Doctoral Thesis

Application of online image guidance for moving tumour treatment using scanned proton therapy

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Publication Date:
2013

Permanent Link:
https://doi.org/10.3929/ethz-a-010158999

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Application of Online Image Guidance for Moving Tumour Treatment using Scanned Proton Therapy

A thesis submitted to attain the degree of

DOCTOR OF SCIENCES of ETH ZURICH

(Dr. sc. ETH Zurich)

presented by

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2013
Abstract

Scanned proton therapy with its physical superiority and clinical flexibility, has been demonstrated as one of the most efficient radiotherapy modality, and seem to be the future of radiation-based cancer treatment. However, currently, this technique is still restricted to static tumour treatments, due to the concerns of the interplay effects as well as the density variations, which could occur in the presence of intra-fractional organ motions. In order to expand its clinical applications for each patient, appropriate motion management approach needs to be determined during treatment planning and needs to be applied during dose delivery.

This dissertation proposes an innovative online image-guide solution, which utilises the Beams’ Eye View (BEV) on-board X-ray imaging system (of PSI-Gantry2) for the clinically implementation of various motion mitigation strategies in the context of scanned proton treatment, for the purpose of maximally reducing motion induced dosimetric deteriorations with the least damage to the surrounding healthy tissues. To achieve this objective, first a dedicated geometry calibration has been performed for the imaging system. Then, two image-based tracking algorithms have been developed to obtain motion from the time-resolved BEV image sequences. However, besides real-time tracking motion at several sparse locations, dense motion information and information on the induced density variation for each pencil beam and each dose calculation position are required for either retrospectively calculating the final dose distribution after each fraction or for deriving beam compensation offsets online. To tackle this trade-off, a patient specific statistical motion model has been employed, which allows to reconstruct deformable motion from the online tracked surrogate motion. The induced density changes can be then derived afterwards. Through extensive simulations of scanned proton treatment using 4D dose calculations with realistic motions, the necessity, feasibility and potential advantage of online image guidance in scanned proton treatment using beam gating and beam tracking have been demonstrated. The results indicate that applicably combining beam gating/tracking with rescanning is beneficial for improving treatment efficiency and reducing dosimetric uncertainties.
Zusammenfassung


This dissertation would not have been achieved without helps and supports from many individuals. First and foremost, I would like to extend my greatest appreciation to my direct supervisor, Prof. Dr. Antony Lomax, for introducing me into the realm of medical physics, and for his innumerable scientific supports and insightful discussions during the last three years. Without him, it would be impossible to participate those advanced developments and obtain the knowledge and experiences in such exceptional proton therapy centre. I sincerely thank him for his confidence in me and continuous encourages, especially during the writing of each paper and this dissertation. Moreover, I want take this opportunity to express my gratitude to Prof. Dr. Gabor Szekely, for allowing me to be a member in his laboratory and supervising this work from ETHz side, and to Prof. Dr. Philippe Cattin for kindly accepting to be my external examiner. This research would not have been carried on without assistances from Dr. Antje-Christin Knopf. My deepest appreciation goes to her, for each detailed discussion, for her availability whenever I meet problems, and for each warm encourage whenever I encounter difficulties and depresses. Furthermore, I also want to show my great gratitude to Dr. Christine Tanner for her meticulous proof-reading of this dissertation, as well as all pertinent suggestions to improve work quality, and to Dr. Monika Zakova for her coordinates and idea sharing during each experiment. Special thanks forward to Dr. Eros Pedroni, for his outstanding innovations of gantry design, which built a solid foundation for the research ideas in this dissertation. Thanks also go to Dr. Sairos Safai and Dr. David Meer for sharing me with their understandings of proton therapy from physics aspects, to Dirk Boye for introducing me various handy tools and for the discussions about motion modelling, to Gabriel Meier for the discussions of proton dose calculation, and to Andreas Schaetti for the discussions of pencil beam scanning. I am also grateful for each technical support I received these years from people both inside and outside PSI, especially to Hans-Ueli Staueble for the calibration phantom construction, to Stefan Danuser for GPPS trouble shootings, to Dr. Harald Paganetti and Dr. Ted Hong for providing 4DCT datasets, to Dr. Uwe Schneider, Dr. Andreas Mack and Jan Hrbacek for helping me with clinical radiography images, and to Dr. Ralf Schneider for kindly providing various fiducial markers for experimental validation.

Life would become very boring and desperate, if there were no accompany to share the moments with happy or sad. My private thanks forward to Antje, Stefania, Maria-Luisa, Margherita, Petra, Greg and all my friends in Switzerland and worldwide, who are treating me like family and who are making my foreign country life as sweet as at home.

Finally, to my fiancée Sicong, my soul mate, who loves me no matter how far away we are, and who supports and comforts me no matter which circumstance we are in front of. Last but not the least, I also want to send my deepest love and thanks to my parents and my family, who have been tolerating my absence for years. Without your love, supports and understandings, I could never complete this milestone in my life.
<table>
<thead>
<tr>
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<tr>
<td>2D</td>
<td>Two Dimensional</td>
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<tr>
<td>3D</td>
<td>Three Dimensional</td>
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<td>4D</td>
<td>Four Dimensional</td>
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<tr>
<td>SI</td>
<td>Superior – Inferior direction</td>
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<td>AP</td>
<td>Anterior – Posterior direction</td>
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<td>LR</td>
<td>Left – Right direction</td>
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<tr>
<td>CT</td>
<td>Computer Tomography imaging</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>OBI</td>
<td>On-Board Imaging system</td>
</tr>
<tr>
<td>EPID</td>
<td>Electronic Portal Imaging Device</td>
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<tr>
<td>BEV</td>
<td>Beam Eye View X-ray imaging system of PSI-Gantry2</td>
</tr>
<tr>
<td>DRR</td>
<td>Digital Reconstructed Radiography</td>
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<td>IGRT</td>
<td>Image Guided Radiation Therapy</td>
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<td>4DDC</td>
<td>Four Dimensional Dose Calculation</td>
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<td>CTV</td>
<td>Clinical Target Volume</td>
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<td>PTV</td>
<td>Planning Target Volume</td>
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<td>ITV</td>
<td>Internal Target Volume</td>
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<tr>
<td>DVH</td>
<td>Dose-Volume Histogram</td>
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<tr>
<td>DDVH</td>
<td>Dose-Difference Volume Histograms</td>
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<tr>
<td>CN</td>
<td>Conformity Number</td>
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<tr>
<td>CDF</td>
<td>Cumulative Distribution Function</td>
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<tr>
<td>WER</td>
<td>Water Equivalent Range</td>
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<tr>
<td>DIR</td>
<td>Deformable Image Registration</td>
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<tr>
<td>PCA</td>
<td>Principle Component Analysis</td>
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<td>DVF</td>
<td>Displacement Vector Field</td>
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<td>MM</td>
<td>Motion Map for 4DDC</td>
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<td>DM</td>
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Background

1. RADIOTHERAPY IN CANCER TREATMENT

Cancer is the second major cause of death after cardiac disease around the world, and it is the only major disease for which the death rates are still increasing (NIH, 2012). Currently, the main therapeutic strategies for curing cancer include surgery, radiation therapy, chemotherapy or any combination of the above. Indeed, the most effective therapy method is surgery, which contributes 22% to overall cure rate. However, for almost 1/3 of patients, the tumour has already spread out before being diagnosed. Radiation therapy, alone or in combination with other treatment modalities, is the second most effective treatment method. Nowadays, approximately 60% of cancer patients are treated using external beam radiotherapy at some point during cancer management (Delaney et al., 2005), and for the foreseeable future, radiotherapy will have an extremely important role to play in cancer therapy.

Energy deposited by radiation can sterilize cells through the production of free radicals in the cell. The higher the delivered dose to the whole tumour, the higher the probability it will be controlled. However, at the same time, normal tissues can also receive radiation or sterilization through similar mechanisms. Thanks to the differences in radiobiological effect between different tissues, normal cells are capable of repairing themselves more rapidly than cancerous cells. Consequently, fractioned treatment, the use of repeated applications of relatively low doses of radiation over many days and weeks rather than a one-shot delivery, has been used for many years to enhance the therapeutic ratio between the dose to the normal and tumour tissues. Despite this, the holy grail of radiation therapy is to concentrate radiation dose to the tumour cell whilst simultaneously sparing surrounding healthy tissue as much as possible. In pursuit of this goal, there has been continuous research into improving radiotherapy delivery techniques, since the start of radiotherapy more than 100 years ago. For example, oncologists have been searching for protocols for defining targets and optimizing the prescribed dosage for maximising outcomes, whilst physicists have been taking use of various kinds of particles and manipulation techniques for improving concentration of dose to the tumour. As such, hundreds of thousands of papers or articles have been published concerning this topic, and there is no doubt that it will continue being a hot topic in the next decades.
In particular, during the last 20 years, radiation therapy has made great steps in developing advanced treatment techniques. For example, Intensity Modulated Radiation Therapy (IMRT) utilizes intensity modulated photon fluencies, instead of homogeneous ones, for conforming dose more precisely to the 3D target shape. Furthermore, different radiation qualities, such as heavier charged particles are being exploited more and more. In particular, protons and carbon ions both have relatively low energy deposited in the entrance path, followed by a pronounced dose maximum in the so-called Bragg Peak region through which superior dose distributions can be obtained, particularly for deep site tumours.

2. RADIOTherapy with PROTONS

1. Rationale and Superiority

In the 1940s, Robert R. Wilson (Wilson, 1946) first proposed the use of protons for radiotherapy. However, at that time, modern computer technology and image technique for treatment planning and precise anatomy description had not been fully developed. As such, the first patients were only treated with proton therapy at the University of California Berkeley in 1954, the Gustav Werner Institute in Uppsala in 1957 and the Harvard Cyclotron Laboratory in 1961.

Compared with photons, protons have a well-defined range when penetrating tissue. The curve can be considered as two parts, a dose plateau and dose peak. In the plateau region, the velocity of the protons is high, so that the deposited doses are relative small, whilst in the peak, the protons slow down and stop, depositing dose in a more concentrated way. The position of this Bragg peak depends on the initial energy of the beam and density of the tissues through which they travel, whilst its height (magnitude) is relative to the number of deposited protons. Its width depends on both range straggling (due to the statistical nature of proton interactions with matter) and the initial energy spectrum of the proton beam. The main advantages of proton therapy is expected to come from this finite range, which provides the potential of reducing the dose burden to surrounding healthy tissues, especially for large tumours with complex shapes. By the end of 2012, there had been more than 100000 patients treated with particle therapy world-wide, of which over 86% were treated with protons (PTCOG1, 2013). Although the portion of particle therapy is currently still low in comparison to conventional photon therapy, this value is expected to substantially increase in the near future (Harald, 2011), due to the large number of on-going facilities planned or under construction (PTCOG2, 2013).

With its long running eye-irradiation program (Goitein and Miller, 1983) and development of spot scanning (Pedroni et al., 1995) since the first patient treatment in 1996, by the end of 2012, over 1400 patients have been treated with this innovative approach, with the main indications being chordomas and chondrosarcomas of the skull base and spinal axis, whose location is relative static during each fraction. Recent analyses of the treatments have shown the drastically promising local control and survival rates (Weber et al., 2005, Ares et al., 2010,
Staab et al., 2011, Weber et al., 2012), and these results compare favourably with results for similar indications from conventional therapy.

![Figure 1-1. Schematic graph of depth dose curve of photon (in blue) and proton (in red) beam](image)

**II. Dose delivery system**

For therapy applications, proton beams can be modulated in two ways (figure 1-2): passive scattering and active scanning. With passive scattering (Chu et al., 1993), a homogenous dose region is generated by the superposition of many Bragg peak layers at different depths to form a so-called Spread Out Bragg Peak (SOBP). Using this technique, the quasi-mono-energetic beam from the accelerator is longitudinally spread out into the SOBP using a fast rotating modulator wheel. In addition, the beam is scattered laterally using either single or dual scattering the systems and then conformed to the target volume by the use of collimators and compensators which are specially manufactured for each field of each patient. As such, apart from the very fast range modulation resulting from the range shifter wheel, the whole target is irradiated simultaneously, in contrast to active scanning, as described next.

Since protons are charged particle, it is not difficult to deflect the proton beam using magnetic fields. As such, the lateral position of a pencil beam can be quickly adjusted by changing magnet currents, whilst longitudinal position (range) can be controlled by direct adjustment of the beam energy or through the introduction of degrading material into the beam. With this scanning approach (Goitein and Chen, 1983, Haberer et al., 1993, Pedroni et al., 1995), the pencil beam is thus manipulated point-by-point and layer-by-layer until the desired dose distribution is achieved.

Compared to passive scattering, there are a number of advantages to active scanning. Firstly, it is capable of delivering intensity modulated proton beams which can provide better conformation of dose in the target and further decrease dose to normal tissues (Lomax, 1999). Secondly, there is a significantly reduced neutron contamination (due to the lack of scatters, collimators and compensators in the beam) which should decrease the risk of treatment related
secondary cancers (Schneider et al., 2002). Most importantly, as active scanning allows for
the individual placement and weighting of many thousands of Bragg peaks, it provides
significantly more flexibility in delivery than passive scattering. There is, however, a potential
downside to active scanning, and that is in the treatment of mobile tumours. In short, when a
tumour is moving, there are essentially two dynamic systems interacting, which of the
scanned beam sequence and that of the mobile tumour. As such, there can be significant
interference effects between the two systems which can lead to substantial dose in-
homogeneities within the tumour volume, an effect known as the ‘interplay’ effect (Phillips et
al., 1992). As such, at the time of writing, we are unaware of any scanned particle therapy
facility that is treating mobile tumours on a regular basis, and by many, this is still considered
to be the main Achilles heel of active scanning.

![Passive scattering diagram](image1)

![Active scanning diagram](image2)

Figure 1-2. Dose delivery systems for proton therapy: passive scattering (upper) and active scanning
(bottom). Images courtesy of Zenklusen (2010)

3. MOVING TUMOUR TREATMENT USING SCANNED PROTON BEAM

I. Motions in radiotherapy

Tumour and/or anatomical motions are considered to be one of most serious uncertainties in
the whole treatment framework (Korreman, 2012), especially for proton therapy (Bert and
Durante, 2011). In general, motions occurring in radiotherapy treatment can be classified into
three types, based on the timescale of the motion. We will first introduce each of them
individually, and then concentrate on the main issue of this project, intra-fractional motion.

1) Position related motion

Positioning related motions are mainly due the variations of the daily patient setup with
respect to that of the reference position used for treatment planning. There are numerous
methods proposed to improve the accuracy of daily patient positioning (Verhey, 1995). One
widely used approach is the use of customized immobilization devices, such as stereotactic head holders, moulds, thermoplastic head masks and Vacuum bite blocks (Song et al., 1996). As their name indicates, these devices are constructed to reduce or restrict a patient's movement in order to keep a relatively constant relationship between the patient and the treatment machine. Such a device can be consistently used for both imaging acquisition and all subsequent dose deliveries, in order to achieve a reproducible position over the entire treatment course (Bolsi et al., 2008). This approach is generally valid for static tumour treatment, typically for skull based tumours. However, this correlation becomes less consistent for the tumour sited in the body region, and the immobilization devices can never stop internal motion. Therefore, it is an advantage of measuring internal tumour location directly. Nowadays, imaging based patient positioning has become a standard in radiotherapy (Jaffray et al., 1999, Jaffray et al., 2002). So called Image Guided Radiation Therapy (IGRT) typically uses On-board Imaging (OBI) systems, such as the Mega Voltage (MV) Electronic Portal Image Device (EPID) or kV X-ray imaging system integrated with the gantry or at least installed in the treatment room (Adler et al., 1994). However, in exceptional circumstances, such imaging can also be performed outside of the treatment room, with the patient subsequently being carefully transported from the imaging to the treatment room (Bolsi et al., 2008). In its simplest form, daily imaging for positioning consists of the acquisition of 2D X-ray images from single or multiple directions, which are then compared to the reference digital reconstructed radiographs derived from the planning CT (Birkfellner et al., 2003). The current trend however, is towards 3D imaging using on-board, cone-beam X-ray imaging devices (Jaffray et al., 1999, Jaffray et al., 2002). In addition, patient positioning can also be performed using ultrasound imaging (Lattanzi et al., 2000, Serago et al., 2002) or surface imaging (Djajaputra and Li, 2005, Bert et al., 2006).

2) Inter-fraction/inter-field motion

In fractionated radiation therapy, the full treatment is divided into multiple fractions delivered every working day over several weeks, and usually the treatment plan is consist of more than one treatment field. During these periods, anatomical changes of the patient and tumour can happen, due to the treatment itself (e.g. tumour shrinkage) or variations of the patients themselves (e.g. weight changes, bladder and rectum filling etc). In principle, these types of motion can be mitigated by regular imaging of the patient (typically with CT, cone-beam CT or possibly MRI) and, as necessary, re-planning the patient based on the new imaging studies, a technique called Adaptive Radiation Therapy (ART) (Yan et al., 1997). As such motions are over a rather long time-scale (days rather than minutes or seconds), these re-planning strategies can be performed off-line.

3) Intra-fraction motion

In many ways, this type of motion is the hardest to deal with, since it occurs within the time it takes to deliver a single fraction or even a single field. Intra-fraction motion is mainly caused by respiratory motion within the dose delivery of each fractionation, although depending on
the treatment site, also heart and other internal motions may be an issue. Respiratory motion affects all tumours in the thorax and abdomen (Bert and Durante, 2011). Yang et al. (2008) reported that amplitude of respiratory organ motion could reach up to 100 mm with a velocity of up to 95mm/s. Particularly, in the thorax and upper abdominal region, tumours can move 10-20 mm, while in the lung, motions of up to 30 mm or more have been observed between inhalation and exhalation (Keall et al., 2006b). Moreover, Chang et al. (2008) found out that 50% of lung tumours have motion amplitudes of at least 5 mm (11% of greater than 10 mm) during one breathing cycle. Also in the liver, peak-to-peak motion amplitudes of over 20mm have been reported under normal breathing condition (Balter et al., 1996). Additionally, Siebenthal et al. (2007b) found that intra-fraction motion could also be caused by organ drift, whose amplitude could possibly reach 10 mm in 30 minute, and Zhao et al. (2011) reported that for gated lung SBRT treatment, baseline shift alone could cause up to 20% probability of tumour moving outside a gating window of 5 mm. A systemic overview of motion characteristics of tumour with different indication can be found in various review articles (Langen and Jones, 2001, Bert and Durante, 2011, Korreman, 2012).

II. Dosimetric impacts of intra-fractional motion

In conventional photon radiotherapy, since the depth-dose curve of photons is rather shallow and therefore insensitive to density variations, dose delivery in the presence of intra-fraction organ motion will generally only cause averaging or blurring of the static dose distribution (Korreman, 2012). However, in the context of particle therapy, an additional dosimetric effect occurs due to motion induced density variation. For passive scattering, Martijn and Christoph (2011) found that the minimum dose in the target can drop from 95% down to 50% for 10mm tumour motion if density variations due to motion are not taken into account. Similarly, Mori et al. (2008) systematically analysed 11 lung cancer patients with varied beam angle and breathing phase, and reported maximum local range variation can reach 10-35mm in Water-Equivalent-Range (WER). Furthermore, when active scanning system is used instead, the so-called interplay effects happen due to the non-synchronization between dynamic scanning delivery sequence and the target motion (Phillips et al., 1992, Bortfeld et al., 2002, Lambert et al., 2005, Bert et al., 2008, Seco et al., 2009, Knopf et al., 2011, Zhang et al., 2012a). Such interplay effects not only generate dose blurring and density variation, but also result in hot or cold spots inside of the dose distribution. Since the inhomogeneity exists inside of the dose coverage, it cannot be generally solved by conventional safety margin approach. In order to avoid redundant descriptions, details about the interplay effects will be profoundly discussed in Chapter 2.

III. Basic framework of 4D treatment

A typical radiation treatment starts with the delineation and definition of the tumour and any relevant organs at risk, together with a dose prescription for the tumour and corresponding dose constraints to critical structures around. In order to deal with positioning uncertainties, the actual tumour volume is extended using a defined safety margin to produce the so-called
Planning Target Volume (PTV). If inter-fraction motion is also expected or observed, this may also include an additional expansion of the volume to the so-called Internal Target Volume (ITV), which is an additional expansion of the initial tumour volume which is designed such that any possible positions of the tumour due to motion are contained within the ITV. Based on this information, appropriate beam directions are selected such that critical structures can be avoided as much as possible, whilst providing sufficient (and generally homogenous) dose coverage to the target. Through the application of a dose calculation algorithm (and related optimisation of the fields), a prediction of the delivered dose distribution to the patient can be calculated and with this, different plan solutions can be compared and evaluated by the responsible clinician. Once selected, the chosen plan will be converted into a format which can be recognized by the treatment machine, and, after the necessary plan specific quality assurance checks, can eventually be delivered to the patient.

However, in the context of treatments in the presence of tumour motions (4D treatment), additional considerations in both the planning and delivery phases have to be addressed.

1) Motion modelling: offline dynamic volumetric motion imaging and quantification

As described above, external beam radiation therapy requires a precise geometric description of the internal patient anatomy. Nowadays, this information can be easily obtained using modern imaging modalities such as X-ray CT and MRI. In particular, X-ray CT is a fundamental component of the treatment planning process, due to the information it provides on the (electron) density of different tissues, which is essential information for the dose calculation process, particularly for particle therapy. Although several groups have shown that, for photon therapy, equivalent treatment plans can be achieved using either CT or MRI image (Chen et al., 2004, Stanescu et al., 2008), this is certainly not the case for particle therapy, and currently, despite its superior soft tissue contrast, the utility of MR imaging in radiotherapy is limited to tumour identification and structure delineation.

Concerning 4D treatments, it is a great advantage to have some form of dynamic, volumetric imaging in order to estimate time-dependent anatomical variations. As such, there is no doubt that the development of respiratory-correlated 4D-CT has been a significant innovation for this purpose (Ford et al., 2003), and this method has rapidly become the standard approach in most modern radiotherapy clinics for imaging motions. In contrast, taking use of 4D MRI imaging duration treatment planning is only just beginning to be investigated (Boye et al., 2013, Tryggestad et al., 2013), but forms the basis for all motion modelling used in this work. As such, the potential advantages of 4D-MRI and limitations of 4D-CT for motion imaging will be discussed in detail in Chapter 2.

2) Beam modelling: 4D dose calculation

4D dose calculations are one of the most important steps in the entire 4D treatment. There are three basic reasons for performing such calculations: to study the potential effects of organ motion on standard spot scanned proton plans, to analyse the potential effectiveness of
different organ mitigation techniques, and finally to potentially be able to reconstruct the actual delivered treatment under conditions of motion. It is these that form the cornerstone of the works presented in this thesis.

All 4D dose distributions used here have been calculated using the in-house developed dose calculation engine (Lomax, 1999, Schaffner et al., 1999) but modified to perform 4D dose calculations based on the deforming dose grid approach (Boye et al., 2013). In short, this algorithm consists of three main components: a nominal, optimised 3D plan calculated on the reference (and static) CT, a set of motion maps (MM), a series of density maps (DM) and a time-stamp (TS) file assigning a specific delivery time to each proton pencil beam to be delivered for each field of the plan. This combination of pencil beam specific spot list and time stamps completely describes the temporal characteristics of the treatment field to be delivered. In a complimentary way, the MM describe the variations of target geometry due to the respiratory organ motion, thus providing a time-varying 3D displacement matrix of each dose grid point. Finally, density maps are generated from the reference CT images by warping this with deformation fields derived for the MM, with the final density variation at each phase being calculated from the differences in radiological path lengths from the time resolved CT to those from the static CT. The 4D dose calculation then uses these MM, DMs and the TS to calculate, and accumulate, the dose at each dose grid point for each pencil beam at each TS.

3) 4D dose delivery: online motion monitoring

One of the most challenging aspects of radiation therapy is to “accurately aim an invisible radiation beam at an invisible target, without missing it and without making the beam so generous that a large volume of normal tissue is irradiated” (Goitein, 2008). This is made particularly difficult as, in principle, the exact location of a tumour cannot be known a priori. Although dynamic imaging techniques such as 4DCT can help to assess the internal organ motion characteristics (such as position, deformation, frequency and phase etc.) over the time of acquisition of the study, these will inevitably vary from cycle-to-cycle and day-to-day. Consequently, the necessity and importance of online motion monitoring has been addressed extensively in conventional radiotherapy (Murphy et al., 2007). The ideal online motion monitoring system should be able to provide direct deformable motion tracking (preferably of the target itself) in real time, and must be compatible with the delivery system on which it is being used for compensating those geometric and dosimetric differences. In addition, the required information from the monitoring system is highly dependent on the chosen motion management approach (see section IV of this chapter).

Motion can be measured online by either external or internal signals. Examples of external motion surrogates are air-flow due to breathing (Zhang et al., 2003) or chest wall motion monitoring, while internal motion monitoring usually requires imaging techniques, such as portal imaging, kV fluoroscopy (Adler Jr et al., 1997, Shirato et al., 1999, Berbeco et al., 2004a, Hoogeman et al., 2009), ultrasound (Hsu et al., 2005, Harris et al., 2006, Xu and
Hamilton, 2006, Harris et al., 2007, Schlosser et al., 2010) and MRI (Lagendijk et al., 2008, Raaymakers et al., 2008, Kerkhof et al., 2011). In addition, internal motion can also be derived using the Electro-Magnetic transponder (Willoughby et al., 2006, Kupelian et al., 2007, Kindblom et al., 2009). However, due to current technical restrictions, motions can currently only be tracked sparsely in real-time, as there is no time resolved volumetric imaging modality available that can extract dense motion field in real-time over the extended period of one treatment fraction. The potential consequences of this limitation for scanned proton therapy will be discussed in detail in Chapters 5 and 7. Moreover, in Chapters 3 and 4, we will comprehensively describe the available image guidance solution currently used in conventional radiotherapy treatment and the purposed on-board imaging systems for scanned proton treatment in our centre.

IV. Motion management of intra-fractional motion

Management of motion is a challenging and important issue. Failure to manage motions could lead to imaging artefacts, poor target coverage, unnecessarily high dose to normal tissues, and dose heterogeneities. Motion management methods for particle therapy can be broadly classified into five major categories (Bert and Durante, 2011): margin-based, breath-hold, beam gating, beam tracking and rescanning. One should realize that there is not one method that is an ultimate solution and significant better than others, and all have their benefits and drawbacks (Knopf et al., 2010).

1) ITV margin

4D dose delivery based on ITV margins is not very different from that of static delivery, but uses an expanded safety margin (called ITV) outside of the CTV which encompasses the largest motion of the tumour (ICRU, 1999). In addition, for particle therapy, there are good arguments that the ITV should actually be field specific in order to take into account the additional effects of range changes due to motion induced density changes (ICRU, 2007, Graeff et al., 2012, Knopf et al., 2013).

2) Breath-hold

Breath-hold is conceptually the simplest method to minimize respiratory motion, as it essentially attempts to stop the physiological process causing motion. Although quite widely used in conventional radiotherapy, it can be limited by the problems of patient cooperation, compliance and reliability in term of the reproducibility of tumour position between each breath-hold. In general, breath-hold techniques can be classified in the following ways:

- Forced Shallow Breathing (FSB)

In this approach, a stereotactic body frame with attached compression plate is employed to restrict the motion of the patient’s abdomen/diaphragm. This technique is mainly used in the abdomen, e.g. for liver irradiation (Lax et al., 1994).
Deep Inspiration Breath Hold (DIBH)

With the DIBH technique, the patient is verbally coached to attain a reproducible deep inspiration breath-hold level. The patient is then asked to hold their breath at this deep inspiration level approximately 10 times during one fraction (Mah et al., 2000) and around 15s for each breath hold (Hanley et al., 1999). DIBH can be performed with/without respiratory monitoring, but usually is helped by restricting nose breathing and preforming only month breathing through the use of a nose-clip.

Active Breathing Control (ABC)

Otherwise known as machine assisted breath-hold, ABC techniques have been proposed and studied for a number of years (Wong et al., 1999, Dawson et al., 2001, McNair et al., 2009, Yoshitake et al., 2009, Wong et al., 2010). In this approach, the patient breathes through a mouthpiece connected to a flow monitor and balloon valve. By closing the valve at a pre-selected phase in the respiratory cycle, breathing can be temporarily halted. ABC is more reliable and repeatable compared to FSB and DIBH and the duration of each breath hold can be longer (up to 15-30s).

Beam gating

In contrast to breath-hold, with beam gating, the patient can breathe freely, but the beam is switched on and off within a predefined window of the breathing cycle. Consequently, tumour motion amplitude is restricted with the beam rather than by restricting the breathing of the patient. Some form of motion monitoring is therefore compulsory for gating, and is performed using either internal or external surrogates. Gating has been successfully employed in photon radiotherapy (Kubo and Hill, 1996, Shirato et al., 2000b, Keall et al., 2006a) as well as in scattered particle therapy (Minohara et al., 2000, Lu et al., 2007, Mori et al., 2010). However, when applying it to scanned particle therapy, one should note that the residual motion within the gating window can still generate interplay effects (Bert et al., 2009). Consequently, it has been proposed to improve gating effectiveness by increasing the overlap of pencil beams (Bert et al., 2009), or by combining gating with rescanning (Furukawa et al., 2007). The potential of gating for scanned proton therapy using online image guidance will be investigated in detail in Chapter 6 of this work.

Rescanning

This technique is only relevant for scanned particle therapy, but as this is the major topic of this work, it is also included in this brief overview. The basic idea of rescanning is that, by applying the scanning pattern several times instead of once, the dose heterogeneities resulting from interplay effects can be smoothed out. A systematic comparison of different rescanning approaches can be found in Zenklusen et al. (2010), and potential of this technique for clinical treatment will be described in detail in Chapter 2 in this dissertation.

Beam tracking
Beam tracking is the term used to describe the method by which the spatial position of the delivered beam(s) are varied dynamically to 'follow' the tumour as it moves. In principle, beam tracking is the best way of minimising ITV margin, whilst meanwhile maintaining a 100% use of the beam during delivery. However, in order to successfully implement beam tracking, several factors need to be considered:

- The target position(s) of each pencil beam should be known at all times;
- The therapeutic beam position must be adjustable at speeds similar or faster than the speed of tumour motion;
- Motion induced dosimetric variations must be compensated;
- All of above requirements should be done automatically and in real time.

In conventional radiotherapy, beam tracking is only being used in a limited way by either a robotic radio-surgery system (Adler et al., 1999, Murphy et al., 2003), the dynamic multi-leaf collimator (Keall et al., 2001, Webb, 2005) or the couch-based movement (Wilbert et al., 2010). For particle scanning, on one side it is somewhat more complicated since extra uncertainties can be introduced due to the sequential dose delivery, but on the other side perhaps the most optimal technique for tracking due to the easier implementation of beam steering. More complicated, because it requires not only the lateral position adaption of each beam, but also an adaption of the range of the Bragg peak in the patient by varying beam energy, more optimal because each individual pencil beam can be adapted quickly using the standard scanning magnets for their delivery (Grözinger et al., 2006). In contrast to the mechanical adjustments required for tracking in photon therapy, particle therapy has the advantages of redirecting pencil beam in an electromagnetic way. From a machine configuration point of view, it will be easier to adjust the position of each pencil beam by parametrically changing the steering file. However, from the motion monitoring point of view, beam tracking for scanned particle therapy requires more precise and highly reliable information on the dense motion and density field. More detail information regarding to the beam tracking can be found in Chapter 7, in which the BEV imaging system will be used as an image guided solution to implement beam tracking for scanned particle therapy.

4. CONTRIBUTIONS AND STRUCTURES OF THIS THESIS

This PhD dissertation was carried out at the Centre of Proton Therapy (CPT) in Paul Scherrer Institut (PSI) between August 2010 and November 2013. The motivation of this project is to perform the necessary clinical and software based ground work that will ultimately allow for safe and accurate irradiation of mobile tumours using actively scanned proton therapy. In order to achieve this objective, this thesis describes an innovative approach for clinically implementing online image guidance for scanning proton therapy using the Beams’ Eye View imaging system of PSI-Gantry2.
The chapters in this thesis have been organized with respect to the 4D treatment framework described in Chapter 1. III.

Chapter 2 concentrates on an issue of 4D planning, which takes use of standard 4DCT liver datasets and two deformable registration methods to investigate the interplay effects and effectiveness of rescanning. The results reveal the potential uncertainties induced by using 4DCT images for liver tumour treatment and highlight the necessity of including utility of 4DMRI into scanned proton treatment planning.

Chapter 3 and Chapter 4 focus on the novel BEV imaging guidance system which can be used as online motion monitoring device for 4D dose delivery. The basic algorithms for imaging system calibration are first described, and then the method and performance of two developed motion tracking algorithms for extracting the surrogate motion measured by this system are detailed.

Chapter 5 proposed a method which allows online reconstruction of deformable motion from the tracked surrogate motion with a statistical motion model pre-built using 4DMRI datasets. Chapter 6 and Chapter 7 respectively study the potential efficacy of two motion mitigation techniques based on the BEV image guidance, namely beam gating and real-time beam tracking/re-tracking, which can be clinically applied for scanned proton beam therapy.

Part of the work in Chapter 2 has been published as a journal article in Physics in Medicine and Biology (PMB) (Zhang et al., 2012a), and parts of that work in this chapter were performed during a previous masters project. The work in Chapter 5 has been published as a journal article in PMB (Zhang et al., 2013c), whilst Chapters 6 and Chapter 7 will be submitted as articles to journals in the near future. In addition, most of the contents in this thesis have been presented in various international or regional conferences during the course of this PhD project (Zhang et al., 2011, 2012b, Zhang et al., 2012c, Zhang et al., 2013b, a).
Chapter 2

Offline motion estimation from 4DCT and its effects on scanned proton beam therapy

1. INTRODUCTION

When applying spot scanned treatment with protons, in addition to dose blurring (ICRU, 2007), interplay effects can also significantly deteriorate dose homogeneity within the target volume. In order to mitigate such effects, sophisticated motion management techniques are compulsory (Knopf et al., 2010, Bert and Durante, 2011). One such approach that we are detailed studying in this chapter is called re-scanning (Furukawa et al., 2007, Zenklusen et al., 2010, Knopf et al., 2011). In this approach, the spot sequence of each field is delivered repeatedly, rather than once, in the hope that dose in-homogeneities resulting from the interplay effects will be ‘washed-out’ over the different rescans. This has been studied in detail for liver cases by Knopf et al. (2011), but only using translation motion model. Obviously however, the successful application of any such approach requires knowledge of the characteristics of the target motion, together with detailed information on the dynamics of the delivery machine. For dose delivery, the beam sequence is deterministic and is therefore well known and easily modified. Motions of tumours, on the other hand, can vary significantly from case to case and even over time for the same patient (Langen and Jones, 2001, Siebenthal et al., 2007b). Consequently, in order to calculate accurate 4D dose distributions under conditions of motion, accurate knowledge of the motion, plus any inter- and intra- fraction variations, is essential.

4DCT is the standard imaging modality in radiotherapy for estimating and modelling motions (Keall, 2004, Trofimov et al., 2005, Bert and Rietzel, 2007), mainly because it is readily available on modern CT imaging systems, but also because the X-ray attenuation data can be accurately converted into high energy photon attenuation maps for subsequent use in photon dose calculations. For similar reasons, CT data is also the standard imaging modality for the calculation of proton therapy treatment plans, and has already been used by a number of authors for 4D dose calculations in proton therapy (Paganetti et al., 2004, Dowdell et al., 2013, Grassberger et al., 2013). Therefore, in this chapter, we investigated both the potential of re-

\[1\text{This chapter was selected from parts of the following published paper, Ye Zhang et al 2012 Phys. Med. Biol. 57 1779 doi:10.1088/0031-9155/57/7/1779 Respiratory liver motion estimation and its effects on scanned proton beam therapy}\]
scanning for mitigating the effects of this interplay effect on scanned proton beam treatments, and the usefulness of 4DCT data for estimating tumour and anatomical motions. In particular, as motion estimations from any form of 4D data require Deformable Image Registration (DIR) techniques to accumulate the dose (either by dose accumulation on a single phase of the 4DCT or through deformation of the dose grid during the calculation), it is important to understand the sensitivity of the motion estimations as a function of the deformation algorithm used. For instance, in conventional radiotherapy, DIR has been used for contour propagation (Chao et al., 2008) and dose distribution warping (Flampouri et al., 2006). However, such techniques are particularly challenging in the liver due to CT providing low contrast image in liver region given limited internal structures for registration. As such, there exists relatively limited work on 4DCT image registration for liver patient cases, especially if no contrast enhancing agent is applied, and the impact of possible mis-registrations on proton therapy has not been quantified and analysed before.

As such, in this chapter we wish to study the following points:

- How effective is re-scanning in the liver under conditions of real motion?
- What are the magnitudes of the spatial differences resulting from different DIR algorithms when estimating respiratory liver motion from 4D CT?
- What is the uncertainty in motion estimation due to the use of different DIR algorithms?
- How much does this uncertainty potentially impact dose distributions in 4D treatment planning for scanned proton therapy?

Consequently, we have applied two different DIR algorithms to 4DCT data sets of three different liver patient cases, and have used the resulting displacement vector fields (DVFs) as input into a 4D dose calculation to estimate the dosimetric effects of ambiguities resulting from the different motion estimations. In order to concentrate on these four points, this analysis has been restricted to the effects of motion alone and for a single fraction (worst-case scenario for motion). As such, no inter-fraction motions or variability have been taken into account.

2. METHODS AND MATERIALS

I. 4DCT dataset

In this chapter, treatment plans for three different liver cases have been investigated, referred to as L1, L2 and L3. 4D CT images were obtained for each patient during free breathing and were reconstructed as a single breathing cycle consisting of ten phases (T00, T10, … , T90). For each case, T00 and T50 correspond to the end of inhalation and end of exhalation respectively. No contrast agent was used for the CT image acquisitions. However, three fiducial markers (denoted as M1, M2 and M3) implanted near the CTV were used, which are
visible in all phases of the 4D CT. CT image resolution was 1x1x2.5mm³. Depending on the tumour type, the GTV has been defined as the tumour which is visible on the CT and/or static MRI (for tumour delineation), and the CTV is generated using an expansion of 0.5–1 cm to account for the microscopic disease at the treating physician’s discretion. All target volumes and organs at risk were contoured on a single reference phase. For cases L1 and L2, whose motion magnitude are less than 10 mm, CT images of T30 were used for contouring. For case L3 whose motion is over 10 mm, T50 is used for contouring (standard clinical protocol at Massachusetts General Hospital (MGH)). The PTV for each of the three cases is a uniform 10 mm expansion of CTV, which accounts for the mean motion extension. In all CT-based figures in this chapter, the CTV and PTV are displayed for each case, but the GTV is not.

As a ‘ground truth’ of the actual motion during the reconstructed breathing cycle, the positions of the three implanted markers in each phase of the 4D CT image have been identified manually. Mean motion in each direction at each time phase have been quantified by averaging over the displacement vectors of the three fiducial markers. Thus, the deformation in each direction is simply quantified by the standard deviation of the displacement vectors over the three markers. Motion information can also be described by other definitions, such as the movements of tumour’s centre of mass. However, due to the lack of contrast in the liver on CT images, the tumour boundary is very difficult to identify. Hence, we considered the information from implanted markers as the only reliable data source to obtain the ‘ground truth’ motion.

II. Motion extraction by deformable registration

DVF of liver motion have been extracted from 4D CT datasets by using two different algorithms: a multi-resolution B-splines transformation model (Rueckert et al., 1999) (referred to as B) and a Demons approach (Thirion, 1998) using an affine transformation for initial alignment (referred to as AD). We chose these two methods since they have been shown to perform relatively well, be comparable in accuracy and have a similar multi-resolution approach (Brock, 2010). For algorithm B, which is a parametric DIR method, five stages of multi-resolution optimization have been performed by a gradual refinement of the image resolution along with a gradual increase in the number of free transformation parameters (called control points). The mean squared difference of intensity was used as a similarity measurement and 100 iterations were performed for each stage. For the AD algorithm, an affine registration was employed at the beginning to obtain a global alignment of the two images. Then, the image intensity histograms are equalized before applying the Demons algorithm. In each iteration, a Gaussian filter with a defined standard deviation was used to smooth the deformation field in order to avoid unrealistic deformation due to the presence of noise in the images.

For both approaches, the 3D CT of the reference phase is defined as the fixed image in the registration framework, while the 3D CTs belong to the other phases are individually used as moving images. For cases L1 and L2, the reference phase was T30, whilst for L3 it was T50,
due to the different contour phases in clinic. Accordingly, the outputs of the DIR for each patient case are displacement fields with vectors for each voxel, pointing from the reference phase (fixed image) toward the other nine phases (moving images). These DVF{s} can then be used as input into the 4D dose calculation engine, which will be explained in more detail in the following section. For the DIR software, we have chosen a well-established open source implementation from Plastimatch (http://plastimatch.org/).

It is difficult to measure the accuracy of deformable registration since there are limited gold standards with which to compare its performance. In this study, the qualitative performances of both DIR approaches have initially been evaluated by visually comparing the liver contours propagated by the DIR from the reference phase to the corresponding phases belong to the nine moving images. Depending on the results of this, the DIR parameters were then further optimized to obtain the best visual estimation of the liver contour with respect to the surface of the liver in the moving CT images. Following this first evaluation, two specific factors have been further investigated, the registration error and the registration ambiguity. The registration error is here defined as the absolute difference between the estimated motion and the ‘ground truth’ motion, which is represented by the landmark (implanted fiducial markers) movements in this study. Specifically, a quantitative validation of landmark-based point tracking was employed, where the Euclidean distance, $e_{t,m}$, for each marker $m$ at each time phase $t$, between the DIR estimated position $(\tilde{x}_{t,m}, \tilde{y}_{t,m}, \tilde{z}_{t,m})$ and the manually identified position $(x_{t,m}, y_{t,m}, z_{t,m})$ in each of nine original moving images was calculated. The performance of each DIR approach is then evaluated by the value $\overline{e}$, where

$$
e_{t,m} = \sqrt{(\tilde{x}_{t,m} - x_{t,m})^2 + (\tilde{y}_{t,m} - y_{t,m})^2 + (\tilde{z}_{t,m} - z_{t,m})^2}$$

$$\overline{e}_t = \frac{1}{3} \sum_{m \in M} e_{t,m} \quad \overline{\overline{e}} = \frac{1}{T} \sum_{t \in T} \overline{e}_t$$

and $T \in \{T00, T10, ..., T90\} \cap T_{fixed}$ and $M \in \{M1, M2, M3\}$.

The registration ambiguity, on the other hand, refers to the fact that different algorithms can generate different deformation fields, leading to an ambiguity in the registration results. This happens because DIR is an ill-posed problem, where correspondences between two images can be estimated differently due to different design criteria of the algorithm itself. This is especially true for image regions containing few structures and when constraining the transformations to be realistic is not straightforward. In this study, this effect will be directly assessed with respect to its influence on the 4D dose calculation.
III. 4D dose calculations

The DVF’s obtained from the two DIR algorithms have been incorporated into our PSI treatment planning system to deform the calculation dose grid in order to perform the time-resolved (4D) dose calculations. In brief, the 4D dose calculation algorithm requires three main components: a 3D dose calculation with pencil beam optimization on the reference phase, a series of displacement maps and a series of density-variation maps. The dose calculation is first performed on the reference CT image by using the ray-casting algorithm of Schaffner et al. (1999) and is optimized using the algorithm described by Lomax (1999). This optimization process ensures that for the static case (and on the reference CT) the target volume is homogeneously irradiated and provides a list of pencil beam positions with relative weights corresponding to this initial distribution. The displacement map of each motion phase is then generated by first geometrically translating and rotating the selected DVF into our machine coordinate system and then sampling it by the dose grid size (5 mm × 5 mm × 5 mm). Thus, the DVF provides a time-varying 3D displacement matrix of each dose grid point. Moreover, density-variation maps are derived from the 3D CT images of the different motion phases using Siddon’s algorithm (Siddon, 1985). A density-variation map for a specific motion phase is then calculated by comparing the radiological path length of this motion phase with the corresponding length in the reference motion phase. According to the corresponding displacement, the density-variation map and the water equivalent range, the dose at each grid point is adjusted at each time instance during the 4D calculation. In this study, we assume that the breathing periods of all three patients are 5 s and their breathing is regular (repeated in the following period).

IV. Treatment planning and plan evaluation

For each of the three liver patient cases (L1, L2 and L3), single- and three-field plans have been calculated on the reference phase. Based on these static plans, 4D plans have subsequently been generated by incorporating either of the estimated motions from the two DIR methods. In addition, 4D distributions have been calculated assuming either a single scan or four times volumetric rescanning with the parameters and speeds being those of Gantry 2 at our institute (Zenklusen et al., 2010). The delivered pencil beams had a full-width at half-maximum of 8 mm at the Bragg peak and were separated in both axes orthogonal to the beam direction by 5 mm. Dead times for moving the pencil beam along these directions (magnetic scanning) are of the order of 4 ms and energy changes have been modelled at 80 ms for a depth change in water of 5 mm. For all fields, field delivery (i.e. delivery of the first pencil beam) started at breathing phase T00 and was performed continuously.

For each plan, dose volume histogram (DVH) curves and D5–D95 values for the CTV have been calculated and used as a measurement of dose homogeneity. In addition, for the plans calculated based on the two different motion estimations, absolute dose differences have been calculated. From these, the maximum/ mean values as well as DVH curves in CTV have also been calculated in order to measure the significance of motion extraction by using either the B
or the AD algorithm. The plan configurations are denoted as $c_{fs\_r}$, where $c$ represents the patient case $c \in \{L1, L2, L3\}$, $f$ stands for the number of fields $f \in \{1f, 2f\}$, $s$ denotes 4D plans and the number of rescanning $s \in \{1s, 4s\}$ and $r$ stands for the used DIR algorithm $r \in \{B, AD\}$. The difference between the plan $c_{fs\_B}$ and $c_{fs\_AD}$ is denoted as $c_{fs\_diff}$.

3. Results

I. Fiducial marker motions

Figure 2-1(a) shows an overall statistics of the 3D magnitudes of all three marker motions along all ten time phases in the form of box plots (McGill et al 1978) for the three cases. The box plots show the median (red line), the 25% to 75% quartile (blue box range), the data range without outliers (black whiskers) and outliers (red crosses). In addition, figure 2-1(b-d) individually show the averaged motion displacements of each case over the three fiducial markers in the left-right (L-R, red), anterior-posterior (A-P, green) and superior-inferior (S-I, blue) directions for all moving images phases with respect to the reference phase. The 3D magnitude, which was computed from the mean of absolute displacements in the three directions is also indicated (dash line in magenta). An uncertainty of manual marker identification due to image voxel and CT artefacts is expected and estimated to be around 1mm (one voxel) in the L-R and A-P direction and 2.5mm (one voxel) in the S-I direction, which is around 3mm in 3D magnitude. From these plots, it can be seen that the motion magnitudes for L1 and L2 can reach 9mm, whilst that of L3 is as high as 17mm. Averaged over the three makers at each phase, the mean 3D motion ranges are of the order of 7mm for L1, 6mm for L2, but over 13mm for L3. Large organ deformation can be observed in both inhalation (e.g. T00-20) and exhalation (e.g. T80-90) phases of case L3, shown as large error bar in figure 2-1(d).

II. Deformable motion extraction from 4D CT

The performance of the two DIR algorithms for each motion phase has been evaluated by visually checking the propagated liver contours and by point-to-point tracking of landmark positions. As an example, resulting contours on orthogonal slices for the time phase T00 are shown in figure 2-2 for all cases, while all other phases have been checked in the same way. In figure 2-3, the statistics of the registration errors for each method and each patient case is shown in the form of box plots. Generally, the larger the motion and deformation are, the more difficult it is for the registration to achieve a good performance. From the results, we can see that the average maximum registration error for moderately moving liver cases (L1 and L2) is no more than 3.5 mm. However, for the larger motions case (L3) the average maximum error can be as high as 7 mm.

An indication of the registration ambiguity can be observed by comparing the corresponding deformation fields. Figure 2-4 shows the DVF$s$ for all patient cases resulting from the two DIR algorithms. The estimated motion magnitude is represented by the vector length as well
as by the colour, while the vector direction indicates the motion directions from the reference phase toward the target time phase (in this example T00). By comparing the resulting DVF in figure 2-4, we can see that different DIR approaches result in non-identical motion maps, even if they were showing similar registration accuracies in figure 2-3.

Figure 2-1. Motion information from implanted fiducial markers manually identified on 4DCTs. (a) box plots showing overall statistics of the 3D motion magnitudes for the three cases over all phases and fiducial markers. Mean and standard deviation of displacements in the different directions for patient case (b) L1, (c) L2 and (d) L3. (y-axis: motion in mm)
Figure 2-2. Contour propagation of liver and CTV using deformable registration for case (top row) L1, (middle row) L2 and (bottom row) L3 for (left) sagittal, (middle) coronal and (right) axial views, showing T00 as background image and contours of (dark blue) reference phase, and after propagation to T00 by registration method (light blue) B and by (yellow) AD.

Figure 2-3. Registration performance based on landmark tracking, showing box plots of the averaged error $\tilde{e}$ for two DIR approaches B and AD for case (a) L1, (b) L2 and (c) L3. (y-axis: error in mm)
III. Static and 4D dose calculations

1) Static dose calculations

Figure 2-5 shows the static 3D dose distributions for the CTV for all plan scenarios. As can be seen, all static plans (including the single field plans) provide adequate to excellent target coverage and dose homogeneity.

2) 4D dose calculations - no rescanning

Figure 2-6 shows the corresponding 4D dose distributions for the single-field plans taking into account motion estimation extracted either by the B method (in the top row) or the AD method (in the lower row). All calculations have been performed assuming a single scan through all pencil beam positions. Compared to the static dose distribution in figure 2-5, motion-induced dose distortions in the form of local over- or under-dosage are evident with both motion estimates. However, the patterns of the dose inhomogeneity differ significantly for the two approaches. The interplay effects are also clearly seen in figure 2-7, where the DVHs of the target volume for these distributions are shown (red and green). These are much shallower than the corresponding DVHs for the static calculations (blue), and correspondingly result in larger D5–D95 values (table 2-1).

Indeed, the D5–D95 values can increase from 8.8% for the static plan to 23.4% when motion is considered (averaged value of L1 over the two motion estimates). In addition, clear differences in the DVHs can be seen in cases L2 and L3 depending on the used DIR algorithm (red and green curves). The somewhat smaller differences for L1 could be due to the presence of liver tissue calcification in this case, which perhaps provides more corresponding...
information for improving the DIR performance, thus potentially reducing the registration ambiguity between the two algorithms.

In order to illustrate potential dose differences due to registration ambiguity, absolute dose differences have also been calculated for all 4D single-field plans and are shown in figure 2-8. Together with table 2-2, this shows that absolute dose differences in the CTV can reach up to 44.6% for any single point and 2.4% on average for case L1. Averaged over all cases, the maximum single point dose difference is 32.8%, and the mean difference is 2.9%. This shows that 4D dose distributions can vary substantially depending on the incorporated motion estimation resulting from different DIR algorithms.

3) The effectiveness of rescanning

Besides single-field plans, multiple-field plans have also been calculated. The use of multiple fields per plan can also be interpreted as a kind of rescanning, since the dose application is divided into several time intervals per fraction. In addition to this, 4x-scaled volumetric rescanning has also been simulated for all plans. The effectiveness of rescanning can be evaluated by comparing the D5–D95 values between the rescanned and single-scan simulations.

Figure 2-9 shows dose distributions after rescanning for case L2. By comparing these to figures 2-6(b)(e), one can note that dose inhomogeneity resulting from interplay effects can be reduced substantially when rescanning is applied. Moreover, the 4D dose distributions for the rescanned three-field plans (figures 2-9(c)(f)) are similar to the static plans in terms of dose homogeneity. This is confirmed by the D5–D95 values in table 2-1, where the averaged mean D5–D95 value over all cases reduces from 17.8% for the single-scan plans to 4.7% for the three-field rescanned plans, approaching the 2.4% of the three-field static plan. This illustrates that although dose distortions due to motion are quite obvious in single-field plans, they can become relatively small when rescanning is applied, either by applying several fields per plan or by splitting the dose delivery into several runs or by both.

In order to investigate the influence of registration ambiguity when rescanning is applied, the absolute dose differences for the 4D dose calculations using the different motion estimations have been calculated. Example slices are shown in figure 2-10, for the single-scanned multiple-field plans (upper row), the rescanned single-field plans (middle row) and the rescanned multiple-field plans (lower row). Compared to the results shown in figure 2-8 (no rescanning), the local dose differences have been substantially reduced. Table 2-2 summarizes the mean and maximum dose differences in the CTV due to the different motion estimations for all plan scenarios and all cases. By using three fields with four times rescanning, maximum point dose differences for case L2 can be reduced from 26.8% to 11.1%, and the mean difference can be reduced from 3.3% to 0.6%. When averaged over all cases, the mean dose difference reduces from 2.9% to 0.6%. Figure 2-11 shows the dose difference DVHs of the CTV for the different plan scenarios, which also confirm that the registration ambiguity-
induced dose differences can become negligible if rescanning is applied. Our results demonstrate that rescanning is effective not only to mitigate motion-induced dose distortion, but also is a robust approach against possible motion estimation uncertainties.

Figure 2-5. Static 3D dose distributions for (top) single-field-plans and (bottom) three-fields-plans for patient case (left) L1, (middle) L2 and (right) L3.

Figure 2-6. 4D dose distribution of one-field-plans (1f) considering organ motion estimated by registration method (top) B or (bottom) AD for case (left) L1, (middle) L2 and (right) L3.
Figure 2-7. DVHs of CTV for all discussed one-field-plan scenarios for case (a) L1, (b) L2, (c) L3. (x-axis: volume in %; y-axis: dose in %)

Figure 2-8. Absolute dose difference of 4D dose distributions of one-field-plans based on motion estimations of different DIR algorithms (a) L1, (b) L2 and (c) L3.

Figure 2-9. Dose distribution after rescanning considering two motion estimations (top) from B and (bottom) from AD for patient case L2 by (left) three-fields one-scan (3f1s), (middle) one-field four-scans (1f4s) and (right) three-fields four-scans (3f4s)
Figure 2-10. Absolute dose difference of all rescanned 4D dose distributions based on the motion estimations from different DIR algorithms for case (left) L1, (middle) L2 and (right) L3, showing (top) 3f1s, (middle) single-field with 1f4s and (bottom) 3f4s.
Figure 2-11. DVH of the dose difference in CTV for case (top) L1, (middle) L2 and (bottom) L3.
(x-axis: volume in %; y-axis: dose in %)

Table 2-1. D5-D95 values of all 4D plan scenarios

<table>
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<tr>
<th></th>
<th>L1</th>
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<th></th>
<th>L3</th>
<th></th>
<th>mean over cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>AD</td>
<td>mean</td>
<td>B</td>
<td>AD</td>
<td>mean</td>
<td>B</td>
</tr>
<tr>
<td>1f1s</td>
<td>23.86</td>
<td>22.87</td>
<td>23.37</td>
<td>19.06</td>
<td>9.32</td>
<td>14.19</td>
<td>19.12</td>
</tr>
<tr>
<td>1f4s</td>
<td>8.05</td>
<td>9.03</td>
<td>8.54</td>
<td>4.88</td>
<td>4.41</td>
<td>4.65</td>
<td>11.95</td>
</tr>
<tr>
<td>3f1s</td>
<td>15.55</td>
<td>12.34</td>
<td>13.95</td>
<td>9.76</td>
<td>5.68</td>
<td>7.72</td>
<td>17.78</td>
</tr>
<tr>
<td>3f4s</td>
<td>6.77</td>
<td>6.28</td>
<td>6.52</td>
<td>2.98</td>
<td>2.53</td>
<td>2.76</td>
<td>4.94</td>
</tr>
<tr>
<td>static 1f</td>
<td>8.84</td>
<td>2.53</td>
<td></td>
<td></td>
<td>7.09</td>
<td>6.16</td>
<td></td>
</tr>
<tr>
<td>static 3f</td>
<td>5.35</td>
<td>2.38</td>
<td></td>
<td></td>
<td>4.66</td>
<td>4.13</td>
<td></td>
</tr>
</tbody>
</table>
Table 2-2. Maximum and mean value of the absolute dose difference in CTV due to different motion estimation for all 4D plans scenarios

<table>
<thead>
<tr>
<th>%</th>
<th>L1</th>
<th>L2</th>
<th>L3</th>
<th>case averaged</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Max.</td>
<td>Mean</td>
<td>Max.</td>
<td>Mean</td>
</tr>
<tr>
<td>1f1s_diff</td>
<td>44.60</td>
<td>2.36</td>
<td>26.80</td>
<td>3.33</td>
</tr>
<tr>
<td>1f4s_diff</td>
<td>30.10</td>
<td>0.89</td>
<td>16.30</td>
<td>0.62</td>
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<td>1.94</td>
<td>10.70</td>
<td>1.54</td>
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<tr>
<td>3f4s_diff</td>
<td>12.40</td>
<td>0.54</td>
<td>11.10</td>
<td>0.57</td>
</tr>
</tbody>
</table>

4. DISCUSSION

From the study of this chapter, it can be observed that the different deformable registration methods applied in this work, the multi-resolution B-splines (B) and the Demons with an initial affine transformation (AD), can acceptably estimate motion based on ten phases of 4D CT data with mean registration errors less than the error level of the ground truth estimation (around 3 mm). Indeed, this registration error can be quantified by comparing the estimated motion with the real motion characterized by the pre-selected corresponding landmarks. However, the sparseness of identifiable landmarks and the deformable nature of the transformation prevent conclusions on the registration error to be applicable to all areas. The registration error is likely to increase for larger motion and deformation, as in our example L3, where the average maximum error can be as high as 7 mm. Brock (2010) reported the results of a comparison study of multi-institutional deformable registration accuracy for multiple organs by a variety of algorithms. There, it was found that most algorithms performed well for contrast-enhanced liver CT images, resulting in mean errors of less than the voxel size (2.5 mm), which is in good agreement with our finding despite our CT images having fewer image features (no contrast agent used). Maximum errors in their study were up to 13.0 mm.

On the other hand, the registration ambiguity cannot be quantified everywhere due to the missing ground truth data in homogenous regions. As shown in figures 2-2 and 2-4, quantifiable features such as liver outline and fiducial markers can be matched (with a tolerable error) if the DIR algorithm is robust enough and parameters are optimized. However, within the homogeneous regions of the liver, where there is little information on how the liver actually moves, the deformation maps can differ significantly, depending on the transformation model and the regularization used by the DIR algorithm. This is due to the intrinsic ill-posed character of DIR, where the additional degrees of freedom of the transformations require denser corresponding image features. Ideally, it is possible that registration errors of the detectable features can vanish, but besides those, the registration ambiguity will always exist in the region with no features, if no supplementary information is provided. Our investigations support the opinion that DIR for non-contrast liver CT data is a difficult problem. The probability of this ambiguity will thus increase in homogeneous areas, and will decrease in regions containing more features, for example in the lung region. Indeed, Brock (2010) also reported improved performance of DIR for lung cases compared to liver
cases, highlighting the necessity of improving the applicability of DIR to other low-contrast anatomic sites. Consequently, for liver CT, the choice of deformable registration algorithm as well as its parameters has great influence on the final deformation field, so that they should be carefully evaluated especially for the 4D dose calculation of scanned proton therapy.

In order to increase the accuracy of liver motion estimation, so as to obtain a more reliable and meaningful 4D dose calculation, an improvement of the DIR performance is required. From a theoretical point of view, this could be achieved for example by including a more realistic regularization constraint into the registration framework to achieve a diffeomorphic correspondence map. The same problem of DIR-induced ambiguity also appeared in other applications of medical image computing, such as for neuro-images and MR breast images analysis. Tanner et al. (2000) and Yanovsky et al. (2007) proposed a solution where the unbiased mapping with logarithmic operations should have an evenly distributed Jacobian matrix to preserve global density constancy for above two applications respectively. From an imaging point of view, supplemental motion information from complementary imaging modalities, such as 4DMRI or 4DUS (ultrasound) from the same patient, could improve the accuracy and reduce ambiguity for motion estimation. Moreover, this additional information would allow investigating the inter-fractional motion variability, an additional effect that we have not studied here. On the other hand, from a clinical point of view, DIR performance can also be improved by implanting more fiducial markers into the target region or by applying contrast agents during image acquisition.

The estimated motion information from deformable registration has additionally been incorporated into our treatment planning for performing 4D dose calculations. The resulting dose distributions, as well as DVH curves for the CTV, confirm that motions can severely affect the dose homogeneity of single-field dose distributions, and that the application of multiple fields per plan and/or rescanning can mitigate these effects (Furukawa et al., 2007, Zenklusen et al., 2010, Knopf et al., 2011). However, we have also demonstrated in this work that different DIR algorithms can result in different motion estimations, and that those in turn can as well have a significant impact on the final 4D dose calculation. Interestingly, however, we have found that rescanning is also a robust approach from the point of view of motion estimation uncertainty, being significantly less sensitive to registration ambiguity than similar calculations assuming single scans. Given that the liver appears nearly homogeneous in a CT scan, the problem of registration ambiguity will be apparent throughout the entire organ. Thus, we believe that the three investigated cases are representative for most tumour locations in the liver. Nevertheless, variations in motion and drift magnitude have been reported for different regions of the liver (Kitamura et al., 2003, Siebenthal et al., 2007b), and it would therefore be interesting to statistically study the robustness of 4D treatment plans as a function of tumour location throughout the liver.

Motion estimation ambiguity resulting from the deformable registration process and the associated uncertainties in 4D dose distributions is inevitable. Thus, we believe that it is
prudent to assess these uncertainties, particularly if 4D dose optimization for a plan is being performed. This could be, for example, the case for beam tracking (Bert et al., 2007) or for motion-based margin adaptation. In the latter case, when incorporating range variations into the optimization of ITV margins, the motion trajectories are used to calculate both lateral and (ideally) distal margins to deal with range changes resulting from motion. For instance, different motion estimations can potentially yield significant variations in motion-adapted ITV margins. On the other hand, with beam tracking, motion trajectories are used to compute the lateral and longitudinal (range) beam adaptation so as to optimally ‘follow’ the tumour trajectory, whilst rotations and deformation of the tumour are dealt with using a dose compensation technique. In both cases, locally varying motion trajectories could potentially result in quite different adaption parameters, which in turn could result in significant dosimetric uncertainties. Indeed, compared to the DIR error-induced dose uncertainties observed in conventional radiotherapy (Salguero et al., 2011), active scanned proton therapy is especially sensitive to DIR uncertainties, since each beam has a sharp gradient in both the lateral and distal directions.

5. SUMMARY

In this chapter, we have applied two deformable image registration approaches to 4DCT studies of three liver patient cases to obtain motion estimates for 4D treatment planning from which the effectiveness of re-scanning for scanned proton beam therapy can be assessed. Although we have shown that re-scanning, as well as being a potentially effective method for reducing the effects of interplay, is also a robust method for dealing with uncertainties resulting from ambiguities between different deformable registrations, we have also shown that (non-contrast) 4DCT data is perhaps not the best modality for extracting accurate motion from the liver region, due to the lack of contrast in the liver in this modality.

As such, in the rest of this dissertation, we will concentrate our analysis on motion data generated from 4DMRI, which provides much more contrast in the liver region and we hope that this reduces the ambiguity of the deformable registration process. In addition, the no-dose characteristics of MRI allow for long-term motion quantification and also allows for imaging to be performed on healthy volunteers. Thus, it is possible to build a comprehensive library of motions from which we can perform our motion analysis. Unfortunately however, 4DMRI does not provide the correct information for proton dose calculations. There is no simple relationship between 4DMRI signals and tissue density, which is the main contributor to proton stopping power of a material. Consequently, to eventually perform 4D dose calculations, we need to somehow combine the motion extracted from 4D-MRI with the ‘density’ data provided by CT. We will do this in the subsequent chapters using the so-called 4DCT(MRI) technique introduced by Boye et al. (2013). In this approach, motion is extracted from 4DMRI data sets and these motions are then used to deform a reference CT such as to generate a so-called 4DCT(MRI) data set. As demonstrated in that paper, such an approach can be used to produce many different 4DCT data sets of good enough quality to perform
accurate 4D dose calculations for pencil beam scanning with protons. Indeed, one of the main advantages of this approach is the potential to be able to monitor patient motions using some form of surrogate and then ‘imply’ the actual 3D motion from these surrogates, based on the prior-knowledge of the motion library extracted from the 4DMRI data sets. In the following two chapters we will investigate the use of one type of clinically available surrogate and show how this can be used with a statistical model to derive anatomical motions using such a 4D motion library.
1. INTRODUCTION

In order to achieve a high precision dose delivery for the treatment of static tumours, accurate information (≤1-2mm) on target locations at the treatment position is essential (Bolsi et al., 2008). Moreover, in the presence of tumour motion, inaccurate target localizations in either space or time can induce even more severe dosimetric consequences (Phillips et al., 1992, Cheung et al., 2013). Therefore, various methods have been developed for monitoring tumour motion. For example, by measuring ventilations of breathing flow (Zhang et al., 2003) or by monitoring chest/abdomen wall movements (Ford et al., 2002) using the RPM system (Varian Medical Systems, Palo Alto, CA), the Anzai belt (Anzai Medical Co, Ltd., Tokyo, Japan) or the VisionRT real-time surface imaging system (Vision RT, London, UK). Although there are some benefits of using such radiation-free monitoring systems, these methods all suffer from the same major drawback that tumour motion is not able to be measured directly. As such, correlation models are usually required, which relate these external, surrogate motions with the internal tumour motion (Gierga et al., 2005, Ionascu et al., 2007). These approaches also need to be updated frequently during the treatment in order to maintain their validity (Kanoulas et al., 2007, Wu et al., 2008, Ren et al., 2012). Furthermore, the reliability of such models is highly patient-specific and their accuracy can very much depend on the tumour indication and location (Gierga et al., 2005, Seppenwoolde et al., 2007). Consequently, here observing any internal motion is of advantage, especially for the sensitive scanned proton therapy.

The new gantry at our institute (Gantry 2) has been developed with the aim of optimising the treatment of mobile tumours with scanned proton beams through fast scanning in all dimensions (Pedroni et al., 2004, Pedroni et al., 2011) but also through the use of an novel Beams-Eye-View (BEV) imaging system for on-board image guidance (OBI) (Pedroni, 2010, Safai et al., 2012). This imaging system is shown schematically in figure 3-1. By using upstream scanning (i.e. before the last 90 degree bending magnet, see Pedroni et al. (2011)), and reducing material in the magnet gap and treatment nozzle to just the essential beam and dose monitoring devices, it has been possible to incorporate an X-ray tube above the bending magnet which can irradiate directly through the nozzle. In this way, X-ray images can be
acquired in the same direction as the treatment field (the most useful direction for assessing motions orthogonal to the proton beam) and crucially on-line during treatment delivery.

The imaging system consists of a 150kV X-ray tube which can be operated in either single-shot or fluoroscopy mode. For image detection, a digital flat panel (Varian PaxScan 4020E), consisting of 3200x2304 detectors with a pitch of 0.127mm, is mounted on an extractable support arm. During the design of this system, the source-to-detector distance (SDD) and the source-to-isocenter distance (SAD) were defined to be 4225mm and 3735mm respectively, providing a field size of 200x250mm² at the gantry isocenter plane. Initially, this OBI system will be used for additional confirmation of the patient’s position at the treatment site after the patient has been positioned previously using an in-room sliding CT. However, in the longer term, we envisage using this system to monitor respiratory tumour motion during dose delivery and to use extracted image features to allow for real-time, dynamic 3D pencil beam adjustments, opening up the possibility of real-time tumour tracking with scanned proton beams (see Chapter 4). It is also the exact motivation and objective of this thesis to profoundly investigate how to apply such image guiding system for scanned proton therapy in context with mobile tumour treatment.

Figure 3-1. Configurations of the Beam's Eye View imaging system of PSI-Gantry2 (Pedroni, 2010) Top: the X-ray tube mounted at the final 90 degree bending magnet. Bottom: the extractable flat panel with the calibration phantom mounted.
To implement this system in clinic, a dedicated calibration process is a pre-request in order to determine corresponding geometry parameters of the imaging system with respect to the treatment system (gantry geometry). This procedure is required for two reasons. Firstly, the rigid mechanical transformation resulting from the gantry rotation will result in geometric variations with respect to the ideal (specified) conditions. Secondly, it must be confirmed that these deformations are reproducible, so that the coordinate system of the BEV imaging system, the proton beam delivery system and the treatment room can be correlated (illustrated in figure 3-2). As soon as this systematic coherence is confirmed, the real geometric parameters of the BEV will be taken into account during the Digital Reconstructed Radiography (DRR) calculations based on the planning CT or 4D-CT data of the patient. Such DRRs provide the reference images for any positioning of the patient, as they are generated directly from the planning CT of the patient, which in turn is the basis for the treatment planning dose calculations. Therefore, to obtain correct DRR calculations, geometry parameter derived from system calibration is compulsory. In addition, and as will be seen in subsequent chapters of this thesis, these DRRs are also an extremely valuable method for simulating BEV images that may be acquired under a whole set of patient and motion specific parameters.
2. METHODS AND MATERIALS

There are basically three steps to perform the geometry calibration: (I) a well-known phantom was first designed and constructed, (II) the characteristics of the BEV image system were modelled as a mathematical representation, (III) a calibration algorithm was developed to derive the real geometry parameters of the imaging system. Each of these processes will be described in detail in the following sections.

I. Design of the calibration phantom

The BEV imaging system has been calibrated using the in-house designed geometry phantom shown in figure 3-3. This consists of 20 precisely localized steel ball bearings (BBs), embedded in a hollow plastic box with a valid size of 180x200x180mm³. Due to the presence of beam line material in the imaging path, with the design phantom size, BBs can be maximally spread out in the whole field of view. Based on the recommendation from Clackdoyle and Mennessier (2011), the BB diameter should be as small as possible, in order to reduce the bias between the projected marker centre and the extracted marker centroid from the X-ray images. Meanwhile, the BBs also need to be large and dense enough in order to generate sufficient contrast such that they can be precisely distinguished from the acquired X-ray images. Besides these two major considerations, together with taking into account pixel size of the BEV image (0.127mm) and the smallest voxel size (1x1x0.6mm³) of the CT images (for the final end-to-end testing), the BBs have been chosen to be 1.5mm in diameter and made of steel (7.85g/cm³). In addition, the plastic phantom has been designed to be sufficiently large to distribute the BBs maximally over the whole volume of interest at all gantry angles. In principle, any kind of BB arrangement can be used as long as the absolute coordinates of each BB (w.r.t gantry isocenter) can be accurately defined. In practice however, the selected distribution should be able to maximally avoid overlaps among the imaged BBs from each beam angle. To derive the projected locations of the BBs in the image coordinate system, the BEV geometry has been parameterized in terms of X-ray tube location $O_X$, EPID detector location $O_D$ and EPID rotation $R_D$ in the STU-beam coordinate system as illustrated in figure 3-4.

II. Modelling of the calibration phantom

In order to build a mathematical model of the geometric phantom, the location of each BB in the beam coordinate system ($M_N(\alpha)$ ($N^{th}$ BB)) for a given gantry angle $\alpha$ needs to be determined. In the room coordinate system, this information ($B_N$) can be easily obtained after properly aligning the phantom with respect to the isocenter $O$, which is indicated by the three room lasers. Since $O$ is the common origin for all three coordinates systems, the BBs’ locations in the beam coordinate system at any desired gantry angle can be derived as,

$$M_N(\alpha) = R(\alpha) \cdot B_N \tag{3-1}$$

where
\[
R(\alpha) = \begin{bmatrix}
1 & 0 & 0 \\
0 & \cos \alpha & \sin \alpha \\
0 & -\sin \alpha & \cos \alpha
\end{bmatrix}
\]

is the rotation matrix, which simulates gantry rotations around the X-axis in room coordinates.

To be more specific,

\[
\begin{aligned}
O_X &= O_X' + dO_X(\alpha) \\
O_D &= O_D' + dO_D(\alpha) \\
R_D &= R_D' + dR_D(\alpha)
\end{aligned}
\]

(3-2)

where \(O_X' = [0, 0, -SAD]\) and \(O_D' = [0, 0, SDD - SAD]\) are the ideal coordinates of the X-ray tube and EPID detectors, \(R_D' = (0, 0, 0)\) for ideal EPID rotation, while \(dO_X(\alpha)\), \(dO_D(\alpha)\) and \(dR_D(\alpha)\) are the geometry correction vectors which need to be determined by this calibration procedure.

The projection function \([s, t, u] = f_{CB\text{-projection}}\) of any incident X-ray beam originating from the X-ray tube position \(O_X\), and penetrating the \(N^{th}\) BB, \(M_N\), can be determined as a line in the STU-beam coordinate system using the following equations,

\[
\begin{aligned}
t &= k(M_{N,1} - O_{X,1}) + M_{N,1} \\
u &= k(M_{N,2} - O_{X,2}) + M_{N,2} \\
s &= k(M_{N,3} - O_{X,3}) + M_{N,3}
\end{aligned}
\]

(3-3)

where \(k\) is the coefficient describing the line function.

In addition, the EPID imager is then considered to be a plane, of which the ideal normal vector can be defined as

\[
\overrightarrow{n_i} = O_D' - O
\]

(3-4)

However, since gantry rotations can induce gravitational variations of both the detector and the extractable mechanical support, the orientation of the imaging panel in reality may not be perfectly parallel to \(\overrightarrow{OO_D}'\). This effect can be modelled by applying a rotation matrix \(R_D\) to the ideal normal vector. Therefore, the normal vector of the imaging detector with any arbitrary rotation can be described as,

\[
\overrightarrow{n} = R_D \cdot \overrightarrow{n_i}
\]

(3-5)

where the rotation centre has been defined as the imaging plane centre \(O_D\) and the rotation axes are defined as W, V and S respectively. The equation of the 3D plane describing the EPID detector can then be represented as,
\[
\vec{n}_1 \cdot t + \vec{n}_2 \cdot u + \vec{n}_3 \cdot s = \vec{n}_1 \cdot O_{D,1} + \vec{n}_2 \cdot O_{D,2} + \vec{n}_3 \cdot O_{D,3}
\] (3-6)

Substituting \(t\), \(u\), and \(s\) in equation (3-6) with the expressions in equation (3-3), we thus obtain,

\[
k = \frac{\vec{n}_1 \cdot (O_{D,1} - M_{N,1}) + \vec{n}_2 \cdot (O_{D,2} - M_{N,2}) + \vec{n}_3 \cdot (O_{D,3} - M_{N,3})}{\vec{n}_1 \cdot (M_{N,1} - O_{X,1}) + \vec{n}_2 \cdot (M_{N,2} - O_{X,2}) + \vec{n}_3 \cdot (M_{N,3} - O_{X,3})}
\] (3-7)

Therefore, by first calculating the coefficient \(k\) in (3-7), the numerical solution of the BEV projection function \(f_{CB,projection}\) can be derived from equation (3-3). Consequently, the projected BB coordinates \(D_N(\alpha)\) in the stu-beam coordinate can be determined thus

\[
D_N(\alpha) = f_{CB,projection}(M_N(\alpha), O_X(\alpha), O_D(\alpha), R_D(\alpha))
\] (3-8)

### III. Calibration algorithm

The main objective of the geometric calibration is to establish the correct correspondences between the object 3D location in space and its imaged 2D location provided by the BEV. Since the geometric characteristics have been parameterized (see equation 3-8 above), the expected location of each BB under any given geometry parameters can be calculated. Once the phantom has been positioned properly with respect to the isocenter, BEV X-ray images can be acquired, from which the real, projected locations of each BB can be extracted from the image. Under ideal conditions, that is without any mechanical deformation during gantry rotations and without any localization error, the detected locations should be identical to those derived by calculation using \(f_{CB,projection}\). However, differences between the analytical calculation and positions derived from the BEV images are observed, due to these inevitable mechanical distortions. Therefore, to derive the realistic geometry parameters therefore, a system calibration has been developed based on an extrinsic 2D/3D registration procedure, which optimizes the correction factor \([dO_X, dO_D, dR_D]\) such that these provide the best match (minimum squared distance) between the expected BB positions and the positions derived from the BEV image. Thus, if \(Q_N(\alpha)\) is the detected location of the \(N^{th}\) BB from the acquired BEV image at gantry angle \(\alpha\), the optimized geometry parameters at this gantry angle can then be deduced by minimizing the following objective function;

\[
[dO_X, dO_D, dR_D] = \text{argmin} \left( \sum ||Q_N - D_N|| \right)
\] (3-9)

Based on this calibration algorithm, we first assessed the influence of each geometric parameter in order to choose the appropriate discrete search space accordingly, and then the geometry calibration procedures were performed at individual gantry angle from -20 to 180 degree with 10 degree intervals.
Figure 3-3. Illustrations of calibration phantom

Figure 3-4. Schematic diagram of geometry of BEV imaging system
3. RESULTS

I. Influences of the geometry parameters

In principle, there are no restrictions to the values for each input argument in equation (3-9), but bounding the inputs helps to increase calculation efficiency. As such, boundary conditions have been introduced by taking into account the measured characteristics of the system (e.g. the distance between the isocenter to the imaging plane centre) or by considering the physical sizes of system components (e.g. the gantry and X-ray tube supporter). First though, the sensitivity of each parameter in \([dO_X, dO_D, dR_D]\) was investigated independently using computer simulation, in order to determine a reasonable searching range and step size for the optimization.

Seven representative BBs simulated in the STU-beam coordinate system, sparsely located in the extremes of the field-of-view of the BEV system. These had the following coordinates (in mm):

- P0: (0 0 0)
- P1a: (-50 0 -200)
- P2a: (-150 0 -200)
- P3a: (-150 -150 -200)
- P1b: (-50 0 200)
- P2b: (-150 0 200)
- P3b: (-150 -150 200).

Point P0 is the isocenter, and it is assumed that this point will be least influenced by geometric variations. P1/2/3a are located at the plane 20cm towards the X-ray tube direction w.r.t the isocenter plane, whilst points P1/2/3b are 20cm from the isocenter away from the X-ray source. Additionally, three different in-plane locations have been considered, with the P1 and P2 points having offsets only along the T-direction and P3 offsets in both the T and U directions.

Figure 3-5, 3-6 and 3-7 show the effects of the simulated translation of imager detector and X-ray tube position, or rotation of the detector on the projected 2D locations of these artificial BBs, as differences from their nominal projected position, as a result of simulated translations of either the X-ray tube or the detector, or rotations of the detector. From these results, we can conclude that detector translation is potentially the most significant effect in comparison with the other two factors (X-ray tube translations and detector rotation). In addition, the projected locations of the isocenter BB (dark blue) are only be influenced by lateral translations in \(t\) and...
u direction of either detector or X-ray tube, and no discrepancy among BBs has been observed due to lateral translations of the detector.

As the slopes in left column of figure 3-5 are close to 1, to achieve pixel size calibration accuracy, the search step in the calibration optimization for determining the parameters relating to lateral translations of the detector have been set to 0.2mm, which is slightly more than one pixel size of the BEV images. In addition, the search range has been restricted to within [-10 10] mm, based on knowledge of the possible physical deformations of the whole system (based on the collision detection system of the gantry). Furthermore, with regards to influences of longitudinal (S-axis) translations of the detector, which will affect the magnification factor, the off-axis distances of the BBs have been shown to be a major factor for determining this effect. For instance, as shown in the right column of figure 3-5, the slopes of the plots increase when a BB is located farther from the S-axis. Since the maximum value of those slopes is less than 0.05, the search step for this parameter has been set to 5mm within the range of [-50 50] mm. Similar selection criteria have been employed for the search space of the X-ray tube position. As indicated by differences in the slopes in figure 3-6, lateral translations will introduce different effects on the projected 2D location, depending on the 3D location along the S-axis. In addition, variations due to longitudinal translations are non-linear, especially for BBs located near the X-ray tube. Finally, realistic ranges for lateral and longitudinal translations of the X-ray tube have been determined as [-200 200] mm with 2mm search step and [-500 500] mm with 20mm search step respectively. The final parameter for which sensitivity needs to be determined is the detector rotation shown in figure 3.7. From these, we can see that potential detector rotations with respect to either the T or U axis can introduce non-linear variations of BBs which have in-plane offsets in both the T and U direction (P3a and P3b), and that 5 degrees of rotation can generate 1mm differences compared to the ideal location. Consequently, the optimization ranges for the detector rotation parameter have been chosen as [-5 5] degree with 0.5 degree interval.
Figure 3-5. Influence of simulated detector translations to projected locations of the example BBs. (upper row: differences in T direction; bottom row: differences in U direction; left column: translation in T-direction; middle column: translation in U-direction; right column: translation in S-direction).

Figure 3-6. Influence of simulated X-ray tube translations to projected locations of the example BBs. (upper row: differences in T direction; bottom row: differences in U direction; left column: translation in T-direction; middle column: translation in U-direction; right column: translation in S-direction)
II. Calibration results

As a first step of the calibration process, the mean differences between the BB locations extracted from the BEV images and those calculated under the ideal conditions (see Chapter 3 section II) have been determined for each gantry angle. These are shown, in the form of box-plots, in figure 3-8. As can be seen, discrepancies of up to 4mm can be found, indicating the need for a gantry specific calibration procedure. The major discrepancies occur in the T-direction, which is to be expected when looking at the relationship of this axis with the mounting of the EPID (see figure 3-2). As the gantry rotates, it is clear that gravitational effects on the extractable support arm of the EPID will be the largest along this axis. However, pronounced variations of offset discrepancy (width of the boxes) have been observed in the U-direction for different gantry angles, which might be due to small disagreements between the real gantry rotation axes to the axis marked by the room lasers.

The discrepancies were then used as the initial values for a set of optimizations which took into account successively more complex geometrical deformations of the gantry and imaging system. These can be categorized as follows:

- 2 Degrees of Freedom (DoF) correction of EPID lateral translation
- 3DoF correction of EPID translation
- 4DoF correction: 3DoF of EPID translation and longitudinal X-ray tube translation
• 6DoF correction of EPID translation and rotation

• 9DoF correction: 6DoF of EPID translation & rotation and 3DoF of X-ray tube translation

Figures 3-9 to 3-13 show the residual discrepancies as a result of each of the correction strategies (2DoF–9DoF) listed above, and figure 3-14 summarises the mean and maximum residual discrepancies of each calibrated gantry angle as a function of correction method. By comparing these results with those shown in figure 3-8, it is immediately apparent that a gantry angle specific calibration procedure is required, and already with the simplest correction (2DoF), discrepancies between measured and calculated BB positions are in the sub-millimetre range over all gantry angles. Indeed, from figure 3-14, it can be seen that although a small improvement is found on average by moving to the 3DoF correction, little extra benefit in accuracy is found using the more complex correction strategies (4DoF – 9DoF).

Figure 3-8. before correction: differences between detected and calculated BB locations with a function of gantry angles (a) RMS, (b) in T-direction, (c) in U-direction, (X-axis: gantry angle (in degree) and Y-axis: (in mm))
Figure 3-9. 2DoF correction: differences between detected and calculated BB locations as a function of gantry angles (a) RMS, (b) in T-direction, (c) in U-direction, and (d) the correction vector for EPID translation in T and U directions. (X-axis: gantry angle (in degree) and Y-axis: (in mm))
Figure 3-10. 3DoF correction: differences between detected and calculated BB locations as a function of gantry angles (a) RMS, (b) in T-direction, (c) in U-direction, and (d) the correction vector for EPID translation in T/U/S direction. (X-axis: gantry angle (in degree) and Y-axis: (in mm))
Figure 3-11. 4DoF correction: differences between detected and calculated BB locations as a function of gantry angles (a) RMS, (b) in T-direction, (c) in U-direction, (d) the correction vector for EPID translation in T/U/S directions and (e)X-ray tube translation in S direction. (X-axis: gantry angle (in degree) and Y-axis: (in mm))
Figure 3-12. 6DoF correction: differences between detected and calculated BB locations as a function of gantry angle (a) RMS, (b) in T-direction, (c) in U-direction, and the correction vector for (d) EPID translation and (e) EPID rotation. (X-axis: gantry angle (in degree) and Y-axis: (in mm/degree))
4. DISCUSSIONS

Theoretically, the more geometric components are under consideration, the more accurate calibration results can be obtained, and ideally the 9DoF geometry correction is the best solution. However, our results indicate that for the BEV imaging system of PSI-Gantry2, comparative results have already been achieved by only taking into account the corrections for detector translation. Given the unique design of this imaging system, where the X-ray tube is nearly 4m away from the detector, the influences from either X-ray tube translation or detector rotation are clinically negligible. This is in contrast to the case with a conventional OBI system, whose SDD is around 1.5m. Moreover, taking into account all other possible
uncertainties during experiment, such as misalignments of phantom position (<0.5mm), the width of the room lasers used for positioning (0.5mm) and the accuracy of 2D BBs’ centroid extraction (<0.5mm), the resulted calibration accuracy using the 3DoF correction can already been considered as sufficient. If one cannot exclude above mentioned experimental setting errors, extending to the more complex geometry model is meaningless. However, from the algorithm improvement point of view, besides the current 9DoFs describing the imaging system geometry, additional 6DoF (translation and rotation) regarding to phantom positioning condition can also be considered in the 2D/3D optimization procedure as extra constrains, describing the inevitable errors from phantom setup. These six parameters should be unique regardless gantry rotations. Additionally, currently calibration was performed at each desired gantry angle independently, so that further considering the inter-gantry relationship may also strengthen accuracy and efficacy of the final calibration results.

5. SUMMARY

In this chapter, a novel BEV X-ray imaging system, as incorporated into the PSI-Gantry2, has been introduced and its potential applications for image guided scanned proton therapy have been explained. It has been shown that, due to inevitable deformations of the gantry mechanics as a function of gantry angle, gantry angle specific corrections must be applied to achieve sub-millimetre geometrical accuracy of the system. As such, an extrinsic 2D/3D registration based calibration method has been developed, from which correction vectors can be deduced. Our results show that a 3DoF correction approach suffices for achieving mean/max accuracies of 0.4/0.9mm over all gantry angles, and no substantial gain has been found when using more complex correction strategies.
Chapter 4

Online surrogate motion tracking from BEV images

1. INTRODUCTION

In Chapter 3, we introduced the Beams-Eye-View on-board imaging system and described the detailed calibration procedure for acquiring spatially accurate images. In this chapter, we will describe the first stage in extracting motion information from fluoroscopic images acquired by this system, from which we can then reconstruct 3D motions using a motion model constructed from 4D-MRI studies (see Chapter 5). In particular, we will describe two feature extraction algorithms developed as part of this work for tracking either implanted fiducials or the motion of the diaphragm in Superior-Inferior (SI) direction.

In computer vision, the difficulties of tracking objects for video analysis have been summarised by Yilmaz et al. (2006). In the context of the BEV system studied in this work, several crucial problems need to be recognised and solved specifically. For example, depending on the imaging parameter settings, gantry directions and patient sizes, resulting image intensities of both the traced target and the background differ substantially. Irregular breathing can cause abrupt motions which break the motion patterns in the previous cycles, and partial or full occlusion can occur when the tumour moves relative to bony structures. Furthermore, motion components along the imaging direction will be lost when a monoscopic imaging system (such as ours) is used, and tumour motion also consists of rotations and deformations besides translations. In the literatures within the realm of radiotherapy, numerous algorithms have been proposed for tracking tumour motions online, but if we focus on strategies using transmission imaging only, such as MV portal imaging, OBI projection or X-ray fluoroscopy, these methods can be generally classified into two categories: marker and marker-less approaches.

Due to the poor contrast of soft tissues on X-ray images, especially for tumours located in abdomen regions, fiducial markers are typically implanted near to the GTV in order to improve the reliability and accuracy of tumour localization. Clinically acceptable fiducial markers can be made of different materials (e.g. gold, carbon or polymer), come in various sizes (e.g. 0.35-1.1mm in diameter and 0.5-5mm in length) and also in diverse shapes (e.g. spherical, cylindrical or coil-shaped, see e.g. (Handsfield et al., 2012)).
Many fiducial-based image tracking techniques have been developed, with most being based on the concept of template matching. For example, Balter et al. (1995) used the marker templates which were generated from the images of the first delivered fraction to derive the marker positions on subsequent fractions by cross correlation. Later, more generic templates can be constructed by incorporating specific marker kernels, such as the MEK filter (Nederveen et al., 2000), Mexican hat filter (Buck et al., 2003), blob detection (Keall et al., 2004) or the improved version of blob detection proposed by Park et al. (2009). Moreover, Pouliot et al. (2001) and Aubin et al. (2003) directly exploited the spatial distribution of marker attenuation profile from portal images in order to identify the locations by their local intensity minimum. In addition, for reducing the probability of false positive detection, as well as increasing the calculation efficiency, all above methods are usually constrained with the well-defined criteria. One typical approach is to introduce a (manually) pre-defined region of interest (ROI) to restrict the search area for the target to include its likely motion. Alternatively, Li and Sharp (2013) have proposed improving the robustness of tracking algorithms by using additionally spatial relationships among multiple markers. Finally, a number of authors have proposed automatic methods based on prior knowledge of 3D marker location from the planning CT and/or DRR (Tang et al., 2007, Mao et al., 2008, Wiersma et al., 2008, Park et al., 2009, Slagmolen et al., 2010, Poulsen et al., 2011).

Generally, fiducial marker boundaries are able to generate strong changes of local image intensities which usually can be identified by edge detection with high accuracy. As such, the resulting edge features are less sensitive to background changes and can carry both shape and appearance information. In addition, for a fixed imaging direction, the marker appearance will not change considerably in time and hence the preselected features are stable. Although small variations might happen if the marker is large and moves significantly along the imaging direction, this can generally be solved by allowing the template parameters to change within limits. However, fiducial based tracking is not without its disadvantages, due to the small but finite risk of pneumothorax (for implants in the lung) and also the possibility of marker migration over the time of the treatment (Kothary et al., 2009). Consequently, a number of groups have also investigated marker-less tracking. For instance, Berbeco et al. (2005a) proposed the use of intensity changes between inhalation and exhalation phase as a respiratory signal for gating. Similar strategies have also been developed to derive one-dimensional gating signals using various machine learning methods, such as support vector machines (Cui et al., 2008), clustering (Cui et al., 2007b) and artificial neural networks (Lin et al., 2009). However, if target locations need to be known precisely, it is preferable to directly track the tumour from the image itself, since less prior information is required. However, these kinds of methods have been primarily applied to lung cases due to the somewhat better contrast between the tumour and surrounding healthy tissues. For example, Cui et al. (2007a) generated multiple motion-enhanced templates from fluoroscopy images and then measured the similarity between the daily images with these templates using Pearson correlation with a voting scheme. Arimura et al. (2009) applied a similar strategy to MV images with a single
template built from the reference portal image and cross correlation used as similarity measurement. Xu et al. (2008) combined template matching with optical flow to rigidly track the tumour centroid frame by frame, from which they were able to trace deformable tumour contours with the help of a pre-generated active shape model (Xu et al., 2007). Furthermore, tumour motion can also be extracted by taking into account other image features. Rottmann et al. (2010) developed a multi-region tracking algorithm which determined landmarks from MV lung images by the use of a local variance filter (Haralick, 1979) and Xie et al. (2013) detected feature points by the use of orientation gradient histograms of local image derivatives, characterising them using a SIFT descriptor (Lowe, 1999, Lowe, 2004).

Finally, instead of trying to track the tumour directly, surrounding visible anatomic structures have also been utilized as surrogates, such as the diaphragm (Cerviño et al., 2009). Such techniques are particularly important in the liver where there is little or no contrast between the tumour and surrounding normal liver tissues on X-ray images. As such, diaphragm motion has been tracked by the well-known Amsterdam shroud method (Zijp et al., 2004, Rit et al., 2012), which extracted SI motions from the so-called AS image, whereas Keatley et al. (2000) proposed to use the active contour algorithm for tracking the diaphragm. It was based on minimizing a joint scoring energy function, which measured the deviation from detected edge features and the preferred shape. More recently, Chen and Siochi (2010) have combined this idea with the dynamic Hough transform for automated hemi-diaphragm detection.

As mentioned above, the BEV imaging guidance system on Gantry 2 has been designed with the aim of determining internal tumour motion characteristics during dose delivery. In particular, we are interested in obtaining real time information on potential breathing irregularities or target base line shifts which may occur during irradiation. Inspired by the above mentioned work in conventional radiotherapy, in this work we have investigated two approaches to feature extraction from our time-resolved BEV kV images, namely fiducial marker and diaphragm tracking, and have developed the corresponding tracking algorithms for extracting such motions online (Zhang et al., 2012c).

2. METHODS AND MATERIALS

In this section, we will first describe the image sequences we have used for validation, and then move on to describe two algorithms which can be used to track fiducials or diaphragm motions.

1. Image sequences

The experimental setup has been shown in figure 4-1(a), with which fluoroscopy sequences have been acquired using the default clinical settings (70kV, 4mA and 2Hz) of the BEV system and an anthropomorphic breathing phantom at two development stages from two different imaging directions (AP and LR) respectively. The anthropomorphic phantom we have used has been developed in collaboration with CSEM (Neuchatel, Switzerland) (Zakova
et al., 2012) and is shown in (c) and (d). It consists of a realistic skeleton of the thorax region and an air-tight lung component into which an artificial tumour can be inserted. Air inflation leads to tumour movements and rib cage expansion, which mimics realistic respiration behaviour and anatomic variations. Moreover, as shown in (b), single Visicoil™ gold markers with 10mm in length and 1.1mm in diameter have been implanted into an artificial silicon tumour, which was then inserted into the artificial lung.

In addition, in order to simulate fluoroscopic images of real patients, time resolved Digital Reconstructed Radiographs (DRRs) have been calculated from 4DCT(MRI) data sets for an example liver patient using the BEV geometry, as shown in figure 4-1(e). These 4DCT(MRI) data sets were generated using the method proposed by Boye et al. (2013), which maps motions extracted from 4D-MRI studies onto a single-phase reference CT, and then deforms this CT image based on the mapped motion field. This step is preliminarily necessary since Gantry 2 is not yet in clinical operation so that we have no real patient data from this imaging system. However, this setup also has the advantage that 3D motion has been known from the volumetric images, which hence allows for quantitative evaluation of the tracking performance.

Table 4-1 summarizes the details of each fluoroscopy sequence used for algorithm validation. The marker tracking algorithm has been validated using all fluoroscopy image sequences, whereas the diaphragm tracking method has been only tested through the three DRR image sequences (dataset 5-7) as there is no realistic diaphragm in our anthropomorphic phantom.

<table>
<thead>
<tr>
<th>Dataset No.</th>
<th>Imaging modality</th>
<th>Target type</th>
<th>Marker amount</th>
<th>Imaging direction</th>
<th>Sequence length (in frame)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BEV in fluoroscopy mode</td>
<td>Phantom 1</td>
<td>1</td>
<td>AP</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Phantom 2</td>
<td>1</td>
<td>AP</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>DRRs from simulated 4DCTs</td>
<td>Patient liver</td>
<td>3</td>
<td>F0</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>F1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>F2</td>
<td></td>
</tr>
</tbody>
</table>
Figure 4-1. Acquisition of BEV fluoroscopy sequences. (a) The experiment setup of moving phantom and imaging system. (b) The inserted gold fiducial marker in the artificial silicon tumour. (c)(d) Anthropomorphic breathing phantoms in the I and II stages. (e) Illustration of reference CT with corresponding three imaging directions for DRR calculation.

II. Fiducial marker tracking

1) Definition of marker’s Region of Interest (ROI)

As a first step, the marker tracking algorithm is initialized by determining marker-specific ROIs. Since the online motion tracking method will only be performed after the patient has been correctly aligned and positioned in relation to the proton beam (and therefore the BEV system), information on the 3D location of the fiducial markers from the planning CT(s) can be used to calculate the expected 2D locations on the BEV images, based on the projection functions derived in Chapter 3. Thus, as indicated in figure 4-2(a-b), a rectangular ROI with a size of 200x300 mm² is generated for each fiducial with its centre located at this calculated 2D location. The size of the ROI has been on designed as sufficient large to encompass maximum motion.
2) Detection of underlying image features

After cropping the image to the defined region of interest, the second step is to measure the characteristics of the fiducials to generate feature sets for detecting and matching the fiducials. Since edge detection algorithms are sensitive to noise, a de-noising method has been applied as a pre-processing step, which combined an adaptive noise-removal filter (Lim, 1990) and a median filter (Keall et al., 2004). Afterwards, a Laplacian of Gaussian (LoG) operator is then used for extracting the marker edges (d) and local binary regions are obtained using a sequence of morphological image operations (e-g). In order to achieve this designed image processing pipeline, the implemented MATLAB routines ‘wiener2’, ‘median2’, ‘edge’ and ‘regionprop’ were used respectively.

3) Determination of fiducial marker image characteristics

On the first image frame, the size of the LoG filter is iteratively optimized until both long edges of the marker are detectable. Based on this, the characteristics of the fiducial marker mask (labelled by the purple arrow in (i)) is quantified in terms of area and roundness, both of which are often used for object representation. Roundness, defined by equation (4-1), is then used to describe the compactness of the object, a property which has been widely used as a discriminator to distinguish objects with different shapes (Gonzalez and Woods, 2002). In addition, the marker mask was diluted to be slightly larger than the whole marker shape, such as to contain sufficient local intensity variations. Finally, these measured characteristics, area and roundness of the marker template as well as the mean/minimum/maximum of the template region, were saved as template features and used later for recognizing each fiducial marker from its surrounding environment in the subsequent image frames.

\[
roundness = \frac{4\pi \times area}{perimeter^2}
\]  

(4-1)

4) Fiducial tracking using derived template features

For each temporally resolved image frame, the pre-processing steps described in 2) were first applied using the same parameters as for the reference images, which are including image cropping, de-noising, edge detection and generation of silhouettes by morphological operations. The area and roundness features were extracted for all candidate objects and then compared to the template values resulted from 3). After eliminating spurious regions (labelled by the orange arrows in figure 4-2(i)) which do not fulfil the selection criteria (area and roundness), the maximum, minimum and mean intensity inside each mask region are calculated and used as an additional check of the remaining regions. As soon as the final marker region has been confirmed, the intensity weighted centroid can be determined. Finally, the marker trajectory is obtained by deducing the detected marker location from the location at the reference phase.
III. Diaphragm tracking

As the diaphragm exhibits strong intensity gradients in the projected X-ray images, we have also developed an algorithm for tracking diaphragm motion from fluoroscopic BEV images. The basic steps of this tracking algorithm are illustrated in figure 4-3. Initially, a rectangular ROI encompassing the expected diaphragm motion has been generated from the planning CT with the same procedures as described for fiducial tracking (see II(1)). Following this, the BEV image at time step \( t \) \( (I_t) \) is subtracted from that of the last time step \( (I_{t-1}) \). In this way and due to motion, the boundary between the lung and liver can be enhanced (b). For each time step, the initial ROI (yellow dashed rectangle in (a)) can be further decreased to a local diaphragm mask (d) by image intensity thresholding. At the same time, edge detection has been employed for extracting the edges of the diaphragm (c). Then, in the step (e) and (f), the boundary of the previously generated local diaphragm mask is then used to exclude surrounding spurious features of the image. Following this, a quadratic function \( f_t(x_n) = c_0 + c_1 x_n + c_2 x_n^2 \) is fitted to the coordinate of the \( N \) detected edges of time step \( t \), such that \( \sum_{n=1}^{N} |f_t(x_n) - y_n|^2 \) is minimized using the least-squares algorithm, where \( x_n \) and \( y_n \) are the coordinates of \( n \)th edge in the T and U direction respectively. The resulting \( f_t(x) \) are used later to quantify the motion in the U direction (\( \Delta y \)) of any specific point of interested \( (x_n) \), such as the apex of the diaphragm.

\[
\Delta y_n = f_t(x_n) - f_{ref}(x_n)
\]
Figure 4-3. Illustration of individual steps of the diaphragm tracking algorithm. (corresponding steps have been described in section 2.III)

IV. Performance evaluation

The two proposed tracking algorithms have been implemented in Matlab (Mathwork, Natick, MA) and validated using BEV X-ray image sequences of both anthropomorphic breathing phantoms and/or simulated BEV (DRRs) sequences of patient data. As soon as the characteristics of the target markers were determined from the first image frame, the criteria for marker recognition were fixed and applied to all following images without adaption. The algorithm performance was then evaluated with respect to the sensitivity of the detections as well as the accuracy. The sensitivity was measured by means of the determination of true positive detection rate, which calculates the proportion of the correctly identified markers (extracted location within the ground truth location) to the actual number of markers. Moreover, the number of false positives were also quantified and used to measure the capability of the algorithm to distinguish between the fiducials and other spurious objects in the images. However, in order to evaluate tracking accuracy, the ground truth locations of fiducials first need to be known. For the BEV fluoroscopy image sequences (acquired for the phantom), marker positions were extracted manually by identifying the ends of the markers from each image frame and calculating from these the coordinates of the marker centre. For the DRR fluoroscopy images on the other hand, the ground truth 3D locations can be directly extracted from the simulated 4DCTs, and therefore their ground truth 2D locations could be calculated using the calibrated BEV system geometry described in Chapter 3. For each correctly detected marker per image frame, the Euclidean distance between the tracked and ground truth locations have been quantified and recorded as the tracking error.
3. RESULTS AND DISCUSSION

I. Fiducial tracking

The fiducial tracking algorithm has been validated using four different BEV sequences, consisting of two imaging directions for each of the two phantoms, providing different image appearances for the evaluation. Figure 4-4 shows the tracked marker motions in either the T or U direction, and a summary of the performance for each dataset can be found in table 4-2.

For the real BEV sequences acquired on the phantoms (dataset 1-4), there was only 1 frame (over 85) in dataset 2 and 2 frames (over 51) in dataset 4 where the expected fiducials could not be successfully detected using the proposed tracking procedure. In addition, only two objects were mis-recognized as fiducials, as labelled by the red arrows in figure 4-4(b). However, one should note that here we were trying to evaluate the true performance of the marker shape extraction and there was no parameter adaptations or temporal restrictions applied. In practice, we believe that these kinds of tracking errors could be easily eliminated by incorporating additional constraints, such as ensuring that the breathing curve should change smoothly in time. Furthermore, compared with the manually identified ground truth locations, a high detection accuracy has been achieved, with a mean (max) tracking error of 0.39(0.71)mm averaged over all four BEV fluoroscopy datasets, which is around 1.5(2.9) times the pixel size of the BEV images (0.254mm in fluoroscopy mode).

For sequences 5-7 (real patient data, but simulated BEV-DRR images) the tracked fiducial motions are shown in figure 4-5(a-c). For the three field directions, corresponding tracked motions indicate field specific motion amplitude, depending on the 3D coordinates of each fiducial. Moreover, significant disparity of motion amplitude among different fiducial markers can be observed in figure 4-5, due to the presence of organ rotation and deformation. Even though the results are acceptable, they are clearly inferior to those of the phantom/real BEV sequences. Although part of the reason could be the more complex anatomy (and therefore more complex images) of real patients in comparison to those of our phantom, it also has to be noted that the quality of the DRR generated BEV images are substantially inferior to those of real BEV images, as their resolution is limited by both the resolution of the originating CT data set (1x1x2.5mm) and blurring of the marker shape due to CT reconstruction. Therefore, the edges of the markers in the BEV-DRR images are substantially less sharp than those in true BEV acquisitions. It is to be expected that the tracking algorithm will perform less well in these sequences. Nevertheless, our analysis shows the potential of our tracking algorithm for real patient geometries even if the reconstructions are being made under less than ideal conditions.

II. Diaphragm tracking

Diaphragm tracking is more challenging than tracking implanted fiducials due to the aperture shape, but, as can be seen in figure 4-6, the algorithm described in this chapter for extracting
the diaphragm motion shows promising results. The extracted diaphragm shape from the fitting a second order polynomial function is shown in the upper row, while the middle row depicts it over the time in the form of a space-time mesh. Visually compared to the DRR images, the diaphragm shapes can be well fitted by the polynomial functions. The red curves are the ground truth moving traces in 2D of the diaphragm apex. They were extracted from the 4DCT datasets and then projected on the BEV images using the projection function described in Chapter 3. The blue curves are the tracked SI motion traces of the diaphragm apex. Since there are fewer features available to build up the corresponding between the fitted 2D curves in time, hence only motion direction orthogonal to the “curve shape” can be extracted. Therefore, here diaphragm motions were simply quantified by the movement in SI direction, which is also the main motion direction. Furthermore, in the plots at the bottom row of figure 4-6, the tracked and ground truth motion in SI direction of the diaphragm apex can be directly compared over time. Quantitatively, the mean (max) error for diaphragm tracking for the F0, F1 and F2 field direction is 1.27(4.30), 1.18(4.32) and 0.89(3.35) mm respectively, which is slightly higher than corresponding values of fiducial marker tracking performance. One should note that this algorithm has been only validated through DRR image sequences, and therefore the parameters used in each step (such as the size of the edge detection filter) might need to be determined for real BEV image sequences. We are aiming to evaluate the real performance of this algorithm more extensively as soon as the BEV system is functional and patient data can be obtained.

Table 4-2. Performances of marker tracking algorithms

<table>
<thead>
<tr>
<th></th>
<th>dataset 1</th>
<th>dataset 2</th>
<th>dataset 3</th>
<th>dataset 4</th>
<th>dataset 5</th>
<th>dataset 6</th>
<th>dataset 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>100</td>
<td>98.8</td>
<td>100</td>
<td>96.1</td>
<td>94.4</td>
<td>90.3</td>
<td>93.1</td>
</tr>
<tr>
<td>false positive detection (times)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>mean/max error (in mm)</td>
<td>0.34/0.55</td>
<td>0.40/0.83</td>
<td>0.37/0.89</td>
<td>0.45/0.67</td>
<td>0.82/2.30</td>
<td>1.18/2.90</td>
<td>1.05/1.80</td>
</tr>
</tbody>
</table>
Figure 4-4. Tracked fiducial marker motion, with respect to the reference (1st) image frame, from BEV fluoroscopy image sequences of (a) dataset 1; (b) dataset 2, (c) dataset 3 and (d) dataset 4.
Figure 4-5. Tracked fiducial marker motion, with respect to the reference (5th) image frame, from DRR fluoroscopy image sequences of (a) dataset 5; (b) dataset 6 and (c) dataset 7. (circle: tracked fiducial positions; cross: ground truth positions)
Figure 4-6. Tracked diaphragm SI motion from (a) dataset 5, (b) dataset 6 and (c) dataset 7.

4. SUMMARY

In this chapter, we have described two algorithms for tracking surrogate motions from X-ray images that can be acquired using our BEV on-board imaging system. The algorithms have been shown to be able to track motions with an acceptable sensitivity and accuracy, by either following implanted fiducials or the diaphragm. In the following chapter, the motions resulting from these tracking methods will be used as surrogates for liver motion. These will be used as input for a statistical model of motions built from a library of 4D-MRI extracted motions, and the accuracy of the tracking/statistical model approach for 3D motion reconstruction will be validated.
1. INTRODUCTION

In Chapter 4, we have described methods for tracking fiducials and diaphragm motions in two and one dimensions using a monoscopic X-ray imaging device. However, as will be shown in this chapter, 2D motions at a few sparse locations are not sufficient for accurately modelling the dense motion field for scanned proton treatment, and more sophisticated methods are required. Such a method will be the subject of this chapter.

Over the last decade in conventional radiotherapy, real-time image guidance has been continuously developed (Shirato et al., 2000a, Berbeco et al., 2004b, Nill et al., 2005, Rottmann et al., 2010) and clinically applied (Adler et al., 1999, Nuyttens et al., 2006, Hoogeman et al., 2009) in order to decrease geometrical uncertainties which are associated with tumour motions during dose delivery. For scattered proton/particle therapy, since dose is delivered to the whole target simultaneously, motion tracking methods currently available in conventional radiotherapy, which have been described in Chapter 4, can all, in principle, be used directly. However, when applying image guidance to particle therapy, it is also important to obtain supplementary spatial information on the 3D deformable motion (dense motion vector field, DVF) for each pencil beam delivery. This is required for two reasons. Firstly, it is well known that the target volume, as well as surrounding tissues in the upper abdomen region, moves in a non-rigid manner, so that any sparse surrogate signals which may be traceable on-line, are generally not sufficient to describe the full deformable behaviour of the entire region of interest (ROI). Secondly, density variations along the beam path, which can significantly affect particle ranges, also need to be known, which means that during delivery, the induced density changes along the beam path also have to be predicted for adapting beam energy.

As discussed in Chapter 2, information on target motions and density changes can be derived from a single 4DCT, on which 4D plans can be generated using deformable registration to accumulate the dose on a single reference phase of the 4DCT data (Kraus et al., 2011, Zhang et al., 2012a). However, significant intra-fraction motion irregularities have been reported...
(Siebenthal et al., 2007a), and it is likely that patient/tumour motion will be different during the delivery to that captured by the single ‘snap-shot’ 4DCT used for planning. These differences can limit the accuracy of pre-calculated 4D plans with respect to the actually delivered dose distribution (Boye et al., 2013). In addition, and also as shown in chapter 2, deformable registration solutions in the liver based on 4DCT can be ambiguous, due to the lack of anatomical features resulting from the low soft-tissue contrast of CT data. Consequently, we believe that on-line deformable motion tracking and prediction in three-dimensions are a pre-requisite for tumour tracking using scanned particle beams, due to the high sensitivity of this technique to both small motions and range changes. However, as there are currently no imaging techniques that can acquire real-time 3D motions, such predictions necessarily have to rely on patient specific or population based models of the motions.

Principle Component Analysis (PCA) is a well-known technique of multivariate analysis which has been used for constructing statistical models for radiotherapy applications by a number of authors. For example, Xu et al. (2007) built an active shape model in order to track deformable tumour contours from fluoroscopic imaging sequences, whereas Tang et al. (2007) and Li et al. (2011) have applied PCA’s to motion fields derived from lung 4DCT and have shown that single markers can be used to derive motions of the whole lung. More recently, Preiswerk et al. (2012) and Samei et al. (2012) have generated a population based liver motion model based on a Bayesian and exemplar framework for predicting tumour motions during high intensity focused ultrasound and have argued that such a technique could also be used for radiotherapy applications (Arnold et al., 2011).

In this chapter, we expand on the statistical modelling work of Arnold et al. (2011) and Preiswerk et al. (2012) to describe and evaluate the potential capability of our BEV fluoroscopic imaging system for reconstructing 3D dense motion fields from traced surrogates extracted from the resulting time resolved images (see previous chapter 4). For this, we propose the reconstruction of deformable motions based on an a-priori acquisition of 4D motion data over an extended period (i.e. over many breathing cycles) using 4DMRI (Siebenthal et al., 2007b) from which a patient specific motion model can be built before treatment, and from which subsequently reconstructed 4DCT data sets can be calculated (so called 4DCT(MRI) data sets, see e.g. Boye et al. (2013)). At treatment time, surrogate motions, directly measured on-line via the BEV system and quantified using the tracking algorithms described in Chapter 4, can then be used as a predictor to reconstruct the 3D motions with the help of this pre-generated motion model.

As such, we wish here to simulate and evaluate the effectiveness of our proposed motion reconstruction scenario as realistically as possible, starting with the generation of patient specific motion models and continuing on to the generation of simulated BEV fluoroscopic studies, as we would expect to acquire on our gantry mounted imaging equipment. In addition, the predictive power of the methods used for automatic extraction of motion surrogates from these images will be assessed, together with a final evaluation of the efficacy of the full
approach through the use of 4D proton dose calculations applied to the motions reconstructed from the extracted surrogates and patient specific model. It should be noted that, in common to other work in this field, we concentrate here on a scenario to reconstruct motions due to breathing alone in order to potentially mitigate the interplay effect only (Li et al., 2004, Paganetti et al., 2005, Grözinger et al., 2006, Water et al., 2009, Bert et al., 2012, Riboldi et al., 2012). As such, we temporally neglect the additional potential effects of baseline shifts due to longer time-scale anatomical motions, and the potential limitation will be discussed later.

Therefore, we thus wish to investigate the following five main questions in this chapter:

- Is it feasible to reconstruct full motion vector fields from surrogate motions extracted from monoscopic imaging systems?
- How accurate are these PCA based reconstructed motion fields?
- Is there any advantage to using stereoscopic imaging systems?
- What are the benefits of online deformable motion prediction in comparison to conventional online motion tracking approaches (i.e. only following the surrogate in 2D)?
- How will errors in these predictions influence dose distributions for scanned proton beam treatments?

2. METHODS AND MATERIALS

An overview of the methods used for this work is shown in figure 5-1. In short, four different processes have been performed:

- Subject specific motion modelling based on 4DMRI training data.
- Simulation of online motion scenarios for generation of ‘ground truth’ motions and 4DCT(MRI) data sets based on motions extracted from the 4DMRI studies.
- Reconstruction of deformable motions from surrogates tracked from BEVs simulated from these ground truth data sets
- Motion prediction validation through the calculation of 4D dose distributions on either the ground truth or reconstructed data sets.

Each of these processes will be described in detail in the following sections.
I. Motion modelling

1) Motion extraction from 4DMRI

As a basis for this study, motions extracted from 4DMRI studies of the right liver lobes of 11 healthy volunteers have been used (http://www.vision.ee.ethz.ch/4dmri/). These were acquired by retrospectively sorting sagittal MRI slices based on the navigator technique with an in-plane spatial resolution of 1.8x1.8mm and slice thickness of 4mm. Temporal resolution ranged from 2.5Hz to 3.5Hz and total acquisition times for each subject ranged from 35-44 minutes (Siebenthal et al., 2007b, von Siebenthal et al., 2007). For this study, data from 130 contiguous breathing cycles randomly selected from each subject, with the first 100 cycles being used to compute the subject specific motion model, and the following 30 cycles being used as the ‘ground truth’ motion for validating the proposed method. Motion Displacement Vector Fields (DVFs) from these data sets were calculated using B-spline based Deformable Image Registration (DIR) (Rueckert et al., 1999), with the first end of exhalation phase being selected as reference (Siebenthal et al., 2007a). In common with conventional 4DCT approach in radiotherapy, motions were interpolated into ten phases per cycle, which means only the inter-cycle variability of motion amplitude is considered here as well as in the following chapters.

2) Motion modelling by Principle Component Analysis
To form the PCA model, liver motion at each time step was first described in vector space. \( v_t \) is the motion DVF at time step \( t \), represented by concatenating the 3D motion vector \((dx_k, dy_k, dz_k)\) of all \( K \) voxels into a single \( 3K \) dimensional vector,

\[
v_t = [dx_1, dy_1, dz_1, \ldots, dx_k, dy_k, dz_k]^T \quad (k \leq K)
\]

where each variable refers to one motion component in the DVF. From this, one can form a data matrix

\[
X = [v_1, v_2, \ldots, v_t]^T \quad (t \leq T)
\]

with each row representing a high dimensional displacement vector at each time step. Subsequently, PCA has been used to decompose the variation of matrix \( X \) into a new space with orthogonal (uncorrelated) coordinates given by,

\[
S = [s_1, s_2, \ldots, s_{T-1}]
\]

which are the principle components (or Eigenvectors), such that the variance of the projection of \( X \) is maximized with respect to the components sequence (Jolliffe, 2002). The resultant coefficients \( D = [\sigma_1^2, \sigma_2^2, \ldots, \sigma_{T-1}^2] \) (Eigenvalues) represent the variance of each principle components in descending order.

Now let \( c \) be the projection of \( X \) in the PCA domain,

\[
c = diag(\sigma_i^{-1}) \cdot S^T \cdot (X - \mu)
\]

where \( \mu = \frac{1}{T} \sum_{t=1}^{T} v_t \) is the mean displacement vector field averaged over all time steps. Since \( S \) is an orthogonal matrix \( (S^T = S^{-1}) \), then each motion displacement vector field \( v \) in the spatial domain can be described as a linear combination of Eigenvectors in the PCA domain with corresponding Eigenvalues.

\[
v = \mu + S \cdot diag(\sigma_i) \cdot c
\]

II. Simulation of online motion scenarios

1) Motion reconstruction from sparse surrogate motion

Since \( X \) contains a set of possible motion instances as prior knowledge, online motion reconstruction is based on the assumption that any particular motion instance is in the span of these possible motions and its prior probability can be statistically estimated based on the correlation of vector components (each column) within \( X \). The Bayesian approach described in Blanz and Vetter (2002) was used to solve this problem as follows.

Let \( r_t \) represent the partial observation of motion instance \( v_t \) at any arbitrary time step \( t \),
\[
\begin{align*}
  r_t &= L \nu_t \\
  & \quad \text{(5-6)}
\end{align*}
\]

where \( L : \mathbb{R}^{3K} \to \mathbb{R}^N \) \((N < 3K)\) is a function which correlates the \( N \) measured motion components with the full motion vector in \( 3K \) dimensions, which cannot be completely online tracked. This \( L \) function can be formulated by determining corresponding column index in \( X \) of the chosen predictor, based on 3D coordinate of each fiducial in the reference CT image. Depending on the type of surrogate motion, as well as the configuration of the OBI system under investigation, these partial observations can be either motion from pre-implanted fiducial markers or from the diaphragm.

Mathematically, the idea of this approach is to find the model coefficient \( c \) in equation (5-4) for the full motion vector \( \nu \), which can provide the partial observation \( r \) with the highest prior probability. Specifically, this means that when a certain motion component is measured online, the whole motion field can be estimated from the motion model based on the correlation of these motion components. Practically, this can be solved by minimizing the objective function

\[
E = ||Qc - r||^2 + \eta||c||^2
\]

with respect to the coefficients \( c \), where \( Q = L \cdot S \cdot \text{diag}(\sigma_i) \) is the reduced version of the Eigenvectors, and \( \eta \) is the regularization factor for balancing matching quality and prior probability in order to avoid over-fitting artefacts. Here, it has been set to 2 in all following predictions, based on the suggestion from Blanz and Vetter (2002).

For the optimum case,

\[
0 = \nabla E = 2Q^T Qc - 2Q^T r + 2\eta c
\]

and therefore

\[
Q^T Qc + \eta c = Q^T r
\]

By applying Singular Value Decomposition (SVD) of \( Q = UWV^T \), we get

\[
Q^T Q = VWU^T UWW^T V = VW^2 V^T
\]

which yields

\[
VW^2 V^T c + \eta c = VWU^T r
\]

where \( W = \text{diag}(\omega_i) \).

By multiplying with \( V^T \) on both sides, it follows that

\[
\text{diag}(\omega_i^2 + \eta)V^T c = \text{diag}(\omega_i)U^T r
\]
The relationship between the most probable coefficients $c$ and the partial observation $r$ can then be determined by,

$$c = V \cdot diag\left(\frac{\omega_i}{\omega_i^2 + \eta}\right) \cdot U^T \cdot r$$

(5-13)

Finally, the overall result can be derived from equation (5-5) and equation (5-13), thus

$$v = \mu + S \cdot diag(\sigma_i) \cdot V \cdot diag\left(\frac{\omega_i}{\omega_i^2 + \eta}\right) \cdot U^T \cdot r$$

(5-14)

2) Simulation of BEV images

In order to validate and quantitatively evaluate this method, time resolved Digital Reconstructed Radiographs (DRRs) have been used for simulating fluoroscopic images that could be achieved with our BEV system. Based on motions extracted from the 30 breathing cycles which have not been used to build the subject specific motion models (our so-called ‘ground truth’ data), multiple 4DCT(MRI) data sets have been generated per subject. This has been performed using the method proposed by Boye et al. (2013), which consists of mapping the extracted MRI motions onto a single-phase reference CT, and then warping this CT image based on the mapped motion field. Thus, from the extracted motions of each subject, and using a single, exhalation phase CT of an example liver cancer patient as the starting point, ‘extended’ 4DCT(MRI) data sets consisting of 300 different time resolved 3DCT ‘instances’ have been generated per subject, extracted over the 30 ‘ground truth’ breathing cycles of the selected subject’s 4DMRI data. This process has been performed on motions extracted from all 11 subjects, to generate 3300, time resolved 3DCT ‘instances’ from the same originating single phase CT data set.

As a next step, multiple, time-resolved DRRs have been calculated from these 4DCT(MRI) data sets using the geometry parameters of our BEV system, which has been described in Chapter 2. For each subject, time-resolved BEV-DRRs for three different field directions have been generated (figure 5-2): Anterior-Posterior (F0), left-lateral (F1) and AP-inferior oblique fields (F2). These field directions have been chosen according to suggestions from a previous study by Knopf et al. (2011), together with considerations of surrogate visibility on DRRs (e.g. avoiding field directions in which markers might overlap with bony structures). Furthermore, for each field, field and subject specific motion models have been constructed by rotating the training DVFs from the original CT coordinate (shown in figure 5-2(a)) to the treatment coordinate system (shown in (b-d)) according to the defined gantry and table angles of each field.

III. Surrogate motion tracking and deformable motion reconstruction

1) Motion tracking and magnification correction

In Chapter 4, we have developed algorithms for tracking either fiducial markers or the diaphragm motion from fluoroscopy image sequences (Zhang et al., 2012c), which have
subsequently been applied to the BEV-DRRs as described above. In addition, the zoom factor resulting from the divergent nature of the imaging geometry needs to be corrected for, as this will be different for different markers, depending on their position along the longitudinal imaging axis. Hence, 2D motions measured from DRRs will generally be slightly larger than the real 2D lateral motion components. In this work, the magnification for each surrogate’s motion has been corrected individually using the corresponding constant magnification factor derived from the reference 3DCT.

Figure 5-2. Online motion monitoring using BEV imaging system of PSI-Gantry2. (a) the reference CT (red volume: PTV (Planning Target Volume); pink volume: right liver lobe) with three selected field directions towards the isocenter (green sphere). The pre-implanted fiducial markers are presented as cylinders located around the PTV. (b-c) configurations of each treatment field.

2) Reconstruction of deformable motion

From the tracked surrogate motions, motion DVFs can be predicted using the subject and field specific PCA models. For this step, a number of motion prediction scenarios have been used, as summarised in table 5-1. For fiducial marker tracking, the effectiveness of BEV (monoscopic) based tracking for three different field directions have been evaluated (P1-P3), as has the effectiveness of dual-orthogonal (stereoscopic) imaging by combining the information from fields F0 and F1 (P4). Furthermore, motions have been estimated assuming either translation mode (P6-P8), in which every point in the liver is assigned the same motion vector calculated from the averaged motion of the fiducial markers, or deformable mode (P1-P3), where full 3D motions are reconstructed from the subject specific PCA motion model. With diaphragm motion as surrogate, there was no significant difference of the tracked SI motion among coplanar fields, and this information cannot be tracked for the non-coplanar field F2. As such, deformable motion prediction has been only evaluated for field F0 from AP direction (P5).

IV. Performance evaluations and 4D dose verifications

1) Accuracy of surrogate motion tracking
In order to first quantify the accuracy of the tracking algorithms, the real 3D positions of the tracking surrogates were extracted from the ‘ground truth’ motions and projected with the geometry parameters of the BEV imaging system (see Chapter 3). These were then compared to the positions extracted from the BEV images by calculating the magnitude of the Euclidean distance between corresponding points. In addition, the ground truth magnification factor of each surrogate at each time step was also calculated and compared to the pre-defined constant value from the reference CT.

Table 5-1. Motion prediction scenarios.

<table>
<thead>
<tr>
<th>No.</th>
<th>Motion Scenario</th>
<th>Motion Type</th>
<th>OBI System</th>
<th>Predictor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>P0</td>
<td>Ground truth</td>
<td>Deformable motion</td>
<td>F0/F1/F2</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>Prediction by PCA model</td>
<td>Deformable motion</td>
<td>BEV-F0</td>
<td>2D markers</td>
</tr>
<tr>
<td>P2</td>
<td></td>
<td></td>
<td>BEV-F1</td>
<td>2D markers</td>
</tr>
<tr>
<td>P3</td>
<td></td>
<td></td>
<td>BEV-F2</td>
<td>2D markers</td>
</tr>
<tr>
<td>P4</td>
<td></td>
<td></td>
<td>dual OBI (F0&amp;F1)</td>
<td>3D markers</td>
</tr>
<tr>
<td>P5</td>
<td></td>
<td></td>
<td>BEV-F0</td>
<td>diaphragm(SI motion)</td>
</tr>
<tr>
<td>P6</td>
<td>Prediction by translation model</td>
<td>Translation motion</td>
<td>BEV-F0</td>
<td>2D markers</td>
</tr>
<tr>
<td>P7</td>
<td></td>
<td></td>
<td>BEV-F1</td>
<td>2D markers</td>
</tr>
<tr>
<td>P8</td>
<td></td>
<td></td>
<td>BEV-F2</td>
<td>2D markers</td>
</tr>
</tbody>
</table>

2) Accuracy of deformable motion reconstruction

Using each of the 300 time resolved DRRs or DRR pairs per subject, the reconstructed deformable motion fields have also been directly compared with the ground truth motions (extracted directly from the 4DMRI data) by calculating the point-by-point Euclidean distance between the corresponding motion vectors in three dimensions. Moreover, for each prediction scenario, cumulative distribution functions (CDFs) of the prediction errors and the inter-subject variations at the 99% confidence level have been quantified and used as a measure of prediction performance for motions extracted from all 11 subjects.

3) Influence of reconstruction errors on 4D dose distributions

As the ultimate goal of this work is to show the feasibility of motion tracking for scanned proton beam therapy using motion surrogates, 4D dose calculations (Boye et al., 2011, Zhang et al., 2012a, Boye et al., 2013) are the most relevant end-point to study and, as has been shown by other authors, are also extremely sensitive to the exact characteristics of the motion (see e.g. Water et al. (2009) and Zhang et al. (2012a)). Thus, they are an ideal metric for studying the accuracy of the motion reconstruction algorithms described above.
In order to maximize the sensitivity of 4D dose calculations to motions, the calculations have been performed for a single field (rather than multiple fields, where effects of motion will tend to smooth out, see e.g. Knopf et al 2011) and no rescanning or other motion mitigation approach has been applied. The scanning parameters used for the calculations are those of Gantry2 at our institute (Zenklusen et al., 2010) and the proton pencil beams have been considered to have a full-width, half-maximum width of 8mm at the Bragg peak and are separated in both axes orthogonal to the beam direction by 5mm. Dead time for moving the pencil beam along each lateral direction is of the order of 4ms, while energy changes have been modelled at 80ms for 5mm changes in water equivalent depth.

An example 4D dose distribution for such a field can be seen in figure 5-3. For comparison, and for each of the 11 motion subjects, 4D calculations have been performed using both the ‘ground-truth’ motion (P0 in table 5-1) and using the predicted motion from each of the scenarios (P1-P8), resulting in a total of 121 4D plans. Differences between 4D dose distributions calculated based on the ground-truth or predicted motions have been quantified in the form of cumulative Dose-Difference Volume Histograms (DDVHs). For the analysis in this paper, DDVHs have been calculated within a volume called the Irradiated Volume (IV) (green contour in figure 5-3) which is the original PTV plus an isotropic 10mm expansion. This volume has been assessed in detail as it contains both the region where dose should be homogenous (in the PTV) plus the regions of the dose distribution where the sharpest dose gradients are present (directly outside the PTV). The DDVHs have been further quantified by extracting the relative volume of the IV for which dose differences are 5% or greater ($V_{\text{dosediff} \geq 5\%}$). Finally, variations between results from the different subjects have been evaluated as error bands of the IV DDVH for each prediction scenario.

Figure 5-3. Exampled 4D ground truth plan with single field and one time scanning for moving target and no compensation for motion (yellow contour: PTV margin; green contour: IV margin for dosimetric evaluation of prediction error).

3. RESULTS

I. Respiratory motion and PCA motion modelling

Figure 5-4 shows example motion patterns (with respect to the first end of exhalation position) over 10 breathing cycles from one subject of the training data, with clear inter-cycle
irregularities being visible. The statistics of the motion filed over the whole liver are represented in the form of a box-plot per time step (a-c), with the variation of the motion over the liver indicated by the extent of the blue boxes (25-75% quartile). The curves (yellow, pink, green and light blue) give information on the tracked surrogate motion either from the diaphragm (yellow) or each of the three pre-implanted fiducial markers (pink, green and light blue). From these plots, we can clearly see that the end inhalation phase gives the largest spatial motion variation (largest blue boxes). In addition, it is also clear that none of the surrogate motions are sufficient to represent the motion in the whole liver region. This point is reinforced in the Cumulative Distribution Function (CDF) plots shown in (d-f) which show the statistics of the motion in the individual direction over all time steps used for building the subject specific PCA models. The set of blue CDF curves show the motion distributions for all points in the liver, while the yellow, pink, green and light blue curves again show the motions of the surrogates.

The PCA model was then applied and the cumulative energy of each principal component was calculated for each subject and each field direction respectively. Depending on the motion dataset, the first 2-15 principal components were selected in order to achieve 99% variability of the original data (Blanz and Vetter, 2002, Jolliffe, 2002).

II. Accuracy of tracked surrogate motion

The tracking algorithms described in Chapter 4 have been applied to all calculated DRRs of each motion subject and field direction. Figure 5-5 shows the results of tracked fiducial markers (a) and diaphragm (b) from example treatment field F0. The detected surrogate motions have been directly compared to the calculated 2D ground truth motions, and errors from the tracking algorithm have been quantified for the three selected fields of all 11 motion subjects over 300 time steps each. In total, over the 29700 time-resolved marker detections, median (max) errors of 0.9(2.9) mm have been achieved. For diaphragm motion, where the tracking algorithm has been evaluated for F0 (AP), slightly higher median (max) errors of 1.5 (3.0) mm were found.

Although the magnification effects have been considered as locally constant, their ‘ground truth’ influences can be analysed retrospectively. Figure 5-5(c) shows the magnitude of the Euclidian distance between projected 2D motions of the inferior fiducial marker (green circle in (a)) for field direction F0 and their corresponding lateral ground truth motion components before and after correction using the constant magnification factor. Figure 5-5(c-2) demonstrates the effectiveness of the simplified magnification correction method, which reveals negligible residual differences. After correction, and taking into account results from all surrogate (three fiducial markers and diaphragm), all field directions, all motion subjects and all time steps, a maximum residual difference of 0.5mm could be achieved, indicating the importance of correcting geometry induced magnification effects before applying the detected surrogate motions to the motion model.
III. Accuracy of deformable motion reconstruction

Figure 5-6 shows the results comparing the reconstructed to the ‘ground-truth’ motions for scenarios P1-3 (monoscopic tracking of fiducial markers for each of the three different fields). The coloured solid lines represent the CDFs of each individual subject if no motion prediction is performed (i.e. the error in position due to motion relative to the first end-exhalation), whilst the dashed lines show the CDFs resulting from the PCA based motion prediction for the same subjects. Inter-subject variations are shown as uncertainty bands (red areas), and it is clearly seen that these become narrower and steeper when the motion is predicted by the PCA model (green areas). More quantitatively, the boxplots in (d) show inter-subject variations at the 99% confidence level in motion prediction accuracy for each field direction. The median (max) 99% prediction error are 2.6/2.5/2.8 (5.6/4.9/6.5) mm for P1/P2/P3 respectively, compared to the median (max) motion magnitude of 11.9(25.5) mm. In addition, only moderate variations of the prediction error are observed among the different field directions.

A similar tendency can be observed for scenario P5, where the SI motion of the diaphragm is tracked. This technique resulted a median (max) 99% prediction error with the magnitude of 2.7(4.2) mm. The similarity between the use of fiducials or the diaphragm as tracking surrogates are further demonstrated in figure 5-7. Here the green/blue error bands represent the statistical analysis of prediction results from field F0 (AP) when fiducial markers (P1) or the diaphragm (P5) motion are used as a surrogate. The similarity of the results imply that fiducial markers may not be compulsory for online respiratory liver motion tracking if a PCA model as described here is used.
Figure 5-4. (a-c) Example motion traces in LR, AP and SI direction as boxplots, with the zoomed pictures in the right showing the variation of motion within the liver for one example breath cycle; (d-f) Cumulative distribution of motion in directions over 1000 training time steps. Each blue curve shows motions from one corresponding point, while curves in colour (of yellow, pink, green and light blue) present motion from the tracked surrogates (x-axis: motion in mm; y-axis: relative cumulated frequency).
Figure 5-5. Example of simulated BEV image (F0) with highlighted features used for online motion tracking (a) pre-implanted fiducial markers (circles in colours) and (b) diaphragm (arc in red); (c) effectiveness of magnification correction: motion differences (marker 3 at F0) between the projected 2D motion and corresponding ground truth 2D motion components (c-1) before and (c-2) after applying the local constant magnification corrections.

Figure 5-6. PCA motion prediction using 2D fiducial markers as surrogate for field direction (a) F0, (b) F1 and (c) F2; (d) boxplot showing the inter-subject variations of the 99% confident level of the error for different prediction scenarios.
IV. Benefits of deformable motion reconstruction

1) PCA model versus translation model

Figure 5-8 compares for one subject, the prediction errors using the PCA model (P1-3) with those using only a translation model based on the averaged 2D marker motion (P6-8). It can be clearly seen that for all field directions, errors from deformable prediction results (b/c/d-1) were substantially lower for all time steps compared to the results from the translation only scenarios (b/c/d-2), especially at inhalation, which typically exhibits the largest deformations. For the example shown, the 75% quartile (max) errors of the deformable prediction are around 2.4(5)mm, compared to 8(13)mm if motion is simply modelled in a translational way. Similar results can be observed for the motions from all subjects, presented in the form of CDF plots in figure 5-9 with an obvious error reduction being achieved using the PCA model (median (max) 99% error magnitude over all subjects of 2.63 (5.67) mm for the PCA approach, 5.82 (11.21) mm for 2D translations).

In addition, the lost motion component in depth due to monoscopic imaging using the BEV imaging system can also be estimated once the PCA model approach is used. Figure 5-10(a) shows an example of prediction errors for scenario P3, where a median 99 percentile motion magnitudes of up to 6mm is present parallel to the imaging direction (F2). Since monoscopic imaging system cannot monitor this ‘lost’ motion component, larger errors may be expected, but this information can be derived from the PCA motion model. Additionally, one should notice that prediction errors in the imaging direction are dependent on how much motion there is in this direction. This can be observed in figure 5-10(b) by comparing the variation between the two boxplots from the same geometry scenarios, which reveals that, although the effectiveness of deformable motion tracking over conventional surrogate tracking is field direction-dependence, its superiority is obvious.
2) Monoscopic versus stereoscopic OBI system

Figure 5-11 shows the inter-subject variation of the 50/99/100 percentiles of the prediction error magnitude over all subjects as a function of OBI geometries and motion models. For the PCA based approach (left part of each figure), similar accuracies have been achieved for both monoscopic and stereoscopic imaging systems. However, for the translation scenarios (right part of each figure), variations between the two OBI configurations are generally more pronounced. This demonstrates that the OBI imaging geometry (monoscopic or stereoscopic) has less influence once a PCA model is used. In other words, the use of a monoscopic imaging system could be sufficient for achieving a comparable prediction performance when used in conjunction with a patient specific PCA motion model.

V. Influences of reconstruction error on 4D dose distributions

Finally, we move on to assessing the effect of prediction errors on 4D dose distributions, in particular by comparing the 4D dose distributions based on the reconstructed motions (predicted 4D plans) to those performed on the ‘ground-truth’ motion (ground truth 4D plans). Figure 5-12 shows examples of absolute dose differences between the ground truth and predicted plans for motion predicted from either the PCA model (a-c) or the translation model (d-f). In this case, the motion was predicted using the fiducial markers as surrogate. Compared to deformable motion reconstruction, the translation only scenario is clearly a very poor approach, with maximum 30% dose differences of over 5% occurring within the IV, whereas maximum dose differences of at most 15% are found using the deformable approach.

Figure 5-13 shows results for all 11 subjects in the form of DDVHs. For the worst field direction (F0), the median (max) $V_{\text{dosediff} \geq 5\%}$ can be reduced to 3.61% (15.13%) if motion is estimated using the PCA model, compared to only 12.85% (29.28%) for the translation only estimation. In addition, the advantages of deformable motion reconstruction are further demonstrated in (d), where each colour line represents the results from one motion subject. A substantially incensement of $V_{\text{dosediff} \geq 5\%}$ values can be observed when motions were estimated by only following the average translation of the markers. A summary of median (max) $V_{\text{dosediff} \geq 5\%}$ quantifications for each prediction scenario can be found in table 5-2.

Figure 5-14 compares 4D plans using either 2D tracked fiducial markers, 3D marker tracking (using dual imaging) or diaphragm tracking. Although the median DDVHs of plans using the diaphragm (red curve) is slightly worse than the 2D fiducial approach (blue curve), the DDVH bands closely match each other. Furthermore, from (b), we can see that there are negligible dosimetric differences existing between surrogate motions tracked by either monoscopic or stereoscopic imaging system, reinforcing the impression that monoscopic imaging using BEV type geometry can be just as effective as a dual imaging system if deformable motion reconstruction based on a patient specific PCA model is used.
Table 5-2. Median(max) values (%) of $V_{\text{diff-5\%}}$ over 11 motion subjects for all predictions

<table>
<thead>
<tr>
<th>scenario field</th>
<th>Translation model</th>
<th>PCA model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean 2D markers</td>
<td>2D markers</td>
</tr>
<tr>
<td>F0</td>
<td>12.85(29.28)</td>
<td>3.61(15.13)</td>
</tr>
<tr>
<td>F1</td>
<td>3.71(9.15)</td>
<td>1.15(5.34)</td>
</tr>
<tr>
<td>F2</td>
<td>11.65(26.26)</td>
<td>0.88(5.89)</td>
</tr>
<tr>
<td>mean</td>
<td>8.79(21.56)</td>
<td>1.88(9.41)</td>
</tr>
</tbody>
</table>

Figure 5-8. Predictions for each field direction of one example subject: error (magnitude) from PCA deformable motion v.s. 2D translation motion of each time steps (left column) and their CDFs of the prediction error (right column).
Figure 5-9. Statistical comparison of prediction errors magnitudes from either PCA model or 2D translation model for field direction (a) F0, (b) F1 and (c) F2; (d) Boxplots show inter-subject variations of 99% confident level of errors magnitudes for different prediction scenarios.

Figure 5-10. Prediction errors in the field direction. (a) CDFs of errors from PCA prediction in comparison to no prediction for scenario P3 (F2); (b) Boxplots show inter-subject variations of 99% error, in the context of different field (imaging) directions.
Figure 5-11. Statistical comparison (over 11 cases): boxplot of (a) 50%, (b) 99% and (c) 100% of prediction errors from PCA reconstructed deformable motion (left column) and 2D translation motion model (right column) with respect to difference OBI system geometries.

Figure 5-12. Absolute dose difference of 4D dose distributions considering ground truth motion versus reconstructed motion from either the PCA model (top) or the 2D translation model (bottom) prediction for field F0 (left), F1 (middle) and F2 (right) with the arrows indicating the field direction.
Figure 5-13. (a-c) Statistical comparison DDVHs (in the IV) between ground truth plans and predicted plans with motion from PCA model (areas in blue) or 2D translation model (area in red). (d) Inter-subjects variation of $V_{dose<5\%}$ of those DDVHs (in the IV) in context with prediction model for three treatment field directions (dashed, coloured line represents each subject).
Figure 5-14. Comparison DDVHs between ground truth plans and PCA predicted plans for different surrogates: (a) 2D markers (area in blue) vs. diaphragm (area in magenta) and (b) 2D markers (area in blue) vs. 3D markers (area in cyan) with boxplots showing the inter-subjects variation of $V_{\text{DoseDiff}}>5\%$.

4. DISCUSSION

In this chapter, we have proposed and validated (through simulations) an approach of tracking deformable motion based on time-resolved 2D on-line imaging. It has been demonstrated that, in the liver region at least, deformable 3D motions can be accurately reconstructed from sparse surrogate motions acquired from an on-board imaging system, if a patient specific PCA motion model can be constructed a-priori.

In order to assess how accurate such motion reconstructions can be, two possible surrogate signals have been extracted from the motion of 11 different subjects, each consisting of 300 time steps. Then, the reconstructed motions have been compared to the ‘ground-truth’ motions of these subjects extracted directly from their 4DMRI acquisitions. Comparing the results between the different predictors, we have found that diaphragm motion in the SI-direction is a comparative surrogate for predicting respiratory motions with a median (inter-
subject) accuracy of 2.7mm for 99% of considered samples within the liver. By using diaphragm motion as a surrogate for tracking the tumour, the problematic issues concerning fiducial implants (Arslan et al., 2002) and their potential dosimetric effects on proton treatments (Newhauser et al., 2007) could be avoided. Furthermore, we have also compared the accuracy of the proposed deformable motion prediction with a much simpler 2D translation motion assumption, based on the average motion of the visible fiducial markers. This has clearly shown that incorporation of deformable motions is essential if accurate motion predictions in three-dimensions are to be achieved. To evaluate the dosimetric effects of the resulting residual prediction errors, 4D dose calculations have been performed both on the ‘ground-truth’ motions and on motions reconstructed from the different motion surrogate scenarios. Although dose differences have been found, these are rather small and their magnitudes have been found to be independent of whether monoscopic or stereoscopic imaging was simulated, or whether the surrogate motion was tracked from implanted markers or the diaphragm. It should also be remembered that all 4D dose calculations were performed for a single field and without any motion mitigation approach. As has been demonstrated elsewhere (see e.g. Knopf et al. (2011) and Zhang et al. (2012a)), the use of additional fields and/or rescanning would be expected to reduce these dose differences even more.

The subject specific models used by the PCA have been generated from extended 4DMRI acquisitions of volunteers. Compared to models built from 4DCT (see e.g. Li et al. (2011)), 4DMRI has a number of advantages. First, images can be acquired over a long duration, and thus capture more information on inter-cycle variability, potentially resulting in better predictive performance, especially in the presence of irregular breathing. Second, MRI liver images provide a superior image contrast compared to 4DCT, which is beneficial for deformable registration when estimating motion fields in the liver region, the problem that we investigated for 4DCT in Chapter 2. Third, in order to implement such a technique clinically, a patient specific model of motions would have to be acquired as part of the pre-treatment preparation. This is also an advantage of the 4DMRI technique that we use here. We envisage that for such treatments, patients could be imaged with 4DMRI over an extended period (20-30 minutes) as part of the pre-treatment preparations (i.e. on the day of the planning CT) to provide the input for the patient specific PCA model. If done at the treatment facility, then these studies could be acquired in treatment position and, if possible, using exactly the same fixation devices as will be used during therapy. This way, any systematic differences in motion between imaging and treatment could be minimized. However, we do not exclude the possibility that, after data from enough patients has been acquired, we could not also move to a population based model, maybe therefore removing completely the need for pre-treatment MRI imaging.

In order to achieve high spatial prediction accuracy, online measured surrogate motions need to be tracked as accurately as possible. While tracking performance has been assessed for simulated BEVs, it still needs to be determined how accurately these can be extracted in reality. First, errors can be introduced from imprecise detection of the surrogate locations. The
shape of the fiducial markers allows for the incorporation of prior shape knowledge and point localization, facilitating accurate localization and extraction of 2D motion, while the diaphragm permits only estimation of 1D motion due to its curve-like shape. Also, it should be pointed out that the motion extraction from the surrogate motion in this chapter is based on DRR (simulated BEV) images instead, whose resolution is limited by the resolution of the originating CT (1x1x2.5mm). As has been shown in Chapter 4, the actual BEV images acquired on-line would have a substantially better resolution with an image pixel size of around 0.254mm, while having similar image contrast. Hence, edges of the fiducial markers and the diaphragm can be obtained much easier, which should increase the efficiency and accuracy of the algorithms for surrogate tracking. Second, all OBI systems have cone-beam geometry and the divergence of the beam can introduce varying magnification when surrogates move. For the BEV imaging system described here, we have demonstrated the effectiveness of a simplified correction method, which assumes that the magnification factor is locally constant during respiration. However, it should be noted that larger variations are expected for a conventional OBI system, which has shorter source-to-detector distances. Thus, the accuracy of the proposed correction method for other OBI systems needs to be validated further. Although the work presented here is based on simulations of 2D images, these simulations have been necessary in order to be able to evaluate the efficacy of the technique against a well-known and quantifiable ‘ground-truth’ motion, which is impossible to determine in real patients or from real imaging studies. In addition, through our technique of using 4DMRI, and using the motion extracted from these studies to generate many hundreds of 4DCT(MRI) data sets, we can investigate many more motion scenarios than would be the case on real data sets, allowing us to more thoroughly investigate the ‘phase space’ of possible motions that could occur in a population of patients. Although the 4DMRI data used here is based on volunteer, rather than patient data, we think this is not a great problem. As stated throughout the chapter, the proposed method is based on the generation of a ‘subject’ specific model, and we therefore see no reason why the method could not be applied to patients who may have disease specific ‘motions’ (e.g. resulting from ascites or cirrhosis). Indeed, apart from the motion simulations and 4D plan validations, all the other tools developed here (the PCA motion model, surrogate marker tracking, reconstruction of motion etc.) could be applied directly to real patient treatments.

However, this proof-of-concept study is somewhat limited by the fact that we have divided the original MRI datasets into two parts, with the dense motion fields in the second part being reserved for validating the performance of the motion reconstruction. Compared to clinical workflow in reality, this might be a simplification, since motion model cannot be built immediately before dose delivery. Therefore, it is possible that the patient and tumour motion can be slightly different to that in treatment planning. However, these inter-fractional motion problems can be somehow reduced using volumetric imaging for patient positions and introducing plan adaptation approaches. The temporal resolution of respiratory motion has been modelled as 0.5s (2Hz) (similar as the time resolution of conventional 4DCTs), and
motion states within each time interval were linearly interpolated for the 4D dose calculations. Indeed, increasing imaging frequency is beneficial for improving accuracy of the motion modelling, and ideally motion should be monitored online with the same temporal resolution as the pencil beam scanning (4ms). However, selecting appropriate imaging parameters is absolutely essential for controlling the additional imaging dose. Using the default setting of our BEV imaging system in fluoroscopy mode (70kV, 4mA and 2Hz) and approximately estimated from the published data by Shimizu et al (2001), less than 20 mGy imaging dose is expected for the example patient case. Nevertheless, the experimentally measured values from our system will be reported in a future paper.

Finally, we have not attempted here to perform temporal motion predictions yet, but have shown that the tracking of motion surrogates can accurately reconstruct the full 3D motion field of the right liver lobe. Thus, we believe that true tracking, which would require in addition some temporal prediction algorithm due to the system latency of tracking, could be simply performed by applying existing temporal prediction algorithms (see e.g. (Verma, 2011b)) directly to the tracked surrogate motions here. Nevertheless, even without temporal prediction and true tracking, this method could still be employed for retrospective calculations of 4D dose distribution. For instance, for treatments involving other motion mitigation techniques (e.g. re-scanning, gating etc.), the reconstructed motion fields resulting from the techniques described here could be considered as an in-vivo record of the patient’s motions during treatment. Together with the delivered log files from the treatment machine (which could log the exact time of delivery of each pencil beam), the use of such models may allow for the reconstruction of 4D dose distributions on a fraction-by-fraction basis.

5. SUMMARY

In this chapter, we have proposed and validated a method which allows for the reconstruction of 3D dense deformable motions from sparse surrogate motions traced via on-board imaging systems with the help of a patient specific PCA motion model. Our results show a good agreement between the predicted and the ground truth motion fields, which have been validated through 4D dose calculations of scanned proton beam therapy. The benefits and effectiveness of deformable motion prediction have been shown, and we also demonstrated that a monoscopic OBI system could be sufficient to perform online image guidance for scanned treatments. Moreover, the diaphragm motion has been shown to be a good predictor for respiratory motion prediction in the liver region, implying that fiducial markers might not be compulsory for online motion tracking if a PCA model is used. In the following chapter, we move on to use BEV surrogate imaging, together with the models developed in this chapter, to study the potential efficacy of two additional motion mitigation techniques that can be used for scanned proton beam therapy, namely gating (chapter 6) and real-time tumour tracking and re-tracking (chapter 7).
Chapter 6

Scanned beam gating with BEV image guidance

1. INTRODUCTION

Beam gating has been extensively proposed and clinically employed for motion mitigation in both conventional radiotherapy (Kubo and Hill, 1996, Berbeco et al., 2005b, Dietrich et al., 2005) as well as passively scattered particle therapy (Lu et al., 2007), due to its relatively simple implementation. By limiting dose delivery to a certain pre-defined gating window of the patient’s breathing cycle, relative displacements between the irradiation and the target can be reduced, thus reducing dose blurring effects at the edge of the target dose and consequently allowing for reduced ITV margins. Although shorter beam-on periods per breathing cycle should reduce motion during irradiation, it is also essential that the total treatment time does not increase unduly. Thus, a balance between gating window size and an acceptable duty cycle (defined as the ratio of beam-on time to overall treatment time) has to be found in clinical practice. In addition, for pencil beam scanning with particles, dose blurring is not the only problem. The residual motions within the beam-on window could still lead to substantial interplay effects, whilst related density changes could also lead to range variation of each pencil beam (Bert et al., 2009).

In literature, numerous studies have been performed for exploring the benefits of gating through both simulations and experiments. However, most of the relevant studies were performed based on either simplified target geometries and/or simplified organ motions (Bert et al., 2009). Although 4DCTs can provide both geometric and density changes and are essential for calculating dose distributions in patients, the single-respiration-cycle nature of these data sets cannot fully represent the variation of motion that may occur during beam delivery. On the other hand, in order to study the potential effects of breathing irregularities, either simplified motion models or real motion trajectories extracted from any sparse internal (Matsuura et al., 2013) or external surrogates (Gierga et al., 2005) have been use. The latter have always been combined with rigid motions of the whole target or of the simplified phantom shapes (e.g. spheres or boxes).

We have previously explained the advantages of 4DMRI and 4DCT(MRI) data sets for extensively modelling motions in a way which can take both geometric and density changes into account, but which can also capture the variations of these as a result of inter-breath variations over extended time periods (see Chapter 5). A first example simulation using
motion extracted from 4DMRI motion to validate gating for scanned proton therapy has been performed by von Siebenthal (2008), but without considering motions induced density variations for accurate proton dose calculations. Thanks to the 4DCT(MRI) and 4D dose calculation (4DDC) methods developed by Boye et al. (2013), we can now for the first time perform extensive simulations of the effectiveness of beam gating, taking into account both geometric and temporal changes in the breathing-patterns of patients.

In order to implement beam gating for patient treatments, real time motion monitoring is compulsory, from which the system control signal for beam gating can be obtained. The potential advantages of the BEV imaging system over other motion monitoring devices for this have already been discussed in Chapter 3. In this chapter, we use 4DDC and the ground truth 4DCT(MRI) datasets generated as part of the studies in Chapter 5 to simulate BEV image guided beam gating for scanned proton treatment, so as to investigate the clinical necessity, the dosimetric benefits and the treatment efficiency of scanned beam gating using realistic patient motions and geometry. In addition, we also look into the effectiveness of a combined motion mitigation approach of gating and re-scanning, with the hypothesis that moderate amounts of re-scanning will help to deal with the residual motions effects that may present within the gating window.

2. METHODS AND MATERIALS

I. Motion data and gating windows

For this study, we have chosen three representative motion cases (A, B and C), together with their ground truth motion/density fields from 4DCT(MRI) data sets (see Chapter 5), to study the dosimetric effects of gating and combined gating/rescanning combined methods. The inter-cycle averaged motion ranges are of the order of 10mm, 15mm and 20mm (for A, B and C respectively).

Using the methods described in Chapter 4, breathing signals have been derived for each case. Their origin has been set to be the position of the chosen surrogate at the reference (first) end-of-exhalation observation (Shirato et al., 2000b). The size of the gating window was then defined from the first breathing cycle of each subject. Subsequently, for each time step, the tracked surrogate location of either fiducial markers or the diaphragm, were compared to this reference location, and then the absolute differences were quantified and finally used to determine beam gating signals. The scenarios of dose delivery without gating and four different gating window sizes have been simulated for each case, namely 20%, 30%, 40% and 50% of the maximum motion magnitude of the first breathing cycle.

II. 4D treatment planning

For each subject, the 4DDC for beam gating has been simulated by taking into account, only the portion of the 4DCT(MRI) data sets that temporally lies within the selected gating window. As shown in figure 6-1, the worst case scenario of a single anterior field with field
direction orthogonal to the major axis of motion (superior-inferior) was simulated, and 4DDCs were performed for both single, three-times and six-times volumetric rescanning (Zenklusen et al., 2010). In order to deal with dose blurring in the non-gated or no-rescanning scenario, a Planning Target volume (PTV) was defined through a 15mm isotropic expansion of the Clinical Target volume (CTV), in order to be able to distinguish dose inhomogeneity due to the interplay effects from those of dose blurring at the edges.

Figure 6-1. Configuration of the 4D plans

III. 4D plan evaluation

To evaluate the results of the gated and gated/rescanned 4DDCs, the Dose Volume Histograms (DVHs) were calculated for each 4D plan, from which the homogeneity of the dose within the CTV was measured in terms of the difference between the D5 and D95 points of the DVH (D5-D95). The steeper the DVH is, the smaller the D5-D95 value is, and the more homogeneous the plan is. Since a relatively large ITV margin has been used, any deterioration in the D5-D95 value is mainly due to over- and under dosages resulting from residual interplay effects.

Furthermore, in order to quantify dose conformity, the conformity number at 95% of the prescribed dose has been calculated. This value is used to evaluate the differences in irradiated volume (the total volume of tissue irradiated above 95% of the target dose). The Conformity Number (CN) was originally proposed by van Rit (1997) and is defined as,

\[
CN = \frac{V_{CTV,95\%}}{V_{CTV}} \times \frac{V_{CTV,95\%}}{V_{95\%}}
\]

(6-1)

where \( V_{CTV,95\%} \) is the volume of the CTV receiving a dose equal or higher than 95% of the prescribed dose, \( V_{CTV} \) is the volume of the CTV, and \( V_{95\%} \) is the total tissue volume irradiated to a dose of 95% or higher. The CN value is thus made up of two components. The first term measures the conformation of dose distribution with respect to the CTV, with higher values (1 at most) for more homogenous distributions. The second part quantifies the level of healthy tissue involvement (e.g. volumes outside the CTV) relative to the CTV, with higher values for
less tissue being unnecessarily irradiated. In summary, the nearer the CN is to 1 (or 100%), the better the treatment.

As mentioned in the introduction, one drawback of beam gating is the extended treatment time. The total field delivery time will be the sum of the beam-on time and the beam-off time, and thus treatment time will increase as the gating window size reduces. To reflect this, the treatment efficiency has been quantified in terms of the duty cycle, which has been defined by the percentage of beam-on time over the total duration of dose delivery. However, due to different motion appear among different breathing cycle, this value can be different per breathing cycle dependent on breathing patterns. For the three motion cases, temporal motion resolution was modelled as 0.5s, and 300 timestamp (150s) motion data in total were used as inputs. If the overall treatment duration is longer than 150s, motion data will be repeated from the beginning (due to the restriction of data size in our planning system currently). We compared the 4D plan scenarios using five different gating window sizes, combining with three different scanning approaches, in order to achieve an optimal solution for maximally mitigating motion effects. The determined approach should be able to appropriately balance target dose homogeneity and coverage with the shortest treatment time. The scanning parameters used for the calculations are those of Gantry2 at our institute (Zenklusen et al., 2010) and the proton pencil beams have been considered to have a full-width, half-maximum width of 8mm at the Bragg peak and are separated in both axes orthogonal to the beam direction by 5mm. The dead time for moving the pencil beam along each lateral direction is of the order of 4ms, while energy changes have been modelled at 80ms for 5mm changes in water equivalent depth.

3. RESULTS

I. Gating window

The left column of figure 6-2 shows the mean fiducial motions as a function of time, which was extracted from simulated BEV images with respect to the first end-of-exhalation observation. Each of the coloured horizontal lines indicates one defined gating windows, which was calculated by different portions of the chosen surrogate motion range of the first breath cycle. In the right column of the same figure, gating signals from the example Case A are shown as a function of window size. The temporal difference of breathing patterns can be clearly observed, especially for the scenarios with large window size. The gating efficacy (measured by duty cycle), resulting from different gating windows and surrogate types (fiducial or diaphragm motion) has been respectively compared in figure 6-3(a). Due to the asymmetry of the breath curves, 50% amplitude gating window results in duty-cycles of 50-70%, while if the gating window is reduced to 20%, this corresponds to a duty cycle of around 35-50%. When comparing across different motion cases, as expected, smaller motion (Case A, cyan) is always associated with the highest duty cycle and the lowest residual motion, regardless of surrogate types. However, for larger motions (Case C, red), the duty cycle was actually higher than for moderate motions (Case B, green), since more motion states were
located at the end-of-exhalation phases. Furthermore, given the same amplitude-based gating window, maximum residual motions have been found to be larger for diaphragm tracking than for fiducial tracking. Although this effect is rather small for the smaller motion cases, these differences are quite dramatic for the largest motion case due to the extensive deformations of the liver along with respiration. The comparison of maximum residual motions (of fiducials) for different surrogates and cases has been found in figure 6-3(b). In order to obtain a meaningful comparison, when diaphragm was used (dashed line) as surrogate, corresponding residual fiducials motions is calculated and then compared to the scenarios when fiducials were directly used as gating signal. For large motion (case C in red), residual motions were up to 30% higher when diaphragm tracking was used as a gating surrogate compared to those resulting from fiducial tracking, and the residual motions resulting from only a 20% diaphragm based gating were similar to those for a 40% window based on fiducial motion. This indicates that a smaller gating window needs to be considered if the diaphragm is selected as the surrogate for gating applications.

II. Effectiveness of beam gating and impact of residual motions

Figure 6-4 compares the quality of dose distributions, in term of the DVHs in the CTV, as a function of gating windows using the tracked surrogate motion of either fiducial (a-c) or diaphragm (d-f). Generally, for all scenarios, the smaller the gating window is, the steeper the DVH can be, indicating improved dose homogeneity across the CTV as the gating window narrows. This tendency has been confirmed for all scenarios, regardless of surrogate type. For the smallest motion (case A) and fiducial based gating shown in figure 6-4(a), differences of DVH steepness due to the decreasing window sizes is less pronounced than for the other two cases (c-d). Correlating these results to the motions plotted in figure 6-3(b), it can be seen that the residual motions of this case were less than 5mm for all gating windows and reduced by only about 3mm when the window size decreased from 50% to 20%. Moreover, from all DVHs in figure 6-4, it is clear that gating alone cannot fully restore the dose homogeneity of the static case, even with the smallest gating windows, indicating the high sensitivity of scanned proton beam to even small residual motions and density variations. For the case with the largest motion (Case C), D5-D95 only decreases from 57% to around 25% for 50% amplitude gating, and subsequently reduced to 15/13/9% for 40/30/20% gating windows respectively, in comparison with a D5-D95 of only 2% for the static plan. For cases A and B, the best dose homogeneities that could be achieved (both with the 20% gating window) were 6% and 8% respectively. These results highlight the interests in combining beam gating with other motion management strategies to further improving plan quality, particularly for cases with larger motions.
Figure 6-2. (left) Mean fiducial motions with different gating windows and (right) the exemplar beam gating signals for motion Case A.
Figure 6-3. (a) Duty cycle and (b) maximal residual surrogate motion as a function of gating windows size, gating surrogates (solid: fiducials; dash: diaphragm) and motion subjects (cyan: Case A; green: Case B; red: Case C). Note that no gating is shown as a 100% gating window.

Figure 6-4. DVHs (in CTV) of 4D plans with different gating windows, when (a-c) fiducials or (d-f) diaphragm motion used as gating surrogate. (x-axis: Dose (%); y-axis: Volume(%) )

III. Combining beam gating with rescanning

Figure 6-5 shows the D5-D95 and rCN (relative CN with respect to corresponding static plan) values of the 4D dose distribution for gating alone (purple), 3x (red) and 6x rescanning (blue), all as a function of gating window sizes. For all values in this figure, the mean fiducial motions were used as surrogate to derive beam gating signals.

1) Gating and rescanning compared

As shown in Chapter 2, rescanning has been demonstrated (at least through simulations) as an effective approach to restoring dose homogeneity in the presence of motion and, as mentioned
above, gating has also been used extensively to mitigate motion in both conventional therapy and passive scattered particle therapy. In this section, we first directly compare the two methods based on the three motion cases described above.

Table 6-1 lists dose homogeneity (D5-D95) and rCN values for all three cases using either gating alone (using the 20% window) or rescanning alone (without gating). As discussed above, even for the 20% gating window and the smallest motions (case A), gating alone cannot achieve the dose homogeneity or the rCN value of the static calculation (6% and 94%). However, by combined using three times rescanning with 20% gating, D5-D95 value within 1% of the static value can be achieved. For the medium and large motions (cases B and C), rescanning alone appears not to be sufficient for either dose homogeneity (12% and 15% respectively) or conformity (77% and 65% respectively). Although homogeneity can be improved somewhat by increasing to 6 times rescanning (reducing the D5-D95 values for both cases to below 10%), the rCN values are only improved marginally. For large motion, gating has been found to be more effective for improving rCN value than 6x rescanning. Consequently, in order to achieve results similar to the static case for medium to large motions, neither gating nor rescanning appears to be sufficient on their own, and combining motion mitigations seems to be compulsory.

<table>
<thead>
<tr>
<th>(%)</th>
<th>Homogeneity (D5-D95)</th>
<th>Conformity (rCN)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case A</td>
<td>Case B</td>
</tr>
<tr>
<td>Static</td>
<td>2.05</td>
<td></td>
</tr>
<tr>
<td>No mitigation</td>
<td>29.7</td>
<td>41.5</td>
</tr>
<tr>
<td>20% gating</td>
<td>6.3</td>
<td>6.9</td>
</tr>
<tr>
<td>3x rescanning</td>
<td>3.4</td>
<td>12.2</td>
</tr>
<tr>
<td>6x rescanning</td>
<td>3.4</td>
<td>9.4</td>
</tr>
</tbody>
</table>

2) Gating combined with rescanning

The impact of residual motion within the gating window have already been analysed, and clearly contributes to the less than optimal results seen for gating or rescanning alone in the previous section. However, as seen in all plots of figure 6-5, by combining rescanning with beam gating (red and blue lines in the plot, and gating window < 100%) both dose homogeneity and conformity can be substantially improved. Averaged over all three motion cases, the use of 3x rescanning together with a 50% gating window can reduce D5-D95 values to ~8%. Indeed, for case A (small motion), there appears to be no advantage to further reduce gating windows or increasing the number of rescanning, once these are combined, since the D5-D95 values are very similar (max. difference 2.9%) over all windows sizes when combined with 3x or 6x rescanning. However, for the cases with larger motions, there seems to be an advantage in using higher orders of rescanning, particularly for case C and 50%
gating window. In summary, it appears that adding rescanning to gating can significantly improve the plan quality over and above what can be achieved by gating alone. Similar conclusions can also be drawn for the effects of combined gating and rescanning on dose conformity (lower row of figure 6-5).

![Figure 6-5](Image)

Figure 6-5. (top) Homogeneity and (bottom) relative conformity (rCN) of 4D plans (fiducial based gating) with and without rescanning for (left to right) case A, B and C. Gating windows of 0(100) % represents no motion (no gating).

3) Plan quality versus treatment duration

Both gating and rescanning are motion mitigation methods that will tend to increase the total treatment time. For gating, this is dependent on the duty cycle, which will be smaller for smaller gating windows, whereas for rescanning, this is due to the increased dead time (time to move from spot to spot) accumulated in visiting all target positions multiple times. However, for either gating or rescanning, the total beam-on time remains constant, only correlating with the planned dose amount, irrespective of the number of re-scans or gating window size. Therefore, the total treatment time increases sub-linearly with the rescan factor or gating efficiency. Thus, as gating and rescanning influence total treatment time differently, there may be an additional advantage of combining rescanning and gating from the point of view of overall treatment time. This issue will be discussed in this section.

Figure 6-6 compares the D5-D95 and rCN values of each 4D plan, but now as a function of the total treatment duration. Without any form of gating or rescanning, the time required to deliver single field is about 100s, which successively increases to 135s and 212s for 3x and 6x rescanning respectively. As the target volume is the same for all cases (only the motion characteristics have been changed between cases A, B and C), these times is valid for all plans, gating and motion scenarios. In contrast, the increased treatment duration in the presence of
beam gating, whilst highly dependent on the size of the gating window, is also dependent on the breathing pattern and period during dose delivery, and thus varies somewhat for each case and, to a lesser extent, between different breathing cycles. Over all cases, the mean (std) of the durations for gated delivery (without rescanning) were 163.8(14.3), 178.8(27.5), 206.0(30.7) and 234.2(43.6) seconds for 50, 40, 30 and 20% gating windows respectively.

We now move on to assess the total treatment duration for the scenarios which combined beam gating with volumetric rescanning. Assuming we wish to obtain a plan with D5-D95 < 5% and a rCN>95 (indicated by the colour bands in figure 6-6) and consumed the shortest possible delivery time, it is simple to define the optimal case specific combination of gating and rescanning directly from the results shown figure 6-6, where they are marked by the arrows. For case A, although many combinations provide clinically acceptable values of homogeneity and conformity, these can be fulfilled with the minimum treatment time by the combination of a 50% gating window combined with 3x rescanning (blue arrows). This combination would take 194s to complete delivery, so just under twice as long as the nominal field without gating. However, it should be pointed out that almost comparable dosimetric results can be also achieved for 6x rescanning on its own and with a similar, if slightly longer, treatment time of 212 seconds. Given the extra complexity of gated treatments, it is therefore likely that for this case, the rescanning only option would be used, despite the small disadvantages of this approach compared to the ‘optimal’ combined rescanning/gating option. A similar selection procedure can be applied to the other two cases. For Case B (moderate motion), the most time efficient approach would be a 20% gating window with 3x rescanning (labelled by green arrows), requiring a delivery time 367s. For case C, the optimal approach would be a 40% gating window, together with 3x rescanning (total treatment duration, 239s). Thus, for none of the motion scenarios considered does there appear to be an advantage from the point of view of treatment time to increasing the rescanning factor to 6.

4) Fiducial versus diaphragm guided gating

Finally, figure 6-7 compares D5-D95 and rCN values for all 4D plans (static, gating alone, gating combined with 3x and 6x rescanning) when beam gating signal is derived from the tracked diaphragm motion. Since gated dose delivery only requires the relative motion information to obtain a gating signal, the final dosimetric differences is simply related to the motion differences between surrogates. Because diaphragm motions are generally larger than that of internal points of the liver (and therefore the fiducials), given the same percentage of amplitude, the size of derived gating window will therefore likely be larger than the one derived from fiducial motions. Nevertheless and as already shown in figure 6-3, these differences (between the two surrogates) are only pronounced for larger motion cases. Even if generally slightly higher D5-D95 values were obtained with the diaphragm as gating surrogate and the tendency from the results in 6-7 and figure 6-6 is consistency, which demonstrates the feasibility of using diaphragm motion as surrogate to derive beam gating signal, perhaps negating the need to have implanted fiducial markers for BEV based gated treatments.
Figure 6-6. D5-D95 (upper row) and CN (upper row) of 4D plans for different motion mitigation methods using motion surrogate of mean 2D fiducial motions as a function of total treatment duration.

Figure 6-7. D5-D95 (upper row) and CN (upper row) of 4D plans for different motion mitigation methods using surrogate of diaphragm SI motion as a function of total treatment duration.

4. DISCUSSION

In this chapter, we have used simulated BEV images (Chapter 3) and the developed image-based motion tracking methods in Chapter 4, to investigate the potential of this system for online beam gating treatment. In addition, we also simulated two levels of volumetric rescanning.
(3x and 6x) for the same cases, and compared the results of rescanning to the purely gating scenarios. Finally, we have looked at various combinations of these two techniques to determine the optimal combination, which can not only achieve dose homogeneities and conformations of clinically acceptable levels, but also minimise overall treatment time.

The results of 4DDCs have shown that for the two large motion cases investigated (>15mm), the effect of residual motions within the gating window can still significantly affect dose homogeneity within the target volume, with the D5-D95 (in CTV) being ~10% when gating only was simulated. It can be improved to ~6% for the case with small motion, but such dose homogeneities can only be reached using the smallest gating window (20%). In addition to the considerations of dose homogeneity within the CTV, it is also desirable to reduce the amount of healthy tissue involved in the irradiation. The CN values of the 4D plans indicate that dose conformity can be substantially increased when a small gating window is applied, but at the cost of a prolonged treatment duration.

Therefore, in order to reduce interplay effects caused by residual motions within the larger gating windows, whilst maintaining good dose homogeneity, conformation and treatment durations, we have found that for all motion scenarios, it could be an advantage to combine gating with rescanning. Our results show that, at least for the three representative liver motions studied in this chapter and with the limited mitigation methods under the investigations, it is possible to achieve a suitable strategy for each subject which is able to provide D5-D95 values of lower than 5%, together with CN values of better than 95% of the values for the static case, which can also minimise the treatment times below those that could be achieved with rescanning or gating alone (for similar dosimetric parameters). In addition, we have taken into account two motion surrogates extracted from BEV images. Since differences in motion between the diaphragm and fiducials markers are likely to result in somewhat different window sizes for the same breathing cycle, it is somehow meaningless to directly compare the 4D plans with the gating signal derived from either fiducials or diaphragm. However, our results as least demonstrate the feasibility of using the diaphragm motion alone as a gating signal to achieve a comparable plan resulted when fiducials are used as surrogate.

We cannot find any reason for prohibiting applying such patient specific motion mitigation optimization into the clinically implementation, if calculation efficiency of the 4DDC can be eventually improved through incorporating new techniques such as powerful CPU or parallel computing. It somehow extends the idea of current Multi-criteria optimization (Craft, 2013) from 3D into 4D by further taking into account the optimization for different motion mitigations. We believe it can be one interesting research focus in the subsequent work.

One limitation of our current study is that we have ignored the organ drift caused by muscle relaxation (von Siebenthal et al., 2007), due to the relative short beam delivery time (less than 10min, plus the preparation time). However, it is a crucial point for further studies, especially
if hypo-fractionation regimes are considered, where the treatment times would increase due to the higher dose levels that need to be delivered per fraction. Such potential drifts are another important reason why treatment durations should be kept to a minimum. As by keeping these short, the magnitude of such drifts should also be minimised. Nevertheless, it actually highlights another advantage of using the BEV imaging system for beam gating, since the internal motions are detected all the time. If there is any systematic baseline shift of the target, it may be possible to correct this by adapting the reference position of the gating window accordingly. For example, by applying a method similar to that proposed by Aristophanous et al. (2010) if fiducial marker was selected as surrogate. Moreover, since the time scale of organ drift in the inferior part of liver is relatively long, this type of organ motion can be somehow considered as an intermediate status between intra- and inter-fractional motion, more reliable method for solving such problems is acquiring volumetric image from time to time (such as in between of each rescan). This procedure can be performed by using either the in-room sliding CT or the BEV based cone beam CT (such as the case of PSI-Gantry2), but eventually the in-room or the on-gantry MRI should be the ideal solution. One more factor which might limit the conclusions drew in this chapter is that we had modelled the breathing cycle as equal duration (5s) in the 4DDCs. Although the inter-cycle variations in terms of motion amplitude were considered, the temporal irregularity has not yet been taken into account in the simulation yet. Compared to the reality, these differences can slightly influence the calculated beam-off time, but will not much affect the dosimetric quantifications and concluded mitigation optimization tendency in this chapter.

5. SUMMARY

In this chapter, we have used the previously described 4DDC methods, together with 4DCT(MRI) datasets, to perform a proof of concept study of the BEV image guided beam gating for scanned proton treatment. The BEV tracked surrogate motions from either fiducial markers or the diaphragm has been utilized to derive amplitude-based gating windows. A total of fifteen motion mitigation approaches (five different window sizes and three types of scanning modes) have been applied to three representative and free breathing patterns. Our results show that for subjects with averaged motion range over 10mm, it is necessary to combine beam gating with rescanning in order to reduce the residual interplay effects within the gating window. In addition, the combined approach has also been demonstrated as an efficient strategy for decreasing healthy tissue involvement and reducing total treatment times, in comparison to purely gating and purely rescanning strategies.
Chapter 7

Scanned beam tracking with BEV image guidance

1. INTRODUCTION

Previously in this thesis, we have respectively investigated the effectiveness of re-scanning and gating for mitigating interplay effects. Although such approaches are straightforward to implement clinically, as shown in the Chapter 6, treatment duration is inevitably extended and their efficiency is somewhat dependent on the reproducibility of tumour motion between cycles. Breath-hold (not studied in this work) basically shares the same drawbacks as gating, and also requires active patient participation and the ability to maintain a reproducible location of the tumour during each portion of dose delivery, which is clearly not easy. For all these techniques, due to either residual motions (re-scanning/gating/breath-hold) or irreproducible tumour positions between successive irradiations (gating/breath-hold), ITV margins of varying magnitudes are still required in order to assure target coverage, inevitably leading to larger irradiated volumes.

In this chapter, we look into a third motion mitigation technique, namely beam tracking. In this approach, the position of each pencil beam is adjusted dynamically to ‘follow’ the tumour position as it moves. Beam tracking is, in principle, the optimal technique of motion mitigation, as, if done perfectly, it should not lead to excessive treatment prolongation or target volume expansions (Grözing et al., 2006). For scanned proton beam irradiations, beam tracking means both laterally adapting individual pencil beams according to the current target position, and possibly longitudinally adjustments depth of the Bragg peak by varying the beam energy in order to compensate density variations. However, from the dose delivery point of view, scanned beams are ideal for tumour tracking, since the speed at which the beam can be magnetically deflected in to lateral beam directions (~1mm/ms) is much faster than typical anatomical motions. On the other hand, tracking can only be optimally utilised if accurate, real time information on the tumour location is known. Indeed, it is this requirement that is the main challenge for any form of tumour tracking with external beam radiotherapy.

In Chapter 5, we have proposed and validated a method which allows for reconstructing the deformable motions from sparse surrogate motions tracked via the BEV imaging system. Due to the sequential delivery technique and high sensitivity of proton beams to both small motions and range changes, knowledge on 3D motions in real-time, together with the resultant density variations, is a pre-requisite for clinical implementation of scanned beam tracking.
With our pre-built patient specific PCA model, a good agreement between the predicted and the ground truth motion fields has been observed. Moreover, from the aspect of prediction accuracy, the benefits of tracking deformable motion over just translations have been demonstrated. Therefore, we aim to investigate in this chapter the potential of scanned tracking with online BEV image guidance, through the use of our 4D dose calculation and the reconstructed motion/density fields developed in Chapter 5. In particular, we investigate three types of beam tracking strategies applied to three liver cases with different motions, in order to assess the consequences of the uncertainties from both spatial and temporal motion prediction (simulated as random error) for scanned beam tracking. Moreover, we also introduce and look into the use of re-tracking (the tracking with re-scanning) (Water et al., 2009) on the sensitivity of tracking to those uncertainties.

2. METHODS AND MATERIALS

1. 4D dose calculation for scanned beam tracking

The basic framework of 4D dose calculation (4DDC) used in this work has already been introduced in Chapter 2, which will be briefly reviewed here to descript the method developed for simulating scanned beam tracking. The algorithm of 4DDC for scanned proton treatment consists of three main components:

- a nominal optimised 3D dose distribution (3DDC) calculated using the density information of the reference CT, $DM_{\text{ref}}$,
- a series of motion maps $MM_{TS}$,
- a series of density maps $DM_{TS}$.

1) 3DDC

The 3D planning is first performed using the reference CT, which results in a list of $N$ pencil beams, whose Bragg peak position in the STU-beam coordinate system (as introduced in Chapter 3) is given by,

$$PB_{0,n} = (s_{0,n}, t_{0,n}, u_{0,n}) \quad n \in [1, N]$$

(7-1)

Each beam also has a relative weight, $N_{p+,n}$, which is associated with the number of protons planned to be delivered by beam $n$. $N_{p+,n}$ are calculated and optimised on $DM_{\text{ref}}$, which describes the Water-equivalent range (WER) of all $M$ dose calculation position in the same coordinate system. The coordinate of dose grid $m$ can be described as,

$$DG_m = (s, t, u) \quad m \in [1, M]$$

(7-2)

whose centre is usually positioned with respect to the CTV tumour centre. $M$ is the total number of dose calculation positions, which is defined once the treatment field is constructed.
\( DM_{ref} \) is calculated from the planning CT by integrating the density values along the direction of treatment field.

Therefore, dose deposited at \( DG_m = (s, t, u) \) by pencil beam \( PB_{0,n} \) can be described as,

\[
d_n(DG_m) = d_n(s, t, u) = N_{p+n,n}D_{PB_{0,n}}(DM_{ref}(s, t, u)) \frac{1}{2\pi\sigma_t\sigma_u} e^{-\frac{(t_0,n-t)^2}{2\sigma_t^2}} e^{-\frac{(u_0,n-u)^2}{2\sigma_u^2}}
\]

where \( iD \) is the depth-dose curve characterized by the nominal beam energy and the width of the initial energy spectrum. \( \sigma_t, \sigma_u \) are the standard derivation of the Gaussians of the pencil beam in lateral \( t \) and \( u \) directions at the WER which is equal to that of \( DG_m \), describing beam lateral profiles. Consequently, the final dose distribution \( D_{3D} \) contributed by all \( N \) pencil beams can be calculated as,

\[
D_{3D}(s, t, u) = \sum_{n=1}^{N} d_n(s, t, u)
\]

2) 4DDC

In order to extend 3DDC to 4DDC, an individual time stamp (TS) is calculated for each pencil beam, depending on the number of delivered protons, the beam scanning path (SP) and the system specific beam position adjustment time (BPAT), depending on the speed of magnetic deflection and energy changes. The combination of pencil beam specific spot list and time stamp completely describes the temporal characteristics of the dose delivery of certain treatment field. Let \( H \) be the function used for calculating TS, the time resolved spot \( PB_{0,TS} \) can be derived by,

\[
PB_{0,TS} = (s_{0,TS}, t_{0,TS}, u_{0,TS}) = H(PB_{0,n}, N_{p+n,n}, SP, BPAT)
\]

In a complimentary way, \( MM_{TS} \) describes geometry variations of \( DG_m \) due to respiratory organ motion, thus providing a time-varying 3D displacement matrix of each \( DG_m \) position. The lateral motions \( (\Delta t_{TS}, \Delta u_{TS}) \) of \( DG_m \) at each \( TS \) can then be extracted from the corresponding \( MM_{TS} \), thus,

\[
(\Delta t_{TS}, \Delta u_{TS}) = MM_{TS}(s, t, u)
\]

Finally, density maps \( DM_{TS} \) of \( DG_m \) can also be achieved from the warped 4DCTs using the displacement field derived from \( MM_{TS} \). According to the corresponding \( MM_{TS}, DM_{TS}, \) and \( TS \), the dose at each dose grid position and at each \( TS, d_{TS}(s, t, u) \), is calculated during the 4DDC, so that the final 4D dose distribution \( D_{4D}(s, t, u) \) can be achieved by summing up contributions from all pencil beam deliveries at \( TS \), as,
\[ d_{TS}(s, t, u) = N_{p+,TS} D_{PB0,n}(DM_{TS}(s, t, u)) \frac{1}{2\pi \sigma_t \sigma_u} e^{-\frac{(t_0,TS-(t+\Delta t_{TS}))^2}{2\sigma_t^2}} e^{-\frac{(u_0,TS-(u+\Delta u_{TS}))^2}{2\sigma_u^2}} \]

\[ \sigma_t = \sigma_u = \sigma_{PB0,n}(DM_{TS}(s, t, u))\]

\[ D_{4D}(s, t, u) = \sum_{TS=0}^{T} d_{TS}(s, t, u) \quad (7-7)\]

3) 4DDC for beam tracking

In order to simulate scanned beam tracking, the original inputs of \( MM_{TS} \) and \( DM_{TS} \) in equation (7-6) and (7-7) have been considered as two separate parts: a compensated component and a residual component after beam adaptation. The residual motion maps \( eMM_{TS} \) (see equation (7-8)) and their corresponding residual density maps \( eDM_{TS} \) (see equation (7-10)) after adapting the initial \( PB_{0,TS} \) settings (position and energy) can be obtained by respectively subtracting the online tracked motions and density variations of the Bragg peak position from the initial inputs of \( MM_{TS} \) and \( DM_{TS} \). Since online reconstructed motions field \( \overline{MM}_{TS} \) is predicted for all dose grid positions, rather than the pencil beam positions, motion vectors of the most nearest dose grid position \( \overline{PB_{0,TS}} \) is used instead. Due to the evitable prediction errors, \( eMM_{TS} \) has been calculated by subtracting beam lateral position compensation offsets (\( BLP\overline{CO}_{TS} \)) from each of all motion vectors of the ground truth motion field \( MM_{TS} \), in the following way,

\[ BLP\overline{CO}_{TS} = (c\overline{t}_{TS}, c\overline{u}_{TS}) = \overline{MM}_{TS}(\overline{PB_{0,TS}}) \]

\[ eMM_{TS} = MM_{TS}(s, t, u) - BLP\overline{CO}_{TS} \quad (7-8)\]

In order to adjust beam energy (position in depth) as well as estimate the total dosimetric impacts due to beam energy adaption, corresponding density field \( \overline{DM}_{TS} \) needs to be predicted online. From this, the estimated Bragg peak position of each beam can be online calculated. The differences between the predicted value (\( \overline{W\overline{E}R}_{TS} \)) and the initial value (\( \overline{W\overline{E}R}_{ref} \)) can be used to determine the beam energy compensation offsets (\( BEO_{TS} \)), which can be used to on-line adapt the Bragg Peak position in the tumour target.

\[ BEO_{TS} = (\overline{W\overline{E}R}_{TS} - \overline{W\overline{E}R}_{ref}) = \overline{DM}_{TS}(\overline{PB_{0,TS}}) - \overline{DM}_{ref}(\overline{PB_{0,TS}}) \quad (7-9)\]

From this, the residual density field \( eDM_{TS} \) can be derived by subtracting the predicted density variation of pencil beam \( PB_{0}(TS) \) from the ground truth density field \( DM_{TS} \), as,

\[ eDM_{TS}(s, t, u) = DM_{TS}(s, t, u) - BEO_{TS} \quad (7-10)\]
Finally, the 4D dose distribution using scanned beam tracking can be calculated by,

\[ d_{TS}^{TS}(s, t, u) = N_{p+TS} iD(eDM_{TS}(s, t, u)) \frac{1}{2\pi \sigma_t \sigma_u} e^{-\frac{(t_{TS} - (t + \Delta t_{TS} - c t_{TS})^2}{2\sigma_t^2}} e^{-\frac{(u_{TS} - (u + \Delta u_{TS} - c u_{TS})^2}{2\sigma_u^2}} \]

\[ \sigma_t = \sigma_u = \sigma(eDM_{TS}(s, t, u)) \]

\[ D_{4D-tracking}(s, t, u) = \sum_{T_{TS}=0}^{T} d_{TS}^{TS}(s, t, u) \]  

(7-11)

II. Strategies of scanned beam tracking

In scanned proton therapy, beam tracking can be implemented in different modes, depending on how much the motion effects are planned to be compensated online. As such, we here define three such beam tracking strategies, conventional (translation) 2D tracking, deformable 2D tracking and deformable 3D tracking. To analyse the results and efficacy of these strategies, the resulting 4D dose distributions have been respectively compared to the original static dose distribution. In addition, we also looked into the potential effects of prediction errors for these approaches, as well as the residual motion effects after applying beam tracking. An overview of the characteristics of different tracking modes can be found in table 7-1.

However, before describing the different tracking strategies, it is necessary to clearly state a fundamental limitation to tumour tracking with pencil beams. Although the motion models developed in Chapter 5 allow us to reconstruct the full three-dimensional motion of the whole liver, there are only three degrees of freedom for correcting each pencil beam position (the two directions orthogonal to the beam direction, and the pencil beam energy). In other words, the beam is always straight, while the anatomy it passes through can deform. One straightforward approach is to therefore adapt pencil beam positions based only on motions of the planed Bragg Peak positions, due to the highest dosimetric contributions, which is the approach we have taken in this chapter. However, since dose grid positions in the whole treatment field (of both tumour target and surrounding tissue) are moving in a deformable way (i.e. have many more than three degrees of freedom), such a beam adaption can only compensate dosimetric variations due to motions close to the Bragg peak, and not necessarily for the tissues along the entrance path of the pencil beam.
Table 7-1. An overview of different scanned beam tracking modes.

<table>
<thead>
<tr>
<th>4D scenarios</th>
<th>Online compensated</th>
<th>Density variation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lateral motion ((\vec{c}t_{TS}, \vec{c}u_{TS}))</td>
<td>((\overline{WER}<em>{TS} - \overline{WER}</em>{ref}))</td>
</tr>
<tr>
<td>No motion</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>No tracking</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Ideal tracking</td>
<td>from the ground truth motion fields</td>
<td>from ground truth density fields</td>
</tr>
<tr>
<td>Conventional 2D tracking</td>
<td>from the mean motion of the three tracked surrogate</td>
<td>None</td>
</tr>
<tr>
<td>Deformable 2D tracking</td>
<td>from the reconstructed deformable motion fields</td>
<td>None</td>
</tr>
<tr>
<td>Deformable 3D tracking</td>
<td>from the reconstructed deformable motion fields</td>
<td>from the reconstructed density fields</td>
</tr>
</tbody>
</table>

1) Conventional 2D tracking

This mode is perhaps the most straightforward technique, and has been clinically extensively investigated in photon therapy with devices such as the Cyberknife (Hoogeman et al., 2009), the RTRT system (Shirato et al., 2000b) and the IRIS system (Berbeco et al., 2004a) as introduced in Chapter 1. The basic approach of these systems is to make use of the OBI tracked tumour motion in order to adapt the therapeutic beam lateral position accordingly. In these approaches, tumour motions are usually quantified as a series of 2D translations in time (orthogonal to the radiation beam), the whole tumour is considered as a rigid object and no density changes are considered, as these have a rather minor effect on the dose distributions of photon treatments. To simulate this type of beam tracking using scanned proton therapy, the estimated motion field for the 4DDC in equation (7-6), \(\overline{M}_{TS}\), can be determined by directly tracking the fiducial motions and assuming that each pencil beam position can be corrected based on the tracked mean fiducial motion (among three in this study) at each time step. Since the monoscopic BEV system was used in our system, motion in the direction of imaging beam cannot be obtained, and thus no beam energy adaption is applied for this scenario.

2) Deformable 2D tracking

Since pencil beam scanning delivers the total dose to the target sequentially, and deformation of the organ from one pencil beam to the next can introduce additional motion effects, a more advanced tracking technique is to adapt each beam segment with its specific compensation vector, instead of assuming identical motion vectors over the whole field (as is the case with 2D tracking). In this mode, the motion differences between each beam delivery position and the online tracked surrogate position has been taken into account. The online estimated motion field \(\overline{M}_{TS}\) can then be obtained from the deformable reconstructed motion in real-
time as proposed in Chapter 5, which predicts the whole motion field from the measured sparse surrogate motions with the help of the pre-built, patient specific PCA model. Therefore, the 4DDC for this scenario takes into account the residual motions $e_{M_{TS}}$ after compensating the lateral motions of the Bragg peak of each pencil beam according to the 3D motion reconstruction model. However, as with 2D tracking, no tracking in the depth is used with this approach.

3) 3D tracking

In addition to the beam specific lateral motion compensation by deformable 2D tracking, an additional step in complexity is to simultaneously compensate any motion induced density variations by adapting the beam energy as well. As stated previously, besides online predicted motion fields, the density field $\hat{D}_{M_{TS}}$ can also be obtained by warping the reference CT with the inverse motion fields. However, due to the imperfect motion predictions, the derived density information can also differ from the ground truth one, so that the residual $e_{D_{M_{TS}}}$ should be calculated by subtracting the compensated density variation of each beam delivery $(\hat{W_{ERTS}} - W_{ERref})$ from the ground truth density field $D_{M_{TS}}$.

III. Re-tracking: a combination of tracking and rescanning

The technique called re-tracking was first introduced by Water et al. (2009), which takes advantage of beam tracking combined with the robustness of rescanning. As such, it attempts to reduce the sensitivity of pure tracking to the inevitable uncertainties resulting from the online motion tracking process. In that work (Water et al., 2009), from the simulations using a simple phantom, dramatic improvements in terms of increased dose homogeneous were shown when 4x re-tracking was applied. Inspired by that study, in this chapter we have also simulated this approach, but using 4DDCs with real patient motions and geometry. As such, we have also simulated 3x re-tracking for 2D and 3D tracking for all the three cases.

IV. Patient data

Three representative motion cases have been selected for this study, together with their online predicted motion/density fields extracted using the methods described in Chapter 5. These are identified as Cases A, B and C, with average motion range of 10, 15 and 20mm respectively as in Chapter 6. 4D plans have been generated by taking into account the ground truth motion/density and the reconstructed motions/density from the predictions using either the PCA model or 2D translations motions extracted directly from the detected average fiducial motions. In addition, the corresponding $e_{M_{TS}}$ and $e_{D_{M_{TS}}}$ were calculated respectively for the three tracking modes in the way described above. All BEV images were assumed to be acquired with the frequency of 2Hz, with which the pencil beam at the corresponding time was adapted according to the online predicted motion and density variation.

However, in reality there will be an inevitable loss of tracking accuracy due to system latency. That is, there is a finite time required to process the monitoring signal, extract the motion and
then correct the dose delivery device, by which the target points possibly moved to a new position. Because of this, a number of authors have developed temporal motion prediction algorithms to estimate the position of the tumour, based on previous motion pattern, at the eventual time of application of the corrected pencil beam. It is out of the scope of this work to develop new motion prediction algorithms, so we assumed that an existing temporal prediction algorithm (Verma, 2011a) can be applied to our online tracked motions in order to obtain the surrogate location in advance, and that the uncertainty in this process can be modelled as an additional residual motion in the 4DDC (see e.g. Ernst et al 2013). As such, we have artificially added random error components to the surrogate motion at each time step to simulate such prediction uncertainties. For this work, the random error components have been assumed to follow a normal distribution with mean (standard deviation) values of 1(0.5)mm, according to the latest comparison study by Ernst et al. (2013). In addition, in order to capture the effects of these uncertainties, 4DDCs were performed for five simulations of these random errors per motion case and tracking mode respectively.

V. Patient data and 4D treatment planning

For this study, we have used the same representative motion cases as Chapter 6, and the same worst case field direction, AP. The scanning parameters used for the calculations are those of Gantry2 at our institute (Zenklusen et al., 2010) and the proton pencil beams have been considered to have a full-width, half-maximum width of 8mm at the Bragg peak and are separated in both axes orthogonal to the beam direction by 5mm. Dead time for moving the pencil beam along each lateral direction is of the order of 4ms, while energy changes have been modelled at 80ms for 5mm changes in water equivalent depth. The target volume, field configuration and static (nominal) dose distribution are shown in figure 7-1. The dose distribution has been optimized on the PTV (white solid contour), which has a volume of 403ccm. To obtain a quantitative analysis, an Irradiated Volume (IV) (white dash contour) has been defined as a 10mm isotropic expansion of the original PTV, which results a volume of 1016ccm. The total volume of the liver (yellow solid contour) is 2769ccm.

![Figure 7-1. Configurations of the one field plan.](image-url)
VI. Plan evaluation

To evaluate tracking performance, the Dose Volume Histograms (DVHs) for the PTV have been calculated for each tracking mode and for each motion case, and then compared to the DVHs of the static plan. The D5-D95 value has been used as a measurement of dose homogeneity in the PTV. Moreover, the conformity of the 4D dose distribution to the PTV is also essential to assess the effectiveness of beam tracking, since tracking should, at least theoretically, involve the least amount of normal tissue. In order to assess the conformation of the high doses to the PTV, we use the Conformation Number proposed by Riet et al. (1997). In addition, absolute dose differences between the static and each of the 4D plans have been calculated, which have then been quantified in the form of cumulative Dose-Difference Volume Histograms (DDVH’s) in the IV. Moreover, the absolute volume size (in ccm) for which dose differences in comparison to the static plan are 5% or greater ($V_{\text{dosediff}=\geq 5\%}$) are quantified for each 4D plan, and has been used as another criteria to assess the efficiency of beam tracking.

3. RESULTS

1. Spatial prediction errors

Figure 7-2 shows deformable motion prediction error distributions on the liver surface at one end-of-inhalation phase for the three selected motion cases (A, B and C). These figures support the result from Chapter 5 that online reconstruction of deformable motion provides a more accurate estimation of the real tumor movement, in comparison to the simpler approach of using the mean motion from the tracked fiducial markers.

Figure 7-2. Prediction error distributions from the online reconstructed motions of one exemplified end-of-inhalation phase from (upper) PCA model and (bottom) translation model

More quantitatively, the different motion compensation methods (2D translation and 3D deformable) are compared to the ideal (3D deformable) scenario (using the simulated BEV imaging frequency of 2Hz). In figure 7-3a, the two columns show the derived lateral position
compensation vectors (T and U directions) of the pencil beam at each time when a BEV image is acquired, whilst figure 7-3b shows the predicted density variations for 3D tracking (in red) with respect to the ideal values (in blue). Additionally, in figure 7-4, the corresponding errors (in relation to the ground truth motions/density variations) have been quantified and presented in the form of boxplots. From figure 7-3 and figure 7-4, we can see that, in contrast to conventional 2D tracking (cyan), deformable 2D or 3D tracking (red) provides a more accurate compensation for lateral motions compared to the ideal scenario (in blue), whilst only 3D tracking is able to compensate the motion induced density variations. Indeed, as indicated by the boxplots in figure 7-4, density variations tend to increase as a function of motion magnitude, with maximal WER changes of 5, 8 and 10mm occurring for the small, moderate and large motion cases respectively if no range compensation was applied. However, applying range compensation by 3D tracking, these can be substantially reduced to 2-3mm. Nevertheless, it should be remembered that, as observed in Chapter 5, besides possible motions which may be out of the range of the training data for the PCA modeling, the larger the motion is, the larger the organ deformation and the less accurate the deformation model is.

II. Effectiveness and limitation of scanned beam tracking: tracking versus no tracking

By taking into account residual position and density variation errors after applying partial or full beam compensation as described above, 4DDCs have then be used to study the effects of beam tracking using the different modes summarised in Table 7-1. Figure 7-5 shows 4D dose distributions for each of the three motion cases and for each beam tracking mode, while Figure 7-6 shows the corresponding absolute dose differences between the static and each 4D plan. As expected, due to the relatively large motion magnitudes of all cases, considerable over- and under-dosage can be directly observed, when no motion compensation is applied, resulting in D5-D95 values as high as 35, 58 and 79% for Case A, B and C respectively. However, dose homogeneity is substantially improved using all beam tracking approaches, with conventional 2D tracking (cyan) reducing D5-D95 to 17, 19 and 29% for the three motion cases studied. Dose homogeneity can be further improved to 15, 18 and 23% when 3D tracking was employed, in comparison to the D5-D95 value of 9% achieved for the static plan. The effectiveness of beam tracking can also be seen by comparing the corresponding DVHs (PTV) in figure 7-5 as well as the plotted D5-D95 values in figure 7-7(a).

While dose inhomogeneity can be noticeably reduced when beam tracking is applied, dose homogeneity is still compromised in comparison to the static case, even using 3D tracking. This is due to three reasons. First, the BEV based motion reconstruction is not perfect, and there are inevitably residual errors for both motions and density, so that those uncertainties that will degrade the dose homogeneity in relation to the static case. Second, and as shown in figure 7-6, normal tissue motions in the entrance region of each pencil beam cannot be completely compensated if motion is different to that at the Bragg peak (to which we have
tracked the beams. Third, the pencil beams at the distal usually have larger weights, and consequently longer beam-on times within which there may still be residual motions that cannot be completely compensated. Consequently, the D5-D95 values of even ideal tracking have been found to be 5.9, 8.7 and 11.5% higher than those derived from the static plan. In addition, the difference dose volume histograms (DDVHs) in IV shown in figure 7-6 indicated that 29, 37 and 39% of the volume of the IV have dose differences of more than 5% compared to the static case for ideal tracking, which can be compared to 54, 74 and 81% for the case of no tracking. Finally, figure 7-7 summarises PTV dose homogeneity and dose conformation of PTV for all cases and tracking modes.

Figure 7-3a. Lateral motion compensation offsets in (left) T and (right) U directions for Case (top)A, (middle)B and (bottom)C using 2D conventional tracking (in cyan) and 2D/3D deformable tracking (in red) in comparison to the ideal 3D tracking (in blue) (x-axis: time step (in frame); y-axis: motion (in mm))
Figure 7-3b. Density compensation offsets for Case (top)A, (middle)B and (bottom)C with 3D tracking (in red) in comparison to the ideal 3D tracking (in blue) (x-axis: time step (in frame); y-axis: WER (in mm))
Figure 7-4. Statistics of the compensation errors of (left) lateral motion and (right) density variations of all beam deliveries for Case A (top), Case B (middle) and Case C (bottom)
Figure 7-5. 4D dose distributions for example slice and DVHs (in PTV) using different scanned beam tracking modes
Figure 7-6. Distributions of absolute dose difference and corresponding DDVHs (in IV) between static plan and each 4D plan.
III. Comparison of different tracking strategies

1) Conventional 2D tracking versus deformable 2D tracking

Compared to conventional 2D tracking, deformable 2D tracking has advantages in terms of improved dose homogeneity/conformity in the PTV, due to the more precise estimations of organ deformations within the PTV region. However, visible disparities of the DVHs are mainly observed for the largest motion (C). As seen in figure 7-7, in general, the dosimetric benefits of deformable 2D tracking, in terms of the reduction of D5-D95, are less than 1% for cases A and B, but close to 6% for case C. There is no obvious difference among cases for relative CN. However, it should be noted that for the studied three liver cases, the fiducial markers were implanted very close to the PTV, and are therefore good surrogates for PTV motion. If the fiducial markers were implanted further away or if the diaphragm was used as motion tracking surrogate, then conventional 2D tracking might not provide such comparable results as deformable 2D tracking.

2) Deformable 3D tracking versus deformable 2D tracking

As shown in figure 7-7(a), for Case C, the D5-D95 in the PTV decreases by 2.3% when 3D tracking is used instead of deformable 2D tracking, and is also associated with a 9.6% improvement in the relative conformity. However, these advantages are not observed for case A, where improvements in either dose homogeneity or relative conformity are less than 1%. For case B (moderate motion), although there is no obvious improvement in PTV dose homogeneity, the relative conformity improves slightly with 3D tracking by about 3%.

3) Deformable 3D tracking: ideal versus realistic

The results for realistic deformable 3D tracking have been previously shown in figure 7-5 and 7-7. In addition, figure 7-8 shows the absolute dose differences between realistic and ideal (based on the ground truth motions) deformable 3D tracking for the worst case (C). For this case, $V_{\text{dosediff}}=5\%$ is 2.7% in the IV, whereas this parameter is less than 0.1% for cases A and B.
IV. Effectiveness of re-tracking

Figure 7-9 shows a comparison of the resultant 4D dose distributions for case C, simulated using re-scanning alone, conventional 2D and deformable 3D tracking alone, and three-times conventional 2D and deformable 3D re-tracking. Figure 7-10 shows the corresponding PTV DVHs, D5-D95 and rCN values for each scenario. These clearly indicate a general improvement when moving from simple re-scanning, through 2D/3D-tracking and on to 2D/3D re-tracking. For example, for case C, D5-D95 decreases to below 13% when 3D re-tracking is applied, in comparison to 21% from pure 3D tracking and thus approaching that of the static plan (9%). In addition, the differences in dose homogeneity between 2D and 3D re-tracking are less than 0.2%. Relative dose conformity for the different scenarios are also shown in figure 7-10, where conformity increases from 85% to 96% using 3x 3D re-tracking, while this value also reach 92% when 3x 2D re-tracking was applied. From the dose homogeneity point of view, 2D and 3D tracking provide comparable results when combined with 3x rescanning, whereas regarding dose conformity, 3D re-tracking results in a slightly smaller irradiation volume due to the compensated density variation, which increased conformity by 3%. This trend is also evident for cases A and B, where D5-D95 values are around 5% higher for 3x re-tracking with respect to pure tracking, and relative conformity increased by nearly 7% for Case A and 6-8% for Case B.

Our simulations also indicate that 3x conventional 2D re-tracking (based on fiducials implanted near the PTV) could provide a better dose homogeneity inside the PTV than pure deformable 3D tracking, particularly for the large motion Case (C), although this can only be achieved at the cost of slightly prolonged treatment duration and decreased conformity values. Nevertheless, 2D re-tracking can still be considered as potentially the most efficient solution to implement in the clinic, since no prior motion information is needed for this approach. On the other hand, 3x 3D re-tracking provides the best results in general, in terms of the lowest D5-D95 values (10.5, 12.8 and 12.8% for cases A, B and C), together with the highest relative dose conformity (97, 95 and 95% of the static plan values for the three cases respectively). Furthermore, although rescanning can also be quite effective (when enough rescans are...
applied), dose conformity is significantly lower than that of any tracking approach. This is particularly true for the small motion Case A, where 6x rescanning provides a D5-D95 similar to that achieved using either 2D or 3D re-tracking, only comprising with 1-2% worse rCN. For the large motion cases, as shown in figure 7-9, significant under dosage for rescanning can be observed at the lateral field edges of the PTV, which could probably be solved by extending the Internal Target Volume for 3D plan. However, this effect can be almost eliminated when online image guided re-tracking is applied. Finally, for case C, figure 7-11 compares the volumes of the dose distributions with differ >=5% from those of the static case as a function of the different motion mitigation methods. V\textsubscript{dosediff>=5%} inside the PTV can reduce from 122 ccm for pure 3D tracking to only 34ccm for 3D re-tracking, whereas the difference in this value between 3D and 2D re-tracking is less than 3ccm. However, this improvement is associated with a slight increased V\textsubscript{dosediff>=5%} outside of the PTV, 27ccm, if compared purely 3D tracking scenarios with respect to the 3x 3D re-tracking.

Figure 7-9. Comparison of 4D dose distributions on example slice using different motion mitigation strategies for the largest motion (Case C).
Figure 7-10. Comparison of 4D plans (0-7) with/without re-tracking by corresponding DVHs in PTV and the extracted D5-D95 and relative CN values.

Figure 7-11. Volumes with dose differences (w.r.t static plan) >5% as a function of motion mitigation for case C (large motion)
V. Impact of potential temporal prediction errors

Up to now, all 4DDC results have been simulated assuming that the tracked fiducial motions can be used to instantaneously correct pencil beam positions with or without energy adaption. In practice however, temporal motion prediction algorithms will always be required in order to be able to predict where the anatomy will be in the near future, to allow for the finite time-lag between the acquisition of the motion surrogate, its analysis and the time to correct the steering components of the pencil beam. Typically, this response time can be a few hundred milliseconds in total, and can lead to additional uncertainties between the true and predicted anatomical position of a millimetre or so (Ernst et al., 2013). In this part of our analysis, we assume that this uncertainty is randomly distributed (1 +/-0.5mm for 300ms latency, see Ernst et al. (2013)), and have therefore added this as a random error to the tracked surrogate motions at each time step, and five 4DDCs were performed to assess the effects of the random error. Figure 7-12 compares the values for dose homogeneity (a) and relative conformity (b) of the 4D plans with and without these uncertainties. For 3D tracking (scenarios 2), the maximal variations (range of each boxplot) due to the presence of temporal prediction errors is within 1.2, 0.8 and 0.6% for D5-D95 and within 1.1, 1.2 and 1.3% for the rCN values for the three cases respectively, and the results without temporal prediction were always within the range of the corresponding results considering temporal prediction. The differences are even smaller than 0.5% for D5-D95 and below 1% for CN, when re-tracking is applied.

4. DISCUSSION

In this chapter, we have used the motions reconstructed from BEV tracked surrogates and the patient specific PCA motion models developed in Chapter 5 to simulate different tracking strategies for pencil beam scanning with protons. Besides considering the inevitable uncertainties resulting from surrogate motion tracking and online deformable motion reconstruction, we have also simulated the potential errors that can result from temporal motion prediction. Compared to our simulations without motion mitigation, dramatic improvements for beam tracking have been shown, in terms of increased dose homogeneity and conformity. However, due to the presence of large tissue deformations and rotations in the liver, even the most comprehensive beam tracking strategy we have investigated (3D), cannot recover the dose homogeneity of the reference static plan, with D5-D95 values being 6-12% higher than the static. Moreover, more than 5% absolute dose differences (between 4D plan and static plan) can be seen in 30-40% of in the IV, of which most occur in the proximal entrance and distal region with respect to the field, while differences are rather limited inside PTV.
Figure 7-12. Evaluation of 4D plans using conventional 2D or deformable 3D tracking/re-tracking with (by boxplots for five 4DDCs) and without (by cyan/green markers) simulated temporal prediction error (1-conventional 2D tracking, 2- deformable 3D tracking, 3-3x conventional 2D re-tracking and 4- 3x deformable 3D re-tracking)

On the other hand, we have shown that the plan quality of the delivered dose distribution under conditions of motion can be improved when more sophisticated tracking methods are employed. The simplest (conventional 2D tracking) directly changes the lateral position of each beam segment according to the surrogate motions tracked via BEV imaging, and thus requires no motion model for its implementation. Deformable 2D tracking extends this approach by using the model-based reconstructed motion to more accurately guide the each pencil beam lateral position adaption, which is able to obtain a more homogenous dose distribution inside the PTV. Deformable 3D tracking takes the most use of the online
reconstructed density field by further adapting each pencil beam’s Bragg Peak according to the predicted WER variation. However, although the superiority of 3D tracking has been demonstrated for all three cases, the improvements are only substantial for the large motion case (C). Since the fiducials were implanted very close to the PTV in these cases, and potential density variations are rather small for the liver in comparison to the lung, the advantage of online deformable motion/density prediction over the conventional 2D motion tracking are less extensive. Nevertheless, if the fiducials were implanted further away or other surrogates were used for online motion tracking (e.g. diaphragm), the benefits of deformable 3D tracking are expected to be more pronounced.

However, it should also be noted that even with 3D tracking, our simulations imply that there may still be problems at the distal edge of the field. This maybe correlates to the high proton fluencies typically applied in this region, which require longer irradiation times and could therefore be more sensitive to inter-irradiation residual motions. Moreover, this study assumed that the BEV online motion monitoring was performed with a frequency of only 2Hz, which is significantly lower than that of typical pencil beam delivery and beam adjustment rate (~200Hz). Thus, the majority of the beam compensations have to be extrapolated. However, this low imaging rate is rather realistic, since it is impossible to obtain fluoroscopy images online with the same frequency as the pencil beam adjustment, and also in order to keep imaging doses to the patient relatively low. Nevertheless, our results demonstrate that, based on realistic liver motions and cases, purely beam tracking alone, at least for a single field and under these tracking conditions, and cannot fully mitigate all motion effects. Beam tracking must thus be combined with additional mitigation methods. In addition, it was also interesting to observe that beam tracking can generate high dose spots in the field proximal entrance due to the relative little moving ribcage in comparisons to the internal tumour motion. For those reasons, we have also investigated the potential effectiveness of what we call re-tracking, the combination of tracking and re-scanning (Water et al., 2009). Our results show that the residual motion effects inside the PTV for 2D tracking can be almost eliminated with 3x re-tracking, even for the largest motions. Compared to the static plan, inside the PTV, both 2D and 3D re-tracking agree to a similar level of ~91% all points being within 5% of the static plan. However, for dose conformity, 3D re-tracking still brings benefits due to a reduced irradiation volume.

In literature, the dosimetric benefits of tumour tracking with particles have been investigated through both simulation (Grözinger et al., 2006, Grözinger et al., 2008) and in simplified experimental set-ups (Bert et al., 2007, Saito et al., 2009, Bert et al., 2010, Luchtenborg et al., 2011, Seregni et al., 2013). For realistic clinical cases, 4D treatment planning for tracking has been explored using 4DCT by (Bert and Rietzel, 2007, Bert et al., 2008). However, as stated in Chapter 2, there are certain limitations to 4DCT, not least the assumption of regular breathing patterns, periods and amplitudes which will likely vary during delivery and over the whole course of a treatment. By using motion extracted from 4DMRI sequences, and generating 4DCT data sets from these motions, we have avoided these limitations, and have
been able to simulate scanned beam tracking under realistic breathing and motion amplitude variations. In particular, instead of determining corresponding compensation offsets from 4DCTs offline and assuming an identical breathing pattern during dose delivery, we took advantage of 4DMRI to better estimate free-breathing motion patterns online, so that the compensation offsets of each beam segment can be achieved specifically at each time step.

Although currently, the temporal motion prediction component of the full tracking framework is still lacking, we have found that tracking is rather robust to random prediction errors of 1±0.5mm, with less than 1.2% and 1.3% deterioration of dose homogeneity and conformity respectively compared to tracking without temporal prediction uncertainties. These can be substantially reduced to less than 0.5% when re-tracking is employed. Nevertheless, these results need to be confirmed by incorporating true motion prediction methods into our treatment simulation. On the other hand, and in common with other chapters in this work, we need to point out that all simulations here have been performed for the worse case of a single field, and we would expect that for multiple-field plans (Knopf et al., 2011), the dose homogeneity in the PTV would always be better than those presented here due to the multiple field smoothing effect.

Last but not the least, subsequent works should be focused on how to best utilise 3D motion information for scanned beam tracking. As discussed above, although organ anatomy can deform, each pencil beam can only be corrected with three degrees of freedom (the two lateral positions and range) and clearly cannot be deformed. As such, the 3D corrections per pencil beam could either be extracted from changes in the position of points immediately in the neighbourhood of the Bragg peak of each pencil beam, or from some averaged offset derived from all points with which the pencil beam interacts. Although here we have simulated the first approach, the second potentially has the advantage of also adapting for changes in all the anatomy through which the pencil beam travels. Investigations into the optimal approach to perform 3D tracking will be the subject of future work in our group.

5. SUMMARY

In this chapter, we have simulated the use of BEV surrogate imaging, together with the motion models developed in chapter 5, to study the potential efficacy of scanned beam tracking. As such, we have investigated three types of beam tracking strategies for liver treatments with different deformable motions, and have evaluated the consequences of residual motion effects as well as the uncertainties in both spatial and temporal motion prediction. Our results have shown that due to the presence of organ deformation, online pencil beam adaption is only able to compensate dose variations at each Bragg peak position, and as such, residual motion effects induced by the motions in the entrance path of the pencil beam cannot be further mitigated. In comparison to conventional 2D tracking, the benefits from deformable 3D tracking have been highlighted, in terms of increased dose homogeneity and conformity, but these improvements are only significant for larger motions. However, by
combining tracking with re-scanning (so-called re-tracking), the robustness of tracking has been shown to be significantly improved, with even conventional 2D tracking providing dose homogeneity in the PTV of almost comparable quality as for a static plan.
Chapter 8

Conclusions and outlooks

Scanned proton therapy with its physical superiority and clinical flexibility, has been demonstrated as one of the most efficient radiotherapy treatment modalities. However currently, scanned proton therapy is mainly restricted to the treatment of static tumours, due to the concerns of interplay effects and density variations that could occur in the presence of organ motion. Therefore, in order to expand the clinical applications of this technique, appropriate motion mitigation strategies need to be determined for each patient specifically. It has been the topic of this PhD work to study, through detailed and realistic simulations, the potential of using the online Beams-Eye-View image guidance as a motion mitigation tool for scanned proton beam treatment.

As a first step, we performed an analysis of the utility of conventional 4DCT data sets as an imaging modality for performing 4D dose calculations (4DDCs) of the scanned proton therapy. In this work, two deformable registration algorithms were used to estimate respiratory motions of three liver patient cases, whose results were compared extensively including the evaluation of dosimetric impacts by motion estimation differences induced by different registration algorithms. Besides assessing the effectiveness of one typical motion management approach, re-scanning, for reducing the interplay effects in clinical cases, the study also revealed certain unavoidable limitations of 4DCTs for such motion estimation. Firstly, as has been previously shown by Boye et al. (2013), 4DCT are essentially ‘single-shot’ motion studies, combining the motions of a few breathing cycles and reducing these into a single representative breath cycle. Given that patient breathing patterns tend to vary over time, it is certainly a major limitation of conventional 4DCT imaging approach. Secondly, we have also shown that motion estimation based on 4DCT is also limited in the liver region due to the lack of image contrast. This has been demonstrated by showing that substantially different 4D dose distributions can be resulted from the same 4DCT data set, depending on the deformable registration algorithm chosen for extracting the dense motion fields which are required by the 4DDC. Based on this initial work, in the rest of this PhD project, we concentrated on using 4DCT(MRI) data sets (as described by Boye et al. (2013)), for both motion estimation and modelling. The advantages of 4DCT(MRI) include a more accurate deformable motion estimation within the liver, which is benefited from the improved soft tissue contrast, and the ability to acquire varied motion data over multiple breathing cycles.

In Chapter 3, we introduced the Beam’s Eye View (BEV) X-ray imaging system of the PSI-Gantry2 and elaborated the geometrical calibration of this system. As such, an extrinsic
2D/3D registration based calibration method has been developed in order to deduce the gantry angle depended correction vectors for spatially exact DRR calculations. Although various complexities of correction strategies (2 degree-of-freedom (DoF) through to 9 DoF) have been analysed, our results have shown that sub-millimetre geometrical accuracy can be achieved by only employing the 3 DoF (translations) imaging detector position corrections, with no substantial benefits being obtained when the more complex corrections were applied. This is mainly due to the unique configuration of the imaging system, where the X-ray tube is nearly 4m away from the detector, minimising the divergence of the system with respect to the iso-centre. However, the developed procedures can be easily adapted and used for the calibration and correction of any other on-board imaging (OBI) systems. Furthermore, derived geometries of the BEV imaging system in this chapter have been then extensively used in subsequent chapters to simulate time-varying online BEV image sequences (DRRs) for patient treatments, to calculate 2D ground truth motion trajectories from 4DCT(MRI) datasets and to derive factors for correcting the magnification effects of tracked surrogate motions.

Chapter 4 then described the first stage of online motion tracking using such fluoroscopic imaging sequences. Two tracking algorithms have been developed for extracting surrogate motion, which were further validated using both real BEV image sequences of a 4D anthropomorphic breathing phantom and simulated Digitally Reconstructed Radiographs (DRRs) calculated from 4DCT(MRI) data sets of real liver patients. Our results have demonstrated that the algorithms are able to track surrogate motions by either following pre-implanted fiducials or the diaphragm with a high accuracy and acceptable success rate. The extracted surrogate motions by these approaches have been utilised in the following three chapters to reconstruct full 3D deformable motion with the help of the statistical liver motion model (Chapter 5), as a surrogate for beam gating treatments (Chapter 6) and finally as surrogate to derive beam compensation offsets for beam tracking treatment (Chapter 7).

In order to online obtain dense motion fields as well as volumetric images for estimating density variations, we have proposed and validated a method in Chapter 5, which allows for reconstructing the 3D deformable motions from the sparse surrogate motion traced by the BEV image sequences with the help of a patient specific motion model pre-built using the Principle Component Analysis (PCA). An excellent agreement between predicted and ground truth motion fields has been achieved, and the accuracy of this dynamic image reconstruction approach has been subsequently validated through 4DDCs of three scanned treatment fields for eleven motion cases. The benefits and effectiveness of deformable motion prediction have been revealed, in comparison to the conventional online motion monitor approach of only following the tracked surrogate transationally. We have also demonstrated that a monoscopic OBI system could be sufficient to perform online image guidance for such treatments.

In the last two chapters (6 and 7), we moved on to investigate the application of BEV based online image guidance for mobile tumour treatment using two motion mitigation techniques, namely beam gating and scanned beam tracking/re-tracking. By incorporating the tracked
surrogate motions into our 4DDC, we took realistic patient geometries and deformable motions into account for evaluating the effectiveness of these motion mitigation solutions. The results show that, although both techniques can considerably reduce the damaging effects of motion, neither of them is sufficient on their own, especially for large motion cases (>10mm). Therefore, in order to further increase the dose homogeneity and conformity but simultaneously maintain (or decrease) the treatment duration and complexity, other two treatment scenarios which combined motion mitigation strategies has also been investigated, namely gating with re-scanning and tracking with re-scanning. We respectively simulated three types of beam tracking approach for three exemplar cases with different deformable motions for studying the dosimetric consequences of the residual motion effects as well as the uncertainties induced by both spatial and temporal motion prediction. Since beam tracking is only able to compensate the dose differences at a certain part of one pencil beam (e.g. at the Bragg peak region in this study), motion effects in the rest parts of the beam (e.g. entrance path) cannot be mitigated completely. Therefore, for clinical cases which consists extensive organ rotation and deformation, it is impossible to restore the static dose distribution by purely using scanned beam tracking. Although our beam tracking comparison study has shown dosimetric benefits of deformable 3D tracking in comparison to the conventional (translation) 2D tracking in general, those advantages are only evident for large motion cases due to the more pronounced target deformation and density variations. However, by appropriately combining tracking with re-scanning (so-called re-tracking), the robustness of beam tracking has been significantly improved, with even 2D re-tracking providing dose homogeneities in the PTV of almost comparable quality as the static plan.

Finally, there are a number of interesting areas of further research that follow-on from the work of this thesis.

- **4D dose reconstruction as a delivery validation tool:**

Based on the PCA based deformable motion reconstruction approach described in Chapter 5 and the developed 4DDC tools for scanned proton therapy, we believe it could be possible to reconstruct the actually delivered dose distribution to the patient on a fraction-by-fraction basis. By synchronizing the time scales of the BEV image acquisition with that of the log-files for individually pencil beam delivery (contain information on the time, energy, position and dose of each beam), we envision to reconstructing the delivered dose distribution under conditions of motions. Such approaches can be considered as an important quality assurance tool for the validation and verification of 4D treatments. From these retrospective calculations and comparisons, the initial treatment plan can be adapted, if necessary, in the following fractions.

- **Beam gating:**

All of the work on gating performed here has been based on simulated BEV image sequences reconstructed from 4DCT(MRI) datasets, or on real BEV sequences of a 4D anthropomorphic
phantom. The next stage of our research will focus on acquiring real BEV images from actual patients as soon as our Gantry 2 is in clinical operation (from November 2013). In addition, we would also like to clinically compare the image guided gating technique (described in this work) with other, non-imaging based gating signals such as pressure belts or optical systems. Furthermore, we would like to investigate the use of adaptive gating windows to deal with possible baseline shifts of the tumour position during treatment delivery, a problem that has not been addressed in this work.

- Beam tracking:

There is still much to do for beam tracking before we could confidently apply such a technique into patient treatment. First, it is essential that algorithms for the temporal prediction of the surrogates’ motion (extracted from our BEV sequences) needs to be implemented. Second, we would like to optimize our beam tracking strategy by better utilizing the online reconstructed dense motion fields. For example, instead of adapting each beam according to the derived compensation offsets of the Bragg Peak position, certain averaged offsets can be calculated from all points with which each pencil beam interacts. However, in order to eventually apply tracking in clinic, it would also be necessary to significantly improve the calculation time for reconstructing density field. We believe that this could only be performed by moving to GPU based implementations. Third, we have to re-state that for this proof-of-concept study, we currently considered each breathing cycle with the same duration in the 4DDCs, and temporarily ignored the potential problem concerning organ drift in the inferior part of liver due to the relative short treatment duration. However, it is no doubt that organ drift can be a crucial uncertainty especially when hypo-fractionation regimes are considered, where the treatment times would increase due to the higher dose levels that need to be delivered per fraction. Nevertheless, since the time scale of organ drift is relatively long, this type of organ motion can be somehow considered as an intermediate status between intra- and inter-fractional motion, more reliable method for solving such problems is to acquire volumetric images from time to time during the treatment and then compared to the reference image which was used for planning. This procedure can be performed by using either the in-room sliding CT or the OBI based cone beam CT (such as the case of PSI-Gantry2), but the in-room or the on-gantry MRI should be the ideal eventual solution especially for tumours sited in the abdomen region. Fourth, we also would like to investigate whether patient specific models are required, or whether a population based model could be used once enough data from enough patients has been acquired. Last but not the least, the clinical implementation of beam tracking still needs to be finalised, including the implementation of on-line pencil beam specific corrections in the control system of our scanning gantries, robust quality assurance tools and tools for the in-vivo validation of such tracked and re-tracked treatments. As such, 4DDCs based on time-resolved treatment log files and BEV guided motion reconstruction (see above) could be of great relevance in the future.
• Extension to other treatment sites:

In this work, we have concentrated on the liver as anatomical site, as liver tumours are the first mobile target that we would like to treat with our new spot scanning gantry at PSI. However, a next step will be assessing many of the same techniques in this thesis for the tumour sited in the lung region. For this, 4D-MRI data sets of volunteers (and eventually patients) need to be acquired in the lung (the first few sets have already been acquired as part of another PhD project), and the validity of the 4DCT(MRI) methods used here need to be tested in this anatomical region. In addition, methods for dealing with large density changes due to motion (an additional problem with proton treatments in the lung region) will have to be assessed.

• Experimental validations:

Finally, apart from the calibration of the BEV system in Chapter 3 and parts of the motion tracking validations in Chapter 4, all the work performed in this thesis has been based on simulations. This has been necessary due to the current challenges of measuring doses in three-dimensions and with high resolution within a patient. As such, 4D dose calculations, combined with accurate estimations of motions in a patient’s anatomy over the duration of treatment, are currently the only way to estimate motion effects, and the effectiveness of mitigation methods, within a patient. Nevertheless, the limitations of such simulations have to be considered, and all the techniques developed and assessed in this work need to be validated experimentally. For this, and in collaboration with another Swiss research centre (CSEM, Landquart), we have developed a comprehensive anthropomorphic 4D phantom, which can be programmed to breath with realistic breathing patterns extracted from our library of 4D-MRI data of volunteers, and has a moving ‘tumour’ insert in which radiation sensitive films can be placed for high resolution, 4D dosimetry. Indeed, this phantom has already been used in this work for validating the fiducial tracking algorithms (Chapter 4). In the future, we wish to use this phantom for detailed and comprehensive experimental validations of the motion mitigation methods developed and assessed in this work.


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