# Required transition from research to clinical application: report on the 4D treatment planning workshops 2014 and 2015

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**Abstract**

Since 2009, a 4D treatment planning workshop has taken place annually, gathering researchers working on the treatment of moving targets, mainly with scanned ion beams. Topics discussed during the workshops range from problems of time resolved imaging, the challenges of motion modelling, the implementation of 4D capabilities for treatment planning, up to different aspects related to 4D dosimetry and treatment verification.

This report gives an overview on topics discussed at the 4D workshops in 2014 and 2015. It summarizes recent findings, developments and challenges in the field and discusses the relevant literature of the recent years. The report is structured in three parts pointing out developments in the context of understanding moving geometries, of treating moving targets and of 4D quality assurance (QA) and 4D dosimetry.

The community represented at the 4D workshops agrees that research in the context of treating moving targets with scanned ion beams faces a crucial phase of clinical translation. In the coming years it will be important to define standards for motion monitoring, to establish 4D treatment planning guidelines and to develop 4D QA tools. These basic requirements for the clinical application of scanned ion beams to moving targets could e.g. be determined by a dedicated ESTRO task group.

Besides reviewing recent research results and pointing out urgent needs when treating moving targets with scanned ion beams, the report also gives an outlook on the upcoming 4D workshop organized at the University Medical Center Groningen (UMCG) in the Netherlands at the end of 2016.

## 1. Introduction

Over the years, the scope of the 4D treatment planning workshop has broadened significantly. Initially focusing on aspects related to the treatment of intra-fractionally moving targets, the 6$^{th}$ and 7$^{th}$ edition of the 4D treatment planning workshop addressed the entire range of motions that can occur, including inter-fractional changes. Motion and geometrical changes on all different time scales were quoted (ms – heartbeat, s – breathing, min – drifts, days – treatment response, weight loss/gain, filling/emptying of cavities) and corresponding treatment planning (TP) approaches were discussed (“plan of the day”, “plan of the beam”, “plan of the segment", “plan of the second”). While in past years mainly scientists and clinicians from particle radiotherapy attended the workshops, the present workshops featured invited speakers and attendees from conventional photon radiotherapy backgrounds as well. Furthermore, researchers from related fields such as biomedical engineering, medical imaging and computer science were represented.

Up to now the treatment of moving targets has been entitled as a “4D problem”. Discussions revealed that as motions on different time scales can happen simultaneously (e.g. a tumour responding to treatment by shrinking is still affected by breathing motion) and thus the problem would be better posed using a higher dimension. The potential knowledge about the actual motion characteristics increases as the imaging options advance. At the same time, progress in the development of new radiotherapy treatment machines increases the possibilities to address the challenges due to motion. However, the treatment of moving targets is an indication-specific,

patient-specific and modality-specific problem and treatment options often span over a large parameter phase space, which reveals the complexity of finding a “simple solution”.

In the 6th edition of the 4D workshop held in 2014, discussing technical aspects of 4D treatment planning and delivery in the context of changing patient geometries, high-light talks were given by Marco Schwarz (Proton therapy Department Trento, Italy) and Martijn Engelsman (HollandPTC, Netherlands), illustrating requests for a proton TP system and a proton radiotherapy facility optimized for the treatment of moving targets. Both talks initiated active discussions in the 2014 workshop and are therefore considered as highlight talks. The poster prize 2014 was awarded to a contribution of Valeriy Vishnevskiy et al. (Computer Vision Laboratory, ETH Zurich) on “Total Variation Regularization of Displacements in Parametric Image Registration” [Vishnevskiy 2014]. Slides of the talks and abstracts of all posters can be found at the 2014 4D workshop webpage (http://4d-treatment-planning-workshop-2014.cs.ucl.ac.uk/index.html).

A high-light talk of the 7th edition of the 4D workshop held in 2015 was given by Francesca Albertini (PSI, Switzerland) emphasizing the need of further developments in commercially available TP planning software in order to treat moving targets with particle beams. Two other keynotes were presented by Daniel Low (UCLA, USA) and Guntram Pausch (OncoRay, Germany) on relating external and internal motion and the advantages of prospective 4D-CT reconstruction and prompt-gamma based in vivo dosimetry and its extension to 4D capability, respectively. The poster prize 2015 was awarded to a contribution of Maxim Makhinya et al. (Computer Vision Laboratory, ETH Zurich) on “Real-time Tracking of Liver Landmarks in 2D Ultrasound Sequences” [Makhinya 2015]. Slides of the talks of the 2015 workshop, the award winning poster and abstracts of all other posters can be found at http://www.oncoray.de/announcements/4d-treatment-planning-workshop-2015/.

This report focuses on novelties and necessities discussed at the last two 4D workshops in regards to the treatment of moving targets mainly considering particle therapy, however also keeping an eye on the developments in conventional photon radiotherapy. Section 2 presents the current status on imaging, modelling, and predicting motion. In section 3, key points for an “ideal” proton facility and an “ideal” planning system in regards to the treatment of moving targets are given. In this context, the need for a 4D error simulation platform is discussed. Section 4 gives an overview on 4D QA and 4D dosimetry and sketches future developments and needs. Finally, section 5 gives a summary and an outlook on the next 4D workshop to be held at the end of 2016.

## 2. Understanding moving patient geometries

### 2.1 Imaging motion

Imaging is crucial when treating moving targets [Bert 2011, Korreman 2012]. For an ideal consideration of motion, the patient geometry (target volume and organs at risk) should be monitored prior to and during treatment delivery. As the last workshop report discussed [Knopf 2014], motion monitoring capabilities during radiotherapy are more advanced in photon therapy than in particle therapy. However, image guidance in proton therapy is slowly beginning to catch up with conventional therapy. In-room imaging in form of in-room CT and CBCT is becoming available [Veiga 2016]. Cone-beam CT based proton dose calculations have been investigated [Veiga 2015b,

Kurz 2015] and the utilization of 4D-CBCT data for dose calculation has been proposed [Cai 2015]. As more in room image guidance options become available for particle therapy in the coming years there will be a greater opportunity to exploit the dosimetric advantages particle therapy has to offer.

For motion evaluation prior to treatment 4DCT imaging is still standard. Recently it has been shown that prospective 4D CT reconstruction is superior to retrospective reconstruction resulting in less artefacts. Dou et al. have proposed a promising implementation that was recently applied clinically [Dou 2015]. In order to capture motion variations and drift effects the value of 4DMR has been pointed out [von Siebenthal 2007, Boye 2013]. During the recent workshops motion monitoring possibilities during treatment delivery without the use of ionizing radiation were discussed. A specific focus was given to the use of ultrasound (US) and magnetic resonance (MR) imaging to help optimizing radiotherapy of moving and deforming targets. Talks during the workshop 2014 featuring these topics were highlighted in a medicalphysicsweb article [medicalphysicsweb 15 December 2015].

In recent years, there has been a trend towards MRI guided radiotherapy. MR offers exquisite soft-tissue contrast and is highly versatile, capable of imaging a wide variety of structures. The ability to visualize lymph nodes, for example, enables the use of stereotactic boost to individual nodes. In the context of moving targets, MRI offers the ability to perform 4D imaging, implemented as a repeated acquisition of 3D image volumes. Currently achieved temporal resolutions are in the order of 2 s to 3 s. Further development is needed to obtain real time 4D data acquisition. However, there has been recent progress on retrospectively reconstructing 4D-MRI datasets from multi-slice acquisitions [Paganelli 2015] and MRI-based 4D-CT generation [Bernatowicz 2016]. It is also believed that online MRI can provide a feedback loop to enable gating and beam tracking in clinical routine [Glitzner 2015, Stam 2013], and there have been initial studies on the effect of the magnetic field on particle beams [Oborn 2015, Hartman 2015], and motion prediction from orthogonal cine MRI [Seregni 2016].

Another approach for non-ionizing, non-invasive imaging of soft-tissue motion is to use US guidance [Fontanarosa 2015, Western 2015]. US offers many advantages over existing approaches for radiotherapy motion management, including superior soft-tissue contrast compared to X-ray imaging, no dose, no need for fiducial markers, high temporal resolution, low cost and theoretical compatibility with particle therapy [e.g. Schwaab 2014]. US imaging in 3D is possible, enabling 4D monitoring of target positions prior to- and/or during treatment. This method is currently being developed into a clinical product (Clarity Autoscan (Elekta Ltd.)) for transperineal prostate motion monitoring [Lachaine 2013]. For other sites there are, however, a number of challenges to consider. Firstly, US waves do not propagate easily through interfaces with high density differences; so direct monitoring of anatomy obstructed by ribs and lungs is challenging [Xu 2006]. The useful maximum depth for accurate US motion estimation is approximately 20 - 30 cm. In addition, the placement of the US probe without impacting the treatment delivery for abdominal sites remains a challenge [Zhong et al 2013]. Also, although US imaging is fast, the delays in the image acquisition/capture and processing pipeline still introduce a lag, e.g., of down to 20-50ms in 2D for current state-of-the-art [Makhinya 2015], often with a trade-off between accuracy and speed. Most current 3D US transducers include a motorized linear or curvilinear array which is swept through a defined acquisition angle to acquire a 3D volume (i.e. a stack of 2D frames). With a swept array approach, acquisition is limited by the motor sweep precision and speed [Harris 2011]. Newer technology,

developed for echocardiology, which uses a 2D matrix array transducer can create one to two thousand volumes per second [Byram 2010]. However, this newer technology is not yet commonly applied within radiotherapy [Bell 2012]. Sub-millimetre motion estimation accuracy has been demonstrated for the prostate [O'Shea 2014] and liver [Harris et al 2010]. A number of interesting approaches for liver feature (blood vessel) tracking have recently been contrasted [De Luca 2015]. Several groups are also currently investigating the full potential of US imaging for setup, gating and beam tracking applications [Bell 2014, Schlosser 2010, Schwaab 2014], including the use of US to track high frequency cardiac motion during (atrial fibrillation ablative) radio-surgery [Bruder 2014].

### 2.2 Modelling motion

#### 2.2.1 Deformable Image Registration (DIR)

Deformable Image Registration (DIR) has become an invaluable tool for 4D TP as highlighted by many poster contributions, including the prize-winning poster at the 2014 workshop. DIR has many potential applications in planning, guiding and assessing RT treatments [Brock 2006, Rietzel 2005, Veiga 2014]. Although it is a powerful tool when used correctly, there was agreement between the speakers and participants of the workshops that care needs to be taken to ensure that it is used and interpreted appropriately. A warning was given not to have overconfidence in registration results, particularly from commercial systems where the inner-working and nuances of the algorithm may not be known.

Understanding the limitations of DIR in relation to its different application is key for its correct use. Some applications require 'descriptive' results, i.e. they must look good, but do not necessarily have to be anatomically correct. For example, when propagating structure delineations from one scan to another [Wang 2008] it is important that the structure boundary is aligned correctly, but it does not matter if the transformation is incorrect inside or outside the structure. For other applications the results must be 'quantitative', i.e. they must be anatomically correct even inside homogenous structures. For example, when warping doses in order to perform dose accumulation [Zhang 2012, Veiga 2015a] any inaccuracies in the transformation will lead to errors in the accumulated dose. Achieving reliable results as well as defining appropriate ground truth data is challenging, and in general is still an unsolved problem and the focus of on-going research. Furthermore it is important that the applied DIR is able to cope with the type of anatomical changes to be expected (e.g. shrinkage of volumes vs. preservation of volumes). Most commonly used registration algorithms assume a smooth continuous transformation, which cannot correctly model sliding between organs or tissue that is present in one scan but not the other e.g. due to tumour growth/regression or weight loss.

It is essential that registration results are validated for each clinical application so that the results can be used with confidence and any uncertainties in the results can be incorporated into the TP process. Offline validation experiments should be performed to estimate the uncertainty in the registration results. These involve estimating the ground truth motion and deformation that has occurred, e.g. by manually locating landmark points [Castillo 2009] and structure boundaries [Veiga 2014] in the images being registered, and comparing these to the motion recovered by the registration. This can be a time consuming and labour intensive process (e.g. it has been shown that to get a good estimate of the registration error in the lungs several hundred well distributed landmarks should be used [Castillo 2009]), which is subject to intra- and inter-observer errors, and is

not possible in homogenous regions of the images. Another approach is to use software or hardware phantoms [Kashani 2008], where the ground truth motion is known or can be accurately measured, but there will always be a question regarding how realistic the phantoms are and how relevant the results are to real clinical data (see also Chapter 4). In addition to offline validation studies, some form of online verification (e.g. visual inspection) should be performed for every registration result, as there is always the possibility of the registration performing significantly worse than in the validation studies. Therefore automatic consistency checks of registration results are highly desirable for application in clinical practice. Although first ideas in this direction have been proposed, this topic seems to be under-investigated so far.

### 2.2.2 Surrogate based correspondence models

During the workshops correspondence models were discussed which relate the internal motion of interest (i.e. of the tumour and OARs) to one or more respiratory surrogate signals, such as the motion of the skin surface, which can be accurately measured during image acquisition and treatment delivery [McClelland 2013]. Such models have a wide range of potential applications in RT, including accounting for motion during image acquisition [Rit 2009], when planning RT [Werner 2012], and when guiding RT delivery [Schweikard 2000], but to date have only seen limited clinical use. Their main clinical use has been in guiding RT delivery where they are used in two commercial systems: the Cyberknife (Accuray) and the Vero SBRT system (Brainlab). An important point about these systems is that they usually model the motion of only a small number of implanted markers. The motion of the implanted markers can be easily determined using stereo x-ray images [Zhang 2013]. This can be used to check the accuracy of the models during treatment, and to update or rebuild the models if required.

There has been much research into correspondence models that can model the motion of an entire region of interest rather than just a few specific points [McClelland 2013]. In this case the motion is usually determined by applying DIR to a 4D dataset, and then fitting the correspondence model relating the registration results to the surrogate signal(s). As such, the afore-mentioned issues in the context of DIR also apply to correspondence modelling and translate into model errors, respectively. In addition one of the main problems with fitting correspondence models to DIR results is acquiring appropriate 4D data. Most currently available 4D imaging methods cannot acquire data over the entire region of interest fast enough to ‘freeze’ the respiratory motion. Instead they acquire data over several breath cycles, and then sort the data into coherent volumes after the acquisition [von Siebenthal 2007, Hugo 2012]. In essence this assumes a particular correspondence model during the image formation (although the model is usually not explicitly calculated), and therefore it is at least questionable to fit other correspondence models to the 4D dataset. One potential solution to this is to use several fast helical CT acquisitions and record the surrogate signal value for each individual slice [Thomas 2015]. Another potential solution is to combine the correspondence model fitting and DIR into a single optimisation [McClelland 2014], which allows the model to be fitted directly to the unsorted ‘raw’ or ‘partial’ data before it is sorted into coherent volumes.

Other topics discussed at the workshops in the context of surrogate based correspondence models included:

- the use of multi-dimensional surrogate data (e.g. 3D skin surfaces) and appropriate fitting methods such as ridge regression, principal component regression, partial least squares, and canonical correlation analysis [Wilms 2014]

- population based models that can be used to estimate the motion for a new subject without needing to image the motion for that subject [He 2010, Preiswerk 2014]

- the wish for a publically available repository of image, surrogate, and validation data that can be used to objectively assess and compare different models (such as is available for DIR at www.dir-lab.com [ Castillo 2009])

- how different sources of error (e.g. surrogate measurement errors, DIR errors) impact the accuracy of the models, how these translate into dose errors, how they can be accounted for when planning and delivering treatment, and what magnitude of errors would be considered clinically acceptable?

**2.3 Predicting motion**

The estimation or forward-prediction of patient anatomy is an important link in the chain of adaptive radiotherapy. Prediction of patient motion can compensate for inherent system latencies, i.e. the lag time between the request of an action and its complete execution. Typical latencies are caused by the image acquisition time, the image-processing time, computing times and the multi-leaf collimator (MLC) travel time among others. Total system latency can add up to anything between tens to hundreds of milliseconds.

A large variety of motion predictors have been studied in the literature: Kalman filters, kernel density estimation, linear regression, Markov models, neural networks and support vector regression to name only a few [Sharp 2004, Krauss 2011, Ernst 2013]. Prediction is mostly limited to the target without considering deformations or the organ-at-risks, which might move differently. Prediction success is usually measured in terms of residual geometric misalignment (error) with the true target motion. Almost all predictors depend on multiple parameters and the optimisation of these parameters is based on a large training sample of previously acquired patient data. Irregular motion presents the biggest challenge to motion prediction. Some models are tuned in a "training phase" just before treatment or even constantly re-tuned according to the current patient motion. This is especially useful for systematic motion events such as baseline shifts.

It is important to keep in mind that these models are inherently mathematical and not physiological which presents a limitation. At the workshop, it was discussed that the development of more and more mathematically advanced motion predictors may have reached the point of diminishing return, and that a better physiological understanding of patient motion would be needed to advance the field further.

**3. Treatment of moving targets with proton beams**

For several years, moving targets have been treated with conventional radiotherapy and with passively scattered particle therapy. Recently, particle centres equipped with scanning started

treating moving tumours. At the MD Anderson cancer centre in Houston and at Scripps proton therapy centre in San Diego a subset of lung patients are treated with active scanning [Chang 2010, Hui 2011, Kadar 2014, Li 2014, Liu 2014]. The same holds true for the University of Pennsylvania in Philadelphia. The proton radiotherapy group in Sapporo will soon start online x-ray image guided scanned proton treatment [Shimizu 2014]. Researchers at Heidelberg Ion-Beam therapy centre (HIT) have treated liver patients with scanned carbon beams [Habermehl 2013] and the group at National Institute of Radiological Sciences (NIRS) started gated scanned treatment for lung and liver [Takahashi 2014, Mori 2014, Mori 2016]. These are only a few examples for the rapid clinical development towards scanned particle treatments for moving targets. Many new proton facilities are solely equipped with scanning and thus will have to use pencil beam scanning SFUD or IMPT plans for static as well as moving indications. Participants of the 4D workshops 2014 and 2015 raised concerns about this potentially rash development.

Scanning comes with the choice of a lot of parameters, whose tuning significantly influences the treatment quality, especially for moving targets. An optimal parameter combination is indication- and patient-specific and to date, there exist no clear guidelines for an optimal parameter choice. The following list of acute needs was compiled by the participants of the 4D workshops, which in their view are essential for a comprehensive and safe clinical implementation of scanned particle treatment for moving targets:

- standards for initial end-to end test for moving targets
- clinical guidelines as to which motion mitigation approach should be used in which situation and what are acceptable uncertainties
- guidelines for internal target volume (ITV) and margin construction
- robust measures to evaluate motion effects (DVHs are not sufficient)
- standards for motion monitoring during treatment delivery
- standards for QA procedures for moving targets
- feasibility of daily retrospective 4D dose reconstruction

Focus topics during the workshops 2014 and 2015 were optimal facility characteristics and features missing in commercially available TP systems for the treatment of moving targets. Especially, gaps between the research world and the clinical reality were alluded. The majority of the 4D workshop audience agreed that for the next years a focus should be on developments, and efforts should be made to bring research outcomes into clinical routine.

### 3.1 The “perfect” proton facility for treating moving targets

Moving tumours have been treated with mainly double-scattered proton / particle beams utilizing gated delivery since several years with promising outcome and low toxicity (Oshiro 2014, Nguyen 2015, Berman 2015). Although most of these patients were treated with double scattered beams and only a fistful of particle centres have the experience of actually treating moving targets, active beam delivery seems to be the preferred option for lung cancer treatment in the future for the majority of particle centres, as revealed by a survey. Likewise, vendors and customers share this view [De Ruysscher 2015].

A state-of-the-art or “perfect” proton facility should be capable to deliver an optimal, secure and effective treatment to patients with various, but probably not all, tumour entities, including mobile

indications. Speakers at the workshop claimed that pencil-beam scanning in combination with motion mitigation techniques like gating, breath hold and rescanning should be capable to address under realistic circumstances approximately 80% of these cases. According to the workshop participants, beam tracking approaches are seen as rather hypothetical and are unlikely to be implemented clinically anytime soon. Essential for a modern proton facility is the availability of gantries in a multiple rooms (2-3) setup with continuous beam-sharing between all rooms. Especially to address moving targets, a scanning system with layer switching times in the order of 0.5 to 1.5 seconds and lag-times (reaction time) below 0.3 s or even lower for large amplitudes [Prall 2014] should be realized.

Important for the handling of moving targets are appropriate imaging capabilities. Orthogonal x-ray imaging systems, as implemented for the majority of photon treatment facilities, were pointed out to be insufficient in the context of treating moving targets with protons as they do not provide accurate enough 3D information. Cone-beam or diagnostic CT would be desired instead, preferably to enable in-room imaging at the iso-centre. For dose validation, online dose recalculation should be enabled with additional techniques in place to assess the effectiveness of dose degradation management techniques [da Silva 2015a, da Silva 2015b]. Options currently discussed for range verification are prompt gamma or in-vivo PET measurements.. In order to evaluate the wide parameter phase space in the context of the treatment of mobile targets with scanned particles, it was suggested to develop a community-supported freeware platform to perform comprehensive 4D error simulations (see also summary of discussed topics in section 2.2).

To realize a state-of-the-art or “perfect” proton facility it was pointed out that a close collaboration between research, development and the clinic is essential. In the recent years a gap between research and development has been established. Current research often focuses on limited parts of a problem and rarely provides comprehensive, technologically mature solutions. While new exciting findings get published and praised, the development until implementation of new findings often remains unrewarded and undone. Furthermore, tight clinical schedules, financial pressures and the reluctance to move on to new protocols hinder developments. To overcome these struggles, participants of the workshop agreed that clinical, academic and commercial organisations have to work closely together. A competition in terms of the applied clinical treatment quality should be prevalent and should predominate publication contents.

### 3.2 The “perfect” planning software for treating moving targets

Different TP strategies for mobile targets have been investigated in the last years, including beam-specific target volumes [Knopf 2013, Lin 2015], optimized spot scanning patterns [Brevet 2015, Li 2015b, Liu 2015], and various motion mitigation techniques [Schätti 2014a, Schätti 2014b, Dueck 2015, Gassberger 2015, Zhang 2015]. The clinical implementation of developed algorithms into certified TP systems, however, still lags behind. Available are quasi-static approaches that calculate dose on different phases of a 4DCT, on an average CT or based on a maximum intensity projection CT. For a realistic evaluation of motion effects it is essential to consider the geometrical changes in the patient (and the timeline of the delivery in the case of scanned proton therapy) in a dynamic way. To do so reliable dose accumulation algorithms are needed based on standardized DIR algorithms [Zhang 2012].

Features that are desired for the treatment of moving targets with particle beams are:

- DVH uncertainty bands: Simulations have shown that small changes in the initial conditions can have a significant impact on 4D dose distributions. Therefore it is recommended to compute 4D dose distributions for a meaningful set of initial conditions and present dose distributions with error bars. DVH uncertainty bands have been proposed long time ago [Goitein 1985] and their importance has been highlighted in recent publications [Trofimov 2012, Hild 2013]. However they are still not available in commercial TP systems.

- Dedicated margin recipes: ITV definitions used in photon radiotherapy are insufficient as pointed out in the past [Rietzel 2010, Graeff 2012]. Due to particle specific range uncertainties, beam-specific margin concepts have been suggested [Knopf 2013, Lin 2015], but have not been implemented clinically to assist target volume definition during TP.

- 4D optimization: Several approaches have been studied over the years. Eley et al. investigated the possibilities of 4D optimization in beam tracking with a scanned carbon beam [Eley 2012]. Graeff et al. developed a more general framework for 4D optimization based on subdividing the target volume to ease the technical demands in the optimization [Graeff 2013]. Worst case robust optimization for lung cancer has recently been shown to result in treatment plans not only robust against setup and range error but also improving insensitivity against anatomy changes throughout therapy [Li 2015a]. However, 4D optimization approaches only start to get incorporated in commercial TP systems.

In the context of moving targets, an essential requirement for TP systems is efficiency and computational speed. To efficiently cope with the increased amount of medical images in the context of moving targets, contouring procedures have to be automated and contour propagation has to become more robust. This again demands reliable and standardized DIR algorithms. A 4D TP system should be capable to adapt the dose on a daily basis without causing delays in the general treatment workflow. Preferably, this would include the capability to perform online re-planning in order to instantaneously react to a changing patient geometry [Hild 2016].

While most TP systems rely on analytical beam models, Monte Carlo dose calculation methods might improve the exactness of the resulting dose distributions [Paganetti 2012]. Generally, MC calculations come at the expense of increased calculation time which needs to be countered by the use of modern computer architecture [Jia 2012, Souris 2014]. However, Monte-Carlo computation time does not have to scale with the number of CT phases in a 4D CT, and might therefore become beneficial for 4D robust TP in the future.

During the workshops, representatives of commercial vendors of TP systems were faced with the various demands by the research community, emphasizing the need of further development.

**4. 4D QA and 4D dosimetry**

A recurrent topic of discussion at the 4D workshops is the question of what is available and what is still needed in terms of 4D QA and 4D dosimetry. Motion management techniques such as ITV concepts, gating, beam tracking and rescanning require validation. Independent dose recalculations that allows for 4D dose reconstructions have been proposed for 4D plan QA. Meier et al. showed that QA based on independently reconstructed dose distributions is favorable to pencil beam by

pencil beam comparisons for the detection of delivery uncertainties and the estimation of their effects [Meier 2015].

In vivo dosimetry is of immanent importance, especially in particle therapy. There is a noticeable interest of vendors to participate and collaborate actively in the integration of at least 3D particle therapy dosimetry in terms of hardware development e.g. for prompt gamma measurements and algorithmic implementations like the prediction of treatment plan specific PET distributions in a commercial TPS. This was one of the reasons why it was selected as special focus for the 2015s edition of the workshop. Among the studies that have been performed, mostly 4D-PET has been investigated, taking into account patient motion during the post-treatment acquisition. In-beam PET is still challenging for clinical applications due to the high signal rate and limited time resolution of the detectors [Sportelli 2014]. In this context, the measurement of prompt gammas and charged secondary particles emitted along the beam path during the irradiation of a single spot is a promising on-line monitoring technique. Currently, prompt gamma based methods are of great research interest using either the spectroscopic, spatial or temporal distribution of the prompt gammas [Verburg 2014, Hueso-González 2015]. This topic gained a big momentum over the last years. In particular, at the beginning of 2007, a single publication existed about prompt gamma imaging [Min 2006]. Now prompt-gammas are commonly recognized as one of the most promising methods for in-vivo range verification in particle therapy. Dose/range monitoring based on the detection of charged secondary particles is a further promising approach. The evidence of the correlation between the position of the Bragg peak in tissues and the emission shape of charged secondary particles produced in the patient has been already demonstrated [Piersanti 2014] and a detector, which is feasible to obtain this information on-line is currently under construction [Marafini 2015].

First in man application of prompt gamma monitoring technique has been demonstrated recently [Richter 2016]. As gammas are promptly emitted and the currently used detectors offer a sufficient timing resolution, an extension to 4D prompt gamma techniques is feasible and should be further investigated. Once the 4D information from in vivo imaging methods will be available, it could be processed and used not only for range or dose distribution monitoring but also for calculation/reconstruction of the 3D dose deposition for each individual pencil beam spot or possibly considered as a motion surrogate. For these reasons, time resolved range monitoring techniques, which are still in an early research and development stage, could become part of the 4D problematics in the future and face similar challenges of 4D treatments in the translation to clinical routine.

4D dosimetry is often performed in physical phantoms. These should mimic the geometry of a typical patient, both in physical properties such as density and stopping power, as well as the physical dimensions and anatomy. Compared to static phantoms geometries, phantoms developed for validating treatments in moving geometries face a much higher complexity. A moving phantom requires, in addition to afore-mentioned criteria, a realistic tumor motion and relative motion of the target with respect to modeled bony anatomy. Some ingenious and complex phantoms have been manufactured and reported in the literature, reproducing the dynamics commonly present in the irradiation of abdominal or thoracic tumours. Phantoms produced by Kashani et al. [Kashani 2007], Vinogradskiy et al. [Vinogradsky 2009], Serban et al. [Serban 2008] and Perrin et al. [Perrin 2014] included a deformable lung, even more closely mirroring realistic patient anatomy. Others have

attempted to use ex-vivo organs [Markel 2015], one of which was reported at the 4D workshop itself [Mann 2015].

For dosimetry purposes it is also essential that the phantom contains compartments or inserts that can accommodate dosimetric devices, for the tumor target. Ideally the dosimeters would have a high spatial resolution, have an online read-out, be water-equivalent and have little or no energy dependence. These criteria are extremely difficult to fulfill in one device. Steidl et al. [Steidl 2012] have reported a promising approach, building a detector head from pinpoint chambers for online absolute dose measurements, and with channels for inserting film, for high spatial resolution measurements, albeit with an arduous offline read-out. Another promising approach from Court et al. [Court 2010] employed MOSFET detectors within a 3D printed tumour, inserted into a anthropomorphic thorax phantom. High spatial resolution detectors with an online readout, suitable for insertion into internal cavities of anthropomorphic phantoms, should be the focus of ongoing research in order to move away from time-consuming and error-prone film dosimetry.

The extension of the dosimetric capabilities to include implantable dosimeters in models of critical normal tissues found in the thorax, such as the lung, heart and esophagus, would increase the power of deformable phantoms to verify candidate treatment plans with different motion management techniques. For example, in proton therapy, planning concepts have been reported in which density override is employed in the ITV [Chang 2014]. The target will be covered at all phases of the respiratory cycle, while there will be significant overshoot of the proton pencil beams in phases when the beam does not meet the tumor along its path. This extra lung dose, not “seen” in the dose distribution performed on 3D CT, should be taken into account. Commercially available dynamic rigid phantoms, such as the CIRS dynamic thorax phantom[1] allow for this, but deformable phantoms should also be developed to fulfill this need.

Dynamic anthropomorphic phantoms can also be used to validate 4D dose calculation techniques. An important step in this type of calculation is to sum up doses in a reference image, and increasingly DIR algorithms are being applied for this step. However, the accuracy of a given DIR is precarious and needs to be benchmarked (see also section 2.1). Phantoms containing a high degree of detail can serve as a ground truth for benchmarking [Kashani 2007, Serban 2008]. Inserted features distributed over the deformable structure were necessary to provide the DIR with enough detail to achieve an accurate registration.

During the workshops it was discussed that for anthropomorphic phantoms there is an inherent trade-off between anthropomorphic behavior, on the one hand, and dosimetric precision and reproducibility on the other. As a case in point, compare the dynamic, anthropomorphic phantom, LuCa, developed at the Paul Scherrer Institute [Perrin 2014], with the thorax phantom, PULMONE, developed at the Institute of Cancer Research [Nioutsikou 2006]. The former, LuCa, is constructed of an inflatable lung within a deformable rib cage frame; the tumor moves passively with inflation and deflation of the lung. The latter, PULMONE, is a solid, water-filled shell with cavities containing sponge-filled accordion-style bottles. Its tumor is coupled to a motion platform, and is moved by stepper motors. LuCa has a 3D nonisotropic lung deformation mimicking the physiological mode of breathing. In both phantoms the motion type is freely programmable, inputted as a list of control points in an ASCII file. However in the LuCa phantom the motion type depends on the day-to-day

[1]Computerized Imaging Reference Systems, Inc. Norfolk, Virginia 23513, USA.

elastic properties of the lung upon inflation and deflation, causing limited reproducibility. PULMONE, on the other hand, can produce precise and reproducible motion patterns. However, due to the fact that there are two main deformable components in LuCa the rib cage and the lung, it produces more realistic conditions for dose verification. Thus, there is a trade-off between precision, reproducibility and anthropomorphic behavior.

In summary, combining the requirements for a dosimetry and imaging in one phantom has proved to be challenging due to conflicting requirements: reproducibility and high precision dosimetry. During the workshops, it was concluded that promising phantoms have been developed and with further work could be improved by employing detectors with online measurements and including more dosimetric points in normal tissue structures.

**5. Conclusion and Outlook**

This report has summarised the different topics discussed during the 4D workshops 2014 and 2015 and the opinions of speakers and participants expressed at these workshops. Options for imaging motion for particle therapy are now starting to catch up with what is available in photon therapy. The uses, and the limitations, of deformable image registration are starting to become better understood. There has been promising research on the use of surrogate driven motion models, though currently they are still the focus of on-going research rather than clinical translation. The workshop participants agreed that the growing number of proton therapy facilities equipped with scanning beam requires a rapid clinical development to enable the treatment of moving targets. Proton gantries offering high beam rates and a quick beam energy switch could be optimal to treat moving organs. The workshop participants agreed that the incorporation of in-room CT and motion monitoring devices should be aimed for. In terms of an ideal TPS, high computational speed, allowing for daily dose adaptation and on-line re-planning, as well as prospective and/or retrospective analysis of different motion mitigation approaches is desired. 4D dose distributions and DVHs should display uncertainties resulting from different motion scenarios and/or different motion mitigation procedure. Furthermore, a recurring topic of the 4D workshops are dedicated anthropomorphic phantoms to perform 4D treatment plan verification. Different models are being adapted or developed to reproduce a realistically moving anatomy, guaranteeing high dosimetric precision and reproducibility of the results.

Talks and poster presentations at the last two 4D workshop  mainly covered a wide range of issues related to characterizing motion (motion imaging, modelling and predicting) and related to the application of time resolved therapy mainly with protons (treatment planning, delivery and verification). In 2014, a special focus of the workshop was on image guided (ion beam) therapy and on motion modelling. At the workshop 2015 workshop, 4D treatment planning using commercial systems, Monte Carlo approaches and robust optimization, and the capabilities of online dose verification for moving targets were discussed as special topics.

The participants of the 4D workshops are convinced that, while there is still much research to be done, more efforts are now required to translate the promising outputs from recent research into clinical application. The formation of an ESTRO workgroup on particle therapy that will also cover 4D aspects will support this direction and focus the needs of clinical practice and communicate them to

the industry, as does the 4D workshop. Along this line the next 4D workshop will take place at the end of 2016 at the University Medical Centre Groningen (UMCG) in the Netherlands. Recently the construction of UMC Groningen Proton Therapy Centre (GPTC) started on the site of the UMCG. The GPTC will consist of a cyclotron and two treatment units with 360˚ gantries, which are dedicated for pencil beam scanning and equipped for image-guided and adaptive proton therapy. GPTC will be one of the centres implementing new 4D treatment concepts in the coming years and thus, Groningen is an ideal venue for the next 4D workshop. If you are interested in receiving details of the next workshop please write an email to 4Dworkshop.aknopf@gmail.com.While the community represented by the 4D workshop is keen on reaching out to the conventional radiotherapy world, a return to the roots of the first workshop focusing mainly on particle therapy is foreseen A small number of representatives of commercial vendors will be allowed to take part at the workshop to accelerate the impact of findings into clinical routine.

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