The IMRT information process—mastering the degrees of freedom in external beam therapy

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REVIEW

The IMRT information process—mastering the degrees of freedom in external beam therapy

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Abstract
The techniques and procedures for intensity-modulated radiation therapy (IMRT) are reviewed in the context of the information process central to treatment planning and delivery of IMRT. A presentation is given of the evolution of the information based radiotherapy workflow and dose delivery techniques, as well as the volume and planning concepts for relating the dose information to image based patient representations. The formulation of the dose shaping process as an optimization problem is described. The different steps in the calculation flow for determination of machine parameters for dose delivery are described starting from the formulation of optimization objectives over dose calculation to optimization procedures. Finally, the main elements of the quality assurance procedure necessary for implementing IMRT clinically are reviewed.

Contents

1. Introduction  382
2. Evolution of the information driven radiotherapy workflow  382
  2.1. From simulators to treatment planning computers  382
  2.2. Algorithm development  383
3. Treatment delivery techniques  384
  3.1. Tomotherapy  384
  3.2. Cone beam IMRT  385
  3.3. Other IMRT techniques  385
  3.4. Positioning and compensation for organ motion  386
1. Introduction

A long-standing key issue for development of radiotherapy technology has been to provide means to concentrate the radiation dose to the tumour while sparing dose burdens to normal tissues. IMRT, or intensity-modulated radiation therapy, is the result of a long evolution where several technological achievements combine to take this final step in providing dose distributions, now about to approach the physical limits for photon beam dose delivery. The evolutionary aspect is illustrated by the fact that no one is actually credited with coining the term ‘IMRT’. The acronym is now well established, although it has come to carry the incorrect physical term ‘intensity’ instead of ‘fluence’.

The IMRT planning and delivery technique offers many degrees of freedom to shape dose distributions for photon beam irradiation. These possibilities now give incentives to improve the control over other parts of the radiotherapy process, from tumour characterization over image based localization to more detailed treatment reporting and patient follow-up. At all stages, relevant computer based representations of the patient make information technology a central aspect for inventions and improvements of the radiotherapy process.

IMRT has had its historical forerunners, and has been reviewed several times from different aspects. The present review sets its perspective from a treatment planning point of view, with an emphasis on the concepts used to formulate and process the information driven radiotherapy workflow governing IMRT. With respect to IMRT in general, there is now a large set of publications that have followed the pioneering works in the 1980s and early 1990s. There are several in depth reviews; see, e.g., Webb (2003, 2004) for a physics background, Galvin et al (2004) for a clinical process guideline, or Guerrero Urbano and Nutting (2004a, 2004b) for a summary of published data of clinical results. A historical review has been included in Purdy et al (2001).

2. Evolution of the information driven radiotherapy workflow

2.1. From simulators to treatment planning computers

The clinical introduction of ‘high energy’ photon radiation from isotope (i.e. $^{60}$Co) machines and bremsstrahlung from betatrons and linear accelerators in the 1950s led to radiotherapy...
workflows where most of the parameters for treatment delivery were determined by means of a radiotherapy simulator. With these one could take x-ray projective images of the patient to check beam angles, their (rectangular) field size and blocking to spare critical organs by means of bone landmarks. The homogeneity of the dose distribution was tuned by use of treatment planning systems providing dose calculations in a two-dimensional (2D) cross section of the patient. In these systems the patient individual shape was typically represented by manually drawn contours, supported by direct measurements with flexible lead rulers, or similar devices. The clinical availability of CT images in the early 1980s provided a high-tech replacement of the rulers and greatly improved the anatomy information. The vision of what later was to be known as three-dimensional (3D) conformal radiotherapy (3D-CRT) was now clear, where each selected beam aperture would be designed to match the projected outline of the target.

It took another decade before computers were powerful enough to allow full implementation of the 3D-CRT vision. Two papers, Goitein et al (1983), and Goitein and Abrams (1983) were particularly influential in spreading interactive visualization concepts such as the beams-eye-view for 3D planning of beam directions. Also, the concept of dose–volume histograms was pivotal for evaluating dose distributions calculated by treatment planning systems (Shipley et al 1979). When 3D-CRT eventually went clinical, the proper definitions of irradiation target volumes became critical. The ICRU report (ICRU50 1993) introduced a series of standard volume concepts that have been widely adopted; see section 4.1.1. Together with margin recipes for considering uncertainties in volume determination and location, see review by van Herk (2004), this now forms the foundation for how to set up the geometrical basis for IMRT treatment planning.

2.2. Algorithm development

In dose calculations, accurate algorithms that are fast enough for practical planning have for many years been an issue. Empirical, factor based algorithms have dominated until recently. Although the basic interactions of photons and electrons have been known for long, a fully reductional transport calculation scheme, as in event-by-event Monte Carlo, has always taken too much CPU time to be practical, motivating the search for more efficient methods. At the 1984 ICCR meeting three speakers independently presented proposals for a new family of dose calculation methods based on scatter kernels pre-calculated with Monte Carlo methods (the first author of this paper had the luck to be re-scheduled as the first speaker). One-and-a-half decade later, kernel based methods had matured into a standard option for treatment planning; see the review by Ahnesjö and Aspradakis (1999). However, for accurate dose calculations, correct modelling of the radiation output of the machine is equally important as modelling the scattering processes in the patient. This was initially much less recognized, but is today a thoroughly investigated area, much due to the dedicated accelerator head simulation software BEAM developed by Rogers et al (1995). Monte Carlo dose calculations have generally been anticipated to replace kernel based methods but with the increased dose calculation load caused by the iterative approach in optimization of IMRT, the current praxis has rather tended towards simplified pencil kernel methods for speed efficiency.

The clinical introduction of 3D-CRT radically changed the radiotherapy workflow from a simulator oriented ‘beam adjustment’ philosophy to an information driven, computer based process where the machine settings for treatment delivery were determined by use of a treatment planning system (TPS) by which realistic calculations could be done. The information process was a main focus of the Nordic collaborative study CART (Westerlund 1988), as well as in commercial TPS development; see, e.g., Jung et al (1997). The number of parameters to set, i.e. the degree of freedom in treatment delivery, was however still limited to
beam energy, directions and field shapes for typically 2 to 4 fields. This amount of information was still possible to manually transfer from the TPS to the treatment machine. Connecting the nodes of information in a clinic into a network holding information management systems, and establishing standards for data structuring, e.g. DICOM (NEMA, 1998), finally paved the way for the treatment planning application to meet the IMRT challenge. Only one piece was missing—algorithms for automated optimization of the beam fluence modulation.

The beam directions, beam weights, field shapes etc, constituting the free variables in 3D-CRT could be manually optimized. However, by conceptually dividing each beam portal into approximately $10^2$–$10^3$ ‘beamlets’ for which the ‘modulation’ (i.e. fluence) could be set independently of all other beamlets led to the formulation of a large-scale optimization problem, intractable by manual procedures. Initially, the optimization was viewed as an inverse problem, partly due to a successful analytical solution of a special problem in rotational therapy (Brahme et al 1982), and partly inspired by the similarities with the inverse basis of image reconstruction in computed tomography (Cormack 1987, Cormack and Cormack 1987). However, the physical lack of negative dose prohibited purely inverse solutions and the problem formulation gradually shifted towards optimization, as illustrated by representative papers from leading research groups during the 1990s, for example Karolinska in Stockholm (Lind 1990, Gustafsson et al 1994, Löf et al 1998, Brahme, 2000), Heidelberg (Bortfeld et al 1990, Bortfeld 1999) and Madison (Holmes and Mackie 1994, Shepard et al 2000). The work of Webb has consistently used the optimization formulation (Webb 1989, 2003). The term ‘inverse planning’, however, is still used. It now refers to the planning workflow where dose distribution goals are input to, and used by, the computer before the dose calculations that determines the treatment delivery parameters are done. This work sequence of dose goal handling is considered reversed as compared to the non-IMRT procedure where explicit dose levels are not processed by the TPS except for documentation and reporting (Brahme 1988).

The hallmark of IMRT is its ability, through extensive calculations in a TPS, to deliver controlled, heterogeneous dose distributions of high resolution. So far this ability has been almost exclusively applied to construct homogeneous target dose distributions by superposing heterogeneous dose from multiple fields of different directions. The degree of freedom to customize the dose from voxel to voxel is now in our hand but remains to be clinically explored. To gain from this freedom we need to adapt, and expand, our knowledge of cancer and radiation biology, cf Brahme (2001), Bentzen (2005a, 2005b) or Yang and Xing (2005), ensuring that radiation oncology will still have be a vital discipline in the future.

3. Treatment delivery techniques

Most of the early scientific work addressed IMRT applied to standard, cone beam C-arm linear accelerators equipped with multileaf collimators (MLC), i.e. the main stream IMRT equipment of today. However, the first IMRT delivery method commercially available for clinical use was an add-on equipment enabling standard linear accelerators to deliver serial, fan beam tomotherapy. Tomotherapy is now also available by dedicated machines based on helical (spiral) delivery of fan beams. A third class of delivery systems comprises special robotic and hybrid techniques that do not readily fit into the other two groups.

3.1. Tomotherapy

Tomotherapy, or rotational fan beam IMRT, can be delivered in two ways, serial and spiral (helical) tomotherapy (Webb 2004). Historically, the serial fan beam IMRT system by MIMiC and CORVUS TPS (Nomos Corporation) was the first commercially available IMRT system
with many installations in hospitals throughout the world. It uses a binary modulated mini MLC, attached to the treatment head of a standard linear accelerator. It irradiates two narrow slices of the patient by rotating a slit collimator through a series of gantry angles. After completing a gantry rotation, the patient is moved to the position of the next two slices and the procedure is repeated until the entire treatment volume has been irradiated.

Later, a dedicated machine and planning software system for helical tomotherapy became commercially available through Tomotherapy Inc. in collaboration with University of Wisconsin; see, e.g., Mackie et al (1993), Welsh et al (2002) or Beavis (2004). Photon radiation is produced by a linear accelerator mounted in a standard, large aperture CT chassis. The accelerator rotates in the gantry around the patient while the couch moves the patient slowly through it thus creating a spiral (helical) pattern of beam delivery. A computer-controlled MLC with two sets of interlaced leaves continuously modulates the radiation beam during the rotation. A special feature of the tomotherapy unit is the capability to acquire megavoltage CT-scans with low doses from the therapy beam, and integrating this image information into the delivery workflow. All moving parts of the machine are encapsulated enabling the high rotation speed needed for high-quality volumetric imaging.

3.2. Cone beam IMRT

The present mainstream IMRT delivery is based on standard C-arm machines for cone beam delivery with MLCs. These collimators were initially designed for block replacement to facilitate the 3D-CRT workflow, but the potential for beam modulation by moving collimators was also early recognized (Kijewski et al 1978, Brahme 1987, 1988). Several papers soon proposed algorithms for realization of arbitrary fluence distributions by means of multileaf field ‘segmentation’ where one by superimposing differently shaped beams (segments) could freely shape the delivered fluence pattern (Convery and Rosenbloom 1992, Bortfeld et al 1994, Svensson et al 1994). Most equipment used for IMRT today is still essentially designed for block replacement with MLC, rather than being dedicated for IMRT. Delivery of multiple field segments (‘subfields’) where the leaves do not move during irradiation, has often been referred to as step-and-shoot IMRT, while modulation by moving the MLC leaves during irradiation is referred to as dynamic MLC (dMLC) technique. The dMLC delivery is generally considered to be faster than the step-and-shoot technique, but calculations are more complicated since the discretization of the beams into well-defined beamlets is not as straightforward as for the step-and-shoot technique. To minimize interleaf leakage MLC leaves are often shaped with thin parts (‘tongues’ and ‘grooves’) overlapping the sides to adjacent leaves. This can yield an unwanted underdosage as the penumbra shaped over the overlapping parts do not add to yield a homogeneous fluence. Much of this tongue-and-groove effect can be removed by synchronized segment patterns, but at the cost of increased treatment time and hence an increased leakage outside the treated area (van Santvoort and Heijmen 1996, Webb et al 1997).

Attenuating metal filters with varying thickness, ‘compensators’, is an alternative to MLC for realization of a modulated cone beam. This technique has long been used to provide homogeneous dose at depth by ‘compensating’ the difference in attenuation through tissue between adjacent rays. It is straightforward and requires neither MLC nor advanced computer control during beam delivery. The filter fabrication and handling, however, is labour intensive and therefore becoming less used.

3.3. Other IMRT techniques

It has been argued that robotic IMRT, where a linear accelerator mounted on a robotic arm can deliver multiple beams to a target from any angle, might become the ultimate IMRT

3.4. Positioning and compensation for organ motion

In recent years increased availability of imaging in the treatment room has boosted interest in the implementation of protocols to increase delivery precision based on image guided radiotherapy, IGRT, and adaptive radiotherapy, ART. In clinical practice, portal imaging with projective images is the present workhorse for checking and correcting patient positioning; see review by Herman (2005). With increased image acquisition and processing capabilities volumetric CT imaging can be done at the treatment couch, which has great potential (Mackie et al 2003, Jaffray 2005, Yan et al 2005). Implementation of protocols fully using the potential from volumetric imaging requires extensive integration of treatment planning data using both rigid and deformable image registration techniques to consider changes in both position and shape (Mackie et al 2003).

The implementation of ART can in principle follow two tracks, either an indirect method where the planning is performed onto the PTV and with online imaging used to reduce the applied margins with no feedback data for explicit re-planning, or a more direct feedback approach where new and updated plans are formed based on the feedback information from previous fractions (including providing compensatory dose for misses in earlier fractions). The first, indirect approach has been used for years, while the more direct approach has been limited to modelling and simulation studies, see e.g. Löf et al (1998), Birknet et al (2003) or Rehbinder et al (2004).

All methods for patient immobilization are aiming to minimize patient movements. Some movements cannot be suppressed completely, e.g. heartbeat and breathing. Breathing is a major problem in the thorax region where important targets are located such as breast and lung cancers. The movements are large and since the speed of the MLC movements are of the same order of magnitude as breathing, movement interference can cause significant deviations between planned and delivered dose. Therefore, IMRT for moving targets require techniques for respiratory control or gating, or must be restricted to 3D-CRT with margins large enough to allow for breathing motions. Several solutions have been proposed for treatments in the respiratory affected regions; see reviews by Keall (2004) and Mageras and Yorke (2004).

4. Handling dose distributions in anatomical space

A single IMRT dose fraction of 2 Gy to a deep seated target induces in the order of $10^{17}$–$10^{18}$ ionization events into the target, and 10 to 20 as many ionizations in surrounding healthy tissues. The cell sterilization action is mediated by breaking DNA strands, most effectively if both strands are broken close to each other (double strand break, DSB). Single strand breaks are repaired more effectively through the structural support by the unbroken strand. The vast majority of the ionizations from x-rays do not induce any irreparable DSB, partly because the cell nucleus fills only a fraction of the cell volume, and partly because most ionizations yield repairable (single) strand breaks. For a dose of 1 Gy, approximately $10^5$ ionizations per cell occur, but the yield of DSB is only about 40 per cell. Several of the DNA bound breakings responsible for DSB might be due to reactions with OH-radicals from hydrolysis of water, and by low energy, non-ionizing events induced at the track-ends of the secondary electrons released in ionizing events (Boudaiffa et al 2000).
Although one in principle can follow individual radiant particles in detail through track-structure simulations, see e.g. Nikjoo et al (2001), the excessive amount of information and computer simulation time requires a different approach to practical treatment planning. Instead of keeping track of individual cells, regions of interest are delineated from anatomical patient images composed of macroscopic physical quantities such as x-ray attenuation (CT) or nuclear spin magnetic resonance imaging (MRI). Instead of keeping track of ionizations, macroscopic distributions of energy deposition, i.e. dose, are calculated. To make the problem tractable, the candidate dose distribution is intersected with relevant regions of interest, and the information is further reduced to a small set of numbers for assessing the plan quality. Logically, final plan judgment should be in terms of likelihood for providing cure without severe side effects (Agren et al 1990, Söderström and Brahme 1993, Brahme 1999). However, direct calculation and maximization of such a quantity for the individual patient involves uncertainties and is currently used on research basis only (Turesson et al 2003). Instead, the current clinical paradigm is to use protocols specifying physical dose levels to targets and tolerance levels for regions at risk.

4.1. Anatomical volumes for treatment planning

Tomographic imaging has evolved from providing pictures of the patient to become digital representations of the patient in the computer. The target determination process has developed into a qualified, computer aided sculpturing process in 3D. However, while CT is an anatomical imaging that solely maps x-ray absorption variations in tissue, emerging imaging technology can map properties related to specific functions of the cells. This ‘functional imaging’ can provide for detailed tumour spatial mapping and biological characterization for prediction of radiation therapy response. As reviewed by Apisarnthanarax and Chao (2005), positron emission tomography (PET) and MRI provide potential to map both hypoxia, proliferation, apoptosis and hormone receptor status. Hence, the dose could be increased to selected confined volumes containing, e.g., hypoxic cells. However, validation of the imaging-pathological relations, and the cost and time of clinical outcome studies will indeed delay the introduction of these promising possibilities into clinical routine.

4.1.1. The ICRU volumes

The currently used target concept for radiotherapy planning, as defined by ICRU (ICRU50 1993, ICRU62 1999), is the PTV (planning target volume) constructed by adding a margin accounting for organ movement and set-up errors to the CTV (clinical target volume), which in turn is defined by the GTV (gross tumour volume) with margin regions to cover assumed spread of invading tumour growth. The PTV concept has been criticized for being dependent on treatment technique arguing that set-up margins would be more logical to define in the machine system than anatomically (Aaltonen et al 1997). Although adding a set-up margin is simple for 3D-CRT, it is less practical for fields modulated by MLC segmentation techniques. The ICRU concepts now dominate for handling both set-up margins and internal movements. This standardization has had a profound influence in establishing a common framework for the radiotherapy community.

4.1.2. Margins for positional uncertainties

As depicted in figure 1, the planning CT study is viewed as a snapshot in time of the patient, and the deviation between the snapshot and (the not available) time averaged CTV position introduces a systematic error present all through the delivery sequence, which requires attention (Stroom and Heijmen 2002). The ICRU reports do not state any particular algorithm for calculation of the margin but several authors have addressed the problem. Stroom et al (1999) chose the margins such that the 95% isodose
should enclose, on average, at least 99% of the CTV. van Herk et al (2000) chose a different approach where 90% of treatment plans should result in a CTV dose that everywhere is greater than 95% of the prescribed dose. The size of the needed margins, applied by a 3D region growing algorithm as proposed by Stroom and Storchi (1997), were similar for both approaches despite the differences in assumptions; cf van Herk (2004).

It is important to realize that any margin algorithm applied to a 3D object must be intrinsically 3D in its implementation. Sequential use of a 2D margin growing algorithm for the slices of a contoured 3D object is not recommended since it can lead to severe margin errors, particularly in the direction perpendicular to the image plane as clearly shown by Stroom et al (1998).

The ICRU reports did also propose an expansion of organs at risk volumes, OAR, into planning organ at risk volumes, PRV. Much less attention has been given to the problem of devising algorithms and protocols for designing a PRV from an OAR. McKenzie et al (2002) have worked out class solution recommendations for organs of ‘parallel’ architecture, and ‘serial’ architecture, respectively. Lung is an example of a parallel organ where small hot spots resulting in local loss of function are much less severe than in a serial organ such as the spinal cord where even small volumes of affected tissue may result in severe side effects. Muren et al (2005) have studied the application of the PRV concept applied to the rectum, which in prostate treatment is a critical organ with rather large positional uncertainties.

4.1.3. Direct modelling of positional uncertainties. The correlation in movement between CTV and OAR is not explicitly considered through the margins inherent in PTV and PRV.
Hence, optimization objectives formulated for the CTV and OAR with positional error modelling integrated in the optimization procedure itself is an interesting approach. By simulating populations of replica instances of the same patient, where the CTV and OAR positions are sampled according to an organ displacement model, the yielded dose–population histograms can be used to more precisely tailor dose compromises between CTV and OAR (Yang et al. 2005, Trofimov et al. 2005). The potential benefit of such optimizations is that sharper gradients of delivered dose can be achieved by giving more dose at the edges of the CTV, assuming that the positional spread will smear the dose heterogeneity over the fractions to yield homogeneous dose in the end.

Convolving the dose with patient geometry variations is a simple way to get the expectation dose values, but the usual number of delivery fractions (approximately 30) is not large enough to reduce the variance of the total dose in gradient regions. Hence, reducing the variance must be part of the optimization objectives. Unkelbach and Oelfke (2004, 2005a, 2005b) have presented a more detailed analysis using estimated probability distributions of possible patient geometries and investigated the influence of uncertainties in those distributions. Baum et al. (2006) used CTV and OAR coverage probabilities as weights to maximize the CTV equivalent uniform dose (EUD) and to keep the EUD of the OAR below a certain threshold in order to shape a robust dose distribution. Extending the optimization procedure in routine planning to cover also patient geometry uncertainties requires more CPU time and/or more approximations in calculations.

Improved positioning methods may in the future reduce the margins such that the difference between a CTV and its PTV will be of less practical importance. If not, methods for CTV based planning to improve the consideration of OAR are at hand. Although the PTV in this type of optimization is no longer needed for dose shaping, the resulting dose envelope to the patient will still be larger than the CTV. Hence, the dose reporting specifications that now are based on the PTV need to be revisited before implementing CTV based planning protocols clinically.

4.2. Treatment plan quality measures

Ranking the quality of competing plans is a prerequisite for both manual plan comparison, and in automated optimization with iterative improvements. The most obvious score to directly reflect a curative intent is the probability of uncomplicated control

\[ P_r = TCP(1 - NTCP) \] (1)

where TCP is the tumour control probability and NTCP is the normal tissue complication probability (assumed uncorrelated in equation (1)). Procedures for maximization of \( P_r \) have been extensively discussed in research papers from the Stockholm group; see, e.g., Brahme et al. (2001), Brahme (2001).

Although many institutions probably use TCP and NTCP for ranking competing nearly equivalent plans, and for evaluating candidate treatment protocols, the scepticism regarding the predicting power of the biological models, together with a perceived higher risk for complications, has hampered their direct application in clinical IMRT. Contributing is probably also the lack of routine methods to quantitatively monitor and score treatment responses. Translating the biological response into terms of \textit{equivalent dose} has instead gained considerable interest. The EUD concept (Niemierko 1997) is defined as the uniform dose causing equal surviving fraction

\[ SF(\text{EUD}) = SF(D(r)) \] (2)
where $D(r)$ is the dose distribution for the volume of interest. The general characteristic of the non-linear dose response has been incorporated into a computation friendly application of the EUD concept based on a power law average proposed by Niemierko (Wu et al. 2002) that has been frequently employed. Mavroidis et al. (2001) proposed a quantity $\bar{D}$, the biologically effective uniform dose linked directly to the response probability through

$$P(\bar{D}) = P(D(r))$$  \hspace{0.5cm} (3)

where $P$ can be either TCP or NTCP. Whatever biological index considered, the biological macroscopic response to radiation is non-linear, and the more heterogeneous $D(r)$ is, the more sensitive to the underlying biological model, and its parameter values, will the result be!

Most plan optimization is done on physical dose–volume criteria aiming for homogeneous dose coverage of the target, and minimal dose outside. Various conformity indices have been constructed to directly score the planning success in terms of dose coverage, as reviewed by Feuvret et al. (2006). A conformity index can be very useful for characterization of a treatment plan, but unlike a biological index as EUD, a conformity index is not aimed for automated optimization engines since direct derivates versus the optimization variables are lacking, or hard to describe quantitatively.

5. From dose sculpturing to machine settings

Besides an appropriate representation of the patient, automated optimization of IMRT requires formulation of the problem into a set of optimization variables that controls the incident radiation, models for converting the irradiation pattern to dose, and a dose distribution quality measure (objective function). Iterative search procedures are used to find the best combination of irradiation control parameters, and it is obvious that the more direct and well behaving influence the optimization variables have on the objective function, the more effective search algorithms can be designed.

5.1. Optimization variables

The DICOM standard for radiotherapy data specifies the data structures that are needed for beam delivery (NEMA 1998). The data have to be structured into control points specifying beam angles, MLC settings and monitor units. However, variation in leaf edge position far from a dose point has a very weak influence on the dose, while the direct photon energy fluence has an almost linear influence. Hence, the most common approach to IMRT optimization is to use a discretization of the beam apertures as optimization variables, although other sets of variables are also possible.

5.1.1. Discrete fluence apertures—bixels. Discretizing a beam aperture into elements, commonly rectangles sized by the width of the leaf times an arbitrary set discrete step length, provides a way to represent the energy fluence distribution of the beam as a set of numbers that can be used as optimization variables. The irradiation through a bixel yields a dose distribution forming a discrete kernel that can be pre-computed to save computation time. The dose to the voxels directly irradiated through a bixel is practically linear to the bixels’ energy fluence (we will in the following use ‘fluence’ for short, instead of the for photon dose calculations more relevant ‘energy fluence’), but scattering processes add dose contribution through contributions from kernels from other bixels of the beam. Normalizing the kernels per incident fluence yields directly the derivative of the dose distribution with respect to the bixel fluence optimization variable.
The number of bixels is in the order of $10^2$–$10^3$ per beam making the optimization a large-scale problem. The use of bixels as optimization variables may cause some drawbacks. There is a tendency that the resulting optimized fluence distribution becomes highly irregular, as a consequence of requesting sharp dose gradients (Alber et al 2002b). The magnitude of the fluence irregularities depends on both the size of the discrete bixels, size of dose voxels as well as on the optimization technique.

As there is no hardware (except attenuating filters) that can deliver modulated fluence profiles directly, the optimal fluence profiles must be converted into machine parameters such as MLC control points. This conversion may deviate from the desired fluence due to approximations in calculations and limitations in MLC settings. Hence, the resulting, deliverable, fluence profile will no longer be optimal. To ensure modelling and delivery consistency, the dose should always be (re)calculated with an appropriate model considering actual beam settings. The corresponding degradation of the plan quality will be more pronounced for large irregularities of the fluence, and its realization will also require more monitor units (MU). Several methods have been proposed that produce smoother, more regular fluence distributions, which are easier to deliver, either by explicitly imposing various regularity constraints on the fluence pattern directly (Chvetsov et al 2005, Coselmon et al 2005), by indirect methods such as modifying the requirements on the dose (Price et al 2003), or by using optimization methods with inherent smoothing properties (Xiao et al 2004).

5.1.2. Machine parameters. One method to avoid the problems associated with fluence optimization is to take the machine settings into account during the optimization. This can be achieved by incorporating the MLC sequencing into the optimization (Alber and Nüsslin 2001) or by optimizing the machine parameters directly (Löf 2000, Tung et al 2005) as depicted in the upper part of figure 2. Gradient based, direct optimization is local and dependent on an initial set of leaf settings. One way to obtain this is to first perform a coarse fluence optimization with a leaf sequencing step. Alternatively, control points can be generated based on geometrical attributes, such as the projection of the target and the OAR.

5.1.3. Beam orientation. Other parameters that can be optimized include the number of beams, and the beam orientation (gantry, couch and collimator angles) and isocentre positions. This increases the complexity of the optimization problem considerably since all bixel variables are dependent on beam orientations. Suggested methods to combat this include speedups for solving the (repeated) fluence optimization, for example by using a clustered dose grid (Scherrer et al 2005) and heuristic choice of candidate beams (Ehrigott et al 2005). Furthermore, the beam orientation can be optimized locally, starting from an initial point given by the planner (Löf 2000). A local optimization cannot guarantee that a global optimum is found, but may still improve the plan significantly.

In conjunction with MLC sequencing, or direct optimization, the collimator angle is an important parameter, and a correct utilization of this degree of freedom can provide increased treatment quality (Chapek et al 2005). In helical tomotherapy optimization, all beam directions within the treatment region are considered, yielding up to about $10^5$ bixels for optimization (Shepard et al 2000), which puts even higher computational demands on the planning system.

5.2. Fluence modelling and dose calculations

For any iterative optimization technique, fast dose calculations are necessary since the dose distribution needs to be calculated repeatedly. The required number of iterations may vary from $10^1$–$10^3$ depending on type of algorithm. The most common way to meet both these demands is to store pre-computed dose distributions from each bixel representing the fluence
Figure 2. The figure illustrates the calculation workflow in treatment planning. Calculations for 3D-CRT start by defining leaf settings (upper left), and end with the calculated dose, that can be improved by manually testing new beam set-ups and repeating the procedure. The IMRT optimization process starts by defining an objective (lower left) for the dose distribution. Guided by this objective, the planning process is automated through an optimization feedback loop (upward directed arrows), where gradients of the objective with respect to dose are used to find new proposals of the fluence pattern directly (middle left directed arrows), or, for direct machine parameter optimization, the gradients are expressed with respect to leaf positions and segment weights (upper loop of hatched arrows). The IMRT optimization can be repeated with new set-ups of the objective to evaluate different clinical compromises in a trial and error process.

discretization. To limit memory needs and computational operations, the kernels are often cut off neglecting distant scatter. The accuracy lost by neglecting scatter can be compensated for by more accurate calculations at intermediate iterations by, e.g., a point kernel method (Ahnesjö 1989). Conceptually, the impact from heterogeneities can be fully regarded during the pre-calculation of pencil kernels (Gustafsson et al 1994), but in practice dose is often approximated by use of correction methods as in 3D-CRT pencil kernel dose calculations, see e.g. Ahnesjö et al (1992) or Bortfeld et al (1993), to shorten the kernel pre-calculation time. Critical for calculation accuracy is the ability to handle the influence imposed by the beam and treatment head geometry, such as scatter from the flattening filter, impact of rounded shape of leaf ends, etc. Of particular interest to IMRT is the modelling and delivery accuracy of small field segments. The small field ‘regime’ prevails when the combined effects of source size blurring (i.e. direct fluence penumbra), and lateral electron transport (including range shift introduced by heterogeneities) are of the same characteristic length as the segment width itself. When this happens, the lateral charge particle equilibrium is lost which makes the dose very sensitive to small changes and errors of leaf positions as demonstrated by LoSasso et al (1998).

Since optimization may enforce ‘more-than-wanted’ approximations of the calculated dose, it is pertinent that the treatment plan evaluation and dose reporting is based on the best possible dose calculations performed with the actual machine settings used for dose delivery, and that due consideration is taken to crucial effects invoked by the segment characteristics (small fields, head scatter output, etc). The difference between the optimized dose distribution and the delivered dose should be as small as possible, requiring that TPS vendors must integrate as much as possible of the beam characteristics into the optimization loops (Reynaert et al 2005).
5.3. Optimization goals

The treatment planning process aims to produce a feasible treatment plan considering specific goals. To drive the optimization the goals must be cast in mathematical form that quantifies the deviation from the goals, and eventual restrictions on the solution. Hence, an optimization problem consists of a set of constraints that must be fulfilled and an objective function to be minimized (or maximized) with respect to a set of independent variables.

5.3.1. Constraints. A constraint is a non-negotiable, *a priori* requirement on an optimization problem, and the objective will be minimized (or maximized) only to the extent allowed by the constraints. Constraints do not have weights, and are not part of the objective function, with high weights or otherwise. Confusingly, the term ‘DVH constraint’ is often used to denote DVH based objectives. The most straightforward application of a constraint is to give absolute precedence to a part of the objective function, for example to guarantee that the dose do not exceed a critical maximum dose level, but they can also be used to define more elaborate optimization problems in order to improve the user interaction; cf section 5.3.3.

The non-negativity requirements of fluence or dose are physical constraints, as well as the interdigitation of MLC settings. The former represents a simple bound, while the latter can be formulated as a linear constraint. Simple bounds and linear constraints are easier to implement into an optimization algorithm, and feasibility can be guaranteed and maintained (Luenberger 1984). With non-linear constraints, such as a TCP constraint, the search path may frequently violate the constraints and feasibility is usually obtained only at the optimum.

5.3.2. Objective functions. The objective function may be composed of any number of functions, combined to produce a single number, usually through a weighted sum. It is difficult to convey the knowledge and experience of a clinician to an optimizer through one or more simple functions. An optimizer will follow the instructions given in the objective function literally: only what is explicitly asked for will be obtained, and anything not explicitly forbidden may appear. The most commonly used objective function, a weighted sum of penalty functions based on satisfying a set of DVH points, may not be ideal for this purpose. A small set of DVH points is often insufficient to avoid undesired properties, and a large set may be overly strict, and force the solution into inefficient compromises. Biological treatment measures like EUD, TCP or NTCP are technically well suited since they all consider the dose distribution for a full volume and not only the parts violating a certain condition.

When using gradient based optimization algorithms, differentiability and convexity are desired properties; see section 5.1.1. The more degrees of freedom an optimizer has to its disposal, the more detailed objectives need to be defined. A beam set-up for prostate avoiding the femoral heads does not need objectives for those, but if the optimizer is free to change the beam configuration, it must be given a more specific objective that penalizes high doses to the femoral heads.

The formulation of efficient and intelligible objective functions is of paramount importance for the planning process requiring effective tools for user interactivity.

5.3.3. User interaction. The iterative process of setting up the optimization problem can be very time consuming, and several attempts can be used to facilitate the process. *Early feedback* of intermediate results enables the user to estimate how the compromises work out, without waiting for a full optimization with MLC sequencing and final dose calculation to be completed. This is facilitated if MLC sequencing is integrated into the loop. *Prioritized treatment goals* can be more intuitive to use instead of an objective function consisting of a
weighted sum of conflicting goals. This method is sometimes referred to as lexicographic optimization, and is based on separating the objectives into categories of importance. First, only the most important category is included in an optimization. Then, the result is transformed into constraints, and the next category is introduced as objectives, and so on. Guided problem modification aims at reducing the number of iterations by providing tools to analyse and modify the problem. Sensitivity analysis has been proposed by Alber et al. (2002a) to give the user information on how much a change in one objective or constraint will affect others. For example, it may provide an estimate on how much the maximum dose in an organ at risk can be reduced by allowing a higher target dose heterogeneity. Other tools include voxel based weighting, in which voxels that received undesired doses can be individually reweighted (Yang and Xing 2004). Evaluation of precomputed plans can help in setting planning compromises by producing a large number of plans with different compromises (possibly overnight) and then choosing one or combining several plans to obtain a usable plan (Küfer et al. 2003). When producing such plans, it is only relevant to consider Pareto efficient plans, i.e. plans where no objective can be improved without worsening another.

5.4. Optimization algorithms

The IMRT optimization problem is a large-scale problem requiring sophisticated algorithms to efficiently navigate the solution space. The most common algorithms for IMRT use deterministic methods to determine search patterns, often by using information about the gradient of the objective function. Gradient based algorithms work iteratively by first selecting a direction, and then search along this direction to find a good point from which to start the next iteration; see, e.g., Luenberger (1984). The simplest algorithms use the gradient directly as a search direction, and then search along this direction to find a good point from which to start the next iteration; see, e.g., Luenberger (1984). The simplest algorithms use the gradient directly as a search direction, and then search along this direction to find a good point from which to start the next iteration; see, e.g., Luenberger (1984). The simplest algorithms use the gradient directly as a search direction, and then search along this direction to find a good point from which to start the next iteration; see, e.g., Luenberger (1984). The simplest algorithms use the gradient directly as a search direction, and then search along this direction to find a good point from which to start the next iteration; see, e.g., Luenberger (1984). The simplest algorithms use the gradient directly as a search direction, and then search along this direction to find a good point from which to start the next iteration; see, e.g., Luenberger (1984). The simplest algorithms use the gradient directly as a search direction, and then search along this direction to find a good point from which to start the next iteration; see, e.g., Luenberger (1984). The simplest algorithms use the gradient directly as a search direction, and then search along this direction to find a good point from which to start the next iteration; see, e.g., Luenberger (1984).
5.5. Leaf sequencing for MLC dose delivery

The fluence optimization results in a fluence distribution that has to be translated into a sequence of control points for the MLC. The process by which these are computed is referred to as leaf sequencing, and can be performed for step-and-shoot or dynamic delivery.

5.5.1. Step-and-shoot delivery. Most leaf sequencing algorithms require a discrete number of fluence values into which the bixel fluence values have to be approximated. Some sequencers let the integers represent equidistant fluence levels, and some use clustering techniques to choose levels such that the error introduced by the approximation is minimized.

Assuming somewhat idealized conditions, leaf sequencing algorithms aim to exactly reproduce the integer matrix created by the discretization. This problem has been well studied, and elegant solutions exist that guarantee that the number of MUs is minimized (Kamath et al 2003). It has been shown that it is practically impossible to guarantee optimality with respect to the number of segments (Kalinowski 2005), but there are many heuristic algorithms that seem to obtain good results; see Siochi (1999), Wu et al (2001) or Bar et al (2001).

Current leaf sequencers are able to incorporate many of the MLC constraints, such as minimum and maximum tip differences and interdigitation, and some are also able to explicitly avoid the tongue-and-groove effect. One powerful method to incorporate these constraints is to regard the segment generation as a transportation problem through a network of connected nodes representing different leaf configurations (Ahuja and Hamacher 2004). Constraints of a more global nature, such as maintaining a minimum segment area, have not yet been efficiently incorporated to the knowledge of the authors of this paper.

There are numerous approximations in leaf sequencing algorithms. Will small field effects with partial source blocking and leaf tip shape and positioning accuracy be critical? Are there small modifications that can be made in the matrix that would allow reducing the number of segments or MUs without causing clinically relevant changes in the dose? How will scattering, transmission and lateral variations in the beam quality affect the difference between the original and the resulting fluence? How can the jaws be utilized to fine-tune the segment edges? Many of these questions can be resolved by optimizing the segments directly, but the optimization algorithms must be very innovative in order to exploit the possibility to add, delete or combine segments and to incorporate beam model and delivery uncertainties.

5.5.2. Dynamic delivery. In dMLC delivery the leaves move continuously while the beam is on. For each leaf pair, trajectories can be computed to generate a stepwise constant fluence profile (Ma et al 1998), much like for step-and-shoot, or to generate a smooth continuous fluence profile (Svensson et al 1994). A common method is sliding window in which the leaves move in one direction with variable leaf separation to modulate the fluence. There are also bi-directional approaches as the close-in technique where the leaves move towards each other, but such techniques may not be more efficient (Kamath et al 2004).

An issue to consider for dynamic mode delivery is the increased MLC leakage. The backup jaws typically do not move during the sequence, and large parts of the field may be blocked by the MLC only for many MUs. The leakage needs to be considered in calculations, and also the beam hardening effect of the MLC (Kim et al 2001).

6. Quality assurance of the IMRT process

IMRT is a complex task all through from imaging over treatment planning to its delivery, and a reliable QA of the dose distribution within the patient is of extraordinary importance (Bogner et al 2004). Besides commissioning and testing of the TPS and the treatment delivery systems,
routine testing QA of the delivery system, and (routine) patient-specific QA are required (LoSasso et al 2001, Galvin et al 2004). The routine parts may be done less frequently with time when confidence and experience of the full procedure is gained. Extensive data gathering for QA also raises particular issues regarding evaluation of test data and setting relevant action levels.

6.1. Commissioning and testing of the treatment planning and delivery systems

In many ways, the issues that must be addressed during commissioning and testing of the treatment planning and delivery systems for IMRT are analogous to those necessary for 3D-CRT (Purdy et al 2001). Compared to 3D-CRT, more of the delivered dose in IMRT will be composed of leaf leakage and penumbras, and small fields. Hence, the commissioning data set must be more carefully examined with respect to data influencing dose in such regions.

6.2. Routine QA of the delivery system

The relationship between monitor unit (MU) setting and radiation dose for IMRT fields is much more complex than for non-modulated fields as the beam portals are composed of many segments. The machine control data are too large for simple manual verification. For small fields and large dose gradients, small errors in the MLC positioning yield significant dose errors (Budgell et al 2000, LoSasso et al 2001, Bogner et al 2004). For dMLC, the gap width is the critical parameter for accurate dose delivery and MLC position calibration and leaf motor fatigue are recognized as primary sources of gap inaccuracy (LoSasso et al 2001). Hence, TPS data and modelling consistency with machine performance characteristics is pertinent.

MLC leaf position variations can be tested to a precision of about 0.2 mm by using match-line uniformity for periodic QA (Galvin et al 2004). Another useful test to semi-quantitatively check the MLC leaf positional accuracy is to expose a film to a sequence that creates 1 mm strips at regular intervals. A fast visual inspection can detect improper positioning to a precision of about 0.5 mm (Galvin et al 2004).

6.3. Patient-specific QA

Implementing a patient-specific QA process complements the delivery system QA, and ensures that the planned MLC data for individual patients are properly documented and correctly transferred and executed by the MLC control system (LoSasso et al 2001). The most applied procedure is to replace the patient by a standard phantom. By exposing the phantom to irradiation using the same MLC segments, leaf trajectories and MU for each field as for the final patient calculation, and do a similar calculation in the TPS, test data can be created and compared to data from dosimeters placed in the phantom (Galvin et al 2004). Although ionization chambers are preferred for point dose checks in IMRT phantoms, they cannot be practically used for scanning 2D or 3D dose distributions since the entire treatment plan must be delivered for each measured point (Purdy et al 2001). Film is therefore a convenient possibility that can provide 2D distributions, either for fluence verification of single beams, or for dose verification in a phantom for the complete treatment. There is only one suitable radiographic film for 2D dose distribution verification (Bogner et al 2004). However, this type of film needs processing, which often deteriorates the reproducibility. More recently, a radiochromic, self-processing film has shown good dose linearity and reproducibility (Devic et al 2005). Electronic portal imaging devices, 2D ionization chamber and diode arrays have also been used for single beam fluence verification (Letourneau et al 2004, Spezi et al 2005, Winkler et al 2005) or for the reconstruction of the delivered dose to the patient (McNutt et al 1996, Steciw et al 2005, Dahlgren et al 2002).
Some errors in calculated data will not be caught by using phantom plans, since the dose distribution in a standard phantom will not be the same as in the patient due to anatomical inhomogeneities not present in the phantom. Alternatives being explored for more complete error mappings are Monte Carlo simulations and gel dosimetry as reviewed by Pawlicki and Ma (2001) and MacDougall et al (2002), respectively. Independent monitor unit calculations, i.e. software that imports field specifications from the TPS and then calculate dose using methods and dosimetry data independent of the TPS, provide a viable alternative to intercept errors and mistakes (Kung et al 2000).

All verification data, measurements or calculations, require comparison with data from the TPS calculations. Evaluations involving distributions can be complex motivating use of data visualization and data reduction methods. The $\gamma$-index method combines dose deviations and spatial differences into one dimensionless quantity that can be scaled for different absolute tolerance levels, often chosen so that 3% dose difference and 3 mm distance to agreement constitutes the acceptance levels (Low et al 1998, Low and Dempsey, 2003). Further data reduction is possible by using index–volume, or index–area, histograms to set appropriate tolerance levels considering their relative importance (Dahlgren et al 2002, Stock et al 2005). Further plan analysis can also be made using modelling accuracy linked modulation complexity index like the leaf step index proposed by Stock et al (2005).

### 7. Conclusions and outlook

In this journal, almost 40 years ago, Barber (1967) reported from a conference on the use of computing machinery for radiotherapy. The conclusion was that “with the increasing capability and accuracy of treatment planning techniques, it was apparent that these had already outgrown the accuracy of tumour localization and diagnosis. These deficiencies are likely to limit the overall efficiency of treatment as the planning stage becomes more effectively automated, unless steps are taken to develop these techniques. There was evident appreciation that the computer was not merely a fast calculating machine but rather a piece of complex decision making equipment to be integrated into an overall system of treating patients . . . . The efficient utilization of computing technology throughout the whole range of hospital activities is one of the exciting challenges of the present day”.

About 5 years after Barber’s report was published, CT was invented and had soon challenged the TPS of that time with an overflow of information on patient anatomy. Since then, the development of 3D-CRT and IMRT has shown that localization of photon dose delivery by means of computers can be efficiently implemented close to its physical limitations. Today, with IMRT leaving its infancy, we are back to the situation 40 years ago where the bottleneck for development of more efficient radiotherapy is to acquire, process and handle more information about the malignancies to treat. Current development in radiobiology and imaging gives better insight into the basic pathways of radiation response and hence possibilities for increasing therapeutic gain by, e.g., using drugs. Maybe this development will make another quantum leap and force us to re-conceptualize the delivery and planning of RT? Meanwhile, full exploration of the IGRT and ART concepts and biological optimization will need the engagement of physicists in medicine and biology. Will reviewing old issues of PMB in 2056 tell the story?

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R398 Review


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Biography

Anders Ahnesjö obtained a PhD in radiation physics from the University of Stockholm in 1991. He has worked at Scanditronix AB, Uppsala, on development of stereotactic treatment planning for Leksell Gamma Units (1981–82); at UDAC, Uppsala University Comp. Center, on development of treatment planning systems (1983–87); at Allan Blair Memorial Cancer Clinic, Regina, Canada, on a visiting research fellowship for 4 months (1986–87); at Helax AB, Uppsala, on development of treatment planning systems (1987–90); and at Helax AB/MDS Nordion/Nucletron, Uppsala, as manager of the research department (1990). He was an Adjunct Professor at Umeå University (2003–2006), and since 2005 an Adjunct Professor at Uppsala University and a research scientist at Nucletron.