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REVIEW

IMRT: a review and preview

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Abstract

The very first cornerstone paper on intensity-modulated radiation therapy (IMRT) was published in *Physics in Medicine and Biology*, and many seminal IMRT works have since appeared in this journal. Today IMRT is a widely used clinical treatment modality in many countries. This contribution to the 50th anniversary issue reviews the physical, mathematical, and technological milestones that have facilitated the clinical implementation and success of IMRT. In particular, the basic concepts and developments of both IMRT treatment planning ('inverse planning') and the delivery of cone-beam IMRT with a multileaf collimator from a fixed number of static beam directions are discussed. An outlook into the future of IMRT concludes the paper.

Introduction

Intensity-modulated radiation therapy (IMRT) has been considered the most exciting development in radiation oncology since the introduction of computed tomography imaging into treatment planning (Bentzen 2005, Nutting 2003). 25 years have passed since IMRT was first 'invented' (Brahme *et al* 1982), and it seems to me that progress is made in IMRT at an ever increasing pace. IMRT is already widely accepted in the clinics in the US. The rate of clinical acceptance increases rapidly both in the US and worldwide. According to a recent survey, 73% of the responding US radiation oncologists used IMRT clinically in 2004—in 2002 the number was 32% (Mell *et al* 2005). In the present paper I will review the developments of inverse IMRT treatment planning and of IMRT delivery using multileaf collimators. I will also give an outlook into the future, which should obviously be taken with a grain of salt: in a presentation at the DEGRO meeting in Munich in 2000 I predicted that it would take until 2005 before IMRT becomes routinely available at many centres, and I thought that that was highly optimistic. The numbers mentioned above (Mell *et al* 2005) prove me wrong in a positive way.

The basic idea of IMRT is easy to understand: modulate the intensity of the incoming beams of radiation, and the added flexibility (compared to conventional beams of uniform intensity) can be utilized to achieve a higher degree of spatial agreement ('conformality') of the resulting dose distribution with the tumour target volume. Typically in IMRT we reduce the intensity of rays that go through particularly sensitive critical structures and increase the

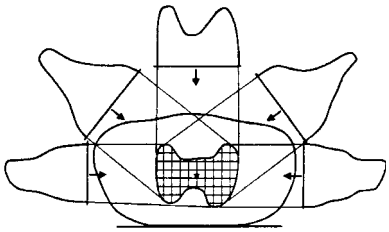

Figure 1. Illustration of the IMRT principle from Brahme (1988). A number of intensity modulated beams (5 in this case) with their intensity profiles are shown. The schematic shows an axial cut through the patient's body where the hatched area symbolizes the target volume. The intensities are typically reduced in those regions where the rays pass through critical structures and increased where the rays 'see' primarily the target volume. (Figure reprinted from Brahme A. 1988. Optimization of Stationary and Moving Beam Radiation Therapy Techniques. *Radiotherapy and Oncology* 12: 129–40, Copyright © 1988, with permission from Elsevier.)

intensity of those rays that see primarily the target volume. An illustration taken from the original work of Brahme is shown in figure 1. The intensity modulation of a single IMRT beam leads to an undesired inhomogeneous spatial dose distribution in the target volume. The resulting hot and cold areas are compensated by corresponding cold and hot areas from intensity-modulated beams from other directions. Thus, IMRT relies heavily on synergistic effects from multiple beams. A universally accepted official definition of IMRT does not exist but I believe most colleagues would concur with the following: 'IMRT is a radiation treatment technique with multiple beams in which at least some of the beams are intensity-modulated and intentionally deliver a non-uniform intensity to the target. The desired dose distribution in the target is achieved after superimposing such beams from different directions. The additional degrees of freedom are utilized to achieve a better target dose conformality and/or better sparing of critical structures'.

The calculation of those non-uniform intensities based on the dose prescription in the target volume and the surrounding critical structures is called 'inverse planning'.

It is an interesting question why it took more than 80 years of radiation therapy practice with uniform beams before the idea of intensity modulation came up. A possible explanation is that, first, for target volumes with simple convex shapes, beams of uniform intensity usually deliver acceptable results and there is no need for intensity modulation. Secondly, advanced volumetric imaging such as computed tomography (CT) had to be developed before such complex target volumes and the surrounding geometry of healthy tissues could be detected, which called for IMRT.

Many of the early landmark papers on IMRT were published in *Physics in Medicine and Biology* (PMB). The whole early 'history' of IMRT is arguably a European history, which can in fact be told by referring to PMB papers alone. Table 1 lists some of the PMB papers that had a significant impact on IMRT. I will discuss the development of IMRT using those papers as guidance and as milestones. I will write this review from my personal perspective and will add some personal statements—note the disclaimer at the end of this review. Note also that a number of excellent historical reviews of IMRT have recently been published from different perspectives (IMRT-CWG 2001, Webb 2003a, 2003b, 2005).

Review: development of IMRT

The 'early history'

The 1982 paper by Brahme *et al* (1982) is generally considered as the cornerstone IMRT paper. It poses the central question: 'Which is the desired lateral dose [intensity] profile in the incident

Table 1. Some early landmark IMRT papers that were published in PMB. Three of these are among the 20 most frequently cited articles in PMB over all years (source: ISI web of knowledge, status January 2006).

1982 (27:1221–1229)	Brahme, Roos, Lax	'Solution of an integral equation encountered in rotation therapy'	• Generally considered as the first seminal IMRT paper • Treatment planning formulated as an inverse problem
1989 (34:1349–1370)	Webb	'Optimization of conformal radiotherapy dose distributions by simulated annealing'	• IMRT planning formulated as an optimization problem • Simulated annealing
1990 (35:1423–1434)	Bortfeld, Bürkelbach, Boesecke, Schlegel	'Methods of image reconstruction from projections applied to conformation radiotherapy'	• Optimization problem solved with fast gradient techniques • Useful solutions with <10 beams
1992 (37:1359–1374)	Convery, Rosenbloom	'The generation of intensity-modulated fields for conformal radiotherapy by dynamic collimation'	• Efficient IMRT delivery with an MLC • Leaf motion in unidirectional 'sweep' mode

beam that produces a desired . . . absorbed dose distribution in the body after one complete rotation?' Today we recognize this as the definition of the inverse planning problem in IMRT. The paper is of mathematical nature, it looks at an idealized case with rotational symmetry: a doughnut-shaped target volume with a circular critical structure at the centre. Under a number of simplifying assumptions it calculates the beam intensity profile that delivers this doughnut shaped dose distribution through a full rotation of the beam. As a result it shows that a highly non-uniform intensity profile is needed to produce a uniform dose distribution in the doughnut shaped target volume.

It is perhaps interesting to note that some of the most important developments in our field started out as abstract modelling studies and made heavy use of mathematics as well. Another well-known example of this kind is the development of CT, which is, for several reasons, closely related to IMRT. For the medical physicist working in the clinic it is sometimes a challenging balancing act to merge the abstract physicist's approach with the concrete clinical needs of a physician treating individual patients. It is clear that groundbreaking developments in medical physics are not usually made by directly responding to clinical requests—in the beginning no clinician asked for CT or IMRT. Rather, researchers in medical physics had to take several steps back from the concrete clinical problem to come up with innovative solutions that found their way into clinical practice many years later. Both in CT and IMRT the original motivation was a clinical one. In IMRT it was to improve the dose distribution for certain head and neck tumours (Lax and Brahme 1982).

There were some forerunners of IMRT and inverse planning. Colleagues at the Joint Center for Radiation Therapy in Boston developed a dynamic rotational/translational treatment technique with conventional collimators, which could generate complex dose distributions, but did not fully utilize or emphasize the potential of intensity variation in the beam (Chin *et al* 1981). Two decades earlier Proimos *et al* developed a gravity-oriented device that allowed for dynamic sparing of critical structures during rotation of the beam around the patient (Proimos 1960). One could argue that, similar to the Joint Center approach and some early multileaf-collimator based techniques from Japan (Takahashi 1965), this device allowed for binary intensity modulation (on-off) but it was not able to deliver the complex intensity patterns that

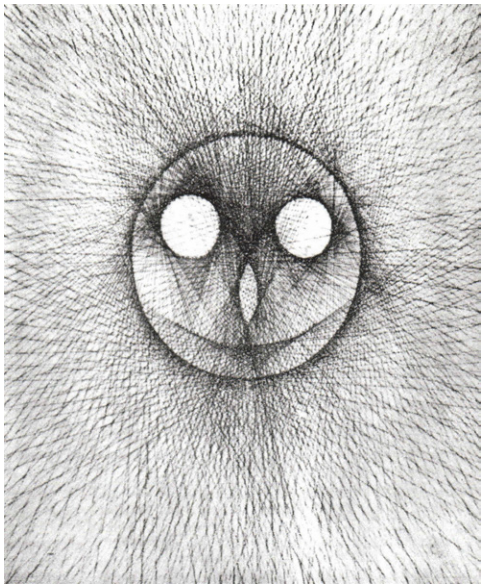

Figure 2. An illustration from the 1940 paper by George D Birkhoff, 'on drawings composed of uniform straight lines'. To construct this type of line diagram is mathematically equivalent to solving the inverse problem of IMRT. (Figure reprinted from Birkhoff G 1940. On drawings composed of uniform straight lines. *Journal de Mathematiques Pures et Appliquees* 19: 221–36, Copyright © 1940, with permission from Elsevier.)

are needed to achieve both a good sparing of critical structures *and* high uniform doses in the target volumes.

Another two decades earlier, in 1940, a mathematical problem that resembled the inverse planning problem of IMRT was solved by George D Birkhoff. In his paper 'On drawings composed of uniform straight lines' Birkhoff derived a mathematical solution of the 'problem' to produce an arbitrary picture with a pencil and a ruler by drawing straight lines with different 'intensities' (grey values), but uniform along each line, on a sheet of white paper (Birkhoff 1940). If we identify the pencil lines with IMRT pencil beams we see the analogy between the two problems. An example from the paper by Birkhoff is shown in figure 2. Unfortunately, and quite understandably, Birkhoff's solution required an eraser. In other words, the intensity of some pencil lines has to be negative, for example to remove the background outside the smiling face in figure 2. Unfortunately a radiation eraser does not exist. Birkhoff's solution is therefore not directly applicable to IMRT. In fact, Birkhoff's work wasn't even known to most pioneers of IMRT. This is no surprise because the mathematical journal in which Birkhoff's work was published is largely unknown to physicists in radiation oncology.

Interestingly, the first person who saw the theoretical potential of Birkhoff's work for IMRT was Allan M Cormack, who in 1979 received the Nobel Prize together with Godfrey N Hounsfield for the development of CT. Cormack provided an interesting geometric interpretation of the inverse problem using a limacon of Pascal (pedal curve) (Cormack 1987). This is discussed in some detail in Webb (1993). Together with his son, Robert A Cormack, he derived a solution for dose distributions with an axis of symmetry using an expansion of the dose and intensity distributions into circular harmonics, which leads to the use of Chebyshev polynomials (Cormack and Cormack 1987). This approach had some similarities with Allan Cormack's original CT reconstruction approach.

The development of 'inverse' treatment planning

The early inverse planning methods were not capable of solving real-world clinical IMRT planning problems. For example, none of the mathematical methods mentioned above was able to handle even the most basic physical phenomena such as scattered radiation. It was realized that IMRT could never become a clinical reality without a practically useful inverse planning 'engine'. Progress in this direction was rather slow initially, mainly because very few people were actually working on the problem. Anders Brahme and his colleagues from the Karolinska Institute in Stockholm initially pursued a deconvolution approach taken from image processing. They defined a point irradiation distribution and tried to decompose ('deconvolve') the desired dose distribution in the patient into such point irradiation distributions. As a result they obtained a point irradiation density. A (back)projection of the point irradiation density yielded the desired intensity profiles for each beam. A related deconvolution approach was developed by Tim Holmes and Rock Mackie in Wisconsin (Holmes *et al* 1991). The deconvolution approach had the potential to solve inverse planning problems for real clinical cases, but it had some conceptual drawbacks and never made it into clinical practice.

Yair Censor in Haifa developed a feasibility search method, which was aimed at finding a plan that fulfils a number of constraints, expressed as lower and upper dose limits in various organs (Censor *et al* 1988). It employed a projection onto convex sets (POCS) algorithm. This method had some features that still exist in today's inverse planning algorithms. Notably, it introduced the concept of a 'dose influence matrix', which pre-calculates the dose contribution from each beam element (nowadays called 'bixel') to each volume element (voxel), such that there is no need to perform dose calculation 'on the fly' during the execution of the algorithm.

Steve Webb at the Royal Marsden Hospital in Sutton, who, in his earlier career, worked on image processing and tomography reconstruction problems, was probably the first who published a paper about the formulation of the inverse problem of IMRT as an optimization problem (Webb 1989), minimizing an objective function or 'cost function'. This concept has become the state of the art in modern IMRT planning. It is clear that the inverse problem has no exact solution. There are simply no physical (i.e., non-negative) intensity modulation profiles that deliver the full prescription dose to the tumour and no dose to the surrounding critical structure. Since there is no exact solution, it is desirable to design the IMRT plan such that it comes as close as possible to the unachievable ideal prescription. This is the basis of the optimization problem formulation. The 'as close as possible' objective has often been defined in mathematical terms as the sum of squared deviations of the delivered dose from the prescription, which is to be minimized.

Steve Webb also introduced the optimization method of simulated annealing, which had success in image processing before, into the field of IMRT (Webb 1989). Simulated annealing simulates the technical process of annealing a metal. With a carefully designed cooling scheme, the properties of the metal can be optimized, and so can the properties of a treatment plan if simulated annealing is used in IMRT. The main advantage of simulated annealing is that it can escape local minima while searching for a global optimum. However, it quickly became clear that the problem of optimizing intensity maps using a typical (for example quadratic) objective function does not have local minima, so much faster downhill methods can be used. Nevertheless, simulated annealing has been implemented in the commercial Peacock planning system (Carol 1995) and was used for the planning of the first patient treated with IMRT in 1994, see also figure 3.

In 1988 I began to work on my PhD project with Wolfgang Schlegel at the Deutsches Krebsforschungszentrum (DKFZ) in Heidelberg. Inspired by Anders Brahme, Wolfgang saw the potential of IMRT and put two PhD students on IMRT-related projects, Josef Bürkelbach

and myself. At that time IMRT was not exactly a hot topic. There was not a lot of excitement about IMRT at scientific conferences. The acronym IMRT wasn't even in use yet. Of course, all of this changed very quickly in the following years. My PhD project was the development of new methods for the solution of the inverse planning problem in IMRT. My goal was to develop methods that could be applied for the benefit of patients in the not too distant future. Independent of Steve Webb, I also developed an optimization formulation of the inverse planning problem. I realized that this problem with a quadratic objective function does not have local minima, so fast gradient descent methods can be used to find its solution. I developed the algorithm, borrowing heavily from image reconstruction methods, and implemented the code, both in 2D and later in 3D. Even on the hardware of that time the algorithm achieved respectable execution times (several minutes for a not too large case (Bortfeld *et al* 1990)). Various forms of gradient descent algorithms have since become the standard of inverse planning algorithms in commercial treatment planning systems. Using the initial algorithm, I analysed the effect of the number of beams on the resulting dose distribution and found that less than 10 intensity-modulated beams are often enough to get to a point of diminishing returns (Bortfeld *et al* 1990). This finding was relevant because most or all investigators at that time assumed the use of many more than 10 beams to simulate a rotational treatment. The reduction of the number of beams paved the way for a practical implementation of IMRT on treatment machines equipped with a multileaf collimator (MLC), which just began to appear on the horizon around 1991.

In subsequent years I revised and extended the algorithm and shared it with others. Eventually the code was completely rewritten by Konrad Preiser, after whom we named the program KonRad (Preiser *et al* 1997). The main goal of the KonRad development was to create a dynamic, interactive IMRT planning system. KonRad also stands for Konforme Radiotherapie—conformal radiotherapy. In 1993, on my way back from my stay in Houston (see below), I stopped in New York where Radhe Mohan and I installed the (pre-KonRad) code at the Memorial Sloan Kettering Cancer Center (MSKCC). There it was employed in the MSKCC planning environment and used for the first MLC-based IMRT in 1995, a prostate treatment (Ling *et al* 1996).

Obviously the inverse planning development did not stop with the first clinical implementations. It would take this entire issue to give a complete overview of the various more recent developments in inverse treatment planning for IMRT. However, the foundation was laid in the late 1980s and early 1990s, and for better or for worse, the basic types of algorithms developed at that time are still being used in today's inverse treatment planning practice. An example of an advanced IMRT dose distribution is shown in figure 3.

Some of the important recent developments in inverse planning should be mentioned. After some early attempts to apply inversely planned IMRT to lung treatments, it was found that inverse planning based on simple dose objectives and constraints did not yield satisfactory results (Mohan *et al* 1994). This has led to or re-activated many discussions about the need for biologically-based IMRT planning (Brahme 1999, Niemierko *et al* 1992, Wang *et al* 1995). On the other hand, lung IMRT plans can also be improved using 'physical' dose–volume limits for healthy lung tissue instead of pure dose limits (Bortfeld *et al* 1997, Spirou and Chui 1998). Today dose–volume limits are implemented in most commercial inverse planning systems. Generally speaking, many of the recent developments in inverse planning aim at a better, more complete, representation of the clinical prescription and objectives, so that the resulting IMRT treatment plans become more clinically meaningful, rather than 'just' mathematically optimal. It turned out that one of the biggest challenges in inverse planning is not only the algorithmic solution of a given inverse planning problem, but the mere definition of the clinical objectives and constraints (Langer *et al* 2003). This point is further discussed in the outlook below.

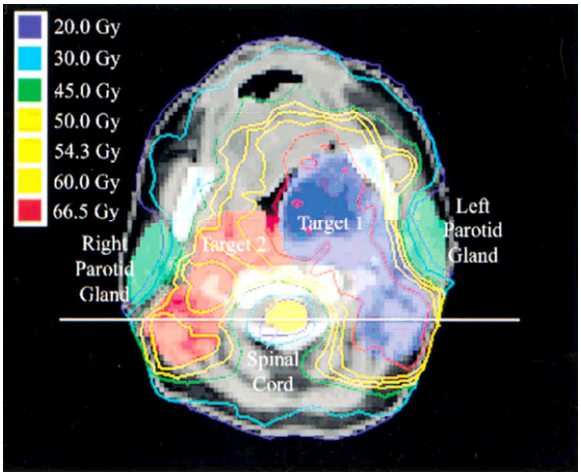

Figure 3. This figure shows a typical head and neck IMRT plan, which would be impossible to achieve with conventional uniform beams. The two target volumes are covered with two different dose levels—the prescription dose levels were 66.5 Gy for target 1 and 54.3 Gy for target 2. Note in particular the sparing of the parotid glands and spinal cord, and the steep dose gradients between the target volumes and the parotid glands. (Figure reprinted from IMRT-CWG. 2001. Intensity-modulated radiotherapy: current status and issues of interest. *Int. J. Radiat. Oncol. Biol. Phys.* 51: 880–914, Copyright © 2001, with permission from Elsevier.)

Figure 4. A multileaf collimator (MLC) consists of a large number of highly absorbing tungsten leaves (in the order of 20–80 on each side) that can be positioned individually to create field openings with complex shapes. The beam orientation is perpendicular to this page. Dynamically moving the leaves while the beam is on will generate intensity-modulated (or rather fluence modulated) fields. (Photo courtesy of Varian Medical Systems of Palo Alto, California. Copyright © [1999-2005], Varian Medical Systems. All rights reserved.)

One intuitive concept that should help to facilitate the definition of the inverse planning problem and the subsequent analysis of dose distributions is the concept of equivalent uniform dose (EUD). EUD is yet another brainchild of Anders Brahme (Brahme 1984) but it has since

been substantially developed by Niemierko (1997, 1999) and others. EUD is the dose which, if given uniformly to an organ or structure, would lead to the same biological/clinical effect as a given non-uniform dose distribution. More recently EUD has been defined as the 'generalized mean' dose. For example, in the lung the EUD is close to the physical mean dose, whereas in 'serial' organs it is closer to the maximum dose. EUD can be considered as being in between pure physical dose objective (or constraints) and biological planning objectives. The use of EUD in IMRT planning has led to promising results (Wu *et al* 2002).

Development of MLC-based IMRT delivery

While the first theoretical inverse planning methods were developed in the 1980s, it was not at all clear at that time how IMRT would eventually be delivered in clinical practice. The use of simple metallic absorbers ('compensators') of variable thickness was an obvious option, but it was generally considered as impractical to fabricate a relatively large number of compensators for every patient, and to switch compensators between the treatments with different intensity-modulated beams from the different directions of incidence. On the other end of the complexity spectrum, completely new radiotherapy treatment devices were envisaged that would magnetically scan a narrow electron pencil beam to directly generate intensity-modulated electron beams, or indirectly produce scanned photon beams for photon IMRT via a bremsstrahlung target (Brahme 1987). Unfortunately, bremsstrahlung at the energies in question (10–50 MeV incident electron energy) inherently produces a broad divergent photon beam, which defeats the purpose of IMRT. To produce an intense narrow photon pencil beam that can be magnetically scanned across a target is a very difficult problem from both a physical and technical point of view. Mechanical beam scanning, on the other hand, is relatively straightforward. A *mechanical* binary intensity modulator was developed as part of the tomotherapy treatment technique (Carol 1994, Mackie *et al* 1993), which delivers rotational IMRT beams. Tomotherapy will be reviewed separately in the article by T R Mackie *et al* in this issue.

Here we will discuss the use of motor-driven multileaf collimators (MLC) for multiple static beam IMRT, as opposed to *rotational* IMRT such intensity-modulated arc therapy (Yu 1995). MLCs began to become commercially available in the early 1990s. Originally the MLC was developed for field shaping in 3D conformal radiotherapy. It consists of a large number of highly absorbing tungsten 'leaves' (about 20–80 on each side of the treatment field) that can be moved against each other and thereby create a large variety of field openings (figure 4), which can be shaped to conform with the projection of the tumour target volume. It has long been known that a movement of a field-shaping device such as a motor-driven MLC under computer control, can be used to produce various forms of intensity modulation (or rather, fluence modulation). The challenge is to make this process time efficient, and to keep the unavoidable leakage radiation within tolerable limits. The latter can be accomplished by requiring that the average field opening be large.

The dynamic mode. An early example of a dynamic treatment technique, i.e., a technique in which mechanical parts move while the beam is on, was the dynamic wedge (Kijewski *et al* 1978). By leaving one leaf stationary and moving the opposite leaf towards this stationary leaf while the beam is on, one can produce wedge-shaped dose distributions. A generalization of this idea was to dynamically 'close-in' the leaves over a local maximum in the intensity distribution. In other words, start with a certain setting of the field opening shaped with the MLC, and then narrow-in the field shape dynamically. This technique can indeed create various shapes of intensity peaks. The slopes on both sides of the intensity maximum depend on the speed of the leaf motion. A combination of such close-in movements at different

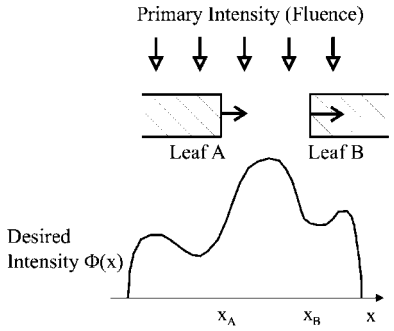

Figure 5. Generation of one-dimensional intensity-modulation with one leaf pair (one row of the MLC from figure 4). For the unidirectional 'sweep' mode (from left to right), the intensity at every point x is proportional to the difference between time $t_B(x)$ when the edge of the leading (B) leaf crosses point x and starts the irradiation, and time $t_A(x)$ when the trailing (A) leaf crosses over point x and stops the irradiation.

locations could potentially, but not very efficiently, produce arbitrary intensity maps (Källman *et al* 1988).

A breakthrough occurred in 1992, when an outstanding new approach was published by Convery and Rosenbloom from the Royal Marsden Hospital (Convery and Rosenbloom 1992). Their proposed scheme would later be used for the first MLC-based IMRT treatment (Ling *et al* 1996) and it is in essence still in use in clinical IMRT today. Convery and Rosenbloom found that arbitrary intensity profiles can be produced with a unidirectional 'sweep' motion of MLC leaves (say, from left to right) and relatively large average field openings (i.e., separations between opposing leaves). They were primarily concerned with the generation of one-dimensional intensity profiles with one pair of MLC leaves (see figure 5). The independent motion of parallel pairs of MLC leaves would then create arbitrary two-dimensional intensity maps. Their observation was that in the unidirectional sweep mode the intensity (fluence) at any point x is proportional to the difference between the time $t_B(x)$ when the leaf edge of the right (B) leaf crosses that point x and starts the irradiation, and time $t_A(x)$ when the left (A) leaf crosses that same point and stops the irradiation. Therefore the leaf motion trajectories must be designed such that $t_A(x) - t_B(x)$ equals the desired treatment time, i.e., the desired intensity or fluence Φ at every point x. There are many possible trajectories that fulfil this constraint. The most desirable is arguably the one that delivers the intensity profile in the shortest time. Convery and Rosenbloom formulated an optimization problem with this objective and the above-mentioned constraint on $t_A(x) - t_B(x)$, plus a constraint on the maximum leaf speed. They solved the problem numerically with a standard linear programming subroutine.

Improvements to the Convery and Rosenbloom approach were developed independently and almost simultaneously by the Karolinska group in Stockholm (Svensson *et al* 1994), the MSKCC group in New York (Spirou and Chui 1994) and the DKFZ group in Heidelberg (Stein *et al* 1994). These investigators found that the leaf trajectory problem, as originally defined and numerically solved by Convery and Rosenbloom, has a simple *analytical* solution, which is illustrated in figure 6. Their insight was that one gets the best possible solution if the A leaf shapes those parts of intensity profile with a positive slope, and the B leaf takes care of the negative slopes. This finding allows one to create the $t_A(x)$ and $t_B(x)$ trajectories easily and directly from the desired intensity map. The leaf motion profiles $x_A(t)$ and $x_B(t)$ are then obtained by inverting $t_A(x)$ and $t_B(x)$, respectively (figure 6(b)). Obviously one has to address some issues such as the infinite slopes of the $x(t)$ profiles in figure 6(b), which would make the leaves move infinitely fast, but those problems are also easily solved. In addition to the

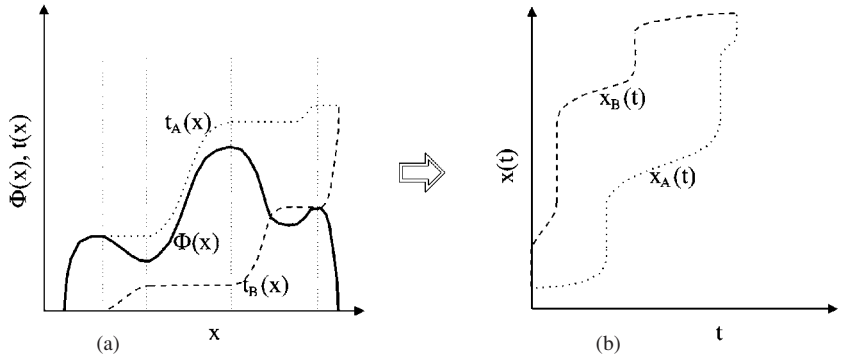

Figure 6. This figure shows the construction of the leaf trajectories for the unidirectional sweep technique from figure 5. The $t(x)$ profiles are constructed directly from the desired fluence profile $\Phi(x)$. Note how the trailing (A) leaf creates positive slopes and the leading (B) leaf creates negative slopes. The difference $t_A(x) - t_B(x)$ equals the desired treatment time, which is proportional to the fluence, at every point x. From the $t(x)$ profiles the $x(t)$ profiles are obtained by inversion (see part (b) on the right-hand side). The latter are used to drive the leaves as a function of time.

original work by Convery and Rosenbloom, the new approaches also took finite acceleration (Svensson *et al* 1994), transmission through the leaves (Spirou and Chui 1994, Stein *et al* 1994) and penumbra effects (Stein *et al* 1994) into account in their models.

Step-and-shoot MLC leaf sequencing. There has always been some reservation against any kind of dynamic treatment technique in radiation therapy, mainly because of safety concerns. In fact, dynamic treatment techniques are a challenge for the control system. In 1991, Art Boyer and colleagues from the MD Anderson Cancer Center in Houston envisaged the delivery of IMRT using an MLC, not in a dynamic mode, but as a succession of discrete field settings ('segments') with a small fluence (i.e., small number of monitor units, MU) delivered to each segment (Boyer *et al* 1991). This discrete mode of IMRT delivery, in which the beam is off while the MLC leaves move to their next position, has later been termed 'step-and-shoot' mode. In 1992/1993 Art invited me to come to Houston for 9 months (avoiding the summer months, for a good reason) with my inverse planning programme, to experiment with step-and-shoot mode IMRT delivery using the then-new Mark 1 version of the Varian MLC.

The first thing we did after my arrival was to develop an efficient step-and-shoot IMRT algorithm that minimized the number of MUs delivered, because we were concerned about increased leakage radiation. Our algorithm also minimized the overall leaf travel, which should help to reduce the wear and tear on the MLC. Yet, this 'Bortfeld-Boyer' algorithm (Bortfeld *et al* 1994b) was very simple. It took us only a few days to develop and implement it. The algorithm was similar to the above-mentioned dynamic sweep technique, except that, by definition, it led to a stair-step intensity pattern.

Independently, Jim Galvin *et al* developed a step-and-shoot intensity modulation technique whose objective was to reduce the total number of segments, which, on some treatment machines, governs the treatment time. Their approach was to 'ablate' the intensity map from top to bottom using segments with ever decreasing MU settings (Galvin *et al* 1993). This technique has later been refined and called 'reducing level technique' (Xia and Verhey 1998). The Galvin *et al* paper was an important piece of work that addressed a number of highly relevant issues ahead of its time. One example is the tongue and groove construction of the MLC leaf leaves and its effect on IMRT dose distributions (van Santvoort and Heijmen 1996).

It is important to note that minimizing the number of monitor units (which primarily affects the undesired leakage radiation) is not equivalent to minimizing the number of segments (which

affects the overall treatment time). Hence, the reducing level technique and the step-and-shoot sweep technique give different solutions to the MLC leaf sequencing problem. Minimizing the number of segments while keeping the number of MUs as small as possible is a very difficult ('NP hard') problem that has been tackled much later (Siochi 2004), but to date it has not been completely solved, except for unrealistically small cases (Langer *et al* 2001).

After developing the leaf sequencing algorithm, I spent the rest of my stay in Houston preparing and executing IMRT phantom experiments. At that time the operation of the treatment machine in the step-and-shoot mode was anything but smooth. We had to manually select the shapes of the MLC segments from the console, one by one, and initiate the delivery of each segment separately. Often the leaves did not reach their intended position or got stuck—due to gravity, some gantry angles were more prone to that than others—and we had to shake them loose by rotating the gantry back and forth. My former colleagues Darren Kahler, Tim Waldron and I spent many evenings and nights in the basement of the MD Anderson Cancer Center on these activities. Initially we proved the feasibility of our step-and-shot technique by delivering saddle-shaped (Art is a horse rider) and other geometrically shaped intensity maps from one direction of incidence. This required around 30 segments and was quite manageable (Bortfeld *et al* 1994b).

Our ultimate goal was to do a prostate-like IMRT phantom treatment. Applying my inverse planning programme to a real prostate case, we created IMRT intensity maps for nine beam angles, and we then used our newly developed step-and-shoot sequencer to create the MLC segments. As a result we obtained 225 segments. For the dose measurement we built a polystyrene slab phantom and stacked it with dose verification film. The treatment of the phantom with those 225 segments was quite an undertaking. Nevertheless, we were able to deliver this 'treatment' successfully in a little more than 3 h. It was arguably the first phantom treatment with MLC-based IMRT (Bortfeld *et al* 1994a). In terms of treatment time it was still several steps away from clinical application. But, we took comfort in the fact that the first phantom CT scans also took several hours to acquire (and days for the reconstruction), whereas today it is a matter of a fraction of a second.

In our field the speed improvements have not been as dramatic as in CT, but since 1993 the vendors of commercial treatment machines (linear accelerator + MLC) have substantially improved their systems. Today treatment times in the order of 10 min for an entire IMRT treatment are achievable. The exact numbers are vendor dependent. Both dynamic and step-and-shoot IMRT delivery are in clinical use. If many segments are used the distinction between dynamic and step-and-shoot delivery becomes somewhat blurry.

Further progress has also been made on the algorithmic side of leaf sequencing, both for dynamic and step-and shoot delivery. Leaf sequencing has now become a mathematical playground. Whole sessions at mathematical conferences have been devoted to the problem. However, the potential to make clinically relevant improvements in this particular field is rather limited. A notable improvement of inverse planning that does affect leaf sequencing and that did have a practical impact has been the introduction of smoothness constraints on intensity maps (Alber and Nüsslin 2001, Webb *et al* 1998).

In some recent inverse planning algorithms the optimization of the intensity maps and the subsequent leaf sequencing step have been abandoned altogether and the MLC segment shapes (apertures) are directly optimized (De Gersem *et al* 2001). This approach has been called direct aperture optimization (Shepard *et al* 2002) or direct machine parameter optimization. The removal of the intensity map optimization as an intermediate step in inverse planning makes the problem much more difficult (non-convex) from a mathematical point of view. Direct aperture optimization algorithms are not guaranteed to find an optimal IMRT solution. In spite of this mathematical difficulty, practical direct aperture optimization algorithms based

on simulated annealing have generated excellent IMRT plans with a small number of segments, especially when fed with a good initial guess of the segment shapes.

Outlook

Today, at the age of 25 years, IMRT has grown up, but it still has a long way to go. The commercial companies continue to put effort (albeit not enough, as some say) into making the various IMRT components and procedures more efficient and integrating them better into the clinical workflow. This is to a large degree an engineering task, which does not require much research.

In this section I will identify areas of IMRT research and development that have the potential to make a significant clinical impact in the next 5 years or so. Clearly, image-guided and adaptive radiotherapy must be mentioned in this context. These areas have lately become the hot topics in our field and are here to stay, so image-guided IMRT is the logical next step (Bentzen 2005). Image guidance is arguably more important in IMRT than in less conformal radiotherapy techniques. But, image-guided strategies can also be usefully applied in conventional radiotherapy or, in fact, in completely different treatment modalities such as surgery. In the discussion below, image guidance will not be a strong focus. However, I will mention some aspects of image guidance that are IMRT-specific—areas, in which there is a real synergy between image guidance strategies and the intensity-modulation capability of IMRT.

From mathematical optimality to clinical optimality

The fact that inverse IMRT planning is commonly defined and solved as an optimization problem does not imply that the resulting plans are *clinically* optimal or even clinically acceptable. To capture the clinical goals and translate them into a complete set of IMRT prescriptions, i.e., mathematical objectives and constraints that provide a comprehensive description of the problem, is a difficult undertaking. It is often the case that the system comes up with unexpected and unacceptable 'solutions' that exploit some weakness or incompleteness in the prescription. Iterative adjustment of the prescription parameters using trial and error in a time-consuming 'human iteration loop' is often necessary to obtain a good IMRT plan. Several solutions to this problem have been proposed. For example, an 'outer optimization loop' has been added that adjusts the weights of importance of different structures or voxels automatically until some clinical goals are met (Cotrutz and Xing 2002).

Another approach is to control the 'output parameters' of the optimization directly, instead of tweaking the prescription. Output parameters are, for example, the maximum dose, mean dose, minimum dose, or the equivalent uniform dose (EUD) in various structures. This can be done with the concepts of multi-objective Pareto optimization, especially in combination with interactive plan navigation tools (Küfer *et al* 2003). This method allows one to explore the unavoidable tradeoffs in IMRT in an interactive way.

A lot of time in the human iteration loop is sometimes spent on the selection of suitable beam angles. Most IMRT planning systems optimize the intensity maps for a given number of fixed beam positions. The selection of beam angles is left to the experience and intuition of the treatment planner. Unfortunately, automatic selection of beam angles is a very difficult problem, which has not been solved so far. Standard beam arrangements can be used in standard cases such as prostate treatments, but these class solutions do not always help, for example, in the head and neck.

Marginal effects of IMRT

Because of its greater dose shaping potential, IMRT can often reduce the margins between the planning target volume (PTV) and the treated volume. An interesting question is whether

IMRT can also shrink the margin between the clinical target volume (CTV) and the PTV, which is used to account for setup errors and internal organ motion. Various aspects of organ motion in IMRT, its detection and reduction of its effect, are discussed in the article by Steve Webb in this issue. The main effect of organ motion, particularly respiratory motion, is a blurring of the dose distribution. If no margin is used, the blurring leads to cold areas near the edges of the target volume. With IMRT there is now an alternative to margins in avoiding those cold areas, namely by increasing the intensity near the field edges (McShan and Frass 2004, Trofimov *et al* 2005, Unkelbach and Oelfke 2004, Zhang *et al* 2004). The correction for dose blurring through IMRT requires good knowledge of the motion characteristics, which can be obtained through new imaging technologies such as respiration correlated CT.

Handling of uncertainties in IMRT planning and optimization

There is a lot of uncertainty in IMRT planning, in addition to the motion problem. Perhaps the biggest uncertainty is in the definition of the target volume and the critical structures, even in the static case. Uncertainty also exists in the dose calculation model, in the treatment delivery with a multileaf collimator, as well as in many other elements of the IMRT planning and delivery chain. In the current IMRT planning practice most of the uncertainties are ignored. The IMRT optimization is done as if all parameters were known with perfect precision. Michael Goitein has often reminded us to perform some kind of error or sensitivity analysis in treatment planning (Goitein 1985). Typically, it is possible to estimate the effect of uncertainty in some parameters, but this is rarely done. The next logical step after the estimation of the effects of the uncertainties is to include those effects in the treatment planning optimization loop, in order to make the resulting plan robust against uncertainties. Coincidentally, robust optimization has recently become an area of active research in mathematical optimization. Some robust optimization techniques have just been translated into the field of IMRT optimization (Chu *et al* 2005), and I hope that they will eventually find their way into clinical IMRT.

Dose painting based on functional and molecular imaging

Tumours are often highly heterogeneous. For example, influential factors such as the clonogenic cell density and oxygenation levels are non-uniformly distributed. One can hypothesize that the optimal dose distribution in the tumour is therefore also non-uniform—more dose is needed in regions with higher clonogenic cell densities and in less oxygenated regions (Ling *et al* 2000). IMRT is an ideal tool to deliver such intentionally non-uniform dose distributions. In fact, this can be done today. The big question is: which dose levels should be prescribed in different regions in the target volumes? Functional or molecular imaging have the potential to image the relevant quantities either indirectly or even directly. The next challenge is then to translate these images into prescribed non-uniform dose distributions for IMRT. The nature of these problems is probably more biological than physical. However, physicists can help in the quantitative modelling of the underlying phenomena. So far a simple linear model to translate functional image information into dose prescriptions has been suggested (Xing *et al* 2002).

IMRT with heavier particles

Intensity modulation has greatly improved the dose shaping capability of external beam photon therapy. In fact, IMRT with photons has challenged proton therapy (see the article by A R Smith in this issue), which has long been recognized as the ultimate (yet expensive) treatment technique in terms of dose conformality and normal tissue sparing. However, by introducing intensity modulation concepts into proton and, more generally, charged particle

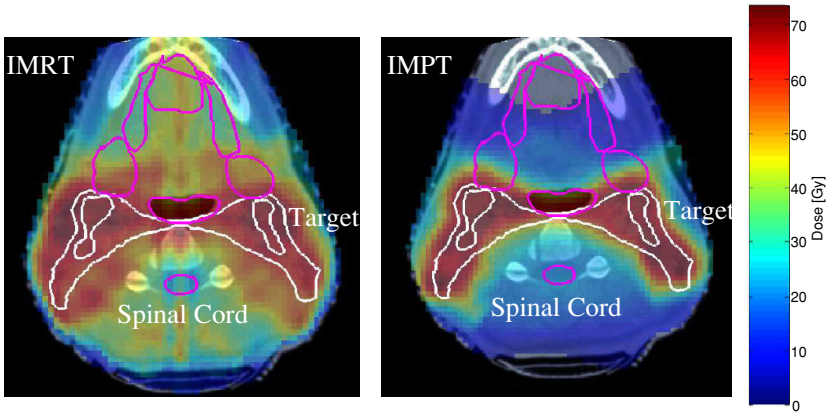

Figure 7. This figure shows the potential of intensity-modulated proton therapy (IMPT) in comparison with IMRT for a nasopharynx case. While IMRT allows for dose conformation to the overall shape of the target volume, a non-negligible amount of dose 'spills over' into normal tissues. The degree of dose conformation in the IMPT plan is much higher. Plans were generated with KonRad. Courtesy of Drs. Annie Chan and Alexei Trofimov, MGH.

therapy one can improve dose distributions further (Lomax 1999). Intensity modulated proton therapy (IMPT) can increase the dose conformality of proton therapy (Oelfke and Bortfeld 2000). IMPT can also be used to reduce the sensitivity of the resulting dose distributions to delivery errors, and some IMPT techniques can reduce the total (integral) dose delivered to the patient. A comparison of IMRT and IMPT dose distributions on a selected CT slice of a nasopharynx case is shown in figure 7.

Concluding remarks

IMRT has made an amazing development from its first conception in the early 1980s to today's widespread clinical application in some countries. While today's clinical implementation of IMRT may be driven in part by economic incentives (Mell *et al* 2005), its original development most certainly was not. It is one example where physicists, supported by mathematicians and computer scientists, have made a major impact on medicine, in this case on the daily clinical practice in radiation oncology. The clinical success of IMRT, which was not the subject of this paper, consists of the reduction of side effects and improved tumour control through dose escalation in certain cancer sites. IMRT continues to be an area of active research and development. Future developments have the potential to lead to further substantial and clinically relevant improvements.

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Disclaimer

In the spirit of this PMB anniversary issue, I wrote the review from a personal perspective, included some personal statements, and emphasized results published in PMB. At the same

time I tried to be as fair and objective as possible. I fear that in this balancing act I may have neglected some important works of colleagues, which was certainly not my intention.

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Biography

Thomas Bortfeld started his career in medical physics at the German Cancer Research Centre and at the University of Heidelberg. Since 1988 he has been instrumental in developing both intensity-modulated radiation therapy (IMRT) treatment planning algorithms and IMRT delivery methods with multileaf collimators. In 2001 Dr Bortfeld accepted a position as the Director of Physics Research in the Department of Radiation Oncology at the Massachusetts General Hospital in Boston, where he is also an Associate Professor at Harvard Medical School. Dr Bortfeld's current research interests include the optimization of IMRT treatments and proton radiation therapy.