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INVERSE PLANNING ALGORITHMS FOR EXTERNAL BEAM RADIATION THERAPY

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Abstract—Intensity-modulated radiation therapy (IMRT) is a new treatment technique that has the potential to produce superior dose distributions to those of conventional techniques. An important step in IMRT is inverse planning, or optimization. This is a process by which the optimum intensity distribution is determined by minimizing (or maximizing) an objective function. For radiation therapy, the objective function is used to describe the clinical goals, which can be expressed in terms of dose and dose/volume requirements, or in terms of biological indices. There are 2 types of search algorithms, stochastic and deterministic. Typical algorithms that are currently in use are presented. For clinical implementations, other issues are also discussed, such as global minimum vs. local minima, dose uniformity in the target and sparing of normal tissues, smoothing of the intensity profile, and skin flash. To illustrate the advantages of IMRT, clinical examples for the treatment of the prostate, nasopharynx, and breast are presented. IMRT is an emerging technique that has shown encouraging results thus far. However, the technique is still in its infancy and more research and improvements are needed. For example, the effects of treatment uncertainties on the planning and delivery of IMRT requires further study. As with any new technology, IMRT should be used with great caution. © 2001 American Association of Medical Dosimetrists.

Key Words: **Intensity-modulated radiation therapy, Optimization, Inverse planning**

INTRODUCTION

Intensity-modulated radiation therapy (IMRT) is a new treatment technique that has the ability to deliver a more conformal dose to the target while providing better protection to the critical organs than conventional 3-dimensional conformal radiation therapy (3DCRT) techniques. In the 3DCRT technique, dose conformation is mainly achieved through the use of beam's-eye view to provide geometrical coverage of the target. Within the field, the intensity distribution is either uniform, as in an open field, or linear, as in a wedged field. In the IMRT technique, the intensity distribution inside the field is nonuniform so as, when combined with other beams, to produce an optimum dose distribution in the patient.

An important step in IMRT is inverse planning, or optimization. This is the process by which the intensity distribution of each beam employed in a plan is determined such that the resultant dose distribution can best meet the criteria specified by the planner. These criteria are typically specified in terms of dose and dose-volume requirements, or biological indices such as tumor control probability (TCP) and normal tissue complication probability (NTCP).

The concept of inverse planning was first suggested by Brahme.[1] Since then, a variety of optimization algorithms have been proposed, based on either dose and dose-volume considerations,[2–9] or on biological indices.[10–13] A number of methods based on dose and dose-volume considerations have already been used to treat a variety of diseases in recent years.[14–20] Methods based on biological indices have not been widely implemented in the clinic, primarily because the radiation-biological models are not well established, although TCP and NTCP values are sometimes calculated for plan evaluation.

The number of rays (or pencil beams) involved in an IMRT plan is typically in the thousands, and the number of points in the targets and critical organs used for optimization is typically in the tens of thousands. The dimensions of each ray depend on the delivery device (such as the multileaf collimator), usually between 0.2 cm to 1 cm along the leaf travel direction, and the leaf width along the leaf width direction. For IMRT to be practical, the computation time required to solve an inverse-planning problem should be within minutes or at most, 30 minutes.

The small size of the ray requires that, in order to obtain accurate dose distributions and beam profiles, a correspondingly fine dose calculation grid be used. Typically, about 30 points/cc are recommended; therefore, the total number of points used is often in the tens of thousands.

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We describe some of the optimization algorithms that are commonly in use at present. We present clinical examples for the treatment of the prostate, nasopharynx, and breast to demonstrate the advantages of IMRT, and also discuss other issues related to the clinical implementation of IMRT.

METHODS

An optimization algorithm can generally be considered to consist of 2 parts: the objective function that encapsulates the clinical objectives of planning and assigns a numerical score to each plan, and a method to minimize (or maximize) the objective function.

The objective function

For dose-based algorithms, the objective function should include the clinical criteria typically used in routine planning. These include: (a) target prescription dose, (b) target dose homogeneity, (c) critical organ maximum dose, and (d) critical organ dose-volume constraints. Dose-volume constraints are generally stated as "no more than q% of the organ may exceed a dose d."

The most commonly used objective function is the quadratic one. In its simplest form it can be written as:

$$F_{obj} = \sum_{i\text{etarget}} (D_i - D_p)^2 + \sum_{i\text{ecritical organ}} (D_i - D_t)^2 \qquad (1)$$

where D_i is the dose to point i, D_p is the target prescription dose, and D_t is the constraint or tolerance dose. The first term includes all the points in the target, and the second term applies to those points in the critical organ with doses greater than D_t. If a dose-volume constraint is imposed, then the second term is further limited to those points that also exceed the volume constraint.

The quadratic form is used primarily for mathematical convenience. It is also reasonable as the objective function increases when the actual dose deviates from the desired dose in the target or exceeds the tolerance in critical organs. However, it should be noted that the quadratic form has no fundamental physical meaning. The objective function can take any other form as long as it is qualitatively consistent with the clinical goals.

The dose to any point D_i can be written in vector form as:

$$D_i = \vec{a}_i \cdot \vec{x} \text{ with } \vec{a}_i = \{a_{ij}\} \text{ and } \vec{x} = \{x_j\},\ j = 1,\ldots,J \qquad (2)$$

where x_j is the intensity or weight of the jth ray, a_{ij} the dose deposited to the ith point from a unit weight of the jth ray, and the dot product is summed over all j. The dose-deposition coefficients a_{ij} depend on the beam energy and on the anatomical geometry between the ray and the point. The quadratic objective function can then be written in terms of the ray weights as:

$$F_{obj} = \sum_{i\text{etarget}} (\vec{a}_i \cdot \vec{x} - D_p)^2 + \sum_{i\text{ecritical organ}} (\vec{a}_i \cdot \vec{x} - D_t)^2 \qquad (3)$$

Simulated annealing

Simulated annealing is a stochastic method that relies, in part, on random sampling. It mimics the way a thermalized system reaches its ground state as the temperature slowly decreases. At each iteration, a small change, either positive or negative and of varying magnitude, is attempted in the ray weights. If the score decreases, then the change is accepted. If the score increases, the change is not automatically rejected, but accepted with a probability of $e^{-\Delta F/kT}$, where ΔF is the change in score, k the Boltzmann's constant, and T the "temperature" at this stage. By accepting changes that actually worsen the dose distribution, the method has the potential to avoid getting trapped in local minima. In the early stages of the optimization, the temperature is relatively high-to provide an opportunity to search the entire solution space. As the process progresses, the temperature slowly drops to reduce the search space. The main advantage of this method is that it is easy to implement and, in principle, it has the ability to escape from local minima. However, it is relatively inefficient compared to deterministic methods.

Iterative method based on dose differences

This is a deterministic method that, at each iteration, updates the solution based on the difference between the dose achieved with the current set of ray weights and the prescription or constraint dose. It is significantly faster than simulated annealing; however, it always proceeds to find the closest minimum and does not have the capability to escape from local minima.

The gradient method is one example of this type of methods. In the simplest implementation of this method, the solution is updated along the gradient of the objective function:

$$\vec{x}^{k+1} = \vec{x}^k + s\vec{G}(\vec{x}^k) \qquad (4)$$

where the superscript k indicates the iteration,

$$\vec{G}(\vec{x}^k) = 2 \sum_{i\text{etarget}} (D_i^k - D_p)\,\vec{a}_i \qquad (5)$$

is the gradient at the k-th iteration and s the size of the step.

Dose and dose-volume constraints to critical organs can be taken into account in a similar manner.

Using the gradient is not the most efficient implementation of this method. For example, if the minimum lies in a long narrow valley, the simple gradient approach will require many small steps to reach the minimum. A more efficient approach is to use the conjugate gradient. The details of this method can be found elsewhere.[8]

Iterative method based on dose ratios

This is also a deterministic method based on the ratio of the current and prescription or constraint doses. It has the same appearance as the maximum likelihood

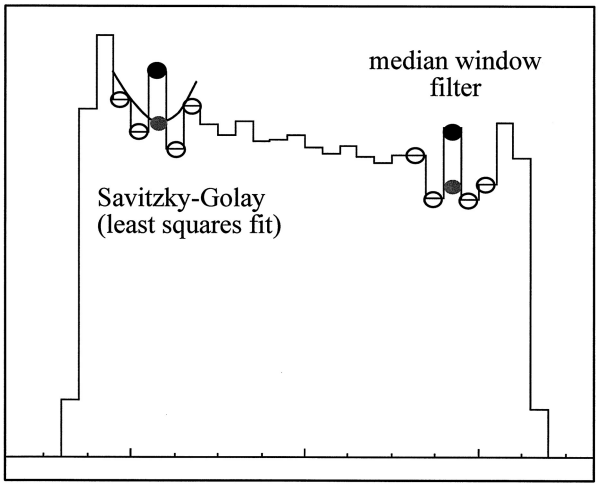

Fig. 1. Smoothing of intensity profile.

method used in nuclear medicine for emission image reconstruction. At the (k+1)th iteration the solution is updated by:

$$x_j^{k+1} = x_j^k \left[\sum_i a_{ij} \frac{D_p}{D_i} \Big/ \sum_i a_{ij} \right] \tag{6}$$

Dose contraints to critical organs can be handled in a similar manner. The details of this method can be found elsewhere.[5]

Other methods

Inverse planning with intensity-modulated beam profiles was preceded by inverse planning with fixed open or wedged beams. In this case, the algorithm would not modulate the intensity within the beam but would determine the optimal weight of each beam. In addition to the methods described above, a number of other methods, such as linear programming and genetic algorithms, were investigated for beam-weight optimization.[21–25] Although the results obtained were promising, the methods were computationally restricted to, at most, a few hundred dose-calculation points. Thus, the applicability of these methods was very limited.

Smoothing of the intensity profile

Regardless of which method is used, the intensity distribution obtained from optimization tends to have local noise (fluctuation) due to numerical artifacts. This noise is undesirable as it increases the delivery time and also makes the delivery more susceptible to treatment uncertainites. Therefore, it is useful to apply smoothing to the intensity distribution. One such method is the "median window filter".[26] This method is illustrated on the right side of the curve shown in Fig. 1. Each point on the intensity profile is evaluated by a set of symmetric points, for example, 2 points each shown as open circles to the left and right of the current point. The value of the current point (shown in solid black) is then changed to the median value (shown in gray) of this set of points. Another method is the "Savitzky-Golay" method, in which a polynomial (typically quadratic) is least-squares fit through these points and the current point is changed to the value on the fitted polynomial. Both of these methods apply the smoothing *after* each iteration. Alternatively, smoothing can be applied *during* each iteration by adding another term in the objective function:

$$F_{obj} = \sum_{i \epsilon \text{target}} (D_i - D_p)^2 + \sum_{i \epsilon \text{critical organ}} (D_i - D_t)^2 + \sum_j (x'_j - x_j)^2 \tag{7}$$

where x_j and x'_j are the ray weights before and after smoothing, respectively. The advantage of this approach is that the intensity profile only gets smoothed where it does not adversely affect the desired dose and therefore sharp gradient can be maintained near the boundary of critical organs.

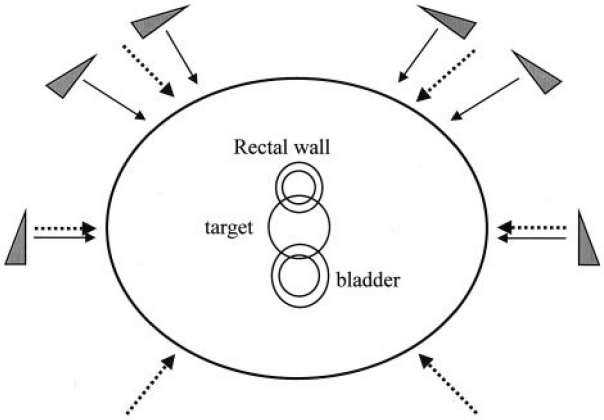

Fig. 2. Conventional conformal plan for prostate treatment.

EXAMPLES

Prostate

The clinical goal for prostate treatment is to deliver a high, uniform dose to the target while keeping the dose to critical organs under a previously established tolerance level. The prescribed dose to the target may be further escalated as long as the protection for critical organs is achieved. Figure 2 shows a conventional conformal plan for the prostate, with the patient in the prone position. In this plan, 72 Gy was first delivered to the target with a set of 6 open fields (shown in dotted lines) followed by a boost of 9 Gy with another set of 6 wedged fields (shown in solid lines) in which the rectum is blocked. The beam arrangement for the IMRT plan is shown in Fig. 3, in which 5 intensity-modulated beams are employed. The isodose distributions for these 2 plans are shown in Fig. 4. The target and the rectum are shown

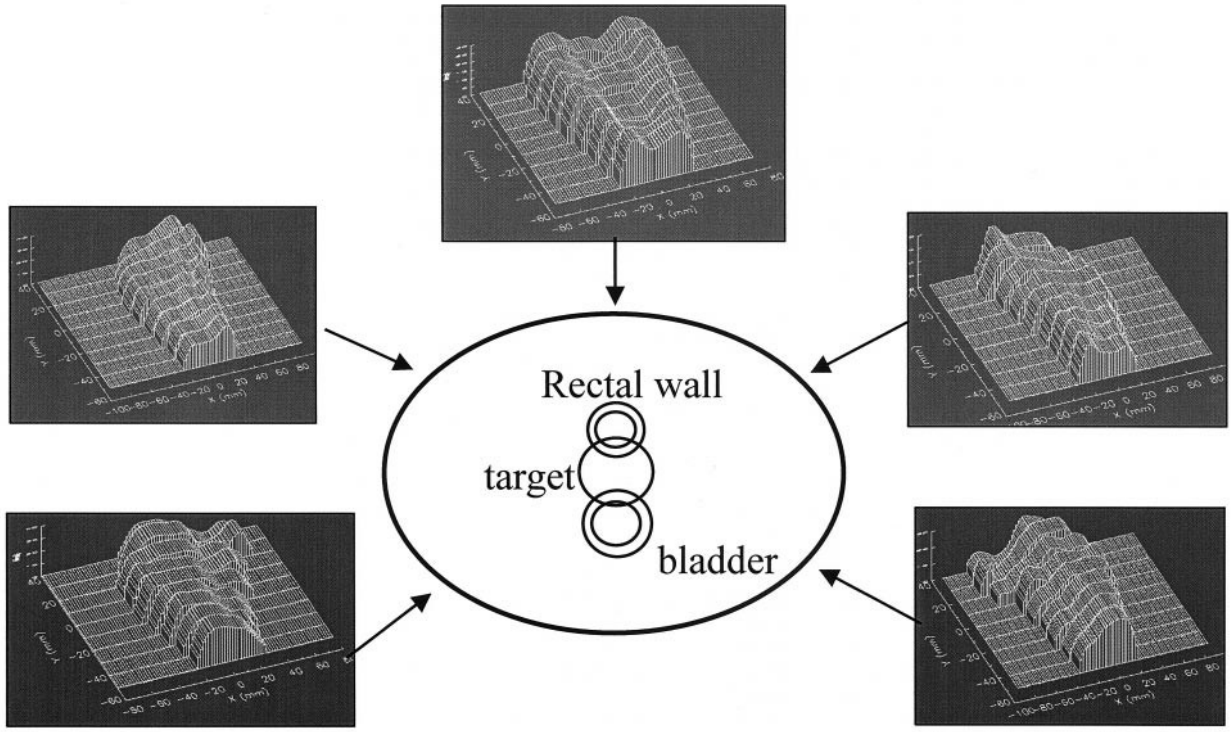

Fig. 3. IMRT plan for prostate.

as dotted lines. It can be seen that the prescribed level, 81 Gy, conforms to the target better for the IMRT plan than for the conventional plan, while avoiding the rectum. Moreover, the hot region (86.4 Gy) is present in the conventional plan but absent in the IMRT plan. This example shows that the IMRT plan can deliver more uniform dose to the prostate while providing the same protection to the rectum as the conventional plan.

Nasopharynx

Nasopharynx tumors, unlike prostate ones, are difficult to treat due to the variability of target shape and size at different body levels and the presence of several dose-limiting critical organs such as the brainstem, spinal cord, parotid glands, eyes, ears, optic chiasm, etc. Consequently, the treatment objectives, such as the target prescription dose, coverage, and dose homogeneity, are determined by the limitations imposed by the critical organs rather than the desired tumorcidal dose.

In this example, both the conventional and the IMRT plans use the same beam arrangement, 7 fields all coming from the posterior direction. The target is to receive 70 Gy, while the critical organs include the brainstem (<45 Gy) and the cord (<40 Gy). The isodose

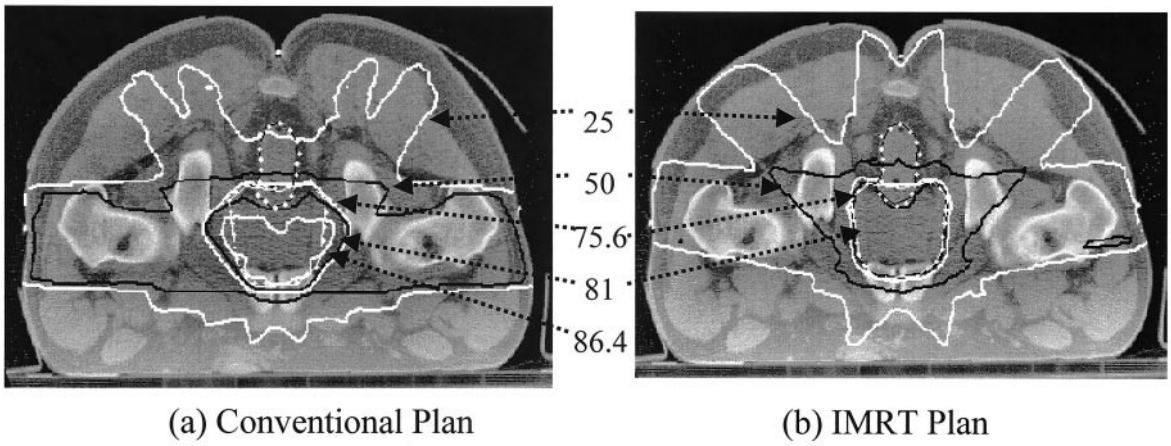

Fig. 4. Isodose distributions for prostate treatment, (a) conventional and (b) IMRT plans.

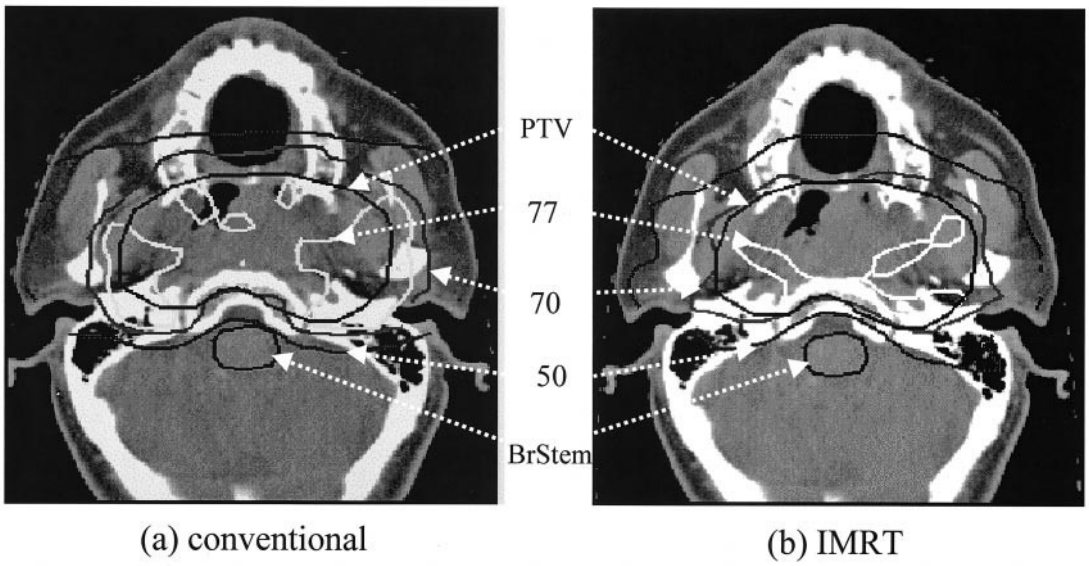

Fig. 5. Isodose distributions for nasopharynx, (a) conventional and (b) IMRT plans.

curves for both plans are displayed in Fig. 5, in which the target and the brainstem are shown as dark lines. The prescribed level, 70 Gy, shown in gray, covers the target for both plans. However, the high dose level, 77 Gy, covers less area for the IMRT plan than that for the conventional plan. Moreover, the 50-Gy level (shown in dark lines) is farther away from the brainstem on the IMRT plan than in the conventional plan, thus providing a better protection.

Breast

The standard treatment technique for breast tumors consists of 2 tangential fields covering the target. The only critical tissue involved is the fraction of the lung close to the breast that is within the field. Consequently, the treatment objective is typically only the dose to the target. Therefore, the optimization problem can be simplified by restricting it to a mid-plane perpendicular to the two opposing beams without including other structures, and simply requesting a uniform dose on that plane. Figure 6 shows the isodose distribution of a conventional plan employing a pair of tangential wedged fields and an IMRT plan using the same beam arrangement. The dose to the target ranges from 100% to 108% for the conventional, compared with 100% to 103% for the IMRT plan. The DVHs for 2 plans are shown in Fig. 7. The IMRT plan delivers a more uniform dose to the target than the conventional plan while providing better protection to the critical organ, the ipsilateral lung. The IMRT technique has a further advantage in that inverse planning is automatically done by the optimization algorithm, while the conventional technique requires the planner to find the best combination of beam weights and wedge angles through a trial-and-error process.

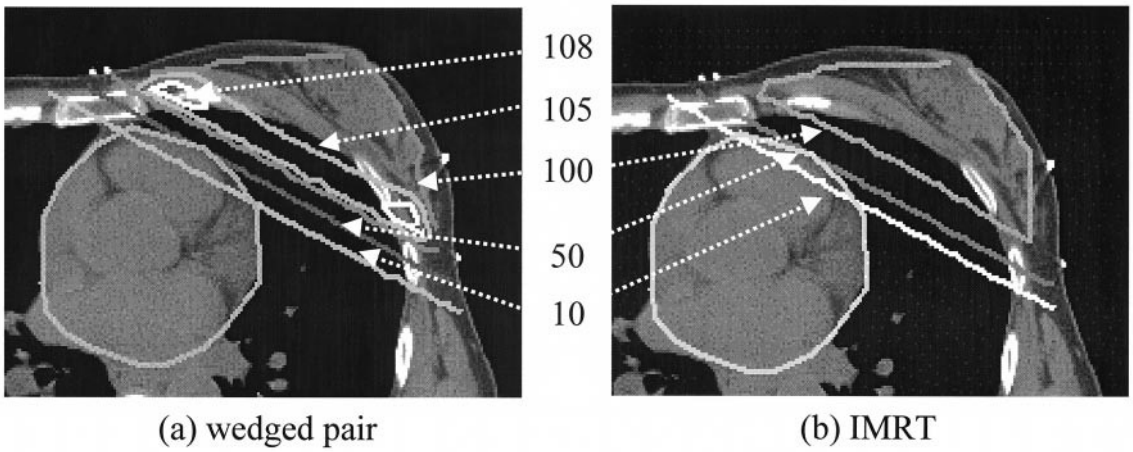

Fig. 6. Isodose distributions of (a) wedged pair and (b) and IMRT treatment of the breast.

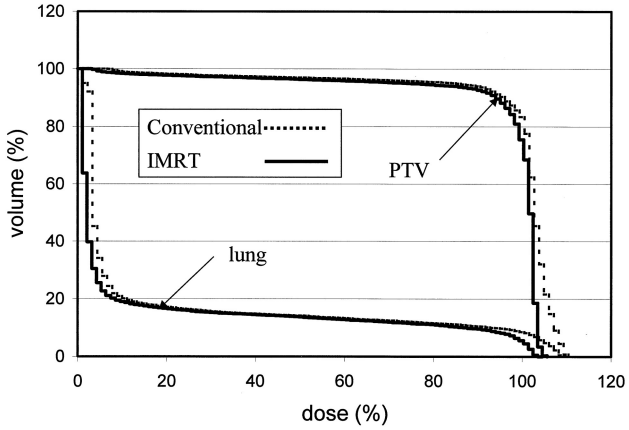

Fig. 7. DVH comparison of a wedged pair and an IMRT treatment of the breast.

OTHER ISSUES

Global vs. local minimum

A frequently asked question in optimization is the possible existence of local minima, and if so, how to find the global minimum among the local ones. We shall use a simple example to show that local minima can, indeed, exist in external beam treatment planning. Figure 8 shows a square phantom containing a square target, represented by points 1 to 5, and a split critical organ, represented by points 6 and 7. For simplicity, only 2 wedged beams are used for this plan. The dose contribution a_{ij} to each point i from a unit weight of each beam j is listed in Table 1. Let us first consider a treatment in which the goal is to deliver a uniform dose of 100 to the target, without any constraints to the critical organ. The objective function for this treatment can be written as:

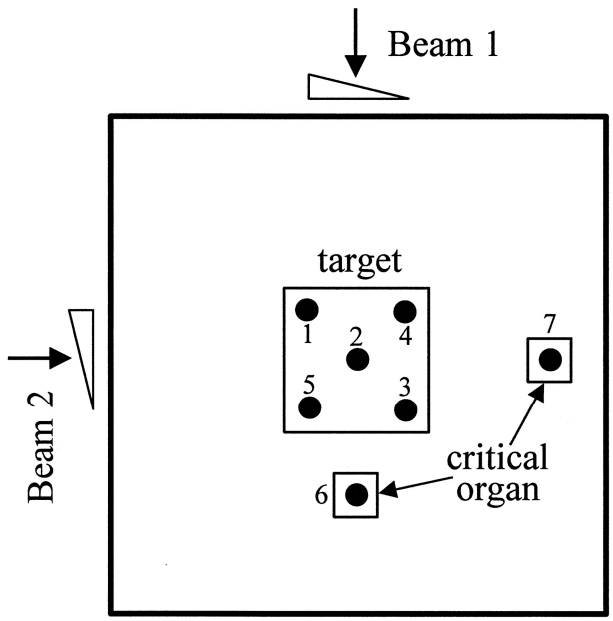

Fig. 8. A square phantom containing a square target; represented by points 1 through 5, and a split critical organ, represented by points 6 and 7.

Table 1. Dose contribution to each point from a unit weight of beam 1 and beam 2

	1	2	3	4	5	6	7
Beam 1	50	50	50	60	40	30	0
Beam 2	50	50	50	40	60	0	20

$$F_{obj} = \sum_{i=1}^{5} (D_i - 100)^2 \quad (8)$$

where $D_i = w_1 a_{i1} + w_2 a_{i2}$, and w_1, w_2 are the weights of beam 1 and beam 2, respectively.

The value of F_{obj} as a function of w_1 and w_2 is shown in Figure 9a as a 2-dimensional (2D) grey-scale display. Clearly, there is only one minimum located at (1,1), that is, equal beam weights, with $F_{obj} = 0$. Now, suppose that a dose-volume constraint is added to the problem, specifying that no more than 1/2 of the critical organ is to exceed the dose of 5, and if it does, a penalty of 50 would be applied. The objective function becomes:

$$F_{obj} = \sum_{i=1}^{5} (D_i - 100)^2 + 50(D' - 5)^2 \quad (9)$$

where the first term represents the target as before, and the second term represents the critical organ if *both* points 6 and 7 receive dose greater than 5. In this case, a penalty of 50 is applied and D' is the minimum of D_6 and D_7. The value of F_{obj} as a function of w_1 and w_2 is now shown in Figure 9b. There exist 2 minima, one at (0.24, 1.5) with $F_{obj} = 1404.5$, a local minimum; and another at (1.5,0.35) with $F_{obj} = 745.7$, the global minimum. This simple example illustrates that local minima can exist in external beam treatment planning. The question then is how to deal with this problem.

As described in the Methods section, there are 2 types of optimization methods: stochastic and deterministic. The theoretical advantage of the former is that it has the ability to escape from a local minimum as a result of random sampling. In practice, however, it is difficult to determine whether a current solution is at a global minimum or a local minimum, regardless of which type of method is used. Therefore, the theoretical advantage of the stochastic methods over the deterministic ones may not be realized in practice. However, this question may not be important in a clinical application. If a solution already meets all requirements specified by the planner, then it is acceptable, although it may not be the best possible solution, that is, at the global minimum.

On the other hand, if the current solution is not adequate, then either (a) no acceptable solution exists, *i.e.*, the clinical requirements cannot be met therefore, they must be relaxed, or (b) an acceptable solution does

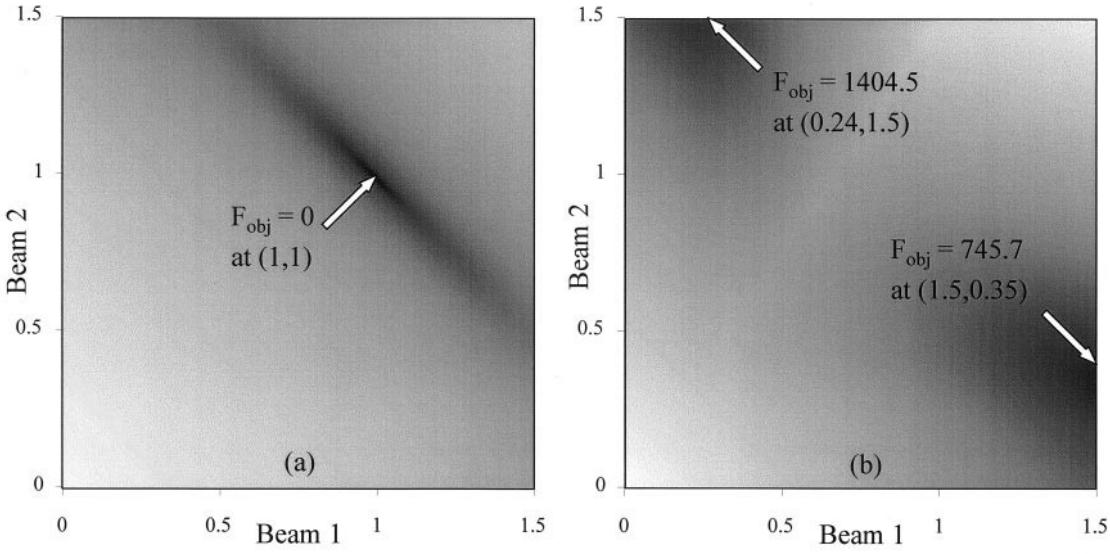

Fig. 9. 2D grey-scale display of the objective function F_{obj} as a function of beam weight 1 and beam weight 2: (a) a single minimum at $(^{1,1})$ with $F_{obj} = 0.0$, (b) a local minimum at (0.24,1.5) with $F_{obj} = 1404.5$ and another local minimum at (1.5,0.35) with $F_{obj} = 745.7$.

exist and may be found with further effort. For the simulated annealing method, for example, more iterations may be needed, perhaps in conjunction with a different annealing scheme. For the deterministic methods, a different initial guess may be used to lead to a different solution.

Dose uniformity in the target

There has been a perception by some that IMRT plans tend to give less uniform dose to the target than conventional plans. Before this issue is addressed, one needs to ask whether this question is clinically important. If it is not important (at least to some physicians for some disease sites), there is no cause for concern. If, however, it is important, then an IMRT plan should, in principle, do no worse than a conventional plan, for the former has more degrees of freedom. In fact, the conventional plan can be seen as a special case of an IMRT plan, where all of the rays are either equal (open beam), or smoothly varying according to the wedge angle (wedged beam).

The improved dose uniformity achieved with IMRT will be illustrated using the example shown in Fig. 10, in

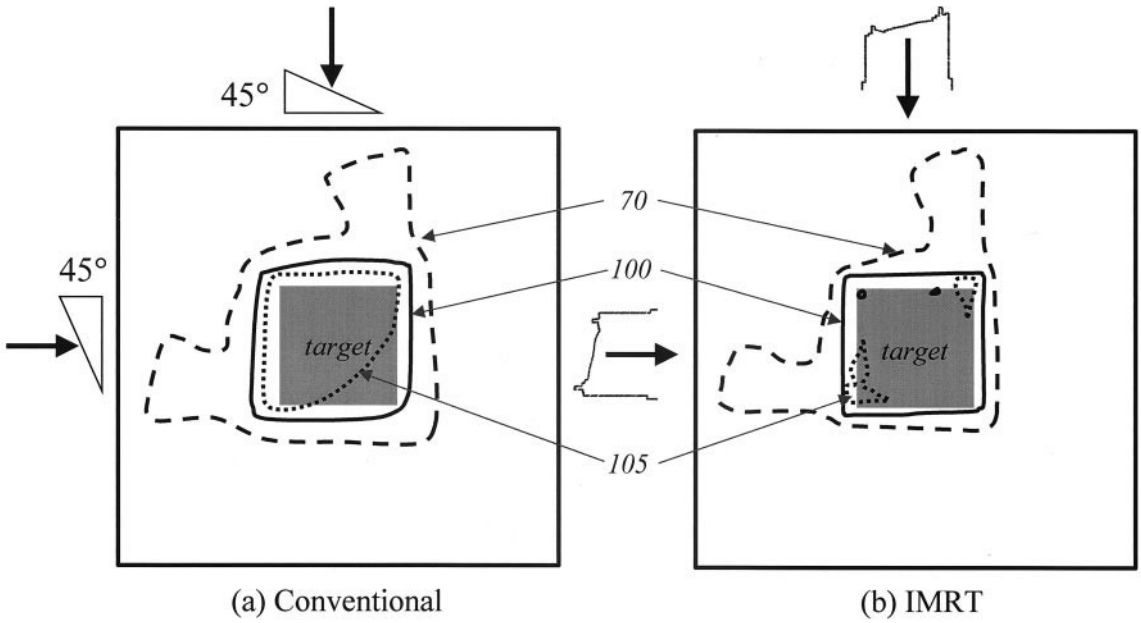

Fig. 10. Isodose distributions of an IMRT plan and a conventional plan for a square target in a square phantom.

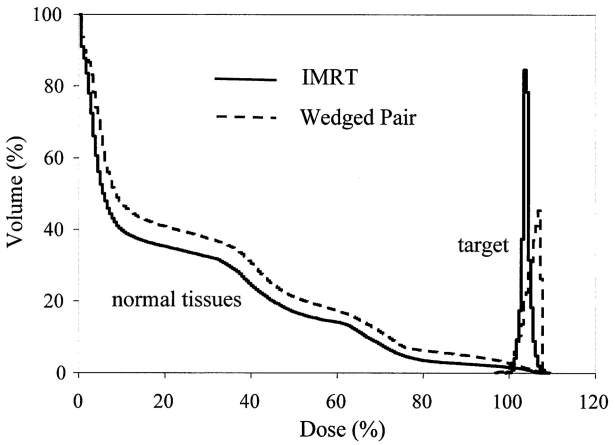

Fig. 11. DVHs of an IMRT plan (solid line) and a conventional plan (dotted line). For clarity, the DVH for the target is shown as differential distribution and the DVH for the normal tissue is shown as cumulative distribution.

which 2 perpendicular beams are used to treat a square target. The conventional plan uses a pair of 45° wedged fields whereas the IMRT plan uses a pair of intensity-modulated fields, with the same beam directions. The prescribed dose, 100% level, is shown in solid lines. A high-dose level (105%) and a low-dose level (70%) are also shown in dotted and dashed lines, respectively. Both plans were normalized so that the target is covered by the 100% level. It can be seen that the IMRT plan has less target volume receiving the 105% level and less normal tissue (the rest of the phantom outside the target) covered by the 70% level than the conventional plan. This comparison is more evidently clear in the dose-volume histograms (DVHs) in Fig. 11, in which the target DVH is shown as differential distribution whereas the normal tissue DVH is shown as cumulative distribution. For the target, the DVH for the IMRT plan (shown in solid lines) has a sharper peak closer to the prescribed dose 100% than the conventional plan (shown in dotted lines), indicating a more homogeneous dose distribution. For the normal tissues, the DVH for the IMRT plan is consistently lower than that for the conventional plan, indicating better sparing. This simple example shows that the IMRT plan can achieve more uniform dose in the target while at the same time providing better protection to normal tissues than the conventional plan.

Optimization based on biological indices

As mentioned in the Introduction section, only dose and dose-volume-based optimization methods are presently in clinical use. The reason biological indices-based methods have not been used is primarily because the models are not well established. For example, current TCP models would predict that a cold spot in the target would seriously degrade the probability of tumor control. In reality, however, the treatment outcome very much depends on the location of the cold spot, *i.e.*, whether it

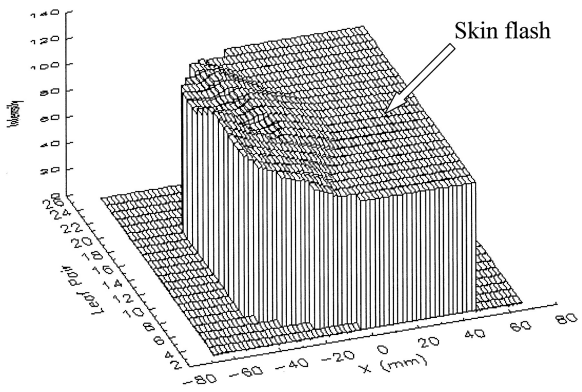

Fig. 12. A medial field used in a breast treatment. A 2-cm skin flash is extended beyond the original edge of the intensity distributions.

is in the periphery or in the middle of the target. This effect is not accounted for in the current TCP models. It is hoped that when more clinical data become available in the future, biological models will be used in the clinic.

Skin flash

Treatment uncertainty is an unavoidable factor that must be taken into account during planning. The standard practice is to include its effects in the delineation of the planning target volume (PTV). However, when the target is sufficiently close to the skin, a "skin-flash" is applied to artificially extend the field edge into the air. This is routinely done for conventional plans of the breast and head/neck regions. For IMRT, however, the intensity distribution as well as the field edge are determined by the optimization process, and therefore no "skin-flash" is automatically included. Ideally, the optimization algorithm should account for treatment uncertainties; however, this is not routinely done. An alternative method is to take the intensity distribution as determined by optimization, and extend the distribution into the air using the intensity level at the skin. One such example is shown in Fig. 12, in which a skin flash is added to the intensity distribution of a medial field used in a breast treatment. The general question of treatment uncertainties has not been adequately addressed in IMRT optimization and should receive more attention.

CONCLUSIONS

IMRT is a new treatment technique that promises to produce superior dose distributions than conventional techniques, in terms of both target coverage and normal tissue sparing. An important step in IMRT is inverse planning, or optimization. This is the process by which the optimum intensity profile of each beam is determined. The goodness of a solution is usually measured by an objective function, which, at present, is dose or dose/volume based. There are 2 types of search algorithms, stochastic and deterministic. The stochastic

methods, in principle, can find the global solution, whereas the deterministic methods may get trapped in a local solution. In practice, however, it is difficult to determine whether a current solution is a global or a local one, regardless of which method is used. For clinical applications, there are other issues that need to be considered, such as smoothing of the intensity profile and skin flash.

The IMRT technique today is still in its infancy, and more research and improvements are needed. For example, the effects of treatment uncertainties on the planning and delivery of IMRT need more attention. Dose response or biological indices-based optimization needs to be established and validated. As with any new technology, IMRT should be used with great caution. Comprehensive quality assurance is essential to ensure accurate and safe delivery of IMRT.

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