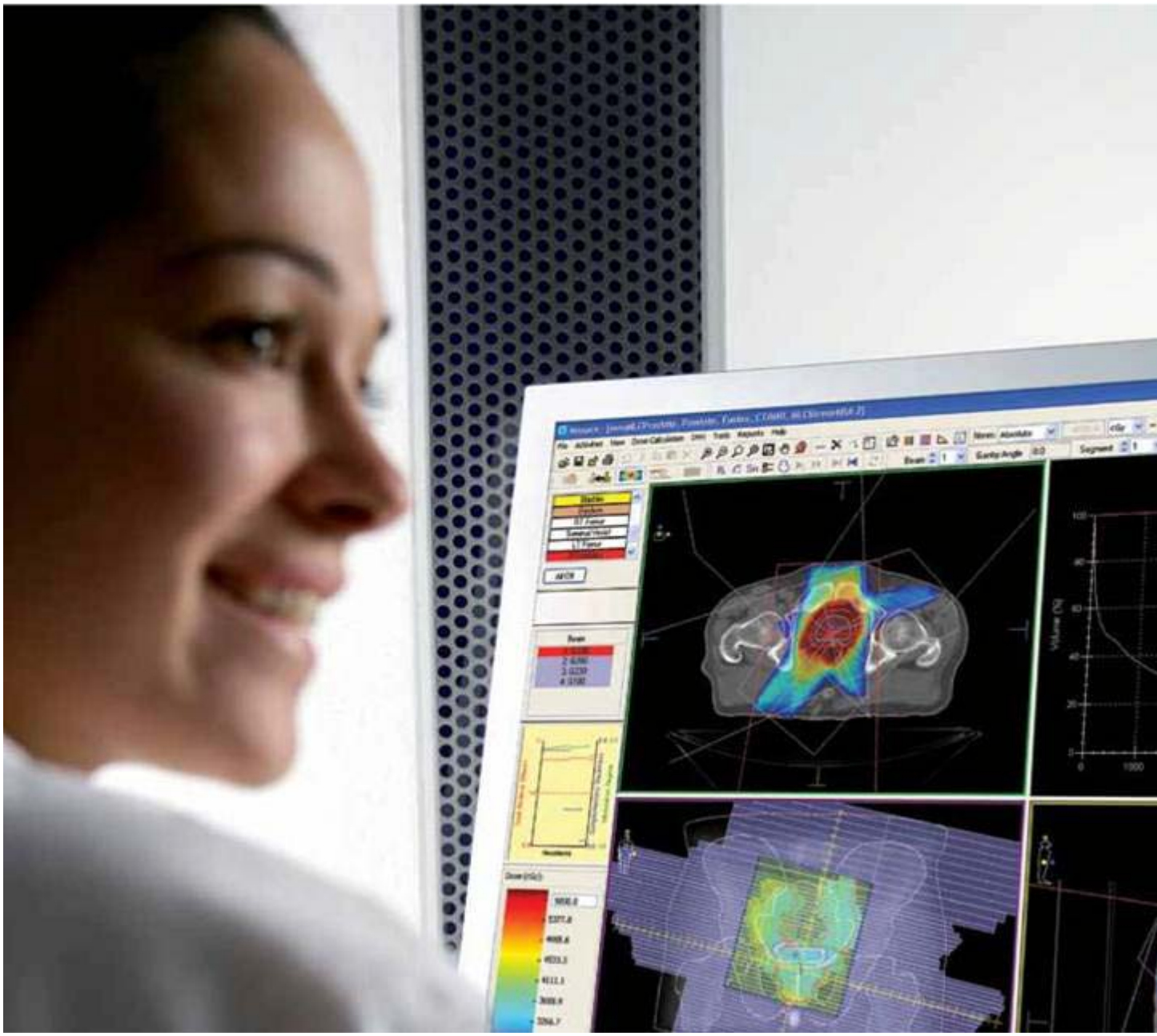
Monaco

Monaco Biological Optimization Technical Reference



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ELEKTA REGIONAL OFFICES

13723 Riverport Drive, Suite 100
Maryland Heights, MO 63043
Sales
Toll Free: +1 800 878 4276
Fax: +1 314 993 0075
Email: sales-na@elekta.com
Customer Support
Phone: +1 800 878 4276
Email: support@elekta.com

Sunnyvale, California
100 Mathilda Place, Fifth Floor
Sunnyvale, CA 94086
Phone: +1 408 830 8000
Fax: +1 408 830 8003
Email: info@elekta.com

Europe, Latin America, Africa and Middle East
Contact Information
Elekta, Inc.
Linac House
Fleming Way, Crawley, West Sussex RH10 9RR
Phone: +44 1293 544 422
Fax: +44 1293 654 321

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Introduction

Dose delivery technology for intensity modulated radiotherapy (IMRT) has made numerical dose optimization a necessity. The price for the new freedom in dose shaping offered by these technologies has to be paid by a loss of transparency of the treatment planning process, the dependence on optimization algorithms and the consequential need to communicate the treatment intentions to a computer[1].

Different formulations of the radiotherapy optimization problem serve the same purpose of expressing the clinical treatment intentions in a concise, numerically expedient, unambiguous and intuitive manner. Hence, it should not come as a surprise that some basic common traits can be identified.

There are two distinct layers of evaluation of a therapeutic dose distribution. Radiotherapy commonly affects both target volumes (TV) and normal tissues (NT).

The individual effects in each NT should be mild. If not, they should be in a justifiable relation to a gain in target effect. Once you quantify effects, you may prioritize them readily when you make decisions. However, for each NT, you must assign a value to a non-homogeneous dose distribution that reflects faithfully the intuitive, implicit rules of clinical experience. Henceforth

- dose evaluation on a per-organ basis with a focus on biological effectiveness shall be termed level one (L1)
- the search for the right balance between a set of TV and NT effects shall be termed level two (L2) evaluations.

Monaco is based on the philosophy that, despite the high degree of non-explicit clinical knowledge and the difficulty to extract solid data from clinical studies, per-organ dose evaluation based on biological effectiveness is best left to the computer and taken out of the hands of the clinician. The dose distribution in a NT volume is a massive amount of data, even if compacted into a dose volume histogram (DVH). Further, it is usually impossible to alter one aspect of a dose distribution without affecting it as a whole, including all other NT and TV. From this inability to control a dose distribution in all its facets, the need for dose-effect models arises. These models serve both as the:

- knobs and levers to steer the dose distribution into a desired direction
- magnifying glasses to raise the awareness for undesirable features in the optimization process.

This document will introduce you to the dose-effect models on which Monaco is based. In addition to these biological cost functions, Monaco also offers an array of physical cost functions, which you can use in combination with the biological cost functions. These will also be presented in this document.

In contrast to L1 dose evaluation, L2 dose evaluation should not, at the time being, be delegated to software. Especially when treatment intentions are mutually exclusive, like sufficient target dose and safe organ sparing, this conflict has to be resolved by the clinician, either in the direction of a safe, less promising or a more risky, aggressive treatment. The best support the computer can give in the frequent case of conflicts like this is to provide for easy navigation of the solution space, exploration of alternative

solutions or offer navigation aids[2,3,4,5,6,7]. The sensitivity tool in Monaco is such a navigation tool and the mathematics behind this tool will also be explained in this document.

Intensity modulated radiotherapy requires higher accuracy of dose computation than conventional radiation therapy. In Monaco the dose optimization for IMRT starts from decomposition of the radiation field into small fluence elements called beamlets and requires the precomputation and storage of the beamlet dose distributions. The weights of individual beamlets are optimized by an iterative algorithm to meet the prescription requirements. The consequence of this scheme is that the actual positions of the collimators are not known during the dose calculation of the beamlets. Therefore the optimized dose is recomputed in Monaco with a dose computation algorithm that includes the MLC model. This concept imposes two main requirements for the dose pre-computation algorithm: (1) speed, due to computation of a large number of beamlet dose distributions and (2) precision, to ensure fast convergence and close proximity between optimized and the final re-computed dose. A fast finite size pencil beam (fsPB) algorithm was developed for Monaco, specifically designed for the purpose of dose pre-computation in IMRT. The algorithm employs an analytical function (fsPB kernel) to describe the cross-profiles of the beamlets. The parameters of the fsPB kernel are determined from broad beam dose distributions computed with the XVMC Monte Carlo code by means of a fitting procedure. To facilitate lateral and longitudinal density corrections the dependencies of those parameters on the density are derived and used to adapt the fsPBK to the given density distribution e.g. in the patient. This pencil beam algorithm is described in the Monaco Dose Calculation Technical Reference. Final dose distributions are calculated with the fast XVMC Monte Carlo algorithm, which is also described in the Monaco Dose Calculation Technical Reference (LRMMON0001).

By reading this technical reference, you will familiarize yourself with important general concepts and specific features of Monaco IMRT. Exact numerical values and numerical limits are rarely mentioned in this document, in favor of general concepts. Information about implementation-specific parameters and the general use of Monaco IMRT can be found in the Monaco Online Help and the "IMRT Training Guide". In addition, you may want to read Ezell *et al,* 2003, whose purpose is "to guide and assist the clinical medical physicist in developing and implementing a viable and safe IMRT program. This report, while not prescribing specific procedures, provides the framework and guidance to allow clinical radiation oncology physicists to make judicious decisions in implementing a safe and efficient IMRT program in their clinics." A recent AAPM task group report TG-166 which pertains to the use of biological models for TPS is another good source of information.[8]

More Sources of Information

Refer to the sources that follow for more information:

- Monaco Online Help
- Monaco Training Guide
- LRMMON0001 Monaco Dose Calculation Technical Reference

Definitions

TV	**target volumes**
NT	**normal tissues**

L1	**dose evaluation with focus on biological effectiveness**
L2	**dose evaluation based on the balance between target and normal tissue**
EUD	**Equivalent Uniform Dose**
IMRT	**Intensity Modulated Radiotherapy**
NTCP	**normal tissue complication probability**
gEUD	**generalized equivalent uniform dose**

Overview

Optimization – Basic Concepts

This chapter is an introduction to optimization concepts and the optimization algorithm in Monaco. As a general rule, the target dose distribution in Monaco is obtained from a minimization of the objective function under a number of hard constraints expressing normal tissue sparing and target dose homogeneity. The sensitivity tool in Monaco relates dosimetric restrictions in normal structures and target volumes to their impact on the target dose distribution in a quantitative manner.

The Optimization Algorithm and Sensitivity Tool

Monaco uses a constraint optimization method[9]. This method requires that all treatment goals concerning normal tissues and the homogeneity of the target dose distribution are expressed by a constraint function and are limited by a constraint boundary. No weight factors need to be specified. If the objective function and constraints are modeled as doses, e.g. equivalent uniform dose (EUD)[10,11,12], mean dose or standard deviation of the target dose, the optimization problem can be expressed as 'maximize the EUD to the target (in Gy) while keeping the constraints at or below their boundaries (in Gy)'.

The exact mathematic optimization method in Monaco is described in great detail in Reference [13]. Here we just want to lay down the framework of the constrained optimization method in Monaco briefly.

Assume that all mandatory treatment goals are expressed by a constraint function $g_i(D), i = 1,...,m$, which assigns a number to a given dose distribution $D(\vec{x})$. This dose distribution is obtained from a modulated fluence weight distribution as:

$$D = \sum_{j=1}^{n} T_j \phi_j \qquad \textit{Equation 1}$$

where

T_j - dose distribution of fluence element *j*

ϕ_j - weight of this fluence element in the total fluence distribution

Let the constant $c_i, i = 1,...,m$, denoted as constraint boundary, be the acceptable maximum level of the respective constraint functions. For the sake of simplicity, assume that there is only one objective function $f(D)$ which expresses the goal of achieving the required target dose. Then, the problem is posed as:

minimize with respect to ϕ

$$f(D) \qquad \textit{Equation 2}$$

such that

$$g_i(D) \le c_i \qquad \textit{Equation 3}$$

Let the solution of this problem be denoted as ϕ^* and the objective function value at the optimum by

$$f^* = f\left(D\left(\phi^*\right)\right)$$ ***Equation 4***

Clearly, the optimum fluence weight profile and dose distribution are functions of the constraint boundaries c_i. The fundamental conflict between the objective of target coverage and the normal tissue constraints is expressed by the function $f^*\left(c_i\right)$. In order to assess the impact of constraints on the target objective and to make decisions regarding the treatment strategy, it is necessary to know how f^* changes with any given c_i, in other words $\partial f^* / \partial c_i$. In Reference 14 and 15, the solution is outlined in more detail. To solve for the constrained problem Equation 2 and Equation 4, an equivalent unconstrained problem is introduced by minimizing with respect to ϕ and using the Lagrange function *L*:

$$L(D,\lambda) = f(D) + \sum_{i=1}^{m} \lambda_i (g_i - c_i)$$ ***Equation 5***

for a suitable set of Lagrange multipliers $\lambda_i, i = 1,...,m$. A pair (ϕ, λ) has to satisfy the following conditions to be a solution to the original constrained problem of Equation 2 and Equation 4:

$$\nabla_\phi L\left(\phi^*, \lambda^*\right) = 0$$ ***Equation 6***

$$g_i\left(\phi^*\right) \le c_i$$ ***Equation 7***

$$\lambda_i^* \ge 0$$ ***Equation 8***

which are known as the Karush–Kuhn–Tucker conditions. The difficulty here is to determine the (unique) set of multipliers λ^* that delivers a solution to Equation 2 and Equation 3. Without going into algorithmic details of finding $\left(\phi^*, \lambda^*\right)$ we just want to assume here some algorithm produces the solution[4]. Combining equations Equation 5 and Equation 6 we find

$$0 = \nabla_\phi f^* + \sum_{i=1}^{m} \lambda_i^* \nabla_\phi g_i$$ ***Equation 9***

The interpretation of this equation implies that at the optimum, the Lagrange multipliers are used to balance the gradients of the constraints and the objective function. In the absence of active constraints, $\nabla_\phi f\left(\phi^*\right) = 0$ is a necessary condition for a minimum, whereas active constraints may counteract such a solution. In this case, the residual gradient of the objective cannot have a component that is tangential to the constraint surfaces $g_i = c_i$, because a change of ϕ in this direction would reduce f^* and leave g_i constant. Hence, if active constraints are present at the solution ϕ^*, it must be possible to express the residual gradient of *f* as a linear combination of the normal vectors of the constraint surfaces. If a constraint has a great impact on the objective, the product of multiplier and gradient must be comparatively large and thus have a large sensitivity as expressed in the sensitivity table during Monaco optimization. Conversely, if it does not influence the solution, its corresponding multiplier is zero which is also reflected in the sensitivity table. A slight perturbation of c_i leads to a change of f^* in the

direction of $\frac{\nabla g_i}{\|\nabla g_i\|}$ by an amount of $\|\lambda_i \nabla g_i\|$. With this consideration and Equation 9, the following relation can be motivated:

$$\frac{\partial f^*}{\partial c_i} = -\lambda_i \qquad \textit{Equation 10}$$

The proof can be found in Reference14 and Reference 15. A straightforward but only approximate extension can be made for multiple objectives $f = \sum_k f_k$

$$\frac{\partial f_k^*}{\partial c_i} = -\frac{\nabla f_k^* \nabla g_i}{\nabla f^* \nabla g_i} \lambda_i \qquad \textit{Equation 11}$$

which modifies the right-hand side of Equation 10 by the projection of the sub-gradient ∇f_k^* onto the gradient of the constraint. Equation 11 directly defines the sensitivity information provided for the user in Monaco. The sensitivity is provided in the form "Raising this constraint by x cGy changes the isoeffect to "Target EUD x" by y cGy".

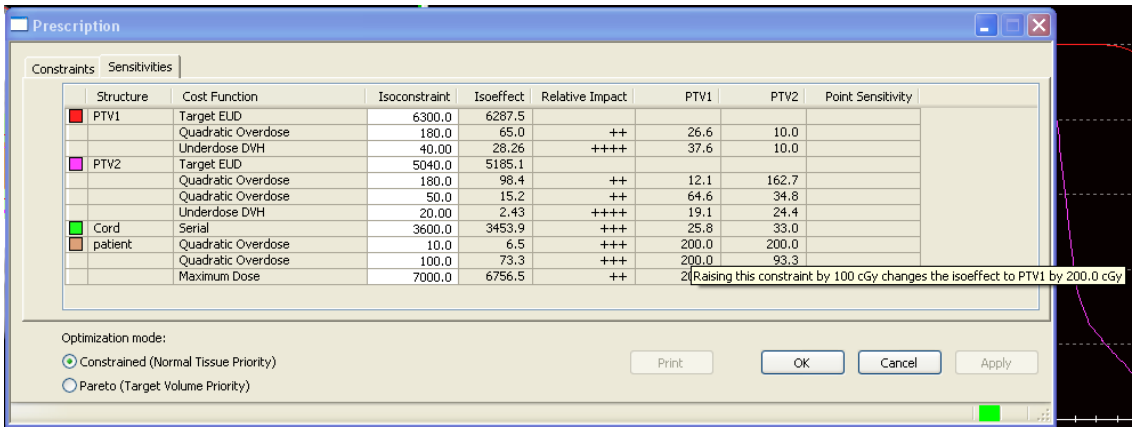

Figure 1: The sensitivity window in Monaco - Conflicts between constraints and goals become numeric quantities.

Naturally, as the sensitivity tool in Monaco offers differential information, the range of this prediction is limited. The sensitivity analysis is of great value if multiple objectives and constraints are defined simultaneously, which is often the case in head and neck treatments. In this situation, it can be quite difficult to guess the compromise the algorithm had to find to arrive at the solution of the problem as both multiple target dose constraints and normal tissue constraints can cause an underdosage in some target volume. Adjusting constraints in case the target dose does not meet the expectation can be very cumbersome if no additional information is provided. The sensitivity analysis can help avoid fruitless trial and error by highlighting the constraints which have the greatest impact. Especially in cases of multiple target volumes with different dose prescriptions, there can be significant cross-talk between target dose constraints.

Cost Functions

As mentioned in the overview, Monaco allows biological dose-effect based optimizations. In addition to biological cost functions, Monaco also offers an array of physical cost functions, which can be used in combination with the biological cost functions.[16]

The concept of biological optimization and local dose-effect measures

As already discussed earlier, for dose optimization, high- and low-dose volumes in the same normal tissue or target volume need to be balanced (L1), and the total effects of various NT and TV need to be weighted against each other (L2). In other words, there have to be mathematical functions that assess the meaning of dose in a sub-volume relative to the total volume of one organ, and other functions that poise the total effect of the dose distribution in one organ against the others, including the targets.

It has been suggested to express the total effect in a TV (NT), denoted as F (G), by summing over all volume elements belonging to the volume in question[10,12].

$$F = \frac{1}{N}\sum_{i=1}^{N} f(D_i) \qquad \textit{Equation 12}$$

$$G = \frac{1}{N}\sum_{i=1}^{N} g(D_i) \qquad \textit{Equation 13}$$

where D_i is the dose to volume element i and $f(D)$ and $g(D)$ are local effect densities for a TV or NT respectively. By convention, $f, g \geq 0$, and the smaller the value the more preferable. Per this definition, the integral effect of a dose distribution in an organ is the sum of the independent effects in all sub-volumes. If the dose in one sub-volume changes, the effect densities in its neighborhood are unaffected. This assumption of locality allows for very fast dose evaluations- and optimization algorithms and makes the effect density practically independent of the voxel size of the chosen patient model.

Having obtained the total effects of n target volumes and m normal tissues, a particular dose distribution can be quantified by the vector

$$(F_1,...,F_n,G_1,...,G_m) \in [0,\infty[^{n+m} \qquad \textit{Equation 14}$$

Clearly, it is not possible to minimize all of these effects simultaneously or else the problem would have the trivial solution $(F_1,...,F_n,G_1,...,G_m) = 0$. Obviously, some combinations of effects cannot be obtained from physical dose distributions. This reflects the practical experience that improving the dose distribution in one volume usually makes it worse in others. The physics of dose deposition introduce a boundary in the solution space that separates feasible from unphysical dose distributions. The optimum solution for a given patient, expressed in its particular combination of achievable F and G values, has to be found on this boundary. Since greater values of F or G mean worse dose distribution properties, any dose distribution whose total effect values lie above the boundary are not optimum, while physical dose distributions cannot lie below.

In order to arrive at a point on this boundary manifold, the standard approach is to identify the effect functions F and G as *cost functions* of an optimization problem, and combine them to a Lagrange function L by virtue of

$$L = \sum_{i=1}^{n} \lambda_i F_i + \sum_{i=n+1}^{n+m} \lambda_i G_{i-n} \qquad \textit{Equation 15}$$

with Lagrange multipliers $\lambda_i \in [0,1], \sum_{i=1}^{n+m} \lambda_i = 1$. By convention, the optimum dose is obtained by minimizing L as discussed earlier in this document. By varying the values of $(\lambda_i)_{1..n+m}$, any possible combination of total effects can be obtained. Recently, the terminology of Pareto optimality attracted attention in this context. The aforementioned boundary is identical to the Pareto frontier P and can be obtained in this framework as a manifold in the $n+m$ dimensional solution space parametrized by $(\lambda_i)_{1..n+m}$

$$P(F,G) = (F_1,...,F_n,G_1,...,G_m)(\lambda_1,...,\lambda_{n+m}) \qquad \textit{Equation 16}$$

Once a solution is found for a particular set of Lagrange multipliers, these may be altered incrementally to navigate on the Pareto frontier to other, more preferable solutions with a different balance of NT and TV effects.

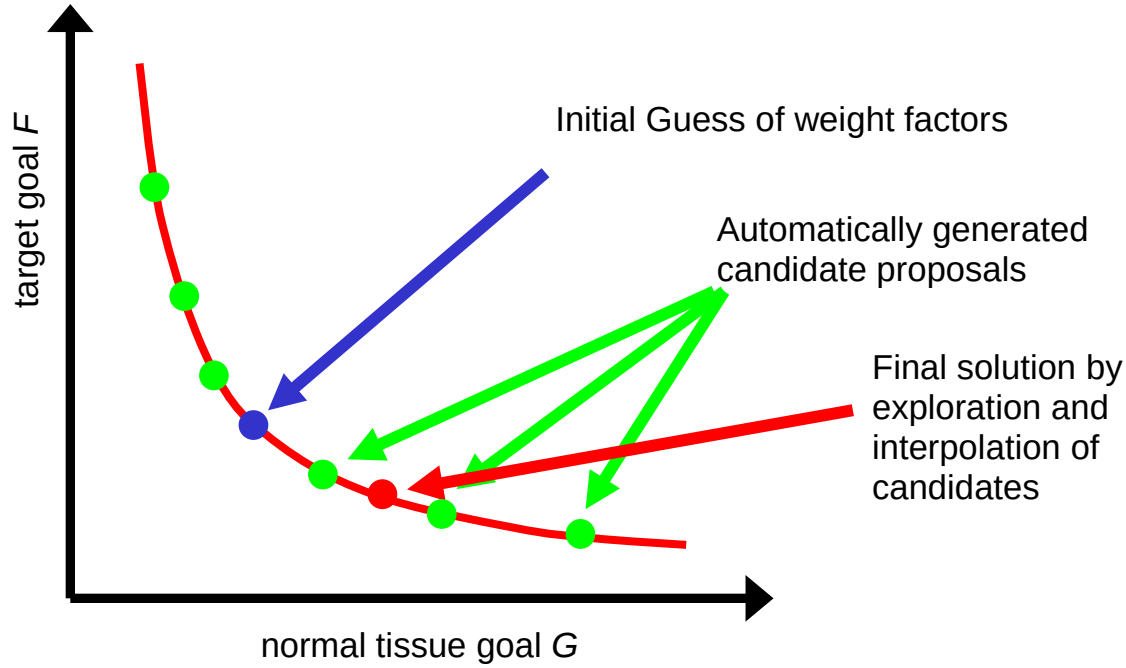

Figure 2: Navigating the solution space as Monaco offers a library of proposals shown in green with the final solution in red. Manually chosen weight factors make the solution space also accessible, but are not well suited for exploring it during the search for the best balance between goals.

The volume effect and equivalent uniform dose

Although the form of Equation 12 and Equation 13 can be motivated by a mean-field approximation of non-local biological effects, the true benefit of this formalism lies in the transparent and effective way by which these effect functions offer control over the shape of the dose-volume histogram of a NT volume. Starting from the notion that the local effect densities g reflect the damage wrought in a volume element of some normal tissue by the applied dose, it is clear that g is a continuous, monotonically increasing function to dose. It is also obvious that g is bounded from above as the maximum damage in a tissue is

limited by its total obliteration. So in general, *g* is of sigmoidal shape. However, this upper bound to the NT effect may not become apparent in clinical dose regions.

The salient feature of *g* is the representation of the typical volume effects of a normal tissue dose response, i. e. its deviation from a step function (no volume effect). The volume effect details how much tissue volume has to be spared in order to gain some added tolerance in a high-dose sub-volume. With a small volume effect, the return on volume sparing is low. The ideal DVH in this case is a steep drop at the tolerance dose.

This kind of behavior is usually preferred for organs showing a serial, chain-like complication mechanism: just as the chain breaks when one link gives way, the complication occurs if a small sub-volume of the organ is destroyed. In contrast, with a large volume effect small volumes may receive very high doses if at the same time large volumes are effectively spared. The ideal DVH in this case shows a steep drop at low to intermediate doses, and levels off to a shallow tail towards high doses. This is often associated with a parallel, rope-like complication mechanism: a fraction of the strands may tear, yet the rope may still hold.

In mathematical terms, the volume effect answers the question: if the homogeneous irradiation of a fractional volume *v* with a dose *D* results in a certain level of toxicity, how does a change of fractional volume *dv* alter the dose *dD*? This is captured in the function $Q(v,D)\rangle\rangle 0$ in the following equation

$$dv = -Q(v,D)dD \qquad \textbf{Equation 17}$$

It is easy to see, for *G*=const., that

$$Q = \frac{vg'}{g} \qquad \textbf{Equation 18}$$

in the local effect formalism. By virtue of this relationship, it is straight-forward to construct an efficient cost function of optimization from normal tissue complication probability (NTCP) models. At the core of any relevant NTCP model lays a representation of the volume effect, which can be laid bare by eq. 6. The particular choice of $g(D) = D^k, k \geq 1$ leads to the generalized equivalent dose model (gEUD), which is the core of the well established Lyman-Kutcher-Burman model. Under the above conditions on *g*, it is always possible to form

$$EUD = g^{-1}(G) \qquad \textbf{Equation 19}$$

The EUD represents the dose that causes the same effect if applied homogeneously to the entire organ volume. The advantage of expressing the effect in terms of a dose is that the numerical value becomes more meaningful, and can be related to clinical experience.

It has been shown that the gEUD – power law model provides a good approximation to the observable volume effect of serial complications, where the volume effect is small. For optimization algorithm purposes, it provides the additional benefit that it is dose-scale invariant. However, it appears as if the power law arises only as an approximation to a more fundamental dose-response in the limit of low doses/low complication rates. The serial reconstruction unit (sRU) model suggests an exponential local effect density $g = \exp(\sigma D)$, with σ being typically in the range of $\approx 0.15 Gy^{-1}$.

It may appear as a contradiction to the previous statement about the boundedness of *g* that both presented effect densities tend to ∞ with dose. This is a consequence of the fact that for most serial complications, the point of inflexion of the sigmoid is well above the clinical dose range so that these functions still

provide a faithful approximation for the convex branch of the sigmoidal dose response. If clinical doses reach the saturation level of the effect density, this means that a partial obliteration of the tissue is acceptable. Hence, the clinical endpoint is not tied to the integrity of the entire organ as in serial complications, but rather to the integrity of a critical subvolume of the organ. Requiring the entire sigmoidal shape of the local effect density is the hallmark of parallel complication mechanisms. Thus, the full sigmoidal dose effect needs to be described. For the gEUD model, this extension to the full range results in

$$g = 1/\left(1 + (D_0/D)^k\right)(pEUD) \qquad \textit{Equation 20}$$

the reconstruction unit model yields

$$g = 1/\left(1 + \exp\left(-\sigma(D - D_0)\right)\right)(pRU) \qquad \textit{Equation 21}$$

The reference dose parameter D_0 marks the point of inflexion.

Serial complication mechanisms

For typical parameters, e. g. $k = 12$, $\sigma = 0.15$, the gEUD and sRU models show a steeply increasing, strongly curved local effect density, and an associated small volume effect. For example, a dose increase by 10 per cent necessitates a reduction of irradiated volume by a factor 0.3. This strongly non-linear behavior has two consequences. Firstly, the total effect will always be dominated by the volume elements receiving the highest doses.

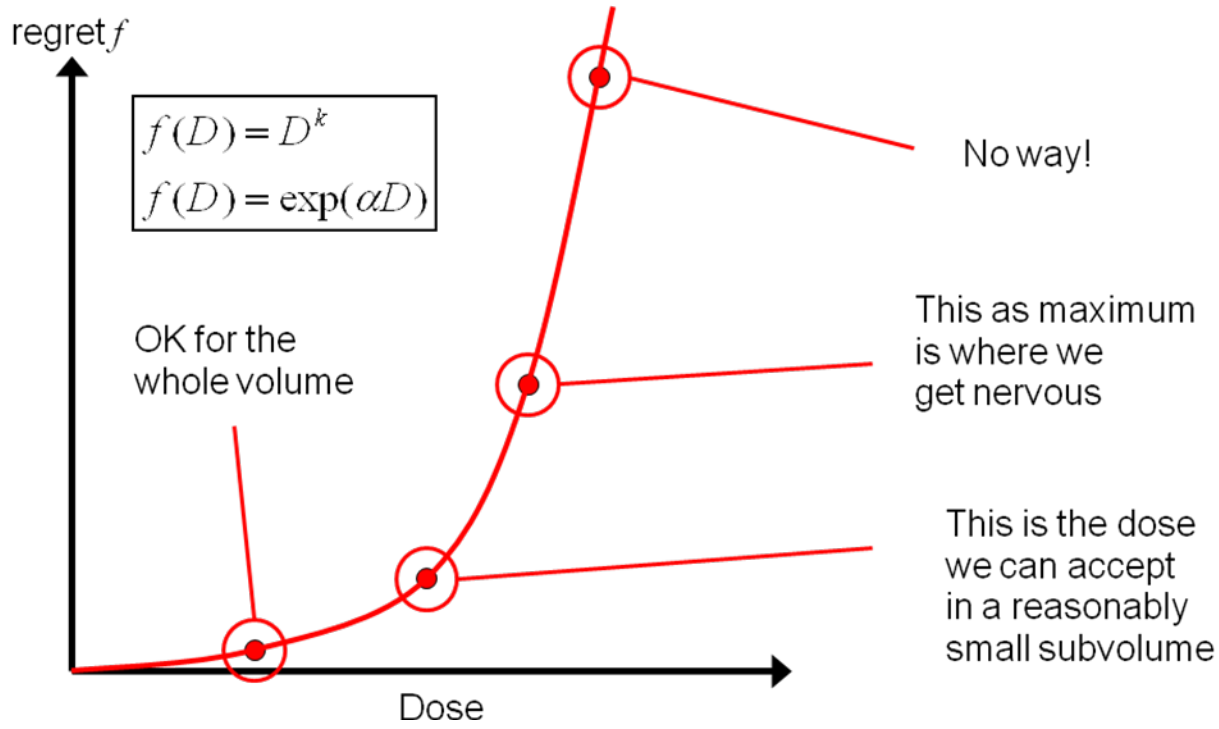

Figure 3: Biological cost function for serial organs.

This effect is so strong that volume elements with less than 80 per cent of the maximum dose in this organ contribute virtually nothing to the total effect. Secondly, the cost of increasing the dose to an already hot sub-volume rises tremendously. Since by virtue of Equation 15 all effects are connected, this rise has to be compensated by a drop in one of the effect functions of other NT, or more likely, a target volume. This ensures that both the risk is spread equally among NT, and that cold spots in a TV are tightly coupled to hot spots in a NT. In consequence, these low-volume-effect cost functions act strictly dose limiting by themselves, which makes the adjustment of the associated Lagrange multiplier less critical. As a corollary, the power-law dependence of the total effect on basically the maximum dose may even serve as a guide to adjust the magnitude of Lagrange multipliers should the total effect of this NT be too high.

This discussion already emphasizes the aspect of controlling the shape of the DVH by the choice of local effect density. The dose distribution of each NT and TV is partly a consequence of the chosen local effect density and the interplay of different NT and TV, mediated by patient geometry and the physics of dose deposition. Total control of the dose distribution in one volume usually means loss of control in all other volumes. Hence, it is important to realize which aspects of a dose distribution are controlled by a particular effect density function, and to which aspects this function is blind. During dose optimization, each cost function will reward a redistribution of dose such that the total effect is diminished. Hence, it is illustrative to look at the drop of local effect density per dose level, dg/dD. In Figure 4 the length of the arrows corresponds to the derivative of the local effect density with respect to dose, signifying the reduction of total effect if this dose bin in the DVH was reduced. In other words, the length of arrows shows the level of control which is exercised by this effect density over the dose distribution. Increasing the value of k or σ will shift the importance further towards high doses, decreasing it will distribute it more evenly as shown in Figure 4. In general, serial-type cost functions are not very powerful to control the mid- and low-dose range. In the gEUD formalism, the lowest value for the exponent $k = 1$, resulting in the evaluation of the mean dose. Here, all dose bins are controlled with equal power. If the low–dose and mid-dose regions do need to be controlled, the complication mechanism is usually parallel.

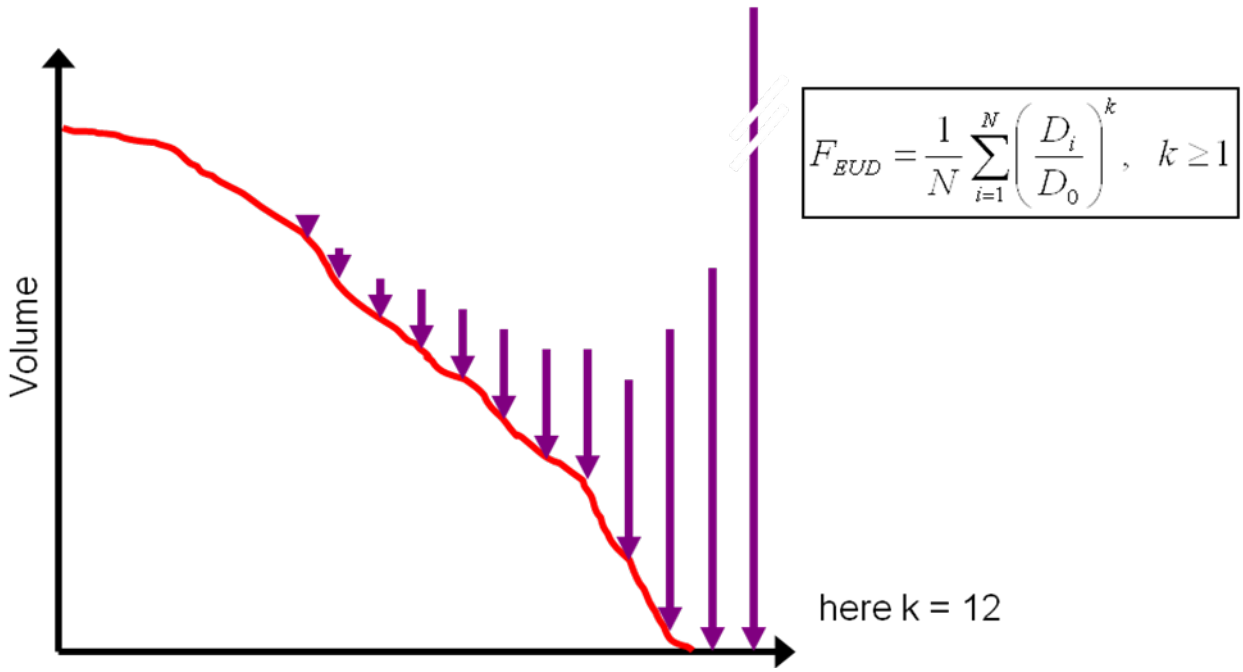

Figure 4: How the serial complication model controls the DVH.

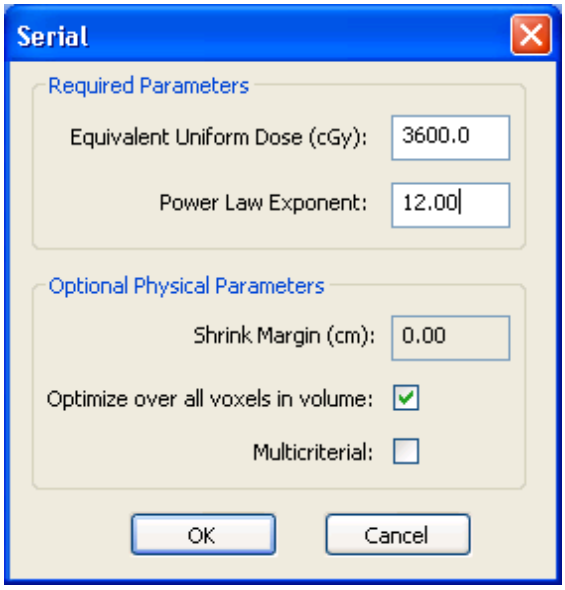

Figure 5: Serial model parameters in Monaco. The power law exponent k and the EUD value tolerated for the organ are the only two parameters needed to control the entire DVH.

Parallel complication mechanisms

Applying the same reasoning to the full sigmoidal local effect density for a parallel complication mechanism, the derivative dg/dD is peaked around the point of inflexion D_0 as shown in Figure 6.

The corresponding weight control arrows in a typical DVH is shown in Figure 7. It becomes apparent that this effect density type acts like a watershed. As the gain of reducing the dose volume elements close to D_0 is greatest, the dose is redistributed towards the extremes, where dose does not mean much harm yet or cannot cause any more damage than already wrought. In consequence, this type of effect density acts as a fuzzy dose-volume constraint for parallel complications. Typical examples are lung, liver, kidney and parotids, where the organ function can be maintained by a sufficiently large critical volume while the remaining volume is sacrificed. Notice, that if g is normalized such that $g = 1$ as $D \to \infty$, the total effect corresponds to the integral loss of function in this organ. It is more meaningful to refer to the total effect in this case rather than the EUD, as parallel responding organs are rarely irradiated with a homogeneous dose so that clinical experience pertains to partial irradiations. The fact that the total effect of such a cost function can be interpreted as the fraction of the functional volume that is obliterated highlights the similarity to dose-volume constraints.

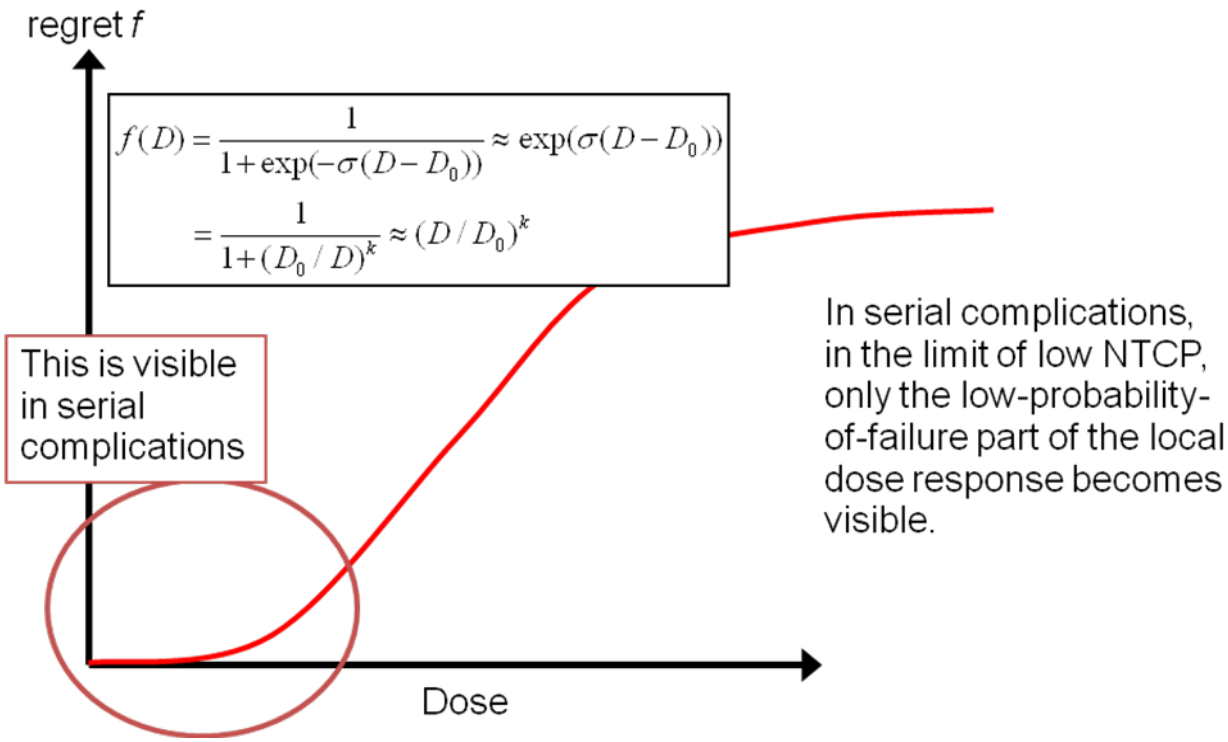

Figure 6: Biological cost function for parallel organs and how parallel and serial complications are related.

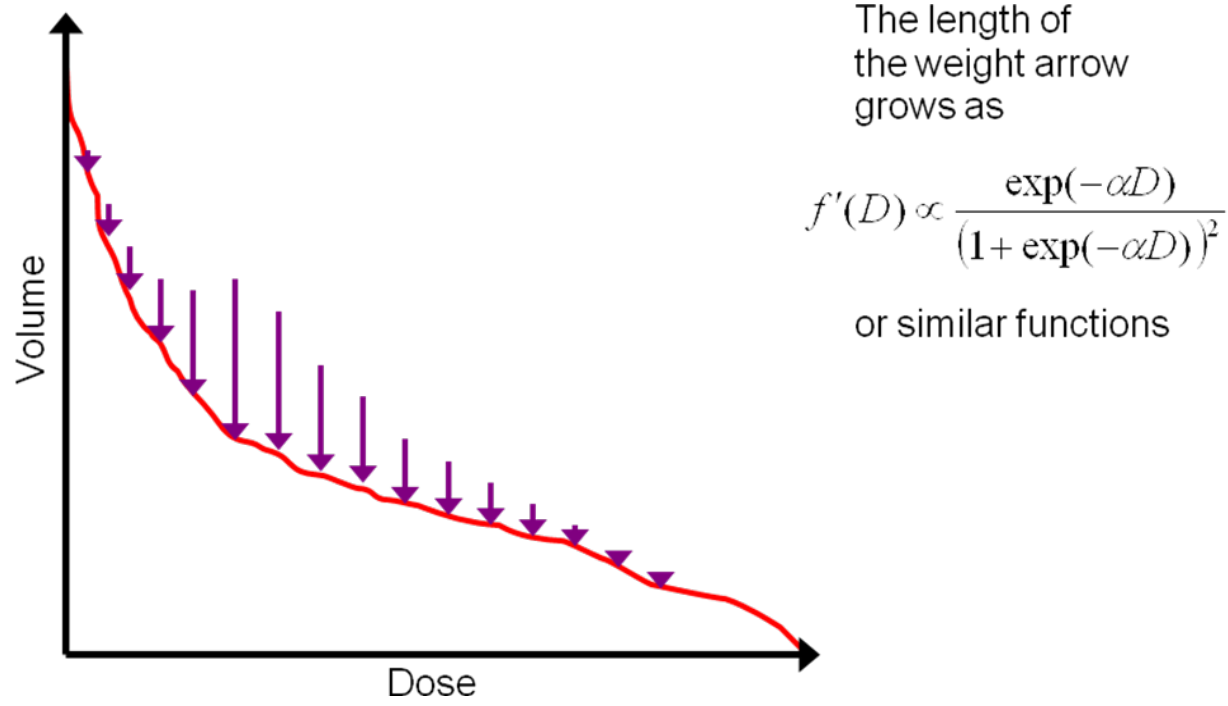

Figure 7: How the parallel complication model controls the DVH.

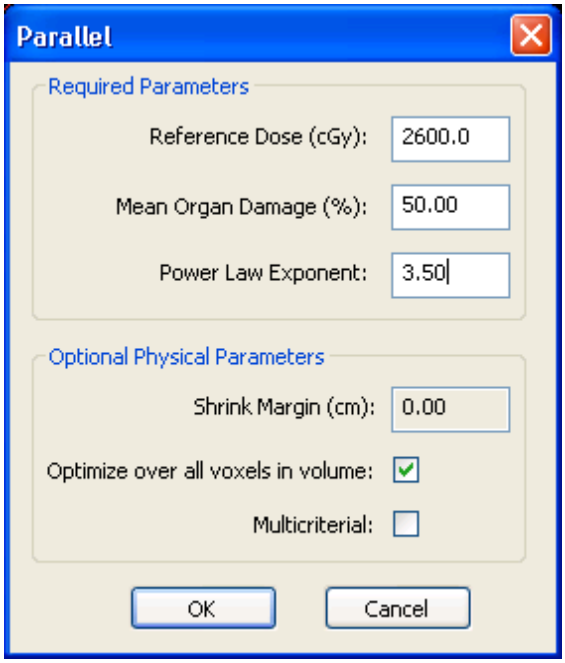

Figure 8: Parallel model parameters in Monaco.

The power law exponent k, the tolerated EUD value for areas of the organ one wants to spare and the percentage of the organ that does not need to be spared are the only parameters needed to control the entire DVH. In the parotid example above voxels of the organ one wants to spare must have a dose less than 26 Gy, but 50% of the organ can receive higher doses without the organ as a total losing its function.

Target volume cost functions – poisson EUD

The local dose-effect measure models may also be defined for targets, e. g. by means of the poisson probability model[17]

$$-\log TCP = \sum_{x_i \in V} \rho_i \exp(-\alpha_i(x_i) D_i(x_i) + \frac{T}{T_i^{pot}})\Delta V \qquad \textit{Equation 22}$$

$$f = \exp(-\alpha D) \qquad \textit{Equation 23}$$

where:

ρ tumor cell density

α cell sensitivity

T^{pot} cell doubling time

This model can be combined with physical cost functions such as quadratic penalties, which fit into the same formalism.

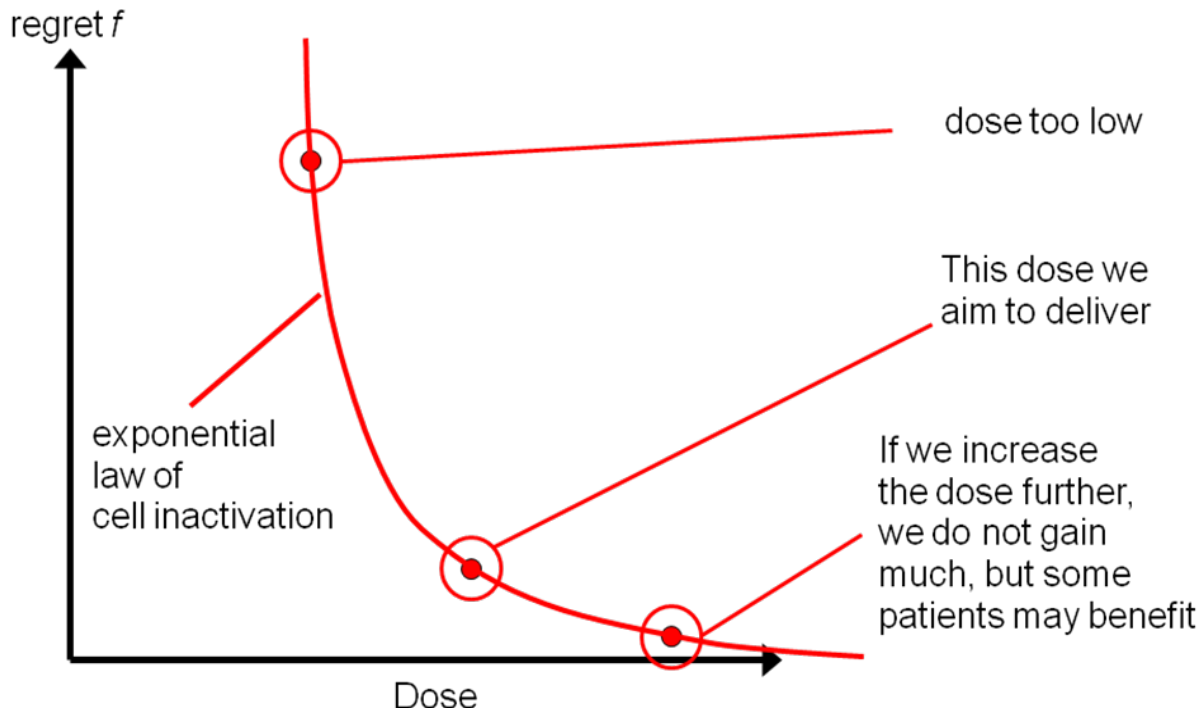

Fig 7: How the Poisson model for target volumes controls the DVH.

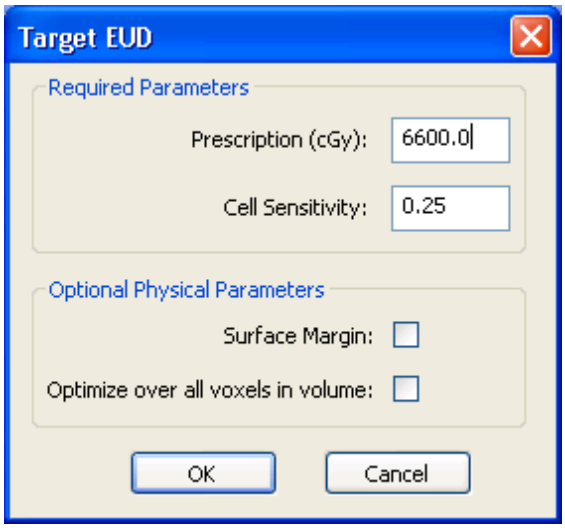

Figure 9: Target EUD (Poisson Cell Kill Properties)

The Poisson Cell Kill model is used for target volumes in Monaco. Besides the dose one aims to deliver (prescription), users can also define the value α for cell sensitivity. If α is larger, then it is less likely to get cold spots in the target volume and the less there is to gain from hot spots in the optimization.

Physical cost functions

As mentioned earlier, in addition to biological cost functions, Monaco also offers a variety of physical cost functions. These are summarized below. The provided figures illustrate how these cost functions affect the DVH of the organ for which they are applied.

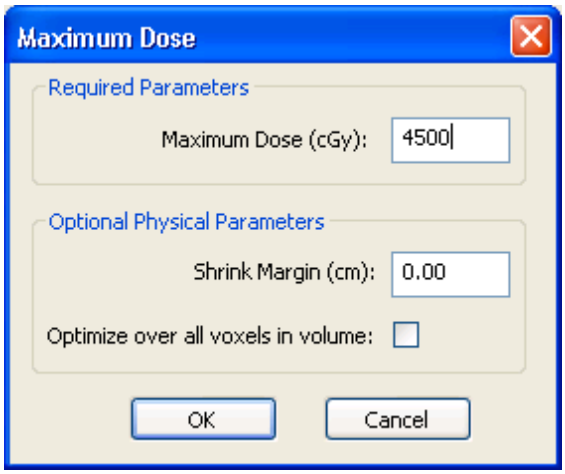

Figure 10: Maximum Dose Properties

This is a hard constraint and defines the absolute maximum dose for every voxel of an organ. It should be used with caution, but can be useful when it comes to organs with dose limits like the spinal cord.

Quadratic under- and overdose cost functions

These are the most commonly used cost functions available in commercial IMRT tools and they are also available in Monaco. The cost function value grows quadratically with dose above (or below) the user defined “minimum (or maximum) dose value”. The “RMS dose deficit (or excess)” values define by how much (cGy) in average voxels below the minimum dose value (or above the maximum dose value) will be allowed to exceed the minimum (or maximum) dose. A smaller number will result in a shorter dose “tail”. It is important to understand that the overall target dose homogeneity cannot be influenced by target dose penalties allow. If the target dose is not homogeneous enough, one might need to reduce normal tissue sparing, or add more beams.

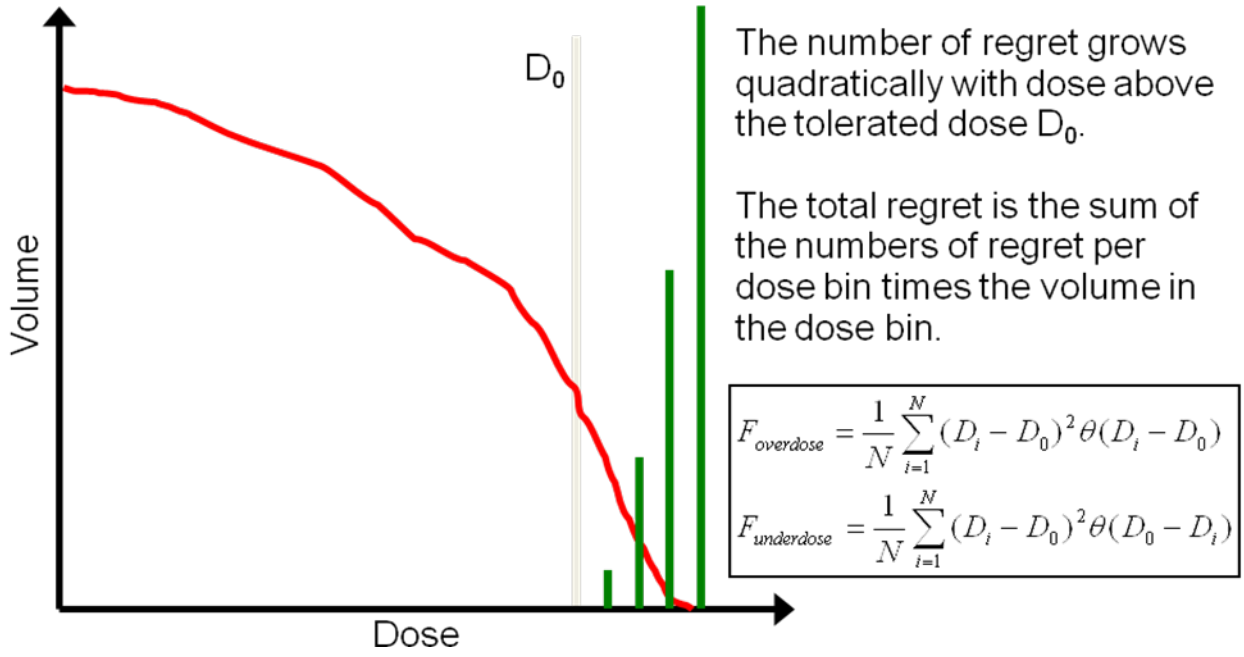

Figure 11: Quadratic Overdose

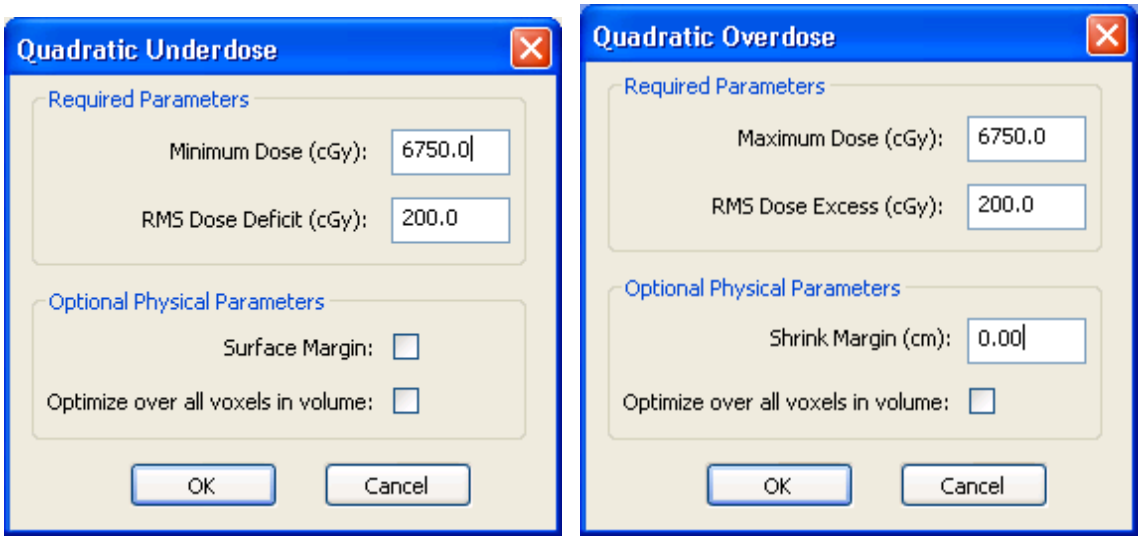

Figure 12: Quadratic Underdose and Overdose Properties

Under- and overdose DVH constraints

These are also two cost functions, which are typically available in commercial IMRT tools and which are available in Monaco as well. Users define a percentage of the organ volume, which has to be above or below a certain threshold dose. DVH constraints are hard constraints in Monaco, similar to the maximum dose constraint. Major drawback of DVH constraints is that they only control one single point of the DVH of an organ, but they can be helpful in conjunction with serial or parallel dose constraints.

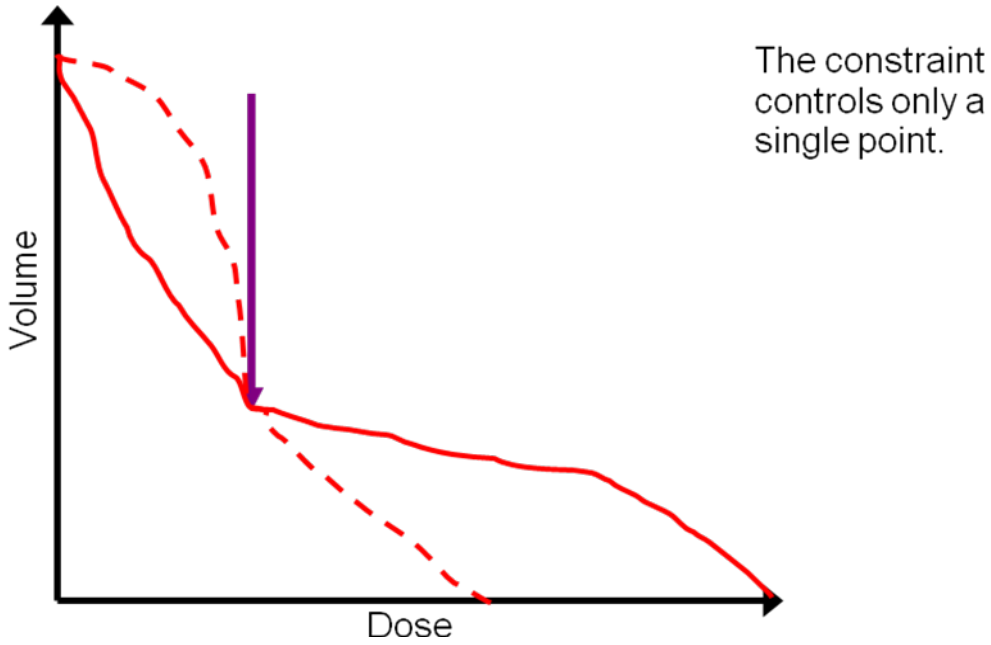

Figure 13: DVH Single Point Constraint

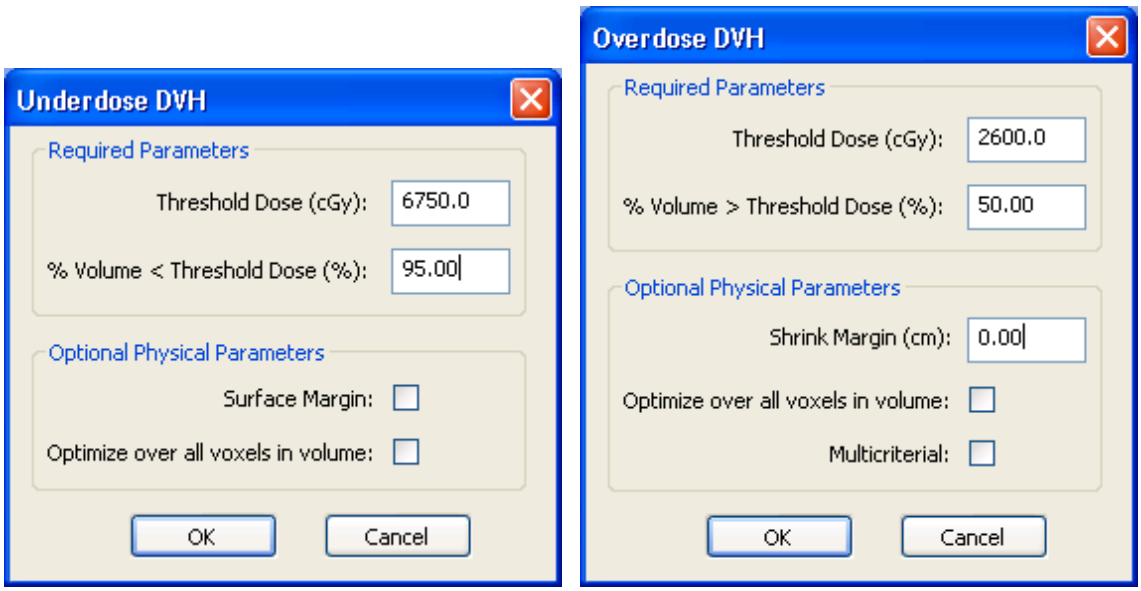

Figure 14: Underdose and Overdose DVH Properties

How to Use Monaco IMRT

Successful inverse planning requires an understanding of the trade offs and limitations inherent in the inverse planning process. Foremost, it is important to understand the interplay between the specification of anatomy contours, beams, and objectives. This should not be surprising as anatomy contours define the structures whose dose we are interested in; beam specifications define how dosage is to occur; objectives set up dose goals and evaluate how well we have achieved them. In addition, the method of IMRT delivery, whether by multileaf collimator (MLC), can affect the dosimetric results. Successful inverse planning also requires an understanding of how to evaluate results, whether it be through dose statistics, isodose displays, dose-volume histograms, or beamlet intensity maps. This chapter provides an introduction to the specification of inverse plans and the analysis of inverse planning results. It is meant to orient the first-time user or hone the skills of the more experienced.

One thing to remember as you engage in inverse planning is that optimizers can do amazing things, but they cannot accomplish the physically impossible.

Inverse Planning Flow

This section is an introduction to Monaco IMRT inverse planning. It centers on the "big picture", introducing inverse planning in Monaco with an annotated flowchart. In subsequent sections, we will steadily expand on this foundation.

Figure15 shows that the inverse planning process can be divided into two stages. During the first stage, the optimizer uses inverse planning objectives, anatomy contours, and beamlets to produce what are called the ideal intensity maps and ideal doses. By "ideal", it is meant beamlet intensities and doses that might be delivered if the realities of treatment delivery could be ignored.

In the second stage, ideal beamlet intensities are converted to a deliverable form; that is, field segments for multileaf collimator (MLC) delivery. New deliverable doses are recalculated and the dose is then reoptimized using the same objectives as in the first stage, but instead of changing individual beamlet intensities, the weights and shapes of deliverable beam segments are modulated. This second round of optimization compensates for some of the effects of changing beamlets to deliverable beams, such as weighting during field segmentation. The outputs of the second stage are deliverable field segments and a Monte-Carlo calculated dose distribution. (See Figure15.)

Detailed descriptions of each step in Figure15 are given with the (#) corresponding to the (#) on the figure.

1 Plan Setup

In order to begin inverse planning, you must:

1. Select a patient
2. Contour anatomy structures requiring inverse planning objectives
3. Carefully select the isocenter location
4. Specify a sufficient number of usually non-opposed, isocentric beams that intersect the target
5. Create objectives that represent your prescription

6. Specify treatment delivery, structure properties and dose calculation parameters (e.g. overwrite density inside structure with contrast during CT, minimum number of MU/segment, dose grid size, variance, minimum segment size …).

2 Stage I Optimization

The optimizer uses knowledge of the location of anatomy structures and the dose from the collection of weighted beamlets to minimize a cost function defined as the sum of inverse planning objectives. The output of Stage I is beamlet ideal intensity maps and ideal doses.

3 Ideal Dose Checking

A basic rule of thumb is that the ideal doses from Stage I optimization must be acceptable in order to continue on to Stage II. Isodose displays as well as dose-volume histograms (DVH) and their accompanying dose statistics should be used to determine if doses are satisfactory.

4 Adjusting Objectives, Contours, and Beams

If doses are unsatisfactory, you will need to change, in order of preference, objectives, beams, or anatomy contours. In addition, bolus can be helpful in situations where targets are drawn very near to the patient's skin. It may be beneficial, using isodose displays, to find locations in the patient where your dosimetric objectives are not being satisfied. Competition between organ at risk (OAR) objectives and target minimum dose objectives is inevitable when using unconstrained optimization methods and much of the effort that you will expend in inverse planning will be in determining which objectives are competing with each other and resolving these conflicts. The sensitivity tool in Monaco will help guide this process.

5 Segment Fields, or determine MLC positions

Ideal beamlet maps must be converted to a form deliverable by MLC. During this conversion process, not all aspects of the ideal dose obtained during Stage I can be retained. For VMAT plans the minimum spacing of control points is specified.

With MLC delivery, allowing more and smaller segments can lead to more faithful reproduction of ideal doses, but this also leads to longer treatment times on certain linear accelerators and may decrease the dose calculation accuracy as well as robustness of the plan.

When the segmentation is accessed the ideal maps will be discretized. The user should re-assess isodose contours and DVHs at this point to see the effects of discretizing the map on the solution. The user may change segmentation parameters and discern what the best trade-off between the number of intensity levels and preserving the "ideal" optimized solution is. Once the optimum set of segmentation parameters has been decided, the user should then proceed to produce segments.

6 Recalculate Beam Doses

After dose delivery issues have been resolved, new beam doses are calculated using Monte Carlo. This dose calculation method is highly accurate. For MLC delivery, the knowledge of leaf positions improves estimates of fluence for beam penumbra, individual field segment penumbra, and head scatter. Thus, many of the limiting approximations of the beamlet representation of the relationship between fluence and dose representation are eliminated.

7 Stage II Optimization

The deliverable beam doses are then reoptimized allowing segment weight and shape changes, which is computed exactly like Stage I optimization, except that optimization is over beam segment doses rather

than beamlets and the final result of the optimization is deliverable dose rather than ideal dose. The final dose estimate represents, as nearly as possible, the actual dose that will be delivered during treatments.

8 Final Dose Checking

Final dose checking is much like ideal dose checking and uses the same dose analysis and visualization tools.

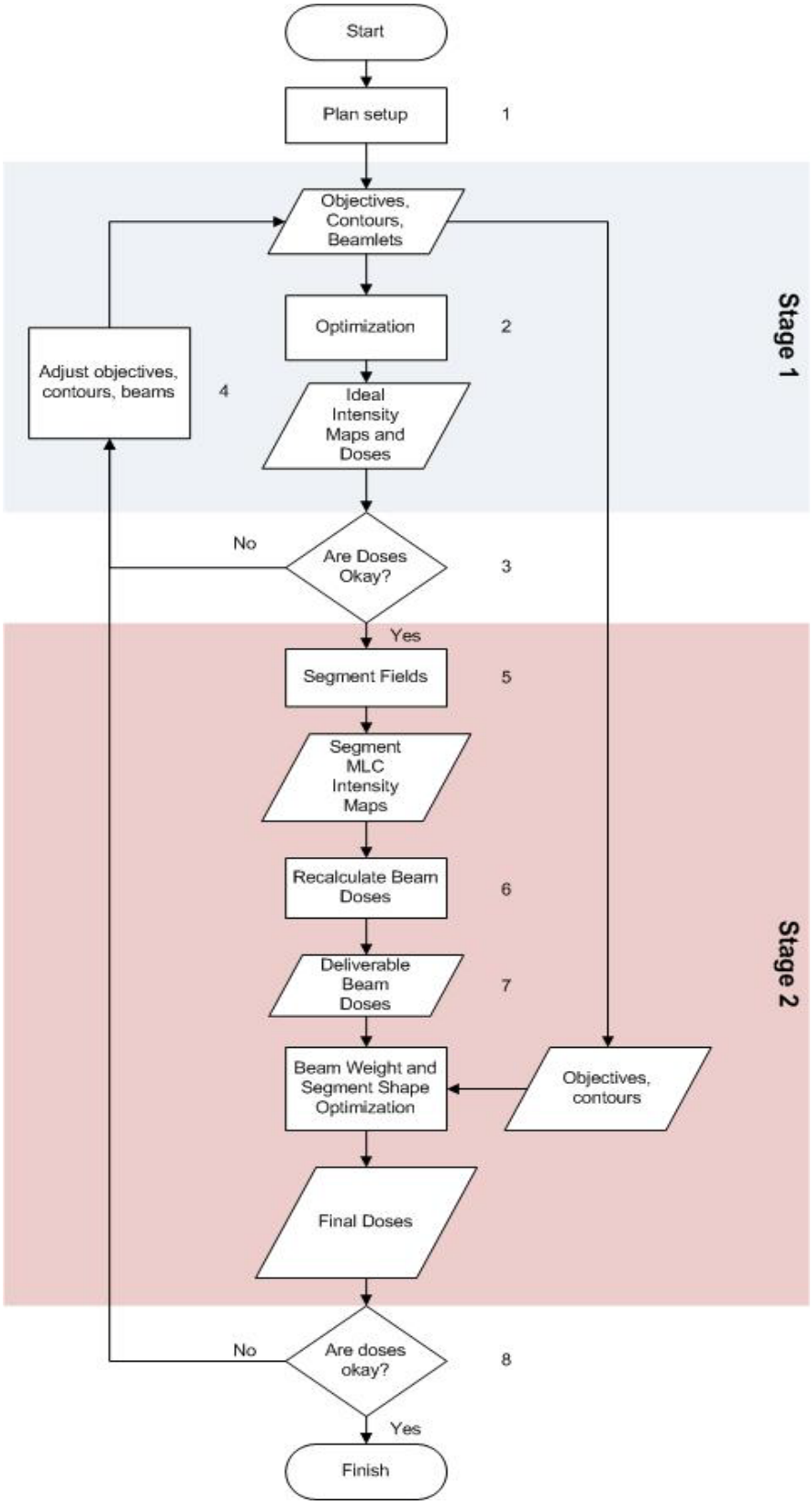

Figure15: Monaco IMRT Inverse Planning

Anatomy Structures

For optimization by inverse planning, the image set must be contoured. Image contours can be imported from external sources, created manually, or created through the automatic tools within Monaco. This includes target volumes and avoidance organs that will have objectives as well as structures for which dose-volume histograms (DVH) will be calculated. Anatomy contours and anatomy rank are used to identify volume elements (voxels) claimed by different objectives. It is very important to contour anatomy carefully, because the optimizer uses contour information exactly as it is specified, and achieving prescription goals may be difficult or impossible with inexact or inappropriate contours. Additionally, CT voxels representing anatomy do not typically conform to the dose voxels. Monaco relies on an algorithm to determine if a particular dose voxel is in fact included in the anatomical structure. Beginning in Monaco release 3.30, a modified algorithm is used to improve accuracy of dose voxel inclusion, this change is described in Appendix B

The next subsections describe potentially problematic contouring issues for inverse planning and tools available in Monaco to deal with those issues without the need to contour additional "dummy" structures to guide the optimization algorithm. The nomenclature of the International Commission on Radiation Units and Measurements (ICRU) reports 50 and 62 is used in further discussions of patient anatomy.

Optional physical parameters

Problems occur when contoured anatomy structures overlap, abut, or are in contact with each other, and have different dose objectives, as shown in Figure 16. Suppose that the mandible maximum dose objective is 54 Gy and that the planning target volume (PTV) minimum dose objective is 70 Gy. Because the mandible and PTV are in contact with each other, neither structure will completely achieve its dose objective, since that would require an instantaneous change in dose; that is, an infinite gradient.

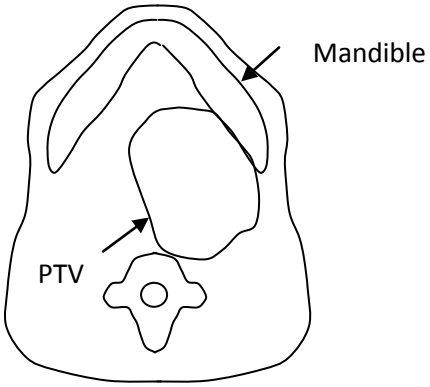

Figure 16: Anatomy Structures with Conflicting Dose Goals

Figure 17 shows a schematic of structures and doses that further illustrates the abutment/infinite gradient problem. When structures are too close to each other or overlap, instead of a perfect step in dose, the optimizer will produce a physically-realizable gradient (as shown by the thick line in the figure) in which the normal tissue is minimally overdosed and the target is minimally underdosed. This behavior is not due to an idiosyncrasy of optimizers; rather, it is due to the continuous nature of dose distributions in tissue and the physical limits of dose modulation.

Figure 17: Infinite gradient problems

To deal with this problem, Monaco offers several optional physical parameters. The lower ½ of the dialog boxes shown in Figure 5, Figure 8, Figure 9, Figure 10, Figure 12, and Figure 14 for each constraint dialog box allow for setting the optional physical parameters. The order in which objectives for different organs are entered is critical in case organs overlap. In this situation, Monaco assigns voxels to the organs in their order in which optimization parameters are listed in the optimization parameter window. In case the spinal cord + margin organ was listed before the spinal cord organ, all voxels would be assigned to the spinal cord + margin and no voxel would be assigned to the spinal cord. As a consequence, any spinal cord constraint would be ignored or – to be more accurate – would be applied to no voxel. In contrary, was the spinal cord organ listed before the spinal cord + margin organ, so would all voxels of the spinal cord become assigned to the spinal cord and only the margin surrounding the spinal cord would be assigned to the spinal cord + margin organ.

Beginning in Monaco 3.0 a partial voxel assignment is allowed such that if ½ the voxel is in the target and ½ the voxel is in the OAR the DVH will be constructed such that the ½ voxel volumes are accounted for in the separate DVHs rather than all in one DVH.

Optimize over all voxels in volume

To change this functionality, a box in the parameter window can be checked. This box is labeled "*optimize over all voxels in volume*". Monaco then assigns voxels in overlapping regions to more than one organ. With the box checked, a spinal cord constraint would not be ignored, even if the spinal cord organ was listed after the spinal cord + margin organ.

Shrink margin

The parameter window allows entering values for a "*shrink margin*". A "shrink margin" creates a contour smaller than the original volume by a specified distance in order to deal with abutting structures or structures which are close to each other. If a shrink margin value is entered for a critical structure, Monaco only applies the constraint to the organ voxels further away than the shrink margin specified for all target volumes listed before the critical organ.

Multicriterial

One other optional physical parameter that may be selected is "*multicriterial*". If this box is checked, Monaco treat the cost function as a secondary objective, which is minimized only if the primary objectives can be met. In short multicriterial should be used when an objective is nice to have, but not worth having if a higher priority criteria cannot be met. This option is only available for cost functions which are associated with an NTCP model. When multiple multicriterial cost functions are selected, their NTCP values are reduced by the same factor.

Global Parameters

Figure 18A shows a contour of a target that is very close to the skin surface. The result of such a contour is that a portion of the target will be in the buildup region of any beam that directly enters the patient near the target (*e.g.*, beams 2 & 5). When a target is in the build-up region of a beam, it is often difficult to achieve minimum dose objectives. Dose to normal tissues may be unnecessarily increased due to increased dose to the target that is required to make up for low dose at the skin surface. Alternatives are either to redraw the target away from the skin surface (which may not be clinically feasible) or to add bolus to the patient at problematic beam entry points.

Figure 19 shows a schematic of two idealized beam doses and their dose sum; it is meant to represent the situation in Figure 18A. The stippled region represents the target and the solid white region on the right

represents a bolus. The left of Figure 19 shows that the beam enters the "patient" directly and that the buildup region of the beam is in the target. On the right of the figure, the buildup region is in the bolus.

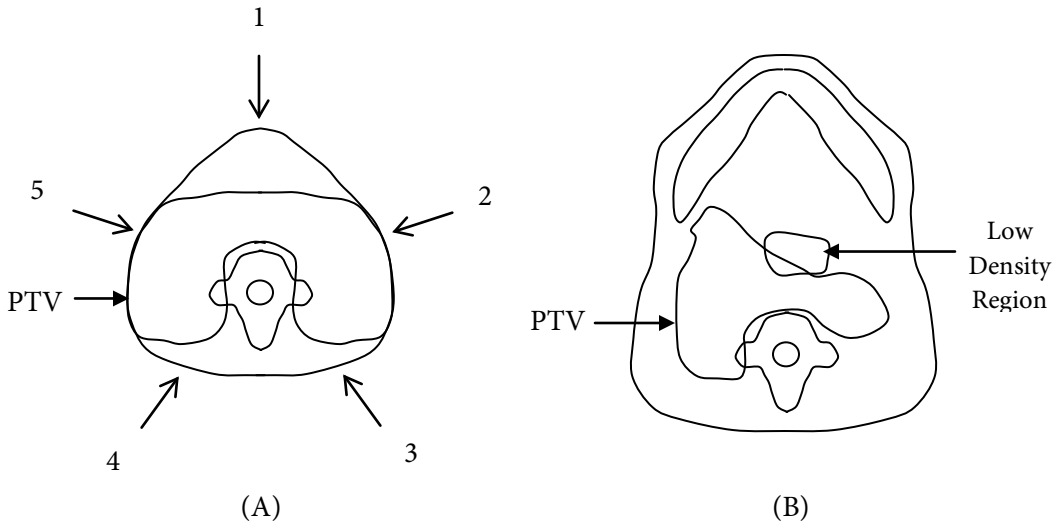

Figure 18: Dose buildup and build down problems

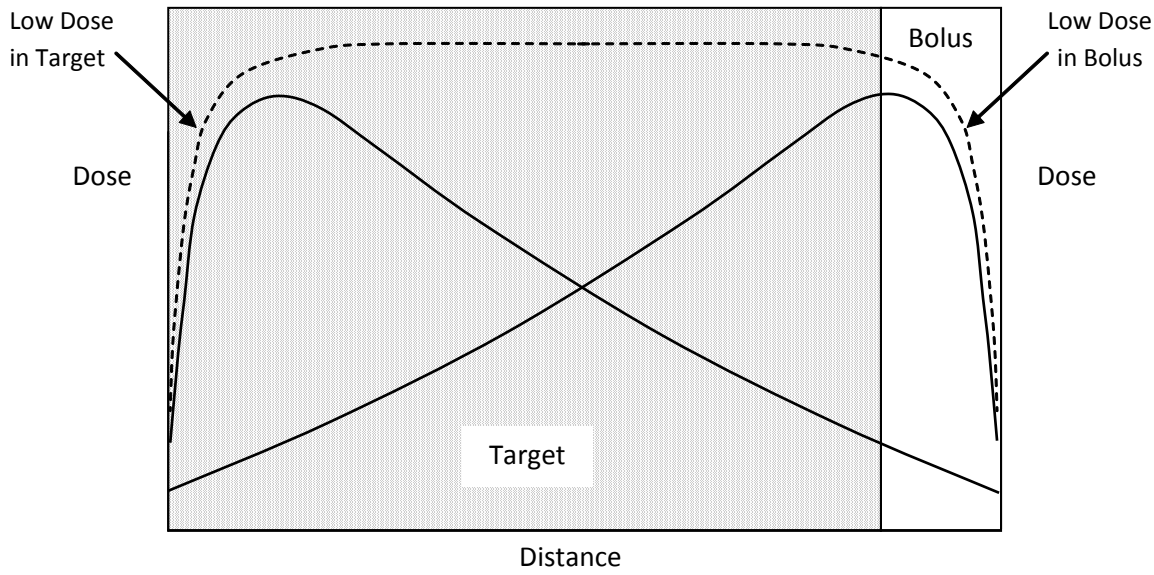

Figure 19: Build up at skin and in bolus

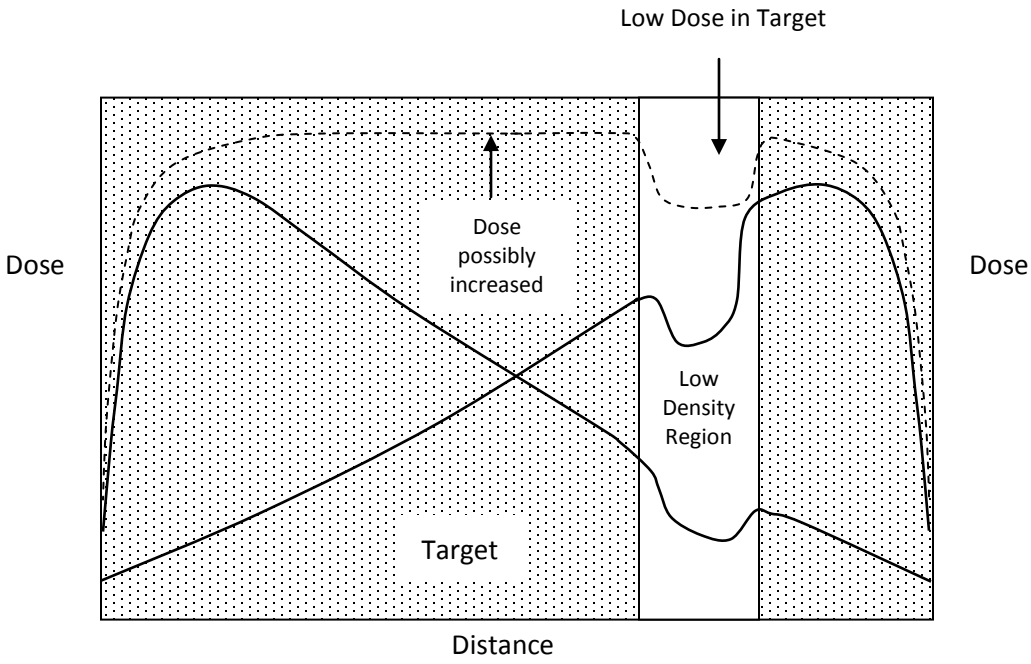

Figure 20: Low density region doses with superposition photon dose calculation

Figure 18B shows another contouring problem – having low density holes or air gaps in a target outline. Ironically, this is only a problem when using homogeneity corrections with photon dose calculation algorithms that *correctly* estimate dose in low density regions (*e.g.* Monte Carlo) as it is the case with Monaco. The final dose calculation should always be completed using Monte Carlo rather than Pencil Beam. One should keep in mind that, Monte Carlo calculated dose distributions and the corresponding DVH calculations need to be interpreted differently than those calculated with convolution or pencil-beam algorithms. They will *correctly* estimate dose in low density regions such that resulting DVH results and PTV coverage may appear worse than those calculated with other calculation algorithms in which dose tends to be overestimated in low density regions. Figure 20 represents such a dose decrease in a low density region.

A depression in the dose in a low density region may be interpreted by the optimizer as a failure to achieve a minimum dose to the target. In reality, the air gap is not part of the target, but unfortunately is part of the contour. The low dose depression may, as with targets in the build-up region, make it difficult to achieve minimum dose objectives and indirectly increase dose to normal tissues. These problems may be especially difficult to avoid when using the automargin expansion option.

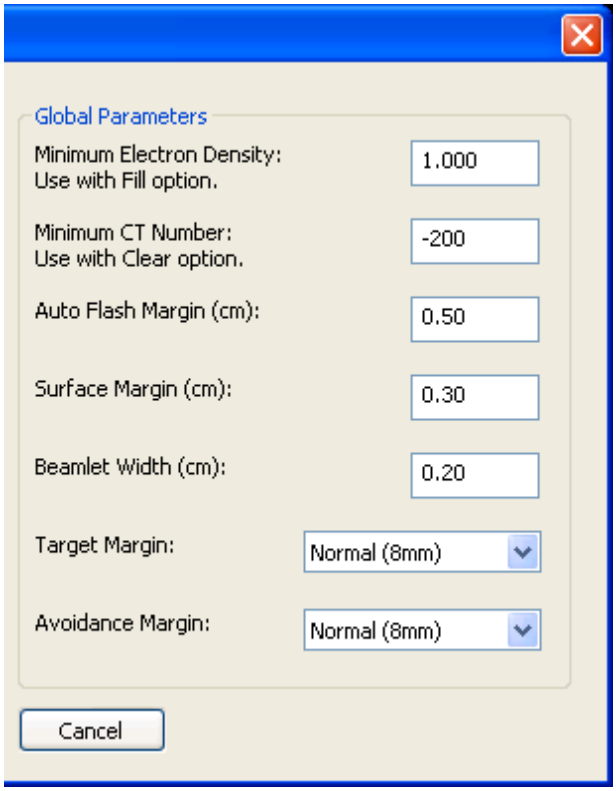

Figure 21: Global Parameters

Monaco offers a variety of global functions and parameters which will be described here.

Minimum Electron Density

This global parameter allows users to overwrite density values for voxels inside a structure with the value entered in the global parameter window. If the *minimum electron density* is used in conjunction with the *uniform* function of an organ, so will Monaco overwrite all density values of voxels inside a given structure with the density value entered. This is useful in cases where patients were scanned with contrast (e. g. bladder contrast) and where density values would need to be corrected as a result to allow for accurate dose calculation.

If the *minimum electron density* is used in conjunction with the "fill" option of an organ, Monaco only overwrites voxels inside a given structure if the CT number of the voxel is below the *minimum CT number*. If the defined *minimum CT number* is for example -200, Monaco replace all areas inside a structure with the *minimum electron density* value entered for voxels with CT numbers of less than -200. This is useful in cases where the PTV volume encompasses air cavities. Under the assumption that those areas need to be included in the PTV structure to allow for a large enough margin around the GTV to account for positioning errors. For example, it is assumed that on some treatment days there will be GTV instead of an air cavity at those locations. One may have good reason to enter values between 0.2-0.4 for such areas.

Minimum CT Number

The *minimum CT number* value can be used in two different ways. If used in conjunction with the *fill* option for structures, the *minimum CT number* value will define a threshold for overwriting CT numbers. If used in conjunction with the *clear* option, the *minimum CT number* value will set a threshold for the

IMRT optimizer, which will ignore areas inside target volumes below the set threshold value. As a result, the optimizer will accept target volume doses below the minimum dose value as long as they are inside low density regions.

Surface Margin

This parameter is similar to the *minimum CT number* value if used in conjunction with the "clear" option. The *surface margin* value defines a distance to the skin surface of the patient. The IMRT optimizer will ignore areas inside target volumes if they are located closer to the skin surface than this value. As a result, the optimizer will accept target volume doses below the minimum dose value as long as they are inside areas too close to the skin surface.

Auto Flash Margin

The *auto flash margin* value is defined and used for target volumes. If the parameter is set for at target volume, it creates a flash volume around the target volume that will cause the fields to extend into air by the value defined. This parameter was introduced into Monaco for use with breast IMRT treatment planning or other mobile surface targets in mind. These fields with flash are needed to account for breathing motion, patient movement or setup variations.

Beams and isocenter placement

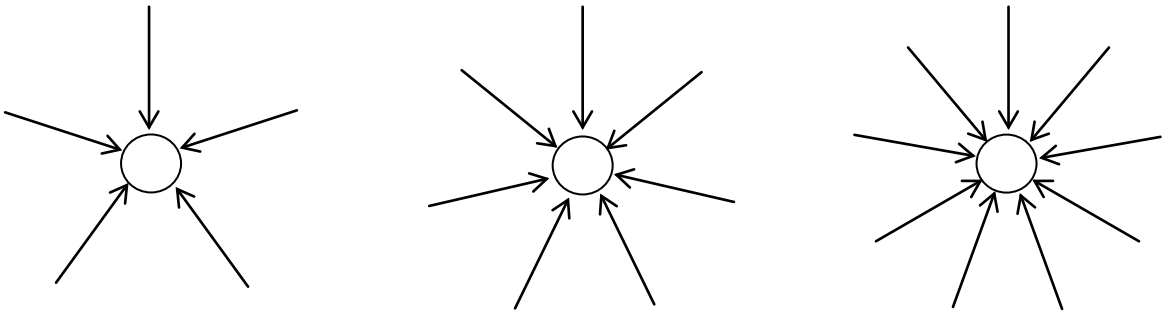

Figure 22: Beam arrangements for 5, 7, and 9 evenly-spaced beams

In many cases, a small, odd number of evenly-angled coplanar beams will yield satisfactory results in inverse planning. At the low end, five beam plans have the advantage of few dose calculations, fast optimization and relatively fast treatment times. As more and more beams are used, the possibility of finer dose shaping increases with the trade off of longer dose calculation time, optimization time. The speed of optimization is linearly related to the number of beamlets and voxels represented by beamlets. Figure 22 shows evenly-angled beam arrangements for 5, 7 and 9 beams. It may be beneficial in some cases to use 11 or 13 beams. Users will find that often an increase in the number of beams results in a decrease in the total number of segments needed. Reason is that beams of an 11 or 13 beam plans often end up being less highly modulated than beams of a 7 or 9 beam plan, which often results in less segments total. As a result, plans with more beams will often result in shorter treatment times.

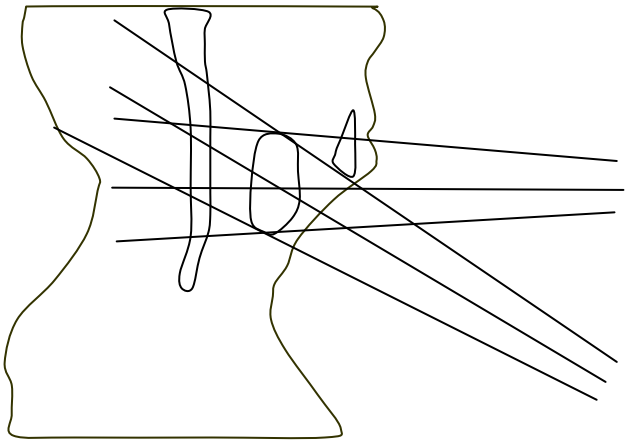

Figure 23: Shortening a beam path using a non-coplanar beam

Non-coplanar beams may also improve results in some instances. One obvious possibility is to use non-coplanar beams to entirely remove an OAR from a beam path. In the case of follow-up treatments this may be very useful if the physician's intention is to eliminate all new dose to a previously-treated OAR. However, in the general case, optimizers can achieve good results limiting dose to OARs, even if they are directly in the path of beams, and it is not necessary to intentionally place beams according to anatomy. Figure 23 shows a case in which using a non-coplanar beam may improve results. It shortens the beam path from the skin to a target, lengthens the path of the exit dose to the cord, and avoids the mandible, all of which lower dose to the cord.

Isocenter placement can also be important. The isocenter should be place such that beams covering target volumes from different beam angles are as symmetric as possible in each direction. Moving the isocenter in superior/inferior direction by one half the widths of the MLCs may also sometimes result in better results. Moving the isocenter by one half the MLC width may for example allow the optimizer to block a small structure like the chiasm with just one MLC instead of two, which would result in a better dose distribution and lead to improved target volume coverage in case the target volume is close to the chiasm.

Independent Beam Dose

Odd numbers of evenly-angled beams provide the optimizer with beamlets that have independent doses. By independent doses, we mean that by changing a specific beamlet's weight, the dose is changed in the patient in a way that is unique and perhaps not possible by any other combination of beamlet changes. This independence allows the optimizer many degrees of freedom in which to affect doses to targets and normal tissues when iteratively changing beamlet weights.

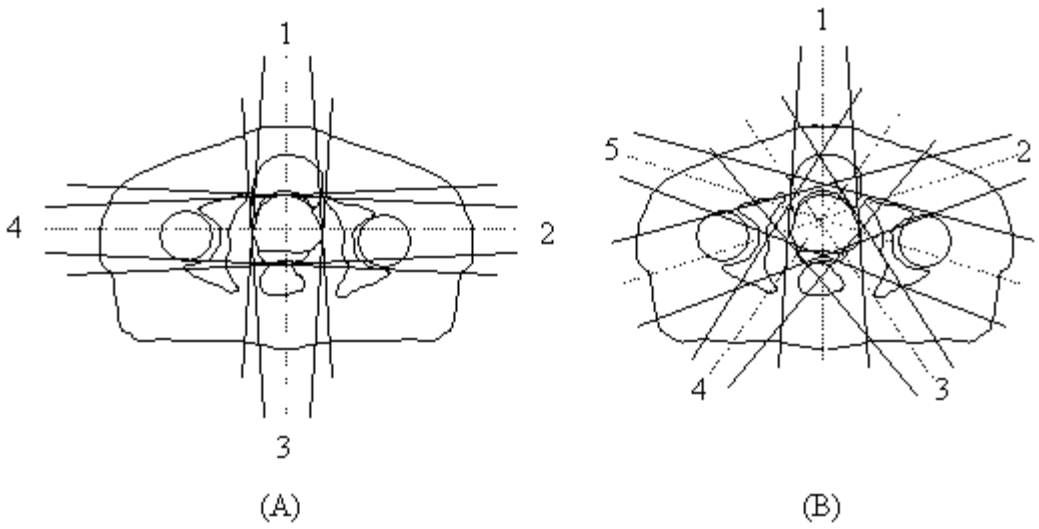

Figure 24: Poor beam angles and good beam angles for inverse planning

The more that pairs of beams approach being parallel or directly opposed, the fewer the degrees of freedom for the optimizer to find a good solution to an inverse planning problem. A good rule of thumb is that beam angles should be at least 15 degrees apart for independence. Figure 24A shows an example of poor beam placement for inverse planning that is very acceptable and, in fact, the norm in many clinics for conventional prostate treatments. The problem with this beam placement for IMRT is that the parallel opposed beams (1 & 3 and 2 & 4) affect doses in very much the same way The five beam arrangement in Figure 24B is more typical in inverse planning for IMRT.

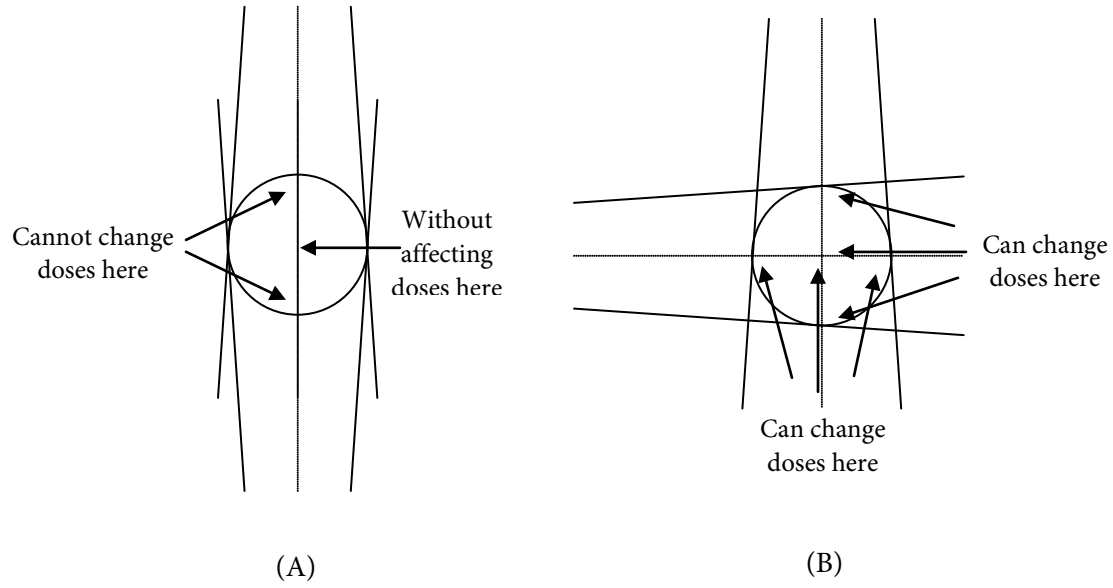

Figure 25: Target doses for dependent and independent beamlet doses

Two beam arrangements that may make the concept of beamlet dose dependence and independence clearer are shown in Figure 25. Suppose that the beams shown in the figure are subdivided into beamlets.

On the left of the figure, it is clear that the doses at the top and bottom of the target are tightly coupled to doses within the target. On the right of the figure, doses at the top and bottom of the target are decoupled from doses on the left and right of the target by virtue of the 90^0 separation of beam angles. From Figure 25B one can see that adding more non-parallel beams will have the effect of creating more ways for the optimizer to modulate dose.

Excessive Beam Paths

Even though evenly-angled beam arrangements are often preferred, as long as beams are separated by at least 15 degrees, good results are possible. One situation where non-evenly-angled beams may be useful is when a beam in a standard configuration traverses an excess amount of normal tissue before it encounters the target. Figure 26 shows a seven beam arrangement in which the two anterior oblique beams are traversing too much normal tissue. Without a maximum dose objective to keep dose to patient unspecified tissues under control, hot spots may occur in the shoulders.

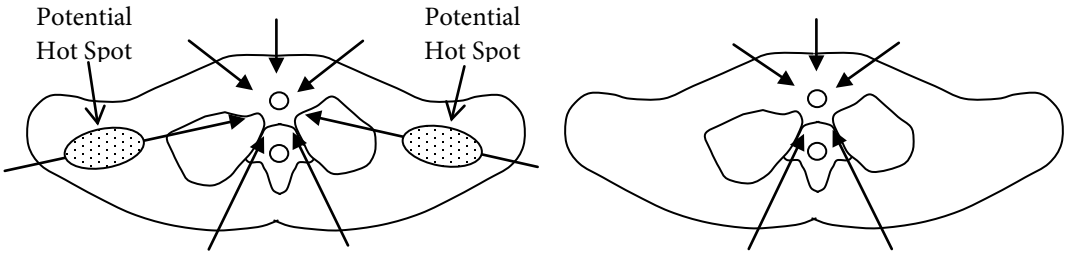

Figure 26: Seven field evenly-angled plan with beams traversing too much tissue and five field improved beam angle selection (0, 55, 154, 206, 305 degrees).

Dose Calculation Parameters

In Monaco IMRT, dose calculations are performed multiple times during inverse planning. When the Stage I optimization begins, dose in the form of beamlets is calculated using the pencil beam algorithm. During Stage I optimization, these beamlet weights are iteratively modified based on objectives set by the user to create the ideal patient dose. When Stage II optimization begins, ideal beamlet intensities are segmented for delivery by a multileaf collimator (MLC) and/or arc. A final deliverable dose is calculated for each beam with the secondary algorithm. Concluding Stage II optimization, segment shapes and weights are re-optimized based upon deliverable beam rules and dose is computed for each beam with the same optimization method and objectives as in Stage I.

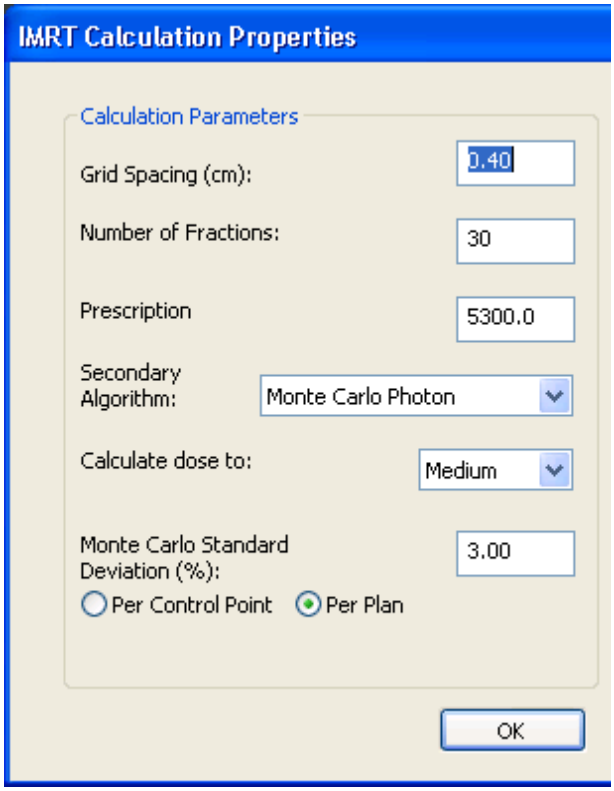

Figure 27: Global dose calculation parameters

Grid spacing between 0.2 and 0.4 would be typical, depending on the problem size and complexity of the problem. For a typical prostate IMRT case, a grid spacing of 0.3 or 0.4 may be sufficient. For the IMRT plan of a small brain lesion a dose grid spacing of 0.2 would probably be more appropriate. A good strategy would be to start with smaller grid spacing and to increase the grid spacing stepwise if optimization times are unacceptably long. SRS treatments typically use a finer grid spacing not larger than 0.2 as recommended by AAPM TG-101[18].

Number of Fractions and *Initial Prescription* are two fields, which allow entering the plan prescription.

The *Secondary Algorithm* field allows choosing between the pencil beam and Monte Carlo Photon algorithm in Monaco for the second phase of the IMRT optimization process and final dose calculation. The pencil beam algorithm is always used during the first phase of the IMRT optimization. It is highly recommended to use the Monte Carlo photon algorithm as the secondary algorithm for clinical IMRT plans, but choosing the pencil beam algorithm may be helpful to run test plans until the best set of constraints has been found for a clinical case.

Calculate Dose to medium has been the default option up until Monaco 3.1 and is still the default calculation. AAPM TG-105 recommends the user be provided with options for calculations both to medium and to water[19]. The user may also select dose to water in which case the heterogeneity properties of the patient are properly accounted for, but the dose is converted to dose to water via the stopping power ratio between water and the medium at the point where the dose is being calculated.

Monte Carlo variance defines the statistical accuracy of completed Monte Carlo calculations in Monaco. Reducing the variance by a factor of two results in four times longer calculation times. In general, a

variance of 3% should be sufficient. Note that in some versions the UI uses the term *Monte Carlo standard deviation*, but the value is actually variance in all versions. The variance can be specified on a per plan or per segment basis meaning that if the UI specified control point variance is set to 3% and the plan has multiple beams then the plan variance will be less than 3%. How much less than 3% is determined by the weight and number of beams. See the Dose Calculation Technical Reference for more details.

Sequencing Parameters

Selection of sequencing parameters is a tradeoff between the ideal dose created during stage one and practical delivery. Different parameter options are available depending on whether the delivery mode is:

- step and shoot IMRT
- dMLC
- VMAT
- Conformal RT.

For example for step and shoot IMRT, the user must appropriately select the minimum segment area, minimum segment width, and minimum change in area between consecutive segments. In addition the size of the segments is a trade-off for creating the ideal dose and having a robust quick to deliver plan. And the minimum MU/segment is required. Multiple options are available for the fluence smoothing including off, low, medium and high depending on the number of segments desired with off producing the most segments.

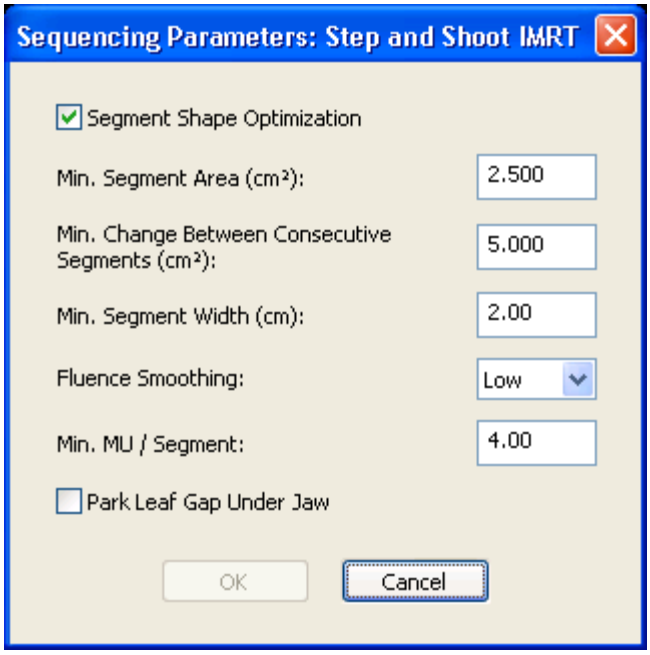

Figure 28: Sequencing Parameters: Step and Shoot IMRT

Practical examples for biological optimization

In the following sections, two clinical scenarios are described, a prostate IMRT case and an H&N IMRT case. The goal of this discussion is to explain why and how certain functions and constraints in Monaco are used in certain clinical situations as well as the strategy and motivation behind the chosen approach.

A Prostate IMRT Case

Figure 29 below represents the Monaco IMRT prescription page, which is where inverse planning objectives are specified. Imagine a prescription with the following objectives:

At least 95% of PTV76 to receive 7560 cGy.

Bladder:

Volume of Bladder receiving at least 6800 cGy is below 30%

Volume of Bladder receiving at least 5000 cGy is b below 50%

Rectum:

Volume of Rectum receiving at least 7000 cGy is below 10%

Volume of Rectum receiving at least 4000 cGy is below 50%

Femurs:

Volume of Rt. Femoral Head receiving at least 5000 cGy is below 10%

Volume of Lt. Femoral Head receiving at least 5000 cGy is below 10%

Limit dose to unspecified tissue as much as possible

(1) (2) (3) (4) (5) (6) (7)

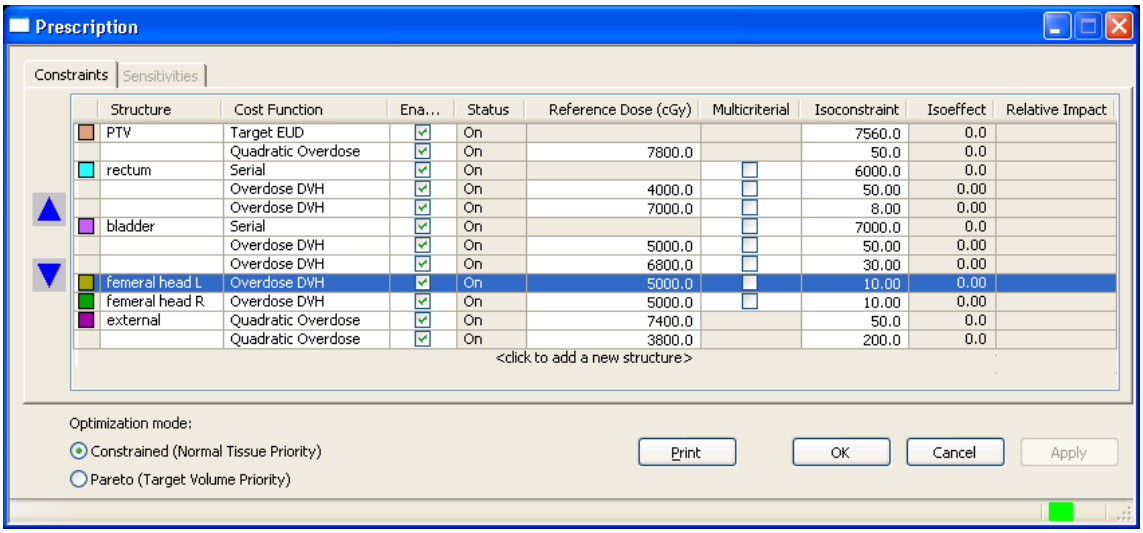

Figure 29: The Monaco IMRT prescription page for a prostate case

(1) Briefly, the Structure column lists all anatomy structures that have been contoured, including the patient exterior. Any contoured anatomy structure can have cost functions. The order in the Structure column specifies how voxels are shared when anatomy contours overlap, unless the *optimize over all voxels* box is checked under structure properties. Typically, targets are listed before OARs. The patient exterior should be listed last, thus excluding all voxels from the patient that belong to other anatomic structures with active objectives. Note that only active structures are considered; thus, what is considered unspecified tissue will be determined by the contoured anatomy as well as the active objectives for the contoured anatomy. A structure listed before another structure have possession of dose voxels in regions where the two structures overlap. Therefore, any cost function for the first structure listed will be affected by doses in the overlap region. Structures listed below another structure will not be affected by doses in the overlap region.

(2) The Cost Function column contains information about the type of cost function selected for the structure.

(3) The Is On column specifies if a cost function is active in the next optimization or not.

(4) The Status column specifies if a cost function is used during optimization. The optimization algorithm can turn cost functions on or off, depending on the effect on or need for the resulting dose distribution.

(5) The Reference dose column specifies the dose limit set in the cost function.

(6) The Multicriterial column indicates whether the multicriterial flag is set to *on* or *off*. On signifies that the cost function is considered only if the primary objective is met.

(7) The Isoconstraint column defines the value specific to the cost function: the set isocontraint value for the poisson statistics cell kill model cost function, the RMS dose excess value defined in

overdose or underdose constraints, dose maximum or minimum values, equivalent uniform dose values for serial organs, or mean organ damage percentage for parallel organ constraints.

Figure 30A shows two structures of different rank and how the voxels in the intersecting region between the structures are owned by the structure of higher rank. Figure 30B shows two structures of the same rank and how they share intersecting voxels.

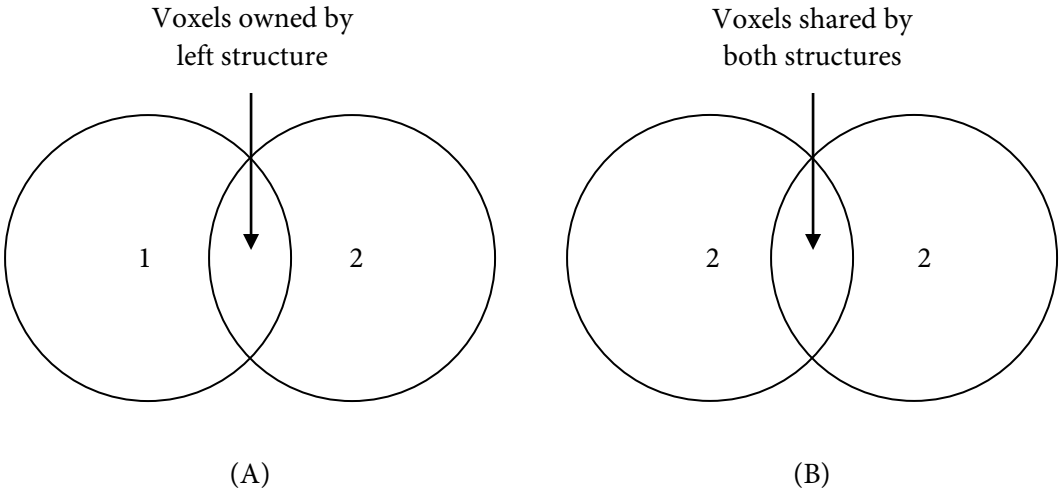

Figure 30 Structure rank and voxel ownership

Each cost function used in this prostate case and the associated parameters are discussed in more detail. Note that each physician will have their own objectives and the following is provided as an example.

For all structures the *Display total volume DVH* box was checked in the structure properties window.

PTV uses two cost functions

The *Poisson Statistics Cell Kill Model* is selected. To ensure that underdosage inside the PTV is kept to a minimum, a high *cell sensitivity* value of 0.5-0.75 should be chosen. As discussed previously this will minimize underdosage at the interface between the rectum and PTV and also reduce the benefit of biological optimization from overdosing the PTV. As a result, the PTV coverage will be more homogeneous with a higher *cell sensitivity* value. For the isoconstraint value, the *Prescription* dose of 7560cGy was set.

The *Quadratic Overdose Penalty* is also selected. To prevent the PTV from being overdosed too much, a maximum dose value of approximately prescribed dose + 200cGy, in this case of 7800cGy was chosen and input into the Reference Dose column. A relatively small *RMS dose excess* value of 50cGy is chosen as the *Isoconstraint* to restrict the dose tightly beyond this dose limit.

Rectum uses three cost functions

Checking the *optimize over all voxels in volume* box is important for all rectum constraints. This will guarantee comparable toxicity levels for different prostate patients with different overlap volume between PTV and rectum without changing the constraints.

You can use multiple *Serial Complication Models* are the only constraints truly needed for optimization. Add a *Serial Complication Model* for high dose to cover the rectum volume exceeding doses of 7000cGy and beyond. Set the *power law exponent* between 8 and 10. Add a second *Serial Complication Model* for midrange doses, between 3,000 and 4,000 cGy. Add a *shrink margin* around the volume and set the *power*

law exponent to 8. If necessary, you can also add a third *Serial Complication Model* to the patient anatomy to control lower dosage with a larger *shrink margin*. If you do not want to use multiple *Serial Complication Models*, you can add a single one with a dose at 3,500 cGy and a *power law exponent* of 1. This will help lower the overall mean dose to the rectum.

Bladder also uses three cost functions

The strategy chosen for the bladder is similar to the one chosen for the rectum. A serial dose constraint combined with two DVH constraints is chosen. If bladder contrast was used, then the box *fill structure with Minimum ED* should be checked. The *optimize over all voxels in volume* box needs to be checked for all bladder constraints. Use of *optimize over all voxels in volume* will guarantee comparable toxicity levels for different prostate patients with different overlap volume between PTV and bladder without changing the constraints.

The *Serial Complication Model* is the first function selected. The serial constraint uses a *power law exponent* (k) of approximately 6.0, and an *equivalent uniform dose (EUD)* value of approximately 7000cGy.

Use the *Quadratic Overdose* cost function to add two DVH constraints . In the above case 50% of the rectum volume is allowed to receive 5000cGy and 30% is allowed to receive 6800cGy. These two DVH constraints reflects typical dose points of clinical relevance. During the optimization checking if the DVH constraints are active or not is recommended. If they are active, then they are battling against the desired PTV coverage and one should be aware of the potential consequences.

Femoral Head requires one DVH constraint

The *Overdose-Volume Constraint* is the one DVH constraint selected for this case. The physician was willing to allow up to 10% of the femoral heads to receive 5000cGy. In most cases this constraint will be easily fulfilled and the constraint will be inactive. Some physicians might like to restrict the dose to the femoral heads even further. Alternatively, instead of the overdose-volume constraint a quadratic-overdose constraint could be selected with a *maximum dose* value of 5000cGy and an *RMS dose excess* value of 150cGy. The larger *RMS dose excess* value will allow some overdose to the femoral head if absolutely necessary to achieve other optimization goals.

External (or undefined voxels) require two constraints

The surface contour of the patient is used to constrain dose to all voxels not included in any structure listed above. Associating the undefined voxels in conformal plan helps ensure that the global hotspot is positioned inside the PTV.

The *Quadratic Overdose Penalty* is selected twice. The first constraint allows for a high *maximum dose* specified in the Reference Dose column of 7400cGy, which is approximately 200cGy below the prescribed target dose. Because the *maximum dose* value is high, a small *RMS dose excess* value of 50cGy is chosen. This constraint should not include a shrink margin and is applied to all voxels outside the PTV, which are not defined as a critical structure. The main purpose of this constraint is to make sure that hot spots are inside the PTV. The second quadratic-overdose constraint has a much smaller *maximum dose* value of 3800cGy, but a larger *RMS dose excess* value of 200cGy and a 1.0-cm shrink margin. The purpose of this constraint is to minimize dose to all voxels with more than 1cm distance to the PTV, or at least below 3800cGy. The 3800cGy is selected because it is about one half of the prescribed dose. The high *RMS dose excess* value gives the optimizer some freedom to produce high-dose areas inside normal tissue if required to ensure good PTV coverage.

The above listed method and constraints will produce good prostate IMRT plans. After some slight modifications to meet specific department's criteria, customers will find that for almost all prostate IMRT patients the same constraints can be used. This is called a class solution and is one advantage of biological optimization constraints. Class solutions are configurations of beams and collections of objectives that seem to work well in solving inverse planning problems for different classes of cancers and disease sites. In Monaco, class solutions, when created, can be saved as Monaco templates.

A Head and Neck IMRT Case

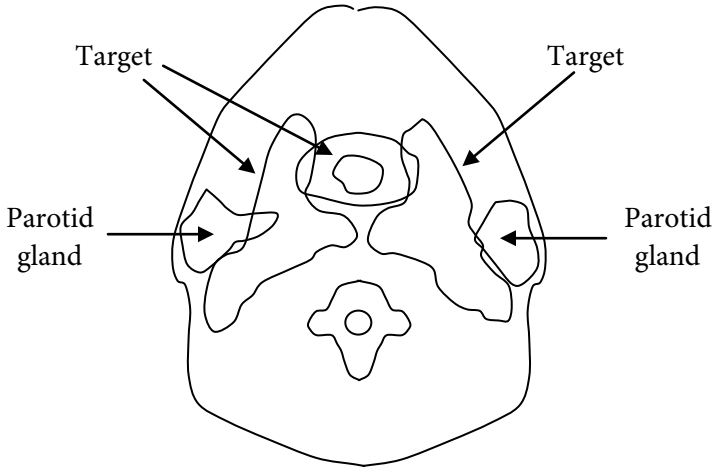

Figure 31: Target volumes overlapping parotid glands

Figure 31 above shows a schematic view of contours as are typical for H&N cases. The Monaco IMRT prescription page, which is where inverse planning objectives are specified, is shown in Figure 32. The prescription for this example has the following objectives:

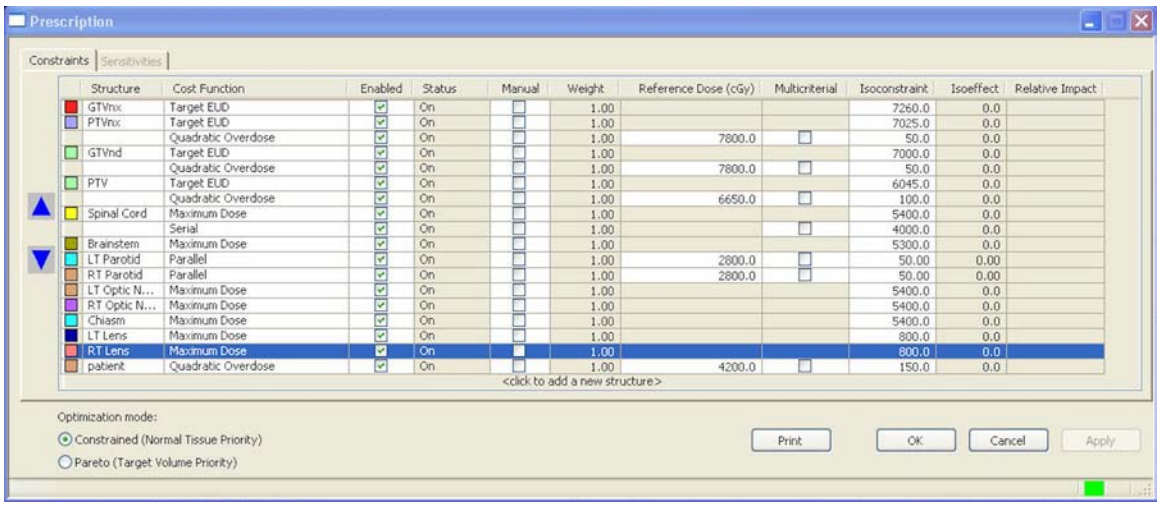

Figure 32: The Monaco IMRT prescription page for a H&N case

Target Objectives:

GTVnx: 95% > 7260 cGy

PTVnx: 95%> 7025 cGy

GTVnd: 95%> 7000 cGy

PTV: 95%> 6045 cGy

Target dose should be uniform, and no high dose as 4000cGY outside 1.5 cm margin of target volume

OAR Objectives:

Brain_stem: Serial-4000cGy

Maximum dose < 5400cGy

Spinal_cord: Maximum dose < 4000cGy

Parotid_L: Volume 3000cGy< 50%

Parotid_R: Volume 3000cGy< 50%

Lens_ L: Maximum dose < 800cGy

Lens_ R: Maximum dose < 800cGy

Optic_nerve_L: Maximum dose < 5400cGy

Optic_nerve_R: Maximum dose < 5400cGy

Optic_chiasm Maximum dose < 5400cGy

Next each cost function used in this H&N example and their parameters are described in more detail. For all structures the *Display total volume DVH* box was checked in the structure properties window.

GTVnx requires only one cost function

Since the GTVnx includes air cavities, the *Clear all voxels below the Minimum CT number* is checked in the structure properties window to force the optimizer to avoid putting dose in the air cavities.

The *Poisson Statistics Cell Kill Model* is selected to ensure that underdosage inside the PTV is kept to a minimum. A high *cell sensitivity* value of 0.5-0.75 should be chosen in order to minimize underdosage inside the GTVnx and also control overdosing as is typical biological optimization. As a result, the GTVnx coverage will be more homogeneous with a higher *cell sensitivity* value. For the isocontraint *prescription* value, the prescribed dose of 7260cGy was set.

No *Quadratic Overdose Penalty* is needed, because the GTVnx is completely inside the PTVnx, and the PTVnx quadratic-overdose constraint will also constrain maximum dose values inside the GTV. Ideally global hotspot will be inside the GTVnx. If a quadratic-overdose constraint was chosen, it would need to have a higher *maximum dose* value than the PTVnx overdose constraint. The prescription doses of both the GTVnx and PTVnx are close enough to allow this strategy if desired.

PTVnx uses two cost functions

Since the PTVnx includes air cavities, the *Clear all voxels below the Minimum CT number* is checked in the structure properties window to force the optimizer to avoid putting dose in the air cavities.

The *Poisson Statistics Cell Kill Model* is again selected to ensure that underdosage inside the PTV is kept to a minimum, a high "cell sensitivity" value of 0.5-0.75 is chosen. This will minimize underdosage at the interface between rectum and PTV and also control overdosing of the PTV. As a result, the PTV coverage

will be more homogeneous with a higher *cell sensitivity* value. For the isocontraint value, the prescribed dose of 7025cGy was set.

The *Quadratic Overdose Penalty* is selected to prevent the PTVnx from being overdosed too much. A *maximum dose* value of 7800cGy was chosen and entered in the Reference Dose column. A relatively small *RMS dose excess* value of 50cGy is chosen to restrict the dose tightly beyond this dose limit. The *optimize over all voxels in volume* box was checked to ensure that the overdose-constraints is also applied to voxels of the GTVnx.

GTVnd uses same cost functions of the PTVnx

The GTVnd includes air cavities, the *Clear all voxels below the Minimum CT number* is checked in the structure properties window to force the optimizer to avoid putting dose in the air cavities.

The *Poisson Statistics Cell Kill Model* is selected to ensure that underdosage inside the PTV is kept to a minimum, a high "cell sensitivity" value of 0.5-0.75 should be chosen. This selection will minimize underdosage at the interface between rectum and PTV and also limit overdosing the PTV. As a result, the PTV coverage will be more homogeneous with a higher "cell sensitivity" value. For the *prescription* value, the prescribed dose of 7000cGy was set.

The *Quadratic Overdose Penalty* is selected to prevent the PTVnx from being overdosed too much. A *maximum dose* value of 7800cGy was chosen. A relatively small *RMS dose excess value* of 50cGy is chosen to restrict the dose tightly beyond this dose limit.

PTV again uses the same cost functions

The PTV includes air cavities, the *Clear all voxels below the Minimum CT number* is checked in the structure properties window to force the optimizer to avoid putting dose in the air cavities.

The *Poisson Statistics Cell Kill Model* is selected to ensure that underdosage inside the PTV is kept to a minimum, a relatively high "cell sensitivity" value of 0.4-0.6 should be chosen. This value is a little bit lower than the values used for the target volumes described above and will allow some underdosage to the PTVnd, which is important because of the proximity of this structure to the parotid glands. For the *Isocontraint* value, the prescribed dose of 6045cGy was set.

The *Quadratic Overdose Penalty* is selected to prevent the PTVnx from being overdosed too much, a *maximum dose* value of 6650cGy was entered as the *Reference Dose*. An *RMS dose excess* value of 100cGy is chosen to restrict the dose beyond this dose limit. A shrink margin of 0.8cm was chosen to make sure that this overdose constraint does not restrict the dose to the GTVnd.

Spinal Cord and brainstem (or spinal cord + margin)

The *Maximum Dose Constraint* is selected to prevent the spinal cord or brainstem from exceeding the allowed dose. The hard maximum dose constraint was chosen and the maximum dose was set in the isoconstraint column to 4000cGy for the spinal cord and 5300cGy for the brainstem.

Alternatively, or in addition, one could choose a serial dose constraint for the spinal cord and brainstem. In that case, a very high power law exponent of 14 would need to be chosen in combination with an *equivalent uniform dose value* of approximately 3800cGy for spinal cord and 4600cGy for brainstem. The advantage of the serial constraint is that the optimizer will reduce the dose to the spinal cord and brainstem beyond the allowed tolerance dose whenever possible without a significant reduction of the PTV coverage. The disadvantage obviously is that even though the high power law component of 14

greatly restricts voxels from getting high doses; the serial dose constraint is not a hard constraint like the maximum dose constraint. A combination of both constraints therefore may be reasonable.

Parotid glands require one cost function

The *Parallel Complication Model* is the most important and effective cost function for the parotid gland. You can use the *Serial Complication Model* with the *Parallel Complication Model* to affect the low-dose or high-dose regions of the DVH curve. . Parotid glands are parallel organs, such that a certain percentage of their volume can be damaged without losing organ function. For the contra-lateral parotid a *Reference Dose* value of 2600-2800cGy is specified. For the ipsi-lateral parotid a slightly higher value of 2800-3000cGy is typically specified. A *power law exponent* of 4 will ensure that all voxels exceeding the specified dose level will be spared as much as possible. However, by setting the *mean organ damage* value to 50% in the isoconstraint column, about half of the parotid volume is allowed to exceed this dose. Use of the Parallel *Complication Model* in combination with the *optimize of all voxels in volume* box checked is important.

Alternatively, one can check this box and use a serial dose constraint with a *power law exponent* of 1 for the parotid. A relatively large percentage of the parotid gland will then be allowed to receive doses above the *reference dose* with similar results to the parallel dose constraint.

Optic nerve, chiasm and lenses require a maximum dose constraint

The *Maximum Dose Constraint* is selected to prevent the chiasm, optic nerves, eyes and lenses from exceeding the allowed dose, the hard maximum dose constraint needs to be selected and the maximum dose needs to be set to the tolerance dose of these organs (5400cGy for the optic nerve and chiasm or 800cGy for the lenses). The quadratic-overdose constraint would not be an alternative, because it is not a hard constraint. A serial dose constraint would also not be useful, since the volumes are in general so small that the only thing that is of interest is the maximum dose value.

Alternatively if these dose restraints are not required for a particular patient, then a similar strategy could be followed as described above for the spinal cord. A serial dose constraint with a high power law exponent of 14 could be added to the maximum dose constraint.

External (or undefined voxels)

The surface contour of the patient is used to constrain dose to all voxels not included in any structure listed above. This guarantees a conformal plan and helps making sure that the global hotspot is positioned inside the PTV.

The *Quadratic Overdose Penalty* is selected in this case. The constraint has a *maximum dose* value of 4200cGy (typical values are between 4000cGy and 4800cGy), but a larger *RMS dose excess* value of 150cGy and a 1.0-cm shrink margin. The purpose of this constraint is to minimize dose to all voxels with more than 1.0-cm distance to any PTV by as much as possible, or at least below 4200cGy where possible. 4200cGy is a little more than one half of the prescribed dose. The high *RMS dose excess* value allows the optimizer some freedom to produce high-dose areas inside normal tissue if required for good PTV coverage.

In addition to the quadratic-overdose constraints, a *Maximum Dose Constraint* with a maximum dose value at around 113% of Rx dose and with the *optimize over all voxels* box checked can be used. The global maximum of the plan will be controlled, which can be a problem with H&N IMRT. In the initial stage, the optimizer will not use this constraint so it will shut off automatically. In the 2nd stage this constraint often kicks in.

Summary

Inverse planning in Monaco IMRT is accomplished in two stages. In the first stage, optimization is over beamlets, and in the second stage, optimization is over deliverable beam doses through use of multileaf collimators (MLC) and arcs. The Monte-Carlo dose calculation MUST always be selected for the final dose calculation. Careful selection of isocenter position and beams must take place before an optimization should be started. Typical prescriptions include a combination of biological and physical constraints and it is important to understand how they impact the optimization result. Experienced users will quickly find class solutions facilitated through use of templates for many IMRT treatment sites or learn quickly how to tweak constraints to achieve the results they want. With practice, one can efficiently produce high-quality IMRT plans, optimized with biological constraints and a Monte Carlo dose calculation.

Appendix A: Useful Tips

Should I use Underdose-Volume Constraints for target volumes?

You have a few different options. You can try to increase the Cell Sensitivity. However, this can lead to a higher maximum dose applied to the target. If you want to try this option, start at 0.5. Increase it if target coverage becomes an issue. In some cases, an Underdose –Volume Constraint cost function will help target coverage.

What values of Cell Sensitivity are good for target volumes?

Try using a higher cell sensitivity value (i.e., 0.5 to 0.75) to reduce cold spots. Use of a higher cell sensitivity value on a target within a target helps push the hot spot inside the high dose target. Increasing the cell sensitivity value may increase optimization time since the optimizer will try harder to eliminate cold spots yet meet the constraints of the OARs making the problem more difficult to solve.

Are there times when one should consider use of a *Maximum Dose Constraint* rather than a *Serial Dose Constraint* for a serial organ?

Consider using a *Maximum Dose Constraint* on small structures (lens, optic nerves, etc.) since there is so little volume to spare.

What are some tips for Parotid Glands?

Pick one parotid to be spared and apply a harder constraint than on the other. The following options for controlling the parotid dose are considered good practice:

Select a *Parallel Cost Function* with the following: A *Reference Dose* of approximately 2600cGy with a *Power Law Exponent* of ~ 4 with a Mean Organ Damage percent of about 40 to 50%. Try *Optimize Over All Voxels* because if you don't you are allowing high doses in the non-overlapping portions of the parotid. *Optimize Over All Voxels* should allow the high doses to occur in the Overlap region and reduce the dose elsewhere. Although in some cases selecting the *Optimize Over all Voxels*, the optimizer can cause a cold spot in the PTV in the region of overlap.

Use a *Serial Cost Function* (to control dose in non-overlap portion) with the following: A Power Law Exponent of about 8 with an Equivalent Uniform Dose which approximately depends on overlap. Do not select *Optimize Over All Voxels* because, you are only controlling the dose in the non-overlap region and trying to keep it low.

Use a *Serial Cost Function* to control mean dose by selecting a *Reference Dose* of about 2000 cGy. Also *Power Law Exponent* should be set to 1 so that the cost function is now working to control mean dose, while low and high doses are less important. From a mathematical standpoint, a *Serial Cost Function* is more agreeable to the Optimizer and thus may be a very good choice of cost functions. Also select *Optimize Over All Voxels*

What Normal Tissue Cost Functions are appropriate?

Use of *Quadratic Overdose* is useful If using two cost functions, the first one should have a Maximum Dose approximately equal to the high dose target with a zero shrink margin. Use care not to constrain the *Quadratic Overdose* cost function so much that you do not allow for doses in the buildup region. Also the *Maximum Dose* cost function can be used to control the global maximum dose. Typically a *Maximum Dose* of 113% of the prescription dose is reasonable while selecting *Optimize Over All Voxels*.

Appendix B: Changes to Patient Model in Monaco 3.30

A change to the dose voxel sampling process was implemented in Monaco 3.30. In summary, this change discontinued interpolated occupancy of structures within the CT voxels for sampling by the dose voxels on creation of the patient model. The effects of this change as it relates to the electron density sampling are fairly obvious. This change will also affect VOI occupancy with subsequent impact to the cost function occupancy. Overall, this change should remove dose voxels outside volumes of interest. This will cause volumes of interest to decrease in volume, particularly at interfaces. As a consequence of this change treatment planning templates may require re-tuning to increase cost function effectiveness or increase blocking margins.

Volume of interest occupancy is directly related to the creation of dose voxels. Dose Voxel creation is discussed at length in the Monaco Dose Calculation technical Reference, LRMMON0001. In the examples shown within this document a wedge shaped contour has been created and copied within the image study set. This creates a triangular prism volume of interest. By copying this contour onto adjacent slices the three dimensional problem is collapsed into a two dimensional problem that is more easily visualized.

To understand the volume of interest occupancy of dose voxels the structure occupancy of CT voxels must be understood. In Monaco, a structure occupies a CT voxel when any portion of the voxel is traversed by the structure contour. There is no partial occupancy of CT voxels, however CT voxels can be occupied by multiple volumes. Figure 33 shows the relationship of the original drawn contour and the occupancy of the CT voxels. The reader will recognize that this approach to CT voxel occupancy always causes a slight expansion of the structure volume when compared to the geometric volume of the drawn contour.

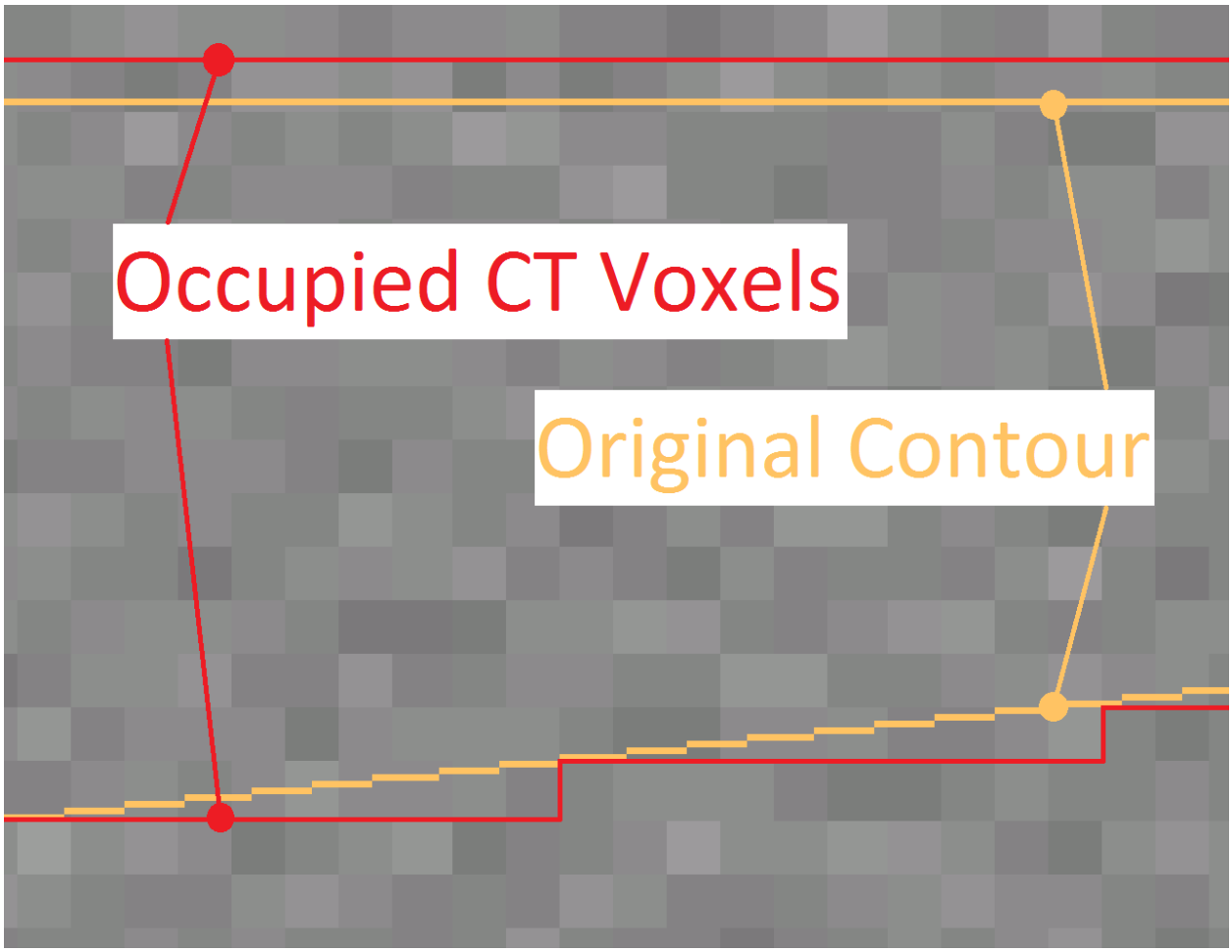

Figure 33 - A figure showing the original contours as drawn as well as the resulting CT voxels occupied by the wedge structure.

In Monaco 3.20.01 and earlier, an additional tri-linear interpolation was applied between CT voxels. This interpolation assigned a value of 1 to the center point of occupied voxels, and assigned a value of 0 to the center point of un-occupied CT voxels. Figure 34 depicts this interpolation. In Figure 34, the red points indicate occupied CT voxels assigned an occupancy value of 1, yellow points indicate un-occupied CT voxels assigned an occupancy value of 0, orange arrows indicate the interpolation between points.

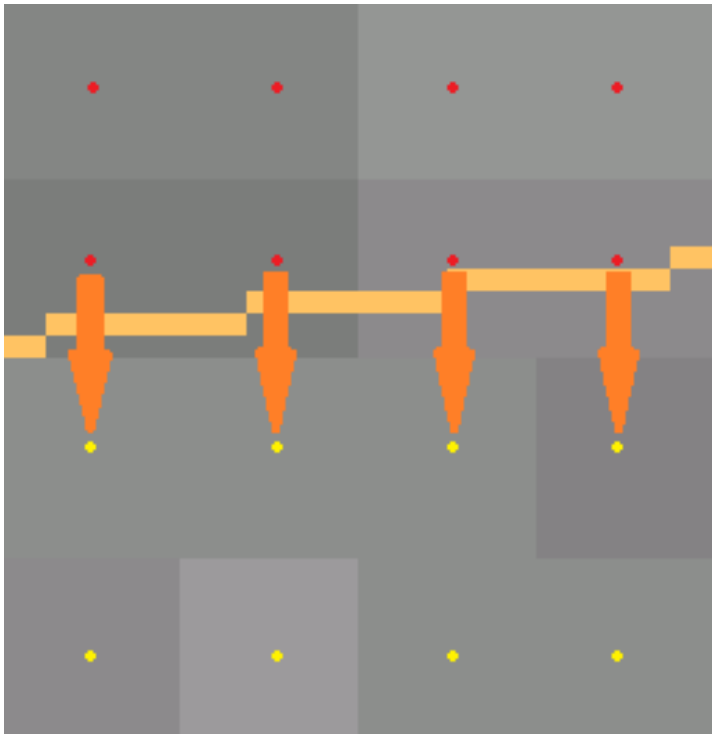

Figure 34 - Illustration depicting CT voxel occupancy and interpolation in Monaco 3.20.01.

Interpolated occupancy was discontinued in Monaco 3.30. Beginning in Monaco 3.30 the entire volume of occupied voxels is assigned a value of 1, the entire volume of un-occupied voxels is assigned a value of 0. A comparison of the CT voxel occupancy is shown in Figure 35.

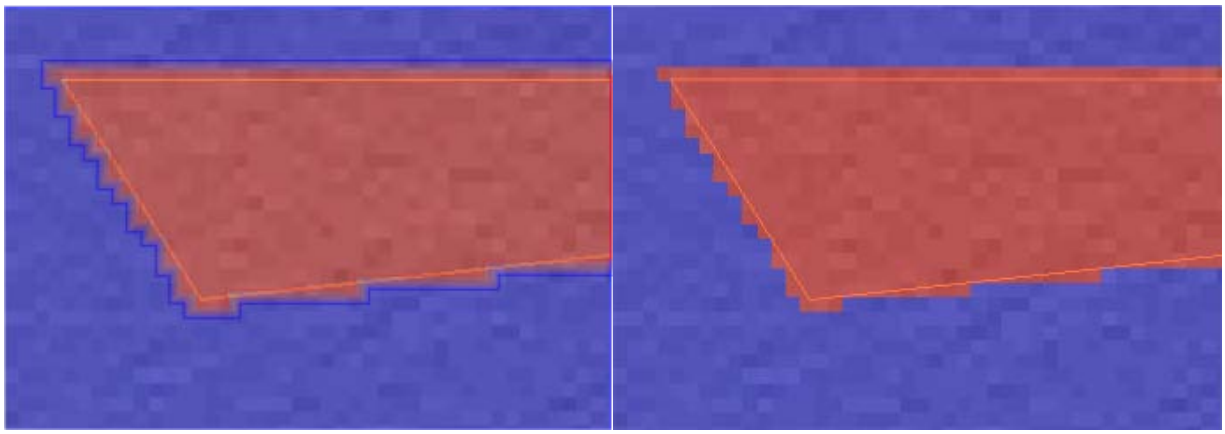

Figure 35 - CT voxel occupancy, comparing results of Monaco 3.20.01 (left) to Monaco 3.30 (right). The extents of Monaco 3.20.01 CT occupancy interpolation is accentuated for clarity.

Close examination of Figure 35 reveals that CT occupancy in Monaco 3.20.01 is increased by one-half CT voxel in all directions as a result of interpolated occupancy This effect is undesirable, and is among the reasons that interpolated occupancy was discontinued in Monaco 3.30.

Monaco dose voxels are created when optimization or calculation routines are called. Dimensions of dose voxels are user defined. The center of a dose voxel will be aligned with the first isocenter. Dose voxels are extended to cover the entire patient contour. Patient data is assigned to dose voxels through a method of super sampling. In this method of super sampling the dose voxel is subdivided into 27 sub-voxels (Figure 36). The underlying CT data is then sampled at the center point of these sub-voxels, the mean of these values is then assigned to the dose voxel.

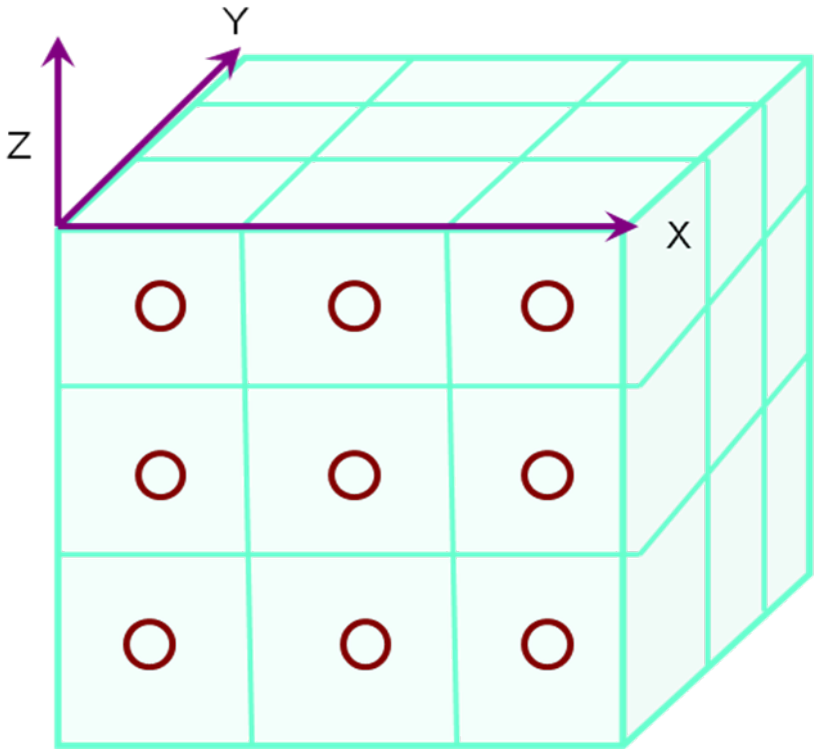

Figure 36 - Artistic depiction of dose voxel subdivided into 27 sub-voxels.

Figure 37 shows the wedge contour with volume of interest occupancy of dose voxels as calculated in Monaco 3.20.01.

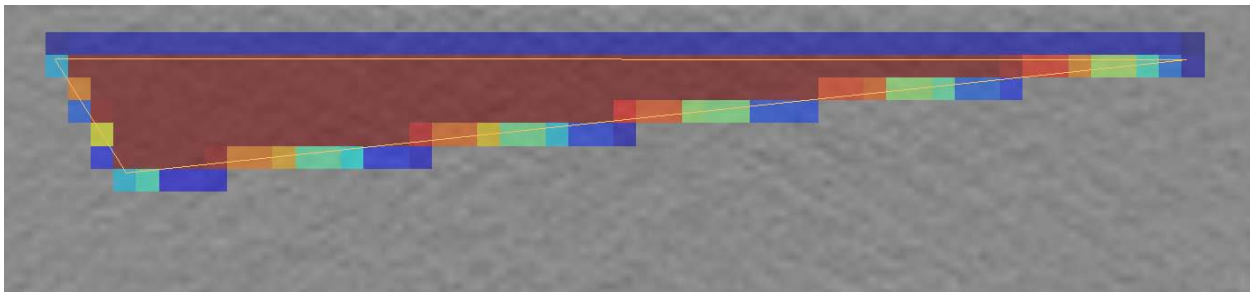

Figure 37 – "Wedge" contour with volume of interest occupancy of dose voxels as calculated in Monaco 3.20.01.

Figure 38 shows the identical wedge contour with volume of interest occupancy as calculated in Monaco 3.30. The reader will notice differences in the volume of interest occupancy calculation. These differences arise solely from the interpolated occupancy of the CT voxels.

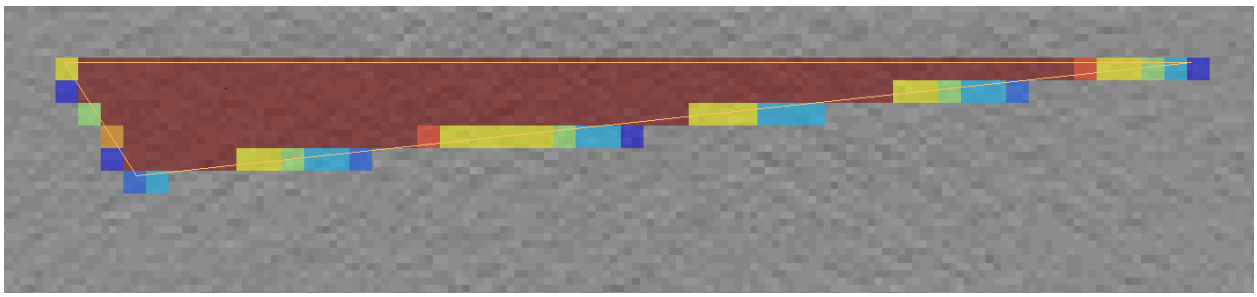

Figure 38 - "Wedge" contour with volume of interest occupancy of dose voxels as calculated in Monaco 3.30.

As described, the change to discontinue interpolation of CT information will impact the Monaco patient model. This change has been implemented to improve the patient model in Monaco. At a visual level, users should expect to see differences in the creation of dose voxels within all patient structures. As these structures are created differently the occupancy of cost functions will also change. As the occupancies of cost functions vary the overall shaping of fields will change. In nearly all cases, volumes will be reduced in size.

Small structures will experience the largest relative changes as a result of VOI occupancy reductions. Larger structures, while experiencing similar absolute VOI occupancy reductions, will experience much smaller relative changes as a result of VOI occupancy reductions.

Clinical examples of the reduction in VOI occupancy are contained in Figure 39 to Figure 41.

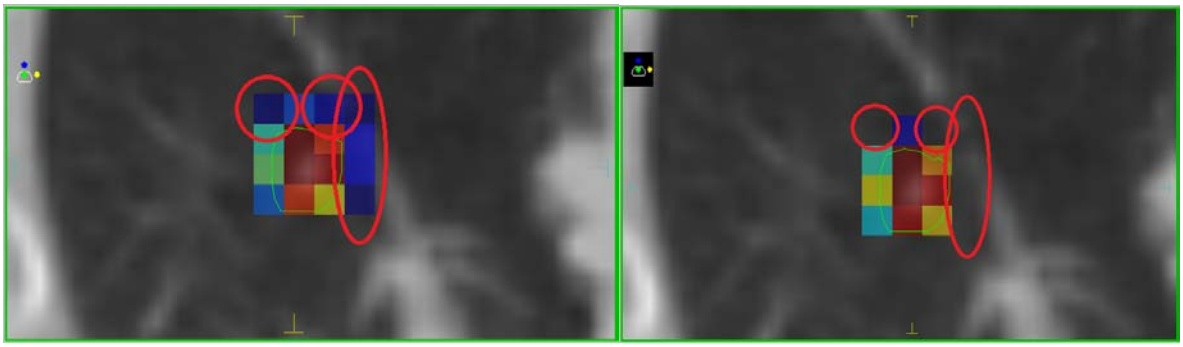

Figure 39 - Transverse view of small volume VOI occupancy, Monaco 3.20.01 (left), Monaco 3.30 (right). Dose voxels assigned to volume in Monaco 3.20.01 but not in Monaco 3.30 are highlighted.

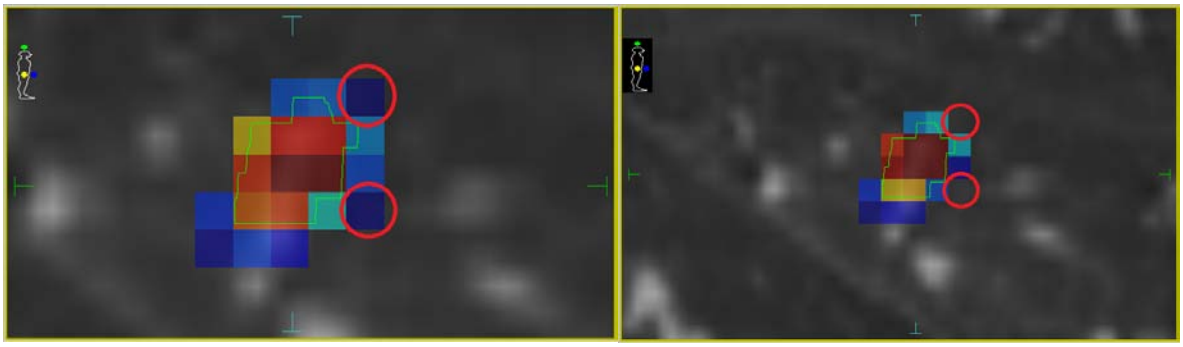

Figure 40 - Sagittal view of small volume VOI occupancy, Monaco 3.20.01 (left), Monaco 3.30 (right). Dose voxels assigned to volume in Monaco 3.20.01 but not in Monaco 3.30 are highlighted.

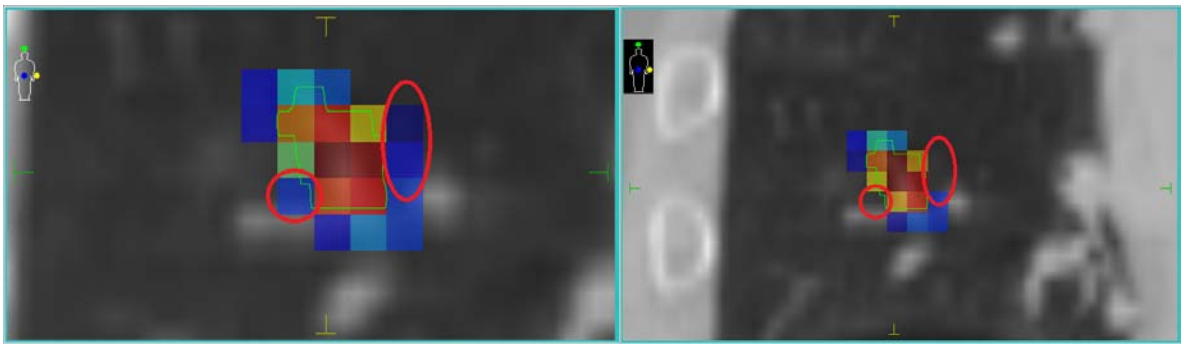

Figure 41 - Coronal view of small volume VOI occupancy, Monaco 3.20.01 (left), Monaco 3.30 (right). Dose voxels assigned to volume in Monaco 3.20.01 but not in Monaco 3.30 are highlighted.

As described, similar effects will be noted for larger volumes, but the relative effects will be much smaller.

Endnotes

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13723 Riverport Drive Suite 100, Maryland Heights, MO 63043

Manufacturer

Elekta Business Area Software Systems

IMPAC Medical Systems, Inc.

13723 Riverport Drive

Suite 100

Maryland Heights, MO 63043

USA

Phone: +1.800.878.4267

Fax: +1 314 812 4491

European Union Authorized Representative

EC REP

Elekta Limited

Linac House, Fleming Way

Crawley, West Sussex

RH10 9RR,

United Kingdom

Phone: +44 129 365 4242

Fax: +44 1293 471347

eu_ar@elekta.com

www.elekta.com

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Corporate Head Office:

Elekta AB (publ)
Box 7593, SE-103 93 Stockholm, Sweden
Tel +46 8 587 254 00
Fax +46 8 587 255 00
info@elekta.com

Regional Sales, Marketing and Service:

North America
Atlanta, USA
Tel +1 770 300 9725
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Europe, Latin America, Africa, Middle East & India
Tel +44 1293 544 422
Fax +44 1293 654 321
info.europe@elekta.com

Asia Pacific
Hong Kong, China
Tel: +852 2891 2208
Fax: +852 2575 7133
info.asia@elekta.com

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