THE CONCEPT OF LOCAL NORMAL TISSUE DAMAGE 
IN THE EVALUATION OF TREATMENT PLANNING
PARAMETER SPACE

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We accept this thesis as conforming to the required standard

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Abstract

At present, there is still no systematic approach to the radiation treatment planning process which aims to provide maximum dose to all the tumour cells while the surrounding, normal but critical tissues are minimally irradiated. In fact, the process of treatment plan selection is usually simply based on experience from a large number of past trial-and-error cases in individual cancer centers. In this thesis, two new concepts are introduced, that are demonstrated to be useful tools to rationalize a systematic planning process.

1. The concept of local normal tissue damage (LNTD) : Using a similar concept to that of “cellular damage” in radiobiological models, a concept of a localized “normal tissue damage” is introduced. This simple model is designed to make the best use of current limited clinical estimates of whole organ complication probabilities while providing a coherent framework that will preserve spatial information as well as condense the information into a numerical score for the plan.

2. The concept of parameter space mapping : Treatment parameter mappings will indicate the tissue-specific effect of the dose distribution resulting for the given parameter values. Such mappings can provide very useful insights for treatment plan selection. The use of this new tool is demonstrated in studying the values of the fixation point coordinates for the treatment of uveal melanoma at TRIUMF. Important insight is gained about the effects of the values of the fixation point coordinates on the probable success of the treatment. Such mappings help make treatment planning more efficient, objective and systematic which allows for a better exploitation of the
full potential of the proton beam.

The above concepts are combined to provide a systematic strategy for treatment planning that will rely on the tissue-specific response to inhomogeneous dose distributions. The $LNTD$ model is used to transform dose distributions into damage maps and then an overall score for that plan can be determined. This score is then used as the information mapped on a fixation point space mapping in order to facilitate selection of a plan. Also, the rationale for the development of multiple-fields is based on the resulting non-linearity of the $LNTD(d)$ curves and hence it is demonstrated that it can be used along with the parameter space mappings in order to successfully plan such a treatment.
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Chapter 1

Introduction

The survival of cancer patients depends on both the removal of the cancer cells and the retention of normal tissue. Hence, the ultimate goal of radiotherapy is to deliver a dose distribution that will eradicate the tumour without causing unacceptable levels of complication in the surrounding normal tissue (NT). Due to the cellular origin of cancer, a recurrence is usually determined by "cold spots" which are regions within the tumour that are under-dosed. Therefore, an ideal radiotherapy treatment plan (TP) should uniformly deliver the prescribed dose to the entire tumour while completely avoiding irradiation of the surrounding NT. In practice, uniform irradiation of the tumour to a tumouricidal dose is not achievable without some level of irradiation to the surrounding tissue. Therefore, a successful TP will be considered one for which the tumour receives as close as possible to a uniform prescribed dose while the NT receives a tolerable dose of irradiation.

The prescribed dose that is necessary to eradicate a specific tumour can be determined by in vitro studies of the dose response of tumourous cells as well as by experience resulting from the study of tumour recurrence in previously treated patients. In fact, the concept
of tumour control probability TCP has been developed [Niemierko and Goitein, 1993] to quantify such a response. TCP is defined as the probability of eradicating all tumour cells and is primarily a function of dose.

However, in order to determine quantitatively the amount of dose the NT can receive with negligible effects resulting, it is necessary to assess the response of NT to dose, at the level of functional breakdown of the whole organ. For a uniform irradiation, it will not only depend on the absolute value of the dose, \( d \), but also on the fractional volume, \( v \), of the NT that receives this dose. In contrast to the dose response of tumourous cells, dose survival response for most normal tissue cells cannot be determined by standard in vitro techniques because these cells are usually differentiated so they do not form colonies. However, since the response of interest is not at the cellular level, the inability to perform in vitro studies is not crucial. In fact, the only data available for tissue response estimations at the level of the whole organ breakdown is derived from the study of previously treated patients [Rubin et al., 1975; Rubin and Poulter, 1978; Emami et al., 1991].

Analogous to TCP, the concept of NT complication probability (NTCP) was introduced [Dritschilo et al., 1978] to quantify this tissue response to dose. This concept is a fundamental one and may be a function of several factors, however, for simplicity, it is has presently been assumed to be a function of only volume and dose in the literature. In fact, \( NTCP(v, d) \) has been defined to be a measure of the probability that a fractional volume, \( v \), of a specific organ or tissue, irradiated to uniform dose, \( d \), will cause the predefined complication to occur. However, since NTCP is taken to be a function of only \( v \) and \( d \), the spatial information, indicating the location of \( v \) irradiated to \( d \), is not considered.
The result is that $NTCP(v, d)$ does not preserve spatial information since any one value for $v$ and $d$ will result in a single $NTCP(v, d)$ value, regardless of the location of $v$ within the $NT$. Presently, most $NTCP$ estimation schemes make use of dose volume histograms ($DVHs$) which are a form of condensing the dose distribution information. The assumption of organ homogeneity leading to the loss of spatial information is inherent in such a representation as well. Therefore, as is noted in the literature [Lyman,1985; Sontag et al.,1991], since it is important to retain the spatial information because many clinical decisions based on the evaluation of plans require a knowledge of the spatial distribution of dose, $DVHs$ cannot replace the original isodose distributions and, hence, both must be used in conjunction.

It is important to note that the complication or end-point considered must be clearly defined in order to assign meaningful $NTCP(v, d)$ values to the observed patient responses to dose. Any subjectivity or ambiguity in this definition will result in an uncertainty in $NTCP(v, d)$ data which serve as the sole basis for many $NTCP(v, d)$ models. Also, the data must be estimated using a large sample population of patients in order to minimize the uncertainty. Inter- and intra-patient variability has been considered in several $NTCP$ models [Niemierko and Goitein,1993; Jackson et al.,1993] and these tend to add even more uncertainty to the present $NTCP(v, d)$ estimates. Keeping this in mind, at present one can only work with these crude tissue response estimates and hope that in the future, better data will allow for improved understanding of dose effects on $NT$. In the meantime, one may argue that these values are only meant to serve as a relative measure of the probable success/failure of a $TP$, in the intercomparison of competing plans, and not as
an absolute scheme to predict normal tissue effects.

In order to understand the tissue specific dose response of NT in treatment planning, it is essential to understand the response of tissue to an inhomogeneous irradiation since most plans will result in such dose distributions. Much work has been done [Kutcher et al., 1991; Lyman, 1985; Burman et al., 1991] to try to deduce NTCP values for such irradiations based on data supplied in the form of dose values \( D_{NTCP}(v) \) for which \( v \) of an organ uniformly irradiated to this dose will have a specified NTCP value (e.g. for \( NTCP = 5\% \) and \( NTCP = 50\% \), these doses are written as \( D_{5}(v) \) and \( D_{50}(v) \) respectively). In most cases, assumptions must be made about the structure and function of the different fractional volumes contained within the organ. A basic assumption made in most NTCP models is that of organ or tissue homogeneity which is consistent with the loss of spatial information. This assumption is justified by noting that if there is very obvious inhomogeneity, then that portion of the organ can be treated as a separate tissue altogether.

Attempts to optimize TPs are often based on maximizing the probability of uncomplicated tumour control \( (P_{UTC}) \) [Kallman et al., 1992a; Agren et al., 1990] which combines the concept of TCP and NTCP and is defined as: \( P_{UTC} = TCP(1 - NTCP) \) for uncorrelated TCP and NTCP [Agren et al., 1990]. Such a function is then used in several optimization algorithms as the objective function which must be maximized. If several competing plans are constrained to uniformly deliver the prescribed dose to the tumour such that \( TCP = 1 \), then \( P_{UTC} \) will be maximum for the plan resulting in the minimum NTCP. In such a case, determining the NTCP values corresponding to any given dose
distribution will allow for a characterization of the specific $TP$ which resulted in the given distribution and, hence, will serve as a relative, quantitative evaluation of the plan. This value alone can then be used to rank competing plans. If more than one type of complication is considered, a relative gravity based on the therapist’s judgement may be used to assign a weight ($w_i$) to each contributing $NTCP_i$ such that $\prod_i (1 - w_i \cdot NTCP_i)$ is maximized [Schultheiss and Orton, 1985].

This leads to another important aspect of treatment planning. It is important to be able to determine the relationship between particular treatment planning parameters and the resulting dose distributions. The value of such parameters will define the $TP$ and will affect the resulting dose distribution along with its associated relative score or rank as given, for example, by the $NTCP$ value for that plan. Once the treatment planning parameters are determined, it can be very informative to study the behaviour of the dose distribution as the parameters are varied. Since each dose distribution may be assigned a corresponding score, there may be relatively desirable or forbidden areas in parameter space that become apparent. If this is the case, such a study would facilitate the choice of parameter values that will ultimately define the optimal plan used for treatment and hence help in decision making. It may also allow for a more systematic and rigorous use of the information presently used in treatment planning.

Finally, while the physical dose distribution in the form of isodose contours is independent of the prescribed dose, the $NTCP(v, d)$, or tissue response in general, will depend on the absolute doses used because of the non-linear relationship between $NTCP$ and dose. Given the treatment planning parameters, the validity of the aforementioned study
would ultimately depend on the accuracy of the dosimetry and the validity of the dose calculations used to anticipate the resulting dose distributions.

These considerations, thoroughly discussed by Ling et al. [Ling et al., 1993], are essential in assuring a successful TP and are the scope of this thesis. For simplicity, the scope of this thesis is limited to the study of NT in radiotherapy treatment planning evaluations and, hence, TCP = 1 is assumed throughout. Both main chapters of this thesis are based on the first two aspects of treatment planning mentioned above and it is emphasized that the validity of any such aspect of treatment planning is indeed dependent on the accuracy of the dosimetry and dose calculations. However, this thesis will not be concerned with the study of dosimetry since that alone is believed to be material enough for an entire thesis. First, a model which preserves spatial information while estimating the dose response of an inhomogeneously irradiated whole organ or tissue is presented in Chapter 2. Most of the material of that chapter has been discussed in a paper submitted for publication to Physics in Biology and Medicine [Lam and Chavez, 1995]. In Chapter 3, a study of the dependence of the quality of a TP on the specific treatment planning parameters, for the treatment of uveal melanoma with protons at TRIUMF, is performed. Finally, Chapter 4 serves to link the main ideas from these two chapters as the model developed in Chapter 2 is incorporated into the treatment planning parameter study of Chapter 3 and the results are used to plan a real case: that of the first patient treated at TRIUMF. Although this work makes use of the software available at the proton facility at TRIUMF, such an approach serves as an example of treatment planning considerations and the results should be applicable to other charged particle facilities as well.
Chapter 2

The Concept of Local Normal Tissue Damage

2.1 Treatment Planning Evaluation Schemes

2.1.1 3-Dimensional Data Display Schemes

In the quantitative evaluation of radiotherapy treatment plans (TP), it is necessary to obtain scores for ranking. Each TP, resulting in a planned dose distribution, must be evaluated in an objective and systematic way. For 3-dimensional treatment planning, the extensive amount of data that must be compared makes the conventional method of displaying planar isodose distributions inadequate, inefficient and, in most cases, not helpful for selecting the best plan. Evaluation schemes have therefore been developed in order to deal with such a complex selectioning process. If a TP is to spare NT from "unacceptable" levels of radiation, the limits of "acceptability" of dose to different regions must be clearly outlined and taken into account when evaluating such a plan. Such was the idea of Shalev et al. [Shalev et al., 1988] who introduced the concept of "images of
regret” which are those regions in the dose distribution, where the NT has been irradiated to an “unacceptable” level as defined by certain preset limits derived from experience. The degree to which they have been overdosed is displayed along with the anatomical spatial information. Such a display emphasizes the tissue’s response to a particular dose distribution and would assist the clinician in assessing the relative merits of rival plans. This “regret” can then be quantified by means of score functions [Shalev et al.,1991].

Another way to deal with the overwhelming amount of data in 3-dimensional TPs is to condense the information in the form of dose-volume histograms (DVHs). The fraction of volume raised to specific dose values is displayed in what is referred to as a differential DVH, while the integral (or cumulative) DVH displays the fraction of volume receiving the stated dose or more. In general, integral DVHs are easier to interpret and appear smoother than differential DVHs. The former are therefore more readily compared when overlayed on the same plot [Drzymala et al.,1991], thus, if unspecified, DVH will refer to this type of histogram throughout this thesis. It is important to note that this condensed form of 3-dimensional or 2-dimensional dose distribution data does not preserve the original spatial information indicating the location, within the NT, of the fractional volume irradiated to a particular dose. Also, since all fractional volumes of the same dose are summed for each dose bin, they are treated as contributing equally to the overall complication, regardless of their location, so tissue homogeneity is intrinsically assumed. Combining the above ideas of DVHs, “images of regret” and score functions, Viggars has developed a computer program to evaluate DVHs in a consistent way for 3-dimensional treatment planning [Viggars et al.,1992]. Attempts have also been made to show how
those voxels\(^1\) in a dose distribution corresponding to a specific part of the DVH can be interactively displayed [Kessler et al., 1994].

### 2.1.2 Review of NTCP Models

**Modelling of the Dose Effect**

Several models have been proposed to describe the sigmoidal shape of the \(NTCP(v, d)\) response as a function of a fixed fractional volume \(v\) irradiated to a uniform dose \(d\). This general shape has been suggested by the crude data available to date. The two models most often used are the probit (or integrated normal) [Lyman, 1985] and the logistic [Schultheiss et al., 1983] models. The logistic model, as used by Schultheiss et al., can be written in closed form and therefore easily manipulated mathematically. For uniform whole organ \((v=1)\) irradiation, this model is written as:

\[
NTCP(1, d) = \frac{1}{1 + (\frac{D_{50}}{d})^k}
\]  

(2.1)

where \(NTCP(1, D_{50}) = 50\%\) and \(k\) is a slope parameter such that at \(d = D_{50}\) the slope is \(\frac{k}{4D_{50}}\) [Schultheiss et al., 1983].

Based on the observation of partial volume irradiation data from Rubin et al. [Rubin et al., 1975], Lyman [Lyman, 1985] presented an empirical function, called the probit or "integrated normal" model, to describe the \(NTCP\) behaviour. For whole organ irradiation, this model is written as:

\[
NTCP(1, d) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx
\]  

(2.2)

\(^1\)Voxels are small volume elements within the tissue, in which some physical quantity (e.g. dose) is measured and displayed.
where \( t = \frac{d - D_{50}}{D_{50}} \), \( x \) is a free variable, \( NTCP(1, D_{50}) = 50\% \) and \( m \) is a slope parameter.

In the above, it is implicit that \( D_{50} = D_{50}(1) \). Both the probit and logistic models can be written for any fractional volume \( (v < 1) \) uniform irradiation by using the corresponding \( D_{50}(v) \) where \( NTCP(v, D_{50}(v)) = 50\% \). Also, \( v = 1 \) may sometimes be defined to represent a partial reference volume \((v_{ref})\) and not the whole organ. In that case, all \( v < 1 \) are fractional volumes determined with respect to \( v_{ref} \) (e.g. \( v = \frac{1}{2} \) means the volume considered represents \( \frac{v_{ref}}{2} \) of the whole organ). Such a \( v_{ref} \) may be preferable in the case when the relevant dose information represents only a subsection of the whole organ. For example, if only the dose distribution information contained within a single plane in the whole organ is used to rank plans.

### Modelling of the Volume Effect

If \( D_{50}(v) \) is not known for all \( v \), it would be useful to relate the isodose \( NTCP \) values for the different partial volume irradiations of the same dose. To do so, some assumptions about the role of \( v \) in the organ response must be made and these are usually referred to as the volume effect models. The contribution of \( v \) to the functional breakdown of the organ can only be assessed if the structural, or more exactly, the functional architecture of the organ is identified. A number of such volume effect models have been proposed which can be categorized as "power laws" or "integrated dose" relationships and have been reviewed by some authors [Schultheiss et al., 1983; Wolbarst, 1984]. These models are used to relate the \( D_{NTCP}(v) \) to \( D_{NTCP}(1) \). However, many such relationships are not tissue specific and, in fact, apply only to skin or vascular stroma [Schultheiss et al., 1983].
The tissue specific "power law" written as:

\[ D_{NTCP}(1) = v^n \cdot D_{NTCP}(v) \]  \hspace{1cm} (2.3)

was derived by Schultheiss et al. [Schultheiss et al., 1983] making the assumptions of homogeneous dose distribution and small NTCP value. However, in their model, each \( v \) is assumed to be an essential component of the whole organ function. This results in what is commonly referred to as a "serial" organ structure, where each subvolume must be spared in order for the whole organ to be devoid of the complication or injury. In other words, since \( \frac{1}{v} \) such subvolumes make up the whole organ, using probability theory one can write:

\[ 1 - NTCP(1, d) = (1 - NTCP(v, d))^\frac{1}{v} \]  \hspace{1cm} (2.4)

which leads to:

\[ NTCP(v, d) = 1 - (1 - NTCP(1, d))^v. \]  \hspace{1cm} (2.5)

For \( NTCP(1, d) \ll 1 \), expanding Eq.(2.5) in a Taylor series and taking the first approximation gives:

\[ NTCP(v, d) = v \cdot NTCP(1, d) \]  \hspace{1cm} (2.6)

If the logistic model is used for \( NTCP(v, d) \) [Schultheiss et al., 1983] in Eq.(2.6), it will result in the tissue specific "power law", as given by Eq.(2.3), with \( n = \frac{1}{k} \). In the "critical element" model of a "serial" organ, using the logistic model, Eq.(2.6) is shown to hold only for \( D_{NTCP}(1)/D_{50}(1) \ll 1 \) which is shown to be an even more restrictive condition [Niemierko and Goitein, 1991].

Another possible structural architecture considered is that of a "parallel" organ where
all subvolumes must be killed or incapacitated in order for the whole organ to exhibit
the complication [Jackson et al., 1993; Yorke et al., 1993]. This results in what is called an
"integral dose response".

**NTCP as a Function of Dose and Volume**

Combining the above volume and dose effects on the NTCP value of a uniform irradiation,
3-dimensional $NTCP(v, d)$ surfaces can be generated from just a few data points for
different organs by fitting them to the multi-parameter equations of the aforementioned
models [Burman et al., 1991]. These surfaces can then be used to assign NTCP values
given any $v$ and $d$ values, where the dose $d$ is uniform inside the fractional volume $v$.

### 2.1.3 **NTCP for Inhomogeneous Dose Distributions**

**Analytic Equations Derived for Serial Organs**

Virtually all TPs will result in inhomogeneous dose distributions in the NT. If the above
models for uniform irradiations of different partial volumes of NT are to be clinically
useful, they must be extended to account for more realistic, inhomogeneous distributions.
Many different schemes have been developed to deal with such inhomogeneous distribu-
tions by making use of the basic ideas resulting from $NTCP(v, d)$ for uniform irradiation.

Following the assumptions of a "serial" organ structure, it has been suggested [Wolbarst
et al., 1980] that for a particular plan $P$, which assigns a different value $d_i$ to each of $N$
equally spaced grid points $i$ (representing the uniform dose received by the corresponding
$N$ voxels) of a reference volume ($v = 1$), the corresponding $NTCP$ for such an inhom-
geneous irradiation can be written:

\[ NTCP(P_{inhomo}) = \sum_{i=1}^{N} v_i \cdot NTCP(1, d_i) \]  

(2.7)

where the NTCP contribution from each subvolume is weighted by its volume \( v_i \). This has been shown to follow from the formulation for a "serial" architecture [Schultheiss et al., 1983] for which Eq.(2.4) gives:

\[ NTCP(P_{inhomo}) = 1 - \prod_{i} (1 - NTCP(1, d_i))^{v_i} \]  

(2.8)

Making, for every value of \( i \), the same type of approximation that was made to derive Eq.(2.6) from Eq.(2.5), Eq.(2.8) will yield Eq.(2.7) for \( NTCP(1, d_i) \ll 1 \forall i \). However, it is also noted that such a condition will probably not be satisfied for most curative radiotherapy TPs since therapists often rely on the fact that small regions of an organ can usually tolerate irradiations much greater than the whole organ could withstand [Schultheiss et al., 1983].

**DVH Reduction Schemes**

The prevailing schemes that allow determination of \( NTCP(P_{inhomo}) \) are based on the condensed form of dose information: DVHs. In a scheme suggested by Lyman and Wolbarst [Lyman and Wolbarst, 1987], multiple step DVHs, resulting from inhomogeneous irradiations, are reduced to a single step indicating the effective dose \( (d_{eff}) \) that the reference volume of the organ \( (v = 1) \) would have to receive in order to produce the same NTCP. The reduction scheme is based on a linear interpolation between steps (i.e. weighting the NTCP by the corresponding \( v \)) using the “power law” of Eq.(2.3), along with the \( NTCP(1, d) \) curve, to determine the value of NTCP associated with each step.
Another such $DVH$ reduction scheme using the "power law" was proposed [Kutcher and Burman, 1989] which reduces a multiple-step $DVH$ to a single step indicating the effective volume ($v_{eff}$) that would have to be irradiated to the maximum dose ($d_{max}$) in order to produce the same $NTCP$.

For the above schemes, $NTCP(1, d_{eff})$ and $NTCP(v_{eff}, d_{max})$ respectively, can be read off a predetermined, 3-dimensional $NTCP(v, d)$ surface for uniform irradiation.

### 2.1.4 Assumptions Inherent in Present $NTCP$ Schemes

Very elaborate mathematical models have been developed to derive $NTCP$ values for inhomogeneous dose distributions so that these may be used clinically to rank competing plans. Niemierko and Goitein [Niemierko and Goitein, 1993] present a sophisticated biophysical model which takes into account variations in tissue radiosensitivity and architecture of an organ for a single patient and for a patient population. Their model combines many of the previously mentioned ideas along with new concepts in a very thorough piece of work. However, such an elaborate biophysical model incorporates many parameters but is ultimately based on very crude data which makes it very difficult to test the model and justify this high level of sophistication. This emphasizes a need for improvement in the acquisition of such data before further development of such a model can be justified.

Many assumptions, inherent in other models as well, are explicitly discussed and acknowledged by these authors in a previous paper [Niemierko and Goitein, 1991] where, for small $NTCP : D_{NTCP}(1) \ll D_{so}(1)$, the empirical $DVH$ reduction models are shown to be equivalent. The important assumptions made are the following:
• the organ consists of a number of identical elements (this is consistent with the assumption of organ homogeneity)

• the responses of the individual elements are uncorrelated

• the elements are in "series" therefore, each one is "critical" to the functioning of the whole organ.

These elements are referred to by several other terms, the most common being "functional subunits" (FSU). There is however some ambiguity in the definition of an FSU since sometimes they are defined structurally (e.g. nephrons in a kidney) and other times they are defined functionally as the largest unit of cells regenerated from a surviving clonogenic cell without losing the specified function [Niemierko and Goitein,1991; Withers et al.,1988]. However, since the elements of the "critical element model" are assumed to have a certain functional role within the organ, it is the functional definition of an FSU that is most relevant.

In comparing the "serial" and "parallel" architectures, it is noted in the literature [Niemierko and Goitein,1991] that the behaviour would differ. There would be no expected volume threshold behaviour for the former since: "... stochastic effects do not exhibit a threshold behaviour." However, the latter would require a certain amount of volume incapacitated before expression of an injury to the whole organ would result. Complex structures of combined "parallel" and "serial" elements as described by their "relative seriality" [Kallman et al.,1992b] have been suggested, since complex biological systems

\footnote{The word "identical" here must refer to the \textit{biological function} of these elements and not necessarily their \textit{physical structure} since it is their contribution to the whole organ function and their response to dose that is postulated to be the same.}
would seem to be more appropriately modelled this way.

2.2 Local Normal Tissue Damage: \textit{LNTD}

2.2.1 Motivation

From the above review of current \textit{NT} dose response models, many problems become apparent. The need to understand and predict how an organ will respond to a specific dose distribution is essential when planning a treatment, since the dose distribution, which is the sole information used to characterize a specific plan, is not tissue specific. Also, dose is a local quantity which is defined as the amount of energy deposited per unit mass at that location while, on the other hand, tissue response is much more difficult to define locally since it is the functional breakdown of the whole organ that is considered. However, since most \textit{TPs} will result in inhomogeneous irradiations, a need to predict the effect of local dose variations on an organ's response will necessitate an understanding of the tissue response on a local level. The role each local unit of organ has to maintain in order to spare the tissue of a given complication must therefore be determined. In all the aforementioned models that have been developed to deal with inhomogeneous \textit{NT} irradiations, the spatial information contained in the original dose distributions is lost as all the dose information is condensed into a single \textit{NTCP} value. Ideally, once competing plans have been ranked according to their respective \textit{NTCP} values, the therapist would also like to have the spatial information indicating where the most affected part of the tissue lies within the organ. This may be important if two competing plans result in
very similar NTCP values, since then the location of the damage may serve as the sole criterion used to select the best plan.

2.2.2 Introduction to the LNTD Model

In many clinical situations, the choice of TP is based on the relative amount and location of damage to the NT adjacent to the tumour. It has been emphasized [Drzymala et al., 1991; Kessler et al., 1994] that DVH analysis should be accompanied by spatial information for appropriate evaluation of TPs. In this chapter, a basic scheme is developed, reconciliating the two basic pieces of information required for successful TP evaluations: (i) NT response to dose, referred to as "local NT damage" (LNTD) and (ii) spatial information in the form of damage maps. This model is based on the same assumptions as other serial structure models for NTCP, extended to apply on a local scale:

- organ homogeneity
- independence of local response
- "critical" function of each local unit (i.e. the organ behaves serially).

It is shown to be analogous to the ideas of "radiation damage" and "survival curves" currently used in radiobiology but applied on a whole organ scale rather than at the cellular level. The formulation is compared to that of the "Theory of Dual Radiation Action" [Kellerer and Rossi, 1972] which provides the familiar linear quadratic dose response relationship from the measurement of the microscopic dose distribution using the technique of microdosimetry [Rossi, 1959].
The local units are referred to as serial subunits (SSUs) to emphasize the importance of their role within the organ and to avoid any ambiguity in their definition that may be associated with FSUs. It is also pointed out that although most authors assume that any given organ is associated with a particular fixed architecture, this need not be the case. This assumption may result from the structural FSU definition, since then the FSUs obviously do not depend on the irradiation. However, functionally, the role of a subvolume may depend on the size and shape of that subvolume, which would in turn, depend on the direction of irradiation. For example, the spinal chord is commonly referred to as a serial structure [Niemierko and Goitein, 1991]. However, this assumes a complete transverse irradiation where \( v \) is determined only by the length \( (l) \) of chord irradiated such that one could write: \( v = l \cdot A \) where \( A \) is the cross-sectional area of the chord. If, for the sake of argument, the irradiation was longitudinal and did not cover all of \( A \), categorizing the spinal chord as serial would not seem justified. Such a consideration leads to the conclusion that any organ may be modelled by finding its particular SSU for the particular irradiation as long as one allows: \( 0 < \text{SSU} \leq 1 \). From a conceptual point of view, the SSU will be the smallest fractional volume of the reference organ \( (v = 1) \) which, if irradiated to a high enough dose, may cause the whole organ breakdown. For an organ responding in a purely "parallel" fashion to the particular irradiation, the whole organ is then the SSU for that organ.

Translating an isodose distribution map into an isodamage map on a point by point basis would be meaningful as long as the SSU is at least as small as the voxel size used for dose evaluation and that the dose for each voxel can be considered homogeneous.
If the SSU is much smaller than the voxel size then, grouping several, proximal SSUs would result in a larger subunit that still behaves serially and hence, the voxel can be considered as the SSU for the structure in all such cases. For a purely “parallel” organ where the SSU is the whole organ (SSU = 1), this model could only assign a damage value for uniform whole organ irradiation and hence the term “local” must be carefully interpreted: the LNTD of an organ can only be as “local” as the SSU. In cases where the SSU is not very small, the requirements for isodose distribution map translation may not be satisfied (e.g. voxel size < SSU) and thus, it may not be possible to produce an isodamage map.

It should be emphasized that the terms subunit and local do indeed imply: SSU ≪ 1. This is because the goal of this model is to introduce a new concept of local tissue response. If the organ does not respond to infinite levels of irradiation on a local level, which is the case for SSU not very small, then this new concept does not appear applicable. However, it should still be relevant as a working model since, in such cases, if several adjoining voxels receive non-zero dose then the average dose received by a subunit equal to the SSU for that organ will yield a non-zero NTCP value. Hence, although this model does not attempt to predict the response of NT to irradiations of v smaller than an SSU, in practice, if we do not know the size of the SSU, it is suggested that it should be taken equal to the voxel size, until it is experimentally determined. In fact, if for instance the SSU is twice the size of the voxel, the error in setting it equal to the voxel size will be the difference between: $\frac{LNTD(D_1) + LNTD(D_2)}{2}$ and $LNTD(D_1 + D_2)$, which will depend on the difference between $D_1$ and $D_2$. In addition, in contrast to that stated by Niemierko and
Goitein [Niemierko and Goitein, 1991] (see section 2.1.4), a threshold response would be possible since by definition of an SSU, irradiation to \( v < SSU \) would result in \( NTCP = 0 \) even for infinitely large doses. This phenomenon could be explained biophysically as a compensation mechanism whereby damage to any \( v < SSU \) can be repaired by adjacent tissue. Such behaviour may well characterize the dose response of some tissues [Niemierko and Goitein, 1991] and such a critical volume has been suggested [Kutcher et al., 1991; Lyman and Wolbarst, 1989]. Since in general, \( NTCP(v, d) \) for \( v < 1 \) is not negligible for infinite \( d \), this suggests that most NTs will have \( SSU < 1 \) and hence some form of serial functional infrastructure can be assumed.

### 2.2.3 Development of the LNTD Model

When \( SSU \ll 1 \), the concept of a true local damage exists since \( LNTD_{SSU}(d) \) is a measure of the number of "initiating events"\(^3\) occurring on average when an SSU is irradiated to a uniform dose \( d \).

Since the probability that the whole organ will express the injury or complication when a single SSU is irradiated to \( d \) is small if \( SSU \ll 1 \), it may be described by a Poisson statistical process as:

\[
1 - NTCP(SSU, d) = e^{-LNTD_{SSU}(d)}
\]  

(2.9)

which defines the relationship between the old concept of \( NTCP \) and the new concept of

---

\(^3\)Initiating events were referred to by Schultheiss [Schultheiss et al., 1983], as those events caused by radiation that will eventually lead to the expression of injury in the NT.
Solving for $LNTD_{SSU}(d)$ gives:

$$LNTD_{SSU}(d) = -\ln(1 - NTCP(SSU, d))$$

which demonstrates a highly non-linear relationship between $LNTD$ and dose if the usual sigmoidal shape for $NTCP(v, d)$, as a function of dose for a fixed volume (i.e. $v = SSU$), is assumed.

For an inhomogeneous irradiation, resulting from a plan $P$, where each of the $\frac{1}{SSU}$ subvolumes receives a dose $d_i$ ($i = 1, 2, \ldots, \frac{1}{SSU}$), since each $SSU$ must be spared in order to spare the whole organ, one can write:

$$1 - NTCP(P) = \prod_{i=1}^{\frac{1}{SSU}} e^{-LNTD_{SSU}(d_i)}$$

which can be written:

$$1 - NTCP(P) = e^{-\sum_i LNTD_{SSU}(d_i)}.$$  

Defining the total $NT$ damage ($TNTD$) as the sum of the $LNTD$:

$$TNTD(P) = \sum_i LNTD_{SSU}(d_i)$$

Eq.(2.12) becomes:

$$1 - NTCP(P) = e^{-TNTD(P)}$$

The $LNTD$ are therefore additive and the $TNTD(P)$ will be independent of the size of $SSU$. In the above, $NTCP(P_{inhomo})$ has been written as $NTCP(P)$ for simplicity, since the equations hold for any given plan $P$, yielding a homogeneous or inhomogeneous irradiation. Since all equations that apply to an inhomogeneous irradiation also hold for a homogeneous irradiation, but the reverse is not true, throughout the rest of this chapter,
(P) will imply any dose distribution while a uniform irradiation of a volume v to a dose d will be explicitly noted as (v, d).

It should be noted that the choice of this description is not arbitrary. It is analogous to the "Theory of Dual Radiation Action" [Kellerer and Rossi, 1972] where the survival response S(D) of a whole cell irradiated to an average, macroscopic dose D, is given as a function of the total yield of local lethal lesions⁴ (E(D)) and following a Poisson statistic: \[ S(D) = e^{-E(D)} \]. E(D) thus totals the local lesions, ε, produced on a sub-cellular scale as a function of the microscopic dose, z, called the specific energy. Due to statistical variations in energy deposition, there is a distribution, f(z; D), of the microscopic dose for a given macroscopic dose D. This distribution is measured by microdosimetry techniques [Rossi, 1959]. Analogously, in the case of whole organ dose response, the \( TND(P) \) represents the total of all the local damage, \( LNDSSU \), produced on a whole organ (or \( v_{ref} \)) scale as a function of the uniform dose, \( d_i \), received by the \( i^{th} \) SSU (\( i = 1, 2, \ldots, \frac{1}{SSU} \)). The distribution of \( LNDSSU(d_i) \) will correspond to the spatial distribution of dose for the particular plan P and will be as "local" as the SSU.

### 2.2.4 Practical Applications of the LND Model

From the property of additivity of the LND(d_i) for inhomogeneous irradiations and Eq.(2.14), the NTCP value for a particular TP resulting in an inhomogeneous dose distribution can easily be calculated. Also, differential DVHs can be used to easily determine \( TND(P) \) as long as the volume steps, \( v_j \) (\( j = 1 \ldots \) total number of steps),

---

⁴Lethal lesions are defined with respect to the killing of the whole cell. They are produced directly by intratrack action and indirectly by intertrack action through the interaction of sublethal lesions.
are larger or equal to the size of an SSU. In such a case, the TNTD(P) can be written as:

\[ \text{TNTD}(P) = \sum_j \text{LNTD}_{ssu}(d_j) \cdot n(d_j; P) \]  \hspace{1cm} (2.15)

where \( n(d_j; P) = \frac{\nu_j}{\text{SSU}} \) is the number of SSUs irradiated to a uniform dose \( d_j \) for a particular plan \( P \).

Once again, this formulation is analogous to the “Theory of Dual Radiation Action” where the total yield of lesions \( E(D) \) for a nonuniform average dose \( D \) is calculated by a linear summation as: \( E(D) = \int e(z) \cdot f(z; D) dz \), where \( z \) is the specific energy, \( e(z) \) represents the local lesions produced by \( z \) and \( f(z; D) \) is the specific energy distribution for a macroscopic average dose \( D \). Comparing this with Eq.(2.15), it can be seen once again that \( \text{LNTD}_{ssu}(d_j) \) is analogous to \( e(z) \), \( n(d_j) \) is analogous to \( f(z; D) \) and \( E(D) \) is analogous to \( \text{TNTD}(P) \). The analogy between the \( \text{LNTD} \) model and the “Theory of Dual Radiation Action” (TDRA) is given in Table 2.1.

Besides serving as a tool for quick NTCP assessment for inhomogeneous irradiations, the concept of \( \text{LNTD} \) can be used to translate isodose distribution maps into isodamage distribution maps. This feature is unique to this model since it preserves spatial information, thus allowing for the possibility of obtaining a pictorial representation of the tissue’s response to a specific dose distribution. For previously mentioned reasons, this may prove to be very useful in the evaluation of TPs.
Table 2.1: Analogy between the “Theory of Dual Radiation Action” (TDRA) and the “Local Normal Tissue Damage” (LNTD) model.

<table>
<thead>
<tr>
<th>TDRA model</th>
<th>LNTD model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D$</td>
<td>$P$</td>
</tr>
<tr>
<td>$z$</td>
<td>$d_i$</td>
</tr>
<tr>
<td>$f(z; D)$</td>
<td>$n(d_j; P)$</td>
</tr>
<tr>
<td>$e(z)$</td>
<td>$\text{LNTD}(d_i)$</td>
</tr>
<tr>
<td>$E(D)$</td>
<td>$\text{TNTD}(P)$</td>
</tr>
<tr>
<td>$S(D)$</td>
<td>$1 - \text{NTCP}(P)$</td>
</tr>
</tbody>
</table>

$S(D) = e^{-E(D)} \quad 1 - \text{NTCP}(P) = e^{-\text{TNTD}(P)}$

$E(D) = \int e(z) \cdot f(z; D) dz \quad \text{TNTD}(P) = \sum_j \text{LNTD}_{SSU}(d_j) \cdot n(d_j; P)$

2.2.5 Data “Pooling” for LNTD Determination

Since the $NT$ dose response data is presently scarce and very crude, the corresponding $LNTD$ values calculated from this model will also be crude. However, assuming they will improve in the future, the available data may be used to demonstrate the applicability of this model without making any statements about the accuracy of the results.

From Eq. (2.14), it is easy to see that for a uniform irradiation of $v$ to a dose $d$ one can write:

$$\text{TNTD}(v, d) = -\ln(1 - \text{NTCP}(v, d)).$$

(2.16)

Also, since there will be $\frac{v}{SSU}$ SSUs receiving this dose while $1 - \frac{v}{SSU}$ receive no dose,
using Eq.(2.13) and the fact that $LNTD_{SSU}(0) = 0$ by definition, one may write:

$$TNTD(v, d) = \frac{v}{SSU} \cdot LNTD_{SSU}(d).$$

(2.17)

Equating Eq.(2.16) to Eq.(2.17) gives:

$$LNTD_{SSU}(d) = \frac{SSU}{v} \cdot \ln(1 - NTCP(v, d))$$

(2.18)

where $LNTD_{SSU}(d)$ should be, in fact, independent of $v$. As stated in section 2.2.2, this translation of a set of $NTCP(v, d)$ data points into an $LNTD_{SSU}(d)$ data point leads to the “pooling” of $NTCP(v, d)$ data for uniform irradiation of different partial volumes of a given organ, into one single $LNTD_{SSU}$ vs $d$ plot. However, as is evident in Eq.(2.18), the absolute value of $LNTD$ will depend on the value of $SSU$.

From the data for different partial uniform irradiation collected by Emami et al. [Emami et al., 1991], which is given in the form of doses for 5% and 50% $NTCP$ ($D_5(v)$ and $D_{50}(v)$) for $v = 1, \frac{2}{3}$ and $\frac{1}{3}$, Eq.(2.18) can be used to determine $LNTD$ vs $d$ curves for the different organs. Unfortunately, the value of the smallest $SSU$ for such irradiations as well as the value of the voxel size used is not known. It is hence assumed, for simplicity, that $SSU = \frac{1}{100}$. This small value was chosen since the aim of this model is to preserve the local information from dose distributions and the smaller the $SSU$, the more “local” the translated dose information can be. Since the choice of this value will only scale the absolute values of the $LNTD$ curves, it cannot invalidate such a data “pooling” scheme in that it will not change the shape of the $LNTD(d)$ curve nor the value of $TNTD(P)$ and hence the resulting $NTCP(P)$ as calculated using Eq.(2.14). The resulting set of points, for each organ, will alone determine the validity of the assumptions inherent in
this model in that they may or may not form a smooth curve and \( LNTD(d) \) may or may not be the same for different \( v \) irradiated to the same \( d \). In either of these cases, Eq.(2.18) is not justified for that particular organ and irradiation. Fig.2.1 shows an example of the "pooling" procedure for the stomach.

\[
\begin{align*}
\text{(a) Dose: } & \quad \text{STOMACH} \\
\text{(b) Dose: } & \quad \text{STOMACH}
\end{align*}
\]

Figure 2.1: (a) \( NTCP(v, d) \) data points from Emami et al. (b) "pooling" of \( NTCP(v, d) \) data into one smooth curve for the stomach \( LNTD(d) \). Here \( LNTD \) values are for \( SSU = \frac{1}{100} \).

Such a data "pooling" scheme was performed on all the latest available data [Emami et al., 1991] which has also been the basis for some other \( NTCP(v, d) \) fitting procedures [Kutcher et al., 1991; Burman et al., 1991]. Several organs resulted in smooth plots (see section 2.2.6) suggesting our model may indeed account for the behaviour of some organs.

2.2.6 Fitting of \( LNTD(d) \) to an Analytic Function

In order to make use of the resulting \( LNTD(d) \) behaviour observed for the different organs from the data "pooling" scheme described above, it is necessary to describe the
relationship by an analytic function that can be used to calculate \( LNTD \) for any value of \( d \) in a plan \( P \). To do this, the "pooled" points for each organ must be fit by an organ specific function. This function can then be used to generate isodamage maps from isodose distribution maps and to calculate the corresponding \( NTCP(P) \).

Eq.(2.18) shows how \( NTCP(v, d) \) data is directly used to obtain the \( LNTD_{SSU}(d) \) data points. Since much work has already been done to fit \( NTCP(v, d) \) data by sigmoidally shaped functions, the simplest approach is to make use of one of these functions to derive an appropriate \( LNTD_{SSU}(d) \) fitting function. For this purpose, the use of the logistic model for \( NTCP(v, d) \) (Eq.(2.1)) is chosen, since it is easy to manipulate mathematically. Since Eq.(2.18) is satisfied \( \forall v \), choosing \( v = 1 \) in Eq.(2.1) to substitute for \( NTCP(1, d) \), Eq.(2.18) becomes:

\[
LNTD_{SSU}(d) = -SSU \cdot \ln(1 + \left( \frac{d}{D_{50}} \right)^k).
\]

This result, with \( D_{50} = D_{50}(1) \) implicit, provides a 2-parameter \( (D_{50} \text{ and } k) \), organ specific equation for the fitting of \( LNTD_{SSU}(d) \) data. Such a fit was performed for several organs as shown in Fig.2.2, where the resulting tissue specific parameters are indicated in each case. The fitting was done using the Gauss-Newton method which proceeds by iterative means until the sum of squares of the differences between the data points and the function being fitted converges to a minimum (see PLOTDATA manual for details).

The above fitting procedure was performed with no error analysis or standard measure of "goodness of fit" since large, unspecified uncertainties are associated with the \( D_5(v) \) and \( D_{50}(v) \) data as mentioned earlier. It is therefore not justified to treat the resulting \( LNTD \) data points as being accurate enough to warrant more sophisticated methods than.

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Figure 2.2: “Pooling” of $NTCP(v, d)$ data, from Emami et al., into single $LNTD(d)$ plots for various organs. Here $LNTD$ values are for $SSU = \frac{1}{100}$. The points were then fit to a two parameter tissue specific function, Eq.(2.19), which was derived from the “logistic” model for $NTCP(v, d)$. The resulting fit is indicated by the solid line and the tissue specific parameters, $D_{50}$ and $k$, are shown in each case. Note, T-M stands for temporo-mandibular.
determining the adequacy of the fits by eye.

2.2.7 Comparison of the LNTD Model with other Models

The resulting $D_{50}$ and $k$ from this LNTD fitting procedure should be compared with other such organ specific parameters found in the literature, since their values will lead to predicted dose responses of NT which may, or may not, coincide with those resulting from other fitting schemes. For example, the parameters found here may be compared with those that Burman et al. [Burman et al., 1991], obtained by fitting the same data to Lyman's empirical $NTCP(v, d)$ model, described by Eq.(2.2) with the four parameters: $v_{ref}$, $D_{50}$ (where $D_{50}$ implies $D_{50}(v_{ref})$ such that $NTCP(v_{ref}, D_{50}) = 50\%$), the slope parameter $m$ and the volume dependence parameter $n$ resulting from the "power law" relationship of Eq.(2.3). For all organs presented in Fig.2.2, $v_{ref}$ is the whole organ [Emami et al., 1991] which implies $D_{50} = D_{50}(1)$ is for whole organ irradiation and, hence, $v_{ref}$ does not act as a free parameter in this case. The $D_{50}(1)$ dose value is actually a given point of the data and despite the fact that, for the $NTCP$ fits, it was fixed to the given value while for the LNTD fits, it was treated as a free parameter, very small (i.e. negligible) differences between the values obtained from the two fitting procedures were observed (Table 2.2).

In contrast to other purely empirical fitting procedures applied to this data [Burman et al., 1991; Kutcher et al., 1991], the LNTD fitting procedure was derived from a model where specific assumptions about the functional behaviour of the infrastructure of the organ have been made. However, although the fits of Burman et al. were meant to be
<table>
<thead>
<tr>
<th>ORGAN</th>
<th>( D_{50}[Gy] )</th>
<th>( D_{50}[Gy] )</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOMACH</td>
<td>65</td>
<td>65.20 ( \approx ) 65</td>
</tr>
<tr>
<td>BRAIN</td>
<td>60</td>
<td>62.60 ( \approx ) 63</td>
</tr>
<tr>
<td>LIVER</td>
<td>40</td>
<td>41.58 ( \approx ) 42</td>
</tr>
<tr>
<td>TMJ</td>
<td>72</td>
<td>70.96 ( \approx ) 71</td>
</tr>
<tr>
<td>BRP</td>
<td>75</td>
<td>75.23 ( \approx ) 75</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>68</td>
<td>68.43 ( \approx ) 68</td>
</tr>
</tbody>
</table>

Table 2.2: Comparison of the \( D_{50}(1) \) parameter values. Column (1) is the parameter value used by Burman et al. in their NTCP fitting procedure. It is equal to the given data point \( (D_{50}(1)) \) [Emami et al., 1991]. Column (2) is the parameter value resulting from the \( LNTD \) fitting procedure, treating it as a free parameter.

purely empirical, assuming the “power law” volume dependence holds actually implies a certain relationship between the \( NTCP \) vs \( d \) curves (for fixed \( v \) values). More specifically, if the parameter \( n \) is known, Eq.(2.3) allows each \( D_{NTCP}(1) \) value, associating a whole organ dose to an \( NTCP \) value, to result in a \( D_{NTCP}(v) \) value, for \( v < 1 \). In other words, all \( NTCP \) vs \( d \) curves, for any value of \( v < 1 \), can be derived from the single \( NTCP(1, d) \) curve. In effect, the “power law” assumes the \( NTCP(v, d) \) curves (for \( v < 1 \)) will simply result from a scaling of the dose axis by \( \frac{1}{v^n} \) with respect to the \( NTCP(1, d) \) curve. The slopes at \( NTCP = 50 \), referred to as \( s_{50}(v), \forall v \), will therefore be related as : \( s_{50}(v) = v^n \cdot s_{50}(1) \). These are the unstated assumptions introduced by the “power law” to the model of Burman et al., which was meant to be purely empirical.
Due to the above considerations, it would seem that fitting procedures derived from clearly stated assumptions about the functional behaviour of the infrastructure of the organ would be more appropriate if a relationship between the \( NTCP(v, d) \) curves, for fixed values of \( v \), is to be used. Such fitting procedures are suggested here and the resulting parameters are compared, in an attempt to understand the effect of the assumptions on the resulting curves. The results may help to compare the parameters \( (m \text{ and } n) \) determined by Burman et al. with the \( k \) values presented in this thesis.

The "power law" has been shown to result from a "serial" organ model if only small \( NTCP \) values are considered [Niemierko and Goitein, 1991]. In such a case, if the dose responses are described by the logistic model, one obtains the relationship : \( n = \frac{1}{k} \). The parameter \( n \) can thus be compared to \( k \) only when exclusively small \( NTCP \) values are being considered. Otherwise, \( n \) will simply indicate the scaling factor : \( \frac{1}{\sqrt{n}} \), that, when applied to the dose axis of the \( NTCP(1, d) \), will result in a \( NTCP(v, d) \) curve (for \( v < 1 \)) that most closely fits the given data points.

If one assumes a "serial" organ and uses the logistic model to describe \( NTCP(1, d) \) (as given by Eq.(2.1)), using Eq.(2.5) to determine \( NTCP(v, d) \) and then setting the condition : \( NTCP(1, D_{NTCP}(1)) = NTCP(v, D_{NTCP}(v)) \) will result in the following :

\[
D_{NTCP}(1) = (((\frac{D_{NTCP}(v)}{D_{50}(1)})^k + 1)^v - 1)^\frac{1}{k} \cdot D_{50}(1)
\]  

(2.20)

which is similar to the form derived by Schultheiss et al. [Schultheiss et al., 1983] and by Niemierko and Goitein [Niemierko and Goitein, 1991]. This is referred to as the isoeffect (i.e. same \( NTCP \)) relationship between \( D_{NTCP}(v) \)s for whole organ (or \( v_{ref} \)), \( v = 1 \), and partial organ , \( v < 1 \), irradiations. Eq.(2.20), with \( D_{50}(1) \) fixed to a specific value, can be
used to fit the data of Emami et al. First, this fitting procedure was performed on only the small NTCP (NTCP = 5%) data and then on the full set of data. The resulting k values are shown in Table 2.3. In this table, the $\frac{1}{k}$ values, resulting from the isoeffect fits to NTCP = 5% data only, are compared to the values of n, obtained from the fits of Burman et al. since, for small NTCP, Eq.(2.20) reduces to the "power law" with $n = \frac{1}{k}$. These $\frac{1}{k}$ values obtained are very similar to the n values of Burman et al., since Burman et al. weighted the NTCP = 5% data points more heavily and, thus, essentially the same fitting procedure was performed in both cases. However, in the scheme of Burman et al., the "power law" relationship is assumed to hold for all values of NTCP.

If all the data points are used, the isoeffect fitting procedure consistently results in significantly larger k values (Table 2.3 (3)). Unfortunately, these values cannot be compared to the n parameter, since they do not represent a "power law" relationship. Nevertheless, the discrepancy in the k values resulting from the two isoeffect fits does suggest that the simple "power law" assumption, fit primarily to the small NTCP data points, will predict different NTCP(v, d) curves, for fixed v, than those resulting from the isoeffect fit to all data points. In particular, since the slope of the NTCP vs d curves at $d = D_{50}(v)$ is $\frac{k}{4D_{50}(v)}$, for any fixed v, the larger k values imply steeper sloped NTCP vs d curves at $d = D_{50}(v)$.

The resulting parameters from the isoeffect fits can be compared to the resulting k values from the LNTD fitting procedure since Eq.(2.20) was derived using the same assumptions that are inherent in the LNTD scheme. Since the LNTD fits were performed using all the data points, in order to be consistent with the observation mentioned in the
previous paragraph, one would expect the resulting $k$ values to be larger than those found using only the small NTCP data. In fact, since LNTD is a logarithmic function of NTCP and the LNTD points are fit on this scale, the greater NTCP values will be more heavily weighted and one would expect a greater increase of $k$ than that observed for the isoeffect fit to all NTCP data points. This is indeed the case observed for all the LNTD fits (Table 2.3 (4)). This phenomenon seems to result from the fact that, in order for a smooth curve to pass through the high LNTD-valued points, the curves must, in general, pass below the low LNTD-valued points, resulting in a steeper sloped LNTD vs $d$ curve at $d = D_{50}(1)$ (see Fig.2.2). Since the slope of LNTD($d$), as given by Eq.(2.19), at $d = D_{50}(1)$ can be shown to equal $\frac{kS_
u}{2D_{50}}$, the larger slope (steeper curve) will indeed result in a larger predicted $k$ value.

Having accounted for the differences observed in the $k$ parameter values resulting from different fitting procedures to the same data, in order to compare these values with the $m$ and $n$ from the literature, the following must be considered.

The reduction of the two parameters in the fits of Burman et al. to the single $k$ parameter of the LNTD fits is a direct consequence of the "seriality" assumption which results in Eq.(2.4), relating NTCP($v,d$) for $v < 1$ to that for $v = 1$. Two different phenomenological models have been proposed to describe the NTCP vs $d$ curves, for any fixed $v$: Lyman's probit (or integrated normal) model [Lyman,1985] and the logistic model of Schultheiss et al. [Schultheiss et al.,1983]. Each model uses the single parameter, $m$ and $k$ respectively, to describe the steepness of the NTCP($v,d$) curves, for fixed $v$, as long as $D_{50}(v)$ is known. In fact, for a given value of $D_{50}(v)$, they have been shown
Table 2.3: Comparison of the $m$ and $k$ parameter values resulting from fitting of the same $NTCP(v, d)$ data to different models. Column (1) is the parameter value determined by the $NTCP$ fitting procedure of Burman et al. Column (2) is the parameter value resulting from the isoeffect fitting of the $NTCP = 5\%$ data only to Eq.(2.20). Column (3) is the parameter value resulting from the isoeffect fitting of all the data to Eq.(2.20). Column (4) is the parameter value resulting from the $LNTD$ fitting procedure.

$$m = \frac{1}{1.647} \cdot \left(1 - \frac{D_5(1)}{D_{50}(1)}\right).$$  

The value is thus determined by the $v = 1$ data and assumed to be constant for all other $NTCP(v, d)$ curves for fixed values of $v < 1$. However, since $s_{50}(v) = \frac{1}{\sqrt{2\pi} \cdot m \cdot D_{50}(v)}$ for the probit model [Niemierko and Goitein, 1991], the $m$ and $n$ parameter values will both...

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determine the slopes to the $NTCP$ vs $d$ curves since the “power law” gives:

$$s_{50}(v) = \frac{v^n}{\sqrt{2\pi \cdot m \cdot D_{50}(1)}} \quad (2.22)$$

Burman et al. primarily used the $v = 1$ data points to determine the $m$ parameter value since, from Eq.(2.22), it is clear that the slope of the whole organ ($v = 1$) dose response is independent of $n$ since for $v = 1$, $v^n = 1 \forall n$. The comparison of the $m$ parameter alone (determined by Burman et al.) to the $k$ parameter (for the isoeffect fits and the $LNTD$ fits) values can, therefore, serve as an indication of the slopes of the predicted $NTCP(1,d)$ curves only.

If the “logistic” model is used to describe the $NTCP(1,d)$ relationship, then, given any two values of $NTCP$ ($NTCP(v,d_1)$ and $NTCP(v,d_2)$) for the same organ and the same volume, $v$, irradiated to two different doses $d_1$ and $d_2$, $k$ may be determined by:

$$k = \frac{\ln((\frac{1}{NTCP(v,d_1)} - 1)/((\frac{1}{NTCP(v,d_2)} - 1))}{\ln(\frac{d_2}{d_1})} \quad (2.23)$$

[Schultheiss et al., 1983] which, for $NTCP_1 = 50\%$, $NTCP_2 = 5\%$ and $v = 1$, becomes:

$$k = \frac{\ln 19}{\ln(D_{50}(1)/D_5(1))} \quad (2.24)$$

Fitting the $D_{50}(1)$ and $D_5(1)$ data of Emami et al. to Eq.(2.24), resulted in $k$ values (Table 2.4) which, when comparing to the $m$ values of Burman et al., gave the familiar relationship $m \approx \frac{1.6}{k}$. These are the $k$ values that would result in the same values of $s_{50}(1)$ for both models.

In order to compare the predicted $NTCP(v,d)$ curves, for $v < 1$, resulting from different fitting schemes, the $n$ parameter cannot be ignored. The $s_{50}(v)$ resulting from
Table 2.4: Comparison of $k$ and $m$ values. Column (1) is the parameter value resulting from fitting data ($D_{50}(v)$ and $D_5(v)$ of Emami et al. for $v = 1, 2, 3$) to Eq.(2.24) which is derived assuming the logistic model for NTCP. Column (2) is the parameter value determined by the NTCP fitting procedure of Burman et al.

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these fits will be compared since it will be a good indication of the steepness of the resulting NTCP vs $d$ curves. Burman et al. predicted $NTCP(v, d)$ curves where $s_{50}(v)$ is given by the values of the two parameters, $n$ and $m$, as described by Eq.(2.22). For the isoeffect fits to all the data points and the $LNTD$ fits, the predicted $s_{50}(v)$, $\forall v$, can be written as:

$$s_{50}(v) = \frac{k}{4 \cdot D_{50}(1)} \cdot \left(2^v - 1\right)^{-\frac{1}{k}} \tag{2.25}$$

where $s_{50}(v) = \frac{k}{4 \cdot D_{50}(v)}$ has been used with $D_{50}(v)$ resulting from Eq.(2.20). The slopes of the resulting $NTCP$ vs $d$ curves, at $d = D_{50}(v) \forall v \leq 1$, can now be compared for the four different fitting schemes performed on the same data:

1. The empirical fitting scheme of Burman et al.
2. the isoeffect fitting scheme for the $NTCP = 5\%$ data only

3. the isoeffect fitting scheme for all data points

4. the $LN_{TD}$ fitting scheme.

Both of the above expressions for $s_{50}(v)$ (Eq.(2.22) and Eq.(2.25)) depend on $v$, hence, in order to compare the behaviour of the slopes of the different predicted curves (at $d = D_{50}(v)$), $s_{50}$ is plotted as a function of $v$ for each of the above fitting schemes in Fig.2.3.

From Fig.2.3, much steeper $NTCP$ dose response functions are seen to result from the $LN_{TD}$ scheme than those predicted by the isoeffect fits. Also, the $LN_{TD}$ and the models of Burman et al. do indeed predict a similar behaviour of $s_{50}$ as a function of $v$: a sharp rise for small $v$ and then a leveling off into a plateau region where $s_{50}$ varies very little for increasing $v$. However, for most organs, the empirical fitting procedure of Burman et al. has underestimated the $s_{50}(v)$ with respect to the $LN_{TD}$ model for most values of $v$. Predicting a larger slope for the $NTCP$ vs $d$ curves means that the tissue's non-linear dose response will be emphasized. Low responses in the smaller-sloped $NTCP$ vs $d$ region, where $d < D_{50}$, will be attenuated and larger responses in the steep-sloped $NTCP$ vs $d$ region, where $d > D_{50}$, will be amplified. The effects at very small $v$ may not even be relevant since as $v$ gets very small, it might be approaching the size of the SSU. Below this value, the aforementioned curves have no meaning since the $NTCP$ vs $d$ will be flat and equal to zero $\forall d$. Although the predictions of Burman et al. do not show such an underestimation for the cases of the liver and brain, this may be explained as follows.

From Table 2.4, the discrepancy between the $\frac{16}{k}$ value and the $m$ value suggests that
Figure 2.3: Plots of $s_{50}$, in units of $\text{NTCP}_{\text{gy}}$, as a function of $v$ for several schemes and resulting parameters. $s_{50}(v)$ was given by Eq.(2.22) and Eq.(2.25) and depended on the scheme and resulting parameters used. Scheme (1) is that of Burman et al. where the resulting parameters, $n$ and $m$, and Eq.(2.22) have been used. Schemes (2), (3) and (4) are the isoeffect fitting scheme for the NTCP = 5% data only, for the full set of data and the fitting scheme for the LNTD model respectively. For these, the resulting $k$ parameters and Eq.(2.25) are used. Note, T-M stands for temporo-mandibular.
the \( m \) values estimated by Burman et al. were not estimated using exclusively the \( v = 1 \) data. In fact, setting the \( m \) values to be equal to \( \frac{1.6}{k} \) as given in Table 2.4, resulted in a slight shift of the \( s_{50}(v) \) graphs corresponding to the predictions of Burman et al., as shown in Fig.2.4.

![Figure 2.4: Plots of \( s_{50} \), in units of \( NTCP \), as a function of \( v \) for several schemes and where \( m \) is set to the value of \( \frac{1.6}{k} \) for Burman et al.'s scheme. \( s_{50} \) was given by Eq.(2.22) or Eq(2.25). Scheme (1) is that of Burman et al. where the resulting parameters, \( n \) and \( m \), and Eq.(2.22) have been used. Here, \( m \) is set to the value of \( \frac{1.6}{k} \) as given in Table 2.4. Schemes (2), (3) and (4) are the isoeffect fitting scheme for the \( NTCP = 5\% \) data only, for the full set of data and the fitting scheme for the \( LNTD \) model respectively. For these, the resulting \( k \) parameters and Eq.(2.25) are used.](image)

Considering Fig.2.4, the only organ for which the \( LNTD \) model does not predict the steepest rise in \( NTCP \), for most \( v \) values, is the liver. This can be explained by the following two considerations. The fits to the given data for the \( LNTD \) scheme (see Fig.2.2) as well as for Burman et al.'s scheme [Burman et al.,1991] were quite poor. From Fig.2.2, if the \( LNTD(d) \) curve was made to pass through the \( D_5(\frac{1}{3}) = 50\text{Gy} \) data point, the slope of the predicted \( LNTD(d) \) for the liver, would be much steeper which would result in a larger predicted \( k \) value. This, in turn, would result in greater value for \( s_{50}(v) \) \( \forall v \) according to Eq.(2.25). On the other hand, according to the \( LNTD \) scheme, this poor
fit may indicate that the required assumptions, as discussed in section 2.2.5., do not hold for the liver data.

In summary, for the case of the $LNTD$ fitting procedure, clear assumptions have been identified in order to account for the volume effect while the parameters $k$ and $D_{50}$ are adjusted to fit all the data points (on a logarithmic scale) in order to account for the dose effect. In contrast, in the fitting procedure of Burman et al., the parameters are extracted from different subsets of the data pool. The $D_{50}(1)$ data points are, essentially, assumed to be free of error since the corresponding parameters are fixed to these values for every organ and no clear assumptions about the infrastructures of the various organs are made. Instead, the "power law" is assumed to hold for all values of $NTCP$ although the parameter describing such a relationship ($n$) is derived from a fit to the $NTCP = 5\%$ data points primarily. Finally, the $m$ parameter is derived from the $v = 1$ data points and assumed to be a constant for all other curves ($v < 1$). In general, if the parameter $m$ is indeed derived from the $v = 1$ data points according to Eq.(2.21), the $s_{50}(v)$ resulting from the $LNTD$ scheme will be greater than the $s_{50}(v)$ value predicted by the scheme of Burman et al., for most $v$ greater than some value $< 0.1$.

In general, the resulting $NTCP(v, d)$ 3-dimensional surfaces will depend on the model, and accompanying assumptions used to fit the scarce data. At this stage, since the $NTCP$ data is a set of crude clinical estimates with no error bars, there is no way of knowing which of the many models results in the more realistic, volume and dose, response functions because we cannot apply the standard methods of statistical analysis. However, being able to categorize a particular model as the steepest or flattest estimated response may be
an important consideration, since the ultimate use of such a surface is to extract relative
behaviour of the NT when selecting a TP. The LNTD fitting procedure does appear to
result in the steepest estimation of most NTCP vs d curves (at \( d = D_{50}(v) \)) for most
relevant values of \( v \). It is important to note, at this point, that the comparison between
the parameters resulting from the LNTD model and the model of Burman et al. has
been done assuming the logistic model for \( NTCP(1, d) \). Hence, this general conclusion
about the steepness of the predicted NTCP vs d curves, for most \( v \) values, may or may
not be the same if another model for \( NTCP(1, d) \) is used.

Another benefit of the presented model in this thesis is that, once tissue specific
functions adequately describing the LNTD vs d relationship have been determined, the
NTCP for a nonuniform dose distribution resulting from any plan \( P \) can easily be com-
puted. Eq.(2.13) and Eq.(2.19) give :

\[
TNTD(P) = -SSU \cdot \sum_{i=1}^{SSU} \ln(1 + (\frac{d_i}{D_{50}})^k)
\]  

(2.26)

which, when used with Eq.(2.14), will yield NTCP(\( P \)). If a differential DVH is given
for \( P \), Eq.(2.15) may be used instead of Eq.(2.13) giving :

\[
TNTD(P) = -SSU \cdot \sum_{j} \ln(1 + (\frac{d_j}{D_{50}})^k) \cdot n(d_j; P)
\]  

(2.27)

where \( n(d_j; P) = \frac{v_j}{SSU} \). Hence, there is no need to resort to any DVH reduction techniques
as suggested by Burman et al., since the assumptions inherent in this model take into
account how each \( v_j \) irradiated to a uniform dose \( d_j \) will contribute to the NTCP. This
model is, thus, self-consistent and self-contained in the sense that additional techniques,
with associated assumptions which are often not clear and may be incompatible with the
original set of assumptions, are invoked in order to obtain an NTCP score, from the basic dose distributions, for the plan.

2.2.8 Isodamage Maps

In addition to the above, if an isodose distribution map for a particular plan \( P \) was given for a specific organ, the derived \( LNTD_{SSU}(d) \) function could be used, with \( SSU = \) the voxel size in dose calculation/measurement, to translate the dose to each voxel into an \( LNTD \) value for that voxel and thus generate an isodamage map. This, of course, could only be applied if the conditions stated in section 2.2.2. are met.

A study was done to assess the feasibility and value of such a procedure. The above steps were performed for several of the organs shown in Fig.2.2, where the tissue specific parameters of Eq.(2.19) have been determined. Hypothetical dose distributions were generated using 8X8 grid points (i.e. 64 voxels) to sample the entire reference volume which is assumed to represent the whole organ (i.e \( v = 1 \) is for the whole organ). The voxel size being \( \frac{1}{64} \), \( SSU = \frac{1}{64} \) was used in Eq.(2.19) to translate the dose value, \( d \), of each voxel into an \( LNTD_{\frac{1}{64}} \) voxel value. The resulting \( LNTD \) values were then plotted out in contour maps. Fig.2.5(a) represents the hypothetical isodose distribution map, while Figs. 2.5(b) and (c) represent the corresponding organ-specific isodamage distribution maps for the liver and stomach respectively. Although the absolute values of the isodamage curves are not easily interpreted (since they will depend on the voxel size), the relative spatial distribution of the damage is emphasized in these pictorial displays of tissue specific responses. The “hot” dose spot is emphasized, through the translation, for the stomach.
while it is smeared, through the translation, for the liver.

To best indicate the relative spatial distribution of damage, the $LNTD$ values may be normalized. For example, to compare how much the different locations of a single organ contribute to the overall damage to that organ, an intra-organ response comparison may be desired. For such a study, the $LNTD$ voxel values are normalized with respect to the individual organ's maximum damage value ($LNTD_{\text{max}}$) for that plan (Fig.2.6). On the other hand, for the inter-comparison of different tissue's responses (Fig.2.7) for the same dose distribution, these values are normalized with respect to the overall $LNTD_{\text{max}}$. Obviously, the normalization can be done with respect to any relevant value in order to produce percentage isodamage curves that can be more readily interpreted. However, it is essential that all the damage values, normalized for any given study, always be evaluated for the same size SSU since this affects the absolute $LNTD$ value (Eq.(2.19)). For example, if an SSU is uniformly irradiated to a dose $d_1$, then $LNTD(d_1)$ will result at that location and a contour line of this value would pass at this location. However, splitting it into 2 smaller SSUs would result in two, side by side, values of $\frac{LNTD(d_1)}{2}$ which would give rise to a contour line of half the value of the previous one passing through the same location. Normalizing these two incompatible values by the $LNTD_{\text{max}}$ will yield a difference of 50% when the actual tissue response is the same since the irradiation is the same.

In order to observe the dependence of the resulting isodamage maps on the absolute values of dose, the above translation was repeated, for an inhomogeneous dose distribution where the voxel dose values were increased by 20Gy with respect to that in Fig.2.5(a).
Figure 2.5: Example of transforming an isodose map, with maximum dose value of 60Gy, into tissue-specific isodamage maps. Eq.(2.19) was used to transform the isodose map in (a) into tissue specific raw isodamage maps. The dose, in Gy, was sampled in 8X8 grid points (i.e. 64 voxels). Since the entire field is assumed to represent the whole organ \( v = 1 \), voxel size \( = \frac{1}{64} \). The value of SSU used in Eq.(2.19) was therefore \( \frac{1}{64} \) so each voxel’s dose \( d \) was transformed into an \( LNTD_{\text{voxel}} \) voxel value with units of damage per voxel [dam/voxel]. \( NTCP \) values were then determined for each organ using Eq.(2.20) and Eq.(2.14) and are indicated on the corresponding map. The \( LNTD_{\text{voxel}} \) values were then normalized with respect to each individual organ’s maximum value for intra-organ comparison in (d) and (e). The stomach was also normalized with respect to the overall maximum \( LNTD_{\text{max}} \) value for both organs (in this case \( LNTD_{\text{max}} \) for the liver) in (f) for inter-organ comparison: (d) vs (f).
The resulting isodamage maps for the liver and stomach are shown in Fig.2.6: (b) and (c) represent the raw damage values for the liver and stomach respectively and (d) and (e) represent the *intra*-organ normalized values. The liver and stomach’s isodamage maps were much more similar for this higher valued irradiation. The *inter*-organ normalization was not specifically performed in this case since the raw isodamage maps for both organs had comparable values (i.e. same scale: $10^{-3}$ dam/voxel) and the maximum contour, which was for the stomach in this case, was conveniently of value 100. This simply means that all other contour values already indicated the percentage of this maximum value that they represent. Thus, the raw isodamage maps can be equally read as *inter*-organ normalized isodamage maps for the *inter*-comparison of different structure’s response to the same dose distribution.

This clearly demonstrates the dependence of tissue response on absolute dose value and leads to the observation that as the dose values become very high, the tissue specific responses become more similar and hence the tissue specificity is lessened yielding more comparable $NTCP(P)$ values. Since most $TP$s will aim to minimize the dose to $NT$, lower dose values will result in general. For this reason, the tissue specificity evident in the resulting isodamage maps will indeed prove useful because it will allow these to exclusively convey the spatial dose information that is relevant by eliminating the isodose contours of values too low to cause any effect to the particular $NT$ while reinforcing those corresponding to greater $LNDT$ values for the particular $NT$. 


Figure 2.6: Example of transforming an isodose map, with maximum dose value of 80Gy, into tissue specific isodamage maps. Eq.(2.19) was used to transform the isodose map in (a) into tissue specific raw isodamage maps (b) and (c) as well as intra-organ ((d) and (e)) normalized isodamage maps. The dose, in Gy, was sampled in 8X8 grid points (i.e. 64 voxels). Since the entire field is assumed to represent the whole organ (v = 1), voxel size = \( \frac{1}{64} \). The value of SSU used in Eq.(2.19) was therefore \( \frac{1}{64} \) so each voxel’s dose \( d \) was transformed into an \( LNTD_{\text{max}} \) voxel value with units of damage per voxel [dam/voxel]. NTCP values were then determined for each organ using Eq.(2.20) and Eq.(2.14) and are indicated on the corresponding map.
Chapter 3

A Study of Treatment Planning Parameters

3.1 Motivation

One very important aspect in the process of treatment planning is the determination of the parameters that define the particular conditions under which the treatment will be performed. Although the specific parameters may be unique to a specific facility and treatment, the following study is meant to serve as an example of a general approach by which any treatment planning parameters may be studied. The specific conclusions obtained by such a systematic study are indeed treatment and facility dependent, however, it is expected that any such systematic approach to the study of treatment planning parameters should result in equally useful conclusions.

The importance in the value of the parameters is based on the fact these will define the specific dose distribution that will result for a given plan and hence, will characterize that plan. From the previous chapter, it is clear that one must provide a score for a plan in order to quantitatively rank competing plans and select an optimal plan for treatment. In
order to provide such a plan-specific score, one must be able to predetermine the specific
dose distribution resulting from a specific plan. Therefore, a systematic study of all of
parameter space, along with its associated dose distributions and corresponding scores,
will give some insight into the optimal values of the treatment planning parameters.

For the purpose of this thesis, the particular case that will be studied is the treat­
ment planning for proton therapy of uveal melanoma at the proton facility at TRIUMF
(Tri-University Meson Facility). The rationale behind the use of heavy charged particles
for therapy lies in their characteristic Bragg peak, which results from a finite penetration
range with a greater maximum-depth to entrance dose ratio than for conventional radio­
therapy as well as reduced sideways scatter. Smaller treatment volumes require sharp
boundaries to avoid sensitive normal structures. Therefore, smaller treatment volumes,
such as those required for the treatment of uveal melanoma, are more successfully achieved
by protons than by conventional radiotherapy [Suit and Urie,1992]. In fact, results suggest
that proton irradiation is quite successful in achieving local control of uveal melanoma
[Gragoudas et al.,1987].

Details on how the proton beam at TRIUMF will be made to conform to the tumour
volume will not be discussed here, because they are not handled by the treatment planning
program but by other beam delivery control programs. Instead, it is assumed that the
tumour uniformly receives the prescribed dose and hence, as in Chapter 2, only the amount
of dose received by the surrounding $NT$ for all possible treatment planning parameter
values will be explored.
3.2 Overview of the Treatment Planning Program: EYE

The goal of this study is to predict the best treatment planning parameters, i.e. those that will result in the best dose distribution. The particular version of the treatment planning program used to predict the resulting dose distributions will inevitably determine the set of relevant parameters that may be explored. For the case of the treatment of uveal melanoma at TRIUMF, the treatment planning program, EYE, originally developed by Tom Miller of SIN (now PSI) in Switzerland and Michael Goitein of the Massachusetts General Hospital in Boston, will be used. The version used at TRIUMF is one that has been extensively reworked since it was installed at the Medical Research Council Cyclotron Unit (now Douglas Cyclotron Unit) at Clatterbridge, England. For details, see the EYE program manual [Perret & Sheen, 1992] or the discussion by Goitein and Miller [Goitein & Miller, 1983].

The program calculates the required beam range and modulation so that the entire tumour is uniformly irradiated and assumes such a beam is provided. The specific dose profiles (lateral penumbras as well as distal fall-off) must be supplied so that the program can then use this information to calculate or predict the dose to each of the nodes of each of the modelled structures in the eye.

The first step required in order to begin to plan a treatment is to introduce all the rel-

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1By "best" it is implied "a good one" since there may be more than one dose distribution that will result in indistinguishable minimal NTCP values, given the uncertainty in the dose and the NTCP estimation.

2The energy of the proton beam at the entrance of the eye is varied, so that the Bragg peak will cover the entire tumour.
evant clinical data into the program so that the eye, together with the embedded tumour, of the particular patient can be reconstructed as best as possible. The ophthalmological data required consists basically of the various dimensions of the eyeball, lens, limbus and tumour (height and width as well as the tumour profile).

Once the eye has been modelled, the treatment planning may begin. In this program, the user must determine the following treatment planning parameters:

- fixation point of the eye axis in the beam frame given by the polar and azimuthal angles, $\theta$ and $\phi$ respectively
- the maximum range and the range modulation
- the profile of the beam collimator aperture.

In order to determine the above, the five main steps to be followed are:

1. select a fixation point for the eye axis ($\theta, \phi$)

2. translate the eye, either manually with crosshairs or by entering coordinates, so that the center of the tumour lies along the central beam axis

3. calculate the tumour profile as projected onto the beam's cross-section (an optional safety margin can be set) in order to determine the milling machine coordinates of the collimator

4. calculate the maximum beam range required (with a depth-wise safety margin) as well as the modulation necessary in order to cover the entire tumour depth-wise
5. calculate the dose distributions (in the form of isodose contour maps and/or histograms), to various eye structures, that will result for the given fixation point.

Of the above, only the first two steps will actually require the user's judgement. Steps 3-5 are performed by selecting the appropriate options in the program once a specified margin has been chosen for each profile (i.e. in depth and for the collimator). Since the objective of step 2 is merely to center the tumour on the beam's axis for the convenience of beam delivery, only step 1 will be entirely up to the user and will eventually determine the plan. This means that the only independent parameters are given by the fixation angles \((\theta, \phi)\) since once those have been set, all the other steps with corresponding parameter values, will follow. Step 5 is necessary for plan evaluation. It can be performed by either plotting various planar isodose maps or by looking at the integral \(DVHs\) which can be generated for the 12 most relevant structures: tumour surface, retina, globe volume, inner globe surface, lens periphery, lens volume, ciliary body volume, macula, optic disc, optic nerve length and the rims of the upper and lower eyelids if these have been included.

The method to search for an acceptable treatment plan, as defined by its \((\theta, \phi)\) coordinates, is presently based on trial and error. For some simple cases, choosing a fixation point that will lead to reasonable dose distributions to the critical \(NTs\) may be quite trivial. For example, if the tumour lies in the anterior region of the eye (i.e. anterior to the equator), the eye may be positioned such that the tumour, alone, is placed in the beam while the lens is rotated outside the collimated field and the range of the proton beam is adjusted to stop before the macula and optic nerve. However, in many cases, the determination of an acceptable fixation point or, more specifically, of the best fixation
point possible, may not be as trivial. In fact, cases that are best indicated for proton therapy are those for which the tumour lies in the posterior region of the eye, such that it is difficult to place a plaque for conventional treatment and also, the tumour is close to the macula or optic disc which requires careful positioning. At present, there is no systematic method used to determine the optimal plan at any proton eye treatment facility. The planners usually only guess at 3 or 4 different values for \((\theta, \phi)\), based on experience, and then simply select the best plan amongst those. Clearly, in order to bring out the full benefit of proton therapy, a more systematic determination of \((\theta, \phi)\) is desirable. Fortunately, since there are effectively only two independent treatment planning parameters in the simple case studied here, the parameter space can be displayed in 2-dimensional mappings. Therefore, in this thesis it will be possible to illustrate the effects certain conditions, such as tumour size etc., may have on treatment planning and the selection of these parameters' values.

3.3 Overview of Features Added to EYE

3.3.1 Automation of Parameter Space Mapping

A more systematic determination of \((\theta, \phi)\) would result from an initial coarse mapping of the necessary dose information in all parameter space, followed by a finer mapping in the areas of interest. This would avoid the possibility of overlooking a better fixation point than the one chosen for treatment. In order to incorporate an automated parameter space mapping into the treatment planning program, the first step was to introduce a
self-centering feature which allows for step 2 of section 3.2 (see page 50) to be performed automatically. This step is required at every fixation point since as the eye rotates to fixate a different point, the tumour centre can move away from the beam axis centre. Now, an automated version of the usual planning steps (outlined in section 3.2) was possible whereby the program automatically steps through \((\theta, \phi)\) coordinate space which can extend from \(\theta_{\text{min}} = 0.0^\circ\) and \(\phi_{\text{min}} = 0.0^\circ\) to \(\theta_{\text{max}} = 50.0^\circ\) and \(\phi_{\text{max}} = 359.9^\circ\) with a grid spacing defined by the preset step size. The default step size values are \(\theta_{\text{step}} = 5.0^\circ\), \(\phi_{\text{step}} = 30.0^\circ\). Steps 2-5, from section 3.2, are performed with the defaults (e.g. 2.5mm for the safety margins) selected at each option. For this, the many menus and graphics appearing in the usual interactive mode are skipped since a preset order of steps has already been selected. At this point, it will be noted that there is a parameter “skin” which will indicate how embedded the eyeball is in the socket (which is represented in the program by a plane surface). This value will affect the range of the dose profile in the eye since the beam may intersect the skin of the socket before the eyeball in some regions. This “skin distance” is a very difficult value to measure/estimate for a particular patient. Furthermore, the EYE treatment planning program assumes that the skin of the socket is flat, which results in a very crude model. For these reasons, different eye facilities seem to have different empirical rules for this “skin distance”. At present, the default value of 1.5mm will be used throughout the following studies. If a more appropriate value becomes known, it can easily be changed.

The option of using rectangular fixation light coordinates, \((X, Y)\), to define the fixation point, was also introduced, since a mapping in these coordinates can be more readily
interpreted. This is due to the fact that the \((X, Y)\) coordinates represent the fixation light viewing plane directly and do not wrap around like \((\theta, \phi)\) at 0° and 360°. The \((X, Y)\) coordinates can be determined from the \((\theta, \phi)\) coordinates using the following relations:

\[
X = D \cdot \tan \theta \cdot \cos \phi \\
Y = D \cdot \tan \theta \cdot \sin \phi
\]  

(3.1)  

(3.2)

where \(D\) is the distance from the eye to the fixation light plane. For the beamline set up at TRIUMF, \(D=169.67\) mm. In this case, \((X, Y)\) represents the coordinates of the fixation light on the fixation light plane as seen from behind (upstream). The default values for stepping through this coordinate space, in millimeters, will be: \(X_{\text{min}} = -140, Y_{\text{min}} = -140, X_{\text{max}} = 140, Y_{\text{max}} = 140\) and \(X_{\text{step}} = Y_{\text{step}} = 40\). These values were chosen since \((X, Y) = (\pm140, \pm140)\) will correspond to a value of \(\theta\) equal to 49.4° which is the maximum expected range for any patient even though this will restrict the eye’s motion to \(\theta = 39.5°\) in the up-down \((\phi = 90°\) and 270°\) and left-right \((\phi = 0°\) and 180°\) motions (see Fig.3.1) since this value will probably be sufficient for most patients. In order to transform a point, \((X, Y)\), in this coordinate system, to a point lying on the fixation light plane as seen by the patient, \((X_P, Y_P)\), the \(X\) value must be reflected about the origin: \((X_P, Y_P) = (-X, Y)\).

For such mappings, the dose information that is determined at each step must give a good indication of whether or not that plan is desirable. As discussed in the previous chapter, the concept of \(NTCP\) and \(LNTD\) can be used to quantify how desirable/undesirable a specific plan may be, based on the dose distribution information. However, since the
present data available for eye structures does not justify determining $LNTD(d)$ for those structures, translation of the differential $DVH$s into $NTCP$ values, as outlined in Chapter 2, is not performed at this point. Instead, since all $LNTD(d)$ curves resulted in sharply peaking, concave upwards curves which indicate a kind of threshold dose response, it is assumed, for the moment, that as long as one can reduce the amount of dose to all the voxels (represented by nodes in EYE), in a particular normal structure, to a value that is less than the threshold value, the damage (i.e. $TNTD$) will be minimized thus minimizing the $NTCP$ (see Chapter 2, Eq.(2.14)), resulting in an optimal plan. Unfortunately, this threshold value is not known for the structures considered by the EYE program since $LNTD(d)$ for those structures has not yet been determined. Therefore, in order to determine the relevant dose information that can be used to score a plan, the following was considered.

Due to the gradual monotonic nature of the dose profiles (i.e. penumbra and distal fall-off) resulting from irradiation at a single fixation point, as the eye rotates such that a
particular structure gradually intercepts the radiation field, the maximum dose intercepted will gradually increase. As this occurs, the average dose/node will also gradually increase. Once any region of the structure has moved deeper into the field than the penumbra/distal fall-off, it will be receiving the maximum dose delivered at that particular range. Thus, the maximum dose received by any portion of the structure will no longer increase as it continues to move deeper into the field. However, the average dose/node will continue to increase as a greater region of the structure becomes irradiated by the high dose region of the beam. Therefore, a $DVH$ with a smaller maximum dose bin value will usually represent a smaller average dose/node value and, until the structure receives the maximum dose of the field, either value will indicate how much irradiation a particular structure receives. Afterwards, it is the average dose/node that will indicate how much the structure is irradiated and hence, this value alone will be used to rank a particular single-point plan. For all examples presented in the next section (section 3.5), both the mappings for the average dose/node and for the maximum dose to $\geq 10\%$ of the nodes of a structure followed the same pattern while the average dose/node mappings gave more detail for the high values. Equally, the integral $DVH$s initially increased in both area and maximum dose to the structure, as the structure intersected more and more of the beam. Once the maximum dose region of the beam was intersected, the $DVH$s stopped extending to the right (higher dose values) and only continued to expand in area.

Both of these observations are demonstrated in Fig.3.2 for a particular case (CASE4 of

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3The average dose/node is proportional to the area under the integral $DVH$, therefore, a smaller average dose/node will be associated with a $DVH$ containing a smaller area under the curve.

4This value was arbitrarily chosen to represent a significant portion of any structure. The maximum dose to a structure will therefore only be considered if a significant portion of that structure is affected by it.
section 3.5), for the lens volume. In all cases, the dose values will be normalized with respect to the maximum dose received by any one of the tumour nodes and will, hence, be quoted as percentage dose.

In conclusion, since the average dose/node value will indicate, more precisely, how much dose the structure receives, it is this value that will be considered for all single-fixation-point plans. On the other hand, for a 2-fixation-point plan which is used when there is no overlapping low average dose/node region for all considered structures (see section 3.3.3), the goal will be to lower the maximum dose received by the front structures in order to reduce the damage, regardless of the average dose/node value. In such a case, the maximum dose value will be considered as it is minimized. This will be assumed to result in a superior plan due to the above $LNTD(d)$ considerations even though the exact threshold dose value for the production of damage in the various eye structures is not yet known.

From the above considerations, the values recorded at each $(\theta, \phi)$ step, or $(X, Y)$ step, for each structure, are the average dose/node and the maximum dose received by at least 10% of that structure, therefore, a mapping of either of those two values can be obtained. Fig.3.3 represents the steps automatically undertaken by the EYE program if "Get Optimum" is selected.

### 3.3.2 Automation of Macular-Tumour Wedge Inclusion

The option of including a wedge is already available in the EYE program. The wedge is a piece of material (assumed to be aluminium in this case) that is placed in the beam,
Figure 3.2: Particular case (CASE4 of section 3.5) demonstrating that a plan resulting in a larger maximum dose to $\geq 10\%$ of a structure will usually also have a larger average dose/node (i.e. area under the integral $DVH$). Both the mappings of average dose/node and maximum dose to $\geq 10\%$ of the nodes of the lens volume followed the same pattern at low values and the average dose/node mappings alone gave more details for the high values. Equally, the integral $DVH$s with greater area correspond to a higher value for the maximum dose to $\geq 10\%$ of the lens volume, until a certain maximum value of approximately 72\%. 

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Figure 3.3: Flowchart of automatic parameter space mapping with no wedge. The Yes and No boxes represent answers the user is prompted for and which cause the program to halt. The (1) and (2) boxes indicate that there are 2 possible paths the program may automatically follow, depending on the condition that is indicated by the 'if' statements which are in between parentheses.
in front of the eye. It serves as a "tissue compensator" since its insertion will alter the distal fall-off profile by modifying the range of material the beam must traverse in order to arrive at a certain point in the eye. This may therefore be used to conform the beam to the tumour while sparing the structures lying distal to it (i.e. downstream from it). However, in order to plan with the wedge in EYE, it must be defined, by the user, by entering three points interactively with the cursor: two that will determine the wedge's edge and one which will indicate on which side of this edge the wedge lies. This option was automated for the case of a macular-tumour wedge which aims to spare the macula, since it is a very crucial normal structure [Seddonet al.,1987] that planners will generally try to avoid irradiating. If desired, the user now has the option of using the wedge during the automated parameter space mapping, at each step, in order to reduce the dose to the macula. This structure may, in principle, be spared of any irradiation by such a wedge when treating at a fixation point which causes the macula to be downstream from the tumour as long as it is a sufficient distance (depending on the distal profiles safety margin) away. The macular-tumour wedge edge is therefore defined, given a specific fixation point, as passing through the most distal point on the tumour, perpendicularly to a line connecting this most distal tumour point to the macula. The wedge will then lie on the same side as the macula. Its angle is increased, at each step, until a maximum of 60° (this is the maximum wedge angle presently accepted by the EYE program) or until the average macular dose/node is reduced to (or below) 5% of the maximum tumour dose which is approximately the accuracy to which the dose at a node can be estimated (this value may also be changed if another value is judged to be more suitable). Fig.3.4
represents the steps automatically undertaken by the EYE program if “Get Optimum” is selected with the inclusion of a macular-tumour wedge. The largest wedge angle required at each step is recorded.

The automation of an optic-disc-tumour wedge could be similarly constructed, and this remains to be done since this is another structure that is of crucial importance and that can be made to lie downstream from a tumour. In fact, the EYE program can accommodate 2 wedges being used simultaneously.

### 3.3.3 Planning with Two Equally Weighted Fixation Points

As was stated previously (section 3.3.1), a 2-fixation-point plan may result in a better plan by reducing the maximum dose received by the front structures, thus reducing the damage to these structures. The program has been adapted to allow for planning with two, equally weighted, fixation points for the eye axis. A single \( DVH \) for each structure, corresponding to the combined dose received by that structure for the resulting 2-point plan, can then be obtained. Also, planar isodose mappings may be obtained for the resulting plan. The two fixation points can be entered in either \((X, Y)\) or \((\theta, \phi)\) coordinates as long as both fixation points are in the same coordinate system. The option of using two fixation points is offered when the user requests “FIXATION POINT” from the Main Menu. If this option is not desired, the program will continue as usual. Once the program has returned to the Main Menu and one has selected to plan with two fixation points, certain interactive steps are required in order to obtain the 3 sets of \( DVHs \) or planar isodose maps, for any given structure, resulting from the following 3 treatments: using either fixation point alone.
Figure 3.4: Flowchart of automatic parameter space mapping with wedge. The Yes and No boxes represent answers the user is prompted for and which cause the program to halt. The (1) and (2) boxes indicate that there are 2 possible paths the program may automatically follow, depending on the condition that is indicated by the 'if' statements which are in between parentheses.
throughout the treatment and using both fixation points, each for only half the treatment time. Once the option for planning with two fixation points has been selected, when DVHs or planar isodose maps are generated for treatment at the first fixation point, the program will automatically store the dose information calculated at each relevant node corresponding to treatment at that first fixation point. This information will then be combined with that which results for treatment at the second fixation point when the same DVHs or planar isodose maps are generated. Since both fixation points are weighted equally, the information is combined by halving and then summing the treatment to each fixation point alone. The steps required in order to obtain either DVHs or planar isodose maps for a 2-fixation-point plan are represented in the flowchart of Fig.3.5.

### 3.4 Planning with the Added Features in EYE

In this section, the method of planning a treatment with the use of the additional features described in the previous section (section 3.3) will be outlined. The goal of treatment planning, for this particular case, is to select fixation point coordinates that will result in the best treatment possible. As stated previously, by “best” it is meant that the resulting treatment is “as good as it can be”. There may actually be several fixation points resulting in the same “best” plan and the goal here is just to determine one of those.

To illustrate the use of these added features, the 11 normal structures considered by the EYE program will be split into 3 categories according to position:

1. front structures (located in front of the eye’s equator): lens periphery, lens volume, ciliary body volume, rims of upper and lower eyelids
Figure 3.5: Flowchart of the steps required in order to obtain a DVH or planar isodose map for the 2-fixation-point plan using the EYE program. The (1) and (2) boxes represent two possible paths the user may wish to follow, depending on the condition that is indicated by the 'if' statements which are in between parentheses.
2. back structures (located in back of the eye’s equator): macula, optic disc, optic nerve length

3. global structures (located throughout the eye): retina, globe volume, inner globe surface.

Since the modelling of the eyelids and optic nerve length remain unsatisfactory for reliable dose calculations, these will not be considered in the following. Also, the following will concentrate on determining fixation point coordinates that will result in a dose distribution, for each of the front and back structures, which would presumably have a minimum NTCP value associated with it. The global structures will not be considered because, in general, the mappings for these structures are homogeneous in that they do not reveal any significantly lower regions (in fixation coordinate space) of average dose/node. This is because they cannot be avoided for any fixation point since they refer to the eyeball itself. Also, they are large structures so variations in the fixation point will only result in variations in the irradiation to a small fraction of the nodes of such structures, which will translate into minor average dose/node differences (see examples in Fig.3.6).

Since the tumour is attached to the global structures, these will always (at every fixation point) receive the maximum dose that the tumour receives. This will result in the maximum dose bin always being equal to 100% and a parameter space mapping of this value would not be useful. However, although the parameter space mappings of the global structures will not be considered when selecting the fixation point(s) for the best plan, it can be observed that the region of lower-valued contours of Fig.3.6 will coincide with the lower dose/node region for the front structures (see section 3.5). This is because
Figure 3.6: Examples of average dose/node parameter space mappings for global structures. The cases represented here are those of section 3.5. The contours vary within a range of approximately 10% of the tumour's maximum dose and hence, can be considered fairly homogeneous. The slight differences arise due to the varying collimator shape (i.e. different tumour projections) as well as beam positions with respect to the eye, for different fixation angles.

the spreading of dose over the front structures will also cause a spreading of dose over these global structures, thus reducing the maximum dose received by these structures, possibly reducing their damage as well.

The treatment planning must begin by running the “Get Optimum” option from the “Main Menu” of the EYE program. In the resulting \((X,Y)\) space mappings of average dose/node, the front structures are basically outlined by the highest valued contours (see examples in section 3.5) making it is quite easy to infer, from a couple of \((X,Y)\) contour lines, which regions of parameter space would result in better plans. Therefore,
it is preferable to use \((X, Y)\) coordinates instead of \((\theta, \phi)\) coordinates for the mappings. To begin, a quick determination of the values of average dose/node and maximum dose received by at least 10% of the nodes of a particular structure, should be made for all possible values of \((X, Y)/(\theta, \phi)\), in large steps, for all structures. The default can be used for this, since it covers all of parameter space in coarse steps.

It is important to notice that if the tumour is anterior (located in front of the eye’s equator), there may be a complete absence of dose arriving at the back structures, for all fixation points, since these structures may be spared by the distal beam fall-off. In contrast, regardless of the location of the tumour, there will always exist a fixation point for which the front structures will receive significant dose. Therefore, depending on the position of the tumour, the back structures may be of more or less importance in the selection of a plan. Hence, the first step in a systematic study of parameter space will be to look at the back structures’ mappings, keeping in mind that these structures are much more vital for the functioning of the eye. If these result in insignificant levels\(^5\) of irradiation for all fixation point coordinates, then only the front structures will be of concern and one will have to determine a fixation point that lies in the intersecting regions of low average dose/node for all front structures. Otherwise, one will have to determine a fixation point that lies in the intersecting regions of low average dose/node for all the back and front structures. Since the relevant front structures (i.e. lens and ciliary body) are both centered and symmetric and they are both located at approximately the same depth in the eye, their mappings will have similar shapes resulting in a great overlap of

\(^5\)The exact value (\%) that will be considered insignificant should be predetermined and may be patient/structure specific. In general, a 5% value will be considered insignificant and a 10% value will be tolerated in these studies.
their low dose regions. On the other hand, the back structures are irradiated by protons stopping outside of the tumour region and so will have very different mappings and their low dose regions may not even overlap at all with those of the front structures.

Once the necessary coordinate space region(s) of low dose to all structures have been determined, a limited search resulting in a smaller stepped mapping can be performed in order to get a more detailed determination of the coordinates for a good fixation point. At this stage, one can look directly at the recorded average dose/node values for all structures in order to choose a particular fixation point.

However, if the low dose contour regions of the front and back structures do not intersect, a 2-fixation-point plan should be considered. In such a case, the aim is to reduce the front structures’ maximum dose values by spreading the dose. Therefore, it is the regions of low contour values for the back structures that will guide the selection of the two fixation points’ coordinates since the back structures’ dose values (either average dose/node or maximum dose) are not expected to change significantly for a 2-point plan. To perform the selection of two fixation points, a limited search should be done in two regions of low macular/optic disc contour values that are as far apart as possible. The further apart the fixation points, the more the dose to the front structures will be spread. Once the two fixation point coordinates have been selected, following the steps outlined in Fig. 3.5, one can quite easily determine if the goal of reducing the maximum dose received by at least 10% of the front structures, has been achieved. This can be done by comparing the DVHs or certain planar isodose maps for the 2-point plan with those arising from a single fixation point plan. If the selected 2-point plan has not proven
successful, this may be due to the fact that the only low macular dose regions lie too close to one another and hence the front structures' dose is not sufficiently spread. One may then wish to redo a limited search over a different region of macular dose where the dose may be higher but the distance between the two select regions greater. Since the resulting average macular dose/node is an average of the contribution from both fixation coordinates, a higher macular dose received throughout half of the treatment time may not have a great effect on the resulting macular $DVH$. As long as the selected 2-point plan does not cause a significant increase in the average macular dose/node, it may well be acceptable. The trade-off between the 2-point treatment achieving its goal, by shifting the front structures' $DVH$s to the left (i.e. region of lower dose), and the increase in average macular dose/node, must be specifically considered for each case, one may well outweigh the other.

These are the basic effects that must be considered by all those involved in selecting a successful treatment plan for a particular patient. However, it is very difficult to set a standard rule that can be applied to all patients indiscriminantly so it is important to note that any of the preset values (e.g. percentage volume considered for maximum dose determination) can be modified for the particular patient, as judged by the oncologist/ophthalmologist/treatment planning physicist. Fig.3.7 outlines the suggested strategy used to select a treatment plan when using the added features to EYE. It is important to remember that the basic assumption made throughout this treatment planning strategy is that the tumour is always homogeneously receiving the full prescribed dose. If any of the suggestions (e.g. use a greater wedge angle) cause this assumption to be violated,
they must be immediately discarded as options.

Figure 3.7: Flowchart outlining the suggested strategy used to select the best treatment plan possible when using the added features to EYE. The 'Y' and 'N' indicate the path to follow depending on whether "Yes" or "No", respectively, answers the question.
3.5 Examples of Treatment Planning Using Parameter Space Mappings

3.5.1 Examples of Anterior, Equatorial and Posterior Tumours

In the previous section (section 3.4), the steps for planning a treatment with the automated fixation point mapping and 2-point plan option were outlined. The benefits of using two points or wedges as viewed by the resulting $DVH$s (following $LNTD$ considerations as discussed in section 3.3.1) were studied for several hypothetical cases of tumours, all occurring on an identically modelled eyeball. In this section, the goal is to arrive at the determination of the region of $(X, Y)$ parameter space that corresponds to low dose/node for all concerned structures (i.e. all front and back structures). As mentioned in the previous section (section 3.4), once this region is determined, a limited search in this region, resulting in smaller stepped mappings, can be performed and the recorded values of dose/node can be used to select the best possible fixation point coordinates.

First, three similarly sized tumours (see Table 3.1), varying in position with respect to the eye's equator (see Table 3.2), were studied. An anterior tumour corresponds to one lying in front of the eye's equator, an equatorial tumour lies across the eye's equator and a posterior tumour lies behind the eye's equator.

Fig.3.8 shows the resulting average percentage dose/node mappings corresponding to each case. The average percentage dose/node values are determined with respect to the maximum tumour dose/node value. Anything below 5% is considered negligible due to the inaccuracies in the dose calculation and possible inaccuracy in the actual dosimetry. Any
### Table 3.1: Table indicating the dimensions of three similarly sized tumours which vary in position (see Table 3.2). Row (1) indicates the maximum diameter of the tumour’s circumference. Row (2) indicates the minimum diameter of the tumour’s circumference.

<table>
<thead>
<tr>
<th>Tumour Dimensions</th>
<th>CASE1 (anterior tumour)</th>
<th>CASE2 (equatorial tumour)</th>
<th>CASE3 (posterior tumour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) max dia. of circ.</td>
<td>11.9 mm</td>
<td>11.1 mm</td>
<td>11.5 mm</td>
</tr>
<tr>
<td>(2) min dia. of circ.</td>
<td>8.5 mm</td>
<td>8.5 mm</td>
<td>9.3 mm</td>
</tr>
<tr>
<td>(3) height</td>
<td>3.9 mm</td>
<td>3.9 mm</td>
<td>3.9 mm</td>
</tr>
<tr>
<td>(4) volume</td>
<td>.20 cc</td>
<td>.21 cc</td>
<td>.24 cc</td>
</tr>
</tbody>
</table>

### Table 3.2: Table indicating the location of three similarly sized tumours which vary in position: anterior, equatorial and posterior. Row (1) indicates the distance from the anterior tumour margin to the equator. Row (2) indicates the minimum distance to the macula. Row (3) indicates the minimum distance to the optic disc.

<table>
<thead>
<tr>
<th>Location Information</th>
<th>CASE1 (anterior tumour)</th>
<th>CASE2 (equatorial tumour)</th>
<th>CASE3 (posterior tumour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) dist. from ant. tum. margin to equ.</td>
<td>9.7 mm (anterior)</td>
<td>4.8 mm (anterior)</td>
<td>2.0 mm (posterior)</td>
</tr>
<tr>
<td>(2) min. dist. to mac.</td>
<td>13.7 mm</td>
<td>10.1 mm</td>
<td>3.1 mm</td>
</tr>
<tr>
<td>(3) min. dist. to disc</td>
<td>16.7 mm</td>
<td>13.7 mm</td>
<td>7.4 mm</td>
</tr>
</tbody>
</table>
Figure 3.8: Average percentage dose/node mapping with respect to the maximum dose/node received by the tumour of three hypothetical cases: an anterior, an equatorial and a posterior tumour. Anything below 5% is considered negligible due to the inaccuracies in the dose calculation and possible inaccuracy in the actual dosimetry. Therefore, any value of 10% or less is considered low dose. The relevant low dose regions are shaded for emphasis. For CASE2, low dose/node regions intersect for the 5 considered structures. This would also result for CASE1 except the tumour is obviously too close to the ciliary body and periphery of the lens. CASE3 clearly demonstrates how the regions of low average dose/node for the front and back structures are mutually exclusive suggesting the use of either a macular-tumour wedge or a 2-point plan.
value of about 10% or less is considered quite reasonable and will be henceforth referred to as low dose. The corresponding low dose regions will be shaded in for emphasis. A contour map representing no irradiation of that structure for all fixation point coordinates will be completely shaded and referred to as a “blank contour map”. The contour lines for any one plot are always equally spaced and their values are written in small numbers. However, the largest and lowest values are written larger for clarity, since these are the most relevant values. Also, as stated in section 3.4, the average percentage dose/node will be used as the relevant dose information unless a 2-point plan is being considered.

It is obvious, from the ciliary body and periphery of lens mappings of CASE1, that the tumour is too close to these structures to be able to successfully spare them from significant irradiation (i.e. the smallest average dose/node possible is 22% for the ciliary body and 15% for the periphery of the lens). For CASE2, low dose/node regions intersect for the 5 considered structures. CASE3 clearly demonstrates how the regions of the front and back structures with low average dose/node are mutually exclusive suggesting the use of either a macular-tumour wedge or a 2-point plan. Therefore, Fig.3.8 demonstrates that the low dose regions of parameter space are clearly determined by the location of the structure (front vs back) and of the tumour.

3.5.2 Examples of Posterior Tumours

From the above considerations, it appears that a macular-tumour wedge or a 2-point plan may be beneficial if the tumour is posterior. If the tumour lies close enough to the macula/optic disc, such that their parameter space mappings are not blank, then, if
there is no overlapping low average dose/node region for all front and back structures, two solutions may exist:

1. use a 2-point plan where each fixation point results in low irradiation of the back structures while the damage to the front structures is reduced by spreading the dose over these structures.

2. use a wedge to reduce the range of deposited dose such that a back structure is spared of any dose while fixating a point that will result in a low value for the average dose/node to the front structures.

In order to explore these cases further, two more posterior tumours, of similar dimensions to that of CASE3 (see Table 3.3), were considered. One located directly above the eye’s axis (i.e centered with respect to left and right), the other below (see Table 3.4).

<table>
<thead>
<tr>
<th>Tumour Dimensions</th>
<th>CASE4</th>
<th>CASE5</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) max. dia. of circ.</td>
<td>10.2 mm</td>
<td>10.1 mm</td>
</tr>
<tr>
<td>(2) min. dia. of circ.</td>
<td>9.4 mm</td>
<td>9.3 mm</td>
</tr>
<tr>
<td>(3) height</td>
<td>3.9 mm</td>
<td>3.9 mm</td>
</tr>
<tr>
<td>(4) volume</td>
<td>.20 cc</td>
<td>.20 cc</td>
</tr>
</tbody>
</table>

Table 3.3: Table indicating the dimensions of two more examples of posterior tumours. Row (1) indicates the maximum diameter of the circumference of the tumour. Row (2) indicates the minimum diameter of the circumference of the tumour.

Fig 3.9 demonstrates how front structures are outlined by the highest-valued contour in a region of parameter space that will depend on the location of the tumour. In fact,
Figure 3.9: Average percentage dose/node mappings with respect to the maximum dose/node value received by the tumour of three cases of posterior tumours. All three cases are for posterior tumours lying at different azimuthal positions (i.e. to the right, below and above the macula). The low dose regions are shaded. The highest valued contours outline the front structures and are indicative of the tumour’s location. In CASE3 and CASE4, the low dose regions for the front structures overlap while being mutually exclusive with the low dose regions for the macula. In CASE5, the macular and optic disc mappings demonstrate the tumour is too close to these structures since these cannot be spared of significant dose (i.e. the lowest contour values are 50% and 40% for the macula and optic disc respectively).
### Table 3.4

<table>
<thead>
<tr>
<th>Location Information</th>
<th>CASE4</th>
<th>CASE5</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) distance from anterior tumour margin to equator (posterior)</td>
<td>3.7 mm</td>
<td>5.6 mm</td>
</tr>
<tr>
<td>(2) min. distance to macula</td>
<td>3.0 mm</td>
<td>1.9 mm</td>
</tr>
<tr>
<td>(3) min. distance to disc</td>
<td>5.3 mm</td>
<td>2.2 mm</td>
</tr>
</tbody>
</table>

Table 3.4: Table indicating the location of two more examples of posterior tumours. CASE4 is located above the central axis of the eye (i.e. above the macula) and CASE5 is located below the axis (i.e. below the macula). The optic disc is referred to as disc for simplicity.

This region of high dose will occur close to the fixation point coordinates that would cause the tumour and the central axis of the eye (which is also the center of the symmetric front structures) to become aligned along the axis of the beam. Since this alignment will always occur for the eye looking towards the same direction that the tumour lies in with respect to the macula (i.e. up if the tumour is directly above the macula etc.), the highest valued contours will outline the front structures in the region of parameter space that directly corresponds to the location of the tumour. This emphasizes the following observation: for a given posterior tumour, the mappings of the front structures will, in general, have overlapping low dose regions because they occupy similar positions in the eye. As long as the tumour is far enough away from the back structures, such that the distal and lateral dose profiles (plus safety margins) do not reach them, there will always be a fixation point corresponding to the eye looking “away from the tumour”, that will cause negligible irradiation to these structures. However, it is apparent in Fig.3.9 that, if the tumour is

---

6The patient’s right is actually seen as being left on an $(X,Y)$ plot since $(X_P,Y_P) = (-X,Y)$ as discussed in section 3.3.1.
close to the back structures, the low dose regions for the front and back structures will be, in general (CASE3 and CASE4), mutually exclusive. For this reason, the effect of the macular-tumour wedge on such mappings will be studied (see section 3.5.4). In CASE5, there is no region of low ($ \leq 10\%$) macular nor optic disc contour values suggesting that the tumour lies too close to these structures and no fixation point will be successful in sparing them from significant dose.

3.5.3 Examples Varying the Tumour Size

The above examples were meant to study the effects of the tumour location, on the resulting average dose/node mappings. They were thus performed for similarly sized tumours (see Table 3.1 and Table 3.3). However, in order to examine if the general trends observed for the posterior tumours (e.g. outlining of the front structures) are size dependent, the same mappings were obtained for three posterior tumour cases located as CASE3, CASE4 and CASE5 but with tumour height of 2.0 mm rather than 3.9mm. The resulting cases : CASE6, CASE7 and CASE8, all have the same location and diameter circumference values as CASE3, CASE4 and CASE5, respectively, but their volumes are : 0.14 cc, 0.13 cc and 0.13 cc, respectively. Fig.3.10 shows that the tumour size does not significantly alter the mappings of the front structures, in most cases it simply increases the region of $(X, Y)$ parameter space corresponding to low dose. The same was observed for the mappings of the back structures (Fig.3.11).
Figure 3.10: Front structure mappings of average percentage dose/node (with respect to the maximum tumour dose/node) for six cases of posterior tumours varying in height as well as position. This figure demonstrates the effect the size of the tumour will have on the mappings of the front structures. It can be concluded that the tumour size will not significantly affect the shape of the contour mappings. However, in general, a smaller tumour will translate into a greater low dose region in \((X, Y)\) space.
Figure 3.11: Back structure mappings of average percentage dose/node for six cases of posterior tumours varying in height as well as position. This figure demonstrates the effect the size of the tumour will have on the mappings of the back structures. As for the front structures, it can be concluded that the size of the tumour will not affect the shape of the contour mappings. However, a smaller tumour will translate into a greater low dose region in \((X, Y)\) space, in general.
3.5.4 Examples Using the Macular-Tumour Wedge

If the macula (or the optic disc) lies close to the tumour, this structure may be irradiated by the back corners of the treatment field as shown in Fig.3.12(a). However, if the distance between the tumour and this back structure is greater than the treatment margin, the dose to the macula can be reduced or eliminated by the appropriate use of a macular (or optic disc)-tumour wedge as shown in Fig.3.12(b). In this section, the benefits of using such a wedge are explored for the three cases of posterior tumours presented in the previous section (section 3.5.2).

![Diagram](image_url)

Figure 3.12: Schematic diagram demonstrating the use of the wedge. (a) Schematic diagram demonstrating the case when the macula lies close to the tumour such that it is irradiated by the back corners of the treatment field. (b) Schematic diagram demonstrating that the dose to the macula can be reduced or eliminated by the proper use of a macular-tumour wedge.

For this purpose, the automated version of the EYE program was run with the wedge included and the parameter space mappings of average percentage macular dose/node
were obtained (see Fig. 3.13). For the cases where the wedge was successful in reducing the dose to the macula, a drastic change in the average macular dose/node mapping can be observed since the wedge's angle was increased at each fixation point (until a maximum value of 60°) until the average macular dose/node was ≤ 5%. For CASE5, it is obvious that the use of the wedge was not successful. This can be understood by looking at Table 3.4 which indicates that, for this case, the tumour is so close to the macula that the safety margin in depth (2.5mm) plus the beam's distal fall-off profile (in the order of 1.0mm), were not small enough to spare it at any fixation point. Therefore, as long as the macula is far enough away from the tumour (i.e. at least a distance greater than the distal safety margin plus the distal fall-off profile), the wedge can be shown to be successful in reducing the macular dose at several fixation points, thus creating macular mappings with
a larger region of low dose. It is apparent, when comparing these macular mappings for CASE3 and CASE4 to the mappings of the front structures\(^7\) (Fig.3.9), that the wedge will create overlapping low dose regions for the macula and front structures. The smallest front structure low dose region will represent the most constringent constraint, for all front structures, in the selection of the fixation point coordinates for treatment. Since this occurs, in both CASE3 and CASE4, for the ciliary body, the low dose region for this structure was superimposed on the corresponding average macular dose/node mapping which resulted when the wedge was included (Fig.3.14). In this figure, the shaded region therefore represents the intersecting region of low average dose/node for all front and back structures. A limited search in this region was performed for CASE3 for: \(X_{\text{min}} = 60\) to \(X_{\text{max}} = 140\) with \(X_{\text{step}} = 20\) and \(Y_{\text{min}} = -140\) to \(Y_{\text{max}} = -60\) with \(Y_{\text{step}} = 20\).

\[\text{Figure 3.14: Macular contour mappings with wedge included superimposed by the most constringent contour line for the front structures: the 10\% ciliary body contour line, for CASE3 and CASE4. The shaded regions represent the overlapping low dose regions.}\]

\(^7\)The wedge does not significantly alter the average \% dose/node mappings for the front structures therefore the front structures' mappings of Fig.3.9 are relevant for the case of a macular-tumour wedge as well. However, the wedge will increase the maximum dose to 10\% of a front structure for some fixation points since it will affect the range of material the beam will traverse before reaching certain nodes.
The fixation point coordinates that resulted in the best possible plan according to this scheme were: \((X, Y) = (140, -140)\) or \((\theta, \phi) = (49.4^\circ, 315.0^\circ)\) which resulted in the values written in Table 3.5 for a wedge angle of 30°. The same was performed for CASE4 with a limited search from \(X_{\text{min}} = -140\) to \(X_{\text{max}} = 140\) and from \(Y_{\text{min}} = 60\) to \(Y_{\text{max}} = 140\) in step sizes of \(X_{\text{step}} = Y_{\text{step}} = 20\). The fixation point coordinates that resulted in the best possible plan according to this scheme were: \((X, Y) = (0, 140)\) or \((\theta, \phi) = (39.5^\circ, 90.0^\circ)\) which resulted in the values written in Table 3.5 for a wedge angle of 35°.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Ave. dose/node</th>
<th>CASE3</th>
<th>CASE4</th>
</tr>
</thead>
<tbody>
<tr>
<td>retina</td>
<td>28.63%</td>
<td>20.48%</td>
<td></td>
</tr>
<tr>
<td>surface of globe</td>
<td>20.86%</td>
<td>15.16%</td>
<td></td>
</tr>
<tr>
<td>globe volume</td>
<td>15.46%</td>
<td>15.03%</td>
<td></td>
</tr>
<tr>
<td>macula</td>
<td>4.60%</td>
<td>2.65%</td>
<td></td>
</tr>
<tr>
<td>tumour surface</td>
<td>99.90%</td>
<td>99.80%</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.5: Table listing the average percentage dose/node values for the best fixation point coordinates. The following structures have not been included since they were not at all irradiated: lens volume, periphery of the lens, ciliary body, optic disc and optic nerve.

The success with which the macular-tumour wedge is capable of reducing the average macular dose/node for a fixation point will depend only on the minimum distance between the tumour and macula. Since this distance was maintained for the shorter tu-
mour versions of CASE3, CASE4 and CASE5 referred to as CASE6, CASE7 and CASE8 respectively, one can predict that the wedge will be successful for CASE6 and CASE7 but will fail for CASE8. Therefore, the size of the tumour alone will not affect the wedge results.

3.5.5 An Example of Planning a 2-Fixation-Point Plan

In the previous sections, it has been shown that in some circumstances the low dose regions for the front structures and that for a back structure, such as the macula, will be mutually exclusive (i.e. will not overlap). In such a case, if the back structure in question is the macula, a macular-tumour wedge has been shown to possibly reduce the macular average dose/node in some regions of parameter space, thus allowing for macular low dose regions of parameter space to overlap with that of the front structures.

However, if such a wedge is not available then the only achievable, reasonable plan may result from spreading the dose over the front structures while assuring a low dose to the back structures. The benefits of reducing the maximum dose to a significant portion of a structure, although maintaining a constant average dose, is based on the concept of LNTD discussed in Chapter 2 and has been discussed previously (see section 3.3.1). In the following, any plan resulting in the lowest values of maximum dose to at least 10% of each front structure will be assumed to be a best plan (assuming the back structures receive low dose and that the average percentage dose/node for the front structures is constant for all competing plans). The resulting plan will be qualitatively evaluated by looking at relevant DVHs and planar isodose maps.
For the posterior tumour cases of section 3.5.2, it appears (see Fig.3.9) that if no wedge was used for CASE3 or CASE4, it may not have been possible to find a good plan with a single fixation point (i.e. there may not be any overlapping regions of low dose for the front and back structures). For this reason, both the above cases will be examined here in order to demonstrate the benefits of a 2-point treatment plan as well as the steps required to plan with two fixation points, using the added features to the EYE program.

To begin, CASE3 will be studied. Following the strategy suggested in Fig.3.7, the back structures' parameter space mappings of Fig.3.9 are first examined. Since it is clear that, for this case, the optic disc is never irradiated at any fixation point, the macula is the only back structure of concern here. The low dose region for the macula was hence superimposed on the most constringent front structure parameter mapping which, as previously mentioned, is that for the ciliary body (Fig.3.15(a)). This figure demonstrates that there is indeed no overlapping low dose region for the ciliary body and the macula. In fact, one can observe that the smallest-valued average dose/node contour lines for the ciliary body that intersect the low macular dose region are of 15%. Fig.3.15(b) shows that selecting two fixation point coordinates corresponding to this region will actually correspond to maximum dose values of ≥ 60%. If the two fixation point coordinates are far enough away in parameter space such that no ciliary body node is irradiated at both fixation points, then the resulting 2-point plan should be able to reduce this maximum dose to the ciliary body by 50% which would be quite an improvement. Since the other front structures will have similarly shaped parameter space contour mappings, one would expect the maximum dose to be reduced for these structures as well.
Figure 3.15: Parameter space mappings used to select the 2-point plan fixation points’ coordinates for CASE3. (a) Superposition of the macular low dose region on the ciliary body’s parameter space mapping of average percentage dose/node since this front structure’s contours are the most constringent. It is evident that there is no overlap between the low dose regions for the ciliary body and the macula. (b) Superposition of the macular low dose region on the ciliary body’s parameter space mapping of maximum % dose (to ≥ 10% of that structure) contours, equally spaced by 10%. The selected fixation point coordinates, for a 2-point plan, are also shown.

Fig.3.16 demonstrates the effect the 2-point plan will have on the DVHs of the structures of concern. From such a figure, one can observe that the 2-point plan will indeed cause the ciliary body’s DVH to shift towards the left (low dose region) while maintaining relatively the same average dose/node value (see Table 3.6). The other front structures’ DVHs will not demonstrate such a shift since they were already very small in all respects: small in area and not significantly extending to the right along the dose axis (i.e. maximum dose (to ≥ 10%) was 15% for each single point irradiation). It can
also be observed in Fig.3.16 that the 2-point plan did not affect the dose distribution for the macula. Table 3.6 shows that the average dose/node values for all front and back structures were not significantly affected by the 2-point plan. In fact, as expected, the resulting values are simply an average of the values obtained for each of the corresponding single-point plans. The only structure that does not have low average dose/node (i.e. $\leq 10\%$) is the ciliary body and it is hoped that shifting its $DVH$ to the left will improve its chances of not having a radiation-induced complication. However, in order to quantify the true benefit of such a 2-point plan over either single-point plan, the $LNTD(d)$ for the ciliary body would need to be known.

Figure 3.16: Comparison of the integral $DVH$s of the structures of concern for the 2-point plan and the corresponding single-point plans (for CASE3). The 2-point plan causes the $DVH$ of the ciliary body to shift towards the region of lower dose by spreading the dose over such a frontal structure. The $DVH$s for the other front structures are so small (in all respects) for each single-point plan that the 2-point plan does not make a difference.

Next, CASE4 was studied. In this case, the parameter space mapping for the optic disc was not blank (see Fig.3.9). Therefore, the low average macular dose/node region was
Table 3.6: Average percentage dose/node values (for CASE3) for all the structures of concern. Plan 1 refers to treatment at the single fixation point $(X,Y) = (-15,135)$. Plan 2 refers to treatment at the single fixation point $(X,Y) = (-20,-140)$. Plan 3 refers to the 2-fixation point plan where half the treatment time is spent at $(X,Y) = (-15,135)$ and half is spent at $(X,Y) = (-20,-140)$.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Average dose/node</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plan 1</td>
</tr>
<tr>
<td>macula</td>
<td>9.0%</td>
</tr>
<tr>
<td>ciliary body</td>
<td>13.6%</td>
</tr>
<tr>
<td>per. of lens</td>
<td>3.9%</td>
</tr>
<tr>
<td>lens volume</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

In this case, the low dose region for the macula lies completely within the low dose region for the optic disc and hence it can be used to represent the low dose region for both back structures. The low macular dose region was therefore superimposed on the most constringent front structure parameter space mapping, that for the ciliary body (Fig.3.17(b)). Since there are two small overlapping regions of low average dose/node for these back and front structures, a single-point plan could be selected. However, overlaying the low macular dose region on the maximum dose (to $\geq 10\%$ of the structure) parameter space mapping for the ciliary body (Fig.3.17(c)), it becomes apparent that any single fixation point lying in the overlapping regions will result in a maximum dose to $\geq 10\%$ of the ciliary body of $\geq 30\%$ (for the larger overlapping region on the right of Fig.3.17(b))
or $\geq 55\%$ (for the very small overlapping region on the left of Fig.3.17(b)) at best. Since the 2-point plan aims to reduce the maximum dose to the front structures, a 2-point plan may still result in a better plan. If the $LNTD(d)$ or at least the value of the threshold dose for the production of damage were known for all concerned structures, it would be possible to evaluate any suggested single-point plan and determine exactly if a 2-point plan is necessary. However, since a 2-point plan should not affect the macular $DVH$ nor the average dose/node to the front structures, it cannot result in a worse plan, so it will be considered here. Two points lying, as far away as possible, within the intersecting low dose regions of Fig.3.17(b), were selected and are represented by the black dots of Fig.3.17(c). Their coordinates are equal to: $(X, Y) = (-130, -10)$ and $(X, Y) = (130, -30)$.

Fig.3.18 demonstrates the effect that the 2-point plan will have on the $DVH$s of the structures of concern. The $DVH$s for the optic disc resulted in practically flat lines (i.e. it received practically no dose) for all plans so it is not included. From such a figure, one can observe the same result as for CASE3: the $DVH$ for the ciliary body shifted towards the left (low dose region) while maintaining a relatively constant average dose/node (see Table 3.7). Again, the $DVH$s for the other front structures did not demonstrate such a significant shift since they were already very small in all respects. Also, the dose distribution for the macula was not affected by the 2-point plan. Table 3.7 shows that the average dose/node values for all front and back structures were not significantly affected by the 2-point plan. Judging by these values, Plan 2 may have been just as successful as Plan 3. However, if an $LNTD(d)$ curve for the ciliary body was available, it may have demonstrated the benefits resulting from spreading the dose over such a structure.
Figure 3.17: Mappings used to select the 2-point plan fixation point coordinates for CASE4. (a) Superposition of the low dose regions for the back structures. The macular low dose region lies entirely within the optic disc low dose region. (b) Superposition of the low dose regions for the macula and ciliary body. There is some overlap in two different regions (on right and left of the figure). (c) Superposition of the macula low dose region on the parameter space mapping of the maximum (to at least 10% of the structure) dose to the ciliary body. The black dots represent the two selected fixation point coordinates: $(X, Y) = (-130, -10)$ and $(X, Y) = (130, -30)$, which both lie in the overlapping low dose regions of (b).
since the resulting calculated $NTCP$ values for Plan 2 and Plan 3 may have been very
different. This will be considered in the following section since it may have a drastic effect
in selecting the best treatment plan.

![CASE4](image)

Figure 3.18: Comparison of the integral $DVH$s of the structures of concern for the 2-point plan and the
corresponding single-point plans (for CASE4). The $DVH$s for the optic disc resulted in practically flat
lines (i.e. it received practically no dose) for all plans so it is not included. The 2-point plan causes the
$DVH$ for the ciliary body to shift towards the region of lower dose by spreading the dose over such a front
structure. The $DVH$s for the other front structures are so small (in all respects) for each single-point
plan that the 2-point plan does not make a difference.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Average dose/node</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plan 1</td>
</tr>
<tr>
<td>macula</td>
<td>9.3%</td>
</tr>
<tr>
<td>optic disc</td>
<td>0.0%</td>
</tr>
<tr>
<td>ciliary body</td>
<td>11.9%</td>
</tr>
<tr>
<td>per. of lens</td>
<td>1.7%</td>
</tr>
<tr>
<td>lens volume</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Table 3.7: Average percentage dose/node values (for CASE4) for all the structures of concern. Plan
1 refers to treatment at the single fixation point $(X, Y) = (-130, -10)$. Plan 2 refers to treatment at
the single fixation point $(X, Y) = (130, -30)$. Plan 3 refers to the 2-fixation point plan where half the
treatment time is spent at $(X, Y) = (-130, -10)$ and half is spent at $(X, Y) = (130, -30)$.
Chapter 4

Planning with $LNTD$ and Parameter Space Mappings

4.1 $NTCP$ Parameter Space Mappings

In this chapter, the $LNTD$ model will be applied to the quantitative evaluation of treatment plans in order to obtain parameter space mappings indicating the local response of the tissue to the dose it receives for a plan with the corresponding parameter values (i.e. fixation point coordinates). The $NTCP$ data presently available is very scarce for the eye structures of concern in the study of planning a uveal melanoma treatment. However, as noted in the previous section (section 3.5.5), in order to quantitatively assess the benefit of a 2-point plan, the $NTCP$ value associated with the single-point plans as well as the 2-point plan is necessary. Without this quantitative evaluation of such plans there is no way to measure or give a score to these competing plans since the average dose/node is not significantly affected by the use of two fixation points (see Table 3.6 and Table 3.7)
Ultimately, the use of two fixation points is motivated by $LNTD(d)$ and $NTCP$ considerations (see section 3.3.1) and hence if the aim is to determine the plan with smallest $NTCP$ associated with it, a value of $NTCP$ must first be assigned to each plan. This section will therefore make use of the scarce $NTCP$ data in order to obtain some $NTCP$ contour mappings of parameter space. This will be achieved by following the steps outlined in Chapter 2 describing the translation of the differential $DVH$s into $NTCP$ values, going through the $LNTD(d)$ fits and $TNTD$. As mentioned in section 3.3.1, it is the value of $NTCP$ that will give an indication of the effect of the dose distribution resulting from a particular treatment plan on a particular structure. Therefore, ideally, the mappings of parameter space will indicate the $NTCP$ of a plan that results from treatment at the particular $(X, Y)$ fixation point coordinates instead of the average dose/node.

Data are available for only a few structures; they were published by Emami et al. [Emami et al., 1991] and are for the lens, the retina and the optic nerve (see Table 4.1). Since the periphery of the lens as well as the lens volume have been considered throughout the previous $(X, Y)$ space study, the lens will be examined first. The retina and the optic nerve were not considered but the resulting $LNTD(d)$ curves for these structures can also possibly shed some light as to any effect the $NTCP$ mappings may have made on the selection of the best fixation point.

The couple of data points for each structure were fit to Eq.(2.19) with $D_{50}$ and $k$ acting as free parameters. In all cases, the best fits were obtained for $D_{50}$ equal to the given data point. The resulting $k$ values were: 5.0, 11.2 and 8.0 for the lens, optic nerve and
Table 4.1: Table listing the only presently available data for eye structures. The data has been published by Emami et al. in 1991 and is a very crude estimate. As in Chapter 2, $D_5$ and $D_{50}$ represent the dose that, for whole organ (i.e. $v=1$) irradiation, will result in NTCP values of 5% and 50% respectively.

<table>
<thead>
<tr>
<th>Structure</th>
<th>$D_5$ [Gy]</th>
<th>$D_{50}$ [Gy]</th>
</tr>
</thead>
<tbody>
<tr>
<td>lens</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>optic nerve</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td>retina</td>
<td>45</td>
<td>65</td>
</tr>
</tbody>
</table>

retina respectively. Fig. 4.1 shows the resulting fitted curves and the data points. Since the value of $SSU$ is not known, $\frac{LNTD}{SSU}$ is what was fit and what is plotted as a function of dose : $d$ in Fig. 4.1.

Using the values for $k$ and $D_{50}$ that resulted from the fits, the tissue specific functions for $LNTD(d)$ are determined and hence every bin of a differential DVH can be translated into a value of $LNTD(d)$ and summed to give the total normal tissue damage for that plan $P : TNTD(P)$ (see chapter 2, Eq.(2.15)). Therefore, for any given coordinates of the fixation point $(X,Y)$, a value of NTCP can be determined using Eq.(2.14). Of course, the value of NTCP will depend on the absolute value of dose (in Gy) that the tumour will receive which makes this approach very different from what was used earlier since the average percentage dose/node with respect to the maximum tumour dose will not depend on the absolute value of that dose. This procedure was integrated into the EYE program and the NTCP contour mappings for the lens periphery and volume were obtained for CASE3, CASE4 and CASE5 of the previous sections and for a prescribed tumour dose of 60Gy. Due to the nature of the $LNTD$ vs $d$ curves which, although non-
linear, monotonically increase with dose, it would be expected that as the DVHs extend further to the right (higher dose bin values) and expand in area, the corresponding TNTD and hence NTCP values associated with the plans must also increase. This would result in similarly shaped NTCP and average percentage dose/node contours. This is indeed what was observed for the three cases mentioned (see Fig. 4.2).

These results suggest that the use of NTCP contours, rather than average percentage dose/node contours, will not have a great effect on the selection process for a single-point plan since the \((X,Y)\) values for plans resulting in lower NTCP values will also result in lower average dose/node. Therefore, the average dose/node will not only be a good indication of how much dose a particular structure receives from a single-point plan (see section 3.3.1), it can also be used to rank a plan according to the probability of a
Figure 4.2: The percentage NTCP contour mappings vs average percentage dose/node contour mappings of (X, Y) space for the lens volume and the periphery of the lens for CASE3, CASE4 AND CASE5 and for a prescribed tumour dose of 60Gy. As expected, the mappings are of similar shape: the lower-valued NTCP contours are in the low average dose/node regions.
complication arising. However, this will only apply to a single-point plan. As previously mentioned, the average dose/node will not indicate the value of a 2-point plan and hence, to rank a 2-point plan against a single-point plan, the NTCP values associated with such plans must be used.

The $LNTD(d)$ curves above were used to determine the NTCP values for both the single-point plans and the resulting 2-point plan for both cases presented in section 3.5.5. Unfortunately, the DVH that was most affected by the 2-point plan was that of the ciliary body in both cases but there is no data available for this structure. In order to obtain an $LNTD(d)$ curve for this structure, the following was considered. Since the $LNTD(d)$ curve for the lens rises sharply at a lower dose value than those for the retina and optic nerve, the lens would be more damaged than either of the other two structures, given that they all receive the same dose distribution. In fact, if one observes the percentage NTCP mappings of the retina vs the average percentage dose/node mapping of $(X,Y)$ space (Fig. 4.3), it is clear that the effect of the $LNTD$ vs $d$ relationship is to either accentuate the effect of the dose on the structure (for the case of the lens, see Fig. 4.2) or, on the contrary, to attenuate these effects (for the case of the retina) depending on the absolute values of the dose contours associated with a particular plan. The attenuation of the effects of dose on the retina, for a typical tumour dose of 60Gy, also justifies omitting this structure from consideration when comparing competing plans in the previous sections. Although the 2-point plan may reduce the NTCP to the retina, it is already low, in general, for all parameter space values and hence this may not be considered significant.
Figure 4.3: Percentage NTCP contour mappings vs average percentage dose/node contour mappings of (X, Y) space for the retina for CASE3, CASE4 and CASE5 and for a prescribed tumour dose of 60Gy. The mappings clearly demonstrate that the LNTD(d) curve for the retina causes an accentuation of the effect of the irradiation on this structure since, for all three cases, the resulting NTCP parameter space mappings are very homogeneous and low-valued (negligible).

It is plausible that the LNTD(d) curve for the ciliary body would lie somewhere between the curves for the lens and the retina/(optic nerve). Therefore, in order to observe any effect, the 2-point plan will have on the NTCP of the ciliary body, the LNTD(d) curve for the lens was used to compute the NTCP value for this structure. If the retina or optic nerve LNTD(d) curves had been used, the result would have been that all three competing DVHs of Fig. 3.16 and Fig. 3.18 would have translated into negligible NTCP values. If any other curve, lying somewhere between the curves of Fig. 4.1 had been used, the net effect would still be somewhat attenuated with respect to the effect seen if the LNTD(d) curve for the lens is used. Table 4.2 indicates the resulting NTCP associated
to the three $DVH$s of the competing plans for CASE3 and CASE4. It is apparent that the 2-point plan would result in a significantly better plan according to $NTCP$ values for the ciliary body and retina in both cases. As expected, due to the minimal irradiation of the lens at both fixation points for both cases, the $NTCP$ values for the lens are quite negligible for all plans and thus no significant improvement can be observed for these values, for the 2-point plan.

<table>
<thead>
<tr>
<th>Plan $(X,Y)$</th>
<th>$NTCP$ values for CASE3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ciliary body</td>
</tr>
<tr>
<td>(-15,135)</td>
<td>52.3%</td>
</tr>
<tr>
<td>(-20,-140)</td>
<td>48.8%</td>
</tr>
<tr>
<td>2-point plan</td>
<td>26.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plan $(X,Y)$</th>
<th>$NTCP$ values for CASE4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ciliary body</td>
</tr>
<tr>
<td>(-130,-10)</td>
<td>46.3%</td>
</tr>
<tr>
<td>(130,-30)</td>
<td>30.4%</td>
</tr>
<tr>
<td>2-point plan</td>
<td>17.7%</td>
</tr>
</tbody>
</table>

Table 4.2: Table indicating the values of $NTCP$ obtained using Eq.(2.15) of Chapter 2 and the corresponding $LNTD(d)$ curve shown in Fig. 4.1 (the $LNTD(d)$ curve of the lens was used for the ciliary body as well). It is apparent that the 2-point plan would result in a better plan according to $NTCP$ values for the ciliary body and retina in both cases. As expected, due to the minimal irradiation of the lens at both fixation points for both cases, the $NTCP$ values for the lens are quite negligible for all plans.
4.2 Planning a Treatment for the First Patient at TRIUMF

4.2.1 Planning a Single-Point Plan with No Wedges

This final section will be a study of the treatment planning for the first patient treated for uveal melanoma at the proton therapy facility at TRIUMF. This patient was treated the week of August 21st, 1995. The process of reconstructing the eye and tumour was as described in the brief overview of the treatment planning program EYE (section 3.2) and is discussed in detail in the EYE program manual, so it will not be discussed here. The value of the "skin" variable indicating the location of the eyeball in the socket, was estimated by the physicians to be about 5mm in this particular case. Therefore, this valued replaced the default value of 1.5mm and was used throughout the following discussion. The tumour dimensions and location information are shown in Table 4.3

Before discussing the treatment planning, a brief outline of the necessary procedures involved in treating a patient a TRIUMF will be presented. It will become apparent that the work of Chapter 3 has allowed for certain new considerations that may affect future approaches to the preparation before the day that the patient is to be treated.

The patient is first seen by the ophthalmologist at the Eye Care Clinic. Tantalum clips are surgically inserted onto the patient’s eye surface, around the tumour base. This procedure allows one to obtain the required information about the eye structure and the tumour while the position of the clips relative to these are recorded.

The patient is then sent to TRIUMF and a face mask is made for the patient on the
### Tumour Dimensions

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. maximum diameter of circumference</td>
<td>13.4mm</td>
</tr>
<tr>
<td>2. minimum diameter of circumference</td>
<td>12.2mm</td>
</tr>
<tr>
<td>3. height</td>
<td>5.7mm</td>
</tr>
<tr>
<td>4. volume</td>
<td>.46cc</td>
</tr>
</tbody>
</table>

### Tumour Location Information

<table>
<thead>
<tr>
<th>Location Information</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. distance from anterior tumour margin to equator</td>
<td>1.6mm (posterior)</td>
</tr>
<tr>
<td>2. minimum distance to macula</td>
<td>3.2mm</td>
</tr>
<tr>
<td>3. minimum distance to optic disc</td>
<td>7.5mm</td>
</tr>
</tbody>
</table>

Table 4.3: Table indicating the dimensions of the first patient’s tumour as well as the location of the tumour with respect to other eye structures.

treatment chair. At this point, a simulation is performed with the patient on the chair at the treatment position (i.e. with the patient’s eye at the isocentre and rotated by fixating the fixation light at set coordinates) by taking two orthogonal x-ray pictures which will record the position of the clips relative to the beam axis. These x-ray pictures will be used to recreate the patient’s eye and tumour in the program.

However, the day of treatment, new x-ray clip pictures will be taken and these will be compared with those predicted by the treatment planning program EYE. It is clear that the EYE program makes many simplifications and assumptions as far as the modelling of the eye, its structures and the tumour. Hence, one would not expect the predicted
and actual x-ray clip pictures to match exactly unless, of course, the patient's eye was placed in the identical position that it was for simulation, since the recreation of the eye and structures was made to match for that particular set-up. This means that if the comparison of predicted and actual x-ray pictures, made on the day of treatment, is to be used in order to realign the chair and check for misalignments, in order for it to be reliable, the patient's positioning and fixation during the actual treatment should be used for the simulation. However, this clearly presents a dilemma since the treatment planning, which serves to determine the fixation light coordinates, has not yet been performed at the time of simulation. Without the results of Chapter 3, at the time of simulation, the ophthalmologist is required to make an educated "guess" of the fixation point which could be used to treat the specific patient and hope to use very similar coordinates after the trial-and-error process of treatment planning is performed. It seems that such an approach could also bias the trial-and-error procedure as a particular result has already been suggested. Instead, the results of Chapter 3 would allow one to reduce the possible region of fixation point coordinate space by taking into consideration the outlining of the tumours for front structures as was discussed in Chapter 3. Also, a very crude tumour reconstruction could be quickly created, prior to simulation, and the fixation coordinates' space could be used to determine an approximate value of the best treatment. This would allow for an unbiased treatment planning to follow and the simulation and treatment patient positioning would not be very different due to the patterns observed in Chapter 3. In fact, during simulation, often two or three x-ray pictures are taken which would be enough to sample all the possible best treatment fixation point regions of parameter space.
Having discussed the relevance of the results of Chapter 3 in the stages prior to treatment planning, the remainder of this section will concentrate on the actual treatment planning since it is at this stage that those results make their most crucial contribution. The planning follows the suggested method as outlined in section 3.4. First, the "Get Optimum" option is selected from the "Main Menu" of the EYE program with the default values for $X_{\text{start}}, Y_{\text{start}}, X_{\text{end}}, Y_{\text{end}}, X_{\text{step}}$ and $Y_{\text{step}}$ and with no wedge included. The resulting front and back structure parameter space mappings of average dose/node are examined (Fig. 4.4). Since the optic disc does not receive any significant irradiation at any of the fixation point coordinates, the mapping for this structure is not included.

![Figure 4.4: Average percentage dose/node contour mappings of parameter space for back and front structures, for the case of the first patient at TRIUMF, with no wedge included.](image)

From the front and back structure parameter space mappings of average dose/node, it is clear that there does indeed exist a region of overlap for all these structures. In order to determine the exact region, the most constringent of the 10% contour lines of the three front structures (that for the ciliary body) is superimposed on the macular mapping and the overlapping low dose region of parameter space is shaded for emphasis (Fig. 4.5).
The double-lined ellipse is supposed to approximate the possible range of fixation for this particular patient's eye movement. During simulation, the patient’s actual range of motion for the eye was estimated by the physicians. They concluded that any polar angle, \( \theta \), greater than a value of about 30° to the left (at \( \phi = 0° \)) or to the right (at \( \phi = 180° \)) may be difficult to maintain throughout a treatment. In the up and down directions, the range for the eye extended somewhat further (\( \theta > 30° \)). However, looking at the overlapping low dose region of Fig. 4.5, it is clear that the best plan will have \((X, Y)\) lying close to the positive \(X\)-axis and hence it is the right-left motion limits that will be of importance. Therefore, the \((X, Y)\) parameter space corresponding to \( \theta > 30° \) at around \( \phi = 0° \) and \( \phi = 180° \) should not be considered available in this particular case while the up and down motion will not be restricted to less than 40° (the default value), hence the ellipse.

![Diagram](image)

**Figure 4.5:** Parameter space mappings used to select the best single-point plan with no wedge for the case of the first patient treated at TRIUMF. The solid lines represent the average percentage macular dose/node contour mapping of parameter space. The hatched line represents the 10% contour line for the ciliary body and delimits the low front structure region. The shaded region indicates the overlapping low dose region for all front and back structures and the double-lined ellipse represents the restricted available parameter space estimated from the range of motion for the eye of this particular patient.
A limited search in the available overlapping region of: \( X_{\text{start}} = 85 \) to \( X_{\text{end}} = 100 \) with \( X_{\text{step}} = 5 \) and \( Y_{\text{start}} = -30 \) to \( Y_{\text{end}} = 30 \) with \( Y_{\text{step}} = 10 \) was performed. The best resulting plan selected was that for \((X, Y) = (100, -30)\) or equivalently \((\theta, \phi) = (32^\circ, 343^\circ)\) which resulted in the average dose/node values shown in Table 4.4 and the histograms of Fig. 4.6.

<table>
<thead>
<tr>
<th>Best Single-Point Plan with No Wedge for the First Patient</th>
<th>((X, Y))</th>
<th>(100, -30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Ave. dose/node</td>
<td></td>
</tr>
<tr>
<td>retina</td>
<td>30.84%</td>
<td></td>
</tr>
<tr>
<td>surface of globe</td>
<td>25.26%</td>
<td></td>
</tr>
<tr>
<td>globe volume</td>
<td>23.13%</td>
<td></td>
</tr>
<tr>
<td>ciliary body</td>
<td>6.42%</td>
<td></td>
</tr>
<tr>
<td>macula</td>
<td>1.35%</td>
<td></td>
</tr>
<tr>
<td>tumour surface</td>
<td>99.90%</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.4: Table listing the average dose/node values for the best single-point plan. The following structures have not been included since they received no dose: lens volume, periphery of lens, optic disc and optic nerve.

The macula and the ciliary body are the only front/back structures that receive some dose for the selected fixation point. From the table, one can see that the amount of average dose/node for these two structures is indeed low (<10%). However, if one includes the NTCP calculation as was done in the previous section (i.e. using the \(LNTD(d)\) curve
Figure 4.6: For the case of the first patient treated at TRIUMF, integral DVHs of the macula and ciliary body which are the only two front/back structures to receive any dose for treatment at the selected fixation point: \((X, Y) = (100, -30)\) or \((\theta, \phi) = (32^\circ, 343^\circ)\) with no wedge included.

for the lens to represent the damage response of the ciliary body as well), the NTCP for the ciliary body for this plan is 27.6%. The region of the DVH for the ciliary body that extends far to the right contributes greatly to this NTCP value. This reflects the fact that since the maximum bin dose value is high (95%), some portions of the ciliary body will be significantly damaged. This value could, in principle, be lowered by using a 2-point plan to spread the dose over the ciliary body. However, since the area of the overlapping low dose region that is contained within the restricted parameter space is quite small, it would not be possible to determine two fixation points corresponding to the low average dose/node for all front and back structures and yet far apart enough to make the spreading of dose significant. Since the \(LNTD(d)\) curve for the ciliary body is purely speculative at this point, the average % dose/node should be used to decide on a fixation point and hence a lower NTCP value should not be opted for at the expense of increasing the average % dose/node to any of the important structures. However, in the future, if a more reliable \(LNTD(d)\) curve is obtained for the ciliary body, the NTCP
value should be the most relevant value to use to rank a plan and a lower $NTCP$ should take precedence over a lower average % dose/node.

4.2.2 Planning a Single-Point Plan with a Wedge

Since the tumour is sufficiently far away from the optic disc such that the average dose/node for this structure is equal to zero for all values of fixation point coordinates, there is no need for an optic disc-tumour wedge. On the other hand, the macula is within 5mm of the tumour boundary and is thus quite significantly irradiated for many fixation point coordinates. For this reason, the availability of a macular-tumour wedge could indeed make a difference when planning the treatment for this particular patient.

Fig. 4.7 shows the effect of the wedge on the macular parameter space mapping of the average percentage dose/node. As expected, the average dose/node parameter space mappings for the front structures were not significantly altered and are hence not shown here. As for the case of planning a single-point plan with no wedge, the 10% average dose/node contour for the ciliary body is superimposed on the average percentage dose/node parameter space mapping for the macula in Fig. 4.7 and the overlapping low dose region is shaded for emphasis.

The overlapping low dose region is now considerably larger than before. Due to the nature of this region and the restricted eye motion primarily in the left-right direction, two limited searches were performed. One for: \( \theta_{\text{start}} = 20^\circ \) to \( \theta_{\text{end}} = 30^\circ \) with \( \theta_{\text{step}} = 5^\circ \) and \( \phi_{\text{start}} = 315^\circ \) to \( \phi_{\text{end}} = 360^\circ \) with \( \phi_{\text{step}} = 15^\circ \) and the other for \( \theta_{\text{start}} = 25^\circ \) to \( \theta_{\text{end}} = 40^\circ \) with \( \theta_{\text{step}} = 5^\circ \) and \( \phi_{\text{start}} = 270^\circ \) to \( \phi_{\text{end}} = 300^\circ \) with \( \phi_{\text{step}} = 15^\circ \). The best
plan resulted in \((\theta, \phi) = (40^\circ, 285^\circ)\) which is equivalent to \((X, Y) = (37, -137)\) with a macular-tumour wedge of angle equal to 45°. However, if this fixation point is too difficult for the patient to fixate throughout the entire treatment (approximately 1-2 minutes), another plan that will require a macular-tumour wedge\(^1\) and resulting in the average percentage dose/node \(\leq 10\%\) for all the front and back structures is:

\((\theta, \phi) = (35^\circ, 300^\circ)\) which is equivalent to \((X, Y) = (59, -103)\) with a macular-tumour wedge of 30°. The resulting average percentage dose/node values to all structures for these two suggested plans with a macular-tumour wedge are given in Table 4.5 and the DVHs corresponding to the first plan (i.e. \((\theta, \phi) = 40^\circ, 285^\circ)\) and wedge angle of 45° are shown in Fig. 4.8. Comparison of the values in Table 4.5 with those of Table 4.4

\(^1\)The case of “no wedge” is, by definition, a subset of the “wedge” case (which includes wedge angle=0°). Therefore, the previously obtained plan of \((X, Y) = (100, -30)\) with no wedge was again obtained for this limited search but is not referred to again here.
suggests that the plan with no wedge should be used if the first suggested plan with a macular-tumour wedge is not attainable. Using the $LNTD(d)$ curve for the lens to calculate the $NTCP$ for the ciliary body, corresponding to the $DVH$ in Fig. 4.8, one obtains 26.3% which is only slightly lower than the value obtained for the single-point plan with no wedge (i.e. 27.6%).

| Best Single-Point Plans with a Macular-Tumour Wedge for the First Patient |
|-----------------------------------|-----------------|-----------------|
| $(\theta, \phi)$                  | $(40,285)$       | $(35,300)$       |
| $(X, Y)$                           | $(37,-137)$      | $(59,-103)$      |
| wedge angle                        | $45^\circ$       | $30^\circ$       |
| Structure                          | Ave. dose/node   |
| retina                             | 34.21%           | 32.47%           |
| surface of globe                  | 27.01%           | 26.28%           |
| globe volume                       | 26.01%           | 24.91%           |
| periphery of lens                  | 0.00%            | 0.21%            |
| ciliary body                       | 6.32%            | 7.88%            |
| macula                             | 1.40%            | 2.15%            |
| tumour surface                     | 99.92%           | 99.92%           |

Table 4.5: Table listing the average percentage dose/node values for the best single-point plan with a macular-tumour wedge included for the case of the first patient treated at TRIUMF. The following structures have not been included since they received no dose: lens volume, optic disc and optic nerve.
For the case of the first patient treated at TRIUMF, integral $DVH$s of the macula and ciliary body which are the only two front/back structures to receive any dose for treatment at the selected fixation point : $(\theta, \phi) = (40^\circ, 285^\circ)$ with a macular-tumour wedge of wedge angle $45^\circ$.

### 4.2.3 Planning with Two Fixation Points

It is noted here that the only reason that a single-point plan, resulting in low average dose/node values to all structures of concern, was possible, is because the "skin" value was taken to be 5mm. Had the default value of 1.5mm been used instead, such an overlapping region would not exist (see Fig. 4.9). This is due to the fact that the "skin" may serve the same purpose of a wedge in that it will affect the distal dose profile of the beam and may cause it to avoid hitting a structure located downstream from the tumour for certain fixation points. Due to the uncertainty in the value of "skin", if one does not wish to rely on such a value, a 2-point plan is one alternative although, as discussed previously, the value of such a plan will rely on the estimated value of the $NTCP$ associated with the plan.

The steps performed here to plan a 2-point plan will be identical to those presented in the example of section 3.5.5. The low dose region for the macula that does not depend on the "skin" value (i.e. the region in parameter space corresponding to negative $X$ values)
is superimposed on the parameter space mapping of the average percentage dose/node for the ciliary body, and no overlapping region is observed (Fig. 4.10(a)). In fact, one can observe that the smallest-valued contour lines for the ciliary body that intersect with the low macular dose region are of 20% dose/node. However, Fig. 4.10(b) shows that selecting two fixation points corresponding to this region will actually correspond to maximum dose values of $\geq 70\%$. Two fixation points, far apart, in this region were selected: $(X, Y) = (-40, -130)$ and $(X, Y) = (-25, 130)$.

Fig. 4.11 demonstrates the effect the 2-point plan will have on the $DVH$s of the structures of concern. From such a figure, one can observe that the $DVH$s for all the front structures were indeed considerably shifted to the left (lower dose). Using the $LNTD(d)$ curve of the lens for the ciliary body as well, the corresponding $NTCP$ values, associated with each single-point plan and with the suggested 2-point plan, were calculated for the ciliary body, lens periphery, volume of lens and retina (see Table 4.6).
Figure 4.10: Parameter space mappings used to select the best 2-point plan fixation points’ coordinates. (a) Superposition of the macular low dose region on the parameter space mapping of the average percentage dose/node for the ciliary body, since the contours for this front structure are the most constringent. It is evident that there is no overlap between the low dose regions for the ciliary body and the macula. (b) Superposition of the macular low dose region on the parameter space mapping contours of maximum percentage dose to (≥ 10% of) the ciliary body, equally spaced by 10%. The selected fixation point coordinates, for a 2-point plan, are also shown.

From Table 4.6, it is apparent that the 2-point plan would indeed result in a better plan, since the NTCP value for all front structures of concern was decreased, while maintaining basically the same, acceptable, dose distribution to the macula (see Fig. 4.11).

4.2.4 Comparison of Results with the Actual Treatment Plan

Selected

In this last section, the resulting best plans obtained in each of the three previous sections (sections 4.2.3, 4.2.2 and 4.2.1) will be compared to the actual plan that was selected and
Figure 4.11: Comparison of the integral $DVH$s for the back and front structures and for the retina resulting from the 2-point plan and the corresponding single-point plans, for the case of the first patient treated at TRIUMF. The $DVH$ for the retina is included since the $NTCP$ value can be calculated for this global structure due to availability of data and thus a $LNTD(d)$ curve. The $DVH$ for the optic disc is not included since this structure will not receive any dose for the given 2-point plan. This figure demonstrates the effect the 2-point plan will have on the $DVH$s of the structures of concern. One can observe that the $DVH$s for the front structures were considerably shifted to the left (lower dose).
Plan for the First Patient

<table>
<thead>
<tr>
<th>Plan</th>
<th>NTCP for the First Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ciliary body</td>
</tr>
<tr>
<td>(-40,-130)</td>
<td>71.6%</td>
</tr>
<tr>
<td>(-25,130)</td>
<td>69.8%</td>
</tr>
<tr>
<td>2-point plan</td>
<td>48.0%</td>
</tr>
</tbody>
</table>

Table 4.6: Table indicating the values of NTCP obtained using Eq.(2.15) of Chapter 2 and the corresponding LNTD(d) curve shown in Fig. 4.1 (the LNTD(d) curve of the lens was used for the ciliary body as well). It is apparent that the 2-point plan would result in a better plan according to NTCP values for all structures.

used to treat the first patient at TRIUMF. The purpose of this comparison is to determine the real value of such a systematic determination of the treatment planning parameters as opposed to the usual trial-and-error approach.

The fixation point used to treat the first patient at TRIUMF had coordinates: \((\theta, \phi) = (35^\circ, 65^\circ)\) which correspond approximately to: \((X,Y) = (50,108)\). The “skin” distance used was 5mm. This specific plan was obtained after half an hour of trial-and-error. The basic assumption made throughout was that the macula was too close to the tumour to be spared and hence, not taking this structure into consideration, this fixation point resulted in an obvious, comfortable choice for the patient, that would still significantly spare the front structures of dose. The resulting \(DVHs\) are shown in Fig. 4.12. These are compared to the \(DVHs\) resulting for either of the single-point plans (with and without a macular-tumour wedge) determined, within half an hour as well, using the parameter space mappings.

The resulting \(NTCP\) values associated with the lens, optic disc, ciliary body (accord-
Figure 4.12: DVHs for the important structures, resulting from treatment of the first patient at the actual treatment position. These DVHs can be compared to those resulting from the alternative plans mentioned in the previous sections: the single-point plan with no wedges (Fig. 4.6), the single-point plan with a macular-tumour wedge (Fig. 4.8) and the 2-point plan (Fig. 4.11).

ing to the LNTD(d) curve to the lens) and retina are shown in Table 4.7 and compared to the values resulting from the suggested 2-point plan of section 4.2.3.

It is apparent that the NTCP values, for the retina and ciliary body, associated to the actual plan are similar to those that would result for such a 2-point plan. However, the lens periphery and volume are quite a bit more affected by the resulting dose from the 2-point plan than by that resulting from the actual treatment. This effect must be considered in conjunction with the NTCP value for the macula if one is to rank these plans. Unfortunately, the NTCP value for the macula cannot be calculated due to the
lack of data for this structure. Nonetheless, comparing the macular \( DVH \) corresponding to the 2-point plan in Fig. 4.11 with that resulting for the actual treatment plan used as shown in Fig. 4.12, it is obvious that this structure would almost undoubtfully undergo some complication for the given treatment but could have been spared quite significantly by using the 2-point plan. Overall, the 2-point plan could be viewed as providing a successful treatment with greater probability than the treatment that was actually given, due to the greatly improved \( DVH \) for the macula at the expense of increasing the \( NTCP \) value for the lens volume to only 12.6% and that for the periphery of the lens to 42.1%. Both these values are significantly lower than the hypothetical 100% \( NTCP \) value that could be assigned to the macular \( DVH \) of the actual treatment.

In conclusion, parameter space mappings were used to determine the best plan for all three suggested types of treatment:

- single-point plan with no wedges
- single-point plan with a wedge

<table>
<thead>
<tr>
<th>Plan</th>
<th>NTCP for the First Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ciliary body</td>
</tr>
<tr>
<td>(i)</td>
<td>47.4%</td>
</tr>
<tr>
<td>(ii)</td>
<td>48.0%</td>
</tr>
</tbody>
</table>

Table 4.7: Table comparing the values of \( NTCP \) obtained for the actual treatment that was used on the first patient treated at TRIUMF (Plan (i)) with those obtained for the suggested 2-point plan of section 4.2.3 (Plan (ii)). It is apparent that the lens volume and periphery are affected significantly more for the 2-point plan however, the greatly reduced macular dose may well outweigh this effect.
• 2-point plan.

This resulted in $DVH$s demonstrating either a much lower value of average dose/node to all structures of concern (for the single-point plans) or a dose distribution that would result in smaller $NTCP$ values for most structures (for the 2-point plan) than the actual plan selected for treatment, by trial-and-error. This emphasizes the need for such a systematic approach to treatment planning.
Chapter 5

Summary and Conclusions

One of the most important aspects of using radiation for cancer therapy is the planning process which determines the geometric delivery of radiation that will provide the maximum dose to all the tumour cells, while the surrounding, normal but critical tissues are minimally irradiated in order to reduce the chance that the patient will experience radiation-induced complications, affecting his/her long term survival. At present, there is still no systematic approach to the treatment planning process, and so the planning is usually simply based on experience from a large number of past trial-and-error cases in individual cancer centres. In this thesis, two new concepts have been introduced, that can be used as tools to rationalize a systematic planning process.

1. The concept of local normal tissue damage ($LNTD$): Using a similar concept to that of “cellular damage” in radiobiological models, a concept of a localized “normal tissue damage” is introduced. Since dose is equal to the amount of energy deposited, by a radiation, per unit mass, this “normal tissue damage” is local in
the sense that it can be related to the dose associated with a local unit of mass and thus, it too can be associated with a local unit of mass. Nevertheless, the LNTD is defined with respect to the overall integral function of the whole organ of normal tissue. This simple model is designed to make the best use of the current limited clinical estimates of whole organ complication probabilities, while providing a coherent framework that will relate the following two separate, but equally important, considerations that must be taken into account when evaluating treatment plans: (i) preservation of spatial information in the form of damage maps for subjective evaluation by oncologists and (ii) condensation of the plan information into a numerical score representing the overall tissue complication for objective ranking of rival plans.

2. The concept of parameter space mapping: By displaying, on a mapping for which each point completely defines the conditions of the treatment, information indicating the effect of the resulting dose distribution on a particular structure, very useful insights can be obtained. Particularly, such mappings can further our understanding as to why certain structures are hit and how this can be avoided. This new tool of "parameter space mappings" is shown to be particularly useful in studying the values of the fixation point coordinates for the treatment of uveal melanoma, due to the pictorial representation of this 2-dimensional parameter space. Such mappings are applied to the study of planning a proton eye therapy treatment at TRIUMF and a systematic scheme for the rational search of a "best" treatment can be developed. Results from a study of such mappings may include the consideration of a macular-
tumour (or optic disc-tumour) wedge or planning a treatment with two equally weighted fixation points. This tool will therefore help make treatment planning more efficient, objective and systematic which will allow for a better exploitation of the proton beam's full potential.

The above two tools, or concepts, are inter-related in that they can be combined to produce a consistent scheme for treatment planning. The *LNTD* model can be applied to transform a dose distribution resulting on a particular structure, given particular treatment conditions, into a damage map indicating the local *effect* of the dose and hence, preserving the spatial information. In turn, since this damage is defined with respect to the functioning of the whole organ, it is possible to determine the overall effect that the particular dose distribution will have on the structure. This value can then be used to produce a parameter space mapping, indicating the *effect* of the particular plan (defined by the given parameter values) on the particular structure. Also, the rationale for the development of multiple-fields (i.e. 2-point plans) is based on the general non-linearity of the local damage vs dose curves derived in Chapter 2 for various organs. This non-linearity allows for the total damage to a given organ to be sometimes significantly reduced by spreading the same total dose over a larger fraction of the organ. Reconciling the two main concepts of this thesis, as was done in Chapter 4, allowed for a coherent framework to study the treatment planning parameter values, for this special case of proton treatment of uveal melanoma, but, equally well, contributed to some useful insights concerning treatment planning in general.
Bibliography


