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A representation of an NTCP function for local complication mechanisms

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Abstract

A mathematical formalism was tailored for the description of mechanisms complicating radiation therapy with a predominantly local component. The functional representation of an NTCP function was developed based on the notion that it has to be robust against population averages in order to be applicable to experimental data. The model was required to be invariant under scaling operations of the dose and the irradiated volume. The NTCP function was derived from the model assumptions that the complication is a consequence of local tissue damage and that the probability of local damage in a small reference volume is independent of the neighbouring volumes. The performance of the model was demonstrated with an animal model which has been published previously (Powers *et al* 1998 *Radiother. Oncol.* **46** 297–306).

1. Introduction

The mathematical description of normal tissue complication probabilities (NTCP) of radiation therapy has been developed over the last two decades taking two distinct approaches: the phenomenological definition of fit functions (Lyman 1985, Lyman and Wolbarst 1987, 1989) and the mechanistic modelling of dose-response relations (Schultheiss *et al* 1983, Wolbarst 1984, Niemierko and Goitein 1991). The formalism developed in this paper draws on mechanistic concepts to derive a phenomenological description of an NTCP function.

The range of validity of the model and the detail of the description of the dose response is inevitably limited. Common experimental design and radiation therapy practice significantly restrict the variability of the dose response and the available information. Whilst the former is a blessing for any phenomenological approach to NTCP modelling, the latter is a curse for mechanistic models. We assume the standpoint that the mechanistic assumptions in our model ought not be taken further than they can be supported by experimental data or basic reasoning.

Any measurement of complication probabilities will *a priori* be limited to the group of individuals which received that particular treatment. However, a ranking (or NTCP) function is supposed to map a particular treatment onto the conditions of some experiment. The fundamental problem is to identify 'good observables' which describe the dose response sufficiently and self-consistently. The inevitable interpatient heterogeneity of dose response can be built into the model by defining observables which are invariant under

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population averages. The generalization to inhomogeneous dose distributions can be made by requiring certain 'conservation laws' for these quantities, which could be motivated by mechanistic concepts. The validation of the model is then equivalent to proving the validity of these invariance assumptions.

In particular, a formalism is introduced which allows us to go from experimentally established dose–volume relations for *homogeneous* dose distributions to general, inhomogeneous dose distributions. This formalism requires that the ranking of dose distributions be robust against scaling of the dose, and a reference volume. These transformations have been chosen because they are accessible to experimental falsification and hence can substantiate the observables of isoeffective dose and reference volume. This particular set of transformations precludes distinctly non-local, so-called parallel complication mechanisms with a macroscopic functional reserve (or macroscopic redundancy).

In section 2, the formalism which supports the transition from experimental settings to clinical application is introduced. The relationship of the formalism to experiment and clinic is established in section 3.

2. A phenomenological formalism for ranking treatment plans

This section attempts to illustrate the mathematical method which can also be used for a different set of phenomenological assumptions. These assumptions do not pertain to radiobiology: the definition of the volume effect here is merely a mathematical concept which will not be given biological meaning until section 3.

The dose distribution $D(\vec{x})$ is assumed to incorporate all time and fractionation effects by means of a transformation to some standard dose per fraction. Let $V > 0$ be the reference volume, i.e. the volume with respect to which the ranking function is normalized. In its most general form, a ranking function $F(D, V)$ induces an order on the set of all dose distributions by assigning a non-negative real number. For convenience, the ranking function is defined on dose distributions which 'fill' the entire $\mathbb{R}^3$ to avoid boundary problems. The dose can safely be imagined to be zero outside a certain volume of interest A. However, this should not be confused with the reference volume V which is necessary to normalize F since the volume of A need not be constant or universal.

One can require as an important practical quality of a ranking function to make dose distributions comparable to homogeneous dose distributions on certain standard volumes. To achieve this, the notion of an *isoeffective dose* is introduced. This is an intuitive concept borrowed from treatment planning: the ranking of a given dose distribution is compared with the ranking of a homogeneous dose on a *volume of the size of the reference volume*

$$F(D, V) = F(d, V) \tag{1}$$

with d being the isoeffective dose of the dose distribution D. If d exists for all dose distributions D, and is unique, the ranking function is termed *reducible*. The isoeffective dose of D is denoted by $d(D, V)$. Reducibility is equivalent to the assumption that a dose-oriented DVH reduction scheme exists. Notice that this definition of reducibility does not require a volume threshold for the isoeffective homogeneous dose distribution. With this definition complication mechanisms which show the existence of a certain functional reserve are excluded. Conversely, it follows that isoeffective dose is not a good observable for 'parallel' complications.

In the following the volume effect as a function of reference volume and isoeffective dose is established which relates certain transformations of dose and volume. In this development a scaling operation for both is chosen. In order that the volume effect should apply equally to homogeneous and inhomogeneous dose distributions, we require that the ranking is robust

against these transformations, i.e. for any two dose distributions, the order of their ranking must be preserved under these transformations. This is called the concept of faithfulness.

To achieve this, two scaling operators which act on D are introduced. Operator R is a scaling of the dose by a factor $r > 0$:

$$RD(\vec{x}) = rD(\vec{x}) \tag{2}$$

and operator S is a scaling transformation of $\mathbb{R}^3$ with a scaling ratio $s > 0$

$$\text{vol}\,(SX) = s\,\text{vol}\,(X) \tag{3}$$

which in the case of a homogeneous and isotropic dose response is equivalent to a scaling[1] of the reference volume V with s:

$$S : V \to sV. \tag{4}$$

These transformations reflect the most fundamental consideration in treatment planning: how can a greater dose tolerance be achieved by a reduction in the irradiated volume (and *vice versa*)? One way to arrive at a useful means to rank treatment plans or assess treatment outcome is to demand that the ranking function can account for these transformations in a consistent fashion. This requirement is by no means rooted in biological considerations, but in clinical and experimental practice, or even necessity. We will find in section 3 that it can be substantiated by biological observations. The definition of this special kind of 'faithfulness' follows.

The reducible ranking function F is *R-faithful* if

$$F(RD, V) = F(rd, V) \qquad \text{for all } D, R. \tag{5}$$

Likewise, the reducible ranking function F is *S-faithful* if

$$F(DS, V) = F(d, sV) \qquad \text{for all } D, S. \tag{6}$$

If a ranking function is both R- and S-faithful, it is termed faithful. These definitions assure that the isoeffective dose and the reference volume are meaningful observables both for experimental design and treatment planning. If a complication complies with S-faithfulness, one can extrapolate from a dose–volume relation found experimentally for homogeneous doses to a dose–volume relation for arbitrary dose distributions. It must be pointed out that this definition of 'faithfulness' is a severe limitation of the range of the modelling to the subset of complications for which an isoeffective dose *is* a meaningful quantity.

The rationale for these assumptions is two-fold. Firstly, they can be independently falsified with clinical and experimental data. Even if the NTCP function shows a reasonable fit, the underlying mechanistic or phenomenological model assumptions can be wrong and require individual verification. Secondly, despite the enormous effort required to collect clinical data, a great amount of detail will be blurred by inevitable interpatient heterogeneities. The properties of the ranking function necessarily have to be robust against the population averages exhibited by experimental data.

For example, a dose response has to be assumed not to be S-faithful if there exists a volume threshold below which arbitrary doses may be given without causing morbidity (as could be the case in radiation pneumonitis for example (Yorke *et al* 1993, Jackson *et al* 1993, Boersma *et al* 1995, Graham *et al* 1999)). If the dose response is not R-faithful, then a modest increase in total dose could be much more dangerous when the dose distribution is homogeneous than when some part of the volume is completely spared. Non-local dose-response mechanisms will show a violation of faithfulness due to long-range interactions with inherent dose and macroscopic length scales.

[1] For $s < 1$ the irradiated volume vol $A <$ vol SA, $A = \{\vec{x} \in \mathbb{R}^3 : DS(\vec{x}) > 0\}$ is inflated by the scaling.

In order that experimental design elucidates the faithfulness of the underlying physiological dose response, an experiment has to comprise at least a series of various uniform doses given to a set of partial volumes of differing size, each for a group of individuals.

Based on faithfulness, the volume effect function b is defined, which links the dose transformations R to the volume transformations S. First, the set of admissible ranking functions is restricted further. A reducible ranking function $F(D, V)$ is said to be monotonic if it is monotonic in the two scalars d and V. Continuity and differentiability in either argument of a reducible ranking function F are established in the canonical way.

Let F be a monotonic, faithful, continuous and differentiable ranking function. The volume effect

$$b(d, V, r) = s \tag{7}$$

is then defined by

$$\begin{array}{lcl} F(D, V) & = & F(RDB(D, V, R), V) \qquad (8) \\ \updownarrow & \text{faithfulness} & \updownarrow \\ F(d, V) & = & F(rd, b(d, V, r)V) \qquad (9) \end{array}$$

where $S = B(D, V, R)$ is the scaling operator with scaling factor $s = b(d, V, r)$. This function exists and is unique under the conditions given. The volume effect function b links the fractional increase in dose r to a fractional decrease in irradiated volume s at the same level of toxicity. It defines the lines of equal ranking in the (r, s) space at a given (d, V). The function b will be increasing in r. In general, the volume effect function b will be dependent on all its variables, but this dependence may be hidden by population averages and the limited range of clinical dose variation. For the isoeffect, equation (9) reads

$$d(RD, bV) = \text{const.} \tag{10}$$

This definition of volume effect follows clinical considerations. Depending on the objectives, dose and volume are altered along a line $b(r) = s$ at the same level of toxicity; for example, conformal radiotherapy aims to decrease the irradiated volume (increase the reference volume V) in order to be able to increase the dose to that volume. The method of defining the volume effect by pairing transformations of dose and volume which leave the ranking invariant is not restricted to the two transformations chosen here and may be a generally fruitful concept.

In the following, a ranking function is derived with the lowest-order approximation that the volume effect function depends neither on d nor V. In practice, this can easily originate from experiment design in the limit of low complication rate, since neither this assumption nor faithfulness need to hold for very high isoeffective doses or small volumes.

Starting from equation (9), we form the partial derivative of F with respect to r:

$$d' \frac{\partial F(rd', V')}{\partial d} = -\frac{\partial b}{\partial r} V' \frac{\partial F(d', bV')}{\partial V}. \tag{11}$$

In order that this equation be independent of r and b, we use $b(1) = 1$ and arrive at

$$d' \frac{\partial F(d', V')}{\partial d} = -kV' \frac{\partial F(d', V')}{\partial V} \tag{12}$$

for some characteristic constant $k > 0$, since the volume effect b must be increasing with r. Although k is a function of d and V, we use the lowest-order Taylor approximation which is justified by the small range of d and V encountered in practice in the limit of low NTCP approximations. This partial differential equation leads to the most general form of F

$$F(d, V) = G(d^k V^{-1}) \tag{13}$$

$$= G\left(1/V \int D^k(\vec{x})\, \mathrm{d}x^3\right) \tag{14}$$

with G being some differentiable, monotonically increasing function. The corresponding volume effect function reads

$$b(r) = s = r^k \tag{15}$$

and is independent of d and V.

These infinitely many ranking functions share the same volume effect. If G is set to be the identity, we find that the well-known Kutcher–Burman DVH reduction scheme (Kutcher and Burman 1989) is also among these ranking functions. Equation (14) invokes faithfulness which might be, even in spite of experimental evidence for some dose distributions, unsubstantiated. This step is motivated in section 3 by biological model assumptions.

3. A set of mechanistic model assumptions for local complication mechanisms

The formalism developed above forms the framework for a class of NTCP models which is restricted by phenomenological properties of the ranking function F. This function assigns a figure of merit to every dose distribution D in some given volume (e.g. organ) with respect to an *arbitrary* reference volume V. The first model assumption is that such a function exists for the complication in question[2].

For the ranking function, we demand that for any given dose distribution D there be a homogeneous dose distribution d on a volume with size V with the same ranking as D. This concept of an *isoeffective* dose with an independent reference volume restricts the range of the ranking function to complication mechanisms which do not show a macroscopic functional reserve.

It is reasonable to require that the ranking be preserved if the dose distribution is subject to scaling operations of the dose or the reference volume. This choice does not accord to all radiation complications, yet it is necessary to introduce a 'conservation law' for the ranking function to mediate the transition from homogeneous to arbitrary inhomogeneous dose distributions. This idea of invariant ranking under scaling of dose and volume is formalized with the concept of *S*(pace) and *R*(esponse) *faithfulness*. These assumptions are closely related to mechanistic biological assumptions. In contrast to them, the phenomenological assumptions are easily falsifiable.

For practical utility, it should be possible to link a reduction in irradiated volume to an increase in dose tolerance and *vice versa*. This is made explicit with the *volume effect function b*. Quite generally, b is a function of dose d and reference volume V. Here b is approximated to be independent of these quantities in the limit of low complication probabilities. This approximation may be taken to higher orders of d and V if justified by experimental findings. It is possible to derive a family of ranking functions for a given volume effect in equation (13). The ranking function is in essence defined by the 'conservation law' with respect to some transformation, which establishes a certain quantity as a meaningful observable, and the volume effect function which links those transformations. With the particular choice of this paper, the Kutcher–Burman DVH reduction technique is recovered.

All mathematical assumptions are congruous with the local nature of the so-called serial or series type complications (Schultheiss *et al* 1983, Niemierko and Goitein 1991). These complication mechanisms are perceived to be triggered by the loss of function or repair capacity anywhere in the irradiated volume, no matter how small the lesion is initially (biological model assumption I). Furthermore, the series model assumes that the probability p of local occurrence at site $\vec{x}$ of the complication as a function of dose $D(\vec{x})$ is independent of its neighbourhood and

[2] This should not be taken for granted since the ranking of dose distributions may be patient dependent.

is identical at each point of the volume (biological model assumption II). These assumptions are congruous with the former if the concept of functional subunits for these complications is abandoned. Within the framework of the formalism, defining a dose-response function $p(d)$ for an FSU or $P(V, d)$ for the whole organ is tantamount to fixing the volume effect function b *a priori*. This is a rather problematic step since this dose-response is not easily accessible experimentally and the details of the volume effect may only be very difficult to detect in population averaged data. To avoid these difficulties we assume that if FSUs exist, they are too small to influence the dose response on a macroscopic scale by their microscopic partial damage repair capacity. Hence, the dose response does not show an intrinsic length scale, and is therefore invariant under scaling of the volume, in other words it is S-faithful. Conversely, every complication which does show a macroscopic functional interaction necessitates a different choice of invariance property.

If all model assumptions hold, the NTCP function of the series type model is of the form equation (13) and the definite form of G remains to be determined according to the biological concepts. We assume that $q(D) = 1 - p$ is the probability that the complication does not occur in a unit volume v. If n unit volumes are irradiated with the same dose, the probability that the complication does not occur in any volume is $Q = q^n = \exp(n \log q)$. It follows, that the volume dependence of this series model is exponential, and hence

$$F(d, V) = \exp\left(-\frac{nv}{V}(d/d_0)^k\right) \tag{16}$$

with some constant d_0 and a volume effect parameter k. Notice that $\log q < 0$, hence the minus sign in the exponent. The NTCP function P for this model would then be $P = 1 - F(d, V)$.

It is shown in the following that S-faithfulness is invariant under population averages. Following the previous paragraph, we find that the *number* of lesions in n unit volumes is Poisson distributed with mean $\mu = np$ if p is small, as it usually is if the unit volumes are not too big. Equation (16) is recovered as the Poisson probability that no complication occurs. This result stems from biological model assumptions I and II which demand that the complication mechanism be entirely local in its nature, i.e. any interactions within the ensemble of unit volumes are neglected.

By the same token it is possible to arrive at the NTCP function for a larger ensemble: the set of all unit volumes of all individuals who participate in the trial, whose probabilities of complication occurrence are certainly independent. For a group of m individuals all of whom have n unit volumes of some organ irradiated with a dose d, the probability of no occurrence of a complication in any individual is Poisson distributed with mean $\mu = \frac{n}{m}\sum_{i=1}^{m} p_i$. This result implies the same volume dependence of the NTCP function, in other words that S-faithfulness is robust against population averages. If R-faithfulness is invoked, the population averaged NTCP function has the same functional representation as the individual NTCP function, yet with different parameters d_0 and k.

This particular NTCP function is only applicable to complications with a predominantly local complication mechanism. A good candidate is lesions of the spinal cord. The complication mechanism involves the supportive tissue, with the neural damage being secondary to myelitis, necrosis or infarction. Both the neural damage and the primary radiation damage are sufficiently local to be described by equation (16). Figure 1 shows a fit of the model to the complication data obtained by Powers *et al* (1998). Their experiment involved irradiation of canine spinal cord with fields of 4 cm and 20 cm length with several animals per dose level. The two-parameter model was fitted to the 20 cm data with parameters $k = 8.2$ and $d_0 = 60.7$ Gy with reference 'volume' $V = 20$ cm. To prove S-faithfulness, and support the assumption of the simplest possible volume effect, the same fit parameters must also predict the 4 cm data. To show this, a fit for the 4 cm data was obtained which amounts to $k = 8.1$

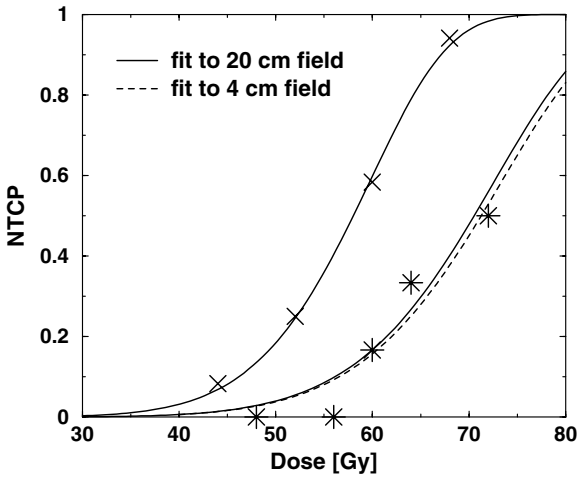

Figure 1. The dose-response curves for the canine spinal cord experiment as in figure 1 of Powers *et al* (1998). The full curve is the fit for the 20 cm data (×), also shown for the 4 cm data (*). The broken curve is the direct fit to the 4 cm data. The good agreement for the 4 cm data supports the assumption of *S*-faithfulness and the simplest possible volume effect for this model.

and $d_0 = 61.2$ Gy. For the direct fit, a χ^2 test delivered $\chi^2 = 0.62$, whereas the parameters of the 20 cm fit delivered $\chi^2 = 0.66$. On the basis of this simple test, neither assumption can be rejected at a confidence level $p \approx 0.1$.

The extension from homogeneous to inhomogeneous dose distributions involves assumptions which have to be substantiated by data obtained from experiments or clinical trials conducted with homogeneous dose distributions. If it is possible to establish *S*-faithfulness for a local dose-response mechanism, as in the example above, the extension may be made safely. From equation (16) it follows that if a volume A is irradiated with dose d_A and a volume B with d_B, the ranking for the volume $A + B$ would be

$$F(D_{(A+B)}, V) = F(d_A, V) * F(d_B, V) \tag{17}$$

$$= \exp\left(-\frac{1}{V}(\mathrm{vol}\,(A)(d_A/d_0)^k + \mathrm{vol}\,(B)(d_B/d_0)^k)\right). \tag{18}$$

By induction it follows that the iso-effective dose and NTCP function reads

$$d = \left(\frac{\int D^k(\vec{x})\,\mathrm{d}x^3}{V}\right)^{1/k} \tag{19}$$

$$\mathrm{NTCP} = 1 - \exp\left[-\left(\frac{d}{d_0}\right)^k\right]. \tag{20}$$

Biological model assumptions I and II are a sufficient condition for *S*-faithfulness (the converse does not hold). There are no equally strong arguments in favour of *R*-faithfulness. From a mechanistic point of view, it is certainly not given in the limit of high doses because it does not comply with the repair capacity of tissues for microscopic lesions. *R*-faithfulness implies dose-scale invariance of the dose response which is inversely related to spatial-scale invariance. If meso- and macroscopic interactions have to be taken into account, both volume and dose-scaling symmetry are broken; this would be the case even for local complication mechanisms in the limit of high doses, or small volumes. It can be conjectured that if the dose-scale invariance did not hold for individuals, the population averages would obliterate

these effects due to the variety of inherent dose-response parameters. The model can account for dose- and/or volume-dependent volume effects by expanding the derivative of the volume effect in equation (12) to higher orders in d and V. This is beyond the scope of this paper, and rather difficult to back up experimentally. In some sense, the power law of the Kutcher–Burman isoeffect is the smallest common denominator in a population dose response.

4. Conclusion

The goal of the model described in this paper was to determine a phenomenological NTCP function with inclusion of mechanistic concepts for predominantly local dose-response mechanisms. The design of the function was determined by the availability of clinical and experimental data where population averages are inherent. It was assumed that the ranking of treatment plans should be independent of the choice of the reference volume and reference dose used for normalization. These steps were embedded in a formalism which is a suitable method for generating model functions under controlled and experimentally accessible assumptions. The formalism was linked to mechanistic concepts which originate from the critical element model. The model is based on properties which are robust against population averages. This is essential if model parameters have to be determined from experimental or clinical data. The invariance properties of the formalism establish practically useful quantities as 'good observables'.

The model has two fit parameters if the dose–volume relation is approximated to the lowest order. More intricate dose–volume relations may be established if indicated by experimental findings. If the assumption of a local complication mechanism is not justified the formalism does not apply. This will certainly be the case for organs showing a high tolerance against partial damage such as lung, liver, kidney or parotid glands. The model was applied successfully to animal spinal cord complication data, yet only similarly conducted experiments can eventually validate it for other tissues.

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