A Stochastic Model for the Normal Tissue Complication Probability (NTCP) and Applications

Theresa Stocks* Thomas Hillen# Jiafen Gong ‡ Martin Burger§

Abstract

The normal tissue complication probability (NTCP) is a measure for the estimated side effects of a given radiation treatment schedule. Here we use a stochastic logistic birth death process to define an organ specific and patient specific NTCP. We emphasize an asymptotic simplification which relates the NTCP to the solution of a logistic differential equation. This framework is based on simple modelling assumptions and it prepares a framework for the use of the NTCP model in clinical practice. As example, we consider side effects of prostate cancer brachytherapy such as increase in urinal frequency, urinal retention, and acute rectal dysfunction.

Key words: normal tissue complication probability, logistic birth death process, tumor control probability, radiation treatment, side effects, TCP, NTCP, brachytherapy, prostate cancer

1 Introduction

The goal of radiotherapy is to deliver a sufficient radiation dose to the tumor to provide a high probability of cure while the surrounding healthy tissue is minimally damaged and left functionally and structurally competent. To achieve this goal, it is necessary to have a method of estimating the probability of normal tissue complication. Quantitative measures for the expected negative side effects on healthy tissue are called *Normal Tissue Complication Probabilities* (NTCP) ([18, 22, 28, 11]). One such model was introduced recently by Hanin and Zaider [11]. Their NTCP model is based on a logistic competition model and it is applied to urethral toxicity of radiation therapy of prostate cancer. The model of [11] is based on an ordinary differential approach, where the model parameters are patient specific. There it is argued that a deterministic model is appropriate, since the relevant population sizes are large and stochastic events are negligible. We confirm this

*Stockholm University, theresa.stocks@math.su.se

#Centre for Math. Biology, University of Alberta, thillen@ualberta.ca

‡University of Toronto, gjf199936097@gmail.com

§Institut für Numerische und Angewandte Mathematik and Cells in Motion Cluster of Excellence, Westfälische Wilhelms-Universität (WWU) Münster, martin.burger@wwu.de

observation, using different methods. We develop the NTCP from a stochastic logistic birth-death process and we consider the limit of large cell populations. In this limit, we find that the mean field equation is a good model for practical use in NTCP calculations. We develop a framework which allows NTCP calculations based on a few parameters of healthy tissue that should be easily obtained. We show how this method can be used to analyze side effects of brachytherapy of prostate cancer. However, several parameters, related to radiosensitivities of the urethra, the bladder and the rectum, have not yet been measured in the literature and we base our modelling on plausible assumptions. We hope that in the future these parameters can be obtained.

The mathematical formulation of a NTCP is similar to the formulation of the *tumor control probability* (TCP), which represents the probability that, after a radiation treatment, no cancer cell has survived in the irradiated domain. The aim of treatment is to achieve a TCP value that is close to one. While the TCP measures the damage to cancerous tissue, the damage of surrounding healthy tissue is not included in a TCP model. Hence here we develop a cousin model, the NTCP, and we use the existing TCP models as guidelines for the development of NTCP models for healthy tissue. Hanin and Zaider [11] argue that a stochastic modelling is not actually needed and an ordinary differential equation (ODE) approach is sufficient. They base this assessment on a calculation of a typical coefficient of variation, which is small. Here we use a stochastic approach, since the clonogenic cells which drive cancer progression, the cancer stem cells, could arise in small numbers. Nevertheless, based on asymptotic scaling methods we also find that an ODE approach can be used for computing the NTCP.

The formulation of a useful NTCP model has many challenges. NTCP models must be patient- and organ-specific. Details of the organ's function, the microenvironment, the biochemical pathways, the geometric structure, and the radio sensitivities are needed. For each organ (and each patient), we need to estimate a critical size of the organ such that it can still function. It is impossible to achieve this in an one-fits-all approach, since organs and patients are different. Here we develop a mathematical framework in which organ specific details can be included in an NTCP model. At the same time, we focus on a model that is not over burdened with complicated mathematics, and rather allows for a simple modelling and transparent presentation of the main results.

Radiation damage to healthy organs and possible organ failures are inherently stochastic events. Furthermore, the organ stem cells, which are responsible for organ regeneration, might occur in low numbers. Therefore, it is reasonable to use the language of stochastic processes to define an NTCP. In this paper we show that

(i) Logistic birth-death models can be used to define a treatment-, patient-, and organ-specific NTCP (see Section 3).

(ii) In the limit of large cell population numbers, the NTCP can be described through the solution of the mean field equations. Furthermore, for small population numbers, the mean field equations still give a good estimate of the transition where the NTCP, as function of dose D, changes from 0 to 1. This allows for an estimation of a maximal tolerable dose D_{max} for each patient (see Section 4).

(iii) The NTCP framework can be extended to include many mechanisms which are left out here, for example, cancer stem cells, cell cycle dynamics, immune responses, various treatment schedules etc. We will discuss these extensions in Section 6.

(iv) We apply the NTCP framework to brachytherapy of prostate cancer using realistic parameters as much as they are available in Section 5. Several important parameters are unknown as of today and a systematic parameter estimation exceeds the purpose of the current paper. We show how the framework can be applied as soon as all parameters are known, where, for now, we choose reasonable values.

(v) Organ- and patient-specific optimization problem for radiation treatment with side effects can be formulated (see Section 6.3). We do not solve them here, but leave it to future research to identify the necessary parameters for each organ/patient, and to perform the optimization.

Since the TCP and NTCP are closely related, we first review some TCP models before extending them to NTCP modelling. One important ingredient is an estimate for the survival fraction $S(d)$ of irradiated cells, given a radiation dose d. We review the corresponding linear quadratic model (LQ-model) in Section 2, where we also review models for the TCP. Section 3 is devoted to our derivation of a stochastic NTCP model based on a stochastic logistic process [1, 6]. It turns out that the mean field equations of this process play an important role in computing the NTCP. Firstly, the mean field equations are of the form of a standard logistic differential equation plus a perturbation which depends on the variance. If this perturbation is small, then the mean field is basically a logistic equation. Secondly, we show that the region where the NTCP becomes critical (i.e. NTCP≈ 1) can be approximated by a Heaviside function, where the location of the jump coincides with the location where the solution of the logistic differential equation falls below a critical level. This relation is surprising, since the NTCP is an intrinsic stochastic concept, but it can actually be estimated from a deterministic differential equation. The same relation arose in the computation of the TCP from Zaider and Minerbo. It was never spelled out in [31], but it was shown in [10] that the Zaider-Minerbo TCP can be computed from the solution of the mean field equations. In Section 4 we motivate the use of a maximal tolerable dose, based on the organ at hand, the patient's radio-sensitivities and the treatment schedule used. In Section 5 we apply the methodology to brachytherapy of prostate cancer. Brachytherapy is one of the best treatments for slow growing prostate carcinoma and it has a success rate of about 94% for 5-year survival and 84% for 10-year survival [20]. However, critical organs near the prostate are affected, leading to side effects that are classified as sexual side effects (erectile dysfunction, reduced libido), urethral side effects (increased urinal frequency, urinal retention, micturition pain, incontinence) and rectal side effects (bleeding, diarrhea, acute and late effects, rectal fistula) [21, 15, 7, 30, 20]. Section 5 focuses on three of these side effects (i) urinary frequency, (ii) urinary retention, (iii) acute rectal dysfunction and we show how the NTCP models confirm the known outcomes. We discuss model extensions in Section 6, which make the modelling approach more realistic. Finally, we close with a conclusion section 7.

2 Previous models of cell survival, TCP and NTCP

A very natural approach to compute normal tissue complication probabilities is a careful statistical evaluation of patient data that are collected after treatment. Two most used statistical approaches are the Lyman NTCP [18] and the critical volume NTCP [22]. In this paper we take a different approach and we derive a mechanistic model that enables us to predict the NTCP during the entire treatment process and beyond. The statistical data mentioned above can then be used to validate the mechanistic predictions. In fact, in [11] such an approach was taken. The authors derived a mechanistic model for radiation-induced damage to healthy tissue and then compared the model to clinical data for prostate cancer side effects. They noted, as we do here as well, that the available data are insufficient to make either a good model validation or a good model prediction. Here we emphasize the fact that the missing model parameters should be measurable in the clinic. We hope that they will become available in the future.

2.1 The linear quadratic model and the hazard function

In this paper we focus on brachytherapy of prostate cancer. We also include the case of constant radiation, since it is the simplest case and it helps us to explain the methodology. Let $\dot{D}(t)$ denote the dose rate of a radiation and D(t) the total radiation up until time t. Then the surviving fraction $S(D(t))$ of irradiated cells is described by the linear quadratic model ([8])

$$S(D(t)) = e^{-\alpha D(t) - \beta G(t) D^2(t)},$$

where α (Gy^{-1}) and β (Gy^{-2}) are radiosensitivity parameters depending on the irradiated tissue types and $G(t)$ is the Lea-Catcheside protraction factor [17, 11]. If the treatment begins at time $t = 0$ and there was no previous radiation, then the Lea-Catcheside protraction factor is given as ([10])

$$G(t) = \frac{2}{D^2(t)} \int_0^t \dot{D}(\tau) \int_0^\tau e^{-\gamma(\tau - s)} \dot{D}(s) ds d\tau, \tag{2.1}$$

where $\gamma > 0$ is the repair rate for DNA single or double strand breaks. In the case of brachytherapy, radioactive seeds are implanted into the prostate. We denote the initial dose to be d_0 and the decay rate to be σ. Explicit values for d_0 and σ can be found in Table 2. Then the dose rate is given by $\dot{D}(t) = d_0 e^{-\sigma t}$ and the total dose up to time t is

$$D(t) = \frac{d_0}{\sigma} \left(1 - e^{-\sigma t}\right).$$

In this case the Lea-Catcheside (2.1) factor becomes

$$G_{\text{brachy}}(t) = \frac{\sigma}{(\gamma - \sigma)(1 - e^{-\sigma t})^2} \left(1 - e^{-2\sigma t} - \frac{2\sigma}{\gamma + \sigma} \left(1 - e^{-(\gamma + \sigma)t}\right)\right)^{1} \tag{2.2}$$

[1] Notice that this formula is identical to the formulation used in the literature, for example equation (16) in [11].

For constant radiation $\dot{D}(t) = \tilde{d}$, we find the Lea-Catcheside factor to be

$$G_{\text{const}}(t) = \frac{2}{\gamma t} + \frac{2}{(\gamma t)^2}\left(e^{-\gamma t} - 1\right).$$

For a given surviving fraction, we can define a corresponding *hazard function* as

$$h(t) = -\frac{1}{S(t)}\dot{S}(t), \tag{2.3}$$

which, in the case of brachytherapy above, gives

$$h_{\text{brachy}}(t) = \alpha d_0 e^{-\sigma t} + \frac{2\beta d_0^2 e^{-\sigma t}}{\gamma - \sigma}\left(e^{-\sigma t} - e^{-\gamma t}\right), \tag{2.4}$$

and for constant radiation gives

$$h_{\text{const}}(t) = \left(\alpha + \frac{2\beta\tilde{d}}{\gamma}\right)\tilde{d}.$$

In Section 6 we discuss other treatment modalities as well as an elegant way to compute the hazard function for any kind of treatment from a differential equation approach, as developed in [10].

2.2 TCP by Zaider and Minerbo

To motivate the TCP model of Zaider and Minerbo [31] we consider a simple ordinary differential equation for the cancer cell number $n(t)$:

$$\frac{dn(t)}{dt} = (b - r(t))n(t), \quad n(0) = n_0, \tag{2.5}$$

with b a constant mitosis rate and $r(t)$ the removal rate. The removal rate can be written as the sum of the natural death rate ρ, which is assumed to be constant here and the radiation dependent hazard function $h(t)$ giving $r(t) = \rho + h(t)$. The solution of this cell population model is given by

$$n(t) = n_0 \exp\Big(bt - \int_0^t r(s)ds\Big), \tag{2.6}$$

with n_0 indicating the initial number of tumor cells.

For a large initial number of clonogenic cancer cells, deterministic models might be appropriate, because with the law of large numbers stochastic events can be neglected and the number of cells converges to the mean number of cells. However, successful therapy aims to diminish the number of cancer cells and for low cell numbers the deterministic formulation no longer applies. Hence we extend the model to include stochastic events via a *birth-death process*.

Following Zaider and Minerbo [31] we let $P_i(t)$ be the probability that i cells are alive at time t with $i \in \mathbb{N}$. The corresponding Master equation for $P_i(t)$ that describes the change in the number of cells is then given as:

$$\frac{dP_i(t)}{dt} = (i-1)bP_{i-1}(t) + (i+1)r(t)P_{i+1}(t) - i(b+r(t))P_i(t), \tag{2.7}$$

with $P_{-1}(t) = 0$ and with initial values $P_{n_0}(0) = 1$ and $P_i(0) = 0$ for $i \neq n_0$. It can be easily checked that the expected number of tumor cells $n(t) = \sum_{i=0}^{\infty} iP_i(t)$ satisfies the above equation (2.5) [31]. Hence (2.5) appears as *mean field* model for the stochastic birth-death process (2.7).
To obtain the TCP we calculate $P_0(t)$. This can be done by the method of generating functions (see [31]). Hence we obtain the *TCP formula of Zaider-Minerbo* as

$$\mathsf{TCP}_{ZM}(t) = P_0(t) = \left[1 - \frac{n(t)}{n_0 + bn_0 n(t)\int_0^t \frac{dr}{n(r)}}\right]^{n_0} \tag{2.8}$$

with birth rate $b \geq 0$ and removal rate $r(t)$. Here $n(t)$ is the solution (2.6) of the mean field equation (2.5).

This framework has been extended to more general linear birth and death Markov processes by Hanin [13, 12], to include active and quiescent cell compartments by Dawson and Hillen [4], non-exponential cell cycle times by Maler and Lutscher [19], and cancer stem cells by Gong [9]. These models follow the same basic principle of stochastic processes, but the resulting TCP formulas are much more complicated. In this paper we base the NTCP-formulation on the Zaider- Minerbo approach, being aware that further generalizations to include cell cycle and stem cells might be needed in the future [29] (see also Section 6).

The description of the TCP by Zaider and Minerbo allows the inclusion of any time-dependent treatment schedule and the parameters are given from a birth-death process of tumor growth. However, so far, there was no cousin model for the NTCP, which is based on an equally detailed description as the Zaider-Minerbo TCP. The model which we develop next, will enable us to compare TCP and NTCP on equal grounds.

3 NTCP based on a stochastic logistic birth-death process

In this section we derive a NTCP model from a stochastic logistic birth-death process. These are well known stochastic processes and detailed expositions can be found in the textbooks of Allen [1] and Nisbet and Gurney [23]. It should be made very clear that here we use the simplest possible model that has non-trivial assumptions. We believe that these assumptions are sufficient to explain the method for deriving an NTCP model. After this has been established, we can extend the model to include stem cells, damaged cells, functional subunits, immune responses, and many other details. We discuss these extensions in detail in Section 6.

Here we make the following assumptions:

1. All healthy tissue cells in the irradiated domain are identical and independent throughout the organ. Here we will not distinguish between organ stem cells and functional cells and we will not consider larger entities such as functional subunits ([22, 28]). These and other extensions will be discussed in Section 6 and they are topic of further research [29].

2. An organ works properly if more than L cells are functionally active.

3. For a small time increment Δt, the expression $\mu \Delta t$ denotes the probability of mitosis in a time interval $[t, t+\Delta t]$, where $\mu > 0$ is the mitosis rate. We will assume that the cell growth is limited by space and nutrition supply so the mitosis rate is dependent on an organ-specific carrying capacity M. An increasing number of cells therefore leads to a decreasing mitosis rate. Mathematically speaking we choose the mitosis rate as follows:
$$\mu_i = \begin{cases} \mu(1 - \frac{i}{M}), & \text{if } i = 1, 2, ..., M \\ 0, & \text{otherwise} \end{cases} \tag{3.9}$$
The carrying capacity M refers to the organ size. If we count cell numbers then M is usually a very large number ($\approx 10^9$). If we consider organ stem cells, then the carrying capacity will be much smaller (depending on the organ at hand).

4. The term $r(t) = \rho + h(t)$ denotes the net cell death rate, where $\rho \geq 0$ denotes natural death of cells and the hazard function $h(t)$ in (2.3) describes death due to radiation. Here we employ the simplifying assumption that dead cells do no longer use nutrients and that their space becomes available for new growth quickly. In [11] a compartment for damaged cells was used to more accurately describe the volume constraint that results from non-functional cells that still linger around.

We denote $P_i(t)$ as the probability that $i \in \mathbb{N}$ normal cells are alive at time t. To define a NTCP we consider the probability that L or less cells are functionally operational, i.e.

Definition 3.1 (NTCP birth-death) *The Normal Tissue Complication Probability based on a birth-death process is defined as*
$$\mathsf{NTCP}_{bd}(t) = \sum_{i=0}^{L} P_i(t). \tag{3.10}$$

The master equation for the probabilities $P_i(t)$ of the number of cells X is given by
$$\frac{dP_i(t)}{dt} = (i-1)\mu_{i-1}P_{i-1}(t) + (i+1)r(t)P_{i+1}(t) - i(\mu_i + r(t))P_i(t), \tag{3.11}$$
with initial values $P_{n_0}(0) = 1$ and $P_i(0) = 0$ for $i \neq n_0$, [6, 1]. For the TCP we were only interested in the solution of $P_0(t)$. In contrast to that we are now interested in solving the system for $P_i(t)$ with $i = 0, ..., L$.

Hanin [13] found an explicit formula for the above sum (3.10) in the setting of a general linear birth and death Markov process, which includes the case of the Zaider-Minerbo TCP,

equation (2.7). This formula has been modified for faster computation in Gong's thesis [9]. We cannot use this formula here, since in our case the mitosis rate, μ_i, is not constant in i. However, the mitosis rate as defined above guarantees that the number of normal tissue cells stays below or equal to the carrying capacity M.

Lemma 3.1 ([6, 1]) *Assume μ_i is given by (3.9). If $P_i(0) = 0$ for $i > M$, then $P_i(t) = 0$ for $i > M$, $\forall t > 0$, i.e. the system (3.11) is finite.*

Another interesting result shows that the mean field function $\mathsf{E}(X(t))$ (with $X(t)$ denoting the random variable which describes the number of healthy tissue cells at time t) obeys a logistic differential equation with a perturbation that depends on the variance.

Lemma 3.2 ([1] Formula (6.28), p. 246)) *Assume μ_i is given by (3.9) and $P_i(0) = 0$ for $i > M$. The series*

$$N(t) = \mathsf{E}(X(t)) = \sum_{i=0}^{M} iP_i(t) \tag{3.12}$$

is the mean field function of system (3.11) and satisfies a differential equation

$$\frac{dN(t)}{dt} = \mu N(t)\left(1 - \frac{N(t)}{M}\right) - r(t)N(t) - \frac{\mu}{M}\mathsf{Var}(X(t)), \tag{3.13}$$

where $\mathsf{Var}(X(t))$ is the variance of the normal tissue cell number and is defined as usual by $\mathsf{Var}(X(t)) = \mathsf{E}((X(t) - N(t))^2)$.

Let us provide some remarks on Lemma 3.2:

1. It is interesting to note that for small perturbation term $\frac{\mu}{M}\mathsf{Var}(X(t))$ we obtain the standard logistic differential equation for the expected number of cells $N(t)$. It should also be noted that under the conditions of Lemma 3.1 the variance is always finite.

2. One could derive an equation for the variance, which then would involve a third moment of X. An equation for the third moment contains the fourth moment and so on. We obtain an infinite hierarchy of models and we are faced with a closure problem. We are not discussing moment closure methods here.

3. Since the variance is non negative, the mean field equation (3.13) is dominated by the logistic equation

$$\frac{dZ}{dt} = \mu Z(t)\left(1 - \frac{Z(t)}{M}\right) - r(t)Z(t), \tag{3.14}$$

   i.e. $N(t) \leq Z(t)$ whenever they have the same initial condition $N(0) = Z(0)$. This fact was already mentioned by Feller in 1939 [6].

4. We rescale the mean field equation (3.13) into a relative occupancy $y(t) := \frac{N(t)}{M}$. Then $y(t)$ satisfies

$$\frac{dy}{dt} = \mu y(1-y) - r(t)y - \mu \,\mathsf{Var}Y(t), \tag{3.15}$$

where the stochastic process Y is defined as $Y(t) = X(t)/M$.

These two previous results give us tools to compute the NTCP for the two complementary cases of M is small and M is large. If M is small (say less than 1000), then we benefit from Lemma 3.1; the system of equations (3.11) is of finite and manageable size, and we can use a direct numerical computation to solve it. This is done in the next Section 3.1. On the other hand, if M is large (larger than 1000, say), then we can use an asymptotic method for $M \to \infty$ to approximate the NTCP as done in Section 3.2. We see that in this case the NTCP is basically given by the logistic differential equation (3.14). If we compare these two methods (for $M = 500$, $M = 5000$ and $M \to \infty$), we find that they coincide surprisingly well, suggesting that the logistic differential equation (3.14) is appropriate in computing the NTCP in all cases. We outline how it can be used in clinical practice in Sections 4 and 5, where we consider side effects of prostate cancer treatments and introduce the organ specific maximal tolerable dose D_{max}.

3.1 Numerical results for small M

After we have seen that the system of ODEs with μ_i is finite, we can now calculate the result numerically. We define $P(t) = (P_0(t), P_1(t), ..., P_M(t))^T$ with $P_i(t)$ from (3.11) and obtain a corresponding *forward Kolmogoroff equation* [1]

$$\frac{dP}{dt} = AP \tag{3.16}$$

with the transition matrix A

$$A = \begin{pmatrix} 0 & r(t) & 0 & ... & 0 & 0 \\ 0 & -(\mu_1 + r(t)) & 2r(t) & ... & & \\ \vdots & & & \ddots & & \\ 0 & 0 & 0 & ... & (M-1)\mu_{M-1} & -M(\mu_M + r(t)) \end{pmatrix}.$$

For the initial values of the ODE system (3.16) we chose a completely healthy organ at the beginning of treatment, i.e. $P_M(0) = 1$ and $P_i(0) = 0 \; \forall i \neq M$. Alternatively we can also consider partially damaged organs such that $P_{n_0}(0) = 1$ with $n_0 < M$. We consider a brachytherapy treatment with ^{125}I and constant radiation. The death rate in the case of brachytherapy is the hazard function (2.4) and is given by

$$r_{\text{brachy}}(t) = \alpha d_0 e^{-\sigma t} + \frac{2\beta d_0^2 e^{-\sigma t}}{\gamma - \sigma}\left(e^{-\sigma t} - e^{-\gamma t}\right). \tag{3.17}$$

In the case of constant radiation we have

$$r_{\text{const}}(t) = \left(\alpha + \frac{2\beta \tilde{d}}{\gamma}\right)\tilde{d}.$$

Case Units	Color	Description	$\tilde{d}$ Gy/day	α Gy^{-1}	β Gy^{-2}	d_0 Gy	γ day^{-1}	μ day^{-1}	M	$l = \frac{L}{M}$
I	blue	Base case	1.16	0.02	0.01	1.68	8.35	0.017	500	1/3
II	magenta	Higher sensitivity	1.16	0.025	0.01	1.68	8.35	0.017	500	1/3
III	green	Slow DNA repair	1.16	0.02	0.01	1.68	2.27	0.017	500	1/3
IV	red	Fast tissue repair	1.16	0.02	0.01	1.68	8.35	0.0346	500	1/3
V	blue, dotted	Larger M	1.16	0.02	0.01	1.68	8.35	0.017	5000	1/3

Table 1: Parameter values for healthy tissues.

Protocol	init. dose d_0 Gy	decay rate σ day^{-1}	total days	half times days	total dose Gy
^{103}Pd	5.71	0.0408	47.63	16.99	120
^{125}I	1.68	0.0117	207.8	59.4	145

Table 2: Parameter values for the radioactive seeds of ^{125}I and ^{103}Pd [21].

The model parameters are given in Table 1 and they have been chosen for the following reasons:

- Instead of using two variables μ and ρ to denote natural mitosis and death rates, we combine both effects in an effective mitosis rate $\mu - \rho$, which we call μ for simplicity.
- The effective growth rate $\mu = 0.017$ for healthy tissue corresponds to an effective doubling time of 40 days. In case IV (Table 1) we consider faster regrowth with $\mu = 0.0346$ and a doubling time of 20 days.
- The ratio α/β was chosen to by 2 for healthy tissue [26, 30].
- DNA repair happens between 2 and 6 h. If we use $T_{1/2} = 2h$ then $\gamma = 8.35$. For $T_{1/2} = 6h$ we have $\gamma = 2.27$, i.e. case III in Table 1.
- A typical fractionated treatment gives a total dose of about 70Gy over 60 days. That is an average dose rate per day of $\tilde{d} = 1.16$ Gy/day, which we chose for the case of constant radiation.
- In Table 2 we list the parameter values for the two isotopes that are used in brachytherapy, ^{125}I and ^{103}Pd. The number of "total days" as reported in Table 2 is the standard way to report brachytherapy treatment duration, see [21], although it is clear that radioactive decay will never reach zero in finite time.

For the solution of the ODE-system (3.16) we used the built-in MATLAB solver *'ode45'*. Fig. 1 shows the simulated NTCP-curves for the five cases listed in Table 1. For cases I, II, III, and V we see that the NTCP starts at zero and, after a while, rises in a relatively short time span to 1. The base case (case I in Table 1) starts to grow significantly at around 55 days. $\mathsf{NTCP} \approx 1$ indicates a large probability of side effects.

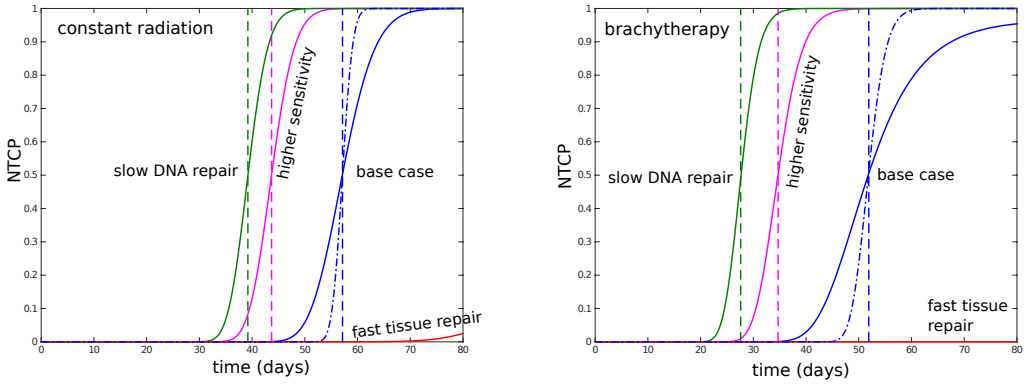

Figure 1: NTCP curves for the five cases listed in Table 1. The left figure shows the case of constant radiation and the right for brachytherapy. The solid lines are the NTCP curves as computed from equation (3.16). The dash-dot blue line corresponds to the fifth case of larger M-value. The dashed lines show the approximation of the jump from 0 to 1 from the asymptotic analysis for large M.

3.2 Asymptotics for large carrying capacity M

As mentioned before, for most cases, the carrying capacity M will be large ($\sim 10^9$) and in that case a direct numerical solution of the system of ODEs (3.16) is no longer feasible. Hence it is useful to consider the asymptotic limit of $M \to \infty$. We will use a rescaling argument to identify the location where the NTCP transfers from 0 to 1. It turns out that the mean field equation (3.14) plays an important role for this transition.

The question we find ourselves confronted with now is if there is an asymptotic limit such that the system of equations becomes independent of the size of the carrying capacity. In this case, the computational limitations would not affect the simulations any longer and we could make capacity-independent predictions. To achieve this aim we will re-parameterize the system of ODEs (3.11). As in the earlier numerical simulations we assume that the initial number of cells is $n_0 = M$. Therefore we get the initial values of the system $P_M(0) = 1$ and $P_i(0) = 0$ for $i \neq M$. For the parameterization we introduce a function $\Phi_M(x,t)$, $x \in [0,1]$ which is a smooth interpolation of the points $x_i = \frac{i}{M}, i = 0, \ldots, M$ as

$$\Phi_M(x_i, t) := M P_i(t), \qquad i = 0, \ldots, M. \tag{3.18}$$

The function Φ_M is an approximate probability density, since $\Phi_M \geq 0$ and

$$\int_0^1 \Phi_M(x,t)dx \approx \sum_{i=0}^{M} \frac{1}{M} \Phi_M\left(\frac{i}{M}, t\right) = \sum_{i=0}^{M} P_i(t) = 1.$$

The NTCP and mean field $N(t)$ can be expressed in Φ_M as

$$\begin{aligned} \mathsf{NTCP}_M(t) &= \int_0^l \Phi_M(x,t)dx \\ N(t) &= M\int_0^1 x\Phi_M(x,t)dx. \end{aligned} \tag{3.19}$$

with $l = \frac{L}{M} \in [0,1]$. We now introduce the rescaling into the master equation (3.11), where we use

$$\frac{i}{M} = x, \quad \Delta x = \frac{1}{M}, \quad i+1 = (x+\Delta x)M, \quad i-1 = (x-\Delta x)M$$

and for the rescaled mitosis rate (3.9) we obtain

$$\tilde{\mu}(x) = \begin{cases} \mu(1-x), & \text{if } x \in [0,1] \\ 0, & \text{otherwise.} \end{cases} \tag{3.20}$$

Using this and (3.18) for (3.11) we obtain by Taylor-expansion with increment $\Delta x = \frac{1}{M}$ (see also [23] eq. (6.2.18) on page 173) that

$$\begin{aligned} \frac{\partial}{\partial t}\Phi_M(x,t) = &-\frac{\partial}{\partial x}\Big[\Big(\mu x(1-x) - r(t)x\Big)\Phi_M(x,t)\Big] \\ &-\frac{\Delta x}{2}\frac{\partial^2}{\partial x^2}\Big[\Big(\mu x(1-x) - r(t)x\Big)\Phi_M(x,t)\Big] \\ &+O(\Delta x^2), \end{aligned}$$

with initial values

$$\begin{aligned} \Phi_M(1,0) &= \Phi_M\Big(\frac{M}{M},0\Big) = MP_M(0) = M. \\ \Phi_M(x,0) &= \Phi_M\Big(\frac{i}{M},0\Big) = MP_i(0) = 0 \quad \text{for} \quad x \in [0,1). \end{aligned}$$

If Δx is small enough, i.e. $M \to \infty$, then we can consider the leading order term $\Phi(x,t)$ of the above expansion. We obtain a hyperbolic partial differential equation for $\Phi(x,t)$:

$$\frac{\partial}{\partial t}\Phi(x,t) = -\frac{\partial}{\partial x}\Big[\Big(\mu x(1-x) - r(t)x\Big)\Phi(x,t)\Big] \tag{3.21}$$

with a singular initial condition

$$\begin{aligned} \Phi(1,0) &= \infty \\ \Phi(x,0) &= 0 \quad \text{for} \quad x \in [0,1). \end{aligned}$$

These initial conditions appear as a Dirac delta distribution

$$\Phi(x,0) = \delta_1(x).$$

In this scaling the NTCP from (3.19) becomes

$$\mathsf{NTCP}_\Phi(t) = \int_0^l \Phi(x,t)dx \tag{3.22}$$

We solve the PDE (3.21) analytically using the method of characteristics. Expanding the spatial derivative we obtain

$$\frac{\partial}{\partial t}\Phi(x,t) + \Big[\mu x(1-x) - r(t)x\Big]\frac{\partial}{\partial x}\Phi(x,t) + (\mu(1-2x) - r(t))\Phi(x,t) = 0.$$

This hyperbolic PDE has the characteristic equations

$$\frac{dx}{dt} = \mu x(1-x) - r(t)x \qquad x(0) = x_0 \tag{3.23}$$

$$\frac{d\Phi}{dt} = -(\mu(1-2x) - r(t))\Phi, \qquad \Phi(x,0) = \delta_1(x). \tag{3.24}$$

With the initial value of Φ being a Dirac delta distribution and (3.24) being linear in Φ, we expect that $\Phi(x,t) = \delta_{x(t)}$ is a weak solution of (3.21). Here $x(t)$ is the solution of (3.23) with the initial value $x_0 = 1$. See [5] for a definition of a weak solution.

Definition 3.2 *$\Phi(.,t) \in \mathcal{D}(\Omega) = \mathbb{C}_0^{\infty^*}(\Omega)$ with $\Omega = [0,1]$ is a weak solution of (3.21), if*

$$\frac{d}{dt}\Big\langle \zeta(x), \Phi(x,t)\Big\rangle = \Big\langle (\mu x(1-x) - r(t)x)\frac{d}{dx}\zeta(x), \Phi(x,t)\Big\rangle$$

for all $\zeta \in \mathbb{C}_0^\infty(\Omega)$.

Here we use the standard notation for the action of a measure on functions:

$$\Big\langle \zeta(x), \Phi(x,t)\Big\rangle = \int \zeta(x)\, d\Phi(x,t),$$

where the integration is with respect to x and t arises as a parameter. We obtain the following theorem:

Theorem 3.3 *Let $x(t)$ be the solution of (3.23) with the initial value $x(0) = 1$. Then $\Phi(x,t) = \delta_{x(t)}(x)$ is a weak solution of the PDE system (3.21).*

Proof. We compute directly for a test function $\zeta \in \mathbb{C}_0^\infty(\Omega)$ that

$$\begin{aligned}
\frac{d}{dt}\Big\langle \zeta(x), \delta_{x(t)}(x)\Big\rangle &= \frac{d}{dt}\zeta(x(t)) \\
&= \frac{d\zeta(x(t))}{dx}\dot{x}(t) \\
&= \frac{d\zeta(x(t))}{dx}(\mu x(t)(1-x(t)) - r(t)x(t)) \\
&= \Big\langle (\mu x(1-x) - r(t)x)\frac{\partial\zeta(x)}{\partial x}, \delta_{x(t)}(x)\Big\rangle.
\end{aligned}$$

□

3.3 Comparison of the two methods for small and large M

The asymptotic method above is particularly designed for the limit of large tumor population, i.e. $M \to \infty$, it does not assume that $\mathsf{Var}(X)/M$ is small. We now want to compare this asymptotic result with the numerical solution from the previous section, cp. Fig.1. Using the solution of Theorem 3.3 we find

$$\mathsf{NTCP}_\Phi(t) = \int_0^l \delta_{x(t)}(z)dz$$

with $l = \frac{L}{M} \in [0,1]$. This integral is 0 if $x(t) > l$, 1 if $x(t) < l$, and it is 0.5 if $x(t) = l$. Hence the NTCP_Φ function is a heaviside function that jumps at $t = x^{-1}(l)$ from 0 to 1. Notice that this value for t might not exist if the characteristic stays above l at all times. The following Figure 2 shows the solutions of the characteristic ODE (3.23), $x(t)$, as function of time for the five cases of Table 1. The threshold value of $l = 1/3$ is indicated as dashed line. As soon as the curves cross the threshold line, the NTCP jumps from 0 to 1. The jump locations have been added to the previous NTCP curves in Figure 1 as dashed horizontal lines of the corresponding color. We see clearly that the jump occurs right in the middle ($\mathsf{NTCP} \approx 0.5$) of the transition of NTCP from 0 to 1. Notice that the case of fast tissue repair does not touch the threshold, hence the NTCP does not jump to 1 for that case.

For the base case we considered two choices of M: $M = 500$ (blue line in Figure 1) and $M = 5000$ (blue dash-dot line in Figure 1). The NTCP for larger M value shows the transition of NTCP from 0 to 1 at the same location, but the gradient of the curve is steeper. For large M the NTCP becomes steeper and steeper, eventually approaching the jump discontinuity. Hence the jump is an excellent indicator of the region where the NTCP rises sharply. The jump was obtained by solving the simple characteristic equation (3.23) instead of the large differential equation system (3.16). Hence (3.23) is a much simpler and efficient model for our purpose.

Besides the parameters shown in Table 1, we tried many other combinations of parameters for fast and slow regenerating tissues, various choices of radio sensitivities, and various choices for M (not shown) and the correspondence of the two NTCP methods was always good.

4 Clinical significance and the maximal tolerable dose

For practical use of this NTCP, we propose an algorithm which is centered around the logistic differential equation (3.14) which we rewrite for convenience:

$$\frac{dZ}{dt}(t) = \mu Z(t)\left(1 - \frac{Z(t)}{M}\right) - r(t)Z(t). \tag{4.25}$$

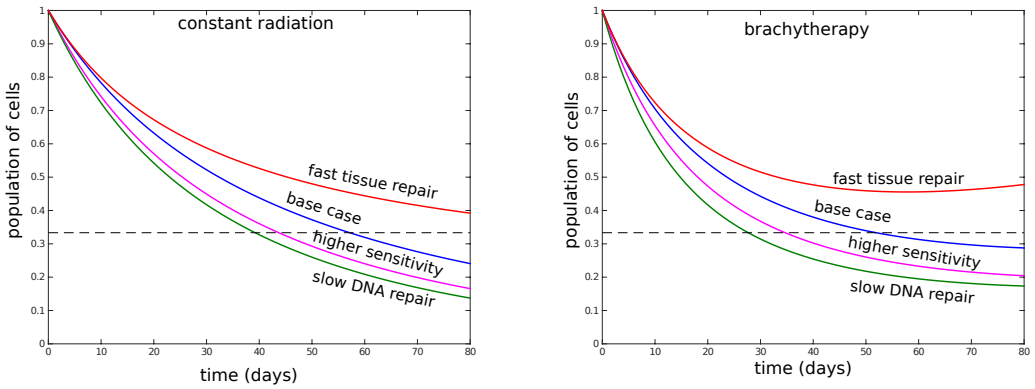

Figure 2: The solid lines show the characteristics $x(t)$ for the five parameter choices from Table 1 for constant treatment (left) and brachytherapy (right). The y-axis indicates the suriving fraction of healthy cells in the irradiated organ. The characteristics start at a fully intact organ $x(0) = 1$ and decrease until they intersect the horizontal line of $x = l$. At that intersection the NTCP jumps from 0 to 1. Notice that the characteristics for cases I and V coincide, since the characteristic equation is independent of M and all other parameters are the same.

As we have seen in Lemma 3.2, this equation approximates the mean field equations (3.13) for a small perturbation term $\frac{\mu}{M}\mathsf{Var}(X)$. Moreover, if we consider the relative abundance $z(t) := Z(t)/M$, then we obtain

$$\frac{dz}{dt}(t) = \mu z(t)(1 - z(t)) - r(t)z(t), \tag{4.26}$$

which coincides with the characteristic equation (3.23) that was used in the asymptotic method for large M. In Section 3.2 we found that the NTCP_Φ jumps from 0 to 1 exactly when the characteristic $x(t)$ meets the threshold value l. Transforming back to the original quantities $Z(t)$, an equivalent condition is

$$Z(t_{\mathsf{max}}) = L, \tag{4.27}$$

where L is the minimal number of cells for an organ to still function and t_{max} is the maximal treatment time, for a given treatment, such that the healthy organ is not damaged too much. In the case of brachytherapy, the radioactive seeds are left inside the organ, hence a maximum treatment time is only an indication of a time point after which the radiation dosage should have reduced to very low levels. Moreover, our method can as well be applied to fractionated treatments, and in those cases the knowledge of t_{max} is quite helpful.

We solve the logistic equation (4.25) until $Z(t_{\mathsf{max}}) = L$ to find the maximal tolerable treatment time t_{max}. The corresponding *maximal tolerable treatment dose* is

$$D_{\mathsf{max}} = D(t_{\mathsf{max}}).$$

	constant radiation		brachytherapy	
case	t_{max} (day)	D_{max} (Gy)	t_{max} (day)	D_{max} (Gy)
I	58	67.28	52	65.45
II	44	51.04	35	48.25
III	39	45.24	28	40.11
IV	N/A		N/A	
V	58	67.28	52	65.45

Table 3: Maximal treatment time t_{max} and maximal tolerable dosages D_{max} for the ten treatments from Table 1.

As an example we use the parameter values from Table 1 for five uniform treatments and five brachytherapy treatments. The NTCP curves were shown in Figure 1. The maximal tolerable dose and the maximal time of exposure in these cases are listed in Table 3. We notice that the maximal dosages for constant treatment and for brachytherapy are very similar. However, the maximal tolerable doses for brachytherapy are a bit smaller, since in brachytherapy a higher dose rate is given at the beginning of treatment.

Notice that for many patients side effects occur only temporarily and they resolve after some time. In our study we only consider the onset of side effects, since these data for the onset of side effects are available.

Summarizing, the parameters that are involved in the computation of the NTCP are the following.

Patient/organ specific:

1. radiosensitivity parameters of the healthy organ; α, β.
2. minimal viable number of cells of the organ; L
3. initial number of cells in the organ; $Z(0)$
4. normal number of cells in the organ; M
5. mean organ repair rate if damaged; μ

We believe that it is possible in the realm of modern medical research to obtain estimates for those parameter values for individual patients.

5 Prostate brachytherapy and side effects

Prostate cancer is treated with a variety of methods including surgical removal, chemotherapy, hormone therapy, external beam radio therapy and brachytherapy [21, 7]. Particularly for low risk prostate cancer patients, brachytherapy is the therapy with the least severe side effects as compared to the other treatments [7]. The toxicity related to sexual dysfunction, rectal effects and severe urethral side effects is lower than compared to surgery

Type	Side effect	toxicity rate Japanese study [30]	toxicity rate Spanish study [7]
Urethral	overall urethral toxicity	78%	89.9 %
	urinal frequency	70%	
	micturition pain	$\sim$ 6 %	
	urinal incontinence	2 %	
	urinal retention	3.7 %	3.4%
		Kishan study [15]	
Rectal	acute response	30-35 %	
	late response	5-7%	
	rectal fistula	0.1%	

Table 4: Occurance of side effects in large cohort studies as reported in the literature.

or external beam radio therapy. However, urinary irradiative obstructive symptoms are more common in brachytherapy [7, 20]. Brachytherapy for prostate cancer is typically performed by inserting radioactive isotopes ^{125}I or ^{103}Pd directly into the prostate. The physical characteristics are listed in Table 2.

Several recent comprehensive reviews evaluate the occurrence of certain side effect after brachytherapy of prostate cancer. The most common side effects relate to sexual performance, to the urethra and to the rectum. Reduced sexual function is a very common outcome of prostate cancer treatment. It affects about 82% of patients treated by surgery or external beam radio therapy and about 52% of patients treated with brachytherapy [7]. Urethral side effects include increase in urinary frequency, urinal retention, micturition pain, and urinary incontinence. Rectal side effects are characterized as radiation proctitis and they occur as acute effects (diarrhea), rectal bleeding, incontinence, rectal fistula and late effects. In a Spanish study about 700 patients were evaluated in 5 year and 10 year follow-up studies [7, 20], and in a Japanese study [30] 218 patients were followed after treatment. Kishan et al. [15] reviews data on rectal toxicities after brachytherapy. In Table 4 we summarize the reported occurrences of side effects. These study only report the onset of a side effect. In many cases these side effects disappear after some time. Since these events are not recorded in the data mentioned above, we do not include the recovery from side effects here.

In Figure 4 we present a sketch of the prostate and related critical organs. We consider the NTCP for three of these: (i) increase in urinary frequency, (ii) urinary retention, and (iii) for rectal proctitis; and we compare those to the tumor control probability (TCP). The relevant parameter values are given in Table 5. We use as many parameters from the literature as are available, however, many of these parameters, especially those related to healthy tissue, are not known. We choose reasonable values to illustrate the NTCP framework and we leave a detailed parameterization for future work.

1. **Cancer TCP.** To calculate the tumor control probability (TCP), we use typical parameter values for prostate carcinoma as collected by Carlson 2004 [3] with $\alpha/\beta =$

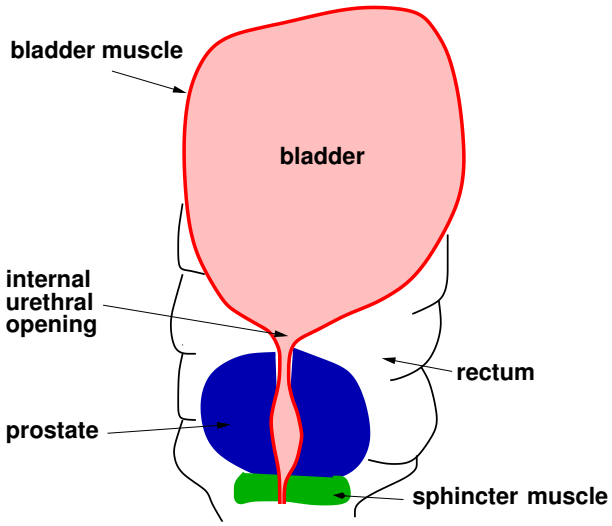

Figure 3: A Mathematicians view of the prostate and the surrounding critical organs (adapted from Wikipedia).

$4, \alpha = 0.2, \beta = 0.05$ and a cancer regrowth rate of $\mu = 0.015$ ($T_{1/2} = 46$ days). Brachytherapy parameters are those of ^{125}I with an initial dose rate of $d_0 = 1.68$ Gy/day, a decay rate of $\sigma = 0.0117$, a total dose delivered as 145 Gy on a treatment time scale of 207.8 days. In all three figures of Figure 4 we show the tumor control probability as function of time in a black dashed line. We see that the TCP starts to increase at about 50 days and well saturates near 1 at the end of treatment, indicating a successful treatment.

2. **Healthy tissue NTCP for urinary frequency.** Increase in urinary frequency affects about 70 % of patients after brachytherapy of the prostate [20, 30]. Hence the NTCP for this case is very high. Urinal urgency is triggered by a combination of effects. Firstly, the epithelial tissue that surrounds the lower part of the bladder is exposed to radiation and becomes raw and sensitive to touch with urine. In addition, radiation damages the muscle tissue that surrounds the bladder and creates scar tissue in the muscles. The bladder cannot expand as much as normal and it looses parts of its flexibility. This leads to an increased sense of urinal urgency even if the bladder is filled at less than 1/4. We assume that the lower bladder region is exposed to about 20% of the full radiation dose rate $d(t)$. The radio sensitivities α and β need special consideration for NTCP modelling. Now we are interested at which doses does epithelial tissue become irritated and raw, rather then when epithelial cells die. In lack of any available data, we choose a five times increased α-value for radio sensitivity related to tissue irritation, i.e. $\alpha = 0.1$. Since the damage is a combination of effects on epithelial and muscle tissue, and since muscle tissue does not fully repair (it forms scar tissue), we use a rather low tissue repair rate of

Case	α Gy^{-1}	β Gy^{-2}	μ day^{-1}	% of total dose	threshold for side effects	tissue type
TCP	0.2	0.05	0.015	100%		prostate
NTCP urinal frequency	0.1	0.01	0.01	20%	60%	bladder
NTCP urinal retention	0.02	0.01	0.05	90%	10%	urethra
NTCP acute rectal	0.1	0.01	0.05	20%	50%	rectum

Table 5: Parameter values for the TCP and NTCP computations.

$\mu = 0.01$ ($T_{1/2}$=70 days). Finally we assume that urgency is prevalent if about 40% of the lower bladder is affected in this way.

To approximate the NTCP, we use the method developed here in Section 3.2. We solve equation (4.26) with the chosen parameters and evaluate the condition $Z(t_{\mathsf{max}}) = L$. The simulation shown in Figure 4 (left) shows the TCP (dashed), the expected functionality of the bladder as function of time and the NTCP threshold as horizontal line. As soon as the blue curve crosses over the threshold line, the probability of urinal frequency increases significantly.

3. **Healthy tissue NTCP for urinal retention.** Urinal retention, or urethral blockage occurs if a part of the urethra is so damaged that urine flow stops ([30, 20]). Particularly critical is the internal urethral opening and the part of the urethra that runs through the prostate. The radioactive seeds are usually placed at a small distance from the urethra, such that it does not receive the full dose. We assume it is exposed to 90% of the full dose rate. The urethra needs to be severely damaged before it can block urine flow, hence we assume a damage threshold of 90%. The radiosensitivities are those of healthy epithelial tissue ([30]) with $\alpha = 0.02, \beta = 0.01$ and a repair rate of $\mu = 0.05$ ($T_{1/2} = 14$ days).

   We observe in Figure 4 (middle) that the mean expected functionality of the urethra stays well above the threshold value, indicating that urethral retention is unlikely (but possible) in brachytherapy.

4. **Healthy tissue NTCP for radiation proctitis.** Similar to the bladder, the rectum is affected in (at least) two ways. Epithelial tissue becomes raw and irritated and the lining muscle tissue of the rectum develops scars and looses part of its flexibility ([15]). We assume that part of the rectum receives about 20% of the radiation dose rate and that acute rectal effects show if about 50% of the irradiated rectum area is damaged. We use the same radio sensitivities as for the bladder, $\alpha = 0.1, \beta = 0.01$ and a repair rate of $\mu = 0.05$.

   We see in Figure 4 (right) that the red curve, indicating the normally functional portion of the rectum, to come close to the red threshold line. This shows that the NTCP for acute rectum dysfunction is less than 50% but still significant. The data show that this occurs in about 30% of the cases.

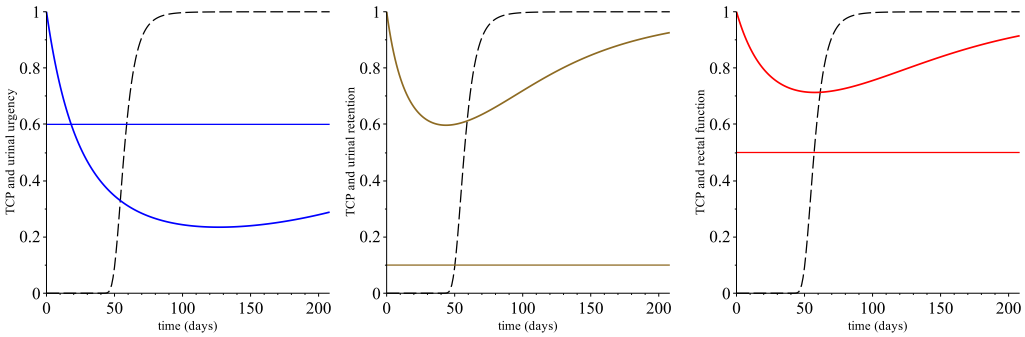

Figure 4: TCP (dashed) and urinary frequency (left), urinary blockage (middle), and rectal proctitis (right). In the left figure we plot the fraction of undamaged tissue in the lower bladder area and the threshold of 60% as straight line. Crossing the threshold indicates a significant risk to develop this side effect. The middle figure shows that the fraction of healthy urethral lining cells stays way above the threshold for urethral retention, indicating that this side effect is least likely. The right figure shows the functioning part of the irradiated part of the rectum. The red curve stays slightly above the threshold, hence acute rectal dysfunction can be expected in several cases (30% according to the data).

6 Model extensions

The above simplified cancer growth model (3.11) was used to introduce our methodology. We wanted to make the point that the transition of the NTCP from 0 to 1 can be approximated for large carrying capacity by a jump discontinuity in the weak solution of the characteristic equation. This allows us to use ODEs for the modelling process.

Certainly, many important aspects of cancer growth have been ignored and should be included. We use this section to discuss some of the relevant model extensions including other treatment schedules, stem cells, and other cell compartments, and we will relate the results to an interesting concept of *functional subunits*.

6.1 Other treatment schedules

If we consider fractionation therapy of n fractions of equal dose d, then we use the standard linear quadratic model

$$S(D) = e^{-(\alpha+\beta d)D}, \qquad D = nd.$$

In [10] we developed a general framework such that the hazard function $h(t)$ can be defined for any treatment schedule $D(t)$. To be precise, we only assume that the dose rate $\dot{D}(t)$ is a piecewise continuous function of time. Such a dose rate can then describe uniform and non-uniform radiation schemes, fractionations with varying dosages, hyper and hypo-fractionations as well as constant radiations, brachytherapies and any combination of the above. The total dose $D(t) = \int_0^t \dot{D}(s)ds$ is then a continuous and non-decreasing function

of time. In [10] we defined a generalized hazard function as

$$h(t) = (\alpha + \beta d_{\mathsf{eff}}(t))\dot{D}(t),$$

with an effective dose rate $d_{\mathsf{eff}}(t)$. The effective dose rate $d_{\mathsf{eff}}(t)$, introduced in [10], depends on the specific treatment schedule and on the underlying cell survival model. For example for fractionation therapy of equal dose d per fraction, we simply use $d_{\mathsf{eff}}(t) = d$ and for brachytherapy we use

$$d_{\mathsf{eff}}(t) = 2\int_{-\infty}^{t} e^{-\gamma(t-s)}\dot{D}(s)ds.$$

It was shown in [10] that this choice of $d_{\mathsf{eff}}(t)$ indeed leads to the correct Lea-Catcheside factor (2.1). Many more models and treatments can be included via $d_{\mathsf{eff}}(t)$ and we consider this formulation a convenient way to use hazard functions for modelling different treatments. Moreover instead of assuming a constant natural death rate, a time dependent rate would be more realistic.

6.2 Other cell compartments, stem cells, cell cycle

- Hanin and Zaider [11] included a compartment of doomed (seriously damaged) cells. These cells although clonogenically dead, can still contribute to the function of the organ and use resources and space. For our purpose we denote the doomed cell number as $V(t)$. Hanin and Zaider consider the logistic system

$$\begin{aligned} \dot{N} &= \mu N\left(1 - \frac{N+V}{M}\right) \\ \dot{V} &= -dV \end{aligned}$$

  and they use it to analyse urethral toxicity of prostate cancer treatment. The inclusion of V would require a simple addition to the above logistic birth-death process above (3.11). Our point is, however, that it is not necessary to use birth-death processes, and we should rather model directly on the level of an ODE, as done, for example, by Hanin and Zaider [11]. In that sense, our framework confirms the ODE approach of Hanin and Zaider from a different perspective.

- Stem cells are known to be the organizing centers of many organs. Stem cells are activated through feedback from damaged organ tissue, initiating tissue repair. The inclusion of stem cell dynamics, feedback mechanisms, differentiation and dedifferentiation is quite difficult on the level of a stochastic birth-death process. This can, however, be done on the level of an ODE, see for example in [2, 16, 25].

- The inclusion of cell cycle dynamics is another interesting challenge. Radiation treatment interferes with the cell cycle and various cell cycle check points are activated by radiation damage [24, 27]. Since the cell cycle phases are not stochastically independent, we leave the realm of Markov processes when studying stochastic models for cell cycle dynamics [14, 19] and an extension to NTCP calculations is an interesting topic for future research.

- The side effects discussed in our paper are only related to the number of functional cells of the organ at hand. As discussed above in the case of prostate cancer treatment, side effects can have many more causes than just cell loss. For example, irradiated epithelial tissue becomes raw and sensitive to touch, tissue might form scars which changed the functionality of the tissue, muscle tissue might not fully recover its original strength, and infections might develop. The inclusion of the nervous system, wound healing, scarring, and the immune response is a huge endeavour. Still, an NTCP modelling based on detailed ODE models, might enable us to include these processes in the future.

- A new idea of Niemierko et al. [22] and Staverv et al. [28] is the introduction of the concept of a *Functional Subunit* (FSU). A variety of organs can still function even when partially destroyed. This fact is called a *parallel organ structure* and appears in organs such as the lung and kidney, because the undamaged parts work independently from the damaged ones. The smallest unit of an organ that is capable to perform biological functions is called a functional subunit (short: FSU) [28]. For example in the kidney the FSU are the renal tubes, in the liver it is the lobules, and the FSU of the lung are the acinuses. As mentioned in [11], the above modelling framework can be formulated in units of FSUs. In that case, the death and reproduction rates no longer relate to individual cells, but to groups of cells, the FSUs. These values are not easily available in the literature.

6.3 Optimization and Optimal Control Problems

The next step is to compare the tumor control probability to the NTCP and formulate a constraint optimization problem and an optimal control problem. These are based on the following patient specific and organ specific parameters:

- radio sensitivities of tumor: α_t, β_t and initial tumor size n_0.

- radio sensitivities of the involved healthy tissue; α_h, β_h

- initial number of healthy tissue cells Z_0, the normal number of healthy tissue cells M, and the minimal tolerable number of the organ cells at hand L.

- tumor growth rate b, and tumor death rate $r_t(t)$ based on a radiation schedule $\dot{D}(t)$

- healthy tissue repair rate μ, and death rate of healthy tissue due to treatment $r_h(t)$, given by a treatment $\dot{D}(t)$, which can include a dose-volume histogram of the exposed healthy tissue.

In the following we denote by $\mathcal{D}$ the set of admissible treatment schedules consisting of certain functions $\dot{D} : [0, t_{\mathsf{max}}] \to \mathbb{R}^+$. Note that $\mathcal{D}$ can include restrictions on the maximal dose in total and per time interval and further a-priori choices on the type of

treatment (e.g. discrete radiation events, continuous radiation, weekends off, etc.). For a given treatment schedule $\dot{D}$ let $(n(\cdot;\dot{D}), Z(\cdot;\dot{D}))$ denote the solutions of

$$\begin{aligned} \frac{dn}{dt} &= (b - r_t(t))n, \qquad n(0) = n_0 \\ \frac{dZ}{dt} &= \mu Z\Big(1 - \frac{Z}{M}\Big) - r_h(t)Z, \qquad Z(0) = Z_0. \end{aligned}$$

Note that the variable $\dot{D}(t)$ enters the radiation induced death rates $r_t(t), r_h(t)$ through the hazard functions.

The goal of the radiation therapy taking into account TCP and NTCP is to achieve tumor control in a certain time interval while restricting the damage. Note that the first means to have TCP close to one at final time t_{max}, which can be expressed already by the formula of Zaider-Minerbo (2.8). The constraint has to be formulated in the whole time interval $[0, t_{\mathsf{max}}]$ however, since too strong damage during the treatment cannot guarantee recovery even if the NTCP is again below a threshold at time t_{max}.

Control problem: Given a fixed target time t_{max} and a target $\mathsf{TCP}_{\mathsf{max}}$ close to 1. Find $\dot{D} \in \mathcal{D}$ such that for all $0 < t \le t_{\mathsf{max}}$:

$$\mathsf{TCP}_{ZM}(t_{\mathsf{max}}) = \left(1 - \frac{n(t_{\mathsf{max}};\dot{D})}{n_0 + bn_0 \int_0^{t_{\mathsf{max}}} \frac{dt}{n(t;\dot{D})}}\right)^{n_0} = \mathsf{TCP}_{\mathsf{max}}, \qquad Z(t;\dot{D}) \ge L.$$

Since it may be difficult or even impossible to achieve exact controllability in a finite time interval, we alternatively formulate an optimization problem rather in the tradition of optimizing treatment schedules:

Optimization problem:

$$\max_{t_{\mathsf{max}}>0, \dot{D}\in\mathcal{D}} \mathsf{TCP}_{ZM}(t_{\mathsf{max}}), \quad Z(t;\dot{D}) \ge L \text{ for all } 0 < t \le t_{\mathsf{max}}.$$

The analysis of this optimization problem and the control problem depends on specific choices of $\mathcal{D}$ and parameters, which exceeds the scope of this paper and it is an interesting problem for future research.

7 Conclusions

We introduced a mathematical model for the normal tissue complication probability (NTCP), which is based on patient-specific, organ-specific and treatment-specific parameters. This of course means that we do not provide a one-fits-all formula. Rather, we present a framework such that in a given situation, a NTCP can be derived. The analysis of the stochastic birth-death process suggests to use the logistic differential equation (3.14) as a good indicator of the NTCP. Hence the model is mathematically simple. There is even

an explicit solution to the logistic equation. Moreover, the number of parameters that are needed is quite limited $(\alpha, \beta, Z(0), M, L)$ and there is real hope that these parameters can be estimated for many healthy tissues in the future. If this is achieved, we will have a biologically-based formulation of the NTCP instead of a statistically based NTCP as the one by Lyman [18], for example.

Acknowledgements: We are particularly grateful to Dr. Nawaid Usmani from the Cross Cancer Institute in Edmonton for his detailed feedback on side effects in prostate cancer brachytherapy. We also appreciate detailed suggestions from Dr. Hanin and two anonymous referees. Research leading to this paper was carried out when the first author was at the WWU Münster (MSc program), visiting University of Alberta (DAAD-PROMOS scholarship), and Stockholm University (PhD program). Parts of this manuscript were written during a research stay of TH at the Mathematical Biosciences Institute in Columbus, Ohio. TH is supported through NSERC. MB acknowledges support by the German Science Foundation DFG via EXC 1003 Cells in Motion – Cluster of Excellence, Münster, Germany.

References

[1] L.J.S. Allen. *An Introduction to Stochastic Processes with Applications to Biology.* Prentice Hall, Upper Saddle River, NJ, 2003.

[2] J. Bachman and T. Hillen. Mathematical optimization of the combination of radiation and differentiation therapies of cancer. *Frontiers in Molecular and Cellular Oncology*, 2012. free online, doi: 10.3389/fonc.2013.00052.

[3] DJ. Carlson, RD. Stewart, XA. Li, K. Jennings, JZ. Wang, and M. Guerrero. Comparison of *in vitro* α/β ratios for prostate cancer. *Phys. in Med. and Biol.*, 49:4477–4491, 2004.

[4] A. Dawson and T. Hillen. Derivation of the tumor control probability (TCP) from a cell cycle model. *Comput. and Math. Meth. in Medicine*, 7:121–142, 2006.

[5] L.C. Evans. *Partial Differential Equations.* American Mathematical Society, Providence, RI, 1998.

[6] W. Feller. Die Grundlagen der Volterraschen Theorie des Kampfes ums Dasein in Wahrscheinlichkeitstheoretischer Behandlung. *Acta Biometrica*, 5:11–40, 1939.

[7] M. Ferrer, F. Guedea, JF. Suarez, B. de Paula, V. Macias, A. Marino, A. Hervas, I. Herruzo, MJ. Oritz, J. Ponce de Leon, G. Sancho, A. Boladeras, A. Ayala, J. Carven-Batle, M. Avila, O. Cunillera, Y. Pardo, J. Alonso, and F. Aguilo. Quality of life impact of treatments for localized prostate cancer: Cohort study with a 5 year follow-up. *Radiotherapy and Oncology*, 108:306–313, 2013.

[8] J. F. Fowler. 21 years of biologically effective dose. *British Journal of Radiology*, 83(991):554–568, 2010.

[9] J. Gong. Tumor control probability models, 2011. PhD thesis, University of Alberta, Canada.

[10] J. Gong, M. M. dos Santos, C. Finlay, and T. Hillen. Are more complicated tumor control probability models better? *Math. Med. Biol.*, 30(1):1–19, 2011.

[11] L. Hanin and M. Zaider. A mechanistic description of radiation-induced damage to normal tissue and its healing kinetics. *Physics in Medicine and Biology*, 58:825–839, 2013.

[12] L. G. Hanin. A stochastic model of tumor response to fractionated radiation: limit theorems and rate of convergence. *Math Biosci*, 91(1):1–17, 2004.

[13] L.G. Hanin. Iterated birth and death process as a model of radiation cell survival. *Math. Biosci.*, 169(1):89–107, 2001.

[14] L.G. Hanin, O. Hyrien, J. Bedford, and A.Y. Yakovlev. A comprehensive stochastic model of irradiated cell populations in culture. *J. Theor. Biol.*, 239(4):401–416, 2006.

[15] AU. Kishan and PA. Kupelian. Late rectal toxicity after low-dose-rate bachytherapy: Incidence, predictors, and management of side effects. *Brachytherapy*, 14:148–159, 2014.

[16] A. Konstorum, T. Hillen, and J. Lowengrub. Feedback regulation in a cancer stem cell model can cause an allee effect. 2016. submitted.

[17] D.E. Lea. *Actions of Radiation on Living Cells*. Cambridge University Press, New York, 2nd edition, 1955.

[18] John T. Lyman. Complication probability as assessment from dose-volume histograms. *Radiation Research*, 104:S13–S19, 1985.

[19] A. Maler and F. Lutscher. Cell cycle times and the tumor control probability. *Mathematical Medicine and Biology*, 27(4):313–342, 2010.

[20] E. Martinez, A. Daidone, C. Gutierrez, J. Pera, A. Boladeras, F. Ferrer, F. Pico, JF. Suarez, A. Polo, and F. Guedea. Permanent seed brachytherapy for clinically localized prostate caner: Long-term outcomes in a 700 patient cohort. *Brachytherapy*, 14:166–172, 2015.

[21] S. Nag, D. Beyer, J. Friedland, P. Grimm, and R. Nath. American brachytherapy society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. *Int. J. Rad. Oncology Biol. Phys.*, 44:789–799, 1999.

[22] A. Niemierko and M. Goitein. Modelling of normal tissue response to radiation: the critical volume model. *Int. J. Rad. Oncol. Biol. Phys.*, 25(1), 1993.

[23] R.M. Nisbet and W.C.S. Gurney. *Modelling Fluctuating Populations*. Blackburn Press, Coldwell, 1982.

[24] B. Novak, A. Toth, A. Csikasz-Nagy, B. Gyorffy, J.J. Tyson, and K. Nasmyth. Finishing the cell cycle. *J. Theor. Biol*, 199:223–233, 1999.

[25] A. Rhodes and T. Hillen. Mathematical modelling of the role of survivin on dedifferentiation and radioresistance in cancer. *Bulletin Math. Biol.*, to appear, 2016.

[26] R. Rockne, J.K. Rockhill, M. Mrugala, A.M. Spence, I. Kalet, K. Hendrickson, A. Lai, T. Cloughesy, E.C. Alvord Jr, and K. Swanson. Predicting the efficacy of radiotherapy in individual glioblastoma patients *in vivo*: a mathematical modelling approach. *Phy. in Med. and Biol.*, 55:3271–3285, 2010.

[27] S.C. Short, M. Woodstock, B. Marples, and M.C. Joiner. Effects of cell cycle phase on low-dose hyper radiosensitivity. *Int. J. Radiat. Biol.*, 79(2):99–105, 2003.

[28] P. Stavrev, N. Stavreva, A. Niemierko, and M. Goitein. Generalization of a model of tissue response to radiation based on the ideas of functional subunits and binomial statistics. *Phy. Med. Biol.*, 46:1501–1518, 2001.

[29] T. Stocks, T. Hillen, J. Gong, and M. Burger. Stem cell modelling of radiation treatment indicators TCP and NTCP. *in preparation*, 2015.

[30] N. Tanaka, I. Asakawa, M. Hasegawa, and K. Fujimoto. Urethral toxicity after LDR brachytherapy: Experience in japan. *Brachytherapy*, 14:131–135, 2015.

[31] M. Zaider and G.N. Minerbo. Tumor control probability: a formulation applicable to any temporal protocol of dose delivery. *Physics in Medicine and Biology*, 45:279–293, 2000.