

ORIGINAL ARTICLE

From cell population models to tumor control probability: Including cell cycle effects

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Abstract

Background. Classical expressions for the tumor control probability (TCP) are based on models for the survival fraction of cancer cells after radiation treatment. We focus on the derivation of expressions for TCP from dynamic cell population models. In particular, we derive a TCP formula for a generalized cell population model that includes the cell cycle by considering a compartment of actively proliferating cells and a compartment of quiescent cells, with the quiescent cells being less sensitive to radiation than the actively proliferating cells. **Methods.** We generalize previously derived TCP formulas of Zaider and Minerbo and of Dawson and Hillen to derive a TCP formula from our cell population model. We then use six prostate cancer treatment protocols as a case study to show how our TCP formula works and how the cell cycle affects the tumor treatment. **Results.** The TCP formulas of Zaider-Minerbo and of Dawson-Hillen are special cases of the TCP formula presented here. The former one represents the case with no quiescent cells while the latter one assumes that all newly born cells enter a quiescent cell phase before becoming active. From our case study, we observe that inclusion of the cell cycle lowers the TCP. **Conclusion.** The cell cycle can be understood as the sequestration of cells in the quiescent compartment, where they are less sensitive to radiation. We suggest that our model can be used in combination with synchronization methods to optimize treatment timing.

In this paper, we concern ourselves with the tumor control probability (TCP), defined as the probability that no clonogenic cells survive the radiation treatment [1]. Expressions for TCP can be derived in a number of different ways. Here, we distinguish between expressions for TCP obtained from statistical models of cell survival and expressions for TCP obtained from stochastic cell population models. We briefly review the former, and focus on the latter.

Expressions for TCP in common use are based on either Poissonian or binomial statistics, in combination with models of cell survival. A strength of these models clearly lies in their simplicity. The models are used widely, and contribute to the analysis of radiobiological data in the lab and the development of clinical treatment schedules. At the same time, there are limitations. In particular, the interaction of the treatment schedules with cancer cell dynamics (cell repair, cell proliferation, sensitivity to radiation, etc.) cannot be represented in full detail.

We argue that cell population models, that is, models that keep track of the number of clonogenic cells using differential equations, can be used to derive new forms of the TCP that will allow a systematic investigation of different treatment schedules and their interactions with cancer cell dynamics. For example, with cell population models, there is a choice in the way that proliferation is modelled (exponential, logistic, Gompertzian, etc.). Similarly, differential effects of radiation can be modelled by dividing the cell population into different compartments [2,3]. In the context of the cell cycle, it makes sense to consider a compartment with actively proliferating cells and another with quiescent cells, since it is known that actively proliferating cells are more sensitive to radiation than quiescent cells. In the context of a solid tumor, it might make sense to consider a compartment of hypoxic cells and another compartment with non-hypoxic cells, since it is known that hypoxic cells are less sensitive to radiation than non-hypoxic cells.

The use of differential equation models is appropriate for large numbers of cells. However, if the radiation treatment is successful, then one expects a small number of cells after some time. In that case, the differential equation model is no longer valid. A more careful modelling approach should include stochastic birth and death events, as modelled through a *stochastic birth-death process*.

Our goal is to present a hierarchical view of expressions for TCP, with increasing sophistication and generality. We begin with TCP curves obtained from cell survival models, and end with a TCP curve obtained by considering a stochastic birth-death process for a cell population model that includes the effects of the cell cycle. We highlight the connections between these models by showing that special cases of the more complex models reduce to previously known models.

TCP curves from cell survival models

A common observation is that the number of cells that survive radiation treatment can be described by a Poisson distribution, which leads to,

$$TCP_p = e^{-n_0 S(D)}, \quad (1)$$

where n_0 is the initial number of cells, and $S(D)$ denotes the fraction of cells that survives the treatment as a function of radiotherapeutic dose D . This formula is valid provided that n_0 is large, that cell survival is a rare event, and that death of each cell is stochastically independent of the other cells.

If n_0 is not large, and survival is not a rare event, then the number of cells that survive radiation treatment follows a binomial distribution. Then the TCP becomes

$$TCP_B = (1 - S(D))^{n_0}. \quad (2)$$

Letting $n_0 \rightarrow \infty$ and $S(D) \rightarrow 0$ such that $0 < n_0 S(D) < \infty$, $TCP_B \rightarrow TCP_p$, that is, the binomial TCP converges to the Poissonian TCP, as expected.

To complete either the Poissonian or the binomial expression for TCP, one needs a model for the survival fraction $S(D)$. There are many theoretical models for cell survival. We will not review these models here, but just mention some major classes of cell survival models, namely target-theory models [4], the linear-quadratic model [5], repair-misrepair models [6], and the lethal-potentially lethal models [7]. Here, we focus on the most commonly used model for cell survival, namely the linear-quadratic model [5],

$$S(D) = e^{-(aD + \beta D^2)}, \quad (3)$$

where a and β are the cellular radiosensitivities that vary with the type of tissue being radiated. In clinical practice, total dose D is given in n fractions, each of dose d . Equation 3 then becomes

$$S(D(n, d)) = \left[e^{-(ad + \beta d^2)} \right]^n = e^{-n(ad + \beta d^2)} = e^{-aD \left(1 + \frac{d}{a\beta}\right)}. \quad (4)$$

The expression

$$BED := -\frac{1}{a} \log(S(D)) \quad (5)$$

has been used in clinical practice as *Biological Effective Dose*, or as *Extrapolated Response Dose* to compare different treatment strategies (e.g., Dale [8]). Although applied with some success, these expressions for cell survival have important limitations. In particular, they do not take into account the temporal protocol of dose delivery. That is, a total dose of say 70 Gy in 35 fractions spread out over seven weeks gives the same cell survival and tumor control probability as the same fractionation spread out over 14 weeks or 21 weeks, etc. By ignoring time as an independent variable, the slow repair mechanisms that restore cells between fractions are ignored, as well as cell proliferation during treatment. Proliferation plays a role especially when the treatment is delivered over a time interval that is long relative to the tumor doubling time. Both of these limitations can be addressed with modified expressions for cell survival and Biological Effective Dose (*BED*).

To incorporate the effect of slow repair mechanisms, the following expression for cell survival is commonly used,

$$S(D) = e^{-(aD + \beta G D^2)}, \quad (6)$$

where G is the generalized Lea-Catcheside dose-protraction factor [9,10],

$$G = \frac{2}{D^2} \int_{-\infty}^{\infty} \dot{D}(t) dt \int_{-\infty}^t e^{-\gamma(t-\bar{t})} \dot{D}(\bar{t}) d\bar{t}, \quad (7)$$

$\dot{D}(t)$ is the dose rate, $D(t)$ is the cumulative dose, and $1/\gamma$ represents the average life time of a double-stranded DNA break ($\gamma > 0$ implies that repair mechanisms are at work).

To incorporate the effect of cell proliferation, cell survival is modified as follows [11, 12]:

$$S(D) = e^{-(aD + \beta D^2)} e^{\frac{\ln 2}{T_p}(t-t_k)}, \quad (8)$$

where T_p is the tumor doubling time, and t_k is the time after treatment ($t=0$) at which proliferation begins. If we use Equation 5 with Equation 6 or 8 we obtain a BED formula which depends on time. The time-delay term has been introduced to describe the effect of accelerated tumor regrowth after treatment has started [13–16]. This last expression can be derived readily from a cell population model, as we review below.

Tucker et al. [17] were among the first to question the appropriateness of the Poissonian description of the TCP. They used Monte-Carlo simulations to show

that the Poissonian distribution of surviving cancer cells underestimates the simulated numbers up to 15%. Yakovlev [18] and later Hanin [19, 20], based on the work of Kendal [21], described the Monte-Carlo simulation through a stochastic birth-death process and they showed analytically that the Poisson distribution may be inappropriate in certain situations. Additionally, Hanin found that the birth-death process can also be understood as a stochastic branching process. In this interpretation, the cell survival distribution follows a generalized negative binomial distribution. He also gives estimates on the convergence to the Poissonian distribution for large cell numbers. Recently, Stavrev et al. [22] used these non-Poissonian models to fit *in vitro* data for radiation damage of tumor cells. We will review the non-Poissonian model of Zaider and Minerbo [23] in the following section.

TCP from cell population models

If we let $n(t)$ denote the number of cancer cells at time t , then one of the simplest cell population models is given by the differential equation

$$\frac{dn}{dt} = [b - d - h(t)]n, \quad (9)$$

where b and d are per-capita rate constants representing birth and death, respectively, and $h(t)$ is known as a *hazard function*, representing death of the cells due to radiation. The hazard function depends on cumulative dose, the dose rate, as the tissue is being radiated. Without radiation (setting $h(t)=0$), the cell population exhibits exponential growth if $b>d$ and exponential decay if $b<d$. By choosing the hazard function to be

$$h(t) = (a + 2\beta D(t))\dot{D}(t), \quad (10)$$

the solution of the differential equation is

$$n(t) = n_0 e^{-(aD + \beta D^2)} e^{\frac{\ln 2}{T_p}(t-t_k)}, \quad (11)$$

where

$$\frac{\ln 2}{T_p} = b - d.$$

The surviving fraction of cells

$$S(D) = \frac{n(t)}{n_0}$$

is the same as the modified linear-quadratic equation shown in Equation 8.

It is important to notice that cancer cell kill due to radiation is in fact a stochastic process. The use of differential equation models is appropriate for large

numbers of cells. However, if the radiation treatment is successful, then one expects a small number of cells after some time. In that case, the differential equation model is no longer valid. A more careful modelling approach should include stochastic birth and death events, as modelled through a *stochastic birth-death process*. Then the differential equation model arises as *mean field* equations for the expected cell number.

In [23], Zaider and Minerbo did exactly that for differential Equation 9, and derived a new expression for the TCP, namely

$$TCP_{ZM}(t) = \left[1 - \frac{S_h(t)e^{(b-d)t}}{1 + bS_h(t)e^{(b-d)t} \int_0^t \frac{dr}{S_h(s)e^{(b-d)s}}} \right]^{n_0}, \quad (12)$$

where

$$S_h(t) = e^{-\int_0^t h(r)dr}$$

is the surviving fraction of cells due to radiation only (assuming $b=d=0$). Noting that the surviving fraction is

$$\frac{n(t)}{n_0} = S_h(t)e^{(b-d)t},$$

we can rewrite $TCP_{ZM}(t)$ as

$$TCP_{ZM}(t) = \left[1 - \frac{n(t)}{n_0 + bn_0 n(t) \int_0^t \frac{dr}{n(r)}} \right]^{n_0}, \quad (13)$$

where $n(t)$ is the solution of the original deterministic population growth model (Equation 9). Note that Zaider and Minerbo's TCP formula is time dependent. In particular, it can accommodate any fractionation schedule, via the dose rate $\dot{D}(t)$ in the hazard function $h(t)$. The procedure to compute the TCP then is straight forward (summarized in steps 6–8 in the next section).

When $b=d=0$, that is, when cell death is due to radiation only, then Zaider and Minerbo's TCP formula TCP_{ZM} reduces to the binomial TCP formula, TCP_B in Equation 2.

The derivation of TCP formulas via birth-death processes, as pioneered by Zaider and Minerbo, also provides a natural way to take into account various factors that influence tumor survival. For example, Zaider and Minerbo's approach can be extended to more sophisticated cell population models. Of interest would be to substitute exponential growth dynamics with Gompertzian or logistic growth, for example, and investigate how different growth laws affect the TCP. In the next section, we

set up a population model that incorporates the cell cycle, and outline the procedure to obtain a TCP formula.

Methods and model setup

Procedure to obtain the TCP from a cell population model

We briefly outline the mathematical steps that are needed to derive a TCP formula from a cell population model (steps 1–5) and then to compute the TCP formula for a given treatment schedule and cancer type (steps 6–8):

Step 1: Begin with a deterministic cell population model, with appropriate proliferation dynamics and a suitable hazard function.

Step 2: Set up the corresponding stochastic birth-death process for $p_i(t)$, the probability that i clonogens are alive at time t , and derive the master equation for $p_i(t)$, for $i=0,1,\dots,\infty$.

Step 3: Verify that the expected values satisfy the population model (mean field equations) from step 1.

Step 4: Solve for the $p_i(t)$:

- (a) Introduce a generating function, and construct the hyperbolic partial differential equation for the generating function.
- (b) Use the method of characteristics to solve the hyperbolic equation for the generating function.

Step 5: Extract the TCP from the generating function, namely $TCP(t)=p_0(t)$.

Step 6: Identify the radiosensitivity parameters for the given tumor, and set up the dose rate function $D(t)$ in the hazard function $h(t)$ for the given fractionation schedule.

Step 7: Solve the deterministic population model (mean field equations) from step 1 (numerically, if necessary).

Step 8: Substitute the solution from the previous step into the TCP formula.

The computation of the TCP via steps 6–8 deserves some special attention. In the context of the cell population model discussed in the previous section, the

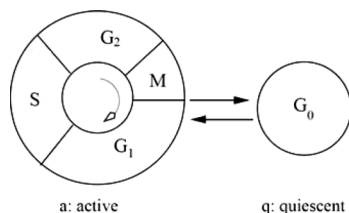


Figure 1. A schematic of cell cycle dynamics. Cells in the G_1 , S , G_2 , and M phases are grouped in one compartment, and labelled active. Cells in the G_0 phase are grouped in a second compartment, and labelled quiescent.

formula for the TCP only depends on the hazard function $h(t)$ in Equation 10 and on the solution of the mean field equation for $n(t)$ in Equation 11. This is a surprising result, since the birth-death process describes the time evolution of probabilities of a stochastic process. However, if we are only interested in the TCP, then it is sufficient to know the mean field, i.e., the *expectation* of P_i . That is, a deterministic model suffices to compute the TCP. This observation can be generalized for more complex models.

Cell population model with cell cycle effects

Dawson and Hillen [24] extended the model of Zaider and Minerbo to include cell cycle dynamics. The basic idea is that a typical tumor consists of cells which are actively proliferating (cells in the G_1 , S , G_2 , or M phase) and cells which are quiescent (cells in the G_0 -phase). Since actively proliferating cells are more sensitive to radiation than quiescent cells, one must keep track of the two subpopulations to make predictions about the total cell population (Figure 1).

In [24], it was assumed that all newly generated daughter cells directly enter the quiescent compartment. Here, we loosen this assumption and allow newly generated cells to become either active or quiescent. With this formulation, we can show that the Zaider and Minerbo model discussed above and the Dawson-Hillen model are special cases of the more general model introduced here.

Let $a(t)$ denote the population of active cells and $q(t)$ the population of quiescent cells. The compartmental population model is

$$\frac{d}{dt}a = 2\mu fa - \mu a + \gamma q - \Gamma_a(t)a, \quad (14)$$

$$\frac{d}{dt}q = 2\mu(1-f)a - \gamma q - \Gamma_q(t)q, \quad (15)$$

where the parameter $\mu > 0$ denotes a constant per-capita birth rate. Note that the population of active cells divide at a rate of μa , giving rise to $2\mu a$ daughter cells, a fraction $0 \leq f \leq 1$ of which remains in the active compartment (the first term in Equation 14), and the rest of which moves into the quiescent compartment (the first term in Equation 15). With birth, there is the loss of the mother cells, represented by the term $-\mu a$ in Equation 14. The parameter $\gamma > 0$ denotes the rate at which quiescent cells become active. This model does not include natural death of cells, since the treatment time is assumed to be short compared to the natural life expectancy of the cells. In addition, $\Gamma_a(t)$ and $\Gamma_q(t)$ are the hazard functions due to radiation treatment for active and quiescent cells, respectively, given by

$$\Gamma_a(t) = a_a \dot{D}(t) + 2\beta_a \dot{D}(t)(D(t) - D(t - \omega)), \quad (16)$$

$$\Gamma_q(t) = a_q \dot{D}(t) + 2\beta_q \dot{D}(t)(D(t) - D(t - \omega)), \quad (17)$$

as proposed by Dawson and Hillen in [24]. The parameters a_a, a_q, β_a and β_q are the radiosensitivities for active and quiescent cells, respectively. The parameter ω represents the time interval over which single-hit events can interact to result in cell fatality, and its value is the mean repair time of a single-hit event. In the limit as $\omega \rightarrow \infty$, the hazard functions have the same form as Equation 10. See [24] for more information on the physical motivation for these hazard functions.

In the Results section, we carry out the procedure described above to obtain a TCP formula for this model.

Case study: Treatment of prostate cancer

To illustrate the use of these TCP models, we consider the treatment of prostate cancer. We compute the time-dependent TCP for two extremal cases, namely the Zaider and Minerbo model ($f=1$) and the Dawson and Hillen model ($f=0$). We use parameter values from the literature as outlined in Table I.

We compute the TCP for three typical radiation treatment schedules (denoted B, C, E) and their corresponding hyperfractionation schemes (denoted b, c, e, respectively). Here, hyperfractionation refers to the corresponding treatment schedule that gives half the radiation twice per day. For all schedules, we consider five treatment days per week (Monday through Friday; weekends off). The schedules are summarized in the first four rows of Table II (the notation of these schedules is based on an earlier work [25]).

Results

Derivation of the TCP for the population model with cell cycle effects

We follow steps 1–5 as outlined in the Methods section. The detailed derivation is available as online supplemental material. We find that the TCP is given by the following expression:

$$\begin{aligned} TCP = & \left(1 - \frac{1}{\Lambda_a(t) + \mu f \int_0^t \Lambda_a(z) dz} \right)^{a_0} \left(1 - \frac{1}{\Lambda_q(t)} \right)^{q_0} \\ & \exp \left\{ -\gamma \int_0^t q(z) \frac{\Lambda_a(z)}{\Lambda_a(t) + \mu f \int_z^t \Lambda_a(y) dy} dz + (1-f) \right. \\ & \left. \left[\mu \int_0^t a(z) \frac{\Lambda_q(z)^2}{\Lambda_q(t)^2} dz - 2\mu \int_0^t a(z) \frac{\Lambda_q(z)}{\Lambda_q(t)} dz \right] \right\}, \quad (18) \end{aligned}$$

Table I. Parameter values and references.

TCP_{ZM}	TCP_{DH}	Value Used	Unit	Reference
$n(0)$	$a(0)+q(0)$	10^6	cells	Villasana and Radunskaia [26]
b	μ	0.0655	1/day	Swanson <i>et al</i> [27]
	γ	0.0476	1/day	Basse <i>et al</i> [28]
a	a_a	0.145	Gy ⁻¹	Carlson <i>et al</i> [29]
	a_q	0.159	Gy ⁻¹	Carlson <i>et al</i> [29]
2 β	2 β_a	0.070646	Gy ⁻²	Carlson <i>et al</i> [29]
	2 β_q	0		Assumption
$\omega=\infty$	ω	57.04	10 min	Carlson <i>et al</i> [29]

where

$$\Lambda_a(t) = e^{-\int_0^t \mu f - (\mu(1-f) + \Gamma_a(z)) dz} \quad \text{and} \quad \Lambda_q(t) = e^{-\int_0^t (\gamma + \Gamma_q(z)) dz}. \quad (19)$$

When $f=1$, we recover the TCP formula of Zaider and Minerbo [23], as stated in Equation 11. Similarly, when $f=0$, we recover the TCP formula of Dawson and Hillen [24], namely

$$\begin{aligned} TCP_{DH} = & \left(1 - \frac{1}{\Lambda_a(t)} \right)^{a_0} \left(1 - \frac{1}{\Lambda_q(t)} \right)^{q_0} \\ & \exp \left\{ -\gamma \int_0^t q(z) \frac{\Lambda_q(z)}{\Lambda_q(t)} dz + \right. \\ & \left. \left[\mu \int_0^t a(z) \frac{\Lambda_q(z)^2}{\Lambda_q(t)^2} dz - 2\mu \int_0^t a(z) \frac{\Lambda_q(z)}{\Lambda_q(t)} dz \right] \right\}, \quad (20) \end{aligned}$$

where now

$$\Lambda_a(t) = e^{-\int_0^t (\mu + \Gamma_a(z)) dz} \quad \text{and} \quad \Lambda_q(t) = e^{-\int_0^t (\gamma + \Gamma_q(z)) dz}. \quad (21)$$

Case study: TCP calculations for the treatment of prostate cancer

To illustrate the use of the TCP formula summarized in Equations 18 and 19, we follow steps 6–8 as outlined in the Methods section to compute the TCP as functions of time and cumulative dose for

Table II. Computed TCP values for six treatment schedules. TCP_{ZM} is computed with Equation 12, and TCP_{DH} with Equations 20 and 21. Values for the model parameters are as listed in Table I.

Protocol	B	b	C	c	E	e
dose/fraction (Gy)	2	1	3	1.5	4	2
times/day	once	twice	once	twice	once	twice
treatment length (days)	50	50	32	32	24	24
total dose (Gy)	72	72	72	72	72	72

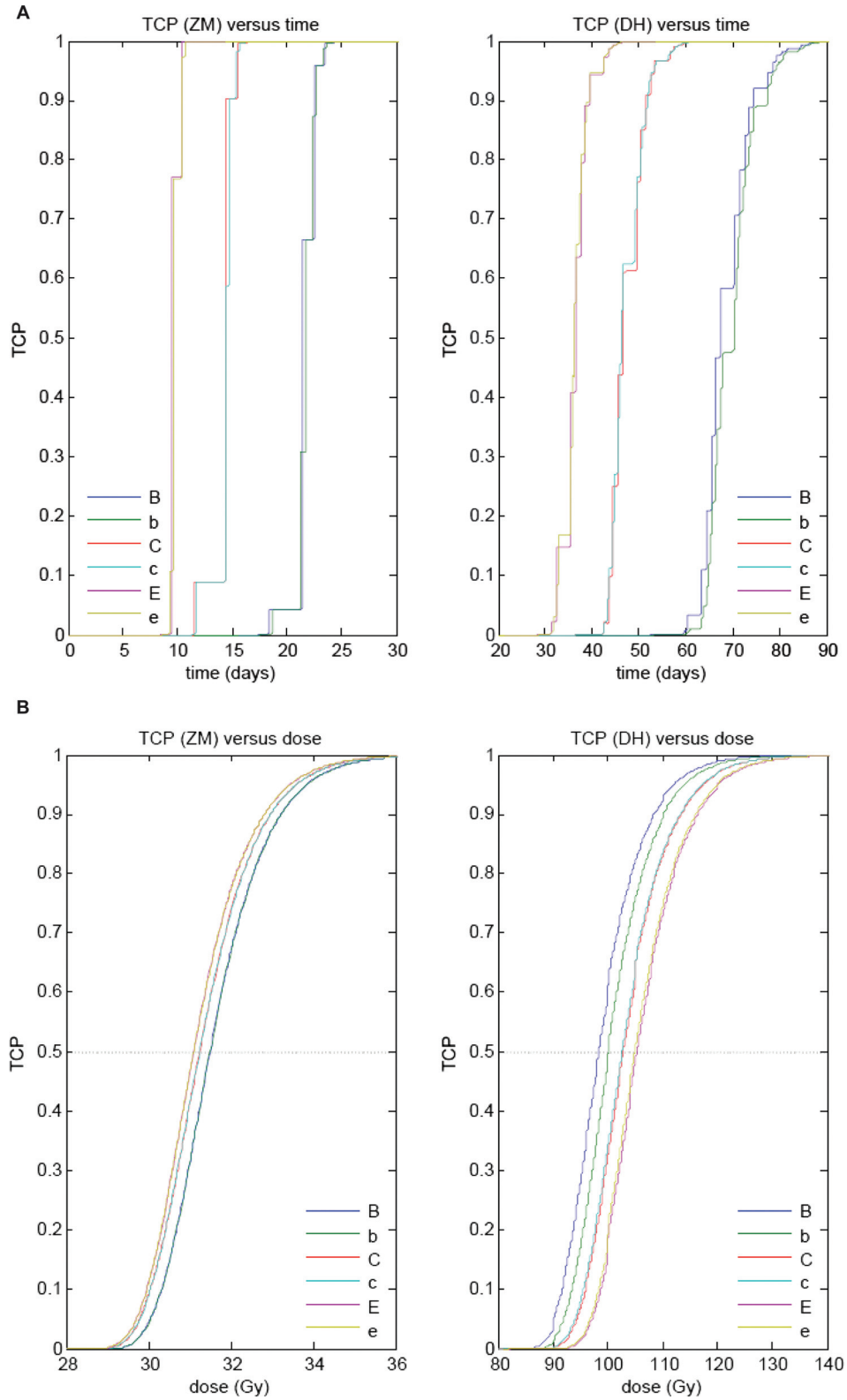


Figure 2. TCP calculations for the Zaider-Minerbo model (Equation 12) and the Dawson-Hillen model (Equations 20 and 21), using the parameter values specified in Table I, for each of the six treatment schedules specified in Table II. The top row shows TCP_{ZM} (left) and TCP_{DH} (right) as functions of time. Note the different time scales. In both figures, the curves (ordered from left to right) correspond to treatment schedules E, e, C, c, B, and b, respectively. The bottom row shows the TCP_{ZM} (left) and TCP_{DH} (right) as functions of dose. Note the different dose scales. For TCP_{ZM} the curves (ordered from left to right) correspond to treatment schedules E=e, C=c, and B=b, respectively. For TCP_{DH} the ordering corresponds to treatment schedules B, b, c, C, e, and E, respectively.

the two extremal cases $f=1$, which recovers the TCP formula of Zaider and Minerbo (TCP_{ZM} in Equation 12), and $f=0$, which recovers the TCP formula for the Dawson-Hillen model (TCP_{ZM} in Equations 20 and 21). We use parameters relevant to prostate cancer (Table I), and compute TCP_{ZM} and TCP_{DH} for the six different treatment schedules specified in Table II. Calculations are continued well beyond the end of the treatment, until each TCP is approximately one (treatment success). To solve the underlying population equation, we use an adaptive time step method, where the time steps range between 0.01 seconds during treatment and 30 minutes on weekends.

The results of the computations are shown in Figure 2. The first row shows the TCP as function of time and the second row the TCP as function of cumulative dose. The curves are sigmoidal, as is typical for TCP curves. The staircase structure in the time-dependent TCP curves shown in the first row of Figure 2 reflects the treatment schedule, with each nearly vertical segment representing a radiation event, and each nearly horizontal segment representing time off between radiation events (the longer horizontal segments represent the weekends). As expected, curves corresponding to the hyperfractionated schedules have a finer staircase structure since radiation is given twice per day.

We observe that the TCP_{ZM} curves exhibit a very steep transition from treatment failure ($TCP=0$) to treatment success ($TCP=1$); they resemble jump functions. This is related to the relatively large number of initial cancer cells of 10^6 . Also, hyperfractionated and standard treatment schedules are indistinguishable. In contrast, the TCP_{DH} curves are less steep and are shifted to the right relative to the TCP_{ZM} curves. This is due to the fact that, with our choice of parameters, the actively proliferating cells in the Dawson-Hillen model are as sensitive to radiation as all the cells in the Zaider-Minerbo model, while the quiescent cells are less sensitive. Essentially, the quiescent cells are sequestered during the initial treatment bursts. To kill those cells as well, more radiation effort is needed. As before, the hyperfractionated and standard treatment schedules are indistinguishable.

If we compute the TCP at the end of treatment (50 days for schedules B and b, 32 days for C and c, and 24 days for E and e), then the TCP_{ZM} equals 1 and the TCP_{DH} equals 0 for all six treatment schedules. Thus, the inclusion of a quiescent compartment can have a drastic effect on the estimate of treatment success. This can also be seen in the second row of Figure 2, where the TCP is shown as function of cumulative dose D . These curves can be used to determine the D_{50} and corresponding γ_{50} values, defined as

$$TCP(D_{50}) = \frac{1}{2}, \quad \gamma_{50} = \left(D \frac{dTCP}{dD} \right) \Big|_{D_{50}}. \quad (22)$$

The D_{50} value represents the cumulative dose at which the TCP is exactly half. The γ_{50} -value is a measure of the sensitivity of the TCP value if dose D is varied close to D_{50} . The D_{50} values are obtained from the intersection of the dashed line $TCP=1/2$ and the TCP curves. For TCP_{ZM} , the D_{50} values are around 31 Gy; for TCP_{DHP} they are around 100 Gy. We emphasize that the parameters were chosen to make *qualitative* rather than *quantitative* observations about the effect of the cell cycle.

Discussion

In this paper, we have presented a hierarchy of TCP formulas, with increasing complexity. We have shown that TCP formulas can be built from detailed cell population models. In particular, we have presented a new cell cycle model, and derived a TCP formula that bridges the gap between the TCP formula of Zaider and Minerbo and the TCP formula of Dawson and Hillen.

The cell cycle effect can be understood as the sequestration of cells in the quiescent compartment, where they are less sensitive to radiation. Therefore, *more* radiation is needed to eradicate the tumor when the cell cycle effect is significant, that is, when cells spend a significant amount of time in the quiescent compartment. Interestingly, we have found with both models, the difference between TCP curves obtained with standard and hyperfractionated schedules is minimal. However, we have not taken early or late responses of healthy tissue into account. It is commonly accepted that a hyperfractionated treatment schedule reduces late side effects, and therefore is beneficial for the patient.

We emphasize again that our results and conclusions are qualitative. The TCP formulas can be used to compare treatment schedules. We find that when no cell cycle is taken into account, the D_{50} values for the six treatments investigated here are relatively close. When the cell cycle is included, as in TCP_{DHP} the D_{50} values cover a range of [90,105]. That is, the precise schedule of the treatment appears to matter less when cell cycle effects are not taken into account. For more quantitative results, careful parameterization of the model is needed, for example as was done by Stravrev and Stravreva for the Poissonian TCP and the Zaider-Minerbo TCP [22,30–32]. We expect that quantitative results will depend on the time scales at which mitosis and activation occur, relative to the time scale on which radiation treatments are applied.

The TCP model based on the cell cycle has the advantage that it can be coupled to synchronization methods. It is known that certain chemotherapy

agents are able to synchronize the cell cycle phases of tumor cells (see [33] and references therein). If all cells are known to be in the same phase, then treatment can be optimized when the cells are radiated during the phase of the cell cycle in which they are most sensitive to the effects of radiation.

Note that we employ a very simple model for the cell cycle. More sophisticated cell cycle models exist in the literature. Such models include a continuous “age” variable for the cell, as well as important biochemical control pathways and checkpoints [33–35]. Recently, Maler and Lutscher [36] designed a stochastic branching process which includes realistic cell-cycle time distributions. For large tumors (10^6 cells and up), their TCP formula yields predictions that are the same as the predictions from the Dawson-Hillen model. For smaller tumors, their prediction is more optimistic. An inclusion of all details in any one TCP model would be unfeasible.

We note that steps 1–5 to derive a TCP formula from a cell population model, as outlined in the Methods section, only apply to models with linear birth and death rates, as we did in this paper. Other approaches, currently under investigation, are needed when non-linear birth and death rates are used, for example when cell proliferation is assumed to be logistic or governed by Gompertz’ growth instead of exponential. TCP formulas from cell survival models when cell proliferation is modelled with the use of non-linear growth rates have been investigated by Usher [37] and McAneny and O’Rourke [38].

In this paper, we have ignored an investigation of the expected complications of the normal tissue surrounding tumors. While this has been done for simple TCP models, for example by Usher [37], an optimization of more sophisticated TCP models with the Normal Tissue Complication Probability constraint [31] is currently under investigation [39].

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Supplemental material

This material accompanies “From cell population models to tumour control probability: Including cell cycle effects” by T. Hillen, G. de Vries, J. Gong, and C. Finlay.

Here, we present the detailed derivation of the TCP formula shown in Equations 18 and 19.

We begin with the following population model with cell cycle effects in Equations 14 and 15:

$$\frac{d}{dt}a = 2\mu fa - \mu a + \gamma q - \Gamma_a(t)a, \quad (14)$$

$$\frac{d}{dt}q = 2\mu(1-f)a - \gamma q - \Gamma_q(t)q, \quad (15)$$

where $a(t)$ denotes the population of active cells and $q(t)$ the population of quiescent cells. The parameter $\mu > 0$ denotes a constant per-capita birth rate, $0 \leq f \leq 1$ is the fraction of newly born daughters remaining in the active compartment, $\gamma > 0$ denotes the rate at which quiescent cells become active, and $\Gamma_a(t)$ and $\Gamma_q(t)$ are the hazard functions due to radiation treatment for active and quiescent cells (shown in Equations 16–17), respectively.

We follow steps 1–5 as outlined in the Methods section to derive the TCP formula.

Step 1: To be able to formulate a birth-death process which corresponds to Equation 14–15, we need to re-arrange the first two terms in Equation 14, and rewrite Equation 14–15 as follows:

$$\frac{d}{dt}a = \mu fa - \mu(1-f)a + \gamma q - \dot{i}_a(t)a, \quad (A.1)$$

$$\frac{d}{dt}q = 2\mu(1-f)a - \gamma q - \Gamma_q(t)q. \quad (A.2)$$

The proliferation terms in Equations 14–15 can be understood as a loss term $-\mu a$ in Equation 14 for mother cells which undergo mitosis and two gain terms $+2\mu fa$ in Equation 14 and $+2\mu(1-f)a$ in Equation 15 of new daughter cells which choose active or quiescent compartment, respectively. The birth terms in (the equivalent) system Equations A.1–A.2 allow a different interpretation: Here a mother cell is only discarded from the active compartment, if it switches to the quiescent state, expressed through $-\mu(1-f)a$ in Equation A.1 and one component of $+\mu(1-f)a$ in Equation A.2. The additional daughter cell has the choice between active and quiescent compartment, which is modelled through $+\mu fa$ in Equation A.1 and $+\mu(1-f)a$ in Equation A.2.

Step 2: Let $P_i(t)$ and $Q_j(t)$ denote the probabilities that i active cancer cells and j quiescent cells are present at time t . For convenience, we assume that

$P_i(t) = 0, Q_j(t) = 0$, for $i, j < 0$. We assume that initially we have active a_0 cells and q_0 quiescent cells such that

$$P_{a_0}(0) = 1, \quad P_i(0) = 0 \text{ for } i \neq a_0, \quad (A.3)$$

$$Q_{q_0}(0) = 1, \quad Q_j(0) = 0 \text{ for } j \neq q_0. \quad (A.4)$$

The master equations describing the dynamics of these probabilities are

$$\begin{aligned} \frac{dP_i(t)}{dt} = & (\mu(1-f) + \dot{i}_a)(i+1)P_{i+1} + \mu f(i-1)P_{i-1} \\ & + \gamma \sum_{j=0}^{\infty} j Q_j P_{i-1} - (\mu(1-f) + \dot{i}_a) i P_i \\ & - \mu f i P_i - \gamma \sum_{j=0}^{\infty} j Q_j P_i, \end{aligned} \quad (A.5)$$

$$\begin{aligned} \frac{dQ_j(t)}{dt} = & (\gamma + \Gamma_q)(j+1)Q_{j+1} + \mu(1-f) \sum_{i=0}^{\infty} i P_i Q_{j-2} \\ & - (\gamma + \Gamma_q) j Q_j - \mu(1-f) \sum_{i=0}^{\infty} i P_i Q_j. \end{aligned} \quad (A.6)$$

Step 3: We can verify by direct computation that the expected values

$$a(t) = \sum_{i=0}^{\infty} i P_i(t), \quad q(t) = \sum_{j=0}^{\infty} j Q_j(t), \quad (A.7)$$

satisfy Equations A.1 and A.2. Hence Equations A.1–A.2 is the system of mean field equations for the above birth-death process.

Step 4(a): The birth-death process in Equations A.5–A.6 can be solved using the following generating functions:

$$V(s, t) = \sum_{i=0}^{\infty} s^i P_i(t), \quad W(s, t) = \sum_{j=0}^{\infty} s^j Q_j(t). \quad (A.8)$$

Multiplying Equations A.5 by s^i and A.6 by s^j and summing, we obtain the following system of hyperbolic partial differential equations for V and W :

$$\begin{aligned} \frac{\partial V}{\partial t} + \frac{\partial V}{\partial s} (s-1)(\mu(1-f) + \Gamma_a(t) - \mu fs) \\ - V \gamma q(t)(s-1) = 0, \end{aligned} \quad (A.9)$$

$$\begin{aligned} \frac{\partial W}{\partial t} + \frac{\partial W}{\partial s} (\gamma + \Gamma_q(t))(s-1) \\ - W \mu(1-f)a(t)(s^2-1) = 0, \end{aligned} \quad (A.10)$$

with initial conditions

$$V(s, 0) = s^{a_0}, \quad W(s, 0) = s^{q_0}. \quad (A.11)$$

The equations for the generating functions coincide with those of Zaider and Minerbo [23] when $f=1$ and

$$q(t) = \sum_{j=0}^{\infty} jQ_j = 0,$$

and with those of Dawson and Hillen [24] when $f=0$.

Step 4(b): We use the method of characteristics to solve the above system, first for V and then for W . To solve for V , let

$$b = \mu f, \quad \delta = \mu(1-f) + \Gamma_a(t). \quad (\text{A.12})$$

Then Equation A.9 has the characteristic equations

$$\frac{ds}{dt} = (1-s)(bs - \delta) = (1-s)(b - \delta) - b(1-s)^2, \quad s(0) = s_0, \quad (\text{A.13})$$

$$\frac{dV}{dt} = \gamma q(s-1)V, \quad V(s_0, 0) = s_0^{q_0}. \quad (\text{A.14})$$

We introduce $y(t) = \frac{1}{1-s}$ to transform Equation A.13 into a linear equation for $y(t)$:

$$\frac{dy}{dt} = \frac{1}{(1-s)^2} \frac{ds}{dt} = (b - \delta)y(t) - b, \quad y(0) = \frac{1}{1-s_0}. \quad (\text{A.15})$$

The solution is

$$y(t) = \Lambda_a^{-1}(t) \left(y(0) - b \int_0^t \Lambda_a(y) dy \right),$$

where

$$\Lambda_a(t) = e^{-\int_0^t (b - \delta(z)) dz}. \quad (\text{A.16})$$

Therefore,

$$\frac{1}{1-s(t)} = \Lambda_a^{-1}(t) \left(\frac{1}{1-s_0} - b \int_0^t \Lambda_a(y) dy \right), \quad (\text{A.17})$$

such that

$$s_0 = 1 - \frac{1}{\frac{\Lambda_a(t)}{1-s(t)} + b \int_0^t \Lambda_a(y) dy}. \quad (\text{A.18})$$

Equation A.14 is linear in V and can be solved directly

$$V(s(t), t) = s_0^{q_0} \exp \left(\gamma \int_0^t q(z) (s(z) - 1) dz \right). \quad (\text{A.19})$$

Since the right-hand side depends on the full characteristic path $s(z)$, we need to replace $s(z)$ through the end point $s(t)$. To do this, we observe from Equation A.18 that

$$s_0 = 1 - \frac{1}{\frac{\Lambda_a(t)}{1-s(t)} + b \int_0^t \Lambda_a(y) dy} = 1 - \frac{1}{\frac{\Lambda_a(z)}{1-s(z)} + b \int_0^z \Lambda_a(y) dy}. \quad (\text{A.20})$$

Hence

$$s(z) - 1 = - \frac{\Lambda_a(z)}{\frac{\Lambda_a(t)}{1-s(t)} + b \int_z^t \Lambda_a(y) dy}. \quad (\text{A.21})$$

Using this expression in Equation A.19, we get an explicit solution for V , namely

$$V(s, t) = \left(1 - \frac{1}{\frac{\Lambda_a(t)}{1-s} + b \int_0^t \Lambda_a(y) dy} \right)^{q_0} \exp \left(-\gamma \int_0^t q(z) \frac{\Lambda_a(z)}{\frac{\Lambda_a(t)}{1-s} + b \int_z^t \Lambda_a(y) dy} dz \right). \quad (\text{A.22})$$

Again, we confirm that for $f=1$, we have $b=\mu$, $h(t)=\Gamma_a(t)$, $q=0$, and $V(s, t) = A(s, t)$ as is consistent with the results of Zaider and Minerbo [23]. Similarly, for $f=0$, we obtain $b=0$, $\delta = \mu + \Gamma_a$, and the generating function for $P_i(t)$ as found in Dawson and Hillen [24].

We now solve for W . Equation A.10 has the characteristic equations

$$\frac{ds}{dt} = (s-1)(\gamma + \Gamma_q(t)), \quad s(0) = s_0, \quad (\text{A.23})$$

$$\frac{dW}{dt} = \mu(1-f)a(s^2-1)W, \quad W(s_0, 0) = s_0^{q_0}. \quad (\text{A.24})$$

The initial condition can be expressed by as

$$s_0 = 1 + (s-1) e^{-\int_0^t (\gamma + \Gamma_q(z)) dz}. \quad (\text{A.25})$$

If we let

$$\Lambda_q(t) = e^{\int_0^t (\gamma + \Gamma_q(z)) dz}, \quad (\text{A.26})$$

then

$$s_0 = 1 - \frac{1-s(t)}{\Lambda_q(t)}.$$

Therefore $W(s(t), t)$ can be expressed as

$$W(s(t), t) = \left(1 - \frac{1-s(t)}{\Lambda_q(t)}\right)^{q_0} \exp\left\{\int_0^t \mu(1-f)a(y)(s(y)^2 - 1)dy\right\}. \quad (\text{A.27})$$

Here we use the fact that

$$s_0 = 1 - \frac{1-s(t)}{\Lambda_q(t)} = 1 - \frac{1-s(y)}{\Lambda_q(y)},$$

and obtain the relations

$$s(y) - 1 = \frac{(s(t) - 1)\Lambda_q(y)}{\Lambda_q(t)}, \quad (\text{A.28})$$

$$s(y)^2 - 1 = \frac{(s(t) - 1)^2 \Lambda_q^2(y)}{\Lambda_q^2(t)} + 2 \frac{(s(t) - 1)\Lambda_q(y)}{\Lambda_q(t)}. \quad (\text{A.29})$$

Then $W(s, t)$ can be expressed as

$$W(s, t) = \left(1 - \frac{1-s}{\Lambda_q(t)}\right)^{q_0} \exp\left\{\mu(1-f)\int_0^t a(y) \frac{(s-1)^2 \Lambda_q^2(y)}{\Lambda_q^2(t)} dy\right\}$$

$$+ 2\mu(1-f)\int_0^t a(y) \frac{(s-1)\Lambda_q(y)}{\Lambda_q(t)} dy\right\}. \quad (\text{A.30})$$

When $f=0$, this solution is the same as the solution found by Dawson and Hillen [24].

Step 5: Based on the explicit solution formulas for V in Equation A.22 and W in Equation A.30, the TCP is

$$\begin{aligned} TCP &= V(0, t) \cdot W(0, t) \\ &= \left(1 - \frac{1}{\Lambda_a(t) + \mu f \int_0^t \Lambda_a(z) dz}\right)^{q_0} \left(1 - \frac{1}{\Lambda_q(t)}\right)^{q_0} \\ &\quad \exp\left\{-\gamma \int_0^t q(z) \frac{\Lambda_a(z)}{\Lambda_a(t) + \mu f \int_z^t \Lambda_a(y) dy} dz\right. \\ &\quad \left.+ (1-f) \left[\mu \int_0^t a(z) \frac{\Lambda_q(z)^2}{\Lambda_q(t)^2} dz - 2\mu \int_0^t a(z) \frac{\Lambda_q(z)}{\Lambda_q(t)} dz \right]\right\}, \end{aligned} \quad (\text{A.31})$$

where Λ_a is given by Equation A.16 and Λ_q by Equation A.26.