Stochastic model for tumor control probability: effects of repair from sublethal damage

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Abstract

Radiation therapy is one of the most widely used treatments for cancer, the aim being to destroy the tumour mass while sparing healthy tissue. Radiotherapy is usually delivered over a period of weeks in a series of daily fraction. Radiation induces lethal and sublethal damage to cancer cells. Cancer cells can repair from sublethal damage between fractions, affecting the treatment efficacy. The tumor control probability (TCP) is the probability that a given dose and a schedule of ionizing radiation eradicates all the tumor cells in a given tissue. In this project, we introduce a model for tumor response to fractionated radiotherapy which includes the effects of repair from sublethal damage (RSD). The cancerous cell population is divided into two classes (affected and unaffected) according to the amount of damage that they receive from the radiation. Affected cells experience sublethal damage and are assumed to be quiescent and recover at a constant rate, while unaffected cells proliferate unaltered by radiation. The model is formulated as a birth-death process for which we can derive an explicit time dependent expression for the tumor control probability (TCP) and a sufficient condition on the parameters for the treatment to be effective, that is, for the treatment to reduce the number of cancerous cells. We consider as a case study, prostate cancer and found that uncertainty in the radiosensitivity parameters and in the probability of unaffected cells to become affected has a significant effect on the TCP than uncertainty in other model parameters. We compare our TCP predictions to those given by Zaider and Minerbo’s one-class model [1] and found significant differences for three typical treatments of prostate cancer. Finally, we consider a modified version of the one-class model that includes RSD in the survival fraction and show that by varying the probability of unaffected cells to become affected, the two-class model can produce the same results as the modified one-class or can give different TCP predictions.
1 Introduction

According to the World Health Organization, cancer is one of the leading causes of death worldwide, particularly in developing countries. For instance, in 2012, there were approximately 14 million new cases and 8.2 million cancer related deaths [2]. Cancer is a class of diseases characterized by uncontrolled cell growth and tissue invasion. Scientists have developed several treatments to fight this disease, the most common being surgery, chemotherapy and radiotherapy [3].

Radiotherapy (RT) is one of the most widely used treatments for cancer, approximately 50% of all cancer patients receive RT as part of their treatment [4]. This treatment involves the use of high-energy radiation (commonly x-rays) and its aim is to destroy the tumor mass while sparing the adjacent healthy tissue. Radiation damages tumor cells principally by inducing lesions in the DNA [5]. Lesions can be either single strand breaks, or double strand breaks. Double strand breaks are caused by either a single event that targets both DNA strands, or by two independent single strand break events that are sufficiently close in time and space [6]. Double strand breaks cause lethal damage to the cells while single strand breaks can usually be repaired by the cell [7]. In practice, several factors reduce the effectiveness of radiotherapy. These include: reoxygenation, redistribution, repopulation, radioresistance and repair from sublethal damage (RSD) which are known collectively as the 5 Rs of radiobiology [8].

For effective treatment planning, one should take into account: biological and radiosensitive parameters, the probability of tumor eradication and the effects on adjacent normal tissue in order to specify a treatment protocol: the rate of dose delivery, the dose of each fraction, the total dose, the overall time, the geometric target domain and the applicator. However, treatments are usually empirically derived and do not account for any mechanical or biological model. Also, the classic method to compare different treatment protocols is via randomized clinical trials which are costly and impractical for studying all treatment variations [5]. The solution to both pitfalls is radiobiological modeling which has received increasing attention during the last decades.

The objective of radiotherapy treatment planning can be mathematically stated as the establishment of a treatment protocol that maximizes the probability of cancer cell eradication and minimizes the probability of normal tissue complication. This gives rise to two key mathematical tools in treatment planning: tumor control probability (TCP) and normal tissue complication probability (NTCP). These tools are used to compare the expected success of different treatment protocols. In this project we focus in TCP models, we do not intend to discuss NTCP models but refer the reader to [9]. We use the remainder of the introduction to review existing TCP models.

The first and simplest TCP model is based on Poisson statistics. Let $X$ be the random variable of the number of surviving cells after radiation and assume it follows a Poisson distribution with mean $nS(D)$ where $n$ is the number of cells before radiation and $S(D)$ is the survival fraction of the tumor mass. The Poisson TCP is the probability that $X = 0$,

\begin{equation}
TCP_P = Pr(X = 0) = e^{-nS(D)}.
\end{equation}

Similarly, assuming that $X$ follows a binomial distribution with parameters $n$ and $p = S(D)$, the binomial TCP has the form

\begin{equation}
TCP_B = (1 - S(D))^n.
\end{equation}

The limitations of both models are widely recognized [10, 11]. To use one of these expressions for the TCP one needs to assume a model for the survival fraction. The most commonly used model is the linear quadratic model [12] which in its simplest form states that the survival fraction of the tumor mass after a radiation dose $D$ is described by the following expression

\begin{equation}
S(D) = exp(-\alpha D + \beta D^2))
\end{equation}

2
where $\alpha (\text{Gy}^{-1})$ and $\beta (\text{Gy}^{-2})$ are radiosensitive parameters that depend on the particular tissue.

The ratio $\alpha/\beta$ is a common characterization of the radiosensitivity of tissues and it divides most tissues into two classes: early responding tissue ($\alpha/\beta \approx 10$) or late responding tissue ($\alpha/\beta \approx 3$). While several authors have been able to derive expression (2) from a mechanistic model [13, 14, 15], however this model was initially derived empirically based on experimental observations [16].

It is important to notice that equation (2) neglects several factors that affect treatment efficacy and several authors have attempted to incorporate the other Rs into the survival fraction expression. A recent review of this work is included in [17]. Since it is relevant to our model, we include the modified version of the LQ model that includes RSD introduced by Thames in [18].

The surviving fraction of cells after a total dose $D$ with an overall treatment time $T$ is given by

$$S = e^{-(\alpha D + \beta GD^2)}$$  \hspace{1cm} (3)

where $D$ and $G$ are given by

$$D = nd$$

$$G = \frac{2}{n\mu T_f} \left[ 1 - \frac{1}{\mu T_f} (1 - e^{-\mu T_f}) \right]$$  \hspace{1cm} (4)

where $d$ is the dose given each fraction, $\mu$ is the repair rate of tumor cells $\mu = \ln(2)/T_r$. $T_r$ is the characteristic repair half-time derived from clinical data and $T_f$ is the dose-delivering time.

Another approach is to calculate the TCP with cell population models. The procedure that has been used is to first consider a cell population model, with appropriate dynamics and a suitable hazard function that models the death of cell due to radiation. The hazard function $h(t)$ describes the decay of the survival fraction for a total dose $D(t)$ absorbed up to a time $t$ as

$$\frac{dS(D(t))}{dt} = -h(t)S(D(t))$$

If radiation treatment is successful, inevitably one deals with small cell numbers; in such cases, the cell population model should be stochastic. In 2000, Zaider and Minerbo [1] introduced the first TCP model of this kind. They considered a homogeneous population of cells that undergoes a stochastic birth-death process and derived a new expression for the TCP, namely,

$$TCP_{ZM}(t) = \left[ 1 - \frac{S_h(t)e^{(b-d)t}}{1 + bS_h(t)e^{(b-d)t}\int_0^t \frac{dr}{S_h(r)e^{(b-a)r}}} \right]^{n_0}$$  \hspace{1cm} (5)

where $n_0$ is the initial number of cell, $b$ and $d$ are the birth and death rate, respectively, and

$$S_h(t) = e^{-\int_0^t h(r)dr}.$$  \hspace{1cm}

Zaider and Minerbo used the following hazard function

$$h_1(t) = (\alpha + 2\beta D(t)) \frac{dD(t)}{dt}.$$  \hspace{1cm} (6)

An important advantage of this model over previous ones is that it can include any time-dependent dose formula and it takes into account proliferation during the treatment. Previous models did not give accurate descriptions especially when treatment was delivered over a time interval longer that the tumor doubling time, as is the case in, for example, brachytherapy [1].
In 2006, Dawson and Hillen [6] extended Zaider and Minerbo’s model to include cell cycle dynamics. The cell-cycle radiation model, they based their model on is

\[
\frac{da}{dt} = -\mu a + \nu q - (d_a + h_a(t))a \\
\frac{dq}{dt} = 2\mu a - \nu q - (d_q + h_q(t))q
\]  

(7)

where \(a(t)\) and \(q(t)\) represent the active and quiescent cells, \(h_a(t)\), \(h_q(t)\) are their hazard function and \(d_a\) and \(d_q\) are the natural death rates, respectively. The term \(\mu u\) models a linear rate for cellular division for which all new daughter cells are assumed to enter the quiescent compartment. Furthermore, cells in the quiescent compartment are assumed to re-enter the active compartment with rate \(\nu > 0\).

The active-quiescent model is extended as a nonlinear birth-death process in order to derive an explicit expression for the TCP, which is given by

\[
TCP_{DH}(t) = \left(1 - e^{-F(t)}\right)a(0)\left(1 - e^{-G(t)}\right)q(0) \\
\exp\left[ -\nu e^{-F(t)} \int_0^t q(y) e^{F(y)} dy \\
+ \mu e^{-2G(t)} \int_0^t a(y) e^{2G(y)} dy - 2\mu e^{-G(t)} \int_0^t a(y) e^{G(y)} dy \right]
\]  

(8)

where

\[F(t) = \int_0^t (\mu + h_a(z))dz, \quad G(t) = \int_0^t (\nu + h_q(z))dz,\]

and \(a(t), q(t)\) solve the cell cycle model (8).

For this model, they found that a large \(\alpha/\beta\) ratio indicates the existence of a long quiescent phase and also confirmed the classical interpretation of the LQ model [6]. In later work, Hillen et al. [19] generalized this model to allow newly generated cells to become either active or quiescent. In 2011, Gong et al [20] compared the Poisson TCP, the Zaider Minerbo TCP, a Monte Carlo TCP and their corresponding cell cycle (two-compartment) model for realistic treatment scenarios for prostate cancer. There was a difference between the one-compartment and two-compartment TCP models due to reduced radiosensitivity of quiescent cells, however among the two-compartment TCP models, there was no significant difference.

In this project, we develop a TCP model that includes repair from sublethal damage. We perform a theoretical analysis of the model and an analysis on the TCP predictions. In Section 2, I give a brief overview of the results we obtained. In Section 3, I describe the contributions the project brought to the field. Finally in the Appendix, I include the draft of the publication.

2 Results overview

We introduced a new model for tumor control probability that incorporates repair from sublethal damage. We consider fractionated treatments and denote by \(t_i\), the time at which the \(i\)th treatment is delivered where \(t_0 = 0 < t_1 < \ldots < t_N\) and \(t_0\) represents the time the patient goes in.

The model has the following assumptions:

- To account for the different types of damage that ionizing radiation can cause, we decompose the cancer cells into two classes: Unaffected (U) and Affected cells (A).
• We suppose that initially all cells are in the unaffected class and that between times $t = t_0$ and $t = t_1$, the population follows a stochastic birth-death process, with linear birth rate $b_U$ and death rate $d_U$.

• At each treatment time, radiation response is modeled as a series of Bernoulli trials in which each cell survives with probability $SF$. Sublethal damage is also modeled as a series of Bernoulli trials where an unaffected cell switches to the affected class with probability $\gamma$.

• Between times $t_i$ and $t_{i+1}$, for $i > 0$, the model follows a stochastic birth-death process with linear rates for the unaffected class $(b_U, d_U)$ as above. We assume the affected class is quiescent and follows a stochastic death process with linear death rate $(d_A)$ and a constant recovery rate from $A$ to $U$, $\eta$.

To examine the advantages of considering a new model, we took as a benchmark a simpler model, Zaider and Minerbo’s model, which we refer as one-class model, and perform every step in our analysis for this model as for the new model.

First, we perform a theoretical analysis that included: description of the probability distribution evolution between treatment times and at treatment times, derivation of explicit formulas of the mean and variance and the derivation of an explicit formula of the TCP.

Taking as a case study prostate cancer, we did an analysis on the TCP predictions by performing a parameter sensitivity analysis and model comparison. In the sensitivity analysis, we found that there were two parameters which play a key role: the radiosensitive parameters and the probability of unaffected cells to switch to the affected class. The TCP curves resulted in being significantly sensitive to these parameters while slightly sensitive to others. Regarding the model comparison, we perform two: one with previous models (Zaider and Minerbo TCP and Dawson and Hillen). By comparing to the one-class model (ZM TCP), we could see that the TCP two-class model had lower prediction than all the other models. We analyze the effect by considering three treatment protocols and saw that as the dose per fraction increased the reduction on the TCP was greater. However this is not the case for the Dawson and Hillen’s model. We also compare our model to a modified one-class model, this modified model has a survival fraction that takes into account RSD. We observed that if we used the same parameters for both models there was a free parameter in our model $\gamma$. We saw that we could fit this parameter for the two-class model to give the same predictions as the modified one-class model but one could also consider other values of this parameter and have different TCP predictions.

3 Contribution discussion

We introduce a TCP model that included the effects of RSD in the state-of-the-art framework of TCP from stochastic cell population models. There are several things we did that contributed to the field and several roads that we can follow now after the analysis we did for the model.

First, we derive an explicit formula for the TCP of a stochastic two-class model. We did this by considering the joint probability distribution of $X$ and $Y$, where $X$ and $Y$ are the random variables that count the number of cells in each class. In previous papers where they derive TCP formula for two compartment model [6, 19], they assumed that $X$ and $Y$ are independent which simplified significantly the derivation of an explicit formula of the TCP. However, in our model, we did not consider the random variables to be independent and we were still able to give an explicit formula for the TCP. Furthermore, we plot Dawson and Hillen TCP assuming independence and not assuming it and we saw that there is a difference in the TCP predictions.
Second, we were able to give an explicit formula for the probability distribution evolution even at treatment times. Therefore, we have explicit formulas of the mean, variance and covariance at all times that enable us to have confidence intervals in our simulations.

Also, we examined what was the effect of uncertainty in the biological parameters. We could identify two parameters that affected the TPC evolution significantly: the radiosensitive parameters and the probability of unaffected cells switching to the affected class, $\gamma$. In our model we had to assume a value of $\gamma$, knowing now the effect on its variation on the TCP, we can advise radiobiologists to measure this parameter. By looking at the mean dynamics, the parameter $\gamma$ can be interpreted as the mean fraction of cells that present sublethal damage.

Finally, clinical data that enables model validation is crucial to increase the impact of the work done.

Acknowledgments

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References


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In this paper, we introduce a model for tumor response to fractionated radiotherapy which includes the effects of repair from sublethal damage (RSD). The cancerous cell population is divided into two classes (affected and unaffected) according to the amount of damage that they receive from the radiation. Affected cells experience sublethal damage and are assumed to be quiescent and recover at a constant rate while unaffected cells proliferate unaltered by radiation. The model is formulated as a birth-death process for which we can derive an explicit time dependent expression for the tumor control probability (TCP) and a sufficient condition on the parameters for the treatment to be effective, that is, for the treatment to reduce the number of cancerous cells. We consider as a case study prostate cancer, and find that uncertainty in the radiosensitivity parameters and in the probability of unaffected cells to become affected, has a greater effect on the TCP than the uncertainty in the other model parameters. We compare our TCP predictions to those given by Zaider and Minerbo’s one-class model [1] and Dawson and Hillen’s two-class model [2] and find significant differences on TCP predictions for three typical treatments of prostate cancer. Finally, we consider a modified version of the one-class model, that includes RSD in the survival fraction, and show that by varying the probability of unaffected cells to become affected, the two-class model can either produce the same results as the modified one-class model or give different TCP predictions.

Keywords: tumour control probability; radiation treatment of cancer; sublethal damage; mathematical modeling of cancer treatment

1. Introduction

According to the World Health Organization, cancer is one of the leading causes of death worldwide, particularly in developing countries. For instance, in 2012, there were approximately 14 million new cases and 8.2 million cancer related deaths[3]. Cancer is a class of diseases characterized by uncontrolled cell growth and tissue invasion. Scientists have developed several treatments to fight this disease, the most common being surgery, chemotherapy and radiotherapy [4].

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For effective treatment planning, one should take into account: biological and radiosensitive parameters, the probability of tumor eradication and the effects on adjacent normal tissue in order to specify a treatment protocol: the rate of dose delivery, the dose of each fraction, the total dose, the overall time, the geometric target domain and the applicator. However, treatments are usually empirically derived and do not account for any mechanical or biological model. Also, the classic method to compare different treatment protocols is via randomized clinical trials which are costly and impractical for studying all treatment variations [6]. The solution to both pitfalls is radiobiological modeling which has received increasing attention during the last decades. The objectives of modeling in radiation oncology are to reveal the critical processes that underlie the response of tumors and normal tissues to radiation and advise on the choice of treatment parameters.

Outcomes in radiotherapy are usually characterized by tumor control probability (TCP). This is the probability that a given treatment protocol leads to eradication of the tumor. We use the remainder of the introduction to review existing TCP models. In Section 2, we introduce first the one-class model of Zaider and Minerbo which we will use as a benchmark. Then, we introduce the two-class model which incorporates SRD. We describe the procedure of obtaining the TCP from the cell population models and introduce prostate cancer as the case study for our model. In Section 3, we introduce explicit formulas for the TCP for both models, we perform sensitivity analysis on the model parameters and find that radiosensitive parameters and the probability of sublethal damage during radiation, affect the TCP significantly while the variation of the other parameters does not. Then, using three prostate cancer treatment protocols, we compare the one-class predictions to the ones from the two-class model in order to examine the effect of the presence of the two classes and the different discrepancies based on the dose amount. We observe that inclusion of the second class lowers the TCP and the reduction is greater as the dose increases. We also compare the two-class model to a modified one-class model with a survival fraction that takes into account RSD. Lastly, in Section 4, we summarize and discuss our results.

1.1 TCP Models

The first and simplest TCP model is based on Poisson statistics. Let \( X \) be the random variable of the number of surviving cells after radiation and assume it follows a Poisson distribution with mean \( nS(D) \) where \( n \) is the number of cells before radiation and \( S(D) \) is the survival fraction of the tumor mass. The Poisson TCP is the probability that \( X = 0 \),

\[
TCP_p = Pr(X = 0) = e^{-nS(D)}. \tag{1.1}
\]

Similarly, assuming that \( X \) follows a binomial distribution with parameters \( n \) and \( p = S(D) \), the binomial TCP has the form

\[
TCP_b = (1 - S(D))^n. \tag{1.2}
\]

The limitations of both models are widely recognized [9, 10]. To use one of these expressions for the TCP one needs to assume a model for the survival fraction. The most commonly used model is the linear quadratic model [11] which in its simplest form states that the survival fraction of the tumor mass after a radiation dose \( d \) is described by the following expression

\[
S(D) = \exp\left(-\left(\alpha D + \beta D^2\right)\right) \tag{1.2}
\]

where \( \alpha \) (Gy\(^{-1}\)) and \( \beta \) (Gy\(^{-2}\)) are radiosensitive parameters that depend on the particular tissue. The ratio \( \alpha/\beta \) is a common characterization of the radiosensitivity of tissues and it divides most tissues into
two classes: early responding tissue ($\alpha/\beta \approx 10$) or late responding tissue ($\alpha/\beta \approx 3$). While several authors have been able to derive expression (1.2) from a mechanistic model [12, 13, 14], however this model was initially derived empirically based on experimental observations [15].

It is important to notice that equation (1.2) neglects several factors that affect treatment efficacy and several authors have attempted to incorporate the other Rs into the survival fraction expression. A recent review of this work is included in [16]. Since it is relevant to our model, we include the modified version of the LQ model that includes RSD introduced by Thames in [17]. The surviving fraction of cells after a total dose $D$ with an overall treatment time $T$ is given by

$$S = e^{-(\alpha D + \beta GD^2)}$$  \hspace{1cm} (1.3)

where $D$ and $G$ are given by

$$D = nd$$

$$G = \frac{2}{n \mu T_f} \left[ 1 - \frac{1}{\mu T_f} (1 - e^{-\mu T_f}) \right]$$  \hspace{1cm} (1.4)

where $d$ is the dose given each fraction, $\mu$ is the repair rate of tumor cells $\mu = \ln(2)/T_r$. $T_r$ is the characteristic repair half-time derived from clinical data and $T_f$ is the dose-delivering time.

Another approach is to calculate the TCP with cell population models. The procedure that has been used is to first consider a cell population model, with appropriate dynamics and a suitable hazard function that models the death of cell due to radiation. The hazard function $h(t)$ describes the decay of the survival fraction for a total dose $D(t)$ absorbed up to a time $t$ as

$$\frac{dS(D(t))}{dt} = -h(t)S(D(t))$$

If radiation treatment is successful, inevitably one deals with small cell numbers; in such cases, the cell population model should be stochastic. In 2000, Zaider and Minerbo [1] introduced the first TCP model of this kind. They considered a homogeneous population of cells that undergoes a stochastic birth-death process and derived a new expression for the TCP, namely,

$$TCP_{ZM}(t) = \left[ 1 - \frac{S_h(t)e^{(b-d)t}}{1 + bS_h(t)e^{(b-d)t} \int_0^t S_h(r)e^{(b-d)r}dr} \right]^{n_0}$$  \hspace{1cm} (1.5)

where $n_0$ is the initial number of cell, $b$ and $d$ are the birth and death rate, respectively, and

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

Zaider and Minerbo used the following hazard function

$$h_1(t) = (\alpha + 2\beta D(t)) \frac{dD(t)}{dt}.$$  \hspace{1cm} (1.6)

An important advantage of this model over previous ones is that it can include any time-dependent dose formula and it takes into account proliferation during the treatment. Previous models did not give
accurate descriptions especially when treatment was delivered over a time interval longer that the tumor doubling time, as is the case in, for example, brachytherapy [1].

In 2006, Dawson and Hillen [2] extended Zaider and Minerbo’s model to include cell cycle dynamics. The cell-cycle radiation model, they based their model is

\[
\begin{align*}
\frac{da}{dt} &= -\mu a + \nu q - (d_a + h_a(t))a \\
\frac{dq}{dt} &= 2\mu a - \nu q - (d_q + h_q(t))q
\end{align*}
\]

(1.7)

where \(a(t)\) and \(q(t)\) represent the active and quiescent cells, \(h_a(t)\), \(h_q(t)\) are their hazard function and \(d_a\) and \(d_q\) are the natural death rates, respectively. The term \(\mu u\) models a linear rate for cellular division for which all new daughter cells are assumed to enter the quiescent compartment. Furthermore, cells in the quiescent compartment are assumed to re-enter the active compartment with rate \(\nu > 0\).

The active-quiescent model is extended as a nonlinear birth-death process in order to derive an explicit expression for the TCP, which is given by

\[
TCP_{DH}(t) = (1 - e^{-F(t)})a(0)(1 - e^{-G(t)})q(0)
\]

exp

\[
\begin{align*}
&-\nu e^{-F(t)} \int_0^t q(y)e^{F(y)} dy \\
&+\mu e^{-2G(t)} \int_0^t a(y)e^{2G(y)} dy - 2\mu e^{-G(t)} \int_0^t a(y)e^{G(y)} dy
\end{align*}
\]

(1.8)

where

\[
F(t) = \int_0^t (\mu + h_a(z))dz, \quad \text{and} \quad G(t) = \int_0^t (\nu + h_q(z))dz,
\]

and \(a(t), q(t)\) solve the cell cycle model (1.8).

For this model, they found that a large \(\alpha/\beta\) ratio indicates the existence of a long quiescent phase and also confirmed the classical interpretation of the LQ model [2]. In later work, Hillen et al. [18] generalized this model to allow newly generated cells to become either active or quiescent. In 2011, Gong et al [19] compared the Poisson TCP, the Zaider Minerbo TCP, a Monte Carlo TCP and their corresponding cell cycle (two-compartment) model for realistic treatment scenarios for prostate cancer. There was a difference between the one-compartment and two-compartment models due to reduced radiosensitivity of quiescent cells, however among the two-compartment TCP models, there was no significant difference.

2. Methods and model setup

In this paper, we consider fractionated treatments and denote by \(t_i\), the time at which the \(i\)-th treatment is delivered and assume the treatment acts instantaneously. We consider the treatment mesh as \(t_0 = 0 < t_1 < \ldots < t_N\) where \(t_0\) represents the time the patient goes in. To track the effect of the treatment, for a function \(f(t)\) related to our model, \(f(t^-)\) and \(f(t^+)\) denotes the function value before and after \(i\)-th treatment.
We will focus on two models: Zaider and Minerbo’s model for a fractionated dose distribution which will be used as a baseline for comparison with our two-class model.

**One-class model**

Zaider and Minerbo’s model, which we refer to as the one-class model, describes a homogeneous population of tumor cells that between \( t_i \) and \( t_{i+1} \) undergoes a stochastic birth-death process with linear birth and death rates, if \( b \) and \( d \) are the birth and death rates respectively, then we can construct the master equation, a differential equation for the evolution of \( p_n(t) \), the probability of having \( n \) cells at time \( t \). This can be done as a probability balance for all the events that can occur during the time interval \((t, t + \Delta t)\). It is straightforward to show that \( p_n(t) \) solves

\[
\frac{d}{dt} p_n(t) = b(n-1)p_{n-1}(t) + d(n+1)p_{n+1}(t) - (b+d)np_n(t)
\]

where we fix \( p_{-1}(t) = 0 \), \( p_n(0) = 0 \) if \( n \neq N_0 \) and \( p_{N_0}(0) = 1 \) where \( N_0 \) is the initial number of cells.

At each treatment time \( t_i \), the treatment is modeled as a series of Bernoulli trials: each cell survives with probability \( SF \). To calculate the probability of having \( n \) cells after treatment, we consider the probability of having \( n + k \) cells before treatment and \( k \) cells dying for all possible values of \( k \). Therefore, we have a binomial distribution at the treatment time,

\[
p_n(t_i^+) = \sum_{k=0}^{\infty} p_{n+k}(t_i^-) \binom{n+k}{k} (1-SF)^k (SF)^n
\]

where \( SF \) is given by the LQ model, equation (1.2).

This way to model the treatment is equivalent to consider Zaider and Minerbo’s hazard function (1.6) and the following dose distribution

\[
D(t) = \sum_{k=1}^{N} dH(t-t_k)
\]

where \( d \) is the dose delivered in each fraction, and \( H(t) \) is a Heaviside function such that \( H(t) = 1 \) for \( t \geq 0 \) and 0 otherwise. With this choice of dose distribution, the hazard function takes the form

\[
h_{ZM}(t) = \sum_{k=1}^{N} (\alpha d + \beta d^2) \delta(t-t_k)
\]

where \( \delta(t) \) is the Delta function.

**Two-class model**

To account for the different types of damage that ionizing radiation can cause, we now decompose the cancer cells into two classes: Unaffected (U) and Affected cells (A), denote the total number of cells \( T(t) = U(t) + A(t) \) and the treatment mesh \( t_0 < t_1 < \ldots < t_N \). For this model we need to define the evolution of the joint probability distribution \( p_{n_U,n_A}(t) \) which is the probability of having \( n_U \) and \( n_A \) cells.
cells at time $t$.

We suppose that initially all cells are in the unaffected class and that between times $t = t_0$ and $t = t_1$, the population follows a stochastic birth-death process, with linear birth rate $b_U$ and death rate $d_U$. In this case, the model possesses a master equation that is similar to that for the one-class model, equation (2.1):

$$\frac{d}{dt} p_{n_U,n_A}(t) = b_U(n_U - 1)p_{n_U-1,n_A}(t) + d_U(n_U + 1)p_{n_U,n_A}(t) - (b_U + d_U)n_U p_{n_U,n_A}(t)$$  \hspace{1cm} (2.3)

where $p_{-1,n_A}(t) = 0 \forall n_A$, $p_{n_U,n_A}(t) = 1$ only when $n_U = N_0$ and $n_A = 0$ and otherwise, $p_{n_U,n_A}(t) = 0$.

At each treatment time, radiation response is modeled as a series of Bernoulli trials in which each cell survives with probability $SF$. Sublethal damage is also modeled as a series of Bernoulli trials where an unaffected cell switches to the affected class with probability $\gamma$. Considering both processes and taking the same considerations as we did for the one-class model, we derive an expression for $p_{n_U,n_A}(t_1^+)$ in terms of $p_{n_U,n_A}(t_1^-)$,

$$p_{n_U,n_A}(t_1^+) = \sum_{k=0}^{\infty} \sum_{j=0}^{n_A} p_{n_U+n_A-j,k,j+1}(t_1^-) \left( \begin{array}{c} j + l \\ l \end{array} \right) \left( \frac{n_U + n_A - j + k}{n_U} \right) \left( \frac{n_A - j + k}{k} \right)$$

$$\times \left( SF \right)^{n_U} \left[ \gamma (1 - SF) \right]^{n_A - j} \left( 1 - \gamma (1 - SF) \right)^k (SF)^j (1 - SF)^l.$$

Between times $t_i$ and $t_{i+1}$, for $i > 0$, the model follows a stochastic birth-death process with linear rates for the unaffected class $(b_U, d_U)$ as above. We assume the affected class is quiescent and follows a stochastic death process with linear death rate $(d_A)$ and a constant recovery rate from $A$ to $U$, $\eta$. The master equation that encodes this process is the following:

$$\frac{d}{dt} p_{n_U,n_A}(t) = -[(b_U + d_U)n_U + (d_A + \eta)n_A]p_{n_U,n_A}(t) + \eta(n_A + 1)p_{n_U - 1,n_A + 1}(t)$$
$$+ b_U(n_U - 1)p_{n_U - 1,n_A}(t) + d_U(n_U + 1)p_{n_U,n_A + 1}(t) + d_A(n_A + 1)p_{n_U,n_A + 1}(t)$$  \hspace{1cm} (2.4)

where $p_{-1,n_A}(t) = p_{n_U,-1}(t) = 0$ for $n_U, n_A > 0$.

**Procedure to obtain TCP and condition to control from a cell population model**

Guided by [18], we now outline the procedure that we use to derive a TCP formula from a cell population model. We include additional steps to derive a sufficient condition for the treatment to be effective (i.e. to reduce the number of cancer cells).

**Step 1:** Consider the probability generating function (PGF) $(G(t,x) = \sum_{n=0}^{\infty} p_n(t)x^n$ in the one-class model, $G(t,x,y) = \sum_{n=0}^{\infty} \sum_{n_A=0}^{\infty} p_{n_U,n_A}(t)x^{n_U}y^{n_A}$ in the two-class model) and construct the associated partial differential equation for the master equation.

**Step 2:** Use the method of characteristics to solve the hyperbolic equation for the PGF.

**Step 3:** Extract the TCP from the PGF ($TCP(t) = p_0(t)$ for the one-class model, $TCP(t) = G(t,0,0)$ for the two-class model).

**Step 4:** Consider the mean field dynamics to obtain a sufficient condition for the treatment to reduce the number of tumor cells (condition for $\langle n(t_1^+) \rangle < \langle n(t_1^-) \rangle$ for the one-class $\langle T(t_1^+) \rangle < \langle T(t_1^-) \rangle$ for the two-class).
2.1 Case Study: Treatment of Prostate Cancer

To develop the parameter sensitivity analysis and compare the models, we consider as a case study prostate cancer. Prostate cancer is a late responding, slow growing tumor. There is a considerable uncertainty in its doubling time, i.e. the time taken for a population of prostate cancer cells to double in number. For example, Wang et al. [20] report doubling times in the range 15-170 days with a median value of 42 days which corresponds to a net growth rate of $0.0165 = \ln(2)/42 (1/\text{day})$. Based on this work and other reviews [21], we estimated the range to be 10-100 days. Following [20], assume that the LQ parameters are within the following ranges

$$\alpha = 0.14 \pm 0.05 \text{ Gy}^{-1}, \quad \alpha/\beta = 3.1^{+2.6}_{-1.6} \text{ Gy.}$$

The recovery rate for prostate cancer cells has been estimated to be 1-2h, although some authors report values as fast as 16 minutes [20]. Estimates of the apoptotic rates for prostatic carcinoma are presented in [22]. However, we will see that the uncertainty in the apoptotic rates with a fixed net growth rate will not turn to be significant for our model predictions.

Unless otherwise stated, we used the parameter values stated in Table 1. For the one-class model, $b = 2d$. For the two-class model, $d_E = 0.0666$, $d_U = 0.03$ and $\theta_U = 0.1129$ which assures a net growth of 0.0165. We use the standard treatment schedule, five days per week and 52 days of treatment. For plotting the TCP curves we defined a mesh in the interval $[0, 52]$ with time step 0.2.

<table>
<thead>
<tr>
<th>Initial cell number</th>
<th>One class model</th>
<th>Two class model</th>
<th>Unit</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N(0) = 10^5$</td>
<td>$U(0) = 10^5$, $E(0) = 0$</td>
<td>$b - d = 0.0165$, $b_U - d_U - d_A = 0.0165$</td>
<td>cells</td>
<td>[20]</td>
</tr>
<tr>
<td>$b - d = 0.0165$</td>
<td>$\eta = 62.382$, $\gamma = .15$</td>
<td>$\alpha = 0.14$, $\beta = 0.0452$, $\beta = 0.0452$</td>
<td>1/day</td>
<td>[19]</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>$\alpha = 0.14$</td>
<td>$\beta = 0.0452$</td>
<td>Assumption</td>
<td>[19] [20]</td>
</tr>
<tr>
<td>$\beta$</td>
<td>$\beta = 0.0452$</td>
<td>$\beta = 0.0452$</td>
<td>$Gy^{-1}$</td>
<td>[20], [19]</td>
</tr>
<tr>
<td></td>
<td>$\beta = 0.0452$</td>
<td>$\beta = 0.0452$</td>
<td>$Gy^{-2}$</td>
<td>[20], [19]</td>
</tr>
<tr>
<td></td>
<td>$\beta = 0.0452$</td>
<td>$\beta = 0.0452$</td>
<td>Assumption</td>
<td>[19]</td>
</tr>
</tbody>
</table>

Table 1. Parameter values for sensitivity analysis and references.

3. Results

**Derivation of the TCP for the population models**

For the one-class model, we follow the approach outlined in the previous section to obtain the following expression for the TCP:

$$TCP(t) = \begin{cases} 
G_0(t, 0) & t \in [0, t_1^-] \\
G_1(t, 0) = G_0(t_1, f_1(t, 0)) & t \in [t_1^+, t_2^-] \\
G_0(t_1, f_1(t_2, f_2(t_2, \ldots f_{i-1}(t_i, (f_i(t, 0)))))) & t \in [t_i^+, t_{i+1}^-] \text{ and } i > 1
\end{cases}$$

(3.1)
where
\[
f_i(t, x) = SF \left[ \frac{(x-1)de^{(b-d)(t-t_i)} - bx + d}{(x-1)be^{(b-d)(t-t_i)} - bx + d} \right] + 1 - SF,
\]
and
\[
G_0(t, x) = \left[ \frac{(x-1)de^{(b-d)t} - bx + d}{(x-1)be^{(b-d)t} - bx + d} \right]^{N_0}.
\]

It is important to notice that the expression (3.1) is calculated for every \( t > 0 \), even at treatment times.

It is also possible to derive the following sufficient condition for the treatment to make a reduction in the mean field dynamics:
\[
SF e^{(b-d)\Delta} < 1,
\]
where \( \Delta \) is the time between treatments.

Detailed derivations of the TCP formula and condition (3.2) are presented in the Appendix A.1.

Carrying out the same procedure for the two-class model yields the following expression for the TCP:
\[
TCP(t) = \begin{cases}
G_0(t, 0, 0) & t \in [0, t^-_1) \\
G_1(t, 0, 0) = G_0(t_1, f_1(t, 0, 0)) & t \in [t^-_1, t^+_1] \\
G_0(t_1, f_1(t_2, f_2(t_0, 0), g_2(t, 0, 0))) & t \in [t^+_1, t^+_2] \\
G_0(t_1, f_1(t_2, f_2(t_3, f_3(t, 0, 0), g_3(t, 0, 0)), g_2(t, 0, 0), g_3(t, 0, 0))) & t \in [t^+_2, t^+_3] \\
\vdots & t \in [t^+_i, t^+_i] \text{ and } i > 1
\end{cases}
\]

where
\[
G_0(t, x, y) = \left[ \frac{(x-1)de^{(b-U-d_U)t} - bx + d_U}{(x-1)be^{(b-U-d_U)t} - bx + d_U} \right]^{N_0},
\]
\[
f_i(t, x, y) = SFX(t - t_i, x) + \gamma(1 - SF)Y(t - t_i, x, y) + 1 - \gamma(1 - SF) - SF,
\]
\[
g_i(t, x, y) = SFY(t - t_i, x, y) + 1 - SF,
\]
in which
\[
X(t, x) = \frac{d_U(1-x)e^{(b_U-d_U)t} + b_Ux + d_U}{b_U(1-x)e^{(b_U-d_U)t} + b_Ux + d_U}
\]
and
\[
Y(t, x, y) = ye^{(d_A+\eta)(t_i-x)} + \frac{d_A}{d_A+\eta} \left[ 1 - e^{-(d_A+\eta)t} \right] + \eta \int_0^t e^{-(d_A+\eta)t'} X(t') dt'.
\]

We can also derive a sufficient condition for the treatment to reduce the number of cancer cells
\[
\left\| \begin{pmatrix}
SF & 0 \\
\gamma(1-SF) & SF
\end{pmatrix} B \right\|_1 < 1
\]
where
\[
B = \begin{pmatrix}
e^{(b_U-d_U)\Delta} & -\frac{\eta\left[ e^{-(d_A+\eta)\Delta} - e^{-(b_U-d_U)\Delta} \right]}{SF} \\
\gamma(1-SF) & SF
\end{pmatrix}.
\]
and $\| - \|_1$ denotes the matrix norm 1 which is the sum of the absolute values of the entries.

Derivations are found in Appendix A.2.

Sensitivity analysis

The model parameters are either related to biological characteristics of the cancer (birth, death and recovery rates, radiosensitive parameters and probability to acquire sublethal damage) or to the treatment protocol parameters (dose per fraction, number of fraction and total dose). Realistic biological parameters are obtained from clinical or experimental data where no unique value is given but rather a confidence interval of the parameters is provided. We analyze what are the effects of varying the biological parameters of prostate cancer in reported confidence intervals from biological studies described in Section 2.1.

First, we vary the $\alpha$ and $\beta$ values in the intervals described in Section 2.1. Using the LQ formula equation (1.2), we have that the value of the survival fraction can be between 0.4 and 0.7. We consider a mesh in the interval $[0.4, 0.7]$ with a step of 0.05 and for each of these values, we plot the TCP curve. The TCP curves vary significantly as can be seen in Figure 1A). As the SF value increases, the TCP curve takes more time to reach 1. Another way to visualize the response of changing the SF value is by considering the time it takes for the TCP curve to be above certain threshold. In Figure 1B) we plot the time it takes for the TCP to be above 0.9 for SF values in the mesh of $[0.4, 0.7]$. We observe there is a linearly increase in the time it takes to reach this threshold going from 23 to 47 days.

![Fig. 1. Sensitivity analysis for survival fraction. A) Plot of TCP curves while varying SF between 0.4 and 0.7. B) Plot of survival fraction values and the time it takes for the TCP to be above 0.9.](image)

We follow the same procedure, now varying the doubling times between 10 to 100 and considering a fixed ratio of the birth and death rate. In this case, the TCP curves do not vary significantly as seen in Figure 2A). Also, by plotting the time it takes for the TCP to be above 0.9 for these doubling times, we observe that for almost all the possible doubling times values, after 43 days the TCP is above 0.9.

To understand the sensitivity in $\gamma$, we notice that when $\gamma = 0$ we recover the one-class model since the probability to change to the affected class is 0 and therefore all cells stay in the unaffected compartment. As we increase $\gamma$, there is more chance that unaffected cells go into the second class. We vary $\gamma$
from 0 to 0.25 with an increase of 0.05. We go up to 0.25 because for the particular protocol that we are considering, for \( \gamma \) values bigger than 0.25, the TCP is the same.

We observe that increasing \( \gamma \) value, makes the TCP have a slower growth as shown in Figure 3 A) On the other hand, we notice that by vaying \( \eta \) in the range of realistic parameters, the TCP does not change ( Figure 3B )

Fixing the net growth rate to 0.0165, we varied the proliferation rate and therefore the apoptotic rate to analyze if the specific values of the birth and death rates are important if only the net growth rate is relevant. We varied the proliferation rate from 0.02 to 0.37 with a step of 0.05. We find that the TCP does not change significantly and that the uncertainty in the specific values of rates is negligible as shown in Figure 4.

**Figure 2.** Sensitivity analysis for doubling times. A) Plot of TCP curves for doubling times from 10 to 100. B) Plot of doubling times and the time it takes for the TCP to be above 0.9.

**Figure 3.** A) Plot of TCP curves for varying \( \eta \) values. (B) Plot of TCP for different \( \gamma \) values One can notice how the TCP is more sensitive to \( \gamma \) values.
Comparison of models

We make two comparisons for our two-class model. First, we contrast the prediction of Zaider and Minerbo's TCP (equation (1.5)), Dawson and Hillen TCP (equation (1.9)) and the two-class TCP (equation (3.3)) using the parameters [2] that are in Table 3. We calculate the TCP for three treatment protocols that are described in Table 2. Protocol A is the standard treatment protocol in the clinic, while Protocol B and Protocol C are new introduced treatment protocols [21]. We can observe that for all the protocols, the two-class TCP is lower than the others while for Protocol B and C, DH TCP is lower than the ZM TCP model and higher for Protocol A, as shown in Figure 5. The difference between the TCP prediction is smaller as the dose per fraction increases.

The second comparison we make is against a modified one-class model where we consider the one-class model formulation with a modified survival fraction that takes into account RSD. We want to analyze if it is necessary to add a class with sublethal damage or if it is enough to consider a modified survival fraction that takes into account RSD. We take into account the one-class model with the survival fraction given by Thames and explained in the introduction section, $S_{FrSD}$ (equation 1.3). We refer to this model as the modified one-class model. If we consider the same parameters for both models, we notice that $\gamma$ is a free parameter for the two-class model. Furthermore, given a protocol, we notice that we can give a particular value for $\gamma$ so the two-class model gives the same curve as the modified one-class model. However, we can also vary this parameter and we can have different behavior. We can see this behavior in Figure 6 A), where we consider protocol A and with $0.15 < \gamma < 0.17$ we get a...
similar curve as the modified one class. Now considering $\gamma = 0$ gives a different TCP curve. The same behaviour occurs by fixing another dose value $D = 4.3$ as shown in Figure 6 B).

4. Discussion

We have introduced a new TCP model that includes RSD. Even when the process to obtain a TCP from a cell population model is easily understood, we made several contributions in our model. First, in previous papers which considered two populations [2, 18] and therefore the evolution of a joint distribution, it was assumed that the random variables that count the number of cells of each population are independent, simplifying significantly the derivation of an explicit formula of the TCP. To see how the TCP is affected by the assumption of independence, we plot DH TCP, under the parameters in Table 3, with the assumption of independence and without it. We are able to plot the TCP assuming independence by using the explicit TCP formula presented in [2]. To plot the TCP without the assumption of independence, we consider an approximation of the TCP by performing a large number of stochastic simulations, where for each realization $i$, we track the time $t_i^*$ at which there are zero cancerous cells and define a function for each realization $TCP_i(t)$ such that $TCP_i(t) = 1$ for $t > t_i^*$ and 0 otherwise. Then,

![TCP curves](image-url)

Fig. 5. TCP curves for three protocols for the one-class model, Dawson-Hillen model and the two-class model. The two-class TCP curve is lower compared to the one-class TCP curve. The reduction is greater as the dose increases.
STOCHASTIC MODEL FOR TCP: EFFECTS OF RSD

Fig. 6. Comparison one-class modified RSD and two-class model.

<table>
<thead>
<tr>
<th></th>
<th>TCPZM</th>
<th>TCPDH</th>
<th>TCPTwo-class</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial cell number</td>
<td>N(0) = 10^5</td>
<td>a(0) + q(0) = 10^5</td>
<td>U(0) = 10^7 E(0) = 0</td>
<td>cells</td>
</tr>
<tr>
<td>Net growth rate</td>
<td>b - d = 0.0273</td>
<td>μ - d_a = 0.0655</td>
<td>b_U - d_U - d_A = 0.0273</td>
<td>1/day</td>
</tr>
<tr>
<td></td>
<td>ν - d_q = 0.0476</td>
<td>η = 62.382</td>
<td>γ = .015</td>
<td>Fraction of unexposed surviving cells</td>
</tr>
<tr>
<td>α</td>
<td>α = 0.1531</td>
<td>α_a = 0.145</td>
<td>α = 0.1531</td>
<td>Gy^{-1}</td>
</tr>
<tr>
<td>β</td>
<td>β = 0.0149</td>
<td>α_q = 0.159</td>
<td>β = 0.0149</td>
<td>Gy^{-2}</td>
</tr>
<tr>
<td></td>
<td>β_a = 0.0353</td>
<td>β_q = 0.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Parameter values for the different TCP models

after M simulations, the TCP_{sto} is defined to be:

\[ TCP_{sto}(t) = \frac{1}{M} \sum_{i=1}^{M} TCP_i(t). \]

In Figure 7, we can see that by assuming independence, the TCP is lower. In our model, we did not consider the populations to be independent and we were able to give an explicit formula for the TCP. We are confident that the formula is correct since one can approximate the true TCP by performing a large number of stochastic simulations, where for each realization i, we track the time t_i^* at which there are zero cancerous cells and define a function for each realization TCP_i(t) such that TCP_i(t) = 1 for t > t_i^* and 0 otherwise. Then, after M simulations, the TCP_{sto} is defined to be:

\[ TCP_{sto}(t) = \frac{1}{M} \sum_{i=1}^{M} TCP_i(t). \]

By considering M = 10^3 and the standard parameters of our model, we plot both TCP curves in Figure 8 and we see they match.
Given the simplicity of the way in which we are modeling radiotherapy, we are able to give a formula for the evolution of the PGF at treatment time. Hence, we are able to give explicit expressions for the mean and variance of the total number of cells for all $t > 0$ that enable us to understand how the variance is affected by the treatment and therefore provide confidence intervals of our predictions.

By performing the sensitivity analysis on the parameters we observed that for prostate cancer, the TCP model was significantly sensitive to the variation of the survival fraction values and $\gamma$ while slightly affected by the variation of the other parameters. This is an interesting result, because if we assume the model correct, it means that clinically one should carefully measure the $\alpha$ and $\beta$ parameters and value of $\gamma$. Also, it tells us that having uncertainty in the other parameters is not as important as the uncertainty in the survival fraction and $\gamma$. Notice that these conclusions are for prostate cancer, with the confidence intervals in this work and assuming the model is correct.

Clearly, the one-class model could be recovered from the two-class model by setting $\gamma = 0$. How-
ever, we wanted to know how the models differ by fixing the net growth rate, so in this case only the presence of the second class will be affecting the dynamics. We analyzed the different TCP curves based on three treatment protocols and saw that the discrepancy of the two models is greater when the dose is greater.

There are several research questions that we can pursue after introducing this model. First, in this paper we assume a specific value for $\gamma$, but we observed in fact that this parameter affects the TCP significantly so it would be interesting to see if this parameter can be measured clinically or experimentally and then one could validate the model. Finally, we think that the large sensitivity to the radiosensitive parameters can be proved analytically using only the TCP formulas.

We have introduced a new TCP model that includes repair from sublethal damage, analyzed it thoroughly (sensitivity to the parameters, explicit formula for the probability distribution and a sufficient condition for the treatment to decrease the number of cells). We find the presence of the second class lowers and slows the TCP and this reduction is magnified as the probability to change to the affected class increases. We analyzed previous models that take into account RSD and seen that our model gives different results depending on the value of $\gamma$. We compared our model to the one-class model introduced by Zaidler and Minerbo and saw that compare to ours, they underestimate the TCP. Model validation is crucial, to see if the model is more realistic than previous ones.

References


A. Derivation of TCP formulas and efficacy condition of treatment

A.1 One-class model

We follow the steps described in Section 2 for obtaining the TCP formula:

**Step 1:** By considering the master equation (2.1), we multiply both sides with \( x^n \) and sum the expression from \( n = 0 \) to \( \infty \). Noticing that \( \frac{\partial G}{\partial x}(t,x) = \sum_{n=0}^{\infty} nx^{n-1} p_n(t) \), we obtain a PDE for the PGF

\[
\frac{\partial}{\partial t} G(t,x) = (bx - d)(x - 1) \frac{\partial}{\partial x} G(t,x).
\]

Since the master equation is only valid between treatment times, we will denote the function \( G(t,x) \) for \( t \in [t_i^+, t_{i+1}] \) as \( G_i(t,x) \).

To have a well-posed problem for obtaining \( G \) we need to define initial and boundary conditions.

For \( i = 0 \), the initial condition is defined by the initial number of cells:

\[
G_0(0,x) = \sum_n p_n(0)x^n = x^{N_0}
\]

and the boundary conditions are given by the fact that we are considering a probability distribution

\[
G_0(t,0) = p_0(t),
\]

\[
G_0(t,1) = \sum_{n=0}^{\infty} p_n(t) = 1,
\]

where \( G_0(t,x) \) solves the following partial differential equation

\[
\begin{cases}
\frac{\partial}{\partial t} G_0(t,x) = (bx - d)(x - 1) \frac{\partial}{\partial x} G_0(t,x) & 0 < t < t_1, \ 0 < x < 1 \\
G_0(0,x) = \sum_n p_n(0)x^n = x^{N_0} & 0 < x < 1 \\
G_0(t,0) = p_0(t), G_0(t,1) = 1 & 0 < t < t_1.
\end{cases}
\] (A.1)

Similarly, we construct a PDE system for \( G_i(t,x) \) for \( i > 0 \). The PDE and the boundary conditions are the same as for \( G_0(t,x) \). For the initial conditions, we need to determine what is the effect of the radiation on the PGF. To determine this, we first describe the effect of the \( i \)th radiation treatment in terms of \( G_{i-1}(t,x) \). This is a straightforward calculation using the properties of PGF. Hence,

\[
p_n(t_i^+) = \sum_{k=0}^{\infty} p_{n+k}(t_i^+) \binom{n+k}{k} (1 - SF)^k (SF)^n
\]

\[
= \sum_{k=0}^{\infty} \frac{1}{(n+k)!} \frac{\partial^{(n+k)}}{\partial x^{(n+k)}} \left( G_{i-1}(t_i,x) \right) \frac{(n+k)!}{n!k!} (1 - SF)^k (SF)^n
\]

(property of the PGF)

\[
= \frac{(SF)^n}{n!} \sum_{k=0}^{\infty} \frac{1}{k!} \frac{\partial^{(k)}}{\partial x^{(k)}} \left( \frac{\partial^{(n)}}{\partial x^{(n)}} G_{i-1}(t_i,x) \right) \bigg|_{x=0} (1 - SF)^k
\]

(Taylor expansion)

\[
= \frac{(SF)^n}{n!} \frac{\partial^{(n)}}{\partial x^{(n)}} G_{i-1}(t_i,x) \bigg|_{x=1-SF}
\] (A.2)
Considering \( G_{i+1}(t,x) = \sum_{n=0}^{\infty} p_n(t_i^+) x^n \) and (A.2), we conclude that
\[
G_{i+1}(t_i, x) = G_i(t_{i+1}, SFx + 1 - SF)
\] (A.3)

therefore, \( G_{i+1}(t, x) \) satisfies the following PDE system
\[
\begin{cases}
\frac{\partial}{\partial t} G_{i+1}(t,x) = (bx - d)(x - 1) \frac{\partial}{\partial x} G_{i+1}(t,x) & \forall t \in I, 0 < x < 1 \\
G_{i+1}(t_i, x) = G_i(t_{i+1}, SFx + 1 - SF) & 0 < x < 1 \\
G_{i+1}(t, 0) = p_0(t_i), G_{i+1}(t, 1) = 1 & t_{i+1} < t < t_{i+2}.
\end{cases}
\]

**Step 2:** There are different ways to solve versions of solving a transport equation via the method of characteristics. We consider the following method:

**Theorem A.1** Let \( u(x,t) \) be the solution of
\[
\begin{cases}
\frac{\partial u}{\partial t} + \frac{\partial}{\partial x} (v(x,t))u(x,t) = 0 & \forall t \in I, 0 < x < 1 \\
u(x,0) = u_0(x) & 0 < x < 1
\end{cases}
\] (A.4)

then, if \( X \) is the solution of the differential equation
\[
\begin{cases}
\frac{dx}{dt} = v(X(t), t) & \forall t \in I \\
X(t_0) = x_0
\end{cases}
\]

The solution of (A.4) is given by \( u_0(X(0)) \) and performing the substitution \( x_0 \to x \) and \( t_0 \to t \).

Using this method, first we need to solve the ODE associated with the characteristic
\[
\begin{cases}
\frac{dX}{dt} = (bX - d)(X - 1) & \forall t \in I \\
X(t_0) = x_0.
\end{cases}
\]

The characteristic then has the following form:
\[
X(t) = \frac{(x_0 - 1)de^{(b-d)t} - bx_0 + d}{(x_0 - 1)be^{(b-d)t} - bx_0 + d}.
\] (A.5)

By considering the initial condition for \( G_0 \) and \( G_i \) (\( i > 1 \)) we determine that these functions have the following form:
\[
G_0(t,x) = \left[ \frac{(x - 1)de^{(b-d)t} - bx + d}{(x - 1)be^{(b-d)t} - bx + d} \right]_{t=0}^{N_0}
\]
\[
G_{i+1}(t,x) = G_i(t_{i+1}, f_i(t_i,x))
\] (A.6)

where
\[
f_i(t_i,x) = SF \left[ \frac{(x - 1)de^{(b-d)(t_i-t)} - bx + d}{(x - 1)be^{(b-d)(t_i-t)} - bx + d} \right] + 1 - SF.
\]

**Step 3:** The previous step gave us a recursive explicit formula for the PGF. To get the explicit formula for the TCP one only considers \( G_i(t,0) \) in formula (A.6).
**Step 4:** By considering the master equation and the evolution at treatment times, we can derive the mean field dynamics:

\[
\begin{dcases}
\frac{d}{dt}\langle n(t) \rangle = (b - d)\langle n(t) \rangle & \quad t_i < t < t_{i+1} \\
\langle n(t_{i+1}^+) \rangle = (SF)\langle n(t_i^-) \rangle & \quad t_i \\
\langle n(0) \rangle = N_0
\end{dcases}
\] (A.7)

where \(N_0\) is the initial number of cells.

Solving this equation, we obtain.

\[\langle n(t) \rangle = \langle n(t_i^+) \rangle e^{(b-d)(t-t_i)}\]

Then, we have that

\[\langle n(t_{i+1}^-) \rangle = SF \langle n(t_i^-) \rangle = SF \langle n(t_i^+) \rangle e^{(b-d)\Delta}.
\]

To ensure \(\langle n(t_{i+1}^-) \rangle < \langle n(t_i^+) \rangle\), we need \(SF e^{(b-d)\Delta} < 1\) which is a sufficient and necessary condition for the mean to decrease at treatment times.

**A.2 Two-class model**

We follow the same steps as for the one-class model:

**Step 1:** We notice that we have two master equations, one for the interval before the treatment (2.3) and another for all the subsequent intervals (2.4). For both equations, we multiply both sides with \(x^{n_U} y^{n_A}\) and sum both expressions from \(n_U, n_A = 0\) to \(\infty\). The PDE associated with the master equation (2.3) is the same as for the one class as expected,

\[\frac{d}{dt} G(t,x,y) = (b_U x - d_U)(x - 1) \frac{d}{dx} G(t,x,y)\]

The PDE associated to the subsequent intervals is the following:

\[\frac{d}{dt} G(t,x,y) = (b_U x^2 - (b_U + d_U) x + d_U) \frac{d}{dx} G(t,x,y) + [- (d_A + \eta) y + d_A + \eta x] \frac{d}{dy} G(t,x,y)\]

We derive the boundary and the initial conditions just as in the one-class model.

The PDE which \(G_0(t,x,y)\) satisfies is

\[
\begin{dcases}
\frac{d}{dt} G_0(t,x,y) = (b_U x^2 - (b_U + d_U) x + d_U) \frac{d}{dx} G_0(t,x,y) & \quad 0 < t < t_1, \quad 0 < x, y < 1 \\
\quad + [- (d_A + \eta) y + d_A + \eta x] \frac{d}{dy} G_0(t,x,y) \\
G_0(0,x,y) = \sum_{n_U=0}^{\infty} \sum_{n_A=0}^{\infty} p_{n_U,0}(0) x^{n_U} y^{n_A} = x^{N_0} & \quad 0 < x, y < 1 \\
G_0(t,0,0) = p_{0,0}(t), \quad G_0(t,1,1) = 1 & \quad 0 < t < t_1
\end{dcases}
\]

Now, for \(G_i(t,x,y)\), we need to establish the initial condition. First we can give a formula for \(p_{n_U, n_A}(t_i^+)\) in terms of \(G_i(t,x,y)\)

\[
p_{n_U, n_A}(t_i^+) = \sum_{j=0}^{n_A} \frac{(SF)^n_U y^{n_U} [y(1-SF)]^{n_A-j}(SF)^j}{j! n_U! (n_A-j)!} \frac{\partial^{(n_U+n_A-j)} \partial^j}{\partial x^{n_U+n_A-j} \partial y^j} G_i(t,x,y)\mid_{x=1-y(1-SF)-SF}.
\] (A.8)
This formula, derived in a similar fashion as in the one-class model, enables us to express the PGF after the radiation in terms of the PGF before the radiation, i.e.

\[ G_{i+1}(t_{i+1}, x, y) = G_i(t_{i+1}, SFx + \gamma(1 - SF)y + 1 - \gamma(1 - SF) - SF, SFy + 1 - SF) \]

where these two formulas were developed in the same way as the one-class model. Hence, \( G_{i+1}(t, x) \) has to solve the following PDE

\[
\begin{align*}
\frac{\partial}{\partial t} G_{i+1}(t, x, y) &= (b_U x^2 - (b_U + d_U)x + d_U) \frac{\partial}{\partial x} G_{i+1}(t, x, y) \\
&+ [(d_A + \eta) y + d_A + \eta] \frac{\partial}{\partial y} G_{i+1}(t, x, y) \\
G_{i+1}(t, 0, y) &= \rho_{0,0}(t), G_{i+1}(t, 1, 1) = 0 < x < 1
\end{align*}
\]

(A.9)

**Step 2:** Following the method of characteristics, first we want to solve the ODE for the characteristic \( X(t) = (X(t), Y(t)) \)

\[
\begin{align*}
\frac{d}{dt} X(t) &= -(b_U X^2 - (b_U + d_U)X + d_U) \\
\frac{d}{dt} Y(t) &= -[(d_A + \eta) Y + d_A + \eta X] \\
X(t_0) &= x_0, Y(t_0) = y_0
\end{align*}
\]

We have that

\[ X(t) = \frac{d_U}{b_U}(1 - x_0)e^{(b_U - d_U)(t_0 - t)} + b_U x_0 + d_U \]

and

\[ Y(t) = y_0 e^{(d_A + \eta)(t - t_0)} + \frac{d_A}{d_A + \eta} \left[ 1 - e^{(d_A + \eta)(t - t_0)} \right] - \eta e^{-d_A + \eta \int_0^t e^{-(d_A + \eta)t'}X(t') dt'}. \]  

(A.10)

Now, we just consider the initial conditions of the PDEs, and the substitutions: \( x_0 \to x, y_0 \to y, t_0 \to t; \) we have that for \( t \in [t_0, t_1], \)

\[ G_0(t, x, y) = \left[ \frac{(x - 1)d_U e^{(b_U - d_U)\eta} - b_U x + d_U}{x - 1) b_U e^{(b_U - d_U)\eta} - b_U x + d_U} \right]^{N_0} \]

and for \( t \in [t_{i+1}^+, t_{i+2}^+], \)

\[ G_{i+1}(t, x, y) = G_i(t_{i+1}, f_{i+1}(t, x, y), g_{i+1}(t, x, y)) \]  

(A.11)

where

\[ f_{i+1}(t, x, y) = SFX(t - t_{i+1}, x) + \gamma(1 - SF)Y(t - t_{i+1}, x, y) + 1 - \gamma(1 - SF) - SF \]

and

\[ g_{i+1}(t, x, y) = SFY(t - t_{i+1}, x, y) + 1 - SF \]

in which

\[ X(t, x) = \frac{d_U}{b_U}(1 - x)e^{(b_U - d_U)\eta} + b_U x + d_U \]

and

\[ Y(t, x, y) = ye^{(d_A + \eta)(-t)} + \frac{d_A}{d_A + \eta} \left[ 1 - e^{-(d_A + \eta)t} \right] - \eta \int_0^t e^{-(d_A + \eta)t'}X(t') dt'. \]
Step 3: The previous step gave us a recursive explicit formula for the PGF. To get the explicit formula of the TCP one only considers $G_i(t,0,0)$ in formula (A.11).

Step 4: By considering the master equation and the evolution at treatment times, we can derive the mean field dynamics:

\[
\begin{align*}
\frac{d\langle n(t) \rangle}{dt} &= (b_U - d_U)\langle n(t) \rangle + \eta \langle n_A(t) \rangle & t_i < t < t_{i+1} \\
\frac{d\langle n_A(t) \rangle}{dt} &= -(d_A + \eta)\langle n_A(t) \rangle & t_i < t < t_{i+1} \\
\langle n_U(t_i^+) \rangle &= (SF)\langle n_U(t_i^-) \rangle, \quad \langle n_A(t_i^+) \rangle = (SF)\langle n_A(t_i^-) \rangle + \gamma(1-SF)\langle n_U(t_i^-) \rangle & \text{at } t_i \\
\langle n_U(0) \rangle &= N_0, \quad \langle n_A(0) \rangle = 0
\end{align*}
\]

(A.12)

and by solving this system we have that

\[
\langle n_A(t) \rangle = \langle n_A(t_i^+) \rangle e^{-(d_A+\eta)(t-t_i)}
\]

\[
\langle n_U(t) \rangle = \langle n_U(t_i^+) \rangle U e^{-(b_U-d_U)(t-t_i)} - \frac{\eta \langle n_A(t_i^+) \rangle}{b_U - d_U + d_A + \eta} \left[ e^{-(d_A+\eta)(t-t_i)} - e^{(b_U-d_U)(t-t_i)} \right].
\]

To assure $T(t_{i+1}^+) < T(t_i^+)$, this is true iff

\[
n_U(t_{i+1}^+) + n_A(t_{i+1}^+) < n_U(t_i^+) + n_A(t_i^+)
\]

and this is true when

\[
\| (n_U(t_{i+1}^+), n_A(t_{i+1}^+) ) \|_1 < \| (n_U(t_i^+), n_A(t_i^+) ) \|_1
\]

where $\| - \|_1$ denotes the matrix norm 1 which is the sum of the absolute values of the entries.

By considering the evolution at treatment times we have

\[
\begin{pmatrix}
  n_U(t_{i+1}^+) \\
  n_A(t_{i+1}^+)
\end{pmatrix} =
\begin{pmatrix}
  SF & 0 \\
  \gamma(1-SF) & SF
\end{pmatrix}
\begin{pmatrix}
  n_U(t_i^+) \\
  n_A(t_i^+)
\end{pmatrix}
\]

and by considering the explicit solutions of the mean field equations, we obtain

\[
\begin{pmatrix}
  n_U(t_{i+1}^+) \\
  n_A(t_{i+1}^+)
\end{pmatrix} =
\begin{pmatrix}
  SF & 0 \\
  \gamma(1-SF) & SF
\end{pmatrix}
\begin{pmatrix}
  e^{(b_U-d_U)\Delta} & -\frac{\eta e^{-(d_A+\eta)\Delta} - e^{(b_U-d_U)\Delta}}{b_U - d_U + d_A + \eta} \\
  0 & e^{(d_A+\eta)\Delta}
\end{pmatrix}
\begin{pmatrix}
  n_U(t_i^+) \\
  n_A(t_i^+)
\end{pmatrix}
\]

where to ensure

\[
\| (n_U(t_{i+1}^+), n_A(t_{i+1}^+) ) \|_1 < \| (n_U(t_i^+), n_A(t_i^+) ) \|_1
\]

is sufficient that the following inequality is satisfied

\[
\left\| \begin{pmatrix}
  SF & 0 \\
  \gamma(1-SF) & SF
\end{pmatrix}
\begin{pmatrix}
  e^{(b_U-d_U)\Delta} & -\frac{\eta e^{-(d_A+\eta)\Delta} - e^{(b_U-d_U)\Delta}}{b_U - d_U + d_A + \eta} \\
  0 & e^{(d_A+\eta)\Delta}
\end{pmatrix}
\right\|_1 < 1.
\]