A STOCHASTIC MODEL FOR PSA LEVELS: BEHAVIOR OF SOLUTIONS AND POPULATION STATISTICS

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Abstract. This paper investigates the partial differential equation for the evolution of prostate-specific antigen (PSA) levels following radiotherapy. We also present results on the behavior of moments for the evolving distribution of PSA levels and estimate the probability of long-term treatment success and failure related to values of treatment and disease parameters.

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1. Introduction

This paper extends an investigation of the continuous stochastic model for the prostate-specific antigen (PSA) levels following radiotherapy undertaken in [1]. Here we address the case in which parameters do not allow for an explicit formula for the evolving PSA density function. We also give a general analysis, including bounds, for the probability density function using maximum principle arguments and conduct an analysis of the moments of the random PSA levels using theoretical and numerical tools.

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In [1] we derived an explicit form for the distribution of future PSA levels (including probabilities of cure) for the case $a = \alpha$, where a is the decay rate of the effect of radiotherapy and α is the (implied) tumor growth rate. In this paper we examine the general case without the restriction $a = \alpha$.

The paper is organized as follows. In §2 we describe the original and transformed initial-boundary value problems. In §3 we summarize results developed in [1] for the case $a = \alpha$, with corresponding formulas for the fundamental solutions. In §4 we use maximum principle arguments to estimate the original and transformed probability density functions for the cases $a \leq \alpha$ and $a \geq \alpha$. In §5 we estimate the probability of cure for these two cases. In §6 we derive an ordinary differential equation for the mean PSA level coupled with the probability of cure and find estimates for the rate of growth of the mean PSA level. We also analyze the time when the minimal mean PSA level is reached and derive appropriate bounds. In §7 we carry out numerical modeling of the mean PSA level and compare our analysis with available clinical data. In §8 we offer conclusions and comments.

2. Initial-Boundary Value Problems

In [1] we introduced the following Chapman–Kolmogorov partial differential equation

$$\frac{1}{2}\sigma^2 \frac{\partial^2 p}{\partial x^2} - \frac{\partial}{\partial x}\left((\alpha x - ke^{-at})p\right) = \frac{\partial p}{\partial t}, \tag{2.1}$$

where $p(x,t) : [0,\infty) \times [0,\infty) \to [0,\infty)$ is, for each $t \in [0,\infty)$, the probability density function in x. Here x represents PSA level and t represents time. The parameters involved are $\alpha > 0$ (tumor growth rate), $a > 0$ (decay rate of the effect of radiotherapy), $k > 0$ (indicator of treatment intensity/effectiveness), and $\sigma > 0$ (volatility of the PSA process). The initial PSA distribution is given by

$$p(x,0) = f(x) \geq 0, \quad f(0) = 0, \tag{2.2}$$

where f is continuous, compactly supported on $[0,\infty)$ and satisfies $\int_0^\infty f(x)\,dx = 1$. We also have an "absorbing barrier" boundary condition (irreversibility of "cure")

$$p(0,t) = 0 \quad \text{for all} \quad t > 0, \tag{2.3}$$

and we impose the growth condition

$$xp(x,t) \quad \text{is bounded as} \quad x \to \infty \quad \text{for each } t. \tag{2.4}$$

The model (2.1)–(2.4) was introduced as an alternative to the deterministic model

$$X'(t) = \alpha X(t) - ke^{-at}, \tag{2.5}$$

$$X(0) = m, \tag{2.6}$$

investigated in [2]. We next develop results leading to the proof of the following theorem.

Theorem 2.1. *The initial-boundary value problem* (2.1)–(2.4) *has a unique smooth solution* $p(x,t)$ *on* $[0,\infty) \times [0,\infty)$.

By (2.4) and the Maximum Principle for parabolic equations,

$$0 \le p(x,t) \le \max p(x,0) = \max f(x) \equiv f^m \quad \text{for all} \quad x \ge 0,\ t \ge 0. \tag{2.7}$$

The transformation

$$\begin{aligned} y &= \alpha\left(x - \frac{k}{a+\alpha}e^{-at}\right)e^{-\alpha t}, \\ \tau &= \frac{\alpha\sigma^2}{2}\left(1 - e^{-2\alpha t}\right), \\ Q(y,\tau) &= \frac{p(x,t)e^{\alpha t}}{\alpha}, \end{aligned} \tag{2.8}$$

was used (cf. [1]) to replace the initial-boundary value problem (2.1)–(2.4) with the one for the transformed probability density function $Q(y,\tau)$ satisfying:

$$\frac{1}{2}\frac{\partial^2 Q}{\partial y^2} - \frac{\partial Q}{\partial \tau} = 0, \quad (y,\tau) \in \mathcal{D}, \tag{2.9}$$

$$Q(y,0) = \frac{1}{\alpha} f\left(\frac{y}{\alpha} + \frac{k}{a+\alpha}\right) \equiv f^*(y) \quad \text{for} \quad y \geq -\frac{\alpha k}{a+\alpha}, \tag{2.10}$$

$$Q(y^*(\tau),\tau) = 0 \quad \text{for} \quad 0 \leq \tau \leq \frac{\alpha\sigma^2}{2}, \tag{2.11}$$

and

$$yQ(y,\tau) \quad \text{is bounded as} \quad y \to \infty \quad \text{for each } \tau, \tag{2.12}$$

where $\mathcal{D} = \{(y,\tau) : 0 \leq \tau \leq \alpha\sigma^2/2,\ y^*(\tau) \leq y < \infty\}$, with

$$y^*(\tau) = -\frac{\alpha k}{a+\alpha}\left(1 - \frac{2\tau}{\alpha\sigma^2}\right)^{\frac{a+\alpha}{2\alpha}}. \tag{2.13}$$

The slope of the tangent line to y^* at $\tau = 0$ is $k/(\alpha\sigma^2)$ and

$$y^{*\,\prime\prime}(\tau) = -\frac{k(a-\alpha)}{\alpha(\alpha\sigma^2 - 2\tau)^2}\left(1 - \frac{2\tau}{\alpha\sigma^2}\right)^{\frac{a+\alpha}{2\alpha}}. \tag{2.14}$$

We note that (2.14) implies that

$$y^{*\,\prime\prime}(\tau) > 0 \text{ if } a < \alpha \qquad \text{and} \qquad y^{*\,\prime\prime}(\tau) < 0 \text{ if } a > \alpha\,. \tag{2.15}$$

The conditions on f outlined after (2.2) imply that there exists $N_0 > 0$ such that $f^*(y) = 0$ outside the compact interval $[-(\alpha k)/(a+\alpha), N_0]$. We note that the first equation in (2.8) implies that $yQ = xp - (ke^{-at}p/(a+\alpha))$. So (2.4) immediately entails (2.12). Conversely, if, for some fixed t, $yQ \leq C$, where $C > 0$, then $xp \leq C + kp/(a+\alpha)$. If there exists a sequence $x_n \to \infty$ so that $x_n p(x_n) \to \infty$, then

$$1 \leq \frac{C}{x_n p(x_n)} + \frac{k}{x_n(a+\alpha)} \to 0 + 0 = 0 \quad \text{as} \quad x_n \to \infty,$$

which is not possible, so xp is bounded.

Theorem 2.2. *The initial-boundary value problem* (2.9)–(2.12) *has a unique smooth solution* $Q(y,\tau)$ *on* $\mathcal{D}$.

Proof of Theorem 2.2. Let $Q_{\max}(y,\tau)$ be the solution of (2.9) on $\{(y,\tau): 0 \le \tau \le \alpha\sigma^2/2,\ y \in \mathbb{R}\}$ with initial values obtained by extending $Q(y,0)$ by zero for $y < y^*(0)$ (cf. Theorem 12, page 25 of [3]). Now let $Q_N(y,\tau)$ be the unique smooth solution of (2.9) on the bounded domain

$$\mathcal{D}_N = \{(y,\tau): 0 \le \tau \le \alpha\sigma^2/2,\ y^*(\tau) \le y \le N\}$$

with the boundary conditions (2.11), $Q(N,\tau) = 0$ for $0 \le \tau \le \alpha\sigma^2/2$, with the initial condition (2.10), and with $N > N_0$. By the (standard) maximum principle for the heat equation in $\mathcal{D}_N$, $Q_{\max} \ge Q_N \ge 0$. In addition, since $Q_{N+1} \ge Q_N = 0$ for $y = N$, the maximum principle can be applied again in $\mathcal{D}_N$ to conclude that $Q_{\max} \ge Q_{N+1} \ge Q_N \ge 0$ on $\mathcal{D}_N$. Thus the sequence of functions Q_n $(n > N)$ converges pointwise in $\mathcal{D}_N$ for every N. A regularity theorem (cf. Theorem 11, page 74 of [3]) implies that each Q_n is C^∞ in $\mathcal{D}_N$ for every N and Theorem 15, page 80 of [3] guarantees that the limit $Q(y,\tau) = \lim_{n\to\infty} Q_n(y,\tau)$ solves the heat equation. This limit satisfies (2.9)–(2.12) in $\mathcal{D}$. □

Furthermore, by (2.12) and the maximum principle

$$0 \le Q(y,\tau) \le \frac{f^m}{\alpha} \quad \text{for all} \quad (y,\tau) \in \mathcal{D}. \tag{2.16}$$

Proof of Theorem 2.1. Transforming back to (x,t)-space, the function obtained in Theorem 2.2,

$$p(x,t) = \alpha e^{-\alpha t} Q(\alpha(x - \frac{ke^{-at}}{a+\alpha})e^{-\alpha t}, \frac{\alpha\sigma^2}{2}(1 - e^{-2\alpha t}))\,,$$

satisfies the original problem. Thus the result follows from Theorem 2.2 and the one-to-one nature of the transform in (2.8). □

3. Original Formulas for Q and p in the case $a = \alpha$

The fundamental solution corresponding to the initial-boundary value problem (2.9)–(2.12) in the case $a = \alpha$ was shown in [1] to be

$$Q(y,\tau;m^{**}) = \frac{1}{\sqrt{2\pi\tau}}\left\{\exp\left(-\frac{(y-m^{**})^2}{2\tau}\right) - \exp\left(\frac{2km}{\sigma^2} - \frac{(y+m^{**}+k)^2}{2\tau}\right)\right\} \tag{3.1}$$

for all $(y,\tau) \in \mathcal{L} \equiv \{(y,\tau) : 0 \le \tau \le \alpha\sigma^2/2,\ y^{**}(\tau) \le y < \infty\}$, where

$$y^{**}(\tau) = \frac{k}{\alpha\sigma^2}\tau - \frac{k}{2}, \tag{3.2}$$

m is the singularity of the fundamental solution at time $t = 0$, and

$$m^{**} = \alpha\left(m - \frac{k}{2\alpha}\right) = \alpha m - \frac{k}{2} \tag{3.3}$$

is the singularity of the fundamental solution in the transformed region $\mathcal{L}$ at $\tau = 0$. The corresponding PSA density function (also developed in [1]) is

$$\begin{aligned} p(x,t;m) = \frac{\alpha e^{-\alpha t}}{\sqrt{\alpha\sigma^2\pi(1-e^{-2\alpha t})}} \Bigg\{ &\exp\left(-\frac{[(k/2) - \alpha m + e^{-\alpha t}(\alpha x - (k/2)e^{-\alpha t})]^2}{\alpha\sigma^2(1-e^{-2\alpha t})}\right) \\ -\exp\left(\frac{2km}{\sigma^2} - \frac{[(k/2) + \alpha m + e^{-\alpha t}(\alpha x - (k/2)e^{-\alpha t})]^2}{\alpha\sigma^2(1-e^{-2\alpha t})}\right)\Bigg\} & \quad \text{for } x \ge 0 \text{ and } t > 0\,, \end{aligned} \tag{3.4}$$

and the solution of a problem with distributed initial values is given by the convolution of those values with the fundamental solution (3.4).

4. Estimates for Q and p for general $a, \alpha > 0$

We start by defining m^*, the singularity of the fundamental solution in the transformed region $\mathcal{D}$ at $\tau = 0$, by

$$m^* = \alpha\left(m - \frac{k}{a+\alpha}\right). \tag{4.1}$$

First, we consider the special case $m^* > 0$. We set $\mathcal{T}^+ \equiv \{(\tau, y) : 0 \le \tau < \alpha\sigma^2/2,\ 0 \le y < \infty\} \subset \mathcal{D}$ (cf. Figures 1 & 2) and use the method of images as described in §3 to find an explicit fundamental solution in $\mathcal{T}^+$. By the maximum principle (with $m^* = m^{**}$), we can obtain a lower bound for the fundamental solution

$$Q(y,\tau;m^*) \ge \frac{1}{\sqrt{2\pi\tau}}\left\{\exp\left(-\frac{(y-m^*)^2}{2\tau}\right) - \exp\left(-\frac{(y+m^*)^2}{2\tau}\right)\right\} \quad \text{for all } (y,\tau) \in \mathcal{T}^+. \tag{4.2}$$

In the (x,t)-domain, the corresponding bound is

$$p(x,t;m) \geq \frac{\alpha e^{-\alpha t}}{\sqrt{\alpha\sigma^2\pi(1-e^{-2\alpha t})}}\left\{\exp\left(-\frac{\alpha\left[xe^{-\alpha t}-m\right]^2}{\sigma^2(1-e^{-2\alpha t})}\right)\right.$$
(4.3)
$$\left.-\exp\left(-\frac{\alpha\left[xe^{-\alpha t}+m\right]^2}{\sigma^2(1-e^{-2\alpha t})}\right)\right\} \quad \text{for} \quad x \geq \frac{k}{a+\alpha}e^{-at}, \;\; t>0.$$

Next we consider the case when $a \leq \alpha$ without restricting m^*. Let $\mathcal{T} \equiv \left\{(y,\tau) : 0 \leq \tau \leq \alpha\sigma^2/2,\; \tilde{y}(\tau) \leq y < \infty\right\}$, where

$$\tilde{y}(\tau) = \frac{k}{\alpha\sigma^2}\tau - \frac{\alpha k}{a+\alpha} \tag{4.4}$$

(cf. Figure 1). Note that (2.15) implies that $\mathcal{D} \subset \mathcal{T}$ and that the line (4.4) is tangent to the curve (2.13) at the point $(0, -\frac{\alpha k}{a+\alpha})$. Again, by using the method of images and the maximum principle, we find an explicit formula that provides an upper bound for the fundamental solution on $\mathcal{D}$:

$$Q(y,\tau;m^*) \leq \frac{1}{\sqrt{2\pi\tau}}\left\{\exp\left(-\frac{(y-m^*)^2}{2\tau}\right) - \exp\left(\frac{2km}{\sigma^2} - \frac{(y+m^*+(2\alpha k/(a+\alpha)))^2}{2\tau}\right)\right\}. \tag{4.5}$$

Now we consider the region $\mathcal{S} \equiv \left\{(y,\tau) : 0 \leq \tau < \alpha\sigma^2/2,\; y^0(\tau) \leq y < \infty\right\}$ (cf. Figure 1), where

$$y^0(\tau) = -\frac{\alpha k}{a+\alpha} + \frac{2k\tau}{(a+\alpha)\sigma^2}. \tag{4.6}$$

The maximum principle now yields a lower bound for the fundamental solution:

(4.7)
$$Q(y,\tau;m^*) \geq \frac{1}{\sqrt{2\pi\tau}}\left\{\exp\left(-\frac{(y-m^*)^2}{2\tau}\right) - \exp\left(\frac{4\alpha km}{(a+\alpha)\sigma^2} - \frac{(y+m^*+(2\alpha k/(a+\alpha)))^2}{2\tau}\right)\right\}$$

for all $(y,\tau) \in \mathcal{S} \subset \mathcal{D} \subset \mathcal{T}$. In the (x,t)-domain, we have corresponding bounds for $p(x,t;m)$:

$$p(x,t;m) \leq \frac{e^{-\alpha t}\sqrt{a+\alpha}}{\sqrt{2\sigma^2\pi(1-e^{-2\alpha t})}}\left\{\exp\left(-\frac{\left[k-m(a+\alpha)+e^{-\alpha t}(x(a+\alpha)-ke^{-\alpha t})\right]^2}{2\sigma^2(1-e^{-2\alpha t})(a+\alpha)}\right)\right.$$
(4.8)
$$\left.-\exp\left(\frac{2km}{\sigma^2} - \frac{\left[k+m(a+\alpha)+e^{-\alpha t}(x(a+\alpha)-ke^{-\alpha t})\right]^2}{2\sigma^2(1-e^{-2\alpha t})(a+\alpha)}\right)\right\} \quad \text{for } x \geq 0 \text{ and } t>0$$

and

$$
p(x,t;m) \geq \frac{\alpha e^{-\alpha t}}{\sqrt{\alpha\sigma^2\pi(1-e^{-2\alpha t})}} \Bigg\{ \exp\bigg(-\frac{\alpha\left[k - m(a+\alpha) + e^{-\alpha t}(x(a+\alpha) - ke^{-\alpha t})\right]^2}{\sigma^2(1-e^{-2\alpha t})(a+\alpha)^2} \bigg)
$$

$$
(4.9) \qquad - \exp\bigg(\frac{4\alpha k m}{(a+\alpha)\sigma^2} - \frac{\alpha\left[k + m(a+\alpha) + e^{-\alpha t}(x(a+\alpha) - ke^{-\alpha t})\right]^2}{\sigma^2(1-e^{-2\alpha t})(a+\alpha)^2} \bigg) \Bigg\} \quad \text{for}
$$

$$
x \geq \frac{k}{a+\alpha}(e^{-at} - e^{-\alpha t}) \ \text{ and } \ t > 0 \,.
$$

Finally, we consider the case when $a \geq \alpha$ without restricting m^*. We can apply similar techniques using the regions $\mathcal{T}' \equiv \{(y,\tau) : 0 \leq \tau < \alpha\sigma^2/2,\ \tilde{y}(\tau) \leq y < \infty\}$ and $\mathcal{S}$. Note that, in view of (2.15), $\mathcal{T}' \subset \mathcal{D} \subset \mathcal{S}$ (cf. Figure 2). By the maximum principle, we have

$$
(4.10) \qquad Q(y,\tau;m^*) \geq \frac{1}{\sqrt{2\pi\tau}} \left\{ \exp\bigg(-\frac{(y-m^*)^2}{2\tau} \bigg) - \exp\bigg(\frac{2km}{\sigma^2} - \frac{(y + m^* + (2\alpha k/(a+\alpha)))^2}{2\tau} \bigg) \right\}
$$

for all $(y,\tau) \in \mathcal{T}'$. The upper bound is given by

(4.11)

$$
Q(y,\tau;m^*) \leq \frac{1}{\sqrt{2\pi\tau}} \left\{ \exp\bigg(-\frac{(y-m^*)^2}{2\tau} \bigg) - \exp\bigg(\frac{4\alpha k m}{(a+\alpha)\sigma^2} - \frac{(y + m^* + (2\alpha k/(a+\alpha)))^2}{2\tau} \bigg) \right\}
$$

for all $(y,\tau) \in \mathcal{D}$. In the (x,t)-domain, the corresponding estimates are

$$
p(x,t;m) \leq \frac{\alpha e^{-\alpha t}}{\sqrt{\alpha\sigma^2\pi(1-e^{-2\alpha t})}} \Bigg\{ \exp\bigg(-\frac{\alpha\left[k - m(a+\alpha) + e^{-\alpha t}(x(a+\alpha) - ke^{-\alpha t})\right]^2}{\sigma^2(1-e^{-2\alpha t})(a+\alpha)^2} \bigg)
$$

$$
(4.12) \qquad -\exp\bigg(\frac{4\alpha k m}{(a+\alpha)\sigma^2} - \frac{\alpha\left[k + m(a+\alpha) + e^{-\alpha t}(x(a+\alpha) - ke^{-\alpha t})\right]^2}{\sigma^2(1-e^{-2\alpha t})(a+\alpha)^2} \bigg) \Bigg\} \quad \text{for } x \geq 0 \text{ and } t > 0,
$$

and

$$
p(x,t;m) \geq \frac{\alpha e^{-\alpha t}}{\sqrt{\alpha\sigma^2\pi(1-e^{-2\alpha t})}} \Bigg\{ \exp\bigg(-\frac{\alpha\left[k - m(a+\alpha) + ((a+\alpha)x - k)e^{-(a+\alpha)t}\right]^2}{\sigma^2(1-e^{-2\alpha t})(a+\alpha)^2} \bigg)
$$

$$
(4.13) \qquad - \exp\bigg(\frac{4\alpha k m}{(a+\alpha)\sigma^2} - \frac{\alpha\left[(a+\alpha)xe^{-\alpha t} - ke^{-(a+\alpha)t} + k + m(a+\alpha)\right]^2}{\sigma^2(1-e^{-2\alpha t})(a+\alpha)^2} \bigg) \Bigg\} \quad \text{for}
$$

$$
x \geq \frac{k}{2\alpha(a+\alpha)}\bigg((a-\alpha)e^{\alpha t} - (a+\alpha)e^{-\alpha t} + 2\alpha e^{-at} \bigg), \quad t > 0 \,.
$$

Note that the estimates above allow bounds to be determined for the probability of absorption (cure), $1 - M(t)$, where

$$
(4.14) \qquad M(t) \equiv \int_0^\infty p(x,t)\,dx = \int_{y^*(\tau)}^\infty Q(y,\tau)\,dy \,.
$$

We are specifically interested in the treatment failure rate, L, which we define as

$$L \equiv \lim_{t\to\infty} M(t) = \lim_{t\to\infty} \int_0^\infty p(x,t)\,dx = \lim_{\tau\to\left(\frac{\alpha\sigma^2}{2}\right)^-} \int_{y^*(\tau)}^\infty Q(y,\tau)\,dy\,. \tag{4.15}$$

Note that $M(t)$ is a nonnegative decreasing function (cf. (6.5)) with $M(0) = 1$. It decays to the limit $L > 0$ (cf. §5). So

$$0 < L \le M(t) \le M(0) = 1 \quad \text{for all } t \ge 0\,. \tag{4.16}$$

5. Estimates for the treatment failure rate

As in the previous section, we start with the special case $m^* > 0$. By (2.13), (4.2), and (4.14), we have

$$M(t) \ge \frac{1}{\sqrt{2\pi\tau}} \int_0^\infty \int_0^\infty \left\{\exp\left(-\frac{(y-m^*)^2}{2\tau}\right) - \exp\left(-\frac{(y+m^*)^2}{2\tau}\right)\right\} f^*(m^*)\,dm^*\,dy\,, \tag{5.1}$$

where τ and t are related via (2.8). Passing to the limit in (5.1) as $\tau \to \left(\frac{\alpha\sigma^2}{2}\right)^-$ and, using (4.15), in case of fundamental solution we obtain

$$L \ge L_1\,, \tag{5.2}$$

where

$$L_1 \equiv \mathrm{Erf}\left[\frac{\alpha(m(a+\alpha)-k)}{(a+\alpha)\sqrt{\alpha\sigma^2}}\right] > 0\,, \tag{5.3}$$

and where Erf is the standard error function.

Next, we consider the case $a \le \alpha$ without restricting m^*. From (2.13), (4.5), (4.7), (4.14), (4.15) (cf. Figure 1) and, using the technique described in the beginning of this section, we have

$$L_2 \le L \le L_3 \le L_4\,, \tag{5.4}$$

where

$$L_2 \equiv \frac{1}{2}\left(\mathrm{Erfc}\left[\frac{\alpha(k-m(a+\alpha))}{(a+\alpha)\sqrt{\alpha\sigma^2}}\right] - \exp\left(\frac{4km\alpha}{(a+\alpha)\sigma^2}\right)\mathrm{Erfc}\left[\frac{\alpha(k+m(a+\alpha))}{(a+\alpha)\sqrt{\alpha\sigma^2}}\right]\right)\,, \tag{5.5}$$

$$L_3 \equiv \frac{1}{2}\left(\mathrm{Erfc}\left[\frac{\alpha(k-m(a+\alpha))}{(a+\alpha)\sqrt{\alpha\sigma^2}}\right]-\exp\left(\frac{2km}{\sigma^2}\right)\mathrm{Erfc}\left[\frac{\alpha(k+m(a+\alpha))}{(a+\alpha)\sqrt{\alpha\sigma^2}}\right]\right), \tag{5.6}$$

and

$$L_4 \equiv \frac{1}{2}\left(\mathrm{Erfc}\left[\frac{k-2m\alpha)}{2\sqrt{\alpha\sigma^2}}\right]-\exp\left(\frac{2km}{\sigma^2}\right)\mathrm{Erfc}\left[\frac{k+2m\alpha}{2\sqrt{\alpha\sigma^2}}\right]\right). \tag{5.7}$$

Here $\mathrm{Erfc}(x)=1-\mathrm{Erf}(x)$.

Finally, we consider the case $a \geq \alpha$ without restricting m^*. From (2.13), (4.10), (4.11), (4.14), and (4.15) (cf. Figure 2), we have

$$L_4 \leq L \leq L_2\,. \tag{5.8}$$

Theorem 5.1. *$L_2>0$, $L_3>0$ and $L_4>0$ for all positive α, σ, a, m, and k.*

To prove the result, we begin with the following lemma:

Lemma 5.2. *Let*

$$F(A,B) \equiv \frac{1}{2}\left(\mathrm{Erfc}\,(B-A)-e^{4BA}\,\mathrm{Erfc}\,(B+A)\right) \tag{5.9}$$

Then $F(A,B)>0$ for all $A>0$ and $B>0$.

Proof of Lemma 5.2. Note that $F(0,B)=0$ and $F(A,0)=\mathrm{Erf}(A)$. We claim that $F(\cdot,B)$ is increasing on $[0,\infty)$. To show the claim, we note that

$$\frac{\partial F}{\partial A}(A,B)=2e^{4AB}\,G(A,B) \quad \text{where} \quad G(A,B)=\frac{1}{\sqrt{\pi}}e^{(-(A+B)^2)}-B\,\mathrm{Erfc}(A+B)\,. \tag{5.10}$$

Now, $G(A,B)$ approaches zero as $A\to\infty$ and

$$\frac{\partial G}{\partial A}(A,B)=-\frac{2}{\sqrt{\pi}}Ae^{-(A+B)^2}<0 \quad \text{for all } A>0\,. \tag{5.11}$$

Thus $G(\cdot,B)$ is a positive function on $[0,\infty)$ decreasing to zero with

$$G(0,B)=\frac{1}{\sqrt{\pi}}e^{-B^2}-B\,\mathrm{Erfc}(B) \quad \text{and} \quad \frac{\partial G(0,B)}{\partial B}=-\mathrm{Erfc}(B)<0\,. \tag{5.12}$$

Note that $G(0,0) = 1/\sqrt{\pi} > 0$, that $G(0,\cdot)$ is decreasing on $[0,\infty)$ by (5.12), and that $G(0,B)$ approaches zero as $B \to \infty$. So $G(0,B) > 0$ for all $B > 0$. The claim follows from positivity of G and from (5.10). Therefore $F(A,B) > 0$. □

Proof of Theorem 5.1. First, $L_2 = F(A,B)$ if we set

$$A = \frac{\sqrt{\alpha}}{\sigma} m \quad \text{and} \quad B = \frac{\sqrt{\alpha}}{\sigma}\frac{k}{a+\alpha}\,.$$

So $L_2 > 0$ by Lemma 5.2. Next, $L_4 = F(A,B)$ if we set

$$A = \frac{\sqrt{\alpha}}{\sigma} m \quad \text{and} \quad B = \frac{k}{2\sqrt{\alpha\sigma^2}}\,.$$

So $L_4 > 0$ by Lemma 5.2. Finally, by (5.4), $L_3 \geq L_2 > 0$. □

We note that in the case when $m^* > 0$ and $a > \alpha$ both (5.2) and the first inequality in (5.8) provide a lower bound on L. In practice, one could evaluate L_1 and L_4 and pick the best of the two. In addition, both of these lower bounds can be improved by analyzing a one-parameter family of suitable rectilinear regions $\mathcal{T}(s) \subset \mathcal{D}$, where

$$\mathcal{T}(s) \equiv \left\{(y,\tau) : 0 \leq \tau < \alpha\sigma^2/2,\ \tilde{y}(\tau,s) \leq y < \infty\right\}\,, \quad 0 \leq s \leq k\,, \tag{5.13}$$

with the corresponding one-parameter family of tangent lines $y(\tau,\cdot)$ along the curve (2.13) given by (cf. Figure 2)

$$\tilde{y}(\tau,s) = \frac{s}{\alpha\sigma^2}\tau - \frac{s}{2} + b(s) \qquad \text{where} \qquad b(s) = \frac{k(a-\alpha)}{2(a+\alpha)}\left(\frac{s}{k}\right)^{\frac{a+\alpha}{a-\alpha}}\,. \tag{5.14}$$

The respective family of fundamental solutions can be written as

(5.15)

$$\begin{aligned} &Q(y,\tau,s;m^*) \\ =&\frac{1}{\sqrt{2\pi\tau}}\left\{\exp\left(-\frac{(y-m^*)^2}{2\tau}\right) - \exp\left(\frac{s}{\alpha\sigma^2}(2m^*+s-2b(s))\right)\exp\left(\frac{(y+m^*+s-2b(s))^2}{2\tau}\right)\right\}\,. \end{aligned}$$

The set of lower bounds is then

$$L(s) = \frac{1}{2}\left(\text{Erfc}\left(\frac{b(s)-m^*}{\sqrt{\alpha\sigma^2}}\right) - \exp\left(\frac{s}{\alpha\sigma^2}(2m^*+s-2b(s))\right)\text{Erfc}\left(\frac{s+m^*-b(s)}{\sqrt{\alpha\sigma^2}}\right)\right)\,. \tag{5.16}$$

Note that $L(0) = L_1$ and $L(k) = L_4$. If we differentiate (5.16) and simplify the derivative at $s = 0$ and $s = k$, we obtain

$$L'(0) = \frac{1}{\sqrt{\alpha\sigma^2}}\left(\frac{1}{\sqrt{\pi}}e^{-\left(\frac{m^*}{\sqrt{\alpha\sigma^2}}\right)^2} - \frac{m^*}{\sqrt{\alpha\sigma^2}}\,\mathrm{Erfc}\left[\frac{m^*}{\sqrt{\alpha\sigma^2}}\right]\right) \tag{5.17}$$

and

$$L'(k) = -\frac{m}{\sigma^2}\,\exp\left(\frac{2km}{\sigma^2}\right)\,\mathrm{Erfc}\left[\frac{2\alpha m + k}{2\sqrt{\alpha\sigma^2}}\right]. \tag{5.18}$$

Note that $L'(k) < 0$, and $L'(0) > 0$ by (5.12) and by the remark that follows it. So we have proved the following result:

Lemma 5.3. *Let $a > \alpha$ and $m^* > 0$. Then $L(s)$, defined in (5.16), attains its maximum value at some $s \in (0, k)$.*

The maximum can be located numerically (cf. the discussion in the end of §7).

6. The Coupled Moments Equations

For the analysis in this section, we define

$$R(s,t) = \int_0^\infty e^{-sx}p(x,t)\,dx, \quad s \geq 0\,. \tag{6.1}$$

Multiplying the original partial differential equation (2.1) by e^{-sx}, integrating by parts from zero to infinity (which amounts to formally applying the Laplace transform), and using the boundary condition (2.3) we obtain

$$\frac{\partial R}{\partial t} - \alpha s\frac{\partial R}{\partial s} = \frac{1}{2}\sigma^2 s^2 R - \frac{1}{2}\sigma^2\frac{\partial p}{\partial x}(0,t) + ske^{-at}R - ke^{-at}p(0,t)\,, \tag{6.2}$$

where we have used (when $s > 0$)

$$\frac{\partial p}{\partial x}(x,t) \quad \text{is bounded as} \quad x \to \infty \quad \text{for each } t \tag{6.3}$$

and (2.4). Note that (2.4) implies

$$p(x,t) \to 0 \quad \text{as} \quad x \to \infty \quad \text{for each } t. \tag{6.4}$$

Recall that in (4.14) we defined $M(t) = \int_0^\infty p(x,t)\,dx$, and that we have the absorbing barrier condition (2.3), $p(0,t) = 0$ for all $t \geq 0$. Using the fact that $M(t) = R(0,t)$, and evaluating (6.2) at $s = 0$, we obtain

$$\frac{dM}{dt} = -\frac{1}{2}\sigma^2 \frac{\partial p}{\partial x}(0,t) \leq 0 \tag{6.5}$$

with the inequality following from the fact that $\dfrac{\partial p}{\partial x}(0,t) \geq 0$ in view of (2.3) and (2.7). Differentiating (6.2) with respect to s, we have

$$\frac{\partial R}{\partial t \partial s} - \alpha \frac{\partial R}{\partial s} - \alpha s \frac{\partial^2 R}{\partial s^2} = \sigma^2 s R + \frac{1}{2}\sigma^2 s^2 \frac{\partial R}{\partial s} + k e^{-at}(R + s\frac{\partial R}{\partial s}). \tag{6.6}$$

Setting $s = 0$ in (6.6), we obtain

$$\frac{d\mu}{dt} = \alpha\mu - k e^{-at} M(t)\,, \tag{6.7}$$

where $\mu(t)$ is the first moment of the probability density function $p(x,t)$ given by

$$\mu(t) \equiv \int_0^\infty x p(x,t)\,dx = -\frac{\partial R}{\partial s}(0,t)\,; \tag{6.8}$$

that is, $\mu(t)$ is the mean PSA level at time t.

To develop additional results regarding the first moment $\mu(t)$, we will need some preliminary lemmas.

Lemma 6.1. *Let $f(\cdot)$ be continuous and let $g(\cdot)$ be differentiable and monotonic on $[a,b]$. There exists $\xi \in [a,b]$ such that*

$$\int_a^b g(x)f(x)\,dx = g(a)\int_a^\xi f(x)\,dx + g(b)\int_\xi^b f(x)\,dx\,.$$

Proof of Lemma 6.1. Let $F'(x) = f(x)$. By the Intermediate Value Theorem (g is monotonic), there exists $\xi \in [a, b]$ such that

$$\int_a^b F(x)g'(x)\,dx = F(\xi)\int_a^b g'(x)\,dx = F(\xi)(g(b) - g(a)).$$

Using $\int_a^\xi f(x)\,dx = F(\xi) - F(a)$, $\int_\xi^b f(x)\,dx = F(b) - F(\xi)$, and integration by parts, we have

(6.9)

$$\begin{aligned}\int_a^b f(x)g(x)\,dx = \int_a^b F'(x)g(x)\,dx &= F(b)g(b) - F(a)g(a) - \int_a^b F(x)g'(x)\,dx \\ &= F(b)g(b) - F(a)g(a) - F(\xi)(g(b) - g(a)) = g(a)(F(\xi) - F(a)) + g(b)(F(b) - F(\xi)) \\ &= g(a)\int_a^\xi f(x)\,dx + g(b)\int_\xi^b f(x)\,dx\,. \qquad \square\end{aligned}$$

Lemma 6.2. *Let μ, k, a, M, α and p be as described earlier. For any $\varepsilon > 0$, there exist ξ_1, ξ_2, and ξ_3 with $0 \le \xi_1 \le \xi_2 \le \varepsilon$ and $0 \le \xi_3 \le \varepsilon$ such that*

$$\frac{d\mu}{dt} \ge \left(\alpha\varepsilon - ke^{-at}\right)M(t) + \frac{\alpha\varepsilon\xi_2}{2}(p(\xi_2, t) - p(\xi_1, t)) - \frac{\alpha\varepsilon^2}{2}p(\xi_3, t)\,. \tag{6.10}$$

Proof of Lemma 6.2. Let $\varepsilon > 0$. From integration by parts we have

$$\int_0^\varepsilon (\varepsilon - x)xp_x(x, t)\,dx = -\varepsilon\int_0^\varepsilon p(x, t)\,dx + 2\int_0^\varepsilon xp(x, t)\,dx\,. \tag{6.11}$$

Using (6.7) and (6.11), and estimating from below the improper integral of $xp(x, t)$ in the following equation, we obtain

$$\begin{aligned}\frac{d\mu}{dt} &= \alpha\mu - ke^{-at}M(t) = \alpha\int_0^\infty xp(x, t)\,dx - ke^{-at}\int_0^\infty p(x, t)\,dx \\ &= \alpha\left(\int_0^\varepsilon xp(x, t)\,dx + \int_\varepsilon^\infty xp(x, t)\,dx\right) - ke^{-at}\left(\int_0^\varepsilon p(x, t)\,dx + \int_\varepsilon^\infty p(x, t)\,dx\right) \\ &\ge \left(\alpha\varepsilon - ke^{-at}\right)\int_\varepsilon^\infty p(x, t)\,dx + \left(\frac{\alpha\varepsilon}{2} - ke^{-at}\right)\int_0^\varepsilon p(x, t)\,dx \qquad (6.12)\\ &\quad + \frac{\alpha}{2}\int_0^\varepsilon (\varepsilon - x)xp_x(x, t)\,dx + \frac{\alpha\varepsilon}{2}\int_0^\varepsilon p(x, t)\,dx - \frac{\alpha\varepsilon}{2}\int_0^\varepsilon p(x, t)\,dx \\ &= \left(\alpha\varepsilon - ke^{-at}\right)\int_0^\infty p(x, t)\,dx + \frac{\alpha}{2}\int_0^\varepsilon (\varepsilon - x)xp_x(x, t)\,dx - \frac{\alpha\varepsilon}{2}\int_0^\varepsilon p(x, t)\,dx\,.\end{aligned}$$

Applying Lemma 6.1 with $g(x) = \varepsilon - x$ and $f(x) = xp_x(x,t)$ for fixed t, we have that there exists $\xi_2 \in [0, \varepsilon]$ such that

$$\int_0^{\varepsilon} (\varepsilon - x) x p_x(x,t)\, dx = \varepsilon \int_0^{\xi_2} x p_x(x,t)\, dx. \tag{6.13}$$

One more application of Lemma 6.1 with $g(x) = x$ and $f(x) = p_x(x,t)$ for fixed t yields $\xi_1 \in [0, \xi_2]$ such that

$$\int_0^{\xi_2} x p_x(x,t)\, dx = \xi_2 \int_{\xi_1}^{\xi_2} p_x(x,t)\, dx = \xi_2 (p(\xi_2,t) - p(\xi_1,t)). \tag{6.14}$$

Combining (6.12)–(6.14) and recalling that $M(t) = \int_0^\infty p(x,t)\, dx$, we have

$$\frac{d\mu}{dt} \geq \left(\alpha\varepsilon - ke^{-at}\right) M(t) + \frac{\alpha\varepsilon\xi_2}{2}(p(\xi_2,t) - p(\xi_1,t)) - \frac{\alpha\varepsilon^2}{2} p(\xi_3,t)\,. \tag{6.15}$$ □

Now we note that the second term on the right-hand side of (6.15) can be estimated as

$$\frac{\alpha\varepsilon\xi_2}{2} |(p(\xi_2,t) - p(\xi_1,t))| \leq \alpha\varepsilon^2 \max_{x\in[0,\varepsilon]} p(x,t) \leq \alpha\varepsilon^2 f^m e^{-\alpha t},$$

while the third term is less than or equal to $(\alpha\varepsilon^2/2) f^m e^{-\alpha t}$ by application of (2.8) and (2.16). Thus we have

$$\frac{d\mu}{dt} \geq \left(\alpha\varepsilon - ke^{-at}\right) M(t) - \frac{3}{2}\alpha\varepsilon^2 f^m e^{-\alpha t}\,. \tag{6.16}$$

Applying $0 < L \leq M(t) \leq 1$ for all $t \geq 0$ (cf. (4.16)), we can write

$$\frac{d\mu}{dt} \geq \alpha\varepsilon L - ke^{-at} - \frac{3}{2}\alpha\varepsilon^2 f^m e^{-\alpha t}\,. \tag{6.17}$$

Since (6.17) holds for all $\varepsilon > 0$, for each fixed t we can maximize its right-hand side with respect to ε, obtaining $\varepsilon = Le^{\alpha t}/(3f^m)$, and thus

$$\frac{d\mu}{dt} \geq \frac{\alpha L^2}{6f^m} e^{\alpha t} - ke^{-at}\,. \tag{6.18}$$

Note that the right-hand side of (6.18) tends to infinity as $t \to \infty$.

Theorem 6.3. *The mean PSA level, $\mu(t)$, remains positive for all $t > 0$ and there are two alternatives in the evolution of the mean PSA level. Either $\mu'(t) > 0$ for all $t > 0$, or there exists a unique $T > 0$ such that $\mu' < 0$ on $[0, T]$ and $\mu' > 0$ on $[T, \infty]$. We call such T "the turning time."*

Proof of Theorem 6.3. Suppose that there exists a finite time T^0 with $\mu(T^0) = \int_0^\infty p(x, T^0)\, dx = 0$. Then $p(x, T^0) = 0$ for all $x \geq 0$, and thus $M(T^0) = 0$, which is not possible since $M(t) \geq L > 0$ for each t (cf. (4.16)). Suppose now that $\mu'(t_1) < 0$ for some $t_1 > 0$. Since $L > 0$ (cf. (5.4), (5.8), and Theorem 5.1), by (6.18) there exists $t_2 > t_1$ with $\mu'(t_2) > 0$, and therefore there exists $T \in (t_1, t_2)$ with $\mu'(T) = 0$. Differentiating (6.7), we have

$$\frac{d^2\mu}{dt^2}(T) = \alpha\frac{d\mu}{dt}(T) + kae^{-aT}M(T) - ke^{-aT}M'(T) = kae^{-aT}M(T) - ke^{-aT}M'(T) > 0\,, \tag{6.19}$$

since $M' \leq 0$ by (6.5). It follows that any critical point of μ must be a minimum. In addition, if there were two or more minima, it would imply that there exists a local maximum, contradicting (6.19). Thus the minimum is unique. □

If t^* is defined as the unique solution of

$$\frac{\alpha L^2}{6f^m}e^{\alpha t^*} - ke^{-at^*} = 0, \tag{6.20}$$

then, in view of (6.18), the average PSA, $\mu(t)$, will start increasing before the time t^* and an upper bound for the turning time is

$$t^* = \frac{1}{a+\alpha}\ln\frac{6kf^m}{\alpha L^2}\,. \tag{6.21}$$

We next obtain another upper bound for the turning time, T, using the solution to the deterministic problem (2.5), (2.6) for the case when $m = \mu(0) = \int_0^\infty xf(x)\, dx > k/(a+\alpha)$. Subtracting (2.5) from (6.7), we have

$$\frac{d}{dt}(\mu - X) = \alpha(\mu - X) + ke^{-at}(1 - M(t)) \geq \alpha(\mu - X)$$

with $\mu(0) - X(0) = m - m = 0$. Thus $\mu(t) \geq X(t)$ for all $t \geq 0$ and $\mu'(t) \geq X'(t)$ for all $t \geq 0$. From this we conclude that if t^{**} is a critical point of (2.5), then we have $\mu'(t^{**}) \geq X'(t^{**}) = 0$, and thus the time t^{**} is past the turning point T (cf. Figure 3 and concluding remarks in §7). So we have another upper bound on T:

$$T \le t^{**} = \frac{1}{a+\alpha} \ln \frac{ka}{\alpha(m(a+\alpha)-k)} \,. \tag{6.22}$$

We can also estimate the turning time from below. Since $\mu'(T) = 0$, we have from (6.7)

$$e^{-aT} = \frac{\alpha\mu(T)}{kM(T)} \qquad \text{or} \qquad T = \frac{1}{a} \ln \left(\frac{kM(T)}{\alpha\mu(T)} \right) . \tag{6.23}$$

We note that $M(t) \ge L$ and $\mu(T) < \mu(0)$, so that

$$T = \frac{1}{a} \ln \left(\frac{kM(T)}{\alpha\mu(T)} \right) \ge \frac{1}{a} \ln \left(\frac{kL}{\alpha\mu(0)} \right) \equiv T^* \,. \tag{6.24}$$

The bounds identified above for the time when a relapse in PSA level may occur (turning time T) for the average prostate cancer patient are helpful in determining guidelines for when future treatments should be considered, because lower doses of radiation may be more appropriate if disease levels are low.

7. Numerical Analysis of the Moments

In this section we focus on the numerical approximation of the quantities discussed in the previous sections. We pick $x_0 \ge 0$ and integrate from x_0 to ∞ the partial differential equation (2.1) with respect to x. Using integration by parts and (6.4), we obtain

$$\frac{d}{dt} \int_{x_0}^{\infty} p(x,t)\,dx = -\frac{\sigma^2}{2} p_x(x_0,t) + p(x_0,t) \left(\alpha x_0 - k e^{-at} \right) \,, \tag{7.1}$$

where $p_x = \partial p / \partial x$. Similarly, multiplying (2.1) by x and x^2, respectively, we can obtain

$$\begin{aligned} \frac{d}{dt} \int_{x_0}^{\infty} x p(x,t)\,dx &= \alpha \int_{x_0}^{\infty} x p(x,t)\,dx - k e^{-at} \int_{x_0}^{\infty} p(x,t)\,dx \\ &\quad + \frac{\sigma^2}{2} p(x_0,t) + x_0 \left[-\frac{\sigma^2}{2} p_x(x_0,t) + p(x_0,t) \left(\alpha x_0 - k e^{-at} \right) \right] \,, \end{aligned} \tag{7.2}$$

and

$$\begin{aligned}\frac{d}{dt}\int_{x_0}^{\infty} x^2 p(x,t)\,dx &= 2\alpha\int_{x_0}^{\infty} x^2 p(x,t)\,dx - 2ke^{-at}\int_{x_0}^{\infty} xp(x,t)\,dx \\ &\quad + \sigma^2\int_{x_0}^{\infty} p(x,t)\,dx + \sigma^2 x_0 p(x_0,t) \\ &\quad + x_0^2\left[-\frac{\sigma^2}{2}p_x(x_0,t) + p(x_0,t)\left(\alpha x_0 - ke^{-at}\right)\right].\end{aligned} \tag{7.3}$$

If we define the second moment, $\mu_2(t) \equiv \int_0^\infty x^2 p(x,t)\,dx$, then the above equations yield (6.5), (6.7), and

$$\mu_2'(t) = 2\alpha\mu_2(t) - 2ke^{-at}\mu(t) + \sigma^2 M(t). \tag{7.4}$$

Since it appears that most of the information regarding the success/failure of the irradiation treatment is contained in $M(t) = \int_0^\infty p(x,t)\,dx$ and the moments $\mu(t)$ and $\mu_2(t)$ rather than in the pointwise values of $p(x,t)$, we have focused our attention on the numerical approximation of these three quantities. This then allows us to modify the usual numerical solvers for parabolic partial differential equations to compute the desired quantities efficiently and also somewhat elegantly. In what follows, we will discuss the numerical algorithm for approximating $M(t)$ at equidistant time steps $j\Delta t$, $j = 1, 2, \ldots$; once these approximations are computed, approximations for the solutions of the ordinary differential equations for μ and μ_2 can be computed on the same grid.

Description of the PDE solver. We now consider the partial differential equation (2.1) and describe the numerical algorithm to produce an approximation to $M(t)$ given by (4.14). We first observe that $M(t)$ should not be difficult to approximate; in view of (6.5), if we have an approximation to $p_x(0,t)$, then we can easily solve the ordinary differential equation (6.5). This yields adequate results in many cases, but in some cases an alternative approach, described in the next paragraph, produces more accurate results with the same discretization parameters.

To describe the alternative method, we first observe that equation (7.1) allows one to approximate $\int_{x_0}^\infty p(x, j\Delta t)\,dx$ by solving a simple ordinary differential equation if the value of the integral is known at time $t = 0$ and if the right-hand side of (7.1) can be computed at any time $t \geq 0$ (cf. description of the ODE solver below). The remaining part of $M(j\Delta t)$, the integral $\int_0^{x_0} p(x, j\Delta t)\, dx$, can then be approximated using a computed approximate solution to the partial differential equation (2.1) and an appropriate quadrature rule. Considering the discretization error in the approximate solution to the partial differential equation (see the next paragraph), the trapezoidal rule, which is of second order, is all that will be needed.

The approximate solution to the initial-boundary value problem (2.1)–(2.4) is computed using the Crank–Nicolson finite difference scheme, whose discretization error is of second order in both space and time. This scheme is implicit in time and ensures numerical stability of the results. If we denote the approximation to $p(i\Delta x, j\Delta t)$ by p_i^j, then the numerical scheme has the following form:

$$\frac{p_i^{j+1} - p_i^j}{\Delta t} = \frac{1}{2}\left(D_i p^{j+1} + D_i p^j\right),$$

where $D_i p^j$ denotes the space discretization of the right-hand side of (2.1) at $x = i\Delta x$ and $t = j\Delta t$, so that

$$D_i p^j = \frac{\sigma^2}{2}\,\frac{p_{i+1}^j - 2p_i^j + p_{i-1}^j}{(\Delta x)^2} - \frac{p_{i+1}^j - p_{i-1}^j}{2\Delta x}\left(\alpha x_i - k e^{-aj\Delta t}\right) - \alpha p_i^j.$$

Instead of solving on an infinite domain $(0, \infty)$ for x, we first replace the domain by a finite domain $(0, X)$, $X > 0$, and supply a Dirichlet boundary condition

$$p(X, t) = 0 \qquad \text{for all } t > 0,$$

corresponding to another absorbing barrier at a high PSA level, X.

Description of the ODE solver. After the partial differential equation has been solved and the discrete values $M(j\Delta t)$, $j = 1, 2, \ldots$, have been obtained, we solve the ordinary differential equations (6.7) and (7.4) for μ and μ_2 to obtain the approximations to $\mu(j\Delta t)$ and $\mu_2(j\Delta t)$, $j = 1, 2, \ldots$. Since the values $M(j\Delta t)$ already carry a discretization error of $\mathcal{O}(\Delta x^2 + \Delta t^2)$, nothing more than a second-order numerical scheme is needed to approximate μ and μ_2.

Notice that all three differential equations (6.7), (7.1), and (7.4) are of the form

$$y'(t) = c y(t) + f(t),$$

where c is a constant. In order to avoid instability of the numerical approximation of the solution, $y(t)$, we have chosen an implicit scheme, the trapezoidal method. Denoting the approximations to $y(j\Delta t)$ and $f(j\Delta t)$ by y_j and f_j, respectively, the numerical approximation to the solution is computed by

$$\frac{y_{j+1} - y_j}{\Delta t} = \frac{1}{2}\left[c(y_{j+1} + y_j) + (f_{j+1} + f_j)\right],$$

which is (because of the linearity of the differential equation) easily manipulated into an explicit expression for y_{j+1},

$$y_{j+1} = \frac{2 + c\Delta t}{2 - c\Delta t} y_j + \frac{\Delta t}{2 - c\Delta t}(f_{j+1} + f_j).$$

This expression is then used to compute the approximations to $M(j\Delta t)$, $\mu(j\Delta t)$ and $\mu_2(j\Delta t)$.

The input parameters (m, k, a, and α) for numerical simulation were determined by data fitting based on studies of prostate cancer and its treatments at the University of Michigan Medical School (cf. [2], [4]–[7]). Below we focus on two specific cases. The first case had the input parameters $\mu(0) = m = 28.2093$, $k = 11.8359$, $a = 0.289246$, and $\alpha = 0.131124$. The second case had the input parameters $\mu(0) = m = 47.8178$, $k = 25.7138$, $a = 0.534273$, and $\alpha = 0.0356484$. These two particular cases were also chosen to contrast two situations. In the first case, the deterministic solution of (2.5), (2.6) deviates strongly from the mean PSA level obtained from the stochastic model (2.1)–(2.4). In the second case, the deterministic solution deviates only slightly from the mean PSA level for an extended period of time (cf. Figures 3 and 4). In both cases we used $\sigma = 1$ (cf. [2]). We note that the majority of cases will be confined to the strip $[\mu(t) - \Sigma(t), \mu(t) + \Sigma(t)]$, where $\Sigma(t) = \sqrt{\mu_2(t) - \mu^2(t)}$.

Now we examine (for the cases described above) theoretical bounds on turning times derived in §6. First we estimate L. In both cases $a > \alpha$ and $L_1 > L_4$ (L_1 applies since $k < m(a + \alpha)$), so we use (5.2) and the second inequality in (5.8). We obtain $0.0218 \leq L \leq 0.497$ for the first case and $0.529 \leq L \leq 0.752$ for the second case.

Remark 7.1. While (5.2) produces a better lower bound for L than the first inequality in (5.8), they both can be significantly improved for the first case to obtain $0.432 \le L \le 0.497$ by using Lemma 5.3 and analyzing (5.16) as s decreases from k to 0 (cf. Figure 2). The lower bound on L for the second case can be slightly improved ($0.535 \le L \le 0.752$) by the same method.

We note that since $k < m(a+\alpha)$, the bound (6.22) applies in both cases. We use $f^m = 20/(\sqrt{2\pi}m)$ in (6.21) consistent with the standard deviation in the initial PSA distribution density. For the first case, the upper bounds (6.21), (6.22) on the turning point T for mean PSA level are $t^* = 30.11$, $t^{**} = 16.79$, but (6.24) yields a negative lower bound. For the second case, the upper bounds are $t^* = 13.78$, $t^{**} = 9.69$, and the lower bound is $T^* = 3.89$. The cited bounds are given in months. We note that in both cases (6.22) gives a sharper estimate than (6.21) ($t^{**} < t^*$)[1].

The obtained bounds are in agreement with the numerical approximation of $\mu(t)$, where the turning times are 8.8 months in the first case and 8.93 months in the second case.

8. Conclusion

The stochastic model for the level of PSA following radiological treatment for prostate cancer, first described in [1] and studied in greater depth in this report, has several advantages over the corresponding deterministic "bi-exponential" model used to represent evolving PSA levels in a number of research studies. In addition to the exact solution of the stochastic model found in [1] in the case that $a = \alpha$, we have been able to describe the dynamics of PSA behavior for all parameter combinations, providing estimates for the biomedically important features of the solution. While the deterministic model sometimes allows PSA values to become negative, the use of an "absorbing boundary" condition for the stochastic model assures that the values are always nonnegative. The stochastic model also allows for distributed (rather than fixed) initial conditions, reflecting,

[1] If we use the lower bound on L discussed in Remark 7.1, then for the first case (6.21) provides a sharper upper bound on T than (6.22) ($15.96 = t^* < t^{**} = 16.79$). It also gives a positive lower bound $T^* = 1.12$ for the first case.

for example, the uncertainty in PSA measurements. In addition, the stochastic model allows for simulations that express the potential variability in outcomes for a single patient.

Applied to a population of patients, our analysis of the stochastic model allows for the determination and/or estimation and study of several important measures of treatment effectiveness. The transient fraction of non-cured patients, $M(t)$, and the ultimate treatment failure rate, $L = \lim_{t\to\infty} M(t)$, for which we have derived estimates and bounds, are two such examples. In particular, the bounds for L derived in §5 indicate that the treatment failure rate is always positive but can be shown to be small if the level of treatment k is large enough. Together, $M(t)$ and $\mu(t)$, the mean at time t of possible PSA levels for a given set of parameters and a given distribution of initial values, have been shown to solve a pair of coupled ordinary differential equations that allow for more detailed analysis.

For all parameter sets when the assumptions include a growing cancer, it was shown that $\mu(t)$ will eventually turn up (although this may happen long after a patient has succumbed to an unrelated cause of death). In some cases, the turning point for $\mu(t)$ may be early and is likely to provide a good indication of the time when follow-up treatment should be considered. For these reasons the upper and lower bounds found for the turning point may be important. It was also shown that $\mu(t)$ always exceeds the value of the solution $X(t)$ of the deterministic model for corresponding parameter values and initial conditions. In addition, since $X'(t) \leq \mu'(t)$, if X has a turning point (i.e., $k < m(a+\alpha)$, cf. [1]), then this turning point provides an upper bound for the turning point of μ. Numerical simulations suggest that the turning point for μ can come early or late, depending on the parameter values.

An additional benefit of the stochastic model is the ability to investigate the impact of variability on outcomes, determined in this case by PSA levels. In particular, the mean PSA level, $\mu(t)$, can be shown in simulations to turn up earlier as the model's variance σ^2 is increased or as the variance in the initial distribution grows larger. This is another way in which the stochastic model may provide insight (not possible in a deterministic model) into the manifestations and treatment of cancer.

Although we have not focused here on the estimation of model parameters, that is clearly a necessary and important step in the application of the model. Using PSA time series data made available by the University of Michigan Medical Center, we have found parameter values which allowed for an accurate representation of patient trajectories using the mean PSA level $\mu(t)$. Simulation of random PSA trajectories derived using the same parameter values provides an indication of the extent to which different outcomes might be observed.

References

[1] P.W.A. Dayananda, J. Kemper, M. Shvartsman, A stochastic model for prostate-specific antigen levels, Math. Biosci. 190 (2004) 113–126.

[2] P.W.A. Dayananda, J.M.G. Taylor, D.G. Whiting, Prostate cancer: progression of prostate-specific antigen after external beam irradiation, Math. Biosci. 182 (2003) 127–134.

[3] Friedman A., Partial Differential Equations of Parabolic Type, Prentice Hall (1964)

[4] J.M.G. Taylor, K. Griffith, H.M. Sandler, Definitions of biochemical failure in prostate cancer following radiation therapy, Int. J. Radiat. Oncol. Biol. Phys. 50 (2001) 1212–1219.

[5] M. Yu, N.J. Law, J.M.G. Taylor, H.M. Sandler, Joint longitudinal-survival-cure models and their application to prostate cancer, Statistica Sinica 14 (2004) 819–846.

[6] H.M. Sandler, R.L. Dunn, P.W. McLaughlin, J.A. Hayman, M.A. Sullivan, J. M. G. Taylor, Overall survival after PSA-detected recurrence following conformal radiation therapy, Int. J. Radiat. Oncol. Biol. Phys. 48 (2000) 629–633.

[7] N.J. Law, J.M.G. Taylor, H.M. Sandler, The joint modeling of a longitudinal disease progression marker and the failure time process in the presence of cure, Biostatistics 3 (2002) 547–563.

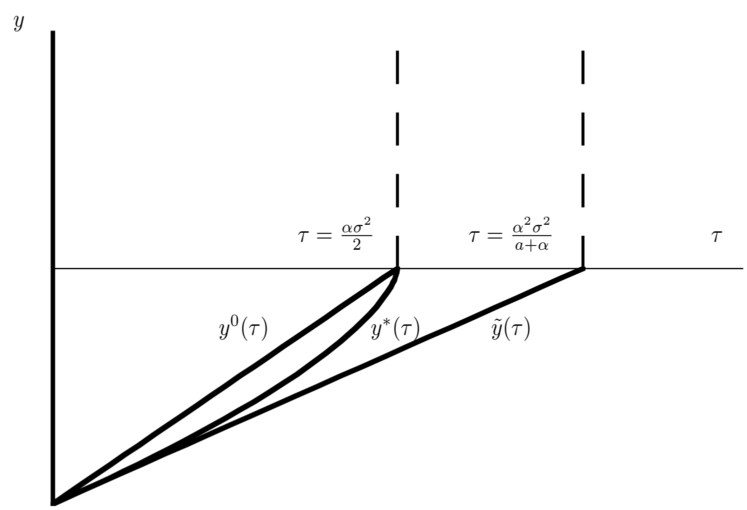

FIGURE 1. Case $a < \alpha$ with $\mathcal{S} \subset \mathcal{D} \subset \mathcal{T}$

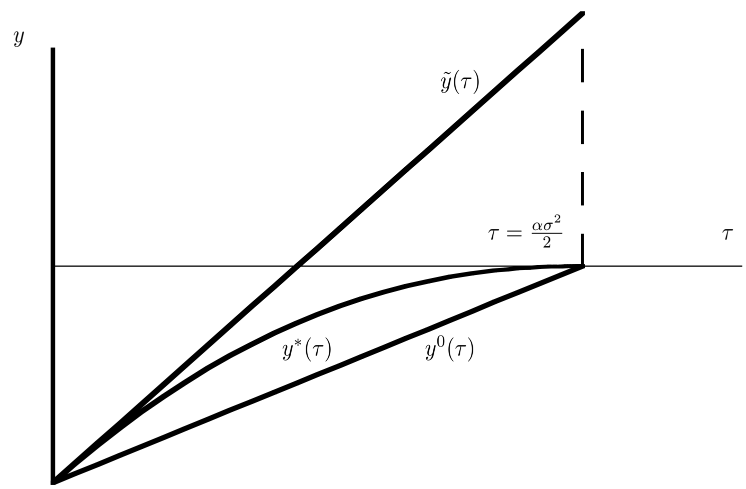

FIGURE 2. Case $a > \alpha$ with $\mathcal{T}' \subset \mathcal{D} \subset \mathcal{S}$ and $\mathcal{T}^+ \subset \mathcal{D} \subset \mathcal{S}$

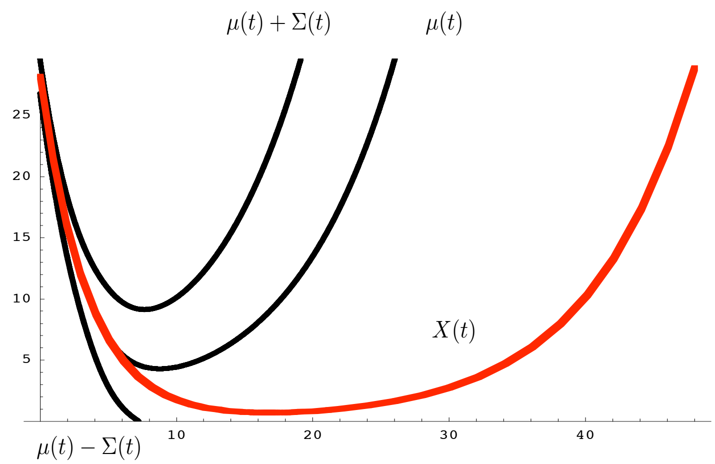

FIGURE 3. Numerical Simulation with $\mu(0) = m = 28.2093$

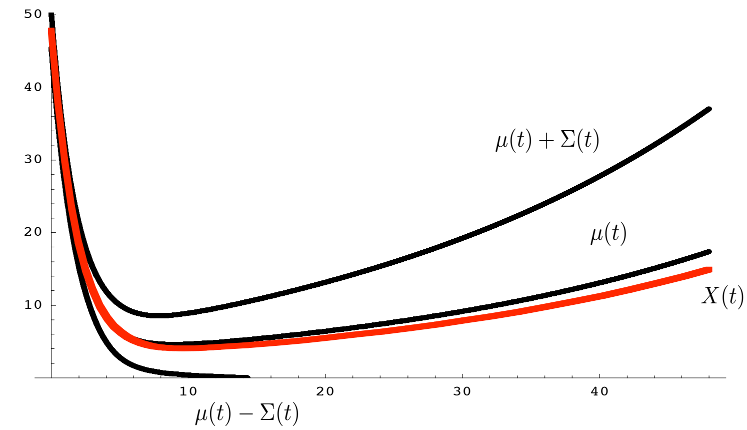

FIGURE 4. Numerical Simulation with $\mu(0) = m = 47.8178$