Mathematical model for the estrogen paradox in breast cancer treatment.

Rachid Ouifki *, Segun I. Oke

[1] *North-West University, Department of Mathematics and Applied Mathematics, Mafikeng campus, Private Bag X2046, Mmabatho 2735, South Africa*

[2] *Department of Mathematics and Applied Mathematics, University of Pretoria, Private bag X20 Hatfield 0028, South Africa*

Abstract

Estrogen is known to stimulate the growth of breast cancer, but is also effective in treating the disease. This is referred to as the "estrogen paradox". Furthermore, short-term treatment with estrogen can successfully eliminate breast cancer, whereas long-term treatment can cause cancer recurrence. Studies highlighted clinical correlations between estrogen and the protein p53 which plays a pivotal role in breast cancer suppression. We sought to investigate how the interplay between estrogen and p53 impacts the dynamics of breast cancer, and further explore if this could be a plausible explanation for the estrogen paradox and the paradoxical tumor recurrence that results from prolonged treatment with estrogen.

For this, we propose a novel ODE based mathematical model that accounts for dormant and active cancer cells, along with the estrogen hormone and the p53 protein. We analyze the model's global stability behavior using the Poincaré-Bendixson theorem and results from differential inequalities. We also perform a bifurcation analysis and carry out numerical simulations that elucidate the roles of estrogen and p53 in the estrogen paradox and its long term estrogen paradoxical effect.

The mathematical and numerical analyses suggest that the apparent paradoxical role of estrogen could be the result of an interplay between estrogen and p53, and provide explicit conditions under which the paradoxical effect of long-term treatment may be prevented.

Keywords: Breast cancer, Estrogen, p53, Estrogen paradox, Mathematical model, Global stability, Bifurcation.

1. Introduction

Cancer is initiated when healthy cells grow beyond control to form a mass known as a tumor. Breast cancer, which affects both humans and other mammals, can take place in the inner lining of milk ducts (ductal carcinomas), or the lobules of the breast (lobular carcinomas) [1]. The most prevalent type of breast cancer is the hormone receptor-positive luminal breast cancer. Worldwide, breast cancer is contracted by 2.1 million women annually, and it is the cause of most cancer-related deaths among women. In 2018, it was appraised that 627000 women died from breast cancer, accounting for about 15 % of the total cancer deaths among women [1, 2].

While these tumors are commonly responsive to endocrine therapy, cellular heterogeneity and the acquired ability of tumor cells to go through cell state switching make it challenging to target these populations completely using conventional methods. This further makes their eradication challenging [1, 2].

It is suggested that increasing levels of estrogen increase the risk of breast cancer development with about 75% of all breast cancers expressing estrogen receptors (ER) and/or progesterone receptors [3], signifying that inhibition of estrogen activity by endocrine treatments may be an effective therapy for patients with breast cancer.

*Corresponding author
Email address: ouifkir@gmail.com (Rachid Ouifki)

Based on a pre-clinical experiment in [4], the authors attributed the estrogen-induced breast cancer to estrogen receptor α, reporting at the same time that, paradoxically, estrogen induces apoptosis in breast cancer cells among postmenopausal women. This finding led them to deduce that estrogen may be used to treat selected postmenopausal breast cancer patients. The therapeutic benefits of estrogen in treating breast cancer were further supported by autopsy studies and computer-based modeling in [5].

Estrogens have been used to effectively treat breast cancer since 1944, when Haddow et al. [6] used diethylstilbestrol (DES) to treat fourteen patients with advanced breast cancer. In the same year, Binnie [7] highlighted the benefits of estrogen in treating advanced breast cancer, especially when used in combination with radiotherapy. This was followed by more research on the use of high-dose estrogen (HDE) in breast cancer treatment [8–12].

Until the antiestrogen drug tamoxifen was introduced by Cole et al. [13] in 1971, HDE was the preferred treatment for postmenopausal women with advanced breast cancer. The use of estrogens for breast cancer treatment was reconsidered in the 1990s when it became evident that HDE has effectively treated patients already exposed to multiple hormone therapies [14–20]. The use of HDE as treatment in selected patients with metastatic breast cancer that have been initially exposed to endocrine was also established [14]. Diverse clinical trials have been carried out using different types of estrogens such as DES, Ethinyl estradiol (EE), estradiol (E2), with highly positive responses, predominantly in patients that were resistant to hormone therapies [21, 22]. Even though the potential for toxicity is higher with estrogen therapy than it is with tamoxifen, the tolerability in most patients with estrogen therapy is better than with chemotherapy [14].

The apparent contradiction between the role of estrogen in the development of breast cancer and its therapeutic benefits in treating this disease was first pointed out in the 1940s by Haddow et al. [6]; it has been termed the "*estrogen paradox*". It should be stressed that another component of the estrogen paradox was reported recently, whereby treatment with estrogen alone for a short term (5 to 9 years) decreased the risk of breast cancer recurrence in [23, 24], while, paradoxically, a study in [25, 26] showed that the risk increased for long-term treatments (more than 20 years).

Several studies have been dedicated to describing the possible mechanisms behind these two components of the estrogen paradox [27–29]. The short-term reduction of estrogen-induced breast tumor was attributed to cell apoptosis of breast cancer cells [27]. Numerous studies have provided insight into the mechanism underlying estrogen-induced apoptosis, see [28, 29] and references therein. According to [29], even after long term antiestrogen therapy, HDE can still restore estrogen signaling which is key for triggering apoptotic tumor cell death. As mentioned in [27], it is generally acknowledged that the paradoxical effect of estrogen can be attributed to: (a) the stimulation by estradiol of expression of breast cancer proliferation genes, (b) estradiol-induced increase in the rate of breast cell divisions, and (c) estradiol enhancement of cell mutations.

Regarding the paradoxical effect of long-term estrogen therapy on breast cancer, the authors in [27] proposed that cancer recurrence can be due to the presence of a reservoir of pre-existing occult breast cancers. This insight was supported by multiple studies using autopsy data, which confirmed the existence of occult undiagnosed breast cancers in approximately 7 % of women dying from unrelated causes, see [30] and references therein.

One of the important stages in tumor progression is tumor dormancy, a stage during which tumors can remain occult and undetected for a long time. During this stage, microscopic metastases are not noticeable before they progress to visible cancer cells over time. In breast cancer, metastases usually manifest asynchronously with the primary tumor, and become clinically obvious over time [31]. It has been reported that approximately 20% to 40% of breast cancers recur in distant organs, and are usually not discovered until several years after the primary tumor has been diagnosed. Such occurrences are particularly prominent in estrogen receptor positive (ER+), which predominantly reappears in bone, mostly several years after initial tumor diagnosis. This prolonged invisibility indicates that the metastasis progression is dormant, leading to cancer cells multiplying slowly or staying quiescent [31]. This observation was supported by autopsy procedures, performed on adults who died from non-cancerous causes, which provided tangible clinical evidence of tumor cells staying dormant throughout an individual's life without becoming active [32–34]. The work done in [32] identified dormant tumors in many organs, such as the breast, prostate, and thyroid. This condition has been described as cancer without disease [34].

Several explanations exist as to how cancer cells survive and remain dormant, and how they get revitalized to exit their dormant status [35–38]. In particular, [39] suggested that estradiol metabolites are directly genotoxic. Using *in vitro* studies, the authors showed that estradiol could be converted to 4-OH-estradiol, which can transform estrogen receptor (ER)-negative benign breast epithelial cells into carcinomas. Moreover, 4-OH-estradiol can also be oxidized to quinone metabolites, which cause mutations by directly altering the DNA, ultimately forcing healthy epithelial cells to become malignant. Estrogen also functions as a mitogen and can trigger cell division in breast tissue [40, 41].

The studies above presented some mechanisms that explain the paradoxical effect of estrogen in breast cancer development and treatment. However, these studies did not account for another factor that plays a key role in tumor suppression; that is the protein p53 which was identified by Arnold Levine in 1979. This protein, referred to as "the guardian of the genome", regulates cell division by keeping cells from growing and dividing too fast or in an uncontrolled way. There are three functions attached to this: growth arrest, DNA repair, and apoptosis [42, 43]. The growth arrest stops the progression of the cell cycle, preventing the reproduction of damaged DNA. The p53 may be activated by the transcription of proteins involved in DNA repair during this function. Apoptosis is the last recourse to avoid the multiplication of cells with abnormal DNA. Usually, the level of the p53 protein in normal cells is low, but DNA damage and other stress signals can prompt its proliferation which induces mutations [44, 45]. Furthermore, mutant p53 aids the multiplication of abnormal cells, which leads to cancer, with about half of all human tumors comprising p53 mutants. While p53 plays a central role in tumor suppression, a high level of it may fast-track the aging process through excessive apoptosis. It is, thus, crucial that the cellular concentration of p53 is strictly controlled.

Clinical correlations between estrogen and p53 have been reported [44, 46, 47]. In [44], the authors highlighted that estrogen, through its estrogen receptor (ERα), inhibits the transcriptional regulation of p53. Additionally, [46] hypothesized that p53 might regulate ER expression. However, [47] suggested that the p53 and ERα are mutually regulated and pointed out the existence of ER-positive breast cancer cases with mutant p53 tumor status, which would not be explained by this hypothesis.

The above studies highlight the ability of p53 to suppress breast cancer cells and the paradoxical role of estrogen in inducing both cancer cells apoptosis and cancer development. Therefore, we sought to investigate the interplay between estrogen, p53 and breast cancer. We are of the opinion that considering p53 alongside estrogen may further help to understand the mechanisms behind the estrogen paradox and its long-term component. Essentially, the competing mechanisms of estrogen and p53 suggest that, depending on which effect might predominate, breast cancer cells may grow or decline. This could explain some of the clinical observations that appeared to be paradoxical.

We propose an ODE based mathematical that accounts for dormant and active cancer cells, the estrogen hormone and the p53 protein. Stemming from the discussions above, the proposed model accounts for estrogen-induced apoptosis and dormant cancer cells' activation and considers the pivotal role that p53 plays in inhibiting the activation of dormant breast-cancer cells and suppressing active ones. The model also takes into account the regulation of p53 by estrogens, but ignores any possible effect of p53 on estrogen due to the lack of tangible clinical or epidemiological evidence [47].

To understand the interplay between the model's variables, we carry out global stability and bifurcation analyses of the model and use them to simulate cancer occurrence, elimination and recurrence scenarios.

The significance of mathematical models and their applications to research works on cancer cannot be overemphasized [40]. Several mathematical studies, including [40, 48, 49] have investigated cancer cells and treatment dynamics. Wei [48] worked on bifurcation analysis of a mathematical model of tumor growth in MCF-7 breast cancer line. The author explored the interactions of tumor cells, estradiol, natural killer (NK), Cytotoxic T lymphocytes (CTLs) cells, and white blood cells. The analysis revealed the coexistence of three equilibrium points that resulted in cancer immunoediting and provided valuable treatment strategies. While recognizing the effectiveness of these mathematical models, we note from reviewed literature that most of the models concentrate on describing tumor-immune system interaction that address cancers in general, and only a few looked into tumor dormancy and activation [34]. However, to this date, no mathematical models have considered the interplay between estrogen and p53 or how they shape the dynamics of breast cancer.

The paper is organized as follow: In the following section we formulate the mathematical model and discuss its underlying assumptions. In section 3 we investigate the model's well-posedness and carry out global stability and bifurcation analyses. Section 4 is dedicated to the model's numerical analysis where we simulate various scenarios relating to the estrogen paradox. The conclusion is presented in section 5.

2. Model formulation:

In this section, we formulate a mathematical model illustrating the relationship between dormant cancer cells, active cancer cells, excess estrogen and p53 tumor suppressor protein.

In formulating our model, we make the following assumptions:

- Both dormant cancer cells, T_d and active ones, T_a populations are assumed to grow logistically.
- Supported by [39–41], we assume that high estrogen levels stimulate dormant cells' activation. Furthermore, following [44, 45] we assume that p53 hinders the activation of such cells. Subsequently, we assume that the activation rate α depends on (E, P) and that the function $\alpha(E, P)$ increases with increasing values of E and decreasing P values.
- Based on [4, 5, 50], we assume that active cancer cells undergo an estrogen-induced apoptosis. Moreover, from [42, 43] we assume that p53 also induces apoptosis in breast cancer cells. Accordingly, we assume that the mortality rate μ depends on (E, P) and is an increasing function of both E and P.
- Estrogen and p53 levels are assumed to grow at a constant rate and decay at a constant per capita rate.
- Finally, to account for the estrogen-induced regulation of p53 reported in [44], we include an estrogen-dependent degradation rate, $\beta(E)$.
- For the sake of the model's biological feasibility, we assume that α, μ and β have positive values and are continuously differentiable with respect to their arguments. This ensures that the system is well-posed and enables us to carry out a global stability analysis of the system.

A schematic representation of the flows between the model's compartments is given in Figure 2.1.

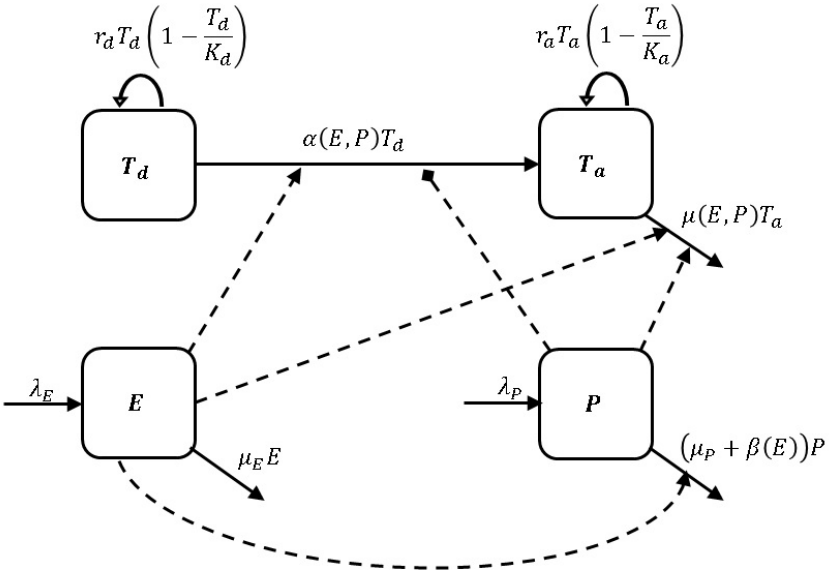


Figure 2.1: Model diagram. Solid arrows correspond to a change of state while the dashed ones represent positive contributions in the corresponding rate of transfer. The dashed line with a diamond end represents a negative contribution to the relevant rate of transfer.

Subsequently, in mathematical terms, we propose the following model equations that capture significant features of the established roles of estrogen and p53 and reflects certain aspects of our proposed hypothesis:

$$\begin{cases} \dfrac{dT_d}{dt} = \underbrace{r_d T_d\left(1-\dfrac{T_d}{K_d}\right)}_{\text{tumor proliferation}} - \underbrace{\alpha\left(E,P\right)T_d}_{\text{actiavtion of dormant cancer cells}} \\ \dfrac{dT_a}{dt} = \underbrace{\alpha\left(E,P\right)T_d}_{\text{actiavtion of dormant cancer cells}} + \underbrace{r_a T_a\left(1-\dfrac{T_a}{K_a}\right)}_{\text{tumor proliferation}} - \underbrace{\mu(E,P)T_a}_{\text{apoptosis}} \\ \dfrac{dE}{dt} = \underbrace{\lambda_E}_{\text{supply of estrogen}} - \underbrace{\mu_E E}_{\text{degradation}} \\ \dfrac{dP}{dt} = \underbrace{\lambda_P}_{\text{growth of p53}} - \underbrace{\beta\left(E\right)P}_{\text{estrogen-induced degradation}} - \underbrace{\mu_P P}_{\text{degradation}} \end{cases} \tag{2.1}$$

We note that the model does not include an explicit term for dormant cancer cells' apoptosis. However, the model can still be used to accommodate the commonly used linear apoptosis rate, because the balance between the proliferation and apoptosis can be transformed through some simple algebraic manipulation into a logistic term.
A description of the model's variables and parameters is presented in Tables 2.1 and 2.2.

Variable	**Symbol**
Dormant cancer cells	$T_d(t)$
Active cancer cells	$T_a(t)$
Estrogen hormones	$E(t)$
Tumor suppressor protein $p53$	$P(t)$

Table 2.1: Description of the model's variables

Description of Parameters	**Symbol**	**Value**	**Source**
Growth rate of dormant cancer cells	r_d	0.5140 per cell per day	[38]
Growth rate of active cancer cells	r_a	0.5822 per cell per day	[41]
Dormant cancer cells carrying capacity	K_d	10^{11} cells	Assumed
Active cancer cells carrying capacity	K_a	1.47×10^{12} cells	[33]
Activation rate of dormant cancer cells to active cancer cells	α	Varies	
Apoptosis rate of active tumor cells	μ	Varies	
Natural death rate of estrogen hormones	μ_E	0.97 per cell per day	[41]
Natural death rate of $p53$	μ_P	0.02, 2.5×10^{-4} per cell per day	[38]
Source rate of estrogen	λ_E	1.3×10^4 per day	Assumed
Source rate of $p53$	λ_P	0.01, 0.5 per day	[41]

Table 2.2: Symbols, values and units of the parameters used in model (2.1).

3. Model analysis:

3.1. Model well-posedness:

Before we proceed with the analysis of the proposed model (2.1), we first prove that it is well-posed in a biologically feasible domain. In fact, by using the variation of constants formula to (2.1), we obtain

$$\begin{cases} T_d(t) = T_d(0)\, e^{\int_0^t r_d\left(1-\frac{T_d(s)}{K_d}\right)-\alpha(E(s),P(s))ds} \\ T_a(s) = \mathcal{U}(t,0)\, T_a(0) + \int_0^t \mathcal{U}(t,s)\, \alpha(E(s), P(s))\, T_d(s)\, ds \\ E(t) = E(0)\, e^{-\mu_E t} + \frac{\lambda_E\left(1-e^{-\mu_E t}\right)}{\mu_E} \\ P(t) = \mathcal{V}(t,0)\, P(0) + \lambda_P \int_0^t \mathcal{V}(t,s)\, ds, \end{cases}$$

where $\mathcal{U}(t,s) = \exp\left(\int_0^t \left(r_a T_a(s)\left(1-\frac{T_a(s)}{K_a}\right) - \mu(E(s), P(s))\right) ds\right)$ and $\mathcal{V}(t,s) = \exp\left(\int_0^t (\beta(E(s)) + \mu_P)\, ds\right)$. This clearly shows that if $T_d(0), T_a(0), E(0)$ and $P(0)$ are positive, then so are $T_d(t), T_a(t), E(t)$ and $P(t)$.

The boundedness of the model's solutions will follow from the global stability results that we will prove in the next section. This ensures that solutions are defined for all time.

Hence, for any given positive initial condition, the corresponding solution is defined and positive for all $t \geq 0$.

3.2. Global stability:

In this section we use the Poincaré-Bendixson Theorem along with results from differential inequalities to analyze the global stability behavior of system (2.1). Let

$$\begin{cases} E_0 = \frac{\lambda_E}{\mu_E}, P_0 = \frac{\lambda_P}{\mu_P+\beta(E_0)} \\ \alpha_{\lambda_P}(E_0) = \alpha\left(E_0, \frac{\lambda_P}{\mu_P+\beta(E_0)}\right) \\ \mu_{\lambda_P}(E_0) = \mu\left(E_0, \frac{\lambda_P}{\mu_P+\beta(E_0)}\right) \\ T_d^* = \frac{K_d\left(r_d-\alpha_{\lambda_P}(E_0)\right)}{r_d} \\ T_a^* = \frac{1}{2}\frac{K_a}{r_a}\left(r_a - \mu_{\lambda_P}(E_0) + \sqrt{(r_a-\mu_{\lambda_P}(E_0))^2 + 4\frac{r_a\alpha_{\lambda_P}(E_0)T_d^*}{K_a}}\right). \end{cases} \tag{3.1}$$

We have the following global stability results:

Theorem 1.
1. *If $\alpha_{\lambda_P}(E_0) \geq r_d$ and $\mu_{\lambda_P}(E_0) \geq r_a$, then $\mathcal{E}_0 = (0,0,E_0,P_0)$ is globally asymptotically stable.*
2. *If $\alpha_{\lambda_P}(E_0) \geq r_d$ and $\mu_{\lambda_P}(E_0) \leq r_a$, then $\mathcal{E}_0$ becomes unstable and $\mathcal{E}^{\#} = \left(0, \frac{K_a\left(r_a-\mu_{\lambda_P}(E_0)\right)}{r_a}, E_0, P_0\right)$ is globally asymptotically stable.*
3. *If $\alpha_{\lambda_P}(E_0) < r_d$, then $\mathcal{E}^* = (T_d^*, T_a^*, E_0, P_0)$ is globally asymptotically stable.*

The proof of this theorem is given in the appendix.

Theorem 1 provides a relationship between λ_P and E_0 that governs the model's global stability behavior. It states that all dormant cancer cells will get activated if the activation rate is high enough ($\alpha_{\lambda_P}(E_0) \geq r_d$). The resulting activated cancer cells will persist if their mortality rate is low ($\mu_{\lambda_P}(E_0) \leq r_a$), but will be eliminated otherwise. Alternatively, if the activation rate is low ($\alpha_{\lambda_P}(E_0) \leq r_d$), dormant cancer cells will persist and serve as sustained reservoir for active cancer cells.

To put these results in the context of the estrogen paradox, we will explore in the next section, a special case of the activation rate α.

3.3. A special case: Estrogen paradox.

The studies in [39–41, 44, 45] suggest that the activation rate $\alpha(E,P)$ increases with increasing values of E and decreasing values of P. In this section, we hypothesize that the activation of dormant cancer cells is a result of a shift in the balance between the levels of estrogen and p53. Due to the lack of details on the activation rate, we assume for simplicity that: i. α is an increasing function of the ratio $\frac{E}{P}$, and ii. activation is only triggered when the ratio $\frac{E}{P}$ is above a threshold value. Subsequently, we replace $\alpha(E,P)$ by $\alpha\left(\frac{E}{P}\right)$ where the function $\alpha(\chi)$ is a continuously differentiable function that satisfies the following assumption:

$(\mathcal{A}_\alpha)$ $\alpha(\chi)=0$ if $\chi \le \chi_c$, for some positive threshold value χ_c and $\alpha(\chi)$ is increasing for $\chi > \chi_c$.

As a consequence of the above assumption we deduce the following properties:

- The function $\alpha(\chi)$ is invertible and increasing on $(\chi_c, +\infty)$, which implies that $\alpha(\chi) \ge r_d$ if and only if $\chi \ge \chi_d := \alpha^{-1}(r_d) > \chi_c$.
- Using (3.1), we have $\alpha_{\lambda_P}(E_0) = \alpha\left(\frac{E_0}{P_0}\right) = \alpha\left(\gamma_{\lambda_P}(E_0)\right)$, where $\gamma_{\lambda_P} := x \to \frac{(\mu_P+\beta(x))x}{\lambda_P}$.

Thus we have the following result:

Theorem 2. 1. *If $\mu_{\lambda_P}(E_0) \le r_a$, then the model always has a globally asymptotically stable active-tumor-endemic equilibrium. More precisely,*
   (a) *If $\gamma_{\lambda_P}(E_0) \ge \chi_d$, then $\mathcal{E}^{\#} = \left(0, \frac{K_a\left(r_a-\mu_{\lambda_P}(E_0)\right)}{r_a}, E_0, P_0\right)$ is globally asymptotically stable.*
   (b) *If $\gamma_{\lambda_P}(E_0) < \chi_d$, then $\mathcal{E}^* = (T_d^*, T_a^*, E_0, P_0)$ is globally asymptotically stable.*

2. *If $\mu_{\lambda_P}(E_0) \ge r_a$, then the model has a globally asymptotically stable active-tumor-endemic equilibrium if and only if $\chi_c \le \gamma_{\lambda_P}(E_0) < \chi_d$. More precisely*
   (a) *If $\gamma_{\lambda_P}(E_0) \ge \chi_d$, then $\mathcal{E}_0 = (0,0,E_0,P_0)$ is globally asymptotically stable.*
   (b) *If $\chi_c \le \gamma_{\lambda_P}(E_0) < \chi_d$, then $\mathcal{E}_0$ becomes unstable and $\mathcal{E}^* = (T_d^*, T_a^*, E_0, P_0)$ exists and is globally asymptotically stable.*
   (c) *If $0 \le \gamma_{\lambda_P}(E_0) < \chi_c$, then $\alpha\left(\frac{E_0}{P_0}\right) = 0$ and $\mathcal{E}^*$ reduces to $\mathcal{E}^{*0} = (K_d, 0, E_0, P_0)$ which is globally asymptotically stable.*

Theorem 2 gives a full description of the global stability and bifurcation behavior of model system (2.1) in terms of E_0. In particular, it states that the active tumor persists if and only if the condition $\mu_{\lambda_P}(E_0) \le r_a$ is satisfied, or the conditions $\mu_{\lambda_P}(E_0) \ge r_a$ and $\chi_c \le \gamma_{\lambda_P}(E_0) < \chi_d$ hold.

We note that the above conditions are implicit. Nonetheless, using monotonicity properties on the function β, the conditions on E_0 that are required for the global stability results can be derived explicitly.

We know from [44] that estrogen inhibits the transcriptional regulation of p53. We thus make the following assumption:

$(\mathcal{A}_\beta)$ The function $E \to \beta(E)$ is increasing.

We deduce from assumption $(\mathcal{A}_\beta)$ that the functions $E \to \gamma_{\lambda_P}(E)$ and $E \to \alpha_{\lambda_P}(E)$ are increasing, which implies that:

- $\alpha_{\lambda_P}(E_0) \ge r_d$ if and only $E_0 \ge E_{0d} := \gamma_{\lambda_P}^{-1}\left(\alpha^{-1}(r_d)\right)$.
- $\alpha\left(\frac{E_0}{P_0}\right) = 0$ if and only if $\frac{E_0}{P_0} = \gamma_{\lambda_P}(E_0) < \chi_c$, that is $E_0 < E_{0c} := \gamma_{\lambda_P}^{-1}(\chi_c)$.
  In this case, $T_a^* = \frac{1}{2}\frac{K_a}{r_a}\left(r_a - \mu_{\lambda_P}(E_0) + |\mu_{\lambda_P}(E_0) - r_a|\right)$, which is equal to 0 if $\mu_{\lambda_P}(E_0) \ge r_a$, and is equal to $\frac{K_a\left(r_a-\mu_{\lambda_P}(E_0)\right)}{r_a}$ if $\mu_{\lambda_P}(E_0) \le r_a$.

With this, the results in Theorem 2 read as follows:

Proposition 3. 1. *If $\mu_{\lambda_P}(E_0) \leq r_a$, then the model always has a globally asymptotically stable active-tumor-endemic equilibrium. More precisely,*
   (a) *If $E_0 \geq E_{0d}$, then $\mathcal{E}^{\#} = \left(0, \frac{K_a\left(r_a - \mu_{\lambda_P}(E_0)\right)}{r_a}, E_0, P_0\right)$ is globally asymptotically stable.*
   (b) *If $E_0 < E_{0d}$, then $\mathcal{E}^* = (T_d^*, T_a^*, E_0, P_0)$ is globally asymptotically stable.*
2. *If $\mu_{\lambda_P}(E_0) \geq r_a$, then the model has a globally asymptotically stable active-tumor-endemic equilibrium if and only if $E_{0c} \leq E_0 < E_{0d}$. More precisely*
   (a) *If $E_0 \geq E_{0d}$, then $\mathcal{E}_0 = (0, 0, E_0, P_0)$ is globally asymptotically stable.*
   (b) *If $E_{0c} \leq E_0 < E_{0d}$, then $\mathcal{E}_0$ becomes unstable and $\mathcal{E}^* = (T_d^*, T_a^*, E_0, P_0)$ exists and is globally asymptotically stable.*
   (c) *If $0 \leq E_0 < E_{0c}$, then $\alpha\left(\frac{E_0}{P_0}\right) = 0$ and $\mathcal{E}^*$ reduces to $\mathcal{E}^{*0} = (K_d, 0, E_0, P_0)$ which is globally asymptotically stable.*

Proposition 3 gives a full description of the global stability and bifurcation behavior of model system (2.1) in terms of E_0, or, equivalently, in terms of λ_E. It suggests that within the domain $\{E_0 : \mu_{\lambda_P}(E_0) \geq r_a\}$, we have three possible outcomes:

1. If the estrogen level is maintained at a reasonably low level ($E_0 < E_{0c}$), then the activation rate α is equal to zero and no dormant tumor gets activated.
2. However, if estrogen levels rise, either by increased endogenous hormone production or hormone therapy, and enter the range $E_{0c} \leq E_0 < E_{0d}$, then dormant tumor cells get activated and some of the resulting active tumor cells will persist. This is because the activation rate α is high enough to activate dormant tumor cells, while the apoptosis rate μ remains too small to eliminate the resulting active tumor cells.
3. In this case, antiestrogen drugs such as tamoxifen can be prescribed to decrease estrogen levels below E_c. Alternatively, if breast cancer cells become resistant to antiestrogen therapy, treatment with HDE can be used to increase estrogen levels beyond the value E_{0d} leading to active tumor elimination (as long as $\mu_{\lambda_P}(E_0) \geq r_a$).

We note that the domains generated by the curves γ_{λ_P} and $\mu_{\lambda_P}(E_0)$ are not clearly depicted at this stage due to their unknown forms or expressions. Further details/assumptions are required to explore the interplay between these curves.

With this regard, we assume that

($\mathcal{A}_\mu$) The function $P \to \mu(E, P)$ is increasing.

With this assumption, we are now able to express explicitly the bifurcation conditions presented in theorem 2 in terms of λ_P. We first note that $\frac{E_0}{P_0} < \chi_x, x = c, d$ if and only if $\lambda_P > \lambda_{P_x}(\lambda_E) := \frac{(\mu_P + \beta(E_0))E_0}{\chi_x}$. Moreover, assumption ($\mathcal{A}_\mu$) implies that the function $\mu_{\lambda_E} : \lambda_P \to \mu\left(\frac{\lambda_E}{\mu_E}, \frac{\lambda_P}{\mu_P + \beta\left(\frac{\lambda_E}{\mu_E}\right)}\right)$ is increasing and thus invertible. Hence, the condition $\mu_{\lambda_P}(E_0) \leq r_a$ is satisfied if and only if $\lambda_P \leq \mu_{\lambda_E}^{-1}(r_a) := \lambda_{P_\mu}(\lambda_E)$.

Thus, Theorem 2 can be written as follows:

Proposition 4. 1. *If $\lambda_P \leq \lambda_{P_\mu}(\lambda_E)$, then the model always has a globally asymptotically stable active-tumor-endemic equilibrium. More precisely,*
   (a) *If $\lambda_P \leq \lambda_{P_d}(\lambda_E)$, then $\mathcal{E}^{\#} = \left(0, \frac{K_a\left(r_a - \mu_{\lambda_P}(E_0)\right)}{r_a}, E_0, P_0\right)$ is globally asymptotically stable.*
   (b) *If $\lambda_P > \lambda_{P_d}(\lambda_E)$, then $\mathcal{E}^* = (T_d^*, T_a^*, E_0, P_0)$ is globally asymptotically stable.*
2. *If $\lambda_P \geq \lambda_{P_\mu}(\lambda_E)$, then the model has a globally asymptotically stable active-tumor-endemic equilibrium if and only if $\chi_c \leq \frac{E_0}{P_0} < \chi_d$. More precisely*
   (a) *If $\lambda_P \leq \lambda_{P_d}(\lambda_E)$, then $\mathcal{E}_0 = (0, 0, E_0, P_0)$ is globally asymptotically stable.*
   (b) *If $\lambda_{P_d}(\lambda_E) < \lambda_P \leq \lambda_{P_c}(\lambda_E)$, then $\mathcal{E}_0$ becomes unstable and $\mathcal{E}^* = (T_d^*, T_a^*, E_0, P_0)$ exists and is globally asymptotically stable.*
   (c) *If $\lambda_{P_c}(\lambda_E) < \lambda_P$, then $\alpha\left(\frac{E_0}{P_0}\right) = 0$ and $\mathcal{E}^*$ reduces to $\mathcal{E}^{*0} = (K_d, 0, E_0, P_0)$ which is globally asymptotically stable.*

3.4. Bifurcation analysis and the estrogen paradox:

In this section, we illustrate the bifurcation diagram of system (2.1) that emerges from the results in Proposition 4. The diagram is constructed by plotting the graphs of the functions $\lambda_{P_\mu}(\lambda_E)$, $\lambda_{P_c}(\lambda_E)$ and $\lambda_{P_d}(\lambda_E)$ in a domain of the positive quadrant (λ_E, λ_P). The aim is to portray the areas where the active-tumor persists and where it is eliminated. For this purpose, we opt to use the following functions:

- The activation rate is given by

$$\alpha(\chi) = \begin{cases} 0 & \text{if } \chi < \chi_c \\ \alpha_1 \left(1 - e^{k(\chi_c - x)}\right) & \text{if } \chi \geq \chi_c. \end{cases}$$

  By using this function, we suggest that: (a) the activation of dormant cells takes place only when the ratio between estrogen and p53 levels is larger than some threshold value χ_c, and (b) as this ratio increases, the activation rate of dormant cells grows smoothly to reach a maximum activation rate α_1. We note that the proposed function, whose graph is presented in Figure 3.1, is smooth enough to ensure the well-posedness of model (2.1).

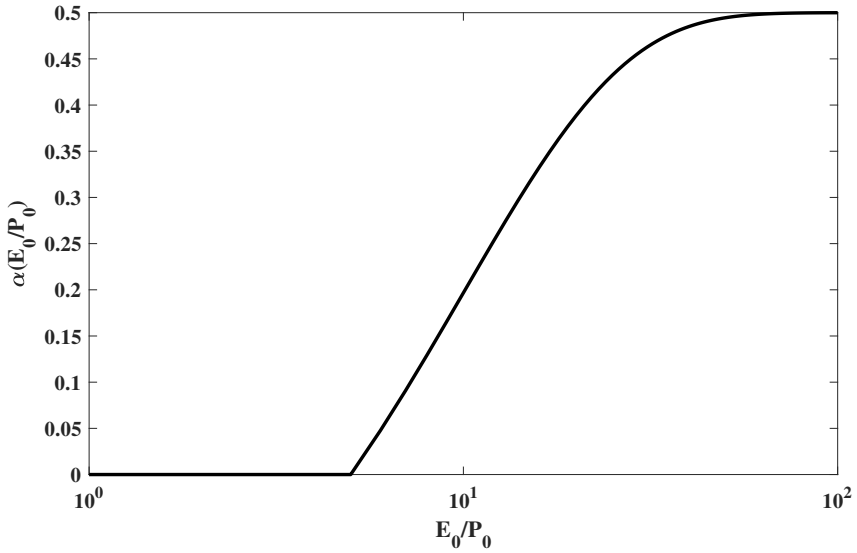


Figure 3.1: Profile of the activation rate as a function of the ratio of estrogen to p53 for $\alpha_1 = 0.5, k = 0.1$ and $\chi_c = 5$.

- To account for the estrogen-induced inhibition of p53 that is reported in [44], we propose that the function $\beta(E)$ is increasing and choose to use, for simplicity, the linear form

$$\beta(E) = \omega E.$$

  In this case, the functions $\lambda_{P_x}(\lambda_E) := \frac{(\mu_P + \beta(E_0))E_0}{\chi_x}, x = c, d$ read as

$$\lambda_{P_x}(\lambda_E) = \frac{1}{\chi_x}\left(\mu_P + \omega\frac{\lambda_E}{\mu_E}\right)\frac{\lambda_E}{\mu_E}.$$

  Clearly, $\lambda_{P_x}(\lambda_E)$ is an increasing function in λ_E, with 0 being the only positive root.

- Finally, we want the function $\mu(E, P)$ to increase with respect to E and P to reflect the biological fact that both estrogen and p53 induce cancer cell apoptosis [4, 5, 42, 43, 50]. We choose the simple linear function

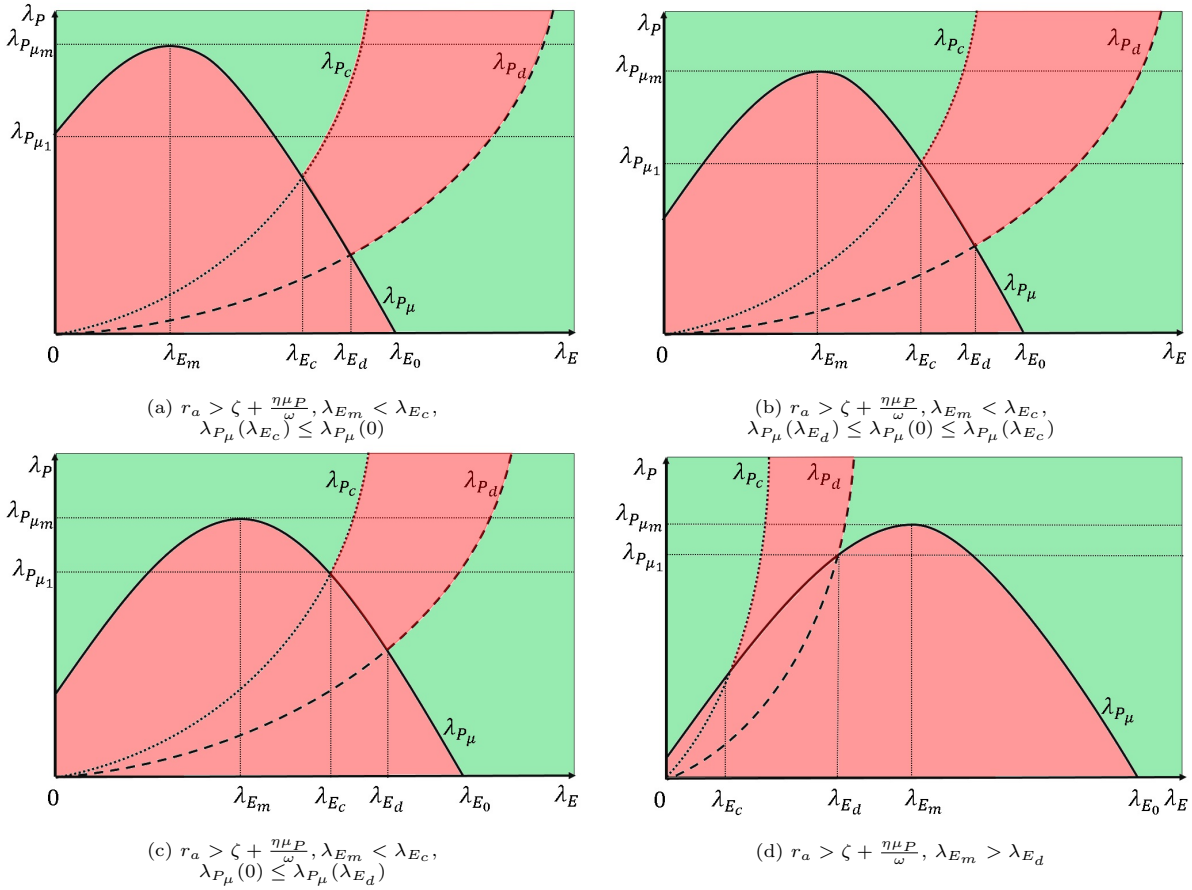
$$\mu(E, P) = \zeta + \eta E + \upsilon P.$$

In this case, the function μ_{λ_E} is given by $\mu_{\lambda_E}(\lambda_P) = \zeta + \frac{\eta\lambda_E}{\mu_E} + \frac{\upsilon\lambda_P}{\mu_P + \frac{\omega\lambda_E}{\mu_E}}$. Clearly, μ_{λ_E} is increasing, which implies that it is invertible, and the condition $\mu_{\lambda_E}(\lambda_P) \leq r_a$ is equivalent to $\lambda_P \leq \mu_{\lambda_E}^{-1}(r_a) = \frac{1}{\upsilon}\left(\mu_P + \omega\frac{\lambda_E}{\mu_E}\right)\left(r_a - \zeta - \frac{\eta\lambda_E}{\mu_E}\right)$.

To depict the bifurcation diagram of system (2.1), we explore the relative positions of the curves $\lambda_{P_c}(\lambda_E), \lambda_{P_d}(\lambda_E)$ and

$$\lambda_{P_\mu}(\lambda_E) := \frac{1}{\upsilon}\left(\mu_P + \omega\frac{\lambda_E}{\mu_E}\right)\left(r_a - \zeta - \frac{\eta\lambda_E}{\mu_E}\right)$$

It is easy to see that if $r_a \leq \zeta$, then $\lambda_{P_\mu}(\lambda_E) \leq 0$, implying that $\lambda_{P_\mu}(\lambda_E) \leq \lambda_{P_x}(\lambda_E), x = c, d$. Moreover, if $r_a > \zeta$, then we obtain from $\lambda_{P_\mu}(\lambda_E) - \lambda_{P_x}(\lambda_E) = \frac{1}{\upsilon}\left(\mu_P + \frac{\omega}{\mu_E}\lambda_E\right)\left(r_a - \zeta - \frac{\upsilon + \eta\chi_x}{\mu_E\chi_x}\lambda_E\right)$ that $\lambda_{P_x}(\lambda_E) \leq \lambda_{P_\mu}(\lambda_E)$ if and only if $0 \leq \lambda_E \leq \lambda_{E_x} := \frac{\chi_x\mu_E(r_a - \zeta)}{\upsilon + \eta\chi_x}$.
We note that the quadratic function $\lambda_{P_\mu}(\lambda_E)$ is an open-down parabola that reaches its maximum $\lambda_{P_{\mu_m}} := \frac{(\omega(r_a - \zeta) + \eta\mu_P)^2}{4\upsilon\eta\omega} > 0$ at $\lambda_{E_m} = \frac{(\omega(r_a - \zeta) - \eta\mu_P)\mu_E}{2\omega\eta}$, which is positive if and only if $r_a > \zeta + \frac{\eta\mu_P}{\omega}$.
Thus, depending on the location of λ_{E_m} with respect to $0, \lambda_{E_x}, x = c, d$, and that of $\lambda_{P_\mu}(0)$ with respect of $\lambda_{P_\mu}(\lambda_{E_x}), x = c, d$, system (2.1) exhibits one of the bifurcation diagrams presented in Figures 3.2 and 3.3.



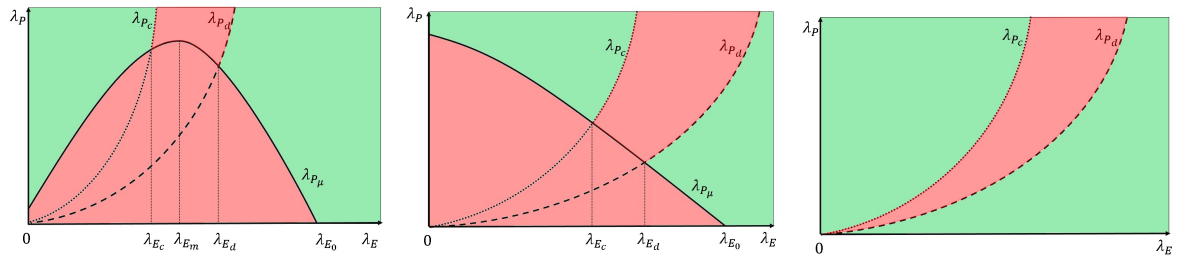
(a) $r_a > \zeta + \frac{\eta\mu_P}{\omega}, \lambda_{E_m} < \lambda_{E_c}$, $\lambda_{P_\mu}(\lambda_{E_c}) \leq \lambda_{P_\mu}(0)$

(b) $r_a > \zeta + \frac{\eta\mu_P}{\omega}, \lambda_{E_m} < \lambda_{E_c}$, $\lambda_{P_\mu}(\lambda_{E_d}) \leq \lambda_{P_\mu}(0) \leq \lambda_{P_\mu}(\lambda_{E_c})$

(c) $r_a > \zeta + \frac{\eta\mu_P}{\omega}, \lambda_{E_m} < \lambda_{E_c}$, $\lambda_{P_\mu}(0) \leq \lambda_{P_\mu}(\lambda_{E_d})$

(d) $r_a > \zeta + \frac{\eta\mu_P}{\omega}$, $\lambda_{E_m} > \lambda_{E_d}$

Figure 3.2: Bifurcation diagrams of model system (2.1). The green and red areas emerge from Proposition 4. Active-tumor cells are eliminated in the green areas and persist in the red ones. The figure shows the estrogen paradox and its paradoxical long-term effect



(a) $r_a > \zeta + \frac{\eta\mu_P}{\omega}$, $\lambda_{E_c} \leq \lambda_{E_m} \leq \lambda_{E_d}$ (b) $\zeta < r_a \leq \zeta + \frac{\eta\mu_P}{\omega}$. (c) $r_a \leq \zeta$

Figure 3.3: Bifurcation diagrams of model system (2.1). The green and red areas emerge from Proposition 4. Active-tumor cells are eliminated in the green areas and persist in the red ones. The figure shows the estrogen paradox without its paradoxical long-term effect

Using Figures 3.2 and 3.3, we put forward plausible biological explanations of the estrogen paradox and the paradoxical tumor recurrence that results from prolonged HDE treatment.
In fact, if we start with a pair (λ_E, λ_P) in any of the green domains located on the left of these bifurcation diagrams and gradually increase λ_E, then one of the following scenarios will take place:

1. In Figures 3.2(a) - 3.2(d) we observe that:
   i. If $\lambda_P \in (\lambda_{P_{\mu_1}}, \lambda_{P_{\mu_m}})$, then as λ_E increases, the pair (λ_E, λ_P) crosses first from the green domain into the red one, then it crosses into the subsequent green domain, after which it enters the red one (either by increasing λ_E or decreasing λ_P). Lastly, the pair crosses into the green domain and stays in it for larger values of λ_E.
   It is worth noting that for realistic parameter values the last crossing to the green domain may not occur, suggesting that the paradoxical role of estrogen in the occurrence, elimination and recurrence of breast cancer may be attributed to the trade-offs between estrogen and p53 represented by the bifurcation curves $\lambda_{P_\mu}(\lambda_E)$ and $\lambda_{P_x}(\lambda_E), x = c, d$.
   ii. If $\lambda_P \notin (\lambda_{P_{\mu_1}}, \lambda_{P_{\mu_m}})$, then as λ_E increases, the pair (λ_E, λ_P) crosses first from the green domain into the red one, then it crosses into the subsequent green domain and remains in it for large values of λ_E.
   This suggests that under certain conditions, the estrogen paradox may occur without its paradoxical long term effect, whereby treatment with HDE may succeed in eliminating breast cancer without the risk of cancer recurring after a prolonged treatment period.
2. In Figures 3.3(a) - 3.3(c) we notice that the behavior described in 1.ii. holds for all $\lambda_P > 0$.

Essentially, the results above attribute the paradoxical role of estrogen in the occurrence, elimination and recurrence of breast cancer to some trade-offs between estrogen and p53 which are described by the bifurcation curves in Figures 3.2 and 3.3. Additionally, and more importantly, these results suggest that the paradoxical cancer recurrence that emerges from prolonged HDE treatment may be prevented if (a) $\lambda_P \notin (\lambda_{P_{\mu_1}}, \lambda_{P_{\mu_m}})$ and the conditions stated in Figures 3.2(a) - 3.2(d) hold, or (b) the conditions in Figures 3.3(a) - 3.3(c) are satisfied. We note that these conditions can be expressed explicitly in terms of the parameters of α, μ and β, by replacing $\lambda_{E_m} < \lambda_{E_x}$ and $\lambda_{P_\mu}(0) < \lambda_{P_\mu}(\lambda_{E_x})$ respectively with the conditions $\omega(\upsilon - \eta\chi_x)(r_a - \zeta) < \eta\mu_P(\upsilon + \eta\chi_x)$ and $\eta\mu_P(\upsilon + \eta\chi_x) < \omega\upsilon(r_a - \zeta)$.

4. Numerical analysis:

In this section, we run some numerical simulations to monitor the impact of the estrogen supply rate on the model's behavior, and corroborate the results presented in Proposition 4. For the sake of our numerical investigation, we chose to use $\chi_c = 5, \alpha_1 = 0.5, k = 0.1, \omega = 0.002, \zeta = 0.3, \eta = 0.002$ and $\upsilon = 0.004$. We first construct the bifurcation diagram of model (2.1) corresponding to these values. Then, building upon the resulting diagram, we run some numerical simulations to monitor the impact of the estrogen supply rate on the model's behavior and confirm scenarios presented in Proposition 4.

In Figure 4.1, we present the bifurcation diagram of (2.1) which is constructed in Matlab by plotting the curves $\lambda_{P_\mu}(\lambda_E)$ and $\lambda_{P_x}(\lambda_E), x = c, d$, using the above parameter values and the values given in Table 2.2.

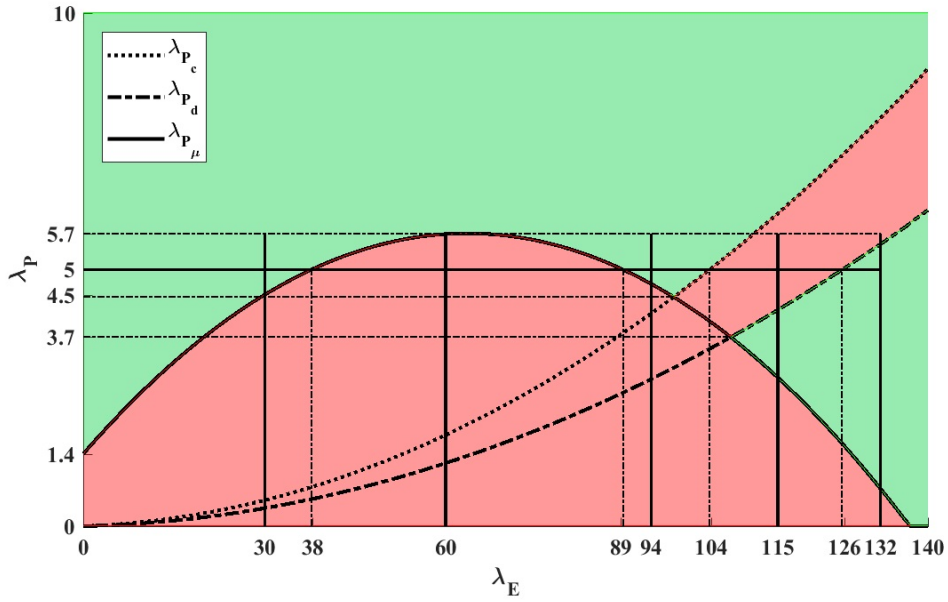


Figure 4.1: Bifurcation diagram of model system (2.1) in a positive domain of the (λ_E, λ_P) plan. The green and red areas emerge from Proposition 4. Active-tumor cells are eliminated in the green area and persist in the red part.

Figure 4.1 shows that when $\lambda_P \in (4.5, 5.7)$, the estrogen paradox occurs alongside the paradoxical tumor recurrence that results from prolonged HDE treatment, while when $\lambda_P > 5.7$ or $1.4 < \lambda_P < 4.5$, the estrogen paradox can occur without its long term paradoxical effect.
We must point out that the biological feasibility of these ranges depends on the parameters of α, μ and β. Hence, it is crucial to accurately estimate the functions α, μ and β in order to determine the interplay between estrogen and p53 that is behind the estrogen paradox and its paradoxical long term effect. However, due to the lack of clinical and experimental data, difficulties arise in obtaining biologically backed expressions for these functions.

4.1. Constant supply rates:

To further elucidate the bifurcation results in Figure 4.1 and their relation to the estrogen paradox, we perform numerical simulations of model (2.1) that emulate scenarios **1.** and **2.** presented in Proposition 4. Particularly, we aim to explore the prospects of cancer occurrence, elimination caused by antiestrogen treatment, elimination due to treatment with HDE, recurrence caused by prolonged HDE treatment, and recurrence generated by a drop in p53 levels. To set ourselves within the framework of simulating the scenarios mentioned above, we use the parameter values given in Table 2.2 and allow λ_E and λ_P to vary in a domain that accommodates all these scenarios.

We start by choosing $\lambda_P = 5$. Noting that the condition $\mu_{\lambda_E}(\lambda_P) = 0$ holds if and only if $\lambda_E = 38$ or $\lambda_E = 89$, and that the condition $\mu_{P_c}(\lambda_P) = 0$ is satisfied if and only if $\lambda_E = 104$, we choose λ_E to be equal to $30, 60, 94, 115$ and 132. Finally, for each of these values of λ_E, we allow λ_P to drop from 5 down to values that accommodate the aforementioned scenarios. We use the Matlab solver ode45, to numerically solve system (2.1) over a large enough period to reflect the long-term evolution of the system towards its equilibrium states. The initial conditions are chosen so that at time $t = 0$, the dormant tumor cells are at 25% of the maximum carrying capacity, and the estrogen and $p53$ levels are assumed to be at 25% of their values at equilibrium. The initial condition for active tumor cells is chosen to be equal to 0, or 10^3 if the

activation rate α is equal to zero, that is when $\dfrac{E_0}{P_0} \leq \chi_c$, where $E_0 = \dfrac{\lambda_E}{\mu_E}, P_0 = \frac{\lambda_P}{\mu_P + \beta(E_0)}$. Accordingly, the initial conditions for all the simulations are given by: $T_d(0) = \frac{1}{4}K_d, E(0) = \frac{1}{4}E_0, P(0) = \frac{1}{4}P_0, T_a(0) = 0$ if $\dfrac{E_0}{P_0} > \chi_c$ and 10^3 otherwise.

Figures 4.2 - 4.8 describe the evolution of dormant and active cancer cells during 10^4 days for the chosen values of λ_E and λ_P. We observe that the population of cancer cells stabilizes at equilibrium points that are equal to the ones derived in Proposition 4. More specifically, we have the following results:

(i) If $\lambda_P = 5$ and the level of estrogen supply is kept bellow 38, then system (2.1) stabilizes at an active-tumor free equilibrium point as shown in Figure 4.2. This is because the activation rate is too small to sustain the activation of dormant tumor cells.

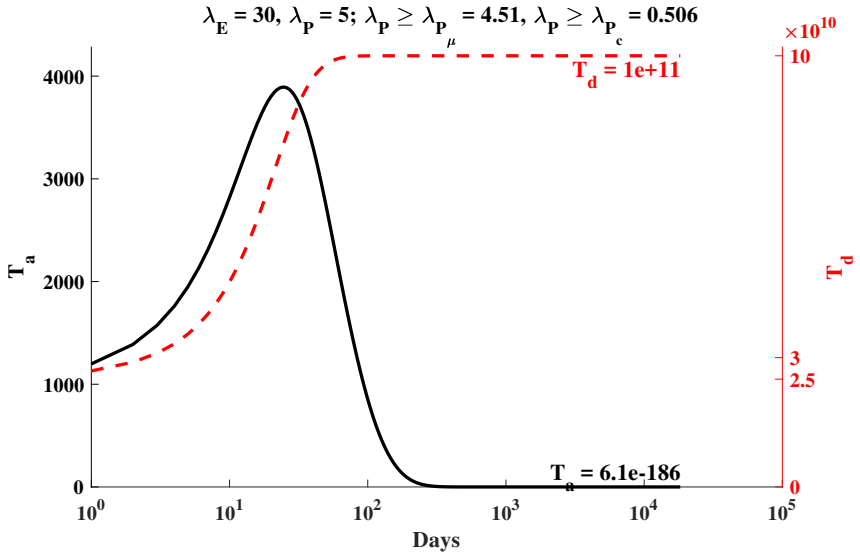


Figure 4.2: Plots indicating the temporal evolution of dormant and active cancer cells for $\lambda_E = 30$ and $\lambda_P = 5$. In this case, we have $\lambda_{P_\mu} = 4.51, \lambda_{P_c} = 0.506$, implying that $\lambda_P \geq \lambda_{P_\mu}$ and $\lambda_P \geq \lambda_{P_c}$. The plots show that the system converges to a dormant-tumor endemic and active-tumor free equilibrium, confirming the result in item **2.c** of Proposition 4.

(ii) However, if λ_P is kept at the same value, but λ_E increases to enter the range $(38, 89)$ - by hormonal therapy or overproduction, or due to lifestyle changes - then, as in Figure 4.3, system (2.1) stabilizes at a dormant-tumor endemic and active-tumor endemic equilibrium point. This is because the activation rate α is high enough to activate dormant tumor cells, while the mortality rate μ is still too small to eliminate the resulting active tumor cells.

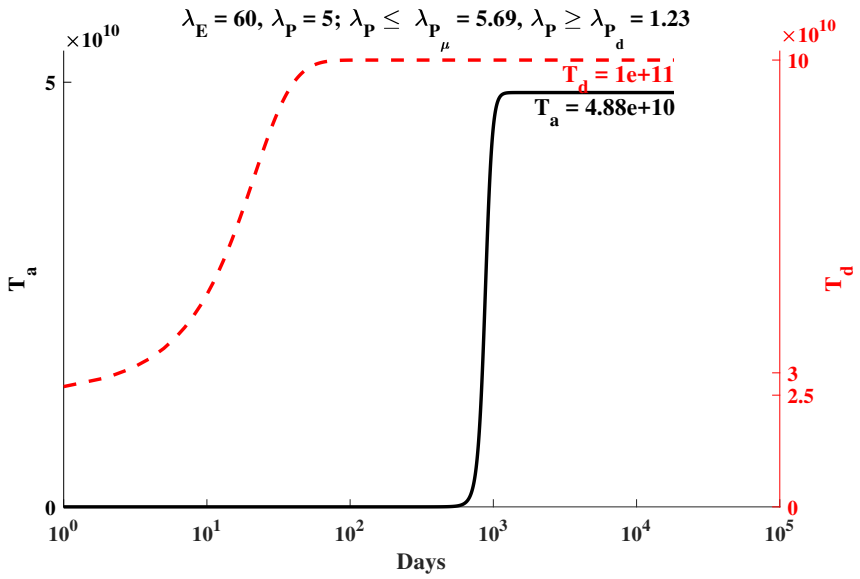


Figure 4.3: Simulations depicting the temporal evolution of dormant and active cancer cells for $\lambda_E = 60$ and $\lambda_P = 5$. In this case, we have $\lambda_{P_\mu} = 5.69, \lambda_{P_d} = 1.23$ implying that $\lambda_P \leq \lambda_{P_\mu}$ and $\lambda_P \geq \lambda_{P_d}$. The plots indicate that the system converges to a dormant-tumor endemic and active-tumor endemic equilibrium, confirming the result in item **1.b** of Proposition 4.

(iii) In case (ii) above, antiestrogen drugs such as tamoxifen can be prescribed to decrease estrogen supply levels below 38 which would result in the elimination of active-tumor cells, as shown in Figure 4.2. If breast cancer cells are resistant to antiestrogen therapy, then treatment with HDE can be used to increase λ_E to the moderately high range $(89, 104)$ where the active-tumor is eliminated, see Figure 4.4. This is inline with the results in [6–12] which states that treatment with HDE causes regression of hormone-dependent breast cancers.

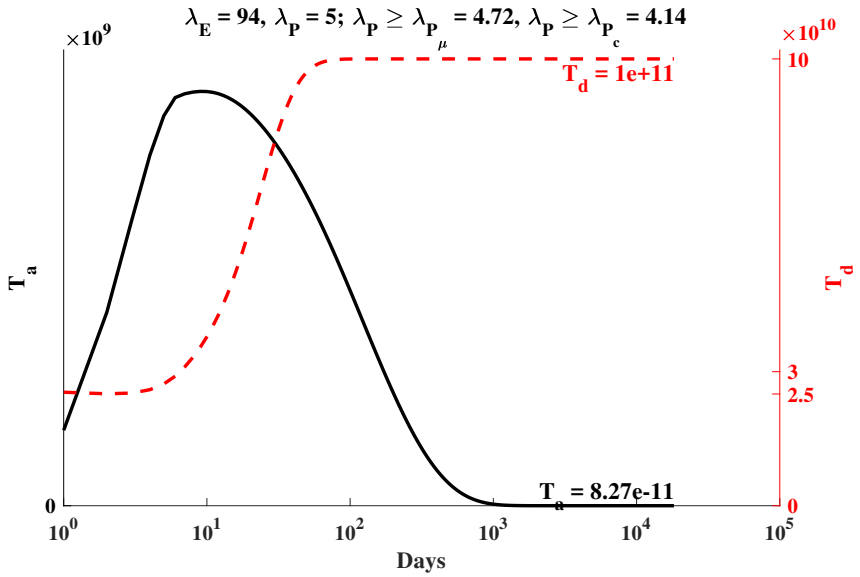


Figure 4.4: Simulations illustrating the temporal evolution of dormant and active cancer cells for $\lambda_E = 94$ and $\lambda_P = 5$. In this case, we have $\lambda_{P_\mu} = 4.72, \lambda_{P_c} = 4.14$ implying that $\lambda_P \geq \lambda_{P_\mu}$ and $\lambda_P \geq \lambda_{P_c}$. We observe that the system converges to a dormant-tumor endemic and active-tumor free equilibrium, confirming the result in item **2.c** of Proposition 4.

(iv) By contrast, Figure 4.5 shows that the tumor relapses again when λ_E is further increased beyond the value 104 (while $\lambda_P = 5$). This occurrence could be due to the fact that although estrogen

increases the rates of both dormant-tumor cells' activation and active-tumor cells' apoptosis, the balance between these two increases favors active-tumor cells' growth.

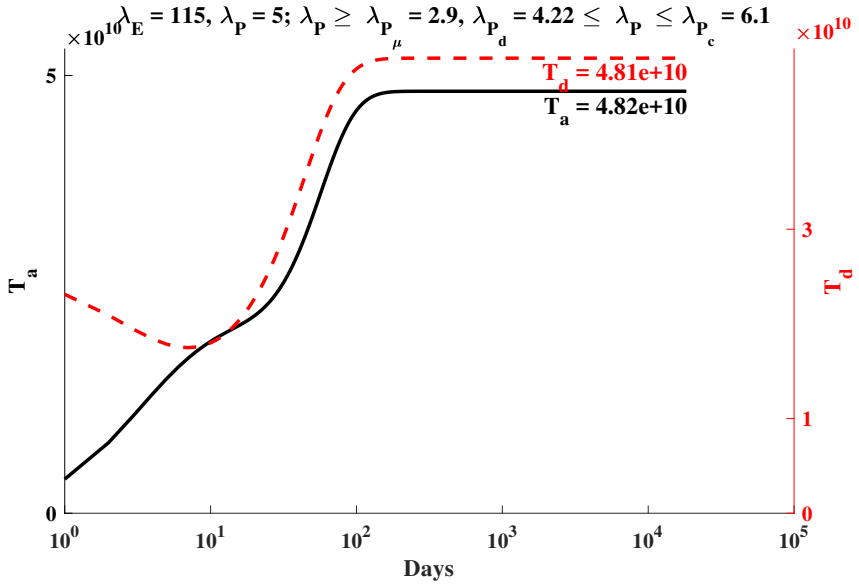
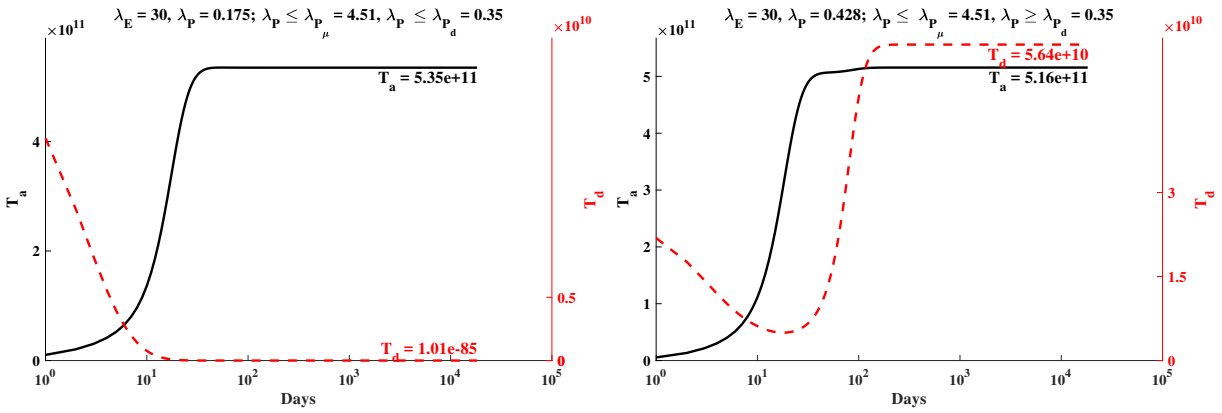


Figure 4.5: Simulations showing the temporal evolution of dormant and active cancer cells for $\lambda_E = 115$ and $\lambda_P = 5$. In this case, we have $\lambda_{P_\mu} = 2.9, \lambda_{P_d} = 4.22$ and $\lambda_{P_c} = 6.1$ implying that $\lambda_P \geq \lambda_{P_\mu}$ and $\lambda_{P_d} \leq \lambda_P \leq \lambda_{P_c}$. The plots reveal that the system converges to a dormant-tumor endemic and active-tumor endemic equilibrium, confirming the result in item **2.b** of Proposition 4.

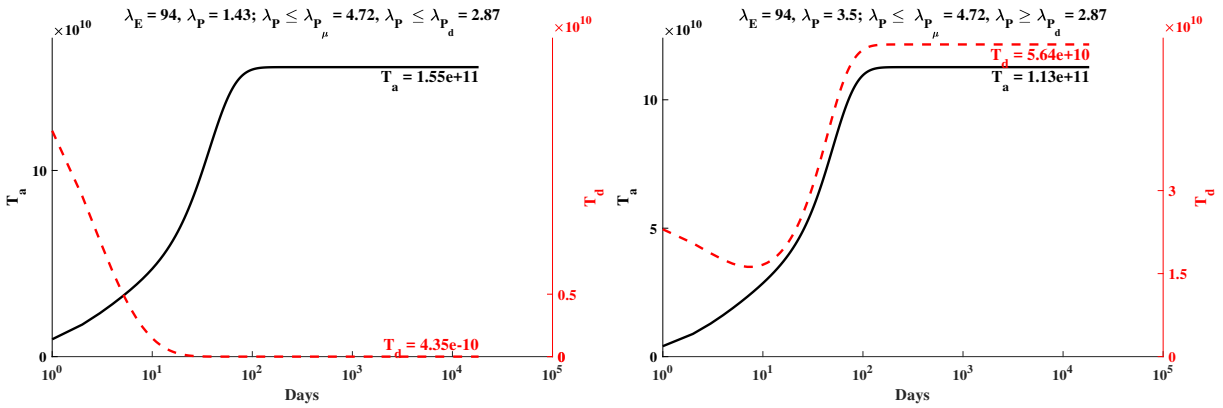
(v) Alternatively to (ii) (respectively (iv)), the supply rate of estrogen could remain equal to $\lambda_E = 30$ (respectively 94), while that of p53 declines until (λ_E, λ_P) falls in the red area of Figure 4.1. In this case, system (2.1) stabilizes at an active-tumor endemic equilibrium point as shown in Figure 4.6 (respectively Figure 4.7). This scenario happens because the drop in λ_P, although reduces tumor cells' apoptosis, it increases the activation rate to such extent that the balance between estrogen and p53 levels shifts in favor of the growth of active-tumor cells.



(a) $\lambda_P = 0.175$;. $\lambda_P \leq \lambda_{P_\mu}$ and $\lambda_P \leq \lambda_{P_d}$.

(b) $\lambda_P = 0.428$. $\lambda_P \leq \lambda_{P_\mu}$ and $\lambda_P \geq \lambda_{P_d}$

Figure 4.6: Simulation illustrating the temporal evolution of dormant and active cancer cells for $\lambda_E = 30$. In this case, we have $\lambda_{P_\mu} = 4.51$ and $\lambda_{P_d} = 0.35$. We observe that the system (2.1) converges to a dormant-tumor free and active-tumor endemic equilibrium (Figure 4.6(a)) and to a dormant-tumor endemic and active-tumor endemic equilibrium (Figure 4.6(b)). This confirms the result in item **1.** of Proposition 4.



(a) $\lambda_P = 1.43; \lambda_P \leq \lambda_{P_\mu}$ and $\lambda_P \leq \lambda_{P_d}$

(b) $\lambda_P = 3.5; \lambda_P \leq \lambda_{P_\mu}$ and $\lambda_P \geq \lambda_{P_d}$

Figure 4.7: Simulation depicting the temporal evolution of dormant and active cancer cells for $\lambda_E = 94$. In this case, we have $\lambda_{P_\mu} = 4.72$ and $\lambda_{P_d} = 2.87$. The plots show that the system (2.1) converges to a dormant-tumor free and active-tumor endemic equilibrium (Figure 4.7(a)) and to a dormant-tumor endemic and active-tumor endemic equilibrium (Figure 4.7(b)). This confirms the result in item **1.** of Proposition 4.

(vi) The tumor will again be eliminated if the estrogen supply rate increases beyond 126 (Figure 4.8).

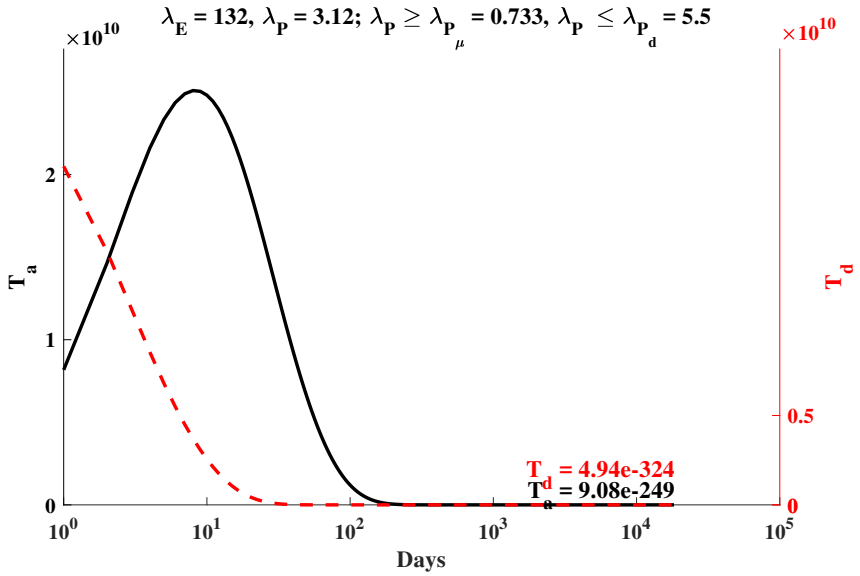


Figure 4.8: Simulation of the temporal evolution of dormant and active cancer cells for $\lambda_E = 132$ and $\lambda_P = 3.12$. In this case, we have $\lambda_{P_\mu} = 0.733, \lambda_{P_c} = 5.5$, implying that $\lambda_P \geq \lambda_{P_\mu}$ and $\lambda_P \leq \lambda_{P_d}$. We observe that the system converges to a dormant-tumor free and active-tumor free equilibrium, confirming the result in item **2.a** of Proposition 4.

The simulations above concern the case where the supply rates of estrogen and p53, λ_E and λ_P, are constant. However, in reality these rates do change with time, it is thus of practical importance to further extend the above simulations to time-dependent supply rates.

4.2. Time-dependent supply rates:

Building upon the bifurcation analysis above, we perform numerical simulation of model (2.1) using time-depend supply rates. Our aim is to investigate the effects of temporal changes in the supply rates of estrogen and p53, on the dynamics of active-tumor cells. The main focus is to explore the following scenarios:

i. tumor development caused by a moderate rise in estrogen levels,

ii. successful tumor elimination caused by a moderately high rise in estrogen levels,
iii. tumor elimination followed by a recurrence that is caused by a very high rise in estrogen levels,
iv. tumor elimination followed by tumor recurrence that is caused by a drop in p53 levels.

For this purpose, we propose the following hyperbolic tangent type function

$$\xi(A, B, \tau, t) = A + \frac{B - A}{1 + e^{-q(t-\tau)}}.$$

This function is infinitely continuously differentiable and has two particular properties; (a) it tends to A (respectively B) for small (respectively large) values of t, and (b) it move from A to B around the time $t = \tau$, with a gradient that is controlled by q. We refer to τ as the jump (respectively drop) point if $B > A$ (respectively $B < A$).
Using this function, we are now able to construct supply rates $\lambda_E(t)$ and $\lambda_P(t)$ that behave like "smoothened" step functions. We chose $q = 0.02$ to ascertain an almost instantaneous, but smooth, jump (or drop) from one value to another at the given jump (or drop) points.
We thus propose the following supply rates:

- $\lambda_P(t) = \xi(\lambda_{P1}, \lambda_{P2}, \tau_P, t)$. This function starts and stays at the value λ_{P1} until time $t = \tau_P$ where it moves to λ_{P2} and remains there for all $t > \tau_P$.
- $\lambda_E(t) = \xi(\lambda_{E1}, \lambda_{E2}, \tau_{E1}, t) + \xi(0, \lambda_{E3} - \lambda_{E2}, \tau_{E2}, t)$. This function starts and stays at the value λ_{E1} until time $t = \tau_{E1}$ where it moves to λ_{E2} and remains at this value until $t = \tau_{E2}$ where it moves to λ_{E3}.

We chose $\tau_P = 365 * 25, \tau_{E1} = 365 * 5$, and $\tau_{E2} = 365 * 12$.

Regarding the values of $\lambda_{E1}, \cdots, \lambda_{E3}$ and $\lambda_{P1}, \lambda_{P2}$, we vary them in a way that accommodates the aforementioned scenarios i. - iv.. The resulting temporal evolution of $\lambda_E(t)$, $\lambda_P(t)$ and $T_a(t)$ is presented in Figures 4.9 - 4.12. More precisely, we simulate the following cases:

i. $\lambda_{E1} = 30, \lambda_{E2} = \lambda_{E3} = 60$ and $\lambda_{P1} = \lambda_{P2} = 5$. In this case, $\lambda_P(t)$ is kept constant, while $\lambda_E(t)$ jumps from 30 to 60 around the 5^{th} year. Figure 4.9 system (2.1) stabilizes at an active-tumor endemic equilibrium. The observed cancer occurrence is attributed to the jump in $\lambda_E(t)$ from 30 to 60.

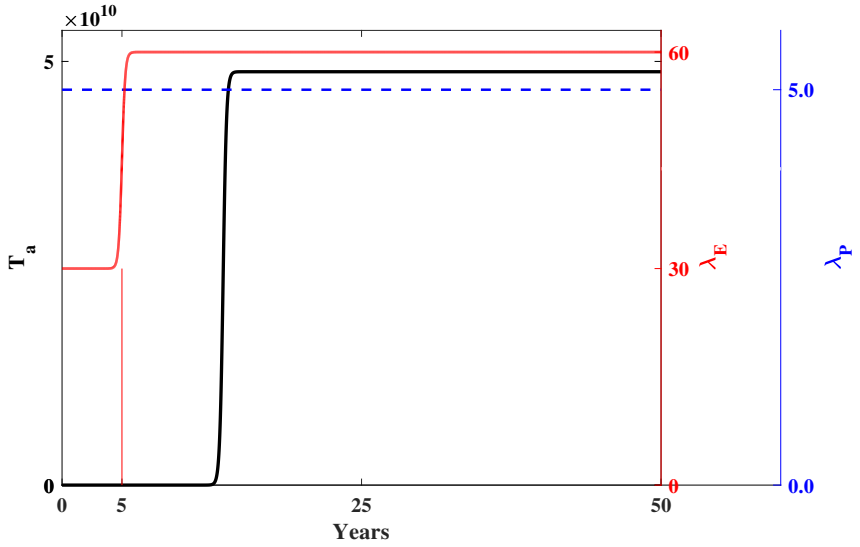


Figure 4.9: Simulation depicting the temporal evolution of active-tumor cells in the case of time-dependent estrogen and p53 supply rates. The graphs show the development of an active-tumor due to a rise in estrogen supply rate.

ii. $\lambda_{E1} = 60, \lambda_{E2} = 94, \lambda_{E3} = 94$ and $\lambda_{P1} = \lambda_{P2} = 5$, then $\lambda_E(t)$ jumps from 60 to 94 around the 5^{th} year, while $\lambda_P(t) = 5$ for all $t \geq 0$. Figure 4.10 shows that the active-tumor is successfully eliminated soon after the higher rise in estrogen level.

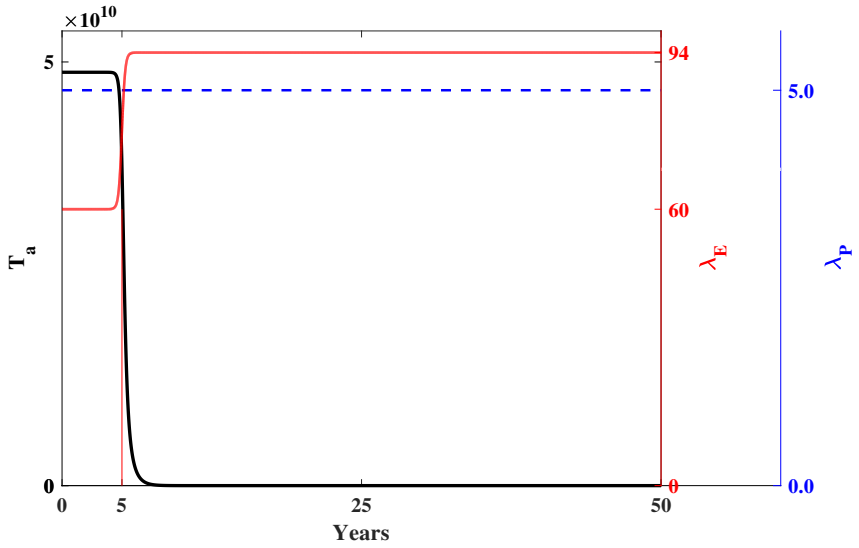


Figure 4.10: Temporal evolution of active-tumor cells in the case of time-dependent estrogen and p53 supply rates. The graph indicates the development of an active-tumor caused by a higher rise in estrogen supply rate.

iii. $\lambda_{E1} = 60, \lambda_{E2} = 94, \lambda_{E3} = 115$ and $\lambda_{P1} = \lambda_{P2} = 5$. In this case, $\lambda_P(t) = 5$ for all $t \geq 0$, while $\lambda_E(t)$ jumps from the moderate value of 60 to the moderately high value of 94 around the 5^{th} year and the very high value of 115 around the year 12. We observe in Figure 4.11 an active-tumor elimination that starts approximately in year 5 and lasts for 7 years, after which we observe a cancer recurrence.

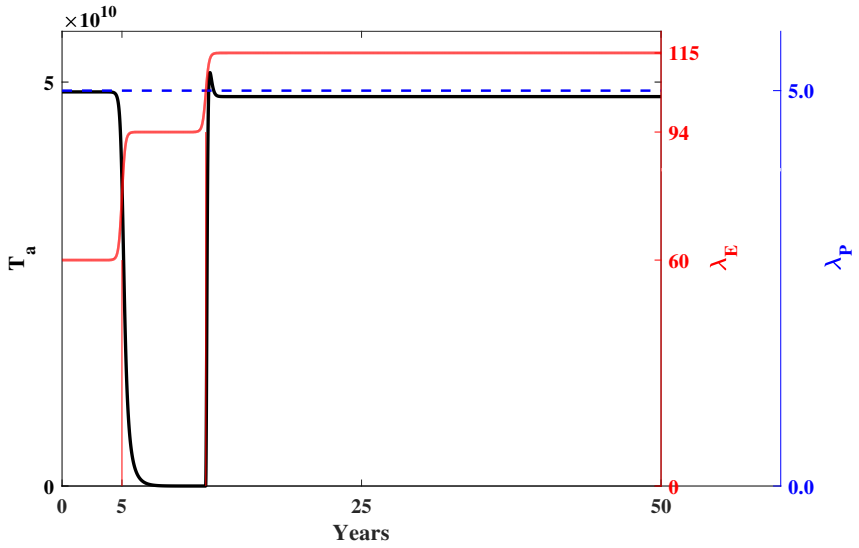


Figure 4.11: Simulation illustrating the temporal evolution of active-tumor cells in the case of time-dependent estrogen and p53 supply rates. The graphs indicate a tumor elimination, caused by a rise in estrogen supply, followed a tumor recurrence caused by higher rise in estrogen supply rate.

iv. $\lambda_{E1} = 60, \lambda_{E2} = 94, \lambda_{E3} = 94$ and $\lambda_{P1} = 5, \lambda_{P2} = 3.5$. In this case, $\lambda_E(t)$ jumps from 60 to 94 at the 5^{th} year, while $\lambda_P(t)$ drops from 5 to 3.5 around the 25^{th} year. Figure 4.12 shows that the tumor

is eliminated shortly after the estrogen supply rate increases to high values. This elimination lasts until year 25, when the supply rate of p53 drops.

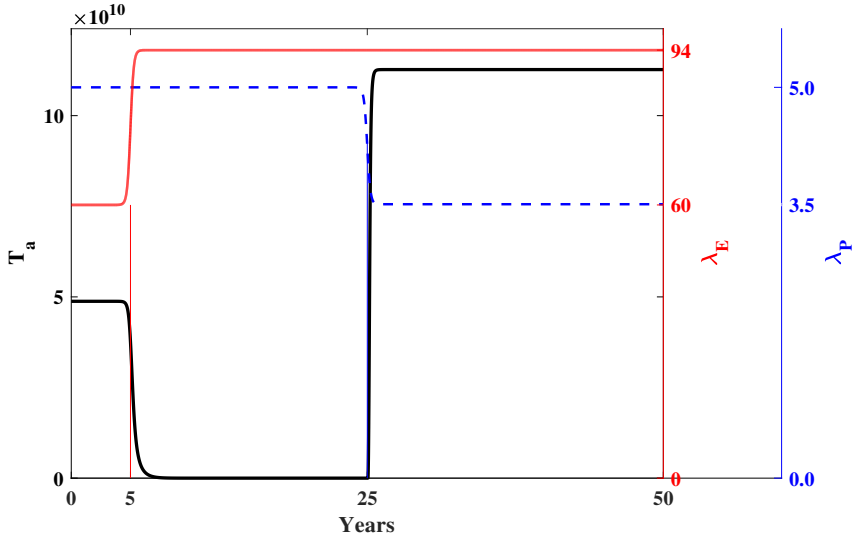


Figure 4.12: Simulation of temporal evolution of active-tumor cells with time-dependent estrogen supply. The graphs show elimination of active-tumor caused by a very high estrogen supply rate. This elimination lasts until the p53 supply rates drops (20 years later).

From the scenarios presented above, we see that for a fixed p53 level, tumor occurrence can happen if the estrogen level is increased from low to moderate values. Further increasing estrogen level to moderately high values can lead to a successful tumor elimination, which will last as long as estrogen and p53 are kept at these levels. Otherwise, if the estrogen level is further increased to higher values, or the p53 supply is decreased, then the active-tumor will recur.

Based on the above, we hypothesize that the interplay between estrogen and p53 levels provides a plausible biological mechanism that could explain the estrogen paradox and its paradoxical long term effect.

5. Conclusion:

In this work we proposed a plausible biological mechanism that explains the estrogen paradox in breast cancer treatment whereby (a) estrogen is one of the risk factors that can cause breast cancer and tumor regression and (b) short-term treatment with estrogen can successfully eliminate breast cancer whereas long-term treatment can cause cancer recurrence. We put forward four important factors that may elucidate the estrogen paradox. These are as follows:

- As in [27, 30], we proposed that there is a reservoir of dormant/occult breast cancers that get activated and become active-tumor cells.
- Motivated by the work in [4, 5, 39–45, 50], we accounted for the important role that estrogen and the protein p53 play in dormant cancer cells activation and active-tumor cells apoptosis.
- More importantly, we hypothesized that the activation of dormant cells only kicks in when the ratio between estrogen and p53 levels becomes sufficiently high.
- Finally, we incorporated the interaction between estrogen and the protein p53 reported in [44].

We developed a novel ODE-based mathematical describing the interaction dynamics between dormant breast cancer cells, active cancer cells, estrogen and p53. The model accounts for the relationship between

estrogen and p53, and their roles in the activation of dormant breast cancer cells and the apoptosis of active tumor cells. We performed a global stability analysis of the model by using the Poincaré-Bendixson theorem and differential inequalities. Further, by building upon the stability results, we constructed a bifurcation diagram in terms of the supply rates of estrogen and p53, λ_E and λ_P. This diagram depicted the areas in the (λ_E, λ_P) positive quadrant where breast cancer can (a) occur, (b) be successfully eliminated, or (c) recur. These findings were further supported by numerical simulations of the model with constant and time-dependent supply rates.

The results of our global stability analysis and bifurcation have provided invaluable insights into the apparent paradoxical role of estrogen in breast cancer treatment. The model suggests that the estrogen paradox and its long-term component could be explained by an interplay (given by the bifurcation curves) between estrogen and p53. In particular, the following points are worthy of note:

- Breast cancer occurrence may result from a rise in estrogen level or a drop in p53 level.
- Successful elimination of breast cancer may be achieved by antiestrogen drugs or by using high dose estrogen (HDE).
- Breast cancer recurrence could be caused by a further rise in estrogen level or by a drop in p53 level, with the recurrence time depending on the levels of estrogen and p53.
- Finally, we provide explicit conditions under which the paradoxical cancer recurrence, that emerges from prolonged HDE treatment, may be prevented.

However, the following important drawbacks prompt further investigation:

- The model ignores the key role that the immune system plays in cancer development and treatment. An extension of this model would be to include an anti-tumoral immune response.
- The model suffers from a lack of clinical and experimental data that are needed for (a) obtaining biologically backed expressions of the activation and death rates, and, more importantly, (b) validating the model.

Nonetheless, we believe that our work opens new possibilities for understanding the biological mechanisms behind the estrogen paradox, and that the theoretical work carried out in this paper provides sufficient grounds for further data collection on the interactions between estrogen, p53 and breast cancer.

Acknowledgments

R. Ouifki acknowledges the support from the DST/NRF SARChI Chair in Mathematical Models and Methods in Biosciences and Bioengineering at the University of Pretoria. S.I. Oke acknowledges the support from the Center of Excellence in Mathematical and Statistical Sciences (DST-NRF COE-MaSS), South Africa. Opinions expressed and conclusions arrived at are those of the authors and are not necessarily attributed to the CoE-MaSS.

Competing interests

The authors declare no competing interests.

6. Appendix

6.1. Proof of Theorem 1

Let us first consider the system formed by the last two equations of (2.1). That is,

$$\begin{cases} \frac{dE}{dt} = \lambda_E - \mu_E E \\ \frac{dP}{dt} = \lambda_P - \beta(E) P - \mu_P P \end{cases} \tag{6.1}$$

One can see that this system has only one equilibrium point given by $\left(E_0, \frac{\lambda_P}{\mu_P+\beta(E_0)}\right)$. Moreover, we have that

$$\frac{\partial\left(\lambda_E-\mu_E E\right)}{\partial E}+\frac{\partial\left(\lambda_P-\beta EP-\mu_P P\right)}{\partial P}=-\mu_E-\beta\left(E\right)-\mu_P<0.$$

Then, by Bendixson's criterion, system (6.1) has no periodic orbits in $\mathbb{R}^2_+$. Thus, by the Poincaré-Bendixson Theorem, $\left(E_0, \frac{\lambda_P}{\mu_P+\beta(E_0)}\right)$ is globally asymptotically stable.
Thus $\lim\limits_{t\to\infty} E\left(t\right)=E_0$ and $\lim\limits_{t\to\infty} P\left(t\right)=P_0$. By the continuity property of α and μ, we deduce that $\lim\limits_{t\to\infty}\mu(E,P)=\mu_{\lambda_P}\left(E_0\right)=\mu_0$ and $\lim\limits_{t\to\infty}\alpha\left(E\left(t\right),P\left(t\right)\right)=\alpha_{\lambda_P}\left(E_0\right)=\alpha_0$. Hence for all $\varepsilon>0$, there exists $T_\varepsilon>0$ such that for all $t>T_\varepsilon$, we have $\left|\mu\left(E\left(t\right),P\left(t\right)\right)-\mu_0\right|<\varepsilon$ and $\left|\alpha\left(E\left(t\right),P\left(t\right)\right)-\alpha_0\right|<\varepsilon$.
Thus, from $(2.1)_1$, we obtain

$$T_d\left(r_d-\alpha_0-\varepsilon-\frac{r_d}{K_d}T_d\right)<\frac{dT_d}{dt}<T_d\left(r_d-\alpha_0+\varepsilon-\frac{r_d}{K_d}T_d\right) \tag{6.2}$$

Applying standard results from differential inequalities to the first differential inequality of (6.2), we obtain

$$\frac{K_d\left(r_d-\alpha_0-\varepsilon\right)}{r_d\left(1-Ce^{-t\left(r_d-\alpha_0-\varepsilon\right)}\right)}<T_d\left(t\right)<\frac{K_d\left(r_d-\alpha_0+\varepsilon\right)}{r_d\left(1-Ce^{-t\left(r_d-\alpha_0+\varepsilon\right)}\right)}\text{ for }t>T_\varepsilon. \tag{6.3}$$

Thus, we have the following cases:

1. If $\alpha_0\geq r_d$, we show that $\lim_{t\to\infty}T_d\left(t\right)=0$.
   (a) In fact, if $\alpha_0=r_d$, then

   $$\frac{-K_d\varepsilon}{r_d\left(1-Ce^{t\varepsilon}\right)}<T_d\left(t\right)<\frac{K_d\varepsilon}{r_d\left(1-Ce^{-t\varepsilon}\right)}\text{ for }t>T_\varepsilon.$$

   which by taking the limit as $t\to\infty$ leads to

   $$0\leq\lim_{t\to\infty}T_d\left(t\right)\leq\frac{K_d\varepsilon}{r_d}.$$

   Thus by taking the limit as ε tends to 0, we obtain $\lim_{t\to\infty}T_d\left(t\right)=0$.
   (b) If $\alpha_0>r_d$, then we choose, for any arbitrary ξ in $\left(0,1\right)$, $\varepsilon=\left(\alpha_0-r_d\right)\xi$ in (6.3). Thus, there exists $T_\xi>0$ such that for all $t>T_\xi$, we have

   $$\frac{K_d\left(-\xi-1\right)\left(\alpha_0-r_d\right)}{r_d\left(1-Ce^{-t\left(\xi-1\right)\left(\alpha_0-r_d\right)}\right)}<T_d\left(t\right)<\frac{K_d\left(\xi-1\right)\left(\alpha_0-r_d\right)}{r_d\left(1-Ce^{-t\left(\xi-1\right)\left(\alpha_0-r_d\right)}\right)},$$

   which by taking the limit as $t\to\infty$ leads to $\lim_{t\to\infty}T_d\left(t\right)=0$.
   Thus, we have $\lim\limits_{t\to\infty}\alpha\left(E\left(t\right),P\left(t\right)\right)T_d\left(t\right)=0$, which by $\lim\limits_{t\to\infty}\mu(E,P)=\mu_0$, implies that

   $$C_-+T_a\left(B_--\frac{r_a}{K_a}T_a\right)<\frac{dT_a}{dt}<AT_a^2+B_+T_a+C_+ \tag{6.4}$$

   where $A=-\frac{r_a}{K_a}<0, B_\pm=r_a-\mu_0\pm\left(\alpha_0-r_d\right)\xi$ and $C_\pm=\pm\left(\alpha_0-r_d\right)\xi$.
   Since for ξ small enough, we have $B_\pm^2-4C_\pm A>0$, then, by Lemma 5, the general solution of

   $$x'=Ax^2+B_\pm x+C_\pm \tag{6.5}$$

   is given by

   $$x_\pm\left(t\right)=\frac{2B_\pm+\left(\sqrt{B_\pm^2-4C_\pm A}-B_\pm\right)\left(Me^{-t\sqrt{B_\pm^2-4C_\pm A}}+1\right)}{2A\left(Me^{-t\sqrt{B_\pm^2-4C_\pm A}}-1\right)}. \tag{6.6}$$

Thus, by using results from differential inequalities [51], we deduce from (6.4), (6.5) and (6.6) that

$$x_{-}(t) \leq T_a(t) \leq x_{+}(t),$$

which by taking the $t \to \infty$, leads to

$$\frac{2B_{-} + \left(\sqrt{B_{-}^2 - 4AC_{-}} - B_{-}\right)}{2A} \leq \lim_{t\to\infty} T_a(t) \leq \frac{2B_{+} + \left(\sqrt{B_{+}^2 - 4AC_{+}} - B_{+}\right)}{2A}.$$

By taking the limit as $\xi \to 0$, we obtain

$$\lim_{t\to\infty} T_a(t) = \frac{K_a}{2r_a}\left((r_a - \mu_0) + |r_a - \mu_0|\right).$$

Hence

i. If $r_a \leq \mu_0$, then $\lim_{t\to\infty} T_a(t) = 0$ implying that $\lim_{t\to\infty} (T_d(t), T_a(t), E(t), P(t)) = (0, 0, E_0, P_0) = \mathcal{E}_0$.

ii. If $r_a \geq \mu_0$, then $\lim_{t\to\infty} T_a(t) = \frac{K_a(r_a-\mu_0)}{r_a}$ implying that $\lim_{t\to\infty} (T_d(t), T_a(t), E(t), P(t)) = \left(0, \frac{K_a(r_a-\mu_0)}{r_a}, E_0, P_0\right) = \mathcal{E}^{\#}$.

2. If $r_d > \alpha_0$, then we choose, for any arbitrary ξ in $(0,1)$, $\varepsilon = (r_d - \alpha_0)\xi$ in (6.3). Thus, there exists $T_\xi > 0$ such that for all for $t > T_\xi$, we have

$$\frac{K_d(1-\xi)(r_d-\alpha_0)}{r_d\left(1 - Ce^{-t(1-\xi)(r_d-\alpha_0)}\right)} < T_d(t) < \frac{K_d(1+\xi)(r_d-\alpha_0)}{r_d\left(1 - Ce^{-t(1+\xi)(r_d-\alpha_0)}\right)}.$$

Taking the limit as $t \to \infty$, we obtain

$$\frac{K_d(1-\xi)(r_d-\alpha_0)}{r_d} < \lim_{t\to\infty} T_d(t) < \frac{K_d(1+\xi)(r_d-\alpha_0)}{r_d}.$$

Hence, by taking the limit as $\xi \to 0$, we obtain

$$\lim_{t\to\infty} T_d(t) = \frac{K_d(r_d-\alpha_0)}{r_d}.$$

This further implies that $\lim_{t\to\infty} \alpha(E(t), P(t)) T_d(t) = \frac{\alpha_0 K_d(r_d-\alpha_0)}{r_d}$, which by $\lim_{t\to\infty} \mu(E,P) = \mu_0$, implies that

$$AT_a^2 + B_{-}T_a + C_{-} < \frac{dT_a}{dt} < AT_a^2 + B_{+}T_a + C_{+} \tag{6.7}$$

where $A = -\frac{r_a}{K_a} < 0, B_{\pm} = r_a - \mu_0 \pm (r_d - \alpha_0)\xi$ and $C_{\pm} = \frac{\alpha_0 K_d(r_d-\alpha_0)}{r_d} \pm (r_d - \alpha_0)\xi$.
Since for ξ small enough, we have, $C_{\pm} > 0$ implying that $B_{\pm}^2 - 4C_{\pm}A > 0$, then by using the same argument as above, we obtain

$$x_{-}(t) \leq T_a(t) \leq x_{+}(t).$$

where

$$x_{\pm}(t) = \frac{2B_{\pm} + \left(\sqrt{B_{\pm}^2 - 4AC_{\pm}} - B_{\pm}\right)\left(Me^{-t\sqrt{B_{\pm}^2-4AC_{\pm}}} + 1\right)}{2A\left(Me^{-t\sqrt{B_{\pm}^2-4AC_{\pm}}} - 1\right)}.$$

Taking the limit as $t \to \infty$ leads to

$$\frac{2B_{+} + \left(\sqrt{B_{+}^2 - 4AC_{+}} - B_{+}\right)}{2A} \leq \lim_{t\to\infty} T_a(t) \leq \frac{2B_{-} + \left(\sqrt{B_{-}^2 - 4AC_{-}} - B_{-}\right)}{2A},$$

which, by further taking the limit as $\xi \to 0$, we obtain

$$\lim_{t\to\infty} T_a(t) = \frac{K_a\left(r_a - \mu_0 + \sqrt{(r_a-\mu_0)^2 + 4\frac{K_d(r_d-\alpha_0)\alpha_0}{r_d}\frac{r_a}{K_a}}\right)}{2r_a} = T_a^*.$$

Thus $(T_d(t), T_a(t), E(t), P(t))$ converge to $\mathcal{E}^* = (T_d^*, T_a^*, E_0, P_0)$.

6.2. Lemma 5 and proof:

Lemma 5. *Using partial fractions we can show that if $B^2 - 4AC > 0$, then the general solution of equation*

$$x' = Ax^2 + Bx + C \tag{6.8}$$

is given by

$$x(t) = \frac{2B + \left(\sqrt{B^2-4AC} - B\right)\left(Me^{-t\sqrt{B^2-4AC}} + 1\right)}{2A\left(Me^{-t\sqrt{B^2-4AC}} - 1\right)},$$

where M is an arbitrary constant.

Proof. If $B^2 - 4AC > 0$, then equation (6.8) can be written as

$$\frac{dx}{dt} = A(x - x_1)(x - x_2).$$

where $x_1 = \frac{-B-\sqrt{B^2-4AC}}{2A}$ and $x_2 = \frac{-B+\sqrt{B^2-4AC}}{2A}$.
Using the method of separation of variables in conjunction with partial fractions decomposition, we find that the general solution of this equation is

$$x = \frac{x_1 - x_2 Me^{(x_1-x_2)At}}{1 - Me^{(x_1-x_2)At}}.$$

Hence

$$x(t) = \frac{2B + \left(-B + \sqrt{B^2-4AC}\right)\left(1 + Me^{-t\sqrt{B^2-4AC}}\right)}{2A\left(Me^{-t\sqrt{B^2-4AC}} - 1\right)}. \tag{6.9}$$

□

References

[1] E. L. Esakov, J. Hale, E. G. Richards, L. Torre-Healy, K. Gullapalli, D. Trivedi, A. Chumakova, O. Wessely, J. Jensen, J. Lathia, *et al.*, "Therapeutic strategies to induce erα in luminal breast cancer to enhance tamoxifen efficacy," *Endocrine-related cancer*, vol. 26, no. 8, pp. 689–698, 2019.

[2] S. B. Mkango, N. Shaban, E. Mureithi, and T. Ngoma, "Dynamics of breast cancer under different rates of chemoradiotherapy," *Computational and mathematical methods in medicine*, vol. 2019, 2019.

[3] R. S. C.K. Osborne, "Mechanisms of endocrine resistance in breast cancer," *Annu Rev Med*, vol. 62, pp. 233–247, 2011.

[4] J. Hugh, L. Haddon, J. M. Githaka, X. Hu, G. Bigras, B. Loney, J. Hanson, Z. Gabos, F. Huang, M. Hitt, *et al.*, "Abstract p2-11-10: Estrogen drives the therapeutic hormonal response in er+ breast cancers," 2020.

[5] R. Santen and W. Yue, "Cause or prevention of breast cancer with estrogens: analysis from tumor biologic data, growth kinetic model and women's health initiative study," *Climacteric*, vol. 22, no. 1, pp. 3–12, 2019.

[6] A. Haddow, J. M. Watkinson, E. Paterson, and P. Koller, "Influence of synthetic oestrogens on advanced malignant disease," *British medical journal*, vol. 2, no. 4368, p. 393, 1944.

[7] G. Binnie, "Regression of tumours following treatment by stilboestrol andx-ray therapy, with notes on a case of breast tumour which regressed withstilboestrol alone," *Br. J. Radiol.*, vol. 17, pp. 42–45, 1944.

[8] I. N. B.J. Kennedy, "Effects of intensive sex steroid hormone therapyin advanced breast cancer," *J. Am. Med. Assoc.*, vol. 152 (12), pp. 1135–1141, 1953.

[9] H. Kautz, "Androgens and estrogen in the treatment of disseminatedmammary carcinoma," *J. Am. Med. Assoc.*, vol. 172 (12), pp. 1271–1283, 1960.

[10] B. Kennedy, "Massive estrogen administration in premenopausal womenwith metastatic breast cancer," *Cancer*, vol. 15, p. 641–648, 1962.

[11] B. Kennedy, "Systemic effects of androgenic and estrogenic hormones inadvanced breast cancer," *J. Am. Geriatr. Soc.*, vol. 13, pp. 230–235, 1965.

[12] B. Kennedy, "Diethylstilbestrol versus testosterone propionate therapy inadvanced breast cancer," *Surg. Gynecol. Obstetr.*, vol. 120, pp. 1246–1250, 1965.

[13] M. Cole, C. Jones, and I. Todd, "A new anti-oestrogenic agent in late breast cancer: an early clinical appraisal of ici46474," *British journal of cancer*, vol. 25, no. 2, p. 270, 1971.

[14] P. E. Lønning, P. D. Taylor, G. Anker, J. Iddon, L. Wie, L.-M. Jørgensen, O. Mella, and A. Howell, "High-dose estrogen treatment in postmenopausal breast cancer patients heavily exposed to endocrine therapy," *Breast cancer research and treatment*, vol. 67, no. 2, pp. 111–116, 2001.

[15] A. Agrawal, J. Robertson, and K. Cheung, "Efficacy and tolerability of high doseethinylestradiol in post-menopausal advanced breast cancer patients heavilypre-treated with endocrine agents," *World J. Surg. Oncol.*, vol. 4, p. 44, 2006.

[16] R. Mahtani, A. Stein, and C. Vogel, "High-dose estrogen as salvage hormonaltherapy for highly refractory metastatic breast cancer: a retrospective chartreview," *Clin. Ther.*, vol. 31, pp. 2371–2378, 2009.

[17] H. Iwase, Y. Yamamoto, M. Yamamoto-Ibusuki, K. Murakami, Y. Okumura, S.Tomita, T. Inao, Y. Honda, Y. Omoto, and K. Iyama, "Ethinylestradiol is beneficialfor postmenopausal patients with heavily pre-treated metastatic breastcancer after prior aromatase inhibitor treatment: a prospective study," *Br. J.Cancer*, vol. 109 (6), pp. 1537–1542, 2013.

[18] P. Chalasani, A. Stopeck, K. Clarke, and R. Livingston, "A pilot study of estradiolfollowed by exemestane for reversing endocrine resistance inpostmenopausal women with hormone receptor-positive metastatic breastcancer," *Oncologist*, vol. 19 (11), pp. 1127–1128, 2014.

[19] G. Zucchini, A. Armstrong, A. Wardley, G. Wilson, V. Misra, M. Seif, W.D.Ryder, J. Cope, E. Blowers, A. Howell, C. Palmieri, and S. Howell, "A phase ii trial oflow-dose estradiol in postmenopausal women with advanced breast cancerand acquired resistance to aromatase inhibition," *Eur. J. Cancer*, vol. 51 (18), pp. 2725–2731, 2015.

[20] M. Ellis, F. Gao, F. Dehdashti, D. Jeffe, P. Marcom, L. Carey, M. Dickler, P. Silverman, G. Fleming, A. Kommareddy, S. Jamalabadi-Majidi, R. Crowder, and B. Siegel, "Lower-dose vs high-dose oral estradiol therapy of hormonereceptor-positive, aromatase inhibitor-resistant advanced breast cancer: aphase 2 randomized study," *JAMA*, vol. 302 (7), pp. 774–780, 2009.

[21] M. Dowsett, J. Cuzick, J. Ingle, A. Coates, J. Forbes, J. Bliss, M. Buyse, M. Baum, A. Buzdar, M. Colleoni, *et al.*, "Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen," *Journal of Clinical Oncology*, vol. 28, no. 3, pp. 509–518, 2010.

[22] V. C. Jordan and A. M. Brodie, "Development and evolution of therapies targeted to the estrogen receptor for the treatment and prevention of breast cancer," *Steroids*, vol. 72, no. 1, pp. 7–25, 2007.

[23] G. L. Anderson, M. Limacher, A. R. Assaf, T. Bassford, S. Beresford, H. Black, D. Bonds, R. Brunner, R. Brzyski, and B. Caan, "Women's health initiative steering committee et al. effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the women's health initiative randomized controlled trial," *JAMA*, vol. 291, pp. 1701–1712, 2004.

[24] M. Stefanick, G. Anderson, K. Margolis, S. Hendrix, R. Rodabough, E. Paskett, D. Lane, F. Hubbell, A. Assaf, and G. Sarto, "WHI investigators et al. effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy," *JAMA*, vol. 295, pp. 1647–1657, 2006.

[25] C. Schairer, J. Lubin, R. Troisi, S. Sturgeon, L. Brinton, and R. Hoover, "Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk," *JAMA*, vol. 283, pp. 485–491, 2000. [Erratum appears in JAMA 2000, **284:**2597].

[26] B. V and M. W. SC., "Breast cancer and hormone-replacement therapy in the million women study," *Lancet*, vol. 362, p. 1160, 2003. [Erratum appears in Lancet 2003, **362:**1160].

[27] R. Santen and D. Allred, "The estrogen paradox," *Nat Rev Endocrinol*, vol. 3(7), pp. 496–497, 2007.

[28] V. C. Jordan, "The new biology of estrogen-induced apoptosis applied to treat and prevent breast cancer," *Endocr Relat Cancer*, vol. 22, no. 1, pp. R1–R31, 2015.

[29] Z. Suba, "The pitfall of the transient, inconsistent anticancer capacity ofantiestrogens and the mechanism of apparent antiestrogen resistance," *DrugDes. Dev. Ther.*, vol. 9, pp. 4341–4353, 2015.

[30] R. Santen, W. Yue, and D. Heitjan, "Occult breast tumor reservoir: Biological properties and clinical significance," *HORM CANC*, vol. 4, pp. 195–207, 2013.

[31] X. H.-F. Zhang, M. Giuliano, M. V. Trivedi, R. Schiff, and C. K. Osborne, "Metastasis dormancy in estrogen receptor–positive breast cancer," 2013.

[32] C. M. Koebel, W. Vermi, J. B. Swann, N. Zerafa, S. J. Rodig, L. J. Old, M. J. Smyth, and R. D. Schreiber, "Adaptive immunity maintains occult cancer in an equilibrium state," *Nature*, vol. 450, no. 7171, pp. 903–907, 2007.

[33] P. Hahnfeldt, D. Panigrahy, J. Folkman, and L. Hlatky, "Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy," *Cancer research*, vol. 59, no. 19, pp. 4770–4775, 1999.

[34] H. Enderling, A. R. Anderson, M. A. Chaplain, A. Beheshti, L. Hlatky, and P. Hahnfeldt, "Paradoxical dependencies of tumor dormancy and progression on basic cell kinetics," *Cancer research*, vol. 69, no. 22, pp. 8814–8821, 2009.

[35] E. Favaro, A. Amadori, and S. Indraccolo, "Cellular interactions in the vascular niche: implications in the regulation of tumor dormancy," *Apmis*, vol. 116, no. 7-8, pp. 648–659, 2008.

[36] B. Quesnel, "Tumor dormancy and immunoescape," *Apmis*, vol. 116, no. 7-8, pp. 685–694, 2008.

[37] E. Lim, O. Metzger-Filho, and E. P. Winer, "The natural history of hormone receptor–positive breast cancer," *Oncology*, vol. 26, no. 8, 2012.

[38] M. W. Retsky, R. Demicheli, W. Hrushesky, M. Baum, and I. Gukas, "Dormancy and surgery-driven escape from dormancy help explain some clinical features of breast cancer," *Apmis*, vol. 116, no. 7-8, pp. 730–741, 2008.

[39] E. Cavalieri, D. Chakravarti, J. Guttenplan, E. Hart, J. Ingle, R. Jankowiak, P. Muti, E. Rogan, J. Russo, R. Santen, and T. Sutter, "Catechol estrogen quinones as initiators of breast and other human cancers: implications for biomarkers of susceptibility and cancer prevention," *Biochim Biophys Acta.*, vol. 1766(1), pp. 63–78, 2006.

[40] S. I. Oke, M. B. Matadi, and S. S. Xulu, "Optimal control analysis of a mathematical model for breast cancer," *Mathematical and Computational Applications*, vol. 23, no. 2, p. 21, 2018.

[41] V. Valayannopoulos, F. Bajolle, J.-B. Arnoux, S. Dubois, N. Sannier, C. Baussan, F. Petit, P. Labrune, D. Rabier, C. Ottolenghi, *et al.*, "Successful treatment of severe cardiomyopathy in glycogen storage disease type iii with d, l-3-hydroxybutyrate, ketogenic and high-protein diet," *Pediatric Research*, vol. 70, no. 6, pp. 638–641, 2011.

[42] D. Eliyahu, D. Michalovitz, S. Eliyahu, O. Pinhasi-Kimhi, and M. Oren, "Wild-type p53 can inhibit oncogene-mediated focus formation," *Proc Natl Acad Sci USA*, vol. 86, pp. 8763–8767, 1989.

[43] C. Finlay, P. Hinds, and A. Levine, "The p53 proto-oncogene can act as a suppressor of transformation," *Cell*, vol. 57, pp. 1083–1093, 1989.

[44] S. D. Konduri, R. Medisetty, W. Liu, B. A. Kaipparettu, P. Srivastava, H. Brauch, P. Fritz, W. M. Swetzig, A. E. Gardner, S. A. Khan, *et al.*, "Mechanisms of estrogen receptor antagonism toward p53 and its implications in breast cancer therapeutic response and stem cell regulation," *Proceedings of the National Academy of Sciences*, vol. 107, no. 34, pp. 15081–15086, 2010.

[45] C. K. Glass and M. G. Rosenfeld, "The coregulator exchange in transcriptional functions of nuclear receptors," *Genes & development*, vol. 14, no. 2, pp. 121–141, 2000.

[46] S. H. Shirley, J. E. Rundhaug, J. Tian, N. Cullinan-Ammann, I. Lambertz, C. J. Conti, and R. Fuchs-Young, "Transcriptional regulation of estrogen receptor- by p53 in human breast cancer cells," *Cancer Research*, vol. 69, no. 8, pp. 3405–3414, 2009.

[47] C. Berger, Y. Qian, and X. Chen, "The p53-estrogen receptor loop in cancer," *Current molecular medicine*, vol. 13(8), pp. 1229–1240, 2013.

[48] H.-C. Wei, "Bifurcation analysis of a mathematical model of tumor growth in mcf-7 breast cancer cell line," in *Proceedings of the 12th International Conference*, vol. 70, pp. 33–40, 2020.

[49] R. E. Stace, T. Stiehl, M. A. Chaplain, A. Marciniak-Czochra, and T. Lorenzi, "Discrete and continuum phenotype-structured models for the evolution of cancer cell populations under chemotherapy," *Mathematical Modelling of Natural Phenomena*, vol. 15, p. 14, 2020.

[50] L. Zinger, K. Merenbakh-Lamin, A. Klein, A. Elazar, S. Journo, T. Boldes, M. Pasmanik-Chor, A. Spitzer, T. Rubinek, and I. Wolf, "Ligand-binding domain–activating mutations of esr1 rewire cellular metabolism of breast cancer cells," *Clinical Cancer Research*, vol. 25, no. 9, pp. 2900–2914, 2019.

[51] J. Hale, *Ordinary Differential Equations*. Dover Books on Mathematics Series, Dover Publications, 2009.