EXAMINATION OF BRAESS' PARADOX ON A REAL DATA-VALIDATED 3-DIMENSIONAL PROSTATE CANCER MODEL

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Esraa Salam Abed AL-HAMADANI

Thesis Advisor
Assist. Prof. Dr. Özlem OZTURK MIZRAK

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Thesis Advisor
Assist. Prof. Dr. Özlem ÖZTÜRK MIZRAK

T.C.
Karabuk University
Institute of Graduate Programs
Department of Mathematics
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I certify that in my opinion the thesis submitted by Esraa Salam Abed AL-HAMADANI titled "EXAMINATION OF BRAESS' PARADOX ON A REAL DATA-VALIDATED 3-DIMENSIONAL PROSTATE CANCER MODEL" is fully adequate in scope and in quality as a thesis for the degree of Choose Degree.

Assist. Prof. Dr. Özlem ÖZTÜRK MIZRAK .....
Thesis Advisor, Department of Mathematics

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Esraa Salam Abed AL_HAMADANI

ABSTRACT

M. Sc. Thesis

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Esraa Salam Abed AL_HAMADANI

Karabük University
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Assist. Prof. Dr. Özlem ÖZTÜRK MIZRAK
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This thesis consists of four parts. The first part contains all the information introductory and the literature review. The second part contains suggested a new model added to the models of Hirata et al., and testing its stability. In the third part, clinical data is given, an explanation of the treatment protocol, and make a comparison between the models by means of numerical simulation. The last part is dedicated to giving concluding remarks.

Key Words **:** Hirata et al model, Real data, Prostate cancer, Braess' paradox, Hormone therapy, linear model, prostate specific antigen.

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ÖZET

Yüksek Lisans Tezi

REEL VERİLERLE DOĞRULANMIŞ ÜÇ BOYUTLU BİR PROSTAT KANSERİ MODELİ ÜZERİNDE BRAESS'IN PARADOKSUNUN İNCELENMESİ

Esraa Salam Abed AL_HAMADANI

Karabük Üniversitesi
Lisansüstü Eğitim Enstitüsü
Matematik Anabilim Dalı

Tez Danışmanı:
Dr. Öğr. Üyesi Özlem ÖZTÜRK MIZRAK
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Bu tez dört bölümden oluşmaktadır. Birinci bölüm giriş niteliğindeki tüm bilgileri ve literatür taramasını içermektedir. İkinci bölüm, Hirata ve diğerlerinin modellerine eklenen yeni bir model önerisi ve kararlılığının test edilmesini içermektedir. Üçüncü bölümde klinik veriler verilmiş, tedavi protokolü anlatılmış ve sayısal benzetim yoluyla modeller arası karşılaştırma yapılmıştır. Son bölüm, sonuç açıklamalarına ayrılmıştır.

Anahtar Kelimeler : Hirata ve diğerleri modeli, Gerçek veriler, Prostat kanseri, Braess paradoksu, Hormon tedavisi, lineer model, prostat spesifik antijen.

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SYMBOLS AND ABBREVIATIONS INDEX

SYMBOLS

λ : Lambda

$\mathbb{R}$: The set of all real numbers

ABBREVIATIONS

ADT : Androgen Deprivation Therapy

DHT : Dihydrotestosterone

IAS : Intermittent Androgen Suppression

CR : Castration-Reluctant

CS : Castration-Sentient

PSA : Prostate-Specific Antigen

AD : Androgen-Dependent

AI : Androgen-Independent

PI : Product Integration

MEASUREMENT UNITS

ng/mL : Nanograms per milliliter

nmol/L : Nanomoles Per Liter

μg/L : Micrograms per liter

PART 1

INTRODUCTION

The prostate is an accessory sex gland in men whose growth and function depend on a constant providing of the hormone testosterone, the most important sex hormone excreted by the testes [10]. Furthermore, under the androgenic steroids effect (such as testosterone), the extent of growth depends on the quantity of dihydrotestosterone shaped in prostate cells from a particular past hormone. The most significant of several enzymatic steps which are likely involve in the metabolic pathway is the 5α-decrease of the hormone testosterone, which leads straight to the structuring of dihydrotestosterone. So that, when a provenance of testosterone is taken away such by operative or medicinal castrate, the concentricity of the dihydrotestosterone inside the cells decreases and prostate shrinking occurs [18]. Principality prostate cancer is a disease that dependent on androgen and is affected by the same arranger mechanisms that the non-malignant cells are affected by. Androgen Deprivation Therapy (ADT) has become the principal therapy for progressed and metastatic prostate tumors since it was discovered that prostate cells depend on the androgen [16,38,43]. The aim of ADT is to either lower androgen levels or stop them from having an impact on prostate cells [11]. Dihydrotestosterone (DHT) and testosterone are the main androgens in the body [11]. The testicles produce the most of androgens, while the adrenal glands only make about 5% of them [16,42]. Lowering androgen levels to prevent it from reaching the cells of prostate cancer leads mostly to cancers shrinking and growing slower, but ADT solely just prolongs patients' lives and does not cure prostate cancer [11]. The principal disadvantage of ADT is the evolution of impedance because of the proliferation of the cells cancer at the repression levels of the androgen [11]. The evolution of resistance can take from slight months to decades [19,43], after which there are only poorer treatments and higher mortality rates [23]. Intermittent androgen suppression (IAS) has been used to postpone the advancement of androgen impedance and got the quality of the patient's life better [3]. During the treatment-free period, patients can recover from ADT's intense side impact [25], and the IAS has been shown by studies it might not

adversely impact the duration of androgen impedance or staying life compared with the continuous ADT [14]. Jackson was the first to research possible paths for androgenetic tumor relapse during ADT [21]. Jackson modeled the mechanisms of the development of prostate cancer that is resistant the castration, by using a set of partial differential equations, the major discovery of his work was ADT apt to fail, and the delays of resistance can only happen within a limited range of the values of the parameter [21]. The dynamics of androgen suppression therapy were then modeled by a large number of researchers. And by a system of ordinary differential equations, Ideta et al. studied the mechanism of ADT [20]. They accounted for androgen levels, castration-reluctant (CR) and castration-sentient (CS) cell groups. Mutations were included in their model from CS to CR cells, and they concentrated on the advancement of cancer cell impedance and on the comparison of continuous versus intermittent treatment. Their outcomes showed that the mutations ratios between cancer kinds have an effect on the timing of the relapse of androgen [20]. By expanding the work of Jackson and Ideta et al., Portz et al. developed an ADT model [33]. Just like Ideta et al. their model contains two cell groups but contained a restricted nutritious-founded tumor growth model as well, via cell quota models [9]. Hirata et al. suggested a model mathematical that can at amount form reproduce the dynamics of the level of serum Prostate Specific Antigen (PSA) for prostate cancer beneath IAS [18]. They took into account three population cells using a piece-wise linear model to appropriate PSA data, where it is modeled the testosterone dynamics with fast shifts among two levels, which are castrated concentrations of the androgen and normal. They used time course data for serum PSA levels during IAS treatment in order to support the validity of the model [3,4,5]. The impacts of hormone therapy on prostate cancer has been mathematically characterized in former publications [20,21,22,39,41], but this is the first model that has been verified from its credibility by clinical data [18]. The model carefully reproduced the activities of a curative decrease of PSA and correctly predicted future nadir level. Also, Hirata et al. provided the best explication for the early advancement of androgen independence by explaining the coexistence of irreversible and reversible changes inside malignant cells [18]. The cells included in their model are CS cells that may change into CR cells, CR cells that may change into the cells CS and the cells CR that may not change back into the cells CS. Considering the above, we see that Hirata's model will be an ideal model for applying Braess' paradox because it is a simple linear model, that uses three populations of cancer cells that are changeable for each other, which gives us a

reticulated shape that paradoxes may occur, also its results are verified by real clinical data for patients with prostate cancer [3,4,5]. The Braess' paradox is a non-intuitive behavioral phenomenon that states that adding a capacity or a path to a network with lines and specific ends can in some cases lead to a decrease in overall performance or the exact opposite happens, as removing or canceling a specific capacity or path leads to increased overall performance which is a surprising detection in contrary to conventional wisdom. It was set by Dietrich Braess for the first time in 1968 in his classic paper which was inspired by a seminar cast by W. Knoedel in Muenster in 1967 while Braess was 29 age [29]. Braess' paper was about the possibility of the happening of counter-intuitive behavior in user-optimized transportation webs. He structured a model for a transportation web consisting of a single origin or destination pair of nodes and two parallel pathways so that when added an extra link for expanding it, gives travelers another way option, the outcome was an increase in travel costs for all users. This unexpected behavior has become known as the Braess' paradox. The paradox is still relevant today, where it has inspired and continues to attract many researchers in an extensive variety of scientific majors, driving more advancements in both theory and practice, like in the science of computers, for the modeling of communication networks and the internet [26,30,35,36], in the engineering of electrical, to study power systems [1,8,44], and the circuits of electronic [31], also in the mechanical case of physics [8], and fluid systems [7], in metabolic networks in biology [28], ecosystems [37] and targeted cancer therapy [12,24], and, interestingly, Braess' paradox analogy matches with the analysis of sports teams, where the removal of a player improves team performance in sports analytics [15,40]. Due to the interest of many majors, Braess et al. published a translation of this article from German to English [2]. The preface Nagurney and Boyce to the translated article include an extra background of how Braess arises with the counterintuitive phenomenon, as well as an explanation of some concepts and terminology [29]. The importance of Braess' paradox lies in the fact that it opened horizons to think in a way that is far from the usual stereotyped methods of addition and deletion for regular networks with moving entities, where it explained that some of the results that are obtained after adding or deleting were reverse and unpredictable. It also works on the concept of system optimization and user optimization for networks. Hirata et al. presented three different scenarios for modeling the relationship between prostate cancer cells, and they adopted the first model as their original model because it is most suitable for the data compared to the other two models

[18]. Based on that, we chose the original model to be our reference in this thesis, we added one capacity (one parameter) to it and obtained a new model. We will compare these two models to investigate whether the new model is more suitable for the data than the original one or it will give us undesirable reverse results thus causing the Braess' paradox.

PART 2

THE SUGGESTED MODEL

2.1. PRODUCING THE NEW MODEL

To initiate IAS in prostate cancer patients, hormonal therapy (androgen deprivation) is used to decrease serum testosterone concentrations to castration levels. One takes notice of PSA levels that correlate with prostate cancer volume. Based on the PSA value, the treatment strategy to control the testosterone level is decided. The treatment will discontinue if the serum PSA level is below 4.0 ng/mL: the give of treatment is not till the PSA level has returned to approx 10 ng/mL and then resuming patients to treatment again. To be able to explain the biphasic degradation of PSA by a model that is linear, requires two variables that are linear with decline different factors, side by side with a factor that is increasing to contain relapse prospect, and also mathematically the models that reproduce PSA dynamics at amount form, must be 3-dimensional at least. Building on that, Hirata et al. tested this formularization for androgen independence that appearance in prostate cancer [18], Figure 2.1. The model takes into account two types of changes, irreversible [11] and reversible [34]. The changes that are irreversible in prostate malignancies may implicate bodily mutations, like those implicating androgen receptors, but others are not excluded either [27,32]. The changes that are reversible may implicate reversible adjustments under the therapy IAS. The 1st variable of the model (State 1) represents the androgen dependent population cells (AD) population cells, the 2nd variable (State 2) represents the androgen independent population cells (AI) produced from changes able to reverse, and the 3rd variable (State 3) represents the population cells (AI) resulting from irreversible changes in gene mutation. Under treatment conditions, cells in state 1 may transition into cells in state 2 or 3, and cells in state 2 may transition into cells in state 3. Under the non-treatment conditions, state 2 cells may revert to state 1 due to reversibility.

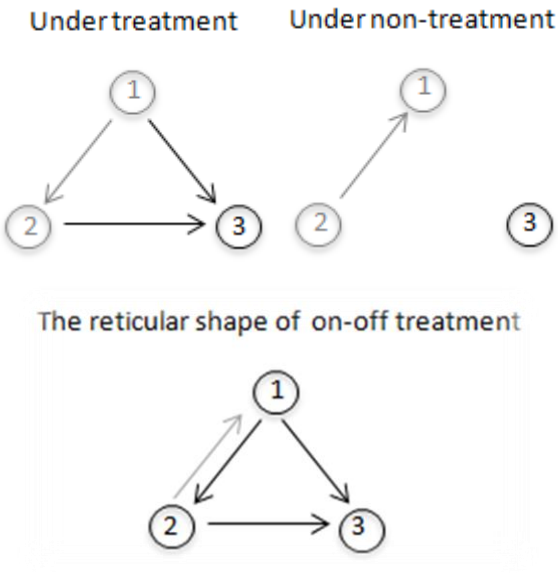

Figure 2.1. Schematic representation of a model of prostate cancer containing irreversible and reversible changes.

The present unanimity is that irreversible and reversible paths may develop inside cancer cell due to mutational and genetic changes and lead to the independence of androgen [34]. Hirata et al. expressed PSA as a sum of weighted of all variables [18]. This model expands on the research done by Ideta et al. [20], which solely took into account mutational changes that could not be reversed [20]. They assume mathematically that the subpopulation of cancer cells in the state i ($i = 1,2,3$) at time t is represented by $x_i(t)$. Then, treatment and non-treatment periods' equations are provided as

$$\frac{d}{dt}\begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = \begin{pmatrix} w_{1,1}^1 & 0 & 0 \\ w_{2,1}^1 & w_{2,2}^1 & 0 \\ w_{3,1}^1 & w_{3,2}^1 & w_{3,3}^1 \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} \tag{2.1}$$

for the treatment period and

$$\frac{d}{dt}\begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = \begin{pmatrix} w_{1,1}^0 & w_{1,2}^0 & 0 \\ 0 & w_{2,2}^0 & 0 \\ 0 & 0 & w_{3,3}^0 \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} \tag{2.2}$$

for the non-treatment period.

Where the population growth rates for states 1, 2 and 3 under the treatment condition are represented by the parameters $w_{1,1}^1$, $w_{2,2}^1$ and $w_{3,3}^1$ respectively, whereas those under the non-treatment condition are represented by $w_{1,1}^0$, $w_{2,2}^0$ and $w_{3,3}^0$. Inflow rates from states 1, 1 and 2, respectively, to states 2, 3 and 3, under the treatment condition are represented by the parameters $w_{2,1}^1$, $w_{3,1}^1$ and $w_{3,2}^1$ while $w_{1,2}^0$ represents the inflow rate from state 2 to state 1 in case non-treatment. According to Figure 2.1, the other matrices' elements are all zero. The pathways from 1 and 2 to 3 can be thought of as mutation rates because they are irreversible. Here, they assume that the castration level of testosterone causes the influx owing to the somatic mutations, hence they do not include $w_{3,1}^0$, $w_{3,2}^0$ and $w_{2,1}^0$ in the model. The same presumption was applied in earlier research [18]. All $w_{i,j}^m$ constants are changes rates per of time. Variables are normalized quantities no-dimensional. For simplicity, the serum PSA level is denoted by the formula $x_1 + x_2 + x_3$. $w_{i,j}^m > 0$ for i ≠ j, i.e., all the elements that are non-diagonal and non-zero are positive. It is necessary to have $w_{3,3}^1 > 0$ in order to reproduce the PSA relapse under CAS. This model was described as one that contained both reversible and irreversible modifications. They had examined and confirmed the model's piecewise linearity, quick change in testosterone level, and model design assumptions. Two additional linear models were also taken into account by Hirata et al. [18]. Only reversible alterations were included in one of these models, and in the other model the irreversible changes only, In Figures 2.2 and 2.3. In the irreversible change scenario, they assumed here all changes are irreversible Figure 2.2. The mathematical model that they used was

$$\frac{d}{dt}\begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = \begin{pmatrix} w_{1,1}^1 & 0 & 0 \\ w_{2,1}^1 & w_{2,2}^1 & 0 \\ w_{3,1}^1 & w_{3,2}^1 & w_{3,3}^1 \end{pmatrix}\begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} \tag{2.3}$$

for the treatment period and

$$\frac{d}{dt}\begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = \begin{pmatrix} w_{1,1}^0 & 0 & 0 \\ 0 & w_{2,2}^0 & 0 \\ 0 & 0 & w_{3,3}^0 \end{pmatrix}\begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} \tag{2.4}$$

for the non-treatment period.

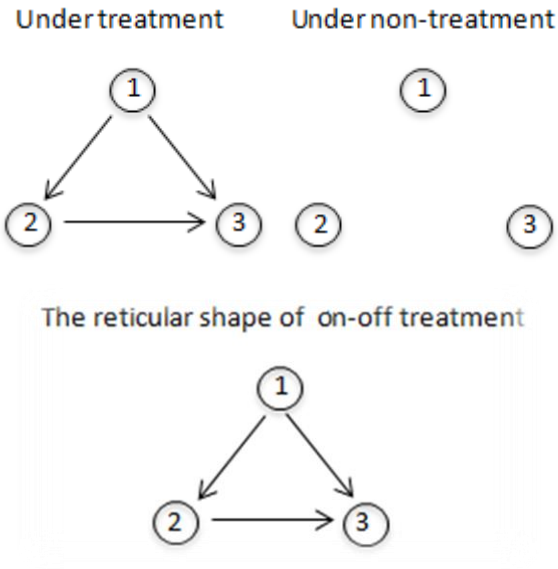

Figure 2.2. Schematic representation of a model of prostate cancer containing the changes of irreversible only. In contrast to Figure 2.1, the model in this figure does not change during the non-treatment period.

In the reversible change model, they examined this scenario under the assumption that all changes are reversible, Figure 2.3. The formulation of the mathematical model in this instance was

$$\frac{d}{dt}\begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = \begin{pmatrix} w_{1,1}^1 & 0 & 0 \\ w_{2,1}^1 & w_{2,2}^1 & 0 \\ w_{3,1}^1 & w_{3,2}^1 & w_{3,3}^1 \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} \tag{2.5}$$

for the treatment period and

$$\frac{d}{dt}\begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = \begin{pmatrix} w_{1,1}^0 & w_{1,2}^0 & w_{1,3}^0 \\ 0 & w_{2,2}^0 & w_{2,3}^0 \\ 0 & 0 & w_{3,3}^0 \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} \tag{2.6}$$

for the non-treatment period.

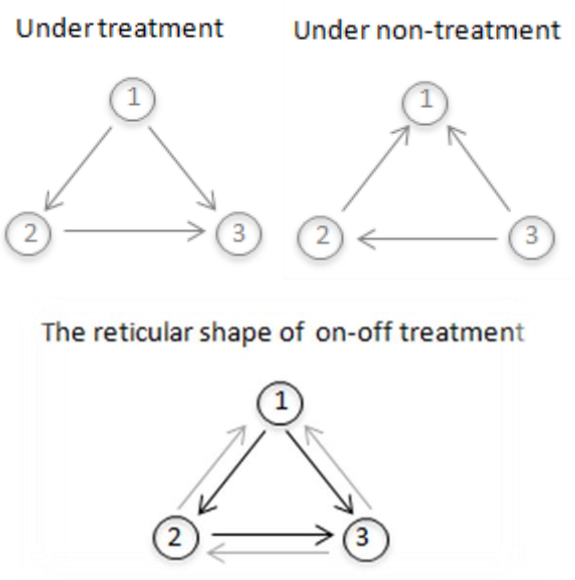

Figure 2.3. Schematic representation of a model of prostate cancer containing the changes of reversible only. In the model of this figure, compared to Figure 2.1, during therapy time all the changes paths in the non-treatment period are reversed.

We considered another linear model derived from Hirata et al. models, this model includes reversible and irreversible changes, which is similar to the first model of Hirata et al. but here in this case we took the changes are reversible in two sub-populations of cancer cells, in states 2 and 3, not just one, where they are 3 influx to 2 and 2 influx to 1 under the case of non-treatment, Figure 2.4. The mathematical model for this case we wrote as

$$\frac{d}{dt}\begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = \begin{pmatrix} w_{1,1}^1 & 0 & 0 \\ w_{2,1}^1 & w_{2,2}^1 & 0 \\ w_{3,1}^1 & w_{3,2}^1 & w_{3,3}^1 \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} \tag{2.7}$$

for the treatment period and

$$\frac{d}{dt}\begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = \begin{pmatrix} w_{1,1}^0 & w_{1,2}^0 & 0 \\ 0 & w_{2,2}^0 & w_{2,3}^0 \\ 0 & 0 & w_{3,3}^0 \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} \tag{2.8}$$

for the non-treatment period.

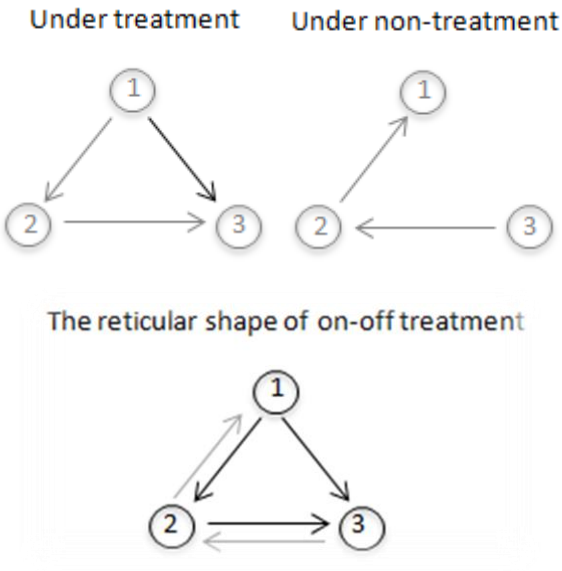

Figure 2.4. Schematic representation of a model of prostate cancer containing irreversible and reversible changes (the suggested model). In this model, the changes are the same as in the model in Figure 2.1, the only difference is that there is an extra path during the non-treatment which is the cells of the cancer of state 3 may change to cells of state 2.

2.2. STABILITY ANALYSIS OF THE NEW MODEL

In this section, we are trying to check the stability of our new model (2.7)-(2.8).

To be able to find the stability of the system, first we have to find the critical point for it:

For on-treatment system

$$f_{x_1} = w_{1,1}^1 x_1 = 0 \rightarrow x_1 = 0.$$
$$f_{x_2} = w_{2,1}^1 x_1 + w_{2,2}^1 x_2 = 0 \rightarrow w_{2,2}^1 x_2 = 0 \rightarrow x_2 = 0.$$
$$f_{x_3} = w_{3,1}^1 x_1 + w_{3,2}^1 x_2 + w_{3,3}^1 x_3 = 0 \rightarrow w_{3,3}^1 x_3 = 0 \rightarrow x_3 = 0.$$

Therefore the critical point is (0,0,0).

For off-treatment system

$f_{x_1} = w_{1,1}^0 x_1 + w_{1,2}^0 x_2 = 0 \rightarrow w_{1,1}^0 x_1 = 0 \rightarrow x_1 = 0.$

$f_{x_2} = w_{2,2}^0 x_2 + w_{2,3}^0 x_3 = 0 \rightarrow w_{2,2}^0 x_2 = 0 \rightarrow x_2 = 0.$

$f_{x_3} = w_{3,3}^0 x_3 = 0 \rightarrow x_3 = 0.$

Therefore the critical point is (0,0,0).

To find out the type of the point if it's stable, asymptotically stable, or unstable, we have to find the eigenvalues of those systems:

$\lambda_1 = w_{1,1}^1, \lambda_2 = w_{2,2}^1, \lambda_3 = w_{3,3}^1$ (the eigenvalues of the treatment system).

$\lambda_1 = w_{1,1}^0, \lambda_2 = w_{2,2}^0, \lambda_3 = w_{3,3}^0$ (the eigenvalues of the non-treatment system).

Based on the first criterion set by Hirata et al. for the prevention of relapse, $w_{3,3}^0 < 0$, and for reproducing the relapse of PSA under CAS therapy, $w_{3,3}^1 > 0$ [18]. It means since $w_{3,3}^1 > 0$, the population cancer cell size of state 3, may decrease if $w_{3,3}^0 < 0$ while the rest diagonal parameters are positive in depending on the second constraint of Hirata et al. which it saying "within the day each cell class can change its volume by 20% at most" [17]. According to the conditions of the linear system to find the type of the critical point, if one of the eigenvalues of the system is positive ($\lambda > 0$) for all $\lambda \in R$, then the point is unstable. Therefore, the cancer-free steady state, (0,0,0), is unstable, for each system under on and off treatment in (2.7, 2.8) that means the CS and CR cells will not die out totally during the IAS.

PART 3

DATA AND NUMERICAL METHODS

3.1. THE CLINICAL DATA AND THERAPY PROTOCOL

In our analysis and calibration of the model, we use data from Bruchovsky et al. [4]. This clinical trial enrolled patients who showed an elevated serum PSA level after receiving radiotherapy and had no proof of malignancy [4]. The implicit criteria were as follows: the disease is in clinical stage T1b/T1c, T2 or T3 at the time of premier diagnosis before radiotherapy; serum testosterone before treatment is within the normal range (6.3–27 nmol/L the PSA serum before the suppression of androgen 46 ng/mL; performance status of 0 or 1; and there is no previous hormonal manipulation. The therapy in each cycle included giving cyproterone acetate as the main therapy for 4 weeks, and then a mixture of leuprolide acetate and cyproterone acetate follows it, for a mean of 36 weeks. If PSA serum by the end of this period is lower than 4 μg/L, the treatment of androgen suppression is stopped. If the PSA serum of the patient remains upper of the threshold, then the patient will be eliminated from the study. After therapy is stopped, the androgen and PSA are watched every four weeks. The treatment is reset when the serum PSA of the patient rises to $\geq 10\mu g/L$ [4]. The collection of clinical data is at [6]. It is worth noting that some of the patients that showed specific properties were eliminated from the study [18]. Patients were valuation in the study till the evolution of the independence disease from the androgen (advancement time), defined as three sequential raises of PSA > 4 ng/mL, in spite of the levels castrated from testosterone in serum. At the end of this study, into cycle one the patients had been in started 103, into cycle two 86, into cycle three 56, into cycle four 26, and 7 into cycle five. And so the study kept to 6 years with a median follow-up average of 4.2 years [5].

3.2. COMPARISON OF MODELS

To get the numerical solutions of the models above (2.1)-(2.2)and (2.7)-(2.8), we suppose a rectangular rule for the frank product integration (PI) [13] to the search process for the best parameters that fit the data for every patient. By the function fmincon in MATLAB (MATLAB 9.4, R2018a) we run simulations in order to compare models, where it employs the Interior Point Algorithm to find each patient's optimal parameters by looking for a minimal value in a range of predefined ranges of parameters, which have been valued from different literary sources. The algorithm is used to reduce the Mean Squared Error (MSE) for the PSA. By the equations below the MSE is computed

$$P_{error} = \frac{\sum_{i=1}^{N}(P_i - \hat{P}_i)^2}{N} \tag{3.1}$$

where the total number of data points, the value of the PSA data, and the value from the model are represented by: N, P_i and $\widehat{P}_i$ respectively. Here, P_{error} is minimized by fmincon.

Table 3.1. Comparing MSE of the PSA for Hirata etc. model and the suggested model for the first 2.5 cycles.

Model	**PSA**		
	Min	**Mean**	**Max**
Hirata etc.	0.070449021	5.714353327	117.3336591
Suggested	0.080291201	3.812043318	40.65153863

Following the methodology expressed above, we selected the same patients every time to check the numerical simulations and to expose a one-to-one comparison between Hirata etc. and suggested models, for example, in Case 1, we took Patient 2 and we saw that the PSA plot of him was in the suggested model much better than Hirata etc model, which is mean the error is less, in Figure 3.1, also we did the same thing for all of the patients in the group without relapse according to Bruchovsky's classification (Case 1) [6] and the patients from the different groups (With metastasis

without relapse (Case 2) and With relapse (Case 3)), and found that there is a discrepancy in preference between the two models, which differs from one patient to another, regardless of the classification, Figure 3.2 and Figure 3.3.

3.2.1. Case 1: Without Relapse (Patients 1, 2, 15, 17)

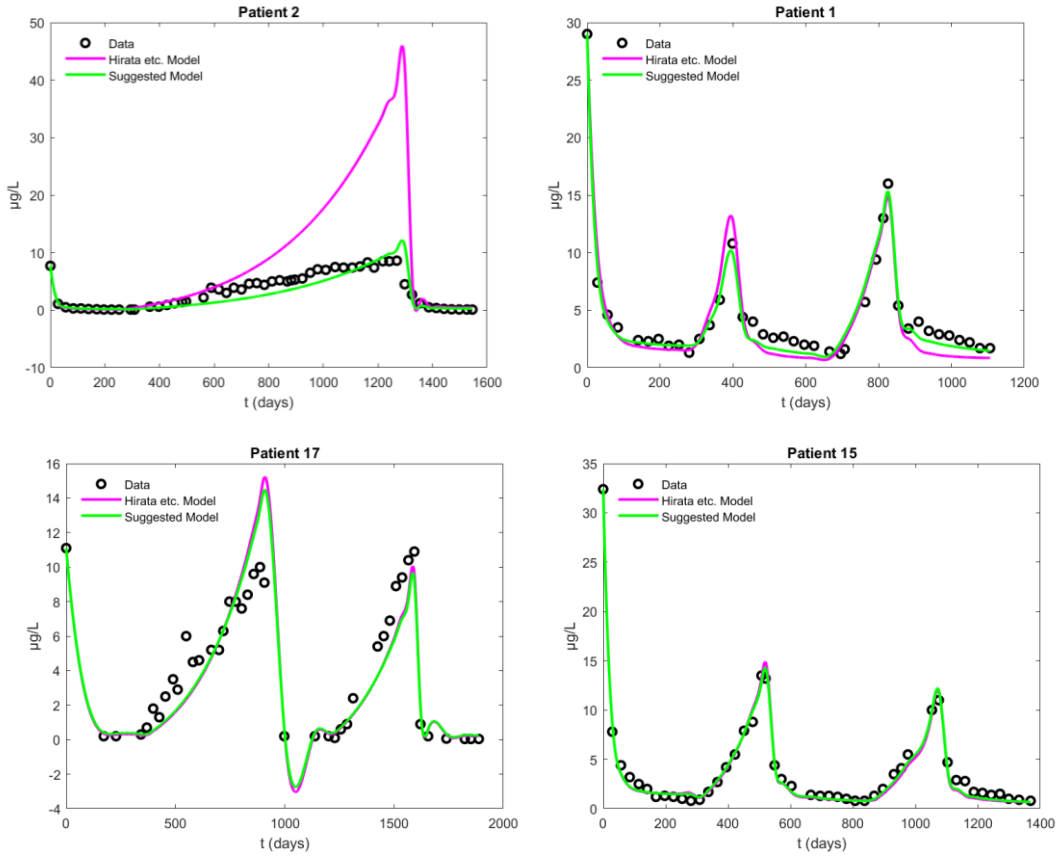

Figure 3.1. Simulation for 2.5 cycles from the therapy for PSA fittings data for both models.

3.2.2. Case 2: With Metastasis Without Relapse (Patients 32, 64, 83)

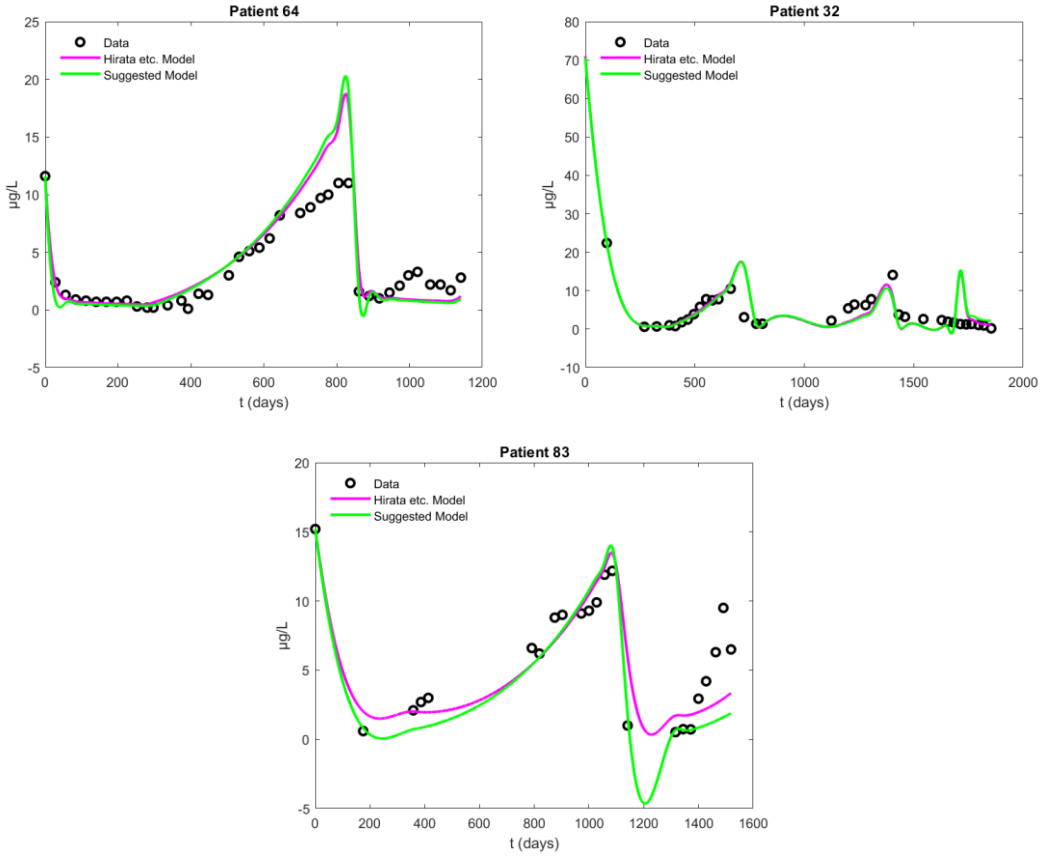

Figure 3.2. Simulation for 2.5 cycles from the therapy for PSA fittings data for both models.

3.2.3. Case 3: With Relapse (Patients 12, 19, 36, 101)

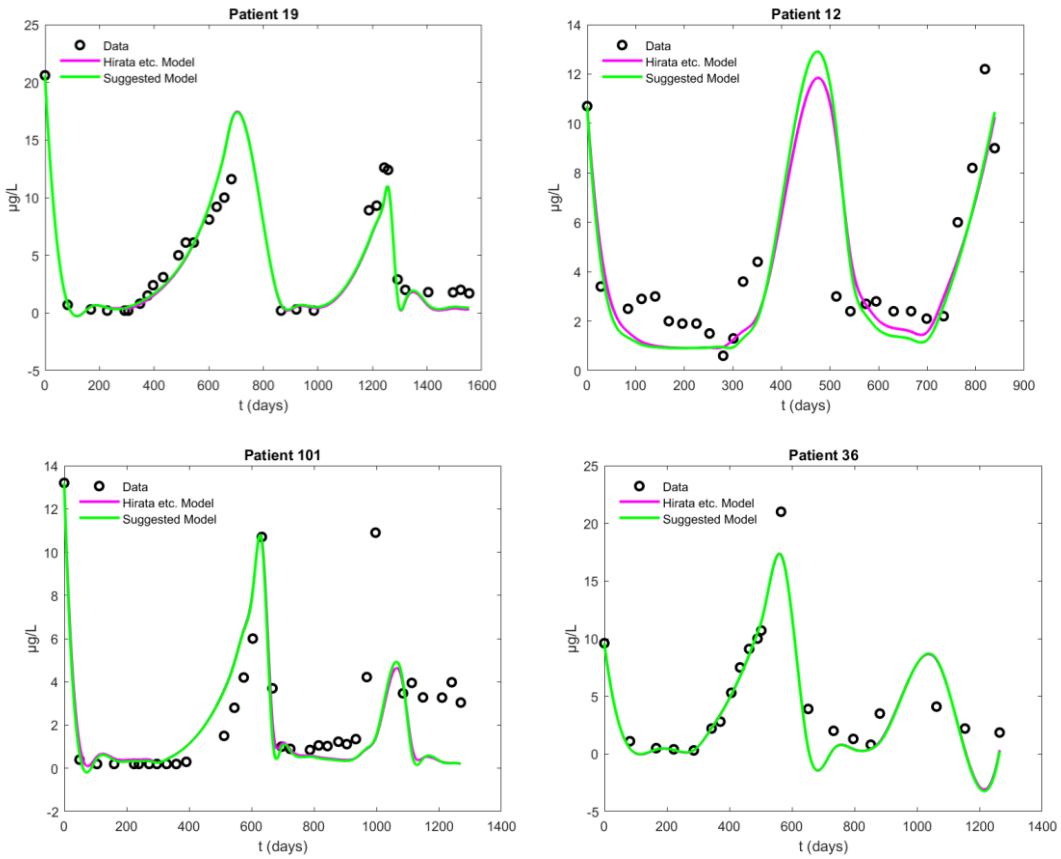

Figure 3.3. Simulation for 2.5 cycles from the therapy for PSA fittings data for both models.

Table 3.2. Hirata etc. X_2 mean and Suggested X_2 mean.

Model	**X_2 mean**		
	Min	**Mean**	**Max**
Hirata etc.	0.079192212	1.097862553	37.7133483
Suggested	0.0952533	1.120053228	37.7133483

Since the addition occurred in the second subpopulation of the cancer cells for the suggested model the result is expected we can notice that the total mean of X_2 of the suggested model is higher than Hirata's etc. model by a very slight difference, table 3.2. However, the implied results of the mean X_2 per patient for the two models differ from patient to patient, like in patient 1 the mean of X_2 in the suggested model is a little bit higher than Hirata's etc. model, and so for some other patients, but for some others, the

mean of X_2 for the suggested model is slightly lower than Hirata's etc. model like in patient 2.

PART 4

CONCLUSION

We conclude from the foregoing that the average error rate for the PSA data is lower in the suggested model than the Hirata's etc model, regardless of the discrepancy between the results of the patients' data in the two models, and because the percentage of error difference between the results of the two models is a small percentage and not a big difference and its preference is due to the suggested model, so the Braes's paradox did not occur between the two models, but this does not mean that the obtained results are satisfactory results, but rather weak results that definitely need broader research support in the field of addition and deletion for such type of models. Perhaps adding another important and influential factor to the suggested model in the future may occur a tangible difference in the results, giving readings that are close to reality.

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RESUME

Esraa Salam Al-Hamadani where she completed both primary and middle studies, and then moved after that to complete her secondary studies in Kufa. She started her bachelor's degree in the Department of Mathematics Science, College of Computer Science and Mathematics at Tikrit University in 2009. After graduation, She worked in several companies in Audit and accounts departments and she volunteered to teach Intelligent mathematics at one of the institutes for intellectual development and creativity. In 2020, she moved to Turkey in order to complete her studies and obtain a master's degree from Karabük University.