NEZİHAL GÖKBULUT

MATHEMATICAL MODELLING FOR THE IMPROVEMENT OF BI-RADS 4 DIAGNOSIS VIA SENSITIVITY ANALYSIS AND OPTIMAL CONTROL

PhD THESIS

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NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF MATHEMATICS

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Supervisor

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Nicosia

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Approval

We certify that we have read the thesis submitted by Nezihal Gökbulut titled **"Mathematical Modelling for the Improvement of BI-RADS 4 Diagnosis via Sensitivity Analysis and Optimal Control**" and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Educational Sciences.

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Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

Nezihal Gökbulut

19/09/2023

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Nezihal Gökbulut

To my parents…

Abstract

Mathematical Modelling for the Improvement of BI-RADS 4 Diagnosis via Sensitivity Analysis and Optimal Control

Gökbulut, Nezihal

Supervisor: Prof. Dr. Evren Hınçal

PhD, Department of Mathematics

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In this thesis, a mathematical model is proposed with the aim of providing efficient techniques in the diagnosis of breast cancer and narrowing the range of cancer risk in BI-RADS 4 subcategories. Concordantly, two of popular mathematical techniques, sensitivity analysis and optimal control theory are employed to the constructed model.

Chapter I specifies the main points and ideas of the presented thesis. General ideas, theorems and definitions supporting the thesis are presented in Chapter II. The study is separated into two sections, broadly.

In Chapter III, the idea of applying sensitivity analysis to the parameters of the basic reproduction numbers is analysed for determining the impact of parameters on BI-RADS 4 subcategories. According to the model, three different globally asymptotically stable equilibrium points are obtained under some circumstances. These points include diagnose-free equilibrium point, BI-RADS 4B&BI-RADS 4C free equilibrium point and endemic equilibrium point. So, from this model it is concluded that it is possible to have a population with no BI-RADS 4 diagnosis, population with no BI-RADS 4B and BI-RADS 4C diagnosis, and manageable population with BI-RADS 4 diagnosis with no epidemic situation. The results of sensitivity analysis revealed that high lactation rate and early menopause causes a decline in BI-RADS 4 diagnosis and breast cancer as well. On the other hand, increase in other parameters including age, palpable mass, bloody nipple discharge, smoking, family history and late menopause leads an increase either in BI-RADS 4 subcategories or breast cancer risk in other BI-RADS categories.

Ascertaining the impact of high lactation rate or a longer time breastfeeding had been a guide so that an optimal control theory is applied to the constructed model

for determining an effective control strategy. The revised version of mathematical model that contains an optimal control is presented in Chapter IV. The results and numerical simulations of this model emphasized the impact of lactation rate on all BI-RADS 4 subcategories.

As a summary, it can be stated that the results of this thesis include significant declarations which should be applied by health professionals and individuals themselves for the control of the diagnosis of breast cancer.

***Key Words**:* mathematical model, sensitivity analysis, optimal control theory, BI-RADS 4 subcategories, breast cancer

Özet

Mathematical Modelling for the Improvement of BI-RADS 4 Diagnosis via Sensitivity Analysis and Optimal Control

Gökbulut, Nezihal

Danışman: Prof. Dr. Evren Hınçal

PhD, Matematik Ana Bilim Dalı

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Bu tezde, meme kanseri tanısında etkili tekniklerin sağlanması ve BI-RADS 4 alt kategorilerindeki kanser risk aralığının daraltılması amacıyla bir matematiksel model oluşturulmuştur. Buna uygun olarak oluşturulan modelde popüler matematiksel tekniklerden ikisi olan duyarlılık analizi ve optimal kontrol teorisi kullanılmıştır.

Bölüm I sunulan tezin ana noktalarını ve fikirlerini içermektedir. Tezi destekleyen genel fikirler, teoremler ve tanımlar Bölüm II'de sunulmuştur. Çalışma genel olarak iki bölüme ayrılmıştır.

Bölüm III'te, parametrelerin BI-RADS 4 alt kategorileri üzerindeki etkisini belirlemek için temel çoğaltma sayılarına ait parametrelere duyarlılık analizi uygulama fikri çalışılmıştır. Modele göre tezde belirtilen bazı koşullar altında üç farklı global asimptotik kararlı denge noktası elde edilmiştir. Bu noktalar arasında teşhis olmayan denge noktası, BI-RADS 4B&BI-RADS 4C serbest denge noktası ve endemik denge noktası yer almaktadır. Dolayısıyla bu modelden BI-RADS 4 tanısı olmayan bir popülasyona, BI-RADS 4B ve BI-RADS 4C tanısı olmayan bir popülasyona ve BI-RADS 4 tanısına sahip, salgın olmayan yönetilebilir bir popülasyona sahip olmanın mümkün olduğu sonucuna varılmıştır. Duyarlılık analizi sonuçları, yüksek laktasyon oranı ve erken menopozun hem BI-RADS 4 tanısında hem de meme kanserinde düşüşe neden olduğunu ortaya koymuştur. Öte yandan yaş, ele gelen kitle, meme ucundan kanlı akıntı, sigara kullanımı, aile öyküsü ve geç menopoz gibi diğer parametrelerdeki artış durumunda ya BI-RADS 4 alt kategorilerinde ya da diğer BI-RADS kategorilerinde meme kanseri riskinde artışa neden olabileceği belirlenmiştir.

Yüksek laktasyon oranının veya daha uzun süreli emzirmenin etkisinin duyarlılık analizi ile belirlenmesi, etkili bir kontrol stratejisinin belirlenmesi adına oluşturulan modele optimal kontrol teorisinin uygulanmasında yol gösterici olmuştur. Optimal kontrolü içeren matematiksel modelin revize edilmiş versiyonu Bölüm IV'te sunulmuştur. Bu modelin sonuçları ve simülasyonları, laktasyon oranının tüm BI-RADS 4 alt kategorileri üzerindeki etkisini vurgulamıştır.

Özet olarak, bu tezin sonuçlarının meme kanseri tanısının kontrolü için sağlıkçılar ve bireylerin bizzat uygulaması gereken önemli noktaları içerdiği ifade edilebilir.

Anahtar Kelimeler: matematiksel modelleme, duyarlılık analizi, optimal kontrol teorisi, BI-RADS 4 alt kategorileri, meme kanseri

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List of Abbreviations

ACR:	American College of Radiology
BI-RADS:	Breast Imaging Reporting and Data System
ODE:	Ordinary Differential Equation
FDE:	Fractional Differential Equation
PDE:	Partial Differential Equation
IVP:	Initial Value Problem
DFE:	Disease Free Equilibrium
EE:	Endemic Equilibrium
NGM:	Next Generation Matrix
US:	United States
USSR:	Union of Soviet Socialist Republics
BVP:	Boundary Value Problem
WHO:	World Health Organization

CHAPTER I
Introduction

For centuries, mathematicians that deal with the epidemiology investigates ways to make contributions in health sciences. Mathematical models are one of the most efficient tools that analyse the structure of the disease and determine significant ways for the diagnosis and/or treatment of diseases. Especially for serious life-threatening diseases, introducing these kinds of powerful tools is quite meaningful. Cancer is one of these life-threatening diseases that affects people's lives worldwide. There exist many types of cancer and breast cancer is one of the leading common cancer types in women. Around 1980s, for uniformity and standardization of mammography and ultrasound results, a categorization system was invented by American College of Radiology (ACR). This system is named as BI-RADS system with the initials of the Breast Imaging Reporting and Data System. Although this system enables some standardization for radiologists, still some strategies and controls are needed for the diagnosis and treatment of breast cancer. In this regard, numerous mathematical models can be created and developed for providing meaningful and useful solutions for breast cancer.

Purpose of the Study

The study is brought forward with the aim of producing valuable solution for the diagnosis of breast cancer. It is realized that BI-RADS 4 diagnosed patients has a wide range of probability of being cancer (2-95%). On that note, BI-RADS 4 subcategories are analysed for narrowing this percentage for the patients with BI-RADS 4 diagnosis with mathematical modelling by introducing sensitivity analysis and some control strategies.

Significance of the Study

In the literature, none of the proposed mathematical models in the field of breast cancer dealt with the BI-RADS 4 subcategories. In other words, the study is the first one that deals with the diagnosis of breast cancer by means of BI-RADS 4 subcategories via mathematical modelling with optimal and sensitivity strategies.

Research Questions / Hypotheses

The main research question of this thesis is by analysing BI-RADS 4, how the wide range of cancer risk (2-95%) can be narrowed and how a mathematical model can be developed so that it can be analysed in which level different parameters affect the percentage of being breast cancer in BI-RADS 4 subcategories. Furthermore, to decide and analyse that is it possible to apply any control strategy to the proposed mathematical model for the prevention of breast cancer for the BI-RADS 4 subcategories patients. As a hypothesis, it is believed that the wide range of cancer risk of BI-RADS 4 category can be narrowed by applying sensitivity analysis to the parameters and with optimal control theory, possible control strategies may prevent breast cancer for the people with diagnosis BI-RADS 4.

CHAPTER II

Literature Review

In this chapter, descriptions, conceptual definitions, theorems, corollaries and information which are already exist in the literature and that are related to the subject of the presented thesis are presented.

Theoretical Framework and Definitions

This section consists of the theories, definitions and information about mathematical modelling process, its relation with health sciences and breast cancer are stated.

Mathematical Modelling

In the last century, mathematical modelling became very popular in the field of applied sciences. Fundamentally, the main idea of mathematical modelling is converting real-life problems into mathematical problems/equations; solving and analysing them with necessary theorems and methods and then applying the results to real life. Due to the complexity of some real-life problems, few approximations or assumptions can be made for finding a solution of a model. In this case, these approximations and assumptions can be stated as limitations of the model (Kapur, 1998). Mathematical modelling is actually a subject of applied sciences. In other words, it is the application of mathematical theorems into real-life problems (Fowler, 1997; Berry & Houston, 1995).

Mathematical models may be continuous or discrete according to the nature of the problem. When the model variables and parameters alter continuously in time and space, model should be continuous and if these changes happen discontinuously, the model should be discrete. Discrete models can be introduced for nonlinear recurrence equations in the field of coding, path finding problems, graphs of production, Markov processes, stochastic problems, etc. (Doorman & Verhage; Fowler, 1997). Continuous mathematical models include differential equations that can be ordinary, fractional, partial, delay, etc. The type of differential equations depends on the structure of the problem (Fowler, 1997). These models can be applied in almost every applied science including health sciences, economy,

social sciences, etc. (Artzrouni, 2005). Continuous models are more cognizable and analysable for human while discrete models are better apprehended by computers (Hall, 1986).

In health sciences, mathematical modelling is a widely used and effective tool. Introducing mathematical models in health sciences focuses on finding cause of diseases, providing early diagnosis and better treatment conditions, predicting the future of diseases and most importantly preventing disease-caused deaths. The first mathematical model in epidemiology was introduced in 17s by Daniel Bernoulli. The model was about vaccination of smallpox which was an endemic at that time. This work was followed by another significant study, spatial and temporal pattern of cholera epidemic in London, by John Snow in 1855. The purpose of both studies was taking the spread of the disease under control and preventing the diseases becoming a pandemic. As a matter of fact, the main target of mathematical models in health sciences is precluding disease-caused deaths and taking the spread of diseases under control. Under favour of the results of these models, it is aimed to affect doctors, radiologists, decision makers, policymakers, etc. for public health (Brauer, 2017; Dündar, Gökkurt, & Soylu, 2012; Porgo, et al., 2019; Kermack & McKendrick, 1927).

For superior understanding of nature/structure/causal factor of diseases, mathematicians mostly prefer studying with compartmental mathematical models. Compartmental mathematical model approach in epidemiology was firstly emerged by Sir R. A. Ross, W. H. Hamer, A. G. McKendrick, and W. O. Kermack in 1900-1935 (Kermack & McKendrick, 1927). Kermack and McKendrick published three papers that explains the transmission of communicable diseases via compartmental model in 1927, 1932 and 1933, which were the basic epidemic models proposed until then (Brauer, 2017).

In compartmental models, the population that is examined is divided into essential number of compartments. Then, to express the change in and transmission between these compartments, differential equations are created. There are many compartmental mathematical models including *SI, SIR, SIS, SEIR, SVIR,* etc. The type of models depends on the structure and transmission of diseases. In these models, *S* denotes the individuals that are susceptible to the disease, *I* denotes the individuals that are infected, *R* denotes either removed of recovered individuals in the population, *E* denotes the exposed individuals in the case of incubation period

of virus/bacteria/parasite and *V* denotes the individuals that are vaccinated if a vaccine exists for the disease (Brauer, 2017; Batista, et al., 2021; Sun, 2016; Hethcote, 1989).

SIR models are created in the case of immunization. That is, when an infected individual (in the compartment *I*) recovers and enters to the compartment *R* with developing immunity, then *SIR* models can be introduced for that disease. For viral infections these models are preferred to be studied such as Cooper et al. (2020), Zakary et al. (2019) and Osthus et al. (2017). When vaccination strategies are one of the leading aims of constructing mathematical models, SVIR type can be created as in Attaullah et al. (2022) and Zhao and Ma (2021). SVIR models are popular in viral infections as well. SIS models are proposed if there exist no immunity for the disease and individuals become susceptible when they get rid of the infection. Ross' malaria model can be given as an example of basic SIS model. Existence of latent period of microorganism that causes the disease is a good sign of constructing SEIR model since the population contains infected but not yet infectious individuals. The details and examples of these models can be found in Shah and Gupta (2013) and Feng (2007). As can be seen from these explanations and papers, mathematical models can be introduced for almost every area of health sciences including medicine, pharmacy, laboratory, etc.

A need for a mathematical model in health sciences appears when a problem arises. The process of mathematical modelling in health sciences is time-drain and may be difficult in some cases. In this area, first step of mathematicians should be investigating the disease via electronic sources and the leading experts of the disease. This step is exceedingly important for understanding the nature and transmission of the disease in the population. Mathematicians generally give their decisions for the number of compartments after gathering this information. After this, the model should be formulated according to the disease and population. While formulating the problem, by adhering the reality, some assumptions and limitations can be added to the model for avoiding complexity in its analysis. At this stage, mathematicians may discuss their model with professionals in medicine for avoiding a mistake in the nature of the disease. The most important part of models is their analysis which makes mathematical models powerful. For these kind of models, similar analyses are applied including existence of steady solutions, stability of equilibrium points, instability of some points, etc. Applying necessary

theorems to constructed models, one can prove the existence of these models in real-life which shows the impact of mathematics. These analyses guarantees that the results of these models can be applied in public and optimal control strategies can be introduced for better health conditions in society. Finally, in mathematical modelling, numerical simulations should be presented for visual convenience for the future trend of diseases. For these simulations, MatLab, Maple, etc. programs can be utilized (Fowler, 1997; Quarteroni & Formaggia, 2004).

For mathematicians, analysing the existence of diseases, understanding under what conditions diseases can spread or die out and predicting their future can be the basis step. However, diversity of mathematics allows researchers to investigate more by introducing mathematical tools into proposed models. As an example, for deciding which parameter is more effective on the disease can be revealed by applying sensitivity analysis to a model with the help of differentiation and basic reproduction number of diseases. If there exist an opinion such that some control strategy can be useful for the control of any disease, then this can be evaluated by introducing optimal control theory. For the improvement of models, new parameters and compartments can be imparted to exist models which allows richer results and makes model more realistic. Any proposed differential equation can be converted to another one including ordinary differential equations (ODEs), fractional differential equations (FDEs), partial differential equations (PDEs), etc. for comparison of results that may contribute discussions about these issues. For the sake of brevity, each constructed model can be improved for better and further contributions to the field of health sciences.

In paper Baleanu et al. (2020), the model proposed in Čelechovská (2004) is improved by adding fractional order to the given integer order model. Both models were about the human liver and comparison of these models revealed that fractional-ordered model is more powerful that integer-ordered model for this study. For determining most effective parameters on COVID-19 with respect to basic reproduction numbers, both the authors of Samui et al. (2020) and Savaşan et al. (2022) applied sensitivity analysis to their constructed models. Vaccination strategies are investigated for rotavirus epidemic, tuberculosis and COVID-19 diseases in Ahmad et al. (2020), Nkamba et al. (2019) and Kaymakamzade et al. (2022), respectively. Optimal control theory is adapted to proposed models in Saad and Hınçal (2018), for bladder cancer, Naik et al. (2020) for Human

Immunodeficiency Virus (HIV) and Abioye et al. (2020) for malaria disease. System of delay differential equations are constructed for tumour growth and cancer in Khajanchi and Nieto (2019) and Sweilam et al. (2021). As it is obvious, mathematical models can be employed for infectious diseases caused by bacteria/virus/parasite, cancer, tumour growth, etc. Moreover, preparing a mathematical model and visualizing results via software programs allows researchers to see where the disease is going. In that way, it can be decided whether it exceeds the threshold of carrying capacity or stays below it. Carrying capacity can be defined biologically as the maximum number that can be reached in a population so that the life goes on with providable resources. Otherwise, if this threshold exceeds, a decline will be obtained in the size of population until the conditions can be satisfied (Hartvigsen, 2017; Hixon, 2008).

Properties of a Mathematical Model

In this section, basic and important properties while constructing and proving a mathematical model are presented with necessary theorems.

Existence of a Mathematical Model. During mathematical modelling process, the system of differential equations is written to describe the changes in compartment in time. For the models, there is another thing that is as important as the creation of models is the existence of solutions of the problems. These solutions may be unique or not. If the solution is not unique, then biologically relevance of these solutions should be proved (Shakil, et al., 2017). In other words, if there exists more than one solution, then these solutions should stay in a feasible region where the solutions are biologically meaningful. Moreover, since these models are related with real-life, solutions should be non-negative. For that purpose, meaningful set of regions should be constructed and with the help of mathematical theorems, mathematicians should show that the set is positively invariant. For such proves, techniques that are used to solve initial value problems (IVPs) can be applied (Sowole, Sangare, Ibrahim, & Paul, 2019).

Uniqueness of Solutions of a Mathematical Model. This section includes necessary definitions and theorems about the unique solutions of any mathematical model.

Definition 1. (Lipschitz continuity) Let $f: X \to Y$ be any function. A function f is said to be Lipschitz continuous if there exist any real positive constant L such that

$$d_Y\big(f(x_1), f(x_2)\big) \leq L d_X(x_1, x_2),$$

for every x_1, x_2 in X. Here, the constant L is called a Lipschitz condition (Hager, 1979).

Theorem 1. (Picard-Lindelöf Theorem of Uniqueness) Given an IVP

$$y' = f(t, y), \qquad y(t_0) = y_0,$$

let f be a continuous and bounded function in a region

$$P = \{(t, y): |t - t_0| \leq a, |y - y_0| \leq b \; for \; a, b > 0\}.$$

Moreover, assume that f is Lipschitz continuous in the second variable. That is,

$$|f(t, y_1) - f(t, y_2)| \leq L|y_1 - y_2|,$$

for each (t, y_i) in P with a Lipschitz constant L.Then, the above IVP has a unique solution defined on the interval $|t - t_0| \leq \delta$, where $\delta = \min\left\{a, \frac{b}{R}\right\}$ for a positive upper bound of f, R.

Proof. (Coddington & Levinson, 1984)

Basic Reproduction Number, Equilibrium Points and Stability. Any dynamical system in mathematical modelling can be formulated as

$$\dot{\boldsymbol{x}} = f(x),$$

where x is a vector of the state of system in $\mathbb{R}^n$ for $n \in \mathbb{N}$. $\dot{\boldsymbol{x}}$ represents the first derivative of the variable x at time t and f is a nonlinear function. For strengthen the constructed model, after proving that the system has solutions that are feasible, equilibrium points of the model should be calculated (Aracil & Gordillo; Ahmed, El-Sayed, & El-Saka, 2007). At the equilibrium points, the population reaches a stable state which can be preserved under some conditions. Hence, at an equilibrium point, there is no change in the

state variables, i.e., the change in state variables equals to zero. This is why the computation of equilibrium points should be calculated by equating the differential equations to zero and finding the values for the state variables at these points (Fantaye, et al., 2022; Auslander, 2003). Generally, for the models, there exist two basic equilibrium points; disease-free equilibrium (DFE) point and endemic equilibrium (EE) point. At disease-free equilibrium point, the population is free of the disease, that is, there is no infected or exposed individuals. On the other hand, at endemic equilibrium point, infected or exposed individuals exist but the spread of the disease is under control; public health is not in danger. At this point, no epidemic or pandemic is expected to occur (Foppa, 2017; Panfilov, Dierckx, & Volpert, 2019). For any constructed mathematical models, other equilibrium points may exist according to the nature of the disease and population.

Mathematical modelling in epidemiology and health sciences includes another important term known as basic reproduction number. It is also called as basic reproduction ratio or basic reproduction rate and denoted by R_0 (Dharmaratne, et al., 2020; Delamater, Street, Leslie, Yang, & Jacobsen, 2019; Brauer, 2017; Heffernan, Smith, & Wahl, 2005).

The concept "basic reproduction number" was first introduced by R. Böckh in the year of 1886 with demographic purposes. He tried to determine what the approximate number of female offspring is which are produced by one female in the duration of her entire life. However, the first mathematical formula for R_0 was formalized by L. J. Dublin and A. Lotka in 1925 as follows:

$$R_0 = \int_0^\infty \mathcal{P}(a).\beta(a)\, da,$$

where $\mathcal{P}$ denotes the survival probability of female and β denotes the fertility rate. As it is obvious, until this time, R_0 was linked to demography (Perasso, 2018).

George MacDonald was the first known scientist that introduced R_0 into the field of epidemiology in the 1950s. He named this value as "basic case reproduction rate" and included the term in his study on malaria and he use the notation z_0 instead of R_0. He defined z_0 as:

"Basic reproduction rate of malaria is the number of infections distributed in a community as the direct result of the presence in it of a single primary non-immune case."

Even though Ross, Kermack and McKendrick's studies involved this threshold quantity, they did not identify or name it. In 70s the notation of basic reproduction number is changed as R_0 with continuing the formula of Lotka. It is definition has also adopted to the field of epidemiology. After this time, it is defined as the expected number of secondary cases caused by primary cases in a fully susceptible population. A mathematical accurate definition for R_0 was finally proposed by O. Diekmann, J. A. P. Heersterbeek and J. A. J. Metz in 1990 as:

"Basic reproduction number is the number of new infections produced by a typical infective individual in a population at a disease-free equilibrium point."

This definition and R_0 was linked to the dominant eigenvalue of the next generation operator. This version is found to be more useful while working with dynamical systems and ODEs. The value of R_0 may be affected by many sociological, biological or environmental factors and it depends on the value of parameters of the proposed models. Hence, it cannot be a constant value since parameters' values change constantly in time. On the other hand, if the spread of the disease can be taken under control, the value of R_0 can be fixed in a small range. Subsequent generations that are developing by means of size results in population growth. This growth factor per population is the growth potential. So, R_0 is actually the mathematical characterization of this growth factor (Dharmaratne, et al., 2020; Delamater, Street, Leslie, Yang, & Jacobsen, 2019; Brauer, 2017; Heffernan, Smith, & Wahl, 2005; Perasso, 2018; Diekmann, Heesterbeek, & Roberts, 2010).

Due to the definition of R_0, for the prevention of any uncontrolled outbreak, the value of R_0 should be less than 1. In this case, $R_0 < 1$ indicates that infected individuals can be infectious for the number of people less than 1 which is meaningless, i.e., infected individuals are not infectious. Under this condition, a decrease will be seen in the disease and it will die out soon. When $R_0 < 1$, the only stable equilibrium point that exists in the population

is generally the disease-free equilibrium point. If $R_0 > 1$, then it can be interpreted as infected individuals can infect more than 1 person in a population. That is, infection exists in the population and an outbreak may occur without any control. In the case of $R_0 > 1$, an endemic equilibrium point may exist and some precautions should be taken to reach the disease-free equilibrium point. When $R_0 = 1$, then it is concluded that each infected individual lead to a new case. The disease will be in the population but no epidemic or outbreak is expected to happen. Therefore, determination of R_0 is crucial and R_0 is a valuable and useful tool for the prediction and upcoming direction of control measures of diseases (Tang, et al., 2021; Delamater, Street, Leslie, Yang, & Jacobsen, 2019; Ma & Earn, 2006; Ramirez, 2023; Breban, Vardavas, & Blower, 2007).

In the course of R_0 calculation, there are mainly two kinds of methods: through dynamical models and driven by data. If the model consists of finite number of compartments, Next Generation Matrix Method (NGM) is habitually preferred to be applied by the researchers which corresponds to the first method of R_0 computation. In this method, next generation matrix (NGM) is constructed by separating the newly infected individuals and other individuals in the compartments/states. With these two matrices are constructed: one that includes newly infected individuals of the system and the other one that contains the rest of the system. After that, the inverse of second matrix is calculated and first matrix and the inverse matrix are multiplied. The dominant eigenvalue of the matrix multiplication will be the formula of R_0. According to the infection or disease there may be more than one R_0 formulas since it can be different for each disease compartment (Diekmann, Heesterbeek, & Roberts, 2010; Keeling & Rohani, 2007; Brouwer, 2021; Guo, et al., 2022).

The basic reproduction number of dynamical systems plays a significant role for the stability of equilibrium points. Stability of equilibrium points is much more important their existence. After finding equilibrium points of the system, it should be decided whether they are stable or not. Some of these points are unstable, locally asymptotically stable and/or globally asymptotically stable. When small disturbances applied, if the constructed

system get a motion away, then the point is said to be unstable. Unstable equilibrium points are not preferred and they reduce the impact of constructed models. Local asymptotical stability of an equilibrium point guarantees that solutions will approach to the equilibrium point if the initial conditions are close to that equilibrium point. However, global asymptotical stability of an equilibrium point ensures that all solutions will eventually approach to the equilibrium point under any initial condition. Hence, it can be concluded that any globally asymptotically stable point is locally asymptotically stable. So, small perturbations do not affect the stability of locally asymptotically stable equilibrium points and this is why local stability will be enough for health sciences if the situation is not an outbreak. On the other hand, especially for the disease-free equilibrium (DFE) point global stability is significant since large perturbations may lead to an epidemic or pandemic. So, if the DFE point of the system can be proved to be globally asymptotically stable, then the decision makers may be relieved since the disease will not be able to persist in public at this point. Thus, stability analysis enables us to know how system will behave when it is far away from the equilibrium points. As a conclusion, global stability of DFE point ensures the elimination of the disease in public and global stability of EE point guarantees that the disease will stay as endemic (Sharov, 1996; Gümüş, 2014; Murray, 2003; Chen & Cohen, 2001).

For analysing the local asymptotical stability of equilibrium points, constructing Jacobian matrix is one of the most popular methods. That is, by taking the partial derivatives of the dynamical system a square matrix, Jacobian matrix, is constructed. Then, the coordinates of the equilibrium point are plugged into the matrix. These coordinates are the corresponding values for the states of the model. As a last step, eigenvalues of the matrix are computed. For the local stability, real parts of the all eigenvalues should be negative definite. Otherwise, the point is unstable. If the analysed point is DFE point, then eigenvalues are negative definite under the condition $R_0 < 1$ and if it is EE point, they are negative if $R_0 > 1$ which makes sense due to the definition of R_0 (Hoang, Ngo, & Truong, 2023; Roussel, 2005). For determining whether the eigenvalues are negative or not, Routh-Hurwitz criterion can be applied (DeJesus, 1987).

Determining global asymptotical stability of equilibrium points can usually be analysed via Lypunov technique. With this technique, one can examine the behaviour of the model when large perturbations happened. The idea for this technique is simply starts with writing a function of state variables which is generally denoted by V. After that, 3 conditions should be checked: the written function should be positive everywhere, it should take the value 0 at the analyzed equilibrium point and its derivative should be negative definite. If such a function can be written and these properties can be proven for a constructed model, then it is concluded that the equilibrium point is globally asymptotically stable. In more general, these can be stated with the following theorem (Sastry, 1999; Mondragón, Gómez, & Leiton, 2014; Roussel, 2005).

Theorem 2. (Lyapunov Stability Theory) Let E be an equilibrium point of the system of ODEs and $V: D \to \mathbb{R}$ be a continuously differentiable function such that $V(E) = 0$ and $V(x) > 0$ for each $x \in D$. Then, if the derivative of V, denoted by $\dot{V}$, is negative definite, the point E is globally asymptotically stable. Such a function is called Lyapunov function.

Proof. (Wang & Zhou, 2007)

Sensitivity Analysis

In health sciences, while dealing with the spread of any disease, determining effective and responsible factors for the transmission and prevalence of the disease is substantially important. In this regard, mathematicians introduced a method called sensitivity analysis. Sensitivity analysis can be applied to a mathematical model for measuring the effects of precariousness on input parameters of a model and the following effect on the output of model (Arriola & Hyman, 2009; Chitnis, Hyman, & Cushing, 2008).

For the analysis, there exist many techniques to be applied according to the type problem setting (Homma & Saltelli, 1996). A popular technique used in diseases analyse the sensitivity indices of basic reproduction number to the parameters of a model. Since R_0 allows researchers to determine the current situation and the future of the disease, with the mentioned technique, crucial and

effective parameters can be decided. Hence, the parameters with high impact on R_0 can be decided and intervention strategies can be planned (Chitnis, Hyman, & Cushing, 2008). When any parameter changes in a model, the relative change in the compartments can be measured with sensitivity analysis. The method for the analysis is given below.

Definition 2. Let the variable R_0 be a differentiable function of the parameter α. The normalized forward sensitivity index of the variable R_0 which differentiably depends on the parameter α can be calculated as:

$$\Psi_{\alpha}^{R_0} = \frac{\partial R_0}{\partial \alpha} \times \frac{\alpha}{R_0}.$$

If the result of the above calculation has a positive value, then it means that increase in the parameter will lead to an increase in the value of R_0, which is not preferred. In the same manner, if the calculation has a negative value, then increase in the parameter will lead to a decrease in R_0 which is preferred and needs to be applicable as an intervention strategy (Rodrigues, Monteiro, & Torres, 2014; Samsuzzoha, Singh, & Lucy, 2013).

In the literature, many researchers applied sensitivity analysis to basic reproduction number while studying with diseases. In Savaşan et al. (2022) the authors analysed the effect of the parameters for the COVID-19 disease with their mathematical model in Mediterranean island. The purpose of their work was to determine what can be done for the control of the spread of COVID-19 in their country. The authors Gokbulut et al. (2022) investigated the effect of parameters on BI-RADS 4 subcategories with the aim of reducing cancer risk in these subcategories. The work of Hurdoganoglu et al. (2022) is performed for applying sensitivity analysis to the constructed mathematical model for the evaluation of ESBL resistance dynamics in *Escherichia coli* isolates. In this study, the authors aimed to determine the effective parameters for antibiotic resistance of the bacteria *Escherichia coli*.

Optimal Control Theory

The theory of optimal control aims to find out control strategies that will either maximize or minimize a given criterion or index of performance while enabling the process to carry out necessary physical constraints. Namely, in terms of mathematics, it is a method that can derive control functions and state trajectories over a time period for dynamical systems for maximizing or minimizing a criterion of performance (Kirk, 2004; Garira, Musekwa, & Shiri, 2005).

History of Optimal Control. 326 years ago, in 1697, Johann Bernoulli who was a professor of mathematics at the local university of the Netherlands, Groningen, had discovered the optimal control. In the June of 1696, Bernoulli had challenged all mathematicians for the solution of *Acta Eruditorum*, also known as brachistochrone problem. At the end, in addition to the Johann's solution, five famous mathematicians more proffered their solutions. On the 16th of June, 1696, Leibniz had solved the problem and submitted it via letter to the Johann. The list of submitted solutions is continued in order of Jakob (elder brother of Johann), Tschirnhaus, l'Hospital and lastly, Newton. It is believed that these events between the years 1696-1697 became significant in the history of mathematics and lead to be an origin of similar works (Sussmann & Willems, 1997).

Before 1696, some optimization problems similar to the mentioned one were studied at least since the Greeks. These problems include finding answers to the questions "What is the shortest path joining two points?" or "What is the plane curve of a given length that encloses the possible largest area?", etc. Actually, in 1685, Newton studied, an accurate "calculus of variations" problem which was determining the shape of a body with minimal drag. However, his work did not get much attention (Sussmann & Willems, 1997). The need of an optimal control had emerged when calculus of variations became inadequate. The calculus of variations can solve optimization problems in the space of all curves while in optimal control problems minimization can be done over a set which can be determined by dynamical constraints. This is one of the reasons that optimal control theory had been developed in early 1960s and today it is mostly and currently used. From

here, it can be concluded that it is an extension of the calculus of variations (Hull, 2003; Kirk, 2004).

According to some beliefs, born of optimal control relies on right after the World War II, also known as Cold War. As soon as the war started, United States (US) and Union of Soviet Socialists Republics (USSR) bore down on for the use of mathematicians and their theories in the analyses of defence. This is because mathematics had been accepted as an efficient tool during the war. Hence, both East and West mathematicians initiated a development process of present theories and studies, and these studies including fighter aircraft's minimum time interception problems, are named as optimal control later on (Pesch & Plail, 2009; Sussmann & Willems, 1997). This belief is strengthened with the work of L. S. Pontryagin and his group work "Pontryagin's Maximum Principle". However, most of the mathematicians stood behind the ideas that this principle was just a minor addition to the "classical calculus of variations" (Berkovitz, 2013; Bryson, 1996).

On the other hand, Pontryagin's maximum principle can be defined as new era of optimal control theory. This is because of providing appropriate conditions for mathematicians while constructing optimization problems if they include differential equations as constraints. Moreover, it makes the present researches richer when the theory is added. Another significant property of the theory is that it can be applied to many fields to study. These fields include finance, business, economy, biology and health sciences, physics, chemistry, etc. (Garira, Musekwa, & Shiri, 2005).

For the development of economic applications and economic growth, author Intriligator (1975) introduced optimal control theory to their constructed model. In the study of Saad and Hınçal (2018), BCG treatment strategy is applied as a control strategy for the bladder cancer. For the plasma in physics and in multistage energy systems, the theory is used in the work of Blum (1989) and Sieniutycz (2000), respectively, as well. As a result, it is applicable into many fields of science and literature for meaningful improvements.

Optimal Control Problem. For the construction of an optimal control problem involves (Kirk, 2004):

1. The mathematical description/model of process that needs to be controlled.
2. Expression of the physical constraints.
3. Indicating performance index or criterion.

Let an ODE be given with an initial condition (IC) as

$$\begin{cases} \dot{\boldsymbol{y}}(t) = \boldsymbol{g}\big(t, \boldsymbol{y}(t)\big), \\ \boldsymbol{y}(t_0) = \boldsymbol{y_0}, \qquad t > 0. \end{cases} \tag{1}$$

Here $\boldsymbol{y}$ and $\boldsymbol{g}$ are vector-valued, continuous and piecewise differentiable functions such that $\boldsymbol{y}$: $\mathbb{R}^+ \to \mathbb{R}^n$ and $\boldsymbol{g}$: $\mathbb{R}^n \to \mathbb{R}^n$ for $n \in \mathbb{N}$. Moreover, $\boldsymbol{y_0} \in \mathbb{R}^n$ holds. The system (1) is a dynamical system of a mathematical model as a state system. For an optimal control problem, a new function, named as control function, should be introduced to the constructed system to make some generalizations. The vector-valued function $\boldsymbol{g}$ will depend on control parameters on any set $B \subset \mathbb{R}^m$. As a result, for $\boldsymbol{u} \in B$ and for $\boldsymbol{g}$ we have

$$\boldsymbol{g}\colon \mathbb{R}^n \times B \to \mathbb{R}^n \ \ and \ \boldsymbol{u}\colon \mathbb{R}^+ \to B.$$

More general, the function $\boldsymbol{u}$ can be defined for $t_0 < t_1 < \cdots < t_n$ and $u_1, u_2, \dots, u_m \in B$ as

$$\boldsymbol{u}(t) = \begin{cases} u_1, & t_0 \le t \le t_1 \\ u_2, & t_1 \le t \le t_2 \\ \quad \vdots & \\ u_m, & t_{n-1} \le t \le t_n \end{cases}.$$

Hence, with the control $\boldsymbol{u}$, an optimal control problem for ODEs or controlled system can be written analogously as follows:

$$\begin{cases} \dot{\boldsymbol{y}}(t) = \boldsymbol{g}\big(t, \boldsymbol{y}(t), \boldsymbol{u}(t)\big), \\ \boldsymbol{y}(t_0) = \boldsymbol{y_0}, \qquad t > 0. \end{cases} \tag{2}$$

The solution of the above system, $\boldsymbol{y}(t)$, is the trajectory of the system which depends on both control an initial condition. Since all $\boldsymbol{y}(t), \boldsymbol{u}(t)$ and $\boldsymbol{g}\big(t, \boldsymbol{y}(t), \boldsymbol{u}(t)\big)$ are vector-valued functions, they can be illustrated as below.

$$\boldsymbol{y}(t) = \begin{bmatrix} y_1(t) \\ y_2(t) \\ \vdots \\ y_n(t) \end{bmatrix}, \boldsymbol{u}(t) = \begin{bmatrix} u_1(t) \\ u_2(t) \\ \vdots \\ u_n(t) \end{bmatrix}$$

and

$$\boldsymbol{g}\big(t, \boldsymbol{y}(t), \boldsymbol{u}(t)\big) = \begin{bmatrix} g_1\big(y_1(t), y_2(t), \dots, y_n(t), u_1(t), u_2(t), \dots, u_m(t)\big) \\ g_2\big(y_1(t), y_2(t), \dots, y_n(t), u_1(t), u_2(t), \dots, u_m(t)\big) \\ \vdots \\ g_n\big(y_1(t), y_2(t), \dots, y_n(t), u_1(t), u_2(t), \dots, u_m(t)\big) \end{bmatrix}.$$

Let $U = \{\boldsymbol{u}: u\ is\ piecewise\ continuous\}$ be the set of all admissible controls of the system with $\boldsymbol{u}(t)$. It is important to note that due to some expected jumps from control, the set does not consist of continuous functions and hence, it can be said that functions are piecewise continuous.

To conclude, on an arbitrary time interval, say $t_0 \le t \le t_f$, a piecewise continuous function $\boldsymbol{u}(t)$ with a range in the region of control U is called as an admissible control. Because of some discontinuities, $\boldsymbol{u}$ is assumed to be continuous except finite number of t. As it is clear from its definition, every admissible control function is bounded.

Any control problem requires a performance criterion or index, or objective function that will be minimized or maximized. An objective function is generally denoted by J and defined as

$$J\big(\boldsymbol{y}(t), \boldsymbol{u}(t)\big) = \omega\left(\boldsymbol{y}\big(t_f\big)\right) + \int_{t_0}^{t_f} f\big(\boldsymbol{y}(t), \boldsymbol{u}(t)\big)dt.$$

In the above equality, $\boldsymbol{y}$ solves (2) for the control $\boldsymbol{u}$. The function $\omega: \mathbb{R}^n \to \mathbb{R}$ denotes the terminal payoff while $f: \mathbb{R}^n \times B \to \mathbb{R}$ denotes the running payoff. Also, f can be named as Lagrangian L. Both of these functions are continuously differentiable.

The main goal after constructing above things is to identify the control u^* which will maximize or minimize the objective function/performance criterion subject to (2). This u^* is called the control of the system. At this step, we need to find u^* such that

$$J(u^*) \ge J(u), \qquad (3)$$

for every control $u \in U$.

Three main formulations exist in an optimal control problem: Bolza, Lagrange and Mayer formulations. The formulation of Bolza of an optimal control is defined by

$$\max_{u \in U}\big[J\big(\boldsymbol{y}(t), \boldsymbol{u}(t)\big)\big],$$

where

$$J\big(\boldsymbol{y}(t),\boldsymbol{u}(t)\big)=\omega\left(t_f,\boldsymbol{y}\big(t_f\big)\right)+\int_{t_0}^{t_f} f\big(t,\boldsymbol{y}(t),\boldsymbol{u}(t)\big)dt,$$

subject to (2). Here $\boldsymbol{y}\big(t_f\big)$ is the value of $\boldsymbol{y}$ at final time t and is can be free or fixed.

Lastly, the third formulation known as Mayer formulation is obtained from Bolza's as well as follows:

$$\max_{u\in U}\big[J\big(\boldsymbol{y}(t),\boldsymbol{u}(t)\big)\big],$$

where

$$J\big(\boldsymbol{y}(t),\boldsymbol{u}(t)\big)=\omega\left(t_f,\boldsymbol{y}\big(t_f\big)\right),$$

subject to (2) (Berkovitz, 2013).

Theorem 3. All Bolza, Lagrange and Mayer formulations are equivalent.

Proof. (Saad, Dynamics and Optimal Control of Cancer Cells, 2019)

Existence of Optimal Control. As in every mathematical problem, proving the existence of solution is much more important than solving and finding a solution. So, in any optimal control problem, it should be proved that such an optimal control exists. In this regard, the following theorem plays a significant role for the existence of an optimal control. That is, it guarantees the existence of an optimal control which will minimize or maximize the optimal control's objective functional that is subject to its physical constraints (Berkovitz, 2013).

Theorem 4. Suppose that there exist an objective functional such that

$$J(u^*)\geq J(u),$$

for every control $u\in U$ where $U=\{\boldsymbol{u}\colon u\ is\ piecewise\ continuous\}$. Let the set of controls be Lebesgue integrable on the interval $t_0\leq t\leq t_f$ in the set of all real numbers. Then, there exists some arbitrary positive constants k_1,k_2,c_1 and c_2 such that:

a. In the admissible control set, $(\boldsymbol{y}_0,\boldsymbol{u})$, i.e., the class of all initial conditions with a control u, is nonempty if each state equation is satisfied.

b. $|\boldsymbol{f}(t,\boldsymbol{y},\boldsymbol{u})|\leq k_1(1+|\boldsymbol{y}|+|\boldsymbol{u}|)$.

c. $\left|\boldsymbol{f}(t,\boldsymbol{y^1},\boldsymbol{u})-\boldsymbol{f}(t,\boldsymbol{y},\boldsymbol{u})\right| \le k_2\left|\boldsymbol{y^1}-\boldsymbol{y}\right|(1+|\boldsymbol{u}|)$.

d. For a closed and convex set U, $f\big(t,\boldsymbol{y}(t),\boldsymbol{u}(t)\big)$ is convex on U and $\boldsymbol{g}(t,\boldsymbol{y},\boldsymbol{u})=\alpha(t,\boldsymbol{y})+\beta(t,\boldsymbol{y})\boldsymbol{u}$.

e. $f\big(t,\boldsymbol{y}(t),\boldsymbol{u}(t)\big) \ge c_1|\boldsymbol{u}|^{\beta}-c_2$ for $\beta > 1$.

If the above conditions hold, then there exists $(\boldsymbol{y}_0^*,\boldsymbol{u}^*)$ which minimizes $J(\boldsymbol{y}_0,\boldsymbol{u})$.

Proof. (Saad, Dynamics and Optimal Control of Cancer Cells, 2019)

Hamiltonian Function. The Hamiltonian of an optimal control theory is developed as a part of maximum principle of Lev Pontryagin. This function allows researchers to solve optimal control problems for dynamical systems. It can be defined as the instant increment of the Lagrangian expression of the optimization problem over a definite time interval. During the development of this function, Pontryagin demonstrated that while solving the optimal control problem for finding the control, control must be selected so that it can optimize the function of Hamiltonian (Sargent, 2000). The definition of the function is given below.

Definition 3. The Hamiltonian function $H\colon \mathbb{R}\times\mathbb{R}^n\times\mathbb{R}^n\times U\to\mathbb{R}^n$ is constructed as

$$H\big(t,\boldsymbol{y}(t),\boldsymbol{\lambda}(t),\boldsymbol{u}(t)\big)=f\big(t,\boldsymbol{y}(t),\boldsymbol{u}(t)\big)+\boldsymbol{\lambda}\boldsymbol{g}\big(t,\boldsymbol{y}(t),\boldsymbol{u}(t)\big)$$

with the adjoint function $\boldsymbol{\lambda}$ (Bellman, 2012).

Pontryagin's Maximum Principle. The maximum principle of Pontryagin was first formulated in the year of 1956 by the mathematician Lev Pontryagin and his students. Initially, it is applied to a rocket system for maximizing its terminal speed. For finding results, Pontryagin and his group took some ideas form the classical calculus of variations. While introducing this principle, the main purpose was to determine necessary conditions for a control to be optimal. In other words, the principle aims to evaluate the best possible control for the problem while transferring the dynamical system between different states when constraints for the state exists (Bongini, Fornasier,

Rossi, & Solombrino, 2017; Vinter, 2013; Kopp, 1962; Gamkrelidze R. V., 2003).

During the discovery of necessary conditions, the principle was reducing the obtained problem to a two-point boundary value problem (BVP). The idea here is to obtain set of differential equations with maximization or minimization condition. It is concluded that the BVP's results and computations can characterize the optimal control (Gamkrelidze R. V., History of the Discovery of the Pontryagin Maximum Principle, 2019). In spite of that, dealing with two-point BVPs can make some confusions and lead to some mistakes for complex examples. Therefore, numerical methods including forward-backward sweep, shooting, trapezoidal, etc. can be employed for the computation of numerical parts of the control problem (Fleming & Rishel, 1975; Schättler & Ledzewicz, 2012).

Theorem 5. (Pontryagin's maximum principle) (Pontryagin, 1987) Let J be an objective functional, $\boldsymbol{u}^*$ be an optimal for the (3) and $\boldsymbol{y}^*$ be the resultant state solution. Then for all $\boldsymbol{u}$ in U and for all t in $[t_0, t_f]$**,** there exists an adjoint function $\boldsymbol{\lambda}$: $[t_0, t_f] \to \mathbb{R}^n$ so that

$$H\big(t, \boldsymbol{y}^*(t), \boldsymbol{\lambda}(t), \boldsymbol{u}(t)\big) \leq H\big(t, \boldsymbol{y}^*(t), \boldsymbol{\lambda}(t), \boldsymbol{u}^*(t)\big), \tag{4}$$

$$\dot{\boldsymbol{y}}^*(t) = \frac{\partial H\big(t, \boldsymbol{y}^*(t), \boldsymbol{\lambda}(t), \boldsymbol{u}^*(t)\big)}{\partial \boldsymbol{\lambda}},$$

$$\dot{\boldsymbol{\lambda}}(t) = -\frac{\partial H\big(t, \boldsymbol{y}^*(t), \boldsymbol{\lambda}(t), \boldsymbol{u}^*(t)\big)}{\partial \boldsymbol{y}}, \tag{5}$$

and

$$\boldsymbol{\lambda}\big(t_f\big) = \mathbf{0}. \tag{6}$$

Proof. (Fleming & Rishel, 1975)

In Theorem 5, the inequality (4) is the maximization principle, the equality (5) is called as the adjoint equations and the equation (6) is the transversality condition. This condition can be used only if y_f is free. With this theorem, optimal control problem is reduced to maximizing Hamiltonian function. Hence, the optimality condition which is the critical point of Hamiltonian can be found as follows:

$$\frac{\partial H\left(t, \boldsymbol{y}^*(t), \boldsymbol{\lambda}(t), \boldsymbol{u}^*(t)\right)}{\partial \boldsymbol{u}} = 0.$$

The result is very crucial, efficient and easy to apply for determining the necessary conditions of an optimal control. In this way, there is no need to solve the integral in the objective function (Gamkrelidze R. V., Discovery of the Maximum Principle, 1999).

Corollary 1. (Bolza version of Pontryagin's principle) Assume that $\boldsymbol{y}^*$ and $\boldsymbol{u}^*$ are optimal for (2). Then for all $\boldsymbol{u}$ in U and for all t in $[t_0, t_f]$**,** there exists an adjoint function $\boldsymbol{\lambda}: [t_0, t_f] \to \mathbb{R}^n$ so that

$$H\left(t, \boldsymbol{y}^*(t), \boldsymbol{\lambda}(t), \boldsymbol{u}(t)\right) \leq H\left(t, \boldsymbol{y}^*(t), \boldsymbol{\lambda}(t), \boldsymbol{u}^*(t)\right),$$

$$\dot{\boldsymbol{y}}^*(t) = \frac{\partial H\left(t, \boldsymbol{y}^*(t), \boldsymbol{\lambda}(t), \boldsymbol{u}^*(t)\right)}{\partial \boldsymbol{\lambda}},$$

$$\dot{\boldsymbol{\lambda}}(t) = -\frac{\partial H\left(t, \boldsymbol{y}^*(t), \boldsymbol{\lambda}(t), \boldsymbol{u}^*(t)\right)}{\partial \boldsymbol{y}},$$

and

$$\boldsymbol{\lambda}\left(t_f\right) = \acute{\omega}\left(y\left(t_f\right)\right).$$

Proof. (Fleming & Rishel, 1975)

In the applications of real life, almost every control is bounded which leads us to propose necessary conditions for the bounded controls. Hence, we have the following corollary.

Corollary 2. For arbitrary constants p and q such that $p < q$, let

$$\max_{u \in U}\left[\int_{t_0}^{t_f} f\left(t, y(t), u(t)\right)dt\right],$$

subject to the system

$$\dot{y}(t) = f\left(t, y(t), u(t)\right),$$

$$y(t_0) = y_0, \qquad for\ \ p \leq u(t) \leq q,$$

be an optimal control problem. Assume u^* and y^* are optimal for the above system. Then for all u in U and for all t in $[t_0, t_f]$, there exists a piecewise differentiable function λ such that

$$H\big(t, y^*(t), \lambda(t), u(t)\big) \leq H\big(t, y^*(t), \lambda(t), u^*(t)\big),$$

$$\dot{y}^*(t) = \frac{\partial H\big(t, y^*(t), \lambda(t), u^*(t)\big)}{\partial \lambda},$$

$$\dot{\lambda}(t) = -\frac{\partial H\big(t, y^*(t), \lambda(t), u^*(t)\big)}{\partial y},$$

and

$$\lambda\big(t_f\big) = \dot{\omega}\left(y\big(t_f\big)\right).$$

Furthermore, the optimal condition can be demonstrated as

$$u^*(t) = \min(\max(\hat{u}, q), p)$$

or more precisely

$$u^*(t) = \begin{cases} p, & \frac{\partial H}{\partial u} < 0 \\ p < \hat{u} < q, & \frac{\partial H}{\partial u} = 0 \\ q, & \frac{\partial H}{\partial u} > 0 \end{cases}.$$

Proof. (Fleming & Rishel, 1975)

Trapezoidal Collocation Method

For the evaluation of results of any model visually, numerical methods are preferred to apply. Trapezoidal collocation method enables researchers to solve nonlinear differential equations numerically via programs like MatLab, Maple, etc. The method chooses a space with finite dimensional of solutions and few points from the domain. Then, it selects the solutions that satisfies the given equations for the points of the domain. As a result, it determines the values of optimal control for the problem. While constructing the program, transversality conditions, adjoint equations, objective functional, initial values of state variables and the equations of the control are needed (Awasthi, 2019).

Descriptive Statistics

Descriptive statistics is basically collecting, grouping, summarizing and analysing the collected data from sample groups. It allows researchers to understand and read data easier with the help of constructed tables, graphics and charts. It can be known as the basis step of researches since it tries to explain data within the groups and titles. Due to the applied field, the results of the statistics highlight

important parameters and guides researchers about what can be done in further steps. The relation between compartmental mathematical models and descriptive statistics can be described as the results of the statistics helps mathematicians to decide which parameters can be used during modelling process (Fisher & Marshall, 2009; Nick, 2007; Marshall & Jonker, 2010).

Cancer

For the centuries, cancer has been the second leading cause of deaths, worldwide. According to the World Health Organization (WHO), only in 2020, 10 million people passed away because of cancer. In 2020, the same statistics revealed that the most common types of the disease include breast, lung, colon and rectum, prostate, skin, and stomach, respectively (Cancer, 2022). All over the world, scientists try to develop techniques and introduce some interventions for providing early diagnosis and better treatment conditions for the patients.

The Natural History of Cancer. In human, the natural history of cancer disease is still indefinite since the truth can be followed up with written records. There are some beliefs without an exact proof that cancer disease exists in animals before the first human in the world in prehistoric times. According to the records, in 3000 BC, it is found that the earliest recorded cancer was breast cancer which was identified in Edwin Smith's papyrus with date 1500 BC. The record belongs to a papyrus from ancient Egypt. At that time, the disease was evaluated as a grave disease and concluded that no treatment exists for the disease. For the treatment of cancer, Egyptians employed knives, salts and arsenic paste till the 19th century. Later on, Hippocrates and Gales, as famous doctors, separated medicine from religion, magic and superstition. Their works claimed that cancer depends on natural causes and it can be diagnosed and treated with medical ways. The origin of the word "cancer" is from the Greek word "καρκὶνοι" which means "crab" in English. The name was given by Hippocrates since the growth of cancerous reminded him a moving crab (Donahue-Taylor, n.d.; Galmarini, 2020; Hajdu, 2011; Foulds, 1958; Sudhakar, 2009).

What is Cancer and its Causes? When an abnormal growth starts to occur in any part of the body including tissue, cells, organs and blood, cancer begins to develop. Even though there exist different types of cancer with unique features, in the lack of treatment, all in cancer types, growth and division of cancer cells are observed. Passing other parts of the body can be seen in some types of cancer through metastasis or the circulation of blood. Cancer cells cannot form independently; they develop in the body since the damage of DNA gives harm to normal cells. Hence, normal cells become cancer cells due to the damage of DNA. This damaged DNA may happen because of environmental conditions or it can be inherited from parents. Under some circumstances, the body structure is eligible to repair damaged DNA. However, this is not the case for cancer cells (Sung, Ferlay, Siegel, Laversanne, & Soerjomataram, 2021; Michor & Beal, 2015).

In any part of the body, cancer emerges as a solid tumour but there are some types of cancer like leukaemia, also known as blood cancer, that does not form tumours since the cells of leukaemia include blood and it circulates along other tissues. On the other hand, not all solid structures diagnosed as cancerous tumour. The structures that do not grow, proliferate or are not life-threatening are named as benign structures while the dangerous, spreadable and have the capacity of growth cancerous tumours are known as malignant tumours (Tabassum, Rosli, & Mazalan, 2019; Weinberg, 1996).

As it is mentioned above, cancer may occur as a result of a damage in DNA. It is discussed that this damage can be hereditary of from the environment. Having a family history is strongly associated with a high risk of cancer (Murff, Spigel, & Syngal, 2004; Love, Evans, & Josten, 1985). The authors Stein and Colditz (2004) established that some of the risk factors of cancer can be modifiable. These factors include tobacco using (smoking), excess amount of alcohol consumption and obesity. They emphasize the importance of change in behaviour for the mentioned parameters for preventing cancer risk. Lack of exercise is also a significant factor so, integrating physical activity into lives will be an advantage for the prevention of disease. WHO revealed that one-third of cancer caused deaths are related with smoking, obesity, excess alcohol consumption and lack of exercise (Cancer, 2022; Siemiatycki, 1991).

Diagnosis and Treatment of Cancer. As mentioned earlier, cancer is a life-threatening disease for centuries and due to this, early diagnosis (primary stage of cancer) is vitally significant. This leads scientists to improve researches for detecting cancer disease before the symptoms show up. There exist many tests for the diagnosis of cancer. First of all, if there are any symptoms, doctors start with investigating whether there is a family history of the patient or cancer history of the patient himself/herself. Screening (MRI, ultrasound, etc.) is a highly recommended prevention technique especially for breast, prostate, long and ovarian cancers. Particularly, the patients with a family history of cancer should regularly undergo medical screening and make necessary laboratory tests that are based on DNA mutations. These laboratory tests include blood tests, urine tests and other body fluids' tests which enables doctors to identify the structure of certain substances. Naturally, laboratory tests are not enough to identify whether the patient has a cancer or not. For precise diagnose of cancer, further implications (especially tumour marker tests and biopsy) are essential (Wardle, Kathryn, Vernon, & Waller, 2015; Warton & Samimi, 2015; How Cancer Is Diagnosed, 2023).

Cancer treatment with chemical substances has a long history. However, the first successful systemic chemotherapy was first used in 1940s. Of course, new agents are discovered and introduced to treatment techniques in following years. According to cancer types, there exist too many treatment types for cancer. Due to the stage and emergence of cancer more than one treatment may be needed. Hormone therapy, chemotherapy, radiotherapy, immunotherapy, surgery are common treatment strategies applied to cancer patients. Unfortunately, some of these like chemotherapy procedures can be a long and painful treatment. This is why drugs are discovered and produced for cancer pain (Nygren, 2001; Benson, et al., 2004; Cancer Treatment, n.d.).

Breast Cancer. Breast cancer occurs when cells in a breast starts to grow and develop out of control in human body. The type of breast cancer may differ according to the place of growth happens. Lobules, ducts and connective tissue are the main three parts of a breast. The growth of breast cancer cells mostly starts inside of the milk ducts or/and breasts' milk

producing lobules. Breast cancer may be invasive and spread out of the breast through lymph and blood vessels. This invasion results in the formation of tumours as lumps or thickening. Invasive cancers may lead a metastasis which may be fatal if no precautions are taken. WHO statistics demonstrated that in 2020, 2.3 million women are newly diagnosed with breast cancer and 685000 people passed away due to the disease (Breast Cancer, 2023; What Is Breast Cancer?, 2023).

Risk Factors, Diagnosis and Treatment of Breast Cancer. Gender is one of the risk factors since the disease occurs in men only with 0.5-1%. As in almost every disease increasing age is another risk factor. The author Singletary (2003) revealed that women aged between 30-80 has a high risk of breast cancer. In the same study, it is reported that alcohol consumption of low level is not related with breast cancer while family history is highly associated with breast cancer. The effect of obesity is significant since insulin level can be high due to obesity and this may lead a growth of cancer cells (Momenimovahed & Salehiniya, 2022). In the paper of Gaudet et al. (2013), it is observed that active tobacco use plays a significant role with the initiation of breast cancer. Hence, active smokers have a higher risk of breast cancer than non-smokers. Because breast cancer is related with hormones, having postmenopausal hormone therapies may increase the risk of breast cancer since the substances of therapy include oestrogen hormone. Another important factors that may increase the breast cancer include late menopause, low lactation rate due to less breastfeeding and early menarche (França-Botelho, Ferreira, França, França, & Honório-França, 2012; Momenimovahed & Salehiniya, 2022; Singletary, 2003; Breast Cancer, 2023).

Until 1980s, there was an inadequacy of uniformity and standardization while reporting MRI, mammography and ultrasound screening results. Distinct evaluation of mammography results of radiologists was lead wide variability of practices and different radiation doses. So, the main problem was inconsistent recommendations and misinterpretations. In this regard, American College of Radiology (ACR) created a categorization system known as the Breast Imaging Reporting and Data System (BI-RADS). The

purpose of the system is to reduce the diversity of the terminology written in MRI, mammography and ultrasound reports (Kim, et al., 2008; Burnside, et al., 2009).

The BI-RADS system consists of 7 different categories starting from BI-RADS 0 till BI-RADS 7. The category 0 is an incomplete category, that is, further and additional evaluations are necessary such as prior mammograms and tests. BI-RADS 1 is the category defined as negative. In this category, no finding (including benign findings) exists in the breast. If 100% of benign findings are present in the breast, then the patient is categorized as BI-RADS 2. In BI-RADS 2, radiologists and doctors do not suggest a time interval to follow up. BI-RADS 3 is an intermediate category in the system. Patients diagnosed as BI-RADS 3 have some structures in their breast and these findings have a high probability of being benign. However, the risk of malignancy exists with 0-2% and so a time interval should be suggested to follow up the structures. The lesions found in the patients diagnosed with BI-RADS 4 have a certain malignancy probability. Hence, a biopsy is needed to evaluate these lesions. Due to the variety and wide range of cancer probability, BI-RADS 4 category is divided into three subcategories: BI-RADS 4A, BI-RADS 4B and BI-RADS 4C. BI-RADS 4A has a low suspicious of malignancy with 2-10%, BI-RADS 4B has a moderate level of malignancy suspicion with 10-50% and the high level of suspicion for malignancy exists in the category BI-RADS 4C with 50-95%. As it is obvious, the category 4 has a wide range of cancer risk which may disturb the patients diagnosed with BI-RADS 4. In the category BI-RADS 5, observed lesions has a high chance of malignancy (95-100%). At this category, further implementations like biopsy are needed and should be done simultaneously. In BI-RADS 6 of the system, malignancy of founded lesions is histologically proved via biopsy. The patient's observed lesions are 100% malignant, i.e., the patient has a breast cancer. Category of patients are identified by radiologists when they evaluate the screening results (Balleyguier, et al., 2007; Obenauer, Hermann, & Grabbe, 2005; Patterson, et al., 2014).

In the breast cancer there are five stages as Stage 0, Stage I, Stage II, Stage III and Stage IV. In Stage 0, cancer is defined as non-invasive and in

medicine language Stage 0 is known as “in situ” since it is the earliest stage. At this stage, abnormal tissue and cell growths occur only in lobules and ducts of the breast; the cancer has not spread yet and can be fully treated by the removal of that region. In Stage I, the cancer become invasive, that is, cancer cells spread in the tissue of breast and the tumour is up to 2 cm. The stage is known as early-invasive stage and the best treatment method is determined as breast conserving surgery since this surgery does not completely remove the breast and it leaves excess healthy tissue of the breast. After the surgery, radiation therapy is necessary to prevent local recurrence. The Stage II is also named as early-invasive stage. However, at this stage cancer cells begin to spread lymph nodes of the breast and the tumour size is between 2-5 cm. In some cases, the tumour size may be above 5 cm with no spread to lymph nodes. Stage III breast cancer or locally advanced breast cancer is an invasive cancer with tumours greater than 5 cm that is extended to lymph nodes, underlying chest wall/skin. At this stage, induction chemotherapy is recommended firstly. Then, local therapy including surgery, radiation therapy, etc. should be applied. The Stage IV is the metastatic stage which may be occurred as a result of relapse after the treatment of early stage of breast cancer. At this stage, cancer cells spread to other organs and tissues. The treatment of cancer at Stage IV differs according to the health conditions of the patient, age, how huge is the spread, etc. (Hortobagyi, 1998; Maughan, Lutterbie, & Ham, 2010; Moulder & Hortobagyi, 2008; Tong, Wu, Cho, & To, 2018).

Related Research

In the literature, there exist innumerous studies that deals with breast cancer via mathematical modelling and statistics. Scientific researchers endeavour to discover effective diagnosis and treatment strategies for breast cancer for centuries. A study proposed in 1996 had developed a mathematical model to determine the effects of risk factors of reproduction on the incidence of breast cancer. The log-incidence model developed for the issue revealed that women’s reproductive life should be limited in time periods (Rosner & Colditz, 1996). The author Euhus (2001) demonstrated that assessment and counselling for the breast cancer can be carried out via mathematical models and epidemiologic obtained data. However, he

emphasizes the importance of introducing more than one model for more accurate results. Solis-Perez and his friends developed an integer-ordered mathematical model for the breast cancer by introducing fractional operator to the system of ODEs. Their work was based on cells, that is, the state variables were cells and hormones. The aim of this work was to enable further information about the complex dynamics of breast cancer (Solís-Pérez, Gómez-Aguilar, & Atangana, 2019). Both mathematical and statistical models are introduced in the work of Roe-Dale et al. (2010) to improve treatment strategies for the breast cancer. For emphasizing the importance of regular screening, a statistical model and a mathematical model are constructed in Shwartz (A Mathematical Model Used to Analyze Breast Cancer Screening Strategies) (1978) and Shwartz (An Analysis of the Benefits of Serial Screening for Breast Cancer based upon a Mathematical Model of the Disease) (1978), respectively. Optimal control theory is applied to a compartmental deterministic model where state variables are cells, immune response and oestrogen in Oke et al. (2018). For minimizing the breast cancer and tumour growth, ketogenic-diet and anti-cancer drugs are added as optimal controls. In the review Clare et al. (2000) two mathematical models are compared which are constructed for molecular biology of breast metastasis. For the BI-RADS categorization system, only papers including statistics and statistical models are developed such as Grimm et al. (2014), Dobruch-Sobczak (2017), Kim et al. (2012).

Framework of the Thesis

The main purpose of this thesis can be summarized as narrowing the wide range of breast cancer risk in BI-RADS 4 subcategories and pointing out the importance of early diagnosis by focusing on determining the effective parameters on BI-RADS 4 subcategories. Moreover, it is aimed to discern a remarkable control strategy in the diagnosis of BI-RADS 4 and hence breast cancer. The summary of the thesis including purpose and significant of the study, and research questions and hypotheses are stated in Chapter I.

For a better understanding of breast cancer, BI-RADS subcategories and the relationship between mathematical model and health sciences, a literature review is done and explained in Chapter II including the mathematical tools (solution techniques, definitions, theorems and corollaries) that are used in the thesis. The data of BI-RADS 4 diagnosed patients is opted for with the aim of designing a

mathematical model. Chapter III consists of the constructed mathematical model with its necessary properties and theorems with proofs. Numerical simulations of the results of the model are also presented in Chapter III. With the findings of Chapter III, an optimal control system is proposed by introducing a control strategy (that should be efficacious) to the constructed mathematical model and presented in Chapter IV. The properties, theorems with proofs and numerical simulations of the results of the mathematical model with optimal control are also included in Chapter IV. The findings of all thesis and discussions are provided in Chapter V with the comparison of other works in literature. Chapter VI comprises the conclusions and recommendations of the thesis. In this chapter, overall conclusions and what can be done in future in this field are discussed.

CHAPTER III
Methodology

In this chapter, the evaluation of BI-RADS 4 diagnosed patients is proposed with the help of mathematical modelling. The aim of this chapter is to construct a mathematical model for the patients diagnosed with BI-RADS 4A, BI-RADS 4B and BI-RADS 4C, to evaluate the relationship between the subcategories and to find the most effective parameters on state variables or compartments via sensitivity analysis. On that note, firstly the design and limitations of the research are given. Then, the obtained data is explained. Lastly, the analysis of the model is illustrated with necessary theorems, proofs and numerical simulations.

Research Design and Limitations

For the research of BI-RADS 4 diagnosed patients, deterministic mathematical model is constructed with ODEs. Later on, proof of existence of solutions and equilibrium points are shown and calculated with computation techniques and theorems. For the examination of the disease, basic reproduction numbers of each compartment are calculated via NGM method. In order to determine the most effective parameters on the risk of breast cancer and BI-RADS 4 subcategories, sensitivity analysis is applied to the parameters and basic reproduction numbers of the model. For visual evaluations, MatLab program is involved to solve the system numerically.

During the construction of the model, it is assumed that diagnosed compartments' transition occurs step by step. That is, BI-RADS 4A patients should be diagnosed as BI-RADS 4B firstly. In other words, they can transfer to BI-RADS 4C compartment only if they diagnosed with BI-RADS 4B after BI-RADS 4A diagnosis. Moreover, as mentioned in Castillo-Garsow and Castillo-Chavez (2020), smoking may increase the risk of breast cancer in a long term. Hence, it is assumed that increase in the rate of tobacco use may increase the risk of diagnosis of BI-RADS 4B and BI-RADS 4C. It does not have a huge effect on the risk of BI-RADS 4A diagnosis. For early menopause, it is considered that an individual should go through menopause before the age 40 while late menopause is considered as after the age of 55.

Data Collection

In this chapter, the data is obtained from the Centre for Breast Health, Near East University Hospital and it captures the data of 107 patients.

Data Analysis

In this section of the thesis, analysis of the obtained data is given.

Descriptive Statistics

In this section, statistics of the obtained data are expressed with tables. In this regard, the data is defined descriptively according to the patients' age, menstrual state, tobacco use, lactation, existence of palpable mass and existence of bloody nipple discharge. The results are given in Table 1 – Table 6. This information is used while determining the parameters of the proposed model.

Table 1.

Distribution of Patients According to Their Age in BI-RADS 4 Subcategories

	Patients younger than 40	Patients older than or equal to 40
BI-RADS 4A	23	33
BI-RADS 4B	10	14
BI-RADS 4C	1	26

Table 2.

Distribution of Patients According to Their Menstrual State in BI-RADS 4 Subcategories

	Regular	Irregular	Menopause
BI-RADS 4A	45	3	8
BI-RADS 4B	19	1	4
BI-RADS 4C	5	3	19

Table 3.

Distribution of Patients According to Their Tobacco Use in BI-RADS 4 Subcategories

	Smokers	Non-smokers
BI-RADS 4A	19	37
BI-RADS 4B	8	16
BI-RADS 4C	6	21

Table 4.

Distribution of Patients According to Their Lactation in BI-RADS 4 Subcategories

	Active lactation	Non-active lactation
BI-RADS 4A	39	17
BI-RADS 4B	14	10
BI-RADS 4C	18	9

Table 5.

Distribution of Patients According to the Existence of Palpable Mass in BI-RADS 4 Subcategories

	Palpable mass exists	Palpable mass does not exist
BI-RADS 4A	16	40
BI-RADS 4B	15	9
BI-RADS 4C	25	2

Table 6.

Distribution of Patients According to the Existence of Bloody Nipple Discharge in BI-RADS 4 Subcategories

	Bloody nipple discharge exists	Bloody nipple discharge does not exist
BI-RADS 4A	1	55
BI-RADS 4B	1	23
BI-RADS 4C	4	23

Mathematical Model and Its Analysis

While constructing the model, the total population, denoted by $N(t)$ at time t, is divided into 4 compartments, that is, the model consists of 4 state variables. These are: susceptible individuals $\left(S(t)\right)$, individuals diagnosed with BI-RADS 4A $\left(4_A(t)\right)$, individuals diagnosed with BI-RADS 4B $\left(4_B(t)\right)$ and individuals diagnosed with BI-RADS 4C $\left(4_C(t)\right)$. For determining the necessary parameters, the obtained data is analyzed. Hence, the model is constructed as follows:

$$\frac{dS}{dt} = \pi - (a + p + b)S + (l_1 + e_1)4_A + (l_2 + e_2)4_B + (l_3 + e_3)4_C - (h_1 4_A + h_2 4_B + h_3 4_C)S - \mu S,$$

$$\frac{d4_A}{dt} = c_1 aS + k_1 pS - (m_1 + l_1 + e_1)4_A + h_1 4_A S - s_1 4_A - \mu 4_A,$$

$$\frac{d4_B}{dt} = c_2 aS + k_2 pS + m_1 4_A - (m_2 + l_2 + e_2)4_B + h_2 4_B S + s_1 4_A - s_2 4_B - \mu 4_B,$$

$$\frac{d4_C}{dt} = (1 - c_1 - c_2)aS + (1 - k_1 - k_2)pS + bS + m_2 4_B - (l_3 + e_3)4_C + h_3 4_C S + s_2 4_B - \mu 4_C.$$

The definitions of state variables and parameters of the model are given in Table 7 and Table 8 below.

Table 7.

Description of Variables used in the Mathematical Model

Variables	Descriptions
S	Susceptible Individuals
4_A	Individuals that are diagnosed as BI-RADS 4A
4_B	Individuals that are diagnosed as BI-RADS 4B
4_C	Individuals that are diagnosed as BI-RADS 4C

Table 8.

Description of Parameters used in the Mathematical Model

Parameters	Descriptions
π	Recruitment Rate
a	Age
p	Palpable Mass
b	Bloody Nipple Discharge
$l_i, i = 1, 2, 3$	Lactation Rate
$e_i, i = 1, 2, 3$	Early Menopause
m_1	Irregular Menstruation
m_2	Late Menopause
$h_i, i = 1, 2, 3$	Family History
s_1	Smoking Rate of the BI-RADS 4A Individuals
s_2	Smoking Rate of the BI-RADS 4B Individuals
μ	Natural Death Rate

For the proof of existence of solutions of the proposed model, the following theorem is stated and demonstrated.

Theorem 6. Let $(S, 4_A, 4_B, 4_C)$ be a solution of the proposed system with the following initial conditions:

$$S \geq 0, 4_A \geq 0, 4_B \geq 0, 4_C \geq 0.$$

Then, the set Λ below is biological feasible, that is, positive and invariant. Moreover, all of the solutions in $\mathbb{R}_+^4$ stay in π with respect to the proposed system (Gokbulut, Hincal, Besim, & Kaymakamzade, 2022).

$$\Lambda = \{(S, 4_A, 4_B, 4_C) \in \mathbb{R}_+^4 : S, C_C, C_I, H_C, H_I, O, G, T \leq \pi\}.$$

Proof. Firstly, all terms of the equations in the system should be added. Then, we obtain

$$\frac{dN}{dt} = \pi - \mu(S + 4_A + 4_B + 4_C).$$

As it is obvious from the above inequality, $\frac{dN}{dt} \leq \pi$. Integrating both sides of the inequality with respect to t, we get

$$N(t)e^t \leq \pi e^t + k,$$

for some arbitrary constant k. Applying Rota and Birkhoff stated in Birkhoff and Rota (1991) to the differential inequality, it is concluded that as t tends to infinity (∞), $0 \leq N \leq \pi$ holds. As a result, all of the solutions of the proposed system enter the region π. Hence, it is concluded that the proposed model is biologically feasible and it will be enough to consider the dynamics on the model in the set Λ.

Equilibrium Points and Basic Reproduction Numbers. As it is mentioned in Chapter II, existence of equilibrium points and their stability improves the strength of mathematical models. For the proposed model in Chapter III, there exist 3 equilibrium points: diagnose-free equilibrium point E_0, BI-RADS 4B&BI-RADS 4C free equilibrium point E_1 and endemic equilibrium point E_2.

The constructed model contains three diagnosis compartments. This results in the existence of three different basic reproduction numbers for each compartment. For the computation of these numbers, NGM method is applied as below. The matrix F contains the model's new diagnosis with BI-RADS 4 subcategories while the rest of the model is included in the matrix V. Hence,

$$F = \begin{bmatrix} h_1 S & 0 & 0 \\ s_1 & h_2 S & 0 \\ 0 & s_2 & h_3 S \end{bmatrix},$$

$$V = \begin{bmatrix} m_1 + l_1 + e_1 + s_1 + \mu & 0 & 0 \\ -m_1 & m_2 + l_2 + e_2 + s_2 + \mu & 0 \\ 0 & -m_2 & l_3 + e_3 + \mu \end{bmatrix}.$$

Computation of basic reproduction numbers should be done by obtaining dominant eigenvalues of the multiplication matrix $F.V^{-1}$. The inverse matrix V^{-1} is

$$V^{-1} = \begin{bmatrix} \frac{1}{m_1 + l_1 + e_1 + s_1 + \mu} & 0 & 0 \\ \frac{m_1}{(m_1 + l_1 + e_1 + s_1 + \mu)(m_2 + l_2 + e_2 + s_2 + \mu)} & \frac{1}{m_2 + l_2 + e_2 + s_2 + \mu} & 0 \\ \frac{m_1 m_2}{(m_1 + l_1 + e_1 + s_1 + \mu)(m_2 + l_2 + e_2 + s_2 + \mu)(l_3 + e_3 + \mu)} & \frac{m_2}{(m_2 + l_2 + e_2 + s_2 + \mu)(l_3 + e_3 + \mu)} & \frac{1}{l_3 + e_3 + \mu} \end{bmatrix}.$$

So, the matrix multiplication is obtained as

$$F.V^{-1} = \begin{bmatrix} \frac{h_1 S}{o} & 0 & 0 \\ \frac{s_1}{o} + \frac{(Sh_2 + s_1)m_1}{oq} & \frac{Sh_2 + s_1}{q} & 0 \\ \frac{s_2 m_1}{oq} + \frac{(Sh_3 + s_2)m_1 m_2}{oqr} & \frac{s_2}{q} + \frac{(Sh_3 + s_2)m_2}{qr} & \frac{Sh_3 + s_2}{r} \end{bmatrix},$$

where

$$o = m_1 + l_1 + e_1 + s_1 + \mu,$$
$$q = m_2 + l_2 + e_2 + s_2 + \mu,$$
$$r = l_3 + e_3 + \mu.$$

The basic reproduction numbers of the constructed model are the dominant eigenvalues of the above matrix. That is,

$$R_{0,A} = \frac{h_1 S}{m_1 + l_1 + e_1 + s_1 + \mu},$$
$$R_{0,B} = \frac{h_2 S}{m_2 + l_2 + e_2 + s_2 + \mu},$$

and

$$R_{0,C} = \frac{h_3 S}{l_3 + e_3 + \mu},$$

for the subcategories BI-RADS 4A, BI-RADS 4B and BI-RADS 4C, respectively.

At the diagnose-free equilibrium point E_0 the subcategories of BI-RADS 4 do not exist in the population. That is, the state variables $4_A, 4_B$ and 4_C are all equal to 0. Hence,

$$E_0(S_0, 4_{A,0}, 4_{B,0}, 4_{C,0}) = \{(S_0, 4_{A,0}, 4_{B,0}, 4_{C,0}) \in R_4^+ : 4_{A,0} = 4_{B,0} = 4_{C,0} = 0\}.$$

As a formulation, it can be written as

$$E_0 = \left(\frac{\pi}{a + p + b + \mu}, 0, 0, 0\right).$$

At the BI-RADS 4B&BI-RADS 4C free equilibrium point $E_1(S_1, 4_{A,1}, 4_{B,1}, 4_{C,1})$, only individuals diagnosed with BI-RADS 4A exist in the community. In other words, no one can be diagnosed with BI-RADS 4B or BI-RADS 4C. This point is important since the subcategory BI-RADS 4A

has the lowest cancer risk when it is compared with other two subcategories. It is obtained with the following calculations.

The solution of S_1 is the solution of the below equation

$$AS_1^2 + BS_1 + C = 0,$$

where

$$A = -h_1(c_1a + k_1p - a - p - b - \mu),$$
$$B = -h_1\pi - (l_1 + e_1 + s_1 + m_1 + \mu)(a + p + b + \mu) + (l_1 + e_1)(c_1a + k_1p),$$
$$C = \pi(l_1 + e_1 + s_1 + m_1 + \mu).$$

The above equation has a solution only if $C \geq 0$ and $B < 0$ which is possible since C consists of addition of nonnegative parameters, so, $C \geq 0$. For $B < 0$, we should show that

$$-h_1\pi - (l_1 + e_1 + s_1 + m_1 + \mu)(a + p + b + \mu) + (l_1 + e_1)(c_1a + k_1p) < 0,$$

or

$$h_1\pi + (l_1 + e_1 + s_1 + m_1 + \mu)(a + p + b + \mu) > (l_1 + e_1)(c_1a + k_1p).$$

At this point, $R_{0,A} > 1$ should hold. That is,

$$h_1\pi > (l_1 + e_1 + s_1 + m_1 + \mu)(a + p + b + \mu). \quad (7)$$

Now, from the inequality (7)

$$\begin{aligned} h_1\pi + (l_1 + e_1 + s_1 + m_1 + \mu)(a + p + b + \mu) &> (l_1 + e_1 + s_1 + m_1 + \mu)(a + p + b + \mu) \\ &+ (l_1 + e_1 + s_1 + m_1 + \mu)(a + p + b + \mu) \\ &= 2(l_1 + e_1 + s_1 + m_1 + \mu)(a + p + b + \mu) \\ &> 2(l_1 + e_1)(a + p + b + \mu) > (l_1 + e_1)(c_1a + k_1p). \end{aligned}$$

Hence, $B < 0$ and the coordinate S_1 exists. For the solution of $4_{A,1}$,

$$c_1aS_1 + k_1pS_1 - (m_1 + l_1 + e_1)4_{A,1} + h_14_{A,1}S_1 - s_14_{A,1} - \mu4_{A,1} = 0,$$
$$(m_1 + l_1 + e_1)4_{A,1} - h_14_{A,1}S_1 + s_14_{A,1} + \mu4_{A,1} = (c_1a + k_1p)S_1,$$
$$(m_1 + l_1 + e_1 + s_1 - h_1S_1 + \mu)4_{A,1} = (c_1a + k_1p)S_1,$$
$$4_{A,1} = \frac{(c_1a + k_1p)S_1}{m_1 + l_1 + e_1 + s_1 - h_1S_1 + \mu}.$$

So, the solution $4_{A,1}$ exists since S_1 exists.

Therefore, the equilibrium point

$$E_1(S_1, 4_{A,1}, 4_{B,1}, 4_{C,1}) = E_1(S_1, 4_{A,1}, 0, 0)$$

exists.

The endemic equilibrium point is where the diagnosis of BI-RADS 4 subcategories exist but under control. This point consists of 4 coordinates, $S_2, 4_{A,2}, 4_{B,2}$ and $4_{C,2}$. For the existence of this point, we need to show that the below equation has a solution S_2.

$$A'S_2^4 + B'S_2^3 + C'S_2^2 + D'S_2 + E' = 0,$$

where

$$\begin{aligned}
A' &= (R - V)h_1h_2h_3,\\
B' &= (B_1V - h_1\pi + C_2R)h_2h_3 + [A_1(R - V) - Q(E + C_3)]h_1h_3\\
&\quad + (R - V)C_1h_1h_2,\\
C' &= A_1[(C_2R + B_1V - h_1\pi)h_3 - (V + R)C_1h_1]\\
&\quad + B_1[(C_1V + h_3\pi)h_2 + (E + C_3)h_3Q]\\
&\quad + C_1[C_2Rh_2 - (h_2\pi + QC_3)h_1] + (E + C_3)DRh_3\\
&\quad - (l_3 + e_3)EQh_1,\\
D' &= A_1B_1(h_3\pi + C_1V) + C_1[A_1(C_2R - h_1\pi) + B_1(QC_3 + h_2\pi)]\\
&\quad + E(l_3 + e_3)(DR + QB_1) + DRC_1C_3,\\
E' &= \pi A_1B_1C_1,
\end{aligned}$$

and

$$\begin{aligned}
R &= c_1a + k_1p,\\
V &= a + p + b + \mu,\\
A_1 &= m_2 + l_2 + e_2 + s_2 + \mu,\\
B_1 &= m_1 + l_1 + e_1 + s_1 + \mu,\\
C_1 &= l_3 + e_3 + \mu,\\
C_2 &= l_1 + e_1,\\
C_3 &= l_2 + e_2,\\
D &= m_1 + s_1,\\
E &= m_2 + s_2,\\
Q &= c_2a + k_2p.
\end{aligned}$$

For this equation, $E' > 0$ always holds since all parameters are positive. For the coefficient A',

$$\begin{aligned}
R - V &= c_1a + k_1p - (a + p + b + \mu) = (c_1 - 1)a + (k_1 - 1)p - b - \mu\\
&< 0.
\end{aligned}$$

Hence, A' is always negative. The coefficient B' is negative if $R_{0,A} > 1, R_{0,B} > 1$ and $R_{0,C} > 1$ as proved below.

$$\begin{aligned} B' &= B_1 V h_1 h_3 + C_2 R h_2 h_3 + A_1 R h_1 h_3 + C_1 R h_1 h_2 - \pi h_1 h_2 h_3 - A_1 V h_1 h_3 \\ &\quad - (E + C_3) Q h_1 h_3 - C_1 V h_1 h_2 \\ &< (C_2 R - \pi h_1) h_2 h_3 + (R - V) C_1 h_1 h_2 < 0. \end{aligned}$$

Similarly, the coefficient C' is always negative if $R_{0,A} > 1, R_{0,B} >, R_{0,C} > 1$ and $h_1 \pi > 3$ which is explained below.

$$\begin{aligned} C' &= A_1[(C_2 R + B_1 V - h_1 \pi) h_3 - (V + R) C_1 h_1] \\ &\quad + B_1[(C_1 V + h_3 \pi) h_2 + (E + C_3) h_3 Q] \\ &\quad + C_1[C_2 R h_2 - (h_2 \pi + Q C_3) h_1] + (E + C_3) D R h_3 \\ &\quad - (l_3 + e_3) E Q h_1 < h_1 h_2 h_3 \pi^2 (3 - h_1 \pi) < 0. \end{aligned}$$

For the coefficient D', it is always positive under the conditions $R_{0,A} > 1, R_{0,B} > 1$ and $R_{0,C} > 1$.

$$\begin{aligned} D' &= A_1 B_1 (h_3 \pi + C_1 V) + C_1[A_1 (C_2 R - h_1 \pi) + B_1 (Q C_3 + h_2 \pi)] \\ &\quad + E(l_3 + e_3)(DR + Q B_1) + DR C_1 C_3 \\ &\quad > A_1 B_1 (h_3 \pi + C_1 V) + B_1 C_1 [V + Q C_3 + h_2 \pi] \\ &\quad + E(l_3 + e_3)(DR + Q B_1) + DR C_1 C_3 > 0. \end{aligned}$$

The equation given above has a real solution S_2 since

$$\begin{aligned} &256 A'^3 E'^3 - 192 A'^2 B D E'^2 - 128 (A' C' E')^2 + 144 A'^2 C D'^2 E' \\ &\quad - 27 A'^2 D'^4 + 144 A' B'^2 C E'^2 - 6 A' B'^2 D'^2 E' \\ &\quad - 80 A' B' C'^2 D' E' + 18 A' B' C' D'^3 + 16 A' C'^4 E' \\ &\quad - 4 A' C'^3 D'^2 - 27 B'^4 E'^2 + 18 B'^3 C' D' E' - 4 B'^3 D'^3 \\ &\quad - 4 B'^2 C'^3 E' < 0 \end{aligned}$$

always hold.

The other coordinates depend on S_2 as below:

$$4_{A,2} = \frac{R}{B_1 - h_1 S_2} S_2,$$

$$4_{B,2} = \frac{(B_1 - h_1 S_2) Q + DR}{(A_1 + h_2 S_2)(B_1 - h_1 S_2)} S_2,$$

and

$$4_{C,2} = \frac{(1-c_1-c_2)a + (1-k_1-k_2)p}{C_1 + h_3 S_2} S_2 + \frac{[(B_1 - h_1 S_2)Q + DR]E}{(A_1 + h_2 S_2)(B_1 - h_1 S_2)(C_1 + h_3 S_2)} S_2.$$

From the above calculations, it is concluded that the endemic equilibrium point E_2 exists only if $R_{0,A} > 1, R_{0,B} > 1$ and $R_{0,C} > 1$.

Theorem 7. The diagnose-free equilibrium point, E_0, of the system is globally asymptotically stable under the conditions $R_{0,A} < 1$, $R_{0,B} < 1$, and $R_{0,C} < 1$.

Proof. For proving the stability of E_0, we will construct a Lyapunov function. Let

$$V(S, 4_A, 4_B, 4_C) = S - S_0 \ln S + 4_A + 4_B + 4_C + K,$$

where $K = S_0 \ln S_0 - S_0$ be a Lyapunov function. It is clear that the state variables are positive and hence, the function V is always positive and it equals to 0 at the equilibrium point E_0. Lastly, it should be checked that $\dot{V} < 0$.

$$\begin{aligned}\dot{V} = \dot{S} - S_0 \frac{\dot{S}}{S} + \dot{4_A} + \dot{4_B} + \dot{4_C} &= \pi - \mu(S + 4_A + 4_B + 4_C) \\ &- [\pi - (a+p+b+\mu)S + (l_1+e_1)4_A + (l_2+e_2)4_B \\ &+ (l_3+e_3)4_C - h_1 4_A S - h_2 4_B S - h_3 4_C S] \frac{S_0}{S}.\end{aligned}$$

Since $\pi = S_0(a+p+b+\mu)$ as calculated above, we get

$$\begin{aligned}\pi - \mu(S + 4_A + 4_B + 4_C) &- [\pi - (a+p+b+\mu)S + (l_1+e_1)4_A + (l_2+e_2)4_B \\ &+ (l_3+e_3)4_C - h_1 4_A S - h_2 4_B S - h_3 4_C S] \frac{S_0}{S} \\ &= S_0(a+p+b+\mu)\left(1 - \frac{S_0}{S}\right) \\ &+ \left[-\mu - (l_1+e_1)\frac{S_0}{S} + h_1 S_0\right] 4_A \\ &+ \left[-\mu - (l_2+e_2)\frac{S_0}{S} + h_2 S_0\right] 4_B \\ &+ \left[-\mu - (l_3+e_3)\frac{S_0}{S} + h_3 S_0\right] 4_C - \mu S.\end{aligned}$$

For the term $1-\frac{S_0}{S}$, we have the followings:

Since S_0 is the point where the population is diagnose-free, whole population stays in that compartment. In other words, for any time t,

$$S_0 > S(t).$$

This implies that

$$\frac{S_0}{S} > 1,$$

$$1-\frac{S_0}{S} < 0.$$

For the other terms, if $R_{0,A} < 1$ at E_0, we have

$$-\mu-(l_1+e_1)\frac{S_0}{S}+h_1S_0 < -\mu-(l_1+e_1)\frac{S_0}{S}+m_1+l_1+e_1+s_1+\mu,$$

since $R_{0,A}(E_0)=\frac{h_1S_0}{m_1+l_1+e_1+s_1+\mu} < 1$.

Then,

$-\mu-(l_1+e_1)\frac{S_0}{S}+m_1+l_1+e_1+s_1+\mu = -(l_1+e_1)\frac{S_0}{S}+m_1+l_1+$

$e_1+s_1 < -(l_1+e_1)\frac{S_0}{S}+l_1+e_1$, since $m_1 > 0$ and $s_1 > 0$. Hence,

$$-\mu-(l_1+e_1)\frac{S_0}{S}+h_1S_0 < -(l_1+e_1)\frac{S_0}{S}+l_1+e_1 = (l_1+e_1)\left(1-\frac{S_0}{S}\right) < 0,$$

since $l_1+e_1 > 0$ and $1-\frac{S_0}{S} < 0$ which is proved above.

Similarly, if $R_{0,B} < 1$ at E_0, we have

$$R_{0,B}(E_0)=\frac{h_2S_0}{m_2+l_2+e_2+s_2+\mu} < 1$$

and so,

$$\begin{aligned}-\mu-(l_2+e_2)\frac{S_0}{S}+h_2S_0 &< -\mu-(l_2+e_2)\frac{S_0}{S}+m_2+l_2+e_2+s_2+\mu\\ &= -(l_2+e_2)\frac{S_0}{S}+m_2+l_2+e_2+s_2\\ &< -(l_2+e_2)\frac{S_0}{S}+l_2+e_2\end{aligned}$$

since $m_2 > 0$ and $s_2 > 0$. Thus,

$$-\mu-(l_2+e_2)\frac{S_0}{S}+h_2S_0 < -(l_2+e_2)\frac{S_0}{S}+l_2+e_2 = (l_2+e_2)\left(1-\frac{S_0}{S}\right) < 0$$

holds since $l_2 + e_2 > 0$ and $1 - \frac{S_0}{S} < 0$ (from above) always hold.

Lastly, under the condition $R_{0,C} < 1$ at E_0, that is, $h_3 S_0 < l_3 + e_3 + \mu$, we get

$$-\mu - (l_3 + e_3)\frac{S_0}{S} + h_3 S_0 < -\mu - (l_3 + e_3)\frac{S_0}{S} + l_3 + e_3 + \mu$$
$$= -(l_3 + e_3)\frac{S_0}{S} + l_3 + e_3 = (l_3 + e_3)\left(1 - \frac{S_0}{S}\right) < 0,$$

since $l_3 + e_3 > 0$ and $1 - \frac{S_0}{S} < 0$ from the previous calculations.

Therefore, the point E_0 is globally asymptotically stable if $R_{0,A} < 1$, $R_{0,B} < 1$, and $R_{0,C} < 1$ hold.

Theorem 8. The equilibrium point, E_1, of the system is globally asymptotically stable under the conditions $R_{0,A} > 1$, $R_{0,B} < 1$, and $R_{0,C} < 1$.

Proof. For the stability, consider the following Lyapunov function

$$W(S, 4_A, 4_B, 4_C) = S - S_1 \ln S + 4_A - 4_{A,1} \ln 4_A + 4_B + 4_C + M,$$

where $M = S_1 \ln S_1 - S_1 + 4_{A,1} \ln 4_{A,1} - 4_{A,1}$. As can be seen, the function W is always positive and equals to zero at E_1. In order to prove stability, we need to show that W is negative definite, that is, $\dot{W} < 0$. Now, we have

$$\dot{W} = \dot{S} - S_1\frac{\dot{S}}{S} + \dot{4_A} - 4_{A,1}\frac{\dot{4_A}}{4_A} + \dot{4_B} + \dot{4_C}$$

$$= \dot{S}\left(1 - \frac{S_1}{S}\right) + \dot{4_A}\left(1 - \frac{4_{A,1}}{4_A}\right) + \dot{4_B} + \dot{4_C}$$

$$= [\pi - (a + p + b)S + (l_1 + e_1)4_A + (l_2 + e_2)4_B$$

$$+ (l_3 + e_3)4_C - (h_1 4_A + h_2 4_B + h_3 4_C)S - \mu S]\left(1 - \frac{S_1}{S}\right)$$

$$+ [c_1 aS + k_1 pS - (m_1 + l_1 + e_1)4_A + h_1 4_A S - s_1 4_A$$

$$- \mu 4_A]\left(1 - \frac{4_{A,1}}{4_A}\right) + c_2 aS + k_2 pS + m_1 4_A$$

$$- (m_2 + l_2 + e_2)4_B + h_2 4_B S + s_1 4_A - s_2 4_B - \mu 4_B + (1$$

$$- c_1 - c_2)aS + (1 - k_1 - k_2)pS + bS + m_2 4_B$$

$$- (l_3 + e_3)4_C + h_3 4_C S + s_2 4_B - \mu 4_C$$

$$= \pi - (a + p + b)S + (l_1 + e_1)4_A + (l_2 + e_2)4_B$$

$$+ (l_3 + e_3)4_C - (h_1 4_A + h_2 4_B + h_3 4_C)S - \mu S - [\pi$$

$$- (a + p + b)S + (l_1 + e_1)4_A + (l_2 + e_2)4_B + (l_3 + e_3)4_C$$

$$- (h_1 4_A + h_2 4_B + h_3 4_C)S - \mu S]\frac{S_1}{S} + c_1 aS + k_1 pS$$

$$- (m_1 + l_1 + e_1)4_A + h_1 4_A S - s_1 4_A - \mu 4_A - [c_1 aS + k_1 pS$$

$$- (m_1 + l_1 + e_1)4_A + h_1 4_A S - s_1 4_A - \mu 4_A]\frac{4_{A,1}}{4_A} + c_2 aS$$

$$+ k_2 pS + m_1 4_A - (m_2 + l_2 + e_2)4_B + h_2 4_B S + s_1 4_A$$

$$- s_2 4_B - \mu 4_B + (1 - c_1 - c_2)aS + (1 - k_1 - k_2)pS + bS$$

$$+ m_2 4_B - (l_3 + e_3)4_C + h_3 4_C S + s_2 4_B - \mu 4_C$$

$$= \pi - \mu(S + 4_A + 4_B + 4_C)$$

$$- [\pi - (a + p + b)S + (l_1 + e_1)4_A + (l_2 + e_2)4_B$$

$$+ (l_3 + e_3)4_C - (h_1 4_A + h_2 4_B + h_3 4_C)S - \mu S]\frac{S_1}{S}$$

$$- [c_1 aS + k_1 pS - (m_1 + l_1 + e_1)4_A + h_1 4_A S - s_1 4_A$$

$$- \mu 4_A]\frac{4_{A,1}}{4_A} - \left[\mu + (l_2 + e_2)\frac{S_1}{S} - h_2 S_1\right]4_B$$

$$- \left[\mu + (l_3 + e_3)\frac{S_1}{S} - h_3 S_1\right]4_C$$

$$= \pi\left(1 - \frac{S_1}{S}\right) - [h_1 S_1 - (l_1 + e_1)S_1 - \mu]4_A$$
$$- [-h_2 S_1 + (l_2 + e_2)S_1 + \mu]4_B$$
$$- [-h_3 S_1 + (l_3 + e_3)S_1 + \mu]4_C$$
$$+ [(c_1 a + k_1 p + h_1)S - m_1 - l_1 - e_1 - s_1 - \mu]4_A < 0.$$

The above equality is negative since

$$\left(1 - \frac{S_1}{S}\right) < 0,$$
$$-h_1 S_1 + (l_1 + e_1)S_1 + \mu < 0 \text{ if } R_{0,A} > 1,$$
$$h_2 S_1 - (l_2 + e_2)S_1 - \mu < 0 \text{ if } R_{0,B} < 1,$$
$$h_3 S_1 - (l_3 + e_3)S_1 - \mu < 0 \text{ if } R_{0,C} < 1,$$

and

$$[(c_1 a + k_1 p + h_1)S - m_1 - l_1 - e_1 - s_1 - \mu]4_A = 0$$

from the second equation of the proposed system of ODEs. Hence, the equilibrium point E_1 is globally asymptotically stable if $R_{0,A} > 1$, $R_{0,B} < 1$, and $R_{0,C} < 1$.

Theorem 9. The endemic equilibrium point, E_2, of the system is globally asymptotically stable if the conditions $\frac{S_2}{S} < \frac{4_{A,2}}{4_A}, \frac{S_2}{S} < \frac{4_{B,2}}{4_B}, \frac{S_2}{S} < \frac{4_{C,2}}{4_C}, \frac{4_{A,2}}{4_A} < \frac{4_{B,2}}{4_B}$ and $\frac{4_{B,2}}{4_B} < \frac{4_{C,2}}{4_C}$ hold.

Proof. Consider the Lyapunov function

$$T = S - S_2 \ln S + 4_A - 4_{A,2} \ln 4_A + 4_B - 4_{B,2} \ln 4_B + 4_C - 4_{C,2} \ln 4_C.$$

From the definition of the function T, it is obvious that the function is always non-negative and equals to zero at the endemic equilibrium point E_2. Lastly, it should be proven that the function is negative definite. In other words, it should be shown that $\dot{T} < 0$. We have

$$\dot{T} = \dot{S} - \frac{S_2}{S}\dot{S} + \dot{4_A} - \frac{4_{A,2}}{4_A}\dot{4_A} + \dot{4_B} - \frac{4_{B,2}}{4_B}\dot{4_B} + \dot{4_C} - \frac{4_{C,2}}{4_C}\dot{4_C}$$

$$= \pi - \mu S - \pi\frac{S_2}{S} + (a + p + b + \mu)S_2 - (l_1 + e_1)\frac{4_A S_2}{S} - (l_2 + e_2)\frac{4_B S_2}{S}$$
$$- (l_3 + e_3)\frac{4_C S_2}{S} + (h_1 4_A + h_2 4_B + h_3 4_C)S_2 - \mu 4_A$$
$$- (c_1 a + k_1 p)S\frac{4_{A,2}}{4_A} + (m_1 + l_1 + s_1 + e_1 + \mu)4_{A,2}$$
$$- h_1 4_{A,2} S - \mu 4_B - (c_2 a + k_2 p)S\frac{4_{B,2}}{4_B} - (m_1 + s_1)4_A\frac{4_{B,2}}{4_B}$$
$$+ (m_2 + l_2 + e_2 + s_2 + \mu)4_{B,2} - h_2 S 4_{B,2} - \mu 4_C$$
$$- (1 - c_1 - c_2)aS\frac{4_{C,2}}{4_C} - (1 - k_1 - k_2)pS\frac{4_{C,2}}{4_C} - bS\frac{4_{C,2}}{4_C}$$
$$- (m_2 + s_2)4_B\frac{4_{C,2}}{4_C} + (l_3 + e_3 + \mu)4_{C,2} - h_3 4_{C,2} S$$
$$< [(l_1 + e_1)4_A + h_1 4_A S]\left(\frac{S_2}{S} - \frac{4_{A,2}}{4_A}\right) + [(l_2 + e_2)4_B + h_2 4_B S]\left(\frac{S_2}{S} - \frac{4_{B,2}}{4_B}\right)$$
$$+ [(l_3 + e_3)4_C + h_3 4_C S]\left(\frac{S_2}{S} - \frac{4_{C,2}}{4_C}\right)$$
$$+ (m_1 + s_1)4_A\left(\frac{4_{A,2}}{4_A} - \frac{4_{B,2}}{4_B}\right) + (m_2 + s_2)4_B\left(\frac{4_{B,2}}{4_B} - \frac{4_{C,2}}{4_C}\right)$$
$$< 0$$

if $\frac{S_2}{S} < \frac{4_{A,2}}{4_A}, \frac{S_2}{S} < \frac{4_{B,2}}{4_B}, \frac{S_2}{S} < \frac{4_{C,2}}{4_C}, \frac{4_{A,2}}{4_A} < \frac{4_{B,2}}{4_B}$ and $\frac{4_{B,2}}{4_B} < \frac{4_{C,2}}{4_C}$ hold. Hence, under the given conditions, the endemic equilibrium point is globally asymptotically stable.

Sensitivity Analysis. In this section, sensitivity analysis is applied to determine the effective parameters of the constructed model. The technique used for sensitivity analysis is to analyse sensitivity indices of obtained basic reproduction numbers to the parameters of the model. The definition 2 given in Chapter III is utilized for the analysis. According to the definition, sensitivity indices of the basic reproduction number $R_{0,A}$ are computed as follows:

$$\Psi_{h_1}^{R_{0,A}} = \frac{\partial R_{0,A}}{\partial h_1} \times \frac{h_1}{R_{0,A}} = 1,$$

$$\Psi_{\pi}^{R_{0,A}} = \frac{\partial R_{0,A}}{\partial \pi} \times \frac{\pi}{R_{0,A}} = 1,$$

$$\Psi_{m_1}^{R_{0,A}} = \frac{\partial R_{0,A}}{\partial m_1} \times \frac{m_1}{R_{0,A}} = \frac{-m_1}{m_1 + l_1 + e_1 + s_1 + \mu},$$

$$\Psi_{l_1}^{R_{0,A}} = \frac{\partial R_{0,A}}{\partial l_1} \times \frac{l_1}{R_{0,A}} = \frac{-l_1}{m_1 + l_1 + e_1 + s_1 + \mu},$$

$$\Psi_{e_1}^{R_{0,A}} = \frac{\partial R_{0,A}}{\partial e_1} \times \frac{e_1}{R_{0,A}} = \frac{-e_1}{m_1 + l_1 + e_1 + s_1 + \mu},$$

$$\Psi_{s_1}^{R_{0,A}} = \frac{\partial R_{0,A}}{\partial s_1} \times \frac{s_1}{R_{0,A}} = \frac{-s_1}{m_1 + l_1 + e_1 + s_1 + \mu},$$

$$\Psi_{a}^{R_{0,A}} = \frac{\partial R_{0,A}}{\partial a} \times \frac{a}{R_{0,A}} = \frac{-a}{a + p + b + \mu},$$

$$\Psi_{p}^{R_{0,A}} = \frac{\partial R_{0,A}}{\partial p} \times \frac{p}{R_{0,A}} = \frac{-p}{a + p + b + \mu},$$

$$\Psi_{b}^{R_{0,A}} = \frac{\partial R_{0,A}}{\partial b} \times \frac{b}{R_{0,A}} = \frac{-b}{a + p + b + \mu},$$

and

$$\Psi_{\mu}^{R_{0,A}} = \frac{\partial R_{0,A}}{\partial \mu} \times \frac{\mu}{R_{0,A}} = \frac{-\mu(m_1 + l_1 + e_1 + s_1 + a + p + b + 2\mu)}{(m_1 + l_1 + e_1 + s_1)(a + p + b + \mu)}.$$

The sensitivity indices of the basic reproduction number $R_{0,B}$ are calculated and given below.

$$\Psi_{h_2}^{R_{0,B}} = \frac{\partial R_{0,B}}{\partial h_2} \times \frac{h_2}{R_{0,B}} = 1,$$

$$\Psi_{\pi}^{R_{0,B}} = \frac{\partial R_{0,B}}{\partial \pi} \times \frac{\pi}{R_{0,B}} = 1,$$

$$\Psi_{m_2}^{R_{0,B}} = \frac{\partial R_{0,B}}{\partial m_2} \times \frac{m_2}{R_{0,B}} = \frac{-m_2}{m_2 + l_2 + e_2 + s_2 + \mu},$$

$$\Psi_{l_2}^{R_{0,B}} = \frac{\partial R_{0,B}}{\partial l_2} \times \frac{l_2}{R_{0,B}} = \frac{-l_2}{m_2 + l_2 + e_2 + s_2 + \mu},$$

$$\Psi_{s_2}^{R_{0,B}} = \frac{\partial R_{0,B}}{\partial s_2} \times \frac{s_2}{R_{0,B}} = \frac{-s_2}{m_2 + l_2 + e_2 + s_2 + \mu},$$

$$\Psi_{e_2}^{R_{0,B}} = \frac{\partial R_{0,B}}{\partial e_2} \times \frac{e_2}{R_{0,B}} = \frac{-e_2}{m_2 + l_2 + e_2 + s_2 + \mu},$$

$$\Psi_{a}^{R_{0,B}} = \frac{\partial R_{0,B}}{\partial a} \times \frac{a}{R_{0,B}} = \frac{-a}{a + p + b + \mu},$$

$$\Psi_{p}^{R_{0,B}} = \frac{\partial R_{0,B}}{\partial p} \times \frac{p}{R_{0,B}} = \frac{-p}{a + p + b + \mu},$$

$$\Psi_b^{R_{0,B}} = \frac{\partial R_{0,B}}{\partial b} \times \frac{b}{R_{0,B}} = \frac{-b}{a+p+b+\mu},$$

and

$$\Psi_\mu^{R_{0,B}} = \frac{\partial R_{0,B}}{\partial \mu} \times \frac{\mu}{R_{0,B}} = \frac{-\mu(a+p+b+2\mu+m_2+l_2+e_2+s_2)}{(m_2+l_2+e_2+s_2)(a+p+b+\mu)}.$$

The sensitivity indices of the basic reproduction number $R_{0,C}$ are computed as below:

$$\Psi_{h_3}^{R_{0,C}} = \frac{\partial R_{0,C}}{\partial h_3} \times \frac{h_3}{R_{0,C}} = 1,$$

$$\Psi_\pi^{R_{0,C}} = \frac{\partial R_{0,C}}{\partial \pi} \times \frac{\pi}{R_{0,C}} = 1,$$

$$\Psi_{l_3}^{R_{0,C}} = \frac{\partial R_{0,C}}{\partial l_3} \times \frac{l_3}{R_{0,C}} = \frac{-l_3}{l_3+e_3+\mu},$$

$$\Psi_{e_3}^{R_{0,C}} = \frac{\partial R_{0,C}}{\partial e_3} \times \frac{e_3}{R_{0,C}} = \frac{-e_3}{l_3+e_3+\mu},$$

$$\Psi_a^{R_{0,C}} = \frac{\partial R_{0,C}}{\partial a} \times \frac{a}{R_{0,C}} = \frac{-a}{a+p+b+\mu},$$

$$\Psi_p^{R_{0,C}} = \frac{\partial R_{0,C}}{\partial p} \times \frac{p}{R_{0,C}} = \frac{-p}{a+p+b+\mu},$$

$$\Psi_b^{R_{0,C}} = \frac{\partial R_{0,C}}{\partial b} \times \frac{b}{R_{0,C}} = \frac{-b}{a+p+b+\mu},$$

and

$$\Psi_\mu^{R_{0,C}} = \frac{\partial R_{0,C}}{\partial \mu} \times \frac{\mu}{R_{0,C}} = \frac{-\mu(l_3+e_3+a+p+b+2\mu)}{(l_3+e_3+\mu)(a+p+b+\mu)}.$$

Numerical Simulations and Results

In this part of the thesis, results and numerical simulations that are obtained with the use of sensitivity indices and the constructed model are provided. With the acquired sensitivity indices and parameter values, sensitivity values for $R_{0,A}, R_{0,B}$ and $R_{0,C}$ are calculated and demonstrated in Table 9, Table 10 and Table 11, respectively.

Figure 1

Distribution of BI-RADS 4 Subcategories According to the Constructed Model

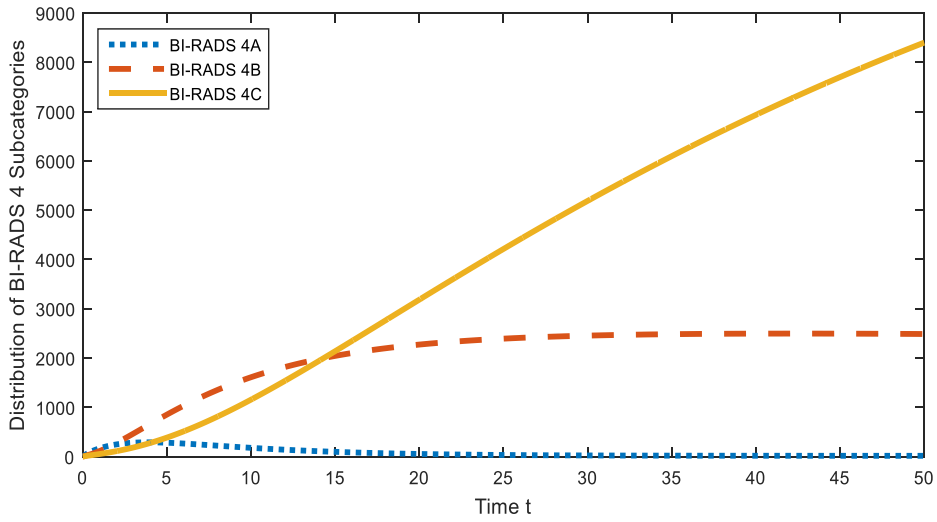


Figure 1 above illustrates that, BI-RADS 4A category is expected to extinct if the current conditions can be preserved (regular screenings, awareness, etc.) and hence BI-RADS 4 category is going to be separated into 2 categories, in time. Therefore, a decrease in the range of cancer probability for BI-RADS 4 is expected. However, existence of BI-RADS 4B and BI-RADS 4C diagnosis is expected and moreover, an increase is observed especially in BI-RADS 4C diagnosed patients.

Table 9.

Sensitivity Values for $R_{0,A}$

Parameter	Value
h_1	1.00
π	1
m_1	-0.063
l_1	-0.683
e_1	-0.25
s_1	-0.003

Table 9 (Continued).

a	-0.511
p	-0.436
b	-0.053
μ	-0.0001

According to the Table 9, increase in the parameters h_1 and π will cause an increase in the $R_{0,A}$ while increase in the rest parameters of $R_{0,A}$ (which are $m_1, l_1, e_1, s_1, a, p, b$ and μ) will result in a decline in $R_{0,A}$. Increase rate of parameters is 10%. Biologically, these can be evaluated as follows:

- Family history has a significant impact on the diagnosis of BI-RADS 4A. If more people have a diagnosis of BI-RADS 4A in the family, then the chance of BI-RADS 4A diagnosis of other family members will increase.
- Increase in the recruitment rate, π, means increase in the susceptible individuals in the population. Hence, increase in this parameter may lead an increase in the compartment 4_A and $R_{0,A}$.
- Irregular menstruation increase will naturally affect the hormones and thus, it will increase the chance of breast cancer risk. So, the cancer risk of people with the diagnosis of BI-RADS 4A will increase and hence people will transfer to other categories (BI-RADS 4B, BI-RADS 4C, etc.) with higher cancer risks. This is why increase in m_1 may cause a decrease in $R_{0,A}$.
- Rise in the lactation rate l_1 is one of the most effective parameters in BI-RADS 4A subcategory and this increase does not cause another increase in the other compartments that are related with cancer risk. Moreover, increase in l_1 causes a decrease in the number of BI-RADS 4A diagnosed patients.
- Since early menopause, e_1, affects hormones positively, increase in this parameter will decrease the number of members diagnosed with BI-RADS 4A. As in l_1, increase in this parameter will not be resulted in cancer risk-related compartments.

- Increase in the smoking rate, s_1, will lead a decrease in $R_{0,A}$. However, increase in the smoking rate causes the patients of BI-RADS 4A to be diagnosed as BI-RADS 4B or even higher category.
- Higher aged people have a lower risk of being diagnosed as BI-RADS 4A which can be related with menopause and hence lower risk of breast cancer. So, the increase in a will cause a decrease in $R_{0,A}$.
- Palpable masses and bloody nipple discharge generally seen in other BI-RADS categories and further investigations are recommended in that case. Hence, individuals cannot be diagnosed with BI-RADS 4A. This is why increase in p and b will decrease $R_{0,A}$.
- Innately, increase in natural death rate μ will decrease the number of people in the population. So, increase in μ naturally causes a decrease in $R_{0,A}$.

Table 10.

Sensitivity Values for $R_{0,B}$

Parameter	Value
h_2	1
π	1
m_2	-0.288
l_2	-0.58
s_2	-0.0035
e_2	-0.128
a	-0.511
p	-0.436
b	-0.053
μ	-0.0001

Table 10, reveals that increase in the rate of h_2 and π will lead arise in the value of $R_{0,B}$ while a decrease is expected in $R_{0,B}$ if the value of other parameters of $R_{0,B}$ (which are $a, p, b, \mu, m_2, l_2, e_2$ and s_2) increase. Increase rate of parameters is 10%. Changes in these parameters can be explained biologically as follows:

- For the diagnosis of BI-RADS 4B, family history has a huge effect so that more people diagnosed with BI-RADS 4B in the family will increase the chance of BI-RADS 4B diagnosis of other family members.
- As expected, increase in the recruitment rate, π, implies an increase in the susceptible individuals in the population. So, increase in π will cause an increase in the 4_B compartment and hence in $R_{0,B}$.
- Higher aged people have a lower risk of being diagnosed as BI-RADS 4B which can be related with menopause and hence lower risk of breast cancer. So, the increase in a will cause a decrease in $R_{0,B}$.
- Palpable masses and bloody nipple discharge generally seen in other BI-RADS categories and further investigations are recommended in that case. Hence, with the further implementations, individuals cannot be diagnosed with BI-RADS 4B. This is why increase in p and b will decrease $R_{0,B}$.
- As it is expected, increase in natural death rate μ will cause a decrease in the number of people in the population. So, increase in μ naturally causes a decrease in $R_{0,B}$.
- Irregular menstruation increase will naturally affect the hormones and thus, it will increase the chance of breast cancer risk. So, the cancer risk of people with the diagnosis of BI-RADS 4B will increase and hence people will transfer to other categories (BI-RADS 4C, BI-RADS 5, etc.) with higher cancer risks. Hence, increase in m_2 may lead a decrease in $R_{0,B}$.
- Increase in the rate of lactation l_2 is one of the most effective parameters in BI-RADS 4B and this increase is meaningful since it does not cause another increase in the other compartments that are related with cancer risk. Also, increase in l_2 decreases the number of BI-RADS 4B diagnosed patients.
- Increase in the smoking rate, s_2, will lead a decrease in $R_{0,B}$. However, increase in the smoking rate causes the patients of BI-RADS 4B to be diagnosed as BI-RADS 4C.

- Since early menopause, e_2, affects hormones positively, increase in this parameter will decrease the number of members diagnosed with BI-RADS 4B. Likewise l_2, increase in this parameter will not be resulted in cancer risk-related compartments.

Table 11.

Sensitivity Values for $R_{0,C}$

Parameter	Value
h_3	1
π	1
l_3	-0.91
e_3	-0.0896
a	-0.511
p	-0.436
b	-0.053
μ	-0.0001

In Table 11, it can be revealed that increase in the rate of h_3 and π will lead an increase in the value of $R_{0,C}$ and a decline is expected in the value of $R_{0,C}$ when the value of other parameters of $R_{0,C}$ (which are a, p, b, μ, l_3 and e_3) increase. Increase rate of parameters is 10%. Changes in these parameters can be explained biologically as follows:

- For the diagnosis of BI-RADS 4C, family history has a significant effect so that more people diagnosed with BI-RADS 4C in the family will increase the chance of BI-RADS 4C diagnosis of other family members.
- As expected, increase in the recruitment rate, π, implies an increase in the susceptible individuals in the population. Thus, increase in π will cause an increase in the 4_C compartment and hence in $R_{0,C}$.

- Higher aged people have a lower risk of being diagnosed as BI-RADS 4C which can be related with menopause and hence lower risk of breast cancer. So, the increase in a will cause a decrease in $R_{0,C}$.
- Palpable masses and bloody nipple discharge generally seen in other BI-RADS categories and further investigations are recommended in that case. Hence, with the further implementations, individuals cannot be diagnosed with BI-RADS 4C. This is why increase in p and b will decrease $R_{0,C}$.
- As it is expected, increase in natural death rate μ will cause a decrease in the number of people in the population. So, increase in μ naturally causes a decrease in $R_{0,C}$.
- Increase in the rate of lactation l_3 is one of the most effective parameters in BI-RADS 4C and this increase is meaningful since it does not cause another increase in the other compartments that are related with cancer risk. Furthermore, increase in l_3 causes a decrease in the number of BI-RADS 4C diagnosed patients.
- Since early menopause, e_3, affects hormones positively, increase in this parameter will decrease the number of members diagnosed with BI-RADS 4C. As in l_3, increase in this parameter will not be resulted in cancer risk-related compartments.

The numerical simulations of the model with sensitivity analysis are illustrated in Figure 2 – Figure 12. Thus, it can be seen what is expected to happen with the increase in parameters (with 10%) in time, visually.

Figure 2

Sensitivity Analysis of the Parameter l_1 in BI-RADS 4A Subcategory

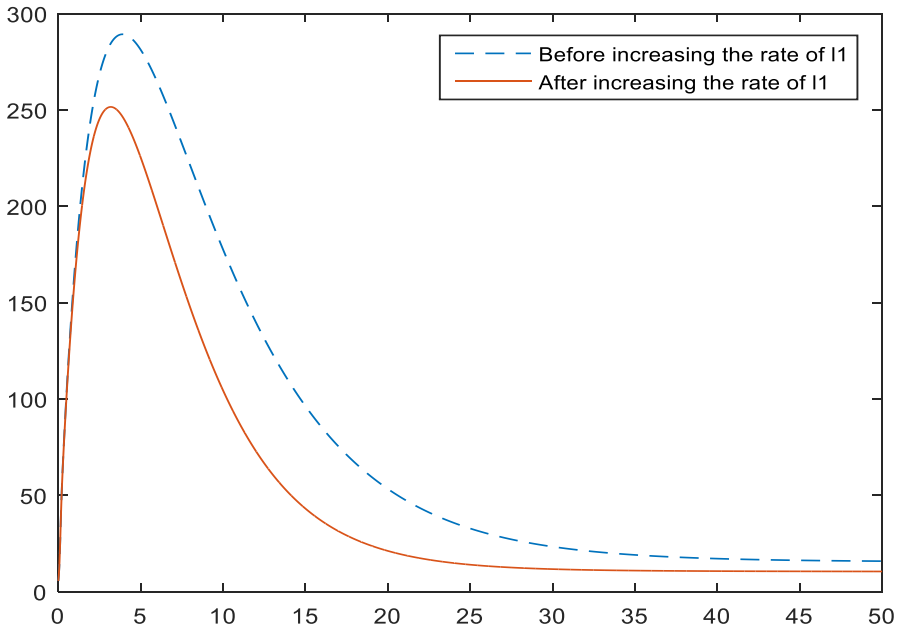


Figure 3

Sensitivity Analysis of the Parameter l_2 in BI-RADS 4B Subcategory

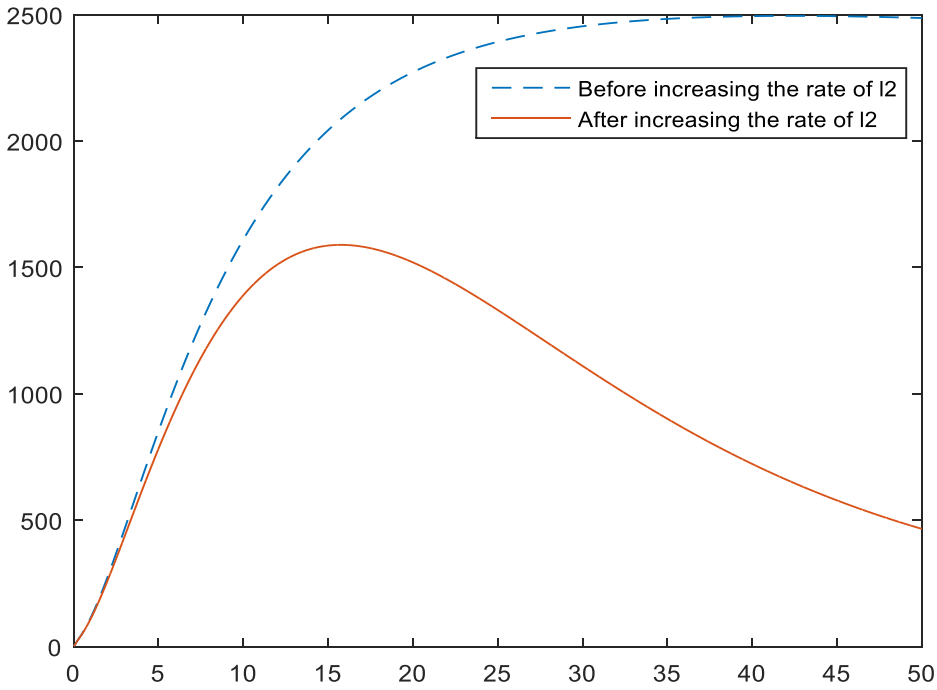
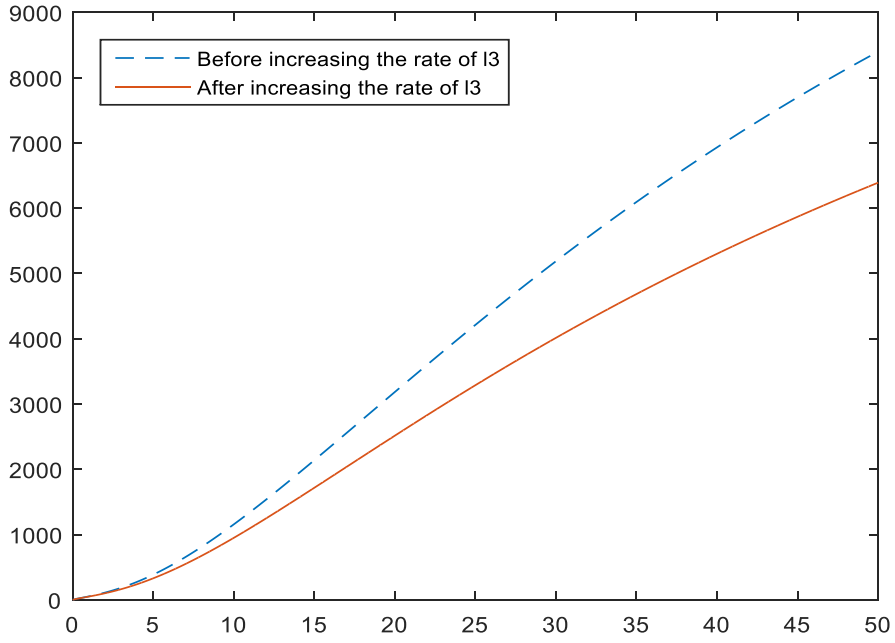


Figure 4

Sensitivity Analysis of the Parameter l_3 in BI-RADS 4C Subcategory



The effect of lactation rate, l_1, l_2, and l_3, on the subcategories of BI-RADS 4 are illustrated in Figure 2, Figure 3 and Figure 4, respectively. The figures revealed that higher lactation rate may lead a significant decrease in BI-RADS 4 subcategories. Especially for the categories BI-RADS 4B and BI-RADS 4C, there is a significant positive impact in the case of active lactation.

Figure 5

Sensitivity Analysis of the Parameter e_1 in BI-RADS 4A Subcategory

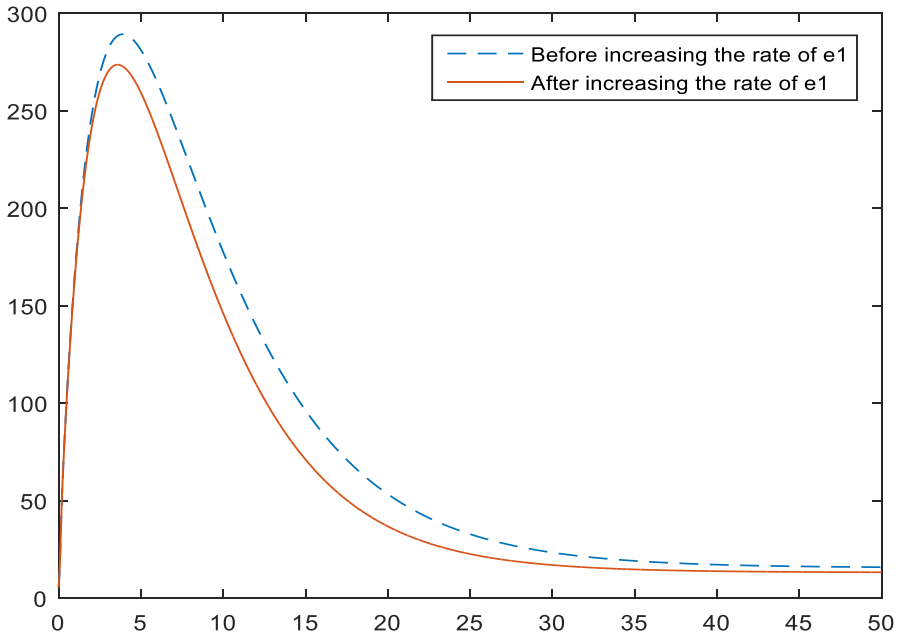


Figure 6

Sensitivity Analysis of the Parameter e_2 in BI-RADS 4B Subcategory

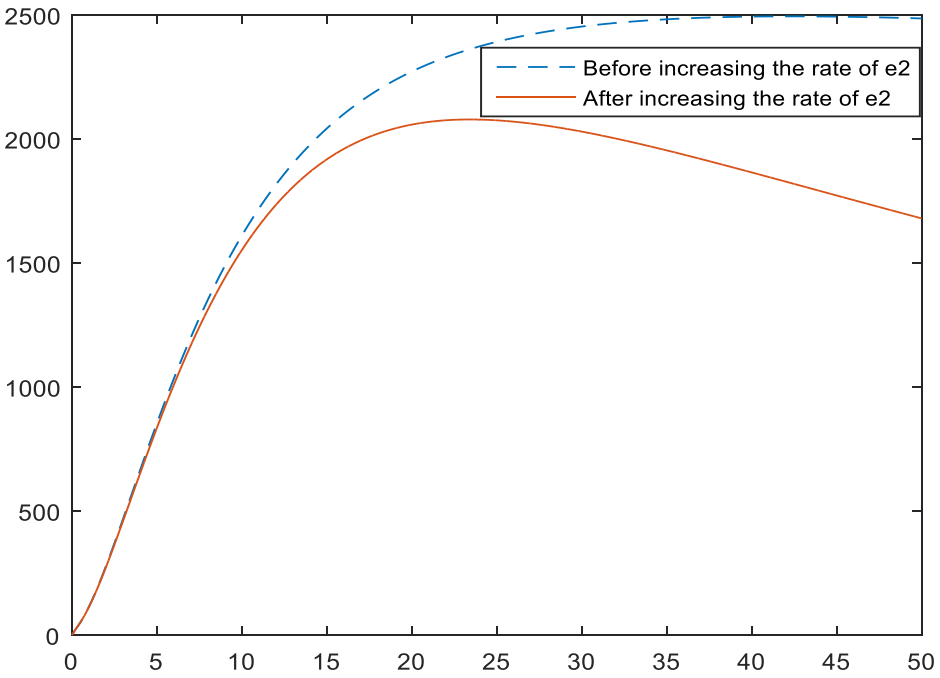
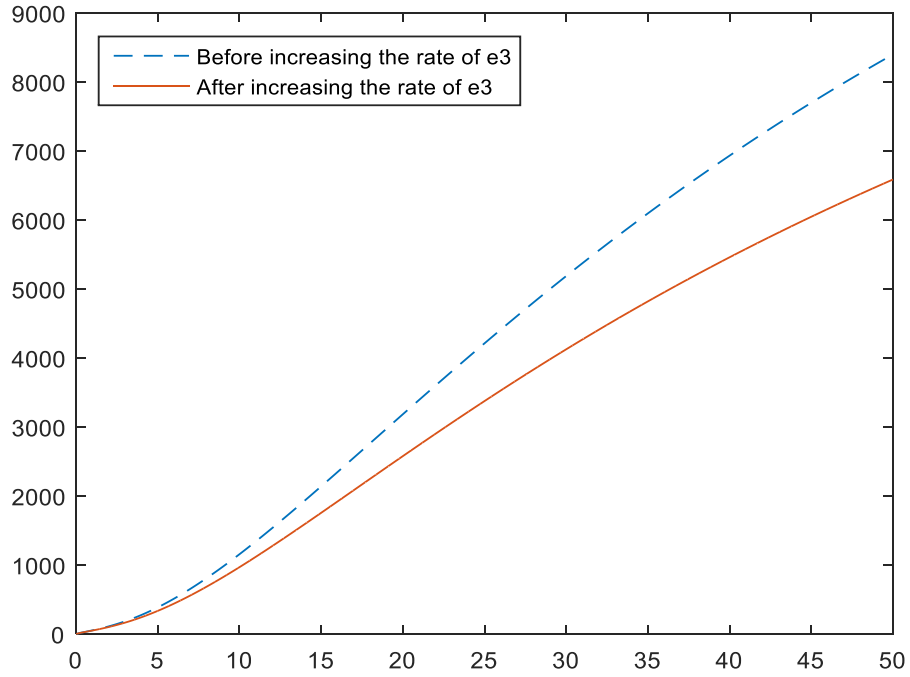


Figure 7

Sensitivity Analysis of the Parameter e_3 in BI-RADS 4C Subcategory



In the Figure 5, Figure 6 and Figure 7, the impact of parameters e_1, e_2, and e_3 on the subcategories BI-RADS 4A, BI-RADS 4B, and BIRADS 4C are respectively presented. According to these figures, early menopause will lead a decline in the subcategories. For all of the subcategories, a meaningful change exists in this situation.

Figure 8

Sensitivity Analysis of the Parameter $\boldsymbol{h_1}$ *in BI-RADS 4A Subcategory*

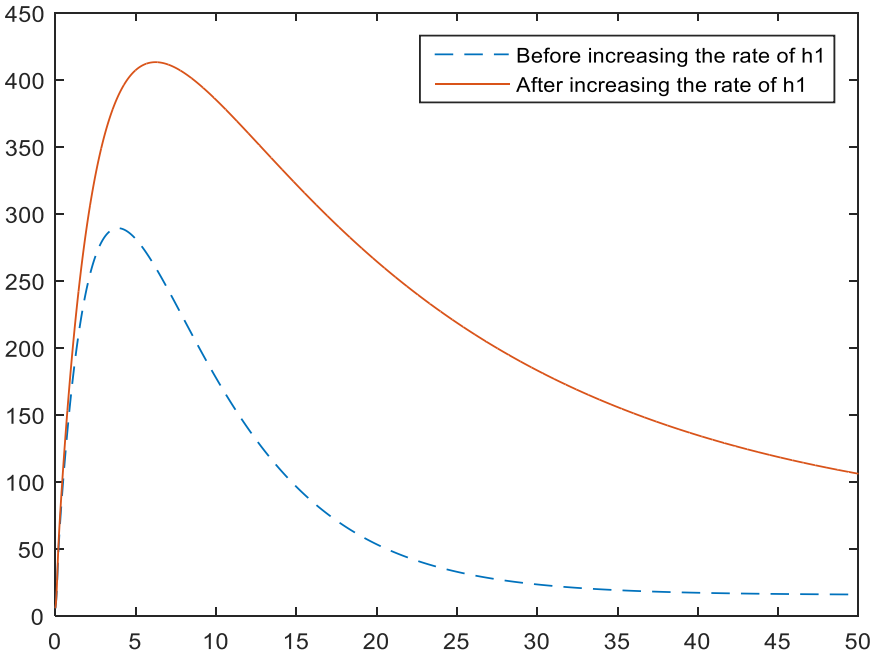


Figure 9

Sensitivity Analysis of the Parameter h_2 *in BI-RADS 4B Subcategory*

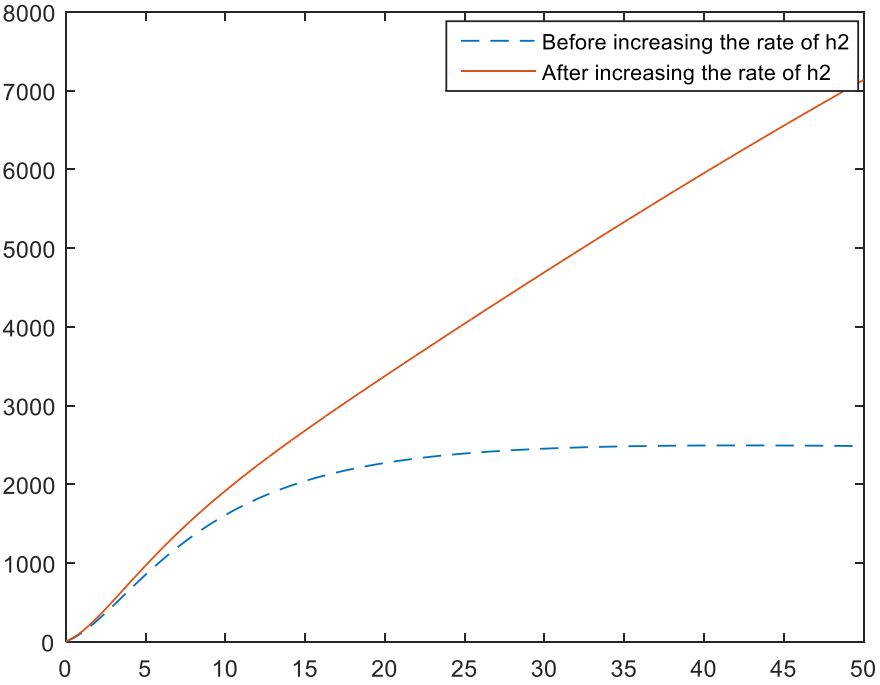
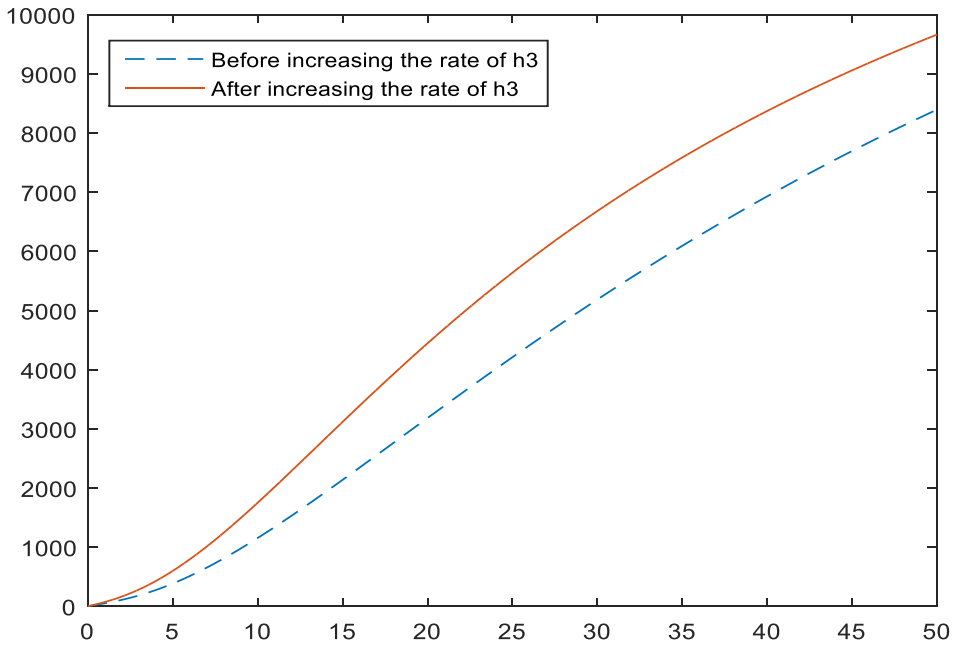


Figure 10

Sensitivity Analysis of the Parameter h_3 in BI-RADS 4C Subcategory



Impact of the parameters h_1, h_2 and h_3, i.e., the family history, on the subcategories of BI-RADS 4 are presented in the Figure 8, Figure 9 and Figure 10, respectively. Family history causes an enormous and meaningful increase in the diagnosis of all BI-RADS 4 subcategories as can be seen from the given figures.

Figure 11

Sensitivity Analysis of the Parameter s_2 in BI-RADS 4C Subcategory

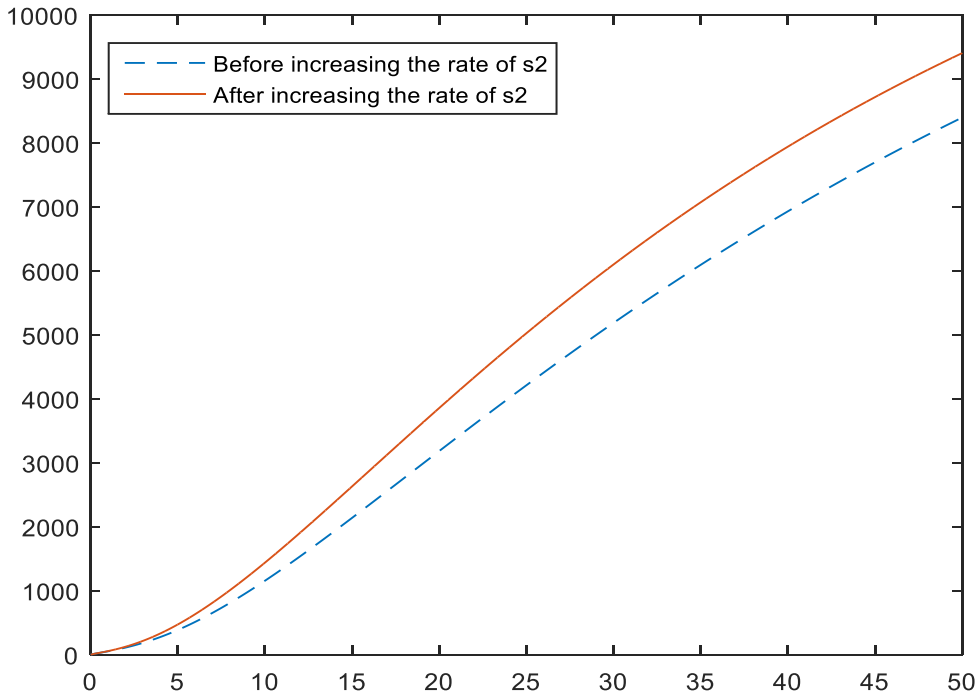
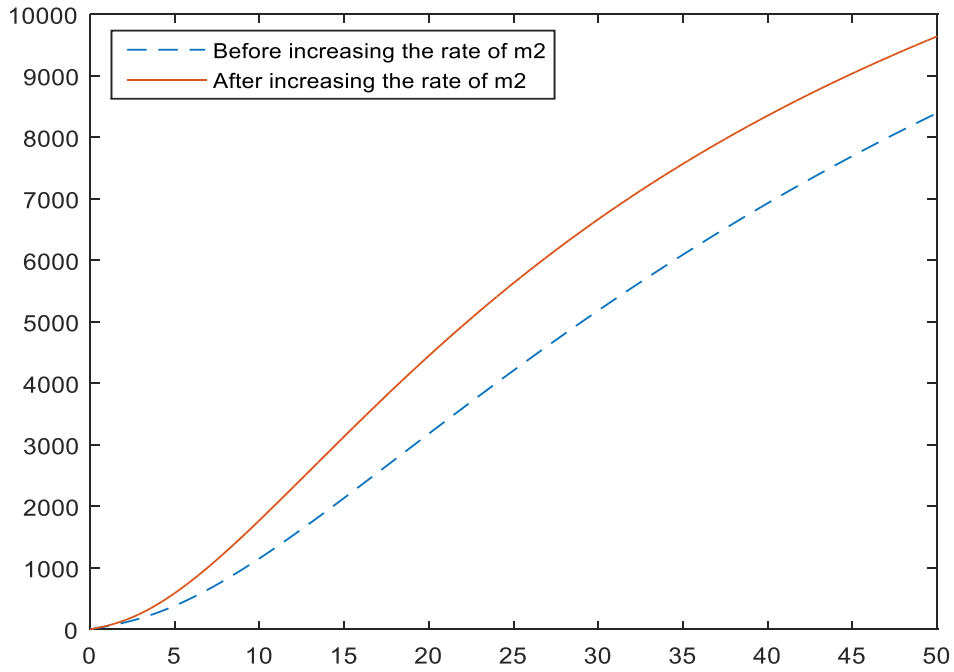


Figure 11 is drawn to determine and show the effect of smoking on the subcategory BI-RADS 4C. Rise in the tobacco usage rate leads an increase in the BI-RADS 4C subcategory, which is naturally expected to happen.

Figure 12

Sensitivity Analysis of the Parameter m_2 in BI-RADS 4C Subcategory



From the Figure 12, the negative effect of late menopause on BI-RADS 4C is illustrated. This figure emphasizes that late menopause and BI-RADS 4C have a substantial relationship.

To sum up, with the constructed model it is obtained that there exist 3 equilibrium points that are globally asymptotically stable under mentioned conditions. This emphasizes that distribution of patients to BI-RADS 4 subcategories can be stable if the conditions satisfied. With these, it is concluded that BI-RADS 4 subcategories can reduce in time with narrower chance of breast cancer risk range. Sensitivity analysis that is applied to the parameters of basic reproduction numbers revealed effective parameters of the model. Calculations of sensitivity analysis showed that increase in h_1 and π will lead an increase in the value of $R_{0,A}$ while increase in $m_1, l_1, e_1, s_1, a, p, b$ and μ will result in a decline in $R_{0,A}$. For the compartment 4_B, it is observed that increase in h_2 and π will cause arise in the value of $R_{0,B}$ while a decrease is expected in the value of $R_{0,B}$ if the value of $a, p, b, \mu, m_2, l_2, e_2$ and s_2 increase. Lastly, the computations for the compartment 4_C showed that rise in the rate of h_3 and π will lead an increase in $R_{0,C}$ and a decline is expected to happen in the value of $R_{0,C}$ when the value of a, p, b, μ, l_3 and e_3 increase.

Numerical simulations of sensitivity analysis emphasized that higher lactation rate and early menopause decreases the number of patients diagnosed with BI-RADS 4 subcategories. On the other hand, having a family history increases the risk of being diagnosed as BI-RADS 4 in all subcategories. Moreover, tobacco use and late menopause increases the chance of diagnosis of BI-RADS 4C.

CHAPTER IV
Methodology

In this chapter, possible and applicable control interventions for BI-RADS 4 patients is introduced with the help of optimal control theory. The aim of this chapter is to introduce control strategy for the patients diagnosed with BI-RADS 4 subcategories and to evaluate the impact of control strategy on these via optimal control function. In this regard, the design and limitations of the research are given at first. Afterwards, the collected data is expressed. Finally, the analysis of the model with control is proposed with necessary theorems, proofs and numerical simulations.

Research Design and Limitations

In order to apply control function into ODEs, effective parameters should be determined firstly. In this manner, the data obtained as a result of sensitivity analysis in Chapter III is utilized. According to those results, it is concluded that lactation rate and hence, breastfeeding plays a significant role in BI-RADS 4 subcategories. Thus, control function in this chapter is assigned as “drug for increasing the lactation rate or longtime breastfeeding”. Later on, this function is added to the constructed mathematical model in Chapter III. For the analysis of newly created model, existence of optimal control, necessary conditions for optimality, characterization of optimal control and uniqueness of solutions are stated. For the evaluation of the control, MatLab program is involved with numerical methods which enables visual results. The limitations of this model are the same limitations given in Chapter III.

Data Collection

In this chapter, the data is obtained from the Centre for Breast Health, Near East University Hospital.

Data Analysis

In this section of the thesis, analysis of the obtained data is given.

Mathematical Model with Optimal Control and Its Analysis

In this section, a mathematical model with an optimal control function is constructed as below. As in Chapter III, the total population (N) is divided into 4 compartments including susceptible individuals (S), individuals diagnosed with BI-RADS 4A (4_A), individuals diagnosed with BI-RADS 4B (4_B) and individuals diagnosed with BI-RADS 4C (4_C).

$$\frac{dS}{dt} = \pi - (a + p + b)S + [l_1u(t) + e_1]4_A + [l_2u(t) + e_2]4_B + [l_3u(t) + e_3]4_C - (h_1 4_A + h_2 4_B + h_3 4_C)S - \mu S,$$

$$\frac{d4_A}{dt} = c_1 aS + k_1 pS - [m_1 + l_1u(t) + e_1]4_A + h_1 4_A S - s_1 4_A - \mu 4_A,$$

$$\frac{d4_B}{dt} = c_2 aS + k_2 pS + m_1 4_A - [m_2 + l_2u(t) + e_2]4_B + h_2 4_B S + s_1 4_A - s_2 4_B - \mu 4_B,$$

$$\frac{d4_C}{dt} = (1 - c_1 - c_2)aS + (1 - k_1 - k_2)pS + bS + m_2 4_B - [l_3u(t) + e_3]4_C + h_3 4_C S + s_2 4_B - \mu 4_C.$$

with the initial conditions $S(0) = S_0, 4_A(0) = 4_{A,0}, 4_B(0) = 4_{B,0}$ and $4_C(0) = 4_{C,0}$. The control function, u, denotes the drug for increasing the lactation rate or longtime breastfeeding. Definitions of parameters and state variables are given in Table 12 and Table 13.

Table 12.

Descriptions of Variables used in the Mathematical Model with Optimal Control

Variables	Descriptions
S	Susceptible Individuals
4_A	Individuals that are diagnosed as BI-RADS 4A
4_B	Individuals that are diagnosed as BI-RADS 4B
4_C	Individuals that are diagnosed as BI-RADS 4C

Table 13.

Descriptions of Parameters used in the Mathematical Model with Optimal Control

Parameters	Descriptions
π	Recruitment Rate
a	Age
p	Palpable Mass
b	Bloody Nipple Discharge
u	Drug for increasing the lactation rate or longtime breastfeeding
$l_i, i = 1, 2, 3$	Lactation Rate
$e_i, i = 1, 2, 3$	Early Menopause
m_1	Irregular Menstruation
m_2	Late Menopause
$h_i, i = 1, 2, 3$	Family History
s_1	Smoking Rate of the BI-RADS 4A Individuals
s_2	Smoking Rate of the BI-RADS 4B Individuals
μ	Natural Death Rate

The objective functional to be minimized is

$$J(4_A, 4_B, 4_C, u) = \int_0^T \left[4_A + 4_B + 4_C + \frac{K}{2}u^2(t)\right] dt.$$

In this part, it is expected to minimize the number of individuals diagnosed as BI-RADS 4A, 4B, 4C and costs of control. K denotes the weight factor representing benefit/cost and the level of patient's breastfeeding or acceptance of drugs. A quadratic control $\frac{1}{2}Ku^2$ is used for convenience in finding an analytic representation of the control $u \in \Omega$. The goal here is to find u^* that will satisfy

$$J(4_A, 4_B, 4_C, u^*) = \min_{u \in \Omega} J(4_A, 4_B, 4_C, u),$$

where

$$\Omega = \{u(t): 0 \leq u \leq u_{max} = b_1,$$

u piecewise continuous function, b_1 is a fixed constant, $t \in [0, T]\}$.

Existence of Optimal Control. Now, it will be proven that an optimal control u^* for the system actually exists. Firstly, it should be shown that the system is bounded for finite time. Afterwards, solutions that are upper bounds (super solutions) of $S, 4_A, 4_B$ and 4_C will be found in the model.

For the compartment S,

$$\frac{dS_{max}}{dt} = \pi,$$

$$dS_{max} = \pi dt,$$

$$S_{max} = \pi t + S_0,$$

where S_0 is the initial condition for S, i.e., $S_0 = S(0)$.

For the compartment 4_A,

$$\frac{d4_{A,max}}{dt} = (c_1 a + k_1 p) S_{max} = (c_1 a + k_1 p)(\pi t + S_0),$$

$$4_{A,max} = \frac{(c_1 a + k_1 p)\pi t^2}{2} + (c_1 a + k_1 p) S_0 t + 4_{A,0},$$

where S_0 and $4_{A,0}$ are the initial conditions for S and 4_A, respectively. That is, $S_0 = S(0)$ and $4_{A,0} = 4_A(0)$.

For the compartment 4_B,

$$\frac{d4_{B,max}}{dt} = (c_2 a + k_2 p) S_{max} + (m_1 + s_1) 4_{A,max}$$

$$= (c_2 a + k_2 p)(\pi t + S_0)$$

$$+ (m_1 + s_1)\left[\frac{(c_1 a + k_1 p)\pi t^2}{2} + (c_1 a + k_1 p) S_0 t + 4_{A,0}\right],$$

$$4_{B,max} = \frac{(c_1 a + k_1 p)(m_1 + s_1)\pi t^3}{6}$$

$$+ \frac{[(c_2 a + k_2 p)\pi + (c_1 a + k_1 p)(m_1 + s_1) S_0] t^2}{2}$$

$$+ \left[(c_2 a + k_2 p) S_0 + (m_1 + s_1) 4_{A,0}\right] t + 4_{B,0},$$

where $S_0, 4_{A,0}$ and $4_{B,0}$ are the initial conditions for $S, 4_A$ and 4_B, respectively. That is, $S_0 = S(0)$, $4_{A,0} = 4_A(0)$ and $4_{B,0} = 4_B(0)$.

Lastly, for the compartment 4_C,

$$\begin{aligned}\frac{d4_{C,max}}{dt} &= [(1-c_1-c_2)a + (1-k_1-k_2)p + b]S_{max} \\ &\quad + (m_2+s_2)4_{B,max} \\ &= [(1-c_1-c_2)a + (1-k_1-k_2)p + b](\pi t + S_0) \\ &\quad + (m_2+s_2)\left\{\frac{(c_1a+k_1p)(m_1+s_1)\pi t^3}{3}\right. \\ &\quad + \frac{[(c_2a+k_2p)\pi + (c_1a+k_1p)(m_1+s_1)S_0]t^2}{2} \\ &\quad \left. + \left[(c_2a+k_2p)S_0 + (m_1+s_1)4_{A,0}\right]t + 4_{B,0}\right\},\end{aligned}$$

$$4_{C,max} = \frac{(c_1 a + k_1 p)(m_1 + s_1)(m_2 + s_2)\pi t^4}{12} + \frac{[(c_2 a + k_2 p)\pi + (c_1 a + k_1 p)(m_1 + s_1)S_0](m_2 + s_2)t^3}{6}$$
$$+ \frac{\{[(1 - c_1 - c_2)a + (1 - k_1 - k_2)p + b]\pi + (m_2 + s_2)[(c_2 a + k_2 p)S_0 + (m_1 + s_1)4_{A,0}]\}t^2}{2}$$
$$+ \{[(1 - c_1 - c_2)a + (1 - k_1 - k_2)p + b]S_0 + (m_2 + s_2)4_{B,0}\}t + 4_{C,0},$$

where $S_0, 4_{A,0}, 4_{B,0}$ and $4_{C,0}$ are the initial conditions for $S, 4_A, 4_B$ and 4_C, respectively. That is, $S_0 = S(0), 4_{A,0} = 4_A(0), 4_{B,0} = 4_B(0)$ and $4_{C,0} = 4_C(0)$. Therefore, by using these bounds, a set of upper bound solutions, denoted by $\bar{S}, \overline{4_A}, \overline{4_B}$, and $\overline{4_C}$, can be formed for the constructed system as follows:

$$\frac{d\bar{S}}{dt} = \pi,$$

$$\frac{d\overline{4_A}}{dt} = (c_1 a + k_1 p)\bar{S},$$

$$\frac{d\overline{4_B}}{dt} = (c_2 a + k_2 p)\bar{S} + (m_1 + s_1)\overline{4_A},$$

$$\frac{d\overline{4_C}}{dt} = [(1 - c_1 - c_2)a + (1 - k_1 - k_2)p + b]\bar{S} + (m_2 + s_2)\overline{4_B}.$$

Hence, a linear and bounded system with bounded coefficients on a finite time interval is obtained. Therefore, obtained super solutions are uniformly bounded and the constructed system is ultimately bounded.

Necessary Conditions for Optimality. In this section, necessary conditions for optimal control will be explained.

Theorem 10. For the objective functional

$$J(4_A, 4_B, 4_C, u) = \int_0^T \left[4_A + 4_B + 4_C + \frac{K}{2}u^2(t)\right] dt,$$

where $\Omega = \{u(t): 0 \le u \le u_{max} = b_1,$ u is lebesgue measurable, b_1 is a fixed constant, $t \in [0, T]\}$, subject to the proposed system with $S(0) = S_0, 4_A(0) = 4_{A,0}, 4_B(0) = 4_{B,0}$ and $4_C(0) = 4_{C,0}$, there exists an optimal control u^* such that

$$J(4_A, 4_B, 4_C, u^*) = \min_{u \in \Omega} J(4_A, 4_B, 4_C, u)$$

if the following conditions hold:

- **a.** The class of all initial conditions with a control in the admissible control set along with all satisfied state equations is non-empty.
- **b.** The admissible control set Ω is closed and convex.
- **c.** In the constructed system of ODEs, right-hand side of each equation is continuous and bounded above by the sum of the bounded control

and the state. Moreover, they can be written as a linear function of Ω with time and state dependent coefficients.

d. The integrand of $J(4_A, 4_B, 4_C, u)$ is convex on Ω and bounded below by $-d_2 + d_1 u^2$ with $d_1 > 0$.

Proof. A result from Lukes (1982) proves that solution exists for the proposed system since it possesses bounded coefficients and the solutions are bounded on the finite time interval. Hence, part (**a**) is proved. From the definition of Ω, it is closed and convex which proves (**b**). For the condition (**c**), the right-hand side of the constructed system is continuous because each term of the equations is nonzero and polynomial. Now, let

$$f(t, \vec{X}, u) = \vec{\varphi}(t, \vec{X}) + u\vec{\beta}(t, \vec{X}),$$

where $\vec{\varphi}$ and $\vec{\beta}$ are vector-valued functions of $\vec{X} \in \mathbb{R}^4$. Then,

$$f(t,\vec{X},u)=\vec{\varphi}(t,\vec{X})+u\vec{\beta}(t,\vec{X})$$

$$=\begin{bmatrix}\pi-(a+p+b)S+e_1 4_A+e_2 4_B+e_3 4_C-(h_1 4_A+h_2 4_B+h_3 4_C)S-\mu S\\ c_1 aS+k_1 pS-(m_1+e_1)4_A+h_1 4_A S-s_1 4_A-\mu 4_A\\ c_2 aS+k_2 pS+m_1 4_A-(m_2+e_2)4_B+h_2 4_B S+s_1 4_A-s_2 4_B-\mu 4_B\\ (1-c_1-c_2)aS+(1-k_1-k_2)pS+bS+m_2 4_B-e_3 4_C+h_3 4_C S+s_2 4_B-\mu 4_C\end{bmatrix}+u\begin{bmatrix}l_1 4_A+l_2 4_B+l_3 4_C\\ -l_1 4_A\\ -l_2 4_B\\ -l_3 4_C\end{bmatrix},$$

$$|f(t,\vec{X},u)|=\left\|\begin{bmatrix}\pi-(a+p+b)S+e_1 4_A+e_2 4_B+e_3 4_C-(h_1 4_A+h_2 4_B+h_3 4_C)S-\mu S\\ c_1 aS+k_1 pS-(m_1+e_1)4_A+h_1 4_A S-s_1 4_A-\mu 4_A\\ c_2 aS+k_2 pS+m_1 4_A-(m_2+e_2)4_B+h_2 4_B S+s_1 4_A-s_2 4_B-\mu 4_B\\ (1-c_1-c_2)aS+(1-k_1-k_2)pS+bS+m_2 4_B-e_3 4_C+h_3 4_C S+s_2 4_B-\mu 4_C\end{bmatrix}+u\begin{bmatrix}l_1 4_A+l_2 4_B+l_3 4_C\\ -l_1 4_A\\ -l_2 4_B\\ -l_3 4_C\end{bmatrix}\right\|$$

$$\leq\left\|\begin{bmatrix}\pi-(a+p+b)S+e_1 4_A+e_2 4_B+e_3 4_C-(h_1 4_A+h_2 4_B+h_3 4_C)S-\mu S\\ c_1 aS+k_1 pS-(m_1+e_1)4_A+h_1 4_A S-s_1 4_A-\mu 4_A\\ c_2 aS+k_2 pS+m_1 4_A-(m_2+e_2)4_B+h_2 4_B S+s_1 4_A-s_2 4_B-\mu 4_B\\ (1-c_1-c_2)aS+(1-k_1-k_2)pS+bS+m_2 4_B-e_3 4_C+h_3 4_C S+s_2 4_B-\mu 4_C\end{bmatrix}\right\|+\left|u\begin{bmatrix}l_1 4_A+l_2 4_B+l_3 4_C\\ -l_1 4_A\\ -l_2 4_B\\ -l_3 4_C\end{bmatrix}\right|$$

$$= \left\| \begin{bmatrix} -(a+p+b+\mu+h_1 4_A + h_2 4_B + h_3 4_C) & e_1 & e_2 & e_3 \\ c_1 a + k_1 p + h_1 4_A & -(m_1+e_1+s_1+\mu) & 0 & 0 \\ c_2 a + k_2 p + h_2 4_B & m_1 + s_1 & -(m_2+e_2+s_2+\mu) & 0 \\ (1-c_1-c_2)a + (1-k_1-k_2)p + b + h_3 4_C & 0 & m_2 + s_2 & -(e_3+\mu) \end{bmatrix} \begin{bmatrix} S \\ 4_A \\ 4_B \\ 4_C \end{bmatrix} \right\|$$

$$+ \left| u \begin{bmatrix} 0 & l_1 & l_2 & l_3 \\ 0 & -l_1 & 0 & 0 \\ 0 & 0 & -l_2 & 0 \\ 0 & 0 & 0 & -l_3 \end{bmatrix} \begin{bmatrix} S \\ 4_A \\ 4_B \\ 4_C \end{bmatrix} \right|$$

$$= \left\| A\vec{X} \right\| + \left\| u\, B\, \vec{X} \right\|$$

$$\leq \|A\| \left\| \vec{X} \right\| + |u| \|B\| \left\| \vec{X} \right\| = (\|A\| + |u| \|B\|) \left\| \vec{X} \right\| = D \left\| \vec{X} \right\|,$$

where D depends on the coefficients of the proposed system. This proves the part (**c**). Since $S, 4_A, 4_B$, and 4_C are non-negative and bounded below, we have

$$\frac{dS}{dt} \geq -(a+p+b+\mu)S,$$

$$\frac{d4_A}{dt} \geq -(m_1+l_1+e_1+s_1+\mu)4_A,$$

$$\frac{d4_B}{dt} \geq -(m_2+l_2+e_2+s_2+\mu)4_B,$$

and

$$\frac{d4_C}{dt} \geq -(l_3+e_3+\mu)4_C.$$

Above inequalities implies that

$$S \geq e^{-(a+p+b+\mu)t+C_S^0} > 0,$$

$$4_A \geq e^{-(m_1+l_1+e_1+s_1+\mu)t+C_A^0} > 0,$$

$$4_B \geq e^{-(m_2+l_2+e_2+s_2+\mu)t+C_B^0} > 0,$$

and

$$4_C \geq e^{-(l_3+e_3+\mu)t+C_C^0} > 0,$$

respectively, where C_S^0, C_A^0, C_B^0, and C_C^0 are constants of the integration. Hence, letting $F = \min\{F_A, F_B, F_C\}$, where

$$F_A = \inf_{t\in[0,T]}\{4_A(t)\}, F_B = \inf_{t\in[0,T]}\{4_B(t)\}, F_C = \inf_{t\in[0,T]}\{4_C(t)\},$$

we get

$$4_A + 4_B + 4_C + \frac{1}{2}Ku^2(t) \geq F + \frac{1}{2}Ku^2(t) = d_2 + d_1|u(t)|^2,$$

where $d_1 = \frac{1}{2}K$ and $d_2 = F$. Besides this, if $L = 4_A + 4_B + 4_C + \frac{1}{2}Ku^2(t)$, then we have $\frac{\partial^2 L}{\partial u^2} = K > 0$. This means that the integrand is a convex function and hence, part (d) is proven. Therefore, optimal control u^* exists.

As the existence of optimal control that will minimize the objective functional J subject to the system with optimal control is proven, characterization of the optimal control will be given with Pontryagin's maximum principle.

Characterization of Optimal Control. For the necessary conditions for optimal control Hamiltonian of the system is defined by

$$H = 4_A + 4_B + 4_C + \frac{1}{2}Ku^2(t) + \sum_{i=1}^{4} \lambda_i f_i,$$

where

$$\begin{aligned} f_1 &= \pi - (a + p + b)S + [l_1 u(t) + e_1]4_A + [l_2 u(t) + e_2]4_B \\ &\quad + [l_3 u(t) + e_3]4_C - (h_1 4_A + h_2 4_B + h_3 4_C)S - \mu S, \\ f_2 &= c_1 aS + k_1 pS - [m_1 + l_1 u(t) + e_1]4_A + h_1 4_A S - s_1 4_A - \mu 4_A, \\ f_3 &= c_2 aS + k_2 pS + m_1 4_A - [m_2 + l_2 u(t) + e_2]4_B + h_2 4_B S + s_1 4_A \\ &\quad - s_2 4_B - \mu 4_B, \end{aligned}$$

and

$$\begin{aligned} f_4 &= (1 - c_1 - c_2)aS + (1 - k_1 - k_2)pS + bS + m_2 4_B - [l_3 u(t) + e_3]4_C \\ &\quad + h_3 4_C S + s_2 4_B - \mu 4_C. \end{aligned}$$

Theorem 11. Given optimal control u^* and solutions $S^*, 4_A^*, 4_B^*, 4_C^*$ of the corresponding state system, there exist adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ satisfying

$$\begin{aligned} \frac{d\lambda_1}{dt} &= \lambda_1(a + p + b + h_1 4_A + h_2 4_B + h_3 4_C + \mu) \\ &\quad - \lambda_2(c_1 a + k_1 p + h_1 4_A) - \lambda_3(c_2 a + k_2 p + h_2 4_B) \\ &\quad - \lambda_4[(1 - c_1 - c_2)a + (1 - k_1 - k_2)p + b + h_3 4_C], \\ \frac{d\lambda_2}{dt} &= -1 - \lambda_1[l_1 u(t) + e_1 - h_1 S] \\ &\quad - \lambda_2[-m_1 - l_1 u(t) - e_1 + h_1 S - s_1 - \mu] - \lambda_3(m_1 + s_1), \\ \frac{d\lambda_3}{dt} &= -1 - \lambda_1[l_2 u(t) + e_2 - h_2 S] \\ &\quad - \lambda_3[-m_2 - l_2 u(t) - e_2 + h_2 S - s_2 - \mu] - \lambda_4(m_2 + s_2), \\ \frac{d\lambda_4}{dt} &= -1 - \lambda_1[l_3 u(t) + e_3 - h_3 S] - \lambda_4[-l_3 u(t) - e_3 + h_3 S - \mu], \end{aligned}$$

and the transversality conditions $\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = 0$. Furthermore,

$$u^* = \min\{max\{0, \Delta\}, 1\},$$

where $\Delta = \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]$.

Proof. The Hamiltonian of the system is

$$H = 4_A + 4_B + 4_C + \frac{1}{2}Ku^2(t) + \sum_{i=1}^{4} \lambda_i f_i$$

$$= 4_A + 4_B + 4_C + \frac{1}{2}Ku^2(t)$$
$$+ \lambda_1\{\pi - (a + p + b)S + [l_1u(t) + e_1]4_A$$
$$+ [l_2u(t) + e_2]4_B + [l_3u(t) + e_3]4_C$$
$$- (h_1 4_A + h_2 4_B + h_3 4_C)S - \mu S\}$$
$$+ \lambda_2\{c_1 aS + k_1 pS - [m_1 + l_1u(t) + e_1]4_A + h_1 4_A S - s_1 4_A$$
$$- \mu 4_A\}$$
$$+ \lambda_3\{c_2 aS + k_2 pS + m_1 4_A - [m_2 + l_2u(t) + e_2]4_B$$
$$+ h_2 4_B S + s_1 4_A - s_2 4_B - \mu 4_B\} + \lambda_4\{(1 - c_1 - c_2)aS$$
$$+ (1 - k_1 - k_2)pS + bS + m_2 4_B - [l_3u(t) + e_3]4_C$$
$$+ h_3 4_C S + s_2 4_B - \mu 4_C\}.$$

The adjoint system will be calculated with below formulas.

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S}, \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial 4_A}, \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial 4_B} \text{ and } \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial 4_C}.$$

That is,

$$\frac{d\lambda_1}{dt} = \lambda_1(a + p + b + h_1 4_A + h_2 4_B + h_3 4_C + \mu)$$
$$- \lambda_2(c_1 a + k_1 p + h_1 4_A) - \lambda_3(c_2 a + k_2 p + h_2 4_B)$$
$$- \lambda_4[(1 - c_1 - c_2)a + (1 - k_1 - k_2)p + b + h_3 4_C],$$

$$\frac{d\lambda_2}{dt} = -1 - \lambda_1[l_1u(t) + e_1 - h_1 S]$$
$$- \lambda_2[-m_1 - l_1u(t) - e_1 + h_1 S - s_1 - \mu] - \lambda_3(m_1 + s_1),$$

$$\frac{d\lambda_3}{dt} = -1 - \lambda_1[l_2u(t) + e_2 - h_2 S]$$
$$- \lambda_3[-m_2 - l_2u(t) - e_2 + h_2 S - s_2 - \mu] - \lambda_4(m_2 + s_2),$$

and

$$\frac{d\lambda_4}{dt} = -1 - \lambda_1[l_3u(t) + e_3 - h_3 S] - \lambda_4[-l_3u(t) - e_3 + h_3 S - \mu].$$

Moreover, from the optimality conditions, we have

$$\frac{\partial H}{\partial u} = 0 \text{ at } u = u^*.$$

That is,

$$\frac{\partial H}{\partial u} = Ku + \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C) - \lambda_2 l_1 4_A - \lambda_3 l_2 4_B - \lambda_4 l_3 4_C = 0$$

$$Ku = \lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)$$

Hence,

$$u = \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)] = \Delta.$$

In other words,

$$u^* = \begin{cases} 0, & if\ \Delta \leq 0, \\ \Delta, & if\ 0 < \Delta < 1, \\ 1, & if\ \Delta \geq 1. \end{cases}$$

Therefore,

$$u^* = \min\{max\{0, \Delta\}, 1\},$$

where $\Delta = \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]$.

Optimality System. In this section, the optimality system will be proposed with the proof of uniqueness of its solutions. The system consists of state equations with initial conditions, adjoint system and transversality conditions. The system is proposed below.

$$\begin{aligned} \frac{dS}{dt} = {} & \pi - (a + p + b)S \\ & + (l_1 4_A + l_2 4_B \\ & + l_3 4_C) \min\left\{max\left\{0, \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C \right.\right. \\ & \left.\left. - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]\right\}, 1\right\} + e_1 4_A + e_2 4_B + e_3 4_C \\ & - (h_1 4_A + h_2 4_B + h_3 4_C)S - \mu S, \end{aligned}$$

$$\begin{aligned} \frac{d4_A}{dt} = {} & c_1 aS + k_1 pS - (m_1 + e_1)4_A \\ & - \min\left\{max\left\{0, \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C \right.\right. \\ & \left.\left. - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]\right\}, 1\right\} l_1 4_A + h_1 4_A S - s_1 4_A - \mu 4_A, \end{aligned}$$

$$\frac{d4_B}{dt} = c_2aS + k_2pS + m_1 4_A - (m_2 + e_2)4_B$$
$$- \min\left\{max\left\{0, \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C\right.\right.$$
$$\left.\left. - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]\right\}, 1\right\} l_2 4_B + h_2 4_B S + s_1 4_A$$
$$- s_2 4_B - \mu 4_B,$$

$$\frac{d4_C}{dt} = (1 - c_1 - c_2)aS + (1 - k_1 - k_2)pS + bS + m_2 4_B - e_3 4_C$$
$$- \min\left\{max\left\{0, \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C\right.\right.$$
$$\left.\left. - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]\right\}, 1\right\} l_3 4_C + h_3 4_C S + s_2 4_B$$
$$- \mu 4_C,$$

$$\frac{d\lambda_1}{dt} = \lambda_1(a + p + b + h_1 4_A + h_2 4_B + h_3 4_C + \mu)$$
$$- \lambda_2(c_1 a + k_1 p + h_1 4_A) - \lambda_3(c_2 a + k_2 p + h_2 4_B)$$
$$- \lambda_4[(1 - c_1 - c_2)a + (1 - k_1 - k_2)p + b + h_3 4_C],$$

$$\frac{d\lambda_2}{dt} = -1 - \lambda_1(e_1 - h_1 S)$$
$$- \lambda_1 l_1 \min\left\{max\left\{0, \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C\right.\right.$$
$$\left.\left. - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]\right\}, 1\right\}$$
$$- \lambda_2(h_1 S - m_1 - e_1 - s_1 - \mu)$$
$$+ \lambda_2 l_1 \min\left\{max\left\{0, \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C\right.\right.$$
$$\left.\left. - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]\right\}, 1\right\} - \lambda_3(m_1 + s_1),$$

$$\frac{d\lambda_3}{dt} = -1 - \lambda_1(e_2 - h_2 S)$$
$$- \lambda_1 l_2 \min\left\{max\left\{0, \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C\right.\right.$$
$$\left.\left. - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]\right\}, 1\right\}$$
$$- \lambda_3(h_2 S - m_2 - e_2 - s_2 - \mu)$$
$$+ \lambda_3 l_2 \min\left\{max\left\{0, \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C\right.\right.$$
$$\left.\left. - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]\right\}, 1\right\} - \lambda_4(m_2 + s_2),$$

$$\frac{d\lambda_4}{dt} = -1 - \lambda_1(e_3 - h_3 S) - \lambda_1 l_3 \min\left\{max\left\{0, \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]\right\}, 1\right\} - \lambda_4(h_3 S - e_3 - \mu) + \lambda_4 l_3 \min\left\{max\left\{0, \frac{1}{K}[\lambda_2 l_1 4_A + \lambda_3 l_2 4_B + \lambda_4 l_3 4_C - \lambda_1(l_1 4_A + l_2 4_B + l_3 4_C)]\right\}, 1\right\},$$

with $S(0) = S_0, 4_A(0) = 4_{A,0}, 4_B(0) = 4_{B,0}, 4_C(0) = 4_{C,0}, \lambda_1(T) = 0, \lambda_2(T) = 0, \lambda_3(T) = 0$ and $\lambda_4(T) = 0$.

Theorem 12. The function

$$u(z) = \min[\max(z, y), x]$$

is Lipschitz continuous in z with $x < y$ for positive parameters x and y.

Proof. (Saad, Dynamics and Optimal Control of Cancer Cells, 2019)

Theorem 13. For the proposed optimality system above, the bounded solutions are unique for sufficiently small T.

Proof. Assume that there exist two different solutions, $(S, 4_A, 4_B, 4_C, \lambda_1, \lambda_2, \lambda_3, \lambda_4)$ and $(S', 4_A', 4_B', 4_C', \lambda_1', \lambda_2', \lambda_3', \lambda_4')$, of the optimality system. Let

$$S = e^{rt}x, 4_A = e^{rt}y, 4_B = e^{rt}z, 4_C = e^{rt}w, \lambda_1 = e^{-rt}q, \lambda_2 = e^{-rt}v, \lambda_3 = e^{-rt}n, \lambda_4 = e^{-rt}f$$

and

$$S' = e^{rt}x', 4_A' = e^{rt}y', 4_B' = e^{rt}z', 4_C' = e^{rt}w', \lambda_1' = e^{-rt}q', \lambda_2' = e^{-rt}v', \lambda_3' = e^{-rt}n', \lambda_4' = e^{-rt}f'.$$

Moreover,

$$u = \min\left\{max\left\{0, \frac{1}{K}(l_1 vy + l_2 nz + l_3 fw - l_1 qy - l_2 qz - l_3 qw)\right\}, 1\right\}$$

and

$$u' = \min\left\{max\left\{0, \frac{1}{K}(l_1 v'y' + l_2 n'z' + l_3 f'w' - l_1 q'y' - l_2 q'z' - l_3 q'w')\right\}, 1\right\}.$$

From the definition 1 and theorem 1, we get

$$u - u' \leq \frac{1}{K}\{l_1[y(v-q) - y'(v'-q')] + l_2[z(n-q) - z'(n'-q')] + l_3[w(f-q) - w'(f'-q')]\}.$$

Substituting $S = e^{rt}x$ and $S' = e^{rt}x'$ into the first equation of the proposed optimality system, we obtain

$$\dot{x} + rx = \pi e^{-rt} - (a+p+b+\mu)x + [l_1u + e_1]y + [l_2u + e_2]z + [l_3u + e_3]w - (h_1y + h_2z + h_3w)xe^{rt},$$

and

$$\dot{x}' + rx' = \pi e^{-rt} - (a+p+b+\mu)x' + [l_1u' + e_1]y' + [l_2u' + e_2]z' + [l_3u' + e_3]w' - (h_1y' + h_2z' + h_3w')x'^{e^{rt}}.$$

Similarly, substituting $\lambda_1 = e^{-rt}q$ and $\lambda_1' = e^{-rt}q'$ into the fifth equation of the proposed system, we get

$$\dot{q} - rq = (a+p+b+\mu)q + (q-v)h_1ye^{rt} + (q-n)h_2ze^{rt} + (q - f)h_3we^{rt} - (c_1a + k_1p)v - (c_2a + k_2p)n - [(1-c_1-c_2)a + (1-k_1-k_2)p + b]f$$

and

$$\dot{q}' - rq' = (a+p+b+\mu)q' + (q'-v')h_1y'e^{rt} + (q'-n')h_2z'e^{rt} + (q'-f')h_3w'e^{rt} - (c_1a + k_1p)v' - (c_2a + k_2p)n' - [(1-c_1-c_2)a + (1-k_1-k_2)p + b]f'.$$

Taking the difference between the equations of x and x', multiplying it by $x - x'$ and then integrating from 0 to T, we obtain

$$\frac{1}{2}[x(T)-x'(T)]^2+(r+a+p+b+\mu)\int_0^T(x-x')^2dt$$

$$=e_1\int_0^T(x-x')(y-y')dt+e_2\int_0^T(x-x')(z-z')dt$$

$$+l_1\int_0^T(x-x')(uy-u'y')dt+l_2\int_0^T(x-x')(uz-u'z')dt$$

$$+l_3\int_0^T(x-x')(uw-u'w')dt$$

$$-\int_0^T e^{rt}(x-x')[h_1(xy-x'y')+h_2(xz-x'z')$$

$$+h_3(xw-x'w')]dt.$$

In the same manner, taking the difference between the equations of q and q', multiplying it by $q-q'$ and then integrating from 0 to T, we get

$$\frac{1}{2}[q(0)-q'(0)]^2-(r+a+p+b+\mu)\int_0^T(q-q')^2dt$$

$$=(c_1a+k_1p)\int_0^T(q-q')(v-v')dt$$

$$+(c_2a+k_2p)\int_0^T(q-q')(n-n')dt$$

$$+[(1-c_1-c_2)a+(1-k_1-k_2)p$$

$$+b]\int_0^T(q-q')(f-f')dt$$

$$+h_1\int_0^T e^{rt}(q-q')[y(q-v)-y'(q'-v')]dt$$

$$+h_2\int_0^T e^{rt}(q-q')[z(q-n)-z'(q'-n')]dt$$

$$+h_3\int_0^T e^{rt}(q-q')[w(q-f)-w'(q'-f')]dt.$$

Similar equations are obtained for 4_A and $4_A{}'$, 4_B and $4_B{}'$, 4_C and $4_C{}'$, λ_2 and $\lambda_2{}'$, λ_3 and $\lambda_3{}'$, and λ_4 and $\lambda_4{}'$. Afterwards, upper bounds / estimates on the right-hand side of all eight integral equations are computed as below. For the compartment S, for example, we have

$$\frac{1}{2}[x(T)-x'(T)]^2+(r+a+p+b+\mu)\int_0^T(x-x')^2dt$$

$$\begin{aligned}
&= e_1\int_0^T(x-x')(y-y')dt + e_2\int_0^T(x-x')(z-z')dt\\
&+ l_1\int_0^T(x-x')\left(uy-u'^{y'}\right)dt + l_2\int_0^T(x-x')(uz-u'z')dt\\
&+ l_3\int_0^T(x-x')(uw-u'w')dt\\
&-\int_0^T e^{rt}(x-x')[h_1(xy-x'y')+h_2(xz-x'z')\\
&+ h_3(xw-x'w')]dt
\end{aligned}$$

$$\leq E_1 \int_0^T [(x-x')^2 + (y-y')^2]dt + E_2 \int_0^T [(x-x')^2 + (z-z')^2]dt$$
$$+ L_1 \int_0^T [(x-x')^2 + (y-y')^2 + (u-u')^2]dt$$
$$+ L_2 \int_0^T [(x-x')^2 + (z-z')^2 + (u-u')^2]dt$$
$$+ L_3 \int_0^T [(x-x')^2 + (w-w')^2 + (u-u')^2]dt$$
$$+ H_1 e^{rT} \int_0^T [(x-x')^2 + (y-y')^2]dt$$
$$+ H_2 e^{rT} \int_0^T [(x-x')^2 + (z-z')^2]dt$$
$$+ H_3 e^{rT} \int_0^T [(x-x')^2 + (w-w')^2]dt,$$

where $E_1, E_2, L_1, L_2, L_3, H_1, H_2$ and H_3 depends on the upper bounds and coefficients of the variables x, y, z and w. In a similar way, we obtain the following inequality for the variable q.

$$\frac{1}{2}[q(0)-q'(0)]^2-(r+a+p+b+\mu)\int_0^T(q-q')^2dt$$

$$=(c_1a+k_1p)\int_0^T(q-q')(v-v')dt$$

$$+(c_2a+k_2p)\int_0^T(q-q')(n-n')dt$$

$$+[(1-c_1-c_2)a+(1-k_1-k_2)p$$

$$+b]\int_0^T(q-q')(f-f')dt$$

$$+h_1\int_0^T e^{rt}(q-q')[y(q-v)-y'(q'-v')]dt$$

$$+h_2\int_0^T e^{rt}(q-q')[z(q-n)-z'(q'-n')]dt$$

$$+h_3\int_0^T e^{rt}(q-q')[w(q-f)-w'(q'-f')]dt$$

$$\leq H_1e^{rT}\int_0^T[(q-q')^2+(v-v')^2+(y-y')^2]dt$$

$$+H_2e^{rT}\int_0^T[(q-q')^2+(n-n')^2+(z-z')^2]dt$$

$$+H_3e^{rT}\int_0^T[(q-q')^2+(w-w')^2+(f-f')^2]dt$$

$$+A\int_0^T[(q-q')^2+(v-v')^2]dt$$

$$+B\int_0^T[(q-q')^2+(n-n')^2]dt$$

$$+C\int_0^T[(q-q')^2+(f-f')^2]dt,$$

where H_1, H_2, H_3, A, B and C depends on the upper bounds and coefficients of the variables q, v, n, f, x, y, z and w. The same computations applied to the rest 6 integral equations. Afterwards, for proving the uniqueness, all of the eight integral inequalities are added side by side as below.

$$\frac{1}{2}[x(T)-x'(T)]^2+\frac{1}{2}[y(T)-y'(T)]^2+\frac{1}{2}[z(T)-z'(T)]^2$$
$$+\frac{1}{2}[w(T)-w'(T)]^2+\frac{1}{2}[q(0)-q'(0)]^2$$
$$+\frac{1}{2}[v(0)-v'(0)]^2+\frac{1}{2}[n(0)-n'(0)]^2$$
$$+\frac{1}{2}[f(0)-f'(0)]^2+(r+a+p+b+\mu)\int_0^T(x-x')^2dt$$
$$+(r+m_1+s_1+e_1+\mu)\int_0^T(y-y')^2dt$$
$$+(r+m_2+s_2+e_2+\mu)\int_0^T(z-z')^2dt$$
$$+(r+e_3+\mu)\int_0^T(w-w')^2dt$$
$$+(-r-a-p-b-\mu)\int_0^T(q-q')^2dt$$
$$+(-r-m_1-s_1-e_1-\mu)\int_0^T(v-v')^2dt$$
$$+(-r-m_2-s_2+e_2-\mu)\int_0^T(n-n)^2dt$$
$$+(-r-e_3-\mu)\int_0^T(f-f')^2dt$$

$$\leq A_0 \int_0^T (f - f')^2 dt$$

$$+ A_1 \int_0^T [(x - x')^2 + (y - y')^2 + (q - q')^2 + (v - v')^2] dt$$

$$+ A_2 \int_0^T [(x - x')^2 + (z - z')^2 + (q - q')^2 + (n - n')^2] dt$$

$$+ A_3 \int_0^T [(x - x')^2 + (y - y')^2 + (u - u')^2 + (q - q')^2$$
$$+ (v - v')^2] dt$$

$$+ A_4 \int_0^T [(x - x')^2 + (z - z')^2 + (u - u')^2 + (q - q')^2$$
$$+ (n - n')^2] dt$$

$$+ A_5 \int_0^T [(x - x')^2 + (w - w')^2 + (u - u')^2 + (q - q')^2$$
$$+ (f - f')^2] dt$$

$$+ A_6 e^{rT} \int_0^T [(x - x')^2 + (y - y')^2 + (q - q')^2$$
$$+ (v - v')^2] dt$$

$$+ A_7 e^{rT} \int_0^T [(x - x')^2 + (z - z')^2 + (q - q')^2$$
$$+ (n - n')^2] dt$$

$$+ A_8 e^{rT} \int_0^T [(x - x')^2 + (w - w')^2 + (q - q')^2$$
$$+ (f - f')^2] dt$$

$$+ A_9 \int_0^T [(y - y')^2 + (z - z')^2 + (q - q')^2 + (n - n')^2] dt$$

$$+ A_{10} \int_0^T [(x - x')^2 + (w - w')^2 + (q - q')^2$$
$$+ (f - f')^2] dt$$

$$+ A_{11}\int_0^T [(z-z')^2 + (w-w')^2 + (n-n')^2$$

$$+ (f-f')^2]dt + A_{12}\int_0^T [(q-q')^2 + (f-f')^2]dt,$$

where A_i's, $i = 0, \dots, 12$, depends on the coefficients and upper bounds of the system's variables. Introducing positivity of solutions of the variables and calculating at both initial and final time the below inequality is obtained with necessary simplifications.

$$(r - Z - Z'e^{2rT})\int_0^T [(x-x')^2 + (y-y')^2 + (z-z')^2 + (w-w')^2$$
$$+ (u-u')^2 + (q-q')^2 + (v-v')^2 + (n-n')^2$$
$$+ (f-f')^2]dt \leq 0.$$

Here, Z and Z' are dependent coefficients and they depend on the solutions of variables x, y, z, w, q, v, n and f. It is obvious that the integrand is always non-negative. Hence, if $r - Z - Z'e^{2rT} > 0$, then the integrand should be zero. Now, if we check the sign of $(r - Z - Z'e^{2rT})$, we have

$$\ln\left(\frac{r-Z}{Z'}\right) > 2rT,$$

since the natural logarithm function is and increasing function. Hence, $r > Z + Z'$ and

$$T < \frac{1}{2r}\ln\left(\frac{r-Z}{Z'}\right).$$

It is obvious that $r - Z - Z'e^{2rT} > 0$ always hold. As a result, we get $x = x', y = y', z = z', w = w', q = q', v = v', n = n'$, and $f = f'$. Therefore, for a small time, the system of optimal has a unique solution.

Numerical Simulations and Results

In Chapter III, the distribution of the population is presented in Figure 1. In this section, the numerical simulations of the model with optimal control are presented. The effect of control function on the state variables $4_A, 4_B$ and 4_C are emphasized in Figure 13, Figure 14 and Figure 15 the trend of control function u is given in Figure 16 and the analysis of control cost is presented in Figure 17.

Figure 13

The Distribution of BI-RADS 4A Diagnosed Patients with Control

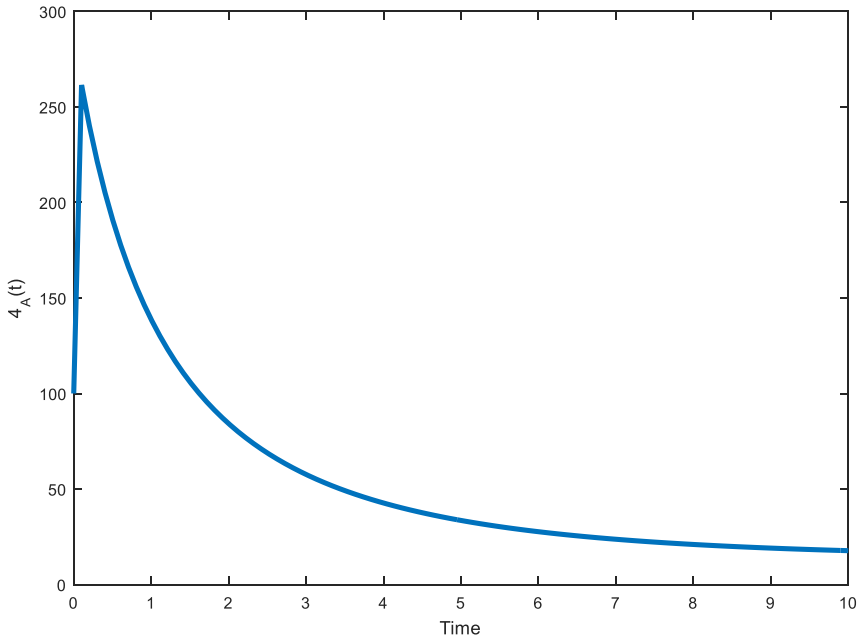


Figure 14

The Distribution of BI-RADS 4B Diagnosed Patients with Control

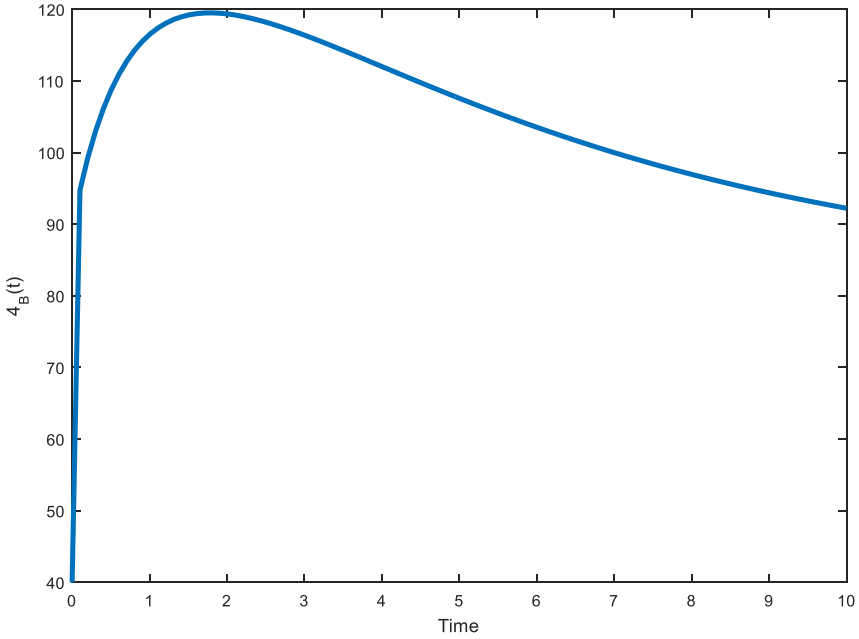


Figure 15

The Distribution of BI-RADS 4C Diagnosed Patients with Control

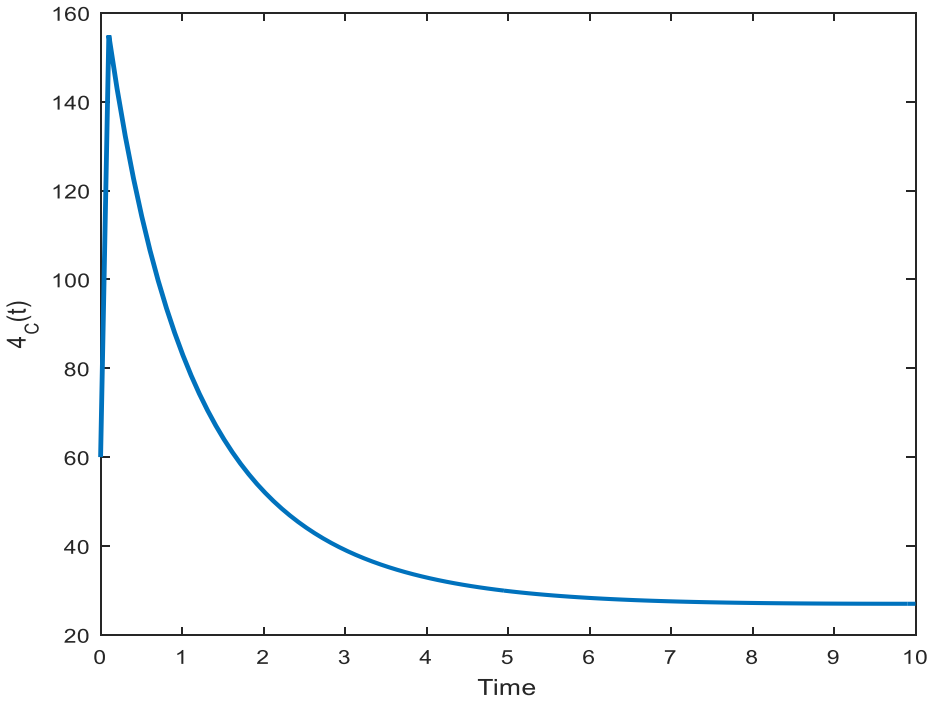


Figure 16

Control Function

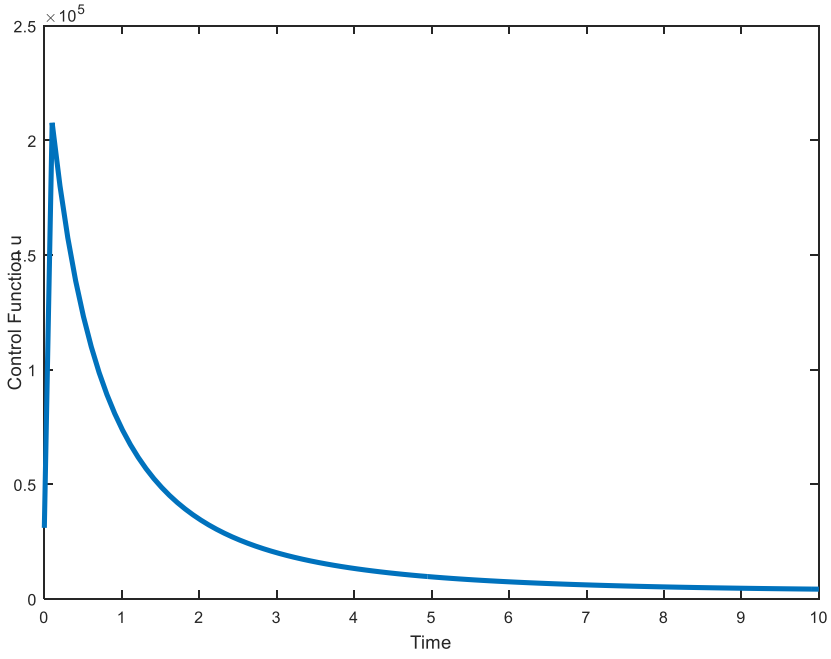
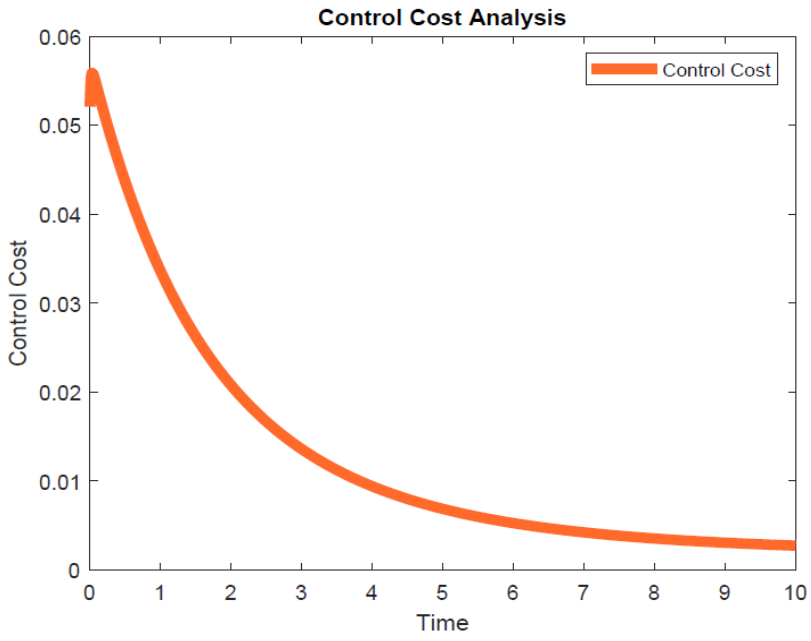


Figure 17

Control Cost Analysis



In Figure 13, Figure 14 and Figure 15, the expected trend of BI-RADS 4A, BI-RADS 4B, BI-RADS 4C diagnosed patients are presented, respectively. As can be seen from the Figure 13, a huge decline is expected to happen in a really short time when the control is applied. With the use of control, there will be an increase in a short time in BI-RADS 4B diagnosed patients. However, after a while, a decrease will be happened in the compartment if the control continues to be applied. Lastly, in the use of control, there will be an enormous decrease in BI-RADS 4C diagnosed patients which has the highest percentage of cancer risk in BI-RADS 4 subcategories. The Figure 16 reveals the nature of control function in time. It represents the dosage that should be used for achieving the desired aim. As it is clear, control should be applied with lower dosages in time which reduces the side effects of control (if it has any). The objective functional J is calculated by integrating the control cost and the number of individuals in the BI-RADS 4A, BI-RADS 4B, and BI-RADS 4C categories over time. It serves as a quantitative measure of the overall performance of the optimal control system and the efficacy of control strategies. The function allows for the comparison of different control interventions and aids in optimizing control strategies to reduce the number of suspicious BI-RADS 4 diagnoses while considering the associated control cost (as shown in Figure 16 and Figure 17). The control cost analysis plot depicted in Figure

17 illustrates the cost associated with implementing control strategies over time. By examining this plot, healthcare providers can assess the efficiency and feasibility of different control measures in minimizing the progression of breast cancer.

To conclude, from the Figure 1 in Chapter III, we observed that an increase is expected in BI-RADS 4B and BI-RADS 4C diagnosed patients in the absence of control. However, when the control is applied, a reduction is foreseen in all diagnosis compartments. This proves the effectiveness of control in BI-RADS 4 subcategories.

CHAPTER V
Findings and Discussion

In this thesis, a compartmental mathematical model is constructed for the analysis of BI-RADS 4 diagnosis in the population of North Cyprus. In this regard, the total population is separated into 4 compartments/state variables which are susceptible individuals (S), individuals diagnosed with BI-RADS 4A (4_A), individuals diagnosed with BI-RADS 4B (4_B) and individuals diagnosed with BI-RADS 4C (4_C). In the analysis of this model, 3 equilibrium points are found; diagnose-free equilibrium point (E_0), BI-RADS 4B&BI-RADS 4C free equilibrium point (E_1) and endemic equilibrium point (E_2). The important side and strength of these equilibrium points is it is proved that all of them are globally asymptotically stable under some conditions. In other words, it is proved that it is possible to reach these equilibrium points and stay as close as necessary under the mentioned conditions.

In the analysis of the proposed model, 3 different basic reproduction numbers are found which are belong to 3 diagnosis compartments, $4_A, 4_B$ and 4_C. Sensitivity analysis is applied to the parameters of obtained basic reproduction numbers to determine the effective parameters on the diagnosis of BI-RADS 4 subcategories. With the constructed model, it is declared that BI-RADS 4A category will become extinct and so, BI-RADS 4 category is going to be separated into 2 categories, in time. Therefore, a decrease in the range of cancer probability for BI-RADS 4 is expected (Figure 1). However, existence of BI-RADS 4B and BI-RADS 4C diagnosis is expected and moreover, an increase is observed especially in BI-RADS 4C diagnosed patients.

As it is expected in the existence of any disease, increase in the recruitment rate in population results in a rise in BI-RADS 4 subcategories which is specified in sensitivity analysis calculations. Both sensitivity analysis calculations and numerical simulations (i.e., Table 9, Table 10, Table 11, Figure 2, Figure 3 and Figure 4) emphasize the impact of lactation rate on BI-RADS 4 diagnosis. It is revealed that rise in the rate of lactation causes a decrease in the diagnosis compartments. There exist papers that suggest longer breastfeeding duration / active lactation for the prevention of breast cancer (Tan, et al., 2018; Qiu, Zhong, Hu, & Wu, 2022). The effect of menopause is discussed in papers Park et al. (2020) and Kim et al. (2020).

In these works, the authors had indicated that there exists a relation between menopause and breast cancer/BI-RADS categories. The results of this thesis revealed that menopause at early age has a significant effect on BI-RADS 4 subcategories so that it reduces the risk of diagnosis of all BI-RADS 4 subcategories (stated in computational and visual way in Table 9, Table 10, Table 11, Figure 5, Figure 6 and Figure 7). On the other hand, as illustrated in Figure 12 and Table 9 – 11, late menopause increases the risk of breast cancer. So, increase in the rate of late menopause decreases the number of BI-RADS 4A&BI-RADS 4B diagnosed patients while increasing the number of BI-RADS 4C diagnosed patients since it has the highest percentage of cancer risk in BI-RADS 4 subcategories. Computations of sensitivity indices indicate that increase in the parameters related with family history will cause an increase in all diagnosis compartments $4_A, 4_B$ and 4_C in time. These computations are supported by Table 9, Table 10, Table 11, Figure 8, Figure 9 and Figure 10. The authors of Colditz et al. (1996) and Pharoah et al. (1997) also had declared the importance and effect of family history on breast cancer. In the works Terry and Rohan (2002) and Lilleborge et al. (2021), the results showed that smoking increase the risk of breast cancer. The results of the sensitivity analysis in this thesis also revealed the importance smoking on the risk of breast cancer. The analysis showed that increase in s_1, will lead a decrease in BI-RADS 4A patients and similarly, increase in the parameter s_2 will cause a decline BI-RADS 4B patients. It is indicated that these decreases happen due to the increasing risk of cancer. In other words, increase in these parameters causes an increase in other BI-RADS categories that have higher chance of cancer risk (given in Table 9, Table 10 and Table 11). This result is shown in Figure 11; increase in smoking will rise the number of BI-RADS 4C diagnosed patients. In the literature, many studies including Kvåle and Heuch (1988), Titus-Ernstoff et al. (1998) and Orgéas et al. (2008) indicated that there is no certain relation between irregular menstruation and breast cancer risk. However, the results of this thesis revealed that irregular menstruation increases the probability of cancer risk and hence, it causes a decline in BI-RADS 4A&BI-RADS 4B diagnosed patients and an increase in BI-RADS 4C diagnosed patients. The impact of age on breast cancer diagnosis and treatment is analyzed in many works including Greenfield et al. (1987) and Adami et al. (1986). Both of these studies showed that the breast cancer can be treated more easier in younger ages. The results of this thesis also showed that in older ages the risk of BI-RADS 4 diagnosis

decreases since the cancer risk is higher at these ages (Table 9, Table 10 and Table 11). In the literature, many studies concluded that having bloody nipple discharges and palpable masses in breast may not be malign; however, increase in them may turn to be a breast cancer and it is an important sign (Donegan, 1992; Klein, 2005; Salzman, Fleegle, & Tully, 2012; Ahmed, Ali, & Almobarak, 2010; Pruthi, 2001; Chen, et al., 2012; Varga, Romero, & Chlebowski, 2002). In this thesis, the computations of sensitivity analysis showed that increase in bloody nipple discharge and palpable masses in the structure of breast definitely increases the risk of breast cancer. Hence, individuals' diagnosis may turn from BI-RADS 4 subcategories to upper BI-RADS categories with higher cancer risk. In this regard, further investigations, screenings and operations are recommended in this case. Also, increase in the natural death rate will cause a decrease in the population and hence, BI-RADS 4 subcategories' diagnosis will be reduced (Table 9, Table 10 and Table 11).

In the continuation of the thesis, the model is improved by introducing control function with the use of optimal control theory. The control function u is selected by analyzing the results of sensitivity analysis. In other words, one of the applicable effective parameters that is found in the sensitivity analysis is chosen to be the control. Hence, due to the effectiveness of lactation rate it is seen that high lactation rate/breastfeeding can be used as a control since it can be applied to the real life. The need of control comes from the continuation of BI-RADS 4 subcategories' diagnosis given in Figure 1.

Concordantly, control function u is described with "drug for increasing the lactation rate or longtime breastfeeding" and added to the constructed model in Chapter III. Necessary theorems including existence and uniqueness of control function with Pontryagin's Maximum Principle are provided and proved in the following sections. The solutions of the proposed optimal control problem are presented in Figure 13, Figure 14 and Figure 15.

In the literature, although there are some studies suggesting that longer duration of breastfeeding may increase the risk of breast cancer like Zhou et al. (2015), most of the studies including Brinton et al. (1995), Lipworth et al. (2000), Lord et al. (2008), Bernier et al. (2000), Gajalakshmi et al. (2009) and Anstey et al. (2017) had revealed that high lactation rate and longer duration of breastfeeding decreases the risk of breast cancer. The results of this thesis also indicated that prolonged breastfeeding

and high lactation rate can be a control measure that decreases the number of patients in BI-RADS 4 subcategories. Figure 13, Figure 14 and Figure 14 are presented to show the expected trends of BI-RADS 4A, BI-RADS 4B, BI-RADS 4C diagnosed patients, respectively. According to the Figure 13, a meaningful decrease is expected to happen in a very short time with the implementation of the control. When the control is applied to the BI-RADS 4B patients, there will be an increase in the diagnosis for a short time; however, after a while, a decrease will be happened in the compartment if the control continues to be applied. Lastly, application of control will cause an enormous decrease in BI-RADS 4C diagnosed patients which has the highest percentage of cancer risk in BI-RADS 4 subcategories. The Figure 16 indicates the nature of control function in time. It represents the dosage that should be used for achieving the desired aim. As it is clear, control should be applied with lower dosages in time which reduces the side effects of control (if it has any). Figure 17 is presented for the analysis of control cost and it illustrates the cost related with implementing control strategies over time. With the help of this figure, healthcare providers can assess the effectiveness and feasibility of different control measures in minimizing the diagnosis of BI-RADS 4. To sum up, from the Figure 1 in Chapter III, it is observed that an increase is expected in BI-RADS 4B and BI-RADS 4C diagnosed patients in the absence of control. However, when the control is applied, a reduction is foreseen in all diagnosis compartments. This emphasizes the effectiveness of introduced control in the diagnosis of BI-RADS 4 subcategories.

CHAPTER VI

Conclusion and Recommendations

In this thesis, the diagnosis of BI-RADS 4 subcategories is evaluated. In this regard, a mathematical model is constructed by introducing related parameters according to the data. For determining the most effective parameters on the diagnosis of BI-RADS 4 subcategories, sensitivity analysis applied to the observed basic reproduction numbers $R_{0,A}, R_{0,B}$, and $R_{0,C}$, which belongs to each subcategory. As a result of this analysis, it is concluded that high lactation rate and early menopause can be helpful and applicable strategies for reducing the risk of BI-RADS 4 diagnosis and hence breast cancer. Unfortunately, it is observed that having a family history increases the risk of diagnosis of BI-RADS 4. Moreover, other parameters including increase in age, palpable masses and smoking rate, existence of bloody nipple discharge, and late menopause causes individuals to be diagnosed with higher BI-RADS categories and so increases the risk of breast cancer. Furthermore, the constructed model revealed that with regular screenings, doctor checks and knowledge of effective parameters, BI-RADS 4 subcategories may be reduced into 2 subcategories with a narrower range of cancer risk.

As high lactation rate is encountered as an effective parameter which can enable breast cancer, it is introduced to the constructed mathematical model as an optimal control strategy. Results of this strategy provide evidence that control measures targeting lactation rate and the duration of breastfeeding have a positive impact on managing the diagnosis of BI-RADS 4. These findings underscore the significance of promoting breastfeeding practices as a potential strategy for controlling breast cancer and highlight the ongoing need for support and encouragement of breastfeeding to alleviate the burden of the diagnosis and cancer.

The presented study captures the diagnosis process of BI-RADS 4 which is a part of breast cancer and it emphasizes the importance of early diagnosis with regular screenings. In future, the study can be extended and higher BI-RADS categories can be added to the model to analyse the relationship between them and to prevent any transition to higher categories with higher risk of breast cancer. Furthermore, what can be done for the treatment of breast cancer can be studied including better and painless treatment conditions. Lately, it is announced by the Washington University that one of the breast cancer vaccines completed its Phase I trials. In this manner,

study of vaccine can be included into mathematical models for determining its effectiveness on patients. Besides, as a popular topic, the relationship between ovarian cancer and breast cancer can be examined to make significance inferences in future since they are found to be related according to some health care professionals.

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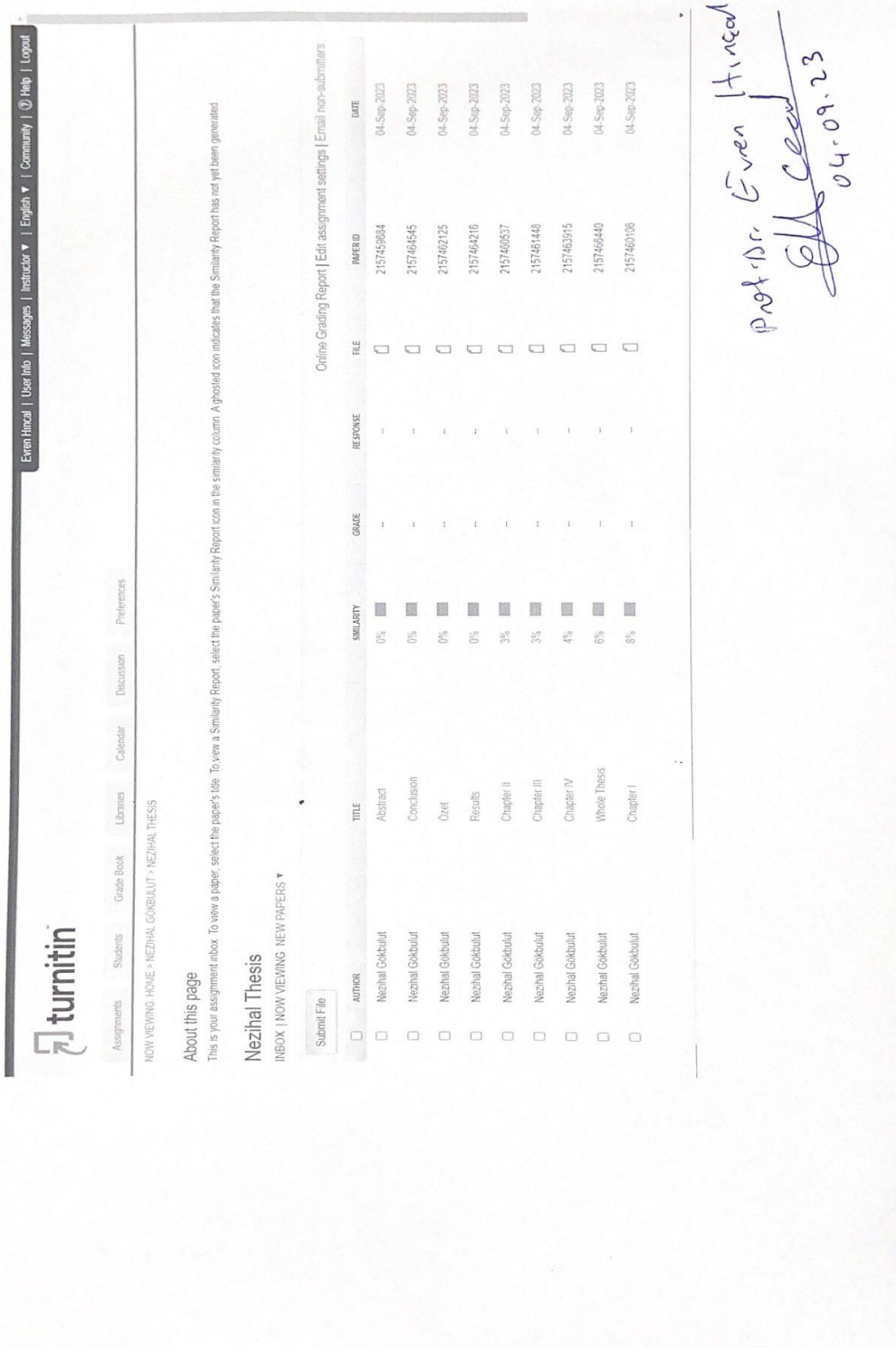
Appendices

Appendix A

Turnitin Similarity Report



Appendix B

CV

Personal Information

Surname, Name:	Gökbulut, Nezihal
Nationality:	Cypriot
Date and Place of Birth:	7 December 1997, Nicosia
Marital Status:	Single

Education

Degree	Institution	Year of Graduation
M. Sc.	Near East University, Department of Mathematics	2021
B. Sc.	Dokuz Eylül University, Department of Mathematics	2019

Work Experience

Year	Place	Enrollment
2019 September – present	Near East University, Department of Mathematics	Lecturer
2019 June – 2019 September	SOS Children's Village	Mathematics teacher, accountant, human resources intern

Foreign Languages

- English, fluently spoken and written.
- Greek, speaks and writes a little.

Honors and Awards

- Young Researcher Award, NEU, 2023
- Young Researcher Award, NEU, 2022
- Young Researcher Encouragement Award, NEU, 2022

Publications in International Referred Journals (in Coverage of SCI/SCI-E)

- Gokbulut, N., Hincal, E., Besim, H., & Kaymakamzade, B. (2022). Reducing the Range of Cancer Risk on BI-RADS 4 Subcategories via Mathematical Modelling. *CMES-Computer Modeling in Engineering & Sciences, 133(1)*, 93-109. Doi: 10.32604/cmes.2022.019782
- Qureshi, S., Soomro, A., Shaikh, A. A., Hincal, E., & Gokbulut, N. (2022). A Novel Multistep Iterative Technique for Models in Medical Sciences with Complex Dynamics. *Computational and Mathematical Methods in Medicine, 2022*. Doi: 10.1155/2022/7656451
- Savasan, A., Kaymakamzade, B., Gokbulut, N., Hincal, E., & Yoldascan, B. (2022). Sensitivity analysis of COVID-19 in Mediterranean Island. *CMES-Computer Modeling in Engineering & Sciences, 130(1)*, 133-148. Doi: 10.32604/cmes.2022.017815
- Sultanoglu, N., Gokbulut, N., Sanlidag, T., Hincal, E., Kaymakamzade, B., & Sayan, M. (2021). A Binomial Model Approach: Comparing the R0 Values of SARS-CoV-2 rRT-PCR Data from Laboratories across Northern Cyprus. *CMES-Computer Modeling in Engineering & Sciences, 128(2)*, 717-729. Doi: 10.32604/cmes.2021.016297

Publications in International Referred Journals (in Coverage of WOS and SCOPUS)

- Kaymakamzade, B., Hincal, E., Gokbulut, N., & Sanlidag, T. (2022). Analyzing the Relationship Between Covid-19 and Proportions of Vaccine & Mobility: Effect of Vaccine and Mobility on Covid-19. *Decision Analysis Applied to the Field of Environmental Health,* 65-76. Doi: 10.1007/978-3-030-96682-9_8
- Gokbulut, N., Sultanoglu, N., Sanlidag, T., Sayan, M., & Hincal, E. (2022). Reliability of Covid-19 PCR Test Results with Statistical Distributions.

Decision Analysis Applied to the Field of Environmental Health, 107-112. Doi: 10.1007/978-3-030-96682-9_12

- Kaymakamzade, B., Hincal, E., & Gokbulut, N. (2022). Importance of Carrying Capacity While Fighting with COVID-19. *Decision Analysis Applied to the Field of Environmental Health,* 77-88. Doi: 10.1007/978-3-030-96682-9_9
- Hincal, E., Kaymakamzade, B., Suren, F. N., & Gokbulut, N. (2021). Estimating Covid-19 deaths by using binomial model. *AIP conference proceedings, 2321(1)*. Doi: 10.1063/5.0040303
- Muhammad, S. M., Hincal, E., Kaymakamzade, B., & Gokbulut, N. (2021). Sensitivity analysis on the SEIR-SEI model for the dynamics of blinding trachoma. *AIP conference proceedings, 2325(1)*. Doi: 10.1063/5.0040299
- Hincal, E., Kaymakamzade, B., Mustapha, U. T., Muhammad, S. M., & Gokbulut, N. (2021). Mathematical modelling of HIV infection with the effect of horizontal and vertical transmissions. *AIP conference proceedings, 2325(1)*. Doi: 10.1063/5.0040304
- Hincal, E., Alsaadi, S. H., & Gokbulut, N. (2021). Existence and uniqueness of solution of fractional order Covid-19 model. *AIP conference proceedings, 2325(1)*. Doi: 10.1063/5.0040302
- Kaymakamzade, B., Hincal, E., Mustapha, U. T., & Gokbulut, N. (2021). Effective reproduction number for North Cyprus fighting Covid-19. *AIP conference proceedings, 2325(1)*. Doi: 10.1063/5.0040307
- Gokbulut, N., Kaymakamzade, B., Sanlidag, T., & Hincal, E. (2021). Mathematical modelling of Covid-19 with the effect of vaccine. *AIP conference proceedings, 2325(1)*. Doi: 10.1063/5.0040301
- Mustapha, U. T., Hincal, E., Yusuf, A., Qureshi, S., Sanlidag, T., Muhammad, S. M., Kaymakamzade, B., & Gokbulut, N. (2021). Transmission dynamics and control strategies of Covid-19: a modelling study. *Bulletin of the Karaganda University,* 92-105. Doi: 10.31489/2021M2/92-105
- Mustapha, U. T., Sanlidag, T., Hincal, E., Kaymakamzade, B., Muhammad, S. M., & Gokbulut, N. (2021). Modelling the effect of horizontal and vertical transmissions of HIV infection with efficient control strategies.

Bulletin of the Karaganda University, 106-114. Doi: 10.31489/2021M2/106-114

- Hincal, E., Kaymakamzade, B., & Gokbulut, N. (2021). Humidity level on Covid-19 with control strategies. *International Journal of Applied Mathematics, 34(4),* 795. Doi: 10.12732/ijam.v34i4.14
- Hincal, E., Kaymakamzade, B., & Gokbulut, N. (2021). Basic reproduction number and effective reproduction number for North Cyprus for fighting Covid-19. *Bulletin of the Karaganda University, 99(3),* 86-95. Doi: 10.31489/2020M3/86-95

Publications in National Referred Journals

- Gokbulut, N., Amilo, D., & Kaymakamzade, B. (2021). Fractional SVIR model for COVID-19 under Caputo derivative. *Journal of Biometry Studies, 1(2)*, 58-64. Doi: 10.29329/JofBS.2021.349.04

Theses

Masters

- Gokbulut, N. (2021). *Mathematical and Statistical Modelling of COVID-19*. Master Thesis, Near East University, Department of Mathematics, Nicosia, Cyprus.

Courses Given

Undergraduate:

Year	Semester	Course Name
2019-2020	Fall	İşletme ve Ekonomi için Matematik II
		Cebir I
		Analysis I
		Abstract Mathematics I
		Algebra I
	Spring	İşletme ve Ekonomi için Matematik II
		Temel Matematik
		Fundamentals of Mathematics
		Cebir II
		Analiz II

		Differential Equations II
2020-2021	Fall	Analiz III
		Analitik Geometri I
		Matematiğin Temelleri
		İşletme ve Ekonomi için Matematik I
		İşletme ve Ekonomi için Matematik II
		Analytic Geometry I
		Abstract Mathematics I
		Basics of Mathematics
	Spring	İşletme ve Ekonomi için Matematik I
		İşletme ve Ekonomi için Matematik II
		Analitik Geometri II
		Temel Matematik
		Cebir II
		Differential Equations II
		Analysis II
2021-2022	Fall	Cebir I
		Analitik Geometri I
		Analiz III
		İşletme ve Ekonomi için Matematik II
		Temel Matematik
		Analytic Geometry I
	Spring	Analiz II
		Cebir II
		Analitik Geometri II
		Abstract Mathematics II
		Differential Equations II
		Real Analysis
2022-2023	Fall	Analitik Geometri I
		İşletme ve Ekonomi için Matematik II
		Analiz III
		Abstract Mathematics I
		Vector Analysis

		Number Theory
		Real Analysis
	Spring	Analiz II
		Soyut Matematik II
		Analitik Geometri II
		Temel Matematik
		Abstract Mathematics II
		Analytic Geometry II
		Fundamentals of Mathematics