DELAY MODEL OF TUMOR-IMMUNE SYSTEM INTERACTIONS WITH HYPERTHERMIA TREATMENT

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DEDICATION

This thesis is dedicated to my beloved late parents Alh. Abdulkareem Adisa and Alh. Habeebat Abdulkareem. It was their wish that I like other children grow in knowledge and wisdom for the benefit of mankind and to the glory of Almighty Allah (SWT). Also to my Wife Alh. Aminat Ibrahim and my children Habeebat, Sumayya, and Habeeb, whose encouragements served as propellers against reluctance encountered.

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ABSTRACT

The interaction of the tumor-immune system was initially based on the immunosurveillance hypothesis that immune cells can identify and kill tumor cells, leading to the use of a prey-predatory model for the description of tumor-immune cell interactions. However, the current biomedical findings reveal a pathway to immunoediting, which hypothesizes the ability of tumors to inhibit, seal, and counteract effector cells. Contrary to the discovery of non-oscillating dynamic biomedicine in solid tumors, existing models show oscillating solutions. Thus, the formulation of an immunoediting model that corresponds to the interaction of the tumor-immune system is sacrosanct in the search for effective malignant tumor treatment. The research suggests an immunoediting delay model of tumor-immune system interactions that combine tumor-immune cytokines derived from tumors to counteract effector cells. Qualitative analysis of this model gives an idea of the conditions for the stability of non-aggressive (benign) tumors and the instability of aggressive (malignant) tumors. The numerical results for these two conditions do not indicate an oscillating solution. Although the elimination of tumors is seen in the case of non-aggressive tumors, the suppression of effector cells and uncontrolled growth of tumors characterize the results for aggressive tumors. To find the best treatment, a sensitivity analysis is performed to ensure the role of the model parameters in the development of the tumor. The analysis reveals the best treatment options to kill tumor cells and strengthen the performance of immune cells. The sensitivity analysis results inform the merger of hyperthermia treatments in the proposed model to investigate the effects of thermal induction on immune cell performance and tumor regression. Discrete-time delays were used to investigate whether hyperthermia treatment was safe for patients who had received other treatments, but no cure occurred. The global stability of hyperthermia treatment is obtained using the Lyapunov function. Furthermore, an optimal heat control strategy for treating malignant tumor hyperthermia is obtained to minimize the effect of heat on normal cells while ensuring the elimination of malignant tumors. This research establishes a unique thermal optimal solution that improves the performance of the effector cell without difficulty.

ABSTRAK

Interaksi sistem imun-tumor pada mulanya berdasarkan hipotesis pengawasan imun bahawa sel-sel imun dapat mengenal pasti dan membunuh sel-sel tumor, yang membawa kepada penggunaan model pemangsa-mangsa untuk gambaran interaksi sel imun-tumor. Walau bagaimanapun, penemuan bioperubatan semasa mendedahkan laluan kepada imunoediting yang membuat hipotesis keupayaan tumor untuk menghalang, mengelak dan juga mengatasi sel-sel efektor. Bertentangan dengan penemuan bioperubatan dinamik bukan berayun dalam tumor pepejal, model sedia ada menunjukkan penyelesaian berayun. Oleh itu, perumusan model imunoediting yang sesuai dengan interaksi sistem imun-tumor adalah sangat penting dalam mencari rawatan tumor malignan yang berkesan. Penyelidikan ini mencadangkan model lengah imunoediting interaksi sistem imun-tumor yang menggabungkan sitokin yang berasal dari tumor untuk mengatasi sel-sel efektor. Analisis kualitatif model ini memberikan gambaran tentang syarat untuk kestabilan tumor bukan agresif (benigna) dan ketidakstabilan tumor agresif (malignan). Keputusan berangka untuk kedua-dua syarat ini tidak menunjukkan penyelesaian berayun. Walaupun penghapusan tumor dilihat dalam kes tumor yang tidak agresif, supresi sel efektor dari terus tumbuh dan pertumbuhan tumor yang tidak terkawal mencirikan keputusan untuk tumor agresif. Untuk mencari rawatan terbaik, analisis kepekaan dilakukan untuk memastikan peranan parameter model dalam perkembangan tumor. Analisis mendedahkan pilihan rawatan terbaik untuk membunuh sel-sel tumor dan menguatkan prestasi sel-sel imun. Hasil analisis sensitiviti memaklumkan penggabungan rawatan hipertermia dalam model yang dicadangkan untuk menyiasat kesan induksi haba terhadap prestasi sel imun dan regresi tumor. Lengahan masa-diskret digunakan untuk menyiasat samada rawatan hipertermia selamat bagi pesakit yang telah menerima rawatan lain tetapi tiada kesembuhan berlaku. Kestabilan global rawatan hipertermia diperoleh menggunakan fungsi Lyapunov. Tambahan pula, strategi kawalan optimum haba untuk rawatan hipertermia tumor malignan diperoleh untuk meminimumkan kesan haba pada sel-sel normal dan juga memastikan penghapusan tumor malignan. Penyelidikan ini mewujudkan penyelesaian optimum terma unik yang meningkatkan prestasi sel efektor tanpa kesukaran.

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LIST OF ABBREVIATIONS

IL-10	-	Interleukin-10
DNA	-	Deoxyribonucleic Acid
DC	-	Dendritic Cells
NK	-	Natural Kille
$CD4^+$	-	Helper T-Cells
$CD8^+$	-	Cytotoxic T-Cells
TGF-β	-	Transforming Growth Factor-beta
Ig	-	Immunooglobulin
TCR	-	T-Cell Receptor
MHC	-	Major Histocompatibility Complex
KDV	-	Korteweg-de Vries
SSE	-	Sum of the Square Error
ODE	-	Ordinary Differential Equation
API	-	Applicaion Programming Interface
DDE	-	Delay Differential Equation
DSB	-	Double-Stranded Breaks
BER	-	Base Excision Repair
MMR	-	Mis-Match Repair
NER	-	Nucleotide Excision Repair
TLS	-	Translesion Synthesis
NHEJ	-	Non-Homologous End Joining
HR	-	Homologous Recombinatio
T-Regs	-	Regulatory T- Cells
mAB	-	Monoclonal Anti-Body
MDSCs	-	Myeloid-Derived Suppressor Cells

LIST OF SYMBOLS

α	-	Proliferation rate of the effector cell
β	-	Surveillance rate of the effector cells against tumor cells
θ	-	Apoptosis rate of the effector cells
γ	-	Counterattack rate of tumor cells against effector cells
ϑ	-	Death rate of the tumor cells
υ_1	-	differentiation rate of the effector cells to suppressive
υ_2	-	Elaboration rate of suppression cells by tumors
υ_3	-	Suppression rate of the effector cells by suppressive T-cells
υ_4	-	Rate at which suppressive cells aid tumors' progression
Υ	-	Death rate of suppressive cells
σ	-	Thermal application rate
Φ	-	Thermal control rate
τ_1	-	Delay in suppression of effector cells
τ_2	-	Delay in tumors derivation of counterattack mechanism
τ_3	-	Delay in the Tumor Elaboration of Suppressive Cells
τ_4	-	Delay in the differentiation of effector cells to Suppressive
ω_1	-	Rate at which heat boost immune cells performance
ω_2	-	Tumors shrinking rate due to heat induction
ω_3	-	Rate at which heat reduces suppressive cells
$\mathsf{J}(\bar{\mathsf{H}})$	-	Objection Function
F	-	Hamiltonian Function
$\bar{\mathsf{H}}$	-	Optimal Control
λ_E	-	Hyperthermia Effect on Effectors Cells
λ_T	-	Hyperthermia Effect on Tumors
λ_S	-	Hyperthermia Effect on Suppressive Cells
λ	-	Root of characteristics Equations

∂	-	Resulting Displacement from the steady point
J_0	-	Jacobean with respect to time t
J_n	-	Jacobean with respect to the corresponding delay-n τ_n
I	-	Th Identity Matrix

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CHAPTER 1

INTRODUCTION

1.1 Introduction

The immune system protection against tumor cells is previously viewed on the hypothesis of immunosurveillance, where immune cells use both specific and non-specific attacks to recognize and eliminate tumors. Recently, biomedical evidence suggests that the immune system interactions with tumors may brew the alteration of immune-cells composition making it less immunogenic variant and facilitating tumors escape [2, 3, 4, 5, 6, 7, 8, 9]. These alterations are mostly through suppressive T-cells Interleukin-10 (IL-10) and/or Transforming growth factor-beta (TGF-β) produce by both the tumor and regulatory T-cells [10, 11, 12, 13].

Interactions between the immune system and tumors occur through complex events that usually climax either in successful tumor eradication or immune evasion [14]. The ability of tumors to counterattack effector cells in the tumor's micro-environment using tumor-derived cytokines has equally been revealed recently [15]. Tumors' escape occurs due to the secretion of inhibitory mechanisms by the tumor to impair antigen presentation, activate negative costimulatory signals, and elaborate immunosuppression [2, 8, 6, 16, 17, 5, 7, 4, 9].

Many therapeutic options such as chemotherapy, radiotherapy, and surgery have been used to eliminate malignant tumors. However, these therapeutic options come with certain side effects which necessitated the search for improved therapeutic options for tumor elimination. Recent findings hint that malignant tumors evolve from the growth of mutated cells which require more energy to survive than normal cells, and the body's blood vessels are unable to match the oxygen and nutrient needs of malignant tumors. This phenomenon resulted in the stimulation of additional blood vessels which are chaotic in structure compared with normal cells. The insufficiency of oxygen makes

the tumor environment hypoxic and perfusion makes it sufficiently difficult to kill the malignant tumor with ionizing radiation or chemotherapy [18].

Hyperthermia takes advantage of oxygen deficiency and irregular perfusion in tumors' micro-environment to damage the plasma, the skeleton, and the nucleus of malignant cells [19]. The promising effect of heat-inductions in the revival of the suppressed effector cells and direct killing of tumors' cells are acknowledged in [20, 21, 22, 18, 23, 24, 25, 26]. The induction of the heat shock proteins (HSP) ensures thermo-tolerance from further heating and subsequent thermal treatments [27, 28, 29, 30]. These inspire continuous research interests in the adoption of hyperthermia treatment for malignant tumors.

One of the most critical and challenging demands in immunology and oncology is the understanding of how the immune system affects tumors' development and progression. In response to these phenomenological dynamics of tumor-immune system interaction, mathematical researchers use mathematical modeling to gain insight into the dynamics and complexities involved in the interaction of the tumor-immune cells. The introduction of continuously incoming experimental observations and clinical findings is usually done by the researchers. This, subsequently led to the adoption and modification of both the prey-predator and the competitive model for tumor-immune system interaction as in [31, 32, 33, 34, 35, 36]. The need for a sufficiently simple mathematical model which describes the tumor growth dynamics under angiogenic inhibition and as well manageable for both real-life applicability and controller design was recommended in [37, 38].

1.2 Motivation

On yearly basis, nearly 10 million deaths are caused by malignant tumors (cancer) and cancer treatments cost over 100 billion U.S. dollars annually. It is projected that by 2040 cancer cases might have risen to 30 million with over 16 million cancer-related cases. The inability to predict malignant tumor (cancer) therapeutics' efficacy and patient response, feasibly endangers the livelihood of people globally.

Cancer trends had prompted much mathematical research works on tumor-immune system interaction including the incorporation of various therapeutics as well as time delay to model biological processes involved in tumor-immune system dynamics. While existing models for tumor-immune cell interactions demonstrate oscillatory dynamics contrary to the immunoediting hypothesis, models with therapies have equally not yielded the expected results in tumor clearance. Therefore, retooling the existing models for more biological conformity will help in identifying the best treatment options for malignant tumors.

Tumors' hypoxic environment and perfusion make killing malignant tumors sufficiently difficult with ionizing radiation or chemotherapy [39]. Recently, findings suggest hyperthermia exploits oxygen inadequacy and abnormal perfusion in tumors' micro-environment to damage malignant tumors' cells and activate an immune response. However, there are concerns on the post-treatment condition of the patient(s) as well as the required thermal dose to avert adversity.

Despite the promising effect of hyperthermia treatment in the direct killing of tumor cells and enhancement of suppressed cells' restoration, there are concerns about the post-treatment condition of the patient(s) as well as the required thermal dose to avert adversity. Therefore, investigating the dynamics of tumor-induced immune suppression with hyperthermia treatment and thermal optimal control strategy to avert adversity mathematically will contribute in great measure to the effective and efficient application of hyperthermia treatments.

1.3 Research Background

Tumor-immune system interaction had passed through some eras, and each of these eras enriches the understanding of the complex dynamics of tumor-immune cells' interaction. The foremost era is with the concept that the immune system can recognize and eliminate nascent malignant cells, originally embodies in the cancer immunosurveillance hypothesis. While the latest era is immunoediting, which illustrates the process responsible for both the elimination and the sculpting of the

immunogenic phenotype of tumors that eventually formed in an immunocompetent host. Tumors and the immune cells interaction as captured in immunoediting theory putting all the unified pictures proffer a notion that tumors cells and immune system interaction is complex and not simply a one-way path [40].

Recently, emerging biomedical shreds of evidence suggest that immune system interaction with tumors may brew the alteration of immune-cells composition making it less immunogenic variant and facilitating tumor growth and immune evasion [2, 3, 4, 5, 6, 7, 8, 9]. These alterations are mostly through suppressive T-cells Interleukin-10 (IL-10) and/or Transforming growth factor-beta (TGF-β) produced by both the tumor and regulatory T-cells [10, 11, 12, 13]. The ability of the tumor to counterattack effector cells in the tumor micro-environment using tumor-derived macrophages/cytokines has equally been revealed in experimental studies recently [15, 41].

Mathematical researchers have used the non-linear dynamical system of both prey-predator and competitive models to suggest different mathematical models in describing the phenomenological dynamics of tumor-immune system interaction. A competitive model to describe the binding and/or detaching of effector cells and tumor cells without damaging cells was proposed in [34], and steady states were obtained for the sneaking through and dormancy state of tumors. Gallach in [42] simplified and modified the work of Kuznetsov [34] by making the immune cells aggressive which modified Kuznetsov [34] work to a prey-predator model.

Many researchers like [36, 31, 43, 44] among others had used the concept of prey-predator to model tumor-immune interactions with little or no distinctions among the variable of their models. Prominently reported in their findings is the existence of periodic solutions and oscillatory dynamics. The presence of periodic solution suggests that the model did not account for the total elimination or escape of the tumor. Kuznetsov et al [45] in the buildup of their model while defining the kinetic constant k_1 "for binding the effector cells and tumor cells without damaging the cells" highlights the non-aggressiveness of their model. The Dulac Bendixson criteria revealed in their model the nonexistence of limit cycles or homoclinic connection in the model.

The introduction of time delay in modeling the biological process in tumor-immune system interaction has attracted more contributions in recent times. Gallach in [42] introduced delay acting on the nonlinear term of a prey-predator-like model to capture the time needed by immune cells to develop a suitable response after the recognition of non-self-cells. Yafia in [46] extended the work of Gallach [42] to study a non-aggressive immune system. A hybrid of prey-predator and competitive model was used by Barnerjee et al in [47] to model the process taken for a resting immune cell to convert to hunting by introducing one delay to the nonlinear term of their model.

Alberto et al in [48] introduced delay to simulate the effect of tumors on immune cells proliferation, the process of proliferation of tumors, and the response of the immune system to the tumor. Bi et al in [49], building on the premises of d'Onforio work [36] added two delays to the linear terms of both tumor and effector domains. A competitive model with two delays was proposed by Khajanchi et al in [50]. They showed analytically that the singular point associated with the co-existence of the three cell populations loses its stability via a Hopf bifurcation.

It is noteworthy that, both the prey-predator and competitive models had not successfully accounted for the elimination or escape of tumors as well as immune suppression as recorded in biomedical findings. The results of these models demonstrate oscillatory dynamics. This indeed contradicts immunoediting hypotheses and is also at variance to the biological realities as oscillatory dynamics are unaware of in solid tumors [51]. The introduction of delay to both prey-predator and competitive models had not effected change in the behaviors of these models as the solution obtained in models without delay remains unchanged with the model with delay.

1.4 Statement of the Problem

A huge responsibility is expected from mathematicians in understanding the scourge of tumors. However, there is a gap between the results of the existing mathematical models and the biological hypotheses. The existing mathematical models demonstrate oscillatory dynamics contrary to immunoediting hypotheses of

possible elimination or escape of tumors. Prominently missing in these models is tumors' counterattack capacity against effector cells which brews immune suppression, inhibition of effector cells by suppressive T-cell, and uncontrollable growth of tumors. Also, time delay has not been employed in studying the process leading to effector cells' suppression or as a control in the dynamics of tumor-immune cell interactions.

Biological literature had suggested immunosuppression as a reason for immune evasion and many therapy options were employed to complement the treatment of clinical cases such as immunotherapy, radiotherapy, and chemotherapy. In response to this, mathematical modelers incorporated chemotherapy to study the impact of different therapies on the dynamics of tumor-immune system interactions.

Recent studies had demonstrated an increase in immunological attacks against tumors after heat induction, which was believed to be achieved through the activation of heat shock proteins (HSPs) and subsequent modulation of the innate and adaptive immune responses against tumor cells. However, the anti-tumor efficacy of hyperthermia alone and its effect on normal cells have not been exploited mathematically. In light of these, the need to develop an immunoediting conformed non-oscillatory model of tumor-immune system interaction with delay and incorporation of hyperthermia treatment in the such model will further address the limitations observed in existing models. The followings are the research questions based on the aforesaid challenges.

1. How would an immunoediting conformed delay model of the tumor-immune system interaction capturing tumor counterattack and inducement of immune suppression by tumors be formulated and analyzed?
2. Would there be an identified best treatment option for tumors' elimination and restoration of suppressed immune cells from such a model?
3. How would hyperthermia incorporation in such a model enhances the anti-tumor efficacy of the suppressed immune cells and as well contribute to the direct killing of tumors?
4. Would hyperthermia treatment of tumors be safe for patients who had received other treatments?

5. Would hyperthermia treatment ensure the global stability of malignant tumors without causing adverse effects on the normal cells due to thermal overdose?

1.5 Objectives of Study

This research aims at developing an immunoediting conformed delay model for tumor-immune system interaction. It also aims at studying the efficacy of hyperthermia in the treatment of malignant tumors. Thus, the followings are the research objectives:

1. To develop and analyze an immunoediting conformed delay model of tumor-immune system interaction.
2. To perform sensitivity analyses on the parameters of the proposed model so as to identify the best treatment option for the restoration of suppressed effector cells and the elimination of tumors.
3. To incorporate hyperthermia into the delay model for possible restoration of suppressed immune cells and direct killing of tumors.
4. To determine if hyperthermia is safe for tumors patience who had received other treatments using a discrete time delay.
5. To determine the global stability condition for hyperthermia treatment of malignant tumors and obtain thermal optimal control to avert adversity on the normal cells.

1.6 Research Scope

An immunoediting conformed delay model of the tumor-immune system would be developed to examine the tumors' counterattack mechanism against effector cells, the role of suppressive T-cells in tumors' uncontrollable growth and effectors cells' suppression, and the elaboration of suppressive T-cells by the tumor. The stability conditions leading to the emergence of the benignant and the malignant will be derived. For the purpose of identifying the best treatment option for the treatment of malignant

tumors and the restoration of suppressed immune cells, the roles of the model parameters in tumors' progression and immune cells' suppression are investigated using sensitivity analysis.

The model will be modified by incorporating hyperthermia treatment to investigate the efficacy of the hyperthermia treatment in the direct killing of tumor cells and thermal enhancement of immune cells' performance. In order to gain insight into the effect of previous treatment control on the hyperthermia treatment of tumors, bifurcation analyses will be performed to determine if there exists the occurrence of a stability switch. The post-hyperthermia treatment conditions of malignant tumors patience will also be assessed and the condition for their global stability will be determined using the Lyapunov function.

Furthermore, the thermal optimal control strategy that will guarantee the complete elimination of tumors without causing an adverse effect on the normal cells will be searched by using the Optimal control theory. A combination of biologically relevant parameter values will be used in the simulation of the model in Matlab using DDE23 and Biftool.

1.7 Significance of the Study

In previous studies, mathematical models were used to study dynamics involve in the tumor-immune system interactions. The biological process involved in the interaction has been modeled by discrete time delays and different therapeutics have been incorporated as well to gain insight into their efficacy. However, the immune suppression and uncontrollable growth of tumors had not been demonstrated by these models as oscillatory dynamics are usual in their demonstrations. While the incorporation of time delays has not brought about any change in the dynamics, the incorporation of different therapeutics also has not brought about the total elimination of tumors.

This study proposes an immunoediting conformed delay model of tumor-immune system interactions. The proposed model will incorporate the ability of tumors to counterattack effector cells in the tumors' micro-environment using tumor-derived cytokines as revealed recently in [15, 41] as well as the role of suppressive T-cells in effector cells' suppression and tumors' uncontrollable growth. This will allow sensitivity analysis to be carried out and thus help in identifying the best treatment option for the restoration of suppressed effector cells and the elimination of tumors. Also, Hyperthermia treatment will be incorporated into the proposed model to reduce tumor cell concentration, improve effector cells performance and control suppressive T-cells.

Discrete-time delays are used to model the previous treatment experience of the patient. The global effect of hyperthermia treatment on patients and thermal dosage will be determined to avert adversity. This work, when completed, would offer among other benefits, the followings:

1. Provide a new direction in modeling tumor-immune system interaction with much conformity to immunoediting hypotheses.
2. Enrich more, clinical knowledge on the management of malignant tumors.
3. Indicate the best treatment option for the elimination of malignant tumors and the enhancement of immune cell performance.
4. Provide a framework for the incorporation of hyperthermia in the treatment of malignant tumors.
5. Provide insight into the thermal dosage and the control required for effective hyperthermia treatment of malignant tumors without causing an adverse effect on the normal cells.
6. Provide a basis for future researchers to explore.

1.8 Research Methodology

The research starts with an extensive review of both biological and mathematical works on tumor-immune cell interaction so as to comprehend the dynamics of the interaction. The reviews of these works suggest that solutions of various mathematical models of tumor-immune cells are variants of the biological hypothesis of tumor-immune cell interactions. While biological hypothesis hints at the likelihood of tumors' elimination or evasion, solutions of various mathematical models exhibit oscillatory dynamics which is not aware of in the case of solid tumors [51]. Owing to this, there is a need for a retooled mathematical model with much more biological conformity.

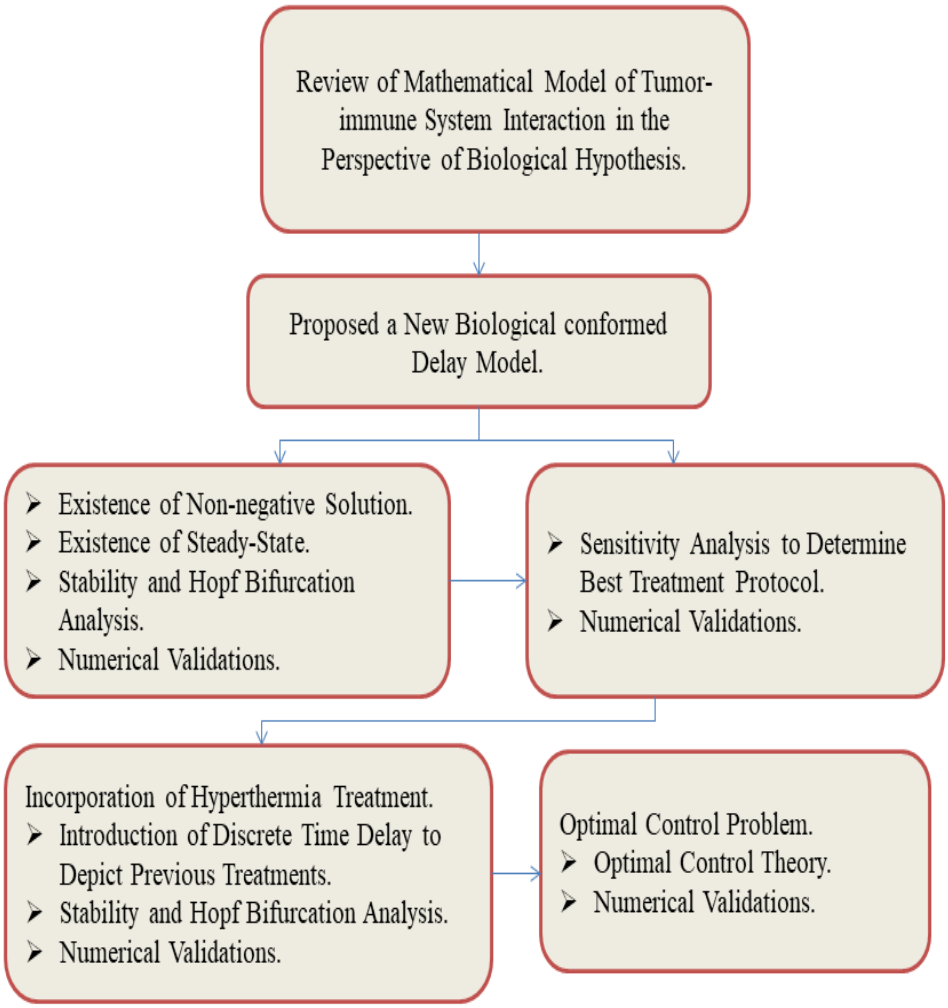

Figure 1.1 Research Methodology

Hence, the formulation and analysis of a delay model of tumor-immune system interaction with conformity to the immunoediting hypothesis. This is done by incorporating the novel tumors' capacity to derive cytokines for counterattacking against effector cells while the role of TGF-β in tumors' progression and effector cells is retained in the model proposed in [52]. Then, the stability analysis of biologically relevant steady-states is carried out, and to obtain possible optimum treatment protocol for tumors, sensitivity analysis is performed to determine the role of model parameters in both the tumor progression and effector cell suppression.

This research further incorporates hyperthermia treatment based on sensitivity analysis and the discrete-time delay is used to model control in immune modulation due to other treatments' experience. In addition, this research also allays the fear of excessive heating which might lead to adversity by formulating thermal optimal control to minimize heat induction during hyperthermia treatment of tumors. The numerical implementation and validation are done at every stage of this research work using a Matlab environment with $dde23$ and bif_tool routine using relevant biological parameter values obtained from the literature. The research methodology is thus summarized in Figure 1.1.

1.9 Thesis Outline

This thesis comprises six chapters, a reference list, and an appendix. This current chapter assesses the existing mathematical models in the context of biological realities of immunoediting hypotheses. Findings in this current chapter established that the existing models demonstrate oscillatory dynamics contrary to biological hypotheses of possible tumor elimination or escape. The gap between biomedical findings and the existing models is highlighted, which formed the motivation for this research. The remaining sections respectively gave in a detailed statement of the problem, the objectives, the scope, the significance of the study, the research methodology, and the thesis outline.

Chapter 2 provides a relevant literature review on tumor-immune system interactions and its mathematical models' works. The biomedical background of tumor and immune system interaction was reviewed to assess the biological likelihood of tumor-immune system interaction outcome. It also put existing mathematical models including the delay model of tumor and immune system into focus and assessed their conformity with biomedical findings. Also, mathematical models with various therapeutics were reviewed in light of the incorporated therapeutics efficacy in both tumor elimination and immunotherapy. These revealed that existing models yield periodic or oscillatory solutions and have not accounted for the possible elimination or escape of tumors as recorded in most of the biomedical findings. The incorporation of delays in these models has not equally shown any effect on the behaviors of the existing models.

Additionally in Chapter 2, malignant tumors therapeutics such as chemotherapy, radiotherapy, surgery, and hyperthermia are reviewed biologically to understand their mechanism, efficacy, side effect, and success rate in malignant tumors' treatment. It was revealed that the tumor was hypoxic and perfusion makes it sufficiently difficult for ionizing radiation or chemotherapy to kill the malignant tumor asides from the side effects. A review of Hyperthermia treatment conveys heat-induced tumor death and an increase in immunological attacks against tumors after heat induction. The increase in immunological attacks is believed to be achieved through the activation of heat shock protein HSPs and subsequent modulation of the innate and adaptive immune responses against tumor cells. The need for improved applications of hyperthermia such as heat-controlled gene therapy or heat-enhanced immunotherapy also manifests in Chapter 2. Consequently, this research work aims to develop a non-oscillatory delay model for tumor-immune system interactions with hyperthermia treatment. The contributions of this research are captured in the succeeding chapters.

Chapter 3 proposes the delay model for tumor, effector cells, and TGF-β interaction with the incorporation of the novel tumor-derived cytokines for counterattacking effector cells as revealed in [15, 41] among others. Since most tumor patients have/are undergone/undergoing one form of treatment or the other to control tumor progression, discrete time delays are used to model treatments' control against

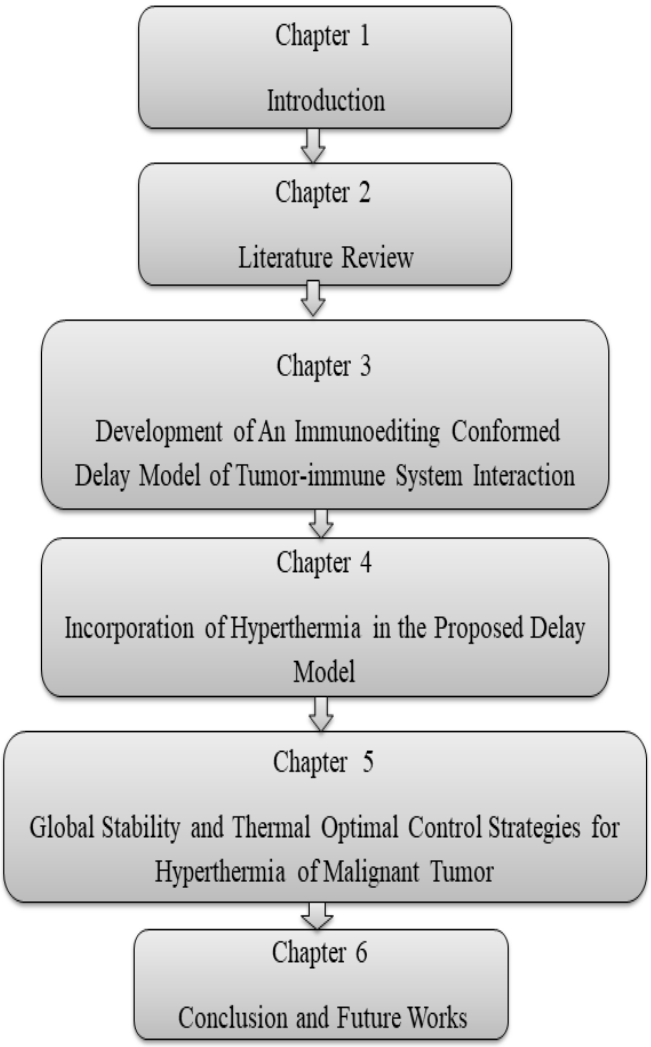

Figure 1.2 Thesis Organization

immune suppression in the dynamics of the interactions. The stability analyses of the model are carried out to obtain the condition for stability or otherwise. In order to obtain a treatment protocol for the treatment of malignant tumors and the restoration of tumor-induced immune suppression, a sensitivity analysis of the model parameters is performed. The numerical simulations are obtained to support the analytical results.

Chapter 4 incorporates hyperthermia treatment into the delay model of tumor-induced immune suppression to study the impact of heat induction on tumor cells as well as the amplifying effect of heat in enhancing effector cells' performance. Discrete-time delay is used to model the control of tumors' counterattack against effector cells, elaboration of suppressive T-cells by tumors, and differentiation of effector cells to

suppressive T-cells due to previous treatments. Also, the longtime behaviors of steady-states through stability and bifurcation analyses are obtained.

Chapter 5 addresses the concern associated with the post-treatment condition of the patient(s) and the fear of the adverse effect of heat on normal cells. In light of these concerns, the global stability of the proposed model with hyperthermia treatment is investigated and a thermal optimal control strategy is developed for the usage of hyperthermia in the treatment of malignant tumor patients.

Chapter 6 contains the summary of the research findings and conclusions derived based on the objectives of the research as contained in Chapters 3, 4, and 5. Also, in this chapter, are suggestions for future research work(s).

1.10 Summary

This chapter starts with an introduction to the evolution of tumors and their clinical implications. Section 1.2, highlights the motivation for this research. Section 1.3 details mathematical efforts toward understanding the dynamics of tumor-immune system interactions. In Section 1.4, the findings of most existing mathematical works on tumor-immune system interaction are assessed in the context of biological realities and research problems are highlighted. Research objectives were captured in Section 1.5. The remaining sections are the scope of the study, the significance of the study, the research methodology, and the thesis outline.

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LIST OF PUBLICATIONS

Journal with Impact Factor

1. Abdulkareem Afolabi Ibrahim, Normah Maan (2019). A Dual-Aggressive Model of Tumor-Immune System Interactions. Int. Journal of Online and Biomdical Engineering, Vol.15 (10) 2626-8493. https://doi.org/10.3991/ijoe.v15i10.10877.

2. Abdulkareem Afolabi Ibrahim, Normah Maan & Khairunadwa Jemon (2020). Stability and Sensitivity Analysis of Tumor-induce imuune Suppression With Time Delay. Journal of Advanced Research in Dynamical & Control Systems. 12(07). Special Issue 2020. https://doi.org/10.5373/JARDS/V12SP7/20202232. (0.316)

3. Abdulkareem Afolabi Ibrahim, Normah Maan, Khairunadwa Jemon & Afeez Abidemi (2022). Global Stability and Thermal Optimal Control Strategies for Hyperthermia Treatment of Malignant Tumor. Mathematics, 10(13), 2188; https://doi.org/10.3390/math10132188. (2.542 Q1)

4. Abdulkareem Afolabi Ibrahim, Normah Maan, Khairunadwa Jemon & Afeez Abidemi. Delay Model of Tumor-Induced Immune Suppression with Hyperthermia Treatment. Submitted to Discrete and Continuous Dynamical Systems Series B (DCDS-B 220408-Maan).