TUMOUR GROWTH MODEL OF CANCER SELF-REMISSION WITH HASSELL-VARLEY FUNCTIONAL RESPONSE

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This work is humbly dedicated to my all valuable treasures in life;

Bapak, Mak and Ah Kee.

Thanks for your endless support!
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In the name of Allah, The Most Gracious, Most Merciful. All praises and thank to Allah, finally, I finished this Master’s project.

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ABSTRACT

Predator-prey like models with functional responses such as Holling type I and II have been studied previously to model the interaction between tumour cells, hunting predator cells and resting predator cells. The aim of this study is to introduce another type of functional response which is Hassell-Varley into predator-prey interaction of tumour model of cancer self-remission. Dimensional analysis, stability analysis and bifurcation analysis are used to analyse the model. Under certain condition, our numerical analysis showed an existence of Hopf-bifurcation for some parameter ranges, which generate periodic solution.
ABSTRAK

Model pemangsa-mangsa dengan tindak balas berfungsi seperti Holling I dan II telah digunakan di dalam interaksi antara sel ketumbuhan, sel pemangsa memburu dan sel pemangsa yang tidak memburu. Matlamat kajian ini adalah untuk memperkenalkan tindak balas berfungsi yang lain iaitu Hassell-Varley ke dalam interaksi pemangsa mangsa tumbesaran ketumbuhan. Kaedah analisis dimensi, analisis kestabilan dan analisis bifurkasi telah digunakan untuk menganalisa pembaharuan sistem ini. Berdasarkan beberapa keperluan syarat, ia menunjukkan kehadiran bifurkasi Hopf di sepanjang siri lingkungan nombor dimana menghasilkan penyelesaian perulangan.
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<td>B</td>
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<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>$M(t)$</td>
<td>Tumour cells population, at time, $t$</td>
</tr>
<tr>
<td>$N(t)$</td>
<td>Hunting predator cells population, at time, $t$</td>
</tr>
<tr>
<td>$Z(t)$</td>
<td>Resting predator cells population, at time, $t$</td>
</tr>
<tr>
<td>$q$</td>
<td>The conversion rate of normal cell to malignant ones</td>
</tr>
<tr>
<td>$r$</td>
<td>The growth rate of tumour cells</td>
</tr>
<tr>
<td>$s$</td>
<td>The growth rate of the resting predator cells</td>
</tr>
<tr>
<td>$d_1$</td>
<td>The natural death rate of hunting cells</td>
</tr>
<tr>
<td>$d_2$</td>
<td>The natural death rate of resting cells</td>
</tr>
<tr>
<td>$k_1$</td>
<td>The maximum carrying capacity of tumour cells</td>
</tr>
<tr>
<td>$k_2$</td>
<td>The maximum carrying capacity of resting cells</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>The killing rate of the tumour cells by hunting cells</td>
</tr>
<tr>
<td>$\beta$</td>
<td>The conversion rate of resting cells to hunting cells</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Hassell-Varley constants for tumour cells population</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Hassell-Varley constants for hunting and resting predator cells population</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>The eigenvalues at each steady-state</td>
</tr>
<tr>
<td>$E_i$</td>
<td>The steady-state of tumour growth model without Hassell-Varley functional response, for $i = 1, 2, 3$</td>
</tr>
<tr>
<td>$F_i$</td>
<td>The steady-state of tumour growth model with Hassell-Varley functional response, for $i = 1, 2$</td>
</tr>
<tr>
<td>$f$</td>
<td>Functions for tumour growth without Hassell-Varley functional response</td>
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<td>$g$</td>
<td>Functions for tumour growth with Hassell-Varley functional response</td>
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<td>$t$</td>
<td>Time</td>
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CHAPTER 1

INTRODUCTION

1.1 Introduction

Over the last century, research in mathematical biology opens up a new challenging problem for mathematicians. The interplay between mathematics and biology has already produced intense successful collaboration that has emerged and developed rapidly. Yet, mathematical modeling bid another research tools proportionally with new powerful laboratory techniques have become increasingly abundant in this field. The mathematical models in this thesis will appoint to the theoretical descriptions of the biology systems that which may be useful for quantitative and qualitative understandings. To describe the interaction of the system, the proposed models are comprised into the ordinary differential equations.

A fundamental model is constructed as an introductory description of biological system, before a more complex mathematical model is provided. We analyze the stability of the model as well as the simple bifurcation behavior. When goes to medical field, specified in oncology, there are many factors which affect the dynamical properties biologically and mathematically of these phenomena. Hence, there are still many unanswered questions related to how the interaction between a growing tumour cell and healthy cell besides the immune system.
1.2 Preliminary of Study

At first glance, we need to know the basic view of tumour and its characteristics as well their common types. Besides, the biologically dynamic mechanism should be presented clearly with reliable model in real life even though still in misery investigation. We do believe that the growth of tumour mechanism may suit to predator-prey like-model. Its common to know that for every predation system lead to different types of interaction. The suitable functional response into the predation system might give crucial meaning about tumour behaviors. In order to investigate deeply the pattern of tumours, some assumption need to made based on previous facts about its remission.

1.2.1 Tumours and its characteristics

Our body is made up of trillions of microscopic cells. The cells grow and divide through time for body development. The reproduction of each cell regulated by the genes in its nucleus. This reproduction virtually reflex from a signals of the environment, their nutrients, an activation of the genes and from the induction of new cell responses. Unfortunately, uncontrolled growing cells and abnormal behavior can form a tumour. A tumour cell can be cancerous (malignant) or non-cancerous (benign). Our body normally creates cells only at the rate needed to replace those that die or to aid an individuals growth and development. The unregulated body control mechanism will trigger the growth of tumour. Obviously, this unregulated control can be seen by looking at its abnormal mass of tissues.

There are growth rate of tumour that can be assessed by sequential measurements of tumour cell and growth rate of the primary tumour throughout the period of the observation and the proliferation kinetics of tumour based on the measurement of the doubling time. The doubling times are significantly correlated with the histological type of tumours. Malaise et al. (1973) who generalized that the
development of a tumour is irreversible in the term of progression concept. A tumour often abruptly in growth rate, histological structure, invasiveness, or responsiveness to extraneous stimuli. For a clear observation, the differentiated term are used to describe of the appearance of the tumour or grading its characteristics. Well-differentiated, moderately-differentiated, poorly-differentiated and undifferentiated are the best descriptions in order to see the behavior of the tumour.

### 1.2.2 Benign and malignant tumours

Benign and malignant tumours are two types of tumours that have respective microscopic features such as resemble pattern (differentiated), growth rate, metastasis process and the invading process in the cells. Non-cancerous tumour cells (benign) grow only locally and cannot invading or undergo metastasis process in the body. A benign tumour is well-defined growth with smooth boundaries that simply grow in the diameter. It can be harmful if the tumour compresses the surrounding tissues against a hard surface in the body. At certain time, benign tumour will grow at relatively slow pace and may stop when it reaches its size. While, cancerous cells (malignant) invading neighboring tissues, enter blood vessels, metastasize, survive and grow in other parts of the body (Hejmadi, 2009). As cancer continue progressing, tissues that have become malignant continue to alter and become more malignant which will harm the normal functioning of organ in the body. A malignant tumour cell grow quite rapidly and it has irregular boundaries and invading the surrounding tissue rather than pressing it aside. This malignant can create another new tumour, shed the cells that travel through the blood vessels in the body. Worse, malignant could displace neighboring organs, causing pain and pressure symptoms. Briefly, Table 1.1 shows the comparison between benign and malignant tumour cell. Whereas, Figure 1.1 shows the benign and malignant tumour cells in a lining of the uterus.
Table 1.1: The comparison of benign and malignant tumour cells.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Moderately-differentiated</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Poorly-differentiated</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rate of growth</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Capsulation</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Does not happen</td>
<td>May be occur</td>
</tr>
<tr>
<td>Mode of growth</td>
<td>Not invade</td>
<td>Invade</td>
</tr>
</tbody>
</table>

Figure 1.1: The comparison of benign and malignant cancer cells in uterus lining (Munksgaard and Blaakaer, 2012).
1.2.3 Prey-predator like model

In natural world, no species can survive alone. While species compete with the other species for food or space or even predated by the other species. These species are compete, evolved and scatter often simply for the purpose of seeking resources to sustain their struggle for their very existence. The predator responses can be influenced by a number of environment variables other than prey abundances, including the characteristic (eg. size) of focal prey, the density and characteristics of the alternatives prey, predators and competitors, environmental factors that can influence predator physiology (eg. temperature) and the habitat architecture (eg. space). In the mid 1920s, Volterra and Lotka were among the pioneering studied on the interacting species by numerically which tense to non-trivial solution but search able mathematical problem (V. Volterra, 1926). The conservation of mass and the rate of the change in birth and death process still well grounded in until today and as attachable principles by many ecologists by T. Zhang and Liao (2016). The model concerned with the dynamic relations between two independent species acting as predator and prey, within an ecosystem. V. Volterra (1926) proposed for a classical model of predator-prey like model as a simple model for the predation of one species by another. If \( N(t) \) is the prey population and \( P(t) \) that of predator population at time, \( t \), the Volterra’s model is

\[
\frac{dN}{dt} = N(a - bP), \tag{1.1a}
\]

\[
\frac{dP}{dt} = P(cN - d), \tag{1.1b}
\]

where \( a, b, c \) and \( d \) are positive constants. One significant component of the predator-prey relationship is the predator’s rate of feeding upon prey. Several authors have used the concept of predator-prey type interactions in tumour studies (Kuznetsov et al., 1994; El-Gohary, 2008; Sarkar and Banerjee, 2005; Kirschner and Panetta, 1998). In tumour system, the prey is considered as the tumour cells and the predator
is the healthy cell which are in resting and hunting stages. Since then, there are numerous dynamic growth rate functions with applicability to tumour growth have been discussed. The Gompertz concept has been shown that the growth rate biologically regressive with its population size. Thus, it is applicable to observed tumour growth slow down with population size.

Figure 1.2: Schematics diagram of the regulation of tumour cell concentration (Sarkar and Banerjee, 2005).

Sarkar and Banerjee (2005) had provided a simpler framework of the interaction among the tumour cells and the healthy cells, where the construction is based on spontaneous tumour regression and progression system as predator-prey like model. The predator is natural killer cells in the immune system, where its has two states, hunting and resting. These natural killer will attacks, destroys or ingests the tumour cell as a prey. The natural killer engulfed tumour cells, eat them and release series of cytokines which activates the resting predator cells that triggered the counter attack. These resting cells cannot kill tumor cells, but they are converted to a special type of natural killer cells and begin to multiply and release other cytokines that continue to stimulate more resting cells. The alteration of hunting and resting cells
will cause in degradation of resting cells which undergoing natural growth and an
activation of hunting cells. In mathematical approaches, the following phenomenon
can be formulated in three equations of the system El-Gohary (2008), which are

$$ \frac{dM}{dt} = q + rM \left(1 - \frac{M}{k_1}\right) - \alpha MN, $$  
(1.2a)

$$ \frac{dN}{dt} = \beta NZ - d_1N, $$  
(1.2b)

$$ \frac{dZ}{dt} = sZ \left(1 - \frac{Z}{k_2}\right) - \beta NZ - d_2Z, $$  
(1.2c)

where $M(t)$, $N(t)$ and $Z(T)$ are the density tumour cells, hunting predator cells and
resting predator cell at time, $t$, respectively. $r$ is the growth rate of tumour cells,
$q$ is the conversion of normal cells to cancerous ones, $k_1$ is the maximum carrying
capacity of tumour cells, $k_2$ is the maximum carrying capacity of resting cells, $\alpha$ is
the rate of predation of tumour cells by the hunting cells, $\beta$ is the rate of conversion
of resting cell to hunting cells, $d_1$ is natural death of hunting cells, $d_2$ is the natural
death rate of resting cells and $s$ is the growth rate of the resting predator cells.

### 1.2.4 Hassell-Varley functional response

The functional response describes the relationship between per capita predator
consumption and prey density. The three main types functional response are Type
I (linear), Type II (decelerating) and Type III (sigmoid) Functional response is a
relationship between individual predator feeding rate and prey density (Holling,
1959a).

Functional response is a vital element in population interaction primarily for
 predator-prey like models. Other than Holling Types, there are many other pioneer
functional response such as Hassell-Varley, Crowley-Martin, Beddington-De Angelis
and Ivlev. The different type of predation drive to different type of interaction.
Apart from that, these functional responses resulted important changes in predation
system. Basically, the functional response Holling type II, $f(N, P) = \left(\frac{aN}{1 + bN}\right)$
describes the average feeding rate of a predator when the predators spends some times searching for prey. Parameters $a$ is \( \left( \text{Units: } \frac{1}{\text{time}} \right) \) describes the effects of capture rate and $b$ is \( \left( \text{Units: } \frac{1}{\text{prey}} \right) \) which describes a handling time. Both $a$ and $b$ are positive constants. It is a description of a predator’s instantaneous, per capita feeding rate, $f$ as a function of prey abundance, $N$, is the classic definition of a predator’s functional response, (Holling, 1959b). Currently, functional response had been used widely in many systems including tumour-immune system. Agrawal et al. (2014) had studied these functional response into tumour system.

\[
\begin{align*}
\frac{dM}{dt} &= q + rM \left( 1 - \frac{M}{k_1} \right) - \frac{\alpha MN}{K_1 + M}, \\
\frac{dN}{dt} &= \beta NZ - d_1 N, \\
\frac{dZ}{dt} &= sZ \left( 1 - \frac{Z}{k_2} \right) - \frac{\beta NZ}{K_2 + Z} - d_2 Z,
\end{align*}
\] (1.3a)

This model is mimics to the model studied by El-Gohary (2008) model dynamics but based on biological evidence, its shows that the hunting cell can lyse the tumour cell quite effectively. This selected functional response, Holling-type II gave a realistic relationship of the killing capacity of hunting predator cell, $\alpha$ and the conversion of resting cell into hunting predator cells in the system, $\beta$.

However, rather than Holling-type, Hassell-Varley functional response could give a different behavior of the system which it may suit the mechanisms of tumour system. Moreover, the numerical response of this functional response represents the change in predator numbers as a function of prey density (Holling, 1959a) and its have similar ratio-dependent forms (forms dependent on $\frac{N}{P}$ rather than $N$). Also, this response has been dispense into a reproductive numerical response (Hassell and Varley, 1969). The predation system with Hassell-Varley functional response is useful for predators that form a groups and applicable in biological control. It is reasonable to assume $\gamma = 1/2$ for terrestrial predator and appropriately $\gamma = 1/3$ for aquatic predators that form a fixed number of tight groups.

A general predator-prey system with Hassell-Varley type functional response
may take following form, \( f(N) = \frac{bN}{N + mP} \). For example Pathak \textit{et al.} (2009), they studied the functional response of Hassell-Varley into a tritrophic food chain model which is given by

\[
\begin{align*}
\frac{dX}{dt} &= r \left(1 - \frac{X}{K}\right) - \frac{\mu XY}{\eta_1 (m_1 Y \gamma + X)}, \\
\frac{dY}{dt} &= \frac{\mu_1 XY}{m_1 Y \gamma + X} - d_1 Y - \frac{\mu XY}{\eta_2 (m_2 Z \delta + Y)}, \\
\frac{dZ}{dt} &= \frac{\mu_2 YZ}{m_2 Z \delta + Y} - d_2 Z,
\end{align*}
\] (1.4)

where \( X(t), Y(t) \) and \( Z(t) \) are prey population density, predator population density and super-predator population density at time \( t \), respectively. \( \eta_i \) is yield constants, \( \mu_i \) is maximal growth rates, \( m_i \) is half-saturation constants and \( d_i \) is death rate of predator and super-predator for \( i = 1, 2 \). \( r \) is a prey intrinsic growth rate. \( K \) is carrying capacity. \( \gamma \) and \( \delta \) are called Hassell-Varley constants. In this project, we are interested to apply Hassell-Varley functional response into the system of tumour growth to describe the predation behaviors between tumour cells and healthy cells.

\subsection*{1.2.5 Cancer self-remission}

In medical field, a Response Evaluation Criteria (REC) in solid tumours is a standard way to measure how well a cancer patients responds to treatments. It is based on whether tumours shrink, stay the same or get bigger in size. The type of response of patients is classified as a Complete Response (CR), a Partial Response (PR), Progressive Disease (PD) and Stable Disease (SD). In other ways, this response can be classified into some natural behaviors of patients remission namely self-partial remission and complete self-remission. These two types of self-remission give contrast symptoms of cancer and signs in the body. For partial self-remission, the signs and symptoms of cancer have disappeared but not all, whereas, in complete self-remission, all signs and symptoms of cancer have disappeared, but the cancer still might be in the body.
Cole (1981) and ORegan and Hirschberg (1992) references to the terms "spontaneous regression" or "spontaneous remission". The behavior of cancer is invariably progress or fatal disease. The more life sophisticated, the more it lost the power of regeneration, regulation and repair whether of wounds or tumour. Apart from this scenario, An apoptosis and angiogenesis process play a vital distributor in growth and development of organisms especially an immune system of the body. An angiogenesis might give a possibility for efficient treatment of cancer because the anti-cancer drugs penetrate into tumour structure much better when distributed via blood. Unfortunately, it is crucial step in the solid tumours transition from the solid form to cancer that are able to metastases and cause lethal outcome of the disease. Besides, tumour environment and DNA suppression also lead to progressive growth of tumour in the body. Thus the control of tumor growth requires special attention.

1.3 Problem statement

Oncology is a wide range field to be predicted but yet still showing progress time to time. However, every system in the oncology specially tumour growth system, currently miserable into huge biological behavior. Specified, into some factors such as handling time of cell capturing, quiet fascinating to discuss about. At most recent, the proposed model have been modified with present functional response lead to many positive progression towards their handling time of cell capturing, such as Holling-type functional response. By the time, the progress towards this system giving effect with the other factors. We must consider about the relevance factors for both prey and predator behaviors along the system. Hence, by modified the system with advance functional response, Hassell-varley, more compatibility system can be predicted for both prey and predator population. This functional response give such complicated behavior into tumour growth system which we interest to predict and investigate fundamentally.
1.4 Objectives

The objectives of this project are to:
1. analyze the system of tumour growth with cancer self-remission using linear stability and bifurcation analyses,
2. introduce Hassell-Varley functional response in the system of the tumour growth with cancer self-remission, and perform stability analysis,
3. compare the system of tumour growth with cancer self-remission with and without the Hassell-Varley functional response.

1.5 Scope of study

The model of tumour growth is constructed as a spontaneous tumor regression and progression which behave similar like as a deterministic predator-prey model. Thus, in our study we only focus on systems of ordinary differential equations (ODEs). Our work is a modified version from that of El-Gohary (2008) where Holling-type I functional response was introduced. In our work, we introduce Hassell-Varley functional response in the model to be compared with the aforementioned model. We analyzed the model by using MATLAB and MAPLE to produce the graphical data of the models and to perform the calculations.
CHAPTER 2

LITERATURE REVIEW

2.1 Research background

Oncology is the study of cancer, its a branch of medicine concerned with cancers including study of their development, diagnosis, treatment and prevention. According to American Cancer report 2013. Cancer remains the second most common causes of death in the US only, accounting for nearly 1 of every 4 deaths. Its major public health problem that profoundly affects more than one million people diagnosed each year. In fact, cancer is a leading cause of death throughout the world. A huge number of experiments has been done over the past few decades about its growth, progression and control, but yet, still not known about its mechanisms while surgery or chemo and radio therapies have played key roles in the treatment. Unfortunately, in the most cases they do not represent a cure, even when patients experience tumour regression. Later, relapse can occur. This anomalous behavior requires a revision of our thinking that cancer is invariably a progressive or fatal disease. Thus, it is very essential to study how the immune system response to the development and progression of tumour. The needs is to address not only preventative measures, but also more successful treatment strategies.

Mathematical modelling of tumour growth is a complex mechanisms, its progressions and development has been studied by many mathematical modelers around the world by developing a variety of models over a last few decades as (Kirschner and Panetta, 1998; Kuznetsov et al., 1994; Sarkar and Banerjee, 2005).
The mathematical modeling of tumour system is not a new approach, but still an enigma when it comes about its growth and control. The approach of systems theory suggests that the problem between the interaction of the micro-systems (the tumour) and the macro-systems (the organism) should be given critical attention. An ordinary differential equation model can be simple model involving a single equation for growth dynamics of cancer cell only. One aspect of complexity can be related to considering multi-equation models (e.g., two-equation, three-equation models, etc.). Basically, these multi-equation represent general predator-prey Lotka-Voltera like models for describing the interactions between the tumour cell and one type of immune cell or tumour cell, immune cell and cytokines (Kirschner and Panetta, 1998). Kuznetsov et al. (1994) define two main populations: effector cells (ECs) and tumour cells (TCs) which mainly ordinary differential equations model were certainly provide a simpler framework within which to explore the interactions among of these cells.

\[
\begin{align*}
\frac{dE}{dt} &= s + \frac{\rho ET}{g + T} - \mu ET - dE, \quad (2.1a) \\
\frac{dT}{dt} &= \alpha T(1 - bT) - nET, \quad (2.1b)
\end{align*}
\]

where \( E(t) \) and \( T(t) \) are the number of effector cells and tumour cells respectively, at any time, \( t \). The rate of change of effector cells is given by the first equation. The growth of the effector cells is stimulated by two factors namely, the constant input \( s \) and the recruitment term \( \frac{\rho ET}{g + T} \) due to the presence of tumour. \( d \) is the natural death of effector cells and \( \mu \) is the rate at which effector cells are killed by tumour cells. The second equation gives the rate of change of tumour cells, whose the growth follows logistic growth function \( \alpha T(1 - bT) \), \( \alpha \) is the intrinsic growth rate and \( \frac{1}{b} \) is the carrying capacity of the tumour cells, \( n \) is the rate at which the effector cells kill the tumour cells.

Also, Kirschner and Panetta (1998) indicated that the dynamics between tumour cells, immune cells and cytokines (e.g., IL-2) can explain both short-term
REFERENCES


