PARAMETERS ESTIMATION FOR A MECHANISTIC MODEL OF HIGH DOSE IRRADIATION DAMAGES USING NELDER-MEAD SIMPLEX AND PARTICLE SWARM OPTIMIZATION

NABIL HAAZIM BIN MOHD AMIRRUDIN

UNIVERSITI TEKNOLOGI MALAYSIA

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NABIL HAAZIM BIN MOHD AMIRRUDIN

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DEDICATION

To my beloved family and friends,
thank you for your love and support

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In the name of Allah the most Merciful and the most Compassionate

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ABSTRACT

Radiotherapy is a treatment that utilizes the high energy waves to treat cancers and tumors. The high energy radiation released from the therapy might directly kill the cancer cell or creates charged particles on the targeted area which consecutively damage the DNA. The damage part of DNA resulted from the high energy radiation will disrupts the growth and division of the cancer cell. However, the high dose radiation may bring side effects as it also may damages the nearby normal cell. The main objective of radiotherapy treatment is to maximize the damage on the cancer cell and minimize its side effect on the surrounding normal cell. Over the years, many mechanistic models had been developed to study the dynamic behavior of the cell population after it had been irradiated by high dose ionizing radiation. Determination of set of parameters of the mechanistic model helps to understand the dynamic behavior of the cell population. The current study aims at estimating parameter for a mechanistic model of high dose irradiation damage using two optimization algorithms which are Nelder-Mead Simplex (NMS) and Particle Swarm Optimization (PSO). The performance and efficiency of both optimization algorithms are compared based on the minimum value of sum of squared error, computational time and number of iteration to compute the objective function. The analysis demonstrates that NMS has higher accuracy and requires shorter time to minimize the objective function. On the other hand, PSO show a quicker convergence to achieve the objective function as compared to NMS.

ABSTRAK

Terapi radiasi adalah rawatan yang menggunakan sinaran bertenaga tinggi untuk merawat kanser dan tumor. Sinaran bertenaga tinggi yang dibebaskan daripada rawatan tersebut boleh membunuh sel kanser secara langsung atau mencipta zarah bercas di kawasan yang disasarkan yang seterusnya akan merosakkan DNA. Bahagian DNA yang telah rosak disebabkan sinaran bertenaga tinggi akan membantutkan pertumbuhan dan pembahagian kanser sel. Walaubagaimanapun, sinaran bertenaga tinggi tersebut boleh juga memberi kesan sampingan dimana ia mampu merosakkan kawasan sel normal di sekitarnya. Objektif utama terapi radiasi adalah untuk memaksimakan kerosakan ke atas sel kanser dan meminimakan kesan sampingan ke atas sel normal disekitarnya. Saban tahun, banyak model mekanistik telah dimajukan untuk mengkaji ciri-ciri dinamik populasi sel yang telah dipancarkan dengan radiasi ion berdos tinggi. Penentuan kumpulan parameter daripada model mekanistik dapat membantu untuk memahami dinamik populasi sel. Kajian ini bertujuan untuk menganggarkan parameter model mekanistik menggunakan dua kaedah pengoptimuman iaitu kaedah *Nelder-Mead Simplex* (NMS) dan *Particle Swarm Optimization* (PSO). Prestasi dan kecekapan kaedah pengoptimuman tersebut akan dibandingkan berdasarkan jumlah ralat persegi (JRP) yang rendah, pengiraan masa dan bilangan lelaran yang diperlukan untuk mencapai fungsi objektif yang ditetapkan. Analisis menunjukkan kaedah NMS mempunyai ketepatan yang tinggi dan memerlukan masa yang sedikit untuk meminimakan fungsi objektif. Sebaliknya, PSO menunjukkan penumpuan yang lebih cepat untuk mencapai fungsi objektif berbanding NMS.

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LIST OF ABBREVIATIONS

CI	-	Confidence Interval
CPU	-	Central Processing Unit
DNA	-	Deoxyribonucleic Acid
DSB	-	Double Strand Break
HCT 116	-	Colon Carcinoma Cell
HR	-	Homologous Recombination
LQ	-	Linear Quadratic
MATLAB	-	Matrix Laboratory
MKM	-	Microdosimetric Kinetic Model
NHEJ	-	Nonhomologous End Join
NMS	-	Nelder-Mead Simplex
ODE	-	Ordinary Differential Equation
PLQ	-	Pade Linear Quadratic
PSO	-	Particle Swarm Optimization
R	-	Registered
SF	-	Survival Fraction
SSE	-	Sum of Squared Error
TM	-	Trademark
UV	-	Ultra Violet
UTM	-	Universiti Teknologi Malaysia

LIST OF SYMBOLS

α	-	Linear Component of cell killing
α_1	-	misrepair rate constant
α_2	-	lethal binary misrepair rate constant
α_{exp}	-	lethal lesions produced by one-track action (experiment)
α_{model}	-	lethal lesions produced by one-track action from model
β	-	Quadratic Component of cell killing
β_{exp}	-	lethal lesions produced by two-track action (experiment)
β_{model}	-	lethal lesions produced by two-track action from model
D	-	radiation Dose
φ	-	reflection ratio
σ	-	contraction ratio
ε	-	expansion ratio
γ	-	repair rate
δ	-	radiosensitivity of the cell
k	-	number of double strand break
m	-	number of misrepair
N	-	number of survival cell
P	-	probability Successful
r^2	-	correlation
s	-	sample standard deviation
V_B	-	Best vertex
V_G	-	Good vertex
V_W	-	Worst vertex
V_M	-	Midpoint vertex
V_{max}	-	Maximum repair rate
V_R	-	Reflection vertex
$\bar{x}$	-	sample mean

CHAPTER 1

INTRODUCTION

1.1 Background of the research

Radiation is the released of energy in the form of moving waves or particles which move through space. Irradiation means exposure to the radiation will cause bad effects to our body and specifically to our biological deoxyribonucleic acid (DNA). Ionizing radiation is a type of radiation which have a large energy that have the capabilities to remove bond of electrons from its orbit which make the atoms become charged or ionized as reported by Ravanat *et al.* [1]. This phenomena if exposed to our body will result in DNA damage.

Nowadays, radiation is widely used in many sectors such as archeology, geology and medical field. An object is said to be irradiated when it is exposed to the radiation. In medical sector, radiation is used as a technique to kill cancer cell. Radiation in medical sector such as x-rays is used to check internal parts of the body or to treat cancer. Beside the objective to kill the cancer cell, the main concern of this radiation therapy is the side effects of the treatment. The radiation might not only targeting the cancer cells but also to its nearby normal tissue. Once our body is exposed to this radiation, it will trigger a self-repair mechanism to repair the damaged part of the body as mentioned by Monson *et al.* [2]. However, the problem arise when the damaged DNA is incorrectly repaired which will develop a secondary cancer cell.

Over the years, many mathematical models have been developed to relate the irradiation effects to DNA. The mathematical models contain parameters which can be manipulated experimentally to understand the cell behavior after irradiation process. Hence, estimating the kinetic parameter values to be used in the mathematical model is important as it can help to solve any related problem in the future.

A mechanistic model has been developed by Siam *et al.* [3] to study the population of cell which has been irradiated by high dose radiation. The mechanistic model which based on structured population model and Linear Quadratic (LQ) framework relates the number of DNA Double strand breaks (DSBs) and misrepair of DSBs after irradiation. The author also developed parameter estimation algorithm in order to understand the behavior of cell activity after irradiation using the existing experimental results.

Optimization algorithms such as Nelder-Mead Simplex (NMS) method, simulated Annealing and Genetic Algorithm had been used to estimate the best parameter values in the mechanistic model suggested by Siam *et al.* [4]. In this study, the parameter estimation procedure using the same mechanistic model of irradiation damage will be established. We will estimate the optimal parameter values for the mechanistic model which are (δ, α_1, α_2, ρ, V_{max}, K_m). The only difference from [4] is the used of another optimization technique called Particle Swarm Optimization (PSO) which to be compared to Nelder-Mead Simplex method. The performance and efficiency of both optimization algorithms in term of the minimum value of sum of squared error(SSE), computational time taken to estimate parameters and number of iteration needed to converge to lowest SSE value.

1.2 Statement of the problem

The main objective of the radiation treatment is to kill the cancer cells, however using the high dose radiation rays might have side effects to our body. The radiation rays not only kill the cancer cells but might also damage the nearby normal tissue. Once exposed to this radiation, a self-repair mechanism is triggered by our body to treat the damaged part of the DNA. The side effects of this treatment might come when the damaged part of DNA is incorrectly repaired by our body system which could lead to the development of secondary cancer cell.

The needs to study the cell population dynamic after irradiation is very crucial so that we can further analyze how many DNA Double strand breaks (DSBs) created, number of misrepair of DSBs and cell death rate occur after the cell is exposed to ionizing radiation. Hence many mathematical models which can fit with these data were developed to help researchers and radiobiologist to understand the dynamic behavior of the cell population.

1.3 Objectives of the study

The objectives of the study are:

1. To estimate the six mechanistic model parameters (δ, α_1, α_2, ρ, V_{max}, K_m) which can explain the physical behavior of the cell population after irradiation by using NMS method and PSO.
2. To compare the performance of NMS method and PSO in estimating kinetics parameter values.

1.4 Scope of the study

The study will focus on the parameter estimation based on the mechanistic model suggested by Siam *et al*. [3]. The model developed will be used to understand the behavior of cell population after irradiation process. NMS will be used as local optimizer and PSO will be used as global optimizer to find an optimal model parameters value. Next, the performance of both methods will be compared and analyzed using MATLAB. Statistical analysis such as the mean $\bar{x}$, the standard deviation s, the correlation r and the confidence interval will also be discussed to further analyse the parameter estimation results obtained.

1.5 Significance of the study

The significance of the study is to give a better understanding on cell population after irradiation using mathematical model. Linear Quadratic relation will be applied in the mathematical model to estimate the kinetic parameters value. Besides, this study aims to suggest the best optimization method between NMS and PSO for the mathematical model used. Finally, the optimal kinetic parameters value of the model obtained could be used as reference to radiologist in radiotherapy planning in the future.

1.6 Thesis outline

This thesis contains of six chapters which consists of introduction chapter, literature review, methodology of the research, the mechanistic model employed, parameter estimation result analysis, conclusion and recommendation for future works. Chapter 1 presents the background of the study followed by the problem statement and objectives of the research. The scope of study and the significance of the study are also discussed in this chapter.

Chapter 2 discusses on the literature review for this research. This chapter highlights the past research on parameter estimation. The previous mathematical model used to study the cell population dynamics after irradiation will also be reviewed in this chapter. Chapter 3 explains the methodology used for this research. Chapter 4 explains in details the mechanistic model used for this research. The ODEs system and the initial condition related to the model were also explained based on [3].

Chapter 5 will discuss in details the performance of the optimization algorithms based on the minimum value of SSE, computational time and number of iteration needed by the optimizers. Statistical formula such as correlation, standard deviation and confidence interval will also be discussed to further justify our results. Finally, the conclusion and recommendations for future research will be stated in Chapter 6.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This chapter will discuss the chronology related to the cell population. It starts with a fundamental introduction about cell, DNA structure and how it can be damaged by radiation. The phenomena of how ionizing radiation can damage the DNA structure will be explained in details. Next, the development of previous mathematical models to relate with this cell population after irradiation will also be discussed.

2.2 Cell and DNA

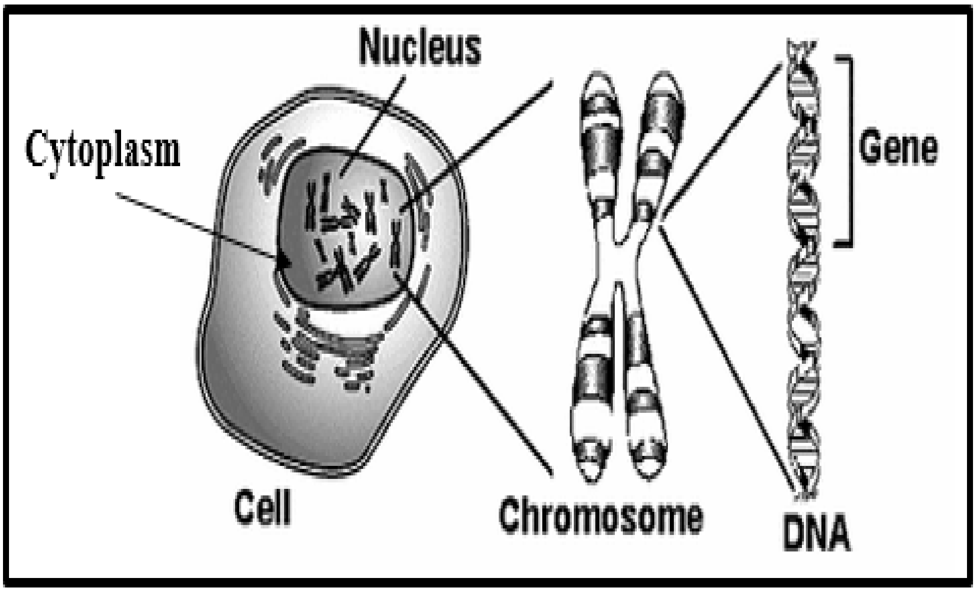

Figure 2.1 The structure of a cell [3].

Figure 2.1 shows the basic structure of a cell which consist of cytoplasm and nucleus which enclosed inside a membrane [5]. Inside the nucleus, genetic information is stored in molecule called as Deoxyribonucleic acid (DNA). DNA contains genetic

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