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# PARAMETERS ESTIMATION FOR A MECHANISTIC MODEL OF HIGH DOSE IRRADIATION DAMAGES USING NELDER-MEAD SIMPLEX METHOD AND GENETIC ALGORITHM

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*To my beloved family and the person who loves me,*

*thanks for your love and support*

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## ABSTRACT

Radiation therapy is one of the cancer cells treatments that use high-energy radiation to shrink tumors and kill cancer cells. Radiation therapy kills cancer cells by damaging their DNA directly or creates charged particles within the cells that can in turn damage the DNA. As a side effect of the treatment, the radiation therapy can also damage the normal cell that located at parts of our body. The main goals of radiation therapy are to maximise the damaging of tumors cell and minimise the damage of normal tissue cell. Hence, in this study, we adopt an existing model of high dose irradiation damage. The purpose of this study is to estimate the six parameters of the model which are involved. Two optimisation algorithms is used in order to estimate the parameters, there are Nelder-Mead simplex method and Genetic Algorithm. Both methods have to achieve the objective function which are to minimise the sum of square error (SSE) between the experimental data and simulation data. The performance of both algorithms are compared based on the computational time, number of iteration and value of sum of square error. The optimisation process is carried out using MATLAB programming built-in functions. The parameters estimation results shown that Nelder-Mead simplex method is more superior than Genetic Algorithm for this problem.

# ABSTRAK

Terapi radiasi adalah salah satu daripada rawatan sel kanser yang menggunakan sinaran bertenaga tinggi untuk mengecutkan tumor dan membunuh sel-sel kanser. Terapi radiasi membunuh sel-sel kanser dengan merosakkan DNA mereka secara langsung atau mencipta zarah bercas dalam sel-sel yang boleh pula merosakkan DNA. Sebagai kesan sampingan rawatan, terapi radiasi boleh merosakkan sel normal yang berada di badan kita. Matlamat utama terapi radiasi adalah untuk memaksimumkan merosakkan tumor sel dan mengurangkan kerosakan sel tisu normal. Oleh itu, dalam kajian ini, kita akan menerima pakai model sedia ada untuk masalah ini untuk menganggarkan parameter yang terlibatkan. Data eksperimen yang kumpul akan digunakan dalam menganggarkan parameter anggaran untuk masalah ini. Kami menggunakan dua penyelesaian berangka dalam masalah ini; Kaedah Nelder-Mead dan Algoritma Genetik. Kedua-dua kaedah perlu mencapai matlamat utama iaitu untuk mengurangkan jumlah ralat persegi (JRP) antara data eksperimen dan bilangan sel hidup. Kami akan membandingkan kaedah ini dengan beberapa faktor; masa pengiraan dan beberapa lelaran pengoptimuman sehingga optima. Prosedur untuk mengumpul data dan simulasi dikodkan menggunakan pengaturcaraan MATLAB dan melaksanakan 100 data secara rawak. Kedua-dua kaedah adalah algoritma yang baik kerana pengoptimum berdasarkan jumlah nilai ralat kuasa tetapi kaedah Nelder-Mead kelihatan lebih unggul sebagai pengoptimum untuk masalah ini.

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| | | |
|---|---|---|
| A | - | Adenine |
| AI | - | Artificial Interlegence |
| ANM | - | Advance Nelder Mead |
| B | - | Best vertax |
| *C* | - | Contraction |
| *CI* | - | Contract Inside |
| *CO* | - | Contract Outside |
| C | - | Cytosine |
| C3H10T1/2 | - | Mouse embryonic cells |
| CI | - | Confident Interval |
| CPP | - | Compound Poisson Process |
| CPU | - | Central Processing Unit |
| D | - | Radiation Dose |
| DNA | - | Deoxyribonucleic acid |
| DSBs | - | Double Strand Breaks |
| *E* | - | Expression |
| *G* | - | Good vertex |
| G | - | Guanine |
| GA | - | Genetic Algorithm |
| GBNM | - | Globalized Bounded Nelder Mead |
| GHz | - | Gigahertz |
| HRR | - | Homologous Recombine Repair |
| ICCM | - | Irradiated Cell Condition Medium |

| | | |
|---|---|---|
| IR | - | Irradiation |
| $k$ | - | Number of DSB |
| $K_M$ | - | Michaelis-menten constant |
| LET | - | Linear Energy Transfer |
| LPL | - | Lethal and Potential Lethal |
| LQ | - | Linear Quadratic |
| $M$ | - | Midpoint |
| $m$ | - | Number of misrepair lesion |
| MATLAB | - | Matrix Laboratory |
| Mel202 | - | Melanona cell |
| N | - | Number of survival cell |
| NHEJ | - | Nonhomologous End Join |
| NM | - | Nelder-Mead |
| NO | - | Nitric Oxide |
| ODE | - | Ordinary Differential Equation |
| $p$ | - | Probability successful |
| PDE | - | Partial Differential Equation |
| $r^2$ | - | Correlation |
| $R$ | - | Reflection |
| RMR | - | Repair Misrepair |
| $S$ | - | Shrink |
| $s$ | - | Sample Standard Deviation |
| SSBs | - | Single Strand Breaks |
| SSE | - | Sum of Square Error |
| T | - | Thymine |
| TGF | - | Transforming Growth Factor |
| UV | - | Ultra Violet |
| UTM | - | Universiti Teknologi Malaysia |
| $V_k$ | - | Vertex |
| $V_{max}$ | - | Maximum repair rate |

| | | |
|---|---|---|
| $W$ | - | Worse Point |
| $\bar{x}$ | - | Sample mean |
| $\mathbb{Z}$ | - | Integer |
| $\alpha_{exp}$ | - | Lethal lesions produced by one-track action from experiment |
| $\alpha_{model}$ | - | Lethal lesions produced by one-track action from model |
| $\alpha_1$ | - | Misrepair rate constant |
| $\alpha_2$ | - | Lethal binary misrepair rate constant |
| $\beta$ | - | Death rate |
| $\beta_{exp}$ | - | Lethal lesions made by two-track action from experiment |
| $\beta_{model}$ | - | Lethal lesions made by two-track action from model |
| $\gamma$ | - | Repair rate |
| $\delta$ | - | Radiosensitivity of the cell |
| $\theta$ | - | Initial parameter set |
| $\theta_o$ | - | Parameter set |
| $\lambda$ | - | Poisson distribution |
| ™ | - | Trademark |
| ® | - | Registered |

# CHAPTER 1

# INTRODUCTION

## 1.1 Background of the Research

All living organism made up of tissue and cell as a basic unit of life. Cell is the basic structural, functional, and biological unit of all known living organisms. In general cells are divided into two part that are animal cell and plant cell. The biggest differences between animal cell and plant cell is the existence of cell wall that decide the shape of the organism. As shown in Figure 1.1, the main component of animal cell main are the membrane cell, the cytoplasm and the nucleus which carries out the activities of the cell. The membrane cell or the plasma membrane is a biological membrane that separates interior part of the cells from the outside environment [1].

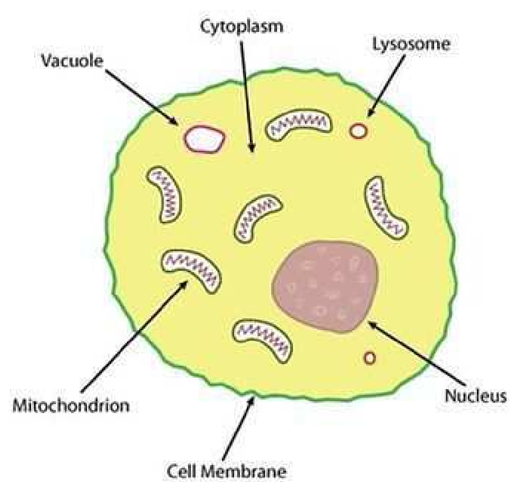


**Figure 1.1** The simple cross section of animal cell.

The cell membrane is selectively permeable to ions that allow the movement of substances in and out of cells. Cytoplasm which is walled by membrane cell consists of thick solution that fills each cell. It mainly composed about 80% water and usually colourless. The last part is nucleus that control the activity of the cell. It contains most of the genetic material to maintain the reliability of these genes present as outsized variation of protein call as Deoxyribonucleic Acid (DNA).

However, we are always surrounded by radiation which can damage DNA molecules. Radiation can be classified physically as an emission of energy in form of waves energy or particles movement through medium [2]. Radiation is often characterized into two parts which are ionising or non-ionising depend on energy of the radiated particles. Ionisation occurs when an electron is ”knocked out” from an electron shell of the atom, which leaves the atom with a net positive charge.The most commonly known types of irradiation are gamma ray and X-ray. In contrast, non-ionising is happen when insufficient energy produce as a part of electromagnetic spectrum such as magnetic field and radio waves. See section 2.3 for detail.

Radiation for medical purpose or known as radiotherapy is a therapy using ionising radiation to control or kill harmful cell in human body. Radiation therapy is commonly applied to the cancerous tumour because of its ability to control cell growth. Ionising radiation works by damaging the DNA of cancerous tissue lead to cellular death of the cell. It is also common to combine radiation therapy with surgery, chemotherapy, hormone therapy and immunotherapy.

During the radiotherapy treatment, our aim is to maximise damages of tumour cell and minimise the damages of the normal tissue. As a result, shaped radiation beams is needed for aiming from several angles of exposure to intersect at the tumour, providing a much larger absorbed dose compared to surrounding health tissue. Because of living cells and, more important the DNA in those cells can be damaged by ionisation radiation, therefore exposure to ionising radiation is considered to increase the risk of cancer [3].

Radiation might be effected nearby tissue located at the treatment area. This living tissue will be affected and can lead to secondary cancer cell. This problem is discussed in detail in [4] to identify the cell population evolution after irradiation. However [5] has claimed that the model in [4] left out too many factors that cause it less accurate.

Parameters are descriptive measures of an entire population. However, their values are usually unknown because it is infeasible to measure an entire population. Because of this, you can take a random sample from the population to obtain parameter estimates. Parameter estimation is the computational numerical values for parameters from the available observation [6]. The parameter estimation term itself refers to the process of using sample data to estimate the parameters of the selected distribution.

Parameter estimation plays a critical role in accurately describing system behaviour through mathematical models such as statistical probability distribution functions. Other than that parameter estimation may act as adaptive filtering where the variable parameters will adjust itself according to optimisation algorithm [7]. Parameter estimation also can identify the model system [8] such as time-series modelling in signal processing theory. Last but not least it can control the mathematical model of the dynamic system by providing the estimated values to the model [9].

As for our parameter estimation part, the model parameter estimation using Nelder-Mead simplex method and Genetic Algorithm which allow us to relate the clinical useful parameter of the LQ relation to aspects of cellular activity that can be manipulated experimentally. The estimated parameters values are also useful which act as a guide in solving real life problem of cell population growth after irradiation.

The goal in this present thesis is to understand a better cell population model suggested by [3] and to estimate the number of cell survived following high dose irradiation. This research will help us in provide the information related to the model for cell population evolution after irradiation. Other than that, this research also provides the information for surviving cell fraction if the parameters in the model vary.

## 1.2 Statement of the Problem

Radiation therapy is one of the most common treatments for cancer. It use high-energy particles or waves, such as x-rays, gamma rays, electron beams, or protons, to destroy or damage cancer cells. In 2011, [10] suggested that irradiation was successful in the novel theranostic technique involving co-treatment with heptamethine dyes to clarify tumour cells and attenuate their growth with minimal side effects.

During the treatment, the radiation can also damage the nearby normal tissue at the treatment areas. Consequently it can lead to development of secondary cancer cell due to damages of genes in DNA.

In 2014, a mechanistic model of high dose irradiation damage on mammalian cell has been proposed by [3]. The model proposed six parameters that involved in cell population evolution after irradiation which explained the dynamics of the problem.

In order to estimate the six parameters, two optimisation algorithms will be employed in this current work. There are Nelder-Mead simplex method and Genetic Algorithm. To investigate the performance of both algorithm, the sum of square error (SSE), computational time and number of iteration will particularly concern.

## 1.3 Objective of Research

The objective of the study are:

1. To estimate the model parameters by using Nelder-Mead simplex method and Genetic Algorithm.
2. To compare the performance of Nelder-Mead simplex method and Genetic Algorithm in term of objective function, number of iteration and computational time.

## 1.4 Scope of the Research

In this research a system of ordinary differential equations (ODE) in [3] which described the cells surviving fraction following high dose irradiation were considered. The model contains of six parameters which are to be estimated. In this work, implementation will be focussing on Nelder-Mead simplex method and Genetic Algorithm to find an optimal model parameters value. By using MATLAB the performance of this two algorithm will be compared.

## 1.5 Significance of the Research

The significance of the study are as follows:

1. Enhance understanding on realistic mathematical model in cell population evolution following high dose irradiation.
2. Describe cell population nature after radiated by irradiation with different doses through cell survival curve.
3. Provide the the best model parameters values for the problem that can be used as a guide for the real related problem.

4. Prove the best optimiser for the problem from the performance between Nelder-Mead simplex method and Genetic Algorithm.

## 1.6 Thesis Outline

The present thesis concentrates on the parameter estimation of model suggested in [3]. It begins with Chapter 1 which is introduction of the study, including the background of the research, problem statement, objective of the research, scope of the research and significance of the study.

Chapter 2 dealt with the literature review on fundamental background of cell population evolution after radiation. Some biological facts will explained so that the reader will understand more about the problem. The related works on model of the problem and implication using ionising radiation were also will reviewed.

Then, Chapter 3 describes and explains in more detail about the research methodology that adopted in this study. The chronology and flow of the study will be explained in order to solve the problem. The methods of solution that used in the research were introduced in this chapter. Some related previous works related to solving method, algorithm and example will explained carefully.

In Chapter 4, the formulation of the model of cell evolution following irradiation suggested by [3] is briefly discussed. In addition the governing equation with the initial conditions for the problem is introduced.

Chapter 5 will summarise and discusses the implementation of Nelder-Mead simplex method and Genetic Algorithm in minimise the objective function (SSE). The real data was introduced and some fundamental information related to the problem was explained. The efficiency for both algorithm will determine the best estimator for the problem. This chapter also includes some discussion on the result that we obtained from MATLAB programming.

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