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NUMERICAL ANALYSIS ON MATHEMATICAL MODEL FOR DRUG DELIVERY SYSTEM ON BLOOD FLOW IN EXTERNAL MAGNETIC FIELDS BY MAGNETIC NANOPARTICLES

Norma Alias[a], Sakinah Abdul Hanan[a*], Akhtar Ali[a], Zakaria Dollah[b]

[a]Department of Mathematical Science, Center for Sustainable Nanomaterials (CSNano), Ibnu Sina Institute for Scientific and Industrial Research, Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor
[b]Department of Mathematical Science, Faculty of Science, Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor

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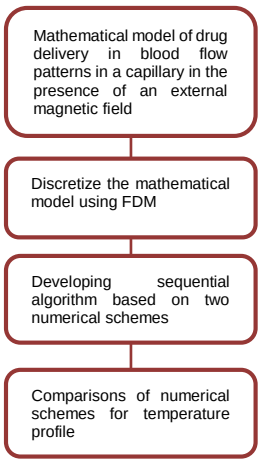
*Corresponding author
sakinahhanan@gmail.com

Graphical abstract



Abstract

A new design of mathematical model of therapeutic compound in blood flow patterns in a capillary attached the magnetic nanoparticles by the external magnetic field which is applied uniformly is considered. The blood flowing through the capillary is dominated to be Newtonian and the flow is assumed unsteady, incompressible and laminar. Based on the present knowledge of the drug delivery, the mathematical models have highly potential to develop by researchers. The implementation of the sequential algorithm is used to model the magnetic nanoparticles drug delivery system. Discretization of the governing equation together with the boundary condition is carried out before they are solved numerically using a finite difference scheme. The sequential algorithms on the mathematical model based on some numerical methods such as Jacobi and Gauss Seidel. The numerical analysis investigates in terms of execution time, accuracy, computational complexity, convergence criterion, root means square error and maximum error. The Gauss Seidel is the superior method compared to Jacobi.

Keywords: Mathematical modeling; drug delivery; sequential algorithm; finite difference schemes; numerical analysis.

1.0 INTRODUCTION

Cancer has become one of the health threatening problems resulting mortality throughout the world. The World Health Organizations (WHO) has reported the statistics where cancer is the leading cause of death in economically developing countries and the second leading cause of death in developing countries [1]. Cancer is the uncontrolled growth of abnormal cells in the body [2]. Indeed, study and research should be conducted to significant impact in the nanoparticle drug delivery system will free up more thoroughly understood. Advances in the delivery of targeted drug systems is alternative nanoparticles in order to maintain the effectiveness of the new drugs developed, potent and complex. Nanoparticles for drug delivery purposes, defined as small particles (< 1μm). The main area of work through the nanoscale is advancing in the drug delivery system. The devices of nanoscale allow the chemotherapeutic drug to discharge the blood vessels and even spread out through the tissue and access to the tumor cells. Today, drug delivery system is notable capability compared to traditional delivery via bolus injection. In others description, nanotechnology can assign with a

size range of structures at 1–100 nm in one dimension (Figure 1).

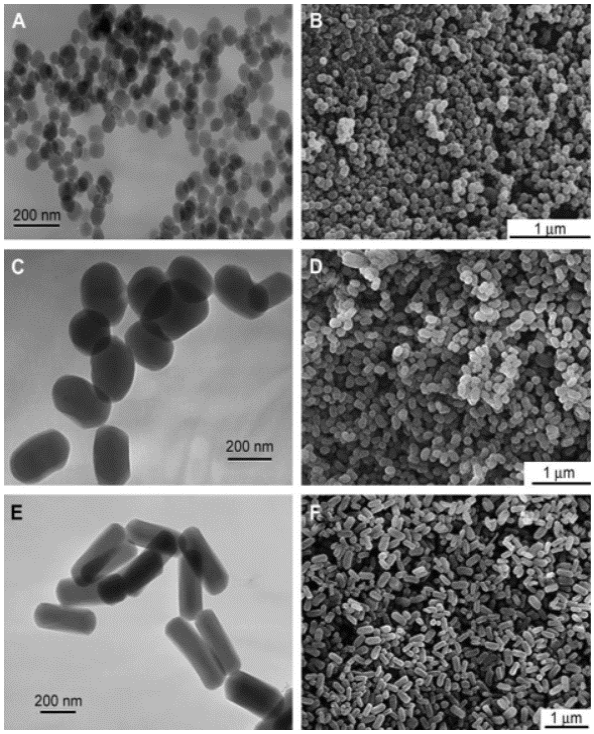


Figure 1 Structure of nanoparticle [3]

Most of the small drug molecule of cancer therapeutics after injected or ingested into the blood stream can only diffuse through the pores and vascular extracellular matrix to achieve the target cell [4]. Brain tumor is one of the dominant cancers in the world and is one of the leading causes of death from cancer [5]. [6] stated that the many type of cell inside human body and individually type of cells has their own specific functions. The potential of nanoparticles delivery systems give the chance to novel drug delivery approaches therapeutic options in treating the cancer disease [7].

Drug delivery system develop by magnetic nanoparticles is new prospects to build the system more effective [8]. At external, the restricted magnetic field gradient may be put on to attract drug particles with magnetic properties from blood flow [9]. Magnetic drug targeting guided has tried to improve the effectiveness and reduce the unpleasant side effects, associated with chemotherapy [10]. Delivery methods make chemotherapy more effective by increasing drug absorption at the site of the tumor to determine the concentration of systemic drugs [11]. An illustration magnetic nanoparticles-based drug delivery is shown in Figure 2. The magnetic nanoparticles for drug delivery are very interesting. Analysis has been reported that magnetically guided nanoparticles for targeted drug delivery into the brain. However there are limitation research the magnetic nanoparticle for drug delivery. In this paper, we will work on the problem in solving mathematical modeling magnetic nanoparticles.

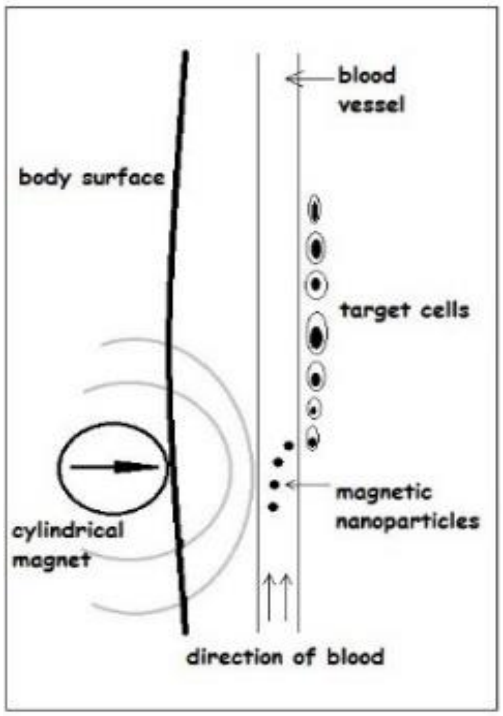


Figure 2 Magnetic nanoparticles-based drug delivery to the direction of blood vessel feeding the target cells.

Based on the real problem to cure the cancer cell treatment, the mathematical models for the drug delivery magnetic nanoparticles to the targeted cells is implement with the real-life problems is studied. This study is to obtain a mathematical model in order to transport and estimate the movement drug delivery. This means that, to relate the continuity and momentum equations with the movement of drug under controlled by electromagnetic field. The partial differential equations with parabolic type is solved by discretizing using central finite-difference technique. Then some numerical methods called Jacobi and Gauss Seidel method are developed to formulate the parabolic PDEs. The discretization is evaluated and analyzed the drug delivery magnetic nanoparticles to targeted cells. The realistic mathematical modelling is represented the importance of biological phenomena. In this study we use C programming to solve the mathematical problems. The implementation of the algorithm and the numerical analysis of the parabolic equation is well suited in estimating the movement of drug delivery for cancer cells treatments.

2.0 MATHEMATICAL MODELING

Magnetic nanoparticles drug concentration is enhanced at the cancer cell and reduced the toxicity and side effects in normal tissue [12]. [13] has studied

that the magnetic force on the magnetic nanoparticles is as follows:

$$F_M = \frac{\chi V_M}{\mu_0}\nabla(B^2) \quad (1)$$

By using the expression

$$B = \mu_0 H \quad (2)$$

and the equation can be transform as:

$$F_M = \mu_0 V_M M \nabla H \quad (3)$$

where $M = \chi H$ is the magnetization feature of bio fluid.

The diameter of the blood capillary in targeting area is very small. So the magnetic force across a capillary diameter is assumed constant. Forces of counteracts the magnetic force on the particle in the blood stream is due to the blood flow and can be calculated using stokes' expression for the drag force on a sphere as:

$$F_D = 6\pi\mu R_M(u - v) \quad (4)$$

where μ is the viscosity of blood, R_M is the radius of the magnetic nanoparticle, u is the velocity of blood and v is the velocity of magnetic nanoparticles.

In this paper we have considered only those portions of blood vessels which are oriented perpendicularly to the direction of the magnetization. The intensity of the magnetic field in the direction of magnetization for the cylindrical magnet is given by [14].

$$H_x = \frac{C_1 a^2}{x^2} \quad (5)$$

where a is the radius of cylindrical magnet and $C_1 = 500000 Am^{-1}$, x is the direction of magnetization oriented perpendicular to the direction of blood vessel feeding the tumor.

The governing equations for blood flow are the mass (continuity) and momentum conservation equation [15]. The equation is integrated each other, where velocity magnetic nanoparticles is depend on velocity of blood flow.

i. Continuity equation

$$m\frac{\partial v}{\partial t} = \mu_0 V_M (M\nabla H)_x + 6\pi\mu R_M(u - v) \quad (6)$$

ii. Momentum equation

$$\rho\frac{\partial u}{\partial t} = -\frac{\partial p}{\partial z} + \mu\left(\frac{\partial^2 u}{\partial r^2} + \frac{1}{r}\frac{\partial u}{\partial r}\right) + \frac{NA}{\rho}(v - u) \quad (7)$$

The initial and boundary conditions given by [16]:

1. It is assumed that no flow takes place when the system is at rest.

$$u = v = \frac{\partial u}{\partial t} = 0 \quad \text{at} \quad t = 0, \quad (8)$$

2. The velocity on the capillary wall is taken as

$$u = 0 \quad \text{at} \quad r = R \quad (9)$$

where R is the radius of the capillary.

2.1 Non – Dimensionalization

Dimensionless equations can reduce the computational complexity of the system. So we rescale the mathematical model in the following manner. The non-dimensional variable is denoted with bar:

$$r^* = \frac{r}{R}, z^* = \frac{z}{R}, x^* = \frac{x}{R}, t^* = \frac{t\mu}{\rho R^2}, u^* = \frac{uR}{v}, v^* = \frac{vR}{v}, H^* = \frac{H}{H_0} \quad (10)$$

where $v = \frac{\mu}{\rho}$ is the kinematic viscosity and H_0 is the intensity of magnetic field at the surface of the magnet.

By applying the variable above, the governing equation (6) until (9) becomes:

$$\frac{\partial \bar{v}}{\partial \bar{t}} = (\omega_1 \nabla \bar{H})_x + \omega_2(\bar{u} - \bar{v}) \quad (11)$$

$$\frac{\partial \bar{u}}{\partial \bar{t}} = -\frac{\partial \bar{P}}{\partial \bar{z}} + \left(\frac{\partial^2 \bar{u}}{\partial \bar{r^2}} + \frac{1}{\bar{r}}\frac{\partial \bar{u}}{\partial \bar{r}}\right) + \emptyset(\bar{v} - \bar{u}) \quad (12)$$

where,

$$\omega_1 = \frac{\mu_0 V_M M H_0 R^3}{mv^2}, \omega_2 = \frac{6\pi\mu R_M R^2}{mv} \quad \text{and} \quad \emptyset = \frac{NAR^2}{\rho v^2}.$$

The initial and boundary equation becomes:

$$\bar{u} = \bar{v} = \frac{\partial \bar{u}}{\partial \bar{t}} = 0 \quad \text{at} \quad \bar{t} = 0, \quad (13)$$

$$\bar{u} = 0 \quad \text{at} \quad \bar{r} = 1 \quad (14)$$

Table 1 Parameter of magnetic nanoparticle and blood equation

u	Velocity of blood (m/s)
v	Velocity of magnetic nanoparticles (m/s)
P	Pressure (Pa)
μ	Viscosity of blood (Kg/m.s)
R_M	radius of magnetic nanoparticles (m)
υ	kinematic viscosity
R	radius of capillary (m)
H	Magnetic intensity
M	Magnetization of particles (A/ m^{-1})
μ_o	permeability of free space
V_M	Volume of MNP
m	Mass of MNP
ρ	density of blood (Kg/m^3)
ρ_p	density of MNP (Kg/m^3)

N	Number density of suspended nanoparticles
A	Stokes's coefficient
t	Time (s)
r	Grid in r direction (m)
x	Grid in x direction (m)
z	Grid in z direction (m)

3.0 DISCRETIZATION

This paper focuses on Finite Difference Method based on the central difference for discretization of models for drug delivery model.

$$\frac{\partial u}{\partial r} = \frac{(u)_{i+1}^{k} - (u)_{i-1}^{k}}{2\Delta r}$$

And (15)

$$\frac{\partial^2 u}{\partial r^2} = \frac{(u)_{i+1}^{k} - 2(u)_{i}^{k} + (u)_{i-1}^{k}}{(\Delta r)^2}$$

While the time derivatives are approximated by

$$\frac{\partial u}{\partial t} = \frac{(u)_{i}^{k+1} - (u)_{i}^{k}}{\Delta t} \quad (16)$$

$$\frac{\partial v}{\partial t} = \frac{(v)_{i}^{k+1} - (v)_{i}^{k}}{\Delta t} \quad (17)$$

The discretization of axial velocity $u\,(r,t)$ and $v\,(r,t)$ is written as $u\,(r_i,t_k)$ and $v\,(r_i,t_k)$ or $(u)_i^k$ and $(v)_i^k$.

We define

$$r_i = (i-1)\Delta r\,; i = 1,2,\dots N+1$$

$$t_k = (k-1)\Delta t\,; k = 1,2,\dots$$

Substitute equation (15) until (17) into (11) and (12) becomes:

$$(v)_i^{k+1} = (v)_i^k + \Delta t(\omega_1 \nabla H)_x + \Delta t\omega_2((u)_i^k - (v)_i^k) \quad (18)$$

$$(u)_i^{k+1} = \left(\frac{\Delta t}{\Delta r^2} - \frac{\Delta t}{2i\Delta r^2}\right)(u)_{i-1}^k + \left(1 - 2\frac{\Delta t}{\Delta r^2} - h\emptyset\right)(u)_i^k + \left(\frac{\Delta t}{\Delta r^2} + \frac{\Delta t}{2i\Delta r^2}\right)(u)_{i+1}^k - \Delta t P_z + \Delta t\emptyset(v)_i^k. \quad (19)$$

Let $h = \Delta t$, $k = \Delta r$ and $r = \frac{h}{k^2}$

$$(v)_i^{k+1} = (v)_i^k + h(\omega_1 \nabla H)_x + h\omega_2((u)_i^k - (v)_i^k) \quad (20)$$

(21)

$$(u)_i^{k+1} = \left(r - \frac{r}{2i}\right)(u)_{i-1}^k + (1 - 2r - h\emptyset)(u)_i^k + \left(r + \frac{r}{2i}\right)(u)_{i+1}^k - hP_z + h\emptyset(v)_i^k.$$

3.1 Iterative Method

The governing equation (6) and (7) which describes the transportation of drug delivery characteristic is solved numerically. Jacobi and Gauss Seidel methods are the selected scheme for solving the discretization of the equation. The transformation of the simultaneous linear system of equations into matrix form is used to solve equation (20) and (21).

3.1.1 Jacobi

Jacobi method is a simple and fundamental iterative method. Jacobi method computed the value of u for each component respect to x

$$u_i^{(k+1)} = \left(b_i - \sum_{\substack{j=1 \\ j\neq i}}^{n} a_{ij}u_j^{(k)}\right) \Big/ a_{ii}, \quad i = 1,2,3 \quad (22)$$

The method is repeated until it reaches the stopping criterion such that $\left|u_i^{(k+1)} - u_i^{(k)}\right| \leq \varepsilon$ where ε is the convergence criterion.

3.1.2 Gauss Seidel

Gauss Seidel method is an enhanced version of the Jacobi method. The calculation of this method is as follows:

$$u_i^{(k+1)} = \left(b_i - \sum_{j=1}^{i-1} a_{ij}u_j^{(k+1)} - \sum_{j=i+1}^{n} a_{ij}u_j^{(k)}\right) \Big/ a \quad (23)$$

$$i = 1,2,3,\dots,n$$

3.2 Sequential Algorithm

There are five steps involved to obtain the algorithm. It started with selection of initial and boundary conditions. Next, the Jacobi and Gauss Seidel is used to execute the numerical method. Then, the iteration of the numerical method will stop if two conditions are satisfied. When the conditions are not satisfied, the step will repeat with increasing the number of iteration. Instead, the update value will be print out when the conditions are satisfied. Hence, the sequential is ended. The steps can be summarized as below and the flowchart of the algorithm represented by Figure 3.

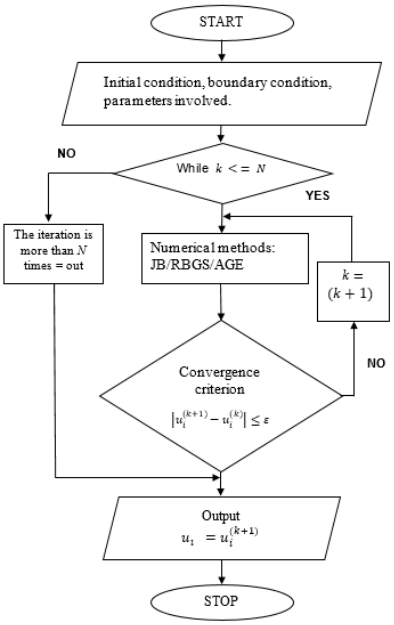


Figure 3 Sequential algorithms for numerical simulation of drug delivery equation.

4.0 NUMERICAL ANALYSIS

In this part, the numerical result is analyzed based on Intel® Core-i7 with window 7 operating system and Microsoft Visual Studio 2010 software with C language. The value of parameters used to solve the mathematical model given by Table 2:

Table 2 Parameter values

$R = 3 \times 10^{-6} m$
$R_M = 10^{-8} m$
$\mu = 0.03501\ kg/ms$
$\rho = 1060\ kg/m^3$
$\rho_p = 5.1 \times 10^3 kg/m^3$
$\mathrm{M} = 450000\ \mathrm{A}/\ m^{-1}$
$\mathrm{N} = 11.69 \times 10^{12}$
$H_0 = 2.1 \times 10^3$
$P = -0.0059\ \mathrm{Pa}$

The graphical numerical results of drug delivery magnetic nanoparticles in blood flow using JB and GS are displayed below. Figure 4 shows the drug delivery magnetic nanoparticles in blood flow. Parabolic curve of the drug delivery magnetic nanoparticle behavior is shown in figure above. Form the all solution methods under consideration, show the drug delivery at the beginning of the magnetic nanoparticles drug delivery process the evolution was smoothly increase until reach peak then velocity decrease after all the drug is diffuse to the targeted cells. The numerical analysis will proved the performances of each method was differences even though the simulation results has smalls different for each iterative methods.

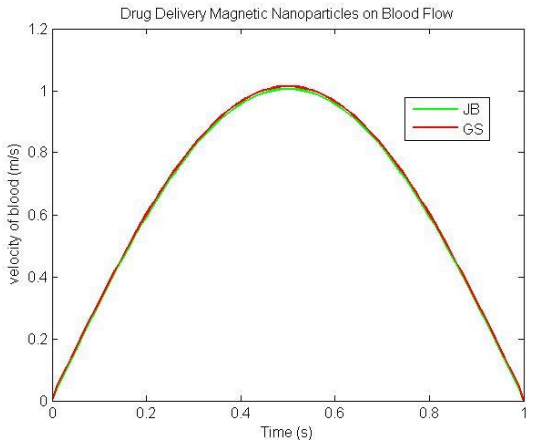


Figure 4 Velocity of blood versus time that contains magnetic nanoparticles

The numerical analysis result is obtained by some iterative methods involving the parameter values in magnetic nanoparticle drug delivery system. Convergence and accuracy is the aspect of the performances analysis of numerical simulation. Result of numerical analysis from iterative method such as number of iteration, execution time, accuracy, maximum error and root means square error (RMSE) are presented in Table 3. Number of iteration can be obtain from the implementation of computer programming while the RMSE is calculate using the formula below;

$$\mathrm{RMSE} = \sqrt{\sum_i^N \frac{\left(u_i^{(k+1)} - u_i^{(k)}\right)^2}{N}} \qquad (24)$$

Table 3 Numerical analysis for each method in magnetic nanoparticles drug delivery simulation

Numerical Analysis N=100, Tolerance=1.0e-10		Jacobi Method	Gauss Seidel Method
Time Execution (s)		0.988127	0.539744
Iteration		98	71
Computational Complexity	+ /−	1078	781
	× / ÷	1470	1065
Maximum Error		0.023091	0.01485
RMSE		1.778139e-6	5.729496e-8

The data size of N=100 and tolerances of 1.0e-10 is use to investigated the convergence comparison among JB and GS iterative methods. Based on Table 3 above, the convergence in term of execution time and the iteration number between JB and GS

methods, showing that, GS method performs faster than JB method. As we can observe from Table 1 above, GS method provides the lowest number of iteration which is 71 as well as give the shortest execution time, which are 0.539744 sec to converge compared with JB method. Number of iteration and computational complexity give a huge impact on execution time of a programming. Since JB method have a large number of iteration, this resulting the execution time also higher compared to GS method. According to [17], the accuracy of algorithm is measured based on RMSE result. The lowest RMSE would indicates the most accurate method as well as algorithm. Through Table 3 above, the lowest RMSE is belong to GS method. Thus GS method resulting the most accurate result.

5.0 CONCLUSION

The application of magnetic nanoparticles for drug delivery model is implication to develop the alternative numerical simulation for solving the cancer cell growth. The application of nanoparticles is assumed as the solver for early detection of tumor cell growth. The model can transport the magnetic nanoparticles towards the targeted cells. The purpose of this study is being able to visualize the transporting drug delivery to targeted cells in one-dimensional space. We have identified the mathematical model based on PDE with parabolic type. Both of the continuity equations and momentum equations are discretize using the central finite difference method. By developing the sequential C programming, the iterative methods namely Jacobi and Gauss-Seidel method is applied to solve the equations. The result of the numerical analysis is compared based on the time execution, number of iteration, computational complexity, maximum error and root mean square error (RMSE). From the result we obtained that, the Gauss Seidel is the superior method compared to Jacobi. The contribution of this study is to successfully prove that the mathematical model is capable to simulate the drug delivery of magnetic nanoparticle to treatment the cancer cells through numerical method approach. The future contribution of this study can be employed to advance numerical methods such as AGE and IADE for solving the mathematical model. The result can be compared with the basic numerical method that employed in this study. Furthermore, can implement the parallel algorithm for these models with large sparse problem.

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