Numerical Method For Differential System With Small Parameter With Applications In Tumours Growth

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Abstract—: Differential equations are of basic importance in cancer diseases because many biological laws and relations appear mathematically in the form of a ordinary differential equation. In this article we presented some applications of mathematical models represented by ordinary differential equations in tumours growth. Cancer is one of the most dangerous diseases of all. Chemotherapy is still one of the most effective methods of treating cancer. Mathematical modeling can be used to find adequate solutions of medicine products for treating cancer. These mathematical models have been developed to describe the tumor growth and find the best treatment by chemotherapy. Differential equation systems based models are useful in cancer biology to study how biological systems change over time. We propose an original mathematical model with small parameter for tumours growth. All the equations system includes small parameter $\varepsilon$ . The smallness of $\varepsilon$ is relative to the size of the solution domain. Numerical results reveal that these high doses should be administered in an optimal period to prevent the destruction of normal tissue. Solution graphs show us that there is an increase in cancerous cells even before the next chemotherapy session.

Keywords—Cancer diseases; Numerical methods; Matlab

I. INTRODUCTION

Cancer is one of the diseases causing most deaths in the world, although medical research has been successful despite all difficulties, at least for a certain pathology of cancer. Currently, the toughest challenges in modelling tumour growth consist in the estimation of parameters in mathematical models. The number of cancerous cells in a tumour is difficult to estimate due to continue changes in time. Neoplastic cells may spread, the rest can be in a condition of rest or might die. The number of live cells only changes when the cells proliferate or die. Tumour treatment may follow two different strategies. A first strategy would be reducing the tumour volume by inducing cell death in cancerous proliferative cells or by reducing tumour support by decreasing the transport capacity. Tumour growth, however, can be blocked in the absence of growth factors and nutrients offered by vascularisation. There are patients who do not die of the total number of cancerous cells from their body, but because the primary tumours invade the tissue locally and spread to other organs causing secondary tumours.

II. MATERIAL AND METHODS

We will take into account an aggressive tumor with two different types of cancer cells, which compete for nutrients. As proliferate cells consume much more oxygen, their consumption rate is much higher than that of healthy cells. The model is represented by a system of ordinary differential equations with small form parameter

$$\begin{align*}
\varepsilon \frac{dx}{dt} &= x(t)[a_1x(t) - y(t)] \\
\varepsilon \frac{dy}{dt} &= y(t)[a_2y(t) - x(t)]
\end{align*}$$

(1)

The mathematical model contains two variables which are $t$ time functions, where $x(t)$, $y(t)$ is the weight of sensitive cells and the mass of cells resistant to chemotherapy. Parameters of ($a_i$, $i = 1,2$) model include the intrinsic rates of increase in sensitive and resistant cells. We assume that the $\frac{1}{\varepsilon}$ parameter (growth rate caused by the competition between cells for oxygen and nutrients) is very long, where $\varepsilon$ is a
small parameter. Chemotherapy destroys $x(t)$ cells sensitive to drugs, but leaves behind a greater proportion of cells resistant to medicine. As the tumor begins to grow again, chemotherapy may fail because the neoplastic left is now more resistant to chemotherapy. Nutritional resources are a focal point of competition between those two types of cells. There is a relationship between limiting concentrations of nutrients and the increase of the two types of cells. The bacterial growth yield is linearly dependent on the initial concentration of nutrients. In the case of cells induced to proliferate, nutrients are needed in abundance for rapid growth. Cancer cells therefore require a plentiful supply of nutrients. Cancer cells are dependent upon exogenous signals for survival, growth, and proliferation.

III. NUMERICAL STUDY

Ordinary differential equations systems describe how properties of a real-world system evolve over time. Most differential linear systems one encounters in practice of nonlinear. Its solution may be obtained numerically by integrating a system of differential—difference equations whose size increases over time. Very often it is almost impossible to find explicitly or implicitly the solutions of a system (1). The intersection point of all the nullclines is called an equilibrium point or fixed point of the system. The $x$—nullclines, $y$—nullclines are given by:

\[
\begin{align*}
\frac{dx}{dt} &= 0 \quad x = 0, y = \alpha_1 x \\
\frac{dy}{dt} &= 0 \quad y = 0, y = \frac{1}{\alpha_2} x
\end{align*}
\]

(2)

The components of the velocity vectors are $x'(t)$ and $y'(t)$. These vectors give the direction of the motion along the trajectories. We have the four natural directions (left, right, up, and down) and the other four directions (left-down, left-up, right-down, and right-up). Hence the $x$—nullcline is the $x$—axis and curve $y = \frac{1}{\alpha_2} x$, and the $y$—nullcline is the $y$—axis and curve $y = \frac{1}{\alpha_2} x$. To draw the phase plane we notice that when we set: $\frac{dx}{dt} = 0$ we got the line: $y = \alpha_1 x$ (this is a line in the $xy$—plane) and when we set: $\frac{dy}{dt} = 0$ we got the line: $y = \frac{1}{\alpha_2} x$.

Thus $(x, y) = (0, 0)$ is the only fixed point.

We rewrite the system as:

\[
\begin{align*}
\frac{dx}{dt} &= f(x, y, \varepsilon) \\
\frac{dy}{dt} &= g(x, y, \varepsilon)
\end{align*}
\]

(3)

When solving differential systems such as (5) we typically have information about the initial state of the system and would like to understand how the system evolves. Numerical Euler method is used to approximate solutions of equations when exact solutions can not be determined via algebraic methods. They construct successive approximations that converge to the exact solution of system (1). We can use the numerical derivative to derive a simple method for approximating the solution to differential equations system (1). Program MATLAB is a perfectly acceptable way to solve Euler’s equation. MATLAB has a variety of numerical operations and numerical graphical display capabilities built. The function euler1storder contains all the code directly related to Euler’s method. We describe some ways of numerically approximating the solution to a system of differential equations (1). Better agreement between the numerical and analytical solution can be obtained by decreasing the time step size $h$. We pick a time step $h$ and attempt an approximation to the solution to (1) at times $t_0 + nh$:

\[
\begin{align*}
x_i &= x_i(t_0 + nh),\ y_i = y_i(t_0 + nh) \\
x(t + h) &= x(t) + hax'(t) + O(h^2) = x(t) + hax^2(t) + O(h^2) \\
y(t + h) &= y(t) + hy'(t) + O(h^2) = y(t) + hy^2(t) - x(t)y(t)
\end{align*}
\]

\[
\begin{align*}
x_i, t) = x_i(t) + hax^2(t) - x_i(t)y_i(t), y_i, t) = y_i(t) + hy^2(t) - x_i(t)y_i(t)
\end{align*}
\]

(4)

Rewriting (1) as:

\[
\begin{align*}
x(t + h) &= x(t) + h \frac{1}{2}[\alpha_1 x^2(t + s) - x(t + s) y(t + s)] ds \\
y(t + h) &= y(t) + h \frac{1}{2}[\alpha_2 y^2(t + s) - x(t + s) y(t + s)] ds
\end{align*}
\]

(5)

We obtain:

\[
\begin{align*}
x(t + h) &= x(t) + h \frac{1}{2}[\alpha_1 x^2(t) - x(t)y(t) + ax^2(t + h) - x(t)y(t + h)] + O(h^3) \\
y(t + h) &= y(t) + h \frac{1}{2}[\alpha_2 y^2(t) - x(t)y(t) + ax^2(t + h) - x(t)y(t + h)] + O(h^3)
\end{align*}
\]

(6)

\[
\begin{align*}
x(t + h) &= x(t) + h \frac{1}{2}[\alpha_1 x^2(t + h) - x(t + h)y(t + h)] + O(h^3) \\
y(t + h) &= y(t) + h \frac{1}{2}[\alpha_2 y^2(t + h) - x(t + h)y(t + h)] + O(h^3)
\end{align*}
\]

(7)
In (6) and (7) we can substitute:

\[
\begin{align*}
    f(x(t + h)) &= f(x(t)) + hf'(x(t)) + O(h^2) \\
    f(x(t + \frac{h}{2})) &= f(x(t)) + \frac{h}{2} f(x(t)) + O(h^2) \\
    g(x(t + h)) &= g(x(t)) + hg(x(t)) + O(h^2) \\
    g(x(t + \frac{h}{2})) &= g(x(t)) + \frac{h}{2} g(x(t)) + O(h^2)
\end{align*}
\]

We obtain the second order accurate difference schemes:

\[
\begin{align*}
    x_{n+1} &= x_n + \frac{h}{2} [f(x_n) + f(x_n + hf(x_n))] \\
    y_{n+1} &= y_n + \frac{h}{2} [g(y_n) + g(y_n + hg(y_n))] \\
    x_{n+1} &= x_n + hf(x_n + \frac{h}{2} f(x_n)) \\
    y_{n+1} &= y_n + hg(y_n + \frac{h}{2} g(y_n))
\end{align*}
\]

Fig. 1. Graphical output from running program in MATLAB. Because many cancer cells tend to grow and divide quickly, they are sensitive to the effects of chemotherapy. The use of a small parameter here is simply for definiteness.

Fig. 2. A cancer cell may be resistant to a chemotherapy drug from the beginning. If cancer cells develop resistance to one chemotherapy drug, they may also develop resistance to other drugs in the same drug family. The parameter values have high impact on the accuracy of the model in representing real biological systems but these values are difficult to estimate experimentally.

Fig. 3. In acquired drug resistance the tumors are initially responsive, but become resistant with continued treatment. The smallness of \( \varepsilon \) is relative to the size of the solution domain. The choice of a small parameter is connected with the order of the solution and the asymptotic sequence which describes the behaviors of the solution as \( \varepsilon \to 0 \).
IV. CONCLUSIONS

The systems of ordinary differential equations containing a small parameter provide a classical framework for dynamic modeling of biomedical systems, using experimental data. The numerical analysis of the model presented in this paper could lead to a deeper understanding of the interaction between cells resistant to chemotherapy and those sensitive to chemotherapy. Chemotherapy resistance remains a major obstacle to improving a cancer patient’s outcome. Simulation of the system of differential equations containing a small parameter depending on various values of $\varepsilon(0 < \varepsilon << 1)$ parameter can generate new work hypotheses work, as well as the motivation to design new models. Obtaining experimental data at well-defined time intervals is essential for the estimation of other sufficiently precise models. The simulations carried out reveal that chemotherapy destroys $x(t)$ cells sensitive to drugs, but leaves behind a greater proportion of $y(t)$ resistant cells to medicine. As the tumour begins to grow again, chemotherapy may not have the expected effects, as $y(t)$ tumor cells left are now more resistant to chemotherapy and multiply uncontrollably. The ordinary differential system (1) can be simulated under new conditions to generate novel hypotheses that drive future experiments. Nonlinear programming and numerical integration techniques with MATLAB were used to solve this differential system.

REFERENCES