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Nonlinear dynamical model for a cancer cell death

Maura Cárdenas-García, Jesús Andrés Areola Flores, Patricia Pardo Ruiz
Facultad de Medicina Benemérita Universidad Autónoma de Puebla,
Calle 13 Sur 2702, Los Volcanes, 72420 Puebla, Pue
maura.cardenas@correo.buap.mx
Facultad de Medicina Benemérita Universidad Autónoma de Puebla,
Calle 13 Sur 2702, Los Volcanes, 72420 Puebla, Pue
jesus.arzola@correo.buap.mx
Facultad de Medicina Benemérita Universidad Autónoma de Puebla,
Calle 13 Sur 2702, Los Volcanes, 72420 Puebla, Pue
mapatrio@hotmail.com

ABSTRACT

The nonlinear biochemical processes and feedback play a crucial role in the physiology of living organism; they are powerful tools that allow us to understand the complex biochemical processes and their dynamics. Nonlinear biochemistry has been used to explain the mechanism of regulation of thyroid hormone, the Krebs cycle and blood pH. Another example of such tools is the process of cell death in various forms. There are mathematical models, which show the dynamics of protein synthesis in the cell; such models demonstrate the nonlinearity of the mechanism showing how the concentration of intracellular and extracellular proteins varies depending on metabolic needs of the cell. These models can be used to describe the dynamics of different biochemical mechanisms involved in cell death. In particular, in this paper we employ nonlinear dynamics to model in a closed system two cells, one normal and one cancerous.

Indexing terms/Keywords

Nonlinear biochemistry, single cell system.

Academic Discipline And Sub-Disciplines

Biomathematics;

SUBJECT CLASSIFICATION

Mathematical Biology Subject Classification

TYPE (METHOD/APPROACH)

Provide examples of relevant research types, methods, and approaches for this field: E.g., Historical Inquiry; Quasi-Experimental; Literary Analysis; Survey/Interview

1. INTRODUCTION

As it is well known, cancer is a multifactorial disease that develops from a cell with genetic changes induced by environmental factors. Cancer occurs in several steps: initiation, promotion and progression. Cancer is clinically detected in the promotion or progression stage, when in some cases it is no longer reversible. However in the initiation stage it can be reversible, as neighboring cells may cut the cancer cell communication by separating the extracellular matrix and prevent the formation of gap junctions. Though the cancer cell is isolated, it still sends the signals of malignancy. To do so, cancer cells harbor mutations, which enable a continuos cellular growthConsidering the above and using nonlinear dynamics, we place two cells in a closed system with constant availability of nutrients, water and oxygen, in the absence of factors of death or malignancy system.

2. NON LINEAL MODEL

Consider the case when two species consume the same resource. An example of such system can be the system consisting of two cell types, one benign and one malignant, that are in the same culture medium. The population dynamics of the species is expressed by the following system of differential equations:

$$\frac{dx}{dt} = x(\alpha_1 - \beta_1 x) - \gamma_2 y,$$

$$\frac{dy}{dt} = y(\alpha_2 - \beta_2 y) - \gamma_1 x.$$

Here "x" and "y" are the size of the population of cancer cells and benign cells, respectively, .alpha..sub.i is the growth rate of the ith species, ßi is a coefficient that describes the influence of the i-th species on itself, and yi is a coefficient that describes the influence from other species. All coefficients are positive.

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This model is a modification to conventional Lotka-Volterra model [1].

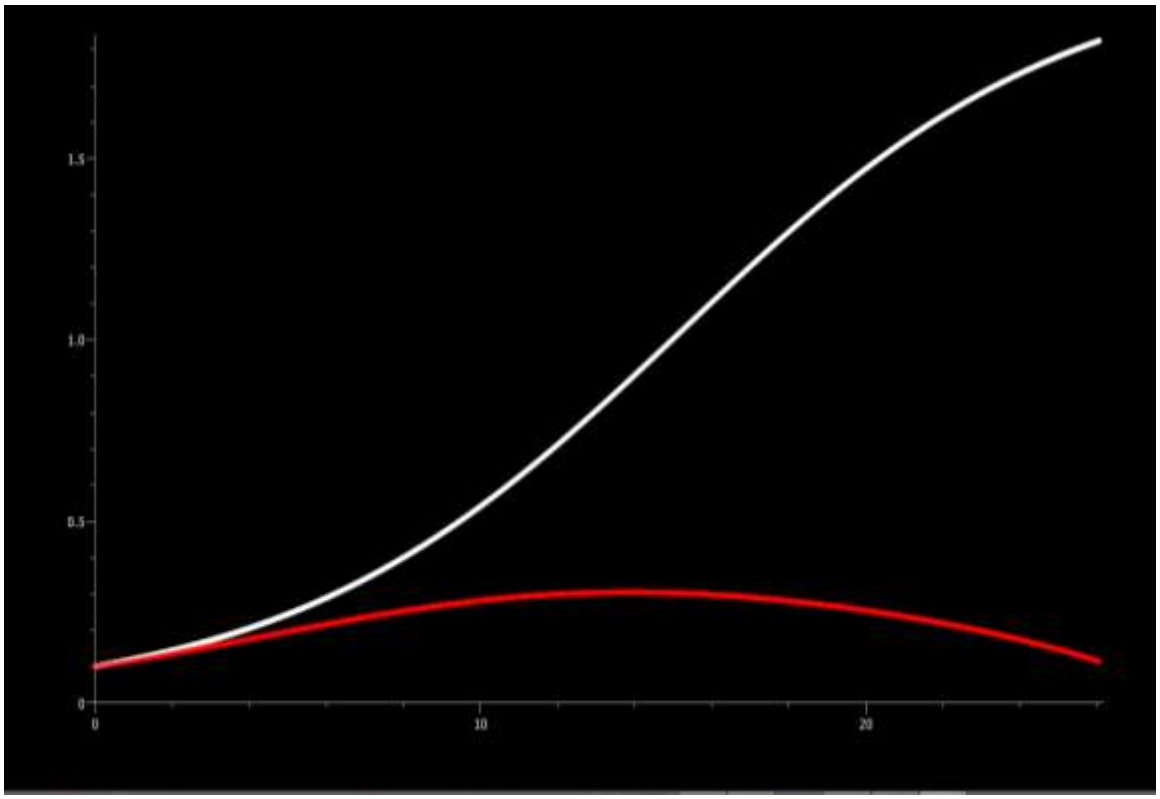

Figure 1. Numerical solution of equations (1a, 1b), computer simulation of cell growth (cell number versus time). The white line corresponds to normal cells growth and red line corresponds to the population growth of cancer cells. α_1=0.2037, α_2=0.240, β_1=0.10, β_2=0.5, γ_1=0.03, γ_2=0.01, dt=0.01, x_0=0.1, y_0=0.1

In Figure 1 it can be seen that the system of equations 1 describes the growth curves of malignant cells (red line) and benign cells (white line). It can be seen that the growth curve of benign cells has an exponential and sustained growth, as reported in the literature. Furthermore, the growth curve of benign cells (white curve) likewise has the 4 stages of normal cell growth reported in the literature (adaptation phase, exponential phase, stationary phase and cell death phase).

In addition to the dynamic system represented by equations 1, the Net-logo software was used to simulate in-silico competition of the two cell lines (malignant cells and benign cells) using a variant of the model Lotka-Volterra predation.

In this software, five control parameters were used to describe the dynamics of the system. The model consists of two types of cells, malignant and benign, both species are found in a culture medium and growth and death rates are well defined. In the model, both types of cells are fed from the culture medium to reproduce and keep their energy; when they run out of energy, both cell types die. But, before the nutrients in the culture medium are finished, it becomes enrich.This model is a variant of the model described by Wilensky and Reisman [1,2].

Model parameters

Initial number of benign cells: initial population of benign cells in the culture medium.

1. Culture medium: How long it takes for the experimenter to change the culture medium? The amount of nutrients is assumed fixed each time the culture medium is enriched i.e., the culture medium is enriched always the same amount of nutrient.
2. Feed rate of cancer cells: speed at which malignant cells are fed to continue their reproductive cycle.
3. Feed rate of benign cells: speed at which feed benign cells to continue their reproductive cycle.
4. Reproduction rate of malignant cells.
5. Benign cells rate reproduction.

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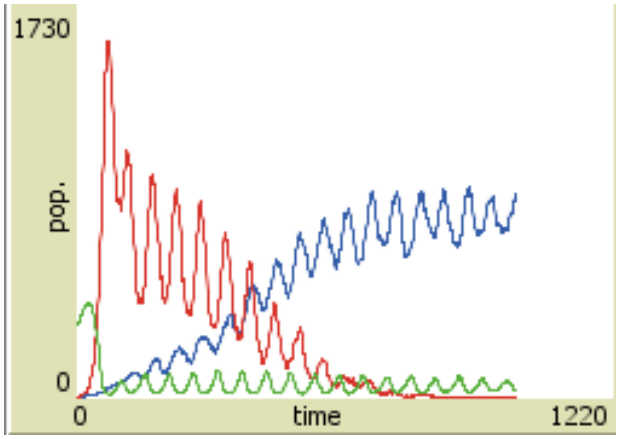


Figure 2. Simulation, Parameter 1=50, parameter 2=10, Parameter 3=6, parameter 4=10%, parameter 5=4%. Initial number of benign cells=3, initial number of malign cells=3. Red line corresponds to malign cells, blue line to benign cells and the green line the turnover rate of the culture medium.

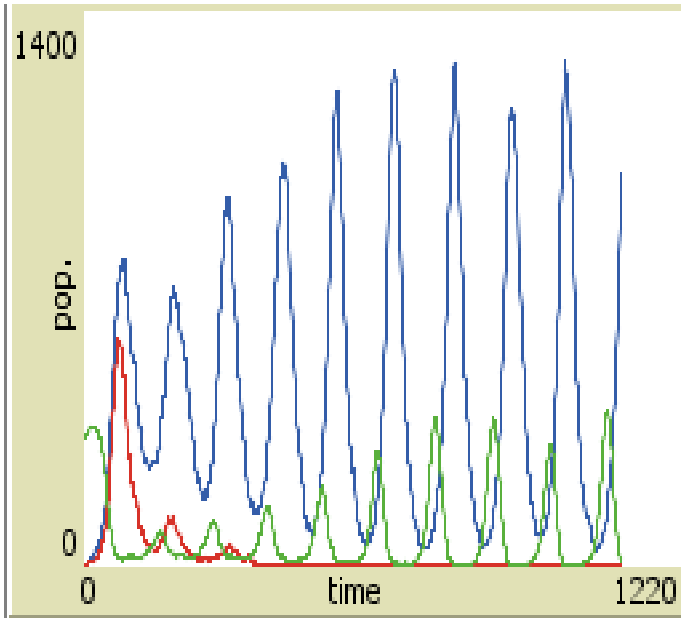
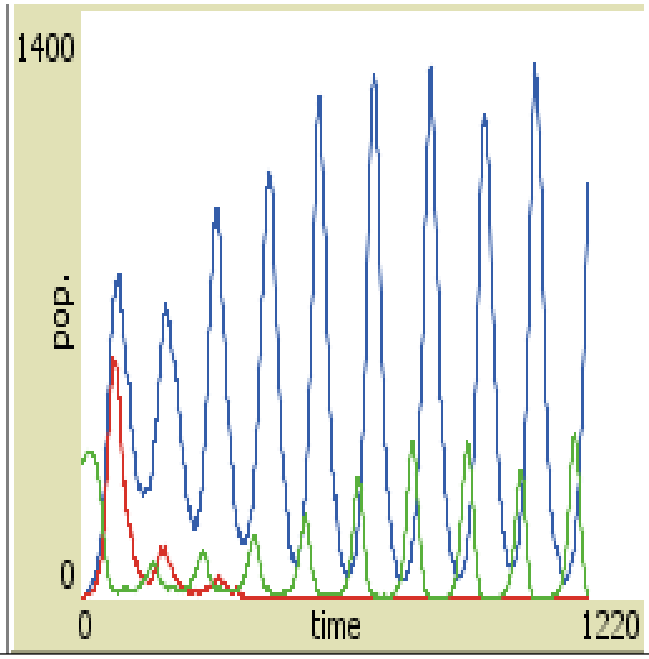


Figure 3. Simulation, Parameters 1= 100, parameter 2= 10, parameter 3=9, parameter 4= 10%, parameter 5=8%. Initial number of benign cells=3, maleficent cells=3. Red line maleficent cells, blue line benign cells the green line the turnover rate of the culture medium.

Multiple experiments were performed with different values of the five control parameters, always arriving at the same result. Figures 2 and 3 show the population of cancer cells decreases resulting in the normal development of benign cells. In mathematics, a critical or equilibrium point of a dynamic system is a system state in which the vector field is canceled or no local flow if the system is continuous, or where the succession of states is constant if the system is discrete. In physics and engineering, a critical point is one in which a system radically changes structure or behavior; for example the point of liquid-solid transition. In both cases, there is one or more control parameters the experimenter can change or adjust to change the structure or behavior. As a counterpart, there are systems that after a while reach a critical state without external controls, only driven by their internal dynamics or cooperative interactions of its components, as in the case of the model represented by Figures 2 and 3. In this case we have a system with self-organized criticality. Theorwtically, cancer cells acculated mutations, and increase growth rate, the healthy cells grow at the constant speed, do not have mutations and the finally survive. However in normal cancer cells consume nutrients so quickly that exceed the growth rate cancer cells.



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Author' biography with Photo

DC Maura Cárdenas García is born in DF province of México. She received bachelor degree, Master degree and Ph. D at Universidad Nacional Autónoma de México. Now she works in Benemerita Universidad Autónoma de Puebla. She has more than 10 published scientific works. Her interesting fields are cancer, cell differentiation, mathematical and computational models, epigenetics and nutrition. She has advised more than 10 Bachelor completed theses.

Ing Jesús Andrés Arzola Flores is born in Puebla province of México. He received bachelor degree in Benemerita Universidad Autónoma de Puebla and in Universidad Nacional Autónoma de México. Now he is Master student at BUAP.

MC Patricia Pardo Ruiz is born in Puebla province of México. She receives bachelor degree and master degree in Benemerita Universidad Autónoma de México. She works in BUAP Professor for 30 years. She was coordinator of Biochemistry academy for 25 years and now is coordinator of Biomedicine Bachelor. She has adviser more than 100 bachelor completed.

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