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HYBRID AUTOMATA: A TOOL FOR REPRESENTING BIOLOGICAL SYSTEMS

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ABSTRACT

Systems biology is an interdisciplinary study field of biological systems from the point of view of integrated systems, resulting mathematical equations that represent biological processes, interactions; all this to obtain models that allow us to save time with simulating scenarios rather than having to recreate in the laboratory and thereby expose predictions about the real world. This work aims to show the hybrid automata model as a tool to manipulate the mathematical modeling of nonlinear dynamic systems of high complexity and discontinuity, which manages systems biology. In this particular case the process of growth of the cancer population were analyzed; addressing first the behavior of the system, based on the mechanism and the mathematical model of the process, then the hybrid automaton model is applied to obtain representation and analyze their behavior.

KEYWORDS: hybrid automata, biological systems, system dynamics, nodes, transitions.

INTRODUCTION

Systems biology aims to provide an understanding of biological systems through the study of the dynamic structure of the processes of these systems with the help of control methods. These biological systems have an intrinsic nature multi-scale in both space and time levels of organization, which makes them so difficult to model even to the extent of not having a formal analysis and appropriate computational model.

This science has a fundamental tool, mathematical modeling, this gives the possibility of treating a biological phenomenon as an abstract complex system. The models obtained from this field of study can make predictions and understandings of the phenomena studied system.

The new paradigm of systems biology are complex networks with thousands of interconnected routes, so integration, representation and modeling system networks require global and systemic analysis; for example system biology has come to understand the functioning of the living cell in the human genome, so we're talking about 25,000 protein-coding genes [6].

At present there are methods and tools for analysis, modeling and simulation of processes, but these are aimed at continuous process or discrete events. It is important to have those that can be used in processes with interactions between the two entities in order to represent highly complex cases like the example above, this is where the hybrid automaton model enters [6].

The hybrid expression refers to anything that is two or more elements of different natures or types, the result is a heterogeneous nature, which is used to define systems with entities or processes of different characteristics. The term hybrid system is used for defining systems with entities or processes of different characteristics; these systems contain signals taking values continuously, and discrete variables taking values in a finite set [7].

SYSTEMS BIOLOGY

As previously mentioned systems biology are understood as general physical systems with great features and characteristics inherent complexity at different levels: organization, development, information, etc. Therefore these systems should be subject to general laws of physics and their behavior should be able to represent through the use of such laws. These biological systems are considered complex because they consist of components interconnected and have an evolutionary dynamics over time [8].

Systems biology involves all components of the system under study, this deep analysis include genes and their interactions within the cell, tissue, organ until the whole body, which makes complex character. All this was achieved thanks to the integration of biology, computation and technology, every day there is a greater motivational force through innovation.

In the study of systems biology in general it can be seen a common denominator that encompasses this complexity and diversity, even peculiar that is its structure and relations of the units that form, they can organize themselves increasing their complexity. These biological systems have the characteristics to be considered as open exchange energy or matter in their environment, have certain restrictions or external pressures that push away from equilibrium. From the dynamic point of view, these features lead to system nonlinearity; but from the physical point of view, this nonlinearity is produced as a result of the existence in the same structure instability mechanisms [8].

Mathematical models made express variables, parameters, and relationships between these entities in order to study behavior of complex systems in difficult situations to observe in reality [1]. The models obtained in this study can be continuous, discrete, or both types, and these should capture the randomness, so you need a powerful tool to work these models, which are computational models [9]. Biological systems are intended to have a mathematical model in order to:

- Predicting the behavior of a complex system (biological phenomenon, economic, etc.).
- To obtain experimental data on the system.
- Improve knowledge of the system.
- Predicting the behavior and dynamics of the system in scenarios of interest.

For the study of these biological processes the classical scientific method is used, in which a hypothesis is proposed and confronts basis of experimental results, first the system or process is identified and then assumptions are made; then the simulation approach is used, which puts the mathematical models obtained to represent the process, with this forecasting biological process is achieved and should correspond to expected experimental results [8].

The global approach that handles this field allows us to understand how works the system or biological process, to understand the internal and external interactions that it has. Any biological process can be studied in systems biology, for example, the growth of a cell, bloodstream, chemical reactions of enzymes, etc. [9].

Population of cancer cells

In this paper as mentioned above the hybrid automata model as a tool for representing the cancer population are used. The term population refers to the entire body of the same species living in a particular space in the same period; the population seems discrete variable, but for large populations can be considered continuous or differential growth, which may be reflected in an equation di reference [1].

One of the deadliest diseases of the modern world is cancer according to the American Cancer Society [3]. Cancer is understood as a cell disease, these cells begin as normal, but then altered so that they lose features and developed a new behavior, changing their appearance, membrane and growth. These cells can replace other and assume their functions that help you blend into the environment of the organ or tissue. After his primary progression, these cells migrate to their place of return (metastases) [4].

Cancer is the final stage of a long and complex evolutionary process caused by a mutation in a single cell exhibiting uncontrolled growth, breaking the cooperation that maintain the integrity of a multicellular organism. Cancer is a disease that involves changes in the genome [2].

Mathematical model of population growth of cancer cells

The mathematical model that describes the behavior of the population of cancer cells in the body we will based on the bio-mathematical model "predator-prey", which exposes two species (normal cells and cells cancer) different but related by natural selection [1]. The following considerations have:

- The system is isolated: no migration, no other cells present.
- The absence of normal cells into cancer cells growing exponentially: the playback speed is proportional to the number of individuals.
- Normal cells only die when they are replaced by cancer cells.
- Normal cells takes place in a medium (system), there is yet another addition to the declared predator model (cancer cells).
- Cancer cells consume only normal cells.

It is a system of two differential equations of the first order, coupled, autonomous and non-linear:

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$$\frac{dx}{dt} = x(\alpha - \beta y) \quad (1)$$

$$\frac{dy}{dt} = -y(\gamma - \delta y) \quad (2)$$

where:
x: normal cells.
y: cancer cells.
α: Rate of growth of normal cells.
β: elimination rate of normal cells by predators.
γ: Rate of growth of cancer cells.
δ: Rate of growth of cancer cells as a result of consumption of normal cells (cancerous growth of population in the system).
Where the speed which varies the population depends on the initial condition of both normal cells and cancer. Combining the effects of the relationship in the system, the rate of change of the population of normal cells is obtained, where the first term of the equation is the normal growth and second are natural and interaction deaths [5]:

$$\frac{dx}{dt} = ax - \beta xy \quad (3)$$

The explained reasoning above is analogous to cancer cells:

$$\frac{dy}{dt} = \delta xy - \gamma y \quad (4)$$

HYBRID AUTOMATA MODEL

The hybrid automata take their origin from the finite automaton model [12]. A finite automaton is a finite state machine allowing the in/out operation of a discrete-event system to be described. This model is simple but insufficient when time has to be taken into account. Therefore, to enrich the previous model, the timed (finite) automaton was proposed by [12].
A timed automaton is a finite automaton with a finite set of real-valued clocks. The clocks can be reset to 0 (independently of each other) with the transitions of the automaton, and keep track of the time elapsed since the last reset.
Thus, the clocks could measure the residence time within each location from the last visit. On the other hand, the timed automata model is not enough if we wish to model more than the timed evolution of the discrete transitions, the continuous evolution of the process variables. Therefore, if we wish to model the process variables evolution, we should utilize the hybrid automata model. By means of the hybrid automaton model, the system discrete state is modeled by the vertices of a graph (called control modes or locations), and the discrete dynamics is modeled by arcs (called control switches or transitions). The continuous state of the system is modeled by points in $\Re^n$ and the continuous dynamic is modeled by flow conditions such as differential equations [10].
One advantage of this model is saving time to understand scenarios rather than recreate in a laboratory and a complete compression of the analyzed system, providing a detailed breakdown of the process and its design [1].

Definition of Hybrid automata

Based on [11] [12], we consider a hybrid automaton $H=(X, S, flow, E, F, \Sigma, init)$ such that:
X: Variables. A finite ordered set $X=\{x_1, x_2, \ldots, x_r\}$ of real-valued variables.
S: Locations. A finite set of n locations $S = \{s_1, s_2, \ldots, s_n\}$.
flow: flow conditions. A labeling function flow that assigns a flow condition $flow(s_i)$ to each location $s_i \in S$ where the continuous dynamic is usually represented by differential equations.
E: Transitions. A finite set E of discrete events called transitions and represented by arcs. Each transition $T = (s_o, s_d)$ identifies a source location and a target location.
F: Jump conditions. A labeling function $F(T)$ that assigns a jump condition to each transition $T \in E$. In general, these conditions are boolean combinations of inequalities.

Σ: Events. A finite set Σ of events. A labeling function event is used to assign an event in Σ to every transition $T \in E$. The events can be used to define the parallel composition of hybrid automata.

init: Initial conditions. A labeling function *init*(s_i) that assigns an initial condition to each location si∈S. In the automata graphical representations, initial conditions appear as labels on incoming arrows without a source location.

HYBRID AUTOMATA MODEL FOR THE BIOLOGICAL SYSTEM

Consider the hybrid automata model defined by:

$$H = (X, S, flow, E, F, init)$$

where:

$X = \{x, y\}$

$S = \{s_1, s_2, s_3, s_4\}$

$E = \{T_1, \dots, T_6\}$

$F = \{F_1, \dots F_{12}\}$

$init = \{x_0 = 10, y_0 = 5\}$

$$flow(s_1) = \begin{Bmatrix} \dot{x} = ax - \beta xy \\ \dot{y} = \delta xy - \gamma y \end{Bmatrix}$$

$$flow(s_2) = \begin{Bmatrix} \dot{x} = ax \\ \dot{y} = \delta xy - \gamma y \end{Bmatrix}$$

$$flow(s_3) = \begin{Bmatrix} \dot{x} = ax - \beta xy \\ \dot{y} = -\gamma y \end{Bmatrix} \quad (5)$$

Three discrete states, s_1, s_2 and s_3 are defined and inside of the states we have a set of continuous equations describing the dynamics of population growth of normal and cancer cells as shown in Figure 1. It starts from an initial state in which the values of the populations of both normal and cancer cells are fixed; then s_1 node, has a dynamic coexistence between the two cells. In the node s_2 have a situation in which there were no cancer cells, normal cells should grow exponentially assuming an organism with saturation limit. In the node s_3 only the dynamics of the cancer cells are present.

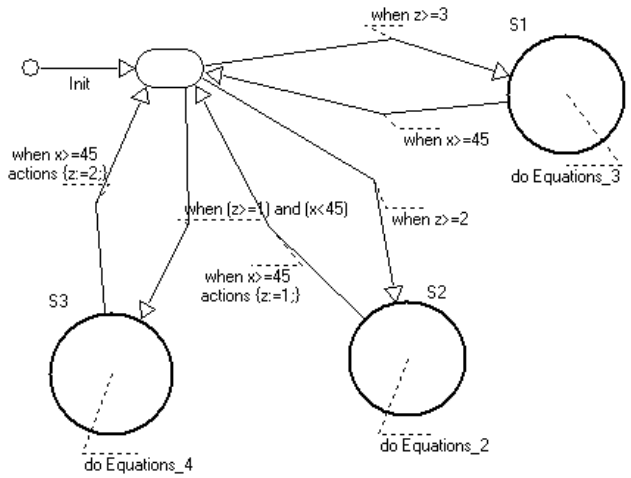

Figure 1. Hybrid Automaton model of population growth to cancer cells

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RESULTS AND DISCUSSION

A simulation was performed using the Model Vision Studium program, with an initial population of normal and cancer cells $x_0 = 10$ and $y_0 = 5$, respectively. The parameters were set for constant for $\alpha = 0.7$, $\beta = 0.2$, $\gamma = 0.1$ and $\delta = 0.3$. The following describes the different behaviors that were obtained using these values.

In Figure 2, we can observe no cancer cells, when $\beta = 0$, the population of normal cells grow exponentially as they have no threat from cancer cells, we assume the system with a saturation limit for the growth, this means the initial population of cancer cells is very small so that the response of normal cells can overcome it.

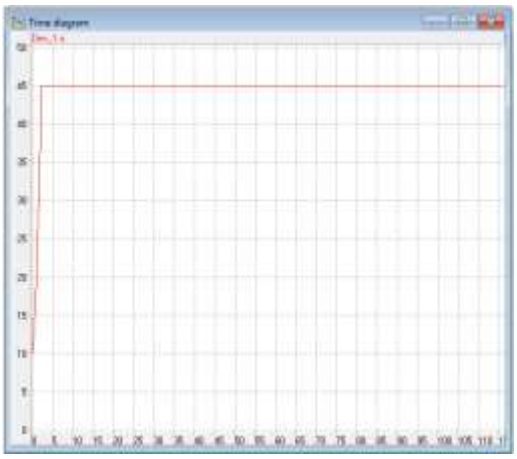

Figure 2. Behavior of normal cells when cancer cells are overcome

In Figure 3 we can see that in the absence of normal cells, when $\delta = 0$, the population of cancer cells decays exponentially because do not have normal cells to consume and increase its population; only it grows until the dynamics change and appear normal cells that can consume.

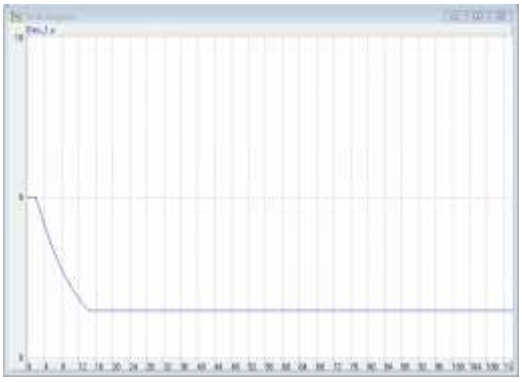

Figure 3. Behavior of cancer cells when the population of normal cells decays to zero

However we can see in Figure 1.5, if the parameters β and δ are different from zero, the population of cancer cells and normal cells coexist, we can see the dynamic system where the variation of one components of the system affects the second and the evolution of the first, achieved the balance in the system.

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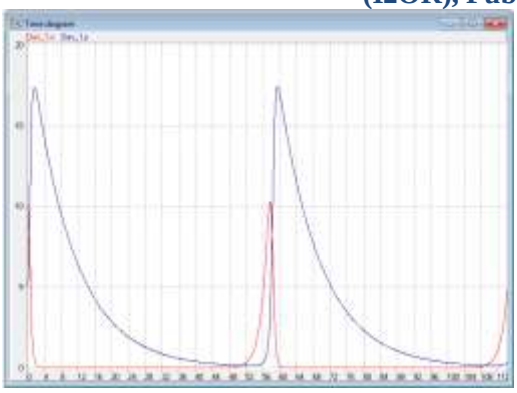

Figure 4. Behavior of cancer cells in coexistence with the population of normal cells

This means that the cancer has a controlled population growth, this is one of the steps in the evolution of the disease, cancer cells initially create a small population, growing by normal cells, they cannot destroy it, even help you. These behaviors carry a qualitative perspective model therefore leads to the following properties:

- Law of periodicity, which explains the evolution of both populations periodically.
- Conservation law of averages, the average size of the two populations are independent in their initial size.
- Disturbance law of averages, in which two populations of cells are reduced to a very small size, the average normal cells and increase of cancer decreases.

In order to verify the first law, the representation of the solution of the first model equations in its phase portrait is used. The superposition of two oscillatory functions can be seen in Figure 5 for the population of cancer cells; in Figure 6 the phase portrait for the population of normal cells is obtained.

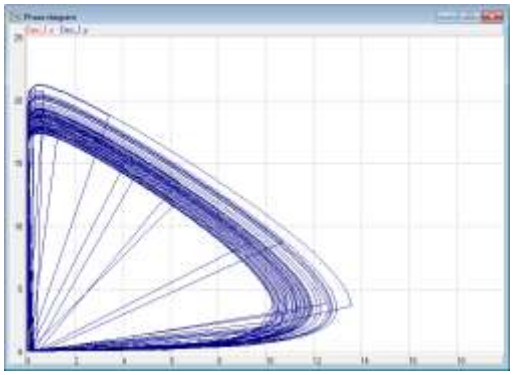

Figure 5. Population cycle of cancer cells

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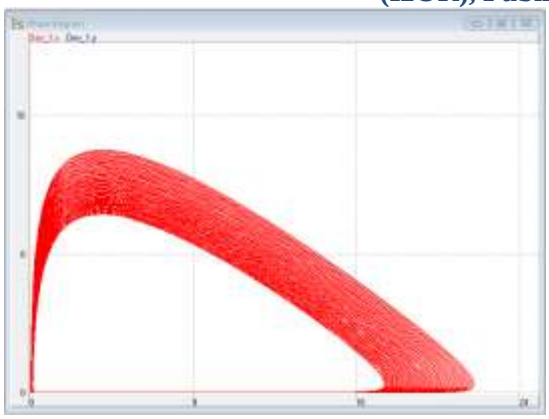

Figure 6. Population cycle of normal cells

CONCLUSION

In systems biology exits processes with hybrid features, where its components are discrete and continuous behaviors, this leads to difficulties in their modeling; it is necessary to have a precise and general tool for the model and analysis of hybrid systems. Thanks to the application of the methodology of the hybrid automata, favorable results are obtained in representing and modeling these systems, besides it includes a tool for analyzing its behavior.

With this tool you can set different conditions for certain discrete transitions, allowing you to visualize changes in this state during the course of the simulation, another important feature is concerned the time saved, because without the hybrid automata would have to work on mathematical model of the system to reduce complexity and have a large margin of error, then with computer programs run the simplified equations and obtained their simulation.

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