NONLINEAR DYNAMICAL FORMULATION FOR DESCRIBING GROWTH OF CANCER CELLS BASED ON INTRACELLULAR CONSTITUENTS

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ABSTRACT

A set of equations characterizing the interactions between RNA, DNA and proteins is postulated to describe the growth of tumor cells. From this set of equations, a method to determine the fixed points of the system is presented including the use of the Jacobian matrix. Assessment of the nonlinear dynamics around these fixed points is provided.

1. INTRODUCTION

It is widely recognized that the common and perhaps only methods to treat cancer involve the modalities radiation treatment [20], chemotherapy, surgery, microwave hyperthermia [4], and combinations of these modalities with the added possibility of immuno-gene therapy using the genetically engineered molecule interleukin-2 (recombinant rIL-2 via DNA slicing) and LAK cells (lymphocytes IL-2 exposed acting as killer cells). All of these modalities have relative merits and disadvantages. But an overriding concern is that they all fail to reduce the number of tumor cells below a level at which they cease to replicate. Thus enough tumor cells seem always to be left which forms the starting population for another nonlinear growth process. There are hundreds of types of cancer [2] and many dozen general categories including lymphoma, mammary [23], prostate [25], myeloma, brain [16], lung, leukemia, melanoma to name a few. Breast cancer [8, 11] comes to mind as one of the most publicized and difficult cancers to understand and treat effectively. In contrast, lymphoma may be treated relatively effectively by surgical removal and a secondary modality if warranted (i.e., chemo or radiation therapy).

The intent of this paper is to outline qualitatively and quantitatively the possibilities of using nonlinear mathematics [12,15,18] in explaining cell growth from a point of view of physics [5-7, 9, 13, 14] and engineering [1, 3, 10, 17, 22, 24]. A specific set of equations characterizing the interactions between RNA, DNA and proteins is postulated to describe the growth of tumor cells. From this set of equations, a method to determine the fixed points of the system is presented including the use of the Jacobian matrix. Assessment of the nonlinear dynamics around these fixed points is provided. It is hoped that this approach will lead to a greater understanding of the behavior of cancer.

2. METABOLIC CELL GROWTH BEHAVIOR

Increase in the number of livings cells, malignant or normal, requires a number of biological processes to happen between two successive cell divisions. Cell mass should approximately double, and the genetic material encoded in the cellular DNA must be provided to the two daughter cells. The time between cellular divisions, the period T, is often divided into three unequal intervals. These three intervals are referred here to as the G_1 interval, the S interval, and the G_2M interval. The G_1 interval involves cellular events which are preparatory to DNA production in the following S interval. Molecular events inside the G_1 interval are not, so we think, as clear as those occurring inside the S and G_2M intervals.

A number of models have been proposed which suggest that it is in the G1 interval that the cell decides to synthesize DNA or enter a quiescent state. And it may be at a particular development level (call it a critical point) in the G_1 interval that the decision whether or not to synthesize DNA occurs. The mechanism for DNA triggering may be delocalized in space with a stochastic flavor caused by random molecular collisions at numerous cellular sites. This may also suggest that the critical point is spread over the G_1 interval with a function describing that characteristic.

The G_1 time interval T_1 is dependent upon the nutrient environment including growth factors Some research information indicates that the sequence of events in the G_1 interval are related to proto-oncogenes, units of genetic information that code for growth factor-like proteins. Oncogenes are expressed one after another during the cell cycle. Expression of a gene begins with the production of a string of mRNA (messenger RNA) This suggests that protein generation results from RNA presence.

After the G_1 interval and before the G_2M interval, is the S interval during which DNA is actually produced. Some consider this the most vital part of cell life. The last interval, the G_2M, constitutes the time span during which the cell prepares for cell division, doing this by separating the DNA into two identical copies and then physically splitting the cell.

Another matter to be aware of is asymmetric cytokinesis, whereby the cell grows and divides into two unequal sized or constituent filled daughter cells. Both RNA and protein are unequally distributed among the daughter cells as a result of this phenomenon. Cells which have more RNA in earlier part of the G_1 interval which immediately follows cell division traverse the cell cycle faster than those that inherited less RNA. It appears that RNA is unequally divided in an apparently random way between daughter cells.

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3. FORMULATION OF NONLINEAR CELLULAR GROWTH EQUATIONS

Following other work [19], it is reasonable as a first approximation to describe the linear interactions between the concentrations of RNA, DNA, and protein by the autonomous - like equations (no explicit time dependence)

$$\frac{dR(t)}{dt} = -a_{11}R(t) + a_{21}P(t) \tag{1}$$

$$\frac{dP(t)}{dt} = a_{12}R(t) - a_{22}P(t) \tag{2}$$

$$\frac{dD(t)}{dt} = \begin{cases} 0 & t < T_1 \\ b[P(t-T_1) - P(0)] & T_1 < t \le T_1 + T_2 \\ 0 & T_1 + T_2 < t \le T \end{cases} \tag{3}$$

Here R(t), D(t), and P(t), are respectively the RNA, DNA, and protein concentrations inside the cell. These equations describe the concentration changes within the cell over time in relation to the total time T it takes for a cell mitosis or division leading to replication. The first part of the process, taking time T_1, is an interval involving no DNA synthesis. The next interval of time , of length T_2, involves DNA synthesis. The last interval again involves no DNA synthesis. This DNA behavior reflects the widely accepted view of what occurs during cellular growth and mitosis. Mitosis is that process whereby the cell duplicates the genetic information to split or divide. The other cellular organelles, proteins, and RNA are also replicated in accordance with this mitotic process.

Coefficient a_{11} gives the reduction of RNA over time and a_{21} gives the increase in RNA due to the ambient protein concentration P(t). Coefficient a_{12} gives the increase in protein concentration due to the ambient RNA concentration R(t). Coefficient a_{22} gives the reduction of protein over time.

The boundary conditions under which equations (1) through (3) are solved are

$$R(0) = P(0) = D(0) = 1 \tag{4a}$$

$$R(T) = P(T) = D(T_1 + T_2) = 2 \tag{4b}$$

Boundary conditions (4) indicate that at time t = 0 the normalized concentrations of RNA, DNA, and protein are unity, that is, there is one cell with its concommitment of constituents, including the required amounts of RNA, DNA, and protein. After the period T elapses, the cell has undergone exactly one cell division, doubling the qunantity of constituents including its RNA, DNA, and protein content. More exactly stated, just before period T, the cell has twice as much RNA, DNA, and protein, which will be used to produce the two new cells originating from the single cell in the mitotic process.

Equations (1) - (3) may be written in a more compact and general form for $T_1 < t < T_1 + T_2$ as

$$\frac{d}{dt}\begin{bmatrix} R(t) \\ P(t) \\ D(t) \end{bmatrix} = \begin{bmatrix} -a_{11} & a_{21} & 0 \\ a_{12} & -a_{22} & 0 \\ 0 & T_c & 0 \end{bmatrix}\begin{bmatrix} R(t) \\ P(t) \\ D(t) \end{bmatrix} \tag{5}$$

where T_c is the translation and subtraction constant operator

$$T_c P(t) = P(t - T_1) - P(0) \tag{6}$$

We may wish to call this system semi-autonomous because of the time translation behavior. Furthermore, the original set of equations (1) - (3) has the third equation giving dD(t)/dt with different expressions in time. This amounts to an explicit time form. Thus the original system is in reality nonautonomous. Only in the interval $T_1 < t < T_1 + T_2$ is the system autonomous with a general form

$$\dot{\mathbf{x}} = \mathbf{f_u}(\mathbf{x}) \tag{7}$$

where the dot above $\mathbf{x}$ indicates a total time derivative and $\mathbf{u}$ is the parameter space vector. $\mathbf{x}$ is the variable space vector given by

$$\mathbf{x} = [R \; P \; D]^T \tag{8}$$

and $\mathbf{f_u}$ is the nonlinear operator and $\mathbf{f_u}(\mathbf{x})$ is a vector. For the linear case of (5), it $\mathbf{f_u}$ reduces to

$$\mathbf{f_u} = \begin{bmatrix} -a_{11} & a_{21} & 0 \\ a_{12} & -a_{22} & 0 \\ 0 & T_c & 0 \end{bmatrix} \tag{9}$$

which is a matrix operator. Clearly,

$$\mathbf{f_u}(\mathbf{x}) = \mathbf{f_u}\,\mathbf{x} \tag{10}$$

The vector representation of $\mathbf{f_u}(\mathbf{x})$ is

$$\mathbf{f_u}(\mathbf{x}) = [f_1 \; f_2 \; f_3]^T \tag{11}$$

where

$$f_1 = -a_{11}R(t) + a_{21}P(t) \tag{12a}$$

$$f_2 = -a_{12}R(t) + a_{22}P(t) \tag{12b}$$

$$f_3 = b[P(t - T_1) - P(0)] \tag{12c}$$

We can postulate nonlinearities of a fairly general nature and modify (5) accordingly. Writing these equations out in an open form like (1) - (3),

$$\frac{dR(t)}{dt} = -a_{11}R(t) + a_{21}P(t) + b_1R^2(t) + b_2P^2(t) + b_{12}R(t)P(t) + \cdots \tag{13}$$

$$\frac{dP(t)}{dt} = -a_{12}R(t) - a_{22}P(t) + c_1R^2(t) + c_2P^2(t) + c_{12}R(t)P(t) + \cdots \tag{14}$$

$$\frac{dD(t)}{dt} = \begin{cases} 0 & t < T_1 \\ b[P(t - T_1) - P(0)] + B_1[P(t - T_1) - P(0)]^2 + \cdots & T_1 < t \le T_1 + T_2 \\ 0 & T_1 + T_2 < t \le T \end{cases} \tag{15}$$

For the interval $T_1 < t < T_1 + T_2$, (13) - (15) can be put into the compact form (7) where

$$f_1 = -a_{11}R(t) + a_{21}P(t) + b_1R^2(t) + b_2P^2(t) + b_{12}R(t)P(t) + \cdots \tag{16a}$$

$$f_2 = -a_{12}R(t) - a_{22}P(t) + c_1R^2(t) + c_2P^2(t) + c_{12}R(t)P(t) + \cdots \tag{16b}$$

$$f_3 = b[P(t - T_1) - P(0)] + B_1[P(t - T_1) - P(0)]^2 + \cdots \quad (16c)$$

The Jacobian matrix operator J_o on $f_u(x)$ produces the Jacobian J

$$J = J_o f_u(x) = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_3} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \frac{\partial f_2}{\partial x_3} \\ \frac{\partial f_3}{\partial x_1} & \frac{\partial f_3}{\partial x_2} & \frac{\partial f_3}{\partial x_3} \end{bmatrix} \quad (17)$$

Using the specific forms for the components of $f_u(x)$, (17) becomes

$$J f_u(x) = \begin{bmatrix} (-a_{11} + 2b_1R + b_{12}P) & (a_{21} + 2b_2R + b_{12}P) & 0 \\ (a_{12} + 2c_1R + c_{12}P) & (-a_{22} + 2c_2R + c_{12}P) & 0 \\ 0 & \partial f_3/\partial x_2 & 0 \end{bmatrix} \quad (18)$$

to second order in the nonlinear terms. Let us evaluate $\partial f_3/\partial x_2$

$$\partial f_3/\partial x_2 = \frac{\partial\{b[P(t - T_1) - P(0)] + B_1[P(t - T_1) - P(0)]^2\}}{\partial P(t)} \quad (19)$$

Notice that the first two equations in (16) are independent of D, the DNA concentration. This presumably makes sense because DNA is finally constructed from protein P and RNA R. Thus for the system as posed, we really have a 2×2 sized problem coupled to a third nonlinear equation. The 2×2 Jacobian J for this system can be extracted from (18) as

$$J = J_o f_u(x) = \begin{bmatrix} (-a_{11} + 2b_1R + b_{12}P) & (a_{21} + 2b_2R + b_{12}P) \\ (a_{12} + 2c_1R + c_{12}P) & (-a_{22} + 2c_2R + c_{12}P) \end{bmatrix} \quad (20)$$

Once the 2×2 system is solved, the nonlinear dynamical behavior of DNA can be found from (16c).

One could also suppose, since $\dot{D} = f_3(P)$ in form, that $\dot{P}$ has terms in D. Maybe, even $\dot{R}$ has D terms. Finally, maybe $\dot{D}$ may not be independent of R and D.

Nonlinear behavior can be determined locally by finding the fixed points of the system, linearizing about those fixed points, and studying the stability characteristics of the particular system under consideration. A fixed point x^* occurs at

$$\dot{x} = 0 \quad (21)$$

so that (7) becomes

$$f_u(x) = 0 \quad (22)$$

Fixed points occur when the system variable motion is zero as (21) states. It is possible to have only part of the variable space motion zero, in which case (21) will only hold for those appropriate components.

$$\dot{x}_i = 0 \qquad i = 1, \cdots, k \le N \quad (23)$$

where the system is N dimensional.

Linearizing (7) about the fixed point x^* gives

$$f_u(x) = f_u(x^*) + \left.\frac{\partial f_u(x)}{\partial x}\right|_{x = x^*} (x - x^*) + \cdots \quad (24)$$

Truncating this equation after the second term and noticing that the coefficient in the second term is just the Jacobian matrix evaluated at the fixed point x^*,

$$J = \left.\frac{\partial f_u(x)}{\partial x}\right|_{x = x^*} \quad (25)$$

(24) can be written as

$$f_u(x) = f_u(x^*) + J(x - x^*) \quad (26)$$

Defining a new variable y in reference to the fixed point

$$y = x - x^* \quad (27)$$

noting that (22) holds, and that

$$\dot{y} = \dot{x} \quad (28)$$

we find that

$$\dot{y} = Jy \quad (29)$$

Linear solution of (29) allows the determination of the types of stability behavior about the individual fixed points. All of the mathematics of linear matrix analysis can be brought to bear on the solution of (29).

4. CONCLUSION

Because the fundamental underlying growth behavior of tumor cells is nonlinear, this paper focused on studying a particular set of equations describing the interactions of DNA, RNA, and proteins in the context of a linear system and its generalization to a nonlinear system. It is hoped that the work here will lead to further research into nonlinear dynamics of cancer cellular growth. There have been many studies which have dealt with the growth of cancer cell population dynamics from an intercellular point of view [26-39], but little work has been done, as this paper has attempted, to derive models for intracellular behavior [40-46] which describe tumor growth.

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