CONTROL THEORETIC APPROACH TO ANALYSIS OF RANDOM BRANCHING WALK MODELS ARISING IN MOLECULAR BIOLOGY

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Abstract: We present two models of molecular processes described by infinite systems of first order differential equations. These models result from branching random walk processes used to represent the evolution of particles in these problems. Using asymptotic techniques based on Laplace transforms it is possible to characterize the asymptotic behavior of telomeres shortening which is supposed to be the mechanism of aging and evolution of cancer cells with increasing number of copies genes responsible for coding causing drug removal or metabolisation. The analysis in both cases is possible because they could be represented by systems with positive feedbacks.

1 PROBLEM STATEMENT

Shortening of telomeres is one of the supposed mechanisms of cellular aging and death. The hypothesis is that each time a cell divides it loses pieces of its chromosome ends. These ends are called telomeres and consist of repeated sequences of nucleotides, telomere units. When a critical number of telomere units is lost, the cell stops dividing. Telomeres are assumed to consist of telomere units repeated sequences of nucleotides. When a chromosome replicates each newly synthesized strand loses one telomere unit at one of its ends. This means that the pair of daughter chromosomes each has one old unchanged strand and one new, one unit shorter. Once a critical number of telomere units is lost a so called Hayflick checkpoint is reached and the cell stops dividing. Under this assumption, only the length of the shortest telomere will matter and thus a chromosome is said to be of type j if its shortest telomere has j remaining units (Arino, Kimmel, Webb, 1995).
The amount of DNA per cell remains constant from one generation to another because during each cell cycle the entire content of DNA is duplicated and then at each mitotic cell division the DNA is evenly apportioned to two daughter cells. However, recent experimental evidence shows that for a fraction of DNA, its amount per cell and its structure undergo continuous change. Gene amplification can be enhanced by conditions that interfere with DNA synthesis and is increased in some mutant and tumor cells. Increased number of gene copies may produce an increased amount of gene products and, in tumor cells, confer resistance to chemotherapeutic drugs. Amplification of oncogenes has been observed in many human tumor cells and also may confer a growth advantage on cells which overproduce the oncogene products (for an overview see e.g. survey in (Stark, 1993)).
We present models of this two phenomena using branching random walk machinery. The asymptotic properties of them could be found using methods of Laplace transforms and spectral analysis. Conclusions resulting from this analysis are general because we demonstrate that the models could be represented by the linear systems with positive feedbacks and therefore we are able to use some well known results from standard control theory of infinite dimensional control systems.

2 MODEL OF TELOMERE SHORTENING

The simplest model of telomere shortening is due to Levy et al.(1992). It is based on the following assumptions:

1. Each chromosome consists of 2 strands: upper and lower, each of them having 2 endings right and left.
2. Number of telomere units on both endings may be written as quadruple (a, b; c, d), where a and c correspond to left and right ending of the upper strand, while b and d correspond to left and right ending of the lower one. The only possible combinations are of the form (n–1, n; m, m) or (n, n; m,m–1).
3. Cells having chromosomes described by a quadruple (n–1, n; m, m) while dividing result in progenies of types (n–1, n–1; m, m–1) and (n–1, n; m, m). The similar rule takes place for the second type leading to the situation in which one of the progenies is always of the same type as the parent cell while the other is missing two sequences each on a different ending of a different strand.
4. The process ends when telomere endings are short enough; without loss of generality it may be viewed as the case (n–1, n; 0, 0) or (0, 0; m, m–1). In this case the cell does not divide and the single progeny is identical with the parent.

The transformation takes the form:

$$(n-1,n;m,m) \quad \begin{cases} \to (n-1,n;m,m) \\ \to (n-1,n-1;m,m-1) \end{cases} \tag{1}$$

$$(n,n;m,m-1) \quad \begin{cases} \to (n,n;m,m-1) \\ \to (n-1,n;m-1,m-1) \end{cases} \tag{2}$$

$$(n-1,n;0,0) \to (n-1,n;0,0) \tag{3}$$

$$(0,0;m,m-1) \to (0,0;m,m-1) \tag{4}$$

We can observe that such "two-dimensional" process may be simplified by introducing indices k and l denoting total number of units on both upper and lower strand for left and right endings respectively.
Denoting:

$$k = \begin{cases} 2n & \text{if} \quad (n,n;m,m-1) \quad \text{appears} \\ 2n-1 & \text{if} \quad (n-1,n;m,m) \quad \text{appears} \end{cases} \tag{5}$$

$$l = \begin{cases} 2m & \text{if} \quad (n-1,n;m,m) \quad \text{appears} \\ 2m-1 & \text{if} \quad (n,n;m,m-1) \quad \text{appears} \end{cases} \tag{6}$$

the feasible transformations are as follows:

$$(k,l) \quad \begin{cases} \to (k,l) \\ \to (k-1,l-1) \end{cases} \tag{7}$$

$$(k,0) \to (k,0) \tag{8}$$

$$(0,l) \to (0,l) \tag{9}$$

Defining $i = \min(k, l)$ leads to the simplest form of the admissible transitions:

$$i \quad \begin{cases} \to i \\ \to i-1 \end{cases} \tag{10}$$

and

$$0 \to 0 \tag{11}$$

Index i describing the state of the cell in the sense of the telomere's length may be called the type of the cell. Dynamics of this model could be represented by a system of state different equations the asymptotic behavior of which has a polynomial form as a function of the number of generation.
Deterministic model treats all cells as homogeneous, not taking into account its variability dealing mainly with different life time. The simplest approaching to real world is to treat cell doubling times as random variables with exponential distribution characterized by the same parameter α. The evolution process becomes a branching random walk with an expected number of cells of type j originated of the ancestor of type i denoted by $N_{ij}(t)$ given by the following state equation:

$$\dot{N}_{ij}(t) = \alpha N_{ij+1}(t), i \geq j \geq 0 \tag{12}$$

For finite number of nonzero initial conditions:

$$N_i(0) > 0, \ \text{i} \leq M \tag{13}$$

we have:

$$N_j(t) = \sum_{i=j}^{M} \frac{\alpha t^{i-j}}{(i-j)!} N_i(0) \tag{14}$$

where $N_j(t)$ is an average number of cells in the state j.
Once more the solution (exact solution and not only asymptotic expansion as it has been the case in the previously discussed discrete model) has a form of polynomial function of time. Moreover if we assume that the random variables representing doubling time has an arbitrary distribution the same in each generation the asymptotic formula for the average number of cells in all states could be also given by (14) with the parameter of exponential distribution substituted by the inverse of the average doubling time resulting from the assumed distribution.

We demonstrate that these rather strange asymptotic characteristics and the generality of their form is related to the positive feedback which could be discovered in all the three models of telomere shortenings.

3 MODEL OF GENE AMPLIFICATION

We consider a population of neoplastic cells stratified into subpopulations of cells of different types, labeled by numbers $i = 0, 1, 2, \ldots$. If the biological process considered is gene amplification, then cells of different types are identified with different numbers of copies of the drug resistance gene and differing levels of resistance. Cells of type 0, with no copies of the gene, are sensitive to the cytostatic agent. Due to the mutational event the sensitive cell of type 0 can acquire a copy of gene that makes it resistant to the agent. Likewise, the division of resistant cells can result in the change of the number of gene copies. The resistant subpopulation consists of cells of types $i = 1, 2, \ldots$.
The probability of mutational event in a sensitive cell is of several orders smaller than the probability of the change in number of gene copies in a resistant cell. Since we do not limit the number of gene copies per cell, the number of different cell types is denumerably infinite.
The hypotheses are as follows:

1. The lifespans of all cells are independent exponentially distributed random variables with means $1/\lambda_i$ for cells of type i.
2. A cell of type $i \geq 1$ may mutate in a short time interval $(t, t+dt)$ into a type $i+1$ cell with probability $b_i\,dt + o(dt)$ and into type $i-1$ cell with probability $d_i\,dt + o(dt)$.
3. A cell of type $i = 0$ may mutate in a short time interval $(t, t+dt)$ into a type 1 cell with probability $\alpha\,dt + o(dt)$, where α is several orders of magnitude smaller than any of b_is or d_is, i.e.
$$\alpha << \min(d_i, b_i), \quad i \geq 1. \qquad (15)$$
4. The chemotherapeutic agent affects cells of different types differently. It is assumed that its action results in fraction u_i of ineffective divisions in cells of type i.
5. The process is initiated at time $t = 0$ by a population of cells of different types.

The mathematical model has the following form:

$$\begin{cases} \dot{N}_0(t) = [1-2u(t)]\,\lambda N_0(t) - \alpha N_0(t) + dN_1(t) \\ \dot{N}_1(t) = \lambda N_1(t) - (b+d)N_1(t) + dN_2(t) + \alpha N_0(t) \\ \ldots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) + dN_{i+1}(t) + bN_{i-1}(t), \\ \qquad\qquad\qquad\qquad i \geq 2 \\ \ldots \end{cases} \qquad (16)$$

where $N_i(t)$ denotes the expected number of cells of type i at time t, and we assume the simplest case, in which the resistant cells are insensitive to drug's action, and there are no differences between parameters of cells of different type ($b_i = b > 0$, $d_i = d > 0$, $\lambda_i = \lambda > 0$, $u_i = 0$, $i \geq 1$, $\lambda_0 = \lambda$, $u_0 = u$).
The first step in the analysis is to evaluate the fate of the drug resistant subpopulation without a constant inflow from the drug sensitive subpopulation. In other words we assume that it is possible to destroy completely the sensitive subpopulation and we are interested only how the drug resistant cancer cells will develop. The analysis can be limited in this case to equations with $i \geq 1$. The asymptotic behavior of the DNA repeats may be analyzed using inverse Laplace transforms and asymptotic formulae for integration of special functions for the case where the initial condition contained only one nonzero element $N_1(0) = 1$, while $N_i(0) = 0$, $i > 1$. It is possible to extend that approach to the case of two or more non-zero elements. The solution decays exponentially to zero in this case, as $t \to \infty$ for:

$$d > 0, b > 0, \lambda > 0, d > b, \qquad (17)$$

$$\sqrt{d} - \sqrt{b} > \sqrt{\lambda} \qquad (18)$$

To analyze the conditions under which it is possible to eradicate the tumor or in other words to ensure that the entire tumor population converges to zero we may represent the model (16) in the form of the closed-loop system with two components. One part of this system is infinite dimensional and linear and represents the drug resistant subpopulation. The second part of the system is given by the first bilinear equation of the model and describes behavior of the drug sensitive subpopulation. The model may be viewed as a system with positive feedback stability of which may be analyzed using generalized Nyquist type criterion (Swierniak, *et al.* , 1999) in the case when we assume a constant therapy protocol. The analysis for other protocols could be also performed using more sophisticated tools of stability analysis.
In the similar way we may consider more general models of anticancer therapy under evolving drug

resistance such as a multi-drug chemotherapy, models including phase specificity in the sensitive compartment or models which take into account partial sensitivity of some neoplastic subpopulations (Swierniak, Smieja, 2005).

4 CONCLUSION REMARKS

In this paper we have studied asymptotic properties of two models of molecular processes each of them modeled by the random branching walk models. The properties of these models are strictly related with their structure which when considered from system theoretic point of view includes always the positive feedback. Moreover although the models have the form of infinite dimensional state equations linear or bilinear the asymptotic analysis may be performed rigorously using control theoretic tools resulting from the closed loop structure of these models. Yet another molecular process which could be analyzed using similar techniques is the evolution of tandem repeats in microsatellite DNA Once more random branching walk could be used as a basis for the model construction. Nevertheless in this case there is no positive feedback which has been used by us to simplify the asymptotic analysis of the two processes considered in this paper.

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