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Asymptotic analysis of three random branching walk models arising in molecular biology

by

Andrzej Swierniak[1], Andrzej Polanski[1], Jarosław Śmieja[1], Marek Kimmel[2] and Joanna Rzeszowska-Wolny[3]

[1] Department of Automatic Control, Silesian Technical University, ul. Akademicka 16, 44-100 Gliwice, Poland

[2] Department of Statistics, Rice University, P.O. Box 1892, Houston TX 77251, USA

[3] Department of Clinical and Experimental Biology, Institute of Oncology Branch Gliwice, 44-101 Gliwice, Poland

Abstract: Using asymptotic techniques based on Laplace transforms, spectral analysis and theory of feedback systems we characterize the asymptotic behavior of the repeat loci in microsatellite DNA and cancer cells with incresasing number of copies of genes responsible for coding proteins causing drug removal or metabolisation as well as telomeres shortening, which is supposed to be the mechanism of aging and death. These three problems are described by models in the form of infinitely many differential linear or bilinear first order equations resulting from branching random walk processes used to represent the evolution of particles in these problems.

Keywords: asymptotic analysis, biomathematical modeling, branching processes, infinite dimensional systems.

1. Problem statement and motivation

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,

this assumption, only the lenght 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. This leads to a model where a type j chromosome gets two offsprings, one of type j and one of type $j-1$. Cells of type 0 do not divide.

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 (1995)). The simplest models of gene amplification in Kimmel and Axelrod (1990) assume the above process. Cells with 2^{j-1} gene copies are said to belong to type j (with 0 gene copies, to type 0). The parameters of the models are the probabilities of gene *amplification* and *deamplification*, and average life times, respectively. The moment of death represents in this case the moment of cell division.

The shortest non-coding repeats of DNA, which are the subject of this presentation are microsatellites. Microsatellites are the repetitive sequences composed of 2 to 5 nucleotide motifs, (for review see e.g. Ramel (1997)). Formation of tandem repeats composed from such short units occurs most probably as a result of DNA replication errors in which slippage through strand occurs. The slippage of polymerase during replication leads to base pairs mismatching and, if not repaired, gives rise to elongation or shortening of the microsatellite with one or more repeated unit. The stability of the number of repeats in microsatellite sequence depends on the intact mismatch DNA repair. The changes in the number of repeats in microsatellites accompany some human diseases. Disorders such as Hutington's disease, spinocerebellar ataxia type 1, syndrome of fragile X chromosome, myotonic dystrophy and other are related to expansion of repeated units in microsatellites lying in the vicinity of some genes Green (1993). In this case we consider a population of individuals stratified into subpopulations with different variants of a repeat sequence, labeled by numbers $i = 0, 1, 2, \ldots$.

In all these processes the simplified time evolution of the population distribution can be described by a branching random walk Athreya and Ney (1972) with an absorbing boundary defined as the multitype branching.

We focus our interest on the stability analysis of the models resulting from the analysis of these three processes.

We use techniques from Swierniak, Kimmel and Polanski (1996) including inverse Laplace transforms for non-rational functions Doetsch (1964) and asymp-

can provide stability conditions for the case of initial conditions with finite support, and they give us conditions for model parameters for our further study. Using the obtained relations between parameters we formulate the model of DNA repeats' evolution as a differential equation in Banach space and we study its stability by examining spectra of the appropriate infinite-dimensional operators. We are able to calculate analytically the resolvent sets and the spectra of the operators and then to obtain analytical stability conditions. These conditions are related to the distribution of the number of repeats or the number of gene copies. The tail of this distribution must decay sufficiently fast in order for the system to be stable. Such problems do not exist in the case of the telomere shortening model because it does not allow for infinite increase of the type of particles. We use also some well-known results for feedback systems to analyse more realistic models of drug resistance evolutions and telomere shortening.

2. Model of telomere shortening

The simplest model of telomere shortening is due to Levy, Allsopp, Futchert, Grieder and Harley (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. The number of telomere units on both endings may be written as the quadruple $(a, b; c, d)$, where a and c correspond to the left and right ending of the upper strand, while b i d corresponds to the left and right ending of the lower one. The sole possible combinations are of the form $(n-1, n; m, m)$ or $(n, n; m, m-1)$.

2) Cells having chromosomes described by the quadruple $(n-1, n; m, m)$, when 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.

3) The process ends when telomere endings are short enough; without loss of generality it may be viewed as the case of $(n-1, n; 0, 0)$ 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:

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

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

$$(n-1, n; 0, 0) \to (n-1, n; 0, 0)$$

$$(0, 0; m, m-1) \to (0, 0; m, m-1)$$

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

By denoting:

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

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

we obtain the feasible transformations as follows:

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

$$(k,0) \to (k,0)$$

$$(0,l) \to (0,l).$$

Defining $i = min(k,l)$ leads to an even simpler form of the admissible transitions:

$$i \begin{cases} \to i \\ \to i-1 \end{cases}$$

and

$$0 \to 0.$$

Index i, describing the state of the cell in the sense of the telomere's length may be called the type of cell. Thus, a particle of type i produces after death two cells, one of type i and the other of type $i-1$, for $i > 0$, while 0 type particle always is substituted by the particle of the same type. In this sense particles of type 0 are immortal but also not creative.

If we denote by $M_i(t)$ the number of cells of type i in the discrete time t we have the following deterministic model of cell evolution with corresponding length of telomeres:

$$M_i(t+1) = M_i(t) + M_{i+1}(t); \quad i, t \geq 0. \tag{1}$$

For the initial condition:

$$M_i(0) = \delta_{ij}, \quad j \geq 0 \tag{2}$$

where δ_{ij} is the Kronecker symbol, we obtain the number of type i cells originating from one cell of type j in time t:

$$M_i(t) = \begin{pmatrix} t \\ \end{pmatrix} \tag{3}$$

assuming $0 \leq j - t \leq i \leq j$.

Thus, the number of cells of type i, originating from different cells defined in $t = 0$ by initial conditions:

$$M_j(0) > 0, \quad j \leq N \tag{4}$$

is given as

$$M_i(t) = \sum_{j=i}^{min(N,i+t)} \binom{t}{j-i} M_j(0). \tag{5}$$

For long horizons it can be approximated by:

$$M_i(t) \sim \frac{t^{N-i}}{(N-i)!} M_N(0) \tag{6}$$

and the sum of cells of all types tends to:

$$M_\Sigma = \sum_{i=0}^{N} M_i(t) \sim \frac{t^N}{N!} M_N(0). \tag{7}$$

The deterministic form of the model treats the whole population as homogeneous, not taking into account its variability associated mainly with different life time. The simplest way of getting closer to the real world is to treat cell doubling times as iid 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 by the ancestor of type i, denoted by $M_{ij}(t)$, given by the following state equation Arino, Kimmel and Webb (1995):

$$\dot{M}_{ij}(t) = \alpha M_{ij+1}(t); \quad i \geq j \geq 0. \tag{8}$$

For the initial condition:

$$M_{ij}(0) = \delta_{ij} \tag{9}$$

the solution is similar to the one resulting from the deterministic model:

$$M_{ij}(t) = \frac{(\alpha t)^{i-j}}{(i-j)!} \tag{10}$$

while for the initial conditions:

$$M_i(0) > 0, \quad i \leq N \tag{11}$$

we have:

$$M_j(t) = \sum^{N} \frac{(\alpha t)^{i-j}}{(i-j)!} M_i(0) \tag{12}$$

where $M_j(t)$ is an average number of cells in the state j.

The case of arbitrary time distribution is much more complicated and does not lead usually to the closed form of the state equations. Nevertheless, if all cells of different type have the common distribution of life time $G(t)$ with mean m, the average number of type j cells originated from ancestor type i are given by Olofsson and Kimmel (1999):

$$M_{ij}(t) = \sum_{n=i-j}^{\infty} \binom{n}{i-j} (1-G) * G^{*n}(t) \tag{13}$$

where $*$ is a convolution, G^{*n} is n-fold convolution of the distribution function, and $\binom{n}{i-j}$ is an average number of type $i-j$ cells in the n-th generation. Time domain analysis of asymptotic behaviour of (13) is near to impossible. Its Laplace transform is given as:

$$\widehat{M_{ij}}(s) = \left(\frac{\widehat{G}(s)}{1-\widehat{G}(s)} \right)^{i-j} \tag{14}$$

From control theoretic point of view it is a cascade of $i-j$ identical systems with the unit positive feedback and main loop transfer function $\widehat{G}(s)$. If

$$\lim_{s \to 0} \widehat{G}(s) = 1 \tag{15}$$

then for small s:

$$\frac{\widehat{G}(s)}{1-\widehat{G}(s)} \sim \frac{1}{ms}. \tag{16}$$

Thus

$$\widehat{M_{ij}}(s) \sim \left(\frac{1}{ms} \right)^{i-j}. \tag{17}$$

For large t the Tauberian theorem (e.g. Doetsch (1964)) leads to the following asymptotic result:

$$M_{ij}(t) \sim \frac{t^{i-j}}{m^{i-j}(i-j)!}, \tag{18}$$

which is consistent with the solution for exponentially distributed intermitotic times with parameter being an inverse of m.

3. Model of gene amplification

In the dynamical process of gene amplification cells of different types are identified with different numbers of copies of the drug resistance gene and differing

the cytostatic agent. Due to the mutational event the sensitive cell of type 0 can acquire a copy of the 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. This factor can have a strong influence on the evolution of drug resistance of cancer cells and in turn becomes one of the most important reason for failure of cancer chemotherapy.

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 the 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 $d_i dt + o(dt)$. 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, ie.
$$\alpha \ll \min(d_i, b_i), \quad i \geq 1. \tag{19}$$
3. 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.
4. The process is initiated at time $t = 0$ by a population of cells of different types.

We denote by $N_i(t)$ the expected number of cells of type i at time t, and for simplicity we assume that the resistant cells are insensitive to drug's action. Moreover, in the simplest case the differences between parameters of cells of different types are small enough to be neglected, leading to parameters independent of the type of cells:

$$b_i = b > 0, \quad d_i = d > 0, \quad \lambda_i = \lambda > 0, \quad u_i = 0, \quad i \geq 1,$$
$$\lambda_0 = \lambda, \quad u_0 = u$$

This leads to the following form of the model for the considered system:

$$\begin{cases} \dot{N}_0(t) = [1-2u(t)]\lambda N_0(t) - \alpha N_0(t) \\ \qquad\quad + dN_1(t), \\ \dot{N}_1(t) = \lambda N_1(t) - (b+d)N_1(t) \\ \qquad\quad + dN_2(t) + \alpha N_0(t), \\ \qquad\quad \dots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) \\ \qquad\quad + dN_{i+1}(t) + bN_{i-1}(t), \\ \qquad i \geq 2, \\ \qquad\quad \dots \end{cases} \tag{20}$$

We assume (as postulated in literature, see e.g. Kimmel and Axelrod (1990)) that the deamplification ratio is greater than the one of amplification $d > b$. It means that the process is subcritical.

Now, assume that the sensitive subpopulation could be completely anihilated by the drug i.e. $N_0(t) = 0$. Moreover assume that at the initial time $t = 0$, $N_k(0) \geq 0$; $k \leq K$, $N_i(0) = 0$, $i > K$, and denote $N(t) = \sum_{i \geq 1} N_i(t)$.

In this case our system is modelled by the following linear state equations:

$$\begin{cases} \dot{N}_1(t) = \lambda N_1(t) - (b+d)N_1(t) \\ \quad + dN_2(t), \\ \quad \dots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) \\ \quad + dN_{i+1}(t) + bN_{i-1}(t), \\ \quad i \geq 2, \\ \quad \dots \end{cases} \tag{21}$$

Using the approach elaborated in Swierniak, Polanski, Kimmel, Bobrowski and Śmieja (1999) (only for $K = 1$), we can investigate the asymptotic properties of $N_1(t)$ and $N(t)$ for the case of arbitrary (but finite) number of nonzero initial conditions. Denote Laplace transforms of $N_1(t)$ and $N(t)$ by $\widehat{N}_1(s)$ and $\widehat{N}(s)$.

Then, for the initial condition:

$$N_i(0) = \delta_{ik} \tag{22}$$

$$\widehat{N}_1(s) = \left(\frac{s - \lambda + b + d - \sqrt{(s - \lambda + b + d)^2 - 4bd}}{2b} \right)^k / d. \tag{23}$$

$$\widehat{N}(s) = \left(-\left(\frac{s - \lambda + b + d - \sqrt{(s - \lambda + b + d)^2 - 4bd}}{2b} \right)^k + 1 \right) \frac{1}{s - \lambda}. \tag{24}$$

Note that

$$((s + b + d) - \sqrt{(s + b + d)^2 - 4bd})^k$$

is the Laplace transform of

$$(2\sqrt{bd}/t)^k I_k(2\sqrt{bdt}) \exp[(-b - d)t],$$

where $I_k(.)$ is the modified Bessel function of order k, see e.g. Doetsch (1964). The system linearity leads to the following result, which generalizes our Theorem 3.1 from Swierniak, Polanski, Kimmel, Bobrowski and Śmieja (1999) obtained using the methods of Swierniak, Kimmel and Polanski (1996), based on the inverse Laplace transforms technique and Laplace asymptotic expansions.

THEOREM 1 *For the initial condition:*

the expected number of resistant cells of type 1 evolves according to the equation:

$$N_1(t) = \sum_{k \le K} (k/d) I_k(2\sqrt{bd}t)(\sqrt{d/b})^k e^{[\lambda-(b+d)]t} N_k(0), \tag{25}$$

while the evolution of the expected number of all resistant cells is given by:

$$N(t) = \sum_{k \le K} (e^{\lambda t} - e^{\lambda t} k(\sqrt{d/b})^k \int_0^t \frac{I_k(2\sqrt{bd}\tau)}{\tau} e^{-(b+d)\tau} d\tau) N_k(0). \tag{26}$$

Moreover, in the case when $k = 1$:

$$N_1(t) \sim \frac{1}{2\sqrt{\pi}\sqrt[4]{(bd)^3}} t^{-3/2} e^{[\lambda-(\sqrt{d}-\sqrt{b})^2]t}, \tag{27}$$

$$N(t) \sim \frac{d}{2\sqrt{\pi}\sqrt[4]{(bd)^3}(\sqrt{d}-\sqrt{b})^2} t^{-3/2} e^{[\lambda-(\sqrt{d}-\sqrt{b})^2]t}. \tag{28}$$

The asymptotic expressions are based on the formulae for asymptotic expansions of $I_1(t)$ and $\int_0^t \frac{I_1(2\sqrt{bd}\tau)}{\tau} e^{-(b+d)\tau}\, d\tau$, given in Lemma 1 and Lemma 2 in Kimmel and Stivers (1994) (obtained via the Laplace method for integrals, de Bruijn (1958)) and are valid only for the subcritical case.

Both (27) and (28) are valid for $t \to \infty$. From (27) and (28), the condition both $N_1(t)$ and $N(t)$ to converge exponentially to zero, as $t \to \infty$, is:

$$\sqrt{d} - \sqrt{b} > \sqrt{\lambda}. \tag{29}$$

The analysis of the asymptotic behavior of the resistant subpopulation was carried out under the assumption that there was no influx from the sensitive compartment. However, using tools of feedback systems analysis we can overcome this unrealistic assumption. Assuming that the initial condition for (1) is zero, $N_i(0) = 0, i = 1, 2 \ldots$, and using calculations similar to those previously performed in Swierniak, Polanski, Kimmel, Bobrowski and Śmieja (1999) we find that the function $N_1(t)$ is a convolution of two functions: $\alpha N_0(t)$, and the free solution for the first state variable $N_1(t)$ of equation (2) (being also the impulse transfer function of the system) in the case analysed in Theorem 1 for $K = 1$. Thus, for the Laplace transforms we have

$$\widehat{N}_1(s) = \alpha \frac{s - \lambda + b + d - \sqrt{(s-\lambda+b+d)^2 - 4bd}}{2bd} \widehat{N}_0(s). \tag{30}$$

Therefore

$$\alpha \frac{s - \lambda + b + d - \sqrt{(s-\lambda+b+d)^2 - 4bd}}{2bd}$$

is the transfer function of the system with input N_0 and output N_1.

The equations of the asymptotic model without cell influx have the same form as a part of the drug resistance model (1). The model including both the sensitive and the resistant parts of the neoplastic population may be treated as a system with positive feedback. In the case of constant dosage of a cytotoxic agent the stability analysis can be based on the Nyquist criterion (see e.g. Zadeh and Desoer (1963)). In this case we have:

$$\widehat{N}_0(s) = \frac{d}{s + \alpha - (1-2u)\lambda}\widehat{N}_1(s). \tag{31}$$

The loop transfer function for the system is

$$K(s) = \frac{\alpha[s - \lambda + b + d - \sqrt{(s-\lambda+b+d)^2 - 4bd}]}{2b[s + \alpha - (1-2u)\lambda]}. \tag{32}$$

The frequency response of (32) is:

$$K(j\omega) = K(s)|_{s=j\omega}. \tag{33}$$

By the analysis of the relation (32), it can be verified that the supremum is achieved for $\omega = 0$, with the condition that both transfer functions define stable systems. As a result we can state the following conditions of exponential stability of the drug resistance model (1):

THEOREM 2 *The model of the drug resistance (1) is exponentially stable if:*

$$\sqrt{d} - \sqrt{b} > \sqrt{\lambda}. \tag{34}$$

(Stability condition for resistant population).
and

$$u > 0.5 + \frac{\alpha}{d - b - \lambda + \sqrt{(b+d-\lambda)^2 - 4bd}} \tag{35}$$

(Stability condition for the feedback loop).

The stability condition of the sensitive compartment ($u > 0.5 - \frac{\alpha}{2\lambda}$) is included in the condition (35). Condition (35) makes sense only if (34) is satisfied. Inequality (35) gives the smallest value u which ensures asymptotic elimination of cancer cell population.

4. Modelling microsatellite DNA repeats

To model the evolution of DNA repeats in microsatellites, we consider a population of individuals stratified into subpopulations, indexed by the number of repeats of the considered motif, described by a branching random walk with an absorbing boundary defined as the following multitype branching process (see

1) There exist denumerably many types of particles, labeled $i = 0, 1, 2, \ldots$.

2) Each particle survives for a random time, distributed exponentially with parameter θ.

3) Upon its death, each particle produces a pair of progeny, each of which independently survives with probability β.

4) Each progeny of an i-th type ($i \geq 1$) is independently distributed among types $i-1, i+1$ or i with probabilities ν, η and $1-\nu-\eta$ respectively.

5) Each progeny of a 0-type particle is of type 0.

$$\begin{cases} \dot{N}_0(t) = \lambda N_0(t) + dN_1(t), \\ \dot{N}_1(t) = \lambda N_1(t) - (b+d)N_1(t) \\ \quad + dN_2(t), \\ \quad \cdots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) \\ \quad + dN_{i+1}(t) + bN_{i-1}(t), \quad i \geq 2, \\ \quad \cdots \end{cases} \tag{36}$$

We assume that there exist $N_i(0)$ particles of each type i at $t = 0$, and $N_i(t)$ is the expected number of particles of type i at time t.

Moreover,

$$d = 2\beta\nu\theta, \quad b = 2\beta\eta\theta, \quad \lambda = (2\beta - 1)\theta \tag{37}$$

and $d > 0, \quad b > 0, \quad \lambda > 0, \quad d > b$

Since equations with $i \geq 1$ do not include $N_0(t)$ and we are interested only in the fate of tandem repeats and not of the whole population (notice that in this model subpopulation of type 0 always grows exponentially), therefore the analysis can be limited to equations with $i \geq 1$ of the form:

$$\begin{cases} \dot{N}_1(t) = \lambda N_1(t) - (b+d)N_1(t) \\ \quad + dN_2(t), \\ \quad \cdots \\ \dot{N}_i(t) = \lambda N_i(t) - (b+d)N_i(t) \\ \quad + dN_{i+1}(t) + bN_{i-1}(t), \quad i \geq 2, \\ \quad \cdots \end{cases} \tag{38}$$

The main point considered is the asymptotic stability of this model, equivalent to the disappearance of the repeat locus.

The asymptotic behavior of the DNA repeats may be analyzed using the results of the previous section. In this case nonzero initial conditions must be, however, finite. In this section we will analyze the stability of the model (38) using the theory of infinite-dimensional systems as this was performed in Kimmel, Swierniak and Polanski (1998) for the gene amplification model. We will allow infinitely many elements $N_i(0)$ not equal to 0. We will formulate the stability analysis problem in the terms of spectral properties of an appropriate

of the previous section, that for finite k the solution starting from $N_k(0) > 0$, $N_i(0) = 0$, $i \neq k$ decays exponentially to zero, as $t \to \infty$:

$$d > 0, \quad b > 0, \quad \lambda > 0, \quad d > b, \tag{39}$$

$$\sqrt{d} - \sqrt{b} > \sqrt{\lambda}. \tag{40}$$

or equivalently

$$\nu > \eta > 0, \quad \theta > 0, \quad \beta > 0.5 \tag{41}$$

$$\sqrt{\nu} - \sqrt{\eta} > \sqrt{1 - 1/\beta}. \tag{42}$$

We denote the solution vector of system (38) by

$$\mathbf{N}(t) = \mathrm{col}[N_1(t), N_2(t), \ldots],$$

and the initial condition by

$$\mathbf{N}_0 = \mathbf{N}(0) = \mathrm{col}[N_1(0), N_2(0), \ldots].$$

The generating function of $\mathbf{N}_0$ is denoted by $\mathcal{N}_0(s) = \sum_{i\geq 1}^{\infty} N_i(0)s^i$. It seems most appropriate to choose the initial condition from space l_1 of the absolutely summable infinite sequences with the norm

$$|\mathbf{N}| = \sum_{i\geq 1} |N_i|. \tag{43}$$

Note that the Hilbert space l_2, which includes l_1 as its subspace, is inappropriate for our analysis. The reason is that the sum of squares of elements of $\mathbf{N}(t)$ does not provide information about the total number of repeat loci. However, the l_1-norm may grow to infinity for some solutions. This suggests formulating the problem in a different space, included in l_1, which imposes additional conditions on the rate of decay of N_i's. Let us write the system (38) in the form

$$\dot{\mathbf{N}}(t) = \mathbf{A}\mathbf{N}(t), \tag{44}$$

where $\mathbf{N}(t)$ belongs to a Banach space B and $\mathbf{A}$ is now a linear operator mapping B into itself. The form of $\mathbf{A}$ is implied by the system of equations (38). We will consider B being the space l_1^R of infinite sequences summable exponentially with base $R > 1$, i.e.

$$\mathbf{N} \in l_1^R \iff |\mathbf{N}|_R = \sum_{i\geq 1} |N_i| R^i < \infty. \tag{45}$$

The analysis based on Theorems 1 and 2 in, Swierniak, Polanski, Kimmel,

THEOREM 3 *The system is exponentially stable* ($\sup\{\Re(\mu) : \mu \in \sigma_R(\mathbf{A})\} < 0$) *for the values of the base parameter* R *in the range* $R \in (s_1, s_2)$ *where* s_1, s_2 *are the roots of the equation:*

$$-bs + (-\lambda + b + d) - \frac{d}{s} = 0. \tag{46}$$

Then, the Banach spaces l_1^R with $R \in (s_1, s_2)$ are stable state spaces for the system (38). Choosing initial conditions from these spaces results in solutions converging to zero.

It is interesting to note that increase of the value R ($R \in [s_2, \infty)$) results in the loss of the exponential stability property. However, one should remember that exponential stability is in terms of the norm in l_1^R, which changes with R.

The results for the infinite dimensional model are important, since any finite approximation of (38) demonstrates only partially the asymptotic properties of the model (see e.g. Mitkowski (1999)).

5. Discussion

In this paper we have studied asymptotic properties of the three molecular processes, each of them being modelled by the random branching walk models. Although all the models have the form of infinite dimensional systems of ordinary linear or bilinear equations, their asymptotic behaviours are different. Under the assumptions arising from biological meaning of the system parameters one can find some additional conditions leading to stable behaviour of the considered parameters. Nevertheless, the particular form of each of the model implies the need of different tools for the analysis. The methods used in this study include the Laplace transforms machinery, spectral analysis for infinite operators, techniques of the theory of feedback systems, and asymptotic expansions of special functions. This study generalizes some previously published results of the authors (see Arino, Kimmel and Webb (1995), Kimmel and Axelrod (1990), Kimmel, Chakraborty, Stivers and Deka (1996), Kimmel and Stivers (1994), Kimmel, Swierniak and Polanski (1998), Swierniak, Polanski, Kimmel, Bobrowski and Śmieja (1999), Swierniak, Kimmel and Polanski (1996), Olofsson and Kimmel (1999)) dealing with only one of the discussed processes, indicates similarities and differences between the models of these processes, techniques of analysis and asymptotic properties. Moreover, it is for the first time that we discuss so extensively the role of positive feedbacks in the considered models. It is worth noting that the models, although looking quite simple, for large range of parameters, beyond the scope discussed in our paper, may manifestate complex behaviour (including chaotic trajectories) (see e.g. Banasiak and Lachowicz (2001)).

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References

O. ARINO, M. KIMMEL and G.F. WEBB (1995) Mathematical modeling of the loss of telomere sequences. *J. Theor. Biol.*, **177**, 45–57.

K.B. ATHREYA and P.E. NEY (1972) *Branching Processes.* Springer, New York.

J. BANASIAK and M. LACHOWICZ (2001) Topological chaos for birth-and-death type models with proliferation. *Math. Models Methods Appl. Sci.* (to be published, now accessible in the *Preprint of Univ. of Natal*, n.4).

N.G. DE BRUIJN (1958) *Asymptotic Methods in Analysis.* North-Holland, Amsterdam.

G. DOETSCH (1964) *Introduction to the Theory and Application of the Laplace Transform.* Springer, Berlin.

H. GREEN (1993) Human genetics diseases due to codon reiteration: relationship to evolutionary mechanism. *Cell*, **74**, 955–956.

M. KIMMEL and D.E. AXELROD (1990) Mathematical models of gene amplification with applications to cellular drug resistance and tumorigenicity. *Genetics*, **125**, 633–644.

M. KIMMEL, R. CHAKRABORTY, D.N. STIVERS and R. DEKA (1996) Dynamics of repeat polyphormisms under forward-backward mutation models: within- and between-population variability at microsatellite loci. *Genetics*, **143**, 549–555.

M. KIMMEL and D.N. STIVERS (1994) Time-continuous branching walk models of unstable gene amplification. *Bull. Math. Biol.*, **56**, 337–357.

M. KIMMEL, A. SWIERNIAK and A. POLANSKI (1998) Infinite dimensional model of evolution of drug resistance of cancer cells. *J. Mathematical Systems, Estimation, and Control* **8**, 1–16.

M.Z. LEVY, R.C. ALLSOPP, A.B. FUTCHERT, C.W. GRIEDER and C.B. HARLEY (1992) Telomere end-replication problem and cell aging. *J. Molec. Biol.*, 225, 951–960.

W. MITKOWSKI (1999) Dynamic properties of chain systems with applications

P. OLOFSSON and M. KIMMEL (1999) Stochastic models of telomere shortening. *Math.Biosci.*, **158**, 75–92.

C. RAMEL (1997) Mini- and microsatellites. *Environmental Health Perspectives*, **105**, 781–789.

G.R. STARK (1995) Regulation and mechanisms of mammalian gene amplification. *Adv. Cancer Res.*, **61**, 87–113.

A. SWIERNIAK, A. POLANSKI, M. KIMMEL, A. BOBROWSKI and J. ŚMIEJA (1999) Qualitative analysis of controlled drug resistance model – inverse Laplace and semigroup approach. *Control and Cybernetics*, **28**, 61–89.

A. SWIERNIAK, M. KIMMEL and A. POLANSKI (1996) Control problems arising in chemotherapy under evolving drug resistance. *Preprints of the 13th World IFAC Congress*, **B**, 411–416.

L.A. ZADEH and C.A. DESOER (1963) *Linear System Theory.* McGraw-Hill, New York, 1963.