Modeling growth as a continuous time stochastic telomere-regulated process and the Gompertzian kinetics

C. Landim∗ † R. D. Portugal‡ B. F. Svaiter§ ¶

Abstract

Telomere are nucleo-proteins located at the end terminal of eukaryotic chromosomes which shorten at each cell division. Recent evidences points to telomere as a cell clock mechanism which limits the total number of cell divisions (Hayflick limit) and decelerates cellular proliferation. In a recent work, simulations of a discrete time stochastic telomere regulated model for cell division produced growth curves similar to those observed in mesenchymal human stem cells and quantitatively very similar to Gompertzian Growth.

In this work we considered the continuous time version of the stochastic telomere regulated model for cultured cell division. Instead of simulations, we obtained the analytic expression for the expected mean cell population. The growth curve obtained is still very close to a Gompertzian growth, within the limit of 2% of the final size. Moreover, Gompertzian growth is retrieved as a limit case. We also evaluate the mean telomere length, which can be checked against cell culture data.

Gompertzian growth is observed in tumors, animals and tissue regeneration but its biological foundations are still unclear. This work adds a possible intrinsic control mechanism for this growth model.

KEYWORDS: telomere, growth, stem cells, model, stochastic, Gompertz.

∗IMPA, Estrada Dona Castorina 110, 22460-320 Rio de Janeiro, Brazil (@impa.br)
†Partially supported by Brazilian CNPq scholarship.
‡Faculty of Medicine, Federal University of Rio de Janeiro
§IMPA, Estrada Dona Castorina 110, 22460-320 Rio de Janeiro, Brazil (benar@impa.br)
¶Partially supported by CNPq grants 300755/2005-8, 475647/2006-8 and by PRONEX-Optimization
1 Introduction

Growth and replicative senescence are very often connected. In cultured cells growth is not observed indefinitely, the division rate slows down and ultimately ceases [26]. A cell clock mechanism based on the shortening of the replica with respect to the DNA template has been proposed in 1970s and was called marginotomy of DNA [39]. There are significant evidences that telomere act as a molecular counting device that regulates the number of cell divisions and limits further division after a critic length is achieved [25]. Replicative senescence of cultured cells is mainly imputed to telomere shortening, which is a mitosis-dependent process [1]. Age dependent telomere shortening is also observed in adult somatic cells [46].

Telomerase synthesizes human hexameric repeats (TTAGGG) onto telomeric ends. This is the main mechanism to overcome telomeric losses of each cell division [15]. Telomere elongation independent of telomerase activity has been described in yeasts [35] but it is not yet documented in animals. Telomerase is present in human embryonic tissues, is not detected in most adult tissues, but is up regulated or reactivated in most of human cancers [45]. Telomerase activity correlated significantly with the Ki-67-expression (a marker of proliferative activity) both in neoplasia [19, 48, 36] and non-cancer cells [51, 32]. It is interesting to note that expression of Ki-67 is routinely used in clinical oncology to access tumor aggressiveness.

A transgenic mouse model (Eµ-myc) of Burkitt’s lymphoma demonstrates that short telomere combined with telomerase inactivity suppress tumorigenesis and this phenomenon is also observed when apoptosis is inactivated, indicating that short telomere negatively affect cellular proliferation [15]. So, telomere driven replicative senescence may be an anti-oncogenic mechanism, preventing replicative errors on the DNA to accumulate indefinitely [47].

A very simple discrete-time stochastic model of telomere regulated growth has been proposed in [42]. Computer simulation of that model produced growth curves strikingly similar to Gompertzian growth. Gompertz model was originally proposed as an actuarial curve [22] to model mortality of an aging population. In fact, this approach still has applications in current survival analysis [7, 12, 24]. One century after its creation, the model surpassed its original realm and was proposed as a biological growth curve [51, 53]. Since then, this function has been successfully used for modelling animal growth [29, 30, 6] and regeneration [11, 52]. Moreover, since the pioneering work of Laird [31], Gompertz curve has been successfully used to model tumor growth [57, 58, 50, 9, 10, 11, 5].
The astonishing fact is not only that Gompertz model fits successfully in many cases of biological growth, but that it’s biological foundation is still not fully understood. Several attempts were made in order to derive the biological explanation of Gompertzian growth model. Some efforts came from the use of allometric relationships and power-law equation [44], cell kinetics that employs quiescence of cells [23, 27], or maturity velocities over the cell population [21] and entropy-based mechanism with thermodynamic characteristics [34].

Here, we take a step further on [42], by studying a continuous-time stochastic telomere-regulated growth model. Now, instead of simulations, we solved analytically the model and obtained the mean growth curve, which is strikingly similar to the Gompertzian growth. Moreover, Gompertzian growth is obtained as a limit of the stochastic model, when the mitosis number/Hayflick limit is high. We also estimated the mean telomere size of the cell population, which can be actually measured in cultured cells.

Is worth of mention that the results obtained here do not depend on the particular division-counting mechanism. So, telomere or any other cell clock may be responsible for the replicative senescence/Gompertzian Growth modeled in this paper.

2 The stochastic model

We will assume that each cell in the initial cell population has its telomere with the same length $L_0$. For the sake of simplicity, we will also assume that a fixed amount of basis is lost by each telomere at each cell division, say $\delta$. This is an approximation of the dynamics of telomere length [33]. Future research may consider more elaborated dynamics. So, after $k$ divisions, the telomere length is

$$L(k) = L_0 - k\delta. \quad (1)$$

Our main biologic assumption is that, for each cell, division (mitosis) is an independent random process which probability depends only on the telomere length and duration of the time interval under consideration. Therefore, at any moment, time to division is a random variable with exponential distribution with parameter $\lambda$ which depends only on the telomere length $L$:

$$\lambda = \lambda(L), \quad P(t) = \lambda e^{-\lambda t}$$

Probability of division shall decrease as the telomere shortens, and reaches 0 for telomere length below a critical value $L_{\text{min}}$. For the sake of simplicity,
we will model this dependence as a linear one \cite{18}:

\[
\lambda = \begin{cases} 
  b(L - L_{\text{min}}), & L \geq L_{\text{min}} \\
  0, & L < L_{\text{min}}.
\end{cases}
\] (2)

Linear approximation is usual in natural sciences and indeed is a first order approximation, whenever we have differentiability of the modeled magnitudes.

To keep the model simple, we will assume that \( L_0 - L_{\text{min}} \) is a multiple of \( \delta \), which, in view of (1), means that when a cell reaches mitotic senescence, its telomere length is exactly \( L_{\text{min}} \). The maximum number of mitosis for the cell in the initial population is

\[ n = \frac{L_0 - L_{\text{min}}}{\delta} \]

and

\[ L_0 = L_{\text{min}} + n\delta. \]

So, using (1) and (2) we conclude that after \( k \) mitosis, the parameter \( \lambda \) is

\[ \lambda_k = b(n - k). \]

Defining \( \beta \) as the parameter \( \lambda \) for the initial telomere length \( L_0 \), we have

\[ \beta = \lambda_0 = bn. \]

Hence

\[ \lambda_k = \beta(n - k)/n, \quad k = 0, 1, \ldots, n \] (3)

Division is not an instantaneous process. Moreover, after a division each cell must synthesize a number of cellular components before it can divide again. Indeed, after a division, the cell mass is divided by 2. Even though, we will assume that these processes occur in a time scale much smaller that \( 1/\beta \), which is the mean division time of the initial cell population. The model:

- The initial state is a single cell with telomere length \( L_0 \).
- This cell can undergo at most \( n \) mitosis.
- Time to next mitosis for each cell is a random process with exponential distribution \( \lambda_k e^{-\lambda_k t} \), where \( k \) is the number of previous mitosis from the initial cell and

\[ \lambda_k = \beta(n - k)/n, \quad k = 0, 1, \ldots, n - 1 \]
Let $X(k, t)$ be the number of the cell population at time $t$ which has undergone exactly $k$ mitosis in his history. The expected value of $X(k, t)$ is
\[
E(X(k, t)) = \sum_{j=0}^{\infty} j P(X(k, t) = j).
\] (4)

Define
\[
x_k(t) = E(X(k, t)), \quad k = 0, \cdots, n.
\] (5)

Then
\[
x_k(0) = \begin{cases} 1, & k = 0, \\ 0, & k = 1, \cdots, n \end{cases}
\] (6)

and
\[
\begin{align*}
d x_0(t)/dt &= -\lambda_0 x_0(t), \\
d x_k(t)/dt &= 2\lambda_{k-1} x_{k-1}(t) - \lambda_k x_k(t), \quad k = 1, \cdots, n.
\end{align*}
\] (7)

where $\lambda_n = 0$. Note that
\[
\lambda_k = \beta(n - k)/n, \quad k = 0, 1, \cdots, n.
\] (8)

In matrix notation, omitting the zero entries, (7) becomes
\[
\begin{pmatrix}
x_0 \\
x_1 \\
\vdots \\
x_{n-1} \\
x_n
\end{pmatrix}
= 
\begin{pmatrix}
-\lambda_0 & 2\lambda_0 & -\lambda_1 & 2\lambda_1 & \cdots & 2\lambda_{n-2} & \cdots & -\lambda_{n-2} & 2\lambda_{n-2} & -\lambda_{n-1} & 2\lambda_{n-1} & -\lambda_n \\
\vdots & 2\lambda_1 & \cdots & -\lambda_n & 2\lambda_n & \cdots & -\lambda_{n-2} & 2\lambda_{n-2} & -\lambda_{n-1} & 2\lambda_{n-1} & -\lambda_n & \vdots \\
x_{n-1} \\
x_n
\end{pmatrix}
\begin{pmatrix}
x_0 \\
x_1 \\
\vdots \\
x_{n-1} \\
x_n
\end{pmatrix}
\]

Hence, defining
\[
x(t) = (x_0(t), \cdots, x_n(t))
\]
and $M \in R^{(n+1)\times(n+1)}$,
\[
M = \{m_{i,j}\}_{i,j=1,\cdots,n+1}, \quad m_{i,j} = \begin{cases} -\lambda_{j-1}, & i = j, \\
2\lambda_{j-1}, & i = j + 1 \\
0, & \text{otherwise}. \end{cases}
\] (9)

equations (6)-(7), becomes
\[
x(0) = (1, 0, \cdots, 0), \quad \frac{d}{dt}x = Mx.
\] (10)
The solution of this linear ODE is

$$x(t) = \exp(tM) \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix} \quad (11)$$

valid for $t \geq 0$. The expected number of cells at time $t$ is given by

$$\sum_{i=0}^{n} x_i(t) = [1, 1, \ldots, 1]x(t).$$

### 3 The dynamics of the stochastic model

In this section we present the analytical solution of the differential equations which governs the expected size of the cell population (10). We compute in particular the matrix $\exp(tM)$.

In order to solve (10), first note that, since $M$ is lower-triangular, the spectrum of $M$ is $-\lambda_0, -\lambda_1, \ldots, -\lambda_n$. Define, for $\gamma \in \mathbb{R}$ and $i, k = 1, 2, \ldots, n+1$

$$a(i, k, \gamma) = a(\gamma)_{i, k} = \begin{cases} 0 & i < k, \\ \gamma^{i-k} \binom{n+1-k}{i-k} & i \geq k, \end{cases} \quad (12)$$

We claim that

$$w_k = (w_{1,k}, w_{2,k}, \ldots, w_{n+1,k}), \quad w_{i,k} = a(-2)_{i,k} \quad (13)$$

is a right-side eigenvector of $M$, corresponding to the eigenvalue $-\lambda_{k-1}$. To check this fact we must evaluate

$$b = \begin{bmatrix} b_{1,k} \\ b_{2,k} \\ \vdots \\ b_{n+1,k} \end{bmatrix} = (M + \lambda_{k-1}I)w_k$$

where $I$ is the $(n+1) \times (n+1)$ identity matrix. Using again the fact that $M$ is lower-triangular and (12) we have

$$b_{i,k} = 0, \quad i < k.$$ 

For $i = k$, since $m_{k,k} = -\lambda_{k-1}$,

$$b_{k,k} = (m_{k,k} + \lambda_{k-1})w_{k,k} = 0.$$
So, if $k = n + 1$ then $b = 0$ and the claim holds.

For the case $k = 1, 2, \cdots, n$ and $i > k$,

$$b_{i,k} = m_{i,i-1} w_{i-1,k} + (m_{i,i} + \lambda_{k-1})w_{i,k}$$

Using also (9) and (8) we have

$$b_{i,k} = 2\lambda_{i-2} w_{i-1,k} + (-\lambda_{i-1} + \lambda_{k-1})w_{i,k}$$

$$= \frac{\beta}{n} [2(n + 2 - i)w_{i-1,k} + (i - k)w_{i,k}]$$

$$= \frac{\beta}{n} 2(n + 2 - i) \left[w_{i-1,k} + \frac{i - k}{2(n + 2 - i)}w_{i,k}\right]$$

Note that, according to (12) for these indexes (i.e. $k < i \leq n + 1$)

$$\frac{w_{i-1,k}}{w_{i,k}} = \frac{a(-2)_{i-1,k}}{a(-2)_{i,k}} = \frac{i - k}{-2(n + 2 - i)}$$

The combination of the two above equations yields $b_{i,k} = 0$, which concludes the proof of the claim on $w_k$ being an eigenvector of $M$ associated with the eigenvalue $-\lambda_{k-1}$

So, defining $A(\gamma), D \in \mathbb{R}^{(n+1)\times(n+1)}$,

$$A(\gamma) = \{a(\gamma)_{i,j}\}, \quad D = \text{diag}\{-\lambda_0, \ldots, -\lambda_{n-1}, -\lambda_n\}.$$ (14)

We have

$$M = A(-2) D \left[A(-2)\right]^{-1}$$

and

$$\exp(tM) = A(-2) \exp(tD) \left[A(-2)\right]^{-1}$$ (15)

To evaluate the above expression we will need two auxiliary results.

**Lemma 1** Let $A(\gamma)$ be as defined in (12). Then, for any $\eta \in \mathbb{R}$,

$$[\eta^n, \eta^{n-1}, \ldots, \eta, 1] A(\gamma) = [(\eta + \gamma)^n, (\eta + \gamma)^{n-1}, \ldots, (\eta + \gamma), 1].$$

**Proof.** Let

$$(u_1, \cdots, u_{n+1}) = [\eta^n, \eta^{n-1}, \ldots, \eta, 1] A(\gamma).$$

Direct calculation, together with (12) yields

$$u_k = \sum_{i=1}^{n+1} \eta^{n+1-i} a_{i,k}(\gamma)$$

$$= \sum_{i=k}^{n+1} \eta^{n+1-i} \gamma^{i-k} \binom{n+1-k}{i-k}$$
To conclude the proof, define $j = i - k$ and use the binomial theorem to obtain

$$u_k = \sum_{j=0}^{n+1-k} \eta^{n+1-k-j} \gamma^j \binom{n+1-k}{j} = (\eta + \gamma)^{n+1-k}$$

\[\square\]

**Corollary 2** For any $\gamma, \mu \in \mathbb{R}$,

$$A(\gamma)A(\mu) = A(\gamma + \mu),$$

and $A(0) = I$. In particular $[A(\gamma)]^{-1} = A(-\gamma)$.

**Proof.** The first equality follows trivially from Lemma 1. The second equality is obtained substituting $\gamma$ by $0$ in (12) and using the definition of $A(\gamma)$ in (14). The last part of the corollary follows directly from the previous ones.\[\square\]

Using Corollary 2, (15) and (11) we obtain

$$x(t) = A(-2) \exp(tD) A(2) \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix}$$

(16)

Note that $e^{-t\lambda_k} = (e^{-t\beta/n})^{n-k}$. Therefore, using (14) we have

$$\exp(tD) = \text{diag}\{e^{-t\lambda_0}, \ldots, e^{-t\lambda_n}\} = \text{diag}\{(e^{-t\beta/n})^n, \ldots, (e^{-t\beta/n}), 1\}.$$  

(17)

From this expressions and (11), we obtain a simple expression for the expected number of cells at time $t$:

$$\sum_{i=0}^{n} x_i(t) = [1, 1, \ldots, 1]A(-2) \exp(tD)A(2) \begin{bmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix}$$

(18)
To evaluate (18), use Lemma 1 and (17) to obtain

\[ [1, 1, \ldots, 1] A(-2) \exp(tD) = [(-1)^n, (-1)^{n-1}, \ldots, -1, 1] \exp(tD) \]
\[ = [(-e^{-\beta t/n})^n, (-e^{-\beta t/n})^{n-1}, \ldots, -e^{-\beta t/n}, 1] \]

Using again Lemma 1 we obtain

\[ [(-e^{-\beta t/n})^n, (-e^{-\beta t/n})^{n-1}, \ldots, -e^{-\beta t/n}, 1] A(2) = \]
\[ = [(2 - e^{-\beta t/n})^n, (2 - e^{-\beta t/n})^{n-1}, \ldots, 2 - e^{-\beta t/n}, 1] \]

Hence, using the above equations and (18) we obtain

\[ \sum_{i=0}^{n} x_i(t) = (2 - e^{-\beta t/n})^n \]
\[ = 2^n \left( 1 - \frac{e^{-\beta t/n}}{2} \right)^n \]

Normalizing the final size to 1 we have

\[ S(t) = 2^{-n} \sum_{i=0}^{n} x_i(t) = \left( 1 - \frac{e^{-\beta t/n}}{2} \right)^n. \quad (19) \]

4 How close are the stochastic and Gompertzian models?

First use (19) to determine the time \( t_* \) at which the (expected) population size is half of the final size:

\[ n \ln \left( 1 - \frac{e^{-\beta t_*/n}}{2} \right) = \ln 1/2 = -\ln 2 \]

Then

\[ -\ln \left( 1 - \frac{e^{-\beta t_*/n}}{2} \right) = (\ln 2)/n. \]

As \( h < -\ln(1 - h) \) for \( 0 < h < 1 \), we have

\[ \frac{e^{-\beta t_*/n}}{2} < (\ln 2)/n. \]
Hence,
\[ \frac{e^{-\beta t^*/n}}{2} = \theta_n (\ln 2)/n, \quad 0 < \theta_n < 1. \]

A Taylor expansion shows that
\[ t^* = \frac{n}{\beta} \log \left( \frac{n}{\log 4} \right) + \frac{\log 2}{2\beta} + o_n(1), \]
where \( o_n(1) \) vanishes as \( n \to \infty \).

Defining the normalized Growth curve
\[ S_{\text{norm}}(\tau) = S(t^* + n\tau) \]
or, alternatively using the change of variable
\[ t = t^* + n\tau, \]
in (19) we get
\[ 2^{-n} \sum_{i=0}^{n} x_i(\tau) = \left( 1 - \frac{e^{-\beta \theta_n \ln 2}}{n} \right)^n \approx \exp \left( -e^{-\beta \theta_n \ln 2} \right). \quad (20) \]

Note that the last expression in the above equation is the Gompertzian growth curve.

To verify how good is the approximation described in (20) we analyzed an instance of the model with parameters in the range of those found in the somatic growth of animals and tumors. Human mesenchymal stem cells in culture can undergo around 30 mitosis before stopping division and usually do not express telomerase activity [55]. Here, we studied the model with \( n = 21 \). As the time scale is arbitrary, we set \( \beta = 1 \). A Gompertzian Growth curve in this case, with final size 1 must have initial size \( 2^{-21} \). So, consider the Gompertzian growth
\[ G(t) = \exp(\exp(-\alpha t) \ln 2^{-21}), \]
where \( \alpha \) is a parameter of the Gompertz curve, and is chosen to give a good fitness. So, we determined the best fitting parameter \( \alpha = 1.116 \) and the maximum error for such \( \alpha \), (and 21 divisions) is 2%. Figure 1 compares both growth curves, using the best fitting \( \alpha \) for the Gompertzian curve.
5 Time evolution of the mean telomere length

In cultured cells, telomere length is not evaluated individually. Instead, what is actually measured is the mean telomere length of a bunch of cells. Therefore, in order to verify the fitness of the stochastic model to real data, we must obtained the expected mean telomere length predicted by the model.

In our model, the telomere length of a cell which has undergone \( k \) mitosis is

\[
L_{\text{min}} + (n - k)\delta.
\]

Therefore, the mean telomere length at time \( t \) is

\[
\frac{\sum_{k=0}^{n}(L_{\text{min}} + (n - k)\delta) X(k, t)}{\sum_{k=0}^{n} X(k, t)} = L_{\text{min}} + \delta \frac{\sum_{k=0}^{n}(n - k) X(k, t)}{\sum_{k=0}^{n} X(k, t)}. \tag{21}
\]

To evaluate this quotient, define for \( \Psi : \mathbb{R} \times \mathbb{R} \to \mathbb{R} \)

\[
\Psi(u, t) = \sum_{k=0}^{n} u^{n-k} X(k, t) \tag{22}
\]
Let $\psi(u,t)$ be the expected value of $\Psi(u,t)$
\[
\psi(u,t) = E(\Psi(u,t)) = \sum_{k=0}^{n} u^{n-k}E(X(k,t))
\tag{23}
\]
As $E(X(k,t)) = x_k(t)$, using (16) we obtain
\[
\psi(u,t) = [u^n, u^{n-1}, \ldots, u, 1] x(t)
\]
\[
= [u^n, u^{n-1}, \ldots, u, 1] \text{A}(-2) \exp(tD) \text{A}(2)
\]
Using Lemma 1 and (17) we obtain
\[
[u^n, u^{n-1}, \ldots, u, 1] \text{A}(-2) \exp(tD) =
[(u-2)e^{-t\beta/n}, (u-2)e^{-t\beta/n})^{n-1}, \ldots, (u-2)e^{-t\beta/n}, 1]
\]
Combining the two above equations and using Lemma 1 again yields
\[
\psi(u,t) = (2 + (u-2)e^{-\beta t/n})^n.
\tag{24}
\]
Note that
\[
E\left(\sum_{k=0}^{n} X(k,t)\right) = \sum_{i=0}^{n} x_i(t) = \psi(1,t).
\]
and
\[
E\left(\sum_{k=0}^{n} (n-k)X(k,t)\right) = \sum_{i=0}^{n} (n-k)x_i(t) = \frac{\partial}{\partial u} \psi(u,t)_{u=1}.
\]
Therefore,
\[
E\left(\sum_{k=0}^{n} (L_{\text{min}} + (n-k)\delta) X(k,t)\right) = L_{\text{min}}(2 - e^{-\beta t/n})^n +
\delta n (2 - e^{-\beta t/n})^{n-1}e^{-\beta t/n}.
\]
The total telomere length of a cell population can be evaluated multiplying the mean telomere length of a sample by the population size. So, it is important to remark that this random variable can be measured in experiments...
of cell culture tissue. Hence, we have an observable quantity which may agree or disagree with the model proposed here, confirming or invalidating respectively the model.

Using the approximation

\[
E \left( \frac{\sum_{k=0}^n (n - k) X(k,t)}{\sum_{k=0}^n X(k,t)} \right) \approx \frac{E \left( \sum_{k=0}^n (n - k) X(k,t) \right)}{E \left( \sum_{k=0}^n X(k,t) \right)}
\]

we obtain the estimation of the expected mean telomere size:

\[
E \left( \frac{\sum_{k=0}^n (L_{\text{min}} + (n - k)\delta) X(k,t)}{\sum_{k=0}^n X(k,t)} \right) \approx L_{\text{min}} + \delta \frac{ne^{-\beta t/n}}{2 - e^{-\beta t/n}}
\]

In Figure 2 we plotted the approximated mean telomere length as a function of the number of population doubles (log\(_2\) of the population) for some biologically feasible parameters [3]. This curve is similar to actual data of cultured mesenchymal stem cells presented in [3, Figure 3].
6 Discussion

We studied an stochastic continuous-time growth model where the number of past divisions determine the probability of the next division. There is biological data supplying evidence that cell do count division, by means of telomere shortening. Moreover, mitosis-dependent telomere shortening is well documented, as well as the fact that cells with telomere length below a critical limit can not divide [16, 33]. Time lengths of S, G2 and M phases of the mitotic cycle are fairly constant. However, the duration of the cell cycle is variable from one cell to another in the same culture and most of this variability lies in G1 [2]. During G1 phase progression there is a checkpoint for cell senescence where telomere length is decisive [8]. Evidences that telomere shortening negatively affect the mitotic rate are still partial [15]. Here we supplied a theoretical evidence of this phenomenon, by proposing a model based on this assumption and which yielded the classical Gompertzian growth. Moreover, population doubling curves and mean telomere length on this model is consistent with actual data supplied by human mesenchymal cell culture [3]. Further validation of the model will be possible as soon as more accurate measures of mean telomere length of cultured cells become available. We regarded telomeric loss as a process with small variance and approximated it by a fixed shortening in each mitosis.

In [43] telomere shortening was modeled as a random process with two different outcomes: a gradual telomere shortening or an abrupt shortening. The second outcome was related to sudden senescence. An aging mechanism based on the combination of telomere shortening, oxidative stress and DNA mutation was proposed in [49]. Here, we modeled cell division as a stochastic process, which probability distribution depends on the telomere length.

Modern cancer therapy is switching from the nonspecific toxic chemotherapy toward specific molecular targeted medicines. Malignant cell usually synthesizes telomerase, which prevents telomere shortening. If telomere shortening (down) regulates mitotic rate, this will have a significant impact in oncology, once specific telomerase inhibitors would act as very specific anti neoplastic agent [41, 17, 40, 14]. For a general review on this perspective, see [28].

References

[1] Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, Greider CW, Harley CB. Telomere length predicts replicative ca-
capacity of human fibroblasts. Proc Natl Acad Sci U S A. 1992; 89:10114-8.

[2] Baserga R. The relationship of the cell cycle to tumor growth and control of cell division: a review. Cancer Res. 1965; 25:581-95.

[3] Baxter MA, Wynn RF, Jowitt SN, Wraith JE, Fairbairn LJ, Bellantuono I. Study of telomere length reveals rapid aging of human marrow stromal cells following in vitro expansion. Stem Cells. 2004; 22:675-82

[4] Baranowitz SA, Maderson PFA, Connelly TG. Lizard and newt tail regeneration: a quantitative study. J Exp Zool. 1979; 210:17-36.

[5] Bassukas ID, Eberle V, Maurer-Schultze B. The growth curve of the first passage xenografts of human tumors in nude mice predicts their transplantation behavior. Oncol Rep. 1998;5:257-9.

[6] Begall S. The application of the Gompertz model to describe body growth. Growth Dev. Aging. 1997; 61, 61-7.

[7] Bender R, Augustin T, Blettner M. Generating survival times to simulate Cox proportional hazards models. Stat Med. 2005;24:1713-23.

[8] Blomen VA, Boonstra J. Cell fate determination during G1 phase progression. Cell Mol Life Sci. 2007; 64:3084-104.

[9] Castorina P, Deisboeck TS, Gabriele P, Guiot C. Growth laws in cancer: implications for radiotherapy. Radiat Res. 2007;168:349-56.

[10] Castro MA, Klamt F, Grieneisen VA, Grivicich I, Moreira JC. Gompertzian growth pattern correlated with phenotypic organization of colon carcinoma, malignant glioma and non-small cell lung carcinoma cell lines. Cell Prolif. 2003;36:65-73.

[11] Chignola R, Schenetti A, Andreighetto G, Chiesa E, Foroni R, Sartoris S, Tridente G, Liberati D. Forecasting the growth of multicell tumour spheroids: implications for the dynamic growth of solid tumours. Cell Prolif. 2000; 33:219-29.

[12] Coe JB, Mao Y. Gompertz mortality law and scaling behavior of the Penna model. Phys Rev E Stat Nonlin Soft Matter Phys. 2005;72:051925.
[13] Demicheli R. Growth of testicular neoplasm lung metastases: tumor specific relation between two gompertzian parameters. Eur J Cancer. 1980; 16: 1603-08.

[14] El-Daly H, Kull M, Zimmermann S, Pantic M, Waller CF, Martens UM. Selective cytotoxicity and telomere damage in leukemia cells using the telomerase inhibitor BIBR1532. Blood. 2005;105:1742-9.

[15] Feldser DM, Greider CW. Short telomeres limit tumor progression in vivo by inducing senescence. Cancer Cell. 2007; 11:461-9.

[16] Greider CW. Telomere length regulation. Annu Rev Biochem. 1996;65:337-65.

[17] Gryaznov SM, Jackson S, Dikmen G, Harley C, Herbert BS, Wright WE, Shay JW. Oligonucleotide conjugate GRN163L targeting human telomerase as potential anticancer and antimetastatic agent. Nucleosides Nucleotides Nucleic Acids. 2007;26:1577-9.

[18] Gupta N, Taneja R, Pandey A, Mukesh M, Singh H, Gupta SC. Replicative senescence, telomere shortening and cell proliferation rate in Gaddi goat’s skin fibroblast cell line. Cell Biol Int. 2007;31:1257-64.

[19] Ikeda S, Shibata T, Eishi Y, Takizawa T, Koike M. Correlation between the expression of telomerase reverse transcriptase and proliferative activity in breast cancer cells using an immunocytochemical restaining method. Pathol Int. 2003;53:762-8.

[20] Mueller S, Hartmann U, Mayer F, Balabanov S, Hartmann JT, Brummendorf TH, Bokemeyer C. Targeting telomerase activity by BIBR1532 as a therapeutic approach in germ cell tumors. Invest New Drugs. 2007;25:519-24.

[21] Frenzen CL, Murray JD. A cell kinetics justification for Gompertz equation. SIAM Journal of Applied Mathematics. 1986;46:614-29.

[22] Gompertz B. On the nature of the function of the law of human mortality, etc. Phil. Trans. Roy. 1825; Soc. 115:513.

[23] Gyllenberg M, Webb GF. Quiescence as an explanation of Gompertzian tumor growth. Growth Dev Aging. 1989;53:25-33.

[24] Halln A. Gompertz law and aging as exclusion effects. Biogerontology. 2007; 8:595-603.
[25] Harley CB, Vaziri H, Counter CM, Allsopp RC. The telomere hypothesis of cellular aging. Exp Gerontol. 1992; 27:375-82.

[26] Hayflick L. The limited in vitro lifetime of human diploid cell strains. Exp. Cell Res. 1965; 37: 614-36.

[27] Kozusko F, Bajzer Z. Combining Gompertzian growth and cell population dynamics. Math Biosci. 2003; 185: 156-67.

[28] Kleideiter E, Piotrowska K, Klotz U. Screening of telomerase inhibitors. Methods Mol Biol. 2008;405:167-80.

[29] Laird AK. Dynamics of relative growth. Growth 1965; 29, 249-63.

[30] Laird AK, Tyler SA, Barton AD. Dynamics of normal growth. Growth 1965; 29, 233-248.

[31] Laird AK. Dynamics of growth in tumors and in normal organism. Natl. Cancer Inst. Monogr. 1969; 30, 15-28.

[32] Leri A, Barlucchi L, Limana F, Deptala A, Darzynkiewicz Z, Hintze TH, Kajstura J, Nadal-Ginard B, Anversa P. Telomerase expression and activity are coupled with myocyte proliferation and preservation of telomeric length in the failing heart. Proc Natl Acad Sci U S A. 2001;98:8626-31.

[33] Lin KW, Yan J. The telomere length dynamic and methods of its assessment. J Cell Mol Med. 2005;9:977-89.

[34] Ling Y, He B. Entropic analysis of biological growth models. IEEE Trans Biomed Eng. 1993; 40:1193-200.

[35] Lundblad V, Blackburn EH. An alternative pathway for yeast telomere maintenance rescues est1- senescence. Cell. 1993; 73:347-60.

[36] Mokbel K, Parris CN, Ghilchik M, Williams G, Newbold RF. A. The association between telomerase, histopathological parameters, and KI-67 expression in breast cancer. m J Surg. 1999;178:69-72.

[37] Norton L, Simon R, Berreth HD, Bogden AE. Predicting the course of gompertzian growth. Nature 1976; 264: 542-45.

[38] Norton L. Gompertzian model of human breast cancer growth. Cancer Research. 1988; 48, 7067-71.
[39] Olovnikov AM. A theory of marginotomy. The incomplete copying of template margin in enzymic synthesis of polynucleotides and biological significance of the phenomenon. J Theor Biol. 1973; 41:181-90.

[40] Mueller S, Hartmann U, Mayer F, Balabanov S, Hartmann JT, Brumendorf TH, Bokemeyer C. Targeting telomerase activity by BIBR1532 as a therapeutic approach in germ cell tumors. Invest New Drugs. 2007;25:519-24.

[41] Parkinson EK, Minty F. Anticancer therapy targeting telomeres and telomerase: current status. BioDrugs. 2007;21:375-85.

[42] Portugal RD, Land MGP, Svaite BF. A computational model for telomere-dependent cell-replicative aging. Biosystems 2008; 91:262-7.

[43] Rubelj I, Vondracek Z. Stochastic mechanism of cellular aging—a abrupt telomere shortening as a model for stochastic nature of cellular aging. J Theor Biol. 1999;197:425-38.

[44] Savageau MA. Allometric morphogenesis of complex systems: Derivation of the basic equations from first principles. Proc Natl Acad Sci U S A. 1979;76:6023-25.

[45] Shay JW. Telomerase in human development and cancer. J Cell Physiol. 1997;173:266-70.

[46] Shiels PG, Kind AJ, Campbell KH, Waddington D, Wilmut I, Colman A, Schnieke AE. Analysis of telomere lengths in cloned sheep. Nature. 1999;399:316-7.

[47] Shin JS, Hong A, Solomon MJ, Lee CS. The role of telomeres and telomerase in the pathology of human cancer and aging. Pathology. 2006;38:103-13.

[48] Shiratsuchi M, Muta K, Abe Y, Motomura S, Taguchi F, Takatsuki H, Uike N, Umemura T, Nawata H, Nishimura J. Clinical significance of telomerase activity in multiple myeloma. Cancer. 2002;94:2232-8.

[49] Sozou PD and Kirkwood TB. A stochastic model of cell replicative senescence based on telomere shortening, oxidative stress, and somatic mutations in nuclear and mitochondrial DNA. J Theor Biol. 2001;213:573-86.
[50] Sullivan PW and Salmon SE. Kinetics of tumor growth and regression in IgG multiple myeloma. J. Clin. Invest. 1972; 51, 1697-1708.

[51] Valenti MT, Sartore S, Azzarello G, Balducci E, Amadio M, Sandri M, Pappagallo GL, Tacchetti G, Bari M, Manconi R, D’Andrea MR, Silvestri B, Vinante O. Human fibroblasts from normal and malignant breast tissue grown in vitro show a distinct senescence profile and telomerase activity Histochem J. 2002;34:403-10.

[52] Wallenstein S, Brem H. Statistical analysis of wound-healing rates for pressure ulcers. Am J Surg. 2004; 188:73S-78S.

[53] Winsor CP. The Gompertz curve as a growth curve. Proc Natl Acad Sci. 1932; 18, 1-8.

[54] Wright S. Book review in J Am Stat Assoc. 1926; 21, 494.

[55] Zimmermann S, Voss M, Kaiser S, Kapp U, Waller CF, Martens UM. Lack of telomerase activity in human mesenchymal stem cells. Leukemia 2003.17, 114649.