Journal of Biological Dynamics
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t744398444

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First published on: 29 October 2009

To cite this Article Olofsson, Peter(2010) 'Can telomere shortening explain sigmoidal growth curves?', Journal of Biological Dynamics, 4: 6, 527 — 538, First published on: 29 October 2009 (iFirst)
To link to this Article: DOI: 10.1080/17513750903377442
URL: http://dx.doi.org/10.1080/17513750903377442

Journal of Biological Dynamics
Vol. 4, No. 6, November 2010, 527–538

Taylor & Francis
Taylor & Francis Group

Can telomere shortening explain sigmoidal growth curves?

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(*Received 22 June 2009; final version received 29 September 2009*)

A general branching process model is proposed to describe the shortening of telomeres in eukaryotic chromosomes. The model is flexible and incorporates many special cases to be found in the literature. In particular, we show how telomere shortening can give rise to sigmoidal growth curves, an idea first expressed by Portugal *et al.* [*A computational model for telomere-dependent cell-replicative aging*, BioSystems 91 (2008), pp. 262–267]. We also demonstrate how other types of growth curves arise if telomere shortening is mitigated by other cellular processes. We compare our results with published data sets from the biological literature.

Keywords: Gompertz function; telomere shortening; branching process

AMS 2000 Mathematics Subject Classification: 60G99; 60K99; 62P10; 92D2

1. Introduction

Shortening of chromosome ends, known as telomeres, is one of the supposed mechanisms of cellular ageing and death, and an explanation for the finite proliferative capacity of cell lines, see [11,14]. Incomplete replication of DNA at the ends of linear chromosomes is predicted from the known biochemical characteristics of DNA replication, the so-called *end-replication problem*, but there is also evidence that oxidative stress plays a role, see [30,35]. Loss of telomeres is counteracted by a mechanism to restore telomeres by the enzyme telomerase. In the absence of telomerase, cells experience progressive shortening of telomeres and eventually stop dividing, entering a *senescent* state.

The role of chromosomal telomere shortening is a fundamental problem in cell biology and medicine and has been studied extensively for many different types of cells, for example, human marrow stromal cells [4], goat's skin fibroblast cells [13], human mesenchymal stem cells [6], and the yeast *Saccharomyces cerevisiae* [5], just to mention a few. The biological process of telomere shortening has also attracted interest from the mathematical modelling community, and several variants of both deterministic and stochastic models have been proposed. Without claiming to produce an exhaustive list, previous mathematical models of the process of telomere shortening include Levy *et al.* [19], Arino *et al.* [1,2], Olofsson and Kimmel [25,26], Rubelj and

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ISSN 1751-3758 print/ISSN 1751-3766 online

DOI: 10.1080/17513750903377442
http://www.informaworld.com

Vondraček [31], Tan [34], Olofsson [23], Sozou and Kirkwood [33], op den Buijs *et al.* [28], Dyson *et al.* [9], and Portugal *et al.* [29].

Sigmoidal growth curves are typical for many cell populations, for example, see [4]. In Portugal *et al*. [29], telomere shortening was suggested as an explanation for such growth curves. More specifically, under certain assumptions, the growth curve was shown to be very closely approximated by the so-called Gompertz function, which is one of several classes of functions whose graphs exhibit sigmoidal shape. The assumptions of Portugal *et al*. can probably be considered unrealistic as they rely on cell cycle times being geometric (or, in the continuous case, exponential) thus having the memoryless property. Nevertheless, their results are mathematically elegant and they seem to be the first to make the connection between sigmoidal growth and telomere shortening.

We will show that sigmoidal growth curves arise under much less restrictive conditions than those of Portugal *et al.* Such curves are typically not of the Gompertz type but, on the other hand, data such as those in Baxter *et al*. [4] are far too crude to assign to any one particular type of sigmoid. Moreover, it turns out that the sigmoidal shape is only approximate as we show below.

Our model is stochastic, in particular, it is developed within the framework of general (or Crump–Mode–Jagers) multitype branching processes. This class of processes provides a model for population dynamics where an individual may give birth many times during their life, and in the next section we provide some of the basics. The exposé is selective and focuses on the definitions and results we will need, leaving out some of the central theory that is not of immediate relevance to our current endeavours. For a comprehensive treatment of general branching processes, see [16,17].

2. General branching processes

In a general multitype branching process, each individual has a type that determines the probability distribution according to which it reproduces. The type is chosen from the type space S which can be quite general; in our applications, the type will correspond to the telomere length that is discrete (measured in base pairs, bp, or nucleotides, nt) and we take the type space to be non-negative integers N_0. One central mathematical object in a general branching process is the *mean reproduction measure*, $\mu(i, j \times [0,t])$, giving the expected number of children of type j born in the age interval $[0,t]$ of a mother of type i. To view μ as a measure, we use the notation $\mu(i, j \times \mathrm{d}t)$. In order to describe the expected population dynamics, we need the convolution powers of μ. More precisely, the operator $*$ is defined to denote convolution in time and the Markov transition on S, so that

$$\mu^{*2}(i, j \times [0,t]) = \mu * \mu(s, j \times [0,t]) = \sum_{k \in N_0} \int_0^t \mu(k, j \times [t-u]) \mu(i, k \times \mathrm{d}u)$$

and the higher convolutions powers defined recursively as

$$\mu^{*n} = \mu^{*(n-1)} * \mu.$$

The zeroth convolution power is defined as $\mu^{*0}(i, j \times \mathrm{d}t) = \delta_{(i,0)}(j \times \mathrm{d}t)$, a point mass at $(i, 0)$. The *renewal measure* ν is defined as

$$\nu(i, j \times \mathrm{d}t) = \sum_{n=0}^{\infty} \mu^{*n}(i, j \times \mathrm{d}t),$$

where $\nu(i, j \times [0,t])$ is the total number of type-j individuals born up to time t if the ancestor is of type i, from now on denoted by $M_{ij}(t)$. The total number of individuals born up to time t

is then

$$\nu(i, N_0 \times [0, t]) = \sum_{j \in N_0} \nu(i, j \times [0, t])$$

from now on denoted by $M_i(t)$. If there is no death, $\nu(i, N_0 \times [0, t])$ also gives the number of individuals alive at time t. If there is death, denote the lifetime of an individual by L and convolve the survival function of L with the renewal measure ν to get

$$M_{ij}(t) = \int_0^t P_j(L > t - u)\nu(i, j \times \mathrm{d}u) \tag{1}$$

and for the total number of individuals alive

$$M_i(t) = \sum_{j \in N_0} M_{ij}(t). \tag{2}$$

The convolution in Equation (1) is a special case of the elegant technique of using *random characteristics*; see [16–18] for details.

3. The branching process model

Cell populations are often modelled by the so-called Bellman–Harris process, where an individual reproduces by splitting at the end of its (random) lifetime. Thus, each mother cell has two daughter cells at the end of her life, which is reasonable when modelling cells that reproduce by binary fission. For cells that reproduce by budding, such as *S. cerevisiae*, there is, however, a clear distinction between the mother and the daughter cell, which is why a general branching process is more adequate in that it lets individuals reproduce several times. We can incorporate binary fission into the general branching process by considering one of the two daughter cells as the surviving mother and the other as the single daughter. If the cells need time to grow or if the mother has experienced any changes (for example, in the telomere length), these factors can be accounted for by the mean reproduction process as we shall see below.

In our branching process model, we let the type of an individual be its telomere length. It is not clear exactly how telomere length triggers senescence, but there is some evidence that it is the length of the shortest telomere that matters, see [15]. However, it has also been claimed that the onset of senescence correlates better with the average telomere length than with the length of the shortest telomere, see [21]. Our model does not hinge upon any one particular theory of the onset of senescence. We denote the type of a cell by an integer i that may represent the length of the shortest telomere or the average telomere length. A daughter cell thus inherits a type j where $j \leq i$. We will often assume for simplicity that telomere shortening is constant so that one 'telomere unit' is lost per replication event. Let 0 denote the critical level; thus, a cell of type 0 is senescent and reproduces no more.

In yeast, it is well known that cells do not keep dividing indefinitely even if they have sufficient telomeres, see [32]. Thus, there is an ageing process due to telomere shortening and another ageing process due to other factors. The number of cell divisions a mother cell goes through is called her (replicative) *lifespan*, not to be confused with her *lifetime* which is the total (chronological) time she is present in the population. Consider an arbitrary cell and let N be its lifespan, that is, the total possible number of daughter cells. Then N has range $\{0, 1, 2, \ldots\}$ and probability mass function $P_i(N = n)$ where i denotes the telomere length. Note that the probability $P_i(N = n)$ needs to take into account both telomere shortening and individual cell ageing.

To arrive at an expression for μ, let the consecutive cell cycle times be $L_1, L_2, \ldots, L_N$, where the L_j are independent and L_j has cdf F_j. In many applications, it might be reasonable to let

all the F_j be the same which we shall assume from now on. There is some evidence, however, that cell cycle times tend to increase with ageing [32], which we could thus easily incorporate, if needed. Next, let τ_k be the time of birth (= the age of the mother) of the kth daughter cell and let σ_k denote the type of that daughter cell. Then

$$\tau_k = \sum_{j=1}^{k} L_j,$$

and we let

$$p_{ij}(k) = P_i(\sigma_k = j) \tag{3}$$

for all k and $j \le i$. If a mother cell maintains the telomere length, the $p_{ij}(k)$ do not depend on k, but if telomeres are lost in both mother and daughter, there is dependence upon k. The mean reproduction process is

$$\begin{aligned}\mu(i, j \times \mathrm{d}t) &= \sum_{n=0}^{\infty}\sum_{k=1}^{n} P_i(\sigma_k = j) P_i(\tau_k \in \mathrm{d}t) P_i(N = n) \\ &= \sum_{n=0}^{\infty}\sum_{k=1}^{n} p_{ij}(k) F^{*k}(\mathrm{d}t) P_i(N = n)\end{aligned} \tag{4}$$

from which the renewal measure ν and the expected number of cells $M(t)$ can be obtained. If there is reason to believe that the L_j have different distributions, $F^{*k}(t)$ is simply replaced by $F_1 * \cdots * F_k(t)$.

4. Special cases

In this section, we examine four special cases of telomere shortening, depending on whether a mother cell has finite or infinite lifespan, and whether a mother cell retains the telomere length or loses telomeres. The relevance of such assumptions depends on the particular situation at hand, and we will point out where they are applicable and have been used in the literature.

4.1. *Example 1: Infinite lifespan, mother retains telomere length*

Let us first assume that $N \equiv \infty$, i.e. cells keep reproducing indefinitely. Assume further that a mother cell retains the telomere length whereas the daughter cell loses one telomere unit. This is the model used in [1,2,19,25] and a special case of the model in Olofsson [23]. The model may be realistic if a single chromosome is followed due to the semiconservative nature of DNA replication, see [19]. This assumption means that we have $p_{i,i-1}(k) = 1$ for all $i > 1$ and all $k \ge 1$, which gives

$$\mu(i, i-1 \times \mathrm{d}t) = \sum_{n=1}^{\infty} F^{*n}(\mathrm{d}t)$$

and the convolution powers become

$$\mu^{*k}(i, i-k \times \mathrm{d}t) = \sum_{n=k}^{\infty} \binom{n-1}{k-1} F^{*n}(\mathrm{d}t)$$

for $k \le i$.

The expression for μ^{*k} can be obtained directly by convolving μ with itself, but it also follows from combinatorial considerations. Any cell of type $i-k$ must be in the kth generation, and if it

is the result of the nth reproduction event (thus preceded by $n-1$ reproduction events), the cdf of the time is F^{*n} and there are $\binom{n-1}{k-1}$ places to 'step up' one generation. For more details regarding this idea of proof, see [25].

The polynomial asymptotics established in [23,25] follow the form of the μ^{*k}. For example, $k = 1$ gives

$$\mu(i, i-1 \times [0,t]) = \sum_{n=1}^{\infty} F^{*n}(t) \sim \frac{t}{E[L]}$$

by the elementary renewal theorem, see Grimmett and Stirzaker [12]. Hence, in this case we do not get a sigmoidal growth curve.

4.2. *Example 2: Finite lifespan, mother retains telomere length*

Assume now that a mother retains the telomere length but is not able to reproduce indefinitely. We still have $p_{i,i-1}(k) = 1$ and get the mean reproduction measure

$$\begin{aligned}\mu(i, i-1 \times \mathrm{d}t) &= \sum_{n=0}^{\infty} \sum_{k=1}^{n} F^{*k}(\mathrm{d}t) P_i(N = n) \\ &= \sum_{k=1}^{\infty} P_i(N \geq k) F^{*k}(\mathrm{d}t)\end{aligned}$$

by changing the order of summation. In particular, if we make the simplifying assumption that $N \equiv n_0$ for some n_0, we get

$$\mu(i, i-1 \times \mathrm{d}t) = \sum_{k=1}^{n_0} F^{*k}(\mathrm{d}t),$$

i.e. the same as in the previous example with ∞ replaced by n_0. The convolution powers are easily found to be

$$\mu^{*j}(i, i-j \times \mathrm{d}t) = \sum_{k_1,\ldots,k_j=1}^{n_0} F^{*(k_1+\cdots+k_j)}(\mathrm{d}t),$$

which gives $M(t)$ by summing over j and adding 1 for the ancestor. Note that

$$\mu(i, i-1 \times [0,t]) = \sum_{k=1}^{n_0} F^{*k}(t) \longrightarrow n_0$$

as $t \to \infty$ since $F^{*k}(t) \to 1$ for all k. This in turn implies that $\mu(i, i-2 \times [0,t]) \to n_0^2$ and so on, and it is easy to realize that the final population size equals

$$\lim_{t\to\infty} M(t) = 1 + \sum_{k=1}^{i} n_0^k = \frac{n_0^{i+1} - 1}{n_0 - 1}$$

for $n_0 > 1$, and $\lim_{t\to\infty} M(t) = 1 + i$ for $n_0 = 1$. The growth curve has a sigmoidal shape as seen in Figure 1. We used $i = 3$ and $n_0 = 3$ to get the final size 40.

Another version of this example is to let $p_{i,i}(k) = 1$ for all k, which means that neither mother nor daughter loses telomeres. This assumption is realistic, e.g. to model populations of telomerase-proficient yeast cells where the telomere length is maintained, see [5]. Such populations grow exponentially with a growth rate that is determined by n_0 and cell cycle parameters.

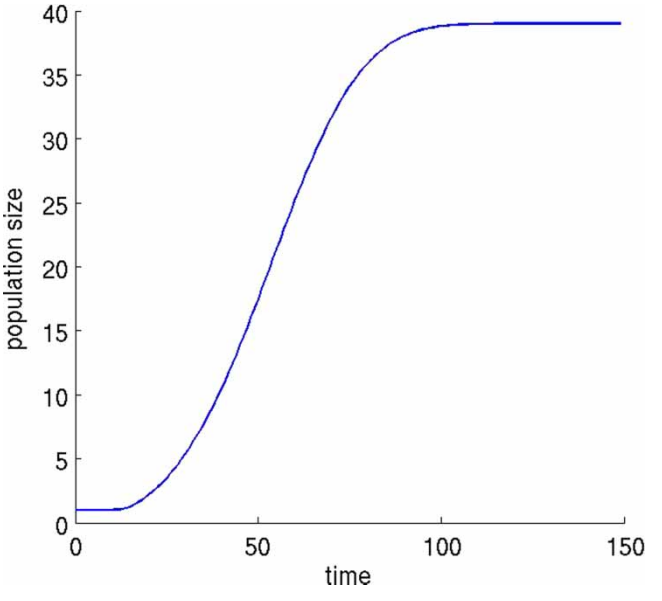

Figure 1. Growth curve for a cell population where mother cells retain the telomere length and have a lifespan of $n_0 = 3$.

4.3. *Example 3: Infinite lifespan, mother loses telomeres*

Now, instead assume that a telomere unit is lost in both mother and daughter, which is the assumption of, for example, Portugal *et al*. [29]. By 'infinite lifespan' we really mean that the replicative lifespan of a cell is affected only by telomere shortening, which means that we now get $P_i(N = i) = 1$ for all i. The first daughter of a type-i mother then has type $i - 1$, the second daughter has type $i - 2$, and so on. In this way, we can account for the fact that the mother's telomere length changes with each reproduction event. We thus have $p_{i,i-j}(j) = 1$ for $j = 1, \ldots, i$ and get

$$\mu(i, i - j \times \mathrm{d}t) = F^{*j}(\mathrm{d}t)$$

and, similarly to Example 1, the convolution powers become

$$\mu^{*k}(i, i - j \times \mathrm{d}t) = \binom{j-1}{k-1} F^{*j}(\mathrm{d}t)$$

for $k \leq j \leq i$. The renewal measure becomes

$$\begin{aligned} \nu(i, i - j \times \mathrm{d}t) &= \sum_{k=1}^{j} \binom{j-1}{k-1} F^{*j}(\mathrm{d}t) \\ &= 2^{j-1} F^{*j}(\mathrm{d}t) \end{aligned}$$

which gives the expected total population size at time t as

$$M_i(t) = 1 + \sum_{j=1}^{i} 2^{j-1} F^{*j}(t),$$

where the initial '1' is the zeroth convolution power corresponding to the ancestor. As $t \to \infty$, $F^{*j}(t) \to 1$ for all j, which gives the final population size 2^i.

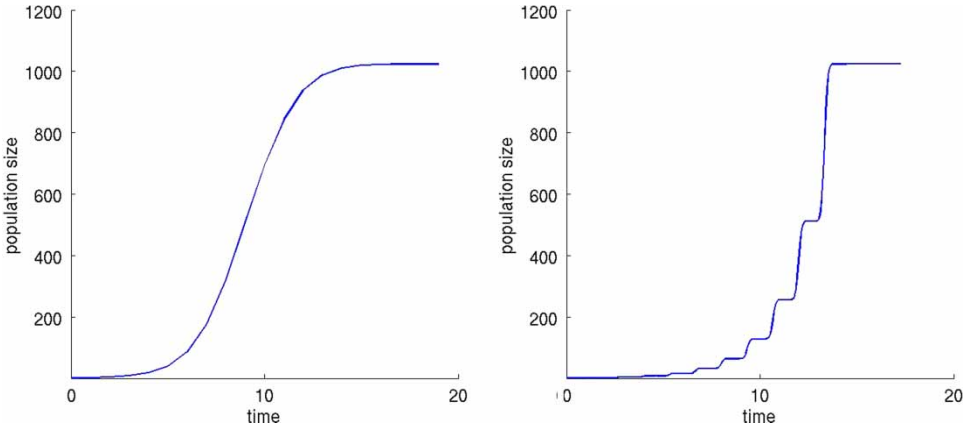

Figure 2. Growth curves for cell populations where mother cells lose telomeres. The variance in cell cycle times is large in the left plot and small in the right plot.

The population growth curve now exhibits a sigmoidal shape as can be seen in Figure 2, left graph. Here $i = 10$, which gives the final population size 1024. Cell cycle times were taken to follow a gamma distribution with mean 1 and variance 1/2. The growth curves obtained in Baxter *et al*. [4] may fit into this example.

Growth curves are not always quite as smooth as they may appear, due to synchronization effects. To illustrate these effects, we instead used a gamma distribution with mean 1 and variance $1/1000$, i.e. the coefficient of variation is only about 3%. With such a small variation in cell cycle times, the population experiences regular growth spurts followed by periods of slow growth, depicted in the right graph in Figure 2. It is well known that cell populations desynchronize so these effects disappear over time but here the final size of 1024 is reached well before any desynchronization effects can be observed. For more on cell cycle desynchronization, see [7,22,27].

4.4. *Example 4: Finite lifespan, mother loses telomeres*

We finish with the most realistic and most interesting case. Assume that a mother loses telomeres and is also limited in reproduction due to her lifespan n_0 (again assumed constant for simplicity). This scenario is realistic for many cell populations, applying, e.g. to *S. cerevisiae* where a mother cell is known to have both a limited lifespan and experience telomere shortening, see [5,32]. The mean reproduction measure is easily obtained as

$$\mu(i, i - k \times \mathrm{d}t) = F^{*k}(\mathrm{d}t)$$

for $k \leq \min(i, n_0)$. The convolution powers are complicated to deal with because reproduction is limited by both telomere length and lifespan. A cell with the telomere length j can produce $\min(j, n_0)$ daughter cells so if the ancestor has a telomere length of $i > n_0$, cells in the first $i - n_0$ generations will be able to reproduce n_0 times and, thereafter, reproduction is limited by the telomere length. Rather than computing convolution powers explicitly, we will arrive at an expression for $M_i(t)$ through an alternative way of reasoning.

The population starts from a single cell of type i and upon completion of the cell cycle, this cell has produced one daughter cell and then both mother and daughter have type (telomere length) $i - 1$. For simplicity, we refer to the two cells as the first 'generation'. Let $m(k)$ denote the expected number of cells in the kth generation. Now note that each cell in the kth generation is present in the population if the sum of k cell cycle times is less than t, but the sum of $k + 1$ cell

cycle times is greater than t. As the probability of this event is $F^{*k}(t) - F^{*(k+1)}(t)$, the expected number of cells from the kth generation that are present at t equals

$$m(k)(F^{*k}(t) - F^{*(k+1)}(t)),$$

and thus the expected total number of cells at time t equals

$$M_i(t) = 1 - F(t) + \sum_{k=1}^{i-1} m(k)(F^{*k}(t) - F^{*(k+1)}(t)) + m(i)F^{*i}(t). \tag{5}$$

Note that we have $m(k) = 2^k$ as long as $k \leq n_0$. For $k > n_0$, we describe a recursive scheme that enables us to compute $m(k)$. To that end, in any given generation, let k_j be the number of cells that are able to reproduce j times. Let us say that these cells belong to class j (and do not confuse 'class' with 'type' which is the telomere length) for $j = 0, 1, \ldots, n_0$. Each cell with $j \geq 1$ produces a daughter cell that is able to reproduce n_0 times and is then itself able to reproduce another $j - 1$ times. Hence, the k_j cells in class j produce k_j cells in class $j - 1$ and k_j cells in class n_0. Cells with $j = 0$ remain unchanged. For $n_0 \leq k \leq n$, the transition from generation $k - 1$ to generation k is therefore as follows:

$$\begin{aligned} &\text{Generation } k-1: \quad (k_0, k_1, \ldots, k_{n_0-1}, k_{n_0}) \\ &\text{Generation } k: \qquad \left(k_0 + k_1, k_2, \ldots, k_{n_0}, \sum_{i=1}^{n_0} k_i\right) \end{aligned}$$

and after relabelling in generation k to $(k_0, k_1, \ldots, k_{n_0})$ again, we have $m(k) = \sum_{j=0}^{n_0} k_j$.[1] The initial configuration in generation 0 is $(0, 0, \ldots, 0, 1)$ since there is one cell that is able to divide n_0 times. Note that if there are $k_0 + N$ cells in generation $k - 1$, there are $k_0 + 2N$ cells in generation k, as expected. For $k \geq i$, all cells are senescent, so $m(k)$ stays constant and we have $m(k) = m(i)$ for $k \geq i$, $m(i)$ thus being the final population size.

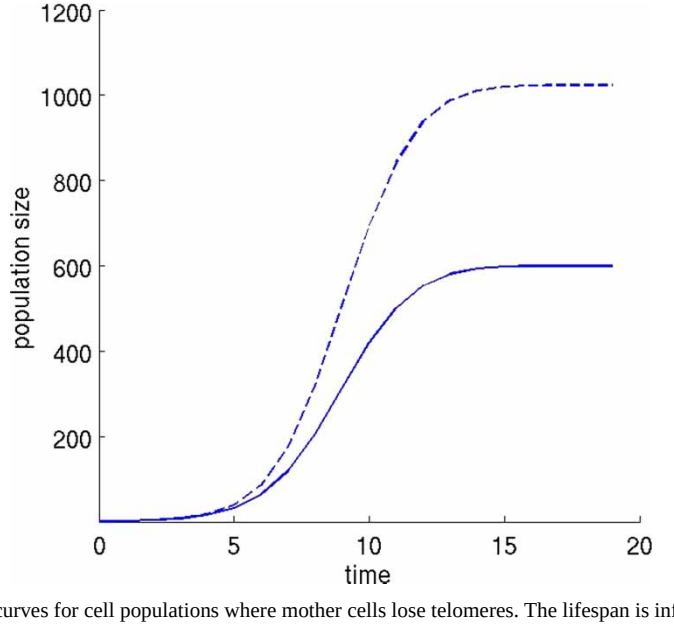

Figure 3. Growth curves for cell populations where mother cells lose telomeres. The lifespan is infinite for the dashed curve and finite for the solid curve.

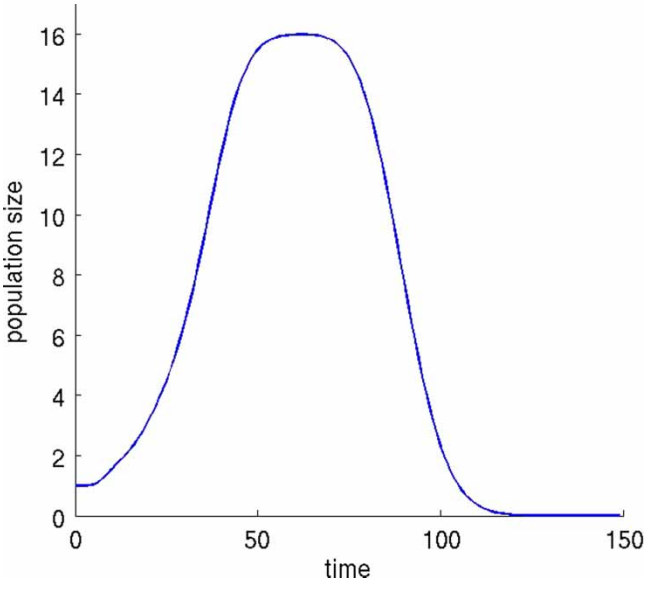

Figure 4. Growth curve for a cell population where senescent cells eventually die.

Figure 3 illustrates the difference between infinite lifespan (Example 3, dashed curve) and finite lifespan (solid curve) when both mother and daughter lose telomeres. The parameters are $i = 10$ and $n_0 = 3$, which give the final population sizes $2^{10} = 1024$ for the dashed curve and $m(10) = 600$ for the solid curve.

5. Cell death

In the examples above, we have assumed that cells do not die but stay in the population as senescent. This assumption may be reasonable in many experimental situations if cells do not die during the course of the experiment. Realistically, however, senescent cells will eventually start dying and we can model such cell death simply by letting a senescent cell have a lifetime L_s with the cdf F_s. The lifetime L of a cell equals the total time spent going through cell cycles plus its additional life: $L = L_1 + \cdots + L_N + L_s$. The population size at time t is obtained by convolving the survival function $P_i(L > t)$ with the renewal measure ν according to Equations (1) and (2).

The growth curve now exhibits the typical phases of exponential growth, stationarity, and death, see Figure 4. By adding an initial quantity to the lifetime of the ancestor, we can also incorporate the initial lag phase present in many observed cell populations such as bacteria; for example, see Baranyi [3].

6. Survivors

An interesting phenomenon observed in both yeast cells and human cells is that cell populations whose growth rates slow down due to telomere shortening have the potential to regain the growth rate, presumably due to a recombination mechanism that enables maintenance of short telomeres, see [5,8]. It is believed that the onset of this mechanism does not necessarily occur in all cells, rather, it is a stochastic event that creates 'survivors' that will later dominate the population.

We thus assume that cells that have reached the zero telomere length have the possibility to become survivors with some probability p and consider the two different scenarios. (1) Survivorship is inherited so each survivor starts a population where the telomere length is maintained and (2) Survivorship is random, so each cell becomes a survivor with probability p at each reproduction event, independently of other cells. To treat the most realistic case, we stay within Example 4 above, where a mother cell loses telomeres and has a finite lifespan n_0.

In Case 1, the population evolves as before until the nth generation when the proportion p turn into survivors. The survivors are unrestricted by telomere length but still restricted by the lifespan n_0. The expected number of cells at time t is now given by the expression

$$M_i(t) = 1 + \sum_{k=1}^{\infty} m(k)(F^{*k}(t) - F^{*(k+1)}(t)), \tag{6}$$

where the only difference from Equation (5) is that the sum over k goes to ∞ rather than i. The typical growth curve displays initial sigmoidal shape but after levelling off for a while, the exponential growth is eventually restored as survivors take over the population. For further details, we refer to Olofsson and Bertuch [23].

In Case 2, the survivorship is not inherited but occurs independently with probability p in each newborn cell. Again, the expected number of cells is given by Equation (6) where the population evolves as before until the nth generation. Thereafter, the expression for $m(k)$ changes because a survivor undergoing a reproduction event may result in 0,1, or 2 survivors, depending on whether the daughter cell gets survivor status and whether it retains its own survivor status. This scenario leads to a recursive relation that is a modified version of the one above in Example 4. As before, let k_j be the number of cells that are able to reproduce j times for $j = 0, 1, \ldots, n_0$ to obtain the transition from generation $k-1$ to generation k as follows:

$$\begin{aligned} &\text{Generation } k-1: \quad (k_0, k_1, \ldots, k_{n_0-1}, k_{n_0}) \\ &\text{Generation } k: \quad \left(k_0 + (2-p)k_1 + 2(1-p)\sum_{i=2}^{n_0} k_i,\ pk_2, \ldots, pk_{n_0},\ p\sum_{i=1}^{n_0} k_i\right). \end{aligned}$$

The expression above reveals that cells in the n_0 category are created from all other cells, each time with probability p. For category j with $0 < j < n_0$, cells are created from cells in category

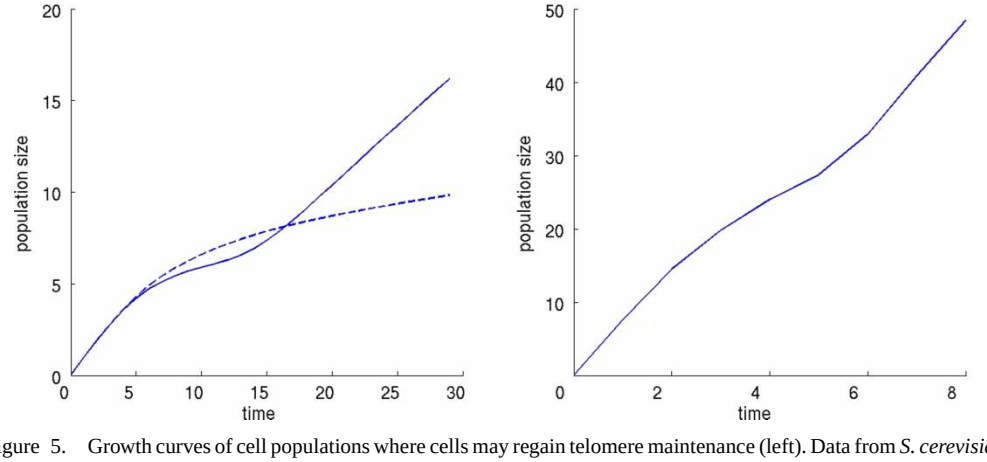

Figure 5. Growth curves of cell populations where cells may regain telomere maintenance (left). Data from *S. cerevisiae* (right).

$j+1$, again with probability p. Cells that fail to become survivors are added to the senescent category zero. Again, note that if there are $k_0 + N$ cells in generation k, there are $k_0 + 2N$ cells in generation $k+1$.

In Figure 5, the left graph shows growth curves for Case 1 (solid curve, $p = 0.01$) and Case 2 (dashed curve, $p = 0.6$). For easier comparison, the curves are on a logarithmic scale and it is clear that the initial growth rate is restored in Case 1 but not in Case 2. The explanation is of course that survivors in Case 1 double their numbers after each generation whereas survivors in Case 2 increase their numbers by a factor $2p$, on average (as long as they are able to reproduce). Since p is large in Case 2, this population initially has many more survivors but as survivorship is not inherited, the population growth quickly falls behind that of Case 1. The right graph shows the average of seven cell populations studied in Bertuch and Lundblad [5], indicating that Case 1 gives the better (qualitative) description in this case.

7. Discussion

We have proposed a class of stochastic models for the shortening of telomeres in chromosomal DNA. The models are stated within the framework of general branching processes where individuals are allowed to reproduce several times during their lives, and where individuals of different types may reproduce differently. In particular, we address the issue of sigmoidal growth curves of cell populations and how these can be explained by telomere shortening. The first paper making such a connection seems to be Portugal *et al.* [29], whose model is a special case of ours. We show that different types of growth curves are obtained depending on assumptions about whether mother cells maintain the telomere length and whether the lifespan is finite or infinite, and also depending on whether telomere maintenance can be restored after an initial period of shortening.

The examples we provide are simplified for clarity and ease of computation. For example, telomeres are lost in units of a fixed size and both telomere shortening and cell cycle times are assumed to be independent of the telomere length. There is evidence that cell cycle times may slow down in older cells [32] and that shortening depends on length [28] and although we ignored such considerations in the examples, they are easily incorporated in the general model by adjusting the quantities in Equation (4). Also the possibility of telomere shortening by oxidative stress [30,35], which might also increase with ageing, can be incorporated in the model by choosing the probabilities in Equation (3) appropriately.

Although the present article is mostly concerned with establishing a general framework to model the shortening of telomeres, we have also considered data sets that corroborate our models, for example, data from human marrow stromal cells [4] and from yeast [5,20]. The data in Bertuch and Lundblad are under investigation for more detailed modelling and analysis in Olofsson and Bertuch [24].

Note

1. Note that the numbers k_j for $j \geq 1$ constitute an 'n_0-nacci' sequence, that is, a generalized Fibonacci sequence where each new number is obtained by adding the previous n_0 numbers, starting from $(0, 0, \ldots, 0, 1)$, see [10].

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