Shortening of telomeres, sigmoidal growth curves, and general branching processes

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Abstract

A general branching process model is proposed to describe the shortening of telomeres in eukariotic 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. (2008). We also demonstrate how other types of growth curves arise if telomere shortening is mitigated by other cellular processes. We compare our results to published data sets from the biological literature.

Keywords: Gompertz function, telomere shortening, branching process, *AMS 2000 Mathematics Subject Classification Codes:* 60G99, 60K99, 62P10, 92D25.

1 Introduction

Shortening of chromosome ends, known as telomeres, is one of the supposed mechanisms of cellular aging and death, and an explanation for the finite proliferative capacity of cell lines, see Harley (1991) and Greider (1996). Incomplete replication of DNA at the ends of linear chromosomes is predicted from the known biochemical characteristics of DNA replication, the so-called

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end replication problem, but there is also evidence that oxidative stress plays a role, see Proctor and Kirkwood (2002). 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 loss 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 [Baxter et al. (2004)], goat's skin fibroblast cells [Gupta et al. (2007)], human mesenchymal stem cells [Bonab et al. (2006)], and the yeast *Saccharomyces cerevisiae* [Bertuch and Lundblad (2004)], just to mention a few. The biological process of telomere loss has also attracted interest from the mathematical modeling 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 loss include Levy *et al.* (1992), Arino *et al.* (1995, 1997), Olofsson and Kimmel (1999, 2005), Rubelj *et al.* (1999), Tan (1999), Olofsson (2000), Sozou and Kirkwood (2001), op den Buijs *et al.* (2004), Dyson *et al.* (2007), and Portugal *et al.* (2008).

Sigmoidal growth curves are typical for many cell populations, see for example Baxter et al. (2004). In Portugal et al. (2008), 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. Also, they make the very specific (and biologically questionable) assumption that mean cell cycle time increases linearly with telomere loss. Nevertheless, their results are mathematically elegant and they seem to be the first to make the connection between sigmoidal growth and telomere loss.

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. (2004) are far to crude to assign to any one particular type of sigmoid. Moreover, it turns out that the sigmoidal shape is only approximate as we will 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 its 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 endeavors. For a comprehensive treatment of general branching processes, see Jagers (1989, 1992).

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, type will correspond to telomere length which is discrete (measured in base pairs, bp, or nucleotides, nt) and we take the type space to be the nonnegative 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 $\mu(i, j \times dt)$. 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 Markov transition on S, so that

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

and higher convolutions powers defined recursively as

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

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

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

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

$$M_{ij}(t) = \int_0^t P_j(L > t-u)\nu(i, j \times du) \tag{2.1}$$

and for the total number of individual alive

$$M_i(t) = \sum_{j \in N_0} M_{ij}(t) \tag{2.2}$$

The convolution in (2.1) is a special case of the elegant technique of using *random characteristics*; see Jagers (1989, 1992) or Jagers and Nerman (1984) for details.

3 The branching process model

Cell populations are often modeled 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 modeling cells that reproduce by binary fission. For cells that reproduce by budding, such as *S. cerevisiae*, there is, however, a clear distinction between mother and 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 an the other as the single daughter. If the cells need time to grow or if the mother has experienced any changes (for example in 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 Hemann et al. (2001). However, it has also been claimed

that the onset of senescence correlates better with average telomere length than with the length of the shortest telomere, see Martens et al. (2000). 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 which may represent the length of the shortest telomere, or average telomere length. A daughter cell thus inherits a type j where $j \leq i$. The distribution of j for given i will not be the same under each of the two hypotheses "shortest" and "average," but qualitative results regarding the shape of the growth curve will not differ. We will often assume for simplicity that telomere loss is constant so that one "telomere unit" is lost per replication event. We 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 Sinclair et al. (1998). Thus, there is an aging process due to telomere loss and another aging 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 and arbitrary cell and let N be its lifespan, that is, the total possible number of daughter cells. Then N has range $\{0, 1, 2, ...\}$ and probability mass function $P_i(N = n)$ where i denotes telomere length. Note that the probability $P_i(N = n)$ needs to take into account both telomere shortening and individual cell aging.

To arrive at an expression for μ, let the consecutive cell cycle times be $L_1, L_2, ...L_N$ 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 aging [Sinclair et al. (1998)] 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

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

for all k and $j \leq i$. If a mother cell maintains telomere length, the $p_{ij}(k)$ does not depend on k but if telomeres are lost in both mother and daughter,

there is dependence upon k. The mean reproduction process is

$$\begin{aligned}\mu(i, j \times dt) &= \sum_{n=0}^{\infty} \sum_{k=1}^{n} P_i(\sigma_k = j) P_i(\tau_k \in dt) P_i(N = n) \\ &= \sum_{n=0}^{\infty} \sum_{k=1}^{n} p_{ij}(k) F^{*k}(dt) P_i(N = n) \qquad (3.1)\end{aligned}$$

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 loss, depending on whether a mother cell has finite or infinite lifespan, and whether a mother cell retains 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 $N \equiv \infty$, that is, cells keep reproducing indefinitely. Assume further that a mother cell retains telomere length whereas the daughter cell loses one telomere unit. This is the model used in Levy et al. (1992), Arino et al. (1995, 1997), Olofsson and Kimmel (1999), and a special case of the model in Olofsson (2000). The model may be realistic if a single chromosome is followed due to the semiconservative nature of DNA replication, see Levy et al. (1992). This assumption means that we have $p_{i,i-1}(k) = 1$ for all $i > 1$ and all $k \geq 1$ which gives

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

and the convolution powers become

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

for $k \leq i$.

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 Olofsson and Kimmel (1999).

The polynomial asymptotics established in Olofsson and Kimmel (1999) and Olofsson (2000) follow from 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 (2001). 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 telomere length but is not able to reproduce indefinitely. We still have $p_{i,i-1}(k) = 1$ and get the mean reproduction measure

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

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

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

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

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

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

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

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 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 can be seen in Figure 1. We used $i = 3$ and $n_0 = 3$ to get the final size 40.

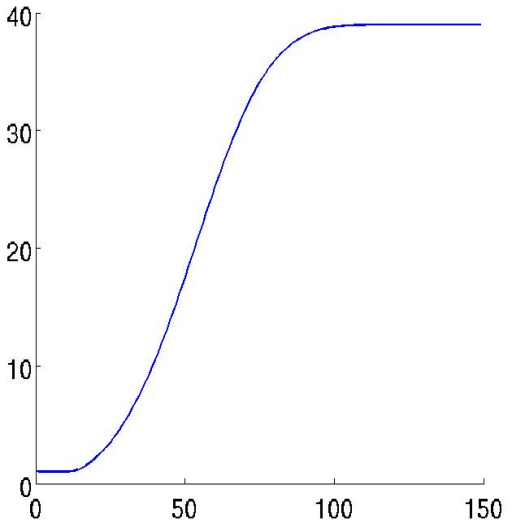

Figure 1: Growth curve for a cell population where mother cells retain telomere length and have a lifespan of $n_0 = 3$.

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 for example to model populations of telomerase proficient yeast cells where telomere length is maintained, see Bertuch and Lundblad (2004). Such populations grow exponentially with a growth rate that is determined by n_0 and cell cycle parameters.

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 (2008). By "infinite lifespan" we really mean that the replicative lifespan of a cell is affected only by telomere loss 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 $j = 1, ..., i$ and get

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

and, similarly to Example 1, the convolution powers become

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

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

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

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 0th 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.

The population growth curve now exhibits a sigmoidal shape as can be seen in Figure 2, left graph. Here $i = 10$ which gives 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. (2004) 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, that is, the coefficient of variation is only about 3%. With such small variation in cell cycle times, the population experiences regular growth spurts followed by periods of slow growth, depicted in Figure 2, right graph. 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 Chiorino et al. (2001), Milotti et al. (2008), and Olofsson and McDonald (2009).

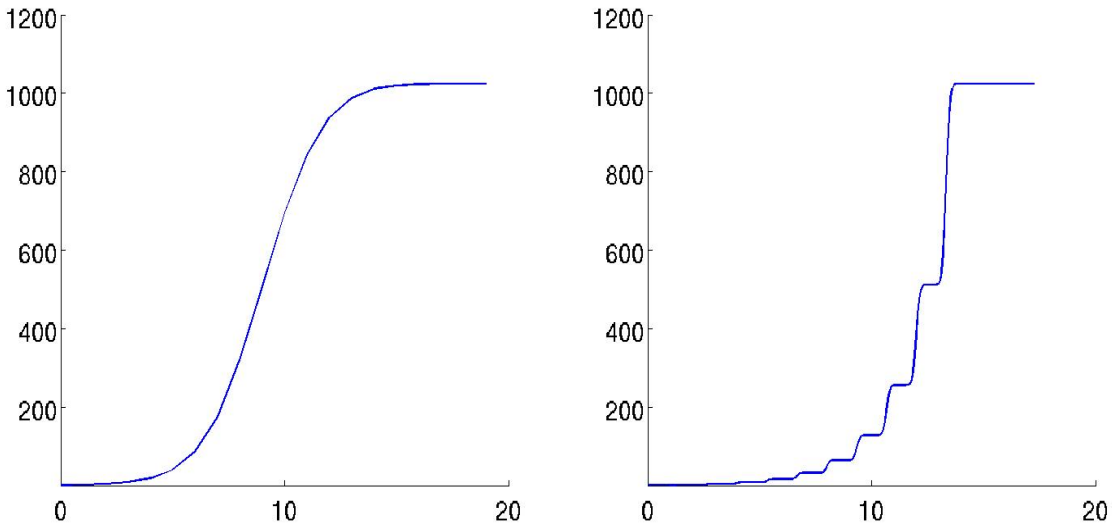

Figure 2: Growth curves for cell populations where mother cells lose telomeres. The variance in cell cycle times is large in the left plot and small in the right plot.

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 for example to *S. cerevisiae* where a mother cell is known to have both limited lifespan and lose telomeres, see Sinclair et al. (1998), and Bertuch and Lundblad (2004). The mean reproduction measure is easily obtained as

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

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 telomere length j can produce $\min(j, n_0)$ daughter cells so if the ancestor has telomere length $i > n_0$, cells in the first $i - n_0$ generations will be able to reproduce n_0 times and thereafter reproduction is limited by 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 has 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

$$m(k)\left(F^{*k}(t) - F^{*(k+1)}(t)\right)$$

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

$$M_i(t) = 1 - F(t) + \sum_{k=1}^{i-1} m(k)\left(F^{*k}(t) - F^{*(k+1)}(t)\right) + m(i)F^{*i}(t) \qquad (4.1)$$

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 for $j = 0, 1, ..., n_0$. 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. 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:

$$\begin{cases} \text{Generation } k-1: & (k_0, k_1, ..., k_{n_0-1}, k_{n_0}) \\ \text{Generation } k: & (k_0 + k_1, k_2, ..., k_{n_0}, \sum_{i=1}^{n_0} k_i) \end{cases}$$

and after relabeling in generation k to $(k_0, k_1, ..., k_{n_0})$ again, we have $m(k) = \sum_{j=0}^{n_0} k_j$.[1] The initial configuration in generation 0 is $(0, 0, ..., 0, 1)$ 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, there are $k_0 + 2N$ cells in generation $k+1$, 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 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, realistically 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 cdf F_s. The lifetime L of a cell equals the total time spent going through cell cycles plus its additional life: $L = L_1 + ... + L_N + L_s$. The population size at time t is obtained by convolving the survival function $P_i(L > t)$ with the renewal measure ν according to (2.1) and (2.2).

[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 $(0, 0, ..., 0, 1)$, see Flores (1967).

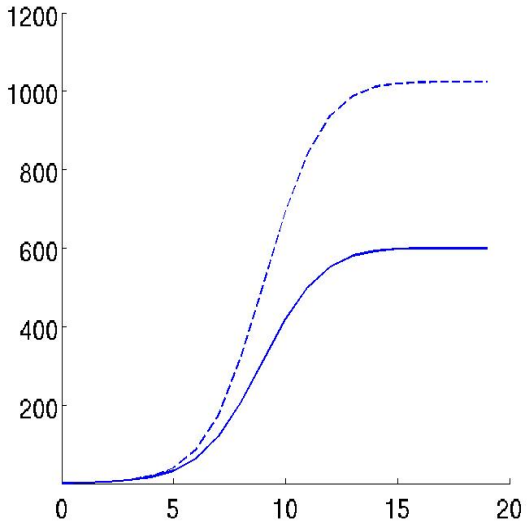

Figure 3: Growth curves for cell populations where mother cells lose telomeres. The lifespan is infinite for the dashed curve and finite for the solid curve.

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, see for example Baranyi (2002).

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 loss have the potential to regain growth rate, presumably due to a recombination mechanism that enables maintenance of short telomeres, see Dunham et al. (2000) and Bertuch and Lundblad (2004). 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 0 telomere length have the possibility to become survivors with some probability p and consider the

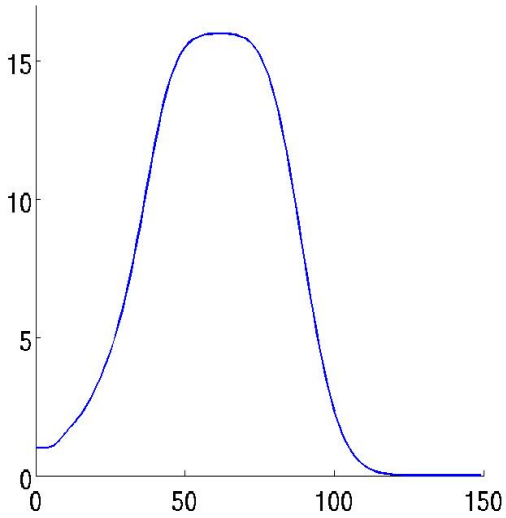

Figure 4: Growth curve for a cell population where senescent cells eventually die.

two different scenarios (1): Survivorship is inherited so each survivor starts a population where 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

$$M_i(t) = 1 + \sum_{k=1}^{\infty} m(k) \left(F^{*k}(t) - F^{*(k+1)}(t) \right) \tag{6.1}$$

where the only difference from (4.1) is that the sum over k goes to ∞ rather than i. The typical growth curve displays initial sigmoidal shape but after leveling off for a while, exponential growth is eventually restored as survivors take over the population. For further details we refer to Olofsson and Bertuch (2009).

In Case 2, survivorship is not inherited but occurs independently with probability p in each newborn cell. Again, the expected number of cells is given by (6.1) 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 its daughter 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 $j = 0, 1, ..., n_0$ to obtain the transition from generation $k-1$ to generation k as follows:

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

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 $j+1$, again with probability p. Cells that fail to become survivors are added to the senescent category 0. Again, note that if there are $k_0 + N$ cells in generation k, there are $k_0 + 2N$ cells in generation $k+1$.

Figure 5, 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 7 cell populations studied in Bertuch and Lundblad (2004), indicating that Case 1 gives the better (qualitative) description in this case.

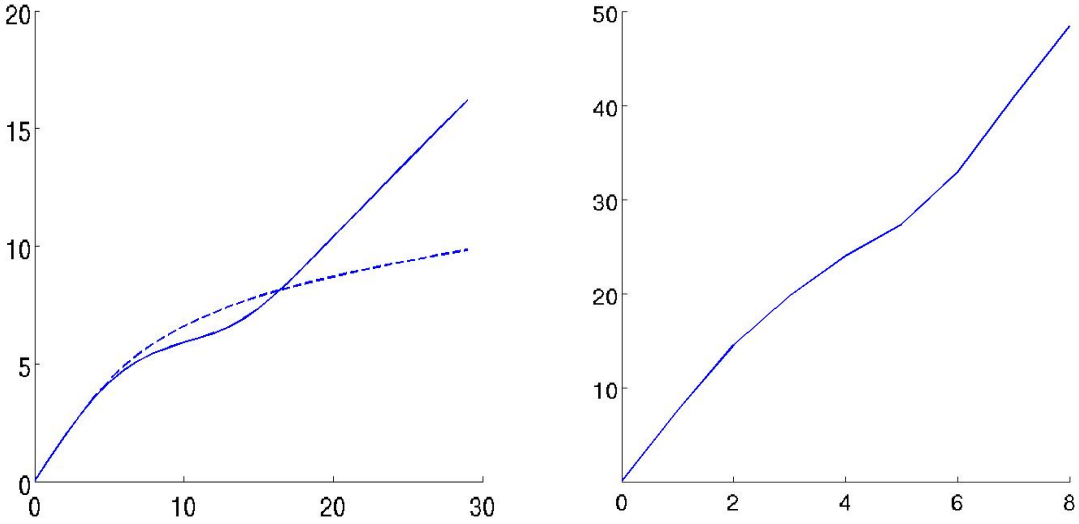

Figure 5: Growth curves of cell populations where cells may regain telomere maintenance (left). Data from *S. cerevisiae* (right).

7 Discussion

We have proposed a class of stochastic models for the loss 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 loss. The first paper making such a connection seems to be Portugal et al. (2008) 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 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 loss and cell cycle times are assumed to be independent of telomere length. There is evidence that cell cycle times may slow down in older cells

[Sinclair et al. (1998)] and that shortening depends on length [op den Buijs et al. (2004)] and although we ignored such considerations in the examples, they are easily incorporated in the general model by adjusting the quantities in (3.1).

Although the present article is mostly concerned with establishing a general framework to model the loss of telomeres, we have also considered data sets that corroborate our models, for example data from human marrow stromal cells [Baxter et al. (2004)] and from yeast [Bertuch and Lundblad (2004)]. The data in the latter is under investigation for more detailed modeling and analysis in Olofsson and Bertuch (2009).

8 References

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