Modeling Telomere Dynamics

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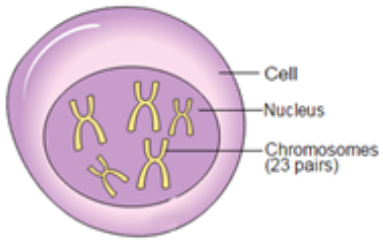
with advice from M.T. Texeira

Nov 21, 2024

Telomeres

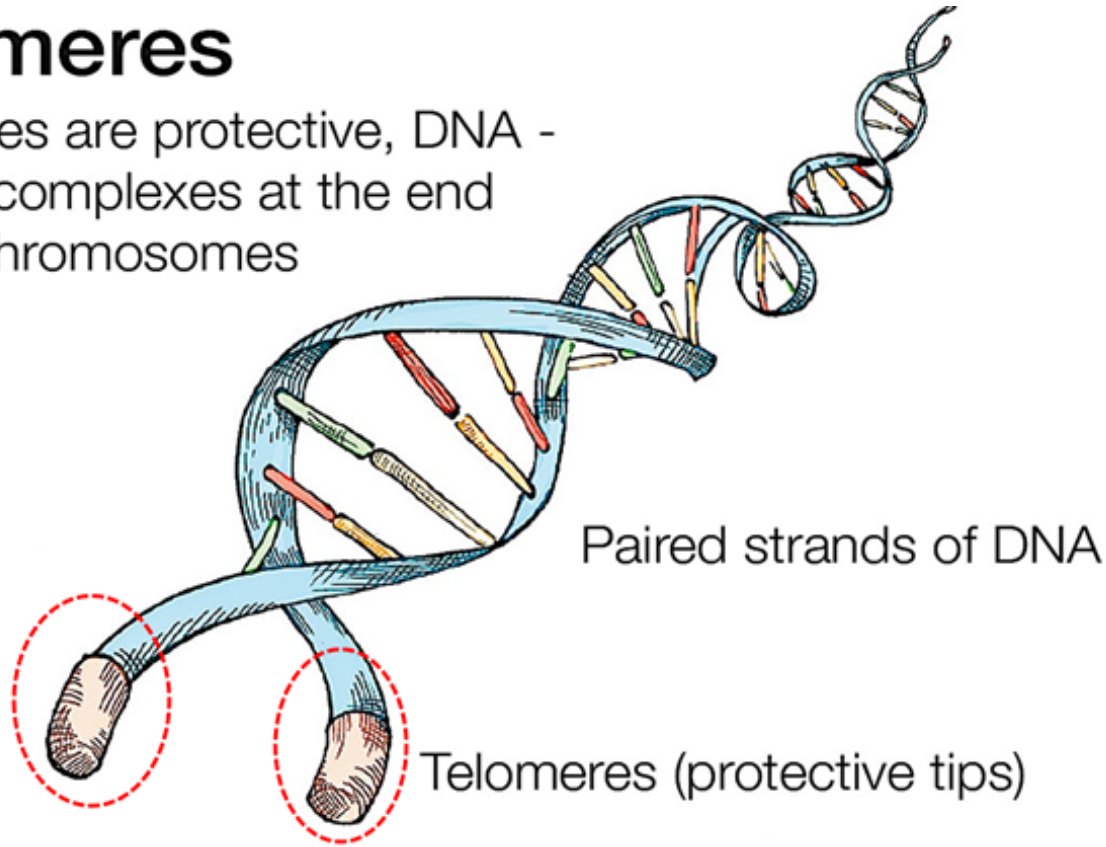
Telomeres

Telomeres are protective, DNA - protein complexes at the end of our chromosomes



$$(23 \times 2) \times 4 = 184$$

(G1 phase)



http://gawler.org/telomeres-long-short/

A Theory of Marginotomy

The Incomplete Copying of Template Margin in Enzymic Synthesis of Polynucleotides and Biological Significance of the Phenomenon†

A. M. Olovnikov

J. theor. Biol. (1973) **41**, 181–190

MARGINOTOMY THEORY OF AGEING

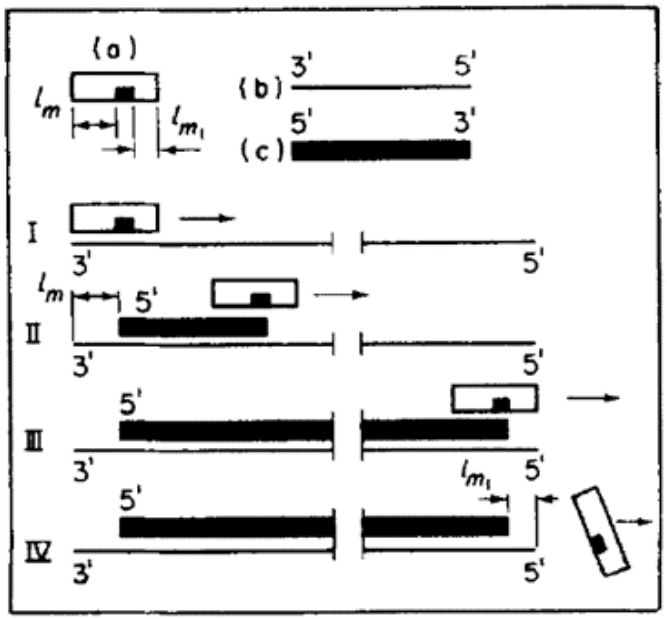
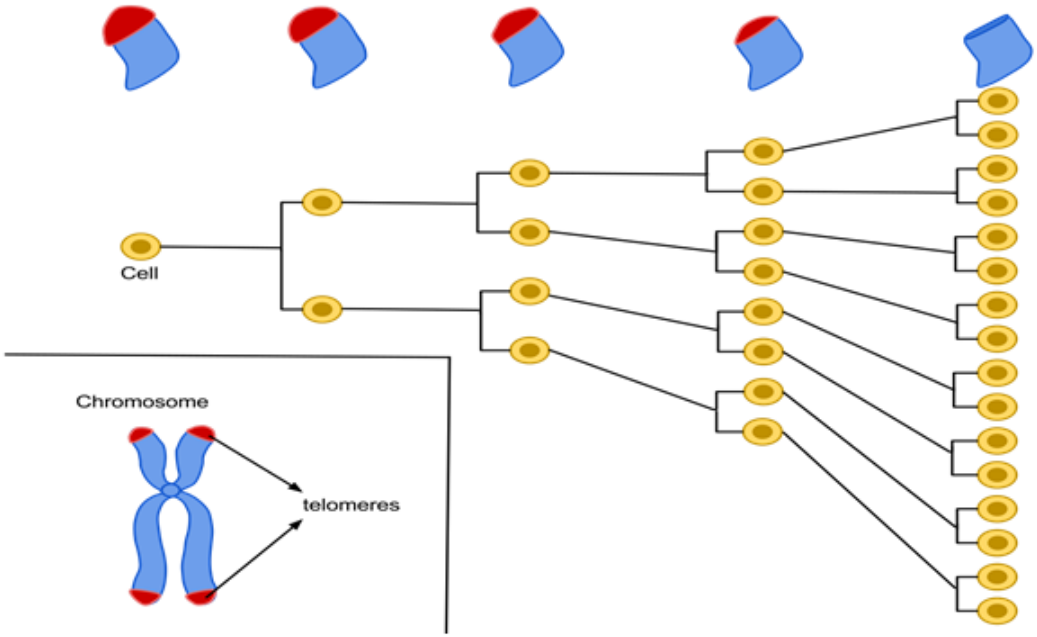


FIG. 1. A schematic representation of marginotomic replication (polymerase-dependent marginotomy). (a) The molecule of single-segment DNA-polymerase. The catalytically active centre is shown in black. Growth of the replica begins without primer and not exactly above the 3′-end of the template but at the point of localization of the catalytically active centre of the enzyme. l_m is the length of marginotomy, i.e. the distance from the end of the enzyme molecule to its catalytic centre. l_{m_1} is the length of marginotomy, i.e. the distance from the catalytic centre to the other end of the enzyme. (b) The template chain of DNA. (c) The replica.

Stages of replication: I, "landing" of the enzyme upon the edge of template DNA; II, the daughter chain appears shorter than the template at its 5′-end by l_m because of marginotomy; III, the enzyme leaves the daughter chain which is not completed by the length l_{m_1} at its 3′-end; IV, the enzyme is dissociated from the template. Latin numerals in all figures (Figs 1 to 4) denote successive stages of DNA replication. Horizontal arrows show the direction of migration of the enzyme from 3′-end of the template.

Consequence of shortening

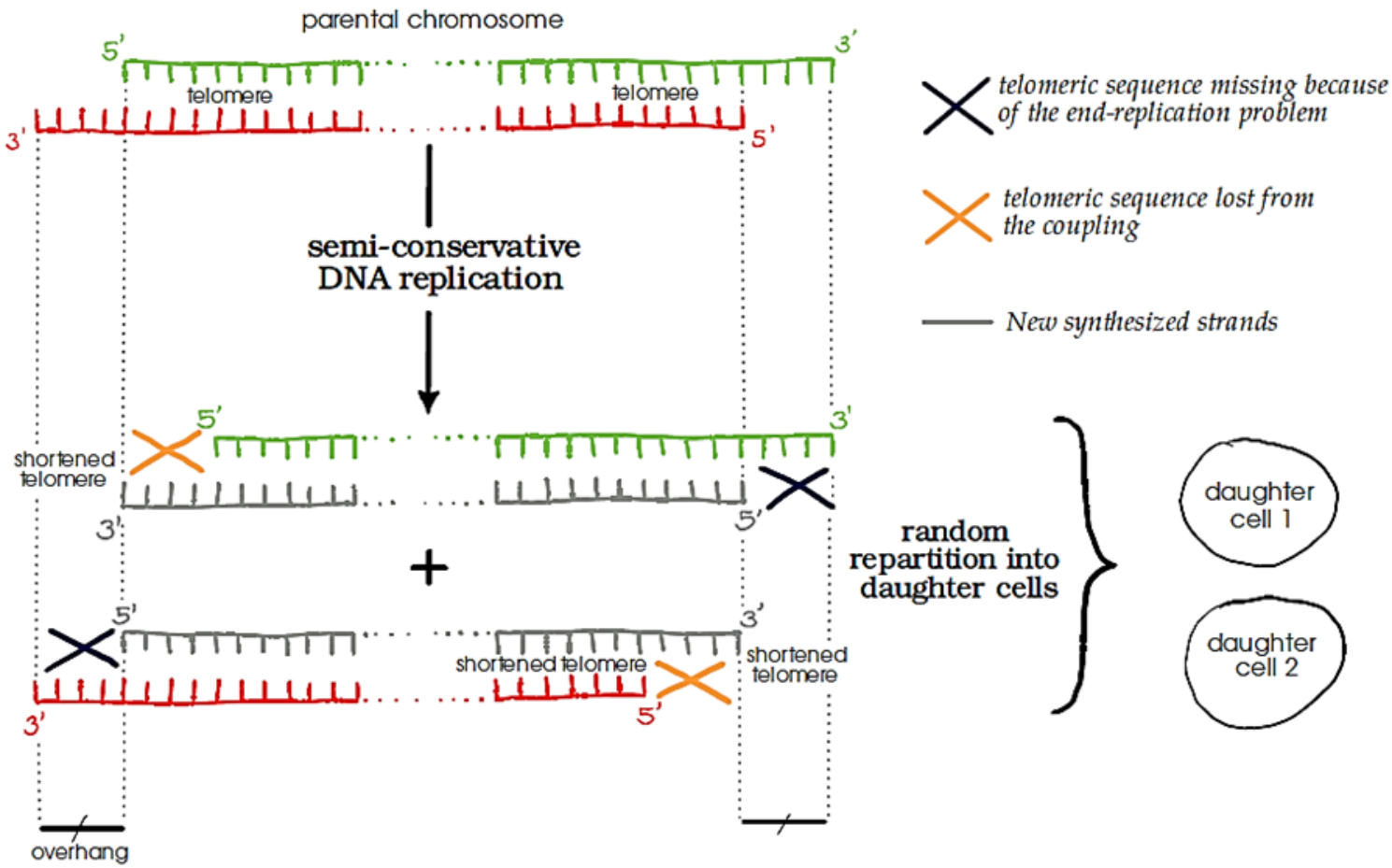
Telomere shortening ultimately leads to "uncapping" of chromosome ends and replication arrest, or even worse



- The average cell divides 50 - 70 times before cell death.
- As the cell divides the telomeres on the end of the chromosome get smaller.
- The Hayflick Limit is the theory that due to the telomeres shortening through each division, the telomeres will eventually no longer be present on the chromosome.
- This end stage is known as senescence and proves the concept that links the deterioration of telomeres and aging.

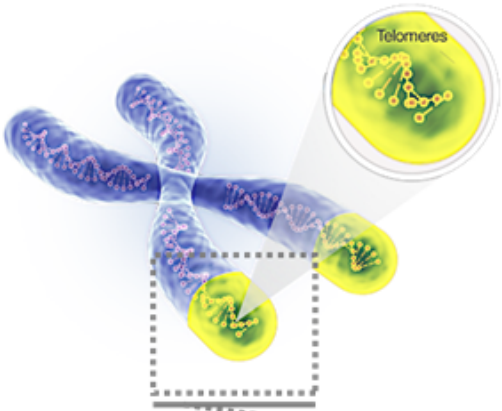
Rules of telomere shortening

From Anais Rat (2024) PhD disertation



Immortalization

The recognized agent to reconstruct telomere ending is the TELOMERASE enzyme. But there are many more ...



Lengths are **maintained** by

(= continual cell replication)

- **Activation of telomerase**
- **Alternative Lengthening of Telomeres (ALT)**

?

Length dynamics &

the connection between mechanisms:

Complicated and still poorly understood!

Immortalization

Basic discrete model for telomere shortening and reconstruction with TMMs activated
MK, Lee (2020) BMB

$$X_{n+1} = (X_n - k)_+ + A_{n+1}$$

here $n = 1, 2, \cdots$, and X_n is a time-homogeneous Markov chain (discrete).

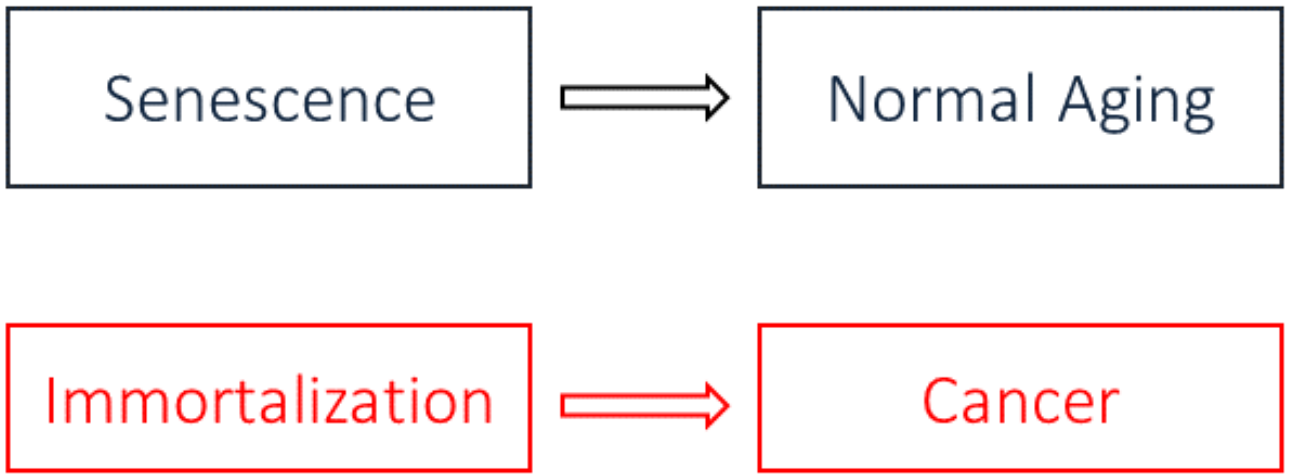
Notation	Definition
X_n	The *shortest* telomere length in a n^{th} cell of a lineage
k	Number of nucleotides ($\in \mathbb{Z}^+$) lost per generation (anchored)
A_{n+1}	$\sim$ *i.i.d.*, non-negative discrete distribution (elongation due to TMMs)
$(x)_+$	$= \max(0, x)$ (In the context of artificial neural networks: *Rectifier*)
Assumption	$P(X_1 = x_1) = 1$
	$X_i \perp A_j \ (i < j)$

11

A more complex model is *Eugène, Bourgeron, Xu. (2017) JTB*

Three modeling questions

- How to model shortening (and reconstruction, as in germ cells) of telomeres?
- How to embed telomere shortening into population structure?
- How to model immortalization of cells in cancer?

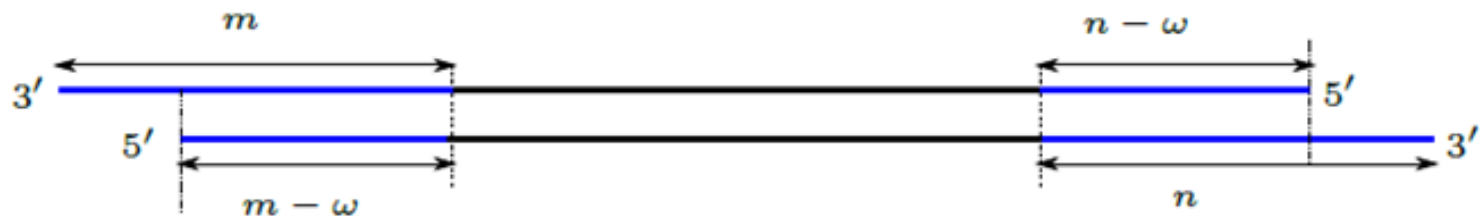


Recent papers with models inspired by telomere dynamics

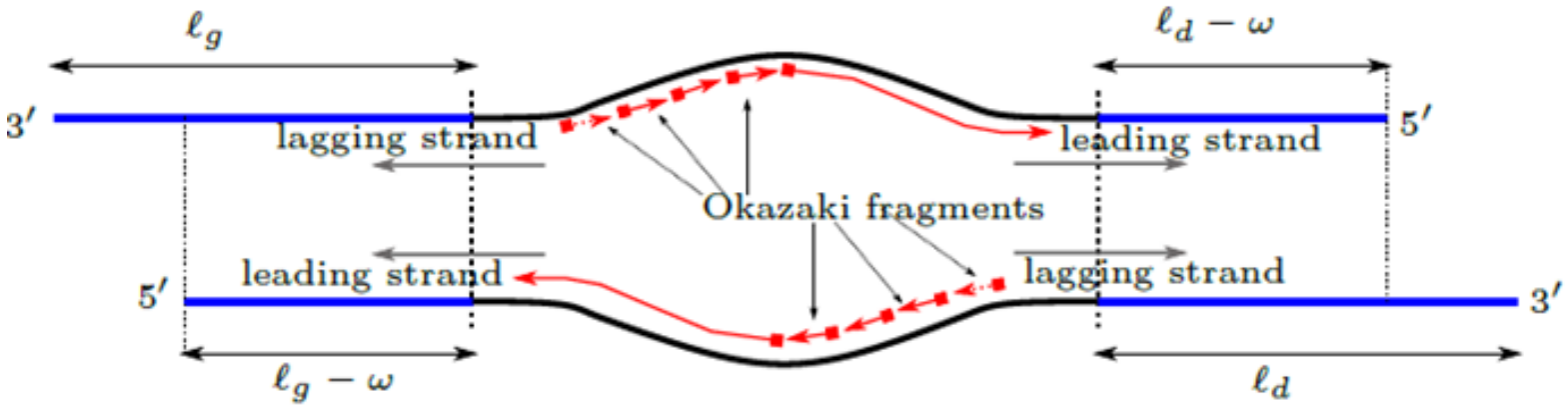
Long-time behaviour of a multidimensional age-dependent branching process with a singular jump kernel
Jules Olayé (CMAP, MERGE), Milica Tomasevic (CMAP, MERGE)
arXiv:2408.02476
[Submitted on 5 Aug 2024]

Stochastic branching models for the telomeres dynamics in a model including telomerase activity
Athanase Benetos (DCAC), Coralie Fritsch (SIMBA, IECL), Emma Horton, Lionel Lenotre (IRIMAS, ARCHIMEDE, PASTA), Simon Toupance (DCAC), Denis Villemonais (SIMBA, IECL, IUF)
arXiv:2407.11453
[Submitted on 16 Jul 2024]

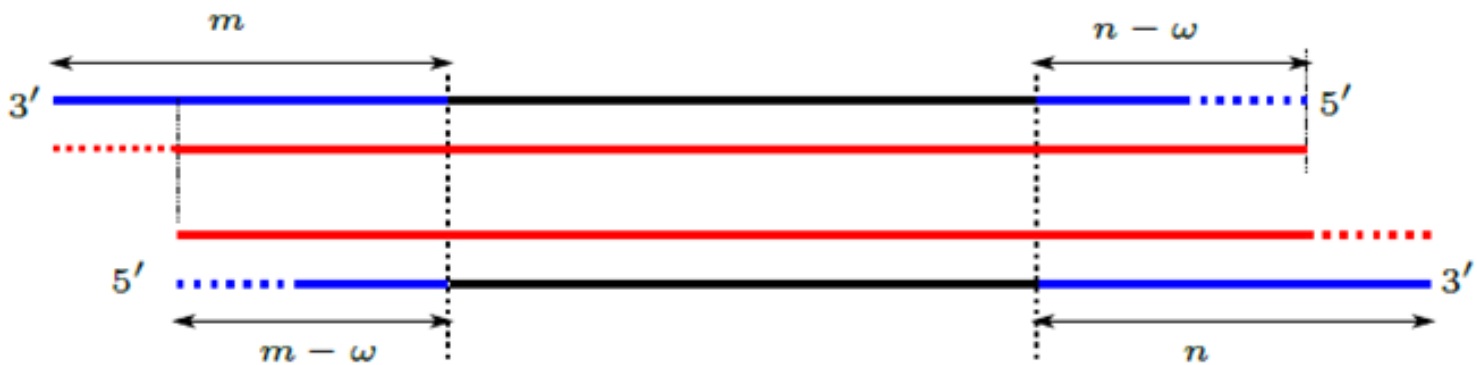
Recent comprehensive model (Benetos et al. 2024 BiorXiv



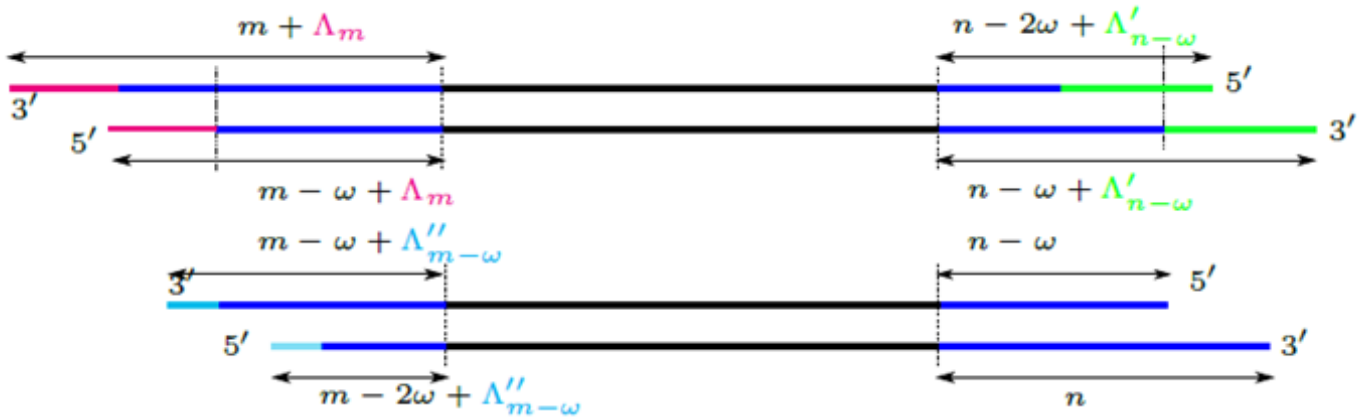
(a) Chromosome before cell division.



(b) Transcription bubble and replication forks



Benetos et al. Model cont.



(d) The two daughter chromosomes after lengthen by telomerase

Notation	Description	Referer
(m, n)	Chromosome indexed by its telomeres	p.6
ω	Overhang	p.6
K	Number of chromosomes per cell	p.6
L_{min}	Minimal telomere length of active cells	p.7
$(c, \mathtt{a}) = \left((m_j, n_j)_{j=1}^K, \mathtt{a}\right)$	Active cell	p.7
$(c, \mathtt{na}) = \left((m_j, n_j)_{j=1}^K, \mathtt{na}\right)$	Non active cell	p.7
c_0	Telomere lengths of each initial cell	p.18
$q(\ell)$	Probability that telomerase acts	p.6
q_0	Parameter of $q(\ell)$	p.21
μ_f	Telomere lengthen law	p.6
M	Maximal telomere lengthen	p.21
$b_{\mathtt{a}}$	Division rate	p.7
$s_{\mathtt{a}}$	Deactivation rate	p.7
r_s	Parameter of $s_{\mathtt{a}}$	p.18
d_x	Removal rate	p.7
N_t	Cell number in the population	p.6
N_∞	Final population size	p.18

Essentials of Olofsson-Kimmel

Originally conceived as a model for 2-ends dynamics

Olofsson and Kimmel, Math Biosci (1999)

Due to outdated view of telomere shortening (overhangs in wrong ends), qualifies as a single-end model only.

However, of some methodological interest, as an example of a reducible multitype branching process.

Main assumptions:

$$k \to \begin{cases} k \\ k-1 \end{cases} ; \quad 0 \to 0$$

i.e., telomere shorter by one unit in one of the progeny cells

- Cell lifetimes iid $\sim G(t)$

- Reproduction laws flexible

More about the OK model

Let the ancestor be of type i (has i t-repeats)

- $M_{i,i-k}(t)$, is the expected number of $i-k$-type cells at time t
- $m_{i,i-k}^{(n)}$, is the expected number of $i-k$-type cells in the n-th generation.
- Basic relation:

$$M_{i,i-k}(t) = \sum_{n=k}^{\infty} m_{i,i-k}^{(n)} (G^{*n}(t) - G^{*(n+1)}(t)), \quad (*)$$

where G^{*n} is the n-fold convolution of the cdf G, or the distribution of the sum of n iid lifelengths.

OK, OK ...

Because,

- at time t, cells from any generation may be present, and
- there are $m_{i,i-k}^{(n)}$ individuals in the n-th generation and each of these is alive at time t with probability $G^{*n}(t) - G^{*(n+1)}(t)$
- Summing over all the generations gives us $M_{i,i-k}(t)$.

Further,

- In particular, if lifelengths are exponential(α), $G^{*n}(t) = e^{-\alpha t} \sum_{k=0}^{n-1} \frac{(\alpha t)^k}{k!} \Rightarrow M_{i,i-k}(t) = e^{-\alpha t} \sum_{n=k}^{\infty} m_{i,i-k}^{(n)} \frac{(\alpha t)^n}{n!}$
- If there is no cell death, $m_{i,i-k}^{(n)} = \binom{n}{k}$ and hence

$$M_{i,i-k}(t) = e^{-\alpha t} \sum_{n=k}^{\infty} \binom{n}{k} \frac{(\alpha t)^n}{n!} = \frac{(\alpha t)^k}{k!} e^{-\alpha t} \sum_{n=k}^{\infty} \frac{(\alpha t)^{n-k}}{(n-k)!} = \frac{(\alpha t)^k}{k!}$$

as in Arino *et al.* (1995).

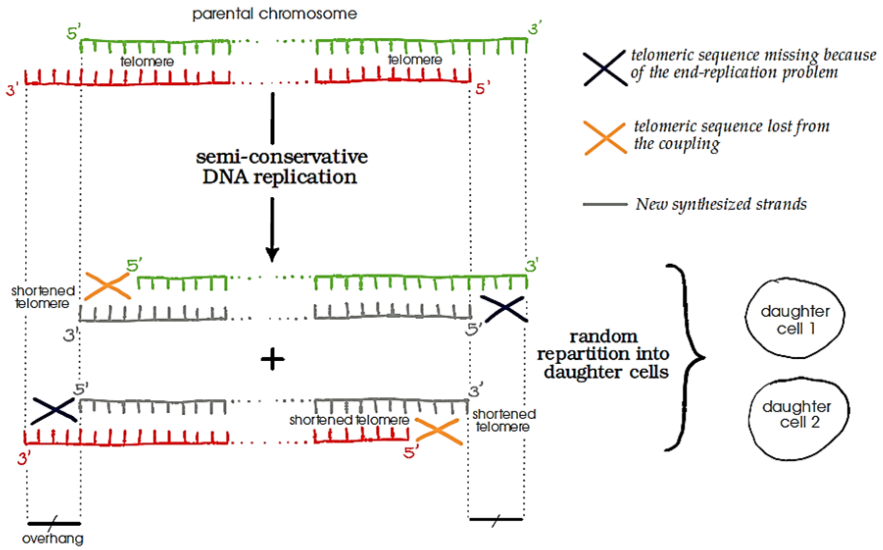
OK, OK, OK ...

If there is cell death, negative exponential terms quench the growth.

In addition, if the lifetimes are non-exponential, literally the same results obtain asymptotically.

However, the telomere shortening model is only OK (note the pun, please!)

Acceptable model?



so that ...

$$\frac{n \qquad m+1}{n+1 \qquad m} \longrightarrow \left\{ \begin{array}{c} \frac{\text{n-1} \qquad \text{m+1}}{\text{n} \qquad \text{m}} \\ \\ \frac{\text{n} \qquad \text{m}}{\text{n+1} \qquad \text{m-1}} \end{array} \right.$$

or, more concisely $(n, \ m) \longrightarrow \left\{ \begin{array}{l} (n-1, \qquad m) \\ (n, \qquad m-1) \end{array} \right.$

Two-dimensional grid flow

$$
\begin{array}{ccccccc}
(n,m) & \longrightarrow & (n,m-1) & \longrightarrow & (n,m-2) & \longrightarrow & \cdots \\
\downarrow & & \downarrow & & \downarrow & & \\
(n-1,m) & \longrightarrow & (n-1,m-1) & \longrightarrow & (n-1,m-2) & \longrightarrow & \cdots \\
\downarrow & & \downarrow & & \downarrow & & \\
(n-2,m) & \longrightarrow & (n-2,m-1) & \longrightarrow & (n-2,m-2) & \longrightarrow & \cdots \\
\downarrow & & \downarrow & & \downarrow & & \\
\vdots & & \vdots & & \vdots & &
\end{array}
$$

Assuming one ancestor in (n, m), no cell death etc., we obtain

$$
m^{(k)}_{(n,m)\to(n-i,m-j)} = \begin{cases} \binom{k}{i} & i+j=k, \;\; i \le n, \;\; j \le m \\ \\ 0 & \text{otherwise} \end{cases}
$$

for the count of cells with nonzero-length telomeres. Accumulation of senescent and dead cells is easily obtained.

Expectations in time

Final expression provides expectations at time t for the counts of cells with given imbalance between telomere deficiencies on both ends of the double helix.

$$M^{(k)}_{(n,m)\to(n-i,m-(k-i))}(t) = \sum_{k=i}^{\infty} m^{(k)}_{(n,m)\to(n-i,m-(k-i))}(G^{*k}(t) - G^{*(k+1)}(t)), \quad ($$

$i = 0, 1, \cdots, n;\ k - i = 0, 1, \cdots, m$

To be continued ...

Alternative telomere lenghtening pathway in yeast

CellPress

Molecular Cell

Article

A unified alternative telomere-lengthening pathway in yeast survivor cells

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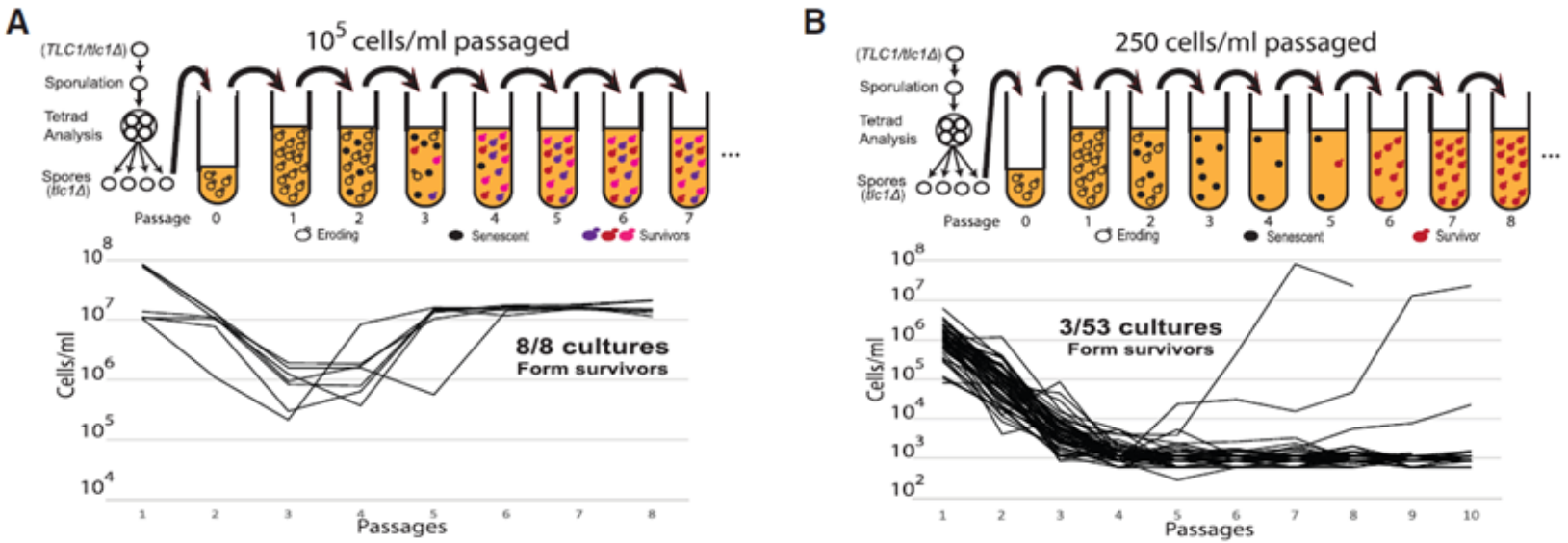
https://doi.org/10.1016/j.molcel.2021.02.004



Summary of findings

- Kockler and Colleagues carried out titration experiments in beer-yeast (MK and PO favorite eukaryotes) cultures without telomerase, to determine frequency of survivers arising.
- Survivor clones arose most likely (8/8 experiments) if a very large number 10^5 cells per ml was used.
- Survivor clones arose less likely (3/53 experiments) if a smaller number 250 cells per ml was used.
- The group carried out interesting (though somewhat vaguely described) simulations supporting diverse aspects of the experiments.
- The ALT telomeres (stable and unstable) found, were thoroughly dissected with a number of interesting conclusions.

Aims (ours)

To investigate if the titration findings are consistent with a simple statistical theory.

To construct a toy (as yet non-calibrated) model of the experiment to understand how the process might be mechanistically working.

Statistical consistency of the experiments

In a population of N individuals each of which has probability p to start a survivor clone, the probability of no survivors arising equals

$$q(p, N) = (1 - p)^N \sim e^{-Np}$$

If we observe experimentally $\hat{q}$, we obtain an estimator for p, defined as

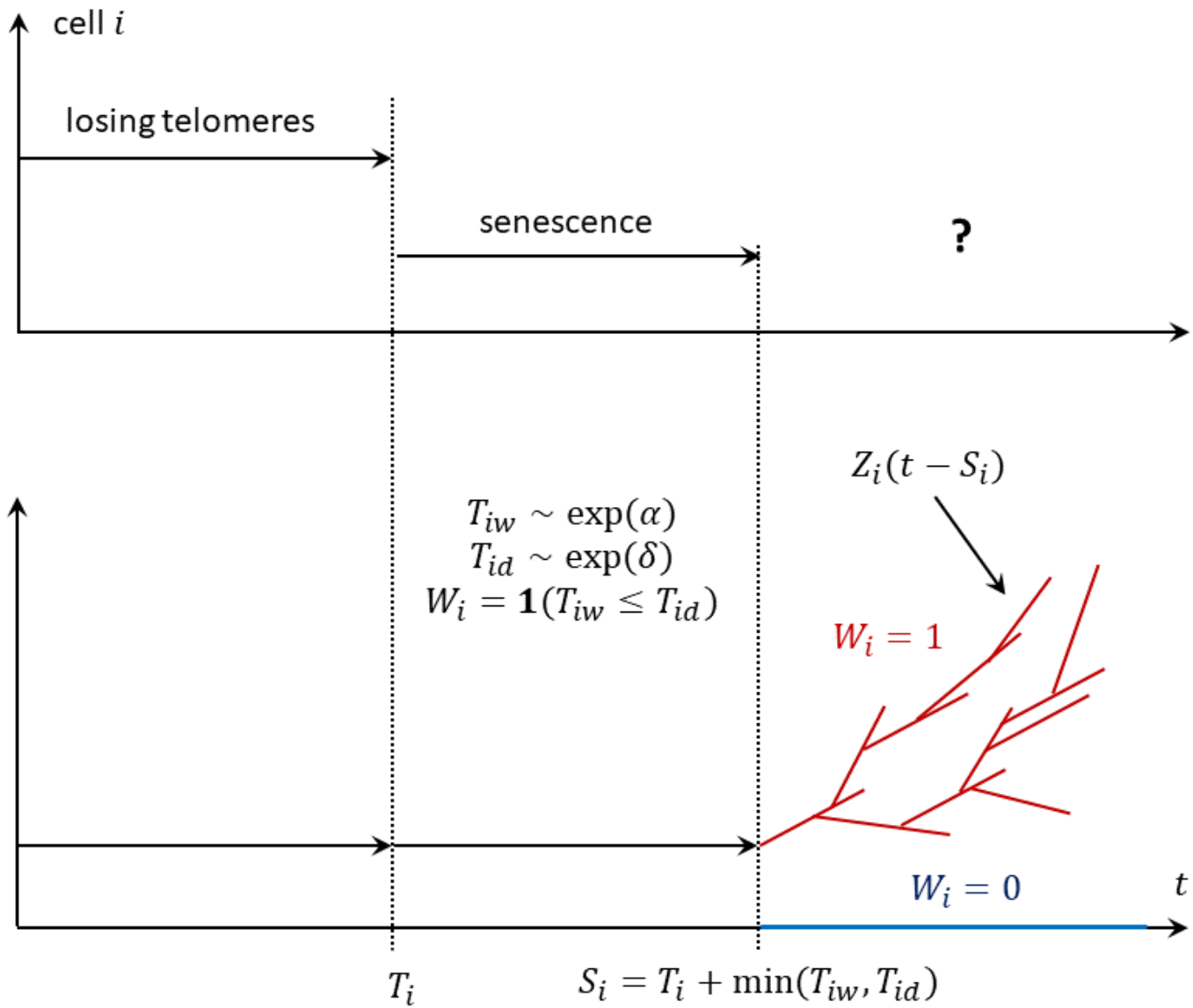
$$\hat{p} = 1 - \hat{q}^{\frac{1}{N}} \approx -\frac{1}{N} \ln q \qquad \text{if} \qquad \ln(q)N \ll 1.$$

Based on the data from Kockler et al., where for $N = 250$ cells and 53 experiments 3 cultures which survived, we obtain $\hat{q} = \frac{50}{53}$, hence

$$\hat{p} \approx -\frac{1}{250} \ln(1 - \frac{3}{53}) \sim 2.33.10^{-4}$$

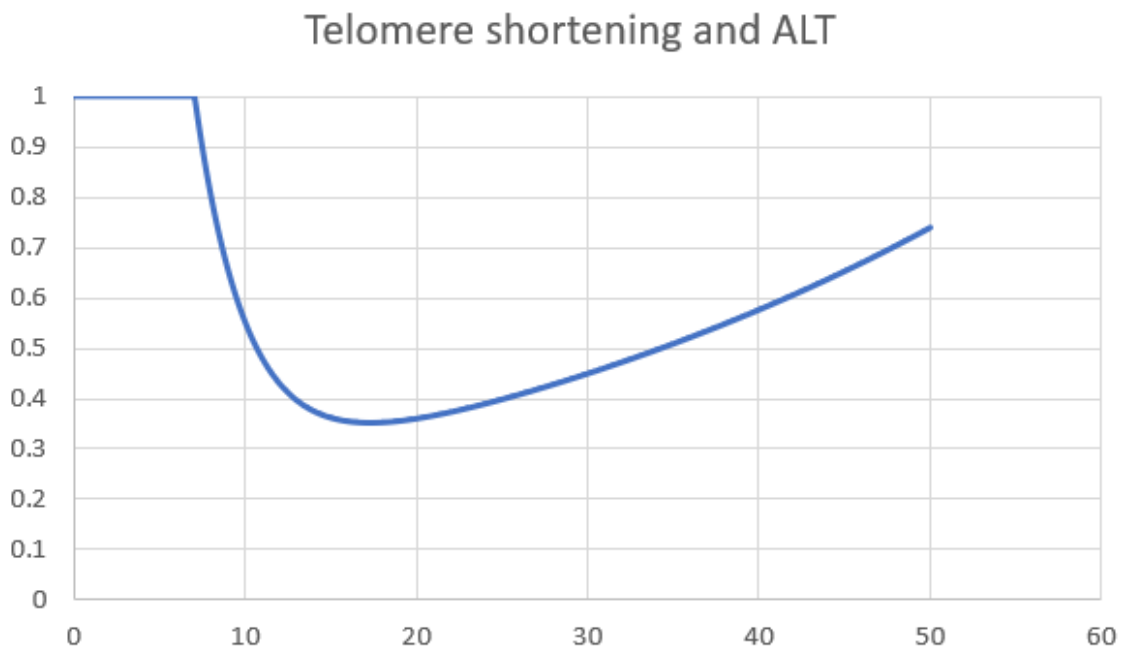
Binomial proportions 0.95 CI for $\hat{q}$ estimate depends on the method, but does not differ much from $q \in [0.8, 0.98]$, hence the 0.95 CI for $\hat{p}$ is not very different from $p \in [8 \times 10^{-5}, 7 \times 10^{-4}]$.
With $N = 10^5$, this makes probability of survivors arising almost equal to 1.

Simplified model of the ALT growth-phase



Expected trajectories of the model

A	10		alpha+delta	55
B	40		(b-a)/K	3
r	1		C	0.358333
xc	3		D	55.025
K	10		(mu-1)*rho	0.025
a	7		1/(alph+del)	0.018182
b	37			
alpha	5			
delta	50			
mu	1.05			
rho	0.5			



Conclusions

Some insights emerge from applications of mathematics to measurements of telomere dynamics.

Still enough to do for everybody ...