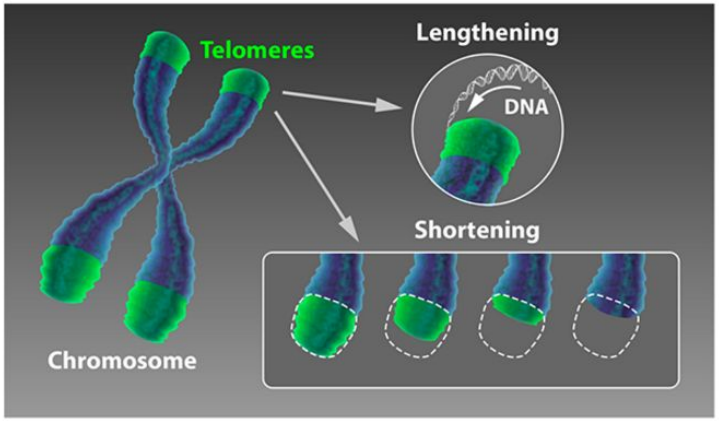
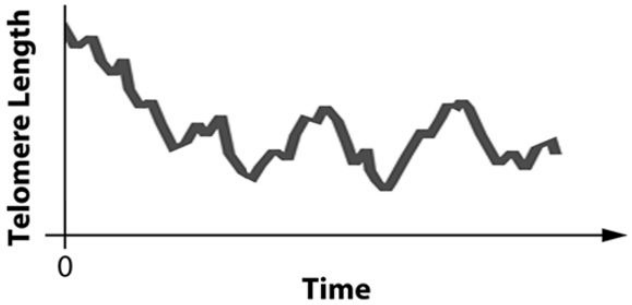




APS/Alan Stonebraker

The Life and Death of Cells

"Computing the Length
of the Shortest Telomere in the Nucleus" *

Chad Germany, Muxin Zhang,
Kexin Yang, Vlad Ghita

Physics 596 Journal Club Nov, 20th 2015

* Duc, K. Dao, and D. Holcman. *Physical review letters* 111.22 (2013): 228104.

What is a telomere?

- Protective chromosome end cap that shortens with each successive cell division
- Act as a buffer during division
- If they become too short, the DNA strand is susceptible to errors
- This results in cell death

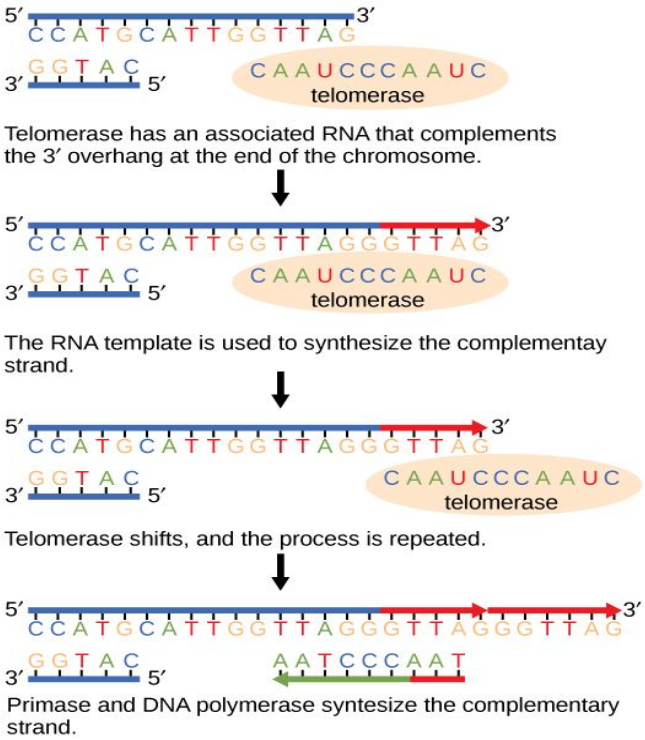
Source: NASA

Telomerase is responsible for adding length to telomeres

Enzyme is a protein which binds to single strands of DNA

Telomere length correlates with cellular aging

- Need a mechanism to regulate it during cell division, otherwise cell ends up dying due to senescence (old age)
- System evolves to a normally distributed steady state of telomere length, independent of initial conditions
- The chemical mechanism is not fully understood yet
- Can extend discussion to cancerous cells in the future - these exhibit prolific enzyme activity and shorter division cycles



Adapted from "Telomere Replication." Boundless Biology. 21 Jul. 2015. Retrieved 19 Nov. 2015

Model used elongation parameter and telomerase inhibition rate to simulate telomere length distribution

Results come from simulations on yeast.

- For a telomere of length L, there are two possible outcomes after a cell division:
- Shortening by 3-4 base pairs (1 bp = 340 pm) or elongation by an amount *y*
- This elongation parameter has a probability distribution *Prob(y) = p Exp(-py),* where p is a fit parameter from experimental data on yeast (1/p = average value of y = 40 bp)
- Effective telomerase inhibition rate = β (chemical rate of inhibition/rate of elongation) is a decreasing function of enzyme concentration
- Steady state length $\rightarrow$ 350 (mean) ± 102 bp (SD), in good agreement with experiment

We can uniquely determine a critical value for the telomerase inhibition rate B if we require 99% of the telomeres to stay above a critical length

- Computation gives 184 ± 25 bp for shortest telomere, 22 bp shorter on average than the second one
- Can explain the onset of senescence if this length drops below a critical length ($\approx$ 120 bp)
- Below this length, telomerase can't regulate the process $\rightarrow$ cell can't divide
- In this model, 1% of all cells drop below the critical length after one division

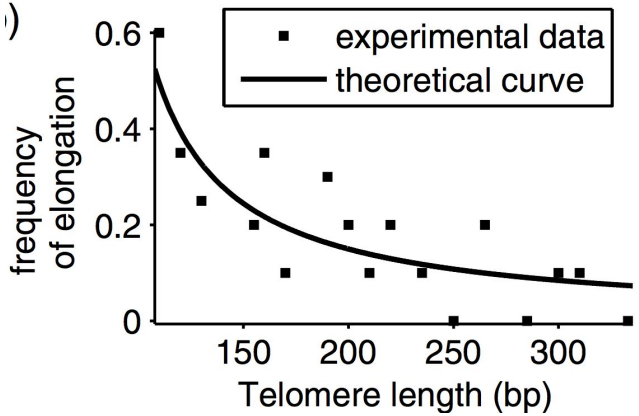
Found $\mathbf{B_c = 0.36}$, but can't easily relate this to amount of telomerase, mainly due to higher-order (non-linear) chemical mechanisms. This represents an area of future work.

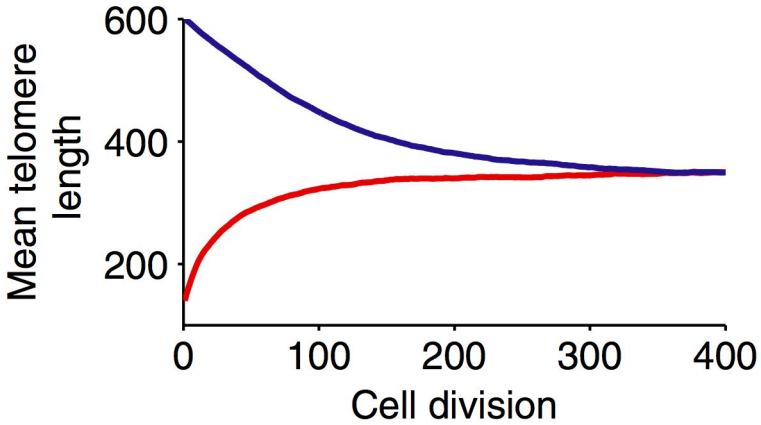
For thriving populations of yeast, senescence is an exceedingly rare phenomenon. That is, cells do not stop dividing, if they have access to nutrients.

Part 1: Compare stochastic model with experimental data

$$L_{n+1} = \begin{cases} L_n & -a \quad \text{with probability } 1 - P(L_n) \\ L_n & +\xi \quad \text{with probability } P(L_n), \end{cases}$$

1) The mean change of telomere length $\langle \Delta(L) \rangle$ is larger for short telomeres than for long ones. Simulation of a population of telomeres shows a steady state distribution of telomere length.
2) Return to equilibrium simulations for both long and short initial conditions have very close parameters to those observed in experiments.



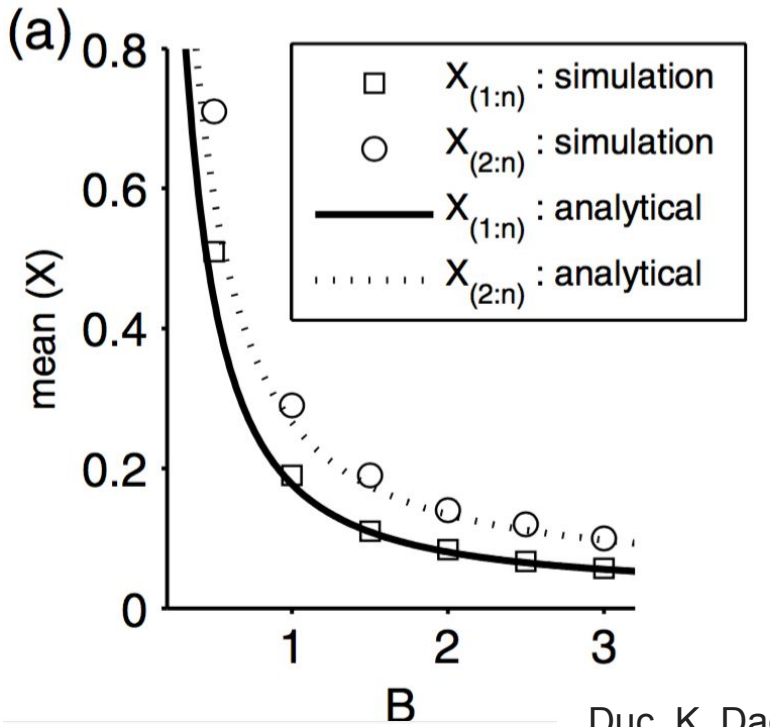


Duc, K. Dao, and D. Holcman. *Physical review letters* 111.22 (2013): 228104.

Part 2: Calculate the distribution of the shortest telomere

Stochastic model to Continuous Probability Density Function:

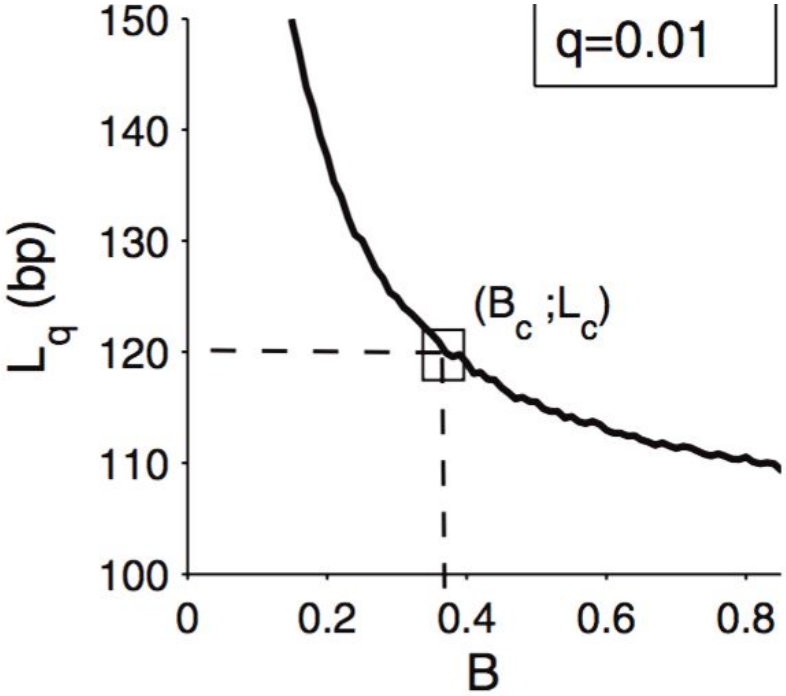
$$\partial_t f = \partial_x f - \lambda(x) f(x,t) + \int_0^l \lambda(y) f(y,t) b(x-y) dy.$$



1) For large elongation parameter B, there is a good agreement between analytical formulas and empirical simulation results.
2) For small B (B<0.5), the mean shortest telomere length is also confirmed by empirical simulation.
3) Results also show accuracy of the analytical approach for estimating the gap between the shortest telomere and the others

Duc, K. Dao, and D. Holcman. *Physical review letters* 111.22 (2013): 228104.

The key factor that determines the aging of cells



In conclusion, the paper presented a stochastic approach to compute the telomere length distribution.

$$P(L_{(1:2n)} < L_q) = q$$

They found a critical condition for elongation parameter B (critical value Bc =0.36) in yeast so that the probability of senescence (aging) for a single cell after one division is 1%.

Duc, K. Dao, and D. Holcman. *Physical review letters* 111.22 (2013): 228104.

Senescence can be influenced by switching of telomere states

Hypothesis: treat uncapping of a telomere as the trigger for cellular senescence

Uncapped state: telomere end is accessible to telomerase
Capped state: telomere end is inaccessible to telomerase

Probability of senescence:

$$P = 1 - \prod_{i=1}^{92} \left(\frac{t_i^{k_2}}{t_i^{k_2} + k_3^{k_2}} \right)$$

t_i : the length of ith telomere
k_2: describe how rapidly telomere switch from capped to uncapped state
k_3: intermediate length at which half telomeres are capped and half are uncapped

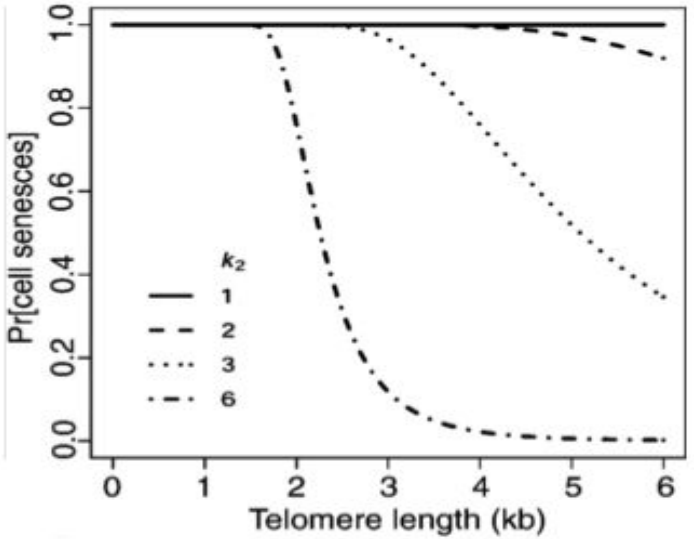


Fig1. Probability of cell senescence is affected obviously by k_2

C. J. Proctor and T. B. Kirkwood, Aging Cell 2, 151 (2003)

The model is a good fit to experiments

Results:

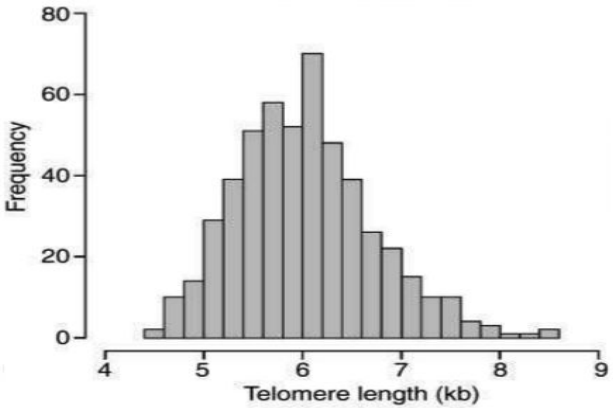


Fig1. Distribution of average telomere length
k_2=6.0, k_3=1000

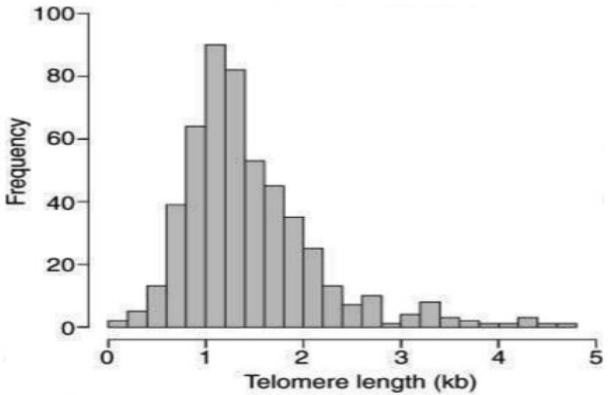


Fig2. Distribution of shortest telomere
k_2=6.0, k_3=1000

C. J. Proctor and T. B. Kirkwood, Aging Cell 2, 151 (2003)

Telomere shortening is length-dependent

Assumption: telomere loss is length-dependent; the percentage of senescence is related to the percentage of telomeres below a critical length

$$\Delta T = -\{(1 - f_s)T + \Delta T_0\}$$

ΔT :Total telomere loss

f_s :Shortening factor

ΔT_0 :Autonomous telomere loss

Case 1: when all n_s below T_c, the cell enters the senescent state

$$v_s = \{N(T_C)\}^{n_s}$$

Case 2: when at least one out of n_s below T_c, the cell enters the senescent state

$$v_s = 1 - \{1 - N(T_C)\}^{n_s}$$

J. op den Buijs, P. P. van den Bosch, M. W. Musters, and N. A. van Riel, Mech. Ageing Dev. 125, 437 (2004).

Mathematical modeling confirms the length-dependency of telomere shortening

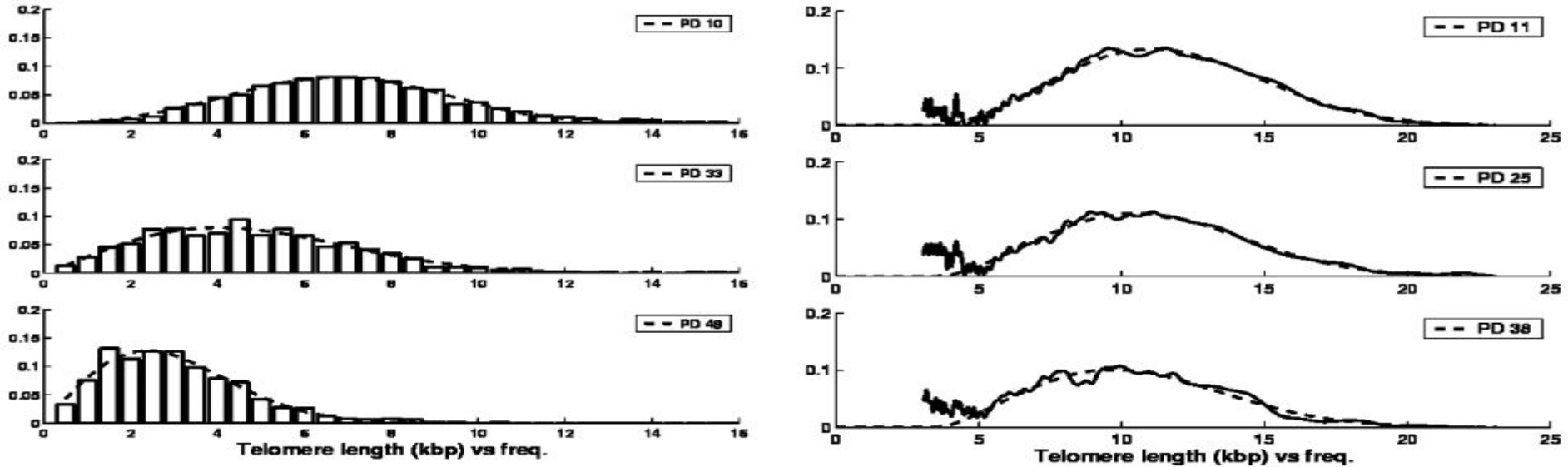


Fig1: Weibull distribution fitted on telomere length measurements in (A) human diploid fibroblasts (Martens et al., 2000) and (B) HUVECs (Zhang et al., 2000)

J. op den Buijs, P. P. van den Bosch, M. W. Musters, and N. A. van Riel, Mech. Ageing Dev. 125, 437 (2004).

Probability distributions are affected by different factors

Duc K D, Holcman D. Computing the Length of the Shortest Telomere in the Nucleus[J]. Physical review letters, 2013, 111(22): 228104.

3 factors: the length of telomere; shortening rate; elongation rate

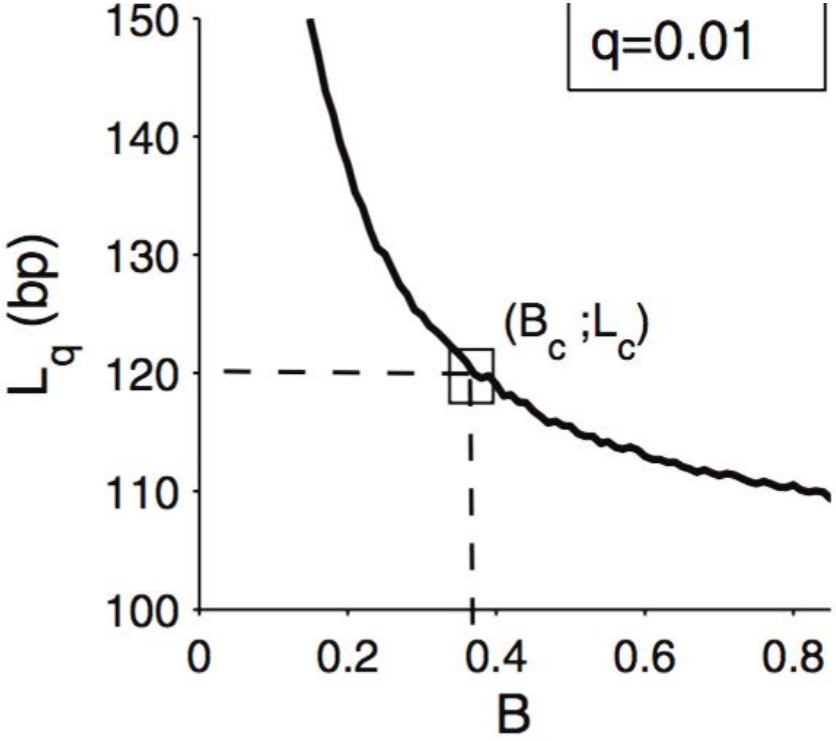
Proctor C J, Kirkwood T B L. Modelling cellular senescence as a result of telomere state[J]. Aging cell, 2003, 2(3): 151-157.

3 factors: length of telomere; intermediate length; switch from capped to uncapped state

op den Buijs J, van den Bosch P P J, Musters M W J M, et al. Mathematical modeling confirms the length-dependency of telomere shortening[J]. Mechanisms of ageing and development, 2004, 125(6): 437-444.

2 factors: critical length and the fraction below critical length

99% of cells will have telomere length greater than Lq

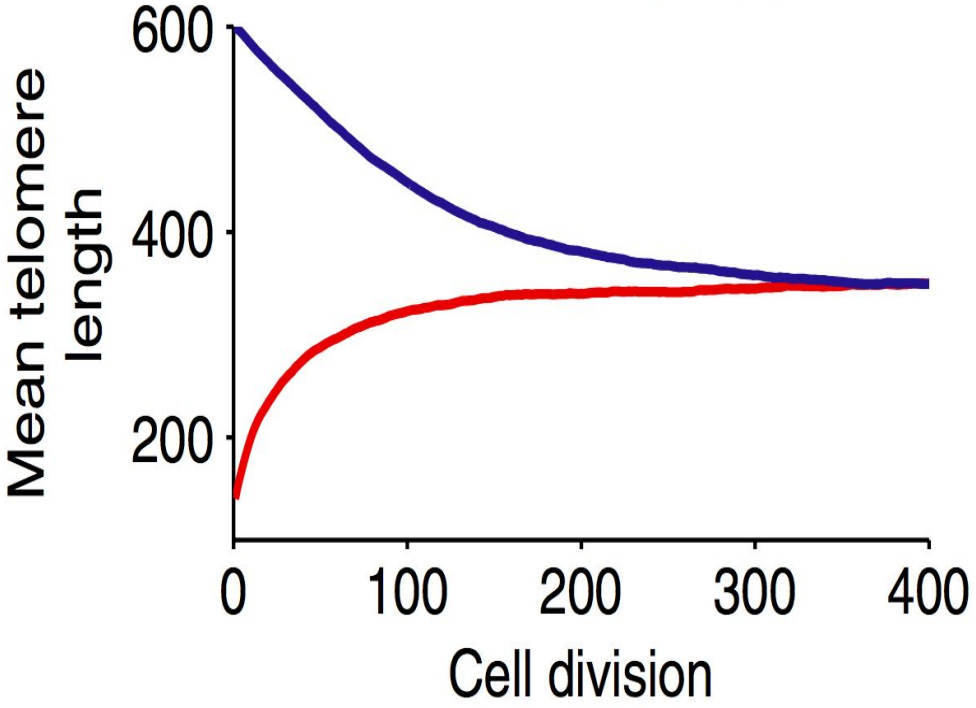


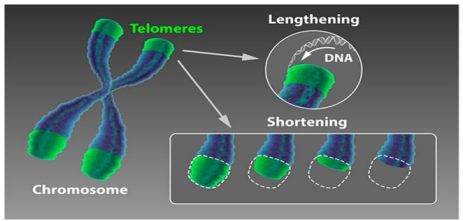
Lq=Lc = some critical length that below which the cell goes through senescence.

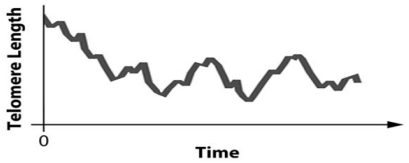
B = elongation probability parameter.

Koller et al. Mathematical model of alternative mechanism of telomere length maintenance, Arxiv: 1402.0430.

The Mean length of the telomere reached some equilibrium







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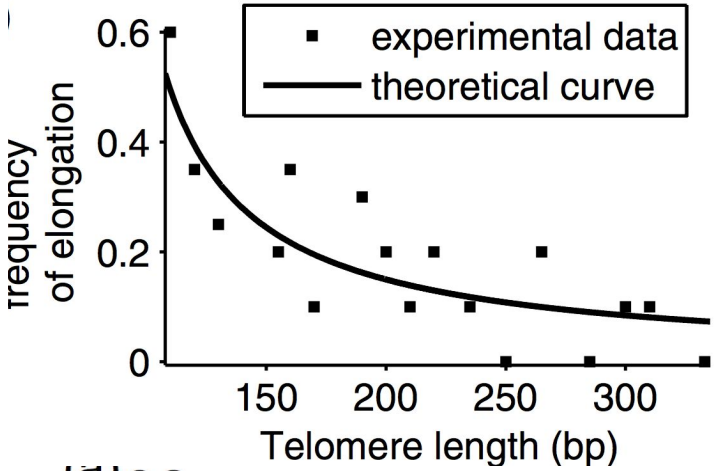
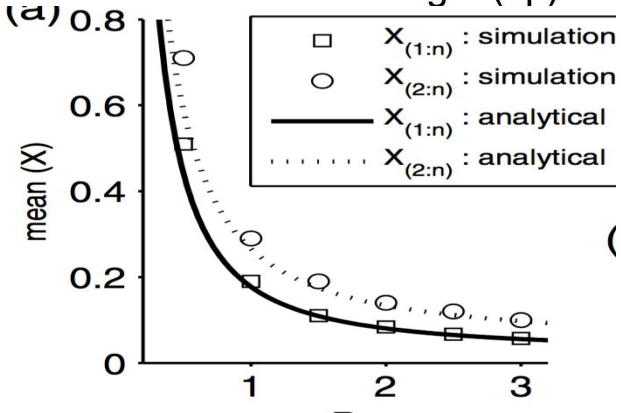
Koller et al. Mathematical model of alternative mechanism of telomere length maintenance, Arxiv: 1402.0430.

Major Criticism





- They lack the necessary error bars on all of their figures.
- The connection between experimental results and analytical calculations is tenuous.
- All of the experiment results are compared to their simulations.

Koller et al. Mathematical model of alternative mechanism of telomere length maintenance, Arxiv: 1402.0430.

List of Citations

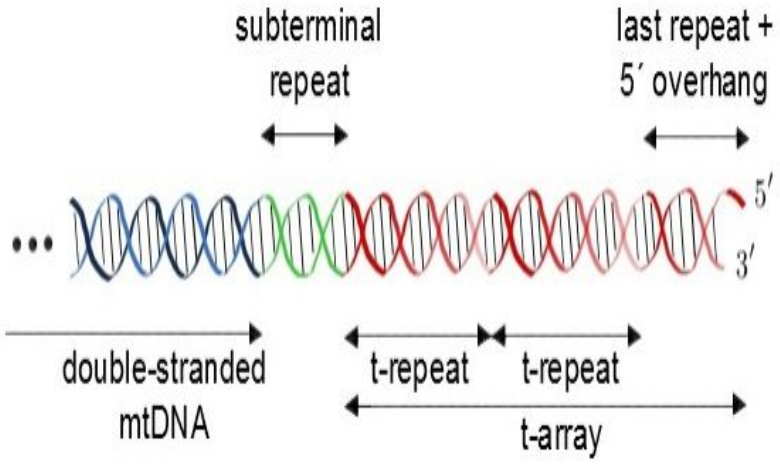


FIG. 3. Telomere structure of the linear mtDNA in yeast *C. parapsilosis*.

Koller et al. Mathematical model of alternative mechanism of telomere length maintenance, Arxiv: 1402.0430.

Therefore we design and analyze a mathematical model of an alternative telomere length maintenance:

(i) In a telomerase independent system.

(ii) On a time scale much shorter than the time scale of cell division.

List of Related Papers

- A Conserved N-Terminal Domain of Rif2 Regulates Telomere Length in Saccharomyces cerevisiae
- Early telomerase inactivation accelerates aging independently of telomere length
- TALEN gene knockouts reveal no requirement for the conserved human shelterin protein Rap1 in telomere protection and length regulation
- Telomere length differences between subcutaneous and visceral adipose tissue in humans
- Midlife racial differences In leukocyte telomere length and in associations between modifiable factors and telomere length
- Minishelterins separate telomere length regulation and end protection in fission yeast
- Association of dimensional psychological health measures with telomere length in male war veterans

What is the connection between the difference in average telomere length and prostate cancer amongst black and white men

- Black men have a 60% higher risk of getting prostate cancer than white males.
- The study tried to access whether or not the average length of the telomere in each race could explain the disparity.
- They measured the length of a single gene from a sample of 43 black males and 56 white males.
- They found that the length of the telomeres did not differ significantly amongst the races.

Meeker et al. Midlife racial differences In leukocyte telomere length and in associations between modifiable factors and telomere length,Cancer Res August 1, 2015 75; 832