Shortening of Telomeres and Replicative Senescence

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joint work with Thibault Bourgeron, Philippe Robert and Zhou Xu

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Outline

Definitions

- Telomere: non-coding sequences at the end of chromosomes
- Replicative Senescence: state of a cell unable to divide

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- Telomere: non-coding sequences at the end of chromosomes
- Replicative Senescence: state of a cell unable to divide

$\Longrightarrow$ the replication machinery implies a shortening of telomeres

$\Longrightarrow$ when too short, the cell enters in replicative senescence (otherwise loss of genetic information)

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Telomeres are involved in:

- Aging

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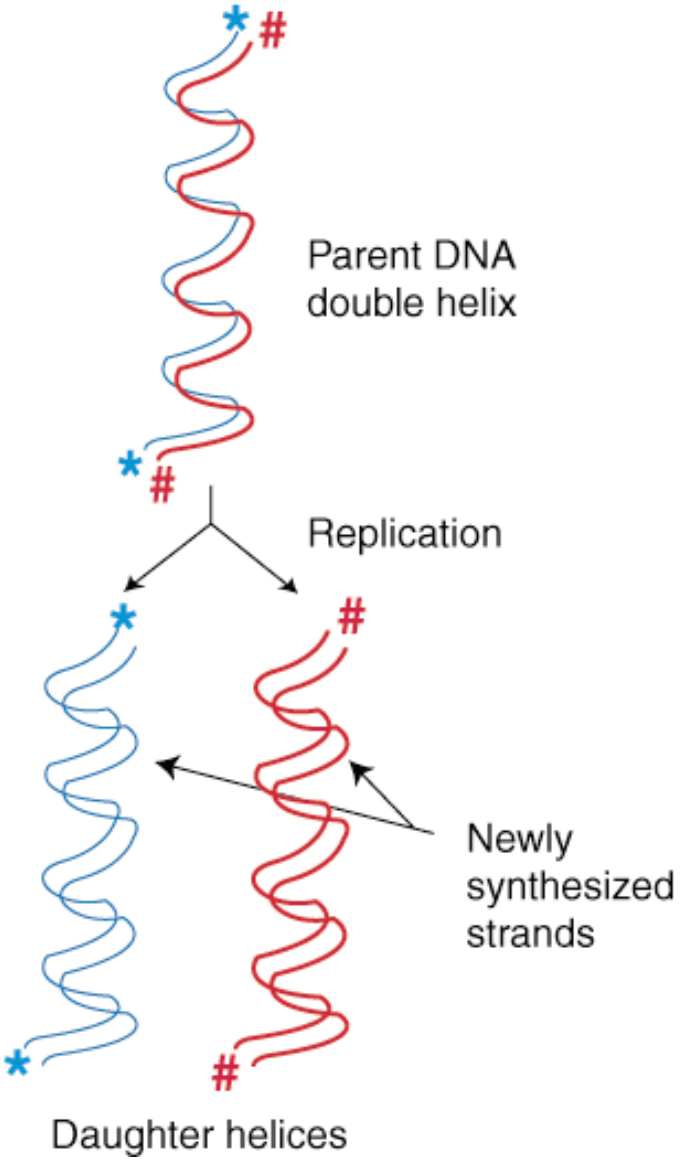
Semi-conservative DNA Replication



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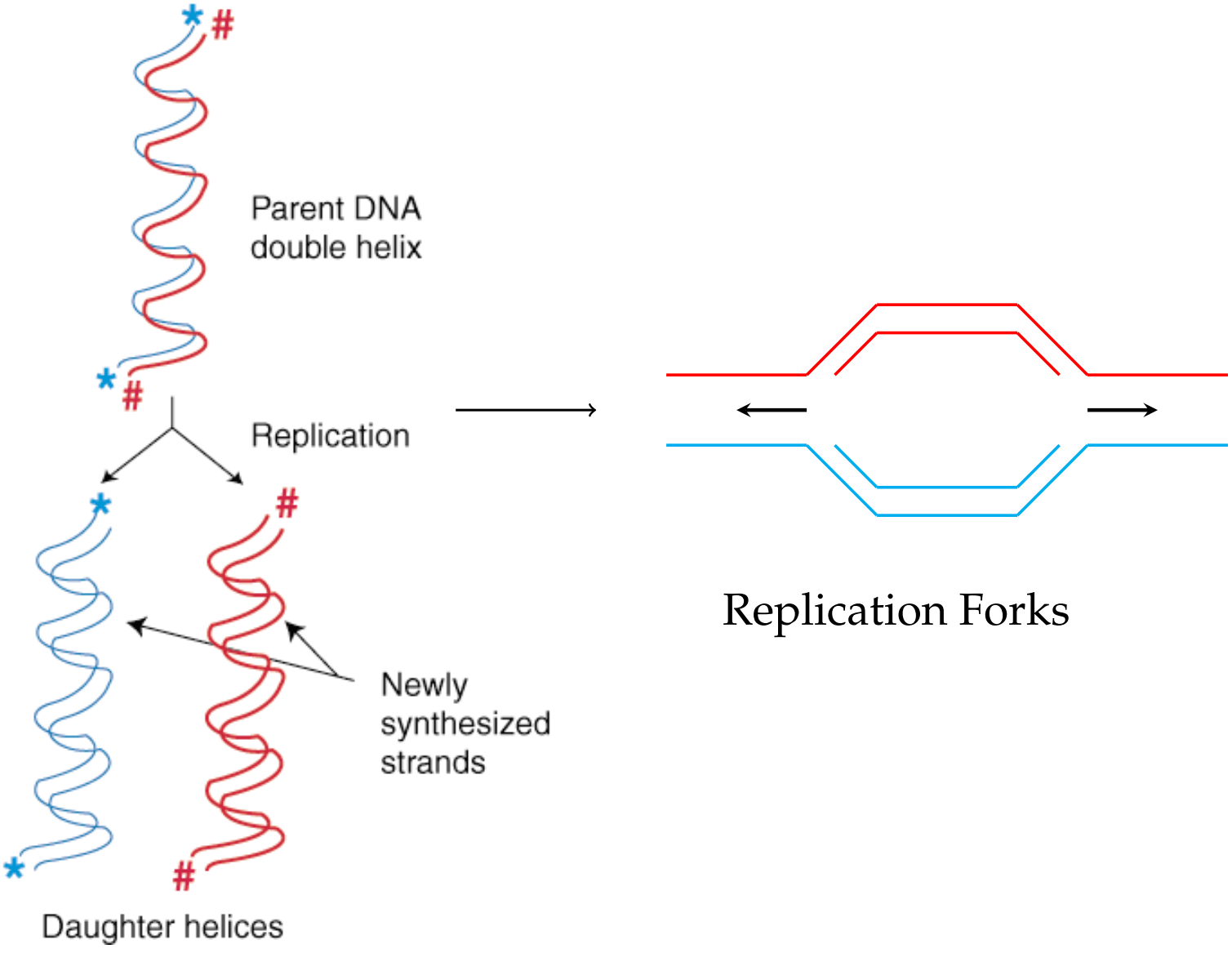

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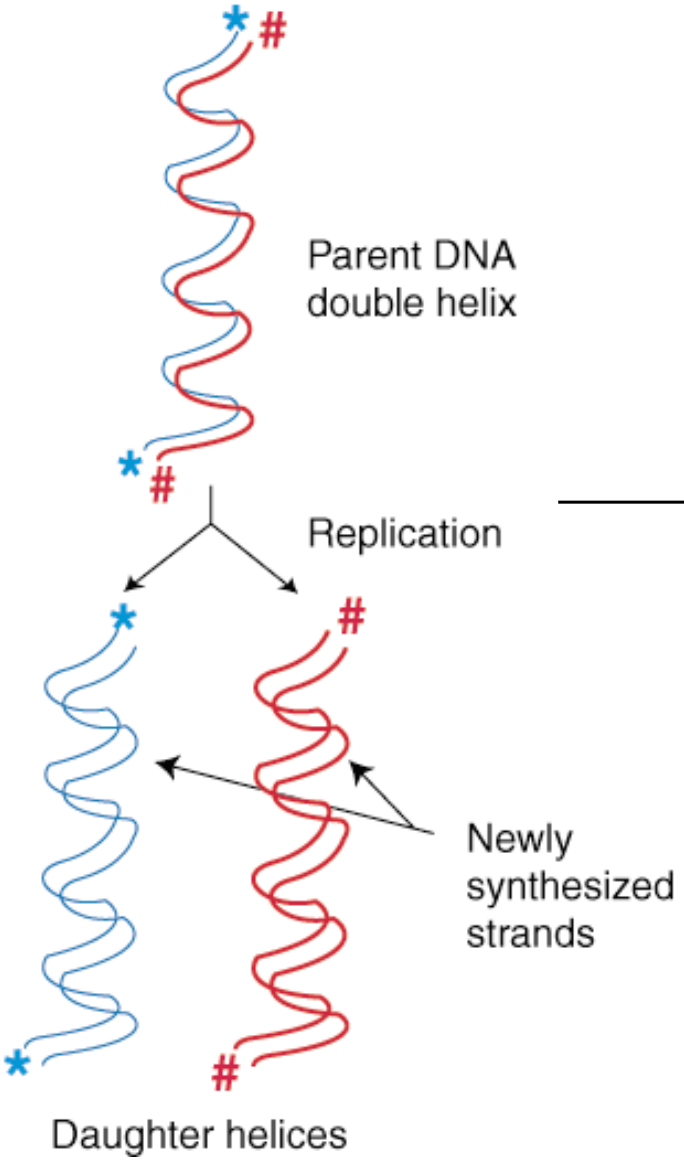
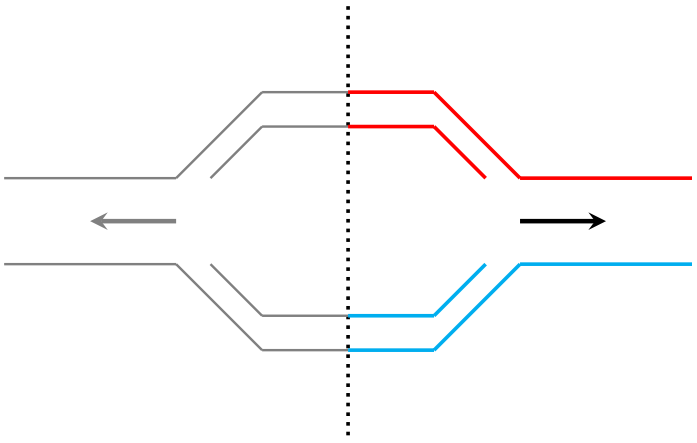
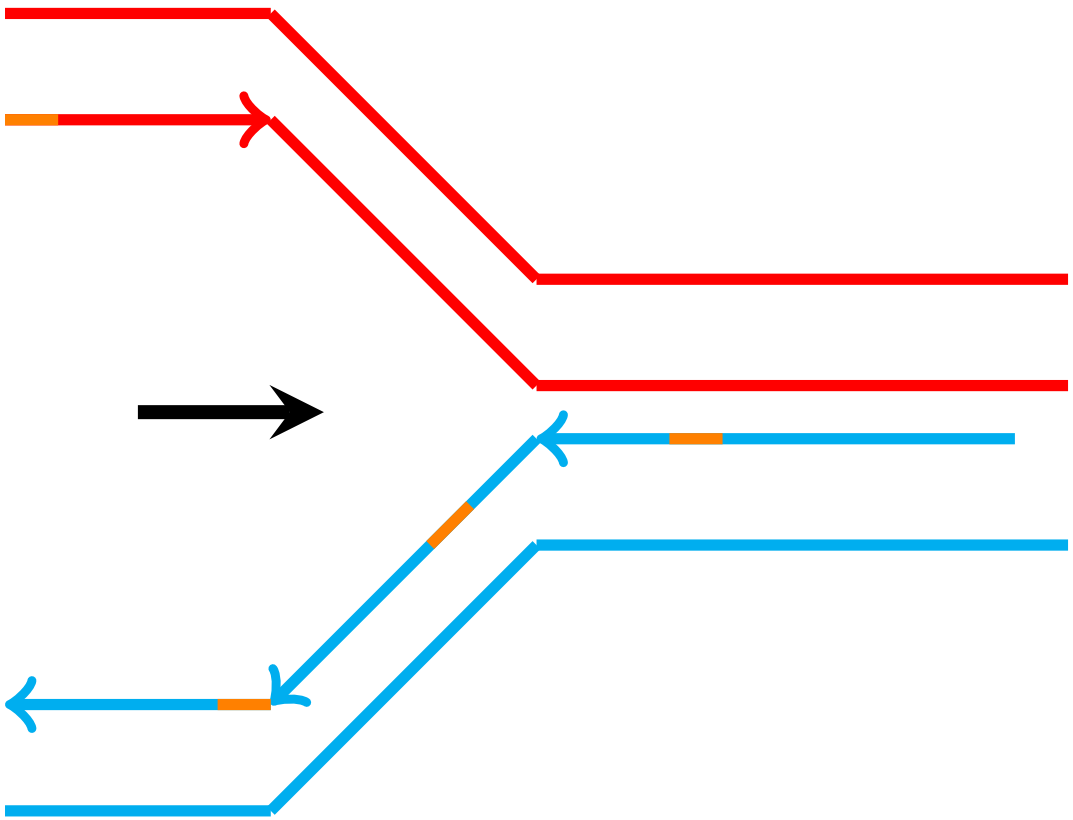




Replication Forks

The Telomere End Problem



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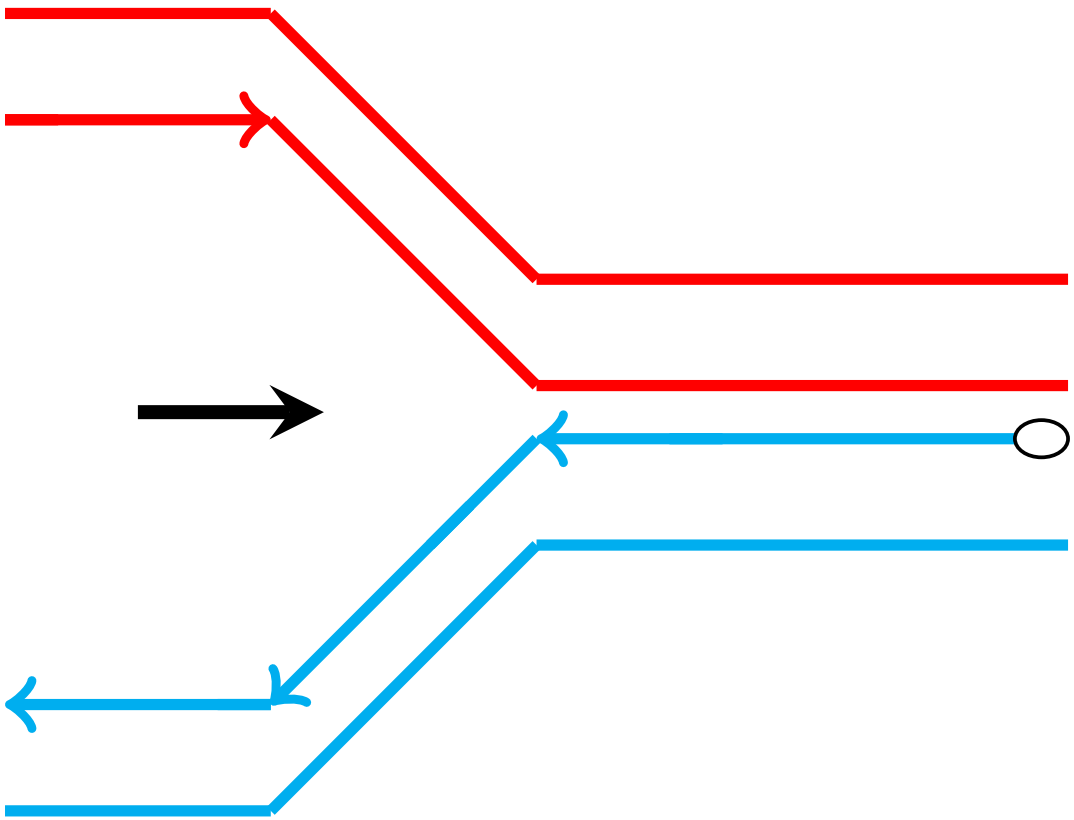

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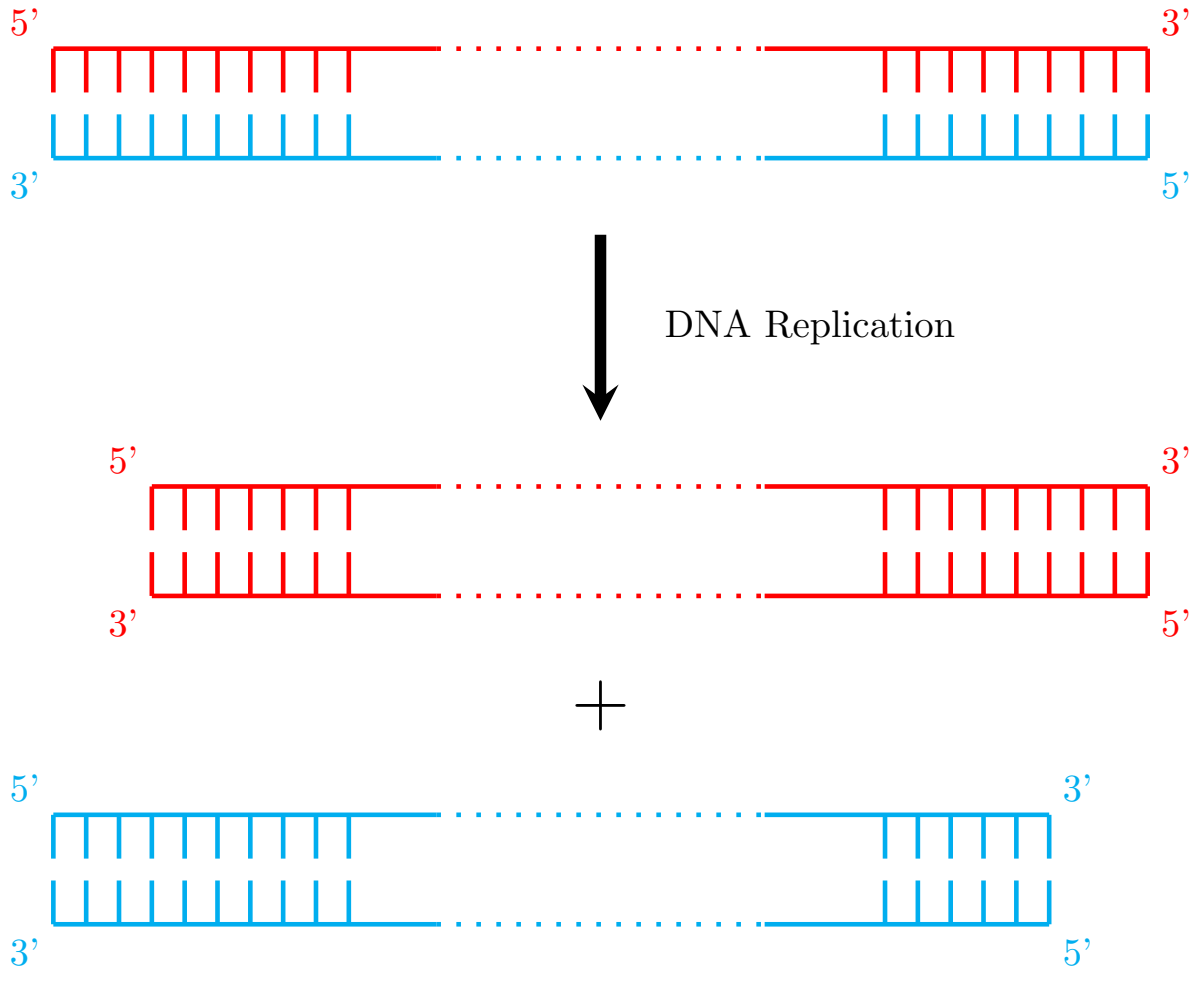

Motivations

- In stem cells and germ cells, telomeres are repaired by a protein, the telomerase

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- In somatic cells, the telomerase is inhibited: the telomeres are only shortened until they are too small to allow replication

EXPERIMENTS

- haploids lineages in Saccharomyces cerevisiae

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- haploids lineages in Saccharomyces cerevisiae
- first: telomeres are repaired by the telomerase ($\leftrightarrow$ beginning of life)
- then: the telomerase is inhibited, the cells enter in replicative senescence ($\leftrightarrow$aging)

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Mathematical Goals

- Model these two phases (obviously)

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Mathematical Goals

- Model these two phases (obviously)
- Describe the equilibrium of the first phase
- From the time of senescence, estimate the parameters of this equilibrium ('inverse problem')

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Outline

Qualitative Behaviour

previous experiments at nucleotide resolution prove that:

- the elongation doesn't depend on telomere length

M. Teixeira et al., Telomere length homeostasis is achieved via a switch between telomerase- extendible and -nonextendible states. Cell, 2004.

If telomeres were always repaired...

- L_n: length of telomere at n^{th} generation
- a: shortening rate
- $\mathcal{G}$: geometric random variable of parameter p (elongation)

Model

$$L_{n+1} = (L_n - a)^+ + \mathcal{G} \tag{1}$$

Equilibrium Distribution

- L_∞ equilibrium distribution of $(L_n)_n$ (if exists)
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Generating function of L_∞

$$\left[(p-1)u^a + p(1+u+u^2+\ldots+u^{a-1})\right]\mathbb{E}\left[u^{L_\infty}\right] = pu^a \sum_{k=0}^{a-1} \pi_k \left(1 + \frac{1}{u} + \ldots + \frac{1}{u^{a-k}}\right)$$

EQUILIBRIUM: IDENTIFYING $(\pi_0, \ldots \pi_{a-1})$

Normalisation condition

$$p \sum_{k=0}^{a-1} \pi_k (a - k + 1) = ap - (1 - p)$$

Rouché's Theorem:

$\left[(p-1)u^a + p(1 + u + u^2 + \ldots + u^{a-1})\right]$ has $a - 1$ roots in the unit disk iff $ap > 1 - p$,

Equilibrium: Identifying $(\pi_0, \ldots \pi_{a-1})$

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Qualitative Behaviour

previous experiments at nucleotide resolution prove that:

- the elongation doesn't depend on telomere length
- tendency to elongate rather short telomeres

M. Teixeira et al., Telomere length homeostasis is achieved via a switch between telomerase- extendible and -nonextendible states. Cell, 2004.

More Accurate Model

- L_n: length of telomere at n^{th} generation
- a: shortening rate
- B: Bernouilli random variable parameter $1/2$
- $\mathcal{G}$: geometric random variable parameter p (elongation)
- i_S: elongation threshold

Model

$$L_{n+1} = (L_n - a.B)^+ + \mathcal{G}\mathbb{1}_{\{L_n \leq i_s\}} \tag{2}$$

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Generating function of L_∞

$$\mathbb{E}(u^{L_\infty}) = \frac{(1-p)(1+u)}{1-u(1-p)} \sum_{k=0}^{i_s} u^k \pi_k + \frac{p}{1-u(1-p)} \pi_0 \qquad (3)$$

The $i_s + 1$ first states determine the whole chain:

Identifying $(\pi_0, ...\pi_{i_S})$

$$\forall\, 1 \leq k \leq i_s,\ \pi_k = \left(\frac{2(1-p)}{p}\right)^k \pi_0$$

$$\forall\, k > i_s,\ \pi_k = p(1-p)^k \left(\frac{2}{p}\right)^{i_s+1} \pi_0$$

$\Longrightarrow$ geometric distribution with two regimes

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Conclusion

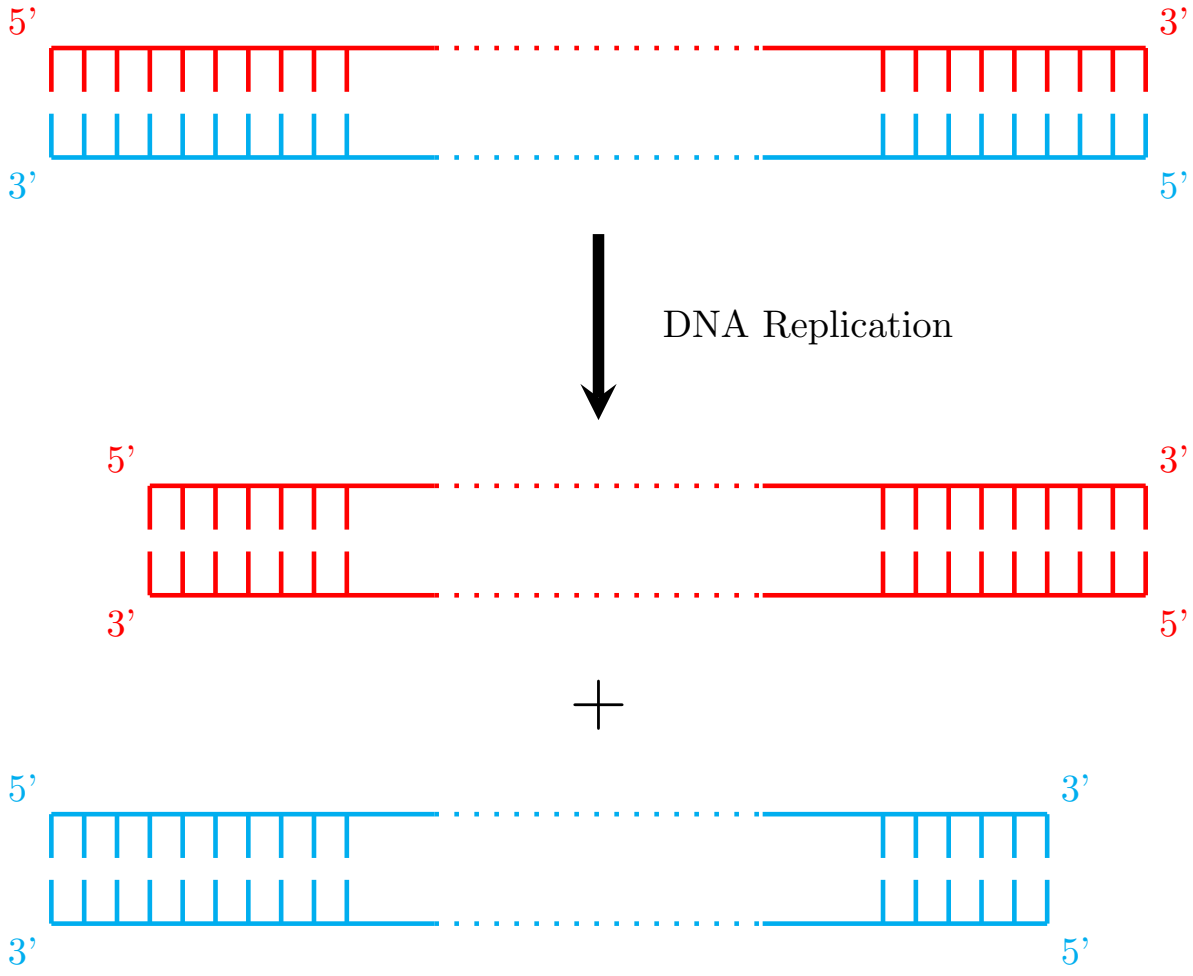
- the equilibrium is theoretically identified
- the parameters (i_S, p) are unknown (no experiments available)

Outline

Motivation

- Experiments allow to estimate the distribution of the time of senescence
- Goal: from these data, estimate the parameter of the previous equilibrium distribution

Two telomeres of the same chromosome are paired



Model of Shortening for the Whole Cell

- the telomerase is switched-off: no reparation
- 16 chromosomes $\Longrightarrow$ 32 telomeres $\Longrightarrow$ 16 independent couples $(X_n^i, Y_n^i)_{1 \leq i \leq 16}$
- initially distributed according to the previous equilibrium:

$$\forall i, X_0^i \overset{dist}{\sim} L_\infty \sim \pi$$

Model for one chromosome

$$\begin{pmatrix} X_{n+1} \\ \\ Y_{n+1} \end{pmatrix} = \begin{pmatrix} (X_n - a \cdot B)^+ \\ \\ (Y_n - a \cdot (1-B))^+ \end{pmatrix}$$

Model for the whole cell

16 independent couples (X_n, Y_n)

Model of Replicative Senescence

Senescence

The first time when the shortest telomere is below an (unknown) threshold S. ($S = 0$ in the following calculations)

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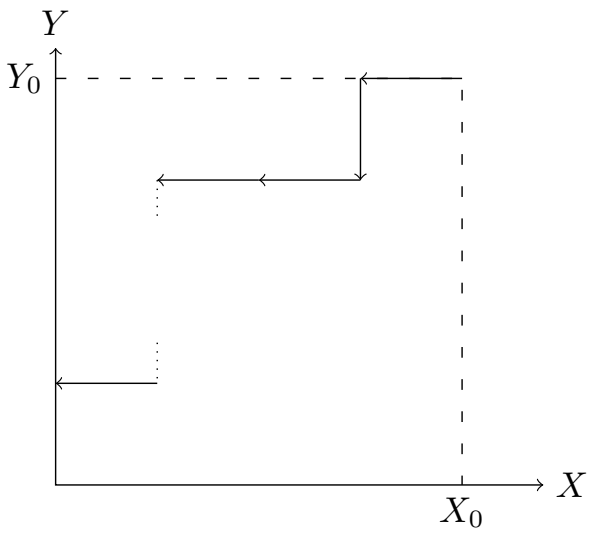
Time of Senescence

$$T = \inf\{n \geq 0, \min_{1 \leq i \leq 16} \left[\min(X_n^i, Y_n^i)\right] < 0\}$$

$$\Longrightarrow \text{ distribution of } T \text{ ?}$$

One Chromosome



$$\begin{aligned} X_n &= X_{n-1} - a.B \\ &= X_0 - n.a.B \\ &= X_0 - a.\mathcal{B}in(n, 1/2) \end{aligned}$$

$$Y_n = Y_0 - n.a + a.\mathcal{B}in(n, 1/2)$$

The Whole Cell

Expected Time of Senescence (a=1)

$$\mathbb{E}(T) = \sum_{n=0}^{\infty} \left[\sum_{k+l \geq n} \pi(X_0 = k)\pi(Y_0 = l) \frac{1}{2^n} \sum_{t=n-l}^{k} \binom{n}{t} \right]^{16}$$

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$\Longrightarrow$ too difficult to handle for an inverse problem

How does the mean of the initial state influence the time of senescence?

- Deterministic and Constant Initial State:

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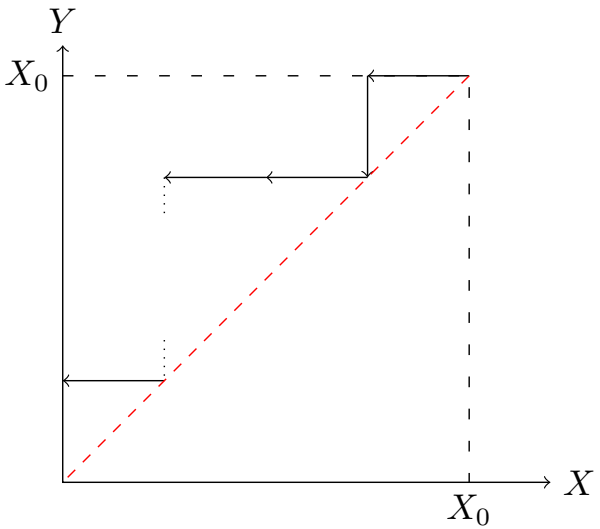

Asymptotitic Expected Time of Senescence

$$\mathbb{E}_{X_0}(T) \underset{X_0 \to \infty}{\sim} 2X_0$$

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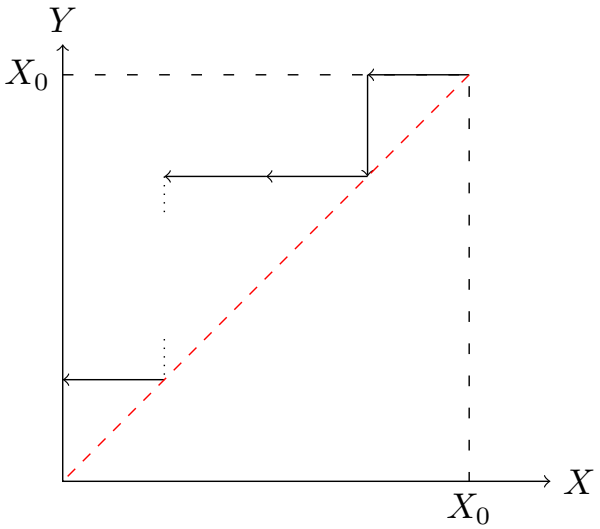


Asymptotitic Expected Time of Senescence

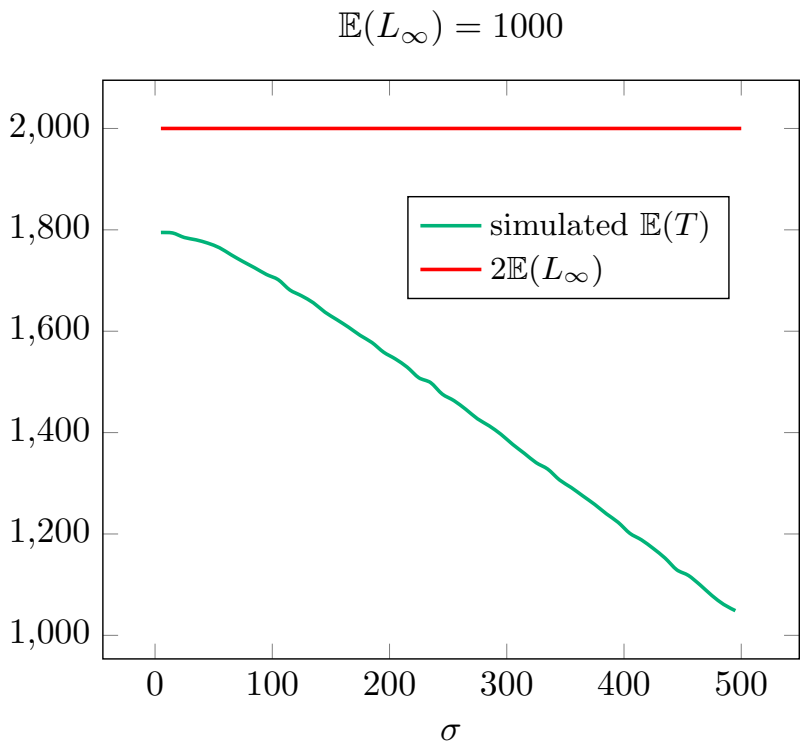
$$\mathbb{E}_{X_0}(T) \underset{X_0 \to \infty}{\sim} 2X_0$$

$\Longrightarrow$ Problem: the initial is NOT infinite at all (~ 100). Second order?

How the variance of the initial state influences the time of senescence? (ongoing work)

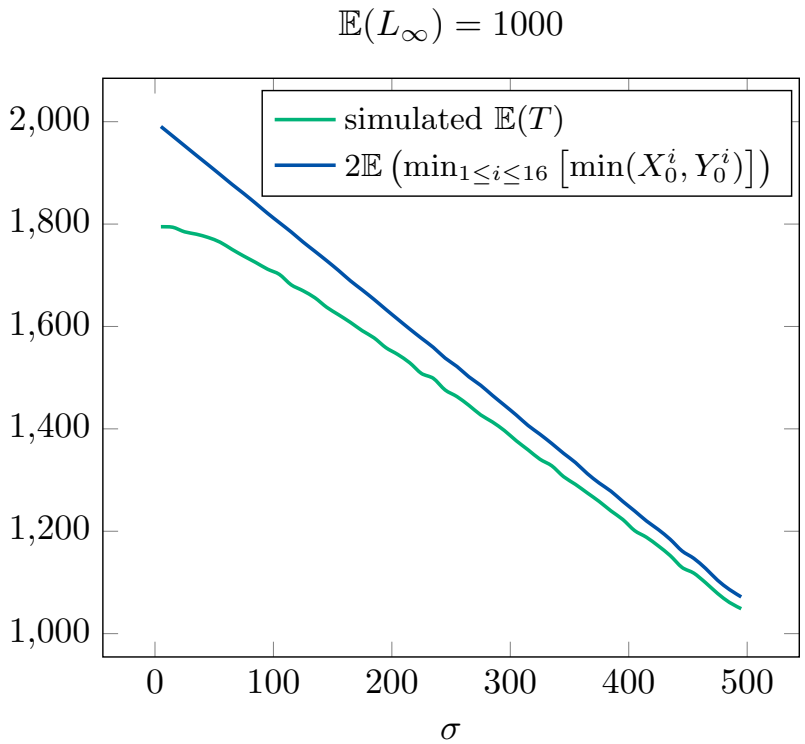
Uniformly distributed initial state: $\forall i \in \{1, .., 16\}$,

$$X_0^i \sim Y_0^i \sim \mathcal{U}nif\left[\mathbb{E}(L_\infty) + \sigma, \mathbb{E}(L_\infty) - \sigma\right]$$



Random initial state (conjecture)

$$\mathbb{E}(T) \sim 2\mathbb{E}\left(\min_{1\leq i\leq 16}\left[\min(X_0^i, Y_0^i)\right]\right)$$



Conclusion

- Explicit form of initial condition
- Explicit form of expected time of senescence
- Inverse Problem?

Future Work

- Information about the initial distribution from measures of time of senescence
- Asymptotics are not enough: the initial is NOT infinite at all (~ 100). How does the second order influence the time of senescence?