The synergy of damage repair and retention promotes rejuvenation and prolongs healthy lifespans in cell lineages

S3 Text: Computational guidelines

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1 Fixed parameters and conventions

| name                          | parameter | value   | ref. |
|-------------------------------|-----------|---------|------|
| size proportion              | s         | 0.6370  | [1]  |
| damage resilience            | Q         | 2.5526  | [1]  |
| growth factor                | g         | 1.05    | [1]  |
| random effects in rate parameters | σ       | 0.005   | [1]  |
| no retention                 | re        | 0.0     | 63.70% |
| retention                    | re        | 0.2957  | this study, 74.43% |
| unlimited repair capacity    | R         | 10⁷     | this study |
| decline in repair capacity   | R         | π⁻¹     | this study |
| maximal generation in lineage|           | 3       | this study |
| critical threshold defining the health span | Dc       | 0.5     | this study |
| threshold for healthy cells   | h_c       | 0.3     | this study |

Table 1: Fixed parameters and conventions used in the paper.

Note that the value of $R$ for unlimited repair is an approximation for $R \to \infty$. $P$ and $D$ are bounded by 1 and within that regime the deviations are neglectable.

2 Create lineage

In most simulations, we generate lineages up to 3 generations. The ODEs of a cell are not coupled to any other cell. Therefore, each cell can be solved individ-
In case there is some coupling between the cells, e.g. time or shared food resources, all ODEs of alive cells have to be solved at the same time instead and dead cells have to be removed from the system.

Algorithm 1 Create lineage (uncoupled cells)

1: Define all relevant parameters
2: Initialise $n$ founder cell(s) with identifiers 1, ..., $n$
3: Set (dynamic) lineage size $N \leftarrow n$
4: Set maximal generation number $M$

5: for $i \in 1..N$ do
6: \hspace{1em} while true do
7: \hspace{2em} Solve ODE of cell $i$ until it divides ($P(t) = 1$) or dies ($D(t) = 1$)
8: \hspace{2em} Keep track of all wanted properties
9: \hspace{2em} if $P(t) = 1$ then
10: \hspace{3em} Reset protein content of mother cell according to division rules
11: \hspace{2em} else if $D(t) = 1$ then
12: \hspace{3em} break
13: \hspace{2em} end if
14: \hspace{1em} end while
15: \hspace{1em} if daughters are in generation $m < M$ then
16: \hspace{2em} Add $rls$ new daughter cells to the lineage according to division rules with identifiers $N + 1, ..., N + rls$
17: \hspace{2em} $N \leftarrow N + rls$
18: \hspace{1em} end if
19: end for
20: Save all wanted information
21: Analyse population properties

3 Finding wildtype cells in the parameter space

In order to find parameter combinations in the $k_1$, $k_2$ and $re$ space that lead to 24 divisions we use an iterative process with adaptive step size. Typically, we fix two of the three dimensions to a value and find the third one. Algorithm 2 shows an example for adapting $k_2$ if all other parameters are set.
Algorithm 2 Finding wildtype cells

1: Define all relevant parameters
2: Set initial conditions of cell to $P(0) = 1 - s$, $D(0) = 0$
3: Set wanted replicative lifespan $rls^* = 24$
4: Set initial value of the parameter to adapt $k_2 = 0$
5: Set initial step size $\Delta k_2$ and minimal step size $\Delta k_2 \geq \delta$
6:
7: Coarse search :
8: \textbf{while} true \textbf{do}
9: \hspace{1em} $k_2 \leftarrow k_2 + \Delta k_2$
10: \hspace{1em} Run single-cell model
11: \hspace{1em} \textbf{if} ($rls > rls^*$) \textbf{then}
12: \hspace{2em} break
13: \hspace{1em} \textbf{end if}
14: \textbf{end while}
15:
16: Fine search with adaptive step size :
17: \textbf{while} true \textbf{do}
18: \hspace{1em} $\Delta k_2 \leftarrow \Delta k_2 \cdot 0.5$
19: \hspace{1em} Run single-cell model
20: \hspace{1em} \textbf{if} ($rls == rls^*$ or $\Delta k_2 < \delta$) \textbf{then}
21: \hspace{2em} break
22: \hspace{1em} \textbf{else if} $rls > rls^*$ \textbf{then}
23: \hspace{2em} $k_2 \leftarrow k_2 - \Delta k_2$
24: \hspace{1em} \textbf{else}
25: \hspace{2em} $k_2 \leftarrow k_2 + \Delta k_2$
26: \hspace{1em} \textbf{end if}
27: \textbf{end while}
28:
29: wildtype is found if $rls == rls^*$ and the corresponding parameter is $k_2$

In the same manner, one can start with many cells and allow for parameter variations in $k_1$ and $k_2$ according to non-linear mixed effects (equation (2) in the paper) and check if the average value of the respective parameter is around the wanted replicative lifespan with some tolerance. The algorithm does not necessarily have to be 24 as it is for the wildtype yeast cells, but works for any preset replicative lifespan. Note that when varying the retention factor, it is computationally more efficient to start from a high value and reduce it stepwise. Corresponding signs have to be adapted.

In the paper, we often compare four cases, which correspond to following
parameter combinations. We chose to fix the damage formation rate $k_1 = 0.4$ and adapt the repair rate correspondingly (see also S1 Fig).

| repair mechanism      | retention | $(re, \bar{k}_1, \bar{k}_2, R)$ |
|-----------------------|-----------|---------------------------------|
| unlimited repair capacity | retention | $(0.2957, 0.4, 0.09219, 10^3)$   |
|                       | no retention | $(0.0, 0.4, 0.02438, 10^3)$ |
| decline in repair capacity | retention | $(0.2957, 0.4, 0.13750, \pi^{-1})$ |
|                       | no retention | $(0.0, 0.4, 0.03125, \pi^{-1})$ |

Table 2: Parameter combinations for wildtype populations.

The range of values of $k_1$ and $k_2$ (Fig 2) generating wild-type cells is in agreement with previous computational and experimental work [2–4] underlining the validity of the conclusions. However, often the estimation relies on various assumptions. Most importantly, experiments usually contain one specific type of damage such that we have to assume that the rate is similar even for other types. Further parameters are sometimes estimated indirectly and we have to assume that the underlying dependency is linear, which is not necessarily true. Clegg and colleagues implemented a similar damage formation term using values in the same range as we do [2]. The response of chaperones to damage formation measured by Saarikagas and colleagues ($\approx 0.11h$), can be interpreted as the increase of the damage while the clearance rate of protein deposits ($\approx 0.07 \sim 0.15\frac{1}{h}$) as the repair rate [4]. Further, the estimated aggregation formation rate by Paoletti et al ($\approx 0.21\frac{1}{h}$) can be interpreted as the damage formation rate [3]. In E.Coli, another organism often used in ageing studies, a value of $\approx 0.72\frac{1}{h}$ for the rate of protein misfolding has been obtained [5].

Note that $k_1$ and $k_2$ in our model are non-dimensionalised, such that these values have to be multiplied by the growth rate $\mu$ ($\approx 0.5\frac{1}{h}$, estimated in [6] assuming full availability of resources) to go back to full dimension and to be compared with experimental values. Consequently, we can justify that the order of the values in our model is realistic.

4 Average initial conditions in a cell lineage

For all population studies the founder cells start with initial conditions $\mathcal{P}(0)$ and $\mathcal{D}(0)$ which are specific to a set of parameters. Starting with an average cell gives rise to more realistic populations and facilitates the analysis since it is not necessary to simulate a large number of generations to get a representative view of the populations. The initial conditions are found according to algorithm 3. The algorithm converges independent of the age of the founder cell up to a
certain precision. With $\epsilon = 10^{-3}$ no numerical issues were faced and the values are sufficiently precise for our purpose.

**Algorithm 3** Finding average initial conditions

1: Define all relevant parameters
2: Set initial conditions of founder cell to $P(0) = 1 - s$, $D(0) = 0$
3: Set tolerance $\epsilon$
4:
5: while true do
6: Create founder cell with $P(0)$ and $D(0)$
7: Run population model and obtain lineage
8: $\overline{P}(0) \leftarrow$ average intact protein content at birth in lineage
9: $\overline{D}(0) \leftarrow$ average damaged protein content at birth in lineage
10: if $(|\overline{P}(0) - P(0)| \leq \epsilon \text{ and } |\overline{D}(0) - D(0)| \leq \epsilon)$ then
11: break
12: else
13: $P(0) \leftarrow \overline{P}(0)$
14: $D(0) \leftarrow \overline{D}(0)$
15: end if
16: end while
17: $\overline{P}(0)$ and $\overline{D}(0)$ are the average initial conditions

**References**

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