Adaptive damage retention mechanism enables healthier yeast population

Qasim Ali[1 2], Riccardo Dainese[1,3], Marija Cvijovic[1*]

[1]Department of Mathematical Sciences, Chalmers University of Technology and University of Gothenburg, Gothenburg, Sweden

[2] Department of Mathematics, North Carolina State University, NC 27607, USA (current affiliation)

[3] Laboratory of Systems Biology and Genetics, Institute of Bioengineering, School of Life Sciences, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland (current affiliation)

*Corresponding author

Marija Cvijovic

Department of Mathematical Sciences

Chalmers University of Technology and University of Gothenburg

Chalmers tvärgata 3

SE-41296 Gothenburg, Sweden

Phone: +46 31 772 53 21

Email: marija.cvijovic@gu.se

Abstract

During cytokinesis in budding yeast, Saccharomyces cerevisiae, damaged proteins are distributed asymmetrically between the daughter and the mother cell. Retention of damaged proteins is a crucial mechanism ensuring a healthy daughter cell with full replicative potential and an ageing mother cell. However, the protein quality control (PQC) system is tuned for optimal reproduction success that suggests optimal health and size of the population, rather than long-term survival of the mother cell. Modelling retention of damage as an adaptable mechanism, we propose two damage retention strategies to find an optimal way of decreasing damage retention efficiency in order to maximize population size and minimize the damage in the individual yeast cell. A pedigree model is used to investigate the impact of small variations in the strategies over the whole population. These impacts are based on the altruistic effects of damage retention mechanism and are measured by cost function whose minimum value provides the optimal health and size of the population. We showed that fluctuations in the cost function allow yeast cell to continuously vary its strategy, suggesting that optimal reproduction success is a local minimum of cost function. Our results suggest that a rapid decrease in the efficiency of damage retention, at the time when the mother cell is almost exhausted, produces fewer daughters with high levels of damaged proteins. In addition, retaining more damage during the early divisions increases the number of healthy daughters in the population.

43 *Table 1: Nomenclature*

Abbreviations	Description
$RE_{div/dist}$	Division / distance strategy of damage retention
g	Division number
α, n	repressor activation constant, repressor Hill constant
τ_I, τ_D	Time required for intact/damage component to reach division/ death
I_{div}	Intact component threshold
R_t	Ratio between the times required for division and death threshold
I_g and D_g	Intact and damage component of mother cell after division
re	Damage Retention with altruist effect
re_{max}	Maximum possible damage retention
A	Altruist value to make variation in the strategy
D, D_{death}	Damage variable, Damage threshold
$N_{daugh/mot/pop}$	Daughter/mother/accumulated cells
P_{daugh}, P_{mot}, P	Population distribution for daughter/mother/accumulated
$D_{daugh/mot/pop}$	Damage in daughter/mother/accumulated cells population
$C_{daugh/mot/pop}$	Cost function for daughter/mother/accumulated cells population

44
45

Introduction:

Aging is a conserved scale-invariant phenomenon that exploits entire organism simultaneously, from the organelles involved in the cellular processes to the organs and body structure. Aging factors like damage accumulation and its asymmetric segregation through retention mechanism during growth and division processes respectively have been frequently studied in the past few decades and are proposed to promote ageing from simple unicellular organism like budding yeast to higher eukaryotes (Bufalino et al., 2013; Erjavec et al., 2007; Hill et al., 2016; Katajisto et al., 2015; Kennedy et al., 1994; Kruegel et al., 2011; Zhou et al., 2014). Retention of damage during the process of cell division is an evolutionary conserved mechanism whose efficiency decreases gradually and leads to the senescence state where basic cellular processes are unable to produce enough proteins to have subsequent divisions (Aguilaniu et al, 2003; Ackermann et al., 2003; Erjavec et al., 2008; Rujano et al., 2006). Budding yeast, *Saccharomyces cerevisiae* (*S. cerevisiae*) has been widely studied in aging research and has contributed to the identification of many genes involved in mammalian aging (Longo et al, 2012). Ageing in yeast can be studied by two main approaches: replicative aging, which is measured by the number of divisions that a cell performs before senescence, and chronological aging, which corresponds to the time before a cell enters senescence in a non-dividing state (Longo, 2012). Experiments targeting replicative aging showed that yeast cells give rise to a limited number of daughter cells, usually around 20–25 (Mortimer and Johnson 1959, Longo, 2012). Throughout its lifespan, a cell accumulates different types of ageing factors, like extra chromosomal RNA circles (ERCs), increased intracellular oxidative stress, mitochondrial dysfunctions and accumulation of damaged proteins (Aguilaniu 2003, Sinclair 1998). It has been shown that asymmetric distribution of damaged proteins in the unicellular organisms is evolutionary beneficial for the whole progeny thus ensuring the highest level of fitness for the daughter cells (Waddington, 1953; Eshel and Matessi, 1998; Crispo, 2007, Kaberlein, 2010). This unequal distribution of damage results in an ageing mother cell and a rejuvenated daughter with full replicative potential (Eglimez and Jazwinski, 1989). In the early divisions, a mother cell is able to retain most of the damage, giving rise to fully healthy daughter cells. However, in the late stages of a mother cell's lifespan, damage retention becomes less effective, and aging factors begin to be passed to the daughters which, thus, are born prematurely old (Kennedy et ak, 1994; Sinclair et al, 1998a; Sinclair et al, 1998b). This

77 trend reaches a climax in the last 5% of a mother's lifespan when divisions are often symmetric
78 and the daughter inherits a consistent amount of cellular damage from the mother. The
79 gradual decline in the organelles performance during replicative aging results in cells with a
80 unique way of damage retention that is well conserved across natural selection and provide a
81 distinctive reproduction strategy among the different yeast strains (Erjavec et al., 2008;
82 Kirkwood and Rose, 1991; Nyström and Liu, 2014).

83 From the evolutionary perspective of Darwinism, the variation in the genetic material of a trait
84 is a random process that is passed on to its progeny by means of natural selection. These
85 variations are negligible preserving the structure and function during the lifespan of a
86 particular species (Konieczny et al., 2014). However, there are several characteristics, e.g. age,
87 size and reproduction, which are uniquely identifiable within the same species. Bringing all
88 the characteristics together outlines an evolutionary survival strategy of the population that
89 leads to its reproduction success (Berg et al., 2002; Brooks and Garratt, 2017).

90 Optimal reproduction success is vaguely understood terminology used to define replicative
91 lifespan of a yeast cell that has evolved the organelles to adapt a finest route for the healthy
92 survival of yeast population. A population's success is in the asymmetric division of cells while
93 keeping the damage low in the progeny and having a long replicative lifespan (Chao et al.,
94 2016; Nyström and Liu, 2014). However, healthy progeny and long replicative lifespan are
95 inversely proportional to each other since it is asserted that, during the replicative lifespan,
96 yeast strains sacrifice their long-term survival over the health of their progeny by retaining the
97 aging factors (Aguilaniu et al., 2003; Hill et al., 2017; Kirkwood and Rose, 1991). Therefore, it
98 is interesting to find a strategy for optimal retention of aging factors in such a way that yeast
99 population accumulates less damage in the living cells and provides maximum population.

100 Theoretical models have played a critical role in understanding ageing process in the
101 unicellular organisms (Ackermann et al., 2007; Chao, 2010; Chao et al., 2016; Clegg et al., 2014;
102 Coelho et al., 2014; Erjavec et al., 2008; Lindner et al., 2008; Stewart et al., 2005; Vedel et al.,
103 2016). A recent theoretical study has shown that symmetric division alone can lead to a
104 senescence state where cell can no longer divide while some stochastic effects on the damage
105 distribution between mother and daughter cells can protect cells from early damage (Chao et
106 al., 2016). Moreover, the natural selection adapts the protective mechanism into the

subsequent progeny in a genetically controlled manner. The asymmetric division in yeast cells increases the population fitness in case of high damage propagation rates and therefore increases the proliferating capacity of the progeny (Erjavec et al., 2008). It has been suggested that the optimal aging strategy is to repair the transcriptional errors and mal-functionalities by recycling the damaged material to maintain the quality rather than segregating the damaged portions (Clegg et al., 2014). However, the protein quality control system is not sufficiently effective to maintain the proteostasis and therefore cellular health is sacrificed over the continuous production of proteins (Nyström and Liu, 2014; Orgel, 1963). Therefore, the segregation of damaged proteins in spatially sequester regions of a cell becomes a necessity in order to maintain the performance of the organelles involved in the fundamental cellular processes (Hill et al., 2017; Tyedmers et al., 2010).

In previously computational models, retention of damage is, due to simplicity, assumed to have the same efficiency throughout the cells replicative life, thus it is treated as a constant (Erjavec et al., 2008; Clegg et al., 2014). Here, based on several experimental evidences reported in yeast (Kennedy et al, 1994; Sinclair et al, 1998a; Sinclair et al, 1998b), we consider that damage retention, like many other processes, loses its efficiency during the replicative lifespan of yeast cell. However, the exact mechanisms of damage retention still remain unclear. We propose two strategies named as *distance strategy* and *division strategy*, to investigate the efficiency and stability of damage retention during the replicative lifespan of single cell. We ask whether it be possible that any two yeast strains following different strategies of damage retention converge to a unique optimal reproduction success. We also investigate whether a yeast population following a well-defined strategy of damage retention reaches a specific optimal reproduction success that her fellow mutated species cannot reach until it follows the same strategy.

Mathematical Modelling

Mathematical model presented here is built on a model published by Erjavec et al, 2008 and comprises of division and growth processes for each cell using discrete-continuous model (Appendix 1). Each cell increases its intact and damaged components during the growth process and asymmetrically distributes these components between the dividing cells (mother and daughter cells) during the division process. The damage retention mechanism allows

mother cell to retain part of the damage proteins from the daughter cell and, in return, give part of the intact portion. The efficiency of damage retention decreases during the whole replicative lifespan in a specified manner, termed as strategy of premiere cell. This strategy is followed by the cell and its whole progeny during their respective replicative lifespans. A pedigree-tree model follows the whole population and provides a discrete population distribution function over the damaged component.

In this work, we consider, two yeast strains following distinct strategies of decreased efficiency of damage retention during the cell division. These strategies are based on the assumption that each strain is tuned for a long replicative lifespan and not for its own long-term survival (Kirkwood and Rose, 1991; Nyström and Liu, 2014). Small variations in a strategy are implanted to alter the way of decreasing the efficiency of damage retention. It is considered that each variation in the strategy represents an altruistic behaviour of a mother cell for her progeny. However, for each variation, whole pedigree-tree model is simulated and cost functions are calculated. These cost functions are based on the damage proportion of the alive cells and their population size.

Damage retention strategies

Retention parameter can be varied considerably in multiple ways while each one can provide a significant effect on the population in the long run. However, it is not feasible to follow all plausible ways of reducing the efficiency of damage retentions due to computational limits. Therefore, it is inevitable to develop strategies by means of well-defined functions for the efficiency of damage retention. Two strategies, named as *division strategy* and *distance strategy*, are defined to investigate the efficiency of damage retention during the replicative lifespan of single cell. Strategies have been developed in such a way that a mother cell following distance strategy retains more damage than a mother cell following division strategy during the early divisions.

Division Strategy

In a division strategy we define retention efficiency as a repressor Hill function in the following way

$$RE_{div}(g+1) = 1 - \frac{g^n}{g^n + \alpha^n} \quad (1)$$

where $\alpha > 0$ and $n \geq 1$ are constants. Increasing these constant values can slow down the decrease in the efficiency of damage retention in the subsequent divisions of the mother cell (Figure 1). r

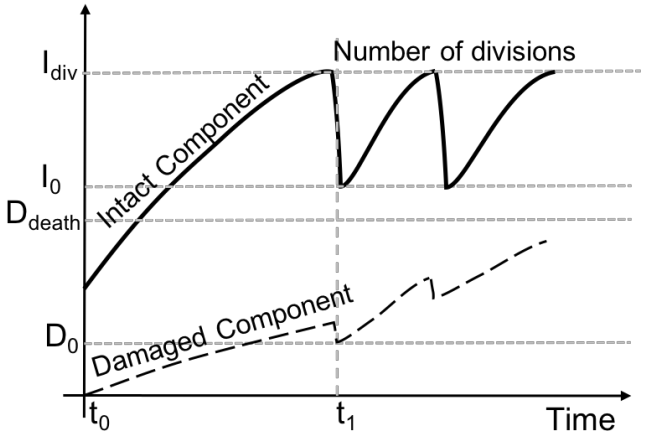


Figure 1: Division strategy: Efficiency in damage retention decreases with the increase in number of divisions. Mother cell is able to retain maximum damage in the beginning but loses its efficiency of damage retention as the number of divisions increases. The intact component decreases from its threshold I_{div} to $I_{g=0}$ after division and the damaged component decreases to $D_{g=0}$. The cell death threshold is represented by D_{death}.

Distance Strategy

In distance strategy the efficiency of retaining damage (RE) decreases with the increase in the number of cell divisions and is also modelled by repressor Hill function as:

$$RE_{dist}(g+1) = 1 - \frac{R_t^n(g)}{R_t^n(g) + \alpha^n} \quad (2)$$

The parameters $n > 1$ and $\alpha > 0$ can be set according to the R_t value; however, these parameters are the same as in the previous strategy (see Appendix 1). The variable R_t is the ratio between the time required for intact component to reach division level (τ_I) and the time required for damage component to reach cell death (τ_D).

$$R_t = \frac{\tau_I}{\tau_D} \quad (3)$$

Due to the increase in damage during the replicative lifespan of a cell, the retention becomes more difficult. After every division cell anticipates the possibility of next division. If the damage is high enough such that next division is not possible then cell further decreases its retention to the minimum level (RE_{dist} = 0) as in the division strategy. The required times (τ_I and τ_D) are calculated by taking ratio between remaining distance and the mean rate of change in the corresponding intact $(Avg(\dot{I}))$ and damage $(Avg(\dot{D}))$ component.

$$\tau_I = \frac{I_{div} - I_g}{Avg(\dot{I})}, \tau_D = \frac{D_{death} - D_g}{Avg(\dot{D})} \quad (4)$$

In the distance strategy (Figure 2), cell composition is divided into two components which are increasing during their growth process. The increase in the damage component is represented by long-dashed lines (— —) that starts from zero and passes through D_0 and intact component by continuous lines that starts from minimum amount of intact proteins. At time t_1, the cell reaches the division threshold (I_{div}) where it is ready to bud a daughter with asymmetric distribution of intact and damage component. After division, mother cell has intact component I_g and damage component D_g. At this point the distance strategy comes into action. The parametric value of retention set by the strategy is used to anticipate the success in completing next division by the above defined procedure (see Eq. 2). If the next division is possible then the cell will divide according to the defined strategy. Otherwise the cell will decrease the retention to its minimum value so that next division becomes possible.

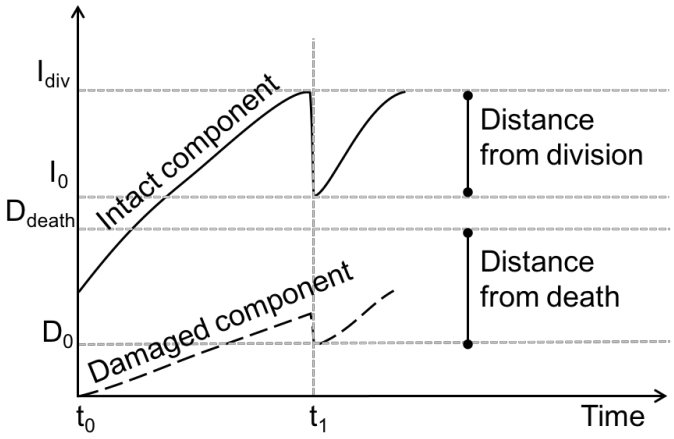


Figure 2: Mother cell decreases damage retention by anticipating her next reproduction success. Cell increases its initial intact and damage component from t_0 and divides at time t_1. The intact component decreases from its threshold I_{div} to $I_{g=0}$ after division and the damaged component decreases to $D_{g=0}$. The cell death threshold is represented by D_{death}.

Altruistic Variation in the Efficiency of Damage Retention

The strategies provide a unique way of decreasing the efficiency of damage retention which can be varied by using an altruist factor (A) as defined in Eq. (5). The parameter A is based on the consequences of the actions performed for replicative lifespan of a mother cell and for reproductive fitness of the offspring that is measured by determining their health status. The parameter A = 0.5 is defined as a neutral value when it has no effect on the strategies of damage retention and therefore follows the asymmetric division as defined in Eqs. (1) and (2). For A < 0.5, cells show selfish behaviour to their progeny by retaining less damage than being neutral during their replicative lifespan, whereas for A > 0.5, cells show selfless behaviour by retaining more damage than the one defined in a neutral strategy. At the extreme values, the cells show either no retention (re = 0) or full retention (re = 1) during their replicative lifespan.

At the time of division, damage retention is set in two stages. Firstly, RE(g) is calculated by means of defined strategy (distance or division strategy). Secondly, altruism parameter is used to alter the strategy. At the moment when no more divisions are possible, the retention decreases to zero allowing another division without taking the altruist effect into account. The equation for altruist retention is written as:

$$re(A,g) = RE(g) + 2\left(A - \frac{1}{2}\right)\left((1-A)RE(g) + A(re_{max} - RE(g))\right) \quad (5)$$

The parameter *re* is altruism-dependent efficiency of damage retention and re_{max} is the maximum attainable retention, i.e. 1.

Pedigree-tree model

Here we develop a pedigree-tree model to follow complete population with variable retention parameter (Appendix 1). The cellular growth is represented by increase in the number of intact and damage components and the division is represented by asymmetric distribution of growth components (intact and damage) between mother and daughter cells. Advantage of this model is that the cells are instantly counted when bud out from their mothers while their growth components are tracked throughout their replicative lifespan. At the end of simulation, the cells are distributed according to their intact and damage components in a discrete manner. Moreover, the variable retention of a single cell during its lifespan can be applied over the whole population in an appropriate manner. Following this procedure leads us to find the population distribution function for damage component and to investigate the differences between strategies by using cost functions.

Population distribution function for intact/damage component

Each cell is born with a specific level of damage and intact components and grows accordingly until it reaches division threshold that leads to its asymmetric binary division. The division leads to a new daughter cell which follows the same growth and division strategy as her mother. During this process the population increases, generating cells with diverse level of intact/damage components. These components can be distributed over the whole population at any time $t = t_0$ and can be represented by a population distribution function $P(A, D)$. Therefore, for each altruist value A and accumulated damage D, the population distribution function for damaged component is written as,

$$P(A,D) = \frac{\sum_{D=a}^{D=b}\left(N_{daugh}(A,D) + N_{mot}(A,D)\right)}{N_{pop}(A)}. \quad (6)$$

where a and b are the minimum and maximum accumulated damage. The functions $N_{daugh}(A, D)$ and $N_{mot}(A, D)$ represent the number of daughter and mother cells with $D \in [0, D_{death}]$

amount of damage component at a given altruist value A. The population distribution function is normalized by total population of alive cells $N_{pop}(A) = \sum (N_{daugh}(A, D) + N_{mot}(A, D))$. The variation in N_{pop} due to altruism A is well-intended to ensure the total size of the population at any time $t = t_0$. Similar kind of distribution functions can be defined for the normalized population distribution of daughter cells, $P_{daugh}(A, D)$, and mother cells, $P_{mot}(A, D)$ as follows:

$$P_{mot}(A,D) = \frac{\sum_{D=a}^{D=b} N_{mot}(A,D)}{\sum_D N_{mot}(A,D)},$$
$$P_{daugh}(A,D) = \frac{\sum_{D=a}^{D=b} N_{daugh}(A,D)}{\sum_D N_{daugh}(A,D)}. \quad (7)$$

Cost Functions

The calculation of cost function is performed at the end of discrete-continuous model while the objective is to find the minimum cost function so that smallest amount of damage and maximum number of cells exist in the population. The damaged component and the total population is calculated for the virgin cells – the cells that have not undergone any division yet, for the mother cells and for the whole population. These calculations are then normalized, defined by $\tilde{N}(X)$, where X is any population distribution of either mother, daughter or total cells with a given altruist value and damage D. This helps to eliminate the redundancy between the cellular components and the population. $\tilde{N}(X)$ can be defined as,

$$\tilde{N}(X) = \frac{X - X_{min}}{X_{max} - X_{min}}$$

The normalization is carried out by finding the extreme values from the deterministic model for the total damage in the cells and the total population. The extreme values for each cost function exist at unique values of altruism $A \in [0,1]$.

Cost function at any given altruism value A in case of daughter cells is the sum of normalized accumulated damage of all the daughter cells, $\tilde{N}$ ($\sum_{D_{daugh}} D_{daugh}(A)$), and difference between normalized maximum number of daughter cells during $A \in [0,1]$, i.e. equals to 1, and normalized alive daughter cells, $\tilde{N}(N_{daugh}(A, D))$, present in the system at any time $t = t_0$.

$$C_{daugh}(A) = \tilde{N}\left(\sum_{D_{daugh}} D_{daugh}(A)\right) + \left(1 - \tilde{N}\left(\sum_{D} N_{daugh}(A, D)\right)\right) \quad (8)$$

The cost function for damage component in the mother cells at a given value of *A* is similar to the cost function defined for damage component in the daughter cells. The only difference is that we calculate damage in those cells that have been divided at least once. We write this cost function as,

$$C_{mot}(A) = \tilde{N}\left(\sum_{D_{mot}} D_{mot}(A)\right) + \left(1 - \tilde{N}\left(\sum_{D} N_{mot}(A, D)\right)\right) \quad (9)$$

Damage in a mother cell is denoted by D_{mot} and total population of the mother cells is N_{mot}. For the damage proportion in the total yeast population at a given altruism *A*, $N_{\text{pop}}(A)$, the cost function is the sum of the normalized damage in the total population, $\tilde{N}(D_{\text{pop}})$, and the difference between the normalized maximum and the normalized current population sizes, i.e. $1 - \tilde{N}(N_{pop})$. It is given by the following formula,

$$C_{pop}(A) = \tilde{N}\left(\sum_{D_{pop}} D_{pop}(A)\right) + \left(1 - \tilde{N}\left(N_{pop}(A)\right)\right) \quad (10)$$

Variation in Altruism

Altruism parameter *A* is varied deterministically as well as stochastically. The deterministic way is quite straight forward as it formulates the normalized distribution of cells at discrete values of *A* and calculate cost functions for each value of *A* that varies in the interval [0,1]. These cost functions are further used in the stochastic model to help find the minimum value of cost function.

The stochastic settings involve individual based modelling approach in which altruist parameter *A* is randomly chosen from its neighbouring values. Small variations bring changes

in the strategy of damage retention and mimic the concept of mutation which directly affects the cost function. The cost of following an individual's strategy of damage retention by its progeny is deterministically calculated by using Eqs. (8), (9) and (10) which involves simulation of pedigree-tree model for a specific period of time. The method allows the cell to follow the direction where it finds minimum cost function. The direction of the altruist value is chosen on the basis of current and preceding cost functions by using the signum function while the magnitude of the variation is set by choosing random value in the interval of [0, ε].

$$A_{i+1} = A_i \pm rand(0, \varepsilon)\, sgn(C(A_{i-1}) - C(A_i)) \tag{11}$$

This process continues for a set period of time and is terminated by the following criteria,

$$\sum_{i=S_N+l}^{S_N+j+l} \left|A_{i-j} - A_{i-(j+k)}\right| < \varepsilon. \tag{12}$$

In the above equation, sign $\pm$ are set according to the direction of altruist value and the index of altruism A indicates the strategy variation number. The positive sign is used when direction of altruism is upward, i.e. $A_{i-1} < A_i$, whereas the negative sign is used in case altruism is decreasing, i.e. $A_{i-1} > A_i$.

Results:

Initially, there is a single daughter yeast cell present in the system that has sufficient amount of intact proteins to grow and doesn't contain any damaged proteins. A general behaviour of the model is described in Figure S1.

In the course of this work we sought to establish relationship between strategies followed by distinct yeast strains and relationship among yeast strains following the same strategy. The former is followed deterministically to find the reproduction success by using the given cost functions whereas in the later the optimality is investigated by making stochastic variations in the strategies.

Relation Between Strategies

Damage retention strategies follow a defined way to decrease the retention efficiency of a mother cell. However, there are unique routes associated to each value of altruism that are followed according to their intrinsic behaviour represented by Eqs. (1) and (2). The distance strategy keeps the damage retention high and decreases the efficiency at an increasing rate whereas the division strategy was defined in an opposite fashion by showing a sharp decrease during the early replicative lifespan of a mother cell.

The strategies are defined using Hill function in the equations (1) and (2) with $\alpha = 1$ (Figure 3). A comparison between the symmetric and asymmetric cell divisions has been performed to observe the effect of strategies over the number of divisions while choosing different sizes of the cells. The variations in the strategies is given by altruist parameter *A with* $A_{max} = 1$. It is interesting to note that both strategies provide same behaviour at the end points of *A*, i.e. 0 and 1 (Figure 3).

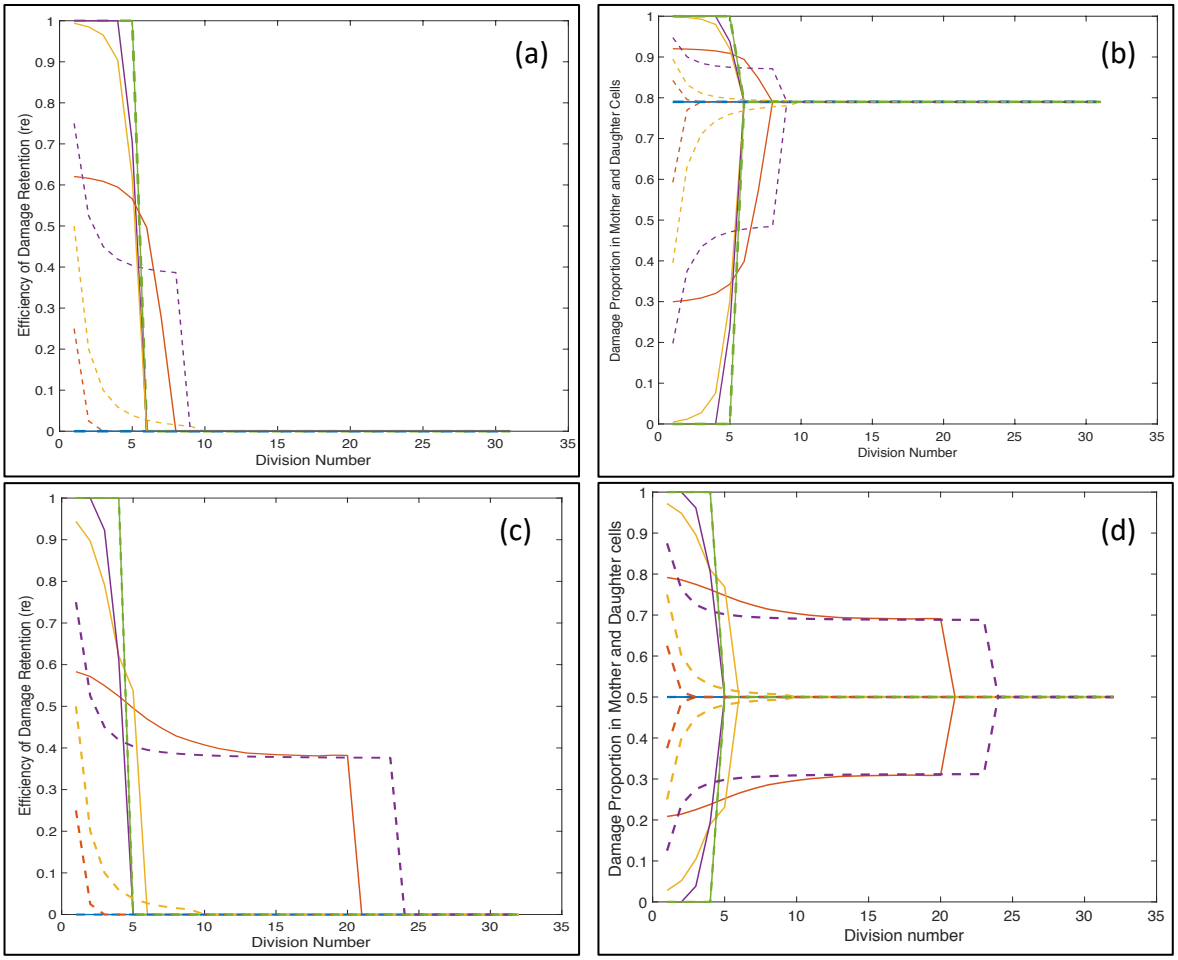


Figure 3: Damage retention efficiency (RE) for altruist parameter values A = 0 (blue), 0.25 (red), 0.5 (yellow), 0.75 (violet) and 1 (green). The dashed lines represent division strategy and continuous lines represent distance strategy. Colours are drawn to match the altruist parameter values between the two strategies. Left hand side panels (a) and (c) shows the damage retention by mother cell while the right-hand side panels (b) and (d) are obtained by relating size-wise damage distribution among mother and daughter cells. The cell sizes after division of cells are chosen asymmetric (Rm = 0.79) for panel (a) and (b) and symmetric (Rm = 0.5) for panel (c) and (d).

At A = 0, yeast cell does not retain any damaged portion (re (0, g) = 0) during its replicative lifespan and therefore share damage with her daughter according to the division size of the cell R_m. Consequently, yeast survives for a longer replicative time and buds off 31 daughters when R_m = 0.5 and 32 daughters when R_m = 0.79 (Figure 3). On the other hand, at A = 1, yeast cell retains all the damage (re (1, g) = 1) and buds a completely healthy daughter cell each time which affects its lifespan and brings it to 5 divisions. For all the other altruist values, i.e. 0 < A < 1, A does not provide same retention function for both strategies. It can be observed

that cell with division strategy retains less damage than distance strategy; however, the former retains damage for a longer period of time during its lifespan. After the critical damage level when no more retention possible, the cell loses all the retention and share the damage according to the cell sizes.

Population Distribution of Damaged Proteins

The pedigree-tree model provides large population of cells where intact and damage components are individually tracked throughout their replicative lifespan. This provides a non-uniform distribution of alive cells over damaged components. Therefore, the cell population is clustered according to the accumulated damage in each cell (with cluster size of 60 and number of clusters of 10 in the interval [0, 600]) for five values of altruism A = 0, 0.25, 0.5, 0.75 and 1 (*Figure 4*, *Figure 5* and *Figure 6*). The maximum attainable damage is bounded by the threshold D_{death} = 600; however, the figures show that the cell could have accumulated damage at most in the interval [480, 540). These clustered populations are normalized in order to calculate the proportion of cells with respect to the total population. Moreover, the error bars are drawn to find the mean and standard deviation of the proportion of cells attaining specific proportion of accumulated damage at the four simulation times t = 1.5, 1.75, 2 and 2.25.

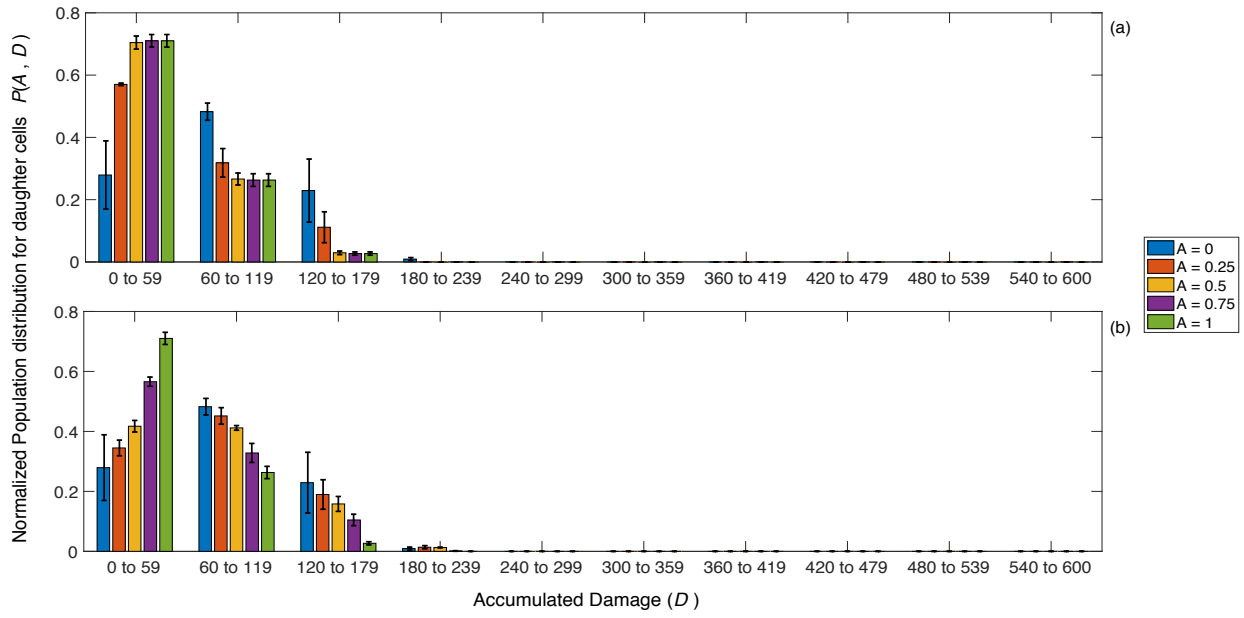


Figure 4: Mean and standard deviation of the daughter distribution of damaged proteins by using distance (a) and division (b) strategies, see Eq. (7). Mean of the distribution is taken for the simulation

time t = 1.5, 1.75, 2, 2.25. The accumulated damage in the span of 600 is clustered into subintervals each of length 60.

The population distribution of daughter cells is present only in the first three clusters of damage component (*Figure 4*). In the first cluster, $D_{daugh} \in [0, 59]$, mean proportion of cells, $P(A, D)$, increases when altruism A goes from 0 to 1 while the succeeding clusters show a reverse behaviour. The error bars represent the standard deviation of the mean distribution values for simulation time t = 1.5, 1.75, 2, 2.25. For A = 0, the standard deviation is quite high because the cell proportion was higher in the first and third clusters ($P(A = 0, D = [0, 60)) \approx$ 0.38) during the early simulation time, t = 1.5. However, it decreased to below 0.2 in the later simulation time, t = 2.25. Moreover, for $A \geq 0.5$, the proportion of cells with least damage is much high and have a very small standard deviation.

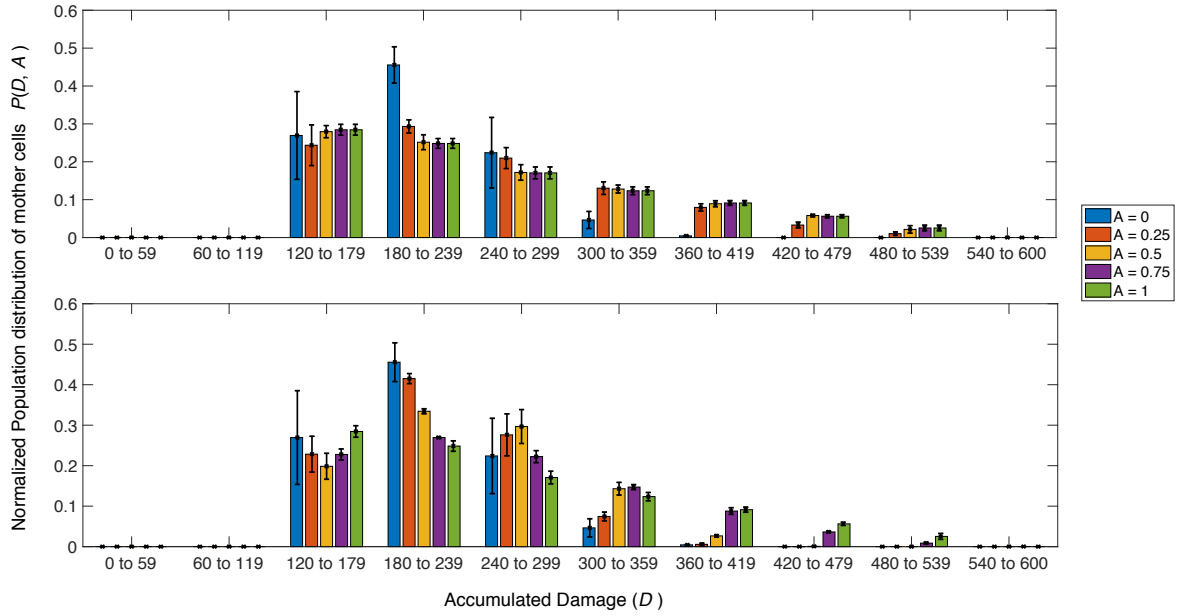


Figure 5: Mean and standard deviation of the mother distribution of damage proteins by using distance (a) and division (b) strategies, see Eq. (7). Mean of the distribution is taken for the simulation time t = 1.5, 1.75, 2, 2.25. The accumulated damage in the span of 600 is clustered into subintervals each of length 600 is clustered into subintervals each of length 60.

The number of daughter cells gradually increases in the first cluster of accumulated damage as A goes from 0 to 1 however it shows opposite behaviour in the second and third cluster (*Figure 4*b). It can be observed that the mean proportion of daughter cells following the distance strategy is higher than the mean proportion following the division strategy in the first cluster for all values of A, except the extreme values where both strategies provide same result. However, the behaviour is opposite in the next two clusters. This suggests that the

distance strategy, i.e. keeping the retention high in the early divisions, accumulates less damage in the population.

Mother cells distribution for damaged component is also normalized and its mean and standard deviation is calculated for the given simulation times t = 1.5, 1.75, 2 and 2.25 and altruism values A = (0, 0.25, 0.5, 0.75, 1) and accumulated damage component in mother cells is shown in the third and succeeding clusters (*Figure 5*). This means that cells become mother in the third cluster of damage accumulation however the highest proportion of cells are present in the fourth cluster where damage is in the interval [180,240). The standard deviation of the mean proportion of mother cells is similar to the mean proportion of daughter cells and therefore cellular health becomes better as A goes from 0 to 1. In comparison between the two strategies, the mothers following the distance strategy have higher damage than mothers following division strategy. In addition, the mean proportion of mother cells containing high damage is comparatively lower than the ones containing low damage.

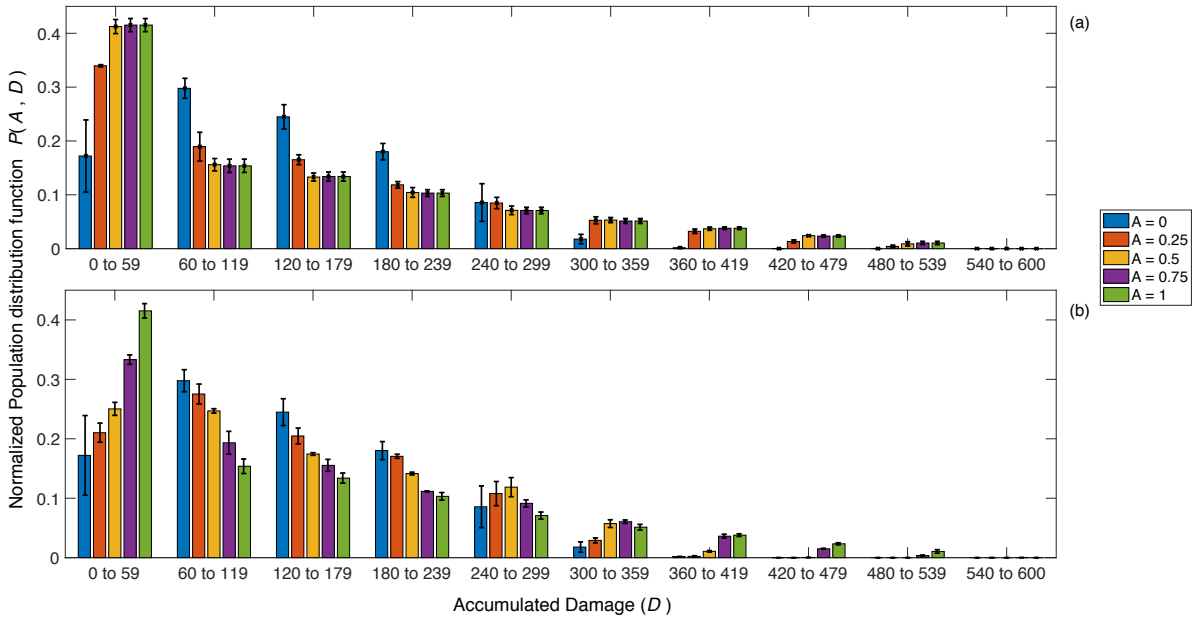


Figure 6: Mean and standard deviation of the normalized population distribution of damaged proteins by using (a) distance and (b) division strategies as defined in Eq. (6). Mean of the distribution is taken for the simulation time t = 1.5, 1.75, 2, 2.25. The accumulated damage in the span of 600 is clustered into subintervals each of length 60.

Mean and standard deviation of the normalized distribution of cells over the accumulated damage in alive cells show the behaviour similar to the above distributions at different values of A, however there is a significant decline in the proportion of healthy cells, i.e. first cluster

(*Figure 6*). At $A = 0$, the standard deviation gives comparatively high values. This is due to the fact that premier cells do not have enough damage to share with their daughter cells for short time scale ($t = 1.5$) and therefore most of the daughter cells born with damage are grouped in clusters 1 and 2. Moreover, the proportion of cells is significantly decreased to below 0.2 when time duration is increased to $t = 2.25$.

Optimal Reproduction success

Models are simulated in deterministic as well as stochastic settings to find the cost functions. These cost functions represent reproduction success by taking into account the cellular health status and population size. The deterministic model provides cost for predefined values of altruism A whereas the stochastic model tracks the minimum value for cost function by taking random steps towards the lowest value of the cost function.

Deterministic outcomes

Deterministic modelling approach is used to evaluate the cost functions by varying the altruist parameter A between 0 and 1 with the step size $\Delta A = 10^{-3}$. The results are obtained for the cost functions defined in Eqs. (8), (9) and (10) and are presented in Figure 7 (for daughter cells), in Figure 8 (for mother cells) and in Figure 9 (for total number of alive cells) respectively each at four different times t = 1.5, 1.75, 2 and 2.25. Computationally, it becomes very expensive to go beyond time point t = 2.25. Therefore, this is the maximum time point chosen. Other time points are chosen to understand the behaviour of cost function over the altruism parameter A. The cost function is modelled by taking this fact into consideration that the replicative lifespan decreases with the increase in damage retention by the cell. In such scenario, it would be interesting to see the effect of replicative lifespan over the damage accumulation in the population.

Altruistic effects on the daughter cells provide a time variant response to its cost function. Due to asymmetric division, mother cells require less time to reproduce than the daughter cells. Therefore, longer lifespan of mother cells will quickly increase the population; however, in case of low damage retention, high amount of damage is passed on to the newly born daughter cells. In case of distance strategy, this phenomenon quickly increases the damage in the population and raises the cost function to high level during the early time, i.e. $t = 1.5$ and

1.75 (Figure 7, Figure 8 and Figure 9). However, with the progression of time, i.e. *t* goes to 2 and 2.25, the cost function gives a surprising outcome by replacing the high values with the lower ones, exposing that for large time scale, population size can dominate over the total damage present in the population. For instance, the distance strategy (continuous lines) near $A = 0.3$, the cost function that was at maximum, i.e. $C_{daugh} = 1.2$ at time $t = 1.5$, goes below the value of $C_{daugh} = 1$ at time $t = 2.25$.

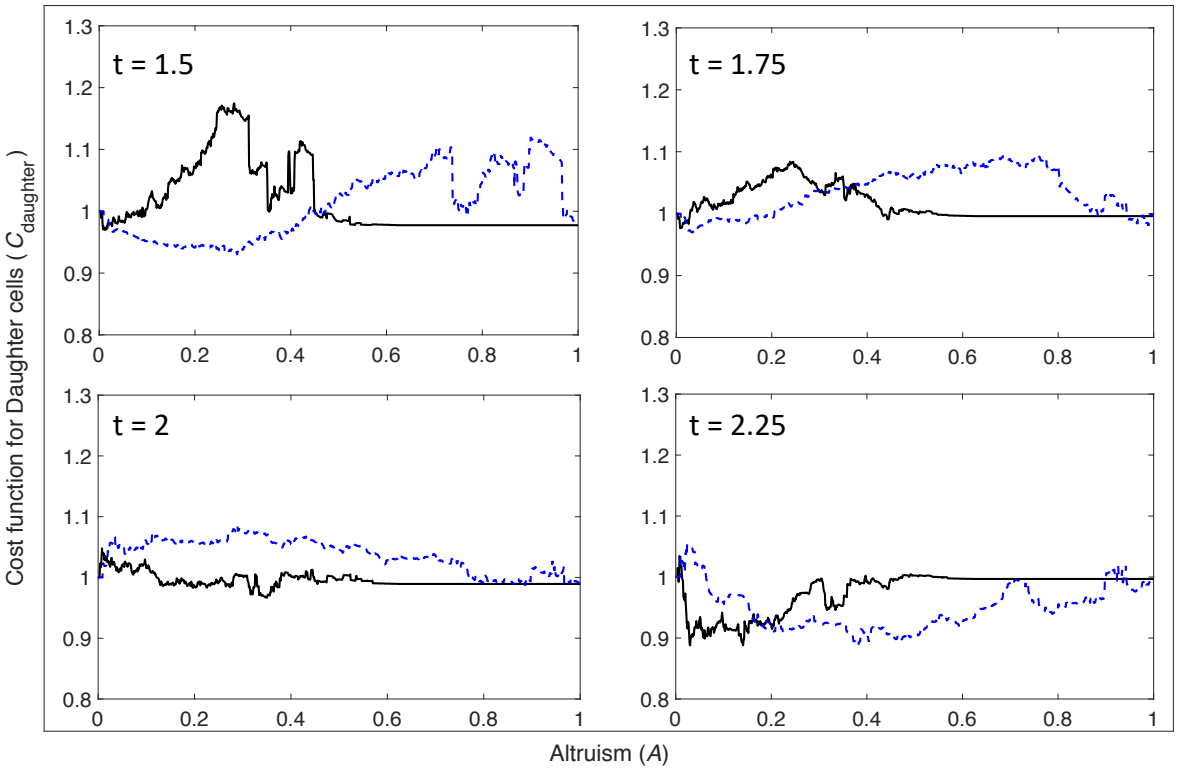


Figure 7: Cost function for the distance (continuous lines) and division (dashed lines) strategies of daughter cells C_{Daugh} at four time-points t = 1.5, 1.75, 2 and 2.25 against the altruist values A in the interval [0,1] and step size 0.001. Cost function is defined in Eq. (8) while the deterministic model used to simulate the results is described in the Appendix 1.

Division strategy provides opposite response than the distance strategy during the early simulation time by showing a small decrease in the payoff function for early altruism values. The reason is clearly that the proportion of cells in the population decreases slightly slower than the increase in the proportion of damage accumulation (

Figure S4: Proportion of daughter cells and their damage in the population for time t =1.5, 1.75, 2 and 2.25. The continuous lines represent distance strategy while dashed lines represent division strategy. The lines moving from 0 to 1 are the daughter cells proportion while the lines moving from 1 to 0 are the damage proportion.

439

440

441

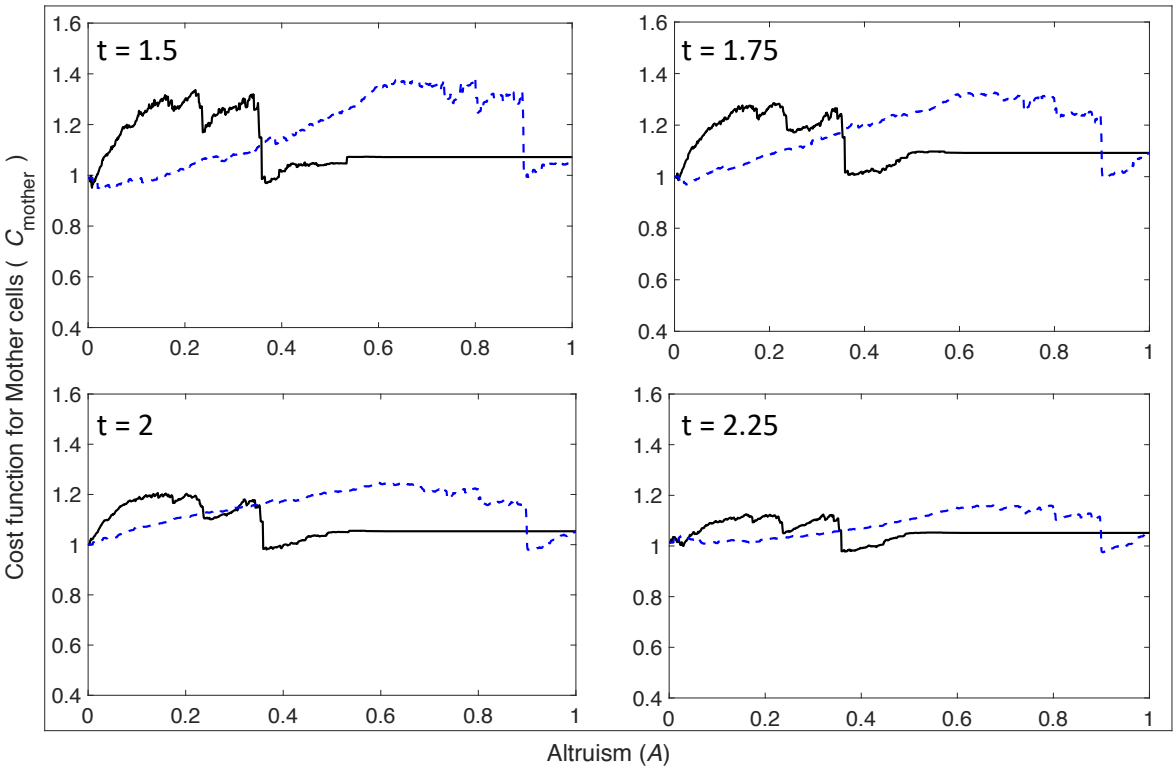
442

443

444

445). For longer period of time, t = 2.25, both strategies decrease their cost function for early
446 values of A, however, their optimal reproduction success varies.

447



448 Figure 8: Cost function for the distance (continuous lines) and division (dashed lines) strategies
449 of mother cells C_{Mot} at four time-points t = 1.5, 1.75, 2 and 2.25 against the altruist values A in
450 the interval [0,1] and step size 0.001.

Taking the final time into consideration, the results provide several interesting outcomes regarding the least value for the cost function, i.e. the optimal reproduction success. First of all, the optimal reproduction success for both strategies require selfish behaviour of mother cells when altruism parameter $A < 0.5$. However, a complete selfish behaviour is not a good strategy which may increase the damage in the population. It is also worth enough to mention here that the cost function varies significantly from one simulation time to the next one, e.g. $t = 2$ to 2.25 which means that the cost function is not in an equilibrium state. Conversely, it is interesting to note that the cost function is squeezing around $C_{Daugh/Mot/Tot} = 1$ by reducing the drastic changes. These drastic changes cause fluctuations in the cost function whose local minimum is termed as "evolutionary ditch". These ditches may not provide the least cost function; however, it becomes difficult to come out from such ditches since these are surrounded by high values of cost functions.

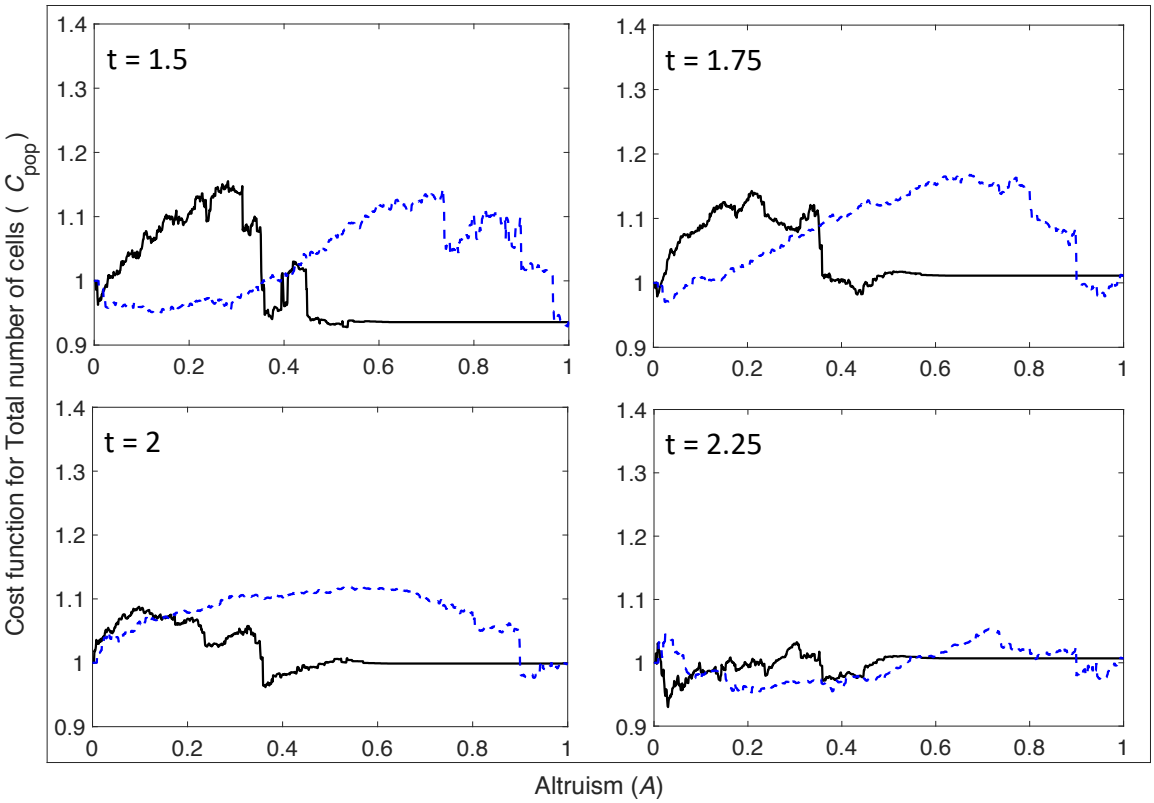


Figure 9: Cost function for the distance (continuous lines) and division (dashed lines) strategies of total cells C_{pop} at four time-points t = 1.5, 1.75, 2 and 2.25 against the altruist values A in the interval [0,1] and step size 0.001.

Stochastic Simulations

Stochastic settings are implemented to observe the behaviour of cost function for total cells calculated at the simulation time t = 1.5. The strategies starting points are chosen for altruist values A between 0 and 1 with a step size of 0.1 (*Figure 10*). At each altruist value, cost functions are calculated which are then compared to their previous values. The strategies vary in the direction where small values of cost function are found by using Eq. (11). However, the least value is not predefined in the stochastic settings and therefore the simulation continues even after reaching the least cost function. The cost function is very sensitive in the sense that a small variation in altruist parameter can vary the yeast efficiency of retaining damage which may result in the decrease/increase in the yeast cell population and damage accumulation in the population. This fallouts fluctuation in the cost function which sets the direction by varying altruism values as shown in the *Figure 10*. In the simulations, an important aspect to analyse is that most of the fluctuations occurred at some specific altruism values. The stopping criteria is implemented after 1000 variations, strategy variation number (S_N) = 1000, by the following inequality

$$\sum_{i=S_N+l}^{S_N+j+l} \left|A_{i-j} - A_{i-(j+k)}\right| < \varepsilon \qquad (12)$$

The index values are j = k = 10 and the epsilon ε = 0.02. The parameter epsilon provides the maximum possible variation in the altriusm value and is used in the Eq. (11). The stopping criteria is defined by the summation expression that stops the simulation if the ε condition is fulfilled consecutively for five values of index l.

The altruist effects on distance strategy (Figure 10a), have revealed clear differences between the values of A chosen above and below the neutral one, i.e. 0.5. For a yeast population following its strategy with altruism $A \geq 0.5$, the cost function decreases as A increases and eventually A reaches to the maximum value. On the other hand, when $A < 0.5$, the strategy varies most of the time around the values A = 0 and 0.4 that are surrounded by evolutionary ditches. Since strategies are tuned to keep varying A in the direction where least value of cost function (minimum of cost function) is found, therefore, the sensitivity in cost function against

the altruist values allows cells to alter their strategy which creates a safe escape from the evolutionary ditch. In a similar way, these strategies escape from the least values of the cost function. Such escapes are made possible due to the involvement of randomness in the altruism.

The division strategy also shows similar behaviour as distance strategy however the strategy is more frequently observed around the extreme values of altruism, i.e. A = 0, 0.1, 0.9 and 1 (*Figure 10*b). The simulations show that strategy started around $A \leq 0.4$ could not escape from the local minimum of the cost function while the starting value of A above 0.8 eventually reached to their evolutionary ditch.

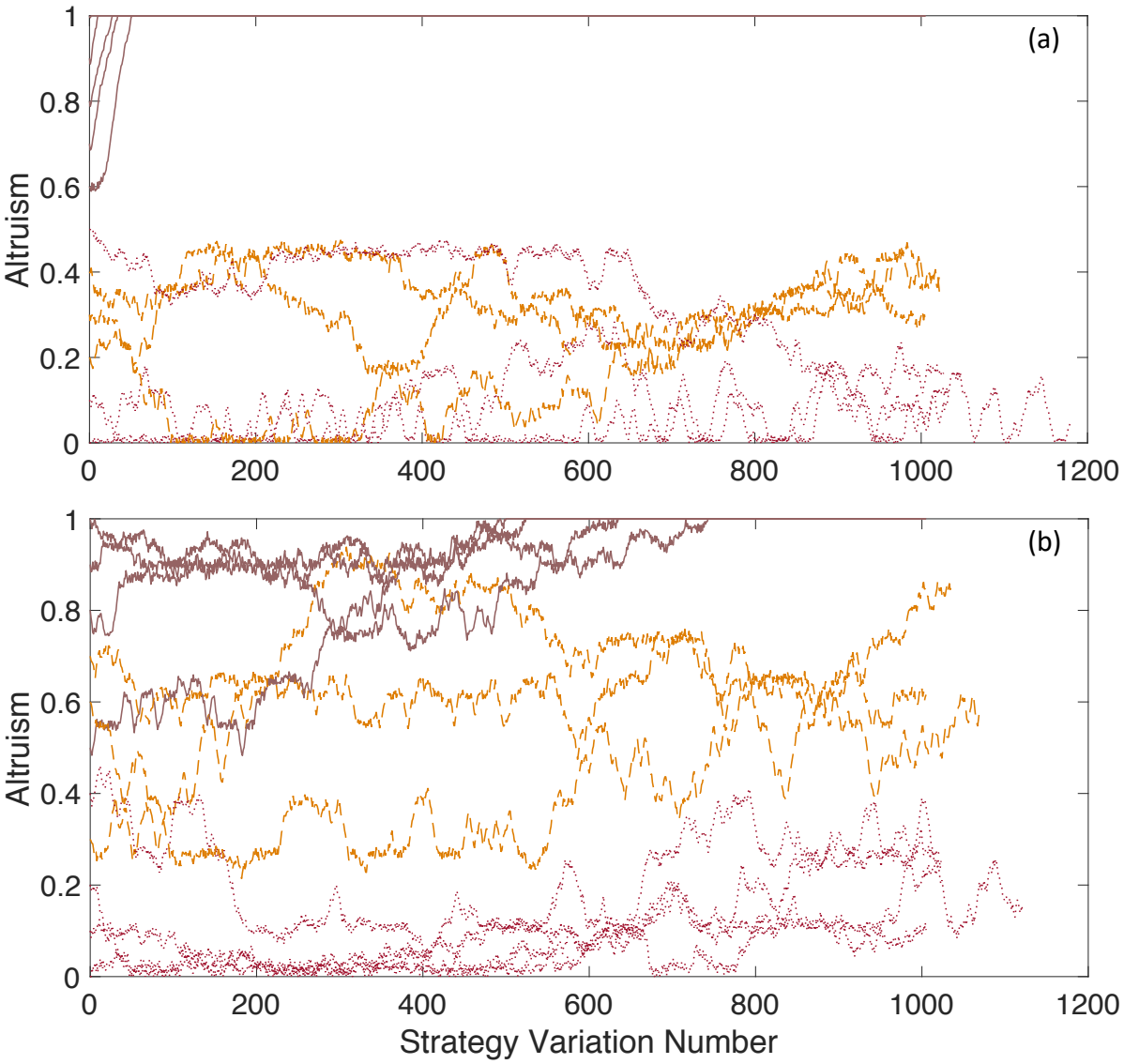


Figure 10: Stochastic simulations of (a) distance and (b) division strategies at time t = 1.5. The altruism parameter A is varied randomly for each strategy variation number in the interval [0, ε = 0.02]. The lines styles are used to clear up the tracking of each simulation.

Conclusions

Efficiency of damage retention provides a monotonically decreasing function in which mother cell retains lower amounts of damage in each subsequent division. The defined strategies have provided unique ways for decreasing the efficiency during cell replicative lifespan of a budding yeast while the altruism factor was used to make deviations in the strategy. For each deviation, a well-defined cost function is computed. Deterministic settings were adopted to analyse the behaviour of cost functions for each strategy. It has also provided the extreme values of the cost function which were further used under the stochastic settings. The cost functions were varied by means of random altruistic effects given to the strategies. These variations were tuned to find the optimal reproduction success of population. However, the strategies that started at different altruist values, ended up optimizing in a local fashion rather than approaching a global minima of cost function.

Distance vs Division Strategy

Our results showed that retaining more damage in the beginning provides healthy daughter cells which plays a significant role in maintaining accumulated health of the population. Moreover, the daughters born with high damage did not replicate as often as daughters born with low damage. In case of division strategy, the mother cell shared more damage in the early divisions, leading to poor health of progeny. At the later stage of replication, when the damage efficiency is low, the mother cell shared high level of damage with its daughter cells. Consequently, these daughter cells could not provide healthy progeny to the population.

Altruism Provides Healthy but a Small Population

Increase in the altruist values increases the efficiency of damage retention of the mother cell. A complete altruist behaviour allows a mother cell to retain all the damage at the time of division which reduces its replicative lifespan while giving birth to completely healthy daughter cells (Figure 3). In case of whole pedigree, the same phenomenon is followed (Figures S1). When both factors, health and population size are considered (Figures 7 – 9), the cost functions of each strategy provided different global minima, while the distance strategy provides lower cost than the division strategy. This shows that a yeast following division

strategy can never achieve a better health and population status than a yeast following a distance strategy.

Population size and population health have shown reverse behaviours. Increasing population size affects the health of the population and brings more damage in the cells while a better health keeps the population size small. In addition, yeast cells with altruistic behaviour do not give a boost to the population health as compared to selfish yeasts who although increase the damage but doubles the size of the population. Providing good health to new buds significantly increases damage in the mother cells which results in an early senescence state where no more replications are possible (Aguilaniu et al., 2003; Denoth Lippuner et al., 2014; Jazwinski and Wawryn, 2001; Liu et al., 2011; Spokoini et al., 2012). On the other hand, the selfish behaviour allows a long replicative lifespan.

Optimal Reproduction Success is Plausible to Local Minima of Cost Function

Strategies were adopted for continuous search of the minimal value of the cost function. Since the function values could not be anticipated in the stochastic simulations, the altruist value varied continuously to search for it. Therefore, the cost function never converged to any specific value. This interprets the physical phenomenon where mutations in a yeast strain could vary the strategy that is followed by its progeny. It is observed that when yeast varied its state from the minima of cost function, the subsequent mutations could not reverse mutation due to stochastic effects and therefore the trait is able to reach local minima of the cost function. Thus, the optimal reproduction success would never be able to show stable behaviour near the minima of cost function. At the same time, when cells opted for minimum value of cost function, the optimal reproduction success trapped for long period of time to local minima which were surrounded by high cost functions.

Evolutionary Ditches can make a Trait Maladaptive

Evolutionary ditches became evolutionary traps in certain cases when the yeast species were unable to escape from local minima because the cost function is surrounded by higher values. With distance strategy, the cost function at $A = 1$ is lower than $0.5 < A < 1$, however it is sufficiently higher than the minimum value of cost function (Figures 7 – 9). Consequently, in the stochastic simulation, the cells with $A > 0.5$, have rapidly adapted complete altruist

behaviour, $A = 1$, and couldn't manage to escape from there. This behaviour showed sufficient potential in the yeast strategy to follow an extinction, especially when it is competing against the other species with lower values of cost function. In summary, our results suggest that damage retention during the early divisions (distance strategy) increases the number of healthy daughters in the yeast population. In addition, a rapid decrease in the efficiency of damage retention, at the time when the mother cell is almost exhausted, produces less daughters with very high amount of damage. Next, the two proposed strategies have distinct cost functions, implying that a strategy may not attain the same minima of cost function as the other. The minimum value attained by distance strategy has provided the minimal value of cost function. And finally, fluctuations in the cost function allow yeast cell to continuously vary its strategy, suggesting that optimal reproduction success is a local minimum of cost function.

Acknowledgment

This work was supported by the Swedish Foundation for Strategic Research.

Appendix 1

Mathematical model for yeast cell growth and division processes

In aging theory, replicative lifespan of a yeast cell is comprised of two major processes: cellular growth in which the intact and damage components of a cell increase, and cell asymmetric division in which cell buds out a new daughter cell. A pedigree-tree modelling approach is used so that the cellular processes can be tracked for each cell individually. A similar modelling approach has been used in the literature where the retention parameter was kept constant (Erjavec et al., 2008), however it followed the fate of the progenitor and the progeny, separately, through a number of generations. We could thus draw a "mother lineage" and a "daughter lineage", whereby we would, after every division, follow respectively the next generation of mothers only, or the next generations of daughters only. However, these do not represent a realistic population that consists of intermediated branches as well. Thus, in the model presented here, we simulate the realistic population, including all intermediated branches and mixed-linages.

During the growth process, the number of healthy protein (intact protein) molecules increases in the cell at the rate constant k_1 and dissolves into the system due to half-life phenomenon at the rate equals to k_2. At the rate k_3 damage proteins are formed. The degradation rate for damaged molecules is denoted by k_4. The modelled equations can therefore be written as,

$$\dot{I} = k_1\left(1 - \frac{I + D}{K}\right) - k_2 I - k_3 I$$
$$\dot{D} = k_3 I - k_4 D \qquad \text{Eq. 1}$$

The increase in the number of damaged proteins D becomes lethal if the cell reaches death threshold value $D = D^*$ whereas the intact component I increases inside the cell to division threshold $I = I^*$. If the cell reaches division threshold first, the cell divides and produces a daughter cell with a mother to daughter cell size ratio $R_m : 1 - R_m$. During the early cell divisions, the mother cell retains maximum damage while its retention efficiency decreases in the later divisions until it reaches the minimum value $re(g)$=0, i.e. no retention.

Parameter	Description	Values	Assumptions and source
I^*	cell division threshold, in number of intact proteins	1500	amount of intact proteins (Erjavec et al., 2008)
D^*	cell death threshold, in number of damaged proteins	600	
k_1	rate maximal protein production	1.5 x 10^4	adjusted by hand to allow steady-state (Erjavec et al., 2008)
k_2	rate of degradation of intact proteins	ln2	half-life of 1 time unit (Erjavec et al., 2008)
k_3	rate of damaging of intact proteins	[0.1,2.3] by 0.75	(Erjavec et al., 2008)
k_4	rate of degradation of damaged proteins	ln2	half-life of 1 time unit (Erjavec et al., 2008)
K	carrying capacity	2500	adjusted by hand
re	retention coefficient	[0, 1] by 0.125	(Erjavec et al., 2008)
R_m	size of the progenitor after division	0.79	$R_m + R_d = 1$ (Erjavec et al., 2008)
R_d	size of the progeny after division	0.21	$R_m + R_d = 1$ (Erjavec et al., 2008)

602 Table 1: **Model parameters with default values and assumptions made**

603
604

The division process is modelled as discrete set of equations for mother and daughter cells. For the mother cell, the intact and damage portions can be calculated as:

$$I_{in}\,(g+1) = I_{end}\;(g)\cdot R_m - D_{end}\,(g)\cdot R_d\cdot re(g)$$
$$D_{in}\,(g+1) = D_{end}\,(g)\cdot R_m + D_{end}(g)\cdot R_d\cdot re(g) \qquad \text{Eq. 2}$$

The intact and damage portions for daughter cells have the similar equations

$$I_{in}\,(g+1) = I_{end}\;(g)\cdot R_d + D_{end}\,(g)\cdot R_d\cdot re(g)$$
$$D_{in}\,(g+1) = D_{end}\,(g)\cdot R_d - D_{end}(g)\cdot R_d\cdot re(g) \qquad \text{Eq. 3}$$

where the parameter $R_d = 1 - R_m$ size of the daughter cell after division and g is division number. The index terms *in* and *end* are the initial value after division and end value before division respectively. The equations 2 and 3 are based on the principle of mass conservation over generations (Erjavec et al., 2008). In particular, this means that the total cellular content (*I+D*), in the original cell equal the sum of the total cellular content of the mother and daughter cell. The conditions are also based on mass conservation with respect to intact component *I* and damage *D*.

General behaviour of Model

The processes described in the above model involving cellular growth and division processes are simulated in the *Figure S1*. The figure describes a general behaviour of the modelled system without including the strategies and their altruist behaviour. Three parameters are investigated at different values to understand their effect on the overall dynamics of the modelled system. We observe that cell undergoes more number of divisions with the decrease in the values of k_3, R_m and *re*. In case of finite replications, cell generally takes more time in the later divisions to grow and reach the division threshold. On the other hand, increasing the cell size ratio from mother to daughter cells (R_m) decreases the time to next division. Damage retention also plays an important role in replicative lifespan of a cell. However, this parameter is chosen constant here for the sake of simplicity. It is interesting to observe that total number of divisions drastically decreases with the increase in retention parameter. We study the retention parameter as variable, dependent upon number of divisions of the mother cell.

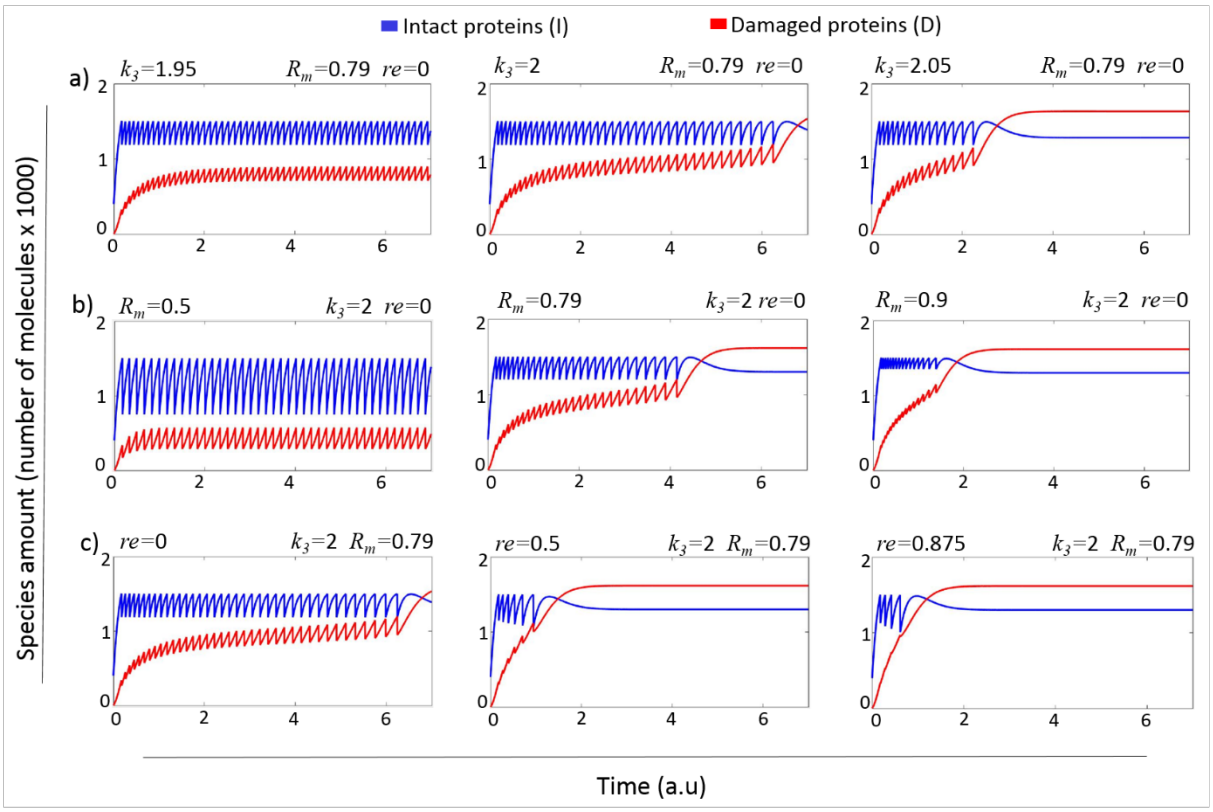


Figure S1: Intracellular species dynamics of a single cell a) damage accumulation rates b) size of the mother and c) retention coefficients. Red and blue lines describe the dynamics of damaged and intact cellular components, respectively. re(g) = Re (a constant).

Pedigree-Tree Diagram

Pedigree-tree model follows growth and division process of each individual cell. The process starts with a single cell that grows its intact and damaged component. At the growth threshold, cell buds its first daughter cell. At this time point, the budding cell is considered as mother while the budded cell is considered as daughter cell. Now mother cell and daughter cell both undergoes the growth process to reach the division threshold, see *Figure S2*. Hence cell population increases while each cell is tracked during its replicative lifespan or until the simulation ends. Population is discretely distributed over the total intact and damage portions of each cell as described in the main text.

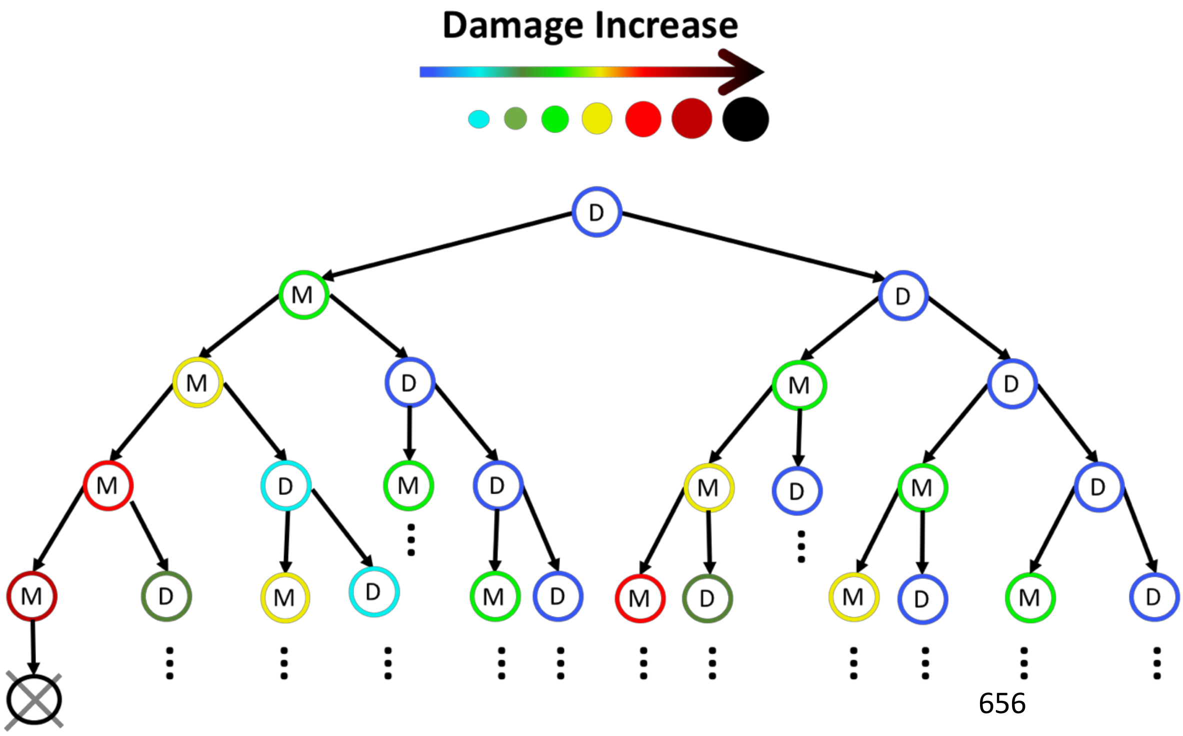


Figure S2: Schematic representation of pedigree-tree model. Each circle represents a cell. D stands for daughter whereas M stands for mother. Blue color is damage free cells while black color is for dead cells (no more divisions possible).

Appendix 2

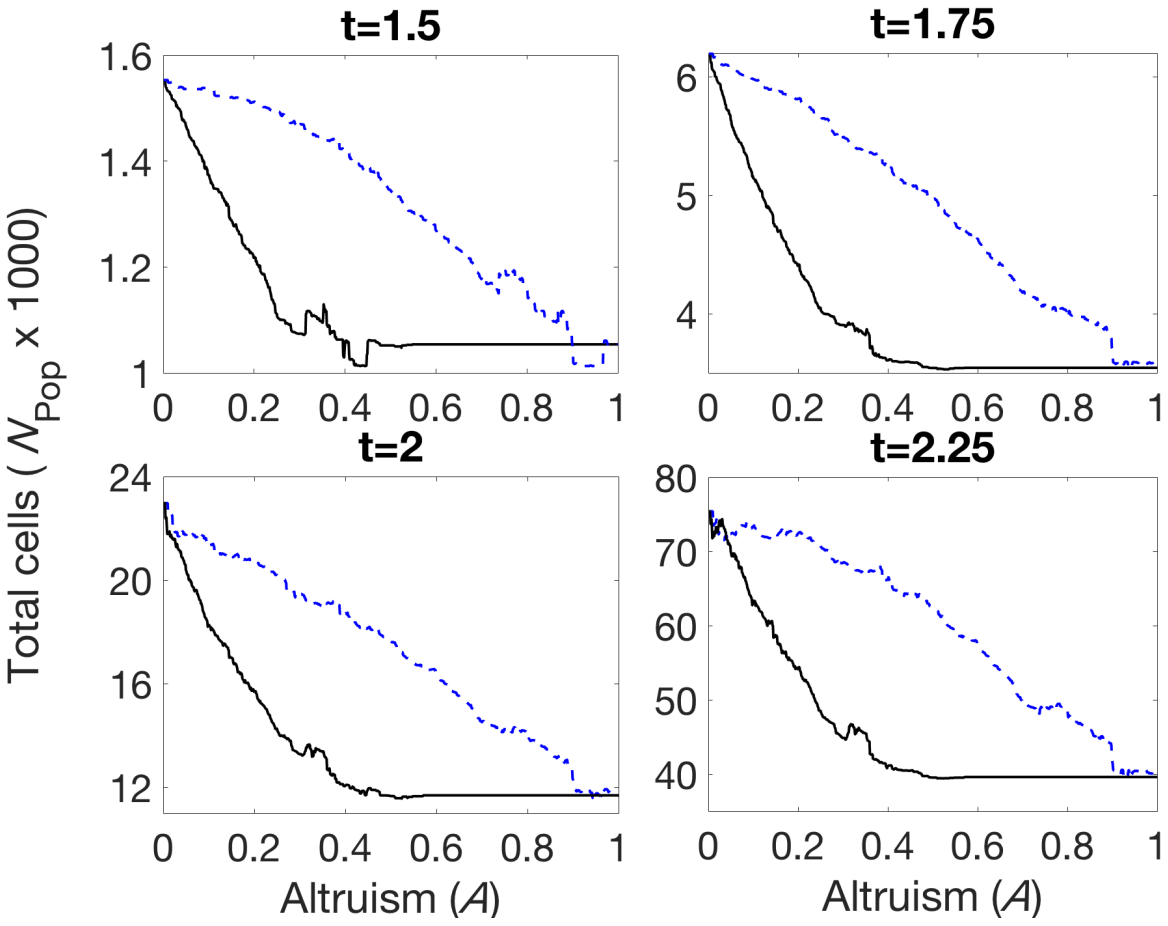


Figure S3: Total number of cells against the altruism values at four simulation times t = 1.5, 1.75, 2, 2.25. Lines represents population with distance strategy whereas the dashed lines represent the population with division strategy.

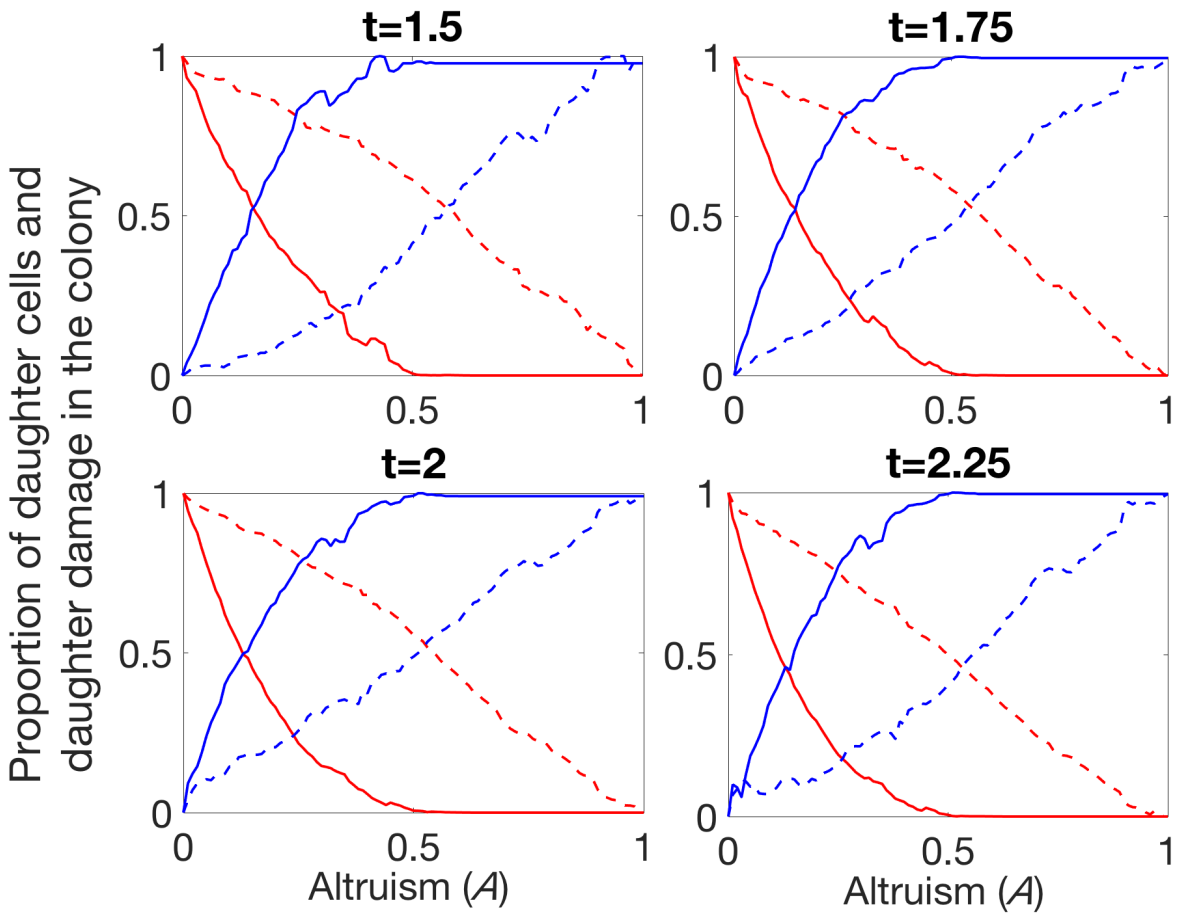


Figure S4: Proportion of daughter cells and their damage in the population for time t =1.5, 1.75, 2 and 2.25. The continuous lines represent distance strategy while dashed lines represent division strategy. The lines moving from 0 to 1 are the daughter cells proportion while the lines moving from 1 to 0 are the damage proportion.

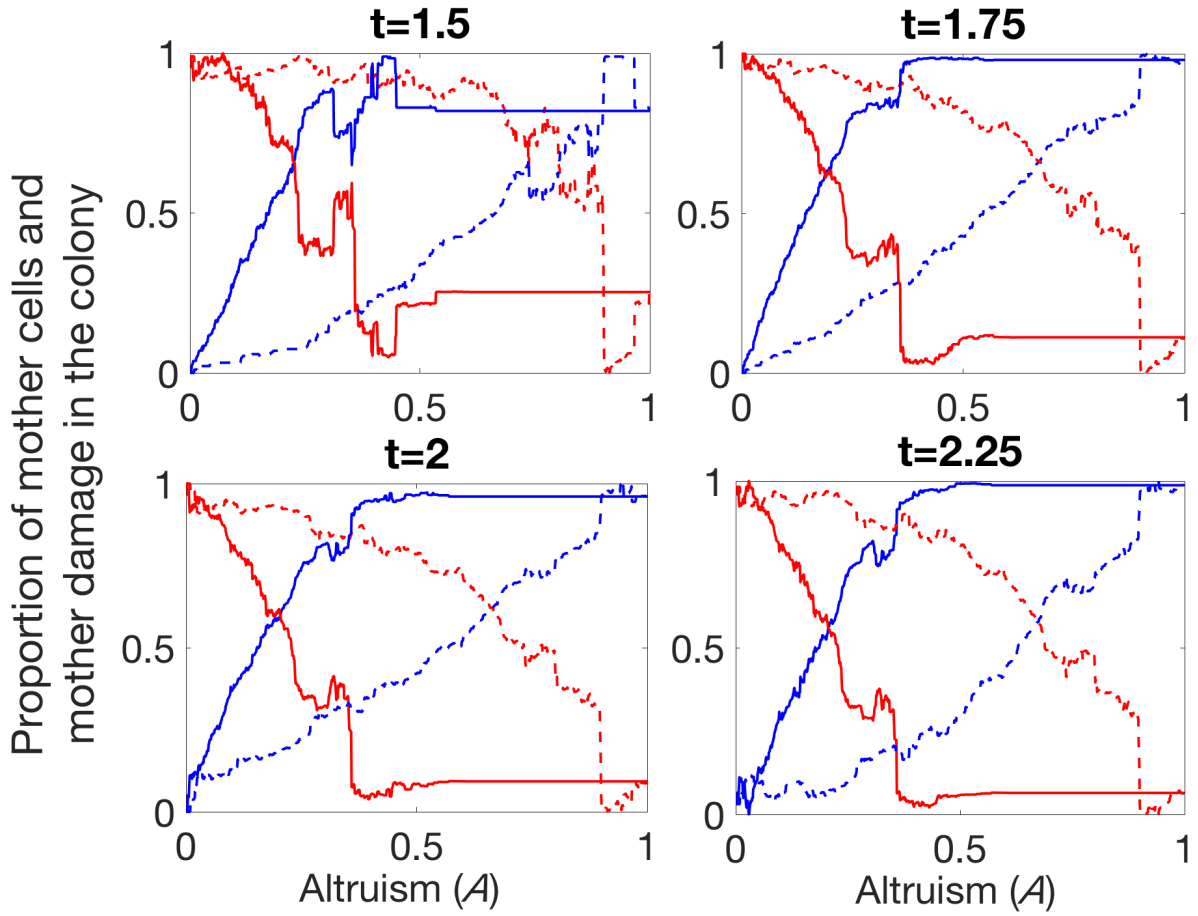


Figure S5: Proportion of mother cells and their damage in the colony at time t =1.5, 1.75, 2 and 2.25. The continuous lines represent distance strategy while dashed lines represent division strategy. The lines moving from 0 to 1 along y-axis are the mother cells proportion while the lines moving from 1 to 0 are the damage proportion.

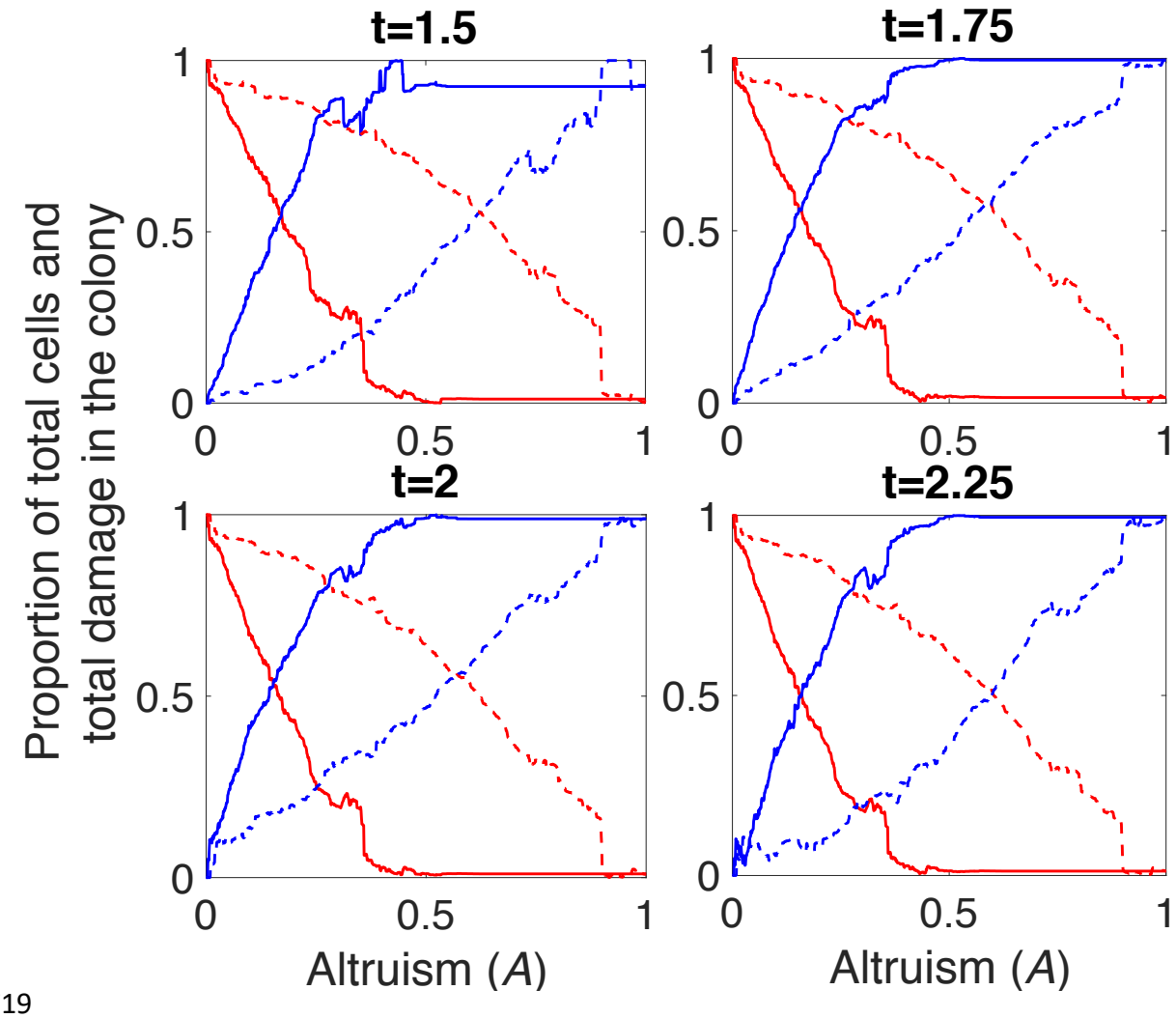


Figure S6: Proportion of total cells and their damage in the population for time t =1.5, 1.75, 2 and 2.25. The continuous lines represent distance strategy while dashed lines represent division strategy. The lines moving from 0 to 1 are the total cells proportion while the lines moving from 1 to 0 are the damage proportion.

References

Ackermann, M., Chao, L., Bergstrom, C.T., Doebeli, M., 2007. On the evolutionary origin of aging. Aging Cell 6, 235–244. https://doi.org/10.1111/j.1474-9726.2007.00281.x

Ackermann, M., Stearns, S.C., Jenal, U., 2003. Senescence in a bacterium with asymmetric division. Science 300, 1920. https://doi.org/10.1126/science.1083532

Aguilaniu, H., Gustafsson, L., Rigoulet, M., Nyström, T., 2003. Asymmetric inheritance of oxidatively damaged proteins during cytokinesis. Science 299, 1751–1753. https://doi.org/10.1126/science.1080418

Berg, J.M., Tymoczko, J.L., Stryer, L., 2002. Evolution Requires Reproduction, Variation, and Selective Pressure.

Biesalski, H.K., 2002. Free radical theory of aging. Curr. Opin. Clin. Nutr. Metab. Care 5, 5–10.

Brooks, R.C., Garratt, M.G., 2017. Life history evolution, reproduction, and the origins of sex-dependent aging and longevity. Ann. N. Y. Acad. Sci. 1389, 92–107. https://doi.org/10.1111/nyas.13302

Bufalino, M.R., DeVeale, B., van der Kooy, D., 2013. The asymmetric segregation of damaged proteins is stem cell-type dependent. J. Cell Biol. 201, 523–530. https://doi.org/10.1083/jcb.201207052

Chao, L., 2010. A model for damage load and its implications for the evolution of bacterial aging. PLoS Genet. 6. https://doi.org/10.1371/journal.pgen.1001076

Chao, L., Rang, C.U., Proenca, A.M., Chao, J.U., 2016. Asymmetrical Damage Partitioning in Bacteria: A Model for the Evolution of Stochasticity, Determinism, and Genetic Assimilation. PLoS Comput. Biol. 12. https://doi.org/10.1371/journal.pcbi.1004700

Clegg, R.J., Dyson, R.J., Kreft, J.-U., 2014. Repair rather than segregation of damage is the optimal unicellular aging strategy. BMC Biol. 12. https://doi.org/10.1186/s12915-014-0052-x

Coelho, M., Lade, S.J., Alberti, S., Gross, T., Tolić, I.M., 2014. Fusion of protein aggregates facilitates asymmetric damage segregation. PLoS Biol. 12, e1001886. https://doi.org/10.1371/journal.pbio.1001886

de Grey, A.D., 1997. A proposed refinement of the mitochondrial free radical theory of aging. BioEssays News Rev. Mol. Cell. Dev. Biol. 19, 161–166. https://doi.org/10.1002/bies.950190211

Denoth Lippuner, A., Julou, T., Barral, Y., 2014. Budding yeast as a model organism to study the effects of age. FEMS Microbiol. Rev. 38, 300–325. https://doi.org/10.1111/1574-6976.12060

Egilmez, N. K, and Jazwinski, S.M., 1989. Evidence for the involvement of a cytoplasmic factor in the aging of the yeast Saccharomyces cerevisiae. J Bacteriol 171: 37–42.

Erjavec, N., Cvijovic, M., Klipp, E., Nyström, T., 2008. Selective benefits of damage partitioning in unicellular systems and its effects on aging. Proc. Natl. Acad. Sci. U. S. A. 105, 18764–18769. https://doi.org/10.1073/pnas.0804550105

Erjavec, N., Larsson, L., Grantham, J., Nyström, T., 2007. Accelerated aging and failure to segregate damaged proteins in Sir2 mutants can be suppressed by overproducing the protein aggregation-remodeling factor Hsp104p. Genes Dev. 21, 2410–2421. https://doi.org/10.1101/gad.439307

Hill, S.M., Hanzén, S., Nyström, T., 2017. Restricted access: spatial sequestration of damaged proteins during stress and aging. EMBO Rep. 18, 377–391. https://doi.org/10.15252/embr.201643458

Hill, S.M., Hao, X., Grönvall, J., Spikings-Nordby, S., Widlund, P.O., Amen, T., Jörhov, A., Josefson, R., Kaganovich, D., Liu, B., Nyström, T., 2016. Asymmetric Inheritance of Aggregated Proteins and Age Reset in Yeast Are Regulated by Vac17-Dependent Vacuolar Functions. Cell Rep. 16, 826–838. https://doi.org/10.1016/j.celrep.2016.06.016

Jazwinski, S.M., Wawryn, J., 2001. Profiles of random change during aging contain hidden information about longevity and the aging process. J. Theor. Biol. 213, 599–608. https://doi.org/10.1006/jtbi.2001.2434

Kaeberlein, M., 2010. Lessons on longevity from budding yeast. Nature 464: 513–519.

Katajisto, P., Döhla, J., Chaffer, C., Pentinmikko, N., Marjanovic, N., Iqbal, S., Zoncu, R., Chen, W., Weinberg, R.A., Sabatini, D.M., 2015. Asymmetric apportioning of aged mitochondria between daughter cells is required for stemness. Science 348, 340–343. https://doi.org/10.1126/science.1260384

Kennedy, B.K., Austriaco, N.R., Guarente, L., 1994. Daughter cells of Saccharomyces cerevisiae from old mothers display a reduced life span. J. Cell Biol. 127, 1985–1993.

Kirkwood, T.B., Rose, M.R., 1991. Evolution of senescence: late survival sacrificed for reproduction. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 332, 15–24. https://doi.org/10.1098/rstb.1991.0028

Konieczny, L., Roterman-Konieczna, I., Spólnik, P., 2014. The Structure and Function of Living Organisms, in: Systems Biology. Springer, Cham, pp. 1–32. https://doi.org/10.1007/978-3-319-01336-7_1

Kowald, A., Kirkwood, T.B., 2000. Accumulation of defective mitochondria through delayed degradation of damaged organelles and its possible role in the ageing of post-mitotic and dividing cells. J. Theor. Biol. 202, 145–160. https://doi.org/10.1006/jtbi.1999.1046

Kruegel, U., Robison, B., Dange, T., Kahlert, G., Delaney, J.R., Kotireddy, S., Tsuchiya, M., Tsuchiyama, S., Murakami, C.J., Schleit, J., Sutphin, G., Carr, D., Tar, K., Dittmar, G., Kaeberlein, M., Kennedy, B.K., Schmidt, M., 2011. Elevated proteasome capacity extends replicative lifespan in Saccharomyces cerevisiae. PLoS Genet. 7, e1002253. https://doi.org/10.1371/journal.pgen.1002253

Lindner, A.B., Madden, R., Demarez, A., Stewart, E.J., Taddei, F., 2008. Asymmetric segregation of protein aggregates is associated with cellular aging and rejuvenation. Proc. Natl. Acad. Sci. U. S. A. 105, 3076–3081. https://doi.org/10.1073/pnas.0708931105

Liu, B., Larsson, L., Franssens, V., Hao, X., Hill, S.M., Andersson, V., Höglund, D., Song, J., Yang, X., Öling, D., Grantham, J., Winderickx, J., Nyström, T., 2011. Segregation of protein aggregates involves actin and the polarity machinery. Cell 147, 959–961. https://doi.org/10.1016/j.cell.2011.11.018

Longo, V., Shadel, G. S., Kaberlein, M., Kenndy, B., 2012. Replicative and Chronological Ageing in Saccharomyces cerevisiae Cell Metab. 16(1): 18-31 https:// doi: 10.1016/j.cmet.2012.06.002

Nyström, T., Liu, B., 2014. Protein quality control in time and space - links to cellular aging. FEMS Yeast Res. 14, 40–48. https://doi.org/10.1111/1567-1364.12095

Orgel, L.E., 1963. The maintenance of the accuracy of protein synthesis and its relevance to ageing. Proc. Natl. Acad. Sci. U. S. A. 49, 517–521.

Rujano, M.A., Bosveld, F., Salomons, F.A., Dijk, F., van Waarde, M.A.W.H., van der Want, J.J.L., de Vos, R.A.I., Brunt, E.R., Sibon, O.C.M., Kampinga, H.H., 2006. Polarised asymmetric inheritance of accumulated protein damage in higher eukaryotes. PLoS Biol. 4, e417. https://doi.org/10.1371/journal.pbio.0040417

Spokoini, R., Moldavski, O., Nahmias, Y., England, J.L., Schuldiner, M., Kaganovich, D., 2012. Confinement to organelle-associated inclusion structures mediates asymmetric inheritance of aggregated protein in budding yeast. Cell Rep. 2, 738–747. https://doi.org/10.1016/j.celrep.2012.08.024

Stewart, E.J., Madden, R., Paul, G., Taddei, F., 2005. Aging and Death in an Organism That Reproduces by Morphologically Symmetric Division. PLoS Biol. 3. https://doi.org/10.1371/journal.pbio.0030045

Tyedmers, J., Mogk, A., Bukau, B., 2010. Cellular strategies for controlling protein aggregation. Nat. Rev. Mol. Cell Biol. 11, 777–788. https://doi.org/10.1038/nrm2993

Vedel, S., Nunns, H., Košmrlj, A., Semsey, S., Trusina, A., 2016. Asymmetric Damage Segregation Constitutes an Emergent Population-Level Stress Response. Cell Syst. 3, 187–198. https://doi.org/10.1016/j.cels.2016.06.008

Zhou, C., Slaughter, B.D., Unruh, J.R., Guo, F., Yu, Z., Mickey, K., Narkar, A., Ross, R.T., McClain, M., Li, R., 2014. Organelle-based aggregation and retention of damaged proteins in

828 asymmetrically dividing cells. Cell 159, 530–542.
829 https://doi.org/10.1016/j.cell.2014.09.026

830