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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 a 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 the 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.

Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
No data was used for the research described in the article

CHALMERS | GÖTEBORGS UNIVERSITET

Gothenburg, November 5, 2018

Journal of Theoretical Biology, editorial board

Dear Professor Chaplain,

On behalf of the authors, I thank you and the referees for the careful assessment of resubmission. As both reviewers noted, we have clearly improved our manuscript. We now submit a second revised version where we have addressed the points raised as outlined in our response to reviewers.

We have received the comments from two reviewers:

Reviewer 2 Was very positive with our revision and had minor cosmetic comments regarding the figure and model description. We have taken these two points into the consideration and have updated our manuscript accordingly.

Reviewer 3 Was also positive with our latest improvements of the manuscript and had comments related to the language and conclusions. Several typos are now corrected, however some concerns and comments raised by this reviewer left a feeling that s/he doesn't possess a knowledge on yeast ageing and is more focused on mathematical conclusions. Although this is completely understandable and we agree with it, we would like to draw attention that reviewers comments should be taken with consideration.
In both first and now second revision, we have provided extensive biological motivation for the problem we are analyzing and cannot agree with some of the points raised.

Our responses to all the points raised are detailed in the Rebuttal. We hope that with these changes, you will find our manuscript suitable for publication.

Thank you for your consideration.
Sincerely,

Marija Cvijovic, on behalf of all authors

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***2. Response to Reviews (for Revision)**

Reviewer #2: The authors have addressed the major concerns by the reviewer.
We would like to thank to the reviewer for careful and thorough evaluation of our revision.

I have a couple of minor discretionary revisions:

(1) Figure 3 is too busy, and difficult to follow. Maybe the authors can select the most important curves that illustrate the feature of the models they wish to highlight.
After testing several versions of this figure, we decided to keep the original version.

(2) The paper might benefit of moving the model from the appendix/supplementary material to the body of the paper. There is an interruption in the flow of the manuscript by having core features of the model in the appendix instead of the body of the paper.
We have now included an abbreviated summary of the model in the main text.

Reviewer #3: This manuscript is much improved. Two significant concerns remain, however.
We would like to thank to the reviewer for careful and thorough evaluation of our revision.

Language: Throughout, the use of English needs improvement. Much of this is minor, but in some places it obscures meaning. These need to be resolved.

Specifics from the first few pages:

line 85: 'rejuvenated daughter'. Odd choice of words: the daughter has just been born. 'Re'-juvination is not possible.
The term ‘rejuvenated daughter’ is widely used in ageing research, meaning that the daughter’s age is ‘reset to zero’ when it arises from an ageing mother.
For yeast specifically, first-born daughters are referred to ‘rejuvenated-daughters’ as they are born damage-free with full replicative potential. The last daughters are born with substantial amounts of damage and are referred to as ‘prematurely old’ and they exhibit reduced replicative potential.

line 104 'is vaguely understood the terminology used…'
This is not corrected

line 106: 'A population's success is in the asymmetric division…'
This is not corrected

line 121: '_The_ natural selection …._The_ asymmetric division' (Articles not needed.)
This is not corrected

line 130: 'in spatially sequester regions…"
This is not corrected

line 133: 'In previously computational models…'
This is not corrected

line 152: damaged
This is not corrected

Conclusions: The main conclusions are still largely intuitive statements. E.g. from the abstract: "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." No mathematical analysis is needed to reach these conclusions. I recommend reorganizing the document to highlight your less intuitive findings (on e.g. altruism and local minima).

We cannot agree with the reviewer on this comment. Experimentally it is still not feasible to understand mechanisms of damage retention, more specifically to what level mother cell is retaining damage and more importantly when it starts to pass damage to her daughters. We tried to answer these questions theoretically, and even though results might sound intuitive they represent an important contribution to the understanding of yeast ageing. During the first revision, we have provided detailed (biological)reasoning for these questions. Also, these findings can be very useful in designing new targeted experiments to test this hypothesis. For example, with the development of microfluidics systems, we hope that this work can serve as a starting point for experimental design and can pinpoint to the specific mechanism to look at experimentally.

Analysis of Altruism concluded that distance strategy provides healthier populations then division strategy (see section Altruism Provides Healthy but a Small Population). In case of global minima of cost function we conclude that the distance strategy is preferred. The cost function for the species following either of the two strategies can never stay at the global minima as species keep looking for a better choice.

Adaptive damage retention mechanism enables healthier yeast population

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Highlights

- retaining more damage by a yeast cell during the early divisions increases the number of healthy daughters in the population
- 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 damage
- fluctuations in the cost function allow yeast cell to continuously vary its strategy, suggesting that optimal reproduction success is a local minimum of the cost function

Keywords: yeast, asymmetrical division, damage retention, dynamical modelling, pedigree-tree model

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 a 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 the 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.

56 *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 a 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

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58

Introduction:

Aging is a conserved scale-invariant phenomenon that exploits the 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 evolutionarily 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 al, 1994; Sinclair et al, 1998a; Sinclair et al, 1998b). This

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

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

Optimal reproduction success is a term used to define the replicative lifespan of a yeast cell that has evolved the organelles to adopt the finest route for the healthy survival of the yeast population. A success of the population is in the asymmetric distribution of damage during the cell division that ensures the low amount of damage in the progeny and its long replicative lifespan (Chao et al., 2016; Nyström and Liu, 2014). However, healthy progeny and long replicative lifespan are inversely proportional to each other since it is asserted that, during the replicative lifespan, yeast strains sacrifice their long-term survival over the health of their progeny by retaining the aging factors (Aguilaniu et al., 2003; Hill et al., 2017; Kirkwood and Rose, 1991). Therefore, it is interesting to find a strategy for optimal retention of aging factors in such a way that yeast population accumulates less damage in the living cells and provides maximum population.

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

(Chao et al., 2016). Moreover, natural selection adapts the protective mechanism into the subsequent progeny in a genetically controlled manner. 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 sequestered 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 previous 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 the yeast cell. However, the exact mechanisms of damage retention 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 the 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 the discrete-continuous model. We provide here an abbreviated summary (for detailed derivation and parameters see Appendix 1).

Each cell increases its intact (I) and damaged (D) components during the growth process (Eq. 1) and asymmetrically distributes these components between mother R_m (Eq.2) and daughter R_d (Eq.3) cells during the division process.

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

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

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

The damage retention mechanism allows mother cell to retain part of the damaged 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 a 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, the 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 the 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

$$RE_{div}(g+1) = 1 - \frac{g^n}{g^n + \alpha^n} \tag{4}$$

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).

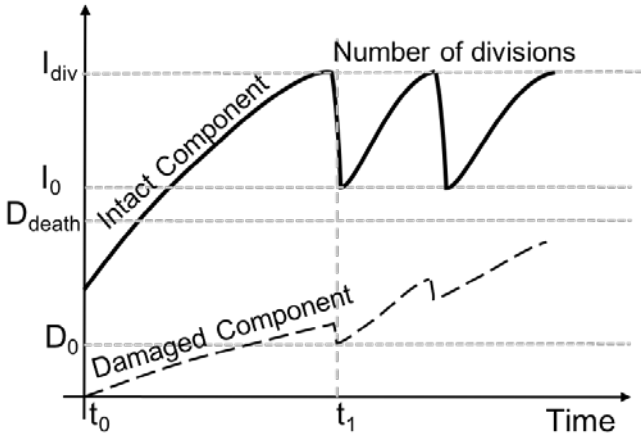

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Figure 1: Division strategy: Efficiency in damage retention decreases with the increase in number of divisions. Mother cell is able to retain maximum damage in the beginning but loses its efficiency of damage retention as the number of divisions increases. 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}.

185 Distance Strategy

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

$$RE_{dist}(g+1) = 1 - \frac{R_t^n(g)}{R_t^n(g) + \alpha^n} \tag{5}$$

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

$$R_t = \frac{\tau_I}{\tau_D} \tag{6}$$

192 Due to the increase in damage during the replicative lifespan of a cell, the retention becomes
193 more difficult. After every division cell anticipates the possibility of the next division. If the
194 damage is high enough such that the 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 the ratio between remaining distance and the mean rate of change in the corresponding intact ($Avg(\dot{I})$) and damage ($Avg(\dot{D})$) component.

$$\tau_I = \frac{I_{div} - I_g}{Avg(\dot{I})}, \tau_D = \frac{D_{death} - D_g}{Avg(\dot{D})} \quad (7)$$

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 a 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 the next division by the above-defined procedure (see Eq. 5). 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 the next division becomes possible.

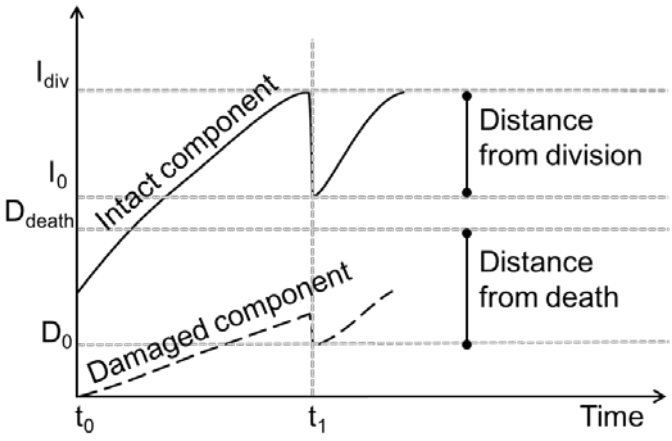


Figure 2: Mother cell decreases damage retention by anticipating her next reproduction success. Cell increases its initial intact and damage component from t_0 and divides at time t_1. The intact component decreases from its threshold I_{div} to $I_{g=0}$ after division and the damaged component decreases 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. (8). The parameter A is based on the consequences of the actions performed for the replicative lifespan of a mother cell and for the 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. (4) and (5). 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 a defined strategy (distance or division strategy). Secondly, altruism parameter is used to alter the strategy. 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:

$$re(A, g) = RE(g) + 2\left(A - \frac{1}{2}\right)\left((1 - A)RE(g) + A(re_{max} - RE(g))\right) \qquad (8)$$

The parameter re is the 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 the complete population with variable retention parameter (Eq(1-3) and Appendix 1). The cellular growth is represented by an increase in the number of intact and damage components and the division is represented by the asymmetric distribution of growth components (intact and damage) between mother and daughter cells. The 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 the 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 the 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 a 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 the damaged component is written as,

$$P(A,D) = \frac{\sum_{D=a}^{D=b}\left(N_{daugh}(A,D) + N_{mot}(A,D)\right)}{N_{pop}(A)}. \quad (9)$$

where a and b are the minimum and maximum accumulated damage, respectively. 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:

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

$$P_{daugh}(A,D) = \frac{\sum_{D=a}^{D=b} N_{daugh}(A,D)}{\sum_{D} N_{daugh}(A,D)}. \quad (10)$$

Cost Functions

The calculation of cost function is performed at the end of the discrete-continuous model while the objective is to find the minimum cost function so that smallest amount of damage and a 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, $\tilde{N}$ ($\sum_{D_{\text{daugh}}} D_{\text{daugh}}(A)$), and difference between normalized maximum number of daughter cells during $A \in [0,1]$, i.e. equals to 1, and normalized alive daughter cells, $\tilde{N}(N_{\text{daugh}}(A, D))$, present in the system at any time $t = t_0$.

$$C_{daugh}(A) = \tilde{N}\left(\sum_{D_{daugh}} D_{daugh}(A)\right) + \left(1 - \tilde{N}\left(\sum_{D} N_{daugh}(A,D)\right)\right) \quad (11)$$

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,

$$C_{mot}(A) = \tilde{N}\left(\sum_{D_{mot}} D_{mot}(A)\right) + \left(1 - \tilde{N}\left(\sum\nolimits_{D} N_{mot}(A, D)\right)\right) \quad (12)$$

Damage in a mother cell is denoted by D_{mot} and a 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,

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

Variation in Altruism

Altruism parameter A is varied deterministically as well as stochastically. The deterministic way is quite straightforward as it formulates the normalized distribution of cells at discrete values of A and calculates 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 using Eqs. (11), (12) and (13) which involves simulation of the 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 a random value in the interval of $[0, \varepsilon]$.

$$A_{i+1} = A_i \pm rand(0, \varepsilon)\, sgn(C(A_{i-1}) - C(A_i)) \quad (14)$$

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

$$\sum_{i=S_N+l}^{S_N+j+l} \left|A_{i-j} - A_{i-(j+k)}\right| < \varepsilon. \quad (15)$$

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 the 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 a 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 a 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 with each value of altruism that is followed according to their intrinsic behaviour represented by Eqs. (4) and (5). 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 (4) and (5) 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 are given by altruist parameter *A with* $A_{max} = 1$. It is interesting to note that both strategies provide the same behaviour at the endpoints of *A*, i.e. 0 and 1 (Figure 3).

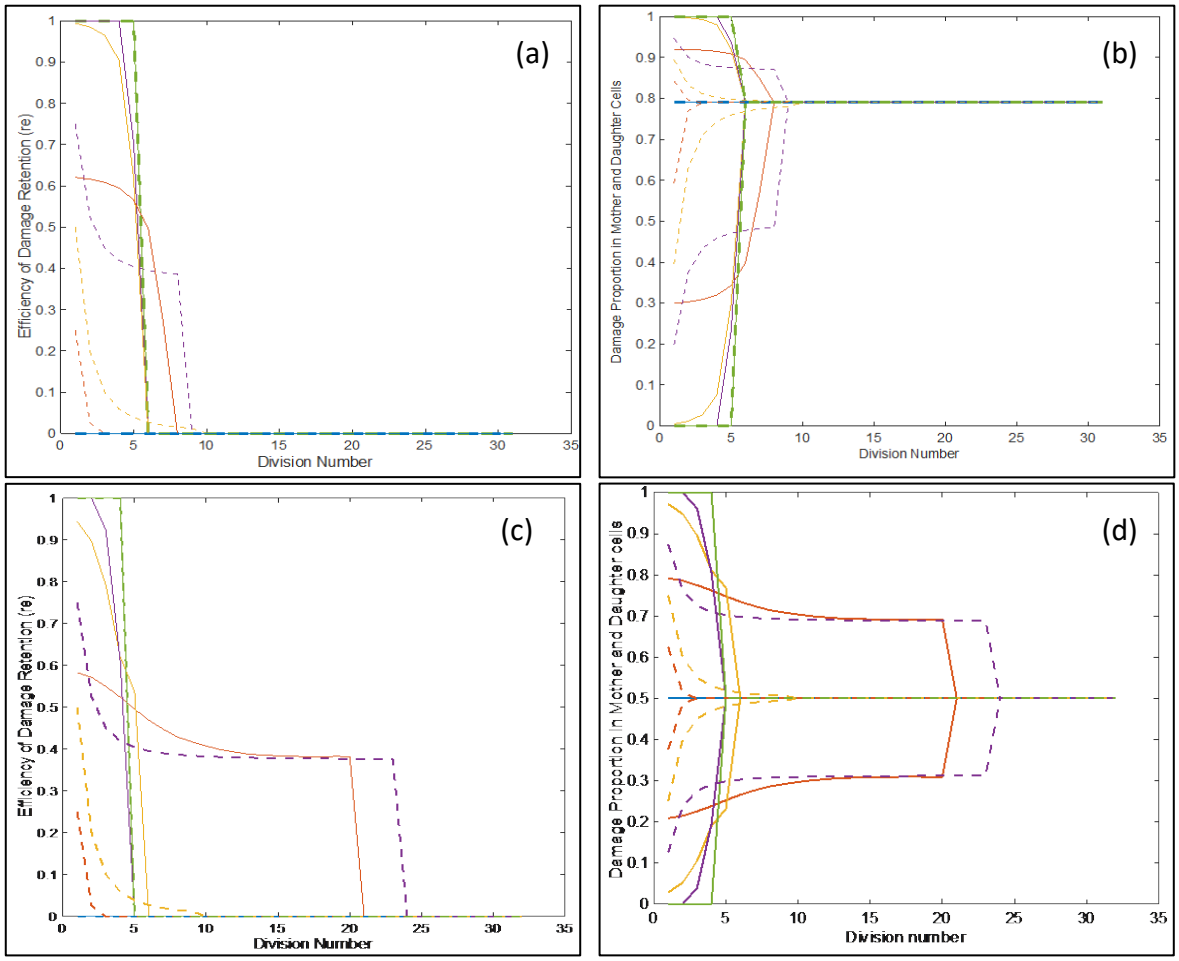
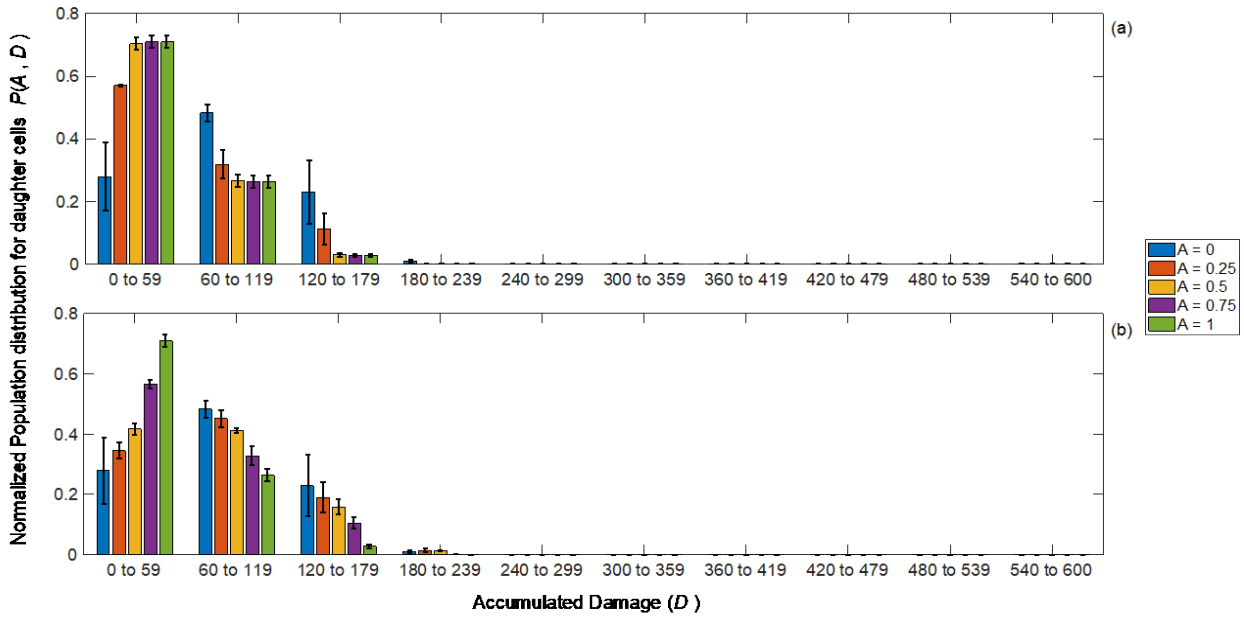


Figure 3: Damage retention efficiency (RE) for altruist parameter values A = 0 (blue), 0.25 (red), 0.5 (yellow), 0.75 (violet) and 1 (green). The dashed lines represent division strategy and continuous lines represent distance strategy. Colours are drawn to match the altruist parameter values between 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 the 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 a 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.



356

357 *Figure 4: Mean and standard deviation of the daughter distribution of damaged proteins by using*
358 *distance (a) and division (b) strategies, see Eq. (11). Mean of the distribution is taken for the simulation*
359 *time t = 1.5, 1.75, 2, 2.25. The accumulated damage in the span of 600 is clustered into subintervals*
360 *each of length 60.*

361 The population distribution of daughter cells is present only in the first three clusters of
362 damage component (Figure 4). In the first cluster, $D_{daugh} \in [0, 59]$, the mean proportion of
363 cells, $P(A, D)$, increases when altruism A goes from 0 to 1 while the succeeding clusters show
364 a reverse behaviour. The error bars represent the standard deviation of the mean distribution
365 values for simulation time t = 1.5, 1.75, 2, 2.25. For A = 0, the standard deviation is quite high
366 because the cell proportion was higher in the first and third clusters ($P(A = 0, D = [0, 60)) \approx$
367 0.38) during the early simulation time, t = 1.5. However, it decreased to below 0.2 in the later
368 simulation time, t = 2.25. Moreover, for $A \geq 0.5$, the proportion of cells with least damage is
369 much high and have a very small standard deviation.

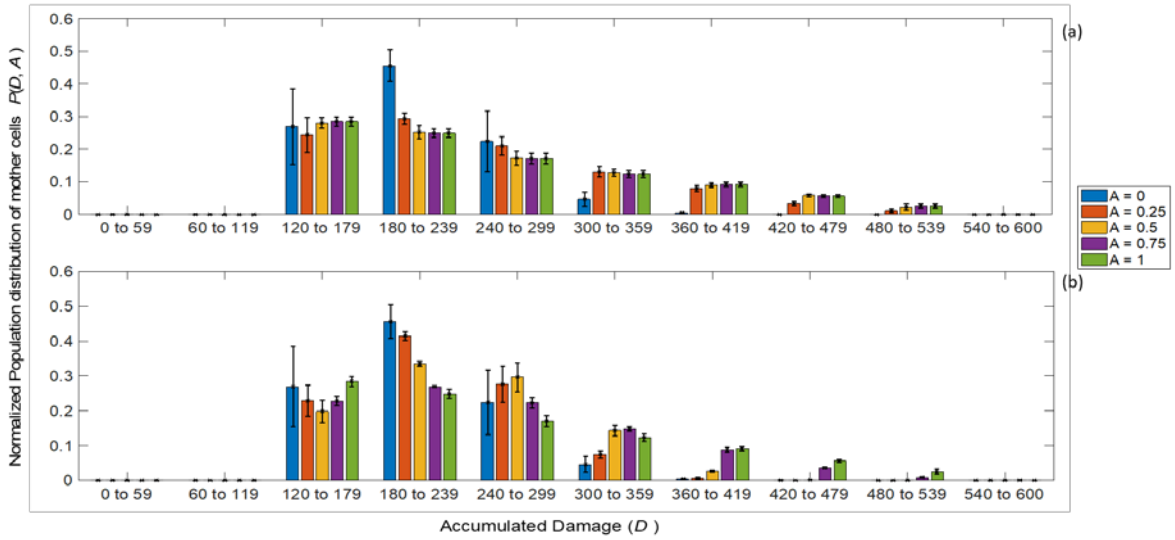


Figure 5: Mean and standard deviation of the mother distribution of damaged proteins by using distance (a) and division (b) strategies, see Eq. (10). Mean of the distribution is taken for the simulation time t = 1.5, 1.75, 2, 2.25. The accumulated damage in the span of 600 is clustered into subintervals 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 4b). 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 the 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 a 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 the low damage.

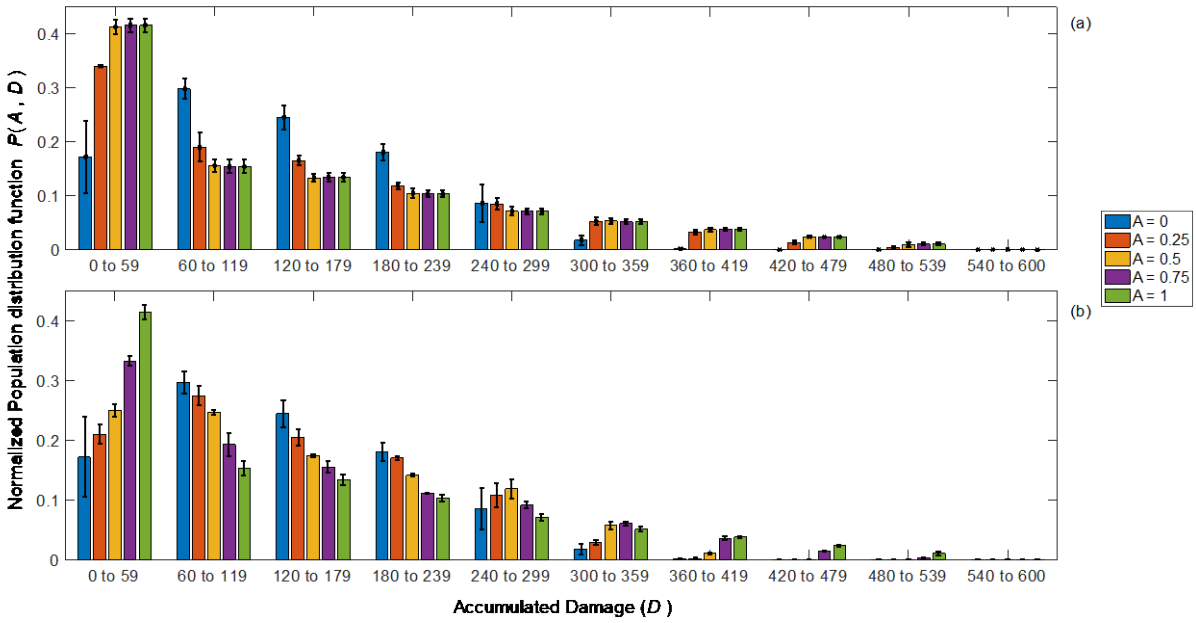


Figure 6: Mean and standard deviation of the normalized population distribution of damaged proteins by using (a) distance and (b) division strategies as defined in Eq. (9). Mean of the distribution is taken for the simulation time t = 1.5, 1.75, 2, 2.25. The accumulated damage in the span of 600 is clustered 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 a cost for predefined values of

411 altruism *A* whereas the stochastic model tracks the minimum value for cost function by taking
412 random steps towards the lowest value of the cost function.

413 ## Deterministic outcomes

414 The deterministic modelling approach is used to evaluate the cost functions by varying the
415 altruist parameter *A* between 0 and 1 with the step size $\Delta A = 10^{-3}$. The results are obtained for
416 the cost functions defined in Eqs. (11), (12) and (13) and are presented in Figure 7 (for
417 daughter cells), in Figure 8 (for mother cells) and in Figure 9 (for a total number of alive cells)
418 respectively each at four different times t = 1.5, 1.75, 2 and 2.25. Computationally, it becomes
419 very expensive to go beyond the time point t = 2.25. Therefore, this is the maximum time point
420 chosen. Other time points are chosen to understand the behaviour of cost function over the
421 altruism parameter *A*. The cost function is modelled by taking this fact into consideration that
422 the replicative lifespan decreases with the increase in damage retention by the cell. In such a
423 scenario, it would be interesting to see the effect of replicative lifespan over the damage
424 accumulation in the population.

425 Altruistic effects on the daughter cells provide a time-variant response to its cost function.
426 Due to asymmetric division, mother cells require less time to reproduce than the daughter
427 cells. Therefore, the longer lifespan of mother cells will quickly increase the population;
428 however, in case of low damage retention, high amount of damage is passed on to the newly
429 born daughter cells. In case of distance strategy, this phenomenon quickly increases the
430 damage in the population and raises the cost function to a high level during the early time, i.e.
431 t = 1.5 and 1.75 (Figure 7, Figure 8 and Figure 9). However, with the progression of time, i.e. t
432 goes to 2 and 2.25, the cost function gives a surprising outcome by replacing the high values
433 with the lower ones, exposing that for large time scale, population size can dominate over the
434 total damage present in the population. For instance, the distance strategy (continuous lines)
435 near A = 0.3, the cost function that was at maximum, i.e. C_{daugh} = 1.2 at time t = 1.5, goes below
436 the value of C_{daugh} = 1 at time t = 2.25.

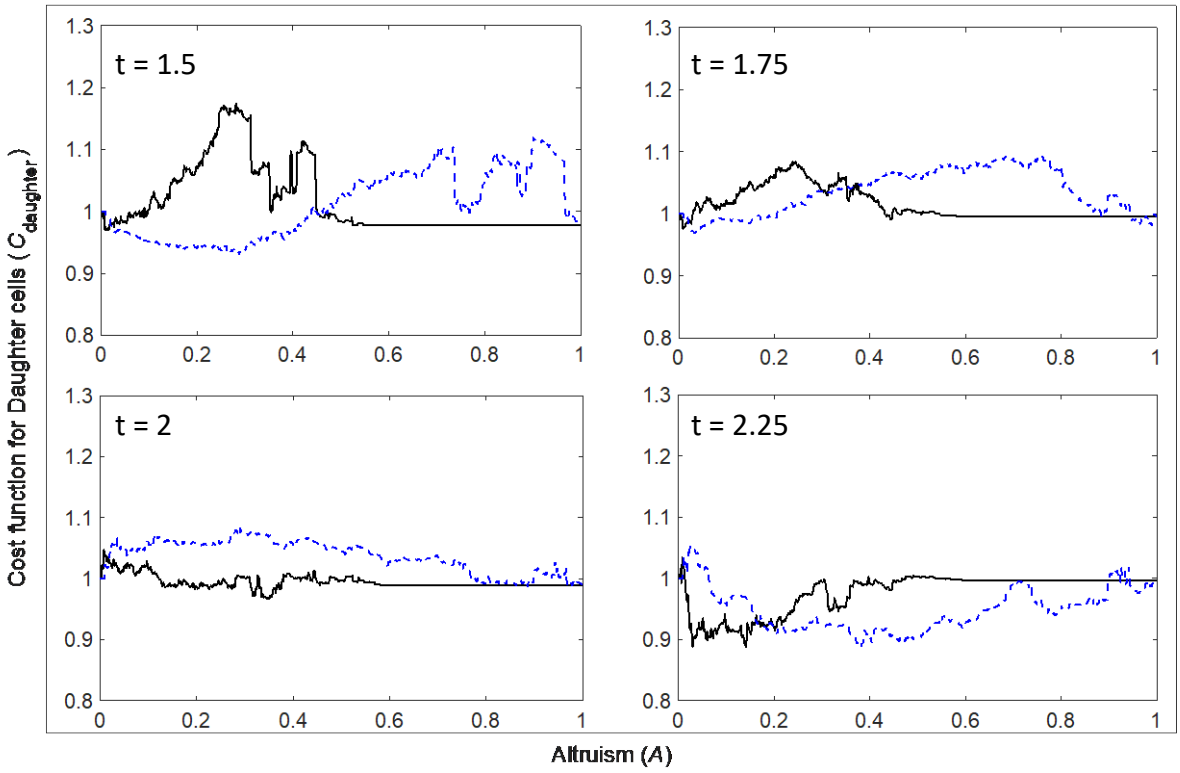
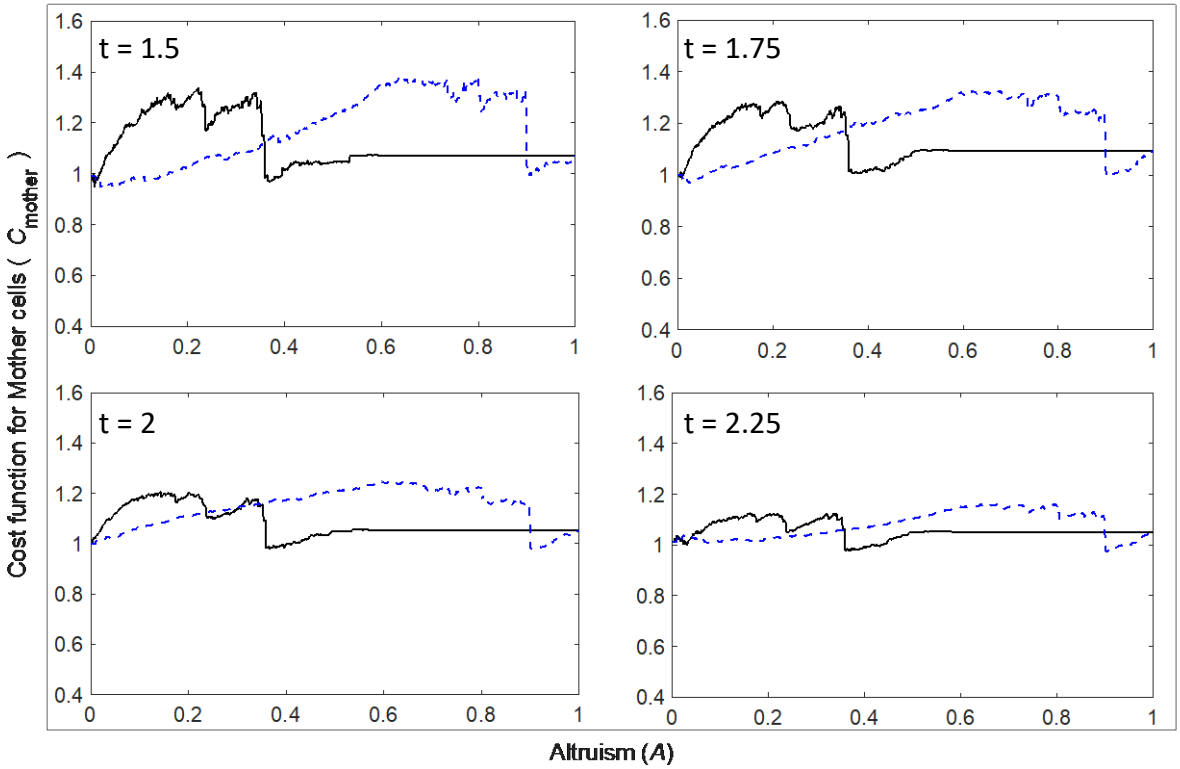


Figure 7: Cost function for the distance (continuous lines) and division (dashed lines) strategies of daughter cells C_{Daugh} at four time-points t = 1.5, 1.75, 2 and 2.25 against the altruist values A in the interval [0,1] and step size 0.001. The cost function is defined in Eq. (11) while the deterministic model used to simulate the results is described in Appendix 1.

Division strategy provides the 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 S2). For a longer period of time, t = 2.25, both strategies decrease their cost function for early values of A, however, their optimal reproduction success varies.



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

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

464

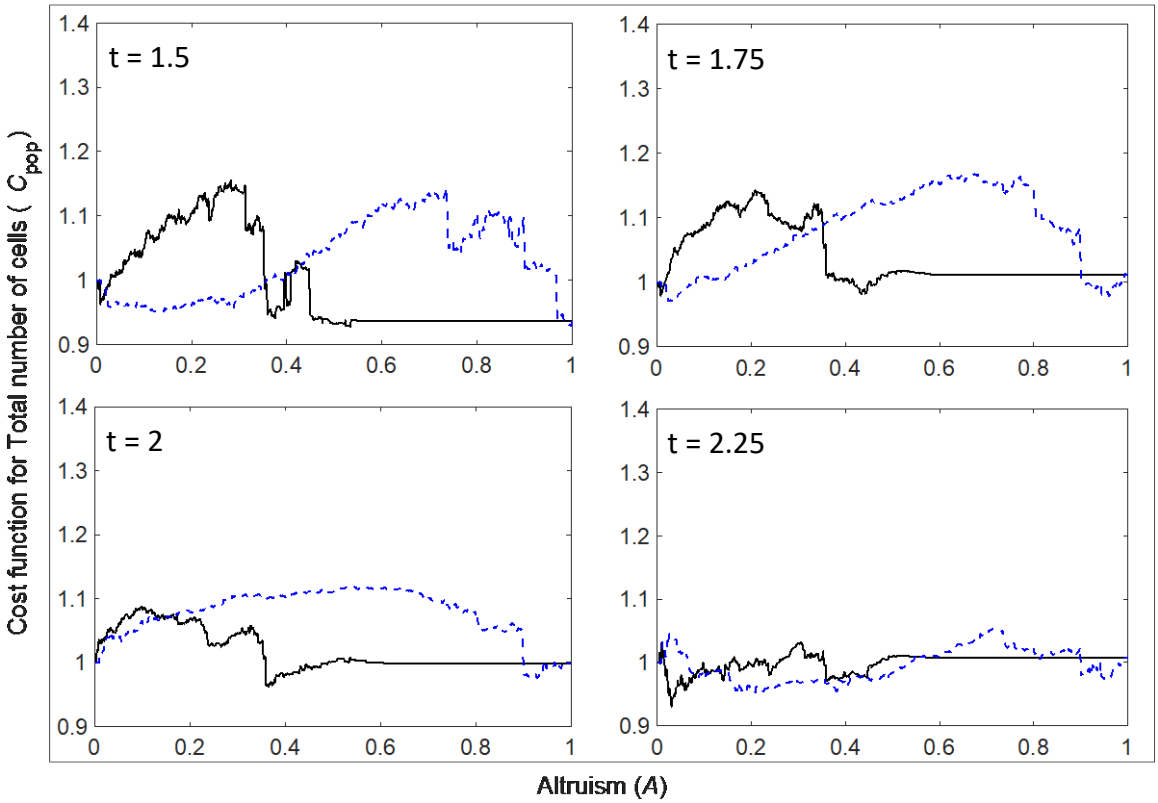


Figure 9: Cost function for the distance (continuous lines) and division (dashed lines) strategies of total cells C_{pop} at four time-points t = 1.5, 1.75, 2 and 2.25 against the altruist values A in the interval [0,1] and step size 0.001.

Stochastic Simulations

Stochastic settings are implemented to observe the behaviour of the 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. (14). 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 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

$$\sum_{i=S_N+l}^{S_N+j+l} \left|A_{i-j} - A_{i-(j+k)}\right| < \varepsilon \qquad (15)$$

The index values are $j = k = 10$ and the epsilon $\varepsilon = 0.02$. The parameter epsilon provides the maximum possible variation in the altruism value and is used in the Eq. (14). The stopping criteria are 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 the 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 10b). 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.

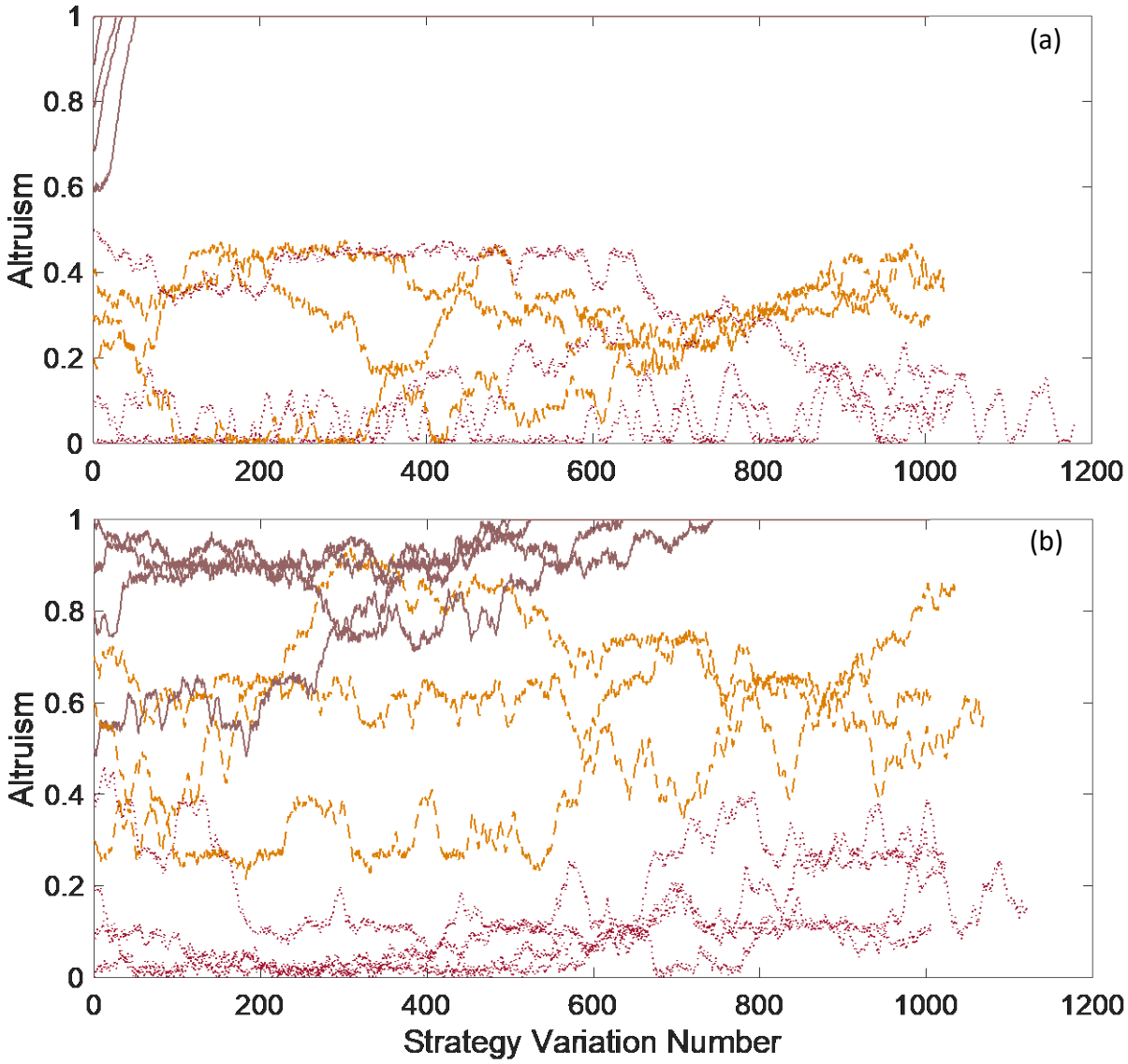


Figure 10: Stochastic simulations of (a) distance and (b) division strategies at time t = 1.5. The altruism parameter A is varied randomly for each strategy variation number in the interval [0, ε = 0.02]. The lines styles are used to clear up the tracking of each simulation.

Conclusions

The efficiency of damage retention provides a monotonically decreasing function in which a 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 the population. However, the strategies that started at different altruist values, ended up optimizing in a local fashion rather than approaching a global minima of the cost function.

Distance vs Division Strategy

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

Optimal Reproduction Success represents Local Minima of Cost Function

Strategies were adopted for the continuous search for 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 the 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 the cost function. At the same time, when cells opted for a minimum value of cost function, the optimal reproduction success trapped for a 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 the 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 fewer daughters with a 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 the cost function.

Acknowledgement

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

Appendix 1

A mathematical model for yeast cell growth and division processes

The 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 the 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	the rate of degradation of intact proteins	ln2	the 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	the rate of degradation of damaged proteins	ln2	the 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)

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

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

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

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

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

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

616 **The general behaviour of Model**

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

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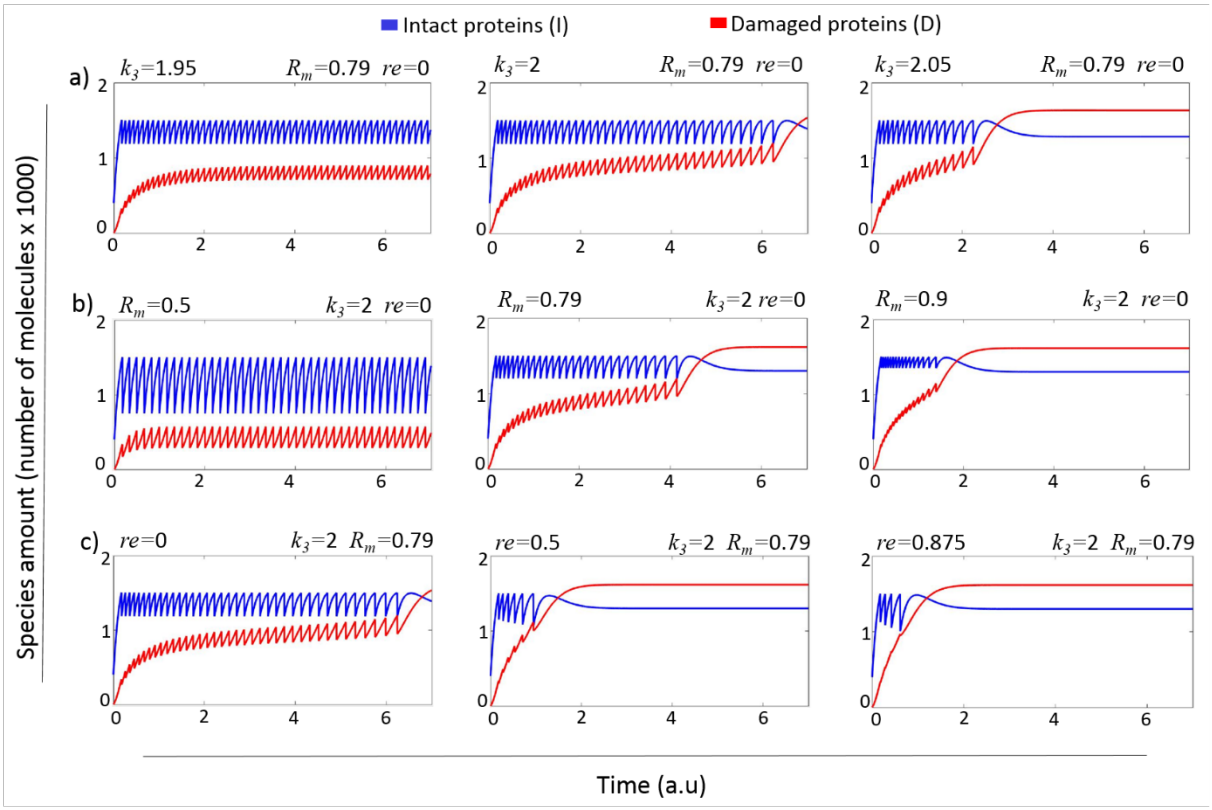

Figure S1: Intracellular species dynamics of a single cell a) damage accumulation rates b) size of the mother and c) retention coefficients. Red and blue lines describe the dynamics of damaged and intact cellular components, respectively. re(g) = Re (a constant).

Pedigree-Tree Diagram

Pedigree-tree model follows the 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 a mother while the budded cell is considered as a daughter cell. Now, mother cell and daughter cell both undergo 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. The population is discretely distributed over the total intact and damage portions of each cell as described in the main text.

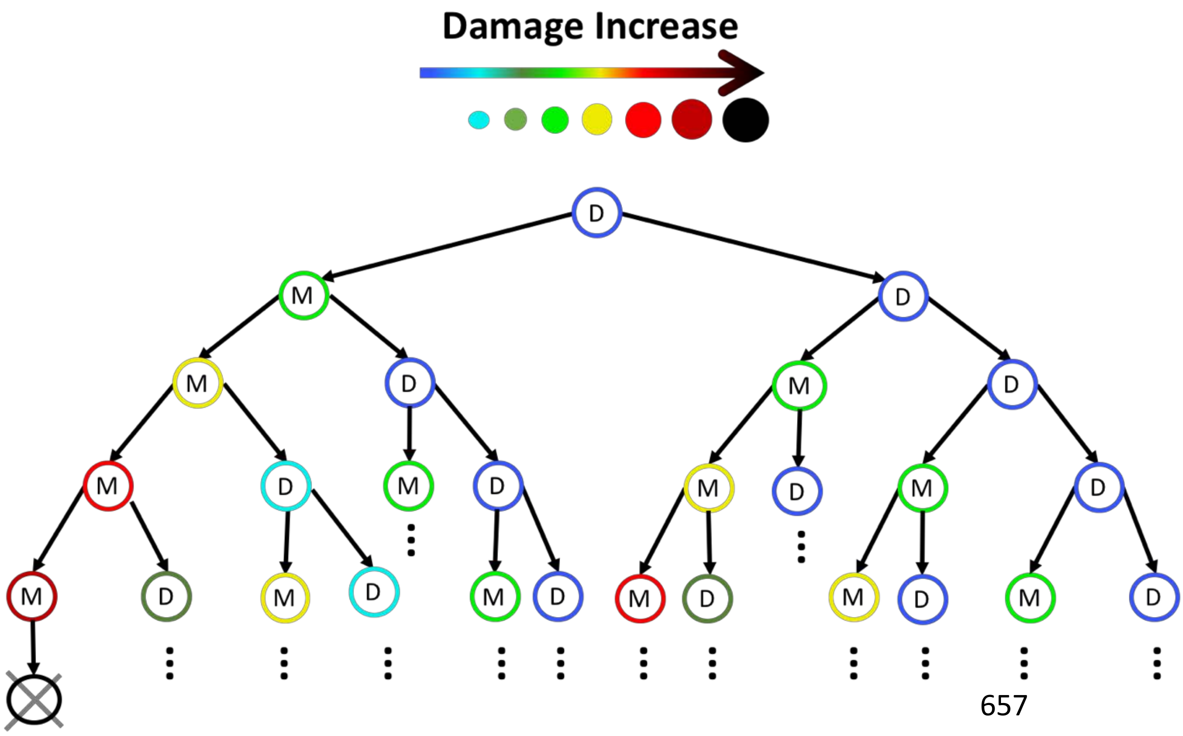

Figure S2: Schematic representation of pedigree-tree model. Each circle represents a cell. D stands for daughter whereas M stands for mother. Blue color is damage free cells while black color is for dead cells (no more divisions possible).

Appendix 2

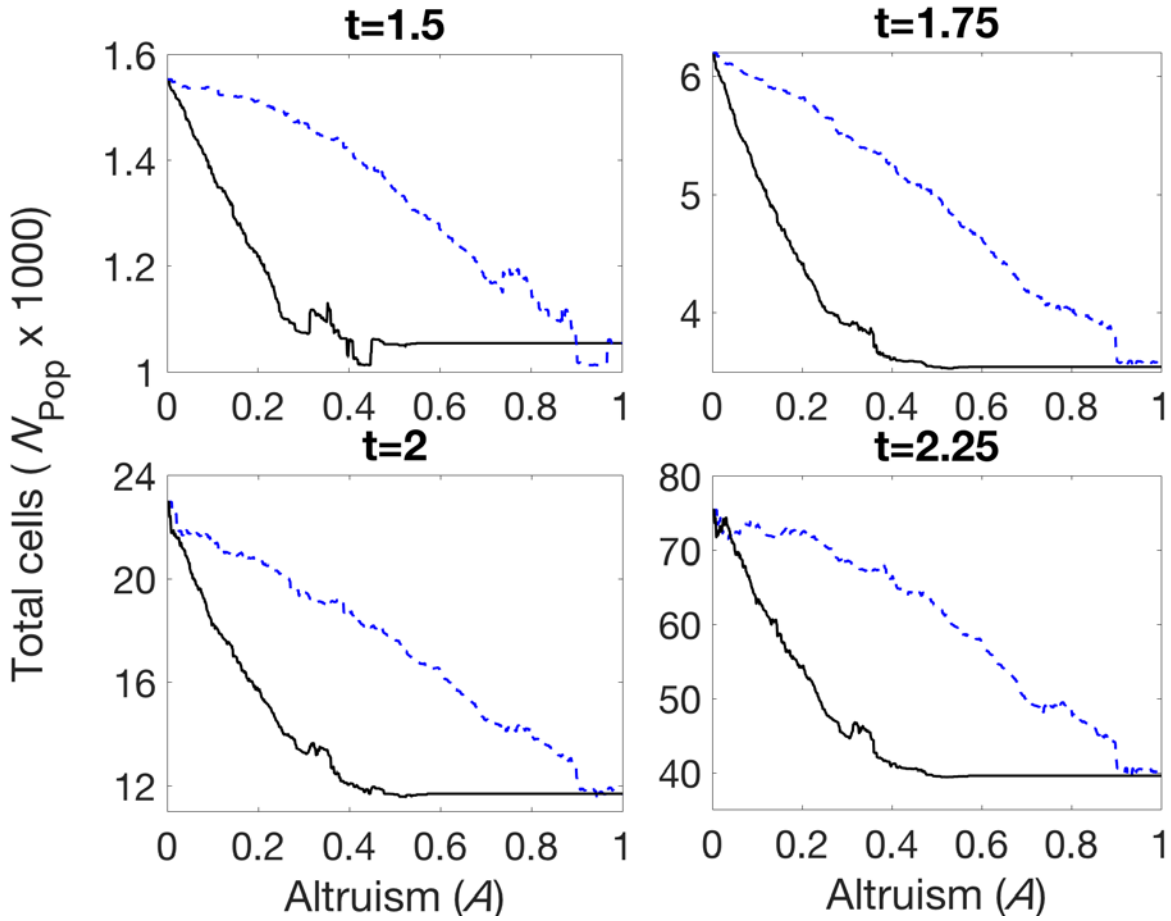

Figure S3: Total number of cells against the altruism values at four simulation times t = 1.5, 1.75, 2, 2.25. Lines represents population with distance strategy whereas the dashed lines represent the population with division strategy.

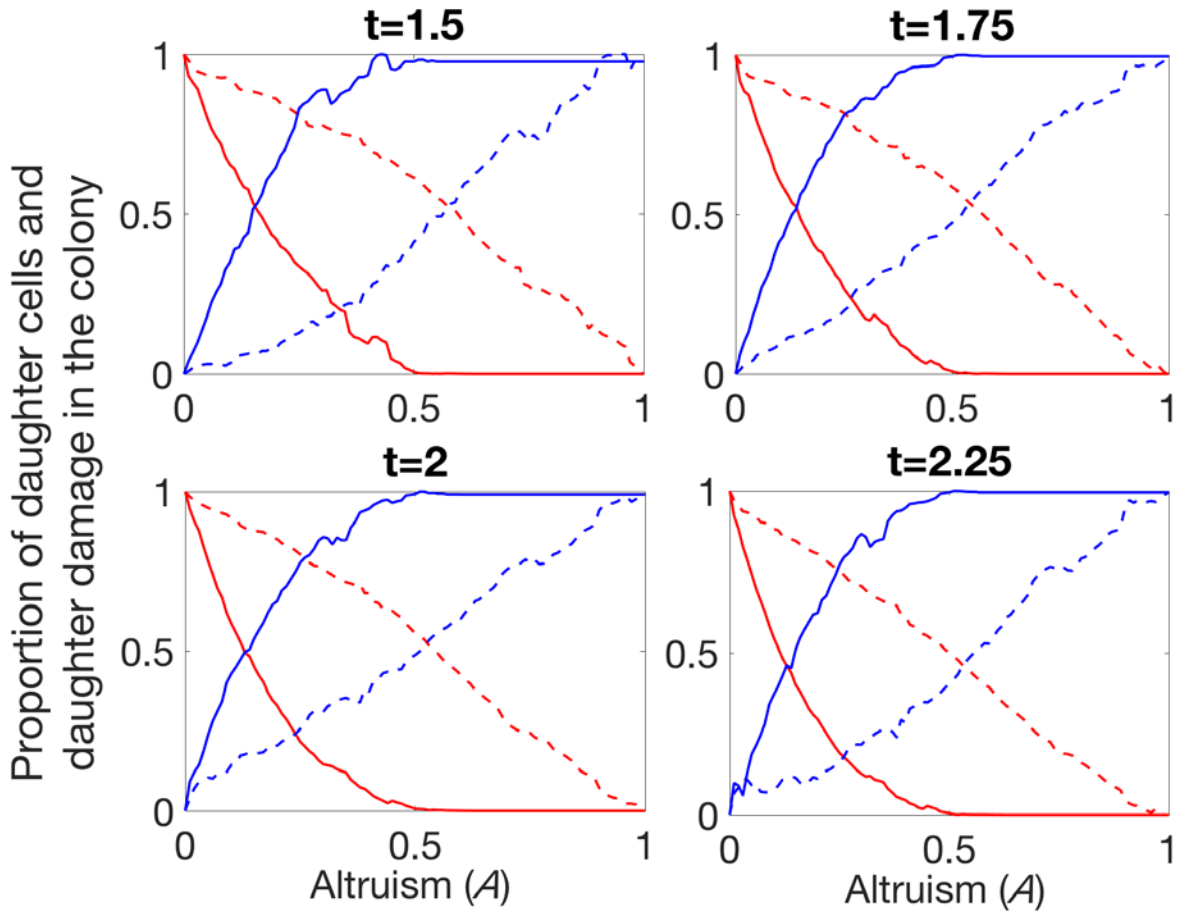

Figure S4: Proportion of daughter cells and their damage in the population for time t =1.5, 1.75, 2 and 2.25. The continuous lines represent distance strategy while dashed lines represent division strategy. The lines moving from 0 to 1 are the daughter cells proportion while the lines moving from 1 to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

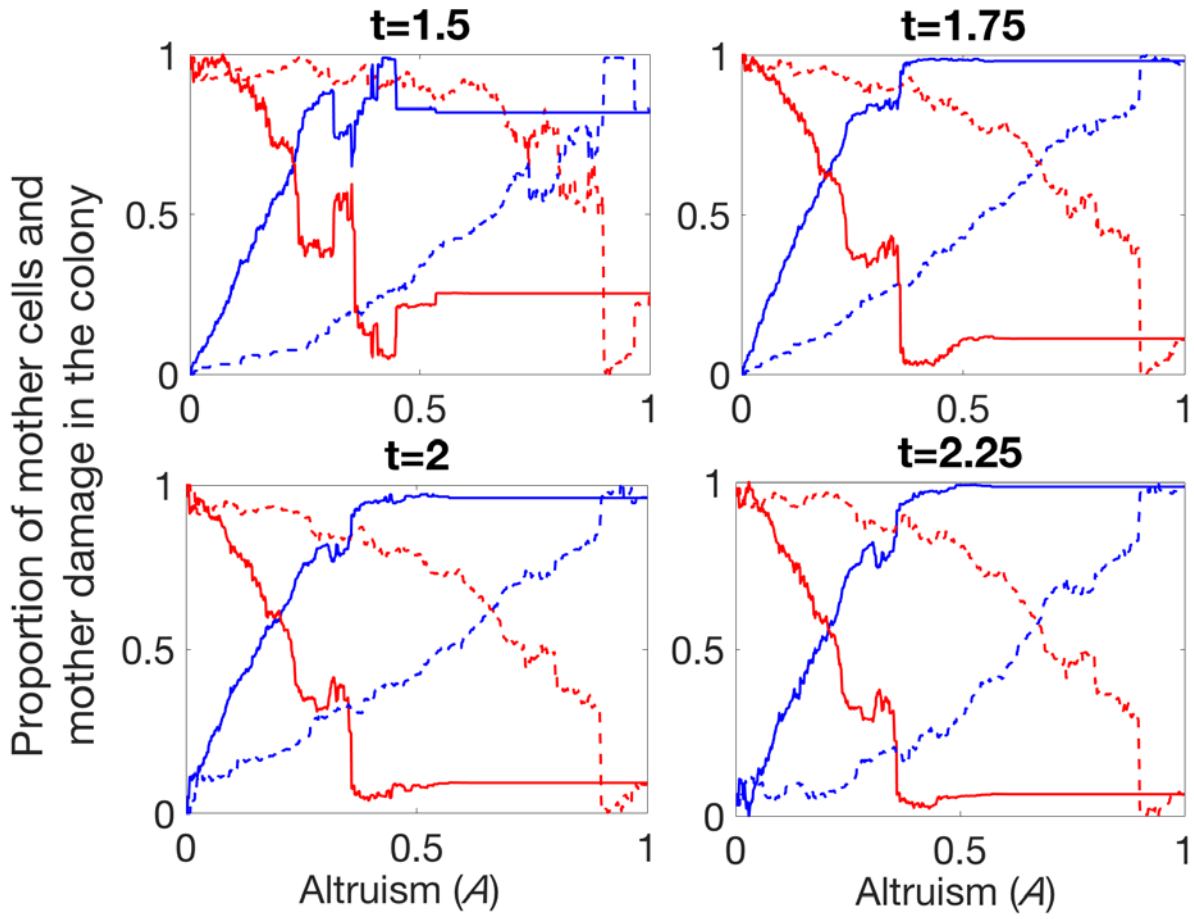

Figure S5: Proportion of mother cells and their damage in the colony at time t =1.5, 1.75, 2 and 2.25. The continuous lines represent distance strategy while dashed lines represent division strategy. The lines moving from 0 to 1 along y-axis are the mother cells proportion while the lines moving from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

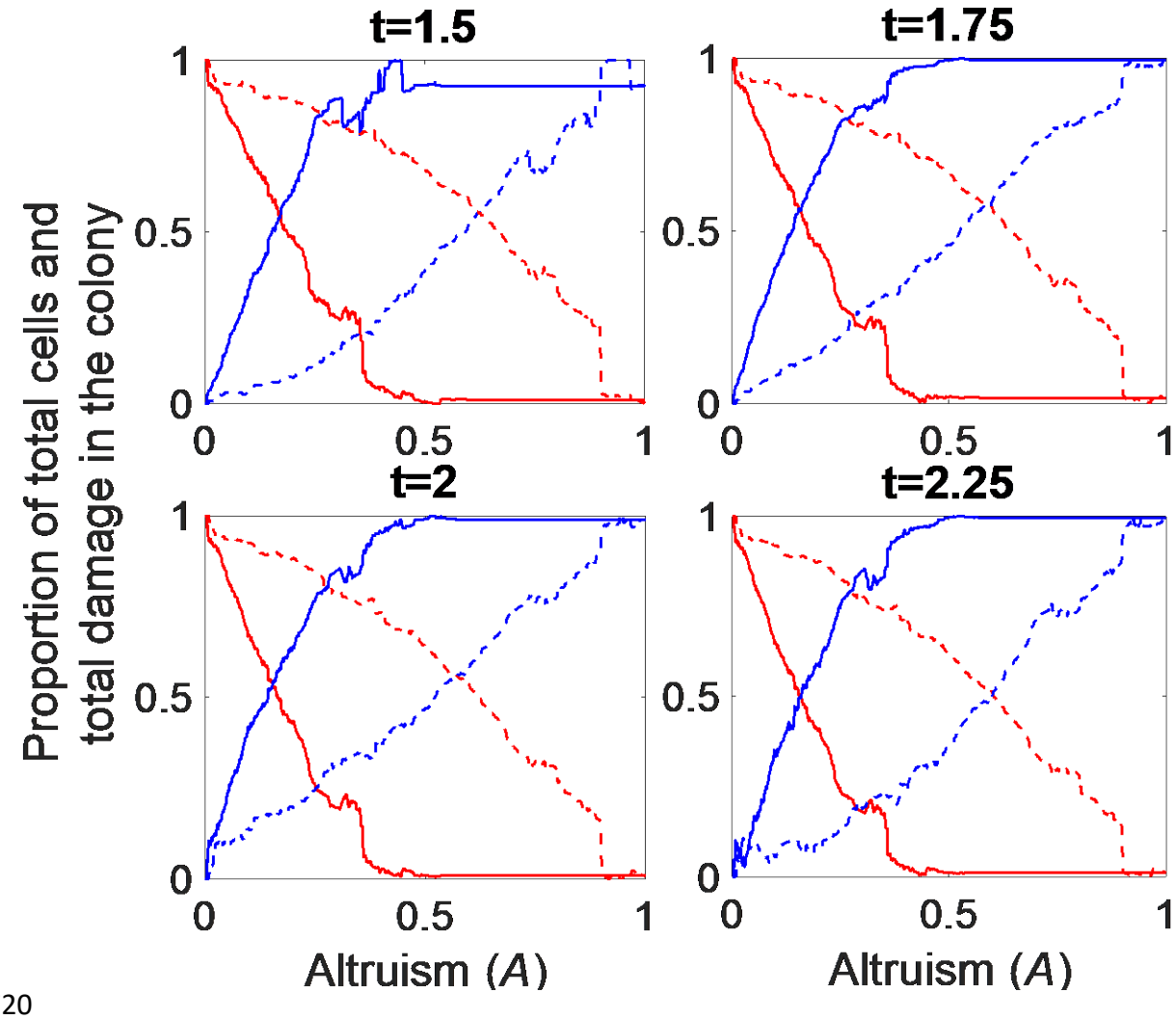

Figure S6: Proportion of total cells and their damage in the population for time t =1.5, 1.75, 2 and 2.25. The continuous lines represent distance strategy while dashed lines represent division strategy. The lines moving from 0 to 1 are the total cells proportion while the lines moving from 1 to 0 are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

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Adaptive damage retention mechanism enables healthier yeast population

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Highlights

- retaining more damage by a yeast cell during the early divisions increases the number of healthy daughters in the population
- 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 damage
- fluctuations in the cost function allow yeast cell to continuously vary its strategy, suggesting that optimal reproduction success is a local minimum of the cost function

Keywords: yeast, asymmetrical division, damage retention, dynamical modelling, pedigree-tree model

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 a 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 the 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.

56 *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 a 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

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Introduction:

Aging is a conserved scale-invariant phenomenon that exploits the 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 evolutionarily 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 al, 1994; Sinclair et al, 1998a; Sinclair et al, 1998b). This

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

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

Optimal reproduction success is a term used to define the replicative lifespan of a yeast cell that has evolved the organelles to adopt the finest route for the healthy survival of the yeast population. A success of the population is in the asymmetric distribution of damage during the cell division that ensures the low amount of damage in the progeny and its long replicative lifespan (Chao et al., 2016; Nyström and Liu, 2014). However, healthy progeny and long replicative lifespan are inversely proportional to each other since it is asserted that, during the replicative lifespan, yeast strains sacrifice their long-term survival over the health of their progeny by retaining the aging factors (Aguilaniu et al., 2003; Hill et al., 2017; Kirkwood and Rose, 1991). Therefore, it is interesting to find a strategy for optimal retention of aging factors in such a way that yeast population accumulates less damage in the living cells and provides maximum population.

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

(Chao et al., 2016). Moreover, natural selection adapts the protective mechanism into the subsequent progeny in a genetically controlled manner. 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 sequestered 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 previous 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 the yeast cell. However, the exact mechanisms of damage retention 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 the 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 the discrete-continuous model. We provide here an abbreviated summary (for detailed derivation and parameters see Appendix 1).

Each cell increases its intact (I) and damaged (D) components during the growth process (Eq. 1) and asymmetrically distributes these components between mother R_m (Eq.2) and daughter R_d (Eq.3) cells during the division process.

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

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

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

The damage retention mechanism allows mother cell to retain part of the damaged 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 a 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, the 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 the 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

$$RE_{div}(g+1) = 1 - \frac{g^n}{g^n + \alpha^n} \tag{4}$$

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).

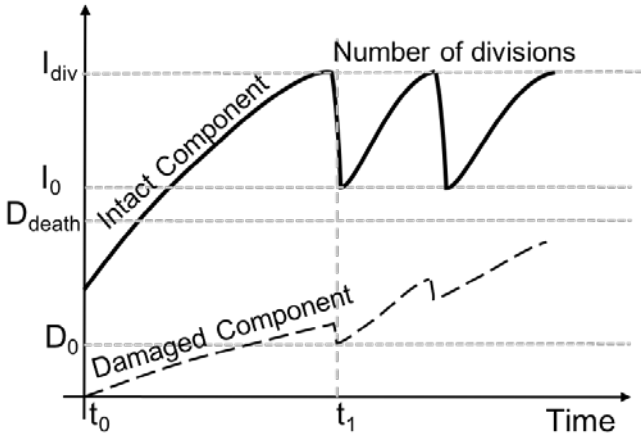

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Figure 1: Division strategy: Efficiency in damage retention decreases with the increase in number of divisions. Mother cell is able to retain maximum damage in the beginning but loses its efficiency of damage retention as the number of divisions increases. 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}.

185 Distance Strategy

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

$$RE_{dist}(g+1) = 1 - \frac{R_t^n(g)}{R_t^n(g) + \alpha^n} \tag{5}$$

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

$$R_t = \frac{\tau_I}{\tau_D} \tag{6}$$

192 Due to the increase in damage during the replicative lifespan of a cell, the retention becomes
193 more difficult. After every division cell anticipates the possibility of the next division. If the
194 damage is high enough such that the 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 the ratio between remaining distance and the mean rate of change in the corresponding intact ($Avg(\dot{I})$) and damage ($Avg(\dot{D})$) component.

$$\tau_I = \frac{I_{div} - I_g}{Avg(\dot{I})}, \tau_D = \frac{D_{death} - D_g}{Avg(\dot{D})} \quad (7)$$

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 a 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 the next division by the above-defined procedure (see Eq. 5). 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 the next division becomes possible.

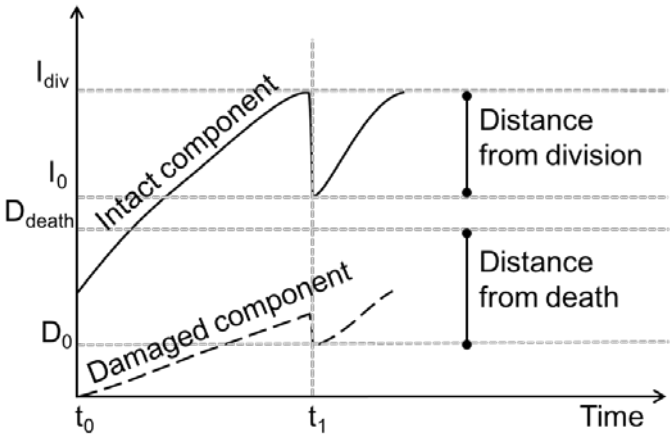


Figure 2: Mother cell decreases damage retention by anticipating her next reproduction success. Cell increases its initial intact and damage component from t_0 and divides at time t_1. The intact component decreases from its threshold I_{div} to $I_{g=0}$ after division and the damaged component decreases 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. (8). The parameter A is based on the consequences of the actions performed for the replicative lifespan of a mother cell and for the 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. (4) and (5). 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 a defined strategy (distance or division strategy). Secondly, altruism parameter is used to alter the strategy. 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:

$$re(A, g) = RE(g) + 2\left(A - \frac{1}{2}\right)\left((1 - A)RE(g) + A(re_{max} - RE(g))\right) \qquad (8)$$

The parameter re is the 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 the complete population with variable retention parameter (Eq(1-3) and Appendix 1). The cellular growth is represented by an increase in the number of intact and damage components and the division is represented by the asymmetric distribution of growth components (intact and damage) between mother and daughter cells. The 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 the 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 the 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 a 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 the damaged component is written as,

$$P(A,D) = \frac{\sum_{D=a}^{D=b}\left(N_{daugh}(A,D) + N_{mot}(A,D)\right)}{N_{pop}(A)}. \quad (9)$$

where a and b are the minimum and maximum accumulated damage, respectively. 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:

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

$$P_{daugh}(A,D) = \frac{\sum_{D=a}^{D=b} N_{daugh}(A,D)}{\sum_{D} N_{daugh}(A,D)}. \quad (10)$$

Cost Functions

The calculation of cost function is performed at the end of the discrete-continuous model while the objective is to find the minimum cost function so that smallest amount of damage and a 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, $\tilde{N}$ ($\sum_{D_{\text{daugh}}} D_{\text{daugh}}(A)$), and difference between normalized maximum number of daughter cells during $A \in [0,1]$, i.e. equals to 1, and normalized alive daughter cells, $\tilde{N}(N_{\text{daugh}}(A, D))$, present in the system at any time $t = t_0$.

$$C_{daugh}(A) = \tilde{N}\left(\sum_{D_{daugh}} D_{daugh}(A)\right) + \left(1 - \tilde{N}\left(\sum_{D} N_{daugh}(A,D)\right)\right) \quad (11)$$

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,

$$C_{mot}(A) = \tilde{N}\left(\sum_{D_{mot}} D_{mot}(A)\right) + \left(1 - \tilde{N}\left(\sum\nolimits_{D} N_{mot}(A, D)\right)\right) \quad (12)$$

Damage in a mother cell is denoted by D_{mot} and a 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,

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

Variation in Altruism

Altruism parameter A is varied deterministically as well as stochastically. The deterministic way is quite straightforward as it formulates the normalized distribution of cells at discrete values of A and calculates 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 using Eqs. (11), (12) and (13) which involves simulation of the 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 a random value in the interval of $[0, \varepsilon]$.

$$A_{i+1} = A_i \pm rand(0, \varepsilon)\, sgn(C(A_{i-1}) - C(A_i)) \quad (14)$$

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

$$\sum_{i=S_N+l}^{S_N+j+l} \left|A_{i-j} - A_{i-(j+k)}\right| < \varepsilon. \quad (15)$$

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 the 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 a 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 a 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 with each value of altruism that is followed according to their intrinsic behaviour represented by Eqs. (4) and (5). 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 (4) and (5) 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 are given by altruist parameter *A with* $A_{max} = 1$. It is interesting to note that both strategies provide the same behaviour at the endpoints of *A*, i.e. 0 and 1 (Figure 3).

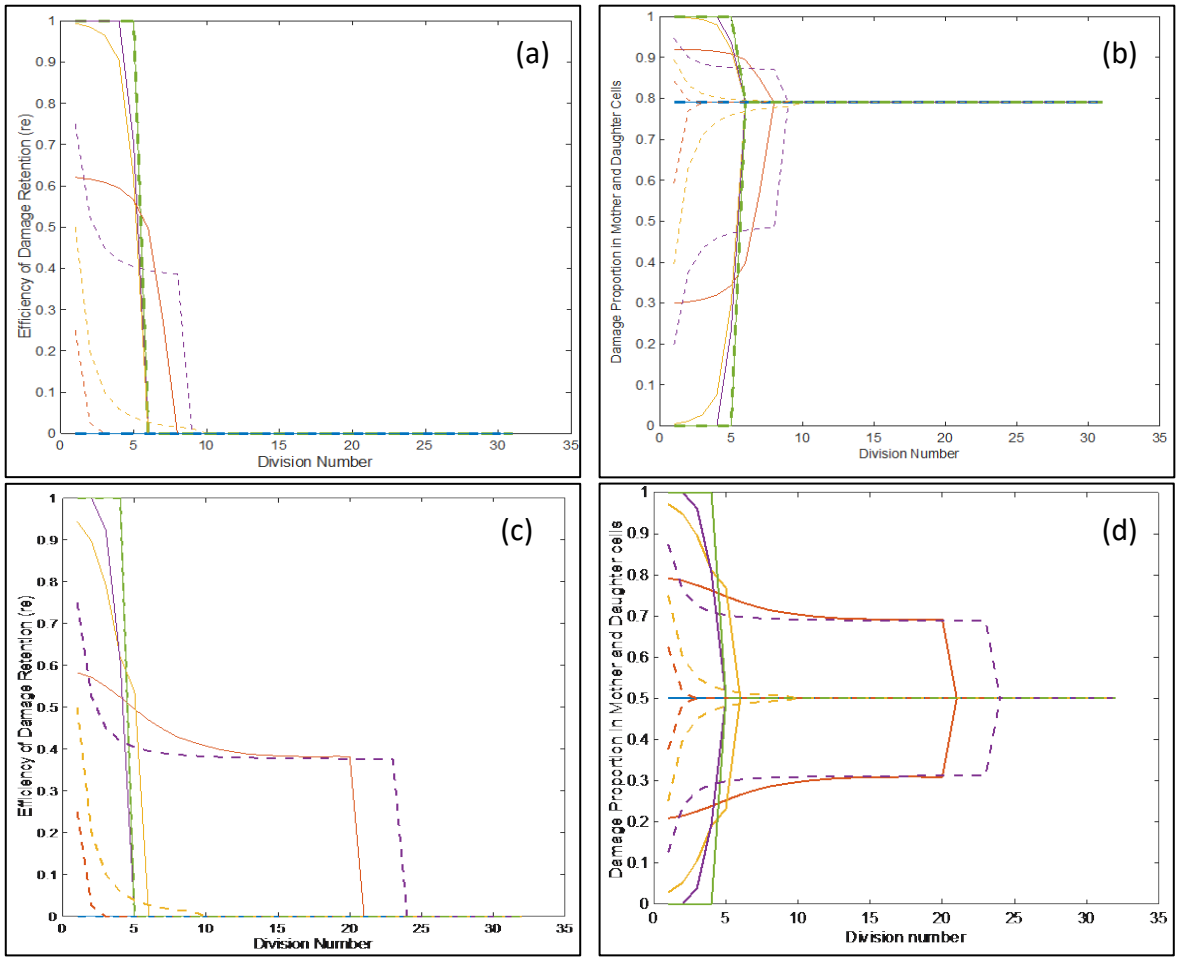
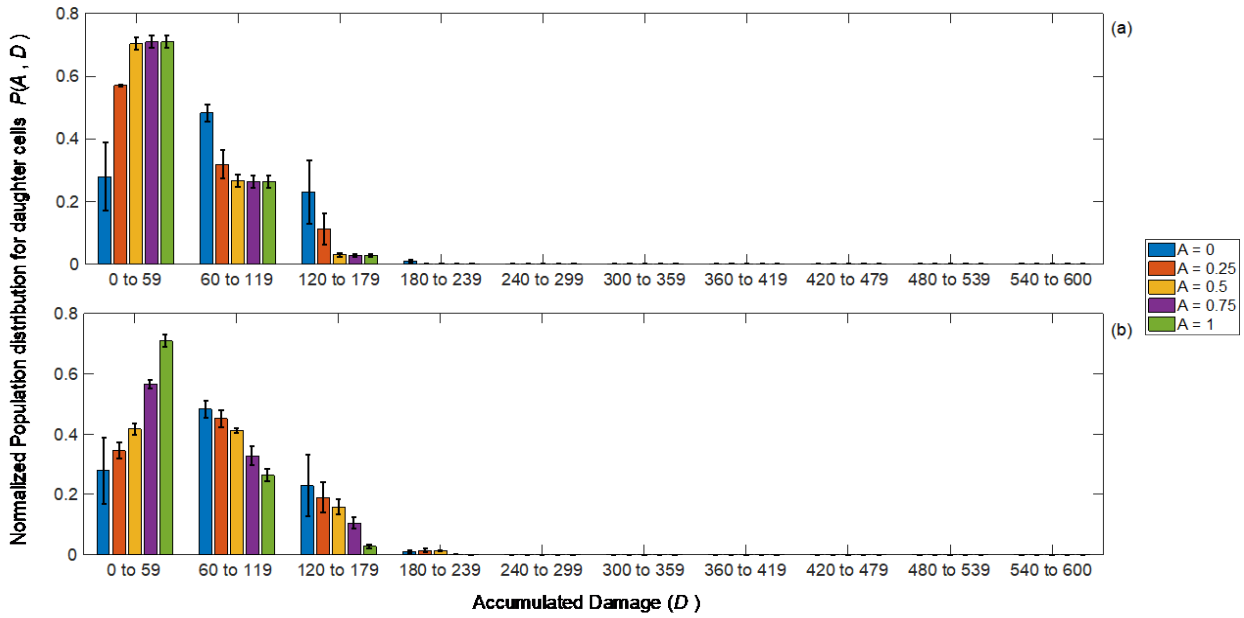


Figure 3: Damage retention efficiency (RE) for altruist parameter values A = 0 (blue), 0.25 (red), 0.5 (yellow), 0.75 (violet) and 1 (green). The dashed lines represent division strategy and continuous lines represent distance strategy. Colours are drawn to match the altruist parameter values between 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 the 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 a 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.



356

357 *Figure 4: Mean and standard deviation of the daughter distribution of damaged proteins by using*
358 *distance (a) and division (b) strategies, see Eq. (11). Mean of the distribution is taken for the simulation*
359 *time t = 1.5, 1.75, 2, 2.25. The accumulated damage in the span of 600 is clustered into subintervals*
360 *each of length 60.*

361 The population distribution of daughter cells is present only in the first three clusters of
362 damage component (Figure 4). In the first cluster, $D_{daugh} \in [0, 59]$, the mean proportion of
363 cells, $P(A, D)$, increases when altruism A goes from 0 to 1 while the succeeding clusters show
364 a reverse behaviour. The error bars represent the standard deviation of the mean distribution
365 values for simulation time t = 1.5, 1.75, 2, 2.25. For A = 0, the standard deviation is quite high
366 because the cell proportion was higher in the first and third clusters ($P(A = 0, D = [0, 60)) \approx$
367 0.38) during the early simulation time, t = 1.5. However, it decreased to below 0.2 in the later
368 simulation time, t = 2.25. Moreover, for $A \geq 0.5$, the proportion of cells with least damage is
369 much high and have a very small standard deviation.

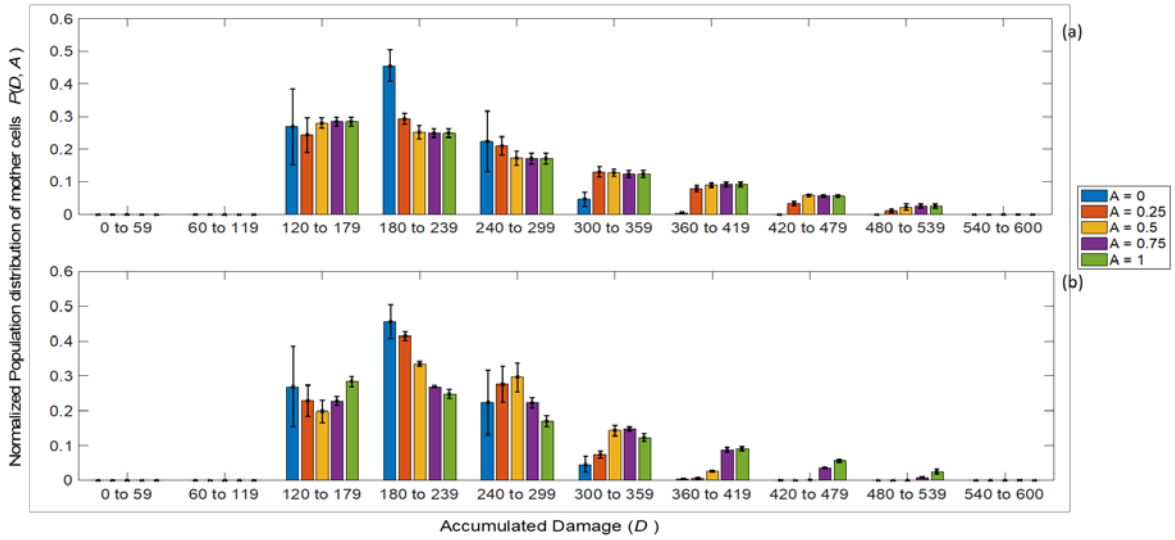


Figure 5: Mean and standard deviation of the mother distribution of damaged proteins by using distance (a) and division (b) strategies, see Eq. (10). Mean of the distribution is taken for the simulation time t = 1.5, 1.75, 2, 2.25. The accumulated damage in the span of 600 is clustered into subintervals 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 4b). 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 the 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 a 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 the low damage.

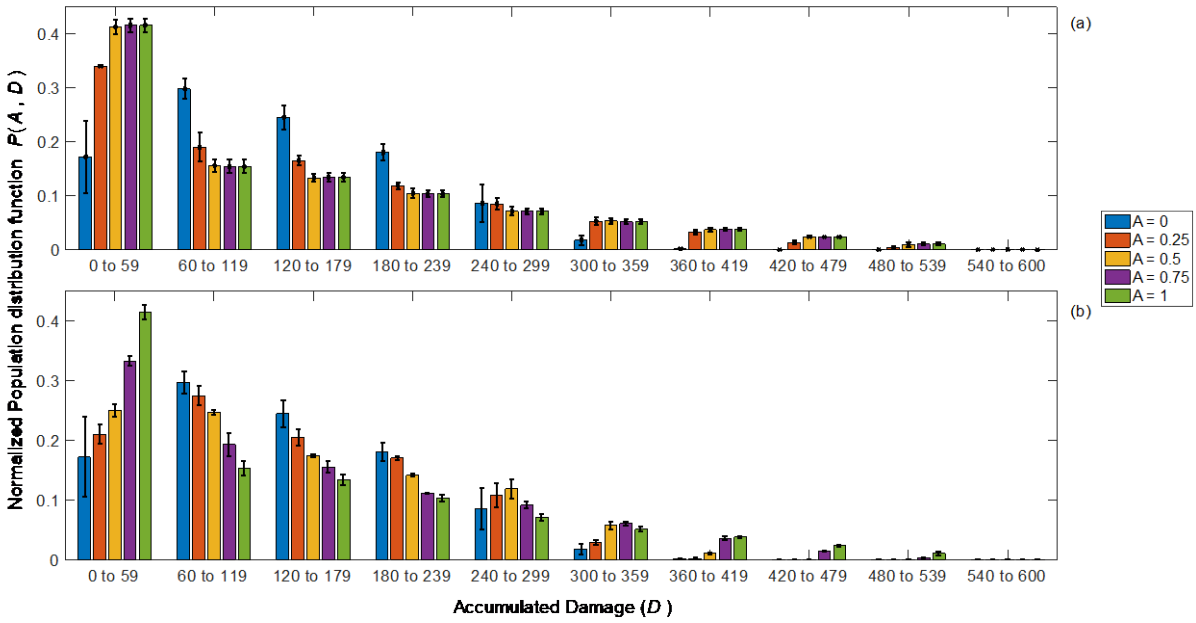


Figure 6: Mean and standard deviation of the normalized population distribution of damaged proteins by using (a) distance and (b) division strategies as defined in Eq. (9). Mean of the distribution is taken for the simulation time t = 1.5, 1.75, 2, 2.25. The accumulated damage in the span of 600 is clustered 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 a cost for predefined values of

411 altruism *A* whereas the stochastic model tracks the minimum value for cost function by taking
412 random steps towards the lowest value of the cost function.

413 ## Deterministic outcomes

414 The deterministic modelling approach is used to evaluate the cost functions by varying the
415 altruist parameter *A* between 0 and 1 with the step size $\Delta A = 10^{-3}$. The results are obtained for
416 the cost functions defined in Eqs. (11), (12) and (13) and are presented in Figure 7 (for
417 daughter cells), in Figure 8 (for mother cells) and in Figure 9 (for a total number of alive cells)
418 respectively each at four different times t = 1.5, 1.75, 2 and 2.25. Computationally, it becomes
419 very expensive to go beyond the time point t = 2.25. Therefore, this is the maximum time point
420 chosen. Other time points are chosen to understand the behaviour of cost function over the
421 altruism parameter *A*. The cost function is modelled by taking this fact into consideration that
422 the replicative lifespan decreases with the increase in damage retention by the cell. In such a
423 scenario, it would be interesting to see the effect of replicative lifespan over the damage
424 accumulation in the population.

425 Altruistic effects on the daughter cells provide a time-variant response to its cost function.
426 Due to asymmetric division, mother cells require less time to reproduce than the daughter
427 cells. Therefore, the longer lifespan of mother cells will quickly increase the population;
428 however, in case of low damage retention, high amount of damage is passed on to the newly
429 born daughter cells. In case of distance strategy, this phenomenon quickly increases the
430 damage in the population and raises the cost function to a high level during the early time, i.e.
431 t = 1.5 and 1.75 (Figure 7, Figure 8 and Figure 9). However, with the progression of time, i.e. t
432 goes to 2 and 2.25, the cost function gives a surprising outcome by replacing the high values
433 with the lower ones, exposing that for large time scale, population size can dominate over the
434 total damage present in the population. For instance, the distance strategy (continuous lines)
435 near A = 0.3, the cost function that was at maximum, i.e. C_{daugh} = 1.2 at time t = 1.5, goes below
436 the value of C_{daugh} = 1 at time t = 2.25.

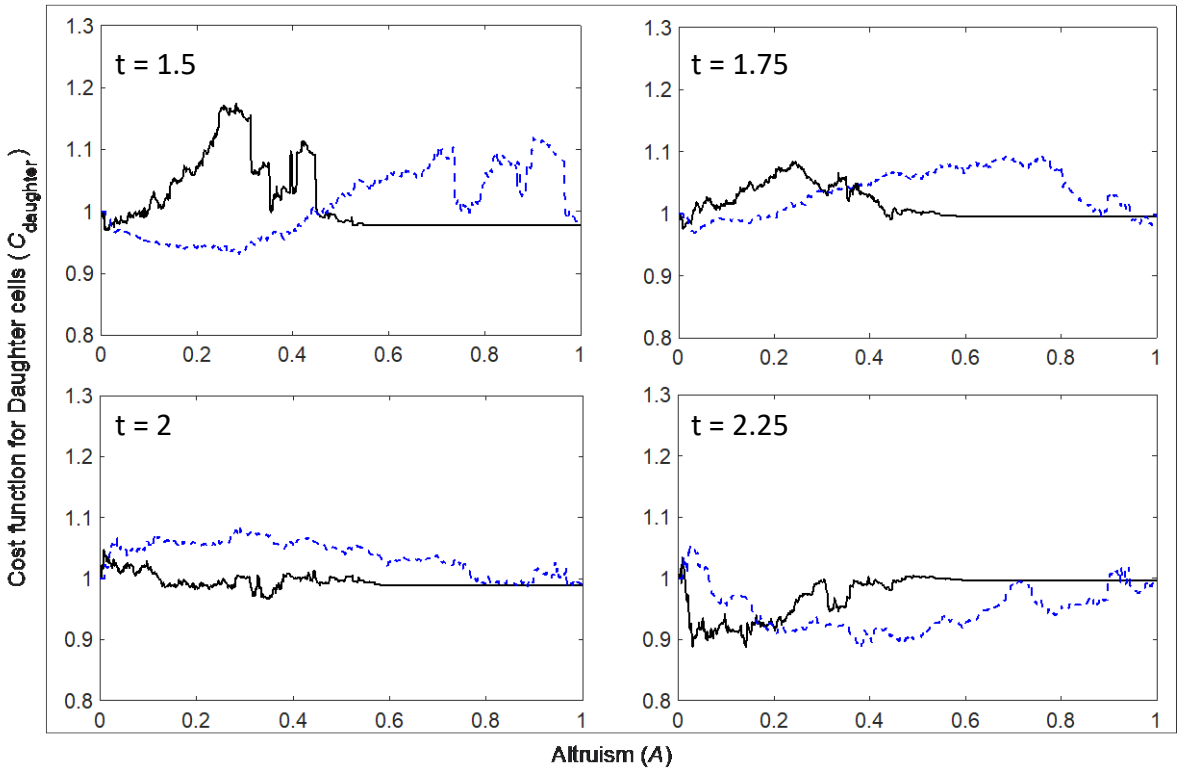
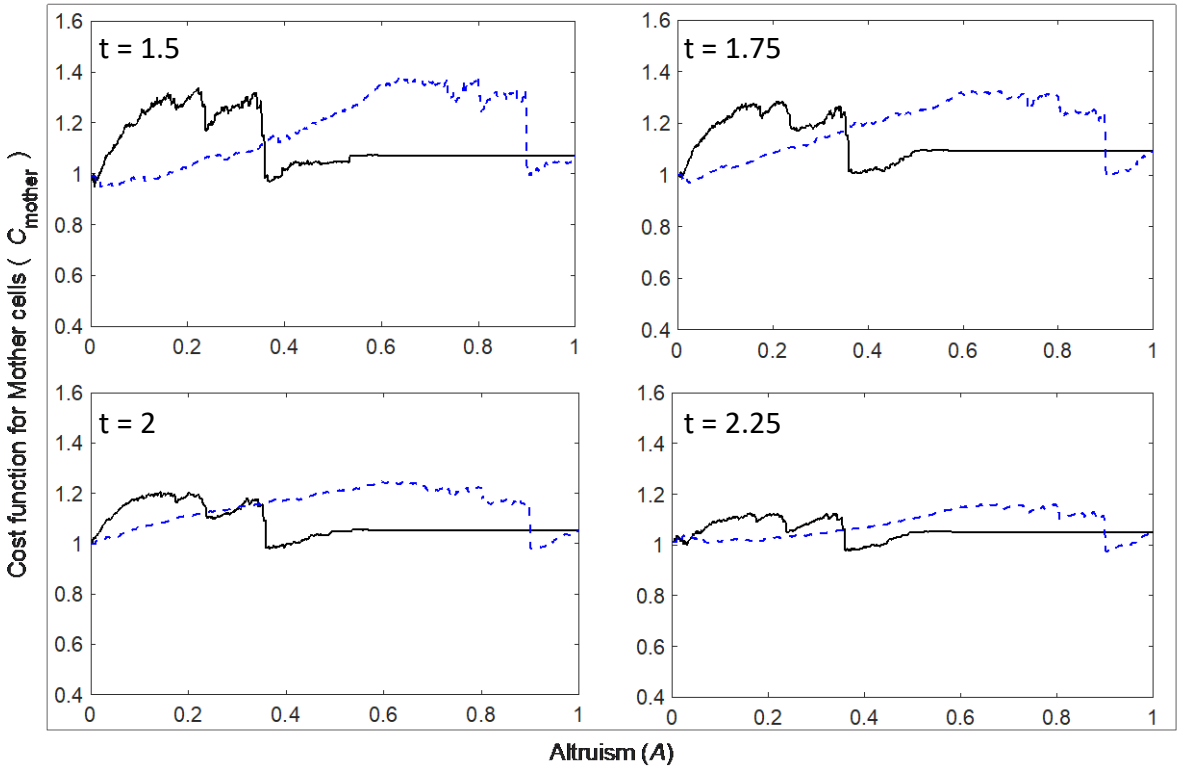


Figure 7: Cost function for the distance (continuous lines) and division (dashed lines) strategies of daughter cells C_{Daugh} at four time-points t = 1.5, 1.75, 2 and 2.25 against the altruist values A in the interval [0,1] and step size 0.001. The cost function is defined in Eq. (11) while the deterministic model used to simulate the results is described in Appendix 1.

Division strategy provides the 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 S2). For a longer period of time, t = 2.25, both strategies decrease their cost function for early values of A, however, their optimal reproduction success varies.



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

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

464

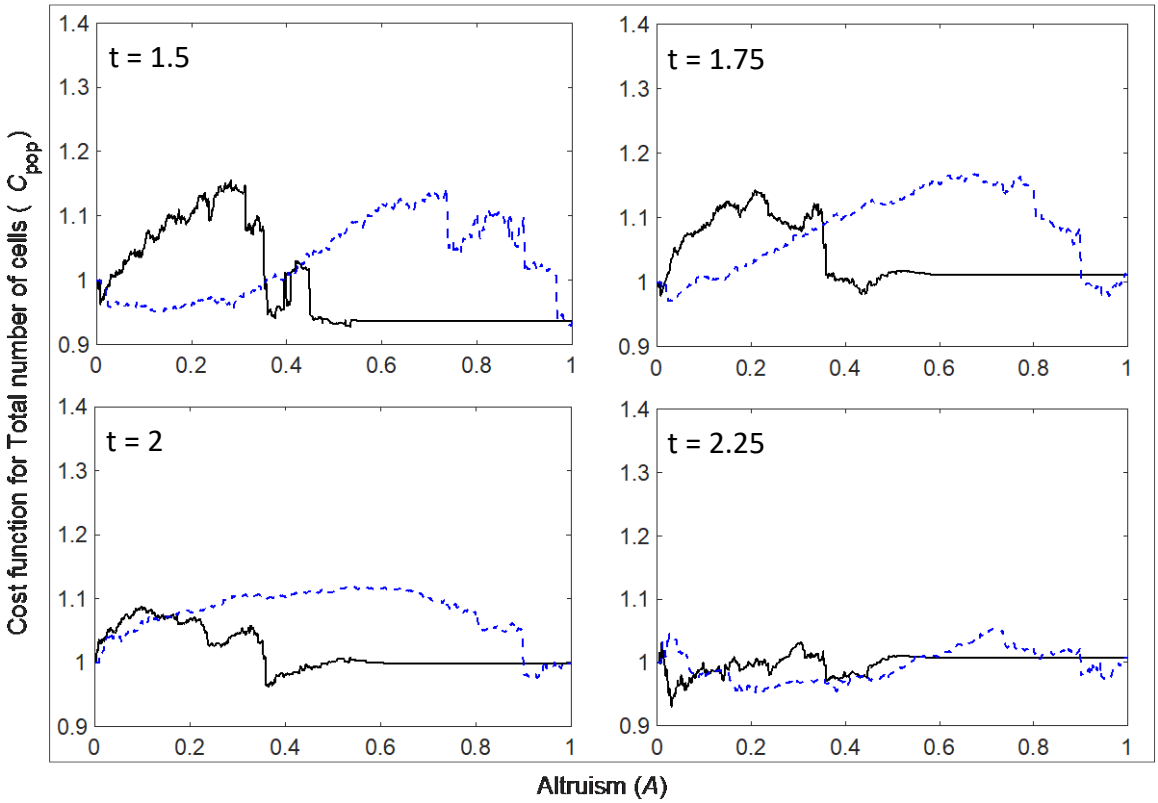


Figure 9: Cost function for the distance (continuous lines) and division (dashed lines) strategies of total cells C_{pop} at four time-points t = 1.5, 1.75, 2 and 2.25 against the altruist values A in the interval [0,1] and step size 0.001.

Stochastic Simulations

Stochastic settings are implemented to observe the behaviour of the 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. (14). 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 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

$$\sum_{i=S_N+l}^{S_N+j+l} \left|A_{i-j} - A_{i-(j+k)}\right| < \varepsilon \qquad (15)$$

The index values are $j = k = 10$ and the epsilon $\varepsilon = 0.02$. The parameter epsilon provides the maximum possible variation in the altruism value and is used in the Eq. (14). The stopping criteria are 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 the 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 10b). 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.

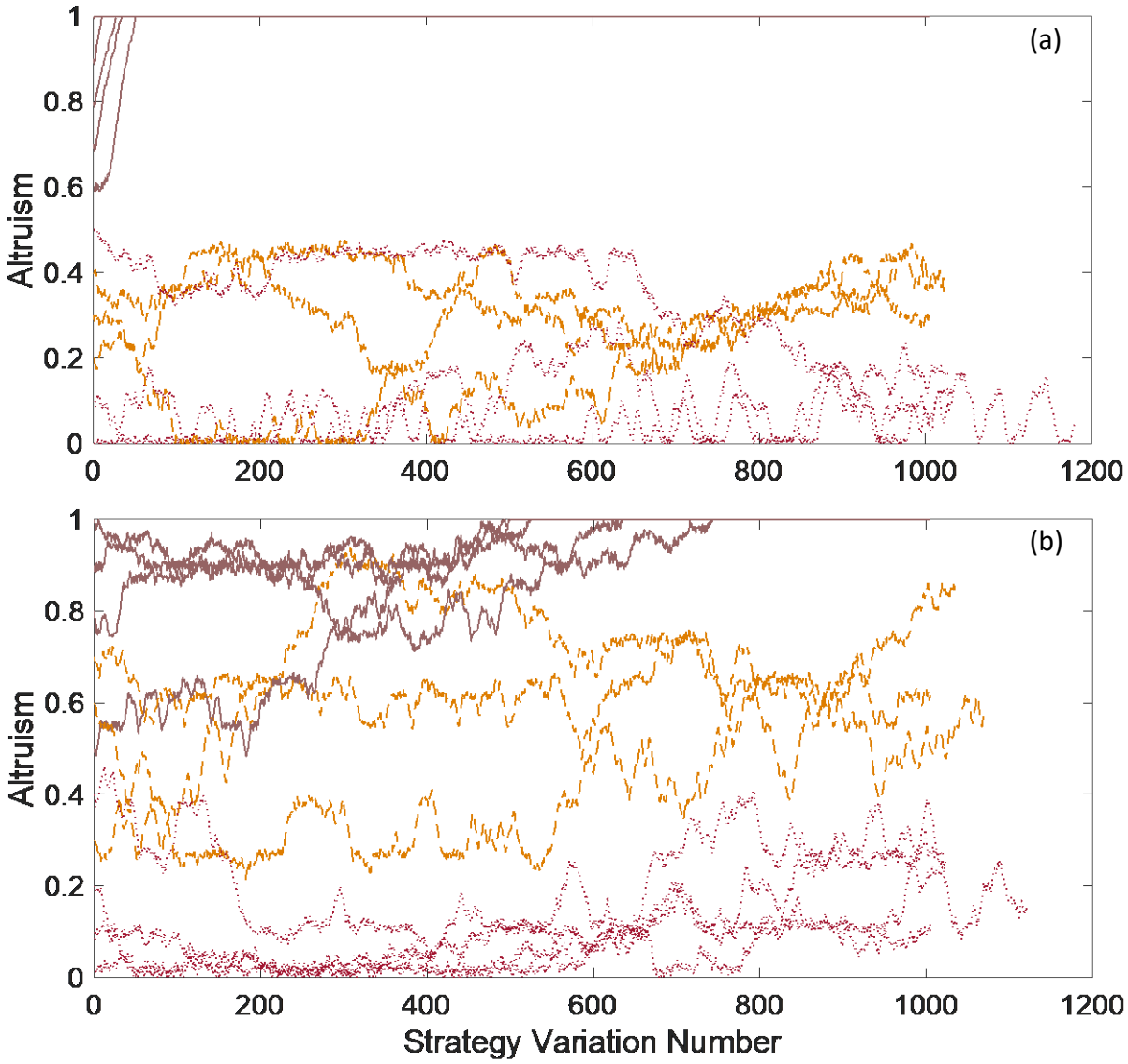


Figure 10: Stochastic simulations of (a) distance and (b) division strategies at time t = 1.5. The altruism parameter A is varied randomly for each strategy variation number in the interval [0, ε = 0.02]. The lines styles are used to clear up the tracking of each simulation.

Conclusions

The efficiency of damage retention provides a monotonically decreasing function in which a 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 the population. However, the strategies that started at different altruist values, ended up optimizing in a local fashion rather than approaching a global minima of the cost function.

Distance vs Division Strategy

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

Optimal Reproduction Success represents Local Minima of Cost Function

Strategies were adopted for the continuous search for 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 the 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 the cost function. At the same time, when cells opted for a minimum value of cost function, the optimal reproduction success trapped for a 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 the 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 fewer daughters with a 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 the cost function.

Acknowledgement

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Appendix 1

A mathematical model for yeast cell growth and division processes

The 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 the 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	the rate of degradation of intact proteins	ln2	the 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	the rate of degradation of damaged proteins	ln2	the 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)

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

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

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

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

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

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

616 **The general behaviour of Model**

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

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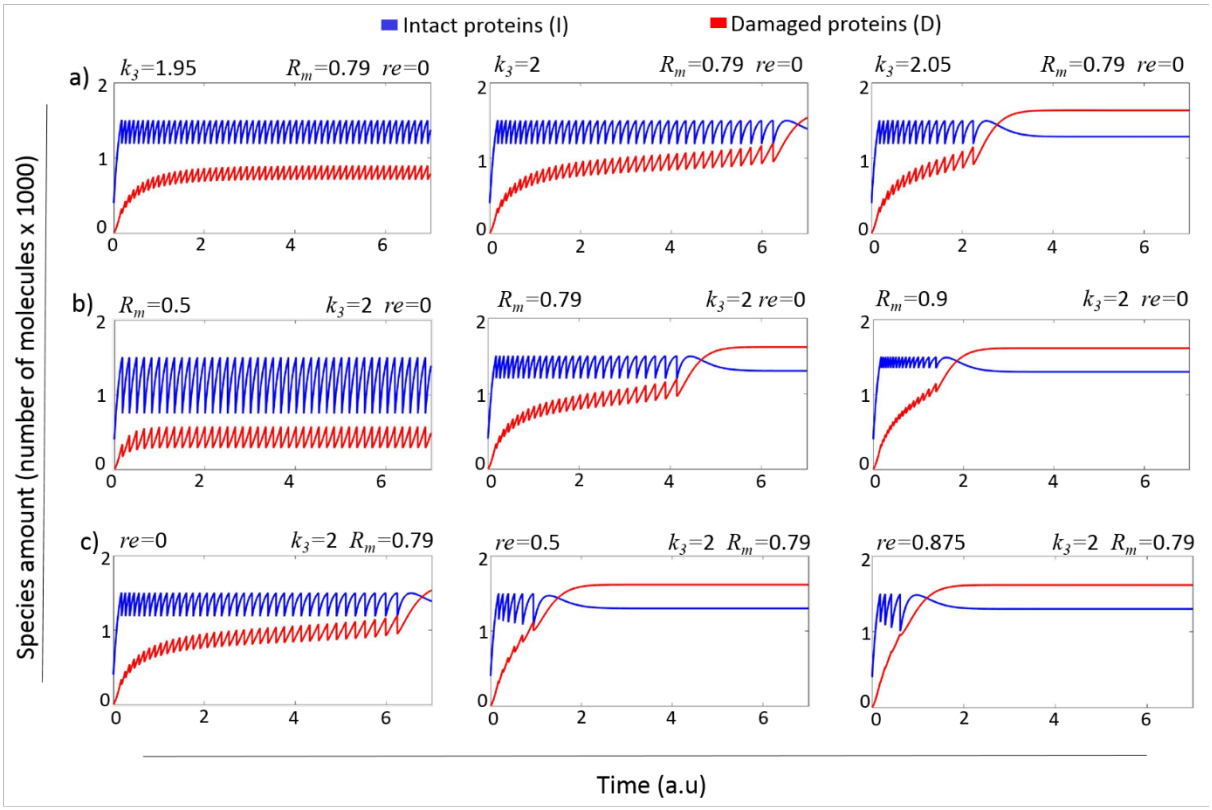

Figure S1: Intracellular species dynamics of a single cell a) damage accumulation rates b) size of the mother and c) retention coefficients. Red and blue lines describe the dynamics of damaged and intact cellular components, respectively. re(g) = Re (a constant).

Pedigree-Tree Diagram

Pedigree-tree model follows the 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 a mother while the budded cell is considered as a daughter cell. Now, mother cell and daughter cell both undergo 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. The population is discretely distributed over the total intact and damage portions of each cell as described in the main text.

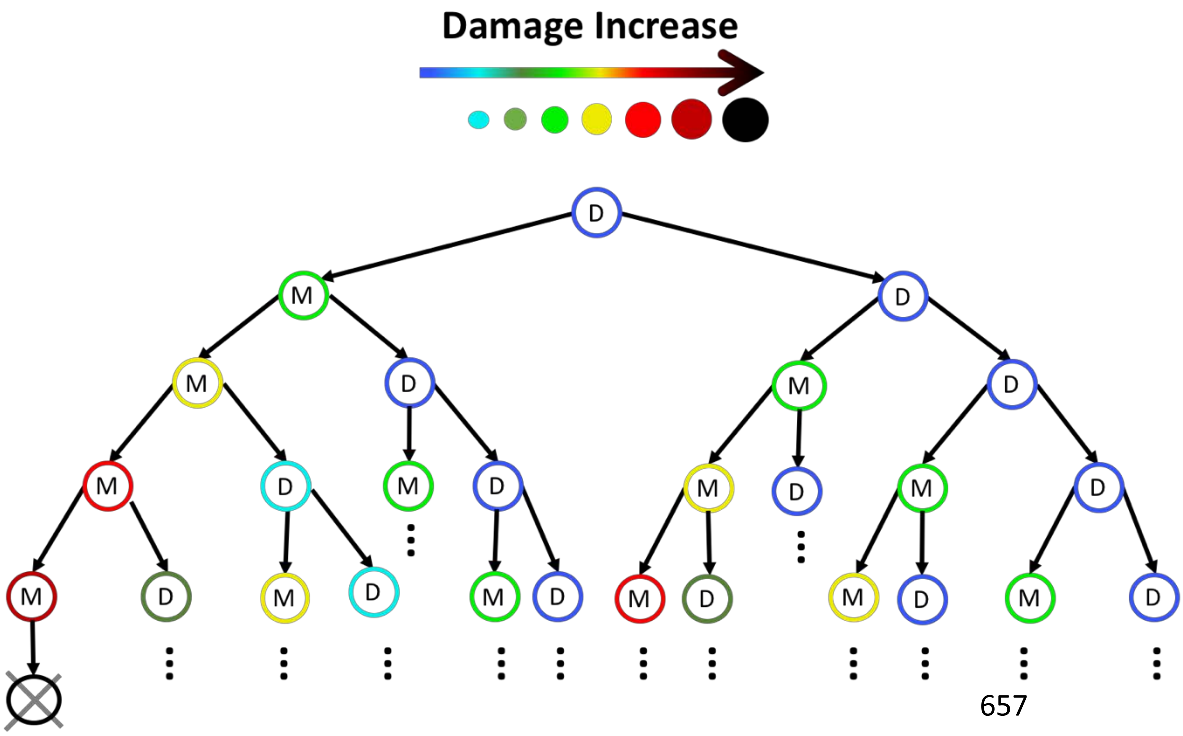

Figure S2: Schematic representation of pedigree-tree model. Each circle represents a cell. D stands for daughter whereas M stands for mother. Blue color is damage free cells while black color is for dead cells (no more divisions possible).

Appendix 2

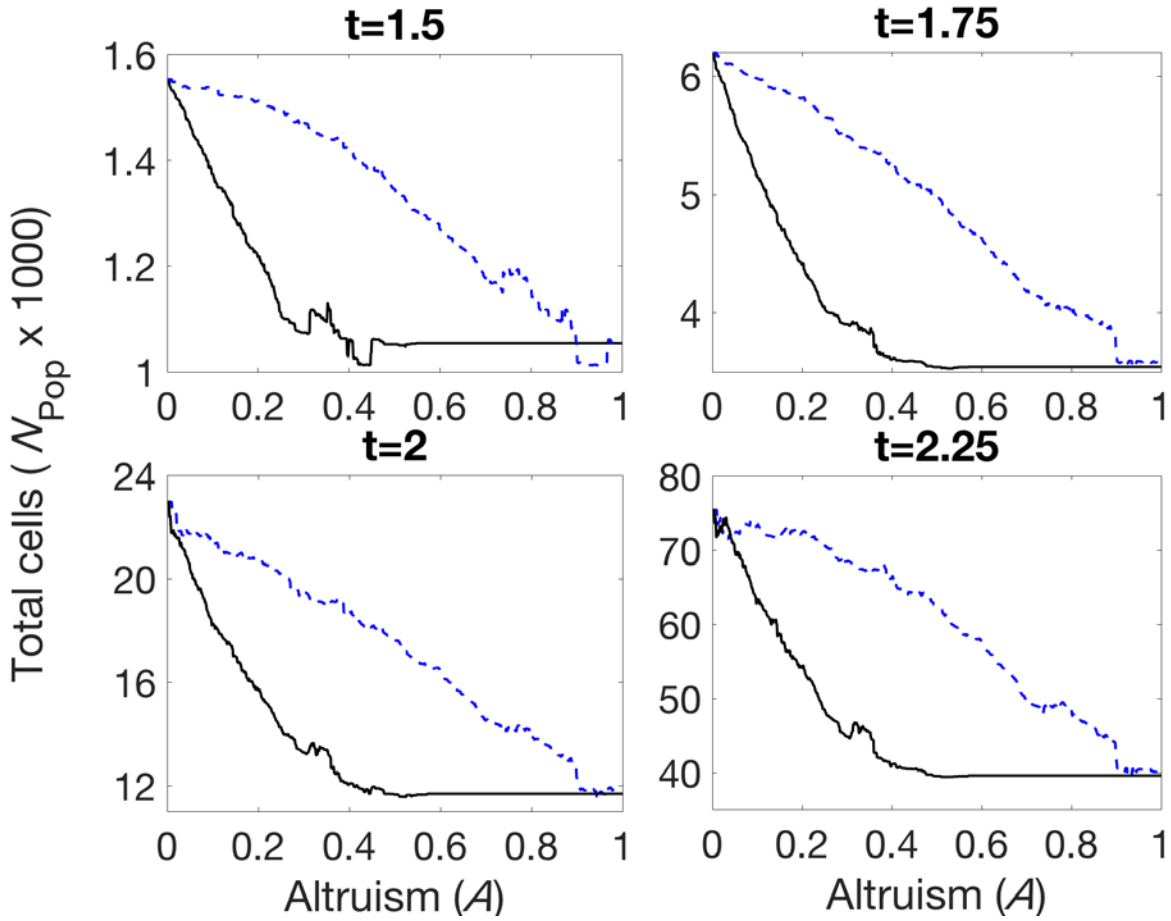

Figure S3: Total number of cells against the altruism values at four simulation times t = 1.5, 1.75, 2, 2.25. Lines represents population with distance strategy whereas the dashed lines represent the population with division strategy.

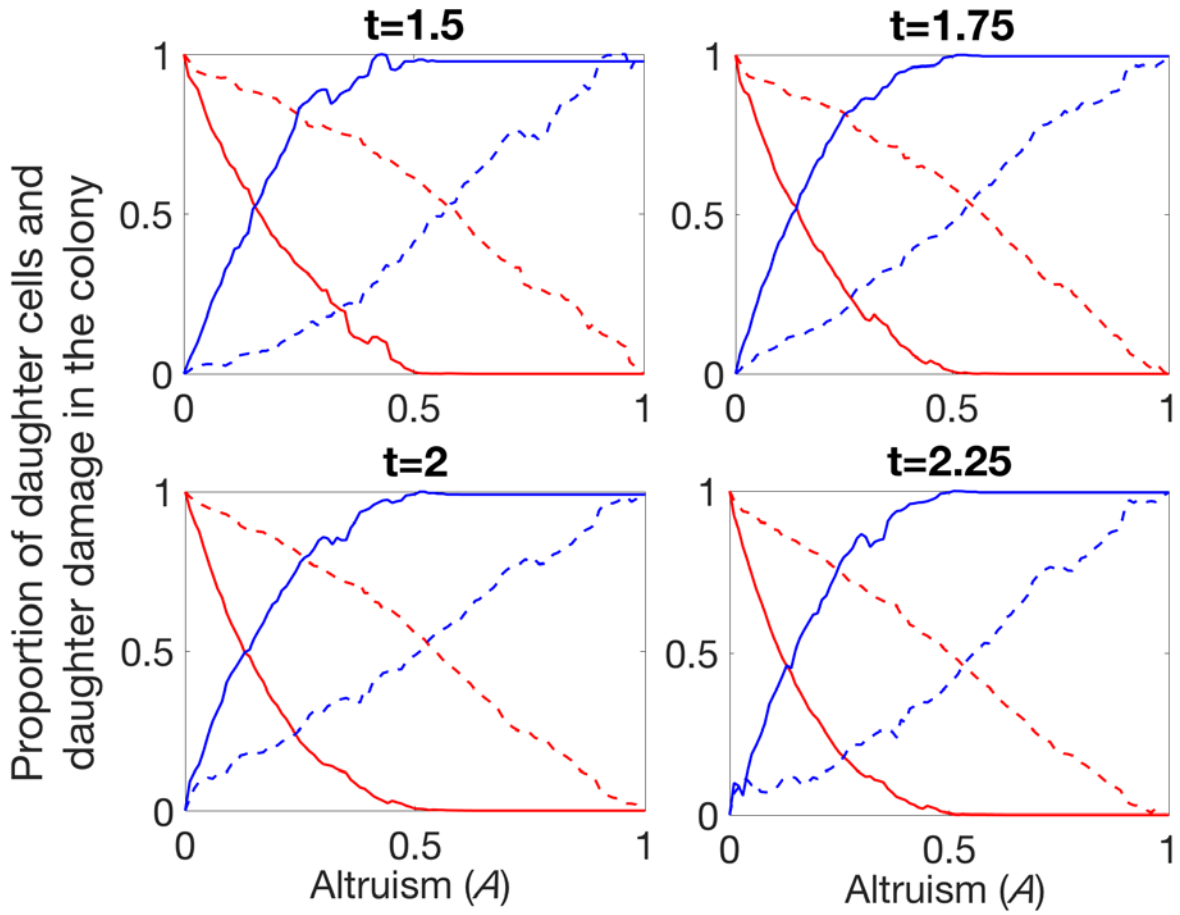

Figure S4: Proportion of daughter cells and their damage in the population for time t =1.5, 1.75, 2 and 2.25. The continuous lines represent distance strategy while dashed lines represent division strategy. The lines moving from 0 to 1 are the daughter cells proportion while the lines moving from 1 to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

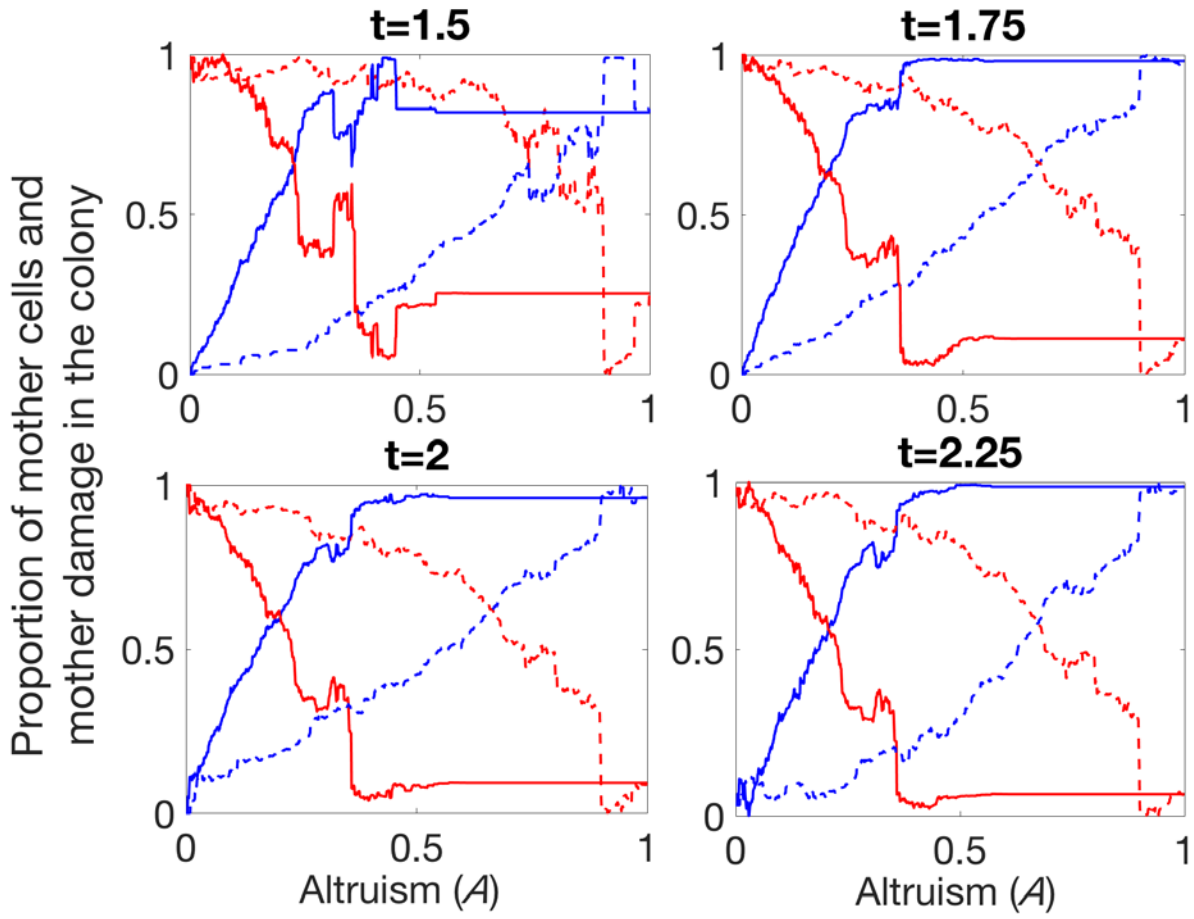

Figure S5: Proportion of mother cells and their damage in the colony at time t =1.5, 1.75, 2 and 2.25. The continuous lines represent distance strategy while dashed lines represent division strategy. The lines moving from 0 to 1 along y-axis are the mother cells proportion while the lines moving from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

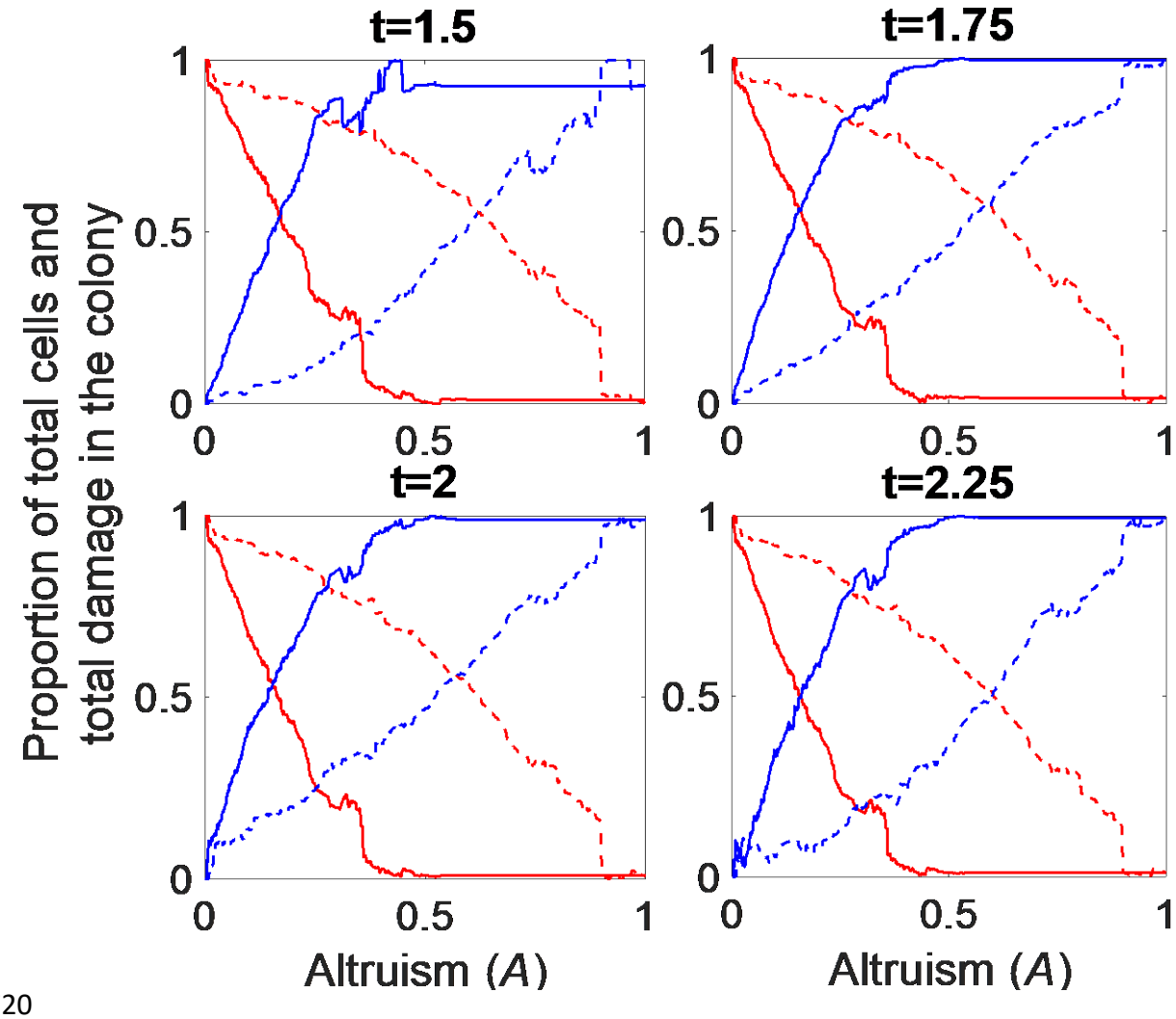

Figure S6: Proportion of total cells and their damage in the population for time t =1.5, 1.75, 2 and 2.25. The continuous lines represent distance strategy while dashed lines represent division strategy. The lines moving from 0 to 1 are the total cells proportion while the lines moving from 1 to 0 are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

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***Highlights (for review)**

Highlights

- Asymmetrically dividing budding yeast can increases the number of healthy daughters in the population by retaining more damage during the early divisions

- Retention of damaged proteins is a crucial mechanism ensuring a healthy daughter cell with full replicative potential and an ageing mother cell
- 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

- 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 damage

- 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