Lessons from yeast: synergistic effects of damage formation, repair, retention and resilience in the context of cellular rejuvenation and health span

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Becoming a systems biologist

Associate professor (2015), Department of Mathematical Sciences, University of Gothenburg

Assistant professor (2011), Department of Mathematical Sciences, University of Gothenburg

PhD Mathematics (2008) Systems Biology
Max Planck Institute for Molecular Genetics
Berlin Germany

University of Bordeaux, France
Virgina Tech (VT), USA

Postdoc (2008-2010), Metabolic Engineering, Chalmers

MSc Bioinformatics (2005), Chalmers

BSc Mathematics (2003)
Belgrade University, Serbia

dry wet

VR-SSF Arena

Lasse Ray

George

PK/PD modelling

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AstraZeneca

Jacob Leander

Methods for parameter estimation in mixed-effects models

Julia Larsson

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Vetenskapsrådet

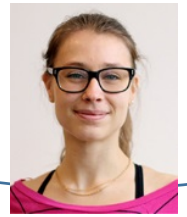
Systems Biology signalling branch

Osmotic stress and metabolic imbalance (sensing and adaptation)

Patrick Reith

Dynamic regulation of central metabolism and cell signalling

Sebastian Persson



Linnea Österberg

Systems Biology ageing (damage accumulation and polarization) branch

Barbara Schnitzer

Cell-to-cell heterogeneity in the aging process

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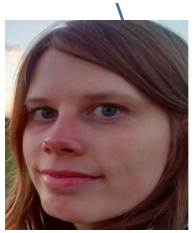


Svenja Braam

Theoretical aspects of ageing and cellular rejuvenation

Johannes Borgqvist

Mapping metabolic alterations during ageing to age-related syndromes and diseases

Niek Welkenhuysen

What is Ageing?

ageing
/ˈeɪdʒɪŋ/

noun

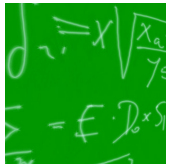
1. the process of growing old.
   "the external signs of ageing"

adjective

1. (of a person) growing old; elderly.
   "an ageing population"

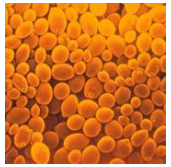
You know you are getting old when the candles cost more than the cake.

Bob Hope



Mathematical definition:

The likelihood of death of individuals within a population increases exponentially with age.



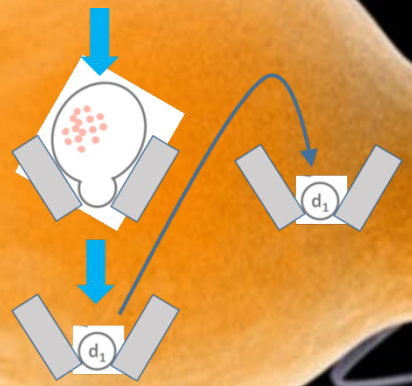
Biological definition:

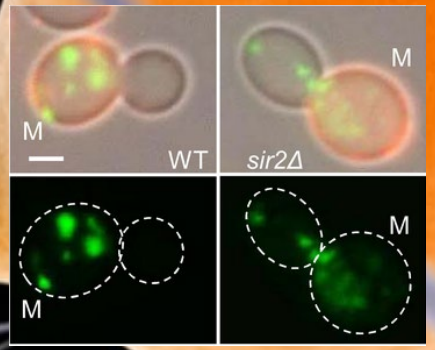
Ageing is simply the age - or time -dependent changes that occur to biological entities.

How and why we age?

The role of damage formation, repair and retention

Microfluidics + optical tweezers + yeast genetics + math

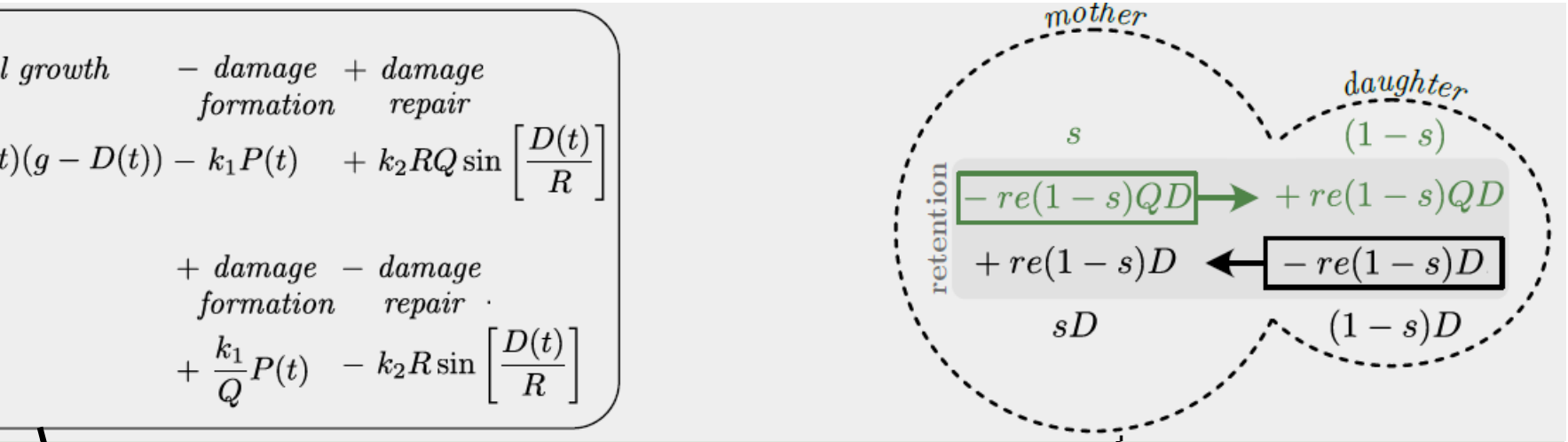


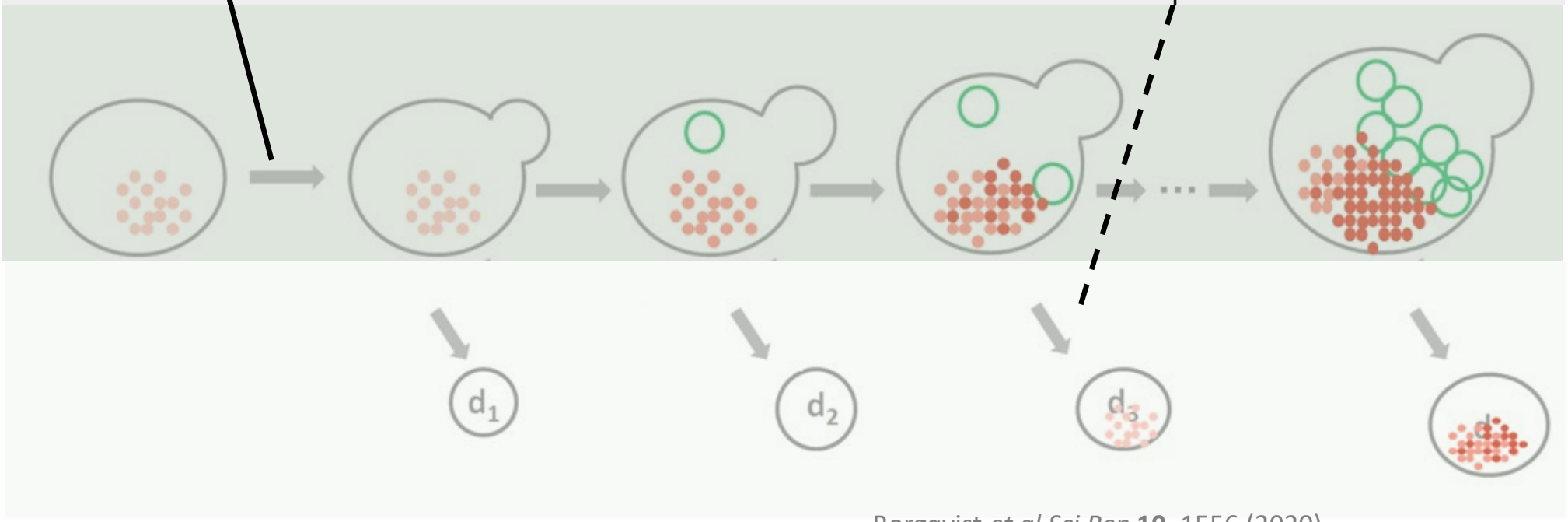


Single cell model of replicative ageing

$$\dot{P}(t) = \textit{cell growth} - \textit{damage formation} + \textit{damage repair}$$
$$= P(t)(g - D(t)) - k_1 P(t) + k_2 RQ \sin\left[\frac{D(t)}{R}\right]$$

$$\dot{D}(t) = + \textit{damage formation} - \textit{damage repair}$$
$$+ \frac{k_1}{Q} P(t) - k_2 R \sin\left[\frac{D(t)}{R}\right]$$





Borgqvist *et al Sci Rep* **10,** 1556 (2020)
Schnitzer *et al bioRxive* https://doi.org/10.1101/2020.03.24.005116 *(2020)*

Nondimensilonalisation of the model

Rescaling of parameters and variables

- Simplify the system without changing the qualitative behaviour

UPDATING RULES

$$t \leftarrow \mu t \qquad k_1 \leftarrow \frac{k_1}{\mu}$$
$$D \leftarrow \frac{D}{D_c} \qquad k_2 \leftarrow \frac{k_2}{\mu D_c}$$
$$P \leftarrow \frac{P}{P_c} \qquad R \leftarrow \frac{R}{\pi}$$
$$Q \leftarrow \frac{D_c}{P_c}$$

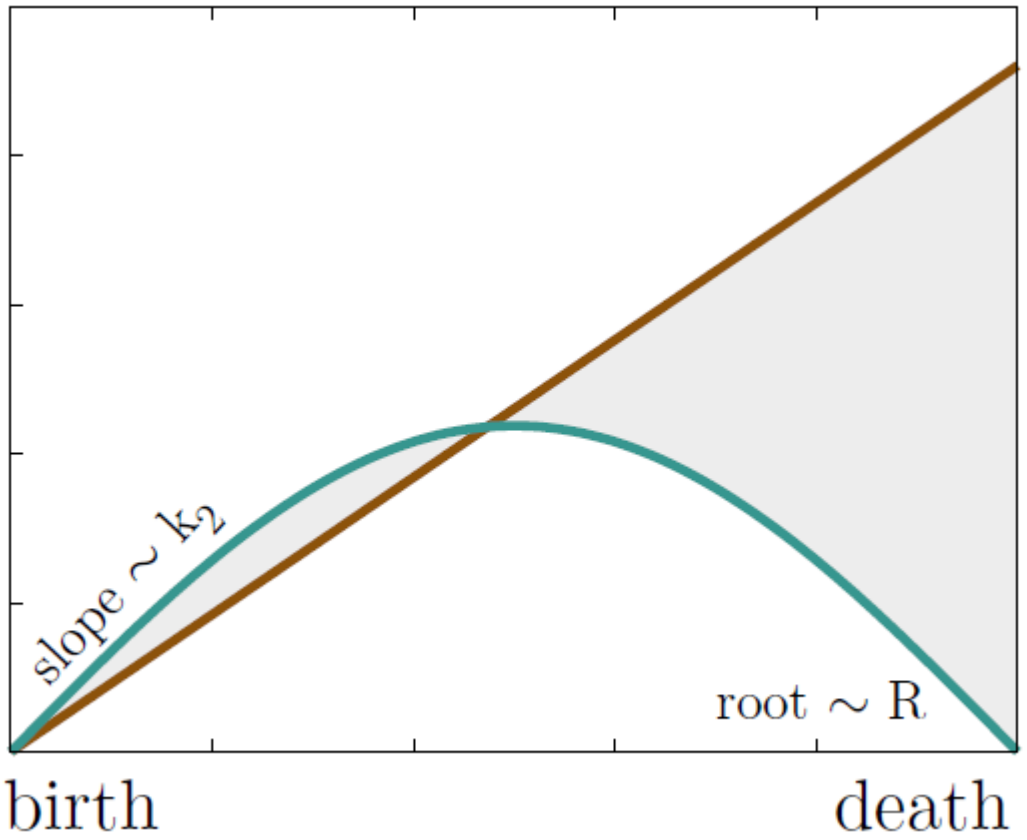
model	original	non-dimensionalised
$\dot{P}(t)$	$\mu P(t)\left(g - \frac{D(t)}{D_c}\right)$	$P(t)\,(g - D(t))$
	$-k_1 P(t)$	$-k_1 P(t)$
	$+\frac{k_2 R}{\pi}\sin\left[\frac{\pi}{R}\frac{D(t)}{D_c}\right]$	$+k_2 RQ\sin\left[\frac{D(t)}{R}\right]$
$\dot{D}(t)$	$+k_1 P(t)$	$+\frac{k_1}{Q}P(t)$
	$-\frac{k_2 R}{\pi}\sin\left[\frac{\pi}{R}\frac{D(t)}{D_c}\right]$	$-k_2 R\sin\left[\frac{D(t)}{R}\right]$
parameter	$P \in [0, P_c], \quad D \in [0, D_c]$	$P \in [0,1], \quad D \in [0,1]$
bounds	$g \geq 1, \quad \mu, k_1, k_2 > 0$	$g \geq 1, \quad k_1, k_2 > 0$
	$R \geq 1$	$R \geq \pi^{-1}$

Damage repair ($r(D)$)

$$\dot{P}(t) = \text{cell growth} - \text{damage formation} + \text{damage repair}$$
$$= P(t)(g - D(t)) - k_1 P(t) + k_2 R Q \sin\left[\frac{D(t)}{R}\right]$$

$$\dot{D}(t) = + \text{damage formation} - \text{damage repair}$$
$$+ \frac{k_1}{Q} P(t) - k_2 R \sin\left[\frac{D(t)}{R}\right]$$

$$r(D) = k_2 R \sin\left[\frac{D(t)}{R}\right]$$



decline in repair capacity — unlimited repair capacity

Resilience to damage (Q)

$\dot{P}(t) =$ *cell growth* $-$ *damage formation* $+$ *damage repair*

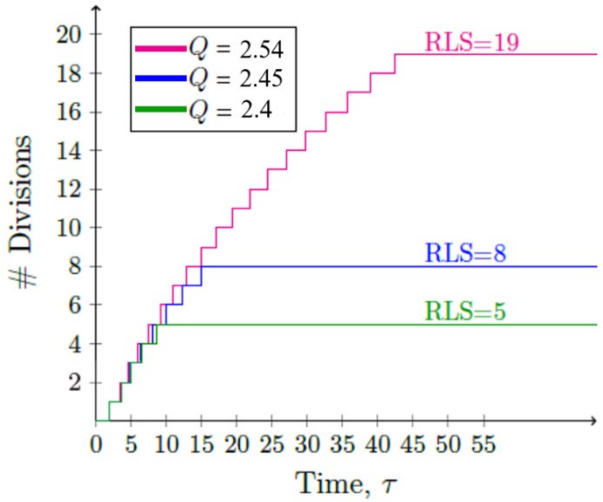
$= P(t)(g - D(t)) - k_1 P(t) + k_2 RQ \sin\left[\frac{D(t)}{R}\right]$

$\dot{D}(t) =$ $+$ *damage formation* $-$ *damage repair*

$+ \frac{k_1}{Q} P(t) - k_2 R \sin\left[\frac{D(t)}{R}\right]$

Defined as the quotient between the death and division thresholds, i.e. and can be interpreted as the capacity of the cell to cope with damage:

$$Q = \frac{D_{\text{death}}}{P_{\text{div}}}$$

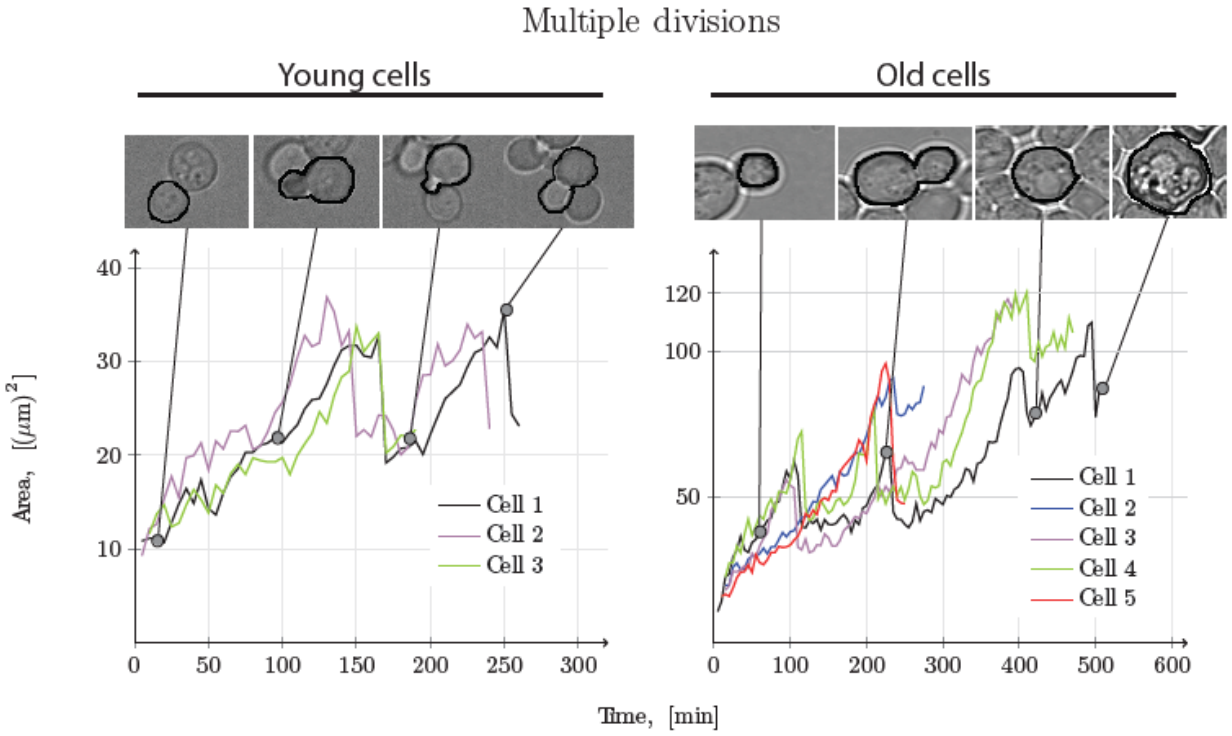


Damage resilience corresponds to the increase in size of an old cell compared to a young cell

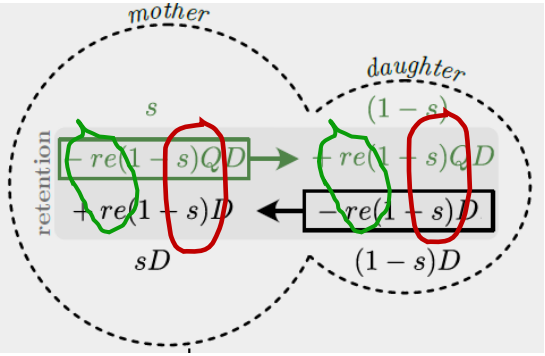
$$\text{cell area} \propto P + D$$

An old mother cell: $y = 1 + Q$

Data suggests that this area is appx 3.5 ➡ $Q \approx 2.5$

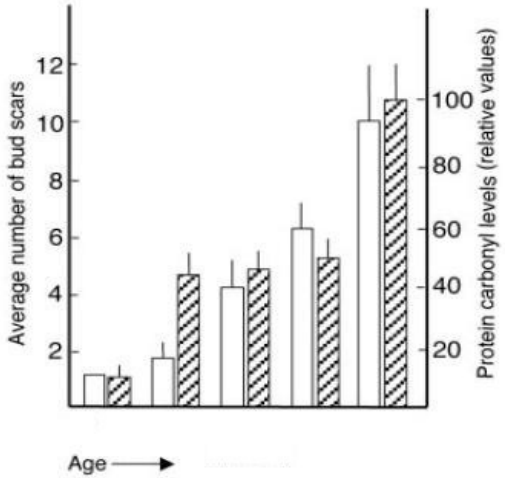


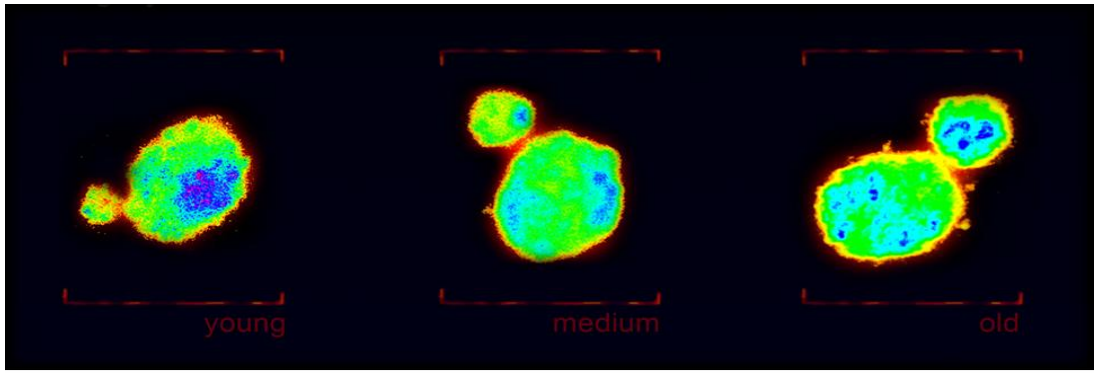
Cell size (*s*) and damage retention (*re*)



Cell size: Yeast divides asymmetrically where mother is approx. 3 times larger then its daughter

Damage retention: active mechanism; age-related damage retained within the mother cell at each division

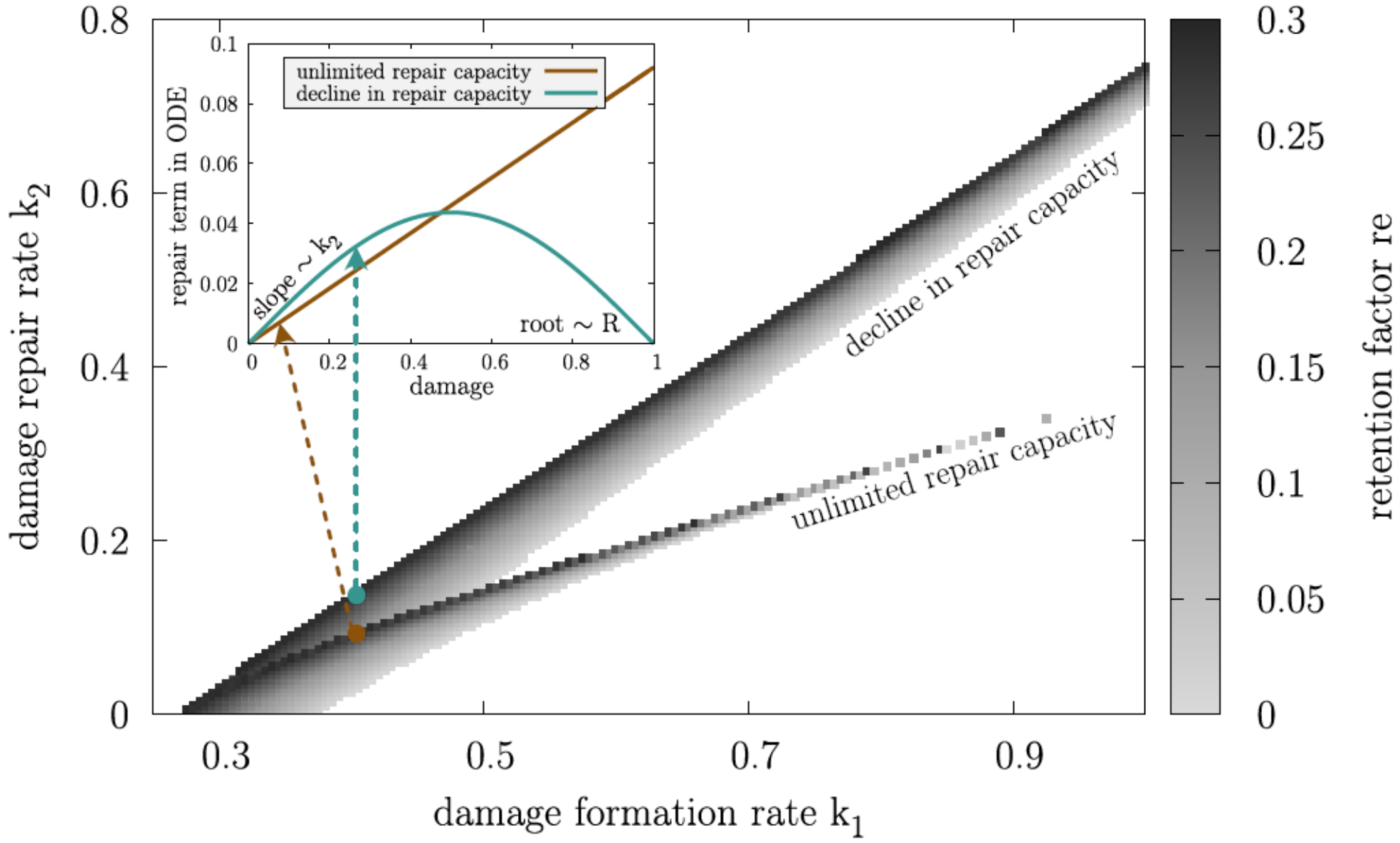




Replicative lifespan (RLS): Number of divisions before cell death. Measure of age of a single yeast cell.

Aguilianiu et al , 2003

Synergy between repair and retention



Interplay between Retention, Resilience, Damage and Celle size

Assumption:
Minimal amount of intact proteins that a cell is required to have after cell division

$$P_{0,\min} = (1 - s)$$

retention

size

$$0 \leq \mathrm{re} \leq \frac{1}{Q}\left(\frac{2^s - 1}{1 - s}\right)\frac{1}{D}$$

damage

resilience

(1) How much damage can a mother cell retain?
(2) How does the capacity to retain change with age?
(3) What factors limit the amount of damage a mother cell can retain at cell division?
(4) How does the degree of asymmetry in the cell division affect the capacity to retain damage?

Asymmetric division allows for retention of damage which comes at the price of a lower resilience to damage

(1) The capacity to retain damage decreases as the amount of damage increases $\mathrm{re} \propto 1/D$

(2) Investing resources in the capacity to retain damage comes at the cost of a lower degree of resilience to damage

for the individual cell $\mathrm{re} \propto 1/Q$

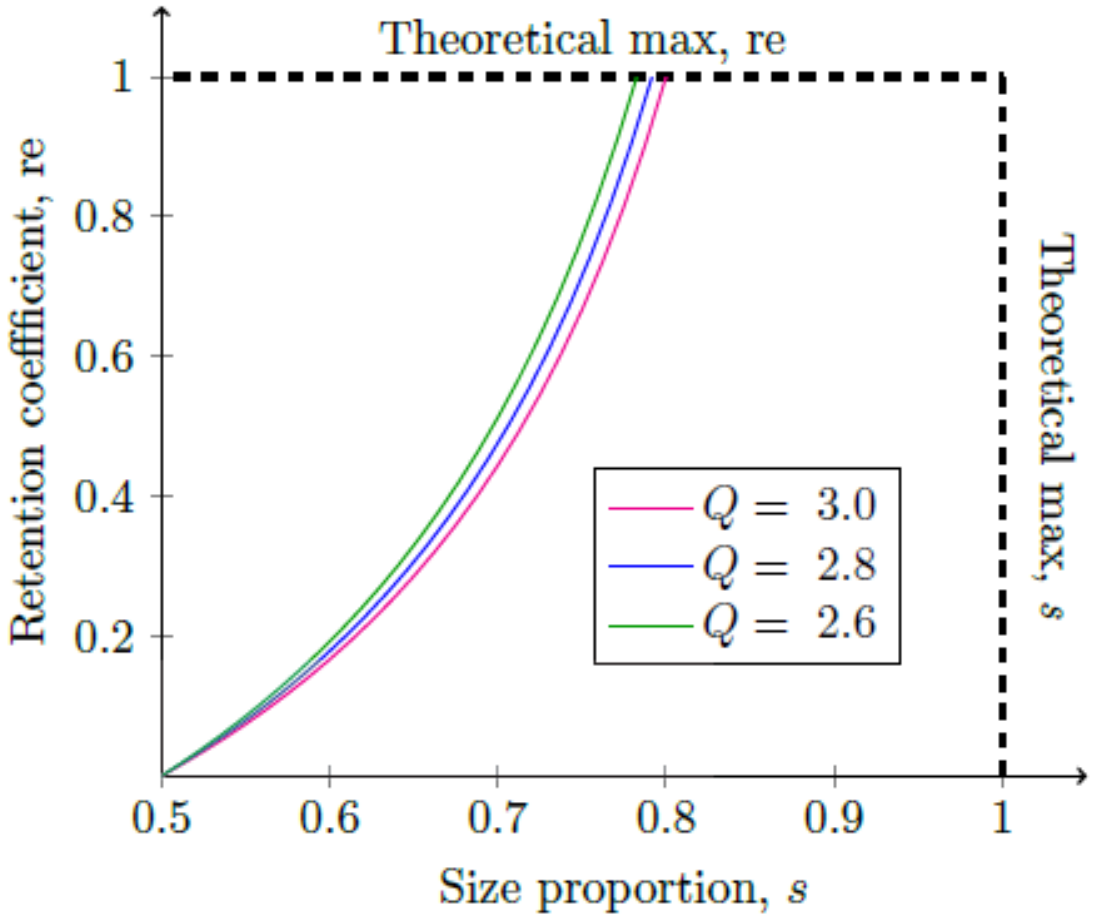
(3) a) Retention is a by-product of asymmetric division

$$0 \leq \mathrm{re} \leq \frac{1}{Q}\left(\frac{2s-1}{1-s}\right)\frac{1}{D}$$

b) The maximum degree of retention is proportional to the degree of asymmetry $\mathrm{re} \propto s$

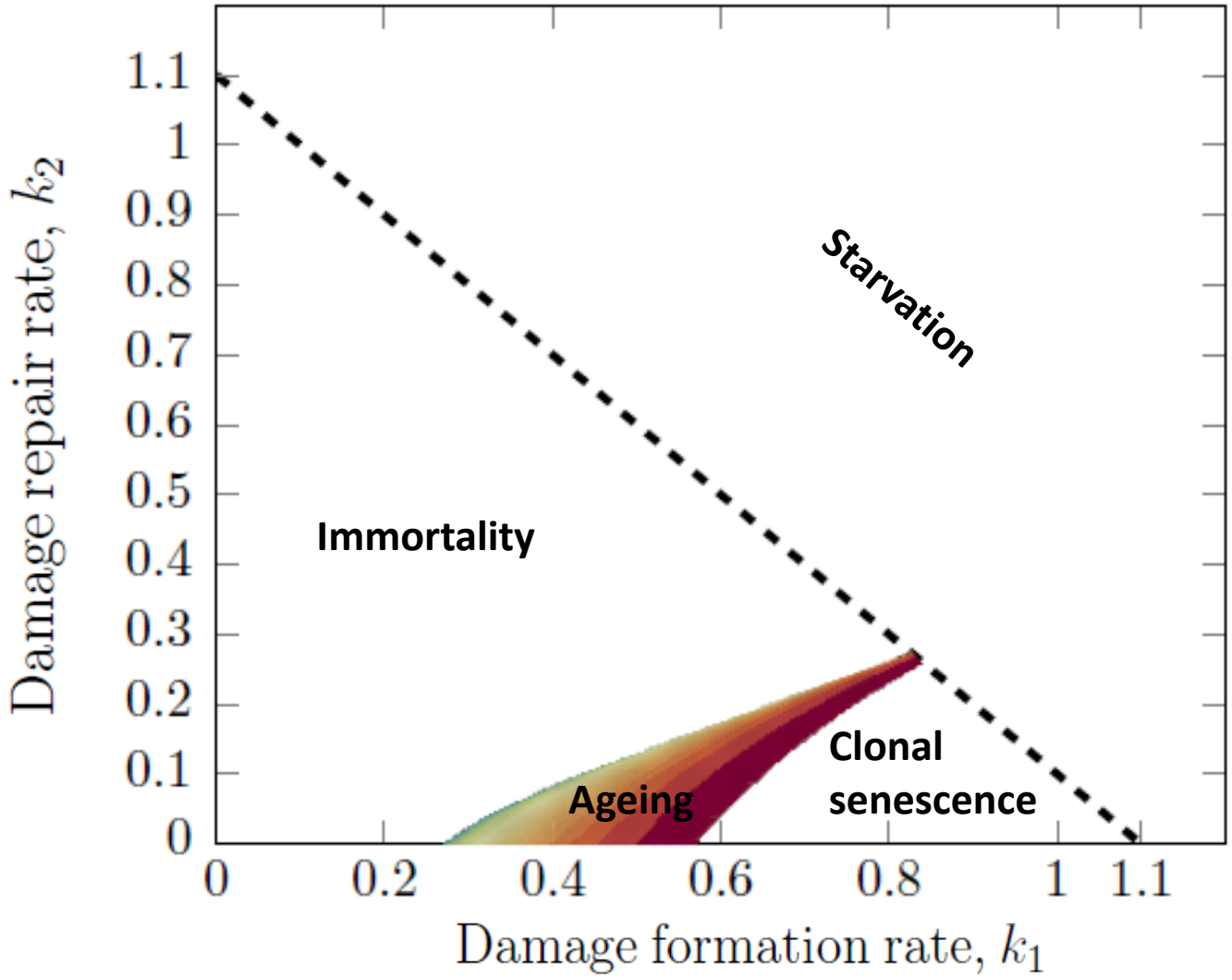
c) Maximal degree of asymmetry at which a cell can divide

$$s_{\max} = \frac{Q+1}{Q+2}, \; s_{\max} = 0.8$$

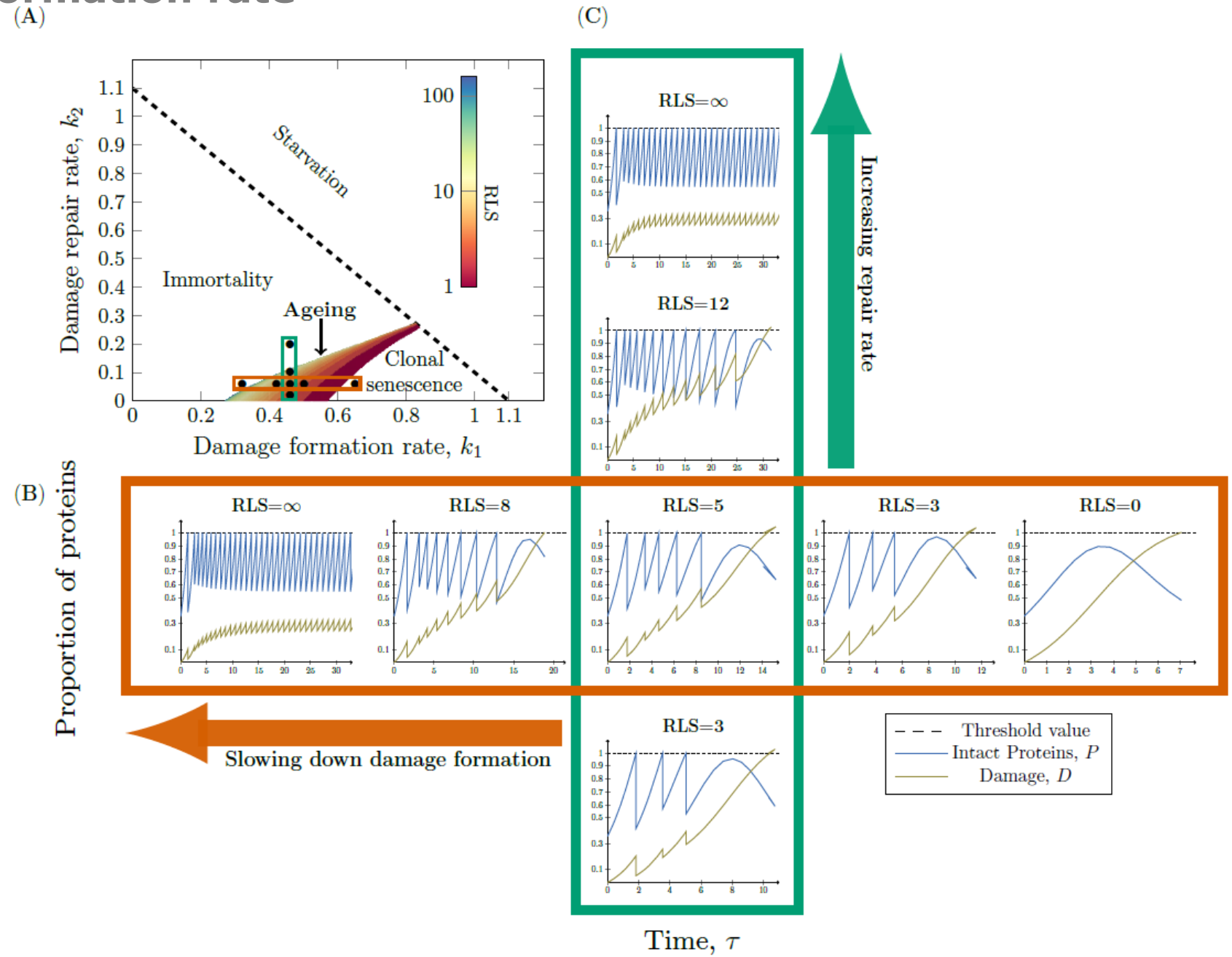


“Triangle of Ageing”

- Given enough food, the cells should grow and as a consequence of cell growth damage should accumulate
- Every cell has a finite replicative life span and should therefore die after a finite amount of cell divisions



Replicative lifespan can be altered either by increased damage repair rate or by slowing damage formation rate

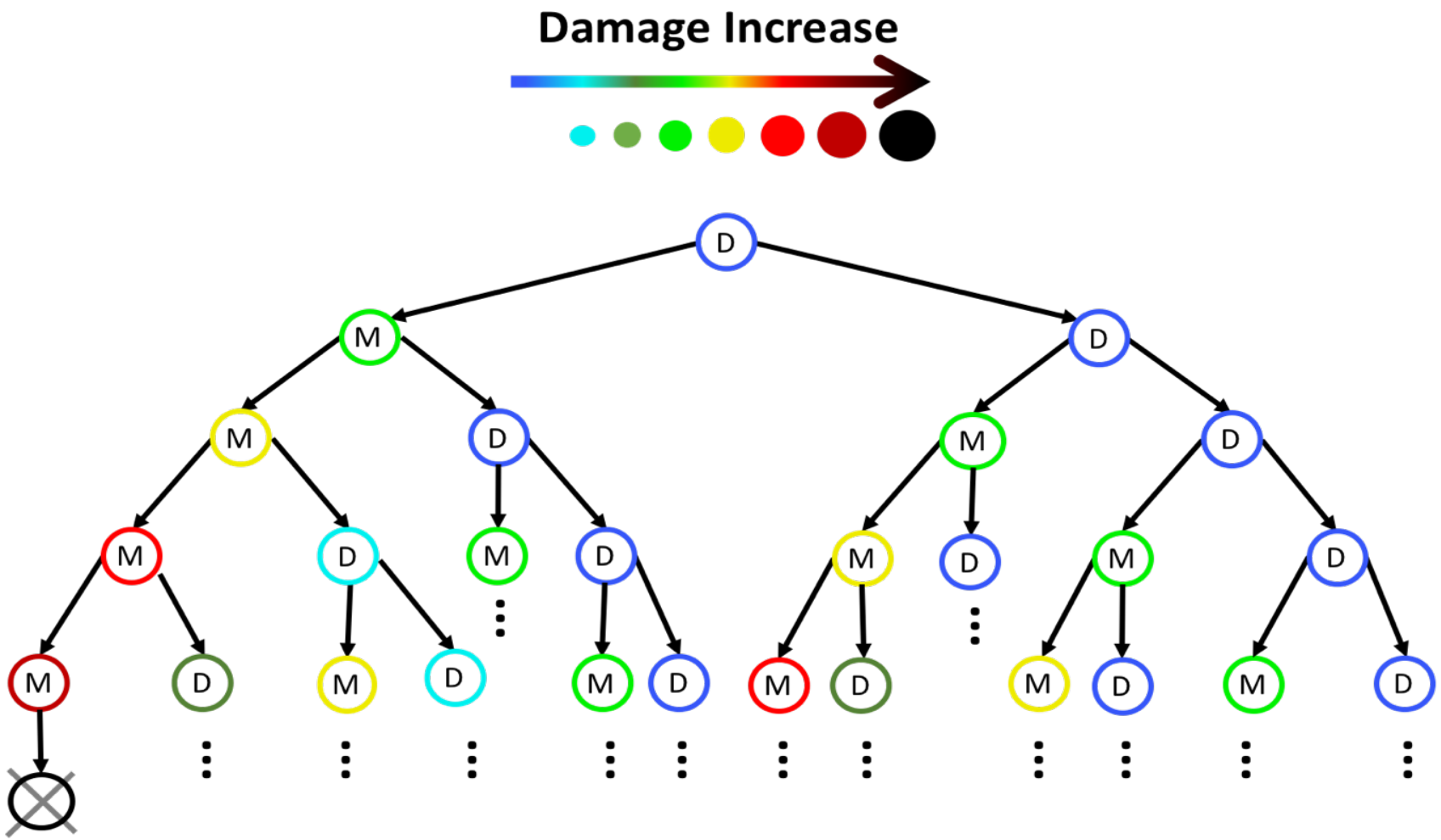


How ageing of the individual cell contributes to the ageing of the whole population: Towards the whole population model

Challenge:

Biology: traditional experiments do not provide means to systematically assess the whole population

Modelling: computationally very expensive to efficiently simulate linages



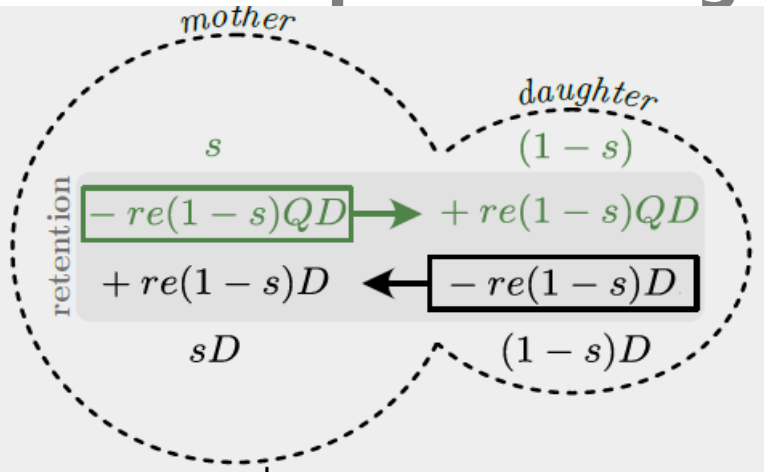
From single-cell to a whole population model of replicative ageing

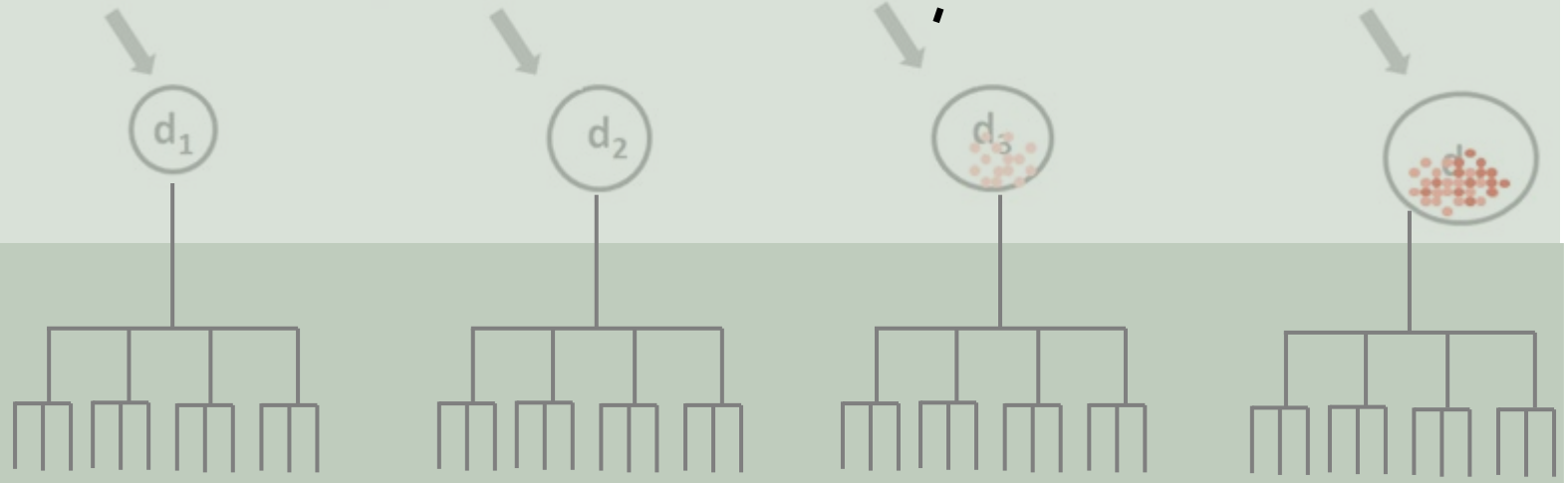
$$\dot{P}(t) = \underset{}{\text{cell growth}} - \underset{\text{formation}}{\text{damage}} + \underset{\text{repair}}{\text{damage}}$$

$$= P(t)(g - D(t)) - k_1 P(t) + k_2 R Q \sin\left[\frac{D(t)}{R}\right]$$

$$\dot{D}(t) = + \underset{\text{formation}}{\text{damage}} - \underset{\text{repair}}{\text{damage}}$$

$$+ \frac{k_1}{Q} P(t) - k_2 R \sin\left[\frac{D(t)}{R}\right]$$



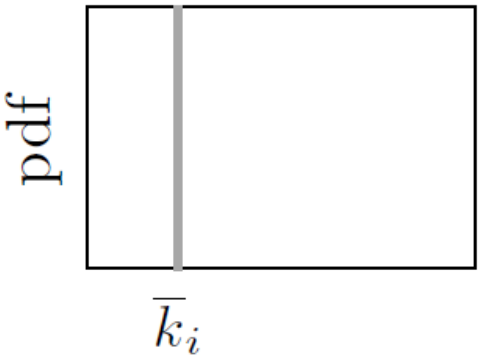


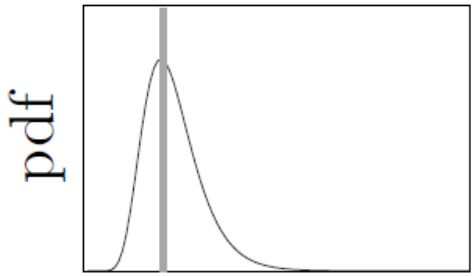
Individuality of cells in the population by introducing non-linear mixed effects

The individuality is reflected in the cell growth, damage formation k_1 and damage repair k_2

Non-linear mixed effects model accounts for individuality of cells

- damage formation rate (k_1)
- damage repair rate (k_2)



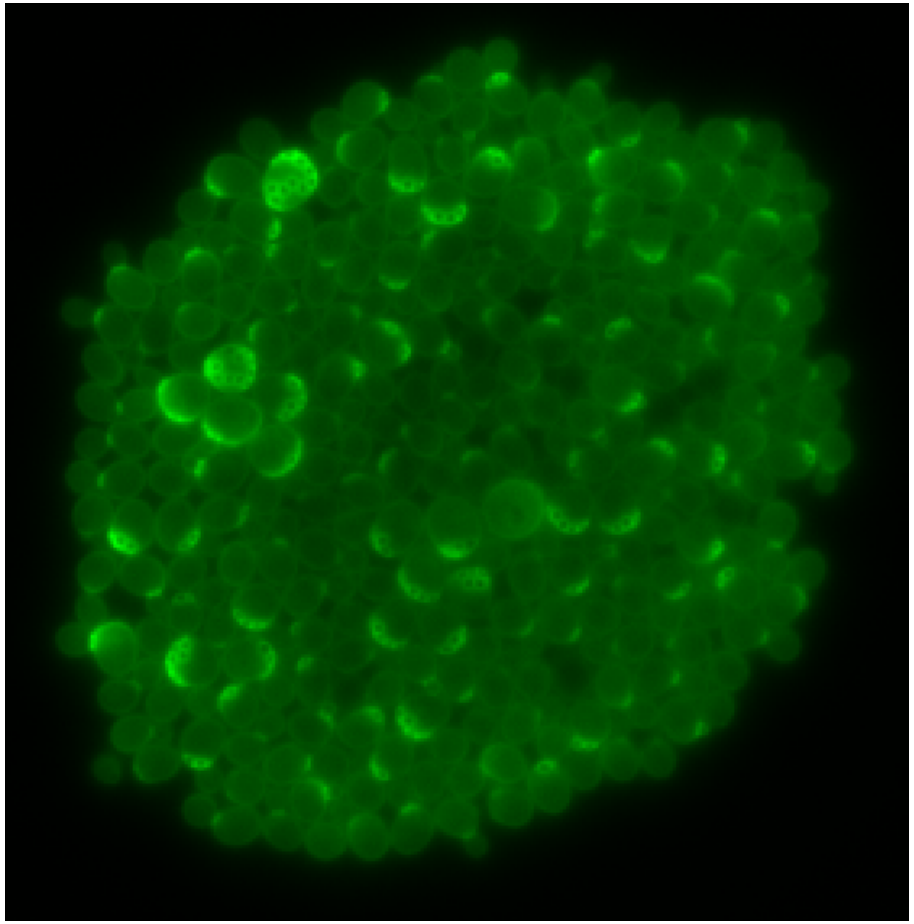


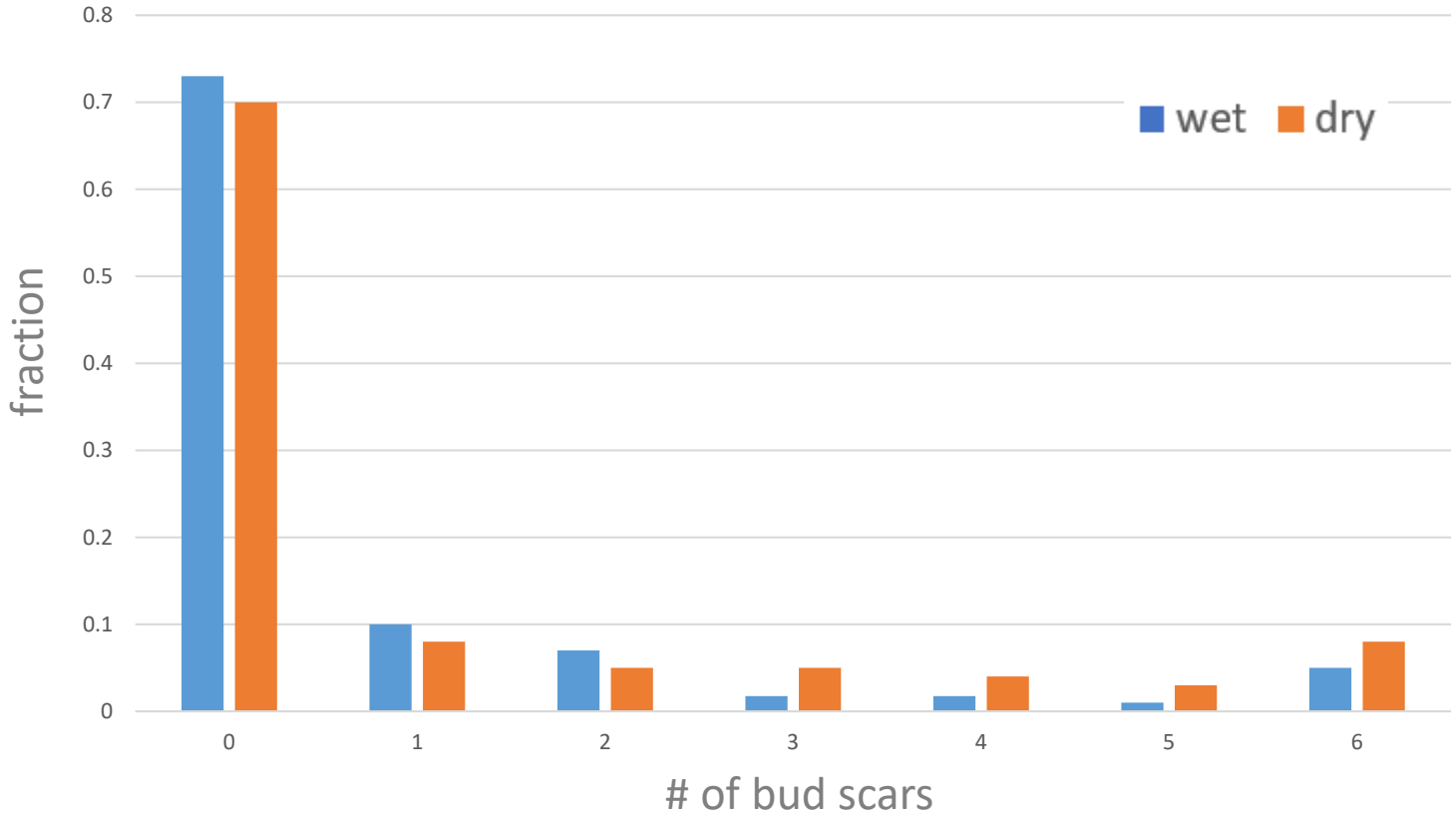
$$k_1 = \overline{k}_1 \exp[\eta_1]$$

$$k_2 = \overline{k}_2 \exp[\eta_2]$$

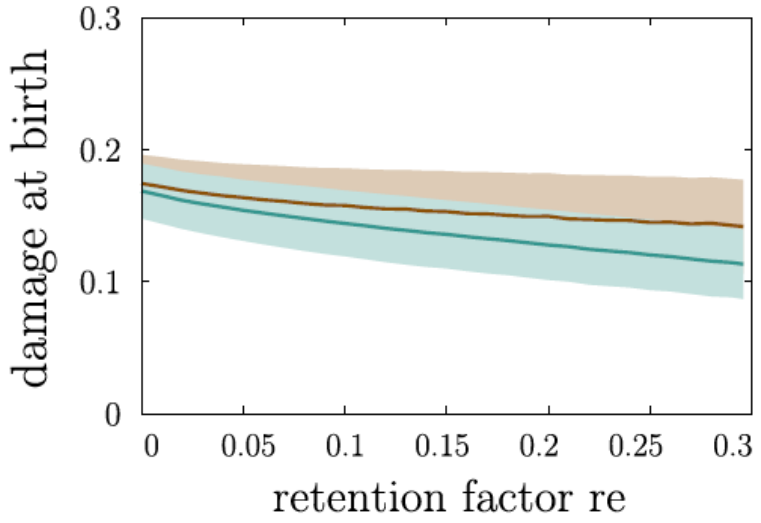
$$\eta_1, \eta_2 \sim \mathcal{N}(0, \sigma^2)$$

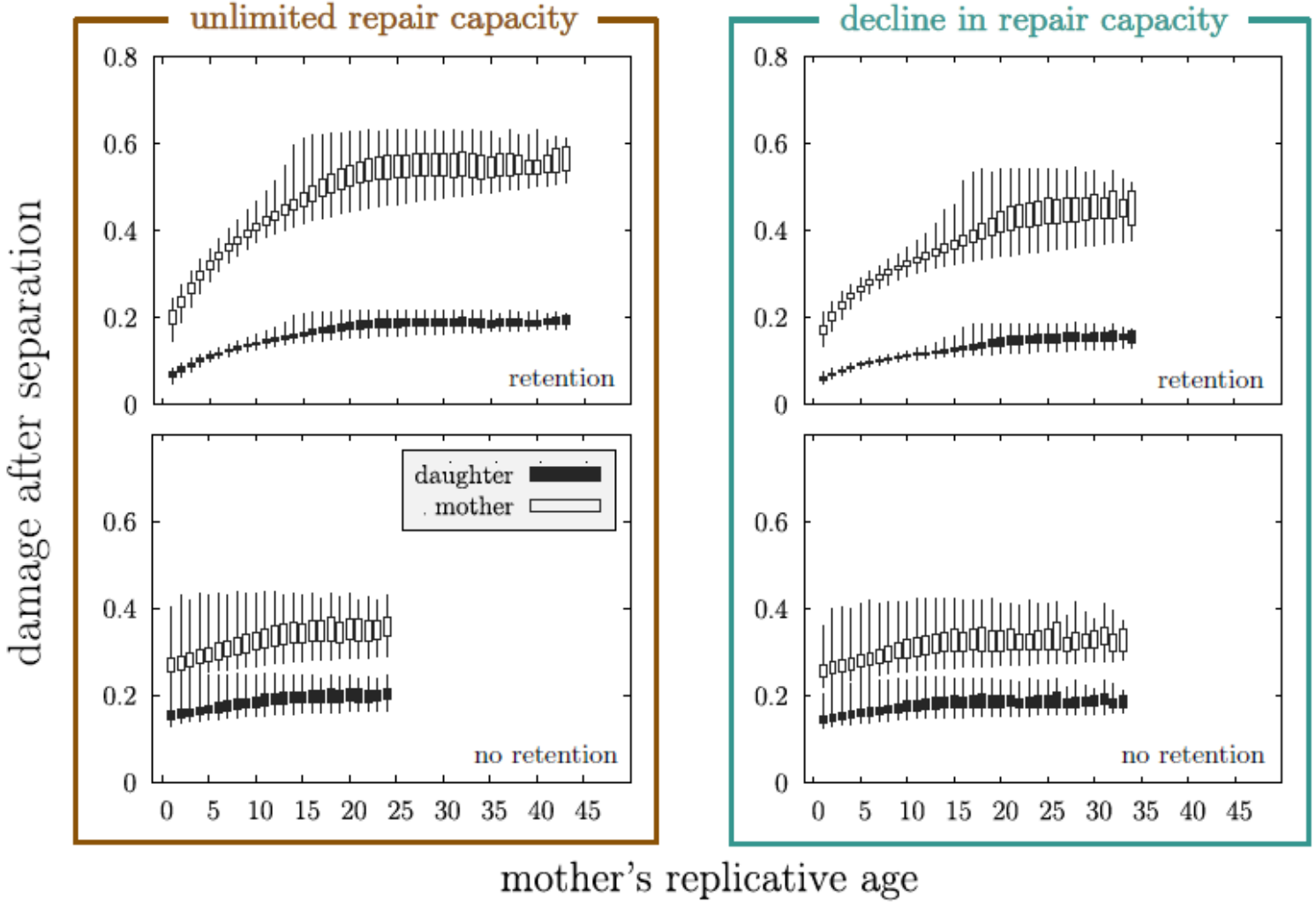
The model captures age distribution





Retention leads to bigger populations with lower damage levels at birth



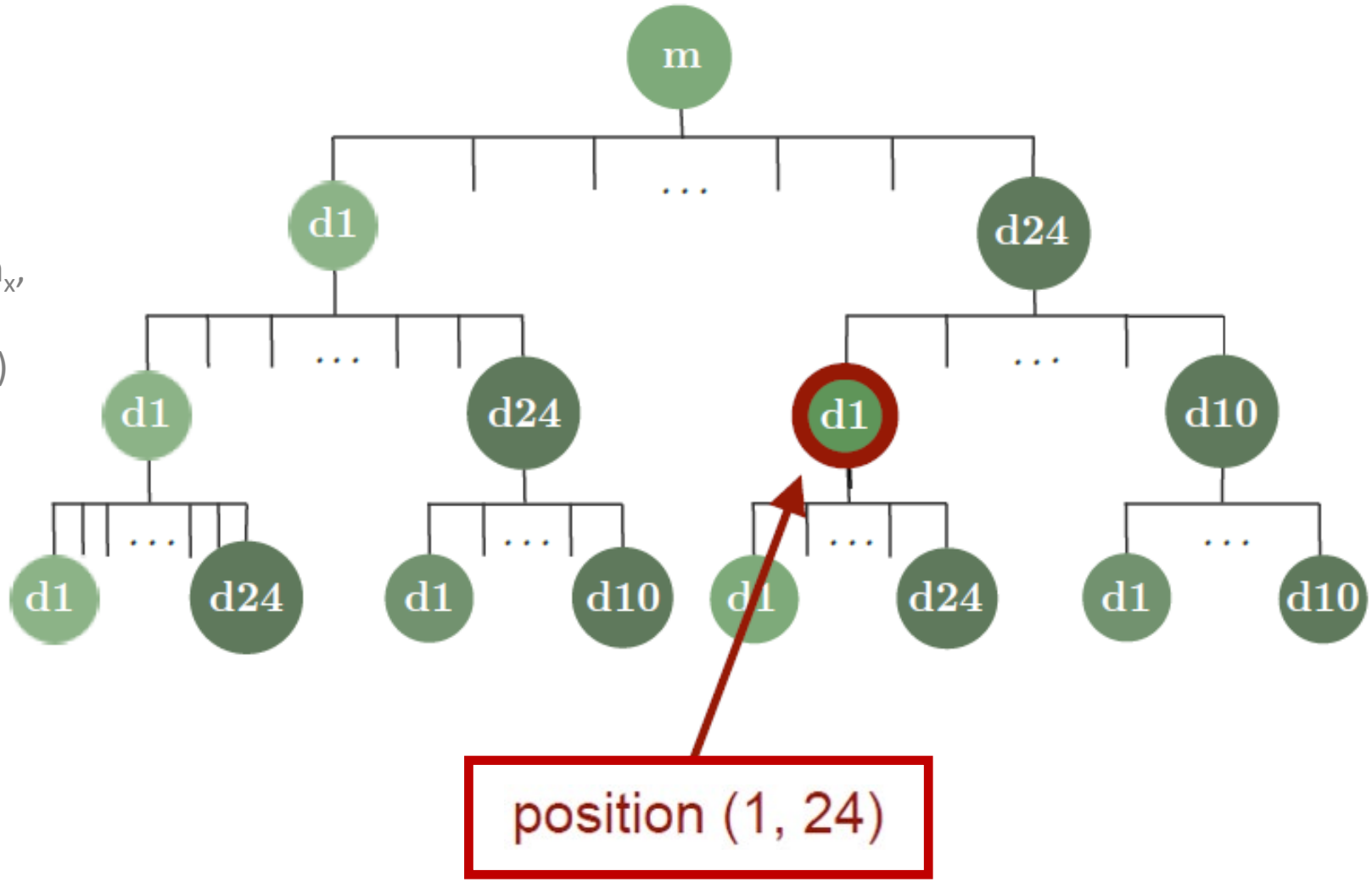


decline in repair capacity — unlimited repair capacity

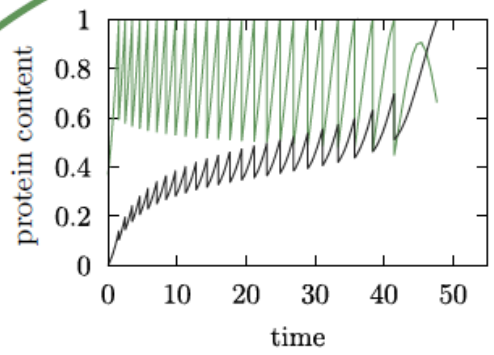
Dissecting population

For each cell x in the population, we define:

Lineage position (i, j):
Cell x is the i^{th} daughter of its mother m_x,
which is the j^{th} daughter
of its mother m_{m_x} (cell's x grandmother)



Measurable properties of individual cell and the whole population



complete time evolution of intact (P) and damaged proteins (D)

exact position and relationship with all cells in the lineage

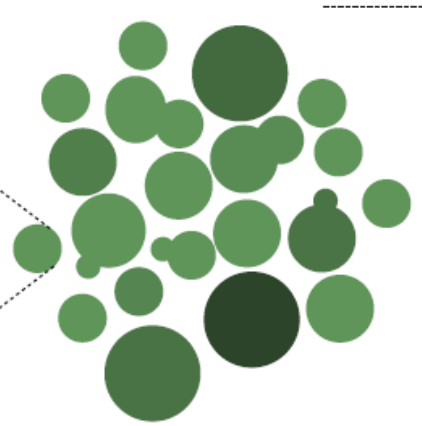
generation times and growth

replicative lifespan

rejuvenation index

health span

repair strategy



retention

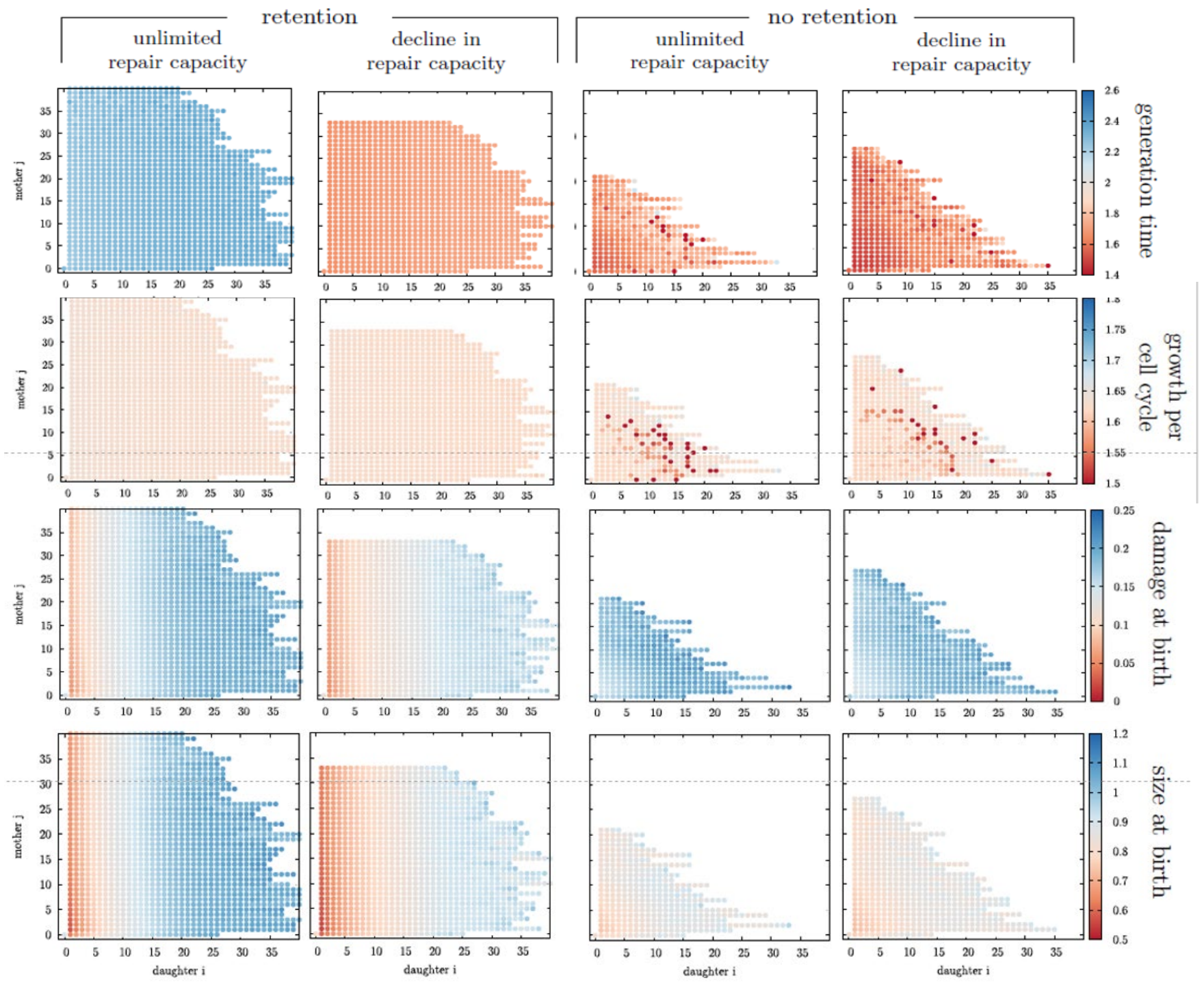
population size

fraction and degree of rejuvenation

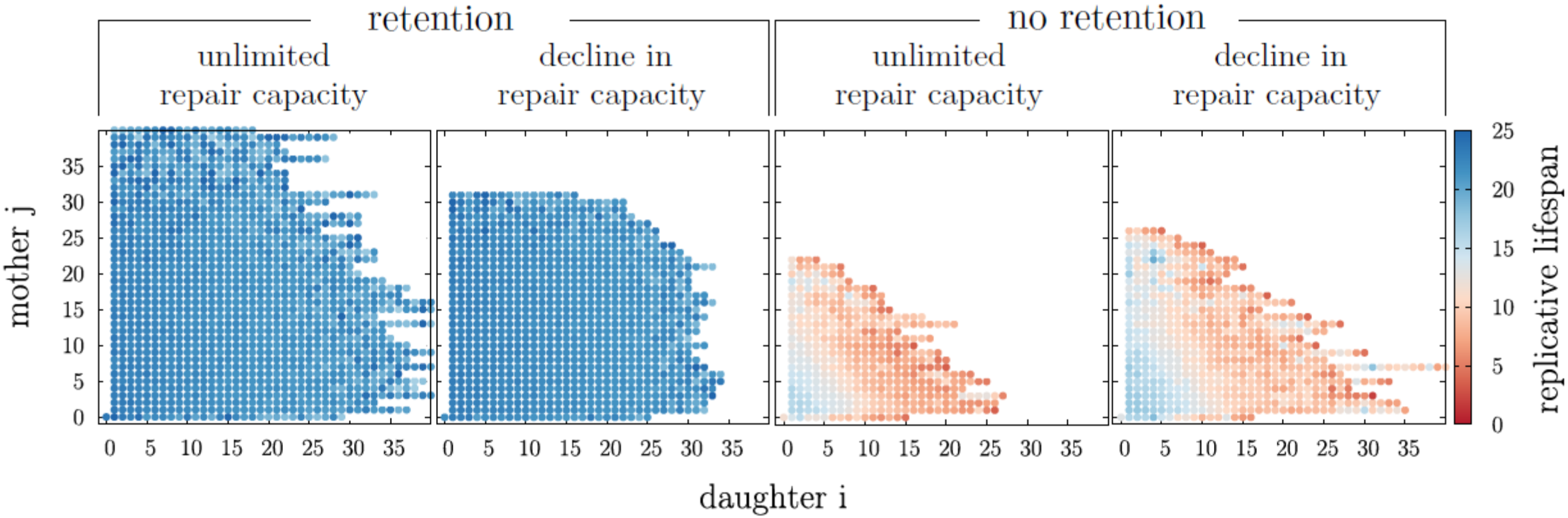
health of cells

doubling time

Properties of the population



Retention decreases the variability across the lineage



rejuvenate

/rɪˈdʒuːvəneɪt/

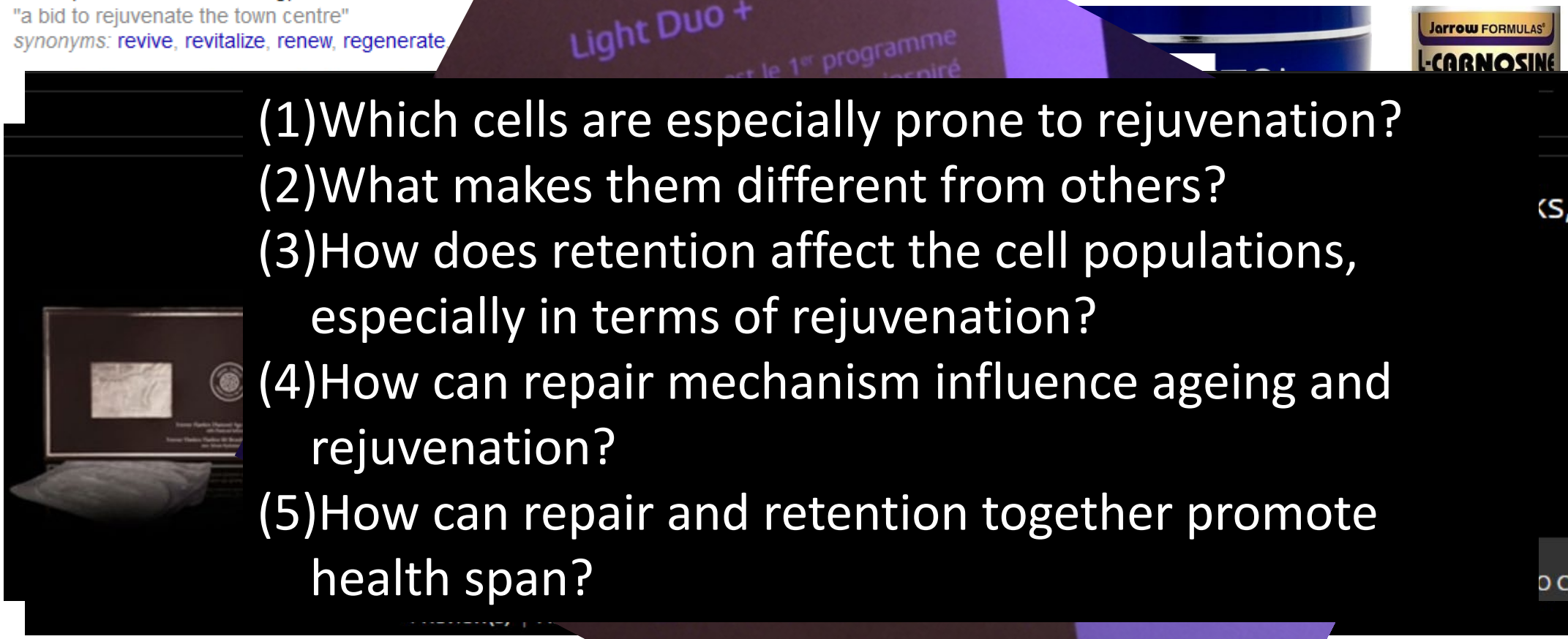
verb

make (someone or something) look or feel better,

"a bid to rejuvenate the town centre"

synonyms: revive, revitalize, renew, regenerate

"It is now possible for the first time ever to ke control of aging and indeed health at the level"



(1)Which cells are especially prone to rejuvenation?

(2)What makes them different from others?

(3)How does retention affect the cell populations, especially in terms of rejuvenation?

(4)How can repair mechanism influence ageing and rejuvenation?

(5)How can repair and retention together promote health span?

- 10 years younger in 28 days. Doctor End
- 11 of the most powerful Anti-Aging and NueroPep

Luxair

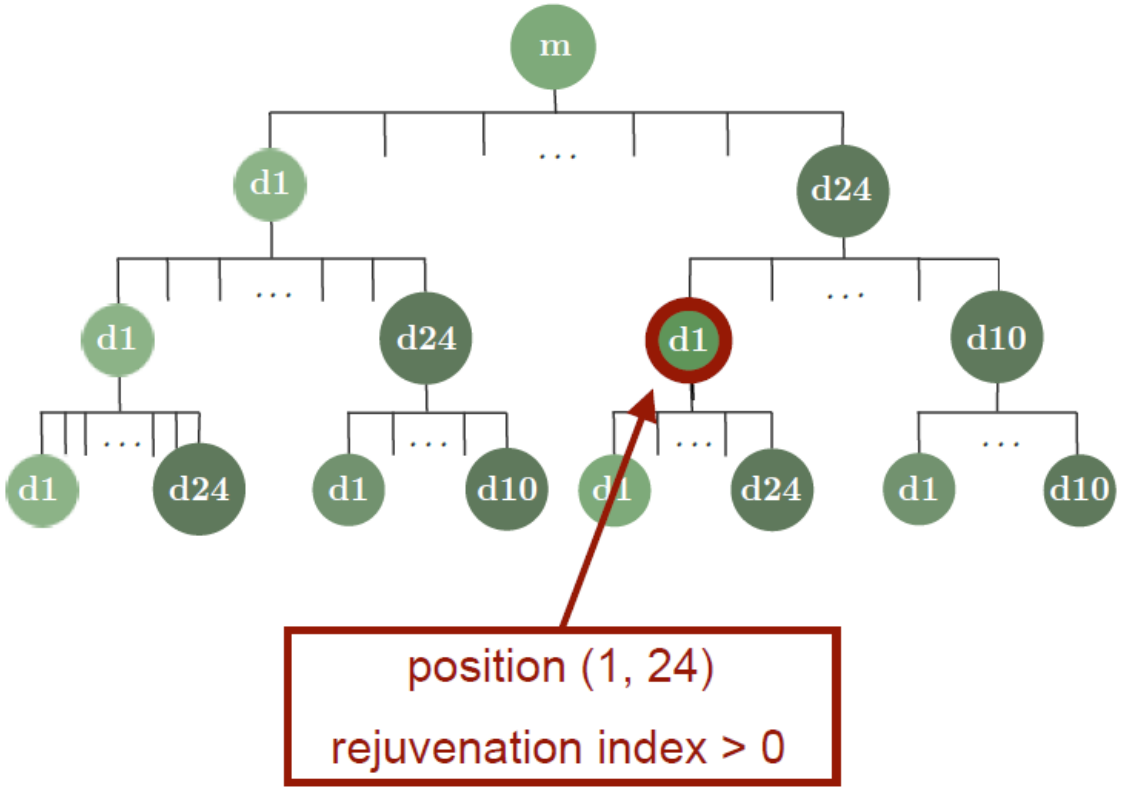
telomere - a part of your DNA structure. It's th ecret lie
telomeres get shorter. The shorter they get, the mo s how it
Rejuvenation Cream helps maintain telomeres and stop t g dryer, m
tissue... extending the youth span of the skin to reduce all vis lus, it enha
not just wrinl

Measuring rejuvenation in the populations

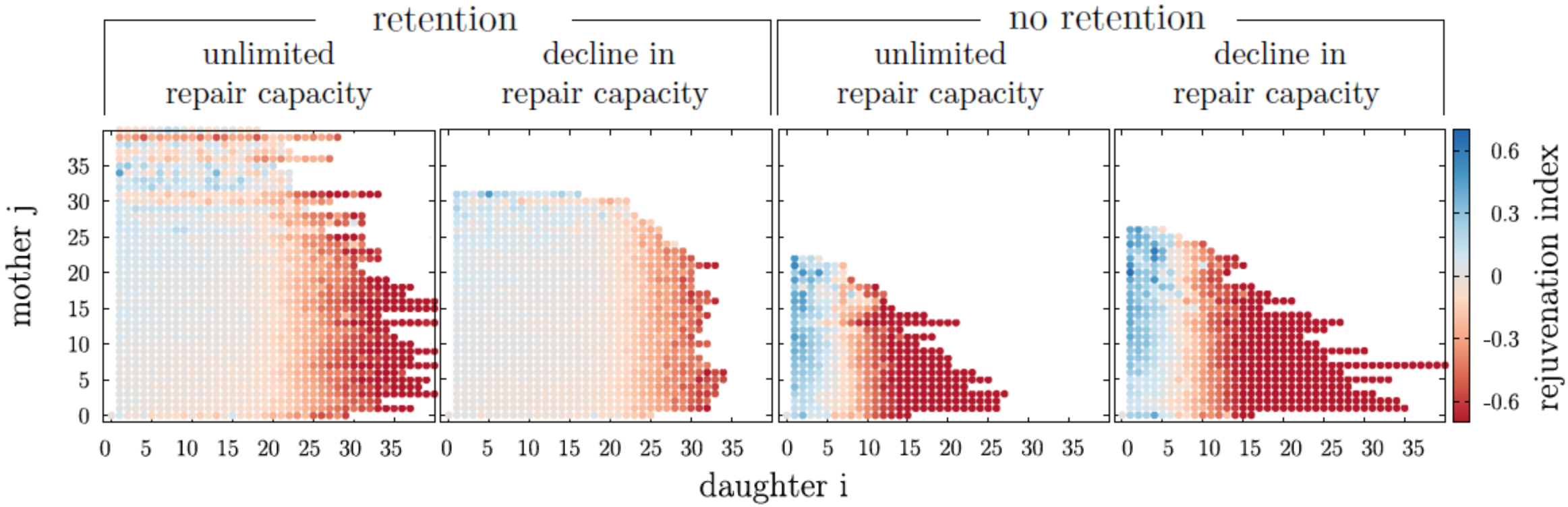
For each cell x in the population, we define:

Rejuvenation index: $\frac{rls(x) - rls(m_x)}{\overline{rls}}$

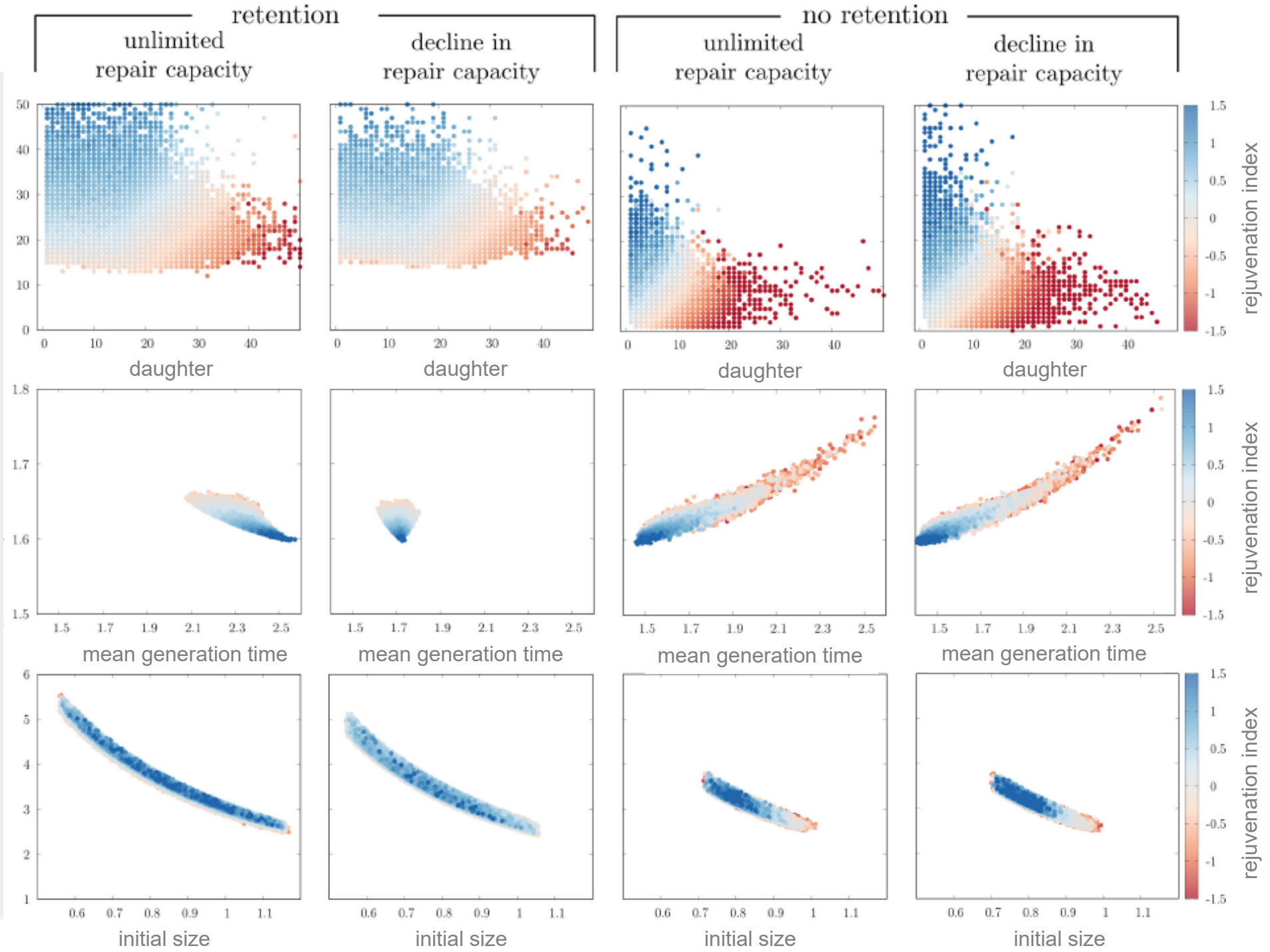
where rejuvenated cell has a positive rejuvenation index



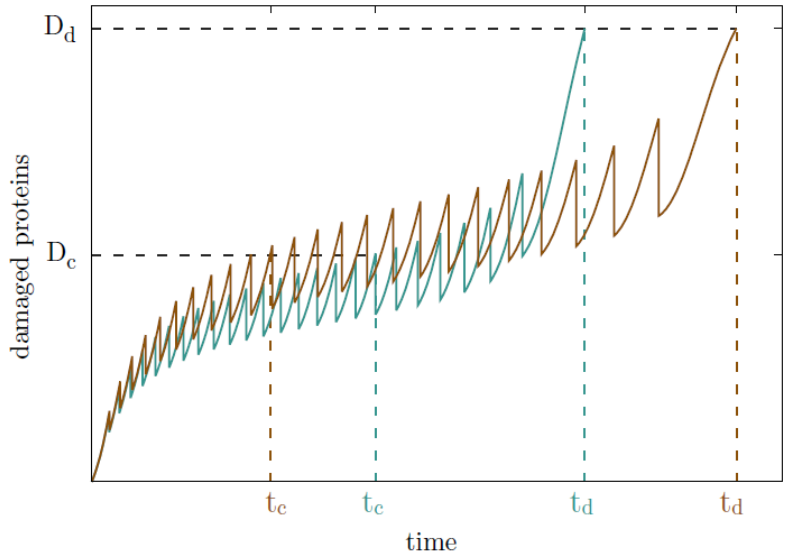
Your grandma determines your ability to rejuvenate



Properties of rejuvenating cells



Measuring health span: pinpin korori in yeast

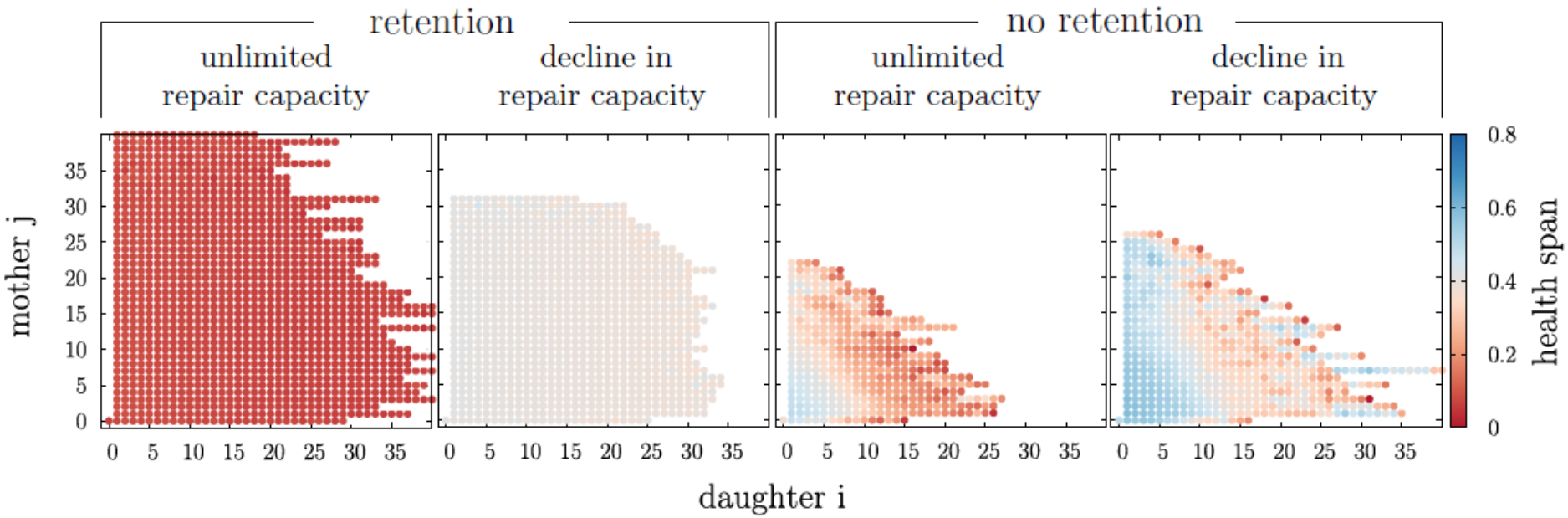


For each cell in the population, we define:

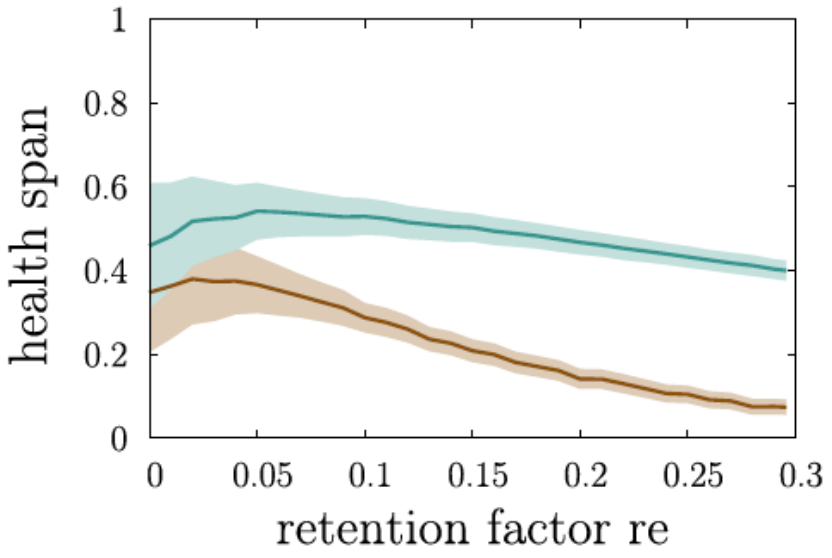
Health span: $$\frac{t_c}{t_d} \cdot \frac{rls_c}{rls_d}$$

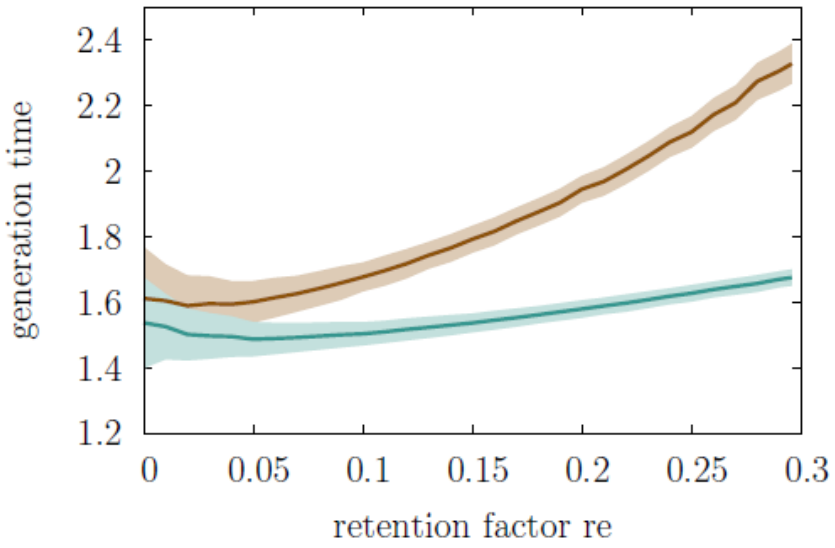
Having a long health span means :

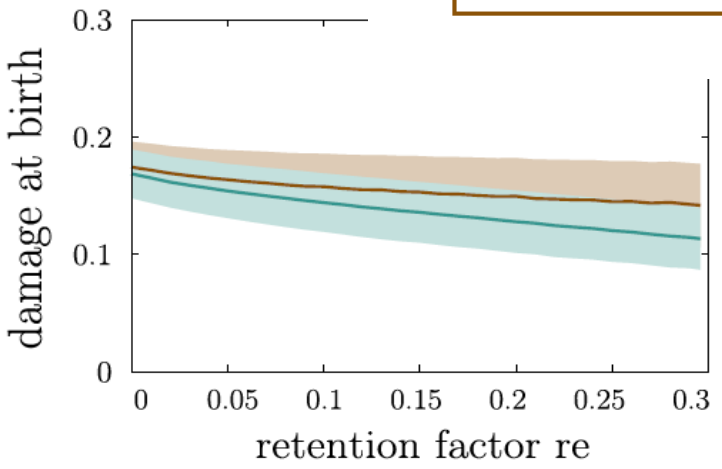
- low damage levels as long as possible
- many divisions when damage levels are low

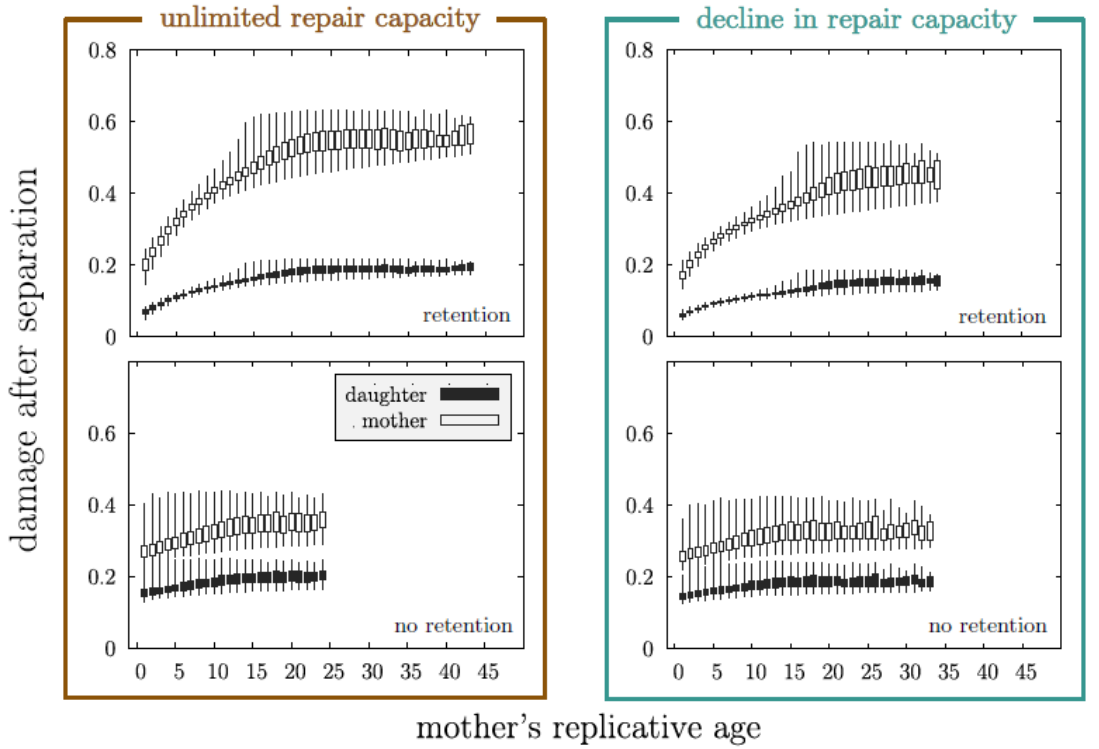


Decline in repair capacity prolongs the health span by increasing generation time and lowering damage levels









decline in repair capacity — unlimited repair capacity

Towards healthy ageing : lessons learned from yeast

investing in yourself

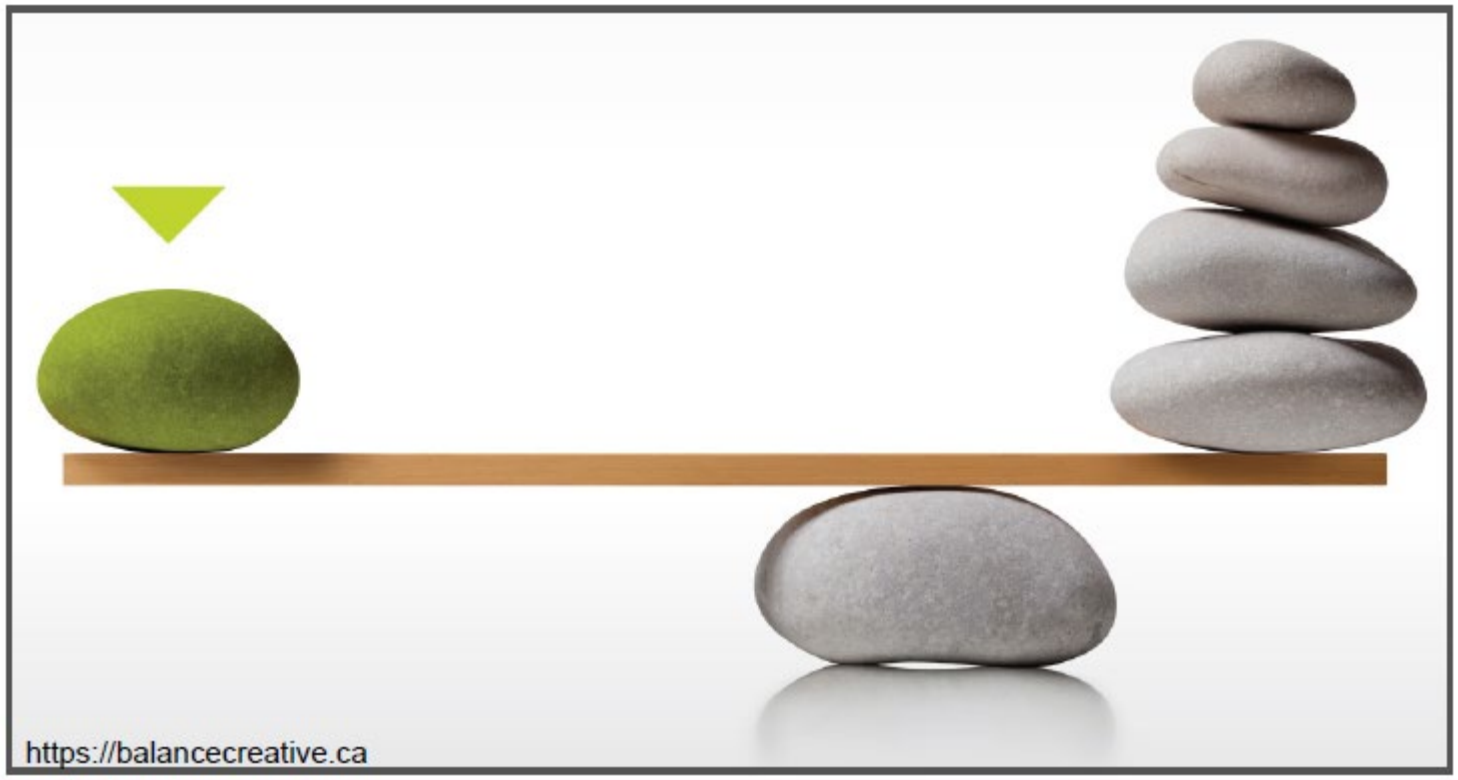
investing in repair early in life

↓

fast divisions with low damage levels

↓

when damage takes over and repair deteriorates, cell stops dividing and dies



investing in your progeny

retention of damaged proteins

↓

homogenous populations with rejuvenation distributed across whole population

► **longer health span**

► **larger population size**

What did we learn

- The capacity to retain damage deteriorates with high age
- Asymmetrical division allows for an optimal trade-off between damage resilience and damage retention (A high resilience to damage corresponds to a cell that can obtain a high age and retention corresponds to a sacrifice of fitness for the individual cell for the sake of its offspring)
- Rejuvenation occurs to a greater extent when retention is present
- Retention leads to more homogenous populations which are larger and have lower damage levels
- Rejuvenation is always present in asymmetrically dividing cells but only together with retention it can be fully exploited
- Investing in repair early in life compensates the decline of repair during ageing and at the same time prolongs the health span of the cell
- The repair mechanism does not influence rejuvenation
- Healthy ageing is promoted by investment in repair in early life together with retention of damage