Ageing: what the Smurf?

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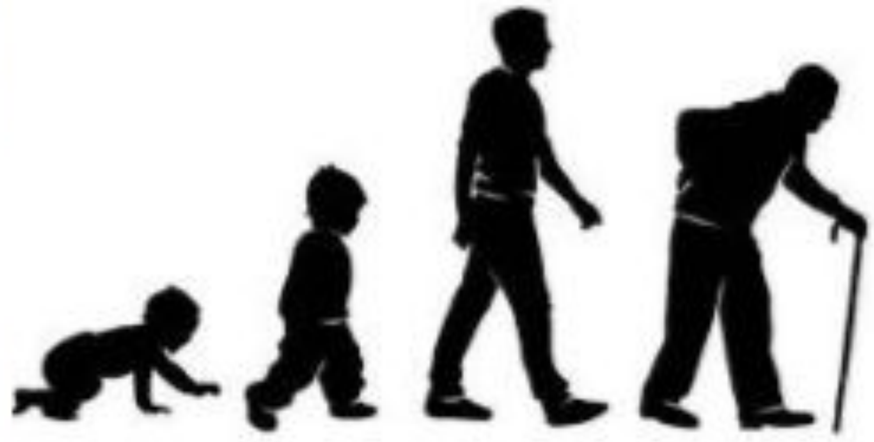
INSERM – Université de Paris

ATIP/Avenir group leader – CRI Core Fellow

A general presentation of ageing



Intuitive definition of ageing

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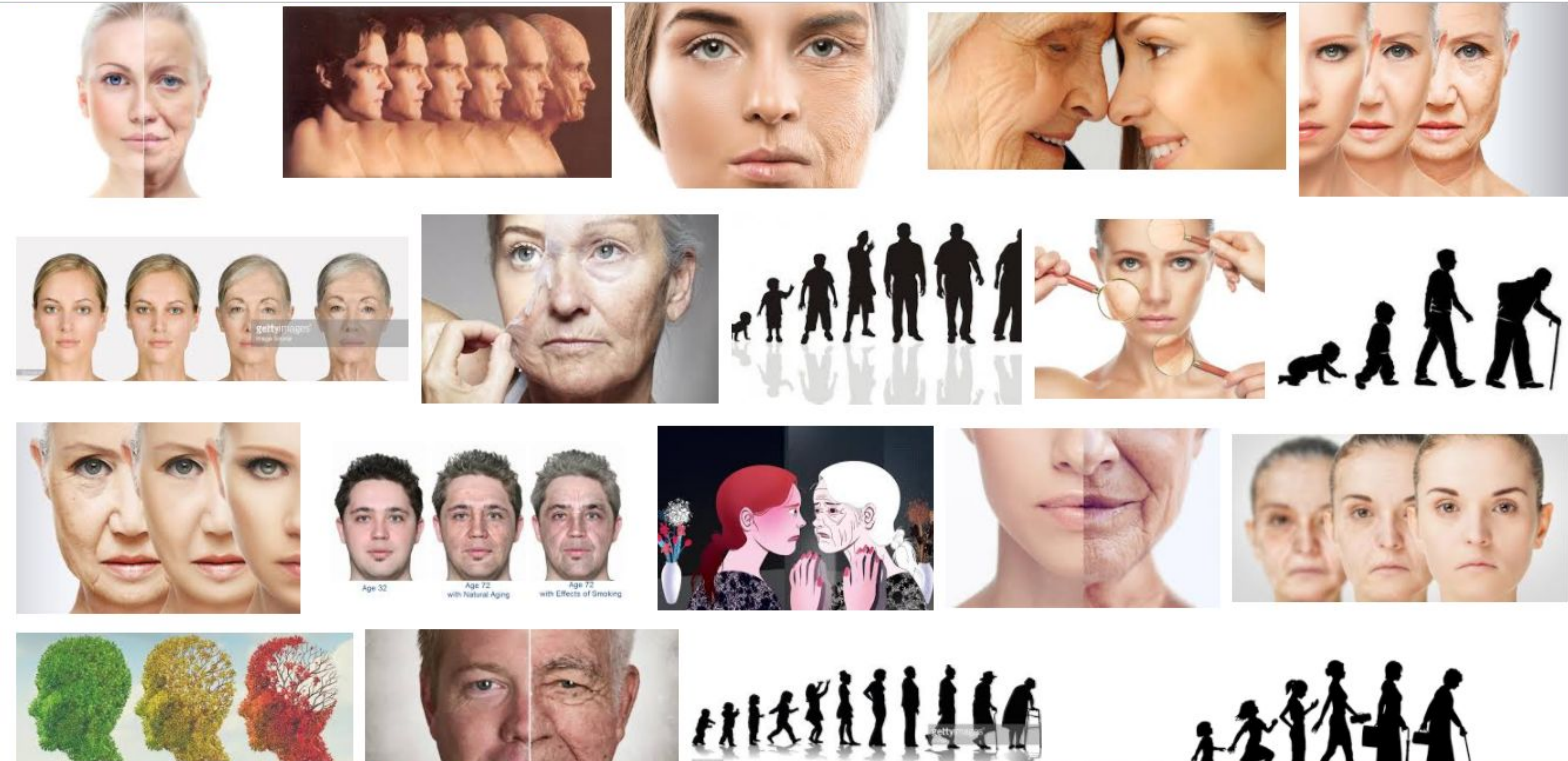

Ageing: a definition

" ..the time-dependent functional decline that affects most living organisms [..], leading to impaired function and increased vulnerability to death."

López-Otín et al, 2013

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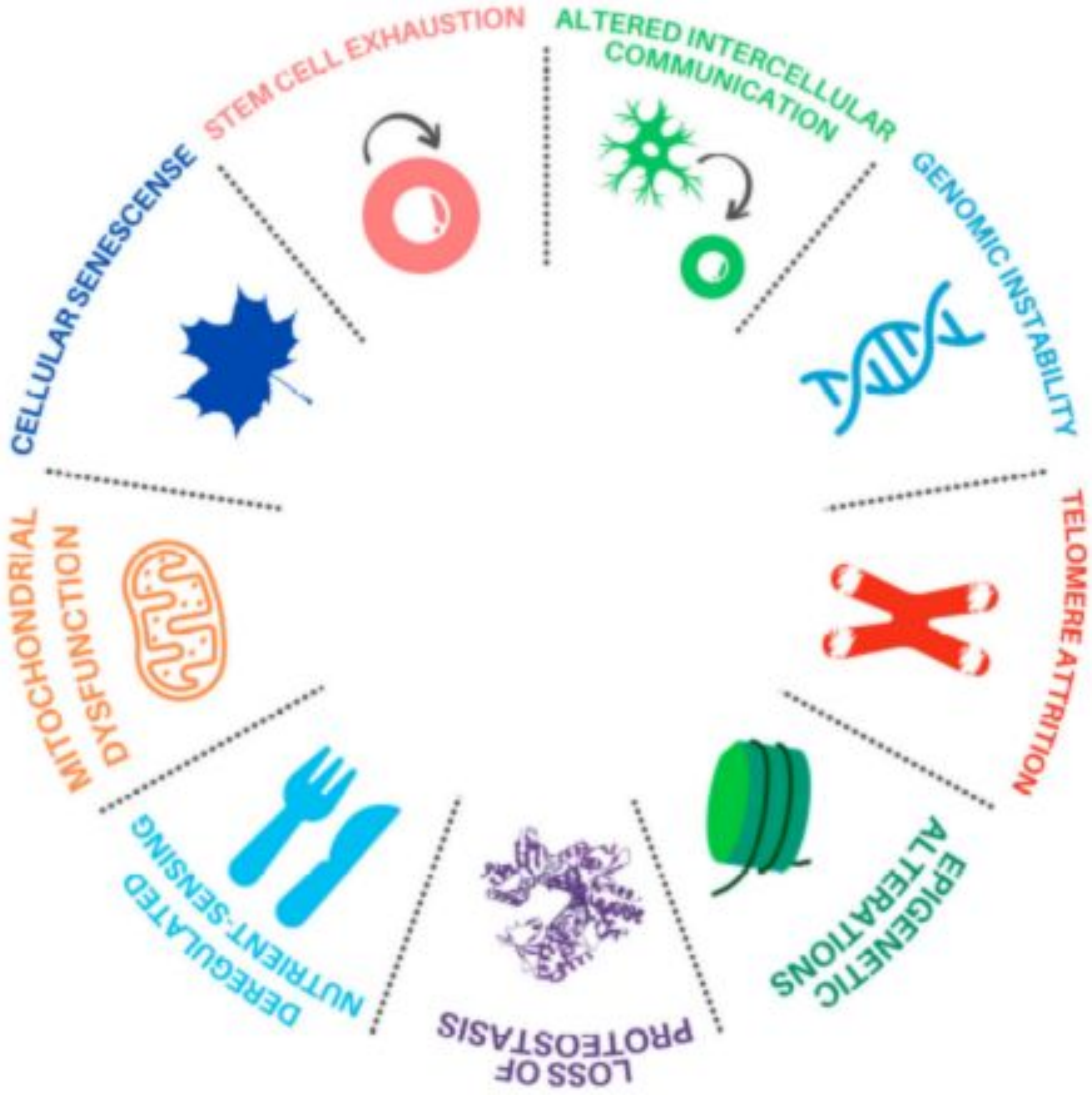

figure adapted from Guimarães et al, 2021

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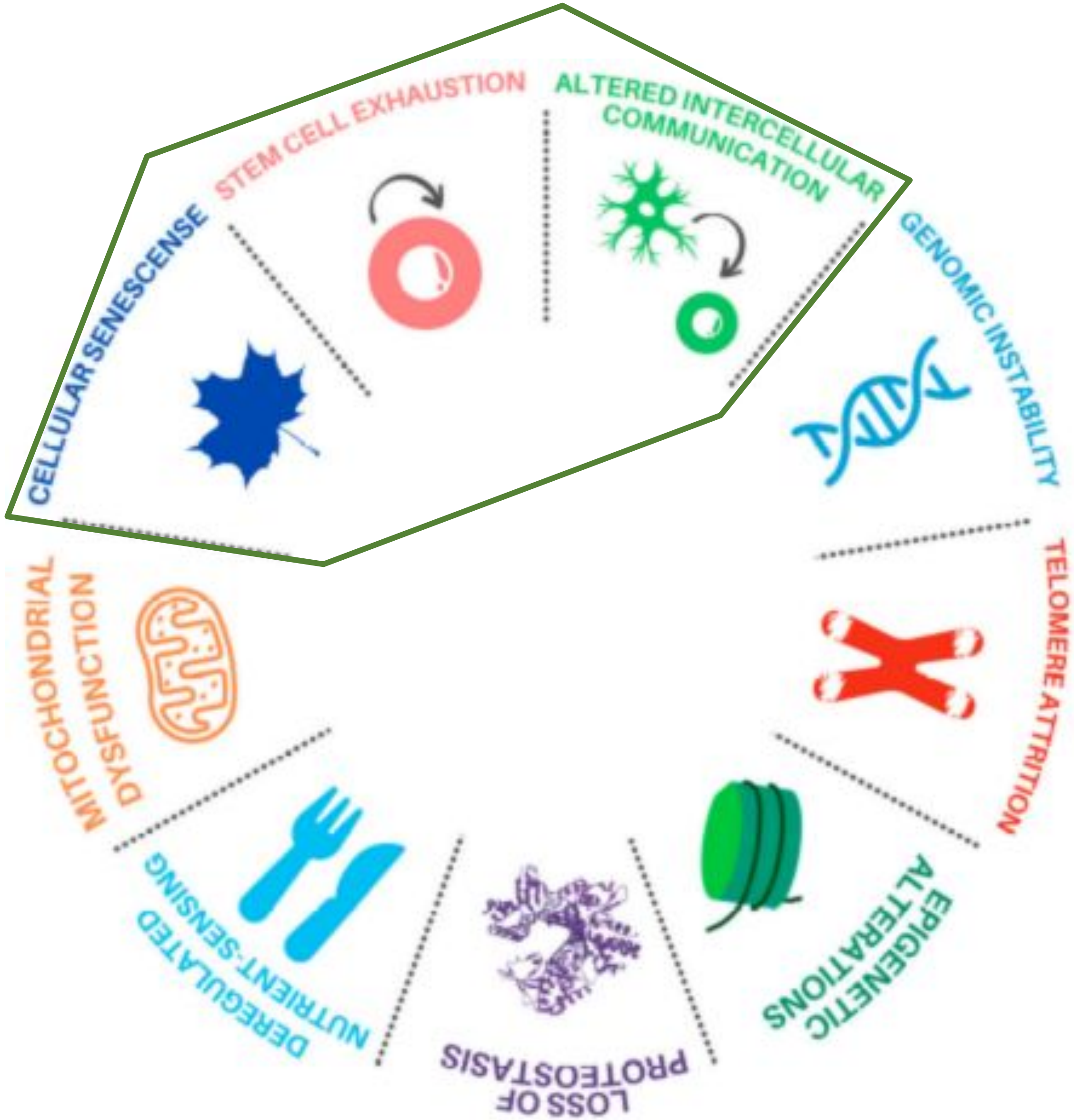

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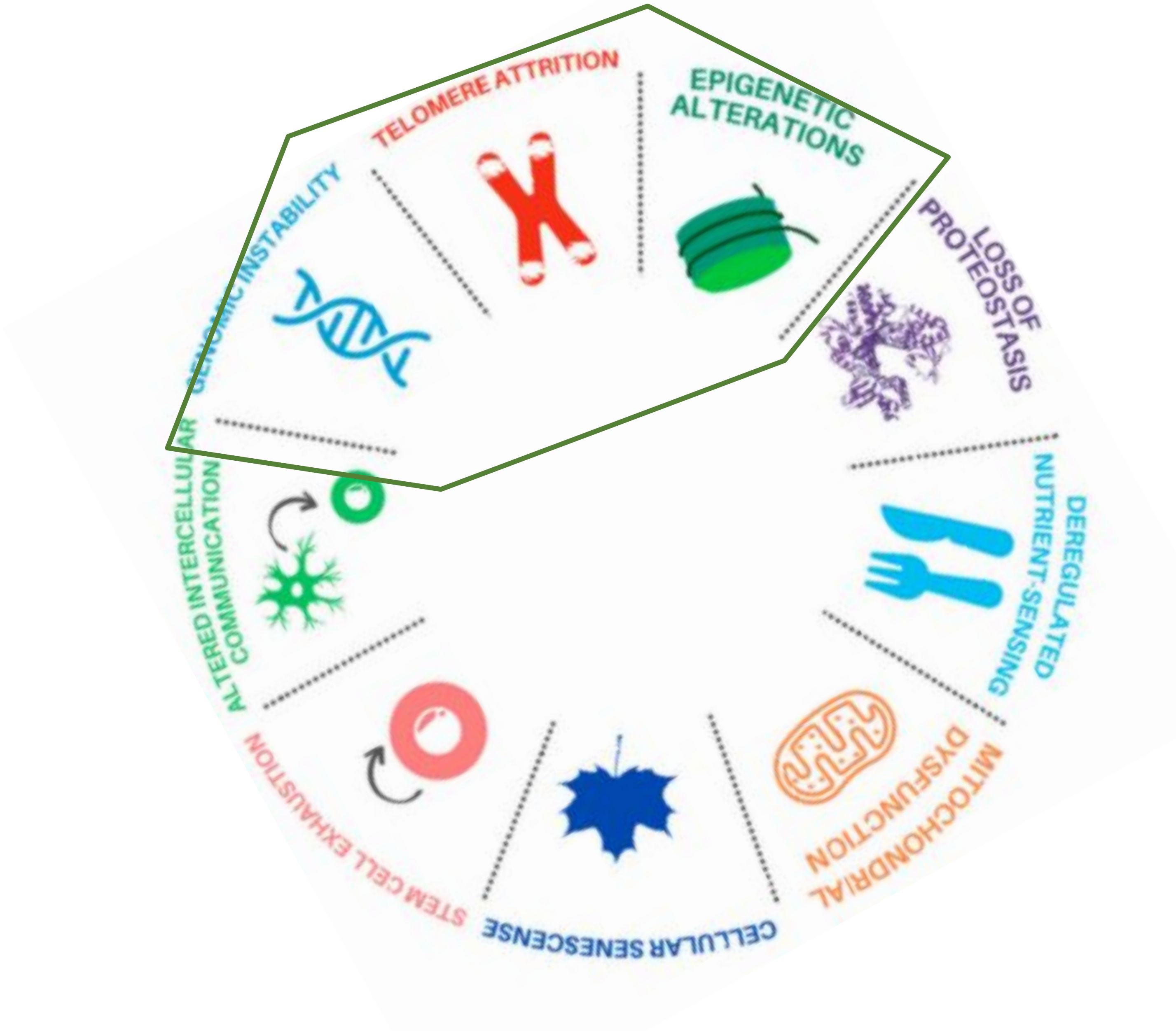

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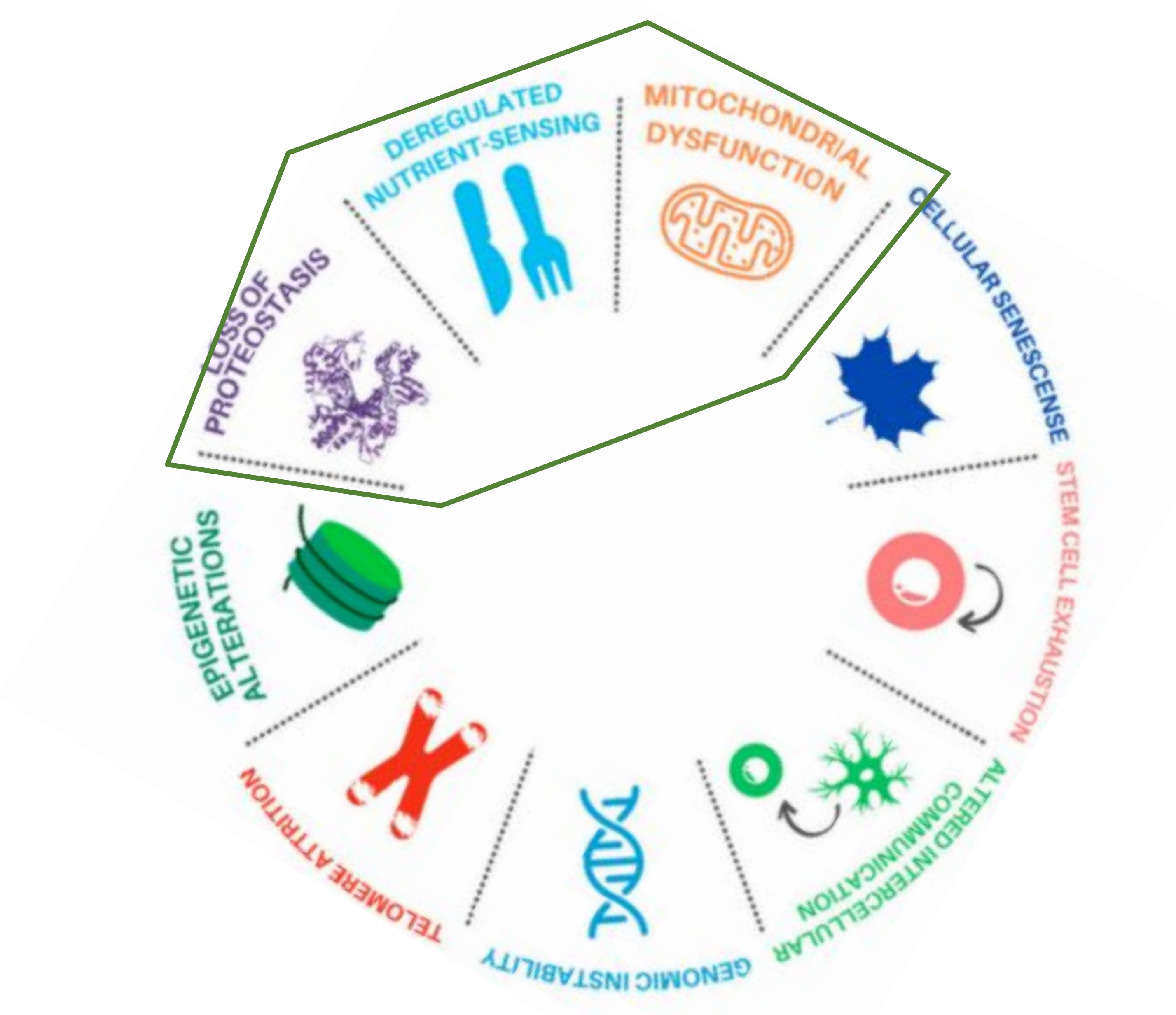

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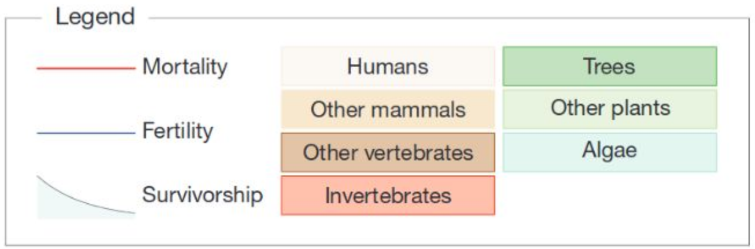
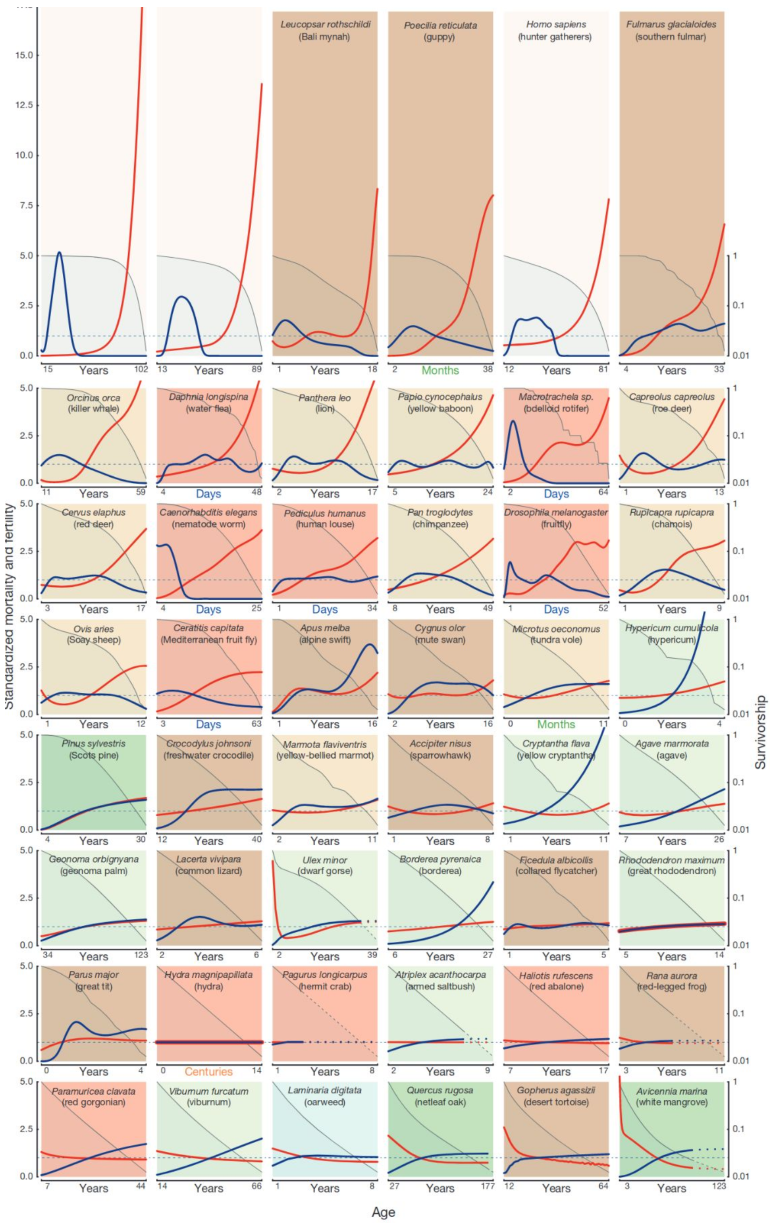
Ageing: diversity across the tree of life

$$-\frac{1}{N} \times \frac{dN}{dt}$$





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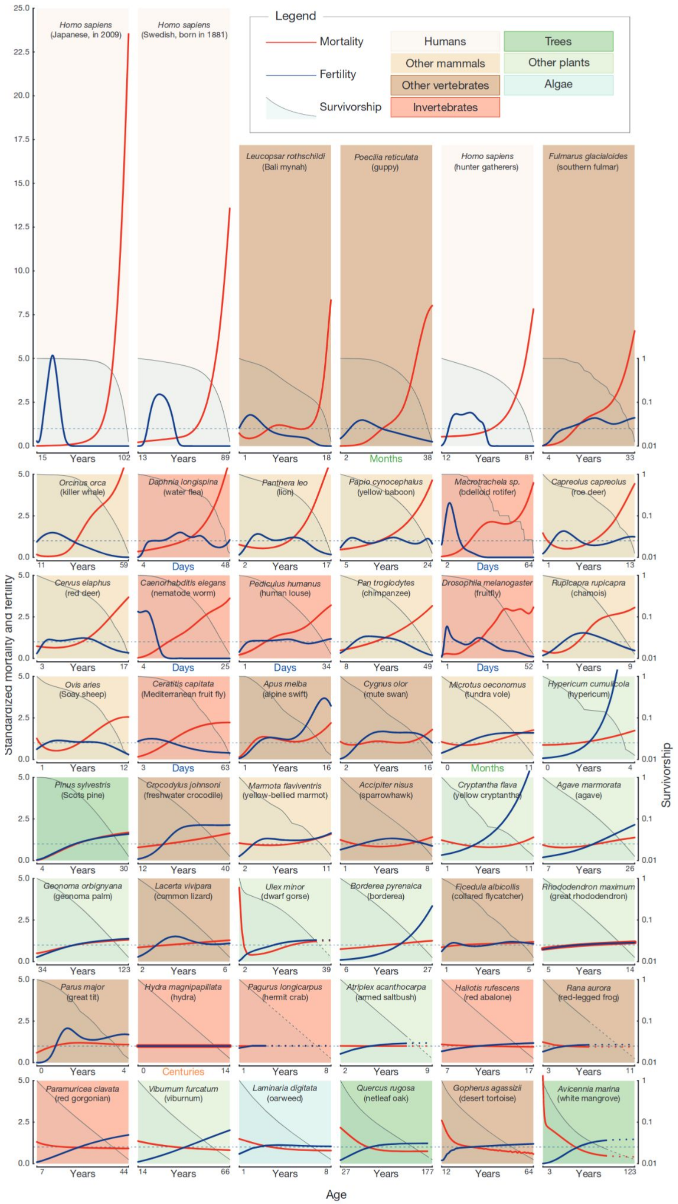

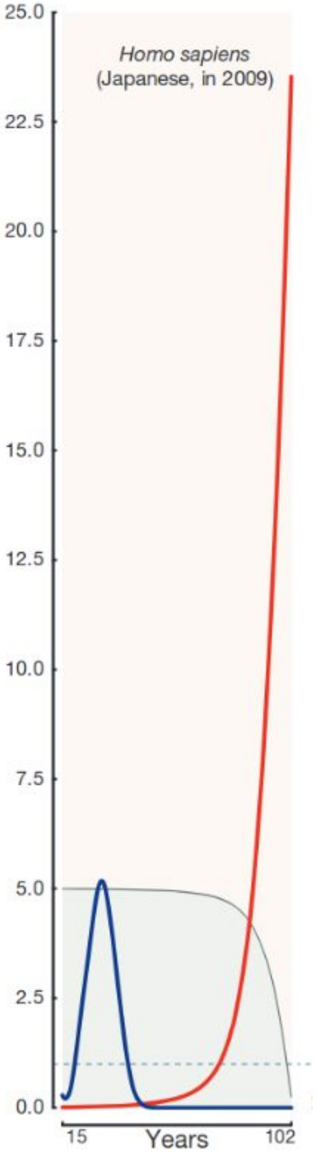

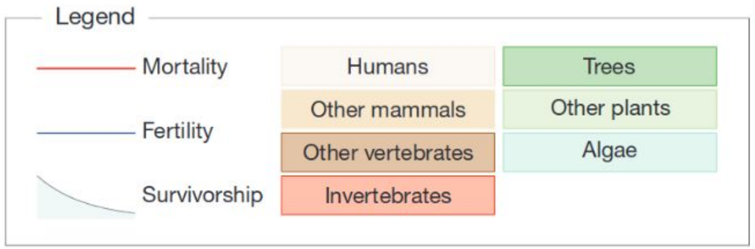

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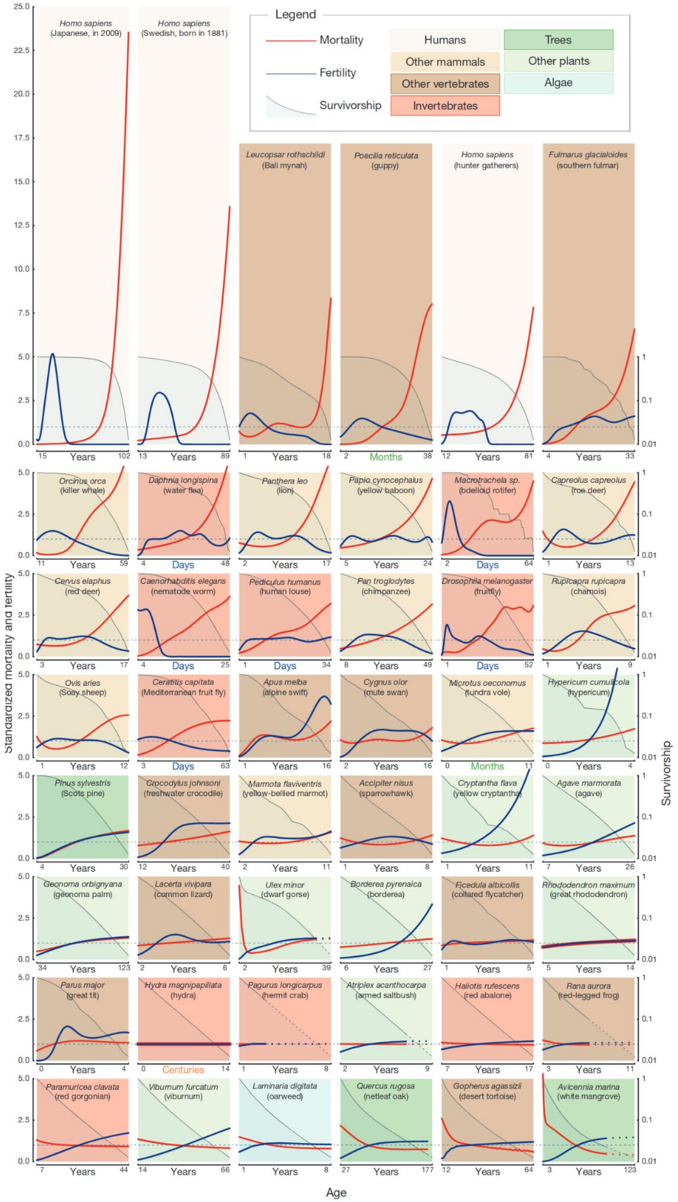

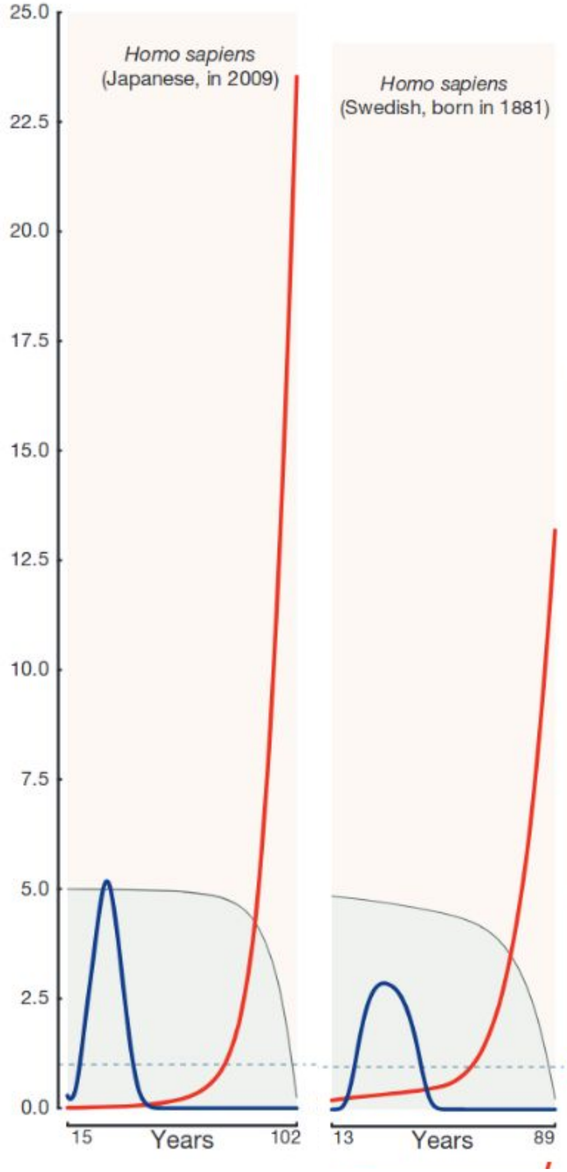

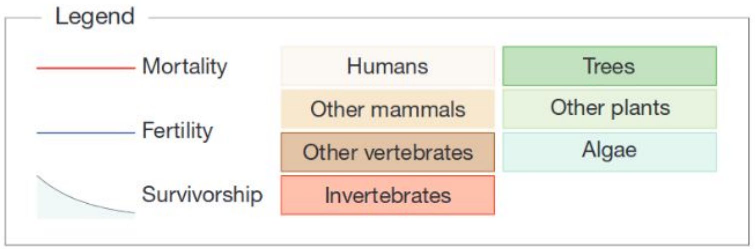

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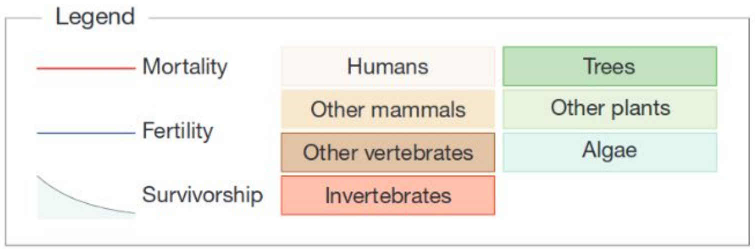

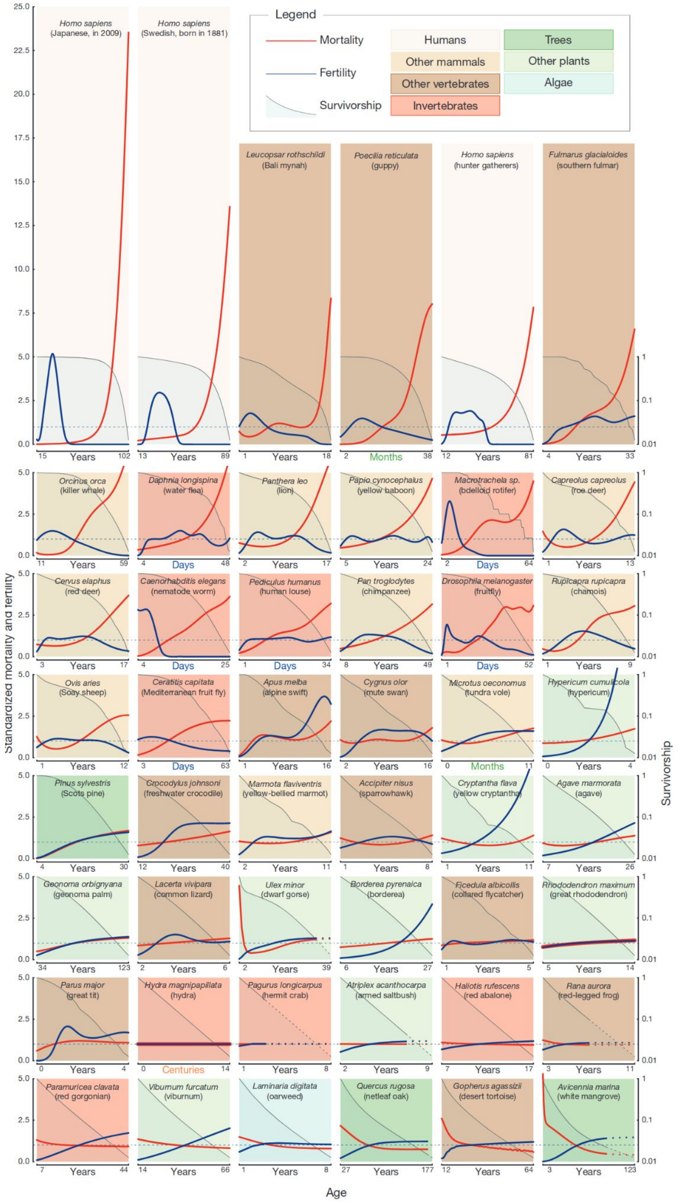

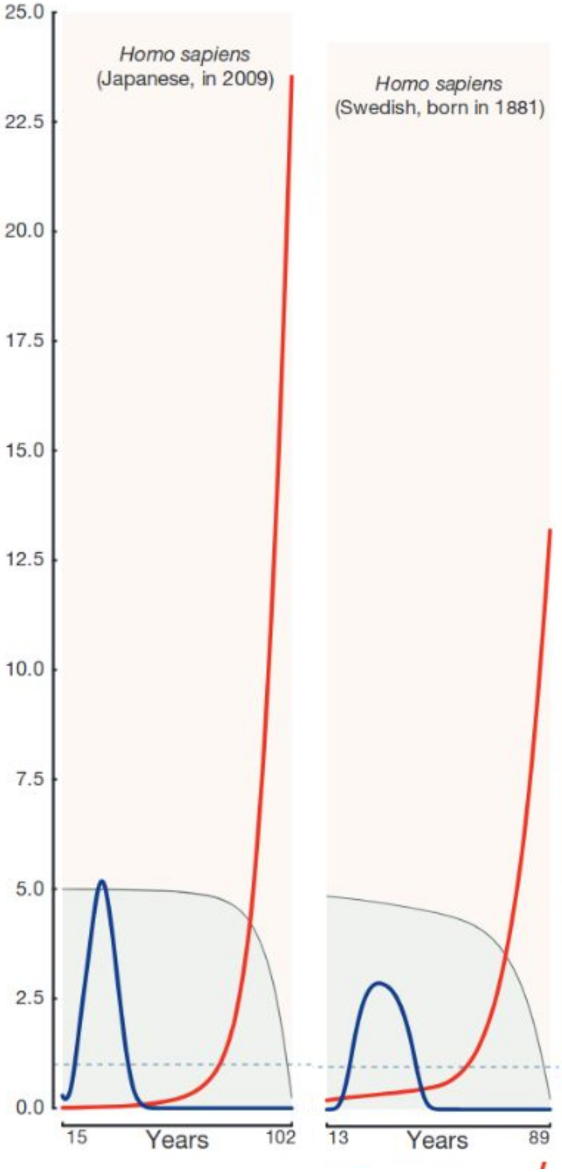

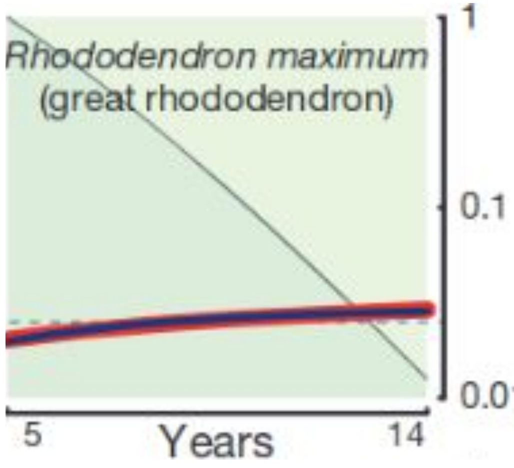

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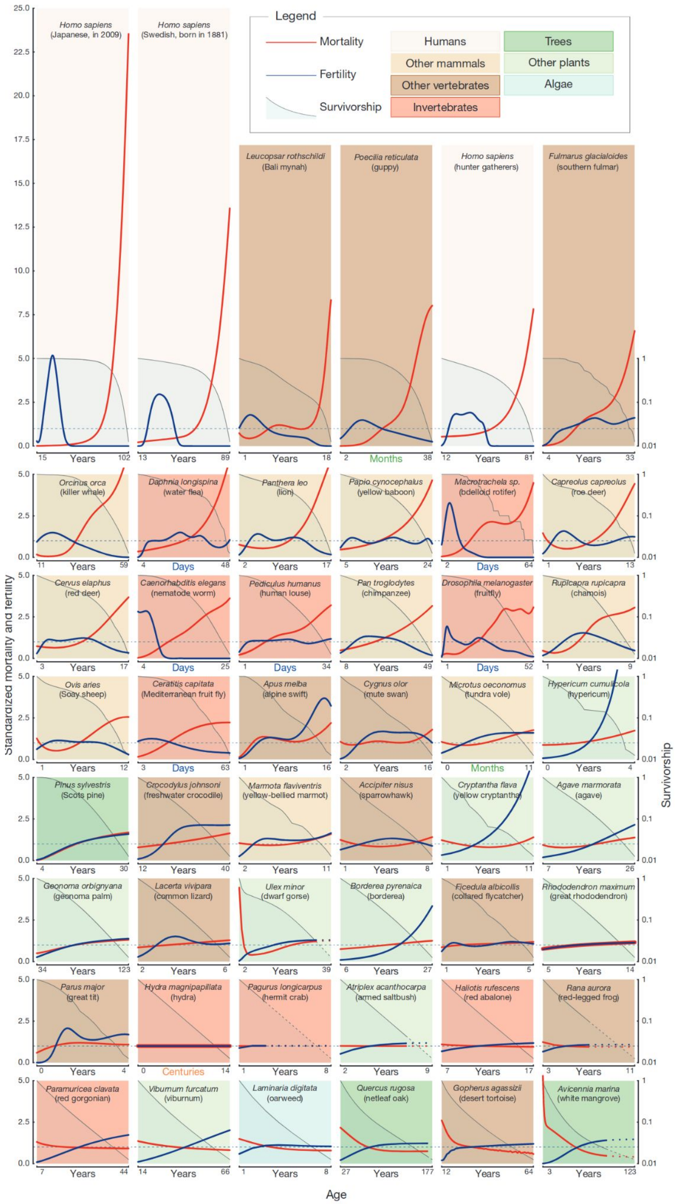
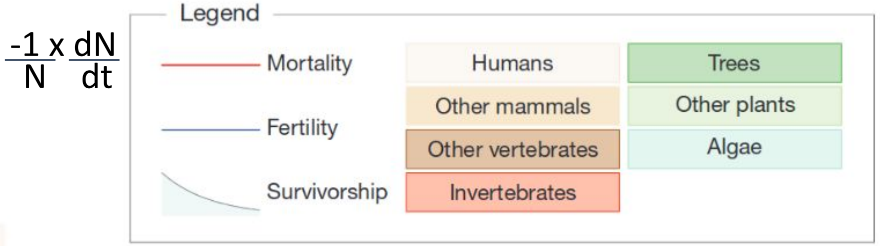
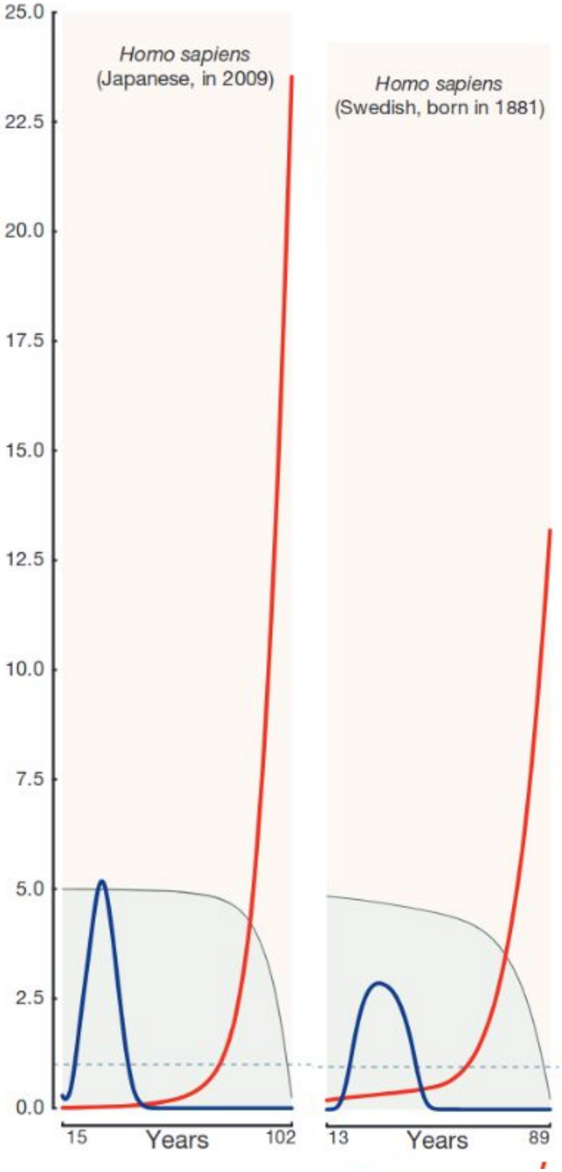
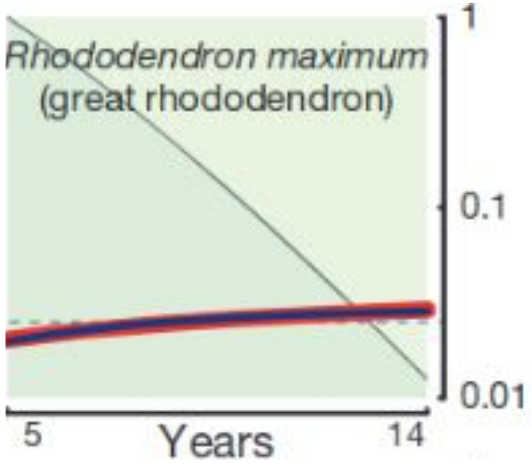
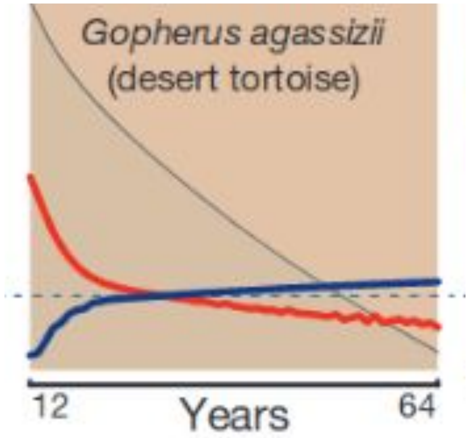




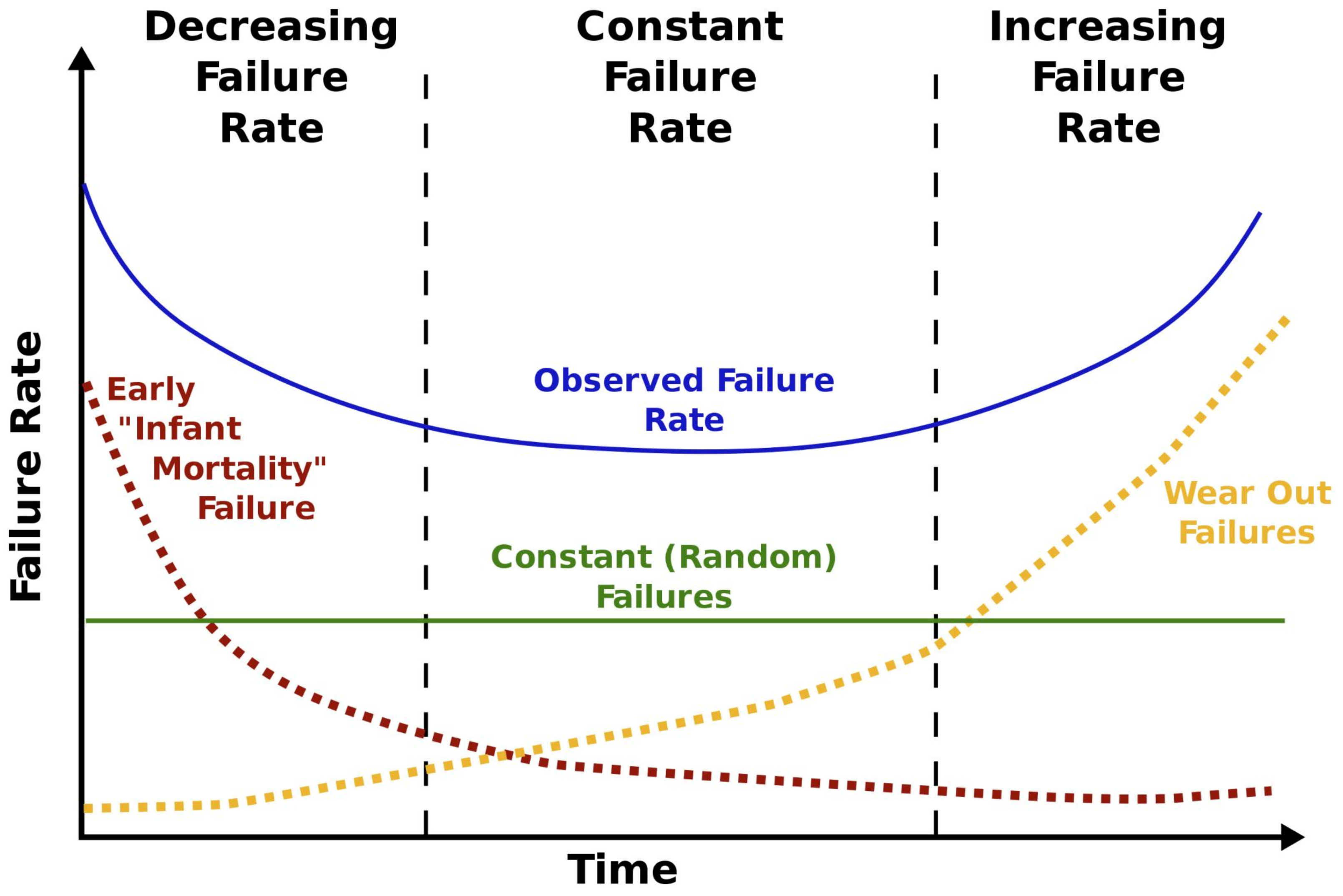






Jones et al., 2014

Ageing: a matter of reliability?

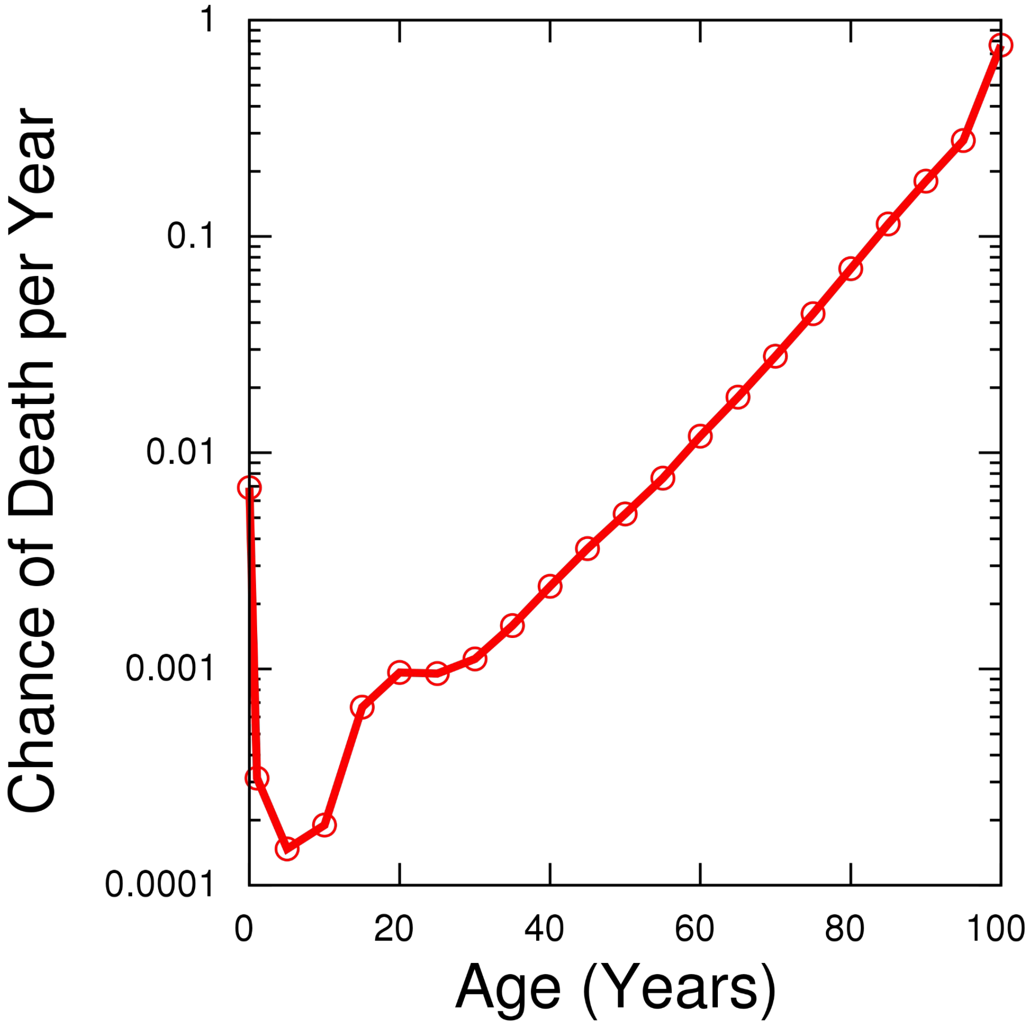


Jones et al., 2014

Mathematical modeling of ageing: Gompertz-Makeham

hazard function for the Gompertz-Makeham:

$$h(x) = \alpha e^{\beta x} + \lambda$$



How is ageing affected by environmental conditions?

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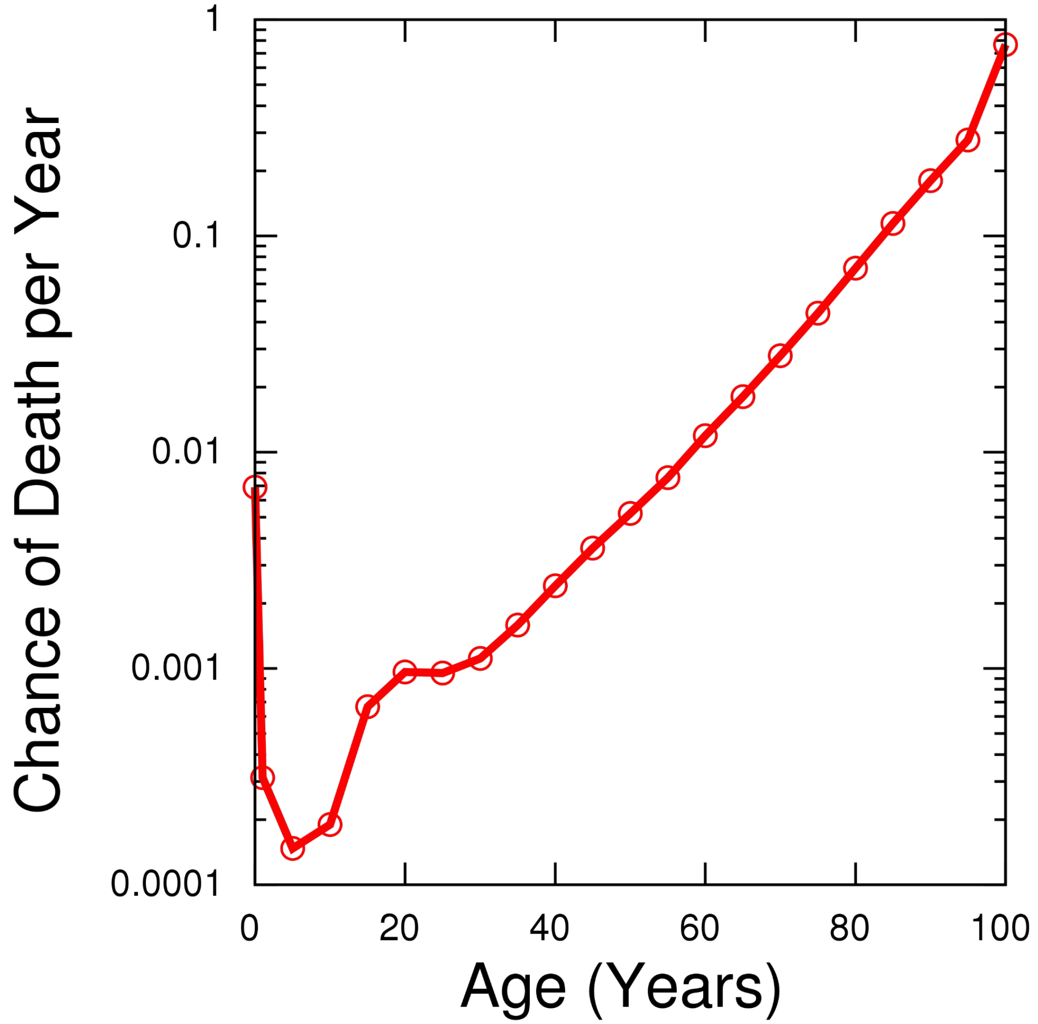
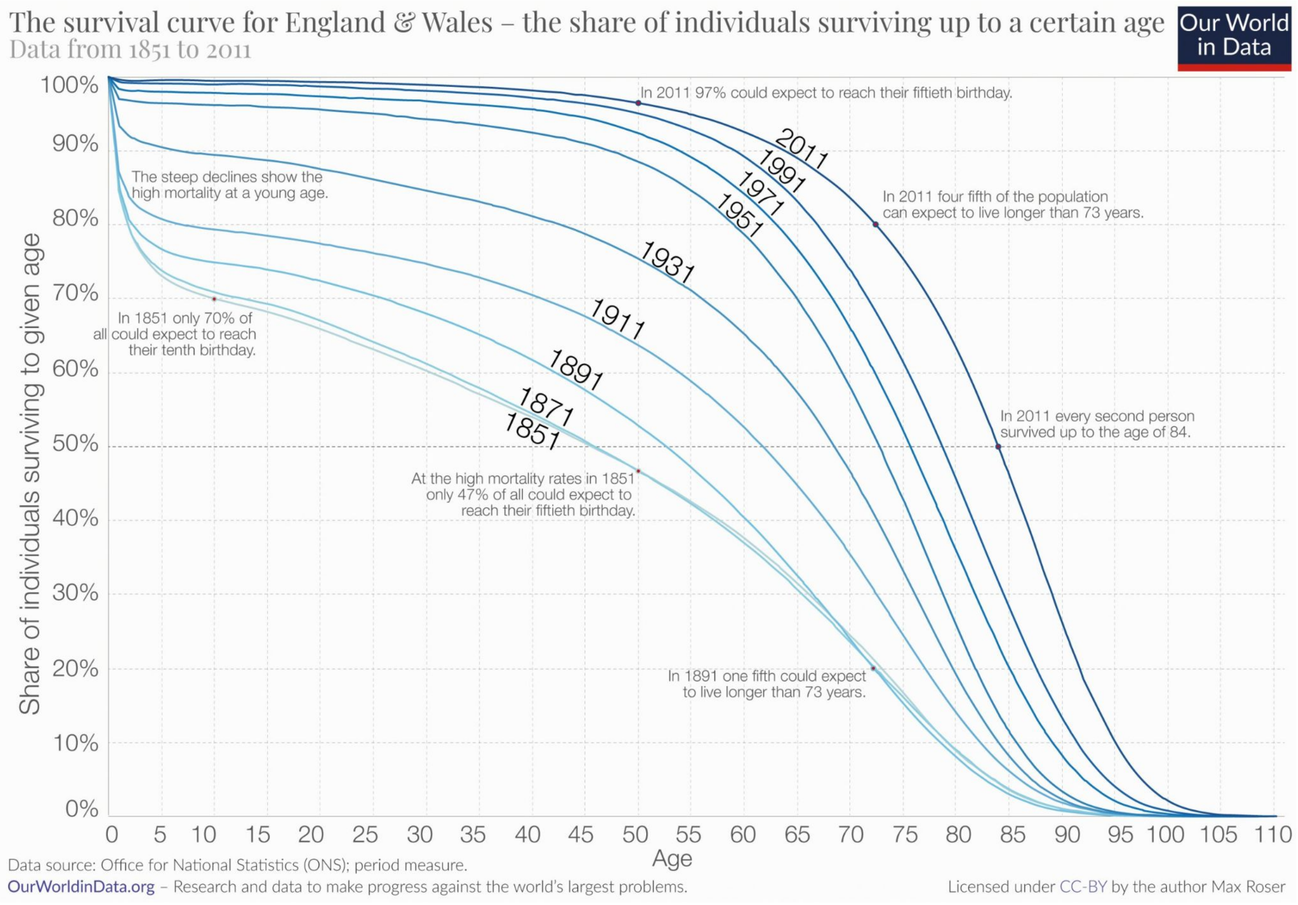
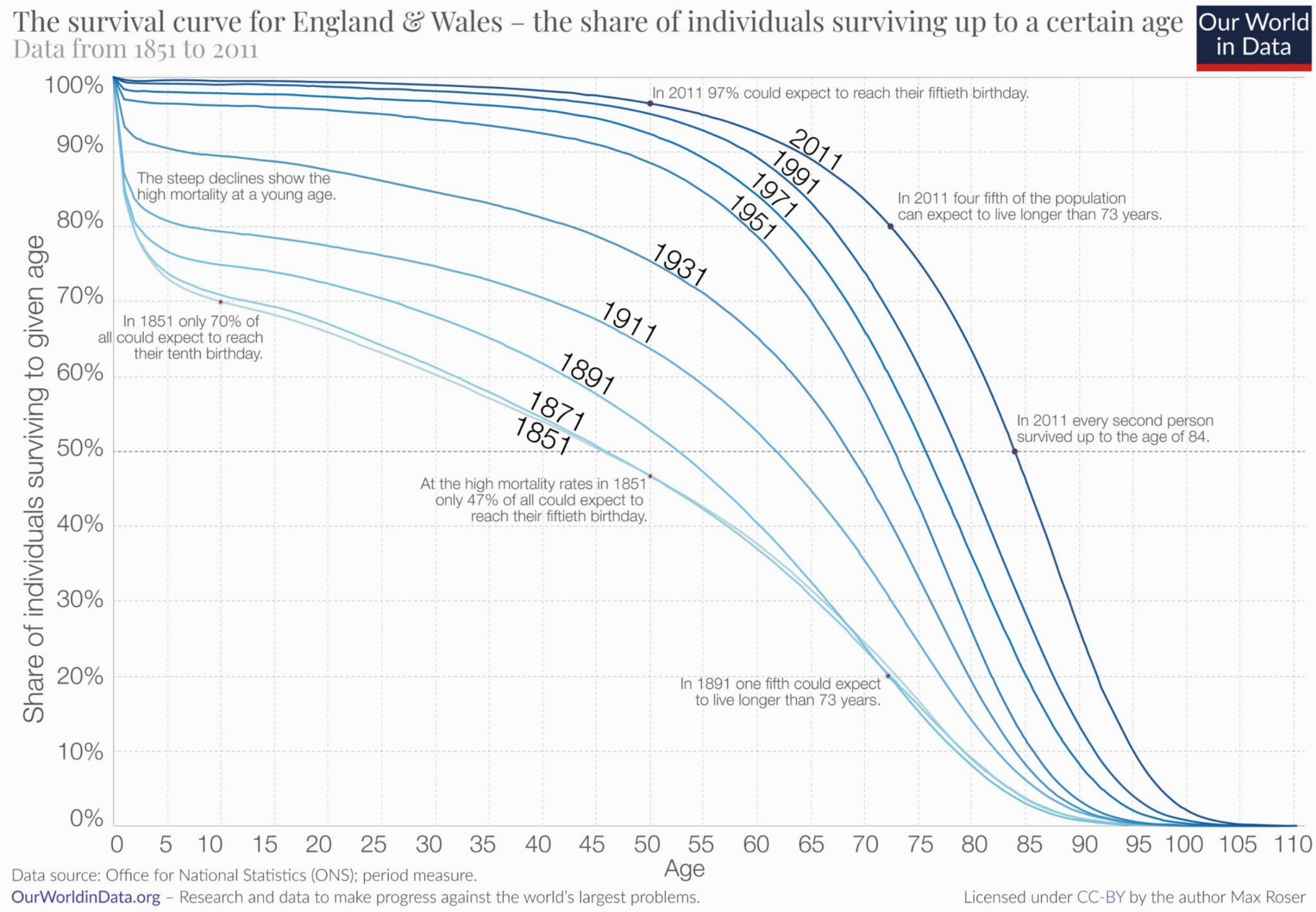
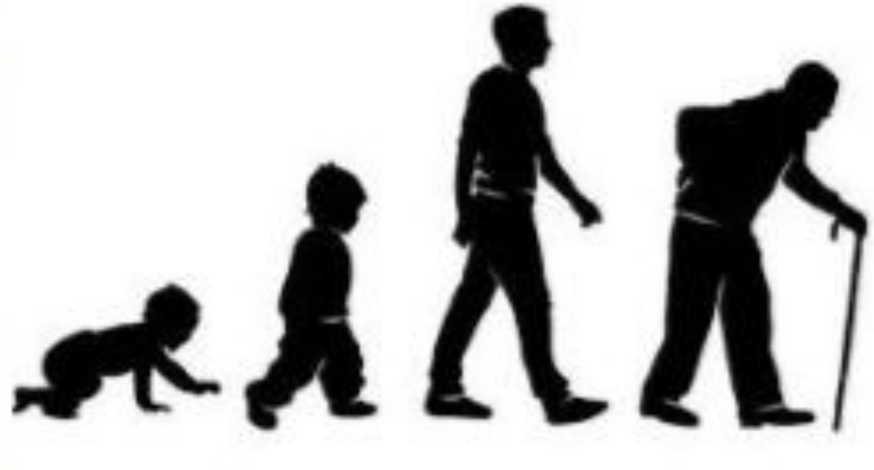




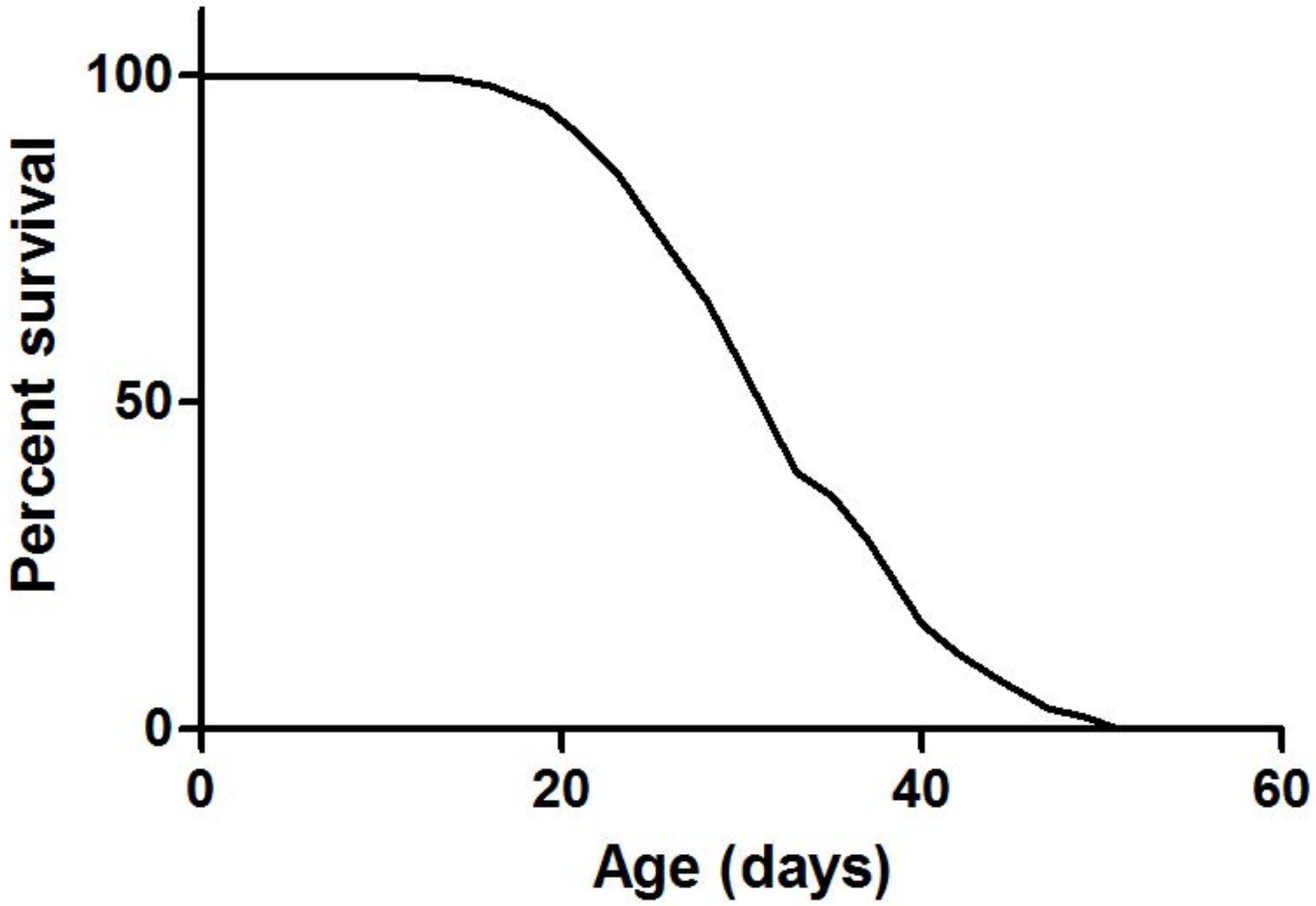
Lifespan, healthspan and life expectancy



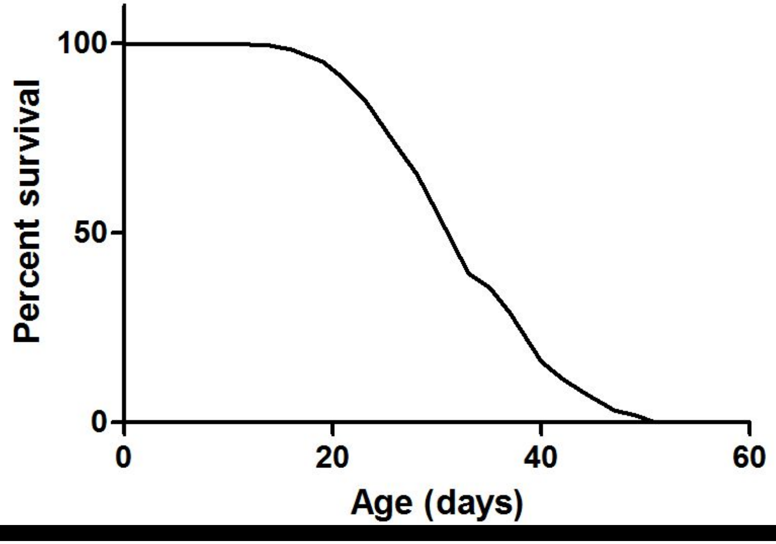
Studying ageing experimentally: a continuous process



Classical approach for studying ageing

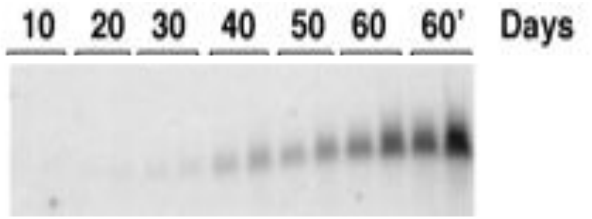


Hallmarks of ageing in a continuous ageing process



Death

Increasing systemic inflammation



- Continuous changes

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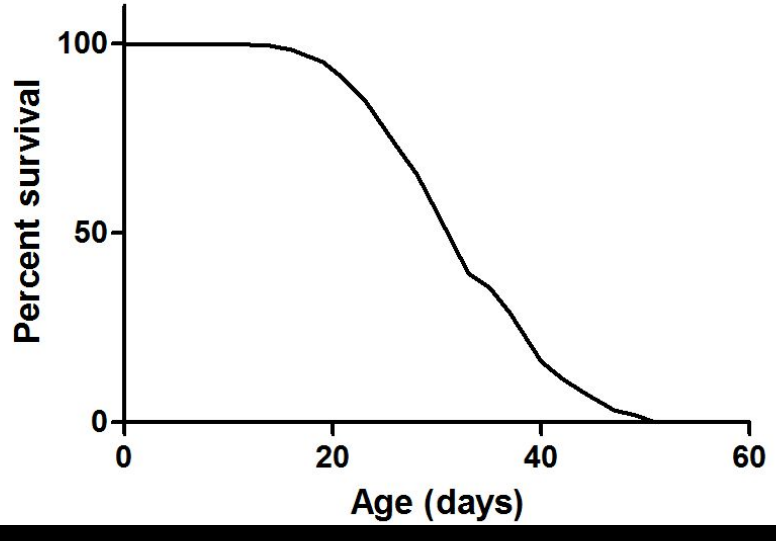
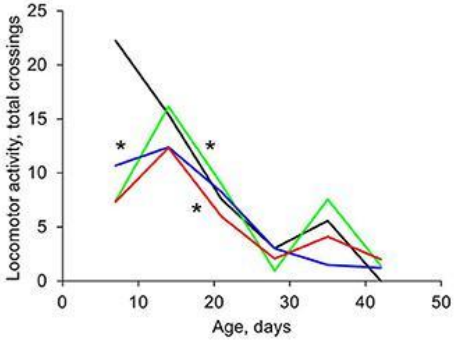


Death

decreasing motor activity



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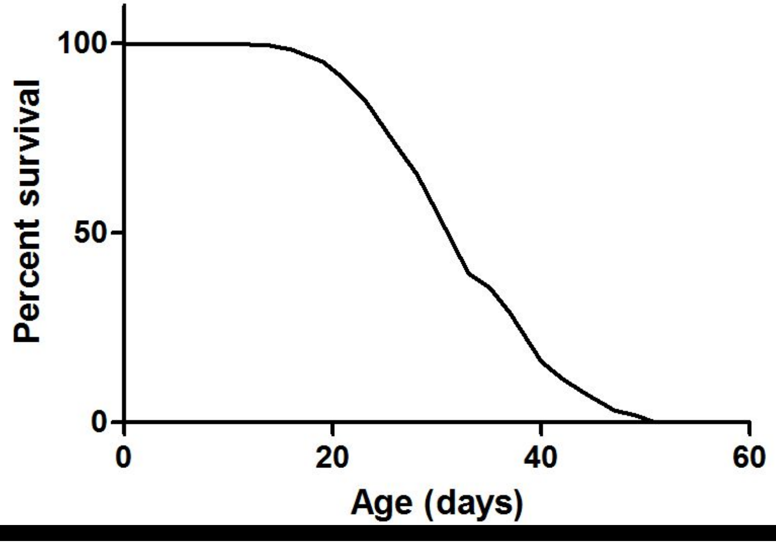
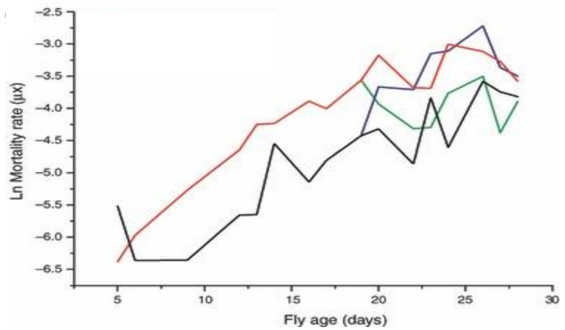


Death

exponential increase of mortality rates



- Continuous changes

Theories of ageing: why and how

Theories of ageing and its evolution: based on age changes

Structural stabilization and cross-linkage theories	
Accumulation of heterogeneous cross-links	Bjorksten (1958, 1974); Sinex (1964)
Accumulation of cross-links in collagen	Verzar (1956, 1957)
Stabilization and inactivation (insolubilization) of intercellular structural proteins	Nagorny (1940)
Accumulation of –S–S, inter- and intra- molecular bonds	Oeriu (1964)
Accumulation of protein-DNA cross-links and progressive stabilization of chromatin complexes	Nikitin (1954); von Hahn (1966, 1970)
Cross-links between DNA molecules	Cutler (1976)

Structural post-translational changes and modifications in proteins	
Progressive demethylation of proteins	Parhon & Oeriu (1962)
Progressive deamination of glutaminyl and asparaginyl residues in proteins	Robinson (1974); McKerrow, (1979)
The age-altered enzymes theory (age-related accumulation of conformational changes in protein leading to the inactivation of enzymes)	Gershon (1979); Rothstein (1979, 1984)
Decrease of phosphorylation and acetylation of chromatin proteins as the cause of defects and decline in transcription	Kanungo (1980)

Theories based on quantitative changes of proteins	
Loss of irreplaceable molecules or enzymes	Butschli (1882); Sinex (1957)
Relative increase of inactivated non-renewable metaplasmic proteins	Nagorny (1940)

Changes in protein biosynthesis (translation)	
Accumulation (gradual) of random errors of protein synthesis	Medvedev (1961, 1962)
The error catastrophe theory	Orgel (1963)

Age changes of RNA and DNA	
Accumulation of single and double breaks and other changes of DNA	Vilenchik (1970), Price & Makinodan (1973), Chetsanga *et al.* (1975)
Decrease of DNA methylation	Holliday (1985)
Accumulation of metal ions and adducts in DNA	Goldstein *et al.* (1968); Cutler (1976)
Age changes of RNA processing	Medvedev (1986)

Age changes at genetic and cellular level	
Accumulation of somatic mutations and chromosomal aberrations	Szilard (1959); Failla, (1960); Curtis (1966)
Selective loss of ribosomal RNA genes	Johnson *et al.* (1972)
Accumulation of transposable elements in somatic cells	Murray & Kirkwood (1984)
Loss of adaptive cellular mechanisms	Adelman (1975)
Accumulation of viral genomes	Gaidusek (1972)
Accumulation of insoluble waste products (lipofuscin and others) in differentiated cells	Sheldrake (1974); Sohal (1981); Yiengst *et al.* (1959); Strehler (1964)
The mitochondrial theory	Miguel *et al.* (1980); Harman (1983); Rochter (1988)
The cell membrane theory	Carpenter & Loynd (1968); Zs.-Nagy (1978, 1987)
Loss and irreplaceable cells and stem cells	Kohn (1965); Hayflick (1975); Rohme (1981)

Age changes at organ and functional levels	
Immunobiological theories	Walford (1969); Burnet (1970)
Endocrine theories	Korencheysky (1961)
Hormone/neurotransmitter, receptor changes theories	Finch (1976); Roth (1979); Frolkis (1982)
The connective tissue changes theory	Bogomolets (1947)
Impairment in physiological control mechanisms	Shock (1974, 1977)
Failure of the adaptive physiological mechanisms	Frolkis (1968)

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Theories of ageing and its evolution: primary damages

Wear-and-tear theories	Sacher (1966)
Damage factors of metabolic origin and toxic theories	
Ageing is a result of autointoxication	Metchnikoff (1904, 1907)
General toxic theory of ageing	Muhlmann (1924); Metalnikov (1937); Korenchevsky (1956)
Waste products theory of ageing	Sheldrake (1974)
Calciphylaxis (calcium petrification)	Selye (1962)
Absence of perfect coordination between different metabolic pathways	Komarov (1966)
Errors of protein synthesis	Medvedev (1962); Orgel (1963)
Side-reactions of intermediate metabolites	Milch (1963)
Side reactions and leaks of lysosomal proteases and DNAases	Allison & Paton (1965); Hansford (1983)
Damage factors intrinsic for chemical and biological reactions in general	
The general free radical theory of ageing	Harman (1956, 1981)
Oxygen radical-mitochondrial injury and other variants of the free-radical theory	Miguel-Fleming (1986)
Micro-thermal releases during chemical reactions as age-damage factor	Strehler (1959)
Ageing as entropy	Sacher (1967); Bortz II (1986)
The 'hit' theory and somatic mutation theories	Szilard (1959); Curtis (1966)
External and environmental damage factors	
Damaging effects of heavy water (D_2O) on metabolic reactions	Hakh & Westling (1934); Griffith (1973)
Damaging effects of D-isomers of normal metabolites	Alpatov (1948); Kuhn (1955); McKerrow (1979)
Cosmic and environmental radiation	Alexander (1957)
Damages from ions of heavy metals	Eichorn (1979)
The stress damage theory	Selye (1970)

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Theories of ageing and its evolution: genetic programs

Active morphogenetic programme switched on by reproduction processes	
Suggested for monocarpic plants, some invertebrates (octopus), some fish species (Pacific salmon, freshwater eels, etc.), Australian marsupial mouse	Orton (1929); Woolhouse (1967); Berdyshev & Protsenko (1972); Kirkwood & Cremer (1982); Diamond (1982)
Active morphogenetic programme of ageing linked to changes of environment	
Seasonal factors (shorter days, dry season, temperature) switch on ageing of tree leaves, many insects and other invertebrates)	Krenke (1940); Leopold (1961); Woolhouse (1967); Rockstein *et al.* (1977)
The programmed suicide	
Suggested as an explanation of nematode death by cell suicide, or formation of adult forms (from larva) with some functions (eating) missing	Evans & Womersley (1980); Hedgecock *et al.* (1983)
Passive, slow morphogenetic ageing	
Theories of ageing as a continuation of differentiation, deterministic mechanism of ageing, ageing as over-differentiation, ageing as an increase of gene repression	Minot (1908); Metalnikov (1937); Vilenchik (1971); Krooth (1974)
Theory of random (noisy) residual morphogenesis due to uncomplete repression of developmental programme	Medvedev (1964, 1966)
Theory of ageing as dysdifferentiation, or loss of gene repression, 'leaky' genes, dysregulation of sequential transcription, etc.	Kanungo (1980); Smith & Lumpkin (1980); Cutler (1982, 1985); Sarkander (1984)
Codon restriction theory of development and ageing	Strehler *et al.* (1971)
Theories of existence of specific and non-specific genes of ageing	
Late acting pleiotropic deleterious genes as a cause of ageing	Medawar (1957); Williams (1957)
Ageing rate as a balance between action of mutator and anti-mutator genes	Presber *et al.* (1976); Lints (1978); Deerberg *et al.* (1980).
Programmed synthesis of mitotic inhibitor and transcription and translation inhibitors which switch on function deterioration	Strehler (1980)
Identification of ageing accelerating mutations	Brown (1979)
Theories of genetic syndromes of premature ageing (Progeria, Down, Werner, and other syndromes)	Martin (1978); Umansky (1982)

Theories of the existence of specific genes of longevity (longevity determinant genes, anti-ageing genes)	
Identification of genes prolonging life in low eukaryotes	Lints (1978); Munkres *et al.* (1984)
Theories which show that the substantial increase of human longevity in evolution of primates was linked with only a few new genes	Sacher (1975); Cutler (1975); Strehler (1979)
Theories which try to identify genes of longevity in mammals by hybridization selection and other methods	Clarke & Maynard Smith, (1955); Russell (1978); Cutler (1982)
Existence of genetic programme for extra-correction which is switched on in germ cells and in immortal cell lines	Orgel (1973); Kirkwood (1977)
Theories of existence of biological clock (pace-maker) for ageing	
Temporal genes theory. Ageing as the loss of temporal organization. Relations between biological rhythms and ageing	Samis (1968); Samis & Capobianco (1977); Flodin (1984); Brock (1985)
The endotomy theory. Shortening of DNA during replication or marginotomy in post-mitotic cells as a timer	Olovnikov (1971, 1973); Smookler, Reis & Goldstein (1980)
Sequential methylation of repeated DNA sequences as a molecular timer	Holliday & Pugh (1975)
Finite replication capacity of Protozoa. Limited potential of cell division *in vitro* and *in vivo* as a cell clock	Maupas (1888); Hayflick (1965, 1977, 1980)
The commitment theory of cellular ageing	Holliday *et al.* (1977)
Theories of neuroendocrine master clock or hepothalamic timer of ageing	Frolkis (1982); Everitt (1980)

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Theories of ageing and its evolution: species-specific difference

The rate of living theories of longevity

Theories of inverse correlation between lifespan and metabolic rate per unit of growth rate	Rubner (1908); Pearl (1928); Sacher (1959); Sahal (1976)
Inverse correlation between environmental temperature and lifespan in poikilothermous animals. Life-extension effects of stupor and hibernation	Strehler (1959, 1961); Maynard Smith (1962); Shaw & Bercaw (1962); Sucher (1967)
Theories originated from the increase of maximal lifespan in rodents by calorie restricted diets	McCay (1934, 1939)

Theories which suggest correlation between growth rate and ageing rate

Ageing of mammalians is more rapid after the growth cessation: longer growth period or growth delaying diet increases lifespan	McCay *et al.* (1935); Sacher (1965, 1975); Comfort (1979)

Positive correlation between the duration of development and lifespan

Longer-lived species develop at slower rates. (Species with a longer period of development and maturation need longer lives to provide parental care and protection.)	Sacher (1975); Cutler (1976); Economes (1982*ab*); Dilman (1986)

Size–lifespan correlation theories

Body weight correlates positively with the longevity in mammals	Sacher (1959)
Brain size–lifespan correlations. Larger brains make evolutionary selection of longer lifespan necessary	Sacher (1975)
Positive correlation between size, height and longevity among tree species. Protective role of large sizes from disease, predators, etc.	Todd (1978)

Lifespan correlations with changes at the molecular level

The hypothesis which suggests higher fidelity of syntheses of macromolecules in longer-lived species and cellular clones	Kirkwood & Holliday (1979)
Immortal germ cells may have more comprehensive repairs and may have higher accuracy of synthesis than somatic cells	Kirkwood (1977, 1981); Medvedev (1981)
The efficiency of the DNA repair correlates positively with species-specific longevity	Hart & Setlow, (1974); Hart *et al.* (1979*a,b*)

Correlations between ageing rate and changes at the genetic level

Higher rate of somatic mutations correlates with higher rates of ageing	Curtis (1966)
Longer-lived species may have higher levels of redundancy of vital genes. Correlation between genome size and longevity	Medvedev (1972, 1983); Cutler (1974)
Theory of the life assurance genes	Sacher (1968); Hart & Turturro (1981)
The longer-lived species have a higher number of beneficial genes (the genetic instability theory)	Strehler (1986)

Lifespan correlations at the cellular level

Polyploidization (hepatocytes and other cell types) increases the lifespan of differentiated cells	Gahan (1977); Uryvaeva (1981)
Correlation between maximal longevity potential and the activity of anti-oxidant enzymes (superoxide dismutase, etc.)	Tolmasoff *et al.* (1980); Cutler (1982, 1984)
Correlation between the intracellular and extracellular concentration of natural antioxidants (urate, ascorbate, carotene, vitamin E, etc.) and longevity	Harman (1981, 1982); Cutler (1982, 1984)
Correlation between lifespan and species-specific activity of detoxification enzymes (longer-lived animals have higher efficiency of detoxification and are more resistant to environmental toxins)	Pashko & Schwartz (1982)

Correlation between the lifespan variations and the tissue regeneration, cellular proliferation

Shorter-lived species (nematodes, insects and other invertebrates) show a complete loss of cell proliferation activity. Longer-lived species have cellular turnover in most of their tissues	Strehler (1977)
Role of informational functional and organ redundancy. The overlap of functions between tissues and more than one organ with similar functions are typical for longer-lived species	Strehler & Freeman, (1980); Cutler (1984)
The disposable soma theory. Some repair-and-error correction systems are switched off in somatic cells for energy saving reasons	Kirkwood (1977); Kirkwood & Holliday (1979, 1981)
Limited stem cell proliferation, capacity as an evolutionary clock that times senescence. Longer-lived species have higher cell doubling potential	Hayflick (1965, 1977, 1970); Hayflick *et al.* (1974); Cristofolo (1972); Rohme 1981)

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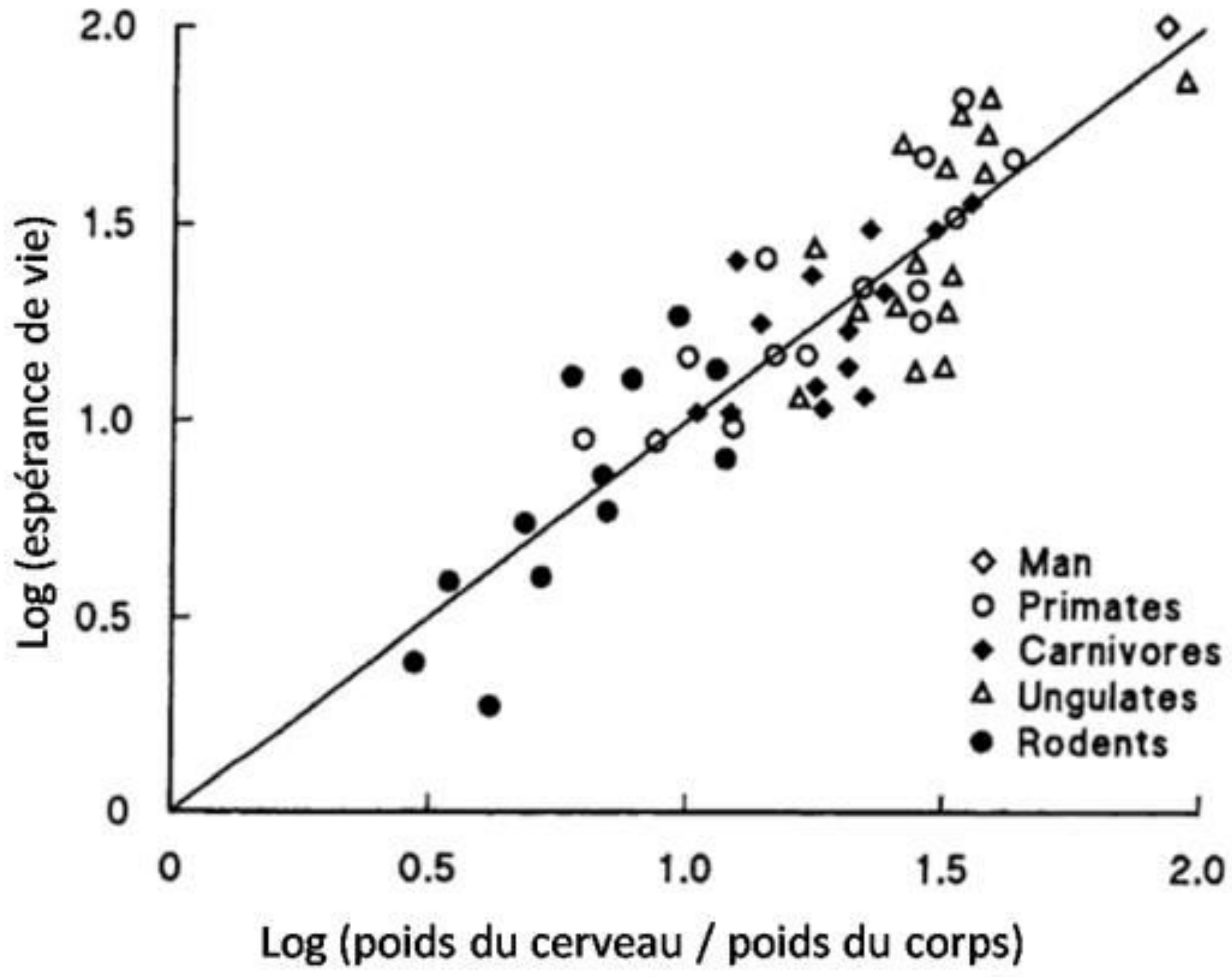
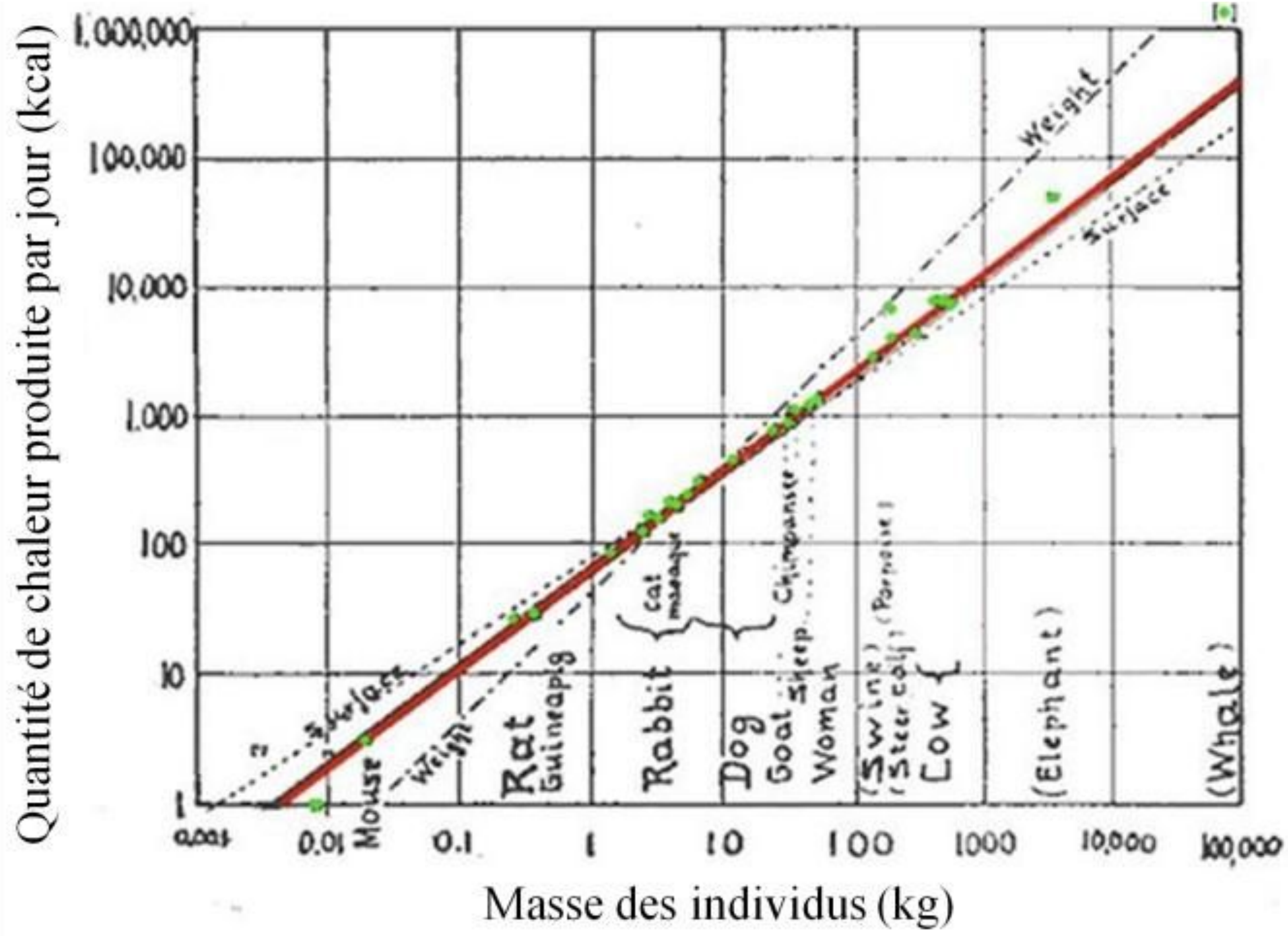
Allometry and ageing : size matters



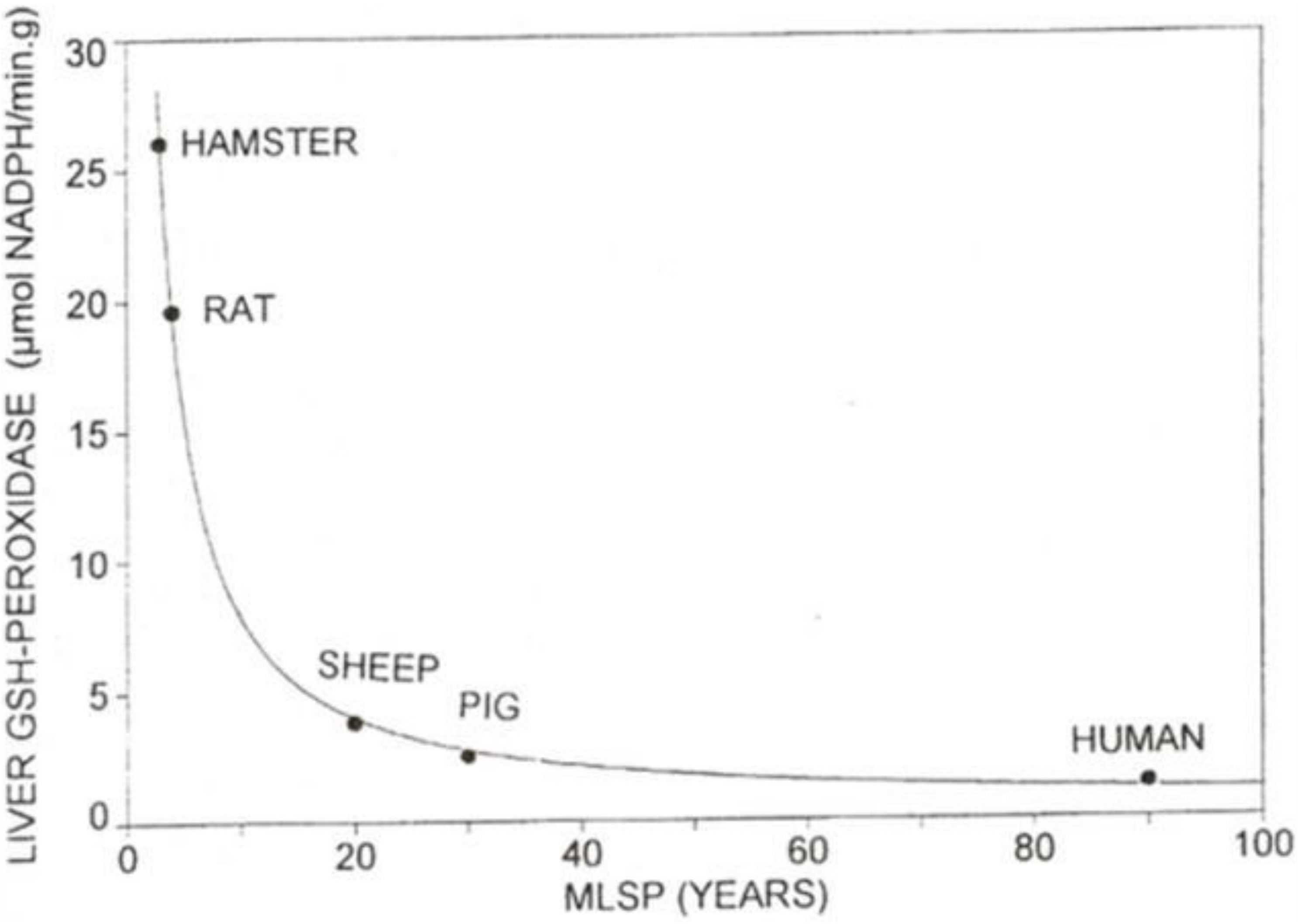
Wickens, 1998

Allometry and ageing : energy dissipation



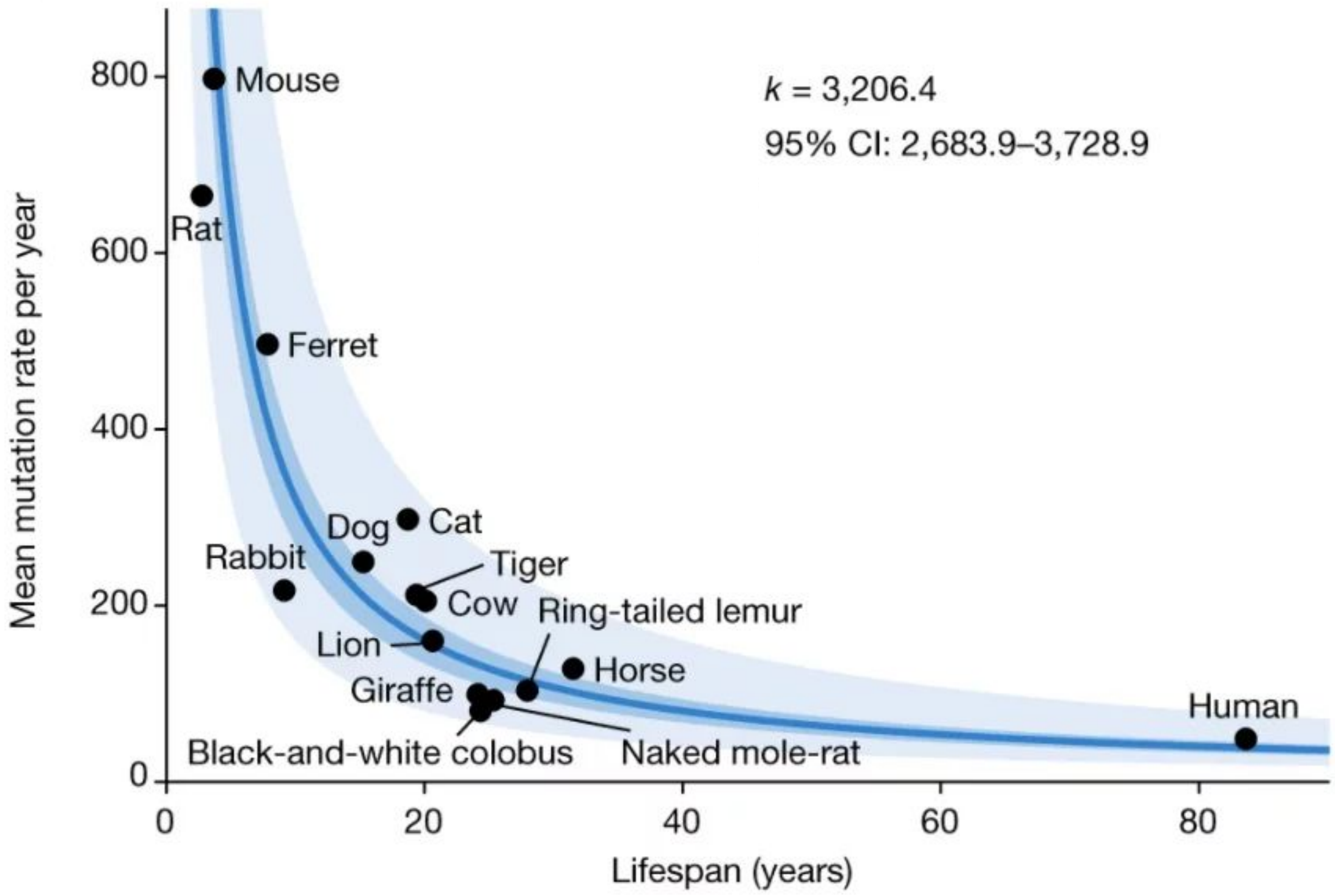
Kleiber, 1947

Allometry and ageing : reduced oxidative stress?



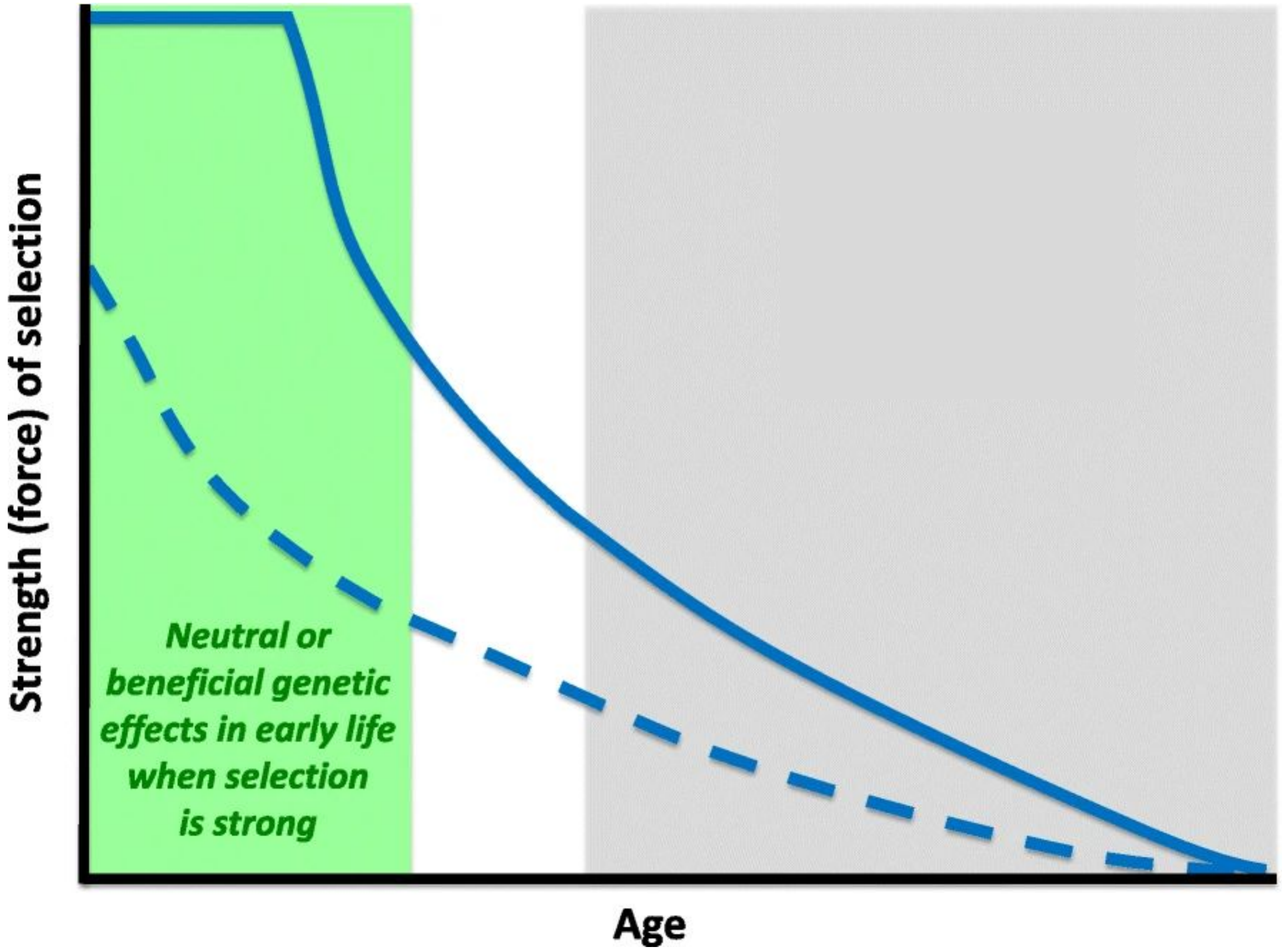
Perez-Campo et al., 1997

Allometry and ageing : reduced mutation rates?



Cagan et al., 2022

Classical model: ageing is a by-product of evolution



Flatt and Partridge, 2018

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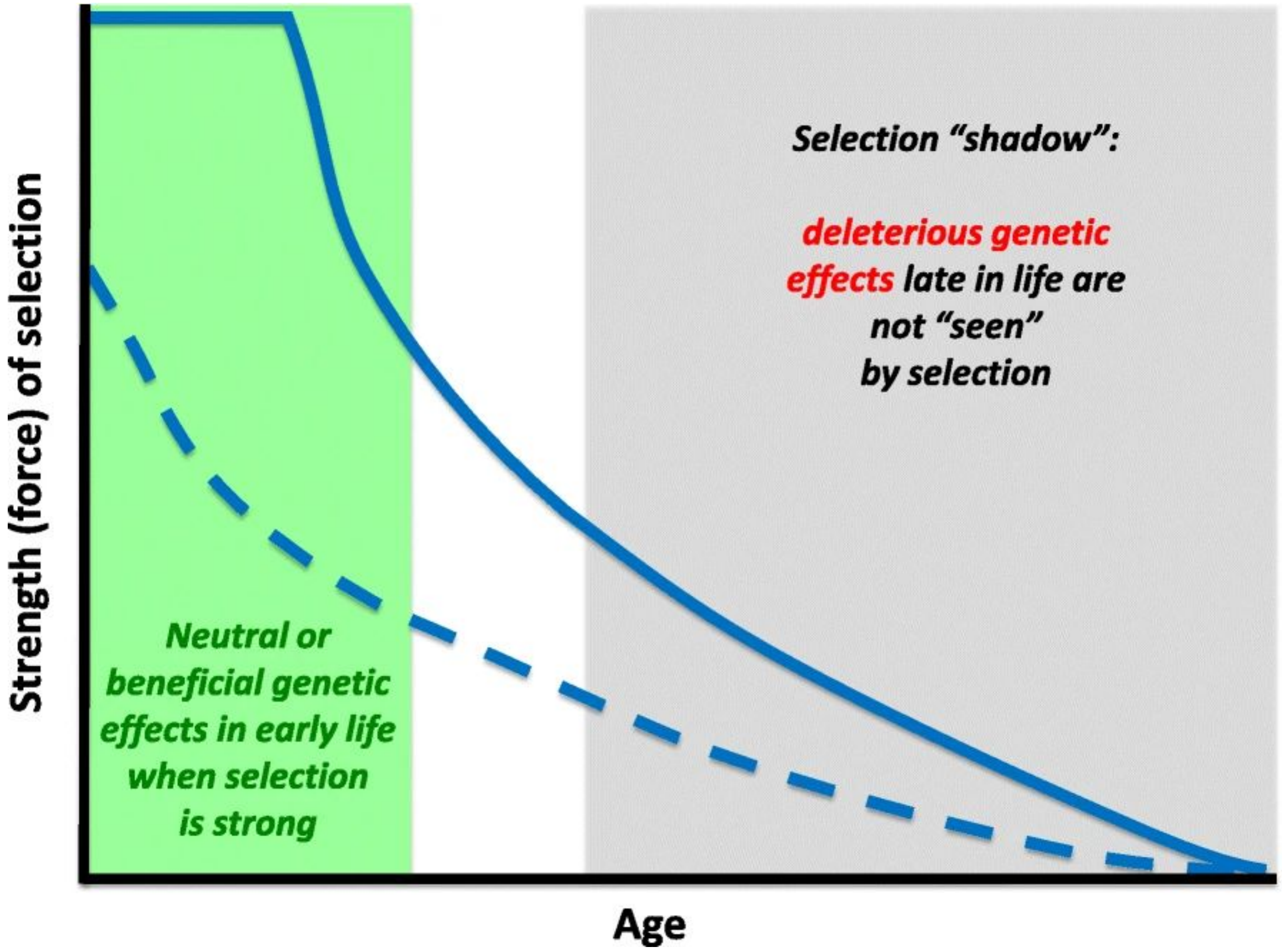
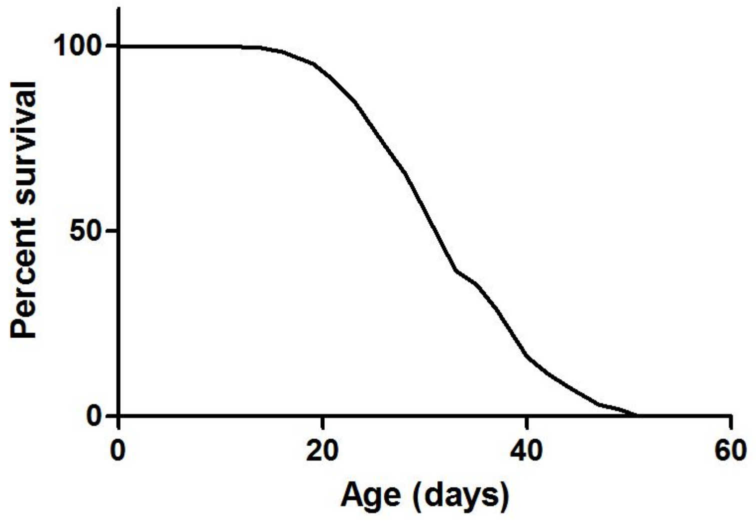


Flatt and Partridge, 2018

Introduction on ageing: summarizing questions

- are all individuals affected equally?



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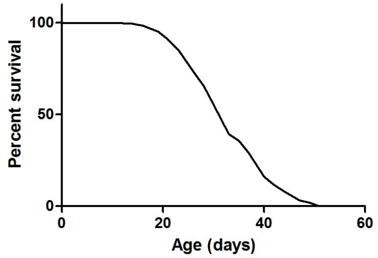
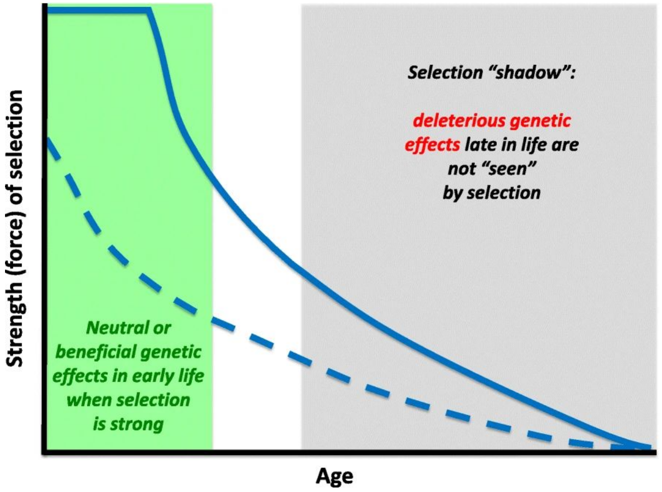


- is ageing really a by-product of evolution?



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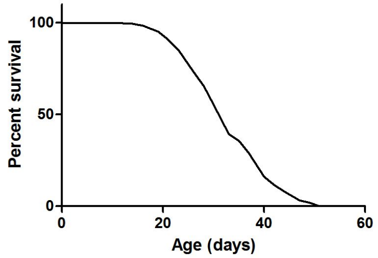

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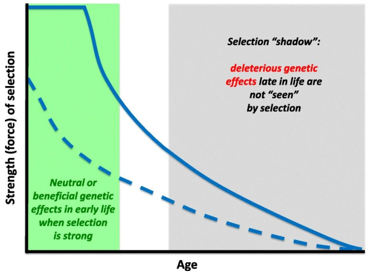
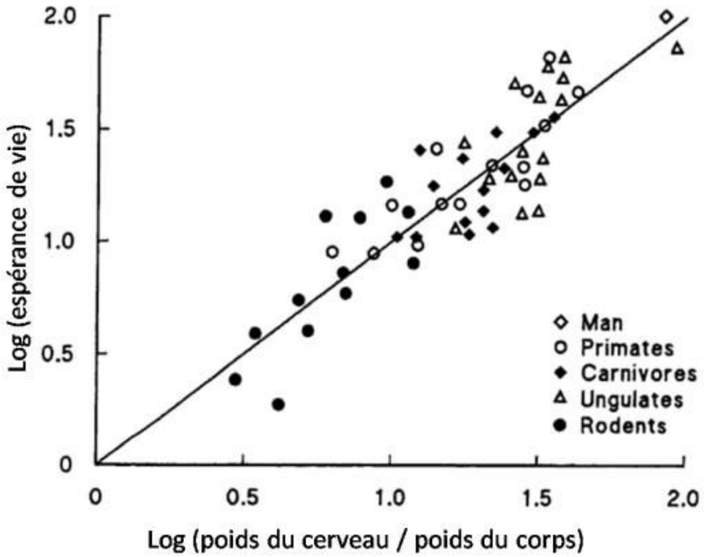


- what is hiding behind allometric properties?

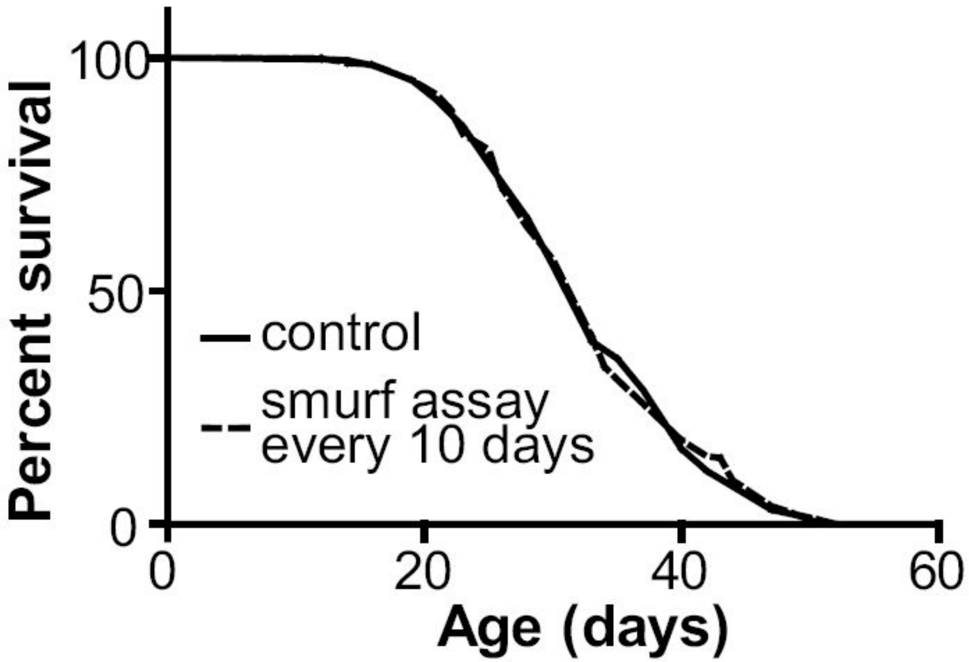


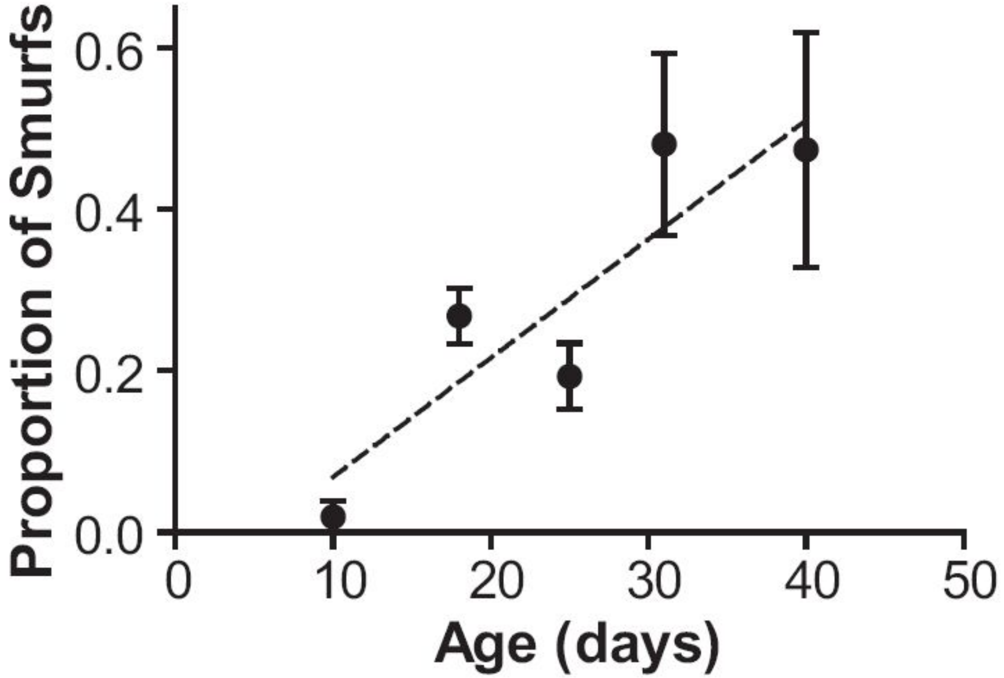
Studying ageing as a two-phase, discontinuous process

A Simple Assay To Identify Individuals About To Die Of Natural Causes

- *in vivo*
- measurement of intestinal permeability
- non-toxic food dye
- non-absorbed food dye
- ‘Smurf’ phenotype

Smurfness is an age-dependent phenotype

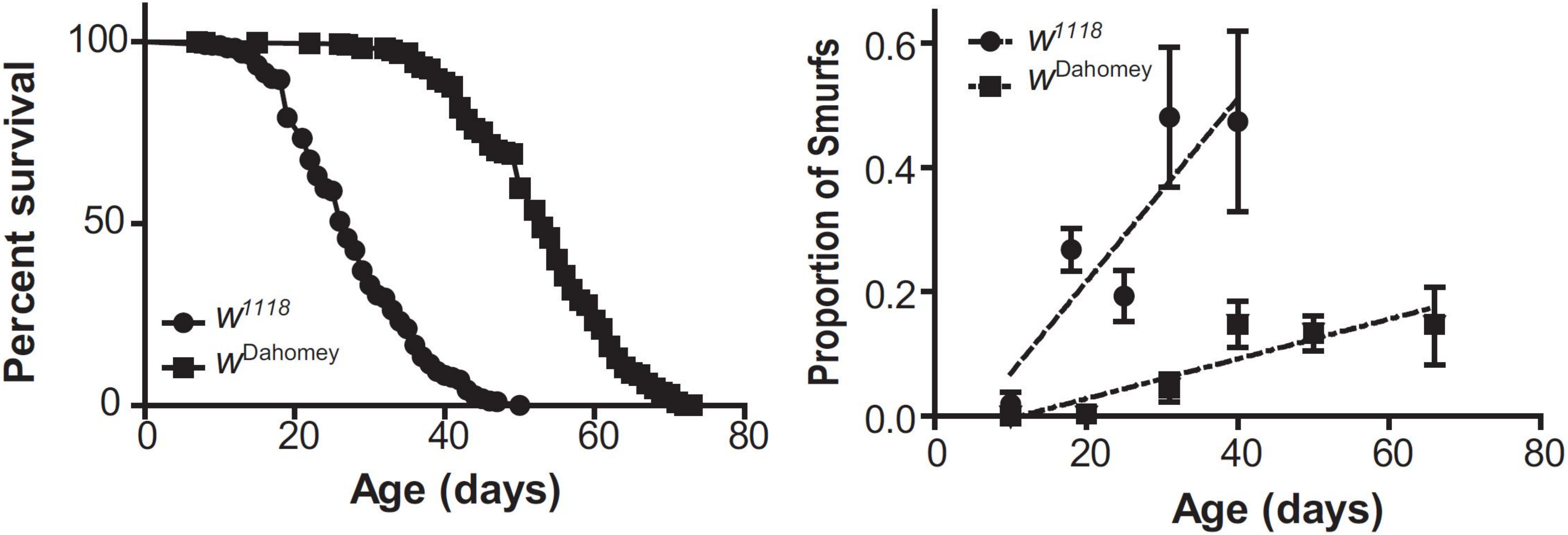




The proportion of Smurfs increases with time…

Rera et al., 2012

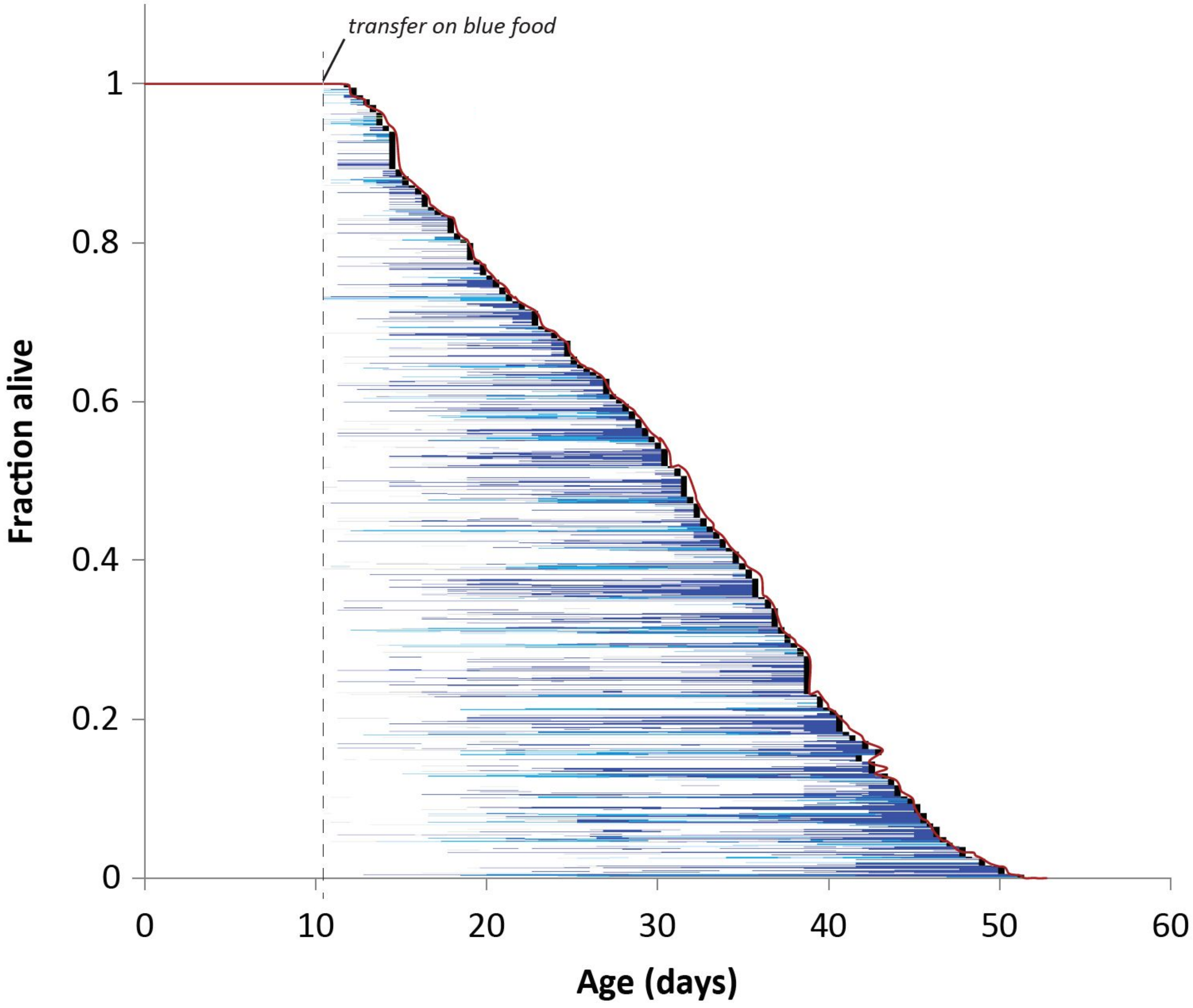
Smurfness is a « physiological age »-dependent phenotype



… the rate of increase is a function of physiological age

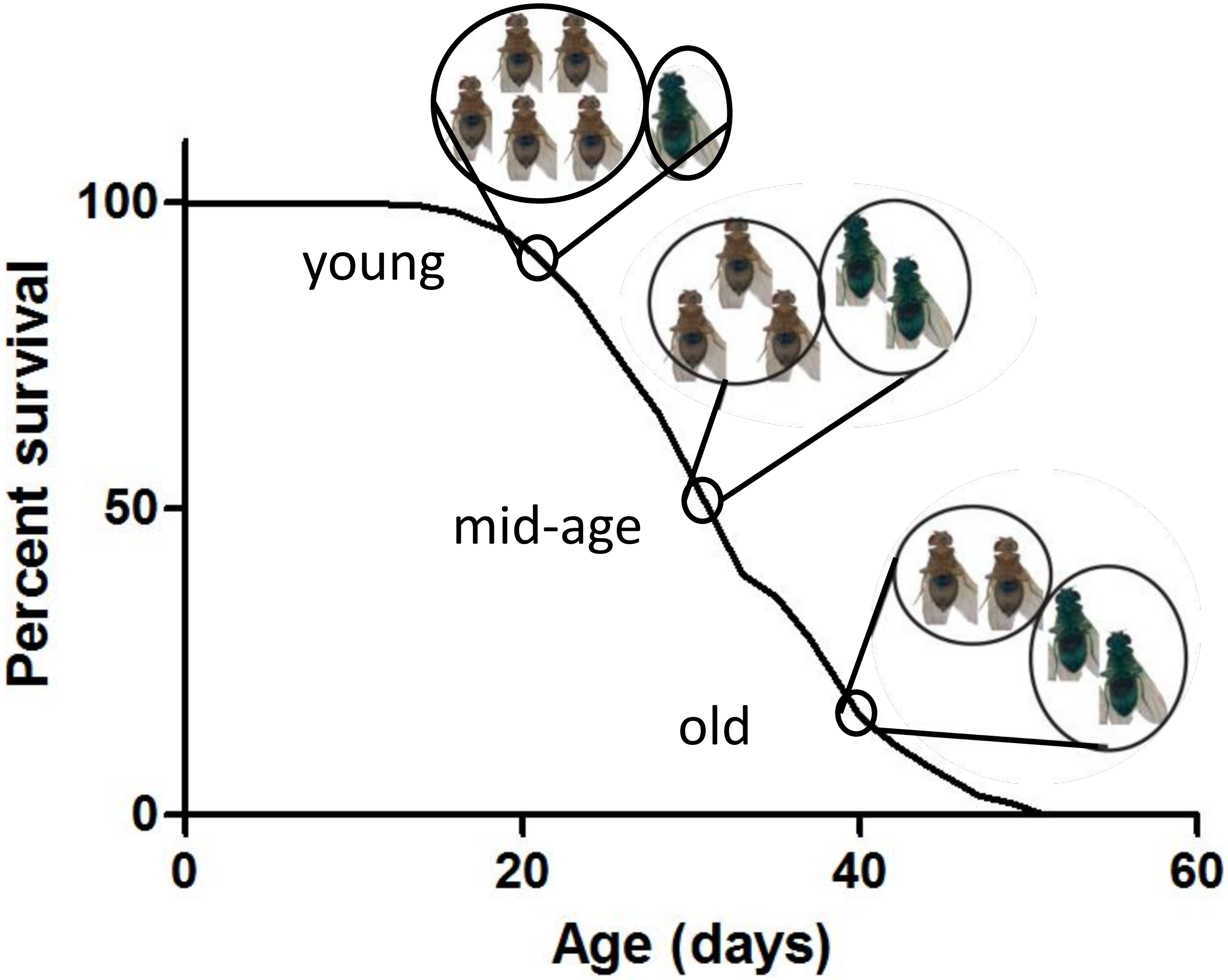
Rera et al., 2012

Every individuals turns Smurf prior to death

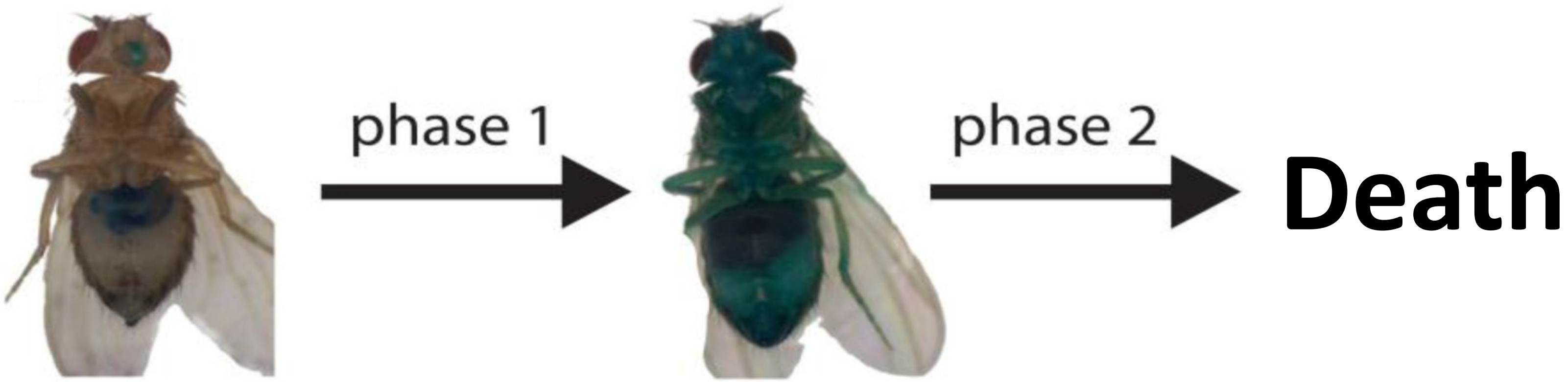


Tricoire and Rera, 2015

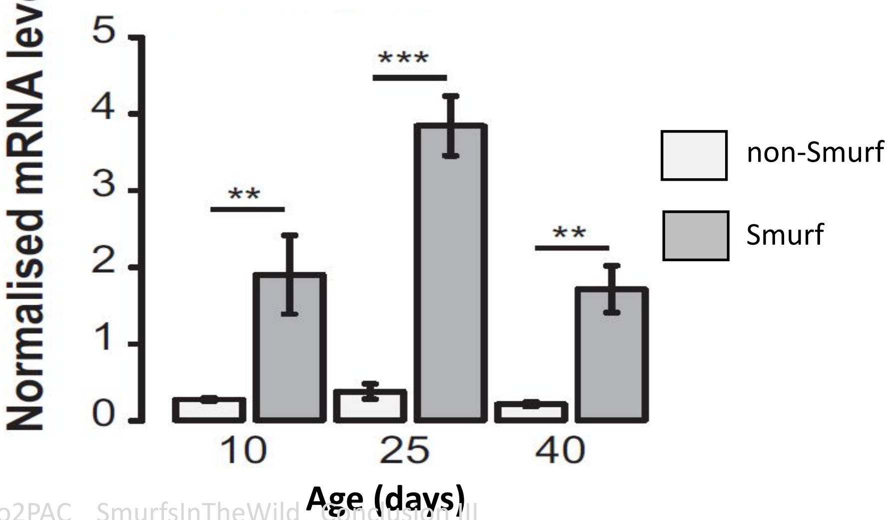
The 2-Phase Model Of Ageing



Hallmarks of ageing in the 2-Phase Model



systemic inflammation



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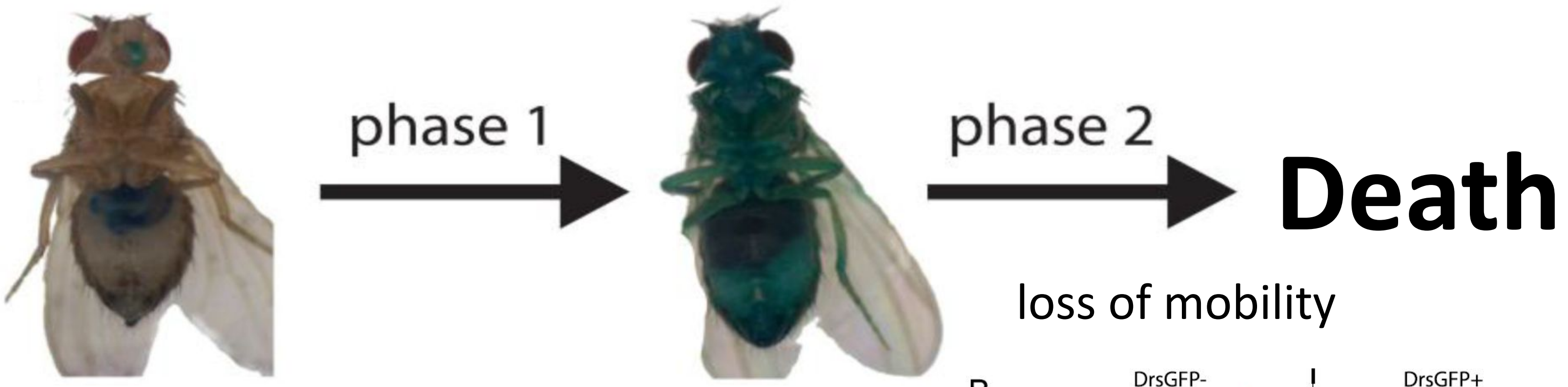
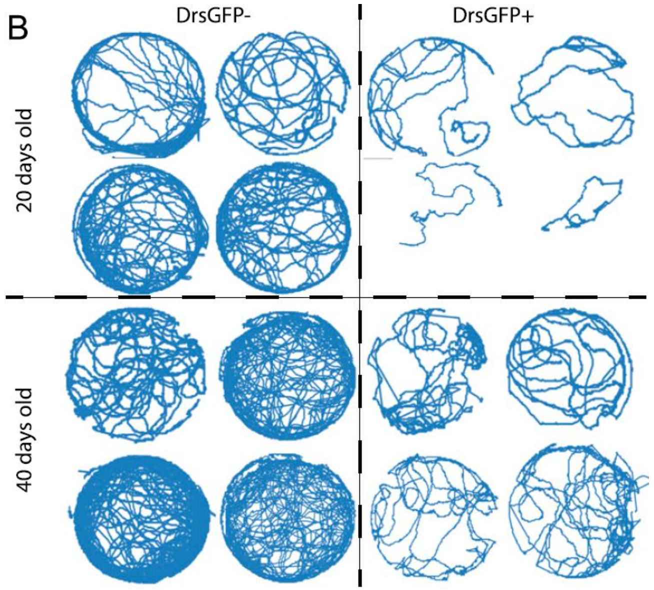


loss of mobility



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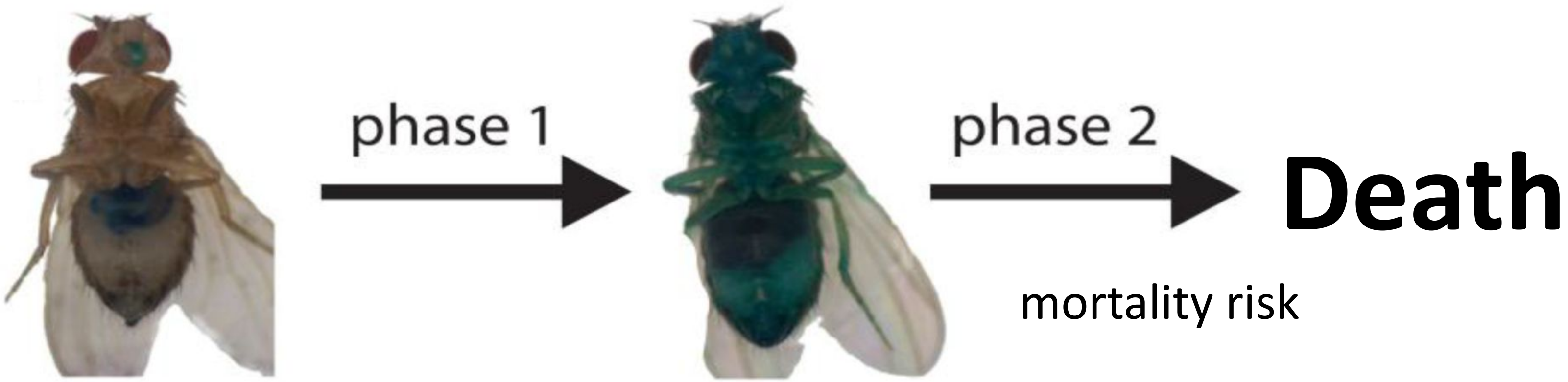
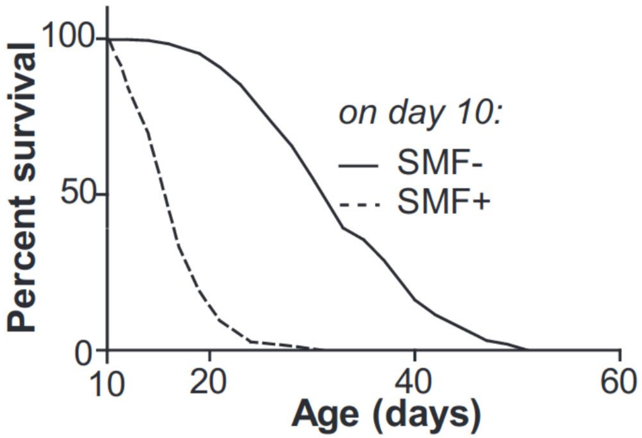
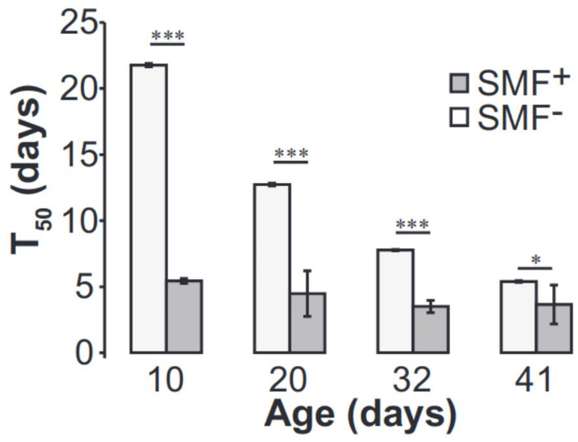
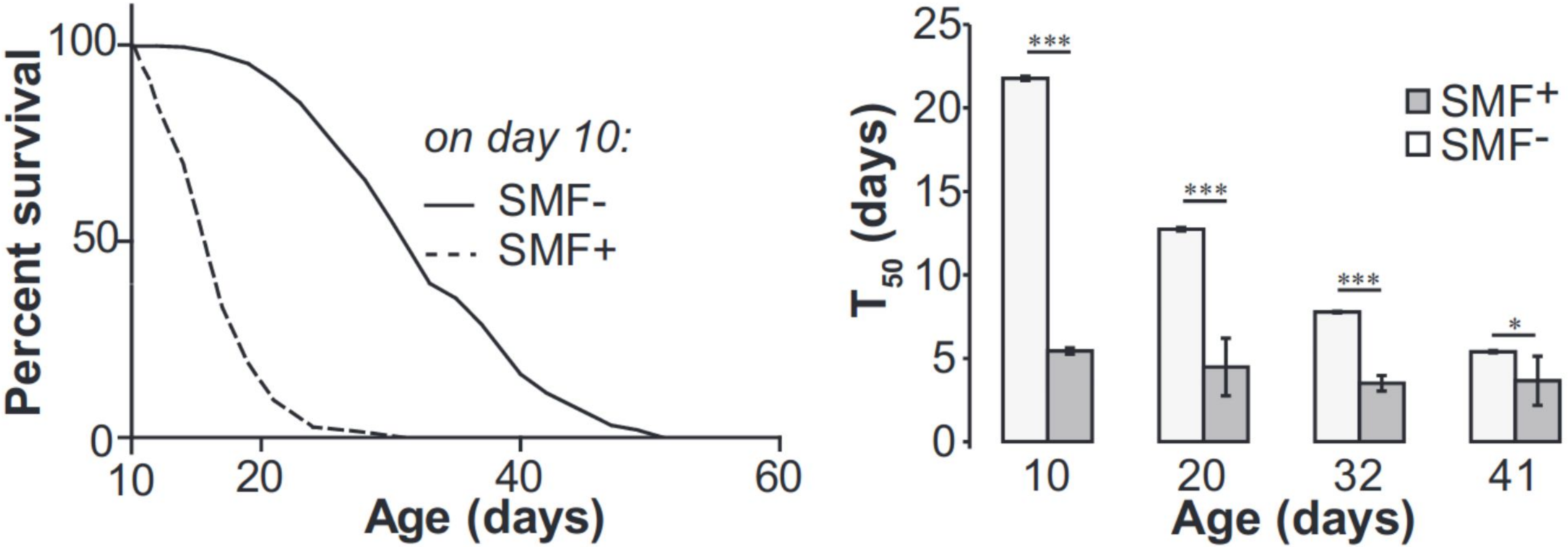






Rera et al., 2012

An age-related phenotype predicting CONSTANT risk of impending death



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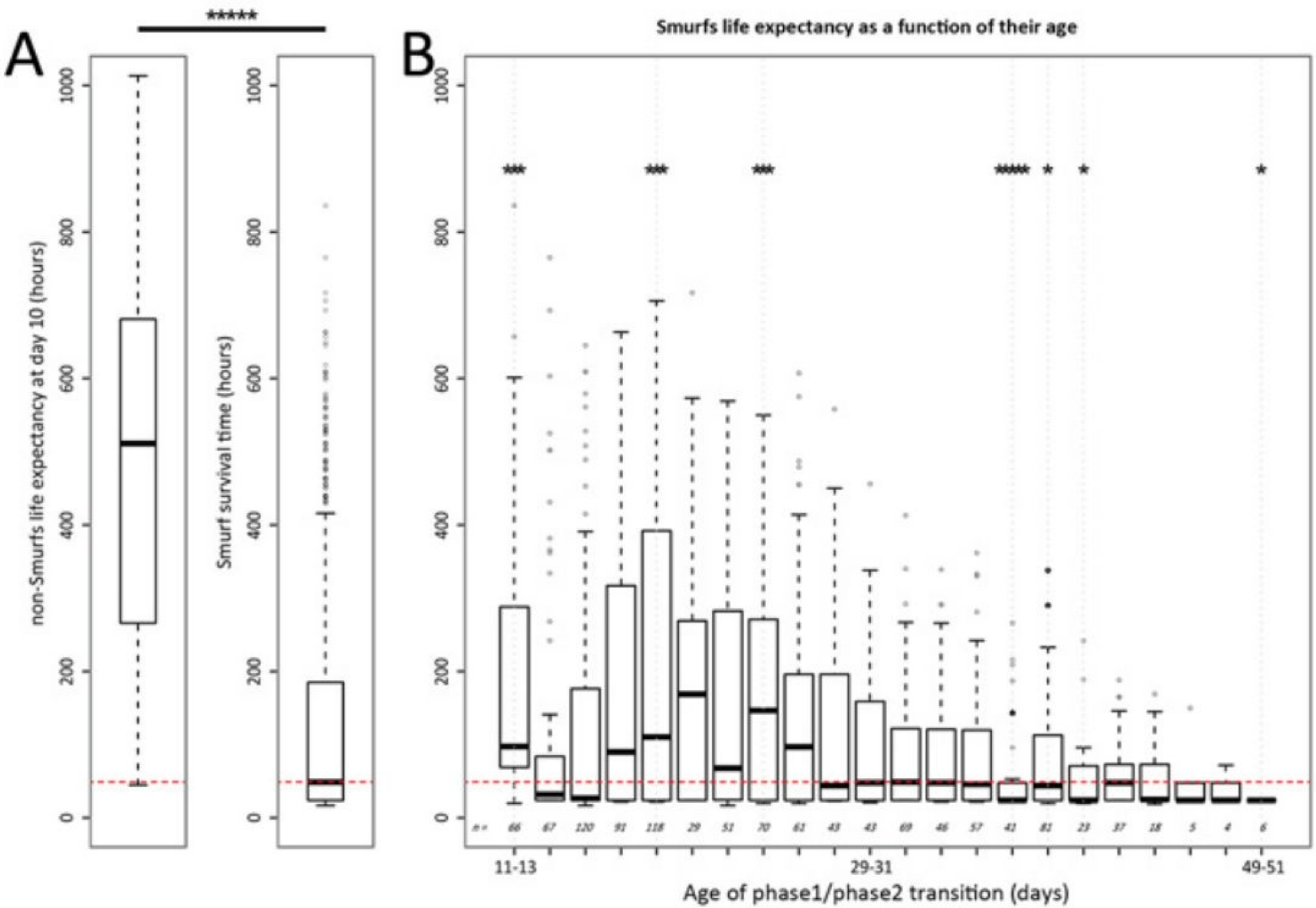
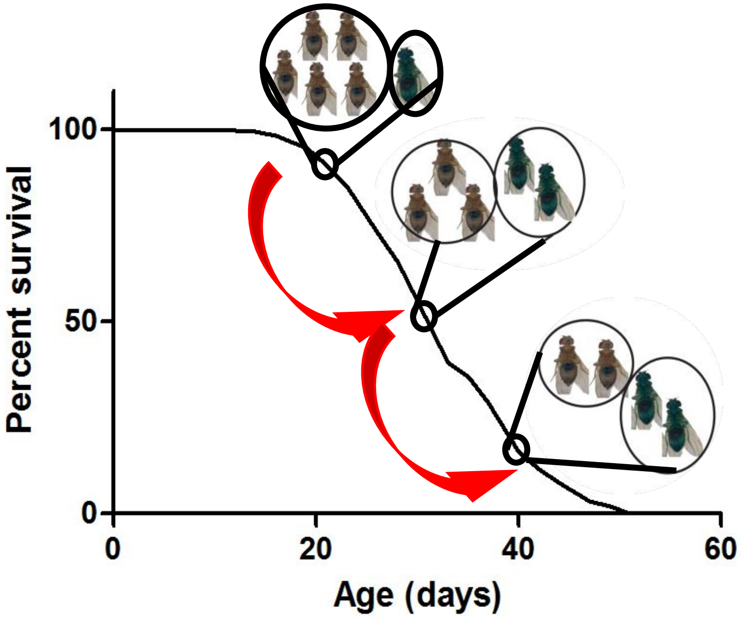
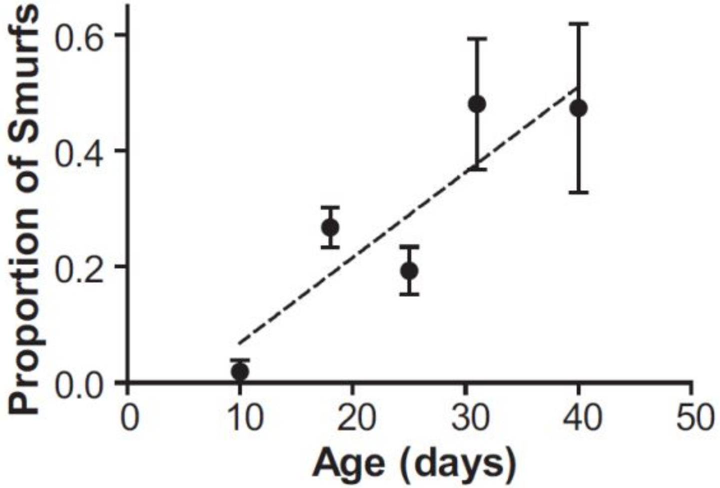


Tricoire et Rera, 2015

Our approach separates chronology and physiology



Understanding the increase in age-dependent risks



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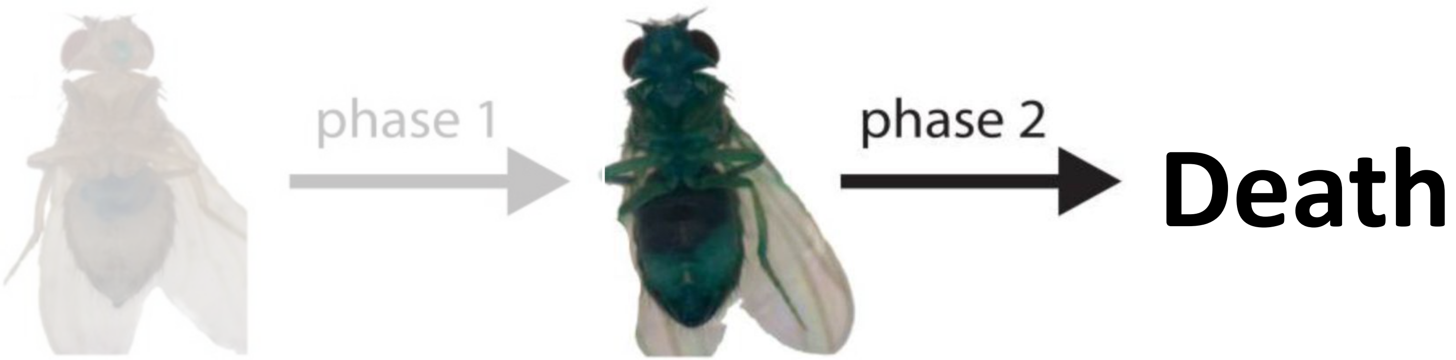
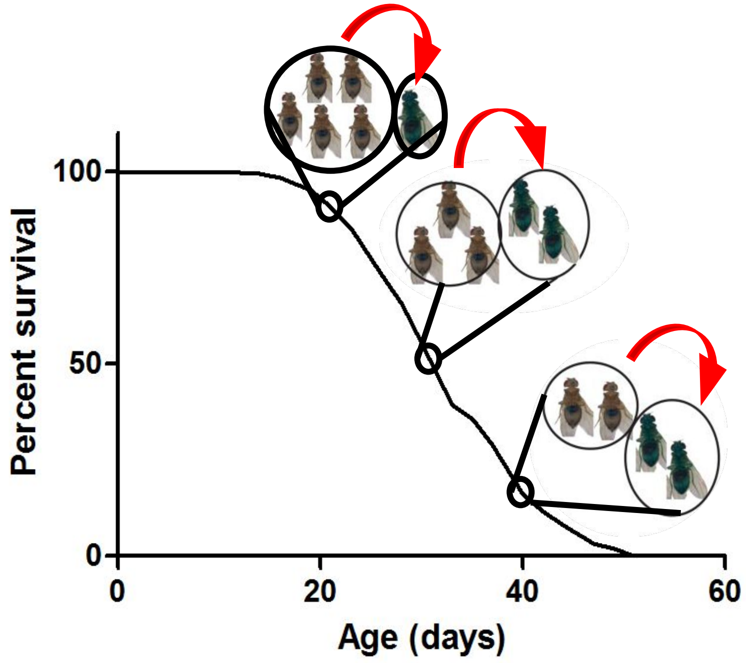
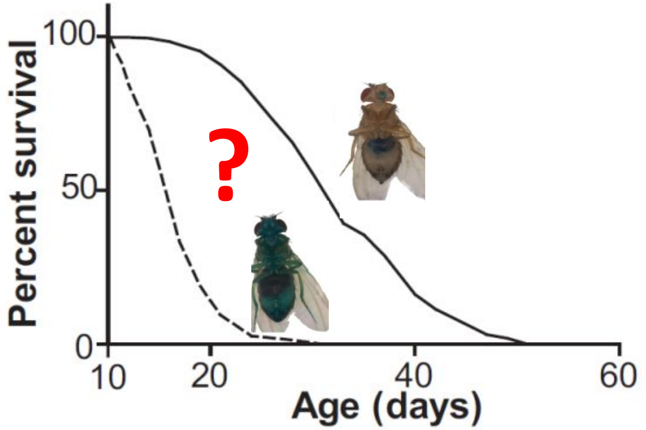
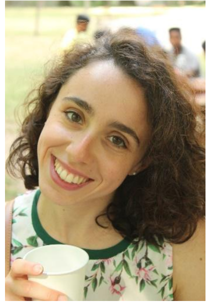




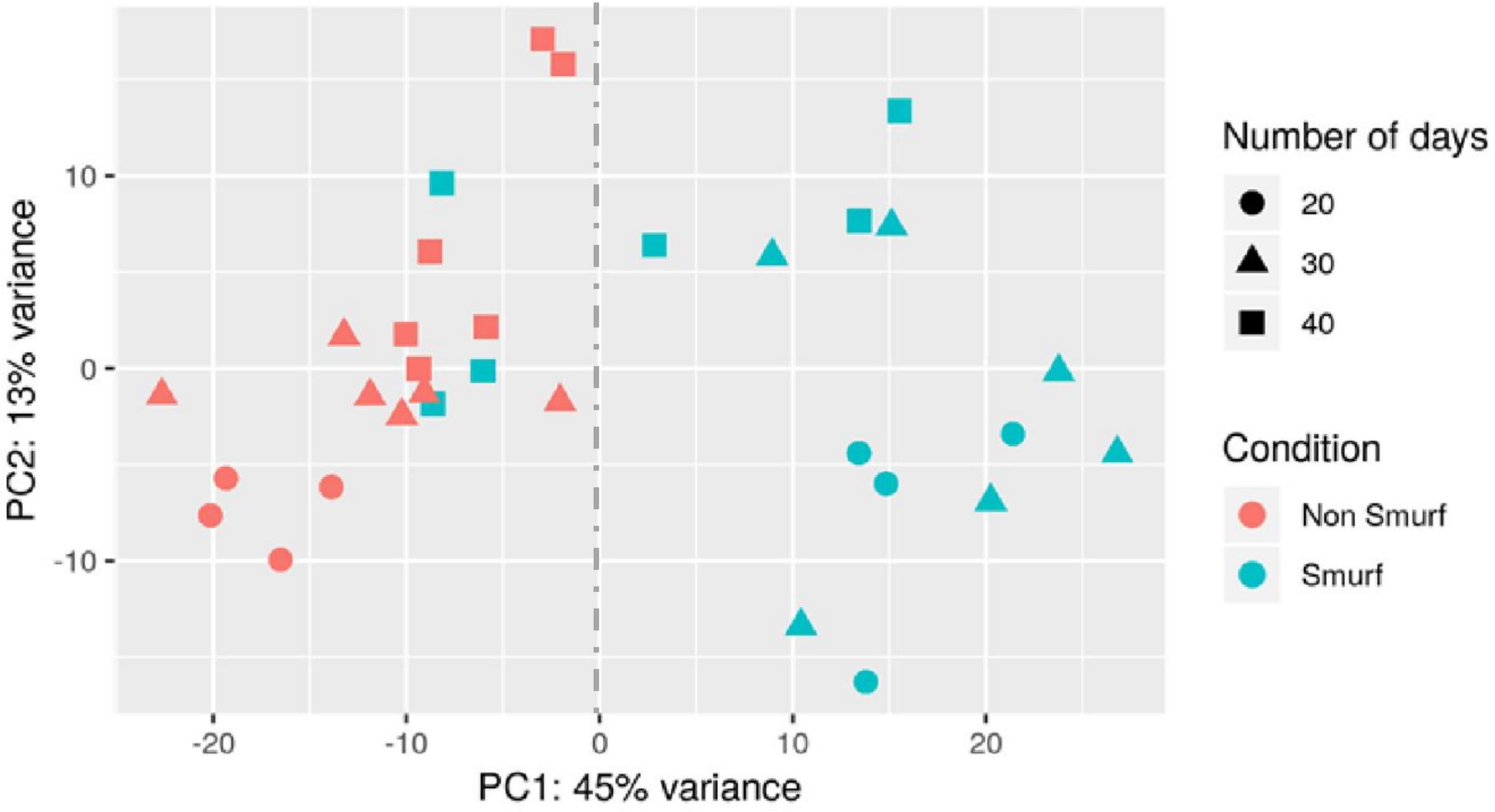
Understanding the
high risk of impending death



There is a Smurf-specific signature

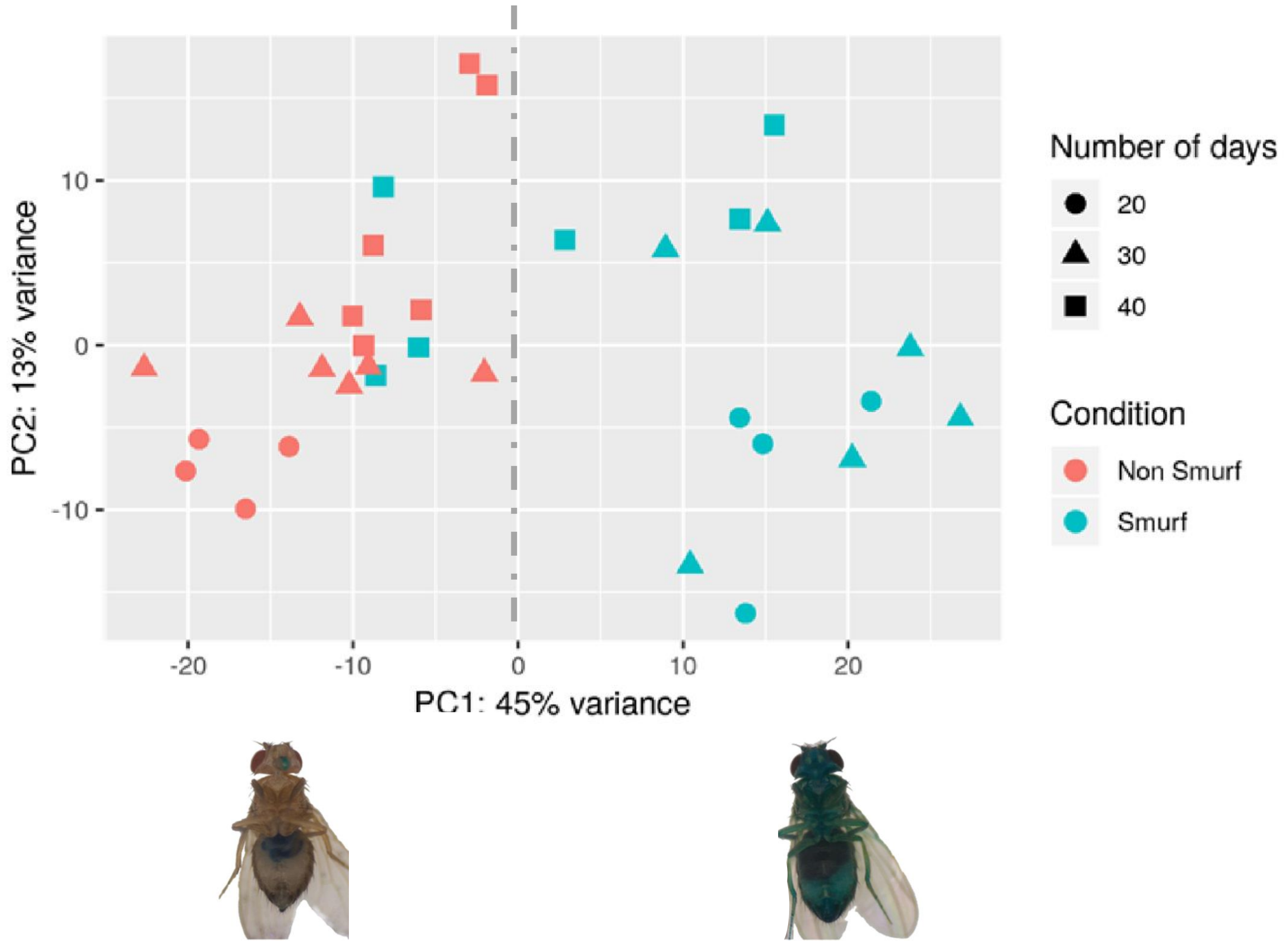


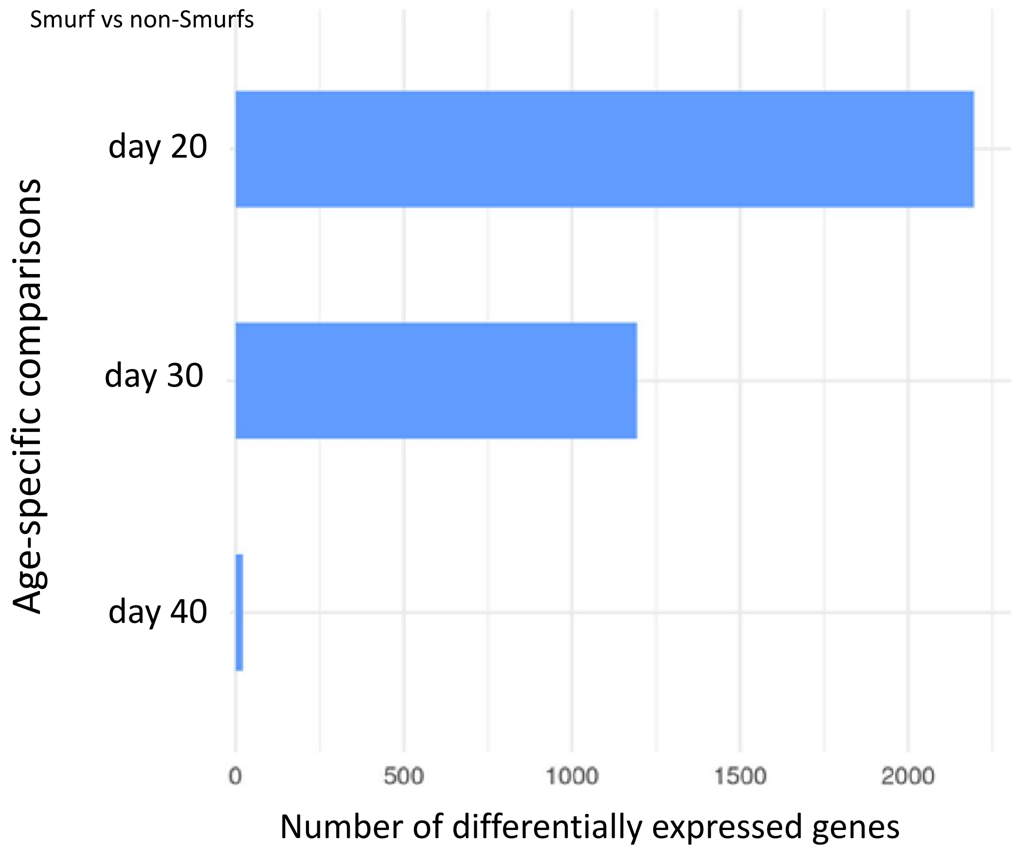
Flaminia Zane
PhD 12/05/22



Zane et al., in preparation

Aged non-Smurfs are close to Smurf





Zane et al., in preparation

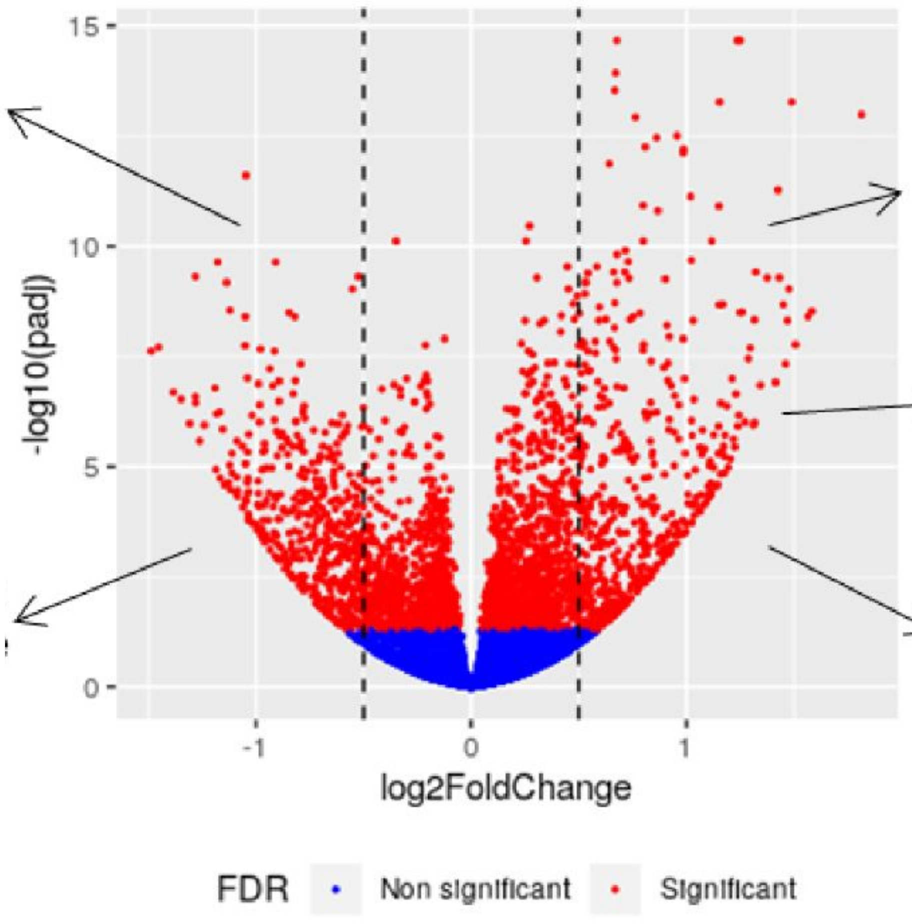
Smurfness recapitulates transcriptional ageing signature

3108 Differentially Expressed Genes (DEGs) / 15364 identified genes

Lipid metabolism

Proteostasis

Mitochondrial respiration



Immune response

Stress responses (GSTs, HSPs); UPR^{ER}

Cell motility

Zane et al., in preparation

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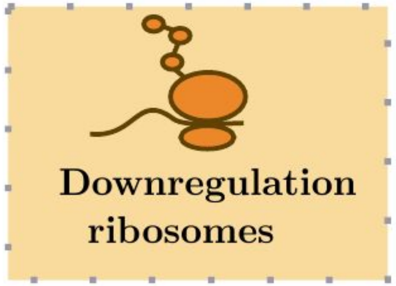

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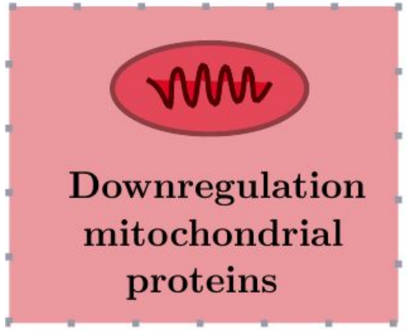

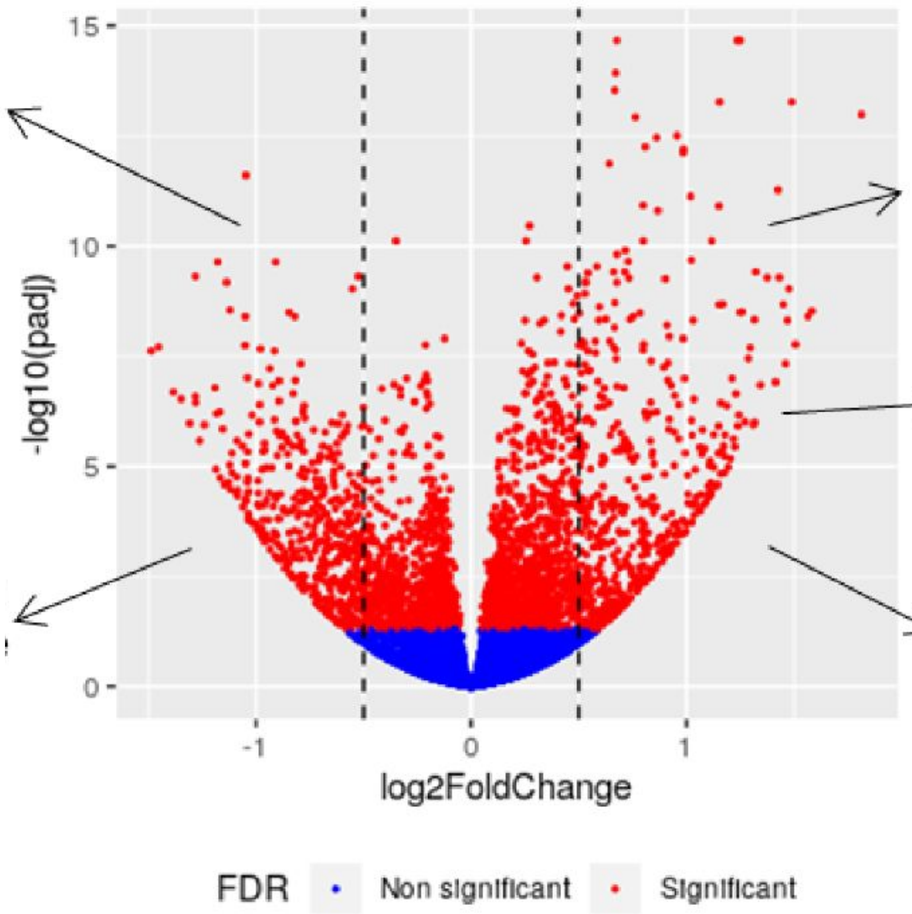

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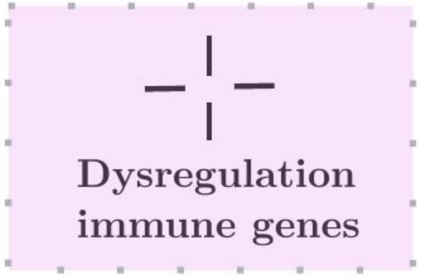

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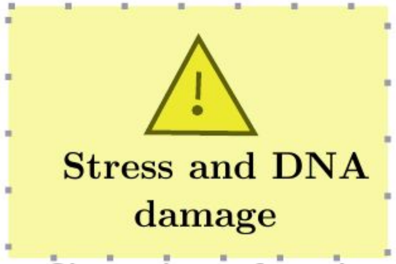
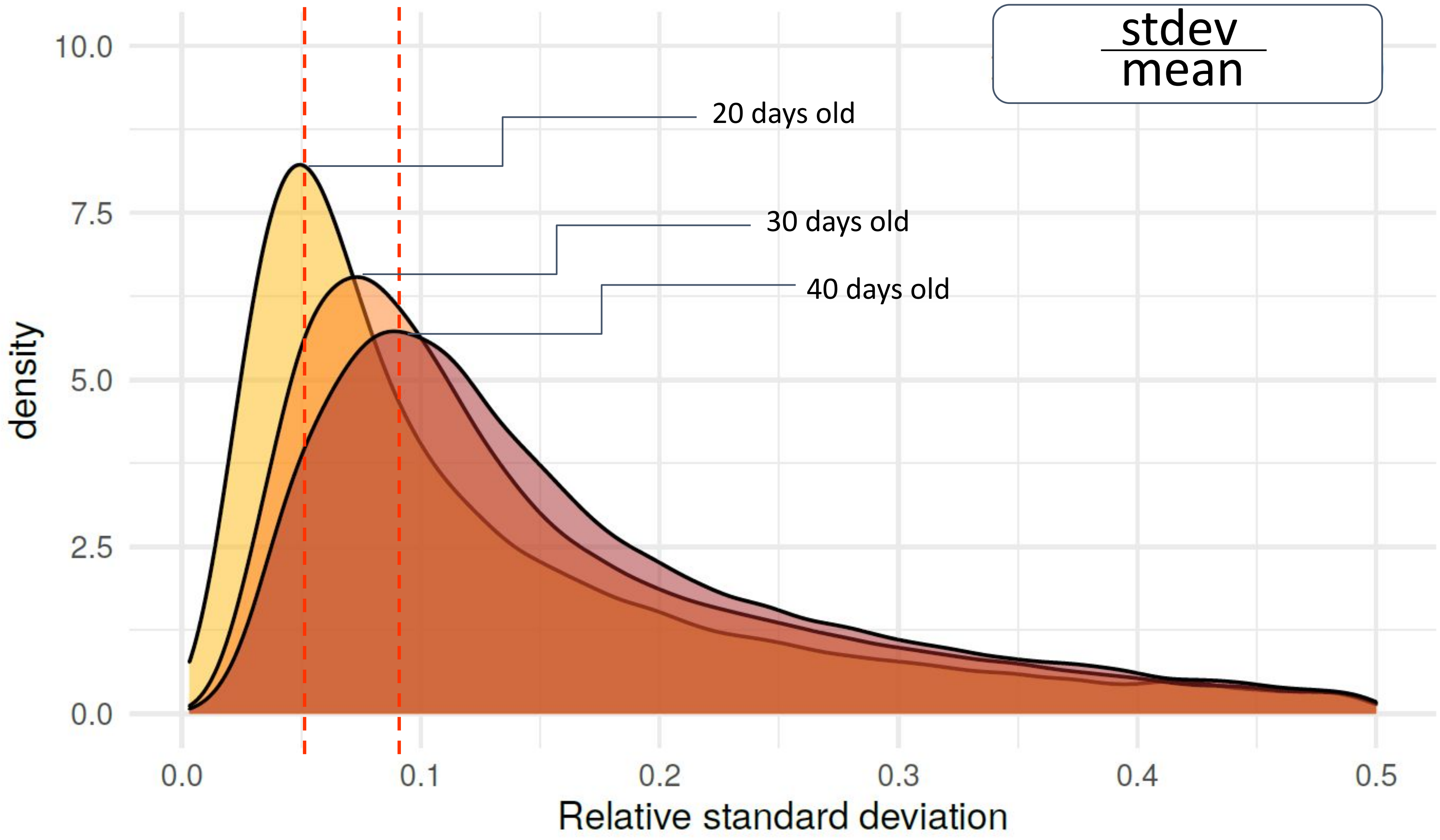


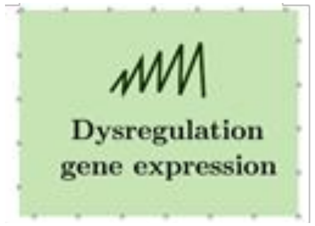
Six markers of aged transcriptome

Frenk & Houlsey (2018)

Zane et al., in preparation

Ageing non-Smurf transcriptome accumulates expression noise





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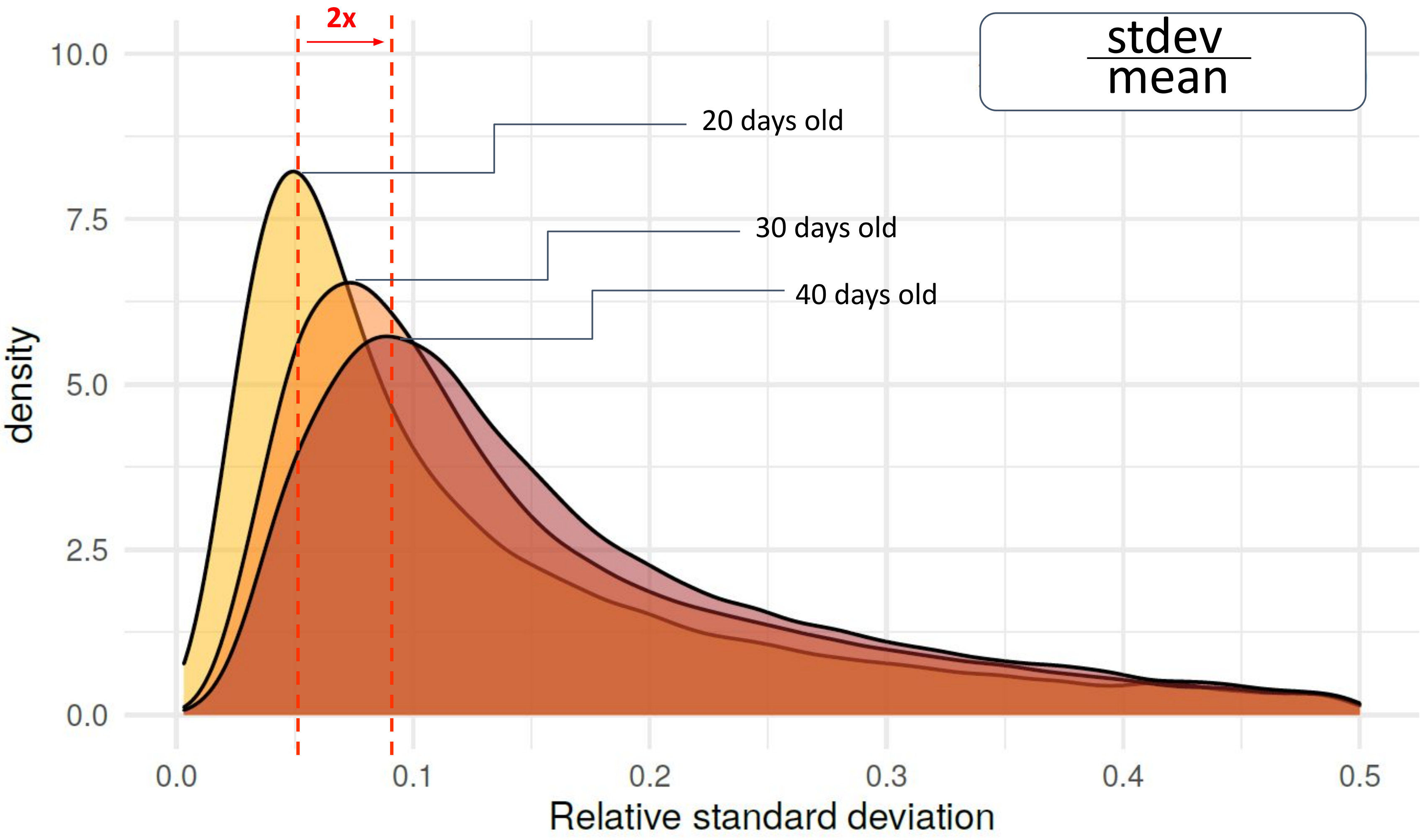
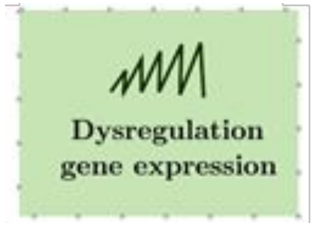
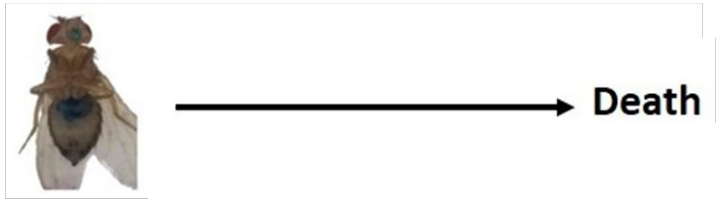




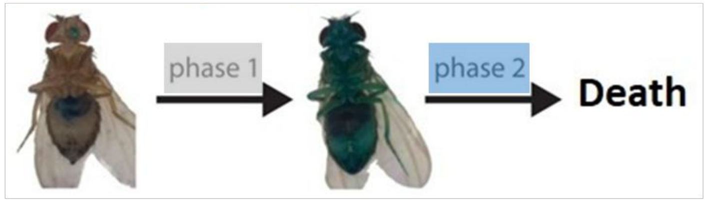
Zane et al., in preparation

Changing paradigm

Classic framework



2-phase ageing framework



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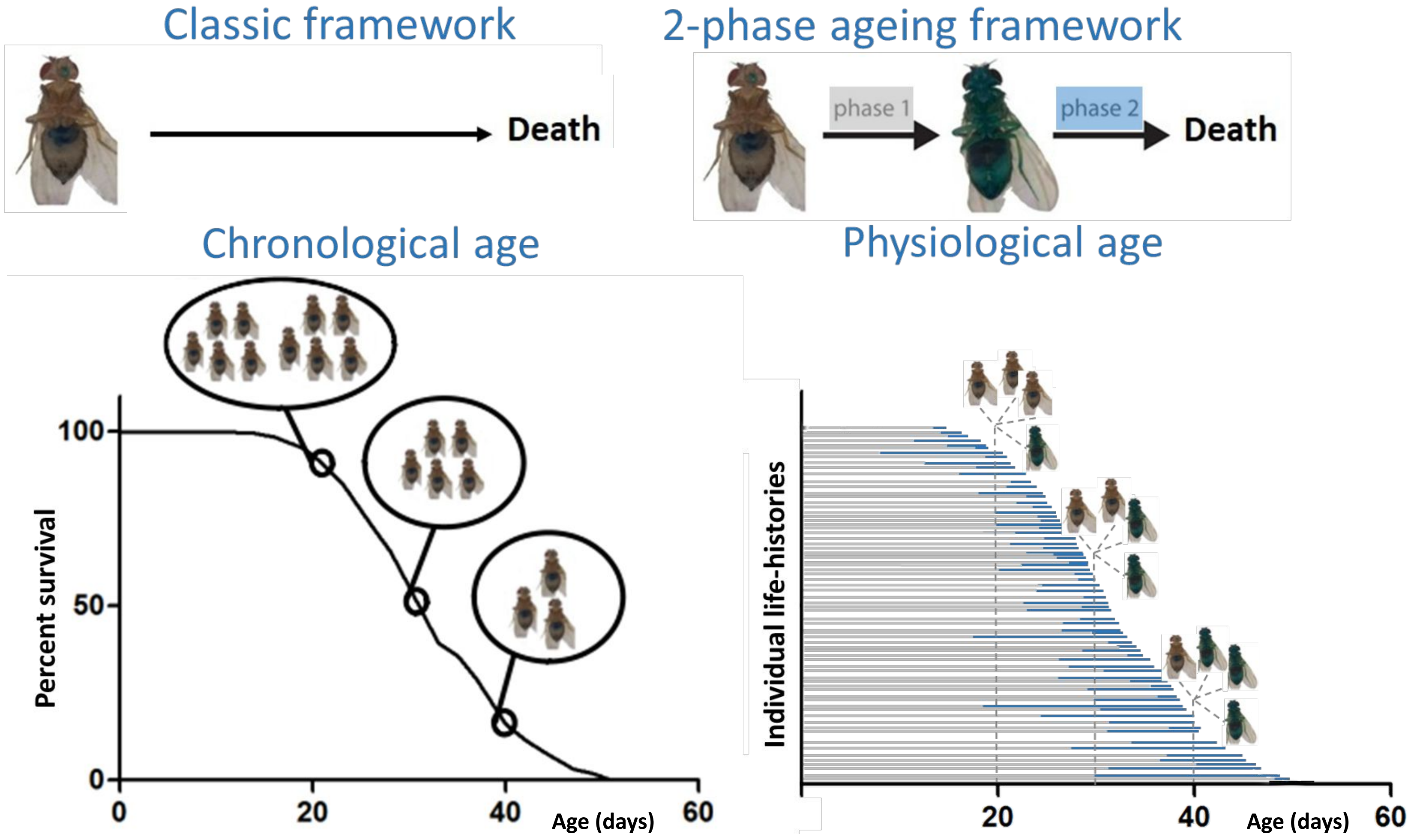

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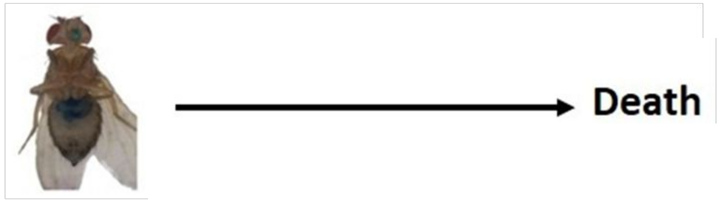

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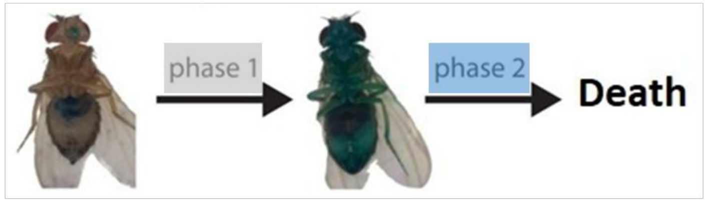
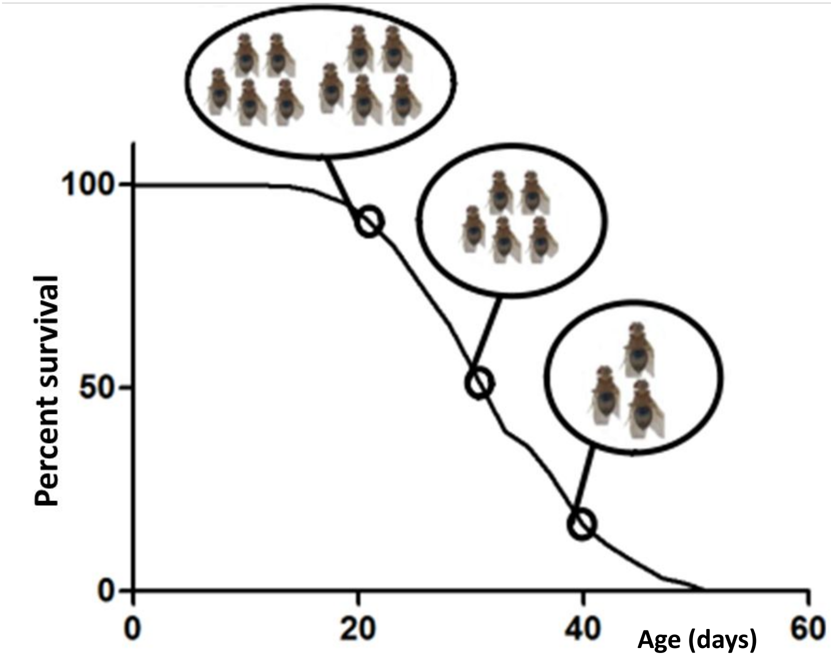
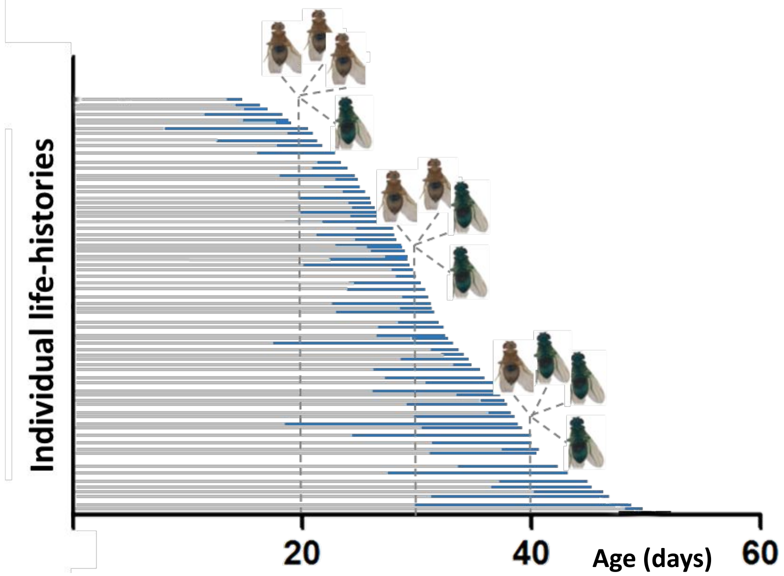


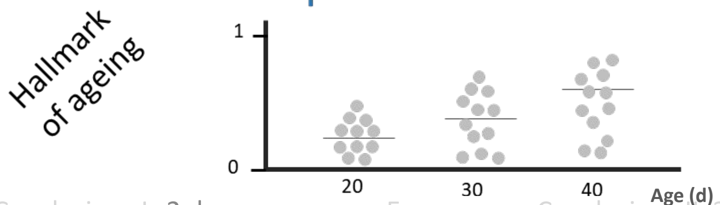
Chronological age



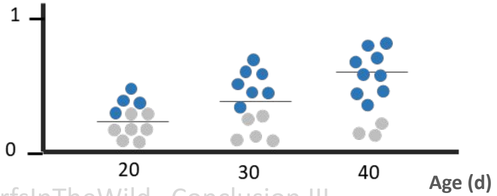
Physiological age



Population-based



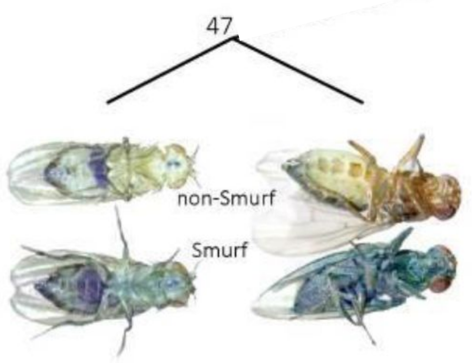
Individual-centered



Is the model evolutionarily relevant?

An evolutionarily conserved End-Of-Life phenotype

The 2-Phase Model of Ageing is evolutionarily conserved



Drosophila

Adapted from Dambroise et al., 2016 Scientific Reports

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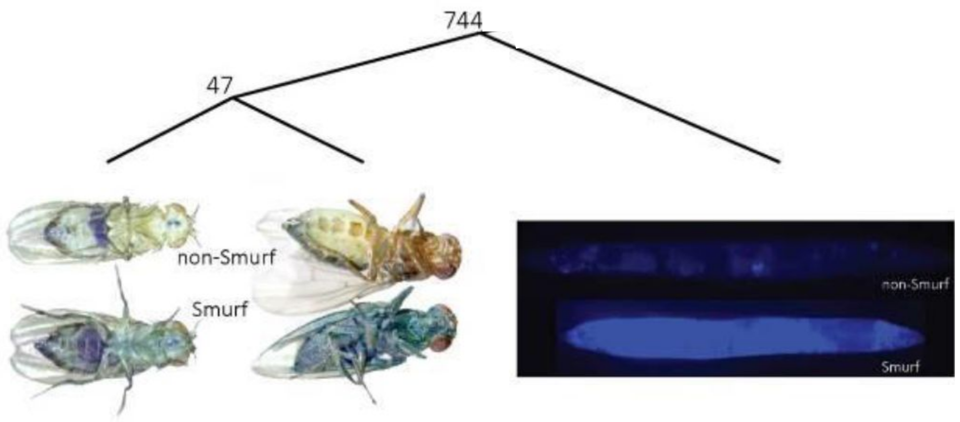

Drosophila Nematode

Adapted from Dambroise et al., 2016 Scientific Reports

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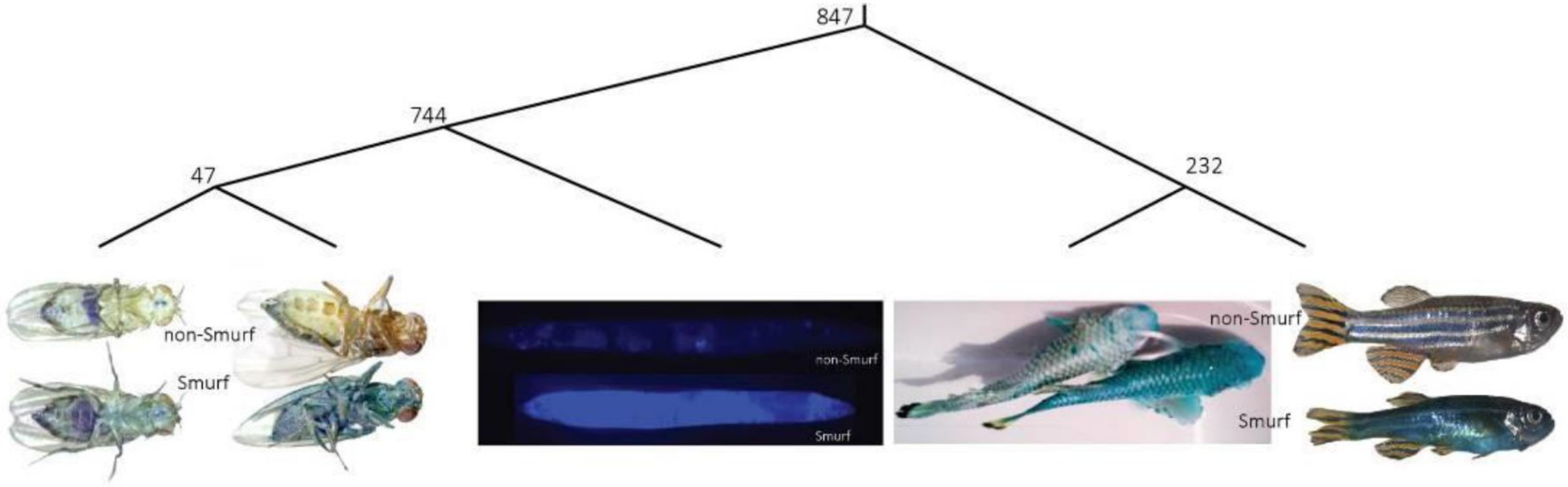

Drosophila Nematode Killifish Zebrafish

Adapted from Dambroise et al., 2016 Scientific Reports

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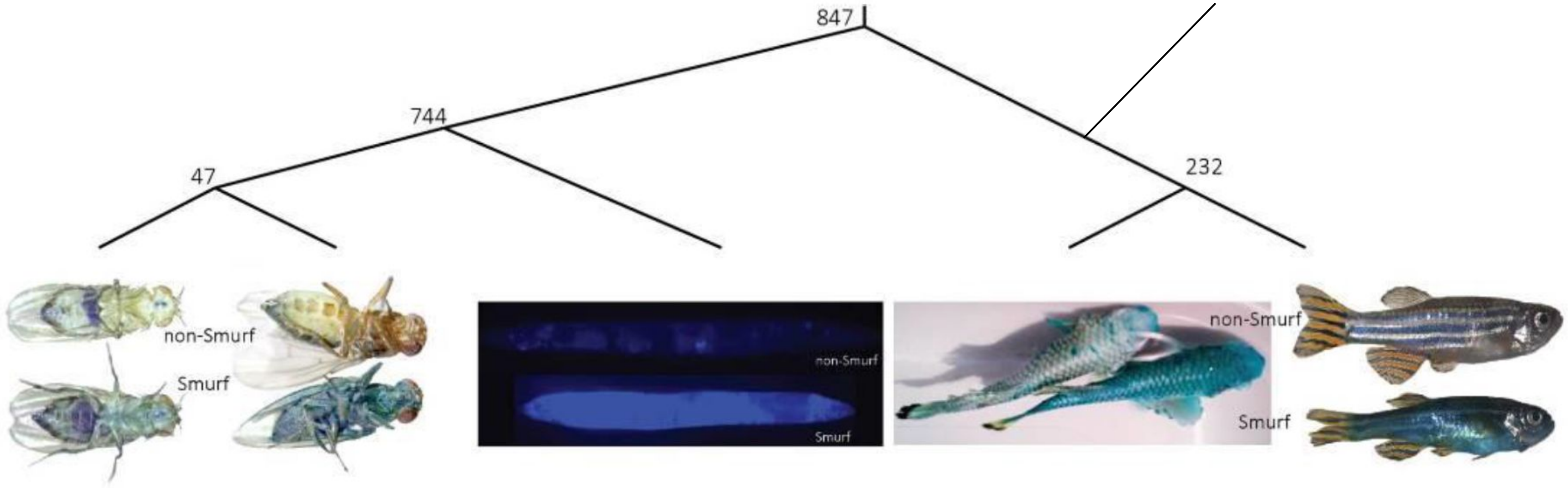
?



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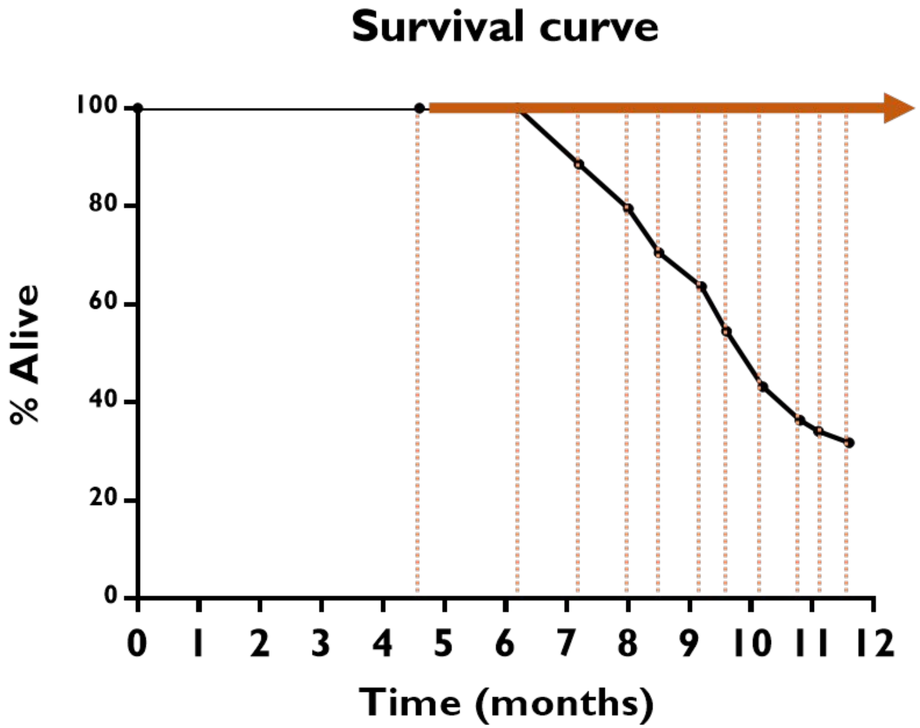
Validating the two-phase model in mice

Fanny Bain

Céline Cansell



-Intestinal permeability test

- ❑ Permeability T1h
- ❑ Permeability T3h

-Measurements :

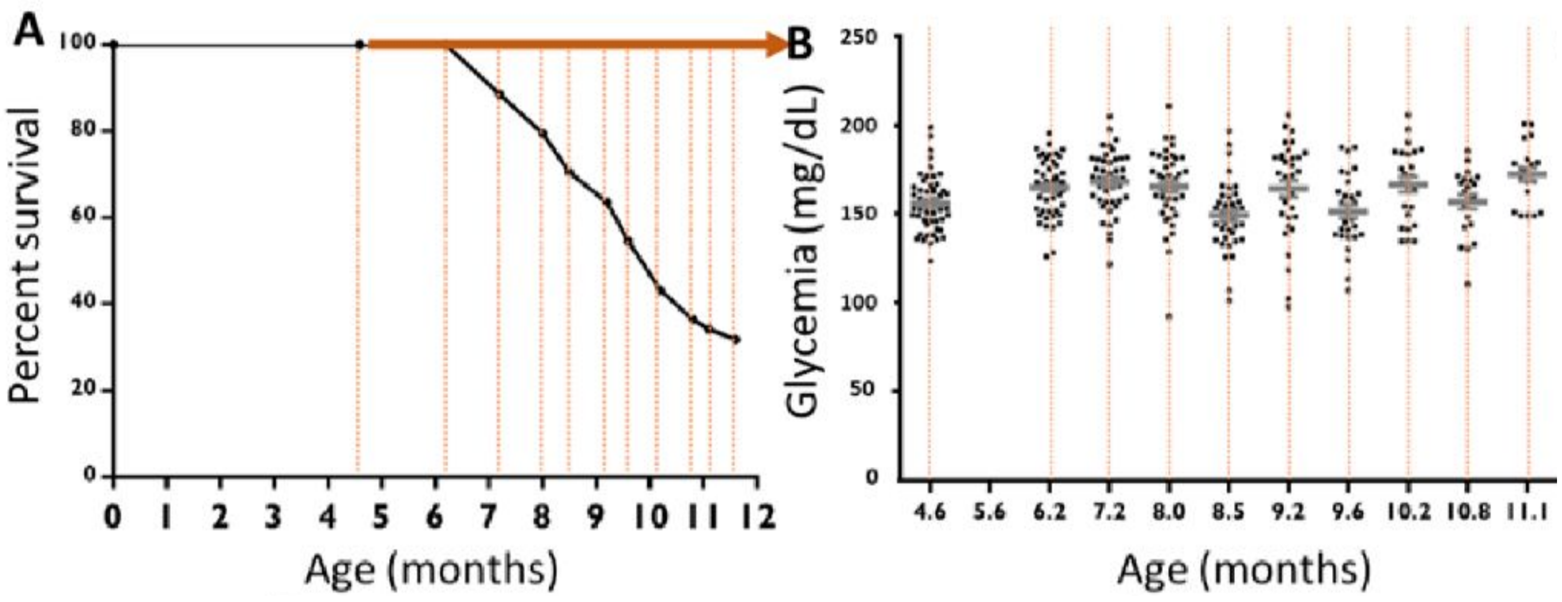
- ❑ Body Weight
- ❑ Fat and lean mass
- ❑ Body temperature
- ❑ Glycemia

-Metabolic recordings

- ❑ Food intake
- ❑ Locomotor activity
- ❑ Energy expenditure

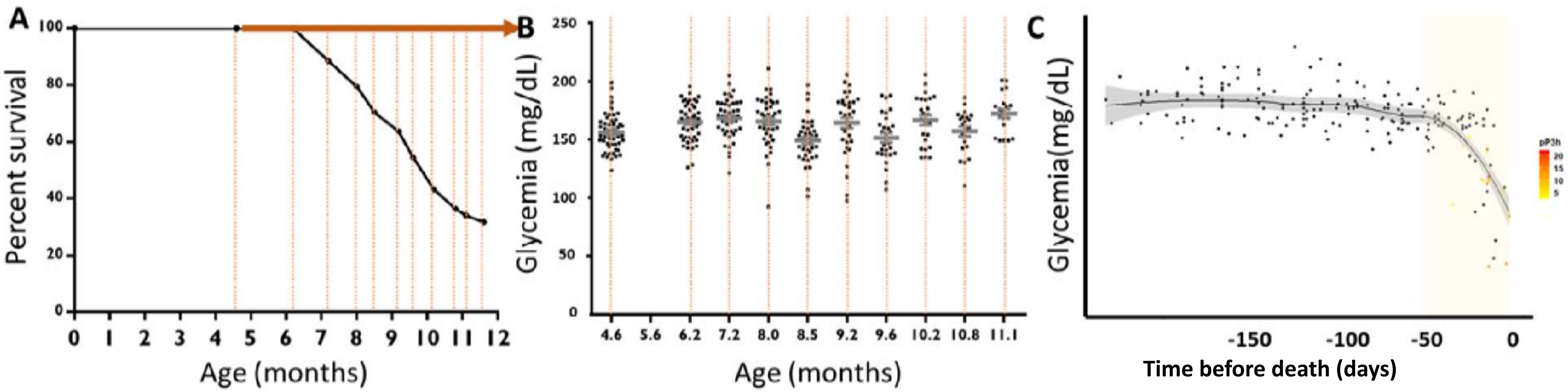
under review Cansell et al., 2022

Stable physiological parameters as a function of time



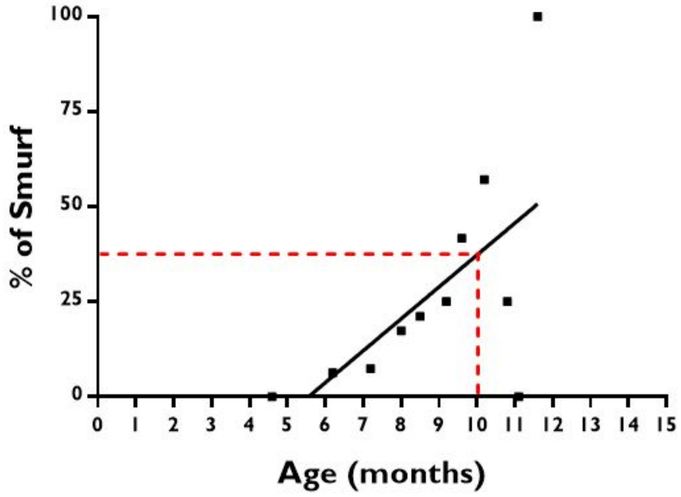
under review Cansell et al., 2022

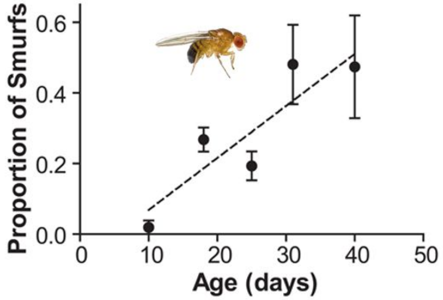
Show a biphasic behaviour as a function of physiological age



under review Cansell et al., 2022

The 2-Phase Model of Ageing applies to mice





under review Cansell et al., 2022

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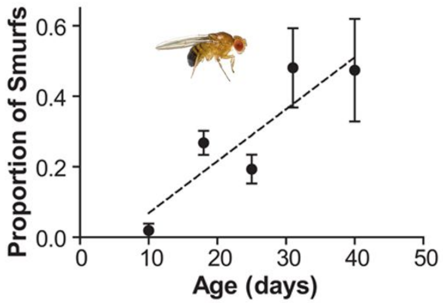
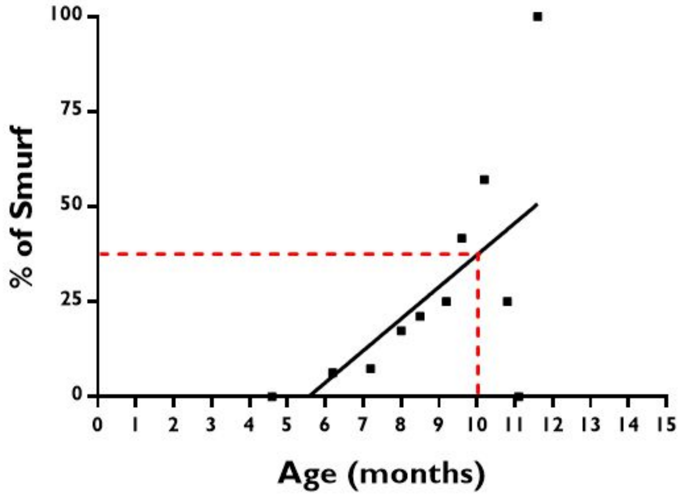
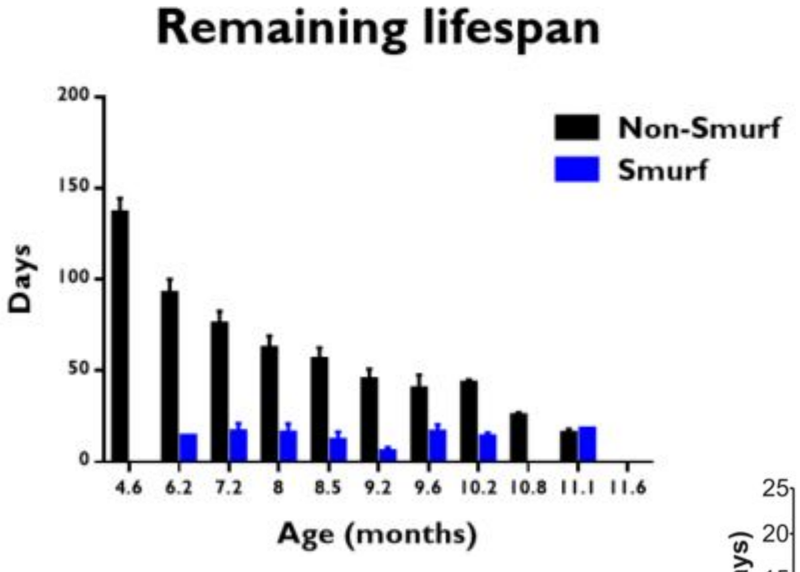
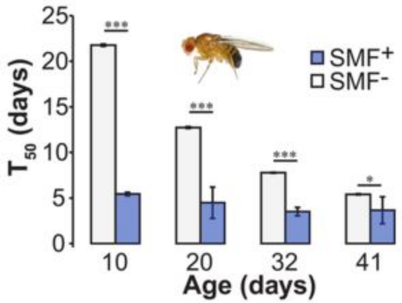


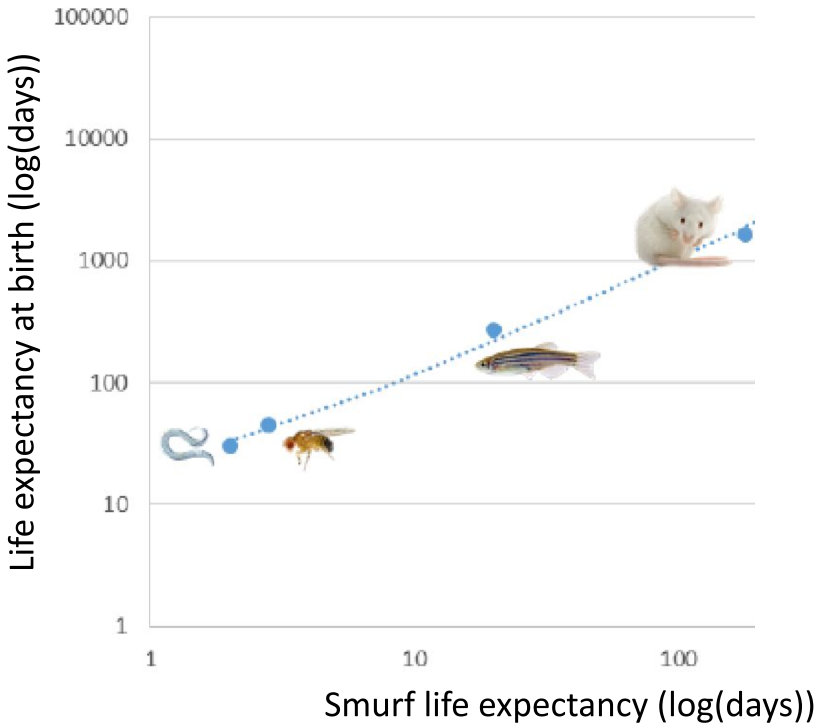




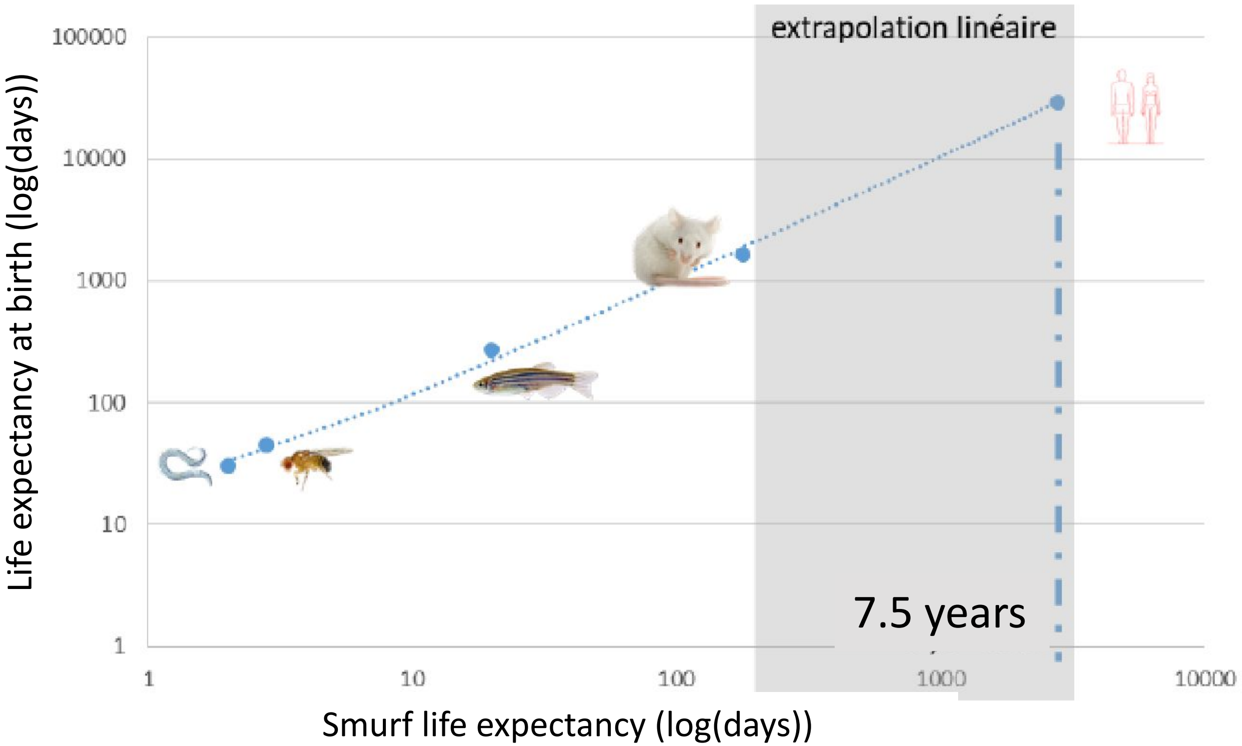


under review Cansell et al., 2022

Relevance of the model to the human risk of impending death



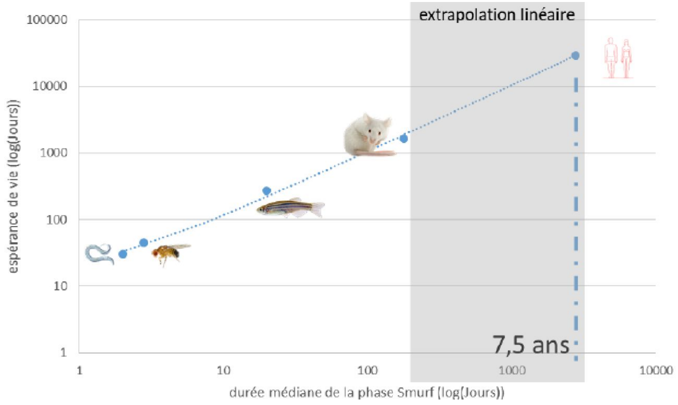
Relevance of the model to the human risk of impending death



Relevance of the model to the human risk of impending death

Grip Strength Predicts Cause-Specific Mortality in Middle-Aged and Elderly Persons

Hideo Sasaki, MD, PhD,[a,b] Fumiyoshi Kasagi, PhD,[c] Michiko Yamada, MD, PhD,[a] Shoichiro Fujita, PhD[d]



Biomarker Profiling by Nuclear Magnetic Resonance Spectroscopy for the Prediction of All-Cause Mortality: An Observational Study of 17,345 Persons

Krista Fischer, Johannes Kettunen, Peter Würtz, Toomas Haller, Aki S. Havulinna, Antti J. Kangas, Pasi Soininen, Tõnu Esko, Mari-Liis Tammesoo, Reedik Mägi, Steven Smit, Aarno Palotie, Samuli Ripatti, [...], Andres Metspalu

[view all]

Published: February 25, 2014 • DOI: 10.1371/journal.pmed.1001606

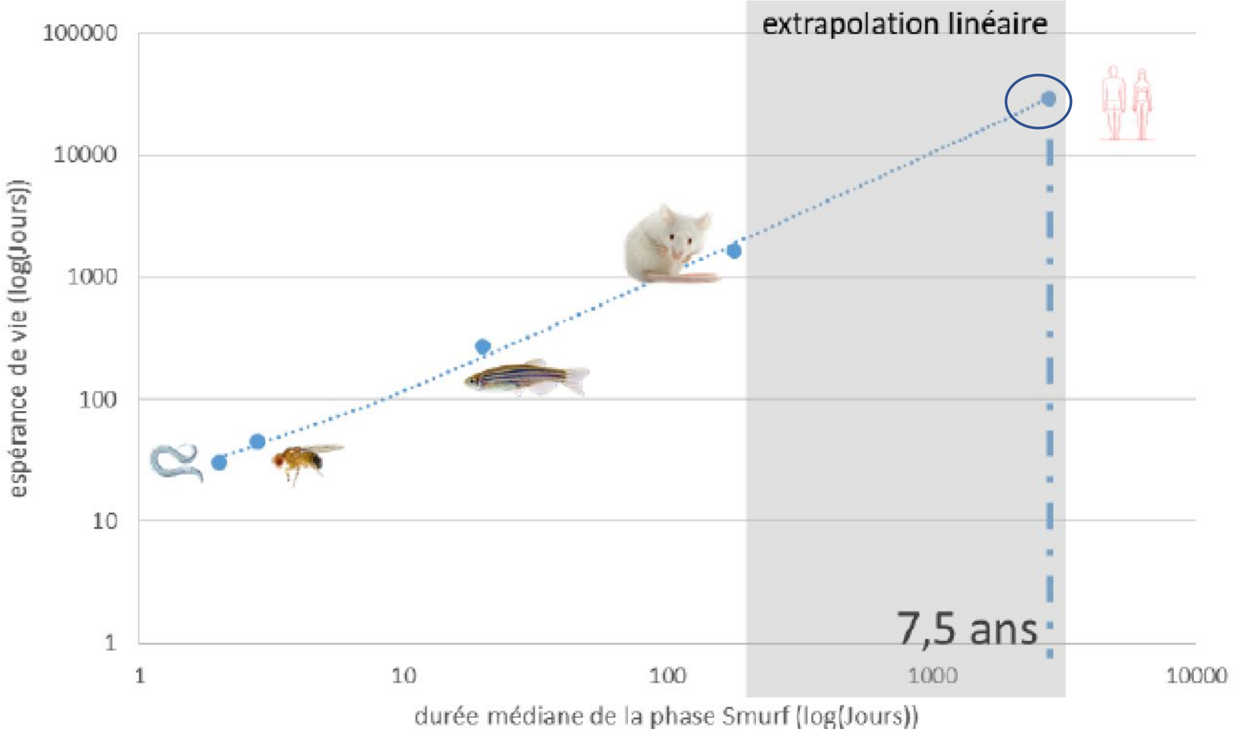
Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states

David Furman[1,2], Junlei Chang[3], Lydia Lartigue[4], Christopher R Bolen[5,11], François Haddad[6], Brice Gaudilliere[5], Edward A Ganio[5], Gabriela K Fragiadakis[5], Matthew H Spitzer[5], Isabelle Douchet[7], Sophie Daburon[7], Jean-François Moreau[7], Garry P Nolan[5], Patrick Blanco[7], Julie Déchanet-Merville[7], Cornelia L Dekker[8], Vladimir Jojic[9], Calvin J Kuo[3], Mark M Davis[1,10] & Benjamin Faustin[7]

Relevance of the model to the human risk of impending death

Clément Dubost
Réa Bégin

- ICU patients, Smurfness and ICU scores



- Scientific council IHA Bégin ✓
- Research division SSA ✓
- IRB (CPP)

Fondation Bettencourt Schueller
Reconnue d'utilité publique depuis 1987

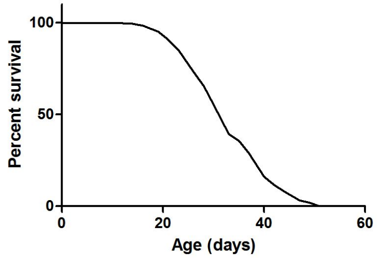
Service de santé des armées

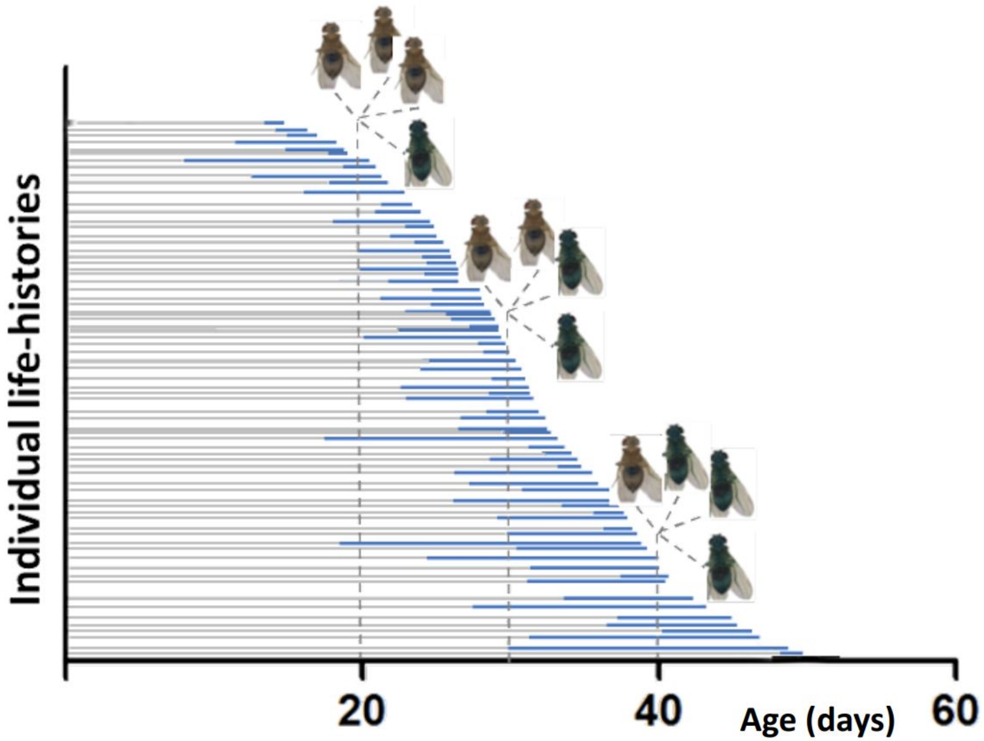
An alternative model for ageing : summarizing questions

- are all individuals affected equally ?

- is ageing really a by-product of evolution?

- what is hiding below allometric properties?





An alternative model for ageing : summarizing questions

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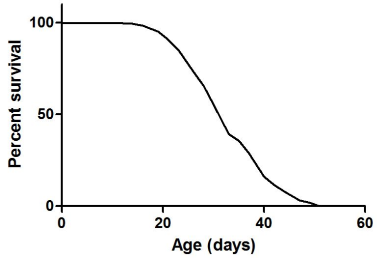

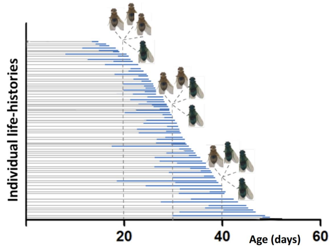

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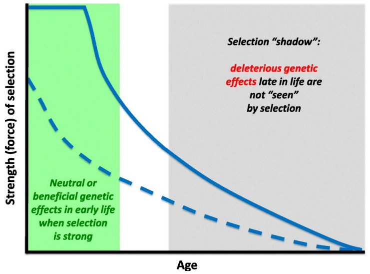

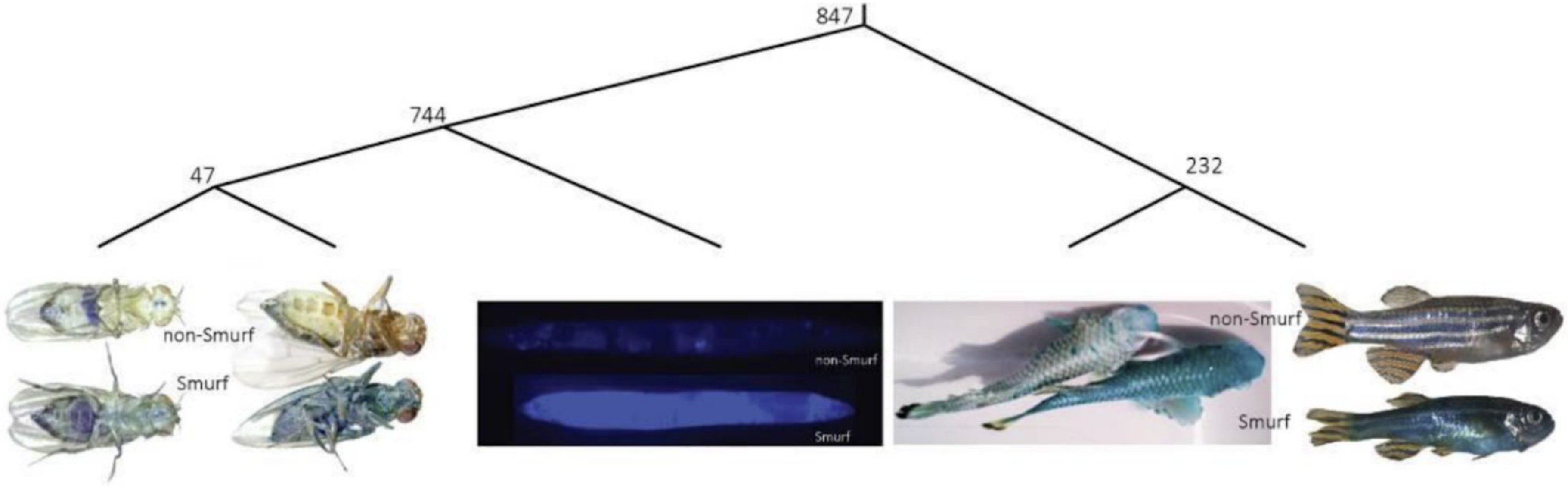

An alternative model for ageing : summarizing questions

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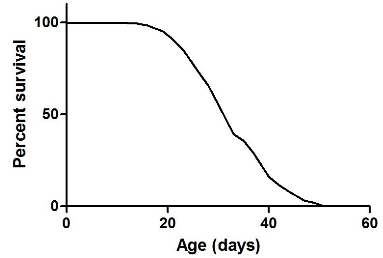

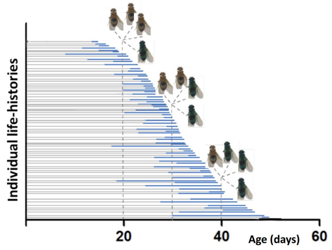

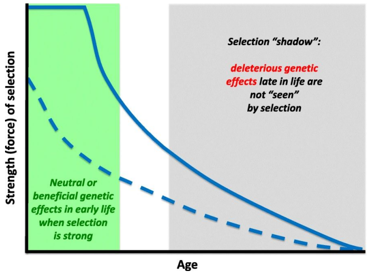

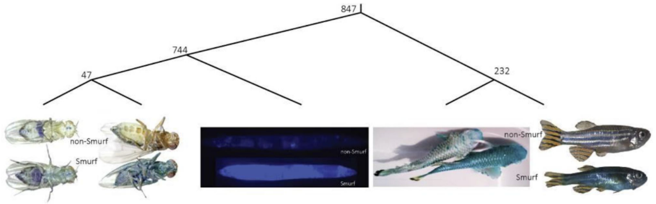

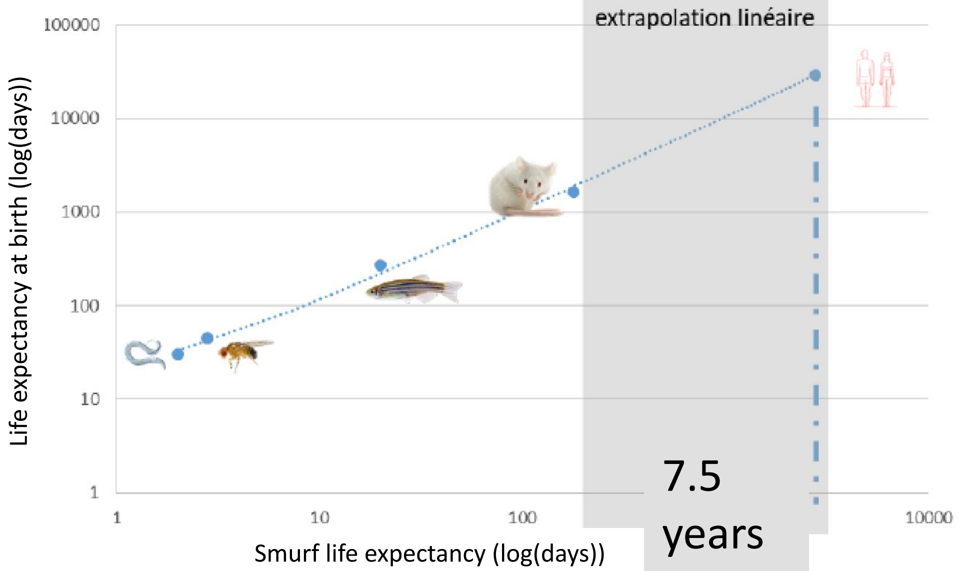

An alternative model for ageing : summarizing questions

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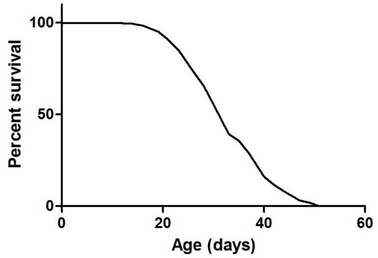

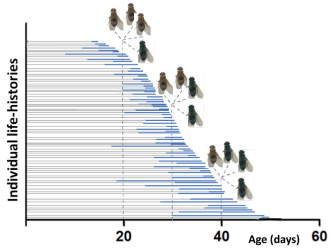

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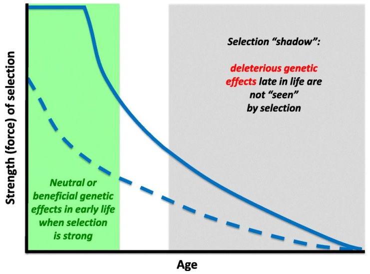
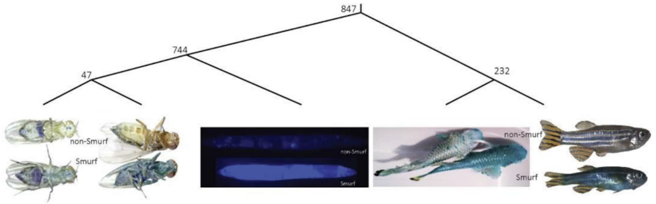
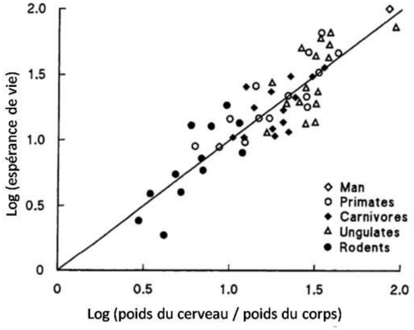
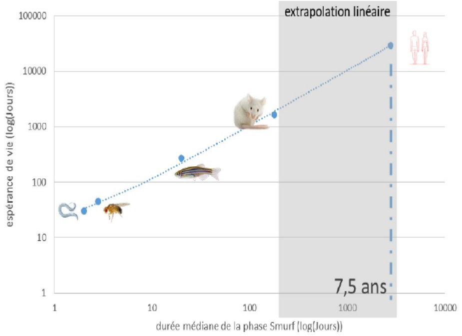


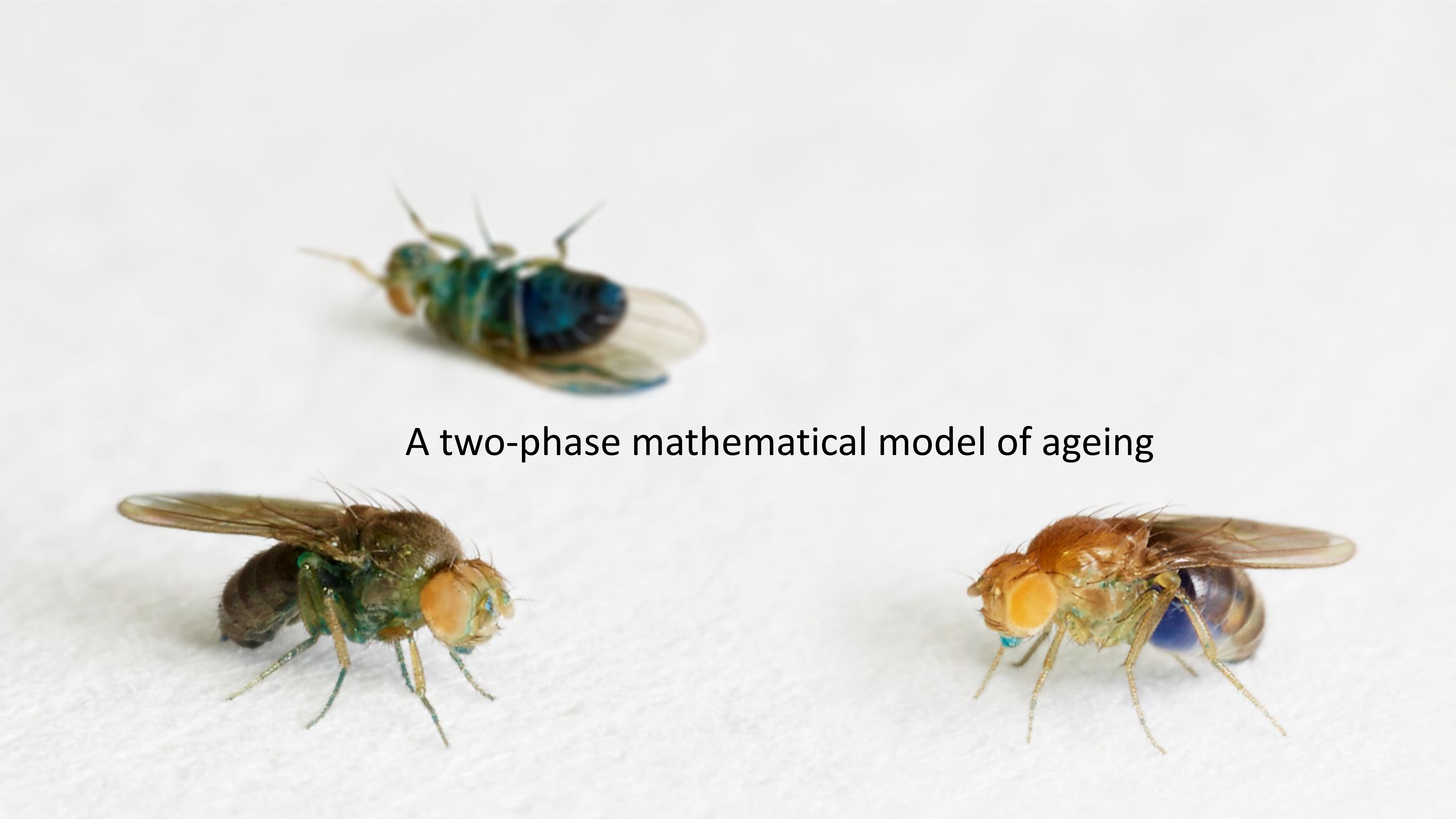


- what is hiding below allometric properties?

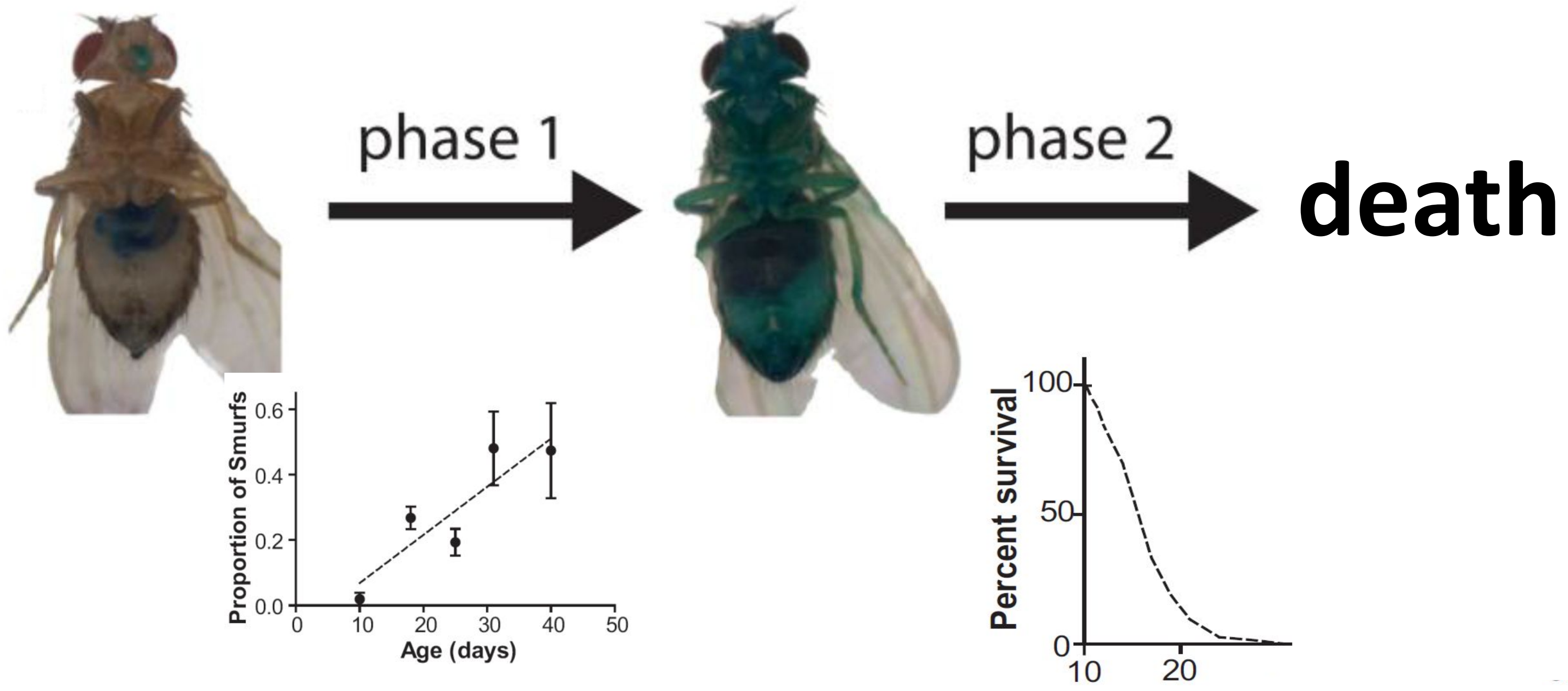




- can we model survival differently?


A two-phase mathematical model of ageing

Rethinking the mathematical structure of ageing

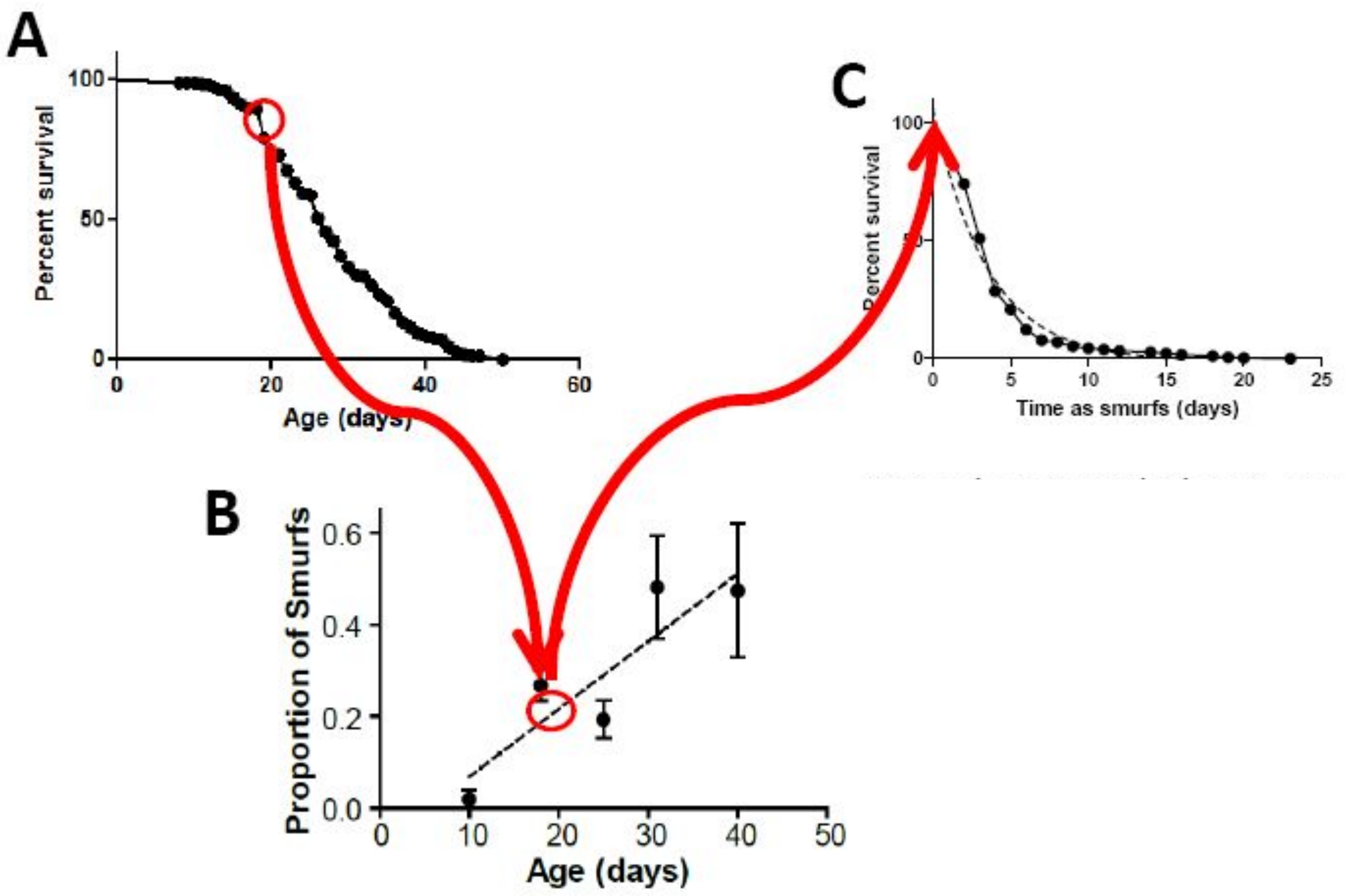


Smurfs = a*t + b

Smurf survival $= e^{-k*t}$

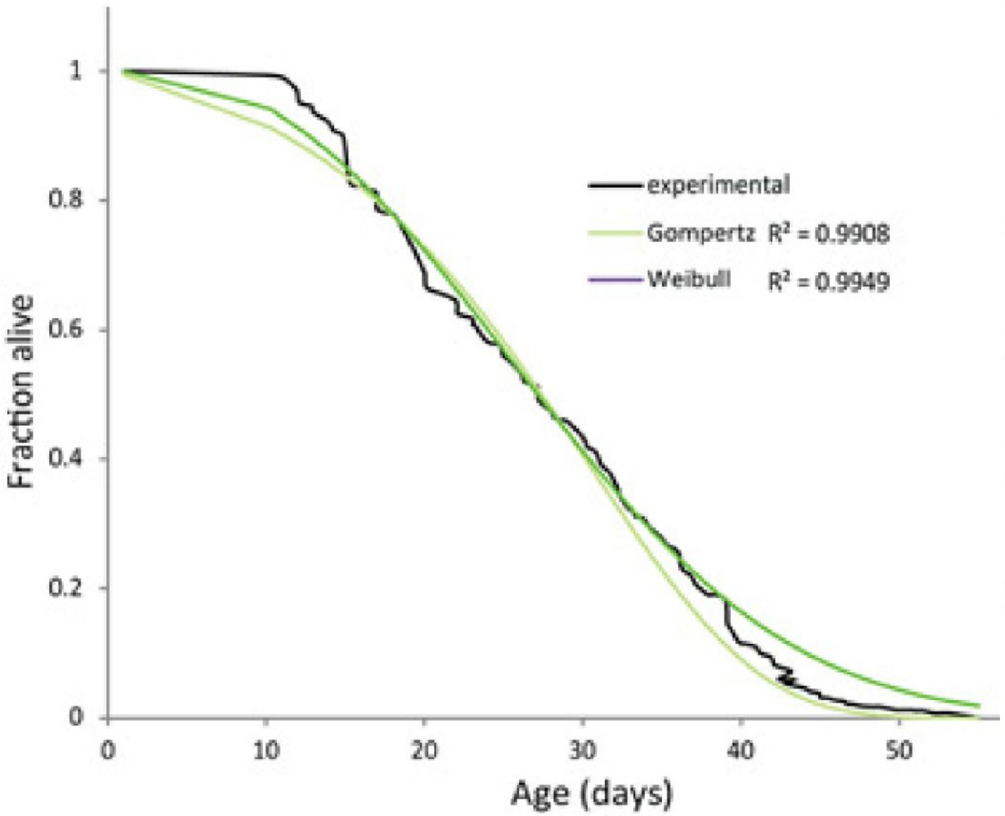
H. Tricoire, M. Rera 2015

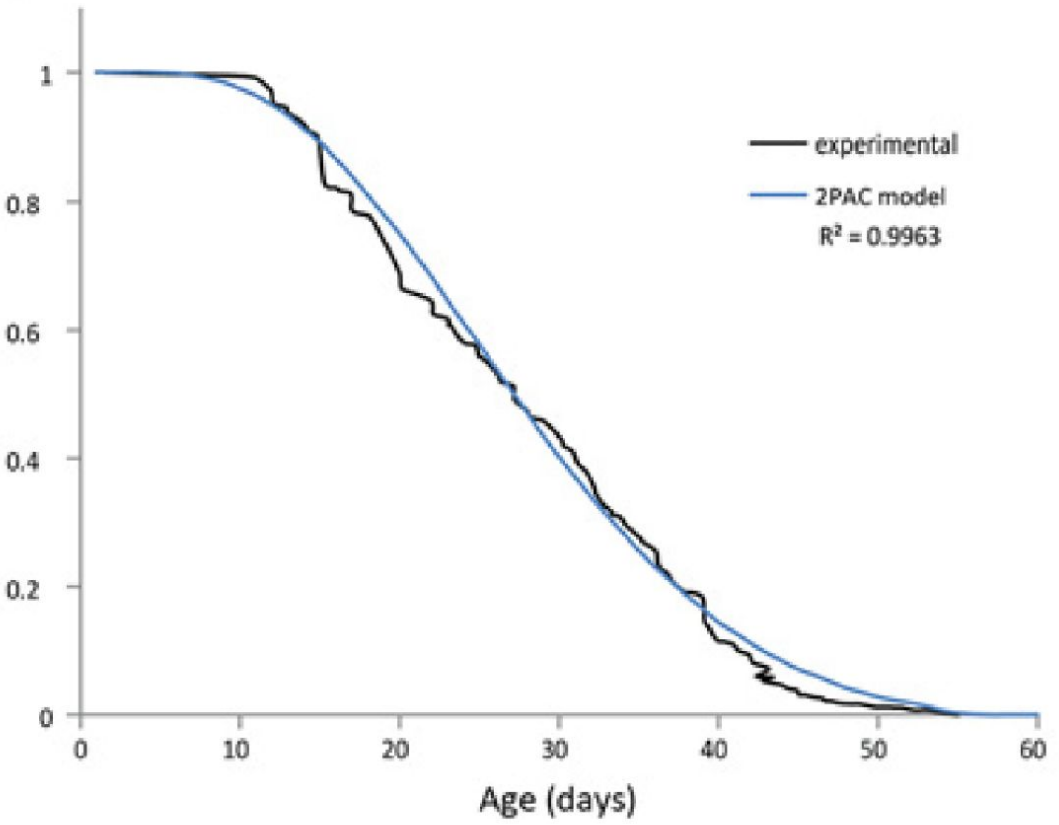
Rethinking the mathematical structure of ageing



H. Tricoire, M. Rera 2015

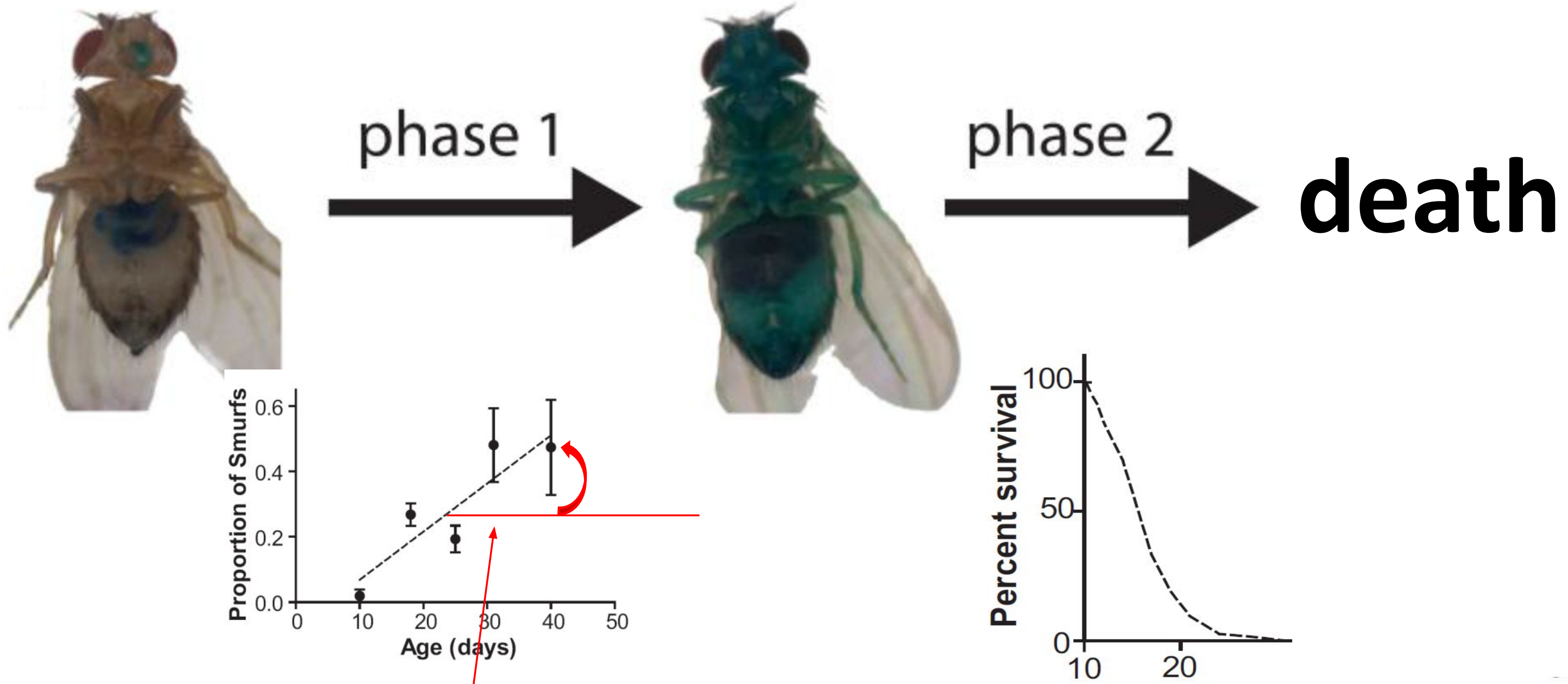
A new powerful mathematical model





H. Tricoire, M. Rera 2015

Experimental parameters that are easy to estimate and interpret



Smurfs = $a*t + b$

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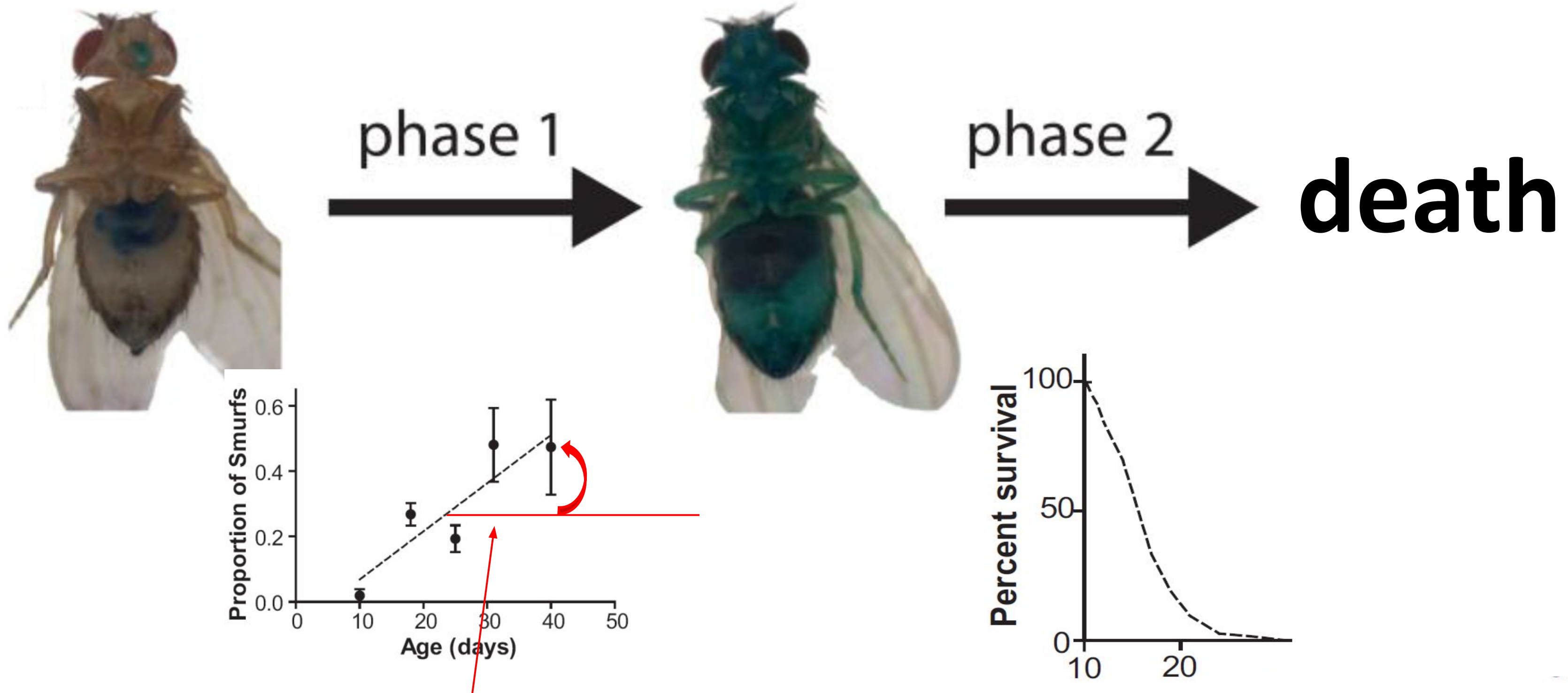
Experimental parameters that are easy to estimate and interpret



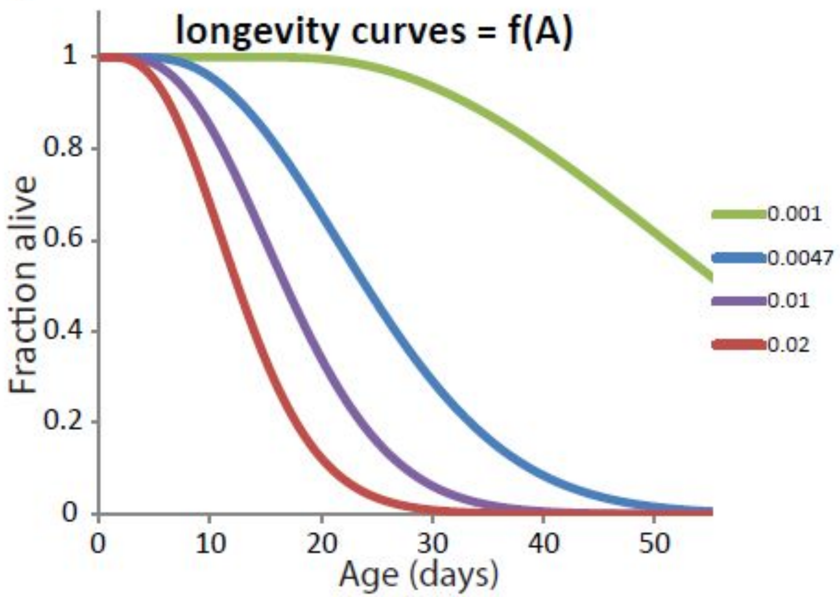
Smurfs = a*t + b

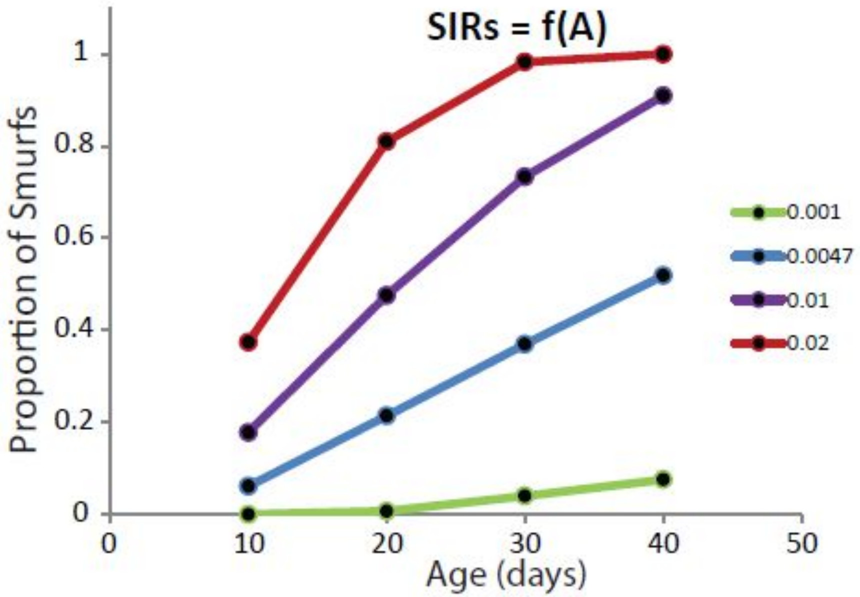
Smurf survival $= e^{-k*t}$

daily failure rate

Experimental parameters that are easy to estimate and interpret

Effects of the parameter <u>A</u> on





H. Tricoire, M. Rera 2015

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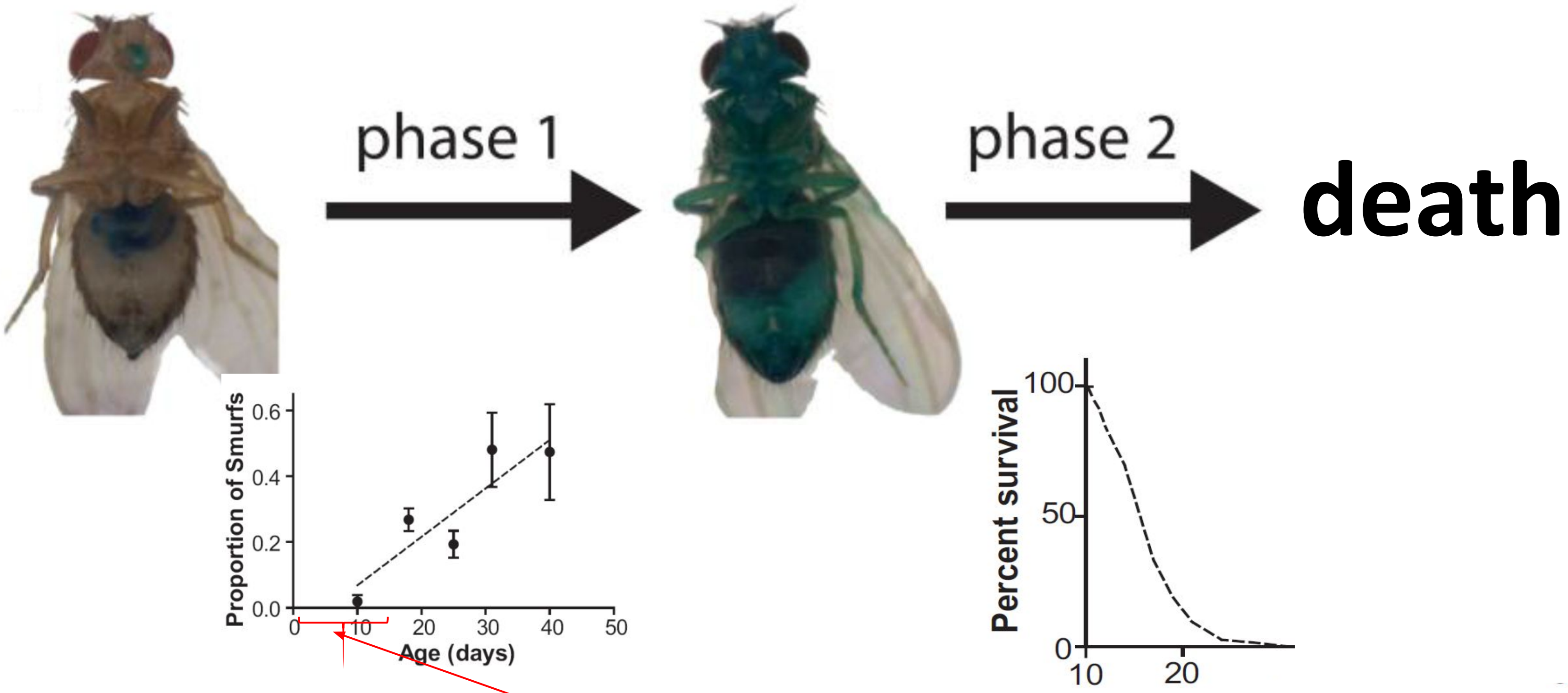
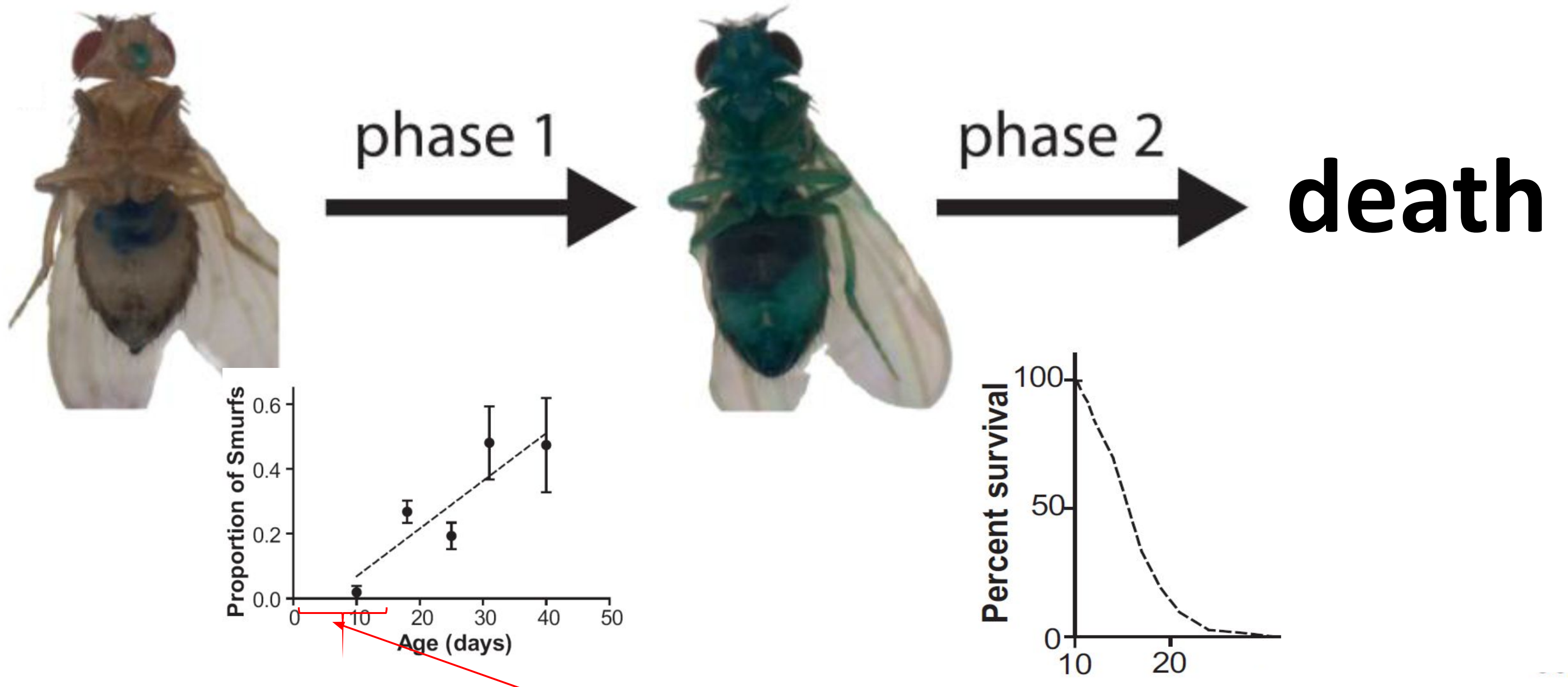


Smurfs = a*t + b

Smurf survival = e^{-k*t}

Experimental parameters that are easy to estimate and interpret



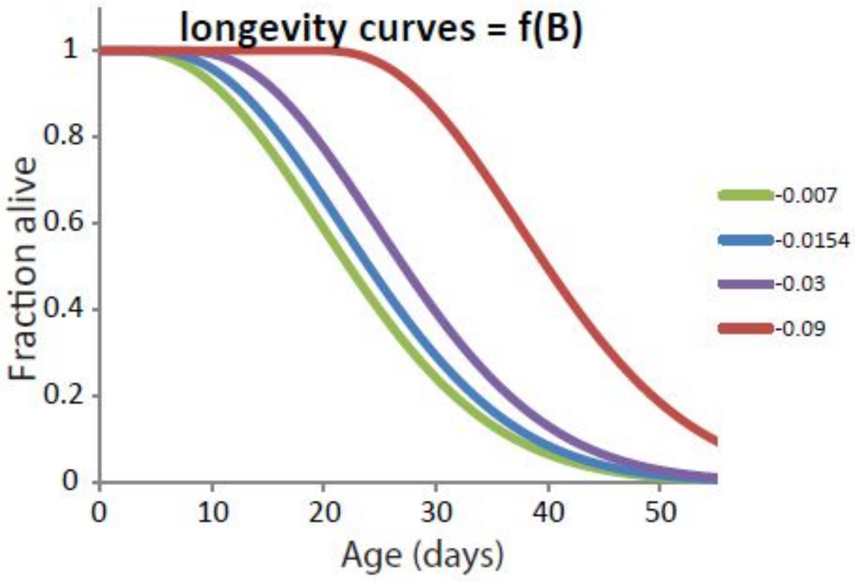
Smurfs = a*t + b

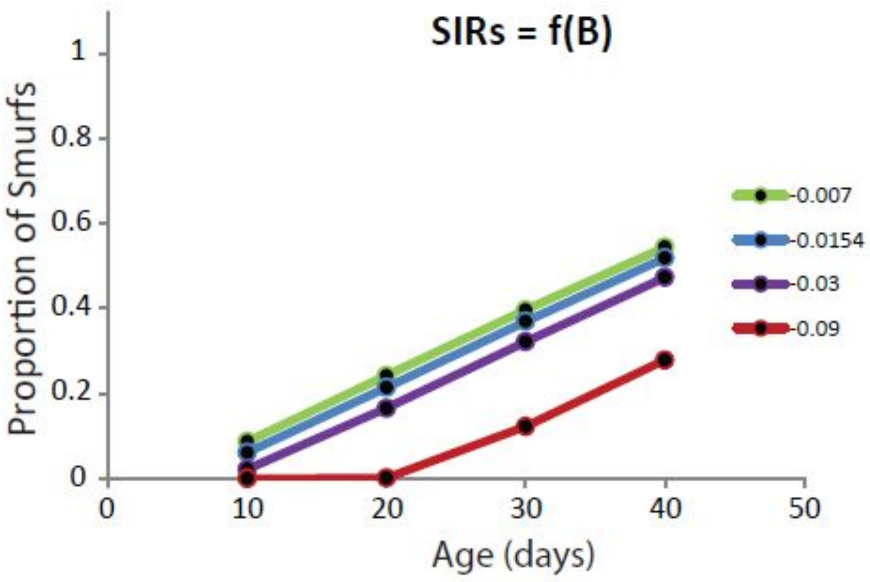
Smurf survival = e^{-k*t}

failure tolerance

Experimental parameters that are easy to estimate and interpret

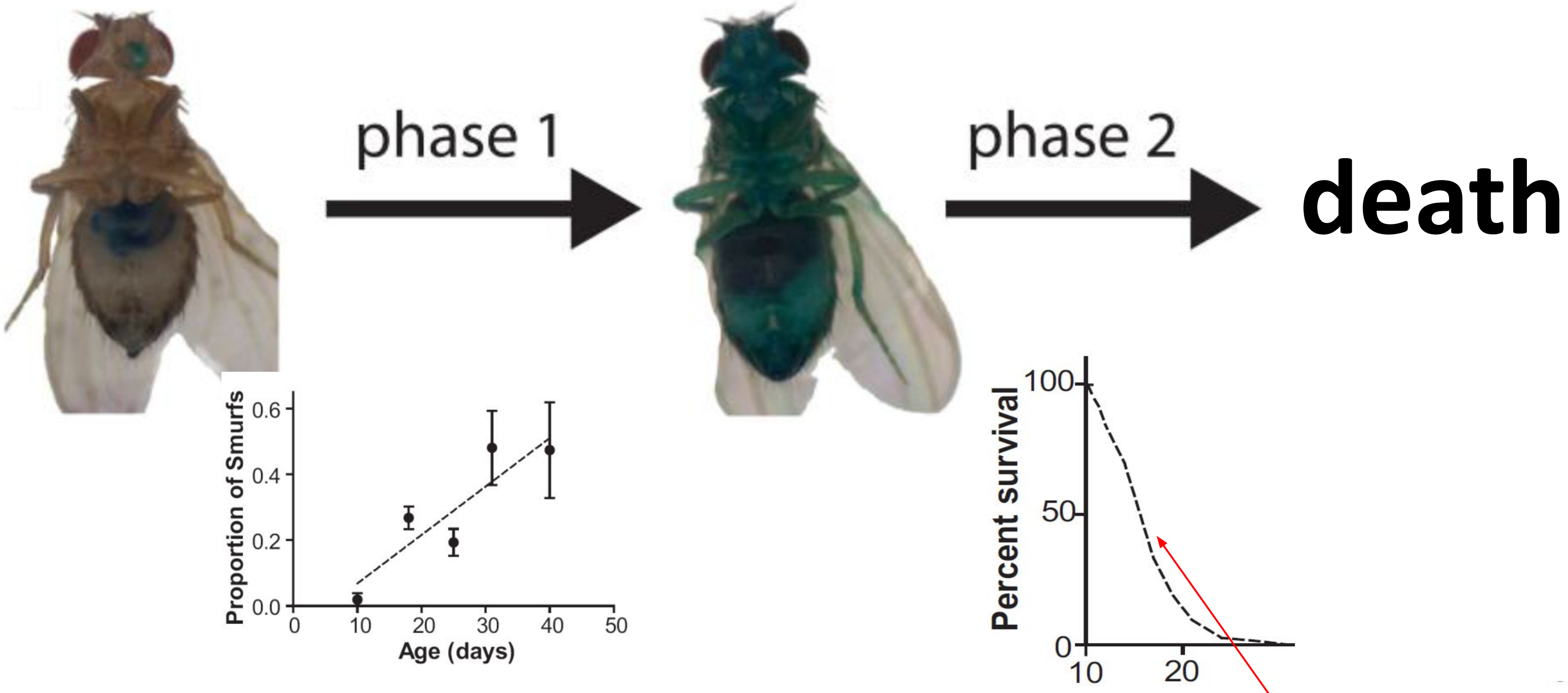
Effects of the parameter ***B*** *on curves*





H. Tricoire, M. Rera 2015

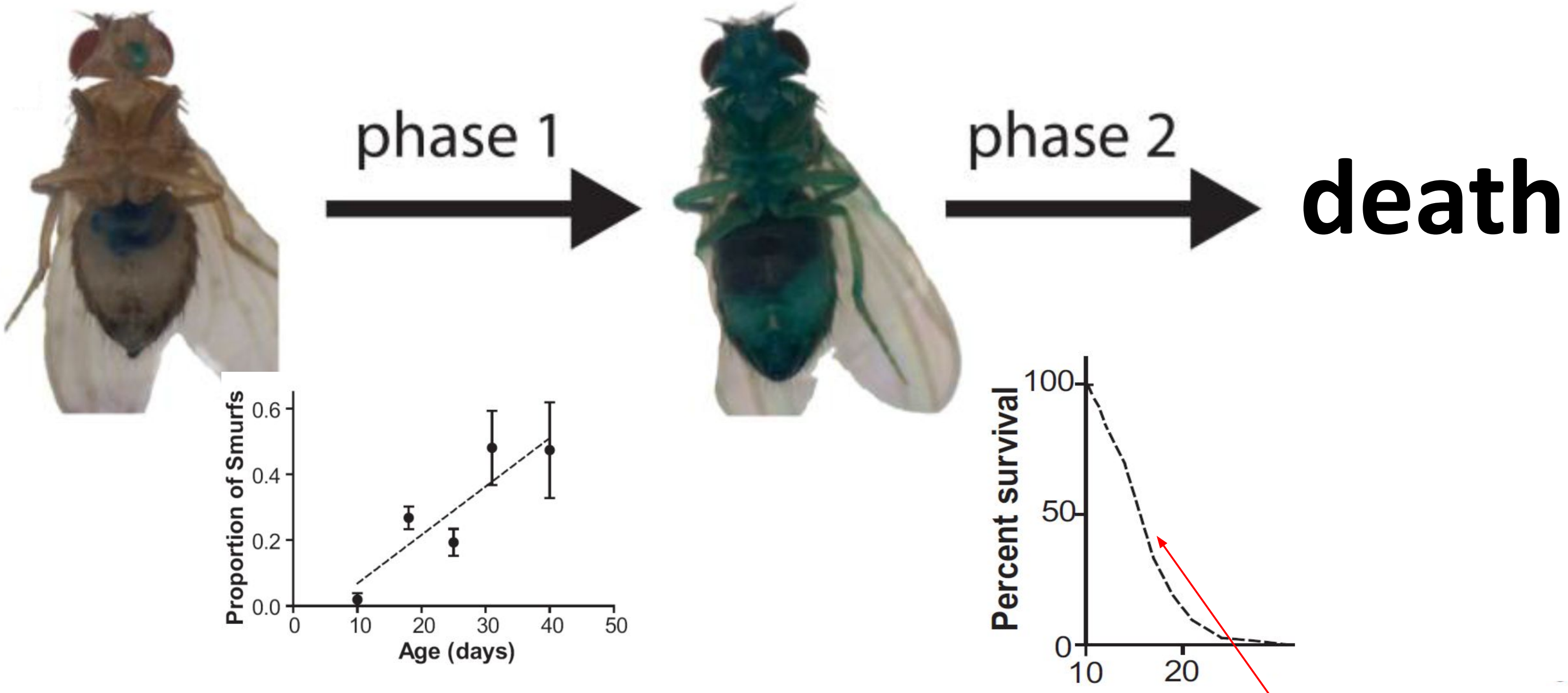
Experimental parameters that are easy to estimate and interpret



Smurfs = a*t + b

Smurf survival $= e^{-k*t}$

Experimental parameters that are easy to estimate and interpret



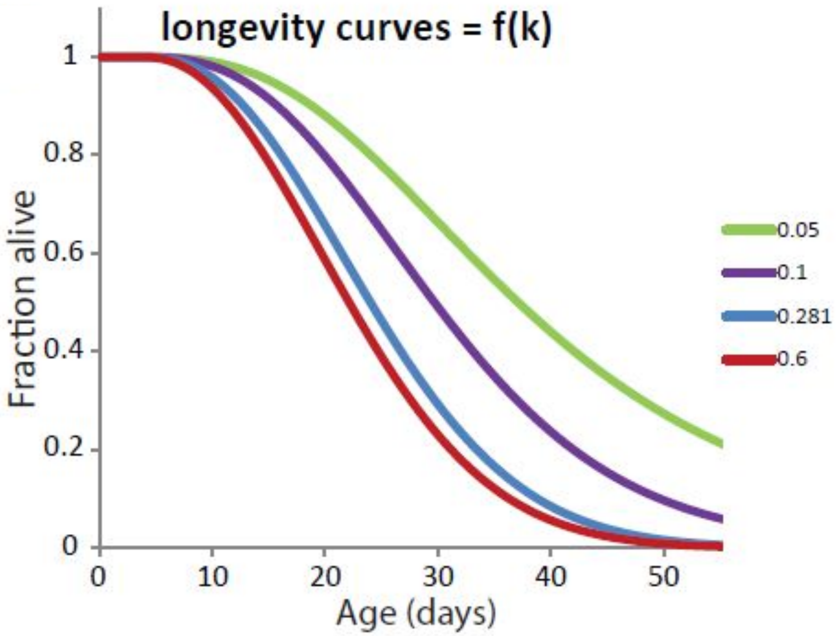
Smurfs = a*t + b

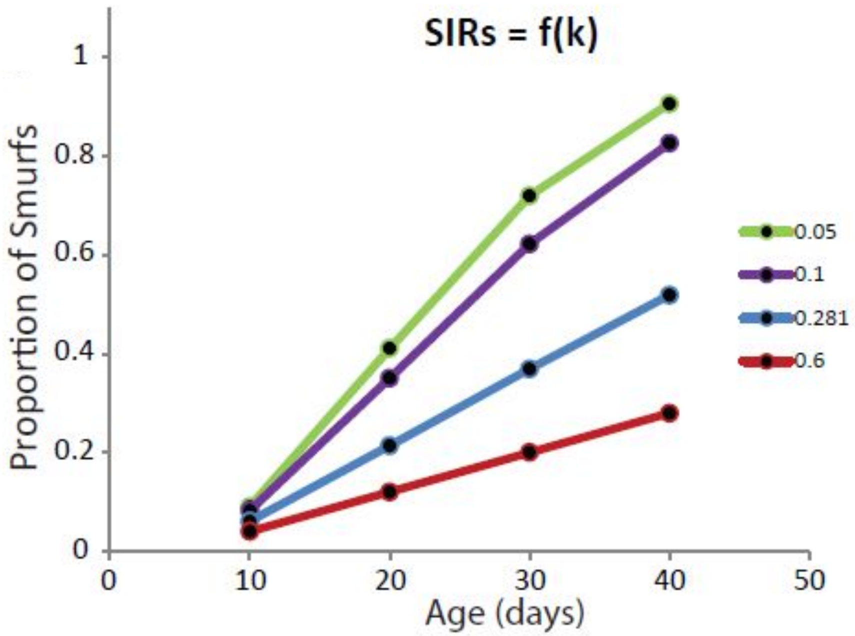
Smurf survival = e^{-k*t}

mortality rate

Experimental parameters that are easy to estimate and interpret

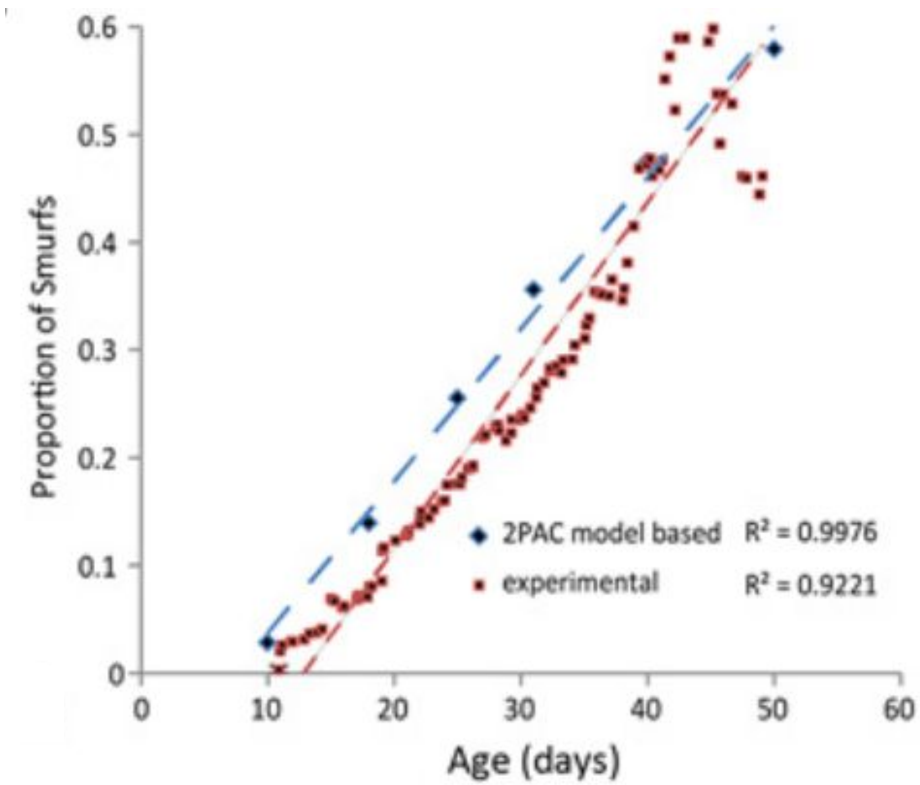
*Effects of the parameter **k** on curves*





H. Tricoire, M. Rera 2015

Improving the model



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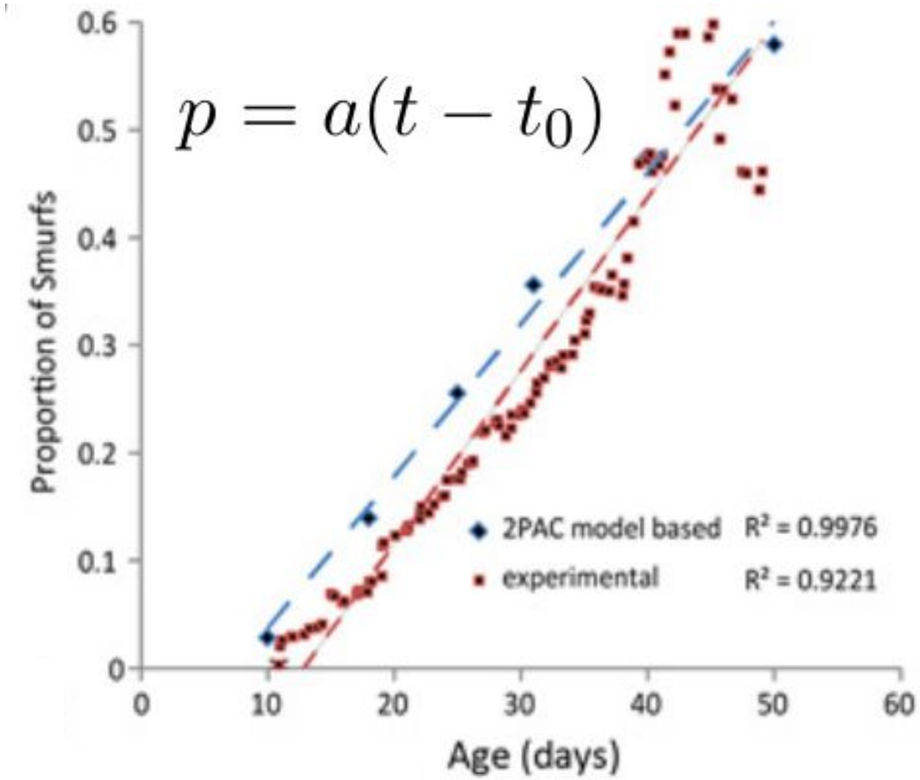
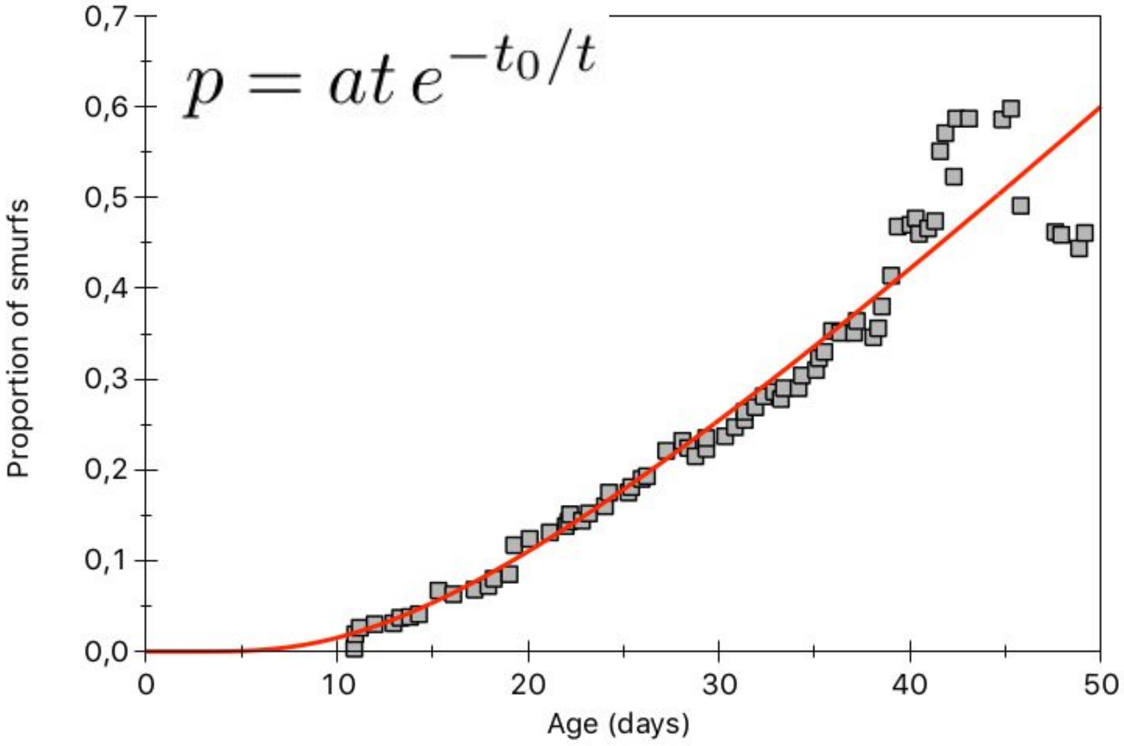
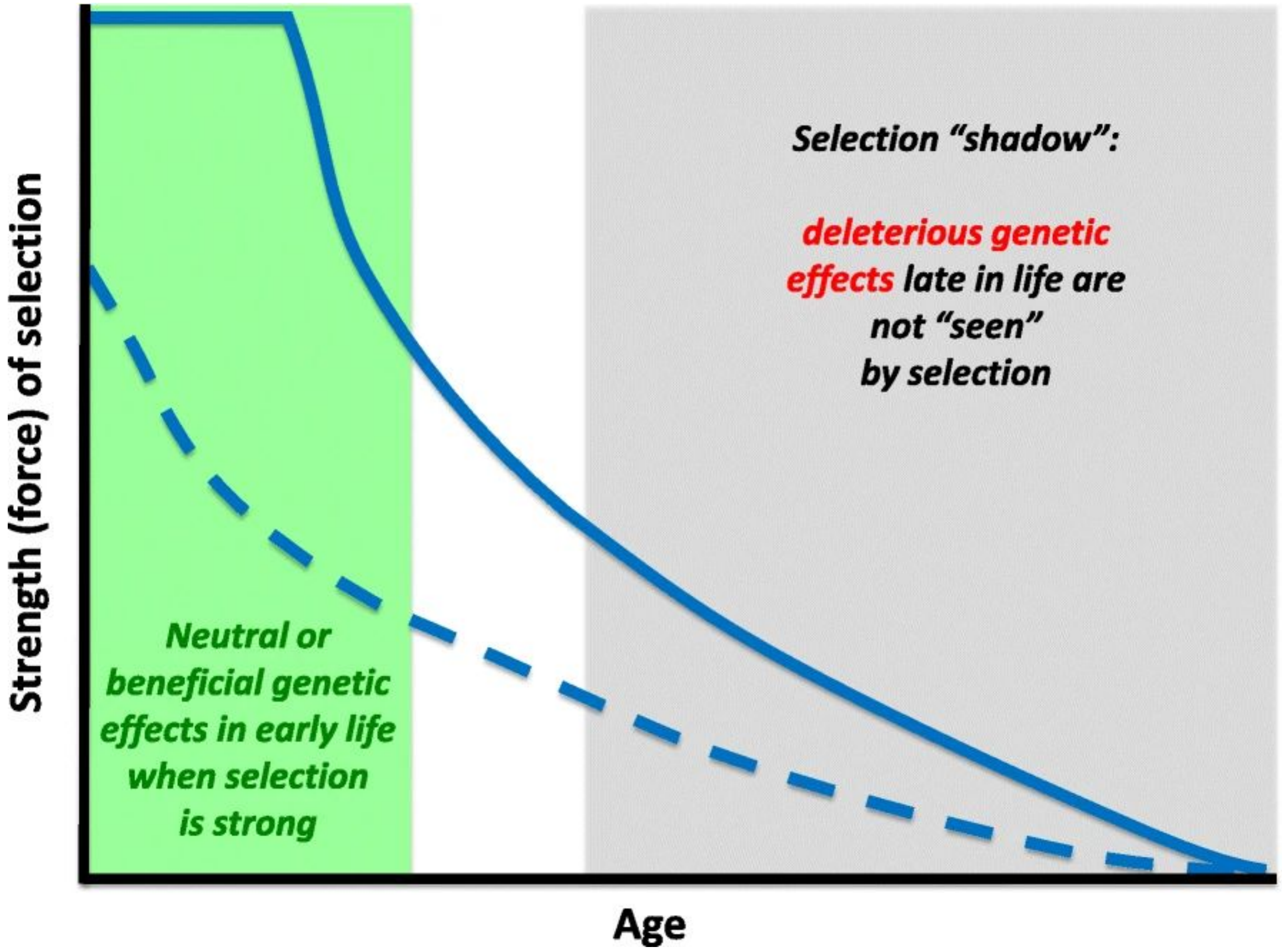




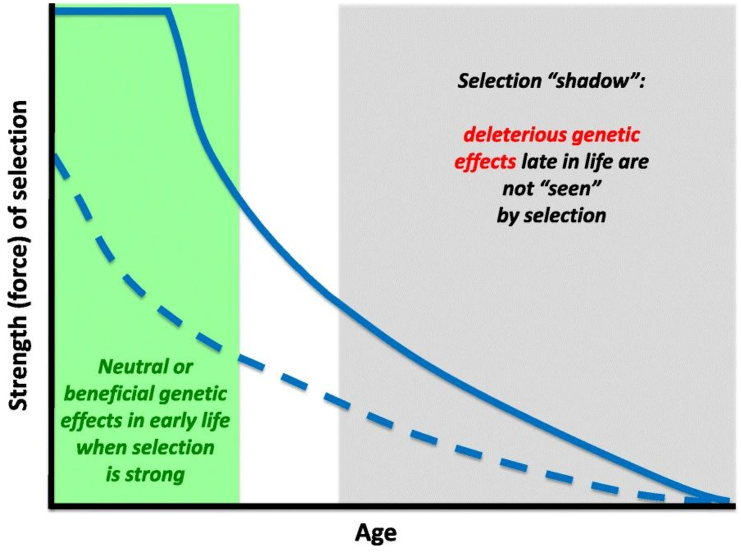
JM Di Meglio, unpublished

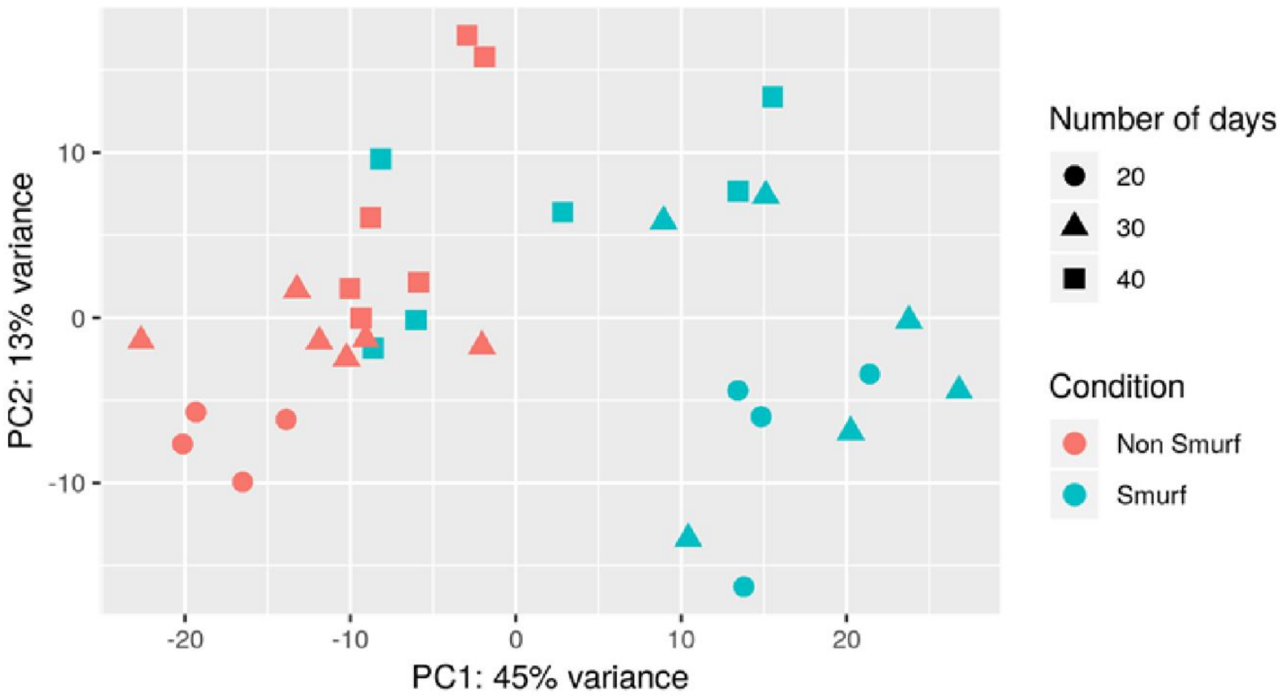

Is a two-phase ageing process selected for by evolution?

Classical model: ageing is a by-product of evolution



Classical model: ageing is a by-product of evolution but…





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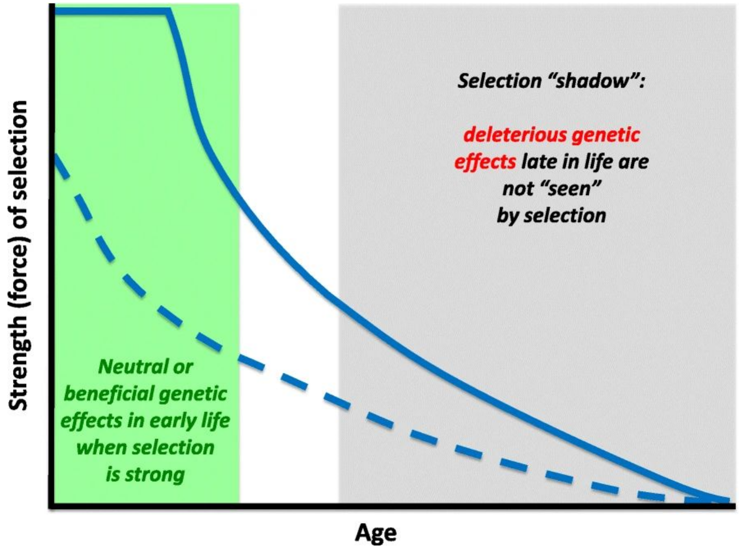
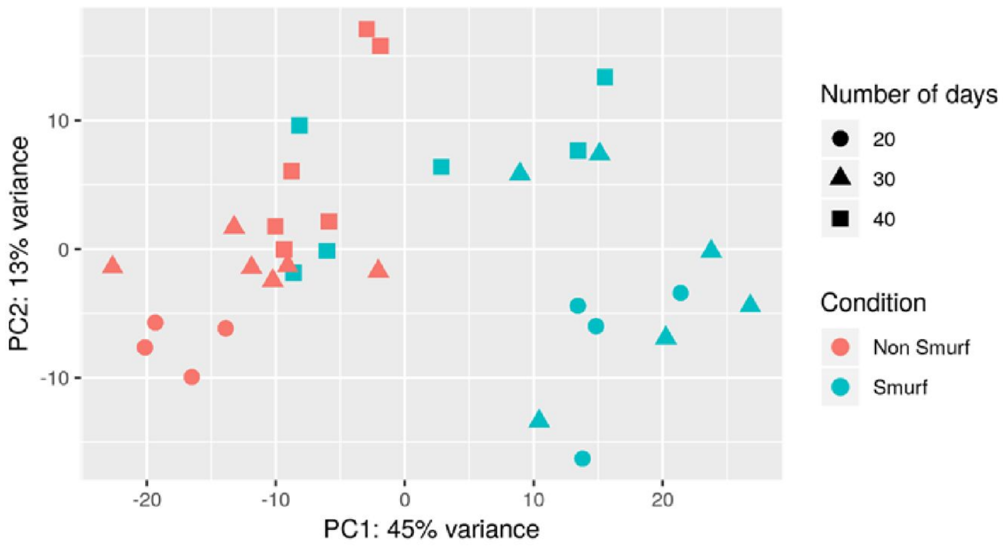
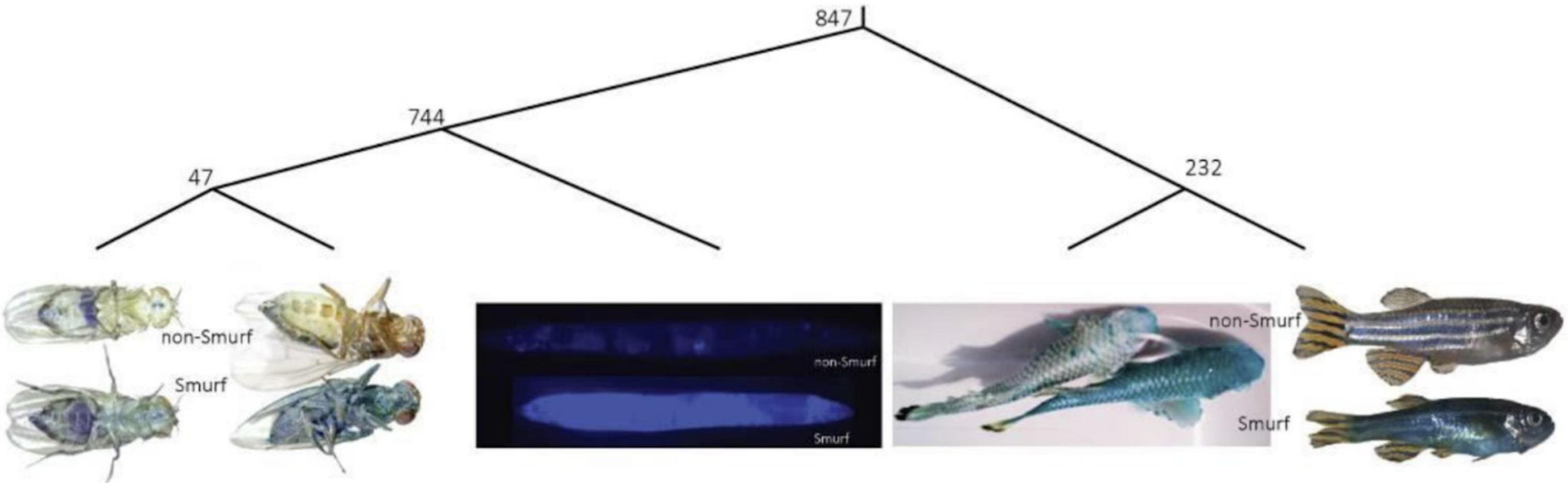
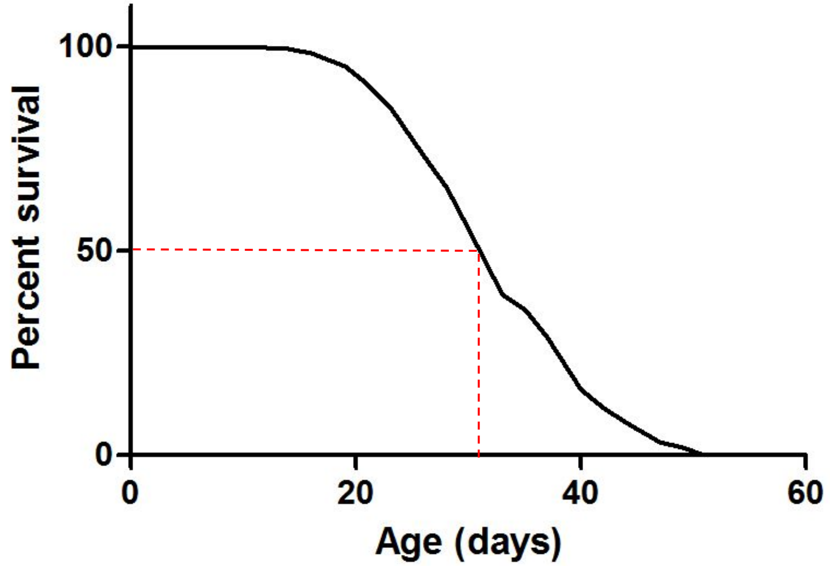
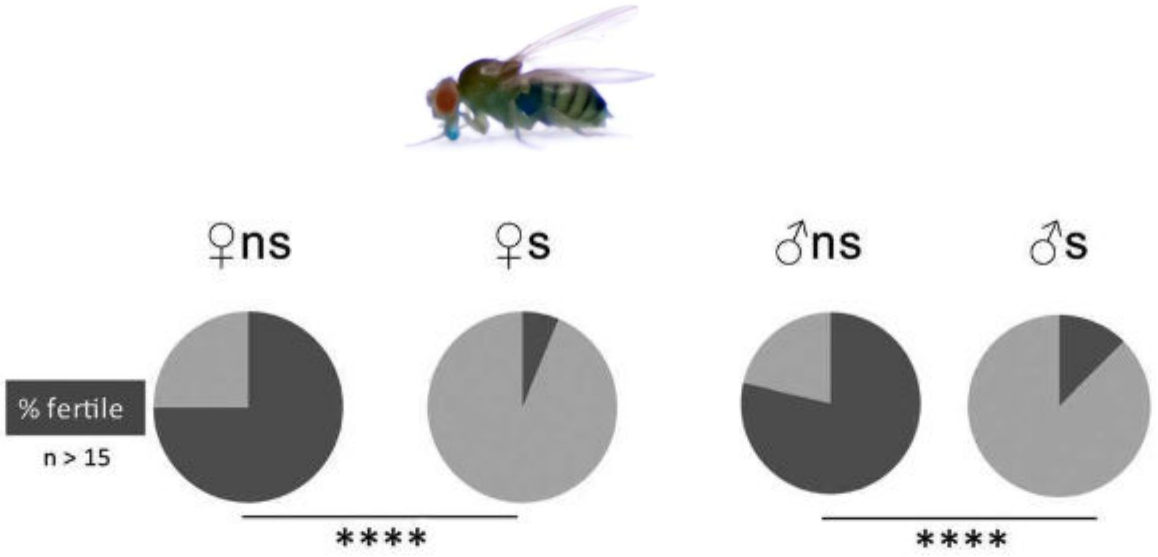






Can a two-phase ageing process appear and be selected for?





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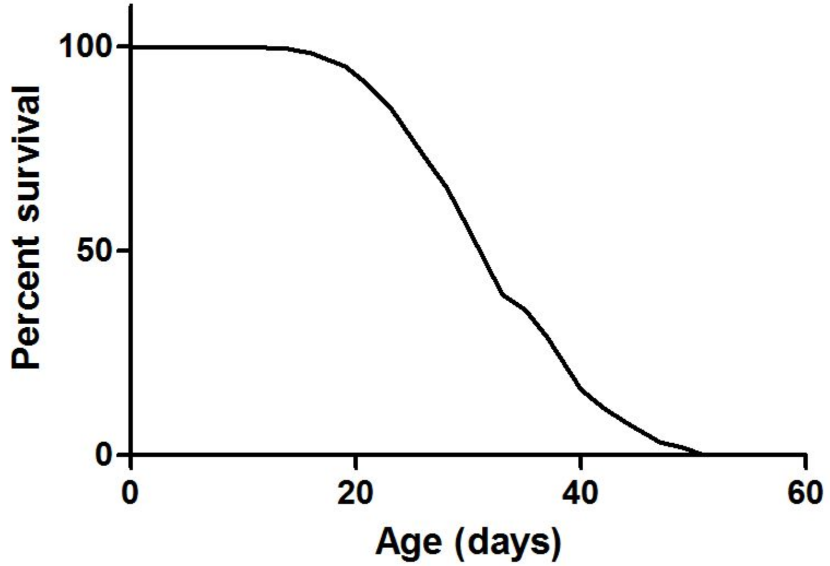
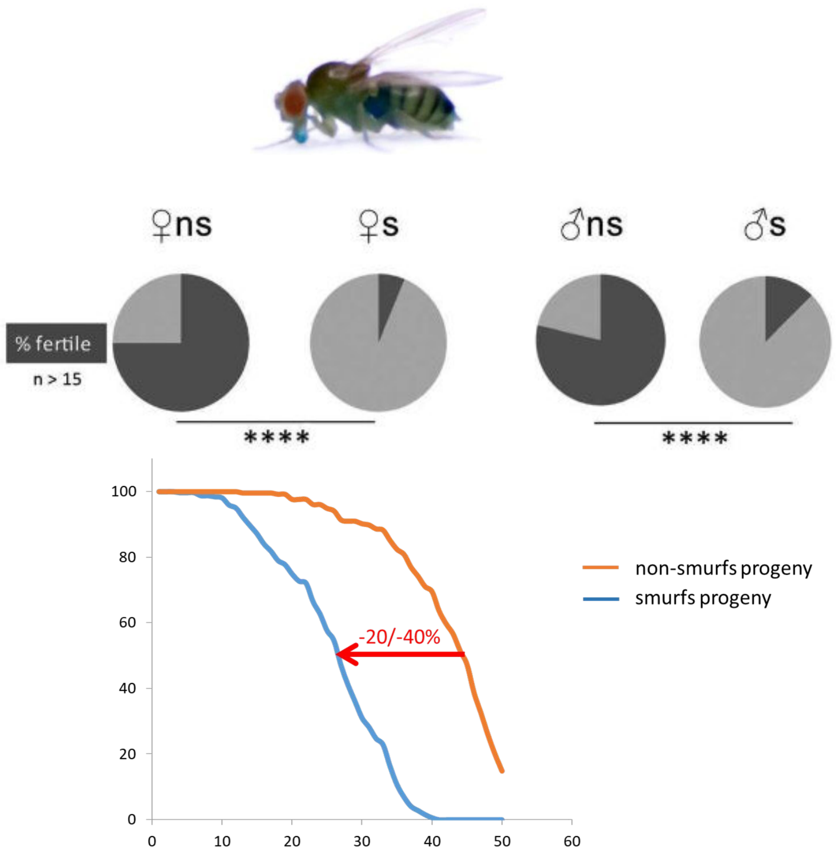


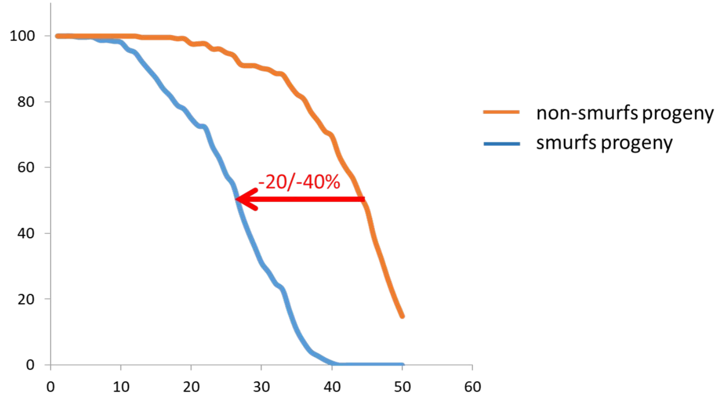


unpublished

The Lansing effect

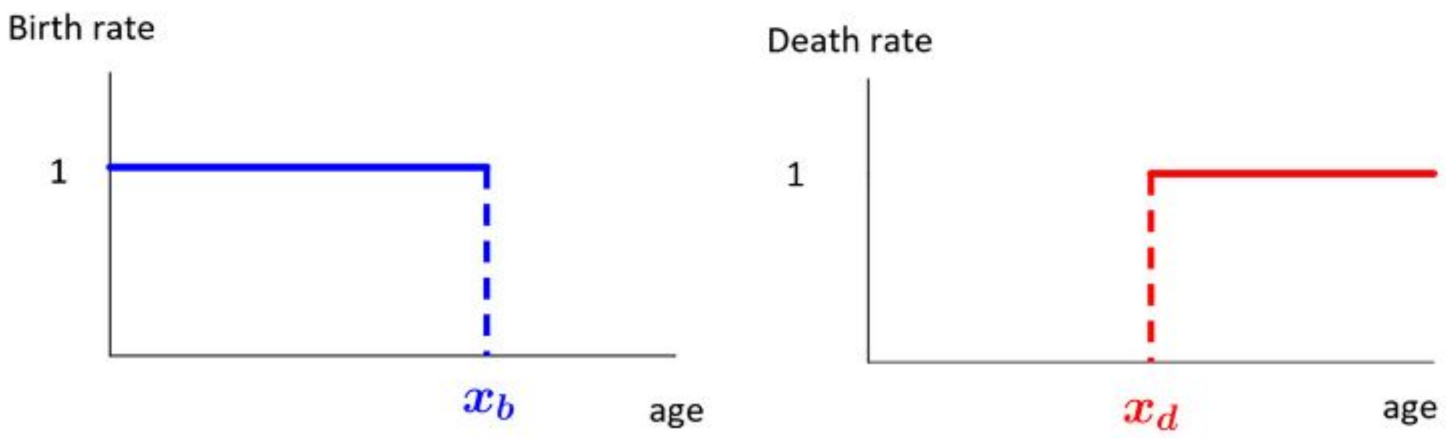
Lansing, 1954

3 independent lines



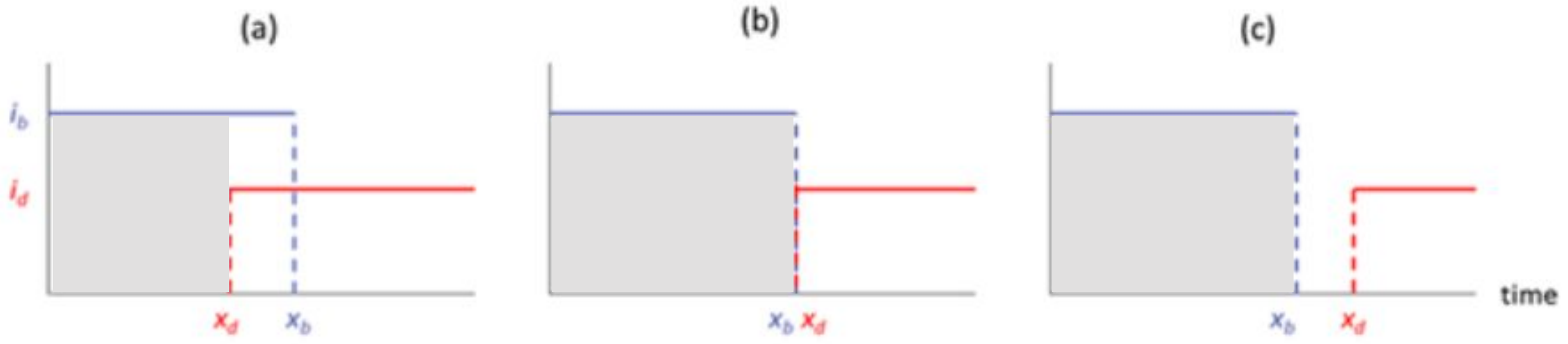
unpublished

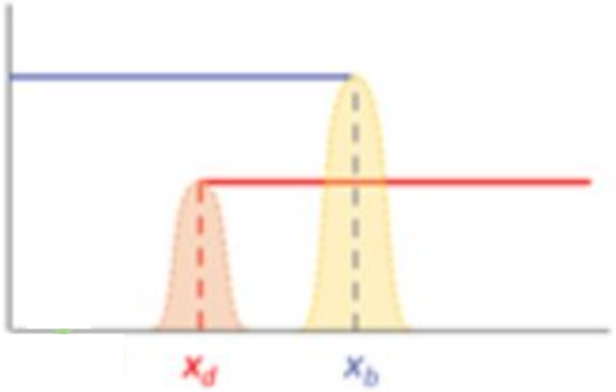
Proposing a simple birth-death model



Roget et al., 2019

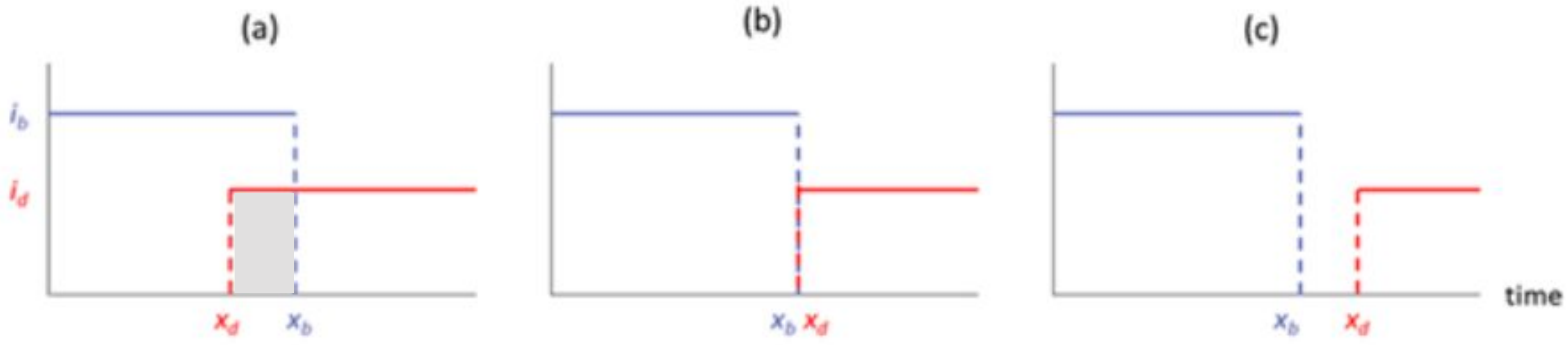
Reproduction rules

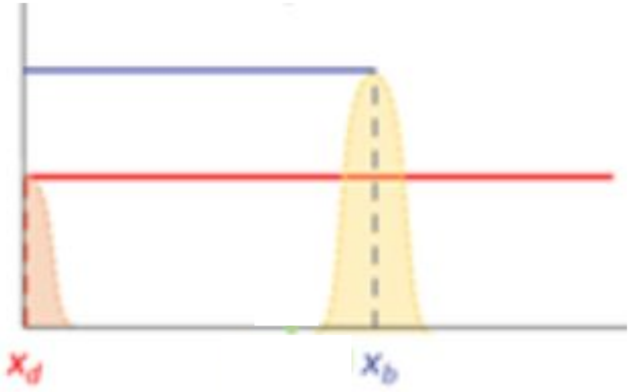




Roget et al., 2019

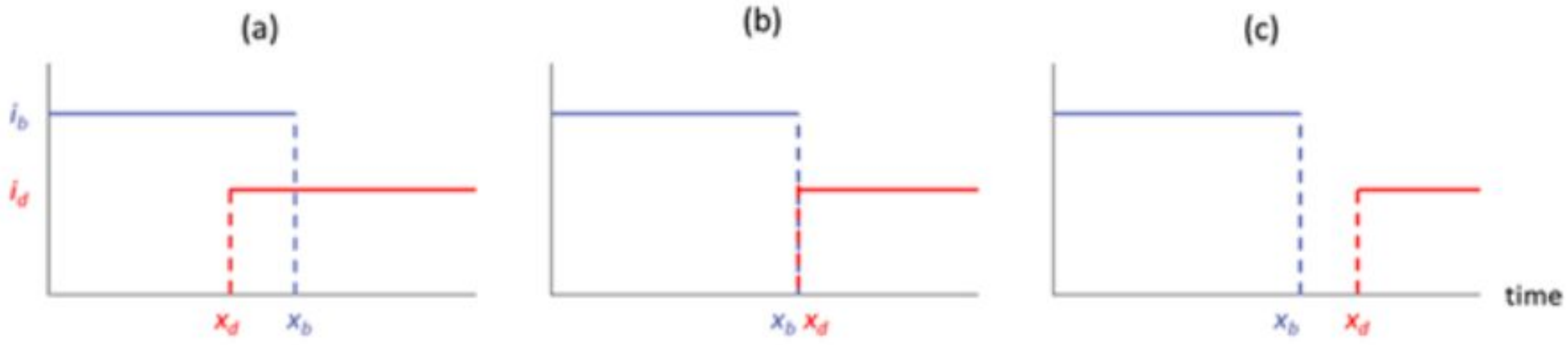
Reproduction rules : implementing the Lansing effect





Roget et al., 2019

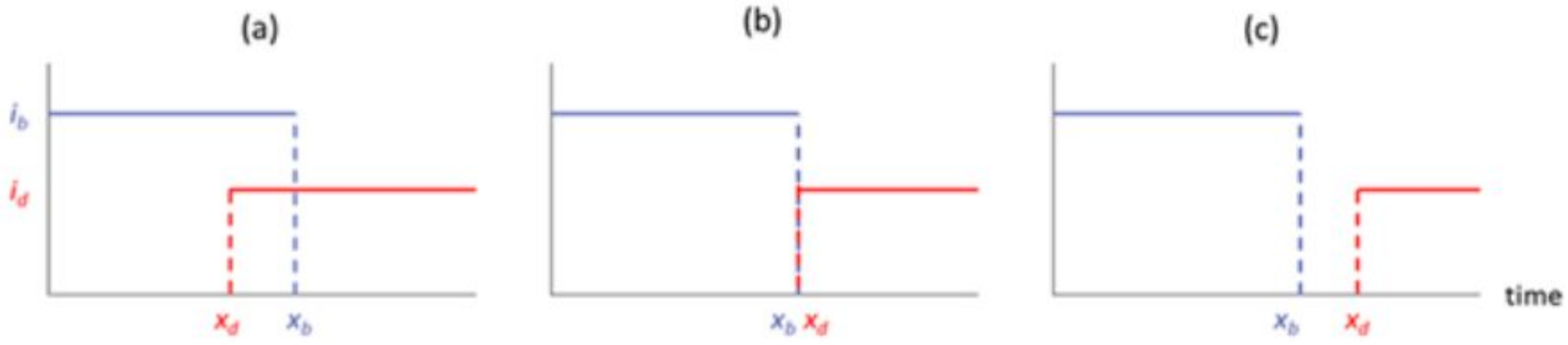
Evolution of the system

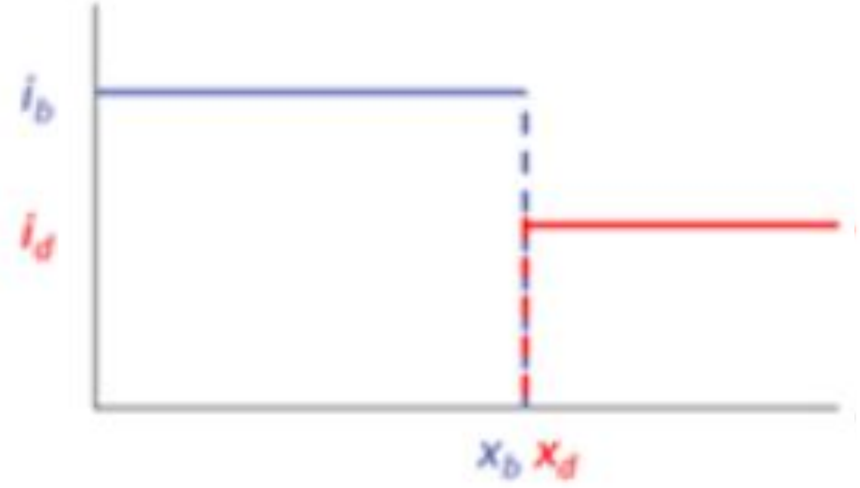


?

Roget et al., 2019; biorxiv Roget et al., 2022

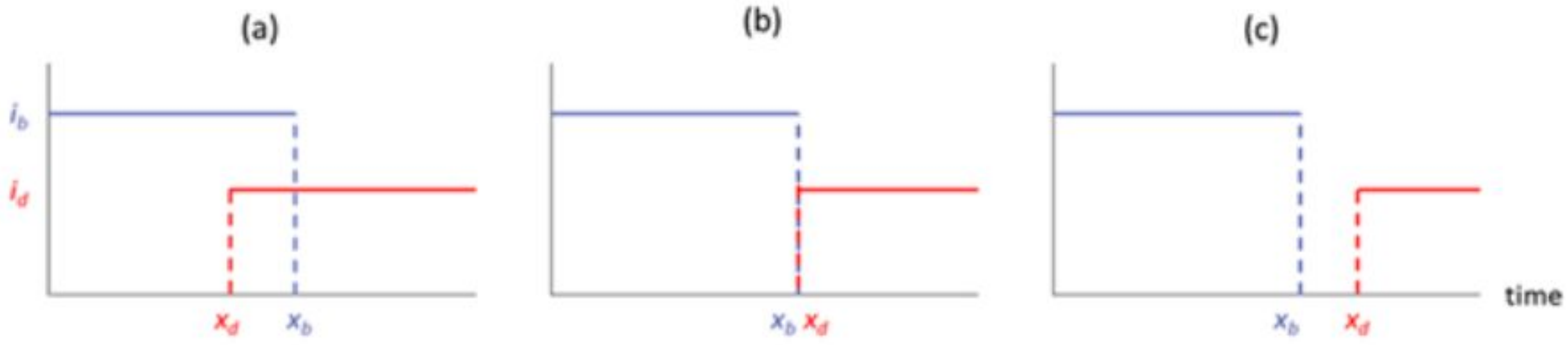
Evolution of the system : with Lansing effect





Roget et al., 2019; biorxiv Roget et al., 2022

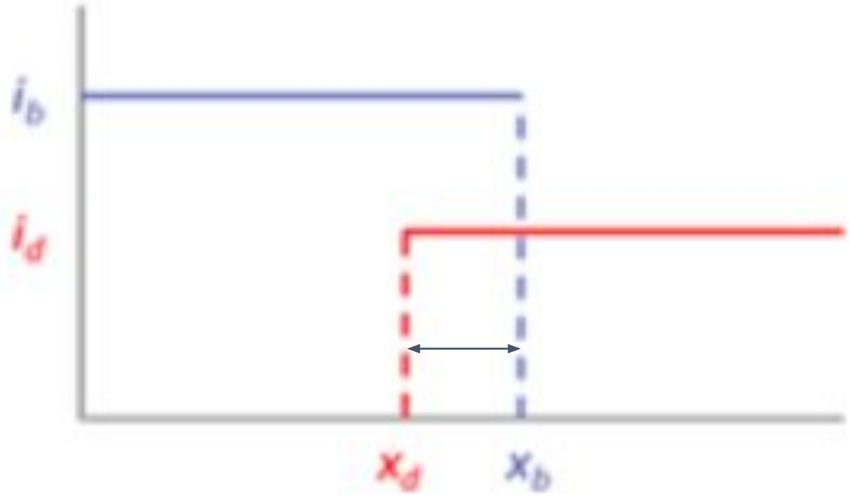
Evolution of the system : without Lansing effect



$$\lim_{t \to +\infty} (x_b - x_d)_t = \frac{\log\left(1 + \frac{i_b + i_d}{i_d}\right)}{i_b + i_d}$$

Roget et al., 2019; biorxiv Roget et al., 2022

Evolution of the system : implications for living organisms



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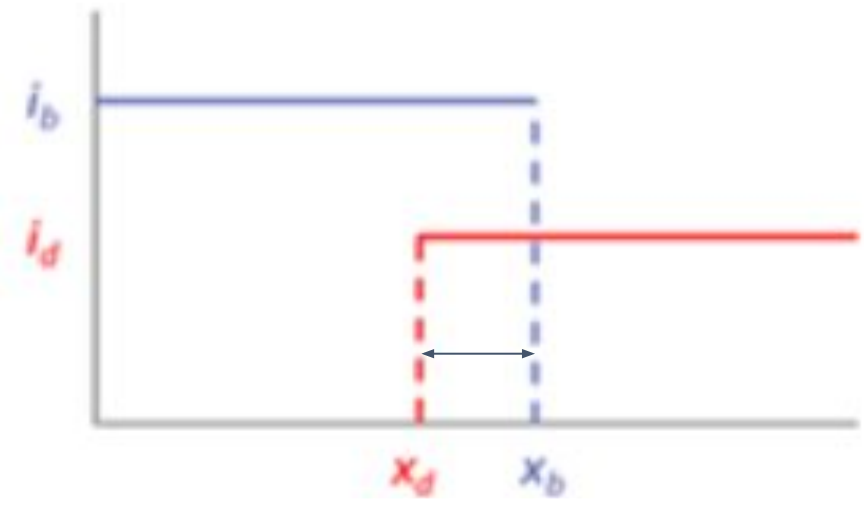
Evolution of the system : implications for living organisms



$$\lim_{t \to +\infty} (x_b - x_d)_t = \frac{\log(1+\frac{i_b + i_d}{i_d})}{i_b + i_d}$$

Roget et al., 2019; biorxiv Roget et al., 2022

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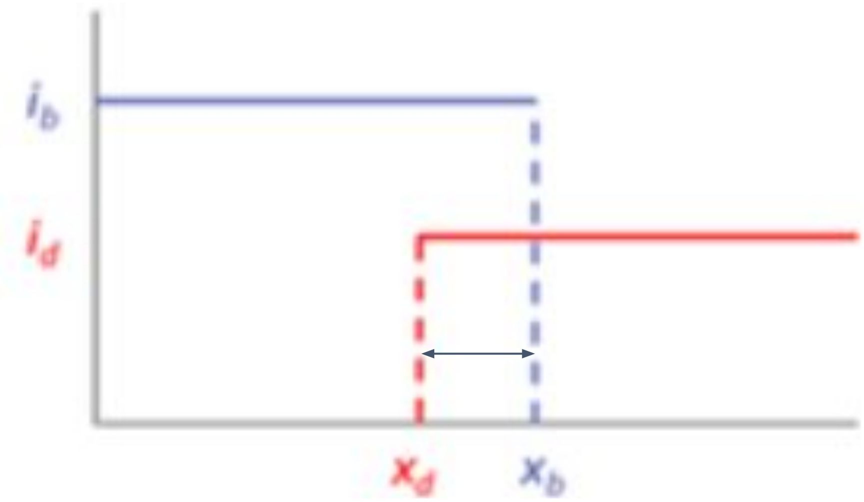

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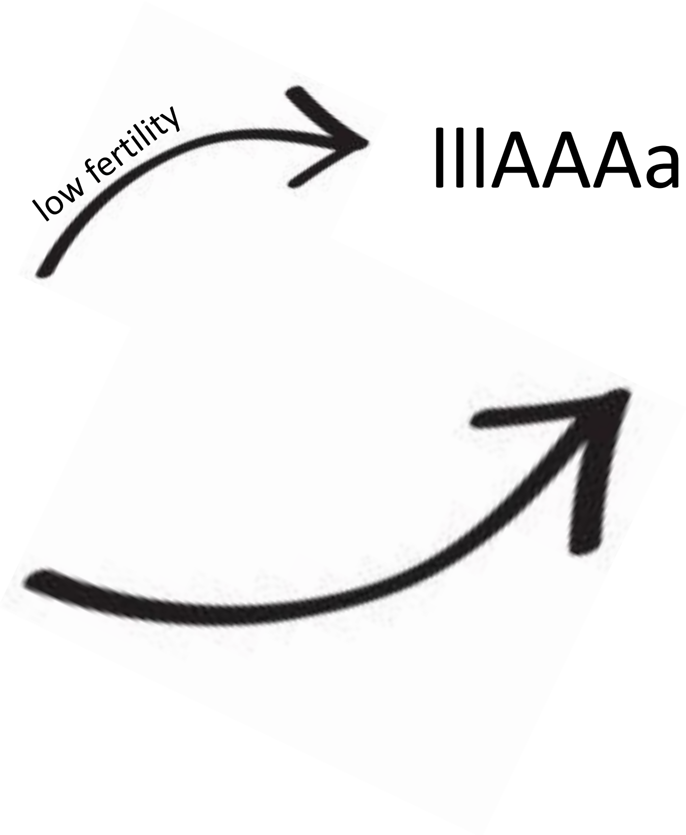


lllAAAarge x_b

lllAAAarge x_d

Roget et al., 2019; biorxiv Roget et al., 2022

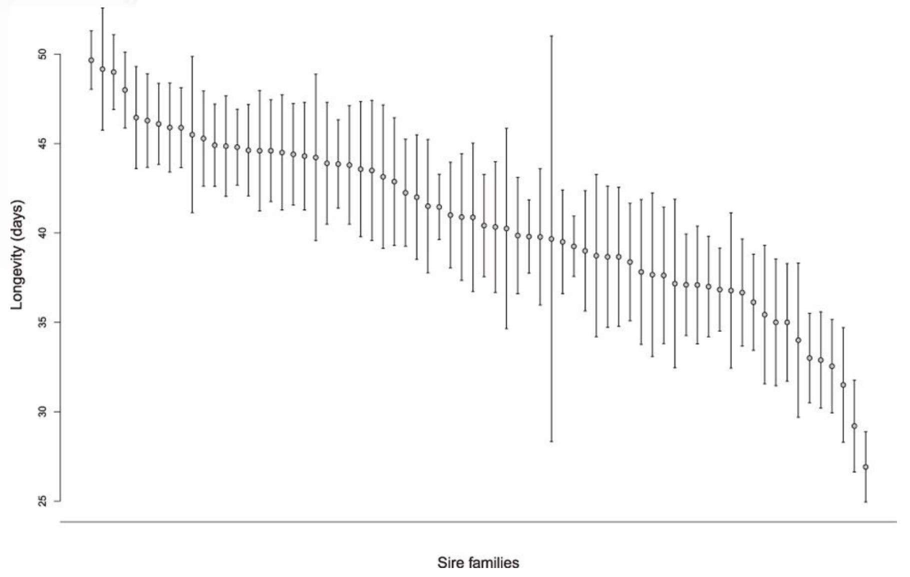
Evolution of the system : implications for living organisms

$$\lim_{t \to +\infty} (x_b - x_d)_t = \frac{\log(1+\frac{i_b + i_d}{i_d})}{i_b + i_d}$$

lllAAAarge fertility

small X_b

small X_d



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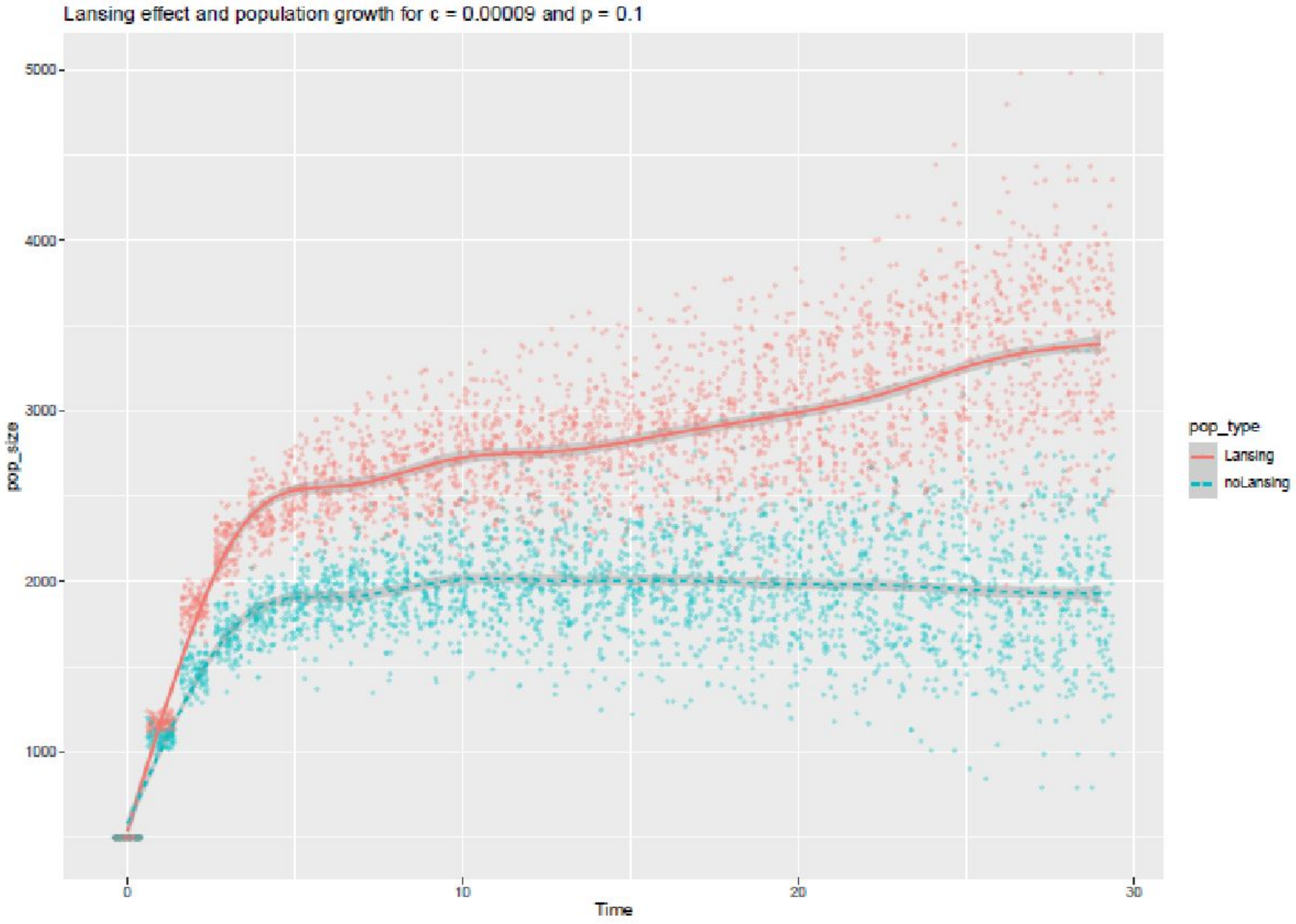
Evolution of the system : competing with and without Lansing effect



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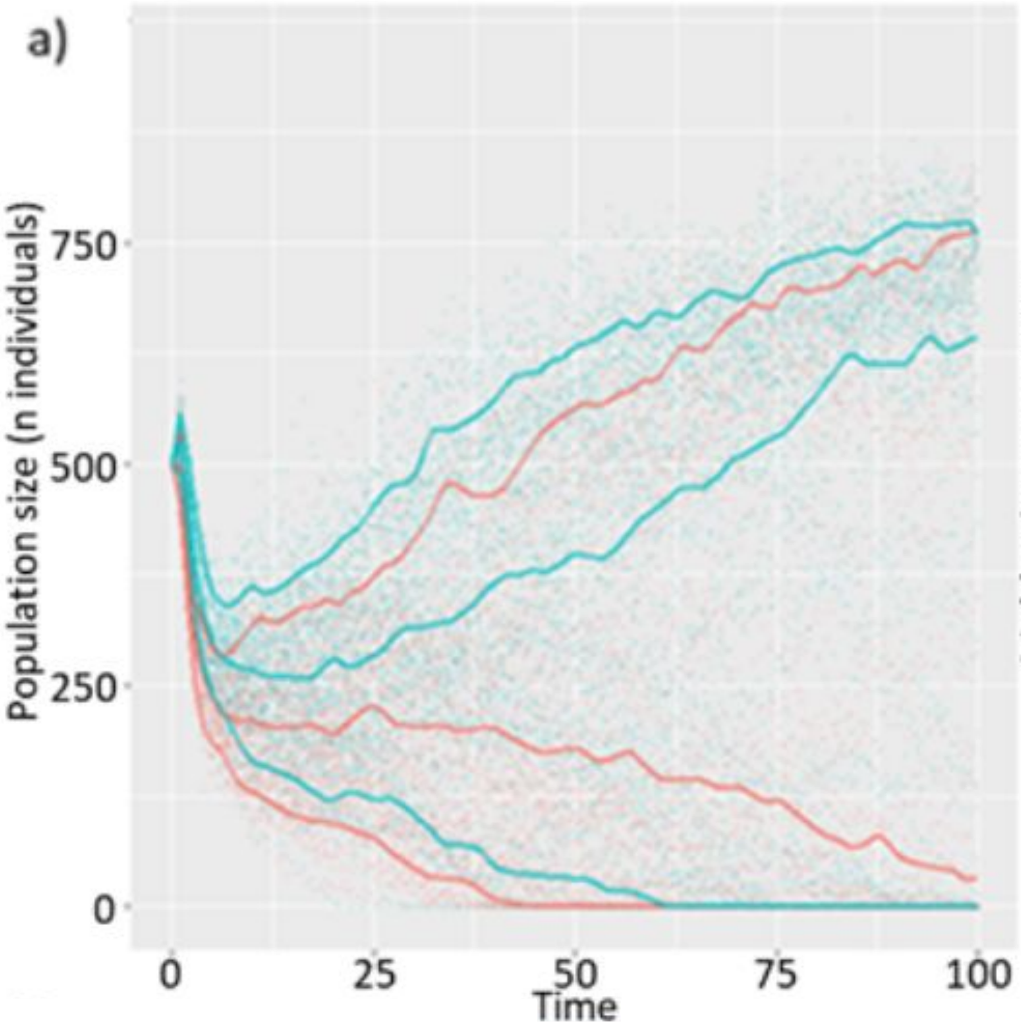

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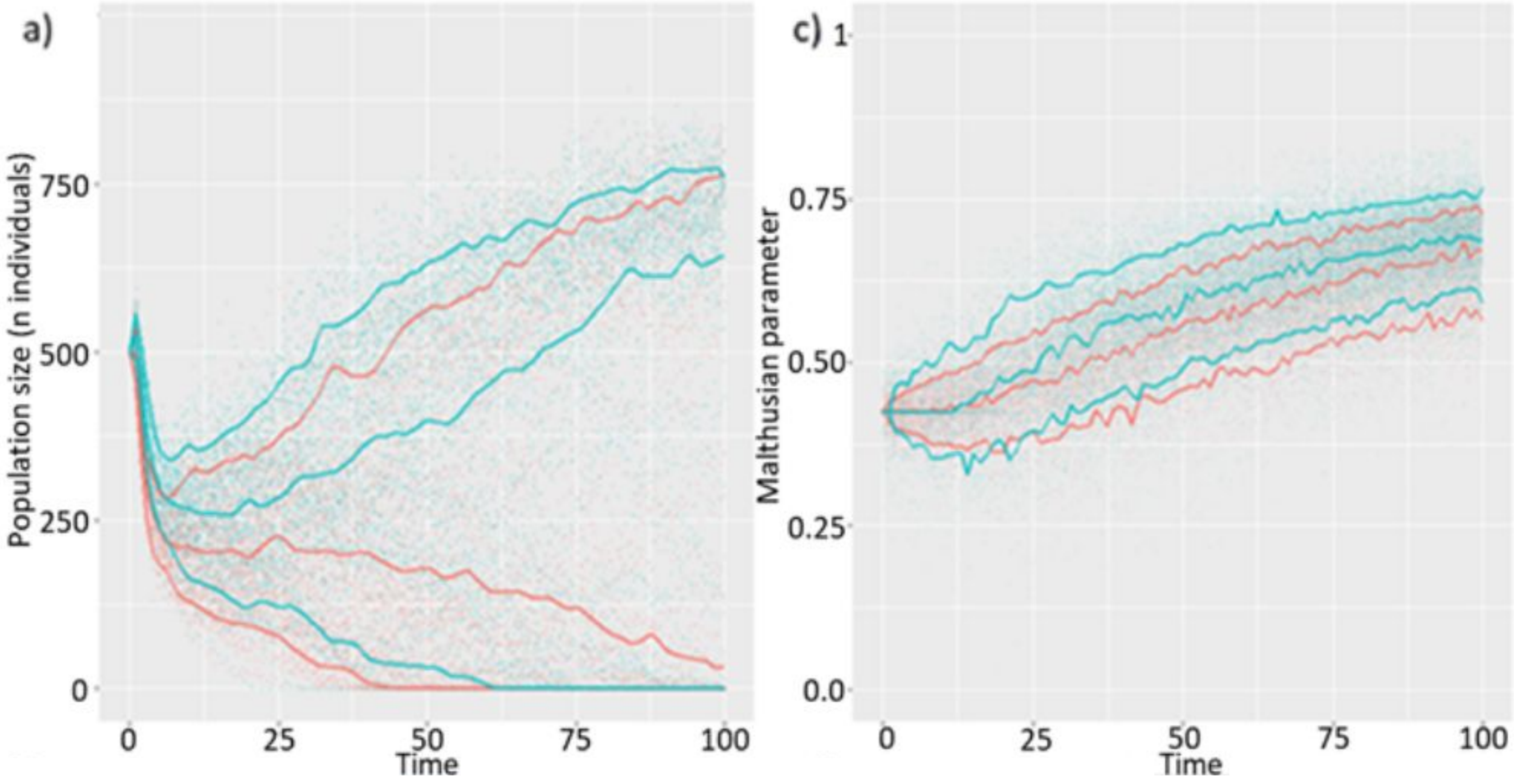

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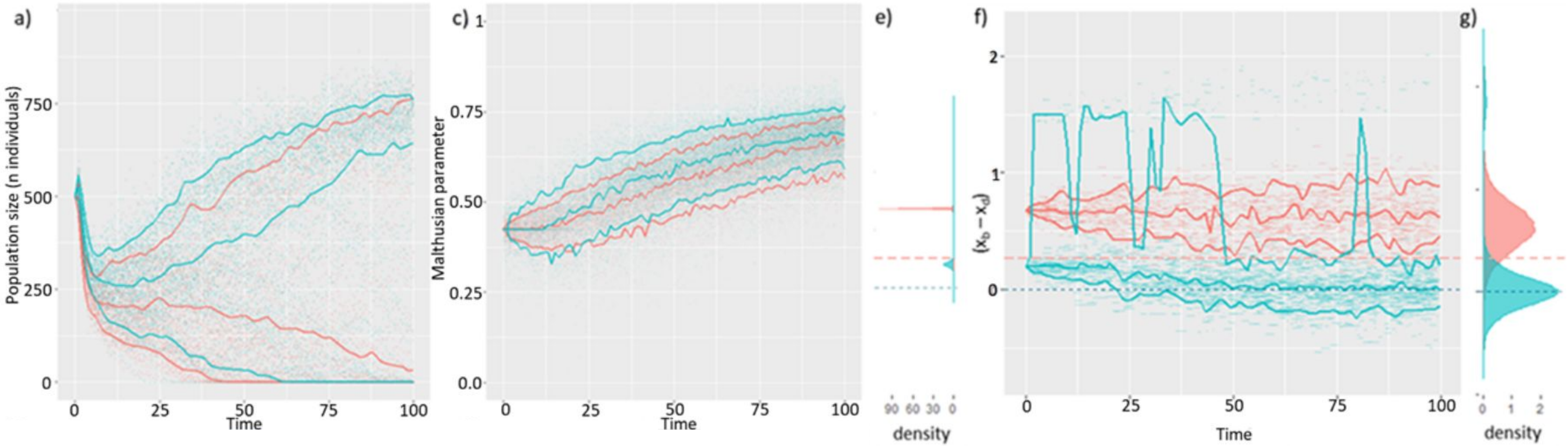


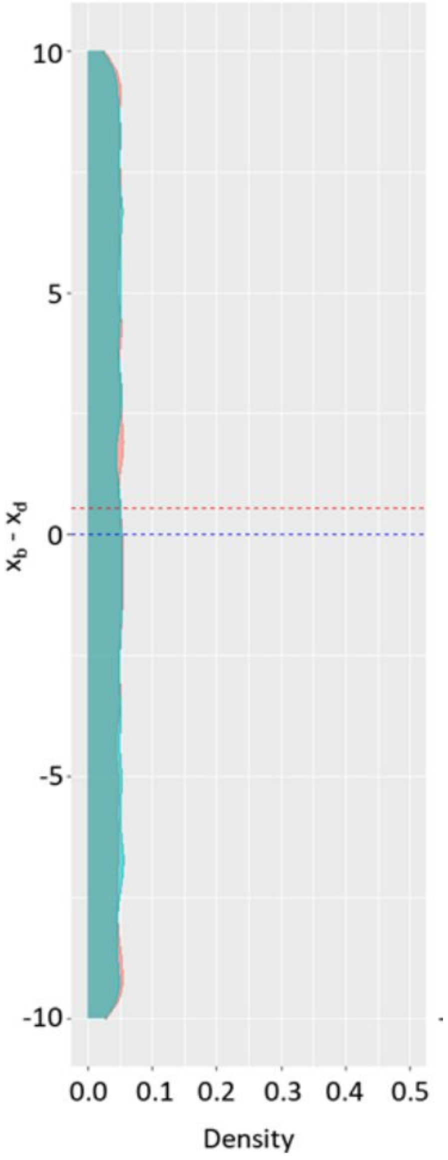
biorxiv Roget et al., 2022

Evolution of the system : competing with and without Lansing effect

		Mutation probability							
		0	0.1	0.5	1	0	0.1	0.5	1
		Lansing/non-Lansing collapsed population				Lansing/total population size			
Competition	9.10^{-5}	-	-	-	-	0.57	0.64	0.62	0.59
	9.10^{-4}	1.02	0.62	0.56	0.66	0.49	0.62	0.60	0.55
	9.10^{-3}	1.00	1.05	1.13	1.03	-	0.43	0.44	0.49

biorxiv Roget et al., 2022

Evolution of the system : competing with and without Lansing effect



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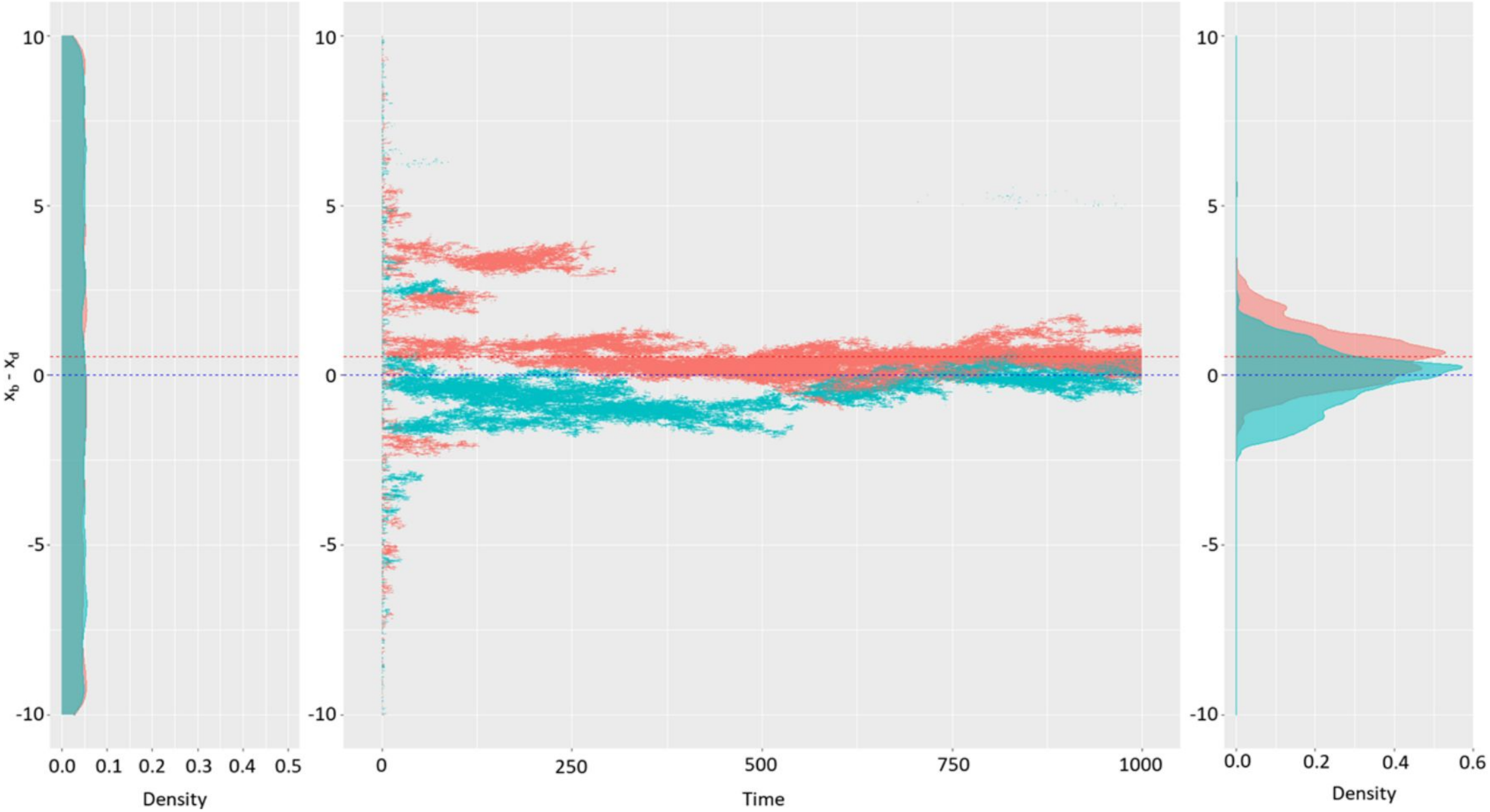
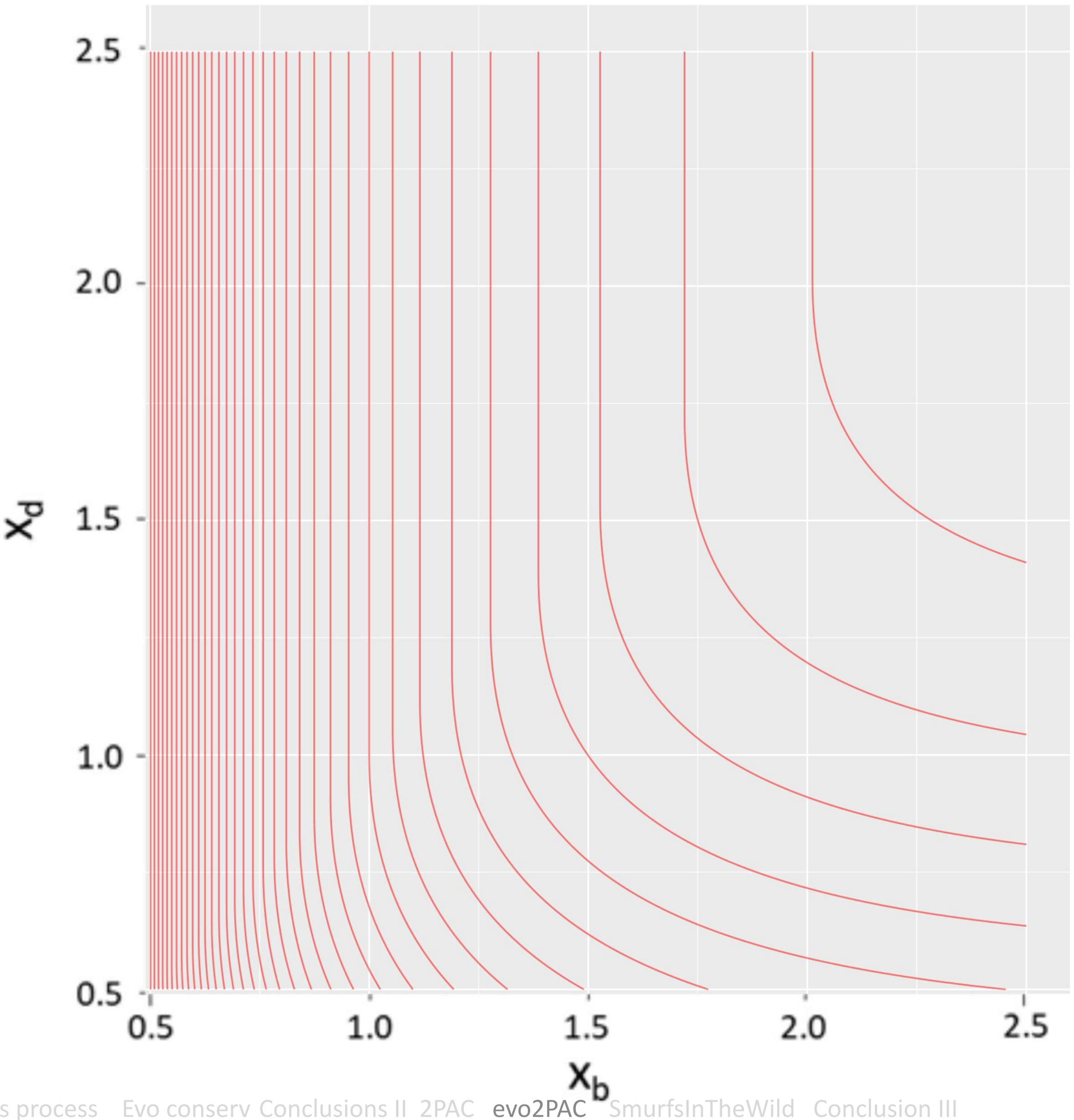


biorxiv Roget et al., 2022

Fitness landscape of non-Lansing populations



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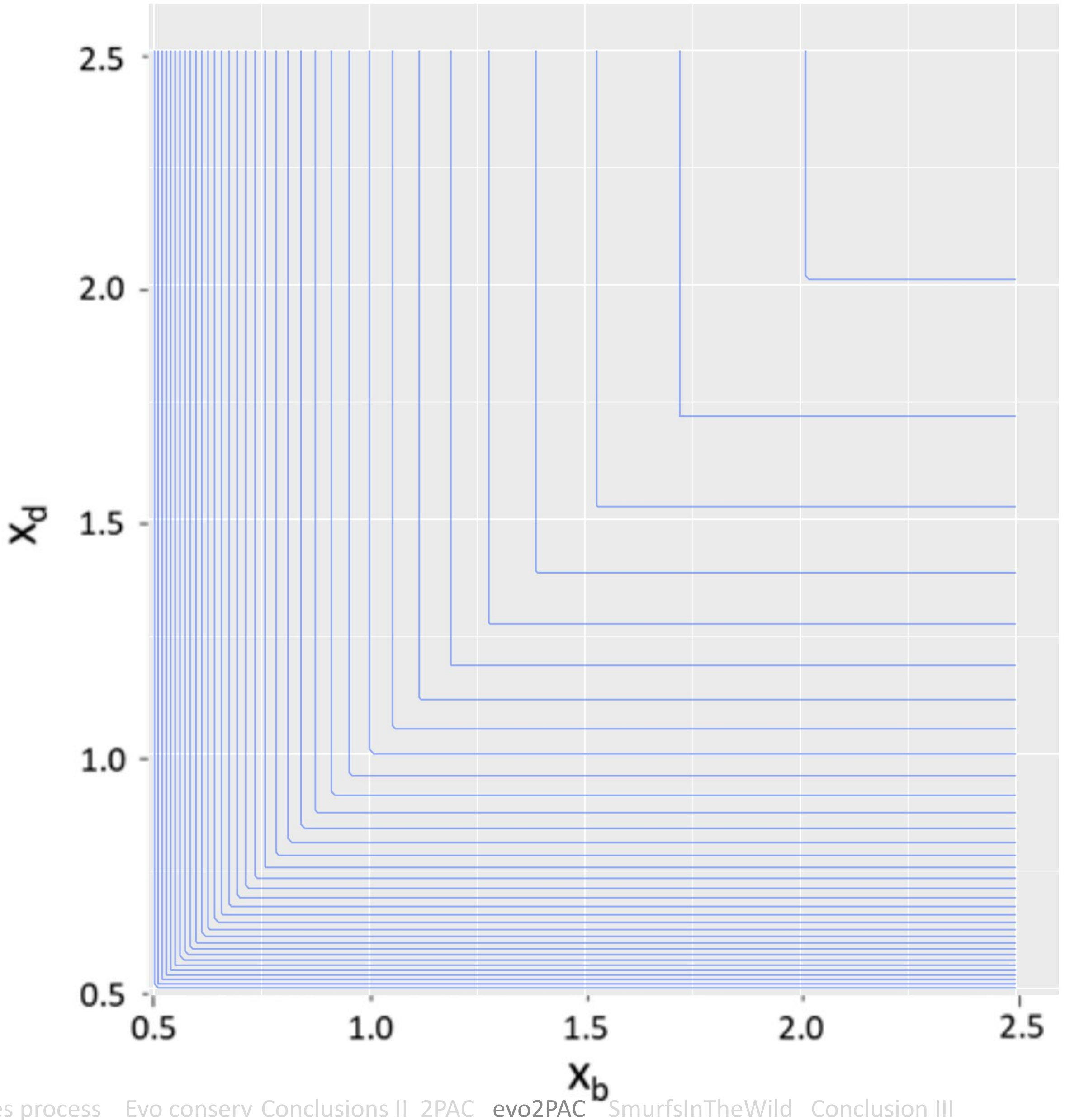
Fitness landscape of Lansing populations



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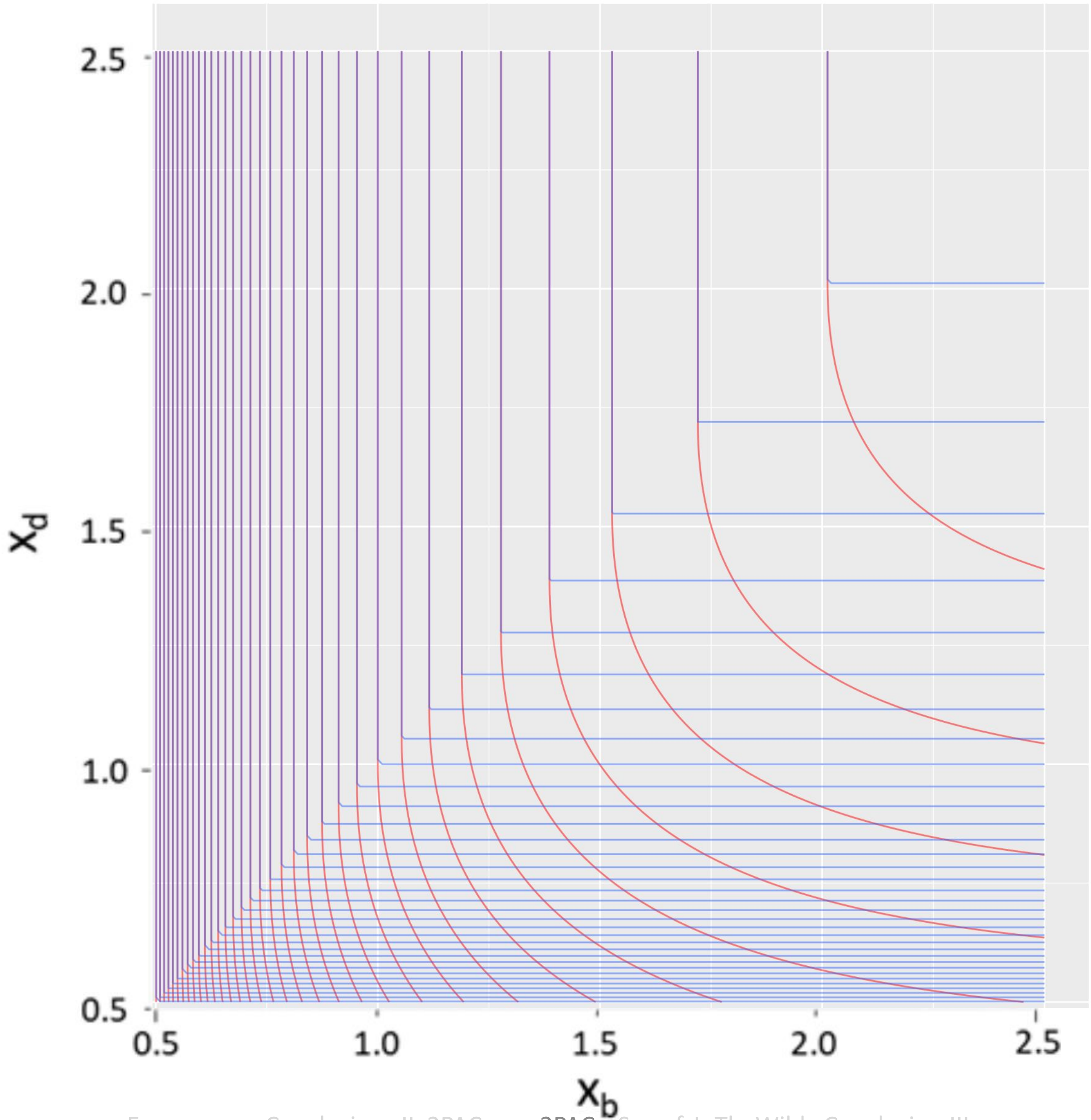
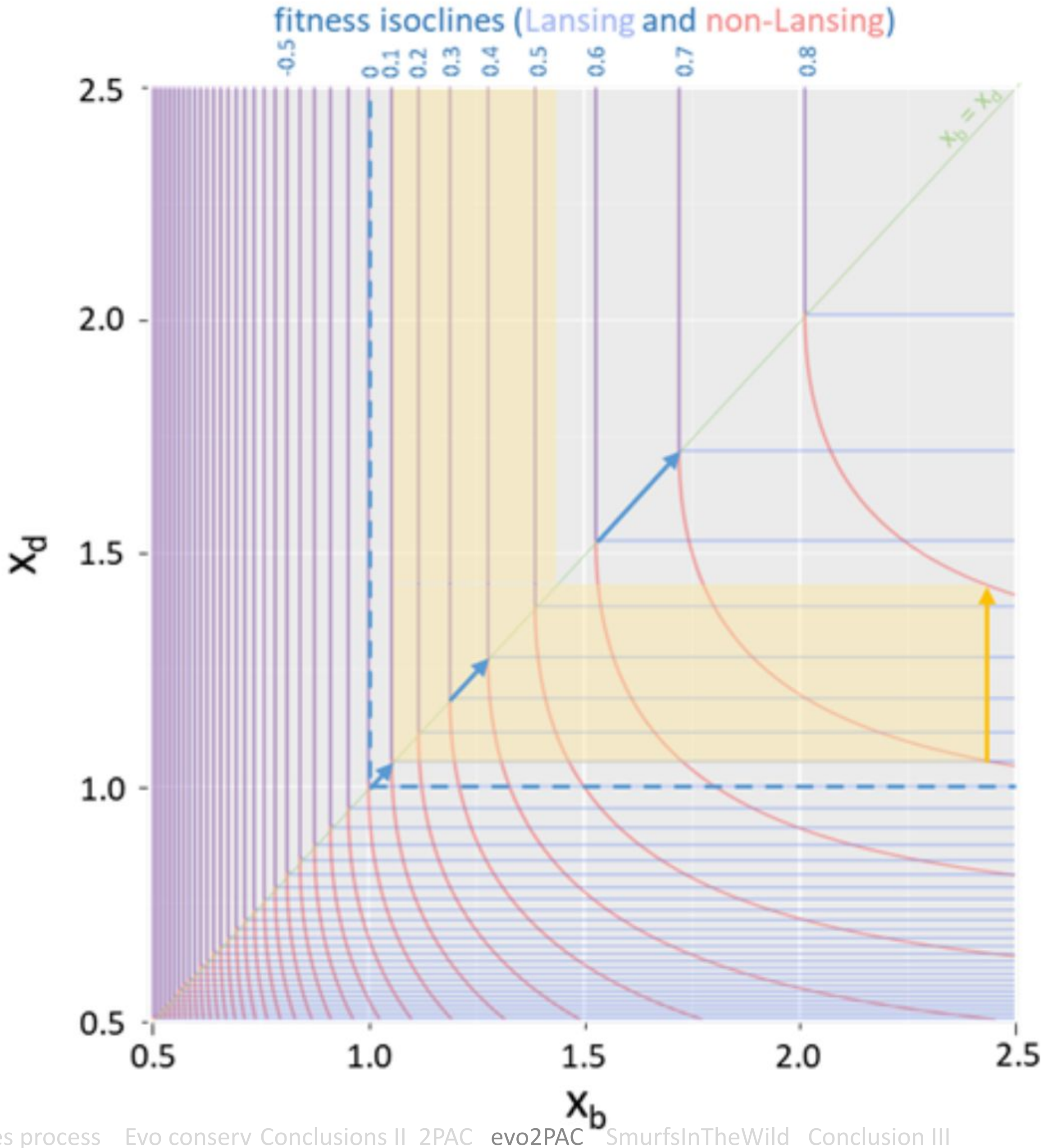
Comparing fitness landscapes



biorxiv Roget et al., 2022

How to explain this relative success? Ageing increases fitness gradient!



biorxiv Roget et al., 2022

Concluding remarks on the evolution of ageing

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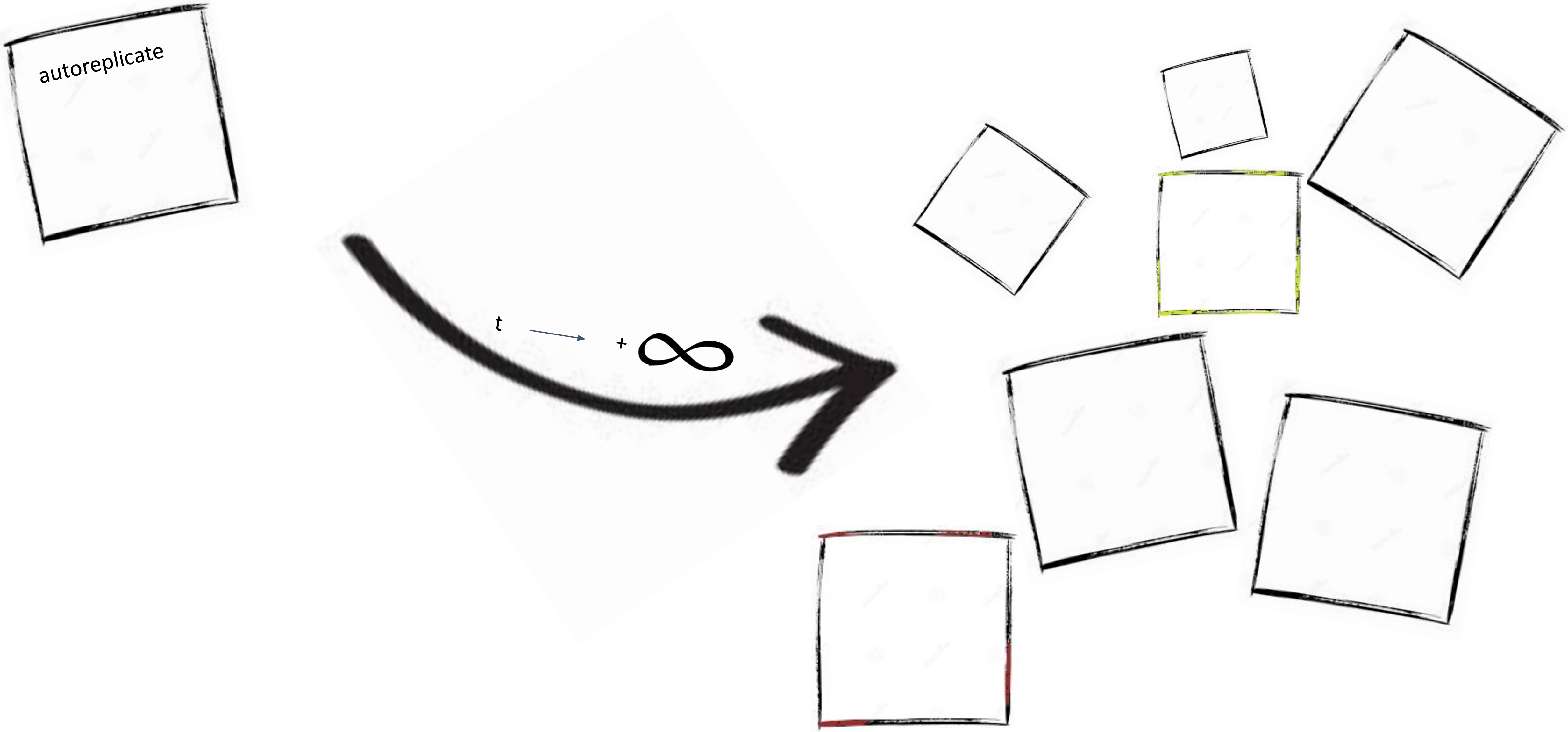
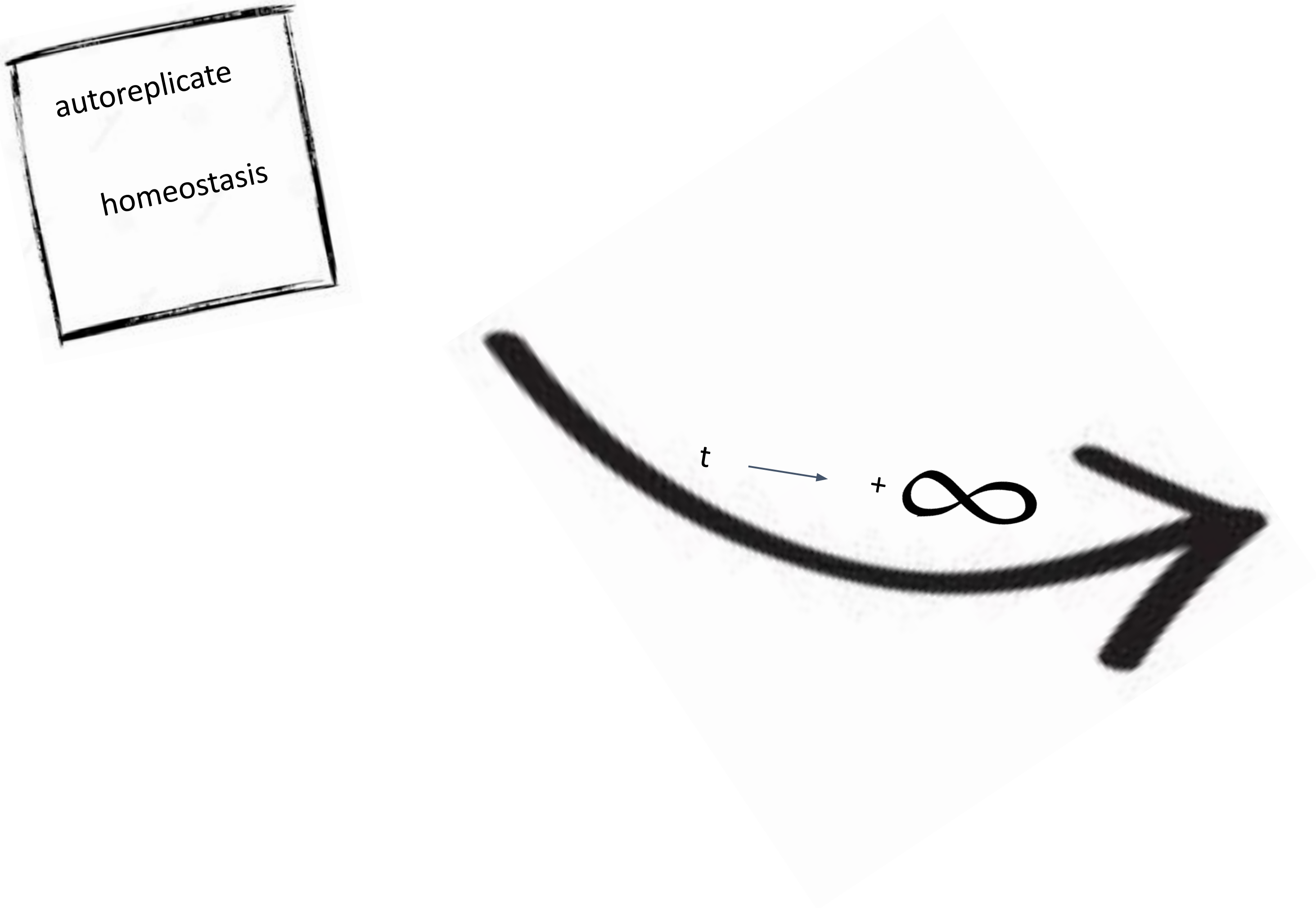
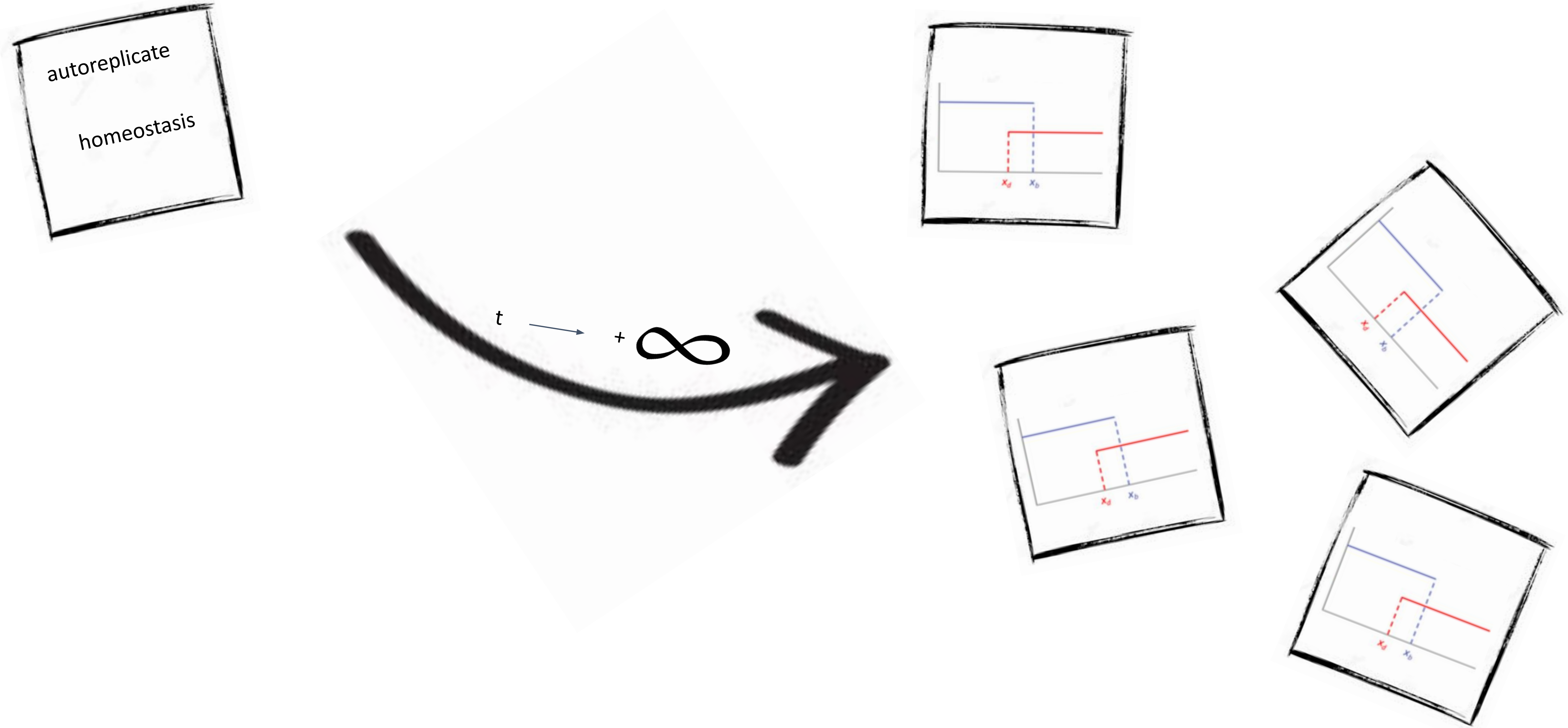


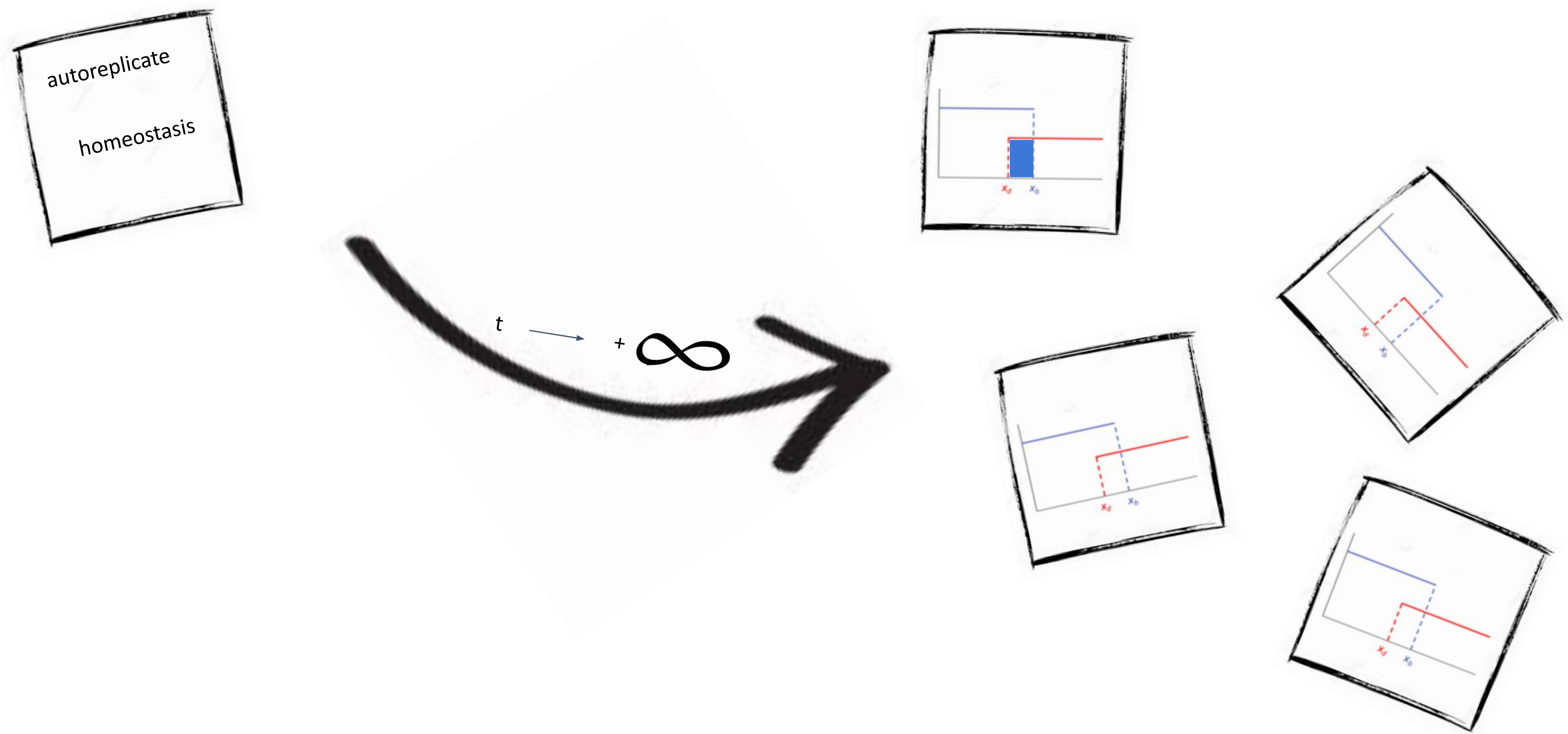
Concluding remarks on the evolution of ageing



Concluding remarks on the evolution of ageing



Concluding remarks on the evolution of ageing



What's next?

- make evo2PAC, diploid, sexual

- make 2PAC for real populations

- implement population health prediction based on field assessment of Smurf proportion

- what is the impact of ageing on populations dynamics and evolution?

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Funding:

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