A new 2-phases model of aging that fits to different organisms

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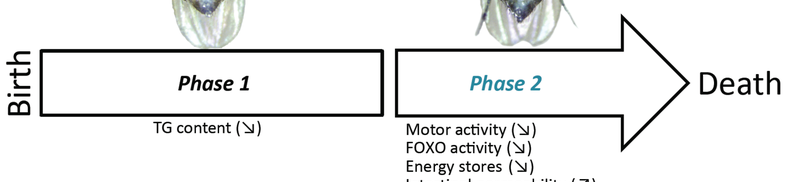
Abstract: *Aging is commonly described as being a continuous process progressively affecting organisms as time passes. This process results in a decrease in individuals' fitness through a wide range of both organismal and molecular phenotypes. We recently described an event characterized by a dramatic increase of intestinal permeability to a blue food dye in aging flies. Importantly, flies showing this so called 'Smurf' phenotype are the only ones, among a population, to show various age-related changes and exhibit a high-risk of impending death – individuals showing that phenotype are committed to die within a few days – whatever their chronological age. Thus, these observations suggest that instead of being one continuous phenomenon, aging may be a discontinuous process well described by at least two distinguishable phases. Here, we addressed this hypothesis by implementing a new 2-Phases of Aging mathematiCal model (2PAC model) to simulate longevity curves based on the simple hypothesis of two consecutive phases of lifetime presenting different properties. We first present a unique equation for each phase and discuss the biological significance of the 3 associated parameters. Then we evaluate the influence of each parameter on the shape of survival curves. Overall, this new mathematical model, based on simple biological observations, is able to reproduce many experimental longevity curves, supporting the existence of 2-phases of aging exhibiting specific properties and separated by a dramatic transition that remains to be characterized. Moreover, it indicates that Smurf survival can be approximated by one single constant parameter for a broad range of genotypes that we have tested under our environmental conditions. Finally, we present here for the first time results showing that the age-dependent intestinal failure called 'Smurf' phenotype is evolutionarily conserved amongst different clades including vertebrates.*

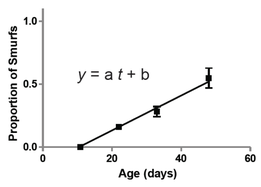
AGING IS CHARACTERIZED BY A DRAMATIC SWITCH

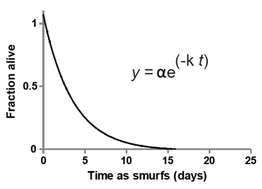
>MOLECULARLY



A simple *in vivo* assay allows to identify individuals that underwent a dramatic transition during aging. Those individuals are characterized by increased intestinal permeability to a food dye as well as numerous molecular changes classically described as 'hallmarks of aging'

>MATHEMATICALLY



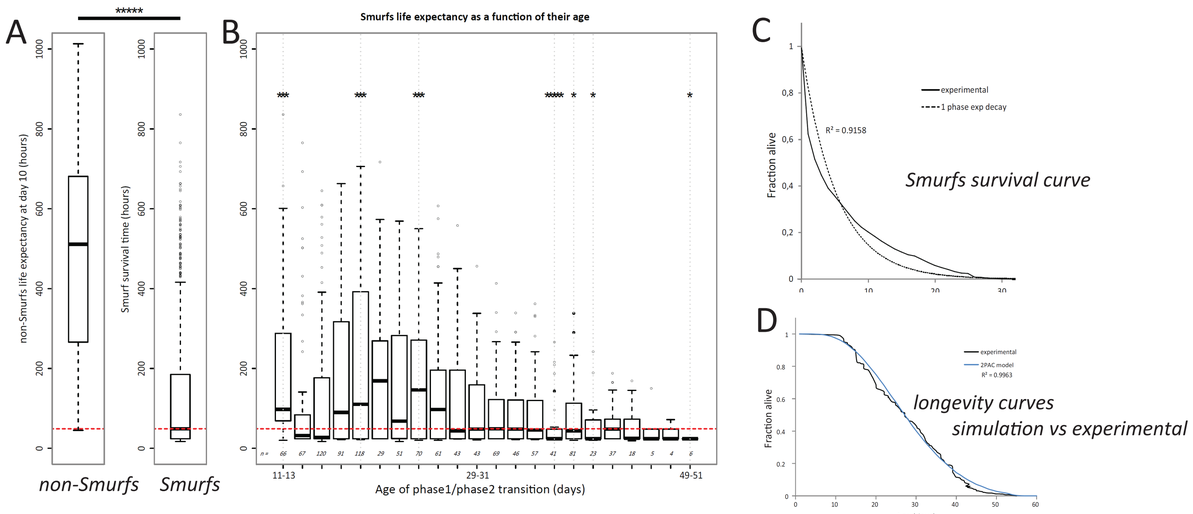


Left panel: the proportion of Smurfs in a given population increases linearly as a function of chronological age. Its age-dependent evolution can thus be simulated using a linear function rule by the two parameters ***a*** and ***b***.

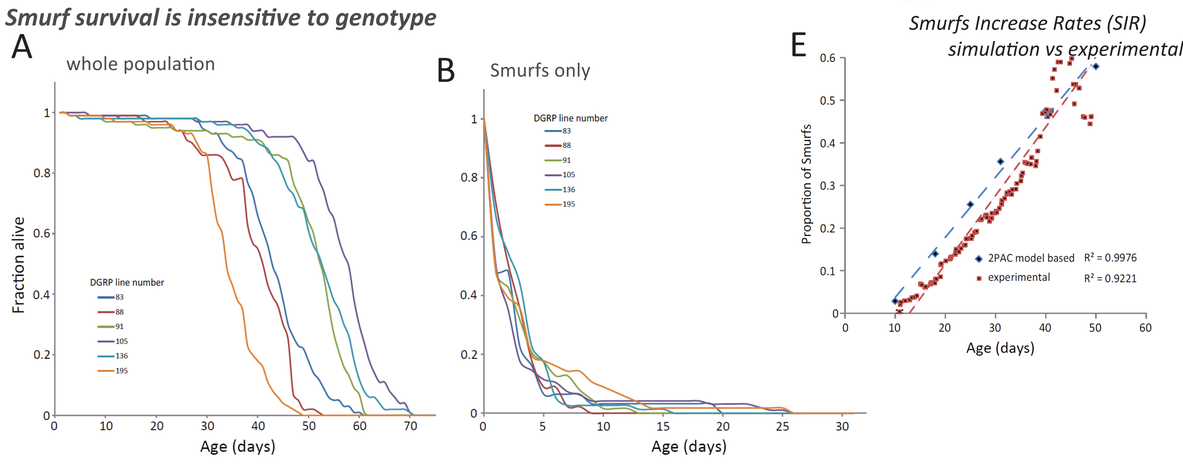
Right panel: once individuals have turned Smurf, their population dies following a one phase phase exponential decay characterized by the only parameter ***k***.

PHASE 2 DURATION IS AGE AND GENOTYPE INDEPENDENT

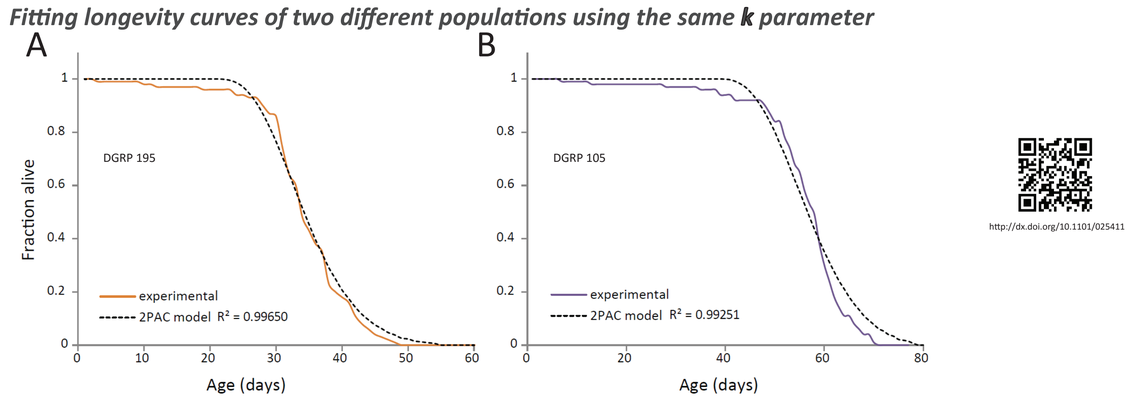
Smurf survival is MOSTLY insensitive to chronological age



Smurf survival is insensitive to genotype



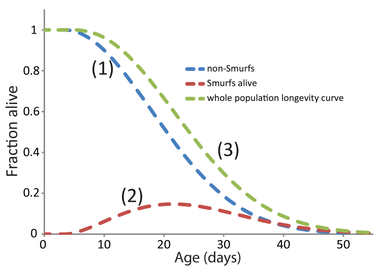
Fitting longevity curves of two different populations using the same k parameter



http://dx.doi.org/10.1101/025411

AGING CAN BE DESCRIBED BY 3 SIMPLE PARAMETERS

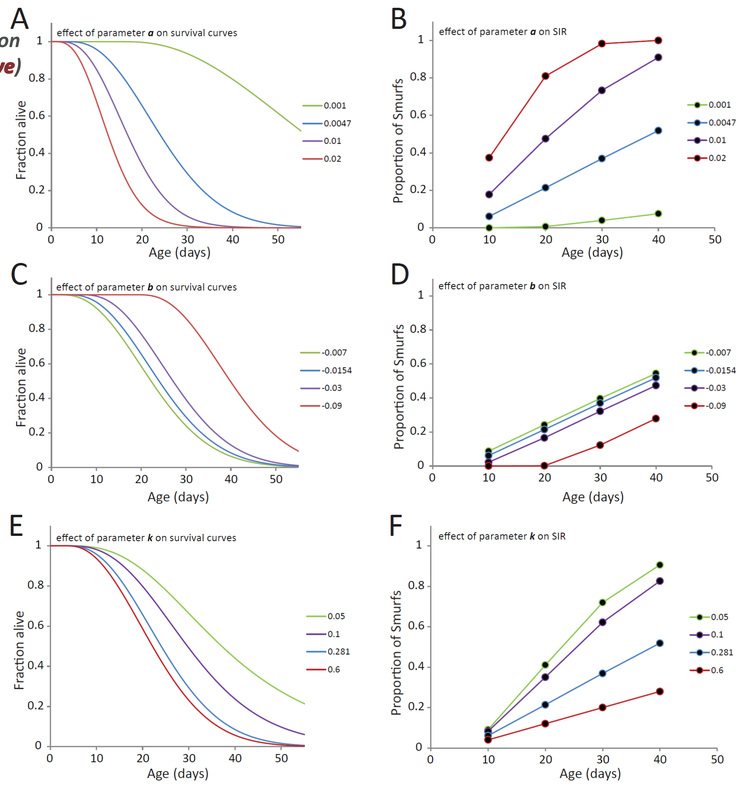
For every chronological age, any population can be defined as a mix of smurfs(red curve) and non-Smurfs (blue curve).



$$(1)\quad N = P_0\, e^{\left(-a\frac{t^2}{2}\right)}$$

$$(2)\quad \begin{cases} \frac{dS}{dt} = -kS + a\,P_0\,t\,e^{\left(-a\frac{t^2}{2}\right)} \\ = 0 \text{ for } t < -\frac{B}{a} \end{cases}$$

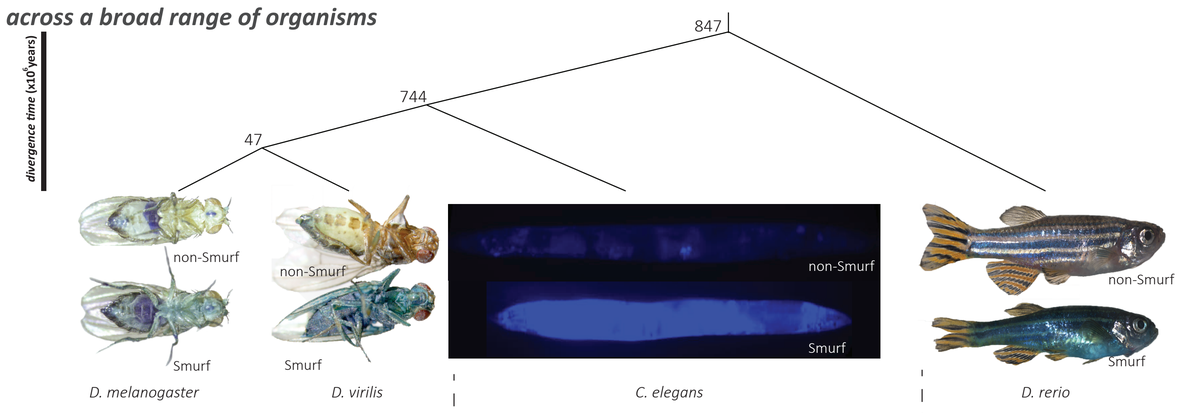
$$(3)\quad N = N + S$$



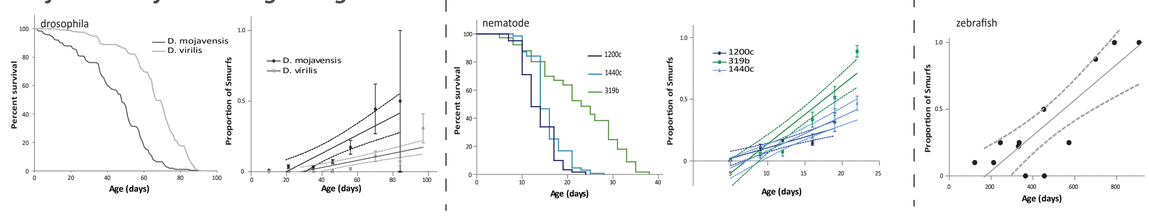
Effects of the different 2PAC model parameters on lifespan. (Only one parameter is modifiedat once)
A, B. As ***a*** increases, lifespan decreases and Smurf Increase Rate (SIR) increases.
C, D. When ***b*** increases, lifespan increases without affecting the SIR but the first Smurfs appear later.
E, F. An increase of ***k*** decreases both lifespan and the SIR. Thus, by measuring lifespan and SIR of flies in two distinct conditions indicates which parameter is affected by the treatment.
a is the rate at which individuals undergo the phase 1/phase 2 transition in a given population. It is the ***daily failure rate***.
b defines the time t at which individuals start to undergo that transition in the given population (t > - b / a).
It thus represents the ***tolerance*** of the population to the changes leading to phase 1 / phase 2 transition.
k is the constant that drives the death of Smurfs appeared at any given time in the population. It is the ***death rate constant.***

SMURF TRANSITION IS EVOLUTIONARILY CONSERVED...

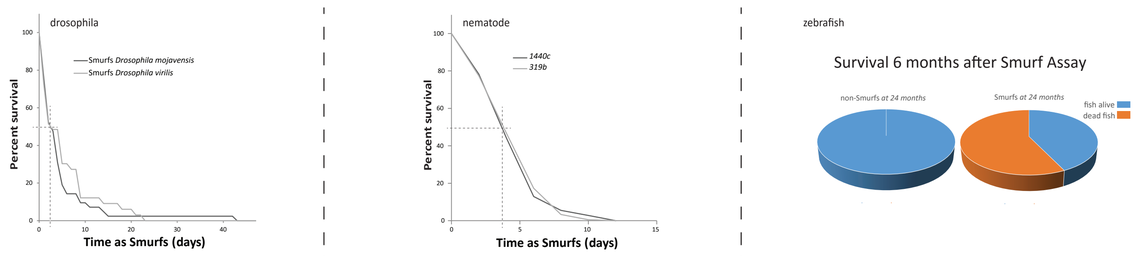
across a broad range of organisms



as a function of chronological age...



and is a predictor of impending death NATURALLY occuring during NORMAL aging



CONCLUSIONS*: It is possible to explain longevity curves by dividing aging in two distinct phases separated by a dramatic transition. Each phase is characterized by specific molecular and mathematical features. This new model is based on experimental data showing that, in our controlled laboratory conditions, individuals in phase 2 of aging die at a pace that is mostly not influenced by the chronological age nor by the genotype of individuals. In addition, the evolutionary conservation of these two phases across a broad range of species allows us to think it is a phenomenon of major importance during aging. Thus, we ask the following questions:*

- What does control the phase 1/ phase 2 transition? Is it programmed?
- Can we prevent/revert that transition?
- What is the role of that transition?