Stretching and squeezing time

Walter Fontana

Systems Biology

Harvard Medical School

walter@hms.harvard.edu

Nick Stroustrup

Winston Anthony

Javier Apfeld

Adam Gomez

Vivek Gowda

Isaac F. López-Moyado

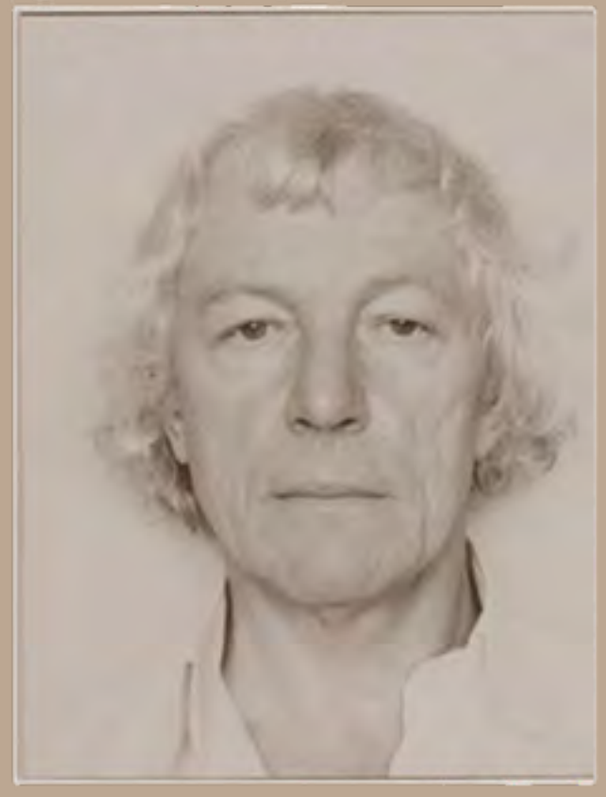
Zachary M. Nash

Bryne Ulmschneider

Stroustrup, N., Anthony, W.E., Nash, Z.M., Gowda, V., Gomez, A., López-Moyado, I.F., Apfeld. J. and Fontana, W. *Nature*, 320: 103-107 (2016)

"...progressive disappearance"





Roman Opałka (1931 – 2011)

Measuring (the process of) organismic aging

Aging is often viewed as a process of “physiological decline”…

What might that mean?

Measuring “capabilities”, i.e. properties such as

- wound healing
- acuity of senses
- physical strength
- endurance
- cellular regeneration
- …

reporting on the structure and functioning of basic physiological systems.

Snag: what we wish to measure is undefined

For a specific aspect of a physiological system or a specific form of damage
to qualify as an observable of the aging *process*,
it must be shown to be related to the aging process,
either as a causal factor or as a consequence faithfully tracking the process.

The problem is that there is no characterization of the aging process to begin with.

The problem is not solved by shifting to the molecular level.
It is only compounded.

We've been there before

Take for example the measurement of temperature.

How can we test whether the fluid in our thermometer expands regularly with increasing temperature, without a circular reliance on the temperature readings provided by the thermometer itself?

How did people without thermometers learn that water boiled or ice melted always at the same temperature, so that these phenomena could be used as "fixed points" for calibrating thermometers?

Hasok Chang, *Inventing Temperature—Measurement and Scientific Progress*, OUP, 2004

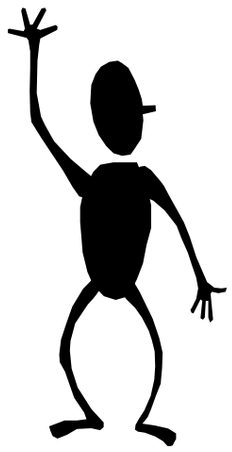
The way out (no pun intended)

Rather than defining a process *explicitly*, define it *implicitly* by reference to its endpoint.

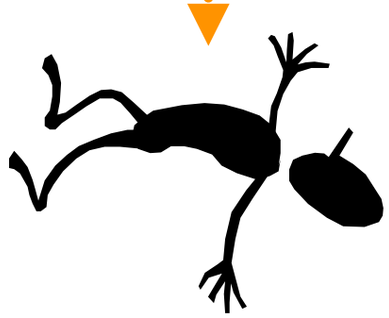
So, let's hang on to what we can agree on:
The endpoint of organismic aging is death

$T = 0$

prepare



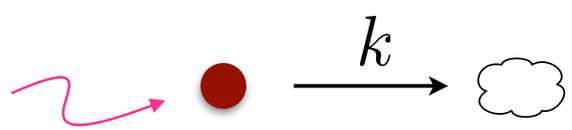
unobserved aging process



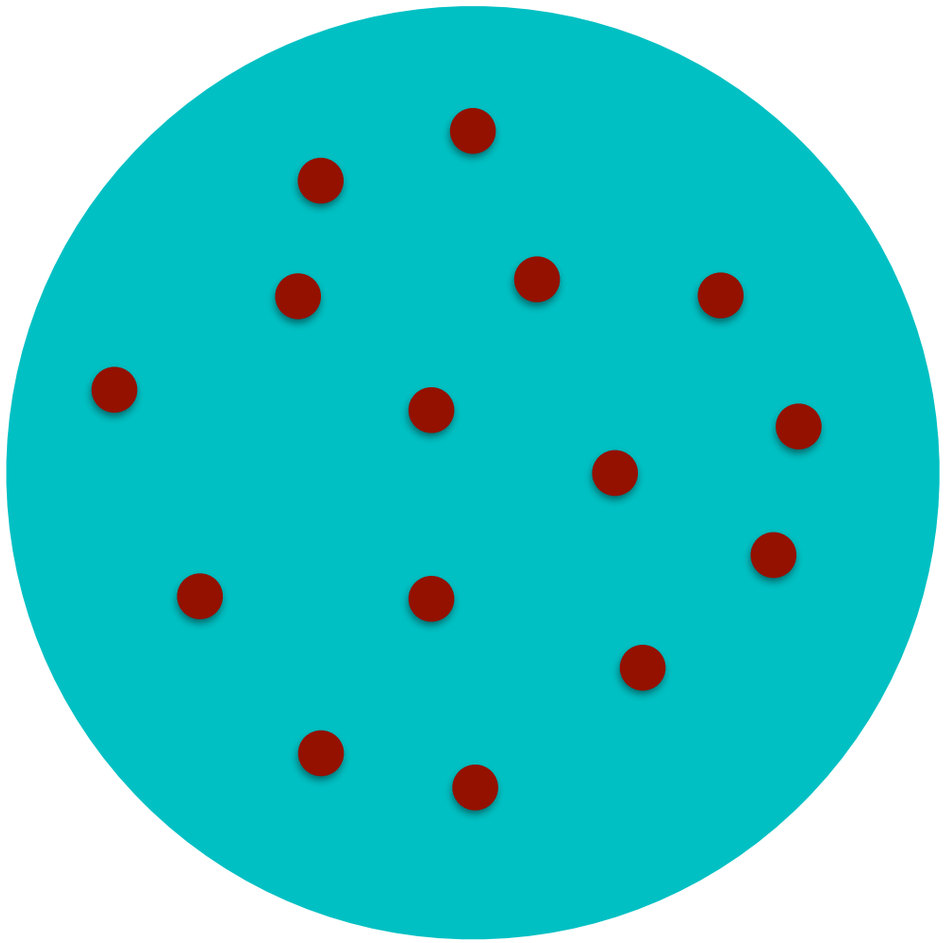
observe endpoint

$T = t$

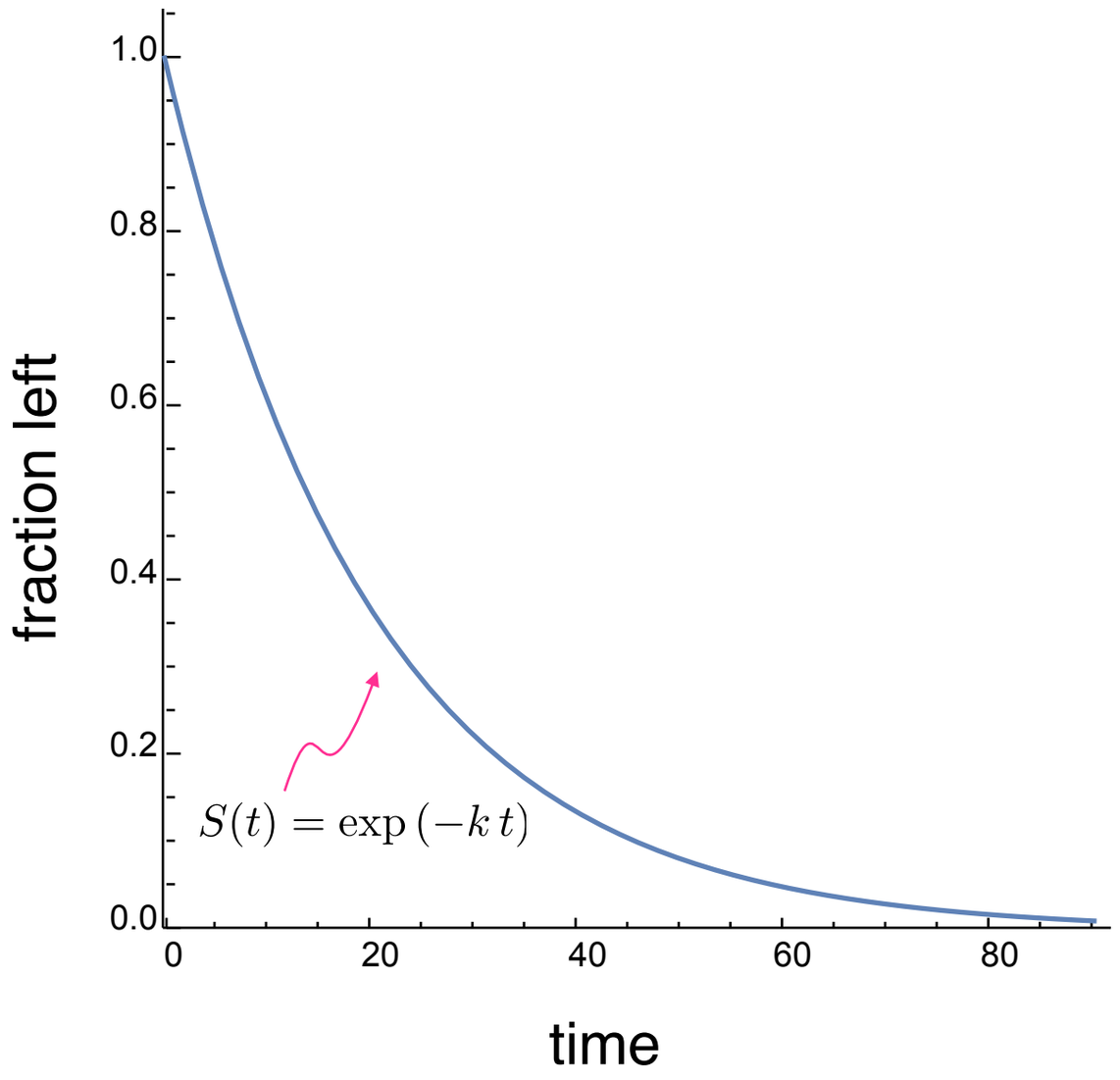
Degradation kinetics

an “elementary” thing 

$$-\frac{d}{dt}S(t) = k\,S(t)$$

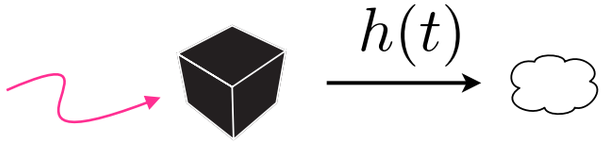


controlled environment



Death kinetics

a “complex” thing
with a process inside

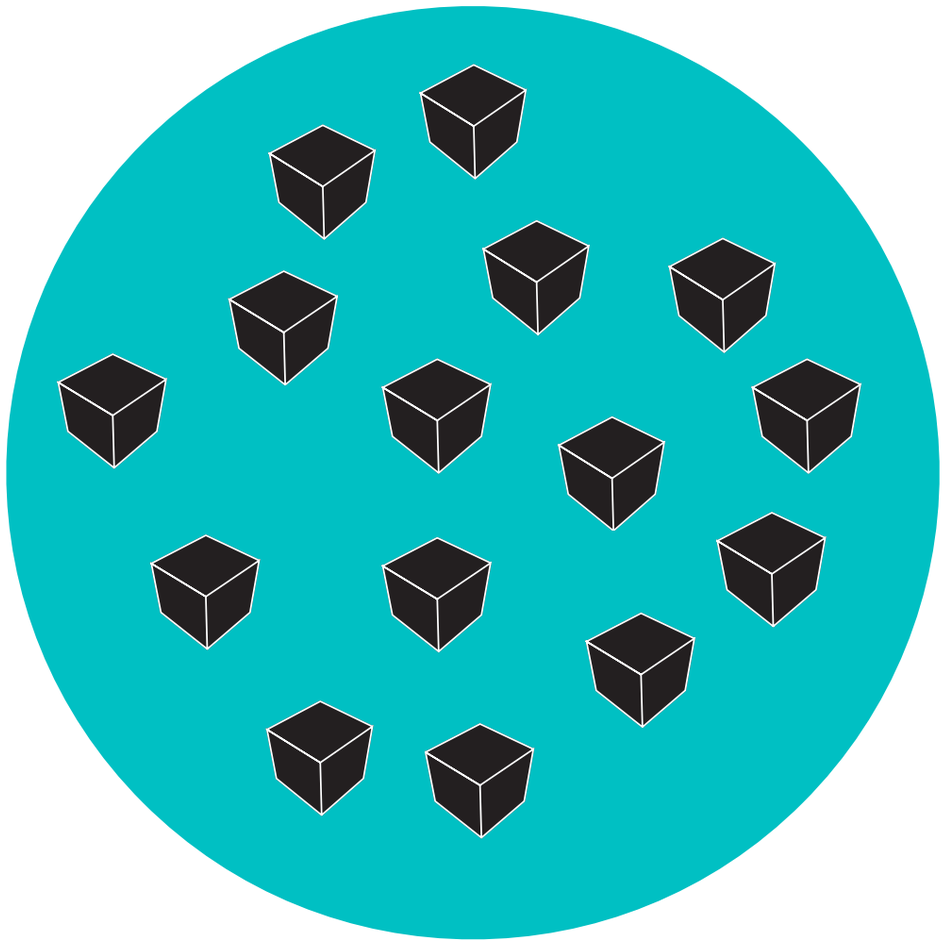


$$-\frac{d}{dt}S(t) = h(t)\,S(t)$$

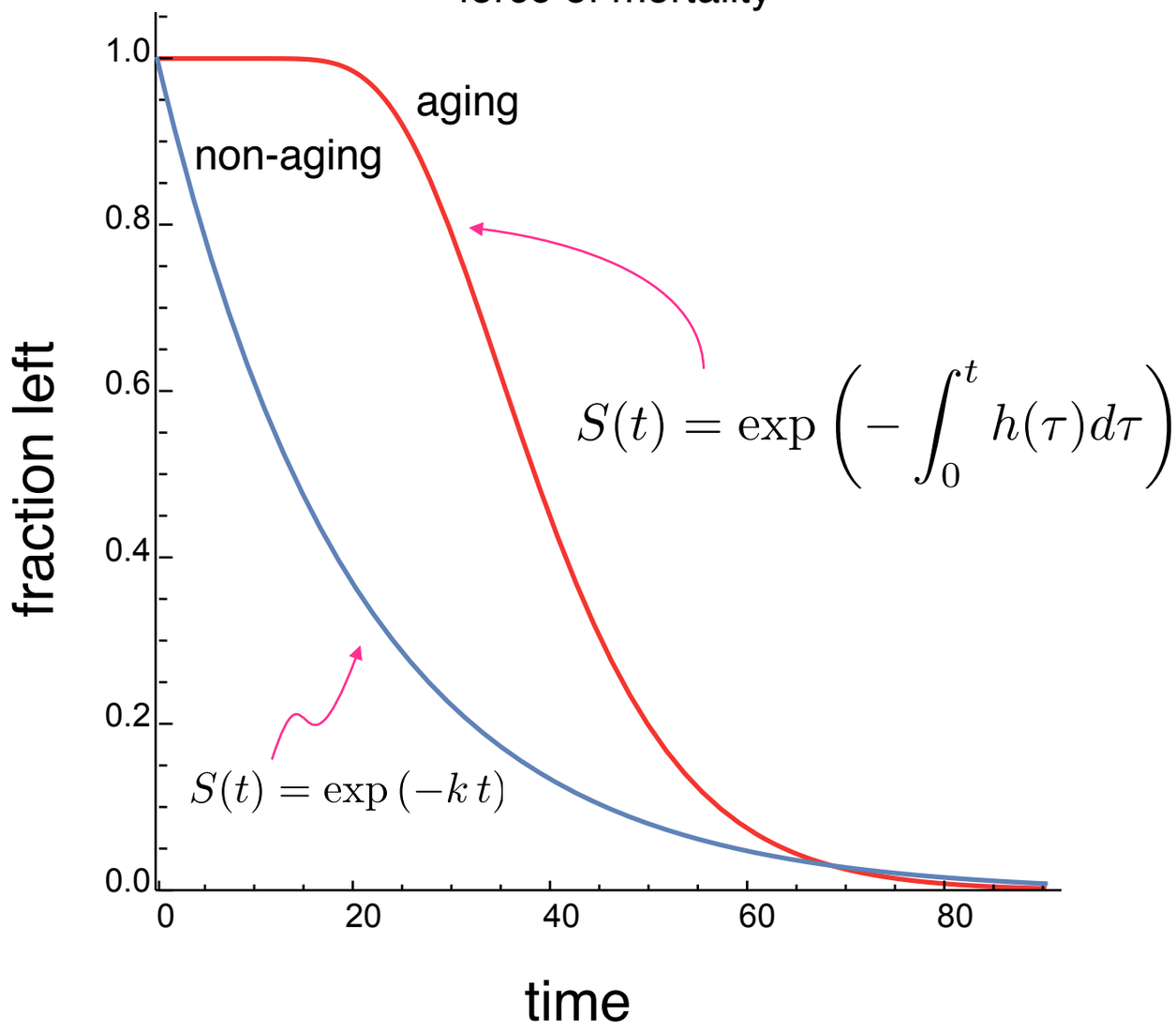
lifespan density

risk
hazard
force of mortality

survival function



controlled environment



Basic mortality statistics

$$-\frac{d}{dt}S(t) = h(t)\,S(t)$$

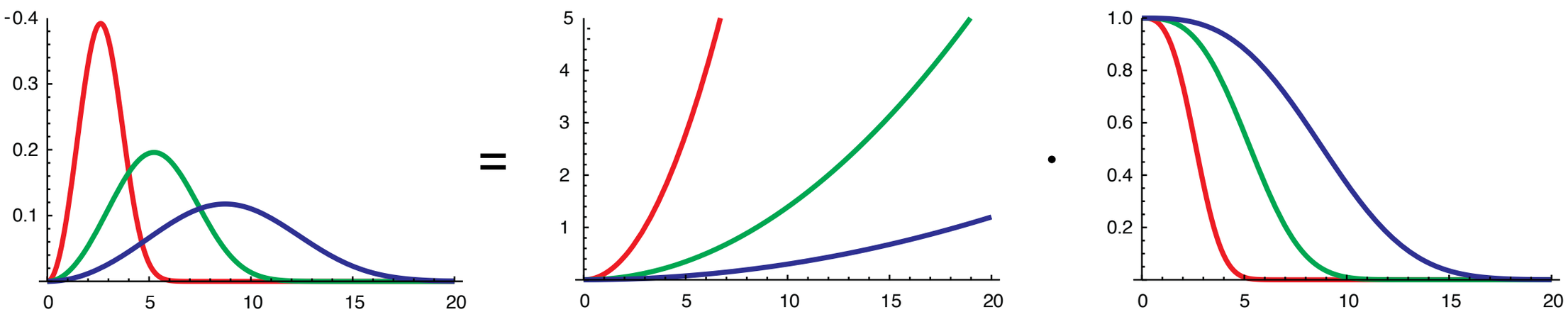
let T, the time of death, be a random variable

$$\text{Prob}(t < T < t + dt) \quad = \quad \text{Prob}(t < T < t + dt \,|\, T > t) \qquad \text{Prob}(T > t)$$

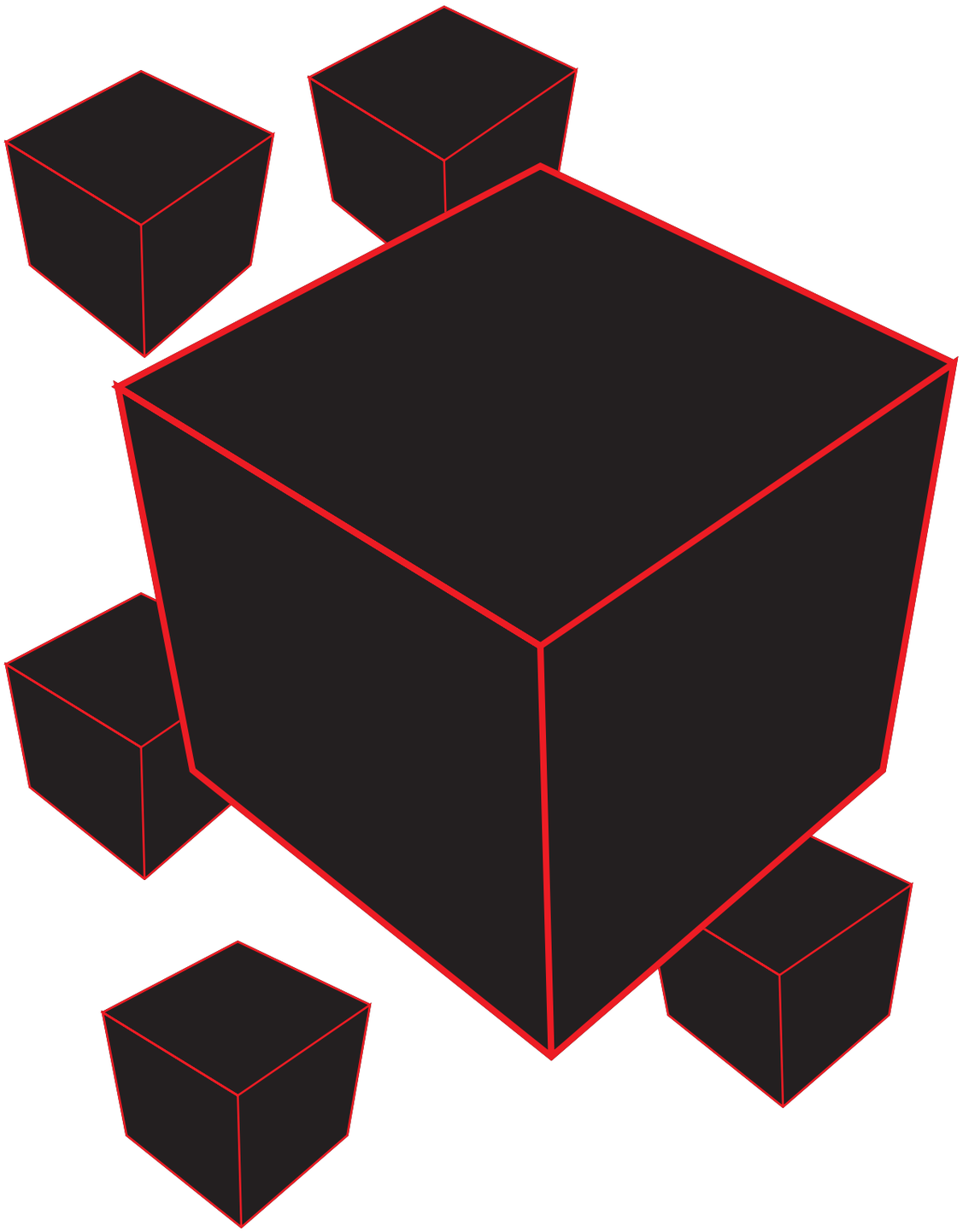
prob density of lifespan

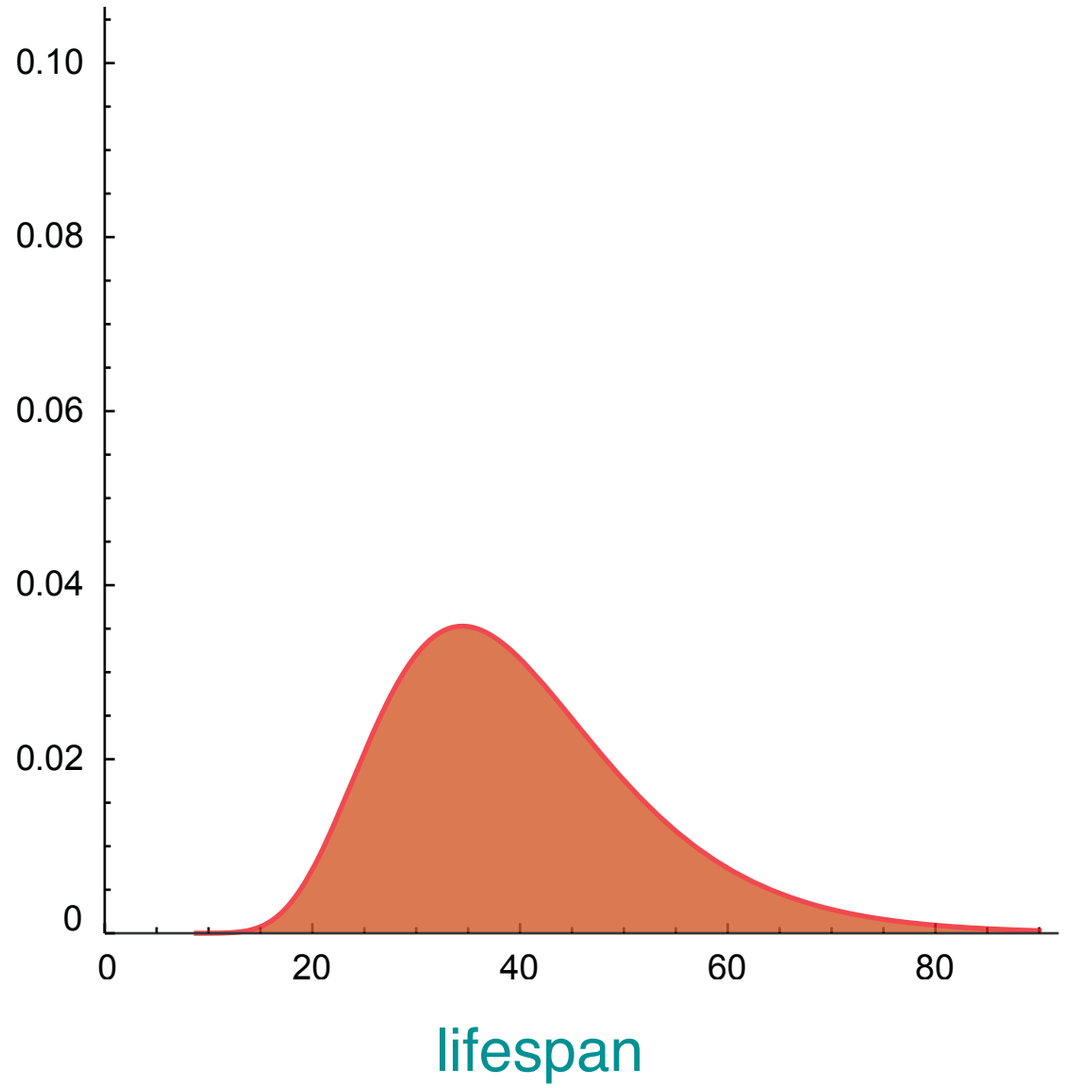
hazard rate

survival function



The key is to measure the whole distribution





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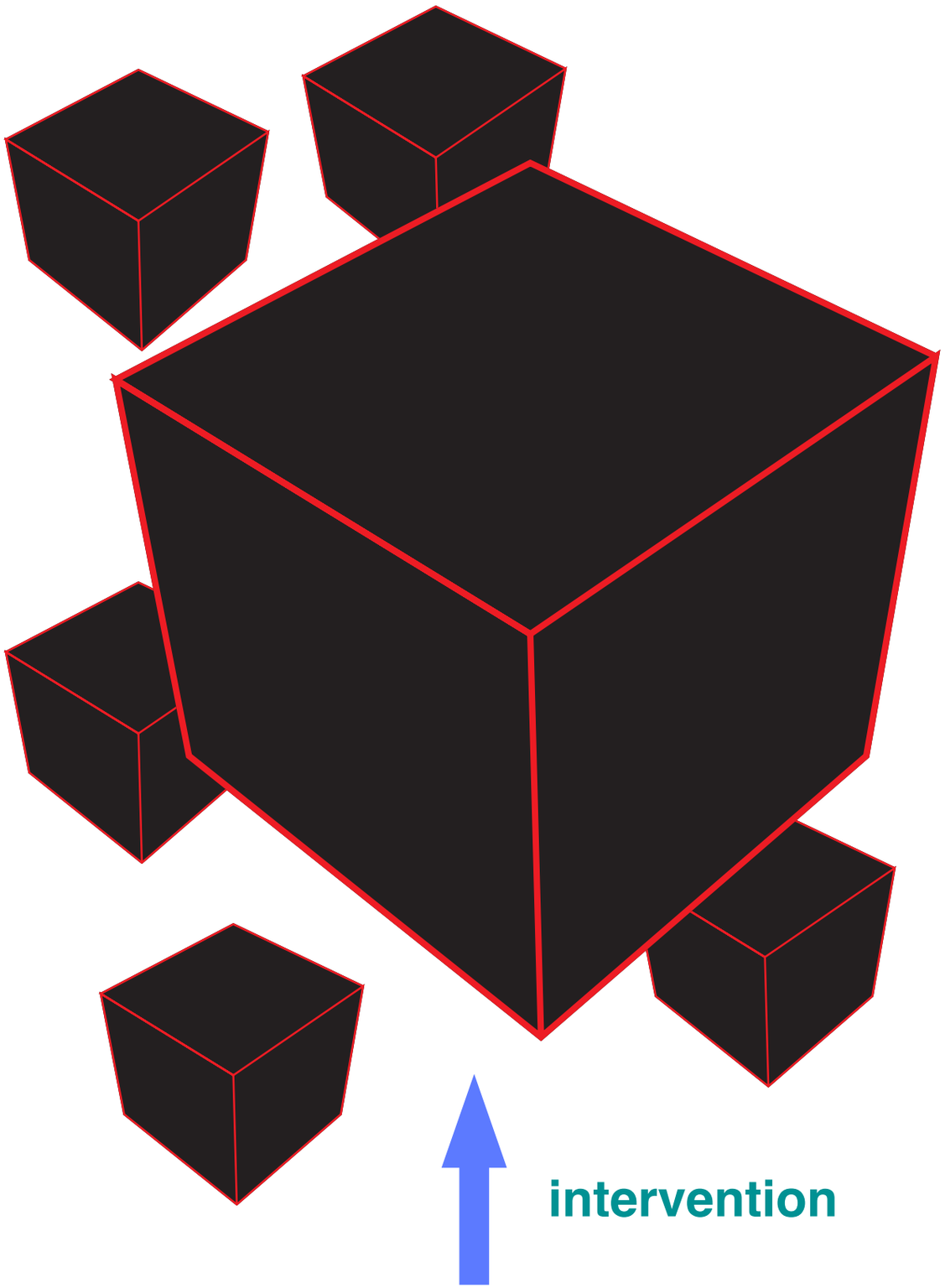
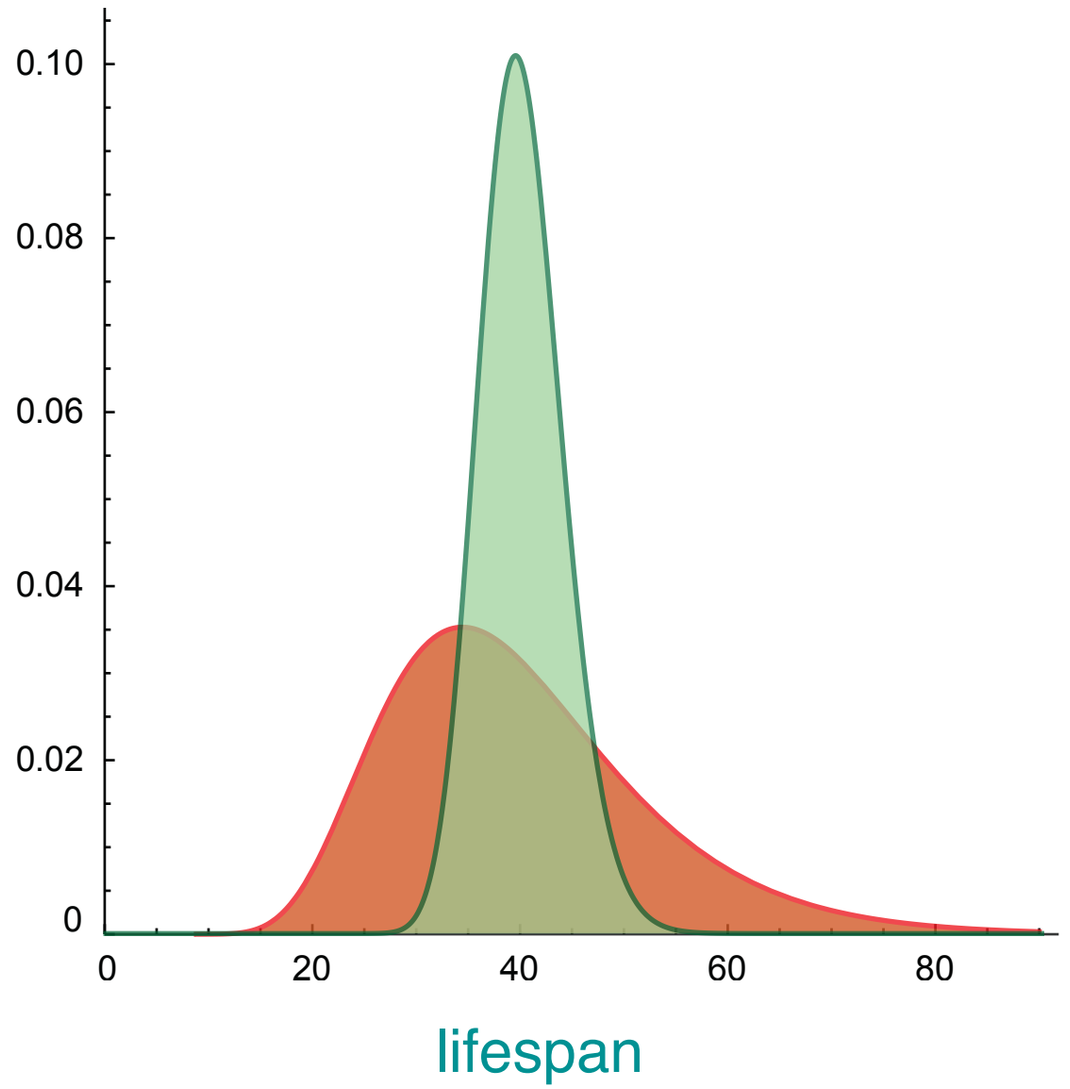
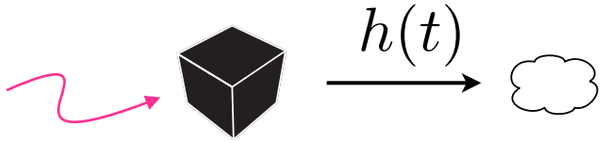
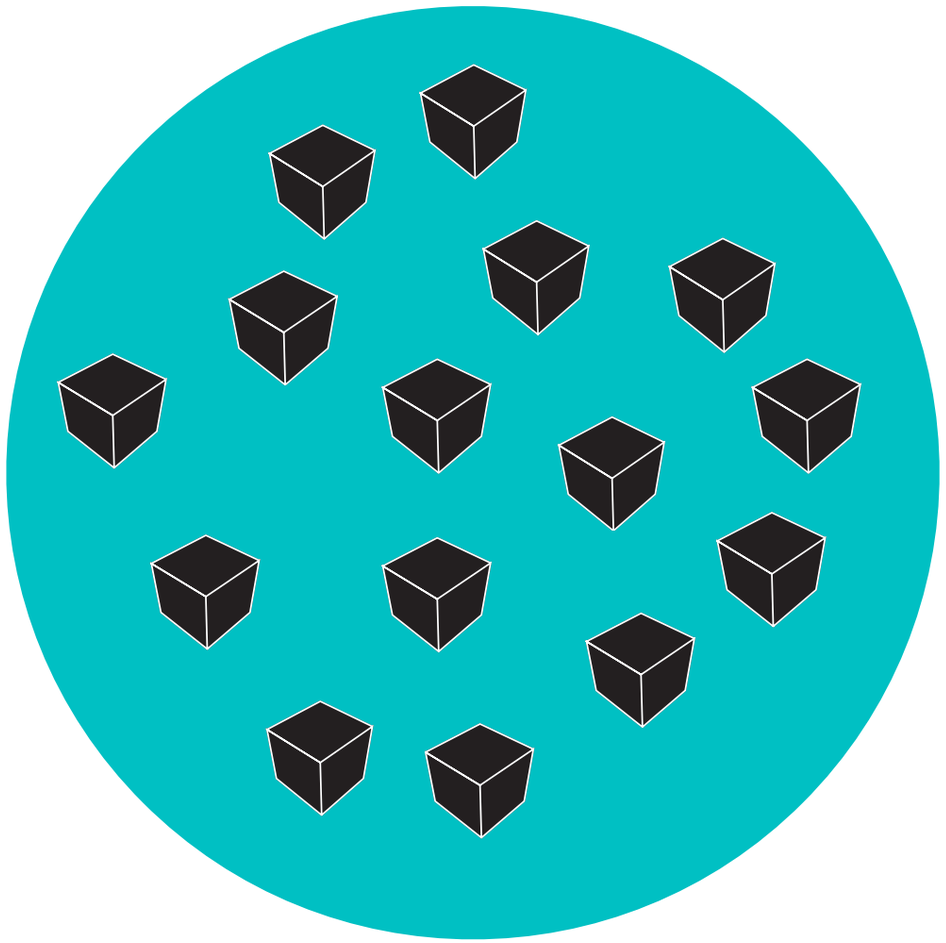




The general experimental frame

a “complex” thing
with a process inside

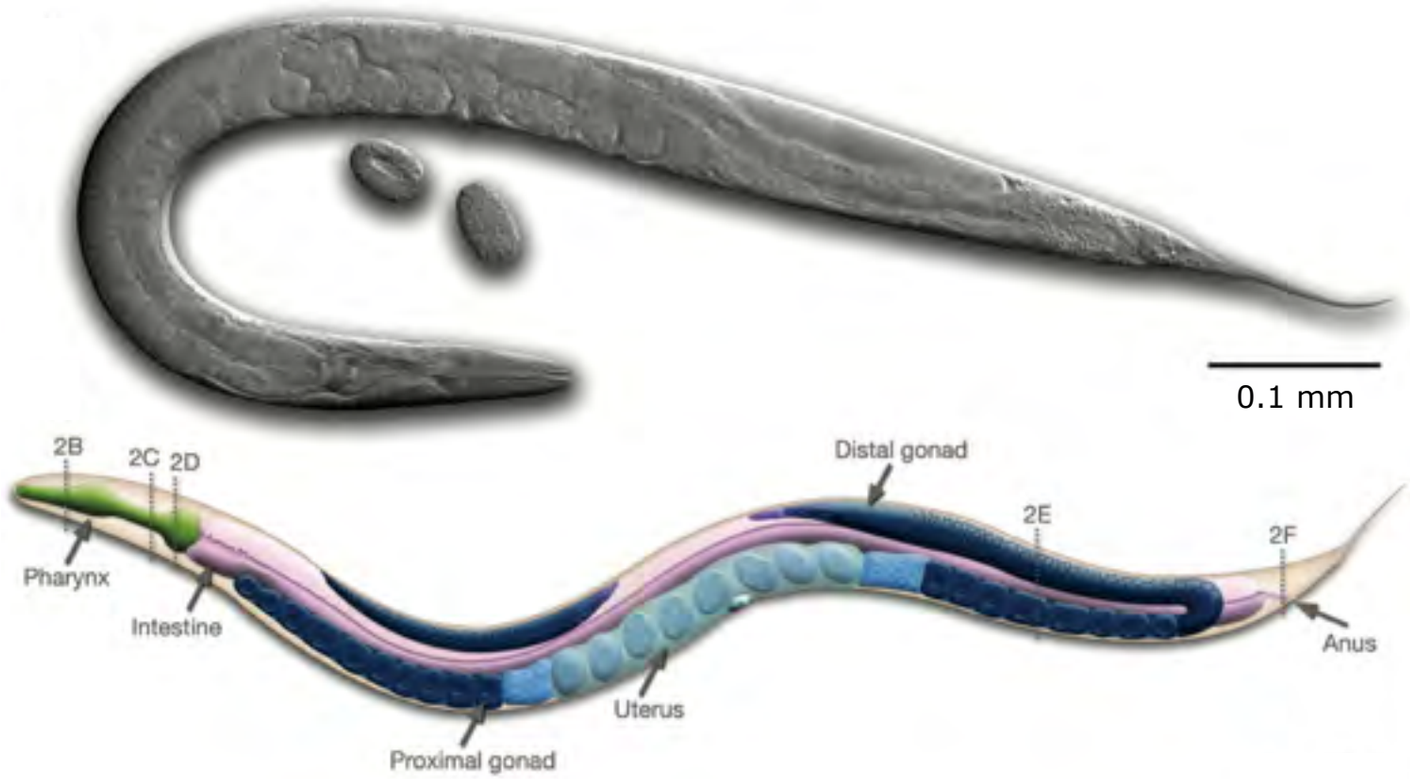




controlled environment

- “all-cause” mortality
  - agnostic about proximal causes of death
  - agnostic about “disease”
  - agnostic about “causes”
- “intrinsic” risk

C. elegans, the essence of life: a stomach and a gonad



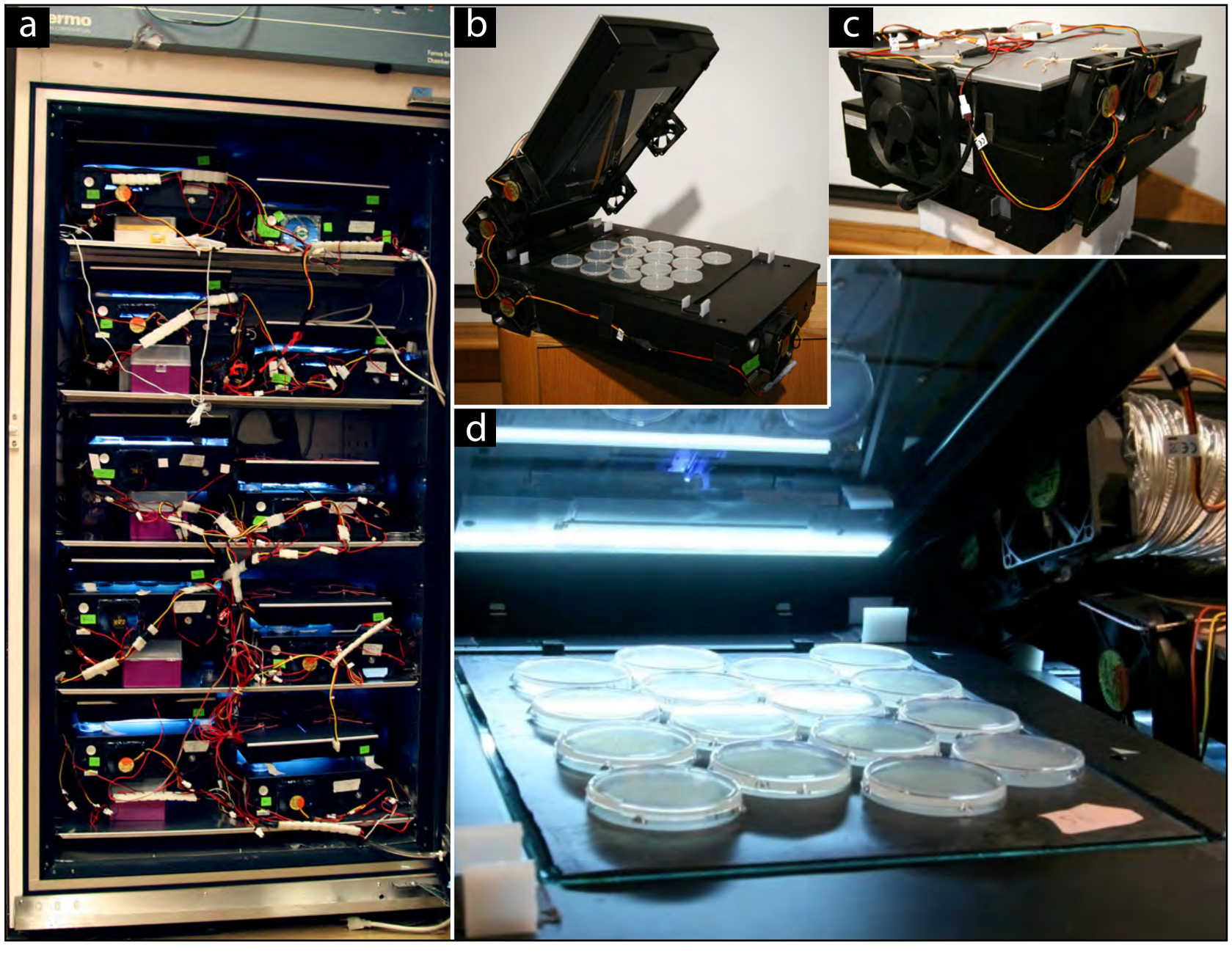
- ~ 1 mm in length
- ~ 70 microns in diameter
- 959 cells (302 neurons)
- 100M bp, 19000 ORFs
- 2 weeks average life span

- transparent
- complete parts list
- complete developmental lineage
- great genetics
- model organism status

Z. F. Altun & D. H. Hall
www.wormatlas.org

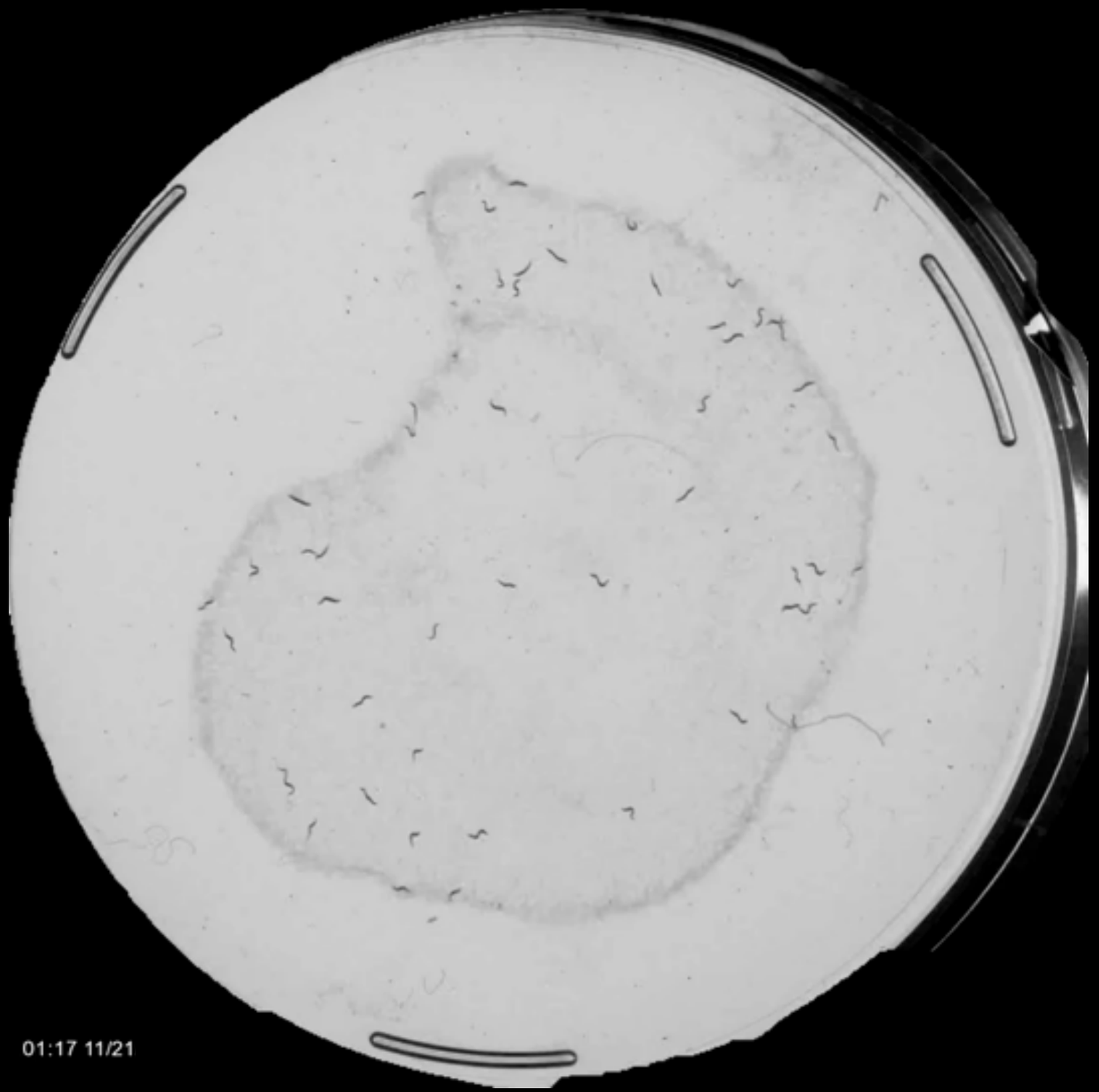
The Lifespan Machine

acquisition of high-resolution lifespan statistics with
a distributed scalable time lapse microscope based on flatbed document scanners



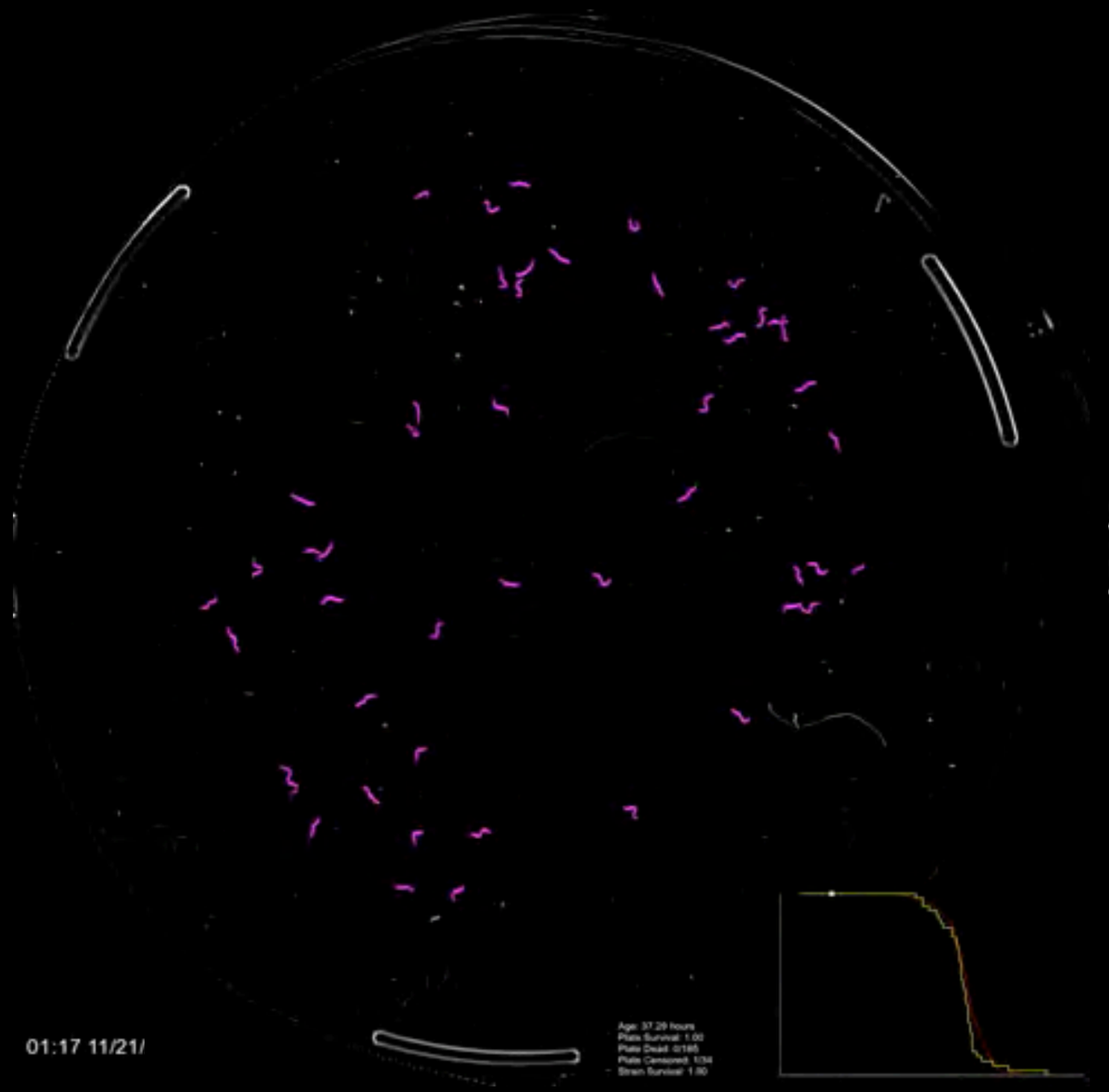
N. Stroustrup et al., "The *C. elegans* Lifespan Machine", *Nature Methods*, **10**, 665-670 (2013)

wildtype in brightfield



wildtype N2

age1(hx586)



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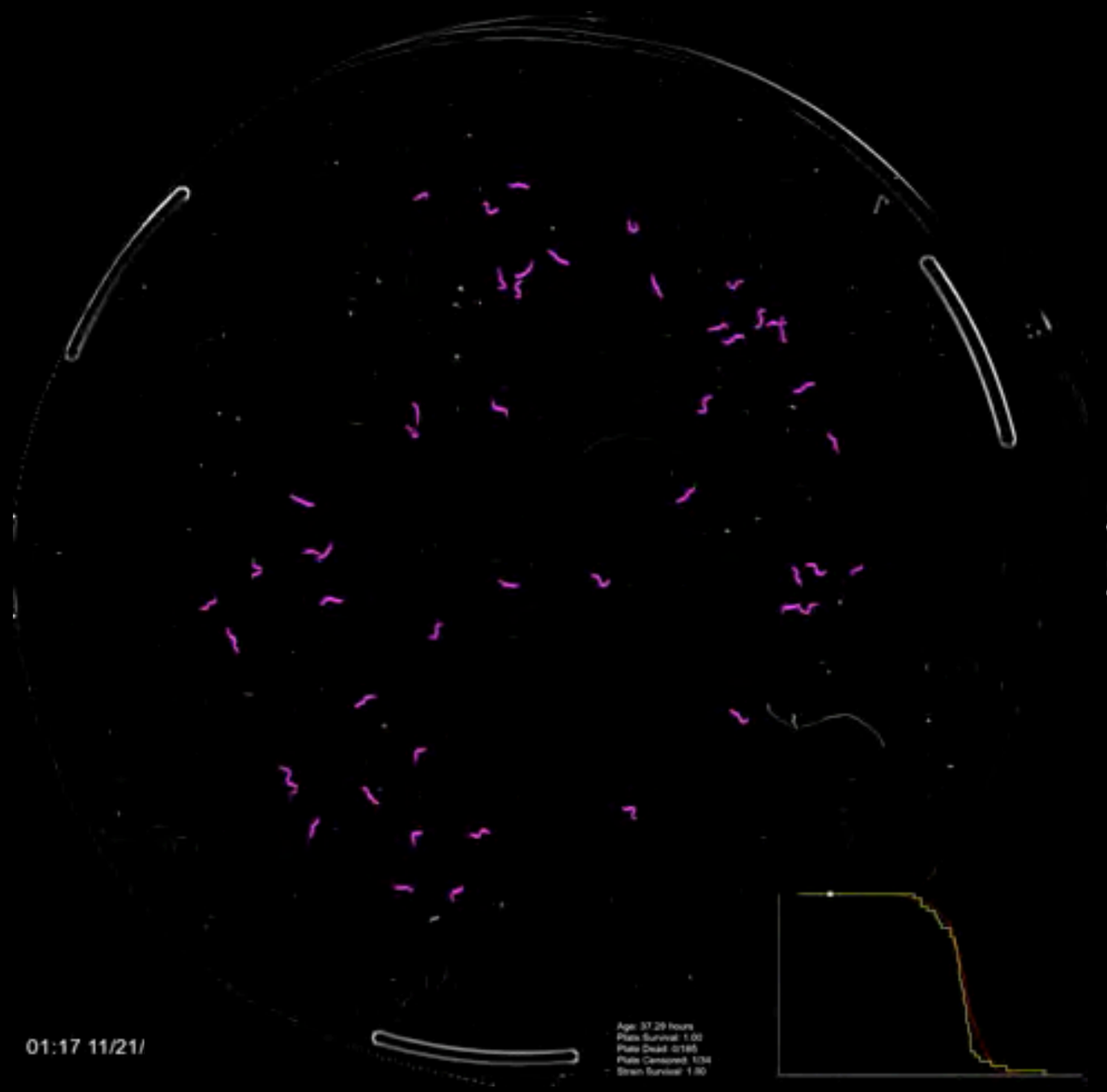
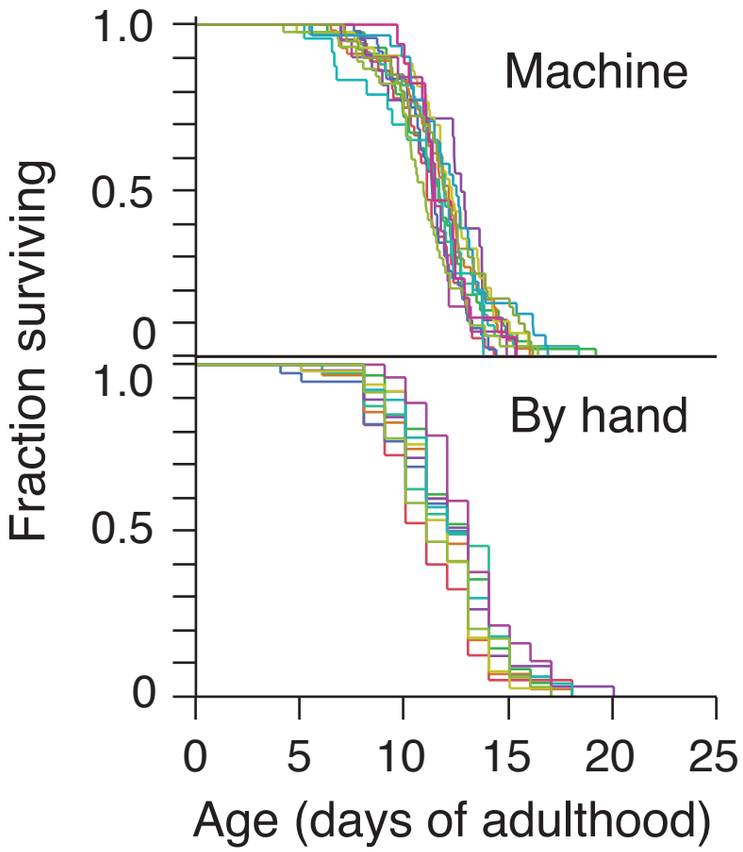
age1(hx586)

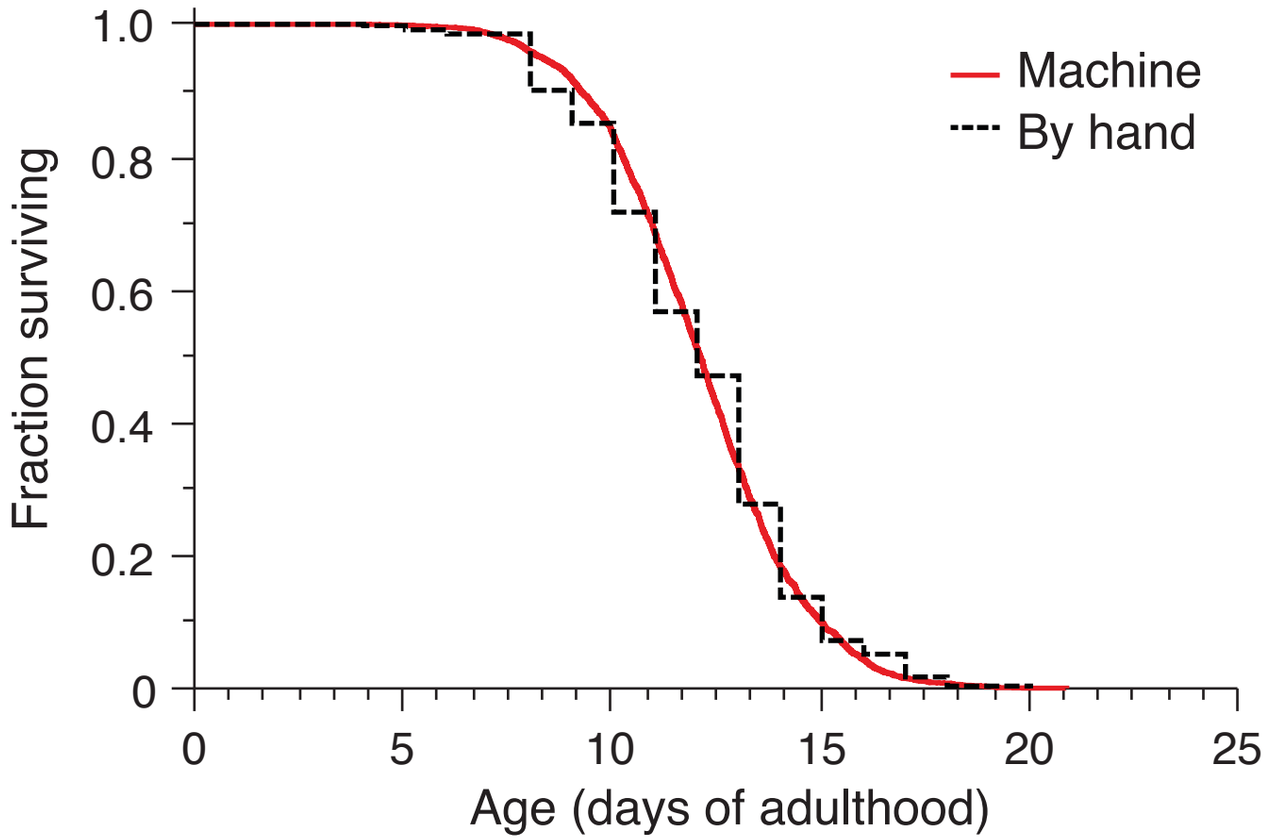


Precision and accuracy

484 death events
on a single scanner

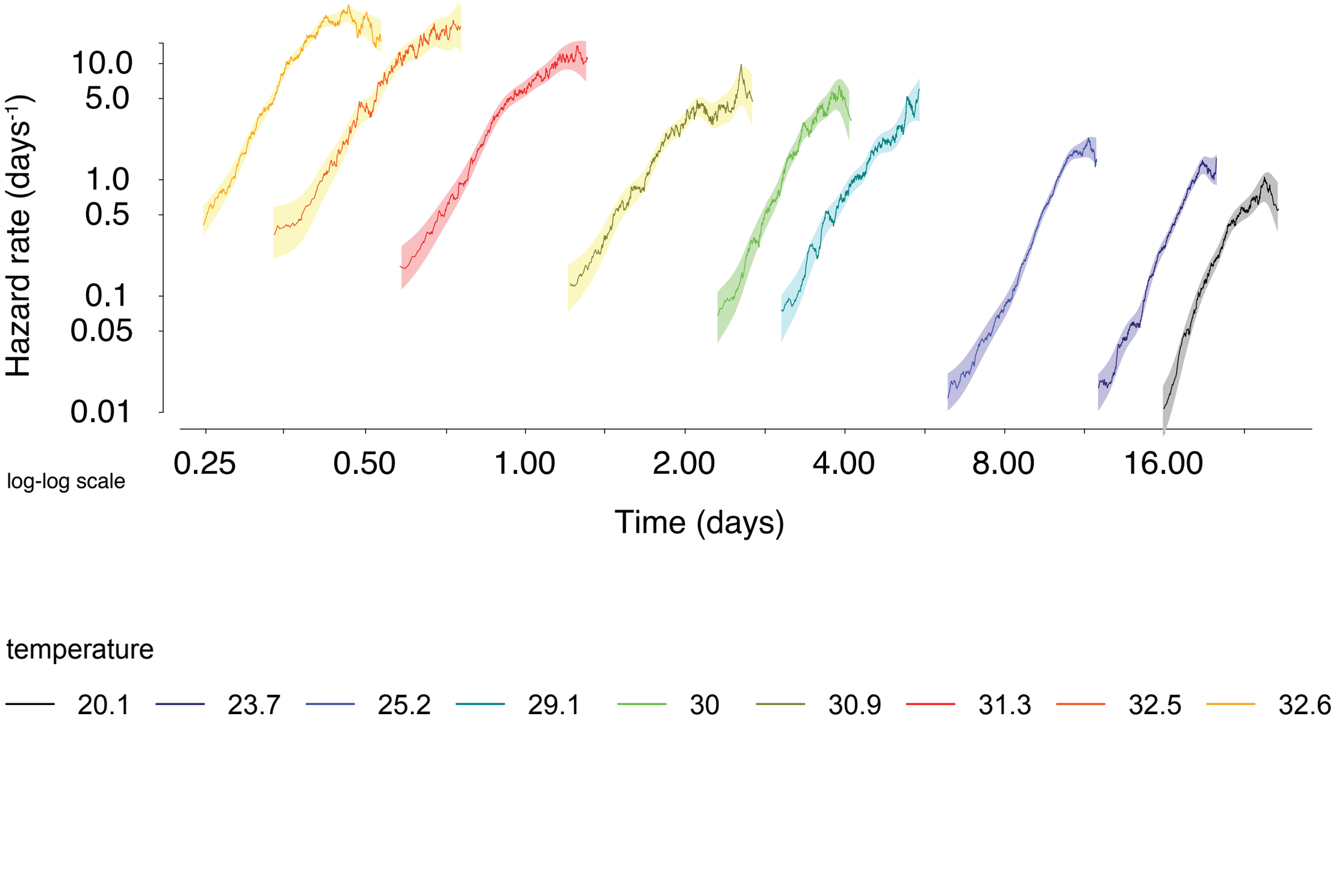


513 death events
observed manually



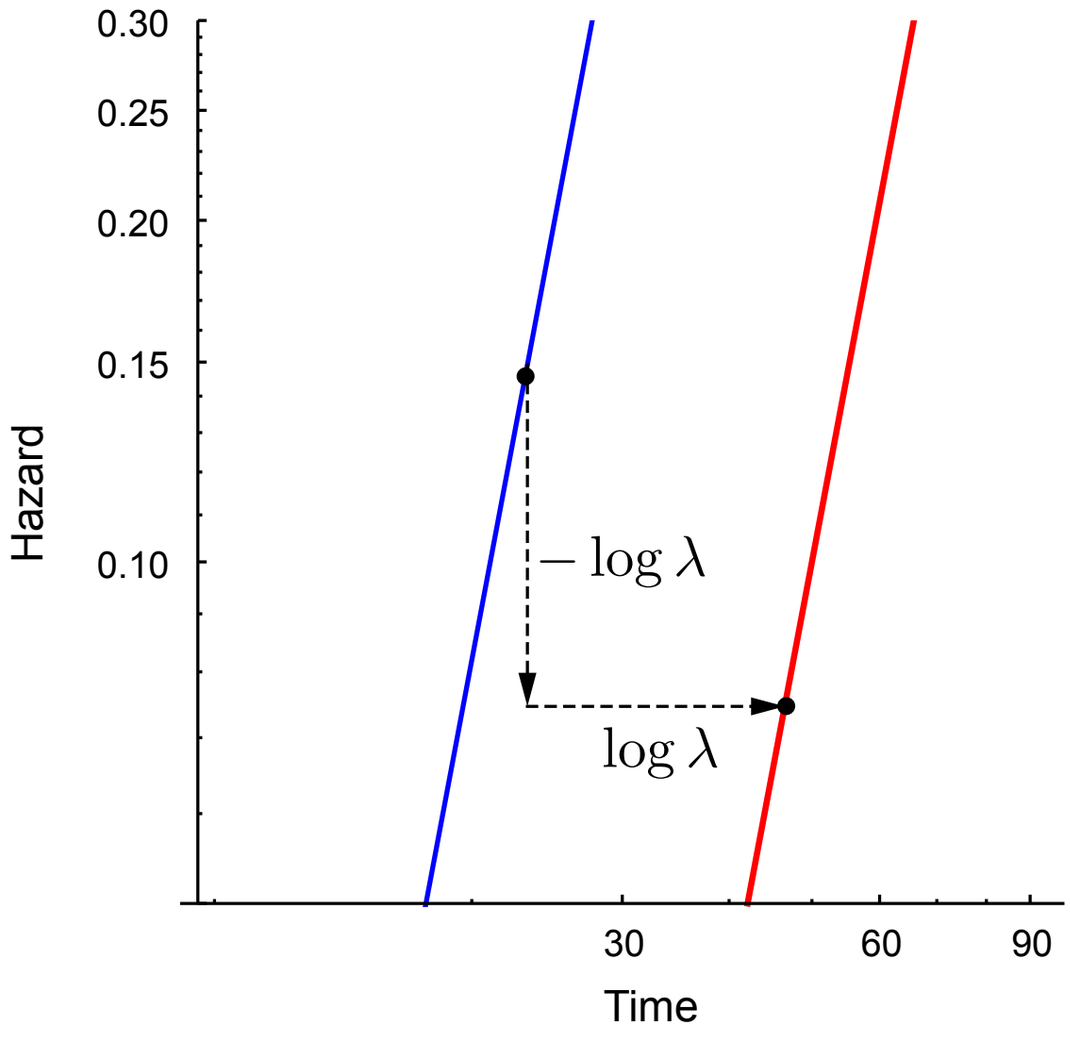
3,578 death events observed
on 10 scanners, aggregated

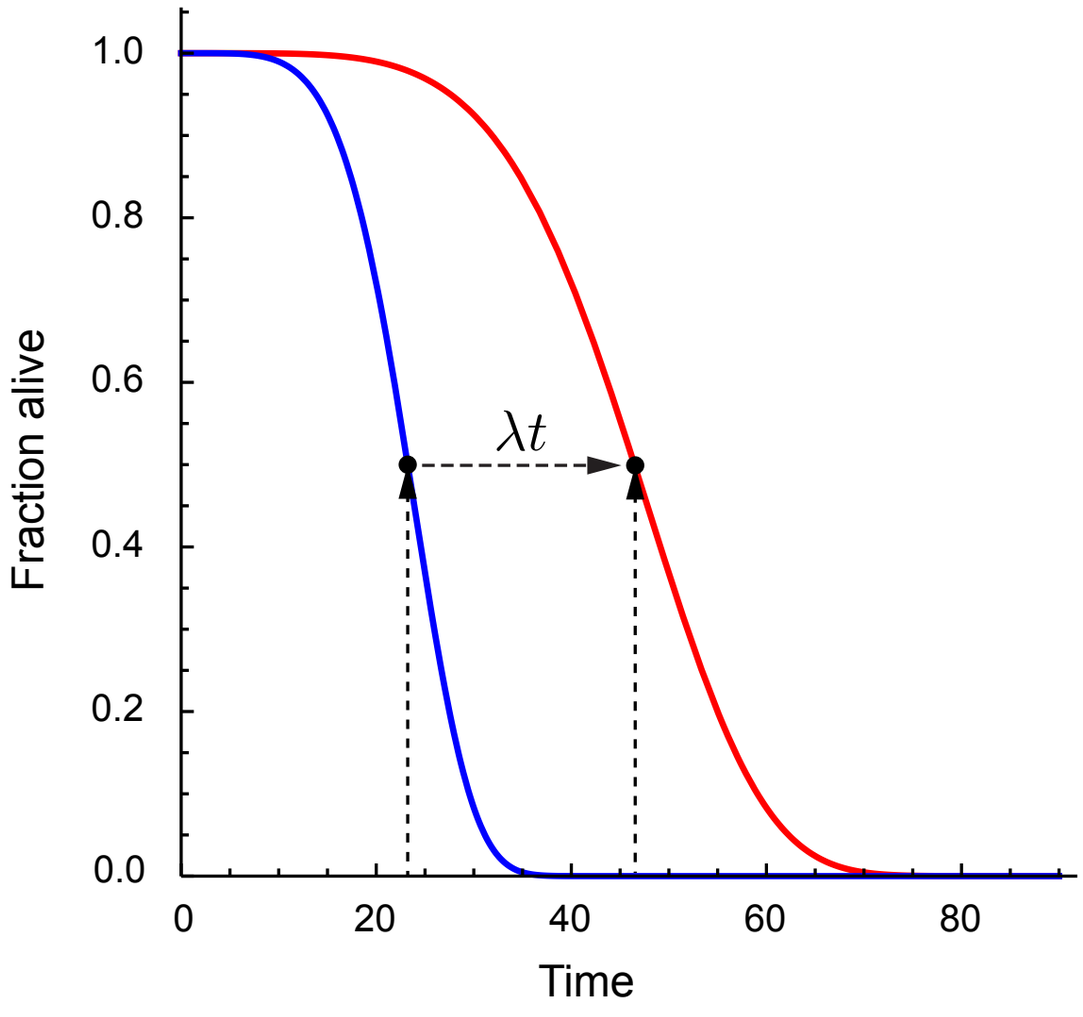
Temperature series



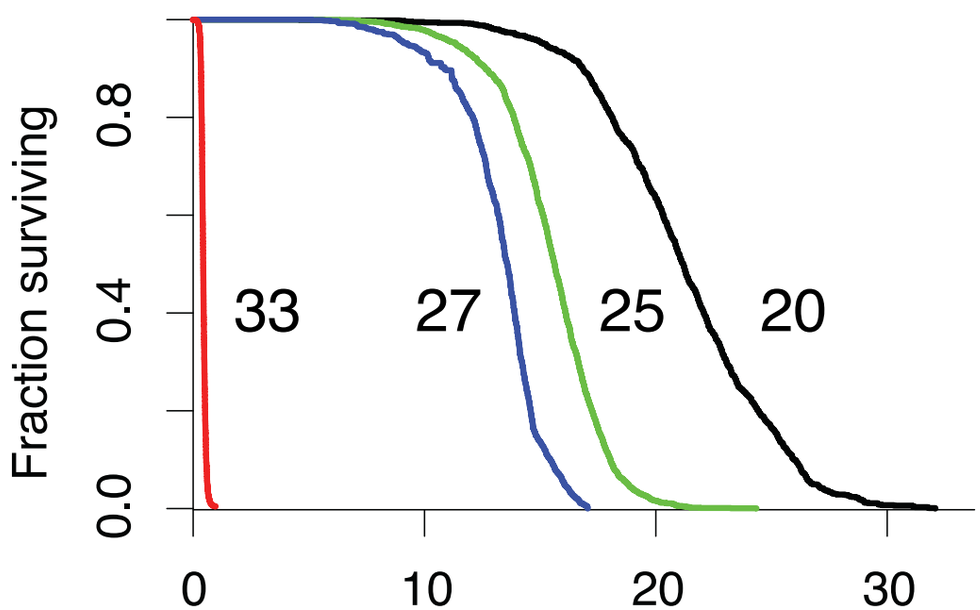
Temporal scaling

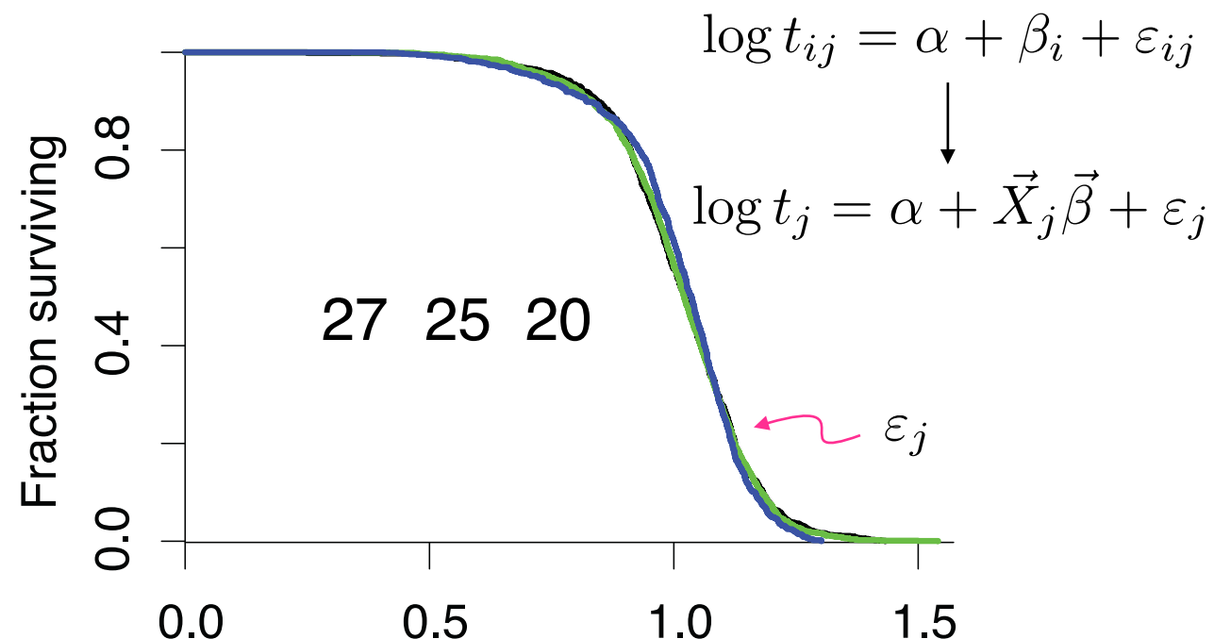
$$h_1(\lambda t) = \frac{1}{\lambda} h_0(t) \quad \text{or} \quad h_1(t) = \frac{1}{\lambda} h_0\left(\frac{1}{\lambda} t\right) \qquad \Longleftrightarrow \qquad S_1(\lambda t) = S_0(t) \quad \text{or} \quad S_1(t) = S_0(\lambda^{-1} t)$$

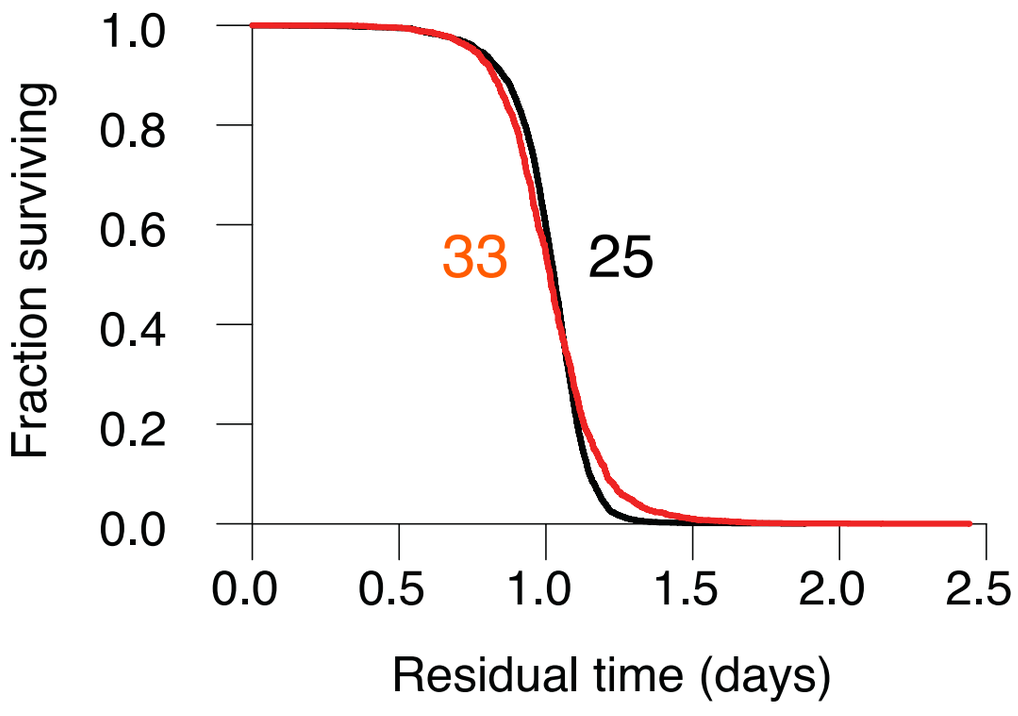


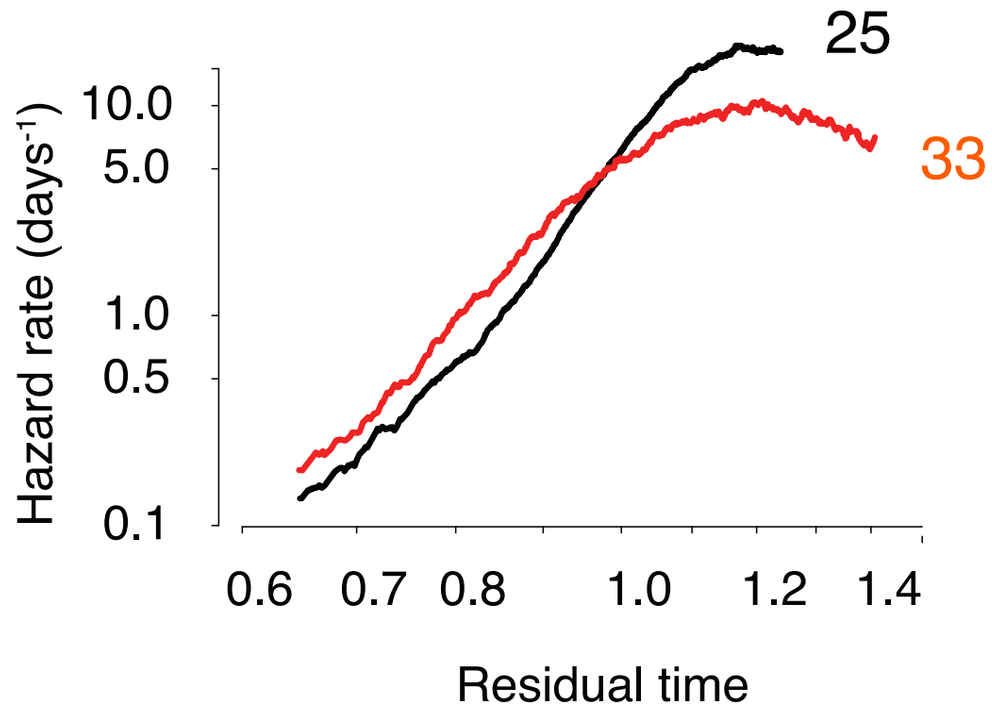


Temperature results in residual time

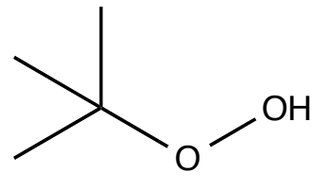


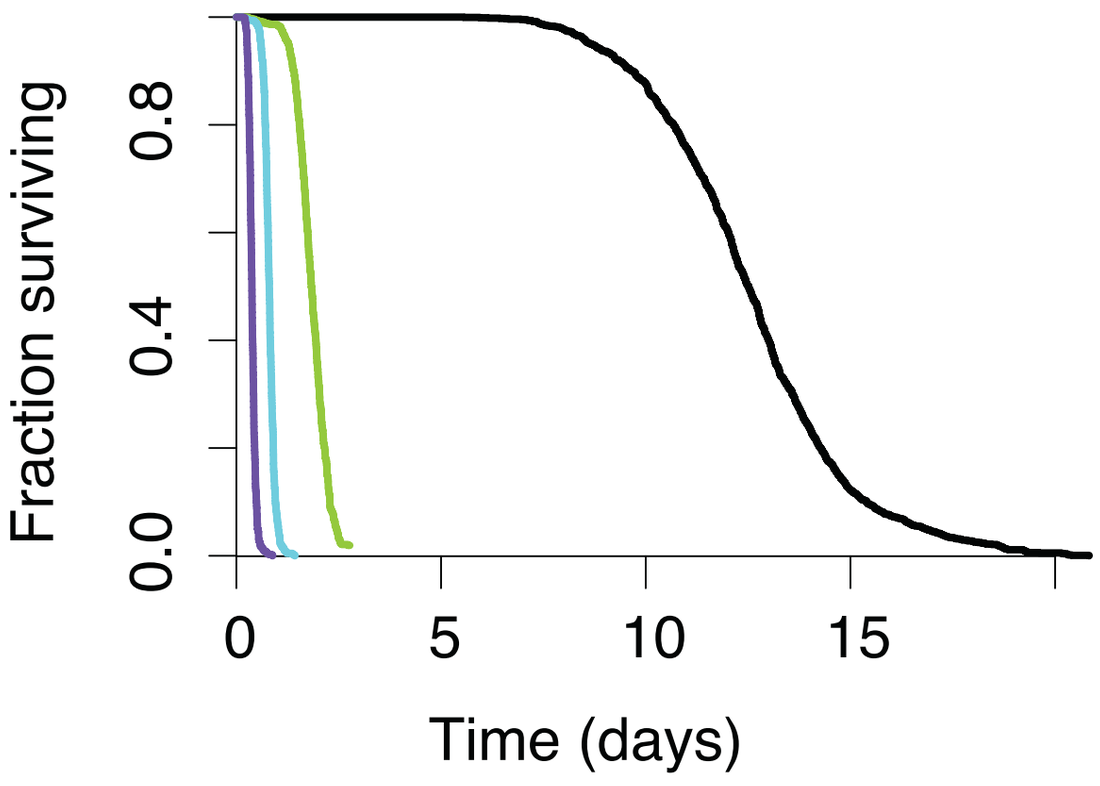


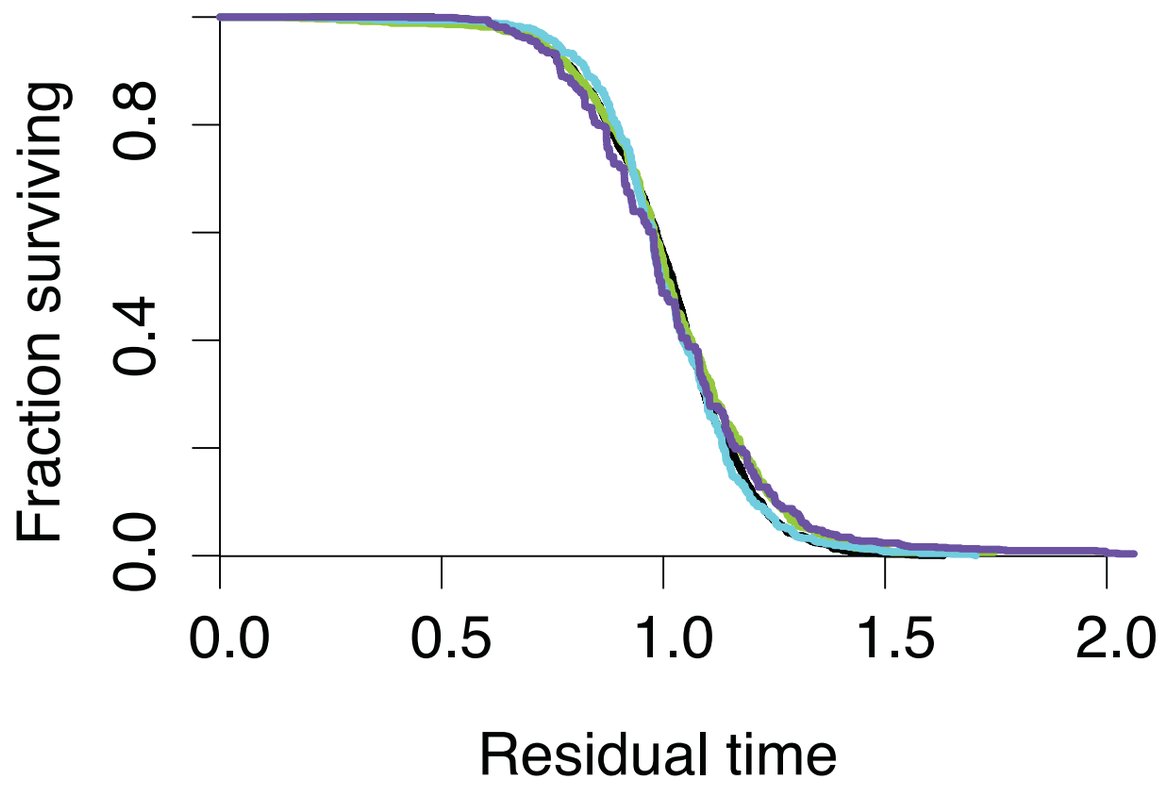




t-butyl-peroxide rescales time

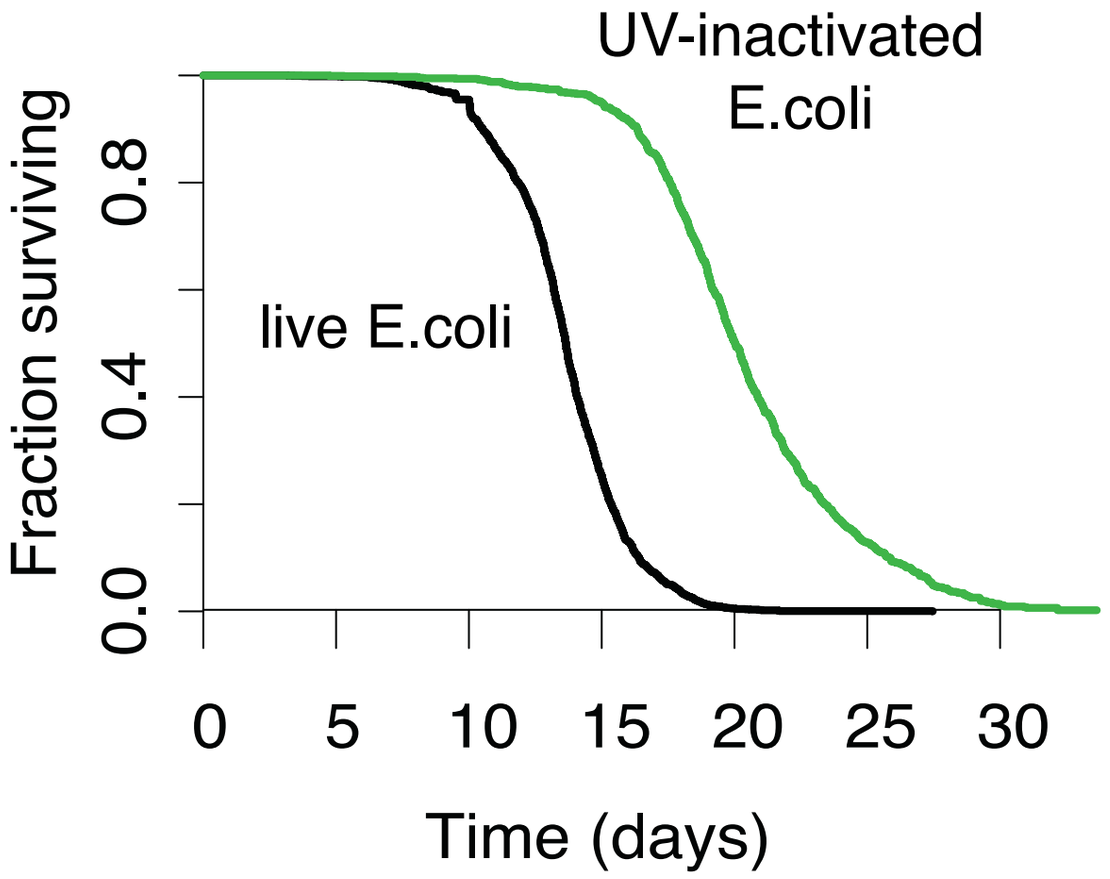
oxidative stress with 

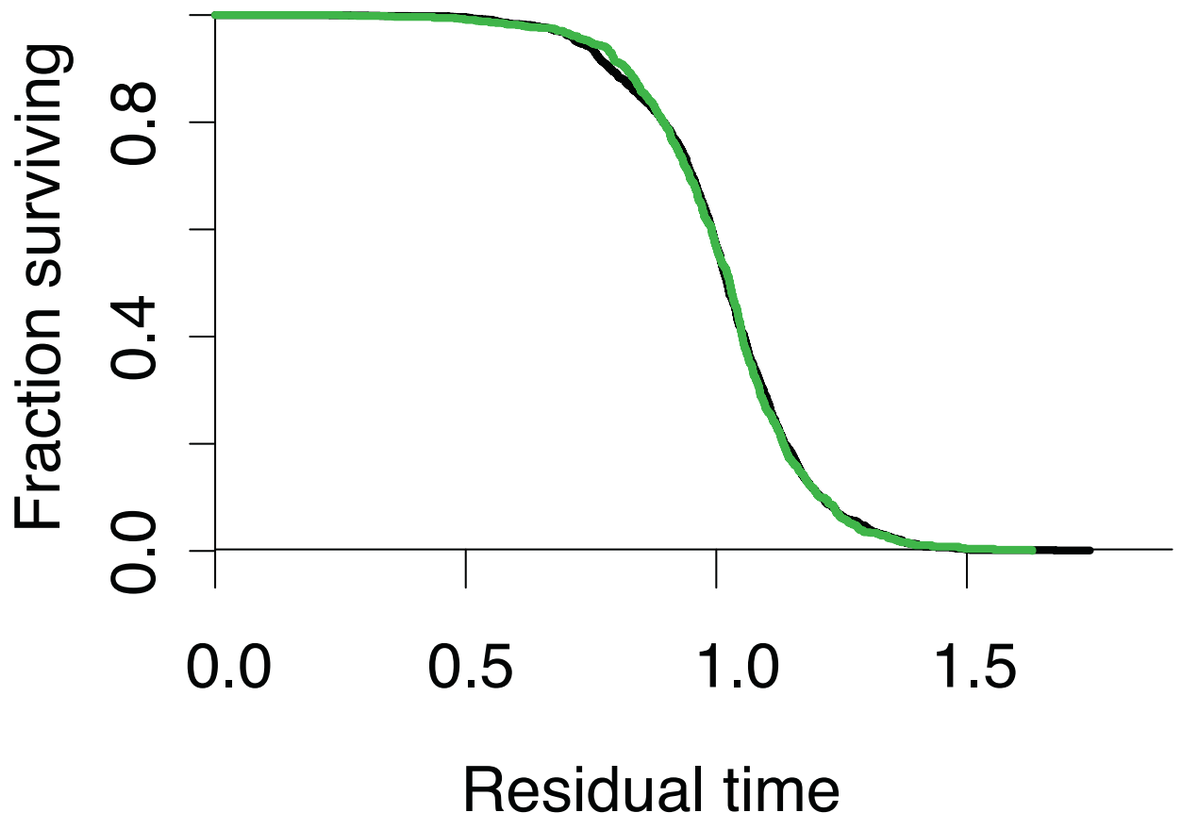




6 mM 3 mM 1.5 mM 0 mM t-butyl-hydroperoxide

Diet rescales time

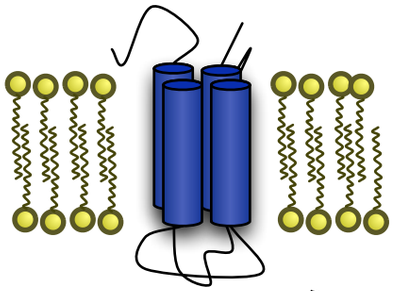




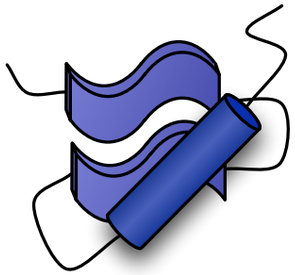
DAF-2/IGF signaling

DAF-2 [insulin receptor]

activation by insulins

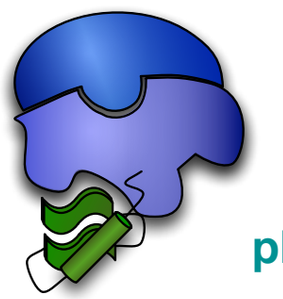


activation



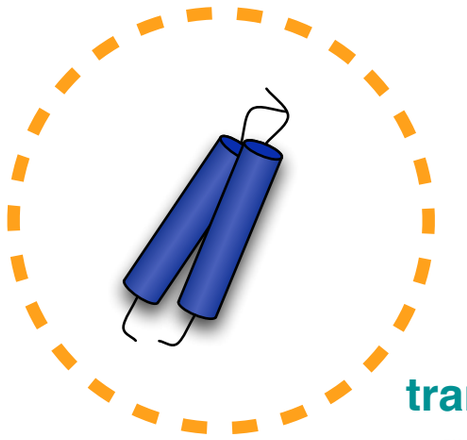
AGE-1 [PI3K]

activation (via PIP3 and PDK-1)



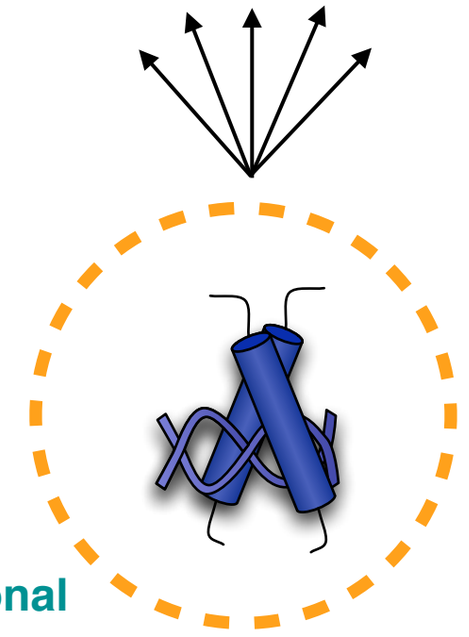
phosphorylation

translocation



transcriptional modulation

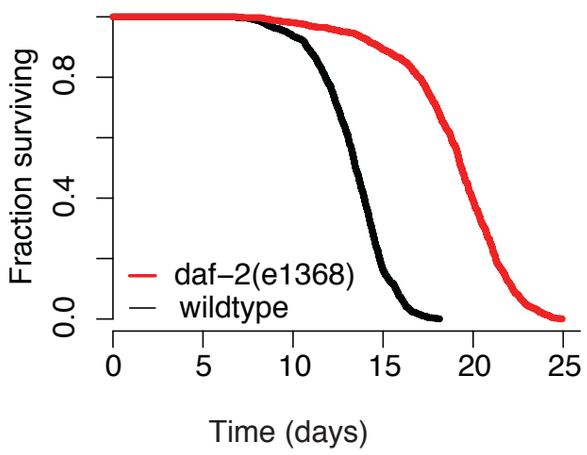
“stress response”

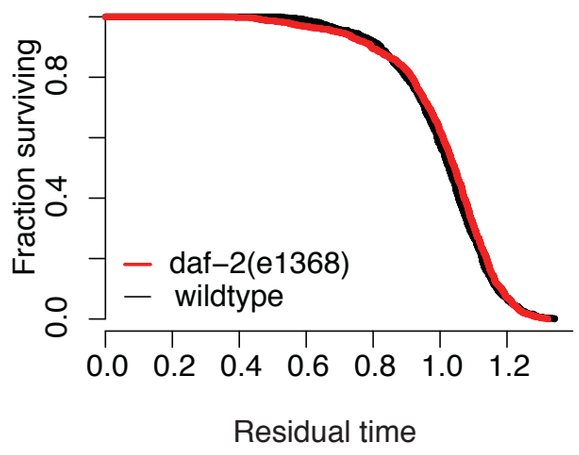


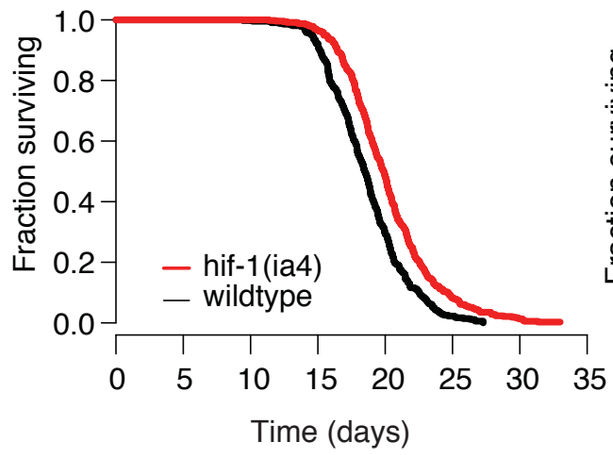
AKT-1/AKT-2

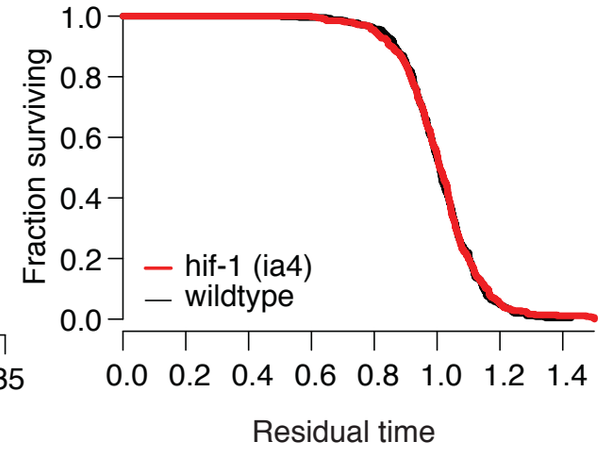
DAF-16 [forkhead TF]

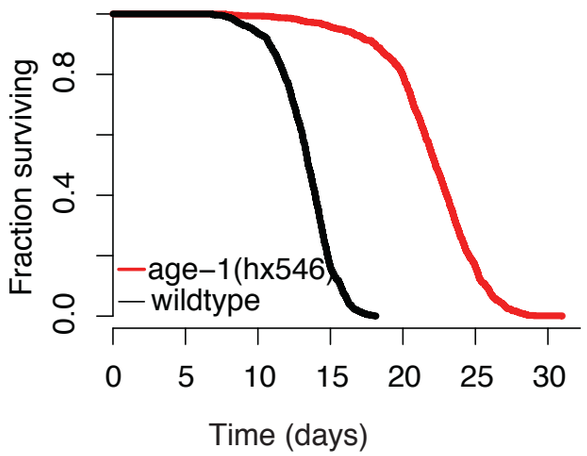
Mutants that rescale time

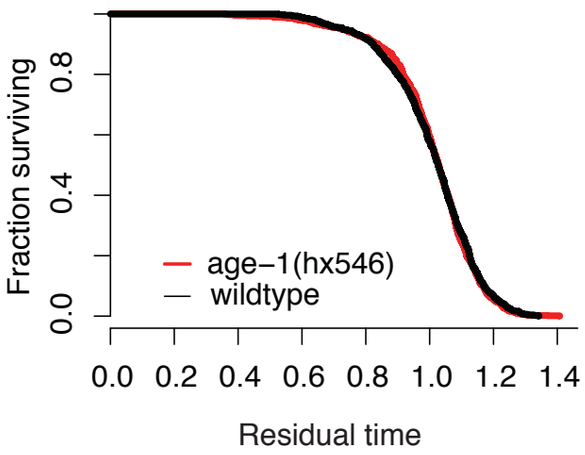


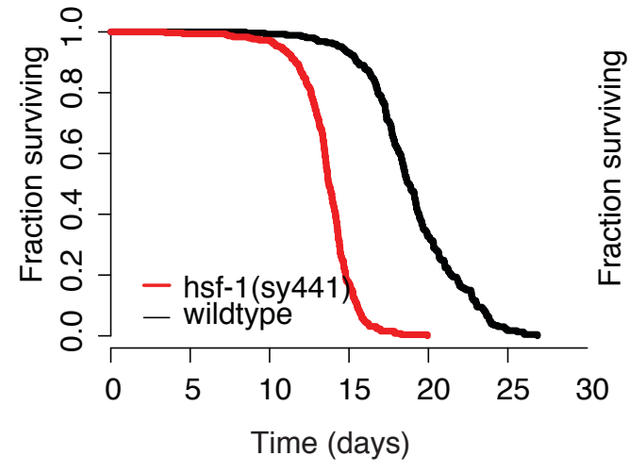


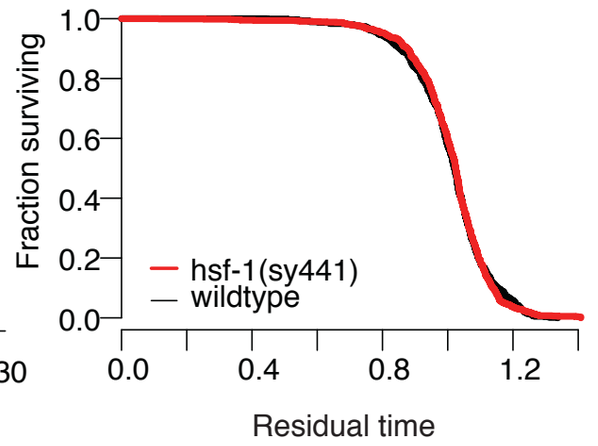


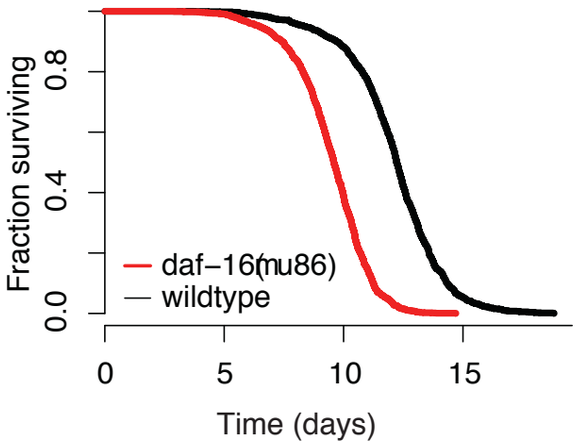


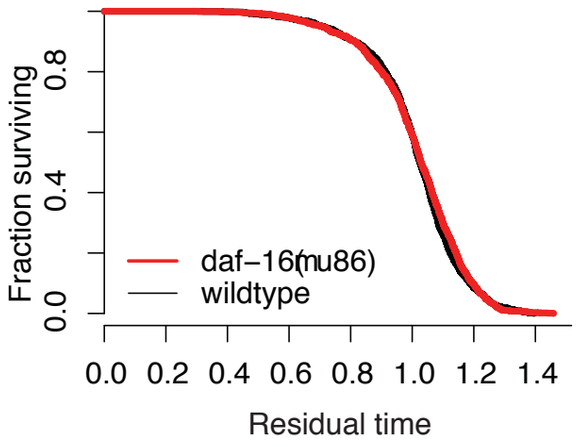










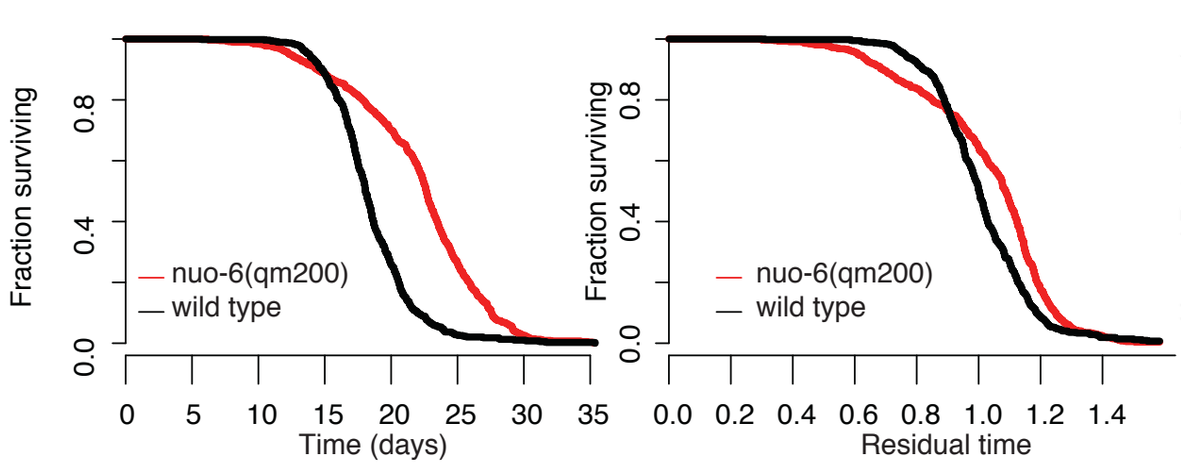


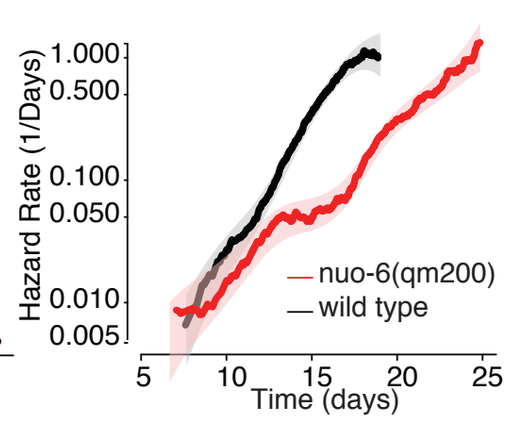
daf-2, age-1, daf-16: IGF pathway

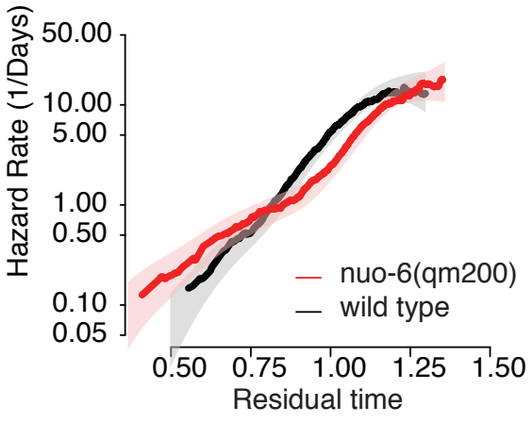
hif-1: hypoxia-inducible factor

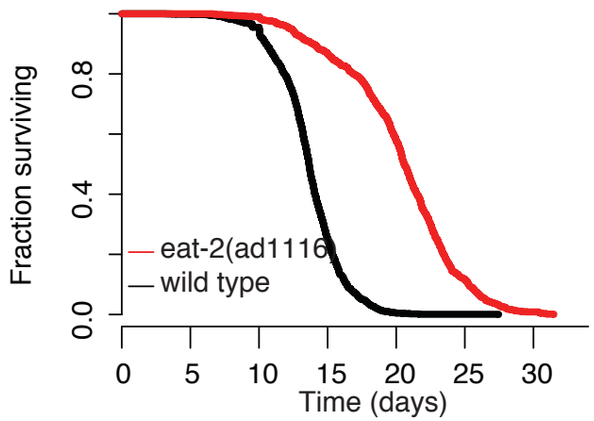
hsf-1: heat-shock factor

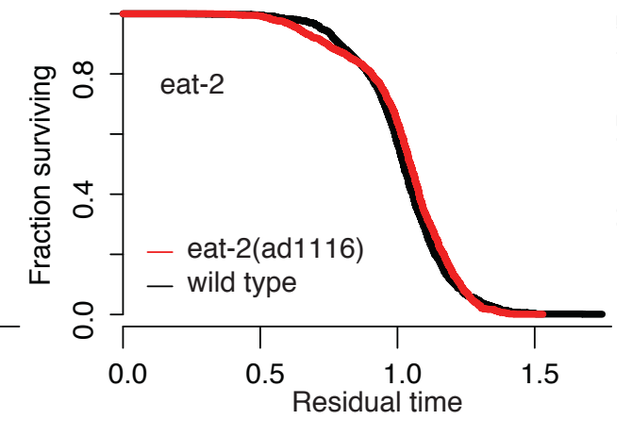
Mutants that break scaling

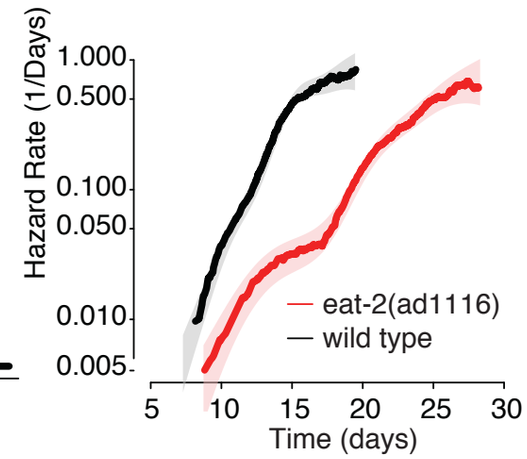


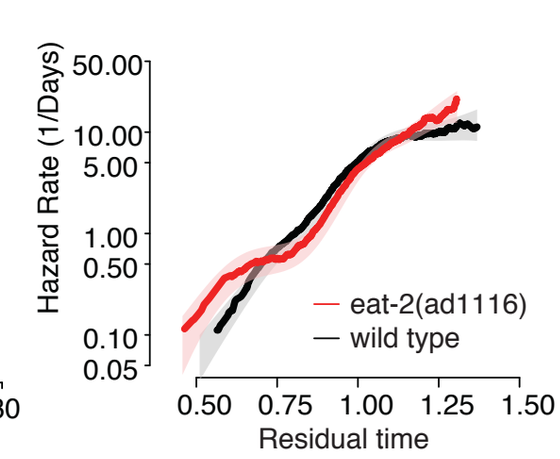


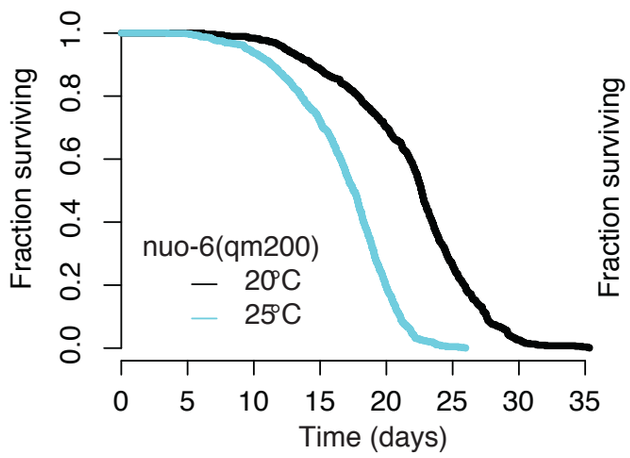


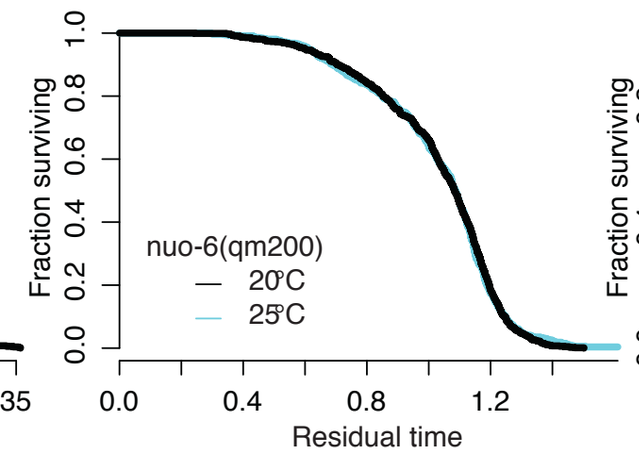


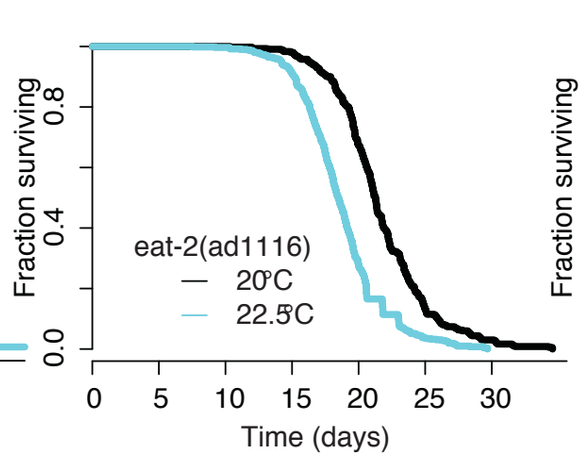


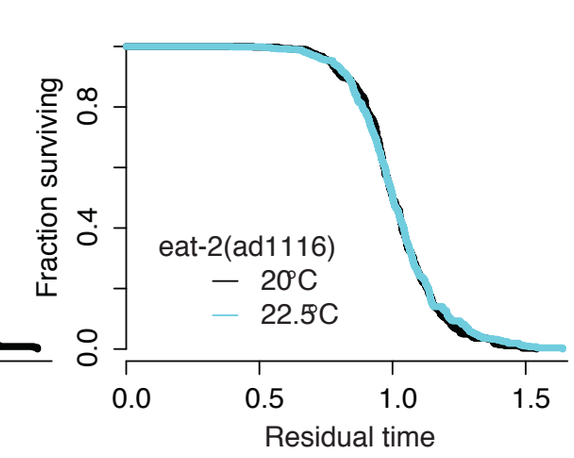




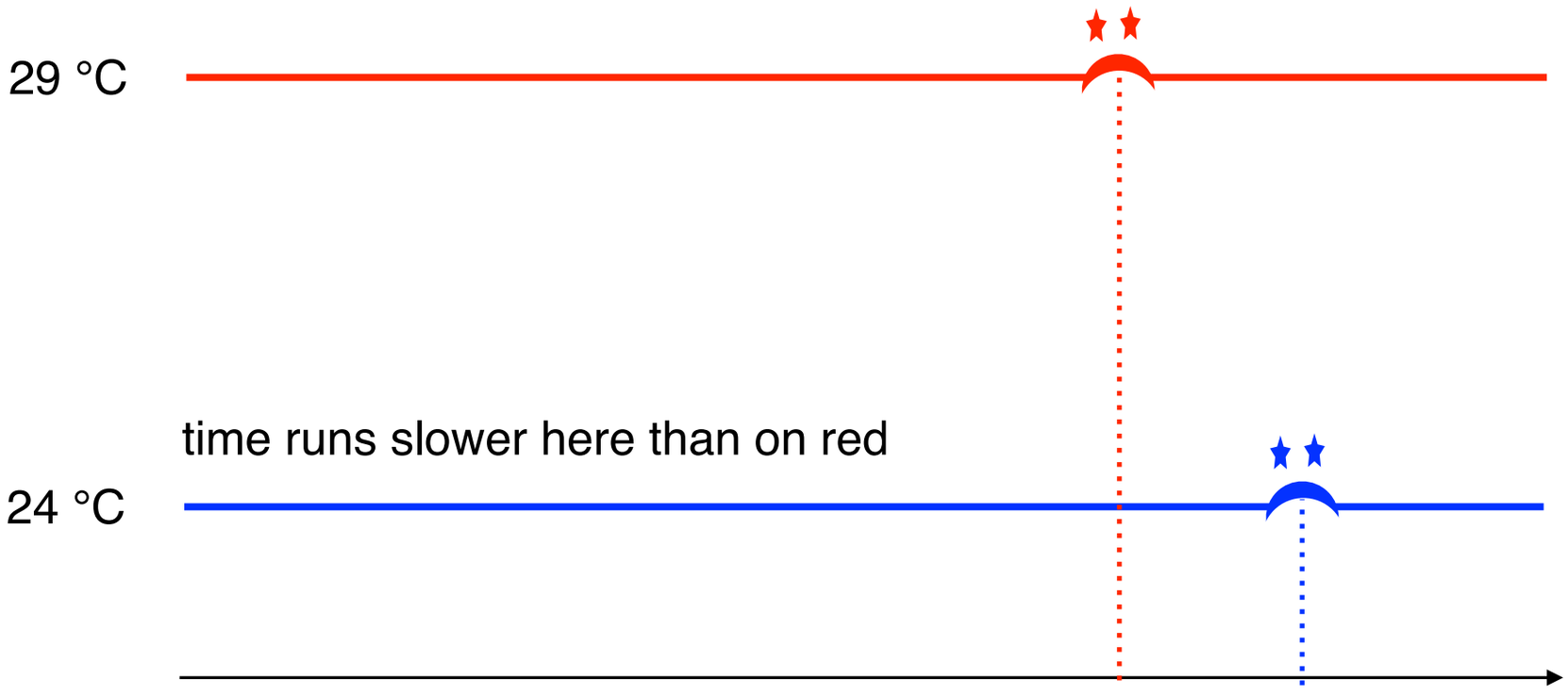


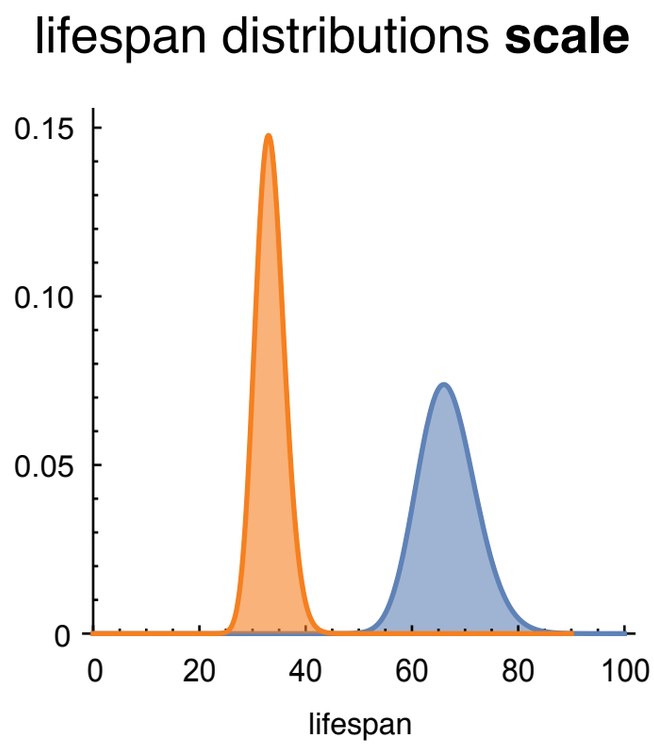




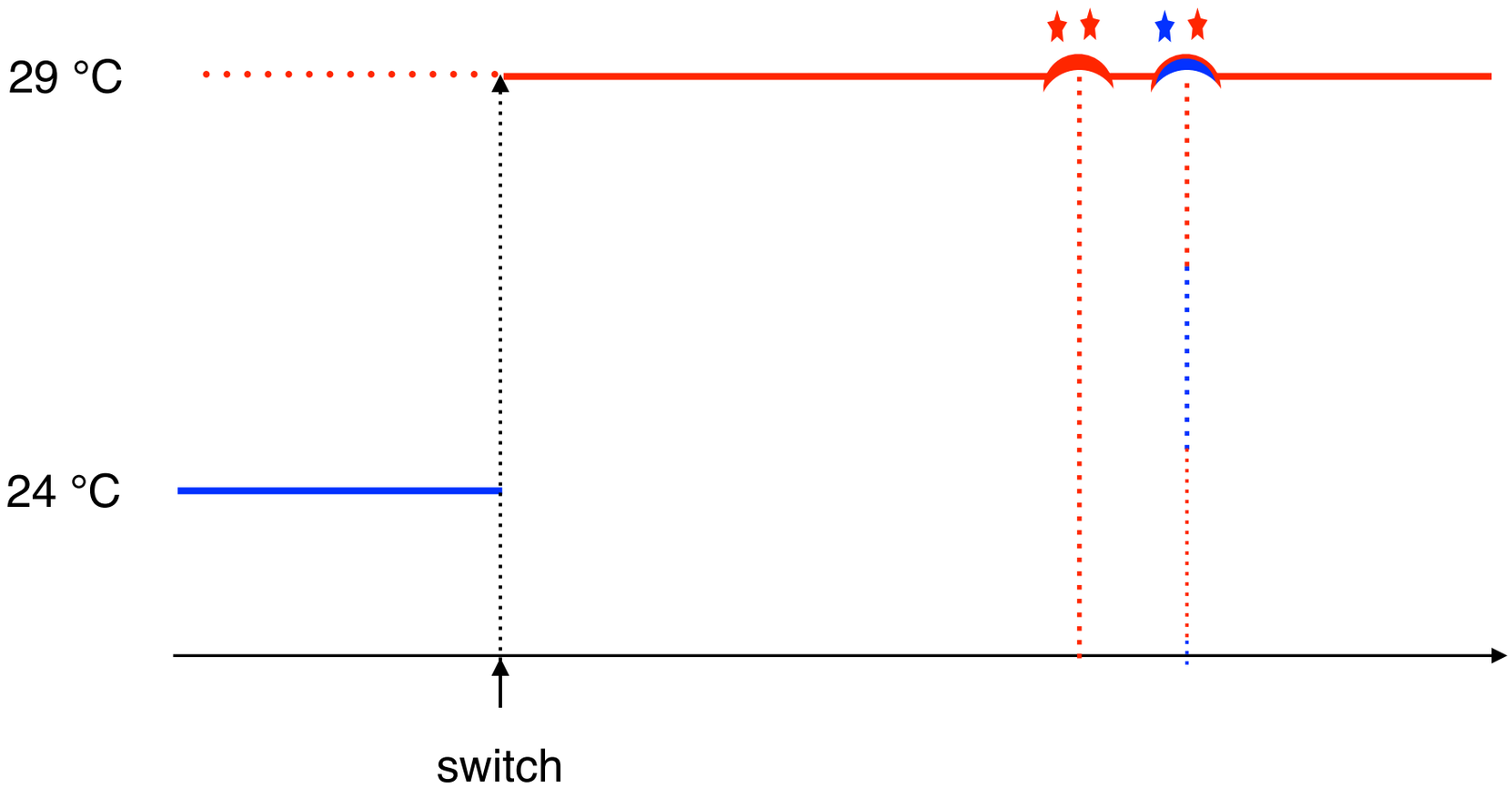


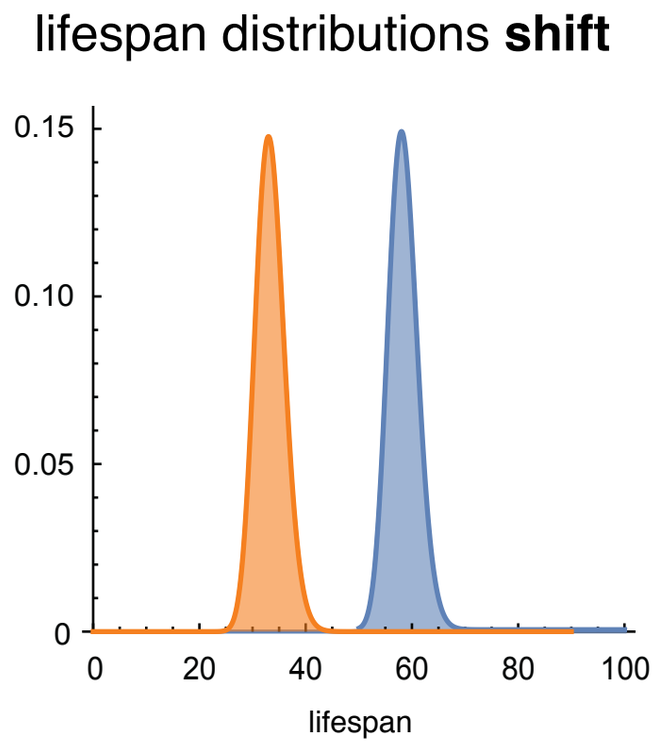
Scaling and shifting





Scaling and shifting





Scaling and shifting

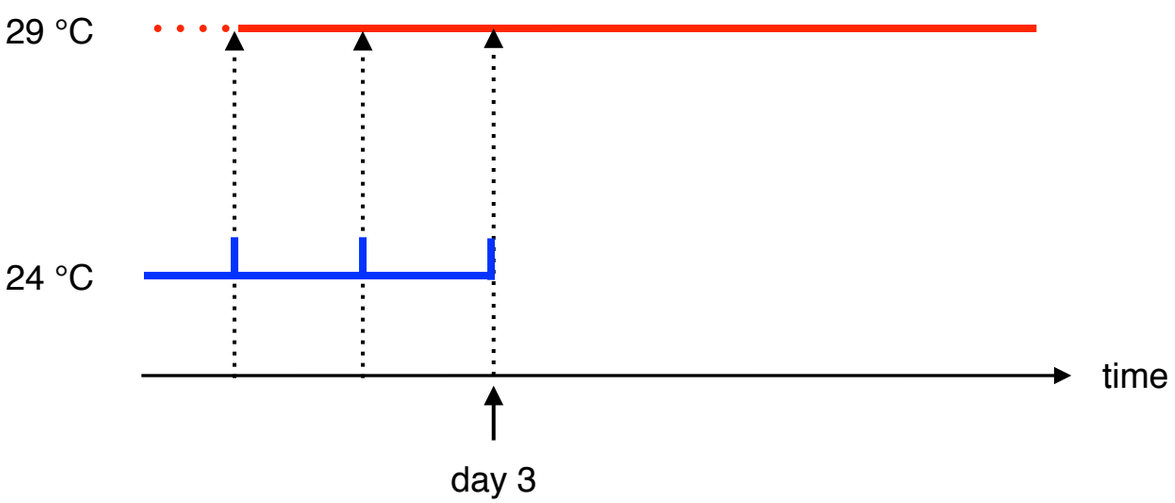
The theory of the switch experiment predicts that *if scaling holds*

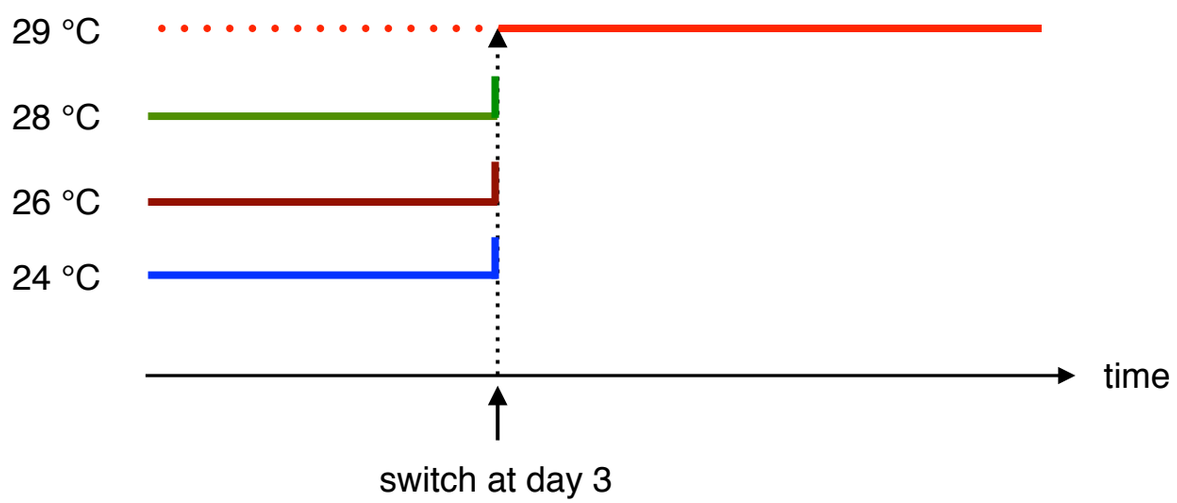
$$\Delta(t) = E_0(Y \mid Y > t/\lambda) - E_0(Y \mid Y > t) + t(1 - 1/\lambda)$$

shift magnitude — time of switch — conditional lifespan expectation of the (non-switched) control population

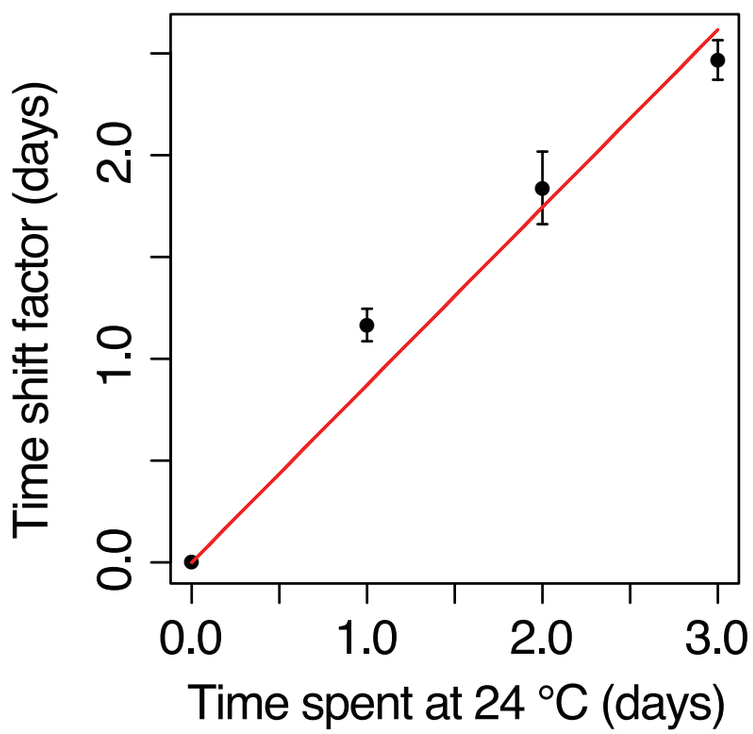
In particular, if switching occurs before any deaths have occurred:

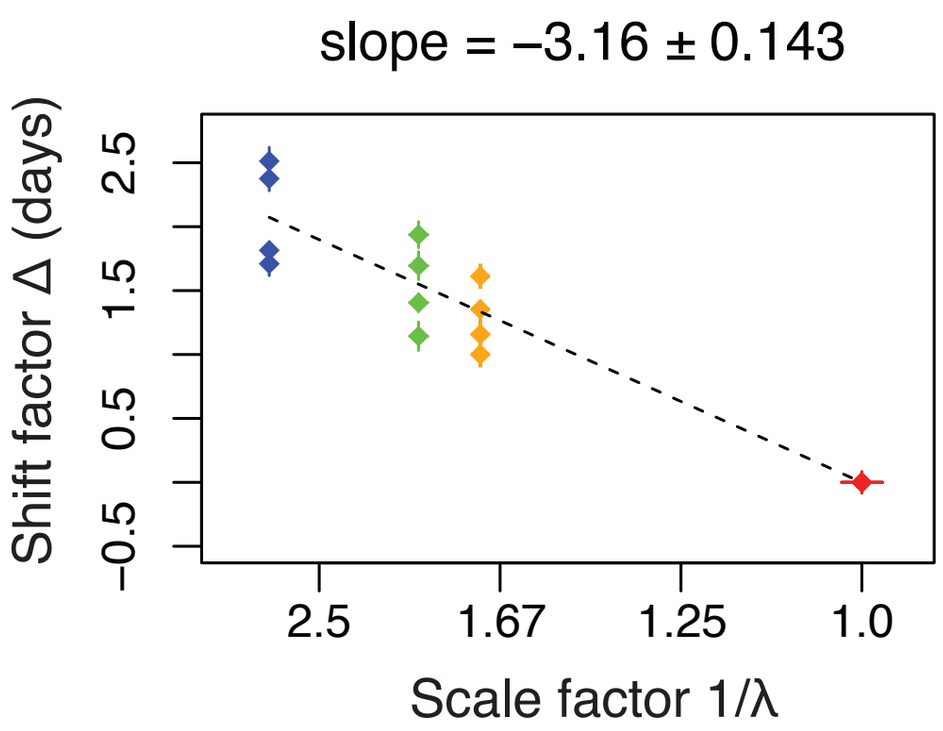
$$\Delta(t) = t(1 - 1/\lambda)$$

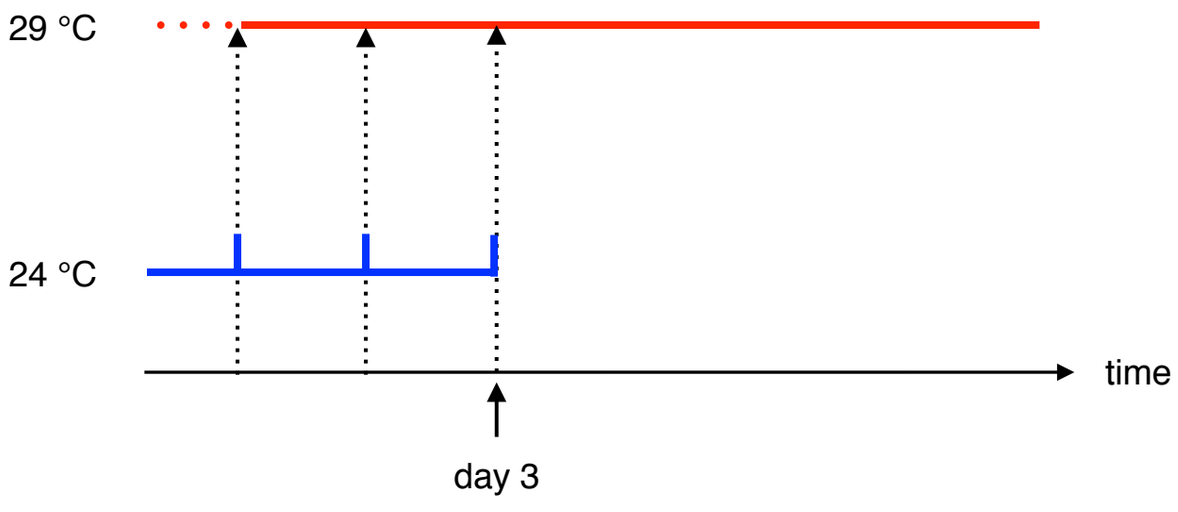


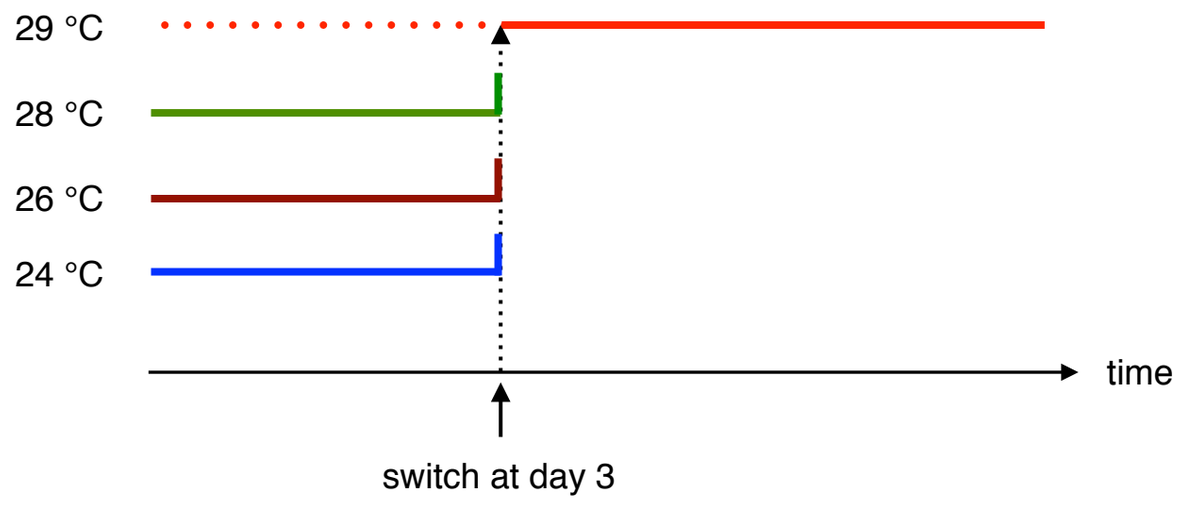


Shifting confirms scaling









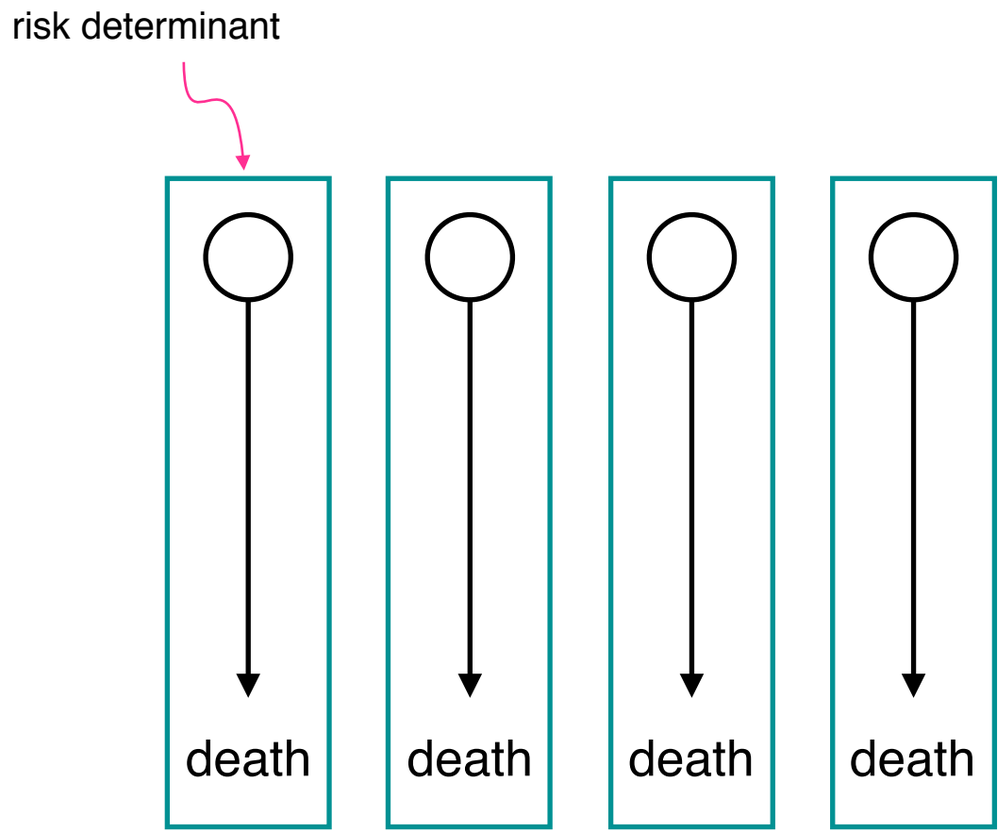
Main observations

- Interventions of distinct modalities and intensities simply rescale time in the mortality statistics of the worm.

- The aging process is remarkably uniform and is ongoing long before any deaths are observed in the population.

What does temporal scaling mean?

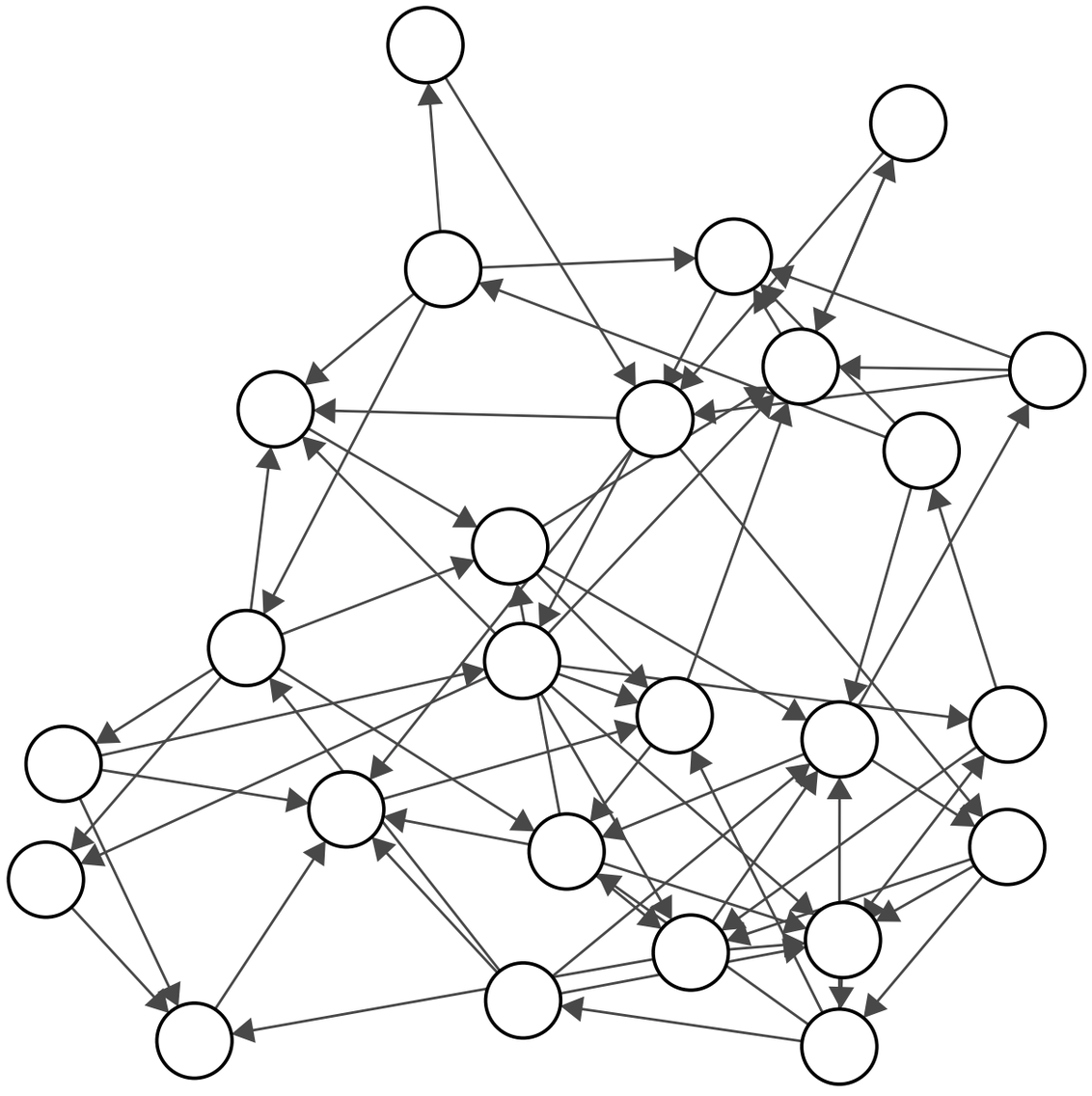
Scaling of mortality requires that all risk factors rescale equally (*) in response to an intervention regardless of its nature and targets.



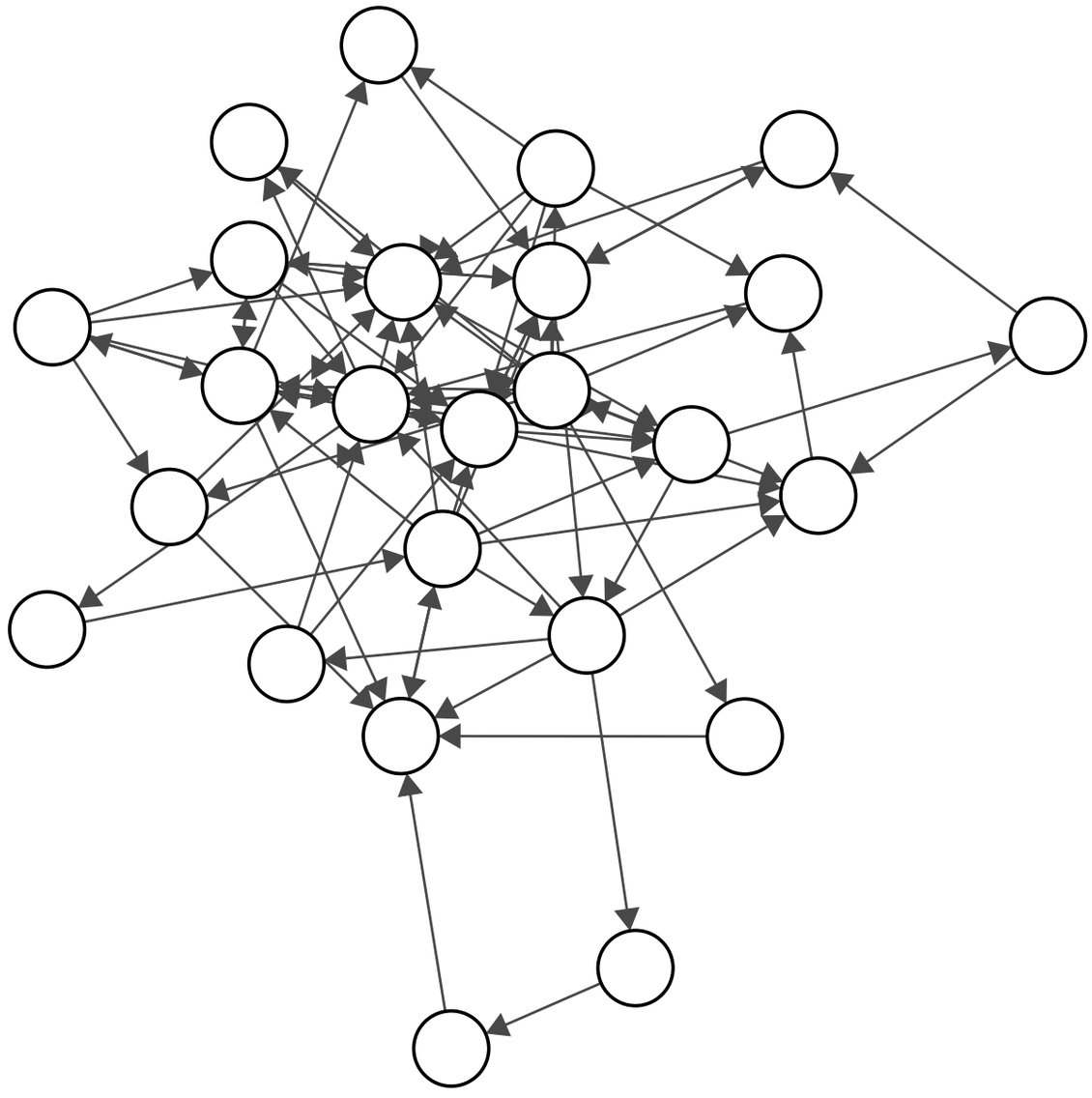
competing (independent) risks model

(*) Exception: risk factors need not rescale *equally,* if they are Weibull, but this would be highly implausible

Dependency network models



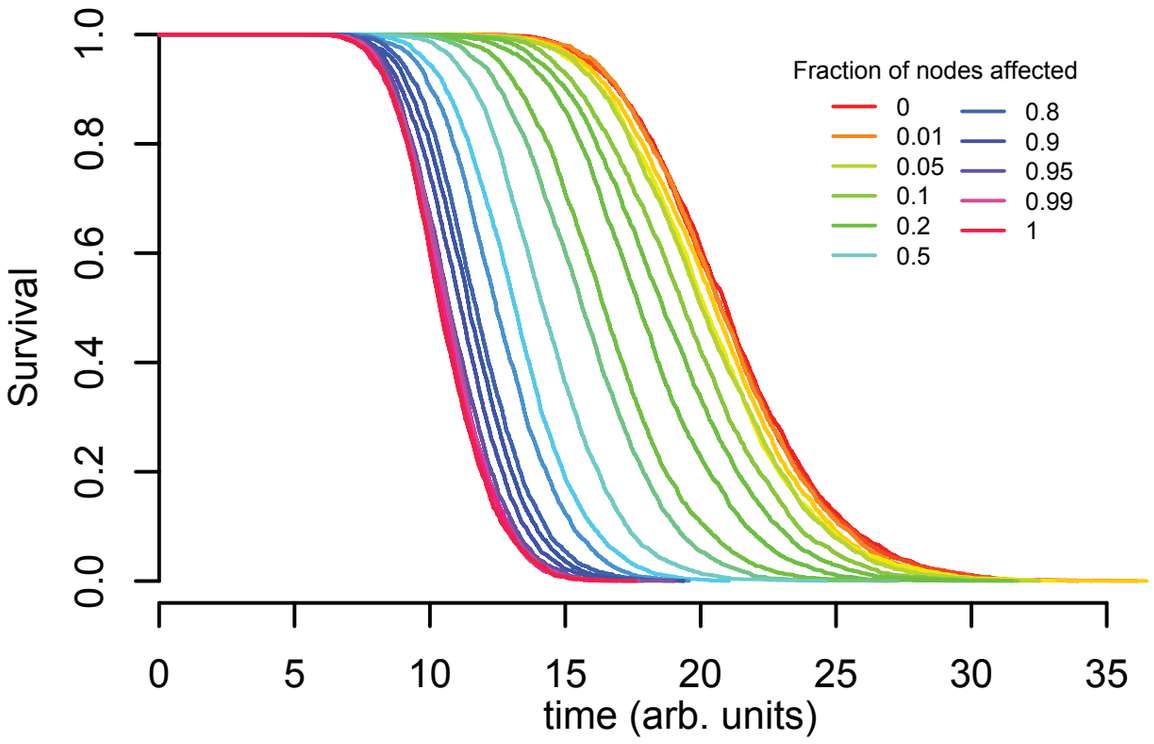
random

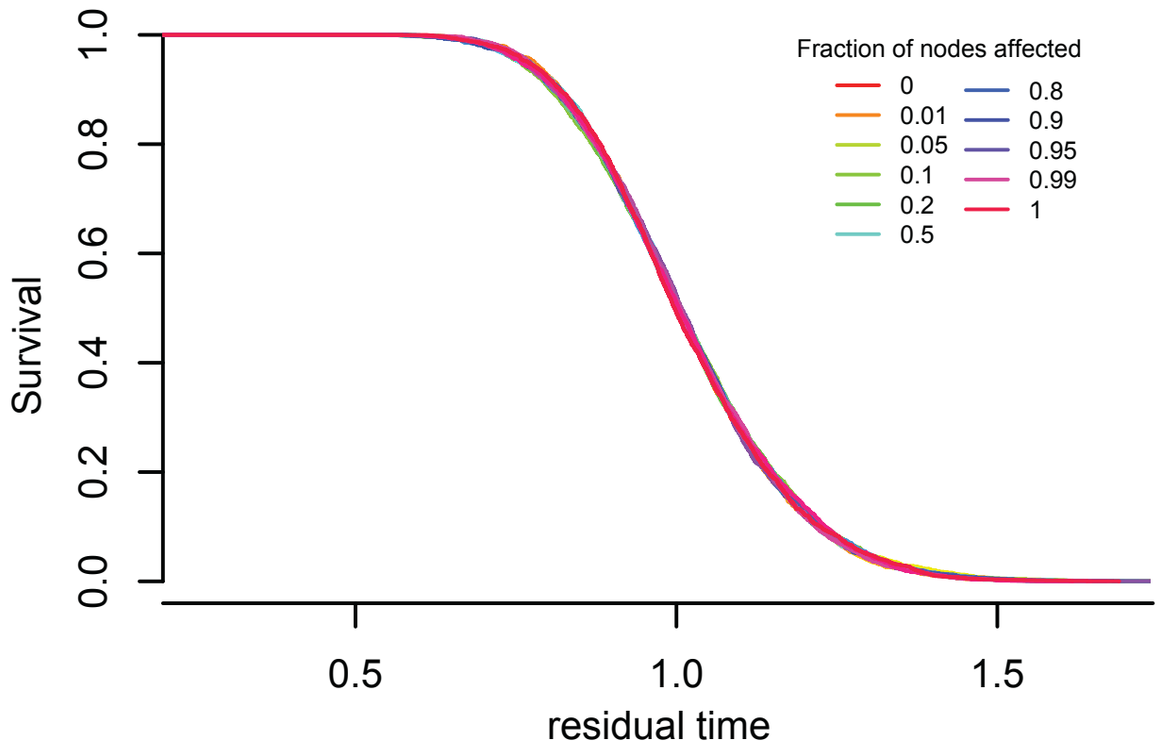


scale-free

Vural, D. C., Morrison, G. & Mahadevan, L. Aging in complex interdependency networks. *Phys. Rev. E* **89**, 022811 (2014)

Perturbing dependency networks





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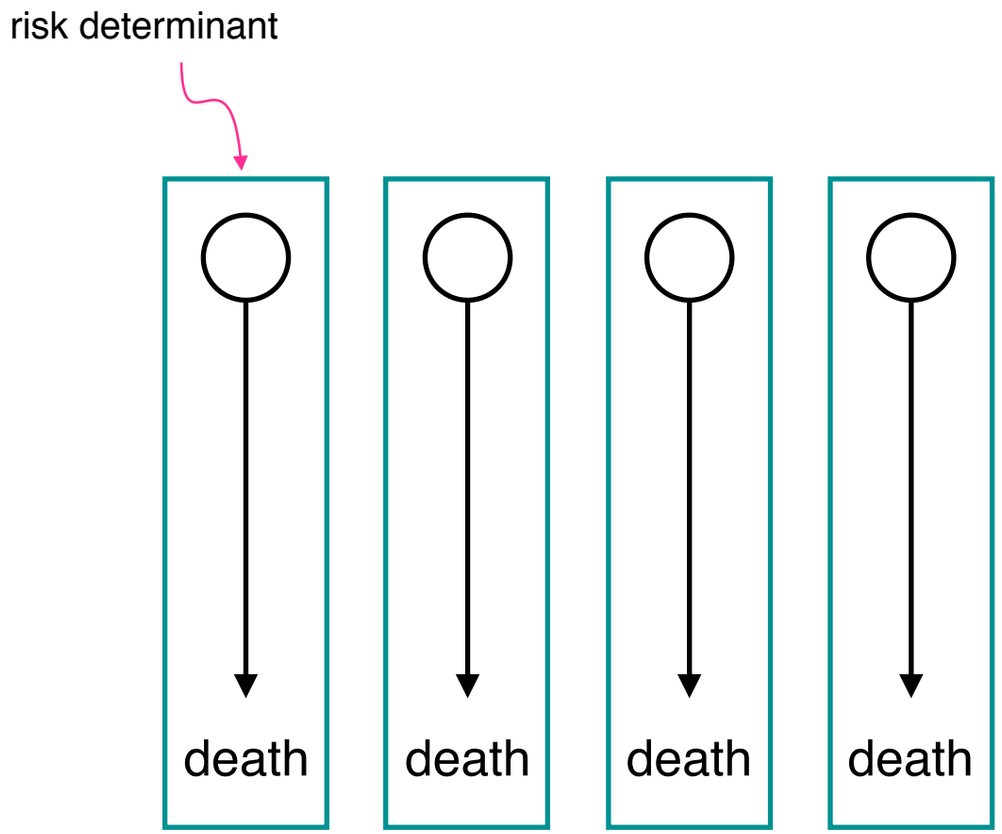
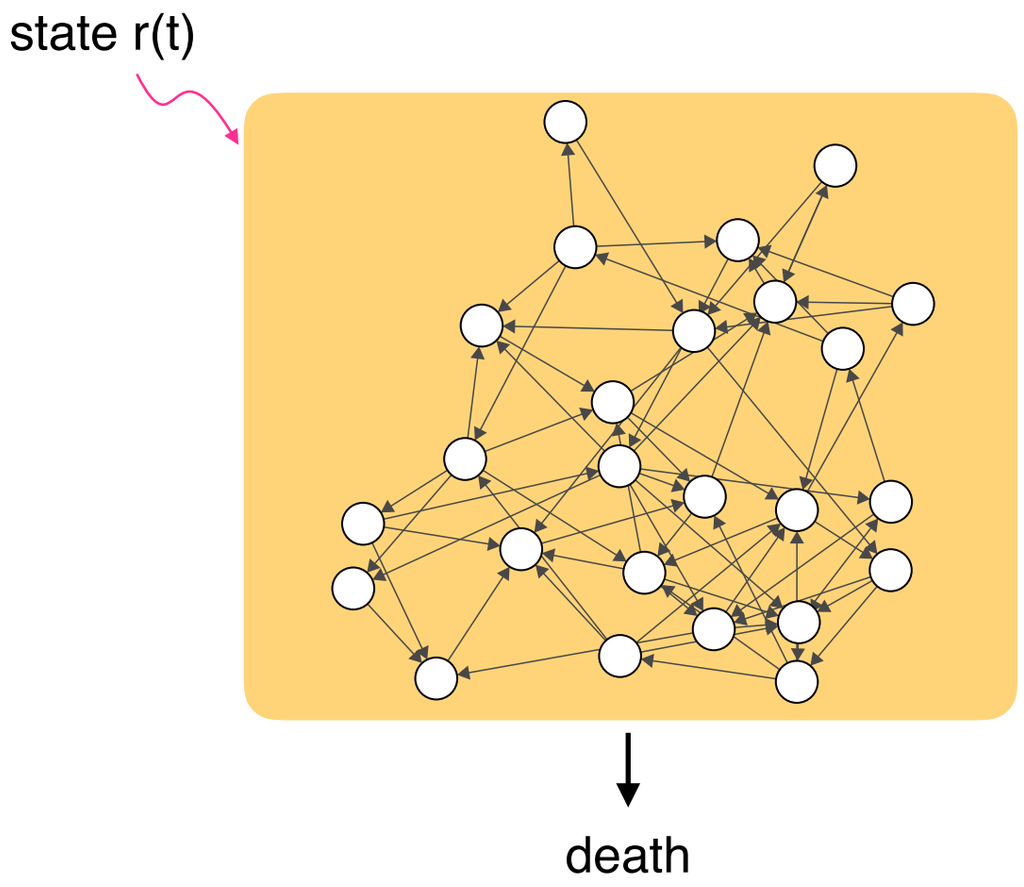


competing (independent) risks model



dependency network model

DNM suggests a state description of organismic aging independent of molecular details.

What does temporal scaling mean?

The *process* of aging can be described in terms of a state variable and must be invariant to time scale transformations.

state variable ("resilience" or some such)

$$-\frac{d}{dt}r(t) = k_r \; F[r(t)]$$

possibly

$$-\frac{d}{dt}r(t) = \frac{1}{\lambda} \; k \; F[r(t)]$$

biology
(of damage control)

physics
(of damage production)

Thank you!

Nick Stroustrup

(in nominal order)

Winston Anthony	→	WUSTL
Javier Apfeld	→	Northeastern
Adam Gomez	→	UCLA
Vivek Gowda	→	Dana Farber
Isaac F. López-Moyado	→	UCSD
Zachary M. Nash	→	UNC Chapel Hill
Bryne Ulmschneider	→	UCSF

Glenn Foundation

Millions of *C. elegans* →