Skolkovo Institute of Science and Technology

Senescent cell turnover slows with age providing an explanation for the Gompertz law

Computational biology of aging final project

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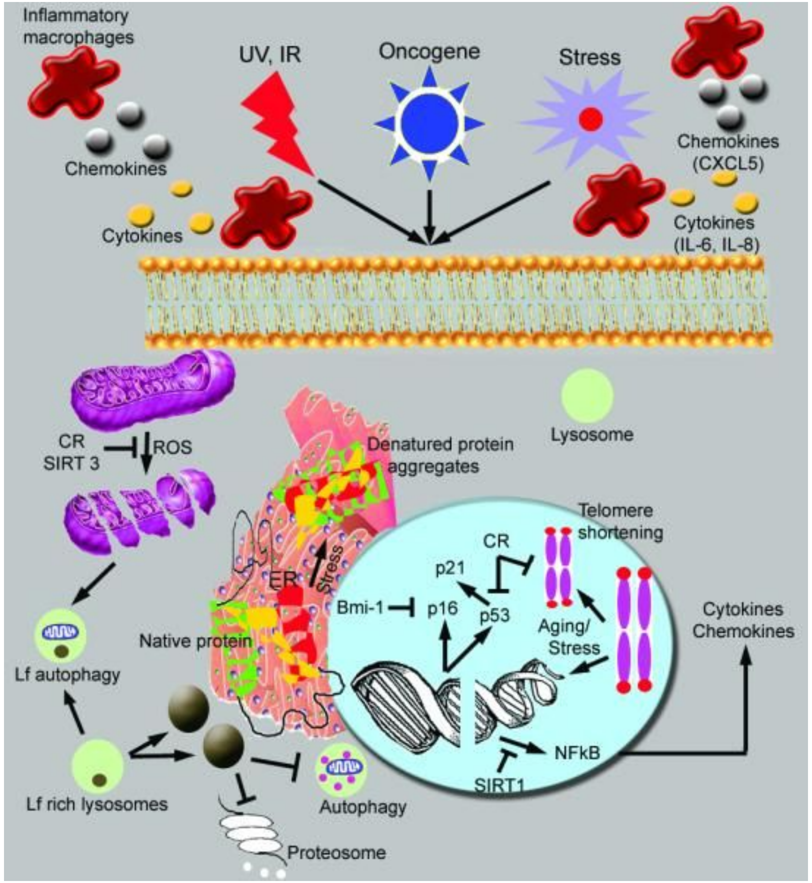
Moscow, 18th December, 2023

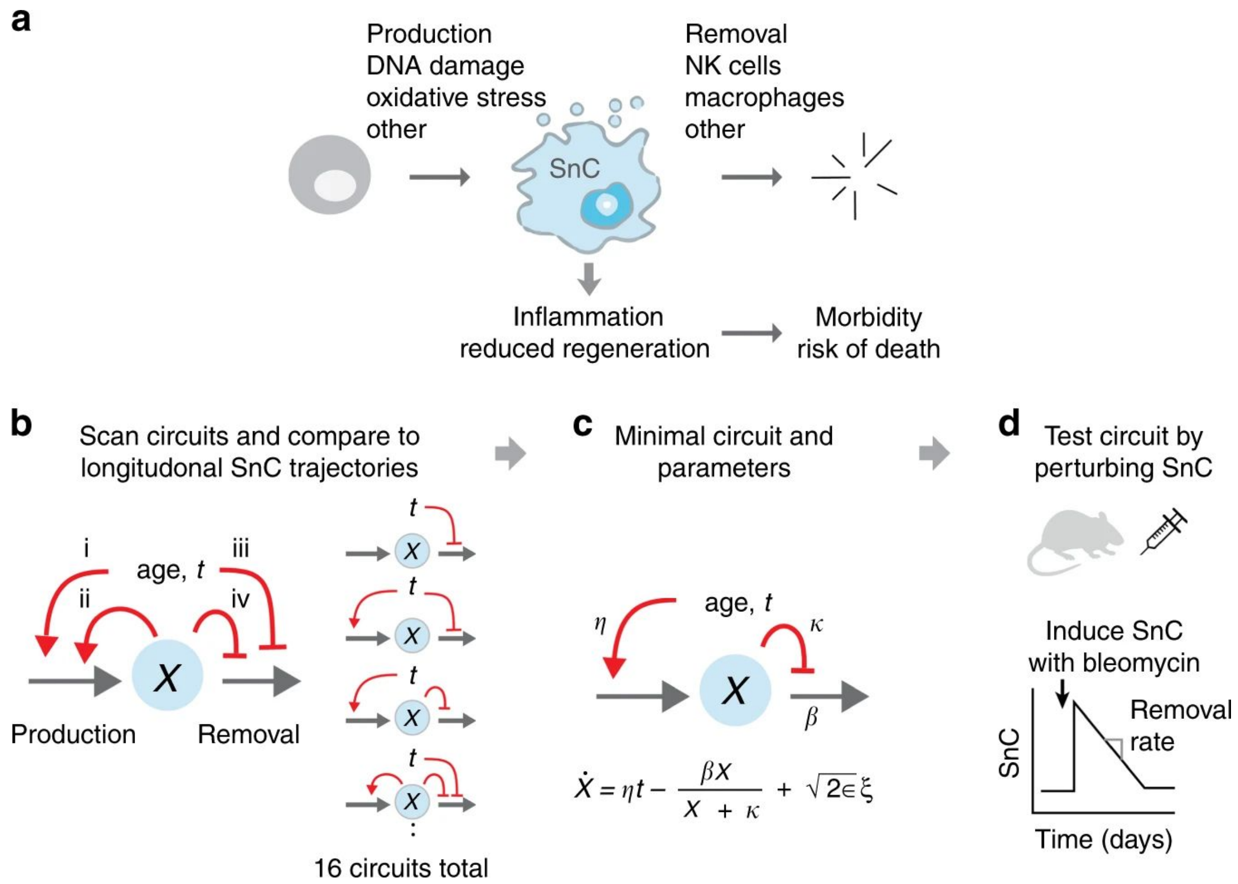
Chief premises of research

1. Implicitly, aging and generation of senescent cells is a stochastic process
2. Death is modeled as a first-passage time process
3. SnC abundance was measured using a luciferase reporter for the expression of p16^{INK4a} and SA-β-Gal



Rayess, Hani et al. "Cellular senescence and tumor suppressor gene p16." *International journal of cancer* vol. 130,8 (2012): 1715-25. doi:10.1002/ijc.27316

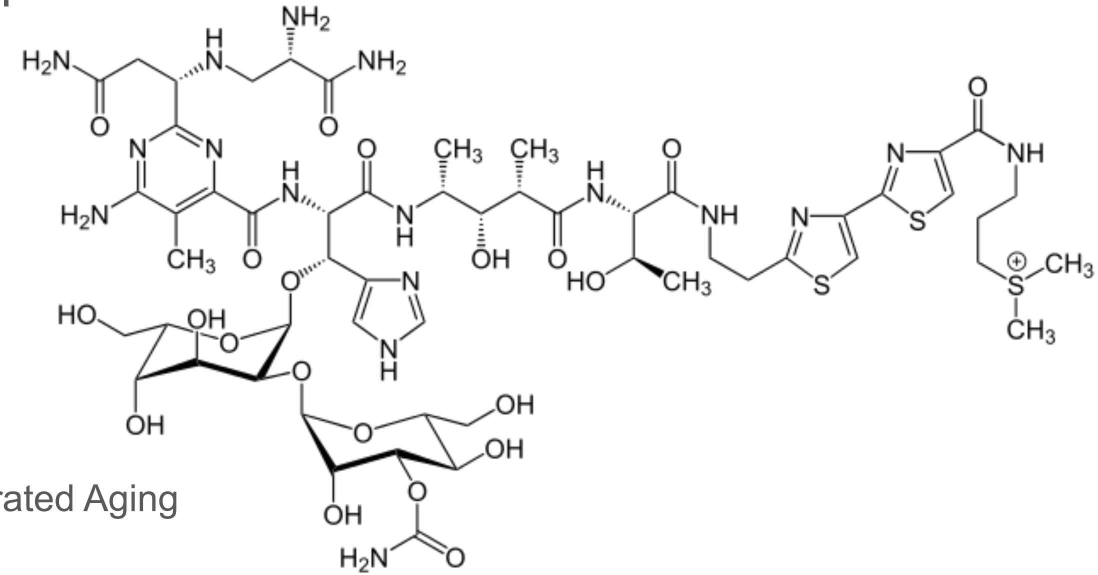
Workflow



Karin, O., Agrawal, A., Porat, Z. *et al.* Senescent cell turnover slows with age providing an explanation for the Gompertz law. *Nat Commun* 10, 5495 (2019).
10.1038/s41467-019-13192-4

Weak points - molecular biology

- Systematic vs. organ specific models of senescence
- Why choose lungs?
- Single-dose bleomycin may show spontaneous regression after 28 days, better use multi-dose protocol



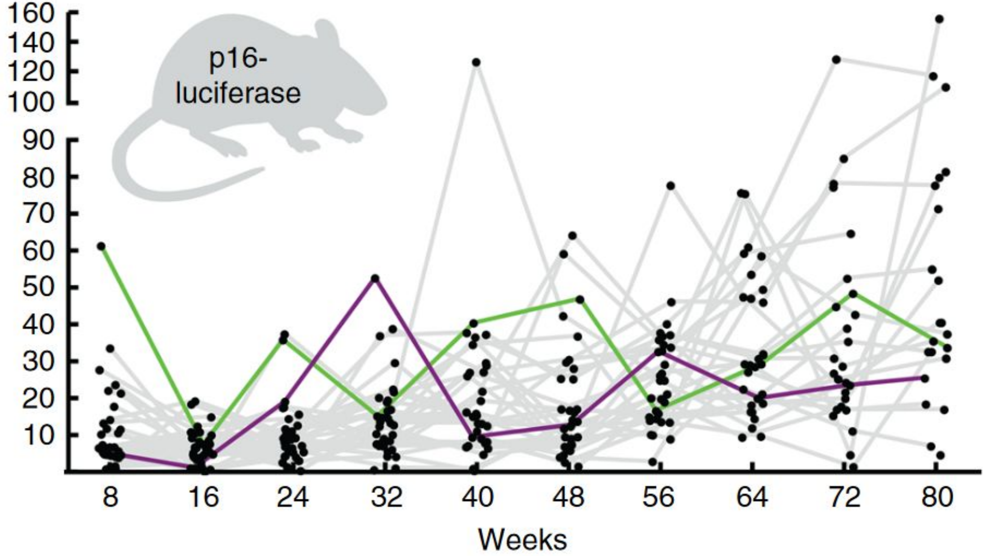
Cai, N.; Wu, Y.; Huang, Y. Induction of Accelerated Aging in a Mouse Model. Cells 2022, 11, 1418. doi:10.3390/cells11091418

Stochastic modeling, longitudinal trajectories SnCs in mice

Basic SR (saturating removal) model

$$\dot{X} = \eta t - \frac{\beta X}{\kappa + X} + \sqrt{2\epsilon}\,\xi_t$$

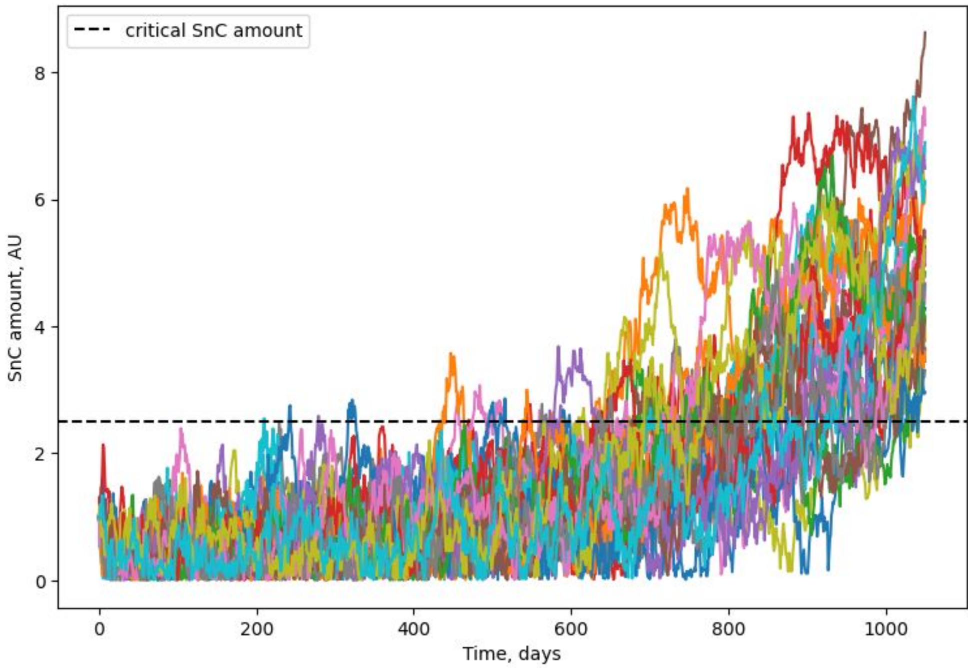
Grid search parameters:
□ - e^{-10}, e^{-9}, …, e^{0}, e^{1}
ϵ - e^{-10}, e^{-9}, …, e^{0}, e^{1}
η - e^{-10}, e^{-9}, …, e^{0}, e^{1}
κ - e^{-10}, e^{-9}, …, e^{0}, e^{1}
> 20k parameters in total, 200 simulations for every sub-trajectory

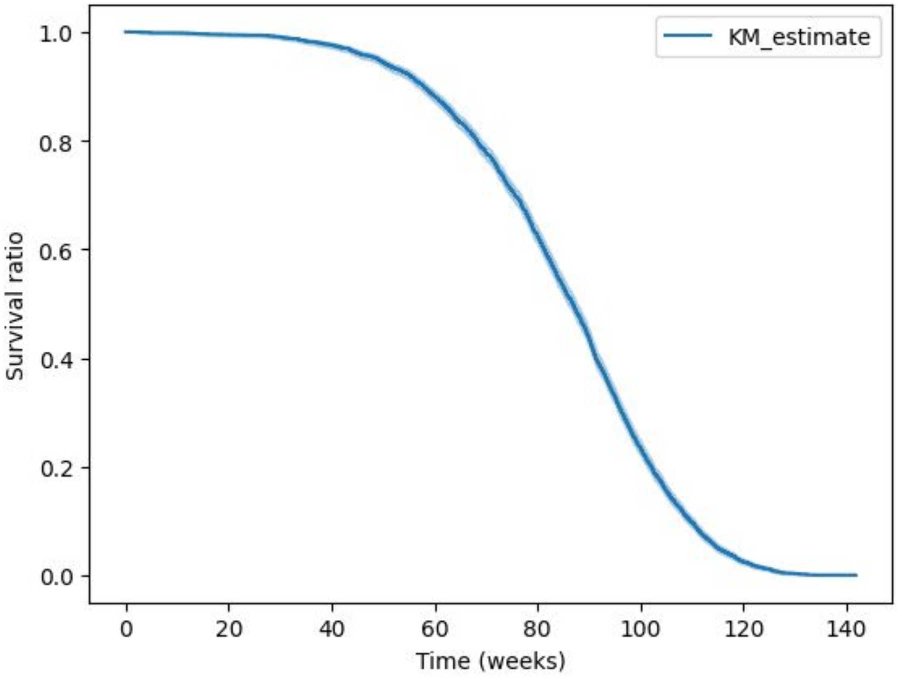


Log-likelihood estimation of parameters: □ - 0.135, η - $1.23*10^{-4}$, κ - 1.00 , ϵ - 0.0183

Karin, O., Agrawal, A., Porat, Z., Krizhanovsky, V., & Alon, U. (2019). Senescent cell turnover slows with age providing an explanation for the Gompertz law. Nature Communications, 10, 5495.

Gompertz law as first time passage consequence





Simulation of Drosophila survival curve.

Drosophlia

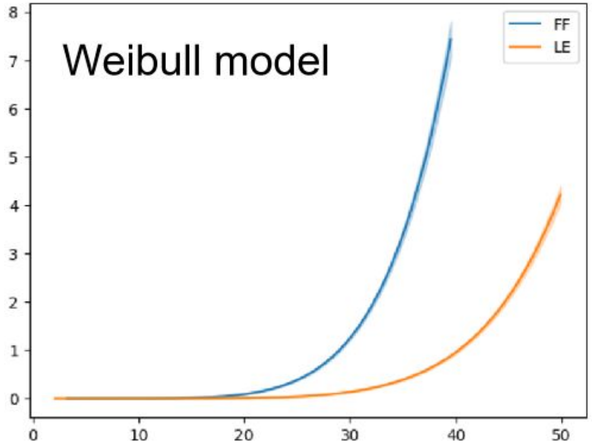
Fully Fed (FF)

- β = 1 h−1
- κ = 1
- ε = 1 h−1
- η = 0.03 day -1 h−1
- XC = 15

Lifespan-extending (LE) dietary

- β = 1 h−1
- κ = 1
- ε = 1 h−1
- η = 0.02 day -1 h−1
- XC = 15

- Simulate data of 4000 individuals.



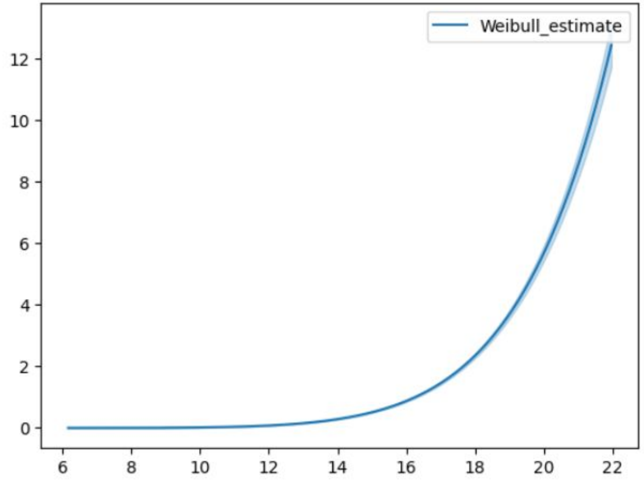
- Drosophlia's Data were extracted from the figures of the original manuscripts

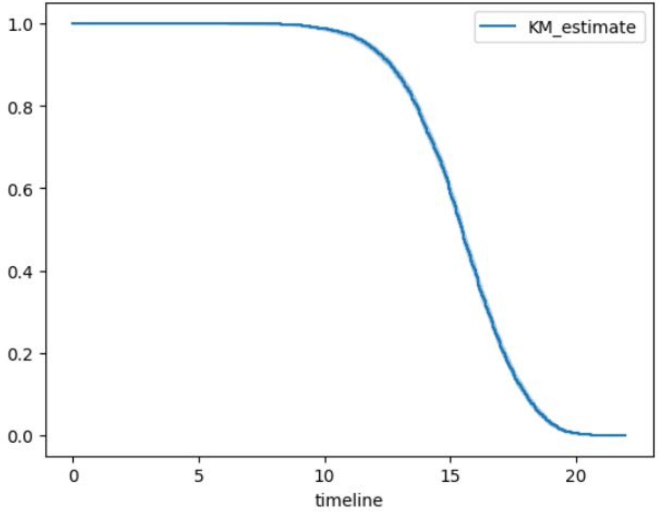
Simulation of C. elegans survival curve.

C.elegans

- β = 1 h−1
- κ = 1
- ε = 1 h−1
- η = 0.07 day -1 h−1
- XC = 20

- Simulate data of 4000 individuals.





Improvements

- Experimental setup should have been fine-tuned
- Spatial and temporal resolutions should be taken into account
- In the simulated survival curve analysis of Drosophila and C. elegans, β, κ and ε were initially set, and there may be certain problems in looking only for eta. So a better approach is to be like mice.

Contributions

- Busygin Sergei - experimental setup analysis
- Song Zhenzhen - fly and worm survival curves simulations based on SR model
- Voropaev Ivan - SR model implementation via Ito process simulation, parameters search for mice, mice survival curves based on SR model