Health, mortality and Human Aging

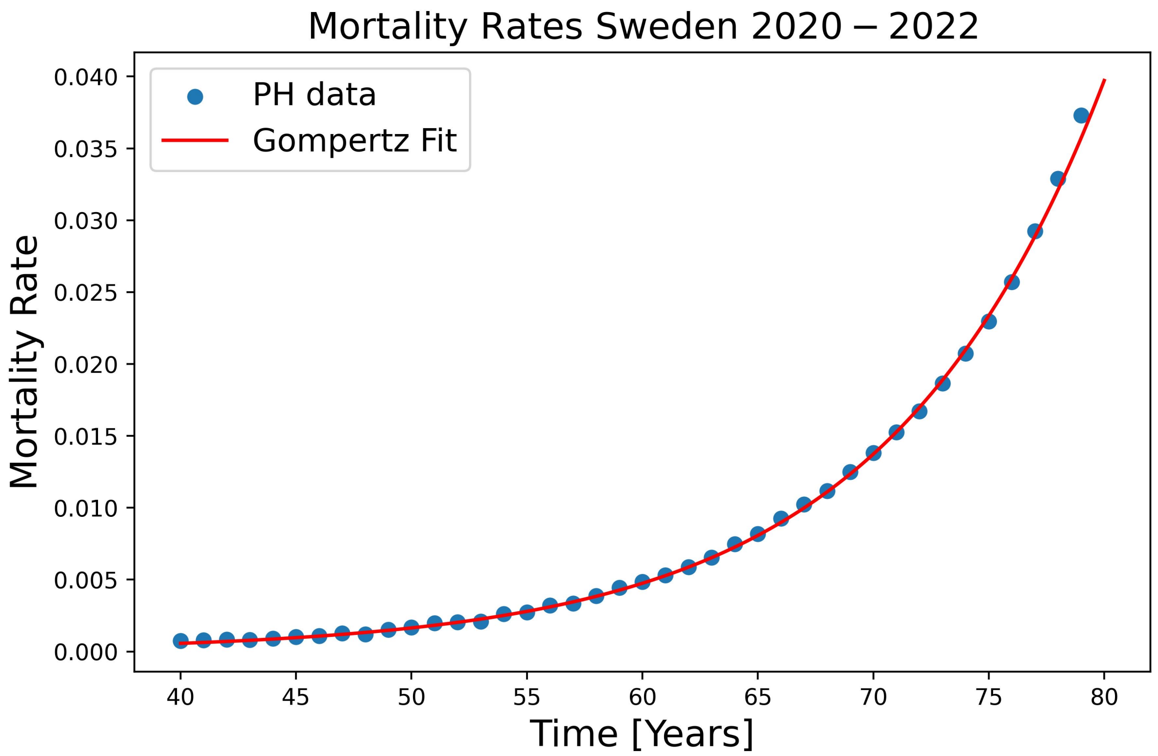
Rafael Enrique Velásquez Rojas

DALHOUSIE UNIVERSITY

Gompertz Law to model the exponential increment

$$\boxed{\mu(t) = R_0 e^{\beta t}}$$

Gompertz Law exponential mortality



Strehler-Mildvan Correlation

$$\boxed{\mu(t) = R_0 e^{\beta t}}$$

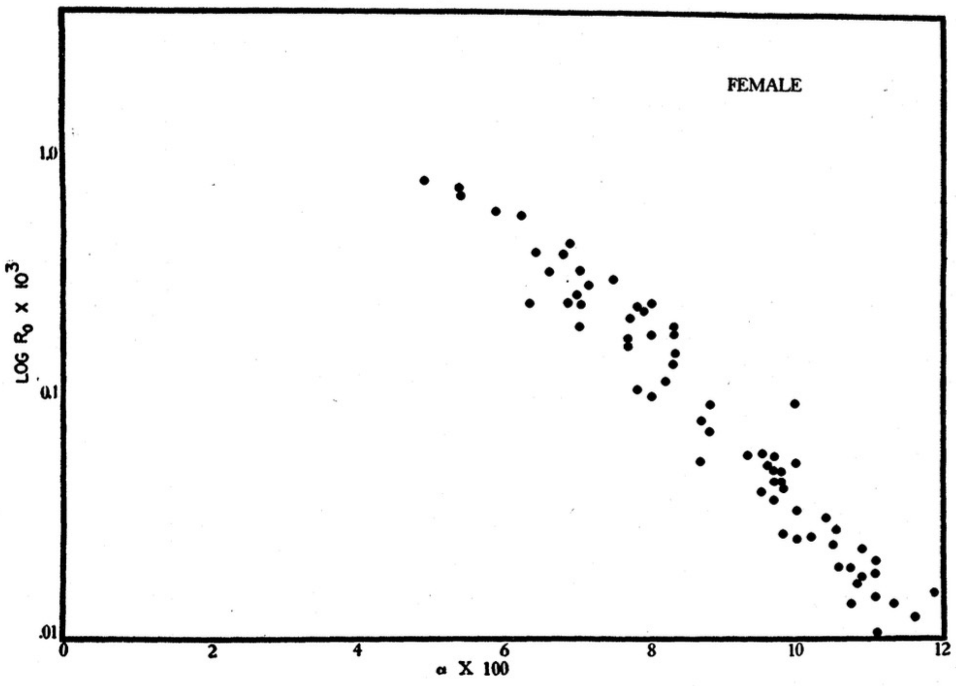
Gompertz Law exponential mortality

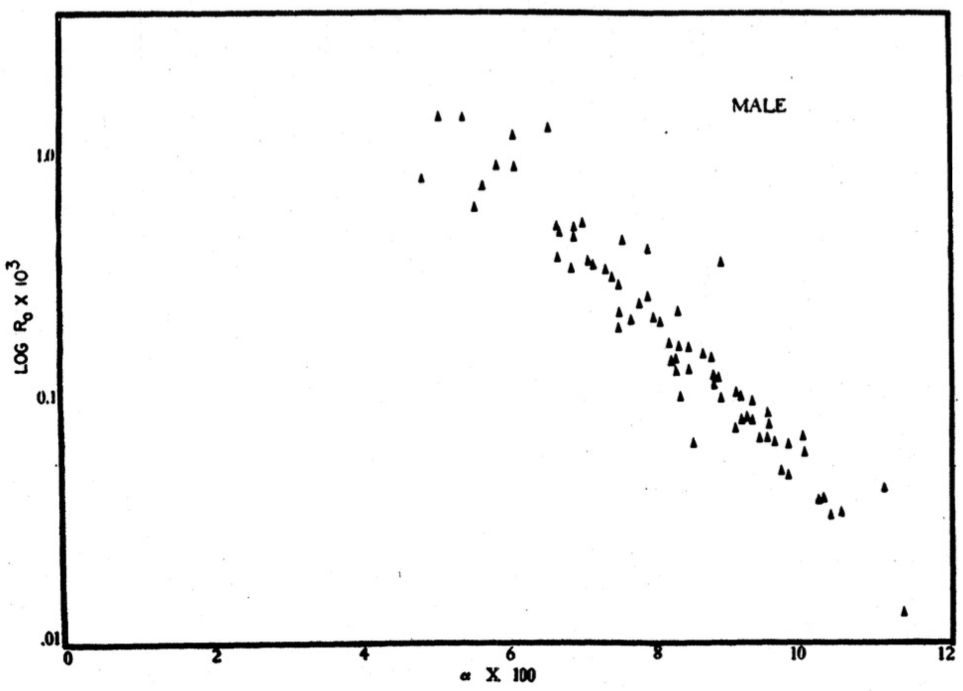
$$\boxed{\ln(R_0) - \ln(K) = -\frac{\beta}{B}}$$

Correlation between two parameters of Gompertz Law

High initially mortality rate $\ln(R_0)$ is associate with a low rate of increase of mortality rate β

Strehler-Mildvan Correlation





$$\boxed{\ln(R_0) - \ln(K) = -\frac{\beta}{B}}$$

High initially mortality rate $\ln(R_0)$ is associate with a low rate of increase of mortality rate β

Developing a model for frailty index and mortality

$$\frac{df}{dt} = (1 - f) \cdot a \cdot (1 + bt) - f \cdot r \cdot (1 - st)$$

Option 1 for frailty index model

$$\frac{df}{dt} = (1 - f) \cdot a \cdot (1 + bf) - f \cdot r \cdot (1 - sf)$$

Option 2 for frailty index model

$$\mu = \mu_0 f(t)^c$$

Option 1 for mortality rate model

$$\mu = \mu_0 e^{d \cdot f}$$

Option 2 for mortality rate model

Why these proposals for the models?

Why these proposals for the models?

Abstract As an organism ages, its health-state is determined by a balance between the processes of damage and repair. Measuring these processes requires longitudinal data. We extract damage and repair transition rates from repeated observations of binary health attributes in mice and humans to explore robustness and resilience, which respectively represent resisting or recovering from damage. We assess differences in robustness and resilience using changes in damage rates and repair rates of binary health attributes. We find a conserved decline with age in robustness and resilience in mice and humans, implying that both contribute to worsening aging health – as assessed by the frailty index (FI). A decline in robustness, however, has a greater effect than a decline in resilience on the accelerated increase of the FI with age, and a greater association with reduced survival. We also find that deficits are damaged and repaired over a wide range of timescales ranging from the shortest measurement scales toward organismal lifetime timescales. We explore the effect of systemic interventions that have been shown to improve health, including the angiotensin-converting enzyme inhibitor enalapril and voluntary exercise for mice. We have also explored the correlations with household wealth for humans. We find that these interventions and factors affect both damage and repair rates, and hence robustness and resilience, in age and sex-dependent manners.

Farrell, S., Kane, A. E., Bisset, E., Howlett, S. E., & Rutenberg, A. D. (2022). Measurements of damage and repair of binary health attributes in aging mice and humans reveal that robustness and resilience decrease with age, operate over broad timescales, and are affected differently by interventions. *Elife*, *11*, e77632.

Repair and damages nodes model

$$\frac{d}{dt}f_i(t) = (1 - f_i)\lambda_i^d(t) - f_i\lambda_i^r(t)$$

$$f_i(t) = \frac{N_{damage}}{N_{total}}$$

$$(1 - f_i) \stackrel{\text{def}}{=} attributes\ available\ for\ damage$$

$$f_i \stackrel{\text{def}}{=} attributes\ available\ for\ repair$$

Connection with our proposed model

$$\frac{d}{dt} f_i(t) = (1 - f_i)\lambda_i^d(t) - f_i\lambda_i^r(t)$$

$$\frac{df}{dt} = (1 - f) \cdot a \cdot (1 + bt) - f \cdot r \cdot (1 - st)$$

Number of Repaired and Damage Nodes

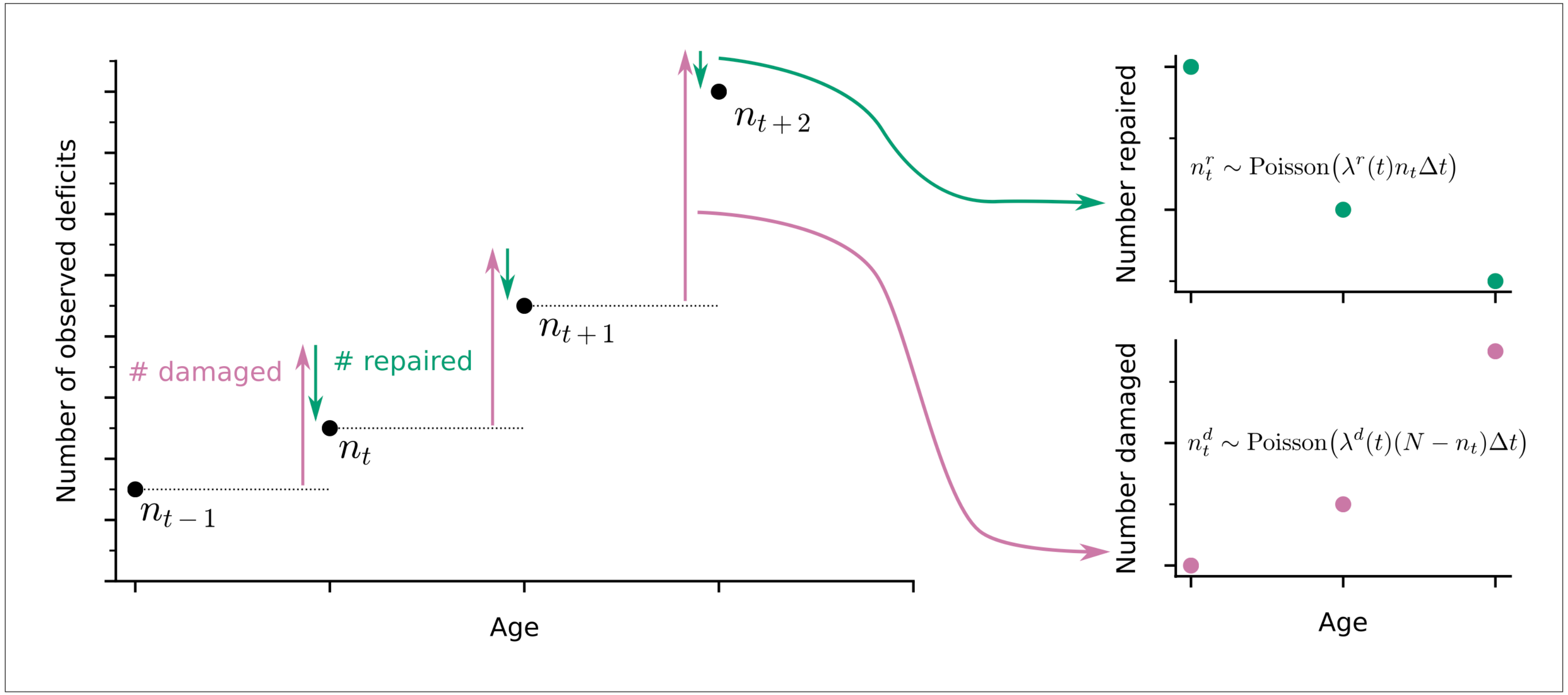
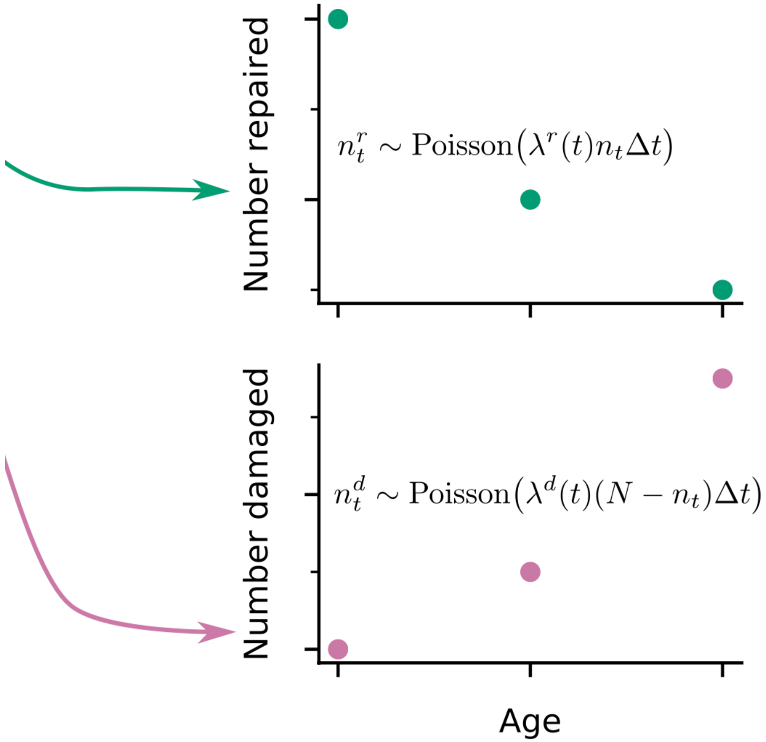


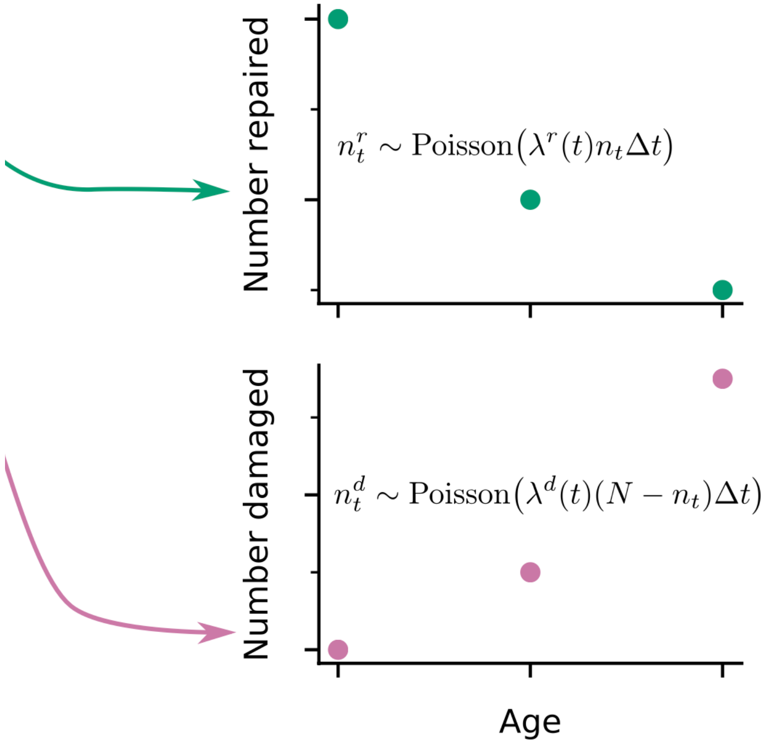
Figure 1. Extracting damage and repair from the longitudinal observation of binary health deficits. Instead of just considering the Frailty Index (FI) or net count of deficits at each age n_t (i.e. FI multiplied by the total number N of deficits considered) as a measure of health, we separately consider the number of deficits damaged n_t^d or repaired n_t^r within a time interval Δt. Time-dependent damage $\lambda^d(t)$ and repair $\lambda^r(t)$ rates are extracted using Poisson models for the counts of repaired or damaged deficits.

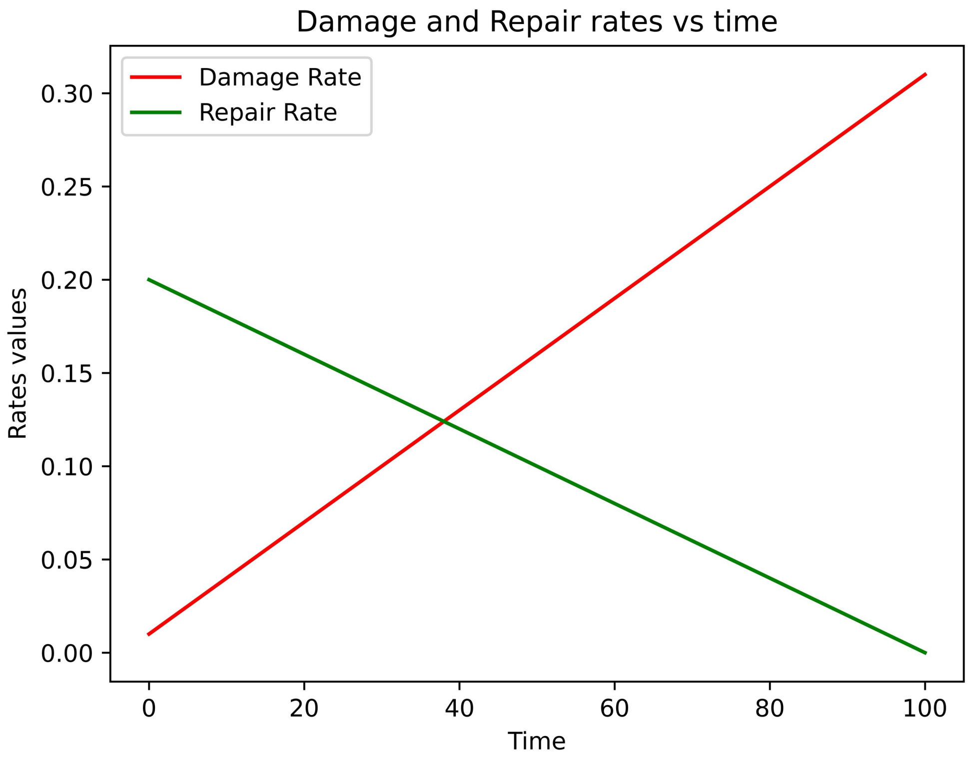
Number of Repaired and Damage Nodes



This is the behavior of the repair and damage rates that we need to obtain the desired behavior for the model.

Number of Repaired and Damage Nodes





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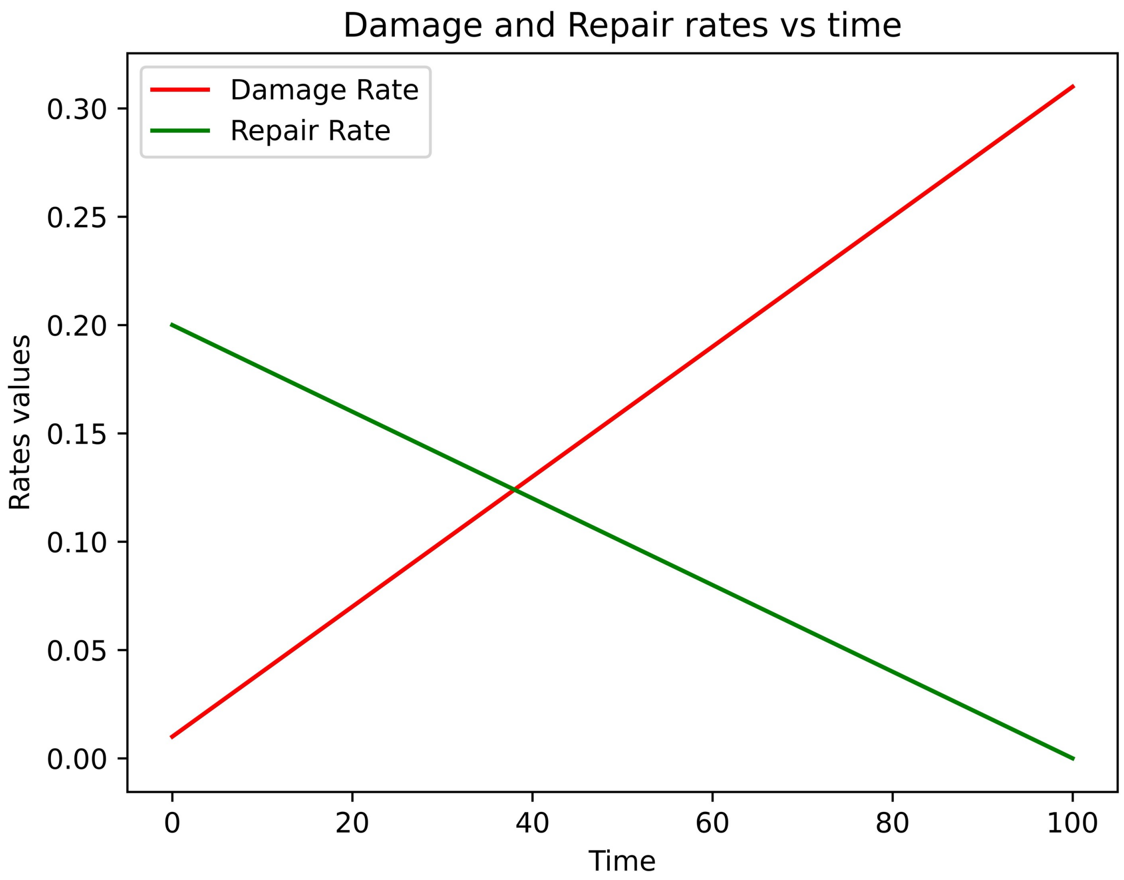
Number of Repaired and Damage Nodes



$$\lambda_i^d(t) = a \cdot (1 + bt)$$ **Damage rate function**

$$\lambda_i^r(t) = r \cdot (1 - st)$$ **Repair rate function**

This is the behavior of the repair and damage rates that we need to obtain the desired behavior for the model.

Guesses for the parameters

1) Both the repair and damage rate must be positive for all times.

$$\lambda_i^d(t) = a \cdot (1 + bt) \quad \geq 0$$

$$\lambda_i^r(t) = r \cdot (1 - st) \quad \geq 0$$

$$\boldsymbol{a} \geq \mathbf{0} \qquad \boldsymbol{b} \geq \mathbf{0}$$

$$\boldsymbol{r} \geq \mathbf{0} \qquad \mathbf{0} \leq \boldsymbol{S} < \frac{\mathbf{1}}{\boldsymbol{t_{max}}}$$

Guesses for the parameters

2) The rate of repair should be greater than the rate of damage at the onset of age.

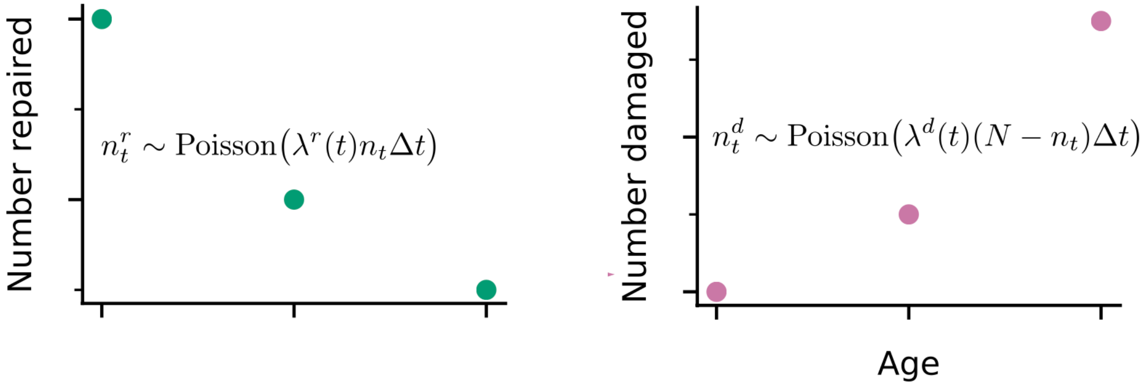
At least a t = 0

$$\lambda_i^r(t=0) \geq \lambda_i^d(t=0)$$

Why?

$$r \cdot (1 - st) \;\geq\; a \cdot (1 + bt)$$

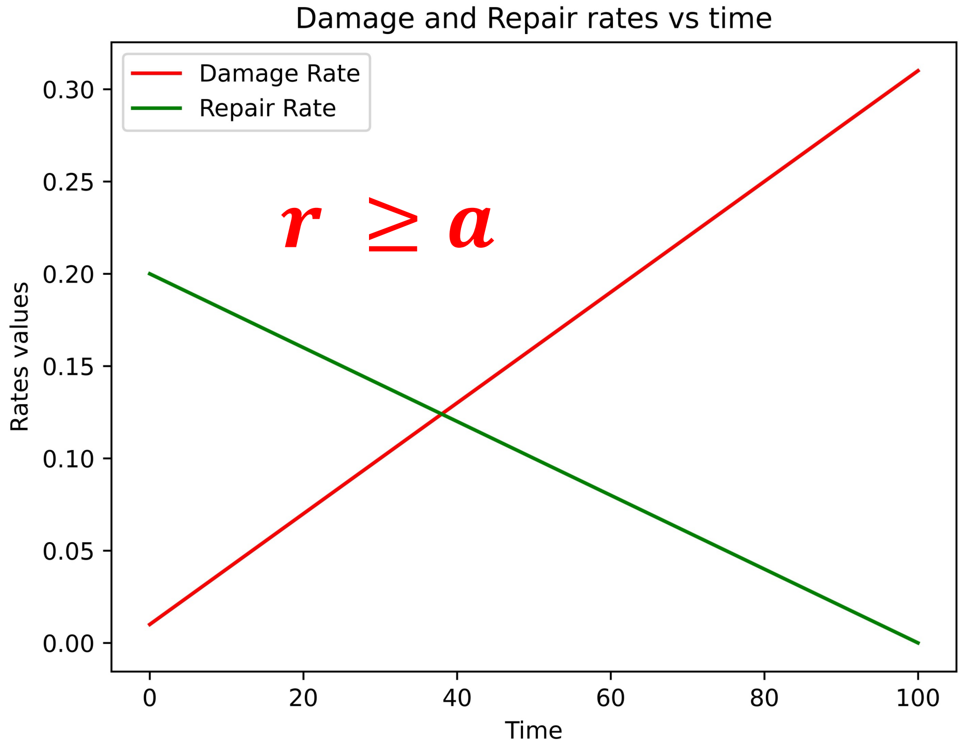
$$\boldsymbol{r \geq a}$$



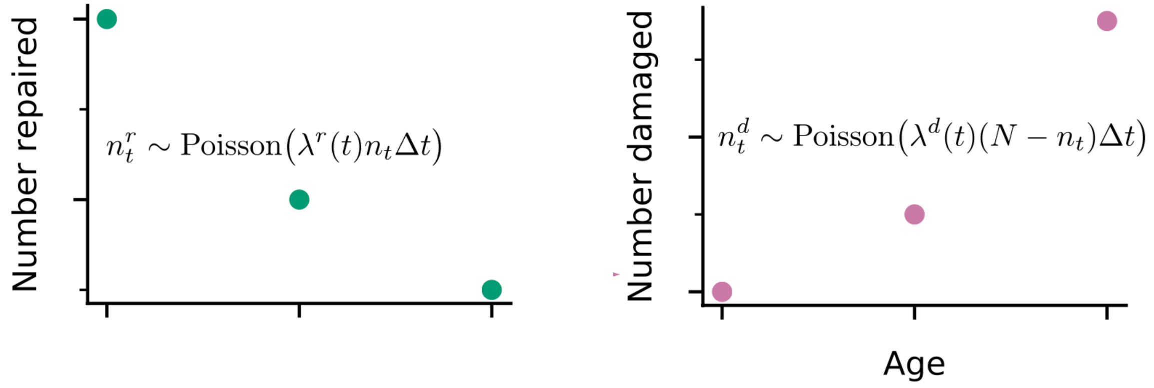
Guesses for the parameters

2) The rate of repair should be greater than the rate of damage at the onset of age.

At least a t = 0



Why?



Guesses for the parameters

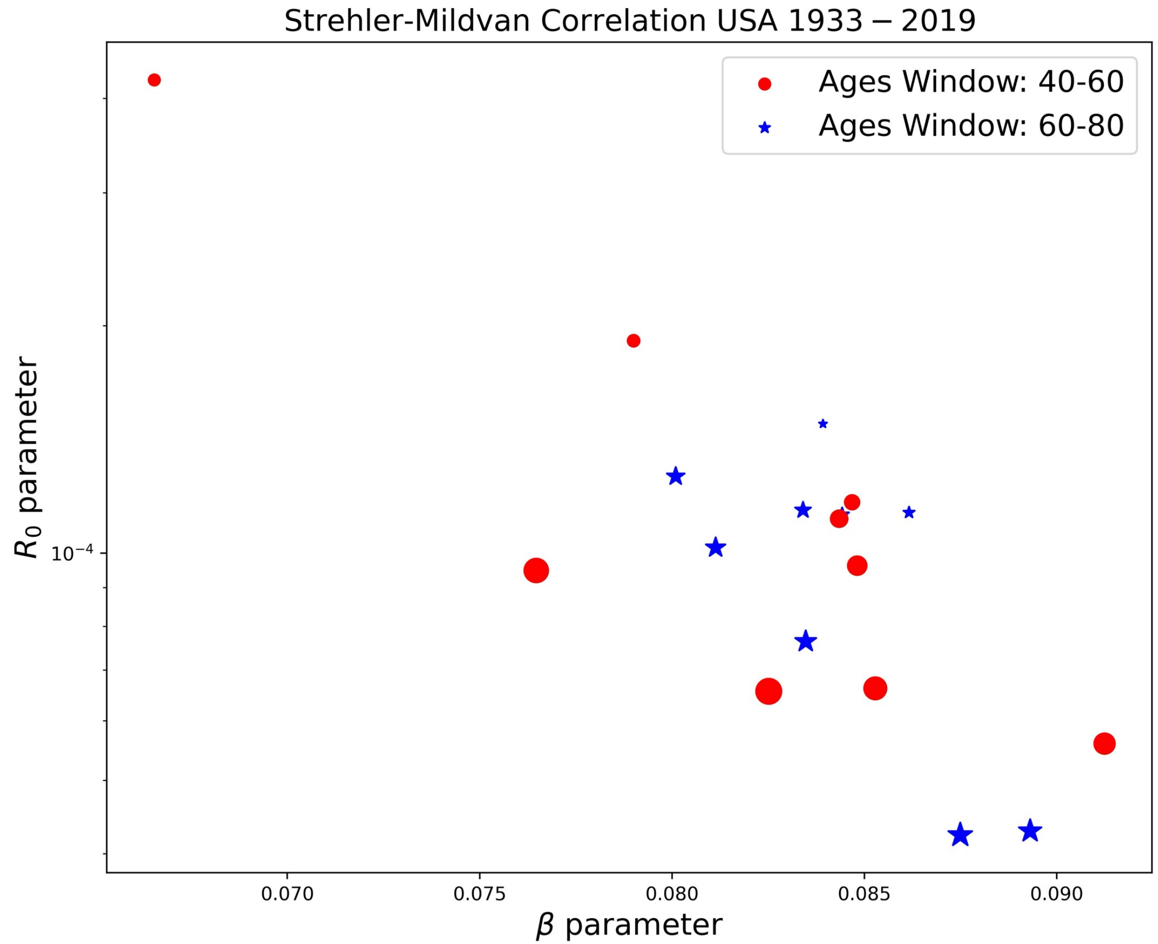
3) The rate of decrease of most physiological functions of humans beings is between 0.5 and 1.3 percent per year (???).

$$\lambda_i^d(t = 30) \geq 0.5$$

$$\lambda_i^d(t = 100) \leq 1.3$$

3) The rate of decrease of most physiological functions of human beings is between 0.5 and 1.3 percent per year after age 30, and is fit as well by a straight line as by any other simple mathematical function (5, 6) (see Fig. 2).

SM correlation is not a strong result



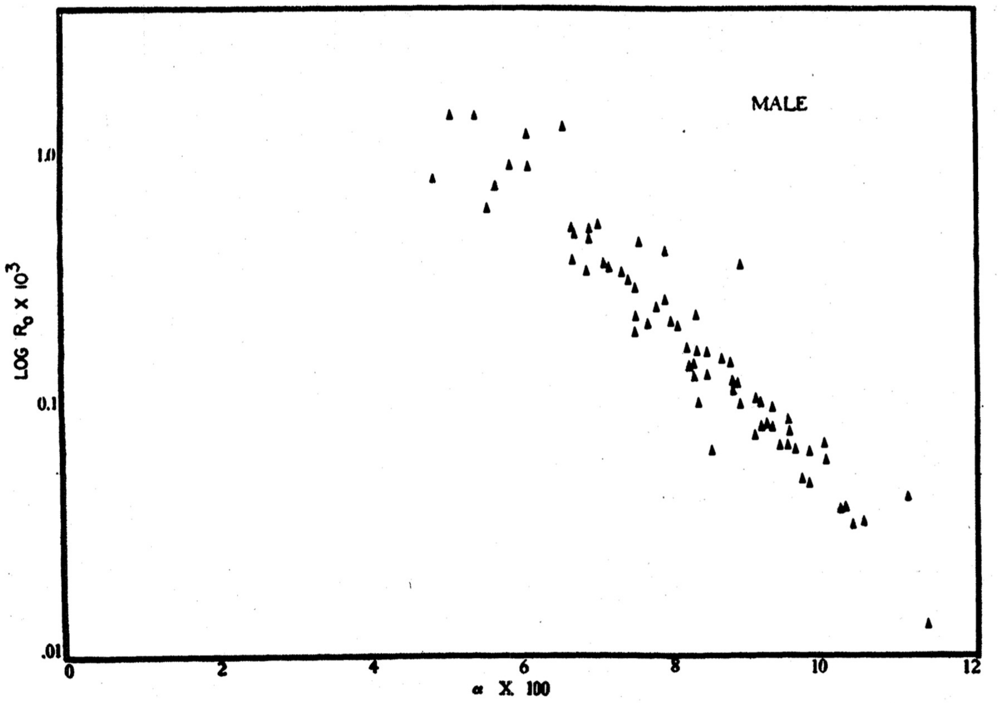
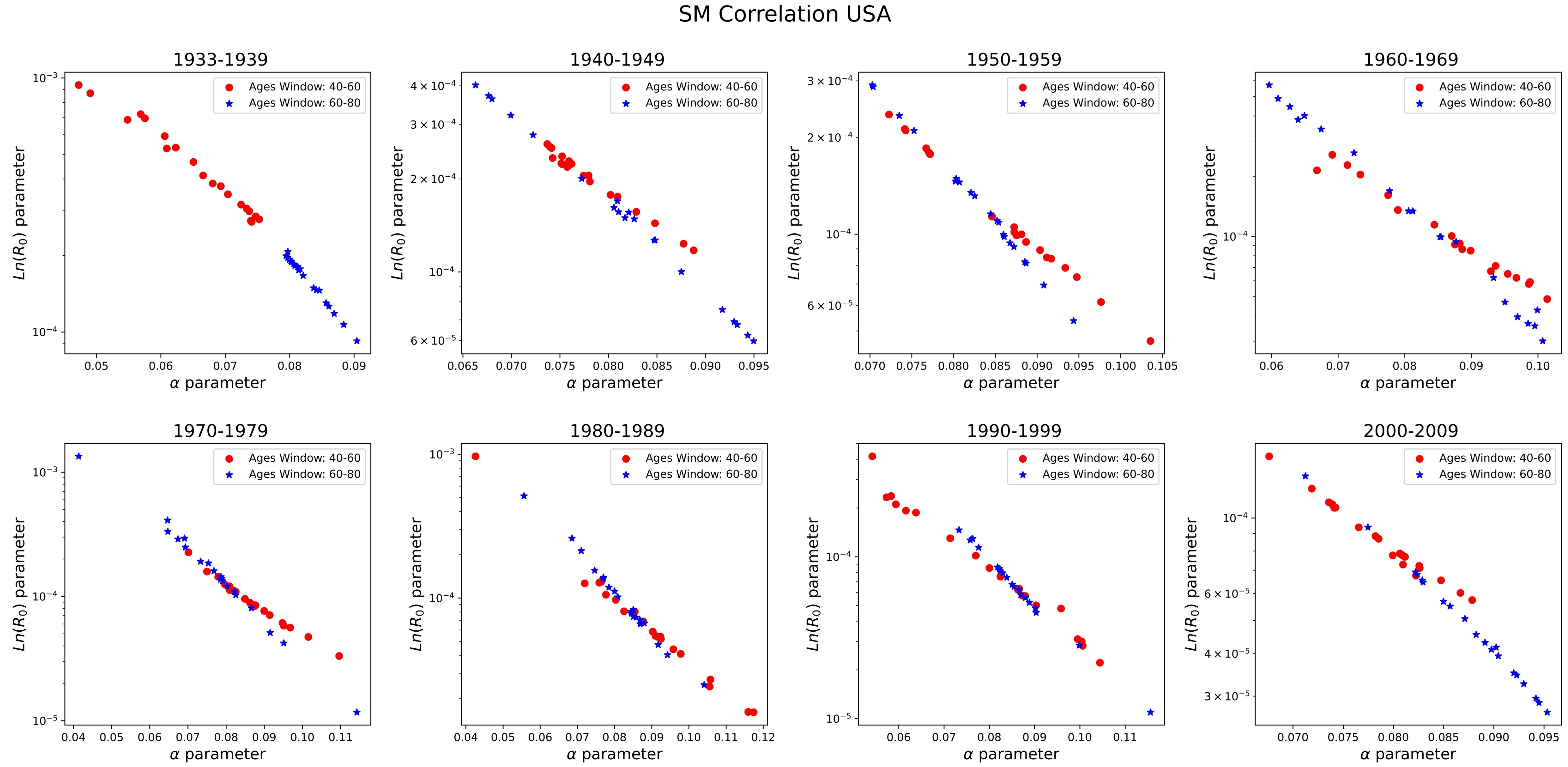
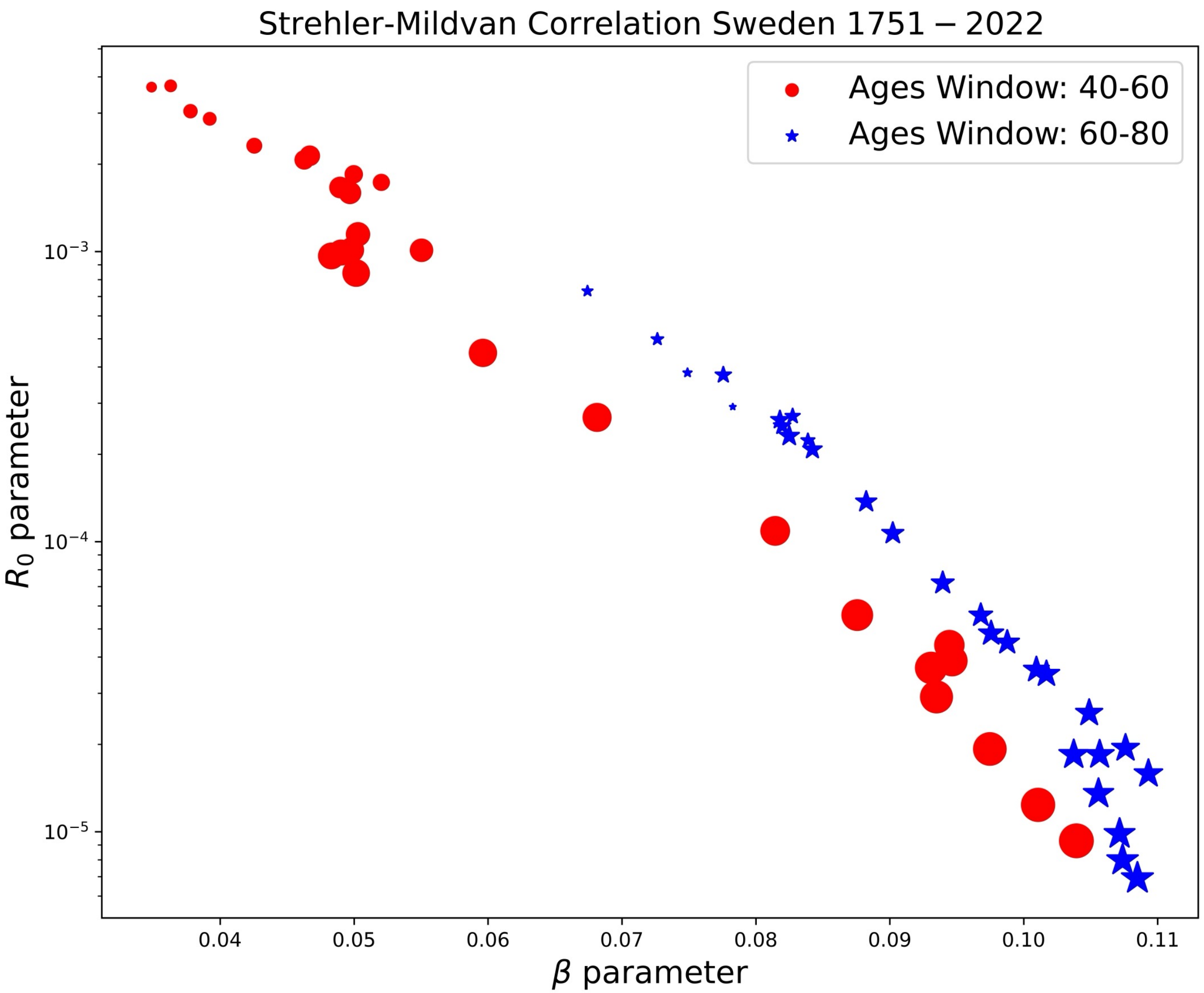


Fig. 3. Gompertz slope (α) versus logarithm of extrapolated hypothetical mortality rate at age 0 (ln R_0) for males of all countries for which adequate data are available (22). Each country's mortality rate was plotted individually on semi-log paper. A straight line was drawn between points from 35 to 85 (or 50 to 70, if large departures from linearity occurred), and the slopes and intercepts were measured or calculated. Only a few countries, whose Gompertz plots exhibited great irregularities, were excluded.

SM correlation is not a strong result



SM correlation is not a strong result



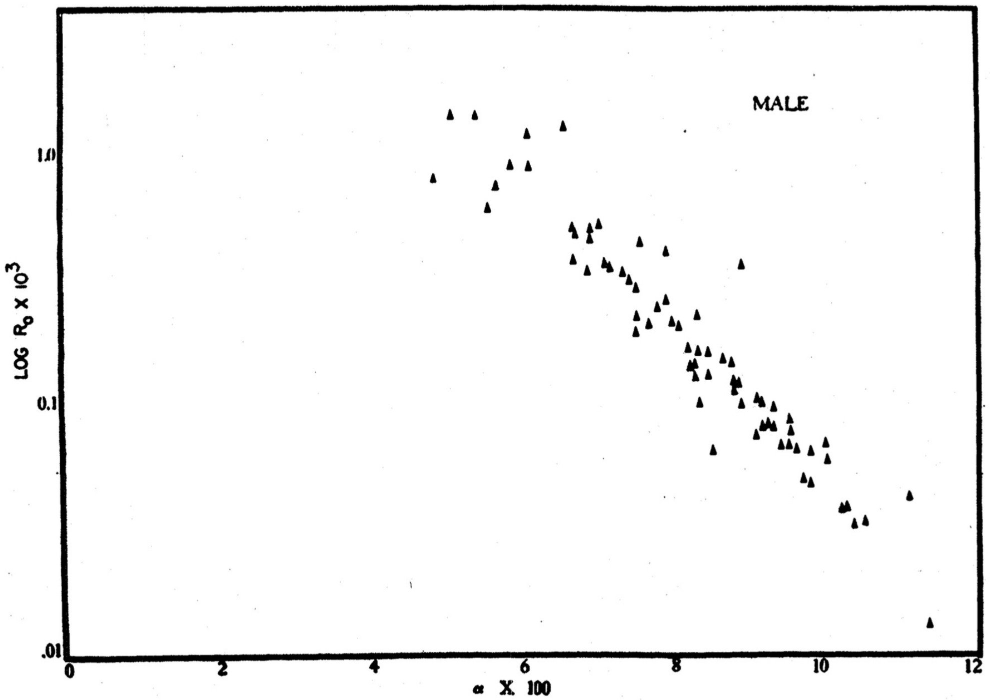
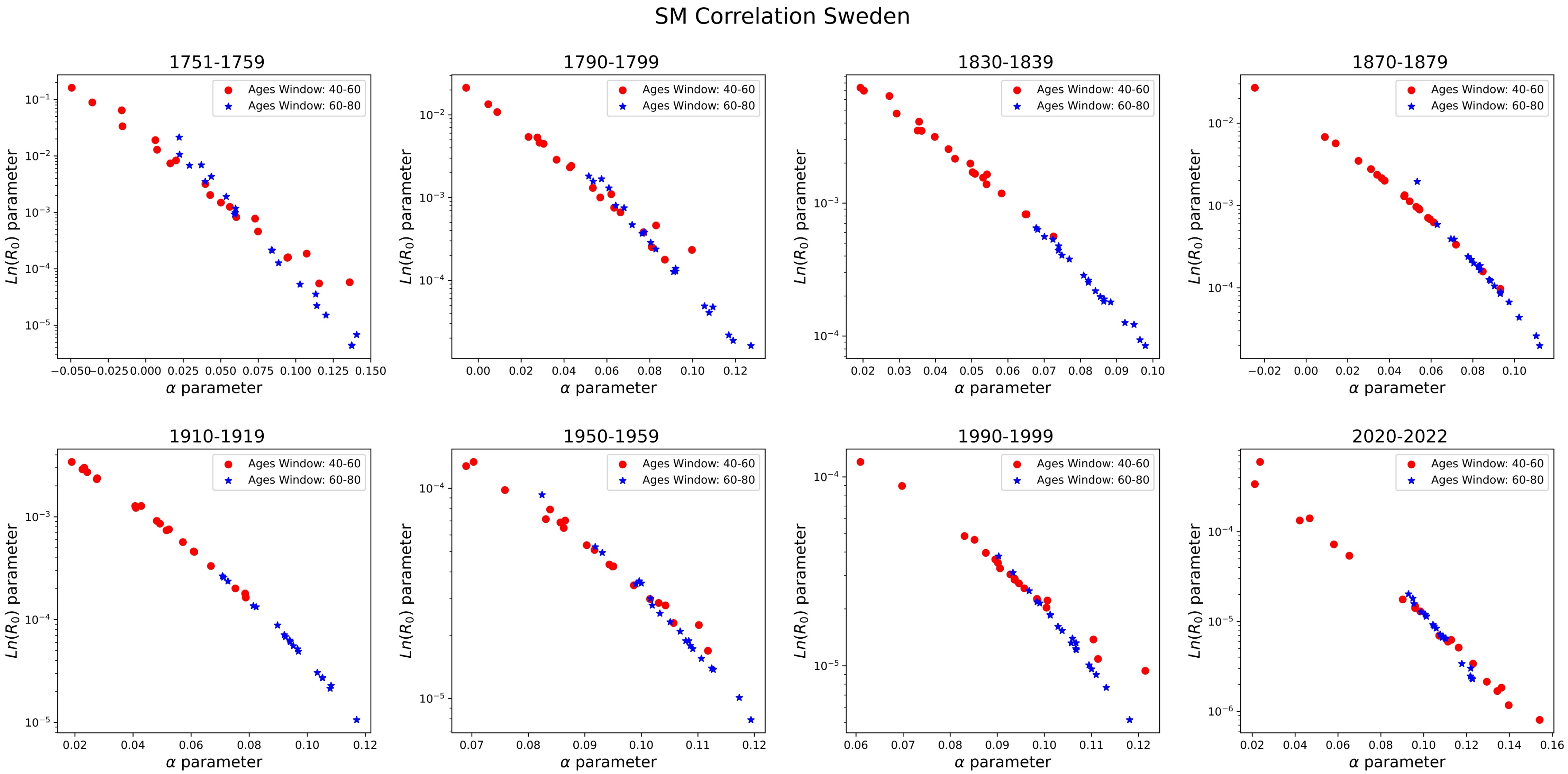


Fig. 3. Gompertz slope (α) versus logarithm of extrapolated hypothetical mortality rate at age 0 (ln R_0) for males of all countries for which adequate data are available (*22*). Each country's mortality rate was plotted individually on semi-log paper. A straight line was drawn between points from 35 to 85 (or 50 to 70, if large departures from linearity occurred), and the slopes and intercepts were measured or calculated. Only a few countries, whose Gompertz plots exhibited great irregularities, were excluded.

SM correlation is not a strong result



SM correlation is not a strong result (???)

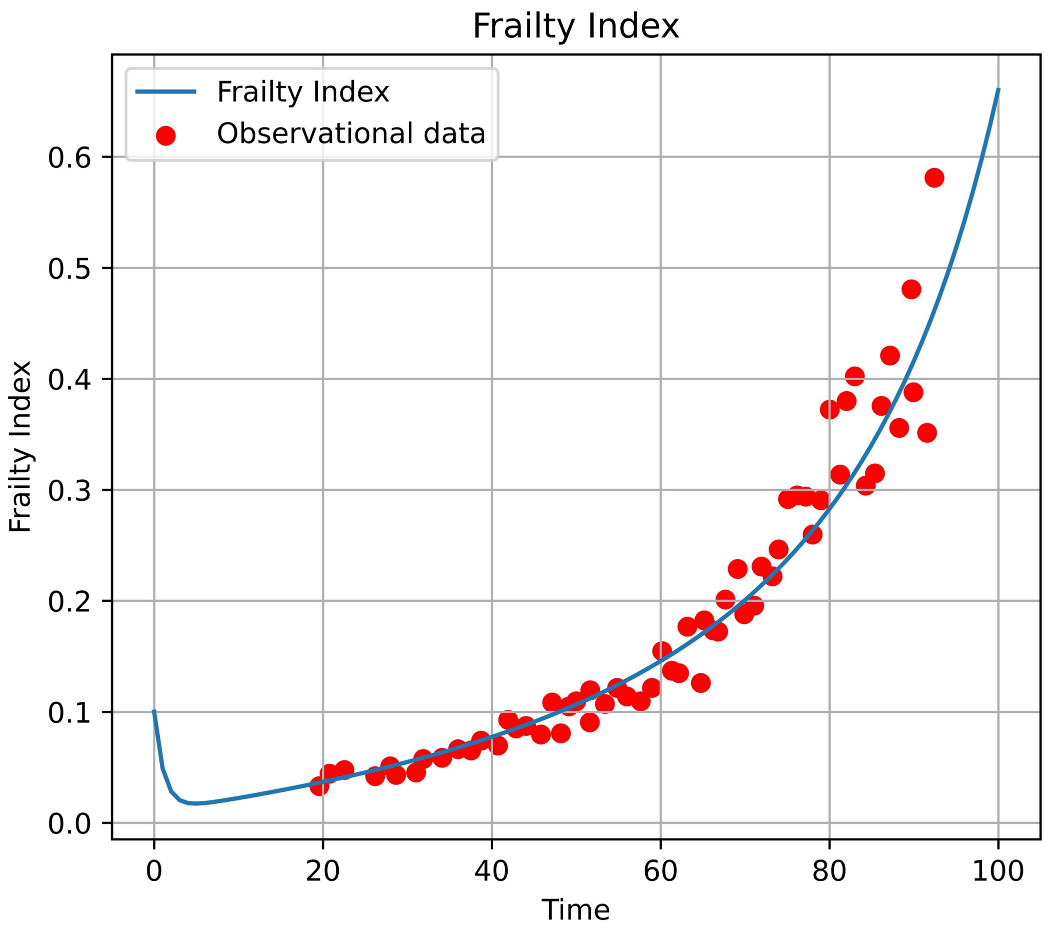
The reason why we should not calculate the SM correlation as in the

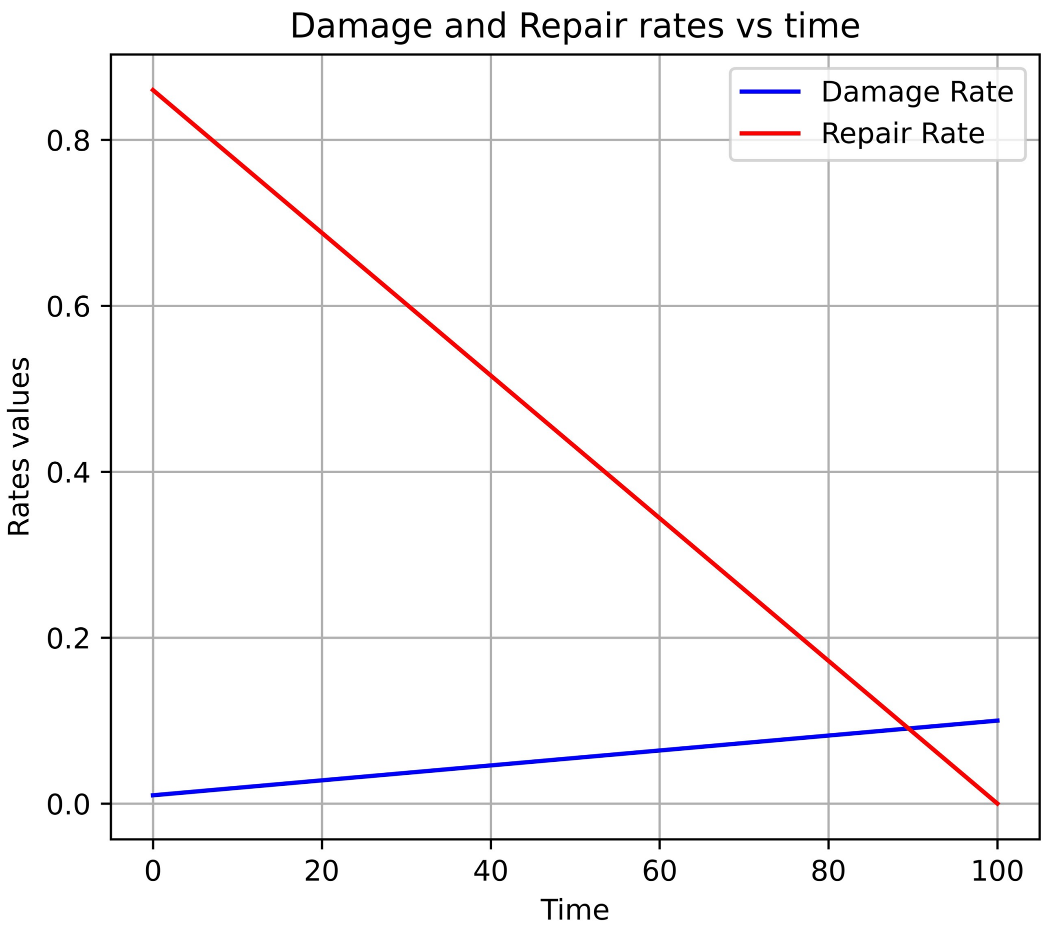
1960 paper is because:

- α can change over time along the same Gompertzian trajectory.
- R_0 can change over time along the same Gompertzian trajectory.

5) Continuous exposure of experimental animals to high-energy radiation tends to increase the Gompertz slope (α) by an amount proportional to dose rate, whereas exposure to a single dose of ionizing radiation does not appreciably affect α, but does increase $\ln R_0$ proportionally to dose (*9–11*).

Model results for SM correlation





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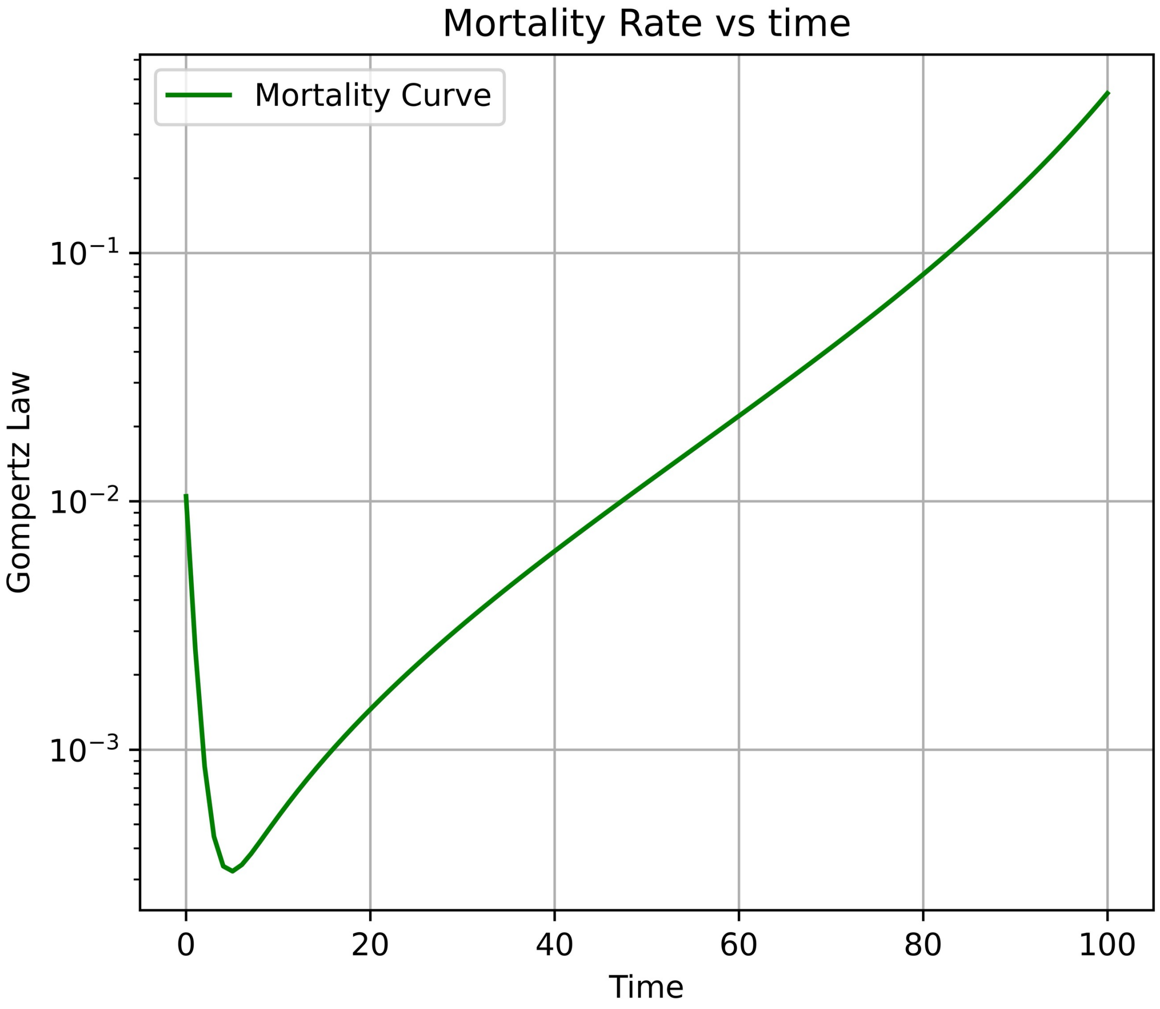

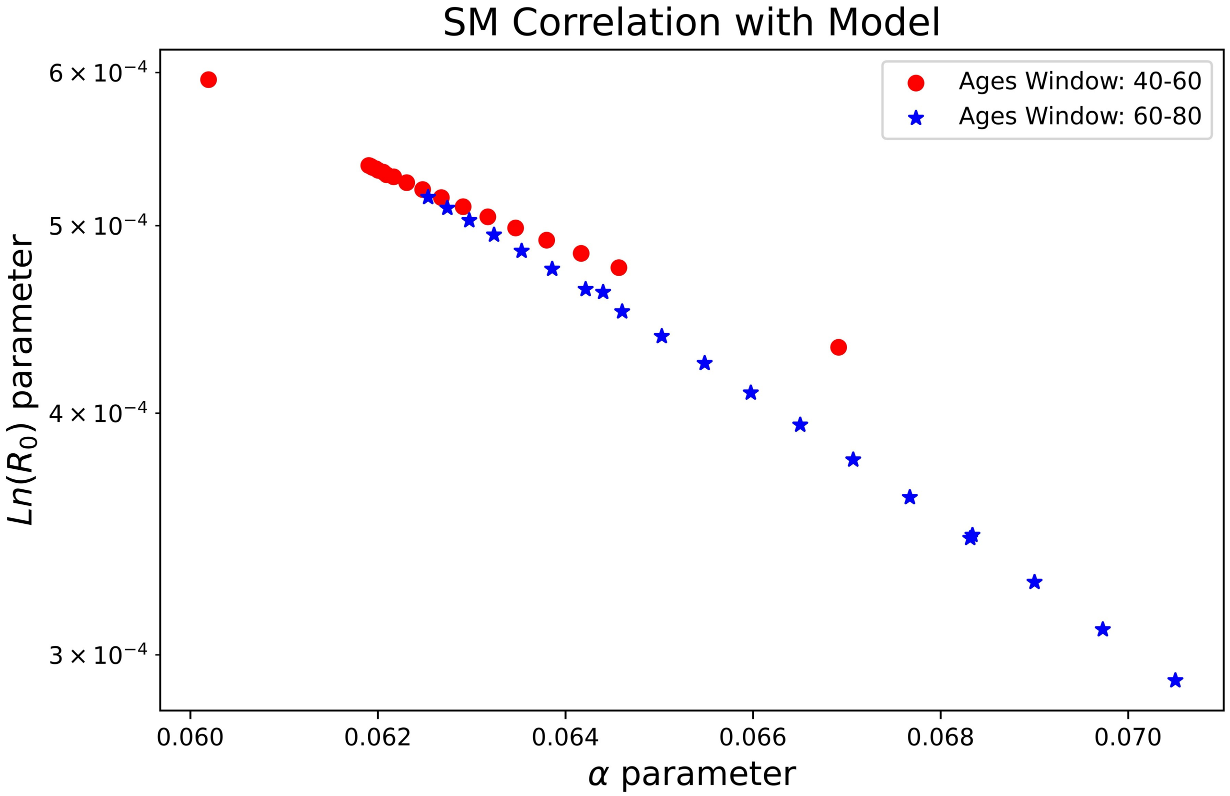

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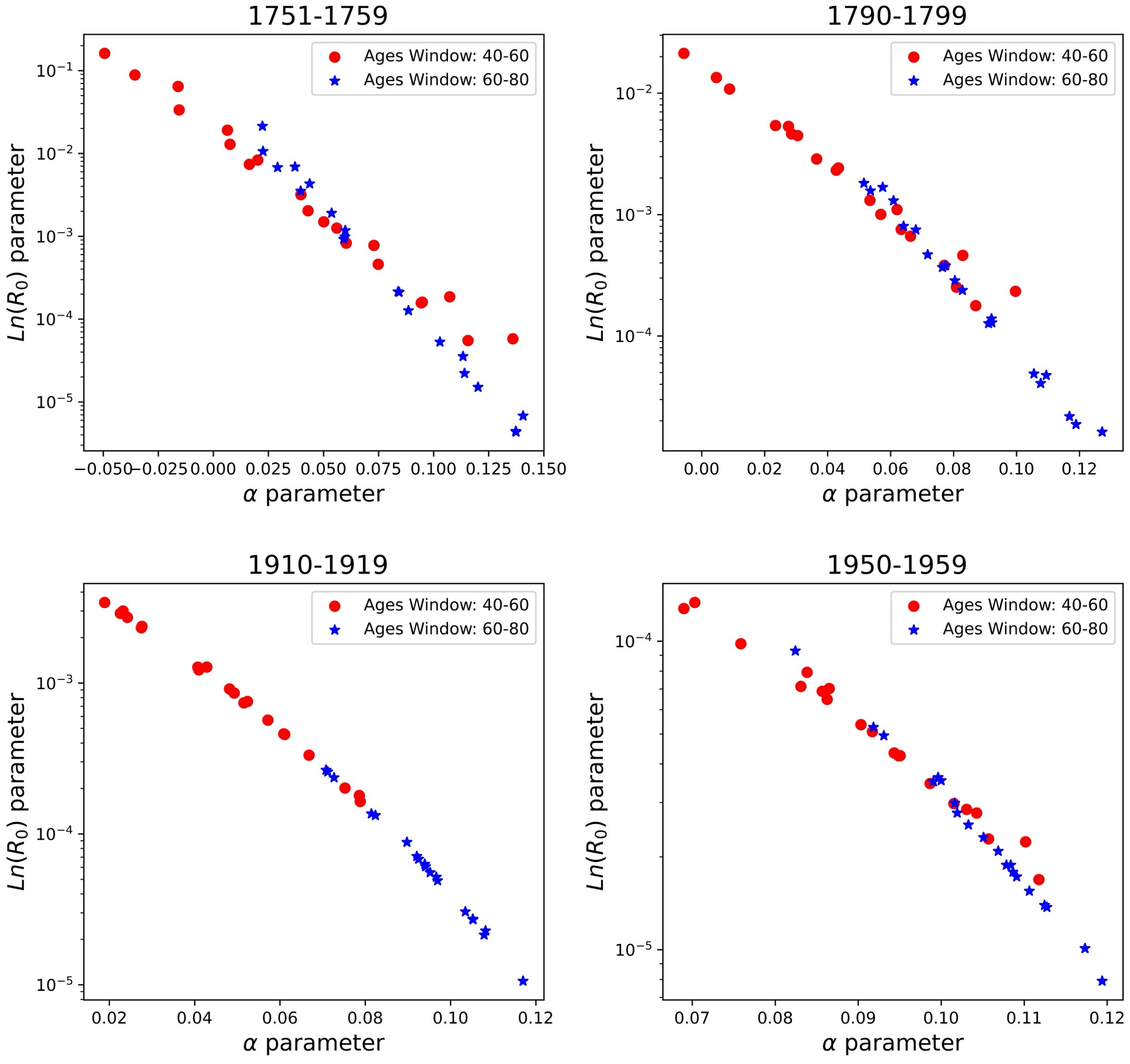

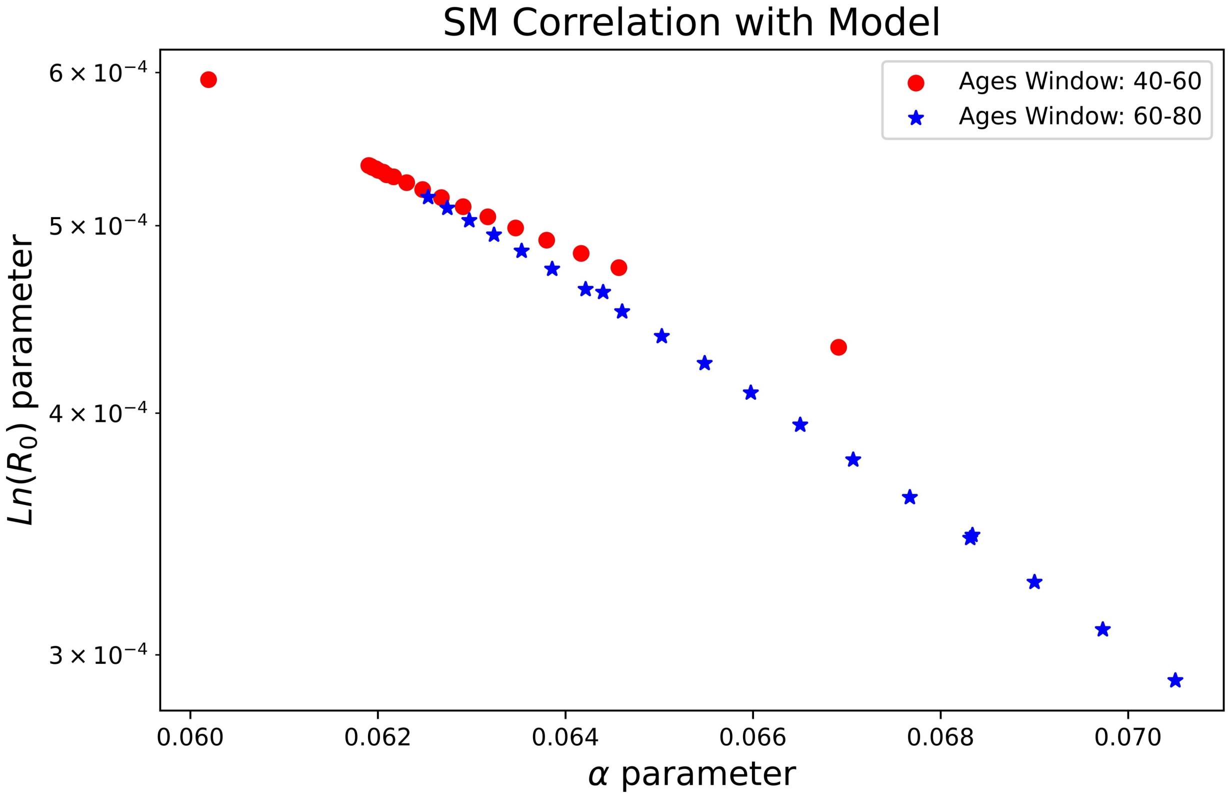

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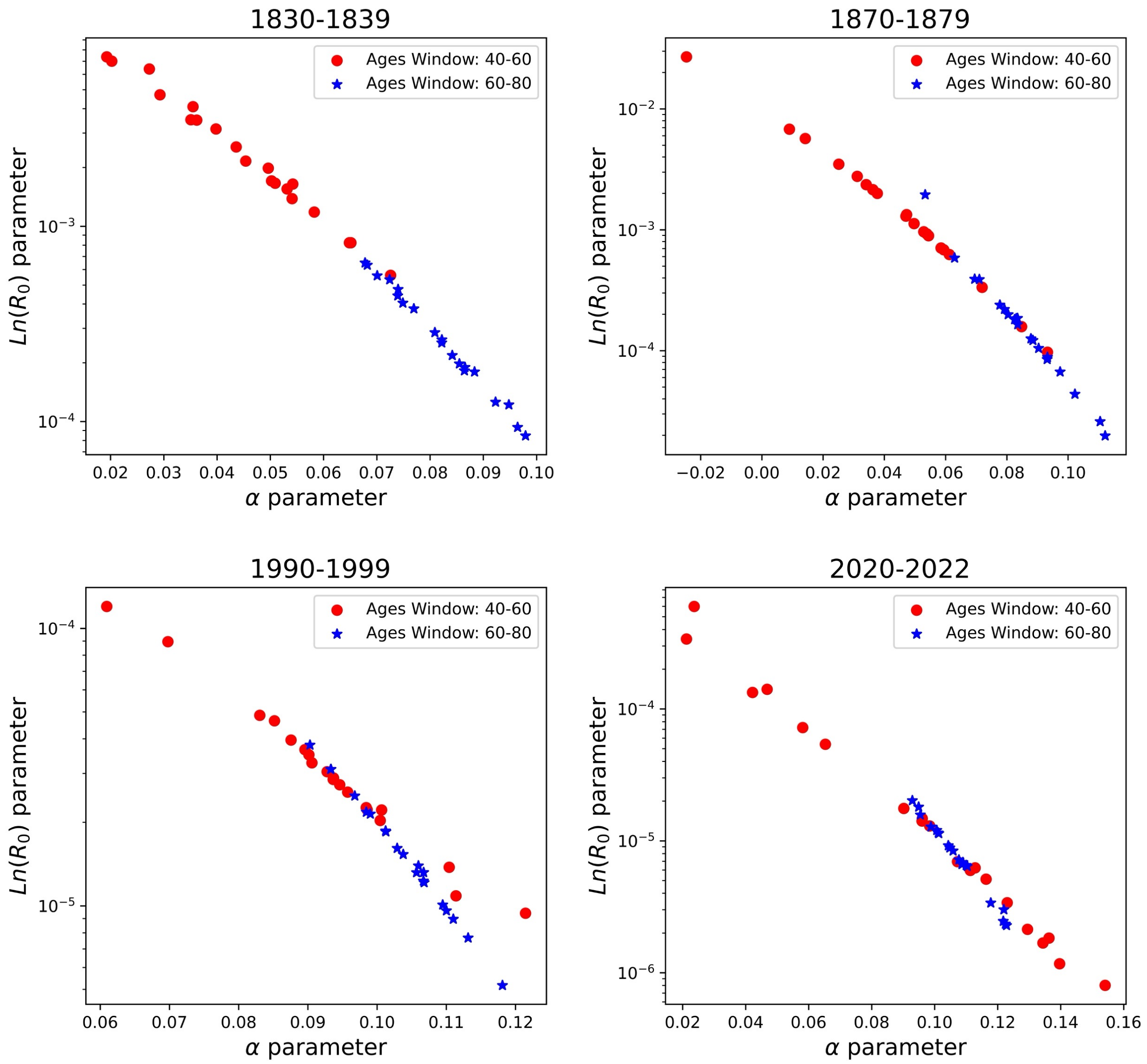

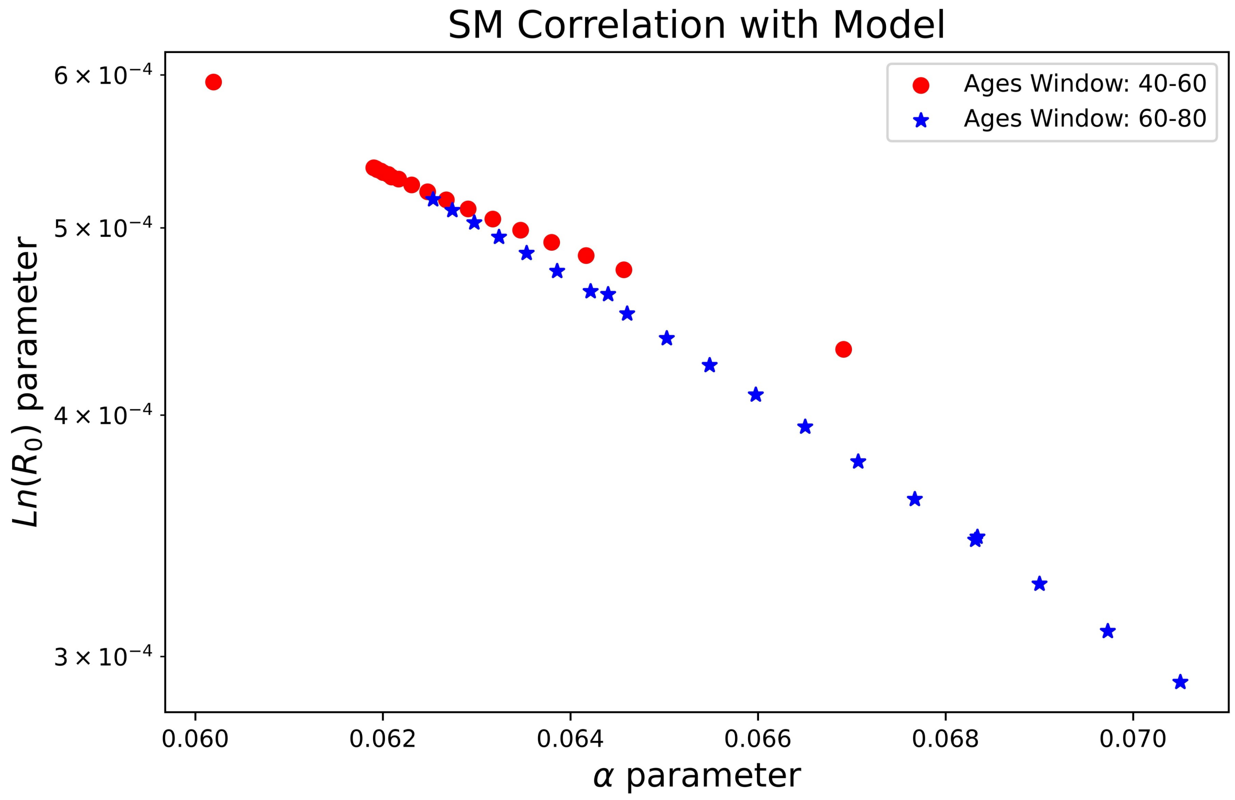

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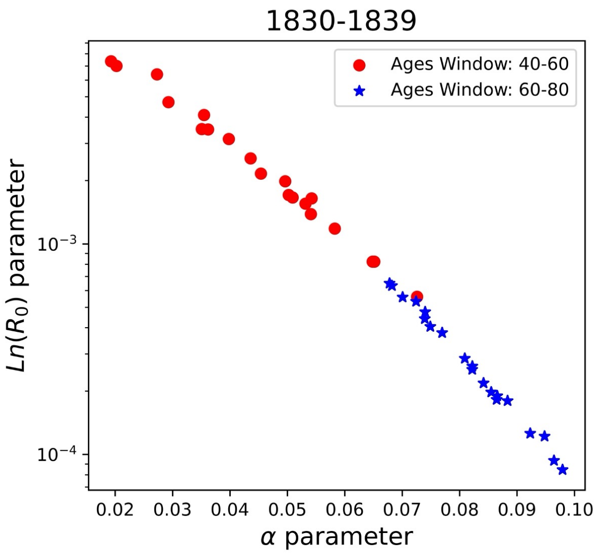
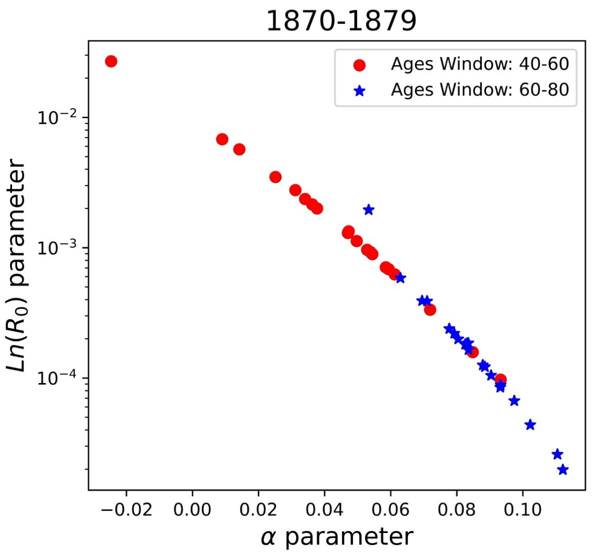
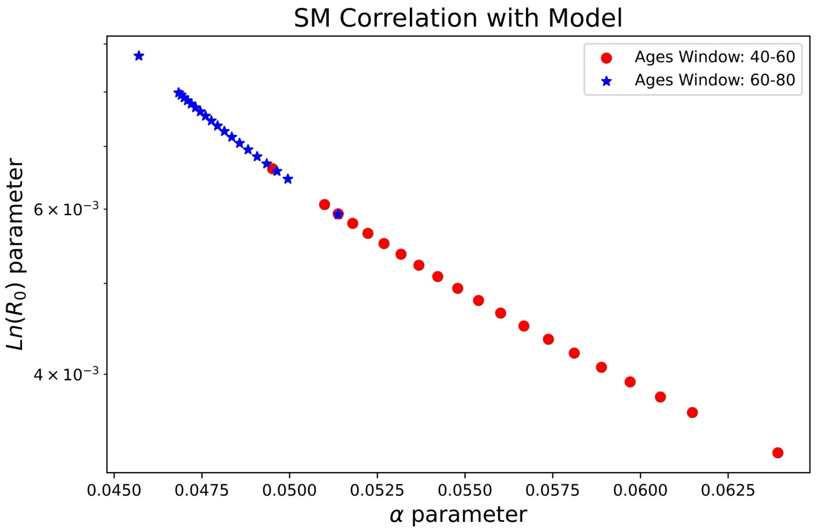
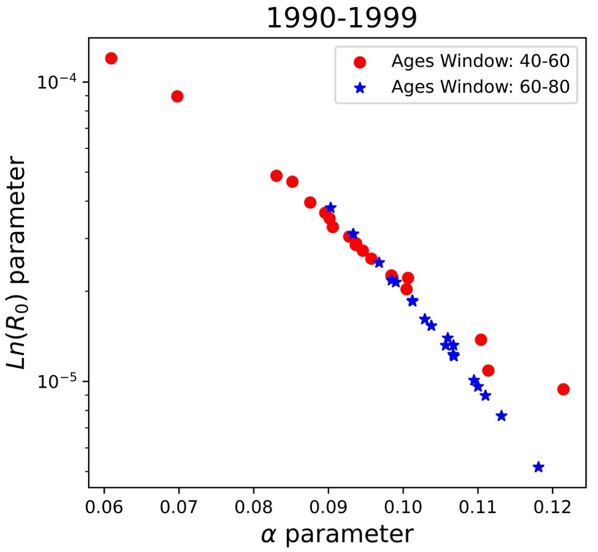
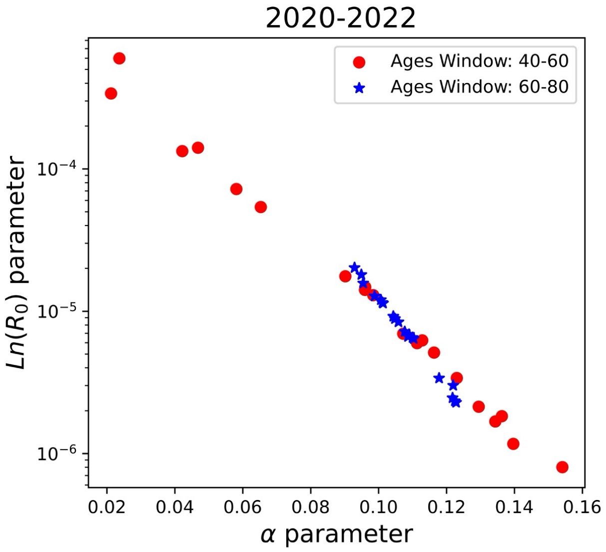
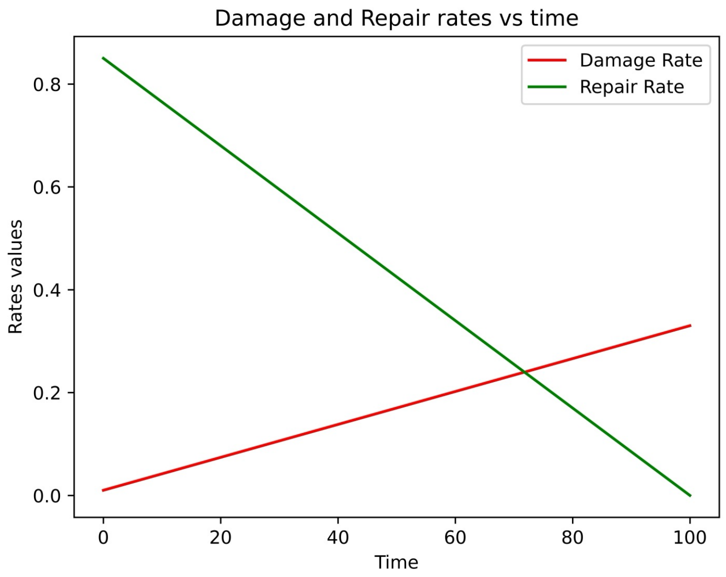












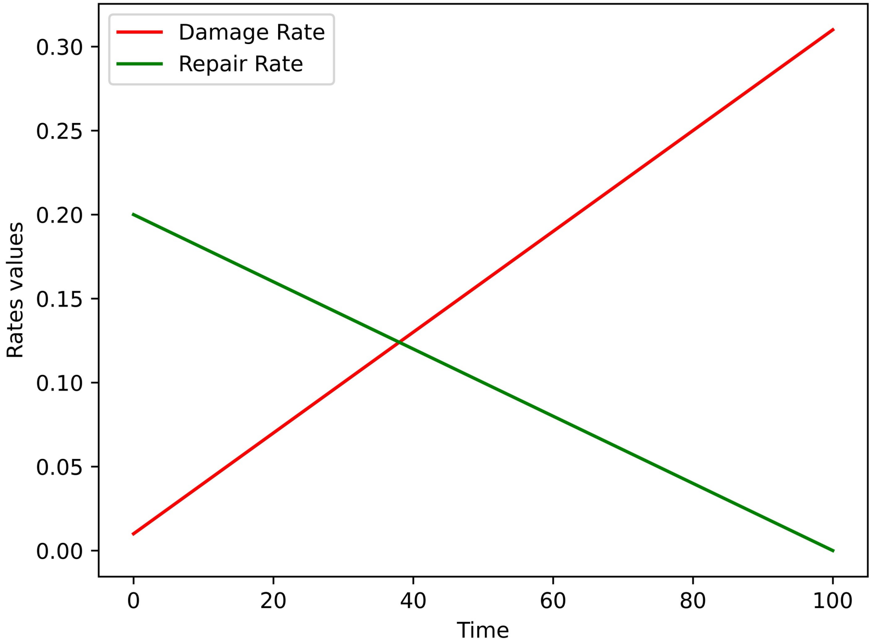
Stochastic Simulation

$$\Gamma_{T(t)} = \frac{(N_T - N_{D(t)})\Gamma_{D(t)} + N_{D(t)}\Gamma_{R(t)}}{N_T} + \mu_0(\frac{N_{D(t)}}{N_T})^C$$

Current rate

$$\Gamma_{max(t)} = \frac{(N_T - N_{D(t)})\Gamma_{D(t=current)} + N_{D(t)}\Gamma_{R(t=0)}}{N_T} + \mu_0(\frac{N_D}{N_T})^C$$

Maximum rate



Stochastic Simulation

$$if\ \ random > \frac{\Gamma_{max(t)} - \Gamma_{T(t)}}{\Gamma_{max(t)}}, \qquad 0 > random > 1$$

Decision State

Invariance in the behavior with N_T (???)

$$\lambda_i^d(t) = a \cdot (1 + bt)$$

$$\lambda_i^r(t) = r \cdot (1 - st)$$

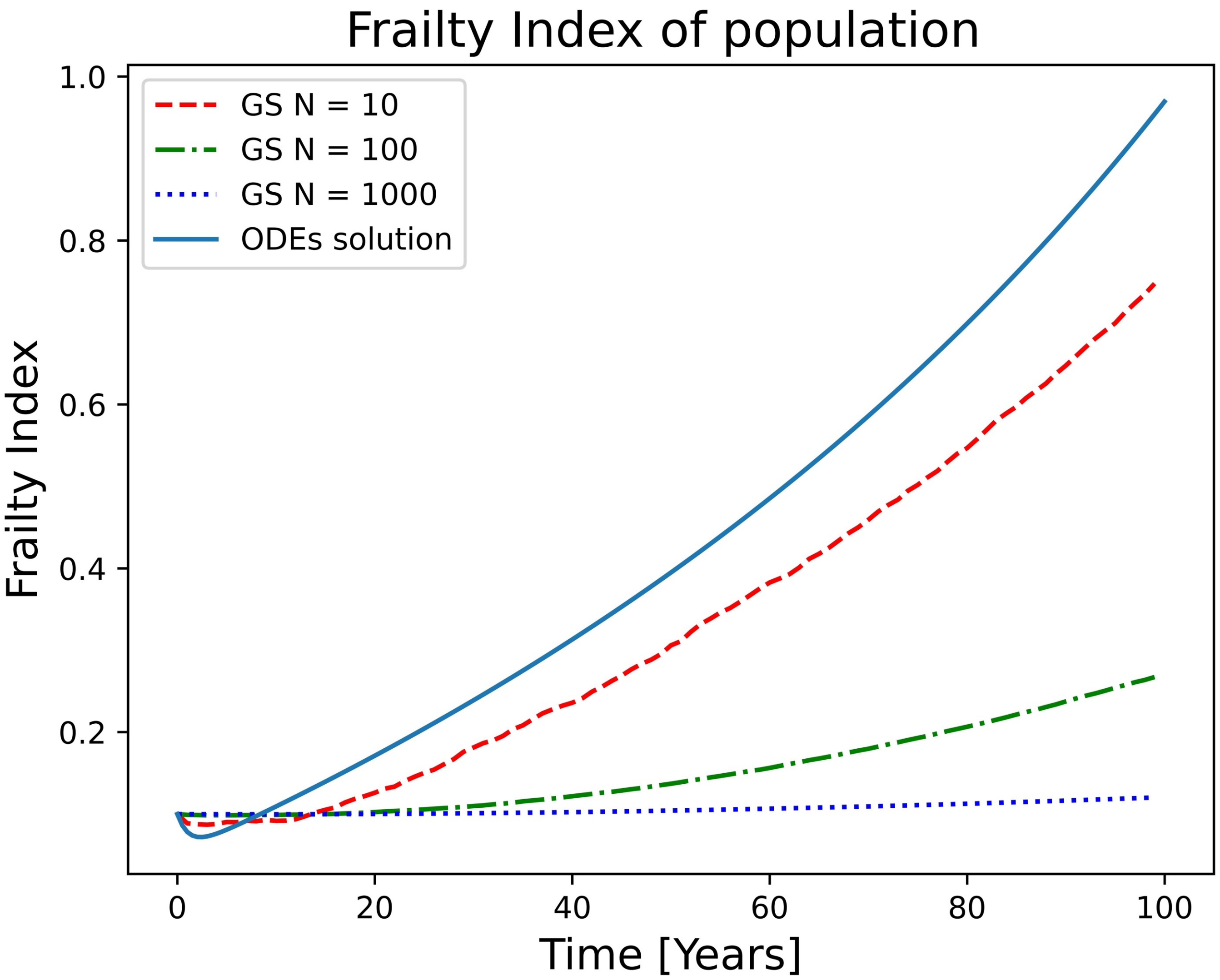
It is not the same a = 0.2 with $\boldsymbol{N_T = 10}$ as it is to $\boldsymbol{N_T = 1.000}$ **(???)**

Stochastic Simulation

Invariance in the behavior with N_T (???)

$$\lambda_i^d(t) = a \cdot (1 + bt)$$

$$\lambda_i^r(t) = r \cdot (1 - st)$$

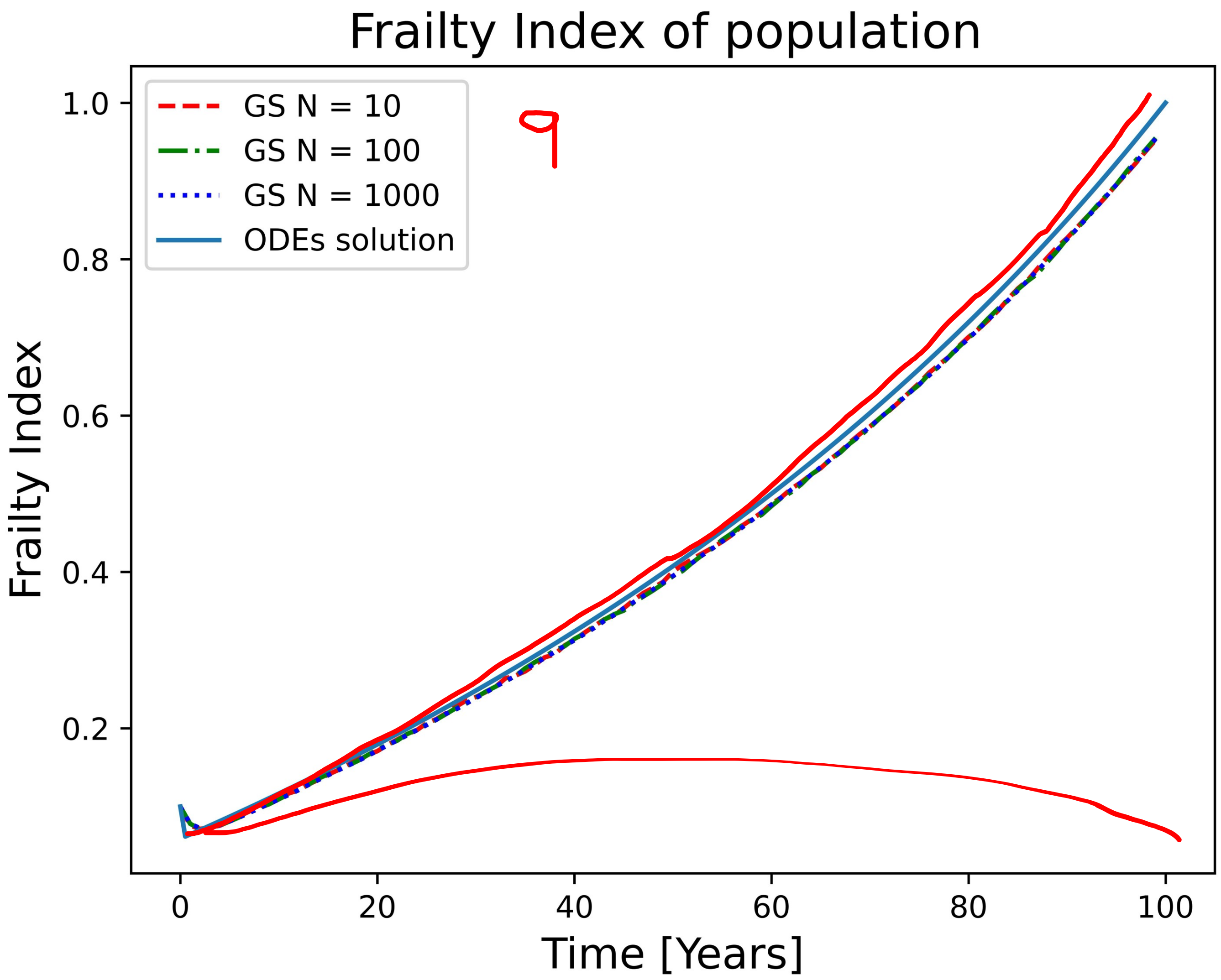


Stochastic Simulation

$$\lambda_i^d(t) = \boxed{N_T} \cdot a \cdot (1 + bt)$$

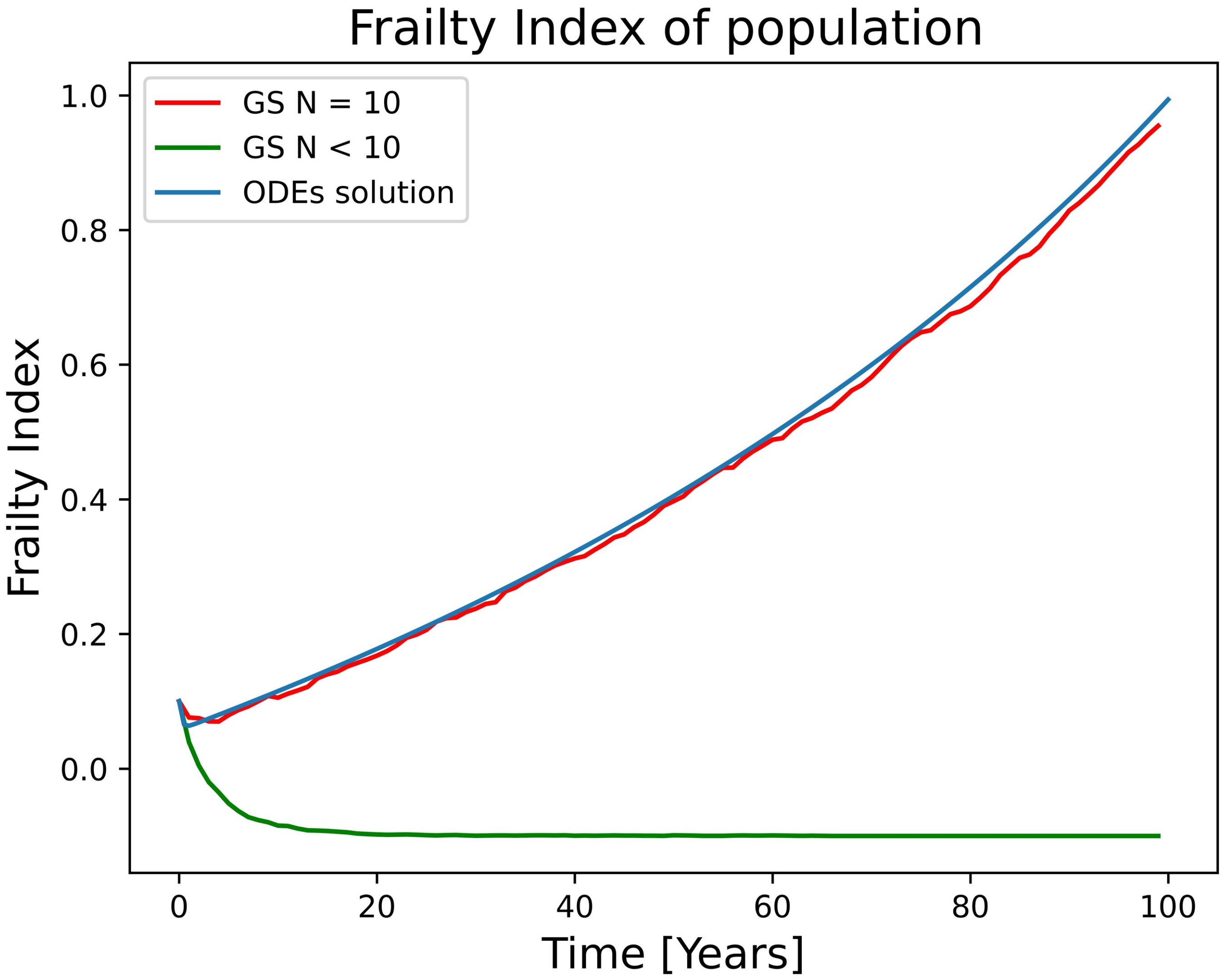
$$\lambda_i^r(t) = \boxed{N_T} \cdot r \cdot (1 - st)$$

Invariance scale with damage and repair rates proportional to N_T



Stochastic Simulation

The minimum number of nodes with which the simulation reproduces the ODEs result is $\boldsymbol{N_T = 10}$



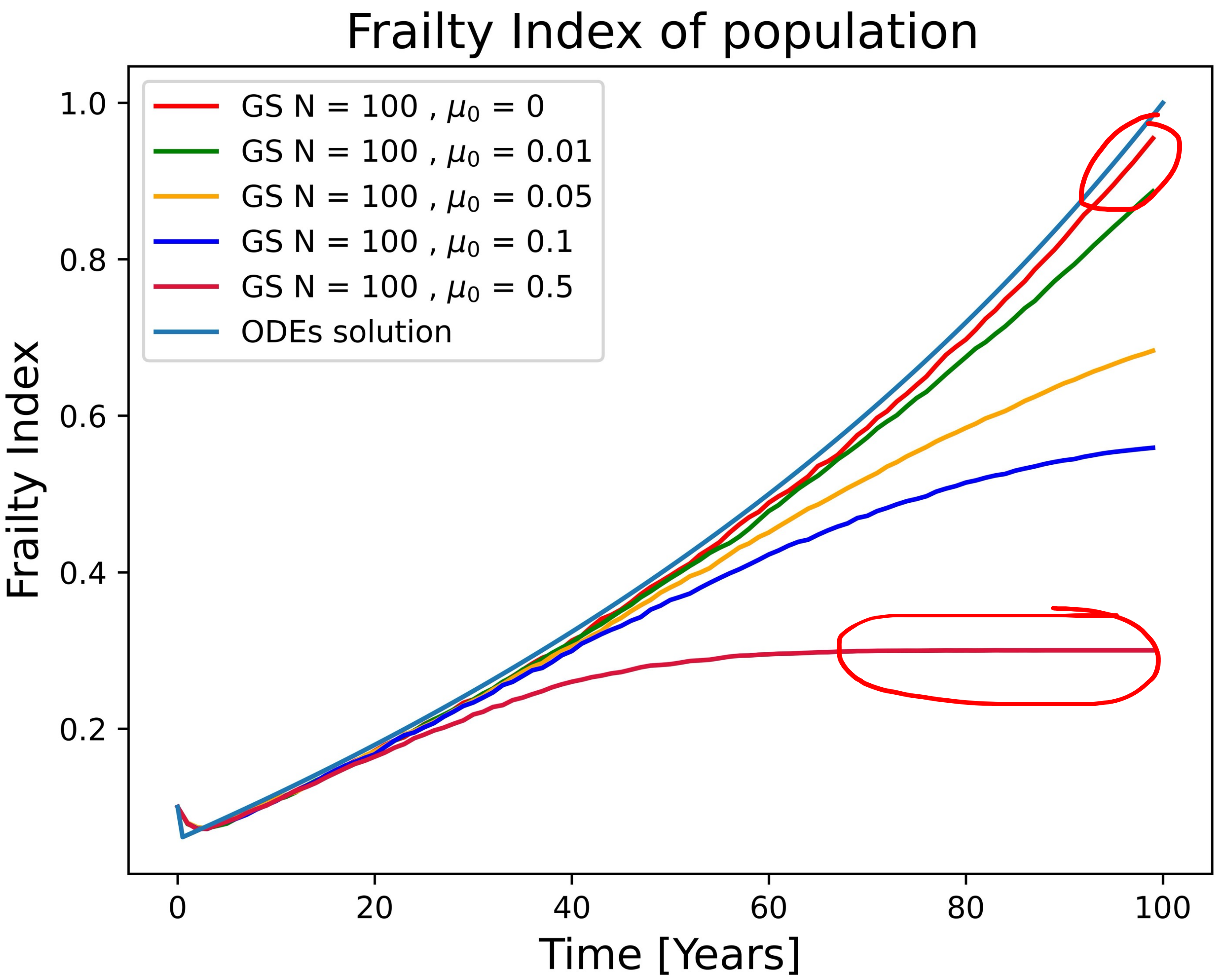
Stochastic Simulation

Increasing the number of total nodes in the system increases stochastic variability. That is, health state distributions become more dispersed.

Stochastic Simulation

Both results have the same behavior when mortality is zero $\boldsymbol{\mu_0 = 0}$

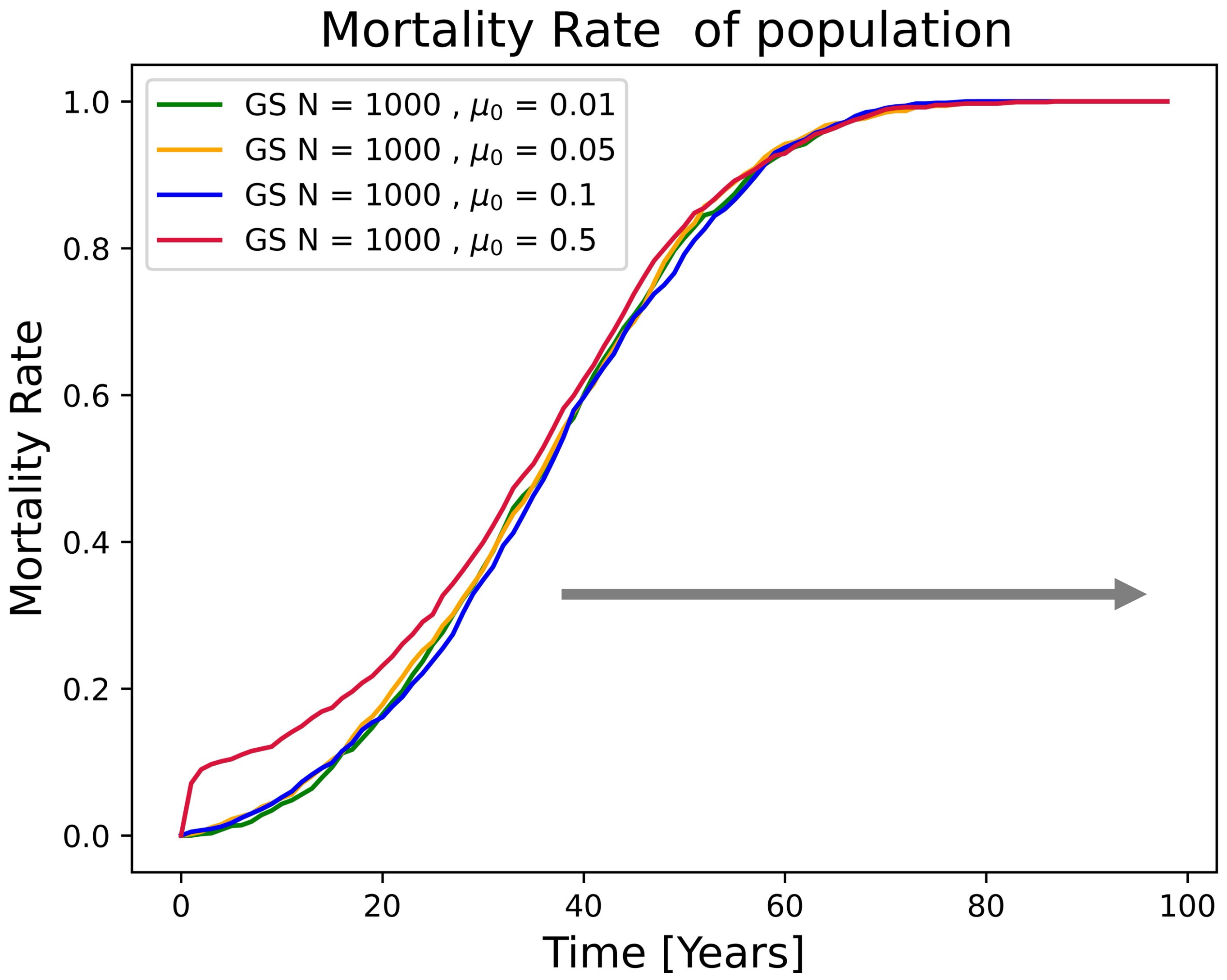
Our stochastic simulation is a joint model between health state (frailty) and mortality as in nature, but the ODEs does not have this coupling



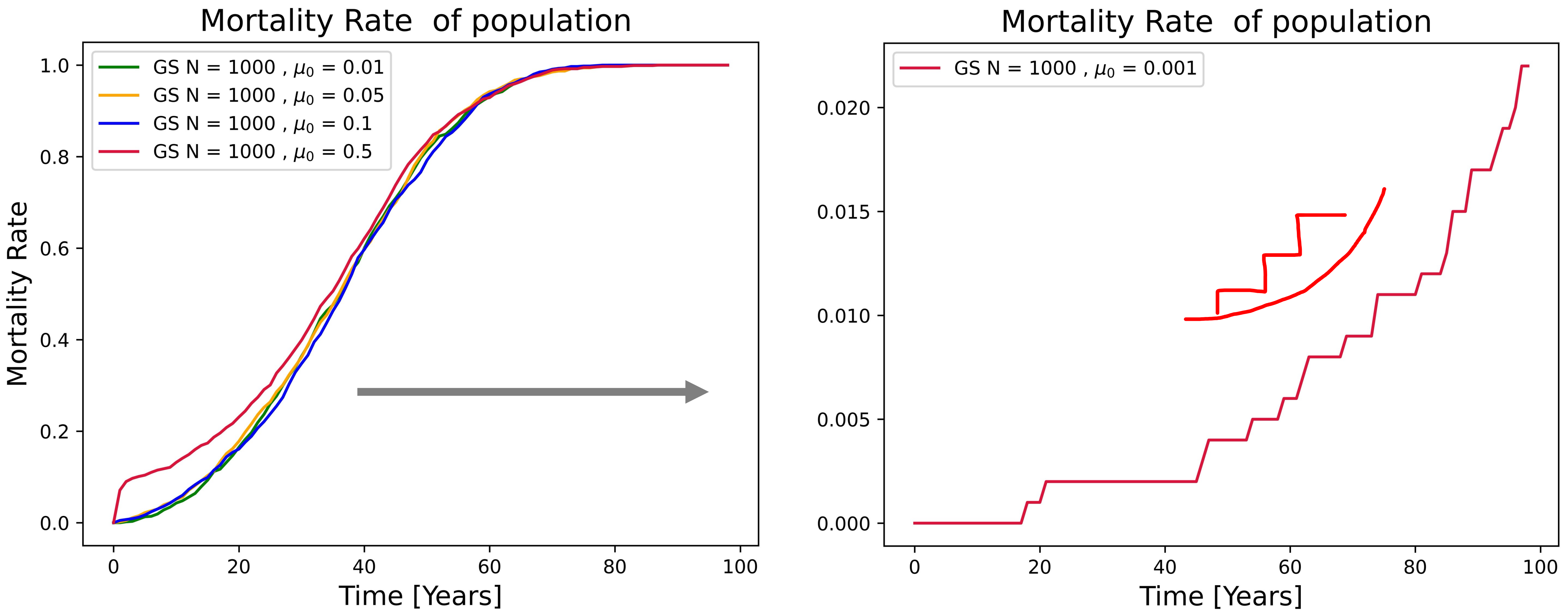
Stochastic Simulation

The mortality coefficient modifies the mortality curves obtained from the simulation

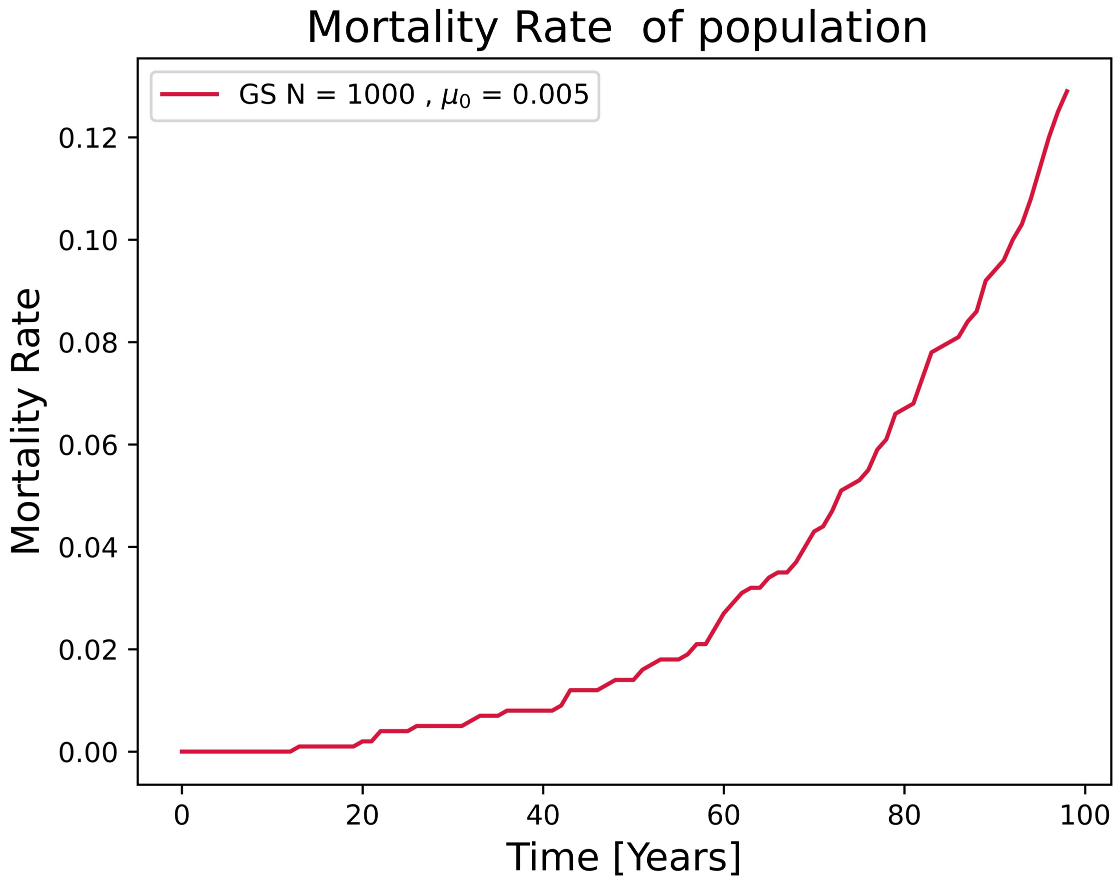
Higher values cause the population to die at an earlier age with lower frailty index values

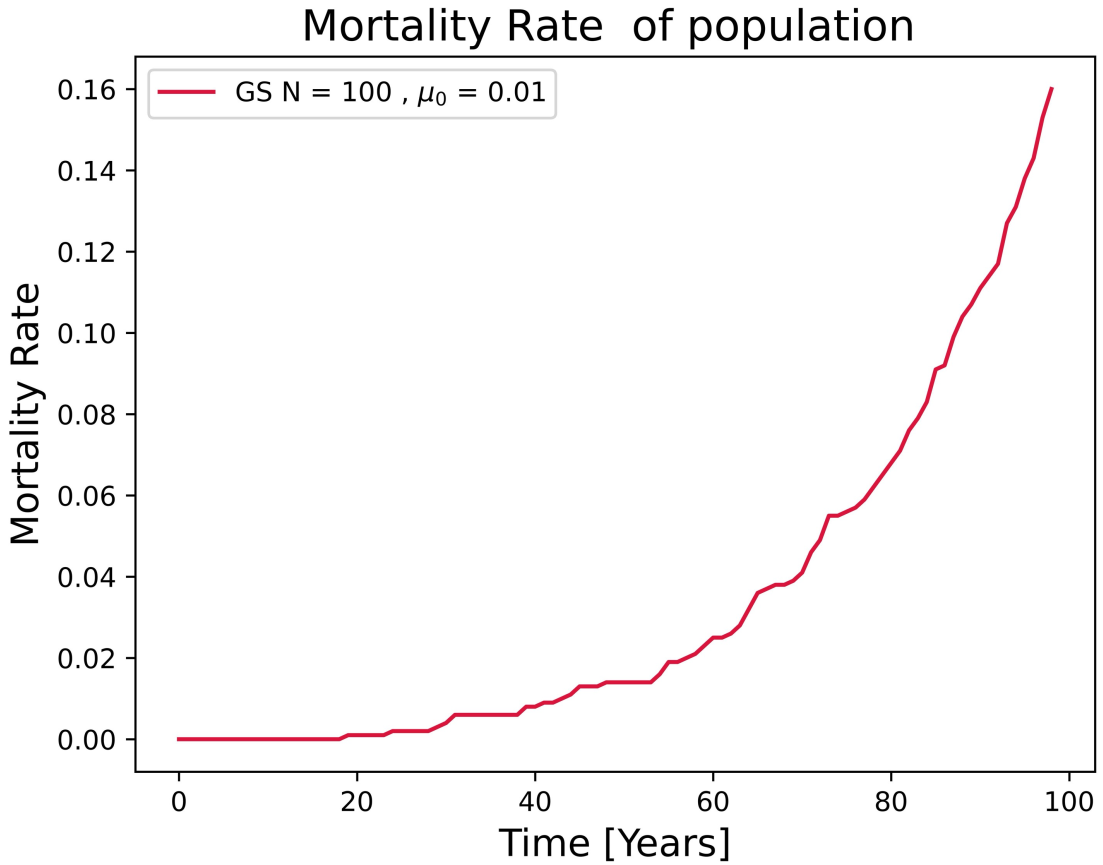


Stochastic Simulation

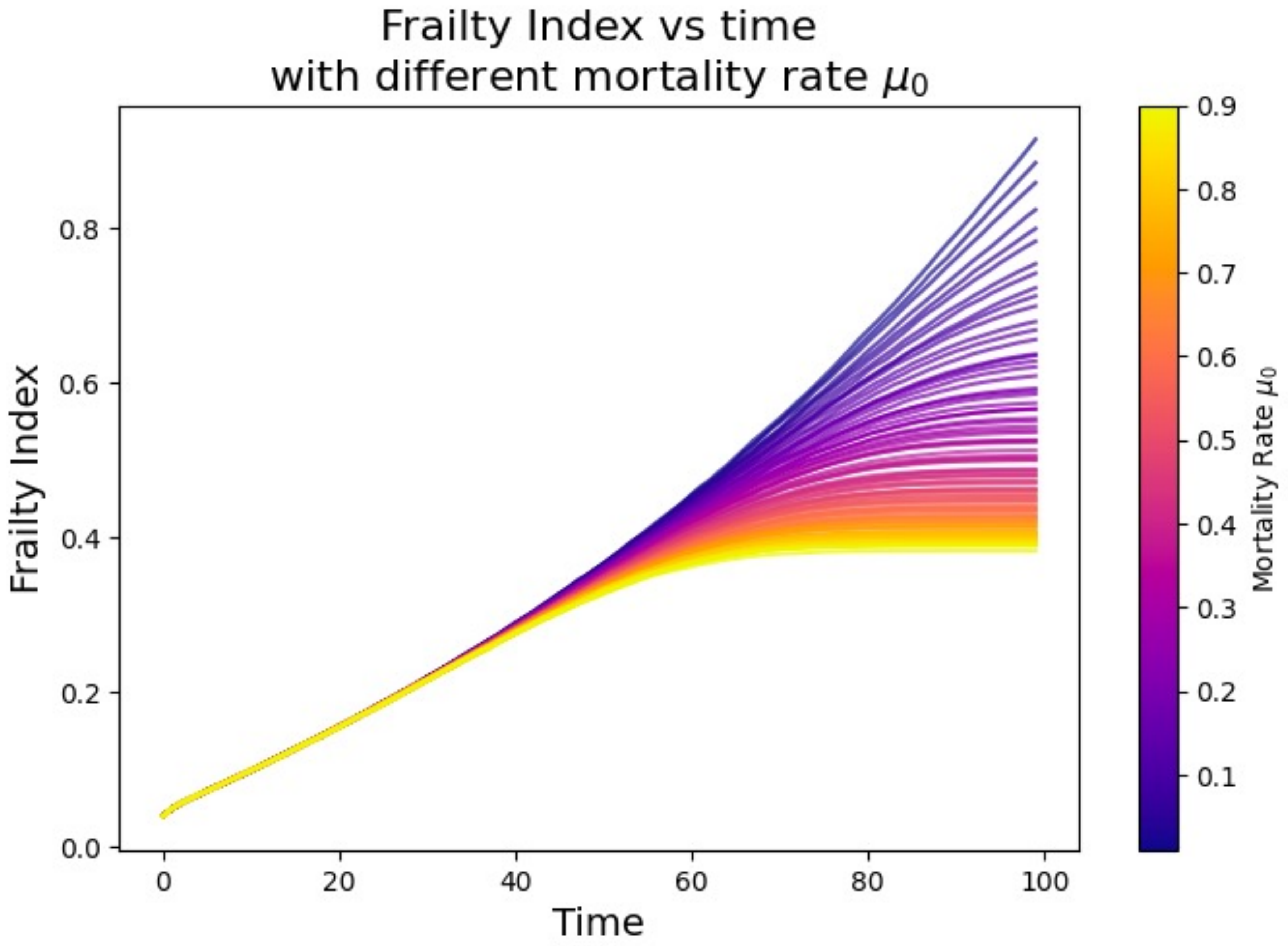


Stochastic Simulation

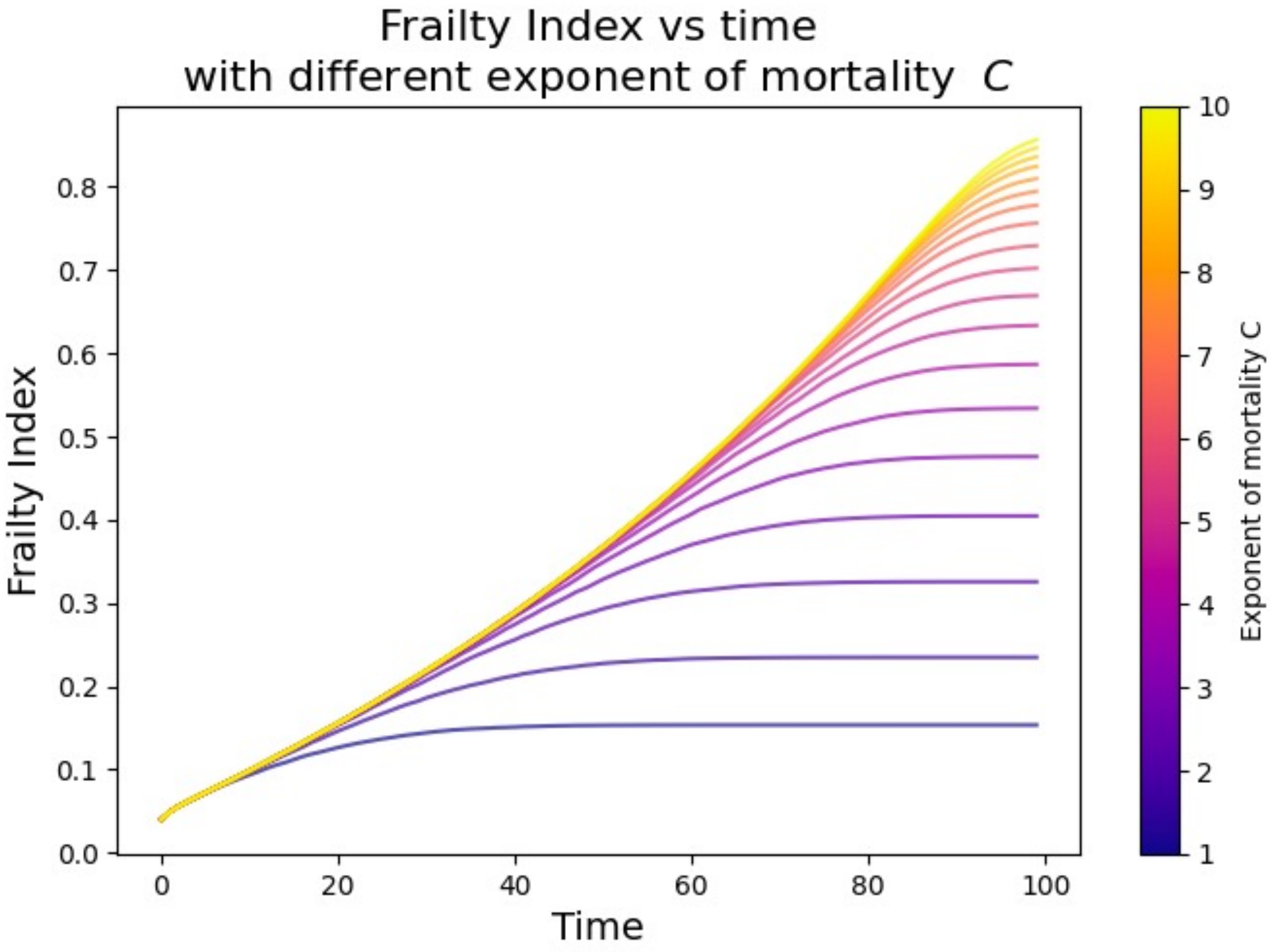




We can recover behaviors exponentially as stated in the gompertz law



Frailty Index vs time
with different mortality rate μ_0
Frailty Index
0.0
0.2
0.4
0.6
0.8
Time
0
20
40
60
80
100
Mortality Rate μ_0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9



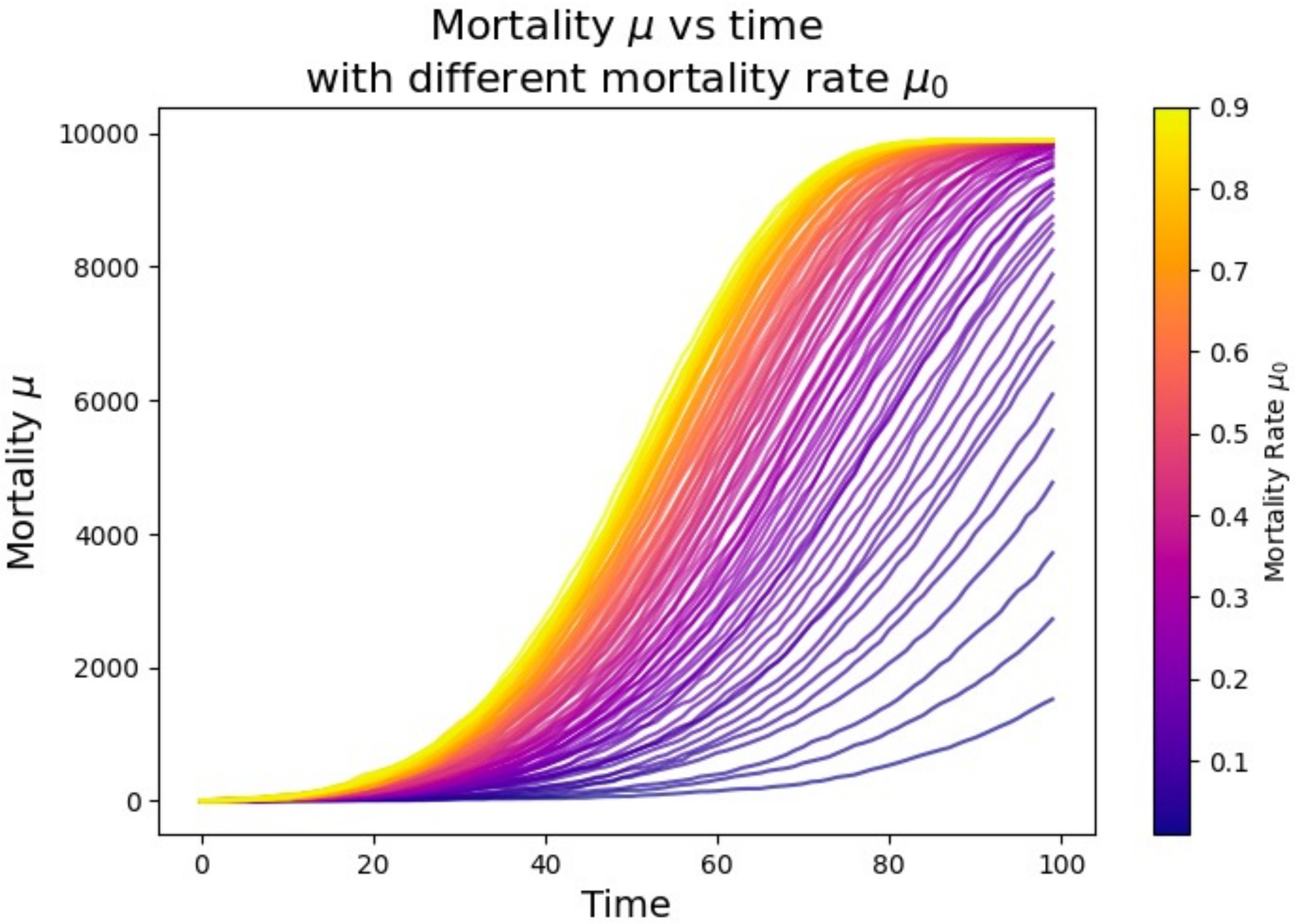
Exponent of mortality modifications

Human Mortality Database

Data resource on mortality in +40 developed countries

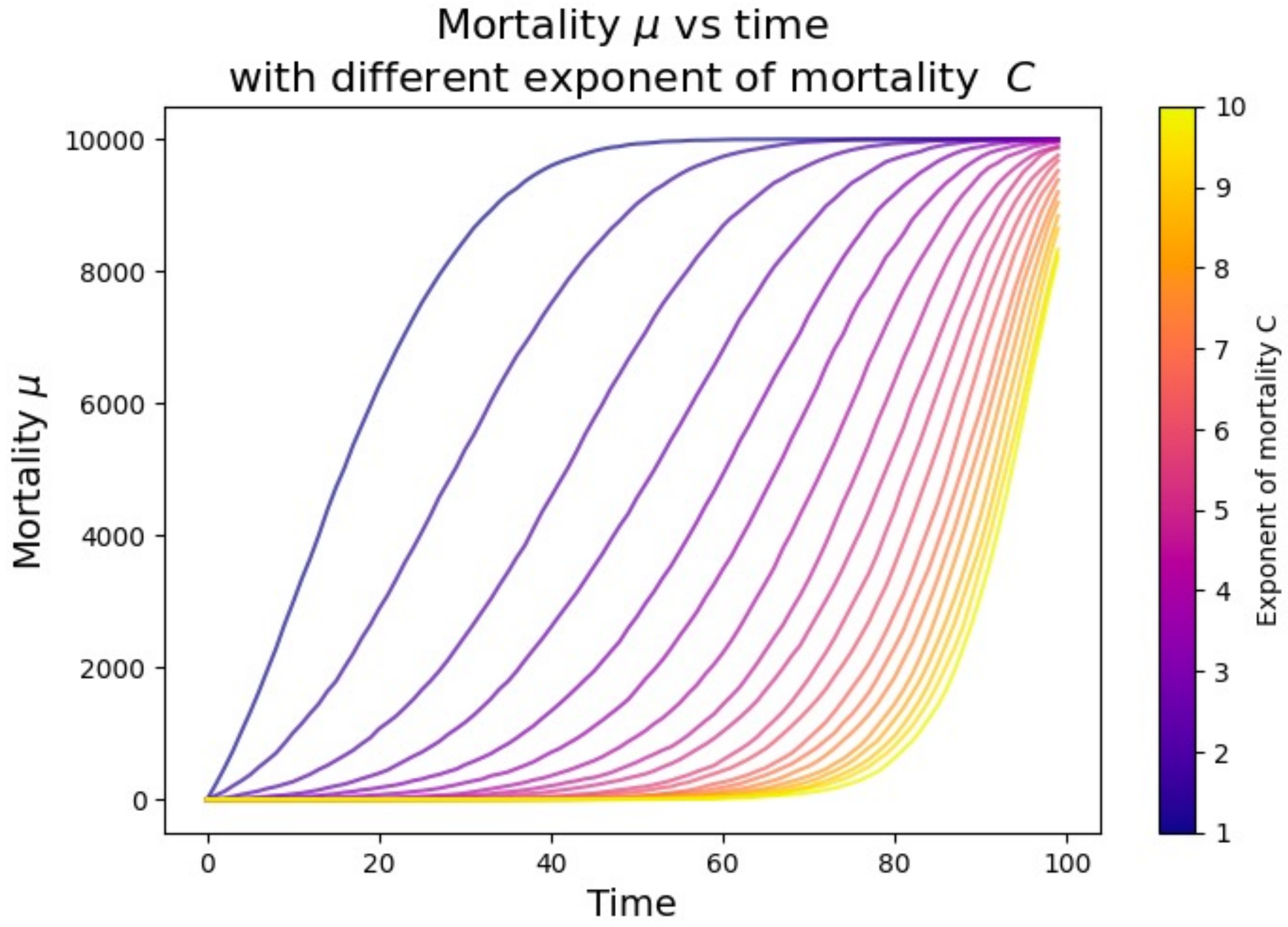
Data of:

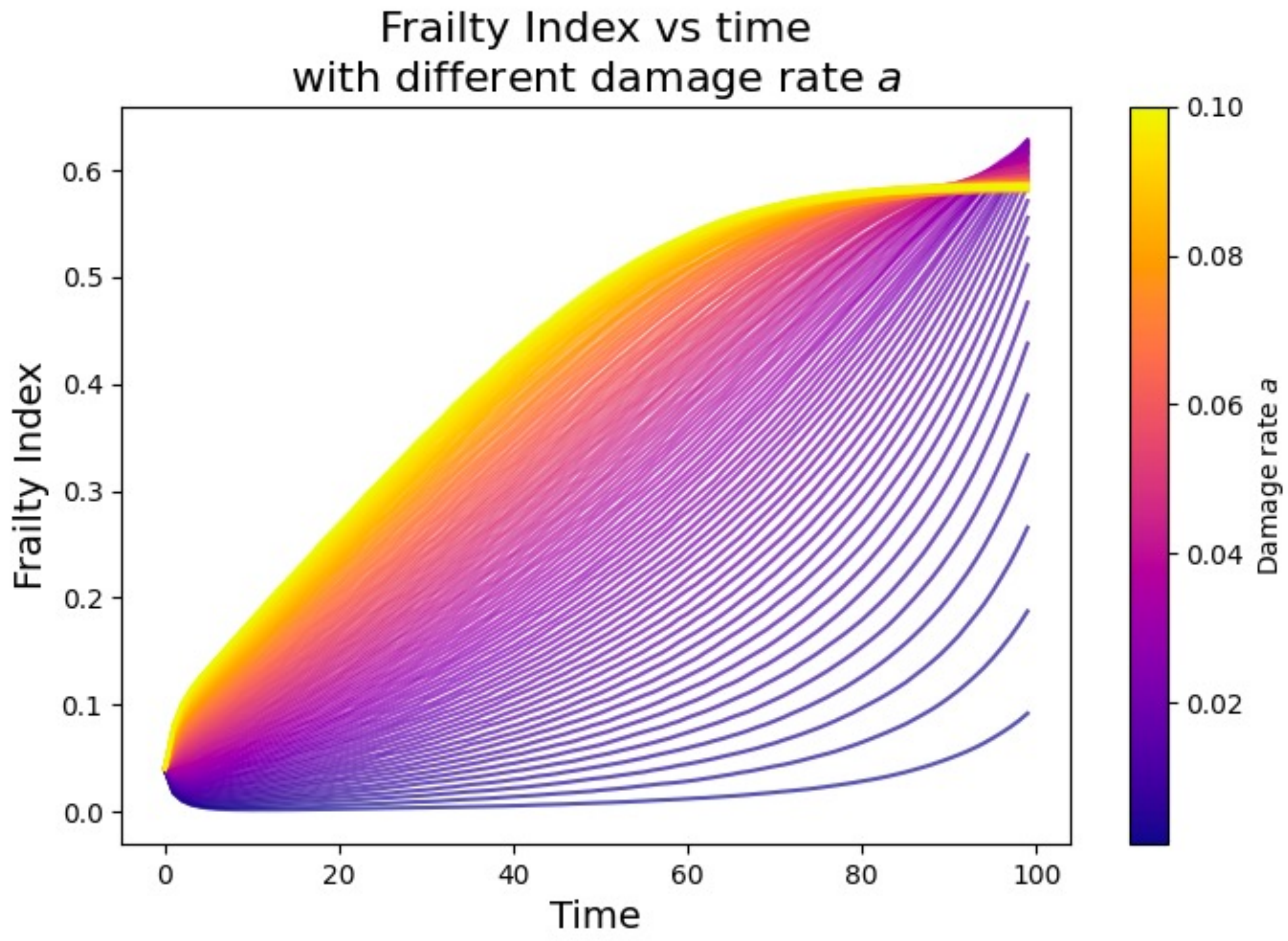
- Deaths
- Population Size
- Death Rates
- Exposure to risk

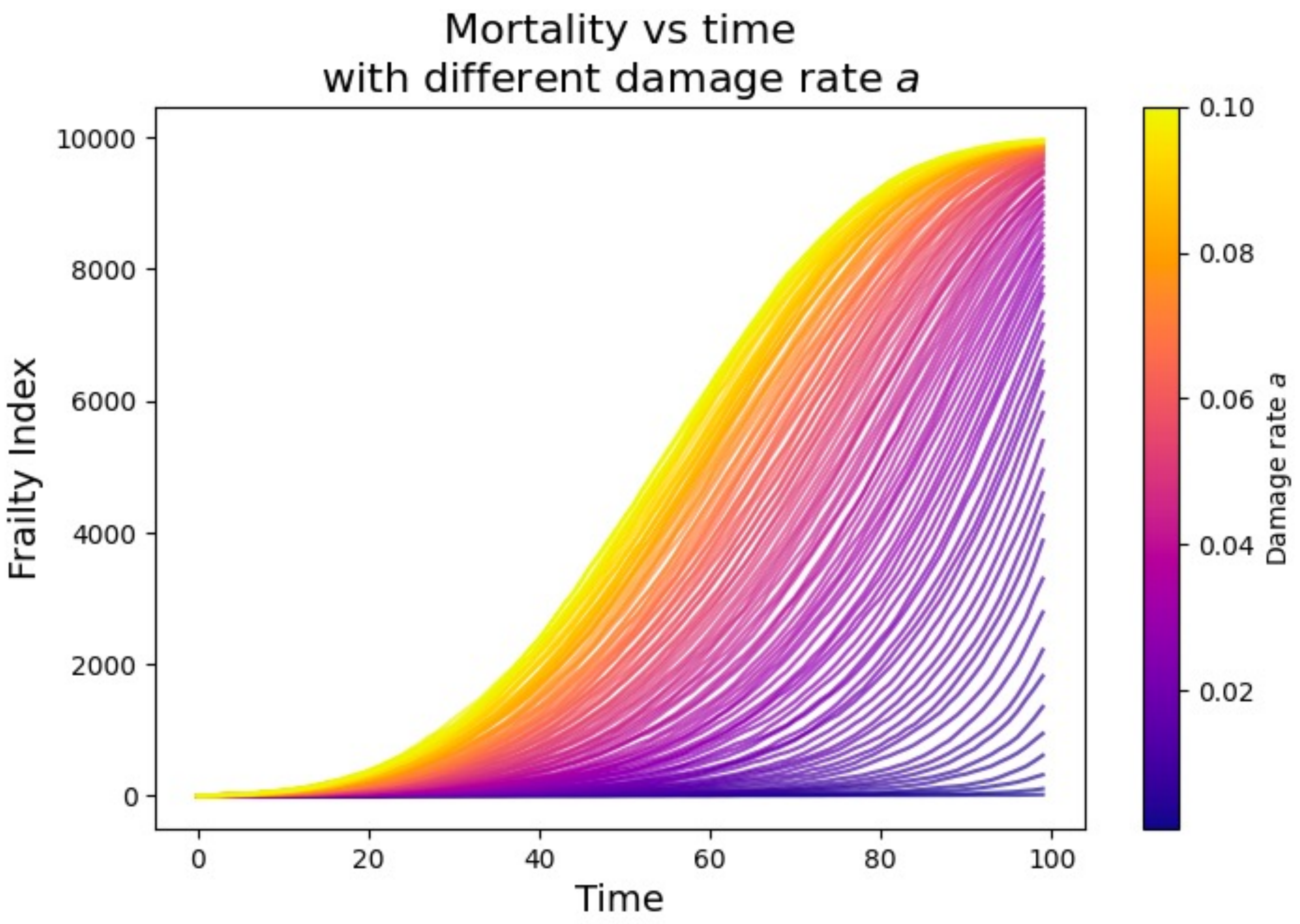


Mortality μ vs time
with different mortality rate μ_0
Mortality μ
Time
Mortality Rate μ_0
0
2000
4000
6000
8000
10000
0
20
40
60
80
100
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9

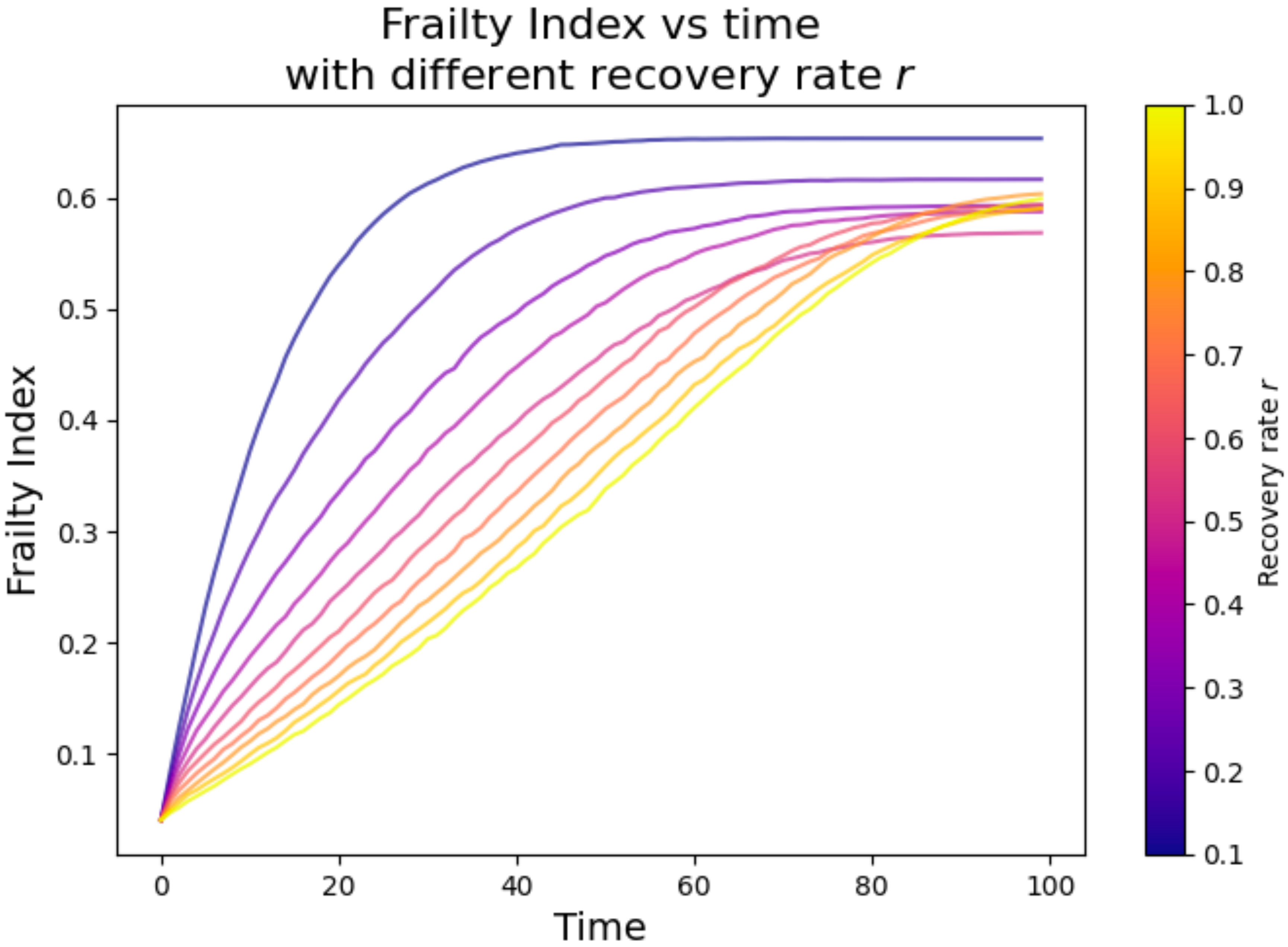
Mortality Rate modifications



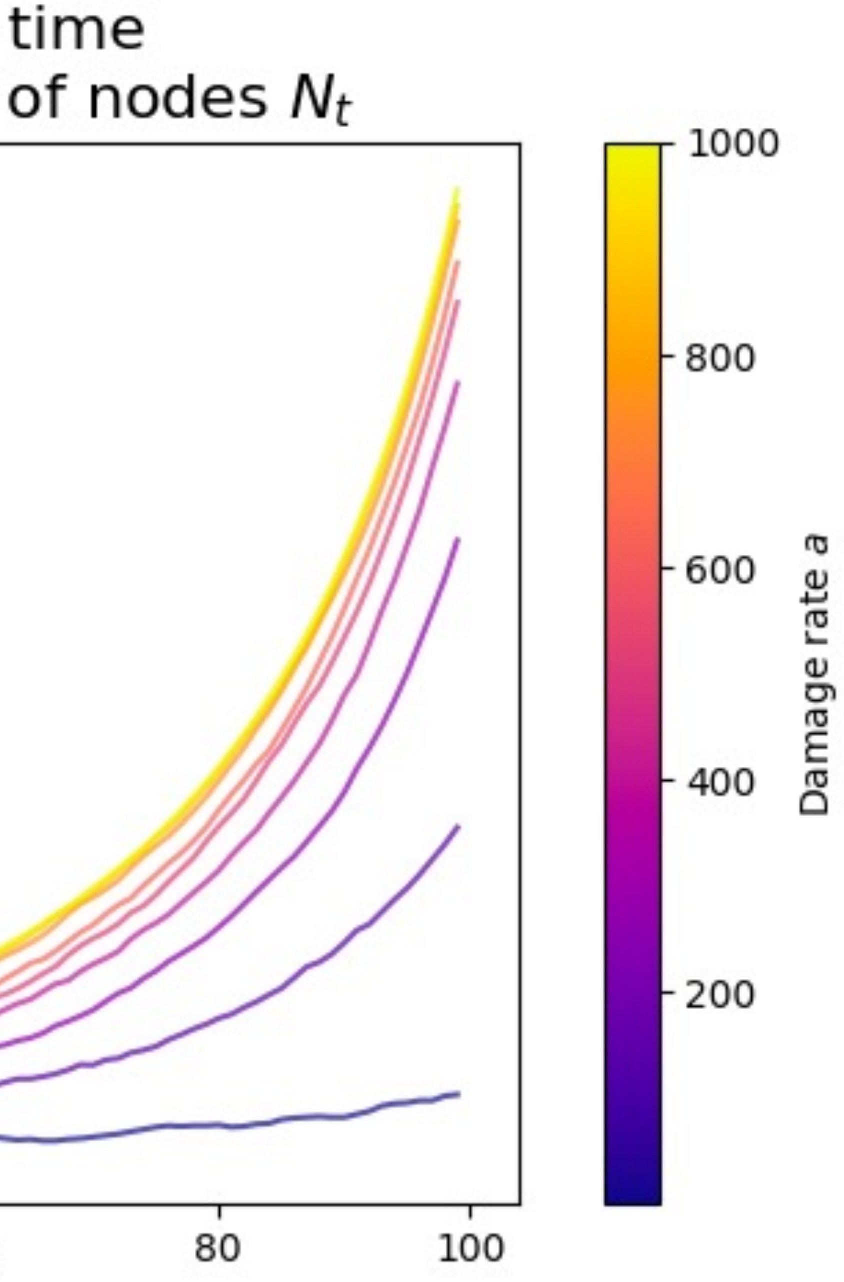

Frailty Index vs time
with different damage rate a
Frailty Index
Time
Damage rate a
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
20
40
60
80
100
0.02
0.04
0.06
0.08
0.10



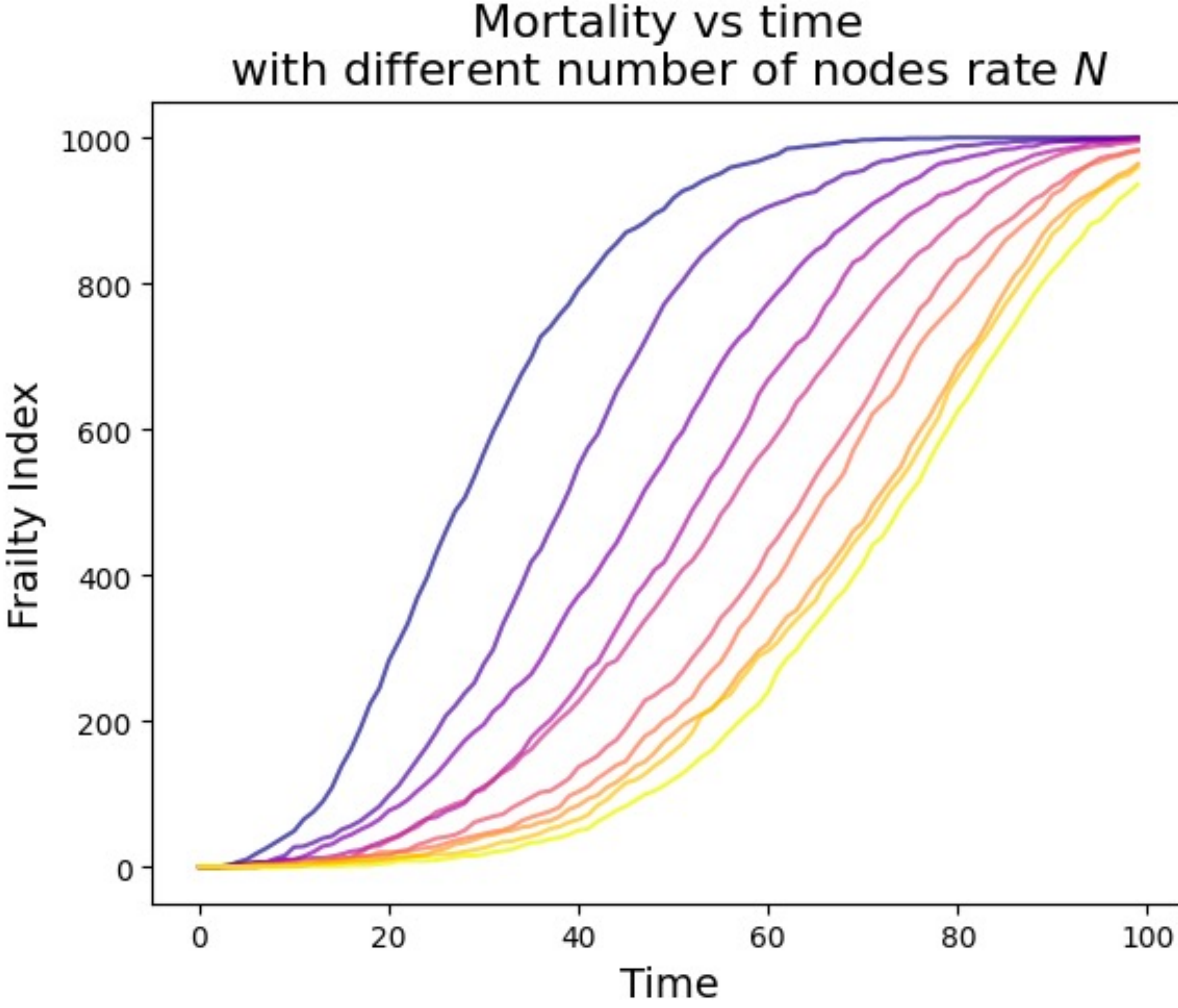
Mortality vs time
with different damage rate a
Frailty Index
10000
8000
6000
4000
2000
0
0
20
40
60
80
100
Time
0.10
0.08
0.06
0.04
0.02
Damage rate a



Frailty Index vs time
with different recovery rate r
Frailty Index
Time
Recovery rate r
0.1
0.2
0.3
0.4
0.5
0.6
0
20
40
60
80
100
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0



time
of nodes N_t
80
100
1000
800
600
400
200
Damage rate a

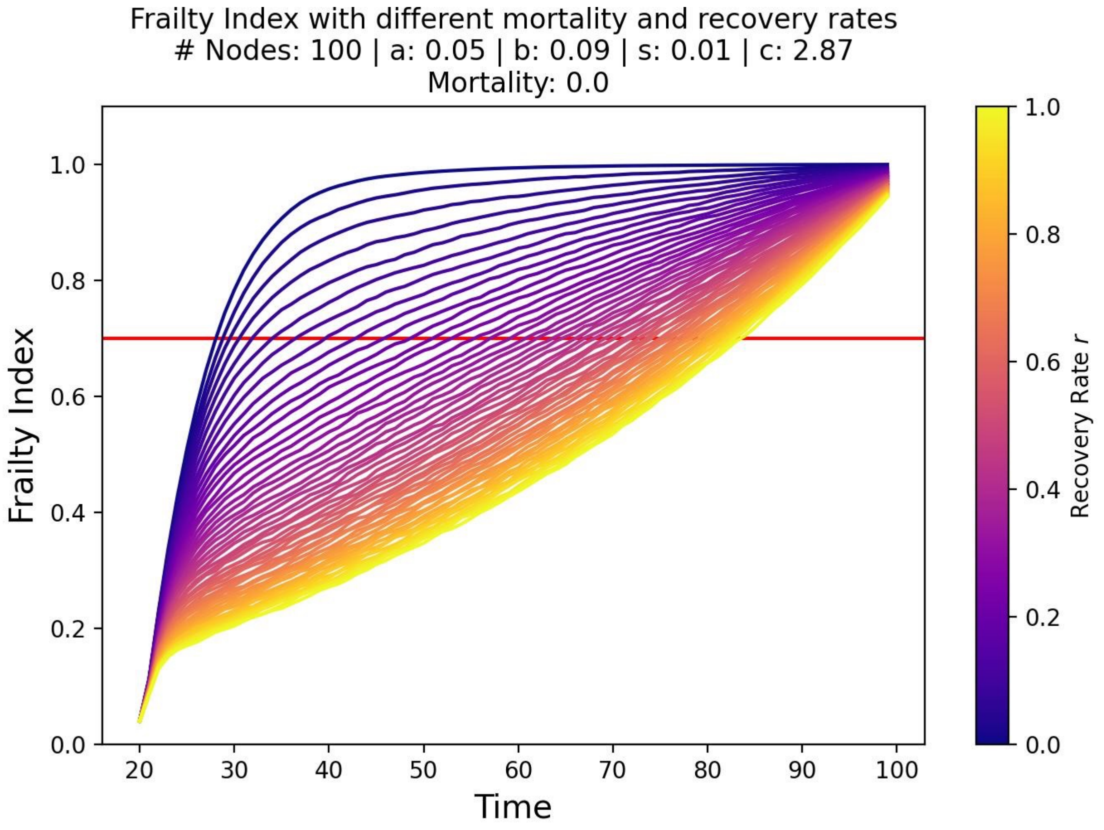


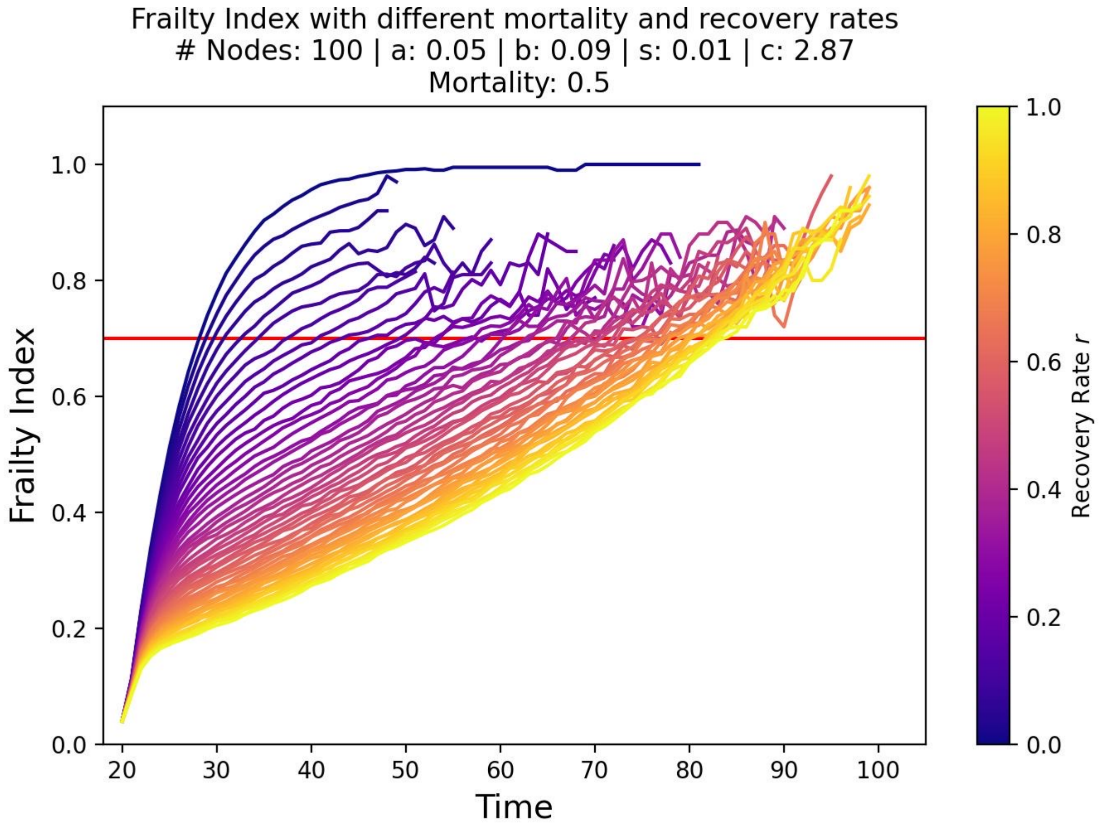
Mortality vs time
with different number of nodes rate N
Frailty Index
Time
0
200
400
600
800
1000
0
20
40
60
80
100

January 22 Meeting

- Hypotheses on the maximum observed frailty index
- Mortality curves behave like Gompertz's law and changes with recovery rate
- Changes in the SM correlation dynamics
- Stochasticity of the frailty Index with mortality

Frailty Index Saturation (???)

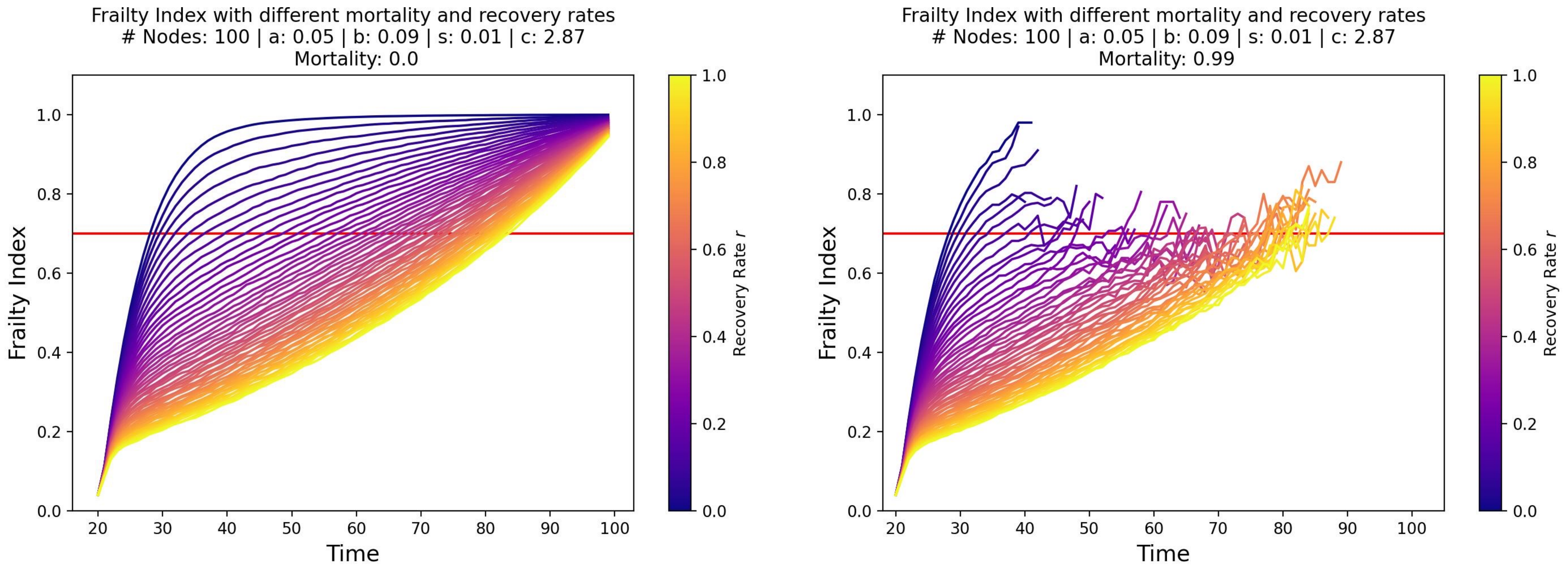




The frailty index also shows a consistent, sub-maximal limit at about 2/3 of the deficits that are considered [1].

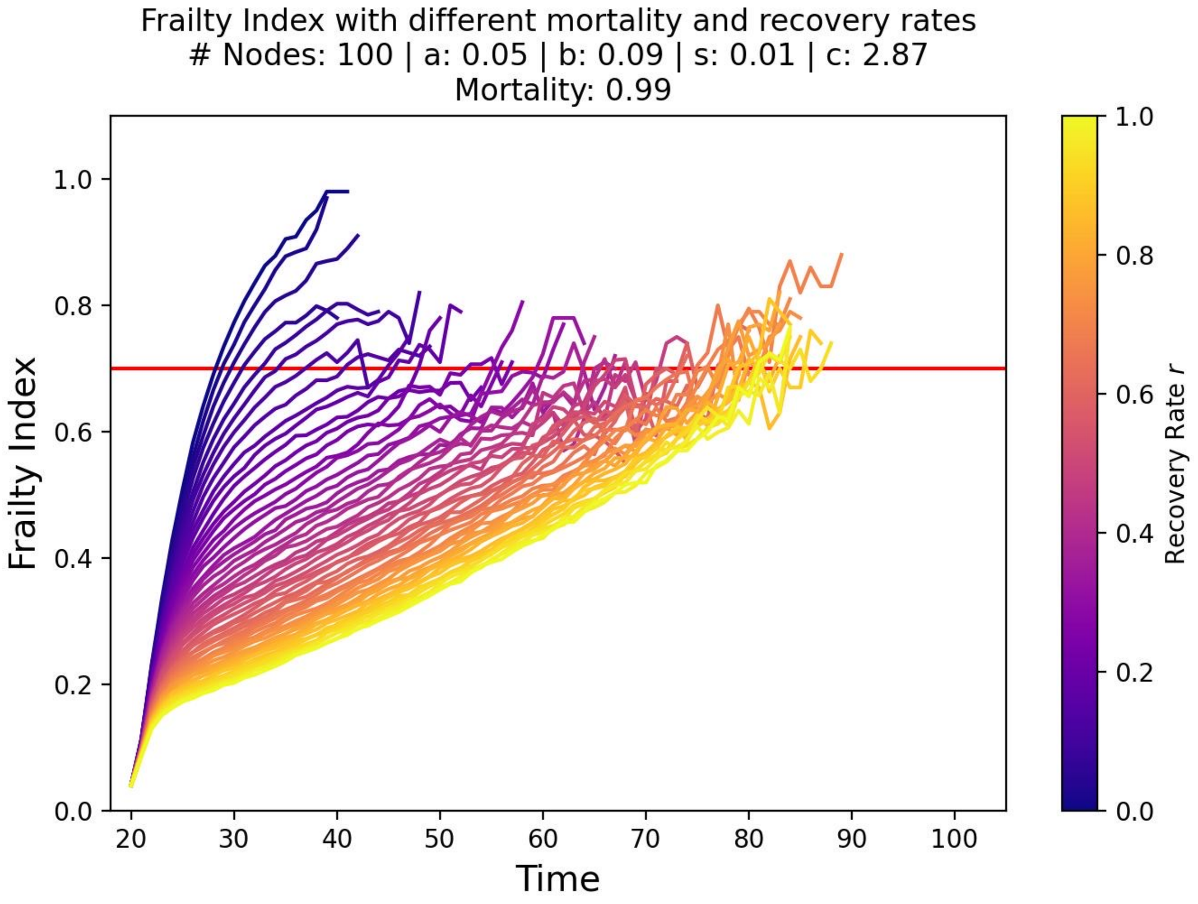
[1] Rockwood, K., & Mitnitski, A. (2007). Frailty in relation to the accumulation of deficits. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *62*(7), 722-727.

Frailty Index Saturation (???)



The observed upper limit of the frailty index may be due to the joint selection for mortality in the dynamics. When a specific value of frailty index is reached (around a maximum) mortality becomes large enough for the individual to recover and die **(???)**.

Frailty Index Saturation (???)



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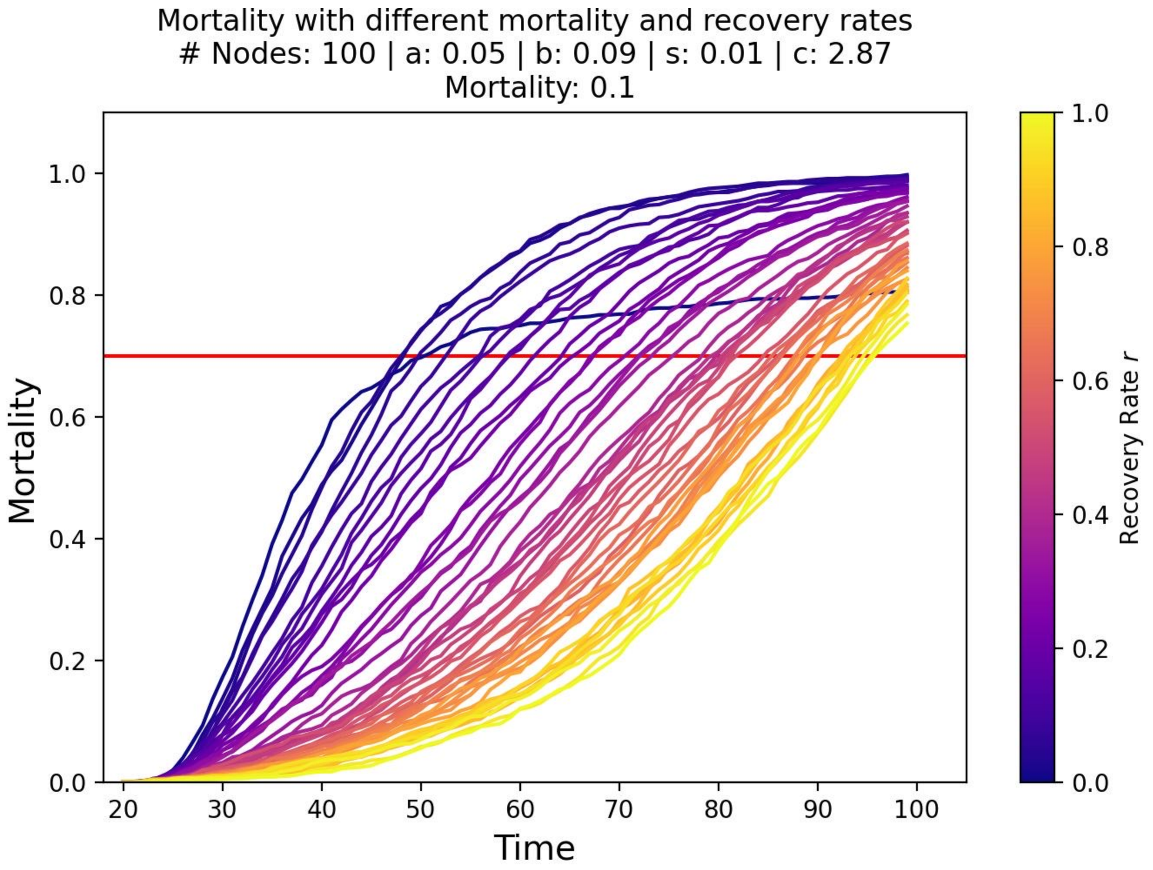
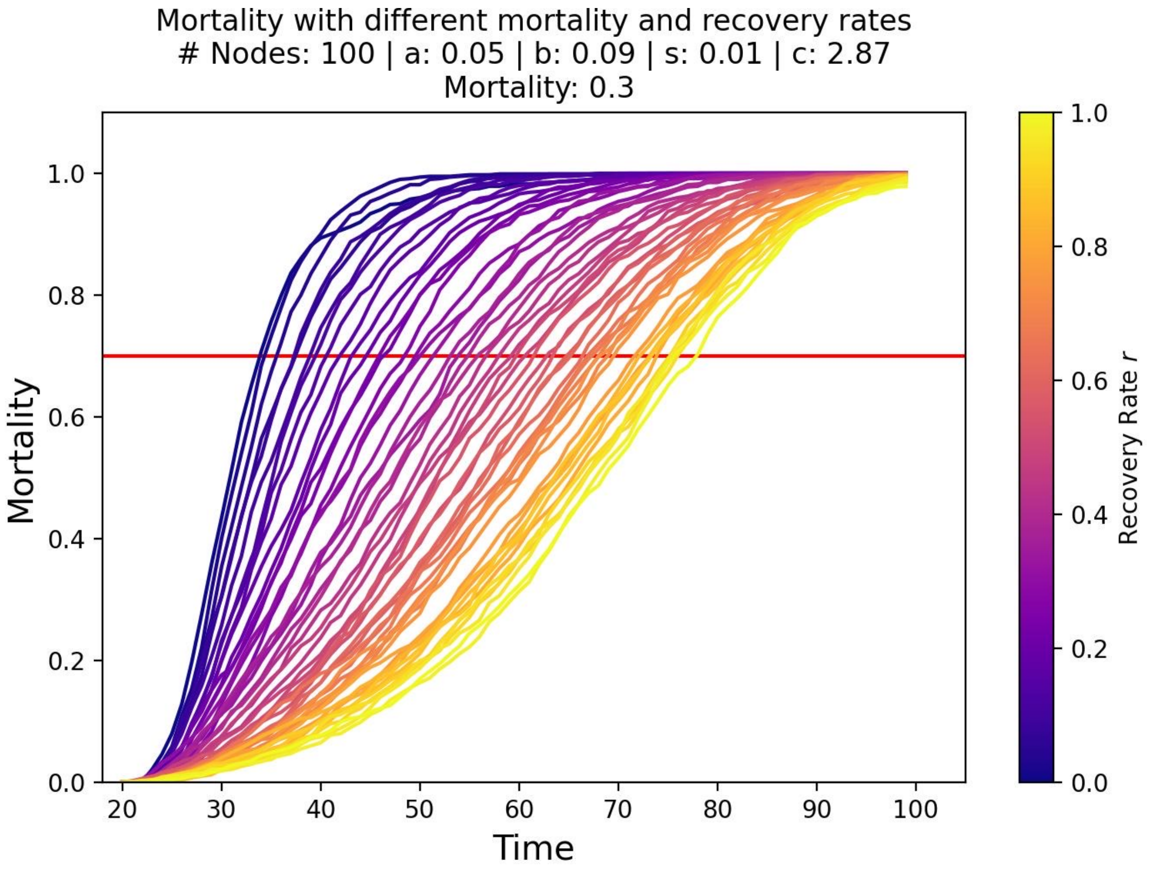
Recovery does not affect whether or not there is a maximum limit, but it does determine the time position of the maximum limit (Moves forward in time). Can we see from clinical data over the years how this boundary has changed in position?. **(Changes in the SM correlation ???)**

Mortality process

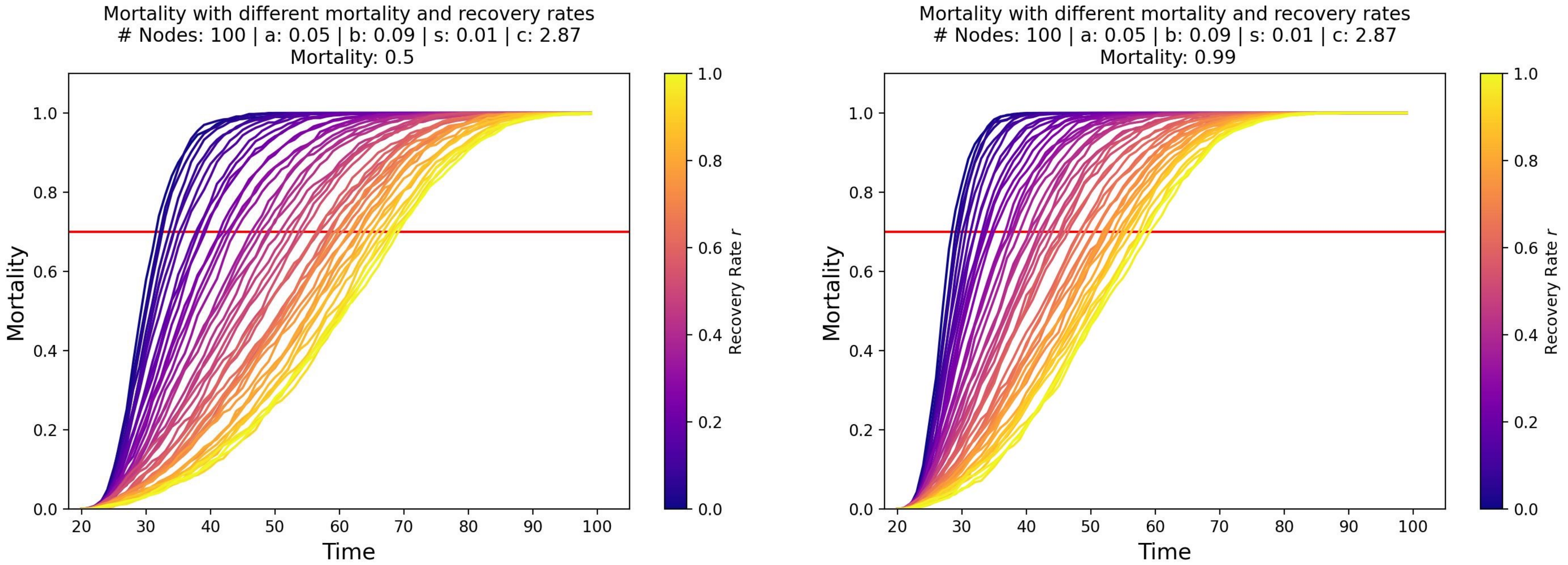




Mortality dynamics with high recovery rates (r>0.7) allow to obtain behaviors such as Gompertz's law.

The recovery rate can determine the shape of the curve, **so could it significantly affect the shape of the SM correlation?**

Mortality process



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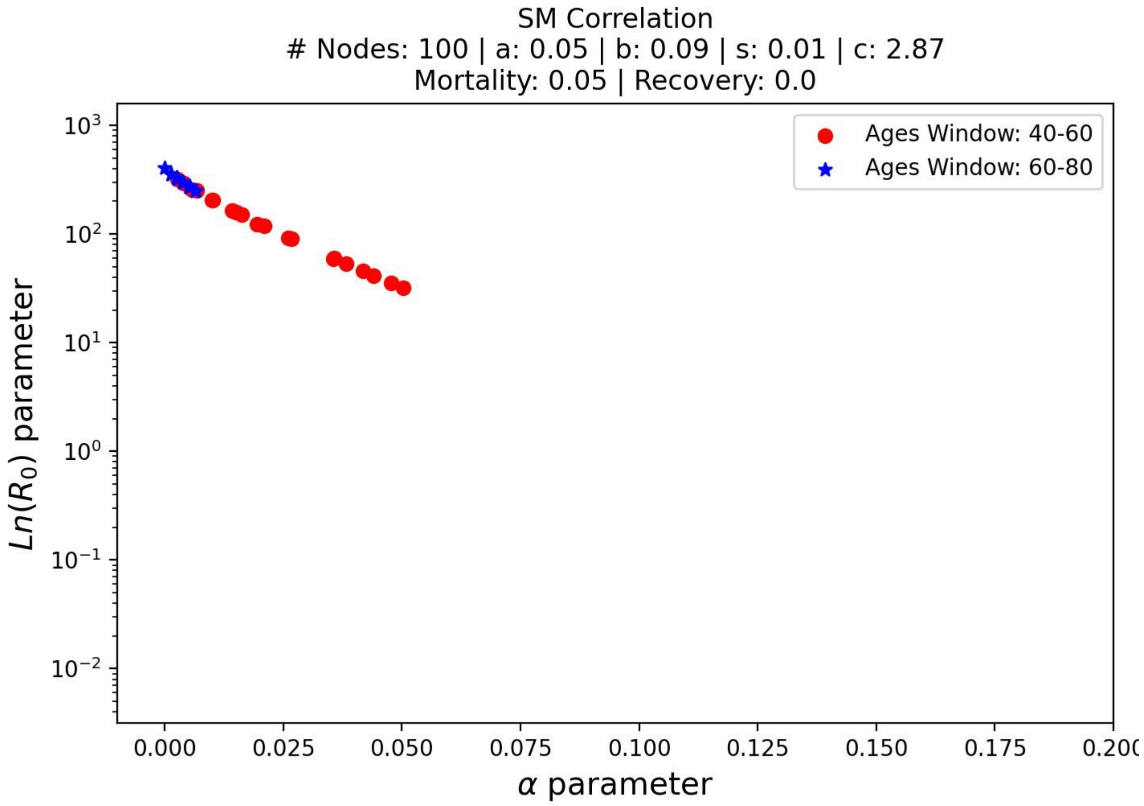
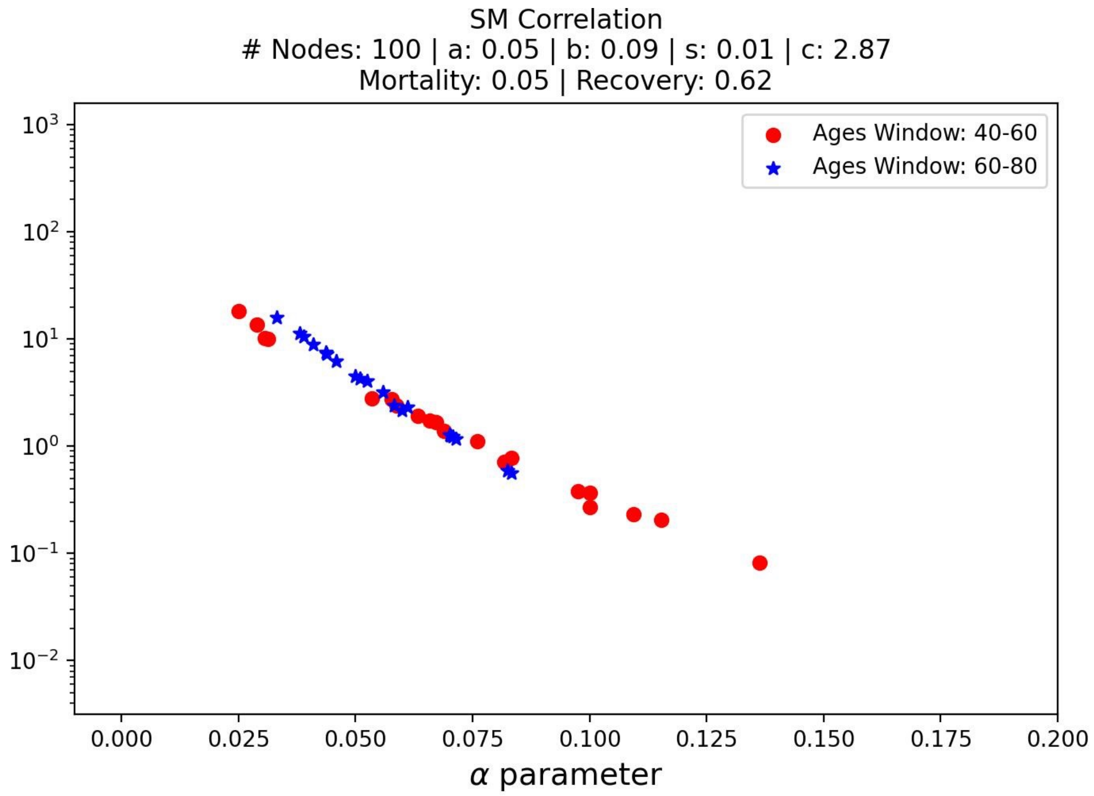
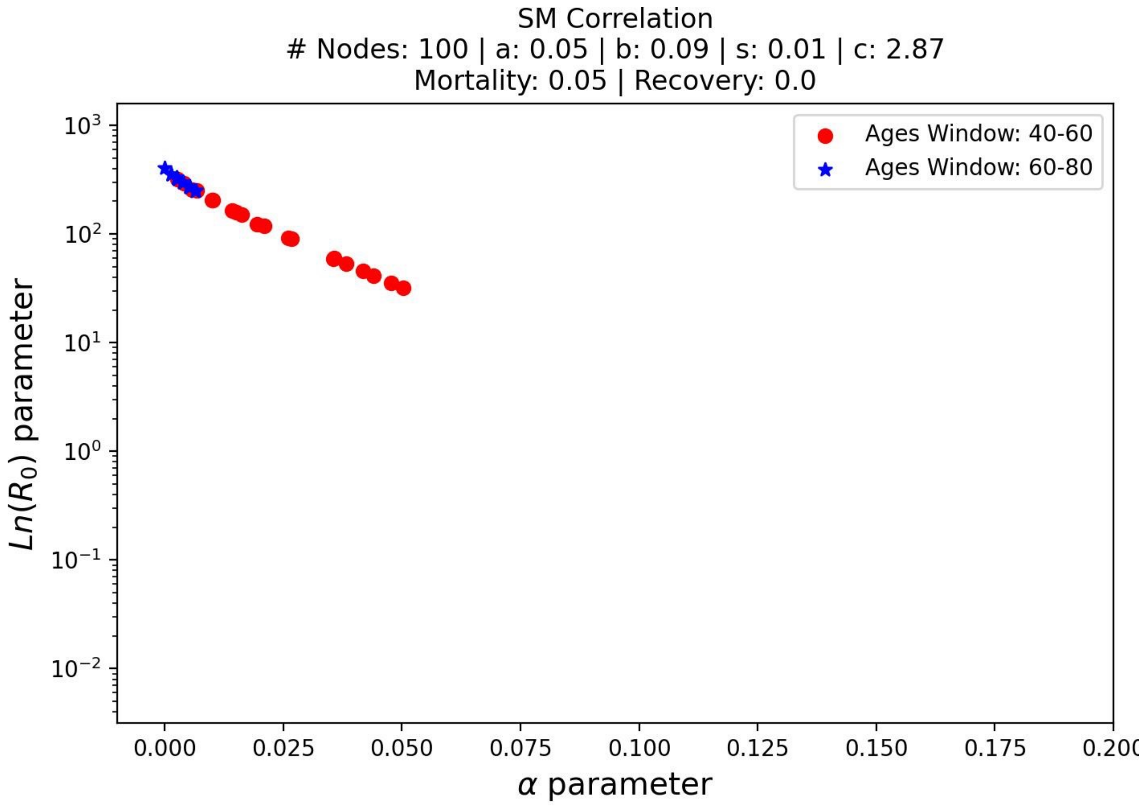
SM Correlation

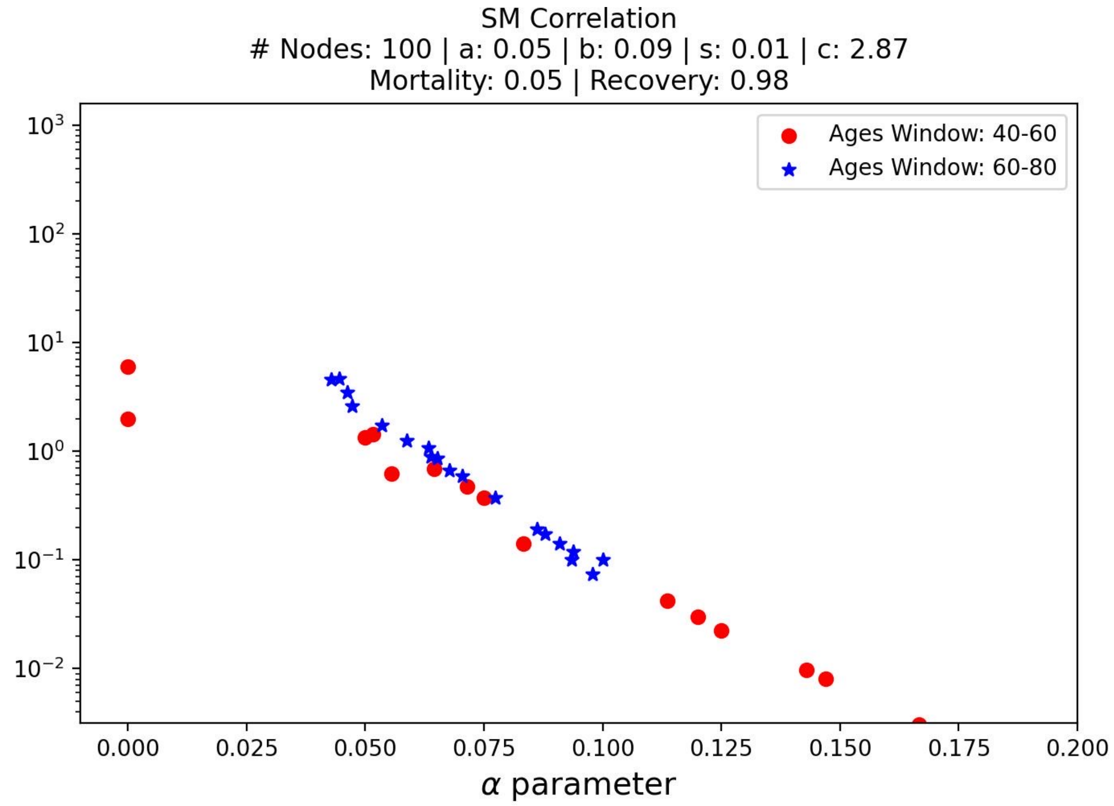




Higher recovery rate values with a constant mortality rate generate an increase in the alpha parameter and a decrease in the R parameter.

SM Correlation





High recoveries and low mortality make both observation groups have more similar SM correlations with each other **(Stochasticity of the frailty index ???).**

SM Correlation

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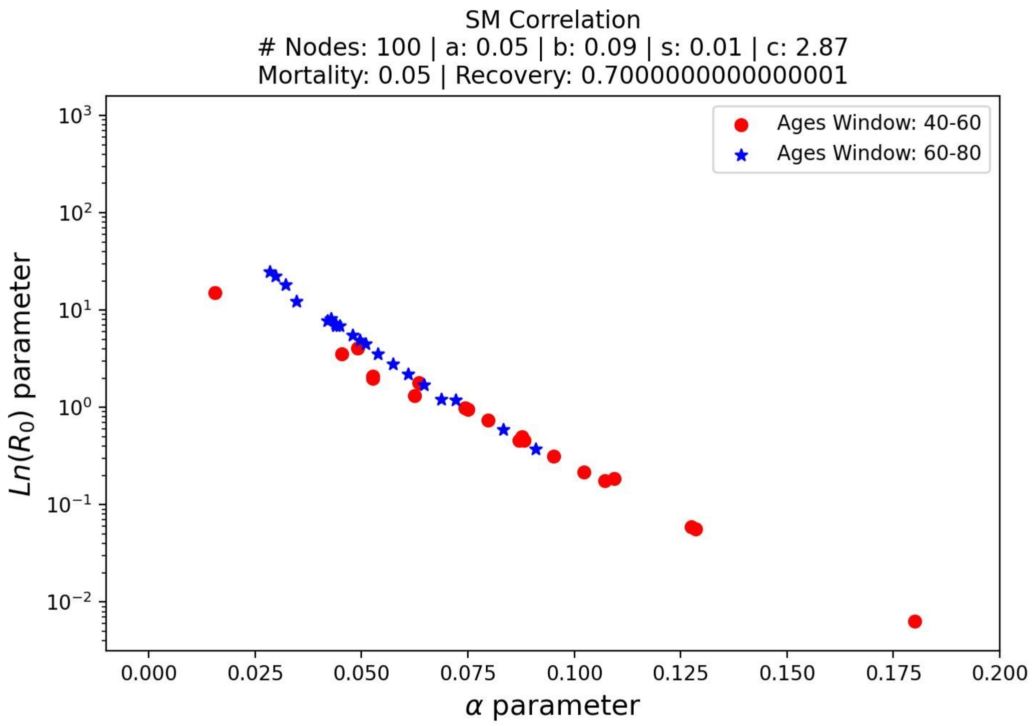
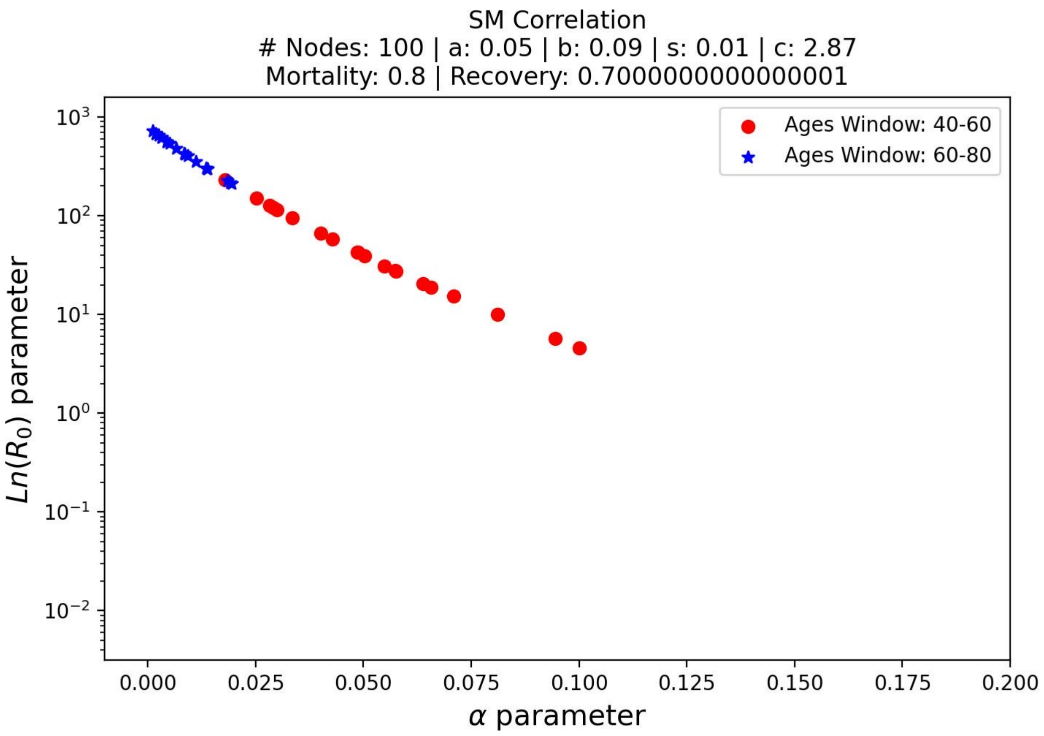
1. If there is greater stochasticity of the frailty index, then there are greater differences between age groups. High mortality increases stochasticity at younger ages, i.e., as mortality increases, people at younger ages are affected.





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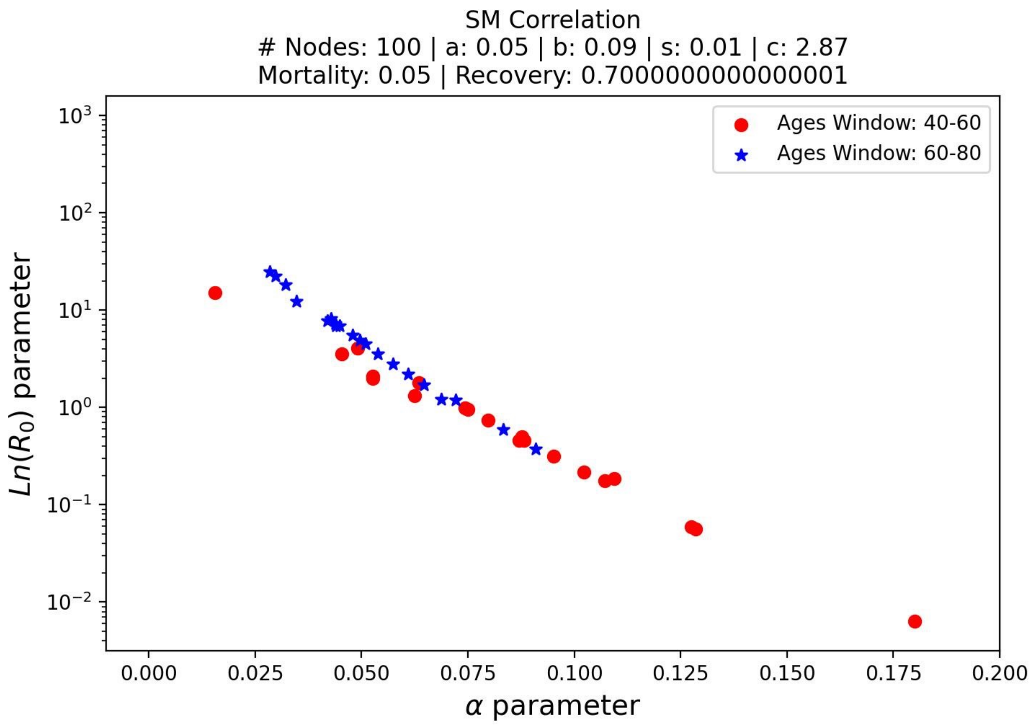
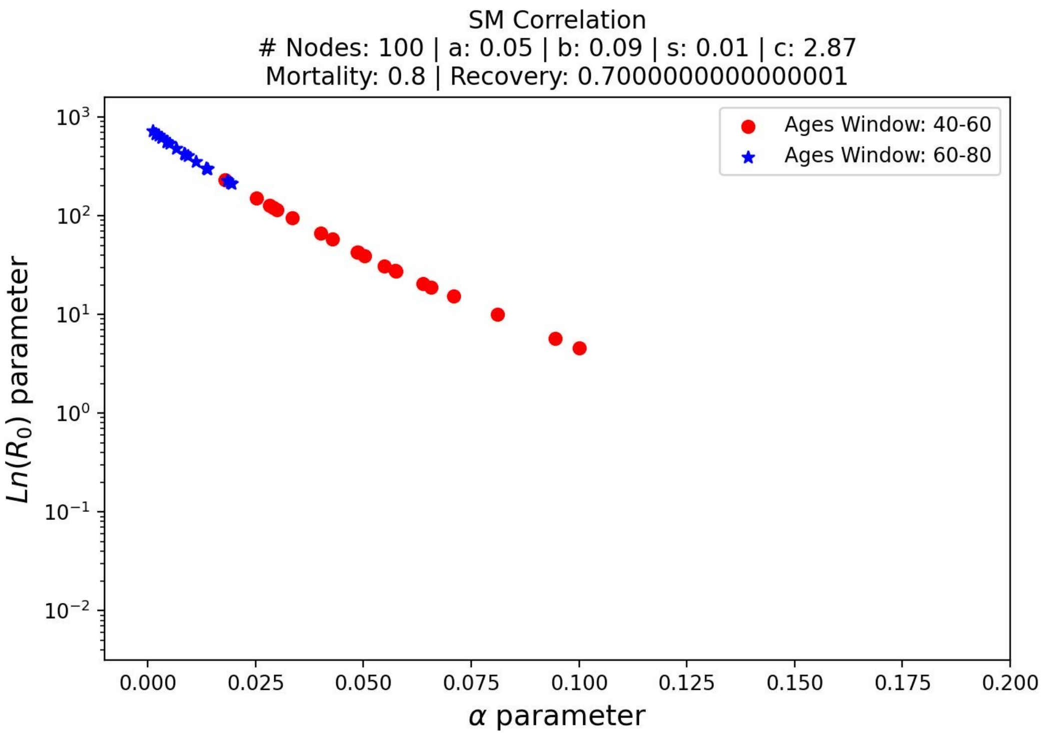
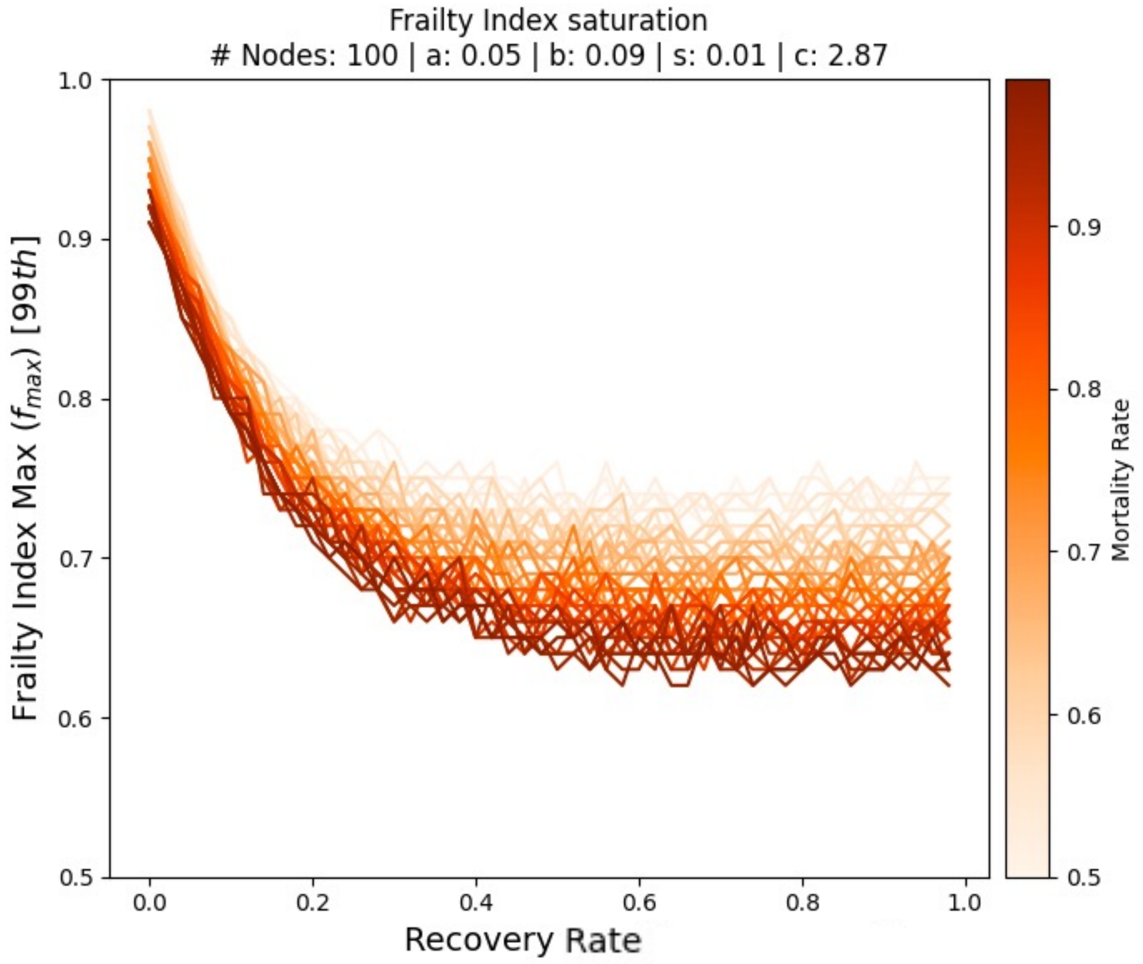
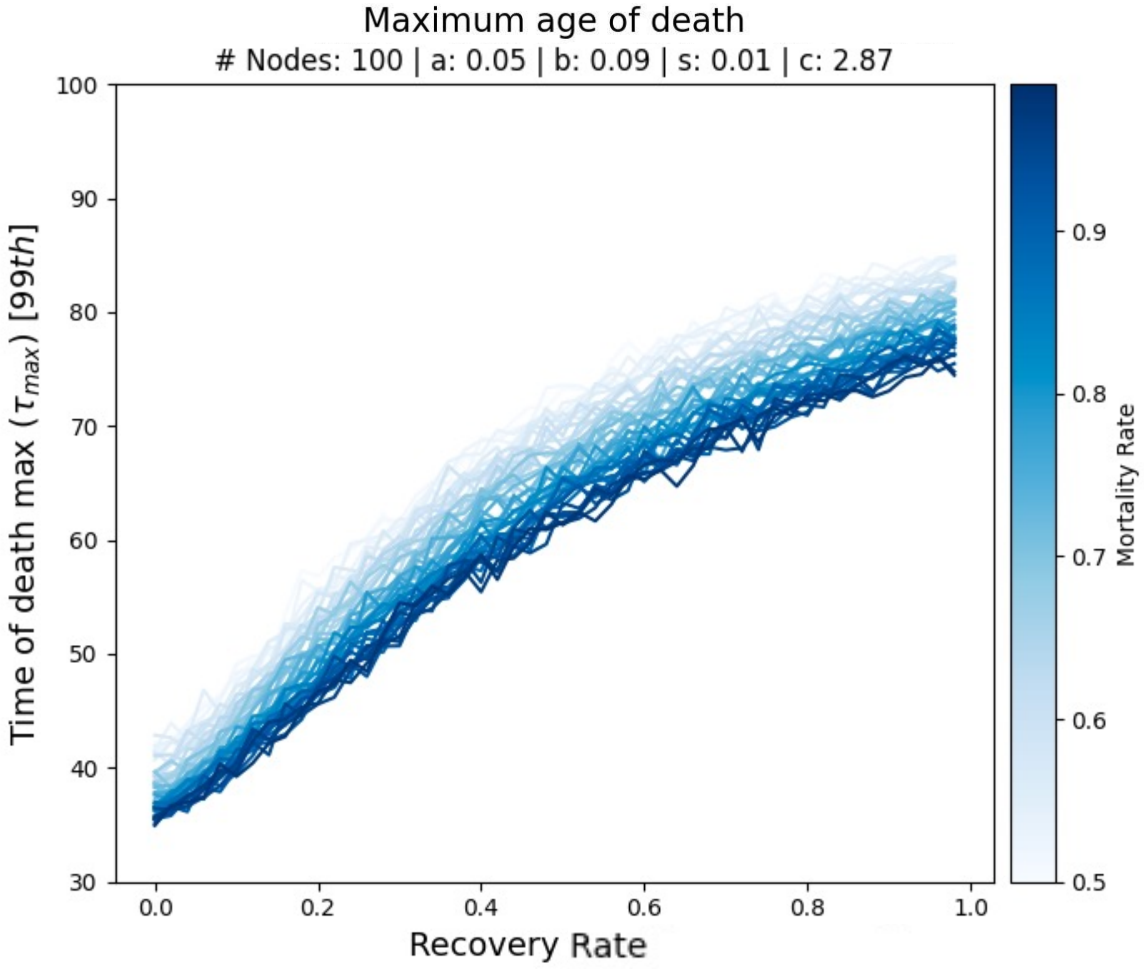




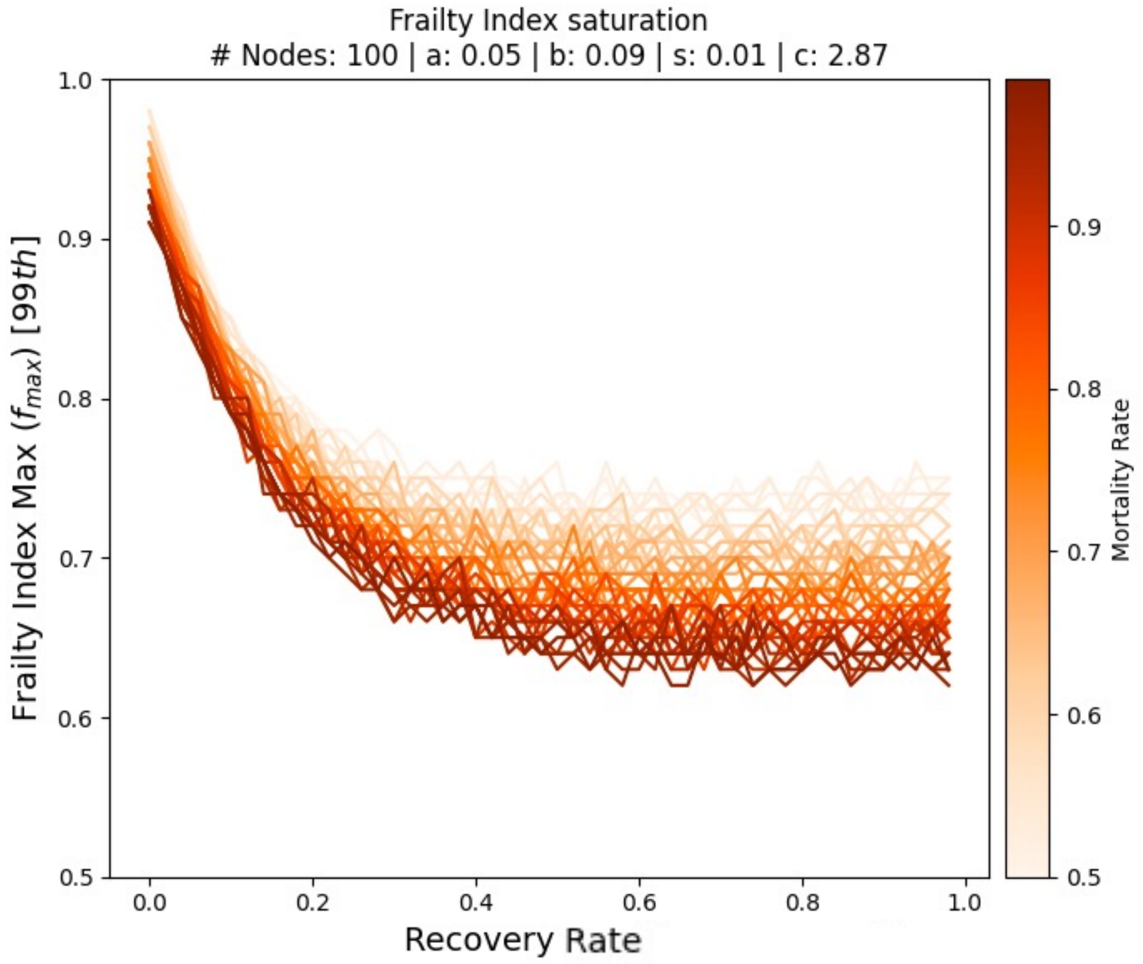
Frailty Index Saturation

Shapes of the Frailty Max and Age Max with different values of recovery rate and mortality rate





Frailty Index Saturation



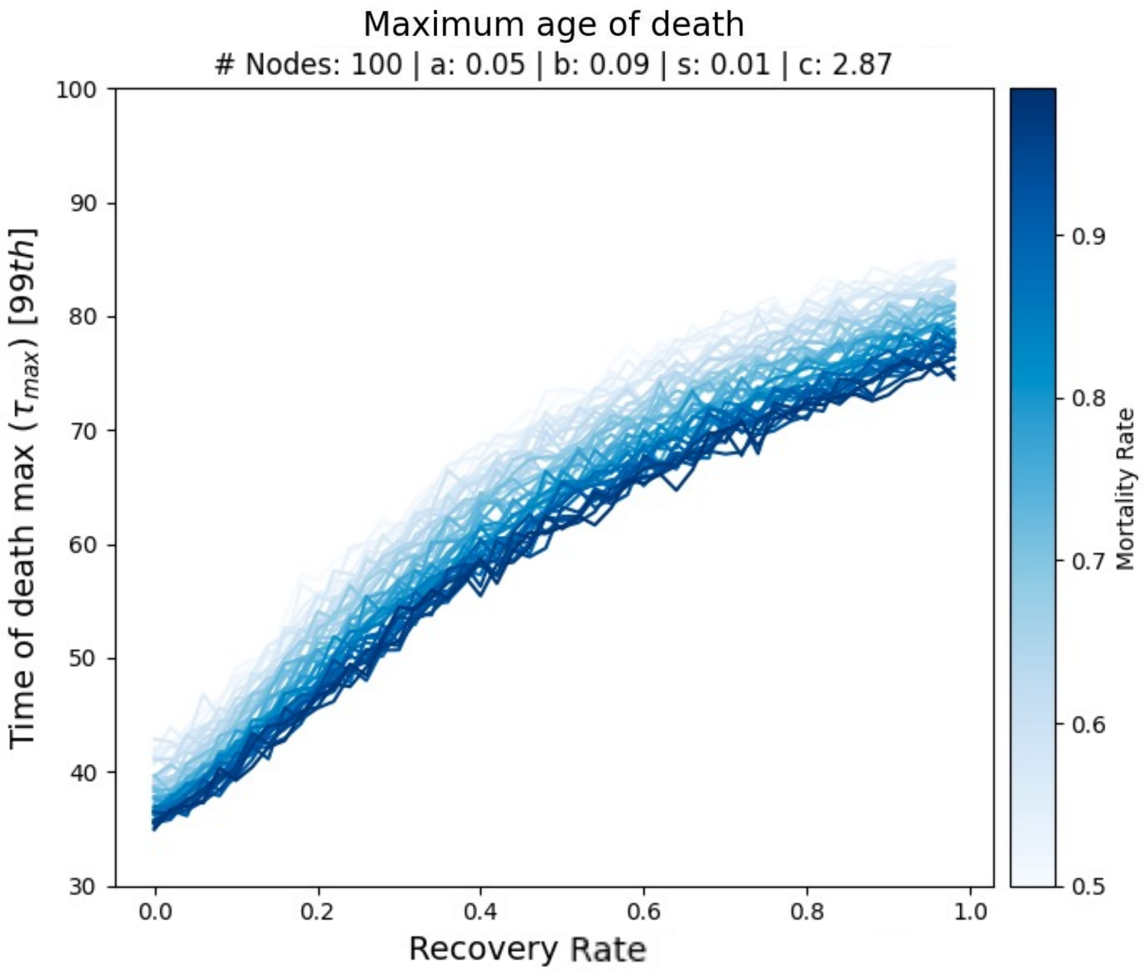
Populations with higher mortality rates require a lower frailty index to die for a fixed recovery rate.

In a population with a fixed mortality rate, having higher recovery rates does not imply having a higher frailty index at the time of death.

Higher resilience

People die with less damage to their bodies throughout their lives because they have a greater capacity for recovery.

Frailty Index Saturation

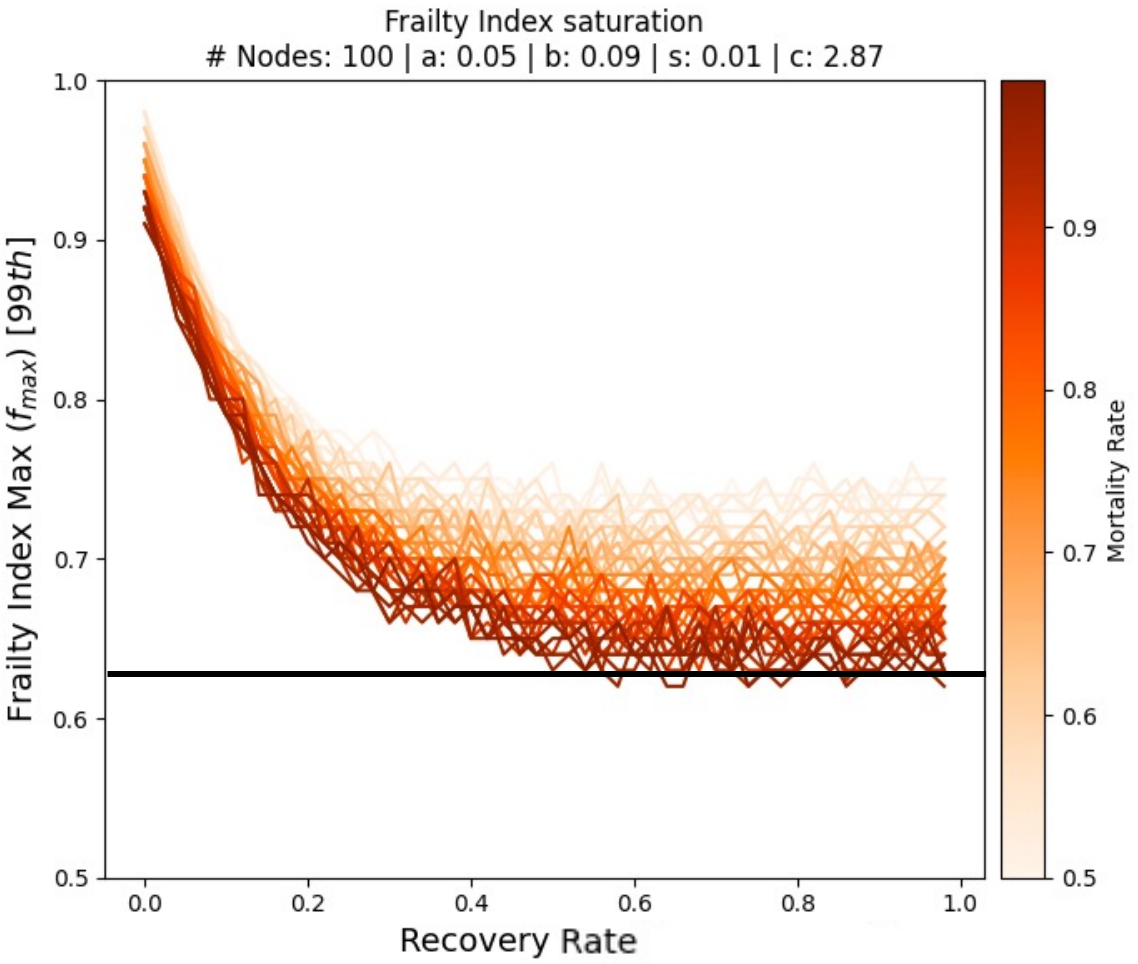


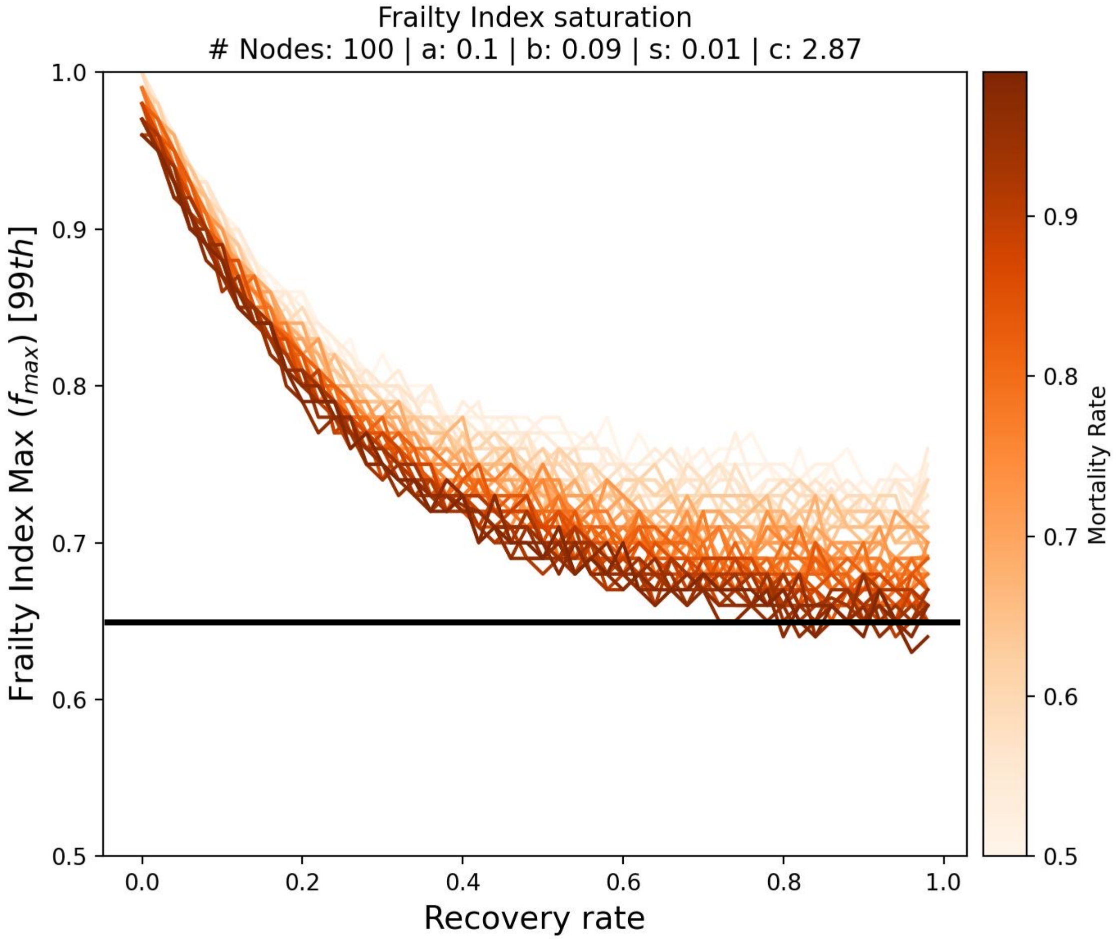
The recovery rate contributes to people living for a longer time, whereas high mortality rates have the opposite effect.

People who die at an early age do so with high frailty indices, whereas those who die with lower frailty indices do so at an older age.

Frailty Index Saturation

Bigger value of damage rate





Frailty Index Saturation

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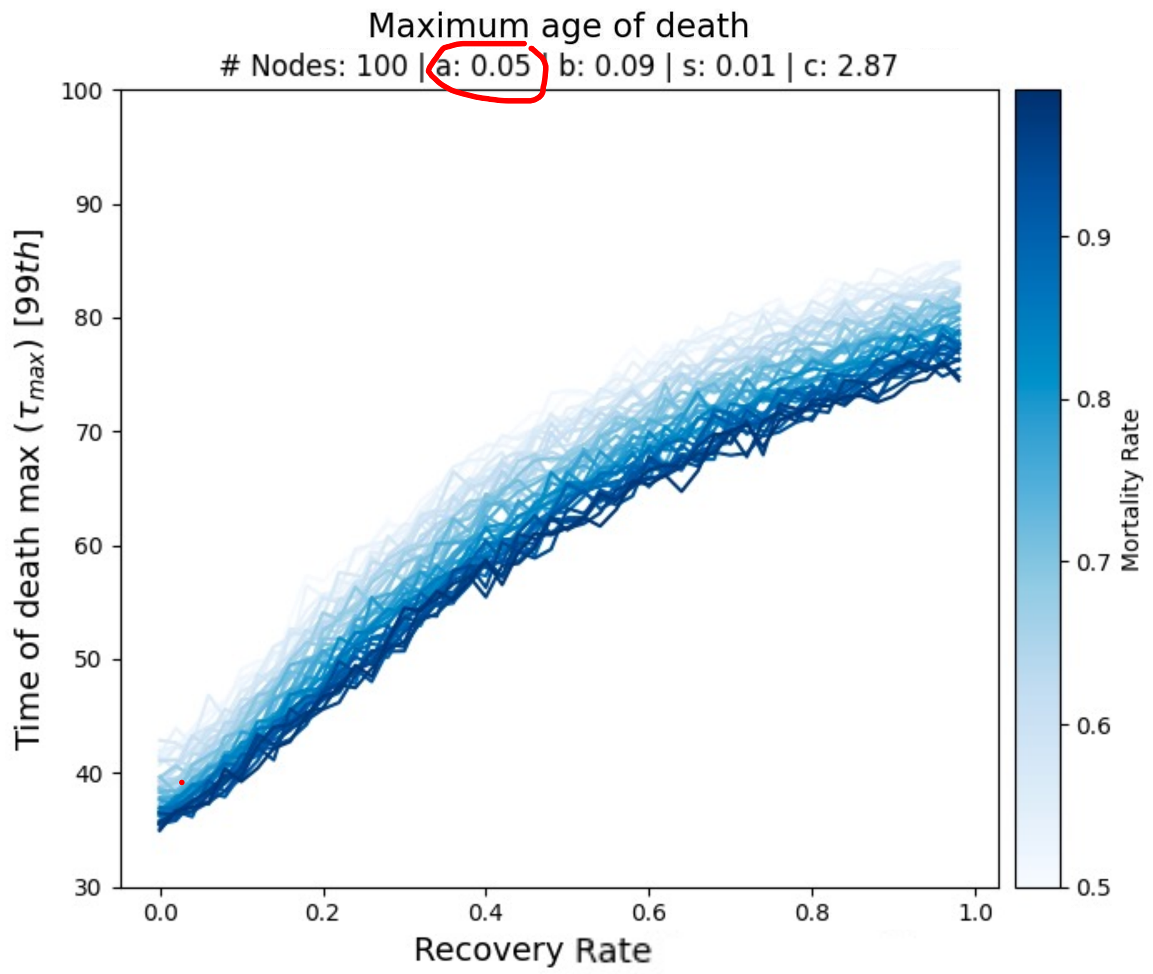
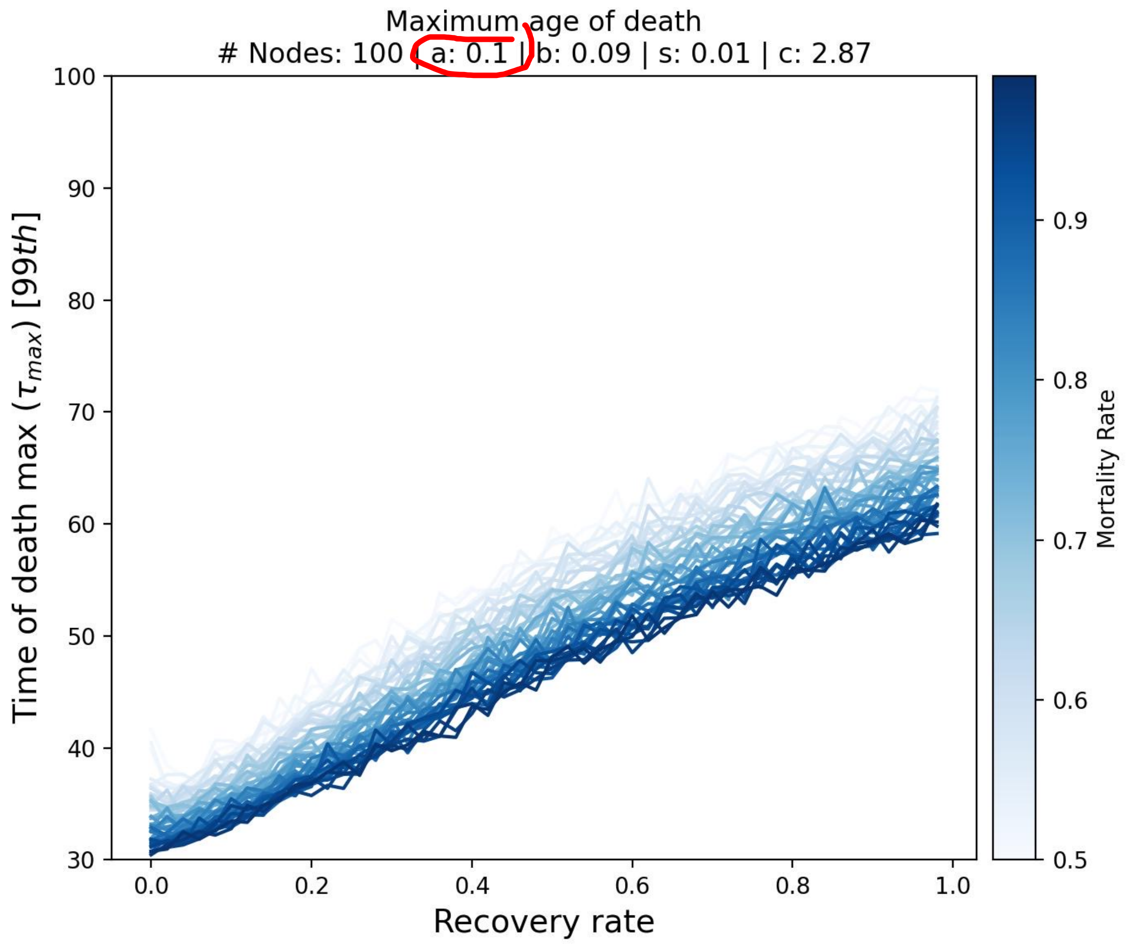
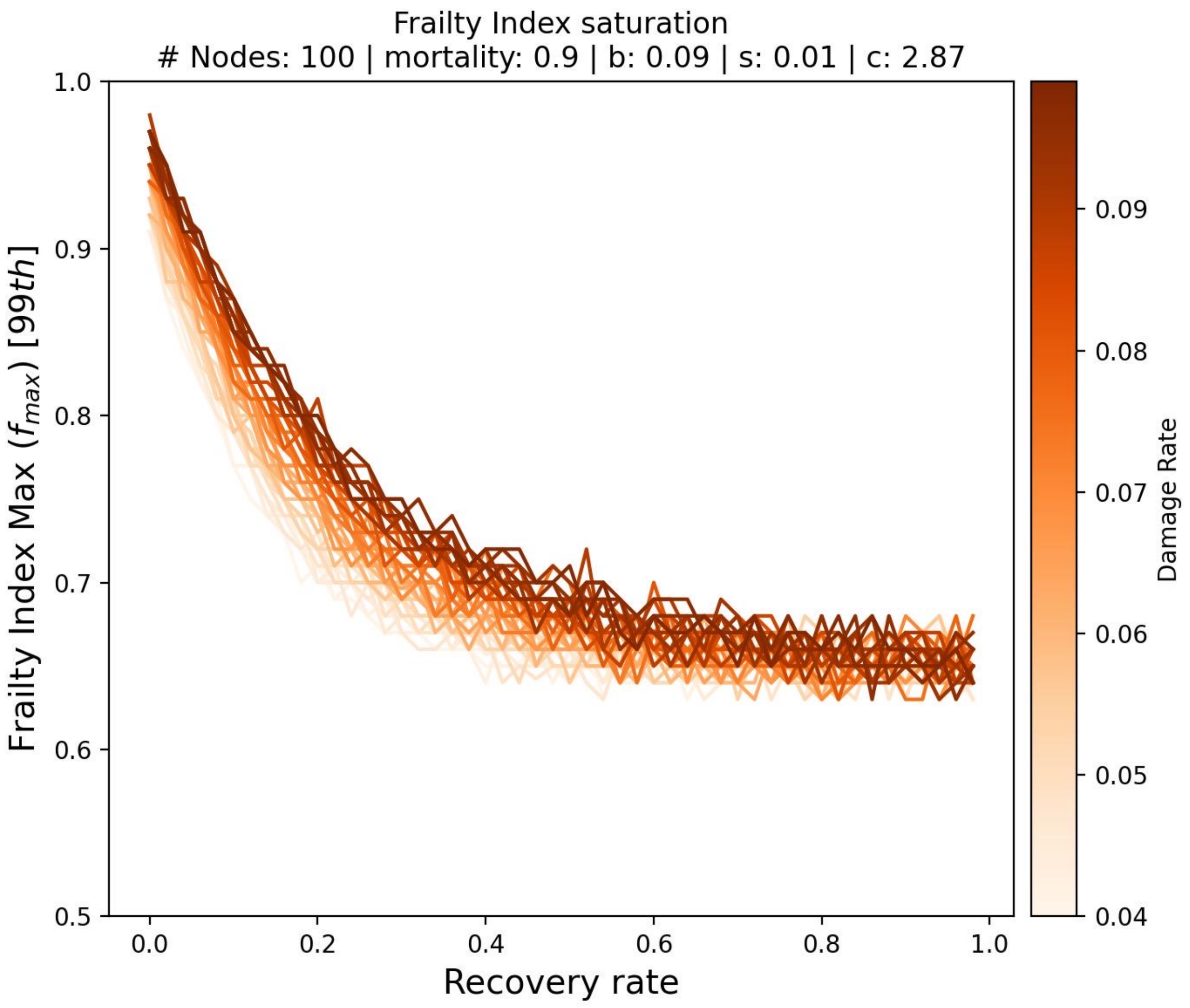
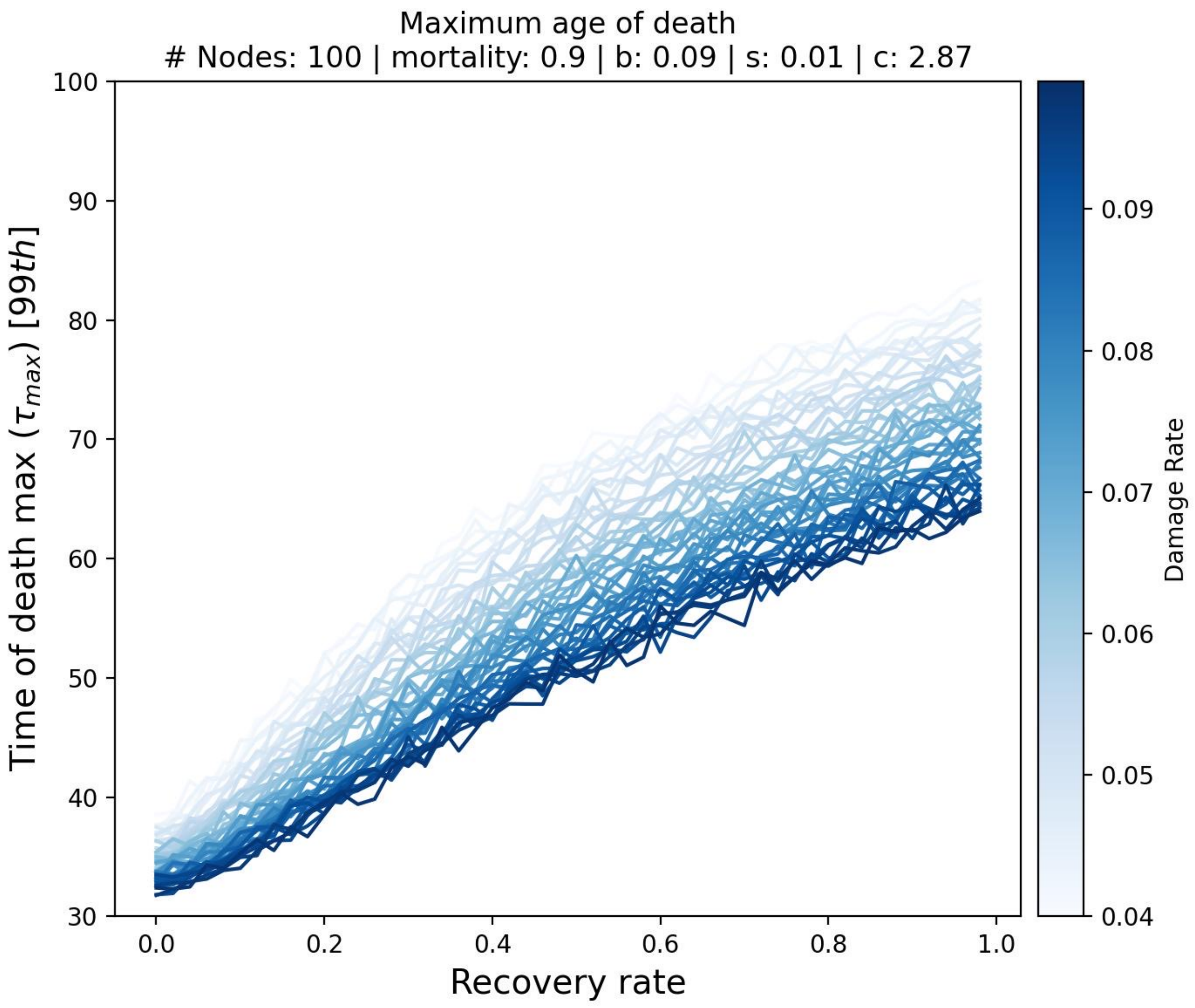




Frailty Index Saturation

Shapes of the Frailty Max and Age Max with different values of recovery rate and damage rate





Frailty Index Saturation

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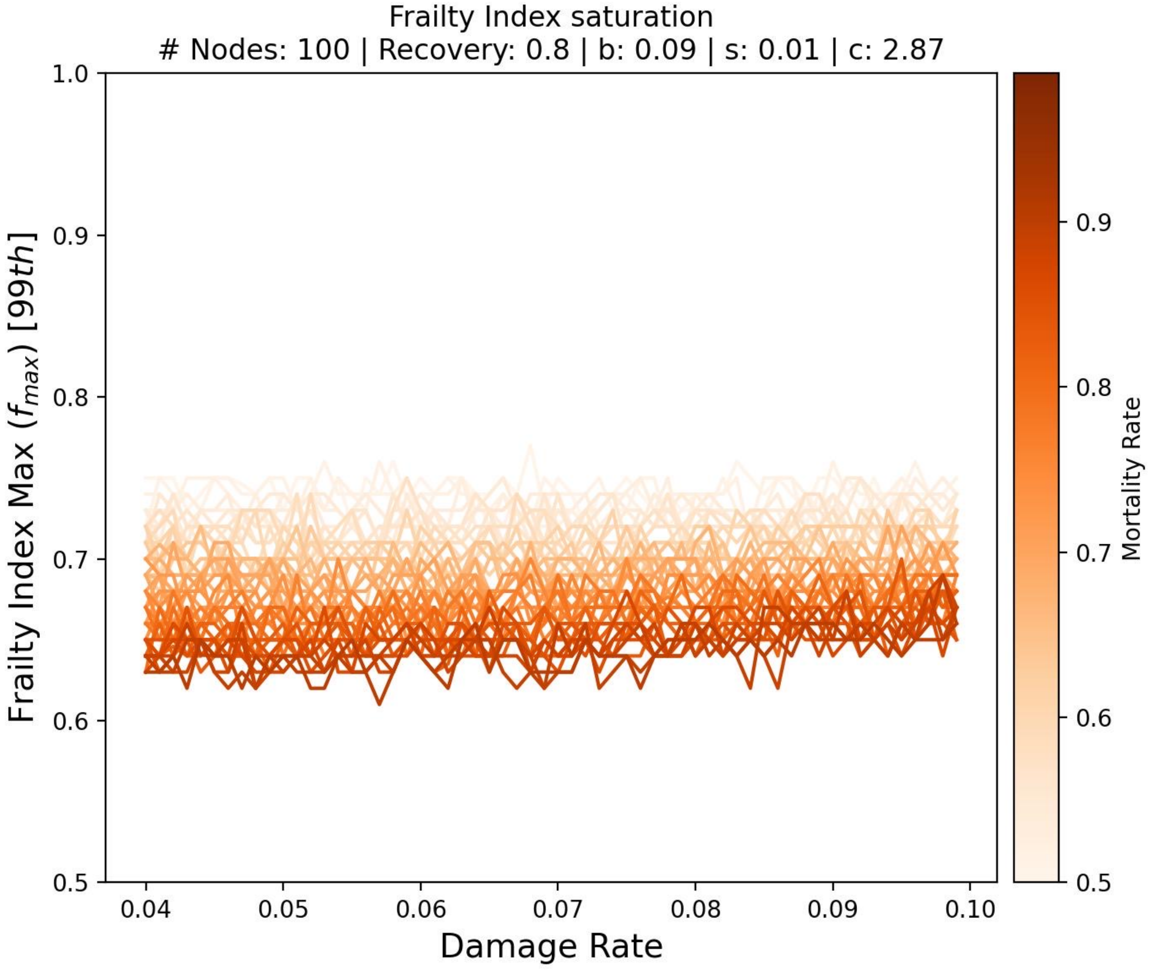

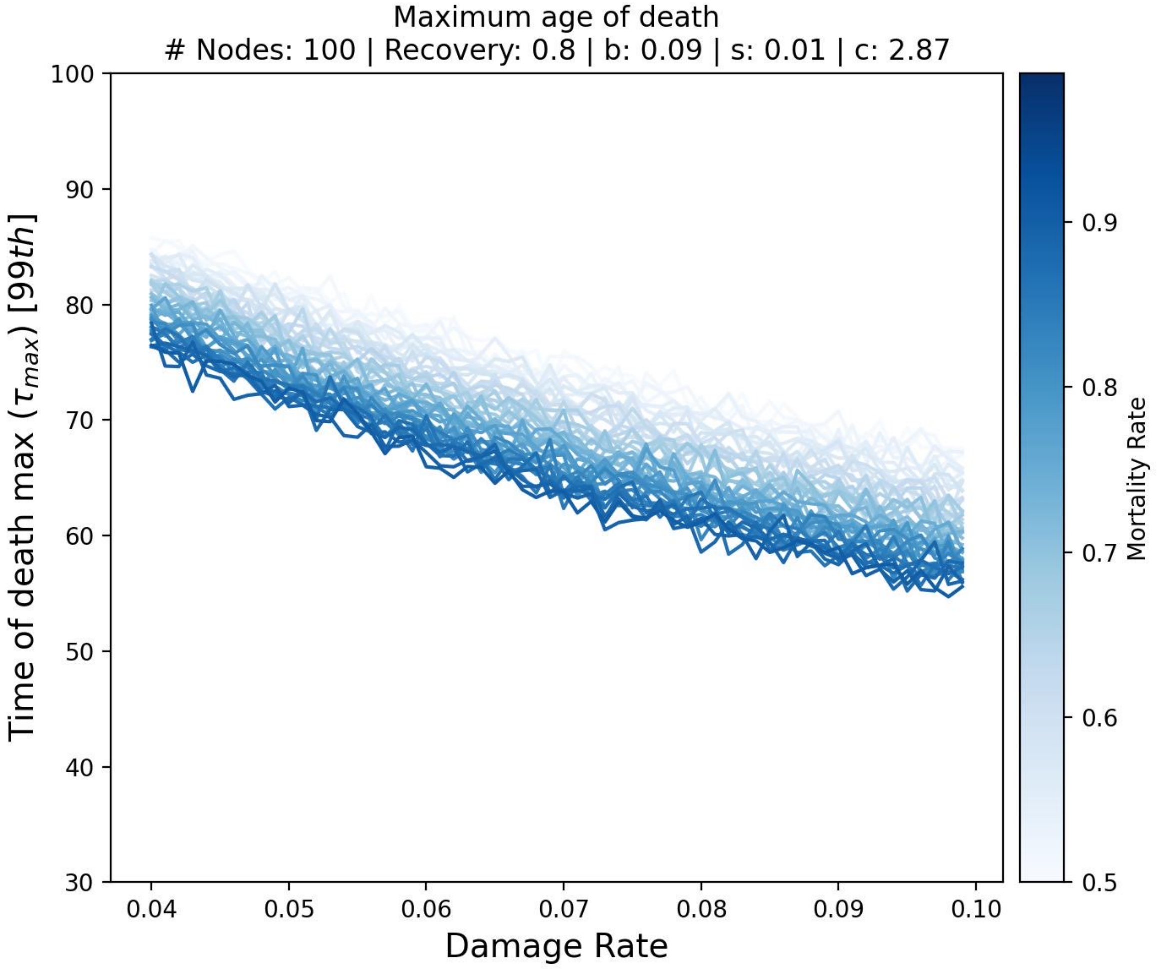

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