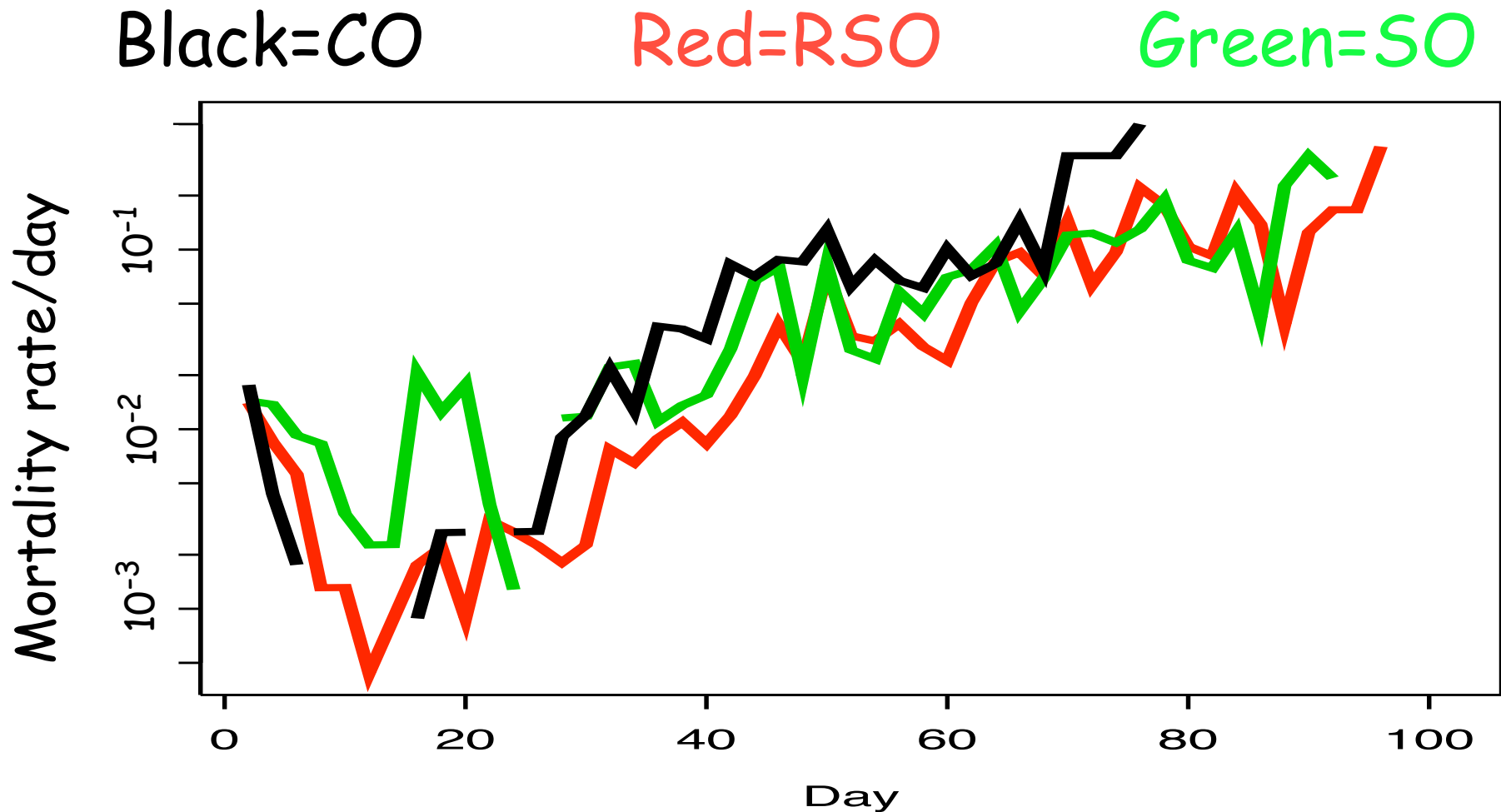


Mortality in heterogeneous populations

Part II: Experiments and Changing frailty models

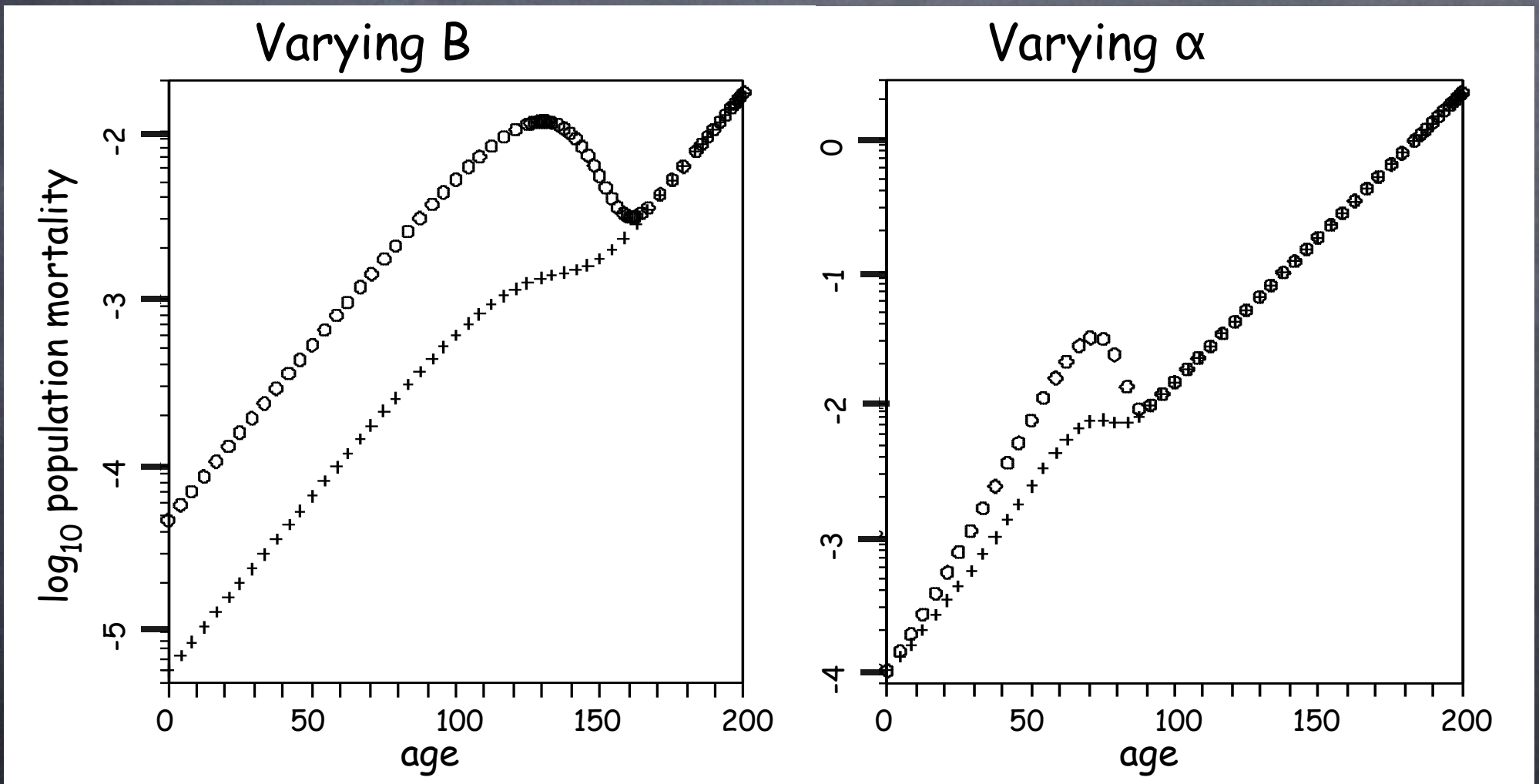
Population heterogeneity has already been tested.

Drapeau et al. "Testing the heterogeneity theory of late-life mortality plateaus by using cohorts of *D. melanogaster*" (2000)



Fixed frailty: $h(x) = Be^{\alpha x}$

Example: two subpopulations



$B_1=10^{-4}$

$B_2=10^{-6}$

$\alpha=.05$

o starts with 50% robust (type 2)

+ starts with 90% robust (type 2)

$B=10^{-4}$

$\alpha_1=.1$

$\alpha_2=.05$

Male			Female		
CO	RSO	SO	CO	RSO	SO
42	76	44	50	78	46
0.11	0.21	0.07	0.10	0.14	0.07
42	44	44	50	66	52
0.10	0.07	0.05	0.13	0.15	0.08
46	68	70	46	52	72
0.13	0.11	0.10	0.12	0.07	0.16
44	44	44	50	52	46
0.12	0.08	0.07	0.15	0.10	0.09
44	44	72	52	52	46
0.10	0.08	0.19	0.12	0.09	0.07

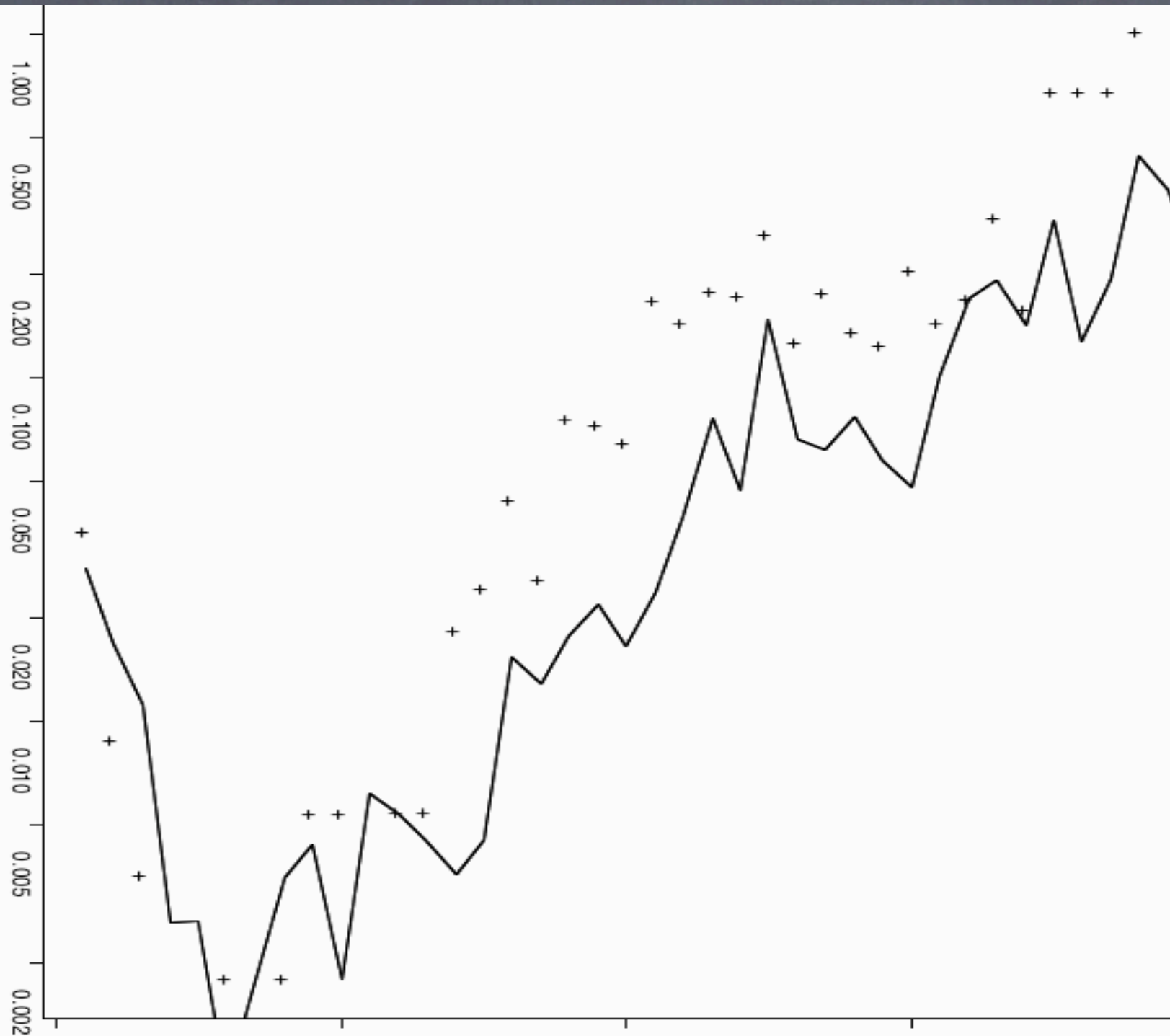
Estimated plateau mortalities and
"breakdays" in five trials

Male			Female		
CO	RSO	SO	CO	RSO	SO
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44	44	72	52	52	46
0.10	0.08	0.19	0.12	0.09	0.07

Estimated plateau mortalities and
"breakdays" in five trials

Mortality rate

0.05
0.2
0.1
0.05
0.02
0.01
0.005
0.002
0.001

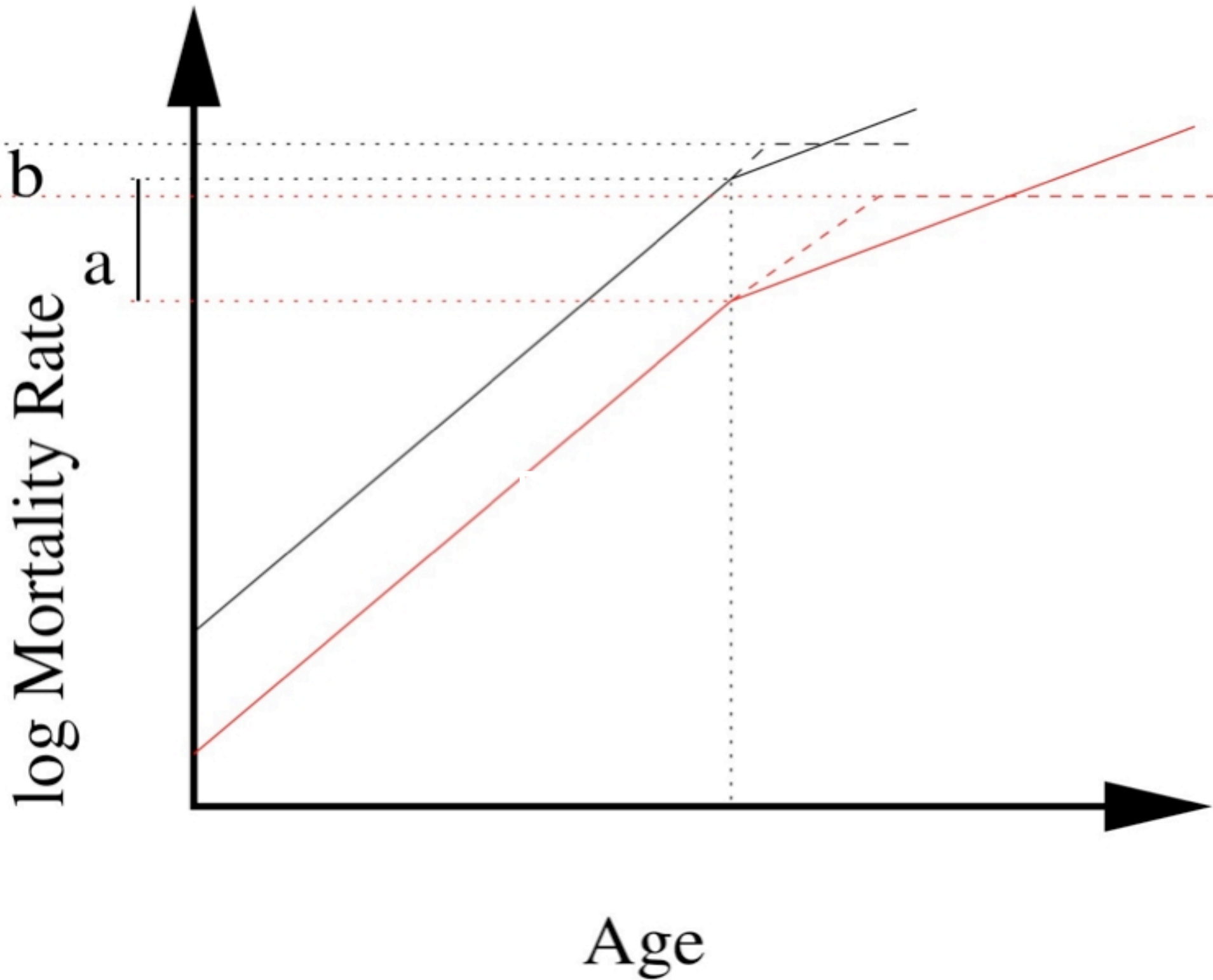


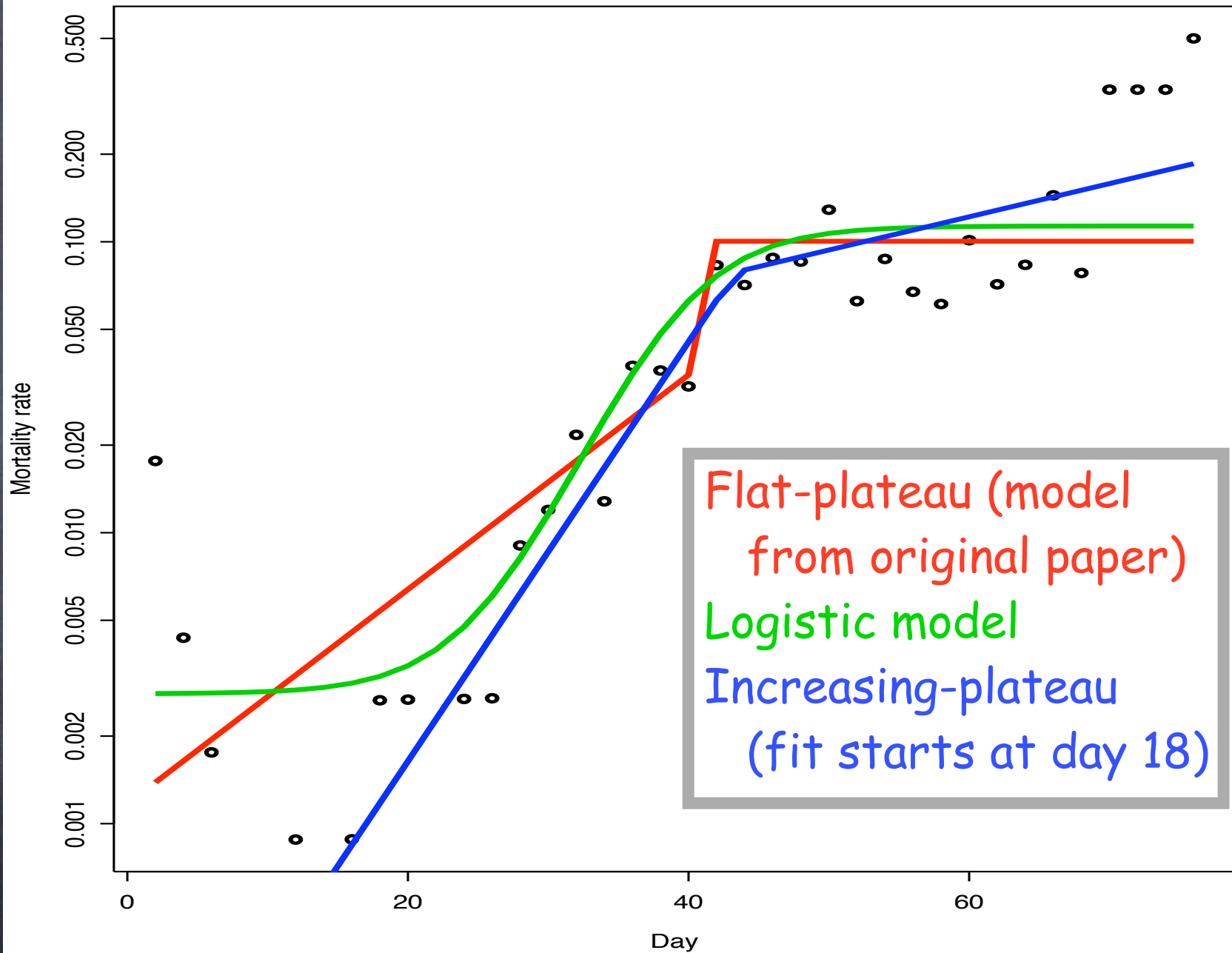
Day

20

40

60





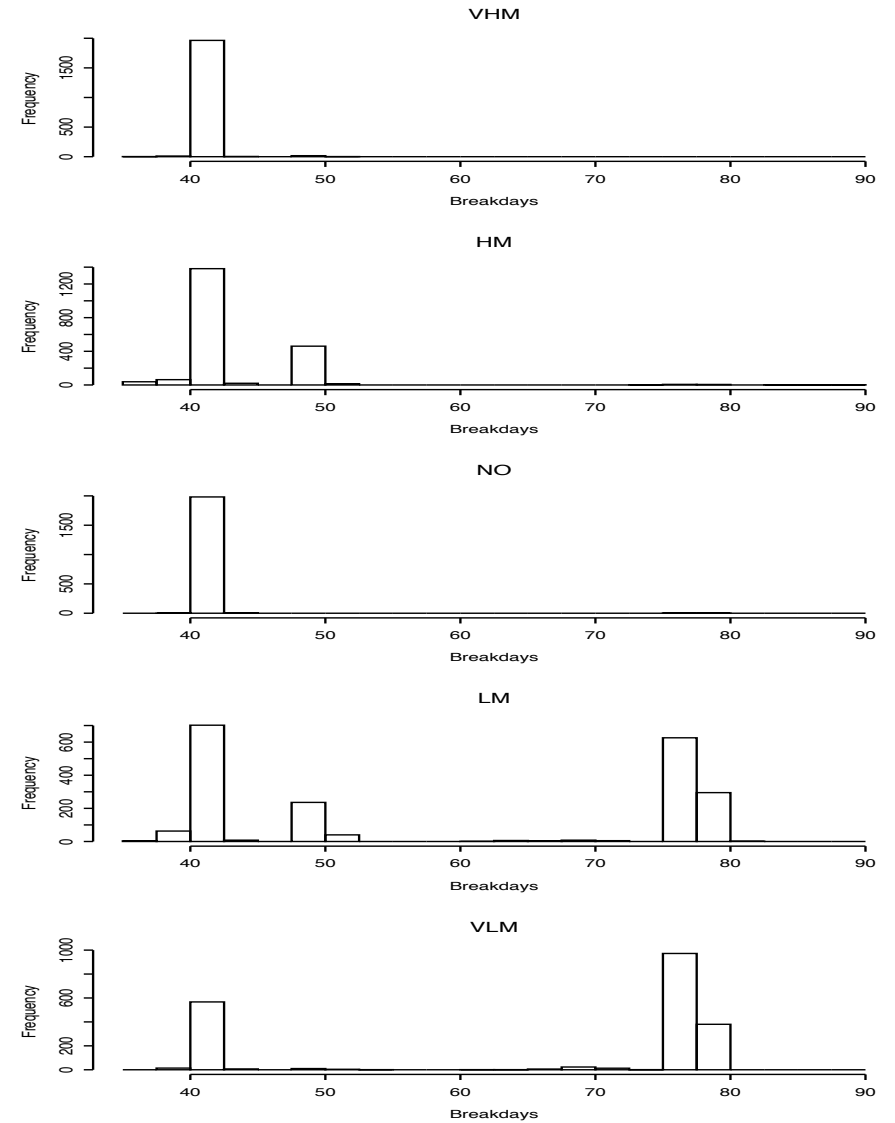
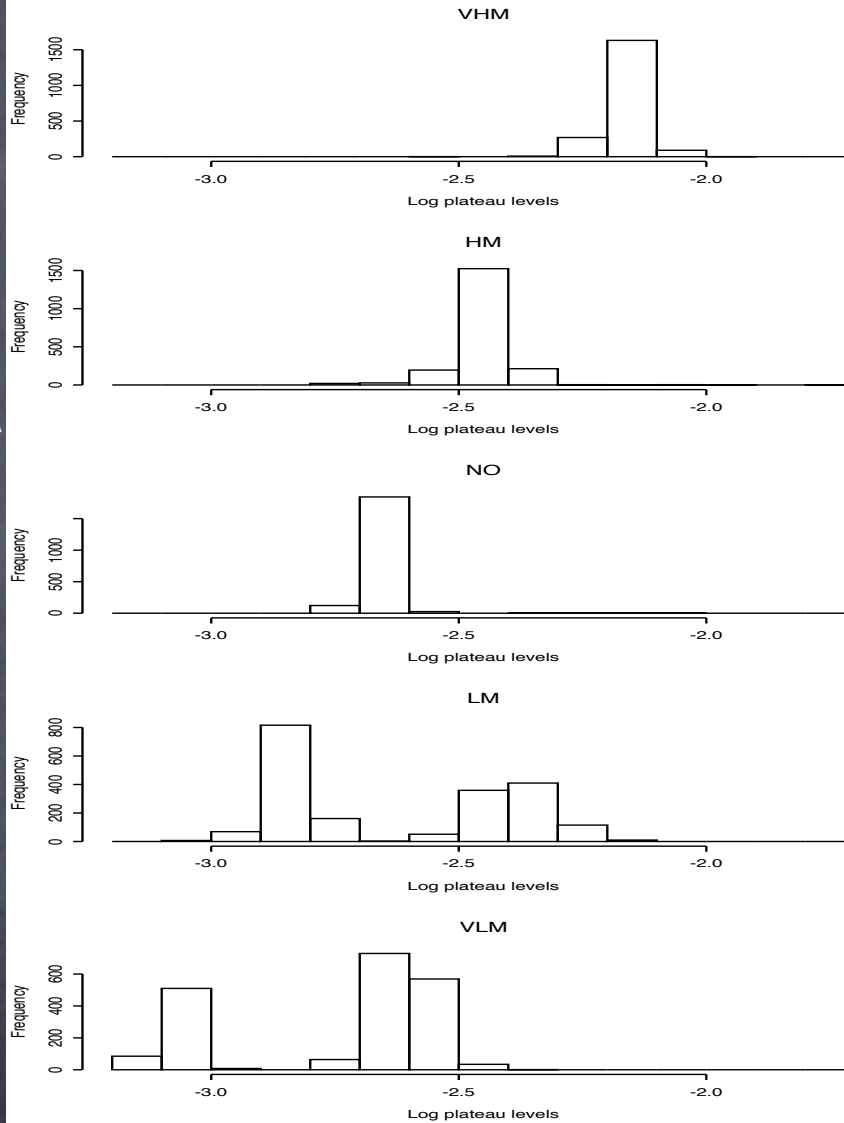
Fitting three different models

Simulation procedure

- Form five virtual strains: NO has average mortality rate over all experimental strains. VHM and HM have mortality rates raised by factor of 1.67 and 1.25. VLM have mortality rates lowered by the same factor.
- Run 2000 simulated survival experiments, starting with 1000 of each strain.
- For each trial, fit all three models. Tabulate breakdays and plateau levels.

Estimates from 2000 simulated populations

Increasing mortality



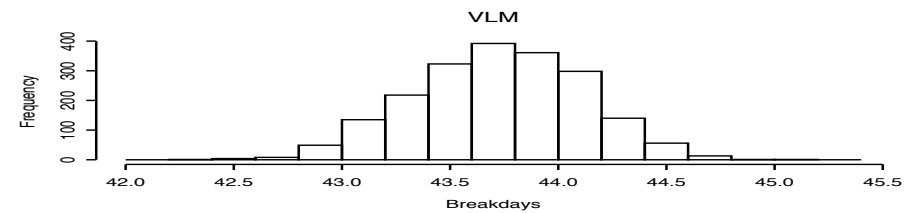
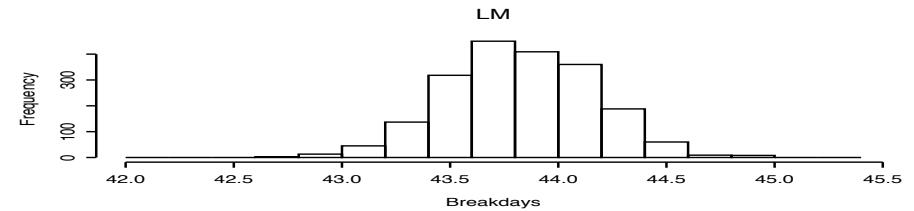
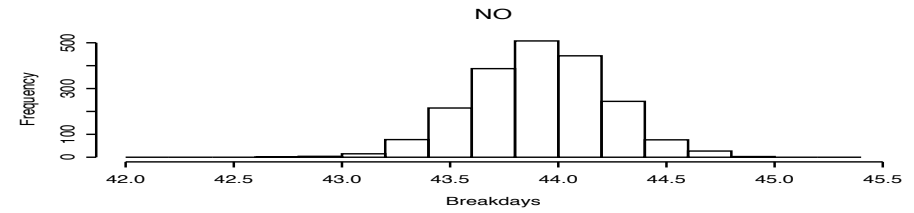
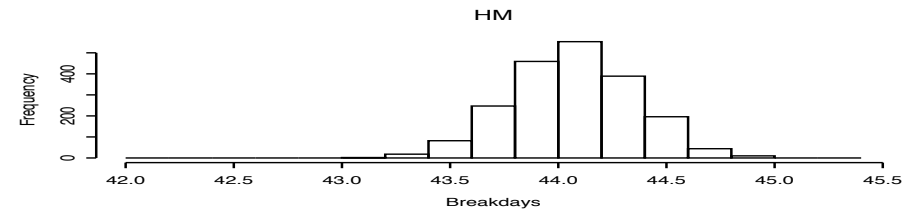
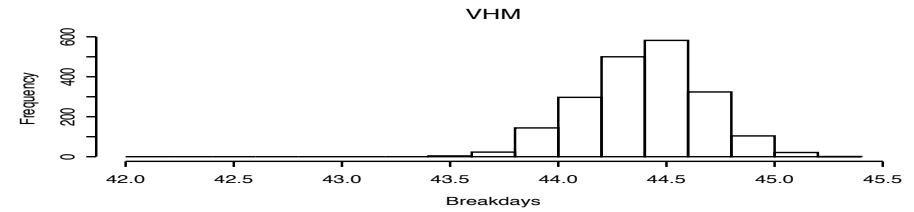
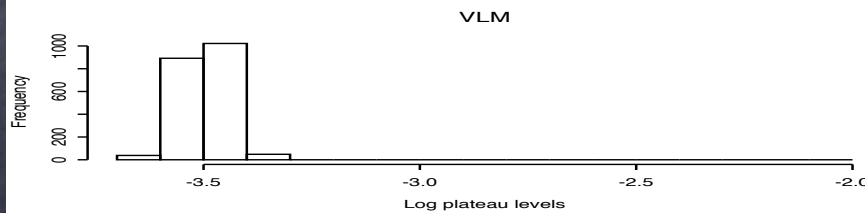
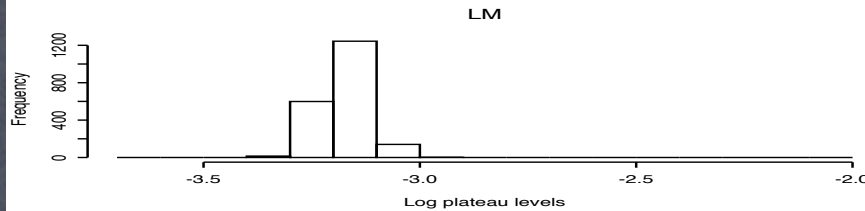
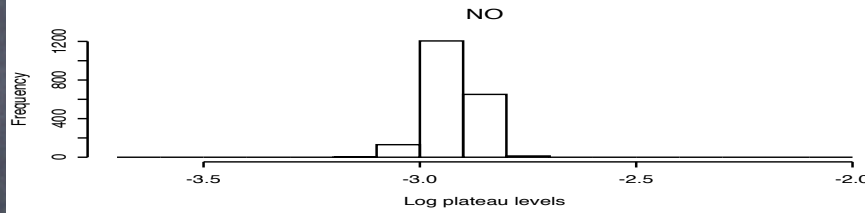
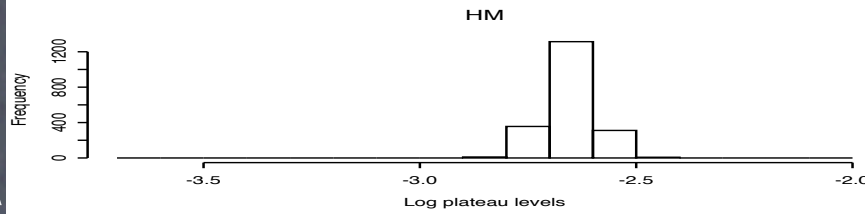
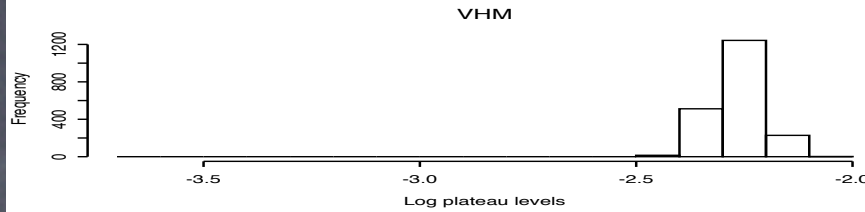
log plateau levels

breakdays

Flat-plateau model

Estimates from 2000 simulated populations

Increasing mortality



log plateau levels

breakdays

Increasing-plateau model

"Reevaluating a test of the heterogeneity
explanation for mortality plateaus."

Experimental Gerontology, 40:1-4 (Jan/Feb 2005)
pp. 101-13.

Traditional explanations for plateaus:

- population heterogeneity: Population composed of distinct frailties. Flattening from selection.
- temporal heterogeneity: Whatever drives the physical aging process slows down at advanced ages. Example: Cancer growth.
- Changing frailty models

Changing-frailty models: Try to reproduce general features of mortality curves from a Markov mortality model.

- Reliability models (Gavrilovs, Witten, Koltover, others)
- Le Bras "cascading failures"
- Diffusion models (e.g., Weitz-Fraser PNAS, 2002)

Gavrilov & Gavrilova's reliability model

• m critical organs, n redundant elements

• Elements fail independently, rate α

• Compute:
$$h(t) = \frac{mn\alpha e^{-\alpha t} (1 - e^{-\alpha t})^{n-1}}{1 - (1 - e^{-\alpha t})^n}$$

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For small t : $\approx mn\alpha^n t^{n-1}$

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For small t : $\approx mn\alpha^n t^{n-1}$

Caution: Approximation depends on

$$1 - e^{-\alpha t} \approx \alpha t$$

Reverse-engineering Gompertz

- Ansatz: Biological systems have most of their components nonfunctioning from the beginning. Number of functioning components in each organ is Poisson.

$$h(t) \approx m \sum_{n=0}^{\infty} \frac{e^{-\mu} \mu^n}{n!} n \alpha^n t^{n-1} = m \alpha \mu e^{\mu(\alpha t - 1)}$$

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Hurray! Exponentially increasing!

This must be right.

Oops!

Let p_n be the probability that there are n components initially, and $F_n(t)$ the distribution of the time of death, conditioned on n components.

The hazard rate is

$$h(t) = \frac{-F'(t)}{1 - F(t)} = \frac{-\sum_{n=0}^{\infty} p_n F'_n(t)}{\sum_{n=0}^{\infty} p_n (1 - F_n(t))}.$$

G & G have computed

$$\sum_{n=0}^{\infty} p_n \frac{-F'_n(t)}{1 - F_n(t)}.$$

"Cascading failures" model

- Start at senescence state $X_0=1$.
- Rate of jumping to next higher state λX_t .
- Rate of killing μX_t .
- Le Bras (1976) pointed out that when $\lambda \gg \mu$, the mortality rate is about $\mu e^{\lambda t}$ for small t .
- Not surprising: Acts like $dX_+/dt = \lambda X_+$.

More on the Le Bras model:

Actually has hazard rate

$$h(t) = \frac{(\lambda + \mu)\mu e^{(\lambda + \mu)t}}{\lambda + \mu e^{(\lambda + \mu)t}}$$

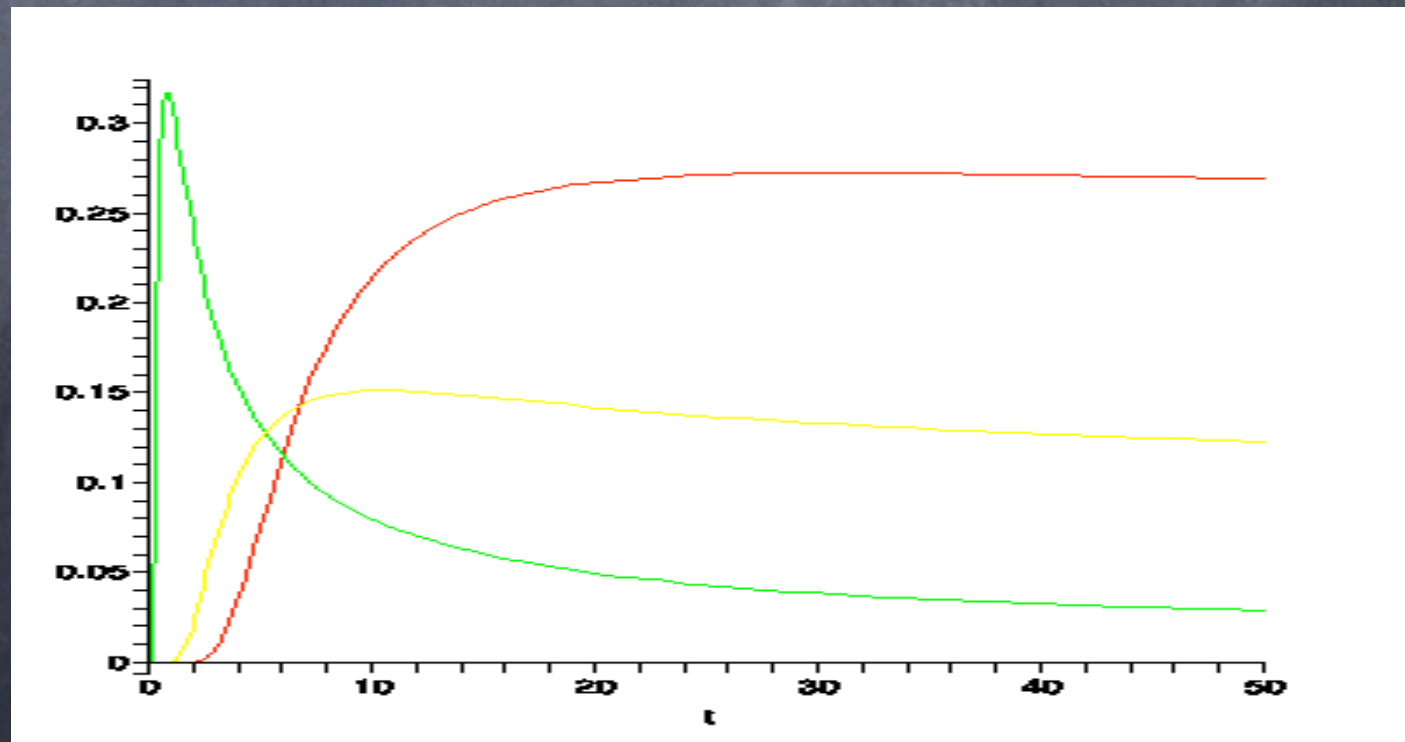
Mortality plateau.

Weitz-Fraser Diffusion Model

- "Vitality" at age t is a Brownian motion (continuous random walk) with constant downward drift.
- "Death" is the time when vitality reaches 0.
- Time of death has "inverse Gaussian" distribution.

Weitz-Fraser Diffusion Model

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- Time of death has "inverse Gaussian" distribution.



What does this mean?

- Are the general features (e.g., mortality plateaus) a consequence of the specific setup of these models, or more generic?
- If generic, what is the underlying principle?

What is happening to the frailty of survivors in the cascading failures model?

Markov processes

- There is a state space S
- The future behavior of the process is random, but depends only on the present state, not on the past
- If S is discrete, there is a transition probability $P_t(x, y) = P\{X_{t+s} = y \mid X_t = x\}$.
- More generally, there is a transition "kernel" $P_t(x, A) = P\{X_{t+s} \in A \mid X_t = x\}$.

Examples: Le Bras Model

- State space = positive integers
- Suppose $X_t = x$. There is a random exponential time T with rate $(b+k)x$.
- At time $t+T$ the process dies with probability $k/(b+k)$, or jumps to state $x+1$ with probability $b/(b+k)$.
- How can we describe the transition probabilities?

Reliability model

- State space= set of m -tuples of integers $\{0,1,\dots,n\}$
- If $X_t=(x_1,\dots,x_m)$ with no 0's, wait for an exponential time T with rate $\alpha(x_1+\dots+x_m)$.
- At time $t+T$, pick one of the x_i 's, with probability $x_i/(x_1+\dots+x_m)$, to decrement by 1.
- If this reduces x_i to 0 then stop.

Simple Example

- Two states
- Suppose $X_t=1$. Let T be an exponential waiting time with rate 1. At time $t+T$, the process jumps to state 2.
- Suppose $X_t=2$. Let T be exponential with rate 2. At $t+T$, the process jumps to 1.
- Because exponential is "memoryless", this process has the Markov property.
- Any discrete-state Markov process has jumps separated by exponential waiting times.

How do we describe the transition probabilities?

- $P_t(x,y)$ is a 2×2 matrix.
- What is $P_{t+dt}(1,1)$? What is the prob. of being in state 1 at time $t+dt$?
- We could have been in state 1 at time t and failed to move (prob. $1-dt$), or we could have been in state 2 at time t and then moved (prob. $2dt$).

$$P_{t+dt}(1,1) = (1 - dt)P_t(1,1) + 2dtP_t(1,2).$$

$$\begin{aligned}
& \begin{pmatrix} P_{t+dt}(1, 1) & P_{t+dt}(1, 2) \\ P_{t+dt}(2, 1) & P_{t+dt}(2, 2) \end{pmatrix} \\
&= \begin{pmatrix} P_t(1, 1) & P_t(1, 2) \\ P_t(2, 1) & P_t(2, 2) \end{pmatrix} \begin{pmatrix} 1 - dt & dt \\ 2dt & 1 - 2dt \end{pmatrix} \\
&= \begin{pmatrix} P_t(1, 1) & P_t(1, 2) \\ P_t(2, 1) & P_t(2, 2) \end{pmatrix} \cdot \left[\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} + \begin{pmatrix} -1 & 1 \\ 2 & -2 \end{pmatrix} dt \right] \\
&= P_t [I + Qdt]
\end{aligned}$$

where $Q = \begin{pmatrix} -1 & 1 \\ 2 & -2 \end{pmatrix}$

$$\frac{d}{dt} P_t = P_t \cdot Q.$$

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$$\frac{d}{dt} P_t = P_t \cdot Q.$$

Solution: $P_t = e^{tQ}$. Q is the "generator".

What is the exponential of a matrix?

If A is diagonal,

$Q = \begin{pmatrix} -1 & 1 \\ 2 & -2 \end{pmatrix}$ has eigenvalues 0, -3
left eigenvectors (2 1), (-1 1)

$$Q = \begin{pmatrix} 2 & 1 \\ 1 & -1 \end{pmatrix}^{-1} \begin{pmatrix} 0 & 0 \\ 0 & -3 \end{pmatrix} \begin{pmatrix} 2 & 1 \\ 1 & -1 \end{pmatrix}$$

$$P_t = e^{tQ} = \begin{pmatrix} 2 & 1 \\ 1 & -1 \end{pmatrix}^{-1} \begin{pmatrix} e^{0t} & 0 \\ 0 & e^{-3t} \end{pmatrix} \begin{pmatrix} 2 & 1 \\ 1 & -1 \end{pmatrix}$$

If we start in state 1 with prob. p , the distribution at time t is $(p \ 1-p) P_t$.

$$(p \quad 1 - p) \cdot \begin{pmatrix} 1/3 & 1/3 \\ 1/3 & -2/3 \end{pmatrix} \begin{pmatrix} 1 & 0 \\ 0 & e^{-3t} \end{pmatrix} \begin{pmatrix} 2 & 1 \\ 1 & -1 \end{pmatrix}$$

$$(p \quad 1 - p) \cdot \left[\begin{pmatrix} 2/3 & 1/3 \\ 2/3 & 1/3 \end{pmatrix} + e^{-3t} \begin{pmatrix} 1/3 & -1/3 \\ -2/3 & 2/3 \end{pmatrix} \right]$$

For large t , the second term vanishes.

The first term is independent of p .

The distribution $(2/3 \quad 1/3)$ is the "stationary distribution". It is the left-eigenvector with eigenvalue 0. No matter what state we start in, the distribution converges to this.

Stationary Distributions

Finite-state Markov processes converge to stationary distributions.

Generator Q : Q_{ij} = rate of jumping to j from i .

For positive t , $P^i \{X_t = j\} = (e^{-tQ})_{ij}$.

By Perron-Frobenius, top eigenvalue (which is 0) is simple, with a positive left-eigenvector π .

Then

$$\mathbb{P}^i \{X_t = j\} \xrightarrow{t \rightarrow \infty} \pi_j.$$

What happens when we
add killing?

What happens when we add killing?

- Say state 1 is "healthy", state 2 is "sick".

What happens when we add killing?

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- When the process is in state 2 it has mortality rate 1.

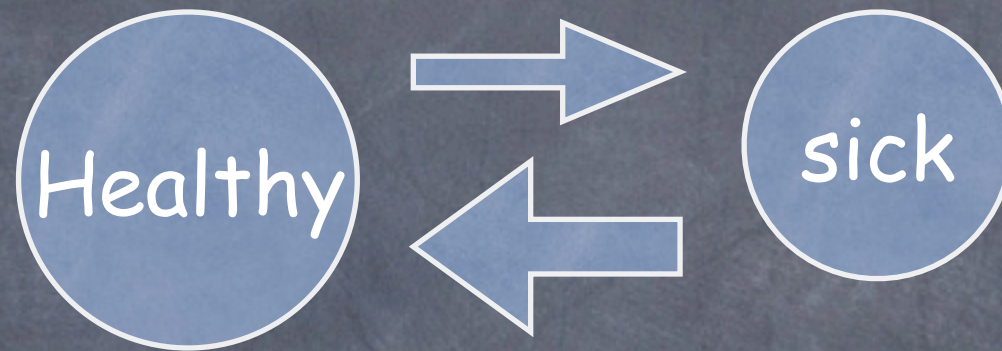
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- What is the asymptotic mortality rate?

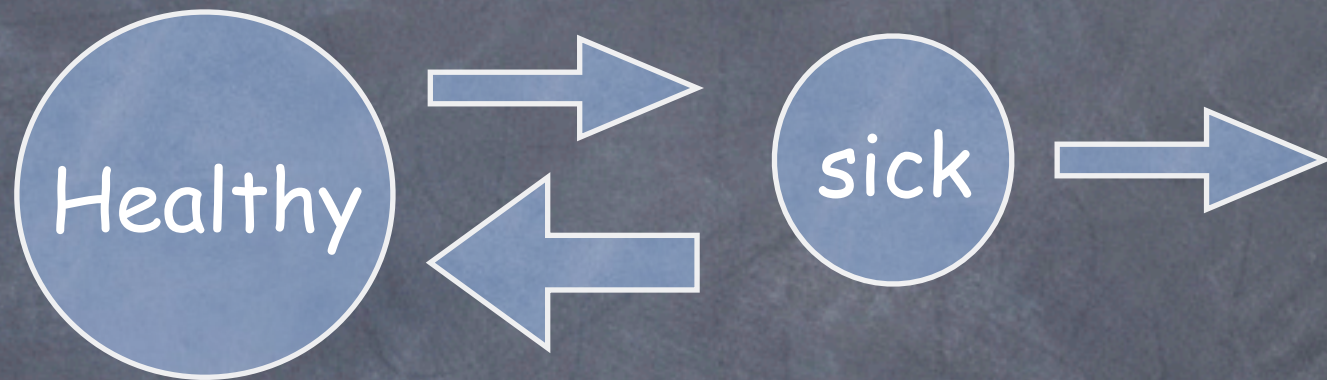
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- Say state 1 is "healthy", state 2 is "sick".
- When the process is in state 2 it has mortality rate 1.
- What is the asymptotic mortality rate?
- Intuitive argument: After a while, $1/3$ of individuals are sick. They have mortality rate 1. Therefore, population mortality converges to $1/3$.

This is wrong.



This is wrong.



State 2 loses share of population
because of outflow to death

State 1 healthy,
state 2 death rate 1.

$$Q = \begin{pmatrix} -1 & 1 \\ 2 & -3 \end{pmatrix}$$

$$e^{tQ} = \begin{pmatrix} 0.789e^{-.268t} + 0.21e^{-3.73t} & 0.289e^{-.268t} - 0.289e^{-3.73t} \\ 0.577e^{-.268t} - 0.577e^{-3.73t} & 0.211e^{-.268t} + 0.789e^{-3.73t} \end{pmatrix}$$

After a while, the ratio of healthy to sick is
.789/.289=.577/.211=2.73. The mortality rate
is then about .268.

Quasistationary Distributions

Finite-state sub-Markov processes conditioned on long-time survival converge to quasistationary distributions.

Generator Q : Q_{ij} = rate of jumping to j from i .

For positive t , $P^i \{X_t = j\} = (e^{-tQ})_{ij}$.

By Perron-Frobenius, top eigenvalue $-\lambda$ (which is negative) is simple, with a positive left-eigenvector π , and positive right-eigenvector v .

Then

$$e^{\lambda t} P^i \{X_t = j\} \xrightarrow{t \rightarrow \infty} v_i \pi_j.$$

Conditional Convergence

Let τ_{∂} be the time when the process is killed. Then

$$P^i \{X_t = j \mid \tau_{\partial} > t\} \xrightarrow{t \rightarrow \infty} \pi_j.$$

$$P^i \{\tau_{\partial} > t + s \mid \tau_{\partial} > t\} \xrightarrow{t \rightarrow \infty} e^{-\lambda s}.$$

Conclusion: Any finite-state Markov mortality model has a "mortality plateau". That is, the mortality rate for the surviving population converges to a constant?

What about Le Bras?

Problem: There is no reason why the process needs to settle down. It could run off to infinity.

"Markov mortality models: Implications of quasistationarity and initial distributions."
Theoretical Population Biology 65:4, June 2004. S. and Evans.

What about Le Bras?

Problem: There is no reason why the process needs to settle down. It could run off to infinity.

Fact: A one-dimensional Markov process converges to a quasistationary distribution if the mortality rate at infinity is greater than the quasistationary killing rate.

"Markov mortality models: Implications of quasistationarity and initial distributions."
Theoretical Population Biology 65:4, June 2004. S. and Evans.

What about Weitz-Fraser?

- "Vitality" at age t is a Brownian motion (continuous random walk) with constant downward drift.
- "Death" is the time when vitality reaches 0.
- Time of death has "inverse Gaussian" distribution.

Brownian Motion

- State space= positive real numbers.
- Independent increments.
- Conditioned on B_t , $B_{t+s}-B_t$ is normally distributed with variance s and mean 0.
- Limit of a random walk, as jump size and time intervals both go to 0.

What is the generator of Brownian motion?

- The generator takes a distribution, and turns it into the instantaneous change
- For finite state spaces, the distribution is a vector, and the generator is a matrix
- For Brownian motion, the distribution is a continuous function, and the generator is...
- ... the second derivative
- Instead of eigenvalues, eigenfunctions:
 $d^2\varphi/dx^2 = \lambda\varphi.$

One-dimensional diffusions

Diffusion rate $\sigma(X_t)$
(assume $\sigma=1$).

Drift $b(X_t)$.

Killing rate
 $\kappa(X_t)$.

Generator

$$\mathcal{L}^* \phi(x) = \frac{1}{2} \phi''(x) - (b(x)\phi(x))' - \kappa(x)\phi(x)$$

If ϕ is the starting density, the density of X_t is $e^{t\mathcal{L}^*} \phi$.

(Technically, this is the "adjoint generator".)

Example -- Continuous version of the

Le Bras model: $\sigma(x) = \sigma x,$

$b(x) = bx,$

$\kappa(x) = \kappa x.$

Reflected at 1.

Example -- Weitz-Fraser model:

$\sigma(x) = 1,$

$b(x) = b,$

$\kappa(x) = 0.$

Killed at 0.

Example: Continuous version of the Le Bras model

$$\sigma(x) = \sigma x,$$

$$b(x) = bx,$$

$$\kappa(x) = \kappa x.$$

Reflected at 1.

$\kappa(x) \rightarrow \infty$, so convergence to quasistationary distribution, corresponding to the top eigenvalue of the generator.

(In this case, eigenfunctions are computable.)

What do we mean by "top eigenvalue"?

$\phi_\lambda(x)$ is the unique eigenfunction

$$\mathcal{L}^* \phi := \frac{d}{dx} \left\{ \frac{1}{2} \frac{d\phi}{dx} - b\phi \right\} - \kappa\phi = -\lambda\phi$$

with boundary conditions

$$\phi_\lambda(0) = p, \quad \phi'_\lambda(0) = 1 - p(1 - b(0)).$$

$\underline{\lambda}$ = largest λ such that ϕ_λ is nonnegative.

The problem of computing the killing rate is now a problem in ordinary differential equations.

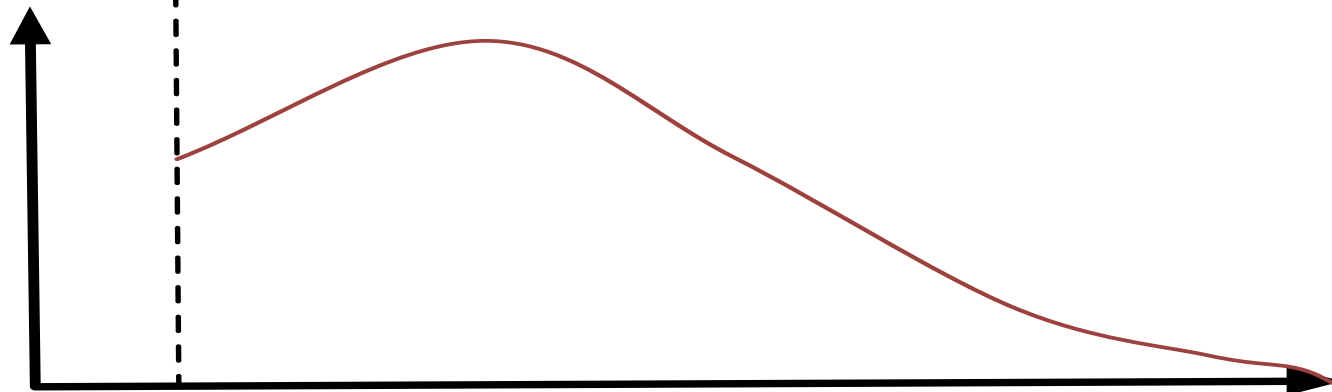
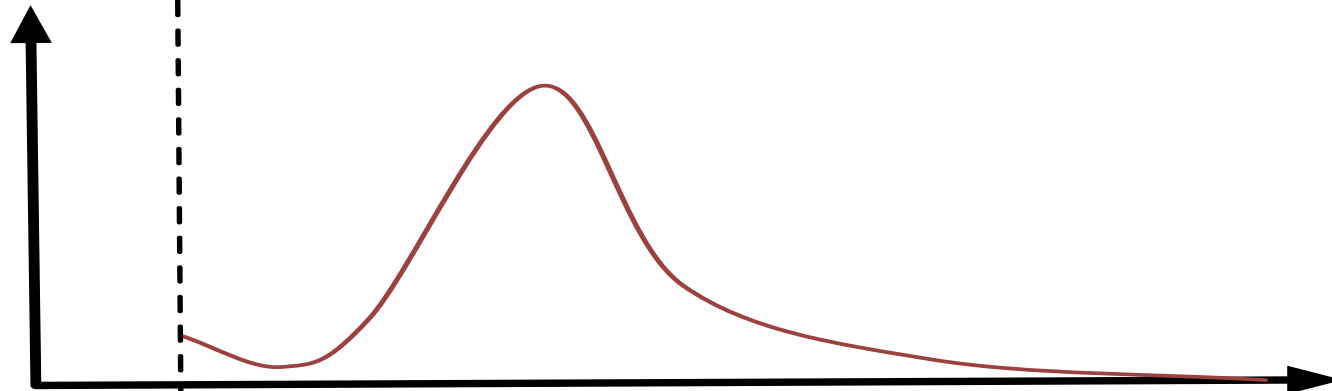
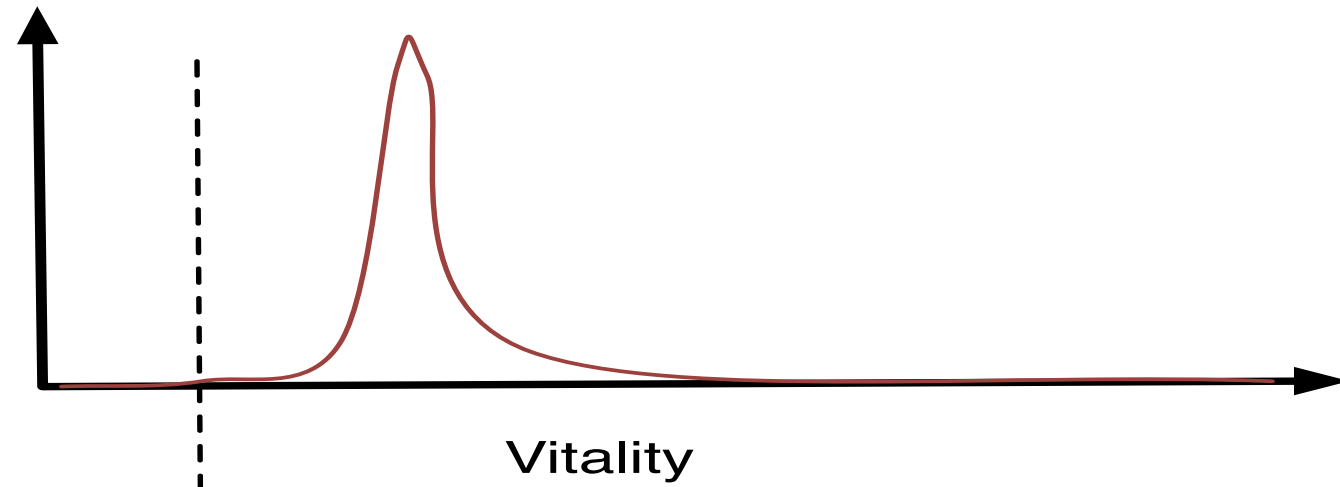
What does this mean?

Traditional explanations:

- population heterogeneity
- temporal heterogeneity
- New idea "Evolving heterogeneity": Late-life mortality flattens out because of an equilibrium between the drift toward lower vitality, and the culling of mortality

Explanatory link between abstract models and the real phenomenon. Possibly testable.

Le Bras evolution



Reaches equilibrium between spread and killing.