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A new model of ageing and mortality

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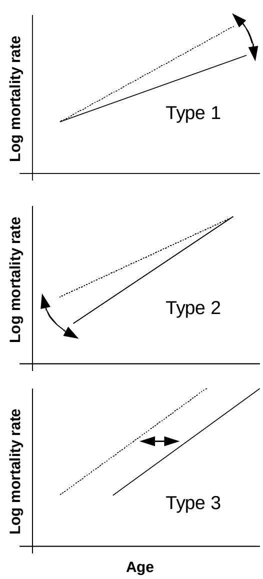
Derivation and design

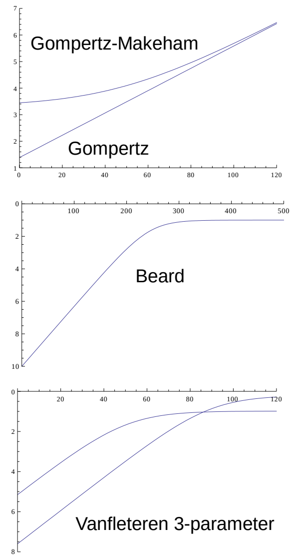
- Intended to be a model of individual risk, rather than a model of population risk
- Assumes inter-individual heterogeneity as a cause of certain population patterns



There appear to be three basic types of 'difference' in semi-logarithmic mortality curves. These differences may be seen between strains or populations of a species, in the same strain under different conditions, or in the 'same' population over time.

Type 1 and 2 differences involve changed gradient, which is widely held to indicate and altered ageing rate. Others argue that any fall in mortality may represent slower ageing.

Standard models of ageing generally exhibit type 1 and type 3 changes with changes in single parameters. However, type 2 changes necessitate adjustment in more than one parameter in order to 'fix' the apparent pivot point in later life.



Actuarial modifications (such as Makeham or Beard) to basic models (such as Gompertz) adjust for non-linearity of early to mid-life patterns, or for mortality deceleration to a plateau in late life.

Makeham has been interpreted by many as an additive component of individual risk, though this may be an ecological fallacy.

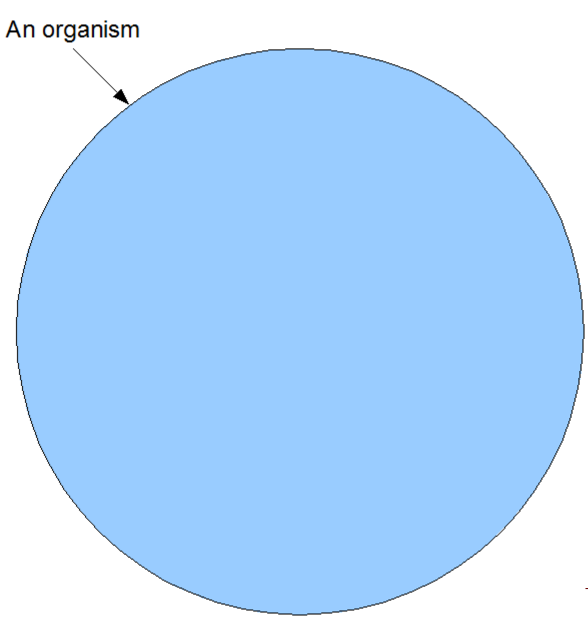
Early and late life deviations from a regular pattern may be manifestations of heterogeneity rather than expressions of modal individual risk.

A comprehensive theory of ageing:

- Should explain why most species deteriorate with chronological age.
- Should explain exponential rises in mortality.
- Should explain [type 2] changes in mortality curves
- Should account for loss of exponentiality, plateaux, and deceleration at older ages.

(paraphrased from Gavrilov & Gavrilova 2006)

BASIC PRINCIPLES



Any organism at any instant has a given probability of failing per unit time

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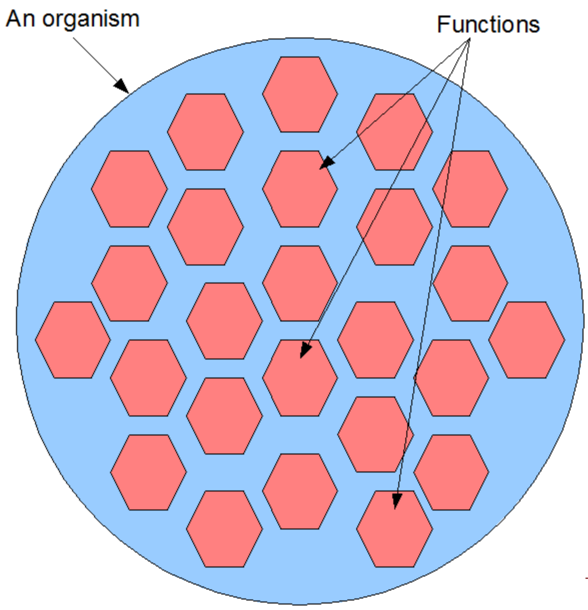
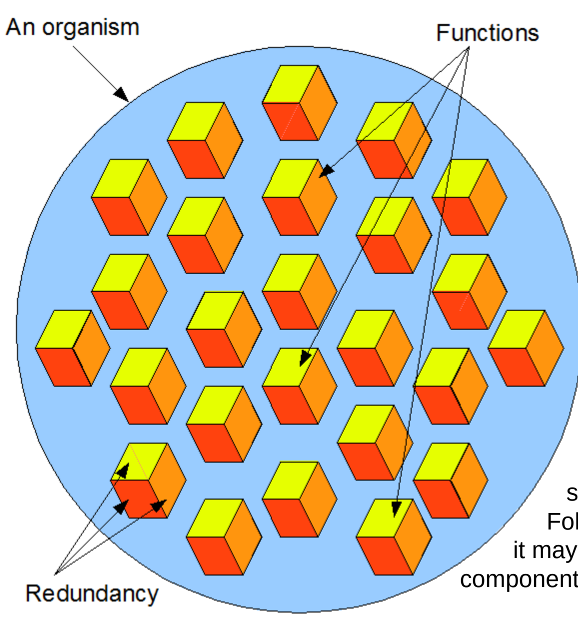


Any organism comprises a set of vital functions.

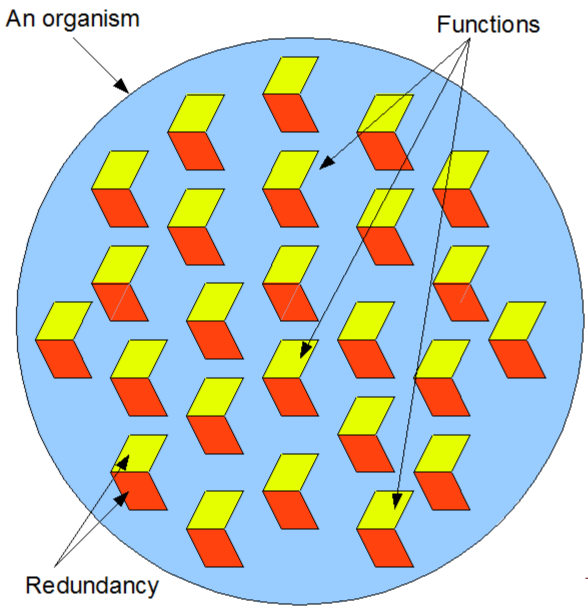
If any function fails the organism dies, so the net probability of organism death depends upon the probability of all functions surviving that given period of time.



Each function has a degree of redundancy such that the normal delivery of the function can be achieved with only part of its full capacity.

For a function to fail, all of its redundant components must fail at the same time.

Failure of function is not the same as loss of a component. Following failure of a component, it may be repaired while remaining components sustain that function.



Components may fail many, many times and be repeatedly repaired.

However, with increasing age, the redundancy of functions diminishes.

Key point:
Component failure and component decay are not the same thing.

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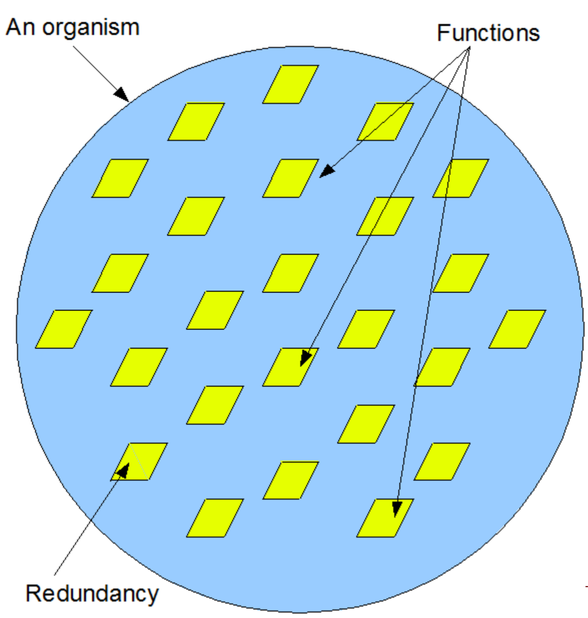

Until, eventually, the organism has very little redundant reserve to protect it from dangerous interactions with its environment.

Crucially, the decay of redundancy with age is:

a) **Linear**
b) **Largely invariable**

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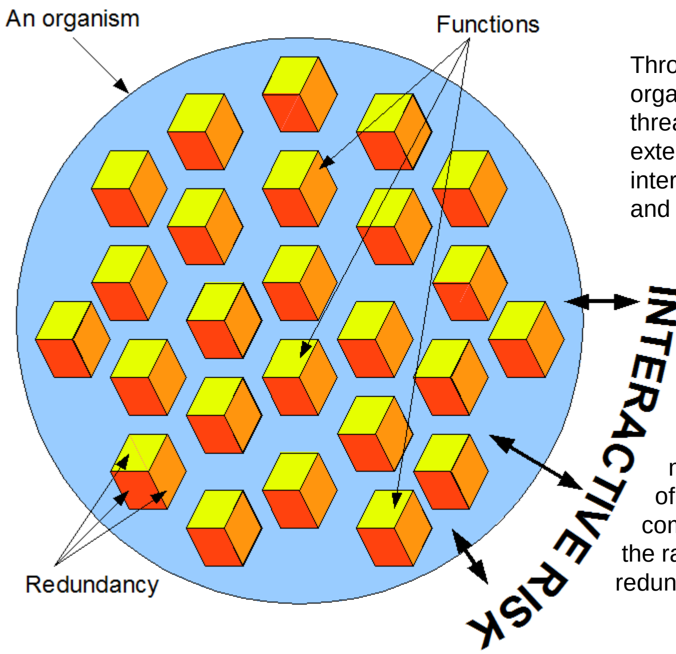

Throughout life, the organism is threatened by external hazard and internal vulnerability, and these interact.

Interactive risk determines the mean time to failure of redundant components. **BUT NOT** the rate of decay of redundant components.

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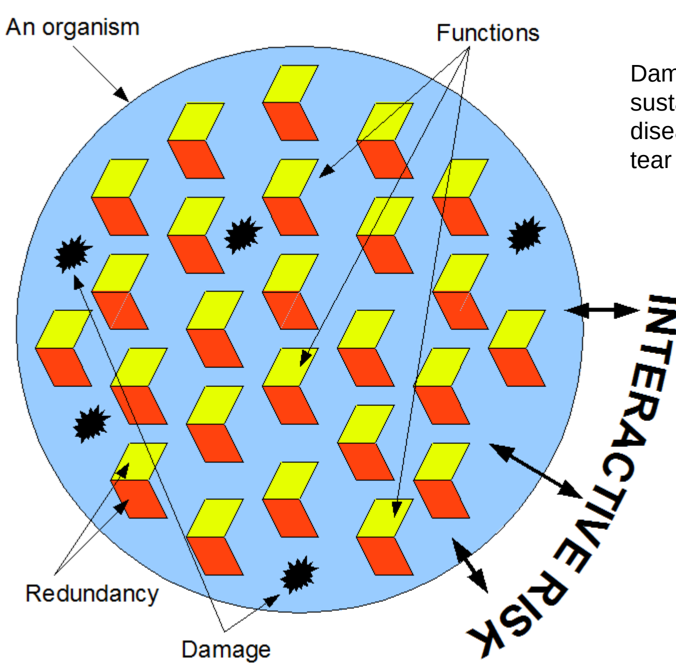

Damage is sustained through disease, wear and tear etc.

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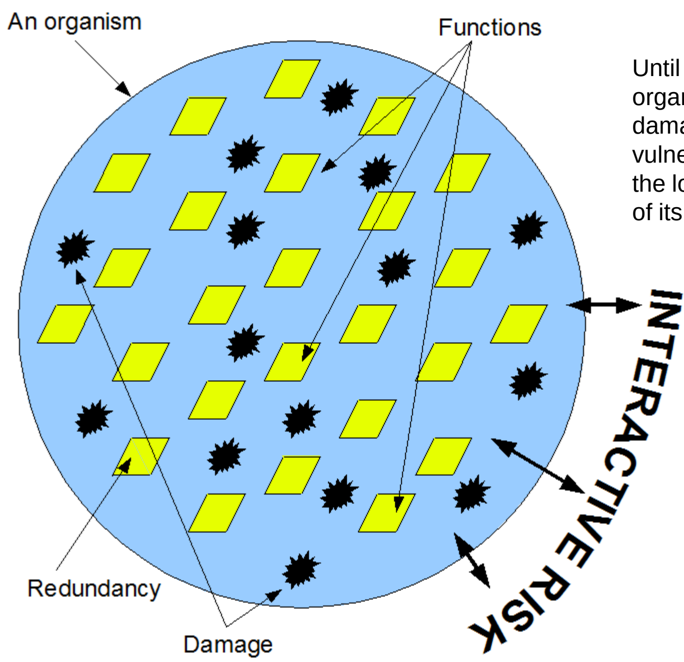

Until the aged organism is both damaged and vulnerable through the low redundancy of its functions.

The nested binomial model

- Divides age-related risk into two distinct partitions:
  - Redundancy decline, which is linear and largely invariable.
  - Interactive risk, which is markedly variable and describes all other influences upon mortality risk.

The nested binomial model

- Assumes that:
  - organisms may be regarded simply as a set of (***n***) vital functions connected in series
  - each function has an initial species or strain-specific quantity (***s***) of redundancy which declines linearly at a largely invariable rate (***a***) throughout life
  - net risk of dying depends upon both the redundant state of the organism's functions and a level of interactive risk (***k***) which varies independently of the redundant state

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Milne EMG. The natural distribution of survival. Journal of Theoretical Biology 2008;doi:10.1016/j.jtbi.2008.07.021

$$\mu_c = -\mathrm{Ln}\left(1 - \left(1 - 0.5^{\frac{1}{r_c \mathrm{k}}}\right)^{r_c}\right)^{n}$$

Where redundancy (***r***) at the current age (***c***) is described by:

$$r_c = s - \frac{c}{a}$$

s = theoretical redundancy level ***r*** in arbitrary units at age 0
a = time taken for decay of 1 unit of redundancy in the same units as age
k = interactive risk parameter = the unit-specific half-life when ***r*** = 1
n = number of functions that comprise the organism
c = current age

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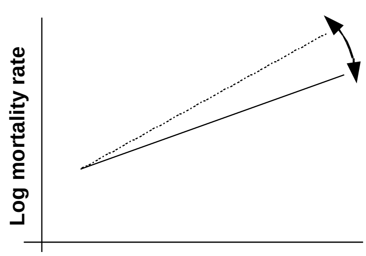
$$\mu_c = -\mathrm{Ln}\left(1 - \left(1 - 0.5^{\frac{1}{r_c \mathrm{k}}}\right)^{r_c}\right)^n$$

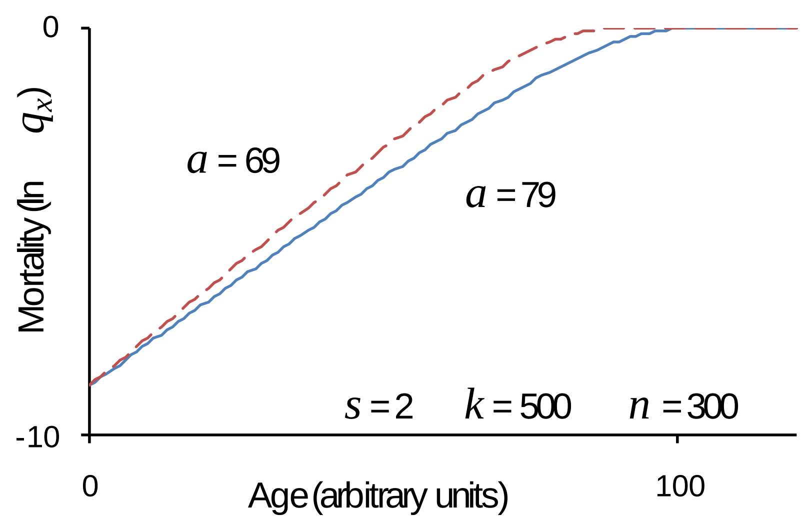
Interactive risk (parameter ***k***)

$$r_c = s - \frac{c}{a}$$

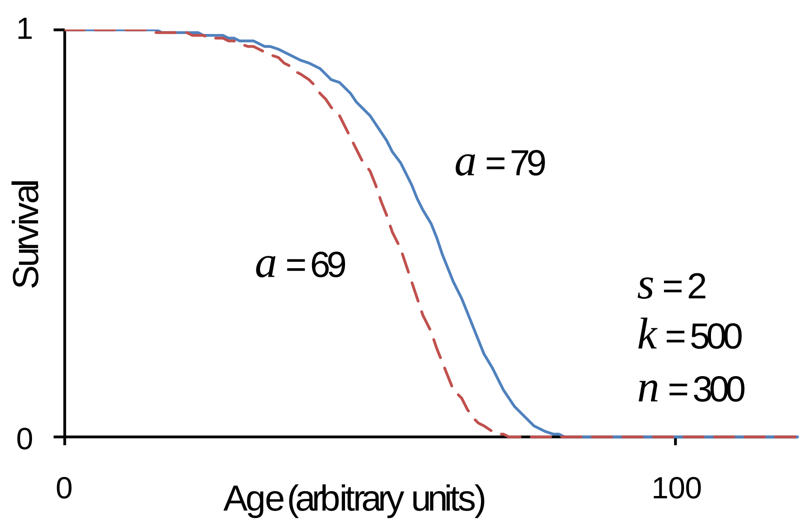
Determinant of the rate of redundancy decline (parameter ***a***)

PARAMETER *a* – *type 1 change*

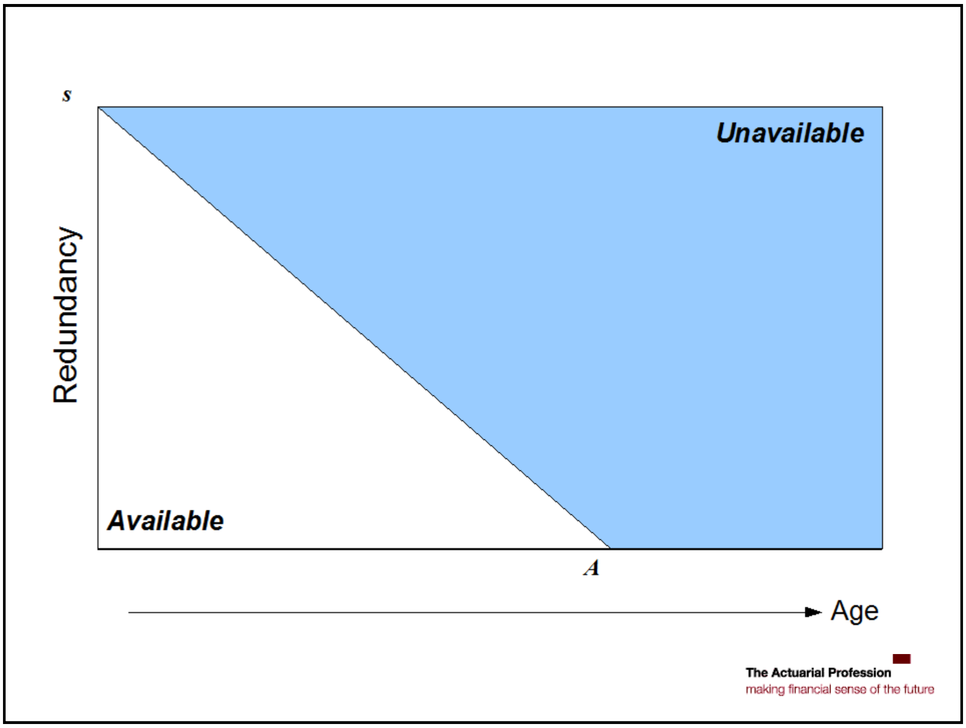




0
-10
Mortality (ln q_x)
$a = 69$
$a = 79$
$s = 2$ $k = 500$ $n = 300$
0
100
Age (arbitrary units)



1
0
Survival
$a = 79$
$a = 69$
$s = 2$
$k = 500$
$n = 300$
0
100
Age (arbitrary units)


s
Unavailable
Redundancy
Available
A
Age
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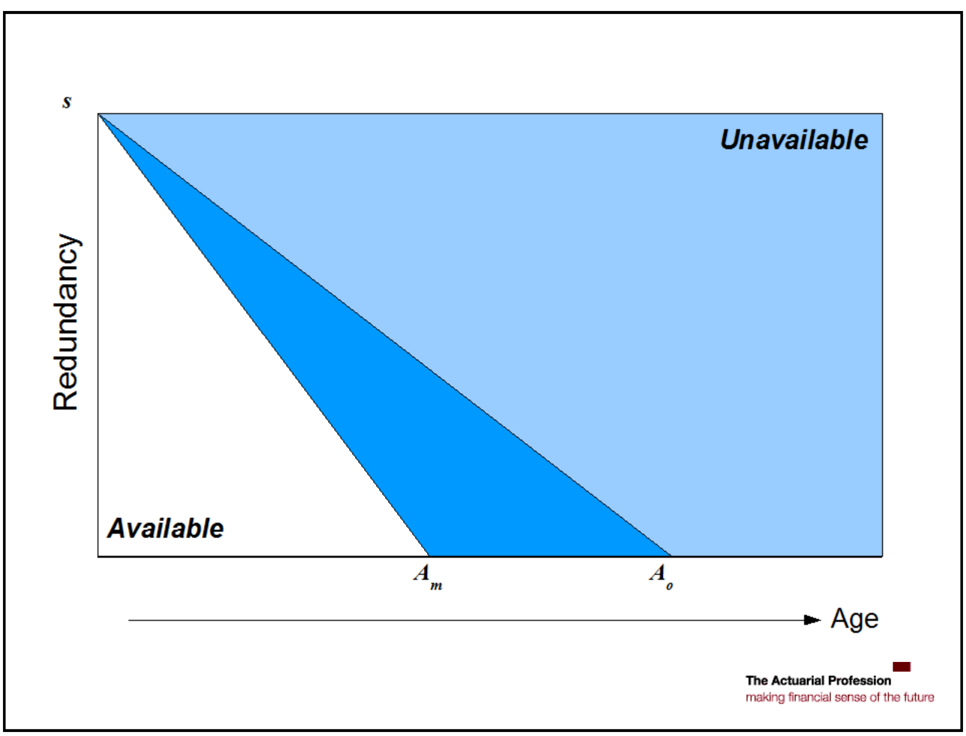
s
Unavailable
Redundancy
Available
A_m
A_o
Age
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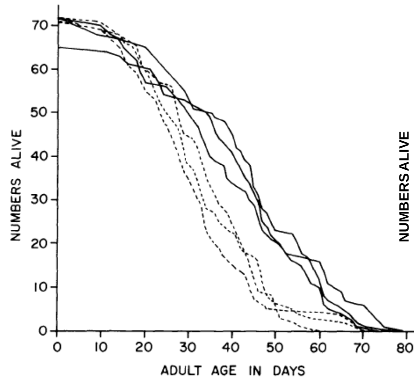

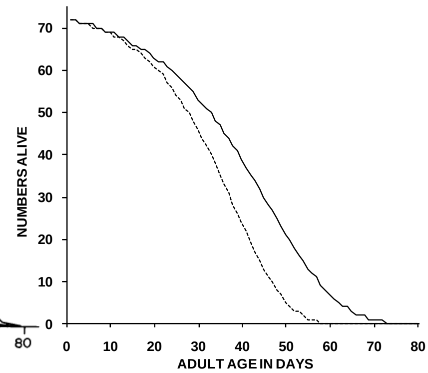

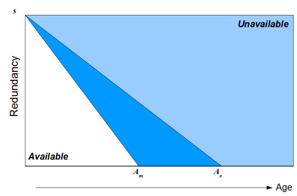

Rose MR. Laboratory Evolution of Postponed Senescence in Drosophila-Melanogaster. Evolution 1984;38(5):1004-1010

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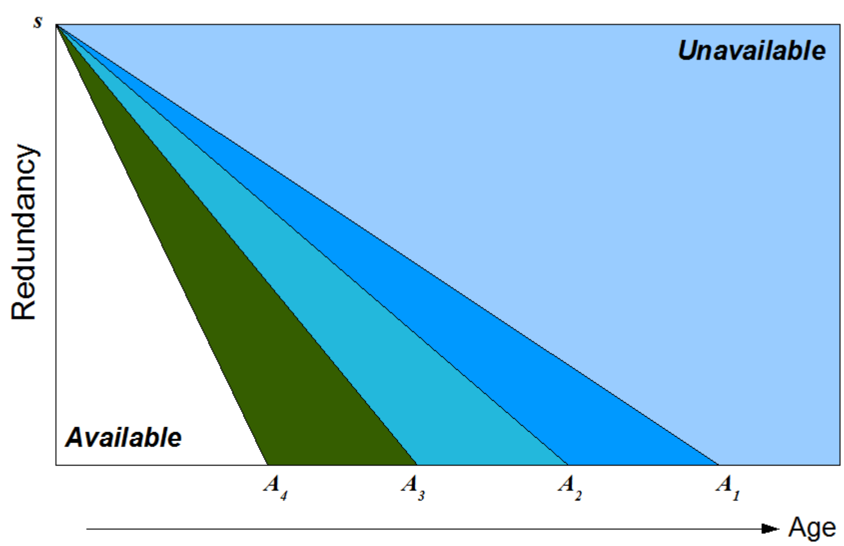

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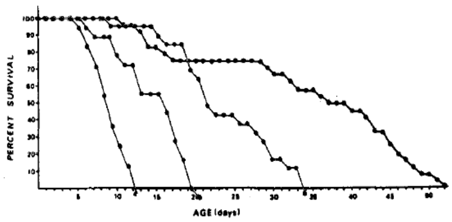
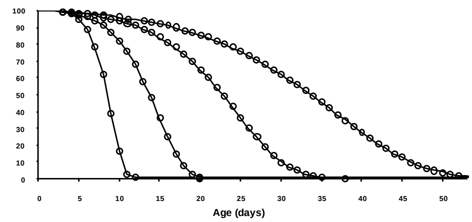
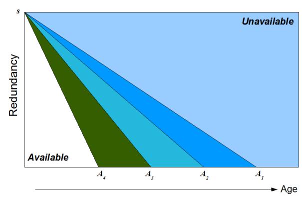
Klass MR. Aging in the nematode Caenorhabditis elegans: major biological and environmental factors influencing life span. Mech Ageing Dev 1977;6(6):413-29







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Parameter ***a***

- Describes the rate of redundancy decline
- Is largely invariable

  BUT
- Varies with temperature (also with dietary restriction, oxygen tension – not illustrated)
- Is the element of the model that changes with evolved longevity

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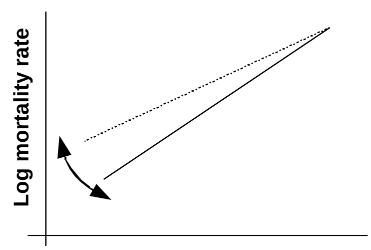
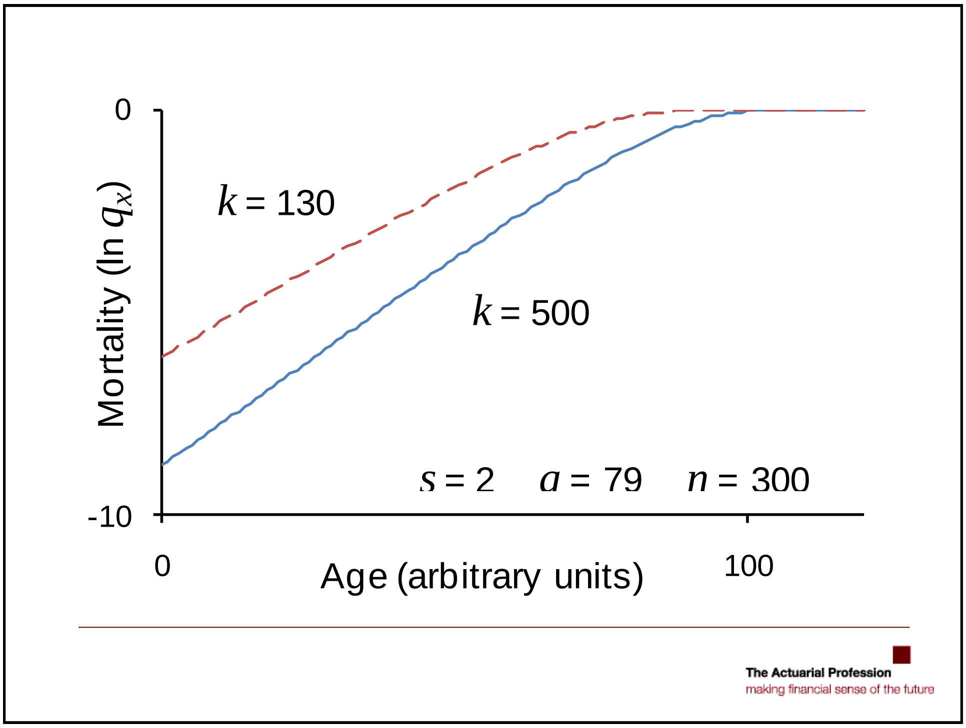
Parameter *a*

- Has similarities to “senescence” (Finch) or “ageing” (Hayflick)
- Determines the structure and scale of the mortality curve

PARAMETER *k* – *type 2 change*





0
-10
Mortality (ln q_x)
k = 130
k = 500
s = 2 a = 79 n = 300
0
100
Age (arbitrary units)
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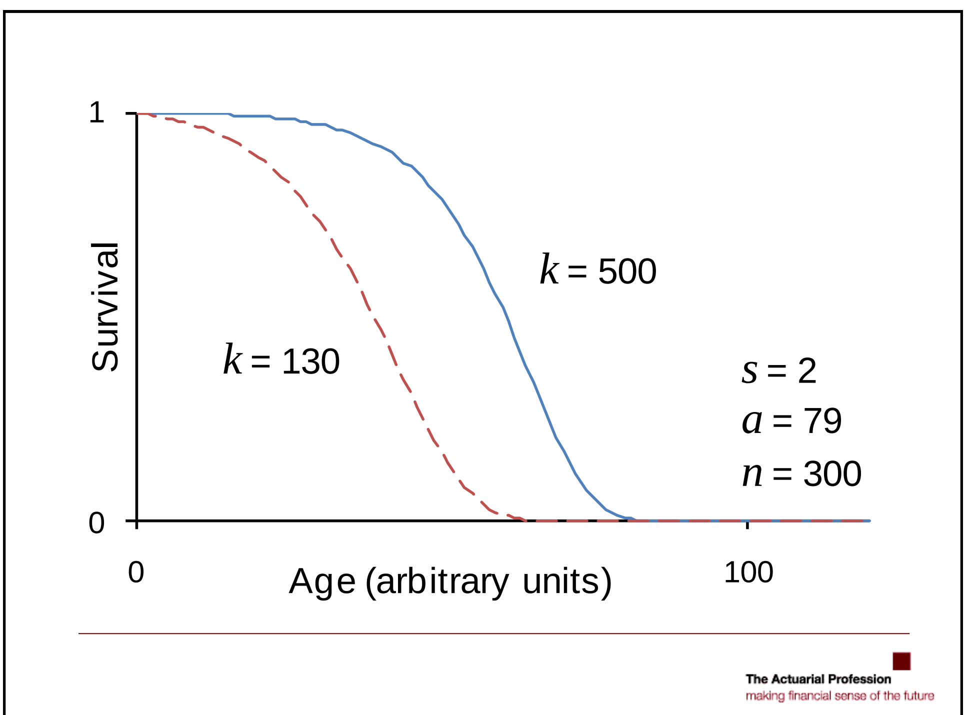

1
0
Survival
k = 500
k = 130
s = 2
a = 79
n = 300
0
100
Age (arbitrary units)
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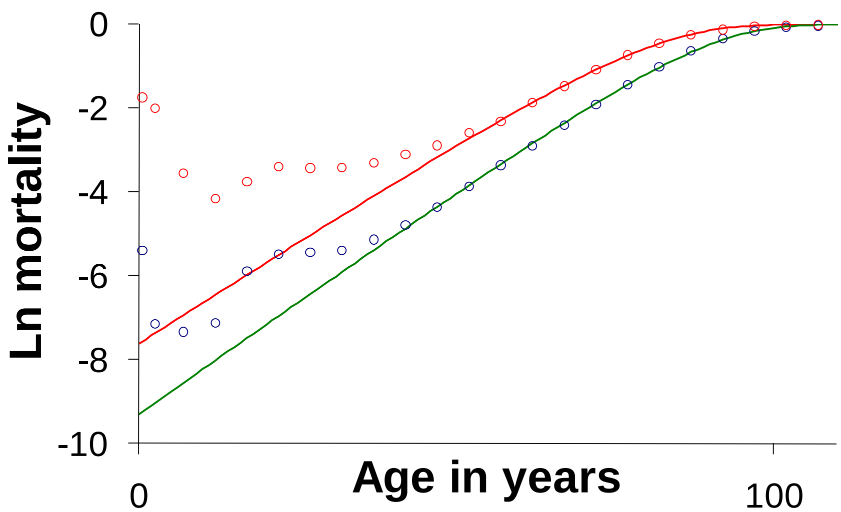

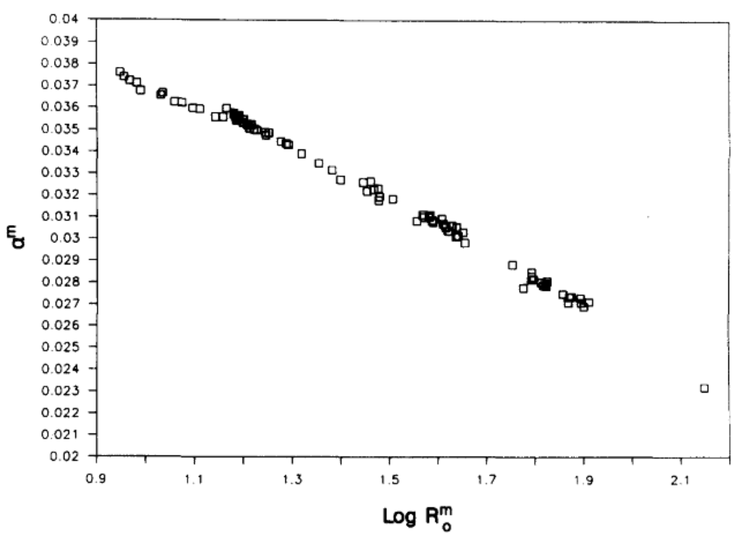

Fig. 2. Graph of α *vs.* log R_0 for men (m) in the United States from 1900 to 1986.

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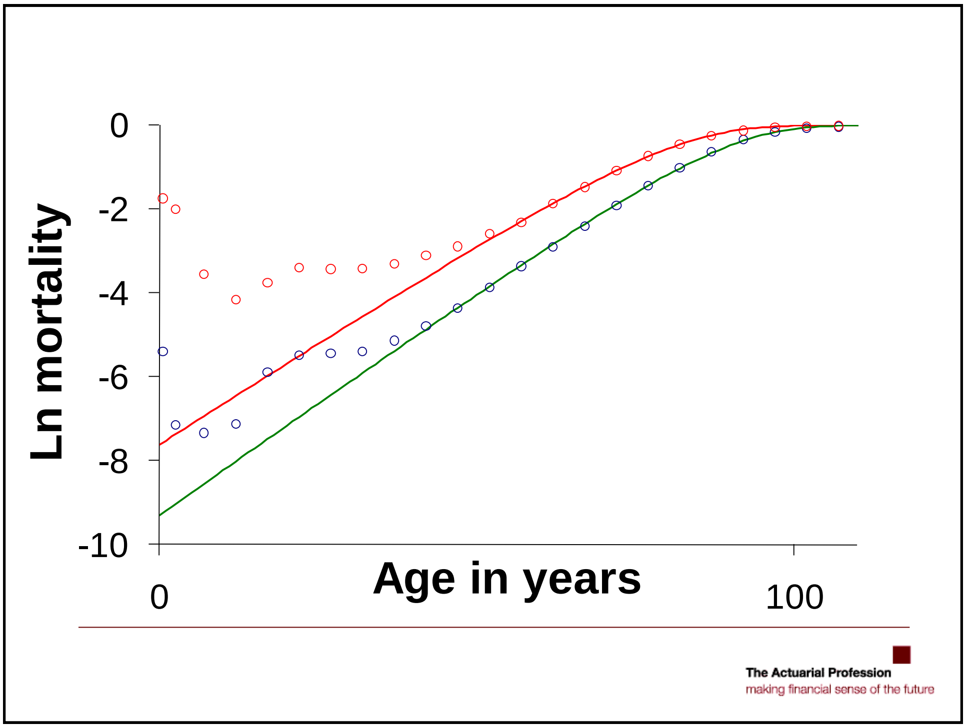
0
-2
-4
-6
-8
-10
Ln mortality
0
Age in years
100
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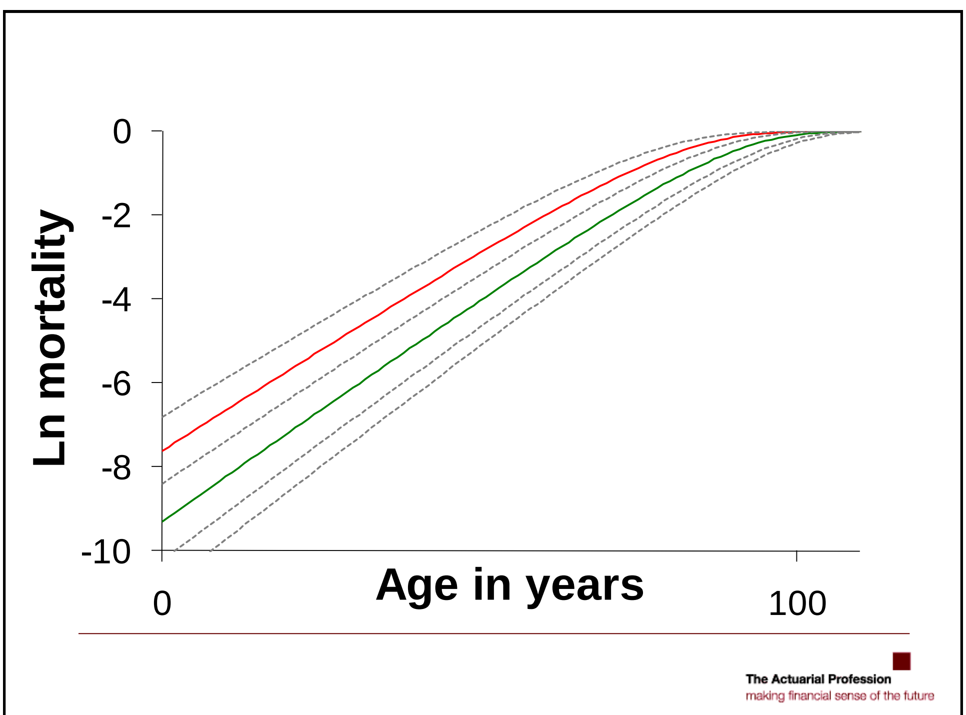
0
-2
-4
-6
-8
-10
Ln mortality
0
Age in years
100
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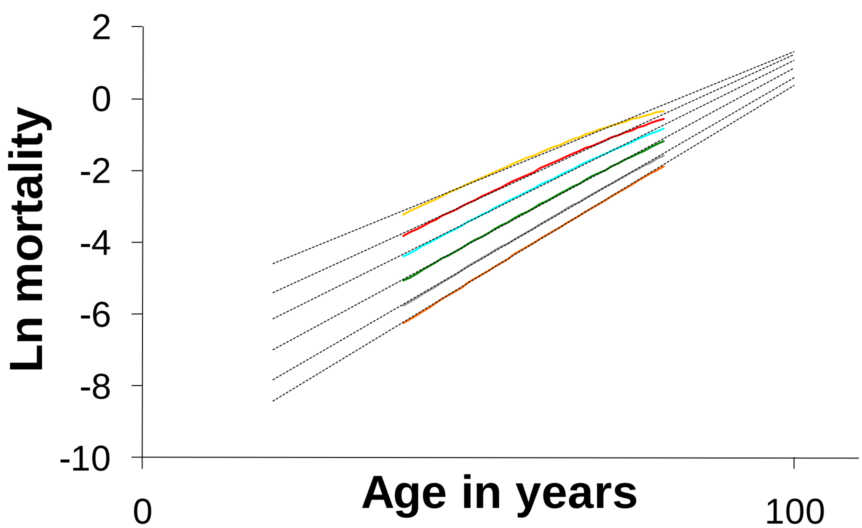

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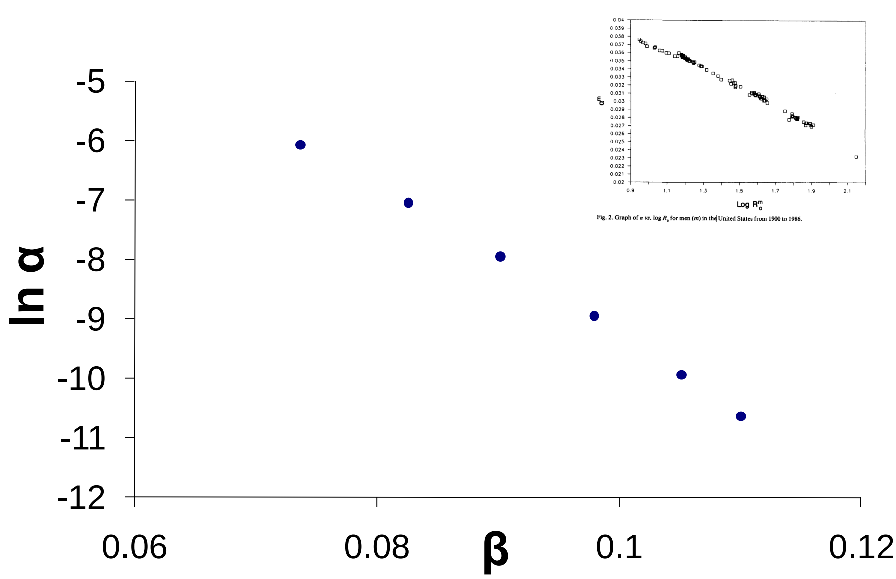

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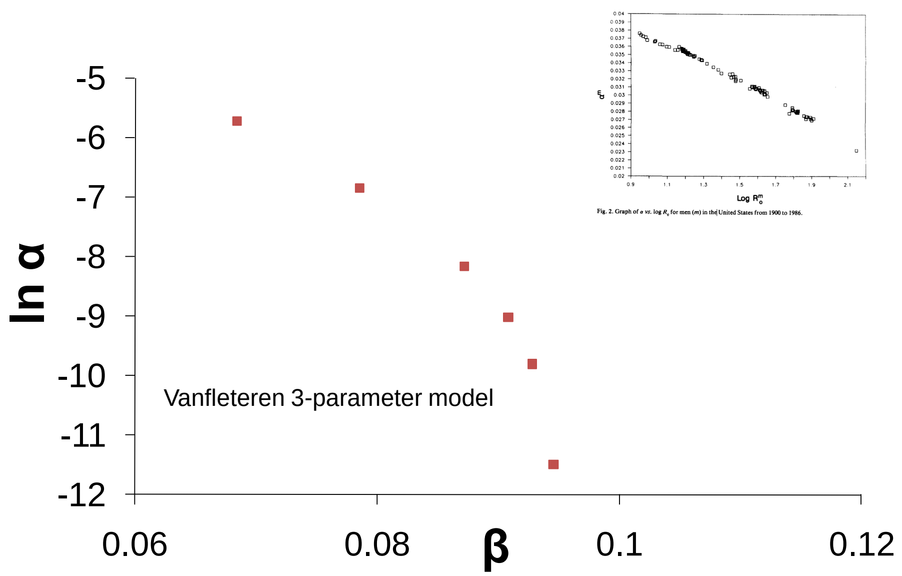
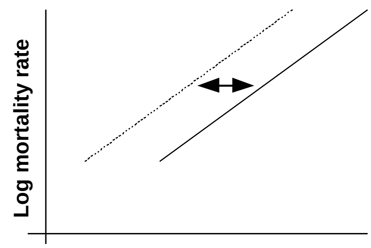
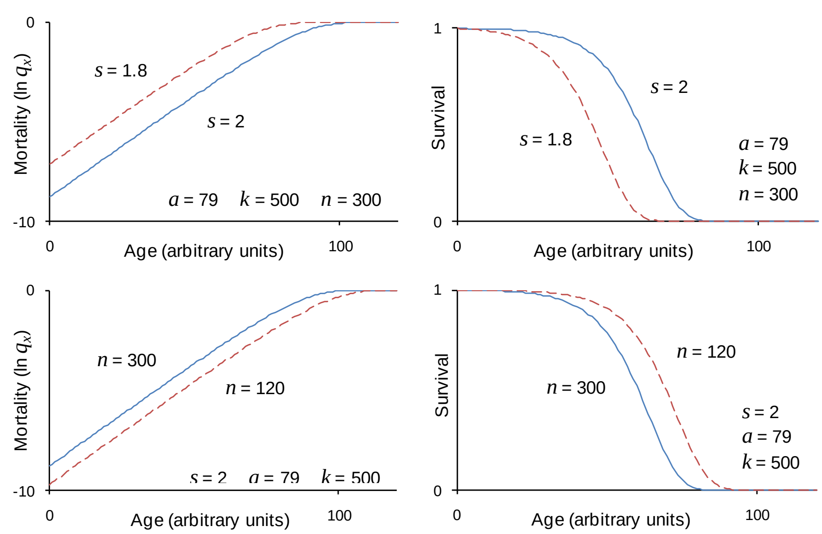


Parameter ***k***

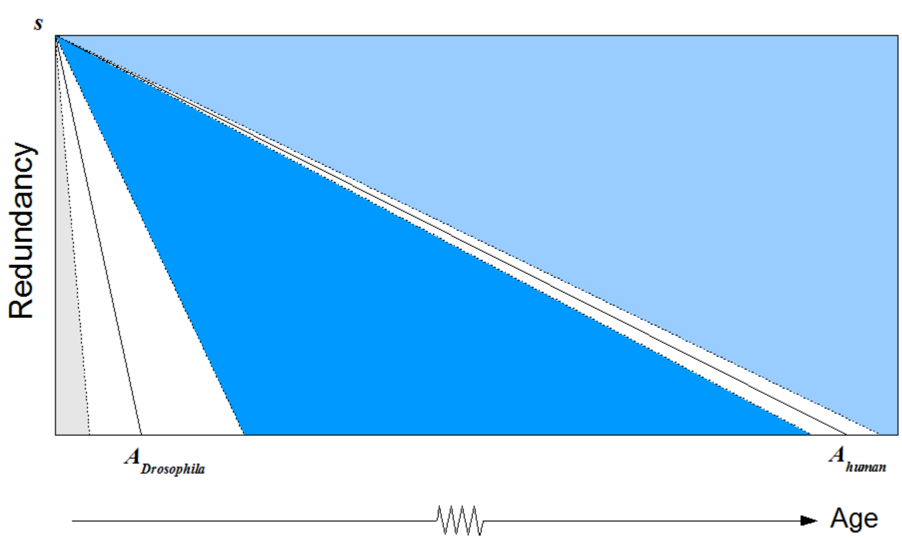
- Describes interactive risk - the aggregate of all other variable, individual and environmental risks including cumulative and (non-senescent) genetic risks.
- The derivation of parameter ***k*** is that it is the half-life of “1 unit” of redundancy, therefore:
  - Low parameter ***k*** = high risk
- Is the element that is changed when organisms age in different environments, and with different external risk exposures.

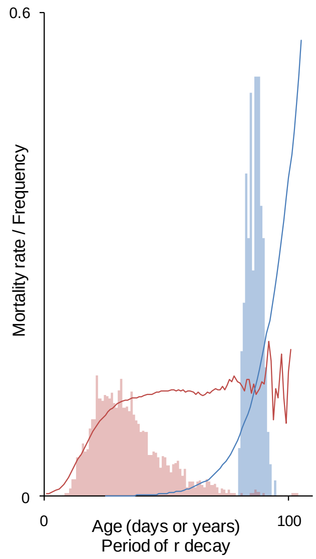
PARAMETER *s & n – type 3 change*





PARAMETER a HETEROGENEITY



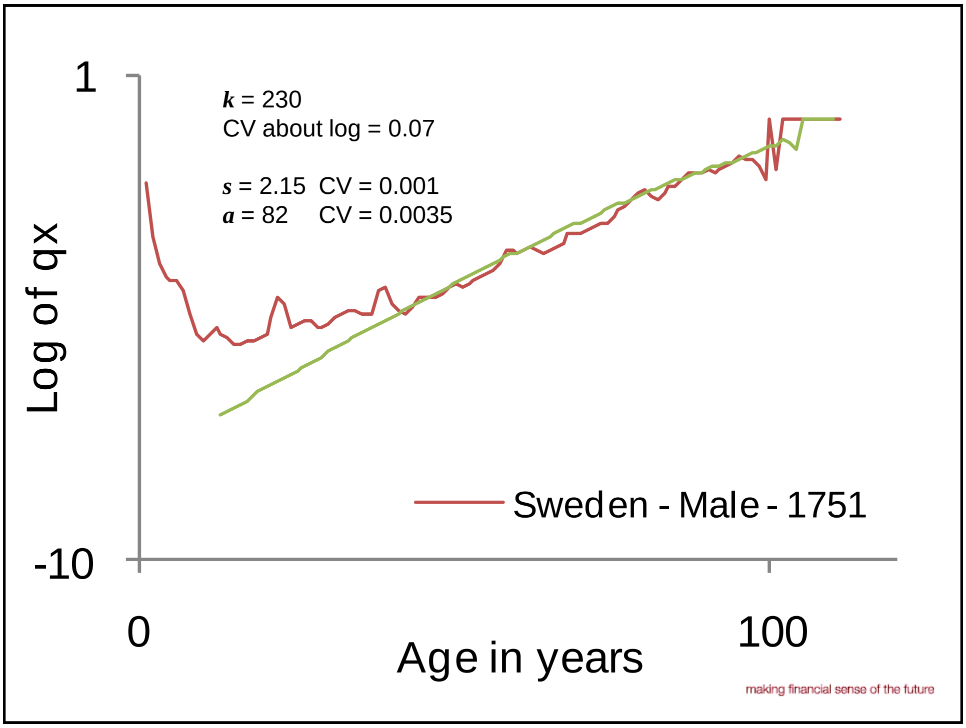


Parameter ***a***
When parameter ***a*** distribution is wide, skewed and its period is short, plateaux of mortality appear.

Conversely, when the distribution is relatively narrow and the period is long, the mortality curve is dominated by an exponential rise.

Thus, loss of exponentiality, plateaux and deceleration of mortality can be accounted for by heterogeneity in parameter ***a.***

PARAMETER *k* HETEROGENEITY



1
-10
Log of qx
k = 230
CV about log = 0.07
s = 2.15 CV = 0.001
a = 82 CV = 0.0035
Sweden - Male - 1751
0
100
Age in years
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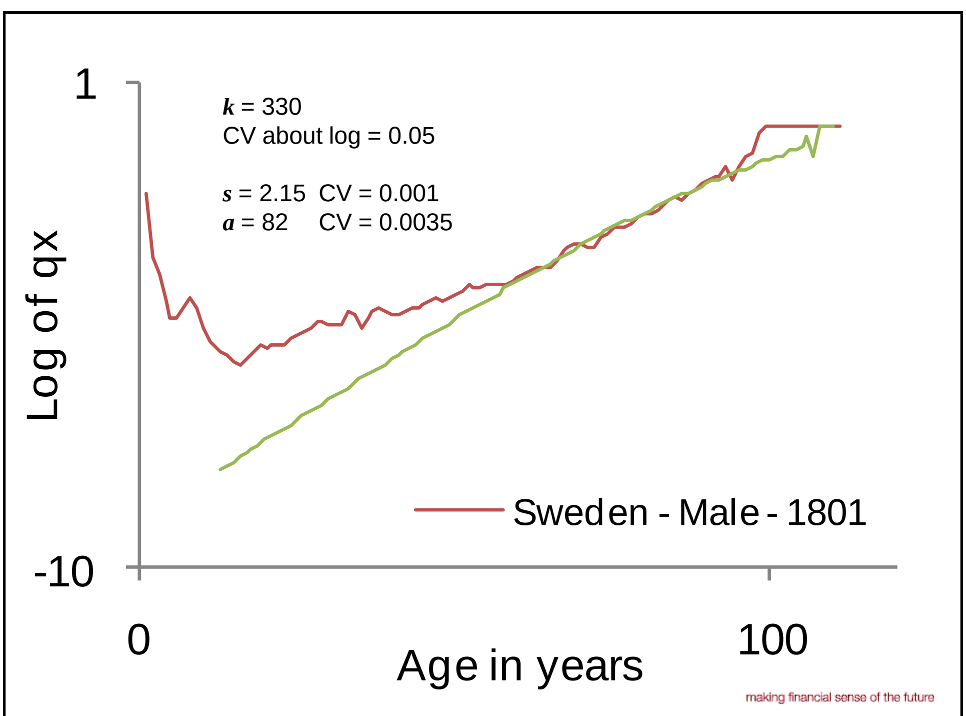

1
-10
Log of qx
k = 330
CV about log = 0.05
s = 2.15 CV = 0.001
a = 82 CV = 0.0035
Sweden - Male - 1801
0
100
Age in years
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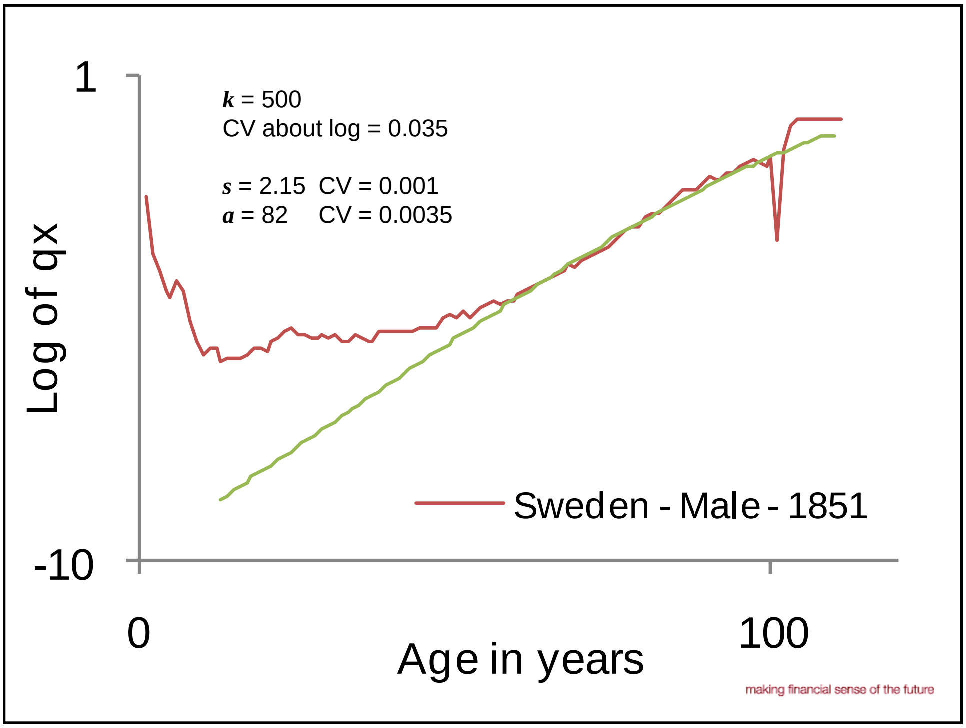

1
-10
Log of qx
k = 500
CV about log = 0.035
s = 2.15 CV = 0.001
a = 82 CV = 0.0035
Sweden - Male - 1851
0
100
Age in years
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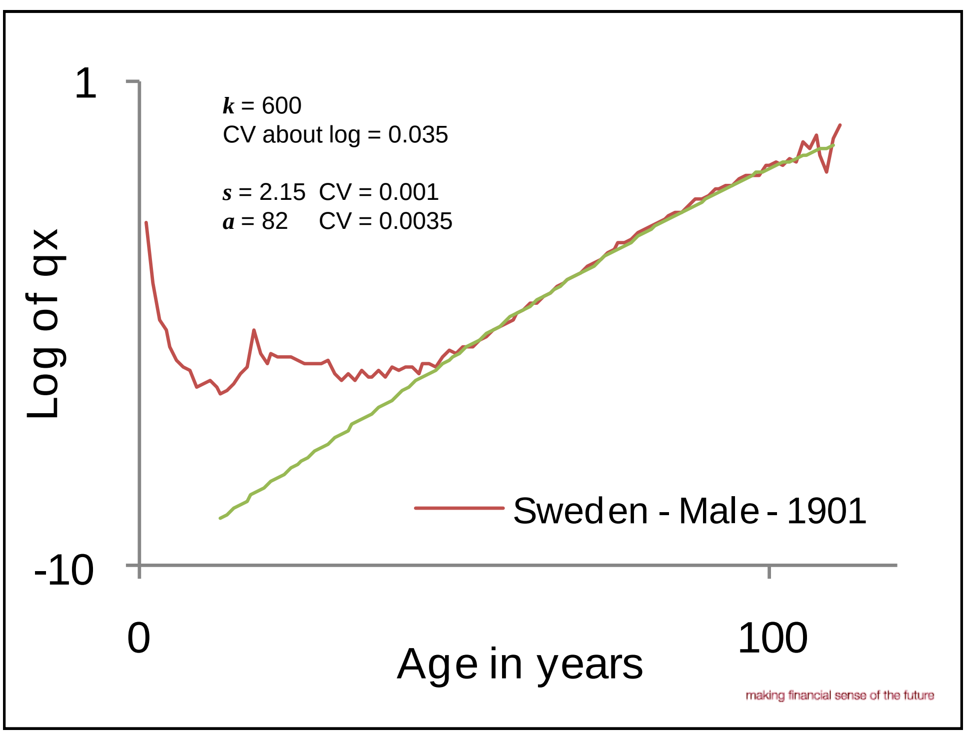

1
-10
Log of qx
k = 600
CV about log = 0.035
s = 2.15 CV = 0.001
a = 82 CV = 0.0035
Sweden - Male - 1901
0
100
Age in years
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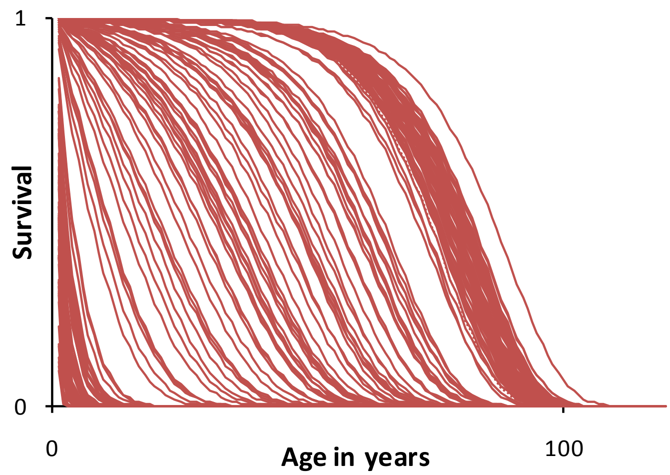
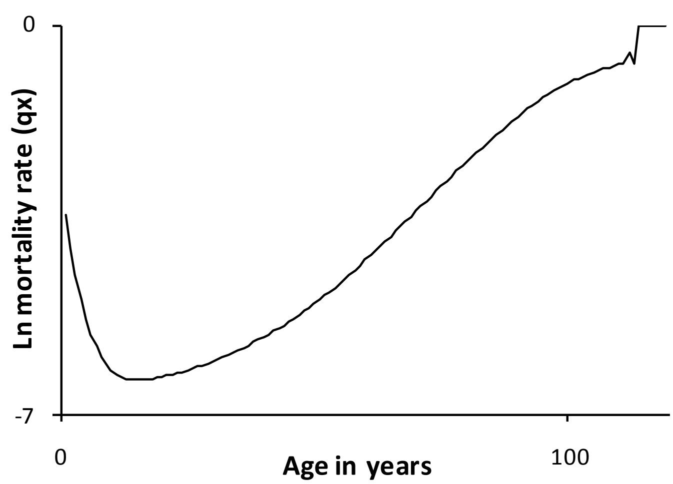
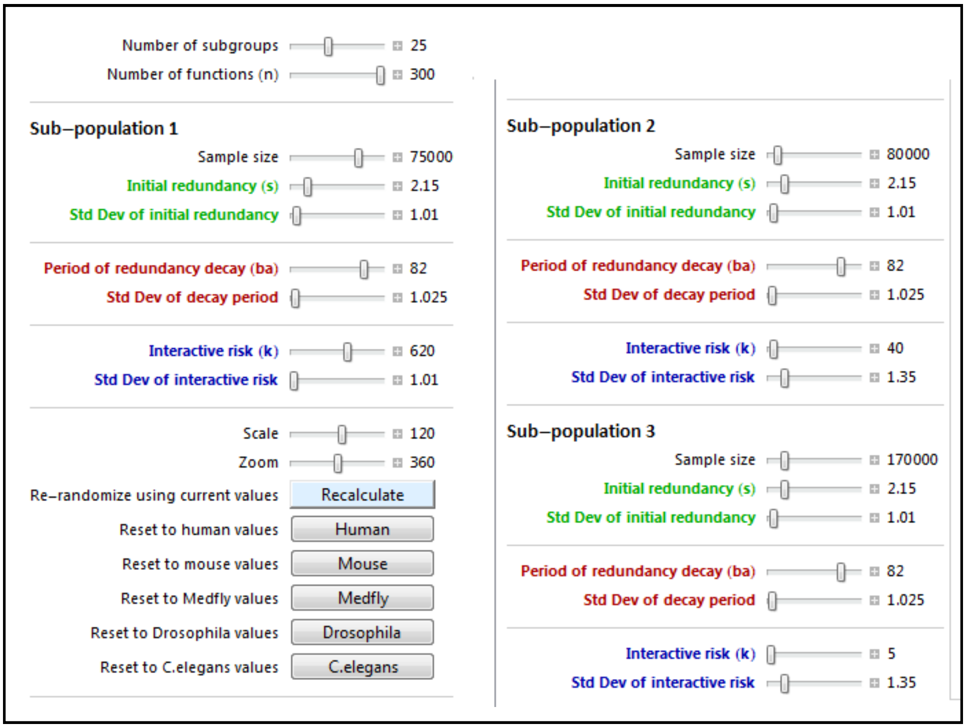
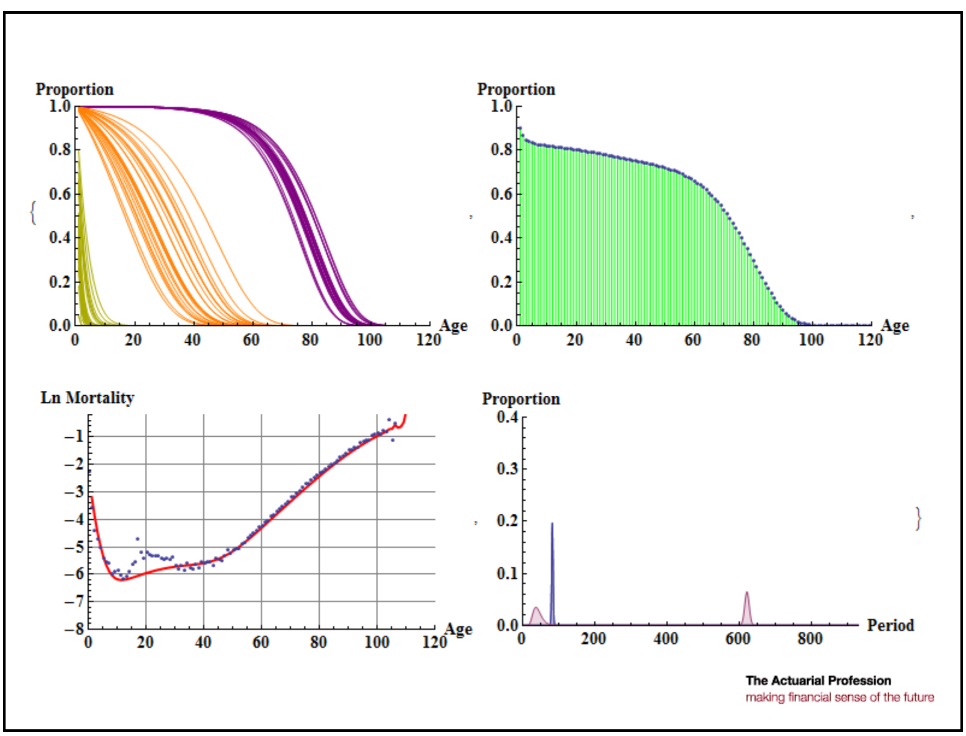

1
0
Survival
0
100
Age in years


0
-7
Ln mortality rate (qx)
0
100
Age in years



Number of subgroups 25
Number of functions (n) 300
Sub–population 1
Sample size 75000
Initial redundancy (s) 2.15
Std Dev of initial redundancy 1.01
Period of redundancy decay (ba) 82
Std Dev of decay period 1.025
Interactive risk (k) 620
Std Dev of interactive risk 1.01
Scale 120
Zoom 360
Re–randomize using current values
Recalculate
Reset to human values
Human
Reset to mouse values
Mouse
Reset to Medfly values
Medfly
Reset to Drosophila values
Drosophila
Reset to C.elegans values
C.elegans
Sub–population 2
Sample size 80000
Initial redundancy (s) 2.15
Std Dev of initial redundancy 1.01
Period of redundancy decay (ba) 82
Std Dev of decay period 1.025
Interactive risk (k) 40
Std Dev of interactive risk 1.35
Sub–population 3
Sample size 170000
Initial redundancy (s) 2.15
Std Dev of initial redundancy 1.01
Period of redundancy decay (ba) 82
Std Dev of decay period 1.025
Interactive risk (k) 5
Std Dev of interactive risk 1.35



Proportion
Age
Proportion
Age
Ln Mortality
Age
Proportion
Period
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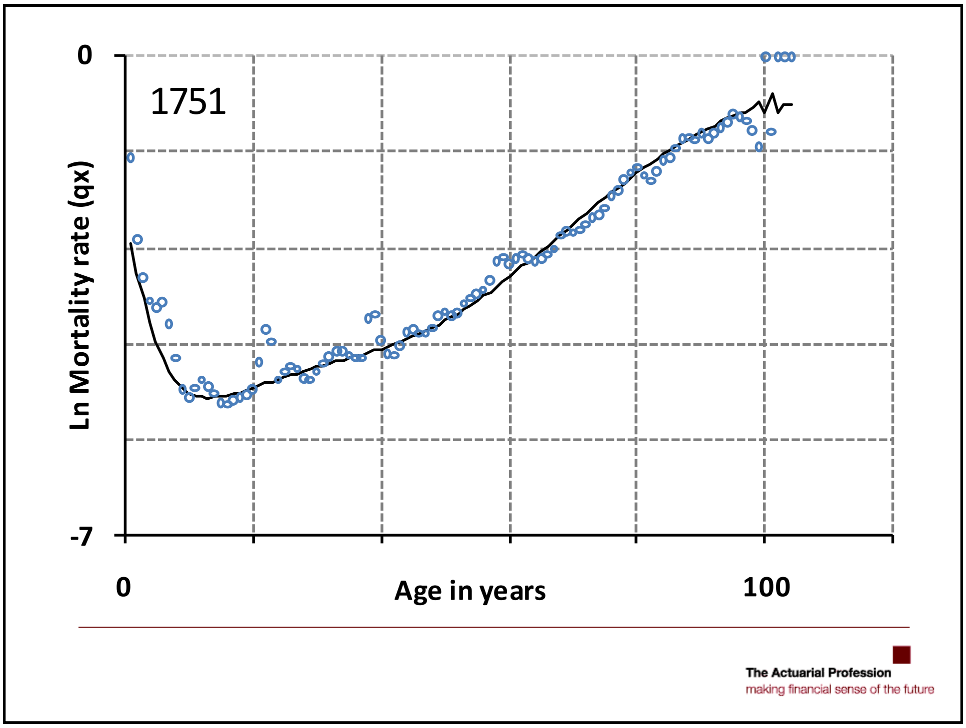
0
1751
Ln Mortality rate (qx)
-7
0
Age in years
100
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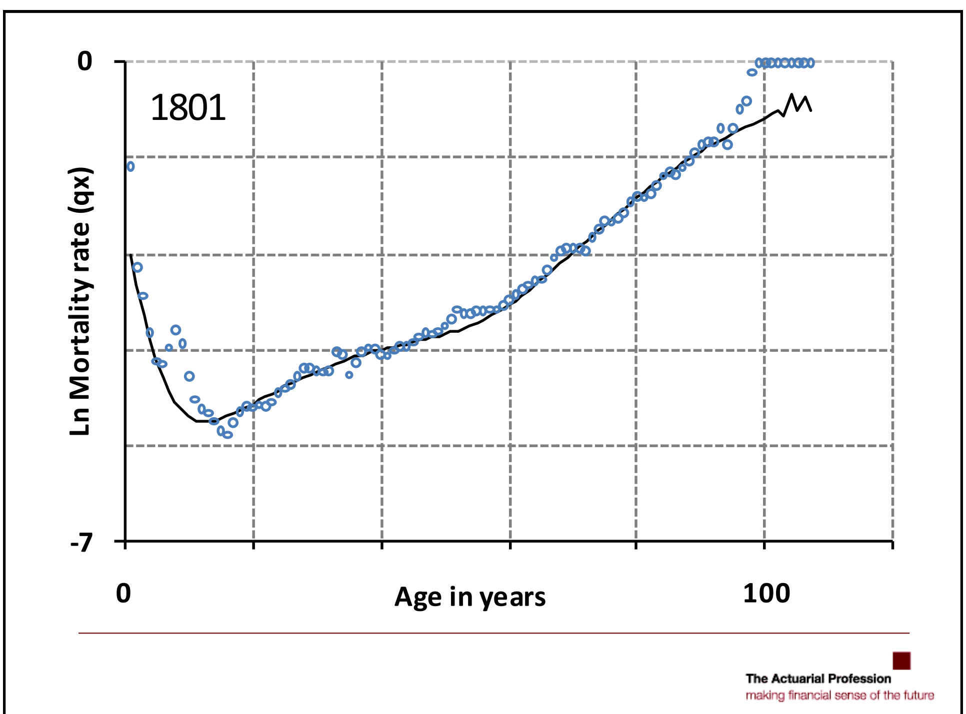
0
1801
Ln Mortality rate (qx)
-7
0
Age in years
100
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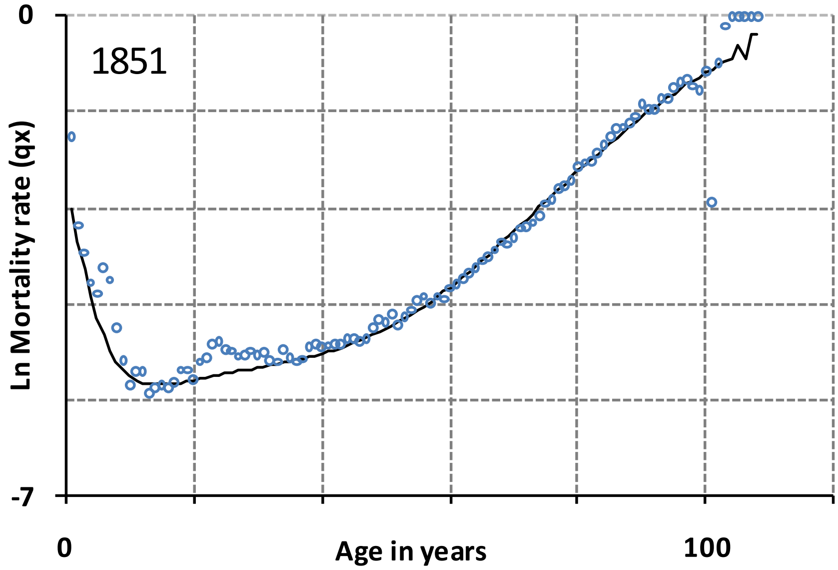

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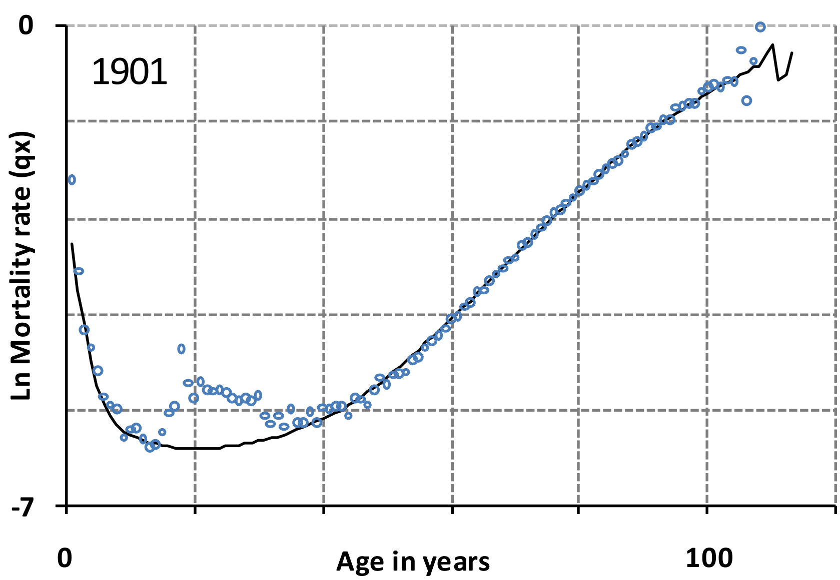

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Summary – Basic Principles

- The NBM:
  - allows modelling of mortality and survival curves, late-life mortality deceleration, S-M correlation, mortality plateaux and slowing of mortality .
  - partitions mortality risk into two main elements: redundancy decay and interactive risk.
  - No single parameter represents 'ageing' although parameter $\boldsymbol{a}$ is closest to the definition commonly used by gerontologists (e.g. Hayflick)

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Human mortality

- Once a fixed human value for parameter a is assumed, variation in historical mortality can be modelled relatively simply by variation exclusively in parameter k.
- So what does parameter a / redundancy actually represent?

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Questions?

- Thanks to:
- Stephen Singleton
- Oliver Milne
- Tom Kirkwood
- Daryl Shanley

Funding and support:

NHS North East

Newcastle University

Human Mortality Database

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