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A NEW MODEL OF AGEING AND MORTALITY

By Eugene M. G. Milne

ABSTRACT

The Nested Binomial Model presented in this paper is a new approach to modelling mortality and survival in humans and other species that seeks to reconcile individual life course risk trajectories and those population mortality patterns that arise from inter-individual heterogeneity. In describing individual trajectories it partitions mortality risk into two main elements: 'redundancy' and 'interactive risk'. Interactive risk is volatile, increasing or decreasing with time and circumstance, while redundancy is a quantity which declines in a linear and largely invariable fashion throughout life. Although a biological correlate for redundancy is not identified, this assumption allows strikingly realistic modelling of mortality and survival curves, late-life mortality deceleration, Strehler-Mildvan correlation, mortality plateaux and slowing of mortality. Simple assumptions with regard to heterogeneity of parameters within the model allow close approximation to the entire human mortality curve, and provide a rationale for observed and otherwise paradoxical population mortality phenomena. As such, it fulfils biodemographic criteria for a comprehensive theory of ageing. Future challenges are to reconcile its theoretical structure with empirical findings in the biology of ageing and to render it in a form that can become a usable actuarial tool.

KEYWORDS

Mortality Laws; Survival Models; Gompertz; Makeham; Biological Models

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1. Introduction

1.1 Many mathematical models of population mortality have been proposed since the time of Gompertz. Generally these have aimed to describe the manner in which *population* risk changes with age. Often, however, those patterns observed in populations have been interpreted as expressions of *individual* ageing risk. Gompertz himself suggested that a law of individual ageing was revealed through the net pattern of human mortality data (Gompertz, 1825). Makeham, similarly, in modifying the original Gompertz formula appears to have done so partly with a biological explanation in mind (Makeham, 1867).

1.2 The history of such approaches has been reviewed elsewhere and will not be laboured here (Olshansky & Carnes, 1997). However, it is clear that a

key problem in biodemographic interpretations of population mortality data is the danger of perpetrating an 'ecological fallacy' — that is, the error of attributing the mean characteristics of a population to individual members of that population. Any biological interpretation of population mortality should address the question of which elements of its patterns are genuinely characteristic of individuals and which are the net consequences of non-age-related risk or of population heterogeneity.

1.3 Carnes and Olshansky approach this problem by attempting to separate 'intrinsic' and 'extrinsic' mortality. Following the lead of Makeham, they assume that such a distinction exists — and suggest that by stripping away 'extrinsic' causes of death one is left with a population pattern that reflects an 'intrinsic mortality schedule', reflecting the increasing vulnerability of individuals with increasing age (Carnes & Olshansky, 1997).

1.4 Such a categorical separation of 'intrinsic' and 'extrinsic' mortality is, however, unsatisfactory since no death is ever entirely one or the other. Indeed, all deaths are more properly seen as a mixture of both in varying proportions. Even road traffic accidents — ostensibly the most 'extrinsic' of events — become fatal only when their force exceeds the (variable) resilience of human anatomy, and their pattern through the life course is influenced by, for instance, hormones and the recklessness of youth.

1.5 An alternative approach, explored in this paper, is to consider not only the shape, but also the dynamics of mortality curves and how these arise.

2. Dynamic Characteristics of Mortality Curves

2.1 Gompertzian increases in mortality are commonly seen in certain parts of the life course not only in humans but in many species. These patterns appear as straight lines when plotted semi-logarithmically, but their slopes and intercepts vary between and within species, strains, and populations under varying conditions and over time.

2.2 For humans the period of log-linearity is commonly considered to extend from the age range of 35-40 to about 85-90 years, though it clearly applies to some populations from earlier ages, and may commence below the age of 20 when certain traumatic causes of death are excluded from analysis (Dolejs, 1997). For actuarial purposes, the period of close compliance with log-linearity may be considered to be the age range 60-90 years (Richards, 2010).

2.3 Taking the human life course as a whole, it is useful to regard log-linearity merely as one of at least six phases of mortality. Six identifiable phases, (Milne, 2009), are :

— birth & childhood;
— sexual maturity and early adult life;

— the 'Makeham' phase;
— Gompertzian mortality;
— late-life deceleration & extreme old age; and
— 'manufactured survival'.

Indeed, these might be subdivided further, or augmented by phases specific to particular times and circumstances.

2.4 The Gompertzian phase, however, is attributed particular significance. Biological interest in this pattern arises from its ubiquity and its robustness. It is a pattern of mortality to which even heavily disrupted populations tend to return; a classic example being the mortality pattern of Australian prisoners-of-war in Japanese concentration camps during World War II (Finch, 1990). More recently, the reversion to log-linearity of African mortality curves disrupted by the emergence of AIDS illustrates the same phenomenon. With reference to this tendency, it has been said that while machines tend to fail according to a Weibull distribution, organisms 'prefer' to die in accordance with Gompertz (Gavrilov & Gavrilova, 2006).

2.5 As a consequence, log-linear patterns of mortality have been widely attributed biological significance in ageing research, thus: "*the age-related acceleration of mortality rate is measured by the mortality rate doubling time, MRDT, and is held to be a fundamental measure of senescence*" (Finch, 1990). This view is not universally held, and there are good reasons to doubt it. It is, however, a behaviour that requires explanation.

2.6 In comparing populations over time, geographical distribution, under different conditions or even between species, we can describe three fundamental differences in the log-linear components of their mortality curves. These three fundamental differences are described in Figure 1 as differences of type A, B or C (Milne, 2009). Types A and B involve changes in gradient, but differ in that they demonstrate what may be broadly characterised as rotations of the semi-logarithmic curve about pivots that lie, respectively, to the bottom left and top right of their plots. Type C differences, in contrast, represent a changed position of the curve without alteration in gradient.

2.7 Under Finch's definition of log-linearity as 'a fundamental measure of senescence', differences in gradient have often been considered to represent alterations in the 'rate of ageing'. Type A differences have been seen as particularly important in this regard, since lowering of the slope has been described in some dietary restriction experiments (Wilmoth & Horiuchi, 1999). However, the presence of type B differences in human mortality has presented a conundrum — namely that, as mortality has fallen, the gradient of mortality appears to have increased, suggesting that the 'rate of ageing' has accelerated (sometimes referred to as the 'compensation law of mortality'). As a consequence, some commentators have suggested that any

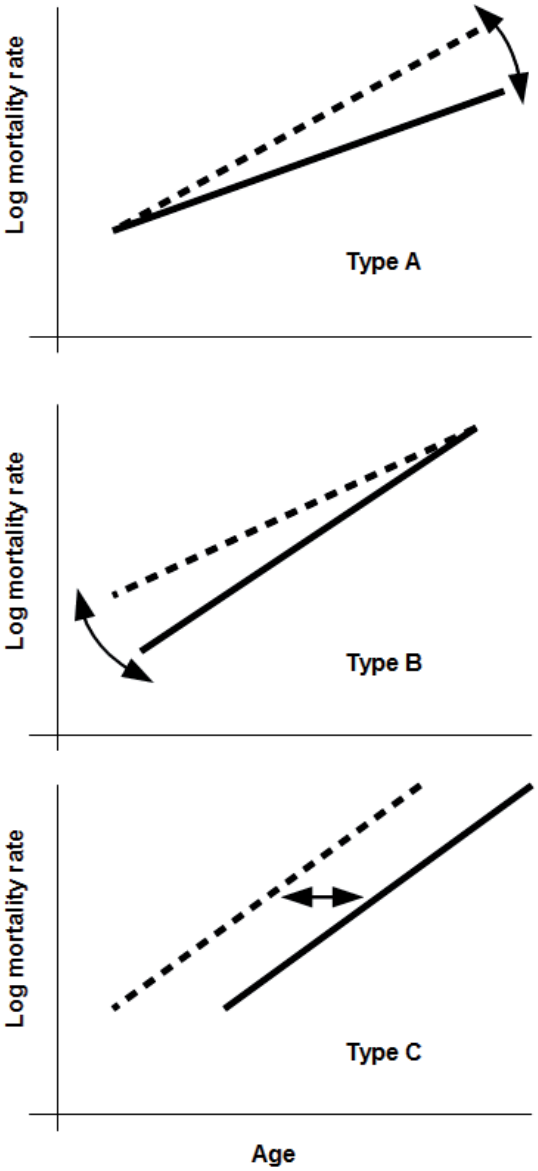

Figure 1. Three principal types of difference in mortality curves (reproduced from Milne 2009)

generalised age-specific reduction in mortality, regardless of the slope, should be regarded as a slowing of ageing (Masoro, 2006).

2.8 Type B differences also, by virtue of their apparent convergence upon a point in late life, have the characteristic of exhibiting 'Strehler–Mildvan correlation'. This refers to an inverse linear correlation between the Gompertz slope parameter and the log of the intercept parameter in such families of curves (Strehler & Mildvan, 1960).

2.9 If we accept the assumption that the Gompertzian pattern is fundamentally a reflection of individual ageing, while observing that it emerges as a population characteristic in humans and in other species only for part of the life course, it becomes necessary also to explain its absence during other phases of mortality.

2.10 There are, essentially, two alternatives here: either that other phases reflect population heterogeneity of risk such that the innate risk patterns of individuals are obscured, or that individual risk has different characteristics during those phases.

2.11 In general, ageing researchers have tended to regard early life as a phase of non-ageing, during which risk is governed by programmed development. Some have explicitly seen the commencement of ageing as the point at which population mortality starts to rise (Hayflick, 1984). Certainly, there has been a general assumption that pre-pubertal risk differs from subsequent mortality. Witten addressed this by assuming transition through the life course between three risk distributions — neonatal failure, Gompertzian failure and old-age failure — having concluded that neonatal deaths exhibited exponential (constant risk) failure kinetics but that no combination of individual constant risks could generate Gompertzian patterns (Witten, 1988).

2.12 There is certainly no good reason to suppose that the processes of ageing do not apply prior to puberty, and a complete theory of individual mortality risk should account for patterns of mortality in childhood as well as later life (Milne, 2006).

2.13 Mortality in the phase of sexual maturity and early adult life and of the 'Makeham' pattern have been attributed to external factors rather than intrinsic patterns, and the pattern of mortality during the 'manufactured survival' phase is seen as a consequence of medical interventions (Olshansky *et al*., 1998).

2.14 Debate about late life mortality deceleration and extreme old age, on the other hand, has more vigorously considered whether deviations from a Gompertzian pattern might reflect changes in individual patterns of ageing or simply population heterogeneity. The latter has been described as 'culling' — defined by the Oxford English Dictionary as "*the selective killing of surplus or inferior animals*". But, as Wachter has observed, "*it takes a lot of heterogeneity to make hazard functions visibly bend or drop … one can compute how low the lifelong hazards have to be among the least frail few percent of*

individuals compared to the hazards for the median individual or most frail few percent if simple culling is to explain all the observed tapering ... [but m]any authors find these ratios too extreme to be plausible" (Wachter, 2003). Accordingly, greater significance has been attached to explaining this phase than others, since it has been considered possibly to reflect a genuine deceleration of individual ageing.

2.15 This is reflected in the *Handbook of the Biology of Aging*, which proposes four criteria that any "*comprehensive theory of ageing*" should satisfy (Gavrilov & Gavrilova, 2006). Paraphrased, these state that the theory should:

(i) Explain why most species deteriorate with age.
(ii) Explain exponential rises in mortality.
(iii) Explain the 'compensation law of mortality' (i.e. type B differences).
(iv) Account for loss of exponentiality, plateaux and deceleration of mortality at older ages.

Implicit in these criteria is an assumption that all four characteristics are reflections of individual ageing.

2.16 An earlier set of criteria for ageing theories proposed by Mildvan overlaps with the list above, but incorporates also (in keeping with what was then contemporary thought on acceleration of ageing) the effects of radiation (Mildvan & Strehler, 1960). We might also add, in the light of animal studies, consideration of the effects of dietary restriction, oxygen tension and temperature (Milne, 2008).

2.17 Combining and summarising these criteria (paragraphs 2.15 and 2.16) with the considerations outlined earlier, I propose that a persuasive theory should:

(1) explain why most species deteriorate with age;
(2) explain exponential rises in mortality;
(3) provide a rational explanation for differences of type A, B and C either in terms of individual risk or through a plausible mechanism of heterogeneity — ideally associating each with a separate model parameter, and accounting for Strehler–Mildvan correlation;
(4) for its application in humans, provide a plausible explanation for all six phases of mortality listed in paragraph 2.3; and
(5) provide a context for the interpretation of data from ageing and other risk-related studies.

3. Limitations of Existing Models

3.1 There is no shortage of models seeking to describe mortality more extensively across the life course than is achieved with the Gompertz law. Richards has recently described and compared sixteen models used in

actuarial analysis and survival modelling and his list may not be exhaustive. I do not propose to examine all of those models here, but it is worth briefly considering the Makeham–Beard model which, of those reviewed, provided the best fit to mortality data (Richards, 2010).

3.2 The Makeham–Beard model has a logistic-shaped hazard, determined by four parameters, yielding a representation of three phases of mortality, namely those referred to in 2.3 as Makeham, Gompertzian and late-life. Its Gompertzian phase easily exhibits type A and C differences by manipulation of single parameters, but it shows Strehler–Mildvan correlated type B differences only insofar as they are generated by the Makeham factor, or by manipulation of more than one parameter (see later). The late-life component describes resolution toward a fixed hazard in extreme old age. It is effective as a description of significant parts of mortality curves, but does not clearly distinguish between individual and population risk, or provide much insight into underlying causes of those patterns. Beard himself was clearly aware of this problem and sought approaches based more upon individual risk, noting: "*mathematical relationships of the type found are essentially descriptive formulas and although various attempts have been made to provide some physical interpretation of the formulas most of them have been in terms of vague concepts which have not led to any scientific developments. It is reasonable to ask whether the emphasis on the rate of mortality which has naturally followed from the needs of the actuary in his problems and from the calculus developed to enable him to deal with them has not been a retarding factor in the study of mortality for its own sake*." (Beard, 1964)

3.3 These problems appear to apply to a greater or lesser extent to all current models of mortality, and reflect their origins as actuarial models rather than models of individual risk.

3.4 While many mortality models replicate the patterns of type A and type C differences with alterations in single parameters, no existing model appears to replicate type B differences with a single parameter change. Instead, to effect a type B difference requires simultaneous changes in two or more parameters in order to 'fix the pivot' implied by that pattern of difference. Crude approximations to type B differences can be modelled using the Gompertz-Makeham model, or the Vanfleteren 3-parameter logistic model, but neither of these provides a very satisfactory approximation to Strehler–Mildvan correlation (Vanfleteren *et al*., 1998).

3.5 It is, I suggest, of crucial importance that a definitive model of ageing should accommodate type B differences. The existence of such differences in historical human mortality data argues strongly for some form of 'schedule' (though not necessarily a program in the conventional sense) to ageing, and provides a key clue to the underlying architecture of mortality risk.

4. The Nested Binomial Model

4.1 This, and following sections, provide an overview of a new approach that aims to avoid ecological fallacy by working theoretically from the 'organism up' rather than from the 'population down' and to obviate the question of 'intrinsic' and 'extrinsic' causes by assuming that all deaths are a result of interactions (Milne, 2008).

4.2 Ultimately, the aim of such an approach is to produce a unifying model that will both accommodate our increasing understanding of the specifics of ageing biology and link them with observations at population level, thereby allowing better interpretation of experimental findings and, potentially, better prediction of mortality patterns.

4.3 Constructing such a model has not been constrained by current understanding of the biology of ageing, since the one thing that is known for certain is that our knowledge is imperfect. Instead, the modelling approach aims to address the question of how organismal risk would *need* to be constructed in order collectively to produce patterns of population mortality such as those observed in nature.

5. Basic Principles of the Model

5.1 An organism, at any instant, has a given probability of surviving or failing per unit time. Envisage an organism as comprising a set of vital functions such that, by their nature, the organism will die if any function fails. Thus, the probability of the organism's survival is the product of the probabilities of survival of its vital functions.

5.2 Now envisage that each function has a degree of redundancy such that the normal delivery of that function can usually 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 a function is distinct from failure of a redundant component.

5.3 A failed component may be repaired and restored to use while other, similar components sustain the function. Indeed, components may fail many, many times and be repeatedly repaired. With age, however, the redundancy of functions is assumed to decay, and is postulated to do so in a linear fashion, until eventually the organism has little redundant reserve to protect it from dangerous interactions with its environment (see Figure 2).

5.4 Crucially, in this model, component failure and decay are distinguished from one another. Failure is repairable, decay is not. Moreover, and perhaps counter-intuitively, the rate of decay is considered to be quite independent of failure rates, and to be largely invariable in its linear trajectory of decline.

5.5 Throughout life the organism is threatened by external hazard and internal vulnerability and these interact. Interactive risk determines the mean

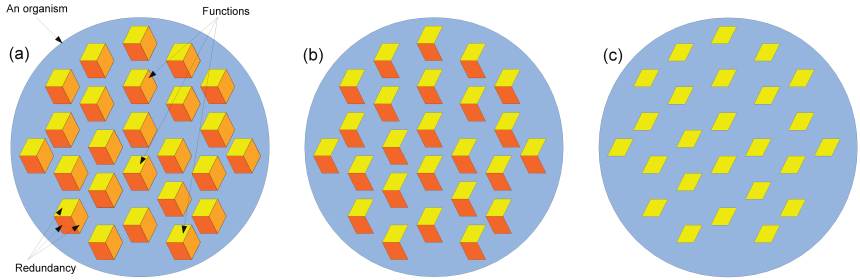

Figure 2. Conceptual model of redundancy decay (a to c) in a theoretical organism with multiple functions

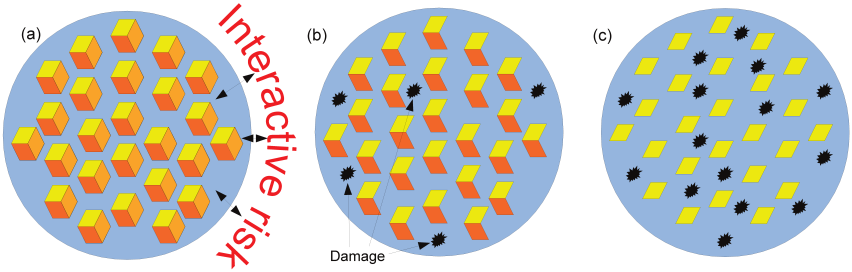

Figure 3. Conceptual model of a theoretical organism experiencing redundancy decay (a to c) and increasingly damaged by interactive risk. This separation of regularly progressive redundancy decay and volatile interactive risk is proposed to be fundamental to the architecture of lifelong mortality risk

time to failure of redundant components but does not affect the rate of decay of those components. Throughout life, damage is sustained through disease, wear and tear, until the organism is both damaged and vulnerable through the low redundancy of its functions (see Figure 3).

5.6 This approach, therefore, divides risk to the organism into two distinct partitions, namely:

— Redundancy decline, which is linear and largely invariable.
— Interactive risk, which is markedly variable and describes all other influences upon mortality risk.

It is this partitioning of risk that is embedded in the model and proposed to be fundamental to the architecture of mortality curves.

5.7 At its heart, the mathematics of this approach is based upon binomial probabilities, and for this reason I have called it a 'nested binomial model' (NBM). It makes the assumptions that:

— Organisms may be regarded as a set of (n) vital functions connected in series — for convenience we may treat these functions as identical.
— Net risk of dying depends upon both the redundant state of those functions and upon a level of interactive risk (k) that varies independently of the redundant state.
— The measure of interactive risk (parameter k) is proportionally related to the half life of redundant components within each function; thus, component half life is short when at high risk and long when at low risk.
— For any given level of interactive risk, additional redundancy has a multiplier effect upon the component half-life.
— A redundancy of 1 is defined arbitrarily as that level of redundancy at which its multiplier effect is 1. The half life is extended by levels of redundancy above this level and reduced by levels below.
— For any function to fail, all of its redundancy must fail simultaneously.
— As a consequence, a function with greater redundant reserve comprises not only redundant components that have longer half lives, it also has the capacity to tolerate temporary 'outages' of a proportion of those redundant components. We may assume that such outages are normally repaired completely, restoring the level of redundancy to pre-outage levels.
— Each function is assumed to have an initial species or strain-specific quantity (s) of redundancy which declines in a linear fashion at a largely invariable rate (determined by parameter a — the period of decay of 1 unit of redundancy) throughout life.

5.8 Mathematically, the instantaneous risk for such a model may be described thus:

$$\mu_x = -\ln\left(1-(1-0.5^{\frac{1}{kr_x}})^{r_x}\right)^n \tag{1}$$

where redundancy at age (x) is:

$$r_x = s - \frac{x}{a} \tag{2}$$

where:

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; a value equivalent to the unit-specific half-life when $r = 1$;
n = number of functions that comprise the organism; and
x = current age.

5.9 It is worth noting that this provides an *exact* estimation of instantaneous risk rather than the approximation commonly used in deriving instantaneous risk from life tables which is expressed as:

$$\mu_{x+0.5} \cong -\ln(1 - q_x). \tag{3}$$

This is because with this approach we are not attempting to estimate underlying risk from real data. Instead we are modelling exact risks to *approximate* observation.

5.10 It may also be noted that the form of equation (1) specifically reflects the theoretical biological model described above, but may be one of the broader class of mathematical models:

$$\mu_x = -\ln(1 - (1 - f(k, r_x))^{r_x})^n \tag{4}$$

where $f(k, r_x)$ is a decreasing function with respect to both k and r_x. However, it is axiomatic of the approach advocated in this paper that any alternatives within that class should be capable of directly relating their variables to biological postulates, and must preserve the mimicry of observed differences in mortality curves exhibited by equation (1).

5.11 The typical pattern generated by equation (1), assuming a moderate or low, constant level of interactive risk throughout life, tends to be one of mortality risk increasing with age on a trajectory which is almost, though not exactly, exponential. In fact, this trajectory 'decelerates' progressively and marginally from a truly exponential course with increasing age (and, hence, decreasing redundancy) until redundancy approximates to zero, at which point risk rises steeply to infinity.

5.12 Within the model, parameter n is treated as a constant for each species, but the remaining three parameters, s, a, and k, are assumed to show a degree of biological variation within each species. A further development of the approach will be to incorporate parameters for such variation into the equation. However, the examples and demonstrations shown in this paper are derived from probabilistic computer models (generated using Wolfram Mathematica), whereby large populations individually exhibiting NBM behaviour are iteratively decayed across a lifetime. For simplicity of modelling, these populations are assumed to contain a number of subgroups (for the examples here there are 25 subgroups in each instance) with similar parameter values, the parameter values in each case being generated randomly from distributions which are assumed to be log-normal. Using this

approach, the examples shown incorporate heterogeneity (for examples of the model without heterogeneity, see Milne, 2008).

5.13 The parameters of particular interest are the rate of redundancy decay (a) and of interactive risk (k). The following sections consider the patterns of mortality that are associated with variation in these parameters.

6. Model Behaviour — Type A Differences

6.1 From the perspective of ageing research, type A differences are, perhaps, of greatest interest, given the emphasis that has hitherto been given to the reduction of log-mortality slope as a supposed indicator of the rate of ageing or senescence — that is to say that clockwise type A differences have been considered to indicate slowed ageing.

6.2 As illustrated in Figure 4, an increase in parameter a causes a clockwise type A difference in the semi-logarithmic projection of a mortality curve, reducing mortality risk at all ages and increasing lifespan.

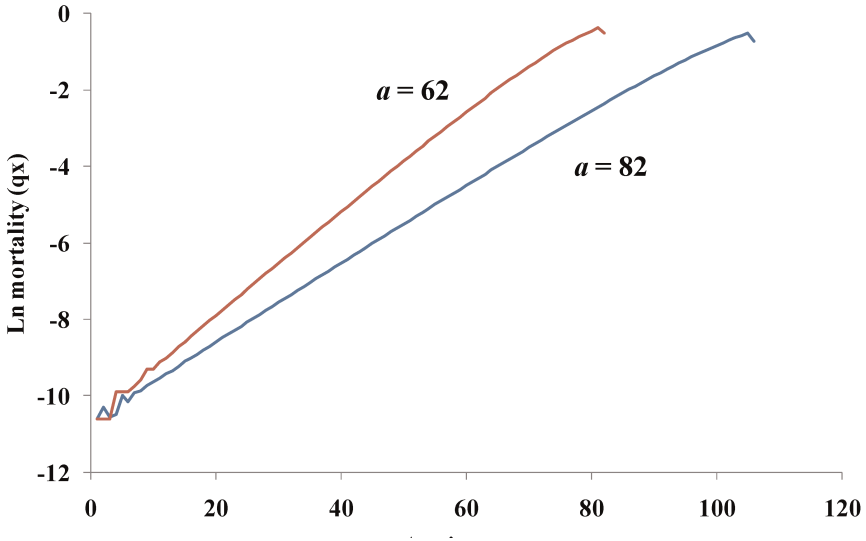

Figure 4. Mortality trajectories modelled for two populations differing only in their value of parameter a demonstrate type A difference in the curves. Figures were derived from populations of 1 million with 25 subgroups and parameters $n = 300$, $s = 2.15$, $k = 700$. Parameters s, a and k are assumed to be log-normally distributed, in this instance with standard deviation of ln(0.001) in each case

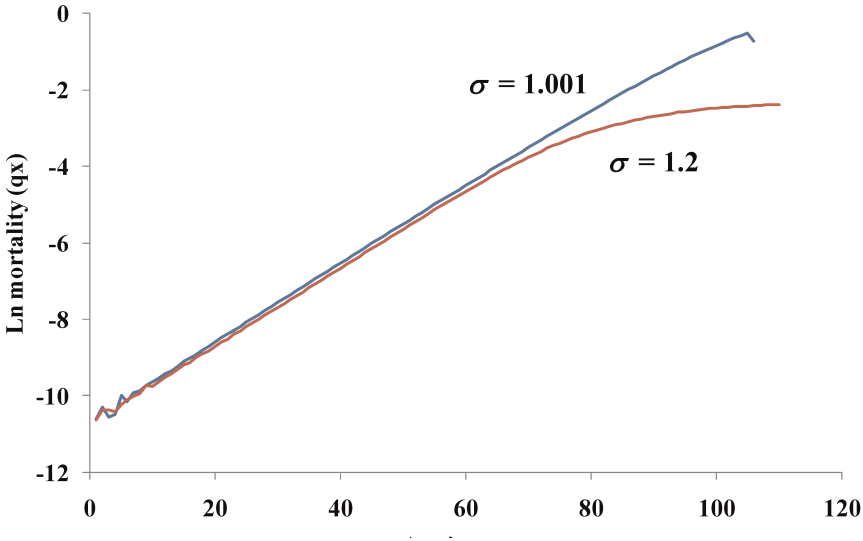

Figure 5. Increasing variance in parameter *a* causes late life deceleration of the mortality curve and can lead to plateau formation with larger variances

6.3 When the variance in values of parameter *a* is small, the mortality trajectory approximates to a Gompertzian increase for much of its length. However, increasing variance curtails this pattern and causes deceleration of the mortality curve (see Figure 5).

6.4 Mortality trajectories in animal studies are well recognised to show plateaux, which appear in this model as the variance of parameter *a* becomes larger, and declines in mortality, which tend to appear if the distribution of parameter *a* values is discrete or granular rather than broadly smooth. As the focus of this article is on human patterns, these features are not further explored here, but it is worth noting that this cross-species concordance is in keeping with the aim of the model to be a general description of lifetime mortality risk.

6.5 Type A changes have been demonstrated in various animal studies, but appear to be rare or absent in human data. Similarly, mortality plateaux and declines are considered not to be a feature of recorded human experience. The degree of mortality deceleration that is seen in human late life is consistent, within the NBM approach, with a narrow variation in parameter *a* across the species. This is, perhaps, unsurprising, given the recognised genetic homogeneity of humans relative to other species.

7. Model Behaviour — Type B Differences

7.1 Type B differences, in contrast to type A, appear ubiquitous in historical human data. Arguments have been made that, in part, this appearance is a consequence of external factors and neglect of Makeham's contribution to our understanding of mortality. However, even after exclusion of 'external' causes of death, type B differences persist — paradoxically suggesting that while mortality has fallen over time, the rate of ageing, as it has conventionally been interpreted, has increased.

7.2 Increasing parameter k while other parameters are held constant causes reduction in modelled mortality, and vice versa. As the value of parameter k approaches zero, the mortality curve approximates to the horizontal trajectory of exponential decay. At a k value of zero, the risk of death would be infinitely large.

7.3 The effect of variation in parameter k is illustrated in Figure 6, and it can be seen that as it increases, the mortality curve falls, but also exhibits

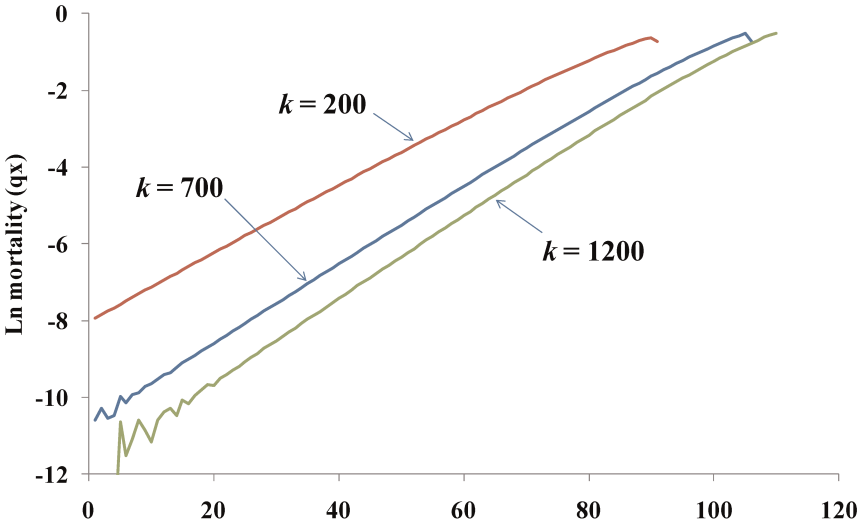

Figure 6. Mortality trajectories modelled for three populations differing only in their value of parameter k demonstrate type B difference in the curves. Figures were derived from populations of 1 million with 25 subgroups and parameters $n = 300$, $s = 2.15$, $a = 82$. Parameters s, a and k are assumed to be log-normally distributed, in this instance with standard deviation of ln(0.001) in each case

an anticlockwise pivoting pattern with respect to a fulcrum at the upper right of the curve — a type B difference.

7.4 Crucially, the deflection of the mortality curve associated with changes in k demonstrates Strehler–Mildvan correlation. This can be demonstrated by applying Gompertzian lines of best fit to data generated in the model (for illustration see Milne, 2008).

7.5 From this perspective, the paradox of reduced human mortality with increased slope is resolved. If falls in mortality result from reduced interactive risk, while redundancy decay is unaltered, such a pattern would be expected.

7.6 The effect of heterogeneity in parameter k also differs from that of parameter a. If we assume constancy of parameter k across the life course, then increasing variance in that parameter causes the type of difference illustrated in Figure 7. This pattern is logical if one considers that greater variance in k indicates a greater degree of inequality of interactive risk being experienced by that population. Under these circumstances a proportion of the population will have markedly higher mortality in early life, while the more privileged long term survivors — selected by their survival — will tend to show lower mortality in old age.

7.7 And it is interesting to note that if one considers the mortality

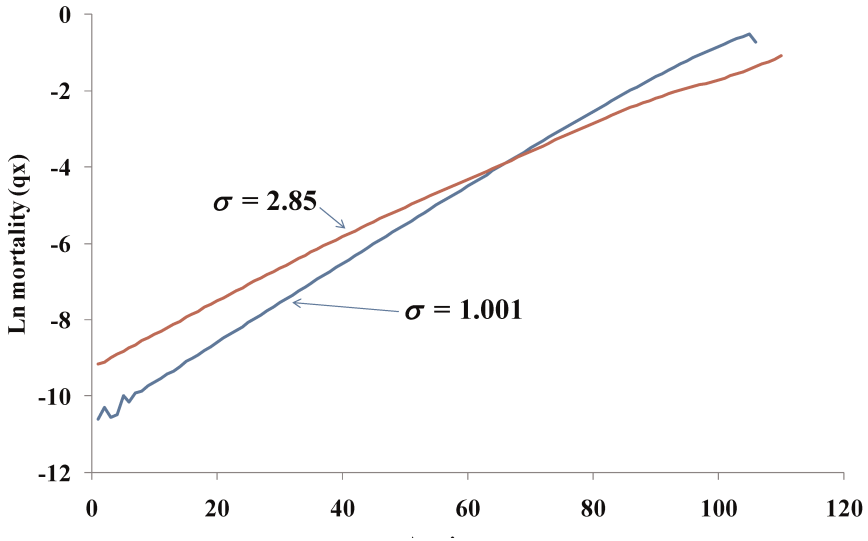

Figure 7. Increasing variance in parameter k produces increased curvature of the mortality curve, with elevation of population mortality in early life and reduction in late life

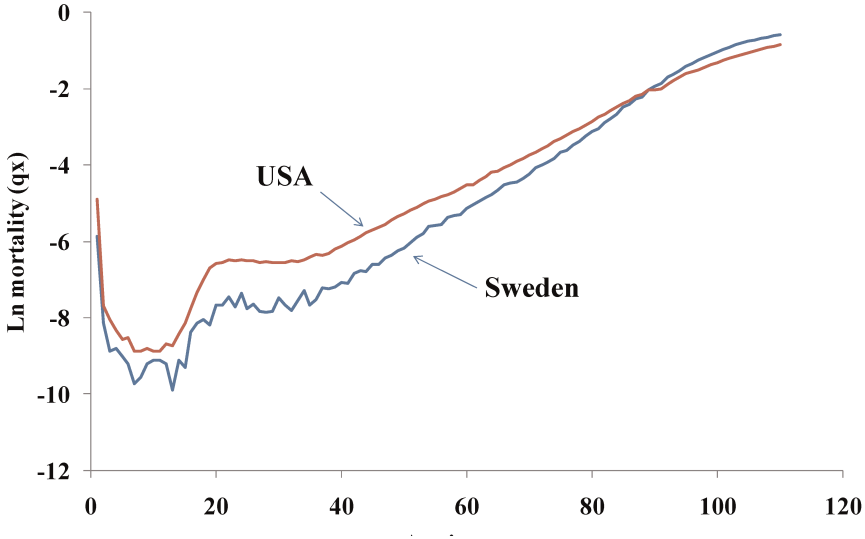

Figure 8. Comparison male mortality (period data for 2006) of a notably equal society with a relatively unequal society appears to illustrate the pattern of greater variance in parameter k shown in Figure 7

experience of two developed nations (Figure 8), one with a notably equal society and one that is comparatively unequal — in this instance Sweden and the USA — the relative positioning of their mortality curves resembles the pattern of parameter k heterogeneity from Figure 7. A lower level of heterogeneity in Swedish interactive risk seems a far more plausible explanation for the differences in these curves than lower mortality with faster ageing.

8. Parameter k Life Course and Inter-Individual Variation

8.1 Since parameter k is a measure of interactive risk — a mixture of variable internal and external factors — it follows that the level of parameter k affecting any individual at any time may be highly variable. At a population level this will generally be masked, since mortality will reflect the mean pattern rather than individual *asynchronous* fluctuations. However, notably in early childhood the predominant influence upon mortality rates stems from these asynchronous variations in parameter k — that is to say that deaths are predominantly of individuals whose interactive risk is markedly different from the average (for example in individuals with severe congenital anomalies).

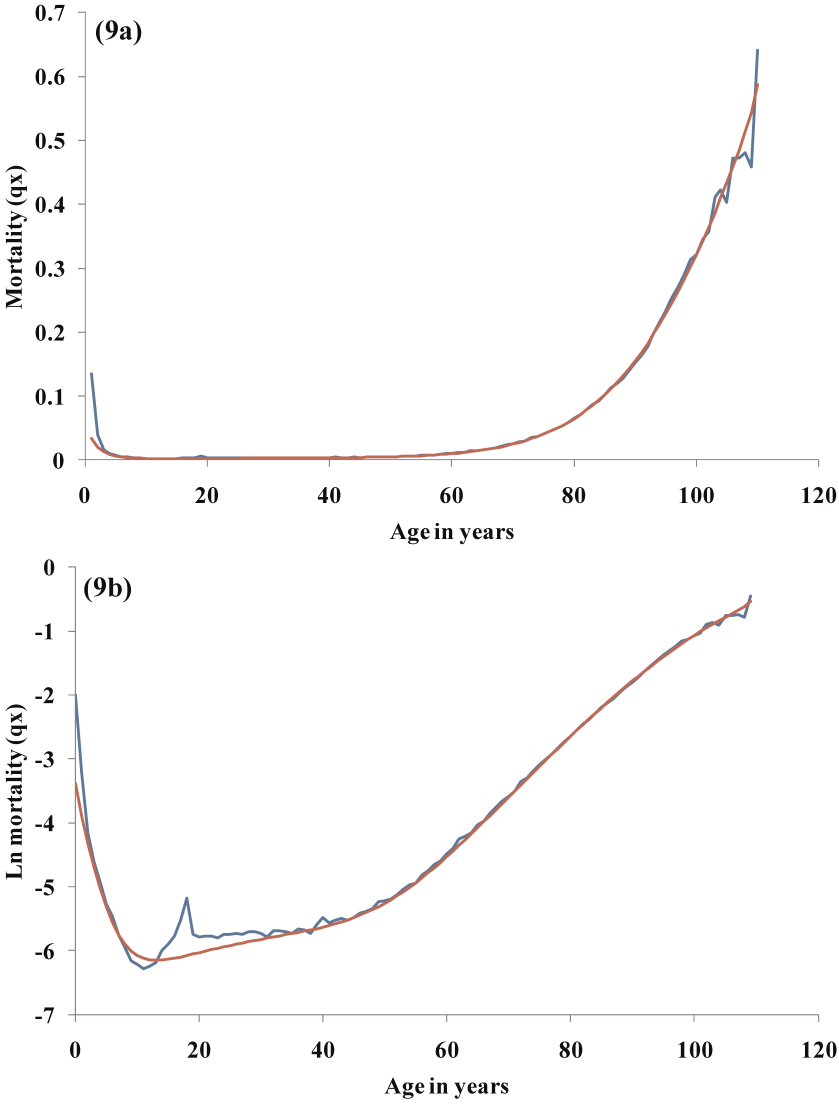

Figure 9. (a) Cohort mortality for women born in England in Wales in 1900 (the slightly irregular line) overlaid with data generated using the nested binomial model (smooth line), and (b) the same data presented in semi-logarithmic projection. Model data are the means of ten consecutive model runs using values judged to provide a good visual fit

8.2 At birth, however, it is also the case that parameter k will be very low for all individuals, and would be expected to climb as a child becomes more robust and resilient in the face of environmental challenges. Similarly, at adolescence, when individuals become more autonomous and driven to take greater risks, parameter k would be expected to fall, at least temporarily. These are examples of what in a cohort would be *synchronous* fluctuations of parameter k (a further example appears in Figure 9(b) at the age of 18 where mortality spikes as a consequence of the influenza pandemic of 1918-19).

8.3 The characteristic shape of human mortality curves in infancy and in early adult life is thus formed by a mixture of asynchronous and synchronous fluctuations.

8.4 In modelling, we could subject each individual to a fluctuating level of parameter k across the life course. However, it is much simpler instead to treat all individuals as if they have a constant level of k throughout life, while sampling those levels of the parameter from several subpopulations. Thus, we can model a population that has a subset of individuals with very low levels of parameter k throughout life, a subset with intermediate levels, and a robust general population with relatively high levels. There is, of course, no particular reason why one should use only three subsets, and one could argue for more. However, three are sufficient to produce a strikingly close approximation to the entire human mortality curve. Figure 9 shows mortality for women in England and Wales in the cohort born in 1900, overlaid with an NBM approximation derived using three population subsets. Between the ages of 40 and 100 the two lines are correlated such that $R^2 = 0.9998$, from ages 2 to 110 the equivalent figure is $R^2 = 0.9956$ and across the whole life course $R^2 = 0.9896$. This approach is explored in more detail and with further examples elsewhere (Milne, 2009).

8.5 The principal deviation from the modelled curve in this instance is in the first two years of life. There may, thus, be a need to include within the model a very specific element addressing infant mortality.

8.6 A visible deviation during the years of fertility (see Figure 9(b)) may reflect synchronous fluctuation of parameter k associated with the risks of childbirth in the early 20th century. However, the contrast between Figures 9(a) and 9(b) emphasises that the differences between the model and actual figures in this period are, in absolute terms, very small.

9. Model Behaviour — Type C Differences

9.1 Type C differences are of much less interest than types A and B, but should be mentioned for completeness. Changes in both the initial level of redundancy (parameter s) and the assumed number of functions (parameter n) bring about type C differences in mortality curves (Figures 10 and 11).

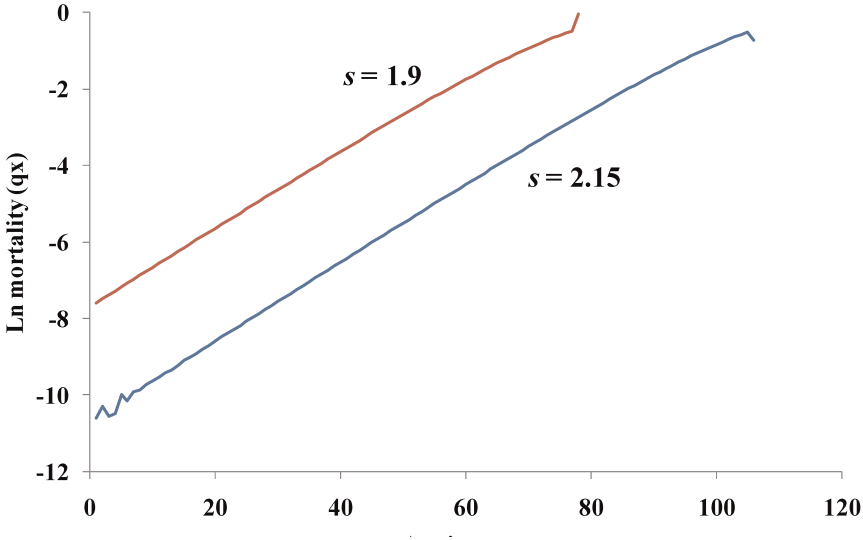

Figure 10. Mortality trajectories modelled for two populations differing only in their value of parameter s demonstrate type C difference in the curves. Figures were derived from populations of 1 million with 25 subgroups and parameters $n = 300$, $a = 82$, $k = 700$. Parameters s, a and k are assumed to be log-normally distributed, in this instance with standard deviation of ln(0.001) in each case

9.2 It is interesting to note that in applying the NBM to a variety of species, mortality curves appear generally to be modelled by consistently low and relatively similar (though not identical) values of parameter s. Values that work in modelling human mortality appear to be lower than those that work best in, for example, Drosophila. This might imply that in evolutionary terms, longevity has been associated not with acquisition of greater initial redundancy, but rather by an immense slowing of its decline. Whereas Figure 10 makes clear that a relatively small increase in initial redundancy would increase robustness markedly, we may speculate that the metabolic costs of a larger redundancy render it a less favoured option than better maintaining an initially smaller quantity.

9.3 A key implication to be drawn from the pattern of difference associated with parameter n changes is that the NBM, given the assumptions outlined above, may be applied to an organism with few functions in exactly the same way as to an organism with many. Such a circumstance must surely apply in nature if the same rules govern the mortality trajectories

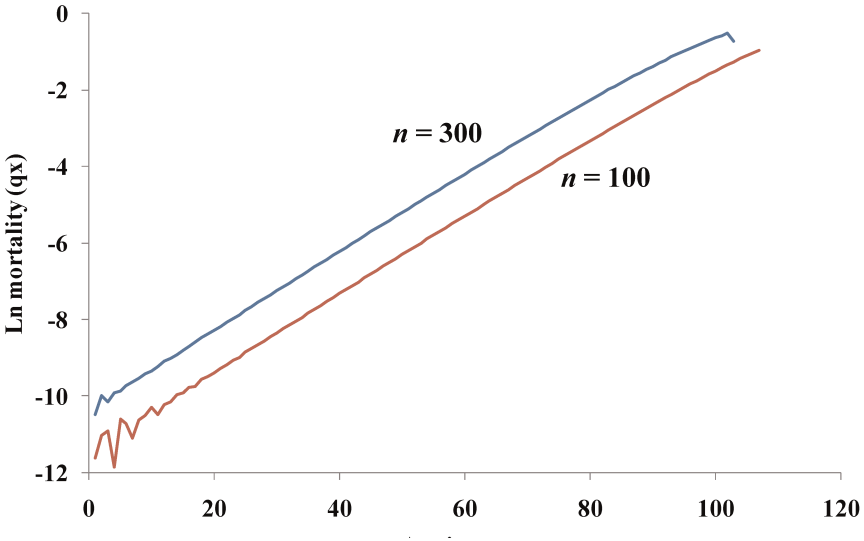

Figure 11. Mortality trajectories modelled for two populations differing only in their value of parameter n demonstrate type C difference in the curves. Figures were derived from populations of 1m with 25 subgroups and parameters $s = 2.15$, $a = 82$, $k = 700$. Parameters s, a and k are assumed to be log-normally distributed, in this instance with standard deviation of ln(0.001) in each case

of very simple and very complex animals and is consistent with the broad observation of similarities in mortality trajectories across many species.

10. Conclusions

10.1 The ultimate aim of the approach described in this paper is to produce a unifying model that will both accommodate our increasing understanding of the specifics of ageing biology and link them with observations at population level, thereby allowing better interpretation of experimental findings and, potentially, better prediction of mortality patterns.

10.2 The model proposed can be evaluated by the criteria for a persuasive theory of ageing proposed in 2.17. It can readily be seen that the NBM:

(1) incorporates a progressive loss of redundancy to account for the deterioration with age seen in most species;

(2) generates exponential rises in mortality for significant periods of the lifespan in populations whose redundancy characteristics are similar;
(3) produces mortality curves that demonstrate differences of type A, B and C with each type being associated with individual parameter changes, and with Strehler–Mildvan correlation arising as a consequence of parameter k changes;
(4) provides or accommodates an explanation for all six phases of human mortality listed in 2.3; and
(5) offers a new context for interpretation of data from ageing and other risk-related studies. It has still to be properly tested against these. A key issue to address is its compatibility with current scientific knowledge of, for example, cellular damage by reactive oxygen species, telomere depletion, signalling pathways and the effects of dietary restriction.

10.3 A fundamental question in addressing the latter issue is to determine whether a biological correlate for redundancy and its decline exists and to understand its nature. Although various candidates for this role may be postulated, none yet explored by the author behaves unequivocally in the manner described in this model.

10.4 As a bridge between actuarial and biological approaches to ageing it falls, as yet, between two stools. The examples in this paper are generated by probabilistic computer modelling. This is clearly not adequate for actuarial use and the model needs to be developed further to provide a form that will serve that purpose. On the other hand, it describes (as noted in section 4) a biology that would be 'needed' in order to construct organismal risk as it is observed. This it does well, providing a coherent account of why mortality patterns appear as they do. Yet its theoretical 'biology' is at odds with currently favoured theories of ageing. If the biological quantity described in the NBM as redundancy exists, we do not yet know what it is, nor why it should appear to act in so sequestered and consistent a fashion.

10.5 These then are the two key challenges for advancing this new model: to reconcile its necessary elements with empirical biology and to develop an actuarial tool that fulfils its evident promise for forecasting mortality.

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