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*Research Article*

### **A matrix approach to the statistics of longevity in heterogeneous frailty models**

**Hal Caswell**

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## Table of Contents

1	Introduction	554
2	The matrix formulation of the gamma-Gompertz model	556
2.1	Constructing transition matrices and the vec-permutation model	558
2.2	The absorbing Markov chain	559
3	Analysis of the model	559
3.1	The marginal survival and mortality functions	560
3.2	The marginal fundamental matrix	560
3.3	Longevity, variation, and disparity	561
3.4	Projecting the distributions of age, frailty, and mortality	562
4	An example: Swedish females	564
4.1	Statistics of longevity	565
4.2	Dynamics of frailty	566
4.3	Effects of the G-G parameters	567
4.4	Numerical reliability	571
5	Generalizations and extensions of the model	572
5.1	Models for baseline mortality	573
5.2	Models for the effects of frailty	574
5.3	Models for the distribution of frailty	575
5.4	Models for the dynamics of frailty	575
5.5	Some animal mortality patterns	577
6	Heterogeneous frailty vs. individual stochasticity: partitioning variance in longevity	578
7	Conclusions	580
7.1	Some pleasant properties of the matrix formulation	581
8	Acknowledgments	582
	References	584
	Appendix A: Gamma-Makeham and Gamma-Siler models	588
	Appendix B: Parameters for animal species	592

## **A matrix approach to the statistics of longevity in heterogeneous frailty models**

**Hal Caswell**<sup>1</sup>

### **Abstract**

#### **BACKGROUND**

The gamma-Gompertz model is a fixed frailty model in which baseline mortality increases exponentially with age, frailty has a proportional effect on mortality, and frailty at birth follows a gamma distribution. Mortality selects against the more frail, so the marginal mortality rate decelerates, eventually reaching an asymptote. The gamma-Gompertz is one of a wider class of frailty models, characterized by the choice of baseline mortality, effects of frailty, distributions of frailty, and assumptions about the dynamics of frailty.

#### **OBJECTIVE**

To develop a matrix model to compute all the statistical properties of longevity from the gamma-Gompertz and related models.

#### **METHODS**

I use the vec-permutation matrix formulation to develop a model in which individuals are jointly classified by age and frailty. The matrix is used to project the age and frailty dynamics of a cohort and the fundamental matrix is used to obtain the statistics of longevity.

#### **RESULTS**

The model permits calculation of the mean, variance, coefficient of variation, skewness and all moments of longevity, the marginal mortality and survivorship functions, the dynamics of the frailty distribution, and other quantities. The matrix formulation extends naturally to other frailty models. I apply the analysis to the gamma-Gompertz model (for humans and laboratory animals), the gamma-Makeham model, and the gamma-Siler model, and to a hypothetical dynamic frailty model characterized by diffusion of frailty with reflecting boundaries.

The matrix model permits partitioning the variance in longevity into components due to heterogeneity and to individual stochasticity. In several published human data sets,

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heterogeneity accounts for less than 10% of the variance in longevity. In laboratory populations of five invertebrate animal species, heterogeneity accounts for 46% to 83% of the total variance in longevity.

## 1. Introduction

The gamma-Gompertz (hereafter, G-G) model is one of a class of models that investigate the effects of hidden heterogeneity — heterogeneity that is either unobservable or unobserved — on mortality rates. It calculates various consequences of that heterogeneity for the dynamics of cohorts (e.g. Vaupel, Manton, and Stallard 1979; Vaupel and Yashin 1985; Yashin, Iachine, and Begun 2000; Vaupel 2010; Wienke 2010; Missov 2013). I refer to this heterogeneity as *frailty*, making no assumptions about its causes. The goal of this paper is to present a matrix formulation that permits easy computation of all the properties of the G-G and other frailty models.

Frailty models can be characterized by their components:

1. the baseline mortality rate,
2. the effects of frailty on the baseline mortality rate,
3. the dynamics of individual frailty over time, and
4. the initial distribution of frailty.

The baseline mortality rate in the G-G model is the Gompertz model, in which mortality increases exponentially with age  $t$ ,

$$\mu(t) = ae^{bt}. \quad (1)$$

Frailty affects mortality as a proportional hazard. If  $Z$  (a non-negative random variable) denotes frailty, and  $z$  its realization, then the mortality of an individual with frailty  $z$  at age  $t$  is

$$\mu(z, t) = z\mu_0(t) \quad (2)$$

where  $\mu_0(t)$  is the baseline mortality schedule. The frailty  $z$  is a fixed property of the individual, and the initial distribution of frailty is a gamma distribution.

Many other frailty models can be created by changing one or more of these four components. As we will see, the matrix formulation applies directly to all of them. Other pleasing properties of the matrix formulation will be discussed in Section 7.

The dynamics at any age of a heterogeneous cohort depend on the distribution of frailty within the cohort. The dynamics differ from the dynamics of any frailty class because the distribution of frailty changes as the cohort ages (Vaupel and Yashin 1985).

The more frail individuals tend to die sooner, and the cohort is progressively dominated by individuals of lower frailty.

To summarize some well known facts about the G-G model (Wienke 2010; Vaupel and Missov forthcoming), because frailty is unobserved, observations on the cohort reveal not the individual mortality schedules, but rather the marginal mortality rate

$$\mu^*(t) = \int \pi(z, t)\mu(z, t)dz \tag{3}$$

where  $\pi(z, t)$  is the distribution of frailty at age  $t$ . The survivorship function of an individual of frailty  $z$  is

$$S(z, t) = \exp\left(-\int_0^t \mu(z, x)dx\right) \tag{4}$$

and the marginal survivorship function of the cohort is

$$S^*(t) = \int \pi(z, 0)S(z, t)dz. \tag{5}$$

The distribution of frailty at age  $t$  is obtained by multiplying the initial probability density for frailty  $z$  by the probability that an individual with frailty  $z$  survives to age  $t$ , and then scaling the result by dividing by the integral:

$$\pi(z, t) = \frac{\pi(z, 0)S(z, t)}{\int \pi(z, 0)S(z, t)dz}. \tag{6}$$

The G-G model assumes that frailty is a fixed individual property and that the cohort begins life with frailty distributed according to a gamma distribution,  $z \sim \text{gamma}(k, \lambda)$  with shape parameter  $k$  and scale parameter<sup>2</sup>  $\lambda$ . The mean and variance of  $z$  are  $E(z) = k/\lambda$  and  $V(z) = k/\lambda^2$ . Thus, when  $E(z) = 1$ , the distribution is given by  $\text{gamma}(1/\sigma^2, 1/\sigma^2)$ .

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<sup>2</sup>The probability density function is

$$\text{gamma}(k, \lambda) = \frac{1}{\Gamma(k)\lambda^k} z^{k-1}e^{-z/\lambda}. \tag{7}$$

Note that two parameterizations of the gamma distribution are widely used. Equation (7) is common in demography. MATLAB uses the parameterization

$$\text{gamma}(k, \theta)$$

where  $k$  is a shape parameter and  $\theta$  is a rate parameter. In this parameterization,  $E(z) = k\theta$  and  $V(z) = k\theta^2$ . Thus in MATLAB the distribution with mean equal to 1 is  $\text{gamma}(1/\sigma^2, \sigma^2)$ .

The marginal mortality rate (3) for the G-G model is a sigmoid function of age,

$$\mu^*(t) = \frac{ae^{bt}}{1 + \frac{a\sigma^2}{b}(e^{bt} - 1)} \quad (8)$$

(Yashin, Vaupel, and Iachine 1994), converging to an asymptote at  $b/\sigma^2$  as  $t$  gets large. Thus, the G-G model is an attractive explanation for the widely observed pattern of decelerating increase in mortality with age, in both humans and other species (e.g., Vaupel et al. 1998; Horiuchi 2003; Vaupel 2010; Missov and Finkelstein 2011).

Although it is simple to state, and widely used, deriving the consequences of the G-G model is mathematically challenging. Only recently has Missov (2013) obtained an expression for life expectancy at birth, by integrating the survivorship function (5). The result, a function of the Gompertz parameters  $a$  and  $b$  and the gamma distribution parameters  $k$  and  $\lambda$ , is

$$e_0(a, b, k, \lambda) = \frac{1}{bk} {}_2F_1\left(k, 1; k + 1; 1 - \frac{1}{b\lambda}\right) \quad (9)$$

where the function  ${}_2F_1(\cdot)$  is the Gaussian hypergeometric function.<sup>3</sup>

Life expectancy, however, is only one of many demographic properties implied by a mortality model. My goal here is to present a matrix formulation that provides not only the mean, but all the moments of longevity, various measures of life disparity, and the full dynamics of the joint distribution of age and frailty. It will become apparent from the construction of this model that it applies equally to a much broader class of frailty models, and I will present examples.

The organization of this paper is as follows. Section 2 derives the matrix model, using methods developed for populations in which individuals are jointly classified by age and stage. Section 3 derives the fundamental matrix, the moments of longevity, the distribution of age at death, and other indices from the matrix model including (Section 3.4) the dynamics of the frailty distribution over the life of the cohort. Section 4 analyzes an example, using parameter estimates for Swedish females taken from Missov (2013). Section 5 discusses some interesting generalizations, with examples. Section 6 uses the model to partition variance in longevity into components due to individual stochasticity and heterogeneous frailty. Section 7 concludes by presenting a protocol for computation and discusses further extensions.

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<sup>3</sup>For more on the Gaussian hypergeometric distribution, see Abramowitz and Stegun (1965, 15.1.1) or the online version in the NIST Digital Library of Mathematical Functions, <http://dlmf.nist.gov/15>.

## 2. The matrix formulation of the gamma-Gompertz model

**Notation.** In what follows, matrices are denoted by upper-case boldface letters, and vectors by lower-case boldface letters. Where necessary, the dimensions of matrices and vectors are denoted by subscripts; thus  $\mathbf{I}_n$  is an identity matrix of order  $n$  and  $\mathbf{1}_n$  is a  $n \times 1$  vector of ones. The vector  $\mathbf{e}_i$  is the  $i$ th unit vector. The diagonal matrix with  $\mathbf{x}$  on the diagonal and zeros elsewhere is denoted  $\mathcal{D}(\mathbf{x})$ . The symbol  $\circ$  denotes the Hadamard, or element-by-element product. The symbol  $\|\mathbf{x}\|$  denotes the 1-norm of the vector  $\mathbf{x}$ . The number of age classes is  $\omega$  and the number of frailty groups is  $g$ .

The matrix G-G model is an age-stage classified model in which stages correspond to frailty classes. Age-stage classified matrix models have been analyzed in other contexts by Caswell (2009, 2011, 2012) and Caswell and Salguero-Gómez (2013). The model is created using the vec-permutation formalism (Hunter and Caswell 2005) and analyzed using absorbing Markov chain theory (Caswell 2006, 2009, 2013)

To construct the matrix G-G model, let us introduce some notation. Age is described by a set of discrete age classes  $1, \dots, \omega$ . The baseline mortality rates are contained in a vector  $\boldsymbol{\mu}_0$  of dimension  $\omega \times 1$ . For the Gompertz mortality model, the baseline mortality rate vector is

$$\boldsymbol{\mu}_0 = a \begin{pmatrix} e^{0b} \\ e^{1b} \\ e^{2b} \\ \vdots \\ e^{(\omega-1)b} \end{pmatrix} \quad (10)$$

Frailty is described by a set of  $g$  discrete frailty classes; the frailty values of these classes are given by a  $g \times 1$  vector  $\mathbf{z}$ . To create the frailty classes, first specify a maximum frailty, where the cumulative gamma distribution reaches some high value; say, 0.9999. Since very high values of frailty are rapidly eliminated, this end of the distribution is, in practice, not very important. Then specify a minimum value of frailty as some very small number; for the applications reported here, a value on the order of  $10^{-7}$  was adequate. Since individuals with very low frailty will persist for a long time in the population, it is important that  $z_{\min}$  be small.

Experience suggests that logarithmically spaced values between  $z_{\min}$  and  $z_{\max}$  work well, because they provide more detail in the frailty distribution at the low end, precisely where individuals will persist the longest. An alternative is to evenly divide the inverse of the cumulative distribution function, so that values are most closely spaced where the concentration of initial probability is greatest. Given the vector  $\mathbf{z}$  of frailty classes, the vector of mortality rates by age, for frailty class  $i$ , is

$$\boldsymbol{\mu}_i = z_i \boldsymbol{\mu}_0 \quad (11)$$

The distribution of individuals among frailty classes at age  $t$  is given by the vector  $\boldsymbol{\pi}(t)$ ; the initial frailty distribution of the cohort is given by  $\boldsymbol{\pi}(0)$ . In the matrix G-G model,  $\boldsymbol{\pi}(0)$  is a discrete gamma distribution with mean of 1 and a specified variance.

## 2.1 Constructing transition matrices and the vec-permutation model

To construct the age-stage model, define a survival matrix for each frailty class, and a matrix of frailty transitions for each age class, as follows.

1. Create a survival matrix  $\mathbf{U}_i$  for each frailty class  $i$ . It contains survival probabilities on the first subdiagonal and zeros elsewhere, and is of dimension  $\omega \times \omega$ .

$$\mathbf{U}_i = \begin{pmatrix} 0 & 0 & \cdots & 0 \\ e^{-\mu(z_i,0)} & 0 & \cdots & 0 \\ \vdots & \ddots & & \vdots \\ 0 & \cdots & e^{-\mu(z_i,\omega-1)} & 0 \end{pmatrix} \quad (12)$$

2. Create a matrix  $\mathbf{D}_j$  describing transitions among frailty classes for each age class  $j$ . In the gamma-Gompertz model, frailty does not change, so  $\mathbf{D}_j = \mathbf{I}_g$  for all  $j$ .
3. Create block-diagonal matrices  $\mathbb{U}$  and  $\mathbb{D}$  by placing the  $\mathbf{U}_i$  (respectively,  $\mathbf{D}_j$ ) on the diagonal with zeros elsewhere. Both matrices are of dimension  $\omega g \times \omega g$ .

$$\mathbb{U} = \begin{pmatrix} \mathbf{U}_1 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \mathbf{U}_g \end{pmatrix} \quad \mathbb{D} = \begin{pmatrix} \mathbf{D}_1 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \mathbf{D}_g \end{pmatrix} \quad (13)$$

In the gamma-Gompertz model,  $\mathbb{D} = \mathbf{I}_{\omega g}$ .

The state of the cohort at age  $t$  is given by a vector  $\tilde{\mathbf{n}}(t)$ , which is derived from the array

$$\mathcal{N}(t) = \begin{pmatrix} n_{11} & \cdots & n_{1g} \\ \vdots & & \vdots \\ n_{\omega 1} & \cdots & n_{\omega g} \end{pmatrix} \quad (14)$$

that describes the abundance of all age-frailty categories. The population vector is

$$\tilde{\mathbf{n}} = \text{vec } \mathcal{N}^T; \quad (15)$$



that is,

$$\tilde{\mathbf{n}} = \begin{pmatrix} n_{11} \\ \vdots \\ n_{1g} \\ \vdots \\ n_{\omega 1} \\ \vdots \\ n_{\omega g} \end{pmatrix} \tag{16}$$

The  $i$ th block of entries in  $\tilde{\mathbf{n}}$  contains a sub-vector giving the abundance of the frailty classes within age class  $i$ .

The joint age-frailty composition of the cohort is projected as

$$\tilde{\mathbf{n}}(t + 1) = \tilde{\mathbf{U}}\tilde{\mathbf{n}}(t) \tag{17}$$

where the projection matrix is

$$\tilde{\mathbf{U}} = \mathbb{D}\mathbf{K}\mathbf{U}\mathbf{K}^T \tag{18}$$

In equation (18),  $\mathbf{K}$  (to be more precise,  $\mathbf{K}_{\omega,g}$ ) is the vec-permutation matrix, or commutation matrix (Magnus and Neudecker 1979; Henderson and Searle 1981). See (Hunter and Caswell 2005; Caswell 2012) for more about models of the form (18).

Because frailty is fixed in the gamma-Gompertz model,  $\tilde{\mathbf{U}}$  reduces to  $\tilde{\mathbf{U}} = \mathbf{K}\mathbf{U}\mathbf{K}^T$ . However, it is good practice to retain the matrix  $\mathbb{D}$  as a reminder of its potential use when frailty is dynamic rather than static.

## 2.2 The absorbing Markov chain

The matrix  $\tilde{\mathbf{U}}$  in (17) is the transient matrix of an absorbing Markov chain (Feichtinger 1971; Caswell 2001, 2006, 2009; van Raalte and Caswell 2013). The transition matrix of this chain is

$$\mathbf{P} = \left( \begin{array}{c|c} \tilde{\mathbf{U}} & \mathbf{0} \\ \hline \tilde{\mathbf{M}} & \mathbf{I} \end{array} \right) \tag{19}$$

where  $\tilde{\mathbf{M}}$  is a mortality matrix describing the transitions from transient (i.e., living) states to absorbing (i.e., dead) states. The fundamental matrix of the chain is

$$\tilde{\mathbf{N}} = \left( \mathbf{I}_{\omega g} - \tilde{\mathbf{U}} \right)^{-1} \tag{20}$$

with dimension  $\omega g \times \omega g$ . The  $(i, j)$  entry of  $\tilde{\mathbf{N}}$  is the expected number of visits to state  $i$ , conditional on starting in a state  $j$ , where states describe the full joint age $\times$ frailty

distribution. From the fundamental matrix we can compute all the statistics of the cohort survival properties. We turn now to these analyses.

### 3. Analysis of the model

The fundamental matrix  $\tilde{\mathbf{N}}$  of the joint chain contains all the information necessary to derive the marginal survival function  $\mathbf{s}^*$  (a vector of dimension  $\omega \times 1$ ) and the corresponding marginal fundamental matrix  $\mathbf{N}^*$  (of dimension  $\omega \times \omega$ ).

#### 3.1 The marginal survival and mortality functions

To obtain the marginal dynamics of the cohort age distribution, first average the columns of  $\tilde{\mathbf{N}}$  over the initial frailty distribution. If, as in the gamma-Gompertz case, the initial frailty distribution has positive support only in the first age class, the result is

$$\tilde{\mathbf{s}} = \tilde{\mathbf{N}} [\mathbf{e}_1 \otimes \boldsymbol{\pi}(0)].$$

This column vector gives the expectation, over  $\boldsymbol{\pi}(0)$ , of the number of visits to each age-frailty state by an individual in the first age class.

Next, sum the rows of the vector  $\tilde{\mathbf{s}}$  within each frailty class to obtain the marginal mean number of visits to each age class for an individual in the initial cohort. Because the underlying demographic model is age-classified, a transient state (i.e., an age class) *can be visited at most once; hence the mean number of visits to age class  $i$  is the probability of visiting age class  $i$ , which is the survivorship to age class  $i$ .* Thus the marginal survivorship function  $\mathbf{s}^*$  is

$$\mathbf{s}^* = (\mathbf{I}_\omega \otimes \mathbf{1}_g^\top) \tilde{\mathbf{s}} \tag{21}$$

$$= (\mathbf{I}_\omega \otimes \mathbf{1}_g^\top) \tilde{\mathbf{N}} [\mathbf{e}_1 \otimes \boldsymbol{\pi}(0)] \tag{22}$$

The marginal mortality rate vector  $\boldsymbol{\mu}^*$  is given by the difference in the log of subsequent terms of  $\mathbf{s}^*$ ,

$$\mu_i^* = -\log \left( \frac{s_{i+1}^*}{s_i^*} \right) \tag{23}$$

### 3.2 The marginal fundamental matrix

The fundamental matrix  $\tilde{\mathbf{N}}$  gives the number of visits to each age-frailty class. We need the marginal fundamental matrix  $\mathbf{N}^*$ , which gives the expected number of visits to each age class. To obtain  $\mathbf{N}^*$ , note that the vector  $\mathbf{s}^*$  is the first column of  $\mathbf{N}^*$ , and that the full matrix is

$$\mathbf{N}^* = \begin{pmatrix} s_1^* & 0 & 0 & \cdots & 0 \\ s_2^* & \frac{s_2^*}{s_2^*} & 0 & \cdots & 0 \\ s_3^* & \frac{s_3^*}{s_2^*} & \frac{s_3^*}{s_3^*} & \cdots & 0 \\ s_4^* & \frac{s_4^*}{s_2^*} & \frac{s_4^*}{s_3^*} & \cdots & 0 \\ \vdots & \vdots & \vdots & \cdots & 1 \end{pmatrix} \quad (24)$$

(Keyfitz and Caswell 2005, Eq. 10.5.4)<sup>4</sup>, which can be written

$$\mathbf{N}^* = \left[ \mathbf{s}^* \mathbf{1}_s^T \mathcal{D} (\mathbf{s}^*)^{-1} \right] \circ \mathbf{Y} \quad (25)$$

where  $\mathbf{Y}$  is a lower triangular matrix with ones on and below the diagonal and zeros elsewhere.

### 3.3 Longevity, variation, and disparity

Many statistics of longevity can be obtained from the marginal fundamental matrix  $\mathbf{N}^*$  (e.g., Caswell 2001, 2006, 2009, 2013; van Raalte and Caswell 2013; Engelman, Caswell, and Agree 2014). These statistics describe the marginal results for the cohort starting with the initial frailty distribution  $\boldsymbol{\pi}(0)$ , including:

1. The moments of the number of visits to each of the transient states. Because transient states (age classes) in an age-classified model can be visited no more than once, these moments may be less interesting in the G-G model than in models with more complicated stage structure. Letting  $\mathbf{N}_i^*$  be the matrix of the  $i$ th moments of the number of visits,  $\mathbf{N}_1^*$  is given by (24), and the higher moments include

$$\mathbf{N}_2^* = (2\mathbf{N}_{dg}^* - \mathbf{I}) \mathbf{N}_1^* \quad (26)$$

$$\mathbf{N}_3^* = \left[ 6 (\mathbf{N}_{dg}^*)^2 - 6\mathbf{N}_{dg}^* + \mathbf{I} \right] \mathbf{N}_1^* \quad (27)$$

$$\mathbf{N}_4^* = \left[ 24 (\mathbf{N}_{dg}^*)^3 - 36 (\mathbf{N}_{dg}^*)^2 + 14\mathbf{N}_{dg}^* - \mathbf{I} \right] \mathbf{N}_1^*. \quad (28)$$

<sup>4</sup>It seems appropriate to note that Keyfitz presented this result in the first edition of the book in 1977.

where  $\mathbf{N}_{\text{dg}}^*$  is a diagonal matrix with the diagonal elements of  $\mathbf{N}_1^*$  on the diagonal and zeros elsewhere (e.g., Caswell 2006, 2009, 2013); for a mathematical source see Iosifescu (1980).

2. The moments and statistics of longevity. Longevity is equivalent to the time until absorption in one of the absorbing states. The vector  $\boldsymbol{\eta}_1$  of mean longevity (i.e., life expectancies) of each age class is given by the column sums of  $\mathbf{N}^*$ , and subsequent moments are as follows, where  $\boldsymbol{\eta}_i$  is the vector of  $i$ th moments of longevity:

$$\boldsymbol{\eta}_1^\top = \mathbf{1}_\omega^\top \mathbf{N}^* \quad (29)$$

$$\boldsymbol{\eta}_2^\top = \boldsymbol{\eta}_1^\top (2\mathbf{N}^* - \mathbf{I}) \quad (30)$$

$$\boldsymbol{\eta}_3^\top = \boldsymbol{\eta}_1^\top \left[ 6(\mathbf{N}^*)^2 - 6\mathbf{N}^* + \mathbf{I} \right] \quad (31)$$

$$\boldsymbol{\eta}_4^\top = \boldsymbol{\eta}_1^\top \left[ 24(\mathbf{N}^*)^3 - 36(\mathbf{N}^*)^2 + 14\mathbf{N}^* - \mathbf{I} \right]. \quad (32)$$

(Caswell 2006, 2009, 2013). These moments provide a complete set of longevity statistics, including the variance, standard deviation, coefficient of variation, and skewness of longevity:

$$V(\boldsymbol{\eta}) = \boldsymbol{\eta}_2 - \boldsymbol{\eta}_1 \circ \boldsymbol{\eta}_1 \quad (33)$$

$$SD(\boldsymbol{\eta}) = \sqrt{V(\boldsymbol{\eta})} \quad (34)$$

$$CV(\boldsymbol{\eta}) = \mathcal{D}(\boldsymbol{\eta}_1)^{-1} SD(\boldsymbol{\eta}) \quad (35)$$

$$Sk(\boldsymbol{\eta}) = \mathcal{D}(V(\boldsymbol{\eta}))^{-3/2} [\boldsymbol{\eta}_3 - 3\boldsymbol{\eta}_1 \circ \boldsymbol{\eta}_2 + 2\boldsymbol{\eta}_1 \circ \boldsymbol{\eta}_1 \circ \boldsymbol{\eta}_1] \quad (36)$$

3. The joint and marginal distributions of age and stage at death. Because the matrix G-G model is an age-stage structured model, the joint and marginal distributions of age and frailty class at death are obtained using the mortality matrix  $\tilde{\mathbf{M}}$  in (19). If  $\tilde{\mathbf{M}}$  is created by defining absorbing states corresponding to the age and frailty class at death, then  $\tilde{\mathbf{M}} = \mathcal{D} \left( \mathbf{1}_{\omega g}^\top - \mathbf{1}_{\omega g}^\top \tilde{\mathbf{U}} \right)$ . Then column  $j$  of the matrix

$$\tilde{\mathbf{B}} = \tilde{\mathbf{M}}\tilde{\mathbf{N}} \quad (37)$$

gives the joint distribution of age and frailty at death, conditional on reaching the age-frailty combination in column  $j$  (Caswell 2012).

Averaging the first  $g$  columns of  $\tilde{\mathbf{B}}$  over the initial frailty distribution gives a vector  $\tilde{\boldsymbol{\phi}}$  containing the distribution of age and frailty at death of a cohort with initial frailty distribution  $\boldsymbol{\pi}(0)$ :

$$\tilde{\boldsymbol{\phi}} = \tilde{\mathbf{B}} \left[ \mathbf{e}_1 \otimes \boldsymbol{\pi}(0) \right] \quad (38)$$

The marginal distributions of age and of frailty at death are obtained by summing over the appropriate rows of  $\tilde{\phi}$ ,

$$\phi_{\text{age}}^* = (\mathbf{I}_\omega \otimes \mathbf{1}_g^\top) \tilde{\phi} \tag{39}$$

$$\phi_{\text{frailty}}^* = (\mathbf{1}_\omega^\top \otimes \mathbf{I}_g) \tilde{\phi} \tag{40}$$

### 3.4 Projecting the distributions of age, frailty, and mortality

The population vector giving the abundance by age and frailty class is projected by the matrix  $\tilde{\mathbf{U}}$  in (18):

$$\tilde{\mathbf{n}}(t + 1) = \tilde{\mathbf{U}}\tilde{\mathbf{n}}(t) \tag{41}$$

If, as in the G-G model, the initial cohort has support only in the first age class, with distribution  $\pi(0)$ , then  $\tilde{\mathbf{n}}(0) = (\mathbf{e}_1^\top \otimes \mathbf{I}_g) \pi(0)$ .

Let  $\tilde{\mathbf{p}}(t)$  be the vector giving the *proportional* age-frailty distribution at time  $t$ . It is given by

$$\tilde{\mathbf{p}}(t + 1) = \frac{\tilde{\mathbf{U}}\tilde{\mathbf{p}}(t)}{\|\tilde{\mathbf{U}}\tilde{\mathbf{p}}(t)\|}, \tag{42}$$

with  $\tilde{\mathbf{p}}(0) = \tilde{\mathbf{n}}(0)/\|\tilde{\mathbf{n}}(0)\|$ .

The marginal age vector and the marginal proportional age distribution vector are obtained by summing over frailty classes within age classes, as was done in (39) for the death distribution. They are given by

$$\mathbf{n}^*(t) = (\mathbf{I}_\omega \otimes \mathbf{1}_g^\top) \tilde{\mathbf{n}}(t) \tag{43}$$

$$\mathbf{p}^*(t) = (\mathbf{I}_\omega \otimes \mathbf{1}_g^\top) \tilde{\mathbf{p}}(t) \tag{44}$$

The marginal frailty vector and the marginal proportional frailty distribution are obtained by summing  $\tilde{\mathbf{n}}$  and  $\tilde{\mathbf{p}}$  over age within each frailty class, as was done in (40) for the death distribution:

$$\mathbf{m}^*(t) = (\mathbf{1}_\omega^\top \otimes \mathbf{I}_g) \tilde{\mathbf{n}}(t) \tag{45}$$

$$\pi(t) = (\mathbf{1}_\omega^\top \otimes \mathbf{I}_g) \tilde{\mathbf{p}}(t) \tag{46}$$

The marginal distribution vector  $\pi(t)$  corresponds to the frailty distribution as a function of age given in (6). From  $\pi(t)$ , the statistics, particularly the mean and variance, of frailty and of any quantity that is a function of frailty, can be calculated, to quantify the effects of selection as a function of age. For example, the mean frailty at age  $t$  is given by  $\mathbf{z}^\top \pi(t)$ , and the second moment is given by  $(\mathbf{z} \circ \mathbf{z})^\top \pi(t)$ , where  $\mathbf{z}$  is the vector of frailty values.

Cha and Finkelstein (2013) have recently discussed the interesting problem of the moments and statistics (variance, CV) of age-specific mortality in an aging cohort. The

marginal mortality rate  $\mu^*$  in (23) is the first moment; we can calculate all the moments, and hence such statistics as the variance, CV, skewness, etc. as follows.

First, use the frailty model to create hazard matrices  $\mathbf{H}_m$  containing the  $m$ th powers of the mortality rates,

$$\mathbf{H}_m = \begin{pmatrix} \mu_{11}^m & \cdots & \mu_{1g}^m \\ \vdots & & \vdots \\ \mu_{\omega 1}^m & \cdots & \mu_{\omega g}^m \end{pmatrix} \quad (\omega \times g) \quad (47)$$

The form of  $\mathbf{H}_m$  will depend on the chosen frailty model; in the special case of the G-G model,

$$\mathbf{H}_m = \underbrace{(\boldsymbol{\mu}_0 \mathbf{z}^\top) \circ \cdots \circ (\boldsymbol{\mu}_0 \mathbf{z}^\top)}_{m \text{ times}} \quad (48)$$

where  $\boldsymbol{\mu}_0$  is the baseline mortality vector and  $\mathbf{z}$  the vector of frailty values for the  $g$  frailty classes.

Then, create a matrix  $\mathbf{\Pi}$  containing, as columns, the frailty distributions obtained from (46),

$$\mathbf{\Pi} = \left[ \boldsymbol{\pi}(0) \cdots \boldsymbol{\pi}(\omega - 1) \right] \quad (g \times \omega) \quad (49)$$

The vector containing the  $m$ th moments of the marginal mortality is the diagonal of  $\mathbf{H}_m \mathbf{\Pi}$ ,

$$\boldsymbol{\mu}_m^* = \text{diagonal of } \mathbf{H}_m \mathbf{\Pi} \quad (50)$$

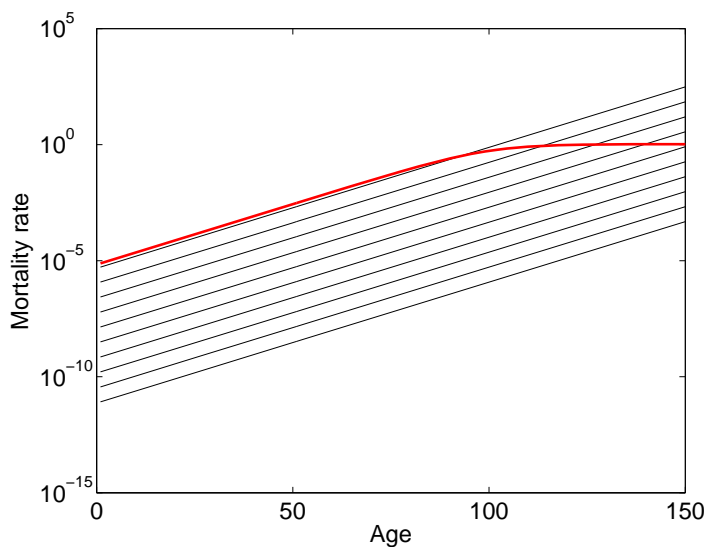
$$= \left[ \mathbf{I} \circ (\mathbf{H}_m \mathbf{\Pi}) \right] \mathbf{1} \quad (51)$$

#### 4. An example: Swedish females

An example of the calculations is provided by using the G-G parameters  $a$ ,  $b$ , and  $k$  estimated by Missov (2013) from period mortality data on Swedish females from 1891 to 2010. I used these parameters, for the arbitrarily selected year 1950, to create the matrices  $\mathbf{U}$  and  $\mathbf{D}$  ( $\hat{a} = 0.0340$ ,  $\hat{b} = 0.1200$ ,  $\hat{k} = 8.2300$ ). Calculations were carried out with  $\omega = 150$  age classes and  $g = 100$  logarithmically spaced frailty classes. A MATLAB program to carry out these calculations is available in the Supplementary Material to this paper.

The marginal mortality rate  $\mu^*(t)$  is shown in Figure 1. It increases nearly exponentially until about age 75, at which point the effects of selection on mortality become apparent and the increase decelerates; mortality converges to an asymptote at about age 100.

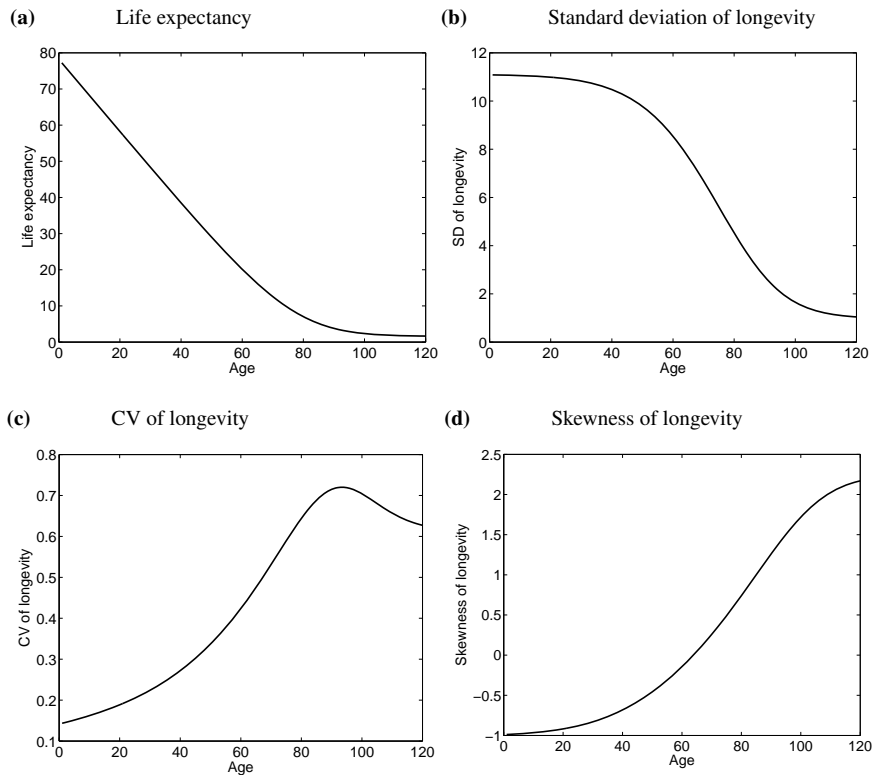
**Figure 1:** Gamma-Gompertz mortality rate  $\mu(t)$  as a function of age,  $t$ . Straight black lines show the age-specific mortality rates for a few of the frailty classes in the model. The curved red line shows the marginal hazard  $\mu^*(t)$ . Parameters for Swedish females as reported in Missov (2013) for the year 1950



#### 4.1 Statistics of longevity

The mean, standard deviation, coefficient of variation, and skewness of longevity, computed from  $\mathbf{N}^*$  using equations (33)–(36), are shown in Figure 2. The remaining life expectancy and its standard deviation both decrease with age, but the relative variation, as measured by the coefficient of variation, increases up to about age 90 and then decreases slightly. The distribution of longevity goes from negative to positive skewness with increasing age.

**Figure 2:** Statistics of longevity for the gamma-Gompertz model, as a function of age, using parameters reported in Missov (2013) for the year 1950. (a) Life expectancy. (b) Standard deviation of longevity. (c) Coefficient of variation of longevity. (d) Skewness of longevity. This and all subsequent figures, unless otherwise noted, computed with  $g = 100$  and  $\omega = 150$



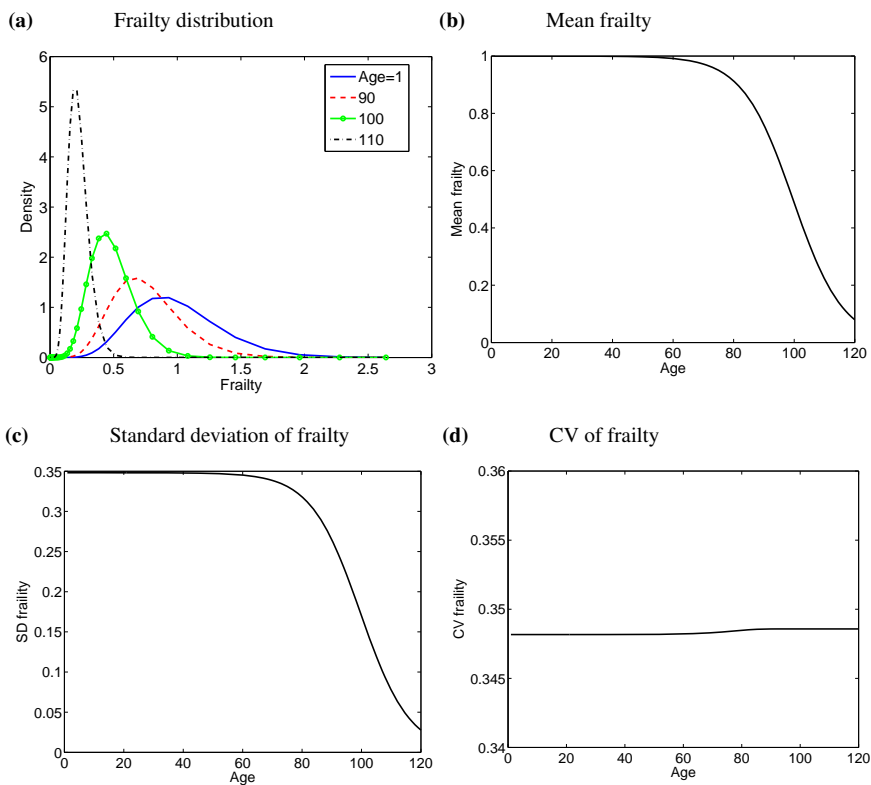
## 4.2 Dynamics of frailty

The selection against more frail individuals is seen in the dynamics of the distribution of frailty  $\pi(t)$  (Figure 3). Both the mean and the standard deviation of frailty decrease with age, with the decline becoming visually evident after about age 50. The CV of frailty is



known to remain constant with age in the G-G model (Wienke 2010, p. 75). In the matrix calculation, it is very nearly constant, increasing slightly at about age 75.

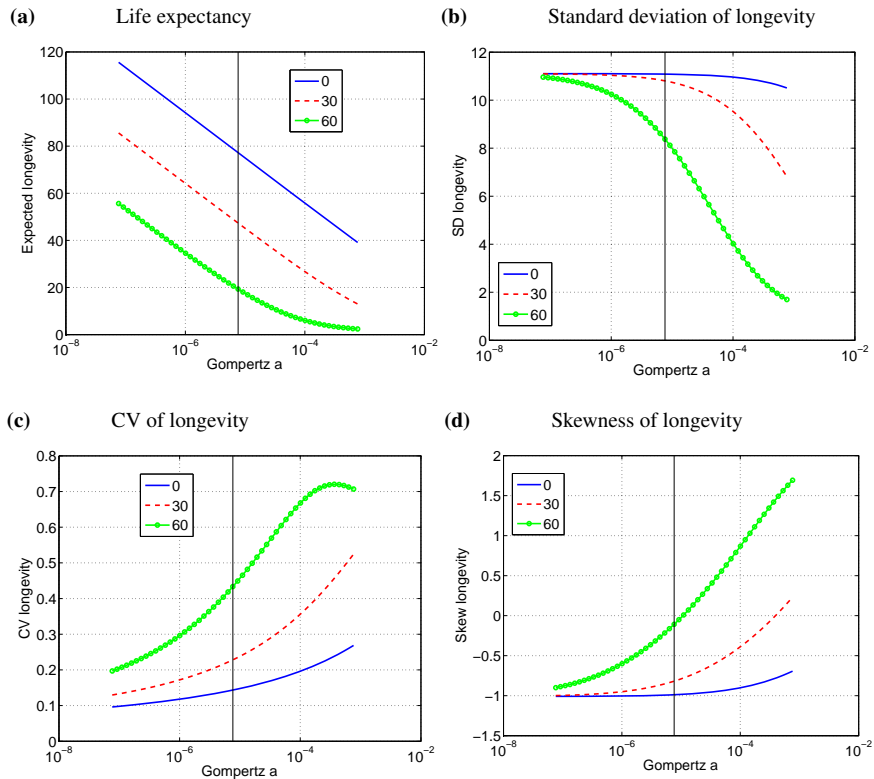
**Figure 3: Changes due to selection in the distribution of frailty, and in the mean, CV, and skewness of that distribution, over the life of a cohort. Parameters for Swedish females, as reported in Missov (2013) for the year 1950**



### 4.3 Effects of the G-G parameters

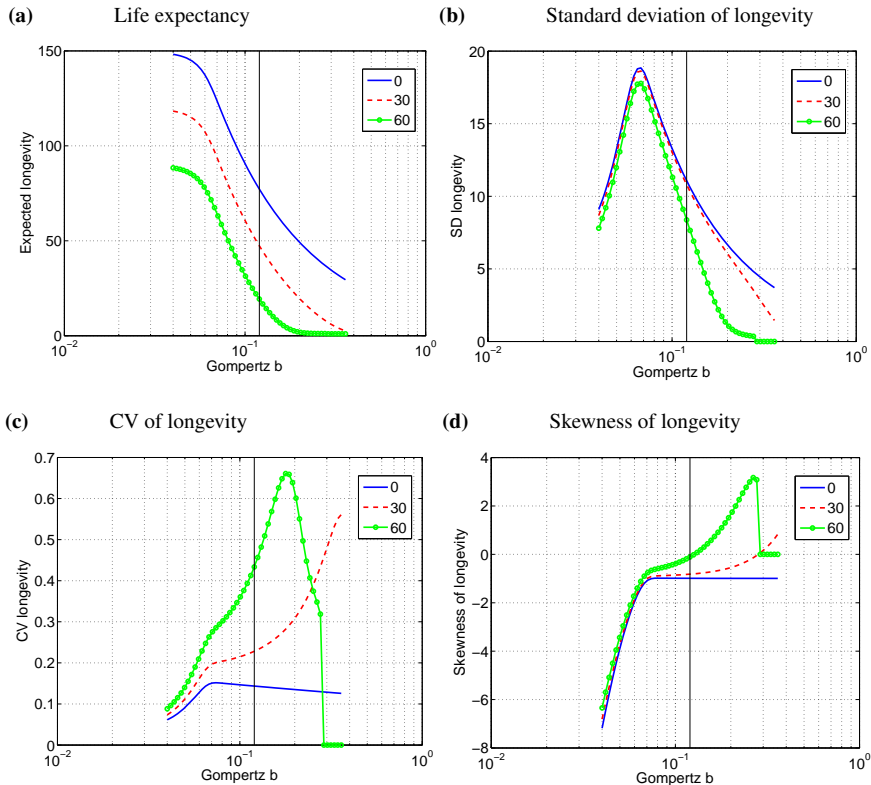
Figures 4–6 show the effects of varying  $a$ ,  $b$ , and the variance,  $1/k$ , of the initial frailty distribution over several orders of magnitude centered on the values for Swedish females in 1950.

**Figure 4:** Statistics of longevity for the gamma-Gompertz model, using parameters reported in Missov (2013) for Swedish females in 1950, as a function of the Gompertz parameter  $a$



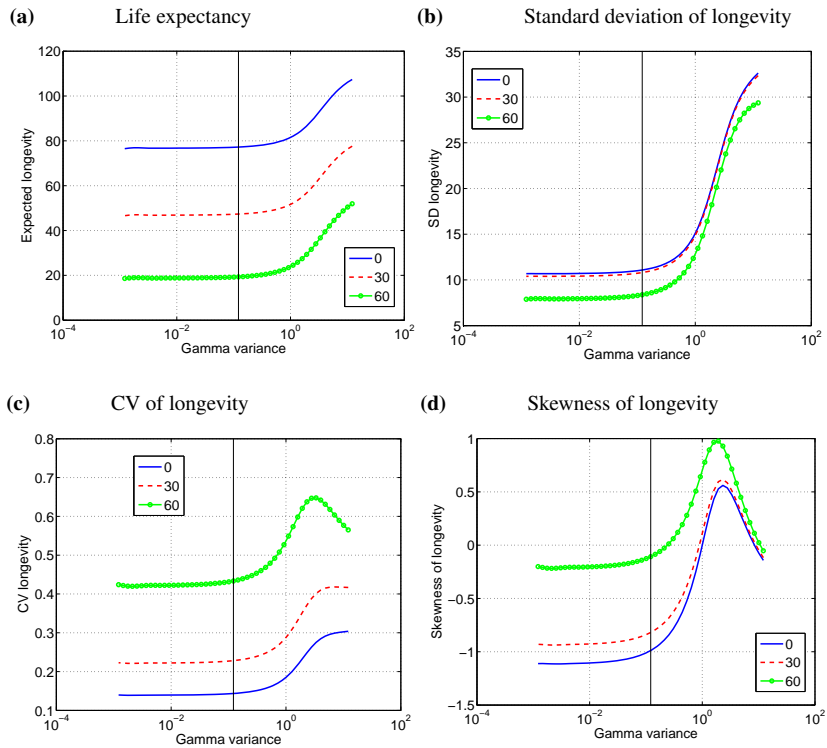
Not surprisingly, life expectancy declines with increases in  $a$ ; roughly speaking, a 10-fold increase in  $a$  reduces life expectancy at birth by about 10 years (Figure 4). The standard deviation of longevity also declines with increasing  $a$ , more dramatically at older ages. Together, these changes lead to a coefficient of variation that increases with  $a$ . The skewness of the distribution of longevity also increases with  $a$ . When measured at birth, it is negative, but by age 60 skewness changes from negative to positive as  $a$  increases.

**Figure 5: Statistics of longevity for the gamma-Gompertz model, using parameters reported in Missov (2013) for Swedish females in 1950, as a function of the Gompertz parameter  $b$ , for ages 0, 30, and 60 years**



Increases in  $b$  also reduce life expectancy (Figure 5). The standard deviation of longevity peaks at an intermediate value of  $b$ , and declines sharply at higher or lower values. The coefficient of variation of longevity increases with  $b$  until at older ages it eventually declines. At very high values of  $b$  the expectation and standard deviation of longevity at older ages become zero and the coefficient of variation is undefined.

**Figure 6:** Statistics of longevity at ages 0, 30, and 60 years for the gamma-Gompertz model as a function of the variance in the gamma distribution of frailty (equal to  $1/k$ ). Parameters as reported in Missov (2013) for Swedish females in 1950. The vertical lines indicate the observed value of variance



The effects of changes in the variance  $\sigma^2 = 1/k$  of the initial frailty distribution  $\pi(0)$  are shown in Figure 6. Expected longevity is relatively insensitive to  $\sigma^2$  until it becomes much higher than that observed for Swedish females, at which point the mean, variance, and coefficient of variation of longevity all begin to increase with  $\sigma^2$ . The skewness of longevity increases to a peak (at values much higher than those observed), and then declines again at extremely high values of  $\sigma^2$ .

#### 4.4 Numerical reliability

Based on his results using the Gaussian hypergeometric function (9), Missov (2013) reports a life expectancy of 77.29 years for Swedish females in 1950. Evaluating his formula with the Gaussian hypergeometric function as implemented in MATLAB or in Wolfram Alpha gives a result of 76.22 years. The matrix calculation yields 77.23 years or, when adjusted by 0.5 years to correspond to a trapezoidal integration of the survival function, 76.73 years. The differences among the various implementations of the calculation are small (Table 1).

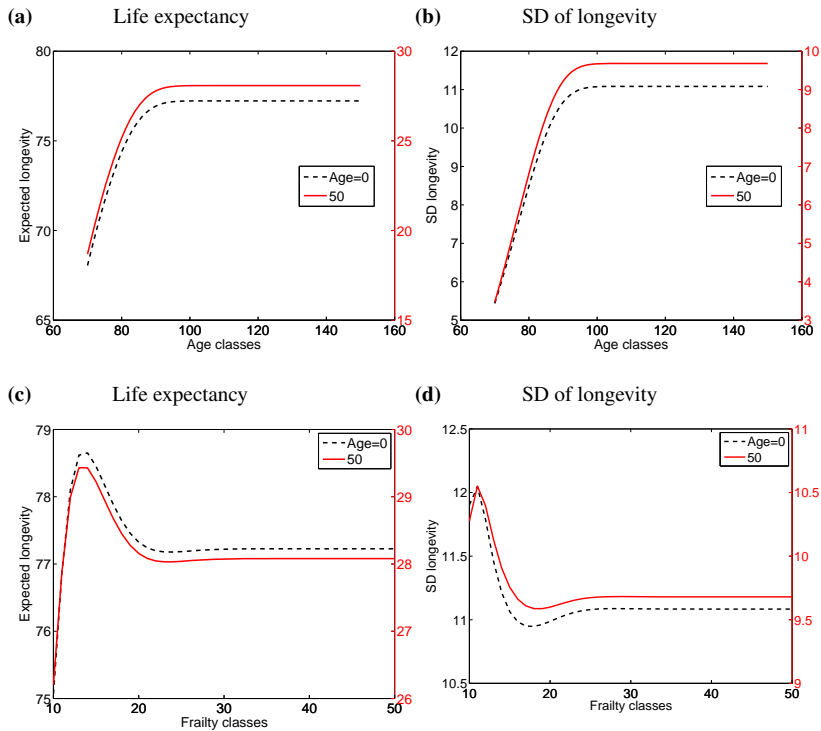
**Table 1:** Comparison of life expectancy results from Missov (2013), from this paper, and from Missov's theorem implemented in MATLAB and calculated using Wolfram Alpha. The adjusted value from this paper has had 0.5 years subtracted to make the result directly comparable to a trapezoidal computation of the integral of  $S^*(t)$ . For the matrix calculations,  $\omega = 150$  and  $g = 100$

Source	Expected longevity
Missov (2013)	77.29
Missov via Matlab	76.22
Missov via Wolfram	76.22
Matrix method	77.23
Matrix method (adjusted)	76.73

Because the matrix calculation is a discrete model, the results are influenced by the number of frailty classes  $g$  and the number of age classes  $\omega$  included in the model. The number of frailty classes determines how closely  $\pi(0)$  can approximate a gamma distribution, and the ability of  $\pi(t)$  to capture the distribution of frailty at late ages when selection has been operating for a long time. The number of age classes determines the extent to which the longevity statistics are influenced by the death of all remaining individuals at age  $\omega$ , which is not part of the G-G model, but must appear in any finite state approximation.

Figure 7 shows the effect of  $\omega$  and of  $g$  on the expectation and the standard deviation of longevity. For this example, choosing  $\omega > 100$  and  $g > 40$  provides reliable estimates of both the mean and the variation of longevity for this data set. Too small a value of  $\omega$  reduces both the mean and the standard deviation, because the survival curve is truncated at age  $\omega$ .

**Figure 7:** Effect of the number of age classes ( $\omega$ ) and the number of frailty classes ( $g$ ) on the estimates of life expectancy and the standard deviation of longevity, at ages 0 and 50. (a) and (b) show the effects of age classes, with  $g = 100$ . (c) and (d) show the effect of the number of frailty classes, with  $\omega = 150$



## 5. Generalizations and extensions of the model

The calculations of  $N^*$ ,  $s^*$ , and all the quantities derived from them depend only on the vec-permutation model structure (18). As a result, the analysis can be extended from the G-G model to other models for baseline mortality, other models for the effects of frailty, other frailty distributions, and other models for the dynamics of frailty.

### 5.1 Models for baseline mortality

The baseline mortality schedule  $\mu_0$  is used to create the frailty-specific mortality schedules  $\mu_i$  in equation (11). These schedules are used to create the matrices  $U_i$  that appear in (13). The Gompertz model is only one possible choice of a baseline schedule. Here, I examine some alternatives; the results, in the same format as Figures 2, 3, and 4–6 are collected in Appendix A.

The Gompertz-Makeham model

$$\mu(x) = ae^{bx} + c, \tag{52}$$

is obtained by adding an age-independent mortality hazard  $c$  to the Gompertz model. The gamma-Makeham model results from incorporating a proportional frailty effect

$$\mu_i = z_i (ae^{bx} + c) \tag{53}$$

where the  $z_i$  have a gamma distribution at age 0.

Modifying  $\mu_0$  in equation (11) transforms the G-G model to the gamma-Makeham model, with

$$\mu_0 = \begin{pmatrix} e^{0b} \\ \vdots \\ e^{(\omega-1)b} \end{pmatrix} + c \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix} \tag{54}$$

All analyses of the gamma-Makeham model then follow from  $\tilde{N}$ , computed from  $\mu(z)$ , just as with the G-G model.

Zarulli et al. (2013) estimated the parameters in the gamma-Makeham model as part of an analysis of the effects of education on the mortality of male and female cohorts in Turin, Italy, from 1971 to 2007. I analyzed their data for the baseline cohort of women, for which AIC calculations indicated that the gamma-Makeham model was much more well-supported by the data than the G-G model (Zarulli et al. 2013). Figure A.1 shows the expectation, standard deviation, CV, and skewness of remaining longevity as a function of age. The patterns are qualitatively similar to the gamma-Gompertz results for Swedish females (Figure 2). Selection reduces the mean and the standard deviation of frailty as age approaches 100, and the log of the marginal mortality rate increases with age in a sigmoid fashion (Figure A.2).

There is no reason to stop at the gamma-Makeham model. Gage (1998) and Engelman, Canudas-Romo, and Agree (2013) have added gamma-distributed frailty to the Siler model for mortality

$$\mu_0(x) = e^{a_1-b_1x} + e^{a_2+b_2x} + e^{a_3} \tag{55}$$

where  $\exp(a_1-b_1x)$  is a declining force of infant mortality,  $\exp(a_2+b_2x)$  is an increasing force of old age mortality, and  $\exp(a_3)$  is a constant force of background mortality. An

analysis of the gamma-Siler model requires only substituting this expression for  $\mu_0$  for the gamma-Gompertz mortality function in (10).

Engelman, Canudas-Romo, and Agree (2013) estimated parameters of a gamma-Siler model for cohorts of Swedish females born from 1875–1916. Here I show results for the 1900 cohort. The expectation, standard deviation, CV, and skewness of remaining longevity are shown as functions of age in Figure A.3. The patterns differ from those of the G-G and gamma-Makeham models mainly in that they show the effects of the infant mortality term. This effect is also apparent in the marginal mortality function (Figure A.4c) which declines sharply after birth, remains low, and then increases, eventually reaching a plateau at older ages.

These examples use parametric functions for the baseline mortality schedule, but they can easily be extended to semiparametric or nonparametric estimates. The estimated mortality function simply needs to be incorporated into the matrices  $\mathbf{U}_i$ .

## 5.2 Models for the effects of frailty

In the G-G model, frailty affects mortality as a proportional hazard. Other models for the effects of frailty can be incorporated into the construction of the matrices  $\mathbf{U}_i$ , by replacing the proportional hazard formulation in (11) with an expression appropriate to the frailty effects.

Vaupel and Yashin (2006), for example, briefly considered a model in which frailty acted to accelerate aging, with

$$\mu(z, x) = \mu_0(zx). \quad (56)$$

They pointed out that, if the baseline mortality schedule is Gompertz, then small changes in  $z$  can have large effects on the mortality, especially at later ages. Figure 3 of Vaupel and Yashin (1985) shows an example with two frailty classes.

Accelerated failure time (AFT) models typically specify frailty in terms of its effect on the survival function, so that

$$s(z, x) = s(zx) \quad (57)$$

which implies that

$$\mu(z, x) = z\mu(zx). \quad (58)$$

(e.g., Anderson and Louis 1995; Keiding, Andersen, and Klein 1997; Klein, Pelz, and Zhang 1999; Pan 2001).

To incorporate such a model in the matrix calculations require only an appropriate change in the the expression (11) for the mortality rate of each frailty class.



### 5.3 Models for the distribution of frailty

The gamma distribution is attractive as a distribution of frailty for its mathematical properties, and theoretical results suggest that it is likely to underlie mortality trajectories that reach a plateau at old ages (Missov and Finkelstein 2011). However, any non-negative initial distribution  $\pi(0)$  can be incorporated in the calculation of the marginal survival  $s^*$  in (22), and the dynamics of the frailty distribution generated by (46). This includes other parametric distributions as well as specification of discrete frailty classes (e.g., Vaupel and Carey 1993).

### 5.4 Models for the dynamics of frailty

In the G-G model, frailty is a fixed property of an individual. However, individual heterogeneity may be dynamic, increasing (debilitation) or decreasing (recuperation) over time due to stress, disease, etc. The matrix model readily incorporates any finite-state Markov chain as a model for dynamic heterogeneity, by properly specifying the matrices  $\mathbf{D}_i$ , for  $i = 1, \dots, \omega$ .

For example, Vaupel and Yashin (2006) considered a model with two frailty states,  $z_1$  and  $z_2$ . Individuals begin life with frailty  $z_1$  and mortality  $\mu_1(x)$ , and change from state one to state two at a rate  $\lambda(x)$ . The second frailty state might represent a morbid event such as a heart attack. This model generalizes to a model considered by Le Bras (1976) and Gavrilov and Gavrilova (1992) with a countably infinite number of frailty classes. The mortality rate in frailty class  $i$  is  $\mu_i = \mu_0 + z_i\mu$ , and frailty increases at the rate  $\lambda_0 + z_i\lambda$ . The debilitation process leads to a stochastic increase in individual frailty over time. The resulting sigmoid trajectory of marginal mortality cannot be distinguished for that produced by the G-G model with an additive Makeham term (Yashin, Vaupel, and Iachine 1994; Yashin, Iachine, and Begun 2000).

Yashin, Vaupel, and Iachine (1994) considered a model in which the cohort starts with some initial frailty distribution, and then frailty of each individual proceeds in accordance with the LeBras model. Vaupel, Yashin, and Manton (1988) modelled the dynamics of frailty as a diffusion process, in which individuals may, with equal probability, become more frail or recuperate to a lower frailty level.

As an example of a model with dynamic heterogeneity, consider a hypothetical scenario where individual frailty changes as a diffusion process with reflecting boundaries. Frailty is as likely to increase as to decrease, but it cannot decline below 0 or increase above some maximum limit. If the changes in frailty follow a diffusion process, then the discrete time transition matrix  $\mathbf{D}$  can be written

$$\mathbf{D} = e^{k\mathbf{Q}} \quad (59)$$

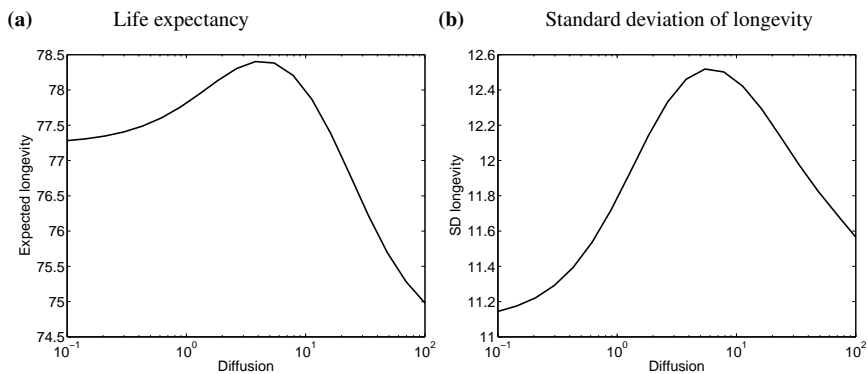
where  $\mathbf{Q}$  is the intensity matrix of a continuous-time, nearest-neighbor random walk with

$$q_{ij} = \begin{cases} 1 & j = i - 1 \\ -2 & j = i \\ 1 & j = i + 1 \\ 0 & \text{otherwise} \end{cases} \quad (60)$$

except that, at the boundaries,  $q_{1,1} = q_{g,g} = -1$ . The coefficient  $k$  adjusts the speed of diffusion (e.g., Kondor and Lafferty 2002). Unlike the LeBras model, this diffusion model does not change the rate of indisposition or recuperation as the frailty changes, but such dynamics could easily be incorporated.

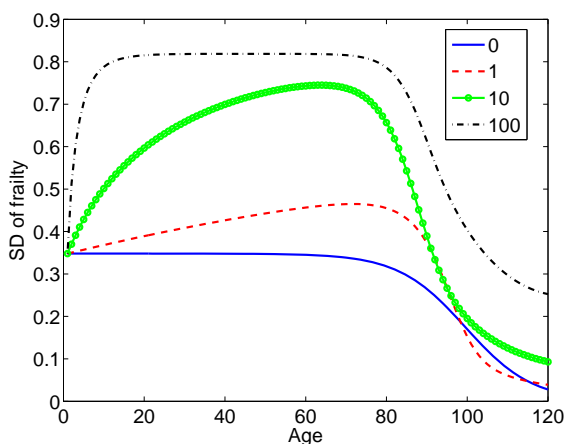
Using the matrix  $\mathbf{D}$  from (59) to create the block matrix  $\mathbb{D}$  in (13), and combining this with the Gompertz mortality for the Swedish females, gives the results shown in Figure 8. Both life expectancy and the standard deviation of longevity are maximized at intermediate values of diffusion. There is a balance between creation of diversity by diffusion, and removal of diversity by selection (a balance familiar from mutation-selection calculations in population genetics). At sufficiently high rates of diffusion, individual move among frailty levels so rapidly that they cannot avoid exposure to high levels of frailty (this reduces life expectancy), and because all individuals experience this random movement the variance in frailty is also reduced.

**Figure 8:** The expectation and the standard deviation of longevity at birth for the gamma-Gompertz model with added diffusion of frailty. Parameters as reported in Missov (2013) for Swedish females in 1950, using  $g = 120$  and  $\omega = 150$



The interaction between the creation of heterogeneity by diffusion and its elimination by selection is shown in Figure 9. The standard deviation of frailty increases from its value at birth, under the impact of diffusion. Eventually, mortality increases enough to reduce the variation by selection. As diffusion declines to zero, the increase in heterogeneity is smaller, and its reduction due to selection more prominent.

**Figure 9:** The standard deviation of frailty in a gamma-Gompertz model with diffusion of frailty, at zero, low ( $k = 1$ ), medium ( $k = 10$ ), and high ( $k = 100$ ) values of diffusion. Parameters as reported in Missov (2013) for Swedish females in 1950, using  $g = 120$  and  $\omega = 150$



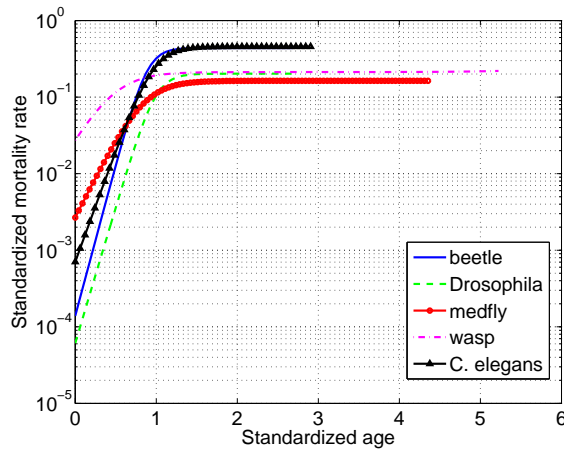
## 5.5 Some animal mortality patterns

In an exploration of the effects of heterogeneity on the distribution of age at death, Horiuchi (2003) estimated G-G parameters from data on laboratory populations of five species of invertebrate animals: a bean beetle (*Callosobruchus maculatus*), the medfly (*Ceratitis capitata*), the fruit fly *Drosophila melanogaster*, the nematode *Caenorhabditis elegans*, and a parasitoid wasp (*Diachasimimorpha longicaudata*.) Because the estimated G-G parameters for these species do not appear in the original paper, they are listed here in Table B.1.

These species exhibit considerably greater variance in frailty than do the human examples considered so far, ranging from 0.90 to 2.18. In contrast, estimates of the initial variance for Swedish females from 1891 to 2010 range from 0.10 to 0.14 (Missov 2013). Figure 10 shows the marginal mortality rate for each species as a function of age, with age and mortality rate both standardized relative to life expectancy at birth. The marginal

mortality rates reach a plateau at an age of about 1 life expectancy, at a standardized mortality rate of 0.1 to 0.5. Further interspecific analyses would be interesting.

**Figure 10:** The marginal mortality rate  $\mu^*(t)$  as a function of standardized age  $t$ , for five species of invertebrate animals, based on G-G parameters estimated by Horiuchi (2003). The age abscissa is scaled by dividing age by the life expectancy at birth. The mortality rate is standardized by multiplying by the same life expectancy

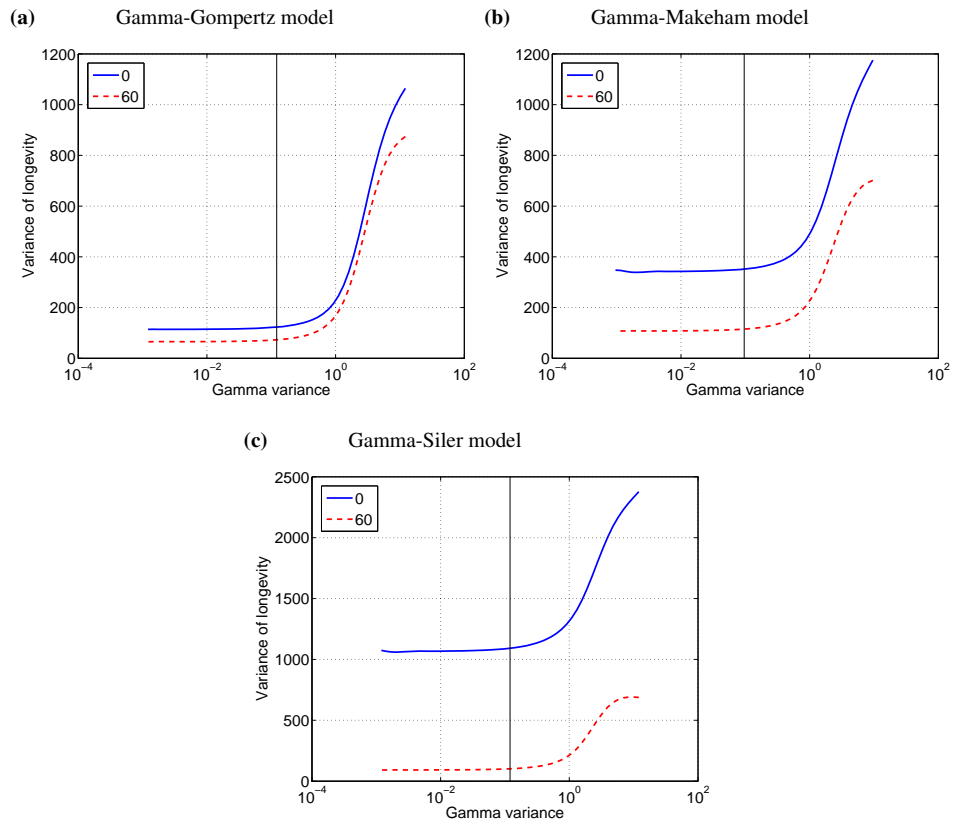


## 6. Heterogeneous frailty vs. individual stochasticity: partitioning variance in longevity

Inter-individual variance in longevity is often taken to be evidence of heterogeneity or inequality among individuals in their mortality risks. However, variance also arises from *individual stochasticity*, the random variation to which the fates of individuals are subject even if they experience exactly the same risks at every stage of the life cycle (Caswell 2009, 2011; Tuljapurkar, Steiner, and Orzack 2009). The only way to evaluate the contribution of heterogeneity is to partition the variance into components due to heterogeneity and to individual stochasticity. Frailty models permit us to do so.

The variance in longevity shown in Figure 11 arises from both individual stochasticity and heterogeneous frailty. However, as the variance in the initial frailty distribution  $\pi(0)$  approaches zero, the remaining variance in longevity is due only to individual stochasticity. Figure 11 shows that only a small fraction is due to heterogeneity; most of it is due to individual stochasticity.

**Figure 11:** The variance of longevity, at ages 0 and 60, as a function of the variance of the initial frailty distribution. (a) The gamma-Gompertz model, calculated from parameters reported by Missov (2013) for Swedish females in 1950. (b) The gamma-Makeham model, calculated from parameters reported by Zarulli et al. (2013) for a cohort model of the female population of Turin. (c) The gamma-Siler model, calculated from parameters reported by Engelman, Canudas-Romo, and Agree (2013) for Swedish females born in 1900. The vertical lines indicates the observed values of initial variance in frailty



This is not always the case. Table 2 compares the decomposition of the variance for Swedish females (using the G-G, gamma-Makeham, and gamma-Siler models) with that for the animal species from Horiuchi (2003). In the human populations, heterogeneity accounts for only 2–7% of the variance in longevity. In the experimental animal data, heterogeneity accounts for 46% to 83% of the variance in longevity. These patterns deserve further empirical investigation.

**Table 2: Decomposition of the variance in longevity for human populations and laboratory populations of invertebrate species. The variance  $\sigma^2$  in initial frailty, the variance  $V(\eta)$  in longevity and the components of  $V(\eta)$  due to individual stochasticity and to heterogeneous frailty, and the proportion of the variance due to heterogeneity. Species are listed in order of increasing initial variance in frailty. Data from Horiuchi (2003)**

Species	$\sigma^2$	$V(\eta)$	Stochasticity	Heterogeneity	Proportion
Sweden 1950 G-G	0.122	122.9	114.1	8.72	0.071
Turin G-M	0.096	351.6	347.3	104.3	0.012
Sweden 1900 G-S	0.120	1091.7	1074.1	17.60	0.016
nematode	0.90	18.0	9.7	8.3	0.46
fruit fly	0.94	88.1	46.1	42.0	0.48
beetle	1.31	12.7	5.2	7.5	0.59
medfly	1.34	81.8	29.5	52.3	0.64
wasp	2.18	30.3	5.1	25.2	0.83

## 7. Conclusions

The gamma-Gompertz and other frailty models provide a powerful way to analyze the mortality of heterogeneous cohorts (Wienke 2010; Vaupel and Missov forthcoming), by capturing the interacting effects of changing mortality with age and selection among individuals with different frailty states. The G-G model is a special case in which the baseline mortality rate follows the Gompertz model (1) and frailty affects the baseline as a proportional hazard, as in (11). The frailty dynamics are fixed, so that  $\mathbb{D}$  in (13) is an identity matrix, and the initial distribution  $\pi(0)$  is a gamma distribution with a mean of 1. As we have seen, many other models can be created by changing one or more of these components. The vec-permutation matrix model (18) methodically keeps track of both age and frailty, and makes it easy to calculate the properties of the joint age×frailty distribution,

the marginal age-specific mortality and survival functions, and a complete set of statistics of longevity.

Table 3 gives a step-by-step protocol for the analysis of the G-G and other frailty models. Other choices of baseline mortality rate (e.g., the Makeham model or the Siler model considered in Section 5.1), the action of frailty (e.g., accelerated failure time models), the dynamics of frailty (e.g., the frailty diffusion models discussed in Section 5.4), or the initial distribution of frailty require only simple modifications of the appropriate steps in Table 3.

**Table 3: A protocol for analysis of the gamma-Gompertz model**

1. Specify the Gompertz parameters  $a$  and  $b$ , and the gamma distribution parameter  $k$ . Choose values for the numbers of age classes  $\omega$  and the number of frailty classes  $g$ .
2. Generate the baseline mortality vector  $\mu_0$  from (10)
3. Specify the frailty classes  $z_i$ ,  $i = 1, \dots, g$ , and the discrete approximation to the gamma distribution  $\pi$ . Logarithmically-spaced frailty classes are recommended.
4. Create the matrices  $\mathbf{U}_i$ , for  $i = 1, \dots, g$ , as in equation (12).
5. Create the block diagonal matrices  $\mathbb{U}$  and  $\mathbb{D}$  according to (13).
6. Create the joint transition matrix  $\tilde{\mathbf{U}}$  according to (18).
7. Analyze the model
  - (a) Compute the fundamental matrix  $\tilde{\mathbf{N}}$  from (20).
  - (b) Compute the marginal survival function  $s^*$  from (22).
  - (c) Generate the marginal fundamental matrix  $\mathbf{N}^*$  from (24).
  - (d) Generate life expectancy and other indices of longevity from  $\mathbf{N}^*$  using (25)–(36).
8. Project the dynamics of the age-frailty distribution  $\tilde{\mathbf{n}}(t)$  with (41). Obtain the marginal age abundance vector  $\mathbf{n}^*$  using (43) and the marginal age distribution vector  $\mathbf{p}^*$  using (44).
9. Obtain the marginal frailty abundance vector  $\mathbf{m}^*$  using (45) and the frailty distribution  $\pi(t)$  from equation (46).
10. If desired, create the mortality matrix  $\tilde{\mathbf{M}}$  and generate the distributions of age and of frailty at death from equations (38)–(40).

### 7.1 Some pleasant properties of the matrix formulation

Too often, analytical methods are treated as competitors, as if there was one best way to carry out a calculation. This is generally false, usually counterproductive, and a tempta-

tion to be resisted. Although the matrix formulation of frailty models has many pleasant properties, it complements, rather than replaces, other formulations (e.g., matrix notation is unlikely to lead to easily interpretable symbolic results). Some properties worth noting include the following.

1. **Easy computation:** all the statistics of longevity, and all the dynamics of the joint age-frailty distribution, are readily computed. A MATLAB script to compute the results for the Swedish example from Missov (2013) is included in the Supplementary Material to this paper.
2. **Variance decomposition:** because the matrix formulation clearly separates the heterogeneity from the stochastic process of mortality, it facilitates decomposition of the variance in longevity into their contributions.
3. **Generality:** the analysis extends to any age $\times$ frailty model (Table 3) and, indeed, to stage-classified (e.g., educational status, health status) or multi-stage models as well as age-classified models.
4. **Population growth and stable population theory:** the matrix formulation has the potential to incorporate heterogeneous frailty into models of population growth, and hence into stable population theory (Caswell 2012).
5. **Sensitivity analysis:** because the results are obtained by matrix operations, they are directly amenable to sensitivity analysis using matrix calculus methods (e.g., Caswell 2006, 2007, 2008, 2009, 2012, 2013; van Raalte and Caswell 2013; Engelman, Caswell, and Agree 2014) Such methods will provide the levels of sensitivity of the moments of longevity, the joint distribution of age and stage at death, and the survivorship and mortality functions to changes in any of the parameters of the model. Results will be presented elsewhere.
6. **Likelihood and parameter estimation.** The formulation as an absorbing Markov chain may potentially contribute to the computation of likelihood functions from data on individuals. Such approaches have been used by animal ecologists analyzing mark-recapture data (e.g., Caswell and Fujiwara 2004) and implemented in some software packages (Pradel 2005; Choquet and Nogue 2010). Because frailty is inherently unobserved, issues of identifiability arise, which can also sometimes be addressed using the Markov chain formulation (Hunter and Caswell 2009).

## 8. Acknowledgments

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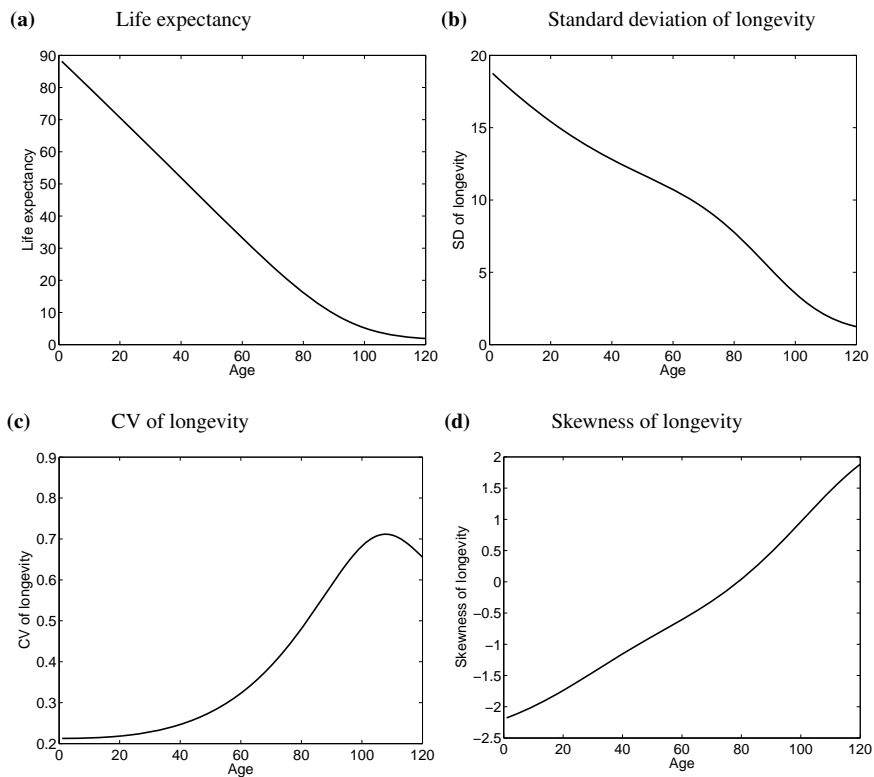
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## Appendix A: Gamma-Makeham and Gamma-Siler models

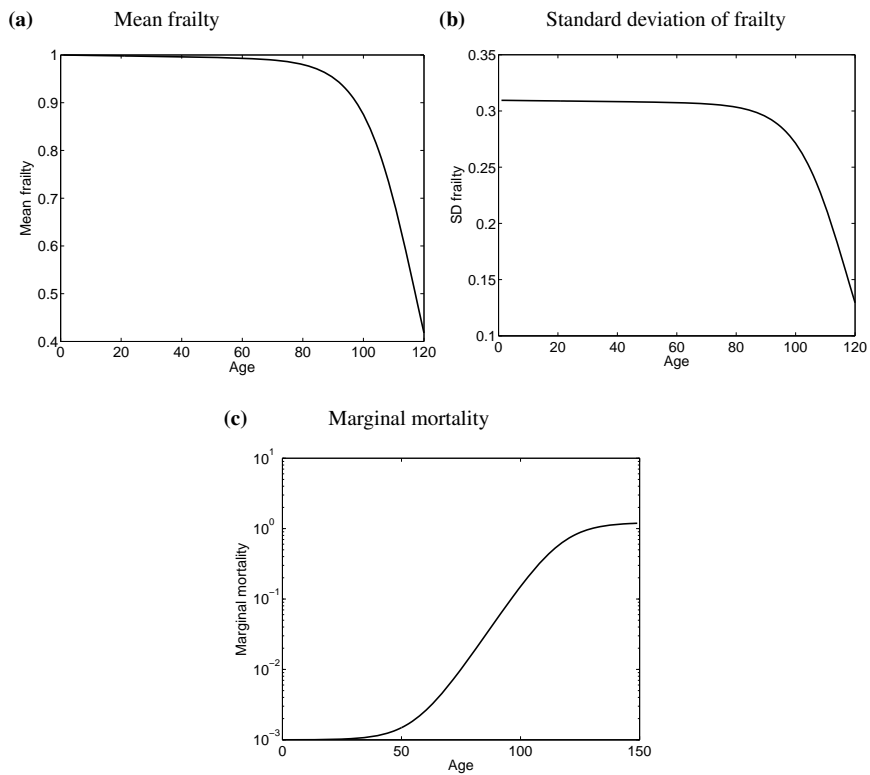
This appendix collects results on the statistics of longevity and the dynamics of frailty for the gamma-Makeham model and the gamma-Siler model, in the same format used for results from the G-G model in Figures 2 and 3.

### A.1 Gamma-Makeham

**Figure A.1:** Statistics of longevity for the gamma-Makeham model, as a function of age. Calculated from parameters reported by Zarulli et al. (2013) for a cohort model for the female population of Turin

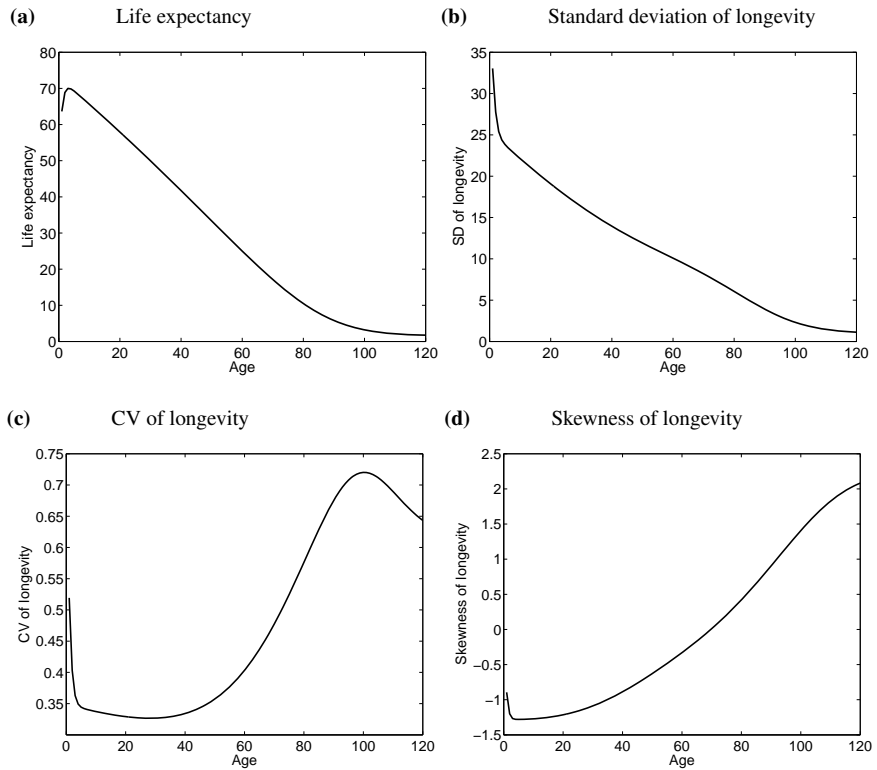


**Figure A.2: Statistics of frailty, and marginal mortality rate  $\mu^*$ , for the gamma-Makeham model, as a function of age. Calculated from parameters reported by Zarulli et al. (2013) for a cohort model for the female population of Turin**



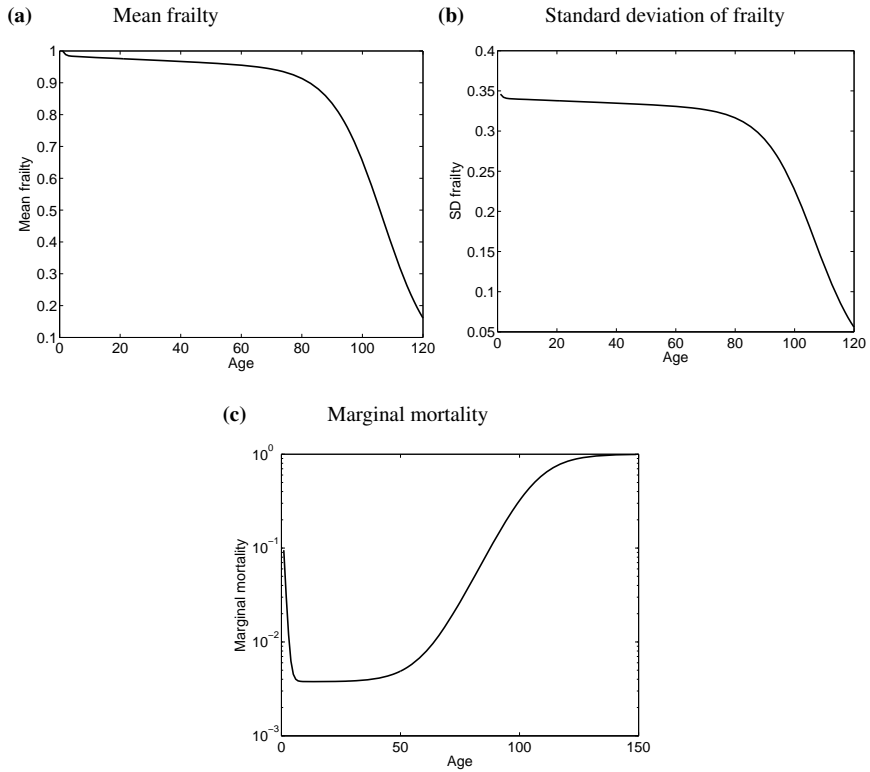
## A.2 Gamma-Siler

**Figure A.3: Statistics of longevity for the gamma-Siler model, as a function of age. Calculated from parameters reported by Engelman, Canudas-Romo, and Agree (2013) for Swedish females born in 1900**





**Figure A.4:** Statistics of frailty, and marginal mortality rate  $\mu^*$ , for the gamma-Siler model, as a function of age. Calculated from parameters reported by Engelman, Canudas-Romo, and Agree (2013) for Swedish females born in 1900



## Appendix B: Parameters for animal species

**Table B.1: Gamma-Gompertz parameters for the invertebrate animal species analyzed by Horiuchi (2003); data provided by Horiuchi (personal communication)**

Species	$a$	$b$	$k$
Medfly	0.0027	0.2168	0.7530
Nematode	$6.9970 \times 10^{-4}$	0.4059	1.1264
Wasp	0.0278	0.4575	0.4640
<i>Drosophila</i>	$6.0558 \times 10^{-5}$	0.1878	1.0796
Beetle	$1.3760 \times 10^{-4}$	0.5671	0.7721