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Beyond the proportional frailty model: Bayesian estimation of individual heterogeneity on mortality parameters.

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Today we know that demographic rates can be greatly influenced by differences among individuals in their capacity to survive and reproduce. These intrinsic differences, commonly known as individual heterogeneity, can rarely be measured and are thus treated as latent variables when modelling mortality. Finite mixture models and mixed effects models have been proposed as alternative approaches for inference on individual heterogeneity in mortality. However, in general models assume that individual heterogeneity influences mortality proportionally, which limits the possibility to test hypotheses on the effect of individual heterogeneity on other aspects of mortality such as ageing rates. Here we propose a Bayesian model that builds upon the mixture models previously developed, but that facilitates making inferences on the effect of individual heterogeneity on mortality parameters other than the baseline mortality. As an illustration, we apply this framework to the Gompertz-Makeham mortality model, commonly used in human and wildlife studies, by assuming that the Gompertz rate parameter is affected by individual heterogeneity. We provide results of a simulation study where we show that the model appropriately retrieves the parameters used for simulation, even for low variances in the heterogeneous parameter. We then apply the model to a dataset on captive chimpanzees and on a cohort life table of 1751 Swedish men, and show how model selection against a null model (i.e. without heterogeneity) can be carried out.

Key words: Bayesian inference; Frailty; Individual heterogeneity; Mortality; Survival analysis;

1 Introduction

Today it has been well established that the age patterns of mortality and fertility observed in natural populations are determined by a multitude of genes and phenotypic pathways (Kirkwood and Holliday, 1979; Partridge, 2010). As a results, it is expected that genetic or phenotypic differences among individuals in their capacity to survive and reproduce, known as individual heterogeneity, should influence mortality and fertility (Vaupel et al., 1979; Vaupel and Yashin, 1985; Service, 2000; Fox et al., 2006; Kendall et al., 2011; Marzolin et al., 2012), while contributing to the regulation of populations under stochastic environments (Kendall et al., 2011). It is commonly assumed that these individual differences, often known as frailty, are determined from birth and remain constant throughout each individual’s lifetime and, furthermore, that they affect mortality proportionally (Vaupel et al., 1979; Royle, 2008; Gimenez and Choquet, 2010). However, we have not yet understood the extent to which individual heterogeneity can affect baseline mortality other than proportionally, for instance by influencing ageing rates, this is the rate of change of mortality with age.

An important challenge in the estimation of the effect of individual heterogeneity on mortality in natural populations is the lack of individual level information that could account for differences in frailty

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among individuals. As a result, each individual’s frailty is often treated as a latent variable where individual heterogeneity is modeled by means of mixed effects (Royle, 2008; Gimenez and Choquet, 2010) or mixture models (Vaupel et al., 1979; Aalen, 1994; Burnham and Rexstad, 1993; Pledger and Schwarz, 2002; Abbring and Van den Berg, 2007). Modelling individual heterogeneity in survival using mixed effects models can be challenging in the absence of individual level covariates. As Lebreton (1995) and other authors recognize, mortality is a one time event, which limits the model’s ability to detect heterogeneity in mortality.

Alternatively, Vaupel et al. (1979) formalized a method for human mortality that incorporated individual heterogeneity into the estimation of life tables. Although they acknowledged that an individual’s frailty might not remain at the same level for the duration of its lifetime, they showed that variations in individual frailty throughout life were in fact negligible on a life table of Swedish women born in 1875. This assumption was further constrained by implying that frailty should affect mortality proportionally, where the hazards rate of an individual at age \( x \) and with frailty level \( z \) is \( \mu(x|z) = z\mu_0(x) \), where \( \mu_0(x) \) is the risk of death for an individual with frailty \( z = 1 \). Since then, this general class of models have been denoted “frailty models”, and are generally defined as random effects models where the level of unobserved frailty, \( z \), is modelled as random effect that modifies the hazards multiplicatively (Vaupel et al., 1979; Clayton and Cuzick, 1985; Oakes, 1989; Hougaard, 1995).

There are two general categories of frailty models, namely univariate and multivariate. The first assumes that frailty is a random variable that affects individuals independently of each other (Vaupel et al., 1979). The multivariate implementation, on the other hand, assumes that individuals belong to groups with non-independent frailties (Clayton and Cuzick, 1985; Oakes, 1989). In this case, random effects are included under a Cox proportional hazards framework (Clayton and Cuzick, 1985; Vaida and Xu, 2000), or different frailty distributions are assigned to individuals belonging to different groups (Yashin et al., 1995; Walker and Mallick, 1997; Parner, 1998). Several approaches have been proposed to estimate the parameters of the frailty distributions such as non parametric maximum likelihood (Parner, 1998), semi-parametric estimation with EM algorithms (Klein, 1992), or Bayesian models with non-parametric priors for the random effects (Clayton, 1991; Walker and Mallick, 1997). However, irrespective of the implementation, frailty models generally assume that the frailty random variable modifies baseline mortality multiplicatively, this is that mortality changes proportionally as a function of an individual’s frailty. This strong assumption limits the possibility to test hypotheses on the effect of frailty, or individual heterogeneity, on mortality other than as a multiplicative effect.

The model we present here focuses on the univariate case of frailty models. One of the most widely used univariate frailty models is the gamma-Gompertz model proposed by Vaupel et al. (1979). They showed that, given two random variables \( X \) for ages at death and \( Z \) for the level of frailty of an individual where \( Z \sim \text{Ga}(1/\gamma, 1/\gamma) \) with support \( z > 0 \) and \( \text{E}(Z) = 1 \) and \( \text{Var}(Z) = \gamma \), and for \( \mu_0(x) = ae^{bx} \) with \( a, b > 0 \), the marginal risk of death for age \( X \) results in a logistic mortality function of the form

\[
\mu_X(x) = \frac{ae^{bx}}{\gamma \frac{2}{3} (e^{bx} - 1)^{1/3}}.
\]  

(1)

They found that the mortality function (1) provided a close approximation to the mortality and its progress in humans since the mid nineteenth century. Other mixture models have been proposed in the context of capture-mark-recapture data, such as the Beta distributed mixture of yearly survival probabilities proposed by Burnham and Rexstad (1993) or the finite mixture model by Pledger and Schwarz (2002) and Pledger et al. (2003).

Although the gamma-Gompertz model and other frailty models can help to improve the estimation of mortality in humans and a few other species under laboratory conditions such as fruit flies (Service, 2000; Zajitschek et al., 2014) and in wild populations (Fox et al., 2006; Colchero et al., 2017), it is not clear if the assumptions that frailty acts as a proportional change in the baseline mortality is true for all species. Vaupel and Yashin (1985) and later Aalen (1994) showed cases in which different assumptions on the effect of
individual heterogeneity could dramatically affect the observed marginal age-specific mortality patterns at
the population level. Here we present a Bayesian modelling approach that builds upon the mixture models
previously developed but that allows testing the effect of individual heterogeneity on any mortality para-
ter, for instance on ageing rates. First, we describe the general framework for parametric survival analysis.
Subsequently, we explain our proposed modelling approach and a Bayesian implementation which allows
to determine the effect of individual heterogeneity any parameter of the mortality function. Then, we il-
lustrate our approach on a simulation study on the Gompertz-Makeham mortality model Gompertz (1825);
Makeham (1860), where we assume that individual heterogeneity affects the Gompertz rate parameter. Fi-
ally we present an application on a captive dataset on chimpanzees and on a life table of 1751 Swedish
men.

2 Basic Properties of Age-Specific Survival Analysis

We define a random variable $X$ for ages at death, where any given age is represented by $x$. A typical
age-specific survival analysis requires us to define the parametric mortality or hazards rate

$$\mu_X(x|\theta) = \lim_{\Delta x \to 0} \frac{\Pr(x < X < x + \Delta x | X > x, \theta)}{\Delta x} ,$$

(2)

where $\theta^T = [\theta_1, \ldots, \theta_p]$ is a $p$-vector of mortality parameters to be estimated. The cumulative hazards
function is given by

$$H(x|\theta) = \int_0^x \mu_X(t|\theta)dt .$$

(3)

From equations (2) and (3), we can calculate the survival function as

$$S_X(x|\theta) = \Pr(X > x|\theta) = \exp[-H(x|\theta)].$$

(4)

3 Estimating Individual Heterogeneity on mortality parameters

Individual heterogeneity accounts for the variability in frailty levels among individuals in a population. In
the absence of individual level covariates that could explain these differences, frailty is commonly treated
as a latent (unobserved) variable that can affect mortality by altering the observed population (marginal)
level of mortality. Here we illustrate our method by modeling individual heterogeneity as a function of the
a given parameter, $\theta_j \in \Theta$ for $j = 1, \ldots, p$. We define a random variable $\Theta$ with PDF $f_{\Theta}(\theta_j|\gamma)$, where
$\gamma \in \mathbb{R}^k$ is a $k$-vector of parameters for the distribution of $\Theta$. The conditional PDF of $\Theta$ for all individuals
still alive at a given age is

$$f_{\Theta|X}(\theta_j|X > x) = \frac{S_{X|\Theta}(x|\theta_j)f_{\Theta}(\theta_j)}{\int_0^\infty S_{X|\Theta}(x|\theta_j)f_{\Theta}(\theta_j)d\theta_j} .$$

(5)

Following the conventions for the construction of cohort life-tables (Preston et al., 2001), we aggregate
deaths within discrete age intervals $[x, x + \Delta x)$, where we assume that $\Delta x = 1$. The number of deaths in
a given age interval is represented by the random variable $D_x \sim \text{Bin}(q_x, l_x)$ with observations $d_x =
0, 1, \ldots, l_x$ for $x = 0, 1, \ldots, \omega$, where $\omega$ is the maximum age in the population and where $q_x \in [0, 1]$ is the
probability that death occurs within the interval and $l_x \in \mathbb{N}_0$ is the number of individuals still alive at the
beginning of the interval. We define the joint probability of death in the interval $[x, x + 1)$ and of having a
given value of $\theta_j$ as

$$q(x, \theta_j) = p(x < X < x + 1, \theta_j|X > x)
= p(x < X < x + 1|\theta_j, X > x)p(\theta_j|X > x)
= q_{X|\Theta}(x|\theta_j)f_{\Theta|X}(\theta_j|X > x) ,$$

(6)
where
\[
q_{X|B}(x|\theta_j) = 1 - \exp \left[ - \int_x^{x+1} \mu_{X|\theta}(z|\theta_j)dz \right]
\]
\[
= 1 - \frac{S_{X|\theta}(x+1|\theta_j)}{S_{X|\theta}(x|\theta_j)}.
\]

Thus, we have that the joint probability (6) becomes
\[
q(x, \theta_j) = \left[ 1 - \frac{S_{X|\theta}(x+1|\theta_j)}{S_{X|\theta}(x|\theta_j)} \right] \times \frac{S_{X|\theta}(x|\theta_j)f_{\theta}(\theta_j)}{\int_0^\infty S_{X|\theta}(x|\theta_j)f_{\theta}(\theta_j)d\theta_j}
\]
\[
= \frac{S_{X|\theta}(x|\theta_j) - S_{X|\theta}(x+1|\theta_j)}{\int_0^\infty S_{X|\theta}(x|\theta_j)f_{\theta}(\theta_j)d\theta_j},
\]
\[
= \frac{[S_{X|\theta}(x|\theta_j) - S_{X|\theta}(x+1|\theta_j)]f_{\theta}(\theta_j)}{\int_0^\infty S_{X|\theta}(x|\theta_j)f_{\theta}(\theta_j)d\theta_j}.
\]

To find the marginal probability \(q(x)\), we integrate \(q(x, \theta_j)\) over \(\theta_j\) as
\[
q(x) = \int_0^\infty \left[ S_{X|\theta}(x|\theta_j) - S_{X|\theta}(x+1|\theta_j) \right] f_{\theta}(\theta_j)\,d\theta_j
\]
\[
= 1 - \int_0^\infty \left[ S_{X|\theta}(x|\theta_j) - S_{X|\theta}(x+1|\theta_j) \right] f_{\theta}(\theta_j)\,d\theta_j.
\]

The integrals in probability (9) can be approximated with a simple midpoint quadrature. This marginal probability of death corresponds then to the observed population level mortality probability. The likelihood function is given by
\[
L(\theta_1, \ldots, \theta_{j-1}, \theta_{j+1}, \ldots, \theta_p, \gamma|x, l, d) = p(x, l, d | \theta_1, \ldots, \theta_{j-1}, \theta_{j+1}, \ldots, \theta_p, \gamma)
\]
\[
= \prod_{x=0}^{l_x} \left( \frac{l_x - d_x}{d_x} \right) q(x)^{d_x}[1 - q(x)]^{l_x - d_x},
\]
where \(x = [0, 1, 2, \ldots, \omega]\) is the vector of discrete ages at death with \(\omega\) being the maximum recorded age for the population, \(l = [l_1, \ldots, l_\omega]\) and \(d = [d_1, \ldots, d_\omega]\) are vectors of observed number of individuals alive and death, respectively, per age interval.

We propose a simple Bayesian model for inference formulated as
\[
p(\theta_1, \ldots, \theta_{j-1}, \theta_{j+1}, \ldots, \theta_p, \gamma|x, l, d) \propto p(x, l, d | \theta_1, \ldots, \theta_{j-1}, \theta_{j+1}, \ldots, \theta_p, \gamma)
\]
\[
\times p(\theta_1) \ldots p(\theta_{j-1})p(\theta_{j+1}) \ldots p(\theta_p)
\]
\[
\times p(\gamma_1) \ldots p(\gamma_k),
\]
where the terms in the right-hand-side of equation (11) correspond to the likelihood function as in (10) followed by the priors for the unknown parameters. Thus, inference requires estimating the vector of unknown parameters given by \(\theta^* = [\theta_1, \ldots, \theta_{j-1}, \theta_{j+1}, \ldots, \theta_p]\) and \(\gamma^* = [\gamma_1, \ldots, \gamma_k]\).

The Bayesian model (11) uses Metropolis-Hastings sampling (Metropolis et al., 1953; Chib and Greenberg, 1995) within an MCMC framework. We assume that the priors are normally distributed truncated at 0. The Metropolis-Hastings part of the algorithm for a given parameter \(\theta \in \theta\) consists of proposing a new parameter value \(\theta^*\) at every iteration and accepting or rejecting it with probability
\[
p(\theta, \theta^*) = \min \left\{ 1, \frac{p(x|\theta^*)p(\theta^*)J(\theta^*|\theta)}{p(x|\theta)p(\theta)J(\theta|\theta^*)} \right\},
\]
where
\[
J(\theta^*|\theta) = \frac{\theta^*}{\theta},
\]
\[
J(\theta|\theta^*) = \frac{\theta}{\theta^*}.
\]
where the elements in the numerator on the right-hand side of equation (12) are the conditional posterior for the new parameter, $\theta^*$, and in the denominator we have the conditional posterior for the parameter in the previous step, $\theta$ and where $J(\theta|\theta^*)$ is the jump density for $\theta$ with mean value $\theta^*$. We use a normal jump density truncated at 0.

To determine if the model is ergodic, we run different MCMC simulations with varying starting parameters. From the resulting parameter chains we calculate the potential scale reduction for each parameter to estimate convergence (Gelman et al., 2013). This diagnostic is calculated as $\hat{R} = \sqrt{\text{Var}^+ (\theta|x)/W}$, where $W$ is a measure of the within-sequence variance and $\text{Var}^+ (\theta|x)$ is a weighted average of the between-sequence variance ($B$) and $W$. Convergence is attained when $\hat{R}$ is close to 1.

The Martingale residuals (Barlow and Prentice, 1988; Aalen et al., 2008) can be used as a visual method to verify the goodness of fit of the model, calculated as

$$\hat{M}(x) = N(x) - \hat{A}(x),$$

where $N(x)$ is the observed number of events (i.e. number of deaths) in the interval $[0, x]$ and $\hat{A}(x)$ is the expected number of events based on the mortality model, commonly known as the cumulative intensity process. This last can be calculated as

$$\hat{A}(x) = NF(x|\hat{\theta}),$$

where $F(x|\hat{\theta})$ is the CDF of ages of death given the estimated model and $N$ is the initial number of individuals in the cohort. This approximation can be used for a cohort data with a stationary population.

We also use the Kaplan-Meier estimator (Kaplan and Meier, 1958) given by

$$\hat{S}(x) = \prod_{T_j \leq x} \left(1 - \frac{1}{Y(T_j)}\right),$$

where $Y(x)$ is the number of individuals at death risk before age $x$.

We use posterior predictive checking (Rubin, 1984; Meng, 1994; Gelman et al., 1996) as a measure of model fit, for which we generate replicated data under the model and compare it with the observed data. This method requires estimating the posterior predictive distribution, given by

$$p(d_{xp}^{rep}|d_x) = \int_{\Theta} p(d_{xp}^{rep} | \theta)p(\theta | d_x) d\theta,$$

where $d_{xp}^{rep}$ are replicated values of the number of individuals dying at age $x$, generated from the sampled parameter sets at each iteration after convergence. Let $T(d_x | \theta)$ be a test statistic for the number of observed deaths, we can then calculate two-tailed posterior $p$-values for the test statistic given the replicated distribution of $d_{xp}^{rep}$ as

$$p_0(d_x) = \min[1 - \Pr(T(d_x | \theta) \geq T(d_{xp}^{rep} | \theta)), \Pr(T(d_x | \theta) \leq T(d_{xp}^{rep} | \theta))].$$

After assessing proper convergence, we calculate the deviance information criterion (DIC; Spiegelhalter et al. 2002), as a measure of support for the model given the data. Alternatively, predictive loss, $D_m$, as proposed by Gelfand and Ghosh (1998) can be computed from the replicated values of $d_x$ used for posterior predictive check. Predictive loss provides a measure of model fit that combines a value of goodness of fit calculated as the sum of squares of the error in estimation of the $d_x$ values, and a penalty term given by the sum of the predictive variances.

For hypothesis testing of the effect of individual heterogeneity on the Gompertz rate parameter we propose a null model where $\theta_j$ is constant. Thus, the likelihood for the null model is

$$L(\theta | x, l, d) = p(x, l, d | \theta) = \prod_{x=0}^{x} \left( \frac{l_x}{d_x} \right) g_0(x)^{d_x} [1 - g_0(x)]^{l_x - d_x},$$

(17)
where \( q_0(x) = 1 - \exp \left( - \int_x^{x+1} \mu(x|\theta) \right) \). Inference for the parameters of the null model follows the same procedure as for the model with heterogeneity. Higher support for the model with heterogeneity with respect to the null model is achieved when \( \Delta \text{DIC} = \text{DIC}_h - \text{DIC}_0 > 0 \), where \( \text{DIC}_h \) and \( \text{DIC}_0 \) are the deviance information criterion for the model with heterogeneity and for the null model, respectively.

## 4 Simulation study

To illustrate our method, we used the Gompertz-Makeham mortality model (Gompertz, 1825; Makeham, 1860) which has been shown to fit well the adult mortality of most primate species (Bronikowski et al., 2011). The hazards rate or mortality function for the Gompertz-Makeham model is given by

\[
\mu(x|\theta) = \alpha e^{\beta x} + \kappa
\]

with survival function

\[
S_X(x|\theta) = e^{\alpha/(1 - e^{\beta x}) - \kappa x},
\]

where \( \theta^T = [\alpha, \beta, \kappa] \) and where \( \alpha, \beta > 0 \) and \( \kappa \geq 0 \) are the baseline, the rate and the age-independent mortality parameters, respectively.

We modelled individual heterogeneity as a function of the Gompertz rate parameter, \( \beta \) (Fig.1). As we show in Fig. 1, the model assumes that, by acting on the rate parameter, individual heterogeneity acts by differentially affecting the rate of actuarial ageing, where robust individuals age more slowly than frail individuals. Thus, we define a random variable \( B \sim \log N(\log \beta_0, \sigma^2) \) with PDF \( f_B(\beta) \) for \( \beta > 0 \) where \( \beta_0 \) is the median frailty level in the Gompertz rate parameter at age 0, and \( \sigma^2 \) is the heterogeneity driven dispersion in \( \beta \). Because evolutionary theories of ageing state that all multicellular organisms with clear separation between soma and germ lines should undergo actuarial senescence (Kirkwood and Melov, 2011), the rate parameter \( \beta \) is commonly assumed to only take positive values. This is why we used a log-normal distribution for \( \beta \), however, other continuous distributions with support \( \mathbb{R}_{>0} \) can be used.

Thus, the model in Eq.(11) becomes

\[
p(\alpha, \kappa, \beta_0, \sigma^2|x, l, d) \propto p(x, l, d | \alpha, \kappa, \beta_0, \sigma^2) \times p(\alpha)p(\kappa)p(\beta_0)p(\sigma^2).
\]

In this case inference requires estimating the vectors of unknown parameters given by \( \theta^T = [\alpha, \kappa] \) and \( \gamma^T = [\beta_0, \sigma^2] \).

We performed a simulation study where we generated 1,000 datasets of \( n = 500 \) by randomly sampling ages at death from a hypothetical population. We set the “real” parameters at \( \alpha = 0.001, \kappa = 0.001, \beta_0 = 0.1 \) and repeated the simulations for varying values of \( \sigma \in \{0.01, 0.1, 0.25, 0.5\} \), where \( B \sim \log N(\log(\beta_0), \sigma^2) \). We initiated each simulation by randomly drawing \( n \) values of \( \beta \) from a log-normal distribution with mean \( \log(\beta_0) \) and variance \( \sigma^2 \). We used these individual \( \beta \) values to simulated ages at death by means of inverse sampling as

\[
x_i = F_X^{-1}(u_i|\beta_i),
\]

where \( x_i \) is the age at death for individual \( i \) and \( u_i \) is a random uniform variable such that \( u_i \sim \text{unif}(0,1) \).

We used vague priors for each of the unknown parameters (i.e. \( \theta \sim N(0.1, 25) \) for \( \theta \in \theta \)) and ran each MCMC simulation for 75,000 steps with a burn-in of 25,000. The MCMC simulation chains for each parameter (i.e. parameter traces) converged satisfactorily (i.e. \( 1 < R < 1.01 \), see Fig. 2) for all the simulations and, upon visual inspection of model fit by means of the Kaplan-Meier curve and Martingale residuals, we confirmed that the model provides a close fit to the data (Fig. 3).
Age, \( x \)

log-mortality, log\[ \mu (x) \]

Robust

Frail

Conditional hazards (unobserved)

Marginal hazards (observed)

Figure 1  Graphical representation of the effect on mortality of individual heterogeneity affecting the rate parameter \( \beta \) in Eq. (18). The grey lines represent the unobserved conditional hazards given the level of frailty, and the red thick line represents the observed marginal hazards.

For hypothesis testing we found that for low values of \( \sigma \) the model with heterogeneity in \( \beta \) has equal support as the null model (Fig. 4). As the magnitude of \( \sigma \) increased, the DIC values for the model with heterogeneity were consistently lower than for the null model. We also found that the parameter posterior densities from the model with heterogeneity in \( \beta \) included the “real” parameters within their 95% credible intervals for 95% of the simulations for values of \( \sigma \geq 0.1 \), while most parameters were also included within the interval for 95% of the simulations with \( \sigma = 0.01 \), except for \( \beta_0 \), which was included in 90% of the simulations.

Source code to reproduce the results is available as Supporting Information on the journal’s web page (http://onlinelibrary.wiley.com/doi/xxx/ suppinfo)

5 Real Data Application

We tested our model on a dataset of female captive chimpanzees (\( Pan troglodytes \)) provided by the organization Species 360. This dataset consists of ages at death of 319 females born in captivity. In addition, we analyzed data from a cohort life table for Swedish men from 1751 provided by the Human Mortality Database (Human Mortality Database, 2018). For both datasets we conditioned our analysis on adult individuals such that only those that survived beyond 15 years of age were included, which corresponds to the age at sexual maturity, since it has been shown that the Gompertz-Makeham model provides an appropriate fit for adult mortality in both species (Golubev, 2004; Bronikowski et al., 2011). It is important to note that, by conditioning on individuals that survived beyond age at maturity, the model estimates the distribution of the heterogeneous parameter at the age at maturity and not at birth. Furthermore, in both datasets all individuals were followed from birth, thus we do not have left-truncation. We used the same vague priors as for the simulation study.
Figure 2  Example of parameter traces (top row), where the different colours correspond to the different MCMC runs (parallel chains), and posterior densities (bottom row, red polygons) for one of the simulations with $\sigma = 0.1$, where the dashed lines depict the parameter values used to simulate the ages at death.

In both cases the Markov chain traces converged appropriately (i.e. $\hat{R} \in \mathbb{C}(1, 1.01)$). In the case of the chimpanzee dataset, the null model had lower DIC ($DIC_0 = 235.47$) than the model with heterogeneity ($DIC_h = 237.17$), which suggests that the effect of individual heterogeneity in the Gompertz rate parameter $\beta$ is negligible (Table 1).

Table 1  Results for the model with heterogeneity on the captive female chimpanzee dataset.

<table>
<thead>
<tr>
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<th>Mean</th>
<th>SE</th>
<th>2.5%</th>
<th>97.5%</th>
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</thead>
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<td>0.012</td>
<td>0.00091</td>
<td>0.043</td>
</tr>
<tr>
<td>$\kappa$</td>
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<td>0.015</td>
<td>0.00220</td>
<td>0.053</td>
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<tr>
<td>$\beta_0$</td>
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<td>0.130</td>
<td>0.01000</td>
<td>0.470</td>
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</table>

For the Swedish men data we found that the model with individual heterogeneity had slightly lower DIC ($DIC_h = 1303.16$) than the null model ($DIC_0 = 1303.78$). As we show in the simulation study, such low differences in DIC arise when the magnitude of $\sigma^2$ is low (Table 2). In Figures 5 and 6 we show the posterior predictive checks for the model with heterogeneity on the chimpanzee and 1751 Swedish men datasets, respectively. Notably, Figure 6 shows a large amount of over-dispersion unaccounted for in the model on the 1751 Sweden life table. This over-dispersion is most likely the result of “age heaping”, also known as “digit preference”, which arises when individuals do not report their ages accurately, or when ages from historical documents such as death certificates had been rounded to the closest digit or by intervals of five years (Myers, 1954; Lee and Lam, 1983).
Figure 3  Graphical verification of model fit by means of the Kaplan-Meier curve (top) and the Martingale residuals (bottom, red points) for the model with individual heterogeneity in $\beta$ (left) and the null model (right). This example corresponds to one simulation with $\sigma = 0.25$.

Table 2  Results for the model with heterogeneity on the 1751 Swedish men life table.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SE</th>
<th>2.5%</th>
<th>97.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
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<td>0.00110</td>
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<tr>
<td>$\kappa$</td>
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<td>0.000087</td>
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<tr>
<td>$\beta_0$</td>
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<td>0.000820</td>
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<td>0.005200</td>
<td>0.00062</td>
<td>0.0190</td>
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</table>

6 Discussion

Individual heterogeneity as a measure of the variability in frailty among individuals has long being acknowledged as an important element driving observed mortality patterns in natural populations (Vaupel and Yashin, 1985; Aubry et al., 2011; Vaupel and Missov, 2014). In most applications, frailty is assumed to affect mortality proportionally (e.g. under a proportional hazards framework, see for example Vaupel...
and Missov (2014)), thus modifying the baseline mortality. Here we have developed a modelling framework that facilitates the estimation of the effect of individual heterogeneity on other mortality parameters, particularly those affecting the rate at which adult mortality changes with age. We have shown that the model retrieves accurately the unknown mortality parameters as well as those that determine the distribution of frailty on the rate parameter. Still, further improvements on the model are necessary such as the inclusion of covariates, the possibility to test the effect of individual heterogeneity on both, the baseline mortality parameter and the rate parameter. In addition, for some over-dispersed datasets it is necessary to develop a more flexible modeling framework that facilitates accounting for over-dispersion. Nonetheless, this modeling framework provides enough flexibility to be generalised to other mortality functions such as the Weibull mortality model (Pinder III et al., 1978) and other distributions for the heterogeneous parameter. We believe that our model provides a reliable basis to test hypotheses on the effect of individual heterogeneity in natural populations and how it can affect ageing rates. Shedding light on these processes can have important implications for a wide number of disciplines, ranging from ecology and evolution to actuarial sciences.

**Figure 4** Difference in the deviance information criterion (DIC) between the model with heterogeneity ($DIC_h$) and the null model ($DIC_0$) for different values of the variance in the distribution of $\beta$. Negative values indicate that the DIC for the model with heterogeneity is lower and thus has higher support than the null model.
Figure 5  Posterior predictive check for the model with heterogeneity in the Gompertz $\beta$ parameter on the chimpanzee dataset. Here age $x = 0$ corresponds to 15 years of age. Posterior predictive check for the model with heterogeneity in the Gompertz $\beta$ parameter on the 1751 Swedish men life table. Here age $x = 0$ corresponds to 15 years of age. The left vertical axis depicts the range of values for the posterior $p$-values, which are drawn with the vertical grey and dark red bars, these last showing when these $p$-values are less than 0.05 (i.e. the real $d_x$ value is not contained within the 95% predictive intervals). The right vertical axis provides the range of values of the number of deaths, $d_x$ at each age, which correspond to black dots for the data $d_x$ and the green polygons for the 95% predictive intervals. The solid green line shows the mean predicted value of $D_x$.

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Conflict of Interest
The authors have declared no conflict of interest.

References
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