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Research Article

Unobserved population heterogeneity: A review of formal relationships

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Unobserved population heterogeneity: A review of formal relationships

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Abstract

BACKGROUND

Survival models accounting for unobserved heterogeneity (frailty models) play an important role in mortality research, yet there is no article that concisely summarizes useful relationships.

OBJECTIVE

We present a list of important mathematical relationships that govern populations in which individuals differ from each other in unobserved ways. For some relationships we present proofs that, albeit formal, tend to be simple and intuitive.

METHODS

We organize the article in a progression, starting with general relationships and then turning to models with stronger and stronger assumptions.

RESULTS

We start with the general case, in which we do not assume any structure of the underlying baseline hazard, the frailty distribution, or their link to one another. Then we sequentially assume, first, a relative-risk model; second, a gamma distribution for frailty; and, finally, a Gompertz and Gompertz-Makeham specification for baseline mortality.

COMMENTS

The article might serve as a handy overall reference to frailty models, especially for mortality research.

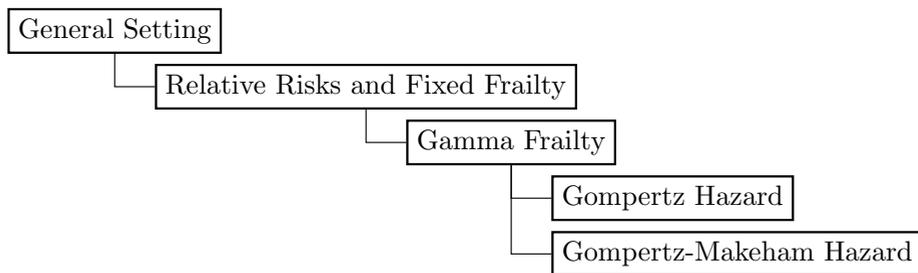
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1. Population heterogeneity

Unobserved heterogeneity plays an important role in shaping mortality trajectories for populations. An overview of unobserved heterogeneity in demographic research can be found in Yashin, Iachine, and Begun (2000) and Vaupel and Yashin (2001b,a, 2006). Vaupel and Yashin (1985) present a number of examples in which hazards of individuals or subpopulations and the hazard of the entire population follow different trajectories. We do not review that material here and we do not discuss applications to the analysis of empirical data; the aim of this article is to present the key mathematical relationships that hold in models with unobserved heterogeneity. We start with the general case and introduce increasingly restrictive assumptions about the distributions of baseline mortality and unobserved heterogeneity (see Figure 1). We present short proofs and derivations as well as some brief qualitative interpretations.

Figure 1: Structure of the presentation of relationships



2. Notation and terminology

In frailty models we distinguish between the mortality schedules for individuals and the entire population. The model for individuals depends on a random variable Z , called *frailty* (Vaupel, Manton, and Stallard 1979), that is unobserved. As a result individual mortality is captured by a conditional (on frailty) distribution. For a given realization z of frailty Z we denote the *force of mortality* (also known as the *intensity of mortality*, the *hazard of death*, the *hazard function*, or simply the *hazard*) for individuals by $\mu(x, z)$, and the corresponding survival function by $s(x, z)$. Canonical notation designates these functions by $\mu(x | z)$ and $s(x | z)$, but we prefer the version with a comma for easier readability. The two functions are linked by the following well-known relationships:

$$s(x, z) = \exp \left\{ - \int_0^x \mu(t, z) dt \right\} \quad \text{and} \quad \mu(x, z) = - \frac{d \ln s(x, z)}{dx}. \quad (1)$$

We assume that the distribution of frailty among survivors to age x is characterized by a probability density function (p.d.f.) $\pi(x, z)$. The p.d.f. of frailty at the starting age of analysis is $\pi(0, z)$.

The hazard for the population

$$\bar{\mu}(x) = \int_0^{\infty} \mu(x, z) \pi(x, z) dz \quad (2)$$

and the survival function for the population

$$\bar{s}(x) = \int_0^{\infty} s(x, z) \pi(0, z) dz \quad (3)$$

are often designated by $\mu(x)$ and $s(x)$, but we prefer the version with a bar-sign on top as these functions are “averages” with respect to the frailty distribution. We will refer to (2) and (3) as the *population, marginal, or aggregate (population) hazard/survival function* and use these terms interchangeably. They are linked to one another by relationships that are analogical to (1).

We designate the age-derivative and the relative age-derivative of a function by a dot and an accent, respectively; e.g., for $\bar{\mu}(x)$ we denote

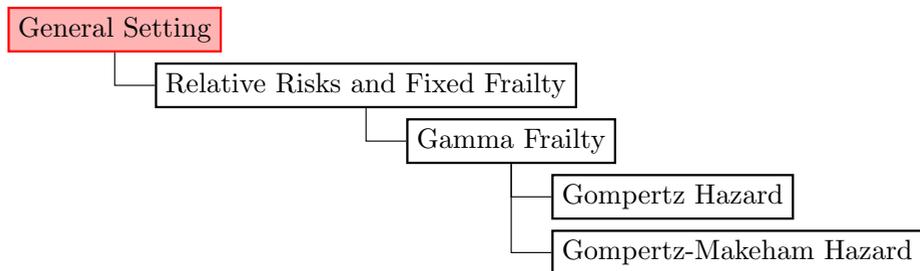
$$\dot{\bar{\mu}}(x) = \frac{d}{dx} \bar{\mu}(x) \quad \text{and} \quad \acute{\bar{\mu}}(x) = \frac{d}{dx} \frac{\bar{\mu}(x)}{\bar{\mu}(x)}. \quad (4)$$

This notation is not new; it can be traced back to Vaupel, Manton, and Stallard (1979) and Vaupel (1992). Many important demographic relationships have been expressed in such notation (see, e.g., Vaupel and Canudas-Romo 2003; Vaupel and Zhang 2010). Table A.1 summarizes the basic notation and terminology we use in the following sections.

We present many mathematical relationships: we place an asterisk after the equation number, e.g., (17*), to denote relationships that we believe are important additions to knowledge about population heterogeneity. We prove many of the known and new relationships. Some of these are classic proofs, in which case we provide a citation. Others are new, at least as far as we know, or so straightforward that we did not scour the literature to determine if they had been published before. We welcome feedback from readers about citations we should add in revised versions of this Primer. Finally some proofs are

so easy that we did not feel that a formal proof was necessary. Again if readers disagree, we will provide additional proofs in future versions of the Primer. One of the advantages of publishing in Demographic Research is that articles can be revised as appropriate.

3. General results



Suppose, in a population, individuals are characterized by Z , a random variable accounting for unobserved heterogeneity, with p.d.f. $\pi(0, z)$ at a given starting age. We will use Z to denote a random variable and z to denote a particular value of this random variable for an individual. Suppose the individuals die or otherwise exit according to a schedule specified by hazard $\mu(x, z)$ and survival function $s(x, z)$. Then the following relationships hold:

- 3A. Cohort survivorship in a population $\bar{s}(x)$ is the weighted average of conditional survival functions $s(x, z)$ that correspond to all profiles $\pi(0, z)$ in the study population:

$$\bar{s}(x) = \int_0^{\infty} \pi(0, z) s(x, z) dz . \quad (5)$$

If the population is stratified into a countable number of subgroups, i.e. when $\pi(0, z)$ is discrete, (5) becomes

$$\bar{s}(x) = \sum_z \pi(0, z) s(x, z) , \quad (6)$$

where the support of Z could be finite or countably infinite.

3B. The density of the frailty distribution among survivors to age x is given by

$$\pi(x, z) = \pi(0, z) \frac{s(x, z)}{\bar{s}(x)}. \quad (7)$$

This can be rewritten as

$$s(x, z) = \frac{\pi(x, z)}{\pi(0, z)} \bar{s}(x), \quad (8)$$

a formula, due to Vaupel (1992), used in “fixed attribute dynamics” to study, e.g., the survival of persons with some genotype based on data on the prevalence of the genotype at two successive ages (Gerdes et al. 2000; Zeng and Vaupel 2004).

3C. If $e(0, z)$ denotes life expectancy at birth for the subpopulation with $Z = z$, then life expectancy at birth for the entire population $\bar{e}(0)$ is a weighted average of $e(0, z)$ across all profiles (Vaupel 1988):

$$\bar{e}(0) = \int_0^{\infty} e(0, z) \pi(0, z) dz. \quad (9)$$

3D. The population hazard $\bar{\mu}(x)$ is the weighted average of the hazards $\mu(x, z)$ of all subpopulations at age x , weighted by the distribution $\pi(x, z)$ at x :

$$\bar{\mu}(x) = \int_0^{\infty} \mu(x, z) \pi(x, z) dz. \quad (10)$$

It is the negative relative derivative of the population survivorship $\bar{s}(x)$:

$$\bar{\mu}(x) = -\frac{d}{dx} \frac{\bar{s}(x)}{\bar{s}(x)} = -\dot{\bar{s}}(x). \quad (11)$$

3E. An identical relationship holds for remaining life expectancy $\bar{e}(x)$ at age x – only those individuals that survived to x count (Vaupel 1988):

$$\bar{e}(x) = \int_0^{\infty} e(x, z) \pi(x, z) dz. \quad (12)$$

- 3F. The derivative of the population hazard can be expressed as (Vaupel 1992; Vaupel and Zhang 2010)

$$\dot{\mu}(x) = \bar{\mu}(x) - \sigma_{\mu}^2(x), \quad (13)$$

where

$$\dot{\mu}(x) = \frac{d}{dx} \bar{\mu}(x) = \frac{d}{dx} \int_0^{\infty} \mu(x, z) \pi(x, z) dz,$$

is the change in the hazard for the entire population at age x ,

$$\bar{\mu}(x) = \int_0^{\infty} \frac{d}{dx} \mu(x, z) \pi(x, z) dz$$

is the average change in all individual hazards $\mu(x, z)$ at x , and

$$\sigma_{\mu}^2(x) = \int_0^{\infty} \mu^2(x, z) \pi(x, z) dz - \bar{\mu}^2(x)$$

is the variance of $\mu(x, z)$ across all profiles. Eq. 13 implies that individuals age faster than populations: $\bar{\mu}(x) > \dot{\mu}(x)$.

Proof. This is a special case of the more general relationship for derivatives of averages (see Price 1970; Vaupel 1992; Vaupel and Canudas-Romo 2003). The proof follows from simple differentiation of

$$\bar{\mu}(x) = \frac{\int_0^{\infty} \mu(x, z) s(x, z) \pi(0, z) dz}{\int_0^{\infty} s(x, z) \pi(0, z) dz}$$

by expressing $\frac{d}{dx} s(x, z) = -\mu(x, z) s(x, z)$.

□

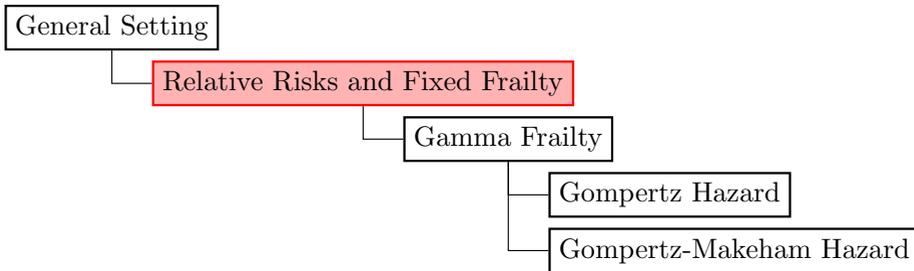
- 3G. The difference between the values of the population hazard at two different ages can be usefully decomposed in the following way:

$$\bar{\mu}(x_2) - \bar{\mu}(x_1) = [\bar{\mu}(x_2) - \tilde{\mu}(x_1)] + [\tilde{\mu}(x_1) - \bar{\mu}(x_1)] \quad (14)$$

$\forall x_2 > x_1 \geq 0$, where $\tilde{\mu}(x_1)$ is the population hazard at age x_1 of survivors to age x_2 . The first term on the right-hand side of (14) captures the change in the

population hazard among survivors to x_2 , and the second term measures the change in the composition of the population due to differential survival. Relationship (14) was introduced by Rebke et al. (2010) for any average characteristic of a population.

4. Relationships for relative-risk models with fixed frailty



The results presented above hold for any population in which the value of Z for an individual is independent of the value of Z for any other individual. The index z could pertain to a fixed number (realization of a random variable) or vector of numbers (realization of a random vector). Indeed, an individual might have a vector $z = (z_1, z_2, \dots)$ that uniquely defines a stochastic mortality or attrition trajectory. In this section we restrict ourselves to a fixed single frailty parameter that acts multiplicatively on the baseline hazard. We do not specify, though, any parametric distribution for it. In a multiplicative (proportional-hazard, relative-risk) fixed-frailty model (Vaupel et al. 1979), Z can be interpreted as “frailty”, and the individual force of mortality is defined as

$$\mu(x, z) = z \mu(x), \tag{15}$$

where $\mu(x) \equiv \mu(x, 1)$ is the baseline hazard. In this setting, the following relationships hold:

- 4A. The population hazard $\bar{\mu}(x)$ at any age x is a function of the baseline hazard $\mu(x)$ and the average frailty $\bar{z}(x) = \int_0^\infty z \pi(x, z) dz$ among survivors to this age (Vaupel, Manton, and Stallard 1979)

$$\bar{\mu}(x) = \bar{z}(x) \mu(x). \tag{16}$$

Because frailer individuals die out first, $\bar{z}(x)$ decreases with age x and, as a result, the force of mortality for individuals increases faster than the force of mortality for the population as a whole.

- 4B. A similar relationship links the changes in the hazards of individuals and the population:

$$\bar{\dot{\mu}}(x) = \bar{z}(x) \dot{\mu}(x). \quad (17^*)$$

As $\bar{z}(x)$ declines, the change in the force of mortality for the population becomes smaller than the change in the baseline hazard.

Proof.

$$\bar{\dot{\mu}}(x) = \int_0^{\infty} \dot{\mu}(x) z \pi(x, z) dz = \bar{z}(x) \dot{\mu}(x)$$

□

- 4C. The variance of the conditional hazard at age x equals the product of the squared baseline hazard and the variance of the frailty distribution at x

$$\sigma_{\mu}^2(x) = \mu^2(x) \sigma_z^2(x), \quad (18^*)$$

where $\sigma_z^2(x) = \int_0^{\infty} z^2 \pi(x, z) dz - \bar{z}^2(x)$.

Proof.

$$\begin{aligned} \sigma_{\mu}^2(x) &= \int_0^{\infty} z^2 \mu^2(x) \pi(x, z) dz - \left[\int_0^{\infty} z \mu(x) \pi(x, z) dz \right]^2 = \\ &= \mu^2(x) \left\{ \int_0^{\infty} z^2 \pi(x, z) dz - \left[\int_0^{\infty} z \pi(x, z) dz \right]^2 \right\} = \\ &= \mu^2(x) \sigma_z^2(x) \end{aligned}$$

□

A simple corollary is that the squared coefficients of variation of conditional mortality and frailty are equivalent at any age x :

$$\text{CV}_{\mu}^2(x) = \text{CV}_z^2(x). \quad (19^*)$$

Proof.

$$CV_{\mu}^2(x) = \frac{\sigma_{\mu}^2(x)}{\bar{\mu}^2(x)} = \frac{\mu^2(x) \sigma_z^2(x)}{\bar{z}^2(x) \mu^2(x)} = CV_z^2(x)$$

□

4D. The relative derivative of the population hazard can be expressed as

$$\dot{\bar{\mu}}(x) = \dot{\mu}(x) - \bar{\mu}(x) CV_z^2(x). \tag{20*}$$

Proof. Divide both sides of (13) by $\bar{\mu}(x)$ and take advantage of (17*) and (19*). □

Eq. 20* has a useful implication (Missov and Vaupel 2014). Suppose the population hazard levels off after age x^* , i.e.

$$\bar{\mu}(x) = \bar{\mu}^* \equiv const \quad \forall x \geq x^* > 0. \tag{21}$$

Then the (relative) derivative of the population hazard vanishes

$$\dot{\bar{\mu}}(x) = \dot{\mu}(x) = 0 \tag{22}$$

and (20*) is reduced to

$$\dot{\mu}(x) = \bar{\mu}^* \cdot CV_z^2(x). \tag{23}$$

Although this equation has infinitely many solutions, two special cases offer straightforward demographic interpretation:

1. $\dot{\mu}(x) = CV_z^2(x) = 0$, which implies a homogeneous population exposed to a constant hazard, and
2. $\dot{\mu}(x) = b \equiv const$ and $CV_z^2(x) = \gamma \equiv const$, which implies a Gompertz baseline and gamma-distributed frailty (Missov 2012; Missov and Vaupel 2014).

4E. The average frailty of the dead at x

$$z^{\dagger}(x) = \frac{\int_0^{\infty} z \mu(x, z) \pi(x, z) dz}{\int_0^{\infty} \mu(x, z) \pi(x, z) dz} \tag{24}$$

can be expressed (Vaupel, Manton, and Stallard 1979) as

$$z^{\dagger}(x) = \bar{z}(x) [1 + CV_z^2(x)]. \tag{25}$$

Proof. Follows by substituting (15) under the integrals in (24) and reorganizing terms. \square

The major analytical advantage of assuming relative risks is that the marginal distribution can be expressed from the conditional distribution through the Laplace transform (Laplace 1782, 1785), the properties of which have been thoroughly studied by Doetsch (1937, 1950, 1955, 1956). The Laplace transform of a function $f(z)$ is defined as

$$\mathcal{L}(s) = \int_0^{\infty} e^{-sz} f(z) dz. \tag{26}$$

If $f(z)$ is a p.d.f. of a random variable Z , then (26) is the expected value of the random variable e^{-sZ} . In this case the Laplace transform is also denoted by \mathcal{L}_Z and is called the *Laplace transform of Z* or the *Laplace transform of the distribution of Z* .

4F. Population survival at age x is the Laplace transform of the frailty distribution calculated at the baseline cumulative hazard

$$\bar{s}(x) = \mathcal{L}_Z(H(x)), \tag{27}$$

where $\mathcal{L}_Z(\cdot)$ is the Laplace transform of the frailty distribution at the initial age and $H(x) = \int_0^x \mu(x) dx$ is the baseline cumulative hazard. The hazard of the population $\bar{\mu}(x)$ can be then expressed via the same Laplace transform and the baseline hazard:

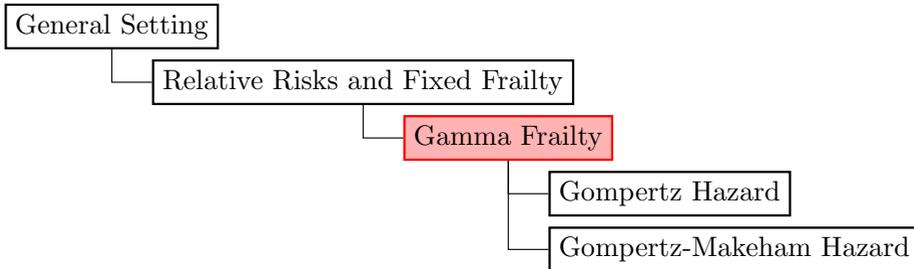
$$\bar{\mu}(x) = -\mu(x) \left. \frac{d}{ds} \ln \mathcal{L}_Z(s) \right|_{s=H(x)} = -\mu(x) \left. \dot{\mathcal{L}}_Z(s) \right|_{s=H(x)}. \tag{28}$$

Proof. The expression for $\bar{s}(x)$ follows by expressing $s(x, z)$ in terms of $H(x, z) = zH(x)$

$$\bar{s}(x) = \int_0^{\infty} s(x, z) \pi(0, z) dz = \int_0^{\infty} e^{-zH(x)} \pi(0, z) dz = \mathcal{L}_Z(H(x))$$

and the expression for $\bar{\mu}(x)$ results from taking the negative relative derivative of the expression for $\bar{s}(x)$. \square

5. Relationships for relative-risk models with gamma-distributed fixed frailty



All results in the previous section hold when frailty acts multiplicatively on the baseline hazard. In this section we will make the additional assumption that frailty is gamma-distributed (Vaupel, Manton, and Stallard 1979). The gamma distribution $\Gamma(k, \lambda)$ with positive parameters k, λ has a density

$$\pi(0, z) = \frac{\lambda^k}{\Gamma(k)} z^{k-1} e^{-\lambda z}. \tag{29}$$

Frailty is often assumed to be gamma-distributed for several reasons. First, the gamma distribution has a flexible shape and converges to a normal distribution as $k \rightarrow \infty$ (direct corollary of the central limit theorem). Second, the gamma distribution has a simple Laplace transform $(1 + s/\lambda)^{-k}$ (Mellin 1900), which makes working with the marginal distribution convenient. Third, $\pi(x, z)$ is gamma distributed at all ages x with the same k and $\lambda(x) = \lambda + H(x)$. Finally, the gamma distribution has a regularly varying density, which is the property frailty distributions possess in a wide family of survival models with unobserved heterogeneity (Missov and Finkelstein 2011). If $\pi(0, z)$ is a regularly varying density, then $\pi(x, z)$ will approach a gamma distribution as $\bar{s}(x)$ approaches zero (see Abbring and van den Berg 2007; Missov and Finkelstein 2011; Missov and Vaupel 2014). In relative-risk models with gamma-distributed fixed frailty, the following relationships hold:

- 5A. 1. The average frailty of survivors to age x or, formally speaking, the expected value of the frailty random variable at age x , equals (Vaupel, Manton, and Stallard 1979)

$$\bar{z}(x) = \frac{k}{\lambda + H(x)}. \tag{30}$$

Proof. Using (7) and $s(x, z) = [s(x)]^z = e^{-zH(x)}$, we get

$$\begin{aligned}\bar{z}(x) &= \int_0^\infty z \pi(x, z) dz = \frac{1}{\bar{s}(x)} \int_0^\infty z \pi(0, z) s(x, z) dz = \\ &= \left(1 + \frac{H(x)}{\lambda}\right)^k \frac{k\lambda^k}{(\lambda + H(x))^{k+1}} = \frac{k}{\lambda + H(x)}.\end{aligned}$$

□

2. Suppose the frailty distribution at the starting age has a unit expectation $\bar{z}(0) = 1$. This means that the “average” or “standard” individual is subjected to the baseline hazard $\mu(x)$. A mean of one implies $k = \lambda = 1/\gamma$, where γ can be interpreted as the squared coefficient of variation of Z at any age x . Then (Vaupel, Manton, and Stallard 1979)

$$\bar{z}(x) = \frac{1}{1 + \gamma H(x)}. \tag{31}$$

Proof. Follows directly from (30). □

- 5B. 1. Vaupel, Manton, and Stallard (1979) showed that population survival in a relative-risk model with fixed gamma-distributed frailty is given by

$$\bar{s}(x) = \mathcal{L}_Z(H(x)) = \left(1 + \frac{H(x)}{\lambda}\right)^{-k}. \tag{32}$$

In addition, if $\bar{z}(0) = 1$, then

2.

$$\bar{s}(x) = (1 + \gamma H(x))^{-\frac{1}{\gamma}} \tag{33}$$

and

3.

$$\bar{z}(x) = [\bar{s}(x)]^\gamma. \tag{34}$$

Proof. (34) follows directly from (31) and (33). □

5C. If $\bar{z}(0) = 1$, then (Vaupel 2002)

1.

$$\bar{\mu}(x) = \mu(x) [\bar{s}(x)]^\gamma \tag{35}$$

and (Vaupel, Manton, and Stallard 1979)

2.

$$\bar{\mu}(x) = \frac{\mu(x)}{1 + \gamma H(x)}. \tag{36}$$

5D. In a relative-risk model with fixed gamma-distributed frailty the average frailty of the dead can be expressed as (Vaupel, Manton, and Stallard 1979)

$$\bar{z}^\dagger(x) = \bar{z}(x) \cdot (1 + \gamma). \tag{37}$$

Proof. Follows directly from (25) taking into account that the squared coefficient of variation for gamma-distributed frailty at any age x is equal to γ . □

5E. Suppose the baseline hazards $\mu_1(x)$ and $\mu_2(x)$ of two populations are proportional by a factor of R :

$$\mu_2(x) = R \mu_1(x), \tag{38}$$

where, without loss of generality, $R > 1$. Then

1. if frailty is gamma-distributed with mean 1 and squared coefficient of variation γ for *both* populations, the marginal hazards $\bar{\mu}_1(x)$ and $\bar{\mu}_2(x)$ of the two populations converge (Manton and Stallard 1981).

Proof. Eq. 38 implies that $H_2(x) = R H_1(x)$. Using in addition (16) and (31), we get

$$\bar{R}(x) := \frac{\bar{\mu}_2(x)}{\bar{\mu}_1(x)} = \frac{R + R \gamma H_1(x)}{1 + R \gamma H_1(x)}.$$

$\bar{R}(x) > 1$ because $R > 1$ and $\lim_{x \rightarrow \infty} \bar{R}(x) = 1$. □

2. if frailty is gamma distributed with mean 1 for both populations, but the respective squared coefficients of variation γ_1 and γ_2 are such that $\gamma_2 > \gamma_1$, then there is a crossover of the marginal hazards $\bar{\mu}_1(x)$ and $\bar{\mu}_2(x)$.

Proof. On the one hand,

$$\bar{R}(0) = R > 1.$$

and, on the other hand,

$$\lim_{x \rightarrow \infty} \bar{R}(x) = \lim_{x \rightarrow \infty} \frac{R + R\gamma_1 H_1(x)}{1 + R\gamma_2 H_1(x)} = \frac{\gamma_1}{\gamma_2} < 1.$$

Hence there is a crossover at x_0 , at which $H_1(x_0) = \frac{R-1}{R(\gamma_2-\gamma_1)}$.³ □

5F. Suppose there exists an age x^* such that

$$\mu_2(x) = \begin{cases} R\mu_1(x), & x < x^* \\ R^*\mu_1(x), & x \geq x^*, \end{cases}$$

where $R > 1$ and R^* are constants, and frailty is gamma-distributed with mean 1 and squared coefficient of variation γ for *both* populations. Then there is a crossover of $\bar{\mu}_1(x)$ and $\bar{\mu}_2(x)$ if $R^* < \frac{1+R\gamma H_1(x^*)}{1+\gamma H_1(x^*)}$.

Proof. For $x < x^*$

$$\bar{R}(x) = \frac{R + R\gamma H_1(x)}{1 + R\gamma H_1(x)} > 1.$$

At $x = x^*$

$$\bar{R}(x^*) = \frac{R^* [1 + \gamma H_1(x^*)]}{1 + R\gamma H_1(x^*)}.$$

This quantity is less than 1 (i.e., there is a crossover) if

$$R^* < \frac{1 + R\gamma H_1(x^*)}{1 + \gamma H_1(x^*)}.$$

Note that R^* can exceed 1.⁴ □

5G. Demographic models have often two time dimensions (age and period) with a third one (cohort) being their linear combination. As a result survival models in demography are often defined on a surface. The negative relative derivative of $\bar{\mu}(x, y)$ with respect to year y is denoted as $\bar{\rho}(x, y)$ and captures yearly mortality improvement:

³ This proof is original.

⁴ This proof is original.

$$\bar{\rho}(x, y) = -\frac{1}{\bar{\mu}(x, y)} \frac{\partial}{\partial y} \bar{\mu}(x, y).$$

In a relative-risk model with gamma-distributed frailty $\bar{\rho}(x, y)$ can be expressed as

$$\bar{\rho}(x, y) = \rho(x, y) - \gamma \hat{s}_c(x, y) \tag{39*}$$

where $\bar{s}_c(x, y)$ denotes survival to age x for the cohort born in $y - x$,

$$\hat{s}_c(x, y) = -\frac{1}{\bar{s}_c(x, y)} \frac{\partial}{\partial y} \bar{s}_c(x, y),$$

and

$$\rho(x, y) = -\frac{1}{\mu(x, y)} \frac{\partial}{\partial y} \mu(x, y).$$

Hence the rate of progress for the population is less than the rate of progress for the individuals in the population.

Proof. By analogy to the uni-dimensional case (35), we have

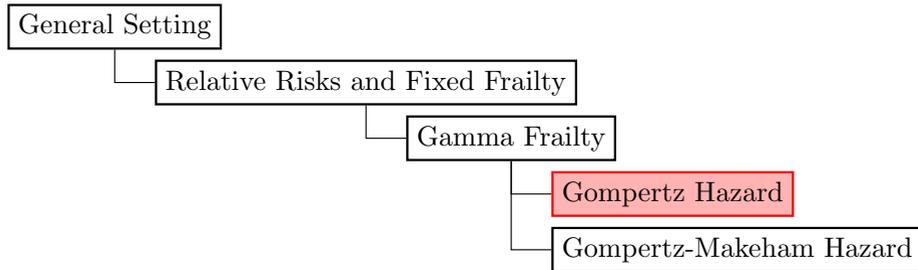
$$\bar{\mu}(x, y) = \mu(x, y) \bar{s}_c^\gamma(x, y).$$

Combining the latter with the definitions of $\bar{\rho}(x, y)$ and $\rho(x, y)$, we get

$$\begin{aligned} \bar{\rho}(x, y) &= -\frac{\frac{\partial}{\partial y} \mu(x, y) \cdot \bar{s}_c^\gamma(x, y) + \mu(x, y) \cdot \frac{\partial}{\partial y} \bar{s}_c^\gamma(x, y)}{\mu(x, y) \bar{s}_c^\gamma(x, y)} = \\ &= \rho(x, y) - \frac{\frac{\partial}{\partial y} \bar{s}_c^\gamma(x, y)}{\bar{s}_c^\gamma(x, y)} = \rho(x, y) - \gamma \frac{\frac{\partial}{\partial y} \bar{s}_c(x, y)}{\bar{s}_c(x, y)}. \end{aligned}$$

□

6. Relationships for relative-risk models with gamma-distributed fixed frailty and Gompertz hazard (gamma-Gompertz (ΓG) models)



A further level of detail in survival models with unobserved heterogeneity can be reached by specifying the baseline distribution. For various theoretical and empirical reasons the Gompertz exponential-increase law (Gompertz 1825) is often assumed as the baseline hazard in models of adult mortality. The Gompertz function can be expressed as

$$\mu(x) = ae^{bx} = be^{b(x-M)},$$

where $a = \mu(0)$ is the hazard at the initial age, b is the rate of increase, and M is the mode (Missov et al. 2014).

On the one hand, the Gompertz distribution is a truncated (at 0) Gumbel distribution (see Gumbel 1958; Lenart and Missov 2014, for a broader discussion), which is a member of the class of generalized extreme value (GEV) distributions. The latter describe distributions of minima or maxima of a set of random variables. Assume a living organism (or an engineered object) consisting of systems, in which each system is comprised of organs (elements). The life of each system is determined by the minimal organ (element) lifetime in it, and the life of the entire organism (engineered object) is determined by the distribution of these minima. It is not surprising then, that the two most popular baseline mortality distributions are the Weibull (also belonging to GEV) and the Gompertz, as they, first, stem from GEV (although, the Gompertz distribution is not a GEV itself), and, second, model aging processes. Empirically speaking, many time-to-event datasets can be fitted with serviceable accuracy by a Gompertz hazard. An extension to the Gompertz model is the Gompertz-Makeham curve $ae^{bx} + c$, which assumes an age-independent mortality component, and often provides a better fit. In both the gamma-Gompertz (ΓG) and the gamma-Gompertz-Makeham (ΓGM) model settings, the force of mortality for the population eventually levels off.

In a ΓG model with $k = \lambda = 1/\gamma$ the following relationships hold:

6A. The population hazard can be represented in several equivalent forms:

1. in terms of the ΓG parameters only (Vaupel, Manton, and Stallard 1979; Missov et al. 2014)

$$\bar{\mu}(x) = \frac{ae^{bx}}{1 + \frac{a\gamma}{b}(e^{bx} - 1)} = \frac{be^{b(x-M)}}{1 + \gamma e^{-bM}(e^{bx} - 1)}. \quad (40)$$

Proof. Follows from (36) taking into account the functional form of the Gompertz baseline cumulative hazard

$$H(x) = \frac{a}{b}(e^{bx} - 1) = e^{-bM}(e^{bx} - 1). \quad (41)$$

□

2. in terms of the baseline hazard, the observed cohort survivorship $\bar{s}(x)$ from the initial age to age x , and the squared coefficient of variation γ of frailty (Vaupel 2002)

$$\bar{\mu}(x) = ae^{bx} [\bar{s}(x)]^\gamma = be^{b(x-M)} [\bar{s}(x)]^\gamma. \quad (42)$$

Proof. Follows from (35) taking into account the expression for the Gompertz hazard $\mu(x) = ae^{bx} = be^{b(x-M)}$. □

3. incorporating information about the mortality plateau

$$\bar{\mu}(x) = \{1 - [\bar{s}(x)]^\gamma\} \bar{\mu}^* + [\bar{s}(x)]^\gamma \bar{\mu}_0, \quad (43^*)$$

where $\bar{\mu}^* = \lim_{x \rightarrow \infty} \bar{\mu}(x) = b/\gamma$ denotes the plateau and $\bar{\mu}_0 = \bar{\mu}(0) = a$ is the mortality level at the starting age.

Proof. We express e^{bx} from

$$\bar{s}(x) = \left(1 + \frac{a\gamma}{b}(e^{bx} - 1)\right)^{-\frac{1}{\gamma}}$$

(a corollary of (33) for a Gompertz baseline) and substitute it in (42). □

6B. The average frailty among survivors to age x also has three equivalent representations:

1. in terms of the ΓG parameters only (Vaupel, Manton, and Stallard 1979)

$$\bar{z}(x) = \left[1 + \frac{a\gamma}{b} (e^{bx} - 1) \right]^{-1}. \quad (44)$$

Proof. Follows from (31) and (41). □

2. incorporating information about the mortality plateau

$$\bar{z}(x) = \frac{\bar{\mu}^* - \bar{\mu}(x)}{\bar{\mu}^* - \bar{\mu}_0}. \quad (45^*)$$

Proof. Follows from (43*) by taking $\bar{z}(x) = [\bar{s}(x)]^\gamma$ into account and reorganizing terms. □

3. rewriting (45*) in terms of parameters b and γ

$$\bar{z}(x) = \frac{b - \gamma\bar{\mu}(x)}{b - \gamma\bar{\mu}_0}. \quad (46^*)$$

Proof. We take advantage of the fact that $\bar{\mu}^* = b/\gamma$. □

6C. Population survivorship can also be expressed in three alternative ways:

1. in terms of the ΓG parameters only (Vaupel, Manton, and Stallard 1979)

$$\bar{s}(x) = \left[1 + \frac{a\gamma}{b} (e^{bx} - 1) \right]^{-\frac{1}{\gamma}}. \quad (47)$$

Proof. Population survivorship is the Laplace transform of the frailty distribution calculated for the baseline cumulative hazard. The relationship follows directly from (33) taking into account the form of the Gompertz cumulative hazard. □

2. incorporating information about the mortality plateau

$$\bar{s}(x) = \left[\frac{\bar{\mu}^* - \bar{\mu}(x)}{\bar{\mu}^* - \bar{\mu}_0} \right]^{\frac{\bar{\mu}^*}{b}}. \quad (48^*)$$

Proof. Follows from $\bar{s}(x) = [\bar{z}(x)]^{1/\gamma} = [\bar{z}(x)]^{\bar{\mu}^*/b}$ and (45*). □

3. rewriting (48*) in terms of parameters b and γ

$$\bar{s}(x) = \left[\frac{b - \gamma\bar{\mu}(x)}{b - \gamma\bar{\mu}_0} \right]^{\frac{1}{\gamma}}. \quad (49^*)$$

- 6D. The rate of aging $\bar{b}(x)$ of a population, known as LAR, the lifetable aging rate (Horiuchi and Coale 1990), is usually defined in demography as the relative derivative of the population force of mortality $\bar{\mu}(x)$ with respect to age x :

$$\bar{b}(x) = \frac{1}{\bar{\mu}(x)} \frac{d}{dx} \bar{\mu}(x). \tag{50}$$

In a ΓG model $\bar{b}(x)$ can be represented in at least two different ways. In both cases the individual rate of aging b exceeds the rate of aging $\bar{b}(x)$ of the population.

1.

$$\bar{b}(x) = b - \gamma \bar{\mu}(x) \tag{51*}$$

Proof. Taking the derivative of $\bar{\mu}(x)$ with respect to x leads to:

$$\bar{b}(x) = \frac{\bar{\dot{\mu}}(x)}{\bar{\mu}(x)} - \frac{\sigma_{\mu}^2(x)}{\bar{\mu}(x)}.$$

The first term on the right-hand side is equal to b for a Gompertz baseline $\mu(x) = ae^{bx}$. The second term can be represented as a product of $\bar{\mu}(x)$ and the squared coefficient of variation of $\mu(x, z)$ (or, using (19*), of frailty) at age x :

$$\frac{\sigma_{\mu}^2(x)}{\bar{\mu}(x)} = \bar{\mu}(x) \frac{\sigma_{\mu}^2(x)}{\bar{\mu}^2(x)} = \bar{\mu}(x) \text{CV}_{\mu}^2(x) = \bar{\mu}(x) \text{CV}_z^2(x).$$

The squared coefficient of variation of the gamma distribution depends only on the shape parameter and equals $1/k$. As the distribution of frailty for all x is gamma with one and the same shape parameter $k = 1/\gamma$, $\text{CV}_z^2(x) = \gamma$, which completes the proof.

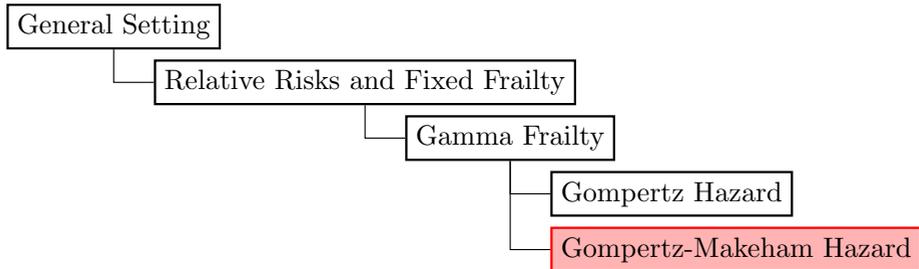
□

2.

$$\bar{b}(x) = b \left(1 - \frac{\bar{\mu}(x)}{\bar{\mu}^*} \right) \tag{52*}$$

Proof. Once again we take advantage of $\bar{\mu}^* = b/\gamma$.

□



7. Relationships for relative-risk models with gamma-distributed fixed frailty and Gompertz-Makeham hazard (gamma-Gompertz-Makeham (Γ GM) models)

A standard extension of the Gompertz model is to add a constant term that accounts for extrinsic mortality, not related to aging processes (Makeham 1860). The resulting gamma-Gompertz-Makeham (Γ GM) fixed-frailty model is defined by a conditional hazard

$$\mu(x, z) = z a e^{bx} + c,$$

which for $k = \lambda = 1/\gamma$ results in the following population hazard (Manton, Stalard, and Vaupel 1981)

$$\bar{\mu}(x) = \frac{a e^{bx}}{1 + \frac{a\gamma}{b} (e^{bx} - 1)} + c. \quad (53)$$

This is an additive-hazards model with a Gompertz age-dependent component affected by frailty, and a constant Makeham component c accounting for non-aging-related mortality. Most relationships derived for the gamma-Gompertz model (adjusted for c) hold in the Γ GM setting, too. The only substantial difference concerns the rate of aging $\bar{b}(x)$ for the population.

7A. Vaupel and Zhang (2010) present an exact expression for $\bar{b}(x)$ in Γ GM models:

$$\bar{b}(x) = \frac{\dot{\bar{\mu}}(x)}{\bar{\mu}(x)} = b \left(1 - \frac{c}{\bar{\mu}(x)} \right) - \gamma \left(1 - \frac{c}{\bar{\mu}(x)} \right) [\bar{\mu}(x) - c]. \quad (54)$$

Proof. One should take advantage of (53) and reorganize terms. □

7B. Vaupel and Zhang (2010) derive a relationship, involving the eventual Γ GM mortality plateau $\bar{\mu}^* = b/\gamma + c$, as well:

$$\bar{b}(x) = b \left(1 - \frac{c}{\bar{\mu}(x)} \right) \frac{\bar{\mu}^* - \bar{\mu}(x)}{\bar{\mu}^* - c}. \tag{55}$$

Proof. At the plateau $\bar{b}(x) = 0$ and $\bar{\mu}(x) = \bar{\mu}^*$, which implies $\gamma = b/(\bar{\mu}^* - c)$. Substituting γ in (54) and reorganizing terms accordingly completes the proof. \square

7C. If in addition $c \approx 0$, i.e., when $\mu(x) \approx ae^{bx}$, then

$$\bar{b}(x) \approx b \left(1 - \frac{\bar{\mu}(x)}{\bar{\mu}^*} \right). \tag{56}$$

This is an approximate multiplicative relationship between $\bar{b}(x) = \dot{\bar{\mu}}(x)$, the rate of aging for the population, and $b = \dot{\mu}(x)$, the rate of aging for individuals. If $c = 0$, then the exact relationship (56) holds.

7D. A widely used demographic indicator in comparative research is the remaining life expectancy at age x , denoted by $e(x)$ and expressed as

$$e(x) = \int_x^\infty t d(t) dt = \frac{1}{s(x)} \int_x^\infty s(t) dt. \tag{57}$$

From a statistics perspective, this represents the first moment (i.e., mean) of the underlying distribution of deaths after age x . Life expectancy in a gamma-Gompertz-Makeham framework equals (Missov and Lenart 2013)

$$e(x) = \frac{(b\lambda)^k e^{-(bk+c)x}}{a^k (bk+c)} {}_2F_1 \left(k + \frac{c}{b}, k; k + \frac{c}{b} + 1; \left(1 - \frac{b\lambda}{a} \right) e^{-bx} \right), \tag{58}$$

where

$${}_2F_1(\alpha, \beta; \gamma; z) = \sum_{j=0}^\infty \frac{(\alpha)_j (\beta)_j}{(\gamma)_j} \frac{z^j}{j!}, \tag{59}$$

is the Gaussian hypergeometric function defined for $\gamma > \beta > 0$ (see, for example, Bailey 1935). For $n \in \mathbb{N}$, $(m)_n = m(m+1) \dots (m+n-1)$ denotes the Pochhammer symbol with $(m)_0 = 1$. Note that for $x = 0$ (58) provides an expression for life expectancy at birth.

Proof. As the proof is very technical, we redirect readers to Missov and Lenart (2013, Appendix A.1., p.33–34). \square

Note that for $c = 0$ and $x = 0$ (58) is reduced to an expression for gamma-Gompertz life expectancy (Missov 2013)

$$e(0) = \frac{1}{bk} {}_2F_1 \left(k, 1; k + 1; 1 - \frac{a}{b\lambda} \right). \quad (60)$$

8. Conclusion

Unobserved heterogeneity should not be overlooked when fitting models to time-to-event data, as this might lead to dubious estimation results (Elbers and Ridder 1982; Heckman and Singer 1982). It can be captured by a random variable (frailty) that accounts for individual susceptibility. We presented a list of relationships, starting from the general setting, in which no assumptions about the baseline hazard or the frailty distribution were made. Then we derived a series of relationships which hold when we add, sequentially, one additional assumption at a time. First, we focused on multiplicative fixed-frailty models. Then we specified a parametric distribution for frailty (gamma), and, finally, we focused on particular parametric baseline hazards (Gompertz or Gompertz-Makeham). The relationships provide a link between the mortality schedule for individuals and the mortality schedule for the entire population, e.g., by comparing the conditional and the marginal distribution of deaths, as well as the rates of aging and mortality improvement for individuals and the population.

In this article we treat unobserved heterogeneity as a random variable that has an *independent* realization for each individual (Vaupel, Manton, and Stallard 1979). Times to event, however, might be dependent within certain subgroups, e.g. twin pairs, households, etc. Fixed-frailty models can be extended to capture such phenomena. Shared frailty models (introduced by Clayton 1978) are based on the assumption that a heterogeneous population is stratified, and all individuals within a cluster share the same frailty. Cluster-specific frailties are considered to be mutually independent. The relationships we present in this article hold for shared frailty models as well. One just has to bear in mind that “individuals” become “clusters”. Correlated frailty models (dating back to Aalen 1987; Marshall and Olkin 1988; Yashin, Vaupel, and Iachine 1995) treat dependencies more flexibly – individuals within a cluster do not necessarily share the same frailty, but their frailties are correlated. Frailties belonging to different clusters are assumed independent. An overview of shared and correlated frailty models is presented in Hougaard (2000); Duchateau and Janssen (2008) and Wienke (2010). Most relationships we present in this article do not hold for correlated frailty models as the relationships do not contain any terms capturing the correlation structure. They also would not hold in

multilevel frailty models (see Sastry 1997; Bolstad and Manga 2001; Manga 2001; Yau 2001), in which the study population is stratified at different levels. The correlation structure in such models is complex and only strong assumptions about it lead to meaningful relationships. Vaupel and Yashin (2006) briefly discuss the array of different kinds of frailty models, including changing-frailty models.

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Authors' contributions

This research project was initiated by JWV. A list of relationships was prepared by JWV. TIM added several relationships on life expectancy and all relationships involving the Laplace transform; he prepared all presented proofs. TIM wrote all drafts of the article, incorporating extensive comments from JWV.

Correction

The paper was updated on July 9, 2018 to include changes requested by the authors.

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Appendix

Table A.1: Functions used in the main text (column 1), corresponding standard probability theory notation (column 2), most commonly used name in the main text (column 3), and alternative names (column 4).

Function	Canonical Notation	Name	Alternative Names
$\mu(x, z)$	$\mu(x z)$	individual force of mortality	individual hazard (function) conditional force of mortality conditional hazard (function)
$\mu(x)$	$\mu(x 1)$	baseline force of mortality	baseline hazard (function)
$s(x, z)$	$s(x z)$	individual survival function	conditional survival function
$\pi(0, z)$		p.d.f. of frailty at initial age of analysis	p.d.f. of frailty at age 0
$\pi(x, z)$		p.d.f. of frailty at age x ($x > 0$)	p.d.f. of frailty among survivors to age x ($x > 0$)
$\bar{\mu}(x)$	$\int_0^{\infty} \mu(x z) \pi(x, z) dz$	population force of mortality	population hazard (function) aggregate population hazard marginal force of mortality marginal hazard (function)
$\bar{s}(x)$	$s(x)$	population survival function	marginal survival function
$\sigma_{\mu}^2(x)$	$\text{Var}\mu(x Z)$	variance of $\mu(x, z)$	
$\dot{\mu}(x)$	$\frac{d\mu(x 1)}{dx}$	age-derivative of baseline hazard	see entry for $\mu(x)$
$\dot{\bar{\mu}}(x)$	$\frac{d\bar{\mu}(x)}{dx}$	age-derivative of population hazard	see entry for $\bar{\mu}(x)$
$\bar{\dot{\mu}}(x)$	$\int_0^{\infty} \frac{d\mu(x, z)}{dx} \pi(x, z) dz$	average change in $\mu(x, z)$ at age x	
$\dot{\mu}(x)$	$\frac{1}{\mu(x 1)} \frac{d\mu(x 1)}{dx}$	relative derivative of baseline hazard	see entry for $\mu(x)$
$\dot{\bar{\mu}}(x)$	$\frac{1}{\bar{\mu}(x)} \frac{d\bar{\mu}(x)}{dx}$	relative derivative of population hazard	see entry for $\bar{\mu}(x)$
$\bar{b}(x)$	$\frac{1}{\bar{\mu}(x)} \frac{d\bar{\mu}(x)}{dx}$	rate of aging of a population	
$\bar{\rho}(x, y)$	$-\frac{1}{\bar{\mu}(x, y)} \frac{d\bar{\mu}(x, y)}{dy}$	rate of mortality improvement at age x in year y	

