

A Model for Antagonistic Pleiotropic Gene Action for Mortality and Advanced Age

Bruno Toupance,¹ Bernard Godelle,^{1,2} Pierre-Henri Gouyon,¹ and François Schächter³

¹Laboratoire Evolution et Systématique, Université Paris-Sud, Orsay, France; and ²Institut National Agronomique Paris-Grignon, and

³Laboratory of Human Genetics, Pasteur Institute, Paris

Summary

Association or linkage studies involving control and long-lived populations provide information on genes that influence longevity. However, the relationship between allele-specific differences in survival and the genetic structure of aging cohorts remains unclear. We model a heterogeneous cohort comprising several genotypes differing in age-specific mortality. In its most general form, without any specific assumption regarding the shape of mortality curves, the model permits derivation of a fundamental property underlying abrupt age-related changes in the composition of a cohort. The model is applied to sex-specific survival curves taken from period life tables, and Gompertz-Makeham mortality coefficients are calculated for the French population. Then, adjustments are performed under Gompertz-Makeham mortality functions for three genotypes composing a heterogeneous cohort, under the constraint of fitting the resultant mortality to the real French population mortality obtained from life tables. Multimodal curves and divergence after the 8th decade appear as recurrent features of the frequency trajectories. Finally, a fit to data previously obtained at the angiotensin-converting-enzyme locus is realized, explaining what had seemed to be paradoxical results—namely, that the frequency of a genotype known as a cardiovascular risk factor was increased in centenarians. Our results help explain the well-documented departure from Gompertz-Makeham mortality kinetics at older ages. The implications of our model are discussed in the context of known genetic effects on human longevity and age-related pathologies. Since antagonistic pleiotropy between early and late survival emerges as a general rule, extrapolating the effects measured for a gene in a particular age class to other ages could be misleading.

Introduction

Genetic influences on human longevity have been widely documented, and rapid progress in human genome mapping renders the project of trying to sort out these influences feasible (Schächter et al. 1993). Differential survival values of polymorphic genes must result in a reshaping, with age, of the genetic structure of any population, so that, after mortality selection, the population of “survivors,” whose genetic composition should provide information on genetic factors relevant to survival, remains. The Chronos collection of French centenarians currently includes >800 subjects who were ≥ 99 years of age when first recorded, therefore providing a useful population in which to search for genes associated with longevity.

Association studies to identify genetic components of longevity rely on a comparison between two age groups and ignore intervening dynamics. In contrast with diseases for which epidemiological features such as odds ratios or relative risks are calculated for restricted age classes, longevity is a quantitative trait that integrates all prior influences on survival. Demographic approaches, which emphasize the relationships between death rates and age classes for different populations at different periods, are therefore appropriate. Reconstruction of life tables from census data provides precise estimates of age-specific quantities such as survival, mortality, and life expectancy. These data generally ignore interindividual variability, except, usually, that of gender.

Known genetic risk factors for major age-related pathologies are obvious candidates for genetic components of longevity. With increasing age, such factors should progressively disappear from cohorts. However, since longevity is the net outcome of cumulative mortality over all age classes, this conclusion is not necessarily warranted for genes with age-specific effects. Indeed, a central feature of evolutionary theories of aging is antagonistic pleiotropy, meaning opposite effects of the same allele at different ages (Williams 1957). At the cohort level, genetic variation in survival potential is likely to have a greater impact on the genotypic composition of a cohort later in life, as the selection gradient becomes

Received November 11, 1997; accepted for publication April 2, 1998; electronically published May 15, 1998.

Address for correspondence and reprints: Dr. Bruno Toupance, Laboratoire Evolution et Systématique, CNRS-URA 2154, Bâtiment 362, Université Paris-Sud, 91405 Orsay Cedex, France. E-mail: Bruno.TOUPANCE@esv.u-psud.fr

© 1998 by The American Society of Human Genetics. All rights reserved.
0002-9297/98/6206-0032\$02.00

steeper because of increasing mortality. Our goal in this study is to provide mathematical support for this intuitive notion and to assess the relationship between mortality and age-dependent changes in the genetic composition of a heterogeneous cohort. We investigate a simple genetic model and show that general assumptions are sufficient to generate complex dynamics and antagonistic pleiotropy for mortality.

Methods

I. Basic Model

Consider a cohort composed of n different genotypes. Let N_{i0} be the number of individuals of genotype i at an initial age x_0 . The initial number of individuals in the cohort is $\bar{N}_0 = \sum N_{i0}$.

The survival function $s_i(x)$ of genotype i is the proportion of the initial N_{i0} individuals surviving at age x : $s_i(x) = N_i(x)/N_{i0}$, where $N_i(x)$ is the number of survivors of genotype i at age x . Similarly, the overall survival function of the cohort is $\bar{s}(x) = \bar{N}(x)/\bar{N}_0$, where $\bar{N}(x) = \sum N_i(x)$ is the total number of survivors at age x .

The initial structure of the cohort is defined by the proportion f_{i0} of each genotype i in the cohort at age x_0 : $f_{i0} = N_{i0}/\bar{N}_0$. Similarly, the frequency $f_i(x)$ of genotype i at age x is

$$f_i(x) = \frac{N_i(x)}{\bar{N}(x)} = f_{i0} \frac{s_i(x)}{\bar{s}(x)}. \quad (1)$$

Age-specific mortality associated with genotypes may be defined either as forces of mortality or as probabilities of death. The conditional probability of death for genotype i in the age interval $[x, x + h]$ ($h > 0$), given survival to age x , is

$${}_h q_{ix} = 1 - \frac{s_i(x+h)}{s_i(x)}, \quad (2)$$

which is usually denoted as “ q_{ix} ” for $h = 1$.

The force-of-mortality function of genotype i is an instantaneous measure of mortality at age x and is defined on the basis of equation (2):

$$\mu_i(x) = \lim_{h \rightarrow 0} \frac{{}_h q_{ix}}{h} = -\frac{d s_i(x)}{s_i(x) dx}. \quad (3)$$

We may notice that, unlike the force-of-mortality function $\mu_i(x)$, the conditional probability ${}_h q_{ix}$ is up-bounded by 1. When mortality is low, $\mu_i(x)$ is small and can be approximated by q_{ix} .

Integration of equation (3) yields

$$s_i(x) = \exp \left[- \int_{y=x_0}^x \mu_i(y) dy \right]. \quad (4)$$

The overall force-of-mortality function, age-specific probability of death, and survival function are the weighted means of the corresponding genotype-specific functions:

$$\bar{\mu}(x) = \sum f_i(x) \mu_i(x), \quad (5)$$

$$\bar{q}_x = \sum f_i(x) q_{ix}, \quad (6)$$

and

$$\bar{s}(x) = \sum f_{i0} s_i(x). \quad (7)$$

II. Variation of Genotypic Frequencies

Changes in the frequency trajectory of genotype i in the cohort are described by changes of the sign of the first derivative of $f_i(x)$. From equations (1), (3), (5), and (7), it is immediately clear that

$$\frac{d f_i(x)}{dx} = f_i(x) [\bar{\mu}(x) - \mu_i(x)] \quad (8)$$

or

$$\frac{d \log[f_i(x)]}{dx} = \bar{\mu}(x) - \mu_i(x),$$

which, when the frequencies of two genotypes, i and j , are compared, is also equivalent to

$$\begin{aligned} \frac{d \log \left[\frac{f_i(x)}{f_j(x)} \right]}{dx} &= \frac{d[\log[s_i(x)] - \log[s_j(x)]]}{dx} \\ &= \mu_j(x) - \mu_i(x). \end{aligned} \quad (9)$$

III. Age-Specific Mortality Data

Age-specific mortality data were obtained from the complete-period life tables for the French population in 1990–92 (INSEE 1993), which provide conditional probabilities of death, q_x , and survival functions, $s(x)$, for males, females, and the overall population, on a 1-year scale, for ages 0–100 years. For ages >100 years,

life tables from the Fondation Institut de Produits de Synthèse et d'Extraction Naturelle (Fondation IPSEN) survey (Allard et al. 1993) were used.

A heterogeneous cohort composed of males and females exhibiting these age-specific mortalities was built. The change, with age, of the frequencies of males and females (eq. [1]) was calculated by use of the survival-functions data, $s_i(x)$ for both sexes and with the assumption that the initial frequencies (f_{i0}) at birth ($x_0 = 0$ years) were .512 for males and .488 for females. The overall survival function was calculated from equation (7).

IV. Assumption of Gompertz-Makeham Model for Mortality

For a wide variety of human and animal populations, age-specific mortality after maturation is well modeled by the Gompertz-Makeham equation (Sacher 1977; Comfort 1979; Finch 1990; Gavrilov and Gavrilova 1991). Force-of-mortality functions may then be written as

$$\mu(x) = m + a \exp(\alpha x), \quad (10)$$

where m is the background mortality and a and α are two age-independent parameters corresponding, respectively, to the initial mortality and the exponential coefficient of mortality increase. This model accounts for the phenomenon of senescence in adults—that is, the acceleration of mortality, with age, after maturity.

With the notations previously introduced in the model of heterogeneous cohorts, equation (10) becomes

$$\mu_i(x) = m + a_i \exp(\alpha_i x), \quad (11)$$

where the index i denotes a given genotype. We assumed that the background mortality m was genotype independent. Integrating equation (11) into equation (4) yields

$$s_i(x) = \exp \left\{ \frac{a_i}{\alpha_i} [\exp(\alpha_i x_0) - \exp(\alpha_i x)] + m(x_0 - x) \right\}. \quad (12)$$

Within the framework of equation (11), different situations could be modeled, depending on the independence of the parameters for the genotypes. Equations with equal α_i and different a_i parameters resulted in parallel curves and constant relative risks between genotypes, meaning that genetic variation induced only differing initial mortalities and did not affect change, with age,

in mortality. Conversely, equations with equal a_i and different α_i parameters resulted in diverging curves and exponentially increasing relative risks among genotypes, meaning that initial mortalities were identical but that change in mortality with increasing age was genotype dependent. Both hypotheses were used to account for complex mortality patterns (Kowald and Kirkwood 1993; Vaupel and Carey 1993) but implied that the relative-risk status of genotypes remained qualitatively unchanged throughout life—that is, a genotype causing deleterious effects at some age caused the same or even worse effects later in life. More-interesting parameter sets are thus obtained when both a_i and α_i are allowed to differ among genotypes, accounting for the effects of antagonistic pleiotropy on survival.

V. Estimation of Gompertz-Makeham Parameters for French Mortality Data

Data on male, female, and overall-population age-specific mortalities in the French population in 1990–92 (Allard et al. 1993; INSEE 1993) were adjusted separately to the Gompertz-Makeham model (eq. [10]). In each case, the fittest set of parameters (a , α , and m) was found by a nonlinear fitting procedure based on the generalized-reduced-gradient (GRG) method, as implemented in GRG2 code (Lasdon et al. 1978). The algorithm minimized the sum of squares of the differences between logarithms of age-specific probabilities of death data ($q_{x\text{-data}}$) and the age-specific probabilities of death ($q_{x\text{-Gompertz-Makeham}}$) calculated from integration of equation (10): $\sum_{x=x_1}^{x_2} [\log(q_{x\text{-data}}) - \log(q_{x\text{-Gompertz-Makeham}})]^2$. The fit was performed for the age range of x_1 (age 20 years) to x_2 (either age 69 years or the maximum age available in life tables [age 109 years for women and the overall population and age 106 years for men]). Starting values of the parameters were obtained by the linear method, as described elsewhere (Gavrilov and Gavrilova 1991).

VI. Fit of a Heterogeneous Cohort's Mortality to Period Life Tables

The force-of-mortality functions and survival functions of three genotypes (AA , BB , and AB) at a biallelic locus were modeled according to the Gompertz-Makeham model (eqq. [11] and [12]). We assumed that the genotypic structure was in Hardy-Weinberg equilibrium at the initial age ($x_0 = 20$ years) and that the three sets of genotype-specific parameters (a_i and α_i) were independent, in order to allow for possible antagonistic effects on survival. Under these assumptions, the genotypic structure of the cohort at any age was completely determined by eight parameters: one initial allelic frequency, the genotype-independent background mortality parameter (m), and the three genotype-specific sets of

two parameters (a_i and α_i). The GRG method described above was used to find sets of these eight parameters that minimized the sum of squares of the differences between logarithms of the French-population age-specific probabilities of death data ($q_{x-\text{population data}}$) and the overall age-specific probabilities of death ($\bar{q}_x$), calculated from equation (6): $\sum_{x=x_1}^{x_2} [\log(q_{x-\text{population data}}) - \log(\bar{q}_x)]^2$, with $x_1 = 20$ years and $x_2 = 109$ years. Starting values of the seven parameters (m , a , and α) were set to the corresponding estimations (m , a , and α) obtained for the overall-population age-specific mortality data. Different starting initial allelic frequencies were used.

VII. Fit to Angiotensin-Converting Enzyme (ACE) Data

The fitting algorithm described above was used to obtain parameter sets in accordance with genotypic data reported for the insertion/deletion (*I/D*) polymorphism at the human *ACE* locus. Such adjustments were obtained by addition of two constraints in the fitting procedure:

1. The frequency trajectories of genotypes *II*, *DD*, and *ID* were constrained to make them compatible with genotypic frequencies observed in two age groups (Schächter et al. 1994): adults (20–70 years old) and centenarians. Because frequencies may vary dramatically across narrow age intervals, especially at advanced ages, the frequency of each genotype i in the modeled cohort, for a given age interval, was calculated by

$$f_{i0} \frac{\sum s_i(x)}{\sum \bar{s}(x)}, \quad (13)$$

where the sums were calculated for every 1-year age point in the age interval, according to equations (7) and (12). The age intervals were 20–69 years and 99–119 years for the adult and centenarian groups, respectively. A χ^2 distance between the observed genotypic numbers (Schächter et al. 1994) and the genotypic numbers calculated from equation (13) was derived. A maximum of this distance was set and used as a constraint in the fitting procedure.

2. The force-of-mortality functions were constrained to make them compatible with the odds ratios reported for the myocardial infarction risk during middle age (Tiret et al. 1993). In our model, the relative risks for death were calculated as the ratios of the forces of mortality at age 50 years: $RR_{DD/II} = \mu_{DD}(50)/\mu_{II}(50)$ and $RR_{ID/II} = \mu_{ID}(50)/\mu_{II}(50)$. In the fitting procedure, these values were bounded by the 95% confidence intervals reported for the respective odds ratios: 1.2–5.6 and 0.9–3.9 for *DD/II* and *ID/II*, respectively.

Results

Changes, with Age, in Composition of a Heterogeneous Cohort

The model developed in this paper considered a heterogeneous cohort composed of individuals that belong to defined groups—for example, relevant genotypes—differing in their susceptibility to death. Equation (1) shows that the genotypic structure of the cohort at any age could be deduced from the initial genotypic structure and the survival functions associated with each genotype and thus would be changed with age, as a result of different mortalities among genotypes.

Two important properties concerning the age-related dynamics of the cohort structure could be derived from equations (8) and (9). First, as long as the difference

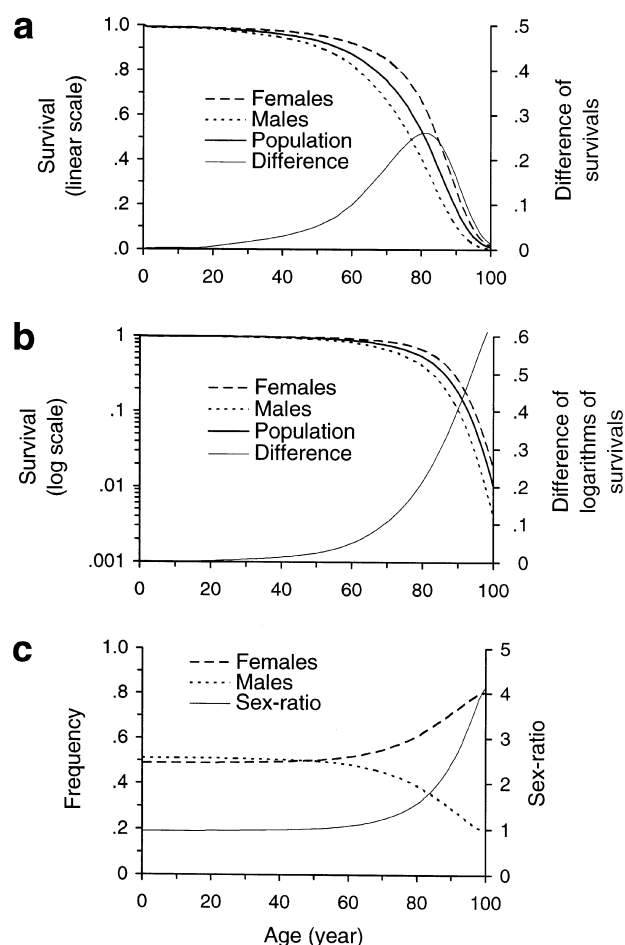


Figure 1 Survival curves from 1990–92 period French life tables, showing separately males, females and their difference (females minus males). *a*, Survival curves, linear scale. *b*, Survival curves, logarithmic scale. The difference is the difference of the logarithms of survivals. *c*, Sex-ratio (females / males) change and frequency trajectories of both sexes in the same cohort.

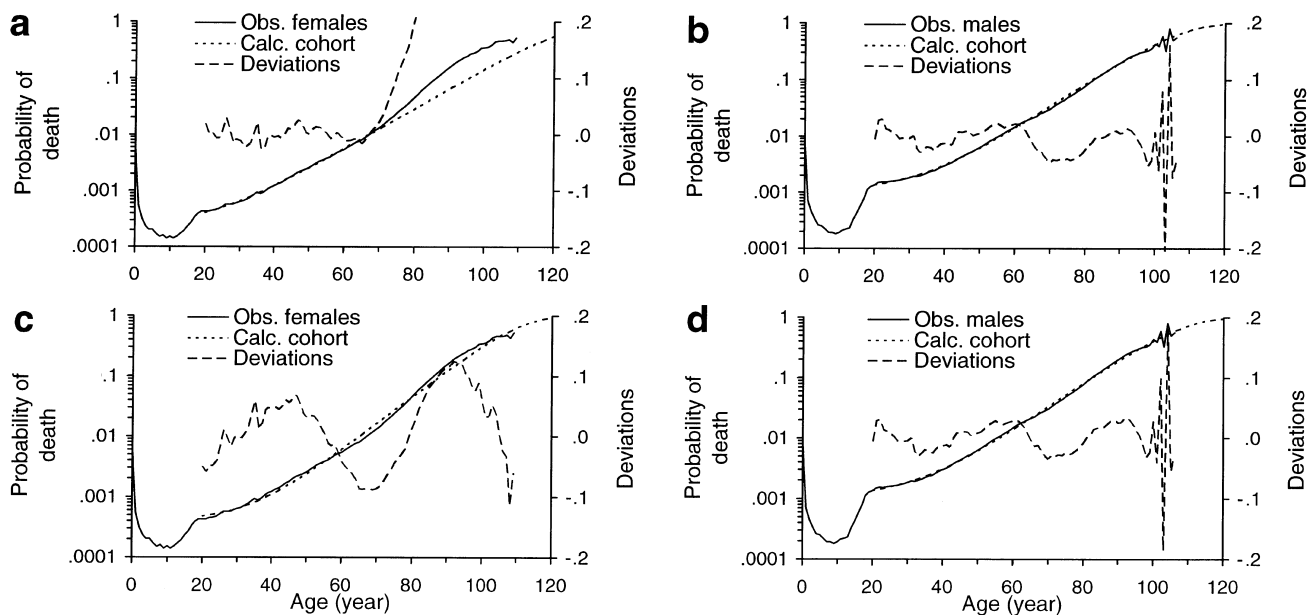


Figure 2 Adjustment of the 1990–92 French females and males age-specific mortality data to Gompertz-Makeham equations on differently fitting age ranges. Deviations between the observed and calculated curves are shown. *a*, Females fitting age range 20–69 years. *b*, Males fitting age range 20–69 years. *c*, Females fitting age range 20–109 years. *d*, Males fitting age range 20–106 years.

between the mortalities of two genotypes retained the same sign, the ratio of their frequencies was a monotonic function of age. This property of divergence meant that frequency ratios between any two genotypes increased or decreased steadily with age if their mortality functions did not intersect. The corollary of the first property was that an extremum of the ratio between frequencies was reached at the intersection point of the respective mortality curves. Similarly, an absolute extremum of the genotype frequency was reached when the genotype and the overall mortality curves intersected. Such points marked an inversion in the change in genotype frequencies. If this occurred more than once for one genotype relative to any other, its frequency exhibited a multimodal distribution with age. Equation (9) shows that the difference between logarithms of survival functions, rather than the difference between survival functions, was relevant to frequency dynamics, so that it was of interest to plot the curve of the former. This effect and the divergence property are illustrated by variation in the age-dependent sex ratio, as described below.

Age-Dependent Changes of the Sex Ratio

Figure 1 shows the survival curves extracted from the 1990–92-period life table for the French population (INSEE 1993), both on a linear scale (fig. 1*a*) and on a logarithmic scale (fig. 1*b*). The age-specific sex ratio in a cohort was calculated from equation (1), by use of the sex-specific survival-functions data. The sex ratio is a

monotonic function of age, with a very sharp increase at older ages (fig. 1*c*). At age 100 years, the ratio is $\sim 4:1$, whereas the true ratio in a population of centenarians is $\sim 7:1$ (Allard et al. 1993). This excess of women in the real population probably stems, however, from extrinsic causes—such as wars—that have decimated the male population and that were not taken into account in the 1990–92-period life table. The difference between female and male survival curves increased from birth, to a maximum at age ~ 80 years, and then decreased, whereas the difference between the logarithms of survival functions continued increasing until age ≥ 100 years. Variation in the sex ratio was greatest not when the difference between survivals was maximal but when the overall survival was lowest. Equation (1) illustrates this, showing that the frequency-ratio variation not only followed the same trend as long as the difference between the respective mortality functions had the same sign but also accelerated when this difference increased—which was likely to occur as forces of mortality increased sharply in the senescent-age range.

Gompertz-Makeham-Parameter Estimations for Age-Specific Mortality Data

The age-specific mortality data (q_x) for males, females, and the overall population were separately fitted to the Gompertz-Makeham model (eq. [10]). Adjustments were made for ages spanning the range from 20 years to either age 69 years or the maximum available age

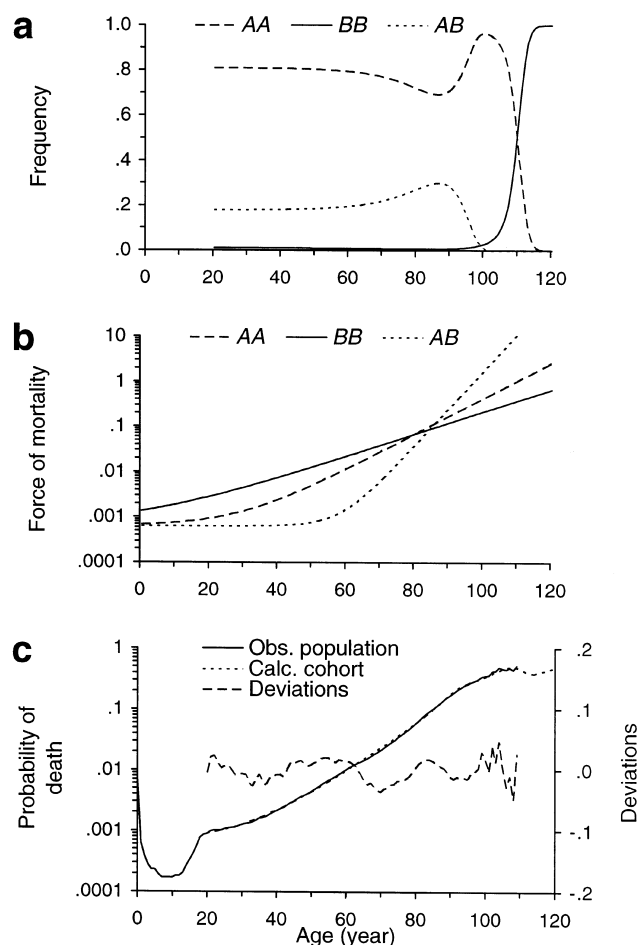


Figure 3 Change, with age, of the genotypic structure of an heterogeneous cohort composed of three genotypes—AA, AB, and BB—exhibiting Gompertz-Makeham mortality phenotypes. *a*, Frequency trajectories of the three genotypes. *b*, Force-of-mortality curves for the three genotypes AA, AB, and BB, modeled by Gompertz-Makeham equations (for values of parameters, see text). *c*, Calculated cohort-mortality curve, observed 1990–92 overall-population mortality data curve, and their difference, in logarithmic scale.

(age 106 years for men and age 109 years for women and the overall population). Figure 2 displays the observed and the adjusted Gompertz-Makeham curves for the two sexes, as well as their difference. The best-fitting sets of parameters were $m = 2.16 \times 10^{-4}$, $a = 3.44 \times 10^{-5}$, and $\alpha = .0836$, for females in the age range 20–69 years (fig. 2*a*); $m = 1.06 \times 10^{-3}$, $a = 4.58 \times 10^{-5}$, and $\alpha = .0936$, for males in the age range 20–69 years (fig. 2*b*); $m = 3.88 \times 10^{-4}$, $a = 1.06 \times 10^{-5}$, and $\alpha = .1038$, for females in the age range 20–109 years (fig. 2*c*); and $m = 1.05 \times 10^{-3}$, $a = 4.81 \times 10^{-5}$, and $\alpha = .0925$, for males in the age range 20–106 years (fig. 2*d*). It was possible to obtain a very good fit over the entire life span, while a characteristic pattern of difference between the observed and modeled mortality curves appeared for each sex. Women exhibited a definite increase

in the first derivative of $\log(q_x)$ during the 8th decade of life, corresponding to a “hump” in their logarithmic mortality curve, at age ~75–95 years, which was not seen in men. The erratic variation of the difference curve in men of age >100 years reflected sampling fluctuations that were due to the low number of available observations, the annual mortalities for centenarians being extracted from the Fondation IPSEN survey, which included only 97 males (Allard et al. 1993). Whereas parameters of the mortality function for men changed slightly with the age range, those for women changed markedly. The exponential coefficient and the initial mortality were most affected, with an increase in the former compensated by a decrease in the latter, account-

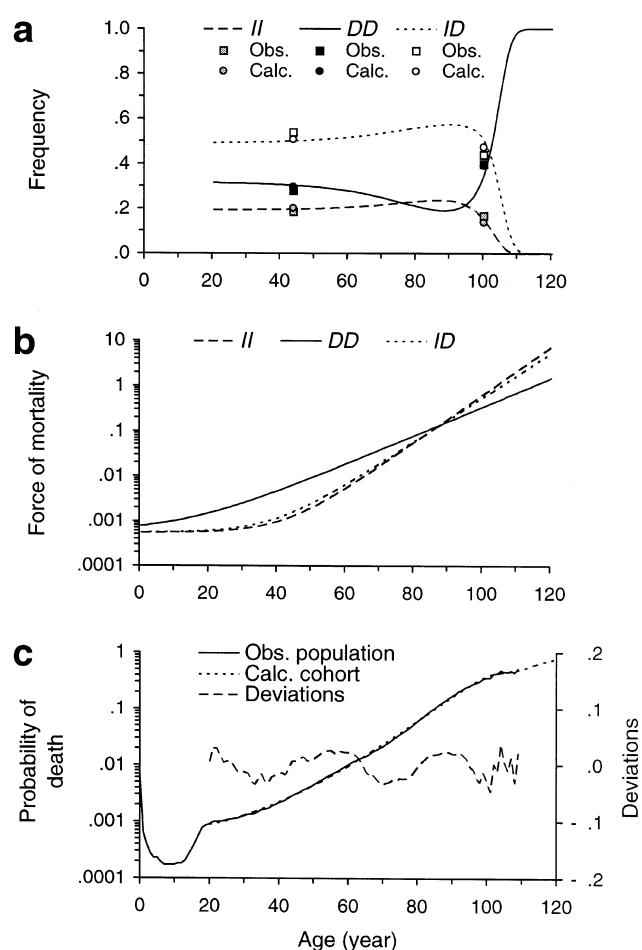


Figure 4 Fit of the genotypic data reported for the three genotypes—DD, II, and ID—at the ACE locus in two age groups (adult and centenarian), under Gompertz-Makeham equations for age-specific mortality. *a*, Frequency trajectories of genotypes DD, II, and ID. Squares and circles denote, respectively, the observed and calculated frequencies of the genotypes in the two age groups. *b*, Force-of-mortality curves for genotypes II, DD, and ID, modeled by Gompertz-Makeham equations (for values of parameters, see text). *c*, Calculated cohort-mortality curve, observed 1990–92 overall-population mortality curve, and their difference, in logarithmic scale.

ing for the mortality increase at age >70 years. As expected, the fitting procedure performed on mortalities of the overall population (curves not shown) yielded parameter estimations intermediate between those of males and those of females: $m = 6.39 \times 10^{-4}$, $a = 4.13 \times 10^{-5}$, and $\alpha = .0892$ in the age range 20–69 years and $m = 7.32 \times 10^{-4}$, $a = 2.94 \times 10^{-5}$, and $\alpha = .0948$ in the age range 20–109 years.

Simple Genetic-Heterogeneity Model

We then considered a hypothetical locus with two alleles *A* and *B* acting on survival capacities. Because of the lack of accurate genotype-specific survival-functions data, we assumed that the force-of-mortality functions of the three genotypes *AA*, *BB*, and *AB* conformed to Gompertz-Makeham equations (eq. [11]) and that $\mu_{AB}(x)$ was independent of $\mu_{AA}(x)$ and $\mu_{BB}(x)$, to allow for a possible change in dominance, with age, for the mortality phenotype.

Given the sole constraint that the initial distribution of genotypic frequencies at age 20 years was in Hardy-Weinberg equilibrium, the eight parameters of the model were numerically adjusted by minimization of the deviations between the observed French-population mortality curve and the resultant curve that the parameters generated. The exploration of parameter space yielded numerous sets of parameters compatible with mortality data, depending on the initial genetic structure. Figure 3 shows an example of such adjustment. In this case, the fitted values of the parameters were $f_{A0} = .894$ (initial frequency of allele *A* at age $x_0 = 20$ years), $m = 6.45 \times 10^{-4}$, $a_{AA} = 4.54 \times 10^{-5}$, $\alpha_{AA} = .0908$, $a_{BB} = 6.76 \times 10^{-4}$, $\alpha_{BB} = .0571$, $a_{AB} = 9.22 \times 10^{-9}$, and $\alpha_{AB} = .1890$. The composition of the three genotype-specific mortality functions resulted in an accurate fit to the real data, as shown in figure 3c. Frequency trajectories are shown in figure 3a: the frequency distribution remained stable until age ~70 years, changed smoothly at age 70–90 years, and thereafter underwent drastic changes. The initially rare *BB* genotype eventually invaded the population of late survivors. Genotype-specific mortality curves intersected at age ~85 years (fig. 3b). Many adjustments gave similar observations (data not shown): (1) trajectories of genotypic frequencies showed a succession of peaks, with, at most, two maxima, although more extrema were obtained when more genotypes per cohort were considered; (2) greater difference in genotype frequency became evident with increasing age, particularly at age >90 years; and (3) mortality curves for the different genotypes intersected at age 80–100 years.

Model Adjustment to ACE-Locus Data

ACE is a peptidase, cleaving, as its major substrates, angiotensin I and bradykinin, two peptides important in vascular-tone regulation (Cambien et al. 1994). There

exists in the *ACE* gene an *I/D* polymorphism, and the *D* allele appears to be a risk factor for coronary artery disease and myocardial infarction (Cambien et al. 1992). Furthermore, a codominant effect of the two alleles is observed with regard to this latter risk, as quantified by odds ratios: 2.6 for *DD* versus *II* and 1.9 for *ID* versus *II* (Tiret et al. 1993). Since circulatory diseases are a leading cause of death, especially at advanced ages, the frequency of *D* alleles should decrease in groups of increasing age. Surprisingly, the *D* allele and *DD* genotypes are more frequent in exceptionally long-lived individuals than in adult controls (Schächter et al. 1994). For adults in the 20–70-year age range, the odds ratios of becoming centenarian were 0.51 for *ID* versus *DD* and 0.90 for *ID* versus *II*, with respective 95% confidence intervals of 0.33–0.79 and 0.54–1.50. The heterozygous genotype thus had a lower survival probability from middle to very old age, compared with both homozygous genotypes, although the difference was not statistically significant.

The model presented above was used to fit the observed *ACE* genotypic frequencies in the adult group (age 20–70 years) and the centenarian group. Figure 4 shows the frequency trajectories and the age-specific mortality curves generated by the fittest set of parameters: $f_{I0} = .440$ (initial frequency of allele *I* at age $x_0 = 20$ years), $m = 5.46 \times 10^{-4}$, $a_{II} = 3.10 \times 10^{-6}$, $\alpha_{II} = .1215$, $a_{DD} = 2.10 \times 10^{-4}$, $\alpha_{DD} = .0735$, $a_{ID} = 6.52 \times 10^{-6}$, and $\alpha_{ID} = .1127$. The calculated relative risks of death at age 50 years were 4.6, for *DD* versus *II*, and 1.3, for *ID* versus *II*. These values are consistent with odds ratios for the risk of cardiovascular diseases (Tiret et al. 1993). The *DD* genotype had a higher initial mortality, accounting for its appearance as a risk factor for adults until their late 80s, when its mortality function intersected the others (fig. 4b). Thereafter, the *DD* genotype's frequency increased at the expense of the two others' (fig. 4a). As a result of potent mortality-driven selection operating among genotypes at very old ages, there was a marked reduction in the exponential increase of mortality at the cohort level (fig. 4c). The cohort curve converged toward the curve of the only remaining *DD* genotype and fitted the mortality data at advanced ages. The use of Gompertz-Makeham equations explained a very rapid increase in *DD* genotypes. A modified model, assuming linearly (rather than exponentially) increasing mortality at age >90 years, led, with similar optimization, to less dramatic changes at very old ages, although the qualitative effect remained the same (data not shown).

Discussion

By modeling how differential mortalities shape the genetic composition of an aging cohort, we have revealed striking properties. Our basic model of a heterogeneous

cohort subdivided into genotypes differing in their mortality functions showed the following: The ratio of any two genotypic frequencies is a monotonic function of age as long as the difference between their respective mortality functions retains the same sign. Furthermore, if these differences increase in absolute value, as was found for French males and females, then frequency variation accelerates with age. A frequency trajectory reaches an extremum and reverses only when the associated mortality curve intersects the global mortality curve. Therefore, dramatic changes in population structure may be expected as mortality increases as the population ages.

Our model employing genotype-specific mortality functions in Gompertz-Makeham form uses independent parameters, which allows mortality curves of different genotypes to cross, indicating the existence of antagonistic pleiotropy for survival. Most previous models of heterogeneous aging cohorts assumed that individuals are born with a given relative age-independent susceptibility to death, called “frailty” (Vaupel et al. 1979). Individual forces of mortality are proportional to a standard hazard function, and the relative effect of an individual genotype on survival acts in the same direction throughout life. Clearly, antagonistic pleiotropy for survival, at different ages, cannot occur in this framework. In contrast, a simple cohort of individuals with three genotypes at a biallelic locus *A/B* and having different mortality functions revealed striking features of age-dependent dynamics of genotype frequencies. First, genetic composition may undergo dramatic changes with age, such that a rare genotype rapidly becomes the most frequent at age >100 years, making it appear to be a “longevity genotype.” Second, age-dependent antagonistic pleiotropy for survival does occur when mortality curves intersect at an advanced age. We suggest that this intersection is the result of our fitting procedure using Gompertz-Makeham equations to model age-specific mortalities. The adult-mortality curve of the French population exhibits a triphasic shape: an initial phase, which can be accurately fitted by a unique Gompertz-Makeham equation for ages 20–70 years; a second phase of acceleration in the mortalities, which increases in the age range of 70–90 years; and a third phase, of deceleration, for ages >90 years. Sets of Gompertz-Makeham curves accounting for this pattern would then correspond to at least two crossing curves, one curve mainly accounting for the initial phase and one curve mainly accounting for the final phase. A modified mortality model, assuming linearly rather than exponentially increasing rates at age >90 years, yields similar adjustments. This tends to strengthen this result.

Antagonistic pleiotropy in evolutionary theory usually refers to opposite effects of a genotype on fecundity and survival (Rose 1985; Kirkwood and Rose 1991). The

existence of trade-offs between these two components of Darwinian fitness was proposed to explain the evolution of senescence and the maintenance, via the creation of a heterozygous advantage, of polymorphism at loci involved in the determination of both traits. In our model, antagonistic pleiotropy involves, instead, relative survival values of a genotype at different ages, as originally proposed by Williams (1957). However, given the very late ages at which mortality curves intersect in our examples, the antagonistic effects on survival are unlikely to contribute to the net fitness of genotypes, as a consequence of the neutrality of genetic effects expressed at advanced ages (Hamilton 1966; Charlesworth 1980). Because age-specific mortality at age <20 years cannot be modeled by Gompertz-Makeham equations, our model assumes that genotypes have identical probabilities of survival to this age. Furthermore, given that the genotype-independent background mortality is the major parameter determining the value of mortalities for young age classes and that mortalities are relatively low in the reproductive period, the genetic heterogeneity in mortalities is probably quasi-neutral with regard to natural selection.

In our model, antagonistic pleiotropy for survival is the result of crossing mortality functions conforming to Gompertz-Makeham equations. Analyses of life tables from many human populations reveal that age-specific mortality curves appear to converge to the same age, referred to as the “species-specific life span,” λ (Gavrilov and Gavrilova 1991). We suggest that λ , estimated as being 95 years for humans, represents a point of reversal, since any genotype that has an effect on survival prior to this age would exhibit the opposite effect after this age. This may provide an explanation for puzzling results for *HLA-DR*, in which, for some alleles, significant differences between nonagenarians and centenarians are found (Ivanova et al. 1998). Antagonistic pleiotropy for survival would thus be a general rule, although some exceptions, such as mutations causing early-onset diseases, certainly exist.

Most interestingly, this model accounts for data considered paradoxical, including the increased frequency of the “risk-associated” *ACE/DD* genotype in centenarians. This genotype is associated with common myocardial infarction, dilated cardiopathy, and sudden death (Marian et al. 1993; Schunkert et al. 1994). The latter phenotype, with hypertrophy of the left ventricle, mimics the natural state of very aged hearts (Hammond et al. 1971; Gunby 1995), suggesting that an age-related adaptation may occur that is favored by the *ACE/D* allele. Moreover, Chagas disease patients display similar features, and those who escape early death live longer than controls. Genotyping such patients, as well as elderly athletes who have also undergone intensive cardiac adaptation, could add support to the purported age-

related adaptive role of the *ACE/D* allele. This illustrates one example of antagonistic pleiotropy for survival. Changes in *APOE/4* allele frequencies in cohorts of different ages (Poirier et al. 1993), as well as varying frequencies of different *HLA* alleles in elderly populations (Proust et al. 1982; Takata et al. 1987), could also be interpreted in this light.

The range of Gompertz-Makeham parameters found in our adjustments may seem unrealistically large. However, even more extreme values have been proposed to fit complex mortalities (Kowald and Kirkwood 1993; Vaupel and Carey 1993). Furthermore, Gompertzian parameters exhibiting as much as a fourfold difference in exponential coefficient and as much as a one-order-of-magnitude difference in initial mortalities have been found for different genotypes in *Caenorhabditis elegans* (Johnson 1990). Human genetic conditions such as Down syndrome or muscular dystrophy have large effects on survival. Altogether, these data appear to support the existence of a genetic component to the rate of change of age-dependent mortality, rather than only to the susceptibility to age-related pathologies. This has been suggested for *Drosophila* (Hughes and Charlesworth 1994) and *C. elegans* (Johnson 1987; Kenyon et al. 1993). It may be argued that our knowledge of age-related pathologies in *D. melanogaster* or in *C. elegans* is yet very scant. Relevant to the thorny issue of distinguishing between hypothetical “intrinsic” aging and age-related pathology is the “compensation effect” described by Gavrilov and Gavrilova (1991), whereby mortality effects due to different diseases compensate for each other. Pathological causes of mortality in various populations appear to fall into categories interrelated by positive or negative correlations. Our model, per se, does not allow us to differentiate between mortality due to “aging” and that due to disease.

Whether the Gompertz law generally holds at very old ages is unclear, since several studies have found that mortality levels off toward the end of the life span (Carey et al. 1992; Curtsinger et al. 1992). Two reasons may explain this observation. First, after the turning point where mortality curves intersect, those genotypes with low mortality increase in frequency, thereby decreasing the resultant acceleration in mortality (Kowald and Kirkwood 1993; Vaupel and Carey 1993), as illustrated in figures 3c and 4c. Second, individuals may adapt to their own aging. Mortality functions result from the increase in individual vulnerability with advancing years, under the assumption that levels of environmental stress remain constant. However, aging persons may reduce environmental perturbations, by decreasing movement, food ingestion, etc. For example Jeanne Calment, who died in 1997 at age 123 years, was motionless and ate almost nothing in her last years, thus reducing her basal metabolism. This effect of adaptation to aging could

attenuate the differences in mortalities among genotypes, while also contributing to an overall reduction of mortality increase near the end of the life span.

Our model clearly shows that simple mathematical equations can generate complex changes in gene frequency over short age intervals near the end of life, which has consequences on the sampling strategy for studies of genetic factors influencing survival. This model may provide a bridge between demography and quantitative genetics, fields generally considered separate, allowing formulation of a comprehensive theory of aging (McClearn 1987, 1997). The widespread notions of “risk factor” and “relative risk” should be reappraised, with account being taken of their age dependence. Finally, antagonistic pleiotropy for survival, resulting from crossing mortality curves, suggests that, although the reverse has been widely assumed, the genetics of late survival may well shed light on the genetics of age-related pathologies.

Acknowledgments

We thank J. Shykoff and C. Finch for comments on the manuscript. This work has been funded by CNRS and Fondation Jean Dausset.

References

- Allard M, Vallin J, Andrieux J-M, Robine J-M (1993) In search of the secret of centenarians: a French demographic and medical survey about centenarians. Paper presented at the IUSSP Seminar on Health and Mortality Trends among Elderly Populations: Determinants and Implications, Senai City, Japan, June 21–25
- Cambien F, Costerousse O, Tired L, Poirier O, Lecerf L, Gonzalez MF, Evans A, et al (1994) Plasma level and gene polymorphism of angiotensin-converting enzyme in relation to myocardial infarction. *Circulation* 90:669–676
- Cambien F, Poirier O, Lecerf L, Evans A, Cambou JP, Arveiler D, Luc G, et al (1992) Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. *Nature* 359:641–644
- Carey JR, Liedo P, Orozco D, Vaupel JW (1992) Slowing of mortality rates at older ages in large medfly cohorts. *Science* 258:457–461
- Charlesworth B (1980) Evolution in age-structured populations. Cambridge University Press, Cambridge
- Comfort A (1979) The biology of senescence, 3d ed. Churchill Livingstone, Edinburgh, London
- Curtsinger JW, Fukui HH, Townsend DR, Vaupel JW (1992) Demography of genotypes: failure of the limited life-span paradigm in *Drosophila melanogaster*. *Science* 258:461–463
- Finch CE (1990) Longevity, senescence, and the genome. University of Chicago Press, Chicago, London
- Gavrilov LA, Gavrilova NS (1991) The biology of life-span: a quantitative approach. Harwood Academic, Chur, Switzerland
- Gunby P (1995) Aging heart adapts to change: researchers

- begin to unravel some mechanisms involved. JAMA 274: 597–598
- Hamilton WD (1966) The moulding of senescence by natural selection. J Theor Biol 12:12–45
- Hammond EC, Garfinkel L, Seidman H (1971) Longevity of parents and grandparents in relation to coronary heart disease and associated variables. Circulation 43:31–44
- Hughes KA, Charlesworth B (1994) A genetic analysis of senescence in *Drosophila*. Nature 367:64–66
- Institut National de la Statistique et des Etudes Economiques (1993) Annuaire statistique de la France: résultats de 1992. Vol 97. INSEE, Paris
- Ivanova R, Hénou N, Lepage V, Charron D, Vicaut E, Schächter F (1998) HLA-HR alleles display sex-dependent effects on survival and discriminate between individual and familial longevity. Hum Mol Genet 7:187–194
- Johnson TE (1987) Aging can be genetically dissected into component processes using long-lived lines of *Caenorhabditis elegans*. Proc Natl Acad Sci USA 84:3777–3781
- (1990) Increased life-span of *age-1* mutants in *Caenorhabditis elegans* and lower Gompertz rate of aging. Science 249:908–912
- Kenyon C, Chang J, Gensch E, Rudner A, Tabtiang R (1993) A *C. elegans* mutant that lives twice as long as wild type. Nature 366:461–464
- Kirkwood TBL, Rose MR (1991) Evolution of senescence: late survival sacrificed for reproduction. Philos Trans R Soc Lond B Biol Sci 332:15–24
- Kowald A, Kirkwood TB (1993) Explaining fruit fly longevity. Science 260:1664–1665
- Lasdon LS, Waren AD, Jain A, Ratner M (1978) Design and testing of a generalized reduced gradient code for nonlinear programming. Assoc Comput Machinery Trans Math Software 4:34–50
- Marian AJ, Yu QT, Workman R, Greve G, Roberts R (1993) Angiotensin-converting enzyme polymorphism in hypertrophic cardiomyopathy and sudden cardiac death. Lancet 342: 1085–1086
- McClearn GE (1987) The many genetics of aging. Basic Life Sci 42:135–144
- (1997) Prospects for quantitative trait locus methodology in gerontology. Exp Gerontol 32:49–54
- Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S (1993) Apolipoprotein E polymorphism and Alzheimer's disease. Lancet 342:697–699
- Proust J, Moulias R, Fumeron F, Bekkhoucha F, Busson M, Schmid M, Hors J (1982) HLA and longevity. Tissue Antigens 19:168–173
- Rose MR (1985) Life history evolution with antagonistic pleiotropy and overlapping generations. Theor Popul Biol 28: 342–358
- Sacher GA (1977) Life table modification and life prolongation. In: Finch CE, Hayflick L (eds) Handbook of the biology of aging, 1st ed. Van-Nostrand, New York, pp 582–638
- Schächter F, Cohen D, Kirkwood T (1993) Prospects for the genetics of human longevity. Hum Genet 91:519–526
- Schächter F, Faure-Delanef L, Guénot F, Rouger H, Froguel P, Lesueur-Ginot L, Cohen D (1994) Genetic associations with human longevity at the APOE and ACE loci. Nat Genet 6: 29–32
- Schunkert H, Hense HW, Holmer SR, Stender M, Perz S, Keil U, Lorell BH, et al (1994) Association between a deletion polymorphism of the angiotensin-converting-enzyme gene and left ventricular hypertrophy. N Engl J Med 330: 1634–1638
- Takata H, Suzuki M, Ishii T, Sekiguchi S, Iri H (1987) Influence of major histocompatibility complex region genes on human longevity among Okinawan-Japanese centenarians and nonagenarians. Lancet 2:824–826
- Tiret L, Kee F, Poirier O, Nicaud V, Lecerf L, Evans A, Cambou JP, et al (1993) Deletion polymorphism in angiotensin-converting enzyme gene associated with parental history of myocardial infarction. Lancet 341:991–992
- Vaupel JW, Carey JR (1993) Compositional interpretations of medfly mortality. Science 260:1666–1667
- Vaupel JW, Manton KG, Stallard E (1979) The impact of heterogeneity in individual frailty on the dynamics of mortality. Demography 16:439–454
- Williams GC (1957) Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398–411