size. The issue is not whether the error is inflated at the tail of the survivorship distribution, but whether the Gompertz model fits actual observations better than alternative models of mortality. We found that a two-stage Gompertz model, with almost no increase in mortality rate at older ages, fits the observed data significantly better than a simple single-stage Gompertz model (*2*). Model fits were obtained by maximum likelihood methods, which take into account differential sample sizes as the cohort ages. The simulations by Kowald and Kirkwood provide no information that lead us to question the value of maximum likelihood fitting of alternative models to mortality data. We did not say that we were estimating morality curves for individuals; our research (*1–3*) discusses the role of heterogeneity in producing non-Gompertzian mortality for cohorts. Furthermore, it is a misrepresentation of these reports to suggest that one addresses the sample size problem and the other addresses the heterogeneity problem; both consider heterogeneity, and the *Drosophila* study (*2*) was sufficiently large to discriminate among alternative models of mortality.

Robine and Ritchie suggest that medfly survival appears similar to that of prehistoric man or of people in India from 1921 to 1930. This type of comparison between the survival schedules of a human and a nonhuman population does not shed light on the nature of mortality at older ages because survival curves are poorly suited for summarizing mortality patterns, as we stated in (*1*). Death rates for humans continue to increase at advanced ages; death rates for medflies and *Drosophila* level off or decline. Moreover, the medfly system was not designed to serve as a miniature *replica* for humans (or any other species), but rather was used as a model biological *system* for addressing fundamental questions about the nature of mortality at older ages.

Robine and Ritchie state that medflies in cups and cells (*1*) and *Drosophila* had death rates similar to the theoretical Gompertz curve. This is incorrect: the death rates leveled off at older ages (*1, 2*). Such leveling off is inconsistent with a species-specific life-span limit. Robine and Ritchie dismiss the drop in mortality at the extreme tail of the mortality curve as being based on "the tiny proportion of aged survivors." However, one of the main purposes of the medfly study was to examine the tail which, by definition, is some small fraction of the initial number. This "tiny proportion" consisted of over 2000 medflies contained in 156 cages (an average of 16 flies per cage for cages in which some medflies were still alive). That this number is a small proportion of the total starting number is irrelevant.

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Compositional Interpretations of Medfly Mortality

Death rates for a cohort of 1.2 million Mediterranean fruit flies (*Ceratitis capitata*) rose and then fell with age (Fig. 1) (*1*). If this pattern reflects age changes for individuals, biological theories of aging may have to be rethought (*2*). On the other hand, the age trajectory may be an artifact of the evolving structure of the population (*3*). Death changes the composition of a cohort by differentially removing the frail. It is possible that the age trajectory of mortality for medflies at any specific degree of frailty actually rises steadily with age.

We have closely fitted the observed medfly mortality pattern (*1*) with mixtures of increasing Gompertz (*4*) or Weibull (*5*) curves. Let $\bar{s}(x)$ denote the proportion of a cohort that survives to exact age x, where $\bar{s}(0) = 1$, and where the cohort is extinct or no longer observed at age ω. Assume that the hazard of death at age x for individuals with fixed frailty z is given by $\mu(x, z)$. If $s(x, z)$ denotes the proportion of individuals with frailty z who survive to exact age x, then

$$s(x, z) = e^{-\int_0^x \mu(t,z)dt} \quad (1)$$

Assume that frailty can be described by an n-point discrete distribution with probabilities $p(z)$. Then

$$\bar{s} = sp \quad (2)$$

where $\bar{s}$ is an ω-element column vector, s is an n-by-ω matrix, and p is an n-element column vector.

If a hazard function μ and vectors z and p are specified, then estimated values of $\bar{s}$ can be calculated, using a formula similar to Eq. 2, by letting s be the matrix of elements $s(x, z)$ as defined by μ and by the values of z, as indicated in Eq. 1. An optimization algorithm can be used to estimate the vectors z and p that minimizes the discrepancy between the actual and estimated survivorship vectors.

To model the age-trajectory of medfly mortality, assume that

$$\mu(x, z) = z\mu^0(x) \quad (3)$$

where μ^0 is the baseline hazard function. This proportional-hazards specification is widely used in survival analysis (*6*). More specifically, assume that the baseline hazard function in Eq. 3 is a Gompertz curve, where

$$\mu^0(x) = 0.003e^{0.3x} \quad (4)$$

The proportion of the initial population of 1,203,646 flies that survived to day $x = 1$ to 121 defines the vector $\bar{s}$. (Deaths were not

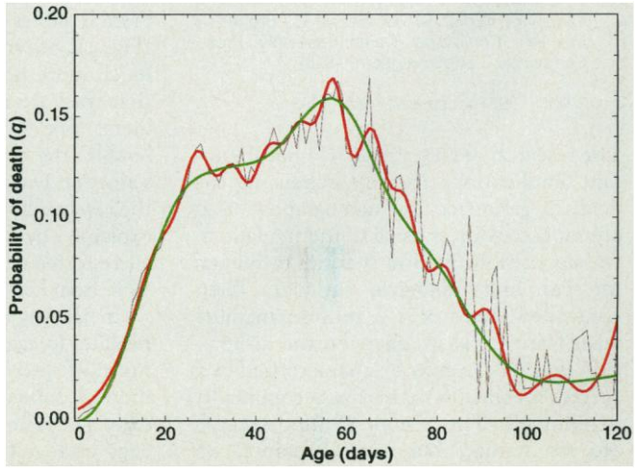

Fig. 1. Daily probability of death for a cohort of 1.2 million medflies. The thin line traces the observed trajectory of death rates. The red line was calculated with the use of the Gompertz model described in the text. The green line was calculated with the use of the Weibull model described in the text.

Table 1. Values of frailty z and proportions p of flies at each level of frailty for the Gompertz and Weibull models described in the text.

Gompertz model		Weibull model	
z	p	z	p
3.7	0.41	5.2	0.47
0.75	0.38	2.2	0.39
0.17	0.13	0.74	0.14
0.03	0.046	0.24	0.0039
0.0093	0.020	0.016	0.00010
0.0020	0.0082		
0.00036	0.0017		
0.000074	0.00046		
0.000011	0.00013		
0.0000014	0.000053		
0.000000058	0.000013		
0.00000000073	0.000043		

counted on day 0, the day of emergence, and after day 121, when only 37 flies were still alive, death rates swing erratically between 0 and much bigger values, producing a noisy pattern.) Experiments with different numbers of subpopulations suggested that 12 groups were sufficient to capture the observed pattern of mortality (Fig. 1 and Table 1).

Other parameters can be used in the Gompertz function specified in Eq. 4 to give fits that are as close or closer than the fit shown in Fig. 1. If the Gompertz slope parameter is big enough, the values of the vector of frailty z will be so dispersed that a fly's frailty will, in effect, be sufficient to predict the fly's life-span to the day. Then, if the number of subpopulations equals the number of days of observation, the empirical curve can be precisely duplicated by the model.

Instead of using the Gompertz hazard described above, one can use a Weibull hazard. With the quadratic model

$$\mu^0(x) = 0.001x^2 \qquad (5)$$

for instance, one can approximate the observed medfly mortality trajectory using five subpopulations (Fig. 1 and Table 1): a frail group that constitutes almost half the population; a normal group that represents just under two-fifths of the population; a robust group of 14% of the population; and two small, very robust groups. The life expectancy of the frail group is 16 days whereas the life expectancy of the most robust group is 110 days. By day 100, virtually all of the frail and normal flies are dead as are most of the two somewhat robust groups. For the exceptionally robust group, however, the chance of surviving to day 100 is almost 60%. This group, which contains only a ten-thousandth of the initial population, constitutes 96% of those still alive on day 100.

Radically different accounts of individual aging and mortality are consistent with observed population death rates: the population can be assumed to be homogeneous, with the chance of death for each individual given by the population death rate; or all individuals can be assumed to have been born with a predetermined life-span. Population death rates in the latter account merely reflect the distribution of allotted life-spans. To move beyond such unlikely extreme explanations, further information and knowledge are required to supplement ordinary survival data (*7*). If a model is appropriately restricted, the age trajectory of mortality and the distribution of frailty can be uniquely identified (*8*). The restrictions, however, are severe, and substantial knowledge of underlying mortality and heterogeneity patterns would be required to justify them.

Researchers should be cautious when drawing conclusions about individual aging from population death rates. Although it has been known at least since Halley's work in the 17th century (*9*) that changes in population composition can affect population death rates, countless researchers have leapt from population data to conclusions about individual trajectories of aging (*10*). Any change in a population statistic may be a result of individual or compositional change (*3*). Our method of calculating frailty distributions provides an engine for generating concrete compositional counterexamples to any direct attribution of observed changes in population hazard rates over age, time, or duration (*11*) to corresponding changes in the characteristics of individuals.

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10. Gompertz, for instance, inferred the pattern of "a man's" aging from data about human populations. Observing a roughly exponential increase in adult mortality. Gompertz surmised that "the average exhaustions of a man's power to avoid death were such that at the end of equal infinitely small intervals of time, he lost equal portions of his remaining power to oppose destruction" [(*4*), p. 281].
11. Deeper understanding of the importance of direct as opposed to compositional explanations hinges on progress in describing individual trajectories of hazard rates and the degree of population heterogeneity. Analyses of how death rates change under different environmental conditions and following mortality shocks may be helpful. A. D. Foster, *Demography* **28**, 619 (1992); J. W. Vaupel, A. I. Yashin, K. G. Manton, *Math. Pop. Stud.* 1(2), 21 (1988).
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