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Letter to the Editor

Rules of evidence for models on trial

In a recent paper de Grey (2003a) raises several questions concerning our analysis of mortality data and its implications for theories of mortality plateaus (Mueller et al., 2003). In our paper we examined the ability of variants of the Gompertz equation to explain the leveling of mortality rates (plateaus) that are observed at advanced ages in laboratory populations of *Drosophila melanogaster*. In particular, Mueller et al. (2003) used a model, called the heterogeneity-in-α model, in which the age-dependent parameter of the Gompertz equation is assumed to vary randomly within a population. We concluded from our analysis that the heterogeneity-in-α model predicts many more long-lived individuals than are actually observed and thus the model fails predictively. From this failure, we suggested that other models should be considered for late life. The major thrust of de Grey's suggestion is that by using different techniques for fitting this model, different conclusions could be reached, including a better fit to actual data. We comment on the details of de Grey's arguments below.

(1) We first note that the model used by de Grey (2003a) bears no resemblance to the model we examined in Mueller et al. (2003). The standard form of the Gompertz equation sets the instantaneous mortality of an individual aged x to, $A\exp(\alpha x)$. In the heterogeneity-in-α model, the parameter α is assumed to have a gamma distribution. In the model used by de Grey, the natural log of α is assumed to have a binomial distribution (de Grey, 2003b). Furthermore, his actual fitting algorithm assumes that for any particular value of α the chance of dying between ages $x - 1$ and x is equal to, $A\exp(\alpha x)$. But the correct probability of dying between ages $x - 1$ and x, according to the Gompertz equation (Mueller et al., 1995), is

$$1 - \exp\left\{ \frac{A\exp(\alpha x)(1 - \exp(\alpha))}{\alpha} \right\}$$

The practical implication of de Grey's erroneous formulation of the Gompertz probabilities is that the estimates of the parameters A and α obtained by de Grey will not be related to our model, nor will they be related to any known variant of the Gompertz equation. For example, after pooling our results for the ACO females, the estimated values of A and α for the heterogeneity-in-α model in the ACO females are 0.0062 and 0.11, respectively. The estimates obtained by de Grey were 0.015 and 3.6. This is

just one example of the many discordances between de Grey's model and a heterogeneous Gompertz model.

(2) Nevertheless, we will consider whether the statistical points made by de Grey have any value, even though the particular model he used bears little resemblance to the models we and others (e.g. Pletcher and Curtsinger, 2000) have used. de Grey argues that since mortality plateaus happen late in life, we should focus our attention only on these age-classes. Ultimately de Grey accomplishes this focus through his goodness of fit measure, which we discuss in (4) below. However, for now we simply point out that we reject this idea. The Gompertz model under consideration is used to predict rates of mortality at all adult ages. Thus, one should use data from the entire adult life span to fit these models since they must be able to predict mortality at all adult ages. It is obvious that arbitrarily fitting a model to a subset of ages will give different estimates of model parameters. When this subset is chosen post hoc, then a considerable improvement in the fit of the model to the data *for this subset* should be possible.

(3) In Mueller et al. (2003), maximum likelihood techniques are used to estimate the three parameters of the heterogeneity-in-α model. The maximum likelihood techniques rely on the number of deaths in each census period to estimate model parameters. With those estimates in hand, we then used computer simulations to estimate the chance of surviving to any particular age. We needed to resort to computer simulations because the heterogeneity-in-α model assumes random variation in the age-dependent parameter of the Gompertz. The complicated manner in which this random variable enters the Gompertz equation prevents us from finding a closed form solution for the chance of surviving to a particular age, though this can be done with the standard Gompertz equation. These simulations then let us predict the chance of surviving to particular ages. These results were presented in our Fig. 7 (Mueller et al., 2003). We should emphasize that the probability of surviving to a particular age or greater is a prediction of the heterogeneity-in-α model but this statistic was not used by us to estimate the model parameters.

(4) de Grey rejects the use of maximum likelihood techniques for reasons that are not clearly articulated. In any case, he chooses to use regression techniques that minimize the absolute difference between the observed age-specific survival rates and the model's predicted rates. As we pointed out in point (1) above, de Grey does not actually use the Gompertz model and ultimately fits the parameters of his

model to the probabilities of surviving to a particular age directly. The method used by de Grey to estimate model parameters minimizes the sum of the absolute value of the differences between the observed chance of surviving to any age and the model prediction. The function to be minimized is presented in an earlier paper by de Grey (2003b, Eq. (3)). This function gives equal weight to each age class. However, the units of observation in these experiments are individuals. There are many more individuals dying at middle ages than at a very young or a very old age, thus we have better information at the middle ages. de Grey's procedure will give different model estimates from ours, because the weighting of the observations is quite different. de Grey's procedure will tend to give more weight to the advanced ages when there are very few individuals left alive. Thus, de Grey's presentation of a model that fits the advanced ages better is by and large a consequence of fitting parameters to age-classes, not his choice of underlying model. In fact when survival probabilities follow a multinomial distribution, Mueller et al. (1995) showed that maximum likelihood was superior to least squares regression for estimating Gompertz parameters.

(5) de Grey's final conclusion that the heterogeneity model doesn't appear all that bad is based on an eye-ball test that is the visual assessment of the predicted curves and observations. In our original paper (Mueller et al., 2003), we display the raw data and the fitted model, and then go on to objectively determine if the model adequately predicts the number of very long-lived flies (see Table 3, Mueller et al., 2003). A formal assessment of these complicated models cannot rely on subjective observations of the goodness of fit. If that were appropriate then our best models would always be interpolating polynomials.

(6) de Grey's rejection of maximum likelihood and his choice of regression techniques suggest that the statistical analysis of data is a free-for-all in which we should disregard well-established techniques. Sometimes this will be harmless, because different estimation procedures will give the same results. For linear models, for example, it is well known that when errors are normally distributed least-squares parameter estimates are the same as maximum likelihood estimates. But some nonlinear models will not have this property, making haphazard analytical choices risky.

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