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Authors' Response to Commentaries on "Two-Parameter Logistic and Weibull Equations Provide Better Fits to Survival Data From Isogenic Populations of *Caenorhabditis elegans* in Axenic Culture Than Does the Gompertz Model"

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ALTHOUGH the classical Gompertz model has been the standard for over a century, recent research has shown definitely that this model often fails to predict survival at old ages. Also our analyses reported in this article showed that the Weibull and 2-parameter (2-p) logistic functions provide better fits to the extremes of the survival curves of *C. elegans* in axenic cultue (1). As a commentator argues, individual differences in the Gompertz dynamics of aging processes can generate a 2-p logistic survival curve for the entire population. The biological interpretation is obvious in the case of genetically heterogenous populations. For strict isogenic populations such as *C. elegans,* the presumed heterogeneity would be restricted to non-genetic innate or acquired differences. This problem is hardly amenable to experimental analysis. We are aware, however, that our pooling of data in Figure 2 of our article may have inflated the fitting ability of the 2-p logistic. The use of a single, very large cohort would alleviate the need of pooling data to increase the population size, but is technically not possible, because life expectancy of this worm decreases as population density increases. Still, we have monitored survival of a cohort of approximately 92,500 worms cultured in 75 ml (3 tissue culture flasks of 75 cm^2, each containing 25 ml) of axenic medium, because the decrease of life expectancy is small as long as population density does not exceed 1,500 worms/ml. This experiment also necessitated the addition of autoclaved *E. coli* cells to avoid dauer formation and to support a more uniform developmental rate. Proper synchronization of juvenile growth is needed because FUdR (added to prevent reproduction) must be added shortly before maturation to minimize possible side effects on larval development. Both effects of increased population density and improved culture conditions (the standard axenic culture medium lacking *E. coli* cells is generally thought to impose calorie restriction) tend to decrease life span. Mean life span measured for this cohort was 25.8 days, i.e., a reduction by approximately 15–20% relative to standard axenic culture conditions.

The survival curve for this cohort is shown in Figure 1. Of the 2-p models, the Weibull function provides the best fit to the data. The classical Gompertz fails to fit the tail of the curve, and the 2-p logistic and the Gompertz growth model (2) fail at both ends of the curve. Whereas the classical Gompertz and Weibull equations produce competitive fits for over 95% of the population, the logarithm of the mortality rates fails to increase linearly with age (see Figure 1, insert). Between the ages of 29 and 38 days, the number of surviving worms declines from 7,841 to 464, a decline large enough for deriving reliable death rates. Logically, statistical fluctuation becomes very important as the cohort approaches extinction.

In this particular experiment, the Weibull function was a better descriptor for survival than the 2-p logistic. We cannot conclude from this and our former experiments which model, Weibull or 2-p logistic, describes the dynamics of aging of *C. elegans* in axenic culture more accurately. First, this is a single experiment, and second, we do not know what the impact of changing the standard axenic medium might be. In this respect, we concur with the commentary that environmental conditions may change the shape of survival curves. We have indeed used axenic culture conditions to reduce environmental differences attempting to focus on the intrinsic dynamics of senescence.

It should be stressed that the survival of short- and long-lived mutant strains of *C. elegans* could be predicted using both Weibull (not shown in our article) and 2-p logistic models by only varying the parameter that controls life span midpoint, whereas the classical Gompertz model requires adjustment of both parameters.

We conclude that there are two competing 2-p equations that give relatively good fits to survival curves of *C. elegans* in axenic culture. Three or more parameter equations may perform slightly better, but the task of intepreting the curve parameters in terms of the dynamics of biological senescence increases accordingly. As outlined by the commentators, the Weibull hazard process and the Gompertz growth model imply a slowing of mortality due to changes

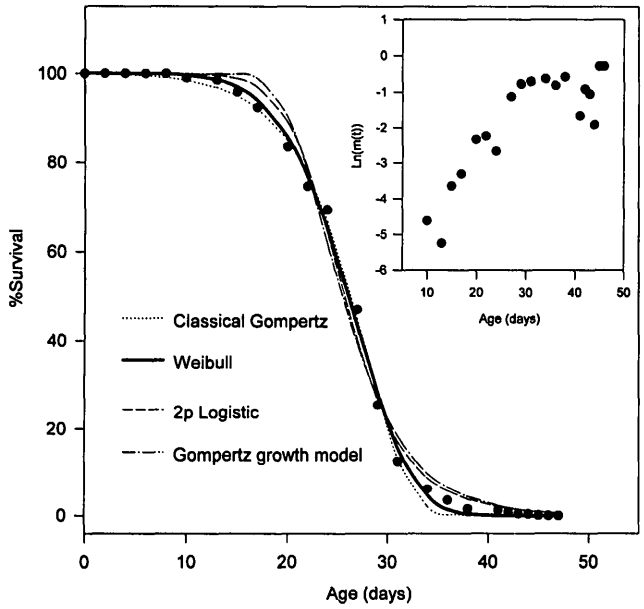

Figure 1. Survival curve.

in the aging process, whereas the logistic assumes mortality selection of individuals from a fixed risk distribution. This is conceptually quite different, and it would be most rewarding knowing the precise dynamics of the worms' senescence in tightly controlled and subtly altered culture conditions. For example, if the final outcome were that the Weibull hazard function accurately describes aging of *C. elegans* in axenic culture when environmental influence is minimized, it would mean that this organism essentially senesces as machines do. The genetic program that determines life span would then not specify the aging process (in this concept a mere stochastic, thermodynamic process) itself, but only the potential to resist wear and tear, such as degenerative changes resulting from accumulating oxidative damage. This task is not easy; the aim is perhaps illusive. Even so, the simple worm *C. elegans* offers many advantages for experimental and genetic analysis of longevity and, although there is no a priori reason why this should be so, we do hope that better knowledge of life-span determination and senescence in this organism may help researchers to understand general principles of aging in more evolved animals, including humans.

References

1. Vanfleteren JR, De Vreese A, Braeckman BP. Two-parameter logistic and Weibull equations provide better fits to survival data from isogenic populations of *Caenorhabditis elegans* in axenic culture than does the Gompertz model. *J Gerontol Biol Sci.* 1998;53A:B393–B403.
2. Easton DM. Gompertz survival kinetics: fall in number alive or growth in number dead? *Theor Popul Biol.* 1995;481:1–6.