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Letter

Statistical kinetic approach for modeling lifespan

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Abstract

Lifespan regulation through gene expression involves complex biochemical processes. Unfortunately, current mathematical models for treating lifespan data afford little insight into the mechanisms that control longevity. In this work, we demonstrate the use of a novel kinetic model to successfully fit the lifespan curves of the nematode, *Caenorhabditis elegans*. Our findings show that population aging may be treated analogously to a dispersive chemical process [P.J. Skrdla, R.T. Robertson, J. Phys. Chem. B 109 10611 (2005)]. Much like the Gompertz model, only two fit parameters, α and β, are needed to adequately describe the entire data set for each nematode population. These parameters relate a 'global first-order time constant' and a 'global second-order rate constant', with units of (time) and $(\text{time})^{-2}$, respectively. In *C. elegans*, the increased longevity resulting from DAF-16 (a transcription factor) activity in the intestinal tissue correlates with a larger α value and a smaller β value; the opposite is true for animals with shorter lifespans. A basic physical interpretation of the two parameters is provided.

Keywords: Statistical; Dispersive; Kinetic model; Longevity; Lifespan; *Caenorhabditis elegans*; Acceleratory reaction; Gompertz Survival; Mortality

In the realm of studies aimed at determining the genetic origins of lifespan regulation, the insulin/IGF-1 (insulin-like growth factor 1) pathway has recently been found to control longevity in various species, including mammals [1]. For example, coupling mutations that inhibit insulin/IFG-1 signaling with removal of the germline precursor cells in the nematode *Caenorhabditis elegans* can dramatically extend the lifespan of the animal [2].

Kenyon et al. reported that the transcription factor, DAF-16, can promote longevity in *C. elegans* in response to germline ablation or reduced insulin/IGF-1 signaling [3]. In their work, various tissues were tested for their activity toward DAF-16 in determining the lifespan of the animal. Data showing the effects of DAF-16 activity on the lifespan of *daf-16(–); daf-2(–)* germline-defective mutants, in the intestinal tissue (also the animal's adipose tissue), is reproduced in Fig. 1. The data shows that DAF-16 activity in the intestine is sufficient to extend the lifespan of these mutants by 50–60%.

However, Kenyon et al. also report that it is likely "an intricate network of feedback regulation and cross-communication in different tissues that may coordinate the expression of downstream longevity genes, thus specifying the animal's aging rate as a whole" [3]. We believe that very simple kinetic models or phenomenological (i.e. empirical) mathematical treatments of aging kinetics do not help in our understanding of these complex processes. The importance of developing an accurate, stochastic or semi-empirical model to treat lifespan data is three-fold: (1) the use of half-life, which has been widely employed to date for this purpose, relies entirely on a single data point from plots of fraction alive vs. age, thus it disregards other potentially valuable information contained within these curves (in the author's opinion, the use of half-life should be limited to the treatment of simple exponential decays and should not be used for the characterization of often complex, asymmetric sigmoids), (2) a stochastic/semi-empirical model for aging may provide a physical basis for the origin of the aging process, which cannot be obtained from a phenomenological model and (3) provided an adequate database for calibration, a general 'aging model' can allow one to

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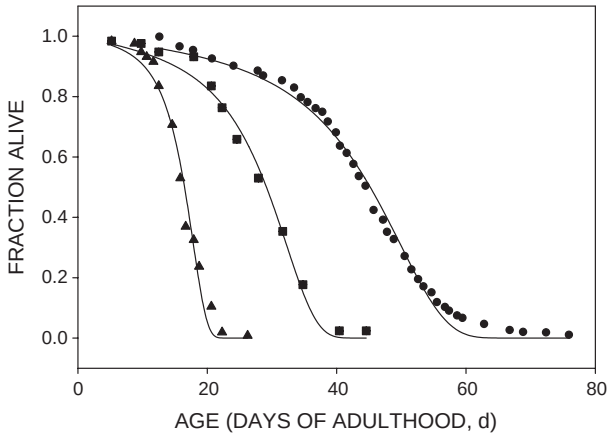

Fig. 1. Effect of intestine (Pges-1) DAF-16 activity on the *C. elegans* lifespans of *daf-16(mu86)*; *daf-2(e1370)* mutants (data taken from Ref. [3]). Intestinal DAF-16 increases *daf-16(mu86)*; *daf-2(e1370)* lifespan by 50–60%: ▲ *daf-16;daf-2-S*, ■ *daf-16;daf-2, Ex285*, ● *daf-2* (see Ref. [3] for details). The solid lines represent regression fits of Eq. (1) to the data points. For ▲: $R^2=0.982$, $\gamma=0.39\pm0.13$ d and $\beta=(1.25\pm0.11)\times10^{-2}$ d^{-2}, ■: $R^2=0.992$, $\gamma=1.5\pm0.3$ d and $\beta=(3.1\pm0.2)\times10^{-3}$ d^{-2}, and ●: $R^2=0.994$, $\gamma=2.21\pm0.19$ d and $\beta=(1.33\pm0.04)\times10^{-3}$ d^{-2}.

accurately predict the longevity of a given population (i.e. wild type or mutant). In this work, we propose a new treatment of aging kinetics, which finds origin in our previous treatment of dispersive or 'statistical' chemical kinetics [4].

In classical chemical kinetics (i.e. disregarding the phenomenon of tunneling), the activation energy represents an energy barrier which the reagent molecules must overcome in order for a given reaction to occur. The Arrhenius equation, which dates back to the late 19th century (yet it is still widely employed today), assumes that all of the reagent molecules react with a single activation energy, ε_a. However, this is not a valid assumption in cases where molecular dynamics (i.e. differences in pathlength, speed and trajectory between individual reagent molecules) create dispersion in ε_a. If a given reaction occurs on a time-scale that is comparable to, or shorter than, that of the internal mixing of reagent molecules, then such dispersion is observed. Dispersion in ε_a gives rise to a *distribution of activation energies* for the reagent molecules, which manifests itself as a time-dependence in the rate constant for the process [4,5]. This time-dependent rate constant typically produces sigmoidal concentration-time ($x-t$) transients for various chemical conversions. Quite recently, dispersive kinetic approaches have been developed to treat complex systems [e.g. [5]]. Our 'statistical kinetic' approach represents a new treatment of dispersive kinetics, in which we specify explicitly that the ε_a distribution for a given chemical system has the functional form of a Maxwell–Boltzmann (M–B) distribution [4]. Doing so allows one to *quantize the activation energy barrier*, on the basis of translational molecular motion (i.e. we believe that it is important to consider the gain or loss in entropy—depending on whether the observed kinetics are generally deceleratory or acceleratory in nature—that is associated with each reagent molecule in an ensemble as it transitions over the activation energy barrier) [6]. Our goal here is to show that our statistical kinetic approach may be valid for modeling a complex biological phenomenon, aging, in addition to modeling dispersive chemical reactions and phase transformations.

Typical longevity curves for *C. elegans*, extracted from Ref. [3], are shown in Fig. 1. To fit these curves, we utilize the statistical kinetic equation we recently derived to model an acceleratory chemical phase transformation [4]:

$$x = \exp\{[-\gamma/t]\left[\exp\left(\beta t^2\right)-1\right]\}. \quad (1)$$

Eq. (1) is based on an integrated first-order kinetic model (the majority of known chemical reactions obey first-order kinetics, or they can be reduced to 'pseudo first-order' through appropriate selection of experimental variables) which uses a M–B distribution of activation energies for the reagent molecules (the M–B distribution is widely used in gas-phase kinetics to describe motion in a molecular ensemble at a constant temperature and pressure, but we have found that its form may be useful for describing kinetics in other phases of matter as well [4]) to define the time-dependent rate constant for the process [7]. For our present purpose, x can be considered to represent the fraction of the animal population remaining alive at any given time, t. The two fit parameters, γ and β, have units of days (d) and days^{-2} (d^{-2}), respectively. These units allow us to consider them analogously to rate parameters in a chemical reaction: γ (or perhaps more precisely, α) represents the *reciprocal* of a '*global* first-order rate constant' and β describes a '*global* acceleratory rate constant'.

From a survey of the literature, we noticed that Eq. (1) has a similar form to the popular 'Gompertz Survival Model' [8]. The phenomenological Gompertz model may be written as:

$$x = \exp\{[-\alpha/\beta][\exp(\beta t)-1]\}. \quad (2)$$

As per our model (in which $\gamma=\alpha/2\beta$), Eq. (2) also has only two fit parameters. The parameters, α and β, affect the mortality in an age-independent and an age-dependent fashion, respectively. Interestingly, one can show that the deviration of the Gompertz model parallels that of our derivation of Eq. (1) [9]. However, the physical origin of the acceleration in the mortality rate, over time, in the Gompertz model remains less clear.

The good fit of the plots in Fig. 1 to Eq. (1) (and Eq. (2); data not shown) suggests that lifespan may be described analogously to a chemical process with dispersive kinetics; the net conversion may be written as: 'live animals → dead animals'. The implication of this finding is that it may be

possible to distinguish factors that affect either the average lifetime of a population or the degree of variance (i.e. dispersion) in the lifetimes associated with that population. The dispersion in the longevity of the population may have the general shape of a M–B distribution. A narrower distribution represents a population with very similar lifespans; the opposite is also true. Since death is not immediate (for most individuals in a given population), there must exist an equivalent of a 'genetically determined activation energy barrier' which must be overcome for death to occur. As the barrier height is proportional to the longevity of each individual, by eliminating certain gene expression pathways in a given population, one can extend the overall lifespan of that population by forcing the 'reaction' to proceed via less efficient mechanisms.

From the data in Fig. 1, in general, enhanced longevity for each population can be seen to correlate with a larger γ (i.e. α) value and lower β value: the former parameter describes the *inverse rate* of the onset of death whereas the second dictates the *acceleration* in the demise of the population of animals as the average lifespan is reached (note: the broadness or sharpness of the distribution of 'activation energies' is related mainly by the β term). Similarly, shorter lifespans correlate with a smaller α value and a higher β value. As an aside, in considering the fractal nature of dispersive chemical kinetics and some biological processes [10], it is possible that the general shapes of the plots in Fig. 1 also mirror (theoretical) curves representing the loss of life-sustaining processes, over time, for *each individual* in a given population.

From a database of α and β values extracted from a series of lifespan curves in which the populations are subjected to controlled genetic alterations/treatments, it is foreseeable that either Eq. (1) or Eq. (2) may be used to successfully predict the lifespan of *C. elegans* on the basis of gene expression and the role of the various tissues in the animal. In addition, the fractional population remaining at any given time may be accurately forecast, provided an adequate calibration of these models. More fundamentally, in this work we demonstrate the usefulness of a novel 'statistical' approach for modeling aging kinetics, which we hope has provided some insight into a possible origin of the widely-used Gompertz model. In doing so, we show that it may be possible to draw parallels between biological aging and chemical reaction.

Though not specifically examined in this work, we believe that Eq. (1), like Eq. (2), may also find application in modeling longevity of higher (i.e. mammalian) species, such as rats: the population aging curves of rats appear to be very similar in shape to those of the nematode presented in this work (e.g. [11]), thus they may potentially be modeled with a similar mathematical function. For future work, it may be of interest to investigate whether Eq. (1) or Eq. (2) is generally more successful in modeling the aging characteristics of various species. In the case of the latter (Gompertz) model, the physical origin of the acceleration in the mortality rate should be further clarified.

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[6] The author believes that all reaction kinetics are fundamentally dispersive; only in cases where the analytical measurement used to monitor the conversion is not of appropriate time-scale to simultaneously detect the dispersion in ε_a do classical kinetic treatments (i.e. models) apply. In support of this claim, in the development of Eq. (1), as described in Ref. [4], it is easy to show that if dispersion in ε_a is not detected, the equation reduces to a simple first-order exponential decay as would be predicted from the Arrhenius equation.

[7] To derive the (isothermal) semi-empirical kinetic model in Eq. (1), it is necessary to integrate the time-dependent expression for the overall rate constant of the conversion, $k'(t)$, with respect to t, using the following integrated form of the rate expression (describing reagent loss) for a first-order process having multiple activation energies:

$$x = \exp\left[-\int k'(t)dt\right]$$

where the integration limits for t are 0 and t. The general form of $k'(t)$ in the above equation, for an acceleratory process, is given by:

$$k'(t) = \left[\alpha\exp\left(\beta t^2\right)\right]$$

where the rate parameters, α and β, are defined at a fixed temperature and pressure. Note that this time-dependence of $k'(t)$ comes as a direct result of defining a M–B distribution of activation energies for the process in which the corresponding values of the molecular rate constants vary linearly with time; see Ref. [4].

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