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Experimental Aging Research

An International Journal Devoted to the Scientific Study of the Aging Process

ISSN: 0361-073X (Print) 1096-4657 (Online) Journal homepage: https://www.tandfonline.com/loi/uear20

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To cite this article: Emine Güven, Sevinç Akçay & Hong Qin (2019): The Effect of Gaussian Noise on Maximum Likelihood Fitting of Gompertz and Weibull Mortality Models with Yeast Lifespan Data, Experimental Aging Research, DOI: 10.1080/0361073X.2019.1586105

To link to this article: https://doi.org/10.1080/0361073X.2019.1586105

EXPERIMENTAL AGING RESEARCH
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The Effect of Gaussian Noise on Maximum Likelihood Fitting of Gompertz and Weibull Mortality Models with Yeast Lifespan Data

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ABSTRACT

Background/study context: Empirical lifespan data sets are often studied with the best-fitted mathematical model for aging. Here, we studied how experimental noises can influence the determination of the best-fitted aging model. We investigated the influence of Gaussian white noise in lifespan data sets on the fitting outcomes of two-parameter Gompertz and Weibull mortality models, commonly adopted in aging research.

Methods: To un-equivocally demonstrate the effect of Gaussian white noises, we simulated lifespans based on Gompertz and Weibull models with added white noises. To gauge the influence of white noise on model fitting, we defined a single index, δ_{LL}, for the difference between the maximal log-likelihoods of the Weibull and Gompertz model fittings. We then applied the δ_{LL} approach using experimental replicative lifespan data sets for the laboratory BY4741 and BY4742 wildtype reference strains.

Results: We systematically evaluated how Gaussian white noise can influence the maximal likelihood-based comparison of the Gompertz and Weibull models. Our comparative study showed that the Weibull model is generally more tolerant to Gaussian white noise than the Gompertz model. The effect of noise on model fitting is also sensitive to model parameters.

Conclusion: Our study shows that Gaussian white noise can influence the fitting of an aging model for yeast replicative lifespans. Given that yeast replicative lifespans are hard to measure and are often pooled from different experiments, our study highlights that interpreting model fitting results should take experimental procedure variation into account, and the best fitting model may not necessarily offer more biological insights.

ARTICLE HISTORY
Received 28 August 2017
Accepted 1 August 2018

Background

Aging is defined as an increase in failure (mortality) rate over time. The budding yeast *S. cerevisiae* has been considered the prototypic eukaryotic model for cellular aging studies, as they are ideal to uncover many of the fundamental mechanism of eukaryotic

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lifespan regulation (Breitenbach, Jazwinski, & Laun, 2011; Gershon & Gershon, 2000; Longo, Shadel, Kaeberlein, & Kennedy, 2012; Sinclair, Mills, & Guarente, 1998). Budding yeast has proven to be an important organism for identifying conserved factors that influence lifespan (Kaeberlein, 2010; Longo et al., 2012; Powers, Kaeberlein, Caldwell, Kennedy, & Fields, 2006; Yiu et al., 2008).

There are two approaches for measuring lifespan in budding yeast. One is chronological lifespan (CLS), which refers to the length of time that a mother yeast cell can stay alive without dividing. Another is the replicative lifespan (RLS) of a cell, defined as the number of generations a cell divides before death, which is a model for dividing cells. RLS measurements based on individual cells are often subject to maximal likelihood analysis, which is the focus of our study here.

The Gompertz and Weibull mortality models assume that the mortality rate increases in different modes during aging. The mortality rate in biological aging typically increases exponentially – this is known as the Gompertz model of aging (Boxenbaum, 1991; Kennedy, Austriaco, & Guarente, 1994; Qin & Lu, 2006; Vaupel, 1986). In contrast, the Weibull model assumes the mortality rate increase with a power function.

Previous studies have shown that the RLS of budding yeast follows the Gompertz model of aging (Qin & Lu, 2006; Steffen, Kennedy, & Kaeberlein, 2009). The probability density function (PDF) of the Gompertz model is defined as,

$$f_{R,G}(t) = Re^{Gt}\exp\left[\frac{R}{G}\left(1 - e^{Gt}\right)\right]$$

where R is the rate parameter and G is the shape parameter.

Mortality rate, or failure rate, in machine aging typically follows a power law, or the Weibull model of aging (Klein & Moeschberger, 2005; Wilson, 1993, 1994). The Weibull model with a given PDF is defined as,

$$f_{\theta,\gamma}(t) = \gamma\theta^{\gamma}\ t^{\gamma-1}\ \exp(-\theta t)^{\gamma}$$

where θ is the scale and γ is the shape parameter.

The mortality model that best fits empirical observation is often considered to represent the implicit causes of increasing mortality rate over time, and hence is usually preferred by gerontologists (Juckett & Rosenberg, 1993; Ricklefs & Scheuerlein, 2002; Wilson, 1994). In addition, the Gompertz and Weibull models are important to understanding the emergent property of aging during early life (Qin, 2013). Although the Gompertz and Weibull models are commonly used to interpret experimental results in aging research (Juckett & Rosenberg, 1993; Ricklefs & Scheuerlein, 2002; Wilson, 1994), it is still unclear how experimental variations may influence how we determine the best fitting model, and in turn, influence our interpretation of the biological mechanism of aging (Lithgow, Driscoll, & Phillips, 2017). To address this gap of knowledge, we used yeast replicative lifespan data with added Gaussian white noise to simulate the effect of experimental variation on model fitting. We performed maximum likelihood estimations on both aging models and compared the differences between their maximum log-likelihood. Finally, we designed

a systematical study in the parameter space to assess the uncertainty in empirical data (Briggs et al., 2012; Kreutz, Raue, Kaschek, & Timmer, 2013).

To illustrate the basic principles of model fitting, we simulated random lifespans based on Gompertz and Weibull probability distributions using the inverse transform method (Fishman & Concepts, 1996; Jodrá, 2009; Luc, 1986; Schmeiser & Devroye, 1988). Because an analytical approach to compare maximum likelihood fitting was not available, we adopted a numerical approach. We developed a simple measurement $\boldsymbol{\delta}_{LL}$ based on the log-likelihood difference between the Weibull and Gompertz models. Overall, our study suggests that experimental variations should be considered when distinguishing between models of aging, i.e. the best fitting model may not necessarily offer more biological insights.

Materials and Methods

Sample Preparation and Simulation

Our overall workflow is shown in Figure 1. To identify the effect of additive Gaussian noises $N(0, \sigma^2)$ with a known variance σ^2 on lifespan data, we compared lifespan samples drawn from the Gompertz and Weibull probability distributions. We used the maximum likelihood technique for the parameter estimations of both models.

An analytical approach of the estimation of parameters requires an explicit formula for the maximum likelihood investigation (El-Gohary, Alshamrani, & Al-Otaibi, 2013; Garg, Rao, & Redmond, 1970; Pletcher, 1999; Scholz, 2006). Usually, such formulas are not available because the equations of log-likelihood functions do not reveal a unique solution and, in general, cannot be solved analytically (Lenart, 2012; Odell, Anderson, & D'Agostino, 1992; Rockette, Antle, & Klimko, 1974). The numerical technique of maximum likelihood can be used to estimate parameters, predictions, or validation of numerical parameter values which are in one-dimensional space. In this study, we assigned specific numeric values to each unknown parameter based on the empirical parameters of simulations. A list of key variables is summarized in Table 1.

We generated Gompertz and Weibull random numbers as simulated lifespans using the inverse transform method (Fishman & Concepts, 1996; Jodrá, 2009), which can be found through the cumulative distribution function of the Gompertz distribution,

$$F_{R,G}(t) = 1 - \exp\left[\frac{R}{G}\left(1 - e^{Gt}\right)\right]$$

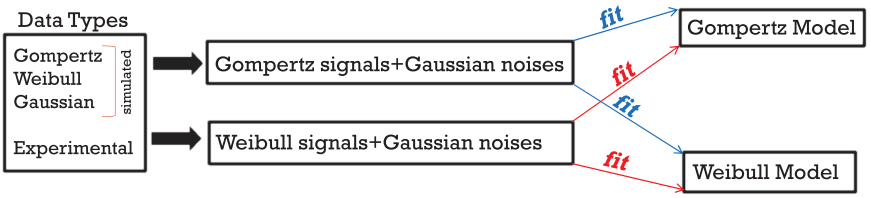

Figure 1. Overview of the computational research.

Table 1. Summary of key symbols and variables.

t	Time measured in days
f	f(t) probability density function (PDF) of time (t)
F^{-1}	$[F(t)]^{-1}$ the inverse probability distributions function of time (t)
R	Gompertz model rate parameter
G	Gompertz model shape parameter
θ	Weibull model scale parameter
γ	Weibull model shape parameter
η	noise scale
N	Population size of mother yeast cells in RLS
t_G	Gompertz generated lifespan of a yeast population
t_W	Weibull generated lifespan of a yeast population
L	$L(R, G\|t_i)$ likelihood function of Gompertz PDF
	$L(\theta, \gamma\|t_i)$ likelihood function of Weibull PDF
LL	$LL(R, G\|t_i)$ log-likelihood function of Gompertz PDF
	$LL(\theta, \gamma\|t_i)$ log-likelihood function of Weibull PDF
δ	δ_{LL_G} difference of log-likelihood values of Weibull and Gompertz models of t_G
	δ_{LL_W} difference of log-likelihood values of Weibull and Gompertz models of t_W

where R is the rate parameter and G is the shape parameter. We then simulated the Gompertz random lifespan, the Gompertz signals, using the inverse cumulative distribution function as follows:.

$$[F_{R,G}(t)]^{-1} = \frac{\log\left(1 - \left(\frac{G}{R}\log(1-U)\right)\right)}{G}$$

Here, U represents uniformly distributed random numbers that take values in the (0,1) interval using the runif() function of R stats package (R Development Core Team, 2015). We took a fixed number representing the population size of unique lifespan data throughout our simulations. The cumulative distribution of the Weibull distribution is,

$$F_{\theta,\gamma}(t) = 1 - \exp(-\theta t)^{\gamma}$$

where θ is the scale and γ is the shape parameter. We can simulate the Weibull lifespan, or Weibull signals, using the inverse cumulative distribution function as follows:.

$$[F_{\theta,\gamma}(t)]^{-1} = \theta(-\log(1-U))^{-\gamma}$$

First, we asked how sensitive Gompertz signals are to Gaussian noises. In other words, if simulated biological lifespans are drawn from Gompertz distributions with additive white noise, how often does the Gompertz model give the best maximum likelihood estimate (MLE) compared to the Weibull model? We simulated the R, G parameters and Gaussian noise scale η for situations that may arise in actual empirical data. We then validated the equivalency of the simulated lifespan and experimental data sets based on their means and standard deviations.

The lifespan t_G defined by Gompertz signals with added white noise is given by

$$t_G = \text{Gompertz signals} + N(0, \text{sd}(\text{Gompertz signals}))\eta, \quad (1)$$

where η represents noise scale to simplify notations in the numerical simulations. Here, the Gaussian noise term is explicitly defined as $Gaussian\ noise_{tG} = N(0, sd(Gompertz\ signals))\eta$. The Gompertz signals were random numbers drawn from Gompertz distributions. We took

a total of 2000 random numbers from the inverse of the cumulative distribution functions of each model. Lifespans were generated by varying G between the [0.05,0.25] range, R between [0.001,0.04] and noise scale (i.e. η) between [0,3]. We then fit each lifespan data set with both models. Parameter estimations were done using the maximum likelihood estimation method, and the MLEs of Gompertz and Weibull models were compared by calculating the difference of their maximum likelihoods (detailed below).

Secondly, we examined how sensitive the Weibull model is to Gaussian white noises. Akin to the aforementioned Gompertz model study, we simulated the Weibull random lifespan with added white noise. We simulated the γ, θ parameters, and *n*oise scale η and estimated the model parameters. The simulated lifespan t_W composed of Weibull signals and white noise is given by

$$t_W = \text{Weibull signals} + N(0, \text{sd}(\text{Weibull signals}))\eta \quad (2)$$

where η is used as a noise scale, the Weibull signals are random numbers drawn from the Weibull distribution, and the Gaussian noise term is defined as $N(0, \text{sd}(\text{Weibullsignals}))\eta$. We let γ vary between [1,30], θ between [25, 30] and noise scale η between [0,3]. We compared MLEs of Gompertz and Weibull model fitting results.

Thirdly, for comparison, we asked how sensitive the Gaussian distribution is to white noise. These Gaussian lifespans were generated using the same population size for a mean varying between [5, 50] and for the noise (i.e. standard deviation) ranging between [1, 5]. We again fit each lifespan data set with both Gompertz and Weibull models, and compared their maximum likelihoods.

Finally, we used lifespan measurements of wild type yeast laboratory strains as empirical data sets to demonstrate the implications of our simulation studies.

Definition of the Delta Log-Likelihood (δ_{LL})

Once we fit the simulated lifespan data with the Gompertz and Weibull aging models, we calculated the difference between the maximum log-likelihood of these two models. The log-likelihood function of the Gompertz for the given PDF is as follows:.

$$log(L(R, G|t_i)) = LL(R, G|t_i) = \sum_{i=1}^{N} \log\left[f_{R,G}(t_i)\right]$$

$$LL(R, G|t_i) = \sum_{i=1}^{N} \left[log\ (R) + G\ t_i + \log\left(\frac{R}{G} + \left(1 - e^{G\ t_i}\right)\right)\right]$$

We obtained the log-likelihood function of the Weibull distribution as.

$$log(L(\theta, \gamma|t_i)) = LL(\theta, \gamma|t_i) = \sum_{i=1}^{N} \log\left[f_{\theta,\gamma}(t_i)\right]$$

$$LL(\theta, \gamma|t_i) = \sum_{i=1}^{N} \left[log\ (\gamma\theta^{\gamma}) + (\gamma - 1)\log(t_i) - (\theta\ t_i)^{\gamma}\right]$$

We used an optimization procedure in R to obtain the MLEs of R and G (or θ and γ).

There are other approaches to evaluate model fittings such as AIC (Akaike Information Criterion) and likelihood ratio tests. Our approach is principally similar to AIC. In fact,

a difference of AIC $= 2 * \boldsymbol{\delta}_{\mathrm{LL}}$. However, for our purposes, $\boldsymbol{\delta}_{\mathrm{LL}}$ is a direct measurement. The likelihood ratio test is not used as it requires nested models and here Gompertz and Weibull aging models are non-nested.

For Gompertz simulated lifespan t_G, we define $\boldsymbol{\delta}_{LLG}$, the difference of maximum likelihood of the two model fittings, as

$$\boldsymbol{\delta}_{LLG} = max\{LL(W, t_G)\} - \max\{LL(G, t_G)\},$$

where t_G is a randomly generated lifespan using the Gompertz distribution with added Gaussian noise as defined in Equation (1).

Analogously, for Weibull simulated lifespan t_W, the difference of maximum likelihood between model fittings is,

$$\boldsymbol{\delta}_{LLW} = max\{LL(W, t_W)\} - \max\{LL(G, t_W)\}$$

where t_W is randomly a generated lifespan using the Weibull distribution with added Gaussian noise as defined in Equation (2)

Data and Analysis Codes

Simulation, fitting and analysis were conducted in the R statistical environment. Sample codes of simulated data and analysis of empirical data can be found at https://github.com/emineguven/modelComparison2018. Maximum likelihood estimations were performed using the flexsurvreg() functions in the flexsurv package (Jackson, 2016). The parameter search spaces for generating Gompertz random lifespan data were shape parameter, G = [0.05, 0.08, 0.1, 0.12, 0.15, 0.17, 0.2, 0.25], rate parameter, R = [0.001, 0.002, 0.003, 0.005, 0.01, 0.02, 0.03, 0.04], and noise scale, η = [0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 1, 2, 3]. As a result, we had |G|x|R|x|η| = 704 simulations in total with the Gompertz random lifespans data set. In the second set of simulations, we generated Weibull random lifespan data using the following parameter search spaces: shape parameter γ = [1, 2, 3, 4, 5, 6, 10, 15, 30], scale parameter θ = [25, 26, 27, 28, 29, 30, 35, 40, 50], and noise scale η = [0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0]. As a result, we had $| \gamma|x|\theta|x|\eta| =$ 704 simulations in total with the Weibull random lifespans data set. To generate the Gaussian random lifespan, the parameter search space used were mean μ = [5, 10, 15, 20, 35, 40, 50] and standard deviation σ = [1, 2, 3, 4, 5], resulting in $| \mu |x | \sigma|$ =35 simulations in total. RLS of wildtype BY472 strain were generously shared by the Kaeberlein group (personal communication). The RLS of the BY4742 strain was measured in 2108 experiments, and the RLS of BY4741 wild type strain was measured in 381 experiments.

Results

Effect of Gaussian Noise on Simulated Lifespans

Sensitivity of the Gompertz model to white noises was examined using the difference of maximum log-likelihoods between Weibull and Gompertz models fitted to Gompertz signals with additive Gaussian noises (Figure 2). Because there were three parameters, we iteratively fixed one parameter and varied the other two, as presented in three rows of

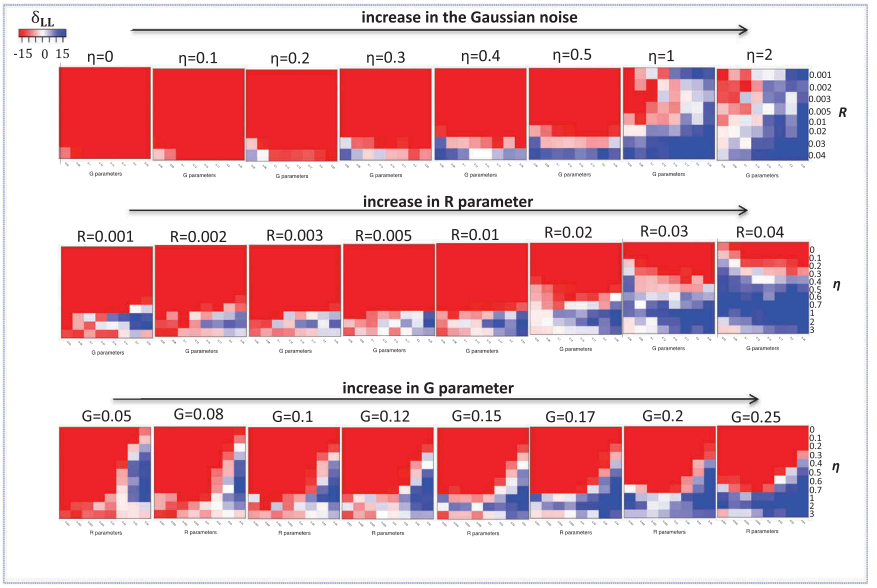

Figure 2. Comparison of Gompertz and Weibull models by δ_{LL} values using simulated Gompertz signals with Gaussian white noises (t_G). Here, parameters for simulation runs are G = [0.05, 0.08, 0.1, 0.12, 0.15, 0.17, 0.2, 0.25], R = [0.001, 0.002, 0.003, 0.005, 0.01, 0.02, 0.03, 0.04], and noise scale η = [0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 1, 2, 3].

heatmaps in Figure 2. In each row, the fixed parameter was gradually increased to cover a range of possible yeast replicative lifespans. Red cells representing negative δ_{LL} values indicated that the Gompertz model fits better than the Weibull model in those parameter sets, whereas blue cells representing positive δ_{LL} values indicated that the Weibull model is a better fit. Recalling that Gaussian noise is N(0,sd(Gompertz signals))η, increasing scale η values represent increasing levels of white noise. Blue cells occur more frequently with higher η values from left to right in the top row, and from top to bottom in the second and third rows. Hence, we conclude that the Weibull model generally fits lifespan t_G better than the Gompertz model as white noise increases. The Gompertz model's sensitivity to noise also depends on the R and G parameters.

Likewise, the Weibull model's sensitivity to white noise data was examined using δ_{LL} = max {LL(W, t_W)} – max{LL(G, t_W)} values (Figure 3). Again, there were three parameters to consider, and we iteratively varied them as depicted in Figure 2 above. The Weibull simulated lifespan t_W can tolerate η up to 1 ~ 1.5, whereas the Gompertz lifespan t_G often loses its Gompertz signal feature when η is in the range of 1 ~ 1.5, as shown in Figure 2. Hence, the results show that the Weibull model is generally more tolerant to white noises than the Gompertz model.

To further examine the Weibull model's tolerance to white noise, we fit the Gaussian random lifespan t_Φ with both the Weibull and Gompertz models. In this case, we only needed to vary the mean and standard deviation of the Gaussian distribution for the parameter space. We calculated δ_{LL} = max {LL(W, t_Φ)} – max{LL(G, t_Φ)}, as presented in Figure 4.

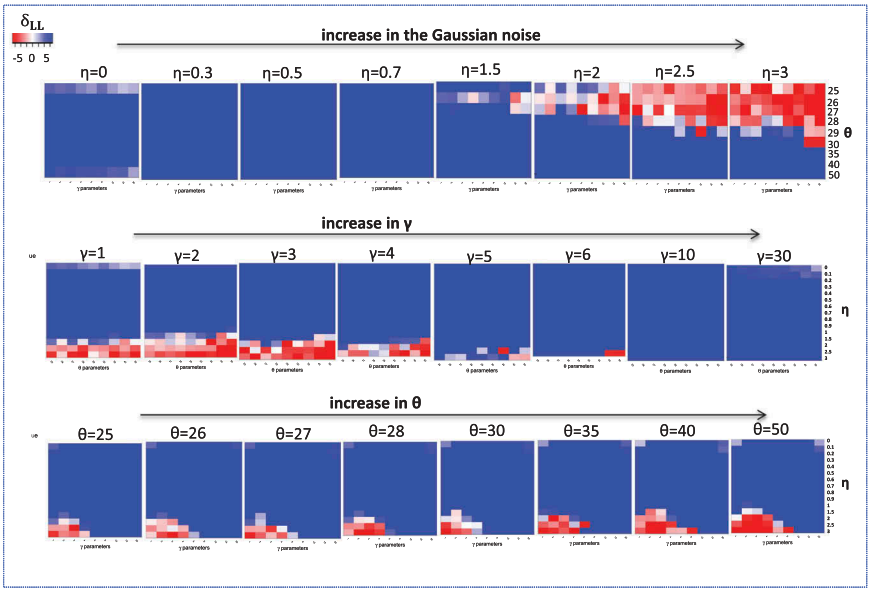

Figure 3. Comparison of Gompertz and Weibull models by δ_{LL} values using simulated Weibull signals with Gaussian white noises (t_W). The parameter ranges of simulation runs are shape parameter γ = [1, 2, 3, 4, 5, 6, 10, 15, 30], scale parameter θ = [25, 26, 27, 28, 29, 30, 35, 40, 50], and noise scale η = [0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0].

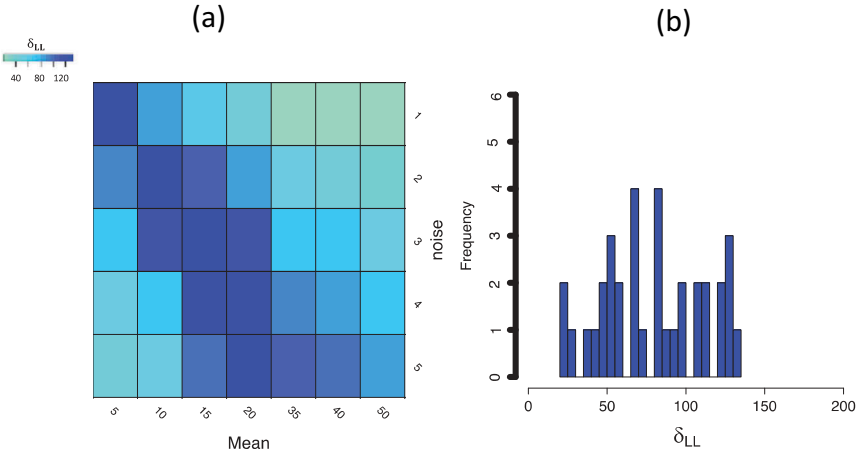

Figure 4. Comparison of Gompertz and Weibull models by δ_{LL} values using simulated Gaussian lifespans. Parameter ranges are mean μ = [5, 10, 15, 20, 35, 40, 50], and standard deviation σ = [1, 2, 3, 4, 5].

All of the calculated δ_{LL} are positive, indicating the Weibull model is always a better fit to Gaussian random lifespans than the Gompertz model.

Overall, the Weibull model fits the lifespan data of Gompertz signals with added Gaussian noise better than the Gompertz model, as the Weibull signals can tolerate higher levels of noise than Gompertz signals.

Experimental Data Analysis

The Kaeberlein group generously shared 2108 RLS experiments for BY4742 and 381 experiments for BY4741 (personal communication). In this case, we calculated δ_{LL} as:

$$\boldsymbol{\delta}_{LL} = max\{LL(W,t)\} - \max\{LL(G,t)\}.$$

Most of the experimental RLS data sets were better fitted with the Weibull model than the Gompertz model, as shown by the positive δ_{LL} values in Figure 5(a,b). We further visualized the relationship between the parameter estimates for the Gompertz model and δ_{LL} values in a three-dimensional scatter plot in Figure 5(c,d). The scatter plots show that the estimated Gompertz parameters, G and R, were within the ranges of the simulation studies shown in Figure 2. They also show that positive and negative δ_{LL} values inter-mingled in all ranges of G and R parameters. More experimental RLS data sets were better fitted with the Weibull model than with the Gompertz model. This does not necessarily suggest that the Weibull model is mechanistically more insightful than the Gompertz model because we have shown

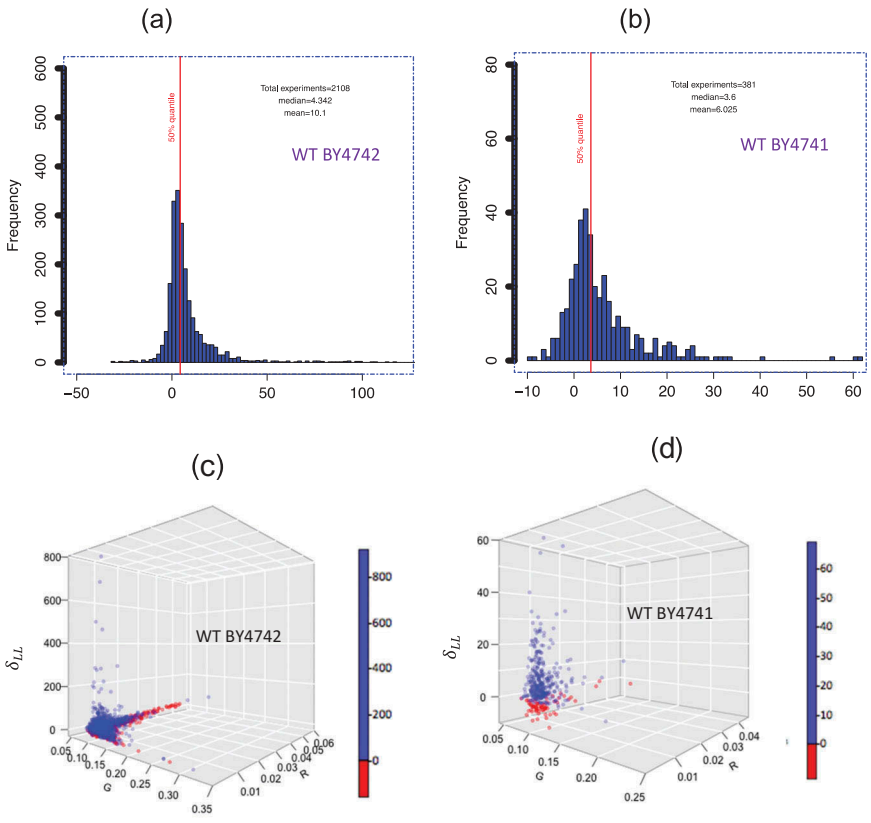

Figure 5. Comparison of Gompertz and Weibull model using RLS experimental data sets for BY4741 and BY4742. (a) and (b) Distributions of the δ_{LL} values of the experimental data sets for BY4742 and BY4741. (c) and (d) 3D scatter plots of the estimated G, R, and δ_{LL} values for wildtype BY4742 and BY4741 yeast strains. Here, the shape parameter G and the rate parameter R of the Gompertz were estimated from fitting experimental RLS data. The Weibull fitted better in most experimental data set than the Gompertz model as indicated by the positive δ_{LL} in blue dots.

the Weibull model is more tolerant to Gaussian noises. As suggested by Lithgow et al. (2017), lifespan measurements are often noisy with experimental variations. Based on our simulation studies, we argue that caution should be taken when determining which mortality model better describes the biological nature of the aging process and more attention should be paid to control the experimental variations during lifespan assays.

Discussion

In this study, we found that the Weibull model is generally more tolerant to Gaussian noise than the Gompertz model based on two lines of evidence. First, the fitting of Weibull signals increases as white noise increases, indicating Weibull signals are more tolerant to Gaussian noises than Gompertz signals. Second, an intuitive understanding of the error-tolerant property of the Weibull model may be achieved with the linear regression of Gaussian lifespan data. Because the Weibull model indicates a linear correlation of log-transformed mortality rate and log-transformed life span and the Gompertz model indicates a linear correlation of log-transformed mortality rate and lifespan, experimental noise in lifespan measurements would be suppressed in the log-log plot for the Weibull model.

The model organism *S. cerevisiae* has contributed significantly to the basic biology of aging (Janssens & Veenhoff, 2016; López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013). When measured in years, reported Gompertz parameters of human aging, R = 0.01 and G = 0.1 ~0.15, are similar to the estimates in yeast RLS (Kirkwood, 2015). Hence, though designed with yeast RLS in mind, this simulation study is relevant for the Gompertz model fitting of human lifespans, as well.

Reproducibility in experimental aging research is a challenging task (Lithgow et al., 2017). Sources of variations may include "subtle tinkering" in biology experiments, such as the idiosyncratic techniques of individual researchers, and un-anticipated heterogeneity, such as different modes of aging in some cohorts of worms. As suggested by our simulation study, experimental variations of lifespan may influence the evaluation of mortality models. The implication of our simulation study to the research community can be seen in a recent study on the mortality model for nude mole-rats (Ruby, Smith, & Buffenstein, 2018). Ruby and co-authors pooled over 3000 lifespan measurements of nude mole-rats from historical data and found that age-specific mortality did not increase with age. There may be substantial experimental variation among past experiments of nude mole-rats, and these experimental noises may influence the model comparison between constant mortality rate model and the Gompertzian models.

The Gompertz mortality model has left a significant impact on the biology of aging (Kirkwood, 2015; Olshansky & Carnes, 1997). In comparison to non-parametric approaches, the Gompertz model offers an appeal of a general "rule" for the biology of aging. Deviations from the Gompertz model have been frequently observed in experimental measurements of mortality rates, especially in late life, and many alternative aging models have been proposed (Gavrilov & Gavrilova, 2001; Li, Yang, & Anderson, 2013; Mueller & Rose, 1996; Vaupel, Manton, & Stallard, 1979; Witten, 1983). Alternative methods are often adopted in part to improve fitting to empirical data (Juckett & Rosenberg, 1993; Horiuchi and Wilmoth, 1998; Koopman et al., 2015; Wilson, 1993; 1994). Our study suggests that caution should be paid to the models' sensitivity to noises when empirical data are evaluated by different mortality models.

Acknowledgments

The authors appreciate the anonymous reviewers for their valuable comments and suggestions during the revision of this manuscript.

Funding

This study was partially supported by the University of Tennessee at Chattanooga start-up fund and by the National Science Foundation Award #1453078 (transferred to #1720215).

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