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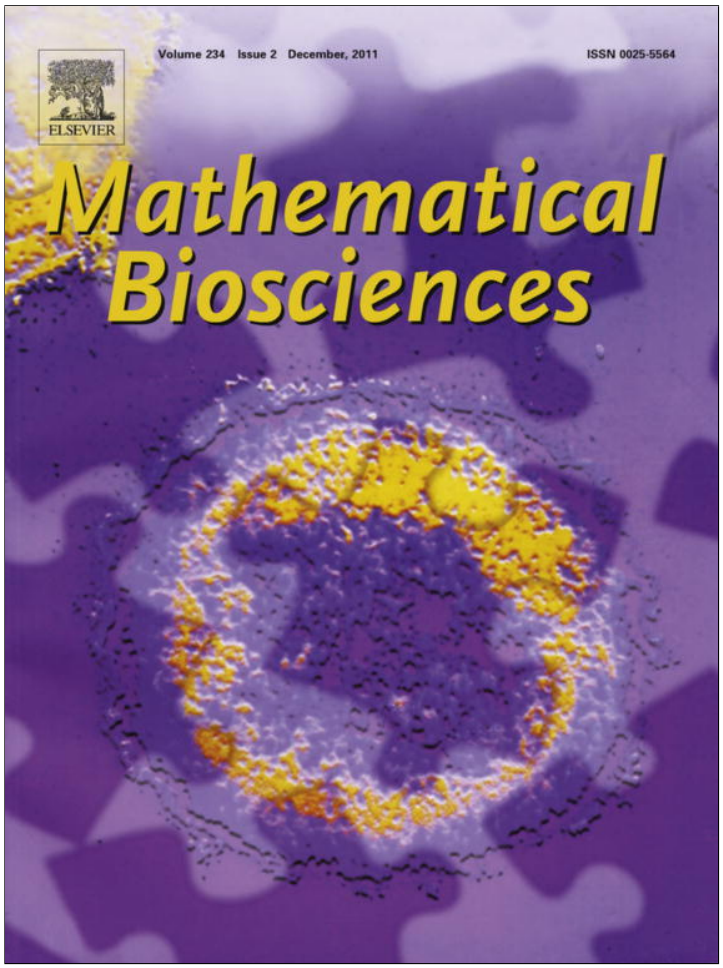

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Modeling and estimating bacterial lag phase

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ABSTRACT

A branching process model of a bacterial population with initial lag phase is developed. Approximations are established in order to facilitate parameter estimation. The validity of approximations and estimation procedures is tested with simulated data.

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1. Introduction

When a bacterium is inoculated into a new environment it typically needs time to adjust before it can start reproducing. This time is referred to as the *lag phase* and it is succeeded by the *exponential growth phase* (or "log phase"). Accurate mathematical modeling and statistical estimation of the lag phase is of great importance in the field of food microbiology and many papers have been devoted to this task. For an overview, see Swinnen et al. [11]. The definition of lag phase varies in the literature but its practical definition seems to be simply "the time until the population is in exponential growth." An older definition is "the time for the initial population to increase twofold" from Buchanan and Solberg [5]. A very simple definition is to denote the logarithm of the number of individuals at time t by $y(t)$ and lag phase by λ, and introduce the biphasic function

$$y(t) = \begin{cases} 0 & \text{if } t \leqslant \tau \\ \alpha t - \alpha\tau & \text{if } t \geqslant \tau \end{cases} \tag{1.1}$$

where α is the *specific growth rate* of the population in the sense that, asymptotically, the population grows proportionally to $e^{\alpha t}$ as $t \to \infty$ (rather, this is how the population would grow if it could sustain exponential growth indefinitely). This definition is overly simplistic as it neglects the fact that there is also a noticeable period between the end of lag phase and the beginning of exponential phase (strictly speaking, exponential growth is an asymptotic phenomenon).

A more sophisticated mathematical definition was suggested by Buchanan and Cygnarowicz [4], namely

$$\lambda = \min\{t \geqslant 0 : y'''(t) = 0\}$$

with the interpretation is that the change in growth rate is maximal at the time this third derivative equals 0. Another definition was suggested by Kutalik et al. [10], namely,

$$\lambda = \lim_{t\to\infty}\left(t - \frac{y(t) - y(0)}{\alpha}\right) \tag{1.2}$$

This last definition seems to be the most common and is the one that is used in several papers by Baranyi and collaborators [2,3], one of the leading research groups in mathematical modeling of bacterial lag. In both definitions, "number of individuals" should be replaced by "expected number of individuals" if the model is stochastic rather than deterministic.

Our approach is to model the bacterial population as a branching process in which we consider the *individual lag*, τ, which is the time a bacterium spends in adjustment to the new environment before it starts its normal life cycle.

2. Branching processes

Consider a population started from one bacterium at time 0. This bacterium lives for a random time that has some distribution function F, then splits into two bacteria, and so on and so forth. Assume that bacteria have lifetimes that are i.i.d. random variables with the common distribution function F which we assume to be absolutely continuous so that its pdf f exists. Denote by Y_t the number of bacteria present at time t, and let $Y_0 \equiv 1$. The process $\{Y_t\}$ is then a simple example of a *Bellman–Harris branching process* (note

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that we disregard the possibility of bacterial death). By a standard convergence result for branching processes, we have

$$E[e^{-\alpha t}Y_t] \to c \tag{2.1}$$

as $t \to \infty$. Here, α is the *Malthusian parameter* and c is a constant, both depending on the lifetime distribution. The Malthusian parameter is the unique solution to the equation

$$2\int_0^\infty e^{-\alpha t}f(t)dt = 1 \tag{2.2}$$

and the constant c equals

$$c = \left(4\alpha\int_0^\infty te^{-\alpha t}f(t)dt\right)^{-1} \tag{2.3}$$

In fact, a stronger result holds, namely,

$$e^{-\alpha t}Y_t \to cW \tag{2.4}$$

almost surely as $t \to \infty$, where W is a random variable with mean $E[W] = 1$. For details and more general results, see Jagers and Nerman [9].

If there is lag, the actual process does not start at time 0. Therefore, let Z_t denote the number of bacteria observed at time t in a branching process where the ancestor has lag τ. Because the branching process does not start until time τ, the true time is $t - \tau$ so if $\{Y_t\}$ is a regular branching process, started at time 0 without lag, Z_t has the same distribution as $Y_{t-\tau}$:

$$Z_t \stackrel{d}{=} Y_{t-\tau} \tag{2.5}$$

Most realistically, τ is a random variable, but for the time being we shall assume it to be constant. By (2.1) and (2.5) we now get

$$E[e^{-\alpha t}Z_t] = e^{-\alpha\tau}E[e^{-\alpha(t-\tau)}Y_{t-\tau}] \to e^{-\alpha\tau}c$$

as $t \to \infty$. In other words, with lag τ we have

$$E[Z_t] \sim ce^{-\alpha\tau}e^{\alpha t} \tag{2.6}$$

with equality if and only if lifetimes follow an exponential distribution with rate α (mean $1/\alpha$), in which case $c = 1$. Without lag we have

$$E[Z_t] \sim ce^{\alpha t}$$

The factor $e^{-\alpha\tau}$ that appears due to the lag is termed the "initial physiological state" parameter by Baranyi [1]. Until now we assumed τ to be constant. If τ is a random variable we get instead the conditional expectation

$$E[Z_t|\tau] \sim ce^{-\alpha\tau}e^{\alpha t}$$

with expected value

$$E[Z_t] \sim cE[e^{-\alpha\tau}]e^{\alpha t} \tag{2.7}$$

assuming that $Y_{t-\tau}$ is independent of τ. Here we recognize $E[e^{-\alpha\tau}]$ as the Laplace transform of τ, evaluated at the point α. If we start from n_0 individuals, we have

$$Z_t = \sum_{k=1}^{n_0} Z_t(k) \tag{2.8}$$

where $Z_t(k)$ is the size of the population started from the kth ancestor so that the $Z_t(k)$ are independent, identically distributed random variables. By additivity of expected values and (2.7):

$$E[Z_t] \sim cn_0E[e^{-\alpha\tau}]e^{\alpha t} \tag{2.9}$$

Let us again assume constant lag τ. Recall the Definition 1.2 of the lag phase λ. By (2.6) we get the connection between τ and λ if we let $y(t) = \log(E[Z_t])$ so that $y(0) = \log n_0$. Then

$$y(t) \sim \alpha t + \log c + \log n_0 - \alpha\tau$$

so that

$$\lambda = \lim_{t\to\infty}\left(t - \frac{y(t) - y(0)}{\alpha}\right) = \lim_{t\to\infty}\left(t - \frac{\log c - \alpha\tau + \alpha t}{\alpha}\right) = \tau - \frac{\log c}{\alpha} \tag{2.10}$$

Although there is no theoretical upper bound for the constant c, for most realistic lifetime distributions (for example the gamma distribution with shape parameter $a > 1$) we will have $c < 1$ in which case $\lambda > \tau$. Note in particular that $\lambda > 0$ even if $\tau = 0$ due to the constant $\log c$ which measures how long it takes the population to "catch up" with exponential growth. If τ is a random variable, (2.7) gives, for any value of $y(0) = \log n_0$,

$$\begin{aligned}\lambda &= \lim_{t\to\infty}\left(t - \frac{y(t) - y(0)}{\alpha}\right)\\ &= \lim_{t\to\infty}\left(t - \frac{\log c + \log E[e^{-\alpha\tau}] + \alpha t}{\alpha}\right)\\ &= -\frac{1}{\alpha}(\log E[e^{-\alpha\tau}] + \log c)\end{aligned} \tag{2.11}$$

which agrees with Formula (5) in Kutalik et al. [10], in the case $c = 1$. The reason for the absence of the constant c in Kutalik et al. [10], is that they implicitly assume that bacterial lifetimes follow an exponential distribution. Indeed, in Appendix A, they give the formula

$$Z_t = I\{\tau > t\} + I\{\tau \leqslant t\}e^{-\alpha(t-\tau)}$$

where I denotes indicator function. The formula is correct only if lifetimes are exponential with rate α (mean $1/\alpha$), assuming that Z_t is interpreted as an expected value. The general formula is

$$Z_t = I\{\tau > t\} + I\{\tau \leqslant t\}Y_{t-\tau}$$

recalling the relation (2.5) between the observed process Z_t and the delayed process Y_t. As mentioned below (2.6), $E[Y_t] = e^{\alpha t}$ precisely when lifetimes follow an exponential distribution, otherwise $E[Y_t] \sim ce^{\alpha t}$ as $t \to \infty$.

3. Estimation

In order to estimate the individual lag and other population parameters we propose to use the exact expression $E[Z_t]$ and fit parameters using nonlinear least squares. Let us first consider the population without lag Y_t and apply the standard technique of decomposing the population by generation. There are 2^n individuals in the nth generation and such an individual is present at time t with some probability $p_n(t)$. Hence

$$E[Y_t] = \sum_{n=0}^\infty 2^n p_n(t)$$

To get an expression for $p_n(t)$, recall that lifetimes are independent and have the common cdf F. A given cell in the nth generation is present at time t if and only if the sum of n lifetimes does not exceed t while the sum of $n + 1$ lifetimes does exceed t. In standard notation for convolution powers, we thus get

$$p_n(t) = F^{*n}(t) - F^{*(n+1)}(t)$$

where by convention $F^{*0}(t) \equiv 1$. Hence

$$E[Y_t] = \sum_{n=0}^\infty 2^n\left(F^{*n}(t) - F^{*(n+1)}(t)\right)$$

and with lag τ, (2.5) gives conditional expectation

$$E[Z_t|\tau] = \sum_{n=0}^\infty 2^n\left(F^{*n}(t-\tau) - F^{*(n+1)}(t-\tau)\right) \tag{3.1}$$

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A first approximation of the unconditional expected value $E[Z_t]$ is to let $\mu = E[\tau]$ and note

$$E[Z_t] \approx \sum_{n=0}^{\infty} 2^n \left(F^{*n}(t-\mu) - F^{*(n+1)}(t-\mu)\right)$$

an instance of the 0th order Taylor approximation of the mean of a function of a random variable, $E[g(\tau)] \approx g(\mu)$. This means we are effectively assuming τ to be constant and we shall make this assumption from now on. As it turns out, estimates of the mean lag $\mu = E[\tau]$ work quite well under this assumption even if τ is random. If the population starts from n_0 ancestors, we get

$$E[Z_t] \approx n_0 \sum_{n=0}^{\infty} 2^n \left(F^{*n}(t-\mu) - F^{*(n+1)}(t-\mu)\right) \tag{3.2}$$

On the logarithmic scale, we are getting observations of $\log Z_t$ and the least-squares fit should thus be done by fitting the curve $E[\log Z_t]$ which is hard to get explicitly. A first approximation is the obvious

$$E[\log Z_t] \approx \log E[Z_t]$$

but since the logarithm is a concave function, Jensen's inequality tells use that $E[\log Z_t] < \log E[Z_t]$ for $t > 0$, so we are systematically overestimating the true expected value. A refined approximation is given next, proved in Section A.1.

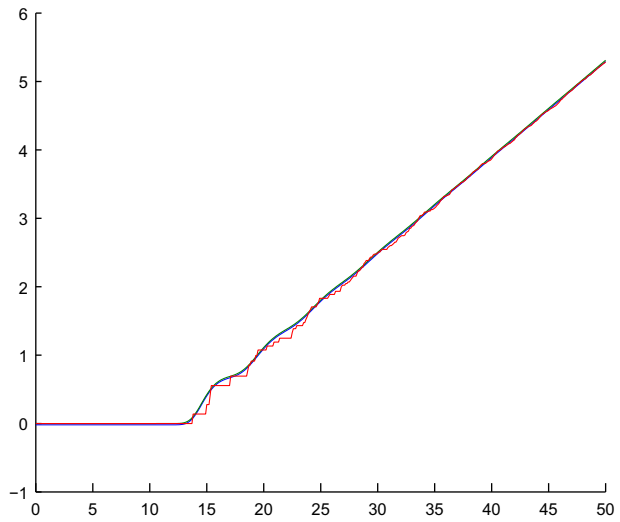

Fig. 1. Average of simulated data (red) and expected values with variance correction term (blue) and without variance correction term (green).

Proposition 3.1. *For Z_t in the exponential growth phase with n_0 ancestors*

$$E[\log Z_t] \approx \log E[Z_t] - \frac{\mathrm{Var}[W]}{2n_0}$$

and

$$\mathrm{Var}[\log Z_t] \approx \frac{\mathrm{Var}[W]}{n_0}$$

where W is the limiting random variable from (2.4).

To assess the accuracy of our approximations, data were simulated and compared to the expression given by Proposition 3.1. In the simulations, bacterial lifetimes and lag times followed different gamma distributions. Thus, lag times are not constant in the simulations (in order to mimic real life data) but as we use (3.2) to approximate $E[Z_t]$, lag times are assumed constant in the approximation, see the discussion above right before (3.2). For a comparison of the approximation and simulated data, see Fig. 1 with details given in Fig. 2. Note that the additional term introduced in Proposition 3.1 may actually make the approximation worse for small t since, for example if $n_0 = 1$ we get $E[\log Z_0] = \log E[Z_0] = 0$. However, as observations are obtained in the exponential growth phase this effect can be neglected. The fact that the variance is constant in exponential growth phase warrants using unweighted nonlinear least squares, see Bickel and Doksum [6]. For the gamma distribution, $\mathrm{Var}[W]$ is given in (6.2). Our model can be used to estimate unknown parameters from observed population count data. To check the validity of such estimation, we ran simulations and observed the population size $L(t) = \log Z_t$ at 3 time-points. From the pairs $(t_1, L_{t_1}), (t_2, L_{t_2}), (t_3, L_{t_3})$ we ran a nonlinear least-squares fit (in Matlab) of the expression for $E[\log Z_t]$, using (3.2) together with Proposition 3.1 to estimate the mean lag $\mu = E[\tau]$ and the mean initial population size n_0. We let the initial population size be random with a Poisson distribution with mean n_0 and the lag be random with a gamma distribution with mean $\mu = 10$ and variance 1. In the estimation, we used the approximation that both quantities are constant. Lifetimes followed a gamma distribution with mean 5 and variance 1. Table 1 gives estimated values of n_0

Table 1
Estimating lag times from simulated data. Standard errors in parentheses.

Initial size	n_0	μ (ind. lag)	λ (pop. lag)
$n_0 = 3$	2.99 (0.15)	9.95 (0.14)	12.21 (0.14)
$n_0 = 5$	4.74 (0.18)	9.92 (0.17)	12.17 (0.17)

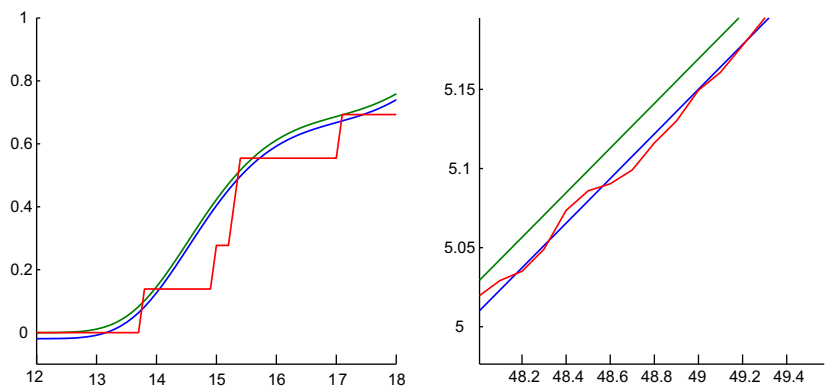

Fig. 2. Details from Fig. 1, early times (left) and late times (right). Average of simulated data (red) and expected values with variance correction term (blue) and without variance correction term (green).

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and $\mu = E[\tau]$ from 100 simulations runs, for different values of n_0. By the least-squares fit we can also estimate the parameters a and b in the gamma distribution for the lifetimes, and by the expressions in Section A.3, we can get estimates of the Malthusian parameter α and the constant c, thereby obtaining estimates of the population lag λ, using (2.10). The true value of λ was 12.22, computed from Eq. (2.11). Notice that our approximations are crude, so the estimates obtained are quite good. Several more simulations with different parameter values gave similar results. More sophisticated estimation methods based on a more careful analysis of the model, including modeling τ as a random variable, will likely improve estimation. Once crucial parameters have been estimated, we can also predict for example the expected time until the bacterial population reaches a certain level which may be of interest in food safety analysis.

4. Stable population theory

An alternative view of a population with lag is to notice that the ancestor has a different lifetime distribution than other individuals. Thus, suppose the ancestor has lifetime distribution G and all other individuals F. Assume binary splitting and no death. Then

$$Z_t = I_{\{L>t\}} + \left(Z_{t-L}^{(1)} + Z_{t-L}^{(2)}\right) I_{\{L\leqslant t\}}$$

where L is the lifetime of the ancestor. Condition on L to get the expected value

$$E[e^{-\alpha t}Z_t] = e^{-\alpha t}(1 - G(t)) + 2\int_0^t e^{-\alpha(t-u)}E[Z_{t-u}]e^{-\alpha u}G(du)$$

For any cdf F, denote the Laplace transform of its induced probability measure, evaluated at the point α, by $\widehat{F}$, that is,

$$\widehat{F} = \int_0^\infty e^{-\alpha t}F(dt)$$

to get the asymptotics

$$E[e^{-\alpha t}Z_t] \to c \cdot 2\widehat{G}$$

In particular, if there is initial lag with cdf H and we assume this lag to be independent of the subsequent lifetime, we have $\widehat{G} = \widehat{H}\widehat{F}$ and since $2\widehat{F} = 1$ by the definition of α, we get

$$E[e^{-\alpha t}Z_t] \to c\widehat{H}$$

in accordance with (2.7). More realistically, the remaining lifetime after lag phase is over does not follow cdf F because it is the remaining lifetime of a cell sampled from a (stable) population. Denote the cdf of this remaining lifetime by F_α to obtain

$$E[e^{-\alpha t}Z_t] \to 2c\widehat{H}\widehat{F}_\alpha \tag{4.1}$$

and as it can be shown that $2c\widehat{F}_\alpha = 1$, we have shown:

Proposition 4.1. *In a branching process with lag τ and an ancestor sampled from a stable population,*

$$E[e^{-\alpha t}Z_t] \to \widehat{H}$$

as $t \to \infty$.

For a proof, see Section A.2. We get the linear approximation

$$\log E[Z_t] \approx \alpha t + \log \widehat{H}$$

and with the further 0th order Taylor approximation $\log \widehat{H} \approx -\alpha\tau$ we get

$$\log E[Z_t] \approx \alpha t - \alpha\tau$$

which, quite interestingly, agrees with the simple biphasic model stated in (1.1). We will not pursue this approach further in the present article, but in future refined estimation procedures, it ought to be taken into account that once the individual lag phase is over, the remaining life does not follow the individual cdf F but rather F_α.

5. Discussion

Accurate modeling and estimation of bacterial lag phase is important in the food sciences. We introduced a branching process model where lifetimes are assumed to follow a gamma distribution and individuals reproduce by splitting. The gamma distribution is flexible and does not make the (sometimes implicit) no-aging assumption of the exponential distribution. We obtained both exact and asymptotic formulas for the expected population size $E[Z_t]$ at a given time t, and also an approximation formula for $E[\log Z_t]$. Simulations indicated that our approximation formula agrees well with data. We also estimated the expected initial size, n_0, and the mean length of lag phase, μ. Although our estimates were done with nonlinear regression using crude approximations, they turned out to be reasonably accurate. In the future, we propose to develop more sophisticated estimation procedures by more careful analysis of the model. The most obvious extension is to let τ be a random variable and make assumptions about its distribution, aiming to estimate parameters of its distribution. The considerations in Section 4 regarding the special features of the ancestor should also be further developed, in particular in the case of more than one ancestor.

Acknowledgments

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Appendix A

A.1. Proof of Proposition 3.1

First recall the Taylor expansion of the natural logarithm of a random variable X with mean μ and variance σ^2

$$\log X \approx \log \mu + \frac{1}{\mu}(X - \mu) - \frac{1}{2\mu^2}(X - \mu)^2$$

which gives

$$E[\log X] \approx \log \mu - \frac{\sigma^2}{2\mu^2}$$

In particular, we choose $X = Z_t$ and recall that Z_t has the same distribution as $Y_{t-\tau}$ where we assume that τ is constant. By (2.6) and (2.8) we have

$$E[Z_t] \sim cn_0e^{-\alpha\tau}e^{\alpha t}$$

and as it can be shown that the convergence in (2.4) holds also in L^2 (see [9]), we have

$$\mathrm{Var}[Z_t] \sim c^2n_0e^{-2\alpha\tau}e^{2\alpha t}\mathrm{Var}[W]$$

as $t \to \infty$, by additivity of variances for independent random variables. We now get

$$\begin{aligned} E[\log Z_t] &\approx \log E[Z_t] - \frac{\mathrm{Var}[Z_t]}{2E[Z_t]^2} \sim \log E[Z_t] - \frac{c^2n_0e^{-2\alpha\tau}e^{2\alpha t}\ \mathrm{Var}[W]}{(cn_0e^{-\alpha\tau}e^{\alpha t})^2} \\ &= \log E[Z_t] - \frac{\mathrm{Var}[W]}{2n_0} \end{aligned}$$

For the variance, use the Taylor expansion

$$\log X \approx \log \mu + \frac{1}{\mu}(X - \mu)$$

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so that

$$\mathrm{Var}[\log X] \approx \frac{\sigma^2}{\mu^2}$$

which gives

$$\mathrm{Var}[\log Z_t] \approx \frac{\mathrm{Var}[Z_t]}{E[Z_t]^2} \sim \frac{c^2 n_0 e^{-2\alpha\tau} e^{2\alpha t}\mathrm{Var}[W]}{(c n_0 e^{-\alpha\tau} e^{\alpha t})^2} = \frac{\mathrm{Var}[W]}{n_0}$$

Hence, the variance of $\log Z_t$ is approximately constant in the exponential growth phase. □

A.2. Proof of Proposition 4.1

Let us first prove a preliminary lemma dealing with the remaining lifetime of the ancestor who is sampled from a stable population.

Lemma 6.1. *The cdf of the remaining lifetime of the ancestor equals*

$$F_\alpha(t) = 2\alpha \int_0^\infty e^{-\alpha s}(F(s+t) - F(s))ds$$

There is a general procedure to find asymptotic probabilities of which we present the special case needed for our application. To that end, consider some individual property of interest, call it A. We want to find the asymptotic probability $P(A)$ in an exponentially growing population. Let $P(A,s)$ denote the probability that an individual of age s has property A; then,

$$P(A) = 2\alpha \int_0^\infty e^{-\alpha s} P(A,s)ds \tag{6.1}$$

The factor 2α is the reciprocal of the asymptotic probability that a randomly sampled individual is alive, and the integral is the asymptotic probability that the individual is alive and has property A. For details and more general results, see Jagers and Nerman [9]. In our case, denote the remaining lifetime of an individual by Y, fix t, and let A be the property that $Y \leqslant t$. Thus, we need to figure out the probability that an individual of age s has $Y \leqslant t$. Denoting the lifetime of the individual by L, we get

$$P(Y \leqslant t, s) = P(s \leqslant L \leqslant s+t) = F(s+t) - F(s)$$

and hence

$$P(Y \leqslant t) = 2\alpha \int_0^\infty e^{-\alpha s}(F(s+t) - F(s))ds$$

which proves the lemma.

If integration under the integral sign is allowed, we can also get the pdf $f_Y(t)$. By Leibniz integral rule, this is the case if the pdf f of F is continuous. If f is not continuous, the interchange of differentiation and integration may still be allowed if

$$\int_0^\infty e^{-\alpha s} f(s+t)ds < \infty$$

by Theorem (2.27) in Folland [7]. Both these conditions are satisfied for the gamma distributions, as well as any other distribution that is likely to arise in applications. Thus, for all practical intents and purposes, the pdf of Y is

$$f_Y(t) = 2\alpha \int_0^\infty e^{-\alpha s} f(s+t)ds$$

We can now prove Proposition 4.1 which we restate for sake of readability:

$$E[e^{-\alpha t} Z_t] \to \widehat{H}$$

where

$$\widehat{H} = E[e^{-\alpha\tau}]$$

the Laplace transform of the lag τ. We will use (4.1) and show that $2c\widehat{F}_\alpha = 1$. Note that

$$\begin{aligned}\widehat{F}_\alpha &= \int_0^\infty e^{-\alpha t} f_Y(t)dt = 2\alpha \int_0^\infty \int_0^\infty e^{-\alpha(s+t)} f(s+t)dsdt \\ &= 2\alpha \int_0^\infty \int_t^\infty e^{-\alpha u} f(u)dudt = 2\alpha \int_0^\infty \int_0^u e^{-\alpha u} f(u)dtdu \\ &= 2\alpha \int_0^\infty u e^{-\alpha u} f(u)du\end{aligned}$$

and by (2.3), $2c\widehat{F}_\alpha = 1$ which concludes the proof.

A.3. Formulas

In the case of lifetimes being $\Gamma(a,b)$, we can get explicit expressions for the main parameters. The pdf for the $\Gamma(a,b)$ distribution is

$$f(t) = \frac{b^a}{\Gamma(a)} e^{-bt} t^{a-1}, \quad t \geqslant 0$$

where $\Gamma(a)$ is the gamma function. The integral in (2.2) for the definition of the Malthusian parameter α is easily computed as

$$2\int_0^\infty e^{-\alpha t} f(t)dt = \frac{2b^a}{(\alpha+b)^a}$$

which set equal to 1 gives

$$\alpha = b(2^{1/a} - 1)$$

The constant c is defined in (2.3) and can be shown to equal

$$c = \frac{2^{(a+1)/a}}{4a(2^{1/a} - 1)}$$

Finally, the variance of the limiting random variable W equals

$$\mathrm{Var}[W] = \frac{4\int_0^\infty e^{-2\alpha t} f(t)dt - 1}{1 - 2\int_0^\infty e^{-2\alpha t} f(t)dt}$$

see Theorem 19.1, Chapter VI, in Harris [8]. For our gamma distribution we get

$$\mathrm{Var}[W] = \frac{4\left(\frac{1}{2^{\frac{a+1}{a}}-1}\right)^a - 1}{1 - 2\left(\frac{1}{2^{\frac{a+1}{a}}-1}\right)^a} \tag{6.2}$$

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