

The Accumulation Theory of Ageing

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Abstract

Lifespan distributions of populations of quite diverse species such as humans and yeast seem to surprisingly well follow the same empirical Gompertz-Makeham law, which basically predicts an exponential increase of mortality rate with age. This empirical law can for example be grounded in reliability theory when individuals age through the random failure of a number of redundant essential functional units. However, ageing and subsequent death can also be caused by the accumulation of “ageing factors”, for example noxious metabolic end products or genetic anomalies, such as self-replicating extra-chromosomal DNA in yeast.

We first show how Gompertz-Makeham behaviour arises when ageing factor accumulation follows a deterministic self-reinforcing process. We go then on to demonstrate that such a deterministic process is a good approximation of the underlying stochastic accumulation of ageing factors where the stochastic model can also account for old-age levelling off of mortality rate.

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1. Introduction

Very simple organisms do not age, that is they do not show a deterioration of significant life functions with age. Instead they seem to simply break, when one of their essential functions happens to fail. If such failures occur independently with a constant rate λ – that is failures follow a Poisson process – then their corresponding survival function $S(t)$ decays exponentially with time, and lifespans are distributed exponentially – this is just a simple conclusion from mathematical reliability theory and other formally similar processes such as radioactive decay.

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More complex organisms however do age, ie show a deterioration of life functions, for example regarding regeneration after injury, reproduction, metabolic activity and so on, and their mortality rates $\lambda(t)$ tend to increase in time. For many different species, it has been empirically established that mortality rates $\lambda(t)$ increase exponentially with time, following the famous empirical Gompertz-Makeham law of mortality

$$\lambda(t) = \lambda_0 + \alpha e^{\beta t}, \lambda_0, \alpha, \beta > 0, \quad (1)$$

at least approximately (Gavrilov and Gavrilova, 1991) where α, β are constants and λ_0 the age-independent death rate. Notable deviations are usually for very young ages t when “childhood diseases” lead to higher mortality and also for old ages where empirically the mortality rate increases slower than exponentially or even levels off to a constant value.

In this paper we will assume that the driver of ageing, and ultimately death, is the accumulation of Ageing Factors (AFs), which for example plays a major role in the ageing of yeast (Sinclair et al., 1998a). We will demonstrate generically that when such AFs are produced in an auto-catalytic or self-reinforcing process, then Gompertz-Makeham behaviour of the mortality rate follows. Such self-reinforcing processes are quite generic, for example in auto-catalytic chemical or biological reactions or also in self-replicating genetic anomalies, and show typically exponential behaviour. The term *Ageing Factor (AF)* will therefore generically stand for any substance or anomaly that is thought to cause ageing in a specific organism. AFs could come in discrete (even “macroscopic”) chunks or be a continuous quantity. They could be measured in absolute numbers of Ageing Factor Units (AFU s) or as a concentration.

We proceed as follows: We will firstly take the naive point of view that creation and replication of AFs is a deterministic process and mortality proportional to the abundance of AF. This straight-forwardly leads to an exponentially increasing mortality rate (with no old-age levelling). We then go on and assume that the creation and replication of the AFs are stochastic when the AF comes in discrete units and in small numbers. If mortality rate is assumed to be proportional to the probability that an organism has an AF abundance above a critical level, then it follows that the mortality rate increases (more than) exponential for middle ages while it levels off to a constant value at old-ages.

2. Background

2.1. Mortality Models

The above equation eq. (1) is primarily descriptive and empirically derived from data, however does not in itself indicate a reason *why* mortality should increase exponentially with age (at least for middle ages) or any underlying mechanism(s) of ageing. However any such mechanism would need to be quite general since lifespan of so many different species often surprisingly well fit the Gompertz-Makeham law. Therefore various attempts have been undertaken to ground Gompertz-Makeham behaviour in underlying processes that could give

an explanation as to why the mortality rate should increase exponentially with time.

One prominent such attempt follows Gavrilov and Gavrilova (2001). These authors ground the Gompertz-Makeham (and Weibull) laws in reliability theory. Their basic assumption is that complex organisms have a block of redundant functional elements for each essential function. Each such element does not age and hence fails with a constant rate. The organism as a whole fails (or dies) if all redundant elements for a single function have been exhausted. Depending on the number of redundant elements and their failure state at birth, a Gompertz-Makeham or Weibull law of mortality results. This model of ageing also nicely explains the levelling off of the mortality rate at old ages.

A second attempt to ground the Gompertz-Makeham law in a biological mechanism is Shklovskii (2005) starting from the assumption that the ability of an organism to neutralise defective cells (or noxious substances for that matter) is based on random encounters of these harmful items with some neutralising antagonist. If the expected number of such encounters sinks linearly with time, again the Gompertz-Makeham law follows. However no attempt is made to explain old-age longevity or to make plausible why the frequency of such random encounters should decrease linearly in time.

While the two models above are individual-based, ie when an individual dies is determined by its life history, there is finally the Penna model (Łaszkiwicz et al., 2005, Penna, 1995, Stauffer, 2007). This, too, can explain an exponentially increasing mortality rate, albeit on a population level. The Penna model assumes that genetic defects come to bear at different ages, and individuals die if they have accumulated a certain number of genetic defects – in that sense it is similar to ageing in yeast below. However how many defects have been acquired and when they come to bear is predetermined genetically for each individual, and only a population equilibrium of individuals with different defective genes leads then to a Gompertzian exponentially increasing mortality rate.

2.2. Ageing in Yeast

Our approach is motivated by systems that age through accumulating an AF. Yeast (*Saccharomyces cerevesiae*) has in this respect been studied extensively and served as model for ageing in higher organisms (Sinclair et al., 1998a). Albeit a single-cell organism, yeast divides asymmetrically, so that mother and daughter cells can be identified. Mothers eventually cease producing daughter cells, stall and subsequently die. Extensive experimentation has shown that so-called Extra chromosomal rDNA circles (ERCs) are a probable cause of ageing (Sinclair and Guarente, 1997). Finally, lifespan of yeast is best measured in number of generations, that is how many times a mother cell has already divided. While the absolute time between two such divisions depends on the environmental conditions, lifespan distribution measured in generational age is constant for different environments.

An ERC is a snippet of a repetitive section of chromosomal rDeoxyribonucleic Acid (DNA) that is excised from the chromosome sponta-

neously with a low rate, and subsequently forms an extra-chromosomal DNA ring. Excision can happen several times independently with approximately constant low rate since the DNA section in question contains about 100 repeats of the snippet. As the snippet has its own begin-of-replication sequence, once excised it replicates with a certain probability in each cell cycle – and hence replicates in a self-reinforcing process.

At cell division, the mother cell retains almost all of the ERCs and does not share them – eg proportional to cell volumes – with the daughter cells, so that ERCs accumulate in mother cells whereas daughters usually start life free of ERCs. Cell death then is assumed to occur because replication of a high number of ERCs (in the order of 1000) exhausts cell resources needed for replication of the core chromosomal DNA.

For very old mother cells ERC retention capability seems to saturate, so that ERCs are shared with daughters, effectively decreasing the mother’s ERC replication rate and producing prematurely aged daughters with a reduced life span. Modelling the effects of retention saturation is beyond the scope of this paper. From figures discussed in the literature (Gillespie et al., 2004, Sinclair and Guarente, 1997, Sinclair et al., 1998b), it seems however that the reduction in ERC number is minor compared to their absolute number and/or rate of replication, so that mothers’ lifespans are extended around one or two generations at most. It does however significantly reduce the expected lifespan of daughters of old mothers that have received a portion of the mother’s ERCs. The model discussed below can straight-forwardly be modified to take into account birth with a number of ERC but for sake of simplicity we will only deal with populations that start life from a clean ERC-free state as has been the case in many experiments (Sinclair and Guarente, 1997).

Experiments suggest as well that for yeast, cells live on quite happily when they have low or medium numbers of ERCs but die when they have reached a critical level of ERCs so that there does not seem to be a linear increase of mortality rate with number of ERCs as we will naively assume in the deterministic model. Instead the underlying assumption seems to be that mortality shows an increase at or around a critical number of ERCs (Sinclair et al., 1998b).

To conclude, ageing (in yeast and other organisms, Sinclair, Mills, and Guarente 1998a) can be caused by an AF that comes in discrete chunks and where individuals initially start up with no or a very small number of such AF. The number of such AF increases due to two processes: initial creation of such AFs (in yeast by excision from chromosomal DNA) and subsequently self-reinforcing replication (for yeast once in the cell cycle). Finally mortality is correlated with the abundance of such AFs.

In the next section we will present two formalisations of these processes. The first is naive, straight-forward and deterministic. The second however is more complicated and based on stochastic processes. This stochastic model serves also to justify the naive approach. These approaches are certainly motivated by the experimental data for yeast, but we will formulate them quite generally as auto-catalytic processes are an ubiquitous phenomenon in nature, thus might well play a role in ageing processes in many organisms.

3. Models

Let $c(t)$ denote the abundance of an AF at time t . The abundance could either stand for the (discrete) absolute number of Ageing Factor Units (AFU s) if the AF comes in discrete chunks and absolute numbers are low, or for a (continuous) concentration if absolute numbers are high or the factor itself is a continuous variable. We shall assume that $c(t)$ changes in time due to two processes: 1. Creation with rate $p(t)$, ie new AFU s come into existence independently of existing ones. This could be from internal processes such as a product of a chemical or metabolic reaction or the excision of snippets of DNA as in yeast, but also external such as a DNA defects due to UV light and so on. 2. Replication with rate $r(t)$, ie once some AFU s have been acquired there is an auto-catalytic process that produces more AFU s, linearly depending on the abundance $c(t)$ of AF already present, ie $\Delta c(t) \sim c(t)$. Typical examples of such processes are auto-catalytic chemical reactions where the product at the same time is also an educt of the reaction, or the replication of a DNA snippet independently of the core genome as happens with the ERCs in yeast. These processes could be happening in continuous or discrete time, on an absolute time scale or tied to an internal time scale. For yeast for example, ERC replication is synchronised with the cell cycle.

3.1. Deterministic Production of AFs

As it is simpler and instructive, we first consider the case where the AF comes in large quantities in each individual and creation and replication processes have high rates. This means that while individual creation and replication processes may well be stochastic, we can assume – due to the high rates and high numbers of AF involved – that creation and replication proceed deterministically, and variations of AF around its instantaneous mean are negligible.

We will in addition assume continuous time. Mathematical argument is often easier in continuous time than in discrete time, and the inaccuracies incurred by transforming equations between discrete time and continuous time are small when the involved quantities are smooth.

Formalising creation and replication processes in continuous time, $c(t)$ follows an inhomogeneous linear Ordinary Differential Equation (ODE):

$$\frac{dc(t)}{dt} = r(t)c(t) + p(t) \quad (2)$$

with solution for initial value $c(0) = c_0$ (see Appendix A):

$$c(t) = \int_0^t p(\tau) e^{\int_\tau^t r(\tau') d\tau'} d\tau + c_0 e^{\int_0^t r(\tau) d\tau} \quad (3)$$

$c(t), p(t), r(t)$ are non-negative functions, and it is obvious that $c(t)$ increases essentially exponentially with t when $r(t) > 0$. For discrete time, $c(t)$ would be the solution of a similar difference equation which again increases exponentially (geometrically) in time.

For simplicity let us assume $r(t) = r$ and $p(t) = p$ are constant, so that both creation and replication processes of AF do not change with time, and eq. (3) simplifies to

$$c(t) = \frac{p}{r}(e^{rt} - 1) + c_0 e^{rt} \quad (4)$$

However time-varying $r(t)$ and $p(t)$ could also easily be accommodated and would not essentially change the arguments belows.

If we assume the death is only due to the AF, then a natural assumption is that the mortality rate is proportional to $c(t)$, ie:

$$\lambda(t) = zc(t), z > 0 \quad (5)$$

where z is the proportionality factor. Then quite straight-forwardly, inserting eq. (4) into eq. (5) provides a Gompertzian time development of t with some additional terms to adapt to initial conditions. For higher t , $\lambda(t)$ increases exponentially with t , and does not level off to a constant value either for very high t .

3.2. Example: Lifespan of Yeast

Experimental data is often in the form of lifespan distributions rather than mortality rate per se. The lifespan distribution is given by the survival function $S(t)$ which is the probability that an individual survives at least until t . It is related to the mortality rate $\lambda(t)$ via the following ODE with initial condition $S(0) = 1$:

$$\frac{dS(t)}{dt} = -\lambda(t)S(t). \quad (6)$$

This is again of the form as in Appendix A and inserting eq. (4) and eq. (5) and solving for $S(t)$ (see eq. (B.2)) we get:

$$S(t) = e^{-\int_0^t \lambda(\tau) d\tau} = e^{-\frac{zp}{r} \left[\frac{e^{rt}-1}{r} - t \right]} e^{-\frac{zc_0}{r} [e^{rt}-1]}. \quad (7)$$

This form of $S(t)$ can now straight-forwardly be fitted to experimental data, see fig. 1.

As p and c_0 do not enter eq. (7) independently of z , their absolute value cannot be estimated from data unless further biological assumptions are taken into account. r can be seen as the average or effective rate of increase of the AF. The fit is surprisingly good even though it does not take into account the levelling of the mortality rate $\lambda(t)$ observed for many species for high t so it underestimates the frequency of very high lifespans.

3.3. Stochastic Production of AFs

While eq. (7) often yields a good fit as we have seen, it starts from the assumption that the AF comes in high numbers with high rates p and r , so that the process of AF is largely deterministic. The deterministic model does also not account for the levelling off of mortality rate with time. For example for yeast it is however known that the AF comes only in discrete units and

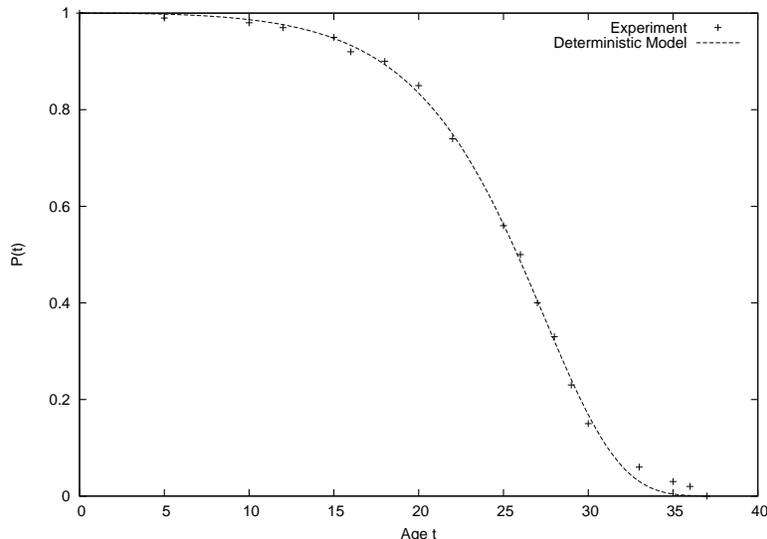


Figure 1: Fitting the survival curve of yeast: A least squares fit for $p' := zp$ and r of eq. (7) against Sinclair et al.'s data 1998b (Fig. 1). c_0 was set to 0, as experiments started with ERC clean cells. Also no age-independent mortality rate λ_0 was used, as accidental death is often negligible under lab-conditions. Best least squares fit for $p' = 0.00011$, $r = 0.22$, $SSR = 0.0034$, $RMS = 0.014$. Note the (expected) underestimation of old-age longevity.

individuals acquire them one by one, and numbers stay smallish throughout life-time. All this does not warrant a deterministic approach. Hence for such discrete AFs in small numbers, creation and replication should be treated as *stochastic processes*. For simplicity of argument here, we will assume discrete time in the following.

The stochastic creation process of discrete AFU s is easily modelled as a (constant or varying rate) Poisson or Bernoulli process, so for constant rate p the expected number of AFU increases as pt with variance pt . In the following we will assume that p is constant. This is simpler and there is also no biological indication to contrary.

The replication process is more complicated and best be described in the framework of branching processes (Haccou et al., 2005), a type of stochastic process suited to model growth processes. We will first look at a pure branching process that corresponds to the stochastic AFU replication in isolation, and subsequently combine replication and creation processes.

In the following capital letters such as X denote random variables. $\Pr(\cdot)$ denotes the probability (density) of an event, $\mathbb{E}(\cdot)$ and $\text{Var}(\cdot)$ the expectation value and variance of a random variable respectively. For further background – such as relations of conditional expectations and variances or approximations of the Q- and erf-function – we refer the reader to good textbooks with an introduction to probability theory, for example Cover and Thomas (1991) or Haccou et al. (2005).

3.4. Replication Process Only

In this section we concentrate on the replication process per se, and assume that initially one AFU is already present: $c(0) = 1$. Then existing AFU s replicate with mean rate r in each time step. This means each single AFU at t gives rise to one (itself) or two AFU s (itself and its replication) at $t + 1$ with probabilities $1 - r$ and r respectively. Formally individual replication is a random variable Ξ with probabilities $\Pr(\Xi = 1) = 1 - r$ and $\Pr(\Xi = 2) = r$, and all other outcomes have probability zero, and we define short symbols for mean and variance of the number of successors of a single AFU : $m := \mathbb{E}(\Xi) = 1 + r$ and $s^2 := \text{Var}(\Xi) = r(1 - r)$.

As the replication process itself is random, also the abundance of the population $c(t)$ at time t is a random variable and – to mark that the abundance is now a random variable in discrete time – we replace symbol $c(t)$ with C_t and call it the population size.

In fact, the sequence of (C_t) forms a *branching process* (see Appendix C) and C_t is the C_{t-1} -fold sum of the individual replication process Ξ (with i.i.d. outcomes; we refrain from distinguishing the individual Ξ in order not to overburden the notation): $C_t = \sum_{i=1}^{C_{t-1}} \Xi$. The expectation value $\mu(t) := \mathbb{E}(C_t)$ and variance $\sigma^2(t) := \text{Var}(C_t)$ of the population sizes C_t then follow from expectation value and variance of individual offspring Ξ as (see Appendix C):

$$\mu(t) = m^t, \quad \sigma^2(t) = s^2 \frac{m^t(m^t - 1)}{m(m - 1)} \quad (8)$$

with the initial condition that we start from a single AFU at $t = 0$, ie $C_0 = 1$.

In the case of deterministic growth, the mortality rate $\lambda(t)$ was assumed proportional to $c(t)$. We could in principle also here set $\lambda(t) \sim \mathbb{E}(C_t) = m^t$ with the same results as above, loosing again the levelling off of $\lambda(t)$ for old ages. Experiments indicate that for yeast, cells with a relative low number of ERCs do not have an altered instantaneous mortality rate from cells with no ERCs. The mortality rate seems to increase only when the number of ERCs has reached a critical level. Hence in this stochastic process setting, it is more natural to assume that the mortality rate $\lambda(t)$ is proportional to the probability that an individual has more AFU s C_t than a fixed critical level c_{\dagger} , ie

$$\lambda(t) = z \Pr(C_t \geq c_{\dagger}), z > 0. \quad (9)$$

This agrees also with the type of mortality criteria used in computer simulations of ageing processes (Gillespie et al., 2004). More complicated dependencies are of course possible, but would typically show a similar dependency on an upper quantile of C_t .

In order to calculate $\lambda(t)$ explicitly, we would need to know the distribution of C_t for all times t . To our knowledge this problem has not been solved explicitly. We can however make a series of approximations for small times t , large times t and middle times t to demonstrate that this setting for the mortality rate $\lambda(t)$ yields Gompertz-Makeham behaviour for middle t and a constant mortality for very old ages.

Small t. We assume that at time $t = 0$ there is one AFU, $C_0 = 1$. As each AFU can have at most two successors (itself and its offspring), we know that for $t < \log(c_{\dagger})/\log(2)$, $\Pr(C_t \geq c_0) = 0$. So depending on c_{\dagger} there will be more or less long an initial period for which the mortality rate is zero.

Approximation with normal distribution. Generally the precise form of $\Pr(C_t)$ is not known. Knowing only its $\mu(t)$ and $\sigma(t)$ we assume that C_t follows approximately a normal distribution with mean $\mu(t)$ and variance $\sigma^2(t)$. This is plausible as C_t ultimately in our setting is a sum of binomial distributions (each individual either replicates or not and survives itself into the next generation, so $C_{t+1} = C_t + B(C_t, r)$) which themselves can be approximated by a normal distribution – however the C_t are not independent. Also quantities related to C_t such as $\Pr(C_t|C_{t-1})$ have been shown to approximate a normal distribution (Quine and Szczotka, 1994). Hence for mildly large t we approximate:

$$\Pr(C_t \geq c_{\dagger}) \approx Q\left(\frac{c_{\dagger} - \mu(t)}{\sigma(t)}\right) = \frac{1}{2} - \frac{1}{2} \operatorname{erf}\left(\frac{c_{\dagger} - \mu(t)}{\sqrt{2}\sigma(t)}\right) \quad (10)$$

where $Q(x) = 1/2 - 1/2 \operatorname{erf}(x/\sqrt{2})$ is the Q-function that gives the mass of a standard normal distribution above x (ie the probability of getting a value larger than x).

Large t $\gg 0$. For large very large $t \gg 0$,

$$\lim_{t \rightarrow \infty} \frac{c_{\dagger} - \mu(t)}{\sigma(t)} = \lim_{t \rightarrow \infty} \frac{c_{\dagger} - m^t}{s \sqrt{\frac{m^t(m^t-1)}{m(m-1)}}} = -\frac{1}{s} \quad (11)$$

as both $\mu(t), \sigma(t)$ grow exponentially with the same rate. Hence

$$\lim_{t \rightarrow \infty} \lambda(t) = Q(-1/s) > 0, \quad (12)$$

ie the mortality rate $\lambda(t)$ levels off with age to a constant positive value, hence $\lambda(t)$ shows the experimentally observed old-age deviation from the Gompertz-Makeham law.

Middle t. We have established that $\lambda(t) = 0$ for small t and $\approx \text{const} > 0$ for large t . As each AFU survives into the next time step, $C_{t+1} \geq C_t$, ie the number of AFU s is non-decreasing. This means that $\lambda(t) = z \Pr(C_t \geq c_{\dagger})$ is non-decreasing as well. Hence $\lambda(t)$ has roughly the form of a (discrete) sigmoid.

If approximation of C_t with a normal distribution is valid also for middle t such that $0 \ll \mu(t) < c_{\dagger}$, where $P(C_t > c_{\dagger}) > 0$ but the expected number $\mu(t) = m^t$ still less than the critical value c_{\dagger} , we go on to show that increase of $\lambda(t)$ must be steeper than m^t , in other words we have an exponential growth of the mortality rate for intermediate ages.

If $x := c_{\dagger} - \mu(t)/\sigma$ is not too close to zero, ie $\mu(t)$ still much smaller than c_{\dagger} , then $Q(x) \approx \frac{1}{\sqrt{2\pi}x} e^{-\frac{1}{2}x^2}$ for $x > 0$ and hence

$$\lambda(t) \approx Q\left(\frac{c_{\dagger} - \mu(t)}{\sigma(t)}\right) \approx \frac{\sigma^t}{\sqrt{2\pi}(c_{\dagger} - \mu(t))} e^{-\frac{(c_{\dagger} - \mu(t))^2}{\sigma^2(t)}}. \quad (13)$$

For $c_t > \mu(t)$, the exponential is increasing towards 1. The denominator of the pre-factor is decreasing, and its numerator increasing exponentially approximately as m^t (since $\sqrt{\frac{m^t(m^t-1)}{m(m-1)}} \approx m^t$ for not too small t). Hence there are intermediate t for which $\lambda(t)$ approximately increases more than exponentially:

$$\lambda(t) \gtrsim zm^t \quad (14)$$

3.5. Creation and Replication

Unless born out of very old mother cells, new-born yeast cell usually do not have any ERC, ie $C_t = 0$ so creation and replication process need to interact to cause ageing. Before replication of AFU s can start, first some must be produced, ie we have a combination of two stochastic processes. This combination is more cumbersome to deal with, but we demonstrate below that (asymptotic) growth rates of $\mathbb{E}(C_t)$ and $\text{Var}(C_t)$ are unaltered, so that the same approximations and asymptotic considerations are valid for this more complicated process as were in the case of replication only.

Let C_t denote the AFU population size as before, and Ξ again the individual AFU replication process with the same distribution. Finally let X_t be the creation process with constant rate p , ie $\Pr(X_t = 0) = 1-p$ and $\Pr(X_t = 1) = p$. Then $\mathbb{E}(X) = p$ and $\text{Var}(X) = p(1-p)$.

The random number C_{t+1} of AFU at time $t+1$ is then the sum of the replication of the previous number of AFU s $\sum_{i=1}^{C_t} \Xi$ plus the number X_t of newly created AFU s:

$$C_{t+1} = \sum_{i=1}^{C_t} \Xi + X_t \quad (15)$$

Utilising independence of the individual Ξ and X_t we can calculate a recursive equation for $\mathbb{E}(C_t)$ as in the case above, see Appendix D:

$$\mathbb{E}(C_{t+1}) = m \mathbb{E}(C_t) + \mathbb{E}(X_t) \quad (16)$$

with explicit solution for initial value $C_0 = 0$:

$$\mathbb{E}(C_t) = \frac{p}{m-1}(m^t - 1). \quad (17)$$

Comparison of (16) and (17) with (2) and (4) also makes it clear that the process C_t is the stochastic time-discrete analogue to the deterministic continuous time equation in section 3.1 (with $r = \log(m)$).

Likewise a recursive formula for $\text{Var}(C_t)$ can be obtained:

$$\text{Var}(C_{t+1}) = m^2 \text{Var}(C_t) + s^2 \mathbb{E}(C_t) + \text{Var}(X_t). \quad (18)$$

This has a rather tedious explicit solution, see Appendix D. For large t however it is clear from the dependency of $\text{Var}(C_t)$ on $\text{Var}(C_{t-1})$ and because $\mathbb{E}(C_t)$ only grows like m^t for large t , that the growth of $\text{Var}(C_t)$ will asymptotically be like m^{2t} . Ie both $\text{Var}(C_t)$ and $\mathbb{E}(C_t)$ grow asymptotically as in the case before.

Hence again under the assumption that C_t can be approximated well enough with a normal distribution, the same considerations as above for small, middle and large follow, ie $\lambda(t) = 0$ for small t , $\lambda \gtrsim zm^t$ for middle t and $\lambda(t)$ constant for large t .

4. Discussion

The production processes and death criteria considered in this paper arise from experimental observation of ageing in yeast mother cells where ERCs seem to be drivers of ageing and death. It is remarkable indeed that the deterministic equation eq. (7) already yields such a good fit with experimental data, even though the underlying process model is deterministic, uses a non-biological death criterion and finally does not take any detailed properties of the underlying AF production processes into account such as sharing of ERCs between old mothers and daughters. It only relies on the exponential accumulation of AFs. The model does not take into account either that ageing in yeast need not necessarily only take place through accumulation of ERC.

In the stochastic model, we have demonstrated that the mortality rate increases with time roughly like a discrete sigmoid and $\lambda(t) \gtrsim zm^t = ze^{rt}$, $r = \log(m)$ for middle t . The good fit of an exponential mortality rate with data (eg in fig. 1) shows that usually $\lambda(t)$ does not increase significantly faster than exponentially or that such faster increase has no significant effect on the form of the survival function. If we do not care about the overestimation of mortality old ages, we can extend the exponential approximation of $\lambda(t)$ also to greater t . Finally we know that $\Pr(C_t \geq c_{\dagger}) = 0$ strictly for young ages. Extending the approximation of C_t with a normal distribution also to these young ages would lead to a $\Pr(C_t \geq c_{\dagger}) > 0$. However as then also $c_{\dagger} \gg m(t)$ this is often negligibly small (and would for example be masked by a constant age-independent death rate λ_0). Hence the deterministic approach $\lambda(t) \sim e^{rt}$ can be justified for all ages t as an approximation of the stochastic approach $\lambda(t) \sim \Pr(C_t \geq c_{\dagger})$.

Gillespie et al. (2004) set out to understand ageing in yeast with the help of numeric computer simulations. Essentially they simulated a stochastic process such as in section 3.5. Their simulation also modelled the old-age ERC sharing between mothers and daughters. Simulation parameters, such as replication rate r or excision rate p were estimated from data in the literature. With these estimated parameters, their simulation yielded a fairly good fit which however was not quantified. The best fit was achieved by assuming that $p(t) \sim t^2$, ie a non-constant creation rate which seems to be an ad-hoc choice to improve the fit over a constant excision rate. In light of the good fit of eq. (7) which was derived with a constant p , it is quite surprising that Gillespie et al. did not obtain a good fit under the same assumption.

Finally the rate with which ERCs in yeast are replicated has been estimated as about $m = 1.6$ (Sinclair and Guarente, 1997) – this follows as an average rate from an average lifespan of 15 generations once the first ERC has been acquired and a critical level in the order of 1000, as $m \approx 1000^{1/15} = 1.585$ and hence $r = \log 1.59 \approx 0.46$, this is about twice the r estimated from the data in fig. 1.

Last but not least, eq. (7) and its good fit to the data also confirm quantitatively a qualitative conjecture of Sinclair et al. (1998b), namely that the survival function for yeast is a “sum” of a decay process (due to excision) and subsequent exponential accumulation of ERCs, albeit the combination of these two processes is a more involved sum than Sinclair et al. implied, namely that of two stochastic processes in eq. (15).

5. Conclusion

In this paper we have demonstrated that mortality rates similar to those in the Gompertz-Makeham law can be derived when we assume an AF is produced in an auto-catalytic process. Such processes in turn lead to an exponential (or synonymously geometric) increase of the abundance of AFs. In the case of deterministic production of AFs, with mortality assumed proportional to the AF abundance a plain Gompertz-Makeham law follows with the usual underestimation of longevity for old ages. In the stochastic case, not only does a Gompertz-Makeham law follow, but also the levelling off of mortality rates is derived if mortality is assumed proportional to the probability that an individual has reached a critical level of AFs.

All in all the paper establishes a useful and interesting relation between mortality rates that follow a Gompertz-Makeham law and an underlying auto-catalytic process. For yeast ageing driven by ERCs the model and data are in qualitative agreement. However discrepancies between the rate of replication estimated here and within other experimental contexts need to be examined.

The derived relation is general and applicable to all organisms where ageing is based on exponential accumulation of an AF – this nicely contrasts and complements Gavrilov and Gavrilova’s approach (2001) for which ageing is based on the exhaustion of parallel redundant functional elements.

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Appendix A. General Linear ODE

In the present paper the linear inhomogeneous ODE plays a role:

$$\frac{dx(t)}{dt} = a(t)x(t) + b(t) \tag{A.1}$$

where $a(t)$ can be thought of as a time-variant rate of growth of $x(t)$ and $b(t)$ as a time-variant external influx to $x(t)$. The generic solution can be obtained – under some smoothness assumptions – for example using the Green’s function approach. We refer the reader to a generic textbook on ODEs and just state

the generic solution below. The reader can check the correctness of the solution through differentiating with respect to t and inserting into eq. (A.1).

In the homogeneous case, i.e. $b(t) = 0$, the general solution of eq. (A.1) with initial value $x(0) = x_0$ is

$$x(t) = x_0 e^{\int_0^t a(\tau) d\tau}. \quad (\text{A.2})$$

In the inhomogeneous case $b(t) \neq 0$, the general solution with initial value $x(t) = x_0$ is:

$$x(t) = \int_0^t p(\tau) e^{\int_\tau^t r(\tau') d\tau'} d\tau + x_0 e^{\int_0^t r(\tau) d\tau} \quad (\text{A.3})$$

For example if $a(t) = a$, $b(t) = b$ are constant and $x(0) = 0$ the solution is:

$$x(t) = \frac{b}{a} (e^{at} - 1) \quad (\text{A.4})$$

Appendix B. Lifespans and mortality rate

Let $\lambda(t)$ be the instantaneous mortality (or failure) rate, ie the rate with which an individual dies/fails at t , then is it related to the distribution of lifespans or survival function $S(t)$ (ie the probability for an individual to survive until time t) via:

$$\frac{dS(t)}{dt} = -\lambda(t)S(t) \quad (\text{B.1})$$

with initial condition $S(0) = 1$. This equation is of the form of eq. (A.1), hence solved for $S(t)$ we obtain:

$$S(t) = e^{-\int_0^t \lambda(\tau) d\tau}. \quad (\text{B.2})$$

If we have independent processes that cause death with rates $\lambda_1(t)$ and $\lambda_2(t)$ and corresponding survival functions $S_1(t), S_2(t)$ and combine them as $\lambda(t) = c_1 \lambda_1(t) + c_2 \lambda_2(t)$, then due to linearity of integration and because the exponential transfers sums into products:

$$S(t) = S_1^{c_1}(t) S_2^{c_2}(t). \quad (\text{B.3})$$

This is handy when dealing with different terms in a complex $\lambda(t)$ separately. For example adding constant age independent mortality rate λ_0 to a $\lambda(t)$ means that the corresponding $S(t)$ acquires an additional factor $e^{-\lambda_0 t}$.

Appendix C. Branching Processes

Intuitively a branching processes is a model for stochastic reproduction of individuals in discrete time and follows the population size C_t in time. Each individual lives for one time step (or generation), and produces a number of offspring according to a random variable (rv) Ξ with mean of $m := \mathbb{E}(\Xi)$ and variance $s^2 := \text{Var}(\Xi)$ according to a fixed probability distribution. Given the

population size C_t , the number of individuals in the next generation C_{t+1} is a random number that is the sum of all offsprings produced randomly and independently by all individuals in C_t , ie $C_{t+1} = \sum_{i=0}^{C_t} \Xi$. The sequence of $(C_t)_{t \geq 0}$ forms a stochastic process, ie a sequence of interdependent random variables (Haccou et al., 2005).

Let $\mathbb{E}(X)$ denote the expectation value of a random variable X and $\Pr(X)$ and $\text{Var}(X)$ its probability and variance. For given expectation m of an individual's offspring and initial population $C_0 = 1$, one can then calculate the expectation values $\mu(t) := \mathbb{E}(C_t)$ of expected population sizes. Since $\mathbb{E}(C_{t+1}|C_t) = \sum_{i=0}^{C_t} \mathbb{E}(\Xi) = mC_t$ it follows:

$$\begin{aligned} \mu(t+1) &= \mathbb{E}(C_{t+1}) = \mathbb{E}(\mathbb{E}(C_{t+1}|C_t)) = \\ &= \mathbb{E}(mC_t) = m\mathbb{E}(C_t). \end{aligned} \quad (\text{C.1})$$

Utilising this recursiveness, it follows with initial value $C_0 = 1$:

$$\mu(t) = m^t. \quad (\text{C.2})$$

A similar but more lengthy argument yields (see for example Haccou, Jagers, and Vatutin 2005) or compare to the more complex argument below for eq. (D.8))

$$\sigma^2(t) := \text{Var}(C_t) = s^2 \frac{m^t(m^t - 1)}{m(m - 1)}. \quad (\text{C.3})$$

For $t \gg 0$, this can be approximated as

$$\sigma^2(t) \approx s^2 m^{2t} \quad (\text{C.4})$$

Hence for a branching process expectation $\mu(t)$ and its standard deviation $\sigma(t)$ both increase exponentially with m^t .

“Individuals” and “offspring” in a branching process as above can correspond to “individuals” in the biological sense but also to other discrete units that reproduce. In the main text, an individual is an AFU that reduplicates with probability r in a time step and also survives into the next time step with certainty. An individual AFU then has either one (itself, no replication) or two successors (itself and its replication), ie individual reproduction Ξ into the next time step is governed by the following probability distribution:

$$\Pr(\Xi = 1) = (1 - r), \quad \Pr(\Xi = 2) = r \quad (\text{C.5})$$

and probabilities for all other outcomes zero. The individual reproduction process Ξ then has mean $m = 1 + r$ and variance $s^2 = r(1 - r)$. Note that this branching process cannot die out ($\Pr(C_t > 0, \forall t) = 1$), as there is at least one successor for each individual (ie $\Pr(\Xi \geq 1) = 1$). In fact the process will be non-decreasing $C_{t+1} \geq C_t$.

Appendix D. Combined Production Process

The full stochastic production process of AFU s is the combination of a standard Galton-Watson branching process that governs AFU replication and a Bernoulli process (a discrete time Poisson process) that governs AFU creation.

Let C_t denote the population size at t , and Ξ the individual AFU replication process with mean $\mathbb{E}(\Xi) = m$ and variance $\text{Var}(\Xi) = s^2$ as before. Let further X_t be the Bernoulli creation process with constant rate p , ie $\Pr(X_t = 0) = 1 - p$ and $\Pr(X_t = 1) = p$. Then $\mathbb{E}(X_t) = p$ and $\text{Var}(X_t) = p(1 - p)$ at each time step. The process we are interested in is given by the sequence of recursively defined random variables C_t

$$C_{t+1} = \sum_{i=1}^{C_t} \Xi + X_t. \quad (\text{D.1})$$

Utilising independence of the individual Ξ s and X_t we can calculate a recursive equation for $\mathbb{E}(C_t)$. First we note that

$$\mathbb{E}(C_{t+1}|C_t) = \sum_{i=1}^{C_t} \mathbb{E}(\Xi) + \mathbb{E}(X_t) = C_t m + p. \quad (\text{D.2})$$

Then making use of $\mathbb{E}(A) = \mathbb{E}(\mathbb{E}(A|B))$ it follows:

$$\mathbb{E}(C_{t+1}) = \mathbb{E}(\mathbb{E}(C_{t+1}|C_t)) = m \mathbb{E}(C_t) + p. \quad (\text{D.3})$$

With initial condition $C_0 = \mathbb{E}(C_0) = 0$ this can be resolved in closed form:

$$\mathbb{E}(C_t) = \frac{p}{m-1}(m^t - 1). \quad (\text{D.4})$$

Consequentially $\mathbb{E}(C_t)$ increases with m^t for large t . For the variance, we set $Z_t := \sum_{i=1}^{C_t} \Xi$, hence $C_{t+1} = Z_t + X_t$ and utilising again the independence of Z_t and X_t :

$$\text{Var}(C_{t+1}) = \text{Var}(Z_t) + \text{Var}(X_t) \quad (\text{D.5})$$

and further using the variance partitioning formula $\text{Var}(A) = \mathbb{E}(\text{Var}(A|B)) + \text{Var}(\mathbb{E}(A|B))$:

$$\text{Var}(Z_t) = \mathbb{E}(\text{Var}(Z_t|C_t)) + \text{Var}(\mathbb{E}(Z_t|C_t)) \quad (\text{D.6})$$

$$= \mathbb{E}(C_t s^2) + \text{Var}(m C_t) = s^2 \mathbb{E}(C_t) + m^2 \text{Var}(C_t), \quad (\text{D.7})$$

and hence we get the recursive formula:

$$\text{Var}(C_{t+1}) = m^2 \text{Var}(C_t) + s^2 \mathbb{E}(C_t) + \text{Var}(X_t). \quad (\text{D.8})$$

We have already a closed solution for $\mathbb{E}(C_t)$. Inserting eq. (17) into (D.8) we (or rather `maxima` with some subsequent manual simplification) can solve this

for $\text{Var}(C_t)$ with initial condition $\text{Var}(C_0) = 0$ (from $C_0 = 0$):

$$\text{Var}(C_t) = m^{2t} \left(p(1-p) \frac{1-m^{-2t}}{m^2-1} + ps^2 \frac{1-m^{-t}}{m(m-1)^2} - ps^2 \frac{1-m^{-2t}}{(m-1)(m^2-1)} \right) \quad (\text{D.9})$$

This is rather cumbersome, and we refrain from further simplification as it is obvious that for $t \rightarrow \infty$ $\text{Var}(C_t) \sim m^{2t}$. As also this C_t is non-decreasing, the same argumentation as in section 3.4 can be applied to the full process in section 3.5.

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