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Modelling Perspectives on Aging: Can Mathematics Help us Stay Young?

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We survey several types of mathematical models that keep track of age distributions in a population, or follow some aspects of aging, such as loss of replicative potential of stem cells. The properties of a class of linear models of this type are discussed and compared. We illustrate the applicability of such models with a simple example based on hypothetical stem cell dynamics developed to address age-related telomere loss in the human granulocyte pool. We then describe the contrasting behaviour of nonlinear systems. Examples are drawn from the class of "dynamical diseases" to illustrate some of the aspects of nonlinear systems. Applications of these, and other models to the problems of aging and replicative aging are discussed.

1. Introduction

This paper provides a brief review of a number of mathematical models, ranging from classical to recent, that address issues related to the biology of aging. A recent example will focus on replicative aging in tissue with continued cell turnover. The purpose of the paper is to address whether, and under what circumstances, modelling and mathematical methods could be a useful tool to add to pre-existing tools of the discipline of aging-related biology.

Many of the models described here have appeared at a greater level of mathematical detail or biological depth elsewhere, with a different target audience in mind. While this paper is neither a comprehensive review, nor a definitive survey of all current relevant work, we hope to highlight a few of the key ideas in the realm of modelling, in the context of relatively simple examples, with the aim of exposing both potential strengths and weaknesses.

We start with models that serve predominantly as book-keeping devices, and that can be used to follow aging populations of individuals or cells. We then discuss some of the recent advances from the field of nonlinear dynamics and possible applications to physiology and aging biology.

2. Linear Dynamics of Populations: From Cells to Organisms

The collection of models in this section span several levels of organization. The common theme is that models can provide a quantitative framework for keeping track of various ages, stages of growth or cell division classes. The level of detail that one chooses to include is arbitrary in many respects, and should be guided to a large extent by the biological data against which the models are to be validated.

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Models for age-structured populations are part of the classical lore in the modelling literature, and have been described in detail in numerous sources. Those used here for the purpose of illustration also fit into a class that can be described by the term "linear" models. This means, essentially, that rates of change are simply proportional to variables describing the state of the system—i.e. interactions are largely ignored. Mathematically, this makes the models very easy to analyse and understand. To a mathematician, the words *linear* and *nonlinear* convey rich meaning: linear systems are largely predictable, and easily classified into a few well-known categories of behaviour (exponential growth or decay with or without simple oscillatory fluctuations). Nonlinear systems hold many surprises: the study of nonlinear dynamic behaviour has spawned a rich mathematical discipline in itself, and areas of application span many scientific disciplines.

Below, several examples of population models in which aging or age-structure are described.

2.1. DEMOGRAPHICS AND AGE STRUCTURE

Various phenomenological quantitative models that quantify and predict human mortality have been developed. The idea behind such demographic models was not necessarily to affect our understanding or control of the aging process, but often simply to predict actuarial risks and profitability.

2.2. LAWS OF MORTALITY

"Laws of mortality" were first quantified in 1825 by Benjamin Gompertz, a British actuary (reprinted by Smith & Keifitz, 1977). The Gompertz equation, as it is now known, consists of a simple variation on the idea of the Malthusian exponential growth (or mortality) equation:

$$\frac{dN}{dt} = -\gamma(t)N(t), \quad \frac{d\gamma}{dt} = a\gamma,$$

where t is the time (= age of cohort), $N(t)$ is the population size of a cohort at time t, $\gamma(t)$ is the mortality, and a is the time rate of increase of mortality with age (equivalent to assuming that mortality increases exponentially with age). We know this to be a naive assumption (see, for example, the paper by Azbel, this issue). The equations can be easily integrated to predict the population of the cohort starting from some size N_0 at time $t = 0$ and into the future. We can easily generalize the model to include cohorts of many distinct ages. This leads to the next example in our hierarchy of age-structured models, in which several age classes are considered simultaneously.

2.3. AGE STRUCTURE IN A POPULATION

2.3.1. *Discrete Models*

We can describe the age structure of the population by keeping track of the numbers of individuals in a given age class. (See Fig. 1 for notation and basic structure of the model.) Suppose that L is the maximal lifespan, and that n is some arbitrary number of distinct age classes to be followed (for example, $n = L$ means we follow aging year by year). The Leslie Model, developed in the 1940s then allows us to follow changes in the population as births and mortalities occur. Let $P_0(t), P_1(t), \ldots, P_j(t), \ldots, P_n(t)$ denote the number of females in a population in age classes 0 (newborn), 1, …, j, …, n. Daughters can only be "born into" age class 0, and thereafter have some age-dependent mortality, μ_j at age j. A given age has some age-dependent fecundity, σ_j associated with it. If we define σ_j as the average number of daughters born to a female while she is in the j-th age class, and μ_j as the fraction of females in that age class that do not survive to the next age class, then the Leslie model would read

$$P_0(t+1)_1 = \sigma_1 P_1(t) + \sigma_2 P_2(t) + \cdots + \sigma_j P_j(t) + \cdots + \sigma_n P_n(t),$$

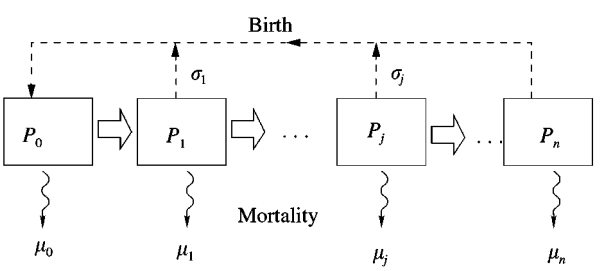

FIG. 1. Diagram summarizing the age-structured model represented by the system of differential equations (1), P_j represents the size of the population currently at age j. μ_j is the mortality and σ_j is the birth rate from stage j.

$$
\begin{aligned}
P_1(t+1) &= (1-\mu_0)P_0(t),\\
&\vdots\\
P_j(t+1) &= (1-\mu_{j-1})P_{j-1}(t),\\
&\vdots\\
P_n(t+1) &= (1-\mu_{n-1})P_{n-1}(t). \qquad (1)
\end{aligned}
$$

Here, time, t, is measured in units of L/n. The first equation keeps track of births, while subsequent equations track mortality from various age classes (see Fig. 1).

From the model, we can make a few elementary quantitative predictions about the behaviour of the process:

- If there is no mortality and no births from the intermediate classes, then the whole population just moves as a group from one class to the next, with no changes in relative proportions. The cohort just "ages" with time, and the initial age structure is preserved for up to n time steps. (After this, one has to make further assumptions about what happens to individuals when they enter the last stage.)
- If there is no mortality and constant fecundity $\sigma > 0$ from each age class (unrealistic for humans), then the total population $P = P_0 + P_1 + \cdots + P_n$ increases by a factor σ at each time step. This leads to exponential growth.
- If there is constant mortality $0 \leqslant \mu \leqslant 1$ at all ages (unrealistic but intuitively appealing) and no births, then the total population decreases by a factor $1 - \mu$ at each time step. Thus, after t steps, there would be a multiplicative factor of $(1-\mu)^t$ times the initial population, so the population decays exponentially.
- If both mortality and fecundity are constant, then the total population is scaled by the factor $P(\sigma + 1 - \mu)$, so behaviour depends on whether $\sigma - \mu$ is positive (growth) or negative (decline).

The above predictions are trivial, and the scenarios far from realistic. (But see comparison with models in the following sections for further insights.) However, the far more interesting cases of age-dependent mortalities and fecundities can easily be handled in such models. Part of the attraction of the Leslie models is that they can tap well-developed mathematical tools of linear algebra. In vector notation, the system of equations are written as

$$\mathbf{P}(t+1) = \mathbf{M}\mathbf{P}(t),$$

where $P = (P_0, P_1, \ldots, P_n)$ is the vector of population sizes in each age class and $\mathbf{M}$ is the matrix of coefficients that fall into a well-defined mathematical setting. It can be shown that, provided $\sigma_j \geqslant 0$ and $0 < \mu_j \leqslant 1$, one can find a growth rate λ (the *dominant eigenvalue* of the matrix M) and a stable age distribution $\bar{\mathbf{P}}$ (corresponding *eigenvector*) such that

$$\mathbf{P}(t) \sim c\lambda^t \bar{\mathbf{P}},$$

that is, the population grows in an exponential way, while the relative proportions of people in the various age brackets approaches a well-defined stable distribution. Both the growth rate and the stable distribution can be obtained, given the birth and mortality parameters [see, for example Caswell (2001) for details].

In the Leslie Matrix model, the population in one class will be transferred to the next age class every time unit L/n, simply by virtue of the passing of chronological time. This is not necessarily the case in other situations, for example, if we consider stages of development, or numbers of divisions that cells have undergone. In that case, different individuals (or cells) may undergo a transition at random, but with some average *residence time* in a given stage. If the size of the sample population is large, this type of transition can be described by differential equations in which time is continuous, rather than discrete, and where transitions are modelled much like flows through compartments.

2.3.2. *Continuous Models*

We first consider again the simple example in which there is no mortality, and no births, but only a simple transition to successive stages of differentiation or successive classes. For example, this would apply to a population of cells that go through a variety of stages before emerging at

some fully differentiated form. As further simplification, we take the case that mean residence time in a given stage is constant and equal for all classes. We let $(S_0, S_1, \ldots, S_n)$ be the number of cells at a given stage at time t and scale time in units of the mean residence time. This leads to the system of differential equations:

$$\begin{aligned}
\frac{dS_0}{dt} &= -S_0, \\
\frac{dS_1}{dt} &= S_0 - S_1, \\
&\vdots \\
\frac{dS_j}{dt} &= S_{j-1} - S_j, \\
&\vdots
\end{aligned} \tag{2}$$

The equations require some additional information about the starting state (initial data), i.e. we must specify the numbers of cells of each type at the beginning of the process. Setting $S_0 = N$, where N is some constant total naive (stage 0) cells initially, and $S_j = 0$ for all other classes, we can solve the system of equations successively with the result that the number of cells in the j-th class is given explicitly by a formula (see the Appendix). The results are shown in Figs 2 and 3. We can comment on a number of features of this simple example worth noting:

1. The total number of cells here, namely $S = S_0 + S_1 + \cdots + S_n$ is constant, to a good approximation (see the Appendix for details). This means that the cells are merely growing older and older, i.e. "flowing" into more advanced division classes. Loss would occur only if we assume that after some finite number of divisions, n, the cells are lost or simply die. In this, the model corresponds to what was seen earlier in the context of the discrete Leslie Matrix model.

2. The number of naive cells, S_0 drops off exponentially: i.e. with age, there are fewer and fewer of these.

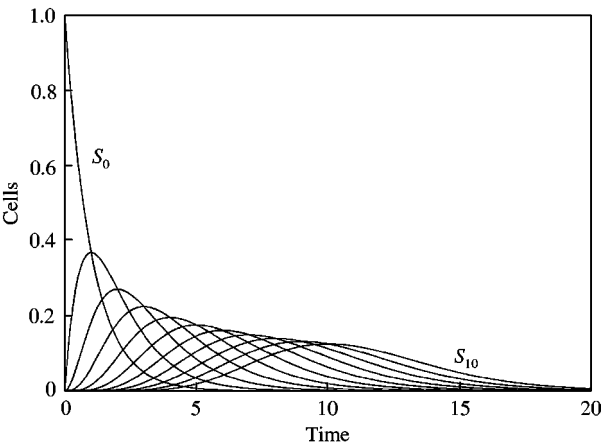

FIG. 2. Behaviour of a simple model for differentiation stages in a population of cells, in which there is no mortality and no new cells, as given by eqns (2). The number of cells in the first ten differentiation stages $S_0, S_1, \ldots, S_{10}$ are shown by the curves plotted here vs. time. The number of cells in class S_0 decreases exponentially. In each other class, the number builds up, peaks, and declines. Results of the same model are shown in Fig. 3.

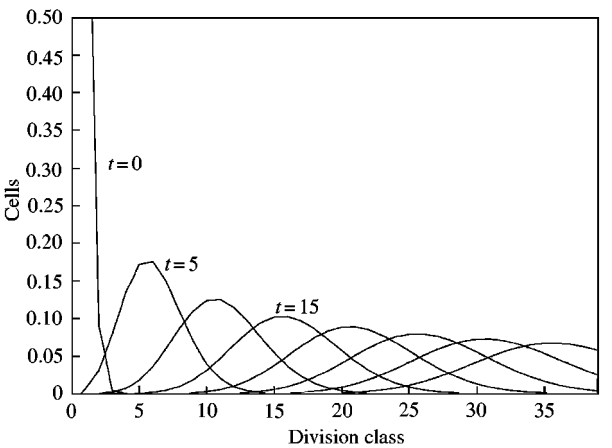

FIG. 3. The distribution of cells by generation at times $t = 0, 5, 10, 15, \ldots, 35$ are shown for the model given by eqns (2) and Fig. 2. Initially, most cells are in the youngest class. With time, the peak of cells moves to higher classes. The distribution also broadens over time.

3. Initially, most division classes are empty: it takes time for these to fill up, as cells keep dividing. This also means that the distribution of the cells is fairly narrow at the beginning.

4. For a given division class, there is some time when it contains some largest number of cells: in other words, the "crest of the wave" of cells passes successively through division cycles.

5. The mean number of divisions that cells have undergone increases with time at a roughly constant rate (see the appendix).

6. The age distribution at any given time has a peak, but the distribution of cells of different generations widens: initially most cells are at most 1–2 divisions away from their naive state, but after a while there are cells at practically all generation classes. This results from the fact that a cell division (unlike a chronological marker, such as a birth date) can occur at any time. The model captures the fact that there is a distribution of individual residence times so that a spread in the distribution occurs with time.

A survey of such models and their applications is given in Caswell (2001). Another variant which fits into the same class is the continuous age-structure model such as the Von-Foerster McKendrick equation

$$\frac{\partial N}{\partial t} = -\frac{\partial N}{\partial a} - \mu(a)N,$$

where $N(a,t)$ is the population age-density at time t and age a, μ is age-dependent mortality. (In this variant, there are no discrete stages, but rather a continuous progression through age or degree of maturity.) This partial differential equation is a "conveyor belt" representation of the process shown in Fig. 1. The birth terms are lumped together in what is referred to as a boundary condition, i.e. a specification of what happens at $a = 0$.

These three models are closely related, even though the detailed techniques used to analyse them might differ. Furthermore, the basic standard model forms can be refined and made more detailed by assumptions about how births and mortalities depend on environmental conditions, genetic factors, etc., possibly at the expense of ease of analysis. Since mathematicians have an impressive arsenal of simulation techniques at their disposal, such refinements are rarely an obstacle to making predictions.

3. Application: Population Dynamics of Stem Cells

In this section, we discuss one application of ideas of stage and age-structured population modelling to a problem which is related to aging biology from yet another perspective, namely, the process by which cells of a single individual may age and have reduced replicative potential over time. A distinction is generally made between aging resulting from the decline in the function of non-dividing cells (e.g. in neurons) and the decline in the function of tissues with continued turnover such as the skin, gut and blood. Loss in the ability to divide affects the latter and our model addresses only this aspect of aging.

Some cells in the body are relatively quiescent, and divide rarely, while others must be replaced constantly. Cells of the blood, skin, and digestive tract constantly wear away and must be replaced by new cells. According to Potten and Loeffler (1990), stems cells of the gut divide more than 5000 times. The number of blood cells produced daily in a normal adult human is 10^{11}–10^{12}, or roughly 4×10^{16} per lifetime (Lansdorp, 1997). A minimum number of 55 cell doublings would be needed to supply this population (since $2^{55} = 4 \times 10^{16}$). A specialized pool of cells, called pluripotent stem cells, is responsible for replenishing the entire pool of blood cells over the lifetime of the individual. The two equally important criteria are that (1) a sufficient supply of differentiated cells are to be produced as needed on a continual basis and (2) the supply of stem cells must self-renew so that future supplies of cells are ensured.

There is controversy in the literature about how many times stem cells can and do divide (see Kay, 1965; Rufer *et al.*, 1999). Stem cells were initially considered to be immortal but now this idea has come into question: it is thought that there is a finite replicative potential, and that aging correlates with loss of competent stem cells (Lansdorp, 1997). Stem cells themselves are currently both too few and too cryptic to identify and count directly, but some of their progeny can be identified, tracked, and counted. Rufer *et al.* (1999) used fluorescence *in situ* hybridization (FISH) techniques to measure the length of telomeres in granulocytes and T lymphocytes from over 500 individuals of all ages to address the question of what underlying dynamics are at work in the stem-cell pool. They discovered that there is a clear decrease in telomere length with age, which, despite considerable scatter, points to

some continual change in the pool of stem cells from which these cells have descended.

Telomeres are ends of chromosomes, known to contain repeats of the form $(TTAGGG)_n$. Each cell division results in the decrease of telomere length in a cell (some exceptions occur). In humans, telomeres shorten by 50–200 bp (on average 100 bp) per division. According to Hayflick (1965), normal somatic cells can undergo a finite number of divisions before they enter into a state called replicative senescence. Harley (1991) proposed that replicative senescence could be explained because the telomere repeats are eventually depleted (however, see the discussion below). Rufer *et al.* (1999) postulated that the length of telomeres in a stem cell would, in principle, correlate with the number of times that the stem cell has undergone self-renewal cell division (i.e. a division that produces new stem cells). Assuming that the number of divisions separating stem cell from differentiated blood cell (e.g. granulocyte) is constant, e.g. 20 divisions, one could infer that the loss of telomere repeats in the granulocyte pool over the lifespan of an individual results from successive self-renewal divisions in the stem cell pool. According to Rufer *et al.* (1999), the data is best fit by a bisegmented line: the length of telomeres in the granulocyte pool decreases by about 3052 bp per year during the first half-year of life, and by about 34 bp per year thereafter.

Population dynamics in an age-structured population have an analogue in cell population dynamics. (This highlights part of the power of mathematics: the ability to generalize from one situation to another, and to extract lessons learned in one system to that of another, seemingly unrelated system.)

Consider the possibility that stem cells can self-renew: i.e. divide to produce two daughter stem cells (with rate p expressed as number of divisions per year) or undergo "tangential division" to produce one stem cell and one daughter destined to differentiate (with rate f, similarly expressed as number of divisions per year). These rates of division undoubtedly vary over time, with age, and in response to many biological factors which the aggregate data in Rufer *et al.* (1999) does not reveal. We can at best hope to arrive at some ideas about mean rates of division,

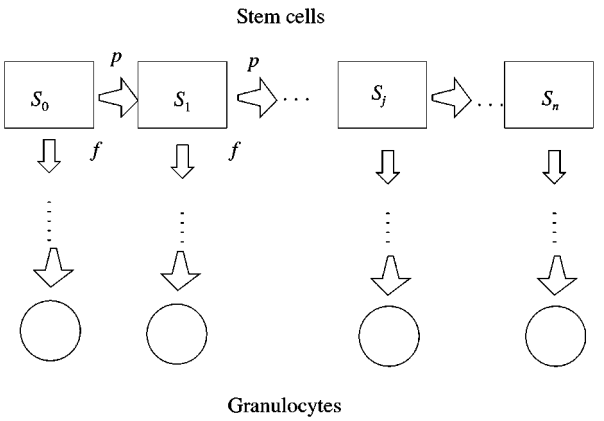

FIG. 4. Diagram summarizing hypothetical stem cells dynamics. Horizontal flow: stem cells undergo self-renewal divisions at rate p, each time producing two daughter stem cells. Subscripts refer to the number of cell divisions that these cells have undergone. Vertical: the stem cells also undergo asymmetric divisions at rate f, producing one blood precursor and one new stem cell. Expansion by a factor of roughly 2^{20} produces the final pool of blood cells. Telomere fluorescence is measured in the granulocyte pool, represented by circles. The tapered arrows represent expansions of a given population.

with those means taken over a large number of data points from distinct individuals at distinct ages, and over a time-scale comparable to a typical lifespan.

Let $S_0(t), S_1(t), \ldots, S_n(t)$ denote the population of stem cells that have already undergone $0, 1, \ldots, n$ self-renewal divisions at time t. (See Figure 4 for the notation and basic structure of the model.) (Initially, at a sufficiently young age, most of these classes are empty, i.e. there are only stem cells with low division numbers present.) We consider simple models of possible cell dynamics, and what these would imply in the examples given below.

3.1. NULL MODEL: SUCCESSIVE DIFFERENTIATION WITH NO BIRTH OR MORTALITY

If there is no self-renewal, then $p = 0$. Selecting time units that are multiples of the mean generation time (so that $f = 1$) leads to the system of differential equations precisely as shown in eqns (2), but this system would be inadequate as a model for stem-cell dynamics for two reasons: (1) cells are not expanding, as the stem-cell pool is believed to do and (2) cells are not being lost to either mortality nor to differentiation, as would

be the case for production of blood cells. We therefore consider the possibility below.

3.2. EXAMPLE 1: SELF-RENEWAL AND DIFFERENTIATION DIVISIONS

Consider the case that stem cells can both self-renew (produce two stem-cell daughters) or undergo an asymmetric division (one stem cell and one differentiation-destined progeny per division). The first type of division leads to an expansion of the stem-cell pool, since each cell doubles. This will show up in the resulting growth of the population predicted by the model with previous definitions of p and f (Fig. 4). The model reads

$$\begin{aligned}
\frac{dS_0}{dt} &= -(p+f)S_0, \\
\frac{dS_1}{dt} &= (2p+f)S_0 - (p+f)S_1 \\
&\vdots \\
\frac{dS_j}{dt} &= (2p+f)S_{j-1} - (p+f)S_j, \\
&\vdots
\end{aligned} \tag{3}$$

In the above equations, the factors $(2p+f)$ represent the fact that each symmetric division (rate p) produces two cells in the successive division class, whereas each asymmetric division produces only one such new cell. At the same time, the "parent" is removed. Starting from some initial number of cells, N, concentrated in the first division class, S_0, we find that the total number of stem cells now increases exponentially with growth rate p (see the Appendix for details). It seems that if we had an independent estimate of the total number of stem cells at any given time, this fact would allow us to determine the parameter p. (Such independent data is not currently available, but even if it were, it is unlikely that such a fit can be made, as the assumption of exponential increase is likely a gross simplification.)

The solution to this system is shown in Figs 5 and 6. The mean telomere length in this scenario decreases by roughly $100(2p+f)$ bp per year in a large population (see the Appendix for details). In order to fit the trend given by data in Rufer *et al.* (1999), for the non-infant rate of telomere shortening (on average, 34 bp shortening per year), p and f must satisfy the relationship

$$100(2p+f) = 34.$$

For example, $p = 0.15$, $f = 0.04$ divisions per year would satisfy this relationship, and was used

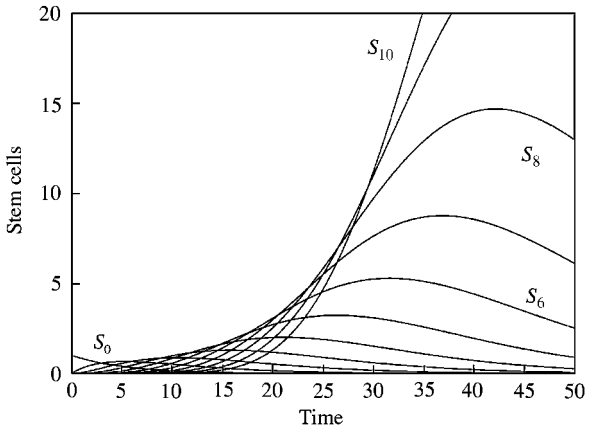

FIG. 5. The number of j-th generation stem cells, $S_0, S_1, \ldots, S_{10}$ is plotted against time (in years) for the model given by eqns (3). We used $S_0 = 1$ at $t = 0$ and assumed constant values of the division rates, $p = 0.15$, $f = 0.04$ per year. (These rates satisfy the relationship $100(2p+f) = 34$, based on data in Rufer *et al.* (1999). Note that for a given division class, the numbers build up over time up to some maximum, and then decrease, as the "crest of the wave" of cells passes through a given division class.

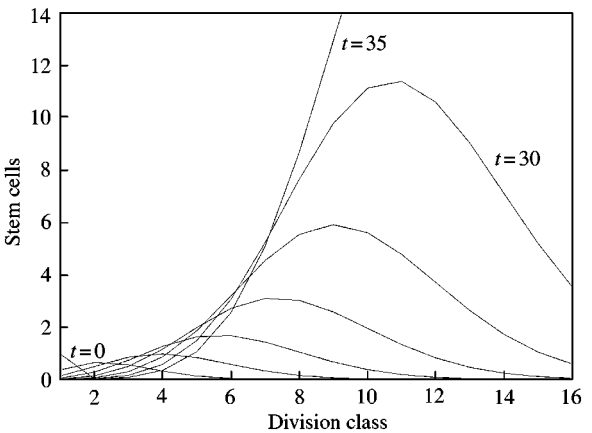

FIG. 6. The distribution of stem cells at successive times, $t = 0, t = 5, t = 10, \ldots, t = 35$ (in years) corresponding to eqns (3) and to the behaviour shown in Fig. 5. Each curve represents the distribution of cells over division classes. The same parameter values were used here [to fit data in Rufer *et al.* (1999)] as in the previous figure.

in the simulations that produced Figs 5 and 6. However, the data does not allow us to uniquely define the division rates p and f.

The parameters p and f in this model govern the dynamics of the stem cells and also prescribe the rate that differentiated products of these cells would accrue. One simple assumption is that there is a fixed number of divisions between a stem cell and a granulocyte (or, for that matter, any other progeny). The rate that the first differentiated blood cell precursors are produced is $fN(t) = fN_0 e^{pt}$ and this number would be magnified by some factor to account for expansion that occurs between the stem cell and the granulocyte level (e.g. 2^{20} assuming 20 cell doublings between these levels).

3.3. REFINEMENTS AND OTHER EXAMPLES

The basic model discussed previously can be modified or adapted in a variety of ways. We briefly highlight the results of varying some of the hypotheses or lifting the restriction that division and differentiation rates are constant.

1. If the self-renewal type of stem-cell division changes gradually over the lifetime of an individual, e.g. $p(t) = p_0 - rt > 0$, where t is time, then f is also non-constant, e.g. a relationship of the form $100(2p(t) + f(t)) = 34$. In this case, the rate of differentiation divisions would increase with age. The total number of stem cells, $S(t)$ can be shown to increase over time, but at a decelerating rate, $S(t) = N_0 + p_0 t - rt^2/2$. The total production of blood cells would be an increasing function of time. This is reasonable up to adulthood, but not necessarily throughout life.

2. If cell-renewal division probability decreases with the number of divisions that a cell has already undergone, i.e. $p(j) = p_0 - rj > 0$, where j is the division class of the cell (i.e. how many divisions it has undergone), then the differentiation division would also be stage-dependent, e.g. $100(2p(j) + f(j)) = 34$. In this case, it can also be shown that both the stem-cell pool and the blood precursor pool would continually increase. The average age of the blood precursors would increase linearly with slope 0.34 to account for the 34 bp per year change in telomere length.

3. To avoid the unlimited growth predicted by the above linear models, it is necessary to impose some kind of size limitation or interaction term. We discuss this in greater detail in the following section dealing with nonlinear models.

3.4. CRITIQUE

In his commentary on Rufer *et al.* (1999), Hodes (1999) raises a number of important considerations. First, he notes that multiple factors can result in significant deviations from normal telomere loss in somatic cells. One set of factors could include mechanisms (such as telomerase) that increase telomere length, not only in germline but also in certain somatic cells. A second factor is a variation in the rate of shortening over cell type and conditions, with exceptionally rapid shortening occasionally observed. Hodes points to two divergent interpretations of the rapid loss of telomere length in childhood: Rufer *et al.* (1999) attribute this to changes in the turnover rate of cells, whereas Frenck *et al.* (1998) suggest that it correlates with a changing rate of telomere loss per cell division. Currently, it is not yet possible to distinguish between these two possibilities. Other models that specifically address telomere shortening include Levy *et al.* (1992), Rubelj & Vondracek (1999), and Olofsson & Kimmel (1999).

At present, longitudinal studies in humans (which would require blood samples over the lifetime of individuals) are not yet available. Although there is a clear correlation between age and the loss of telomere repeats in granulocytes, the rate of loss is not a simple linear relationship, and the variations in telomere length between subjects is large. This means that, at best, the experimental data is approximate. A greater impediment is that the type of data currently available is insufficient to constrain the model or distinguish between several competing hypotheses: undoubtedly, the rate of divisions of stem cells may depend on the division-class of the cell, chronological age of the individual (time), interactions with other cells (e.g. feedback through cytokines or other forms of cellular communication) or possibly other constraints. The models presented above are among the simplest of their

kind. Many more detailed versions have appeared in the literature (see Section 4.2). However, the availability of data severely constrains the ability to distinguish between multiple hypotheses.

Since this article aims to address biology of aging, a natural question is to what extent telomere shortening seen in the data of Rufer *et al.* (1999) has a functional significance in aging. Hodes (1999) addresses this point in his commentary, and sounds several cautionary notes. First, it appears that some cells do not show replicative senescence, indicating that a direct correlation between telomere shortening and replicative senescence does not exist for all cell types. In an even more extreme statement, Miller (2000) wrote that the idea that telomere shortening in lymphocytes leads to replicative failure in old age is one of the few ideas that "can, with a fair degree of confidence be considered incorrect". It would be interesting to follow the eventual development of these divergent points of view on the subject. Even if a direct functional correlation exists, we are still not in a position to envision manipulating telomeres to alleviate problems of aging, nor is it clear that this can be done without also unleashing adverse affects such as cellular immortality in the form of malignancy.

4. Nonlinear Models

As the examples in the previous section reveal, linear models have a relatively benign repertoire of behaviour. They are suitable for describing flows through compartments, (as well as a limited set of periodic phenomena not discussed here). Most of the really interesting biological systems are inherently nonlinear due to interactions between components of a system (not just simple interconversions). As the chemical law of mass action demonstrates, the interaction of components introduces dependence on products of the variables, or other expressions involving more than one variable in a nonlinear way.

In this section, a brief review is undertaken of some of the notable applications of nonlinear dynamics to physiology, and, in particular, to the biology of aging. Before doing so, we comment on the fact that two elementary models for population growth are the Malthusian model, $dN/dt = rN$ and the Logistic (density-dependent) model $dN/dt = rN(1 - N/K)$. The former is linear, and has the unrealistic feature of unlimited exponential growth. The latter is nonlinear by virtue of the quadratic dependence on N on the right-hand side of the equation. Its solutions have a plateau at a population level, $N = K$, called the carrying capacity. Significantly more bizarre in behaviour, the delayed logistic or discrete logistic equation, $N(t + 1) = rN(t)(1 - N(t)/K)$, also has a variety of oscillatory and chaotic solutions as the parameter r (which, incidentally, governs steepness of the response) increases. This equation has an inbuilt delay, i.e. the reaction to a change takes time. It is a well-established fact that equations incorporating delays can give rise to unstable behaviour, oscillations, and in the case of this discrete logistic, to chaos. (This equation spawned the interest in chaos dating back to the mid-1970s, though its relevance to biological systems *per se* is tenuous at best.)

4.1. FEEDBACKS AND NONLINEARITIES IN STEM CELL MODELS

In the previous section, we described a number of the essentially linear models for stem-cell differentiation and self-renewal divisions. Interactions between cells of various classes, renders such models nonlinear.

One hypothesis we explored is that the surface area inside the long bones, which acts as the reservoir of the stem-cell pool, has a limited size, and hence causes renewal divisions to be limited. Since this surface area scales as (body mass)$^{2/3}$, we assumed that the rate of self-renewal divisions is $p(t) = h(km^{2/3} - S)$ where $m = m(t)$ is mass of the individual, and $S = S(t)$ is the total number of stem cells at time t. This assumption means that there is a feedback from current stem-cell pool to its own expansion, but does not account for other feedbacks, e.g. from pools of blood cells.

Aside from this feedback assumption, the model equations were essentially identical to system (3). Data for average growth in mass over time were taken from a growth chart (Castlemead

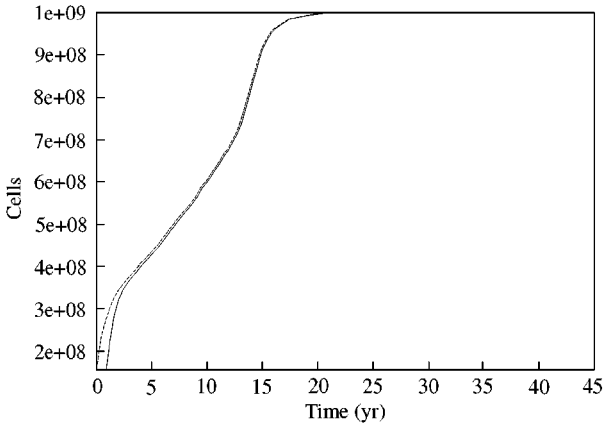

FIG. 7. Behaviour of the nonlinear model for stem cell dynamics discussed in Section 4.1, where the renewal divisions are controlled by a limited capacity for stem cells. Stem cell number increases during growth, then remains constant throughout adulthood. Capacity $= k$ mass$^{2/3}$. (——) Stem cells (total); (------) capacity.

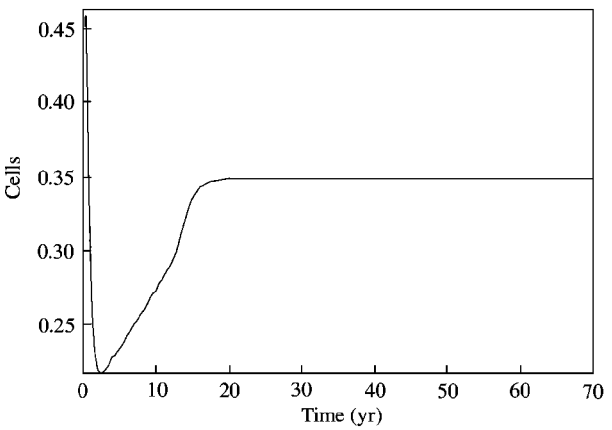

FIG. 8. A plot of $f(t)$, i.e. of the average rate of blood cell precursor per stem cell resulting from the model of Section 4.1.

Publications Chart No GDB11A). This nonlinear model was investigated numerically. We found that the total number of stem cells increased initially during growth, and then stabilized at some constant level through adulthood (see Fig. 7). This means that the average rate of blood cell production *per stem cell* declines over the first year or two, but then eventually increases to reach a steady constant level in adulthood [see Fig. 8, a plot of $f(t)$]. In this instance, the division rate $f(t)$ is not a solution to $100(2p + f) = 34$ as in the previous models discussed in Sections 3.2 and 3.3. The assumption of a physiological

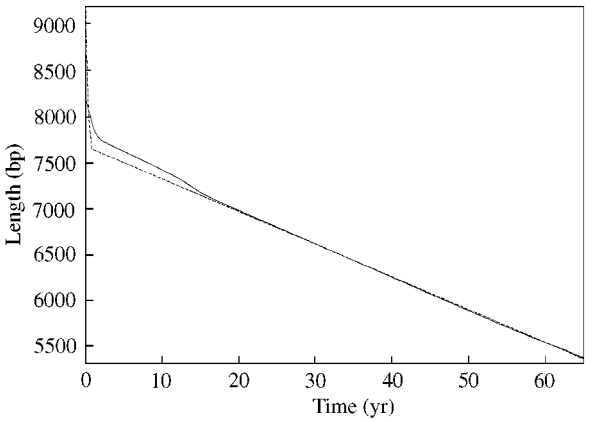

FIG. 9. Granulocyte telomere lengths predicted by the results of the model in Section 4.1. Data line is best fit from Rufer *et al.* (1999). (——) Model; (------) data.

requirement for blood cells proportional to body mass (with blood cells needed divided by stem cells present) determines $f(t)$. The implications for telomere lengths in the mature blood cells (granulocytes) are shown in Fig. 9 along with best-fit lines for the experimental values published in Rufer *et al.* (1999). Fig. 9 shows that by adjusting the parameters h and k, we can get close to satisfying the relationship $100(2p + f) = 34$ anyway, even when it is not pre-assumed.

4.2. OTHER MODELS FOR STEM-CELL DYNAMICS

One of the best reviews of the original literature on stem-cell dynamics, suitable for non-mathematicians appears in Wichmann (1983). Wichmann describes modelling efforts dating back to the early 1960s. In many of the models (including more recent ones), a distinction is made between resting and actively dividing cells. In other cases, the effects of feedback due to growth factors, or other influences are incorporated.

As described in the review by Wichmann (1983), the compartment structure of a model is not particularly important in the sense that it simply provides an (arbitrary) subdivision of the system into a particular number of classes. However, the types of interaction and feedback terms are highly significant. For example, the model above assumes that the activation of stem cell division is regulated by the total stem cell population. Other models have also included feedback

of the downstream differentiated cells, for example, incorporate activation of extra cell divisions when there is a deficiency in the cell population. The dose–response of regulators on the production and differentiation rates of the cells is also an important factor in the behaviour of the system. As an example, some models (for later stages of erythropoiesis) incorporate regulation by cytokines such as erythropoietin (EPO) and others. In fact, it has been shown that simply making dose–response curves steeper can lead to oscillations in cell production, whether or not the compartmental structure of the model is changed (Wichmann, 1983).

Oscillations can be expected to occur with any of the following factors: (1) more extreme or sharper feedback responses, (2) a longer time delay between cause and effect (e.g. feedback of cells far down stream of the regulated compartment), (3) cell death. All of these factors have been explored mathematically in a variety of settings, see for example, Mackey (2000), who describes detailed stages, including transitions between proliferating and resting cell cycle phases; Hearn *et al.* (1998), who modelled cyclical neutropenia (period 19–21 days in humans, 11–15 days in the grey collie); Belair *et al.* (1995a), Mahaffy *et al.* (1998), who have also combined the feedback effects of cytokines such as EPO on the production of blood cells, and the effect of delays.

4.3. DYNAMICAL DISEASES

Most physiological systems are controlled by feedback mechanisms that ensure homeostasis, or, in some cases, regular cyclic behaviour. In pathological states, the constant outputs of some systems may break down into oscillatory behaviour: an example is tremor that accompanies purposeful movements in Parkinson's disease. Other physiological systems may either cease to cycle (as in the oestrous hormonal cycle) or acquire irregular, inappropriate frequency oscillations, or potentially more bizarre aperiodic dynamics. The investigation of *dynamical* behaviour of biological control systems has led to the idea that some diseases stem not from defective single components, but from changes in strengths of connections, changes in slopes or threshold levels in stimulus–response curves, or in delay time for receiving or processing a signal. Succinctly put, such effects correspond to parameters of intact control systems that are operating outside of the range of normal dynamical behaviour. The qualitative changes in behaviour that accompany these correspond to bifurcations in the underlying nonlinear systems. This idea, termed "dynamical diseases" (Mackey & Glass, 1977; Glass & Mackey, 1979) received widespread attention in the modelling community (Mackey & Milton, 1987, Glass *et al.*, 1988, Kaplan & Glass, 1995), though somewhat less wide recognition in the biological community. [See Belair *et al.* (1995a,b) for a good review and insights.]

4.3.1. *Cheyne–Stokes Respiration*

A simple example of a "dynamical disease" is Cheyne–Stokes respiration (Mackey & Glass, 1977). The level of CO_2 in the blood is governed by production (through metabolism) and loss (via ventilation). The latter depends on CO_2 level via feedback control in brain-stem receptors, with a sigmoidal stimulus–response. A delay of up to about $\tau = 0.2\,\text{min}$ is normal (Mackey, pers. comm.) this accounts for the time it takes for circulation from lungs to reach the brain stem. A model of this simple feedback mechanism by the above authors revealed that the system has a stable steady state (or "set point") (e.g. 40 mm Hg partial pressure for CO_2 and about $7\,\text{l}\,\text{min}^{-1}$ for ventilation rate) for a range of parameter values. However, increased CO_2 production, increased delay (e.g. due to congestive heart failure or similar circulatory defects) or a sharpening of the slope of the response curve can lead to instability, and dramatic fluctuations in breathing pattern and blood CO_2 levels, typical of Cheyne–Stokes Respiration.

4.3.2. *Parkinson's Disease*

In many of the more recent investigations of periodic or dynamical disease conditions, the details of the underlying control mechanism are not so clear-cut. Beuter & Vasilakos (1995) investigated the possibility that the oscillations in muscle control that show up as tremor in Parkinson's disease can be considered as a

dynamical disorder: abnormal oscillations appear (tremor), normal rhythms disappear (e.g. reduced swinging of arms in walking) and new periodicities develop; all these features are suggestive of the hypothesis of a dynamic disorder. The idea proposed by Beuter & Vasilakos (1995) is that central and peripheral feedback loops interact dynamically to control limb position, the former having greater impact, and the latter responsible for minor corrections. Changes in the coupling between these systems over time could lead to the changes in dynamics. A simplified model for interactions between central and peripheral systems with a delay due to finite conduction velocity in the nervous system and nonlinear sigmoidal responses showed behaviour similar to experimental observations. However, the detailed mechanisms of the interacting loops are not known, nor can they be inferred easily by studying the dynamics of the experimental system. Parkinson's is a complex disease with multiple facets, and not easy to dissect with an elementary model.

4.3.3. *Diagnostic and Therapeutic Tools*

Milton & Black (1995) investigated some 32 diseases with interesting dynamics. In only a few cases are the systems sufficiently simple or well-understood to intervene directly and suggest ways of resetting physiological parameters to their normal levels. However, even without knowing details of the underlying mechanisms, some dynamical considerations can suggest therapeutic measures. As an example, epileptic seizures can be brought under control by precisely timed input stimuli, e.g. a loud noise at a critical time determined via electroencephalogram monitoring. As described in the excellent review by Belair *et al.* (1995, b), the irregularities in physiological data which could stem from both noise and deterministic factors can also be used to distinguish between subgroups of individuals who are at risk for certain life-threatening conditions. Simply collecting the data and analysing it, either as time series, or with more advanced autocorrelation or power spectra methods can provide signature patterns that are identified with abnormal conditions.

4.3.4. *Power Spectra as "Signatures"*

In the healthy organism, control systems operate at many levels, from the neuronal and hormonal to the subcellular. These are characterized by many disparate time scales, and, in many cases, by cycles of vastly different periodicities. A power spectrum is a succinct summary of the numerous frequencies that make up a system. A particularly striking example of this "signature" data analysis is the work of Lipsitz (1995) on heart rate power spectra using measures of the "complexity" of cardiovascular dynamics. The measures he investigated are based on a number of quantifiers such as *approximate dimension* and *approximate entropy*, used in studying complex dynamics of nonlinear systems in broader contexts. (These indicate, roughly speaking, the predictability of the system.)

4.3.5. *Age-related Changes in "Complexity"*

According to Lipsitz, it is important to understand changes in the dynamics of heart rate and blood pressure, not just their mean values. (Mean values are nearly the same in young and old, while dynamics are strikingly different.) Normal healthy aging is accompanied by a reduction in the sensitivity of the baroreflex response that acts as feedback to regulate both beat-to-beat blood pressure and heart rate. This leads to a decrease of variability over age, and particularly, a loss of the higher-frequency fluctuations. Loss or decline of complex physiological heart rate variability can be used as a marker of abnormality and as a diagnostic or prognostic tool in conditions such as congestive heart failure, coronary disease, and others. In this case, even though the detailed mechanisms that are responsible for the dynamics are not known in detail, the lessons of complexity learned in the course of a more general investigation of nonlinear dynamics could bear fruit.

4.4. CRITIQUE

As discussed by Beuter & Vasilakos (1995), many of the periodic diseases or dynamical behaviours in disease can be observed, but may not lead to direct insights into the details of underlying dynamics. In such cases, it is hard to consider

therapeutic measures in which interventions could correct for the abnormal dynamics. As stated by Milton & Black (1995), the nature of the relevant control parameters is still mysterious in many cases. A good review of both the accomplishments and the challenges facing the dynamical disease research is given in Belair *et al.* (1995a, b). Practical problems include the fact that most of the data with observed time series on which to base the models is too short and confounded by the influence of noise. Debates about optimal techniques for analysing the data are still unresolved, and most of the bottom-up approaches of constructing models based on what is known mechanistically has focused on relatively simple bare-bones examples. According to Belair *et al.* (1995b), this has lead to a paucity of practical applications of the theories to date.

4.5. OTHER PHYSIOLOGICALLY BASED MODELS

Mathematical models have addressed numerous nonlinear problems in physiology, ranging from conduction of electrical signals in neurons, to cardiac dynamics, to kidney function (see recent review in Keener & Sneyd, 1998). Some of these models have led to new disciplines, a notable example being the Hodgkin–Huxley model for action potential in neurons, and its role in inspiring modern neurophysiology. There is as yet a paucity of physiologically based models that specifically address aging biology. Here, it is interesting to point out one or two promising directions.

The mathematics of pacemakers, and coupled oscillators is a rich and exciting field, a subset of dynamical systems in which sophisticated mathematics interfaces aptly with biological experiments and theoretical predictions. The recent decades have seen some remarkable success stories in this field (see e.g. Kopell, 1995, 2000). Some of this theory is now taught as a standard part of undergraduate mathematics and is introduced in an eminently readable form by Strogatz (1994), Kaplan & Glass (1995).

At the same time, biological cycles are a vital part of normal physiology. Hormonal systems are notoriously driven by fluctuations, and oscillations, rather than constant basal levels. For example, gonadotropins such as follicle stimulating hormone (FSH) and lutenizing hormone (LH), responsible for reproductive capacity in humans are secreted by the pituitary in response to periodic pulses of gonadotropin release hormone (GnRH) from the hypothalamus. Typically, such pulses occur once per hour. If the frequency of these pulses is incorrect, secretion does not occur. Both ovary, and brain act as pacemakers—rhythmic producers of signals. According to Wise *et al.* (1996), with age, the natural rhythm of the system may deteriorate, either through changes in the inherent rhythm of the components, or changes in the way that they are connected (or coupled) to one another. This can disrupt the delicate balance, with a resulting loss of function leading, for example, to menopause. An analysis of pacemakers and their interactions is a possible contribution that modellers can make to this area.

Further, a second set of models in the literature may be similarly relevant to the topic of menopause. These models focus on the process of follicular maturation and follicle selection. (A small fraction of the follicles in the ovary—a mere 500 or so—will ever complete the full maturation cycle. Most are fated to die after degenerating.) According to Wise *et al.* (1996) "Reduction in the number of follicles in the ovarian pool which occurs normally during middle age disrupts the dynamic equilibrium between dormant and growing pool of follicles." This disruption is also a part of the aging-related phenomenon of menopause.

Some modelling of follicular dynamics dates back to Lacker (1981, 1988), who modelled interactions of growing follicles, estrogen, LH, and FSH. For analytical tractability, Lacker assumed that follicles have identical responses and follow identical growth laws. Some of these restrictive assumptions were later relaxed, e.g. by Chavez-Ross *et al.* (1997). The models describe the competition of the follicles for dominance and maturation. Recent papers (Faddy & Gosden, 1996; Faddy *et al.*, 1992) fit simple exponential decay to data in their treatment of the decline in follicle number and menopause. Although the more detailed mechanistic models for follicle maturation have not yet addressed the phenomenon of menopause, they provide a framework in which such an investigation could be undertaken.

5. Models of the Aging Process

As of the writing of this paper, the literature of models that have addressed the biology of aging *per se* is hardly extensive. Partly, this may result from the fact that much of that biological core of knowledge is, to some extent, still descriptive, rather than quantitative. What quantitative observations do exist may be comparisons of young and aged individuals, rather than full appreciation of the entire dynamic process of aging. In this section, we briefly describe an exception to this situation, that of network models by Kowald and co-workers.

5.1. NETWORK MODELS FOR AGING

Some of the qualitative views of aging as an accumulation of errors have been incorporated in detailed models for the interactions of normal and defective proteins, free radicals, antioxidants, and the protein production machinery in the cell. These models, given by Kowald & Kirkwood (1994, 1996), Kirkwood & Kowald (1997), have been called the network theory of aging, as they illustrate the network-like interconnections of many components of the system that are required to control cellular homeostasis. A typical model in this collection consists of sets of differential equations for correct and erroneous proteins, ribosomes, RNAs, and their interactions with radicals. The difficulty in constructing such models is that many specific assumptions about radical disposal, energy consumption, and detailed effects must be assembled. Some, but certainly not all, of these assumptions can be derived from experimental or biological data. A typical model also contains a large number of parameters (e.g. 30 or more) and estimates for these require painstaking work.

A network model such as that of Kowald & Kirkwood (1994), while being conservative in detail as far as the biologists are concerned, is complex and non-trivial as far as a mathematician is concerned. As a result, investigative work of this type is mainly done with simulations, rather than analysis. How to effectively explore the relevant parameter space in such a large-scale model is a challenge. To paraphrase Wichmann (1983), high complexity in a model (i.e. a high level of detail) does not always mean high quality. A tradeoff exists between the inclusion of numerous interactions, whose parameters are not well-measured, or subject to large error (in which case the predictions of the model have a large uncertainty) and oversimplification which neglects key features. Nevertheless, certain results of such models are instructive; for instance, Kowald & Kirkwood (1996) have shown that aging leads to increases in inactive proteins, in the persistence time of the protein, in the fraction of damaged mitochondria, while decreasing the amount of energy produced per mitochondrion. They also observe gradual cumulative changes (e.g. in mitochondria) that eventually, by virtue of interaction with the cytoplasm, lead to error.

Kowald & Kirkwood (2000) model delayed degradation of defective mitochondria (suggested by de Grey, 1997) as a possible cause of deterioration in aging cells. Damaged mitochondria replicate more slowly, but also have a slower rate of degradation according to this theory (Kowald, 1999). This results in the buildup of damaged mitochondria. Their model incorporates two major classes of mitochondria, with and without DNA damage, and further subdivide these into subclasses depending on the extent of membrane damage (low, medium and high) with transitions between classes. From this perspective, the model bears parallels with some of the compartmental modelling described earlier in this review. However, Kowald and Kirkwood assume that free radicals produced by the mitochondria affect those transitions between classes, so that the model is nonlinear. Their results point to the fact that the effect of mitochondrial degradation is significant: if the turnover rate is too low or too high, there is an instability. The model contains roughly 20 parameters whose values are based on experimental results, calculations, or guesses. According to Kowald & Kirkwood (2000), an important consequence of the model is that post-mitotic cells accumulate damaged mitochondria more quickly than mitotically active cells. Thus, rapid cell division could slow the decline of the mitochondrial population.

6. Discussion

From this review, it may be apparent that the mathematical modelling currently holds no

magic bullet or cure for aging. Indeed, the extent of effort directed at specific phenomena associated with aging is still in its infancy in the modelling community.

However, it should be noted that physiological, cellular, population, and disease modelling is in a healthy and vigorous state, empowered by advances in mathematical and simulation methods, and enlivened by the recognition that the work is best done with close consultation between theoretical and experimental scientists.

It is to be hoped that some of this work will extend perspectives to address the specific age-related phenomena. Some of the areas are ripe for such extensions. It only remains to broaden the questions, focus on the effects of age, and find willing partners in the biological and theoretical communities to carry forward such research.

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APPENDIX

For the model given by the system of equations (2), an explicit solution can be obtained by solving the first equation to obtain $S_0 = Ne^{-t}$, substituting this function into the term S_0 in the second equation and solving the resulting (non-homogenous) linear equation to obtain S_1. By repeating a similar process step-by-step, we obtain solutions for all of the variables. The resulting formula for the number of cells in class j is

$$S_j(t) = \frac{N}{j!} t^j e^{-t}.$$

So, for example, $S_0(t) = Ne^{-t}$, $S_1(t) = Nte^{-t}$, $S_2(t) = \frac{1}{2}Nt^2e^{-t}$, $S_3(t) = \frac{1}{6}Nt^3e^{-t}$. The total number of cells $S = S_0 + S_1 + S_2 + \cdots$ can be found by adding the equations:

$$\frac{d}{dt}(S_0 + S_1 + S_2 + \cdots)$$

$$= (-S_0) + (S_0 - S_1) + (S_1 - S_2) + \cdots .$$

The terms on the right-hand side cancel successively, so that

$$\frac{dS}{dt} \approx 0.$$

This approximation holds well if there are many differentiation classes so long as few cells are at terminal stages of differentiation. Once the cells accumulate in some end-stage, S_N, this formula will no longer reflect the situation accurately, i.e. it would depend on what happens at that stage.

For eqns (2), the mean differentiation stage (mean number of divisions) in the population at time t would be defined as

$$D(t) = \frac{1}{S(t)} \sum jS_j(t),$$

where $S(t)$ is the total number of cells. We can determine the behaviour of this quantity by noting that

$$\frac{dS_j}{dt} = S_{j-1} - S_j,$$

so that

$$j\frac{dS_j}{dt} = jS_{j-1} - jS_j = (j-1)S_{j-1} + S_{j-1} - jS_j.$$

Adding up equations of this form for $j = 0, 1, 2, \ldots$ leads to

$$\frac{d}{dt}\sum jS_j = \sum (j-1)S_{j-1} + \sum S_{j-1} - \sum jS_j.$$

The summation is taken for $j = 0 \cdots N$. This means that the first two sums on the right-hand side start with no contribution for $j = 0$, since $S_{-1} = 0$. These sums also do not take into account the contribution of the cells in class N to the total population and to the mean number of divisions. However, if cells are initially concentrated in class S_0, it takes time for any to accumulate in class S_N, so for initial stages of the process the omission of this term would have minimal effect. In that case, we find that

$$\frac{d}{dt}\sum jS_j \approx D + S - D = S,$$

and, dividing both sides by S, which is constant,

$$\frac{dD}{dt} \approx 1.$$

(This approximation holds as long as the cells are still in the early phases of divisions. Later, the fact that there are finitely many divisions will introduce a correction due to the contribution of the final division class.)

We can similarly understand the behaviour of eqns (3). By summing all equations, we can easily show that

$$dS/dt \approx pS.$$

This means that $S(t)$ grows exponentially, and that $S(t) = Ne^{pt}$, where N is the initial number of cells. (The approximation is, as before, neglecting the final division class, and holds well for the stages before cells arrive at that final class.)

We now find how the mean length of telomeres $\bar{L}(t)$ behaves over time for eqns (3). First, let L_0 be the average length of telomeres initially (for cells in class S_0) and suppose that telomeres are lost at about 100 bp per division. Then, the length of telomeres for cells in class S_j would be $L_0 - 100j$, and the mean telomere length for all cells combined would be

$$\bar{L}(t) = \frac{1}{S(t)}\sum (L_0 - 100j)S_j(t) = L_0 - 100\frac{L(t)}{S(t)},$$

where $L(t) = \sum jS_j(t)$.

To find the rate of change of the total telomere length L (and hence of the mean length $\bar{L}$) we multiply each equation in eqn (3) by j:

$$\frac{d(jS_j)}{dt} = (2p+f)(jS_{j-1}) - (p+f)(jS_j)$$

and add the equations, to obtain

$$\frac{dL}{dt} = (2p+f)\sum ((j-1)S_{j-1} + S_{j-1}) - (p+f)\sum jS_j.$$

This can be simplified to

$$\frac{dL}{dt} \approx (2p+f)L + (2p+f)S - (p+f)L$$

$$= pL + (2p+f)S,$$

where the approximation has neglected the final division class. Simplifying, and using the results to compute the derivative of $\bar{L}$ leads to

$$\frac{d\bar{L}}{dt} = -100(S(t)\frac{dL}{dt} - L(t)\frac{dS}{dt})/S^2(t)$$

$$\approx -\frac{100}{S^2}[S(pL + (2p+f)S) - pSL].$$

After cancellation and algebraic simplification, this leads to

$$\frac{d\bar{L}}{dt} \approx -100(2p+f).$$

Thus, the mean telomere length decreases by $100(2p+f)$ bp per year.