Chapter 8
Modeling Cellular Aging: An Introduction – Mathematical and Computational Approaches

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Abstract In this chapter we examine a variety of modeling approaches that have been historically used to understand the sub-cellular and cellular biology of aging. We find that there are a large array of methods from discrete to continuous and from deterministic to stochastic. This chapter is not meant to be a comprehensive coverage of all of the modeling efforts but rather a buffet introduction to what has been done in the field over the last 50–60 years.

Keywords Replicative senescence • Cell cycle • Serial passaging • Mathematics • Modelling • Repair • Longevity • Cancer

8.1 Models of Cellular and Subcellular Aging

> "Each particular discipline contains only as much science as it contains mathematics... Immanual Kant, in Metaphysical Foundations Of Science"

Living systems are ubiquitous. Moreover, most of them are so complex that it is difficult to understand their behavior. Experimental science works from the obvious historical perspective of reductionism. Break the organism apart and hope (1) that you can understand how the pieces work and (2) that if you are lucky, you can put the pieces back together again and perhaps understand more about how the whole organism works. However, sometimes it is impossible to test an experimental hypothesis. Perhaps the equipment doesn't exist or it's too expensive. Sometimes we just don't quite know how the pieces should fit back together and we would like to examine a number of different hypotheses. We might want to determine the most important genes in a very large known network. However, knocking them out – one by one – would be time-consuming and expensive. One way to handle problems of such a complex nature is to make use of mathematical and computational

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models. The literature in mathematical modeling and computer simulation, like living systems, is also ubiquitous. New books and papers appear regularly. It is beyond the scope of this short chapter to cover this literature. Some excellent starting texts can be found in references (Hannon and Ruth 1997; Murray 1989; Meerschaert 1993; Jacquez 1985; Godfrey 1983; Tautu 1990; Goel and Richter-Dyn 1974).

8.1.1 Thinking About, Building and Analyzing Mathematical Models and Computer Simulations

Modeling in aging has been around for as long as demography and survival theory have been disciplines; certainly since the famous Benjamin Gompertz and subsequent mortality theorists (Carnes et al. 2006). Circa the 1960s, mathematical and computational methods began to be applied to other areas of aging dynamics. Brain/body-mass and metabolic rate vs. maximum lifespan relationships (Cutler 1982) were two of the earliest of the non-demographic applications of simple mathematical modeling. In complexity theory, these are called scaling relationships (West and Bergman 2009). More recently, there has been a growing interest in graph theoretic/network methods to understand how longevity-related genes and proteins are linked together in networks and how those networks behave (Witten 2014; Wimble and Witten 2014). Graph theoretic methods lead to systems biological approaches that apply differential equation modeling (Jones and Sleeman 1983; Dalle Pezze et al. 2014) and simulation to various pathways in order to better understand their dynamics (Glass 1975). Today, mathematical modeling and computer simulation have been applied to a far larger variety of aging-related problems across all scales of the aging hierarchy, from molecular through population levels.

One area of great interest, in part because of the early ability to make experimental measurements and now to be able to obtain additional data through the use of "omic" methods, is the modeling of sub-cellular, single cell and cell population dynamics. In this chapter we will focus on applications of aging-related modeling in these areas.

8.1.2 Constructing a Model

Mathematical and computer modeling might be seen as the comprehensive processes of representing real world phenomena in terms of mathematical equations or computer equations and subsequently extracting from those frameworks potentially useful information that could further the understanding of the system of interest. The process of mathematical and computer modeling does not have a specific set of rules. It is still as much of an art as it is a science. This isn't to say that there are

not useful guiding principles and approaches to constructing models. An excellent discussion of the process of constructing a mathematical/computer representation of a living system is presented in Kirkwood et al. (2006).

Thinking About the Time Variable

Time, one of the major means by which aging is measured, discussed and by which dynamical systems are studied, is fundamental to any analysis of aging processes. The following citations address the concept of time from various perspectives (Denbigh 1981; Featherman and Peterson 1986; Witten 1984; Vrobel 2011). When we consider modeling cellular aging, we are typically constructing some sort of relationship between a collection of dependent variables such as $N(t)$ the number of individuals at time t or the amount of waste $w(t)$ in a cell at time t. Time is usually expressed as a continuous variable t or as a discrete variable t_n where the subscript indicates the nth timepoint. The timepoints t_n could be the population doubling times or the generation number of yeast buds. It is also possible to describe time t as a random or stochastic variable (Witten 1984, 1994) such as time to failure of a pathway or intermitotic times and even as a fractal (Vrobel 2011). In this chapter I will focus on just discrete and continuous time models of aging.

Thinking About the Dependent Variable(s)

For the most part, a dependent variable will be a variable of interest that depends upon time or age in some way. It will also take on either a discrete, continuous or probabilistic/stochastic demeanor depending upon what you choose to describe. For example, a simple model of cell growth in an unlimited resource could be modeled by a continuous time – continuous dependent variable differential equation of the form

$$\frac{dN(t)}{dt} = bN(t) \tag{8.1}$$

$$N(0) = N_0 \tag{8.2}$$

where $N(t)$ is the number of individuals at time t, b is the per capita net growth rate, and N_0 is the initial population size. We could choose to model the same system using a discrete time – continuous independent variable model as follows

$$N_{n+1} = bN_n \tag{8.3}$$

$$N_0 = \textit{given as initial information} \tag{8.4}$$

where N_n is the number of cells at population doubling point n, b is the per capita net doubling rate, and N_0 is a known initial amount of cells in the population. We can

also have models where one variable, say time t is continuous and the other variable, say $R(t)$ is discrete. For example, we might like to look at how many receptor sites are occupied on a cell at time t. Here, clearly t is continuous but the number of receptor sites $R(t)$ is discrete.

Alternatively, we might also ask for the probability that there are N divisions in a given time interval. We choose to examine probabilities because we recognize that if we were to repeat the experiment over and over, we would not get the same exact numbers of doublings at the timepoints that we measure. Defining $P_N(t)$ to be the probability that there will be N doublings at a given timepoint, it can be shown that the doubling equation (under certain assumptions of course) can be expressed as follows

$$\frac{dP_N(t)}{dt} = bP_{N-1}(t) - bP_N(t) \tag{8.5}$$

$$P_N(0) = 0 \tag{8.6}$$

which is an equation that describes a continuous time, discrete state (N), continuous random variable $P_N(t)$ model. The solution to Eq. (8.5) is the Poisson function $P_N(t)$ given by Eq. (8.7)

$$P_N(t) = \frac{(bt)^N e^{-bt}}{N!} \tag{8.7}$$

All of these models are deterministic models because they have no randomness in them. We could, however, easily introduce randomness in a number of ways. For example, randomness may be directly included as a *noise* term in our model system. For example, we don't expect the net reproductive rate to be exactly the same at each timepoint t, so we may then suppose that the growth rate b in Eq. (8.1) was not constant but rather varied about some mean value b_0, we might assume $\omega(t)$ where $\omega(t)$ was a mean zero variance σ^2 noise process. Under this assumption, we would re-express Eq. (8.1) as follows

$$\frac{dN(t)}{dt} = b_0 N(t) - \omega(t)N(t) \tag{8.8}$$

$$N(0) = N_0 \tag{8.9}$$

In this case, while we wish to solve for $N(t)$ and we have expressed our equation in that form, it is not possible to solve for $N(t)$ exactly. Instead, we must solve for a probability of a particular value of $N(t)$ at time t. Consequently, $N(t)$ is a stochastic variable (Witten 1994). Obviously, we can do the same type of alteration in our discrete model as well. It should be noted that one has to be more careful about constructing discrete time models because they can exhibit behaviors that differential equation models cannot. Consider the following two very simple differential equation models for cellular growth in a limited food environment (density-dependent cell growth). Model 1, the continuous model would be expressed as

$$\frac{dN(t)}{dt} = bN(t)\left[1 - \frac{N(t)}{K}\right] \tag{8.10}$$

$$N(0) = N_0 \tag{8.11}$$

where K is the maximum number of cells that the food resource can support. Similarly, the discrete model would look as follows

$$N_{n+1} = bN_n\left[1 - \frac{N_n}{K}\right] \tag{8.12}$$

$$N_0 = \textit{given as initial information} \tag{8.13}$$

It can be shown that there is no possible way that Eq. (8.10) can oscillate. However, Eq. (8.12) can. Consequently, part of the modeling process is understanding the types of behaviors that the experimental system can exhibit and making sure that those dynamics are demonstrated by the model. Once that is done, then we can examine any unknown behaviors displayed by the model and see if they exist in the experimental system.

More Than One Dependent Variable

Obviously, biological systems are more complex than one independent variable. For example, if we were interested in the total amount of waste in a cell as a function of time, we would be interested in a set of equations; one that describes the waste rate of change and the other that describes the number of cells at a given time. This would be easily described by a system of differential equations as discussed in Hirsch (1978, 1986) and Hirsch et al. (1989). We call this a system of coupled differential equations because the dependent variable of one equation can be found in the other equation or equations. For example, Zheng (1991) discusses a mathematical model that describes the proliferative senescence of cells in a cell culture. The model is based upon the DNA damage hypothesis of cellular aging and is able to account for both the limited and unlimited in vitro proliferative potential of normal and transformed cells. In this model the author uses a system of coupled differential equations (a matrix differential equation system) that describe the transition of a cell population vector through the cell cycle.

More Than One Independent Variable

The dynamics of growing systems of cells (and of people) has been of interest for decades and many mathematical models have been created to describe various aspects of such systems. One of the most famous of these is the Volterra-Lotka equation describing $n(t, a)$ the number of organisms (in this case it was originally people), having age a at time t in the population. Demographers of aging have been using this system for over 100 years (Carnes et al. 2006). I will not go through the

derivation of the equation system. One of the first researchers to use this system as a means of explaining cellular dynamics was Trucco (1965a,b,c). Instead, I will show the Von Foerster system and discuss its general meaning. The system is given by

$$\frac{\partial n(t,a)}{\partial t} + \frac{\partial n(t,a)}{\partial a} = -\mu(t,a,\ldots)n(t,a) \tag{8.14}$$

$$n(t,0) = \int_0^\infty \lambda(t,a,\ldots)n(t,a)da \tag{8.15}$$

$$n(0,a) = n_0(a) \tag{8.16}$$

where $n(t,a)$ is the number (or density) of individuals of age a at time t, $\mu(t,a,\ldots)$ is the per capita mortality rate, $\lambda(t,a,\ldots)$ is the per capita birth rate, and $n_0(a)$ is the initial population distribution and is a given. This type of equation is called a partial differential equation because it has partial derivatives instead of the derivatives you learned in Calculus 1 and we note that there is a derivative related, in the same equation, to each of the independent variables a and t. Demographers have been using this form of equation for decades. The first equation (the partial differential part) describes how individuals of age a at time t exit the population through death; note the mortality rate term on the right hand side of the equation. The second equation describes how newborns arrive in the population. It calculates the total number of newborns by integrating over the whole age distribution in the population. Obviously, this isn't entirely realistic, but its a start. And one thing about modeling is that you have to start very simple otherwise it is very easy to get lost in the model and never really be able to come up with believable results. The third equation simply describes the starting distribution; how many individuals there were of age a at time $t = 0$. Again, note that this is a deterministic equation system as there is no randomness in the model. However, you can include it. But that makes it very hard to solve. As you probably thought while you were reading this, these must be impossible to solve unless you are a brilliant mathematician. Well, not quite but they are hard and require some serious mathematical background if the modeler is going to go this route. A recent application of equation system (8.14) may be found in Stukalin et al. (2013).

The problem with the previous modeling formulation is that both age a and time t are related to each other in demographic models. This is problematic for cellular models because chronological age of a cell is not necessarily related to biological age. Rubinow (1968) and Lebowitz and Rubinow (1974), in a now classic series of articles, introduced the maturity μ of a cell as a possible variable of interest. The Rubinow model is generally difficult to implement in that it is challenging, if not impossible, to assign a biological meaning to the *cellular maturity* of a cell, it has allowed for the introduction of the concept of maturation or change in a *cellular variable*. The partial differential equation portion takes on the form

$$\frac{\partial n}{\partial t} + \frac{\partial (vn)}{\partial \mu} = -\phi(\ldots)n(\mu,t) \tag{8.17}$$

where v is the individual cellular growth rate, ϕ represents the death rate and μ is the maturity variable. Many authors have looked at a variety of formulations of this basic model.

The sum and substance of our discussion is that mathematical and computer simulation models come in a wide variety of types and there is not necessarily a correct or unique approach for modeling or simulating a given physical system. So how then do we go about the actual modeling effort given all of these ambiguities and philosophical difficulties? Start with a simple model and see what kind of behaviors you get. Interact with the experimentalists regularly and read the literature. Understand and be able to explain the limits of your model. Identify the most important dependent and independent variables first. Draw lots of pictures describing the known experimental results. Now we can talk about some of the modeling.

8.2 Senescence at the Sub-cellular and the Single Cellular Levels

As technological progress invades the biosciences, scientific innovation allows us to ask increasingly more precise and detailed questions about the complex workings of cells. These rapid technological advances have made it possible to address issues of aging at the molecular level.

As early as 1967, Strehler addressed the issue of irreplaceable components; components which allowed "the adult organism to persist only as long as the irreplaceable elements continued to function in a manner commensurate with life." He related these elements to molecular/genetic mechanisms in living systems. These issues were further addressed in Strehler and Freeman (1980) and Strehler (1986). We cannot hope to address the myriad of molecular aging theories, their experimental validity, and their mathematical treatment. In this chapter, we will address only some of the historical hypotheses that had mathematical or computational models associated with them.

- **Somatic Mutation Theory**: Aging is due to changes (of various types) in the DNA of somatic cells.
- **Error Catastrophe Theory**: Aging is due to a progressive accumulation of DNA errors leading to protein errors, etc.
- **Differentiation Theory**: Aging is due to changes in gene regulation which control differentiation. Altered gene expression might subsequently lead to aging processes.
- **Mitochondrial Mutation Theory**: Aging results from the accumulation of mutations in the mitochondrial genome.
- **Codon Restriction Theory**: Aging is a result of increasing inability to decode the genetic material.

- **General Theories**: Aging is the result of the gradual *wear and tear* of subcellular components or of the **accumulation and/or depletion** of some necessary material, component, product, or operation.

8.2.1 Mathematics of Somatic Mutations

In an excellent review paper on the subject, Hirsch (1978) points out that somatic mutations have been a major focus of aging research for a number of years. The initial arguments for a somatic mutation theory of aging grew out of the view that aging in mammals was due to a gradual accumulation of somatic mutations; mutations due to radiation in the environment. The theory proposes that aging is due to additions to, losses from, or other changes in the DNA base sequence of somatic cells.

The mathematical modeling methods used in somatic mutation models hinge upon concepts involved in *target theory*. Namely, one asks for the probability that a certain number of sites (of some type) are knocked out by a radiation or other event such as a chemo-mutagenic event. This probability is then related, via some sequence of mathematical arguments, to the probability that the whole system under investigation will survive. The survival of the system is assumed to depend upon the fact that a certain number of sites must receive a certain number of *hits*, in order for the system to *fail* or be unable to survive. Let us now briefly examine the target theory approach and some of its extensions.

Let $P(n,t)$ be the probability that the target area receives n hits at time t. Assume that the system survives as long as it does not receive the environment. We will not specify the nature of these hits for the moment. Let us call this critical number of hits n_c. Hence, the probability that the system

$$P_{SURV}(t) = P(0,t) + P(1,t) + P(2,t) + \ldots + P(n_c - 1, t) \tag{8.18}$$

We can see that Eq. (8.18) is true as the probability of any hit number n occurring is independent from the occurrence of any other hit 2 hits and 3 hits as that is equivalent hits. Hence, from basic probability theory, the probability that the system survives $P_{SURV}(t)$ is equal to the sum of all of the individual hitting probabilities $P(n,t)$ whose number of hits n is strictly less than n_c. Since Eq. (8.18) describes the probability that the system survives, we can – from basic probability theory – find the failure probability. This is given by

$$P_{FAILS}(t) = 1 - P_{SURV}(t) = 1 - \sum_{n=0}^{n_c} P(n,t) \tag{8.19}$$

Suppose, however, that it is required that not only must the system receive a critical number of hits, but also a certain critical number of hits must be received by each of

p target sites in the system. That is, in order for the system to fail, each of the p sites in the system must receive the required critical number n_c hits. Since, within reason, it is justifiable to assume that failure of one target site does not induce failure in another target site, we may write the probability of system failure as follows

$$P_{FAILS}(t) = [1 - P_{SURV}(t)]^p \tag{8.20}$$

Equation (8.20) represents the culmination of a general discussion of what a simple mathematical model might be like, if we required that a transformation to senescence would necessitate that a system of the form specified by Eq. (8.18) have p targets each requiring n_c hits. This is a very simple model. It assumes that the p targets are all homogeneous in their behavior. That is, they all require the same minimum number of hits before they fail. It might be that different targets require a different number of hits before they fail. It might be that a certain fraction of the target population requires $n_c^{(1)}$ while the other fraction of the population requires $n_c^{(2)}$. We might require that the total accumulated number of hits not exceed η by time t. In other words, Eq. (8.20) describes an extremely simplified target model for consider a more complex version of this model. In order to further analyze Eq. (8.20), it next becomes necessary to give a mathematical form to the probability of receiving n hits at time t; $P(n, t)$. There are two ways of looking at the form of $P(n, t)$. If we consider the hitting agent as radiation related, then the natural choice for the hitting probability is the Poisson probability distribution. The particular reason for this choice has to do with the methodology which one uses to create a mathematical model for radiation emission. However, the general form for the probability that n hits are received at time t, given a radiation argument is

$$P(n, t) = \frac{(IAt)^n \exp(-IAt)}{n!} \tag{8.21}$$

where A is the target area, I is the average number of ionizing events per unit time, and t is the given time. In this case, combining Eqs. (8.19), (8.20), and (8.21) yields a general radiation model hitting model. In the simple case where $n_c = 1$ the model is very simple and can be written as

$$P_{FAILS}(t) = 1 - \exp(-IAt) \tag{8.22}$$

For the p target model we would have a probability of failure given by

$$P_{FAILS}(t) = [1 - \exp(-IAt)]^p \tag{8.23}$$

as the probability that the system fails. Consequently, for the p target model, the probability of survival is given by

$$P_{SURV}(t) = 1 - [1 - \exp(-IAt)]^p \tag{8.24}$$

Biological systems, even at the molecular level, are considerably more complex systems than the simple system that we have just described.

Such a model is extremely complex and depends upon knowledge of a number of pieces of information about the structure of the biological system to which it will be applied. For example, how does one define the biological equivalent of sites and components? One might conceivably argue that the target sites are the DNA bases themselves, while the components are the genes. However, one might also argue that the genes are the target sites and the chromosomes are the components. Then, within the framework of the application, one would need to estimate how many sites and components are relevant to the model. Let us now consider an alternative approach to the mathematical modeling of somatic mutations.

The arguments that we will now discuss arise out of the modeling of carcinogenic processes – or more generally – the development of disease. Suppose that, in order to initiate a given disease, r distinct mutations must occur. These mutations give rise to a clone of cells whose subsequent growth gives rise to the disease. If we assume that attaining the disease state is equivalent to system failure, then a cell is said to fail when it receives r mutations. Or, if we wish, when r of the subsystems are said to fail.

Suppose that we assume that λ_j is the mutation rate at the jth locus/cell/unit time. We may then show that the probability of a mutation at the jth locus of a given cell, in the time interval $(0, t)$ is just

$$Prob[j\text{th locus mutation in } (0,t)] = \lambda_j t \tag{8.25}$$

If $\lambda_j t$ is small then, for any given cell, the probability that there will be r mutations before time t (that is, in the interval $(0, t)$) is just

$$Prob[\text{r mutations in } (0,t)] = (\lambda_1 t)(\lambda_2 t)\ldots(\lambda_r t) \tag{8.26}$$

or, more compactly,

$$Prob[\text{r mutations in } (0,t)] = \left(\prod_{k=1}^{r} \lambda_k\right) t^r \tag{8.27}$$

Equation (8.27) gives us the probability that a single cell (or target subsystem) will receive r mutating or damaging events before time t. If we now assume that the given system has m_c of these subsystems, then the *average number of damaged clones* (if we think of the systems as cells) at time t is given by

$$\eta = m_c t^r \left(\prod_{k=1}^{r} \lambda_k\right) = \beta t^r \tag{8.28}$$

As we know the average occurrence rate of the senescence inducing clones (Eq. (8.28)), it is natural to assume that they are distributed in a Poisson-like manner.

That is, the probability that there are n senescence inducing clones in the time interval $(0, t)$ is Poisson with mean η. We may then ask the question of how long will it take for the first occurrence of the disease? In our case, how long will it take for the first occurrence of "senescence"? Such a question is answered by knowledge of the cumulative distribution function for the waiting time to the first occurrence of interest. Under our given assumptions, this is approximated by

$$Prob[\text{first occurrence is in } (0, t)] = 1 - \exp(-\beta t^r) \tag{8.29}$$

As before, we assume that r mutations are necessary to damage the target. However, we also assume that m_c targets must fail before senescence may be initiated. That is, each of m_c targets must receive r mutation events in order that the senescence process may be initiated. In this case, Eq. (8.29) may be generalized to

$$Prob[\text{first occurrence is in } (0, t)] = [1 - \exp(-\beta t^r)]^{m_c} \tag{8.30}$$

A closing alternative to the target theory approach to modeling senescence is the so-called *forbidden clone* theory (Hirsch 1974). In this modeling approach, cells are assumed to transition through a sequence of states, in an irreversible manner. As the cells transition through these states, they are assumed to be transitioning towards a state of senescence. These models are often called Markov models (See also Kirkwood and Proctor 2003). In the next section we will discuss the concepts of error catastrophe and error propagation and how they have been modeled.

8.2.2 Mathematics of Error Catastrophe

Mistakes in the translation of genetic information provide a theoretical mechanism/argument for the variety of age related changes seen in the experimental literature. While *error catastrophe* and *error propagation* are accumulation theories of aging (that is they are based upon the accumulation of a toxic effect upon the cell), the large body of mathematical modeling in this particular area warrants the separation of these two theories under a separate heading. In a subsequent section, discuss more general accumulation/depletion theories. Mistakes in the translation apparatus can lead to two distinct types of *error theory*: (1) *Error Catastrophe* and (2) *Error Propagation*.

Orgel (1963, 1970) proposed that errors in the translation of genetic information contain an element of positive incidents of mistakes and therefore increase the probability of subsequent mistakes. This mechanism, is based upon the assumption that the initial presence of errors in enzymes involved in the transcription/translation process may lead to further to cell death.

The issue of stability of the proof-reading apparatus, the fidelity of cellular translation and DNA synthesis, and the possible variations in proteins as related

to aging processes have been discussed by a number of authors. With this in mind, let us begin to make some simple models of error catastrophe.

As a preliminary approach to error catastrophe modeling, let us denote the number of errors at time t as $\mathscr{E}(t)$. Let us denote the rate of error accumulation as $r(t)$. Then, if Δt is small, and if the errors are not depleted, the number of errors at time $t + \Delta t$ is just

$$\mathscr{E}(t + \Delta t) = \mathscr{E}(t) + r(t)\Delta t \tag{8.31}$$

If we allow Δt go to zero, we obtain the following differential equation for the number of errors $\mathscr{E}(t)$.

$$\frac{d\mathscr{E}(t)}{dt} = r(t)\mathscr{E}(t) \tag{8.32}$$

While Eq. (8.32) may be solved for the general case where $r(t)$ is arbitrary, let us consider a specific choice for $r(t)$ as motivated by biological considerations. The Orgelian hypothesis is that errors create more errors. Therefore, let us assume that the error accumulation rate $r(t)$ is proportional to the number of errors $\mathscr{E}(t)$. Consequently, we would expect the rate of accumulation of errors to be proportional to the current amount of errors. If we wish, we might assume, more generally, that $r(t)$ is some function of $\mathscr{E}(t)$ and then we can examine the system's behavior. For example, we might assume that when there are no errors, the system grows at a constant exponential rate r_0 however, as the errors increase, we can assume that it eventually stops growing.

While the theory of error catastrophe has fallen by the biological wayside, a number of more complex mathematical models were developed to test the various hypotheses involved in the error catastrophe theory of aging. These models attempted to be much more rigorous as well as biologically faithful in their construction. And, as such, are worthy of discussion. Further, they introduce the concept of *error propagation* rather than *error catastrophe* as a possible model for a sub-cellular theory of aging.

The major "biologically faithful" models are the models found in Hoffman (1974), Kirkwood and Holliday (1975a,b), Goel and Yças (1975) and Goel and Islam (1980). Briefly, Hoffman (1974) argues that the fidelity of translation, denoted q_{n+1}, of the $(n + 1)$st generation is related to the fidelity of the nth generation by the formula

$$q_{n+1} = \frac{(S-1)\, q_n^m + 1}{(S-1)\, q_n^m + \lambda} \tag{8.33}$$

where S is a dimensionless specificity coefficient for a perfect translation apparatus, λ is the number of amino acids from which the translation apparatus chooses its assignments, and m is the critical number of sites in the translation apparatus where substitution of any of the $\lambda - 1$ incorrect amino acids is assumed to reduce the

value of S to one (Gallant and Prothero 1980). In Kirkwood and Holliday (1975b), the authors extend the previous model to include another parameter R, the relative overall activity of a translation apparatus that has been rendered non-specific by amino acid substitution in one of the m critical sites. This new model analysis leads to the more complex fidelity equation given by

$$q_{n+1} = \frac{q_n^m\,[\lambda S - R(S-\lambda-1)] + R(S+\lambda-1)}{q_n^m\,[\lambda(1-R)(S+\lambda-1)] + R(S+\lambda-1)} \tag{8.34}$$

The formulations of these two models assume that a single mistake in the apparatus can produce a non-specific translation apparatus in one fell swoop (Gallant and Prothero 1980). The work of Goel and Yças (1975) and Goel and Islam (1980) relaxes this constraint by assuming that y of the m sites must be required for a loss of specificity. For the purposes of understanding these models, let us briefly cover the construction of this model. A given synthetase model is allowed to remain functional only as long as a certain number of amino acid sites on that molecule remain unchanged. Functionality is defined to be the ability to attach the correct amino acid to the correct t-RNA molecule. The activity of a synthetase molecule is defined to be the rate at which it attaches the correct amino acid to the correct t-RNA molecule. The sites of attachment may be assumed to be different for each of the different synthetases. Let i be the subscript which of the indexes which synthetases that we are discussing $i = 1, \ldots, N$. Let j index the sites of attachment. Next, define x_{ij} to be the number of such sites of an amino acid a_j in the ith synthetase.

Let q_i, q_i', q_i'' denote the fractions of normal, erroneous, and inactive ith synthetase molecules. Observing that the actions of an erroneous molecule are not site specific, the normal fraction $q_1(t+1)$ of normal synthetase for amino acid a_1 is given by

$$\left(\frac{q_1}{q_1 + q_1' + q_1''}\right)_{t+1} = \mathcal{Q}(1)_t^{x_{11}}\,\mathcal{Q}(2)_t^{x_{12}} \cdots \mathcal{Q}(N)_t^{x_{1N}} \tag{8.35}$$

where

$$\mathcal{Q}(j) = \frac{q_j}{q_j + q_j'} \tag{8.36}$$

The authors argue that Eqs. (8.35) and (8.36) follow from the fact that the errors will be distributed in a binomial fashion. Therefore, the fraction of molecules with amino acid a_1 at the specified x_{11} locations is given by the first term on the r.h.s. of Eqs. (8.35) and (8.36). The fraction of molecules with amino acid a_2 at specified x_{12} locations is given by the second term, etc.

If we now assume that there are y_{ij} sites which are occupied by incorrect amino acids. Suppose that we now wish to obtain an equation for the fraction of erroneous synthetases. The authors further argue that, if one assumes that the occupation of y_{ij} sites by any of the incorrect amino acids produces an erroneous synthetase, then the

fraction of erroneous synthetases in generation $t+1$ is given by $q_1'(t+1)$ and may be expressed by the following equation

$$\left(\frac{q_1'}{q_1+q_1'+q_1''}\right)_{t+1} = \mathcal{Q}(1)_t^{z11}\mathcal{Q}(1)_t'^{y11}\mathcal{Q}(2)_t^{z12}\mathcal{Q}(2)_t'^{y12}\cdots\mathcal{Q}(N)_t^{z1N}\mathcal{Q}(N)_t'^{y1N} \tag{8.37}$$

where

$$\mathcal{Q}(j)' = \frac{q_j'}{q_j+q_j'} \tag{8.38}$$

and $z_{ij} = x_{ij} - y_{ij}$.

Finally, Goel and Yças (1975) introduce the following change of variables which allows them to simplify their system of equations. Letting

$$Q_i = \ln\left(\frac{q_i(t)}{q_i'(t)}\right) \tag{8.39}$$

they are able to reduce the complex system of N equations to a simple linear matrix system of the form

$$Q_i(t+1) = \sum_{j=1}^{N} y_{ij}Q_j(t) \qquad i = 1,\ldots,N \tag{8.40}$$

The models of Goel and Yças and Goel and Islam predict a variety of dynamical behaviors. In particular, they predict that *error catastrophe* is one of a number of possible outcomes in a model of this sort. Of great importance is the fact that *error propagation* is also a possible outcome. The search for the *error catastrophe* has, however, lead to the search for errors in the more general sense. In the next section of this chapter, we will continue our discussion of mathematical models of errors from the viewpoint of *error propagation*. And, in doing so, we will return to the error catastrophe papers to see which of the models hold true, in light of the known experimental data.

8.2.3 Mathematics of Error Propagation

An elegant review of the various mathematical models of error propagation may be found in Gallant and Prothero (1980). The elegance of this paper derives from the mathematical simplicity of the model and its subsequent predictive power when applied to a specific biological system; error-promoting drugs in a bacterial system. Let us briefly review the formulation, which grew out of the paper of Orgel (1970).

In this paper the author proposed that a given generation n produces the next generation's $n + 1$ proteins. Letting e_n denote the aggregate error frequency in generation n, and letting E be the residual error frequency inherent in the translation machinery. The authors argue that the aggregate error at generation $n + 1$ is given by the finite difference equation

$$e_{n+1} = E + \alpha e_n \tag{8.41}$$

where α is a proportionality constant. If we know the initial aggregate error in the system, denoted e_0,

$$e_n = E\frac{1-\alpha^n}{1-\alpha} + \alpha^n e_0 \tag{8.42}$$

As we are interested in the time course of the aggregate errors, it is natural to inquire as to what happens to the frequency when we examine the system after a large (infinite) number of generations have past. Without that the system error equilibrium given by

$$e_{eq} = \frac{E}{1-\alpha} \tag{8.43}$$

if the value of α satisfies $\alpha < 1$. Otherwise, the system will suffer an error catastrophe; the aggregate error $e_n \to \infty$ as $n \to \infty$.

Next, the authors demonstrate how this simple model of error propagation may be used to discuss mistranslation of a specific UUA codon in *E. coli*. They demonstrate that their data fits the model when $\alpha \approx 0.5$. They further demonstrate that changes in the dose of streptomycin change E; thus raising the eventual error equilibrium but not changing the eventual dynamics of the system. Their conclusion is that, for *E. coli*, the translation system functions at a safe distance ($\alpha \approx 0.5$) from the region of instability ($\alpha \geq 1$). Therefore, there is no error catastrophe. Rather, there is a propagation of errors leading to an eventual equilibrium error level. reject the error catastrophe hypothesis for somatic cells.

8.2.4 Mathematics of Recombination

The concept of tandem gene strings as an evolutionary strategy is an old one. The argument for tandem gene string involvement in an evolutionary theory follows along the line of thought that a newly arisen tandem gene sequence will be, more or less, physiologically superfluous. Hence, mutations in the tandem regions would be less likely to be disastrous to an organism than if they had occurred in a non-tandem region. Thus, duplications may be looked upon as resource material for evolution of new gene sequences; new organismic biological complexity.

In order to discuss how tandem genes might be involved in aging/evolutionary strategies, it becomes necessary to have a mathematical description of how tandem gene repeats would be dispersed/diluted/amplified in an evolving cellular system. We begin by letting m be the tandem repeat number of a hypothetical gene. Using a deterministic approach, we would model $N(m,t)$; the number of cells having a tandem gene sequence of length m at time t. The simplest way to construct such a model is to consider time t to be in MPDT's or Mean Population Doubling Times. Further, we assume that the cells are dividing synchronously. Hence, we wish to relate the number of cells with various repeat sequences at time $t = n$ to the number of cells, one MPDT later or $t = n + 1$, with various repeat sequences. Let us briefly examine how we might construct such a relationship.

We follow the discussion in Witten (1980) begin by assuming that we are given some initial gene distribution , which we shall denote as $N(m, 0)$. This is the number of cells having tandem gene sequences of length m at time $t = 0$. Further, assume that the longest initial tandem gene sequence is of length m^*. If we assume that a gene sequence of length m may undergo a recombination event which can lead to a new sequence of length 0 to $2m$, then we may define $P_m(n,t)$ to be the associated probability that a gene sequence of length m will give rise to a recombinant gene sequence of length n where $0 \leq n \leq 2m$. Since cells with 0 or 1 gene cannot recombine, it is important to realize that we must keep track of these portions of the gene population separately. Cells with a 0 gene sequence are assumed to be dead. The number of cells containing an n-gene sequence, which results from a recombination, is obtained in two steps: First, we assume that there is a population of cells which will undergo a recombination event, and second, we observe that not all cells in the recombining portion of the population will yield daughters of the required n-gene sequence length. If we let $R(n,t)$ be the fraction of m-gene sequence cells that undergo a recombination event at time t, then we may obtain the following equation for $N(m,n,0)$

$$N(m,n,0) = P_m(n,0)R(m,0)N(m,0) \quad 2 \leq m \leq m^* \quad ; 0 \leq n \leq 2m \tag{8.44}$$

where $N(m,n,0)$ represents the number of cells with a repeat length n arising from a parent of repeat length m which divided at time $t = 0$. Remember, however, that the total number of daughter n-gene sequences resulting from the recombination is arrived at by totaling the production of n-gene sequences from all possible m-gene parent sequences of length $m = 2, 3, 4, \ldots, m^*$ in that portion of the cell population undergoing recombination events. Hence, the total number of new n-gene daughter sequences is given by the following expression

$$N(n,0) = \sum_{m=2}^{m^*} N(m,n,0) \quad 0 \leq n \leq 2m \tag{8.45}$$

This results in a recombinant daughter distribution which describes the distribution of tandem genes of length n as generated from all of the dividing cells which

were allowed to undergo a recombination event. It is important to realize that the daughter distribution must be combined with the distribution of parent cells that did not undergo a recombination event, in order to obtain the final and complete distribution of new n-gene sequences.

Before we close our discussion of this type of model, we must realize that tandem genes may confer on the cell containing them

- A growth advantage which allows them to replicate in a shorter timespan than cells with less genes and,
- A survival advantage which allows them to better compete for available resources.

That is, a cell with three genes may double three times in the time that it would take a cell with one gene to double. Details of the mathematical development and analysis of this formalism may be found in Witten (1980).

The results of these models support a variety of dynamical outcomes. Briefly, when there is no recombination, gene sequences compete only through survival and growth advantage. Thus, if the overall advantage is for cells containing the longer gene repeats(tandem repeats), then the population will tend to a final population distribution containing only cells with the longest possible repeat length. This result is independent of the initial distribution of repeat lengths in the population. Likewise, if the short repeat lengths are to be considered advantageous, then the population will tend to a final distribution containing only the shortest repeat length. This result is also independent of the initial distribution of repeat lengths in the population.

In the event we choose to include recombination effects, the complexity of possible behaviors becomes increasingly great. The inclusion of recombination can slow trends to a limiting distribution or it can allow a system to sustain distributions of genes over to multi-model or unimodal distributions. Or they may not tend to a final equilibrium at all. Let us now discuss some of the different probabilistic models of recombination. A similar model with stochastic components was proposed by Lumpkin and Smith (1980).

Probabilistic models of recombination seek to describe the probability $P_{n_i}(t)$ that there are n_i copies of the ith gene in a cell. If we consider having n_i copies of the ith as equivalent to being in state s_{n_i}, then we may make use of a class of mathematical model known as a Markov model. Perelson and Bell (1977) make use of a Markov model to describe transitions between various states. To construct their model, Perelson and Bell make use of the following series of arguments. Suppose that the ith gene can exist in any one of a number of states denoted s_{n_i} where s_{n_i} is the state in which the ith gene has n_i copies of itself in the cell. Further, they assume that n_i may take on the values $n_i = 0, 1, 2, \ldots$. They next assume that they are looking at a time interval $(t, t + dt)$ small enough so that the only way to reach state s_{n_i} is to be in state s_{n_i-1} (meaning that there are $n_i - 1$ copies of the ith gene) and a recombination event occurs, adding an additional copy of the copy of the ith gene. Or, they may be in state s_{n_i+1} and a copy of the ith gene is deleted by a recombination event. They then define $\lambda_{n_i}(t)$ to be the probability that an addition recombination

occurs per unit time, and $\mu_{n_i}(t)$ to be the probability that a subtraction recombination occurs per unit time. They show that the following system of differential equations describes the probabilities $P_{n_i}(t)$.

$$\frac{dP_{n_i}(t)}{dt} = -\left[\lambda_{n_i}(t) + \mu_{n_i}(t)\right] P_{n_i}(t) \tag{8.46}$$

$$+ \lambda_{n_i-1} P_{n_i-1}(t) + \mu_{n_i+i}(t) P_{n_i+1}(t) \quad n_i \geq 1 \quad i = 1, 2, \ldots, N_0 \tag{8.47}$$

$$\frac{dP_0(t)}{dt} = -\lambda_0(t) P_0(t) + \mu_1(t) P_1(t) \tag{8.48}$$

$$n_i = 0 \quad i = 1, 2, \ldots, N_0 \tag{8.49}$$

where the initial conditions are specified as $P_{n_i}(0) = 1$ if $n_i = 1$ otherwise $P_{n_i}(0) = 0$. To make the model tractable for analysis, assume that, at $t = 0$ there is only one copy of each gene in the population. The solution to the model depends, intimately, upon the form one chooses for the functions $\lambda_{n_i}(t)$ and $\mu_{n_i}(t)$.

8.2.5 *Mathematics of Accumulation/Depletion*

The variety of aging theories leads to a variety of models for aging processes in mammalian systems. One major class of model is the accumulation/depletion model which argues that senescence is the result of some gradual accumulation or depletion of various mysterious (or not so mysterious) cell functions, cell products, cellular debris (waste), or other cellular activities and more recently discussed in Grűning and Vinayak (2011).

One of the earliest of the "waste" papers was Hirsch (1978). This paper discusses the dilution of "cellular waste" due to symmetric or asymmetric cell division. A discussion of the modeling of asymmetric cell division may be found in Hirsch (1977). In Hirsch (1978), the author makes use of a differential equations approach to the modeling of the dilution of a cellular waste product. He assumes (1) that waste is created at a rate which is either constant or proportional to the waste already formed, (2) that waste is neither destroyed nor transported across cell walls, and (3) that the rate of cell division at large values of time is inversely proportional to some power of the waste per cell. A review of the literature justifying these assumptions may be found in the aforementioned paper.

The growth of our cell population is governed, as Hirsch (1978) points out, by the cell division rate which may be a function of cell density, waste level, and time. Letting $w(t)$ be the total waste at time t, and letting $n(t)$ be the total number of cells at time t, and assuming that the cells are undergoing density dependent growth, we may write the cell division rate as

$$\frac{1}{n(t)} \frac{dn(t)}{dt} = b(t) k(w) \left(1 - \frac{n(t)}{E}\right) \tag{8.50}$$

where $b(t)$ is the time dependent reproductive rate, $k(w)$ is the waste-cell interaction function, and E is the environmental carrying capacity. More accurately, $b(t)$ is the net per capita birth rate minus death rate. Hirsch (1977) demonstrates that it is more natural to assume that the cell division rate is an explicit function of the waste per cell, denoted $w'(t)$, rather that the overall waste $w(t)$. That is, as $w'(t)$ increases, the cell division rate should decrease. Further, for the sake of simplicity, we assume that the cell division rate is a power function of the waste per cell. That is, the waste-cell interaction function $k(w)$ is of the form

$$k(w) = \frac{1}{w'(t)} \tag{8.51}$$

and the waste per cell is given by

$$w'(t) = \frac{w(t)}{n(t)} \tag{8.52}$$

Combining this with our Eq. (8.50) we obtain the following equation for the cell division rate.

$$\frac{1}{n(t)}\frac{dn(t)}{dt} = b(t)\left(\frac{n(t)}{w(t)}\right)^j\left(1 - \frac{n(t)}{E}\right) \tag{8.53}$$

Equation (8.53) may be rewritten as follows.

$$\frac{dn(t)}{dt} = b(t)n(t)\left(\frac{n(t)}{w(t)}\right)^j\left(1 - \frac{n(t)}{E}\right) \tag{8.54}$$

While Eq. (8.54) is sufficiently general, it does not allow for any obvious biological insights. Let us begin by making the simplification that $b(t) = b_0$ a constant. Further, let us assume that there is no waste effect on the cells. This would correspond to the case where $j = 0$. Replacing these assumptions into Eq. (8.54) we obtain the very familiar equation

$$\frac{dn(t)}{dt} = b_0 n\left(1 - \frac{n}{E}\right) \tag{8.55}$$

the logistic growth equation; the standard mathematical model for density-dependent cell growth in a cell culture environment. This equation has a solution given by

$$n(t) = \frac{E}{1 + \left(\frac{E}{n_0} - 1\right)\exp\left(-b_0 t\right)} \tag{8.56}$$

where n_0 is the initial number of cells at time $t = 0$. Hence, on the basis of our simple assumptions, we see that our model describes known cellular growth phenomena. Let us now examine the possible effects of waste in the model.

We begin this investigation by considering how to describe the production of the waste material. That is, we wish to write an equation for $w(t)$. As an initial assumption, it is reasonable to assume that the waste production is simply proportional to the number of cells at any given time t. That is,

$$\frac{dw(t)}{dt} = r_0 n(t) \tag{8.57}$$

Equations (8.53), (8.54), and (8.57) constitute a simple model for waste production and its interaction with a population of cells which are growing in a density-dependent environment such as a cell culture dish.

Suppose that we wish to determine whether or not our model makes any biological sense. One easy way to do this is to assume that the waste does not affect cell growth (Eq. (8.55)) and see what happens to the waste production over time. If we let our equations be Eqs. (8.55) and (8.57) then, after much algebra, one can show that the solution to the waste equation is given by

$$w(t) = w(0) + E\left(\frac{r_0}{b_0}\right) \ln\left[\frac{n_0}{E}\left(\exp\left(b_0 t\right) - 1\right) + 1\right] \tag{8.58}$$

where $w(0)$ is the initial amount of waste in the system. Observe that we may obtain this solution by replacing $n(t)$ in Eq. (8.57) with the solution for $n(t)$ as given in Eq. (8.56).

We then simply integrate the resultant differential equation to obtain Eq. (8.58). We may simplify Eq. (8.58) as follows. If we assume that t is large enough, then Eq. (8.58) may be approximated by

$$w(t) \approx w(0) + E\left(\frac{r_0}{b_0}\right)\left[\ln\left(\frac{n_0}{E}\right) + b_0 t\right] \tag{8.59}$$

Rearranging Eq. (8.59) leads to

$$w(t) \approx w^*(0) + E r_0 t \tag{8.60}$$

where $w^*(0)$ is given by

$$w^*(0) = w(0) + E\left(\frac{r_0}{b_0}\right) \ln\left(\frac{n_0}{E}\right) \tag{8.61}$$

Notice that Eq. (8.60) says that if cells are growing logistically (in a density-dependent manner), and waste does not affect their growth, then the total waste in the cell system must increase without bound; even though the number of cells

in the cell culture plateaus out to the value of the carrying capacity E. Hence, the asymptotic waste per cell can be shown to be given by

$$w'(t) = \frac{w(t)}{n(t)} \approx \frac{w^*(0)}{E} + r_0 t \tag{8.62}$$

which also grows without bound. Clearly, this cannot be the case. Hence, we must assume that there is a waste-cell interaction or else our model is incorrectly formulated.

Sheldrake (1974) has suggested that the rate of waste production might be proportional to the amount of waste per cell already accumulated. This would require that we utilize a waste equation of the form

$$\frac{dw(t)}{dt} = a_0 w(t) \tag{8.63}$$

where a_0 is a proportionality constant. Considering this waste production model, along with our logistic growth model (8.56), we find that the waste per cell is given by

$$w'(t) = \frac{w(0)}{E} \exp(a_0 t) + \frac{w(0)}{E}\left(\frac{E}{n_0} - 1\right) \exp[(a_0 - b_0)t] \tag{8.64}$$

As $a_0 > 0$ we see that $w'(t)$ grows without bound. Whether $a_0 > b_0$ is irrelevant to the large time dynamics of the waste per cell. Again, in the this model, we see that it is biologically unreasonable to assume that there is no waste interaction. In both cases, under this assumption of no interaction, the waste per cell accumulates without limit.

Let us now take a look at the case where $j \neq 0$. That is, we wish to examine the case where there exists a waste-cell interaction. As $w'(t)$ is given by

$$w'(t) = \frac{w(t)}{n(t)} \tag{8.65}$$

then taking the derivative of both sides of this equation leads to the differential equation

$$\frac{dw'(t)}{dt} + b_0 (w'(t))^{1-j}\left(1 - \frac{n(t)}{E}\right) = \frac{1}{n(t)}\frac{dw(t)}{dt} \tag{8.66}$$

In the case of exponential growth ($E \to \infty$), Eq. (8.66) reduces to the simpler equation

$$\frac{dw'(t)}{dt} + b_0 (w'(t))^{1-j} = \frac{1}{n(t)}\frac{dw(t)}{dt} \tag{8.67}$$

which is discussed in Hirsch (1978). The author demonstrates that for a waste equation where the waste production is proportional to the number of cells (Eq. (8.57)), a variety of population dynamics may occur; governed by the value of j. Of interest is the fact that the finite lifespan of WI-38's can be described by waste models of this type only if $j > 1$; though $j = 1$ will work for appropriately chosen values of b_0 and r_0 satisfying $r_0 > b_0$. Hirsch (1978) also shows that a Sheldrake model for waste production (Eq. (8.63)) can lead to models displaying a senescence-like behavior.

This work is further extended in Hirsch et al. (1989) which discusses how the waste production may be affected by the requirement for an underlying resource which is a precursor for the waste product. Preliminary results show that by controlling the resource, it is possible to control waste levels; and thereby control cell growth. This type of model may have applications in the study of dietary restriction.

Other accumulation/depletion models may be found in the work of Strehler et al. (1971). This work argues that clonal aging processes are explicable as the consequences of irreversible and reversible repressor accumulation on plasma membranes. The authors propose a simple equation describing the kinetics of accumulation. Letting X_n be the fraction of repressors which are irreversibly bound to the membrane/generation, they show that the ratio of repressors/cell between the nth generation and the first generation is given by the following equation

$$\rho_n = \frac{2^n - X_n}{2^{n-1}(2 - X_n)} \tag{8.68}$$

They then go on to demonstrate how this model is consistent with a variety of known experimental results in clonal aging processes.

8.3 Concluding Chapter Thoughts

The dynamics of aging offers a wealth of potential mathematical and computational modeling challenges. This review has touched upon just a small portion of them. The modeling of the cellular dynamics of aging and its interface with tumorigenic processes is an open question with only a few papers written about it. Mathematical models of cellular population dynamics abound in the literature. Historically, this literature does not describe the propagation of a vector of general properties through a population of cells and how those properties might affect the propagation of the cell line. This extension has important ramifications in studying the dynamics of numerous cell system such as aging, cellular co-culture, embryogenesis, and feeder layer dynamics. As such, it represents the next natural level of cellular modeling.

In this chapter, I focused upon the historical literature in the mathematical modeling of cellular level processes. Starting with some of the basic theories of sub-cellular aging processes, we discussed various methods which one can use to

create models designed to study those same aging processes. We observed that some approaches used simple iterative (recursive) models while others used differential equation models; both single and multi-equation. Other forms of model utilized deterministic probability calculations while others used matrix approaches. We also saw that some models used partial differential equations. More recently, systems biological approaches have been used Kowald and Klipp (2013) and Dalle Pezze et al. (2014). These models involve understanding the actual biological pathways (graph theoretic structures) and turning them into differential equation models. Others have modeled focused cellular systems such as aging in the bone (Mehr et al. 1993), the hematopoetic system (Marciniak-Czochra et al. 2009) or yeast (Gillespie et al. 2004). Others have focused on modeling the dynamics of sub-cellular components such as the chaperones (Proctor et al. 2005) or the mitochondria (Kowald and Klipp 2013) and yeast. In summary, we have seen a variety of modeling approaches applied to a diverse collection of biological aging processes. We see that there are numerous mathematical and computational approaches to creating models of aging and the cellular and cell-population levels and we find that there is no one correct way to build one of these models. However, it is essential that we understand the biology of our system to the best of our ability and that we carefully formulate our questions so that they can be turned into models.

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References

Carnes BA, Holden LR, Olshansky SJ, Witten TM, Siegel JS (2006) Mortality partitions and their relevance to research on aging. Biogerontology 7:183–198

Cutler RG (1982) The dysdifferentiative hypothesis of mammalian aging and longevity. In: Giacobini E, Giacobini G, Filogamo G, Vernadakis A (eds) The aging brain. Raven Press, New York

Dalle Pezze P, Nelson G, Otten EG, Korolchuk GI, Kirkwood TBL (2014) Dynamic modelling of pathways to cellular senescence reveals strategies for targeted interventions. PLoS Comput Biol 10(8):e1003728

Denbigh KG (1981) Three concepts of time. Springer, New York

Featherman DL, Peterson T (1986) Markers of aging. Modeling the clocks that time us. Res. Aging 8(3):339–365

Gallant JA, Prothero J (1980) Testing models of error propagation. J Theor Biol 83:561–578

Gillespie CS, Proctor CJ, Boys RJ, Shanley DP, Wilkinson DJ, Kirkwood TBL (2004) A mathematical model of aging in yeast. J Theor Biol 229:189–196

Glass L (1975) Classification of biological networks by their qualitative dynamics. J Theor Biol 54:85–107
Godfrey K (1983) Compartmental models and their application. Academic, New York
Goel NS, Islam S (1980) Error catastrophe in and the evolution of the protein synthesizing machinery. J Theor Biol 68:167–182
Goel NS, Richter-Dyn N (1974) Stochastic models in biology. Academic, New York
Goel NS, Yças M (1975) The error catastrophe hypothesis with reference to aging and the evolution of the protein synthesizing machinery. J Theor Biol 54:245–282
Grűning A, Vinayak A (2011) The accumulation theory of aging. arXiv:1110.2993v2 [q-bio.QM] 17 Oct 2011
Hannon B, Ruth M (1997) Modeling dynamic biological systems. Springer, New York
Hirsch HR (1974) The multistep theory of aging: relation to the forbidden-clone theory. A theoretical article. Mech Aging Dev 3:165–172
Hirsch HR (1977) The dynamics of repetitive asymmetric cell division. Mech Aging Dev 6:319–332
Hirsch HR (1978) The waste-product theory of aging: waste dilution by cell division. Mech Aging Dev 8:51–62
Hirsch HR (1986) The waste-product theory of aging: cell division rate as a function of waste volume. Mech Aging Dev 36:95–107
Hirsch HR, Coomes JA, Witten M (1989) The waste-product theory of aging: transformation to unlimited growth in cell cultures. Exp Geront 24:97–112
Hoffman GW (1974) On the origin of the genetic code and the stability of the translation apparatus. J Mol Biol 86:349–362
Jacquez JJ (1985) Compartmental analysis in biology and medicine. University of Michigan Press, Ann Arbor
Jones DS, Sleeman BD (1983) Differential equations and mathematical biology. George Allen & Unwin Publishers, London
Kirkwood TBL, Holliday R (1975a) Commitment to senescence: a model for the finite and infinite growth of diploid and transformed human fibroblasts. J Theor Biol 53(2):481–496
Kirkwood TBL, Holliday R (1975b) The stability of the translation apparatus. J Mol Biol 97(2):257–265
Kirkwood TBL, Proctor CJ (2003) Somatic mutations and ageing in silico. Mech Aging Dev 124:85–92
Kirkwood TBL, Boys RJ, Gillespie CS, Procter CJ, Shanley DP, Wilkinson DJ (2006) Computer modeling in the study of aging. In: Masoro EJ, Austad SN (eds) Handbook of the biology of aging, 6th edn. Academic, Burlington
Kowald A, Klipp E (2013) Mathematical models of mitochondrial aging and dynamics. Prog Mol Biol Transl Sci 127:63–92
Lebowitz JL, Rubinow SI (1974) A theory for the age-time distribution of a microbial population. J Math Biol 1:17–36
Lumpkin CK, Smith JR (1980) A stochastic model of cellular senescence. Part I: theoretical considerations. J Theor Biol 86:581–590
Marciniak-Czochra A, Stiehl T, Wagner W (2009) Modeling replicative senescence in hematopoietic development. Aging 1(8):723–732
Meerschaert MM (1993) Mathematical modeling. Academic, San Diego
Mehr R, Abel L, Ubezio P, Globerson A, Agur Z (1993) A mathematical model of the effect of aging on bone marrow cells colonizing the thymus. Mech Aging Dev 67:159–172
Murray JD (1989) Mathematical biology. Springer-Verlag
Orgel LE (1963) The maintenance of the accuracy of protein synthesis and its relevance to aging. Proc Natl Acad Sci USA 49:517–521
Orgel LE (1970) The maintenance of the accuracy of protein synthesis and its relevance to aging: a correction. Proc Natl Acad Sci USA 67:1476
Perelson AS, Bell GI (1977) Mathematical models for the evolution of multigene families by unequal crossing over. Nature 265:304–310

Proctor CJ, Sőti C, Boys RJ, Gillespie CS, Shanley DP, Wilkinson DJ, Kirkwood TBL (2005) Modelling the actions of chaperones and their role in aging. Mech Aging Dev 126:119–131
Rubinow S (1968) A maturity-time representation for cell populations. Biophys J 8:1055–1073
Sheldrake AR (1974) The aging, growth, and death of cells. Nature 250:381
Strehler BL (1967) The nature of cellular age changes. Symp Soc Exp Biol 21:149–178
Strehler BL (1986) Genetic instability as the primary cause of human aging. Exp Gerontol 21:283–319
Strehler BL, Freeman, MR (1980) Randomness, redundancy, and repair: roles and relevance to aging. Mech Aging Dev 14:15–38
Strehler B, Gusseck D, Johnson R, Bick, M (1971) Codon-restriction theory of aging and development. J Theor Biol 3:429–474
Stukalin EB, Aifuwa I, Kim JS, Wirtz D, Sun SX (2013) Age-dependent stochastic models for understanding population fluctuations in continuously cultured cells. J R Soc Interface. doi:http://dx.doi.org/10.1098/rsif.2013.0325
Tautu P (1990) Stochastic modeling in biology. World Scientific Press, Singapore
Trucco E (1965a) Mathematical models for cellular systems: the Von Foerster equation – part 1. Bull Math Biophys 27:285–304
Trucco E (1965b) Mathematical models for cellular systems: the Von Foerster equation – part 2. Bull Math Biophys 27:449–471
Trucco E (1965c) On the use of the Von Foerster equation for the solution and generalization of a problem in cellular studies. Bull Math Biophys 27:39–48
Vrobel S (2011) Fractal time. Studies of nonlinear phenomena in life sciences, vol 14. World Scientific Press, Singapore
West GB, Bergman A (2009) Towards a systems biology framework for understanding aging and healthspan. J Gerontol: Biol Sci Med Sci 64A(2):205–208
Wimble C, Witten TM (2014) Modeling aging networks: a systems biology approach – applications. In: Yashin AI, Jazwinski SM (eds) Aging and health. A systems biology perspective. Karger Press, New York
Witten TM (1980) Some mathematics of recombination: evolution of complexity and genotypic modification in somatic cells-a possible model for aging and cancer effects. Mech Aging Dev 13:187–199
Witten M (1984) Time abberation in living organisms: stochastic effects. Math Model 5:97–101
Witten M (1994) Might stochasticity and sampling variation be a possible explanation for variation in clonal population survival curves? Mech Aging Dev 73:223–248
Witten TM (2014) Modeling aging networks: part 1 introduction to the theory. In: Yashin AI, Jazwinski SM (eds) Aging and health a systems biology perspective. Karger Press, New York
Zheng T (1991) A mathematical model of proliferation and aging of cells in culture. J Theor Biol 149:287–315