Chance Events in Aging

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Senescence has traditionally been understood (Strehler et al., 1959) as the suite of physiological changes that are Universal, Progressive, Intrinsic, and Deleterious. Adding the criterion that they be Cumulative created the popular acronym CUPID (Arking, 2006). While this definition has helped to focus research efforts, by distinguishing normal aging from other biological processes with predictable life-course trajectories, it does tend to obscure the stochastic component of aging. Aging is at all levels a random process: random in its physical origin at the level of genetic mutations, of the interactions of genes and cellular structures, of tissue-scale stochastic disorganization, and of adequate or misfired responses to infection and injury; random in its realization through varying genetic and developmental endowment contending with unpredictable wear and tear, and through the daily risk of catastrophe that may admit the individual to gradually decline into decrepitude at a variable time. The cumulative, universal, and progressive nature then appears as a supervening hull, driven by random mutations and random demographic and ecological events, shaped by natural selection to provide an adaptively optimum shape to the chaos—including the chaos of the evolutionary process itself.

Two decades ago a celebrated treatise, *Chance, Development, and Aging* (Finch and Kirkwood, 2000), made a rare attempt to conceptualize systematically the role of randomness in the individual aging process. They construed their task to "propose *intrinsic chance* as a third factor to the conventional two factor model, which attributes genes and environment as the main determinants of life history." While we do not wish to neglect the chance elements in genes and environment themselves, this "third factor" deserves particular attention. Randomness has always been a feature of theoretical models of aging, and of the basic tools used in their study, which are changing rates and probabilities of essentially random adverse events. Our goal here is to clarify the distinction between a process that is monotonic, and a process that is merely directed—in the sense that it may change its speed and reverse its course many times due to intrinsic chance events, even while drifting inexorably toward its ultimate fate. We also seek to distinguish trends that are predictable on an individual level from those that are merely predictable on the level of the population. These probabilistic outcomes of aging in turn shape the landscape on which natural selection acts, preventing life histories from being simply optimal.

The mere presence of randomness does not inevitably entail a random impact on the organism. All physical processes originate in randomness. What we call "deterministic" or "predictable" are those processes whose large-scale effects are determined by a sufficiently large number of individually random events that the overall process becomes a foreseeable consequence based on the probabilities of the component events. For example, randomness may lead to a particular protein misfolding during synthesis but in most cases this protein will be refolded, repaired, or rapidly tagged for degradation, limiting its impact. Precisely because these random events are so common, natural selection has folded them into processes that limit their effects: While the microscopic details are unpredictable, the macroscopic results are not. In the event that the cellular regulatory mechanism fails to detect multiple misfolded copies of an essential protein, then their impact may not be negligible. This is of particular importance for proteins occurring in low-copy numbers but is not limited to them. A stochastic single-molecule event can cause a change in the lactose operon regulation and therefore determines alternative phenotypes (Choi et al., 2008).

Given the huge number of proteins synthesized every second in even the simplest cell, damaged proteins should accumulate as steadily as silt on a continental shelf. Genetic variants that shift the accuracy of folding up or down, or change the efficiency of error

detection and repair, should adjust the rate of misfolding in predictable ways. But the interactions within the cell that allow for correction, can also amplify random errors, not only when the damage happens to fall upon the least redundant and most crucial structure, the nuclear genome.

Biological systems are organized hierarchically: cells within tissues, tissues within organs, organs within organisms, and then organisms within populations and ecosystems. At every level, redundancy and interaction sweep up small-scale stochasticity into something like large-scale stasis or clocklike regularity—as when senescent cells undergo programmed cell death (apoptosis) and are cleared out by macrophages. However, the same interactions can also amplify random events—as when the gradually growing residue of uncleared senescent cells serves as a matrix for the sudden explosion of a malignant tumor (Davalos et al., 2010).

The Stochastic Levels of Aging

Stochasticity is manifest at four logically distinct levels of the aging process:

1. Random endowments—genetic, epigenetic, environmental, and demographic—that shape the individual aging trajectory from early in the life course (e.g., the particular mix of alleles an individual has).
2. Small-scale random processes driving senescence at a basic biological level, such as protein misfolding;
3. Larger-scale random events that alter the trajectory of senescence within an individual, and manifest in the hidden condition of the organism, as when an extreme stressful event might accelerate an individual's aging;
4. Random genetic, environmental, and demographic events that shape a species' or taxon's life history over evolutionary time, as when temporary environmental conditions might cause fixation of a certain physiological strategy, that is then passed down to descendant lineages.

Stochastic Slings and Arrows and the Evolution of Senescence

Since Schrödinger's 1943 "What is Life?" lectures, themselves drawing on Boltzmann's original speculations on the consequences of the Second Law of Thermodynamics, the definition of life as a twilight struggle to bail out a rising tide of entropy has undergirded most thinking about the physics of life and life histories. Although a thermodynamic perspective on biological systems has been criticized (Stoward, 1962), this idea spurred the development of some of the earliest evolutionary theories of aging. One such example is the so-called "wear and tear theory" (Weismann, 1882), which is grounded on the observation that a physical organism—the *soma*, in the terminology that Weismann introduced—could never be secure against the random natural shocks that flesh is heir to. Random damage accrues in every cell in the form of miscopied DNA, leaky mitochondria, and misfolded proteins, and on the level of tissues and the organism in the form of senescent cells, chronic infections, scars, and plaques. The finely balanced system loses coherence. In her *tour d'horizon* of female reproductive aging in humans, Wise (1998) gives this summary: "Multiple studies demonstrate that the temporal order and the pattern of multiple signals are altered during aging. These observations suggest that the dampening and desynchronization of the precisely orchestrated ultradian, circadian, and infradian neural signals lead to miscommunication between the brain and the pituitary-ovarian axis." Responding to all these pressures, Weismann argued, the germline is selected to shuffle off its mortal soma, rather than lingering to eat the bread out of the mouths of its more vigorous offspring.

More recent theories have sloughed off Weismann's group-selection taint, but maintained his core insight, replacing foraging competition with the younger generation by competition within the organism between investment of resources among growth, self-maintenance, and reproduction (Kirkwood and Rose, 1991). But there remains a critical weakness of this theory—which Weismann himself came to recognize—and which was perhaps best expressed in the seminal paper of George Williams on senescence: "It is indeed remarkable that after a seemingly miraculous feat of morphogenesis a complex metazoan should be unable to perform the much simpler task of merely maintaining what is already formed" (Williams, 1957). This same insight had led Medawar (1952) to the most radically stochastic theory of senescence, now known as the *mutation accumulation* theory. According to Medawar, instead of the usual presumption that systematic regularities of life and life histories result from evolutionary adaptations, we should view senescence as, in essence, a failure of adaptation. A random pattern of deleterious mutations drops into the germline, each one requiring on average one excess death (or lost offspring) to be purged. If the age-specific harms have low probability of causing death or lost reproduction, or make themselves felt after the completion of normal reproduction, the mutant allele will persist over many generations. The allele makes itself felt only in the selected few who survive to experience its effects in old age.

Williams's essay offers a complementary theory, now referred to as *antagonistic pleiotropy*, which seems superficially more directed and deterministic: genetic variants that push mortality to later ages may be passed on to more offspring, even if the late degeneration is substantially more extreme than the early compensation (Williams, 1957). Such variants will eventually become fixed in the population. One way of interpreting this is to consider the cost of entropy (or random unpredictability) in lifespan. A nonaging life history, subject to constant hazard rate of death, maximizes the entropy of the age at death, among all those distributions with a fixed average lifespan. A shift toward mortality rates increasing with age reduces entropy, and so reduces the resources wasted in years of life prepared for but never realized.

Bet-Hedging and the Evolution of Longevity

A shift from constant mortality toward mortality rates decreasing with age also reduces entropy, and this may provide a clue to explain the common U-shaped pattern of mortality curves that also characterize the human life-course. Economists such as Lee (2003) have explored the links between the evolution of age-specific mortality rates and the efficient sharing and accumulation of resources. Sharing among diverse individuals smooths consumption over the lifespan, opening up the space of life histories with larger and longer investment in offspring quality. Unsurprisingly, such investment has been found to be linked to longer lifespans. Sharing resources also breaks the tight link between individual reproduction and reproductive value that drives rapid senescence in traditional evolutionary models (Hamilton, 1966)—the famous "grandmother hypothesis" for protracted human longevity (Pavard et al., 2008).

The evolution of lifespan and aging is intimately linked to environmental variation and environmental stochasticity, but the relationship is hardly a simple one. Organisms spend varying portions of their life histories in "r-selected" or "K-selected" modes; respectively, where population growth is unlimited—so that fitness corresponds to growth rate r—and where population growth is constrained by environmental carrying capacity K. Switching among these modes, fitness corresponds to success in holding one of the limited number of places (limited by K), for oneself and one's offspring. In a stable environment the carrying capacity K remains fixed, allowing selection for the most competitive offspring, and so rewarding long lives that support this investment in competitiveness. The more random the environment, the more often, and the more radically, the carrying capacity K will shift, rewarding those who can respond quickly to favorable conditions, but who also can sustain poor conditions.

Stochasticity in population size and variation in phenotype may be amplified, as discussed below, by more frequent turnover of the generations. The same effect may be achieved by spreading offspring over a broader range of phenotypes, so called "bet-hedging," to cope with unpredictable stochastic environmental variation. Paradoxically, this production of a broad range of phenotypes may have the effect of reducing the uncertainty for the population and the lineage as a whole when the optimal phenotypic condition is in flux, as shown in detail by the influential mathematical model of Bull (1987). The general principle, in any case, is that longevity evolves as part of a process that matches life-history randomness to the ineluctable randomness of the organism's internal and external environment.

Stochasticity, Reproduction, and Aging

Underlying Williams's challenge—and hence, underlying all of the evolutionary theory of aging—is the aleatory function of reproduction as a generator of novel traits and mixtures of traits. Organisms do not persist unchanging, like rocks, but as shifting populations of transient individuals.

Analyzing the apparent "aging" of isoclonal protozoan populations—the subject of a major strand of research in the early 20th century and revived since the ground-breaking work on *Escherichia coli* by Stewart et al. (2005)—Graham Bell drew two kinds of conclusions. Bell's earlier book (1988) describes the deterioration of protozoan populations when propagated from randomly selected individuals generation after generation. He argues that this zero-growth condition makes manifest the role of random variations ceaselessly tested by the environment in correcting the damage that accumulates through normal metabolism. Since there is no possible external template, the environment itself must serve as a template, exponentially amplifying the individuals that are randomly most fit. In the experiments described by Bell, bacterial conjugation—exchange of genetic material—was found to serve as an alternative source of randomness that could revive a defunct population. In the experiments of Stewart et al. (2005), inheritors of bacterial components that had physically persisted through more generations showed declining vitality. Again, most lines will show this declining vitality, and we are left to explain why the reproductive process is so structured as to produce two offspring with substantially unequal starting conditions (Steiner et al., 2019; Wang et al., 2010).

A mathematical model (Evans and Steinsaltz, 2007) may shed some light on these processes. This model represents individuals as points positioned each at its own level of "damage." As time passes, damage accumulates in each individual in the population and is repaired, randomly, but with a tendency to increase. At random times the cell may die, or it may fission, dividing its damage in some way between the two offspring. Fission rates decline with rising damage levels, and mortality rates increase. The crucial conclusion is that there is an optimal level of randomness in damage accumulation, at which the population growth rate is maximized. If the inherent randomness is too low the population would be able to increase its growth rate while still accumulating damage at the same rate, simply by the expedient of sharing out the damage less equally between the daughter cells.

Bell's later paper (1993) argues specifically for the role of parasites in driving the evolution of senescence, and it serves as a direct response to Williams's question. Organisms are gradually colonized by all manner of parasites, viruses, and bacteria, which themselves evolve to be better adapted to exploit the particular ecosystem of their host. The only way to expel them is to abandon the body and strike out in a random new direction. Here too, the emphasis is on declining vitality, and the need for randomness to reset the conditions, even if the average result may be worse than the condition of the parent.

Nonselective Stochastic Stage Dynamics

Natural selection depends upon differences in individual life courses, that at the population level shape senescence patterns, being linked to differences in genetic inheritance. Researchers have sought, over the past decade, to quantify the scope of intrinsic chance—in this context also called *dynamic heterogeneity*—in determining the range of individual life courses.

One approach (Tuljapurkar et al., 2009) represents "neutral" life courses as Markov chains—memoryless stochastic processes that transition to a new life stage or to death at each time period, according to probabilities determined by the current state. The idea is that all individuals are born equal, and that all individuals in a given state experience the same probabilities to survive or transition to another stage. There are no genetic differences (or maternally transmitted non-genetic differences) among individuals at birth, and no genetic differences exist that influence later development. Such neutral models, or neutral theories of life histories, are obviously wrong for any natural population where selective genetic differences occur, but they provide null hypotheses against which adaptive explanations for variation in life histories should be tested (Steiner and Tuljapurkar, 2012). Interestingly, trait distributions generated by these neutral models often succeed well in reproducing the observed trait distributions, at least up to the limits of available data quantity and quality. More extensive and detailed data will be needed to differentiate between fixed genetic contributions and stochastic dynamic contributions to variability in phenotypic traits and life courses. Theoretical and empirical support for the predominant contribution of intrinsic randomness to phenotypic variability and diversity in life courses continues to accumulate (Caswell and Vindenes, 2018; Hartemink et al., 2017; Jouvet et al., 2018; Snyder and Ellner, 2018; Steiner et al., 2019; Steiner and Tuljapurkar, 2012), even while these neutral theories have been sharply challenged in recent years (Cam et al., 2016).

Fixation Within Lineages

Differences in the aging process can easily be observed across major clades of organisms. For example, metabolic dysfunction related to glucose metabolism appears to be a principal aging mechanism in mammals, but birds can tolerate glucose levels that are toxic to mammals without any apparent ill effects (Holmes et al., 2001). Many of these differences were presumably fixed early in the evolution of these clades. For example, the mammalian ancestors were apparently small and short-lived, and were confined to more restricted niches than those they occupied after the end of the Cretaceous. Mammalian physiology, including the physiology of aging, is thus likely constrained by traits that were fixed under quite different circumstances from those encountered by many current mammal species. In an important sense, the fixed physiological aging process common to a clade may be interpreted as a random variant generated by the current niche and selective environment upon the background life-history constraints—the *phylogenetic inertia* (Orzack and Sober, 2001)—imposed by its deeper evolutionary history. Such processes may play out at both macro- and microevolutionary timescales, with effects of local demographic and environmental events having an impact at shorter scales. This provides the theoretical justification for a kind of statistics of species (or other taxonomic levels) that separates out the more recent variation from the phylogenetic inertia. Recent theoretical modeling of trade-offs demonstrated that under a variety conditions alternative physiological strategies may produce equally adaptive life history strategies (Cohen et al., 2017), such that the final strategy fixed within a species lineage contains an influential stochastic component.

Stochastic Mechanisms of Aging

Gene Expression and Aggregates

Aging, as we have discussed, arises from the encounter between the immovable randomness of biological processes and the irresistible force of natural selection. Gene expression—the complex sequence of activities, from transcription to protein folding and transport, that underpins all essential functions of living cells—is one of the core processes whose errors are folded into the aging phenotype. The process is fundamentally noisy, in the physicists' sense of being subject to continuous random fluctuations. Importantly, this noise is present in almost every step. Miscopies during DNA transcription—the generation of RNA from the DNA template—can lead to the flawed translation from RNA to polypeptide, which can then result in a protein that does not present the appropriate chemical composition to ensure correct folding. Even with perfectly accurate preceding steps, translation and folding can fail by themselves (Lindner and Demarez, 2009). Observation of the variation in levels and quality of gene expression products among cells, demonstrated for example by Elowitz et al. (2002), can provide insight into the process itself. The nature of this variation is attributed both to local density of relevant chemicals (e.g., high levels of chaperone proteins), as well as the impact of random events directing the occurrence and order of relevant reactions (Cai et al., 2006). Despite this, highly redundant self-regulation maintains homeostasis with extraordinary reliability. One of many examples we could list is correct protein folding that is stabilized by molecular chaperones, which may also mark misfolded proteins for degradation.

Yet errors do occur, and random damage accumulates. For example misfolded proteins can fail to be detected, and accumulate in the cell, forming "aggregates" (Tyedmers et al., 2010)—with some evidence that protein homeostasis declines with age (López-Otín et al., 2013; Taylor and Dillin, 2011). This homeostatic failure seems to be negatively associated with protein synthesis rate and resulting overall quantities of the protein required (Taylor and Dillin, 2011; Toyama and Hetzer, 2013), with long-lived proteins contributing more to age related homeostatic failure (Toyama and Hetzer, 2013). Proteins present only in small quantities are more heavily impacted by random events driving homeostatic failure as evidenced for instance by bistable stochastic phenotypic switching regulated of the lactose operon repressor, LacI, that has copy numbers of <20 (Robert et al., 2010). The actual success and functionality of the various regulatory pathways is also far from clear. Autophagy, for example, was originally thought to delay senescence by removing problematic molecules, and its efficiency was believed to decline during aging. Yet recent work has suggested that this removal process may actually provide the cell with building blocks that promote the activation of senescence pathways, suggesting a complex interaction between autophagy and aging (Kwon et al., 2017). Some association has been found

between age-related disease and protein aggregates in humans (Selkoe, 2003), although doubts have been raised as to the causal role of such aggregates in neurodegenerative diseases such as Alzheimer's disease (Fülöp et al., 2013; Itzhaki et al., 2016).

A correlation between aggregates of misfolded proteins and senescence is illustrated in bacterial systems, though a causal relation has not been proven. Slower growth and reduced division rates, as well as higher levels of aggregates were demonstrated to be disproportionately present in "old cell-pole" bacterial cells, that is, cells that have inherited the original maternal cell pole as opposed to a newly synthesized one (Coquel et al., 2013; Lindner et al., 2008). The rate of aggregate accumulation, and their segregation following cell fission, seem largely stochastic.

Feedback and Nonlinear Effects

One popular class of mechanistic accounts of aging starts from the emergent properties of complex regulatory networks that need to maintain homeostasis. Life consists of organisms composed of cells that are controlled by molecular networks, and these networks are self-regulating. If the feedback loops collapse there is often no possibility of external rescue, so natural selection has fine-tuned the regulation to maintain homeostasis across as wide an array of conditions as possible. Such systems are referred to as highly optimized tolerance (HOT) systems (Kriete, 2013), but can never be optimized for all possible conditions, with trade-offs between resistance to frequent versus rare adverse conditions. When something goes wrong beyond the capacity of the system to correct itself the organism dies or suffers a permanent derangement of the regulatory network.

A particularly straightforward example is the glucocorticoid stress response in vertebrates. Glucocorticoids are a broad class of steroid hormones, some of which play a role in suppressing the immune system in response to stress. Under acute stress, where the hormone levels rise rapidly and just as quickly subside to baseline, this response is highly adaptive, but under chronic stress the return to baseline is incomplete. The downstream damage to multiple other regulatory systems is thought to accelerate aging (Sapolsky et al., 1986). Aging reflects the impossibility of indefinitely maintaining homeostasis in a complex network that must interact with the diversity of conditions the world throws at it (Cohen, 2016). We call these aging mechanisms *dysregulation mechanisms*.

Dysregulation mechanisms are not entirely separate from wear and tear, cellular senescence, or the age-specific effects genetically programmed by antagonistic pleiotropy. Among the stochastic challenges to which homeostatic processes must imperfectly and unpredictably respond are the existing damaged cells. Dysregulation exacerbates the inefficiency and incompleteness of repair processes.

In a HOT system, such as an organism, natural selection has presumably created substantial redundancy and capacity to resist a diversity of challenges that may be individually rare, buffering the impact of stochasticity upon individual aging trajectories. A major outstanding question is the effectiveness of such mechanisms, relative to the inexorable burden of homeostatic dysregulation. This likely varies across species: In cases where buffering mechanisms are effective but costly, and at the same time the burden of homeostatic dysregulation is high, selection on these network-based physiological mechanisms likely follows the same principles that other mechanisms would based on mutation accumulation and antagonistic pleiotropy, adjusting the buffering based on trade-offs, selection's shadow, etc. However, there may be cases where effective buffering mechanisms are unavailable, or inevitably carry high external costs, in which case aging rate could manifest as a constraint relatively impervious to trade-offs or selective environment; as well as cases where the dysregulation burden is low and aging may be largely absent. Indeed, as discussed by Steinsaltz and Goldwasser (2006), the increasing variability of internal state at advanced ages inherently tends to erode the pressure of natural selection toward preserving effective homeostasis indefinitely.

Dysregulation is a highly nonlinear process, and so tends to amplify slight stochastic fluctuations in the aging process. A single highly stressful event can provoke a persistent dysregulation in the glucocorticoid system, that in turn disrupts many other processes (Glover et al., 2006). Amplification of small stochastic events means that the law of large numbers will not average out the stochastic effects into large-scale determinism. Dysregulatory processes are likely a major cause of the large variances in lifespan observed even for genetically identically individuals under nearly identical conditions.

Telomerase and Cancer

Perhaps nowhere is the complex interplay between random insults and a programmed framework more conspicuous than in the age-specific incidence of cancer. Tumors are quintessentially stochastic manifestations of the aging process, but their randomness has been the subject of much debate in recent years. Once the origin of cancer in somatic mutations was understood, the most straightforward conclusion was that a small number of oncogenic mutations combined in a single cell would form the unstoppable seed of a tumor. If a malignant neoplasm is a result of a copying error or a cosmic-ray strike shattering a chromosome, in a cell that then fortuitously evades T-cell scrutiny, then it is an unpredictable random event that could originate at any time. Current "chromosomal instability" theories maintain this stochastic character.

More recent research has depreciated the responsibility of the single cell, tending to see cancers as ailments of the entire organism, which must first protect the seed cell, then nourish it, and ultimately enable it to spread. Tumors implanted in youthful tissue are much less likely to metastasize, and the secretory phenotype (SASP) that characterizes senescent cells is known to promote tumor growth in neighboring cells (Rodier and Campisi, 2011). At the same time, cell senescence inhibits cancer, serving as a final brake on unrestrained cell division.

The genetics of carcinogenesis are thus another amplifier of stochasticity, translating the clocklike accumulation of senescent characters into increasing rates of unpredictable events. Oncogenes—genes whose mutations contribute to tumor initiation, growth, or spread—serve, in their unimpaired form, to activate cell senescence or programmed cell death (apoptosis), but might also have adverse effects on cell death (Lowe and Lin, 2000).

Especial interest in recent years has fallen upon the role of telomerase in the trade-off between senescence and cancer. The shortening of telomeres—"caps" made up of highly repetitive DNA that preserve the physical integrity of eukaryotic chromosomes—has been found to drive the exit from the cell cycle that Hayflick and Moorhead (1961) discovered, and that has come to be called "replicative senescence" or "cellular senescence." Telomeres shorten at every cell division, unless they are actively lengthened by the activity of the enzyme telomerase. In complex metazoans this enzyme is active only in germ cells, stem cells, and a few other specialized cell types. However, most human cancers are found to have significant telomerase activity, indicating that telomere-shortening is an essential roadblock in a cell's mutation pathway to the immortal phenotype that originates a malignant tumor.

Telomere length has been shown to be sensitive to stressful life events, toxin exposure, and disease. Telomeres may therefore be one stochastic clock, accumulating unpredictable insults over the life course, and translating them into increased likelihood of future age-related disease and rising mortality rates. While the connection of cellular senescence to senescent phenotypes at the other end of the organism's structural hierarchy has been a matter of much debate and controversy since Hayflick's discovery, in recent years the accumulation of senescent cells—precipitated in large part by shortened telomeres—is coming to be understood as in and of itself a major cause of many of the characteristic deleterious changes associated with aging (Blackburn et al., 2015).

The repression of telomerase activity appears then as a fundamental genetically programmed trade-off, though different from that foreseen in the original formulation of antagonistic pleiotropy theory: it is not trading youthful vigor against longevity, but balancing different risks to maximize healthy lifespan. The effect, though, contributes to the characteristic long declining likelihood of health and survival.

The Stochastic Trajectories of Senescence

Having examined at length the stochastic sources of senescence, both in its evolutionary origins and its physical causes, we delve now into the stochastic manifestations of senescence.

While salmon and mayflies have famously rigid life histories, randomness is the norm. Models of age-structured population growth invariably presume that the fates of individuals will be random, with an orderly aging process observable, if at all, on the level of age-dependent rates. Mortality rates vary substantially among related species (Jones et al., 2014); and within species among different clonal strains of rodents and nematodes (Yen et al., 2008) and even *E. coli* (Jouvet et al., 2018); and may be subject to environmentally-driven fluctuations or to trends (as in humans over the past two centuries). There is at least some evidence of genetic variation in the general rate of aging in humans (Melzer et al., 2007). We would like to go beyond this, to measure individual variation in mortality rates and mortality-rate trajectories, and to distinguish congenital (due to genetic differences or developmental accidents) variation from adventitious (due to unpredictable life events that cumulatively contribute to the pace of future events or changes) variation in life trajectories. Here we run into significant theoretical and methodological challenges, since mortality rates are really only defined as properties of populations.

A process driven by random noise may still be essentially deterministic in its pace and extent. If there are age-specific changes within organisms, time must be kept by an internal clock. Rigorous timekeeping in biological systems, as in the circadian rhythms, or in the photoperiodic cycles common to many flowering plants, and some animals, depend upon elaborate and highly evolutionarily conserved biochemical networks (Brady, 1982). This is not at all what we would expect to find in the sort of *faute de mieux* adaptation that we posit for the evolution of senescence.

Ultimately, the determinacy of a progressive process is a function of the scale of random fluctuations, and on the number of random influences that it cumulates. What appears to be a smooth, progressive process on a population level may in fact be the product of sudden collapses on an individual level, occurring randomly, hence spread out over time. For instance, bacteria show classical senescence patterns, resembling those of humans and many other metazoans, with an exponential increase in mortality early in life followed by a late age mortality plateau. Underlying this smooth pattern at the population level are two stochastic processes at the individual level: a process resembling random accumulation of damage within a cell, and stochastic transmission of an (unidentified) aging factor at cell fission (Steiner et al., 2019). Whether there is an individual stochastic aging process—so that a major portion of the age-related decline in vitality is an accumulation of large stochastic events—is the subject of current investigation, and even precise formulation of the question is a major challenge. There is some evidence for a substantial adventitious component in bacterial aging. While complex metazoans seem to have far too many individual components for their senescence trajectories to be noticeably random, evidence has been accumulating (Schultz and Sinclair, 2016) to show that it is the senescence of limited populations of stem cells, much more than that of the great mass of somatic cells, that determines the aging of tissues, hence of organs, hence of the whole organism.

Population-Level Consequences of Stochastic Trajectories

One place where the hidden heterogeneity in individual aging can make itself conspicuous is in the development of population-level mortality at extreme ages. Consider the phenomenon of mortality plateaus, the flattening out of mortality rates at advanced ages, which is by now reasonably well-established in many species, ranging from bacteria, to fruit flies, to humans (Steiner et al., 2019; Vaupel et al., 1998), despite recent suggestions that this phenomenon may not be as universal as some have supposed (Jones et al., 2014). Lacking a compelling reason for the observed rate of mortality acceleration through early adulthood we cannot, of course, insist that deceleration requires a special explanation. But the major explanations that have been proposed depend on random individual variability. Missov and Vaupel (2015) and Steinsaltz and Wachter (2006) have shown that congenital variation in mortality risk or in aging rates will tend to yield mortality plateaus. Alternatively, Steinsaltz and Evans (2004) and Weitz and Fraser (2001) have shown plateaus to be the generic outcome when individuals decline over time toward physical states of increasing mortality, but with appreciable random fluctuations in the individual rate of decline. This assumes no variability among the population at birth: heterogeneity in condition evolves over the life course, as the population vitality distribution drifts downward and is clipped at its lower end by the increasing force of mortality. Eventually, the small subset of survivors will settle into a compromise equilibrium distribution of decrepitude, with its corresponding equilibrium mortality rate.

Genetic Variability and Parental Endowment in the Aging Process

There has long been intense interest in exploring the extent to which variation in longevity might be heritable, particularly in humans. That genetic variation reveals evidence both of the mechanisms of current aging, and of the evolutionary forces that shaped it, of course heightens the fascination, on top of the natural human concern with family histories and predicting individual fate. Broadly speaking, we expect senescence driven by mutation accumulation to result in a more heritable aging process, determined in each individual by a large number of alleles, each one shared with a small portion of the population, hence perhaps also subject to more of an inbreeding penalty. At the same time, it would probably be fair to say that no one has yet managed to derive predictions about patterns of genetic variability that could serve as an unambiguous test of any extant theoretical model.

Human longevity has been found to have a significant heritable component, though quantifying this has proven difficult, and depends significantly upon the precise operational definition of aging, and the choice of methodology to isolate genetic from shared environmental influences. Traditional approaches to genome-wide association studies (GWAS) for single nucleotide polymorphisms (SNP) have little power to detect rare variants, and indeed have so far turned up variants incontrovertibly linked to the rate of aging in only a few genes, most prominently Apolipoprotein-E (APOE), whose ε4 allele is a major risk factor for early onset Alzheimer's disease. One study has suggested that this one genetic polymorphism is alone responsible for about 15% of genetic variability in mortality rates after age 65 among several western European countries (Ewbank, 2004). The discovery that this same allele may strengthen the blood-brain barrier against malaria has provoked speculation that it may be a bona fide product of antagonistic pleiotropic selection (Kassa et al., 2016). In addition, there are several rare genetic variants known for their links to progerias, diseases of extremely accelerated aging.

Convincing proof for broad heritability of variability in aging and longevity has come from studying relatives of longevous individuals. One of the most striking results was the discovery of reduced mortality among 2092 siblings of New England centenarians (Perls et al., 2002). At all ages, even through their 1980s and 1990s, these siblings had only about half the mortality rate of their birth cohorts, a result that seems unlikely to be explained by the shared early-life environment or shared socioeconomic status.

Genetic variability has also been invoked to explain mortality plateaus (Vaupel and Carey, 1993). Plausibly, a heterogeneous population comprised of multiple genetic types, with fixed differences in mortality rates would see population-level mortality rates bend downward during the transition to homogeneity, as the less robust type dies out. That this cannot be the whole story—and that there must be a genuinely stochastic element to the fundamental drivers of senescence—may be inferred from the observation that isoclonal populations raised under highly controlled conditions display mortality rate curves of very similar shape to those of more diverse populations (Steiner et al., 2019; Vaupel et al., 1998).

In simple organisms, such as the bacteria and yeast discussed earlier, "age" seems to consist mainly of an endowment of maternally transmitted aging factors, whose differential inheritance contributes to the heterogeneity of lifelong aging trajectories. Despite this obvious transmission of an aging factor between the aged old pole cell and their new pole cells, no correlation between the lifespan of the old pole cell and their new pole cell could be detected (Steiner et al., 2019). A similar pattern of maternally transmitted age has been found in a few studies on more complex model organisms, such as *Caenorhabditis elegans* (Perez et al., 2017), though it has not yet been possible to identify a precise mechanism.

Nongenetic maternal effects have also been linked to significant variation in rates of typical age-related diseases in humans. Finch and Kirkwood (2000) have highlighted a range of research suggesting that differences in individual endowment with nonreplaceable cells, especially oocytes and specialized neurons but also the small reserves of multipotent stem cells, influence the later life-course of their fertility and mortality rates. Such prenatal influences are random on a wide range of scales, from individual infections at critical moments in gestation and stressful experiences, through chronic exposure to toxins, and up to whole-environment-level exposure to famine, which has been found to accelerate age-related development of hypertension, heart disease, and diabetes. These contribute significantly to the stochasticity of senescence trajectories that we observe on a population level.

Caution is needed, however, to distinguish aging from age-related diseases. It is far from clear that major chronic diseases in the modern world existed at all among our ancestors—heart disease, for example, appears to be completely absent in a Bolivian horticulturalist population, despite high levels of purported "risk factors" such as inflammation and low HDL cholesterol (Vasunilashorn et al., 2010). Likewise, many chronic diseases, including cancer, heart disease, and diabetes, are largely the end products of processes that start during young adulthood. It has been argued that much research on human aging risks confounding an age-related increase in rates of chronic diseases that is specific to modern human societies with a more basic mammalian aging process. How to deal with this problem is a subject of ongoing discussion (Franceschi et al., 2018), and we urge prudence in interpretation in the meanwhile.

Conclusion

> *Thou canst help time to furrow me with age,*
>
> *But stop no wrinkle in his pilgrimage.*
>
> William Shakespeare, Richard II 1.3.231-2

> *But time and chance happen to them all.*
>
> Ecclesiastes 9:11

Organisms are subject to a wide range of unpredictable and entirely random forces, intrinsic and extrinsic, on all levels of time, space, and biological organization. An inexorable process of aging, shaped by natural selection, gives form to this randomness. Individual vitality shows predictable patterns with age, and huge variation among individuals, while the patterns themselves interact, in ways still poorly understood, with unpredictable environments and the peculiar demands of each species' foraging and reproduction requirements.

A key challenge of recent decades of aging research, and of the coming decades, has been to organize conceptually the many interwoven levels of randomness. The goal is, of course, to shed light on the mysterious ontogeny of current aging patterns; but also to wield the residues of chance as a tool both for research and for medical practice. Through better analysis and quantification of chance in mortality and aging we may hope to tame chance for our descendants and their environment, and so provide better chances to survive and to flourish.

Random factors mark out the boundaries of ignorance—and hence the boundaries of possible knowledge—but they also mark what is not quite fixed, the points of leverage where change might be effected. When we find that aging patterns are a selective response to environmental unpredictability, we learn how the biosphere may respond to rapidly rising climate chaos. And we recognize, at the same time, the slack that has arisen in the web of interactions in our stabilized human environment, that may permit some manipulation of human aging, free of the original selective trade-offs. Genetic variants that delay or accelerate aging are purely random in their arising and persistence, but each one points out a feature of the biological process that could be made better or worse. A vibrant supercentenarian is proof that some quirks of fate can radically slow the ticking of the biological clock.

In the study of aging, the hope is not that science will enable us suddenly to escape our fate into immortality. The hope is, rather, for patiently helping us to align some of these quirks and flukes in our favor. And as much as any other area of biology the study of aging, its universal patterns and its individual variations, allows us to explore the stable eddies amidst the turbulent stream that are life's primal creation.

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Further Reading

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