AGING AND TOTAL QUALITY MANAGEMENT: EXTENDING THE RELIABILITY METAPHOR FOR LONGEVITY

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Abstract. Reliability models of longevity can be usefully extended by examining both the limitations as well as the potential of repair processes. Engineering principles may impose constraints in addition to those of cost. Reparability itself may impose biological costs in reliability and efficiency, and may not always be advantageous. Rather than simply optimizing parameters within a structure that is tightly defined *a priori*, it is illuminating to examine interactions between high- and low-level design decisions, by analogy with the engineering principle of "Total Quality Management." Because the repair of damage is often incomplete or imperfect, the accumulation of repair increases the disorder within the system over time, decreasing the effectiveness of the local controls over repair. Asymmetry and sequestration appear to be ways of channeling the disorder to parts of the systems that are reparable.

1. Introduction

The accumulation and the repair of damage are essential to theories of senescence. Typically neglected are the consequences of reparability as a designed property. We analyse some of these consequences, with an eye toward informing more complete models.

Current theories of aging hold markedly divergent views of the role of repair. Most mechanism-based theories assume that wear and tear is an inevitable consequence of existence, for living objects no less than nonliving ones, and senescence represents little more than the accumulation of that damage. In this view, mechanisms of repair, however they may be honed by evolution, remain blunt instruments that may retard senescence but not fundamentally alter its progress. In contrast, popular evolutionary theories imply that all damage is in principle reparable, that natural selection can shape the lifetime trajectory of damage and repair, constrained only by the energy budget. In this view, senescence results from life-history decisions about the allocation of finite resources in ways that maximize selective fitness, regardless of the particulars of physical materials.

The evolutionary view is elegant and powerful, but it has not incorporated constraints on repair that are known to be significant. Not all damage can be reversed or prevented simply by investing enough resources. Damage to central nervous system and heart tissue, for instance, is usually irreversible. The regeneration of whole limbs or organs is rare among vertebrates.

Mechanistic theories, generally built on the analogy of mechanical reliability, tend to be quite open about constraints. In pursuit of a bridge between the two kinds of theories, Gavrilov and Gavrilova (2001) suggest that

> [Reliability theory] offers a promising approach for developing a comprehensive theory of aging and longevity that integrates mathematical methods with biological knowledge including cell biology[,...] evolutionary theory [,...] and systems repair principles.

The reliability metaphor holds the possibility of broadening the discussion of tradeoffs, which underlie the evolutionary theory of aging. So far, though, reliability-based models have neglected the problem of repair.

There are three directions in which we believe this metaphor needs to be extended. First, we need to embed repair processes realistically within physiology. It is not simply that repair draws off resources that could be used for other organismal functions. There are internal tradeoffs: ratcheting up repair may entail changes that are more fundamental than simply reallocating resources. Second, we need structural models that take account of the reparability or lack thereof as an evolved feature. Finally, we need to take a global view of reliability, which the engineer's concept of "Total Quality Management" helps to illuminate. Natural selection may not only optimize the allotment of energy to preordained repair mechanisms, but may also determine and modify the nature of repair that is possible.

We describe one new mathematical model, following these principles, in section 4.4, whose analysis may be found in a separate paper (Evans and Steinsaltz, 2006). Most of the discussion is on a more descriptive level, the core of which is four neglected constraints on repair presented in section 4. In brief, these are

- Reparability is a design decision that carries its own costs, even in the absence of active repair.
- Active repair mechanisms may create problems by, for instance, continuing to operate when they are not needed.

- Repair does not recreate the original condition of the organism. There is a gradual loss of structural integrity.
- The impossibility of perfect endogenous repair. There is no unvarying template, to which the organism may compare its current state. Some damage cannot be repaired, therefore, but can only be purged by natural selection.

We hope that the ideas presented here will suggest new approaches to incorporating damage and repair into models, mathematical and otherwise.

2. Conflicting demands

Particularly since the advent of T. Kirkwood's "disposable soma" concept (Kirkwood, 1977), most interest in tradeoffs has focused on the competing segments of organismal housekeeping, as totted up in a nominal "energy balance." In particular, the requirements of present growth and reproduction are weighed against repair and maintenance for the future. Kirkwood and co-authors produced a number of elaborate dynamical systems models of an aging cell (Kowald and Kirkwood, 1994; Kowald and Kirkwood, 1996; Kowald and Kirkwood, 2000; Sozou and Kirkwood, 2001), showing that, under reasonable conditions, repair sufficient to maintain the cell in perpetuity would absorb most of the energy budget. More abstract dynamical models, starting with P. Abrams and D. Ludwig (Abrams and Ludwig, 1995), and elaborated by M. Cichón and others (Cichón, 1997; Mangel, 2001; Cohen and Mangel, 1999; Mangel and Munch, 2005; Chu and Lee, 2006) of the repair–growth–reproduction tradeoff have further elucidated the nature of the evolutionary optimum.

The tradeoffs between reproduction and longevity have attracted particular attention, turning up some striking confirmation in nematodes (Gems and Riddle, 1996), fruitflies (Partridge and Farquhar, 1981), and humans (Gavrilova et al., 1998), but the general picture has turned out to be somewhat murky (Partridge and Harvey, 1985; Glazier, 1999; Gavrilova et al., 2004). Surely much of the difficulty springs from the confounding with population heterogeneity (van Noordwijk and de Jong, 1986; de Jong and van Noordwijk, 1992; Glazier, 1999), but this problem is not merely one of ecological correlations. In seeking optimum levels of repair, growth, and reproduction by age, within a constrained energy budget, the tend to ignore are the inherent structural and *a priori* constraints on repair. And yet, A. Barnes and L. Partridge (2003) have pointed out that the whole corpus of experimental results on life-span in *C. elegans* with oblated gonads is

hard to square with a purely resource-allocation tradeoff. Once we move beyond resource-allocation, we see many other forces shaping life-histories. Just as growth, reproduction, and repair each must be balanced against the others, there are limits on the effectiveness of each one of these due to hard physical constraints, as well as internal tradeoffs. A great deal of theoretical (Partridge et al., 1991; Arendt, 1997; Yearsley et al., 2004) and empirical (Glazier, 1999; Zera and Harshman, 2001) study has exposed the tradeoffs internal to reproduction (clutch size vs. quality, mate choice, and so on) and growth (for instance, rapid vs. robust growth), but repair has been left relatively unexamined. One tradeoff that comes close to reparability is that between mechanical strength — the ability of a tree to survive intermittent storm stresses — and other growth, explicitly modelled in (Cohen and Mangel, 1999). Investment in robust growth is equivalent to investment in the ability to carry out "minimal repair"; that is, to return to the *status quo ante* after a battering.

Consider the struggle against oxidative damage, which looms so large among the putative mechanisms of aging. In Kirkwood's cellular models, repair is represented by the metabolically expensive production of antioxidants, inhibiting the nocive influence of reactive oxygen species (ROS). These models assume no drawback to cranking out unlimited supplies of antioxidants, save the need to balance the energy budget. Recent research has found, though, that ROS play important roles in intracellular signalling pathways, which can be disrupted by overproduction of antioxidants. S. G. Rhee (Rhee, 2006) surveys the evidence for an intricate role of H_2O_2 in intracellular signalling. L. Stryer (Stryer, 1988)[1] points out that elevated levels of the ROS scavenger urate provoke another kind of age-related body failure, namely gout. Repair and maintenance, it seems, are not isolated processes, but may be understood only within the context of physiological interactions, from the level of coarse mechanics down to the biochemistry of individual enzymes and the complex web of tradeoffs that they entail. (It should be mentioned that the precursor to the disposable soma theory, the "commitment theory" of aging (Holliday et al., 1977), is much more in the spirit that we advocate here, focusing as it does on inherent limits to repair, even though it is not explicit about what the tradeoffs are.)

Even more direct is the antagonism between cellular maintenance and immune protection. Inflammation reactions, a first line of immune defense, have been implicated in the etiology of many chronic diseases and disorders, including atherosclerosis (Libby et al., 2002; Desvarieux et al., 2005; Libby, 2002), Alzheimer disease (Monsonego and Weiner,

2003), diabetes (Lazar, 2005), multiple sclerosis (Noseworthy et al., 2000), and cancer (Marx, 2004; Coussens and Werb, 2002), in addition to its direct role in degenerative conditions such as arthritis. (At the same time, there is evidence that the inflammation associated with multiple sclerosis may have, at least in part, a neuroprotective effect (Kerschensteiner et al., 1999; Hohlfeld et al., 2000).) A major source of ROS are neutrophils, which produce them in large quantities for their cytotoxic effects on pathogens. (For another view of the role of ROS in immunity see (Reeves et al., 2002).) Recent research (Miller, III et al., 2005) has found indications that high doses of dietary antioxidants may actually increase mortality rates.

Beyond this tradeoff between durability and repair, there is a host of other fundamental conflicts that limit the evolution of repair mechanisms. Unlike a machine, organisms cannot be shut down and taken apart for repair: basic life support must be maintained without pause. It has been proposed that sleep may be, in part, a repair-promoting partial shutdown, but experiments have contradicted this supposition (Horne, 1985; Landis and Whitney, 1998). This constraint may be expected to be particularly salient in organs whose coordinated uninterrupted function is crucial, in particular the heart and the brain, both of which are known to have only very limited repair capacity. The very sensitive structure of the brain would seem particularly prone to damage from even the most precise repair mechanisms. The evidence that machinery for repairing heart and brain is present in humans, but actively inhibited down to very low levels (Schwab et al., 1993; Gurgo et al., 2002; Orlic et al., 2001), supports the argument that the repair of these organs is constrained not solely by energetics, but by more direct kinds of tradeoffs.(Compston, 1995)

3. Reparable system reliability and Total Quality Management

Reliability theory as a part of engineering has been applied to many of the functional theories, and it provides links to causative theories as well. The link between the wearing out of mechanical devices and the senescent decline of organisms has been treated as the intuitively obvious foil to more sophisticated theories at least since Weismann (Weismann, 1892). Only in recent years has this analogy itself budded into specific theories, making use of the theoretical links between subsystem reliability and global system failure. This approach appears to have sprouted independently in the U.S. and Eastern Europe in the late 1970s — and perhaps multiple times within each of those domains, to

judge by the lack of mutual citation. Early pioneers of reliability models in Eastern Europe were L. Gavrilov and N. Gavrilova (1978; 1978; 1991; 2001), V. Koltover (1981; 1982; 1997), and S. Doubal (1982); their counterparts in the west include R. Rosen (1978), J. Abernethy (1979), and Witten (1985). All presented elementary stochastic models that aimed to reproduce increasing age-specific mortality from nonaging components.[2] Some of the aspirations and accomplishments of this program have been summarized by L. Gavrilov and N. Gavrilova (2004). Another strain of reliability theory strives to connect the failure rates of mixed populations to the failure rates of individuals. Among the most sophisticated applications of these ideas to biological reliability have been (Finkelstein, 2005; Finkelstein and Esaulova, 2006).

Much of the reliability modeling in biodemography is based on traditional engineering models that did not substantially consider reparability. More recently, engineers have focused their attention on the reliability theory of repairable systems. An early textbook on the subject (Ascher and Feingold, 1984) defines a "repairable system" as "a system which, after failing to perform one or more of its functions satisfactorily, can be restored to fully satisfactory performance by any method, other than replacement of the entire system." The problems of reparability are somewhat different from those of maintenance. Maintenance imposes ongoing costs, which reasonably need to be weighed against other pressing needs. Focusing on reparability as an evolvable property may help us to understand why organisms tend toward an end state from which only complete replacement and not repair is possible.

That organisms decay with age seems hardly mystifying in a world of inexorable deterioration. Early theorists of aging, most famously A. Weismann (1882), stumbled over the temptation to include such an obvious fact among the axioms of their theories. The problem, as well stated by G. Williams, is that

> the breakdown of human artifacts is strictly mechanical and is readily cured by mechanical repairs. The system is a static one, since the same material is continuously present, and there is no endogenous change with the passage of time. An organism, on the other hand, is an open system in a state of material flux. Even such structures as bones maintain constant exchanges with the environment. Moreover, an organism produces itself by a morphogenetic process. 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)

There are really two questions here. The first is, given that organisms are constantly repairing themselves, why should they ever wear out? Not wearing out would not require perfection, but merely a stable state, where new damage is balanced by ongoing repairs. The second is, what sort of design principles would develop processes powerful enough to create an organism, but incapable of maintaining it?

The reliability models applied to biodemography typically assume a fixed structure (for example, a fixed set of tradeoffs between repair and reproduction) and then seek to show that the optimal — or evolutionarily accessible — running parameters for the model include senescence. Contrast this to the modern engineering ideal, stated in A. Birolini's textbook (Birolini, 1997)

> Quality and reliability assurance, in the context of *Total Quality Management* (TQM), allows the *optimization* between *performance parameters, reliability,* and *life-cycle cost.* Obviously, quality and reliability, as well as maintainability, availability, and safety have to be *designed* into an item. To do this, a set of specific engineering and management activities must be performed during *all* life-cycle phases of the item considered, from its conception to its use.

TQM (Rao et al., 1996) is consistent with standard Darwinian principles.[3] Operations research has focused considerable technical ingenuity on so-called scheduling problems: given a complex device, with its structure of redundancies, defects, and susceptibilities, and the various costs of maintenance, repair, down time, etc., what is the optimal schedule for repair, maintenance, and outright replacement? Less well studied, because less amenable to formalization, is the design problem itself. How should the device have been designed to maximize the benefits, allowing for the expected repair, maintenance, and replacement costs that result from the most beneficial schedule? To model such processes it appears that we would need only to line up all the potential designs according to their scores, derived from the optimal scheduling problem. A moment's reflection, though, reveals a vast space of potential designs, making this task prohibitive. Like a chess player, we need principles and rules of thumb to direct us toward serviceable, if not precisely optimal, solutions.

Natural selection is not merely in the position of fine-tuning maintenance schedules and energy balances, but it also structures those

schedules and balances. Indeed, natural selection confronts a far more intricate problem than any human engineer, since the very machinery which carries out the maintenance and repair is part of the design, and subject to interactions with the rest of the organism. The rules of thumb become all the more necessary if we are to make useful models of the evolution of reparability.

4. Some principles and metaphors

We wish to address this issue conceptually, by posing a question that has, at some time or another, occurred to most denizens of wealthy industrial societies: why are so many gadgets impossible to repair, but must be tossed on the trash and replaced by new ones when some minor part wears out? It seems terribly wasteful, dumping an essentially functional toaster because the on-off switch has shorted out and can't be removed without cracking the casing. At the same time, it seems unlikely that such devices would be so widespread were they not somehow economically superior to more reparable ones. The toaster has been designed as well as necessary before being launched on its ballistic trajectory to the junkyard.

To analyze the question along the lines of the disposable soma theory would take us only as far as to point out that the toaster will last (let us say) three years without any maintenance work, and that the cost of such work over that time would outweigh the replacement cost. The question, though, is why the toaster is so designed that it runs into an end state from which the only rescue is to dispose of perfectly functional components and replace the entire device. A computer, for comparison, is designed to have many parts — power supply, hard disk, CPU — replaced individually. Still, there is always a smallest level of component meant to be replaced rather than repaired. Thus, when the hard disk malfunctions, only an enthusiast attempts to open it up and tinker with the innards. More typical is to sacrifice the component, sight unseen, and save the larger device.

The essential point here is that the disposable devices are not burning their candles at both ends, forgoing life-extending maintenance in favor of other functions. The chosen lifespan may arise, not from a balance of resources, but rather from a balance of structural and engineering properties, of which resource demands are only a subset, but all of which impose their own tradeoffs. Such properties include reliability, modularity, efficiency, rapidity, and preservation of information. The tradeoffs for each of these properties and for their interactions may stem from the interesting ways that the consequences of design play out over

time. We discuss several such consequences, focusing in particular on reliability.

4.1. **Discontinuities in designs for reparability.** Consider the difference between a disposable camera and a standard one.[4] The body of the disposable camera is flimsy — cardboard, or thin plastic — and the shutter is built to withstand only a small number of motions. Each of these traits saves a small amount on materials cost, but in a continuous way: that is, a small increase in device reliability would presumably be attainable for a comparably small increased expense. In contrast, the differences in other features are qualitative. The standard camera has more or less elaborate latching systems, allowing access to the most frequently manipulated components, the film and the battery. The disposable camera is typically sealed with plastic hooks, so that prying it open will cause permanent structural failure. Further, when the standard camera is opened, more sensitive components — the electronics, the lens, and shutter mechanisms — are shielded from prying hands. Were we to attempt to extend the life of a disposable camera by direct repair, catastrophic failure might be caused by short circuits and breakage of the optics or the shutter. No incremental steps, but only a leap to a different design, could truly render the camera reparable. In key ways, a design that allows for repair is qualitatively different from one that does not.[5]

The toaster provides another example. The switch is welded into place, as is the power cord, and the whole chassis is a single piece of molded plastic. These design choices strengthen the device and make it more durable, at the cost of preventing repairs. A bit more investment in materials might purchase a bit more stability, but would have no effect (or even a negative effect) on reparability.

This kind of nonreparable structure is not uncommon in biology. The cuticle of insects is relatively rigid, and serves as a skeleton for support and for muscle attachment. At the same time, it is made of nondividing cells, so that cuts and scrapes are not repaired, but simply persist for the remainder of the individual's life. The use of diatomaceous earth, a substance with sharp and abrasive surfaces, as an insecticide takes advantage of this vulnerability. The rigidity of insect cuticle has other consequences: because the cuticle cannot expand, it must be molted as the insect grows, and the moltings structure the life histories of many kinds of insects. The physical limits of exoskeletons impose limits as well on the maximum sizes to which insects can grow.

4.2. **The decision to repair.** Ascher and Feingold (1984, p. 67) cite a study of policies for repairing intermittent symptoms, finding that

the maintenance engineer "*always* takes corrective action, and, in our data sample [...] the system would have been much better off if he had never taken corrective action." An analogy to the statistician's Type I/Type II error dilemma illustrates the problem here. When the organism lowers its Type II error rate, reducing the number of genuine defects that persist, it automatically raises its Type I error rate, erroneously repairing components that are functioning properly.

These unnecessary repairs have a cost. Maintenance and repair consume energy that could be applied elsewhere. Repairs interfere with the continuous functioning of a device; the loss of continuity may be important for mechanical devices and is clearly crucial for biological organisms, which cannot be taken offline, fixed, and then powered up again. Even without a loss of continuity, time devoted to repair cannot easily be recaptured. Repairing everything than can possibly be repaired is not necessarily a workable means of ensuring longevity.

Repair processes first recognize damaged or underperforming components as such, and then initiate an appropriate response, whether repair, replacement of the damaged parts, or no response at all. The sensitivity of the recognition and triggering systems must balance the costs of the two types of errors. Research on the evolution of the immune system [dP93] has recognized the fundamental importance of this tradeoff, but it has not generally been acknowledged among the forces that shape senescence.

4.3. **Software reliability and uncertain repairs.** A problem persists even if the decisions about repair are always correct, and the question of software reliability provides a good illustration of the problem. At first blush, it seems odd that software, particularly large software projects, should suffer deterioration over time. Software has no parts that wear out, and is not subject to physical constraints in the way that hardware, bridges, and cells are. Yet, as IBM software engineer Frederick Brooks (Brooks, 1975) recognized in the early days of software engineering, complicated software has a finite lifetime, and exhibits the bathtub-shaped failure-rate curve that is common to complex mechanical devices and to most organisms. After a period of testing and repair, the rate of software failures declines to a minimum, and then reverses and starts to climb.

> The fundamental problem with program maintenance is that fixing a defect has a substantial (20–50 percent) chance of introducing another. So the whole process is two steps forward and one step back.

> Why aren't defects fixed more cleanly? First, even a subtle defect shows itself as a local failure of some kind. In fact, it often has system-wide ramifications, usually nonobvious. Any attempt to fix it with minimum effort will repair the local and obvious, but unless the structure is pure or the documentation very fine, the far-reaching effects of the repair will be overlooked [. . .]
>
> All repairs tend to destroy the structure, to increase the entropy and disorder of the system. Less and less effort is spent on fixing original design flaws; more and more is spent on fixing flaws introduced by earlier fixes. As time passes, the system becomes less and less well-ordered. Sooner or later the fixing ceases to gain any ground. Each forward step is matched by a backward one[. . .] A brand-new, from-the-ground-up redesign is necessary.

Another factor complicates the decisions. Unlike a quintessentially static mountain or rock, organisms are in dynamic equilibrium. The environment changes, as do the other species in an ecological community; what worked great last year may fare poorly this year. Organisms, like software, never have the chance to converge to perfection, because the target—to the degree that it is even well defined—is constantly shifting.

As with software, repairs do not restore an organism to its original state. This imperfection is not entirely negative: the undamaged state of the organism is not necessarily its most robust. More to the point, though, is the accumulation of damage, not despite the repairs, but because of them. This principle is generally recognized by engineers (Ascher and Feingold, 1984). Not only are maintenance, overhauls, and repairs imperfect, even when they do return the system to proper functioning, they increase the randomness in the state. This randomness impairs the precise synchronization of metabolic and signaling processes, and complicates future repairs.

This increase in randomness is part of an answer to Williams's (1957) question. The cell cycle as well as morphogenesis contain numerous checkpoints that buffer the larger process against random fluctuations at lower levels. Some aging might be seen as a consequence of defects that arose from fluctuations in the development of the embryo (Finch and Kirkwood, 2000), just as cracks in girders and beams grow over time from microscopic nucleation sites that are present from the outset

(Petroski, 1992, Chapter 10). The particular patterns of defects demanding attention at any moment is unique, while, in the absence of a global blueprint, repair processes employ only general rules of thumb, albeit complicated ones, to identify and repair damage. As the individual ages, the layers of accumulated damage and partial repair become increasingly idiosyncratic. It is not only the quantity of damage that is key, but also its unpredictability and its increasing connections throughout the body, that lead to senescence.

During its lifetime the organism applies its metabolism against the natural drift toward higher entropy. As the microstate of the organism grows more unpredictable, though, the evolutionarily conditioned responses become less appropriate. Repair mechanisms, like all physiology, have been shaped over millennia by innumerable encounters with the ancestors' fates. The older the organism, the less predictable is its precise state, hence the less closely the state matches the evolutionary memory, and the less likely are its repair responses to suit the exigencies of the moment. At advanced ages, just which the force of selection is less and less effective, the task of the body's repair mechanisms also becomes progressively more difficult.

Some justification for the view that increasing disorder hampers the response to damage may be found in the peculiar fact that some serious disorders of the elderly can be alleviated merely by overriding the body's control of basic processes. A good example is the havoc wreaked by high blood pressure. In a young body, blood pressure is closely matched to the vicissitudes moment by moment. In the elderly, though, this feedback process not uncommonly runs off the rails. Typically, this poor response results from the insensitivity of autonomic blood pressure control to the reduced arterial flexibility. ACE inhibitors or calcium-channel blockers force the blood vessels to relax, a response that, in principle, could be triggered by self-regulation without additional energetic cost or material investment. A possibly related example is the recent discovery that connecting the circulatory systems of young and old mice accelerates wound healing in the old (Conboy et al., 2005).

4.4. **Exogenous repair: Death as a repair mechanism.** Were it not that we have observed life to maintain itself in a continuous line for billions of years, the trick of eternal self-repair would seem to be impossible. Inevitably, damage must arise — such as nucleotide substitutions, excisions, or insertions — that cannot be repaired because the information necessary for a repair is lost, and there is no external template. The solution is to use generational turnover and selection

as a repair process. This is what G. Bell (Bell, 1988, Chapter 10) defined as "exogenous repair", because the instructions for repair reside not within the organism, but in the external world that performs the test. Within any individual line of descent, there is a tendency toward accumulation of damage, but the lines that succumb to this tendency contribute ever less to the total population. Selection combines with random inheritance of damage to produce a virtual repair mechanism, keeping the damage in bounds. The evolutionary optimum may be to have neither the greatest stability nor the most effective endogenous repair mechanisms, if it is possible instead to trade greater damage accumulation for a more complete segregation of damage. Of course, as Bell suggested, sexual recombination is one way to increase the randomness in the next generation, but it is not the only way.

S. Evans and D. Steinsaltz (2006) present a mathematical model of this mechanism, which offers some insight into this tradeoff. The model describes an evolving population of bacteria. During its life, an individual acquires and repairs damage. The net damage accumulation fluctuates randomly, but with an average tendency to increase. When it fissions, the damage may be divided unequally between the daughters. Fissioning rates decline and death rates increase with the extent of accumulated damage. The main results of the analysis are:

- The population growth rate converges to a fixed rate;
- If this asymptotic growth rate is positive, the distribution of the population damage level converges to a fixed distribution;
- The effect of increasing damage segregation in the model (which causes one daughter cell to have more damage and the other one less damage than the parent) is equivalent to increasing the randomness of the damage-accumulation process;
- In general, the optimum level of combined damage randomness and damage segregation (as measured by the growth rate) is not 0, but is some finite nonzero level;
- Consequently, if the damage diffusion rate were suboptimal, a mutant line could obtain a selective advantage by increasing the level of damage segregation. Damage segregation could be a worthwhile investment even if it came at the cost of a slight overall increase in damage accumulation.

Evidence for such a mechanism may perhaps be seen on the level of individual chromosome replication in mice (Armakolas and Klar, 2006), and its significance is made visible in films of misfolded proteins in *E. coli*.[6] The Taddei lab tracked the segregation of damaged proteins through many generations of *E. coli*. The damage accumulates strongly

in certain lines, which become quiescent or die out, while the relatively pristine lines expand in the population. The differences between lines appear to be connected to the discovery that the growth rate of an *E. coli* line falls with the number of old poles it has inherited (Stewart et al., 2005). Those observations are evidence for the segregation of damage preferentially into one of two daughter cells, and evidence that the quantity of damage makes itself felt in the reproductive capacity of a line. The asymmetry between daughter cells in *E. coli* is not a failure of "immortality" (as the popular press (New Scientist, 2005) has accounted it), but is instead one bulwark against the uncontrolled increase in entropy, consequently allowing the preservation of a functioning lineage over unbounded time. L. Johnson and M. Mangel (2005) considered this "aging" in bacterial lines, determining that the costs could be minimal. This is only half of the picture, though. Once we accept that damage accumulation — aging, in a sense — is inevitable, the question becomes not whether some lines are lost, but whether any can be saved. The results of (Evans and Steinsaltz, 2006) show that allowing one daughter to retain its youth at the expense of the other may be a viable strategy.

5. Conclusion

In their book (Finch and Kirkwood, 2000), Finch and Kirkwood argue persuasively for "attending to the noise" when explaining the variations in aging among individuals. It is but a small step to explain the regularities in aging as being, at least in part, a product of random noise. Organisms channel the randomness of the environment into predictable outcomes; reproduction and development — with its canalization toward a sharply defined juvenile state (Waddington, 1942; Stearns, 2002; Siegal and Bergman, 2002; Scharloo, 1991) — may be seen as processes of reducing disorder and returning to a more predictable state.

The particular way that randomness is channelled presumably reflects the evolutionary history of each lineage. Our understanding of the ways that selection might translate into life histories would probably benefit from the application of engineering design principles, but such principles are as yet incompletely formulated even within engineering. It would be instructive to elicit a codification of the unwritten rules of thumb that product engineers apply to find good solutions in their vast and uncharted design spaces. As the bard of civil engineering Henry Petroski has written,

> Design involves assumptions about the future of the object designed, and the more that future resembles the past the more accurate the assumptions are likely to be. But designed objects themselves change the future into which they will age. (Petroski, 1992, p.219)

The cycle of influence between characteristics of objects and their future environment applies at least as strongly to organisms as it does to the products of human engineering.

Unlike consumer products, though, organisms are patchworks of reparable and nonreparable systems. This heterogeneity in reparability may itself be significant in light of the role of asymmetry in dealing with damage. Heterogeneity may be a means of allowing organisms to channel damage into systems that can handle it the best, systems for which not only is repair easy, but for which reparability also does not impose too many tradeoffs. The exploitation of these asymmetries, protecting nonreparable systems by channelling damage preferentially into reparable ones, may be a ploy that puts biology one step ahead of the engineers.

Acknowledgments

We thank Ken Wachter and Ron Lee for helpful discussions. Both authors were supported by NIA grant # K12-AG00981. David Steinsaltz was supported as well by an NSERC Discovery Grant.

References

Abernethy, J. D. 1979. The exponential increase in mortality rate with age attributed to wearing-out of biological components. *Journal of Theoretical Biology*, 80:333–54.

Abrams, P. A. and Ludwig, D. 1995. Optimality theory, Gompertz' law, and the disposable soma theory of senescence. *Evolution*, 49(6):1055–66.

Arendt, J. D. 1997. Adaptive intrinsic growth rates: An integration across taxa. *The Quarterly Review of Biology*, 72(2):149–77.

Armakolas, A. and Klar, A. J. 2006. Cell type regulates selective segregation of mouse chromosome 7 DNA strands in mitosis. *Science*, 311:1146–1149.

Ascher, H. and Feingold, H. 1984. *Repairable Systems Reliability: Modeling, inference, misconceptions, and their causes*. Marcel Dekker, Inc.

Barnes, A. I. and Partridge, L. 2003. Costing reproduction. *Animal Behaviour*, 66:199–204.

Bell, G. 1988. *Sex and Death in Protozoa : The history of an obsession*. Cambridge University Press, Cambridge.

Birolini, A. 1997. *Quality and Reliability of Technical Systems*. Springer-Verlag, Berlin, second edition.

Brooks, F. 1975. *The Mythical Man-month : Essays on software engineering*. Addison-Wesley, Reading, Mass.

Chu, C. Y. and Lee, R. D. 2006. The co-evolution of intergenerational transfers and longevity: an optimal life history approach. *Theoretical Population Biology*, 69(2):193–2001.

Cichón, M. 1997. Evolution of longevity through optimal resource allocation. *Proceedings of the Royal Society of London, Series B: Biological Sciences*, 264:1383–8.

Cohen, D. and Mangel, M. 1999. Investing for survival of rare severe stresses in heterogeneous environments. *Evolutionary Ecology Research*, 1:987–1002.

Compston, A. 1995. Brain repair. *Journal of Internal Medicine*, 237(2):127–34.

Conboy, I. M., Conboy, M. J., Wagers, A. J., Girma, E. R., Weissman, I. L., and Rando, T. 2005. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature*, 433:760–4.

Coussens, L. M. and Werb, Z. 2002. Inflammation and cancer. *Nature*, 420:861–7.

Darwin, C. 1872. *The Origin of Species by means of Natural Selection; or, the Preservation of Favoured Races in the Struggle for Life*. John

Murray, London, 6th edition.

de Jong, G. and van Noordwijk, A. J. 1992. Acquisition and allocation of resources: Genetic (co)variances, selection, and life histories. *The American Naturalist*, 139(4):749–70.

Desvarieux, M., Demmer, R., Rundek, T., Boden-Albala, B., Jacobs, D. R., Sacco, R. L., and Papapanou, P. N. 2005. Periodontal microbiota and carotid intima-media thickness: The oral infections and vascular disease epidemiology study (invest). *Circulation*, 111(5):576–82.

Doubal, S. 1982. Theory of reliability, biological systems and aging. *Mechanisms of Ageing and Development*, 18:339–53.

Evans, S. N. and Steinsaltz, D. 2006. The damage segregation in descent model. Preprint: arXiv q-bio.PE/0608008.

Finch, C. E. and Kirkwood, T. B. L. 2000. *Chance, Development, and Aging*. Oxford University Press, New York.

Finkelstein, M. 2005. On some reliability approaches to human aging. *International Journal of Reliability, Quality and Safety Engineering*, 12(4):337–46.

Finkelstein, M. and Esaulova, V. 2006. Asymptotic behavior of a general class of mixture failure rates. *Advances in Applied Prabability*, 38(1):244–62.

Gavrilov, L. A. 1978. A mathematical model of the aging of animals. *Doklady Akademii Nauk SSSR*, 238:490–2.

Gavrilov, L. A. and Gavrilova, N. S. 1991. *The Biology of Lifespan: A Quantitative Approach*. Harwood Academic Publishers, Chur, Switzerland.

Gavrilov, L. A. and Gavrilova, N. S. 2001. The reliability theory of aging and longevity. *Journal of Theoretical Biology*, 213:527–45.

Gavrilov, L. A. and Gavrilova, N. S. 2004. The reliability-engineering approach to the problem of biological aging. *Annals of the New York Academy of Sciences*, 1019:509–12.

Gavrilov, L. A. and Gavrilova, N. S. 2006. Models of systems failure in aging. In Conn, P. M., editor, *Handbook of models for human aging*, chapter 5, pages 45–68. Elsevier.

Gavrilov, L. A., Gavrilova, N. S., and Yaguzhinsky, L. S. 1978. The main regularities of animal aging and death viewed in terms of reliability theory. *Zhurnal Obshchei Biologii*, 39(5).

Gavrilova, N. S., Gavrilov, L. A., Evdokushkina, G. N., Semyonova, V. G., Gavrilova, A. L., Evdokushkina, N. N., Kushnareva, Y. E., Kroutko, V. N., and Andreyev, A. Y. 1998. Evolution, mutations, and human longevity: European royal and noble families. *Human Biology*, 70(4):799–804.

Gavrilova, N. S., Gavrilov, L. A., Semyonova, V. G., and Evdokushkina, G. N. 2004. Does exceptional human longevity come with a high cost of infertility?: Testing the evolutionary theories of aging. *Proceedings of the New York Academy of Sciences*, 1019:513–7.

Gems, D. and Riddle, D. L. 1996. Longevity in *Caenorhabditis elegans* reduced by mating but not gamete production. *Nature*, 379:723–5.

Glazier, D. S. 1999. Trade-offs between reproductive and somatic (storage) investments in animals: a comparative test of the Van Noordwijk and De Jong model. *Evolutionary Ecology*, 13:539–55.

Gurgo, R. D., Bedi, K. S., and Nurcombe, V. 2002. Current concepts in central nervous system regeneration. *Journal of Clinical Neuroscience*, 9(6):613–7.

Harper, C. A. 2000. *Modern Plastics Handbook*. McGraw-Hill Professional.

Hohlfeld, R., Kerschensteiner, M., Stadelmann, C., Lassmann, H., and Wekerle, H. 2000. The neuroprotective effect of inflammation: implications for the therapy of multiple sclerosis. *Journal of Neuroimmunology*, 107(2):161–6.

Holliday, R., Huschtscha, L. I., Tarrant, G. M., and Kirkwood, T. B. L. 1977. Testing the commitment theory of cellular aging. *Science*, 198(4315):366–72.

Horne, J. A. 1985. Sleep function, with particular reference to sleep deprivation. *Annals of Clinical Research*, 17(5):199–208.

Johnson, L. R. and Mangel, M. 2005. Implications of aging in bacteria. Preprint available at `http://arxiv.org/abs/q-bio.PE/0510001`.

Kerschensteiner, M., Gallmeier, E., Behrens, L., Leal, V. V., Misgeld, T., Klinkert, W. E., Kolbeck, R., Hoppe, E., Oropeza-Wekerle, R.-L., Bartke, I., Stadelmann, C., Lassmann, H., Wekerle, H., and Hohlfeld, R. 1999. Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor in vitro and in inflammatory brain lesions: A neuroprotective role of inflammation? *Journal of Experimental Medicine*, 189(5):865–70.

Kirkwood, T. B. L. 1977. Evolution of ageing. *Nature*, 270(5635):301–4.

Koltover, V. K. 1981. Reliability of enzymatic protection of cells from superoxide radicals and aging. *Doklady Akademii Nauk SSSR*, 156:3–5.

Koltover, V. K. 1982. Reliability of enzyme systems and molecular mechanisms of ageing. *Biophysics*, 27:635–9.

Koltover, V. K. 1997. Reliability concept as a trend in biophysics of aging. *Journal of Theoretical Biology*, 184:157–63.

Kowald, A. and Kirkwood, T. 2000. Accumulation of defective mitochondria through delayed degradation of damaged organelles and its

possible role in the ageing of post-mitotic ad dividing cells. *Journal of Theoretical Biology*, 202:145–60.

Kowald, A. and Kirkwood, T. B. 1994. Towards a network theory of aging: A model combining the free radical theory and the protein error theory. *Journal of Theoretical Biology*.

Kowald, A. and Kirkwood, T. B. 1996. A network theory of aging: The interactions of defective mitochondria, aberrant proteins, free radicals and scavengers in the ageing process. *Mutation research*.

Landis, C. A. and Whitney, J. D. 1998. Effects of 72 hours sleep deprivation on wound healing in the rat. *Research in Nursing & Health*, 20(3):259–67.

Lazar, M. A. 2005. How obesity causes diabetes: Not a tall tale. *Science*, 307:373–5.

Libby, P. 2002. Inflammation in atherosclerosis. *Nature*, 420(6917):868–74.

Libby, P., Ridker, P. M., and Maseri, A. 2002. Inflammation and atherosclerosis. *Circulation*, 105(9):1135–43.

Madu, C. 2001. *Handbook of Environmentally Conscious Manufacturing*. Springer-Verlag.

Mangel, M. 2001. Complex adaptive systems, aging and longevity. *Journal of Theoretical Biology*, 213:559–71.

Mangel, M. and Munch, S. B. 2005. A life-history perspective on short- and long-term consequences of compensatory growth. *The American Naturalist*, 166(6):E155–76.

Marx, J. 2004. Inflammation and cancer: The link grows stronger. *Science*, 306:966–8.

Miller, III, E. R., Pastor-Barriuso, R., Dalal, D., Riemersma, R. A., Appel, L. J., and Guallar, E. 2005. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Annals of Internal Medicine*, 142(1):37–46.

Monsonego, A. and Weiner, H. L. 2003. Immunotherapeutic approaches to alzheimer's disease. *Science*, 302:834–8.

Nesse, R. M. and Williams, G. C. 1996. *Why We Get Sick*. Vintage Books, New York.

New Scientist 2005. Bacteria death reduces human hopes of immortality. *New Scientist*, 2485:19.

Noseworthy, J. H., Lucchinetti, C., Rodriguez, M., and Weinshenker, B. G. 2000. Multiple sclerosis. *New England Journal of Medicine*, 343(13):938–52.

Orlic, D., Kajstura, J., Chimenti, S., Limana, F., Jakoniuk, I., Quaini, F., Nadal-Ginard, B., Bodine, D. M., Leri, A., and Anversa, P. 2001. Mobilized bone marrow cells repair the infarcted heart, improving

function and survival. *PNAS*, 98(18):10344–9.

Partridge, L. and Farquhar, M. 1981. Sexual activity reduces lifespan of male fruitflies. *Nature*, 294:580–2.

Partridge, L. and Harvey, P. H. 1985. Costs of reproduction. *Nature*, 316:20.

Partridge, L., Sibly, R., Beverton, R. J. H., and Hill, W. G. 1991. Constraints in the evolution of life histories [and discussion]. *Philosophical transactions of the Royal Society of London, Series B: Biological Sciences*, 332(1262):3–13.

Petroski, H. 1992. *To Engineer is Human: The role of failure in successful design*. Vintage Books, New York.

Rao, A., Carr, L. P., Dambolena, I., Kopp, R. J., Martin, J., Rafii, F., and Schlesinger, P. F. 1996. *Total Quality Management: A Cross Functional Perspective*. John Wiley & Sons.

Reeves, E. P., Lu, H., Jacobs, H. L., Messina, C. G. M., Bolsover, S., Gabellak, G., Potma, E. O., Warley, A., Roes, J., and Segal, A. W. 2002. Killing activity of neutrophils is mediated through activation of proteases by K^+ flux. *Nature*, 416:291–7.

Rhee, S. G. 2006. H_2O_2, a necessary evil for cell signaling. *Science*, 312:1882–3.

Rosen, R. 1978. Feedforwards and global system failure: A general mechanism for senescence. *Journal of Theoretical Biology*, 74:579–90.

Scharloo, W. 1991. Canalization: Genetic and developmental aspects. *Annual Review of Ecology and Systematics*, 22:65–93.

Schwab, M. E., Kapfhammer, J. P., and Bandtlow, C. E. 1993. Inhibitors of neurite growth. *Annual Review of Neuroscience*, 16:565–95.

Siegal, M. L. and Bergman, A. 2002. Waddington's canalization revisited: Developmental stability and evolution. *PNAS*, 99(16):10528–32.

Sozou, P. D. and Kirkwood, T. B. L. 2001. A stochastic model of cell replicative senescence based on telomere shortening, oxidative stress, and somatic mutations in nuclear and mitochondrial DNA. *Journal of Theoretical Biology*, 213:573–86.

Stearns, S. C. 2002. Progress on canalization. *PNAS*, 99(16):10229–30.

Steinsaltz, D. and Evans, S. N. 2004. Markov mortality models: Implications of quasistationarity and varying initial conditions. *Theoretical Population Biology*, 65(4):319–37.

Stewart, E., Madden, R., Paul, G., and Taddei, F. 2005. Aging and death in an organism that reproduces by morphologically symmetric division. *PLOS (Biology)*, 3(2).

Stryer, L. 1988. *Biochemistry*. W. H. Freeman, New York, 3. edition.

van Noordwijk, A. J. and de Jong, G. 1986. Acquisition and allocation of resources: Their influence on variation in life history tactics. *The American Naturalist*, 128(1):137–42.

Waddington, C. H. 1942. Canalization of development and the inheritance of acquired characters. *Nature*, 150:563–5.

Weismann, A. 1882. *Über die Dauer des Lebens*. G. Fischer, Jena.

Weismann, A. 1892. Ueber die Dauer des Lebens. In *Aufsätze über Vererbung und verwandte biologische Fragen*, chapter 1, pages 1–72. Verlag von Gustav Fischer, Jena.

Williams, G. C. 1957. Pleiotropy, natural selection, and the evolution of senescence. *Evolution*, 11:398–411.

Witten, M. 1985. A return to time, cells, systems, and aging: III. Gompertzian models of biological aging and some possible roles for critical elements. *Mechanisms of Ageing and Development*, 32:141–77.

Yearsley, J. M., Kyriazakis, I., and Gordon, I. J. 2004. Delayed costs of growth and compensatory growth rates. *Functional Ecology*, 18:563–70.

Zera, A. J. and Harshman, L. G. 2001. The physiology of life history trade-offs in animals. *Annual Review of Ecology and Systematics*, 32:95–126.

Notes

[1]Quoted in (Nesse and Williams, 1996).

[2]It must be noted that the well-known attempts to derive the Gompertz mortality pattern in this tradition, including key claims of (Gavrilov and Gavrilova, 2001; Witten, 1985; Abernethy, 1979), for all that they were suggestive and intriguing, were nullified by mathematical errors. The errors of (Witten, 1985) were explained in (Gavrilov and Gavrilova, 1991; Koltover, 1997), while the errors in (Gavrilov and Gavrilova, 2001) — repeated in (Gavrilov and Gavrilova, 2006) — were explained in (Steinsaltz and Evans, 2004). The problem with (Abernethy, 1979) is not so much mathematical error, as the disconnect between the very modest result proved in the mathematical section and the quite broad result claimed in the expository section. Other results, particularly those concerning the compensation law and mortality plateaus in (Gavrilov and Gavrilova, 2006), may have merit.

[3]"Man can act only on external and visible characters: Nature, if I may be allowed to personify the natural preservation or survival of the fittest, cares nothing for appearances, except in so far as they are useful to any being. She can act on every internal organ, on every shade of constitutional difference, on the whole machinery of life." (Darwin, 1872, Chapter 4)

[4]Some information about the electrical systems of disposable cameras may be found in a presentation at `http://hibp.ecse.rpi.edu/~connor/education/IEE/lectures/Lecture\_9_flash_camera.pdf`. *Pace* the remarks here, there seems to be a considerable tribe of enthusiasts interested in extending the life spans of disposable cameras.

[5]One may doubt that technologically intricate components are disposed of after such a brief lifetime, but that seems indeed to be the case. When single-use cameras were introduced in the late 1980s, the entire mechanism was indeed trash once the film had been removed by the photo processor. Interestingly, the Kodak company did painstakingly redesign its cameras for reuse of components. This is not for the sake of profitably reusing the camera bodies or whole components — the bodies are ground up and recycled (Harper, 2000, p. 12.55) — but to assuage environmentalists' concerns about the impact of camera disposal. (Madu, 2001, pp. 17–8)

[6]Unpublished work of F. Taddei *et al.*, presented in October 2004 at a workshop at the Max Planck Institute for Demography in Rostock.

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