



Long-Run Economic Perspectives of an Ageing Society

The Mechanics of Ageing and Death: A Primer for Economists — Part III: Metabolism and Longevity

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The Mechanics of Aging and Death

- A Primer for Economists¹

Part III: Metabolism and Longevity

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Abstract

This study reviews non-evolutionary biological theories of aging. The rate of living theory, being the oldest, proposes that there is a fixed amount of “living” available to biological organisms. We discuss evidence from the literature on allometric scaling, which might provide some support for the premise that there could be a biomechanical explanation for limited maximum life-span of individual species. The last two theories provide insights into biological mechanisms generating aging, and limiting longevity. The free radical theory suggests that oxidative stress leads to cellular damage and thereby organism senescence; the telomere theory considers that cell division and oxidative stress lead to cell senescence and thereby aging of the organism. These theories may be helpful in shedding light on why longevity varies across societies. Some formal statements of the theories, and empirical evidence to their importance to human longevity are presented.

1 Introduction

Below we discuss theories that relate metabolism to longevity. Metabolic theories of aging provides some insights into why maximum life spans is limited for individual species and may provide important clues as to why longevity could differ across societies characterized by different body size. At the same time, the theories discussed below have little to say about the *way* humans age. That is, they do not inform us about why, for instance, mortality rates follows a U-shaped trajectory over the course of life (see Strulik, 2010).

Generally speaking metabolic theories of aging can be said to highlight the influence from environmental factors during life in explaining longevity. A sensible initial question to ask, then, is whether this avenue of influence is likely to be “important”. Indeed, one could imagine genes, or influences while *in utero*, to be (much) more important determinants of longevity.

Hence, we begin by briefly touching upon work aimed at quantifying the importance of genes and environmental influence while being in the mother’s womb for life expectancy. That is, we look at the importance of “prebirth” determinants of longevity. Then we turn to a discussion of “post-birth” determinants of life expectancy; the object of main interest in the present context.

2 Nature vs. Nurture in accounting for Longevity

There are two separate issues worth considering before we turn to the possible link between metabolism during life and longevity. The first issue is the extent to which longevity is determined genetically. If longevity is solely a genetic matter (subject to random events) then an evolutionary approach is called for, rather than an approach which emphasizes the impact from the environment. The second issue is whether the important environmental line of influence is that while *in utero*. If it is, then this too would suggest a change in focus away from postbirth determinants of longevity.

2.1 Prebirth determinants of longevity I: Genes

During the last roughly 150 years human life expectancy has risen tremendously. If measured in terms of the evolution of the country-year pair of highest life expectancy worldwide, human life expectancy has risen by about 1/4 of a year, per year, on average (Oeppen and Vaupel, 2002). This comes to an increase of more than 30 years over the period in question. 150 years is, in evolutionary terms, all but an eye blink. Hence, the “growth record” in life expectancy might in itself suggest that other forces, beyond evolution, hold considerable explanatory power as drivers of human life expectancy.

Naturally, genetic traits may nevertheless be strong determinants of variation in life expectancy *within* populations and between countries. One way to examine the first issue is to examine the longevity of “identical twins”

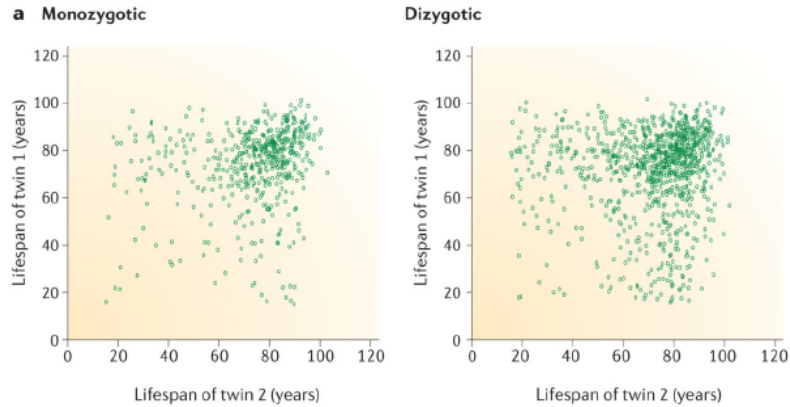


Figure 1: Source: Christensen et al., 2006.

(or, “Monozygotic twins”). If life span is genetically determined one would expect to see a positive correlation between age at death within twin pairs. Figure 1 shows the correlation between identical twins, and twins originating from two separate eggs (“Dizygotic twins”). There is a visually obvious positive correlation. At the same time there is a lot of variation, or noise, to be seen in the figure suggesting that life span is also affected by non-genetic factors, such as life style and luck. Indeed, Christensen et al. (2006) argue that genes account for around $1/4$ of the variation in within country populations. Hence, the genetic make-up of individuals does seem to matter, and by extension, there is ample room for genes to influence cross-country differences in life expectancy (see also Galor and Moav, 2007).

2.2 Prebirth determinants of longevity II: Environmental influences *in utero*

Another possibility is that life expectancy is highly influenced by external factors while *in utero*. This idea, sometimes referred to as “the fetal origins hypothesis”, has had some influence on research in economics. For instance, Van den Berg et al. (2006) document that children born during business cycles booms, as compared to the immediate adjacent bust, live longer. In a similar vein, Doblhammer and Vaupel (2001) document that the birth month seems to matter for longevity; children born (in the Northern Hemisphere) during October-December live longer than children born between April and June. Intriguingly, the results are shifted about 6 month when countries in the Southern Hemisphere are considered, suggesting an impact from the changing seasons. The authors document that these seasonal effects tend to disappear over time, however, when looking at recent cohorts.

In economics the typical bio-marker for early-life influence is the birth weight of children; several studies have used this variable to examine adult outcomes while referring to the fetal origins hypothesis as theoretical foundation.¹ The basic idea which is exploited in economics is that a low birth weight signals initial health, as determined by factors that influenced the foetus.

But a strong causal link between body size at birth and the potential for

¹See Black et al. (2007) and the references cited therein.

successful aging can be questioned. In an interesting paper Christensen et al. (1995) examine the life span consequences of being born as a twin rather than being “single born”. If birth weight matters to longevity *per se* twins should feature higher mortality than single born offspring (later in life), as they on average are considerably smaller at birth; on average twins are about 900 g lighter. Figure 2 shows the mortality patterns for twins and the general population in Denmark. Aside from mortality early in life, which is rather noisy due to relatively few deaths, it seems clear that there is not any particular difference in death rates to be seen. Hence, one may wonder whether birth weight really matters as such. Perhaps a low birth weight is correlated with other factors that influence longevity in a causal manner?²

These concerns notwithstanding, most medical researchers seem to accept the notion that early life influences do have an effect on mortality patterns later in life. The exact magnitude may be hard to assess precisely, but in their survey Vaupel et al. (1998) suggest that about 1/4 of the variation in longevity (within populations) may be accounted for by early life influences.

²Black et al. (2007) exploit variation in birth weight *between* twins in their study. Nevertheless, given the underlying theory for correlation between birth weight and outcomes later in life, it remains difficult to square a causal interpretation of birth weight with the lack of a difference in longevity between single born children and twins, as documented by Christensen et al. (1995).

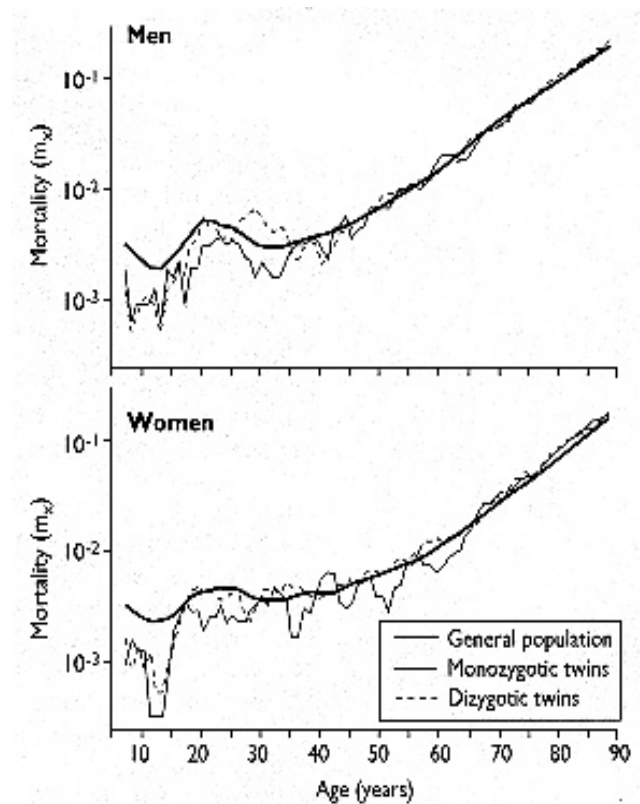


Figure 2: Mortality (three year moving average) among monozygotic twins, dizygotic twins, and the general population in Denmark, age 6-89 years. Mortality was calculated for cohorts born 1870-1900. Source: Christensen et al. (1995).

2.3 Summing up: The quantitative significance of prebirth factors

In summary of the discussion above: the best available evidence suggest that about 1/2 of the variation in longevity within populations is due to genetic factors, and early life influences *in utero*; roughly divided equally between the two. This leaves another 50% of the variation which then must be due to environmental influences during life.

3 Post-Birth Determinants of Longevity

3.1 The rate of living theory

The rate of living theory can be traced back to the writings of Aristotle, who observed:³ “*A lesser flame is consumed by a greater one, for the nutriment, to wit the smoke, which the former takes a long period to expend is used up by the big flame quickly.*” Hence, the basic notion is that there is a certain “amount of living” available, which can be used up quickly or slowly. This biological idea has influenced economic theory. In particular, the theory of optimal capital utilization asserts that a more intensive use of machinery leads to higher user cost of capital through accelerated capital depreciation and thus lowered capital longevity. This is a clear application of the rate of living theory, albeit to a non-biological setting.⁴

There is biological evidence that could be taken to suggest that there exists something like a “fixed amount of living”. We begin with the observation (which stems from the literature on allometric scaling)⁵ that maximum life

³As quoted in Speakman (2005).

⁴The classical reference is Taubman and Wilkinson (1970). The basic machinery has since then found use in business cycle research (e.g., Greenwood, Hercowitz and Huffman, 1988; Burnside and Eichenbaum, 1996) as well as in growth theory (e.g., Dalgaard, 2003; Dalgaard and Hansen, 2005; Chatterjee, 2005).

⁵“Allometric scaling” is a technique used in biology to study how selected biological variables of an organism correlate with the *size* of the organism. The size of the organism is usually summarized by its body mass. See Brown et al. (2004) for a survey.

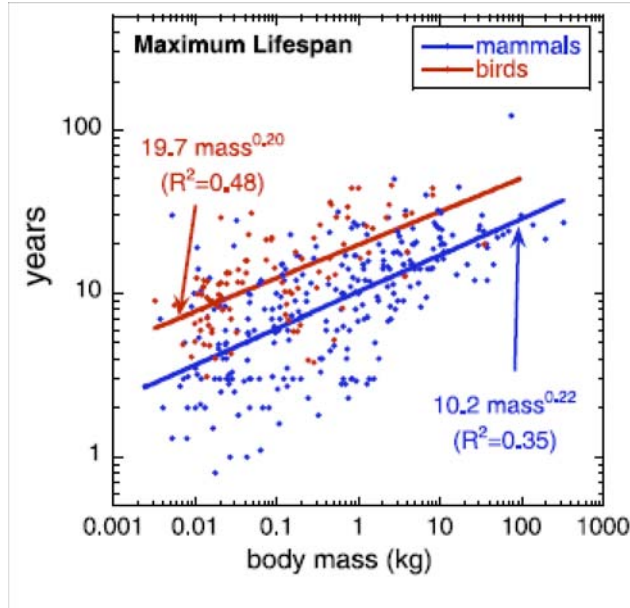


Figure 3: Source: Hulbert et al. (2007).

span⁶ scales approximately with body mass, m , in accordance with

$$T^{\max} = T_0 m^{1/4}, \quad T_0 > 0. \quad (1)$$

That is, comparing different species, life span rises with body mass in accordance with the above log-linear specification. Figure 3 illustrates this regularity, which holds for mammals as well as birds. The basic message is that members of larger species tend to live longer.⁷ Next, we need to invoke another scaling relationship. Namely that between *the heart rate*, h , of a

⁶ “Maximum life span” is an empirical concept, capturing the maximum amount of time a member of an animal group has been observed to survive between birth and death. In many cases data derives from observations of animals that lived out their life in captivity.

⁷In economics its long since been used that even within species (e.g., humans) there appears to be a positive correlation between longevity and body size (see e.g., Fogel, 1994).

mammal (at rest) and its body mass. Empirically, the heart rate declines with the size of the animal in question: $h = h_0 m^{-1/4}$ (e.g., West and Brown, 2005). As a result, *total* heart beats per life time is

$$T^{\max} \cdot h \approx T_0 m^{1/4} h_0 m^{-1/4} = T_0 h_0,$$

and thus size independent. A shrew, a human, and an elephant has about the same number of heart beats per life time. Taken literally, about 955.787.040. Superficially, this is in concordance with the notion of a “given amount of living”, which can be expended fast or slowly, consistent with the rate of living theory.

Extreme care should be taken in not over interpreting this finding. For one thing the relation is approximate. Second, what the scale-invariance of total hearth beats per life time should be taken to suggest is not that life of an *individual* is like a coupon ticket. Instead it should be understood to imply that there seems to be biomechanical constraints that limits longevity of all (mammalian) species. That is, for a species with typical body mass of, say, 80 kg the maximum life span appears to be limited to be counted in 100s of year; but *not* in 1000s of years! In this sense the evidence supports the notion that (for any given species, characterized by a body size) there exists an upper (ultimately, “fixed”) boundary to life span.

But what sort of biomechanical constraint, which must characterize most

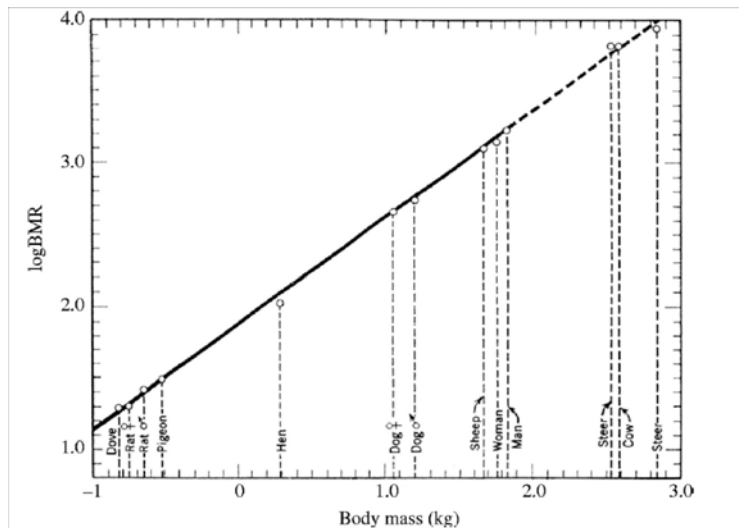


Figure 4: Source: West and Brown (2005).

animals on the planet, can serve to limit life spans in a unifying way? This question takes us to metabolism. To understand why, one needs to introduce a third regularity, known as Kleiber’s (1932) law:

$$B = B_0 m^b, \quad B_0 > 0, b = 3/4, \quad (2)$$

where B is the basal metabolic rate (BMR) and B_0 is a species-dependent constant.⁸ Thus, drawn on log-log paper the energy-body mass relationship is linear with slope of $3/4$, see Figure 4.

A slope of $3/4$ has been verified by Brody (1945) for almost all ter-

⁸“Metabolism” refers to the biochemical processes by which nutrients are transformed into energy, which allows the organs of the body (i.e. ultimately the cells of the body) to function. The “basal metabolic rate” is defined as the amount of energy expended while at rest

restrial animals yielding the famous “mouse-to-elephant curve”. Recently biologists and physicists have managed to provide a theoretical explanation for Kleiber’s law. A living organism needs to feed its cells. For that purpose energy and material is transported through hierarchically branching networks like blood vessels in mammals. The network in use, however, is not of arbitrary structure. Given that organisms have evolved through natural selection, it must be one that minimizes energy used for transport, *i.e.* one that minimizes hydrodynamic resistance. West et al. (1997) have shown that organisms, viewed as energy transporting networks that minimize energy dissipation, fulfill Kleiber’s law. The interesting observation, from the point of view of the above discussion, is that the network model provides a solid foundation for a central implication of Kleiber’s law: *Energy needs per unit of body mass is declining in body size* ($B/m = B_0 m^{-1/4}$). Another way to put this fact is that each cell apparently *needs to work less hard* in larger animals, as larger networks are more efficient. Perhaps this could have bearing on the fact that a longer life span is possible in larger animals, as greater body size might then translate into a slower rate of *cell* aging? The case in favor of this assertion would seem to gain strength if the process of metabolism itself has certain life shortening implications. “The free radical theory” provides just such a causal link.

3.2 Free radical theory

The free radical theory of aging is usually attributed to Gerschman et al (1954) and Harman (1956). The basic idea is that aging is an a consequence of toxic *by-products* of metabolism; the generation of so-called radical oxygen species (ROS) which causes cellular damage. In reduced form, the prediction is that a higher rate of metabolism (per cell) leads to a faster accumulation of damage and thus aging.⁹

There is evidence that the main thrust of the theory might be important in the human species. For one thing, it is by now fairly well established that restricting energy consumption (without causing malnutrition) slows aging (e.g., Ramsey et al., 2000). Moreover, the free radical theory may also explain the declining death rates among the elderly (See Strulik, 2010). In a recent study Ruggerio et. al (2008) examines a sample of Canadians, who were followed over a 40 year period. The study reveals two important facts: (i) BMR declines with age, and at an accelerated rate at older ages, (ii) BMR is a predictor of time of death; higher BMR leads to an earlier time of death. Hence, the study corroborates the link between the rate of metabolism and aging and, moreover, provides some evidence that the theory may be able to account for the (off hand puzzling) declining death rates among the elderly.

In order to see how the free radical theory might produce a link between longevity and body size, with metabolism as the mediator, consider

⁹See Speakman (2005) for a detailed description of the biochemical processes at work.

the following *simplified* version of “damage equation”, discussed in Strulik (2010):

$$\dot{D}(t) = \mu D(t), \quad D(0) \text{ given.} \quad (3)$$

Death is assumed to occur when this damage index reaches a critical level: \bar{D} . The rate at which damage is accumulated is μ . Now, suppose this rate is *determined* by the rate at which the average cell is damaged, which, according to the free radical theory depends on metabolism per cell.¹⁰ Then we have

$$\mu = \mu_0 \frac{B}{N},$$

where μ_0 is an appropriately chosen (mass independent) constant, B is basal metabolism of the entire organism, and N the total number of cells in the body. Since the total mass of an organism is the weight of each cell multiplied by the number of cells, we may write

$$\mu_0 \frac{B}{N} \propto \mu_0 \frac{B}{m} \propto m^{-1/4},$$

¹⁰Going one step back to the underlying premises: (i) We are assuming that damage to each cell grows exponentially over time at the rate μ , (ii) that total damage to the organism as a whole is damage to each cell, multiplied by total cells in the body. As long as body mass is constant, and thus the organism has a constant amount of cells, this leads to equation (3). Hence, the current considerations are likely more relevant for an intermediate age range, thus excluding children (growing body size), and the very old (declining body size) from consideration; we also abstract from individuals that are obese. Moreover, if cellular damage is the cause of the empirically observed growing death probability during life, then μ can also be thought of as the growth rate in the death rate in a Gompertz equation. Note that the Gompertz equation is a fair description of the data precisely in the “intermediate” age bracket. For an introduction to the Gompertz equation, see Strulik (2010).

where the last step employs Kleiber’s law (equation (2)). Finally, maximum life span, T^{\max} , can be seen as the time it takes to reach \bar{D} , starting at $D(0)$.¹¹ Using equation (3) and the equation above:

$$T^{\max} = \log \left[\frac{\bar{D}}{D(0)} \right] \mu^{-1} \propto T_0 m^{1/4}. \quad (4)$$

Hence, by combining the basic free radical theory, the notion of increasing biological damage and Kleiber’s law, one is able to reproduce the biological correlation between body mass and (maximum) life span, see equation (1).

In order to turn the above into a dynamic model of longevity, it is necessary to consider the dynamics of body growth. A general model of body growth is developed by West et al. (2001); this theory has recently been introduced into the economics literature by Dalgaard and Strulik (2010). The point of departure for the West et al model, is the following energy conservation equation

$$E(t) = \kappa N(t) + \psi \dot{N}(t), \quad (5)$$

where $E(t)$ is energy intake during a period, κN are energy needs for maintenance of cells (N) and ψ captures the energy costs of cell creation. Since each cell has a certain mass, ω say, we can convert the right hand side into

¹¹We are necessarily dealing with maximum life span as we are recording the time it takes until the organism *must* collapse due to accumulated damage. In practise, of course, any given mammal may die before then, due to disease, predation or bad luck.

body mass:

$$E(t) = \frac{\kappa}{\omega}m(t) + \frac{\psi}{\omega}\dot{m}(t) \Leftrightarrow \dot{m}(t) = \frac{\omega}{\psi}E(t) - \frac{\kappa}{\psi}m(t).$$

In West et al. energy intake is assumed to equal energy requirements as given by Kleiber’s law; Dalgaard and Strulik determine it through optimization. In the former case, however, the final dynamic equation governing body size becomes (using equation (2) in the equation above):

$$\dot{m}(t) = am(t)^{3/4} - bm(t), \quad (6)$$

with a and b being appropriately defined parameters. Biologically, a and b are species specific, and thus maps into species specific asymptotic body sizes.¹² Moreover, by equation (4), they will map into species specific longevity.

In human populations, it may be reasonable to assume that asymptotic body size is somewhat amendable to an optimally (or suboptimally) chosen trajectory for energy intake, and thus subject to optimization. In addition, however, it will be meaningful to consider scenarios where T^{\max} is affected

¹²A physical reason why the parameters should be species specific is the following. If we consider equation (5) it is clear that all energy “input” finds its use on the right hand side, which does not explicitly allow for *loss*. Heat loss, in other words is implicit in the parameters κ, ψ ; for organisms with greater heat loss the energy costs of, for instance, cell maintenance (κ) is simply thought to be larger. Since heat loss in practise depends on body *shape* (short limbs, for instance, limits heat loss) it is clear that κ would vary across different species, distinguishable by their body shape. It then follows that a and b should vary across species as well.

by technological forces (broadly defined) in addition to biological forces.

3.3 Telomere theory

The idea of Harman (1956), discussed above, that metabolism produces oxygen free radicals which generates cell damage, suggests that something like a biological clock may exist: the process of converting nutrient intake into muscular work effort inevitably leads to aging. The later work of Hayflick (1965) can also be viewed as pointing to the existence of a biological clock, but via a seemingly different mechanism; Hayflick documented that human cells cease to replicate after a certain amount of cell doubling. In other words, there seems to be an upper limit to the reproductive life span of cells: the so-called “Hayflick limit”.

A likely proximate determinant of the Hayflick limit is the gradual reduction in “telomere length”. Telomeres are protein caps that are located at the end of chromosomes. The role of these end-caps is to protect the integrity of the chromosomes during cell division. However, as cells divide the length of the telomeres decline. Eventually their length reaches a critical size, after which cell division ceases; the Hayflick limit is reached (see Olovnikov, 1996).

A layman’s way to think of the role of telomeres is the following analogy. Think about a DNA sequence as a written text on a piece of paper; DNA replication is then conceived as a process whereby the text is photocopied,

and then the copy is copied and so forth. The telomeres are then analogous to the white spaces in between individual letters and words. Now, every time the text is copied the letters of the text will tend to become increasingly blurred; the distance between words and letters will seem shorter. Eventually, the text becomes unreadable and further copying is subsequently pointless. Much like the white spaces in between letters and words is crucial for the readability of a text, telomeres are critical for a meaningful process of cell division.

Some attempts have been made to model this process mathematically. For instance, Aviv et al. (2003) postulate an equation governing the evolution of telomere length, which (in continuous time) can be written

$$\dot{L}(t) = -\phi_1 \cdot \left[\phi_2 \frac{\dot{m}(t)}{m(t)} + \phi_3 m(t) \right],$$

where \dot{L} is the change in telomere length from one instant to the next, m is body mass and ϕ_1, ϕ_2, ϕ_3 are positive parameters. Hence, this equation captures that periods of body growth, which are associated with rapid cell division, work to run down telomere length. Combing this equation with equation (6) provides a simple model of the evolution of telomere length, for initial body size and telomere size given. Finally, Aviv et al (2003) postulate a link between telomere length, and the probability of remaining disease free; the probability declines as L shrinks.

While cell division (arising in the context of body growth, as well as cell maintenance) is one way in which telomere length is reduced, it is increasingly understood that there is another force that also leads to telomere shortening: oxidative stress (von Zglinicki et al., 2000). Hence, the same mechanics that leads to cell damage, as discussed in Section 3.2, may also lead to biological aging of the cell. From a formal perspective, the modelling approach from the last section may then also be a crude reduced form representation in the present context, in that *metabolism* directly is linked to cell senescence and ultimately organism failure.

There is evidence to suggest that telomere shortening is empirically relevant in the context of human longevity. For one thing, accelerated telomere shortening has been shown to be the result of smoking and obesity (Valdes et al., 2005), known sources of oxidative stress and accelerated aging. Epel et al. (2004) find evidence that *psychological* stress is significantly associated with heightened oxidative stress and shorter telomere length, and Kimura et al. (2008) show that telomere length indeed holds predictive power vis-a-vis mortality, in a sample of elderly twins.

4 Conclusions

The (near) mass invariance of heartbeats per life time, and the inability of body cells to keep dividing in perpetuity (cf, the Hayflick limit), suggests the existence of an upper boundary to maximum life span in biological or-

ganisms. Metabolic theories of aging provides some important insights into the nature of what biomechanical constraints that might be responsible for limiting life span of species.

Larger bodies are more efficient in delivering energy to the capillaries and ultimately to the cells of the body. This manifests itself in less energy needs per unit of cell; a lower metabolic rate. According to the free radical theory, and the telomere theory, elevated metabolism is associated with oxidative stress which leads to cellular damage, and telomere shortening. Hence, in smaller bodies one would expect faster cellular aging, and thus (C.P.) faster systemic collapse.

Taken together this literature provides a solid scientific interpretation of the observed positive correlation between longevity and body mass; it can explain why an elephant lives longer than a dog, which in turn lives longer than a mouse. A positive correlation between body size and longevity is also found among humans. It seems possible that the above theories may contribute with an explanation for this regularity.

Hence, it appears possible to improve the modelling of longevity in economic models by paying attention to these mechanisms. A first step is found in Dalgaard and Strulik (2010) in the modelling of human body size; linking framework up with longevity would seem a natural next step.

The theories discussed above may also help shed light on global variation in life expectancy. Given a link between human body size and longevity,

evolutionary differences in stature could explain some of the observed differences across countries in longevity.

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