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# Aging mechanism as the “down side” of adaptation: a network approach

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## Abstract

Many diverse hypotheses on aging are in play. All from “aging genes” over decreasing telomere length to increased level of gene mutations has been suggested to determine an organism’s lifespan, but no one unifying theory exists. As part of a growing interest towards more integrative approaches in the field we propose a simplistic model based on the “use-it-or-lose-it” concept: we hypothesize that biological aging is a systemic property and the down side of adaptation in complex biological networks at various levels of organization: from brain over the immune system to specialized tissues or organs. The simple dynamical model undergoes three phases during its lifetime: 1. General plasticity (childhood), 2. Optimization/adaptation to given conditions (youth and adolescence) and 3. Steady state associated with high rigidity (aging). Furthermore, our model mimics recent data on the dynamics of the immune system during aging and, although simplistic, thus captures some essential characteristics of the aging process. Finally, we discuss the abstract model in relation to current knowledge on aging and propose experimental set-ups for testing some of the theoretical predictions.

*Key words:* Biological systems dynamics, complexity, pruning

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## Introduction

### *Variables correlated with biological aging*

Some basic mechanisms of aging have been proposed, e.g. telomere shortening (Olovnikov, 1973, 1996; Rubin, 2002), stem cell senescence (Sharpless & DePinho, 2004), and oxidative damage (Harman, 1981; Finkel & Holbrook, 2000). These variables have been observed to correlate with aging or cellular senescence in some species and cell lines, but the causality is still widely discussed (Hopkin, 2001; Sozou & Kirkwood, 2001; Rubin, 2002; Weinert & Timiras, 2003; Cristofalo et al., 2004; de Magalhaes, 2005). The specific variables observed to correlate with aging are often either species- or individual specific and this has led to a search for more inclusive system-based models of aging (see e.g. Kirkwood (2005); de Magalhaes (2005)). Free radicals formed during metabolism do cause damage to many parts of the cells (see Balaban et al. (2005); Kirkwood (2005)) but a fundamental question remains whether such random damage is the primary cause of aging (Longo et al., 2005; de Magalhaes, 2005). The universality of the senescent phenotype within and across species could argue against it: though many factors point away from the existence of an actual aging “program” (extensively reviewed in Kirkwood (2005)), aging of biological organisms is still a recognizable developmental stage, as is e.g. infancy and adolescence. It is commonly agreed that these earlier stages are timely organized and reached by developmental mechanisms during the life-cycle of the organism. Similarly, the aging stage is also identifiable at the organism level and in temporal organization during development. This could suggest that, if not a program, then perhaps a common intrinsic mechanism (or principle) of aging is operating across widely different species and taxa. If so, the observed accumulation of random damage with aging may be an important effect of an underlying dynamics rather than the primary cause. Below we follow this hypothesis theoretically and suggest some basic principles involved in the aging process.

### *The evolutionary discussion*

A core question is why biological organisms age at all. Previously, aging was explained as an evolutionary way of making room for the younger members of a population, thereby increasing the adaptability of the population as a whole (originally proposed by Weismann (1889)). It has, however, been argued that in evolutionary history mortality was mostly due to extrinsic hazards. In nature wild animals only rarely live long enough to die of old age (see Kirkwood & Austad (2000)). Two classical but still withstanding theories of aging are *the Mutation Accumulation Theory* (Medawar, 1952) and *the Antagonistic Pleiotropy Theory* (Williams, 1957).

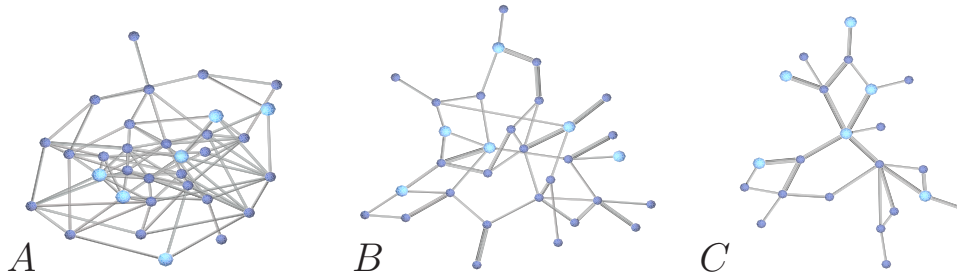


Fig. 1. Illustration of the model. Snapshots of a 32 nodes network at various time points during development. **A**, shortly after the beginning of the adaptive process, **B**, at an intermediary stage and **C**, an “aged” network near the end of development (just prior to the final break-up). Light blue nodes correspond to “active” nodes in the given environment, whereas the dark blue nodes are the “internal” (or “mediator”) nodes of the system. In this figure, the thickness of a link corresponds to its weight,  $w$ , and is thus contributing with  $1/w$  to the shortest path going through that link. For clarity, we present only the largest component of the network and to mimic a lower threshold, only the links with a strength  $\geq 4$  are visualized. See text for description of the extended network model as illustrated in the figure.

Both favor an evolutionary accumulation of late-acting, harmful genes as the cause of aging. The *Mutation Accumulation Theory* argues that aging is due to an evolutionary accumulation of late-acting deleterious mutations, whereas the *Antagonistic Pleiotropy Theory* proposes that the alleles causing aging (i.e., those harmful to the organism in the long run) are positively selected for due to an additional early-acting beneficial function. Specific examples of the latter alleles are, however, quite rare (see Kirkwood (2005)). Furthermore, the causality of most of the genes transcribed in correlation with aging - and thus potentially relevant for the *Mutation Accumulation Theory* - so far remains unclear (see Curtsinger et al. (1995); Pletcher & Curtsinger (2000); Kirkwood & Austad (2000); Kirkwood (2005)).

#### *Focus on single factors versus a systemic approach*

A general approach in gerontology research has been to look for correlations between a specific molecular factor and organism longevity. A more recent approach is to conduct a systemic analysis, where aging is viewed as a dynamical phenomenon based on the interplay between diverse factors during the life of an organism (see e.g. Kirkwood et al. (2003); Promislow (2005)). One example is the *Disposable Soma* theory (Kirkwood, 1977, 2002) in which aging is perceived as the “trade-off” between maintenance and reproduction due to the limited metabolic resources available to the organism during its average lifetime in the wild. In the present study, we have chosen a network approach to model aging in complex biological systems. As in the *Disposable Soma* theory, our focus is on the internal dynamics of the system as the driving force of the aging process. In this work,

however, adaptation at various levels of the organism replaces reproduction as the direct advantage but withholds aging as the unpleasant “trade-off”. We introduce a simplistic model of a network in continuous adaptation to its environment by the biologically relevant process of pruning. Initially, we observe a rapid adaptation/optimization followed by a steady state with increasing rigidity - and an eventual final break down of the system. Interestingly, these theoretical predictions largely mimic the dynamics of recent data on the activity of the adaptive immune system during aging in Baboon monkeys (Jayashankar et al., 2003). Though simplistic, the model thus captures a generic property of aging in biological systems.

## The model

### *Simple adaptive network dynamics*

To conceptually model development and aging of a complex adaptive system we take a network approach and focus on a minimal model based on synapse formation during brain development. Briefly, in the post-natal period a process of apparently disordered synapse formation is taking place in the infant’s brain (see Johnston et al. (2001)). The synapses are subsequently strengthened in an activity-related manner at the expense of weaker ones (i.e. by pruning) (see Penn & Shatz (1999); Johnston et al. (2001)). This process thus leads to an overall decrease in the total number of synapses with time (Bourgeois & Rakic, 1993; Huttenlocher, 1979, 1990; Masliah et al., 1993). As a result, there are twice as many synapses in the cerebral cortex of 2-year-old children compared to adults (see Johnston et al. (2001)).

From this general mechanism we generate a basic model to mimic development of a complex adaptive network. The model is a “top-down” approach, i.e. with focus on systems dynamics rather than the individual entities. Our adaptive network is going from higher complexity and continually reducing the number of links by pruning in response to environmental cues. In Figure 1, an adaptive network at three different time points during its lifetime is shown. The figure shows the development of the *extended network model* described in a later section. Visualized in the figure is the ongoing specialization by pruning resulting in a more sparse network with increasing link strengths which may mimic the aging process in adaptive biological systems. In the following we describe the basic and the extended network models.

### **Basic model assumptions:**

1. The initial network is densely connected with about 20% of all possible links randomly distributed in the network. This was chosen for simplicity and since the occurrence of any preferential neuronal attachment during the initial wiring of the

brain is obscure (see Ahmari & Smith (2002)).

2. In this basic model we define two classes of neurons/network nodes: (1) “active” nodes that contain the start and end-points of pathways activated in the system in response to specific environmental cues, and (2) “internal” nodes that function as signal mediators through the network but neither “receive” nor “end” signal transmission.

3. The “active” subset is defined as a square shaped distribution with width 20%, i.e.  $0.2 * N$  nodes.

4. For simplicity, we assume that the “active” subset is constitutive. This means that the nodes that pick up cues from the specific environment and the endpoints of the activated pathways are fixed, i.e. to a large extent evolutionarily shaped. The specific environment is visualized as nodes 97-159 and the top red line in Figure 2.

### Running the model:

The initial weight of all network links are set to 1. At each time step, a pair of nodes is picked at random from the “active” subset thus defining the start and end points of an activated pathway. Subsequently, the shortest path in the network between the picked pair of nodes is found. Each link on that specific path is then strengthened at the expense of weaker links in the network, i.e. for each unit weight added to the path links, the same weight units are removed at random elsewhere in the system. The length,  $l$ , of the path is the sum of the inverse weights of the links forming that specific path, i.e.

$$l = \sum_{i \in path} 1/w_i,$$

where  $w_i$  = weight (or strength) of a given link  $i$ . Thus, the stronger the link, the shorter the path going through that specific link. A threshold to the maximum strength of each link was chosen to mimic maximum synapse strength (Huttenlocher, 1990). For example, if two nodes picked are separated by a path of length three, three units of weight 1 are removed at random from the rest of the system. Subsequently, each link on the path between the two nodes picked is strengthened provided that their weight is below the given threshold. In this basic model, if an activated link cannot be strengthened further due to the fixed maximum strength of the links, the corresponding weights are still removed from the network. If two nodes are disconnected due to the complete removal of a link they are separated by the distance  $1 = N$  ( $N$  = the total number of nodes in the network).

### Measuring model evolution:

We assume that rapid and efficient signaling through the network in response to environmental cues are important for successful adaptation. To quantify the effects of adaptation in this conceptual theoretical setting, we introduce *Performance* as a node property. Performance is defined as being well-connected and easy to reach, i.e. having a short distance to the rest of the nodes in the network. To quantify the Performance of every network node,  $i$ , in a given environment, the shortest path from node  $i$  to all the rest of the nodes in the network is used, i.e.

$$\langle l \rangle_i = \sum_{j \neq i} l_j$$

In Figure 2, we illustrate how the imposed environment is shaping node performance in a 256-nodes network. Figure 2A shows snapshots of the node specific shortest path,  $\langle l \rangle_i$ , at various time points during development for all nodes  $i$ , each individually represented on the x-axis.  $t = 1$  corresponds to  $N = 256$  updates where one pair of nodes has been picked, which gives a size-independent measure of time. Just by following this simple quantity, three phases in the network development occur.

**Phase 1:** The initial phase (before the onset of pruning) is characterized by a general network plasticity which makes adaptation to any given environment possible.

**Phase 2:** As a consequence of the ongoing pruning, a phase of adaptation to the given environment follows, i.e. from  $t = 0.5$  to  $t = 4$  in Figure 2A (for the network of size  $N = 256$ ,  $t = 0.5$  means 128 updates where two adaptive nodes are picked at random). In this phase, the performance of the subset of nodes “active” in an imposed environment (nodes 97-159) is improving (i.e., length,  $\langle l \rangle_i$ , decreases). In Figure 2B, the *average* shortest path of the “active nodes” (i.e., the nodes that receive or execute signals in the specific environment),  $\langle l \rangle_u$ , and the rest of the nodes  $\langle l \rangle_n$  is plotted versus time,  $t$ . As in 2A, this figure shows that in the adaptation phase the average shortest path of the active nodes,  $\langle l \rangle_u$ , decreases, which means that Performance increases.

**Phase 3:** After some time of adaptation, the Performance of the “internal” network nodes (i.e., nodes 1-96 and 160-256) are decreasing, i.e., path length,  $\langle l \rangle_i$ , increases. Eventually, after some time of ongoing pruning, the Performance of the “active” subset also starts to decrease (see e.g.  $t = 32$  in Fig. 2A). Thus, both the direct in and output to environmental cues and signaling within the network are impaired. Thus, after the network has reached its optimum state defined by the minimum distance between the “active” subset of nodes it enters a phase of “over-optimization”, or the “aging phase”. From this point on ( $t \geq 4$  in Figure 2 A+B), Performance of both the “active” and the “internal” subset decrease, i.e. the length of the shortest



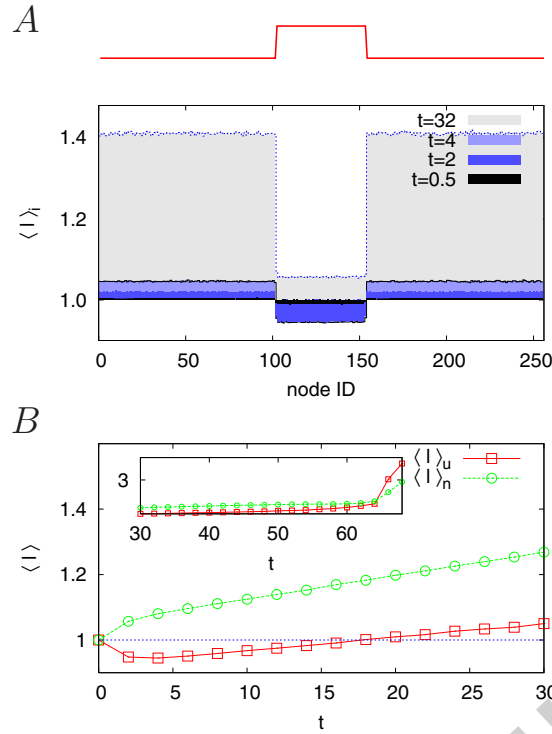


Fig. 2. Illustration of the aging process for a network consisting of  $N = 256$  nodes. In **A** it is shown how the individual Performance,  $\langle l \rangle_i$ , of every node is shaped by the environment (indicated by the top red line) and time. Initially, all nodes are performing equally,  $\langle l \rangle_i = 1$  for all  $i$ . After some time,  $\langle l \rangle_i$  decreases (i.e., Performance improves) for the nodes active in a given environment and is increasing (i.e., Performance decreases) for all the rest of the nodes in the network (see  $t = 0.5$  and  $t = 2$ ). Environment is modeled as the “active” subset of the nodes (as indicated by the top red line). **B** The average Performance of the nodes active in an imposed environment (solid red line with open squares and nodes 97-159 in A) and the corresponding quantity for the “internal” (or mediator) nodes in a given environment (green line with open circles).

path increases with a constant rate until the network becomes very sparse (Fig. 2B at  $t \sim 60$ , see inset). As can be seen from the figure, further pruning has dramatic effects: the network disconnects (or “dies”).

The adaptive network thus rapidly optimizes its response to the specific environmental cues until it reaches a certain point. After this, Performance gradually declines towards final disconnection. This simple conceptual model thus mimics the different developmental stages observed in a complex adaptive system: flexibility, optimization and aging.

### Extended model:

In the basic model presented above the performance of the start- and end-points of

pathways induced by a specific environment initially increases during the adaptive process and subsequently decreases with time. In the next step, we impose more constraints on the model. First, if an activated link cannot be strengthened further due to the fixed maximum strength of the links, we add a link at random in the network. Instead, to mimic the costs of a developing biological system, a fixed low loss rate is maintained. Secondly, to mimic a basal activity level of the network, as is observed in the brain (Shulman & Rothman, 1998), we allow for nodes that are not a part of the “active” (or task-specific) subset to be activated anyway, albeit with a lower probability: the active subset is still defined as a square shaped distribution (with width 10%, i.e.  $0.1 * N$  nodes) but within this subset, the nodes are now picked up with a probability of only 3 times higher than all the rest of the nodes in the network.

In Figure 3, we present Performance versus time of an average of 100 128-node networks with a random link loss rate of 0.1. The network develops in a single environment (or performs a single task) in addition to a basal activity level of all the nodes in the network as described above. As in the basic model the average length between the nodes that form part of the “active” subset (red line) falls drastically in the beginning of the adaptive process. Furthermore, and contrary to the previous model, the “internal” nodes also perform similar dynamics (green line) and the entire network thus seems to adapt to the imposed environment. As time goes, the adaptation saturates reaching a steady state for a while with a subsequent final break up. The final disconnection is visualized by the increasing path length in the figure. Since the figure is an average over 100 runs, disconnection appears as a smooth increase with a different slope after  $t \sim 20 - 25$ . The extended model thus goes through similar developmental stages as the basic model but overall network adaptation improves. In the Discussion we discuss the possible biological relevance of our theoretical findings.

Regarding the observed final break up of the systems it is important to note that in both the basic and the extended model shown in figure 2 and 3, respectively, an on-going loss of links occurs during network development. In the basic model the random removal of links continues although the activated link cannot be strengthened any further due to the imposed threshold. On the contrary, in the extended model if the activated link has already reached the threshold corresponding links are added at random in the network. Instead, a fixed low loss rate is introduced in order to mimic the energy costs of a developing biological system. Interestingly, however, if total links strength is conserved throughout the development of the system, the characteristic dynamics of initial flexibility, rapid adaptation and a final steady state is still observed (see supplementary material Figure S1). In this case, however, the system resides in the steady state after the rapid adaptation showing no final signs of break-up. It could thus be assumed that for the actual break-down of the system to occur an overall energy loss has to occur during development, which is what would be expected for a developing biological system. As discussed previously, the energy loss could either be due to random damage or, as proposed

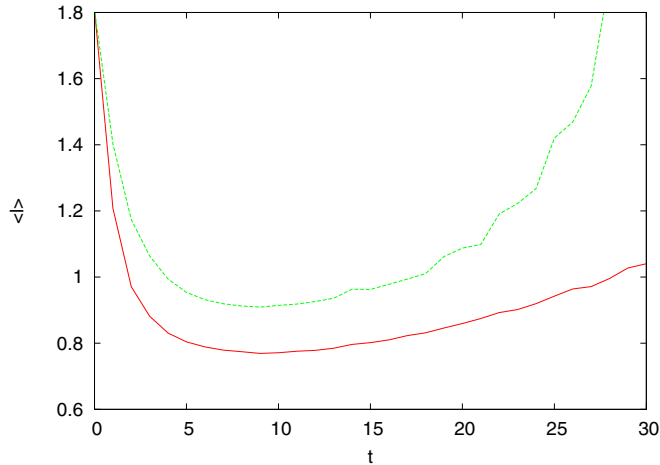


Fig. 3. Dynamics of the extended network model. The average shortest distance,  $\langle l \rangle$ , is decreasing as the network adapts and increases again with aging. Here,  $\langle l \rangle$  is plotted versus time in a 128-node network, i.e.  $t = 1$  corresponds to 128 updates where one pair of nodes has been picked which gives a size-independent measure of time. The maximum strength of the links is 5, and the green and red lines correspond to “internal” and “active” nodes, respectively. A square shaped environment is applied with width 10%, i.e.  $0.1 * 128 = 13$  nodes. This defines the nodes “active” within this environment, and these nodes are picked up with probability 3 times higher than the rest of the nodes in the network. The green line is higher, which means that the “internal” nodes are generally slightly worse adapted than the “active” nodes under these circumstances. The figure shows that in the beginning of the adaptive process, average distance of the network is rapidly decreasing (adaptation). Next, the rate slows down and the network enters a steady state with no (or only very limited) optimization (i.e., the aging phase) and, finally, a systems break up.

in the basic model, an on-going internal mechanism of pruning with imperfect substitution - or perhaps a combination of the two.

## Discussion

In this work we introduce a simple conceptual model on biological aging as an adapting network over time. Adaptation is modeled as the progressive pruning and shaping to optimize an interconnected network of environmental-specific and mediator nodes in a given environment during the developmental process. By following the simple quantity of node performance, a characteristic dynamics in the network progression emerges: initial flexibility followed by rapid adaptation and the aging phase.

*Example: T cell activity*

To compare the model to available biological data we turn to the immune system for a well studied adaptive biological system known to undergo aging. Immunosenescence - the aging of the immune system - is characterized as the observed age-associated decrease in immune function causing increased susceptibility to infectious diseases with age (see Pawelec et al. (1999)). This is a well studied but still widely discussed phenomenon mostly concerning the adaptive immune response and, in particular, the T cell system. Briefly, when the adaptive immune response is first exposed to the specific environment of the organism, the “naive” (yet unspecialized) T cells are highly activated. After an immune response, the pools of activated T cells recognizing the specific environmental antigens that caused the response decreases to about 1%, surviving as resting pathogen-specific cells - the “memory” T cells. By this selective enhancement of the frequency of the previously activated T cell clones, the formation of the memory T cells facilitates the interaction between the APC (antigen presenting cell) carrying the specific antigen and the T cell clone carrying the T cell receptor (TCR) that recognizes the antigen. Upon re-exposure of the antigen, the memory T cells with the relevant antigen-specific TCR are induced to multiply and a directed attack against the intruder is carried out (see Pawelec et al. (1999); Marsden et al. (2006)). By facilitating a step in an environmentally induced signaling pathway of the adaptive system, the formation of memory T cells thus increases the sensitivity of the immune defense against the reappearance of the particular antigen. In our model, this is analogous to the strengthening of one link in a pathway upon activation, which results in a shortening of the specific path involved in the adaptive immune response to the recurrence of the antigen.

If the dynamics of the adaptive immune system is comparable to our conceptual model, we would expect this particular adaptive network to start out with a high average shortest path through the system followed by a rapid decrease, a subsequent steady state and a final increase during the later stages of an organism’s lifetime (as illustrated in Figure 2 and 3). To quantify the average shortest path (and thereby the Performance) of this system, we focus on the pathways induced in the adaptive immune system during development. Since the formation of memory T cells improves the signaling path from APC to T cell, it leads to a shorter response time and thus a more efficient response towards the particular antigen (see Marsden et al. (2006)). We assume that a quicker and more efficient elimination of intruders following the “shorter lengths” of the previously activated paths leads to a shorter overall period of T-cell activation necessary at each attack in the system “trained” (or “pruned”) in a specific environment. If this is correct, the average shortest path of this system will correlate with the overall level of T cell activation. In other words, the more efficient the systemic response the less overall T cell activity will be necessary for eliminating the intruder.

A marker for overall T-cell activation is the serum concentration of the surface receptor IL-2R $\alpha$  (Morris & Waldmann, 2000) and in Figure 4, the serum level of IL-2R $\alpha$  is plotted as a function of age in Olive Baboon monkeys (data from Jayashankar et al. (2003)). As can be seen in the figure, in the beginning of the Baboon's life the level of T-cell activation is high but rapidly decreases within the first 50 months ( $\sim 4$  years) of the baboon's lifetime. After that, the level of IL-2R $\alpha$  stabilizes or slightly increases until it finally seems to break off. Interestingly, the serum level of the IL-2R $\alpha$  receptor thus shows overall dynamics resembling the average shortest path of the adaptive network model in Figure 3 with initial rapid optimization followed by a steady state. Moreover, the observed tendency towards a general higher level of T-cell activity by the end of life could signify a less effective system and thus final signs of break-up as observed in our theoretical settings (Figs. 2 and 3). It could therefore be speculated that the essential specialization and increased efficiency of the adaptive immune system by the formation of memory T cells at the expense of the initial diversity would result in a gradually more rigid system with time, thus contributing to the observed immunosenescence. Indeed, the most characteristic features of aging of the immune system are (1) a decline in naive T cells and (2) an accumulation of memory-phenotype T cells (see Prelog, 2006; Davenport, 2003), as would be predicted from our model.

It is, however, important to stress that several assumptions were taken in the above example which is merely meant as a possible pointer towards an adaptive system where the model could be of relevance for future studies. Though the model is no doubt an oversimplification of the adaptive process in complex biological systems, it might serve as a theoretical tool and perhaps offer useful perspectives on the study of aging. As also discussed in the introduction, the important question remains whether or not the frailty of the aging organism is due to random damage or, as proposed here, because of a general principle at play during organism development. Alternative interpretations of several well-known but still widely discussed observations concerning aging and longevity are suggested below. Furthermore, some experimental tests of our model that might shed some light on core questions are proposed.

#### *Aging as an evolutionary trade-off*

One reason why the down side (the increasing rigidity) of an otherwise advantageous adaptive process would not have been corrected by evolution could be the decline in natural selection with age (i.e., after the reproductive period) (Hamilton, 1966; Kirkwood, 2002). Theoretically, one could imagine a dynamical network that ends the adaptive process at the peak of fitness (around  $t = 4$  in Figure 3) and thus avoids the consequential rigidity of information overload. In real life, however, it is perhaps harder to imagine an organism that ceases to improve in early adulthood. Specialization is most likely needed to cope with the environmental and social de-

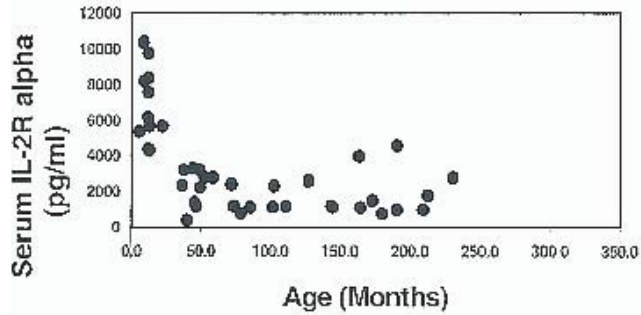


Fig. 4. Data obtained by Jayashankar et al. (2003) showing the relationship between levels of the surface receptor IL-2R $\alpha$  in serum and age in Olive Baboon monkeys. IL-2R $\alpha$  is determined by ELISA and expressed in picograms per milliliter. The serum concentration of IL-2R $\alpha$  is a marker for T-cell activation (Morris & Waldmann, 2000) and the plot thus represents the activity-dynamics in this part of the immune system over time (see text for details). The data shows that the serum level of IL-2R $\alpha$  is initially high with a subsequent rapid decrease during the first 4 years of the baboon's lifetime. After that, the concentration stabilizes with final signs of break-off. As can be seen from the plot, a linear fit is not appropriate, whereas the dynamics seen in our model is closer to the actual dynamics observed in this biological sub-system during senescence (see Figure 3). (Figure modified from (Jayashankar et al., 2003).

mands meeting the maturing organism, as e.g. the parenting of offspring. Thus, aging could be perceived as an evolutionary trade-off or an *antagonistic pleiotropy* (Williams, 1957): the advantage of the adaptive process as the ability to cope with an environment constantly demanding more advanced skills to fill out the role of a maturing organism in the given context - and an inevitable later systemic rigidity as the inevitable trade-off.

### *Cellular senescence*

Though highly abstract, in the framework presented here cellular senescence is comparable to aging of a complex organism. Not due to specific genes, however, but because both could be underlying the same general systemic mechanism of specialization to specific tasks and thus the eventual final rigidity. Interestingly, this is supported by two recent studies showing that both rat nerve precursor cells and rat Schwann cells, which normally exhibit only a limited division capacity in culture (i.e., replicative senescence), grow unlimited in media optimized to prevent differentiation (Tang et al., 2001; Mathon et al., 2001). These results could implicate that if no differentiation or optimization to specific tasks is demanded of the cellular system for continual growth, no (or only very limited) senescence follows.

### *Caloric restriction*

It has been known for quite a while that starvation increases longevity in many species (see Anson (2004); Kirkwood (2005)). If, as suggested in the present study, adaptability and aging is linked, these observations could be due to the slowing down of the adaptive process by caloric restriction. This would increase longevity (by postponing the onset of rigidity) but decrease the overall adaptability of the system. To test this hypothesis empirically, calorically restricted and normal young mice of the same age should be challenged with a new task and the time needed for successful adaptation compared. Alternatively, measures of e.g. brain maturation could be compared at similar ages in calorically restricted and normal model organisms. In support of this view, the effects of caloric restriction show a decrease in the normal rate of maturation in both rodents (Kalu et al., 1984; Merry & Holehan, 1981) and rhesus monkeys (Mattison et al., 2003). Interestingly, caloric restriction seems to have reduced effects on longevity if applied after middle age, i.e. after the period of growth and maturation (Lipman et al., 1998).

### *“Aging genes”*

Genetic mutations that increase mean longevity are often coupled to a decrease in the rate of metabolism (Finch & Ruvkun, 2001). This could indicate that such mutations increase longevity by the same mechanism as the caloric restriction described above, i.e. both the genetic destabilizations correlated with increased longevity and starvation slows down the rate of metabolism and thus adaptation (by pruning). This would maintain the overall plasticity of the system longer and thus the life-time of the organism under non-challenging laboratory conditions. It is, however, currently uncertain whether this growth pattern is favorable under naturally changing conditions where, according the model presented here, a certain adaptation rate would be necessary to optimize to the specific environment of the organism. In support of this hypothesis, a recent study in the round worm *C. elegans* have shown that longer living mutants rapidly die out when grown together with wild type worms, i.e. in a challenging environment (Jenkins et al., 2004).

### *Aging at several organizational levels?*

The flat architecture of our model, the lack of feed-back and the limitation to a single environment are just some of the simplifications of this model compared to the actual dynamics involved in the development of a complex biological system. The model may, however, capture essential characteristics of the adaptive process anyway. Each node can be interpreted as a component interacting with other components at the same level of organization, e.g. as pools of proteins in a differentiating

cell; individual synapse-forming neurons in the brain; groups of cells with specific functions in the immune system, etc.

An empirical test of whether this adaptive mechanism is applicable to the cellular level would be to follow overall transcription during differentiation of a specific cell type. According to our model, the mechanism of adaptation operating at the cellular level would be an initial high number of possible protein-protein interactions (i.e. overall transcription) in the non-differentiated cell followed by strengthening (increased pools) of the nodes (proteins) actually activated in the specific environment. This selective enhancement of the frequency of proteins would occur at the expense of the non-activated protein pools during the “pruning” process. According to the model, diversity of the intracellular proteome would thus decrease during cellular differentiation - comparable to the observed decrease in diversity during maturation of the adaptive immune response (Davenport, 2003) and the brain (Johnston et al., 2001).

Two recent studies have addressed similar topics. Pletcher et al. (2002) followed gene expression in the fruit fly during aging and mostly observed an age-related up-regulation of genes. Their dataset, however, covers the overall expression of the entire fly at different ages. In order to test the model presented here at the cellular level, the expression of the one-cell embryo should be compared to only one cell type at a time during differentiation. Alternatively, structures at the level of the organism, as e.g. the nervous- or the immune system should be analyzed. In the present perspective, Pletcher et al. (2002) and similar studies mix several levels of organization (scales) and thus achieve rather complex data.

Interestingly, however, Golan-Mashiach et al. (2004) followed one cell type and investigated the general design patterns behind embryonic stem cell (ESC) differentiation. They found that ESC gene profiles reveal an elevated complexity with significantly more highly expressed genes than in the derived adult cells. Similar data has previously been observed in the case of hematopoietic stem cell differentiation (Hu et al., 1997). This could indicate that the developmental process in a differentiating cell initiates with a high transcriptional diversity and decreases during the adaptive process dependent on the cellular environment, as would be expected from our simplistic model of adaptation (or differentiation) by pruning.

## **Concluding remarks**

In this work we have outlined a conceptual model of biological aging represented as a simple adaptive network. We suggest that the observed frailty of aged organisms is not primarily due to random damage but rather an inherent consequence of adaptation. If the adaptive strategy preferred by nature is going from diversity to specialization by network pruning, one consequence would be an increased rigidity



and thus an overall decrease in the ability to maintain homeostasis. In this perspective, adaptive networks at several levels of the organism could undergo aging. Thus, the eventual systemic breakdown could occur at various levels (or subsystems) of the organism depending on the specific environment and the particular adaptive process that shaped it - perhaps a parallel to the well known fact that “death from aging” can be a consequence of a wide variety of causes.

In summary, here we modify the classic *Antagonistic Pleiotropy Theory* (Williams, 1957) to concern systemic characteristics rather than individual genes: we propose that an on-going process of pruning in various subsystems of a complex biological organism is a trade-off with multi-level adaptation as the crucial advantage and aging as the inevitable down side. From this perspective aging is, in essence, the systemic rigidity of over-specialization.

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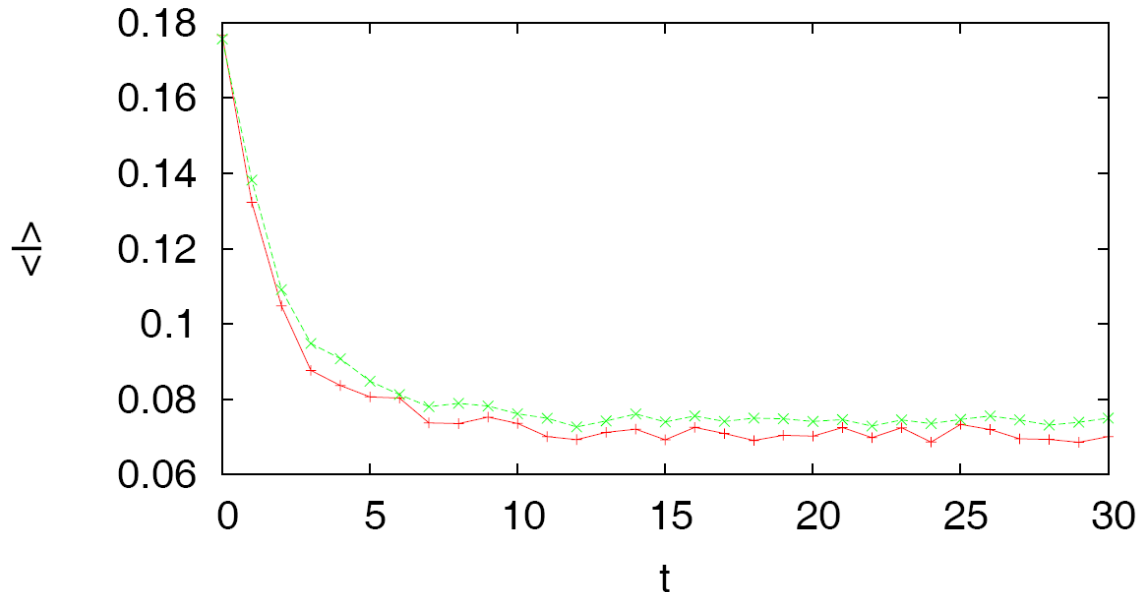
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## Supplementary material for Borup et al.



**Fig. S1.** Dynamics of the extended network model with no overall link loss. The figure shows the dynamics of the extended network model with no fixed loss rate added and thus a total net conservation of link strength in the system during development. As in the previous models, the average shortest distance,  $\langle l \rangle$ , is rapidly decreasing as the network adapts. Here,  $\langle l \rangle$  is plotted versus time in a 128-node network, i.e.  $t = 1$  corresponds to 128 updates where one pair of nodes has been picked which gives a size-independent measure of time. The maximum strength of the links is 5, and the green and red lines correspond to “internal” and “active” nodes, respectively. A square shaped environment is applied with width 10%, i.e.  $0.1 \cdot 128 = 13$  nodes. This defines the nodes “active” within this environment and these nodes are picked up with probability 3 times higher than the rest of the nodes in the network. The green line is higher, which means that the “internal” nodes are generally slightly worse adapted than the “active” nodes under these circumstances. The figure shows that in the beginning of the adaptive process, average distance of the network is rapidly decreasing (adaptation). Next, the rate slows down and the network enters a steady state with no (or only very limited) optimization (i.e., the aging phase). As can be seen in the figure, no signs of final break-up are observed under these conditions. It could thus be assumed that for this to occur an overall “energy loss” must take place during development, which is probably what would be expected for a developing biological system (see text for further discussion).