Biological Aging

> Communication in the field of biogerontology is a minefield because all of the commonly used terms have no universally accepted definitions. In a series of five annual meetings that I chaired recently in an attempt to define common terms, the dozen or more experts who attended could not agree on the definition of almost all of them, including "aging." The committee was disbanded and the communications dilemma remains. ...There is no other field of science in which a similarly bleak situation exists.
> - Leonard Hayflick [1] -

Some theories of **Biological Aging**:

- **Free radical theory of aging**.
- **Wear and tear** (accumulation of damage).
- Genetically programmed aging ("programmed cell death"). There is good evidence now that this theory is wrong for most species, in particular for humans.
- **Rate of living theory**.
- **Evolutionary theories of aging** (e.g. *antagonistic pleiotropy*).
- **Mitochondrial theory of aging**.
- **Disposable soma theory**.
- **DNA damage theory of aging**.
- *Network theory of aging*.
- *Metabolic stability theory*.
- *Cellular theory of aging*.
- *Reliability theory of aging*.

Two modest approaches to aging by the author of this **Wiki-Blog**:

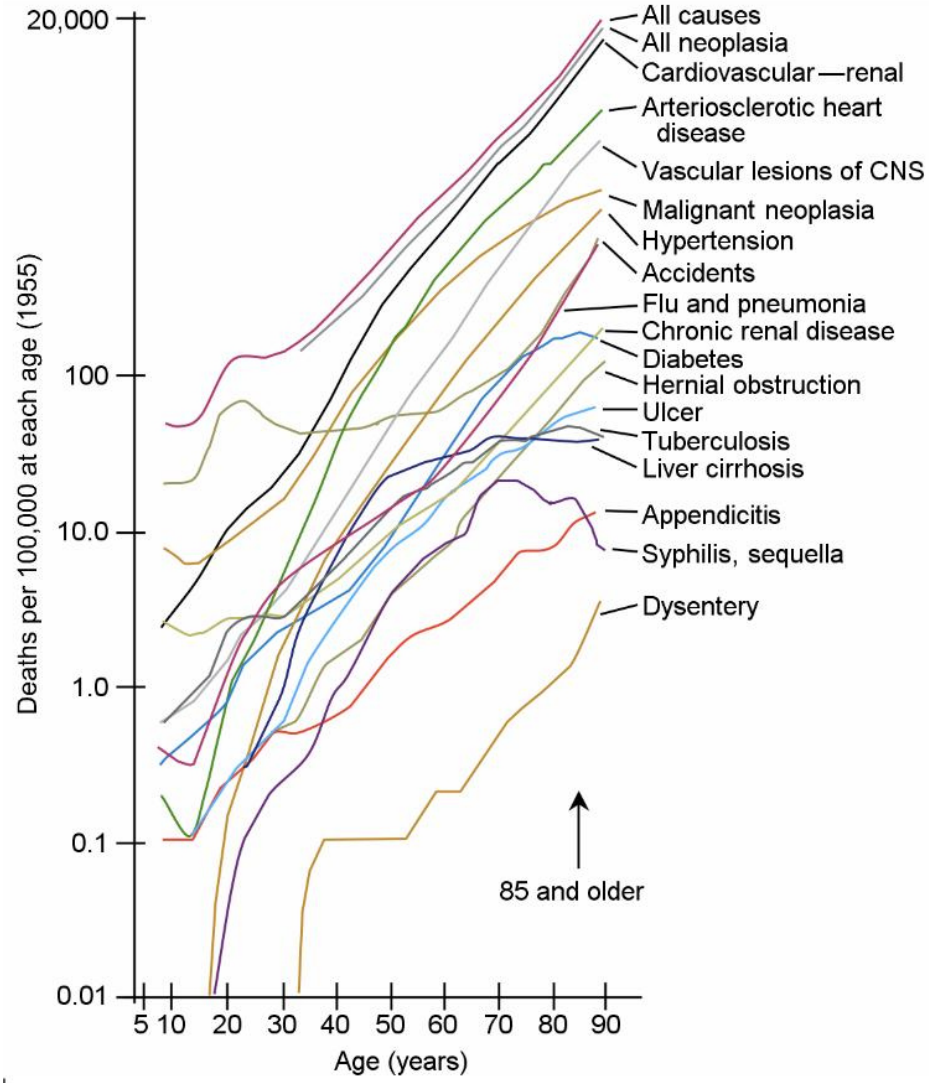
- **Hierarchical theory of aging**.
- **Theory of quasi synchronous aging**.

It's clear that theories of biological aging are in general not mutually exclusive, which makes their discussion and comparison somewhat involved.
In first approximation the rate of living theory predicts the **maximum lifespan** of nearly any animal. I have checked this proposition based on a large dataset (see [2]). This implies that a large part of the aging process takes place on the cellular level and is universal. Therefore the acid test for any claim of a successful intervention in the aging process is the demonstrable prolongation of the maximum lifespan of a species. (An increase of the average lifespan is not relevant in this respect as it merely points to a reduction of suboptimal aging). Moreover, an increase in maximum life span should not depend on a trade off, as for instance is the case in **calorie restriction** or hibernation where the energy throughput is just reduced and as a consequence bodily functionality is considerably altered. E.g. in calorie restriction the outcome is an at least partial

shut down of the reproductive apparatus. (Compare this situation to a car that is kept safely in a garage and never driven, which is not much of a car in the usual sense).
In humans for instance a fundamental increase in maximum lifespan has never ever been achieved. In fact, since ancient Rome [3] the maximum life span has invariably been about 110-120 years.

Aging and disease

Due to the aging process mortality rises exponentially (see also *Gompertz-Makeham law of mortality*). The same applies to age related diseases.



Hence there seems to be only one way to efficiently counter such diseases, namely, instead of merely treating associated symptoms, to tackle the underlying root cause, biological aging.

Some critical remarks

- It has been argued that biological aging is just another problem of everyday

life that needs to be fixed, like a "bug" in a computer program. (This is also the philosophy behind **SENS**). I regard this view as fundamentally wrong. Rather I think that aging is not a problem to a specific biological design, but it is always already in place and life like any other physical system has to deal with it. This view is supported by the fact that virtually everything ages be it animate or inanimate matter. By just focusing on the imperfectness of biological systems, which is inferred from the fact that they age, what I think is sometimes missed or not appreciated enough are the amazing capabilities lively systems possess dedicated to counter aging. An example are the sophisticated **DNA repair** mechanisms. The failure of just one such system can lead to a highly increased pace of aging and to early death as seen in progeria.
Given our biochemical design, it is one thing to modulate lifespan, as can be done by tweaking certain genes, but it is a fundamentally different thing to considerably extend lifespan, which for humans would mean getting way beyond 120 years. (I have not the least idea how this could be practically achieved and my gut feeling is that it will not be possible for a very long time if ever). Hence I predict that there will be no "fix" to aging or "cure" of it but at best a further optimization of our biological design to better counter aging thereby taking more and more the further course of evolution into our own hands.

- In many articles and books on the subject one can read that biological aging is not understood yet. But what does it mean to understand it ? In my opinion understanding boils down to being able to make quantitative predictions. Of foremost importance, I think, is the prediction of the age dependency of **mortality rates** (e.g. the *Gompertz law*). Surprisingly though there is no agreement as to what the biological origin of this law is and even if it holds in any case. (Imagine we would face the empirical exponential decay law of radioactive isotopes but were not able to derive it from fundamental physics - **quantum tunneling** being the answer by the way. Wouldn't that be embarrassing ?). To put it very drastically in the words of Immanuel Kant: "Ich behaupte aber, dass in jeder besonderen Naturlehre nur so viel eigentliche Wissenschaft angetroffen werden könne, als darin Mathematik anzutreffen ist." In the spirit of Kant I would argue that most theories of biological aging are just not science, that being the problem. Rather they are like poetry, telling stories about aging, producing a lot of verbal noise which is not very helpful in making progress in tackling aging. The point is that only if one were able to make quantitative predictions one would have a chance to get a handle on aging, manipulate and modulate it and this way maybe achieve a profound **life extension**. This would open the door to an engineering approach to aging, but as is the case when an engineer constructs a bridge, say, mathematical formulas are desperately needed !

See also:

- **Brain aging**
- *Material aging*

Papers:

- Slowing of Mortality Rates at Older Ages in Large Medfly Cohorts (1992) - J. R. Carey, P. Liedo, D. Orozco, J. W. Vaupel local pct. 563
- [1] Entropy Explains Aging, Genetic Determinism Explains Longevity, and

Undefined Terminology Explains Misunderstanding Both (2007) - L. Hayflick local pct. 74
- Modern Biological Theories of Aging (2010) - K. Jin local pct. 41
- Aging: Why Do Organisms Live Too Long? (2013) - A. A. Maklakov local pct. 1

Documents:

- Theoretische Alternsmechanismen I (1997) - J. Türk local dct. 0
- Theoretische Alternsmechanismen II (2003) - J. Türk local dct. 1

Links:

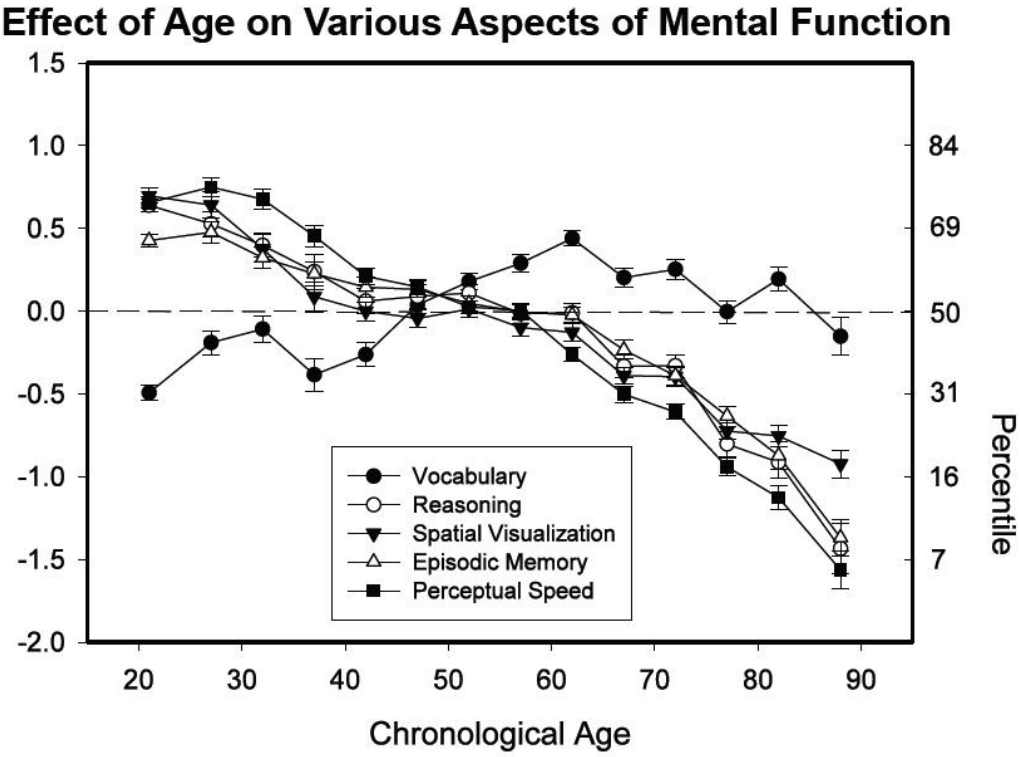
- WIKIPEDIA - Ageing
- [1] Hompage of Markus Maute - Biological Aging
- Human Benchmark (My best score so far: 225ms).
- Watch a man age 27 years in minutes: Artist took a selfie EVERY day to create a chilling video (2014)

Videos:

- The Role of Mitochondria in a Aging and Disease - D. Sinclair
- [3] Roy Walford Interview by M. MacRae
- Building Haystacks and Finding Needles in the Genomics of Ageing (2013) - J. P. de Magalhães

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Brain Aging



See also:

- **Biological aging**
- **Brain**

Videos:

- Cognitive Changes with Aging: What Can You Expect? - M. Greicius

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Calorie Restriction

Papers:

- Body-Mass Index and Mortality among 1.46 Million White Adults (2010) - ... local pct. 674

Links:

- Nature News: Calorie Restriction Falters in the Long Run (2012)

Videos:

- Calorie Restriction

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Disposable Soma Theory of Aging

According to the **Disposable Soma Theory of Aging** (introduced by Tom Kirkwood in 1977 [1]), a life history trade-off exists between early reproduction and late age survival.

The disposable soma theory of aging highlights the relocation of resources from somatic maintenance towards increased fertility, leading to a slow deterioration of the organism.

It is a special case of the *antagonistic pleiotropy theory* and hence it is an **evolutionary theory of aging**.

Links:

- WIKIPEDIA - Disposable-Soma-Theorie

Journals:

- [1] Evolution of Aging (1977) - T. Kirkwood jct. 1057
- The Evolution of Ageing and Longevity (1979) - T. B .L. Kirkwood, R. Holliday jct. 542

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

DNA Damage Theory of Aging

Links:

- WIKIPEDIA - DNA Damage Theory of Aging

Videos:

- Aging of the Genome - J. Vijg

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Evolutionary Theory of Aging

See also:

- **Biological evolution**

Papers:

- Demography of Genotypes: Failure of the Limited Life-span Paradigm in Drosophila Melanogaster (1992) - J. W. Curtsinger, H. H. Fukui, D. R. Townsend, J. W. Vaupel local pct. 386

Links:

- WIKIPEDIA - Evolution of Ageing

Videos:

- Michael Rose's 55 Theses
- How to Control Your Aging - M. R. Rose
- Michael Rose Interview
- Thesciencenetwork - Michael Rose

Audios:

- Genescient's Plan to Extend our Healthy Lives - I. Woolf

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Failure Rate

The **Failure Rate** $\lambda(t)$, also called the **Hazard Rate** $h(t)$, is defined as the relative rate of decline of the **reliability function**:

$$\lambda(t) = -\frac{dS(t)}{S(t)dt} = -\frac{d(\ln S(t))}{dt}$$

The failure rate is equivalent to the **Mortality Force** $\mu(t)$ in demography.

In cases where the failure rate is constant (does not increase with age), one has

a non-aging system (component) which does not deteriorate (does not fail more often) with age. The reliability function of non-aging systems (components) is described by the exponential distribution:

$$S(t) = S(0)e^{-\lambda t}$$

where $\lambda \equiv \lambda(t) = \text{const.}$.
This failure law describes the "lifespan" distribution of atoms of radioactive elements and it is also observed in many wild populations with high extrinsic mortality.
Therefore, in this model, the absence of aging does not imply that a system (organism) is not prone to failing (dying).

If the failure rate increases with age, one has an aging system (component) that deteriorates (fails more often) with age. There are many failure laws for aging systems and the Gompertz law with exponential increase of the failure rates with age is just one of them. In reality, system failure rates may contain both non-aging and aging terms as, for example, in the case of the *Gompertz-Makeham law of mortality*.

Links:

- WIKIPEDIA - Failure Rate

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Free Radical Theory of Aging

Oxidative damage to macromolecules forms the basis of what is arguably the most popular current explanation of **ageing in biology**: the ***Free Radical* Theory of Aging**.
This idea has its origins in the older **rate of living hypothesis** which holds that longevity is directly correlated with expenditure of metabolism.

Papers:

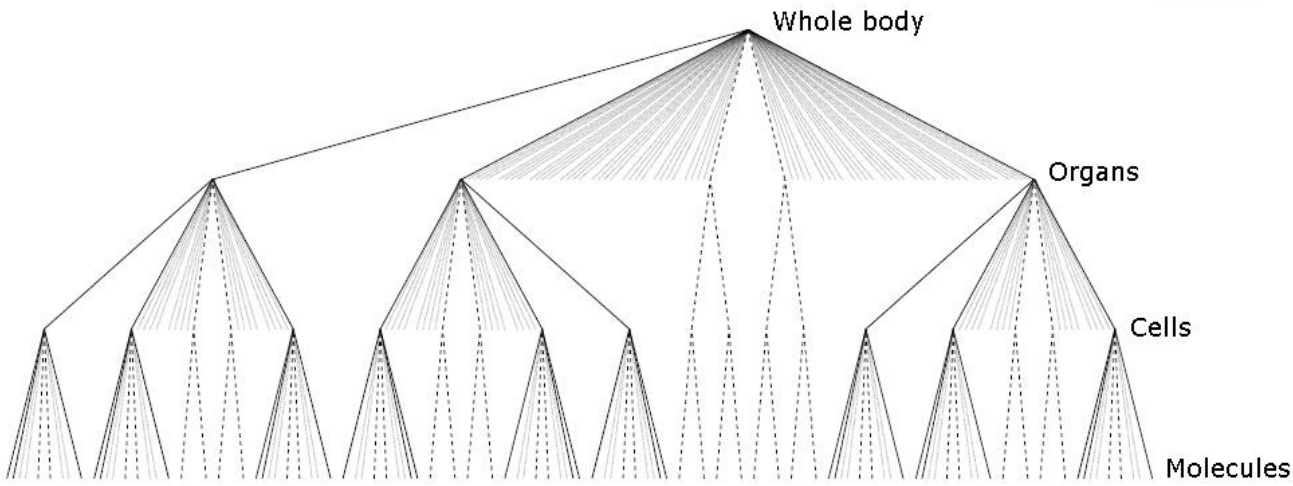
- Aging: a Theory Based on Free Radical and Radiation Chemistry - D. Harman local pct. 5818 - The classic on the free radical theory of aging.
- Ageing and the Free Radical Theory (2001) - A. P. Wickens local pct. 358

Videos:

- How to Build a Human - FOREVER YOUNG

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Hierarchical Theory of Aging



A simplified model of a multicellular organism.

The **Hierarchical Theory of Aging** (HTA) is a theory of **biological aging** proposed by the author of this **Wiki-Blog**.

Its basic ideas are rooted in the *reliability theory of aging* (RTA), yet it differs from it in some aspects:

- The biology is taken into account. I.e. instead of just speaking about components and their **failure rates**, in the HTA an attempt is made to identify these structures and to take into account their topology. The conjecture is that there is a nesting of components, boiling down to a hierarchical (tree-like) structure as a first approximation. Roughly speaking one has the hierarchy: molecules -> organelles -> cells -> organs -> whole body. Superimposed are chemical (**metabolic**) networks which may have to be taken into account too and would complicate the situation. An alternative and possibly more appropriate way to define the hierarchical levels (nodes) is to identify "functional units".

- A connection with the physics of a biological system is made by considering the **thermodynamics of biological aging**. The punchline of the latter is that aging is due to "uncompensated heat", leading to irreversible changes (an increase in **entropy**) in the body. The crucial point is to map these changes to failures of specific structures and locate them in the hierarchy mentioned. As heat is the bulk manifestation of quanta of energy "carried" by the molecules involved, it seems natural to assume that damage caused by the excess heat acts primarily on the molecular level (or exclusively there for all practical purposes) in that energies between molecules are (randomly) exchanged. (Note that the energies of the molecules underlie some probability distribution and there is always a high energetic "tail" of the distribution whose molecules have great potential to do harm).

The consequences of the model are the following:
Aging acts on the molecular level at any stage of life, i.e. more and more bio-molecules get adversely modified. In the language of systems theory this means they "fail". If a critical threshold is reached, the structure one level higher, an organelle in our example, fails. If enough organelles of a cell have failed, the cell fails (a good example are **mitochondria**), and so on. I.e. the effects of aging propagates upwards in the hierarchy as time goes by. This is the key statement of the hierarchical theory of aging. This implies that in a young organism aging mainly plays out on the molecular level and it hardly manifests

itself macroscopically. (In other words, youthfulness rests on a huge redundancy on the molecular level).
Later in life as more and more higher level structures are affected there are typical physiological markers. E.g. a loss of energy as more and more mitochondria "fail" (understood in an appropriate sense).
In late life one expects age related failures on the second highest level, i.e. organ failures (strokes, kidney failures, etc.). This is exactly what is seen.
A hallmark of all of these failures is that a kind of "tension" builds up and once a critical threshold is reached, the disaster happens to a component on a relative short time scale - a kind of "avalanche effect". This also applies to the final manifestation of aging, whole body failure, that is death. (Such an abrupt behaviour is very reminiscent of the one seen in *self-organized critical systems*, but it not clear at this point if there is a connection).

To sum up, the prediction of the HTA is that there is a tendency in life for larger and larger structure to fail and in the end the whole body is doomed to fail, which means death.

How then can one understand the non-zero mortality rate of a young organism ? It is known that the major cause of death in young years are accidents. This means that an insult to one or several higher level structures (in essence to organs) is needed for death to happen in this case. E.g. car accidents, blockage of organs or excessive demands on them as is the case in a fatal alcohol intoxification. According to the HAL, these organ failures are fundamentally different from age related organ failures with regards to their pathology.

Some questions:

- As the theory allows for a mathematical modelling and a simulation on the computer, can one derive observed characteristics of aging, such as the *Gomperts law*, a *late-life mortality plateau*, the **late-life mortality convergence**, **power laws of aging** ? (Maybe one day I'll write a JAVA program and try to figure out). Using general properties of **networks** may serve as a guidance here.
- What is the right way of doing the "blocking" (a.k.a. coarse graining) of components (functional units) ? The scenario is very reminiscent of the one encountered in **renormalisation theory** an *effective field theory*. Can different coarse grainings reproduce known theories of aging, allowing one to interpret them as effective theories of biological aging, with the HAL being the fundamental underlying (microscopic) theory ?
- The omnipresence of **power laws** in biology hints at the presence of self-similar structures. Does this manifest itself in the topology of the network considered here ?

What would be the consequences for **life extension** if the model were right ? Basically one has two options:

- "Downstream fix": One lets the molecular damage happen and tries to remove it one a higher level (an approach taken by **SENS**). An efficient way is to implant new organs, a technology already available in many cases. Less

downstream one can try to apply **stem cell** technology (e.g. practiced in Parkinson's disease, where stem cells are implanted to compensate for missing dopamine-generating brain cells).

- "In situ fix": This boils down to molecular engineering and appears to be hardly feasible with current technology if at all. Although one can already fiddle a bit with the biochemistry with currently available pharmaceutical interventions, something much more radical seems to be required here (e.g. nanobots).

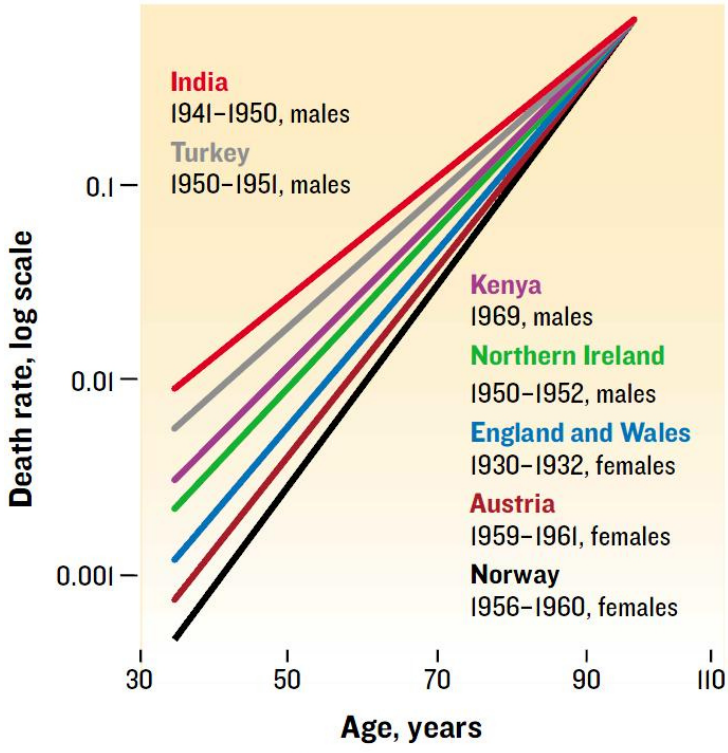
Papers:

- A Hierarchical Model for Aging (1997) - U. Geppert, H. Rieger, M. Schreckenberg local pct. 7

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Late-life Mortality Convergence

Late-life Mortality Convergence (a.k.a. **Compensation Law of Mortality**) refers to the finding that the relative differences in death rates between different populations of the same biological species decrease with age.



GEOGRAPHY IS NOT DESTINY: The compensation law of mortality shows that death rates in different populations converge for older people.

Explaining this behaviour poses great challenges to many **theories of aging**.

One theory that manages to come up with an explanation of the convergence of mortality rates is the *reliability theory of aging*.

Papers:

- The Quest for a General Theory of Aging and Longevity (2003) - L. A. Gavrilov, N. S. Gavrilova local pct. 40

Links:

- WIKIPEDIA - Compensation Law of Mortality

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Maximum Lifespan

Maximum Lifespan (also referred to as **Maximum Lifespan Potential** (**MLSP**) or **Maximum Longevity**), denoted ℓ here, is the longest recorded lifespan among specimen of a species.
Albeit not perfect, it is one of the best available estimators of a species' **aging rate**.
Alternative measures for the rate of aging are:

- **Mortality Rate Doubling Time** (**MRDT**).
- **Maximum Adult Lifespan**.

Although MRDT, like maximum lifespan, is not a perfect measure of the pace of aging at a physiological level, it has been argued that it is the more accurate one, however the debate on this issue has not been settled yet.

Maximum lifespan is affected by the size n of a sample. Some studies have estimated the numeric impact of n on ℓ to be $\ln(\ln(n))$.
Concerning humans, the MLSP is generally quoted as 120 years. This estimate is presumably a rounding of the longest authenticated human longevity record (122 years 164 days in 2004 - Jeanne Calment) to the nearest decade. This human longevity record emerges from hundreds of millions of accurate birth and death records. No other species comes even remotely close to matching this sample size. For example, records for longevity of different dog strains that are derived from pet insurance schemes currently include fewer than 10.000 estimated lifespan records for most dog breeds and these are among the better lifespan data available for mammals. Hence, it is important to take into account that MLSP for humans is an outlier in most analyses, not because humans are exceptionally long lived, but mostly because they are exceptionally well documented and have an enormous sample size.

See also:

- **Biological aging**
- *Gompertz-Makeham law of mortality*

Papers:

- Life and Death: Metabolic Rate, Membrane Composition, and Life Span of Animals (2007) - A. J. Hulbert , R. Pamplona , R. Buffenstein , W. A. Buttemer local pct. 346
- Brain Weight and Life-span in Primate Species (1993) - J. Allman, T. McLaughlin, A. Hakeem local pct. 105
- Correlations Between Physiology and Lifespan - Two Widely Ignored Problems with Comparative Studies (2005) - J. R.Speakman local pct. 75

Links:

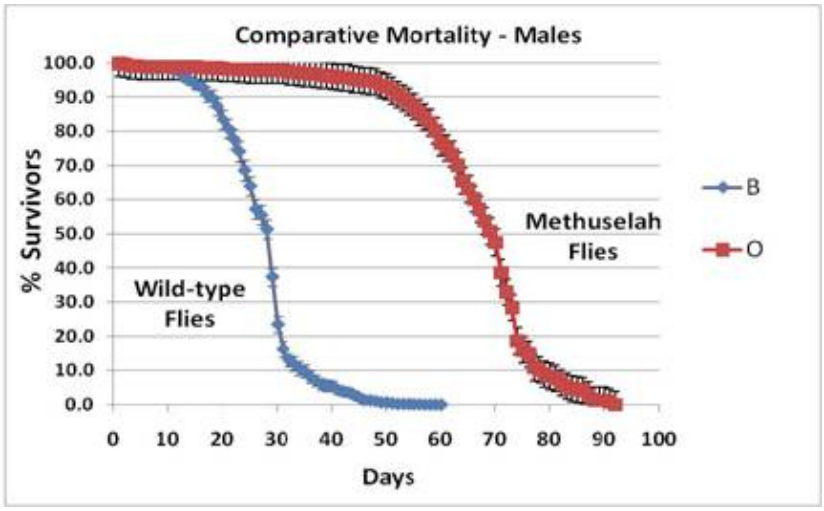
- WIKIPEDIA - Maximum Life Span
- WIKIPEDIA - Rate-of-Living-Theorie

- Homepage of Markus Maute - Biological Aging
- We'll soon all live to 120 years old - but this is probably the absolute limit, claims expert (2014) - V. Woollaston

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Methuselah Fly

In selective breeding experiments it has been demonstrated that the life span of wild type fruit flies (**drosophila melanogaster**) can be extended considerably. The resulting long lived flies are known as **Methuselah Flies** or **"Superflies"**.



Unlike the life extension of flies via the alteration of individual genes that regulate **biological aging**, the long-lived flies demonstrate a huge breadth and depth of genetic differences from ordinary flies. In fact it was shown that several hundred genes have an altered expression in the Methuselah flies.

As fruit flies and humans share most of their genes, including 70 percent of all known human disease genes, these experiments are relevant in regard to a better understanding of the genetic basis of human diseases and **aging**.

See also:

- **Evolutionary theory of aging**

Papers:

- The Effects of Chromosome Substitution on Male Body Weight of Drosophila Melanogaster (1966) - M. B. Seiger local pct. 10

Theses:

- Time Flies : Correlating Life-history Traits, Stress Resistance and Functional

Senescence to Longevity in Drosophila (2012) - J. Wit

Links:

- WIKIPEDIA - Drosophila Melanogaster
- WIKIPEDIA - Indy (Gene)
- Fine-Tuning Your Longevity Genes - B. Villeponteau
- AIs, Superflies, and the Path to Immortality (2010) - B. Goertzel
- Genomic Screens for Longevity Therapeutics

Videos:

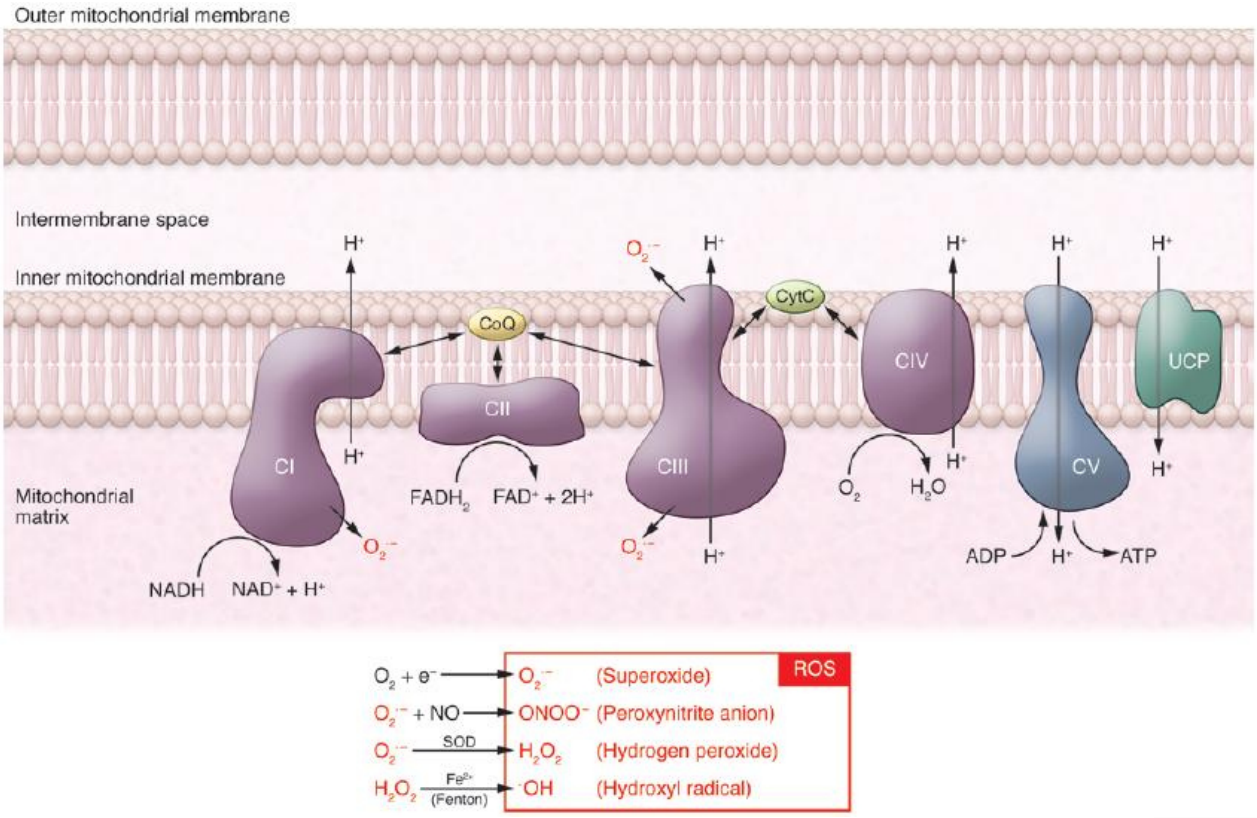
- Why and How do we Age....and is that Process Modifiable (2007) - R. Arking

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Mitochondrial Theory of Aging

The **Mitochondrial Theory of Aging**, which is a version of the **free radical theory of aging**, relates the rate of aging to the rate of damage to mitochondria, and in particular the rate of damage to **mitochondrial DNA** (mtDNA).

The *respiratory chain*, located in the inner mitochondrial membrane, is a main production site of superoxide, an abundant **reactive oxygen species** (ROS) in the cell formed at the level of complexes I and III during electron transport. The superoxide anion is converted to hydrogen peroxide by SOD. Although hydrogen peroxide itself is not a free radical, it can be converted to the highly reactive hydroxyl radical in the presence of transition metals through the Fenton reaction. The hydroxyl radical is considered to be the most damaging form of ROS, as it is highly reactive and causes oxidative damage to virtually every molecule type in the cell, including lipids, proteins, and nucleic acids.
On the other hand, ROS are not simply unwanted byproducts of oxygen metabolism, they also act as important signaling molecules to promote longevity. This possibility is further emphasized by a number of studies suggesting that ROS are important regulators of cell cycle progression, cell signaling, and apoptosis, among other processes. (See also **hormesis** in this context).



Starting in their 40s, every human begins to accumulate a particular mitochondrial mutation, which is severe, removing almost $1/3$ of the mitochondrial genome. It always occurs in the same sequence location, between a pair of 13 bp direct repeats. In addition to the ubiquitous common deletion, there have been hundreds of other different deletions reported in human mtDNA.

Papers:
Papers:

- A Systematic RNAi Screen Identifies a Critical Role for Mitochondria in C. Elegans Longevity (2001) - S. S. Lee, R. Y. N. Lee, A. G. Fraser, R. S. Kamath, J. Ahringer, G. Ruvkun local pct. 661
- New Insights into the Role of Mitochondria in Aging: Mitochondrial Dynamics and More (2010) - A. Y. Seo, A.-M. Joseph, D. Dutta, J. C. Y. Hwang, J. P. Aris, C. Leeuwenburgh local pct. 162
- Mitochondrial DNA and Aging (2004) - M. F. Alexeyev, S. P. Ledoux, G. L. Wilson local pct. 146
- The Role of Mitochondrial DNA Mutations in Aging and Sarcopenia: Implications for the Mitochondrial Vicious Cycle Theory of Aging (2008) - A. Hiona, C. Leeuwenburgh local pct. 135
- The Role of Mitochondria in Aging (2013) - A. Bratic, N.-G. Larsson local pct. 109
- A Midlife Crisis for the Mitochondrial Free Radical Theory of Aging (2014) - J. A. Stuart, L. A. Maddalena, M. Merilovich, E. L. Robb local pct. 9
- Mitochondrial Biogenesis Drives a Vicious Cycle of Metabolic Insufficiency and Mitochondrial DNA Deletion Mutation Accumulation in Aged Rat Skeletal Muscle Fibers (2013) - A. Herbst, C. J. Johnson, K. Hynes, D. McKenzie, J. M. Aiken local pct. 4
- Bioinformatics Applied to Mitochondrial Medicine - D. C. Samuels local pct. 0

Links:

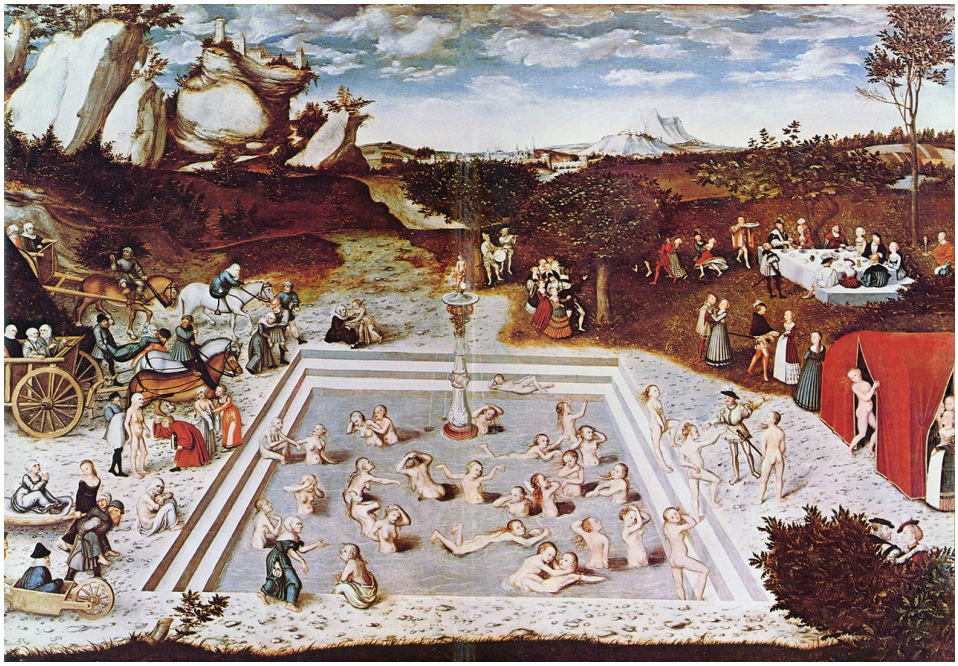
- Steadily Rising Increases in Mitochondrial DNA Mutations Cause Abrupt Shifts in Disease (2014)

Videos:

- Heritable Conditions in Mitochondria and their Genetic Basis in Qi - D. Wallace (starts at 16:00)
- Mitochondrial Paradigm for Degenerative Diseases, Aging and Cancer - D. C. Wallace

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Rejuvenation



In theory, (whole body) **Rejuvenation** of a biological organism means

$$\int_{t_1}^{t_2} \dot{S}_{age}\, dt < 0$$

for a significant period of time $t_2 - t_1 > 0$.
As biological systems are open systems, rejuvenation is not in conflict with the laws of **thermodynamics**.
Assuming a monotonically decreasing modified rate of aging $\dot{S}'_{age} \equiv \dot{S}_{age} - \dot{S}_{rev}$, where $\dot{S}_{age}$ is the "natural" rate of aging and $\dot{S}_{rev}$ is a compensating rate due to technological progress,

$$\dot{S}_{age} < 0, \quad t > t_1$$

with t_1 some time in the future when a "break even" between the natural rate of aging and the compensating rate due to interventions is reached. $\dot{S}_{rev}$ is related to the **Longevity Escape Velocity**, both being zero at t_1.

Much simpler than whole body rejuvenation is rejuvenation of parts of the body

which is already state of the arts in the form of organ transplantations on the level of organs and stem cell therapy on the level of cells.
Big challenges are a rejuvenation on the molecular level and on the organ level when it comes to the **brain**.
Given the problems with a whole brain rejuvenation, there seems to be no way around "going molecular" on the long run in order to be able to do a profound whole body rejuvenation.

See also:

- **Thermodynamics of biological aging**

Links:

- WIKIPEDIA - Rejuvenation
- WIKIPEDIA - Longevity Escape Velocity
- WIKIPEDIA - Fountain of Youth

Videos:

- Young blood rejuvenates older animals, studies show (2014) - A. Cochran
- Battery Rejuvenation by Peter Lindemann - Sep 5, 2013

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Survival Function

The **Survival Function** $S(t)$ (also called **Reliability Function**) describes the reliability of a system (or component) which is the probability that it will carry out its mission until time t.

$S(t)$ is the probability $P(t)$, that the failure time T, is beyond time t. Thus, the reliability function is defined in the following way:

$$S(t) = P(T > t) = 1 - P(T \leq t) = 1 - F(t)$$

where $F(t)$ is a cumulative probability distribution function.

A good illustration of the reliability function $S(t)$ is a survival curve describing the proportion of those still alive at time t.

Examples

(i) Exponential distribution

Survival rate:

$$S(t) = e^{-\lambda t} \equiv S_e(t)$$

This is equivalent to the "decay law" in physics if one sets $S(t) \equiv N(t)/N(0)$ and identifies λ with the decay constant.

Failure rate:

$$\mu(t) = -\frac{\dot{S}}{S} = \lambda = \text{const.}$$

(ii) Weibull distribution

$$S(t) = e^{-\lambda t^{\nu}}$$

$$\mu(t) = \lambda \nu t^{\nu-1}$$

(iii) *Gompertz-Makeham distribution*

$$S(t) = e^{-\frac{a}{b}(e^{bt}-1)} e^{-\lambda t} = e^{-\frac{a}{b}(e^{bt}-1)} S_e(t) = e^{-\frac{a}{b}e^{bt} - \lambda t + \frac{a}{b}}$$

$$\mu(t) = a e^{bt} + \lambda$$

Papers:

- Aging, Natural Death, and the Compression of Morbidity (1980) - J. F. Fries local pct. 3244
- Plasticity and Rectangularity in Survival Curves (2011) - B. M. Weon, J. H. Je local pct. 2

Lectures:

- Mathematical Hazards Models and Model Life Tables Formal Demography (2005) - J. H. Jones local

Links:

- WIKIPEDIA - Survival Function
- WIKIPEDIA - Cumulative Distribution Function

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Theory of Quasi Synchronous Aging

Links:

- Homepage of Markus Maute - Biological Aging

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Thermodynamics of Biological Aging

A living system is an open system far from thermodynamic equilibrium, therefore attempting to describe it by means of **nonequilibrium thermodynamics**

seems to be adequate.
It is a driven system, i.e. for it to stay alive, a continuous input of energy is imperative. This energy must have a comparably low **entropy**. Furthermore, a living system is a **dissipative structure** and it has been conjectured that the **maximum entropy production principle** applies to it. A crucial property of nonequilibrium thermodynamics (compared to **equilibrium thermodynamics**) is that entropy is a local property (i.e. a classical field).
Therefore entropy changes of a living organism are given by the **total differential**

$$dS(\vec{x},t) = \langle \vec{d}\,x|\vec{\nabla}\rangle S(\vec{x},t) + dt\partial_t S(\vec{x},t)$$

which is equivalent to

$$\frac{dS(\vec{x},t)}{dt} = \langle \vec{v}|\vec{\nabla}\rangle S(\vec{x},t) + \partial_t S(\vec{x},t)$$

If one defines an entropy density $s(\vec{x},t) \equiv \frac{dS(\vec{x},t)}{dV}$ and an entropy flux $\vec{v}(\vec{x},t)s(\vec{x},t) \equiv \vec{j}(\vec{x},t)$, the following continuity equation for the entropy density results

$$\frac{ds(\vec{x},t)}{dt} = \langle \vec{\nabla}|\vec{j}(\vec{x},t)\rangle + \partial_t s(\vec{x},t)$$

$\partial_t s(\vec{x},t)$ is an entropy source, describing the internal rate of entropy production and is related to the irreversible phenomena that occur within the living organism (chemical reactions, heat transfer, mass transfer, and so forth), and is nonnegative, that is

$$\begin{aligned} \partial_t s(\vec{x},t) &= 0 \quad \text{(reversible processes)} \\ \partial_t s(\vec{x},t) &> 0 \quad \text{(irreversible processes)} \end{aligned}$$

In fact, due to the omnipresence of thermal fluctuations - as biological system always operate at a temperature way above absolute zero - and due to *quantum fluctuation*, which are however quantitatively negligible here, the equality is never realized.

A hallmark of a living system is its quite distinct boundary, allowing one to clearly distinguish an interior and an exterior, the environment. The interface is the surface of a species, demarcated by its skin, cell membrane, etc., which however is somewhat difficult to define exactly, as it actually is a **fractal**. Yet in the context of thermodynamics a simple geometric approximation relating area and volume can be used (in the most idealized case even a sphere; see also **idealizations in physics**).
Due to the existence of a boundary, the integral form of the continuity equation is of foremost importance, allowing one to talk about entropy budgets (what goes in, what goes out, etc.). It reads

$$\boxed{\frac{dS}{dt} = \int_A \langle d\vec{A}|\vec{j}_{in}\rangle - \int_A \langle d\vec{A}|\vec{j}_{out}\rangle + \frac{\partial S}{\partial t} \equiv \dot{S}_{in} - \dot{S}_{out} + \dot{S}_{gen}}$$

where

- $\dot{S}_{gen}$ is the overall entropy generation rate within the body (including thermal and quantum fluctuations).
- $\dot{S}_{in}$ is the entropy taken up per unit time in the form of food, radiation (thermal radiation, sun light), heat (via convection, conduction), air being

inhaled, radioactive radiation, toxins, carcinogens, harmful bacteria, viruses, etc.
- $\dot{S}_{out}$ is the entropy released per unit time in the form of thermal radiation (and maybe also **biophotons**), air being exhaled, urine, feces, heat (transpiration), etc.

The crucial quantity in regards to **aging** (at least from the perspective of thermodynamics) is the l.h.s., $\frac{dS}{dt} \equiv \dot{S}_{age}$, which reflects the rate of aging. It is the uncompensated part of the entropy which accumulates in the body, increasingly weakening it.
Unfortunately the equation doesn't tell us anything about the actual value of $\dot{S}_{age}$ which is system-dependent. It is the entropy the body cannot get rid off and there are many different ways this can happen, the number of aging theories, trying to pinpoint specific causes, being a reflection of this fact.
Therefore, crucial characteristic parameters of the aging process, like the **maximum lifespan** cannot be computed without further input, which due to the sheer complexity of an organism, and as a consequence of the current impossibility to model it well enough heavily relies on experimental data. The approach therefore must be a highly phenomenological one.
Actually the entropy continuity equation is so general that it applies both to animate and inanimate matter. (E.g. in case of a car, its rate of rusting depends on the quality of its coating).

Some observations, remarks, speculations:

- If $\dot{S}_{age}$ where always zero, the organism would not age at all and if no accidents happened to it, it would be **immortal**.

- One must have $\dot{S}_{age} \ll \{\dot{S}_{gen}, \dot{S}_{in}, \dot{S}_{out}\}$, otherwise the organism would age extraordinarily quickly and life presumably would not be possible (the sophisticated repair mechanisms of cells, e.g. **DNA repair**, being a manifestation of this requirement). If one considers the thermodynamics of an organism on short timescales compared to its typical lifespan $\dot{S}_{age} = 0$ may be a good approximation (e.g. in conventional calorimetry).

- If a biological system would be completely isolated it would rapidly deteriorate and die, as $\dot{S}_{age} = \dot{S}_{gen}$. The critical factor seems to be the uptake of O_2 and the release of CO_2 without which an organism based on *oxidative phosphorylation* presumably dies within seconds or minutes.

- There seems to be an **evolutionary** reason why maximum entropy production applies, at least at times. It is based on the advantage of having the maximum power P possible available in critical situations (e.g. when running away from a lion, or when lifting off the ground in case of insects or birds). I.e. the adaption of an organism to its environment is optimized. Due to the **first law of thermodynamics** $\frac{\dot{U}}{T} \propto \frac{P}{T} + \dot{S}_{gen}$, that is due to the imperfect transformation of internal energy into work, the maximization of entropy production $\dot{S}_{gen}$ is a consequence of the maximization of P. (Like

with modern computers, that almost allow for frying eggs on the CPU :-)).

- Part of $\dot{S}_{in}$ is fixed by the specific environment (e.g. the radiation background), therefore an organism, due to its chemical structure, is first of all required to counter it to avoid rapid aging. Contrary to a stone of granite, for example, which due to its chemical composition ages very slowly, a piece of meat laid into the sun decays very quickly. (And so do people once taken out of the (cooled) morgue).

- Due to the existence of **allometric scaling laws** for organisms, the problem of computing aging related parameters can be reduced to the problem of computing them for a single eukaryotic cell. I.e. the quest is to understand the molecular basis of aging on the level of the cell. Scaling up the cellular parameters to the whole of the organism is quite well understood in terms of the cellular topology of organisms (it's a matter of geometry and not of thermodynamics).

- A characteristic feature of life distinguishing it from many forms of inanimate matter is its potential to *self organize*. For this to happen work is required (energy associated with low entropy), thereby producing heat and dissipation as a byproduct. Therefore $\dot{S}_{gen}$ is expected to be high.

- $\dot{S}_{age} < 0$ means **"rejuvenation"**, which naturally doesn't occur (at least not in mammals and hence in us humans). In order to satisfy this condition, sophisticated interventions would be required (which means overcoming the limited lower level "biochemical intelligence" by higher intelligence of the collective of human **brains**).
  It should be stressed that there is no fundamental reason why $\dot{S}_{age} < 0$ cannot be achieved. This condition should not be confused with the inequality related with the **second law of thermodynamics** which is less general. If in our case $\dot{S}_{in} = S_{out} = 0$, then necessarily $\dot{S}_{age} > 0$ which is nothing but the second law of thermodynamics which shows up as soon as we close the system. (In this situation any biological system would quite rapidly relax to equilibrium as dictated by the second law). That implies that there are roughly two ways to achieve rejuvenation, the one is the manipulation of in- and out fluxes of entropy and the other one the "fiddling" with the internal biochemistry and the **genome**. To summarize: The second law of thermodynamics does not necessitate the aging of a biological organism ! (An argument commonly found, presumably because some people are only familiar with equilibrium thermodynamics and its global properties).

- It seems useful to split up $\dot{S}_{age}$ into a macroscopic and a microscopic term. The macroscopic term mainly describes large scale effects leading to a suboptimal aging, e.g. obstructions of organs. For a population this manifests itself in a deviation of the *Gompertz mortality curve* from a rectangular form. This is where medical interventions can already do quite much. The microscopic term describes the fundamental aging process closely related to a species specific maximum lifespan. Concerning fundamental aging on the molecular level the reach of medicine has been quite limited so far.

Possible health implications

Thermodynamics suggests the following measures in order to slow down aging:

- Keep the output of entropy as high as possible, which means maximizing $\dot{S}_{out}$ by drinking enough water, maintaining a good blood circulation, sweating, detoxification, having a high protein turnover, giving optimal support to the functioning of excreting organs like the liver, kidneys and gut (e.g. avoidance of constipation), etc.
- Keep the influx of entropy as low as possible, which means minimizing $\dot{S}_{in}$ by avoiding toxins and too much x-raying at the doctor, eating a low entropy diet like raw foods and little or no processed foods, etc.
- Keep internal entropy production $\dot{S}_{gen}$ (i. e. the *BMR*) reasonably low. Candidates for achieving this seem to be fasting, **calorie restriction** and sports.
- Prefer foods that are efficiently burnt, like carbohydrates and fats. Proteins are quite inefficiently burnt and thus should be limited to what is required by the body for maintaining its structure and functionality (see also **low protein diet**).
- At first sight eating of *ATP* seems to be the ideal way of substantially decreasing the need for internal entropy production, but there is a big catch to this: One had to eat an amount of ATP a day that is of the order of the whole body mass, which is hardly feasible if not impossible. (Given the market prices for ATP supplements, the costs would be astronomical).

See also:

- **Biological thermodynamics**

Papers:

- Entropy Generation and Human Aging: Lifespan Entropy and Effect of Physical Activity Level (2008) - C. Silva, K. Annamalai local pct. 29
- Entropy Generation and Human Aging: Lifespan Entropy and Effect of Diet Composition and Caloric Restriction Diets (2009) - C. A. Silva, K. Annamalai local pct. 21
- Metabolic Networks Evolve Towards States of Maximum Entropy Production (2011) - P. Unrean, F. Srienc local pct. 18
- Entropy Stress and Scaling of Vital Organs over Life Span Based on Allometric Laws (2012) - K. Annamalai, C. Silva local pct. 2
- The Gouy-Stodola Theorem in Bioenergetic Analysis of Living Systems (Irreversibility in Bioenergetics of Living Systems) (2014) - U. Lucia local pct. 1
- Thermodynamic Approach to the Aging Process of Biological Systems. (2002) - S. J. M. Nieto-Villar, J. Rieumont, R. Quintana, J. Miquel local pct. 0
- Another Way of Looking at Entropy: Entropy and Aging, Evolving Systems (1989) - D. Hershey local pct. 0

Links:

- WIKIPEDIA - Continuity Equation

Videos:

- Do Living Things Defy Entropy?--Consider the Following With Bill Nye

Your comments are very much appreciated. Suggestions, questions, critique, ... ?

Wear and Tear Theory of Aging

The **Wear and Tear Theory of Aging** states that **biological aging** is due to an accumulation of damage over time in a species. In terms of **thermodynamics** this means that the intrinsic **entropy** increases. As biological systems are open systems, part of the entropy produced can be forwarded to the environment.

Part of the intrinsic and local entropy increase can be reversed because the initial information (prior to damage) is still available in some other place (i.e. there is a backup of information, or in other words, biological system exhibit redundancy of information). Such copies of information are harnessed by repair processes (e.g. **DNA repair**). However these reconstructions are limited for the following reasons:

- Repair is never perfect, the repair process itself can be afflicted by spontaneous errors.
- The backup of information can also be corrupt, which is not recognized. This problem increases with time, leading to to a "downward spiral".

Notwithstanding these limitations, repair mechanisms - like DNA repair - can have an impressively high degree of fidelity.

Besides these in principle repairable errors there are errors for which there is no adequate natural biochemical response. Either there was no selection pressure during **evolution** that lead to an implementation of adequate processes or evolution simply couldn't come up with something addressing these damages.

Historical

The wear and tear theory of aging was introduced by Dr. August Weismann, a German biologist, in 1882.
The theory still sounds perfectly reasonable to many people, because wear and tear is what happens to most familiar things around us. Like components of an aging car, it appears as though cells and tissues of the body eventually wear out from repeated use, killing them and then the body.

Papers:

- The Essential Mechanisms of Aging: Irreparable Damage Accumulation of Biochemical Side-reactions (2005) - D. Yina, K. Chen local pct. 123
- Aging Is Not a Process of Wear and Tear (2010) - J. Mitteldorf local pct.12

Your comments are very much appreciated. Suggestions, questions, critique, ... ?