Adaptive ageing theory of faster adaptation and inconsistency of the conventional selection shadow evolutionary theory of ageing.

Arsen Korpetayev.

Newcastle University, School of Computing.

a.korpetayev1@newcastle.ac.uk

KEYWORDS: Evolutionary Biology, Evolution of ageing, Adaptive ageing, Selection shadow.

ABSTRACT: Selection shadow has been the conventional theory of evolution of ageing for decades. I argue that selection shadow is merely a phenomenon by which deleterious mutation will be inevitably passed on if they manifest only after mating. However, to explain prevalence of ageing, the authors of the conventional theory erroneously equated passing on and persistence by interpreting selection shadow as if "selection pressure is decreased after mating" and for the same reason assumed that ageing is deleterious[1,2]. In their conventional framework, although ageing is assumed to be deleterious, it is immune to natural selection, due to happening after mating i.e. being in the selection shadow. In reality selection pressure still remains after mating in form of the need to feed offspring and so also in form of inter- and intraspecies competition and predation avoidance etc. I show that the conventional selection shadow theory is therefore inconsistent, since shadowed counteracting "positive" mutations will inevitably pass with "negative" mutations, resulting in individuals that do not age. And so, since ageing is assumed to be deleterious in this conventional framework, inevitable non-ageing individuals will outcompete ageing ones in intra- and interspecies competition for similar ecological niches. This way the inconsistency of the conventional theory of selection shadow predicts that non-ageing organisms will prevail, which is not what we observe. Recently, some articles incline towards adaptive theory of ageing i.e. ageing as an advantageous mechanism. However, the ground of such inclination has mostly been reduced competition for food and space between parents and offsprings[3,4]. I show that ageing allows for increased reproduction rate, while maintaining optimal population size. As a result of promoted reproduction rate, rate of introduced germline mutations is increased, which means faster adaptation. Faster adapting ageing individuals outcompete non-ageing slower adapting individuals that occupy similar ecological niches, inter and intraspecies. Therefore, since ageing is obviously advantageous, this means that all experimental evidence that supported selection shadow theory of ageing[5–9], also support the proposed adaptive theory of faster adaptation, the difference is interpretation: investigated pleiotropic mutations are not antagonistic after all, and *mutation accumulation* actually accumulates positive germline ageing mutations. Based on genome analysis[10] of the longest living mammal – bowhead whale, I also propose that mutations in DNA repair proteins are a mechanism to tune ageing by natural selection when optimal population size is changed by long lasting shifts in ecosystem, such as new food source. I suggest that DNA repair complexes are purposely of lowered fidelity to allow for somatic mutations to accumulate and so to increase deathrate by ageing leading to faster adaptation.

IMPACT OF AGEING IN THE WILD

Notion that animals rarely die from old age in the wild is erroneous. While, you rarely see a wrinkled lion that has hard time walking, lions grow out of their prime, become slower, weaker and generally deteriorate with age as any other animal, with a few known exceptions such as hydras. In animals, fitness decreases with age, and this kills them, whether they cannot catch enough prey anymore, or run away from a predator, or by weakened immune system, cancer, physiological dysfunctions, retarded tissue repair, or by getting displaced from their social position by younger animals in their prime. There are so many ways ageing kills animals. People are biased to think ageing does not affect animals as much, because comparatively smaller age-related deterioration is enough to make a big difference in the demanding wild, comparatively to what we usually associate with getting old in our comfort environment, where we don't have to be in our physical and physiological prime in order to survive, especially with medicine. For us old is not when you are not in your physical prime, but when your organs start to fail.

INCREASED ADAPTABILITY AS AN EVOLUTIONARY ADVANTAGE OF AGEING.

Now that we established that ageing is a universal sprint toward death, why so? The proposed theory seems to have a strong answer. Since resources are limited, reproduction rate must be balanced by death rate to maintain an optimal population size. Mutations, that disrupt this balance by increasing reproduction, lead to hunger and subsequent death i.e. they are inevitably selected against: a wolf that makes too many pups will not be able to catch enough prey to feed them, and even if enough prey is caught, wolves will run out of prey. However, the more often individuals reproduce, the more germline mutations are explored in a given time, meaning that the species adapts faster. Number of germline mutations in one offspring cannot be increased significantly for better adaptability, because there is a balance between exploring new adaptations and destroying established ones. It was mathematically derived that maximum germline mutations in one offspring that is still compatible with adaptation has to be less than one mutation per genome[11], this fits with data from organisms with recorded germline mutation rate e.g. 0.16 for humans and 0.49 for mice. This is why increasing reproduction rate is essential for faster adaptation. But we have just said that there is a limit to reproduction rate as well, it should not lead to population size

exceeding optimum. This is where ageing comes in. By increasing death rate, ageing allows for higher reproduction rate and so faster adaptation, while still maintaining optimal population size. In the absence of ageing, individuals would only die from predation, injury, deadly disease, climate change and from other environmental causes. Ageing increases death rate significantly, as we have discussed in the first section of the article.

x - number of individuals, $\dot{r}$ - reproduction rate, $\dot{d}$ - death rate from non-ageing causes, $\dot{a}$ - additional death rate caused by ageing

$$\frac{dx}{dt} = \dot{r} - \dot{d}$$

To maintain optimal population size after adding ageing, reproduction rate has to increase

$$\frac{dx}{dt} = \dot{r_2} - \dot{d} - \dot{a}$$

$$\dot{r} - \dot{d} = \dot{r_2} - \dot{d} - \dot{a}$$

$$\dot{r_2} = \dot{r} + \dot{a}$$

As a result of increased death rate from ageing, reproduction rate is allowed to increase, while still maintaining optimal population size. Ultimately, ageing increases turnover. It means that in a given time, there has been more offspring with new germline mutations, therefore ageing organisms will have explored more genetic sequences in search of possible adaptations compared to non-ageing organisms. This way, ageing organisms are faster at adapting to existing and new environments, and after some time they outcompete non-ageing inter- and intraspecies organisms in similar ecological niches, despite having aged individuals. This leads to a conclusion that ageing is a deliberate mechanism that is selected for, contrary to current convention of ageing being merely not selected against enough. Additionally, ageing makes death rate less stochastic and therefore makes it easier to stably maintain optimal population size. I propose a genetic mechanism by which ageing is tuned by natural selection to meet new optimal population size changed by long term shifts in ecosystem, such as new food source. The proposed mechanism is based on genome analysis of long living animals.

GENETIC MECHANISMS FOR TUNING OF AGEING RATE BY NATURAL SELECTION.

Genome analysis of bowhead whales[10], that live past 200 years, revealed bowhead-specific mutations and duplications in genes associated with DNA repair and therefore with cancer and ageing, such as mutations in ERCC1 and duplication of PCNA. This finding suggests an appealing mechanism by which ageing rate can be easily tuned by natural selection to match changes in optimal population size that happen due to long term shifts in ecosystem, such as new food source, climate change and so on. Mutations can increase or decrease performance of DNA repair proteins such as ERCC1. This means that DNA repair mechanisms are deliberately of lowered fidelity i.e. they are tuned to miss mutations from DNA damage or DNA replication at a certain rate. This way, progenitor and stem cells accumulate the damage and somatic mutations over years and start to give rise to mutated differentiated cells, which leads to organs with loss of function and ageing associated disease. In organs with long living differentiated cells, these cells also accumulate the deleterious somatic mutations. The accumulated somatic mutations will disrupt functional proteins, signalling and signal processing (thus cancer) and have many other deleterious effects. Structural proteins such as collagen and elastin will be corrupted and blood vessel and skin will lose elasticity, heart loses structural strength. Signal processing dysfunction cause diabetes, heart arrythmia, cancer etc. Age disease are numerous.

When long lasting environmental changes allow for increase in population size, e.g. new food source, mutations that promote reproduction rate are selected for. After the new optimal size is reached, to maintain it, selection favours mutations that increase ageing rate. It allows to keep reproducing more often, speeding up the search for possible adaptations. Now if there was no ageing, reproduction rate would have to slow down again to maintain the new optimal population size, individuals would have to come back to reproducing less often, therefore slowing adaption.

CRITIQUE OF CONVENTIONAL SELECTION SHADOW THEORY OF EVOLUTION OF AGEING

Currently conventional view of evolution of ageing postulates that ageing is deleterious, but still persists, because “selection pressure is minimised after mating”. The view consists of two main theories developed in the past 50 years or so:

1. *Mutation accumulation*[1]. Germline mutations with negative effects are passed on if the negative effects begin to manifest only after the individual has probably already mated.
2. *Antagonistic pleiotropy*[2]. Pleiotropy is when a gene has more than one distinct phenotypic consequences. The theory says that pleiotropic genes that help to mate, but then manifest negative effects later in life, will still pass on.

The time after mating is called selection shadow, because negative germline mutations will inevitably pass on if they manifest only after mating, but the theories erroneously equate passing on and persisting by stating that selection pressure is minimised in this shadow. Selection pressure still remains in forms of the need to feed offsprings, therefore also in forms of competition for the same ecological niche and avoidance of predation. Therefore, contrary to the convention, shadowed negative germline mutations are not immune to natural selection. The two theories were used to explain why organisms age. They say that negative effects in the selection shadow is what ageing is, that we observe ageing although it is deleterious, because “selection pressure is decreased after mating”, the theories suggest. In evolution, if a germline mutation passes on, it does not at all mean that the mutation will persist in the long term, the logic is obvious. I will show the inconsistency of the conventional shadow selection theory by an example: Negative germline mutations can be counteracted with positive germline mutations, by means of protein inhibition, epigenetic silencing, transcription inhibition, ubiquitination and with many more mechanisms that would silence harmful proteins. Gene duplications of healthy alleles will substitute the silenced harmful allele. In the theories’ framework ageing mutations are negative, and therefore such age-counteracting mutations are positive. Since, both are in the shadow, they will inevitably pass on together. There will be individuals that have these shadowed negative ageing mutations counteracted by positive anti-ageing mutations. So, they will not age, and if ageing is assumed to be deleterious, they simply outcompete ageing individuals in the competition to feed offsprings. We know that it does not happen, because ageing is prevalent, therefore the theories are wrong and inconsistent. The inconsistency stems from assuming that ageing is deleterious and from thinking that selection pressure is decreased after mating and so shadowed negative germline mutations could be immune to

natural selection. Selection shadow is simply a phenomenon when germline negative mutations are passed on if they manifest after mating, however it does not at all mean that they will stay in the population. It just happens that ageing is advantageous on proper evolutionary time scales and therefore negative germline mutations under *mutation accumulation* and *antagonistic pleiotropy* are not after all negative, but positive and persist under standard rules of natural selection. This means that all experimental evidence that supported selection shadow theory of ageing[5–9], also support the proposed adaptive theory of faster adaptation, the difference is interpretation: investigated pleiotropic germline mutations are not antagonistic after all, and *mutation accumulation* accumulated positive germline mutations.

REFERENCES

1. Medawar, P. B. *Unsolved problem of biology*. (1952).
2. Williams, G. C. *Pleiotropy, Natural Selection, and the Evolution of Senescence*. (1957).
3. Muller, A. W. J. Aging is an adaptation that selects in animals against disruption of homeostasis. *Med. Hypotheses* **119**, 68–78 (2018).
4. Werfel, Justin, E. Ingber, D. & Bar-Yam, Y. Programed Death is Favored by Natural Selection in Spatial Systems. *Phys. Rev. Lett.* (2015) doi:https://doi.org/10.1103/physrevlett.114.238103.
5. Lampidis, T. J. & Schaiberger, G. E. Age-related loss of DNA repair synthesis in isolated rat myocardial cells. *Exp. Cell Res.* **96**, 412–416 (1975).
6. Karran, P., Moscona, A. & Strauss, B. Developmental decline in DNA repair in neural retina cells of chick embryos. Persistent deficiency of repair competence in a cell line derived from late embryos. *J. Cell Biol.* **74**, 274–286 (1977).
7. Gensler, H. L. Low level of u.v.-induced unscheduled DNA synthesis in postmitotic brain cells of hamsters: possible relevance to aging. *Exp. Gerontol.* **16**, 199–207 (1981).
8. Vijg, J. Aging genomes: A necessary evil in the logic of life: Prospects & Overviews. *BioEssays* **36**, 282–292 (2014).
9. De Meyer, T. *et al.* Telomere Length as Cardiovascular Aging Biomarker. *J. Am. Coll. Cardiol.* **72**, 805–813 (2018).
10. Keane, M. *et al.* Insights into the Evolution of Longevity from the Bowhead Whale Genome. *Cell Rep.* **10**, 112–122 (2015).
11. Nowak, M. A. *Evolutionary Dynamics: Exploring the Equations of Life*. (Harvard University Press, 2006). doi:10.2307/j.ctvjghw98.