Utrecht University

Doubling the human lifespan

An interdisciplinary approach to longevity extension

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1. Introduction

The elixir of eternal youth, a centuries old concept of a means to obtain everlasting life in a healthy young body. The elixir and similar concepts have persistently returned in fiction, myth, and faith throughout the centuries with different connotations from a virtue to a curse but always something that seemed unobtainable. Already in ancient Egypt, civilization sought to achieve eternal life through means of mummification which was said to make the soul live forever (Pettis, 2010).

In current days, while eternal life is still far from within reach, recent medical and technological advancements have had a significant influence on the duration of our lives. The average life expectancy, the average age at which humans pass away, has steadily been increasing ever since data has been obtained have started obtaining data (Oeppel, Vaupel, 2003). Since this increase does not seem to be slowing down, this suggests that there are no boundaries to the age humans might be able to reach in the future. However, debate exist, as other research points towards a limited maximum age and suggests that clear boundaries exist to the maximum age humans can reach (Dong *et al.,* 2016).

Furthermore, with technology developing at an unprecedented pace, an extension of the human lifespan seems (at least to some extent) to become possible in the future (Kaeberlein & Kennedy, 2009). However, the question of significant longevity extension is more complicated than merely technical feasibility.

Apart from the technical feasibility, more issues arise. Many people believe that tampering with biological mechanisms to such an extent blurs ethical lines and raises questions as to where the thin line between man and machine lies. Ethical issues are also found in health issues that usually go hand in hand with older age.

If, as a society, humans are moving towards a time where longevity extension will be a reality, it is important to take an interdisciplinary approach to the several factors coming into play. Therefore the following question is proposed::

"What needs to be done with respect to longevity extension to achieve a doubling of the healthy human lifespan?"

Disciplinary justification

The increase in the average human lifespan during the last century has mainly been due to our increased understanding of the human body itself and the causes of diseases (Costa, 2005). This increased knowledge has enabled researchers to develop better methods to combat a variety of diseases. For this reason, it is important to involve the field of Biomedical Sciences in this interdisciplinary study. Although our knowledge about the workings of the human body has significantly increased during the last century, it has become even clearer how much knowledge is still missing. To make up for this lack of knowledge, the field of Artificial Intelligence should be involved because of the enormous potential that AI has in providing researchers with new insights (Ramesh, Kambhampati, Monson & Drew, 2004). An example of this is found in the current application of Artificial Intelligence where Artificial Neural Networks (ANN's) assist physicians in making medical diagnosis based on a collection of medical data (Remzi et al., 2003).

Aside from the 'technical' aspects of the central question, it is also important to shed some light on the ethical aspects of this problem. New medical treatments and even the process of developing new medical treatments often lead to complex ethical issues (an example of this is found in prenatal technologies which bring new ethical issues on life and abortion on the table). New Media & Digital Culture has been chosen as a 3rd discipline and it will use philosophy of technology to look at these important ethical aspects of interdisciplinary study.

Disciplinary preludes

By using the insights of these disciplines the goal is to outline the several different issues that arise in achieving longevity extension. Three disciplines have been chosen because they embody three key aspects of longevity.

The field of Artificial Intelligence reaches beyond just the implementation of computational models like ANN's. The field of AI also contains theories and concepts that originate from psychology, philosophy, linguistics, and mathematics. The question that will be addressed is "How can Artificial Intelligence be used to double the human lifespan?". This allows for investigating both the current applications of AI, as well as future applications that might be classified as transhuman.

Through the discipline of Biomedical Sciences, the aging process is addressed. Several different mechanisms of aging exist. Biomedical Sciences seeks to define these mechanisms and gain better insight in the exact ways in which humans age. Biomedical Sciences is an absolutely vital discipline when looking at Longevity extension because, whilst many definitions of aging exist, it is most often defined as a biological process. Biomedical research provides us with better insight into this process and sheds a light on the possible use of therapeutics to increase life. Recently, 9 main biological principles through which humans may age have been addressed. The extent to which each of these principles contributes is not yet fully understood, however, it is thought that collectively these 9 principles are responsible to a significant extent. By specifically using one of these 9 hallmarks as an example, the following question will be addressed: "What are the biomedical possibilities and issues in altering the aging process?"

Through the discipline of Media and Culture Studies, the post-humanistic concept of the cyborg and cybernetic technologies will be explored. These technologies can be used to extend one's life and improve the quality of living. So far the technologies have come as far as providing people with implementations from electronic limbs to the less practical dialysis machines in hospitals. This is an area that still developing and a lot more might be possible in the future. This is also a subject surrounded by a lot of philosophical and ethical debate. The debate entails a lot of different issues and ideals from the extreme that people should ascend humanity and upload their consciousness into a computer to where the line between humans and technology lies. The Media and Culture Studies perspective will be used to look and the most important philosophical and ethical issues in relation to longevity by answering the question "What are the philosophical and ethical issues that need to be addressed before longevity through cybernetic technologies becomes viable?"

2. Artificial intelligence

2.1 Prelude

Due to various techniques within the field, Artificial Intelligence is especially interesting when it comes to medical problems. According to Ramesh, Kambhampati, Monson, and Drew (2004), Artificial Intelligence can be used in three different ways within clinical scenarios: diagnosis, treatment and predicting outcomes. Whether these tasks are carried out by (human) physicians or advanced computer systems, these researchers note that they can be seen as complex problems involving the analysis of complex medical data. The relevance of Artificial Intelligence in the task of doubling the healthy human lifespan is emphasized by their notion of Artificial Intelligence having the potential to be applied in almost every field of medicine. This potential makes the role of AI both important and challenging due to the various ways in which AI might contribute to a solution for the central question:

> "How can Artificial Intelligence be used to double the human lifespan?"

To see how Artificial Intelligence might help in doubling the healthy human lifespan, first the involvement of AI in making medical diagnosis will be investigated, both because AI is already quite extensively being used in this way (Ramesh et al., 2004), and because early and accurate diagnosis is mandatory for the successful treatment of diseases. This will also shed some light on how AI works when it is applied in the medical field. Subsequently, the role of AI in the actual treatment of diseases will be investigated, followed by how diseases might be prevented altogether using AI. Lastly, a more futuristic approach to solve the central problem is investigated that avoids most of the biological problems that prevent the healthy human lifespan from being doubled.

2.2 Application of Artificial Intelligence for making medical diagnosis

Before looking at the possibilities on how Artificial Intelligence might be used to extend the natural healthy lifespan, it is important to see where Artificial Intelligence currently stands within the medical world. Even back in the '50s, researchers were looking at ways to formalize the way of reasoning that was used by physicians when making a medical diagnosis (Ledley & Lusted, 1959, p. 9) and they underlined the potential of computers in the process of making medical diagnosis before computers were even capable of such feats. The researchers Ramesh et al. (2004) note computer systems wouldn't be merely limited to making medical diagnosis: "*The development of medical artificial intelligence has been related to the development of AI programs intended to help the clinician in the formulation of a diagnosis, the making of therapeutic decisions and the prediction of outcome.*" (pp. 334-335). They mention the use of four systems that support workers in the medical field: "*Artificial neural networks (ANN's), fuzzy expert systems, evolutionary computation and hybrid intelligence systems*" (p. 335).

Of these four systems, Artificial Neural Networks are being mentioned exponentially more often in publications during the period from 1965 to 1993 as seen in Figure 1:

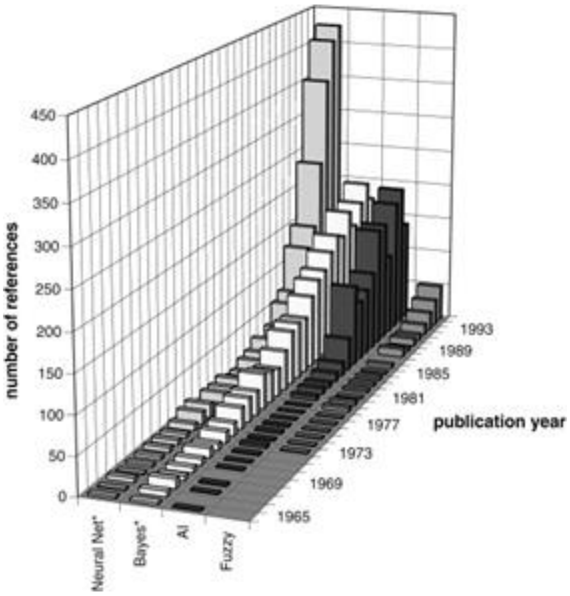


Figure 1. Mentions of 'Neural Networks', 'Bayes', 'Artificial Intelligence and 'Fuzzy' within publications in medicine (Steimann, 2001).

Artificial Neural Networks are described as computational methods inspired by networks of biological neurons (Remzi et al., 2003, p. 458). The use of Artificial Neural Networks stems from their ability to learn based on given examples and their ability to handle imprecise information (Ramesh et al., 2004, p. 335). This makes them especially suited for making medical diagnosis because a diagnosis is always a probabilistic issue (Ledley & Lusted, 1959). One of the current uses that Artificial Intelligence has in making medical diagnosis is found in analyzing CT-scans (Computerized Tomography), where neural networks can improve the accuracy of diagnosis (Matsuki et al., 2002). According to these researchers, the performance of all radiologists who were involved in their study was increased when an ANN was used to assist them ($p < 0.001$). When discussing the possible ways in which Artificial Intelligence might make doubling the healthy human lifespan possible, making accurate diagnosis as early as possible will give patients a higher chance of survival. Especially when people live longer, their vulnerability to diseases increases.

To answer the main question, it is important to look at how Artificial Intelligence is being used for this purpose. One of the techniques necessary to discover patterns that can subsequently be used for decision-making is data mining (Huang, Chen & Lee, 2007). These researchers describe a step-by-step model that is used to extract knowledge from a database (this database could, for example, contain medical data on a vast number of patients) as seen in Figure 2.

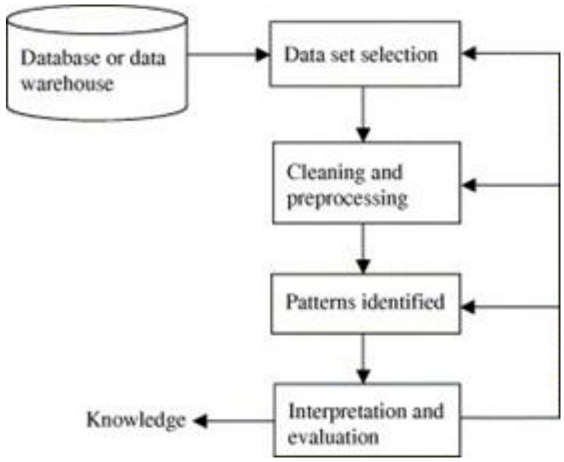


Figure 2. General model to extract knowledge from a database (Huang, Chen & Lee, 2007, p. 857)

To use this knowledge for automating the making of medical diagnosis, the system must be able to deal with changes in the environment (López & Plaza, 1996). They describe that the goal of such as system is to generate a set of sufficiently accurate diagnosis, where the main problem lies in comparing the situation of the current patient to one of the already known patients (it rarely happens that two patients have exactly the same background and symptoms). They refer to this approach as a case-based system, for which they developed a (partial) solution called BORELO.

These cases are represented as being based on pieces of cases and episodes. In BOLERO, a case is strictly "*a sequence of decision steps or episodes*" (López & Plaza, 1996, p. 35) with each episode being a pair of a situation and a plan, where the last plan is the solution of the case. Using this method, BOLERO will start with an initial plan and from there iteratively acquire more information and generate better plans until the diagnosis is known (p. 39). López and Plaza note that one of the strengths of this system lies in its ability to learn from its own experience by adding new cases to its database.

As shown, Artificial Intelligence is being involved increasingly in the medical world. Theories and methods developed within the field of AI can be used to significantly improve the accuracy of medical diagnosis. Due to more data being available for programs to train on, it can be expected that Artificial Intelligence will increasingly contribute to increases in the accuracy of making medical diagnosis. However, the use of Artificial Neural Networks isn't just limited to making medical diagnosis, but can also be found to contribute in treating diseases.

2.3 Treating diseases with the assistance of Artificial Intelligence

ANN's are used in decision support in cancer according to Lisboa and Taktak (2005). Since cancer is one of the diseases that seem to be closely related to someone's age, making better decisions in the treatment of cancer is particularly interesting when trying to extend the healthy human lifespan. The use of ANN's has been proven to be more successful than 'regular' statistical methods such as multivariate logistic regression (LR) (Remzi et al., 2003) within predicting the outcome of prostate cancer. The global architecture of this artificial neural network can be seen in Figure 3.

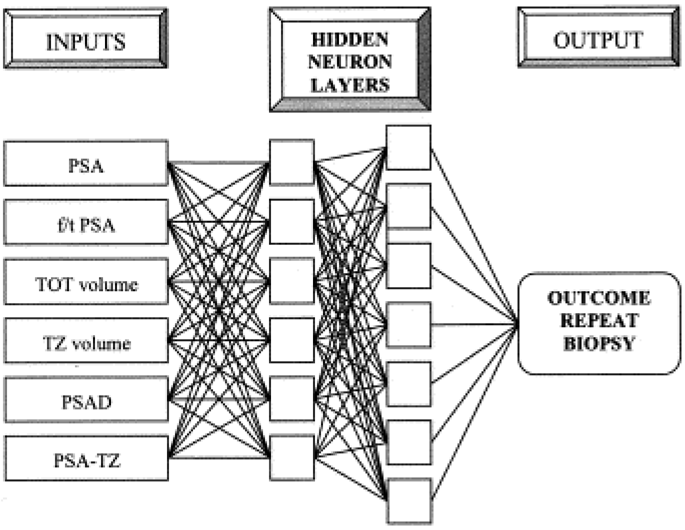


Figure 3. ANN architecture used in early detection of prostate cancer (Remzi et al., 2003, p. 457).

The advantage of using ANN's with their high accuracy for early detection not only increases the patient's chances of survival but can also reduce unnecessary biopsies (Remzi et al., 2003) and therefore reduce patients' anxiety. While it cannot be said that this necessarily means that ANN's will be more successful in each case, it does suggest that ANN's could prove to be invaluable in the near future when it comes to predicting the outcome of cancer, as well as predicting how effective certain treatments will be. This is especially the case because ANN's are becoming more capable every year due to new advances in both hardware and software. Remzi et al. (2003) also emphasize this and mention that the ANN used in their research could have been improved by adding more clinically relevant markers (inputs) such as body mass index. By adding more inputs, the network itself becomes more complex and will require more processing power and more efficient approaches to train them.

An example of how the training time of neural networks might be reduced by using innovative new approaches is provided by Raina, Madhavan, and Ng (2009) where they mention that as neural networks grow more and more complex, their training time on conventional CPU's can become exceedingly long. Therefore these researchers suggested massively parallel methods, which is something that GPU's are very efficient at. The need to parallelize the training of neural networks is further emphasized by the hardware power limit on the raw clock speed of single CPU's (Raina, Madhavan & Ng, 2009, p. 874). One implementation of using the GPU for training neural networks they mention is NVidia's CUDA programming model. Using the GPU does not only have advantages though: One of the disadvantages of using the GPU is the limited bandwidth of the GPU's memory. It should not be too surprising that GPU's still have disadvantages when it comes to training ANN's because the hardware wasn't specifically designed for that purpose. Miranda and Von Zuben (2016) also mention that even though the training of networks has already improved by using graphic processing units (GPU's), the time it takes to train new networks still limits the new methods that can be developed within research and industry. Because of that reason, and because of the increased interest during the past few years in making ANN's more powerful, companies like Google's TNU (Wu et al., 2016) and NVidia's Tesla GPU (Lyakh, 2014) have developed hardware specifically built for training ANN's. Aside from assisting in making medical diagnosis and treating diseases, the third use of Artificial Intelligence within the medical field is found in preventing diseases.

2.4 Preventing (age-related) diseases

As mentioned by Fontana (2009), slowing down or even reversing the ageing process can lead to a significant improvement in health. Not only during someone's normal biological lifetime but also beyond that, because slowing down or even reversing the ageing-process can help people live longer and healthier. Fontana also stresses that "*Additional studies are needed to understand the complex interactions of factors that regulate aging and age-associated chronic disease.*" (p. 1133).

As shown, Artificial Intelligence is already used for increasing the accuracy of medical diagnosis and in optimizing medical treatments, but the subject of preventing diseases in the first place has so far been left untouched. When attempting to prevent a disease, its underlying causes must be understood first. Regarding age-related diseases, these underlying causes are also responsible for the ageing-process itself (one example the accumulation of damage in DNA during someone's lifetime that can eventually lead to cancer). Thus, preventing age-related diseases might very well end up not only preventing these diseases, but also enable humans to stop ageing altogether.

In 2013 a paper was released by Douaud et al. where they described how artificial intelligence was used to help prevent Alzheimer's disease-related gray matter atrophy. It should be noted that their study mainly focused on preventing symptoms relating to Alzheimer's disease instead of preventing the disease in the first place, but preventing symptoms can be considered to be functionally the same as preventing the disease itself. This was done by using a Bayesian network to help discover patterns in their collected data (p. 9527). The workings of a Bayesian network are very well summarized by Friedman, Geiger, and Goldszmidt (1997): "*The problem of learning a Bayesian network can be informally stated as: Given a training set D = {u1,..., uN } of instances of U, find a network B that best matches D.*" (p. 135). In the case of the research performed by Douaud et al. (2013), their training set was data they collected on a group of people (N = 156) diagnosed with Alzheimer's disease (p. 9523). The final network that best matched their data showed that an increase in vitamin B12 slowed down gray matter atrophy which subsequently delayed cognitive decline (p. 9527). Even though this is not a final solution for preventing Alzheimer's disease, this research does show that certain methods developed within Artificial Intelligence can be used to prevent diseases or prevent their symptoms from emerging by creating a better understanding of a system such as the human body.

When more data is available to train (Bayesian) networks on and when better hardware to train these models become more mainstream such as NVidia's Tesla GPU's (Lyakh, 2014), it can be expected that more complex causal relationships can be discovered that show how ageing-related diseases can be prevented more efficiently.

A critical note is that preventing currently known ageing-related diseases wouldn't necessarily mean that people would stop ageing altogether. Even if all ageing-related diseases would be cured, it could well be possible that eventually, other diseases would manifest that usually wouldn't occur within a person's lifetime. Up until now the main focus has been on the human body regarding life extension and curing diseases, but this doesn't reflect the total solution-space.

2.5 Extending the healthy human lifespan through other means

It is possible that the solution to extending the human lifespan isn't found in maintaining the 'normal' biological human body. Especially when considering extending the human lifespan beyond the apparent hard limit, a transhumanistic approach might be the most viable option. Bostrom (2003) says the following about transhumanism: "*It promotes an interdisciplinary approach to understanding and evaluating the opportunities for enhancing the human condition and the human organism opened up by the advancement of technology.*" (p. 493). He also specifically mentions the possibility of eradicating diseases and radical extension of the human health-span. Gene therapy could be considered a transhuman approach because it focuses not solely on returning the human body to a prior state, but instead, focuses on fundamentally changing its properties to improve certain functions. In 1- and 2-year old mice, gene therapy has increased their median lifespan by 24 and 13% respectively without increasing the occurrence of cancer (Bernardes de Jesus et al., 2012).

In the same way that Artificial Intelligence is already being used to prevent symptoms (Douaud et al., 2013) and decision support (Remzi et al., 2003), Artificial Intelligence can help to discover better ways in which to edit the human genome to prolong human lives in a healthy manner.

A more radical approach that doesn't rely on the 'natural' functioning of the human body at all lies in virtual reality. The primary focus on longevity should be on maintaining someone's cognitive and behavioral abilities, but this doesn't necessarily require a biological human body. Athletes with prosthetic limbs have been shown to equal or even exceed the performance of normal athletes (Lechler & Lilja, 2008). As technology advances, it can't be ruled out that eventually every aspect of the human body can be improved through technology. But why stop there? If we assume that the human mind is the only thing that cannot be replaced because it contains our very consciousness, then the most important thing will be to maintain the functionality of our brains and to allow for a way in which the brain can still interact with its environment. Either through providing a virtual reality or the possibility of interacting with the environment through a remote-controlled body, the goal of this approach would be to maintain an experience that is as close to that person's previous life as possible. Of course, such an approach would lead to a whole lot of ethical issues, but since (artificial) realities are already topics of philosophical discussion within the field of Artificial Intelligence such as the Brain in a Vat theory (Putnam, 1981), these more radical approaches shouldn't be left untouched.

2.6 Conclusion

While Artificial Intelligence can certainly contribute a lot to the medical field when it comes to diagnosis, treatments and predicting outcomes, its potential is tightly connected to advances in both software and hardware. When Artificial Neural Networks become increasingly complex, the need for more sophisticated specialized hardware increases. Over the last few decades, companies like Google and NVidia have reflected an increased need for this specialized hardware by developing chips like Google's TPU and NVidia's Tesla GPU's. Artificial Intelligence has already been shown to produce more accurate early detections of certain types of cancer, and since research in the field of AI isn't showing any signs of slowing down, it can be assumed that AI will have a tremendous impact in the medical world during the next few decades.

When answering the central question "*What needs to be done to double the healthy human lifespan?*" from the field of Artificial Intelligence, one of the most obvious answers is that research on specialized hardware and software should continue. But even if AI is used to predict every case of cancer as soon as possible and is able to suggest the best treatments possible, this will most likely not be enough to actually double the healthy human lifespan. In order to do this, more knowledge about how ageing is actually caused is needed, as well as a deeper understanding of the human body as a whole. As shown, generating more knowledge is one of the hallmarks of AI as long as there is sufficient data available. Thus to double the healthy human lifespan, the solution is divided into three sub-goals:

1. The focus of treating diseases like cancer should shift from treatments to preventing the underlying causes of these diseases in the first place
2. As much data as possible should be gathered to train new advanced ANN’s on
3. New advances in hardware and software for ANN’s should be stimulated

When these sub-goals are met, doubling the healthy human lifespan might turn out to be in reach. In pursuing this goal, it is important to also look outside of the usual solution-space that mainly focuses on maintaining the natural human body’s functionality. A more transhumanistic approach that involves Artificial Intelligence might prove to be the most viable option.

On a more critical note, especially because the field of Artificial Intelligence is rather new and because the application of AI in the medical field still seems to be increasing at an exponential rate, there is no good way of telling what Artificial Intelligence can ultimately contribute to the medical field.

3. Biomedical Sciences

3.1 Introduction

Two months ago, Sarah Harper, professor of the Oxford institute of aging stated that current medical advancement extend the average lifespan by 15 minutes every hour. She further elaborated on the subject of longevity by stating that "70 is the new 50" and that kids born today have a life expectancy of 104 (Harper, 2017).

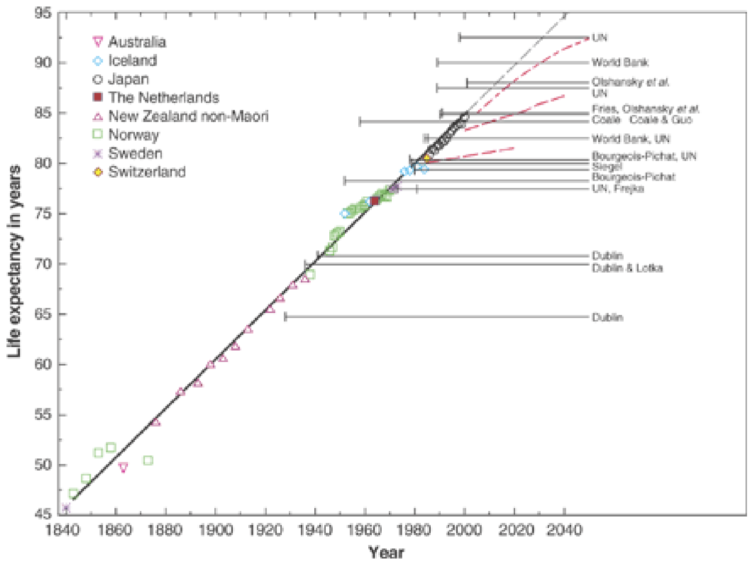


Figure 1. Record life expectancy (female) in several populations(Oeppen, Vaupel, 2002).

Indeed over the past decades an increase in life expectancy has been observed. In fact, data shows a steadily increase of average life expectancy which holds true for multiple different populations.

But does this mean our life expectancy will continuously keep on increasing in future years? Some researchers indeed think so. Oeppen and Vaupel created a linear model based on previously collected data which claims our record life expectancy will steadily keep on increasing (Figure 1.). They fortified this claim by stating that experts contradicting this statement have been proven wrong multiple times in the past. Also they state that, if we were to approach a limit in life expectancy, the increase in life expectancy should be slowing down (Oeppen, Vaupel, 2002).

However, multiple arguments exist against a continuous increase in life expectancy exist. Firstly, a large part of the increase in life expectancy observed over the past years is attributable to a reduction in childhood mortality. This principle, referred to by Omran as The Age of Receding Pandemics, describes how in recent years the receding of pandemics has caused significant reduction in childhood mortality (1971). This reduction in child mortality has had a significant effect on the increase in life expectancy but this effect will decline in the future since pandemics have receded and therefore there is much less improvement to gain in child mortality rates. Even though a decrease in elderly mortality is also observed, its contribution to life expectancy is much lower than the upward shift that was caused by the reduction in childhood mortality.

Secondly, more recent research (Dong *et al.,* 2016) nuances this idea that life expectancy will keep on increasing steadily. Whilst our average life expectancy may steadily increase for several more decades, it is rather unlikely that also our maximum life expectancy –the oldest age any individual can reach- will conjointly increase. When looking at data regarding the yearly highest age of death in different countries–individuals who died aged 110 and older-, no steadily increase in maximum life expectancy is observed. In contrary, since a decade a gradual decline of the maximum age can be observed. This observation holds true also when correcting for possible lack-of-data confounding by including individuals that had the 2nd, 3rd, 4th and 5th highest reported age of death (Figure 2.) (Dong *et al.,* 2016).

Thirdly, it is possible that our increasingly unhealthy lifestyle will completely attenuate the increase in health. It is thought that if the trend in obesity is not halted it may completely abolish health increases gained from a reduction in other unhealthy habits, *i.a.* smoking (Stewart, 2009). Lastly, a major argument against a continuous increase of our life expectancy is the plausible existence of a biological limit to our life expectancy. Olhanksy, has argued that in order for us to break this limit, extreme reductions in mortality rates from all causes of death would be required. To demonstrate the unlikeliness that this would happen: if we would want to have a life expectancy of 50 years old at age 50, it would require an individual aged 50 to have the same mortality risk as a teenager (Olhanksy, 1990).

So what do these arguments tell us with respect to possibilities of longevity extension? In order to understand the trends, possibilities and issues in longevity extension from a more physiological perspective, it is important that first it is defined why we age and what exactly is meant by aging. Whilst many different definitions of the concept of aging exist, generally aging can be defined as: "*a gradual decline in physical functioning with or without mental frailty*" (Myint, Welch, 2012).

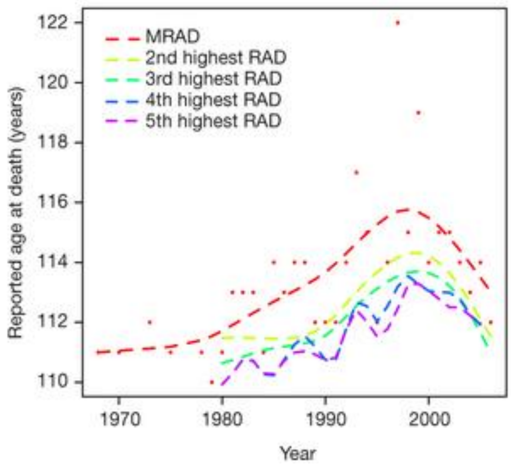


Figure 2. Age of death of individuals aged >100 over time. (Dong *et al.,* 2016)

Aging is caused by many different underlying mechanism. Lopez-Otin *et al.*, recently outlined 9 distinct mechanisms that most likely are the foremost contributors to aging (figure 3.) (2013). These mechanisms are often fundamental mechanisms that, regardless of their role in aging, exert several crucial functions in organisms. To further gain insight in the complexity of these mechanisms and their complex role in longevity extension, I will elucidate one of these mechanisms: proteostasis. By using proteostasis as an example, I will elucidate how complex mechanisms may affect the aging process. Subsequently I will look at (hypothetical) alterations of proteostasis as a means to extend longevity and the issues that arise. Lastly, I will discuss alternative and future methods to induce longevity extension that might be viable in the future

3.2 Proteostasis

The entire collection of proteins that a cell expresses, referred to as the proteome, coordinates the vast majority of cellular processes. Since these proteins fulfil a crucial role in a cell's existence, it is important that a healthy protein homeostasis –also referred to as proteostasis- is maintained.
The cell has multiple mechanisms through which proteostasis is maintained. Firstly, chaperones are able to (re)fold misfolded, unfolded or damaged proteins in an ATP-dependent manner. When chaperone remodelling is insufficient, protein degradation can be achieved through the Ubiquitin-Proteasome System (UPS) or by the lysosomal-autophagy system (Vilchez *et al.,*2014).
The UPS is a system that serves to eliminate misfolded and damaged proteins and prevent them from causing harm to the cell. The first step in the UPS is the labelling of retarded proteins by adding a chain of ubiquitin to the protein. Subsequently, the labelled protein is recognized by the proteasome, which is able to degrade the protein into peptides which can be re-used for new proteins synthesis. Alternatively, labelled proteins can also be degraded in autolysosomes via autophagosomes. (Vilchez *et al.,*2014).

3.3 The role of proteostasis in aging

As stated by Lopez-Otin *et al.,* a distortion in proteostasis is one of the 9 foremost contributors to aging. Aging has several different effects on the different proteostasis mechanisms. Here several of these effects will be discussed.

Chaperones

Correct chaperone functioning is a vital condition for protein homeostasis. However, with age chaperone functioning decreases. In healthy individuals, chaperone synthesis is triggered by the transcription factor HSF1 that becomes activated upon protein damage, a process referred to as a heat-shock response. HSF1 is responsible for activation of several *hsf* genes that carry the heat-shock response. However, with age this heat-shock response decreases, resulting in a lowered synthesis of chaperones (Calderwood *et al., 2009*). The underlying mechanisms of this decline in response are not yet fully

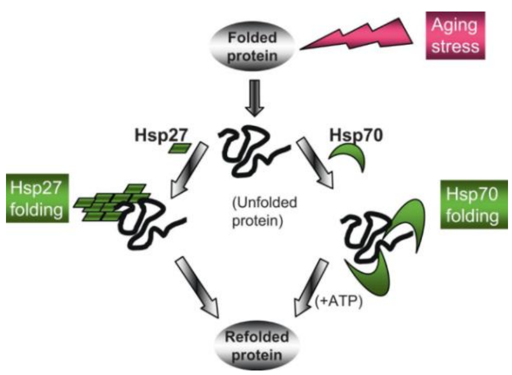


Figure 3. HSP-mediated protein folding (Calderwood *et al.,* 2009)

understood in humans. However, in *C.elegans* models it has been shown that as individuals age, a reduction in the expression of several heat-shock protein genes lowers the efficiency of the heat-shock response (Hsu *et al.,* 2003*)*.
Apart from the reduction in heat-shock response, aging also has influence on the ATP supply to chaperones. AMPK is a kinase that becomes activated in response to depleted ATP levels and subsequently leads to activation of several ATP-production stimulating pathways. In aged mice a reduced AMPK activation than younger mice can be observed (Zong *et al.,* 2002). Since sufficient ATP supply is essential for chaperones to bind proteins which have been selected for (re)folding –not shown in figure 3.-, it is hypothesized that the decreased ATP supply and thus the decreased chaperone efficiency contributes to the loss in proteostasis that in part causes aging (Kaushik, Cuervo, 2015) .

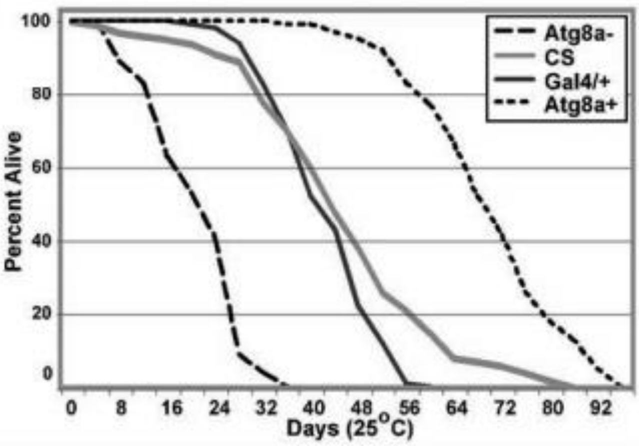


Figure 4. Increasing autophagy can extend lifespan in Drosophila (Simonsen *et al.,* 2008).

Autophagy-lysosomal degradation

Not only chaperone activity decreases with age. Autophagy-lysosomal degradation of potentially detrimental proteins decreases with age (Rubinsztein *et al.,* 2011). Several researchers have tried to analyse the extent to which autophagy contributes to aging. In mice, knockout of the *Atg7* gene, a gene necessary for autophagy, leads to severe accumulation of poly-ubiquitinated proteins. As a result, neuronal cell survival decreased severely and neurodegenerative phenotype was observed (Komatsu *et al.,* 2006). With respect to age, increase of *Atg8* expression in drosophila showed a decrease in protein accumulation. Interestingly, this increase in *Atg8* expression significantly extended Drosophila lifespan in comparison to control groups (figure 4.) (Simonsen *et al.,* 2008).

Ubiquitin-proteasome system

Apart from influencing the autophagy-lysosomal degradation of proteins, aging also influences the ubiquitin-proteasome system. Once linked with ubiquitin chains, proteins will be transported to the proteasome. Different types of proteasomes exist (figure 5). The main proteasome in protein degradation is the 26S proteasome, of which the core is made up by a 20S proteasome particle and the caps consist of 19S particles.

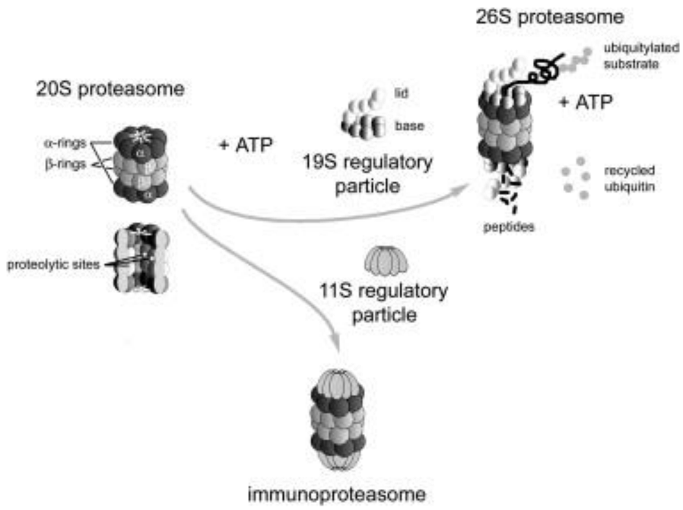


Figure 5. Proteasome structures (Löw, 2011).

Experimental evidence in rats has shown that, with age, the multi-catalytic degradation capabilities of proteasomes decreases over time (Keller *et al.,*2000*)*. More recently, researchers have constructed transgenic mice that have an altered proteasome construction. In these transgenic mice, the 20S core was replaced with a 20S core present in thymus tissue which has a lowered proteolytic activity. The transgenic mice with lowered protein degradation showed phenotypical characteristics similar to those observed in old mice. This provides *in vivo* evidence for the relation between the UPS and aging (Tomaru *et al.,* 2012).

3.4. Longevity Extension through proteostasis: Not that straightforward

An increase in longevity does not necessarily mean that the gained extension is healthy. Aging mechanisms are extremely complex and therefore designing therapies to increase lifespans is a complex process. Whilst some experiments may prove to be effective in extending age, tampering with mechanisms thusly complex may have detrimental side-effects. This principle is addressed below using cancer development as an example.

Hypothesis: Stable HSF-1 expression as a means of longevity extention

As stated before, chaperone activity decreases with age due to the decreased heat-shock response upon stress, a response mediated by HSF1. Since the role of HSF1 in chaperone activation is well-known and decreased protein homeostasis

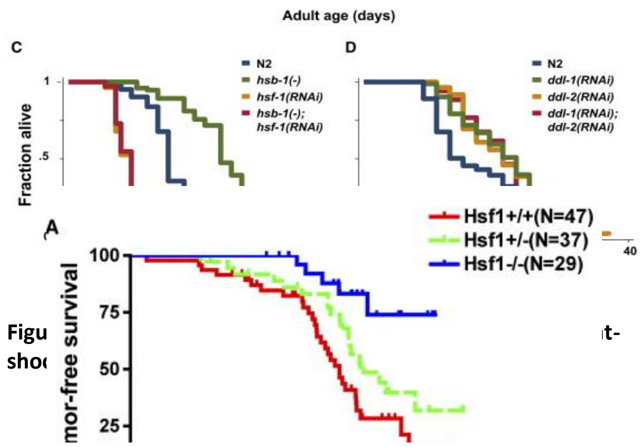


Figure 7. Tumor-free survival for mice with p53 mutations (Dai *et al., 2006)*

is associated with aging, research has focused on HSF1 as a potential target for longevity extension.

In *C. elegans* HSF1 is regulated by DDL1, DDL2 and hsb-1, regulators that all downregulate HSF1 expression. DDL1, DDL2 and hsb-1 are able to form a complex with HSF1, thereby inhibiting its transportation into the nucleus and subsequent gene activation. The important role of HSF1 is confirmed by RNAi inhibition of HSF1 which results in a significant decrease in lifespan figure6. Furthermore, inhibition of any of the three regulators increases *C. elegans* lifespan significantly, yet inhibition of a combination of these regulators does not further increase lifespan. This suggests that all three regulators function through similar pathways (figure 6.) (Chiang *et al.,* 2012.

The previously mentioned increase in *C. elegans* lifespan by genetic interference of HSF1 may at first sight seem a promising therapeutic target to increase human longevity. However, translation of *C.elegans* research to the human is complicated. Hypothetically, if human homologs of DDL1/2 and hsb-1 were to be inhibited, a stable HSF1 expression would be achieved. However, a stable HSF1 expression may have consequences to an individual as well. In mice models, HSF1 was found to be one of the foremost promotors of cell survival and thereby contributed to carcinogenesis. In several different tumours caused by mutations in the tumour suppressor p53, HSF1 enhances tumorigenesis.Knockout of HSF1 in mice with p53 mutations, resulted in a significant increase in the amount of mice that survive tumour-free (figure 7.) (Dai *et al.,* 2006).

As stated a decreased HSF1 expression is involved in a loss of heat-shock response which in turn contributes to aging. However, overly stable HSF1 expression may also be detrimental given the fact that HSF1 drives cell-survival in tumour cells. This illustrates the dualist role that aging mechanisms play. Where stimulation of HSF1 expression may be beneficial to counteract aging, it might also drive detrimental side effects such as tumour-cell survival.

Hypothesis: Stimulation of UPS as a means of longevity extension

As shown in mice, the catalytic degradation capabilities of the proteasome decrease with age which leads to deficient protein degradation and can thereby distort healthy proteostasis. Given the important role of proteostasis in aging, targeting the UPS might provide a means to extend longevity. Indeed, in *C. elegans* the overexpression of RPN-6, a subunit of the 19S capping particle, reduces toxic stress caused by defective proteins and increases longevity (Vilchez *et al.,* 2012). Furthermore, overexpression of ubiquilin-1, a factor that can interact with the proteasome as well as the protein that is selected for degradation and is vital for the UPS-induced protein degradation, can limit protein aggregation and increase the lifespan of mice (Safren *et al,* 2014).

Yet overexpression of the UPS, and thus a strong limitation in protein aggregation, may not be without risk. In patient with colorectal cancer, an increase in carcinoma aggressiveness was found due to an increased UPS-induced degradation of the important tumour-suppressor p27. Colorectal cancer patients with tumours that had decreased p27 levels showed far poorer survival rates than individuals with baseline p27 rates (Loda *et al*., 1997). Furthermore, other research showed increased proteasome activity in breast cancer tissue, suggesting that overexpression of the UPS may fortify tumorous tissue (Chen *et al.,* 2005). Apart from cancer, increased proteasomal degradation has also been observed in other diseases (Coëffier *et al.,* 2010).

Hypothesis: Promotion of autophagy as a means of longevity extension

As mentioned before, autophagy is an important process via which proteostasis can be maintained. Important players in autophagy are the autophagy related genes (atg). Previously, it was mentioned that Atg8 overexpression can significantly extend Drosophila lifespan (Simonsen et al., 2008). The Atg genes can be regulated through many pathways (figure 8.).

Apart from directly influencing Atg expression, sirtuin overexpression can lead to an increase in atg protein synthesis. Sirtuins are histone modifiers that can deacetylate specific histones. By doing so, atg promotor regions become exposed to transcription factors and thus lead to an increase in atg expression. In drosophila, an increase in sir2 (a sirtuin) lead to an increase in lifespan (Rogina & Hefland, 2004). Also p53 is able to modulate autophagy. A knockdown of CET-1, the C.elegans orthologue of p53 was shown to increase autophagy and contribute to extension of lifespan (Tavernarakis et al., 2008).

However, similar to the previous hypothesis, autophagy is a complex and multi-functional process, and therefore strictly balanced. Alterations in such processes may have more effects than the mere extension of lifespan (Madeo et al., 2010). This complex role of autophagy is illustrated by its role in cancer. Whilst autophagy has been known to limit cellular damage and degrade harmful waste products, autophagy is often upregulated in tumorous tissue. Stable autophagy provides a means for tumour cell survival in high stress environments by limiting apoptotic and necrotic cell death (Degenhardt et al., 2006).

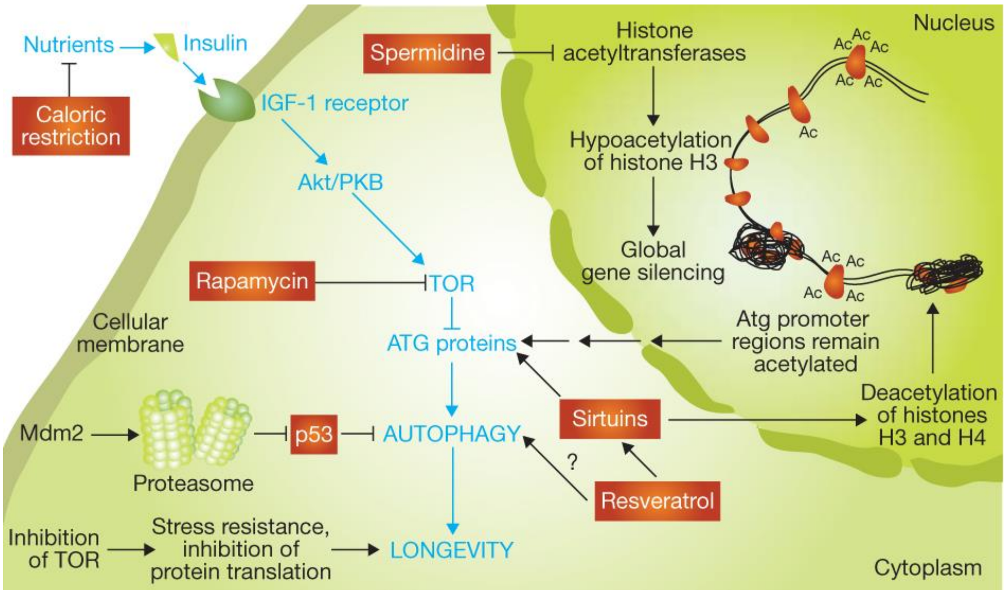


Figure 8. Atg proteins as a central player in longevity. (Madeo *et al.,* 2016)

3.5. Discussion

Proteostasis is one of the 9 hallmarks of aging as defined by Lopez-Otin *et al.* (2013). Proteostasis is maintained through 3 mechanisms: via chaperones, via the UPS and via the lysosomal-autophagy system.

Three hypotheses have been proposed to illustrate the complexity of aging mechanisms and the problems arising with longevity extension. Many of the aging mechanisms function in multiple complexes. These hypotheses have described that, since in model organisms some promising results are shown, life extension may be possible in the future. However, given the complexity of these mechanisms, attempts at longevity extension may have detrimental side-effects.

Furthermore, since many of the proteostatic mechanism are regulators in disease development processes it is possible that a 'trade-off' between age and disease development may occur. With age these mechanisms show more and more defects, therefore it is likely that when life is extended by altering one or multiple of these mechanisms, defects in other mechanisms may occur/increase, thereby leading to novel disease development.

Alternatives

Since direct protein/gene intervention approaches may plausibly be subject to this trade-off, a search for alternative approaches exist. In 2005,researchers discovered a rejuvenation method in mice through parabiosis: the linkage of blood circulation of old mice with young mice seemed to revert aging of already aged cells (Conboy *et al.,* 2005). This sparked the idea that, within juvenile blood, a rejuvenation factor was present capable of inducing rejuvenation of older tissue. However up to now, no conclusive evidence on the existence of such a rejuvenating factor has been found and therefore clinical applicability remains absent.

More alternatives exist. Already in 1986 it was shown that restriction of caloric intake may influence longevity. Mice that had a reduced-calorie diet had significantly longer mean and maximum lifespans than control mice groups (Weindruch *et al*., 1986). It is though that this lifespan extension by caloric restriction is in part caused by a reduction in mitochondrial $O_2^{\cdot}$ free radical production, which is one of the prime causes of aging as established by Lopez-Otin (2013). Regarding caloric restriction in primates, limited data is present. It was shown that caloric restriction in rhesus monkeys was able to slow down the aging process and significantly increase their lifespan (Colman *et al., 2009*). In humans, caloric restriction is shown to have several different beneficial effects. However, conclusive evidence regarding the effect of caloric restriction specifically on longevity extension in humans still remains absent (Fontana, Klein, 2007).

Alternatively, the relatively new research area of biofabrication, which focusses on engineering and printing tissues, may prove to be promising. Current focus of this research area is on the (partial) productions of new specific tissues and entire organs. However, in the future biofabrication may prove to be an alternative approach to longevity extension. Contrary to conventional techniques where old tissue processes are pharmacologically altered, biofabrication may provide a means to actually replace old tissue for the newly created tissue and thereby 'rejuvenate' the body.

Doubling of the human lifespan

When looking at the main question of this interdisciplinary thesis, concering a doubling of the human lifespan, several conclusions can be drawn from the discipline of Biomedical Sciences.
As stated by Olhanksy and many other experimental researchers, a biological limit to average seems to be present and it is extremely unlikely that, without revolutionary unknown biomedical breakthroughs, the human lifespan will significantly surpass this limit let alone be doubled.
Secondly, regardless of an actual doubling of the human lifespan, it must be acknowledged that up to now, whilst some experimental alterations of these processes have shown promising results in model organisms, viable longevity extension is not within grasp in humans in the coming future.

From my personal point of view, I believe that indeed a biological limit to the life expectancy is present and that a doubling of the human lifespan is highly unlikely. However, with technology developing at an unprecedented rate, I do not exclude the possibility that the newer evolving fields like Biofabrication and Regenerative Medicine may provide a breakthrough with respect to longevity extension in the coming future. I do believe however, and this is in line with Olhansky (1990), that at this moment successful longevity extension is still highly unlikely and our focus should not be as much on improving the duration of life yet more on optimizing the quality of life. In agreement with both Olhansky (1990) and Stewart (2009), I believe our focus should be on reducing non-fatal unhealthy habits, such as obesity, since there is much improvement to be gained there.

4.New Media and Digital Culture

This section will look at longevity through theories in the domain of new media and digital culture and will mainly focus on the question; "*What are the moral issues that need to be addressed before longevity through cybernetic technologies becomes viable?*" This is a question which can be answered with the use of philosophy of technology, which is within the domain of new media and digital culture.

To properly look at the moral issues surrounding these technologies, this section will be divided in multiple parts. First, basic ethical theories will be introduced. This will be followed by a philosophical basis to look at cybernetic technologies. The introduced ethical theories and base philosophies will lead to an ethical theory that combines the two in order to properly evaluate the cybernetic technologies for longevity.

In this text, the focus will be on cybernetic technologies that increase the lifespan or increase the quality of life of a human. Quite a few of those technologies exist already, from prosthetic limb, to a dialysis machine, to a pacemaker. These technologies have a big impact on a person's life, that is why the focus will be on these kinds of technologies.

4.1 Traditional Ethics

To understand how to ethically approach the moral issues surrounding cybernetic technologies, it is important to first understand what being ethical means. Therefore, two traditional influential theories on ethics will be introduced here. Many philosophers have explained what they deem truly ethical, but most are not as influential and well known as Immanuel Kant. His theory, simplified, is that he has based his idea of morality on rational thought and in this way the theory serves as an objective morality. He values what is morally good purely on the intrinsic will to do good. If one wants to act a certain way and is led by any other reason than to do good, for instance by profit or pleasure, it is not morally good. In this way Kant constructs an intrinsic obligation to do good. This does not mean one cannot ignore this obligation (Johnson & Cureton, 2017). This is a deontological way to look at morality, meaning that there is a moral obligation to act in a certain way (Alexander & Moore, 2016). Other forms of deontological morality include the morals in religious law.

While this form of morality only looks at the intention of the actions, another form looks at the consequences of the actions. This form of morality is aptly named consequentialism. The basis of this form is how morally justifiable the consequences of one's actions are. One of the movements within consequentialism is named utilitarianism. It quantifies these consequences in the amount of pleasure it brings to the greatest amount of people as defined by John Stuart Mill (Walter, 2015). This, contrary to Kant's morality, does not look at the intentions of the actions. As long as the overall pleasure is increased by the action it is morally justifiable, even if the intentions were not good. There are, of course, more modern interpretations and versions of the forms of morality.

These two influential ethical theories also influence the ethical theories presented later on. Something that is important no matter the theory is the context, position and situation of a moral decision. Something that might be considered ethical in one situation might not be in a different situation. For instance, shooting a person is generally unethical. Yet, if twenty kidnapped victims could be saved by shooting a person, it can easily be considered an ethical action.

4.2 Posthumanism

There is an philosophical and political movement that accepts, yet critiques these technologies, named posthumanism. Posthumanism is a loaded term, involving many different philosophical and/or political points of view. This might be due to its broad etymological origin. The posthumanism intended here is the 'classical' posthumanism which gained popularity through the publications of Donna Haraway (Haraway, 1991; Ferrando, 2013). Her influential Cyborg Manifesto made clear that the lines between human and technology and between human and animals are not that clear. With this blurred distinction, it is no longer clear who has made who in this relation. She sees this as something mostly positive. Her concept of the cyborg is a frame through which humans become more equal, because every human is an amalgamation of human, natural and technological factors (Haraway, 1991). She also critiqued the idea of the cyborg since it stems from militarism and capitalism. However, even though it might be influenced by these harmful factors, she still supports the cyborg since it can be turned into something positive (Haraway, 1991, p. 151). It is important to be mindful of its past and other influences.

Haraway's text has had a large influential reach and recognition and gave a boost to posthumanism. Posthumanism is a broad philosophical movement with many different ideas, the most relevant here being its view on technology. As shown by the Cyborg Manifesto, technology is seen as something closely interwoven with what it means to be human. Technology has been interwoven with humans since the beginning, from sticks and stones to smartphones. In this capacity, technology is one of the essential parts of what it means to be human (Ferrando, 2013).

In this view, the alteration of the human body by cybernetic technology is not a radical change to the human as they were already intertwined with technology to begin with. This is different from more essentialist notions of what it means to be human. Such views might object to alterations to the human body because they might change it into something non-human. This shows that a philosophy that would not object or support these changes, like posthumanism, is necessary to give these technologies a chance.

Yet, it is important to stay critical because it is easy to fall into a techno-utopian rhetoric. When talking about how humans could transcend the limitations of the human body, discussions easily move into the realm of science fiction. Because these views lack critical reflection, they can be quite harmful. Transhumanism, for instance, has a utopic view of humans transcending the physical and mental limitations, such as aging. It tends to reduce human progression to technological progression (Ferrando, 2013). This techno-reductionist approach also tends to shape the way people talk about the human body and mind. Selinger and Engström demonstrate this in their article. They show that the way we talk about these enhancing technologies is similar to terms used in the computational theory of mind, as with discussing the concept of cyborgs (Selinger & Engström, 2008). This theory describes the mind as a computer program with different modules and the body as a piece of hardware. The way in which this is done can be quite dangerous. They show how the computational theory of mind is open to naturalisation and commercialisation, where naturalisation means making it appear is if it is that way by nature (Selinger & Engström, 2008, p. 335-337). This has in turn diminished a critical reflection on these technologies. It is important to stay critical of how we talk about the relation between technology and humans and not state theories as facts before they are proven as such. In this light, the computational theory of mind is only useful as a metaphor of something humanity does not fully understand yet, namely the mind (Selinger & Engström, 2008, p. 340). This and other techno-centric ideas make transhumanism a very one-sided philosophy. To give a broader and more balanced view of humanity and its relation to technology, it might be more advantageous to view it through the philosophy of posthumanism. The latter has its own model to approach the mind, the model of distributed cognition which also takes into account situatedness, embodiment and enaction. The model does not have the pretence to reveal the most inner workings of the mind but is rather a representation of cognition (Hayles, 2010).

This shows that posthumanism is a valid theory, as long as it is grounded it fact. Boström shows that the posthuman is a viable idea by defending it against three of the most common arguments against the posthuman (2005). The most striking argument he mentions is that the posthuman is unnatural and that the natural human being should be respected. He counters that nature itself is sometimes poisoned and should not always be accepted. “Cancer, malaria, dementia, aging, starvation, unnecessary suffering, and cognitive shortcomings are all among the presents that we would wisely refuse” (Boström, 2005, p. 205). Relying on what is natural and what is not, is an outdated way to look at the world. Boström is able to show that human enhancement is not something to be feared or rejected, but he also shows that it is not without its own issues, which need to be kept in mind to be able to properly move forward (2005). This defence of the post human shows that the idea of such human enhancement as longevity is something that can be strived towards as long as there is critical reflection and it is grounded in reality with facts. This way there is also awareness of problems that need solved or addressed before moving forward.

4.3 Morality Of Technology

Now that these underlying philosophies have been addressed, it is clear that an ethical philosophy purely focussing on human agency might not cover everything. In the philosophy of technology there are multiple theories that artefacts like technical devices can have some form of agency or intentionality within them. Adding these actors into the mix of the moral equation makes the philosophy on morality a lot more complex. One of the well-known theories that describes how artefact can have agency is actor network theory by Bruno Latour (Latour, 2002). In this theory artefacts aren't actors in a traditional sense since they cannot act autonomously instead they get agency in relation to other actors. All these relation form an network of actors, hence the name of the theory. One of the easiest examples which is used often, is that of an speedbump. If a driver comes across a speedbump, it forms a relationship with the speedbump. The speedbump then acts upon the driver with the implicit question to slow down. In this way it modifies the intention of the driver. According to Latour it is very important to recognize this. "In this sense, morality is from the beginning inscribed in *the things* which, thanks to it, *oblige us to oblige them*" (Latour, 2002, p. 258).

Dutch philosopher Peter-Paul Verbeek has expanded upon this notion of morality of technologies (Verbeek, 2006a, 2006b, 2008a, 2008b). While Latour shows that this agency and morality is not merely the agency and morality of the designer by proxy, Verbeek points out that the designer nonetheless has an important role in shaping the morality. The technology still has its own morality but the designer can design to exclude as many unwanted moralities as they can. This is important because it might turn out in unexpected ways. "A good example is the revolving door which keeps out both cold air and wheelchair users" (Verbeek, 2008b, p. 100). Verbeek's morality of technology goes deeper than an issue of an revolving door. He uses prenatal technologies like ultrasound and Amniocentesis to illustrate his point. One of the things this technology does, is establish if the foetus has a medical condition like the syndrome of down. It also establishes the foetus as an entity separate from the mother. This shapes the morality around the conception of human life. It shapes the moral questions that can be asked, such as if parents should abort the foetus if it has a chronic medical condition. It also shapes how one sees these moral choices. The framing in medical thinking and norms might invite to abort while the framing of the foetus as its own entity might invite to keep it. These moral issues arise because of the technology. By recognizing the influence of technology, it is a posthumanist morality according to Verbeek

(Verbeek, 2006b).

Because technologies can have such an influence on morality, designing technologies is an inherent ethical practise. Designer should take into account this ethical side of the design process. To avoid unintended forms of mediation, Verbeek constructed a method to analyse how this morality takes form in a design. This method can be used by users to help shape the morality of a final technology. It is, however, not possible to see all the possible expressions of this morality, but designers should try to avoid as many unwanted moralities as they can (Verbeek, 2006a). This is why the moral responsibility cannot solely be placed on the designers. In some cases it might be desirable to regulate the development of some technologies. “The actions and decisions of designers always have public consequences, and therefore these decisions and their consequences should be subject to public decision-making.” (Verbeek, 2008b, p. 102).

Verbeek brings this as a posthuman ethical theory because it recognizes the intimate relation humans and technology has; A relation that becomes more tightly knit the closer the human is to the technology (2006b, p. 56). Once the technology is fused with the human into a cyborg being, the morality is fused as well. The cyborg, either fully or partially, experiences the world as the technology experiences it, and as such experiences the world through the technology with its inscribed morality (Verbeek, 2008a). In this line of thought, the more intimate the relation between human and technology becomes, for example in technologies of longevity, the more important the morality of technology becomes.

4.4 Ethics and fabricated organs

An example of a new technology that could aid in achieving longevity is biofabrication technologies. These are technologies that can fabricate biological tissues, 3D printed organs through 3D bioprinting for example. They could for example replace damaged tissue in the human body and could potentially aid longevity by replacing tissue damaged by aging. It is still a developing technology and has yet to be adopted for regular use on humans. Now is a good time to look at the moral and ethical implications of this new technology.

To dissect these implications, the assessment by dr. Annelien Bredenoord will be reviewed (Otto, Breugem, Malda & Bredenoord, 2016). She is a Dutch professor specialized in medical ethics, who focusses on the ethical issues of new medical technologies. She is on multiple Dutch and international ethics boards. She writes on the ethical issues surrounding new medical technologies and gives advice on how these could be morally approached and implemented. She and three fellow academics wrote on the subject of biofabrication. Here, she was the ethical expert of the four. The resulting paper will be used to illustrate how ethics is used in practise (Otto et al., 2016).

The paper seems to take an approach similar to Verbeek’s and it also briefly references him.

It views biofabrications technologies as things that can change and influence people. It also states that it is important to look at the ethical issues while developing new technologies. Ethics is sometimes seen as a brake on science but the paper states it provides moral guidance and an incentive to review the direction and impact of the new technologies (Otto et al., 2016).

Bredenoord found that the biofabrication technologies already have a moral impact, even in the development stage. Its existence as a technology that still needs medical testing brings with it some ethic issues. The technologies are not as easily tested as other medical procedures and medicines in a standardised test. The medical implications of the procedure are more severe and irreversible. This way these technologies bring the ethical issues of alternate ways of testing onto the table. This exists besides the fact that it also brings with it ongoing ethical issues that arose through previous technologies, like the issue of how to morally obtain human matter (Otto et al., 2016).

Besides the ethical issues of the technology in its developmental phase the article also looks towards the possible future issues the technology might have. For example, can the technology be used for other purposes in the future? Biofabrication technologies could potentially also be used for human enhancement, such as in appearance or performance. Human enhancement is an area with many moral issues that also need to be considered when developing this technology. There are also broader issues that are relevant in this case. Which people have access to such an expansive new technology, for instance, which is important to consider as to not create inequality (Otto et al., 2016).

The article concludes that it is vital to consider the impact of this technology now. They call on scientists and physicians to consider the implications of these technologies and strive for responsible innovations. They control the design of the technologies and with it, shape the impact it can have on society (Otto et al., 2016).

4.5 Conclusion

Now that the example of biofabrication has shown how academics can help advise on the development of new technologies, it is possible to come to a conclusion. In this text, posthumanism is posed as a good philosophical basis to look at longevity and that it is also important to keep critically reflecting as to not wind up in unfounded beliefs of a techno-utopia. One of the more relevant beliefs of posthumanism for cybernetic technologies, is that there is not a clear distinction between humans and technology, and human and nature. Technology is part of what it means to be human. These beliefs support human enhancement through technologies which it is not a big change, since technology was already part of the human. This also forms a foundation to look further into morality.

Also in this text, a model of morality was shown that is more in line with posthumanism than the classical views on morality. This is the model of morality by Verbeek in which technology has a simple form of morality inscribed within it (Verbeek, 2006a, 2006b, 2008a, 2008b). Technology changes the morality of a situation and influences other actors, which needs to be accounted for by designers. It is their job to make sure that it is very unlikely that the technology will result in immoral consequences. These tasks could be neglected or abused. This is why the public impact it might have may also warrant its regulation through policies.

The example of biofabrication technologies shows that academics are already actively advising on policies on new technologies on the basis of morality and ethics. It also considered both the development and final product in these recommendations. A technology can already have moral implications when it is still in development, as the example shows. It can also bring new moral implications with it which have not been seen in previous technologies.

Because each technology can be unique in its moral issues, there is no set of moral issues surrounding all new cybernetic technologies. Each technology has its own morality, which should be considered and analysed. It is therefore important that its morality is properly analysed during development and that there are proper laws and policies in place which allow for a responsible development of technologies for longevity. This way all moral issues regarding these technologies should be resolved, before release to the general public. If they are deemed immoral with this reasoning, they cannot ethically be distributed.

5. Common ground & Integration

The insights from all disciplines can be combined to form a new, more complete insight regarding doubling the healthy human lifespan. To achieve a more comprehensive understanding of these different insights integration techniques as defined by Repko & Szostak (2017) will be used. This will create a greater insight where the whole is greater than the sum of the parts.

Before the insights can be integrated, however, common ground needs to be created. This is done by setting up a collection of theories, concepts, and assumptions on which all disciplines can agree. In order to create this collection, it is important to identify conflicts between the disciplines and resolve them with the methods provided by Repko & Szostak (2017). Apart from addressing conflicts, it is also important to realize what disciplines have in common.

5.1 Identification of insights

Artificial Intelligence provides us with the theory that the use of AI can develop new strategies to solve a problem. Also, AI hypothesizes that aging mechanisms can be precisely defined. Biomedical Sciences provides us with the trade-off theory, stating that altering biological aging mechanisms is often paired with a development of other detrimental outcomes. Furthermore, Biomedical Sciences states that, given current data, extending average lifespan may be possible but extending maximum lifespan is very unlikely. Biomedical Sciences does, however, keep an open approach to longevity extension given the rapid development of new technologies.

The insight of New Media and Digital Culture with its perspective of the philosophy of technology provides a way to ethically evaluate new technologies that might help achieve longevity. It also lays a philosophical foundation to look at these technologies in relation to humans.

5.2 Common ground

In order to create a common ground, 4 distinct techniques exist to connect concepts; the Technique of Redefinition, the Technique of Extension, the Technique of Transformation and the Technique of Organisation. Apart from concepts, theories can also be modified to contribute to the common ground (Repko & Szostak, 2017). By applying these techniques to the concepts and theories it becomes possible to surpass the disciplinary boundaries and create a common ground.

The subjects that will be used for the common ground will be 'Feasibility of human life-extension', 'Human life & Technology' and 'Cognition'. Feasibility of human life-extension was chosen for the common ground since this concept forms the basis of the main question. In order to decide whether something is feasible, it is essential to define when something is considered achieved. The other two subjects, namely Human life & Technology and Cognition, were chosen for the common ground because they influence what methods can and are ethically allowed to be used to achieve an extension of the healthy human lifespan and thus influence this likelihood of achieving longevity extension.

Feasibility of human life-extension

Biomedical Sciences

As stated before Biomedical Sciences and see challenges in healthy aging but do not exclude the idea that this will be achieved in the future. The focus of Biomedical Sciences with regard to the possibilities of extending life, center around extending the average life span. The reason this discipline focuses on extending the average lifespan is that most research points to an absolute limit of the maximum lifespan -as stated in the disciplinary part- and therefore Biomedical Sciences (up to now) mainly focuses on extending average lifespan.

Artificial Intelligence

AI focusses on extending the entire lifespan, including both the healthy and maximum lifespan. Since AI views the human body as a system wherein aging is a consequence of its normal operations, there is no reason for doubling the healthy human lifespan to be seen as an impossible task from within AI. Therefore AI does not hypothesize that extending the maximum lifespan is impossible. The current use of AI combined with the speed at which new technological developments are progressing, doubling the human lifespan seems to be within reach because AI sees aging as a systemic problem that can be solved when it is sufficiently understood.

New Media and Digital Culture

From the perspective of new media and digital culture, new technologies might help overcome some of the limitations of the human body. The judgment on what is possible and what isn't is usually left other sciences which develop these technologies, like Biomedical Sciences. It does however critically reflect on views on future technologies. As illustrated earlier according to the philosophy of technology it is easy to enter the realm of science fiction. It is therefore good to continuously reflect on those perspectives and keep in mind that past results are no guarantee for the future.

Feasibility of human life extension: The technique of Redefinition

It is important to define what is the goal when referring to longevity extension? Indeed, when viewing the human individual as a system with variables, it might be possible to find a way to monitor or alter these variables in such a way that life last longer. However, as illustrated by the underlying trade-off theory within the Biomedical Sciences, an extension in longevity does not necessarily imply good consequences. Especially AI seems to mainly focus on using its theories and methodologies to solve specific problems, without critically looking at possible side-effects these solutions might have. To solve this conflict, the Technique of Redefinition is used, as proposed by Repko & Szostak (2017). The concept of human life extension is redefined to the following: "An extension of the expected lifespan which is not paired with perceived adverse long-lasting physical nor mental side effects".

When using this definition, the conflict between Biomedical Sciences and AI on what form and extent of life extension is possible becomes less emphasized and the focus is more on a healthy way of extending life than extending life in general, and this makes the extension of the human lifespan more feasible. The emphasis in this redefinition lies on the 'perceived' aspect; when there are adverse physical side effects that someone doesn't perceive as adverse, then it shouldn't count as an unacceptable side effect. This new definition broadens the horizon of feasible solutions for human life extension compared to the tradition view from Biomedical Sciences offers.

Human Life & Technology

Biomedical Sciences

From the perspective of Biomedical Sciences, the definition of human is rather straightforward. Within biomedical papers, human or human being refers to a member of the mammalian species *Homo Sapiens.* With respect to the question on staying human in the age of technological developments, a division exists between biomedical researchers. Genetical alterations of embryo's, which is the most discussed example in bioethics, leaves a clear division. Some believe that an alteration of the human embryo through means of technology automatically renders the embryo non-human and states that it can thus be regarded as a bundle of cells (Pearson, 2002). Others, however, take a more nuanced approach and state that, given the fact that the embryo is still a human species, it is unethical to regard it as non-human regardless of the technological aid (O'Mathuna, 2007). Generally, however, technological aids such as pacemakers or prosthesis are not considered to alter the level of being human of an individual.

New Media and Digital Culture

From the perspective of Philosophy of Technology there are multiple views on what makes a human, human. In the posthuman view it is impossible to look at 'the human' in a vacuum. There are many other factors that shape the human. One of which is technology. There is no clear distinction between human and technology. Like shown in the previously shown, one of posthumanism principles is the technogenesis, technology has always been part of what it means to be human.

Artificial intelligence

What it means to be human is a complex and sometimes even obsolete question within the field of AI. The whole field revolves around recreating (human) intelligence by using devices that operate on strict systematic rules. Conservative interpretations of 'human' that are restricted to what a human is in and of itself, have an arbitrary dividing-line between what is human and what isn't. Athletes with prosthetic limbs as well as genetically modified humans could both be considered to be equally 'not human' because of technological interventions, but this would be unpragmatic. Especially because such a division would eliminate any possibility of a 'human' AI from ever existing. Also considering the fact that human beings have been using technology throughout their entire history, technology can be considered as being a part of what it means to be human.

Human Life & Technology: the Technique of Extension

The definition of human as seen from Biomedical Sciences will be extended with the definition of AI and New Media and digital Culture to include technology as part of the human using the method of extension provided by Repko & Szostak (2017). The implementation of technology in human life happens on a daily basis. Although many people seem to fear this idea of technological alterations to human life, it is already being applied to humans with i.e. a pacemaker or an advanced prosthetic. Also, the use of smartphones might be enough to consider ourselves cyborgs because people use technology to extend our perceived world with them. To this extent, technology can be seen as part of what it means to be human and no clear division between the two exist. Seeing technology as part of the human life introduces a positive stance towards technology that ensures more options are left open that might enable the extension of the healthy lifespan.

Cognition

Biomedical Sciences

From the field of Biomedical Sciences, cognition is a broad concept. It is defined by many different aspects of which the most well-known are memory-capacity and ability to learn. Biomedical Sciences researches pathological alterations in these processes that can have a detrimental effect on the aspects of cognition (Weaber, Sweatt, 2002). Generally, it can be said that from Biomedical Sciences cognition is addressed in a biological way and much lesser in an ethical or philosophical way.

New Media & Digital Culture

The posthumanist view used by New Media and Digital Culture uses the extended theory of mind. This concept wasn't explained in depth in the section from New Media and Digital culture but it is important theory nonetheless. This is because firstly, posthumanism was put forward as a foundation to look at longevity technologies and secondly because the view on cognition is intricately linked with technologies that might help achieve longevity. In the extended theory of mind, cognition is is divided over both internal and external cognitive processes. One of the important external factors is that cognition is embodied this means that cognition is tied to observable form like the human body. This means that the human body and other embodiments form cognition. External cognition also means that it can be distributed amongst other embodied agents. Technologies can influence the way people think and act, which is an important thing to consider while looking at potential longevity technologies.

Artificial Intelligence

AI sees cognition mainly as a process, one that isn't by definition restricted to the human brain. Human cognition is directly influenced by biological processes and can, therefore, be influenced by influencing the biological system. The word system is used instead of referring to the human body because cognition could potentially be maintained if the rest of the human body was replaced by technology. Therefore a variation on the brain-in-a-vat theory (Putnam, 1981) could be implemented in the future when such technology is available, where someone could have a remote-controlled body that feels exactly the same to the person, or even an application where the experienced external world is 'replaced' by a computer simulation. Cognition would be maintained despite rigorous changes to the human body.

Cognition: Modification of the theory

New Media and Digital Culture has critique on the brain-in-a-vat theory from AI due to situatedness, embodiment and enaction as mentioned in the extended theory of mind which are not present in the brain-in-vat-theory itself. This does not mean that these theories are completely incompatible.

New Media and Digital Culture finds that it is dangerous to refer to cognition as being a computational process. According to AI, however, the use of computational processes might eventually simulate all bodily senses and thus cognition could be regarded of as being an isolated process. To illustrate this it is useful to look at the following two scenarios; In one scenario a person simply lives their life, in the other scenario the same person lives the same life but it a simulated environment while their brain is in a vat. From the perspective of AI there is no difference in the cognition in the person but from the post-humanistic perspective, there is a big difference. In the second scenario, the vat and its simulation have become part of the cognition of the person. To illustrate this difference further, any change in the simulation would change the cognition of the person according to the post-humanistic perspective. The big difference, therefore, is not if it would theoretically be possible to have a brain in a vat but to single out cognition as an isolated process and consequently to view the surrounding objects as part of the cognition or as a separate system that provides input for the system. The extended theory of mind fits better to the ethical theories from posthumanism in the New Media and Digital Culture section. The difference with AI's theory is mainly that it blurs the distinction between internal and external cognition. It also takes into account the biological view of cognition as part of the internal cognition. According to Repko & Szostak (2017) common ground between theories can be created by choosing the most comprehensive theory that "*requires the least possible modifications*" (p. 416). Therefore from here on the extended theory of mind is chosen as the most appropriate model of cognition.

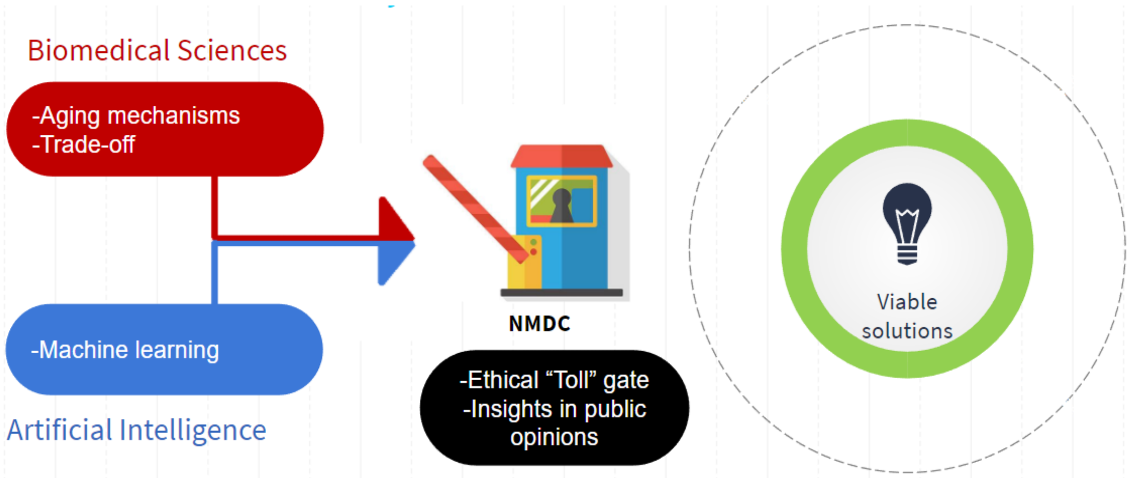
The provided insight into cognition is not only important because it is an important factor within posthumanism, but it also shows us the relationship between longevity technologies and cognition. This way it is possible to make an informed decision on which technologies are viable options with regard to the cognition of an individual.

5.3. Integration

When looking at the feasibility of human life-extension it is clear that both Biomedical Sciences and AI individually lack the complete means to achieve it. Biomedical Sciences lacks the vision that longevity will be possible when looking just from their own perspective and AI lacks the data it requires to discover new methods to make people live longer, therefore a horizontal integration as defined by Repko & Szostak (2017) is needed to combine the insights provided by these two disciplines. This horizontal integration proposes a combination of the biological knowledge concerning aging mechanisms, boundaries and trade-off side-effects with the new AI technologies, that still lack data.

However, for a viable longevity extension solution in our current society, more is required than merely the technical aspects of longevity extension, since ethical issues may arise. The common ground on Human Life & Technology and Cognition has shown that longevity technologies can be more embedded into a human than some might think. New Media and Digital Culture states that the closer the technology is interwoven with the human, the more important its ethical evaluation becomes. This is why the ethical theory can, in turn, be used on the solutions that are generated from the horizontal integration between Biomedical Sciences and AI. In such a system, a multicausal link is formed between New Media and Digital Culture and the other disciplines. Here, the ethical theory provided by New Media and Digital Culture can function as a 'toll gate' in that sense that it decides whether or not possible solutions proposed by AI and Biomedical Sciences are ethically acceptable and viable in our current society.

When combined these two integration-methods together, give a clear meta-insight of all contributing disciplines and how they are combined to lead to more viable solutions that can extend



the human lifespan in a healthy and ethically acceptable manner, as can be seen in Figure 1 below.

***Figure 1*. Schematic representation of the results of the integration between Biomedical Sciences, Artificial Intelligence,**

and New Media & Digital Culture.

5.4 More comprehensive understanding

The integration process as proposed by Repko & Szostak (2017) has led to several novel insights, which collectively are referred to as ‘the more comprehensive understanding:

- The disciplinary boundaries in AI concerning longevity extension may well be overcome by theoretical biological insights from disciplines such as Biomedical Sciences.
- A limit to maximum life expectancy, as observed in several Biomedical Sciences studies, is not conclusive evidence regarding the possibility of longevity extension, since Biomedical Sciences insufficiently draws insights from other more technical disciplines which could potentially enable them to break these limits.
- With technology developing more rapidly than ever before, ethical considerations are also at a more central stage than ever before. Ethical insights, such as drawn from New Media and Digital Culture, should be well communicated with both the disciplines leading technological progression and the society as a whole to create mutual understanding and acceptance.

6. Conclusion

In this interdisciplinary essay, we have sought to outline the possibilities of doubling the human lifespan by gaining several different disciplinary insights and subsequently integrate these to gain novel knowledge by using Repko & Szostak (2017).

Firstly, as a direct answer to the question what needs to be done to potentially achieve a doubling of the human lifespan, more money should be invested in the cooperation between the field of AI and Biomedical Sciences in order to combine their knowledge. Longevity research should no longer be exerted separately per discipline but should instead be done in a cooperative interdisciplinary research environment. By doing so, a bridge is built between both disciplines through which actively a continuous exchange of knowledge is achieved.

Secondly, in order to have a doubling of the human life expectancy to be accepted in our society, it is important to keep reviewing new longevity technologies from an ethical point of view. To achieve this, NMDC should receive the results following from the cooperation between AI and Biomed before they are implemented, and in return, NMDC should play an advisory role in their cooperation. This could be achieved by creating a structure (such as an organization) where focus is put on the transfer of knowledge between all involved disciplines. This way, an advisor can continuously monitor the ethics of the new technologies. If a technology is not up to ethical standards, for example, it should be led to a point where it becomes ethically acceptable and should not be simply halted.

Thirdly, and as briefly mentioned before, the coming of new interdisciplinary technological developments may significantly contribute to the likelihood of achieving a doubling of the human lifespan. For example, biofabrication (a combination between AI, computer science and Biomedical Sciences) may revolutionize longevity research in a way that disciplinary techniques are not able to do.

7. Discussion

Strengths and weaknesses

The strength of this paper is the straightforwardness of the meta-integration. The required structural organisation for a society promoting and constantly monitoring longevity extension techniques is clearly put forward and provides vital advice for future longevity research.

The main limitation of this paper is the inability to explain the specific time and technology through which a doubling of the human lifespan can be achieved. This is mainly due to the fact that at this point it is unknown:

1) how combining knowledge may influence longevity research

2) how the rate at which groundbreaking technological developments relevant to longevity extension may influence the achievability of a doubling. This is also the reason we are neither able to say whether a tripling or a quadrupling may also be possible.

Critical reflections on own disciplines

A disciplinary limitation for Biomedical Sciences is the fact that research in this field often disregards philosophical views with respect to cognition and mainly focusses on the physiological.

A disciplinary limitation for NMDC is that, since longevity extension is not yet present, it is still unclear how the ethical framework we proposed might alter over time and whether current NMDC theories are relevant in the future.

A limitation from AI is that its primary focus lies not on biomedical research, and it views almost everything as a system while public opinions and ethical issues play an important role within a subject like lifespan extension.

These limitations can partially be overcome by the inclusion of additional disciplines, however, this was not possible within the scope of this paper.

Suggestions for other disciplines

Other disciplines could also have provided important insights. The discipline of (Neuro)Psychology might provide additional perspective on cognition (which Biomedical Sciences lacks) and give insight into what people consider to be ‘healthy’ treatments in order to identify when side-effects are considered acceptable .

The disciplines of Economy and political science could have added how projects for longevity could be supported. Economy could find out how these technologies could be developed in a way that is economically viable and has plenty of funding for the projects. Political science could look at the best governmental policies for the support of these projects. Other insights could also have been gained like the drawback on these fields of these projects.

Different integrative approaches

In the common ground, the concepts and theories which appeared the most in all involved disciplines have been chosen, but if other concepts and theories for the common ground had been chosen, different integrative approaches would have been chosen that could potentially lead to a different integration and a better interdisciplinary result.

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