Aging as a Disease

(STS Topic)

Optimizing the biosynthesis of therapeutic compounds in E. coli using computational modeling

(Technical Topic)

A Thesis Prospectus in STS 4500

Presented to the Faculty of the School of Engineering and Applied Science

University of Virginia

In Partial Fulfillment of the Requirements for the Degree

Bachelor of Science in Biomedical Engineering

By

Ben Neubert

12/6/2019

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

Signed: _____Date_____

Approved:_____Date_____

Michael Gorman, Department of Engineering and Society

Introduction

With older individuals forming an ever-increasing segment of the population, aging is coming to the forefront of discussions from a health care, economic, and societal perspective. The desire to increase the number of healthy years within someone's life is central to biomedical research, but processes such as those that cause aging are still treated as inevitable which can hinder research as well as funding. My STS thesis will focus on how aging is viewed within society and scientific communities, the impact these views have on funding for research, and the subsequent effect of increased lifespans on society as a whole.

My technical thesis is being completed through my biomedical engineering capstone design class and involves my work being done within the Papin lab where I am developing a data-driven curation pipeline for genome-scale metabolic models. The gastrointestinal (GI) microbiome represents a diverse set of organisms that play a critical role in human health by contributing to immune system modulation, metabolic functions, and other important activities[1–3]. Metabolism is one of the primary mechanisms by which the GI microbiome interacts with the host organism. Genome-scale metabolic network reconstructions (GENREs) are a powerful computational tool for mathematically modeling the metabolic processes within a cell at a systems-level. The current methodology for manually generating high-quality GENREs requires a great degree of labor and time on the order of several months or even years[4]. Automated methods such as ModelSEED have been able to reduce this figure to approximately 48 hours using only an assembled genome sequence, however, these methods only reach approximately 66% accuracy[5]. Therefore, additional steps must be taken to develop a pipeline through which a high-quality GENRE may be produced while minimizing the time to achieve this quality. In the technical portion of my thesis, I aim to first develop a data-driven model curation pipeline to

reconstruct highly accurate GENREs and apply it to *E. coli* K-12 in an anaerobic growth environment with a focus on pathways resulting in the production of the therapeutic compounds: indole, succinate, and acetate. Second, I aim to validate the accuracy of the proposed pipeline, while also gaining an increased understanding of *E. coli* metabolism in an anaerobic environment in order to find metabolites which increase the production of the aforementioned therapeutic compounds in the gut.

The technical component of my thesis will be displayed through a proposal from my capstone design class. The proposal will be in the form of an NIH-style grant proposal, which contains many sections. Because the proposal is still in progress and unrelated to my STS prospectus, I will not be including this proposal below and instead will be focusing purely on the way in which society views aging as a natural process.

What is Aging?

With the number of people over the age of 60 being projected to approximately double between 2015 and 2050 from 12% to 22%, questions have arisen around aging that range from the socioeconomic impact of this segment of the population to how we perceive aging itself[6]. The aging of the baby boom generation, a growing number of people living with multiple chronic conditions, and the reform of the US health care system all are playing a role in bringing up a discussion on aging in the United States[7]. The broad medical definition of aging is the process of becoming older that is genetically determined and environmentally modulated. At the cellular level, aging is the impact of the accumulation of a wide variety of molecular and cellular damages over time including, but not limited to, telomere erosion, epigenetic alterations, cellular

senescence, and stem cell exhaustion[8]. The collective effect of cellular aging is believed to be a critical component leading to the overall aging of individuals.

Currently, the life expectancy for a baby born in the United States in 2014 is 78.8 years[9]. Through previous studies on twins, researchers were able to determine that 20% of aging is related to genetics and 80% is dictated by lifestyle[10]. Therefore, factors such as where one lives can majorly impact one's lifespan, which is displayed by the discovery of five places around the world where people routinely live to significantly older ages (Loma Linda, CA, USA; Nicoya, Costa Rica; Sardinia, Italy; Ikaria, Greece; Okinawa, Japan)[11]. These areas, known as 'Blue Zones', are demographically confirmed to have the highest percentage of centenarians with the chance of reaching age 100 being 10 times greater than in the United States as a whole. Residents of these areas were determined to have nine specific characteristics, the Power 9, which were conserved across their residents: moving naturally, having a sense of purpose, using stress reduction techniques, following caloric restriction, eating plant-based diets, consuming wine, having a sense of belonging, prioritizing loved ones, and engaging in social circles that supported healthy behaviors. The Power 9 display that aging can be modulated through healthy lifestyle decisions, some of which like caloric restriction are backed by basic science research. Additional research is needed to elucidate the fundamental mechanisms behind aging and to develop novel therapies to combat this process, which is an outcome previously seen as impossible.

Aging as a Natural Process

As a new generation of scientists are emerging, the previously traditional views of aging as an inevitable and natural process are coming into question[12]. The idea that aging is a natural

process has become intrinsically a part of society, without proponents of this belief taking a critical look at whether or not this is truly the case. What society and doctors in particular view as a disease state versus normal changes throughout time as a result of increased mechanistic understanding of the underlying biological processes as well as due to historical context. There are several instances in history of situations being considered disease which would be preposterous to modern society and scientists[13]. For example, drapetomania was considered to be a mental disease that caused slaves to run away in 1851[14]. Homosexuality was considered as a disease as recently as 1973, at which point the American Psychiatric Association removed it from the diagnostic and statistical manual of mental disorders with the latest print of DSM-II[15]. In addition, numerous diseases used to be purely accepted as a natural consequence of aging such as osteoporosis, hypertension, and Alzheimer's disease. With these cases in mind, is aging a natural process or is it a disease?

The question of aging as a natural process should be considered alongside instances within the medical and research communities of conditions that are considered to be diseases. Perhaps the ubiquity in aging is a significant component in why the process is considered by many to be a natural one. However, this cannot be the case considering physiological-level conditions such as muscle atrophy leading to sarcopenia, reduction in bone mass and density leading to osteoporosis, atherosclerosis, dementia, and acne are nearly universal phenomena in humans and yet they are not considered to be natural processes[13]. Cellular level events contributing to aging including the increasing stiffness of collagen fibers, increased frequency of visible chromosomal alterations, disruption of nerve cell nuclei due to clumping of chromatin, among others individually are inevitable consequences of life[16]. Yet these individual occurrences are often treated as departures from what is normal or natural in research labs focusing on these

phenomena, but the cumulative effect of these underlying processes are viewed as natural. Progeria, the rapid aging of a child, is considered to be a disease, but if the same changes are to occur in an elderly individual they are normalized as a natural process that does not require or deserve medical intervention[16]. Opponents of treating aging as a disease take various stances. These arguments include claiming classifying aging as a disease is equivalent to equating cause and effect and aging being too broad of a concept to be reduced to a single specific pathology[12]. Ultimately, the case for aging's classification and its view in society has ramifications that go beyond the philosophical discussion.

The case for classifying aging as a disease stems largely from a point of view that doing so will allow for an increase in funding towards its research and legitimizing medical efforts to do so. The primary source of funding for aging research in the United States is the National Institute of Aging with a budget of $3.08 billion in 2019, which has increased significantly due to an additional $425 million for Alzheimer's Disease research funding[17]. For comparison, the National Cancer Institute(NCI) has $5.74 billion in funding as of 2019[18]. Budgets for scientific research have historically been influenced heavily by the political climate and public support. As a result of increased public support for cancer research and the concerns of those in the medical profession, Richard Nixon declared a "war on cancer". As a part of this intitiative he requested an additional $100 million to be added to the NCI budget and eventually signed the National Cancer Act of 1971, increasing NCI funding and power[19,20]. These developments have ultimately resulted in an increase in the relative survival rate for all cancers of 70%[21]. Therefore, the changing support for research by scientists and the masses is capable of driving change at a societal level, positively impacting research and increasing federal budgets. A change in view

with regards to aging could result in increased funding through grant-awarding bodies for aging research and the development of therapies to combat the effects of aging[13].

Classification as a disease would involve giving aging its own code within the International Statistical Classification of Disease and Related Health Problems (ICD-11), which forms the basis for payment for health services. Further, recognition of aging as a disease would legitimize biomedical researchers pursuing the field and reject the fatalism of the label of natural[22]. In addition, the distinction would also change the regulation of anti-aging therapies from the FDA's regulations for cosmetic products to the more rigorous regulations for disease treatment and prevention[23]. Society and more specifically researchers and funding agencies no longer viewing aging as a natural process would result in positive health outcomes for a growing portion of the population.

The nature of the aging debate lends itself to being analyzed through the lens of normalized deviance. Normalized deviance refers to when an organization becomes insensitive to a deviant practice resulting in it no longer being considered wrong[24]. At an individual level, this occurs when the individual perceives their actions or beliefs as acceptable as a result of the culture within their organization propagating this notion to the point of it becoming a social norm. A characteristic of normalized deviance is when an organization takes an outside, objective point of view to interpret their actions and deems certain behavior as an unacceptable practice or standard. For example, normalized deviance was a critical factor within the Challenger disaster. When NASA was forced to analyze their processes following the Challenger disaster, they determined the failure to be due to an O-ring malfunction. Despite numerous sources of evidence in testing showing the potential for such a failure, abnormal test results regarding the O-rings became normalized due to repeated occurrence and faulty organizational

procedures. Normalized deviance is capable of occurring at larger scales such as at the society-level. While these instances of normalized deviance are not as common due to the number of individuals involved, a lack of scientific knowledge regarding a topic like aging can leave the general public and scientific community to default to the normalized belief without critically evaluating the belief. The fact that taking an objective view of the aging process lends the observer to a perspective in which the phenomenon is a disease draws attention to an occurrence of normalized deviance.

The propagation of the belief that aging is natural in part can stem from the societal passing down of the belief. Medical students are taught by older physicians that there is not anything that they can do to alter the inevitable course of aging[16]. While this could be to help new medical students interact and examine elderly patients, lessons such as these help to propagate a way of thinking about aging as a natural process. Diseases are perceived as a deviation from the normal reference range for an individual based on age and sex[13]. This reference helps to prevent circumstances such as the lack of sperm production in human male neonates from being classified as a disease state, however, the biological reasoning breaks down when stratifying elderly and younger adults. Society and the medical community's view of aging as a natural process coming as a result of self-perpetuation rather than biological reasoning lends the debate to being viewed as a case of normalized deviance.

Conclusion

The way in which scientists, funding agencies, and society as a whole view the process of aging has vast impacts on the development of medical interventions and the focus of research efforts/funds. Traditionally held beliefs about the process of aging as a natural, even inevitable,

process hinder the funding of anti-aging research, which has the potential to combat a plethora of diseases at their roots in a preventative fashion before symptoms arise allowing for a successful increase in the health spans of individuals. The question of how longer life expectancies will impact society as a whole, especially from a social and economic perspective, is a critical aspect of the issue. This question will be explored in my future work for my final thesis to determine the potential long-term impact of increased research towards aging. I plan to look at this problem through the STS framework of normalized deviance in order to analyze how the traditional view of aging came about as well as the means by which this viewpoint can be changed and the effect this will have on research.

References

1. Gilbert, J. A. *et al.* Current understanding of the human microbiome. *Nat. Med.* **24**, 392–400 (2018).
2. Morrison, D. J. & Preston, T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* **7**, 189–200 (2016).
3. Round, J. L. & Mazmanian, S. K. The gut microbiome shapes intestinal immune responses during health and disease. *Nat. Rev. Immunol.* **9**, 313–323 (2009).
4. Thiele, I. & Palsson, B. Ø. A protocol for generating a high-quality genome-scale metabolic reconstruction. *Nat. Protoc.* **5**, 93–121 (2010).
5. Henry, C. S. *et al.* High-throughput generation, optimization and analysis of genome-scale metabolic models. *Nat. Biotechnol.* **28**, 977–982 (2010).
6. Ageing and health. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health.
7. Anderson, L. A., Goodman, R. A., Holtzman, D., Posner, S. F. & Northridge, M. E. Aging in the United States: Opportunities and Challenges for Public Health. *Am. J. Public Health* **102**, 393–395 (2012).
8. Lagunas-Rangel, F. A. & Bermúdez-Cruz, R. M. The Role of DNA Repair in Cellular Aging Process. *DNA Repair- Update* (2019) doi:10.5772/intechopen.84628.
9. Li Yanping *et al.* Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population. *Circulation* **138**, 345–355 (2018).
10. Herskind, A. M. *et al.* The heritability of human longevity: a population-based study of 2872 Danish twin pairs born 1870-1900. *Hum. Genet.* **97**, 319–323 (1996).
11. Buettner, D. & Skemp, S. Blue Zones. *Am. J. Lifestyle Med.* **10**, 318–321 (2016).
12. Gavrilov, L. A. & Gavrilova, N. S. Is Aging a Disease? Biodemographers' Point of View. *Adv. Gerontol. Uspekhi Gerontol.* **30**, 841–842 (2017).
13. Bulterijs, S., Hull, R. S., Björk, V. C. E. & Roy, A. G. It is time to classify biological aging as a disease. *Front. Genet.* **6**, (2015).
14. Willoughby, C. D. E. Running Away from Drapetomania: Samuel A. Cartwright, Medicine, and Race in the Antebellum South. *J. South. Hist.* **84**, 579–614 (2018).
15. The diagnostic status of homosexuality in DSM-III: a reformulation of the issues. *Am. J. Psychiatry* **138**, 210–215 (1981).
16. Caplan, A. L. Death as an unnatural process. *EMBO Rep.* **6**, S72–S75 (2005).
17. NIA Funding Line Policy for FY 2019. *National Institute on Aging* https://www.nia.nih.gov/research/grants-funding/nia-funding-line-policy-fy-2019.
18. NCI Budget and Appropriations. *National Cancer Institute* https://www.cancer.gov/about-nci/budget (2015).
19. Cancer Facts & the War on Cancer | SEER Training. https://training.seer.cancer.gov/disease/war/.
20. National Cancer Act of 1971. *National Cancer Institute* https://www.cancer.gov/about-nci/overview/history/national-cancer-act-1971 (2016).
21. DeVita, V. T. The 'War on Cancer' and its impact. *Nat. Clin. Pract. Oncol.* **1**, 55–55 (2004).
22. Callahan, D. & Topinkova, E. Is Aging a Preventable or Curable Disease? *Drugs Aging* **13**, 93–97 (1998).
23. Gems, D. Tragedy and delight: the ethics of decelerated ageing. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **366**, 108–112 (2011).
24. Vaughan, D. *The Challenger Launch Decision: Risky Technology, Culture, and Deviance at NASA*. (1996).