The information theory of aging: Hacking immortality?

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Abstract:

Humans have sought to cheat death for as long as we have been cognizant of our mortality. History's early explorers of the frontier of immortality include alchemists in the pursuit of an elixir of life and emperors who, ironically, hastened their own death from the consumption of mercurial concoctions. Scientifically grounded approaches to the extension of the human lifespan emerged in the 20th century and were based on hormonal rejuvenation, calorie restriction, and most recently, the consumption of supplements with purported anti-aging effects. A combination of three "longevity drugs" has recently been championed by Dr. David Sinclair, co-discoverer of the lifespan-regulating sirtuin enzymes, and author of the epigenetics-focused Information Theory of Aging (ITA). In this work, we investigate the evidence behind Sinclair's ITA, highlight concerns related to his regimen, and reflect on the possibility that we are at a nexus in time preceding a dramatic increase in human healthspans. Promisingly, if the ITA holds true, individuals will be uniquely empowered to "hack" their own immortality.

Introduction

For at least as long as recorded history, the realization of life's finitude has provoked unease among some people. Mortality is a major theme in the earliest known work of literature, the Epic of Gilgamesh, in which the death of his friend Enkidu prompts Gilgamesh to undertake a quest at whose conclusion he makes peace with his own eventual death [1]. Accepting mortality (or some concept of continued survival in the afterlife) has not proven satisfactory for everyone, however, and practical efforts at achieving immortality have been attempted throughout the centuries.

Perhaps the most notable pre-scientific endeavors are those of alchemists, both in Western esoteric and Daoist traditions. In a famous example, the first Chinese emperor, Qin Shi Huang Di, so feared death that he imbibed various purported elixirs of life which is believed to have hastened his death due the toxic effects of mercury, a key ingredient in the concoctions [2].

In the late 19th and early 20th centuries, the rise of professional science and increasing biological understanding enabled the development of the first scientifically-grounded anti-aging interventions, which were based on the inferred rejuvenating power of hormones (reviewed in [3]). Although such interventions were unsuccessful, several practical approaches to extending both lifespan and healthspan (the period of one's life when in generally good health) have become prominent among later 20th and 21st century longevity enthusiasts, including caloric restriction and anti-oxidant supplementation. [4]

One particular pharmacological cocktail of three drugs has recently gained attention when Dr. David Sinclair, one of the discoverers of the role of sirtuins in lifespan regulation, revealed in a LinkedIn post [5] (posted on June 25th, 2018) and later in his book [6] (published September 19th, 2019) that he was taking these "longevity molecules" every day. The combination consists of the anti-diabetes medication metformin, the mTOR inhibitor rapamycin/resveratrol, and nicotinamide mononucleotide (NMN), a precursor to nicotinamide adenine dinucleotide (NAD^+), an essential co-factor of sirtuin function. Here, we examine the justification for taking these three drugs in context with Dr. Sinclair's mechanistic theory of aging, which he calls the "Information Theory of Aging" (ITA).

Epigenetic control of aging — The Sinclair theory

Biological theories of aging can be divided into two types: *evolutionary* theories aim to explain why aging exists as a phenomenon, while *mechanistic* theories aim to describe the proximal cause of senescence, or age-associated decline in function.

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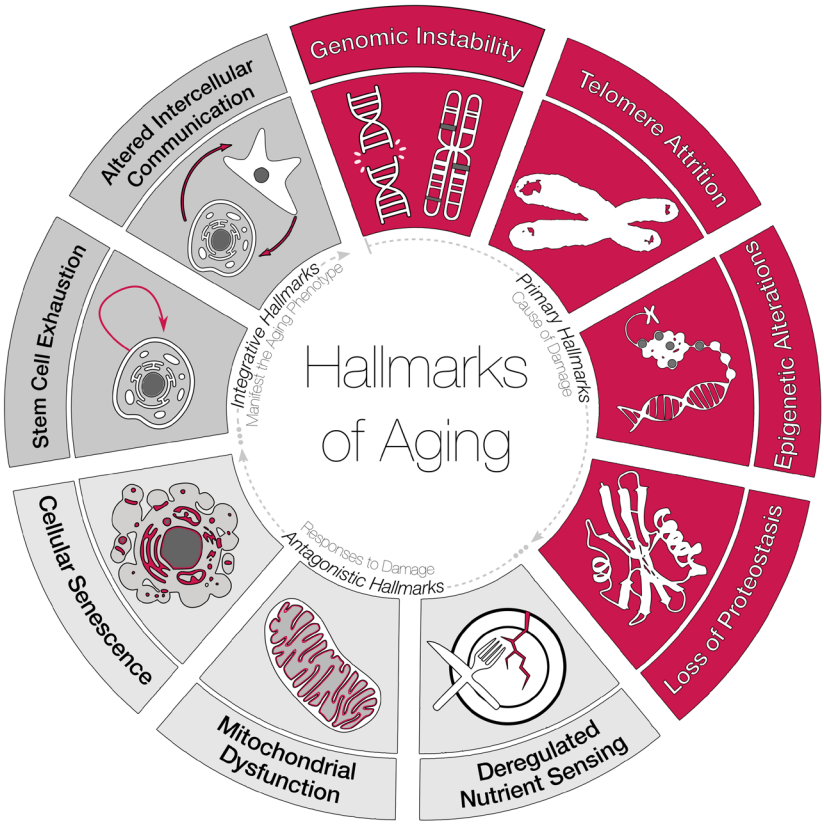

Figure 1 | The nine hallmarks of aging and their functional interconnections. The primary hallmarks (red) are responsible for initial cellular damage which manifests the antagonistic hallmarks (light grey) as a response to mitigate that damage. Together, these hallmarks contribute to the manifestation of the integrative hallmarks (dark grey) which, ultimately, are responsible for the aging phenotype. Figure adapted from [10].

Here, we use the terms aging and senescence interchangeably to signify the functional decline of an organism as a function of calendar time. Senescence, in this sense, is distinct from cellular senescence, which is a narrower term signifying terminal cell cycle arrest and stereotypical phenotypic changes in the cell [7].

The most influential evolutionary theories (reviewed in [8]) have in common the idea of aging as an outcome of specific selective force interaction patterns, but discuss the molecular and cellular mechanisms with a high level of abstraction. Mechanistic theories, by contrast, suggest specific causes of senescence at the molecular, cellular, and organismal levels. Important mechanistic theories can be further divided into programmed aging theories, which consider senescence a programmed response (examples include the endocrine and immunological theories), and damage theories, which explain it as a consequence of accumulated errors or damage (examples include oxidative stress theory, somatic mutation theory, and telomere shortening theory) [9].

The concept that aging is not necessarily inevitable is evidenced by several multicellular taxa (including plants, invertebrate, and vertebrate animals) which do not exhibit an age-dependent increase in mortality, a phenomenon which Caleb Finch termed *negligible senescence* [10, 11]. Thus, it appears that senescence is neither evolutionarily inevitable, nor impossible to overcome at a mechanistic level. To be overcome, however, it must first be understood.

An influential review in 2013 by several leading scientists in the field of aging biology has proposed a list of nine hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [7], illustrated in Figure 1. Of these nine, four are proposed as the "primary hallmarks", or the ultimate causes: genomic instability, telomere attrition, epigenetic alterations, and the loss of proteostasis. The rest are considered either "antagonistic hallmarks" which are responses to damage, or "integrative hallmarks", which are the proximal causes of organismal decline [7] (Figure 1). In other words, the primary hallmarks are biochemical events that trigger local (cellular) responses in the form of antagonistic hallmarks, which in turn result in tissue- and organ-level dysfunction (the integrative hallmarks). This tissue and organ dysfunction is the most proximal (immediate) cause of the phenotypes observed in aged individuals.

In the ITA as proposed by Sinclair, there is one principal cause of aging: loss of epigenetic (non-DNA-encoded gene regulatory) information. In this framework, the aging process is represented by a linear sequence of events, depicted in Figure 2 [6]. While genomic instability, caused by DNA breaks, does precede and cause the epigenetic dysregulation, the ITA considers the loss of epigenetic information as the central cause of aging. In other words, any genetic alterations (mutations) that result from DNA breaks and genomic instability are irrelevant to the downstream events: only the disruption to the epigenome counts.

Today, epigenetics has come to signify non-DNA-encoded heritable information, but it retains much of its original meaning

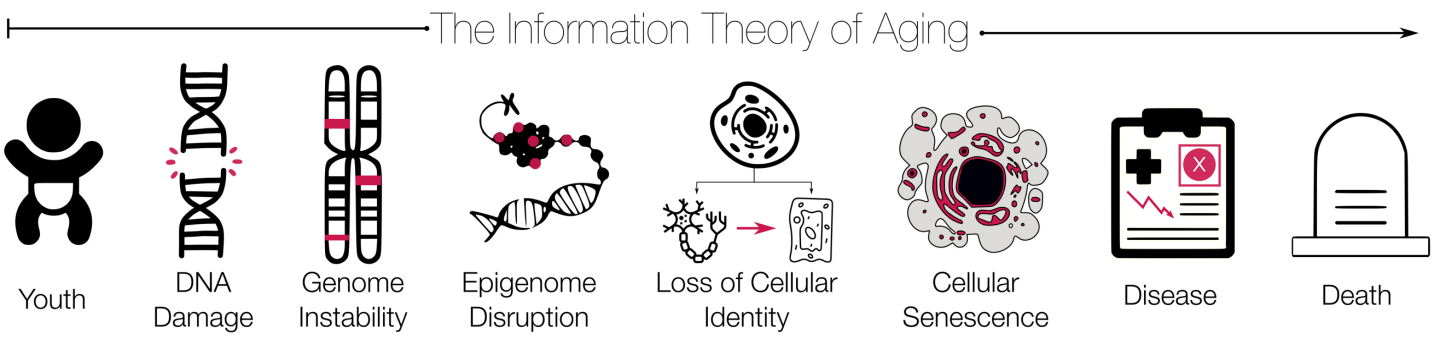

Figure 2 | Illustration of Sinclair's information theory of aging. Adapted from [5].

proposed by Conrad Hal Waddington as the causal mechanisms of multicellular development [12]. Epigenetic mechanisms, it is now understood, control the spatio-temporal patterning of gene expression, which allows cells to maintain a specific identity and coordinate the events of organismal development and later maintenance. Loss of cellular identity, according to the ITA, is directly downstream of the loss of epigenetic information, and is ultimately responsible for organismal breakdown. If the loss of epigenetic information can be either prevented, or the lost information recovered, the ITA predicts that cellular identity can be maintained *in perpetuo*, which would result in negligible senescence.

What constitutes epigenetic information? What are some of the specific hallmarks of epigenetic aging? In a narrow sense, epigenetic information in the nuclear genome is represented by histone marks (chemical moieties present on histone tails) and DNA methylation. Nuclear DNA is tightly wound around nucleosomes-octamers of histone proteins. The number, location, and nature of histone marks (such as acetyl, methyl, ubiquityl, and other functional groups) control the accessibility of DNA to the cellular environment, which has direct consequences for gene expression (when transcription is switched "on" or "off") as well as DNA damage and repair [13]. Typical epigenetic hallmarks of senescence include the loss of histones, the loss of balance between various histone marks, changes in chromatin architecture and the pattern of euchromatin and heterochromatin ("open" and "closed" conformations of DNA and histones), changes in DNA methylation patterns (global hypomethylation and local hypermethylation), and as a result of all these changes, transcriptional dysregulation (reviewed in [14]).

Dr. Sinclair has played a pivotal role with the discovery that the histone (and non-histone) deacetylase SIR2 (Silent Information Regulator 2), which lends its name to the sirtuin enzyme family, is a regulator of lifespan in budding yeast (later confirmed in other animals, including mammals [15]). It is therefore not unexpected that the ITA would elevate epigenetics above the other hallmarks of aging. But what evidence supports this contention?

One stream of support comes from so-called "epigenetic clocks", which is a term that refers both to mathematical estimators of chronological and biological age on the basis of cytosine methylation in the DNA, as well as the cellular processes themselves which give rise to age-related DNA methylation patterns (reviewed in [16]). Three such epigenetic estimators—Hannum's, Horvath's, and Levine's clocks—correlate well with chronological age and other age-related conditions, consistent with the idea that biological aging results from developmental and maintenance programs that generate the characteristic DNA methylation patterns [16].

The second line of evidence comes from Dr. Sinclair's recent work on "ICE" (inducible changes to the epigenome) mice and cells lines, which is currently deposited on a pre-print server [17, 18]. ICE mice and cells contain a tamoxifen-inducible endonuclease I-*PpoI*, endogenous to the slime mold *Physarum polycephalum*, that recognizes approximately 20 sites in the mouse genome. Tamoxifen treatment of ICE mice or cultured cells induces I-*PpoI* expression, resulting in DNA double strand breaks (DSBs). In the experiments reported in the pre-print publications, tamoxifen was added to the food of 4-6 month old ICE and control mice of both sexes for a period of 3 weeks to induce I-*PpoI* [18]. Compared to tamoxifen-treated control mice, tamoxifen-exposed ICE mice display numerous signs of premature aging (decreased weight, increased frailty, pronounced kyphosis, progeroid features in several organs, and neurological impairment). Additionally, the ICE mice were 50% "older" than age-matched controls, according to blood and muscle tissue-validated DNA methylation clocks [18]. Crucially, for the argument that the progeroid phenotypes are caused by epigenetic alterations downstream of DSB induction, neither ICE mouse tissues nor cultured ICE cells display telomere shortening or an increased mutation rate at I-*Ppol* cut sites, off-target sites, or 100,000 random genomic loci [17, 18].

However, questions remain about the mutagenic potential of I-*PpoI* activation. It has been noted on the BioarXiv discussion board that previous work using this system has shown that while I-*PpoI* does not cause point mutations, it has the potential to cause large deletions (up to 1Mb) and generate chimaeric DNA by joining two different I-*PpoI* sites during repair [19]. It is not clear whether ICE mouse tissues are affected by such large deletions. Furthermore, tamoxifen-treated ICE cells show increased levels of LINE-1 retrotransposon RNA [17]. LINE-1 retrotransposition events have been associated

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with at least 65 disease-causing mutations in humans [20] and it is unclear whether the increase in LINE-1 activity may contribute to mutagenesis on genomic sites other than the I-*PpoI* sites or the 100,000 random sites (the mouse genome includes 2.5 billion nucleotides).

Even if the conclusions drawn from ICE mouse experiments are correct and the epigenetic alterations are the sole cause of progeroid phenotypes in this setting, it does not follow that loss of epigenetic information is the sole possible cause of aging in the wild type setting, where somatic mutations, proteostasis, and telomere attrition may play a role together with or independent of the epigenetic alterations. Somatic mutations, in particular, are dismissed by Dr. Sinclair as not important on the argument that the largely normal lifespan of animals created by somatic cell nuclear transfer (SCNT) shows that irreversible genetic changes cannot be the cause of aging [17, 18]. However, the extremely low efficiency of SCNT (<2% per reconstructed oocyte) and the documented role of genetic abnormalities associated with aging phenotypes in several cloned pigs make this a premature conclusion [21].

Regardless of whether the ITA is correct in all particulars, it represents an advance in the understanding of aging biology. Armed with this increasing knowledge, we are on a better footing today than early 20th century hormone researchers or elixir-imbibing ancient emperors to discover pharmacological interventions to combat or reverse the effects of aging.

The Sinclair regimen

The popularity of Sinclair's ITA is due, in part, to its emergence as a promising mechanistic theory of aging. However, the ITA enjoys a widespread acclaim that can be attributed to its marketing as an *actionable* theory of aging. That is, Sinclair himself advocates for a self-prescribed regimen based on his ITA in both his book and in public lectures. Sinclair describes the regimen he developed and adheres to is an effort to extend his own healthspan with an emphatic admission that he is not a medical doctor and offers no assurance that his self-prescribed regimen will result in dramatically improved healthspans. He does, however, disclose that his brother, father, wife, and family dogs each adhere to a version of this regimen and, anecdotally, all have enjoyed improved health outcomes since. Table 1 outlines Sinclair's regimen, augmented with the longevity-related rationale.

As introduced, various stripes of "immortality-hackers" have existed for as long as we have been cognizant of our inescapable mortality. A plethora of supplements and lifestyle interventions of varying degrees of scientific validity exist today, each presenting trade-offs with other comforts of life. One notable example is periodic self-imposed starvation (*i.e.* intermittent fasting) to enforce caloric restriction. Sinclair's regimen presents a paradigm shift in his claims that the stimulation of NAD^+-dependent sirtuin pathways through the consumption

Table 1 | Sinclair's Longevity Regimen, as Outlined in [6].

Type	Intervention	Dose	Specification	Rationale
Chemical	NMN	1,000 mg/daily	Morning (tablet)	Based on ITA
	Resveratrol	1,000 mg/daily	With yogurt; soluble in fat	Correlated with longevity
	Metformin*	1,000 mg/daily	Morning (tablet)	Hypoglycemic effect
	Vitamin D	Daily recommendation	Morning (tablet)	Improves protein homeostasis
	Vitamin K2	Daily recommendation	Morning (tablet)	Linked to decreased mortality [22]
	Aspirin	83 mg/daily	Preventative dosage (tablet)	Cardio-protective
Lifestyle	Limit high carb. intake	Reduced/Eliminated	Specifically: sugar, bread, pasta, and desserts	High carb. food lead to increased blood pressure and heart rate
	Modification of meal number/size	1x daily, reduced size or eliminated	Typically: skipped lunch	Enforces caloric restriction
	Plant-based diet	Meat intake reduced/ eliminated	Exception: meat consumed when exercising	Associated to multiple health benefits
	Regular exercise	Walking/stairs daily, gym on weekends	Mixture of weight training, cardio, and cold-shock therapy	Associated to multiple health benefits
	Toxin/radiation avoidance	N/A	Specifically: non-smoker, avoid UV, X-rays, CT scans, certain plastics	Reduces DNA damage
	Cold exposure	Keep cool daily, nightly	N/A	Hormetic effect
	Maintain BMI	N/A	N/A	Ideal to maintain optimal healthspan

* Typically prescribed, possibly replaceable with over-the-counter Berberine for which studies demonstrate comparable hypoglycemic effects at similar dosages [23]. Note: Sinclair mentions a phlebotomist visit every few months to have his blood drawn and evaluated for several dozen biomarkers to inform adjustments to his diet and exercise.

of NAD+ or its precursors can not only slow the progression of aging, but ultimately reverse it based on experiments in mice. Since sirtuins are activated when in a calorie-restricted state, boosting sirtuin activity through the consumption of an NAD+ precursor, in theory, should provide health benefits without the necessary starvation. Moreover, Sinclair claims that, at a high level, the maintenance of one's epigenome will prevent or delay the onset of many of the most common diseases and causes of death among the geriatric populations (*e.g.* heart disease, diabetes, cancer, *etc.*), thereby extending individual healthspans.

Evidently, a supplement-based anti-aging approach accompanied by minimal commitment to exercise and dietary changes is attractive among the immortality-DIYers and broader public, alike. While the concept of translating senescence-reversing laboratory research into an actionable regimen that enables individuals to mitigate their own aging is certainly widely attractive, a number of weaknesses in the ITA-based regiment must first be addressed.

Hasty generalization from studies in model organisms

Ground-breaking medical research is conducted using model organisms for which genetic makeup and environmental factors are tightly controlled; a reality in stark contrast to the genetic diversity and chaotic environments of *Homo sapiens*. Sinclair himself acknowledges that all aging-related therapies lack the rigorous long-term clinical studies required to understand the breadth of possible health outcomes. Nonetheless, Sinclair claims that the imminence of death justifies this hasty, and possibly detrimental, generalization; ironically echoing a view shared by Qin Shi Huang Di and history's prematurely demised alchemists who pursued the elixir of life.

"N=1" study of regimen efficacy

While many of the sirtuin activating compounds depicted in Figure 3 are undergoing human clinical trials, the anecdotal evidence in support of Sinclair's regimen is derived from a form of "N=1" self-experimental study, where the efficacy of his regimen is concluded from his claimed rejuvenated youthfulness. Ignoring the numerous confounding factors introduced from other longevity-related interventions (*e.g.* intermittent fasting, regular exercise, temperature regulation), an anecdotal, uncontrolled, and possibly biased account of improved healthspan violates the scientific method. Furthermore, the ITA itself focuses on conserving epigenetic health (one hallmark) to prevent a detrimental biological cascade, however the Sinclair regimen incorporates a number of interventions derived from research focused on other aging hallmarks. While the regimen itself is not an explicit test of the ITA, it would be fallacious to attribute its successes solely upon the ITA-based interventions [24].

Commercial conflicts of interest

Finally, Sinclair is integrally involved in the commercial development of therapeutics based upon his research. While several of his affiliated companies are still active, a number of them have terminated for a variety of reasons. His laboratory webpage reports these affiliations [25] and the industry connections which have been disclosed to the National Institute of Health are highlighted in Table 2. As a biotech entrepreneur, Sinclair's extensive commercial involvement presents a two-sided coin: on the one hand, Sinclair's faith in his research justifies significant investment in the pursuit of therapies that hold the potential to dramatically improve the

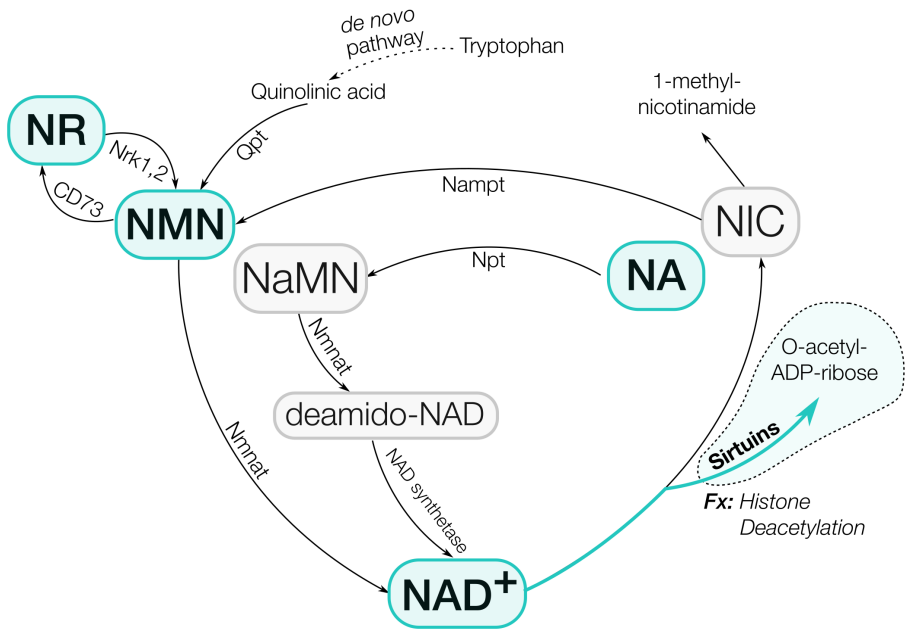

Figure 3 | The NAD+ biosynthetic pathway emphasizing the consumable molecules in support of Sinclair's regimen. The green molecules represent over-the-counter, commercially available molecules in the form of supplements aimed at increasing the production of NAD+ to promote sirtuin histone deacetylation activity. This activity helps to preserve the epigenomic health of an individual and may result in an increased healthspan, as purported by ITA. Abbreviations: NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; NA, nicotinic acid; NAD+, nicotinamide adenine dinucleotide; NaMN, nicotinic acid mononucleotide; NIC, nicotinamide. Adapted from [24].

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Table 1 | Sinclair's ProPublica Reported Conflicts of Interest to the NIH.

Company	Brief Description	Affiliation(s)
OvaScience	Biotechnology company focused on female infertility, based on Jonathan Tilly's research on mammalian oogonial stem cells Sinclair's work on mitochondria.	I
Cohbar, Inc.	Development of mitochondrial-based therapeutics to treat age-related diseases.	F,E,A
Life Biosciences	Parent company for eight daughter companies, each developing commercial solutions for one of the hallmarks of aging (excl. Deregulated Nutrient Sensing).	F,I,E,A,B,IP
Senolytic Therapeutics	Life Biosciences company focusing on the cellular senescence hallmark of aging by developing senolytics: small molecules targeting and inducing death in senescent cells to improve human health.	F,I,E,A,B
Spotlight Biosciences Inc.	A Life Biosciences company developing proteomics services.	F,I,E,A,B,IP
GlaxoSmithKline (acq. Sirtris Pharmaceuticals)	Global healthcare organization that acquired Sirtris Pharmaceuticals, a biotech company co-founded by Sinclair to develop molecules targeting sirtuins.	A,IP
Jumpstart Fertility	Life Biosciences company focusing on restoring egg quality in women of advanced age or experiencing premature infertility.	F,I,E,A,B,IP
Jupiter Orphan Therapeutics	Develops a delivery system for a reformulated resveratrol to alleviate central nervous system symptoms associated with rare diseases and Alzheimer's.	E,A
Liberty Biosecurity	An EdenRoc company developing a variety of biosecurity-related health products based on discoveries in medical genomics.	F,I,E,A,B
Metrobiotech East/Midatlantic, LLC	An EdenRoc company developing NAD+ pharmaceuticals.	F,I,E,A,B

Affiliation Abbr. | F: Founder; I: Investor; E: Equity; A: Advisor/Consultant; B: Board of Directors; IP: Inventor on licensed patents; L: Funding for laboratory

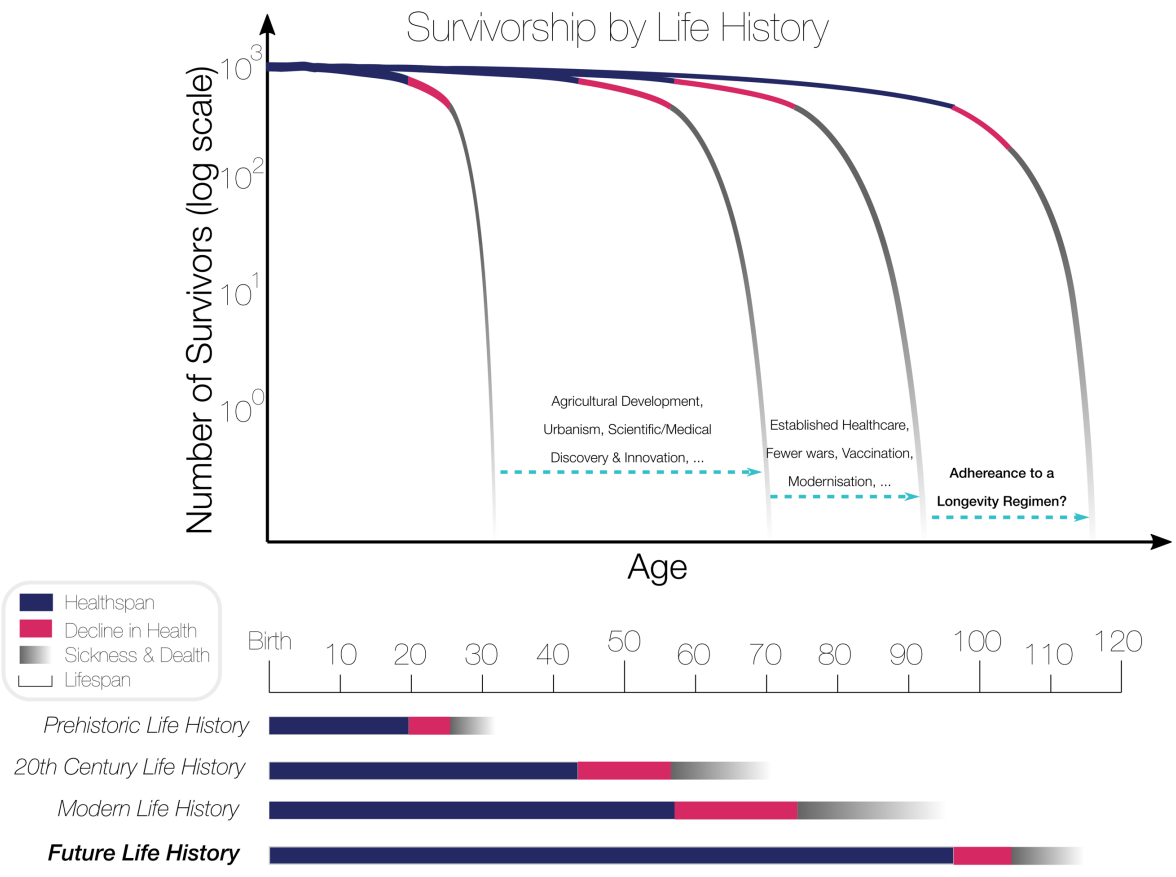

Figure 4 | Simulated survivorship curves for various stages of human life histories.

lives of millions of people; conversely, these commercial interests represent potential biases that challenge the objectivity of the scientific foundation of these studies. While these conflicts of interest themselves are commonplace in the field of biotechnology and are not a weakness of the presented work, the mitigation of potential biases requires rigorous experimental methodology, complete transparency, evidence of reproducibility, and continued disclosure of commercial conflicts of interest.

Contemplated at a high level and ignoring the minutiae, we can theorize whether or not a drastic (or even modest) extension to human lifespan is theoretically possible. Historically, *Homo sapiens* have seen a gradual increase in average life expectancy over the past centuries due to a mixture of technological, social, scientific, and medical innovations. As large mammals, humans exhibit a Type I survivorship curve, characterized by a long lifetime with a low death rate and high survivorship rate, followed by a dramatic increase in death rate. Figure 4 illustrates this concept and highlights the various developments that resulted in considerably improved average life- and healthspans of human populations at various stages in history. However, to date, there is no definitive evidence that the *maximum* human lifespan has increased despite the increase in average lifespans. Sinclair posits that adherence to a longevity regimen that maintains one's epigenomic health will dramatically reduce or prevent the onset of major illnesses prevalent later in life, which ultimately leaves us with the question: do these lifespan increasing methods affect *aging* (*i.e.* achieve negligible senescence *in perpetuo*) or just lifespan (*i.e.* we endure longer with the same kind of "damage")?

Conclusions

In summary, there remains much to investigate and reconcile en route to a fully understood mechanism of aging and the development of efficacious and evidence-based life-extending regimens. A reflection of our shared history reveals dramatic increases in the average human life- and healthspans as a result of scientific innovations; we may now be at the cusp of the next. Much in the way that the development of vaccines eradicated diseases that plagued humanity prior to the 20th century, essentially eliminating diseases that killed the majority of the population, it is not inconceivable that anti-aging regimens might do the same for the major diseases of the present day, improving and extending millions of currently lived lives. Future generations may balk at the idea that humanity ever lived in ignorance of the resultant new limits on lifespan. Unlike the cessation of wars, breakthroughs in medicine, and the implementation of social innovations, this ability to dramatically affect one's own longevity resides with the individual; we have the power to contemplate this emergent research and choose to hack our way to immortality.

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