1 The Eternal Youth of Ageing Research

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1.1 Human Ageing at the Crossroads between North and South, Past and Future, Worry and Hope

Individuals are increasingly likely to live longer in contemporary societies. In Western societies, this is the result of about two centuries of (dis)continuous increase in life expectancy from about 40 years in the middle of the eighteenth century to approximatively 85 nowadays ([1] but see [2]). At the population level, this increase in life expectancy (associated with a decline in fertility) results in a growing proportion of seniors in these populations (i.e. population ageing). It also leads to the appearance of new age classes such as supercentenarians (i.e. individuals who reach 110 years of age or more).

Such population ageing poses crucial societal issues and challenges regarding health policies and the redistribution of wealth between generations [3]. But there is much more at play. Building a society in which a growing number of individuals have an equal chance of living a long and healthy life is, above all, a social and political challenge. This book is a project that legitimizes and makes the case for massive investment in many research areas in order to better understand the biological, social and environmental determinants of ageing, at both individual and population levels.

The tremendous social implications also explain why the question of whether or not there is a biological limit to human longevity arouses such intense and conflicting debate among scientists (see [4] and the multiple commentaries on this article for an illustrative example of the debate). Moreover, the debate around biological limits crystallizes a societal debate on the limits of human progress [5]. Since the second half of the twentieth century, societal and medical progress has allowed people to expect to live longer, but will this continue in the future? Will it be accompanied by a parallel increase in healthspan? And if not, what does this really tell us about the future of our societies?

At the international level, the population ageing of wealthy societies is also changing the relationships they maintain. For instance, in an increasing number of Northern countries, the ageing of the populations has become an important driver of labour migration from the South to the North. In developing societies, on the other hand, seniors are largely forgotten by public policies. For example, the United Nations 2030 Agenda for Sustainable Development promotes a reduction in infant

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and maternal mortality but includes only a few considerations on health, gender disparities and the survival of elderly people [6].[1] However, seniors are subject to many forms of health, socio-economic and environmental vulnerabilities in countries with little or no health-care system favourable to these age groups [7].

At a global scale, there is no doubt that the increase in the life expectancy of a growing number of individuals in developed countries has come at the cost of a large drain on the resources of the planet. Yet globalization, as well as environmental and climatic deterioration, generates new risks for older people, who are more vulnerable to environmental fluctuations, such as climatic changes or epidemics [8]. More rational, equal and sustainable development, as well as the fight against global warming and biodiversity loss, will become major issues in the aim to improve future life expectancy (or even maintain the current level).

But, by contrast, does favouring living long and healthy lives conflict with sustainable development? Fortunately not. First, because actual research on ageing opens new avenues towards late-onset disease prevention and health – for instance in terms of environmental conditions, such as lifestyle and diet, or in terms of socio-cultural practices, such as socialization through family ties and solidarity – that align with environmentally sustainable behaviours. Second, an increasing community of researchers argue that our improved understanding of the evolutionary roots of ageing and its variations between species and populations will lead to findings that allow us to modulate both the onset and rate of ageing in our species [9]. Indeed, a significant part of the recent increase in lifespan results from biomedical progress that allows individuals to survive – at various levels of health – formerly lethal diseases (such as cardiometabolic diseases, cancer or kidney diseases). For many researchers, however, the next step will be to extend lifespan by lengthening healthspan thanks to the development of treatments against ageing (also denoted the fifth epidemiological transition, see [10]). If proved true, this could lead to equal access to low-cost healthspan extension rather than extending life by costly treatments of chronic fatal age-related diseases. Finally, population ageing is the culmination of a demographic transition that, once completed, heralds population demographic stationarity or even decline. Although no biological link between fertility decrease and lifespan increase has been observed during demographic transitions, these issues are nevertheless socio-culturally negatively correlated. It is therefore likely that securing equal access to a long healthy life, within and between countries, is a part of desirable change of the worldwide demography, and will be a factor contributing to slowing global population growth (planned for the next decades [11]) and a decreasing drain on environmental resources.

Living healthier – and perhaps longer – lives thus remains a valid social and political objective of modern democracies, and, far from being in conflict with other

[1] Compared with United Nations Millennium Development Goals, the 2030 Agenda for Sustainable Development states, as its third goal, to ‘ensure healthy lives and promote well-being for all at all ages’ and, as a target, to ‘reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being’; these can be seen as mostly aiming to improve adult health. However, it is noticeable that policies dedicated to old age are not specifically mentioned as a target, in contrast to those concerning children and reproductive women.

contemporary issues, this objective embraces other crucial objectives, whether these involve reducing inequalities between humans or buffering the impacts of human societies on their environments.

1.2 Taking Advantage of the Multidimensional Variability of the Ageing Process

Based on the multiple challenges that ageing societies will meet in the near future (see Section 1.1), one may easily recognize the fundamental importance as well as the timely nature of studying ageing. Given the many facets of the ageing process (e.g. biological, social, mathematical), we believe that the flourishing field of biodemography offers a relevant framework for building integrative research programmes.

In their recent textbook, James Carey and Deborah Roach define biodemography as the 'science concerned with identifying a set of population principles' (see [12], p. 1) through an integrative approach bridging conceptual and methodological advances from life sciences and demography. Focused on ageing, the multidisciplinary nature of the biodemographic approach takes on its full meaning. For instance, upstream of the ageing process, the study of the biological, behavioural and environmental drivers of survival or reproductive performance through the life course is the scientific goal of many research areas (e.g. biogerontology, evolutionary ecology), and downstream, the demographic consequences of ageing at both population and individual levels modulate the expression of age-specific selective forces, leading to complex eco-evolutionary feedback.

Moreover, biodemography allows us, by its essence, to fully embrace the diversity of longevity and ageing trajectories offered by the natural world and thus to expand our horizons in terms of biological models [12]. It allows us to correlate this diversity with several biological, behavioural and environmental factors, putatively shaping ageing patterns, as well as understanding their evolution.

This is why, in the 2010s, we started to see a rise in the number of studies exploring the mechanisms of the ageing process in non-model organisms [13, 14]. The starting point of this increase is rooted in the influential papers or books that have clearly demonstrated that actuarial senescence (the increase in mortality risk with increasing age, also called survival ageing) is widespread across the tree of life, but also highly variable in shape between and within taxonomic groups [13, 15, 16]. For instance, some species display early and rapid increase in mortality risk, while others display intriguing non-continuous patterns of mortality increase with age. Some, even, are characterized by a low and relatively stable mortality risk over the life course [13, 17]. We are only scratching the surface in our understanding of the ecological and biological factors shaping this diversity of actuarial senescence patterns, but the current burst in the field of evolutionary biology of ageing will undoubtedly shed light on the evolutionary roots, as well as the interplay between the evolutionary and demographic consequences of actuarial senescence [18].

Importantly, this inter-specific diversity constitutes an untapped resource for biogerontologists aiming to identify cues for improving healthspan and lifespan, thus calling for integrative research projects. Indeed, even if some ageing mechanisms are shared across species (e.g. insulin/insulin-like signalling and target of rapamycin pathways [19]), the set of cellular mechanisms (or their relative importance) allowing some species to slow down their somatic deterioration and thus to delay and/or buffer the increase in mortality risk over the life course are partly taxa or species-specific [20, 21]. Moreover, in response to some specific sources of mortality, inherent to their Bauplan or ecosystem, some species have evolved sophisticated mechanisms allowing them to limit or even escape the risk of contracting some specific late-onset diseases (e.g. cardiovascular diseases or cancers [22, 23]). The natural world thus constitutes a field of possibilities that likely seize opportunities for the improvement of human healthspan. Yet identifying the most relevant species and candidate mechanisms is a complex task, which requires bridging methodological and theoretical advances from several scientific fields. This will be highlighted throughout the book's chapters.

A first challenge to achieving this is the thorough assessment of the diversity of the ageing process across space and time for a given species. Indeed, the variability in ageing patterns is not limited to the species level and, for a given species, populations often differ in both longevity and actuarial senescence patterns (e.g. [24]). This can be largely explained by some differences in environmental conditions, even if the relative contributions of the diverse ecological traits that can modulate ageing patterns (e.g. temperature, pathogen prevalence and availability of resources) remain to be quantified.

In this context, climate change will undoubtedly have profound consequences on population-specific ageing trajectories. In animals, it has been recently highlighted that global warming can lead lizard populations to extinction through an accelerated rate of telomere erosion [25]. Rapid shifts in ageing trajectories can thus be an accelerator of the biodiversity crisis [26]. Moreover, in the specific case of human populations, global warming can concomitantly hasten ageing trajectories by altering some key cellular and physiological processes underpinning the ageing process and also by directly impairing the health and living conditions of the elderly [27]. Therefore, there is a crucial need for theoretical studies that explore the possible consequences of climate change on population ageing, as well as empirical studies investigating how the multiple ecological traits characterizing a population can influence ageing on the cellular, physiological and demographic levels.

Studying the change in longevity and ageing trajectories through time can also offer relevant insights, especially when it comes to forecasting the future of ageing. Such investigations can be performed at an evolutionary time scale – even if assessing the longevity or ageing trajectories of extinct and fossil species is particularly difficult due to a lack of data (e.g. [28]) and rather rely on phylogenetic reconstructions (e.g. [29]) – or at much shorter time scale (e.g. centuries or decades). For the latter, historical demographic records of human populations across the world constitute invaluable resources that reveal how the modifications of our pathogenic, social and economic landscapes since the nineteenth century have shaped ageing trajectories.

Similar investigations in animals would be highly valuable as these could provide additional information on how environmental conditions can drive the ageing process. As many long-term field studies monitoring individuals from birth to death emerged in the 1960s and 1970s [30], such studies will be soon achievable in both short-lived and long-lived species.

Understanding and predicting population differences along longevity and ageing trajectories is mandatory for establishing public health policies. However, many insights from studies exploring the variability of the ageing process at the individual level can contribute to healthspan improvement, notably through personalized medicine. Within populations, individuals largely differ in terms of physiological conditions, health and longevity prospects. This variability largely depends on (epi) genetic, environmental factors (as well as their interactions) and luck. It is thus important to notice that the study of large cohorts through 'omic' approaches have started to provide key information on the epigenomic and genomic determinants of longevity and health in human populations (e.g. [31, 32]). Social factors (in a broad sense, the quantity and quality of the social bonds, the social level) can also largely contribute to individual differences in health and longevity prospects, as the influence of favourable social environment on hallmarks of ageing (sensu [33]) is increasingly documented (e.g. [34, 35]).

1.3 Overview of the Book's Contents

The present book has multiple objectives. It aims to provide a comprehensive reappraisal of current longevity and ageing research through evolutionary biology and evolutionary demography lenses, and to highlight the promise of this research for dealing with current and future challenges that our societies will face. These book chapters demonstrate that a multidisciplinary philosophy organized by research in biodemography is mandatory for the future of ageing research. This aspect is illustrated in Chapter 2, where Thomas B.L. Kirkwood provides a synthesis of the various theories that have been elaborated so far with regard to the evolution of ageing and demonstrates that theoretical frameworks merging evolutionary biology and biogerontology advances are now badly needed.

Chapters 3 and 4 then focus on the critical question of how to measure longevity (or lifespan). While the concept of 'longevity' is, by its essence, at the core of ageing research, its measurement remains far from trivial and the various metrics used to quantify the duration of life can lead to various (mis)interpretations. More specifically, Victor Ronget, Gilles Maurer and Sarah Cubaynes (Chapter 3) provide the reader with a thorough review of the various metrics that have been proposed to quantify the duration of life between and within species, highlight potential biases intimately linked to each metric and give recommendations for their interpretation. Next, Jean-Michel Gaillard and Nigel Gilles Yoccoz (Chapter 4) specifically focus on the concept of 'exceptional longevity', a term that is widely used in science and media but that lacks a statistically anchored definition. Here, the authors review old and recent approaches that can be used to identify species or individuals who display longevities outwith the range of expected values, and discuss the biological implications of each metric. Taken together, Chapters 3 and 4 offer novel insights on the use and misuse of longevity in evolutionary biology, demography and biogerontology.

In Chapter 5, Annette Baudisch goes beyond the concept of longevity and focuses on full age-specific trajectories. While the occurrence of demographic ageing in survival (i.e. actuarial senescence, the increase in mortality risk with age) across species has already been largely reviewed (e.g. [16]), the author of this chapter specifically focuses on species that show negligible (or an absence of) actuarial senescence. In this carefully organized piece of work, she reviews the current evidence for such an absence of survival ageing and emphasizes the questions raised by these patterns, from both theoretical and mechanistic points of view. Taken together, Chapters 4 and 5 provide new tools and insights for identifying – on the basis of demographic properties – promising model species for ageing research (e.g. species that have potentially evolved cellular mechanisms that enable them to buffer against the increase in mortality with age and to reach a striking longevity). Unfortunately, the current set of wild animal populations for which demographic data to estimate accurate ageing parameters and longevity metrics (i.e. age-specific estimation of mortality trough life) is available remain limited. Since longitudinal follow-up of known-age individuals cannot be reasonably conducted on all species on earth, the rise of demographic (but also physiological) data accumulated in zoo populations appears particularly relevant. In Chapter 6, Morgane Tidière, Johanna Staerk, Michael J. Adkesson, Dalia A. Conde and Fernando Colchero thus demonstrate how zoos and aquariums constitute untapped resources to study ageing at different levels of organization (species, populations, individuals) by implementing approaches combing demography, ecology and biogerontology.

After this set of chapters focused on the ageing process at the demographic level, Chapters 7 and 8 then focus on the genetic, cellular and physiological bases that could underlie the variability observed in longevity and actuarial senescence. These chapters tackle this salient problematic in ageing research through two complementary angles, by focusing predominantly on the inter-specific level (Chapter 7) and intra-specific level (Chapter 8). In the former, Jean-François Lemaître, Jean-Michel Gaillard, Samuel Pavard, François Criscuolo and Fabrice Bertile highlight future avenues of research in the comparative biology of ageing. More specifically, they argue that bridging methodological and conceptual advances in both biological sciences (in particular 'omic' approaches) and demography would provide new insights on the (epi)genetic and cellular mechanisms shaping the diversity of actuarial senescence patterns across the tree of life. This chapter is closely linked to Chapters 4 and 5 as it highlights relevant approaches to identify the mechanistic basis of the evolution of 'exceptional longevity', as well as delayed or slow actuarial senescence across species. In Chapter 8, Pat Monaghan and Jelle Boonekamp focus on biological age, a trait that is gaining increasing attention in both medical and ecological research, as it provides indirect insights on individuals' health and future survival prospects [36]. More specifically, the authors synthetize the various approaches that can be used to assess biological age in wild populations of animals and emphasize the importance of teasing apart chronological and biological age in evolutionary ecology of ageing studies.

Chapter 9 focuses on a long-standing topic that is attracting the attention of scientists from many different research fields: sex differences in longevity and ageing. In this chapter, Jean-François Lemaître, Jean-Michel Gaillard, Dominique Pontier, Hugo Cayuela, Cristina Vieira and Gabriel A. Marais first review the current support for the diverse evolutionary theories that have been proposed to explain the sex differences in longevity and actuarial senescence regularly documented in the animal kingdom. They then extent the current debates on the origin of sex differences on mortality patterns to the sex differences in reproductive and physiological ageing, two aspects that now need to be tackled using a multidisciplinary approach. Given that differences in ageing, healthspan and longevity between sexes are pervasive in human populations, this chapter also embraces the evolutionary roots of sex differences in human disease aetiology (e.g. infectious diseases). It thus sets the scene for the subsequent chapters, which will predominantly focus on human ageing.

Chapters 10–13 indeed turn more particularly to human ageing and longevity and take the reader on a journey through time and space to better understand the factors that have shaped adult mortality throughout evolutionary time, more recently from the Neolithic to historical times, and which are currently at work in societies across the world. More precisely, in Chapter 10, Samuel Pavard and Michael D. Gurven review and organize the literature on the joint evolution between the human life cycle and human cognitive and social capabilities, and discuss the biocultural mechanisms that have decoupled the extended longevity and the short reproductive period in our species, making humans an outlier on most ecological continuums. Michael D. Gurven then extends this discussion (Chapter 11) by a comprehensive review of the scarce and precious data on mortality by age and cause in human forager populations. By doing so, he deconstructs many preconceived ideas about adult mortality and the dynamics of past populations, as well as emphasizing the current challenges faced by these populations, who are sometimes brutally confronted with unchosen environmental and cultural changes. In the pivotal chapter, Chapter 12, Nadine Ouellette and Julie Choquette guide the reader through the changes in longevity resulting from the transition from hunting and gathering to farming, and through more recent demographic and epidemiological transitions. They then introduce the crucial notions of compression of mortality and rectangularization of the human survival curve, the subjacent trade-offs between healthspan and lifespan, and evidence the emergence of a new statistically relevant age class: the oldest olds. The authors thus pave the way to Chapters 14 and 15, which aim at better describing the mortality of these new age classes, and Chapters 16 and 17, which aim at elucidating the factors that enabled these particular individuals to live so long. They conclude by discussing the current disparities on levels of demographic transitions in the Global South and the epidemiological mechanisms behind these. Running with this idea, Géraldine Duthé, Lucie Vanhoutte, Soumaila Ouedraogo and Gilles Pison

(Chapter 13) then discuss how such demographic and epidemiologic transitions theory has to be revised to encompass the current challenges that face countries of the Global South. In many of these countries, adult mortality is indeed the product of the coexistence of communicable and non-communicable or chronic diseases across a complex spatial, cultural and environmental landscape, shaped by urbanization, nutrition and socio-economic conditions.

Chapters 14 and 15 will then turn to the future by questioning – through an epistemological and statistical discussion – the existence and the reachability of a limit to human longevity. Carlo Giovanni Camarda and Jean-Marie Robine (Chapter 14) provide the reader with a comprehensive review of the history of the ideas and the current debate on the limit of longevity, and show how these debates were anchored, first, in natural history and scientific methods and, second, in the development of statistics and data. This discussion is continued in Chapter 15, by Linh Hoang Khanh Dang, Nadine Ouellette, Carlo Giovanni Camarda and France Meslé, who provide a history of the statistical models proposed for exploring mortality trajectories at old ages and these models' respective ability in detecting mortality plateaus and hidden heterogeneity in individuals' frailty – both key to addressing the question of the limit of longevity.

The two following chapters aim at deciphering why some individuals live long lives and why others do not; they thus aim to provide a better understanding of the process behind ageing in our species and also to identify potential levers that could enable future progress in improving lifespan and healthspan. Larissa Smulders and Joris Deelen, in Chapter 16, take a pedagogical approach to explaining the methods used in such phenotypic and genetic comparison, employing data on long-lived individuals and families. They then shed light on how such studies have allowed the identification of key features of healthy long life, such as having a favourable immune-metabolic profile, but have also unravelled deeper questions, such as the absence of clear effects of protective genetic variants (beyond a few ones) and susceptibility alleles to late-onset diseases in modulating survival to very old age. Finally, the authors identify new avenues using 'omic' data on such specific data to investigate ageing from a system biology perspective, as proposed Chapter 7 through comparative biology lenses. By contrast, Gianni Pes and Michel Poulain (Chapter 17) are interested in the overall biological, environmental, nutritional and cultural context that allows certain populations around the world (in the so-called blue zones, BZ) to exhibit lower adult mortality and a higher number of survivors beyond 100 years of age. After a discussion on genetic and hormonal potential explanations, they provide a strong argument for the role played by one's way of life on long healthy ageing, from physical activity and nutrition to social ties and purpose.

Finally, how can modern societies cope with this growing number of seniors, that is, population ageing? This is the question posed by Miguel Sánchez-Romero and Alexia Prskawetz (Chapter 18) in the final chapter of this book. To answer it, the authors apply demo-economic models to country-level data to analyse the impact of increased longevity on the sustainability of intergenerational solidarity. Without omitting the tensions that such increased longevity causes to the economy, the authors also show that when demography, labour market, education, innovation and solidarity are taken into account, modern democracies have all the cards in hand to face these changes. In consequence, increases in healthspan and lifespan may remain indicators of global societies' progress in the future, as much as they have been in the past.

1.4 Conclusion

From the oldest human stories, such as the epic of Gilgamesh (written around 2100–1200 BC), to the works of ancient Greek philosophers such as Aristotle and down to the present day, questions about the length of life, its limits and the deterioration of the body throughout life have been at the heart of philosophy, the arts and the life sciences. Today these issues are more topical than ever, given the social, economic and public health challenges to which they are intimately linked, and require innovative and dynamic scientific research at the crossroads of many scientific disciplines. In recent years, several books have brilliantly summarized major advances in the study of longevity or senescence, whether from the perspective of evolutionary ecology (e.g. [16]) or medical sciences (e.g. [37]). Here, our book builds on the multidisciplinary nature of biodemography to concomitantly summarize the large amount of knowledge accumulated over the past few years in ageing research, as well as to stimulate the development of integrative research projects on ageing. We hope that this book will be an inspiring resource for established academics and, perhaps more importantly, for students, who will be at the forefront of the coming profound changes linked to ageing populations.

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