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Eric Bapteste[1], Philippe Huneman[2], Laurent Keller[3], Jérôme Teulière[1], Philippe Lopez[1], Emma C. Teeling[4], Ariel Lindner[5], Annette Baudisch[6], William B. Ludington[7,8], Claudio Franceschi[9,10].

[1] Institut de Systématique, Evolution, Biodiversité (ISYEB), Sorbonne Université, CNRS, Museum National d'Histoire Naturelle, EPHE, Université des Antilles, Paris, France
[2] Institut d'Histoire et de Philosophie des Sciences et des Techniques (CNRS/ Université Paris I Sorbonne), Paris, France
[3] Department of Ecology and Evolution, University of Lausanne, 1015 Lausanne, Switzerland
[4] School of Biology and Environmental Science, University College Dublin, Ireland
[5] Université de Paris, INSERM U1284, Center for Research and Interdisciplinarity (CRI), Paris, France
[6] Interdisciplinary Centre on Population Dynamics, University of Southern Denmark; 5230 Odense M, Denmark
[7] Department of Embryology, Carnegie Institution for Science, Baltimore, MD 21218, USA
[8] Department of Biology, Johns Hopkins University, Baltimore, MD 21218, USA
[9]Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, 40138 Bologna, Italy
[10]Department of Applied Mathematics and Laboratory of Systems Medicine of Aging, Lobachevsky University, Nizhny Novgorod 603950, Russia

Abstract

How, when, and why organisms age are fascinating issues that can only be fully addressed by adopting an evolutionary perspective. Consistently, the main evolutionary theories of ageing, namely the Mutation Accumulation theory, the Antagonistic Pleiotropy theory, and the Disposable Soma theory, have formulated stimulating hypotheses that structure current debates on both the proximal and ultimate causes of organismal ageing. However, all these theories leave a common area of biology relatively under-explored. The Mutation Accumulation theory and the Antagonistic Pleiotropy theory were developed under the traditional framework of population genetics, and therefore are logically centred on the ageing of individuals within a population. The Disposable Soma theory, based on principles of optimising physiology, mainly explains ageing within a species. Consequently, current leading evolutionary theories of ageing do not explicitly model the countless interspecific and ecological interactions, such as symbioses and host-microbiomes associations, increasingly recognized to shape organismal evolution across the Web of Life. Moreover, the development of network modelling supporting a deeper understanding on the molecular interactions associated with ageing within and between organisms is also bringing forward new questions regarding how and why molecular pathways associated with ageing evolved. Here, we take an evolutionary perspective to examine the effects of organismal interactions on ageing across different levels of biological organisation, and consider the impact of surrounding and nested systems on organismal ageing. We also apply this perspective to suggest open issues with potential to expand the standard evolutionary theories of ageing.

Keywords

Evolutionary theory of ageing; symbioses; microbiomes; networks; pluralism; units of selection

Highlights

Ageing organisms belong to networks of molecular, ecological and social interactions

How surrounding or nested systems impact organismal ageing is yet to be characterized

Focusing on hybridization, (endo)symbioses and social interactions raises open issues

Using concepts of individuality, unit of selection and fitness measures raises issues

Network analyses may help understand the evolution of ageing across the Web of Life

Introduction

Mainstream evolutionary theories of organismal ageing revolve around an important common prediction: that the later periods of any organism's life are less important from an evolutionary viewpoint than their early periods. This asymmetry stems from the consideration that all organisms may eventually die from extrinsic causes, be it by accident, predation, disease or due to harsh conditions (Reichard, 2017). Precisely, as Charlesworth (Charlesworth, 2000) emphasised, Fisher's concept of "reproductive value of individuals of age x" (...) which "measures their contribution to the future ancestry of a population growing at rate r, normalized to a value of unity at the time of conception", had critically contributed to connect the phenomenon of ageing to that of natural selection, and turned evolutionists' attention towards the proportional relationship between ageing and organismal reproductive value (Fisher, 1930). Fisher's work was notably influential for Medawar. Specifically, the Mutation Accumulation theory of ageing (MA), proposed by Medawar in the 1950's (Medawar, 1952), holds that late-expressed deleterious mutations will accumulate in organismal genomes. The reason for this is that the decreasing strength of natural selection fails to purge deleterious late-expressed genes, or to further postpone their expression in the course of an organisms' lifetime. This accumulation contributes to the functional decline of organisms late in their lives. Likewise, the Antagonistic Pleiotropy theory of ageing (AP) (Williams, 1957), fully elaborated by Williams roughly at the same period, predicts that the selection for genes that benefit organisms should be stronger early in their lives, even when genes with early positive fitness effects impair the survival of their bearers later in their lives. Accordingly, organismal ageing would result from trade-offs favouring the reproduction of individuals over their long-term survival. Finally, the Disposable Soma theory (DS) developed by Kirkwood in the late 1970's (Kirkwood and Holliday, 1979; Kirkwood, 1977) assumes an optimal dynamic allocation of resources to life history trade-offs (reproduction, survival) that maximizes organismal lifetime fitness. To summarize, because resources are limited, most organisms will be evolutionarily more successful if they invest their finite energy into their germline and into their reproduction rather than into the maintenance of their soma (Reichard, 2017).

While the contributions of these important, standard theories are invaluable, their explanatory scope may not be fully realized and could be expanded. For example, while an increase in extrinsic mortality (e.g., by predation) usually leads to an evolution of shorter lifespans and earlier reproduction as predicted by classic evolutionary theories of ageing, cases where the reverse happens, and increased extrinsic mortality leads to the evolution of longer lifespans, are also well documented (Chen and Maklakov, 2012; Reznick et al., 2004; Shokhirev and Johnson, 2014). Indeed, MA, AP and DS "designate the organism as the dynamic locus of ageing, and treat the environment as an undifferentiated cumulative source of selective pressures and resources*"* (Johnson et al., 2019). However, it is increasingly acknowledged that a complex network of interactions links an organism to its environment, including other organisms (Bapteste and Huneman, 2018). Thus, mainstream evolutionary theories of ageing leave an important structural and functional aspect of the biological world relatively under-explored, which may limit our understanding of some proximal and ultimate causes of ageing. In particular, these theories do not explicitly model the countless interspecific and ecological interactions, such as symbioses and host-microbiome associations, that shape organismal evolution across the Web of Life, whereas abundant data now demonstrate connections between organismal ageing on the one hand and social interactions, ecological interactions, symbioses, microbiomes, or co-evolution on the other hand, which we review below.

The importance of biological interactions at all scales of biological organisation (from molecules to ecosystems) is not specific to evolutionary theories of ageing. Evolutionary biology in general is currently undergoing various theoretical debates concerning the proper framework to formulate the complexity of biological evolution (Bapteste and Huneman, 2018; Laland et al., 2014; Tozzi, 2014; Witzany and Baluška, 2014). These debates suggest that adopting a greater focus on interactions will enlarge the scope of current evolutionary theories, including those on ageing. Such "theoretical enlargement" (as philosophers of sciences call them) has occurred throughout scientific history for instance when simplifications from Modern Synthesis models such as Wright-Fisher's were relaxed with respect to the original formalization in the Modern Synthesis (Gillespie, 2004), to better account for within-genome interactions (Griffiths and Stotz, 2013), gene–environment covariance (Barker et al., 2013), parental effects (Bonduriansky, 2012), and extended fitness though generations (Lehmann, 2008). Similarly, a "theoretical enlargement" in microbial evolution was proposed to account for the contributions of lateral gene transfers and endosymbioses to the evolution of lineages, adding to the traditional formalism and methods of evolutionary trees, with the advance of phylogenetic networks and other comparative approaches (Koonin et al., 2021; Watson et al., 2020). Thus, outside the field of ageing, network-based analyses are being developed to enhance scientific explanations for the evolution of biological complexity and diversity. For instance, Ciliberti and Wagner used networks of gene regulatory networks to account for evolvability and robustness in evolution (Ciliberti et al., 2007; Wagner, 2005). Alon and colleagues searched gene networks and identified recuring network patterns called motifs whose conservation across lineages casts a light on evolution of complexity (Milo et al., 2002). Together with these ones, many uses of network analyses have been described as shifting our understanding of evolution (Bapteste and Huneman, 2018). These network methods can exploit the rich body of empirical datasets from molecular, cellular, microbiological, organismal,

ecological and evolutionary studies, in ways that better capture the interactions both between and within evolving systems. We argue here that the field of evolutionary ageing studies, while resting on solid grounds, may also benefit from this kind of development.

To evaluate what knowledge may be at stake, in this paper, we review some current grey areas of standard evolutionary theories of ageing that might be enhanced by greater focus on interactions. First, we provide some evidence that ecological interactions and co-evolution matter for ageing. Second, we highlight some systemic aspects of the evolution of ageing that remain a black-box and bring forth important open issues regarding interactions within and between organisms, that affect ageing. We conclude that addressing these open issues could enhance the evolutionary framework of ageing studies, both in terms of phylogenetic scope and by providing a broader framework to consider the role of biological interactions in ageing.

1. Ecological interactions and co-evolution are relevant for ageing studies

1.1. Open issues raised by the connections between microbes and ageing

Starting an article on open issues about ageing with considerations on microbes may seem counterintuitive: the general biology of microbes appears highly different from that of animals, and our understanding of ageing is largely based on animal-centred models. However, from an evolutionary perspective, it is quite natural to consider microbes first, at least for anyone who considers that what is true for the elephant is true for *E. coli*. Investigating ageing in microbes may at the very least help track the deep origins of some pathways associated with animal ageing or longevity.

Indeed, common molecular mechanisms associated with ageing or longevity may be unravelled by following a genetically homogeneous large population of individual organisms under a controlled environment. Advantageously, studying ageing with such microorganisms could be considerably easier than more complex organisms. Thousands of individuals can be followed throughout their lifespan and their survival tested under different nutritional conditions and social conditions. For instance, isolating individual cells in individual micro-size wells or by allowing them to grow as part of a functionally interconnected colony can be performed over time periods easily manageable in the lab. Accordingly, to focus on one model of bacterial ageing, several promising findings have been published on *E. coli,* addressing both chronological and replicative aging.

Addressing replicative ageing, experimental work conducted on *E. coli* has established a stimulating connection between asymmetry of cell division and cellular ageing. In *E. coli,* every cell division generates a daughter cell with one pole that is at least one generation older than the oldest pole of the second daughter cell. Daughter cells of the oldest pole lineage lose reproductivity (Proenca et al., 2018; Stewart et al., 2005) and accumulate misfolded, damaged proteins (Lindner et al., 2008). While this functional asymmetry of damage accumulation in bacteria is a passive mechanism that does not mobilise a dedicated energetic investment (Coquel et al., 2013), other organisms may have evolved such active mechanisms to keep accumulated damage at bay (Nyström, 2011).

Moreover, quantifying age-specific mortality of nutrient-restricted non-growing bacteria, it was discovered that a simple organism as *E. coli* manifests similar ageing properties at the population level to higher social organisms including humans (*e.g.*, Gompertz-like exponential mortality profiles (Yang et al., 2019)). A trade-off between reproduction and survival, mediated by the stress response sigma factor was established, linking the organism's feast and famine lifestyle to an evolved genetic mechanism underlying tuning of ageing rate. What are the stochastic mechanism(s) that trigger the transition from a lively *E. coli* cell to a dying cell is an open question, addressable by following damage (Yang et al., 2022). Further, using the same experimental setup, >100 single gene knockouts increasing longevity were discovered, many of which with hitherto unknown phenotypes (Santos A, Yang Y, Lindner AB (2022), *unpublished*). Interestingly, it is currently unknown whether homologs of such *E. coli* genes, with ability to modulate cellular ageing and rejuvenation play similar role in other members of the prokaryotic world (and possibly beyond), inviting one to consider an application of AP, MA and eventually DS in bacterial lineages.

Furthermore, while bacteria constitute an ancient Domain of life, Archaea are presumed to be equally old. There is a consensus amongst phylogeneticists that the Tree of Life is probably rooted between these two major prokaryotic groups (Dagan et al., 2010). Tackling the issue of ageing in Archaea would however open an entirely new research field. Such an inquiry is warranted by at least two considerations. First, there is evidence of asymmetric cell division in Archaea (upon viral infection in *Sulfolobus* species), coupled to differential fitness between asymmetrically divided cells (Liu et al., 2021). This result makes it conceivable that these archaea can partition damage load as a result of asymmetric cell division. Second, our own species belongs to eukaryotes, which have dual phylogenetic ancestries, i.e., bacterial but also archaeal roots as a result of primary endosymbiosis (Raval et al., 2022). Thus, eukaryotes are evolutionary chimeras: non-photosynthetic eukaryotes harbour mitochondria, which are the descendants of endosymbiotic bacteria acquired during an endosymbiosis involving at least members of an archaeal and a bacterial ancestral lineage. Consequently, eukaryotes, including humans, may have inherited some very ancient features of cellular ageing and rejuvenation that may explain aspects of our current cellular ageing. Empirically tracking the (prokaryotic) phylogenetic origins of gene families associated with ageing and longevity in the human genomes (López-Otín et al., 2023) may be a quantitative way to understand when deeply rooted aspects of ageing evolved, expanding over qualitative studies of this issue (Lemoine, 2021)). Already, it is well recognized that mitochondria, with their non-nuclear genomes, play critical roles in the ageing process (Garagnani et al., 2014).

Moreover, multicellular eukaryotes commonly host microbes. For instance, the human gut encompasses 10^{14} microbial cells (a taxonomic combination of bacteria, archaea and protists) and at least ten times more bacteriophages (Popescu et al., 2021). Taking into account these host-associated microbes adds yet another level of complexity to the genetics of ageing (Biagi et al., 2017, 2010; Garagnani et al., 2014; Gould et al., 2018) and to the issue of its evolution. To what extent these different microbial and microbially-derived genomes contribute to ageing remains therefore an open question. To address this, one can use the tools of phylogenomics, e.g., to assess which ageing-associated genes humans inherited from their deep mitochondrial ancestry. Moreover, one can also wonder what part of human ageing was caused by the

microbial lineages with which we co-evolved. This is for example illustrated by a theory, connecting the taming of fire, microbiomes, and the evolution of *Homo sapiens*. In short, this theory proposes that human ageing was uniquely shaped by our associated microbes, because hominins progressively cooked their food on a routine basis, introducing toxic chemical compounds, derived from the Maillard reaction, into their bodies (Danchin, 2018). The host-associated gut microbiota would have acted as a first line of defence against these toxic compounds. By contrast, an animal species eating raw foods would normally accumulate such compounds slowly over the course of its life, with damaging effects only late in life. The co-evolution between hominins and microbes was here proposed to explain how human-associated microbiomes might have conferred on our species the rare ability to counteract an ageing-related problem, extending human lifespan far beyond that of our great ape cousins. Likewise, it was proposed that interkingdom communication between hosts and microbiomes, mediated by taste-receptors, could allow gut microbiomes to modulate host inflammation in the presence of food (Giuliani et al., 2020). In that later case, evolutionary considerations on interactions encoded beyond the nuclear host genome may help track and highlight the multispecific origins of inflammageing (Santoro et al., 2021). In addition, the CGAS-STING module, which senses pathogen-derived DNA in Vertebrates, is a basic mechanism deeply related to inflammageing, notably in humans. Specifically, in the cytosol, the signal protein cGAS produces a second messenger (cGAMP) that activates the signalling adaptor STING, a protein that evolved in Bacteria and was possibly acquired by ancestral animals more than 600 million years ago (Margolis et al., 2017; Morehouse et al., 2020).

As these few studies illustrate, addressing some questions about ageing requires comparative studies of microbiomes and of organelles along lineages of ageing hosts, e.g., humans and apes, to decipher what makes the contribution of organelles and microbiomes to organismal ageing common or instead unique across species. This complexity also stresses that evolutionary biologists still need to develop methods and concepts to better explain how genes from different kinds of genomes became functionally integrated over time; hence how phylogenetic chimerism affects organismal ageing. As an ultimate case in point, some authors have brought forward aspects of human ageing that may result from the reticulate history of our own lineage, as our history involved hybridization with members of Neanderthalian or Denisovian tribes (Levi et al., 2021). Hence, explanation of ageing processes may benefit from mapping and tracking the connection of externally acquired genes (or alleles) into extant interaction networks and into networks of gene sharing.

However, addressing these challenges is complicated, as we will illustrate below. Indeed, giving a more central place to hybridization events, (endo)symbioses and to the microbiome in the evolution of ageing invites us to question what proper concepts of individuality, units of selection, and fitness measures are relevant to understand the evolution of ageing across the Web of Life.

1.2. Open issues raised by age-distorsion

As a case in point for the difficulty and pay-offs to extend explanations of the evolution of ageing beyond the genetic contribution from a single source, the concept of age-distorters (paraphrasing the notion of sex-distorters in evolutionary biology) was recently coined to

encourage research into evolutionary and genetic causes of ageing, external to a focal ageing species/organism (Teulière et al., 2021). In short, age-distorters are defined as entities that manipulate the biological age of other entities for their own evolutionary interests. For instance, the HIV-1 virus can interfere with the cell cycle by inducing telomerase activity in monocyte-derived macrophages, which turns these infected host cells into resistant viral reservoirs (Reynoso et al., 2012). HIV-1 can also cause immunosenescence (Cohen and Torres, 2017) and provoke stress-induced premature senescence of non-immune cells (Cohen and Torres, 2017) and progressive mitochondrial damages that contribute to accelerated ageing and cellular dysfunction (Schank et al., 2021). Consistently, HIV-1 infection was reported to increase epigenetic age both in brain tissue and in the blood (Horvath and Levine, 2015). In addition, morphological reports identified an acceleration of the normal ageing trajectory in several regions of the human brain, such as the neocortex and the thalamus in HIV-infected individuals with generally good health (Pfefferbaum et al., 2014). HIV-1 infection was also causally connected to cases of osteoporosis and of osteopenia (Seoane et al., 2020).

Phytoplasmas are another example of microbes that modulate host fitness traits for their own advantage. *Phytoplasma asteris* infects aster phloem and releases effector molecules that rejuvenate the plant to make the plants more attractive to leafhopper insects, which serve as vectors (Hogenhout et al., 2008). Furthermore, *Phytoplasmas* can increase fertility and lifespan of the leaf hoppers *Macrosteles quadrilineatus* when they feed on the preferred aster (Hogenhout et al., 2008). Likewise, the obligate intracellular symbiont *Wolbachia*, which primarily resides in the germline cells of its host, but can also be found in its somatic tissues, has been reported to affect the lifespan and the ageing of *Drosophila* in the lab, either by extending or by shortening the longevity of these flies. These lifespan-modulating effects of *Wolbachia* seem to depend on the genetics of the host as well as on that of the symbiont, and there is no clear theory to explain why such opposite effects have been observed. Interestingly, *Wolbachia* is suspected to impact the expression of key longevity-associated genes in *Drosophila* (e.g., stress resistance, immune response, autophagy, oxidative stress defense, etc.), although a systematic and accurate analysis of the involved pathways is still missing (Maistrenko et al., 2016).

Importantly, these very different examples show that the pool of candidate age-distorters is large. It includes viruses, parasites, and symbionts, operating through specific, genetically encoded interferences with their hosts processes and results in co-evolution between manipulative entities and manipulable (ageing) hosts. Accordingly, the notion of age-distorters brings forth (worrying) open issues: what are the age-distorters of humans, their age-distorting genes, and the targets of these genes in humans, if any? (Teulière et al., 2023) What are the loads of such age-distorters in natural populations and their impact on ageing organisms? (Teulière et al., 2021)

Moreover, interspecific interactions altering the normal course of host ageing have no reason to be limited to the human species. The broader phylogenetic scope is illustrated by cases when age-distorters and host evolutionary fates become tightly integrated. For example, when endogenous retroviruses physically disrupt host genomes, they can impact host ageing. Thus, the vast diversity of endogenous viruses found within the bat genome might contribute to the unusually high tolerance of the bat immune system for viral infections (Déjosez et al., 2022), contributing maybe to explain why bats are especially long-lived for their body size (Austad

and Fischer, 1991). Under this hypothesis, the ‘domestication’ of viruses would confer an evolutionary advantage, that extends lifespan of bats by limiting the inflammatory response to pathogens and therefore slowing down the rate of inflammageing and immune driven damage. Consistently, one might wonder whether endogenous viruses generally contribute to host ageing and longevity across the Web of Life? Considering age-distorters asks which organisms have aspects of their ageing driven from outside their own genomes by entities that use their host cells or bodies as their own disposable soma, or are driven from within, when age-distorters become integrated into their host genome? This problem is becoming a hot topic in ageing studies, with the increasing recognition that endogenous retroelements play a role in ageing and in cellular senescence (Gorbunova et al., 2021; Liu et al., 2023; Yushkova and Moskalev, 2023).

From a theoretical viewpoint, the notion of age-distorters supports an extension of traditional evolutionary theories of ageing. When age-distorters interfere with the mechanisms implementing reproduction/maintenance trade-offs in their hosts, age-distorters can be related, by analogy at least, to the Disposable Soma theory. In that case, the manipulated parts of the host can be seen as an expanded disposable soma, exploited by the age-distorters. Moreover, the genomes of age-distorters can be seen as additional sources of mutation accumulation and of antagonistic pleiotropic genes, originally external to the host genome, which expands the scope of the mutation accumulation and of the antagonistic pleiotropy theories (Teulière et al., 2021).

Beyond age-distorters, a growing number of microbial studies of age-related diseases have stressed the possible importance of microbial components to enhance the understanding of organismal ageing, hinting at the general and medical relevance of microbial theories of ageing. Thus, different microbes have been proposed to play a causal role in dependent autoimmune processes associated with atherosclerosis, Alzheimer's and Parkinson's diseases, autoimmune and autoinflammatory diseases. For example, the Cytomegalovirus (CMV) has long been proposed to contribute to immunosenescence (Solana et al., 2012), and the Epstein-Barr virus (EBV) has been proposed to contribute to Alzheimer's disease (Huang et al., 2021).

Such considerations bring biological interactions, and therefore ecological context, to the center of explanations of ageing.

1.3. Open issues raised by the connections between division of labor and ageing

Beyond the issues raised by the above-mentioned ecological and co-evolutionary considerations, another context is already recognized as critical to explain ageing: social interactions also affect ageing and its evolution.

This is particularly true in social species where the evolution of complex societies has been accompanied by a great increase in lifespan, e.g., (Lucas and Keller, 2020). A particularly striking example is provided by the queens of social insects which can live up to nearly 30 years in some species (Keller and Genoud, 1997). Similarly, naked mole rats can also live up to 39 years (Austad, 2010), which is much more than similar-sized rodents (the maximum recorded lifespan of mice is only around four years (Miller et al., 2002). While it was commonly thought that living in social groups does influence the evolution of senescence and longevity because large group size affects key life history parameters such as extrinsic mortality and the cost of reproduction, it seems that this outcome might only be true for species in which life in large

groups is the norm (Lucas and Keller, 2020). By contrast, there seems to be no clear association between survival and social group size in species which have relatively small social groups. Interestingly, the benefits of social life on longevity in co-operatively breeding vertebrates and social insects primarily occurs for high-ranking individuals who benefit from the protection and support of their non-breeding helpers (Lucas and Keller, 2020). In contrast, helpers in these species usually do not show evidence of increased longevity, with the exception of naked mole rats where both breeders and helpers live much longer than related solitary species.

Social life can also lead to changes in the coupling of life-history traits which, in turn, has consequences on lifespan. For example, there is usually a strong relationship between the size of organisms and their lifespan. It is thought that this stems from the coupling between the size of organisms and their metabolism and risk of extrinsic mortality (Austad, 2010; Gaillard et al., 1994; Promislow and Harvey, 1990). However, the relationship between size and lifespan can be modified when social life induces unusual association between size and extrinsic mortality. Thus, in the weaver ant, *Oecophylla smaragdina*, the major (large) workers perform the risky tasks outside the nest, while the minor (small) workers stay within the highly protected arboreal nest. Hence, this pronounced division of labour is associated with minor workers experiencing lower extrinsic mortality than major workers. In line with the prediction that lower extrinsic mortality should lead to higher lifespan, it was shown that, in a protected environment, the minor workers live longer than the major workers (Chapuisat and Keller, 2002). Again, this example illustrates that social life has important consequences on the interaction between organisms and their environment, and as such, can have important implication on patterns of ageing. How social life affects ageing is however still not fully understood (Huneman, 2023). In particular, comparative transcriptomic analyses of genes expressed by organisms in social interactions, e.g., individuals from different casts, such as workers and queens, has potential to unravel whether different pathways or regulations are involved in their differential longevities. Such analyses could inform how a given genome from a given population is able to activate/repress (yet to be discovered) longevity programs, under given social conditions.

Furthermore, one may wonder whether some of the above observations also apply on social organisms outside the animal kingdom, and therefore whether some of the conclusions just presented regarding the evolution of ageing in a social context may have a broader phylogenetic scope than currently assumed. In particular, several species of microbes (e.g., the bacteria *Myxococcus xanthus*, the amoeba *Dictyostelium discoideum*, etc.) are regularly described as implementing social behaviours as part of their reproductive strategies. Because microbial sociality obviously evolved independently from eusociality in insects and in naked mole rats, the lessons from microbes serve to provide hypothetical cases with concrete mechanisms. Yet, these analogies encourage phylogenetically broader analyses of the evolution of ageing in social context. For instance, one may wonder whether social microbes, known to operate transient yet critical forms of labour division, are longer-lived than closely related microbes that do not show evidence of such behaviours?

Moreover, considering that microbes are often found in spatially structured biofilms, and have been proposed to be granted, for some species at least, with some reproductive labour division as a result of asymmetrical cell divisions in their development (Teulière et al., 2020), one may also wonder whether biofilms (that are everywhere in the planet) offer an overlooked

example of socially-structured ageing. For instance, older microbial cells, being more dispensable for the reproductive success of the population, may behave as ant workers do and be especially enriched in the most dangerous areas of biofilms, whereas younger microbial cells, with higher replicative potential, may tend to get better protected, like the queen, and may occupy the most protected areas of biofilms. This hypothesis could be tested by measuring yet-to-be-biomarkers of ageing in spatial sections of microbial biofilms. If conclusive, ageing may provide secondary advantages to a microbial population, and kin selection may be proposed to act upon ageing microbes. Research into microbial ageing may therefore provide additional examples that social interactions can influence ageing across very different branches of the Web of life and unravel phylogenetically ancient processes associated with cellular ageing in a social context, some of which may have been inherited by multicellular eukaryotes during their transitions to multicellularity (Ocaña-Pallarès et al., 2022).

1.4.Open issues raised by the diversity of units of selection in ageing

The sections above hinted at the notion that an individual plant, animal, or even a microbe, being part of an interaction network, may not exactly correspond to the relevant unit of selection, i.e., to the Darwinian individual, upon which natural selection exerts its direct and collateral effects leading to organismal ageing. Therefore, ageing studies in a Web of Life also bring forth open issues about individuality, connected to long-standing active debates in the fields of ecology, evolutionary biology, and philosophy of biology regarding what should be considered as evolving by selection, especially now that naive group selection (i.e., selection aimed at what is good for a group of individuals of the same species) has been rejected in the 1950-1960s by David Lack (Lack, 1954) or Williams (Williams, 1966).

There are currently many competing views on individuality, including ecological views that attract more attention in the context of a Web of Life and may provide additional relevant frameworks for the studies on the evolution of ageing. Thus, after David Hull's influential paper on individuals (Hull, 1980), most views of individuality assume that the individual is a target of selection. Such views have been thoroughly refined since the times of Hull, though this basic connection between individuality and selection remains of the essence. For instance, Ellen Clarke argues that policing mechanisms ensure that selection does not dismantle the individual (Clarke, 2013). Goodnight (Goodnight, 2013) defines grades of individuality in relation to aspects of fitness. Godfrey-Smith (Godfrey-Smith, 2013) supports a dual view, distinguishing evolutionary individuals, defined as replicating entities that respond to selection, from physiological individuals or "organisms", which function as an integrated whole and autonomously reproduce. Recently, a merge between evolutionary and ecological concepts of organisms have also proposed that organisms, as set of cells that includes entities from distinct species (i.e., the microbiome) can be seen as ecosystems (Huneman, 2020). This latter view justifies addressing physiology and some pathologies from an ecological viewpoint (Costello et al., 2012; Scadden, 2006), and may also be applied to study ageing.

Even without embracing notions of ecological individuals as a new standard, from a purely evolutionary perspective, recent theoretical developments on units of selection are encouraging to enhance traditional, organism-centred evolutionary analyses of ageing to the benefit of a broader set of less paradigmatic Darwinian individuals, e.g., a tight association of microbes and

hosts. The theory of evolution by natural selection (ENS) explains biodiversity as the result of the divergence of biological entities with respect to the populations of their last common ancestors by a general evolutionary process common to all life forms, including microbes. In short, ENS requires three conditions: i) the presence of genetic variation within a population, ii) a link between genetic variation and the fitness of the carriers, and iii) the transmission of fitness-related variation from ancestors to descendants (Lewontin, 1970). While it is commonly assumed that the units of selection targeted by ENS must belong to a single species, this assumption is clearly a simplification (Papale et al., 2020). Consistently, it has often been argued that ENS can apply to more complicated entities than simple (monogenomic) lineages, shedding evolutionary light on a variety of otherwise unexplained biological phenomena (Bapteste et al., 2012).

These theoretical developments have thus opened a general issue: what is the diversity of units of selection (and thus of evolutionary individuals) that may evolve by natural selection and therefore may age on the planet, either by antagonistic pleiotropy, or due to a selection shadow? As some units of selection do not simply match traditional organisms within populations, the borders of "evolutionary individuals" (affected by natural selection) may be different from the borders of conventional organisms possibly trespassing the borders of conventional species. In particular, units of selection may be comprised of interacting entities from multiple species. For instance, a host species and some symbionts may be selected together. The Hawaiian bobtail squid, for example, is vulnerable to predation without its light-producing symbiotic bacterium, *Vibrio fischeri*, which in turn gains an advantage in population size and dispersal from the squid (Nyholm and McFall-Ngai, 2021; Visick et al., 2021). In such associations, the impact of natural selection on the ageing of both kinds of components remains to be theorized. Likewise, consider the dynamics of microbial associations associated to ageing hosts, e.g., a host and its gut microbiome. While it is well-known that the microbiome plays a mechanistic role in host ageing, such as inflammageing (Guedj et al., 2019), the role played by the ageing host on the evolution and possible ageing of its own microbial communities are less well-understood (but see (Blaser and Webb, 2014) for some hypotheses).

Again, the main evolutionary theories of ageing do not explicitly model such interspecific interactions, yet, importantly, all these theories postulate that the strength of natural selection acting upon a host decreases with time (Johnson et al., 2019; Reichard, 2017). This "selection shadow", by progressively altering the normal functioning of the ageing host, is therefore likely to alter the selection exerted by the ageing host on its microbiome (Foster et al., 2017). This consideration raises in turn an interesting novel open issue that we call the 'host selection shadow hypothesis'. Namely, if the selection imposed by an ageing host decreases, the host-associated microbiome might be progressively emancipated from the guardianship of its host, which could result in a functional disintegration of the ageing host-microbiome collective, past a given host (biological or chronological) age. Consequently, the host selection shadow hypothesis predicts the accumulation of pathobionts (Rampelli et al., 2013) with genes deleterious to the host late in the life.

Problematically, the host selection shadow hypothesis is currently not explicitly integrated in the classic evolutionary theories of ageing. To test it on empirical grounds, one would need to track the changes in the structure of microbial communities throughout hosts lifespan, e.g., by using temporal series of co-occurrence networks that provide a comprehensive topological

description of the changes that affect host-associated microbiomes in ageing hosts. Such original studies may identify a 'phase transition', after which the structure of host-associated microbial communities changes significantly with host ageing: then the host-microbiome association may not resist host ageing as a unit. In case such a transition occurs, the accuracy of a model where a host-microbiome collective is considered as a unit of selection throughout the entire lifespan of the hosts (as opposed to only from birth to the onset of the selection shadow) will deserve to be questioned.

Furthermore, analysing the relationships between microbiomes and hosts opens an even more fundamental kind of scientific issue. One may wonder whether the ageing of some components within a multi-specific association might contribute to the evolutionary success of that association, hence whether ageing of a single part within a unit of selection may constitute a critical feature for the persistence of the association. If that were to be the case, trade-offs between the repair and maintenance and the reproduction of multi-specific entities within a biological system may be anticipated, generalizing a form of disposable soma theory to systems of species. Indeed, the basic logic of the disposable soma theory proposes that if a motif within a network of interacting parts takes on the role of soma and another motif takes on the role of the germ line, then the former should age and the latter should not, independent of the level of biological organization. Consistently, a focus on molecular interactions occurring within organisms or within associations (e.g., biological systems, holobionts, emerging from networks of interacting components) may help comprehend the issue of modeling ageing across scales. In other words, considering complex systems involving components from multiple biological scales and species raises the open issue of how the ageing at one level of organization constrains ageing at another level of organisation, when both levels are functionally and evolutionarily integrated. However, currently, the ultimate causes that rule the ageing host-microbiome collective, and more generally the ageing of any evolved system, remain to be characterized. In the case of hosts and symbionts, this latter issue invites the development of model systems where the fitness of both host and microbes can be experimentally tracked over the lifespan.

1.5. Open issues when measuring fitness

If fitness measures, i.e., measures of evolutionary success, are critical to test hypotheses on the causes of ageing, quantifying the fitness of an individual is however challenging, especially in an ecological and social context.

The general notion of fitness indeed raises conceptual (what is it?) as well as empirical issues (how to measure it?). Fitness is related to survival and reproduction, and often, to the probability distribution of offspring. But people disagree about whether it is individual fitness or trait fitness (Ariew and Lewontin, 2004) that counts in evolution; whether fitness should be computed over one or more generations; whether ecological fitness as the propensity to thrive in an environment and population genetic fitness as the number of alleles left is identical; or how to interpret the probability concepts involved in fitness (especially, is it a propensity (Mills and Beatty, 1979) or not (Walsh, 2010)), etc. Given that ageing is commonly understood from the perspective of fitness trade-offs, theoretical disagreements about fitness may impact theories of ageing.

Granted, given that population genetics and behavioral ecology have developed positively, notwithstanding foundational disagreements over the concept of fitness, one could think that these disagreements do not matter in ageing theory either. However, the fact that trade-offs are the key concepts here brings about new difficulties.

First, in AP, natural selection trades off survival later for reproduction now. It can be seen as a trade-off between current and later fitness, provided that later survival means the possibility of having late offspring. However, estimating this trade-off presupposes that one knows a discounting rate of fitness (i.e., how it decreases with time) – which cannot be assumed as a universal discounting function. In contrast, the discounting function is very probably itself under selection (Huneman, 2023).

With respect to social structures, Hamilton (Hamilton, 1964) defined inclusive fitness of a behaviour as the sum of the fitness benefit brought by the trait upon its bearer X_0, added to the fitness payoff brought to each other organism in the group X_i, mitigated by the relatedness between X_0 and X_i (See also (Birch, 2017)). This metric allows the fitness of a trait to be assessed at the individual level in the context of a group. However, there are theoretical issues with estimating and defining relatedness (Grafen, 1985; Taylor and Frank, 1996), which is a measure of the statistical correlation between X_i and X_0 at the locus involved in the focal trait. Overall, relatedness allows one to compute how much is the benefit of another individual X_i in relation to the benefit of X_0. It can be seen as a discounting rate (since the less related X_i is from X_0, the less important is this benefit to the genotype delivering it). Quantification of the relatedness between individuals is therefore necessary to calculate social discounting and time discounting in order to make sense of trade-offs in the different theories of ageing, and to unify them in a general theory. Without defining and calculating these rates, a unified trade-off theory of ageing is implausible. Thus, a challenge for the field is whether a unified theory of senescence as a result of fitness trade-offs can be achieved or is even needed (Roget et al., 2022, Huneman 2023).

In addition, as a given organism can interact in different selectable ways with different sets of organisms over its lifetime, organismal ageing can be affected by multiple selection forces. Typically, as discussed above, an animal from a social species can be impacted by natural selection (here for features of ageing that are not biased by sex), by sexual selection (here for aspects of ageing that are sex-biased (Berg and Maklakov, 2012; Bonduriansky et al., 2008; Clutton-Brock and Isvaran, 2007)), by kin selection (for features of ageing that depend from the spatial structure of the population and the behaviour of organisms, i.e., care-giving, cultural transmission (Bourke, 2007; Lee, 2003), and possibly also by selection on persistence, i.e., selection on organismal survival independent of its reproductive success (Bouchard, 2008). This last selection on persistence is expected to be particularly important to the longevity of host-microbiomes associations or to clonally growing organisms (Bouchard, 2014; Edgeloe et al., 2022). Thus, in addition to determining which fitness value best models the evolution of ageing, it is also an open issue to determine which kind of selection exerts the strongest effects on which aspects of ageing over the course of an organism's life. For instance, the strength exerted by natural selection due to predation often decreases as an animal grows in size, while the influence exerted by kin selection on this animal may affect its ageing later in life, if that eusocial organism provides care to the young. The ultimate causes of ageing (and resistance to

ageing by the evolution of longevity programs) before and after the age of last reproduction are therefore likely to be different and require age-dependent modelling.

Finally, one may ask whether the central assumption of the evolutionary theories of ageing, that there exists a selection shadow, is always valid. For populations at equilibrium, Giaimo and Traulsen (2022) have convincingly demonstrated that selection pressure must fall and ageing evolves as long as mutations act age-specifically and do not causally link mortality and fertility (Giaimo and Traulsen, 2022). Yet are natural populations at equilibrium? On the species level, possibly, because if a species were not at equilibrium, it would either at some point spread over the globe or go extinct with respectively positive or negative growth rates, but some species may indeed be heading towards extinction. Locally, however, natural populations may be alternating, being in transition most of the time. In this case, these dynamics would affect the evolution of ageing in natural populations. Accounting for dynamic selection shadow would require extending, not just the phylogenetic scope, but also the ecological scope of existing theories.

1.6. Measuring fitness in ecologically intricate communities

How does such complexity of selection dynamics play out for less familiar units of selection, such as a tight functional multispecies association of a host and its resident microbes?

The effects on host lifespan of non-obligate, commensal microbes in the gut are less clear as is the teleology. Work in *Drosophila* fruit flies has shown that fly genotypes from high latitudes have a slower metabolism than fly genotypes from lower latitudes (Schmidt et al., 2005; Walters et al., 2020), which is reflected in a longer lifespan and longer survival under starvation conditions (Walters et al., 2020). However, depending on the specific gut microbes associated, the survival traits are impacted, for instance in a trade-off between longer lifespan and higher fecundity (Gould et al., 2018; Walters et al., 2020). Interestingly, high-latitude flies are associated with bacteria that promote a slower metabolism (lactic acid bacteria) and, conversely, lower-latitude flies are associated with bacteria that promote a faster metabolism (acetic acid bacteria) (Walters et al., 2020). When the fly genotypes and bacterial origins are swapped, the bacteria can have dominant effects. Specifically, when low-latitude bacteria were associated with high-latitude flies, and high-latitude bacteria were associated with low-latitude flies, the high-latitude flies had faster metabolism than the low-latitude flies (Walters et al., 2020). Thus, gut bacteria can override the genetic predisposition of their host with respect to survival traits. Future models of trade-offs in aging will need to take into account this kind of complexity.

Interactions between bacteria within the host can also affect the fitness traits of the host. Specifically, the trade-off between lifespan and fecundity is modulated by bacterial interactions such that combinations of acetic acid and lactic acid bacteria produce effects that are not necessarily predictable by the effects of the individual bacteria mono-associated with the fly (Gould et al., 2018). This was shown by combinatorial experiments where fly lifespan and reproduction was measured for separate treatments of all species of bacteria found living in the fly gut. By comparing, for instance, the flies associated with a single bacterium with flies associated with a pair of bacteria, the effect on the fly of the interaction between the bacteria

can be measured (Gould et al., 2018). This complexity reflects emergent properties of the host-microbiome association, whereby the interactions produce results that are different from the sum of the individual parts. These observations provide examples of how the unit of selection in ageing-fitness is not always clear because the fitness of the host and the symbionts cannot always be cleanly disentangled. Indeed, experiments measuring lifespan after removal of the bacteria indicate that while some bacteria set the lifespan of the fly only when they are alive inside the fly, others precisely trigger the death timing of their host even when the bacteria were removed in middle age and the hosts maintained under axenic conditions for the remainder of host life (Gould et al., 2018). Thus, the problem of modelling the impact of emergent properties of the host-microbiome association on host fitness and ageing is yet another open issue.

The evolutionary question of how these associations evolved has many grey areas. While it has been clearly argued that fitness is assessed at the level of the organism (Dawkins, 1989), as mentioned above this argument is couched in the context of populations of genetically similar organisms, and what constitutes the best fitness measure is debated. When very different organisms interact, each organism affects the other's fitness. For instance, the fitness of grass affects the fitness of rabbits that eat the grass. When microbes are in tight association with a host, these unrelated organisms can be coordinated so tightly as to be necessary for the survival of the other. Indeed, this is the case of many sapsucking insects and their nitrogen-provisioning symbionts (Smith and Moran, 2020). Sapsucking insects such as aphids maintain an obligate symbiosis with intracellular *Buchnera* bacteria for nitrogen-provisioning. The titter of *Buchnera* varies by aphid lineage with changes in gene expression that correspond to a metabolic tug-of-war (Smith and Moran, 2020), and differences in symbiont load affect the lifespan of the host (Ayoubi et al., 2020). Likewise, the mitochondrion evolved from a once free-living bacterium. With free-living bacteria that are not obligate symbionts, these bacteria often maintain tight associations with a host for the mutual benefit of both, and the maintenance of colonization genes in bacteria clearly argues that the host environment selects on bacterial genes. Thus, the other organism becomes a key environmental determinant of fitness.

In the context of high-diversity ecological communities, the complexities of many interacting genomes affecting their bearers' fitness are another challenge. In this case, one can liken the interaction of genomes to the interaction of genes in what is known as genetic epistasis. The epistasis framework has been extended to higher-order interactions, which accounts for the complexities of many interacting genetic loci (Beerenwinkel et al., 2007). Similarly, bacterial chromosomes can be considered as genetic loci. Thus, frameworks for dissecting higher-order epistatic interactions between genes could be modified to encompass higher-order interactions between bacterial species, and some progress has already been made on this front (Eble et al., 2021, 2019).

This ecological approach constitutes an important research direction that may enhance theories of ageing. To use an analogy, flight has long been hypothesized to explain the long lifespan in bats and birds compared to species of comparable body size that do not fly. Flight can be seen as a structural factor but can also be interpreted in the context of ecological niches. How ecological niches affect whether species age or not remains underexplored. Two models, one for the freshwater polyp hydra (Baudisch and Vaupel, 2010) and one for trees (Seymour and Doncaster, 2007) highlight two separate mechanisms for how negligible ageing could evolve based on available and favorable niches. Ecological niche explanations point directly to

the argument of the holobiont, because microbes could be modeled as the ecological niche of the host (and reciprocally so). Future models may involve trade-offs between survival and reproduction of microbes and their hosts to deduce optimal ageing patterns for the whole host-microbe system. For example, parasitic load may drive ageing, like what has been observed in HIV. An infection and thus the interaction with a microbial species often changes the Kaplan-Meier survival curve for the host. As the immune system needs time to develop, this may explain u-shaped patterns of mortality, where death rates are highest in juveniles and older adults. Including ecological niche arguments and species interactions could reveal new patterns of ageing (Baudisch and Vaupel, 2012). In particular, ageing patterns in taxa for which the distinction between growth and reproduction is not easily marked (i.e., all organisms undergoing asexual fission such as prokaryotes) might turn out to be diverse once these species are viewed as part of an entangled net of interactions among organisms and species, rather than separately evolving entities.

2. Enhancing the evolutionary analyses of systemic aspects of ageing

As we have seen above, traditional theories of ageing tend to treat the ageing organism as a 'unit of ageing', but this 'unity' is not obvious. We mentioned that this was the case because no organism lives alone and possibly ages alone, when discussing the consequences of the fact that organisms belong to ecological networks. In addition, even within organisms, inner networks may not be ageing in a unitary way, at similar paces and rates, as proposed for instance in germen line cells and somatic cells. Some important open issues about the evolution of ageing may therefore also require investigating the impact of surrounding and of nested systems on organismal ageing. In short, original analyses of biological/molecular interactions that take place within (not only between) organisms are probably needed to better connect observations gathered from multiple research fields, such as molecular and microbial -omics, raising issues about ageing at the interface of systems biology and evolutionary biology.

2.1. Bridging the gap between evolutionary theories on organismal ageing and data from other biological scales

Definitions of ageing and mechanisms of current theories cross scales from genetic to physiological to demographic. On the demographic or 'actuarial' level, ageing is defined by the increase of mortality with adult age. This definition is then extended by a causal statement that the increase in mortality results from increasing dysfunction on the physiological level. For instance, modeling the impact of emergent properties of the host-microbiome association between acetic lactic bacteria, lactic acid bacteria, and *Drosophila* described above (Gould et al., 2018) on host ageing is coupled to a second, mechanistic question: what physiological changes were made in the host to produce this lifespan modulation? In that case, it has been observed that colonization modifies host tissues. Lactobacilli have been documented to increase the mucosal thickness of the mouse colon upon colonization (Ahl et al., 2016). A similar expansion of a gut niche is observed in *Drosophila*, where a strain of *Lactiplantibacillus plantarum* binds the foregut and expands the niche for other commensal bacteria (Dodge et al., 2023). Colonization by lactobacilli has been shown to reduce infection and progression of disease by a variety of viral and bacterial pathogens (Britton and Young, 2014; Eaton et al., 2011; Heeney et al., 2018), establishing that commensal bacteria in the gut modulate host traits

with implications for host fitness. The key point here is that key theories to explain the evolution of aging (MA, AP) rely on genetic mechanisms to deduce resulting patterns of mortality over age, creating a large gap between mechanisms and outcomes. Evolution selects variants based on demographic outcomes, that is, surviving offspring and alive or dead parents. In that sense, the causes of reproduction and survival are invisible and selected "under the hood". Importantly, different combinations of causes could lead to the same outcome (Wensink et al., 2014a). A specific single cause might only be selected for or against given the presence of other causes. The diversity of causes results from the many organs, organ systems, and microbial species interacting in the body, each of them with its own rate of ageing (Nie et al., 2022), which together contribute to a focal individual rate of ageing.

For the ultimate outcome of death, ageing rates can only be calculated on the population level as number of deaths per number of individuals at risk. Recent theoretical innovations in formal demographic theory (Vaupel, 2022) open new ways to deduce individual rates of ageing from the population rate of ageing. This will be vital to eventually connect empirical measurement of ageing across scales. "Ageing under the hood" is especially relevant for species that exhibit apparently negligible or negative actuarial ageing, despite the underlying process of physiological ageing (Rera et al., 2012). This mismatch of types of ageing on different levels of biological organization has been demonstrated for the common weed *Plantago lanceolata* (Roach and Gampe, 2004; Shefferson and Roach, 2013), and is indicated by anecdotal evidence for individual tortoises and turtles living in zoos who exhibited typical signs of ageing (loss of senses, death by heart attack) (Austad and Finch, 2022), yet population level data for the respective species show no sign of ageing in the pattern of mortality (da Silva et al., 2022; Reinke et al., 2022).

Another example stresses the need to expand theories and connect them with empirical knowledge on trade-offs, inspired by systemic considerations. Theories argue that life history evolution critically depends on life history trade-offs. Without them, a framework that treats age-specific survival and reproduction independently (Hamilton, 1966) inevitably leads to ageing as the only evolutionary stable strategy possible (Giaimo and Traulsen, 2022). This contrasts with the observed diversity of ageing patterns across the tree of life (da Silva et al., 2022; Reinke et al., 2022; Roper et al., 2021), which is not predicted by existing theories based on the decline in the age-specific force of selection (Hamilton, 1966; Kirkwood, 1977; Medawar, 1952; Williams, 1957). What is missing?

Mutation Accumulation theory (Medawar, 1952) is a purely nonadaptive theory and predicts inevitable ageing. Could this theory predict negligible or negative senescence? MA could possibly predict negligible senescence, if empirical evidence would reveal that genetic effects would not be age-specific but lower or rise mortality at all ages in a similar manner. Mutations in such genes would be under the same selection pressure across ages with no escape into any shade of selection.

Antagonistic Pleiotropy theory (Medawar, 1952; Williams, 1957) evokes the notion of trade-offs, but specifically only among early life and late life. With selection pressure declining

over age, this trade-off favors early life benefits at the expense of late life costs, and thus ageing. Other types of trade-offs, however, are possible and have been shown to allow for the evolution of non-ageing (Baudisch and Vaupel, 2010; Vaupel et al., 2004; Wensink et al., 2014b). Such evolutionary demographic models make the general case for a diversity of ageing patterns, including negligible and negative senescence as evolutionary optimal life history strategies (Baudisch and Vaupel, 2012). They highlight that including alternative trade-offs is a promising extension to existing theories. But existing models are too general to fit empirical data. They do not predict a specific type of ageing for a specific type of species. How can modelers develop more realistic trade-off models? How can models capture ageing in a specific taxon? How can basic principles and determinants of ageing be identified to improve existing theory? Shapes of trade-offs are known to be notoriously difficult to quantify empirically (Roff, 2001; Stearns, 1992). Future theories will have to integrate trade-offs more thoroughly (Omholt and Kirkwood, 2021). And possibly, to understand how these trade-offs act, one should also unravel the molecular processes upon which they rely.

Of note, the disposable soma theory (Kirkwood, 1977) does not only include the notion of trade-offs. Additionally, it also rests on a structural argument, the division of the soma and the germ line. For species with such a separation, it predicts that ageing is inevitable. For species with no such separation, it would seem to predict the absence of ageing, such as for unicellular organisms. Yet, *E. coli* for example, show ageing (Lindner et al., 2008), contradicting that interpretation of the theory. Ageing in *E. coli* emerges from a mechanistic process of asymmetric damage accumulation during cell growth and division. Arguably, other unicellular organisms with a different mode of growth (new material added at the edges, division in the middle leading to random attribution of damage to either one of the daughter cells) may not result in a comparable ageing lineage, but see (Teulière et al., 2020) for the view that ageing is likely to be general across unicellular organisms. What is critical here is that systemic considerations on the role of structure, e.g., organismal structure, remains generally underexplored in existing theories of the evolution of ageing, whereas they would reduce the gap between theories and mechanisms of ageing.

Granted, organismal (and possibly other?) structure defines costs of growth and repair, e.g., modular structure allows for efficient replacement growth of damaged structure by "throw away and grow new" (Baudisch, 2008). It constrains possible modes of reproduction (e.g., asexual *vs* sexual), and it affects the environmental hazard of death, e.g., by the presence of absence of protective, defensive, or escape structures such as shells, poison, or the ability to fly. Organismal structure also dictates a potential future increase in reproductive output, e.g., if body size is proportional to the number of eggs or seeds produced, such as in many fishes or trees. However, organismal structure is underexplored and under-exploited and could be a key dimension to answer why some species age and others not (Cohen et al., 2022). More generally speaking, there is growing evidence that our understanding of the systemic components of mainstream evolutionary theories of ageing can be further elaborated to better explain the theoretical and mechanistic foundations of the evolution of ageing.

2.2. Unravelling the genetic pathways associated with longevity and ageing

Molecular pathways associated with ageing and longevity are another quite natural starting point to try to connect mechanisms of ageing and theories of ageing from a systemic perspective. With the advent of -omics and network sciences, the molecular organisation of these systems is progressively coming within scientific reach, and interactions within and between ageing organisms can be further deciphered. Typically, evolutionary biologists can contribute to identify some pathways associated with ageing and longevity while making some hypotheses regarding their origins and their eventual role in driving ageing (de Magalhães et al., 2009; Li and de Magalhães, 2013). Yet, this apparently straightforward research program brings forth various exciting open issues.

A first intuitive approach to tackle the issue of the evolution of ageing and longevity associated pathways requires to achieve a comprehensive survey of these pathways, in some model species at least. This however actually constitutes a remarkable challenge. For instance, there is a 100-fold variation of longevity across mammals (Tacutu et al., 2018), but the number of genes involved in these differences in organismal longevity are unknown. State-of-the-art methods of genomics and molecular evolution provide valuable strategies to identify some genes with remarkable features that correlate with longevity, e.g., genes under positive selection or highly duplicated in long-lived taxa but not in short-lived taxa for high quality genomes (Doherty and de Magalhães, 2016; Farré et al., 2021; Foley et al., 2018; Gorbunova et al., 2014; Irving et al., 2021; Kacprzyk et al., 2021; Keane et al., 2015; Kolora et al., 2021; Li and de Magalhães, 2013; Orkin et al., 2021; Sahm et al., 2018; Tejada-Martinez et al., 2022; Toren et al., 2020). Interestingly, so far, such methods have reported little overlap in the gene families associated with longevity across mammalian species (Farré et al., 2021). As longevity is predicted by the classic Darwinian theory to be an organismal trait that can be selected for, and can therefore be at least partly genetically programmed, this limited genetic overlap may be reasonably explained if different populations and different species underwent different evolutionary histories because their genes were subjected to distinct selective pressures. An alternative may however be that our methods of detection of longevity genes and genome data quality are still somehow limited. Furthermore, if confirmed, this apparent heterogeneity between the sets of longevity and ageing-associated genes across mammalian species (not to mention even more distantly related groups of Opisthokonta (Teulière et al., 2022)) opens the possibility that mutations with effects on longevity or ageing impact similar functional pathways (if not of the same genes), i.e., DNA damage response, protein homeostasis, etc., and that the evolution of longevity and ageing remains largely convergent over large evolutionary scales (Farré et al., 2021; Muntané et al., 2018; Treaster et al., 2021). Thus, aging -omics analyses across different animals have notably convergently implicated immune and inflammatory processes (Benayoun et al., 2019). Technical developments to make genomics more predictive of longevity- and ageing-associated genes across a broad range of species must still be explored before more definite conclusions can be reached.

Interestingly however, this methodological challenge has already paved the way for alternative approaches to predict longevity and ageing associated genes through the development of network approaches that explicitly take molecular interactions into account. Thus, in the past twenty years, some ageing studies have tried to identify, not only the molecular components of pathways associated with ageing and longevity, but also the molecular

interactions that compose these pathways (Bell et al., 2009; Budovsky et al., 2007; Ferrarini et al., 2005; Fortney et al., 2010; Promislow, 2004; Tejada-Martinez et al., 2022; Wang et al., 2009; Witten and Bonchev, 2007; Zhang et al., 2016). These kinds of studies have the potential to enhance both the mechanistic understanding of how these pathways work but also the ability to predict novel genes and pathways associated with ageing and longevity from interactomics data (Avelar et al., 2020; de Magalhães and Toussaint, 2004; Managbanag et al., 2008; Tacutu et al., 2012; Wuttke et al., 2012), thus fleshing theories of ageing with new molecular evidence. The biological open issues are not only whether we have missed critical, highly central genes involved in ageing and longevity but also whether molecular interactions are possibly evolutionarily conserved and critical for ageing, thus with high translational potential (Teulière et al., 2022).

In short, these network approaches start from experimental predictions that identify sets of genes regulating longevity or ageing, such as those forming the mTOR nutrient-sensing signalling network, using genetically modified model organisms and lifespan assays (Kenyon, 2010; Papadopoli et al., 2019; Templeman and Murphy, 2018). Some of these longevity and ageing-associated genes (LAGs) can even be further classified as pro- or anti-longevity according to the lifespan phenotypes resulting from their genetic loss or gain of function in model organisms (Kenyon, 2010; Tacutu et al., 2018). Next, protein-protein interaction (PPI) networks, reflecting the sum of all known interactions in the proteome of an organism, or interactome, and, as we will see below, gene co-expression networks (GCN) based on transcriptomic data, can be used to understand how LAGs interplay to influence, accelerate or delay ageing in organisms. For instance, proteins encoded by LAGs from model organisms such as *Saccharomyces cerevisiae* and *Drosophila melanogaster* were shown to be significantly central, connected proteins in PPI networks (Fernandes et al., 2016; Promislow, 2004; Tacutu et al., 2018), displaying higher node degree (the number of connections per proteins in the network) than other non-ageing or non-longevity-associated proteins. These metrics were interpreted as a proxy for functional pleiotropy, in support of the AP evolutionary theory of ageing (Promislow, 2004) (Teulière et al., 2022).

Assuming strong conservation between LAGs in human and model organisms, human longevity networks, defined by the protein-protein interactions between longevity- and ageing-associated proteins (LAPs) have also been constructed, and mechanistically connected to age-related diseases (ARD) (Bell et al., 2009; Budovsky et al., 2007; Wang et al., 2009; Zhang et al., 2016). From the analysis of the pro- and anti-longevity genes in four model organisms recorded in the GenAge database, the overlap between LAGs and ARD has been further analysed, and the centrality of LAPs in PPI networks confirmed, indicating such LAPs regulate fundamental processes (Fernandes et al., 2016; Tacutu et al., 2018). Moreover, Fernandes *et al.* have also showed that pro- and anti-longevity proteins are intertwined in the interactome of the worm *Caenorhabditis elegans* (Fernandes et al., 2016). Such an intertwining of LAPs with opposite effects on longevity in interactomes was used to suggest that evolutionarily conserved, fine-tuned molecular interactions are involved in regulating organismal lifespans (Teulière et al., 2022).

Although these previous investigations of ageing processes at the systemic level have been performed using interaction networks, whether other aspects of interaction network topologies and other network metrics convey untapped sources of information related to ageing processes

is another question to be addressed. For example, PPI network comparisons offer a still underexplored research direction to unravel the evolutionary history of ageing processes by uncovering evolutionarily conserved interactions between a much broader set of species than currently investigated (Teulière et al., 2022). A generalized and interdisciplinary comparative strategy, coined phylosystemics or evosystemics, based on the addition of evolutionary knowledge (i.e., from orthology) onto nodes and edges of interaction networks, has been recently proposed to perform such comparative analyses (Teulière et al., 2022; Watson et al., 2020). Using evosystemics approaches, not only conserved but also undescribed ageing-associated processes can be predicted using a process of guilt-by-association in networks (Teulière et al., 2022). For example, additional LAPs and interactions, including medically relevant and/or potentially druggable human genes, can be predicted by identifying proteins with similar neighbours to human LAPs, using the Jaccard index measure to compare ancestral PPI networks or PPI networks from various extant species (Teulière et al., 2022). How many new longevity or ageing associated pathways could still be unravelled by an even more systematic use of evosystemics approaches across the Tree of Life is therefore an exciting open issue.

In addition, transcriptomic data, which provide proxies of gene expression in organismal cells or tissues, bring forth additional questions regarding the evolution of ageing and longevity associated pathways. First, transcriptomic data can be used to unravel more components of longevity or ageing associated pathways (Baumgart et al., 2016; Chiou et al., 2022; Huang et al., 2019, 2016; Somel et al., 2010; Southworth et al., 2009). For example, comparative transcriptomic analyses can in principle serve to establish what genes are both more expressed in long-lived organisms and less expressed in short lived organisms, a pattern suggestive of their conserved association with enhanced longevity. In theory, such opposite patterns of gene expression for taxa with different lifespans could be systematically detected for increasingly phylogenetically divergent sets of taxa, starting with closely related taxa with opposite lifespans, e.g., within bats and then beyond that lineage. However, one methodological challenge must be addressed to move decisively in this direction: longitudinal transcriptomic data must be acquired from organisms with high quality reference genomes, for which molecular biomarkers of ageing can get extracted, ideally through non-lethal sampling in nature.

Moreover, although transcriptomic studies conducted within a focal lineage have provided evidence that gene expression demonstrably changes during ageing (Chiou et al., 2022), the inferential power of transcriptomic studies can also be further enhanced using network analyses. Unravelling how gene co-expression patterns change with ageing, and whether these co-expression changes show some remarkable regularities is far less understood and appears as a scientifically under-explored path to connect general theories of ageing to actual mechanisms (Bernard et al., 2022; Ferreira et al., 2021; Pacifico et al., 2018; Southworth et al., 2009). First, gene co-expression analyses provide a holistic overview of the molecular processes associated with aging. Second, unravelling regularities on gene co-expression would allow to address major fundamental and practical issues.

As a special case of antagonistic pleiotropy, it has been proposed that programs selected for a given purpose early in life may show deleterious effects later in life, causing organismal ageing, due to a lack of selection to turn off the late expression of these programs

(Blagosklonny, 2006; Gems, 2022). In other words, quasi-programs would be predicted instances of antagonistic pleiotropy. Yet, which quasi-programs are indeed involved in human ageing (and beyond our species) has not yet been systematically explored. Network analyses may help unravel candidate quasi-programs as sets of proteins (or genes) that remain constitutively co-expressed with age.

It may be worth noting however that because multiple versions of antagonistic pleiotropy are used in the field of ageing studies, there may be multiple kinds of quasi-programs in ageing organisms. To begin with, antagonistic pleiotropy typically occurs when a given gene has two distinct effects over time. On the one hand, antagonistic pleiotropy can be invoked to explain when in life gene expression exerts a positive effect versus none. On the other hand, antagonistic pleiotropy can produce a situation where a given gene has a positive effect early in life then a negative effect later in life. More generally, either the same effect shifts from positive to negative (such as Williams' example of a gene increasing bone calcification), or a gene can have two distinct effects due to its interactions with other genes that change over the lifespan, causing first positive effects, then negative ones. Therefore, the term 'antagonistic pleiotropy' covers distinct situations, both in terms of the relation between fitness magnitudes, and the characterization of pleiotropy. It is currently unknown which kinds of antagonistic pleiotropy and of quasi-programs prevail in different ageing organisms.

In addition, unveiling regular tissue-specific gene co-expression may hint at tissue-specific clocks, whereas regular gene co-expression with ageing, shared between tissues, may hint at tissue-extrinsic clocks: systemic mechanisms measuring the passage of time in organisms. Unraveling "orchestral" clocks, responsible for structuring the successions of specific biological processes, typically by regulating the (absolute or relative) temporal order of gene expression in organisms, could make a big difference in our understanding of the evolution of ageing. Thus, developmental biologists are familiar with the notion that some developmental programs very likely contribute to individuals' development, from birth to maturation to the adult age. Whether some programs may lead individuals throughout various stages of their lives, typically beyond their age of sexual maturity and possibly until their deaths, is of course much debated (Rando and Chang, 2012). This is a major issue. As noted by T. Kirkwood: "the case for a central clock is weakened, however, by the evolutionary arguments that point to the gradual loosening, and eventual disappearance, of genetic control over the late stages of the lifespan" (Kirkwood, 1997). Yet, importantly, for MA (and to some extent AP) to explain ageing over the entire course of an organism's life, it is constitutive to these theories that some genes can be late-expressed (Medawar, 1952; Williams, 1957). Still, these theories do not explain how such a regular late expression is possible, especially if the organism's functionality, including its capacity to enforce a regulatory clock, reduces during the selection shadow. Thus, these traditional evolutionary theories of ageing raise an issue that is still open: are there 'orchestral programs' that can constrain how gene expression, gene co-expression, and ageing trade-offs unfold over the lifespan?

There are several tentative examples to back up the idea that "orchestral" pathways may exist. Thus, a remarkable unpublished work by Horvath *et al.* (Consortium et al., 2021) reports that DNA methylation profiles set at birth can predict both the age of an individual organism and the longevity of its species across animals. The phylogenetic depth of such predictions is

striking and suggests that a deep, conserved connection exists between aspects of ageing and biological development, as proposed by (de Magalhães, 2012). What developmental processes may set the pace of ageing based on epigenetics is currently unknown and is a fascinating challenge (Raj and Horvath, 2020). Unveiling this connection is not going to be easy, even by relying on epigenetic clocks, because while such clocks (which are computational models, usually a machine learning model like elastic net or LASSO) are fascinating biomarkers of ageing (Bernabeu et al., 2023), it remains to be determined if their inputs (DNA methylation sites that become hypo- or hyper-methylated with age) are causally impactful and result in ageing or are simply downstream effects of other processes.

Here as well, the development of new network analyses may help to tackle this issue. Via developmental programs, natural selection is expected to constrain, hence to introduce some homogeneity in the order of expression of some biological processes at least until individuals reach sexual maturity. By contrast, the expression of biological processes should become more heterogeneous within older conspecific individuals, when natural selection weakens. Indeed, if ageing is not under selection, significantly fewer common biological processes should be detected across networks from older individuals than across networks from younger individuals. However, observing some (or lots of) common biological processes typically associated with older ages, and potentially associated to age-related diseases, would be compatible with either i) the existence of some 'orchestral programs' over the entire lifespan of individuals, or ii) with the (deleterious) continuation of developmental programs past the growth phase, aka quasi-programs. Data are now available to tackle this issue for diverse mammalian species, and rich information about the temporal order of expression of biological processes over individuals' lifetimes will increasingly be deducible from analyses of interaction networks, constructed from transcriptomic data from conspecific individuals at different ages (Bernard et al., 2022). Consistently, it becomes an open issue to know whether conspecific individuals universally express at least some critical biological processes in similarly ordered successions as they age (as suggested in (Chiou et al., 2022)). This in turn would open a new, predictable intriguing question: are such 'orchestral programs' phylogenetically conserved? And can such tissue-specific 'orchestral programs' or tissue-specific quasi-programs explain some of the heterogeneous ageing rates observed between organs within organisms (Nie et al., 2022)?

Likewise, differences in regular co-expression between males and females would show what tissues, in each sex, age fastest (i.e., the tissues that present changes in their typical gene co-expression networks earlier in life), raising questions about sexual selection and these ageing mechanisms. Finally, longitudinal analyses of gene co-expression could show whether ageing is associated with the regular co-expression of age-associated diseases and which ones, uncovering mechanistic connections between age-associated diseases and calendar ageing (Avelar et al., 2020; Fernandes et al., 2016; Rera et al., 2012), questioning whether ageing deserves to be considered as a disease.

Overall, these latter approaches involving the comparison of longitudinal series of gene co-expression networks within and/or between species can enhance evolutionary theories of ageing, because they are informative both on the proximate and the ultimate causes of ageing. GCNs comparison within a species can indeed determine i) how ageing occurs (e.g., what sets

of co-expressed genes are age-specific); ii) when ageing occurs (e.g., which age classes present altered co-expression patterns with aging); and iii) suggest some causes that may drive regular changes in co-expression during ageing (e.g. when evidence of selection recorded in the networks decrease past a given age as a result of the selection shadow) (Bernard et al., 2022). Developing GCN comparison between species can further unravel conserved proximate and ultimate causes of ageing.

Conclusion

We provided some selected examples to show that the evolution of ageing across the Web of Life is not so well-understood (Fig.1) in terms of the conserved genetic determinants of ageing and their evolution. Although our review could not possibly be exhaustive, these examples were sufficient to argue that even for very well-studied extant species, many open issues remain.

Some issues are related to the mosaic nature of evolved entities/mechanisms:

- What are the multi-specific origins of ageing?
- What is the relative contribution of nuclear, organellar, and microbiome genomes in the ageing of multicellular eukaryotes?
- Do endogenous viruses contribute to host ageing and longevity across the Web of Life?
- Do some aspects of human ageing result from the reticulate history of our lineage that involved hybridization with members of Neanderthalian or Denisovian tribes?
- What are the age-distorters of humans, the age-distorting genes, and the targets of these genes, if any?

Other issues are related to the context-dependence of ageing:

- What are the loads of age-distorters in natural populations and their impact on ageing organisms, if any?
- How does social life affect ageing and ageing-associated gene expression?
- Does social life affect organismal ageing outside the animal kingdom?
- Do ‘social microbes’ age in a special way, involving reproductive labour division?
- Does biofilm formation reflect socially-structured ageing?
- Did multicellular eukaryotes inherit phylogenetically ancient processes associated with cellular ageing in a social context?

Other issues concern the systemic nature of evolved entities/mechanisms:

- Do non-canonical units of selection exist in ageing, e.g., multispecies associations of a host and its resident microbes?
- How does host ageing and selection shadow the impact of the microbiome on ageing, and reciprocally, how does microbiome ageing affect host ageing?
- Can a host-microbiome collective be modelled as a unit of selection throughout the entire lifespan of the host, or does that kind of modelling fall short in the case of a selection shadow?
- How does the ageing at one level of organization in a system constrain the ageing at another level of organisation?
- When did constitutive components of ageing systems appear, and when did they start to interact?
- What are the multispecific origins of inflammageing?

- How many genes are involved in the differences in organismal longevity across the Tree of Life?
- How many molecular interactions are involved in the differences in organismal longevity across the Tree of Life?
- What are the stochastic mechanism(s) that trigger the transition from a lively *E. coli* cell to a dying cell?

Finally, other issues bear on more theoretical aspects of ageing studies:

- Can ecological notions of individuality benefit studies on the evolution of ageing?
- Which kind of selection exerts the strongest effects on key aspects of ageing over the course of an organism's life?
- Can a unified theory of senescence as a result of fitness trade-offs be achieved or is this notion fraught?
- Can frameworks for dissecting higher-order epistatic interactions between genes be modified to encompass higher-order interactions between bacterial species that explain ageing?
- Would consideration of ecological niches and species interactions reveal more than the currently described three main patterns of ageing?
- For natural population not at equilibrium, is a selection shadow always observed?
- Can the difference in scales between genetic, physiologic, demographic data be bridged to develop more realistic trade-off models?
- Could the consideration of organismal structure improve existing evolutionary theories of ageing?
- Can new network metrics be developed to convey information about ageing and its evolution in the context of interactions?
- Can candidate quasi-programs be systematically detected?
- Which kinds of antagonistic pleiotropy and of quasi-programs prevail in ageing organisms?
- Do some 'orchestral programs' unfold over the lifespan of organisms with some regularity in spite of the selection shadow?
- What developmental processes, if any, set the pace of ageing? Does this suggest a mechanistic and evolutionary connection between developmental processes, epigenetic changes and ageing?

In the light of the diversity of these open questions, some most respected authors proposed that developing a new paradigm on ageing may be fruitful (Gems and de Magalhães, 2021). This may indeed be a good idea. From a philosophical viewpoint, it is interesting to note that, with the advent of evolutionary biology, the philosophical tradition that provided the most intuitive framework to explain ageing fundamentally already changed once during the history of ageing studies. Namely, there was a shift from the tradition of Providentialism, as ancient as Aristotle, which explained ageing as a price to pay to sustain the economy of Life, to a tradition of Contingency, according to which the ageing process was likely better explained as a form of "evolutionary neglect", as illustrated by the traditional forms of MA, AP and DS. While in the scientific community, the Providentialistic view of ageing was arguably supplanted by the Contingency view of ageing, some ongoing debates, for example around the notion of

"programmed ageing", assess that these two traditions can still, to some extent, conflict in the ageing field (Huneman, 2023). Yet, this conflict is probably no longer the critical root cause for the lack of consensus observed (Cohen et al., 2020). But could there be a single new paradigm about ageing?

Our review shows that current evolutionary explanations of ageing still face several grey areas and could be expanded by tracking functional interactions beyond diverging lineages, social interactions and labour division within populations or systems, and possibly by acknowledging a plurality of *explananda* and of *explanans* (e.g., an alternative way to measure fitness within natural communities, including social and spatial discounting of fitness; the existence of alternative accounts of antagonistic pleiotropy; the multiplicity of ageing individuals/systems that could evolve; the phylogenetic diversity of pathways associated with organismal ageing and longevity across the Web of Life; and the differences in senescence patterns between species, etc.). As such, our review asks a final open question: might the search for a new paradigm lead to a new major shift in epistemic tradition? By bringing multiple open issues about the evolution of ageing under further scrutiny, is the ageing field moving from the Providentialistic and Contingency traditions, towards a Pluralistic view of ageing?

Acknowledgements

We thank 2 anonymous reviewers for their useful comments. PH is supported by the Labex 'Who I Am' and the AgePhiBio project from Paris I Patheon – Sorbonne. J. Teulière was supported by an Emergence grant (EMERG-ESPA) from Sorbonne Université to E. Bapteste. E. Bapteste benefited from a grant ATM MNHN 2022. LK is supported by the ERC grant resiliANT 741491 from the H2020-EU.1.1. - EXCELLENT SCIENCE - European Research Council (ERC) program. ECT is supported a Science Foundation Ireland Future Frontiers 19/FFP/6790. AL thanks the Axa Foundation Chair on Longevity. AB is supported by the ERC Grant Born Once - Die Once 101043983 from the ERC-2021-COG program. WBL is supported by NSF grants IOS 2032985 and 2144342, NIH grant R01DK128454, Scialog award 27912 from the RCSA and the Allen Foundation.

Figure legends

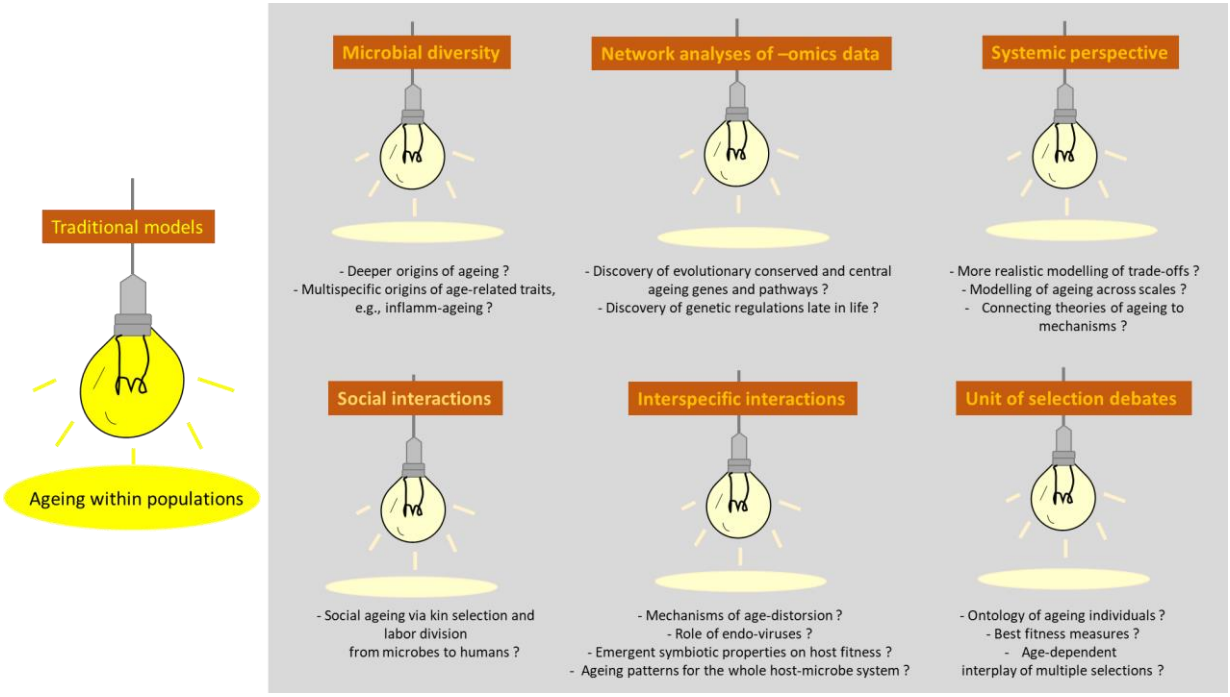

Fig.1: Visual summary of some key sources of open issues about the evolution of ageing

The classic evolutionary theories of ageing are collectively highlighting numerous important issues about the evolution of ageing (yellow bulb), but several open issues (in black font, under lighter bulbs, in the grey area) could benefit from embracing a plurality of additional perspectives (in orange font, over the lighter bulbs). Embracing these perspectives more systematically could ultimately highlight several reticulate dimensions of the evolution of organismal ageing, consistently with a rich scientific literature showing that organismal ageing is affected by interactions from diverse biological systems surrounding the ageing organism and by interactions from biological systems nested within the ageing organism.

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