1. Introduction

Understanding the process of ageing represents one of the key challenges in current basic and applied biological research [1–10]. One reason for this is that ageing is a complicated and multifarious process. The inherent complexity of ageing may be better compre-
hended when considered from an evolutionary perspective. While biogerontological research is centred on functional understanding of the ageing process and seeks potential ways to mitigate its pathologies [3–6], an evolutionary outlook considers functional declines as a consequence rather than cause of ageing. Evolutionary considerations of ageing aim to understand why ageing has evolved, why it is not eliminated by natural selection, and why ageing patterns vary among individuals, populations and species [7–10].

Evolutionary theories of ageing consider the emergence and persistence of functional declines within the broader concepts of evolutionary biology. I believe that such understanding provides critical insights into the practical aspects of biogerontological research, similarly to the advances gained from an evolutionary perspective on disease and medicine [11]. Theodosius Dobzhansky’s assertion that “nothing in biology makes sense except in the light of evolution” [12] has particular relevance in understanding ageing. The prevalence of ageing is inherently puzzling because, in a strikingly wasteful manner, it leads to the destruction of individuals who have successfully managed to develop a complex body from a single cell only to subsequently fail in the seemingly simple task of maintaining what has already been formed [13]. Evolutionary theory offers a satisfactory answer to this puzzle, showing us why this is necessary for some organisms while others may perhaps escape the ageing process. In this review, I treat ageing as an intriguing evolutionary question and demonstrate that, despite major progress in our insights to the origin, diversity and pervasiveness of ageing in recent decades, our understanding of its foundations and variation across the Tree of Life is far from complete.

I first review the classic evolutionary theories of ageing and their empirical tests. By highlighting challenging discoveries, I then demonstrate that many recent challenges can be accommodated within new developments of the classic theories that are their logical extensions. I then summarize more problematic points posed to the current paradigm and provide a summary of alternative views developed primarily by insights from non-model taxa. Finally, I aim to provide a balanced view on whether ageing is indeed universal to all organisms.

2. Classic theories on the evolution of ageing

2.1. Theoretical underpinnings of the classic evolutionary theories of ageing

The classic evolutionary theories of ageing (CETA) hinge on a simple argument explaining how ageing evolved and is maintained. This argument recognizes that all organisms inevitably die from extrinsic sources, be it accident, predation, disease outbreak or bouts of exceptionally harsh conditions. Hence, no individual is immortal, irrespective of the existence of ageing. From an evolutionary viewpoint, this makes later periods of life less important as progressively fewer individuals escape the extrinsic sources of mortality to experience the effects of natural selection [14,15].

This paradigm of the evolution of ageing is rooted in Weismann’s recognition of the fundamental difference between immortal germ line and mortal soma [16]. Later explicit acknowledgment of the genocentric view of evolution [17,18] underscored the fact that the body constitutes a mere envelope – a vehicle – to pass on genes (genetic information), which are the ultimate subjects of selection, through evolutionary time. The germ cells contain the complete genetic information to build a soma and pass it from generation to generation, protected from somatic mutations and other modifications of the information content. Rare mutations within the germ line, along with recombination between parental genetic information, ensure that evolution can act on the resulting variation. This process enables organisms to adapt to changing environments and evolve novel variation. In contrast, somatic cells, less protected from the impacts of the external environment, accumulate errors over an individual’s lifespan [1–3,7].

Traditionally, three main classic evolutionary theories of ageing (CETA) are recognized [13–15]. All of them, sometimes implicitly rather than explicitly, are centred on the distinction between the germ line and soma and use genocentric reasoning. The three theories provide complementary explanations rather than exclusive treatments of the same problem, and all ascribe ageing to an inevitability of extrinsic mortality that erodes the strength of natural selection later in life.

2.2. Mutation accumulation, Antagonistic pleiotropy, Disposable soma

The Mutation Accumulation theory (MA) [14] proposes that mutations with harmful effects on individual condition can accumulate in the genome when they are expressed late enough in life, when most individuals have perished from external sources anyway. Thus, MA suggests the existence of a ‘selection shadow’, resulting in the maladaptive accumulation of senescent changes to organismal performance because natural selection is not effective in purging those mutations from the population. Under MA, a widespread expression of senescent declines should only be manifest when the sources of external mortality are considerably reduced and extended individual survival is achieved. In the real world, removal of extrinsic mortality can be accomplished by keeping animals in protected conditions in captivity or through dramatic reduction of externally inflicted mortality via sanitation, medical care, vaccination and other improvements of life conditions, such as those experienced by many modern day humans. In the absence of protection from extrinsic mortality, senescence is rarely experienced.

The Antagonistic Pleiotropy theory (AP) proposes that ageing can evolve via natural selection rather than being a non-adaptive side effect. Williams [13] suggested that alleles with age-specific pleiotropic effects, that increase early-life fitness at the expense of late-life detrimental effects, could spread across populations. Given that early-life events are under stronger selection (because more individuals are alive before succumbing to extrinsic mortality), such pleiotropic alleles can readily experience positive selection. Hence, AP suggests a clear trade-off between current and future fitness reward and predicts more dynamic evolution of longevity than MA in respect to changing external conditions and the strength of extrinsic mortality.

Both MA and AP assume that higher extrinsic mortality leaves fewer individuals to survive to reproduction at later ages, making selection for longevity relatively irrelevant [1–3]. As a consequence, a higher intrinsic mortality (i.e. more rapid functional senescence) evolves, either simply by a random deterioration (genetic drift) when a “quality check” has little power (MA), or via selection for reallocating resources to early life at the expense of self-maintenance over the long term (AP). In both cases, it leaves populations of ageing individuals with intrinsically limited lifespans even with a contemporary reduction of external sources of mortality (e.g. in captivity). The nature of their evolution (drift or natural selection) implies, however, different predictions related to the association between early-life fitness and the rate of ageing [19]; no correlation for MA but a positive relationship under AP. Further, given the early life benefit of pleiotropically acting alleles, senescent deterioration of vital functions is expected to be commonly detected in natural populations under AP but not under the predictions of MA.

Kirkwood’s Disposable Soma theory (DS) [15,20,21] explicitly highlights the distinction between the germ line (sperm, eggs and
their precursor cells) and other cells that are destined to form temporary bodies that contain, protect and help to propagate the information they share with the germ cells. Somatic cells accumulate mutations, dysfunctions in cellular processes and other functional problems over chronological time [22] and, while their repair is theoretically possible, the cost of keeping complex cellular and organismal machinery in its original state is high. Given that evolution is a competition among sets of genotypic variants [18,23], investment into replication (reproduction) is of a superior long-term return than investment into the perfect maintenance of the current copy. While sometimes seen as a mere extension of the purely genocentric AP to a physiological context, it principally differs by explicitly assuming dynamic optimal allocation of resources within the life history trade-offs (reproduction, survival) to maximize lifetime fitness [21]. Such a definition fits empirical knowledge much better than AP – while evidence for genes with antigenically pleiotropic effects is not strong [24,25], support for generalized trade-offs between reproduction and survival is abundant [7,26–28]. From a survival-reproduction trade-off perspective, ageing can be compared to a sexual selection analogy – while costly adaptations to secure mates (such as elaborate mating signals or lethal male combat) are detrimental to survival, they increase fitness and, therefore, are positively selected for by natural selection.

3. Support of the classic theories

In recent decades, support has accumulated for various predictions derived from the CETA. The association between the force of extrinsic mortality and lifespan has received the greatest support. Broad-scale comparative analyses [29] have demonstrated that taxa with apparently superior protection from sources of extrinsic mortality have longer lifespans than related taxa without such protection. In that sense, poisonous reptiles generally outlive their harmless relatives, birds have longer lifespans than non-flying mammals, bats live longer than similarly sized terrestrial mammals and subterranean rodents outlive their ground-living relatives [30].

The same predictions have been confirmed experimentally at a finer taxonomic scale among closely related species. When transplanted to a benign experimental environment devoid of seasonal limitations, grasshoppers, water fleas and annual fish from environments with a short seasonal duration maintain shorter lifespans than their sister species from longer lasting environments [30]. The support from naturally evolved organisms is pertinent to contrasts between populations within a species. An island population of the opossum (a marsupial mammal), removed from predation pressure for thousands of years, senesced more slowly than the mainland opossum population [31]. Annual killifish populations from pools in a wet region (that naturally last longer), survived in captivity longer than their conspecifics from dry-region pools [32]. Thus experimental evolutionary studies directly confirm that standing genetic variation for lifespan and ageing exists in natural populations and readily responds to artificial selection for longevity [2,33,34].

Survival-reproduction trade-offs among and within species support predictions from DS, with evidence of more rapid actuarial or functional senescence linked to stronger resource allocation to (early) reproduction in both sexes [2,26–28,35]. Data from natural populations of birds and mammals, including human populations, support this general pattern [26,35–37].

4. Challenges to the classic theories

Despite solid corroboration of predictions derived from the CETA, support comes primarily from animals with complex bodies that cease growing at a certain developmental stage. This includes the entire set of common laboratory models of ageing – *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Drosophila melanogaster*, and the mouse *Mus musculus*. All these taxa share a similar life history – a rapid exploitation of explosively available resources that undergo cyclic dynamics of abundance and exhaustion [38–41]. This makes them amendable to breeding in laboratories, but there is a risk that by studying those models we commit to a systematic bias similar to studies on WEIRD (Western, Educated, Industrialized, Rich and Democratic) subjects in social sciences [42]. This approach may be particularly misleading if results are uncritically extended to other species (including humans) that possess a different life history or body form. Indeed, observations from unicellular life forms, plants and modular animals, as well as some observations from animals with complex bodies, are less congruent with the predictions of the CETA (Fig. 1).

Several theoretical and empirical studies have revealed weaknesses and challenge key aspects of the theory. The CETA postulate that ageing is an inevitable outcome of evolutionary forces [17], but there is increasing evidence that ageing and senescence are not apparent in many taxa [2,8,10,43,44]. From a demographic point of view, mortality can only affect senescence if it targets particular ages (or life stages) rather than indiscriminately affecting an organism over its entire lifespan [45]. Constant (or even decreasing) mortality risk over chronological age is theoretically plausible [8] and has been empirically detected across a range of taxa, including animals, plants, fungi and algae [10,44,46].

The most notable challenges pertaining to model animals are represented by the recognition of (i) condition-dependent individual survival and (ii) density-dependent population dynamics. Challenges from other taxa include (iii) the existence of indeterminate (asymptotic) growth and its consequences for lifetime increase in fecundity, (iv) the absence of a universal germ-soma distinction, (v) tissue replacement under modular somatic organization, and (vi) an ability to regress to younger developmental stages. While some challenges can be explained by more elaborated extensions of the classic theories, other facts cannot be accommodated within the CETA as they undermine their basic assumptions.

4.1. Condition-dependent survival, positive pleiotropy and modified mutation accumulation

The CETA consider mortality as a random process, affecting any individual with equal probability. This is clearly not the case and many environmental hazards impact different individuals with a different intensity. The condition-dependent effects of extrinsic mortality are the key principle of natural selection – termed ‘survival of the fittest individuals’ by Charles Darwin [47] and ‘viability selection’ by Ronald A. Fisher [48]. Later theoretical extensions of the CETA [49,50] explicitly treated condition-dependent survival and suggested that it may result in a diverse set of outcomes, depending on the relative strength of condition-dependent effects on survival and fertility, juvenile mortality and their interactions [51]. While this included potential selection for extended rather than reduced lifespan when extrinsic mortality is strong and condition-dependent [49–51], the work went largely unrecognized until experimental work highlighted its importance.

Major support for the importance of condition-dependent survival on the relative strength of ageing comes from a laboratory experiment on wild-derived populations of a small tropical fish, the Trinidadian guppy (*Poecilia reticulata*) [52]. Experimental guppy populations naturally evolve under strongly contrasting rates of predation from piscivorous fishes. The probability of individual survival over a half-year period was 20–30 times higher in populations exposed to low predation than in high predation populations [30]. In a striking contrast to the standard CETA predictions, lifespan differences in the benign captive environment were reversed. Guppies
from high predation sites lived longer, had lower rates of reproductive senescence and were in superior physiological condition. While the study matched predictions from the derived versions of CETA [49,50], it was inconsistent with contemporary experience [53] and inspired research into the complexities of the evolution of ageing.

An apparent paradox in the contrasting roles of condition-dependent and condition-independent mortality on the direction of the evolution of lifespan and ageing has been resolved through a combination of experimental and theoretical research. The major insights have come from experimental selection on Caenorhabditis remanei [34], a non-hermaphroditic relative of an established model nematode C. elegans. Replicated lines of C. remanei were subjected to either condition-independent mortality (executed haphazardly by randomly choosing individuals to contribute to the next generation) or a condition-dependent mortality regime (when survival was implicated by a heat-shock). By selecting lines under high and low mortality treatments, Chen and Maklakov demonstrated that high extrinsic mortality under condition-independent survival selected for higher rates of senescence and shorter lifespans, in accordance with CETA. In contrast, when survival was condition-dependent, high extrinsic mortality selected for slower senescence and longer lifespans [34]. This provided a comprehensive support for the derived modifications of CETA within a single experiment.

Some studies have suggested the existence of positive pleiotropy, recording a lack of life-history trade-offs between early and late reproduction and early reproduction and survival [2,54]. An experimental study on Drosophila melanogaster directly demonstrated a lack of trade-offs between fecundity and lifespan and highlighted the prominence of positive pleiotropy [55]. Despite hundreds of generations of selection on early reproduction, the lifespan of experimental D. melanogaster populations was unaffected, in contrast to the predictions of AP. At the same time, the associated mutation accumulation experiment demonstrated that mutations deleterious for late-life survival were also detrimental to early-life fecundity. Such a case of positive pleiotropy is inconsistent with the predictions of MA as deleterious effects of mutations were expressed throughout the lifespan rather than after a ‘selection shadow’. Together, experimental studies on C. remanei [34] and D. melanogaster [55] have enabled consolidation of earlier suggestions on condition-dependent survival effects at the population level [35,36] with positive pleiotropic effects at the individual level [2,54] and development of a formal framework on how condition-dependent survival, and hence positive correlation between early and late fitness, affects the evolution of ageing [19].

Maklakov, Rowe and Friberg [19] recently summarized the evidence and concluded that alleles with an extremely wide window of negative effects may be common. Unlike under MA and AP scenarios, alleles with deleterious effects across all ages can accumulate in populations if the effect is small at young ages but progressively stronger in later ages. In a verbal model of their Modified Mutation Accumulation hypothesis (MMA), they propose how positively pleiotropic alleles can accommodate predictions for contrasting patterns of the evolution of slower or rapid ageing under increases in condition-independent and condition-dependent extrinsic mortality [19]. The key assumption is that alleles with a negative impact on fitness must increase their impact towards older age; the steeper it increases, the less likely it is selected against and the more likely it contributes to ageing [19]. Minor effects on fitness at an early age enable the persistence of such deleterious alleles in a population. When an increase in the strength of extrinsic mortality is random, more rapid ageing evolves as more deleterious mutations are transmitted to the next generation. However, when extrinsic mortality is non-random and individuals with low fitness genotypes are preferentially removed, the increase in extrinsic mortality results in the evolution of slower ageing [19]. Under the MMA, any potential effects of alleles acting under MA and AP scenarios are likely overwhelmed by positively pleiotropic alleles affecting fitness across all ages [19].

The MMA hypothesis awaits elaboration into a formal model and I propose that future consideration of the MMA should include the role of gene-by-environment interactions (or gene-by-
environment-by-age interactions) to account for the persistence of alleles apparently deleterious to individual fitness across all ages in a population. Alleles with contrasting effects on fitness under specific environmental and ecological conditions are common [56] and conditions experienced by individuals within and across generations often vary enormously. Ultimately, the explicit consideration of gene-by-environment interactions maintains widespread genetic variability in a population and should facilitate the spread and wide persistence of positively pleiotropic alleles with age-specific effects in populations. Given that aging appears strongly associated with complex systems [57,58], an integration of positively pleiotropic alleles to epistatic interactions may additionally strengthen their persistence in the population despite consistently negative effects on some aspects of their expression.

Current support for the positive effects of condition-dependent mortality has been manifested at the intra-specific level. In essence, it implies a strong role of genetic background for the survival of the fittest when mortality risk from external hazards is high. The next challenge is to learn how this intra-specific pattern translates into macroevolutionary trends. I think that many of the broad-scale comparative patterns, originally interpreted as the outcome of the strength of extrinsic mortality, have alternative interpretations in terms of condition-dependence. For example, the capability to fly (e.g. contrasts between birds and mammals or bats and their non-flying relatives) certainly imposes a stronger (and temporarily stable) selection on overall performance and hence condition-dependent survival that may result in a later onset of senescence.

4.2. Density-dependent effects

Density-dependent population dynamics (and age specific impacts of this density dependence) can also modulate basic predictions, with higher extrinsic mortality supporting the evolution of lower rather than higher senescence when density dependence acts primarily on the survival or fertility of later ages [49]. Given that density-dependent fecundity and reproductive success are widespread [59], a set of complex predictions arises and it becomes difficult to define any general predictions on the direction of the evolution of senescence [49,51]. Thus, while density-dependence is often overlooked as a driver of aging – through its impact on survival and fertility – its significance, at least in some taxa, may be substantial and warrants more empirical attention.

4.3. Indeterminate (asymptotic) growth

From an evolutionary perspective, the number and success of an individual's offspring is the ultimate measure of success. While the mere existence of the risk of extrinsic mortality makes future reproduction of a lower importance than current reproductive effort under standard CETA predictions, this assumption is violated if future reproduction can provide a higher fitness gain, such as a major increase in fecundity or offspring survival [81]. Mammals, birds and insects (and many other animals) reach a finite body size, often ceasing growth upon reaching sexual maturity. Yet, many fishes, reptiles, molluscs, fungi, plants and other taxa display asymptotic growth, often inaccurately labelled as indeterminate growth. Asymptotic growth has major consequences for the life history of those species – including the prospect of negligible or even negative senescence [1,8] when reproductive output steadily increases with age. Because many taxa with asymptotic growth display additional traits that violate other assumptions of the CETA (e.g. lack of strict germ-soma distinction and modular body organization in plants, fungi and some animals), I first concentrate on organisms that display asymptotic growth but are compatible with other CETA predictions – complex poikilothermic animals such as fishes, reptiles and molluscs. I address the other taxa in detail in chapters 4.4. and 4.6.

Fecundity and body size are positively related in taxa with asymptotic growth [60]. Hence, a small decrease in current reproduction to the benefit of higher survival can yield large increases in future reproduction. This outcome affects the strength of the fundamental trade-off between current reproduction and somatic growth and maintenance; growth and longevity can undergo much stronger positive selection [8]. For example, fecundity of many teleost fishes can be predicted from body size (mass) and increases as an individual fish grows over its adult lifespan [60]. Such an increase in fecundity with age supports elevated investment into maintenance and survival and may be common among asymptotic growers with relatively low levels of extrinsic mortality. However, when extrinsic mortality is high, relative investment into reproduction can increase more strongly with age than with size, likely at the cost of further growth and self-maintenance. The relative fecundity of the Northern anchovy (Engraulis mordax), a fish with relatively high predation risk, increases with age. A 4-years-old anchovy produces 10 times more eggs than a 1-year-old anchovy, despite only doubling its body mass; effectively producing 5 times more eggs per unit body mass at older age [61]. This is because despite no major increase in batch fecundity (which is constrained by body mass), older anchovies produce more batches per reproductive season, proportional to the relative increase in reproductive output with age. Hence, asymptotic growers, under certain conditions, such as high extrinsic mortality, clearly invest resources into reproduction at a rate that compromises self-maintenance and is expressed as functional senescence [62]. Similarly, the ocean quahog Arctica islandica, one of the flagship species of extreme longevity, survives centuries when living at a slow pace of life in deep subpolar seas, but rapidly accumulates cellular damage and dies within decades in high stress environments in the Baltic Sea [63]. A plastic regulation of somatic maintenance and survival has been suggested as a form of alternative polyphenisms in life histories [64–66].

There is no doubt that species with asymptotic growth are often long-lived [1,2,7,67]. However, lifespan and ageing are not necessarily correlated and long life is no evidence for negligible or negative senescence [68]. Instead, assumptions on negligible or negative senescence may derive from biases caused by such longevity [69]. The onset of senescent declines may simply be delayed rather than weaker or non-existent. The painted turtle (Chrysemys picta), for example, has been cited as a case of negligible senescence [70]. A later analysis of age-specific mortality hazards from long-term longitudinal data on a wild population clearly demonstrated that painted turtles experience declines in survival and reproductive success at old age [69]. Similarly, many fish species display clear functional and reproductive senescence [32,52,62,67]. Longevity of these taxa may thus be misleading. Ageing patterns are often non-linear; ageing is often reduced to a phase of terminal senescence after a long period of decreasing mortality risk [1,2,7,35]. Asymptomatically growing animals are ectotherms and the longest-lived fishes, bivalves and amphibians may simply live slow-pace lives in cold environments [1,2,63,71]. Environmental factors, rather than the lack of senescence, may dictate their longevities. Markers of functional senescence would be especially instrumental to identify how those organisms deteriorate with age [63,72].

It has been assumed that body size (or body mass), rather than chronological age, dictates the timing of crucial life history events and size is a superior predictor of fitness-related trait expression [73]. However, the relationship between size and age is asymptotic rather than linear [74], with important consequences. When the effects of body size and age were modelled separately, using real datasets on reptiles and bivalves, mortality increased as a function of age but not size [74].
Body size is the major predictor of individual capability to compete for mates, food and evade predators [75,76]. Asymptotic growers can, therefore, gain more than increased fecundity from growing larger, making older individuals, who had a longer time to grow to a large size, competitively superior [8,74,76]. Thus, in addition to an increase in female fecundity, large body size may benefit males through sexual selection. Yet, alternative routes to male reproductive success are common [75] and selection on male body size is certainly much weaker than fecundity selection on females [76]. This may, eventually, impose intralocus sexual conflict, leading to a suboptimal lifespan in both sexes [77].

In conclusion, reduced senescence, in terms of much slower functional and reproductive declines compared to mammals or birds, is certainly observable in species with asymptotic growth [69] as the strength of the trade-off between current reproductive effort and residual reproductive value is different than in species with a finite body size. Many organisms, including taxa with finite body size such as mammals, can certainly display negative actuarial senescence over long periods of their adult lifespans. This happens when an increase in body size or experience improves their protection from extrinsic mortality, or while they keep growing over the early periods of sexual maturity to reach peak condition at prime ages [78]. This takes place before functional senescence starts imposing the increase in intrinsic mortality. Nevertheless, consequent terminal senescence can commonly follow regardless of lifetime growth patterns [9,69], as limitations to cellular and functional damage do not appear to be overcome. Yet, when asymptotic growth artificially clusters adjacent age cohort in the analyses, it may mask detection of such terminal declines [69,74], incorrectly leading to the conclusion that asymptotic growers can avoid senescence. Finally, a high cost of germ line maintenance [37] and a lower fitness in older parents’ offspring [79] suggest that ageing in asymptotic growers is inevitable.

4.4. Absence of a universal germ-soma distinction

The separation of germ line and somatic cells early in life is the fundamental assumption of CETA. Protection of the germ line from external risks to genome stability (mutations, viral invasion) is of primary importance, traded off against somatic cell repair [22]. High costs associated with this protection, rather than physiological costs of reproduction, may be the primary reason for functional and reproductive ageing [37]. The germ lines are depicted as immortal lineages, passing genotypes from generation to generation. Yet, they do not represent identical copies, but are modified by recombination during sexual reproduction, rare mutations and inversions [23]. In most animals, the germ line is separated early in embryogenesis, before somatic cell differentiation, and the differentiated somatic cells thus cannot contribute to the next generation. Any mutations to somatic cells (epimutations), therefore, go extinct with the death of the individual soma.

Many organisms defy this universal distinction between the germ and soma. First, prokaryotes and some eukaryotic unicellular organisms reproduce by fission or budding. Second, separation of germ cells occurs late in development in flowering plants. Third, clonal animals with a modular structure may keep recruiting totipotent germ line cells into their bodies. Finally, some filamentous fungi harbour genetically different nuclei within a single ‘individual’, each capable of regenerating into a new organism [46,80].

Unicellular organisms highlight the fact that asymmetrical division is required for ageing to be observed. The CETA implicitly assume age-structured populations and ageing cannot be observed when reproduction by fission produces symmetrical daughter cells. In that sense, many prokaryotic and eukaryotic unicellular organisms were considered immortal. However, whenever cell division is uneven, the larger cell progressively ages and survives only a limited number of divisions, such as in the budding yeast (S. cerevisiae) and some bacteria [81]. Notably, asymmetry in cell division can be achieved by an uneven division of damaged organelles and intracellular substances – making ageing pertain to seemingly symmetrically dividing organisms that completely lack the germ-soma distinction [82].

The life cycle of plants alternates between two heteromorphic generations – a diploid sporophytic generation and a haploid gametophytic generation. Surprisingly, this appears to be largely neglected by many biologists although it has important consequences for germ line development in plants. In bryophytes (i.e. liverworts, hornworts and mosses), the gametophytic generation is dominant. In the angiosperms (flowering plants) the sporophytic generation forms complex bodies while the gametophytic generation is dramatically reduced and represented by only a few cells in the floral organs. Importantly from an evolutionary perspective on ageing, a plant germ line is determined only after formation of the floral organ, or perhaps even later, when gametic and accessory non-gametic cells in the flower are separated [83,84]. It is notable that only a single somatic cell per ovule is usually recruited to form the germ line. It is not fully understood what determines which particular somatic cell initiates germline development (i.e., undergoes meiosis) and what prevents the formation of additional germline cells in the same ovule [84]. A basal angiosperm taxon (Trimenia) forms multiple female gametophytes per ovule. Given that somatic mutations can be readily recruited to plant germ cells, genetically differentiated gametophytes may compete to reach the site of fertilization [85], representing an underappreciated arena for evolutionary conflict.

Sponges differentiate their cells but some cell types retain their totipotency and may de-differentiate [81]. Similarly, some basal metazoan animals such as Hydra (Cnidaria) and Botryllus schlosseri (Tunicata) have no formal separation between the germ line and soma [86,87]. While this capacity is unavailable to most multicellular organisms, probably to protect more complex bodies from cancer, its molecular pathways have been retained (e.g., FOXO transcription factor) and are co-opted to perform other functions [88]. The fact that somatic cells of long-lived mutants of C. elegans that exhibit gene expression patterns contingent on germ line protection of cell integrity include the FOXO transcription pathway suggests that somatic cells of complex animals have the potential to adopt a germ-cell-like character [89].

4.5. Rejuvenation: tissue replacement in modular organisms

An emerging weakness of CETA is their failure to include cyclic phases of rejuvenation. In classic models, the individual moves in time along a unidirectional pathway. It accumulates somatic problems and ultimately needs to restart the body in the form of a newborn individual, freed from accumulated senescent deterioration. The more complex the body formed, the more difficult and expensive the maintenance of its somatic machinery, leading to more pronounced ageing [3,58].

To avoid deterioration of complex bodies, maintenance can act at three levels [86]. Organisms can (i) prevent damage, (ii) repair it, or (iii) replace entire damaged components. These mechanisms act at different levels. Rejuvenation is the reversal of ageing and thus requires replacement of damaged tissue. In a complex organism, prevention and repair of molecular and cellular damage may be efficient, and these mechanisms are likely associated with long-lived species. However, it is impossible to replace components, as the intrinsic complexity essentially disables a temporal dysfunction of one functional unit (e.g., heart or brain). A continuous prevention of damage and the need for somatic repair eventually lead to senescence [20,21].
In contrast, *Hydra*, the iconic organism among those that apparently escape ageing, possesses an extraordinary capacity to replace entire functional elements [86]. The body of *Hydra* has an unusually large number of somatic cells with stem cell attribute, capable of a seemingly unlimited number of cell divisions [90]. Schäuble et al. [86] argue that *Hydra* stem cells may evade accumulation of molecular and cellular damage by asymmetrical damage transmission during division. One of the daughter stem cells is, therefore, effectively rejuvenated by the processes similar to internally asymmetrical bacterial fission [82] and the other cell, enriched by waste products, is differentiated into a disposable somatic cell or eliminated by apoptosis. This mechanism has yet to be tested but provides a stimulating avenue for stem cell research in other taxa.

More complex multicellular organisms may also undergo cyclic rejuvenation. Those taxa are characterized by structural organization of their bodies (genets) in the form of repeated basic subunits (e.g., polyps or leaves), modular organization in their mitotic clonal units (ramets) and a sessile life form [87]. The subunits can be replaced on a cyclical basis, such as annual leaf replacement in many plants [43], and complete physiological modules (ramets) may undergo compensatory turnover [87,91].

A clonal production of ramets in plants can be seen as a form of somatic rejuvenation. In the most extreme case known, a quaking aspen (*Populus tremuloides*) covering over 40 ha and estimated to be at least 10,000 years old [92] can be defined as a single individual genet. Among animals, colonial reef-building corals can also reach large size and comparable age [1,8]. While such individuals were highlighted as the strongest candidates for negative senescence [8], a decline in pollen production, a form of reproductive senescence, was found in the aspen to be associated with genet age but not with ramet age [93]. Consequently, senescence in these extraordinary modular organisms may not be avoided altogether. Rather, it is so much postponed that the chronological age of their genets and ramets must be estimated from a mutation-based molecular clock [93].

Senescence in organisms with indeterminate modular growth may not, therefore, be circumvented but simply occurs over a much larger time scale. For logistical reasons, studies over such a long time scale must clearly be cross-sectional and components of actuarial and reproductive senescence must be deduced from individuals that survived to particular ages [91]. Given heterogeneity in individual quality and condition-dependent survival [2,35,36,52,54], apparent negligible or negative senescence in long-living species may result from a lack of individually-based longitudinal data. To this end, incorporating measures of functional senescence (e.g., oxidative damage, photosynthetic activity or hormone levels) could provide crucial insights to studies on their ageing [63,91,94].

4.6. Cyclic retrogression to younger developmental stages

Another example of regeneration of somatic cells of an individual is cyclic retrogression in herbaceous perennial plants. Retrogression is a return to an earlier ontogenetic stage as a response to damage from external cues (e.g., drought or grazing). In perennial plants, prolonged dormancy of belowground tissues after such external damage returns individuals to a state that appears to be independent of their previous ontogenetic history. This specific form of rejuvenation is apparent breach of the unidirectional course of senescence [95]. Individual plants may repeatedly regrow from meristems, tissues composed of undifferentiated pluripotent stem cells that continue division throughout the plant’s life [91].

Fitting four competing demographic models to long-term data on two species of perennial herbs, Gremer et al. [95] found that a ‘reboot’ model was the best fitting for both species. Interestingly, this result suggests that prolonged dormancy may reset developmental and physiological processes to a stage not dependent on their previous history, a form of rejuvenation [95]. While the lack of evidence for senescent declines in most herbaceous plants [10,43] may be affected by strong limitations from the use of cross-sectional rather than longitudinal datasets [91], induced dormancy is associated with a decrease in senescent deterioration in animals, such as the “dauer” stage in *C. elegans* [7]. In wild type *D. melanogaster*, reproductive dormancy induced consequent decreased mortality, but with a clear cost to reproduction [7]. This is pertinent to observations in one of the two species of “rejuvenated” herbaceous plants, though no reproductive decline was detected in the other [96]. The idea of polyphenol regulation of somatic maintenance and senescence within the framework of the disposable soma theory [21,64] may provide a route to incorporate cycles of rejuvenation into current theories.

5. Outlook on rejuvenation in complex animals

Ostensibly, the ability of some organisms to undergo the process of major structural simplification [87,95], or complete replacement of any body segment from a population of undifferentiated cells [86], provides an avenue for avoiding actuarial senescence (i.e., no automatic increase in mortality risk with chronological age) and functional senescence at organismal level.

While it is possible to complete cyclic retrogression within a single individual in some taxa, it is mediated through reproduction in complex organisms such as vertebrates and most other animals. In an analogy with computers, retrogression is a form of rebooting of the system from a population of stem cells representing a backup copy of the system. All post-zygotic information saved to the “memory” over the lifetime is lost (reset), but the original copy is available from the backup file. In complex systems, post-zygotic information represents complicated interactions between the system (genotype) and external environment. Hence, retaining the same body when rebooting is not possible, though clonal reproduction could be considered as a form of system file continuity. In most taxa, including sexually reproducing animals, an evolutionarily stable strategy appears to include continuous “hardware upgrade” when a new individual combines information from two parents for every system function. Ultimately, the true test of time, sexual reproduction is the most successful strategy for genotypes to cope with perpetually shifting environmental conditions, competition and parasitism.

6. Conclusions

Evolutionary explanations for the occurrence of ageing, and its variation among species and populations, were long considered to match observations from the real world. Recent decades have, however, seen a wealth of new data demonstrating that classical theory is unsatisfactory in explaining the complexity of ageing across the Tree of Life. While some suggest a new paradigm must be defined [8,10,43,46], others consider amendments and refinements to the classic theories to be an adequate way to incorporate these new findings [9,19,30,51,64]. These contrasting approaches perhaps mirrors the debate in evolutionary biology as a whole [97], where new insights into non-genetic inheritance and interactions between organisms and their environment can either be accommodated into the current evolutionary theory (Modern Synthesis) as gene by environment interactions, extended phenotypes, or cultural evolution, or be defined as a novel paradigm (Extended Evolutionary Synthesis).

Empirical data demonstrate that rejuvenation at the organismal level is possible. However, in complex organisms, it is accomplished by rebooting the system from germ line cells, highly protected from
post-zygotic modifications. New somatic material grows from an identical germ line as “the previous version of the body”, a kind of clonal reproduction. Hence, any immortality in complex animals can only be achieved by clonal reproduction or a return to the zygote stage. While this process could retain an identical genotype, individual bodies of complex organisms are formed under coordinated synergy between their genetic background, developmental conditions and environmental factors, and collect and retain information in their somatic tissues. A rebooted version of a particular genotype would be exempt from the defects collected over its previous lifespan but will, correspondingly, lack any information gained during its development. Whether the rebooted version of a complex individual can be considered the same entity is more a philosophical than biological question. Even from a purely biological perspective, genetic information is only a component of an individual entity. A resolution of this question is at heart of the recognition of whether current evolutionary theories of ageing, with their extensions and modifications, are sufficient to explain our understanding of the patterns of ageing across the Tree of Life.

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