3 A Hamiltonian Demography of Life History

Michael R. Rose, Lee F. Greer, Kevin H. Phung, Grant A. Rutledge, Mark A. Phillips, Christian N. K. Anderson and Laurence D. Mueller

Short Summary

We have been developing an approach to the study of life history based chiefly on evolutionary theories that depend on Hamilton's forces of natural selection. After almost forty years of work in this area, we realised that we have been assembling the pieces of an overarching research programme for demography that is distinctively Hamiltonian. Here we attempt to sketch, in an admittedly somewhat allusive and summary form, that overall research programme. We have not completed our work on this fairly broad research programme, and indeed here we point out some components that remain incomplete or barely initiated. To summarise our overview, we delineate here the following elements of our Hamiltonian demography: (1) *a priori* evolutionary genetic theory, (2) numerically generating demographic patterns using such theory, (3) testing the underlying theory using experimental evolutionary biology, (4) applying the findings of this experimental research to wild populations, and (5) inferring ageing phase transitions from demographic data. We do not claim that our research programme reflects a widespread consensus or the only practicable way forward for demography. We do claim, however, that it is one useful way forward for demography.

Introduction

Demography, gerontology, and their cognate fields have been influenced by the widespread notion that biological senescence of entire organisms involves some type of cumulative process of damage or accumulating physiological disharmony that is inherent to life. The influence of this assumption is to be found in the writings of most authors in these fields, starting with Aristotle (fourth Century BCE) in his monograph, 'On the Length and Brevity of Life'. It continues to prevail in most of the popular and academic publications on senescence, from Aubrey de Grey's seven types of damage to innumerable technical works on the supposed molecular machinery of senescence (de Grey & Rae 2007).

Dissenting from this view have been the works of many evolutionary biologists, starting with an obscure note from Alfred Russel Wallace (*ca.* 1870) and the early neo-Darwinian works of August Weismann (1891). Such early evolutionary thinking on the topic began with group selectionist reasoning, in which senescence was conceived in

terms of the benefits it might provide for the evolution of entire species or populations. But soon Weismann was developing early forerunners of more modern evolutionary genetic theories involving the weakening of natural selection (Kirkwood & Cremer 1982). From 1930 to 1957, R. A. Fisher, J. B. S. Haldane, P. B. Medawar, and G. C. Williams articulated and expanded on verbal evolutionary theories of senescence based on the weakening of natural selection at later ages, with only rudimentary mathematical arguments (Fisher 1930; Haldane 1941; Medawar 1946, 1952; Williams 1957). From 1966 to 1980, W. D. Hamilton and Brian Charlesworth developed the first mathematically explicit versions of the idea that senescence evolves because the forces of natural selection decline during adulthood among populations with age-structured demography and no fissile reproduction (e.g. Charlesworth 1970, 1980; Hamilton, 1966). Starting in 1980 and continuing ever since, evolutionary biologists have published a variety of tests of the theoretical ideas of Hamilton, Charlesworth, and others using quantitative genetics and experimental evolution, in effect working within what can now be seen as a Hamiltonian paradigm for ageing research, covering both senescence and post-senescence ageing (Luckinbill et al. 1984; Mueller et al. 2011; Rose 1984; Rose & Charlesworth 1980; Rose et al. 2002).

Up to this point in time, the Hamiltonian approach to gerontological research has seen significant successes in its corroborative alignments of theory and experiment, at least by the standards of both evolutionary biology and gerontology. Although it remains controversial within gerontology, within evolutionary biology the Hamiltonian approach to senescence is seen as paradigmatic for the field as a whole. There is little controversy about it among evolutionists, at least with respect to the core theory and its direct tests.

The basic result provided by Hamilton (1966) was to show the sensitivity of the intrinsic rate of increase r to changes in the log of age-specific survival $P(x)$. Specifically in Hamiltonian terms, he showed that $\delta r/\delta \ln P(x) = s(x)/T$, where T is the generation time, and

$$s(x) = \sum_{y=x+1} e^{-ry} l(y) m(y)$$

and $l(y)$ and $m(y)$ are the familiar age-specific survival and fecundity parameters.

Here we outline an overall programme for Hamiltonian research, with a particular focus on how it can be developed to provide a scientific paradigm for demography over all phases of ageing. We will not be dealing with the salience of Hamiltonian research for mechanistic work on the physiology or genomics of life history here; however, those are topics that we continue to work on (Rose & Burke 2011; Shahrestani et al. 2012a), as do many others (Forsberg et al. 2012; Hoffman et al. 2013; Polosak et al. 2010).

More specifically, we wish to define an arc of connected research strategies that together we believe will eventually provide the foundations of a Hamiltonian demography: (1) *a priori* evolutionary genetic theory, (2) the alternative demographic patterns that such theory can generate, (3) testing the elements of such theory using experimental evolution and other empirical tools of evolutionary biology, (4) implications of experimental research for the predicted demographic patterns of wild populations, and

(5) a look forward toward methods for inferring phase transitions from recently generated large bodies of demographic data. However, it is important to appreciate that this programme of research on the spectrum of life history patterns that arise over the course of ageing is one that is specifically our own. We are not attempting to enunciate a disciplinary consensus, not even for 'evolutionary demography', however that term might be construed. Nor do we wish to suggest that the kind of demography that we are interested in is the only interesting kind.

Hamiltonian Evolutionary Genetic Theory

One way to view the theoretical line of attack pursued by Hamilton (1966) and Charlesworth (e.g. 1980) is that it amounts to a demonstration of the extent to which weakening effectiveness of natural selection at later ages leads to a loss of optimal tuning of age-specific life history characters at later ages. That is, while some theorists (e.g. Abrams & Ludwig 1995) continue to treat every aspect of life history from the standpoint of a Darwinian optimising demon of apparently infinite power and scope, our theoretical work has tended to focus on the extent to which natural selection is of progressively less benefit at later ages and may even produce harmful outcomes at later ages when there is antagonistic pleiotropy (Mueller & Rose 1996; Rose 1985), as both Medawar (1952) and Williams (1957) verbally conjectured.

Hamiltonian evolutionary theory for life history has been developed for relatively simple cases to this point. Hamilton's original 1966 paper did not offer explicit evolutionary genetic models, asymptotic state predictions or evolutionary trajectories. Charlesworth (1980) confined most of his theoretical analysis to evolutionary genetic systems with one segregating Mendelian locus. More recently, theory has been developed for the evolutionary stabilisation of mortality and fecundity rates at late ages (Charlesworth 2001; Mueller & Rose 1996; Mueller et al. 2011; Steinsaltz et al. 2005; Wachter et al. 2013), theoretical research motivated and underscored by the raw demographic phenomenon of late-life stabilisation uncovered in some notably large bodies of age-specific mortality-rate data (Carey et al. 1992; Curtsinger et al. 1992; Greenwood & Irwin 1939), age-specific fecundity data (Le Bourg & Moreau 2014; Rauser et al. 2003; Rauser, Mueller & Rose 2006) and age-specific male virility data (Shahrestani et al. 2012b).

At this point, two basically distinct kinds of Hamiltonian evolutionary theory can be distinguished. The first, and simplest, involves models that assume age structure but generally clonal inheritance. In such models, Mendelian genetic transmission producing large-scale out-crossing and recombination is treated as either absent or rare. Instead, it is assumed that evolution proceeds by the successive fixation of beneficial mutants that modify life history in a well-defined manner. Examples of this type of theory are to be found in Mueller and Rose (1996) and Mueller et al. (2011). These studies have shown that natural selection will permit the establishment of genetic variants with antagonistic pleiotropic effects that increase early-life survival or fecundity as long as the negative fitness effects are relegated to later life. At sufficiently advanced ages when the force of

selection becomes weaker than drift, the age specificity of the evolutionary forces acting on survival and fecundity are lost. This can then lead to the evolution of late-life plateaus for life history characteristics. Most importantly, from an experimental perspective, the age at which these plateaus start is predicted to be a function of the last ages of reproduction and survival and thus subject to evolution as these ages are varied (Rauser et al. 2006; Rose et al. 2002).

The second kind of Hamiltonian evolutionary theory is that which is based on the full apparatus of Mendelian population genetics extended to age-structured populations. This is the work pioneered by Charlesworth (e.g. 1970) in the 1970s, to which he still contributes (e.g. Charlesworth 2001) and which has been recently extended (Wachter et al. 2013). Hamilton's work was a major contribution to the theoretical study of life history evolution even though the theoretical centrepiece of his argument was largely heuristic (Hamilton 1966). Charlesworth extended this theory in important ways by showing that Hamilton's forces of natural selection would properly predict the direction of selection in exact population genetic models (Charlesworth 1980).

Recently, Baudisch (2005, 2008) has returned to the heuristic approach of Hamilton and pointed out that there exist alternative conceivable indicators of the effect of natural selection in an age-structured population – depending on what assumptions about the scale on which mortality effects at different ages should be used. More importantly, Baudisch showed that under certain circumstances, these alternative indicators gave different predictions than Hamilton's. The problem is that there is no direct connection to Baudisch's indicators and exact population genetic models as there is for Hamilton's. For instance, see Charlesworth (1980: chap. 2), which develops such a connection for Hamilton's sensitivity measure. Indeed, Mueller et al. (2011) show that one of Baudisch's indicators gives incorrect predictions about the strength of selection.

Recently, others have made contributions to this field as well (Steinsaltz et al. 2005; Wachter et al. 2013). For example, Wachter et al. (2013) studied conditions under which selection–mutation balance can produce late-life mortality plateaus.

We would like to draw attention to new possibilities for theoretical research in this area. One of them is the transitional evolutionary dynamics that arise for life history when there are environmental changes. Some of these might be transitions in age-specific windows of reproduction, for which Rose et al. (2002) contribute some calculations. Other such transitions involve qualitative transitions in other environmental features that then have age-dependent heterogeneities in phenotypic impact. In particular, Phung et al. (in preparation) show that age-specific adaptation to a novel environment in which the optimal phenotype for survival has changed proceeds at different rates for genetic variants affecting early-life versus late-life phenotypes. The ages at which we expect to see a rapid shift from a maladaptive phenotype to a well-adapted phenotype depend on a number of factors: the time since transitioning to the new environment, the strength of selection acting on new genetic variants, the magnitude of the phenotypic effects among new mutants and the effective population size. The application of the full apparatus of Mendelian population genetics to this spectrum of issues will be challenging but we believe very useful.

Theoretically Generated Hamiltonian Demographies

There is an important bridging theory that has been somewhat neglected within the Hamiltonian research programme: generating predicted demographic patterns from explicit evolutionary genetic models. This type of task was first taken on by Mueller and Rose (1996), to the best of our knowledge, and since significantly elaborated on in Mueller et al. (2003, 2011).

Initially, evolutionary genetic theory for age-structured populations, such as that of Charlesworth (1980), was focused more on how the novel Hamiltonian effects that arise with age structure would affect the evolution of allele frequencies. Interestingly, Hamilton (1966) was more concerned with making predictions about demographic patterns, although he did not supply the type of bridging theory that we are describing here. His inferences with respect to the demographic consequences of his declining forces of natural selection were essentially verbal and intuitive. And in any case, he did not develop the explicit dynamical equations for allele frequency change that Charlesworth (1980) developed, following somewhat the early pioneering work from Norton (1928) and Haldane (1927).

Mueller has deliberately developed demographic predictions from Hamiltonian machinery, where his models have chiefly been of the clonal mutant substitution variety (Mueller & Rose 1996; Muller et al. 2011), as discussed previously. What clearly remains to be done is the development of full-scale Mendelian models in which the machinery of Norton and Charlesworth is extended to produce quantitative theoretical demographies. It is clear from experimental work that changes in the force of age-specific selection can result in relatively rapid changes in patterns of age-specific mortality and fecundity, including the age of onset of late-life plateaus (Rauser, Mueller & Rose 2006; Rauser et al. 2006; Rose 1984; Rose et al. 2002). This evolution is too rapid to be due to the effects of new mutations and is almost certainly a consequence of changes in the frequency of existing genetic variants. Thus, an important goal would be the development of theory based on standing Mendelian genetic variation and balanced polymorphisms in age-structured populations as a means of understanding the extensive experimental results that now exist.

Comparative and Laboratory Tests of Hamiltonian Demography

Comparative Tests of Hamiltonian Theory

It is rare for any type of evolutionary theory to make unequivocal predictions concerning comparative patterns of variation among species, but Hamiltonian evolutionary theory is just such a case. If the evolution of senescence indeed depends on whether or not Hamilton's forces decline in an age-dependent manner, then species in which they do not decline should not exhibit the kind of persistent decline in survival probabilities and fecundities that are the demographic hallmarks of senescence, at least when cohorts are kept under favourable conditions, particularly in the laboratory.

Note that this is a falsifiable prediction that is specific to cohorts that are not undergoing ecological or genetic change. Despite the claims of Jones et al. (2013), there may be entirely exogenous ecological factors that generate patterns of declining survival with age in wild populations: the spread of infectious disease, secular environmental deterioration, inbreeding, depression as a result of declining effective population sizes, and so on. Under some laboratory conditions, cohorts can face declining conditions that artefactually emulate senescence too. Thus the stipulation that senescence almost always needs to be studied in cohorts protected from adversities is foundational, even for comparative research on the phenomenon (Comfort 1979; Rose 1991).

There are anecdotal claims that some laboratory cohorts show no apparent senescence (Comfort 1979), but of greater value are mortality rate studies like those of Bell (1984) and Martinez (1998) using small invertebrates. Such research has found that demographic senescence does not occur among species that have well-established fissile reproduction that is roughly symmetrical: in these laboratory studies, the mortality rates of such cultures are stable and sometimes close to negligible. These are species in which it is likely that Hamilton's forces of natural selection do not decline simply because there is no soma left after each act of reproduction.

However, it should be noted that species with fissile or budding life cycles do not necessarily have the reproductive symmetry required to ensure that Hamilton's forces do not decline. First, asymmetrical budding in the yeast *Saccharomyces cerevisiae* and visibly asymmetrical fission in some bacteria can both allow the evolution of senescence (Ackerman et al. 2007; Jazwinski 1990). Second, even in bacterial species that have morphologically symmetrical fission, such as *Escherichia coli*, asymmetrical partitioning of metabolic wastes can generate a 'soma' lineage that undergoes senescence (Steward et al. 2005). Thus, the central issue is less obvious than it might appear: the evolution of senescence hinges on whether or not there is the possibility of asymmetrical effects on the products of a vegetative act of reproduction. In some cases, determining whether or not such asymmetry has arisen will be tricky.

Quantitative Genetic Studies of Laboratory Senescence

One of the first empirical avenues for Hamiltonian research on ageing was the study of the quantitative genetics of senescence, particularly in *Drosophila melanogaster* (Charlesworth & Hughes 1996; Promislow et al. 1996; Rose & Charlesworth 1981; Shaw et al. 1999; Tatar et al. 1996). This research was motivated by theoretical expectations that depended on two alternative population-genetic mechanisms: mutation accumulation and antagonistic pleiotropy.

With respect to mutation accumulation, Charlesworth (1980) suggested that deleterious alleles with strictly age-specific effects on only one type of life history character, such as age-specific fecundity or age-specific mortality rate, should produce progressively increasing additive genetic variances for these characters as a function of age. Rose and Charlesworth (1980, 1981), however, found no such pattern for daily fecundity in *D. melanogaster*. In the course of research on age-specific mortality rates, Charlesworth and Hughes (1996) showed that varying patterns of dominance and

antagonistic pleiotropy could also produce increasing additive genetic variances for life history characters as a function of age. Further research has been done on this problem by Promislow et al. (1996), Tatar et al. (1996), Shaw et al. (1999), and Moorad and Promislow (2010). It has proven both problematic and demanding to define the conditions under which genetic variances will increase with age in theory and perhaps even harder to detect such patterns in quantitative genetic data. Thus, this line of research has been largely abandoned (for an exception, see Pujol et al. 2014).

By contrast, research on patterns of genetic correlation has been more productive. Antagonistic pleiotropy is a genetic mechanism in which alleles with beneficial effects on some components of fitness have deleterious effects on other fitness components (Rose 1982, 1983). While it has been of particular interest for the evolution of senescence (Charlesworth 1980; Medawar 1952; Rose 1985; Williams 1957), it is a general evolutionary mechanism that is applicable to pleiotropic effects between types of life history characters at the same age as well as antagonistic effects on alternative sexes, although the latter case is often referred to as 'sexual antagonism'. In the context of Hamiltonian quantitative genetic research, the hallmark of antagonistic pleiotropy as a mechanism for the evolution of senescence is negative genetic correlations between early-age life history characters and later-age life history characters, such as those found by Rose and Charlesworth (1981). However, there are several experimental design problems that interfere with the detection of such negative genetic correlations, among them inbreeding depression and genotype-by-environment interaction (Rose 1991). Either of these effects will tend to bias estimates of genetic correlations upward.

Overall, quantitative genetic approaches to the analysis of the genetic foundations of the Hamiltonian evolution of senescence have been pursued relatively little over the last fifteen years. This is probably because of the significant theoretical and experimental challenges that such research poses.

Experimental Evolution of Senescence and Late Life Using Hamilton's Forces

A much less demanding and now more common experimental strategy is the evolutionary manipulation of laboratory populations by shifts in Hamilton's forces of natural selection. This is most often achieved by shifting the timing of windows of reproduction in *Drosophila* populations maintained with discrete generations and then sustaining such shifts for significant periods of laboratory evolution (Chippindale et al. 1997; Luckinbill 1984; Rose 1980; Rose et al. 2002; Wattiaux, 1968a, 1968b). For example, it is a commonplace result that laboratory populations that have had their age of reproduction shifted to later ages soon evolve increased average life spans (Rose 1991). But such shifts in reproductive timing can also proceed by switching evolving populations from later ages of reproduction to earlier ages of reproduction, which results in progressively falling average life span over a number of generations of evolution (Chippindale et al. 1997; Rose et al. 2004; Service et al. 1988; Teotonio and Rose 2002). Other species have been subjected to comparable experimental shifts in reproductive timing (David & Bryant 2000; Nagai et al. 1995; Sokal 1970), with qualitatively similar effects on the evolution of senescence.

One of the more interesting findings of Hamiltonian experimental evolution, from the standpoint of demography, is that both average longevity and age-specific mortality rates shift in ways that are qualitatively predictable from Hamiltonian theory (Rose et al. 2002). Likewise, patterns of age-specific fecundity shift in accordance with changes in the force of natural selection acting on fecundity (Rauser et al. 2003). Thus, patterns in the evolution of late-life mortality and fecundity plateaus can be predicted using Hamiltonian theory, and these predictions have been generally borne out in experimental evolutionary tests (Mueller et al. 2011; Rauser et al. 2003; Rose et al. 2002).

The Late-Life Controversy

The causes of late-life deceleration in rates of mortality remain controversial within gerontology, demography and evolutionary biology (e.g. Mueller et al. 2011; Pletcher et al. 1998; Steinsaltz & Evans 2004; Wachter 1999). The most common and oldest theory for explaining it is lifelong heterogeneity, in which mortality rates slow at later ages entirely because of the elimination of those who have a lifelong greater risk of death due to a within-cohort attrition process (Greenwood & Irwin 1939). One of the earliest quantitative theories of lifelong heterogeneity was proposed by Vaupel et al. (1979). Under their model, the probability of an individual dying is described by a Gompertz equation. These theories further suppose the idea that due to heterogeneity in either the genetic composition of individuals and/or their development, the age-independent parameter of the Gompertz equation shows individual variation. This variation, if sufficiently pronounced, can cause the composite population to show a levelling of mortality rates at advanced ages even though every individual has an exponentially increasing chance of dying with age. We have pointed out several quantitative difficulties with the application of lifelong heterogeneity theories to the explanation of data from *Drosophila* experimental evolution (e.g. Mueller et al. 2003, 2011), especially the extreme levels of such heterogeneity required to explain the observed mortality-rate deceleration of demographically well-characterised large cohorts.

Some recent experiments with *Drosophila* have claimed that the absence of a detectable mortality plateau in some *Drosophila* populations given different diets is consistent with heterogeneity theories and not with evolutionary theories (Zajitscheck et al. 2013). However, these experiments used only 300 individuals of each sex, so it is likely that these experiments were conducted below the minimal sample size needed to detect these phenomena reliably (cf. the 900–1,550 used in Curtsinger et al. (1992) or 1,000–2,800 per sex used in Rose et al. (2002)).

A further difficulty with lifelong heterogeneity theories of mortality plateaus is their reliance on hypothetical underlying ‘robustness’ and ‘frailty’ variables, which are as inherently difficult to measure and study as ‘reproductive effort’ and other hypothetical variables in optimal life history theory. This makes the design of empirical tests of these models especially difficult. Fortunately, both fecundity and virility also show late-life plateaus (Rauser et al. 2003; Shahrestani et al. 2012a), in keeping with Hamiltonian theory (Mueller et al. 2011; Rauser, Mueller & Rose 2006). Lifelong heterogeneity theories for these two kinds of life history characters do not involve as many hidden

variables as mortality, so they can be used to test lifelong heterogeneity theory more readily. Regrettably for such theory, there is no evidence for lifelong heterogeneity effects that might produce late-life life history plateaus for these characters (Mueller et al. 2011;Rauser et al. 2005).

Further Topics for Hamiltonian Demographic Analysis

There is evidence for transient heterogeneity within cohorts in our demographic data, a phenomenon quite distinct from the much-conjectured lifelong heterogeneity. Specifically, we and others have shown that a week or so before death, flies enter a period of physiological decline we have called the 'death spiral' (Mueller et al. 2007; Rauser et al. 2005; Shahrestani et al. 2012b). During this period, both female fecundity (Rauser et al. 2005; Rogina et al. 2007) and male virility (Shahrestani et al. 2012a) decline at a faster rate among dying individuals than among similarly aged individuals not in this final period of life. Consequently, every population will have heterogeneity due to the mixture of individuals that are and are not in the death spiral. This heterogeneity has been incorporated into models of age-specific fecundity (Mueller et al. 2007, 2011) with a noticeable improvement in model fit.

One of the less noticed aspects of the Hamiltonian models offered in Mueller and Rose (1996) is the role of effective population size in the onset of late life. Specifically, inbreeding is expected to produce significant effects on the evolution of life history within the Hamiltonian paradigm. Not only can inbreeding impinge on the measurement of quantitative genetic parameters in life history research (Rose 1991), but effective population size also is a general scaling factor for the effectiveness of selection, much like Hamilton's (1966) forces themselves. The obvious question is how do these two general types of scaling factors for life history evolution and demography interact with each other? This is a question that needs careful theoretical analysis and experimental investigation, particularly given the large population size fluctuations that often occur during laboratory domestication (Santos et al. 2012, 2013), and that have arisen in recent human evolutionary history (Cochran & Harpending 2009).

Another demographic issue of importance for both experimental evolution and human evolution is the role of Hamiltonian scaling in evolutionary responses to environmental change. We have been exploring this issue both theoretically (Phung et al. in preparation) and experimentally (Rutledge et al. in preparation). To this point in our work, we find that early life history is evolutionarily more responsive to environmental change than later adult life, as we had conjectured previously (Mueller et al. 2011). When studying functional health in populations of *D. mealanogaster* consuming both ancestral and more recent diets during laboratory domestication, at early adult ages we find that flies function as well or even better on an evolutionarily recent diet. Furthermore, at later adult ages, these same flies have better survival and reproduction on their ancestral diet compared to the recent diet (Rutledge et al. in preparation). Adaptation to the newer laboratory diet is apparently not sustained into later ages on an evolutionarily recent diet. At such later ages, the better diet for life history characters is apparently a diet that is more similar to their ancestral diet in nature. This may be theoretically attributed to the

weakening of the forces of natural selection with adult age (Phung et al. in preparation), making later fruit fly dietary effects a relic of adaptation to the food available prior to laboratory domestication. However, much more work must be done, both theoretically and experimentally, to clarify and substantiate this pattern.

From the Laboratory to Wild Populations

Recently, there have been attempts to characterise the demography of populations in the wild, with a view towards informing demographic and life history evolution theory (Jones et al. 2013). Our view is that data obtained from wild populations are unlikely to provide strong-inference tests of core theories of life history evolution because of issues of lack of replicability and control of factors such as gene-by-environment (G×E) interactions that have been discussed repeatedly (Mueller et al. 2005, 2011; Rose 1991). Then there is the issue of how well we can apply Hamiltonian demography to the interpretation of data from wild populations, which is a different scientific problem. While this too remains challenging, attempts at such application would be in keeping with a long scientific tradition in physics of going from laboratory experimentation to the modelling and exploration of possible mechanisms for astrophysical dynamics in far-off solar systems and even galaxies.

For example, a long-standing question in Hamiltonian research is whether or not there is evidence of senescence in the demography of wild populations. Nesse (1988) made a pioneering attempt to find quantitative evidence for senescence in wild populations of animals. He concluded that it did in fact occur. Promislow (1991) applied a similar approach to a larger set of wild mammalian populations and again concluded that there was detectable senescence. The substantial problem not addressed by Jones et al. (2013), who report a lack of evidence for senescence in the wild, is that it is typically impossible to control environmental sources of extrinsic mortality in natural populations. To the extent that these extrinsic sources of mortality act in a strictly age-independent fashion, mathematical analysis shows that they will not be relevant to the evolution of senescence (Caswell 2007). Thus, a cohort followed over time may experience extrinsic sources of mortality that also vary over time. If these extrinsic mortality sources cannot be quantified, then any pattern of mortality is possible, and the inference of senescence will be difficult. In a similar fashion, mortality data collected over a short period of time from individuals of many ages in natural populations cannot control for the past heterogeneous histories of these individuals, making mortality patterns collected in this fashion ambiguous. For instance, in *Drosophila*, it has been known for nearly 90 years that larval rearing density can affect later age-specific mortality rates (Pearl et al. 1927).

However, efforts to analyse data from populations in nature continue. Ricklefs (2008) compared age-related mortality patterns in birds in captivity and wild populations. He found that the rate of senescence is similar to that in wild populations despite the absence of exogenous forces of mortality (i.e., predation, disease, etc.) in captivity. Although evolutionary theory suggests that increasing mortality and decreasing fertility with age

are expected, Jones et al. (2013) compared several demographic age trajectories across a number of species including vertebrates, invertebrates, vascular plants, and a green algae, which showed considerable variation in mortality trajectories. Caleb E. Finch, other gerontologists, and some demographers have argued that there is evidence of negligible senescence in natural populations of a number of species, from rockfish to tortoises (Finch 1998, 2009). However, patterns of mortality found in wild populations using 'marked' individuals cannot easily account for extrinsic forces of mortality (Jones et al. 2013; Ricklefs 2008). For example, an observation of constant mortality may be due to increased intrinsic mortality during a period when the environment also became more favourable during the time span of the study, the two effects thereby cancelling out. Without conducting controlled experiments, interpreting the patterns of senescence in wild populations, especially when only one mortality-rate survey with a unique set of temporal data is used, is at a minimum challenging.

What are we to make of these findings? Does evidence of negligible senescence in wild populations suggest that their ageing is of negligible importance for their demography? Or, alternatively, do such data suggest that late-life mortality-rate plateaus arise early enough in the adult lives of wild populations to be detectable in their demography? Perhaps further progress hinges on the development of new methods of analysing demographic data, to which we now turn.

Inferring Life History Phase Transitions from Demographic Data

One of the core problems impinging on Hamiltonian and other demographic research is identifying the ages at which life histories transition between the successive phases of ageing: development, senescence, late life, and dying. Hamiltonian theory predicts *a priori* three distinct phases of life history that arise from the decline of the forces of natural selection with age in a demographic cohort after the onset of reproduction: (1) early high function, (2) senescence, and (3) late life (Mueller et al. 2011). In addition, as already mentioned, we and others have found extensive evidence of a distinctive fourth phase of dying in our data (Mueller et al. 2007, 2011; Rauser et al. 2005; Rogina et al. 2007). If these or any subset of these phases correspond to real phenomena, under sufficiently good conditions they should be detectable directly from abundant high-quality demographic data in cohorts from species that are subject to declines in Hamilton's forces.

Thus, an important problem in Hamiltonian demography is how best to detect these four demographic phase transitions in mortality, survival, fecundity, and virility as they vary with age. The first significant phase transition is the onset-of-senescence boundary. The second phase transition is the end-of-senescence plateau boundary. The third and final phase transition is the start of the death spiral. We are now seeking empirical estimators of the timings of these phase transitions for two kinds of data: (1) new, yet-to-be published replicated cohort studies of mortality and fecundity more than 10 times larger than any of our experiments heretofore and (2) simulated data sets generated from a priori Hamiltonian models, including the crude two-stage Gompertz models, with and

without heterogeneity correction, which have been our standard tools of analysis (Mueller et al. 2011; Rose et al. 2002).

When we can reliably infer the phase transitions of Hamiltonian demography from cohort data, we may, in turn, be better able to apply Hamiltonian reasoning to data collected from wild populations (cf. Jones et al. 2013, Promislow 1991; Ricklefs 2008), the trickiest frontier of all in demographic research. But that remains to be seen.

Conclusion

We have argued here that there are four phases of ageing: development, senescence, late life, and dying. Age-structured population genetics theory shows how Hamilton's forces of natural selection lead to three of these distinct phases of life history. We are endeavouring to develop an overarching scientific programme for this alternative Hamiltonian demography, focusing on the following elements: (1) *a priori* evolutionary genetic theory, (2) the alternative demographic patterns that such theory can generate, (3) testing the elements of such theory using experimental evolution and other empirical tools of evolutionary biology, (4) implications of Hamiltonian experimental research for the predicted demographic patterns of wild populations, and (5) seeking empirical methods of inferring phase transitions directly from demographic data. Our view is that this is a promising way forward for demography conceived as the general scientific study of life history characters in biological populations. However, it remains to be seen if this approach is of much value for the most specific applications of demography to the case of human populations, for which many of our scientific research tactics will not be feasible.

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