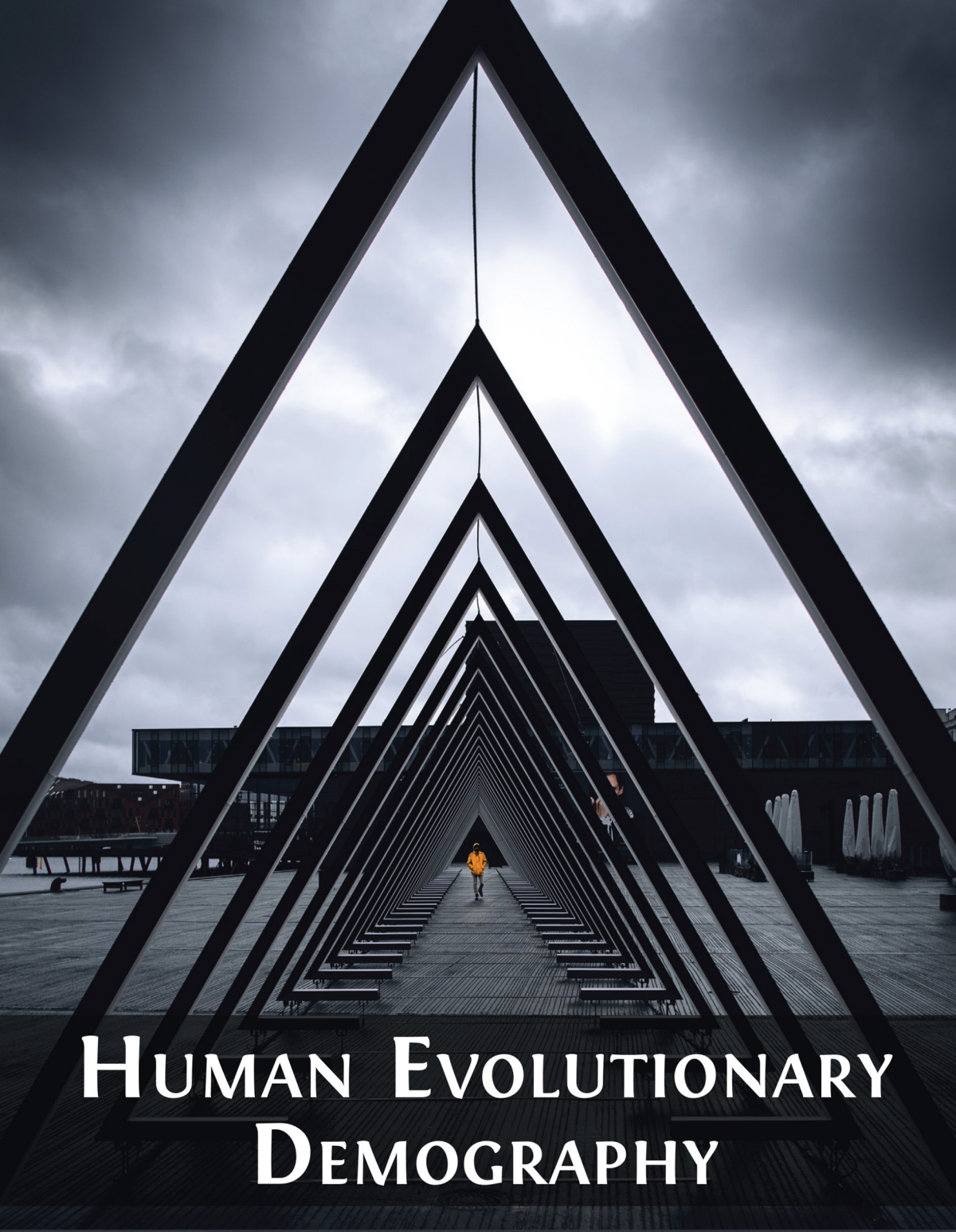

Human Evolutionary Demography

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12. Genetic Evolutionary Demography

Kenneth W. Wachter

Since the 1990s, biodemographers comparing demographic schedules across divergent species have highlighted features in common, plausibly reflecting evolutionary influences in common. Optimal life history models and stochastic vitality models garner inspiration from Darwinian theory. Models for genetic load go further, explicitly incorporating the three fundamental processes of evolution — natural selection, mutation and recombination — and their consequences for genomes. These models draw age-specific demographic implications from assumptions about mutation accumulation. The genetic variants posited by the theory are now coming into observation in genomic data. A search is underway for contemporary effects of genetic load on measures of health, ageing and survival. It may be possible to tell how far an evolutionary heritage from deep in the past persists amid the altered environments of the present, shaping demographic regularities.

Evolutionary Ideas in Demography

With the rise of biodemography, evolutionary ideas have come to play leading roles in demographic thinking. The discovery of tapering mortality rates at extreme ages in Mediterranean fruit flies by James Carey and collaborators (Carey et al., 1992), in Drosophila by James Curtsinger and collaborators (Curtsinger et al., 1992), and in a coordinated set of research projects led by James Vaupel initiated three decades of empirical demographic studies of species with widely ranging body plans and life histories, and uncovered striking commonalities in the shapes of age-specific demographic schedules. It is natural to seek a source of commonalities in what all organisms have in common: Darwinian evolution.

In succeeding years, demographers came into contact with Darwinian thinking and especially with classical evolutionary theories of senescence. In tandem with empirical studies, three main strands of mathematical modelling began to flourish — optimal life history theory, stochastic vitality theory and mutation accumulation theory. These strands draw, respectively, on techniques from economic optimization, reliability statistics and population genetics, and they also contribute to these fields. Initially, the strands took somewhat separate paths. Today, they should be understood in combination.

A description of the three kinds of modelling is given in a paper by Kenneth Wachter, David Steinsaltz and Steve Evans (Wachter et al., 2014). That paper contains an account of many of the ideas in this chapter from a more formal point of view. In this volume, the first strand, optimal life histories, is featured in other chapters. The second strand, stochastic vitality models, enters at various points in other chapters. The third strand, mutation accumulation, is the principal subject of this chapter.

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Mutation accumulation theory differs in one major respect from the other strands: it explicitly models the genetic mechanisms that power evolution, including mutation, recombination and natural selection. It works with a mathematical representation of the genome and a set of formulas that connect genetic determinants with demographic rates. The other strands draw inspiration from Darwinian principles and implement criteria motivated by processes of natural selection, but, in most cases, they do not bring the nuts and bolts of genetics into their formulations. In those strands, arguments do not necessarily depend on genotypic determinants but may refer broadly to strategies and adaptations playing out in daily life.

Mutation accumulation, by contrast, is about genotypic determinants. As large samples of genotypic data become available, the elements of mutation accumulation theory can be confronted with those data and guide hypotheses. Rich empirical opportunities are opening up.

From the early days, biodemographers benefitted from the authoritative 1990 volume *Longevity, Senescence, and the Genome* by Caleb Finch, joined in 2000 by a comprehensive mathematical treatment by Reinhard Buerger, *The Mathematical Theory of Selection, Recombination, and Mutation*. They also built on the extensive works of Brian Charlesworth, (e.g. 1994), leading up to his influential paper (2001). In 1997, under the auspices of the Committee on Population (CPOP) of the U.S. National Research Council, *Between Zeus and the Salmon* (Wachter and Finch, 1997) crystallized biodemography as a field.

In parallel with the assimilation and extension of theory by biodemographers, and under the stimulus and guidance of Richard Suzman at the National Institute on Aging (NIA) groundwork was laid for the collection of genetic markers in social and demographic surveys. CPOP volumes *Cells and Surveys* (Finch et al., 2001) and *Biosocial Surveys* (Weinstein et al., 2008) sponsored by the NIA helped bring this goal to fruition, while *Offspring* (Wachter and Bulatao, 2003) sponsored by the National Institute of Child Health and Human Development expanded the purview from aging to fertility. The current breadth is shown by the latest CPOP-NIA volume *Sociality, Hierarchy, Health* (Weinstein and Lane, 2014) In happy confluence, as the theoretical reach of evolutionary demography has been extended, datasets pairing genomic measurements with social and behavioural variables, so-called "sociogenomic data", have become available in large quantities and high quality to empower empirical research.

Mutation Accumulation in Brief

Genetic variants fall into three categories with respect to natural selection: beneficial, neutral and deleterious. An allele is any one of the forms taken by a variant at a site in the genome. Many though not all variants are Single Nucleotide Polymorphisms (SNPs), differences in what can be pictured as a single letter in the genetic code. Mutations change the variant.

As for beneficial alleles, once introduced through mutation they tend to spread through a population and reach fixation, eventually no longer showing up as genetic variation but helping to determine design features of the organism. Once natural selection has done its job of driving a beneficial mutant allele to fixation, it bows out of the picture. As for neutral alleles, they increase or decrease in frequency at random in a population through the process of genetic drift, more slowly the larger the effective population size. Neutral alleles account for most observed genetic variation. As for deleterious alleles, they systematically decrease in frequency in a population. Mildly deleterious alleles decrease slowly under continual pressure from

natural selection, but their numbers are also slowly renewed by new mutations. They account for much, though not all, of the rest of observed genetic variation.

Mutation accumulation theory is a description of the representation and consequences of mildly deleterious alleles.

Deleterious alleles, always prominent, have recently been brought into the spotlight with the book *Crumbling Genome* by Alexey S. Kondrashev (2017), with its good background treatment of relevant genetics and recent results. For the study of deleterious mutations, a rich repertory of population genetic models exists, but mainly without detailed elements of demography. The model that Steve Evans, David Steinsaltz and Kenneth Wachter developed in an American Mathematical Society monograph (Evans et al., 2013), adds to the repertory by concentrating on and building in age-specific demographic structure. It is the model featured in this chapter. The mildly deleterious alleles it describes are genetic variants changing organisms in small ways that entail slightly less favourable age-specific rates of survival and fertility when their effects are averaged out over varieties of environments and over numbers of generations.

In mutation accumulation, alleles enter the population at slow rates, generation by generation, through new mutations. Alleles carried by parents are shuffled together and dealt out to offspring at each generation by the process of genetic recombination. Alleles are passed to descendants less frequently the lower the rates of survival and fertility they imply, enforcing natural selection. Alleles weeded out by natural selection are replenished by new mutations, and their representation typically reaches an equilibrium, "muation-selection equilibrium".

Sir Peter Medawar (1952) had the insight that bad alleles can be passed on more often if their bad effects are only felt later in the lifespan, after parents have borne and nurtured more of their potential offspring. Natural selection removes late-acting alleles more slowly from the population and leaves more of them around to accumulate at equilibrium. Here is one reason why evolution should favour mortality rates rising with age and fertility rates falling with age: keeping fewer early-acting alleles means being subject to lower mortality and less impaired fertility at early ages. Keeping greater numbers of late-acting alleles means being subject to higher mortality and more impaired fertility at older ages.

The power of this idea is two-fold. Firstly, it implicates something that all species have in common, namely natural selection. Thus, it is a plausible option for explaining cross-species commonalities in demographic outcomes.

Secondly, the mathematics of natural selection plays a central role in the predictions that emerge, to some extent overriding details in particular specifications. The mathematics comes from general principles of population genetics and does not much depend on *ad hoc* assumptions of constraints.

Each individual carries his or her own collection of mildly deleterious mutant alleles. That legacy is called "genetic load". Mutation accumulation theory envisions age-specific genetic load helping shape age-specific risk at the individual level.

Individual-level effects of genetic load are not to be confused with aggregate population-level effects of heterogeneity. Differences in genetic load within a population do constitute a form of heterogeneity. They do contribute to the heterogeneity in frailty and in observable risk factors familiar to demographers (e.g. Wachter, 2014a, pp. 185–97), and the effects of demographic selection within cohorts across the life course are not absent from the model. But they are a sideline, not the main story. Demographic selection occurs within each generation,

leaving its mark not on individuals but only on aggregate rates, whereas natural selection acts generation after generation on variability in genetic load, moulding an age trajectory for senescent mortality that reflects physiology at the individual level.

Mutation and natural selection act slowly, and loads we see today were honed long in the past. In the past, health impairments that are now survivable and even quite tolerable till late in life may then have had lethal consequences earlier in life. In humans, most senescent mortality is found at ages now well beyond the years of childbearing and childrearing. But genetic evolutionary theory proposes that we are seeing patterns in survival at late ages today that were imprinted at earlier ages over evolutionary time.

Concepts and Model

The model for mutation accumulation by Evans, Steinsaltz and Wachter (Evans et al., 2013) requires a fair bit of mathematics for a full description, but the concepts behind it can be explained without resort to formulas, which is the goal of this chapter. Attention is restricted to the setting most studied so far: the application to adult age-specific hazard functions. Each application depends on specification of a "selective cost function", a function that quantifies the difference that carrying a specific load of alleles makes to the chance that carried alleles are passed on to the next generation. Marginal selective cost is the difference that one extra copy of that allele makes to the chance. For the application here, the selective cost function is calculated in terms of decrements to the Net Reproduction Ratio, the "NRR".

Among demographers, the NRR is the most popular measure of population growth from generation to generation. It is also called the Generational Replacement Ratio. Properties are described e.g. in *Essential Demographic Methods* (Wachter, 2014, pp. 79 ff.). The NRR is preferred to the other popular measure, Lotka's intrinsic rate of natural increase, for reasons explained by Charlesworth (2000, p. 930) and by Wachter, Evans and Steinsaltz (Wachter et al. 2013, p. 10146).

Nurture as well as procreation affects the successful formation of each next generation. The NRR can be easily modified to incorporate effects of parental survival on the survival of their offspring. With more effort, selective costs can be defined to take account of grandparental nurturing of grandchildren — individuals who can carry their grandparents' alleles.

In its general form, the model applies widely to fertility and to infant and child mortality as well as to adult mortality. Mating success is as much, or more of a contributor to realized fertility as is fecundity; so complexities abound. The model further applies to alleles with stochastic effects, to sophisticated selective cost functions, and beyond. Such broader applications largely await future development.

How does the model for mutation accumulation work? Each allele is associated with an action profile, a non-negative function of age which is to be added to the hazard function for each individual who carries the allele in his or her genome. Alleles are labelled, not by their sites in the genome, but by their action profiles. They are gathered into teams. The alleles in each team share the same action profile. An individual's genetic load is specified by the number of alleles from each team that the individual carries. The individual's hazard function is calculated by adding up the increments to the hazard from each carried allele, added to a common, population-wide baseline hazard. The state of the population is represented by a probability distribution on the counts of alleles from each of the teams.

As a default option, pending future progress toward better options, the baseline mortality schedule may be chosen to be constant over age, representing extrinsic background risks of death. When alleles affecting fertility are not included in the model, the baseline fertility schedule may be chosen to be a fixed schedule compatible with empirical estimates from present-day hunter-gatherers. In this way, the shape of adult mortality is studied under provisional assumptions about the shape of age-specific fertility and about the levels of fertility and infant survival; that is, about the pace of recruitment in the population.

It may be reasonable to suppose that, over evolutionary time, homeostatic regulation responding to population density and resource availability maintained near-zero long-term population growth. In applications, the level of recruitment is often reset to be consistent with long-term zero growth.

In future research, considerations from other strands of evolutionary demography, from optimal life histories and stochastic vitality may help supply more realistic baseline schedules. These strands surely hold promise for understanding the physiological and adaptive contexts within which the age-specific action profiles of alleles come into being across the life-course.

Different timescales are involved. Stochastic vitality models largely speak to processes within single lifespans. Life history optimization involves trade-offs that may be consequential within one generation or a few generations. The trade-offs may be implemented by short-term phenotypic adjustments and adaptations, channelled by genetically determined pathways of influence, but not necessarily tied down to observable genetic variation. Mutation accumulation plays out over dozens or hundreds or even thousands of generations — long timescales over which natural selection leaves its mark on genetic variation.

It is essential to bear in mind that each new mutation occurs in the genome of an individual. Early humans lived in bands, but a new mutation does not occur simultaneously in the genomes of all members of a band. It occurs in an individual. On average, about half of the individual's children and a quarter of the grandchildren carry the new mutant allele, a little more if beneficial, a little fewer if deleterious, but a small portion of the band.

Beneficial alleles differ from deleterious alleles in their age-specific demographic relevance. Beneficial mutations are much less common than deleterious ones. Striking at random, it is easier to break than to improve. Low numbers mean there is less chance for small beneficial effects to cumulate into noticeable total impacts. Those who study beneficial mutations mainly focus, not on mildly beneficial ones, but on strongly beneficial ones. Strongly beneficial alleles spread quickly toward fixation and leave their mark as what are called selective sweeps. It is true that a mildly beneficial allele at any site runs a risk of extinction before fixation, and the risk does depend on the age-specific action profile. But recurrent mutations at the site blur this dependence. Beneficial alleles now fixed in the genome may derive from mutations so far back in time as to allow for multiple tries before success at fixation. Thus, Medawar's story connecting deleterious mutations to demographic schedules does not have a clear counterpart for beneficial mutations.

Recombination is essential to the demographic dynamics. While one-sex models are useful in some areas of population genetics, they are useless for understanding age-specific consequences of natural selection. Recombination makes it possible for some offspring to inherit lower loads of alleles than their parents, thus keeping a modicum of low-load genotypes in the population. The low-load genotypes anchor equilibria. Without

recombination, counts of deleterious alleles would have to trend upwards. In a finite population, this unhappy process is known as Muller's Ratchet and leads to collapse (Buerger, 2000, pp. 303--305). In infinite population models, a kind of renormalization of loads can let equilibria exist (Steinsaltz et al., 2005), but their properties are no guide to the realistic outcomes from two-sex models with recombination.

Technically speaking, the model for mutation accumulation being described here is an infinite-population model in continuous time. A long proof (Evans et al., 2013, pp. 51–110) shows that it is the limiting form of standard discrete-generation models from population genetics in a limit in which mutation and selection act more slowly than genetic recombination. Recombination is intrinsically a rapid process, with at least one and typically several recombination events per chromosome per generation. Mutations occur in every generation, but most are neutral. Those that act detrimentally, mildly and age-specifically on outcomes like adult survival are only a small subset of all mutations and enter the population at correspondingly modest rates. As for natural selection, mild action denotes, by definition, a slow response to natural selection. Thus, the assumption that recombination is rapid compared to mutation and selection is realistic in this context. The model is meant to apply over the substantial numbers of generations in which loads affecting demographic schedules are being shaped. Genetic drift, genetic dominance and back mutation are not treated in the formulation in the monograph (Evans et al., 2013) but extensions including back mutation are under study by others.

Although mildly deleterious alleles are being found in substantial total numbers in genomes, most alleles are neutral. The alleles relevant to mutation accumulation are sparse (Wachter et al., 2014b, p. 10850). They are well scattered across sites and across chromosomes. Genomic associations between nearby sites due to the process known as linkage disequilibrium can safely be ignored for this demographic application.

Among deleterious mutations, the model of Evans, Steinsaltz and Wachter treats those that mainly matter to the demography: those with effects that are mild, that is, not too strong and not too nearly neutral. Strongly deleterious mutant alleles head toward extinction possibly faster than recombination can thoroughly shuffle them, and possibly faster than the model predicts. Very nearly neutral mutant alleles have very small effects on demographic schedules. For them, the finite sizes over time of real populations matter. Genetic drift, not included in the model, gives extra help in removing the alleles or very occasionally lets them edge upward in frequency toward fixation.

According to the model, a randomly sampled individual carries a randomly sampled, Poisson-distributed load of alleles. The alleles are drawn randomly from each team, teams being labelled by their shared action profile. In fact, the alleles in each team are located at sites in the genome, and individuals can only carry zero, one or two copies at any site. The model envisions the count for a team being summed up over draws from many sites at which the deleterious alleles have low population frequencies. If some sites display high frequencies, differences between Binomial and Poisson sampling could introduce distortions. At each site, intrinsic randomness in family size and survival from generation to generation mean that a new mutant allele may quickly become extinct or may wander randomly upward in frequency for a while. The overall load from a team averages out over these random outcomes, site by site, and takes a smooth path through time predicted by the model.

Implications

Thanks to the simplifications achieved by passing to the limiting-form, continuous-time model, predictions of the demographic implications of mutation accumulation (Evans et al., 2013) are easy to compute. The inputs to such a computation are threefold: (a) a collection of functions of age that serve as profiles of age-specific action for each team of alleles; (b) overall rates of mutation per unit time from wild-type (predominant form) to deleterious form for each team of alleles; (c) baseline age-specific schedules for mortality and fertility. In the background is the assumption that the recombination mechanism satisfies some straightforward conditions, and does outpace mutation and selection.

Implementation requires code that computes hazard functions for the individuals in each subgroup that share the same counts of alleles from each of the teams, along with the implied Net Reproduction Ratios for each such subgroup. Formulas from the model then specify time derivatives of the proportional representation of each team of alleles in the population. In practice, efficient algorithms step through time in discrete intervals which should be seen as covering multiple generations — intervals long enough to show long-term average effects from alleles, but short enough to trace a smooth path of accumulation. A starting state without deleterious alleles under most specifications progresses toward an equilibrium. The population hazard function at equilibrium is the most informative output from the model. Examples of such predictions are presented in a 2009 paper (Wachter et al.).

In 2001, Brian Charlesworth recognized that simple specifications for mutation accumulation led to adult hazard functions tending to rise exponentially with age (Charlesworth, 2001). Such hazards are called Gompertz hazards, harking back to an 1825 paper by Benjamin Gompertz. In 1867, Makeham added a constant, age-independent extra term (Smith and Keyfitz, 2013, pp. 231–40). Gompertz and Makeham hazards for adults are ubiquitous. They are observed in countless species including our own. The question of how to account for them, and for their modification at extreme ages, is a central problem in formal demography. In Charlesworth's picture, the assumed action profiles can be highly stylized. The mathematics of natural selection does the work of turning featureless profiles into exponential hazards. Teams have to differ in ages of onset of the main deleterious effects, providing a mix of early-acting and late-acting alleles to fit into Medawar's paradigm.

Charlesworth made selective cost depend linearly on counts of alleles. Mutation accumulation, however, is an inherently non-linear process. When survival is depressed by the effects of some alleles, the reproductive potential left to be affected by additional alleles is smaller. This non-linearity makes the mathematics more complicated, calling for the extensive machinery and long proofs found in the monograph (Evans et al., 2013).

Happily, however, the most noteworthy implication from Charlesworth's treatment holds up in the full non-linear model: adult hazards mimicking Gompertz and Makeham fits arise naturally from stylized allelic action profiles. Furthermore, something intriguing occurs when action profiles are made just a little less stylized. Instead of assuming no effect at all up to some age of onset, one can assume small effects up to such an age, with the main effects coming afterwards. Such an assumption is generally enough to make hazard function trajectories start to level out at extreme ages. Such levelling out is also predicted in some of Charlesworth's own variants, but for different and less fundamental reasons. Hazard functions that level out are said to reach plateaus. Plateaus are commonly seen in

large populations of model organisms, and evidence for plateaus at extreme ages in carefully validated human datasets is growing (Barbi et al., 2018).

Mutation accumulation is a story about small effects — many and various — which only become visible when they accumulate in large numbers. There is little prospect for measuring the actual action profiles for specific alleles. But for the most part, within limits, the actual functional forms for the action profiles do not matter very much. The dynamics of the Darwinian process reward us with a degree of robustness to details of specification. Alleles with bigger negative effects are weeded out more quickly and are present at smaller frequencies at mutation-selection equilibrium. To a first approximation (before taking non-linear interactions into account), doubling the effect of each allele in a team halves the equilibrium frequency for alleles in the team, and the contribution to the hazard function remains nearly the same. This mechanism of compensation controls the cumulative impact. As a result, the predicted shapes of demographic schedules are being driven less by assumptions about action profiles and more by properties of the mechanism of natural selection itself.

This compensation mechanism does not adjust away any age-specific structure in the mutation rates themselves. Those rates are generally taken to be relatively unstructured, but that remains a hypothesis.

Demographers and statisticians have proposed a number of different explanations for Gompertz and Makeham hazards, along with a number of explanations for plateaus. These should be seen as contributing, rather than competing, explanations. Multiple kinds of processes plausibly play mutually supporting roles. But the striking feature of the explanation offered by mutation accumulation, not shared by most other approaches, is that the same process that predicts exponential rise also predicts tapering at extreme ages. Here is a unified explanation on the table.

There are other implications of the model with empirical importance (Wachter et al., 2014, pp. 10849–10851). They go beyond what can be described in detail here. In one direction, the model allows proof of a generalization to the non-linear setting of the identity known as Haldane's Principle. Haldane's Principle is an equilibrium relationship between the totalled-up selective cost of mutations and the overall mutation rate (Buerger, 2000, pp. 105 ff., 143 ff.). The former represents outflow of deleterious alleles, the latter, inflow, and they come into balance at equilibrium. When selective costs are calculated from demographic schedules via changes in Net Reproduction Ratios, the presence of other alleles alters the cost of any new allele. Outflow is no longer a linear, summed-up function of the separate costs of each allele. However, the non-linear interactions obey a more sophisticated version of Haldane's Principle, allowing inflow at equilibrium to be predicted from evidence bearing on selective costs.

Probabilities of survival cannot exceed one. Mortality rates cannot be less than zero. Consider any given set of age-specific rates of fertility and mortality. We can start with what the Net Reproduction Ratio would be in the absence of all adult mortality. The portion of adult mortality contributed by genetic effects of deleterious alleles brings down the Net Reproduction Ratio by some unknown amount. That is the selective cost of the alleles, when selective cost is being measured by decrements to the NRR. We can then notionally include all the other contributions to adult mortality, external and internal. They further reduce the NRR down to its value in the presence of adult mortality calculated from the age-specific rate schedules. The

reduction to the NRR from some portion of adult mortality has to be less than the reduction to the NRR from all adult mortality, so we have a way of putting an upper bound on the selective cost of those deleterious alleles that affect adult mortality.

Measurements of survivorship and fertility from anthropological field studies of hunter-gatherer populations give some exemplars of age-specific human schedules that could have prevailed over evolutionary time (Gurven and Kaplan, 2007). Combined with an assumption of near-zero rates of long-term population growth, this evidence allows us to implement upper bounds on selective costs, and so, via Haldane's Principle, to obtain bounds on mutation rates for that subset of deleterious alleles affecting adult age-specific hazard rates.

Such calculations show that mutation accumulation theory passes a rough consistency check, since bounds on mutation rates for this subset of deleterious alleles come in below estimates (Kondrashev, 2017, p. 109) for total mutations contributing to genetic load. These estimates of flow can also be compared with estimates of stock: estimates of numbers of mildly deleterious mutant alleles present in the human genome, discussed in the final section of this chapter. Together, estimates of flow and stock can be combined into estimates of average antiquity for alleles observed today.

Common Misunderstandings

In appreciating the place of mutation accumulation in evolutionary demography, it is essential to avoid four common misunderstandings.

Sometimes it is imagined that demographic models for mutation accumulation posit age-specific triggers for action from alleles, requiring an implausible age-based clock. By no means! The age-specific action profiles should rather be pictured as net outcomes that emerge gradually from slight differences in physiological processes. As processes work themselves out over the life-course, small genetic differences leave their mark on the eventual mix of ages at death. Any effect of genes on fitness necessarily has some age-specific signature on fertility and mortality.

A leading framework for understanding senescence is the "disposable soma theory" developed by Thomas Kirkwood (1977) and extended by many others. Sometimes it is suggested that mutation accumulation theory is at odds with disposable soma theory. By no means! The one builds on the other. Prime examples for mutation accumulation are mutant alleles that slightly reduce the efficiency of investments in maintenance and repair, in growth and in reproduction just as described within the disposable soma framework.

Antagonistic pleiotropy is a term that applies where the same genetic variant has multiple (pleiotropic) effects working in opposite (antagonistic) directions at different ages; for instance, trading off advantages at younger ages against debilitation at older ages. Sometimes mutation accumulation and antagonistic pleiotropy are regarded as mutually exclusive alternative explanations of senescence. By no means! The two complement each other. Mutation accumulation accommodates any alleles with a pleiotropic mix of negative and positive effects on fitness, so long as the net effect in relevant environments is negative. Antagonistic pleiotropy takes centre stage when the net effect is positive. In that case, mutant alleles typically head toward fixation. Mutation accumulation emphasizes persisting genetic variation in mutation-selection equilibria. Antagonistic pleiotropy takes over for understanding systemic properties at fixation or headed toward fixation.

Sometimes an impression lingers that mutation accumulation typically brings a threat of population collapse in which hazards diverge over time toward infinity. By no means! Typical predictions are for well-behaved equilibrium states with adult hazards exponentially rising with age and levelling off into plateaus. They mirror patterns familiar for humans and many organisms.

Misleading impressions about the salience of collapse arose when proofs of collapse under contrived conditions were offered in mathematical papers (e.g. Wachter et al., 2013). The proofs were offered for the purpose of dispelling any notion that the new nonlinear models were just fancy ways to obtain the same qualitative predictions as the linear models of Charlesworth that inspired them. The proofs remain of theoretical interest but should not draw attention away from realistic cases. Collapse is easily avoided, and the ease with which it is avoided is itself illuminating.

Genetic Load and Socio-Genomics

The existence of the process of mutation accumulation is well-established. With the burgeoning of genomic data, geneticists routinely observe mildly deleterious alleles, numerous in total, although sparse among all variants. Some are present at sufficient frequencies to qualify as Single Nucleotide Polymorphisms (SNPs) while others at lower frequencies qualify as Single Nucleotide Variants (SNVs). In line with expectations, the loads carried by individuals are heterogeneous. An early comprehensive report is found in a 2012 paper in *Science* (Tennessen et al., 2012).

Any deleterious allele acting over the long term necessarily has some age-specific profile of action, either uniform or structured. It stands to reason that some genetic imperfections manifest themselves earlier in life than others. It is readily imagined that it may be easier for physiological adjustments to postpone rather than eliminate ill effects. Something like ages of onset may show up often in action profiles. As mentioned already, however, the kinds of effects at issue are too small to be observed directly, allele by allele.

Some handfuls of single nucleotide polymorphisms have effects on contemporary measured traits that achieve statistical significance in Genome-Wide Association Studies (GWAS). These are not the kinds of SNPs or SNVs involved in mutation accumulation. Mutation accumulation makes its mark with much larger numbers of much more nearly neutral SNPs and SNVs. They show up in aggregate in the background, likely accounting for the lion's share of so-called "hidden heritability". Hidden heritability is the difference between the heritable portion of variance in a trait inferred from twin studies or parallel methods, and the portion visibly accounted for by genetic variants with effects large enough to be detected. The SNPs and SNVs at stake in mutation accumulation would not achieve genome-wide statistical significance, but they would contribute to the weak pervasive correlations that make constructs called polygenic scores useful predictors of traits like height, educational attainment and cognitive status.

There are arguments (Wachter, 2014b) for expecting that GWAS-significant SNPs reflect interactions between specific features of modern environments and genetic propensities. Alleles with large negative consequences for fitness over hundreds of generations would mostly have been weeded away by natural selection. Any allele now affecting health in detectable ways can mainly only be on the scene today if it is affecting health in new ways.

Newspapers feature speculations about alleles inherited from Neanderthals that were good for surviving Ice Ages and are now bad for patrons of fast-food malls. Varying environments across space, and fluctuating environments across time complicate any attempt at a general account, but, by and large, contemporary conditions may be expected to have a prominent role in the large deleterious genetic effects visible today.

Small imperfections are another matter. Genetic programs for basic biochemical and cellular processes, for systems of resource deployment and for systems for repair have roots far back in evolutionary time. Variants that induce slightly less efficient or resilient versions of these processes could have been affecting health and viability over many generations and still be doing so today.

It therefore seems worthwhile to interrogate genomic data for evidence of associations between genetic load and health and demographic outcomes. For such an investigation, two kinds of measures are needed: firstly, measures that identify sets of mildly deleterious alleles in the genome, and, secondly, measures of present-day traits and conditions that can serve as proxies for components of health and survival that could have been relevant to Darwinian fitness over evolutionary time.

Geneticists have been developing a repertory of methods for distinguishing effectively neutral alleles from deleterious or favourable alleles subject to selective pressure. Seven variants of such methods are used as criteria in the paper already mentioned by Jacob Tennessen and twenty-two co-authors, (Tennessen et al., 2012). The distinction between deleterious and neutral depends on effective population sizes over appropriately early spans of time. Generally speaking, there are two kinds of information to exploit: the first based on the phenomenon of sequence conservation across species, the second on inferred impacts of mutations on protein structure and function. An example of the first is Genomic Evolutionary Rate Profiling (GERP) (Davydov et al., 2010). An example of the second is the Polyphen family of indices (Adzhubei et al., 2010).

The GERP approach takes advantage of the occurrence of stretches of genetic code that are highly similar across a number of species, in this case thirty-four species of mammals. These "conserved sequences" can be aligned with each other. For many sites in the genome, it becomes possible to say which species today share the same allele at that site, either entirely or mainly. These readings can then be combined with reconstructions of the phylogenetic tree of life, detailing how species of today have descended and split off from ancestral species. Statistical methods allow us to work back to guesses at the alleles found in the ancestral species, and so to count how many times across the tree one form has substituted for the other. If the site is one with neutral alleles, then the substitutions are expected to be due to the slow process of genetic drift, and the expected number of substitutions can be predicted. If the site is one with a mildly deleterious allele, natural selection will make it harder for that allele to have drifted to fixation as many times as for neutral alleles. The upshot is a criterion for distinguishing neutral from deleterious alleles.

The Polyphen approach supplements information on conserved sequences with knowledge about the effects of DNA mutations on amino acids and functional properties of proteins. The upshot is an alternative score with a mix of advantages and limitations.

These approaches give demographers analysing genomic data a basis for marking and counting up numbers of mildly deleterious alleles carried by each individual. Different criteria

yield different indices. All indices are subject to wide margins of uncertainty, but geneticists are continually developing new and improved strategies.

The other part of the demographic endeavour is the collection and compilation of measurements of traits. The traits are intended to supply sensible proxies for health conditions that could bear on survival and fitness in the evolutionary settings of long ago. However, sample sizes for single detailed surveys, like the Health and Retirement Study and its counterparts, are too small to allow for estimates of genetic effects that are not underpowered. The only practical option at the present time is to combine measurements of the same trait across a number of large surveys which also collect comparable genomic data. The drawback is that the range of traits measured in comparable ways across surveys is narrow, although rapidly expanding. Educational attainment and cognitive assessments were among the first. Only a few studies have usable data on adult mortality, since respondents who have been recently genotyped had to be alive at genotyping. Present-day longevity would also not necessarily match up with traits crucial for survival under the conditions of long ago.

Counterbalancing these limitations is a piece of technical good luck which can stand demographers in good stead. The outputs produced by the consortia carrying out studies with combined samples typically report coefficients and standard errors for constructs called polygenic scores. As long as these coefficients have been computed in their original simple form, without various complicating refinements, the reported outputs are sufficient for demographers independently to compute regressions and other analyses relating their indices of genetic load to the measured traits.

Pilot studies exploring this research program have been conducted by the present author in collaboration with Iain Mathieson, now at the University of Pennsylvania, and Amal Harrati, now at Stanford Medical School. For the most part, associations of indices of individual genetic load with available traits, educational attainment, and an index of cognitive age have not been statistically significantly different from zero. Those null results remain unpublished. However, the traits so far examined are hardly good proxies for components of evolutionary fitness. Richer and more appropriate data are likely to become available in the future. The line of investigation remains promising.

All the strands of evolutionary demography are rich in theoretical insights and engaged with data of many kinds. Mutation accumulation plays a special role, because the elements explicitly modelled — mutation, recombination and natural selection — are the elements directly reflected in the genomes of members of populations now subject to study. This chapter has described a way in which evolutionary demographic thinking makes contact with today's empirical genetics. Much is to be learned.

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