Mutation Accumulation

Empirical Calibration

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Evolutionary Shaping of Demographic Schedules

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Evolutionary processes of natural selection may be expected to leave their mark on age patterns of survival and reproduction. Demographic theory includes three main strands – mutation accumulation, stochastic vitality, and optimal life histories. This paper reviews the three strands and, concentrating on mutation accumulation, extends a mathematical result with broad implications concerning the effect of interactions between small age-specific effects of deleterious mutant alleles. Empirical data from genomic sequencing along with prospects for combining strands of theory hold hope for future progress.

mutation accumulation | senescence | hazard functions

Darwinian natural selection is a story about demographic success. Creatures pass on their genes thanks to the survival and fertility they achieve as they age across the lifecourse. It makes sense to try to understand the age-specific patterns realized in demographic schedules from species to species in the light of evolution. Three main lines of inquiry are being actively pursued by demographers, mutation accumulation, stochastic vitality, and optimal life histories, described below. Of these, the first, mutation accumulation, draws the most specific connections between genomes and demographic outcomes. The last few years have seen the consolidation of mathematical theory for the demographic consequences of this evolutionary process. This paper situates mutation accumulation within the context of the other demographic approaches, extends a mathematical result with demographic implications, and considers emerging empirical and theoretical opportunities.

Mutation accumulation is an idea of Sir Peter Medawar It posits large numbers of deleterious alleles, each with small age-specific effects on survival, imposing genetic load on the population. Natural selection weeds out more slowly bad alleles that only or mainly affect an organism when its days for procreating, parenting, and grandparenting are running short. More late-acting alleles will be found in any equilibrium state where inflow of new mutations balances outflow in "mutation-selection balance." Basic theory is found in

generalizes fixed frailty; "vitality" changes across life in a stochastic, usually Markovian process.

Large-scale models have been developed over many years by Kenneth Manton, Anatoli Yashin, and many collaborators in the form of "stochastic risk factor models" that are Markov processes with high-dimensional state spaces. States of a system represent large suites of physiological indicators, with transitions estimated from data in longitudinal surveys. Small-scale, stylized models have also proved useful in identifying generic properties and demographic implications of stochastic vitality. In one example easy to picture, vitality is represented by a unidimensional Brownian motion and death by hitting a lower barrier or by remaining below a lower barrier for some random waiting time. Probability models developed to study bankruptcy of firms are enriching the mathematical tools for demographic analysis.

Optimal life history theory, a third approach, is familiar from a long tradition in biology studying organisms making adaptive tradeoffs over the life course to maximize reproductive success. Tradeoffs can be viewed as being programmed into the genome or implemented as dynamic behavioral responses. They could be manifest in genetic variation along the lines of "antagonistic pleiotropy" or they could be found in norms of reaction established by alleles long gone to fixation. The "disposable soma" approach of Thomas Kirkwood has inspired work within this framework emphasizing investments in growth, maintenance, reproduction, and repair.

The demographic side of the enterprise, emphasizes roles for intergenerational and intergroup transfers in social species. Analysis of returns to investments in different background environments give insight into differences among species and taxa, especially into a distinction between "fast" and "slow" life histories. The optimization at issue is optimization under constraints. In practice, in formal models for demographic schedules, constraints tend to have to be invented to produce desired shapes, and the mathematics on its own does not add much predictive power. But the descriptive pictures provided by these models give a wide range of qualitative insights.

Mutation Accumulation

In our model for mutation, selection, and recombination described yesterday by David Steinsaltz, pathologies can be avoided in a sensible way, generating predictions for demographic schedules at mutation-selection balance.

In this talk, I restrict attention to a special class of mildly deleterious mutant alleles, here called MA-alleles, affecting age-specific adult mortality and held in equilibrium.

Empirical Calibration

Questions:

- Flow: How many new MA-mutations per individual per generation ???
- Stock: How many MA alleles on average per individual ???
- Selection: How big is a typical selective cost for an MA-allele ???
- Antiquity: What is a typical average age for MA-alleles ???

Darwin and Demography

Darwinian natural selection is a story
about demographic success.

Age-specific schedules of demographic rates are the proximate determinants of fitness.

Natural selection reshapes age-specific demographic schedules.

Age-specificity forces epistasis upon us.

MRCIA

Most Recent Common Intellectual Ancestors

Epistasis

Weakly selected semi-dominant deleterious mutant alleles under random mating with diploid inheritance but selection on haplotypes. Contrast:

$$\text{Fitness} = NRR(g) = \prod_{j \in g} (1 - s_j) \approx \exp\left(- \sum_{j \in g} s_j \right)$$

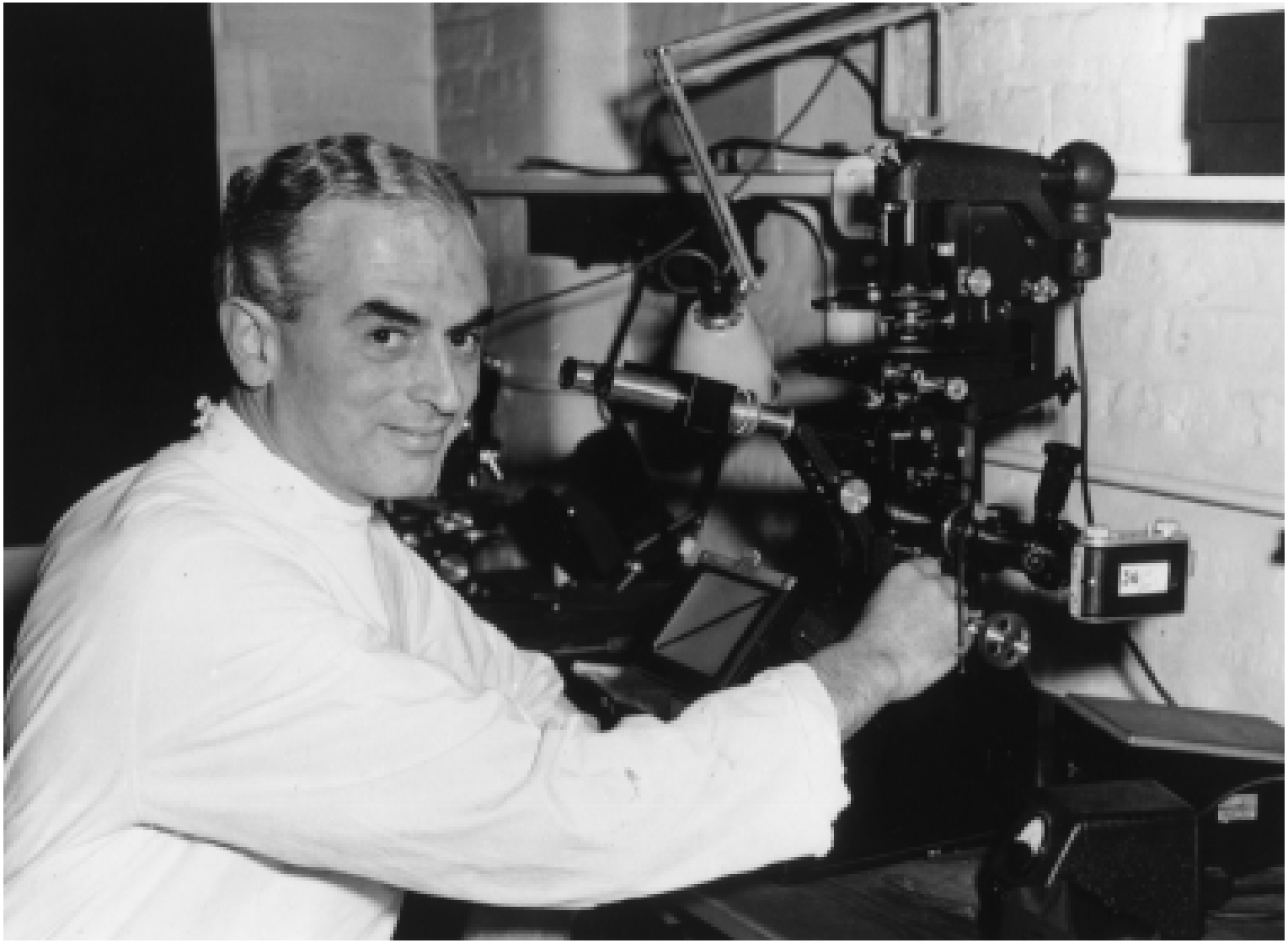
$$\text{Fitness} = NRR(g) = \int \exp\left(- \sum_{m \in g} \theta(m, x) \right) \ell_x(0) f_x \, dx$$

Drawing lessons about discrete-generation outcomes in the world from a continuous-time mathematical model, as I am doing, is not without challenges.

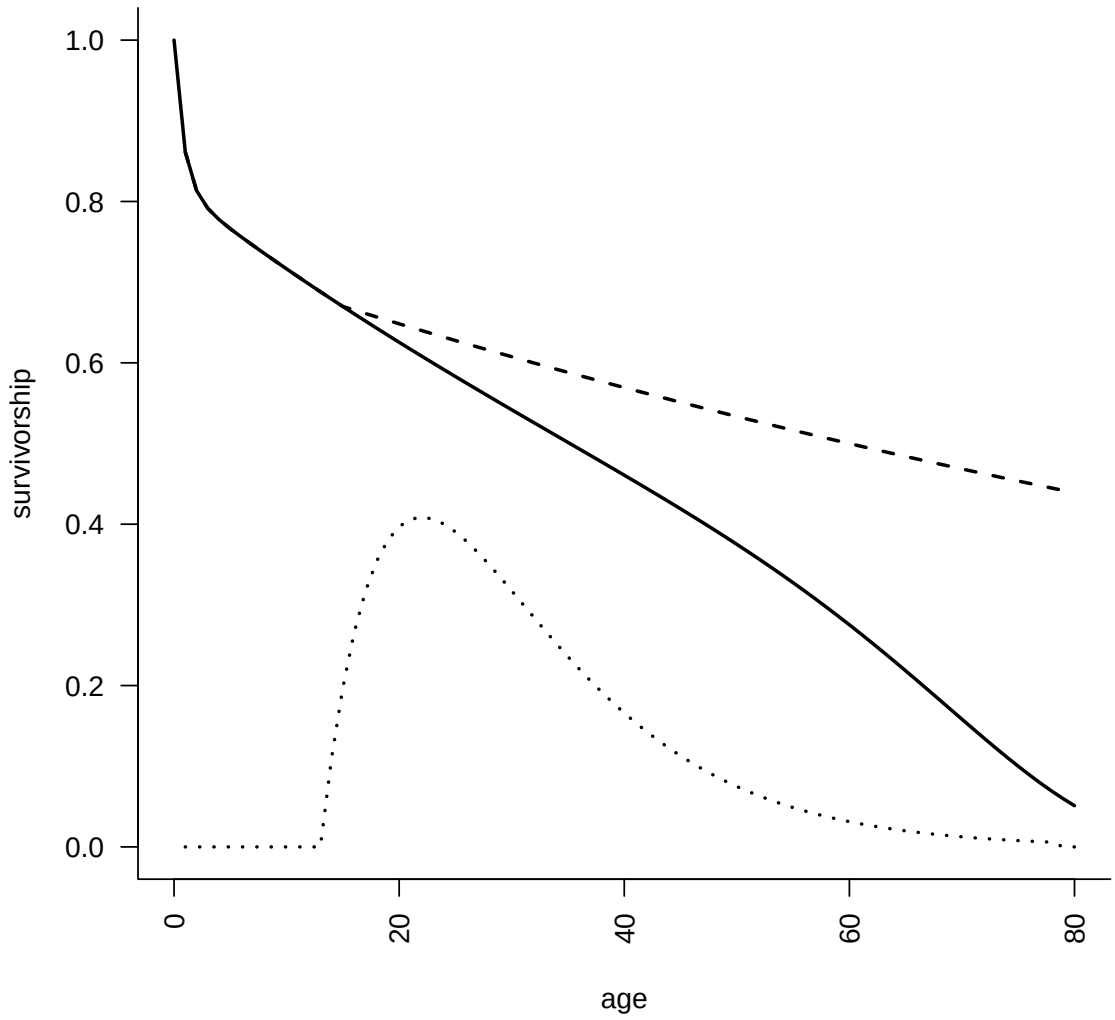
Genetic Load: Spotlight on a Special Subset

1. Each m indexes a "team" of mutant alleles drawn from widely separated sites. The members of a team share an age-specific profile of demographic action.
2. We restrict ourselves to a subset of load, "MA-alleles" with effects on adult mortality rates at mutation-selection balance. This restriction helps bring the notion of a "load-free genotype" and bounds on fitness costs within reach of empirical assessment.
3. There is a closed-form formula for the adjustment due to epistasis in Haldane's Principle relating total loss in fitness to the total rate of new mutations.
4. Prehistoric population growth was kept near zero on average as levels of fertility and juvenile mortality responded to homeostatic feedback mechanisms.

Sir Peter Medawar, 1951, An Unsolved Problem in Biology



Flows: Haldane's Principle and Hunter Gatherers



Michael Gurven and Hillard Kaplan (2007) *Population and Development*

The Generalized Haldane Principle

$$\int q(m)\,dm = \int H_x e^{-H_x} f_x \ell_x(0)\,dx.$$

where

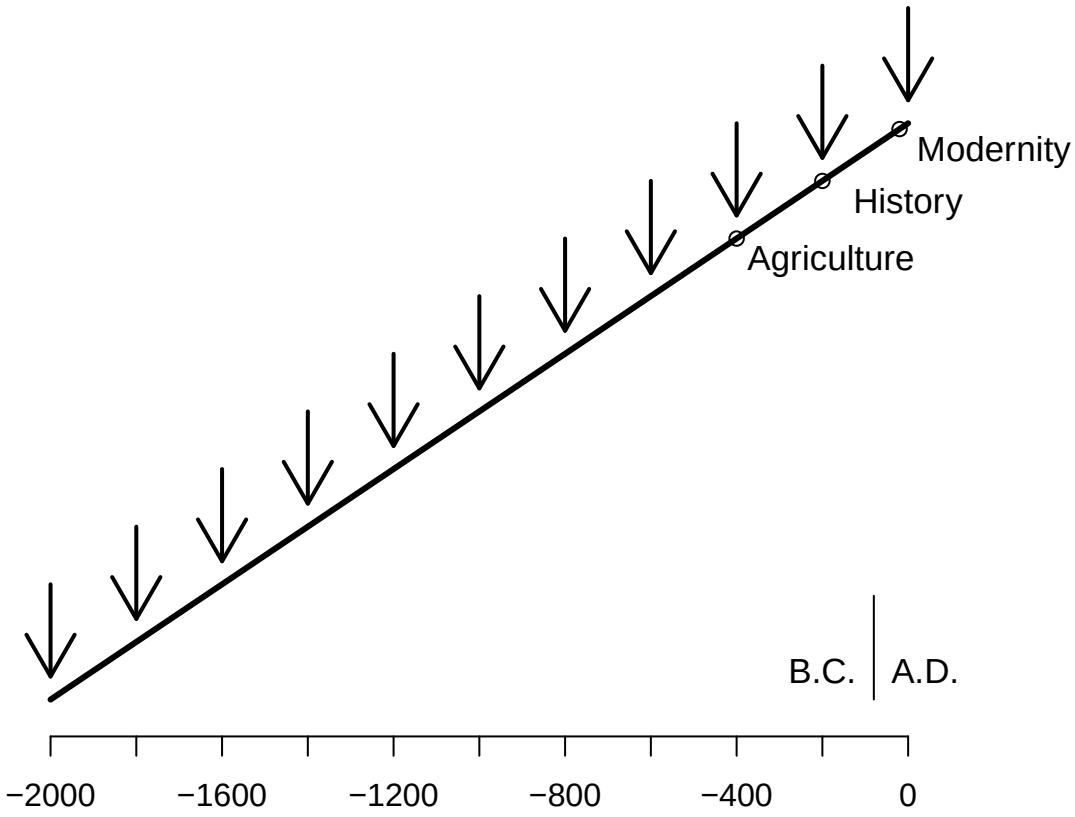
$$H_x := \int_{\mathcal{M}} \left(1 - e^{-\theta(m',x)}\right) r_*(m')\,dm'$$

For example, $0.13 * 1.5 \approx 0.20$.

Stock: Evidence from Tennessen and Co. (2012) *Science*

- Search for Single Nucleotide Variants (SNVs) in the exome in 2044 subjects of European and African descent.
- Individuals carry on average $13,959$ SNVs out of a pool of $503,481$ SNVs
- Most SNVs are classified as neutral or nearly neutral.
- The 23 authors arrive at figures of 318 and 580 for average numbers of functional deleterious SNVs carried per individual by combined criteria of varying strictness.
- Raise these numbers for SNVs outside the exome. Lower these numbers for deleterious alleles that are not MA-alleles.
- For example, $0.20/300 = 1/1500$

MA Alleles and Evolutionary Time



Proposed Calibration

Questions:

- Flow: How many new MA-mutations per individual per generation? ≈ 0.20, i.e. something less than $1/2$.
- Stock: How many MA alleles on average per individual? ≈ 300, i.e. hundreds
- Selection: How big is a typical selective cost for an MA-allele? $\approx 1/1500$, i.e. in the realm of the mildly deleterious
- Antiquity: What is a typical average age for MA-alleles? ≈ 1500 generations, i.e. well back in prehistory.

Zeus and the Salmon