A Theory of Age-Dependent Mutation and Senescence

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ABSTRACT

Laboratory experiments show us that the deleterious character of accumulated novel age-specific mutations is reduced and made less variable with increased age. While theories of aging predict that the frequency of deleterious mutations at mutation–selection equilibrium will increase with the mutation’s age of effect, they do not account for these age-related changes in the distribution of *de novo* mutational effects. Furthermore, no model predicts why this dependence of mutational effects upon age exists. Because the nature of mutational distributions plays a critical role in shaping patterns of senescence, we need to develop aging theory that explains and incorporates these effects. Here we propose a model that explains the age dependency of mutational effects by extending Fisher’s geometrical model of adaptation to include a temporal dimension. Using a combination of simple analytical arguments and simulations, we show that our model predicts age-specific mutational distributions that are consistent with observations from mutation-accumulation experiments. Simulations show us that these age-specific mutational effects may generate patterns of senescence at mutation–selection equilibrium that are consistent with observed demographic patterns that are otherwise difficult to explain.

MUTATION accumulation is a force that is central to shaping adaptation (MULLER 1932; FISHER 1958; MUKAI 1969; KONDRASHOV 1988; KEIGHTLEY 1994; LYNCH *et al.* 1995). It is also of primary importance to evolutionary theories of senescence that seek to explain how and why vitality declines with age. Two popular models of aging, mutation accumulation (MA) (MEDAWAR 1946, 1952) and antagonistic pleiotropy (AP) (WILLIAMS 1957), argue that this decline is caused by late-acting germ-line deleterious mutations that accumulate due to the age-related decline in the strength of natural selection. These genetic explanations consider the balance between the accumulation of age-specific deleterious mutations (which may or may not have beneficial effects early in life) and the capacity for purifying selection to remove those mutations. Age-specific equilibria may be modulated by correlations across ages in the fitness effects of mutations. The AP model requires that late-acting detrimental alleles persist because they confer benefit at early ages. The MA model does not constrain the pleiotropic effects of mutations across ages.

Although AP and MA are not mutually exclusive mechanisms of senescence, population genetic models typically discriminate between them by assigning different representative distributions of age-dependent mutational effects, applying selection determined in large part by demographic structure and then examining the genetic patterns at equilibrium (HAMILTON 1966; ROSE 1982;

CHARLESWORTH and HUGHES 1996; CHARLESWORTH 2001). Much of the empirical investigation into the genetic architecture of aging attempts to determine the relative contributions of these two models to patterns of senescence. In general, quantitative genetic models of aging seek to (1) reconcile these mechanisms with observed patterns of age-specific mortality (usually summarized by a function relating the log-transformed mortality rate to age, the “mortality trajectory”) and (2) identify genetic patterns that are diagnostic of the two putative mechanisms of senescence. These models argue that the MA and AP mechanisms cause divergent patterns of segregating genetic variation and covariation that are manifested in diagnostic differences in age-specific additive genetic variance, dominance variance, inbreeding depression, and genetic correlations across age classes.

Understanding both selection and mutation in age-structured populations is critical to understanding the evolution of senescence. Although existing theories of selection in age-structured populations (HAMILTON 1966; LANDE 1982; CHARLESWORTH 1994) are well developed, the way in which age affects the expression of mutations is poorly understood. As tests of evolutionary theories of aging, classical quantitative genetic approaches have been used to measure changes in genetic variance components for age-specific mortality and fecundity (*e.g.*, HUGHES and CHARLESWORTH 1994; PROMISLOW *et al.* 1996; TATAR *et al.* 1996; SHAW *et al.* 1999; SNOKE and PROMISLOW 2003). QTL studies have also identified segregating loci with age-specific effects (NUZHDIIN *et al.* 1997; LEIPS and MACKAY 2000). These experiments inform us about the temporal distribution

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of polymorphic genetic effects that are already segregating in populations. However, they are useful for understanding past adaptation only as long as the predictive population genetic models are valid. The appropriateness of these models depends on the validity of their underlying assumptions regarding novel mutational effects, which are best tested by measurements of the mutational variance–covariance matrix of traits considered at different ages.

MA and AP models assume that the within-age distribution of mutational effects on fitness is independent of age. To test this assumption, one would need to measure the effects of novel mutations on fitness at different ages. There are many examples of mutation-accumulation studies that have examined the effects of mutations on fitness in various organisms, but usually in the absence of age structure (*e.g.*, MUKAI 1969). However, a few studies in *Drosophila* from three separate labs have examined the age specificity of novel mutations that affect mortality (PLETCHER *et al.* 1998, 1999; YAMPOLSKY *et al.* 2000; GONG *et al.* 2006). These studies find that the effects of novel, deleterious mutations depend upon their age of expression. Specifically, the deleterious effects of novel mutations tend to decrease with age and the variation among mutational effects tends to decrease with age. These observations are problematic because we have no theory to explain why this dependency on age exists, nor do we understand how this age dependency affects the evolution of senescence.

These experiments also suggest the need for new theory to help us understand the role of age-specific mutational effects upon the evolution of senescence. Here we provide such theory by extending Fisher's geometrical model of adaptation (FISHER 1958) to include age specificity of mutational effects. Fisher's model is often used to study how phenotypic complexity influences how mutations affect fitness (FISHER 1958; KIMURA 1983; LEIGH 1987; RICE 1990; HARTL and TAUBES 1996; ORR 1998, 2000, 2006; POON and OTTO 2000; MARTIN and LENORMAND 2006). Here, we use it to model how mutations affect adaptations when individuals senesce—that is, when individuals become *less* well adapted to their environment with age. We assume that the degree of age-specific adaptation for survival diminishes with age, owing to a decline in the force of selection and the subsequent increase in age-specific genetic load (HAMILTON 1966). We demonstrate how Fisher's model, when coupled with this simple assumption, predicts patterns of within-age distributions of mutational effects on mortality consistent with mutation-accumulation experiments and mortality trajectories consistent with demographic observations of natural and laboratory populations.

METHODS

The adaptive fit of a phenotype to its environment follows from the degree to which selection and muta-

tion act on that phenotype. We may view vital rates (*i.e.*, age-specific survival and reproduction) as adaptations, each of which is a complex phenotype determined by numerous genetic and environmental factors. Because the strength of selection declines with age (HAMILTON 1966), we expect differential adaptation leading toward relatively lower rates of early-age mortality and, all else being equal, greater rates of reproduction at younger ages. This perspective views senescence as a manifestation of an age-related loss in adaptation. If mutational effects are themselves dependent upon the degree of adaptation, as suggested by FISHER (1958), then the effects of mutations will depend upon the age at which they act. Mutations will tend to be most deleterious when purifying selection against the mutational load is at its greatest. This positive association between the influx of deleterious mutational load (greatest at early age) and purifying selection (also greatest at early age) will tend to dampen the age-related changes in vital rates at mutation–selection equilibrium. In other words, negative feedback between mutation and selection will cause less senescence than is predicted by the standard mutation-accumulation model of aging. We explore this consequence of Fisher's model on the evolution of age-specific mortality using numerical simulations.

Adaptive geometry: FISHER (1958) argued that because fitness is the result of great physiological and environmental complexity, the trajectory of trait adaptation toward an optimum will be constrained to a serial process of small improvements. To illustrate this point, he introduced a heuristic “geometric model of adaptation.” This model imagines a phenotype represented by a point P that is separated from an optimum O in n -dimensional phenospace by some Euclidian distance z (Figure 1), where n is the number of traits that affect the phenotype and are under selection. This phenospace represents the entire universe of possible multivariate phenotypic configurations. As all points at some distance from the optimum are equivalent, the phenotype can be imagined as a circle, a sphere, or, more generally, a hypersphere with a characteristic radius equal to z . A change in the phenotype, such as might follow from a mutation, will move the genotype away from P by some amount r . Fisher noted that the probability that such a change moves the phenotype closer to the optimum (thereby increasing fitness) decreases with increasing r and n . Specifically, the probability that a mutation is beneficial is approximated by the cumulative standard normal distribution,

$$B(v) \cong \frac{1}{\sqrt{2\pi}} \int_v^{\infty} e^{-t^2/2} dt, \quad (1)$$

where $v = r\sqrt{n}/z$ is the effective size of the mutation and n , the dimensionality of the trait, is very large (FISHER 1958; KIMURA 1983; LEIGH 1987; RICE 1990; ORR 1998). Fisher's model offers a useful heuristic means with

FIGURE 1.—Effects of a mutation depend upon adaptive geometry. Two phenotypes P_1 and P_2 are at distances z_1 and z_2 from the optimum indicated by the star. A mutation occurs with some uniformly distributed effect on each phenotype. Although the expected change in the phenotypes' position is zero on this phenotypic scale, there is a positive expected change in the distance due to the local curvature of the circle defined by z . As adaptation causes the phenotype to approach the fitness optimum, z decreases but the expected fitness cost of novel mutations increases. Here we illustrate the increasingly deleterious character of mutations as a phenotype moves from a position far from the optimum ($z_1 = \frac{3}{2}$) to a position nearer to the optimum ($z_2 = 6$). Note that the proportion of the mutations occurring in the highly adapted phenotype that are beneficial (represented by the disk fraction with dark shading) is less than the proportion of beneficial mutations that occur in the less-adapted phenotype (the fraction with light shading).

which to think about the distribution of mutational effects.

Age structure complicates adaptive geometry: Here, we extend Fisher's model to explore how the distribution of mutational effects might change with age and with the complexity of vital rates. The fit of a phenotype to a particular environment determines the radius of the adaptive geometry. Because the selection that drives adaptation is attenuated with age, more deleterious age-specific mutations are allowed to accumulate at late age (HAMILTON 1966). We expect that the age-specific radii of phenotypes P will consequently increase with age, becoming less well adapted to their age-specific environments. We extend Fisher's heuristic model by adding a temporal dimension x . The result is a series of hyperspheres, each representing the n_x -dimensional adaptive geometry specific to a particular age class. Each age-specific hypersphere has some radius, z_x , which follows from the degree of adaptation characteristic of the age-specific phenotypes. All else being equal, these radii increase with age after reproductive maturity is reached because the intensity of selection lessens with age. Because selection for survival is not expected to change prior to reproductive maturity, all prereproductive hyperspheres will have the same radii provided that

FIGURE 2.—Adaptive geometry of genotypes increases with age. The intensity of selection is greatest and invariant (and the circles are smallest) until the onset of reproduction at some age x' , at which point the strength of selection diminishes with age. All else equal, the degree of adaptation follows from the selection intensity. We visualize the consequence of this process on aging by integrating age-specific geometries ordered along the age axis x . Because the adaptive radii increase with age, senescent life histories are characterized by a funnel-like adaptive geometry, illustrated on the left. Age-specific geometries (see Figure 1) are recovered by taking cross-sections of the funnel at x , as we demonstrate on the right.

the influx of mutational effects does not change (this assumes that n_x is constant—see below).

Previous applications of Fisher's model illustrate the adaptive geometry of a population using the simplest two-dimensional projection of the hypersphere, the circle (e.g., HARTL and TAUBES 1996; ORR 1998, 2006; POON and OTTO 2000; WAXMAN 2006). In keeping with this tradition, we imagine a series of circles with radii that increase with age. We standardize the age-specific radius for dimensionality by dividing each radius z_x by the square root of n_x (Equation 1). When we align the age-ranked circles that represent the radii of reproductive ages along the temporal axis that runs perpendicular to the age-specific radii, we form a truncated cone (a conical frustum). As the intensity of selection on mortality is expected to be constant for all prereproductive ages (HAMILTON 1966) and provided that complexity is constant, the circles for these earliest age classes will form a column with a radius that is equal to the smallest radius of the frustum (Figure 2). We define the adaptive geometry of the whole life course by appending the prereproductive cylinder to the frustum formed by the reproductively mature age classes. Taken together, the age-specific shape of the adaptive geometry appears as a funnel in a three-dimensional projection. The adaptive geometry of a phenotype at a particular age is recovered by taking a cross-section of the funnel perpendicular to the temporal axis.

Geometric interpretations of age-specific mutational effects: At a single age, a mutational effect on this

phenospacial scale can be defined by an n_x -dimensional vector with Euclidean length r . However, the effect of a mutation over all ages is far more complex because a single mutation can have an effect on the phenospace at any or all ages. This effect can vary freely in magnitude and direction, although the tendency to do so depends upon the degree to which an organism's physiology and environment are integrated across ages. In light of the model shown in Figure 2, we can visualize a mutation with identical phenospacial effects at all ages as a line running parallel to the funnel surface. Aside from its effects on this multidimensional phenospacial scale, a mutation may also have an effect on the univariate fitness scale. This is a change in the spatial distance z between the optimum and the new phenotype's adaptive position P . A mutation is consistently beneficial (or deleterious) if it is always within (or always outside) the surface of the volume. These types of mutations will contribute to positive fitness correlations across ages. Mutational effects that enter and exit the volume at different places along x will contribute to negative fitness correlations across ages—a requirement for antagonistically pleiotropic mechanisms for the evolution of senescence.

In the *window-effect* model (CHARLESWORTH 2001), the effects of a mutation are neutral until some age x , have some constant effect over Δx , and then return to neutrality. We can visualize the effect of this form of mutational effect by imagining a line traveling along the surface of the funnel (Figure 3). At some point that corresponds to the earliest age defining the window, the line juts outward (a deleterious mutational effect) or inward (a beneficial mutational effect) in a direction perpendicular to the temporal axis. After traveling some distance corresponding to the magnitude of the effect (the greater the distance, the greater the effect), the line then resumes a course parallel to the surface of the funnel. Upon reaching the end of the window (*i.e.*, the age of last effect), the line returns to the surface of the funnel and continues to run uninterrupted along the surface of the funnel to its terminus. With continuous-time models, the window of time becomes infinitesimally small (*i.e.*, $\Delta x \rightarrow 0$) and the number of age classes becomes infinitely large. We can attribute the frequent use of the window model in theoretical explorations of aging to its apparent simplicity: the duration of the effects of mutations is constrained to the size of the window, which can define a single age class. There can be no genetic correlations across ages either among mutations or among the genetic variants that segregate at mutation–selection equilibrium. As a result, it is straightforward to predict evolutionary trajectories. We consider this model in our simulations.

Numerical simulations of age-specific mortality: We wished to understand how these adaptation-dependent mutational effects influence the evolution of senescence as reflected by declines in survival rates with age. Because

FIGURE 3.—The window-effect model of mutation. A mutation has no effect throughout most of the life of the organism (shaded line along the left side of the funnel). At some age, the mutation has some constant, nonzero effect that lasts for some time, after which the mutation has no effect. Mutations appear to have an effect at some age (point with dark shading extending from the circle at top right) and not at others (point with dark shading at bottom right).

we are particularly interested in the effect of mutations on age-specific mortality, we set the within-age class variance in reproductive output to zero, thereby assuming that the variation in age-specific fitness depends entirely upon three factors—the variation in age-specific survival, reproduction as a function of age, and the age structure of the population. This allowed us to equate the concept of adaptive geometry to a geometry of age-specific survival. We viewed survival at each age (or its negative natural logarithm, mortality) as independent phenotypes made up of many (n_x) traits under selection. The simultaneous effects of window-effect mutations (*i.e.*, a given mutation affects one and only one of the nonoverlapping windows) and selection upon the mean and variance of age-specific survival at mutation–selection equilibrium were explored using deterministic simulation models of an age-structured infinite-size population coded in R 2.5.1 (R DEVELOPMENT CORE TEAM 2007). Our goal was to explore (1) how the mean and variance of mortality (defined as the negative logarithm of survival rates) evolve and (2) how the mean and variance of mutational effects on mortality change with age when the effects of age-specific mutations depend upon the adaptive fit of individuals at each age.

We imagined an infinite population that experienced cycles of reproduction, mutation, and viability selection for some time T sufficient to reach demographic and genetic equilibria. The demographic structure of a population with X age classes at time t was described by the probability density function $\pi_{y,t}$, where y is the age of the cohort. There were $X - 1$ survival traits; each determined the probability that an individual successfully transitioned from age x to age $x + 1$. Mutations acted on single age classes, corresponding to a window-effect model of mutation with $\Delta x = 1$. Each individual

that successfully transitioned from age x to age $x + 1$ contributed offspring to the offspring pool with age-specific fecundity m_x . The probability at time t that an individual belonging to y has an age x -specific phenotype (the distance to the age-specific optimum) equal to z is $p_{z,x,y,t}$. Cohorts expressed these phenotypes when $y = x$. Otherwise the phenotypes were latent, having been expressed before (if $y > x$) or waiting to be expressed in the future ($y < x$). We defined survival as an exponential function of phenospacial distances, $P_z = e^{-z}$, because survivorship mutations are usually considered to act additively on the log scale (HAMILTON 1966; CHARLESWORTH 1994—but see BAUDISCH 2005). Thus, the distance of a phenotype from the optimum defined its age-specific mortality exactly, $z = \mu_x = -\ln(P_z)$.

We explored the case of four age classes ($X = 4$) with three transition traits determining the survival probabilities. The distance z (mortality) ranged from 0.0025 to 10.0025 and was binned into classes of size 0.005. Thus, there were 2000 possible phenotypes available to each individual at each age x . At any time t there were nine phenotypic distributions (three cohorts each with three age-specific phenotypes); we represented each of these with a vertical vector $\mathbf{p}_{x,y,t}$. This is the distribution of distance z for age x among cohort y at time t . Initially, the population's age distribution and age-specific breeding value distributions were uniform: $\pi_{x,1} = 1/X$ and $p_{z,x,y,1} = \frac{1}{2000}$ for all x, y , and z . Differently put, age-specific survival within ages was highly variable but there was no mean change in survival with age (*i.e.*, no initial senescence).

A long-held conclusion of life-history theory is that age-related increases in fecundity will mitigate (but not completely eliminate) the evolution of senescence by increasing the relative intensity of selection on late-age survival (WILLIAMS 1957). To explore the effect of varying late-age selection on survival, we considered three different reproductive functions, $\mathbf{m}_1 = \{0, 1, 1\}$, $\mathbf{m}_2 = \{0, 1, 2\}$, and $\mathbf{m}_3 = \{0, 1, 4\}$ with the expectation that age-specific selection will decline with age most with $\mathbf{m}_1$ and least with $\mathbf{m}_3$. In each treatment, reproduction was delayed until after the second transition. This provided one test of our simulation model: because the decline in selection associated with age was deferred until the onset of reproduction, we expected no change in equilibrium mortality associated with the first two transitions when the mortality effects of mutations were held constant. Any differences in mortality rates at mutation–selection equilibrium between the first two transitions could not be due to differences in selection. We designate the three age-specific survival traits as juvenile survival (transitioning from $x = 1$ to 2), early adult survival (from $x = 2$ to 3), and late adult survival (from $x = 3$ to 4).

Viability selection: Every cohort had $X - 1$ phenotypic distributions, each corresponding to mortality at a different age. At each time step, selection changed the

phenotypic distributions in each cohort that corresponded to mortality at that time, $x = y$. Following our definition of bins and the survival function, age-specific survival could range from a high of 99.75% to a low of $<0.00005\%$. We defined a vertical vector $\mathbf{s}$ in which each element corresponds to the survival of a phenotype, $\mathbf{s} = e^{-\mathbf{z}}$, where $\mathbf{z} = \{\frac{1}{400}, \frac{3}{400}, \dots, \frac{4001}{400}\}$. The distributions of phenotypes currently under selection are described by $\mathbf{p}_{y,y,t}$. After selection, these distributions were reweighted by their phenotype-specific viability,

$$\mathbf{p}_{y,y+1,t+1} = \frac{\mathbf{s} \cdot \mathbf{p}_{y,y,t}}{\mathbf{s}^T \cdot \mathbf{p}_{y,y,t}}. \quad (2)$$

Other distributions $x \neq y$ were shielded from selection. Thus

$$\mathbf{p}_{x,y+1,t+1} = \mathbf{p}_{x,y,t}. \quad (3)$$

We standardized the age distributions to correct for mortality and the production of new offspring. First, we found the unstandardized size of each cohort at time $t + 1$ that followed from viability selection,

$$\pi'_{y+1,t+1} = \pi_{y,t} \cdot \mathbf{s}^T \cdot \mathbf{p}_{y,y,t}. \quad (4)$$

The size of each new cohort $y = 1$ follows from the previous age-structure $\pi_{y,t}$ and the age-specific fecundity function $\mathbf{m}$, $\pi'_{1,t+1} = \sum_{y=1}^Y \pi_{y,t} \cdot m_y$. We standardized the new age structure to account for this new cohort,

$$\pi_{y,t+1} = \frac{\pi'_{y,t+1}}{\sum_{y=1}^Y \pi'_{y,t+1}}. \quad (5)$$

Reproduction and mutation: All surviving individuals reproduced asexually at the end of each time period t . Phenotypes were assumed to be completely heritable, excepting the effects of mutation (like POON and OTTO 2000, we ignore environmental variation). To model the distribution of mutation effects, we followed closely the mutation model of POON and OTTO (2000). The effect of mutation on all phenotypic traits was assumed to be distributed as a set of n independent reflected exponentials (symmetric about zero), each with the same parameter λ . Under this assumption, the magnitude r was distributed as

$$p(r, n) = \frac{\lambda^n e^{-\lambda r} r^{n-1}}{\Gamma(n)} \quad (6)$$

and the angle θ as

$$p(\theta, n) = c' \sin^{n-2} \theta, \quad (7)$$

where

$$c' = \frac{\Gamma(n/2)}{\sqrt{\pi} \Gamma[1/2(n-1)]}. \quad (7a)$$

For some initial distance z , mutational distance r , and effective orientation θ , the distance of the changed phenotype from the optimum was

$$z' = \sqrt{z^2 + r^2 - 2zr \cos \theta}. \quad (8)$$

We rearranged Equation 8 to find the angle of mutational effect that caused the distance to transition from distance z to z' ,

$$\theta(z, r, z') = \cos^{-1} \left(\frac{z^2 + r^2 - z'^2}{2zr} \right). \quad (9)$$

We used Equations 6–9 to find the probability that a mutation at distance z would end up within some distance $\pm \frac{1}{400}$ from every possible value of $\mathbf{z}$. The probability that a mutation shifts the phenotype from z to the interval $z' \pm \frac{1}{400}$ was

$$\Pr \left\{ z + \Delta z - \frac{1}{400} < z' < z + \Delta z + \frac{1}{400} \right\} = \int_{r=\Delta z}^{Z+z} \int_{\theta(z,r,z+\Delta z-(1/400))}^{\theta(z,r,z+\Delta z+(1/400))} p(r, n) p(\theta, n) d\theta dr. \quad (10)$$

Mutations with effect $r > Z + z$ caused the new phenotype to equal Z , making Z an absorbing boundary. By applying Equation 10 to all elements of $\mathbf{z}$, we defined the probability transition matrix for a single mutation $\mathbf{U}(n_x, \lambda)$. The number of mutations n^* introduced in each offspring was Poisson distributed with parameter $u = 1$, a value that conforms to estimates of mutation rates in *Drosophila* (HAAG-LIAUTARD *et al.* 2007). Taking account of the variation in the number of mutations per time unit, the mutational probability transition matrix was

$$\mathbf{U}^*(n_x, \lambda) = \sum_{n^*=0}^{\infty} \Pr(n^*) \cdot [\mathbf{U}(n_x, \lambda)]^{n^*}. \quad (11)$$

Each cohort contributed to each age-specific probability density function (pdf) of phenotypes in proportion to the product of its current fecundity and fractional representation of the population. Given the vertical vector of phenotypic probabilities at time t , $\mathbf{p}_{x,y,t}$, the pdf of mortality phenotypes of the offspring cohort after mutation specific to some age of expression x was

$$\mathbf{p}_{x,1,t+1} = \mathbf{U}^*(n_x, \lambda, u) \cdot \frac{\sum_y \pi_{y,t} \cdot m_y \cdot \mathbf{p}_{x,y,t}}{\pi'_{1,t+1}}. \quad (12)$$

The phenotypic effects of mutations are expected to be greatest with high n and low λ (POON and OTTO 2000). To explore the consequences of changing these mutational parameters on mutation–selection equilibrium and mutation accumulation, we considered each of $\lambda \in \{50, 100, 150, 200\}$. Complexity is a central component of Fisher’s geometric model and some

studies have suggested that the complexity of phenotypic traits may change as an organism ages (KAPLAN *et al.* 1991; LIPSITZ and GOLDBERGER 1992, but see GOLDBERGER *et al.* 2002; VAILLANCOURT and NEWELL 2002). We investigated how complexity affected age-related changes in mutational effects by considering a variety of age-specific functions of n . First, we considered the scenario in which n is constant across all ages (age-independent complexity), with $n \in \{10, 15, 20, 25\}$. In addition, we explored what happens when complexity changes with age (age-dependent complexity). Specifically, we considered what happens if (1) complexity increases between adult age classes, $n_x = \{10, 10, 20\}$, (2) complexity decreases between adult age classes, $n_x = \{20, 20, 10\}$, (3) complexity increases between juvenile and adult age classes, $n_x = \{10, 20, 20\}$, and (4) complexity decreases between juvenile and adult age classes, $n_x = \{20, 10, 10\}$. Scenarios 1 and 2 were investigated to see if changes in complexity caused qualitative shifts in the degree to which senescence evolves in reproductive age classes. Scenarios 3 and 4 were investigated to see how changes in complexity caused equilibrium mortality to diverge between the juvenile and the early adult age classes (recall that selection for both juvenile and early adult survival is equal because juveniles cannot reproduce).

Mutation–selection balance and mutation accumulation:

All simulations were allowed to evolve for T generations, defined as the point at which none of the phenotypic distributions deviated from those at generation $T - 1$ to the resolution limit of R 2.5.1. These distributions defined the mutation–selection equilibrium specific to the population with parameters m_x , n_x , λ , and u . We then removed selection from the populations by changing the survival function to $P_z = 1$ and allowing the populations to evolve for an additional 50 time units. We attributed the changes in the mean and variance of age-specific mortality between generations $T + 50$ and T to the effects of *de novo* mutation accumulation.

RESULTS

Qualitative results of the geometry: As selection relaxes with age, more age-specific, deleterious mutations accumulate at late age than at early age. This causes the adaptive phenospace to increase at late age, thereby decreasing the deleterious nature of novel mutations. These changes in age-specific adaptive geometry mean that a multivariate perturbation in phenospace (such as mutation) that is the same at different ages may nevertheless have different effects on complex traits early *vs.* late in life. The effects of mutations become age dependent.

Mutations are less likely to be deleterious with increased age: As a cohort ages, the phenotypic distance z of the cohort from the optimum, O , increases. All else equal, early-

acting mutations are more likely to be deleterious than late-acting mutations. This property follows from Equation 1, which gives us the probability that a mutation is beneficial. The age-related increase in the probability that a mutation is beneficial is simply the difference of age-specific probabilities described by Equation 1,

$$\Delta B = \frac{1}{\sqrt{2\pi}} \int_{v_2}^{v_1} e^{-t^2/2} dt, \quad (13)$$

where $v_x = r\sqrt{n^*}/z_x$. As long as the effective size of mutations declines with age (as a result of increasing the phenotypic distance to the optimum z), v_1 must exceed v_2 and Equation 13 will be positive, ensuring that late-acting mutations are more likely to be beneficial than early-acting mutations.

Mutations will tend to be less deleterious and less variable at late age: The mean effect of a single mutation on the distance to the optimum lessens with increased initial distance z . However, there will be variation in the phenotypic effect of a single mutation. Furthermore, phenotypes will vary in the number of *de novo* mutations that they experience. Here we demonstrate how the total mean and variance of the phenotypic change is reduced with increased distance from the age-specific phenotypic optimum.

We standardized the initial distance z prior to mutation by the size of the mutation effect r in multivariate adaptive phenospace. We subdivided the population into groups of phenotypes on the basis of the number of mutations experienced by each phenotype. We assumed that the number of *de novo* mutations that affect the phenotypes is Poisson distributed. Thus, the distribution of changes Δz that result from mutation is the mixture of the distribution of single mutations and the distribution of the number of new mutations experienced by each phenotype,

$$\Delta z = \sum_{i=1}^{n^*} \Delta z_i, \quad (14)$$

where n^* is a random draw from a Poisson distribution with rate u and Δz_i is a draw from the distribution of Δz per single mutation. Given the mean and variance of the phenotypic change for a given mutation number n^* (the conditional distribution), the mean and variance of the total mutational change (the marginal distribution) are

$$E_T(\Delta z) = E_{n^*}(E(\Delta z | n^*)) \quad (15a)$$

$$Var_T(\Delta z) = V_{n^*}(E(\Delta z | n^*)^2) + E_{n^*}(V(\Delta z | n^*)), \quad (15b)$$

where E_{n^*} and V_{n^*} are the mean and variance taken on the distribution of mutation number n^* , which we have assumed to be Poisson with rate u .

First, we find the mean of the compound Poisson process. Equation 15a can be restated as a product of the

mean number of mutations and the mean effect of a single mutation,

$$E_T(\Delta z) = E_{n^*}(n^*)E(\Delta z | n^* = 1) = uE(\Delta z | n^* = 1). \quad (16)$$

Rearranging Equation 8 shows us that the change in the distance resulting from a single mutation is $\Delta z(\theta) = -z + \sqrt{z^2 + 1 - 2z \cos \theta}$. Integrating these changes weighted by the distribution of orientations (Equation 7) over all values of θ gives the mean distance change caused by a single mutation as a function of z ,

$$E(\Delta z | n^* = 1) = -z + \int_0^\pi p(\theta, n) \sqrt{z^2 + 1 - 2z \cos \theta} d\theta. \quad (17)$$

The integral is $(1+z)F(-(1/2), (n-1)/2, (n-1), 4z/(1+z)^2)$, where F is the hypergeometric function. At moderately large values of z , the mean change in distance that results from a single mutation is well approximated by

$$E(\Delta z | z) \approx \frac{n-1}{2nz}. \quad (18)$$

Substituting Equation 18 into Equation 16 returns the mean distance change as a function of the mean number of mutations, the initial distance, and the complexity of the phenotype,

$$E_T(\Delta z) \approx u \frac{n-1}{2nz}. \quad (19)$$

Equation 19 tells us that mutations always tend to be deleterious on average. The funnel-shaped temporal extension of Fisher's geometric model predicts that aging causes the initial distance from the age-specific optimum to increase. At great age, where z is presumably high, the mean effects of mutations slowly converge to zero. If aging causes a ratio of phenotypic distances d , then the ratio of mean effects caused by late-acting to early-acting mutations is equal to $1/d$. Increased complexity may also contribute to the reduction of mutational means.

Next, we find the variance of the compound Poisson distribution. Equation 15b can be restated as

$$Var_T(\Delta z) = E_{n^*}(n^*)(V(\Delta z | n^* = 1) + E(\Delta z | n^* = 1)^2). \quad (20)$$

The variance in change $V(\Delta z | n^* = 1)$ is the difference between the mean change squared $E(\Delta z^2 | n^* = 1)$ and the square of the mean change $E(\Delta z | n^* = 1)^2$. By this and the definition of the Poisson distribution, Equation 20 simplifies to the product of the mean number of new mutations and the mean squared effect of a single mutation,

FIGURE 4.—Mutational variance decreases with complexity and distance from the optimum. Trajectories are solved exactly using Equation 23 for $n = 10, 20, 100$. We assume that the number of novel mutations that affect phenotypes is Poisson distributed with mean u . Variance values along the ordinate are standardized by u . Initial distances along the abscissa are standardized by the size r of the mutation in multivariate phenospace.

$$\text{Var}_T(\Delta z) = uE(\Delta z^2 | n^* = 1). \quad (21)$$

We can define this expectation in terms of an integral following the approach taken above in Equation 17,

$$E(\Delta z^2 | n^* = 1) = \int_0^\pi p(\theta, n) \Delta z^2 d\theta. \quad (22)$$

In terms of a hypergeometric function, the variation in mutation effects is

$$\begin{aligned} \text{Var}_T(\Delta z) \\ = u \left(1 + 2z^2 - 2z(1+z)^2 F\left(-\frac{1}{2}, \frac{n-1}{2}, (n-1), \frac{4z}{(1+z)^2}\right) \right). \end{aligned} \quad (23)$$

This is approximately

$$\text{Var}_T(\Delta z) \approx u \left(\frac{1}{n} + \frac{1}{4z^2} - \frac{3}{2nz^2} \right). \quad (24)$$

Figure 4 illustrates the effects of distance z and complexity n upon the variation in mutational effects.

We want to know how senescence (an age-related increase in the initial distance) and age-related changes in complexity will change the mutational variance. First, we take the first derivative of Equation 24 with respect to z ,

$$\frac{d\text{Var}_T\{\Delta z\}}{dz} \approx \frac{u(6-n)}{2nz^3}, \quad (25)$$

which is negative at even moderate values of n . Thus, age-specific mutational variance will decline with increased age. Next, we take the first derivative of Equation 24 with respect to n ,

$$\frac{d\text{Var}_T\{\Delta z\}}{dn} \approx \frac{u(3-2z^2)}{2z^2n^2}, \quad (26)$$

which becomes negative very soon after the premutation phenotype diverges from the optimum. Equation 26 shows us that more complexity will decrease the total mutational variance.

Results of the numerical simulations: All simulated populations reached genetic and demographic equilibria within approximately two thousand generations. As expected, mean mortality did not change between juveniles and adults when complexity was age-independent. Senescence, defined here as the proportional increase in mean mortalities from early to late adulthood, evolved in all treatments with age-independent complexity (Figure 5A). Equilibrium senescence tended to increase with complexity. This effect was reduced when mutational effects were greatest in multivariate phenospace ($\lambda = 50$) and increased late-age individuals' fecundity increased selection for late-age survival ($\mathbf{m}_2$ and $\mathbf{m}_3$). All populations demonstrated phenotypic variation in age-specific mortality that changed throughout the duration of each simulation. Mortality variation did not change from juvenile to early-adult age classes but it always increased from early- to late-adult stages (Figure 5B). Complexity tended to increase the variance ratios, although the ratios did decline slightly with n at $\lambda = 50$, $\mathbf{m}_2$, and $\mathbf{m}_3$. Increased late-age fecundity mitigated the age-related increase in the ratios of mean mortality (senescence) and mortality variance.

All simulated populations were allowed to accumulate mutations for 50 generations after reaching mutation-selection equilibrium. In all treatments, the mean effect of mutation accumulation was detrimental but became less deleterious with age (Figure 5C). Increasing the complexity across treatments tended to exacerbate this effect through much of parameter space; however, the trend seemed to reverse at high n and low λ (but late-acting mutations still were less deleterious than early-acting mutations). In general, increasing the reproduction of late adults increased the deleterious nature of mutations at late adulthood. The mutational variance, defined here as the difference between the variation in mortality before and after mutation accumulation, tended to increase after selection ceased. The variance increased *less* at late adulthood than at early adulthood (Figure 5D). In one case, however, the ratio of mutational variances increased by 4% ($\lambda = 50$, $n = 20$, $\mathbf{m}_3$). These ratios tended to decrease with increased complexity and decreased λ but the pattern became less clear as the effective size of mutational effects in multivariate phenospace became large (high n and low λ). The age-specific mutational variance was observed to decline with age when scaled by the square of the equilibrium mean mortality (see supplemental data).

Aging theory predicts that there is no difference in selection against mortality between juveniles and the

FIGURE 5.—Proportional increase of mortality at mutation–selection balance with age-independent complexity. Data represent the ratio of late-adult to early-adult values for (A) mean mortality at mutation–selection equilibrium, (B) mortality variance at mutation–selection equilibrium, (C) mean effects of 50 generations of mutation accumulation, and (D) variation in mutational effects. Each line follows a particular fecundity function, where the first value of $\mathbf{m}$ is the early-adult fecundity and the second value is late-adult fecundity. The data that we show here follow from $\lambda = 50$ treatments. Other treatments give similar qualitative results.

earliest reproductive age. Our simulation results support this prediction by showing that all mortality distributions were identical between these age classes at equilibrium. Because the properties of mutation accumulation depend upon these equilibrium means and variances, the mutational distributions did not differ between juveniles and early adults. When complexity becomes age dependent, however, equal selection pressures did not guarantee equal equilibrium points because the mutational pressures changed with age. We found that changes in complexity with age gave rise to every possible qualitative age-related pattern of equilibrium mean mortality, equilibrium mortality variation, mean mutation effects, and mutational variance (data not shown). Table 1 summarizes these qualitative results.

DISCUSSION

Fisher’s model of adaptive geometry has frequently been used to study the evolutionary importance of mutations (*e.g.*, LEIGH 1987; WAGNER and GABRIEL 1990; ORR 1998, 2006; WAXMAN 2006). In essence, Fisher’s model suggests that mutations that affect fitness become more deleterious the closer a phenotype gets to its adaptive optimum. This context-dependent behavior of mutations becomes more important as the complexity of the adaptation (the number of its component traits under selection) increases. We have applied this approach to explore the effects of mutations on mortality in age-structured populations by adding a temporal dimension to Fisher’s model. Our models show that age structure will cause distributions of mutational

TABLE 1

Age-dependent complexity changes the evolution of mortality and mutational distributions

n_x	Equilibrium mortality		Mutation accumulation	
	Mean	Variance	Mean	Variance
{10, 10, 20}	$\bar{z}_1 = \bar{z}_2 < \bar{z}_3$	$\sigma_{z_1}^2 = \sigma_{z_2}^2 < \sigma_{z_3}^2$	$\Delta\bar{z}_1 = \Delta\bar{z}_2 < \Delta\bar{z}_3$	$\Delta\sigma_{z_1}^2 = \Delta\sigma_{z_2}^2 < \Delta\sigma_{z_3}^2$
{20, 20, 10}	$\bar{z}_3 < \bar{z}_1 = \bar{z}_2$	$\sigma_{z_3}^2 < \sigma_{z_1}^2 = \sigma_{z_2}^2$	$\Delta\bar{z}_3 < \Delta\bar{z}_1 = \Delta\bar{z}_2$	$\Delta\sigma_{z_3}^2 < \Delta\sigma_{z_1}^2 = \Delta\sigma_{z_2}^2$
{10, 20, 20}	$\bar{z}_1 < \bar{z}_2 < \bar{z}_3$	$\sigma_{z_1}^2 < \sigma_{z_2}^2 < \sigma_{z_3}^2$	$\Delta\bar{z}_1 < \Delta\bar{z}_3 < \Delta\bar{z}_2$	$\Delta\sigma_{z_1}^2 < \Delta\sigma_{z_2}^2 < \Delta\sigma_{z_3}^2$
{20, 10, 10}	$\bar{z}_2 < \bar{z}_3 < \bar{z}_1$	$\sigma_{z_2}^2 < \sigma_{z_3}^2 < \sigma_{z_1}^2$	$\Delta\bar{z}_3 < \Delta\bar{z}_2 < \Delta\bar{z}_1$	$\Delta\sigma_{z_1}^2 < \Delta\sigma_{z_3}^2 < \Delta\sigma_{z_2}^2$

The qualitative results from the simulation evolution of age-specific mortality and mutation accumulation when phenotypic complexity was changed with age are shown. The rows correspond to the different treatments: complexity increases between adult age classes, $n_x = \{10, 10, 20\}$, decreases between adult age classes, $n_x = \{20, 20, 10\}$, increases between juvenile and adult age classes, $n_x = \{10, 20, 20\}$, and decreases between juvenile and adult age-classes, $n_x = \{20, 10, 10\}$. The first two columns show how the complexity treatments affect the ranking of the mean and variance of age-specific mortality at mutation–selection equilibrium. The third and fourth columns show how the mean and variance of age-specific accumulation of mutational distributions rank. The age-independent complexity simulations demonstrated the same qualitative pattern as the {10, 10, 20} treatment.

effects to become age dependent. We make qualitative predictions regarding the distributions of age-dependent mutational effects and segregating genetic effects that fit observations better than the previous population genetic models that assumed that mutational effects were age independent. Below, we discuss the consequence of age-dependent mutation upon the evolution of senescence and its impact on the distributions of mortality factors arising from mutation accumulation. We also explore in more detail how age-related changes in complexity may be evolutionarily important.

Aging decreases the likelihood that a mutation is deleterious: We explored how the age-mediated change in adaptation affects the relationships between mutational effects and age-specific survival. We have argued that age-specific fitness traits, such as survival, are adaptations that fit their environment best at earlier ages when selection is expected to most efficiently move populations toward the age-specific optima (MEDAWAR 1952; WILLIAMS 1957; HAMILTON 1966). At late age, in contrast, selection for survival is weak and mutations are relatively free to accumulate and drive the population further away from the adaptive optimum. Using Fisher's formula for finding the probability that a mutation is beneficial, we derived a simple equation that demonstrates that mutations are less likely to be detrimental as phenotypes move from an adaptive optimum (Equation 13). Since our perspective views aging as akin to lengthening the phenospacial distance from the population to the adaptive optima, this relationship suggests that the probability that a mutation is deleterious must decrease with age, provided that complexity does not decrease with age. The biological meaning of this caveat is discussed below in more detail.

Aging makes mutations less deleterious: Mutation-accumulation experiments have shown that mortality mutations tend to be more deleterious at earlier ages than at later ages in *Drosophila melanogaster* (PLETCHER *et al.* 1998, 1999; YAMPOLSKY *et al.* 2000; GONG *et al.* 2006). We have shown that this pattern could arise as a consequence of the particular funnel-shaped adaptive geometry that has likely evolved in age-structured populations. We derive a simple analytic result (Equation 19) that predicts how the expected distance of a phenotype from its adaptive optimum will tend to increase when changed by mutation. The increase in distance is positively associated with complexity and age. It follows that mutations will tend to move age-specific phenotypes further away from the optimum at early *vs.* late ages. Our simulated mutation-accumulation studies give the same qualitative results over a wide range of parameters. Specifically, the more mutations that accumulate, the weaker their expected effect will be upon age-specific survival. This gives the appearance of "diminishing returns" epistasis (CROW and KIMURA 1970) or "compensatory" epistasis, a result shared with POON and OTTO's (2000) application of Fisher's model

to study mutational meltdown in small populations and our own analytical results (Equation 19).

Aging makes mutations less variable: Mutation-accumulation experiments have shown that mutational variance for mortality accumulates more rapidly at early than at later ages in *D. melanogaster* (PLETCHER *et al.* 1998, 1999; YAMPOLSKY *et al.* 2000; GONG *et al.* 2006). We demonstrate how the adaptive geometry model predicts these findings by showing analytically that an increase in phenospacial distance, such as we might expect with aging, will cause the mutational variation to decrease (Equation 25). This prediction is supported by our simulated mutation-accumulation studies that show decreases in mutational variance with age in most parameter space. We note, however, that our simulations show that the mortality variance increased slightly with age in some parameter space (Figure 5D). A possible reason for this discrepancy is that the theory developed in Equations 14–26 assumes an absence of phenotypic variance prior to mutation. This assumption was necessary to make the effects of mutations a linear function of the number of mutations. However, when the mutational effects were large in multivariate phenospace ($\lambda = 50$, see Figure 5D), simulated populations showed large amounts of segregating variation for mortality at mutation–selection equilibrium. A more complete theory that predicted the relationship between a distribution of initial distances and mutational variance would be far more complicated because the assumption of additivity would need to be relaxed. We conclude that aging will cause age-specific mutational variance to decrease in populations without segregating variation. Large amounts of segregating variation may weaken this tendency. We also note that the results from the mutation-accumulation studies on mortality in *D. melanogaster* are reported on the natural log scale (PLETCHER *et al.* 1998, 1999; YAMPOLSKY *et al.* 2000; GONG *et al.* 2006). Because we expect mortality to increase with age, our predictions made on the untransformed scale will extend to the natural log scale as well.

Changes in trait complexity with age: Fisher's original model of adaptive evolution included a complexity term, defined as the number of orthogonal phenotypic traits that contribute to fitness. In our analysis, we imagined that complexity is the number of traits that are relevant to survival at each age. According to Fisher's model, the effective size of a mutation is proportional to the square root of complexity. If we assume that complexity declines with age, we would expect, *ceteris paribus*, that effective mutation size also declines with age. We need to consider just what is meant by complexity in the context of senescence to fully understand the implications of this result. There seem to be two perspectives on complexity in the aging literature. Some studies consider age-related changes in physiological complexity of specific organ functions. For example, some have applied complexity theory to studies of the human

heart, where physiological complexity is defined by the extent of long-range temporal correlations in the dynamics of heartbeat frequency, which follow a fractal pattern (KAPLAN *et al.* 1991; LIPSITZ and GOLDBERGER 1992). Whether such measures of complexity regularly decline with age, however, is an open and somewhat controversial question (GOLDBERGER *et al.* 2002; VAILLANCOURT and NEWELL 2002).

A second approach, and one explored more recently, is to consider complexity in the context of network structure and function. These studies may include networks defined by explicit spatial structure, like neurons in a brain, or networks whose topological properties are a product of interactions between components, but without an explicit spatial structure (*e.g.*, gene regulatory networks). In some cases, we have clear measures of age-related decline in network complexity, such as DICKSTEIN *et al.*'s (2007) work on neuronal networks in the brain. In the case of molecular networks, age-related declines in complexity are still mainly conjectural. SOTI and CSERMELY (2006) suggest that these declines arise from random molecular damage, which leads to the eventual loss of large numbers of weakly connected nodes in biological networks. Theoretical and molecular studies of networks point to a role of declining complexity to explain age-related changes in network function (DIAZ-GUILERA *et al.* 2007; SOTI and CSERMELY 2007). A recent analysis of age-related changes in gene regulatory networks in mice shows that network complexity declines quite dramatically with age (S. KIM, Stanford University, personal communication). Much empirical work is still needed to determine how and why network structure and function change with age.

Changes in complexity affect the evolution of mortality trajectories: Age-related changes in complexity may explain the dynamics of age-specific mortality observed in both natural and lab-reared populations. Classical senescence theory (HAMILTON 1966; CHARLESWORTH 1994, 2001) explains why mortality rates increase monotonically with age after the onset of reproduction. Two commonly observed phenomena in mortality dynamics are not explained by this theory, however. These are mortality deceleration that occurs late in life, where mortality rates appear to reach a plateau at late ages (CAREY *et al.* 1992; CURTSINGER *et al.* 1992; VAUPEL *et al.* 1998), and the decrease in mortality that occurs early in life (FISHER 1958; HAMILTON 1966; PROMISLOW *et al.* 1996; YAMPOLSKY *et al.* 2000).

Late-life mortality plateaus are often attributed to demographic heterogeneity (YASHIN *et al.* 1985; SERVICE 2000). That is, young individuals within a population may differ in some measure of life-long frailty, even if they all have the same rate of aging. If this measure of frailty is positively correlated within individuals across ages, then as the relatively high-frailty individuals die off early in life, the average frailty in the cohort will decline

with age. This within-cohort selection will thus lead to decelerating mortality rates late in life.

Two group-selection arguments have been proposed as alternative explanations for the early-life decrease in mortality. First, there may be selection for modifiers to quickly eliminate individuals carrying potentially lethal mutations (and so reduce long-term costs of caring for low-quality individuals) (FISHER 1958; HAMILTON 1966). A new offspring can quickly replace a previous one that had a lethal mutation. Second, extended offspring care by parents or other relatives can shift the intensity of selection toward later ages, away from early-age care-dependent offspring (HAWKES 2003; LEE 2003).

Our results suggest that decreases in complexity early in life can cause patterns of age-specific mortality that mimic the early life mortality declines observed in real populations. Differential intensities of selection for survival cannot account for changes in complexity at prereproductive ages. A different process may lead to age-mediated complexity declines in juveniles. Relaxed mutational pressure, such as predicted by reduced phenotypic complexity, may provide one such mechanism. During early life, when genetic pathways that regulate development are active, survival may simply be determined by more genetic factors than at reproductive maturity. Certainly maternal effects are important in early life (RAUTER and MOORE 2002; BARKER *et al.* 2005). Here the influence of a second genome (the mother's) likely makes juvenile survival a more complex genetic trait. This is even more likely if intergenomic epistasis (WADE 1998) is important.

PLETCHER *et al.* (1998) suggest that the narrowing of mutational targets with age may explain the age-related decline in the effects of mutation on mortality observed in their mutation-accumulation experiment. In this scenario, mutations that affect late-age mortality arise less frequently than those that affect early-age mortality because there are fewer targets available for mutagenesis. One way this might happen is if relaxed selection and random genetic drift allowed relatively more inactivation of loci important to late-age survival. If we take the perspective that gene products are traits, then this model has at least two relevant implications to our model. First, it suggests that age-related declines in complexity evolve in concert with senescence (n decreases with age). Second, phenotypically relevant mutations are less likely to occur with greater age because there are fewer functional genes that are available to mutate (u decreases with age). The latter aspect alone is consistent with the reductions in the mean and variance of mutational effects with age observed in mutation-accumulation studies. This age-related change in u might also help explain late-age mortality deceleration. However, it cannot explain prereproductive mortality changes because age-specific purifying selection against deleterious mutational load is constant until reproductive maturity.

Decreased complexity with age is adequate to explain these patterns. Our model tells us that age-related reductions in complexity will exacerbate the age-related widening of the funnel. This can have dramatic effects on the age-specific consequences of *de novo* mutations. Our simulations that include age-related declines in complexity provide an intriguing fit to observed demographic patterns of mortality. Specifically, the simulations show an initial decline in age-specific mortality of prereproductive age classes, rapid increases in early adulthood, and then late-life mortality deceleration. However, our model makes no predictions about whether complexity changes with age in nature. Our models point to the need for empirical research to determine (a) evolutionarily meaningful measures of phenotypic complexity, (b) how this complexity changes with age, and (c) the degree to which any changes in complexity influence the phenotypic consequences of deleterious mutations in nature and, subsequently, the evolutionary trajectory of senescence.

Conclusions: Experiments that measure the temporal distribution of mutational effects are seldom performed, yet they are powerful tools for understanding the evolution of senescence because they offer us a direct means with which to evaluate the age-specific behavior of a critical determinant of the evolutionary mechanisms of senescence. Classical quantitative genetic approaches, in contrast, inform us about the age-specific distribution of genetic effects that are segregating in populations that are assumed to be near mutation-selection equilibria. The latter are useful for understanding past adaptation only as long as the predictive population genetic models are valid. The appropriateness of these models follows from their assumptions, which are best tested by direct measurements of mutation effects over many ages. Newer quantitative genetic approaches, such as microarrays, could be applied to examine changes in patterns of coregulation with age. Furthermore, they could be used to compare control and mutation-accumulation lines to explore age-related changes in network complexity (see RIFKIN *et al.* 2005).

Evolutionary theories of senescence focus largely upon the intricate relationship between age structure and selection. All population genetic models of aging assume that the distributions of mutational effects upon fitness effects are age independent. We might expect that this is a reasonable assumption in the absence of real data, as we have no *a priori* reason to suspect that age might have an effect upon the severity of mutations. However, mutation-accumulation experiments challenge this assumption, revealing that mutations become less deleterious and less variable with age. Because evolutionary theories of aging have assumed that the distribution of mutational effects is age independent (HAMILTON 1966; CHARLESWORTH 1994, 2001), our findings cast doubt upon the quantitative conclusions that follow from these. In particular, population genetic

models might overestimate the decline in physiological function at old age. We have shown here that a rudimentary application of Fisher's model of adaptive geometry predicts distributions of mutations that are consistent with observations from mutation-accumulation studies. Furthermore, it provides relatively parsimonious explanations for why juvenile mortality is greater and late-age mortality lower than predicted by classical theory.

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LITERATURE CITED

- BARKER, M. S., J. P. DEMUTH and M. J. WADE, 2005 Maternal expression relaxes constraint on innovation of the anterior determinant, bicoid. *PLoS Genet.* **1**: e57.
- BAUDISCH, A., 2005 Hamilton's indicators of the force of selection. *Proc. Natl. Acad. Sci. USA* **102**: 8263–8268.
- CAREY, J. R., P. LIEDO, D. OROZCO and J. W. VAUPEL, 1992 Slowing of mortality rates at older ages in large medfly cohorts. *Science* **258**: 457–461.
- CHARLESWORTH, B., 1994 *Evolution in Age-Structured Populations*. Cambridge University Press, Cambridge, UK.
- CHARLESWORTH, B., 2001 Patterns of age-specific means and genetic variances of mortality rates predicted by the mutation-accumulation theory of ageing. *J. Theor. Biol.* **210**: 47–65.
- CHARLESWORTH, B., and K. A. HUGHES, 1996 Age-specific inbreeding depression and components of genetic variance in relation to the evolution of senescence. *Proc. Natl. Acad. Sci. USA* **93**: 6140–6145.
- CROW, J. F., and M. KIMURA, 1970 *An Introduction to Population Genetic Theory*. Alpha Editions, Edina, MN.
- CURTSINGER, J. W., H. H. FUKUI, D. R. TOWNSEND and J. W. VAUPEL, 1992 Demography of genotypes: failure of the limited life-span paradigm in *Drosophila melanogaster*. *Science* **258**: 461–463.
- DIAZ-GUILERA, A., A. A. MOREIRA, L. GUZMAN and L. A. N. AMARAL, 2007 Complex fluctuations and robustness in stylized signalling networks. *J. Stat. Mech. Theor. Exp.* **1**: 1–19.
- DICKSTEIN, D. L., D. KABASO, A. B. ROCHER, J. I. LUEBKE, S. L. WEARNE *et al.*, 2007 Changes in the structural complexity of the aged brain. *Aging Cell* **6**: 275–284.
- FISHER, R. A., 1958 *The Genetical Theory of Natural Selection*. Oxford University Press, Oxford.
- GOLDBERGER, A. L., C. K. PENG and L. A. LIPSITZ, 2002 What is physiologic complexity and how does it change with aging and disease? *Neurobiol. Aging* **23**: 23–26.
- GONG, Y., J. N. THOMPSON, JR. and R. C. WOODRUFF, 2006 Effect of deleterious mutations on life span in *Drosophila melanogaster*. *J. Gerontol. A Biol. Sci. Med. Sci.* **61**: 1246–1252.
- HAAG-LIAUTARD, C., M. DORRIS, X. MASIDE, S. MACASKILL, D. L. HALLIGAN *et al.*, 2007 Direct estimation of per nucleotide and genomic deleterious mutation rates in *Drosophila*. *Nature* **445**: 82–85.
- HAMILTON, W. D., 1966 Moulding of senescence by natural selection. *J. Theor. Biol.* **12**: 12–45.
- HARTL, D. L., and C. H. TAUBES, 1996 Compensatory nearly neutral mutations: selection without adaptation. *J. Theor. Biol.* **182**: 303–309.
- HAWKES, K., 2003 Grandmothers and the evolution of human longevity. *Am. J. Hum. Biol.* **15**: 380–400.
- HUGHES, K. A., and B. CHARLESWORTH, 1994 A genetic analysis of senescence in *Drosophila*. *Nature* **367**: 64–66.
- KAPLAN, D. T., M. I. FURMAN, S. M. PINCUS, S. M. RYAN, L. A. LIPSITZ *et al.*, 1991 Aging and the complexity of cardiovascular dynamics. *Biophys. J.* **59**: 945–949.

- KEIGHTLEY, P. D., 1994 The distribution of mutation effects on viability in *Drosophila melanogaster*. *Genetics* **138**: 1315–1322.
- KIMURA, M., 1983 *The Neutral Theory of Molecular Evolution*. Cambridge University press, Cambridge, UK.
- KONDRASHOV, A. S., 1988 Deleterious mutations and the evolution of sexual reproduction. *Nature* **336**: 435–440.
- LANDE, R., 1982 A quantitative genetic theory of life-history evolution. *Ecology* **63**: 607–615.
- LEE, R. D., 2003 Rethinking the evolutionary theory of aging: transfers, not births, shape senescence in social species. *Proc. Natl. Acad. Sci. USA* **100**: 9637–9642.
- LEIGH, E. G., 1987 Ronald Fisher and the development of evolutionary theory. II. Influence of new variation on evolutionary process, pp. 213–263 in *Oxford Surveys in Evolutionary Biology*, edited by P. H. HARVEY and L. PARTRIDGE. Oxford University Press, Oxford.
- LEIPS, J., and T. F. MACKAY, 2000 Quantitative trait loci for life span in *Drosophila melanogaster*: interactions with genetic background and larval density. *Genetics* **155**: 1773–1788.
- LIPSITZ, L. A., and A. L. GOLDBERGER, 1992 Loss of complexity and aging—potential applications of fractals and chaos theory to senescence. *J. Am. Med. Assoc.* **267**: 1806–1809.
- LYNCH, M., J. CONERY and R. BURGER, 1995 Mutation accumulation and the extinction of small populations. *Am. Nat.* **146**: 489–518.
- MARTIN, G., and T. LENORMAND, 2006 The fitness effect of mutations across environments: a survey in light of fitness landscape models. *Evolution* **60**: 2413–2427.
- MEDAWAR, P. B., 1946 Old age and natural death. *Mod. Q.* **1**: 30–56.
- MEDAWAR, P. B., 1952 *An Unsolved Problem of Biology*. H. K. Lewis, London.
- MULLER, H. A., 1932 Some genetic aspects of sex. *Am. Nat.* **66**: 118–138.
- MUKAI, T., 1969 The genetic structure of natural populations of *Drosophila melanogaster*. VII. Synergistic interaction of spontaneous mutant polygenes controlling viability. *Genetics* **61**: 749–761.
- NUZHDIIN, S. V., E. G. PASYUKOVA, C. L. DILDA, Z. B. ZENG and T. F. MACKAY, 1997 Sex-specific quantitative trait loci affecting longevity in *Drosophila melanogaster*. *Proc. Natl. Acad. Sci. USA* **94**: 9734–9739.
- ORR, H. A., 1998 The population genetics of adaptation: the distribution of factors fixed during adaptive evolution. *Evolution* **52**: 935–949.
- ORR, H. A., 2000 Adaptation and the cost of complexity. *Evolution* **54**: 13–20.
- ORR, H. A., 2006 The distribution of fitness effects among beneficial mutations in Fisher's geometric model of adaptation. *J. Theor. Biol.* **238**: 279–285.
- PLETCHER, S. D., D. HOULE and J. W. CURTSINGER, 1998 Age-specific properties of spontaneous mutations affecting mortality in *Drosophila melanogaster*. *Genetics* **148**: 287–303.
- PLETCHER, S. D., D. HOULE and J. W. CURTSINGER, 1999 The evolution of age-specific mortality rates in *Drosophila melanogaster*: genetic divergence among unselected lines. *Genetics* **153**: 813–823.
- POON, A., and S. P. OTTO, 2000 Compensating for our load of mutations: freezing the meltdown of small populations. *Evolution* **54**: 1467–1479.
- PROMISLOW, D. E. L., M. TATAR, A. KHAZALI and J. W. CURTSINGER, 1996 Age-specific patterns of genetic variance in *Drosophila melanogaster*. I. Mortality. *Genetics* **143**: 839–848.
- R DEVELOPMENT CORE TEAM, 2007 *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna.
- RAUTER, C. M., and A. J. MOORE, 2002 Quantitative genetics of growth and development time in the burying beetle *Nicrophorus pustulatus* in the presence and absence of post-hatching parental care. *Evolution* **56**: 96–110.
- RICE, S., 1990 A geometric model for the evolution of development. *J. Theor. Biol.* **143**: 319–342.
- RIFKIN, S. A., D. HOULE, J. KIM and K. P. WHITE, 2005 A mutation accumulation assay reveals a broad capacity for rapid evolution of gene expression. *Nature* **438**: 220–223.
- ROSE, M. R., 1982 Antagonistic pleiotropy, dominance, and genetic variation. *Heredity* **48**: 63–78.
- SERVICE, P. M., 2000 Heterogeneity in individual mortality risk and its importance for evolutionary studies of senescence. *Am. Nat.* **156**: 1–13.
- SHAW, F. H., D. E. PROMISLOW, M. TATAR, K. A. HUGHES and C. J. GEYER, 1999 Toward reconciling inferences concerning genetic variation in senescence in *Drosophila melanogaster*. *Genetics* **152**: 553–566.
- SNOKE, M. S., and D. E. PROMISLOW, 2003 Quantitative genetic tests of recent senescence theory: age-specific mortality and male fertility in *Drosophila melanogaster*. *Heredity* **91**: 546–556.
- SOTI, C., and P. CSERMELY, 2007 Aging cellular networks: chaperones as major participants. *Exp. Gerontol.* **42**: 113–119.
- TATAR, M., D. E. L. PROMISLOW, A. A. KHAZALI and J. W. CURTSINGER, 1996 Age-specific patterns of genetic variance in *Drosophila melanogaster*. 2. Fecundity and its genetic covariance with age-specific mortality. *Genetics* **143**: 849–858.
- VAILLANCOURT, D. E., and K. M. NEWELL, 2002 Complexity in aging and disease: response to commentaries. *Neurobiol. Aging* **23**: 27–29.
- VAUPEL, J. W., J. R. CAREY, K. CHRISTENSEN, T. E. JOHNSON, A. I. YASHIN *et al.*, 1998 Biodemographic trajectories of longevity. *Science* **280**: 855–860.
- WADE, M. J., 1998 The evolutionary genetics of maternal effects, pp. 5–21 in *Maternal Effects as Adaptations*, edited by T. A. MOUSSEAU and C. W. FOX. Oxford University Press, Oxford.
- WAGNER, G. P., and W. GABRIEL, 1990 Quantitative variation in finite parthenogenetic populations—what stops Muller's ratchet in the absence of recombination. *Evolution* **44**: 715–731.
- WAXMAN, D., 2006 Fisher's geometrical model of evolutionary adaptation—beyond spherical geometry. *J. Theor. Biol.* **241**: 887–895.
- WILLIAMS, G. C., 1957 Pleiotropy, natural selection, and the evolution of senescence. *Evolution* **11**: 398–411.
- YAMPOLSKY, L. Y., L. E. PEARSE and D. E. L. PROMISLOW, 2000 Age-specific effects of novel mutations in *Drosophila melanogaster*—I. Mortality. *Genetica* **110**: 11–29.
- YASHIN, A. I., K. G. MANTON and J. W. VAUPEL, 1985 Mortality and aging in a heterogeneous population: a stochastic process model with observed and unobserved variables. *Theor. Popul. Biol.* **27**: 154–175.

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