UC Irvine

UC Irvine Previously Published Works

Title

The great evolutionary divide: two genomic systems biologies of aging.

Permalink

<https://escholarship.org/uc/item/5k02n871>

Journal

Interdisciplinary topics in gerontology, 40

ISSN

0074-1132

Authors

Rose, Michael R
Cabral, Larry G
Philips, Mark A
[et al.](#)

Publication Date

2015

DOI

10.1159/000364930

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

The Great Evolutionary Divide: Two Genomic Systems Biologies of Aging

Michael R. Rose • Larry G. Cabral • Mark A. Philips • Grant A. Rutledge •
Kevin H. Phung • Laurence D. Mueller • Lee F. Greer

Department of Ecology and Evolutionary Biology, University of California, Irvine, Calif., USA

Abstract

There is not one systems biology of aging, but two. Though aging can evolve in either sexual or asexual species when there is asymmetric reproduction, the evolutionary genetics of aging in species with frequent sexual recombination are quite different from those arising when sex is rare or absent. When recombination is rare, selection is expected to act chiefly on rare large-effect mutations, which purge genetic variation due to genome-wide hitchhiking. In such species, the systems biology of aging can focus on the effects of large-effect mutants, transgenics, and combinations of such genetic manipulations. By contrast, sexually outbreeding species maintain abundant genetic polymorphism within populations. In such species, the systems biology of aging can examine the genome-wide effects of selection and genetic drift on the numerous polymorphic loci that respond to laboratory selection for different patterns of aging. An important question of medical relevance is to what extent insights derived from the systems biology of aging in model species can be applied to human aging.

© 2015 S. Karger AG, Basel

With the advent of whole-genome DNA sequencing and other genomic technologies, biology is now revealing much about the genetic foundations of life that were once obscure. Here, we discuss the relevance of some of these early genomic findings for the systems biology of aging, as well as the design and interpretation of experimental research on aging.

We structure our discussion of these issues in terms of two distinct kinds of population genetic systems: largely asexual reproduction or sexual reproduction with limited outcrossing (system 1), and sexual reproduction with consistent outbreeding (system 2). These two systems have very different consequences for genomes, particularly the relationship between genetic variation and organismal function, includ-

ing aging. Their differing patterns of genetic variation and adaptation produce striking differences in the relationship between genetic variation and aging, with profound consequences for the theoretical explanation and experimental analysis of the genomic foundations for the systems biology of aging.

Rarely Sexual Evolutionary Genetics: Theoretical Expectations for Aging Genomics

Complete asexuality is evolutionarily exceptional. The prokaryotes, for example, may lack frequent mendelian recombination, but nonetheless have parasexual mechanisms of recombination: conjugation, transduction, and transformation. Such parasexual genetic exchange can be largely or wholly removed from laboratory evolution paradigms that use well-understood prokaryotes such as *Escherichia coli* [1]. But in nature, parasexuality doubtless occurs with enough frequency to produce novel genotypes at a greater frequency than mutation within clonal lineages can achieve. Early work showed that bacterial genetic diversity is higher than previously thought, suggesting infectious transfer of genes brings in new genetic variants which are not necessarily purged by directional selection [2]. Indeed, when there is frequency-dependent selection as well as transposable, phage, and plasmid elements, even bacterial populations can maintain significant genetic variation [3].

However, if parasexuality introduces new genetic variation into a population at a sufficiently low rate, then it is roughly like mutation with respect to its impact on functional genetics. That is, if mendelian segregation and recombination among variant alleles do not usually occur in each generation, then conventional theory for clonal selection can address the evolutionary effects of the favorable genetic variants by genetic exchange which is sufficiently rare. Note that this does *not* mean that the genomics of non-mendelian populations would not be significantly different with parasexual genetic exchange. Compared to wholly asexual populations, there should be more genetic variation within parasexual or infrequently outcrossing sexual populations. But if we assume that beneficial genetic variation is only introduced rarely by parasexual recombination or amphimixis, then the low frequency at which genetic variation is introduced over time gives rise to an evolutionary process of adaptation mathematically comparable to that of adaptation sustained by rare favorable mutations subject to clonal selection.

Thus, it is reasonable to examine the scenarios for adaptation and for aging that arise with this evolutionary genetic 'system 1' in terms of the formal theory and experimental findings already available for asexual systems with intermittent favorable mutations. The theory of such evolutionary systems is relatively powerful [4]. Small-effect beneficial variants will often be lost because of genetic drift effects near the fixation boundary, as they will in mendelian populations. Large-effect beneficial variants are much more likely to escape from such sampling effects and sweep to fixation, purging genetic variation along the way due to a genome-wide, rather than local,

hitchhiking effect [cf. 5]. Thus, the process of adaptation itself will tend to purge genetic variation from such systems, genome-wide. The chief exceptions to this genomic purging arise in cases where selection is frequency-dependent, such as arises with micro-niche partitioning among genotypes [e.g. 6]. It is unclear how often such frequency-dependent balancing selection leads to the maintenance of genetic variation in asexual or parasexual populations in nature [but see 3].

The effects of this evolutionary genetic system 1 on the genomics of aging can be interpreted in terms of standard hamiltonian theory for age-specific selection [7, 8]. If there is strictly symmetrical division of the organism during reproduction, then aging is not expected to evolve. It is important to note that the common asexual reproductive system of fission does not ensure such strict symmetry. In both bacteria and eukaryotes, cytologically asymmetrical fission is well known to allow the evolution of aging [9]. Even when cytological asymmetry is not obvious, bacteria like *E. coli* nevertheless have asymmetrical partitioning of waste products after fission, which can lead to the evolution of aging [10]. Nonetheless, under good conditions strictly fissile single-cell species like *Schizosaccharomyces pombe* are known to be free of aging [11], as are *Hydra* kept under good conditions [12], as expected by hamiltonian theory [7–9].

But when there is sufficient asymmetry between products of asexual reproduction, the problem of declining age-specific forces of natural selection is expected to always lead to the evolution of aging in hamiltonian evolutionary theory [7–9]. Dissent from this view has been offered [13], but numerical simulations of asexual evolution suggest that such alternative theory for the evolution of aging in age-structured populations is incorrect [8]. Only the formalism of Hamilton has been shown to be intimately tied with fitness in an age-structured population under some well-defined conditions [8, 14]. No such connection has been made for alternative non-hamiltonian analyses [13].

At the genomic level, mutations with solely deleterious effects at later ages might drift to fixation, a process commonly called mutation accumulation [8, 9, 14]. But because of the intermittent purging of genetic variation by selective sweeps, such drift effects are particularly unlikely for asexual systems. A more likely genetic mechanism for the evolution of aging in asexual species is antagonistic pleiotropy [8, 9, 14, 15], in which mutations that have early life benefits sweep to fixation despite deleterious later-life effects, because the latter will have little effect on fitness compared to the former.

There are some significant issues that arise with evolutionary genomic system 1 for aging which are too often neglected: genotype-by-environment interaction (‘GxE’), rate of approach to evolutionary equilibrium, and age-independent beneficial substitutions. Furthermore, these issues potentially interact with each other. Both adaptation and aging are environment specific, thanks to GxE. That is, a mutant that is beneficial in one environment can be deleterious in another environment. This is well understood for adaptation in evolutionary research, but less appreciated for aging, even though aging is nothing more or less than age-dependent loss of adaptation.

When mutants have beneficial effects that are age-independent, they foster the evolution of indefinitely sustained survival and reproduction, producing the phenomenon of post-aging plateaus after the cessation of aging [8]. But such evolutionary effects are dependent on the number of generations that a population has spent in a particular environment. The approach to mutation-selection equilibrium in asexual populations decelerates over evolutionary time, with some evidence of continuing adaptation as late in evolution as 50,000 generations [16], despite assiduous maintenance of a stable culture regime. This means that asexual populations with age structure will be subject to a protracted process of adaptation with later ages particularly subject to a lack of beneficial effects, which produces aging.

Rarely Sexual Evolutionary Genetics: Implications for the Systems Biology of Aging

The forgoing general theoretical and experimental points have great salience for the design and interpretation of gerontological systems biology research using rarely outcrossing species like *Saccharomyces cerevisiae* and *Caenorhabditis elegans*. In these species, longevity mutants can be isolated by random mutational screens or by screening extant mutant stocks isolated for other purposes. It is not difficult to find mutants with greatly increased longevity in rarely outcrossing species [e.g. 17]. There are several evolutionary genetic mechanisms by which such increased longevity can arise.

First, since these longevity mutants are not generally isolated from asexual stocks that have long adapted to laboratory conditions, unlike those of Lenski [16], they may be mutants that enhance survival and reproduction generally in the evolutionarily novel environment supplied in a particular laboratory. In effect, then, these mutants may be generally beneficial in the specific lab environments in which they are screened. That is, they are broadly adaptive. As such, they are not specifically ‘aging mutants’, even if they increase longevity. There is nothing wrong with the careful study of such genetic mechanisms of adaptation, so long as the experimenters doing so understand that they are studying the genomic foundations of adaptation in general, not something that is notably specific to aging. Evolutionary biologists welcome new recruits to the study of the evolutionary genetics of adaptation, particularly when those new recruits are aware of the strong evolutionary theory that pertains to adaptation.

Second, other longevity mutants might involve cases of striking antagonistic pleiotropy, in which early reproduction or competitive ability are sacrificed in the mutant in exchange for a striking gain in adult longevity, at least in the particular laboratory environment employed by the experimenter. Van Voorhies et al. [18] have argued that this is the case for a number of *C. elegans* longevity mutants. However, the ability to obtain such antagonistic pleiotropy mutants does not demonstrate that aging evolved in such species specifically because of the ‘wild-type’ sequences that have been altered in these longevity mutants.

Evolutionary Genetics of Outcrossing Mendelian Populations: General Genomic Findings

Over the last 30 years, research on the evolutionary genetics of mendelian populations that usually outbreed has been dominated by a 'neoclassical' consensus. Classical evolutionary genetic theory presumed there was very little segregating mendelian variation [19], with rare beneficial mutations that sweep through the genomes of such populations providing the foundation of adaptation. With the discovery of massive genetic variation in outbred mendelian populations beginning in the late 1960s, classical theory was replaced by a neoclassical variant with the following assumptions: (a) a great deal of strictly neutral genetic variation evolves by genetic drift; (b) deleterious genetic variation arises by mutation but is kept at a low frequency by purifying selection, and (c) rare beneficial mutations arise and sweep to fixation [20]. Like the classical theory of evolutionary genetics, neoclassical theories imply that there will be very little segregating genetic variation genome-wide that can readily respond evolutionarily to novel forms of selection. Instead, rare beneficial mutations of large effect are expected to dominate the process of adaptation in outbred mendelian populations, as they are supposed to in the evolution of strictly asexual populations [1].

Long opposed to both classical and neoclassical theories, balance and neobalance theories for evolutionary genetics have hypothesized that there is abundant genetic variation affecting components of fitness. The difference between balance and neobalance theories is analogous to the difference between classical and neoclassical theories. Like neoclassical theory, present-day neobalance theory adds to traditional balance theory the possibility that there is a significant amount of neutral or weakly deleterious genetic variation across the genome. The key difference is that neobalance theory supposes that balancing mechanisms of selection, such as frequency-dependent selection and antagonistic pleiotropy, frequently allow the maintenance of functional genetic variants at high frequencies. Such abundant functional genetic variation is then expected to allow immediate responses to selection at many sites across the genome.

Recent experimental studies of the genome-wide response to selection in laboratory mendelian populations suggest that the neobalance theory has much more validity than has been supposed heretofore. For example, Burke et al. [21] found numerous sites in the genome that respond strikingly to selection for earlier reproduction and faster aging in *Drosophila melanogaster*. Our recent unpublished research has found even more numerous sites in the *Drosophila* genome that respond to selection on aging, thanks to superior replication to that of earlier studies of the genomics of the response to selection in mendelian populations. Thus, there can be a very large number of sites in the genome of a sexual species that respond to selection, implicating the action of widespread balancing selection which sustains functional genetic diversity in outbred populations of species like those of *Drosophila*.

Evolutionary Genetics of Outcrossing Mendelian Populations: Implications for Their Systems Biology of Aging

From a hamiltonian standpoint, aging is the decline in age-specific adaptation due to the declining forces of natural selection, as illustrated by, among other things, the cessation of aging after these forces stop declining [8]. But the genomic machinery that underlies this decline in age-specific adaptation is evidently very different between largely asexual and sexual species, if the neobalance view of the evolutionary genetics of outbred sexual species is correct. If the neoclassical view is correct, there is *no* such differentiation between the genomics of aging in asexual and sexual species: aging in both would depend primarily on selective sweeps of alleles with antagonistic pleiotropic effects that force aging as a price of improved adaptation at earlier ages. The neoclassical theory chiefly has different implications for outbred mendelian populations compared to rarely sexual species with respect to mutation accumulation, because the purging of genetic variation that occurs with selective sweeps is expected to be localized across the genome in outbred species, rather than global [5, 20]. Our view, however, is that this neoclassical view of the evolution of aging in sexual populations is unlikely to be correct, given the observed genomics of the evolution of aging in *Drosophila* [21].

There is thus a clear divide in the genomic underpinnings of aging between largely asexual species and outbreeding mendelian species, a division of great significance for the systems biology of aging. In particular, the kinds of mutants that are generated by mutagenesis and then identified in screens for increased life span do not generally correspond to those identified by us when resequencing outbred laboratory-evolved *D. melanogaster* populations with increased longevity.

This type of finding is apparently not confined to aging research. The prosaic but much studied character of *Drosophila* bristle number likewise shows little correspondence between loci identified by mutagenesis and those identified from studies of genetic variation in wild populations [e.g. 22]. Thus, the functional genomics of outbred system 2 populations are not expected to correspond to the genetics of large-effect mutants on theoretical grounds, and they do not appear to correspond so far in studies of *Drosophila* where a direct comparison can be made. Naturally, this conclusion can only be offered for *Drosophila* at this point, but the history of genetics suggests that many *Drosophila* findings are likely to generalize.

The Two Kinds of Evolutionary Genomics and the Systems Biology of Aging

Systems Biology of Aging in Largely Asexual or Inbred Populations

Considered in, of, and for themselves, evolutionary genetic system 1 species like *E. coli* or *S. cerevisiae* can be usefully studied using large-effect mutants, as shown in figure 1.

Fig. 1. In largely asexual or inbred species, the systems biology of aging is appropriately analyzed using large-effect mutants, transgenics, etc. This research focus arises naturally from the way aging evolves in such species. In the figure, genetic strains of little heterozygosity are indicated by thin lines, with the different types of genetic manipulation indicated by different line fonts.

It is exactly such large-effect mutations which will be important determinants of the evolution of aging in such species, because when they are sufficiently beneficial for fitness they will sweep rapidly toward fixation, purging genetic variation across the rest of the genome. Once they have swept through a population from a largely asexual species, such substitution will change the activity of at least some, and potentially many, gene products from elsewhere in the genome. Such effects on gene activity should be identifiable from gene expression assays, from microarray characterization of translated proteins or from genome-wide transcriptomic assays. Furthermore, such substitutions could then pave the way for further, now beneficial, epistatic substitutions elsewhere in the genome. And such epistatic combinations of substitutions could likewise be studied usefully, whether by direct genetic manipulation or experimental evolution [23].

From data concerning both mutants and the alleles fixed by selective sweeps, including gene expression and other downstream phenotypic effects, it should be possible to build a systems biological model for how some large-effect DNA sequence changes work their way through complex molecular networks to produce specific patterns of adaptation and aging in inbreeding or asexual organisms. In particular, the specific details of the antagonistic pleiotropy likely to be involved in natural selection against most longevity mutants would be a natural theme of such research, as well as any genotype-by-environment dependence in the appearance and disappearance of such effects [see 18]. Overall, this seems like an eminently feasible research project.

Significant challenges face the systems biology of aging in outcrossing mendelian species. Many of these challenges have already arisen in the study of chronic diseases in human GWAS research. It has proven very difficult to identify the majority of specific SNP changes that are responsible for the heritability of such chronic disorders as type 2 diabetes, Crohn's disease, or Alzheimer's disease, although the impact of ApoE and ACE variants on longevity stands out as a notable exception [24]. But the total amount of genetic variation for longevity that is explained by such loci is very small.

As we have already argued in more general terms [25], experimental evolutionary genomics offers a powerful way to begin developing a systems biology for aging in outbreeding mendelian species. Since there are many sites in the genome with sequence variation that affect aging, such variation can be teased out using experimental evolution with resequencing. Experimental evolution can readily change the rate of aging, and even the age of onset of late-life aging plateaus [8–9]. With enough replication of selection lines and enough generations of selection, it is possible to probe the entire genomes of organisms like *D. melanogaster* for the genomic sites that affect aging [cf. 21]. Furthermore, it is then straightforward to use orthology to identify corresponding loci in other outbred mendelian species that affect aging or chronic disease in those species. Figure 2 provides a schematic for this research strategy.

In this sense, the systems biology of aging is easier to probe genome-wide in outbred mendelian populations than it is in inbred or asexual species. It requires much less experimental effort to rapidly screen entire genomes to find a large number of genomic regions that are involved in the response to selection for different patterns of aging. However, recently Tenaillon et al. [23] have shown that very large-scale experimental evolution in asexual populations can come up with comparable genome-wide screening. In their case, they applied high-temperature selection to more than 100 distinct populations for 2,000 generations. By resequencing samples from this huge collection of populations after selection, they were able to identify genomic regions that were repeatedly subject to sequence change as a result of their specific selection protocol. But sustaining longevity or later-life fertility selection among some hundred or more clonal lines over thousands of generations seems like a prohibitively difficult task.

In any case, we already know that this strategy of genomic-site identification works in studies of the experimental evolution of aging in outbred mendelian populations with much less replication [21]. The question is then what to do with information about the many genomic sites that evidently play a role in the system 2 genetics of aging, with respect to the systems biology of aging.

An obvious next step is the use of genome-wide gene expression assays of populations with different patterns of aging over a range of different ages and different environments in order to infer the regulatory interconnections across the numerous sites in the genome. For further resolution, tissue-specific gene expression could also be used, particularly in conjunction with the kind of functional physiological differ-

Fig. 2. Experimental evolution readily shifts patterns of aging when Hamilton's forces of natural selection have their declining phases shifted by changing the time at which outbred sexual laboratory populations are cultured [8]. Such populations are differentiated at many sites across the genome [21]. The systems biological analysis of aging in such settings needs to proceed along very different lines from that which is appropriate for asexual or inbred species.

entiation associated with the evolution of aging in *Drosophila*. Then there is the possibility of metabolomic analysis of whole organisms and specific tissues or organs. Such downstream genomic and functional data would naturally be extremely complex, requiring advanced machine learning software to parse. Any viable systems biological model for aging obtained by this experimental methodology would naturally be extremely complex in turn, a model that would be opaque to human intuition at the detailed level. Nonetheless, it is possible to parse even very complex numerical models using well-developed bioinformatics tools like sensitivity analysis, in which model parameters are systematically varied in simulations for their quantitative impact on model predictions.

This in turn raises the question of how to test such a systems biological model. In our laboratory, we have a number of populations of *D. melanogaster* that have evolved a wide range of differences in DNA sequence, gene expression, and downstream phenotypes. If we were to assemble a systems biological model for aging based on genome-wide changes in sequence and gene expression among a subset of our populations, then we could test the validity of the analysis of such a model by determining whether corresponding variation in populations that were *not* used to construct the initial systems biology model nonetheless shows the predicted patterns of parametric sensitivity.

Application to the Systems Biology of Aging in Humans

Many scientists who work on aging are chiefly interested in patterns of aging in the particular taxonomic group(s) that they study, but most people are more interested in the application of such research to the biomedical problem of aging, as illustrated by the articulate declamations of figures like Aubrey de Grey.

Thus, the question of applying systems biological insights into the genomics of aging among model organisms to the human case is a natural concern. Surprisingly, a large fraction of the loci identified as relevant to aging in *D. melanogaster* have orthologs in the human genome, and some of those loci in turn have been associated with human chronic disease, particularly when human GWAS databases are probed in light of genomic results [26]. Likewise, the various longevity loci identified in studies of largely asexual species can be tested for their relevance to human genomic databases for aging-associated diseases and disorders.

In the end, the question of the medical merit of the systems biology of aging in model species for human aging is empirically answerable with orthology. We are already confident that genomic data from similarly outbreeding mendelian species are, at a minimum, relevant to *understanding* the systems biology of aging in our species, but it has not yet been determined how useful such understanding will be for developing interventions that might *ameliorate* human aging.

Acknowledgements

We thank Jennifer E. Briner for her careful reading and editing of the manuscript.

References

- 1 Lenski RE, Rose MR, Simpson SC, Tadler SC: Long-term experimental evolution in *Escherichia coli*. I. Adaptation and divergence during 2,000 generations. *Am Nat* 1991;138:1315–1341.
- 2 Levin BR: Periodic selection, infectious gene exchange and the genetic structure of *E. coli* populations. *Genetics* 1981;99:1–23.
- 3 Levin BR: Frequency-dependent selection in bacterial populations. *Philos Trans R Soc Lond B Biol Sci* 1988;319:459–472.
- 4 Nagylaki T: Introduction to Theoretical Population Genetics. Berlin, Springer, 1992.
- 5 Maynard Smith J, Haigh J: The hitch-hiking effect of a favourable gene. *Genet Res* 1974;23:23–35.
- 6 Rainey PB, Travisano M: Adaptive radiation in a heterogeneous environment. *Nature* 1998;394:69–72.
- 7 Hamilton WD: The moulding of senescence by natural selection. *J Theor Biol* 1966;12:12–45.
- 8 Mueller LD, Rauser CL, Rose MR: Does Aging Stop? New York, Oxford University Press, 2011.
- 9 Rose MR: Evolutionary Biology of Aging. New York, Oxford University Press, 1991.
- 10 Lindner AB, Madden R, Demarez A, Stewart EJ, Taddei F: Asymmetric segregation of protein aggregates is associated with cellular aging and rejuvenation. *PNAS* 2008;105:3076–3081.
- 11 Coelho M, Dereli A, Haese A, Kühn S, Malinowska L, Desantis ME, Shorter J, Alberti S, Gross T, Tolić-Nørrelykke IM: Fission yeast does not age under favorable conditions, but does so after stress. *Curr Biol* 2013;23:1844–1852.
- 12 Martinez DE: Mortality patterns suggest lack of senescence in hydra. *Exp Gerontol* 1998;33:217–225.
- 13 Baudisch A: Hamilton's indicators of the force of selection. *PNAS* 2005;102:8263–8268.

- 14 Charlesworth B: Evolution in Age-Structured Populations. New York, Cambridge University Press, 1980.
- 15 Rose MR: Life-history evolution with antagonistic pleiotropy and overlapping generations. *Theor Pop Biol* 1985;28:342–358.
- 16 Lenski RE: Evolution in action: a 50,000-generation salute to Charles Darwin. *Microbe* 2011;6:30–33.
- 17 Klass MR: A method for the isolation of longevity mutants in the nematode *Caenorhabditis elegans* and initial results. *Mech Ageing Dev* 1983;22:279–286.
- 18 Van Voorhies WA, Curtsinger JW, Rose MR: Do longevity mutants always show trade-offs? *Exp Gerontol* 2006;41:1055–1058.
- 19 Lewontin RC: The Genetic Basis of Evolutionary Change. New York, Columbia University Press, 1974.
- 20 Burke MK: How does adaptation sweep through the genome? Insights from long-term selection experiments. *Proc R Soc* 2012;B279:5029–5038.
- 21 Burke MK, Dunham JP, Shahrestani P, Thornton KR, Rose MR, Long AD: Genome-wide analysis of a long-term evolution experiment with *Drosophila*. *Nature* 2010;467:587.
- 22 Gruber JD, Genissel A, Macdonald SJ, Long AD: How repeatable are associations between polymorphisms in achaete-scute and bristle number variation in *Drosophila*? *Genetics* 2007;175:1987–1997.
- 23 Tenaillon O, Rodríguez-Verdugo A, Gaut RL, McDonald P, Bennett AF, Long AD, Gaut BS: The molecular diversity of adaptive convergence. *Science* 2012;335:457–461.
- 24 Schachter F, Faurelanel L, Guenot F, Rouger H, Froguel P, Lesueurignot L, Cohen D: Genetic associations with human longevity at the ApoE and ACE loci. *Nat Genet* 1994;6:29–32.
- 25 Rose MR, Mueller LD, Burke MK: New experiments for an undivided genetics. *Genetics* 2011;188:1–10.
- 26 Rose MR, Long AD, Mueller LD, Rizza CL, Matsagas KC, Greer LF, Villeponteau B: Evolutionary nutrigenomics; in Fahy GM, West M, Coles LS, Harris SB (eds): *The Future of Aging: Pathways to Human Life Extension*. New York, Springer, 2010.

Michael R. Rose
 Department of Ecology and Evolutionary Biology, University of California
 321 Steinhaus Hall
 Irvine, CA 92697-2525 (USA)
 E-Mail mrrose@uci.edu