

## BOOK REVIEW

# Fruitflies and the fountain of youth

### **Methuselah flies: a case study in the evolution of aging**

Edited by Michael R. Rose, Hardip B. Passananti and Margarida Matos

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Reviewed by AMITABH JOSHI\*

'Methuselah Flies' is an interesting, informative and useful book, but also in some respects an odd and frustrating one. Interesting, because it deals with ageing and our understanding of how it evolves. Odd, because it is unusual to read a book, other than a 'collected works' compilation, that largely consists of reprints of papers from the primary literature. Informative and useful, because it collates 24 important papers, published between 1984 and 2002, that tested hypotheses about the evolution of ageing using fruitflies, and went on to investigate physiological, reproductive, behavioural and genetic correlates of lifespan and other life-history related traits. These papers are augmented with several chapters written for the present volume, including overview type chapters as well as those reporting previously unpublished data. Finally, I found the book somewhat frustrating at times, partly because some of my favourite papers from the Rose research group at Irvine were not represented, but mostly because the chapters providing an overview to each section of the book were rather cursory. Had those chapters been more detailed, the volume would have been an important source for historians of biology as well as for evolutionary biologists and biologists interested in ageing.

Ageing as a phenomenon, and the possibilities of postponing, reversing or abolishing it, have fascinated humans for a very long time as both mythology and history testify. In the past couple of centuries, medical practitioners have used many methods to study the phenomenology of human ageing in an attempt to understand the proximal causes of the symptoms of ageing, with the hope that understanding will lead to the means of alleviation of those symptoms. A different tradition, going back to Wallace and Weismann in the nineteenth century, has aimed at elucidating the ultimate causes of ageing by seeking to understand how ageing evolves. The early views on the

evolution of ageing, however, were fuzzy and group selectionist: ageing was thought to be for the good of the species, as it weeded out infirm and 'unfit' individuals. With the development of population genetics, and the increasing realization that selection typically acts on individuals rather than groups, clearer theories about the evolution of ageing were put forward by J. B. S. Haldane, P. B. Medawar and G. C. Williams in the mid-twentieth century. These views were then formalized mathematically by W. D. Hamilton, and further refined by B. Charlesworth.

The crux of the evolutionary theories of ageing is the fact that the force of natural selection acting on genes declines with the age at which the phenotypic effect of the gene is expressed. Until the onset of reproduction, all gene effects are subject to the full force of the scrutiny of natural selection. Thereafter, the efficacy of selection at rooting out deleterious genes rapidly and progressively diminishes; genes whose effects are felt at ages after the cessation of reproduction are not 'seen' by selection at all. Based on this underlying fact, two mechanisms, that are not mutually exclusive, have been proposed for the evolution of ageing: antagonistic pleiotropy and mutation accumulation. Antagonistic pleiotropy refers to the situation wherein selection will favour genes with beneficial effects early in life, even if they have harmful effects later on in life; effects that give rise to the symptoms of ageing. Mutation accumulation suggests that deleterious genes with late life effects causing the syndrome of ageing will largely escape selection and could, therefore, rise to high frequency in populations via random genetic drift.

The manner in which the force of natural selection declines with the age of expression of gene effects – relative to the age of first reproduction – immediately suggests a simple yet powerful protocol for generating populations with a genetically increased lifespan. If one progressively postpones the age of effective reproduction over generations, selection should result in the evolution of a population with an increased lifespan. This was the idea behind the creation of Methuselah flies, a popular name deriving from the Hebrew patriarch who supposedly lived to the

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\*Evolutionary & Organismal Biology Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur, Bangalore 560 064, India.  
E-mail: ajoshi@jnca.ac.in.

age of 969 years, given to populations of *Drosophila melanogaster* subjected to selection for increased lifespan in the laboratory. Such populations of fruitflies with increased lifespan were created in several laboratories around the early 1980s, but the most extensive and systematic studies of ageing related issues on such populations have been carried out by Michael Rose and his students and collaborators at the University of California, Irvine. The Rose research group has used these populations to empirically validate the evolutionary theories of ageing, and also to investigate reproductive, physiological, biochemical, behavioural and molecular genetic mechanisms underlying the postponed ageing phenotype.

The book begins with a short introduction, followed by 34 chapters (previously published papers and some newly written chapters) divided among six sections. The introduction and the first chapter in section 1 deal with the benefits of using laboratory selection as a tool to study ageing, as contrasted with other approaches e.g. the use of mutant lines. There is also a very brief history of studies in which age at reproduction was manipulated, leading into a short description of how Methuselah flies were first established in the Rose laboratory and in the Luckinbill/Arking laboratory at Wayne State University. These two chapters also include a very terse rebuttal of recently articulated critiques of using long-term laboratory populations for ageing studies, as opposed to wild-caught populations. I had hoped for a more detailed rebuttal which would also have been helpful to graduate students reading the book.

The first section includes previously published papers covering the initial establishment of the Rose laboratory Methuselah flies and quantitative genetic studies of fitness components in these populations. This section also includes a formal demonstration that the rate of ageing has actually slowed down in the extended lifespan populations, as well as one of three important papers from 1994 exploring the ubiquitous and pernicious effects of genotype-by-environment interactions and the implications of such interactions for experimental design and interpretation in evolutionary studies.

In section 2, the relationship between stress resistance, ageing and metabolic rates is explored through a set of five papers dealing with the evolutionary correlations between starvation and desiccation resistance and lifespan in populations selected for one or the other trait, as well as physiological mechanisms of resistance to starvation and desiccation. This section is followed by one consisting of papers looking at the often observed inverse relationship between reproductive output and lifespan, and showing that the tradeoff between fecundity and lifespan is not an energetically exact one. Many of the studies reported in these papers have implications for our understanding of the evolutionary process, and effective strategies for studying it, that go well beyond the experimental sys-

tem used and the traits studied in any particular experiment.

Section 4 includes studies that go a little deeper into formal genetics and examine the extended lifespan flies, as well as flies selected for rapid pre-adult development and very early reproduction, for differences in frequencies of enzymes such as Cu-Zn superoxide dismutase, alcohol dehydrogenase, phosphoglucosmutase and  $\alpha$ -glycerol-3-phosphate dehydrogenase. Levels of heat shock proteins in the Methuselah flies were also studied, in addition to a general electrophoretic survey of differences in protein profile between the Methuselah flies and their controls. Such studies may appear a little dated today, in the era of microarrays and proteomics, but at the time these were some of the first studies to examine the biochemical and genetic correlates of extended lifespan.

Section 5 is a particularly interesting compilation of studies using reversed or relaxed selection on populations of *D. melanogaster* selected for extended lifespan, rapid development and early reproduction, or resistance to starvation or desiccation. The results from these studies provide evidence for antagonistic pleiotropy between lifespan and starvation resistance (at least in males) on one hand and some early life fitness characters on the other. However, some other traits that also evolved in the extended lifespan populations (e.g. desiccation resistance) do not seem to be related to early life fitness via antagonistic pleiotropy. The variation in the manner and degree to which different traits respond to reversed/relaxed selection in populations with different histories of forward selection in the laboratory also illuminates many aspects of the genetic structure of complex phenotypes, and the possible evolution of genotype-by-genotype and genotype-by-environment interactions in the course of adaptation to a particular selection regime.

The last section brings together papers examining the links between the pre-adult and adult life stages of *Drosophila* by comparing results from age-specific and density-dependent selection experiments, and by looking at how selection on pre-adult traits affects the adult life-history and *vice versa*. This is an active area of ongoing research in *Drosophila* life-history evolution of great personal interest to me, and this section includes one of my favourite papers from the Rose research group (Paper 31 in the book) which first showed evidence for a tradeoff between pre-adult developmental rate and pre-adult viability. This paper also has an excellent discussion of how artifactual results can arise from slight changes in maintenance regimes, leading to inadvertent selection pressures on one life stage that can then have multifarious effects on the response to selection by traits in another life stage. Other papers in this section deal with the evolution of pre-adult and adult life-history related traits in populations selected for rapid development and very early life fecundity, and the last paper has a very nice discussion on how selection

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on pre-adult traits can affect the observed relationships between fitness related traits in the adult life stage.

Overall, the book is a very useful compendium and certainly belongs on the shelf of anyone working on life-history evolution, especially in *Drosophila*. I could also imagine the book being the foundation for an interesting and challenging graduate seminar course in experimental evolution or natural selection. In terms of providing a model of rigour in experimental design and interpretation, many of the papers included in this book are excellent examples for beginning research students in experimental evolution. Similarly, the discussions in many of the papers of the extreme subtlety with which selection and the genetic architecture of fitness related traits interact to produce evolutionary trajectories should be useful not only to students of experimental evolution, but also to students of life-

history evolution and evolutionary ecology in general. Many of the papers are also exemplary in terms of elegant scientific writing. Indeed, several of the papers reprinted here have been used by me in the past to introduce new students in my laboratory to both good experimental design and good writing. However, as a resource for beginning students, the book would have been strengthened by more detailed introductory chapters, and perhaps an overall concluding chapter that stressed the importance of these studies, not only to understanding ageing, but also as an example of the subtle complexities in the adaptive evolution of composite phenotypes that are often obscured by the stark simplicity of selection as a concept. That said, I would still recommend the book strongly, despite its price, to all those who study the evolutionary process: there is much understanding to be mined from its pages!