

CURRICULUM VITAE

HIROSHI AKASHI

Department of Biology
208 Mueller Laboratory
Pennsylvania State University
University Park, PA 16802 USA

Fax: (814) 865-9131
Office: (814) 865-5013
Lab: (814) 863-8577
Email: akashi@psu.edu

EDUCATION

- Ph.D. Ecology and Evolution, University of Chicago, 1996
Advisor: Martin Kreitman
- M.S. Ecology and Evolution, University of Chicago, 1993
- B.A. Biology, Harvard College, 1990
magna cum laude with highest honors in the Department of Biology

PROFESSIONAL EXPERIENCE

- Assistant Professor, Department of Biology, The Pennsylvania State University, Aug. 2000 -
- Visiting Scholar, Center for Information Biology,
National Institute of Genetics, Mishima, Japan, Sept. 2000 – Dec. 2000
Sponsor: Takashi Gojobori
- Assistant Professor, Department of Ecology and Evolutionary Biology,
University of Kansas, Aug. 1998 – July 2000
- Visiting Scholar, Section of Evolution and Ecology,
University of California, Davis, Sept. 1996 - Aug. 1998
Sponsor: John Gillespie
- Postdoctoral Fellow, Center for Population Biology,
University of California, Davis, Feb. - Aug. 1996, Sponsor: John Gillespie

FELLOWSHIPS AND AWARDS

- Japan Society for the Promotion of Science Postdoctoral Fellowship, 2000
- American Society of Naturalists' Young Investigator Award, 1998
- National Science Foundation/Alfred P. Sloan Foundation Postdoctoral Research Fellowship in
Molecular Evolution, Sept. 1996 - 1998
- Center for Population Biology Postdoctoral Fellowship, University of California, Davis, Feb. - Aug.
1996 (terminated to begin NSF/Sloan Fellowship)
- Departmental Award for Outstanding Performance in the General Field of Ecology and Evolution,
University of Chicago, 1996
- Howard Hughes Biomedical Institute Predoctoral Fellowship, 1991 - 1996
- Dean's Merit Award, University of Chicago, 1991-1996
- John Harvard Scholarship, 1987-1988
- Harvard College Scholarship, 1986-1987

EXTRAMURAL FUNDING

National Science Foundation, DEB-0235472 “Translational selection and *Drosophila* genome evolution” Division of Environmental Biology, June 2003-May 2007, \$402,000 (direct + indirect including supplements).

Alfred P. Sloan Foundation Young Investigator Award in Molecular Studies of Evolution, \$100,000, 1998–2003

PUBLICATIONS [ISI citation numbers are given in brackets, >1200 total]

peer-reviewed publications

1. Ko, W. Y., S. Piao, and H. Akashi, Extreme region-specific heterogeneity in base composition evolution on the *Drosophila* X chromosome (submitted to *Molecular Biology and Evolution*).
2. Akashi, H., W.Y. Ko, S. Piao, A. John, P. Goel, C. F. Lin, and A. Vitins, Molecular evolution in the *Drosophila melanogaster* species subgroup: Frequent parameter fluctuations on the time-scale of molecular divergence (submitted to *Genetics*).
3. Akashi, H., P. Goel, and A. John, Ancestral state inference and the study of codon bias evolution: Implications for molecular evolutionary analysis of the *Drosophila melanogaster* species subgroup (submitted to *Genetics*).
4. Akashi, H., 2003 Translational selection and yeast proteome evolution. *Genetics* 164: 1291-1303. [24]
5. Ko, W.Y., R. David, and H. Akashi, 2003 Molecular phylogeny of the *Drosophila melanogaster* species subgroup. *Journal of Molecular Evolution* 57: 562-573. [6]
6. Nielsen, R, and H. Akashi, 2003 Purifying Selection: Action on Silent Sites. In: Cooper DN (ed.) *Nature Encyclopedia of the Human Genome, vol. 4*, pp. 945-948. London: Nature Publishing Group.
7. Akashi, H, and T. Gojobori, 2002 Metabolic efficiency and amino acid composition in the proteomes of *Escherichia coli* and *Bacillus subtilis*. *Proceedings of the National Academy of Sciences, USA*. 99: 3695-3700. [47]
8. Akashi, H., 2001 Gene expression and molecular evolution. *Current Opinions in Genetics and Development* 11: 660-666. [62]
9. Iida, K., and H. Akashi, 2000 A test of translational selection in the human genome: Base composition comparisons in alternatively spliced genes. *Gene* 261: 93-105. [31]
10. Akashi, H. 1999 Inferring the fitness effects of DNA mutations from patterns of polymorphism and divergence: Statistical power to detect directional selection under stationarity and free recombination. *Genetics* 151: 221-238. [54]
11. Akashi, H., 1999 Detecting the "footprint" of natural selection in within and between species DNA sequence data. *Gene* 238: 39-51. [35]
12. Noor, M. A. F., and H. Akashi. 1999 *Drosophila* evolutionary genetics. In: *Embryonic Encyclopedia of Life Sciences*, London: Nature Publishing Group.
13. Akashi, H., R. Kliman, and A. Eyre-Walker. 1998 Mutation pressure, natural selection and the evolution of base composition in *Drosophila*. *Genetica* 102/103: 49-60. [25]
14. Akashi, H., A. Eyre-Walker. 1998 Translational Selection and Molecular Evolution. *Current Opinions in Genetics and Development* 8: 688-693. [41]

PUBLICATIONS (cont'd)

15. Akashi, H., and S. Schaeffer. 1997 Natural selection and the frequency distributions of "silent" DNA polymorphism in *Drosophila*. *Genetics* 146: 295-307. [79]
16. Akashi, H. 1997 Codon bias evolution in *Drosophila*: Population genetics of mutation-selection-drift. *Gene* 205: 269-278. [43]
17. Akashi, H. 1996 Molecular evolution between *Drosophila melanogaster* and *D. simulans*: Reduced codon bias, faster rates of amino acid substitution, and larger proteins in *D. melanogaster*. *Genetics* 144: 1297-1307. [105]
18. Akashi, H. 1995 Inferring weak selection from patterns of polymorphism and divergence at "silent" sites in *Drosophila* DNA. *Genetics* 139: 1067-1076. [222]
19. Kreitman M., and H. Akashi. 1995 Molecular evidence for natural selection. *Annual Review of Ecology and Systematics* 26: 403-22. [120]
20. Dorit, R. L., H. Akashi, and W. Gilbert. 1995 Absence of polymorphism at the ZFY locus on the human Y chromosome. *Science* 268: 1183-1185. [140]
21. Akashi, H. 1994 Synonymous codon usage in *Drosophila melanogaster*: Natural selection and translational accuracy. *Genetics* 136: 927-935. [175]

Short communications and non-peer-reviewed publications

1. Akashi, H., 2003 Metabolic economics and microbial proteome evolution [abstract]. *Bioinformatics* 19: ii15.
2. Noor, M. A. F., J. R. Wheatley, K. A. Wetterstrand, and H. Akashi. 1998 Western North America *obscura*-group *Drosophila* collection data, summer 1997. *Drosophila Information Service* 81: 136-137.
3. Akashi, H. 1997 Distinguishing the effects of mutational biases and natural selection on DNA sequence variation [letter]. *Genetics* 147: 1989-1991. [6]
4. Dorit, R. L., H. Akashi, and W. Gilbert. 1996 Estimating the age of the common ancestor of men from the ZFY intron [letter]. *Science* 272: 1361-62. [3]

INVITED LECTURES/SYMPOSIA

Université Claude Bernard, Lyon, France, 2005
Graduate University for Advanced Studies, Hayama, Japan, 2005
National Institute of Genetics, Center for Information Biology, Mishima, Japan, 2005
Symposium on "Genome and RNA: Expression and Functions" International Society for Molecular Evolution, San José, Costa Rica, 2005
University of Chicago, Department of Ecology and Evolution, 2004
European Conference on Computational Biology, Paris, France, Keynote presentation, 2003
University of Munich, Department Biologie II, Section of Evolutionary Biology, Munich, Germany, 2003
Stanford University, Department of Biology, 2003
International Symposium: Dynamism in Molecular Networks. Nara Institute of Science and Technology, Nara, Japan, 2003
Harvard University, Department of Organismal and Evolutionary Biology, 2002
Joint Genome Institute, Department of Energy, Walnut Creek, California, 2002
University College, London, Biology Department, 2001
Symposium on Natural Selection and the Neutral Theory, Ischia, Italy, 2001

INVITED LECTURES/SYMPOSIA (cont'd)

Symposium on "Neutralism and Selectionism: the end of a debate", Ischia, Italy, 2000
Graduate University for Advanced Studies, Biosystems Department, Hayama, Japan, 2000
National Institute of Genetics, Institutional Biological Symposium, Mishima, Japan, 2000
Kyushu University, Genetics Department, Kyushu, Japan, 2000
Duke University, Program in Genetics, 2000
Rochester University, Department of Biology, 2000
University of California, Davis, Section of Evolution and Ecology, 1999
Symposium on Neutralism and Selectionism, European Society for Evolutionary Biology,
Barcelona, Spain, 1999
University of California at Santa Cruz, Department of Biology, 1999
Symposium on Evolutionary Genomics, International Society of Molecular Evolution, Puntarenas,
Costa Rica, 1999
Young Investigators' Symposium, American Society of Naturalists, Vancouver, BC Canada, 1998
Symposium on Deleterious Mutations, Society for the Study of Evolution, Boulder, Colorado, 1997
Symposium on "Junk" DNA, International Society of Molecular Evolution, Guanacaste, Costa Rica
1997
Harvard University, Population Biology Seminar, 1997
North Carolina State University, Department of Genetics, 1997
Walter M. Fitch Prize Symposium, Society of Molecular Biology and Evolution Conference,
Tucson, Arizona, 1996

CONFERENCE PRESENTATIONS (^Pposter, ^Ooral, ^Sstudent)

Joint Conference: Society of Molecular Biology and Evolution and International Society
of Molecular Evolution, Sorento, Italy, 2002^O
Symposium on Evolutionary Genomics, Atami, Japan, 2001^O
Society of Molecular Biology and Evolution Conference, 2001^O, 2003^O, 2004^{SP}
Annual Drosophila Research Conference, 1994^P, 1996^P
Gordon Conference on Microbial Population Biology, 1995^P
Society for the Study of Evolution Conference, 1992^O, 1994^O, 2000^O
Northeast Ecology and Evolution Conference (NEEC), Penn State University, 2005^{SO}
Eastern Great Lake Molecular Evolution Meeting (EGLME VIII), Cornell University, 2004^{SO}
"Comparative and Functional Genomics", 24th Summer Symposium in Molecular Biology, Penn State
University, 2005^{SP}

PROFESSIONAL SERVICE

Associate Editor: *Journal of Molecular Evolution*, 1999 – 2001

Editorial Board: *Genetical Research*, 1999 –

Contributing Faculty Member, Faculty of 1000 Biology, 2004 –
Online service to evaluate scientific literature

Manuscript reviewer: [>100 grant and manuscript reviews 2000-]

*Science, Nature, Genetics, Proc. Natl. Acad. Sci. USA, Molecular Biology and
Evolution, Public Library of Science – Biology, Gene, Journal of Molecular Evolution,
Nucleic Acids Research, Trends in Genetics, Quarterly Review of Biology, Genetica,
Genetical Research, Insect Molecular Biology, Current Biology, Biochimica et Biophysica
Acta - Gene Structure and Expression, Molecular Microbiology, BMC Evolutionary
Biology, BMC Bioinformatics*

PROFESSIONAL SERVICE (cont'd)

Research proposal reviewer: National Science Foundation, Biotechnology and Biological Sciences Research Council, UK, Science Foundation Ireland
Panelist, 2003, National Science Foundation, Population Biology Panel
Organizing Committee, Annual Meeting for the Society for Molecular Biology and Evolution, Penn State University, 2003

PROFESSIONAL SOCIETIES

Society for Molecular Biology and Evolution, 1994-
Genetics Society of America, 1994-
Society for the Study of Evolution, 1995-
International Society for Molecular Evolution, 1998-
American Association for the Advancement of Science, 1998-
American Society of Microbiology, 2003
Sigma Xi, 1990-

TEACHING EXPERIENCE

Instructor, Department of Biology, Penn State University
Biology 597G: Critical evaluation of scientific literature (w. R. Raina and J. Marden), 2001
Biology 405: Molecular evolution (w. S. Schaeffer, 5 of 45 lectures), 2001
Biology 428: Population Genetics (w. A. Clark, 22 of 45 lectures), 2002
IBIOS 598B: Genomics (4 lecture module on Evolutionary Genomics), 2002, 2003, 2004
Biology 428: Population Genetics, 2003, 2004, 2005
Biology 497G/597G: Computer programming in C: Biological Applications, 2003, 2004
Biology 222: Genetics (w. S. Schaeffer, 10 of 26 lectures), 2005

Instructor, Department of Ecology and Evolutionary Biology, University of Kansas
Biology 404: Introduction to Genetics (sole instructor), 2000
Biology 420: Molecular Evolution (sole instructor), 1999, 2000

Graduate student supervision

Wen-Ya Ko, PhD student, 6th year, (advisor) Department of Biology
Anoop John, MS completed in 2003 (co-advisor) Department of Electrical Engineering
Piyush Goel, PhD student, Department of Operations Research
Vivek Natarajan, PhD student, Computer Science and Engineering
Araxi Urrutia, visiting graduate student, 2002. University of Bath, UK. PhD 2003

Research Interests

Hiroshi Akashi

Identifying the evolutionary forces that have shaped genomes is a central challenge in biology. The Neo-Darwinian theory of evolution proposes that complex adaptations arise from the accumulation of heritable changes with scarcely appreciable effects on the physiology, morphology, and behavior of organisms. My research combines theoretical and laboratory studies to test whether subtle forms of natural selection play a major role in genome evolution.

Weak selection and major codon preference

Synonymous, or "silent", DNA changes were considered to be candidates for neutral evolution because they do not alter the amino acid sequence of encoded proteins. However, a number of species show preferential usage of "major" codons recognized by abundant tRNA's. Such patterns suggest major codon preference; maintenance of codon bias by a balance among mutation pressure, genetic drift, and weak selection favoring translationally superior codons.

I have employed population genetic methods to test the major codon preference model (Akashi 1995; Akashi and Schaeffer 1997). In *Drosophila simulans* and *D. pseudoobscura*, within and between species sequence comparisons demonstrate fitness differences between classes of silent mutations. Maximum likelihood estimates confirm that silent DNA changes are a prevalent class of weakly selected mutations in *Drosophila*.

Patterns of codon usage allow inference of a phenotypic target of selection from DNA sequence comparisons. Biochemical studies have shown that synonymous codon usage can affect the fidelity of protein synthesis. Because the fitness cost of a translational misincorporation depends on how severely it disrupts protein function, selection for translational accuracy should cause associations between codon usage in DNA and protein functional constraint. Higher codon bias at conserved than at non-conserved amino acid positions identifies codon selection to enhance the accuracy of protein synthesis in *Drosophila* (Akashi 1994).

Our recent work focuses on codon usage and protein evolution among closely related species within the *D. melanogaster* species subgroup. Knowledge of the historical relationships among taxa is essential for molecular evolutionary studies and we have obtained strong support for a revision of the phylogeny of these species (Ko, David, and Akashi 2003). Previous analyses identified a dramatic decline of codon bias in the *D. melanogaster* lineage (Akashi 1996) and data from our lab shows codon bias is rarely at equilibrium (Akashi *et al.*, submitted). At least half of the eight lineages examined have undergone apparently genome-wide fluctuations in base composition. Rates of protein divergence are also strongly lineage-specific. Finer-scale analyses have revealed striking localized heterogeneity of codon bias and protein evolution in a ~130kb region of the X chromosome (Ko, Piao, and Akashi, submitted). Both weak selection and departures from steady-state appear to be prevalent features of molecular evolution in *Drosophila*.

Identifying causes of molecular evolution: methodology

Within and between species DNA sequence comparisons are widely employed to identify causes of molecular evolution. I have employed computer simulations to show that combining information from both the frequency distribution of segregating mutations and the number of mutations fixed between populations can confer considerable statistical power to detect selection close to its limit of efficacy. Frequency distribution and divergence (fdd) tests revealed mutation-selection-drift at silent sites and substantial contributions of both adaptive and weakly deleterious protein evolution (Akashi 1999).

Reconstructions of ancestral nucleotide states allow predictions of the fitness effects of mutations and enhance the statistical power to detect selection. Many population genetic studies have employed maximum parsimony methods to reconstruct ancestral states. We have tested the reliability of such inferences through computer simulation. Both asymmetry in substitution rates and departures from equilibrium can lead to strong biases in ancestral state inference, even among closely related species (Akashi, Goel, and John, submitted). Our recent analyses employ a maximum likelihood approach that considerably improves the accuracy of ancestral reconstruction. The *D. melanogaster* subgroup is becoming a focus area for comparative genomics and these findings will benefit future evolutionary studies.

Global forces in protein evolution

Natural selection is thought to act upon protein structures to optimize biochemical properties related to their specific cellular functions. Selection for efficient synthesis of proteins may act globally on the size, amino acid composition, and evolutionary rates of proteins, but are less firmly established. A substantial fraction of bacterial energy budgets are devoted to biosynthesis of amino acids. Synthesis of amino acids entails a dual cost; energy is lost by diversion of chemical intermediates from fueling reactions and additional energy is required to convert precursor metabolites to amino acids. Increases in the usage of less energetically costly amino acids as a function of the expression levels of proteins demonstrate that natural selection to enhance metabolic efficiency affects fundamental features of the *Escherichia coli* and *Bacillus subtilis* proteomes (Akashi and Gojobori 2002).

The primary structures of proteins may also reflect natural selection to enhance the rate and accuracy of their synthesis. In yeast, usage of several amino acids is strongly associated with gene expression. These changes in amino acid composition result in stronger correlations between amino acid composition and tRNA abundances in highly expressed genes than in less expressed loci (Akashi 2003). Translation selection appears to act both within and among synonymous codon families. These studies provide evidence that proteome-wide patterns of amino acid composition reflect natural selection to enhance the overall physiology of cells as well as the specific functions of proteins.

Future interests

Our research has revealed the importance of both weak selection and parameter fluctuations in synonymous DNA evolution. Contrasts between polymorphic and fixed mutations in multiple species from the *D. melanogaster* subgroup will be employed to reveal the causes of lineage-specific codon bias evolution (*i.e.*, changes in mutation biases and/or selection intensity). Because synonymous changes are often employed as a form of internal control to infer natural selection, understanding mechanisms of codon bias evolution is critical for testing claims of widespread adaptive evolution of proteins and non-coding DNA in *Drosophila* genomes.

Global models of protein evolution predict fitness classes of replacement changes that apply across genes. Studies of gene expression and amino acid composition in *Drosophila* will allow us to employ within and between species contrasts to identify mechanisms of proteome evolution.

"Nearly neutral" models have been criticized for their extreme parameter sensitivity. Selection coefficients for synonymous mutations appear to fall in a precise range, near the reciprocal of effective population size, in many microbes as well as multi-cellular eukaryotes. We are employing computer simulations to develop methods to identify how the genomic context of DNA changes determine their fitness effects. Diminishing returns in fitness with the accumulation of beneficial mutations would explain why natural selection frequently acts at its limit of efficacy.