

# UC Irvine

## UC Irvine Previously Published Works

### Title

Walter Monroe Fitch (May 21, 1929 - March 10, 2011): A memorial tribute

### Permalink

<https://escholarship.org/uc/item/8457m541>

### Journal

Infection Genetics and Evolution, 12(7)

### ISSN

1567-1348

### Author

Ayala, Francisco J

### Publication Date

2012-10-01

### DOI

10.1016/j.meegid.2012.07.001

### 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/>

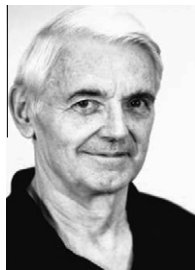
Peer reviewed

Contents lists available at [SciVerse ScienceDirect](#)

# Infection, Genetics and Evolution

journal homepage: [www.elsevier.com/locate/meegid](http://www.elsevier.com/locate/meegid)

## Walter Monroe Fitch (May 21, 1929 - March 10, 2011): A memorial tribute



Walter Fitch is acknowledged as the founder of the discipline of molecular phylogenetics, the reconstruction of evolutionary phylogeny using molecular data, which is now an enormously active field of research and publication, perhaps the most intensely used method of ascertaining the evolutionary history of living organisms and the one method that can incorporate all sorts of organisms, from bacteria and protozoa to plants and animals, using a single all-encompassing trait, a chosen DNA sequence or protein molecule.

In 1967, Fitch and Emanuel Margoliash published “Construction of Phylogenetic Trees” in *Science* (Fitch and Margoliash, 1967), a paper that would forever impact the way in which we reconstruct the phylogeny of living species (Fig. 1). Based on the amino acid sequence of a small protein, cytochrome *c*, Fitch and Margoliash had, astonishingly, constructed a phylogenetic tree of 20 species, from yeast, through insects, fish, reptiles, birds, and mammals, to humans, “remarkably like the classical phylogenetic tree that has been obtained from purely biological data” (p. 279). The possibilities were astounding: organisms carry thousands of genes and proteins, every one recording the same evolutionary history. One and another and another gene or protein could be studied so as to achieve as much precision as wanted in a phylogeny. For determining the phylogeny, Fitch and Margoliash had formulated the minimal “mutation distance,” an “analytical method [that] has general applicability” (p. 279), subject to quantification and statistical analysis.

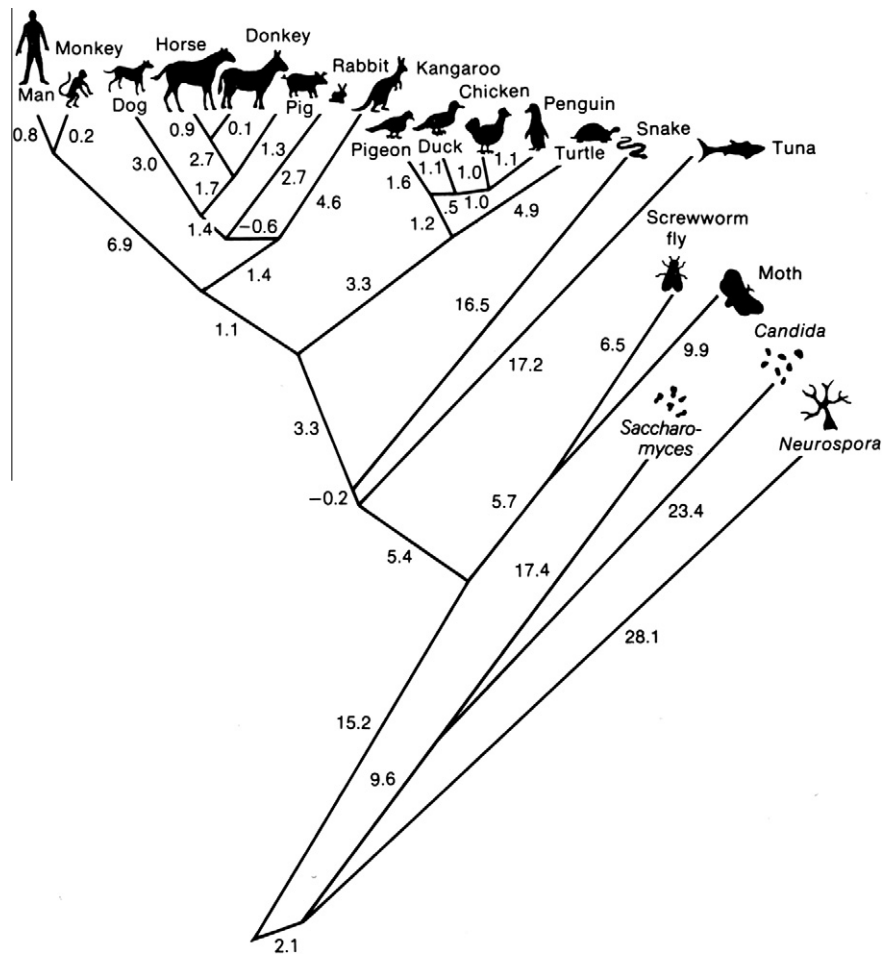
Walter Monroe Fitch was born in San Diego, California, on 21 May 1929. He attended the University of California, Berkeley, where he received his A.B. in chemistry (1953) and his Ph.D. in comparative biochemistry (1958). After a series of postdoctoral appointments, he joined the faculty of the School of Medicine at the University of Wisconsin, Madison, where he was a professor from 1962 to 1986. He then returned to his native California, where he was a professor at the University of Southern California, in Los Angeles for three years (1986–1989), before moving to the Department of Ecology and Evolutionary Biology at the University of California, Irvine (UCI), where he was a professor from 1989 to 2011.

Fitch was a cofounder of the Society for Molecular Biology and Evolution and of its journal, *Molecular Biology and Evolution* (MBE). He was the Society’s first president and editor-in-chief of the journal for its first 10 years, from December 1983 (volume 1, number 1) through July 1993 (volume 10, number 4). In the “Introductory Statement” explaining the scope and justification of a new journal, Walter Fitch called attention to the journal’s title, which included “and”, not “or”, “that is, a paper must contain material about macromolecules *and* about their evolutionary implications.” MBE’s record of significant publications starts with that first issue, which includes papers by Nobel laureate M.F. Perutz, “Species Adaptation in a Protein Molecule,” and by distinguished evolutionists, including, among others, John C. Avise, Howard Ochman, Robert K. Selander, Motoo Kimura, Wen-Hsiung Li, Takashi Gojobori, Barry G. Hall (who would become MBE’s editor starting in September 1993), and by Fitch himself (“Evolution of Antibiotic Resistance Genes: The DNA Sequence of a Kanamycin Resistance Gene from *Staphylococcus aureus*,” in collaboration with Gary S. Gray).

Walter Fitch received distinguished honors throughout his career, including, among numerous others, election to the three most honorific societies for scientists in the United States: the National Academy of Sciences in 1989; the American Academy of Arts and Sciences in 1991; and the American Philosophical Society in 2000. He was elected a Foreign Member of the Linnean Society (London) in 1994, and received a Doctor *Honoris Causa* degree from North Carolina State University in 2001, and in 2005, the UCI Medal, the greatest distinction awarded by the University of California. The “Walter M. Fitch Award” given each year by the Society for Molecular Biology and Evolution to the most deserving young scientists working on molecular evolution recognizes his lasting legacy.

DNA, RNA, and proteins have been called informational macromolecules because they convey evolutionary information in the linear sequence of their nucleotide or amino acid components, similarly as the sequence of letters in an English text conveys semantic information (Vogel et al., 1963). Zuckerkandl and Pauling (1965), among others, had noticed that the number of component differences between homologous (orthologous) molecules obtained from different organisms seemed to be proportional to the time elapsed since the evolutionary divergence of the species, or, in the case of paralogous genes, since the time when a gene duplication may have occurred. In their investigation, focused primarily on different hemoglobin polypeptides from the same or different species, Zuckerkandl and Pauling had postulated that most nucleotide or amino acid replacements would be adaptively neutral and thus “*There may thus exist a molecular evolutionary clock*” (Zuckerkandl and Pauling, 1965, p. 148, their emphasis).

These were important antecedents, but the emergence of molecular phylogeny as a major field of study can be traced to the publication in 1967 of Fitch and Margoliash’s paper in *Science* mentioned above (“Construction of Phylogenetic Trees,” Fitch and Margoliash,



**Fig. 1.** Evolutionary history of twenty species, based on the cytochrome *c* amino acid sequence. The common ancestor (at the bottom) of yeast and humans lived more than 1 billion years ago. The numbers along the branches estimate the nucleotide substitutions occurring in the span of evolution represented by the branch. Although fractional (or negative) numbers of nucleotide substitutions cannot occur, the numbers along the branches are those that best fit the data. More detailed studies would make it possible to determine the exact number of changes along each branch. (After Fitch and Margoliash, 1967).

1967), a paper that would impact forever how the evolutionary history of living organisms is investigated. Margoliash, a distinguished biochemist at the Abbott Laboratories in North Chicago, had obtained for several species the amino acid sequence of cytochrome *c*, a small protein involved in cell respiration, consisting of about 104 amino acids. In collaboration with Walter, Margoliash extended the sequences to a total of 20 species, as noted above. The reconstruction of the evolutionary history of organisms that had shared the last common ancestor more than one billion years ago was a remarkable outcome. More significant yet was the formulation of concepts, algorithms, and statistically reliable methods of wide applicability in the investigation of molecular evolution, subjects to which Fitch would further contribute in the years to follow. We owe to him useful concepts such as “covarions” (concomitantly variable codons), neutral mutation, rate of fixation of nucleotide replacements, orthologous versus paralogous genes, molecular convergence versus divergence, minimal mutation distance, parsimony, and much more. The *Science* paper and Fitch’s ensuing contributions largely account for the rapid expansion of molecular evolution studies, which now account for a sizeable parcel of evolutionary research, particularly concerning molecular phylogeny, rates of evolution and the molecular clock. Witness the rush of publications that followed that paper, such as, for example, some notable contributions of Motoo Kimura: “Evolutionary Rate at the Molecular Level” (Kimura, 1968); “The Rate of Molecular Evolution Considered from the Standpoint of Population Genetics” (Kimura,

1969); and “Protein Polymorphism as a Phase of Molecular Evolution” (Kimura and Ohta, 1972).

Paleontology, comparative anatomy, biogeography and other traditional disciplines continue to be used in the reconstruction of phylogeny, and they have distinctive advantages for certain purposes, notably paleontology for the investigation of the morphology, distribution, and other characteristics of extinct species. But molecular evolutionary studies have three notable advantages over classical disciplines. One is *quantification*, because the molecular information is readily quantifiable. The number of units (nucleotides or amino acids) that are different is easily established when the sequence of units is known for a given macromolecule in different organisms. It is simply a matter of aligning the nucleotides or amino acids between two or more species and counting the differences. The second advantage is *universality*, because comparisons can be made between very different sorts of organisms. There is very little that paleontology or comparative anatomy can say when, for example, organisms as diverse as yeasts, pine trees, and human beings are compared, but there are numerous DNA and protein sequences that can be compared in all three. The third advantage is *multiplicity*. Each organism possesses thousands of genes and proteins, every one of which reflects the same evolutionary history. If the investigation of one particular gene or protein does not satisfactorily resolve the evolutionary relationships of a set of species, additional genes and proteins can be investigated until the matter has been settled.

Walter's contributions to the conceptual and methodological development of molecular evolution extend throughout his career, with a bibliography consisting of more than 180 peer-reviewed papers. It is not possible herein to list his important contributions, because so many of them are. One long paper, chock full of new ideas, precisely defined terms, algorithms, and specific methodologies, is "The Usefulness of Amino Acid and Nucleotide Sequences in Evolutionary Studies" (Fitch and Margoliash, 1970). "Towards Defining the Course of Evolution: Minimum Change for a Specific Tree Topology" (Fitch, 1971) was designated a "Citation Classic" by *Current Contents*.

Walter developed increasingly sophisticated methodologies to evaluate the molecular clock, that is, the constancy of molecular evolution. See, for example, "An Examination of the Constancy of the Rate of Molecular Evolution" (Langley and Fitch, 1974), and "An Evaluation of Molecular Evolutionary Clocks" (Fitch, 1976), or "The Estimate of Total Nucleotide Substitutions from Pairwise Differences is Biased" (Fitch, 1986), and the much more recent "The Superoxide Dismutase Molecular Clock Revisited" (Fitch and Ayala, 1994b).

Notable are Fitch's investigations of the evolution of the influenza virus, which became of great consequence in the development of flu vaccines. Early papers were "Evolution of Influenza A Viruses over 50 years," published in *Science* (Buonagurio et al., 1986a) and "Epidemiology of Influenza C Virus in Man; Multiple Evolutionary Lineages and Low Rate of Change," published in *Virology* (Buonagurio et al., 1986b). Notice also "Positive Darwinian Evolution in Human Influenza A Viruses," published in the *Proceedings of the National Academy of Sciences* (Fitch et al., 1991), and "The Variety of Human Virus Evolution," published in *Molecular Phylogenetics and Evolution* (Fitch, 1996). All important for the development of flu vaccines are several papers co-authored with Robin M. Bush and others, such as "Predicting the Evolution of Human Influenza A," published in *Science* (Bush et al., 1999) and "Effects of Passage History and Sampling Bias in Phylogenetic Reconstruction of Human Influenza A Evolution," in the *Proceedings of the National Academy of Sciences* (Bush et al., 2000). One of his last published papers, published in the *Proceedings of the National Academy of Sciences*, is "A Statistical Phylogeny of Influenza A H5N1" (Wallace et al., 2007).

Walter and I co-authored several papers, mostly dealing with the molecular clock of evolution. Shortly after his joining in 1989 the Department of Ecology and Evolutionary Biology at UCI, Walter and I embarked on the planning of several colloquia sponsored by the U.S. National Academy of Sciences intended to commemorate significant anniversaries of four major books important in the formulation of the Modern Theory of Evolution. Our purpose was to update the knowledge concerning the topics. Also, we sought to enhance the visibility of evolutionary studies among the members of the National Academy of Sciences. The colloquia were held at the Arnold and Mabel Beckman Center of the National Academies, which is just next to the UCI Campus, and the colloquium papers were published by us as co-editors in the *Proceedings of the National Academy of Sciences* (and as separate books published by the National Academies Press). The four colloquia were: "Tempo and Mode in Evolution" in 1994 (Fitch and Ayala, 1994a), commemorating the 50th anniversary of G.G. Simpson's book with the same title. In 1996, "Genetics and the Origin of Species" (Ayala and Fitch, 1996), on the 60th anniversary of Th. Dobzhansky's classic book with the same title. In 2000, "Variation and Evolution in Plants and Microorganisms" (Ayala et al., 2000), on the 50th anniversary of G.L. Stebbins', *Variation and Evolution in Plants*. In 2004, just a few months before Ernst Mayr passed away on February 3, 2005, and 62 years after publication of his classic book with the same title, "Systematics and the Origin of Species" (Hey et al., 2004).

Walter Fitch was a scientific genius: creative, original and incisive, with enormous analytical powers. He was also energetic as

well as humorous, occasionally inclined to play a practical joke and always ready to tell amusing stories, fictional or not.

In the second half of the decade of the 2000s, Walter's health deteriorated owing to various ailments, leading to his retirement in 2009, although he continued to come to his office and to write. He passed away peacefully in his sleep in the early morning of March 10, 2011. The family held a memorial service at the UCI University Club on 8 April 2011. UCI's School of Biological Sciences held a memorial on 26 May 2011, at the Beckman Center of the National Academies in Irvine. He is survived by his wife, Chung Cha, formerly Ziesel, two daughters and one son, two step-daughters, and seven grandchildren.

## References

- Ayala, F.J., Fitch, W.M., 1996. Genetics and the Origin of Species. *Proc. Natl. Acad. Sci. USA* 94, 7691–7806.
- Ayala, F.J., Fitch, W.M., Clegg, M.T., 2000. Variation and Evolution in Plants and Microorganisms. *Proc. Natl. Acad. Sci. USA* 97, 6941–7057.
- Buonagurio, D.A., Nakada, S., Parvin, J.D., Krystal, M., Palese, P., Fitch, W.M., 1986a. Evolution of Influenza A Viruses over 50 years: Rapid, Uniform Rate of Change in NS Gene. *Science* 232, 980–982.
- Buonagurio, D.A., Nakada, S., Fitch, W.M., Palese, P., 1986b. Epidemiology of Influenza C Virus in Man; Multiple Evolutionary Lineages and Low Rate of Change. *Virology* 153, 12–21.
- Bush, R.M., Bender, C.A., Subbarao, K., Cox, N.J., Fitch, W.M., 1999. Predicting the Evolution of Human Influenza A. *Science* 286, 1921–1925.
- Bush, R.M., Smith, C.A., Subbarao, K., Fitch, W.M., Cox, N.J., 2000. Effects of passage history and sampling bias on phylogenetic reconstruction of human influenza A evolution. *Proc. Natl. Acad. Sci. USA* 97, 6974–6980.
- Fitch, W.M., 1971. Towards defining the course of evolution: minimum change for a specific tree topology. *Syst. Zool.* 20, 406–416.
- Fitch, W.M., 1976. An Evaluation of Molecular Evolutionary Clocks. In: Ayala, F.J. (Ed.), *Molecular Evolution*. Sinauer Associates, Sunderland, Massachusetts, pp. 160–178.
- Fitch, W.M., 1986. The Estimate of Total Nucleotide Substitutions from Pairwise Differences is Biased. *Phil. Trans. Roy. Soc. London, B* 316, 317–324.
- Fitch, W.M., 1996. The Variety of Human Virus Evolution. *Mol. Phylog. Evol.* 5, 247–258.
- Fitch, W.M., Margoliash, E., 1967. Construction of Phylogenetic Trees. *Science* 155, 279–284.
- Fitch, W.M., Margoliash, E., 1970. The Usefulness of Amino Acid and Nucleotide Sequences in Evolutionary Studies. In: Dobzhansky, T., Hecht, M.K., Steere, W.C. (Eds.), *Evolutionary Biology*, Vol. 4. Appleton-Century-Crofts, New York, pp. 67–109.
- Fitch, W.M., Ayala, F.J., 1994a. Tempo and Mode in Evolution. *Proc. Natl. Acad. Sci. USA* 91, 6717–6829.
- Fitch, W.M., Ayala, F.J., 1994b. The Superoxide Dismutase Molecular Clock Revisited. *Proc. Natl. Acad. Sci. USA* 91, 6802–6807.
- Fitch, W.M., Leiter, J.M.E., Li, X., Palese, P., 1991. Positive Darwinian Evolution in Human Influenza A Viruses. *Proc. Natl. Acad. Sci.* 88, 4270–4274.
- Hey, J., Fitch, W.M., Ayala, F.J., 2004. Systematics and the Origin of Species. *Proc. Natl. Acad. Sci. USA* 102 (Suppl 1), 6515–6635.
- Kimura, M., 1968. Evolutionary Rate at the Molecular Level. *Nature* 217, 624–626.
- Kimura, M., 1969. The Rate of Molecular Evolution Considered from the Standpoint of Population Genetics. *Proc. Natl. Acad. Sci. USA* 63, 1181–1188.
- Kimura, M., Ohta, T., 1972. Protein Polymorphism as a Phase of Molecular Evolution. *Nature* 229, 467–469.
- Langley, C.H., Fitch, W.M., 1974. An Examination of the Constancy of the Rate of Molecular Evolution. *J. Mole. Evol.* 3, 161–177.
- Vogel, H.J., Bryson, V., Lampen, J.O. (Eds.), 1963. *Information Macromolecules*. Academic Press, New York.
- Wallace, R.G., Hodac, H.M., Lathrop, R.H., Fitch, W.M., 2007. A statistical phylogeny of influenza A H5N1. *Proc. Natl. Acad. Sci. USA* 104, 4473–4478.
- Zuckermandl, E., Pauling, L., 1965. Evolutionary Divergence and Convergence in Proteins. In: Bryson, V., Vogel, H.J. (Eds.), *Evolving genes and proteins*. Academic Press, New York, pp. 97–166.

Francisco J. Ayala  
 Department of Ecology and Evolutionary Biology,  
 University of California,  
 Irvine, CA 92697, USA  
 Tel.: +1 949 824 8293; fax: +1 949 824 2474.  
 E-mail address: fjayala@uci.edu