

Models of the Molecular Clock Hypothesis: *Resolving the Neanderthal Paradox*

by Scott R. Herriott, Ph.D.

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3:30 p.m.
Violette Hall 1200

Recent studies have used pairwise differences in DNA sequences to determine the time elapsed since two lineages had a common ancestor. The most basic mathematical model, analogous to radioactive decay, was modified for genetic dating long ago to account for the possibility that the same nucleotide substitution can occur at the same site in each lineage and that a substitution can be reversed by a later change. Since 1969, progressively more inclusive mathematical models have been developed to account for these unique features of DNA evolution.

This presentation develops an equation and method for calculating the expected percentage of sites that will be common to two lineages as a function of time, making it possible to date the divergence of two lineages. The method permits different rates for all 12 types of observable nucleotide substitution. It thereby generalizes the HKY and Tamura-Nei analytical models that are in current use for genetic dating and provides an analytic solution for the more complex models that are now estimated by maximum likelihood.

The model assumes that nucleotide frequencies are in equilibrium and substitution rates are stationary over time. When the nucleotide substitution rate is homogeneous across DNA sites, the model equation is quadratic in form with exponential components. The model has two free parameters, which must be calibrated from nucleotide substitution data, nucleotide frequencies, and the divergence times and genetic differences of two lineages in relation to the lineage of interest. When the nucleotide substitution rates are heterogeneous across DNA sites, the model equation is a sum of shifted power functions. Routines available in a spreadsheet program can perform the necessary calculations.

I illustrate the model on data for the separation of the Neanderthal and modern human lines (Klings, Stone, Schmitz, Krainitzki, Stoneking, and Paabo, 1997. Neandertal DNA sequences and the origin of modern humans. *Cell* 90, p. 19–30.) My calculated divergence time of 2 million years ago contrasts with their stated conclusion of 600,000 years. The resolution of this paradox gives some insight about the use of mathematical models by molecular biologists and how they should be written up for publication.

The presentation will close with a discussion of two open research questions.

Scott Herriott is a professor at Maharishi University of Management in Fairfield, Iowa. He received his Ph.D. from Stanford University in applied mathematics (Management Science and Engineering.) He is also the author of a new textbook, *College Algebra Through Functions and Models* published by Brooks-Cole.