NONLINEAR MOLECULAR CLOCKS AND APE-HUMAN DIVERGENCE TIMES

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Preference for simple rather than complex hypotheses is axiomatic in science. "Occam's razor" and "parsimony" both express this principle. It is important to note in framing and comparing evolutionary hypotheses that an operational preference for simple explanations does not imply that evolution itself is simple. We study evolution, however complex, by building, testing, and sometimes rejecting progressively more complicated models to account for new observations earlier and simpler models could not anticipate (let alone explain). This process of learning requires inductive hypothesis formation based on a collected body of past observation, followed by deductive testing using newly acquired observations. New observations may corroborate and strengthen the hypothesis under which they were collected, or new observations may require modification of a given working hypothesis. In either case, once made, new observations become a part of the collected body of past observation and the process of learning continues.

This approach to learning, with its continual interplay of induction and deduction, is nowhere more apparent than in the tortuous development of our present understanding of human evolution. A "missing link" is a paleontologist's hypothesis about a stage of evolution not represented by fossils. It is a prediction about what one expects to find. Some missing links are found, corroborating and strengthening models predicting their existence (in which case the "links" are, of course, no longer "missing"). Sometimes the search for missing links yields unexpected results, requiring modification of one's working hypothesis.

Many missing links have been found in sixty years of human paleontology in Africa, beginning with Dart's recognition of the significance of Australopithecus africanus. Other predicted links have been abandoned as new finds rendered their discovery improbable.

My purpose here is not to review the human fossil record, but rather to discuss interpretation of new evidence, originating outside the realm of paleontology, that bears directly on the relationships of humans and extant apes, our closest living relatives. Living African apes are virtually unknown as fossils, and any estimate of the closeness or distance of their genealogical relationship to humans requires comparison based on visible morphology, which is difficult to quantify and interpret, or comparison of structure at a molecular level, which appears easier to measure and relatively straightforward in interpretation.

The current concensus model of molecular evolution, as befits hypotheses in young sciences, is among the simplest of possible models. It is based on a Poisson metric (Zuckerkandl, Pauling 1965) transformed (augmented or corrected) to make it linear. The "neutralist hypothesis" of molecular evolution follows from the Zuckerkandl-Pauling model, indeed it is assumed implicitly in this model. The Zuckerkandl-Pauling model was constructed for blood proteins (globins), and initially calibrated using a single paleontological estimate of the time of human (primate) versus other mammal divergence. Zuckerkandl and Pauling demonstrated at once the great value of paleontological calibration for placing molecular difference in evolutionary context and the potential of a calibrated molecular clock for clarifying unknown molecular or organismal genealogies and divergence times.

Recent studies recognize variation in molecular difference/divergence time ratios, but this is usually assumed to reflect random variation about a linear trend. Reed and Lestrel (1970), Radinsky (1978), and Corruccini et al. (1980) questioned the appropriateness of linear models. Here I shall briefly outline preliminary results of an ongoing effort to test the linear model using multiple calibration points derived from the primate fossil record. These results are important for understanding evolution at the molecular level, and they have an important bearing on molecular clocks used to predict ape-human divergence times.

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Simply stated, the Zuckerkandl-Pauling model predicts that augmented or corrected molecular difference (MD) should be a linear function of divergence time (DT). Algebraically:

$$MD = a(DT) \qquad (1)$$

where a is a constant. A linear model like that in Equation 1 is a special case of the general power function:

$$MD = a(DT)^b \qquad (2)$$

where the exponent b = 1. Linearity can be tested by examining whether an empirically derived b differs significantly from unity. Relative rate tests (Sarich, Wilson 1967) measure internal consistency in a set of molecular data, but they do not bear on the problem of how rates behave in real time. Tests in real time require molecular difference values and geological divergence times for a minimum of two nonzero calibration points.

Primates are the most intensively studied mammals. The fossil record of primate evolution is among the best known for any group, offering the greatest potential for testing the linearity assumption inherent in the Zuckerkandl-Pauling model and the neutralist hypothesis. Three primate divergence intervals are sufficiently well established paleontologically to be of use here. These are Hominoidea-Cercopithecoidea at the Oligocene-Miocene transition (ca. 20-30 myBP), Catarrhini-Platyrrhini at the Eocene-Oligocene transition (ca. 35-45 myBP), and Anthropoidea-Prosimii at the Paleocene-Eocene transition (ca. 50-60 myBP) (Radinsky 1978; Szalay, Delson 1979; Pilbeam 1984; Gingerich 1984). These divergence intervals are bounded on the left by appearance of both descendants in the fossil record and on the right by complete absence of primates of the grade in question known in the fossil record. Central values for each major divergence (25, 40, and 55 myBP) are used in the following analysis. Ape-human divergences, the subject of this study, are open to interpretation paleontologically and thus here considered unknowns to be predicted.

The most widely cited molecular studies predicting ape-human divergence times are those of Sarich (1968, 1970), based on immunological comparisons of primate albumins (Fig. 1). Other studies providing additional measures of molecular difference that can be scaled against the primate
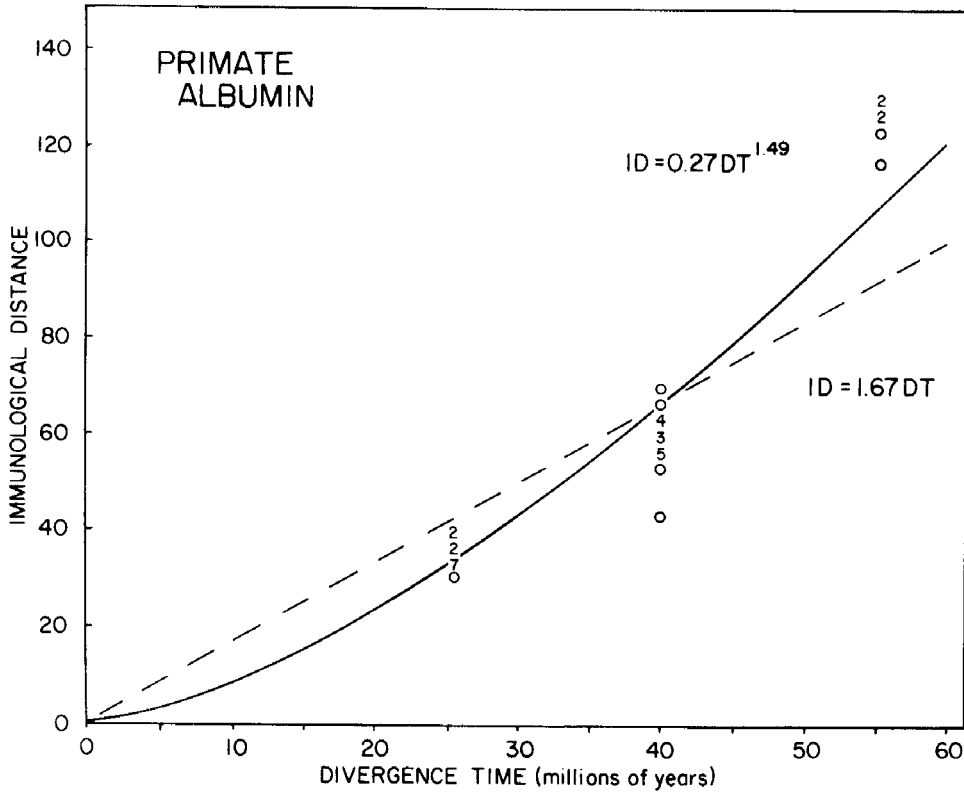
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PRIMATE
ALBUMIN

IMMUNOLOGICAL DISTANCE

$ID = 0.27 DT^{1.49}$

$ID = 1.67 DT$

140

120

100

80

60

40

20

0

DIVERGENCE TIME (millions of years)

0   10   20   30   40   50   60

Fig. 1.   Comparison of Hominoidea-Cercopithecoidea,
Catarrhini-Platyrrhini, and Anthropoidea-Prosimii albumin
immunological distances (ID; from Sarich 1968, 1970) with
paleontologically constrained divergence times (DT) of 25,
40, and 55 myBP (see text).   Exponent 1.49 of power function
fit to data has 95% confidence interval of 1.31-1.67,
significantly greater than unity and precluding linear model
ID = 1.67(DT) employed by Sarich (1970: 194).   Anthropoid-
prosimian divergence at 75 myBP is predicted by Sarich
model, which would require a last common ancestor for
anthropoids and prosimians 20 m.y. older than any known
primate of prosimian grade (and fully 10 m.y. older than any
known mammal of remotely primate grade).   Linear model
predicts recent divergence times that are too young and
ancient divergence times that are too old.   Power function
is more consistent with fossil record over entire range of
primate history and Cenozoic time.   Albumin ID of 7 units
for Homo-Pan yields a predicted DT of 4.2 myBP using Sarich
model and a predicted DT of 8.9 myBP, more than twice as
great, using power function fit to same data.

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Table 1. Predicted divergence times (myBP) for apes and humans, based on temporal scaling of molecular evolution.

Source	Homo vs.:	Pan	Gorilla	Pongo	Hylobates
Immunology					
Albumin (ID)		8.9	10.5	12.8	14.8
(Sarich 1968,1970)					
Transferrin		10.1	-	-	-
(Sarich, Cronin 1976)					
Summed proteins (AD)		7.6-11.2	9.5-10.3	18.9	18.2-21.3
(Dene et al. 1976)					
Nucleic acid hybridization					
DNA (del TS C)		11.2	-	-	-
(Kohne et al. 1972)					
DNA (del TmR C)		7.0-7.3	7.3-7.9	(13.1)	18.1-19.4
(Benveniste, Todaro 1976)					
DNA (del mode C)		10.0	13.3	19.1	20.9
(Sibley in Pilbeam 1983)					
Means		**9.2**	**9.8**	**16.0**	**18.7**
Standard deviations		(1.7)	(2.1)	(3.5)	(2.2)

fossil record to yield ape-human divergence times are listed in Table 1. All have exponents b greater than 1.0, indicating similar nonlinear scaling of MD and DT (sequence data show this pattern but exhibit few ape-human differences). Molecular estimates of ape-human divergence times based on paleontologically calibrated nonlinear clocks suggest humans and chimpanzees diverged 9.2 myBP, humans and gorillas diverged 9.8 myBP, humans and orangutans diverged 16.0 myBP, and humans and gibbons diverged 18.7 myBP.

A linear model and neutralist hypothesis of molecular change may have been justifiable on the basis of simplicity a decade ago, but molecular differences are now sufficiently well documented to permit scaling against the fossil record and geological time. Available evidence supports Goodman's (1963) early suggestion of a slowdown of molecular change during primate evolution. Power functions appear adequate to describe this slowdown at present, but new evidence may show such curves to be oversimplified as well.

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