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WHEN CLOCKS (AND COMMUNITIES) COLLIDE: ESTIMATING DIVERGENCE TIME FROM MOLECULES AND THE FOSSIL RECORD

CHRISTOPHER A. BROCHU,[1] COLIN D. SUMRALL,[2] AND JESSICA M. THEODOR[3]

[1]Department of Geoscience, University of Iowa, Iowa City 52242, [2]Department of Geological Sciences, University of Tennessee, Knoxville 37996, and [3]Department of Geology, Illinois State Museum, Springfield 62703

TRADITIONALLY, DEEP time was the domain of paleontology. Origination time could be assessed only through reference to first appearance data in the rock record. This changed almost from the beginnings of modern molecular biology, when it was realized that molecules could be used to calculate divergence times between living species. Early studies relied on immunological distance information, and the underlying rationale was simple: because evolution involves changes to the genetic code, and because these changes accumulate over time, we should expect the number of accumulated changes (the molecular distance) between living taxa to increase as their time of divergence becomes older (Zuckerkandl and Pauling, 1962). By inferring a rate of evolution of the genetic code, we can place absolute time estimates on divergence points.

Unfortunately, temporal estimates from molecules did not always coincide with first appearance data from the fossil record. This first became apparent with the divergence between humans and living great apes. Based on presumed relationships between fossil and living primates at the time, paleontologists put the human-ape split at roughly 20 million years (Simons, 1961; Pilbeam, 1968). Protein clock studies, and later sequence-based analyses, suggested a much more recent divergence within the past 10 million years (Sarich and Wilson, 1967; Hasegawa et al., 1985).

The outcome of this particular conflict colored the nature of the debate for many years. New fossil discoveries eventually put the human-chimp split much closer to the molecular estimate (Fleagle, 1998). This became the standard textbook example of the molecule-fossil rift, and it seemed to lend credence to claims that molecular approaches were somehow more reliable than those restricted to paleontology. Throughout the 1980s and up to the present, it was not uncommon to see published claims that molecular data were inherently superior to morphology and fossils in phylogeny reconstruction and divergence time estimation (e.g., Sibley and Ahlquist, 1987; Goodman, 1989; Hedges and Sibley, 1994; Givnish and Sytsma, 1997; Douady et al., 2002)—even though molecules and morphology usually support very similar results.

Several other temporal conflicts have come to the surface over the past 10 years. The most prominent involve the origin of living mammalian and avian ''orders.'' Most first appear as fossils in the latest Cretaceous or Paleogene, but are predicted to have much longer roots in the Mesozoic from molecular evidence (Cooper and Penny, 1997; Bromham et al., 1999a; Foote et al., 1999; van Tuinen et al., 2000; Archibald and Duetschman, 2001; Springer et al., 2003). Similarly, the origin of metazoan phyla, most of which first appear during the ''Cambrian Explosion'' 550 ma but which are estimated to have originated as much as 1.5 billion years ago on the basis of mitochondrial data (Wray et al., 1996; Bromham, 2003; Budd, 2003). Other conflicts have received less attention but remain no less perplexing, such as the origin of angiosperms (Doyle, 1998; Wikström et al., 2001) and gavialoid crocodylians (Brochu, 1997; Harshman et al., 2003). These have remained robust to improved data sets and techniques—the more we look at fossils, molecules, or algorithms, the stronger the disparity seems to grow.

What causes these conflicts? We believe part of the problem continues to be a lack of interaction between proponents of fossil-based and molecule-based dating approaches. This is unfortunate, because the centralization of these conflicts and a lack of dialogue mask the basic fact that molecules and fossils often support the same answer, and in some cases, the answers are different because the questions are different (even if we fail to recognize the difference). And both approaches must ultimately refer to the fossil record.

We organized a symposium at the Sixth North American Paleontological Convention entitled ''When Clocks Collide: Calibrating Lineage Divergences from Fossils and Molecules.'' It brought experts together from a wide range of disciplines, specialists on a large array of taxonomic problems, and proponents of a diversity of methods to discuss these issues and try to reach a level of understanding of the sources of the conflict and address some possible solutions. Attendees of that symposium were treated to some remarkable talks and post-talk exchanges. Not surprisingly (to us), very little blood was drawn—the fields of paleontology and molecular systematics are beginning to integrate, as they should.

Ours was not the only such event in recent years (e.g., Hadly, 2003). The number of papers and funded research programs involving the collaboration between molecular biologists and morphologists is growing. This is remarkable considering the lack of dialogue in the years since Colin Patterson (1987) edited *Molecules and Morphology in Evolution: Conflict or Compromise?* We are seeing the synthesis our field has needed for so long.

We here expand on our point that miscommunication is as important as real data conflict in these debates. It is written from a paleontologist's perspective, and is perhaps slanted against misinterpretations of the paleontological literature by neontologists. Paleontologists may feel beleaguered when revised fossil information overturns long-held beliefs and conforms to a molecular estimate, but the unease is misplaced; in many cases, fossils and molecules have never been in conflict. The conflict is a matter of interpretation, and as long as competing hypotheses are not completely understood, the magnitude of the ''conflict'' will be exaggerated. As seen in the papers in this issue, we still have a long way to go to resolve some of the inconsistencies between sources of information—but an integrative approach holds the greatest promise in achieving the one goal of understanding the history of life as thoroughly as possible.

THROUGH A GLASS DARKLY—IMPERFECTIONS IN DATING TECHNIQUES

The classic ''molecular clock'' approach follows from the theory of neutral evolution (Kimura, 1968)—molecular evolution, when not under directional selection, can be treated as a stochastic process. The longer two lineages are separate, the greater the number of nucleotide differences we should find between them. Accumulated stochastic changes will show a uniform rate averaged over extended periods of time, much like a radiometric ''clock.'' The earliest applications relied on immunological distances between proteins, but molecular clock studies today almost

exclusively use nucleotide or amino acid sequence data. Time is the number of base differences divided between two taxa, assuming a given rate of change.

Radiometric clocks are a function of physical laws that apply throughout the universe, and we have good reason to view them as constant. But molecular clocks are not so constrained, and the central assumption of molecular clock studies—that rates of evolution are uniform not only over time, but across taxa—is frequently violated (e.g., Huelsenbeck and Rannala, 1997; Yi et al., 2002; Krieger and Fuerst, 2002; Corneli, 2003). Apparent rates should diminish over time as the number of unobserved substitutions increases (Nei, 1987; Arbogast et al., 2002), and although the evolutionary models used to correct for branch length underestimation are growing more sophisticated, this is still a source of uncertainty. Whether biological factors such as generation time and physiology covary with molecular evolutionary rate is debated in the literature (e.g., Mindell et al., 1996; Barraclough and Savolainen, 2001; Bromham, 2002; Whittle and Johnston, 2003), but the existence of lineage-specific rate variation is no longer debated. If different lineages evolve at different rates, a simple division of differences between taxa will not work.

All molecular clock studies ultimately rely on external (usually fossil) calibrations. But was the fossil calibration chosen from within the ingroup, in which case the estimated rate is likelier to apply to some of the study taxa, but is also subject to statistical independence issues; or was it external, which avoids the independence issue but increases the chances that the rate poorly reflects the true ingroup rate (Smith and Peterson, 2002)? More importantly, should one single calibration be used, or should we use multiple independent calibrations—and what do we do if they support radically different rate estimates (as they sometimes do—e.g., Brochu, this issue; van Tuinen and Hedges, this issue)?

Contemporary methods for estimating divergence time are more sophisticated and relax these assumptions. Timing methods can test and account for rate variation among lineages, genes and sites (Swofford et al., 1996; Felsenstein, 2003); and knowing that unmodified branch lengths are underestimates of the actual number of changes to have occurred over time, branch length estimates are based on a specified model of evolution to account for unobserved multiple substitutions per site. But the tradeoff comes either with the removal of information (e.g., deletion of taxa violating the uniform rate rule to ''linearize'' the tree) or the addition of more assumptions to the analysis.

It is well known that no paleontological calibration point is error-free, and error comes from many aspects of the calibration. All inherently underestimate the actual origination time, and the magnitude of the underestimate will vary among taxa. This can be partially ameliorated by applying multiple independent calibrations to minimize the impact of the error associated with any single calibration, but calibration error remains a significant source of molecular divergence error (Marshall, 1990; Springer, 1995).

For this to work, the independent calibration points (whether they be internal or external) have to be independent, but even where independence is claimed, it does not always exist. The widely cited study of Kumar and Hedges (1998), for example, claimed to have used three independent calibration points. In fact, only one was based directly on the fossil record—the other two were molecular time estimates based on this calibration and then treated as calibrations themselves (Lee, 1999), yet all are dependent on the single fossil occurrence. Additional examples have been cited by Smith and Peterson (2002).

Virtually all fossil-bearing strata are dated with nonabsolute relative age dates. Correlation is based on biostratigraphic principles and radiometric dates are incorporated into this framework by fortuitous discovery and dating of small rock units such as ash beds. Radiometric dates have intrinsic measurement error, and since most fossils come from rock units not directly datable with radiometric methods, the date associated with a fossil will usually be between two radiometric benchmarks, each with its associated error. This is especially true for continental deposits, where biostratigraphically informative fossils are less common and less widespread geographically than in marine contexts. Changes in half life estimation, changes in radiometric technique, new fossils, and new phylogenetic interpretations can alter the calibration, underscoring the importance of following developments in several fields, rather than relying on textbook summaries.

In practice, the confidence intervals associated with radiometric dates (or ranges thereof) will be very small relative to the calibrations being used. Extending the age of a calibration point from 100 to 105 million years is unlikely to have a major impact on a given molecular dating technique (Springer, 1995). But this can prove important for younger calibrations—adding the same five million years to a calibration in the Pliocene will more than double the calibration's age.

Error related to the gap between first appearance datum and actual origination time is harder to quantify. Different methods for assessing sampling error (e.g., Marshall, 1997; Solow, 2003) are based on the distribution of fossils throughout a stratigraphic range (information that does not exist, or is very imprecise, for many fossil groups) and make assumptions about abundance and preservation potential outside the actual stratigraphic range. Changes to these assumptions can have a dramatic impact on the resulting confidence intervals (Marshall, 1999). The nature of this kind of error will obviously vary taxonomically, either because of the nature of the organisms themselves or their ecology. It will also vary temporally with eustatically driven erosional and depositional cycles (Holland and Patzkowsky, 2002). The potential for recovery of fossils from older rocks is limited by the amount of rock present and exposed. Older sediments are more likely to have been destroyed by subduction and erosion. These methods are not widely used, and analyses comparing the various methods with a variety of groups and temporal scales have not been completed. For these reasons, sampling-based stratigraphic error remains a significant unknown.

BARRIERS TO MUTUAL UNDERSTANDING

Conflicting meanings of taxon names.—Taxon names have not been applied as uniformly as many might think. The nineteenth century was dominated by typological approaches in which taxa were somehow ''defined'' by the presence of particular key characters. We now understand taxa to be the products of descent with modification, but whereas taxon names are sometimes formally *expressed* as either stem-based or node-based groups, they may continue to be *applied* as typological categories.

The resulting miscommunication can create the impression of data set incongruence where none exists. For example, Kirchman et al. (2001) conducted a molecular phylogenetic analysis of ground roller birds, finding that if the earliest ground rollers were in the Early Eocene (as indicated in the literature), rates of molecular evolution would be anomalously low. But Mayr and Mourer-Chauvire (2003) showed that these Eocene fossils are not crown-group ground rollers. The divergence among living rollers is much younger than the Eocene, removing the rate anomaly.

A similar situation occurred between molecular and paleontological estimates of the age of the ''true crocodiles'' (*Crocodylus*). Molecular data addressed the last common ancestor of living species, which was estimated to have been in the Neogene (Densmore, 1983), but the name was used by paleontologists as a catch-all for any fossil crocodyliform not obviously belonging to some other established taxon, with a range extending into the Mesozoic (Markwick, 1998). Phylogenetically, the earliest fossils belonging

to the crown genus are of Neogene age, and very few would have suggested that any pre-Oligocene fossil was closely related or ancestral to any particular living species (Brochu, 2000). The two different ''*Crocodylus*'' differ in age by an order of magnitude.

In these cases, the data have always been in close agreement. Fundamentally different applications of the same name prevented recognition of this basic fact. As a result, fundamentally different questions were asked of different data sets.

These distinctions can be important for divergence time calibration. Van Tuinen and Hedges (this volume), for example, show that divergence estimates within birds increase fivefold by regarding certain fossils as members of a crown group and not the base of the stem. Bromham et al. (1999b) argued that the conflict is often between molecular stem-based concepts and morphological crowns—molecules are estimating when the stems diverged, but paleontologists recognize taxa by the appearance of diagnostic characters for the crown.

A related problem is the lag time between cladogenesis and the acquisition of distinctive crown group characters. The ancestors of elephants and dugongs may have looked more or less like modern shrews in outward appearance long before either began to look elephantine or dugongian, even though these lineages were on different evolutionary trajectories. *Divergence* timing need not coincide with *diversification* timing (Bromham et al., 1999a; Alroy, 1999; Cracraft, 2001).

Data versus scenarios.—Disagreements are not between molecules and fossils, but on hypotheses (or scenarios) based on one and the other. When we claim the fossil record to disagree with molecular estimates placing modern mammalian orders deep in the Mesozoic, we refer to a hypothesis in which mammalian orders diversified not long before they first appear in the fossil record. Molecular estimates are consistent with the fossil record—logically, any hypothesis in which true originations precede first appearances is consistent with it—but are inconsistent with a particular scenario based on the fossil record. For this reason, many conflicts are wrongly expressed as ''molecules versus fossils'' when it is the scenarios that are in conflict.

Consider the überexample of molecule-fossil conflict: the human-chimp split. The 20 million year estimate was based on a widespread assemblage of extinct apes now called *Sivapithecus*. *Sivapithecus* was thought to be more similar to humans than to other primates (Pilbeam, 1968), but this was based on fragmentary remains open to multiple interpretations (Fleagle, 1998). The shape of the palate, for example, was thought to be more humanlike than apelike, even though the palate was incompletely known and could be restored with apelike or humanlike features. Confirmation that the fossil record agreed with molecular divergence estimates came with more complete specimens of *Sivapithecus*. These forced a reinterpretation of *Sivapithecus*' morphology. We now regard *Sivapithecus* as a close relative of orangutans. The oldest known fossil hominids are four to seven million years in age, depending on the relationships of newly described fossils older than four million years (Wood, 2002).

Another example involves birds. Molecular evidence predicts the presence of modern avian orders prior to their first appearances in the fossil record, but most such discussions apply a fossil model in which bird orders sprang rapidly from vague ''shorebird'' ancestors at or near the K-T Boundary (e.g., Feduccia, 1995). This is based on a strict reading of the fossil record—many of the earliest crown-group avian appearances are of shorebirdlike animals (not surprising, as shorebirds are likelier to be found near depositional environments), and other bird groups appear later. First appearances by themselves may postdate molecular estimates, but if we look at fossil birds phylogenetically (Cracraft, 2001; Hope, 2002), we find multiple ghost lineages extending back from first appearances in the Early Tertiary to the Late Cretaceous. ''Shorebirds'' are not a primitive pool of basal forms, but a derived assemblage of taxa related to many other lineages that themselves must have occurred in the Cretaceous. Phylogenetically calibrated first appearances still postdate molecular predictions, but the issue is no longer one of whether bird orders are products of a post-Cretaceous explosive radiation.

In these cases, part of the conflict was inappropriately thought to reflect fundamental differences in the data. In the human-chimp example, the problem was one of incomplete data—an issue of concern to all systematists, regardless of where the information comes from. Improvement of our *Sivapithecus* sample corrected the error, just as many molecular hypotheses have been overturned with the addition of a new data. In the avian example, some of the conflict is related to the absence of phylogenetic methodology—again, something of which all must be aware. A phylogenetic hypothesis was being compared with a stratigraphic scenario.

Ad hoc dismissal.—Molecular and fossil data sets are less often in conflict than some may believe, but some intriguing cases of discord remain. A common tendency in the face of conflicting conclusions is to assume that one of the data sets is somehow ''wrong.'' Unfortunately, this sometimes leads to ad hoc explanations that do little than hide oneself from incongruous information.

Consider, for example, common molecular explanations for the controversy over mammalian divergence timing (Easteal, 2001). Molecular information tells us mammalian orders split in the mid-Cretaceous. Obviously, the fossil record is simply incomplete, and we have yet to find the ''right'' fossils. Or the ''right'' fossils were never preserved and will never be found. Or we have them, but they lack the diagnostic features that would allow us to tie them to the morphologically recognizable ''orders'' that first appear in the Cenozoic. Short of actually finding these ''right'' fossils, these are ad hoc explanations little different from just saying ''the fossil record is unreliable and should be disregarded''—an odd position to take, given that calibrations in the molecular realm are taken from the fossil record.

Conversely, paleontologists often dismiss molecular clock methods because they seem irrelevant to their own research (which they actually are in the case of entirely extinct groups) or reject them if they support what appear to be unrealistic divergence times. Fossils from extant mammalian orders appear much later than molecular divergence estimates suggest. Thus, molecular clocks are inconstant. But the methods we have that would account for heterogeneity (or relax the clock) will fail, because there were odd simultaneous rate increases in all of the orders, probably right when the nonavian dinosaurs croaked (Benton, 2001). The scientific equivalent of a miracle happened, and we just have to accept that.

These are really the same argument—one source of information is superior to another. While this is undoubtedly true in some cases, it is not universal. We know molecular clocks are imprecise, and we know first appearances underestimate true originations. The correct answer likely lies somewhere in between, and resolution of the issue will depend on hypothesis testing—and conflicting divergence timing scenarios do generate falsifiable hypotheses. Unfalsifiable explanations to wish conflicting data away do little good.

DISCUSSION

Given that estimation of divergence time is not the primary research focus for most paleontologists, and given that our research is unlikely to result in the single centralized data base of taxon FADs molecular biologists would like to have, it is in our own best interest to improve access to our data by molecular biologists interested in divergence timing. We can do so by providing explicit information on the phylogenetic hypotheses we

use, the methods by which we have generated them, and the sources of error that may impact calibrations drawn from our work.

The absence of testable phylogenetic hypotheses for the vast majority of groups of organisms may seem to make the paleontological literature appear less than adequate to the task of divergence time estimation. Taxon names as applied by paleontologists and molecular biologists are not always mutually intelligible, and the present situation makes miscommunication inevitable. But this must be understood in the context of paleontology as a whole, in which divergence time estimation plays only a very minor part.

Until recently, there has been little perceived reason to establish phylogenetic hypotheses for most extinct groups. But a calibration point is an explicitly phylogenetic statement—it expresses the time when two lineages last shared a common ancestor. We cannot know what those ancestors were without knowing how fossil taxa are related to each other.

This is especially important when a group includes living members. Taxonomic miscommunication can lead to a mismatch between the origin of a character and divergence of the crown group and, ultimately, the use of the same name for different clades. There is a clear need for crown group first appearance data so that calibrations used by molecular systematists actually reflect the clade they are studying.

This is not a matter of altering paleontology to please molecular biology. We happen to be among those who advocate restriction of certain taxon names to crown clades, but this is a controversial point of view. What is needed is a clear understanding of phylogeny, whether or not taxon names are actually changed.

We should go beyond the ''Christmas tree lights'' approach to these conflicts. We see conflict and assume that some aspect of one approach is being misled. A light is out somewhere, and all we have to do is find the bad bulb. But the methods used to find these bulbs often boil down to ad hoc explanations of why a competing hypothesis is fundamentally flawed. We assume that the molecular data are right, that extant bird and mammalian orders arose in the Early Cretaceous, and that our failure to find fossils from these groups reflects imperfections in the fossil record. Or we assume that the fossil record closely approximates the origination times of these orders and that molecular clocks are being misled by mysterious simultaneous speedups of evolutionary rate. As long as the fossil record fails to reveal these fossils, and as long as our methods remain unable to localize the proposed rate changes, neither explanation is at all testable.

A different analogy might be more appropriate. Consider the evolution of the bird hand. Based on the fossil record, birds are unambiguous dinosaurs, and the digits of the hand are unambiguously 1–2–3. Based on developmental data, the digits of the bird hand are unambiguously 2–3–4 (Burke and Feduccia, 1997; Gauthier and Wagner, 1998; Larsson and Wagner, 2002; Kundrát et al., 2002). This was once used as evidence against the dinosaurian nature of birds, but this is no longer a tenable point of view—the fossil evidence is very firm, and the phylogenetic sequence clearly shows the fifth digit diminishing and disappearing, followed by reduction and loss of the fourth. But the developmental anlage of digits 1 and 5 appear and disappear in the embryonic bird wing, leaving the second through fourth. In this instance, both sources of information are ''right''—we can explore the reason for the disparity, but ruling one out as ''off'' is simply not an option. We still do not know the whole story, but the search for the answer is bolstering the integration of paleontology, phylogenetics, and evolutionary developmental morphology.

Perhaps we should approach conflicts in divergence timing the same way—the signals look different, but are reflecting different parts of a group's evolutionary history and are thus both ''correct.'' In this context, some of the ad hoc rationalizations used to dismiss other data sets can be turned into research programs. If molecular divergence estimates reflect real lineage divergences, and if they long predate first fossil appearances, where would we look for fossils filling in the gap? What would they look like? Is there a disconnect between molecular divergence and phenotypic differentiation that would result in a lag between genetic and morphological separation? What are the developmental or molecular mechanisms that would lead to such a disconnect?

Conversely, if fossil first appearance data are approximating the dates of real radiations, what are the implications for molecular dating? Are we somehow overcorrecting branch length? Are some of the major explosive radiations in the fossil record the products of long evolutionary fuses, with the radiations themselves not apparent in molecular analyses with limited taxon sampling? This latter possibility does not necessarily imply that molecules are right and fossils wrong—it reinforces the unquestioned fact that no single source of data, including molecules, can ever tell the whole story.

The integration of molecular biology and paleontology can address many large-scale questions. Are rates of molecular and morphological evolution correlated (Omland, 1997; Bromham et al., 2002)? Do we see covariance in rates of molecular evolution and speciation (e.g., Webster et al., 2003)? Can molecular information guide the identification of problematic fossils (e.g., Waggoner and Collins, this volume)? We stand to learn much by dismissing less and discussing more.

The current climate is conducive to such discussions. The papers presented here illustrate a synthetic approach—examination of all of the evidence is preferable to relying on one source of data over all others. We eagerly look forward to the lessons we will all learn in coming years as paleontologists and molecular systematists find their common ground and walk forward into the history of life.

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