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Guest Editorial

The Zuckerkandl Prize: Structure and Evolution

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The Zuckerkandl Prize, established by Springer-Verlag in 2002 to honor Emile Zuckerkandl and his contributions to molecular evolution, is awarded this year to Gustavo Caetano-Anollés for his paper on "Evolved RNA Secondary Structure and the Rooting of the Universal Tree of Life" (Caetano-Anollés 2002). The editors of the *Journal of Molecular Evolution* have judged this to be the best paper in the journal last year due to its creative use of structure, and the evolution of structure, to reconstruct deep phylogenies.

Caetano-Anollés first aligned RNA topological features based on their context in the entire molecular structure. Alignments were further modified using combinations of folding algorithm predictions, comparative sequence analysis, or iterative rounds of phylogenetic reconstruction and tracing of characters by hand. Homologous topological features (shapes) were then coded by type (such as base-paired stems, hairpin loops, bulges in the midst of stems, and unpaired sequences), and stems were further coded by identifiable features relevant to thermodynamic stability such as length, number of bulges, and number of non-canonical base pairs. Phylogenies were reconstructed under an assumption of polarized characters in which the more thermodynamically stable states are considered ancestral.

This analysis is distinguished by a number of features. In addition to inclusion of an impressive number of RNA molecule types (SRP RNA, Y RNA, RNAse P RNA, snRNA, tRNA, SSU rRNA, LSU rRNA, 5S rRNA, and spacer rRNA), the author is careful to include datasets that represent evolution on different time scales. Clearly, different structural features evolve at vastly different and fluctuating rates, but the importance of time scale comparisons is often overlooked. This work is perhaps most significant for its potential rather than for its specific results. It represents an important step in the quest to embed structure and function directly into phylogenetic analysis. No topological features of ancient relationships are dramatically overturned, and results on rooting are dependent on the arguable assumption that the most stable features are ancestral. It points the way, though, to consideration in a thorough and detailed way how structures evolve from one to the other, how functional understanding can lead to rooting hypotheses, and how to include this information in phylogenetic reconstruction. As the authors point out, more detailed models can and should be developed and evaluated; future approaches will undoubtedly include variable rates and other variable model parameters in a probabilistic (maximum-likelihood or Bayesian) setting.

By linking sequence to shape and structure, this study also points the way to understanding how at least this one set of "morphological" characters can transform among themselves. Such analyses will eventually provide details of correlation among characters that are coded from continuous shapes into discrete units for processing, and perhaps also some insights into the causes of homoplasy in morphological characters. By extending upward from sequence evolution to shape evolution, we can begin to understand how functional selection drives specific sequence changes that alter morphology and bring about functional evolution. This is critical if we are to distinguish the domes of the molecular basilica from

the mosaics on the molecular spandrels that support them.

With proteins as well as RNA, the integration of structure, function, and mechanism into phylogenetic analysis is developing into an important emerging subdiscipline of molecular evolution. Related approaches are beginning to have strong impacts both in predicting and understanding mechanism, and in using that understanding to improve phylogenetic reconstruction. RNA has an important advantage over proteins in the relative accuracy of its secondary structure predictions, and may therefore act as a template for protein scientists on how to approach important issues and test novel techniques. This prize-winning study is a good and creative example of both.

Reference

Caetano-Anollés G (2002) Evolved RNA secondary structure and the rooting of the universal tree of life. J Mol Evol 54:333–345