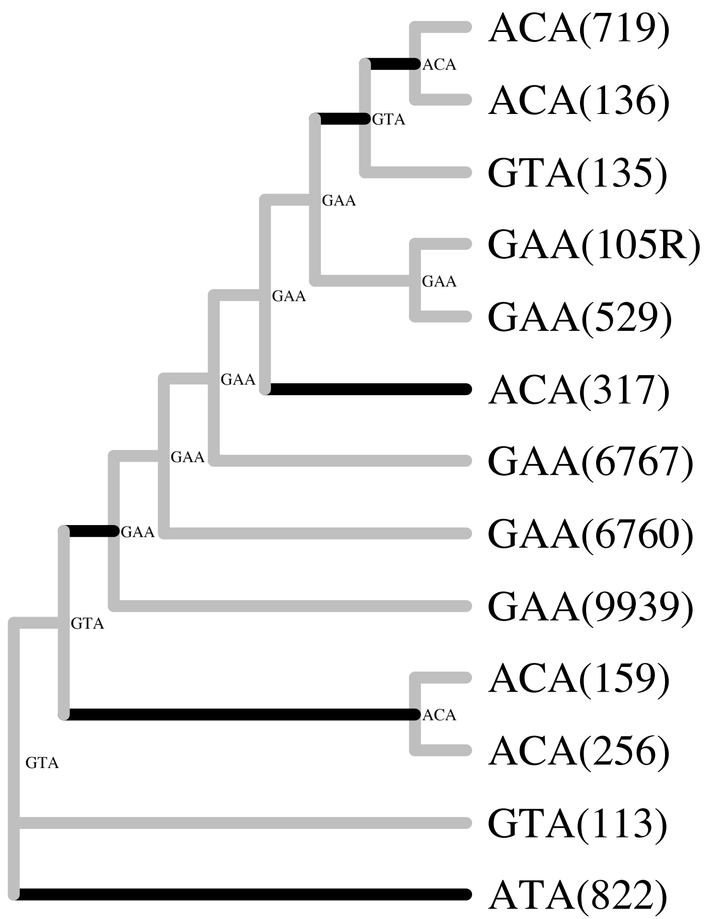

Fig. 1.6. An illustration of SLAC method, applied to a small HIV-1 envelope V3 loop alignment. Sequence names are shown in parentheses. Likelihood state ancestral reconstruction is shown at internal nodes. The parsimonious count yields 0 synonymous and 9 non-synonymous substitutions (highlighted with a dark shade) at that site. Based on the codon composition of the site and branch lengths (not shown), the expected proportion of synonymous substitutions is $p_e = 0.25$. An extended binomial distribution on 9 substitutions with the probability of success of 0.25, the probability of observing 0 synonymous substitutions is 0.07, hence the site is borderline significant for positive selection.

Codon-substitution models

A likelihood approach for comparing synonymous and nonsynonymous nucleotide substitution rates, with application to the chloroplast genome
S. V. Muse and B. S. Gaut
Mol Biol Evol **11** 715-724 (1994)

~800 citations

A codon-based model of nucleotide substitution for protein-coding DNA sequences.
N. Goldman and Z. Yang
Mol Biol Evol **11** 725--736 (1994)

~1820 citations

- In 1994, first tractable mechanistic evolutionary models for codon sequences were proposed by **Muse and Gaut** (MG94), and, independently, by **Goldman and Yang** (GY94) [in the same issue of MBE, back to back]
- Markov models of codon substitution provide a powerful framework for **estimating substitution rates** from coding sequence data, as they
  - *encode our mechanistic understanding of the evolutionary process,*
  - *enable one to compute the phylogenetic likelihood,*
  - *permit hypothesis testing or Bayesian inference,*
  - *systematically account for confounding processes (unequal base frequencies, nucleotide substitution biases, etc.),*
  - *afford many opportunities for extension and refinement (still happening today).*