Codon-substitution models

- 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).

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)

~1000 citations

A codon-based model of nucleotide substitution for proteincoding DNA sequences.

N. Goldman and Z. Yang
Mol Biol Evol 11 725-736 (1994)

~2250 citations

Three example datasets

West Nile Virus NS3 protein

- An interesting case study of how positive selection detection methods lead to testable hypotheses for function discovery
- Brault et al 2007, A single positively selected West Nile viral mutation confers increased virogenesis in American crows

HIV-1 transmission pair

- Partial *env* sequences from two epidemiologically linked individuals
- An example of multiple selective environments (source, recipient, transmission)

SARS-CoV-2 Spike

- Full length spike sequences chosen to represent viral diversity (circa mid 2021)
- Good example for analyzing selection in population samples with many "deadend" intra-host variants