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)

~1000 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)

~2250 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).*

Rate matrix for an MG-style codon model

$$(\text{Rate})_{X,Y}(dt) = \begin{cases} \alpha R_{xy}\,\pi_t dt & , \quad \text{one-step, synonymous substitution,} \\ \beta R_{xy}\,\pi_t dt & , \quad \text{one-step, non-synonymous substitution,} \\ 0 & , \quad \text{multi-step.} \end{cases}$$

X,Y = AAA...TTT (excluding stop codons),
π_t - frequency of the target nucleotide.
Example substitutions:
AAC→AAT (one step, synonymous - Aspargine) αR_{CT}
CAC→GAC (one step, non-synonymous - Histidine to Aspartic Acid) βR_{CG}
AAC→GTC (multi-step).

α (syn. rate) and **β** (non-syn. rate)
are the key quantities for all selection analyses