Computing the transition probabilities

- In order to recover transition probabilities `T(t)` from the rate matrix `Q`, one computes the matrix exponential `T(t) = exp (Qt),` same as with standard nucleotide models, e.g. HKY85 or GTR

- Because the computational complexity of matrix exponentiation scales as the cube of the matrix dimension, codon based models require roughly `(61/4)`³ `≈ 3500` more operations than nucleotide models

- This explains why codon probabilistic models were not introduced until the 1990s, even though they are relatively straightforward extensions of 4x4 nucleotide models

Multiple substitutions

- The model assumes that point mutations alter one nucleotide at a time, hence most of the instantaneous rates (`3134/3761` or `84.2`% in the case of the universal genetic code) are `0`.

- This restriction, however, does not mean that the model disallows any substitutions that involve multiple nucleotides (e.g., **ACT**⟹**AGG**).

  - This can be further relaxed with models supporting multiple nucleotide changes.

- Such substitutions must simply be realized via several single nucleotide steps, e.g., **ACT**⟹**AGT**⟹**AGG**

- In fact the `(i,j)` element of `T(t) = exp(Qt)` sums the probabilities of all such possible pathways of duration **t**, including reversions

- Compare this to the naive NG86 parsimony approach.