Computing the transition probabilities

- In order to recover transition probabilities $\mathbf{T(t)}$ from the rate matrix $\mathbf{Q}$, one computes the matrix exponential $\mathbf{T(t) = exp\ (Qt)}$, 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 $\mathbf{(61/4)^3 \approx 3500}$ 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

Limitations: 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`. (Sparse)
- 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.