Quantifying selection on coding sequences

1.) selectively constrained:
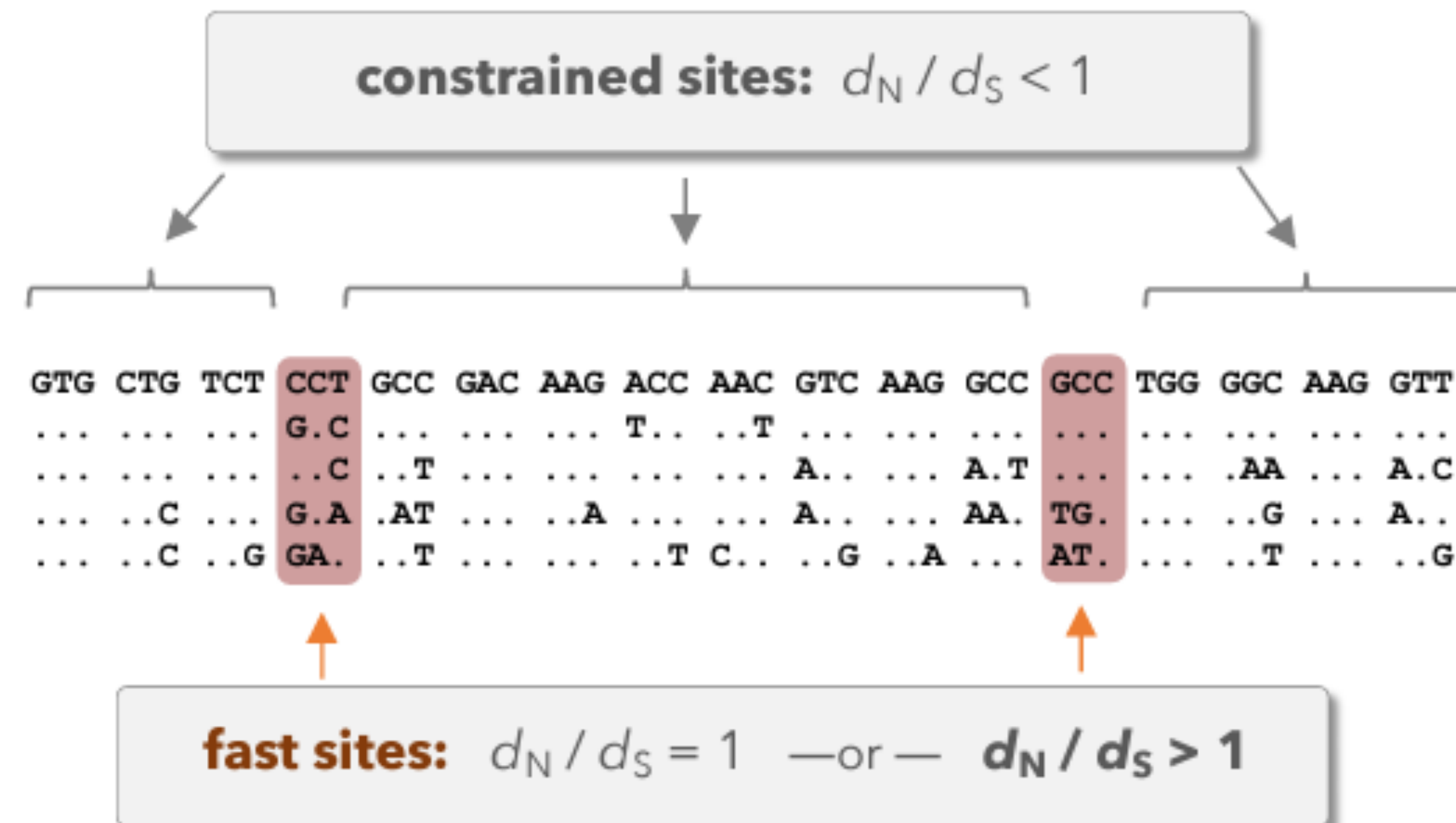
$$d_N / d_S < 1$$

2.) strictly neutral:

$$d_N / d_S = 1$$

3.) adaptive evolution:

$$d_N / d_S > 1$$

constrained sites: $d_N / d_S < 1$

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GTG CTG TCT CCT GCC GAC AAG ACC AAC GTC AAG GCC GCC TGG GGC AAG GTT
... ... ... G.C ... ... ... T.. ..T ... ... ... ... ... ... ... ...
... ... ... ..C ..T ... ... ... ... A.. ... A.T ... ... .AA ... A.C
... ..C ... G.A .AT ... ..A ... ... A.. ... AA. TG. ... ..G ... A..
... ..C ..G GA. ..T ... ... ..T C.. ..G ..A ... AT. ... ..T ... ..G
```

fast sites: $d_N / d_S = 1$ —or— **$d_N / d_S > 1$**

Codon substitution models

the instantaneous rate matrix, Q, is very big: 61 × 61

phenomenological codon models: just a few parameters are needed to cover the 3721 changes between codons!

From codon below:	to codon below:							
	TTT (Phe)	TTC (Phe)	TTA (Leu)	TTG (Leu)	CTT (Leu)	CTC (Leu)	∙∙∙▶	GGG (Gly)
TTT (Phe)	——	$\kappa\pi_{TTC}$	$\omega\pi_{TTA}$	$\omega\pi_{TTG}$	$\omega\kappa\pi_{TTT}$	0	∙∙∙▶	0
TTC (Phe)	$\kappa\pi_{TTT}$	——	$\omega\pi_{TTA}$	$\omega\pi_{TTG}$	0	$\omega\kappa\pi_{CTC}$	∙∙∙▶	0
TTA (Leu)	$\omega\pi_{TTT}$	$\omega\pi_{TTC}$	——		0	0	∙∙∙▶	0
TTG (Leu)	$\omega\pi_{TTT}$	$\omega\pi_{TTC}$	$\kappa\pi_{TTA}$	——	0	0	∙∙∙▶	0
CTT (Leu)	$\omega\kappa\pi_{TTT}$	0	0	0	——	$\kappa\pi_{CTC}$	∙∙∙▶	0
CTC (Leu)	0	$\omega\kappa\pi_{TTC}$	0	0	$\kappa\pi_{TTT}$	——	∙∙∙▶	0
⋮	⋮	⋮	⋮	⋮	⋮	⋮		
GGG (Gly)	0	0	0	0	0	0	0	——

* This is equivalent to the codon model of Goldman and Yang (1994). Parameter $\boldsymbol{\omega}$ is the ratio d_N/d_S, $\boldsymbol{\kappa}$ is the transition/transversion rate ratio, and $\boldsymbol{\pi_i}$ is the equilibrium frequency of the target codon (i).