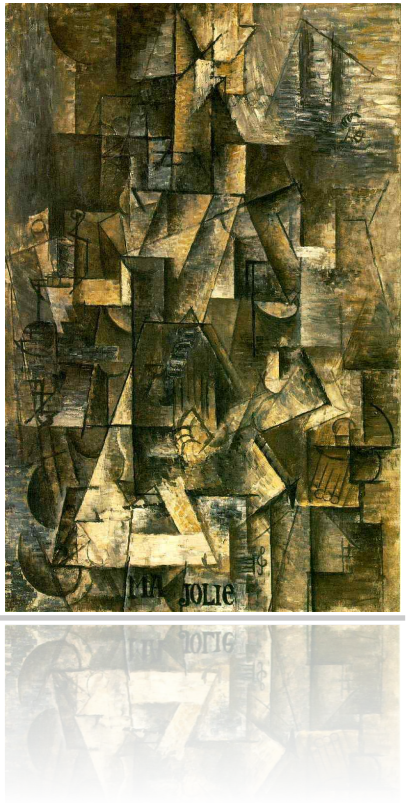
# codon substitution models and the analysis of natural selection pressure

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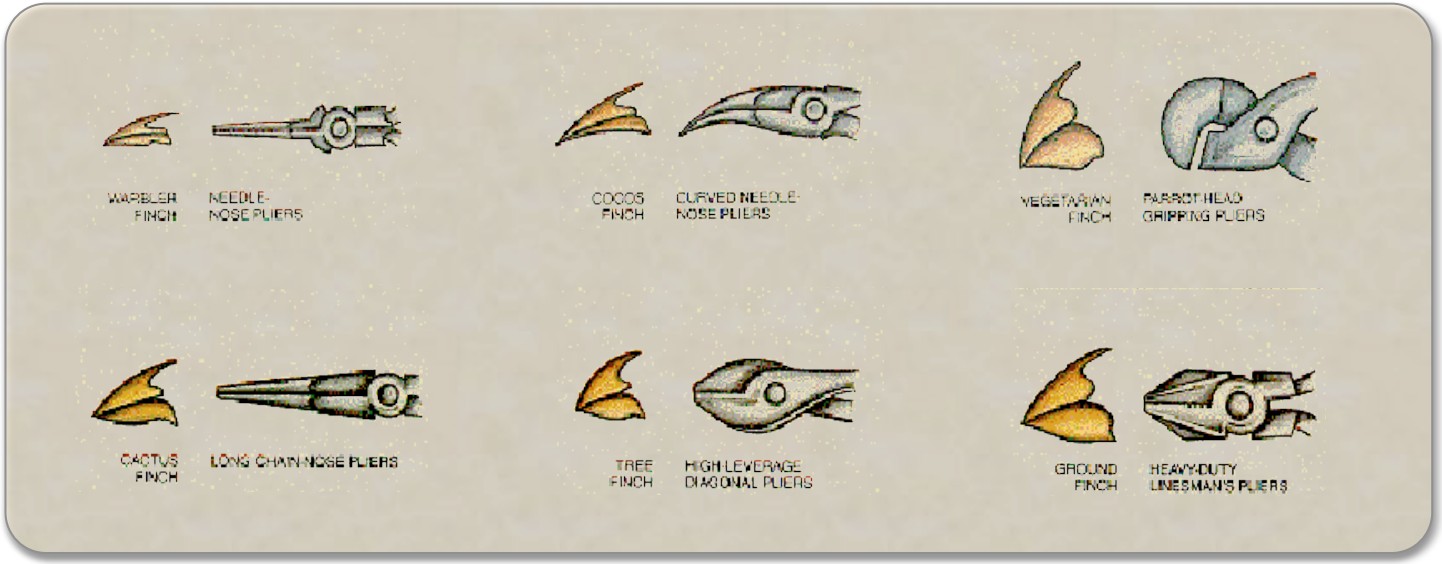
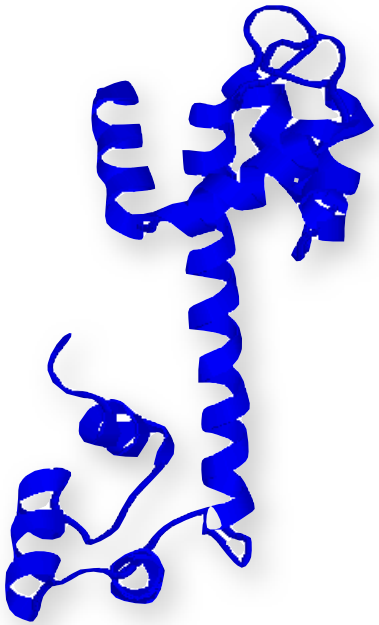
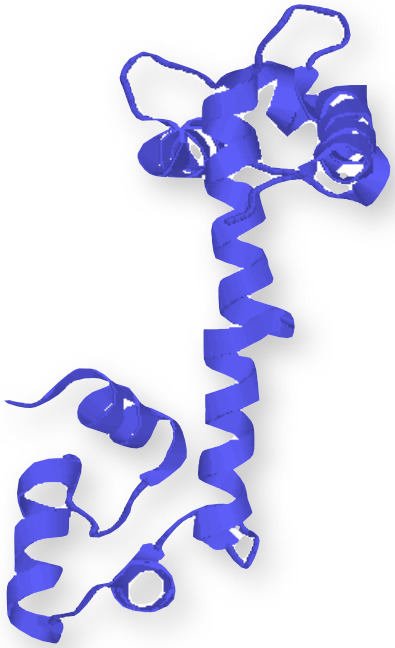
# morphological adaptation



# protein structure



Troponin C: fast skeletal

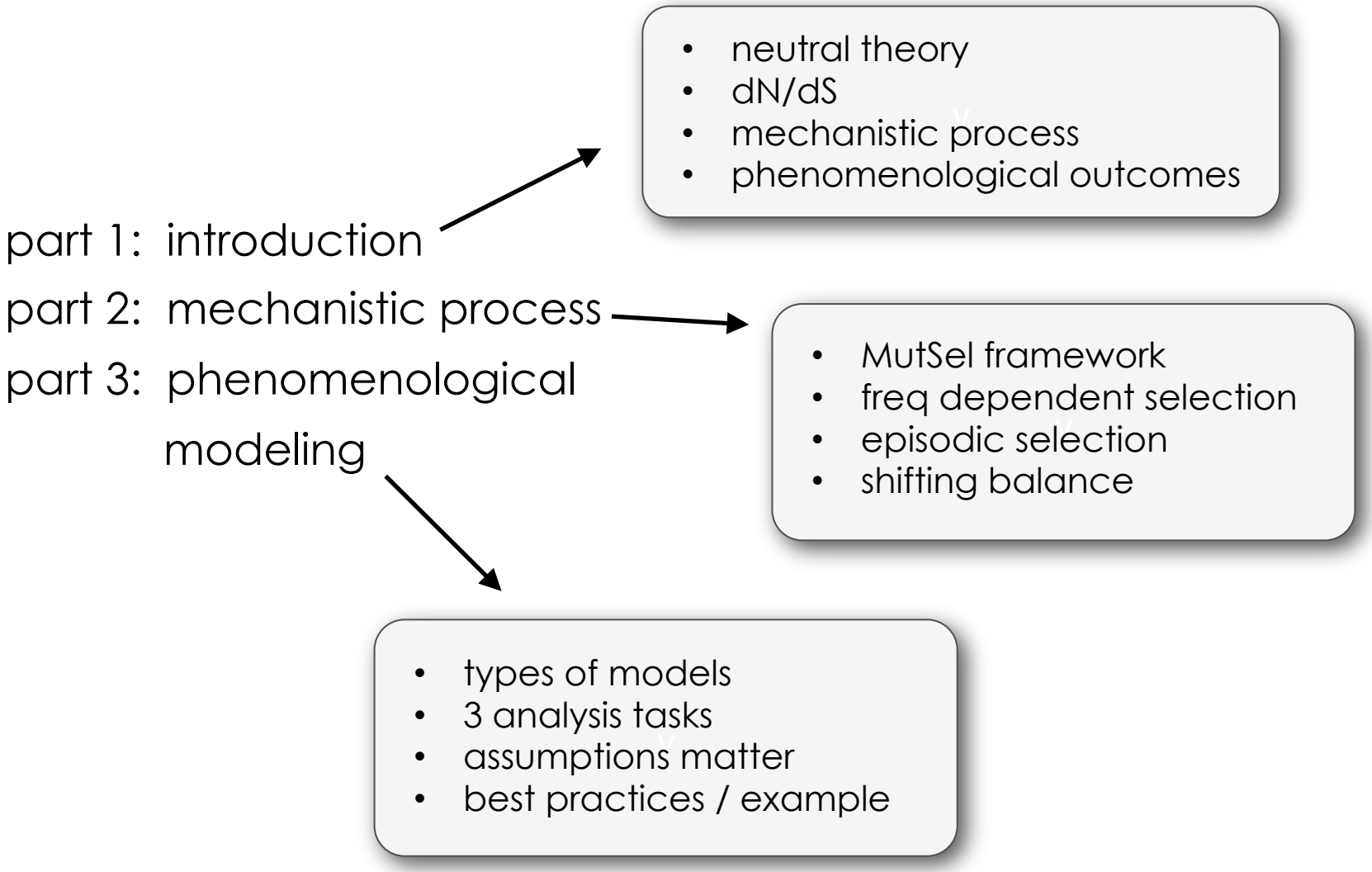


Troponin C: cardiac and slow skeletal

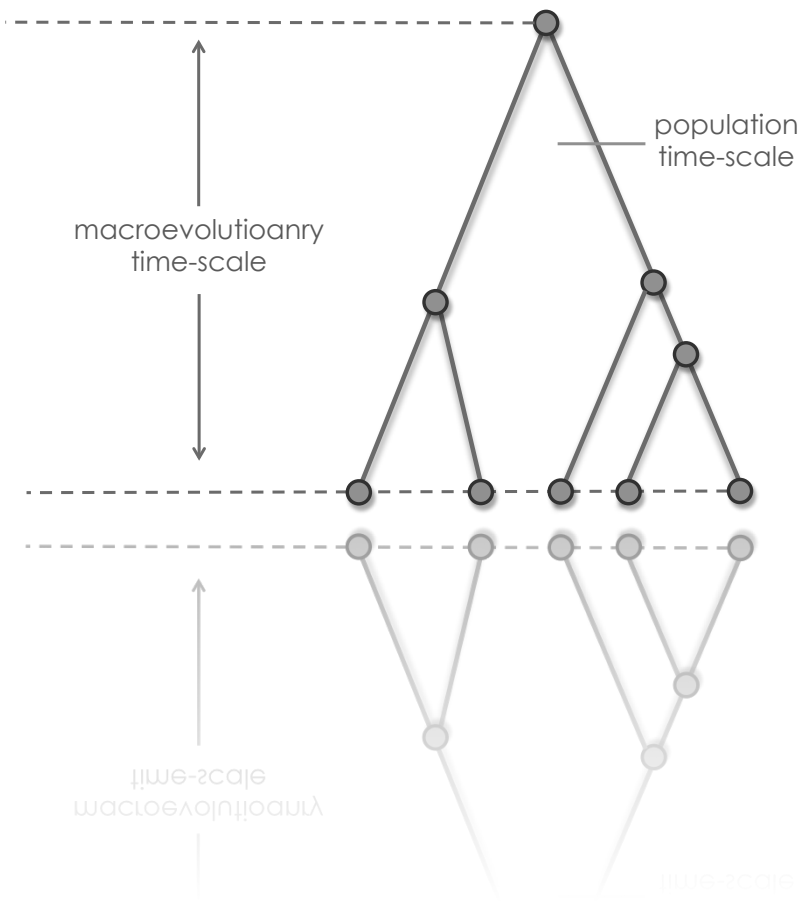
# gene sequences

```
human
cow
rabbit
rat
opossum

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

GCT GGC GAG TAT GGT GCG GAG GCC CTG GAG AGG ATG TTC CTG TCC TTC CCC ACC ACC AAG
... ..A .CT ... ..C ..A ... ..T ... ... ... ... ... ... AG. ... ... ... ... ...
.G. ... ... ... ..C ..C ... ... G.. ... ... ... ... T.. GG. ... ... ... ... ...
.G. ..T ..A ... ..C .A. ... ... ..A C.. ... ... ... GCT G.. ... ... ... ... ...
..C ..T .CC ..C .CA ..T ..A ..T ..T .CC ..A .CC ... ..C ... ... ... ..T ... ..A

ACC TAC TTC CCG CAC TTC GAC CTG AGC CAC GGC TCT GCC CAG GTT AAG GGC CAC GGC AAG
... ... ... ..C ... ... ... ... ... ... ... ..G ... ... ..C ... ... ... ... G..
... ... ... ..C ... ... ... T.C .C. ... ... ... .AG ... A.C ..A .C. ... ... ...
... ... ... T.T ... A.T ..T G.A ... .C. ... ... ... ... ..C ... .CT ... ... ...
..T ... ... ..C ... ... ... ... TC. .C. ... ..C ... ... A.C C.. ..T ..T ..T ...
```

# The goals and the plan



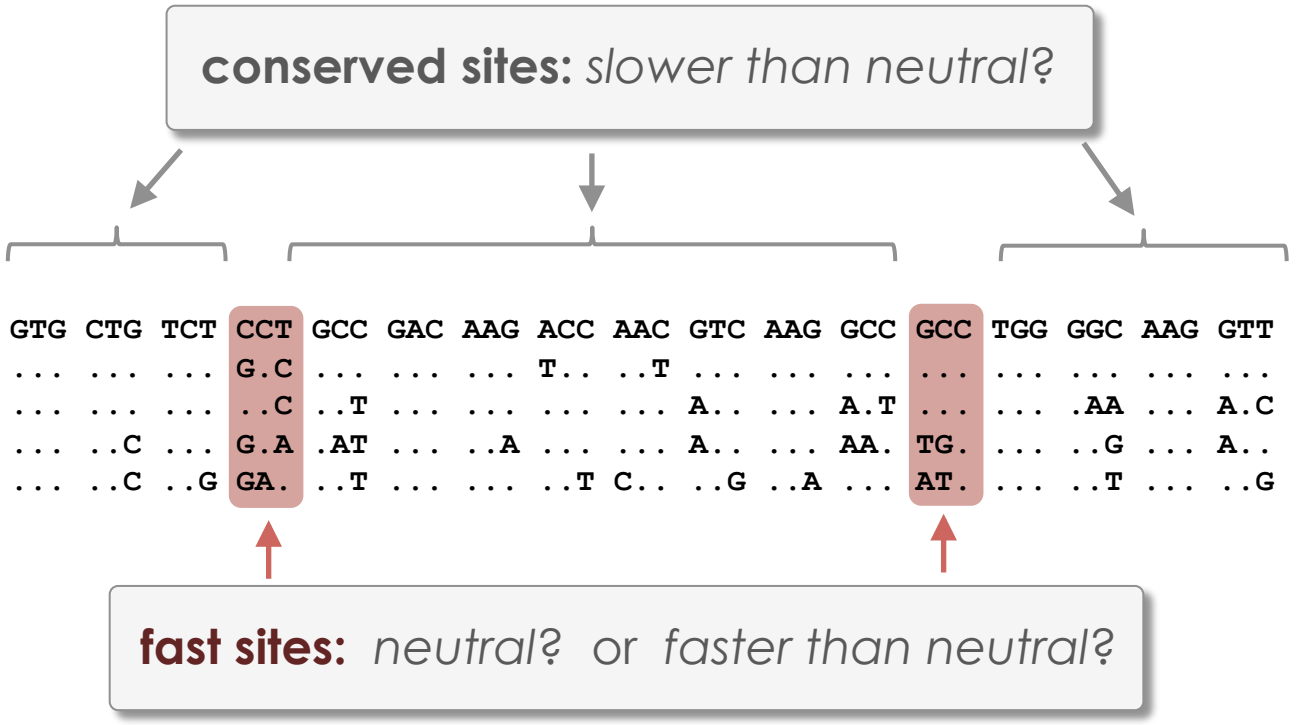
# part 1: introduction



# evolutionary rate depends on intensity of selection

selectively constrained = slower than neutral (drift alone)

adaptive divergence = faster than neutral (drift alone)




What is the neutral expectation?

# neutral theory of molecular evolution (Kimura 1968)

the **number of new mutations** arising in a diploid population

$$2N\mu$$

the **fixation probability** of a new mutant by drift

$$1/2N$$

The **substitution (fixation) rate**, k

$$k = 2N\mu \times 1/2N$$

the elegant simplicity of **neutral theory**: $k = \mu$

# genetic code determines impact of a mutation

| | U | C | A | G | |
|---|---|---|---|---|---|
| **U** | UUU Phe | UCU Ser | UAU Tyr | UGU Cys | U |
| | UUC Phe | UCC Ser | UAC Tyr | UGC Cys | C |
| | UUA Leu | UCA Ser | UAA Stop | UGA Stop | A |
| | UUG Leu | UCG Ser | UAG Stop | UGG Trp | G |
| **C** | CUU Leu | CCU Pro | CAU His | CGU Arg | U |
| | CUC Leu | CCC Pro | CAC His | CGC Arg | C |
| | CUA Leu | CCA Pro | CAA Gln | CGA Arg | A |
| | CUG Leu | CCG Pro | CAG Gln | CGG Arg | G |
| **A** | AUU Ile | ACU Thr | AAU Asn | AGU Ser | U |
| | AUC Ile | ACC Thr | AAC Asn | AGC Ser | C |
| | AUA Ile | ACA Thr | AAA Lys | AGA Arg | A |
| | AUG Met | ACG Thr | AAG Lys | AGG Arg | G |
| **G** | GUU Val | GCU Ala | GAU Asp | GGU Gly | U |
| | GUC Val | GCC Ala | GAC Asp | GGC Gly | C |
| | GUA Val | GCA Ala | GAA Glu | GGA Gly | A |
| | GUG Val | GCG Ala | GAG Glu | GGG Gly | G |

http://www.langara.bc.ca/biology/mario/Assets/Geneticode.jpg

The genetic code determines how random changes to the gene brought about by the process of mutation will impact the function of the encoded protein.

Kimura (1968)

$d_S$: number of synonymous substitutions per synonymous site ($K_S$)

$d_N$: number of nonsynonymous substitutions per nonsynonymous site ($K_A$)

$\omega$ : the ratio $d_N/d_S$; it measures selection at the protein level

# an index of selection pressure

| rate ratio | mode | example |
|---|---|---|
| $dN/dS < 1$ | purifying (negative) selection | histones |
| $dN/dS = 1$ | Neutral Evolution | pseudogenes |
| $dN/dS > 1$ | Diversifying (positive) selection | MHC, Lysin |

## Why use $d_N$ and $d_S$? (Why not use raw counts?)

example of counts:

300 codon gene from a pair of species

5 synonymous differences

5 nonsynonymous differences

5/5 = 1

why <u>don't</u> we conclude that rates are equal (i.e., **neutral evolution**)**?**

# the genetic code & mutational opportunities

**Relative proportion of different types of mutations in hypothetical protein coding sequence.**

| Type | Expected number of changes (proportion) | | | |
|---|---|---|---|---|
| | **All 3 Positions** | **1st positions** | **2nd positions** | **3rd positions** |
| Total mutations | 549 (100) | 183 (100) | 183 (100) | 183 (100) |
| Synonymous | 134 (25) | 8 (4) | 0 (0) | 126 (69) |
| Nonsyonymous | 392 (71) | 166 (91) | 176 (96) | 57 (27) |
| nonsense | 23 (4) | 9 (5) | 7 (4) | 7 (4) |

Modified from Li and Graur (1991). Note that we assume a hypothetical model where all codons are used equally and that all types of point mutations are equally likely.

## Why do we use $d_N$ and $d_S$ ?

same example, but using $d_N$ and $d_S$:

Synonymous sites = 25.5%

$S = 300 \times 3 \times 25.5\% = 229.5$

Nonsynonymous sites = 74.5%

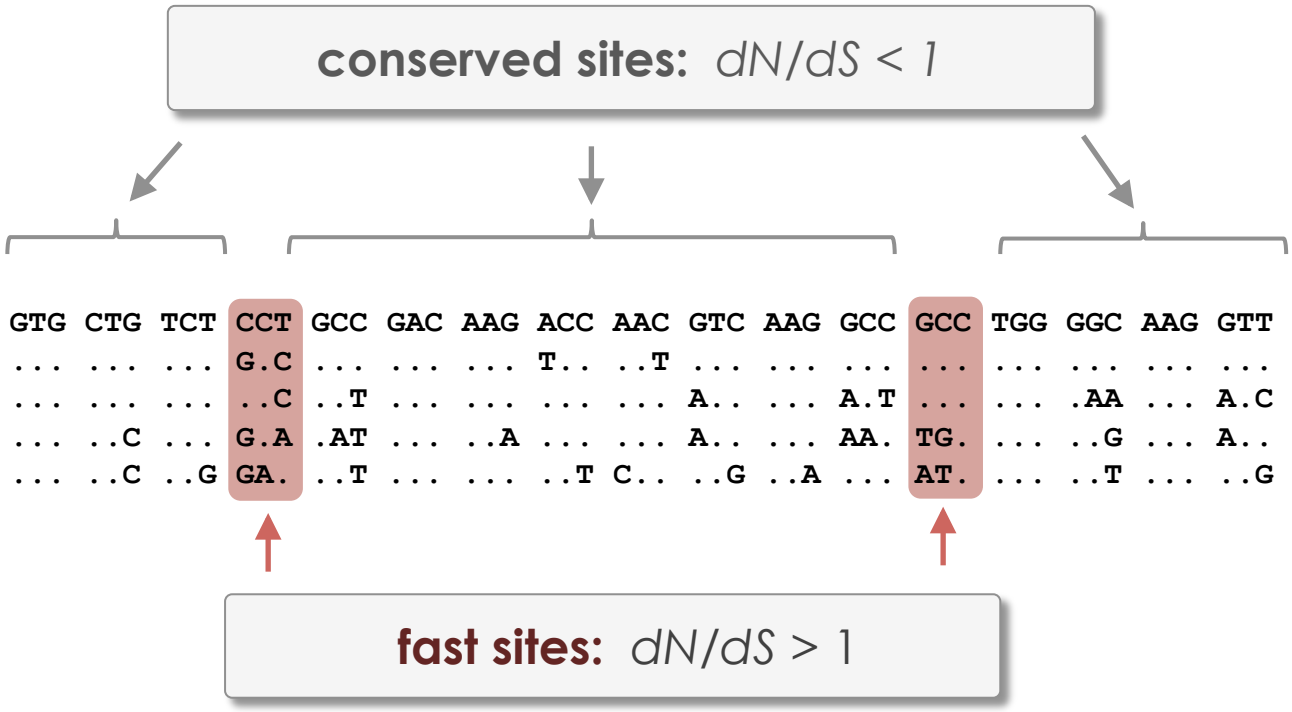
$N = 300 \times 3 \times 74.5\% = 670.5$

So, $d_S = 5/229.5 = 0.0218$

$d_N = 5/670.5 = 0.0075$

$d_N/d_S$ ($\omega$) = 0.34, **purifying selection** !!!

# an index of selection pressure acting on the protein




**conclusion:** *dN* differs from *dS* due to the effect of selection on the protein.

# mutational opportunity vs. physical site

| **Relative proportion of different types of mutations in hypothetical protein coding sequence.** | | | | |
|---|---|---|---|---|
| **Type** | **Expected number of changes (proportion)** | | | |
| | **All 3 Positions** | **1st positions** | **2nd positions** | **3rd positions** |
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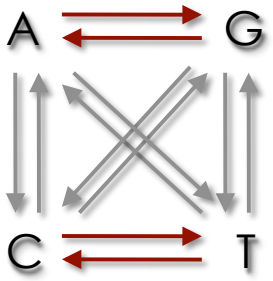
**Note** that by framing the counting of sites in this way we are using a "mutational opportunity" definition of the sites. Thus, a synonymous or non-synonymous site is not considered a physical entity!

**Note** that we assume a hypothetical model where all codons are used equally and that all types of point mutations are equally likely.

# real data have biases (*Drosophila GstD1* gene)

**transitions** vs. **transversions**:




**ts**/tv = 2.71

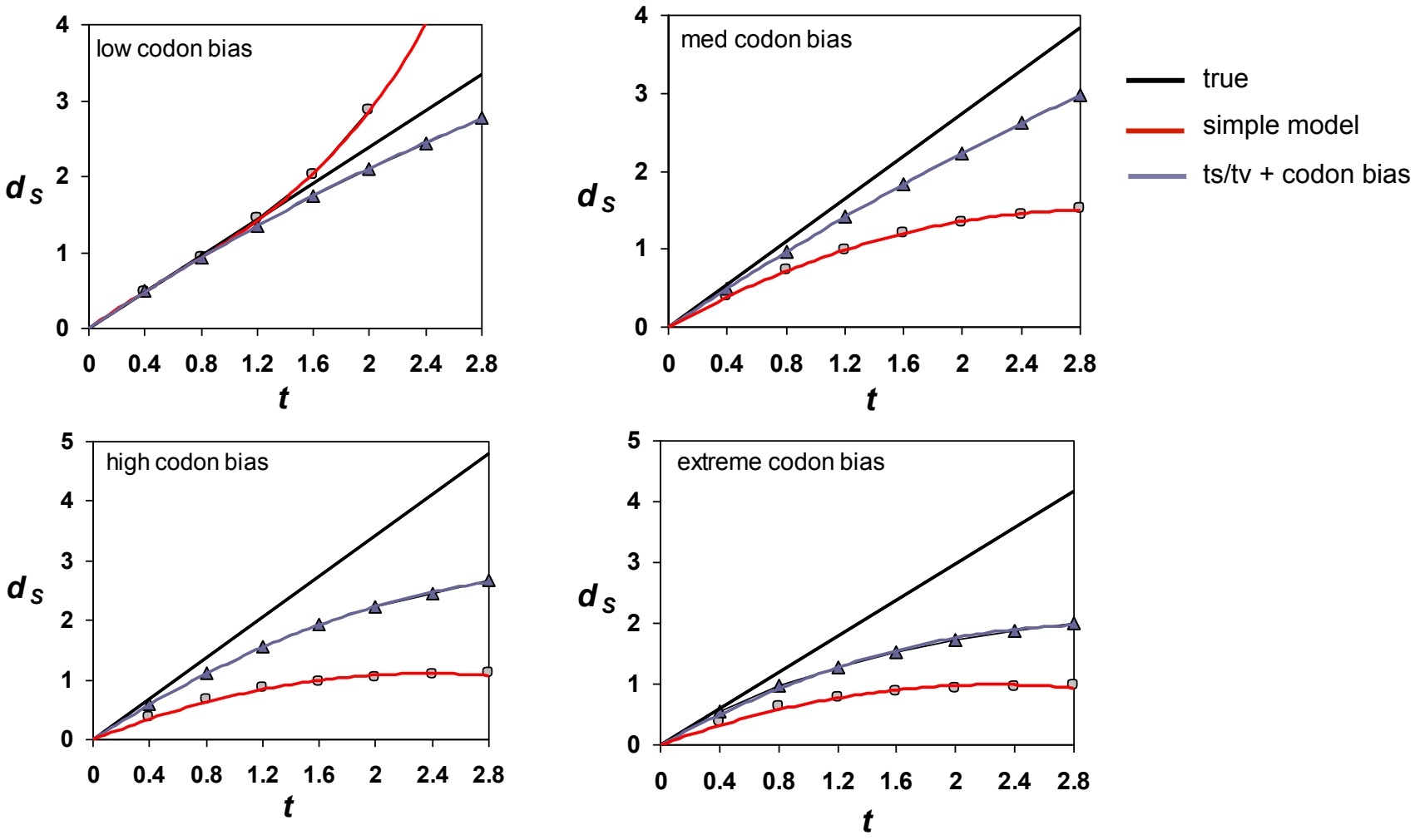
**preferred** vs. **un-preferred** codons:

partial codon usage table for the *GstD* gene of *Drosophila*

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Phe | F | TTT | 0 | Ser | S | TCT | 0 | Tyr | Y | TAT | 1 |
| | | TTC | 27 | | | TCC | 15 | | | TAC | 22 |
| Leu | L | TTA | 0 | | | TCA | 0 | *** | * | TAA | 0 |
| | | TTG | 1 | | | TCG | 1 | | | TAG | 0 |
| Leu | L | CTT | 2 | Pro | P | CCT | 1 | His | H | CAT | 0 |
| | | CTC | 2 | | | CCC | 15 | | | CAC | 4 |
| | | CTA | 0 | | | CCA | 3 | Gln | Q | CAA | 0 |
| | | CTG | 29 | | | CCG | 1 | | | CAG | 14 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cys | C | TGT | 0 |
| | | TGC | 6 |
| *** | * | TGA | 0 |
| Trp | W | TGG | 8 |
| Arg | R | CGT | 1 |
| | | CGC | 7 |
| | | CGA | 0 |
| | | CGG | 0 |

# uncorrected evolutionary bias leads to estimation bias




data from: Dunn, Bielawski, and Yang (2001) Genetics, 157: 295-305

# recap

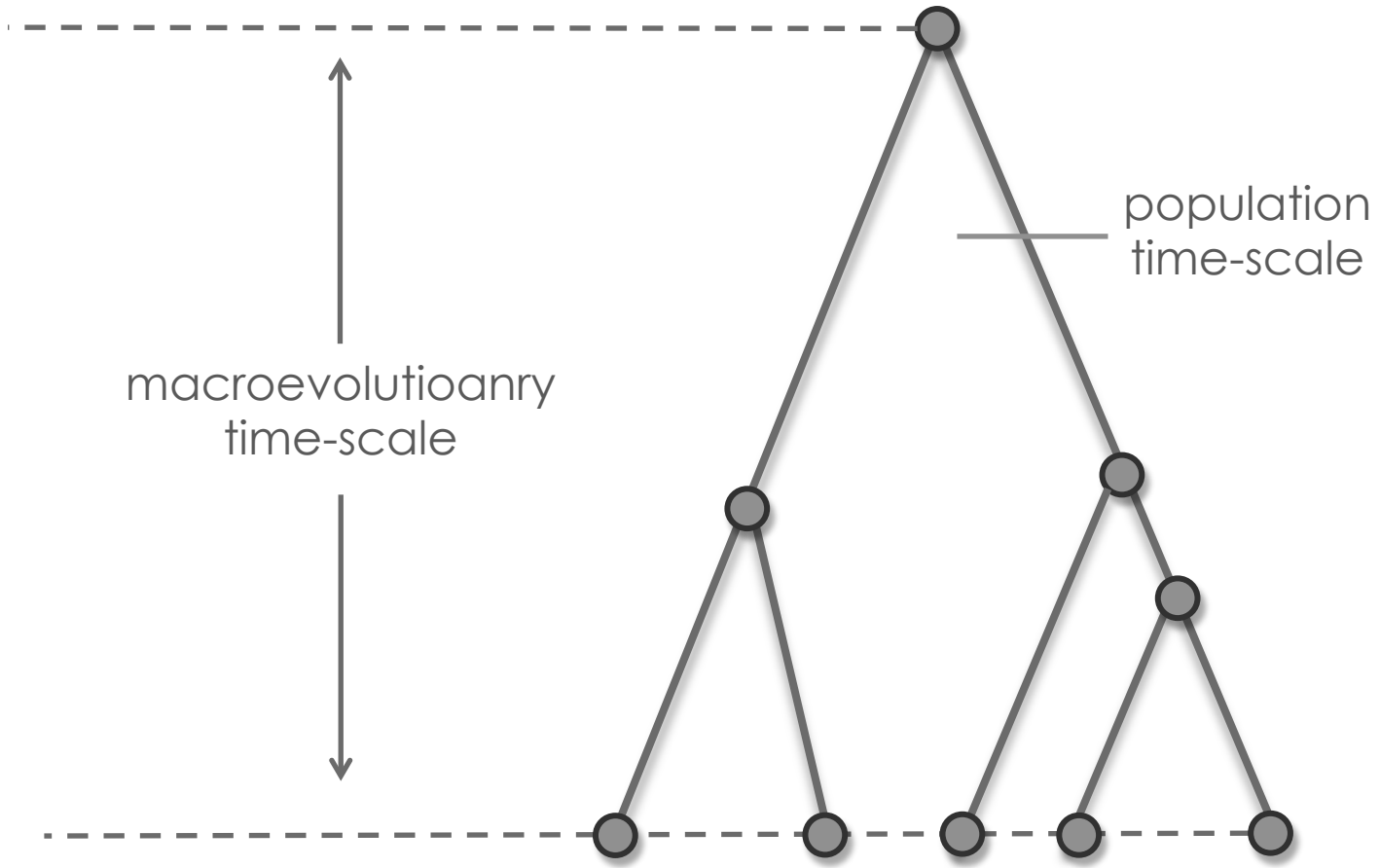
*dS* and *dN* must be corrected for BOTH the structure of genetic code and the underlying mutational process of the DNA

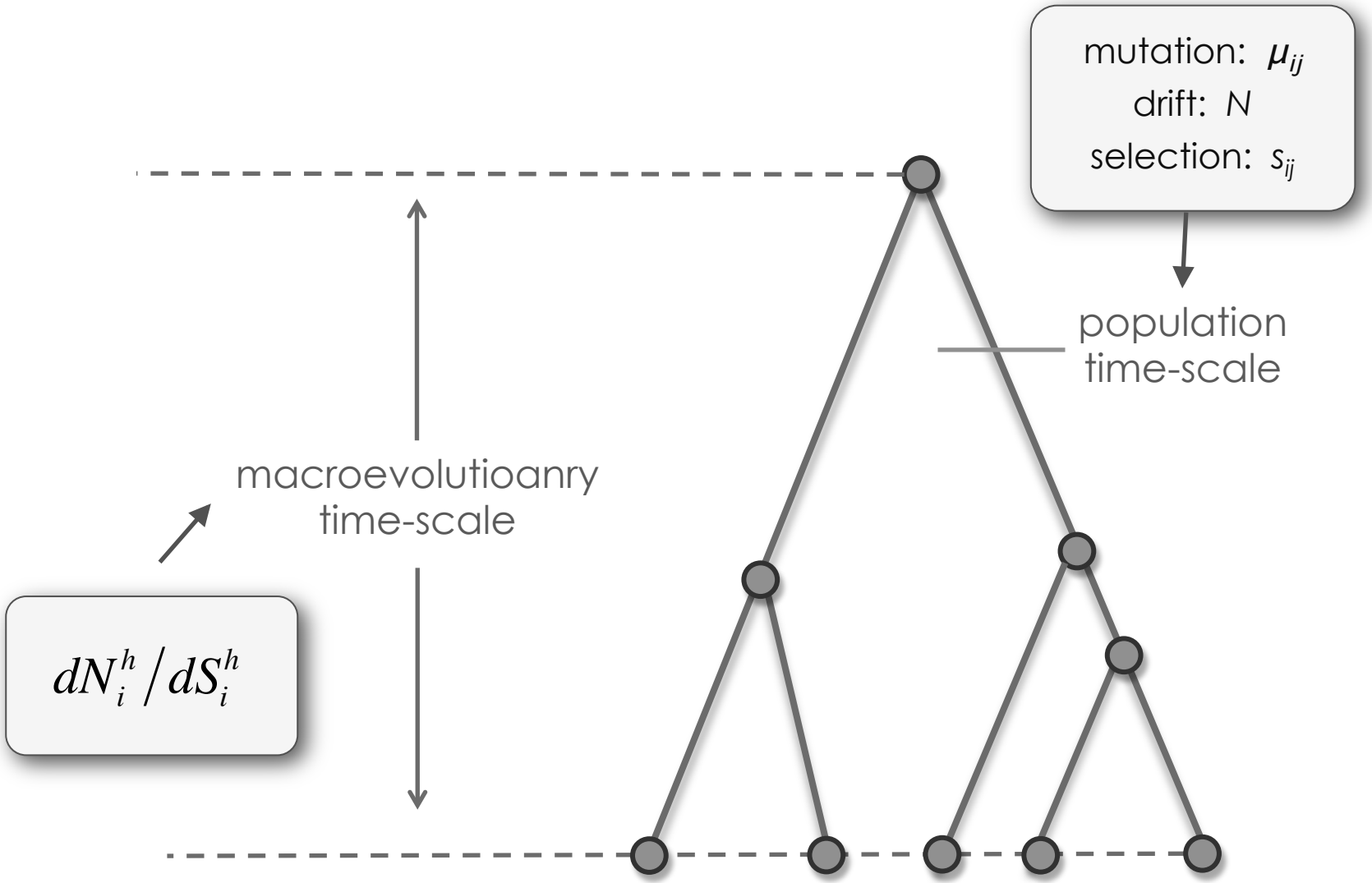
but, this can differ among lineages and genes!

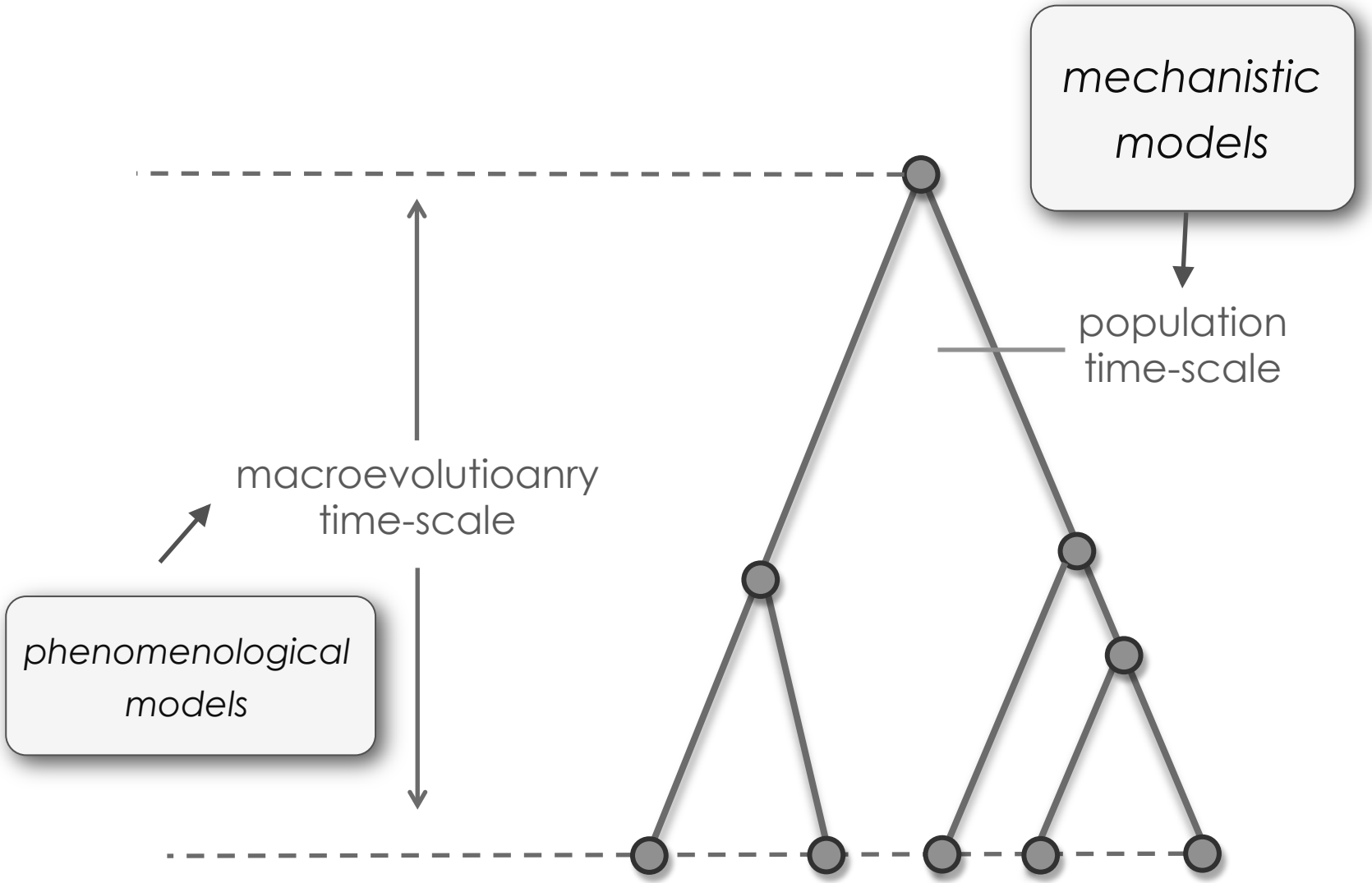
correcting *dS* and *dN* for underlying mutational process of the DNA makes them **sensitive to assumptions about the process of evolution**!

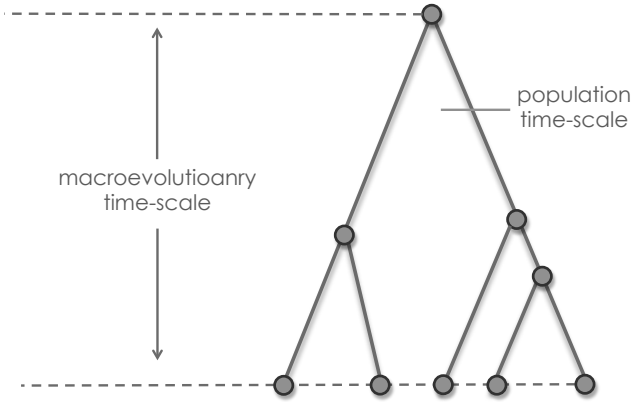
but, the process of evolution occurs at the population genetic level (micro-evolution)

# reconciling evolutionary time scales




mutation: $\mu_{ij}$
drift: $N$
selection: $s_{ij}$
population time-scale
macroevolutioanry time-scale
$dN_i^h / dS_i^h$


mechanistic models
population time-scale
macroevolutioanry time-scale
phenomenological models




*mechanistic models*

## "MUTSEL MODELS"

$$\Pr = \begin{cases} \mu_{ij} N \times \dfrac{1}{N} = \mu_{IJ} & \text{if neutral} \\ \mu_{ij} N \times \dfrac{2 s_{ij}}{1 - e^{-2 N s_{ij}}} & \text{if selected} \end{cases}$$

$$s_{ij} = \Delta f_{ij}$$

Halpern and Bruno (1998)

- Wright-Fisher population
- drift: ***N***
- mutation: ***μ***
- selection: $s_{ij}$
- $s_{ij}$ vary among sites AND amino acids
- expected $dN^h/dS^h$

# fixation probability with selection

population genetics at a single codon site (*h*)

**fitness coefficients**

$$f^h = \langle f_1 , \ldots, f_{61} \rangle$$

**selection coefficients**

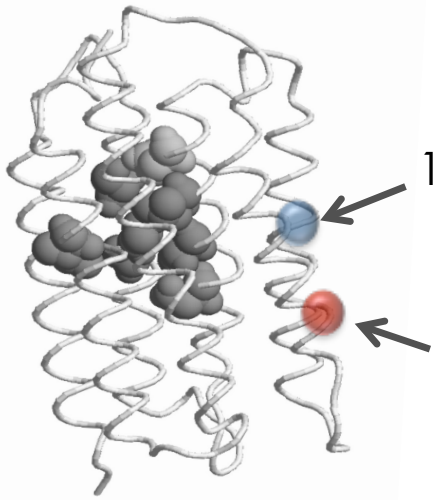
$$s_{ij}^h = f_j^h - f_i^h$$

**fixation probability (Kimura, 1962)**

$$\Pr(s_{ij}^h) = \frac{2 s_{ij}^h}{1 - e^{-2 N s_{ij}^h}}$$

# fixation probability with selection

**MutSel:** selection favours amino acids with higher fitness (if *N* is large enough)

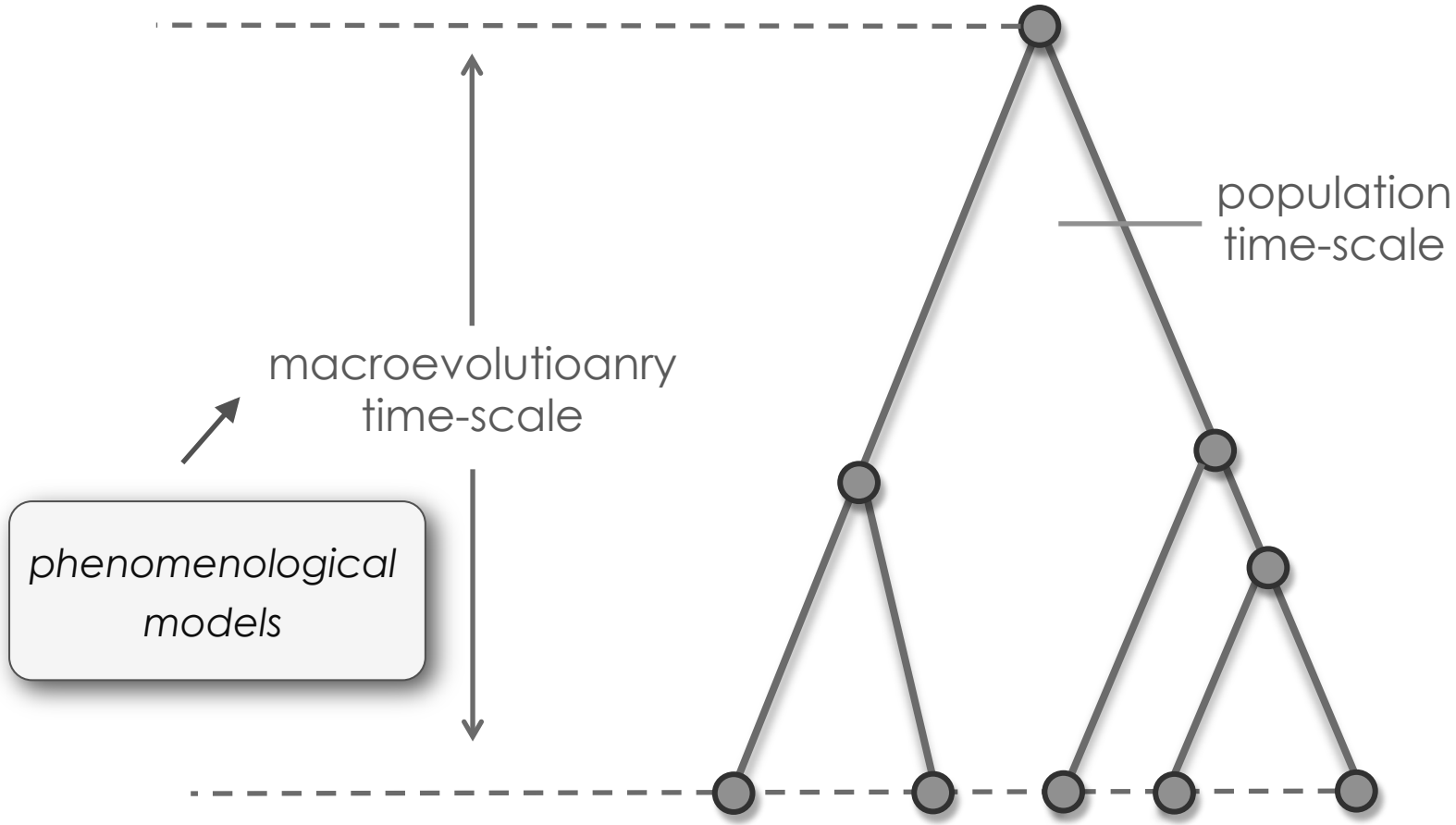


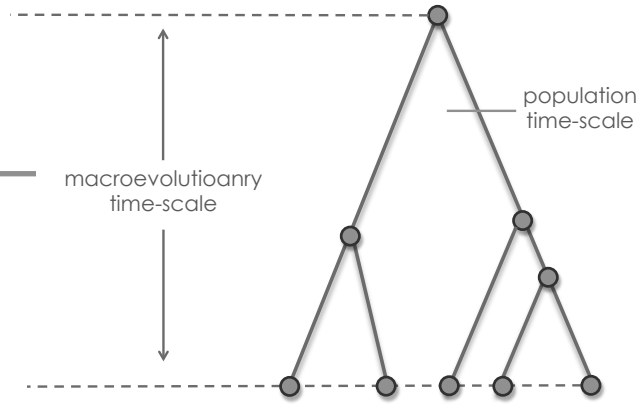
1. **A**TA (**Ile**) ➔ **T**TA (**Leu**): $\Delta f^{h}_{Ile \to Leu}$ (**conservative**)

2. A**T**A (**Ile**) ➔ A**A**A (**Lys**): $\Delta f^{h}_{Ile \to Lys}$ (**radical**)

**realism**: fitness expected to differ among sites and amino acids according to protein function

**the cost of realism**: too complex to fit such a model to real data


population
time-scale
macroevolutioanry
time-scale
phenomenological
models




*phenomenological models*

## "OMEGA MODELS"

$$Q_{ij} = \begin{cases} 0 & \text{if } i \text{ and } j \text{ differ by} > 1 \\ \pi_j & \text{for synonymous tv.} \\ \kappa\pi_j & \text{for synonymous ts.} \\ \omega\pi_j & \text{for non-synonymous tv.} \\ \omega\kappa\pi_j & \text{for non-synonymous ts.} \end{cases}$$

Goldman and Yang (1994)
Muse and Gaut (1994)

- phenomenological parameters
- ts/tv ratio: $\kappa$
- codon frequencies: $\pi_j$
- $\omega = dN/dS$
- parameter estimation via ML
- *stationary process*

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

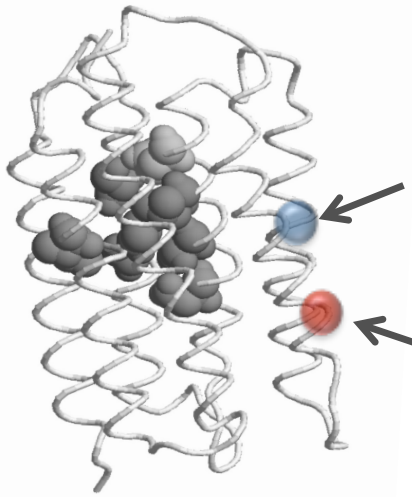
## phenomenological codon models: just a few parameters are needed to cover the 3721 transitions between codons!

| | to codon below: | | | | | | ⋯▸ | |
|---|---|---|---|---|---|---|---|---|
| **From 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 ($i$).

# substitution probability with selection

**intentional simplification**: all amino acid substitutions have the same $\omega$!



1. **A**TA (**Ile**) ➔ **T**TA (**Leu**): $\omega_{ile \rightarrow leu}$ (**conservative**)

2. AT**A** (**Ile**) ➔ A**A**A (**Lys**): $\omega_{ile \rightarrow lys}$ (**radical**)

**contradiction?** selection should favour amino acids with higher fitness.

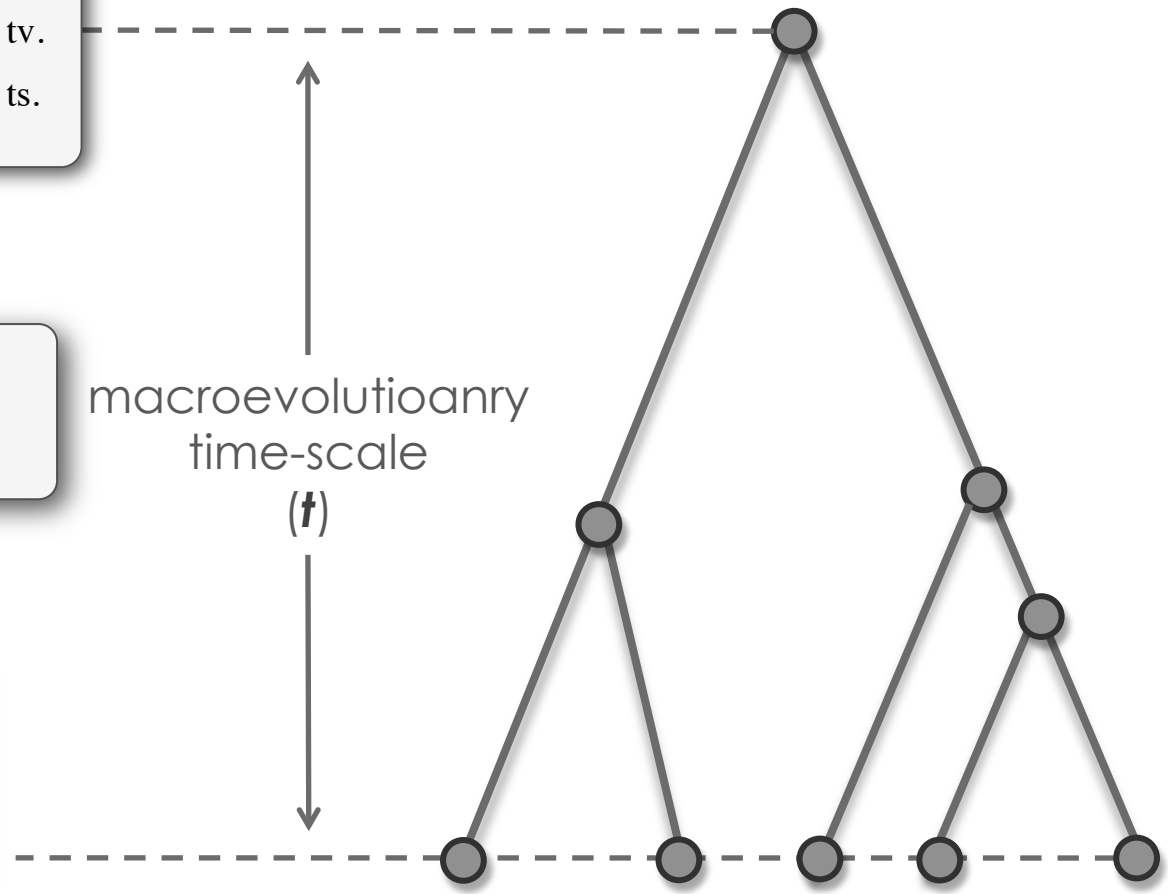
# probability of substitution between codons over time, $P(t)$

$$Q_{ij} = \begin{cases} 0 & \text{if } i \text{ and } j \text{ differ by} > 1 \\ \pi_j & \text{for synonymous tv.} \\ \kappa\pi_j & \text{for synonymous ts.} \\ \omega\pi_j & \text{for non-synonymous tv.} \\ \omega\kappa\pi_j & \text{for non-synonymous ts.} \end{cases}$$

$$P(t) = \{p_{ij}(t)\} = e^{Qt}$$

recall that **Paul Lewis** introduced **Q matrices** and how to obtain **transition probabilities**

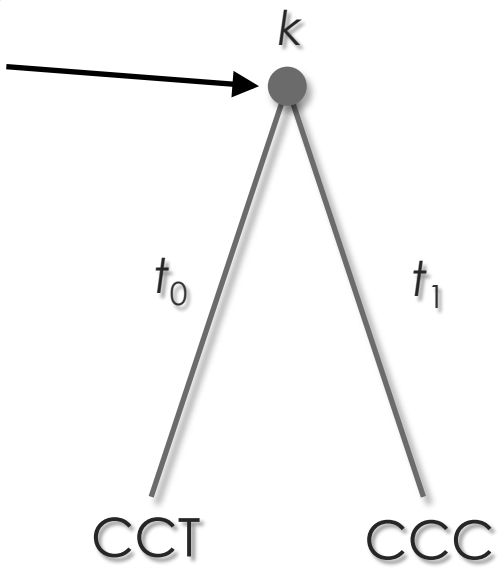
macroevolutioanry time-scale ($t$)



# likelihood of the data at a site

$$L_h(CCC, CCT) = \sum_k \pi_k p_{kCCC}(t_0) p_{kCCT}(t_1)$$

the likelihood is a **sum over all possible ancestral codon states** that could have been observed at node k




recall that **Paul Lewis** described how to compute the likelihood of the data at a site for a DNA model. The only difference here is that the states are codons rather than nucleotides.

note: analysis is typically done by using an unrooted tree

# likelihood of the data at all sites

**Paul Lewis** covered this with the **"AND" rule** in his likelihood lecture.

The likelihood of observing the entire sequence alignment is the product of the probabilities at each site.

$$L = L_1 \times L_2 \times L_3 \times \ldots \times L_N = \prod_{h=1}^{N} L_h$$

See **Paul Lewis's** lecture slides for more about likelihoods vs. log-likelihoods.

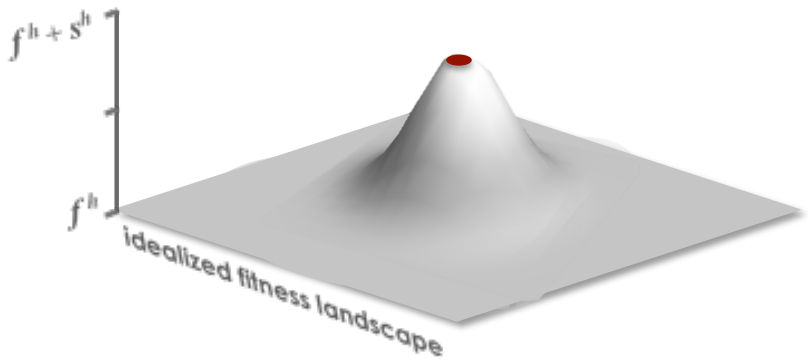
The log likelihood is a sum over all sites.

$$\ell = \ln\{L\} = \ln\{L_1\} + \ln\{L_2\} + \ln\{L_3\} + \ldots + \ln\{L_N\} = \sum_{h=1}^{N} \ln\{L_h\}$$

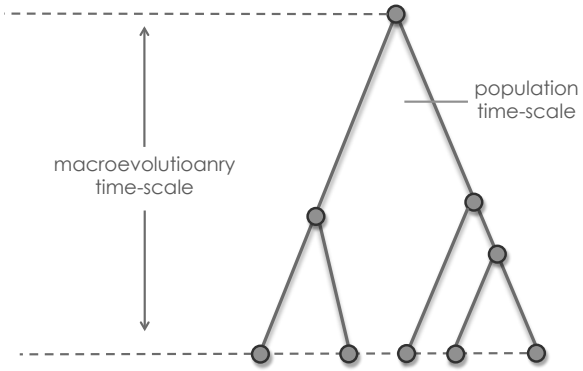
## summary

- *dN*/*dS* is a measure of selection pressure that can be connected to a mechanistic process of population genetic evolution (MutSel models)
- *dN*/*dS* can be estimated from multi-sequence alignments as a parameter ($\omega$) in a phenomenological model of sequence evolution
- estimates of *dN*/*dS* for real data must be corrected for the underlying process of evolution for those data
- estimates of *dN*/*dS* can be sensitive to assumptions about the underlying process of evolution
- phenomenological estimates of *dN*/*dS* are highly simplistic summaries of a much more complex evolutionary process

part 2: mechanistic processes of codon evolution



# site-specific MutSel rate matrix




## MutSel rate matrix

$$A_{ij}^{h} = \begin{cases} \mu_{ij} & \text{if } s_{ij}^{h} = 0 \\ \mu_{ij} N \times \dfrac{2 s_{ij}^{h}}{1 - \mathrm{e}^{-2 N s_{ij}^{h}}} & \text{otherwise} \end{cases}$$

- MutSel time-scale is infinitesimal compared to substitution scale
- MutSel probabilities approximate the instantaneous site-specific rate matrix, A
- $\mu_{ij}$ = nucleotide GTR process (before the effect of selection)

two explicit ways to reconcile **population genetics** and **macroevolution**:

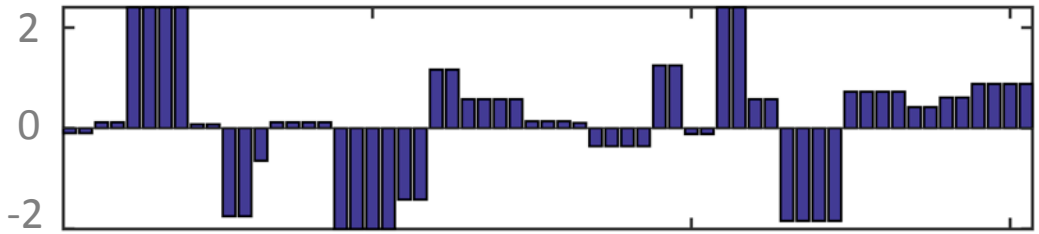
1. map fitness to equilibrium frequencies

2. macroevolution index of selection intensity

# fitness coefficients map to stationary codon frequencies

fitness coefficients

$$f^h = \langle f_1 , \ldots, f_{61} \rangle$$




codon frequencies

$$\pi^h = \langle \pi_1 , \ldots, \pi_{61} \rangle$$

# from fitness coefficients to *dN/dS*

## MutSel rate matrix

$$dN^h / dS^h = \frac{E[\text{evolution w/ selection}]}{E[\text{drift away from equilibrium set by selection}]}$$

$$dN^h / dS^h = \frac{\sum_{i \neq j} \pi_i^h A_{ij}^h I_N}{\sum_{i \neq j} \pi_i^h \mu_{ij} I_N}$$

- *dN/dS* = $\omega$ when matrix $A^h$ is replaced by matrix Q of model M0
- *dN/dS* is an analog of $\omega$ under MutSel

# positive selection: 3 evolutionary scenarios

1. frequency dependent selection
2. episodic adaptation

dynamic fitness landscape

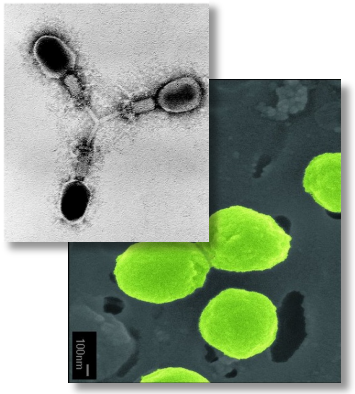
3. shifting balance

static fitness landscape

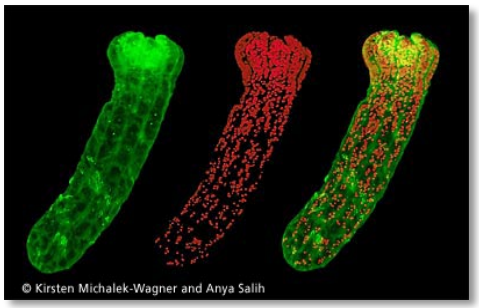
# scenario 1: frequency dependent selection

**1. antagonistic evolutionary interaction**

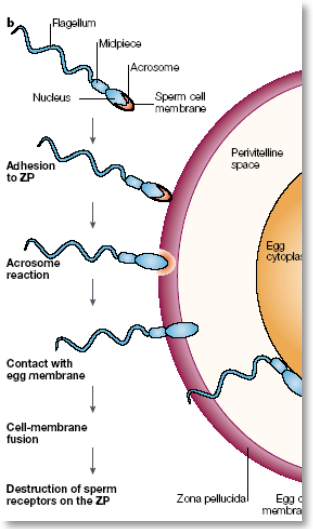
host-pathogen




molecular-interactions

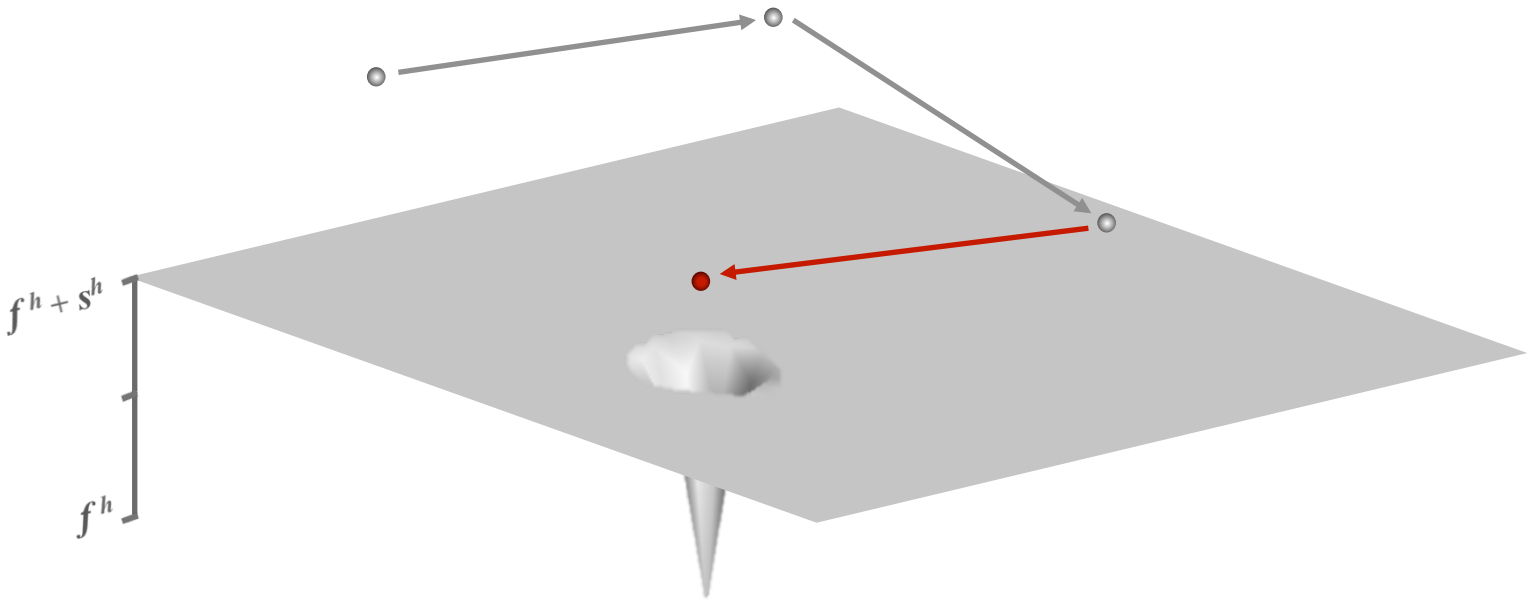



sexual-conflict



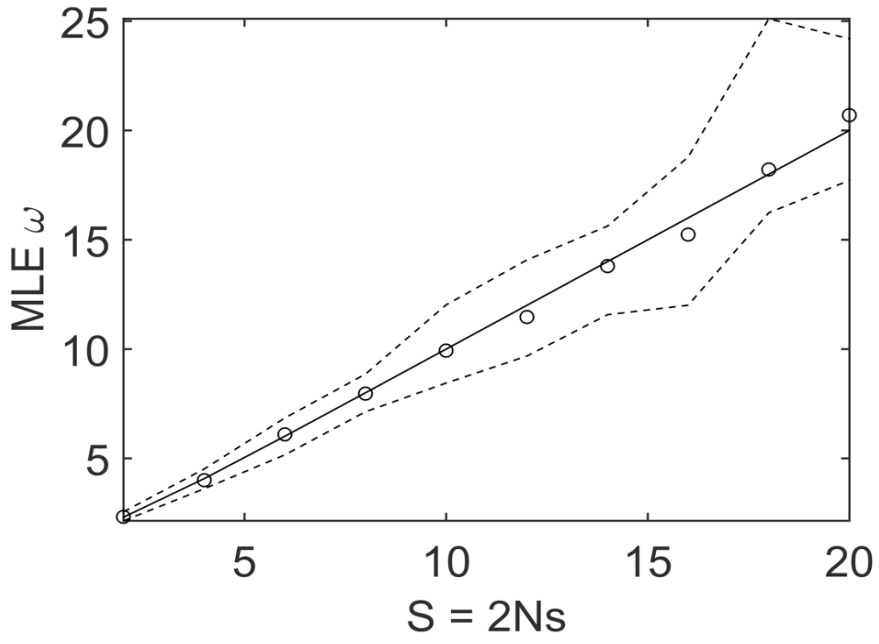
# frequency-dependent selection: MutSelM0

1. amino acid at a site has $f^h$; all others have $f^h + s$
2. fitness values swap when a substitution occurs




**MutSelM0:** (1) and (2) above imply Markov chain properties with the same rate matrix $Q$ as **codon model M0**

# frequency-dependent selection: MutSelM0




**generating process:**

MutSelM0

expectation = $dN^h/dS^h$

symbol = ——

**fitted model:**

model M0

inference = MLE $\omega$

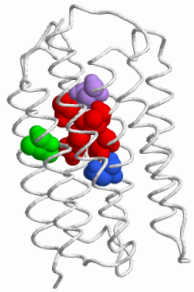
symbol = O

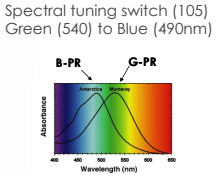
**conclusion:** phenomemologcial codon models assume frequency-dependent selection

# scenario 2: adaptive peak shift

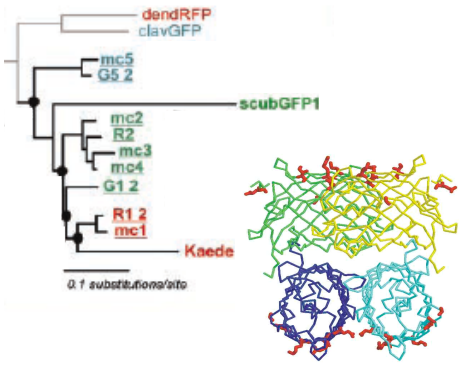
**2. episodic Darwinian adaptation**

exploitation of a new niche

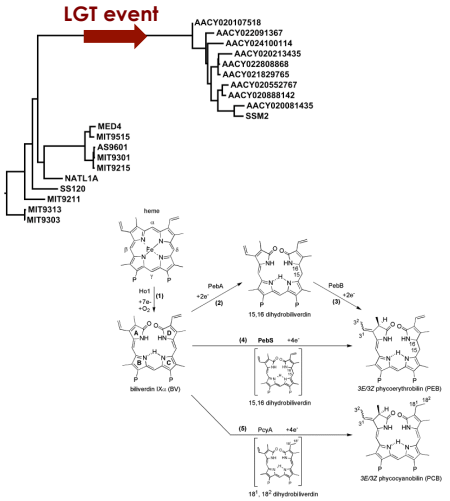





gene duplication

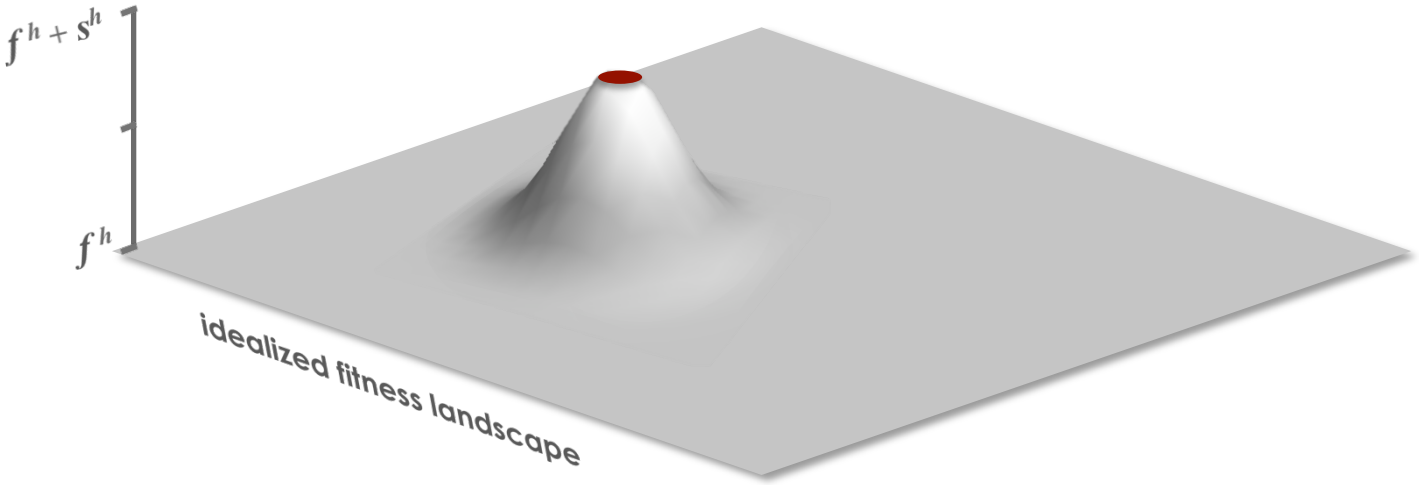



lateral gene transfer (LGT)



# adaptive peak shift: evolution of novel function

optimal function in a stable environment



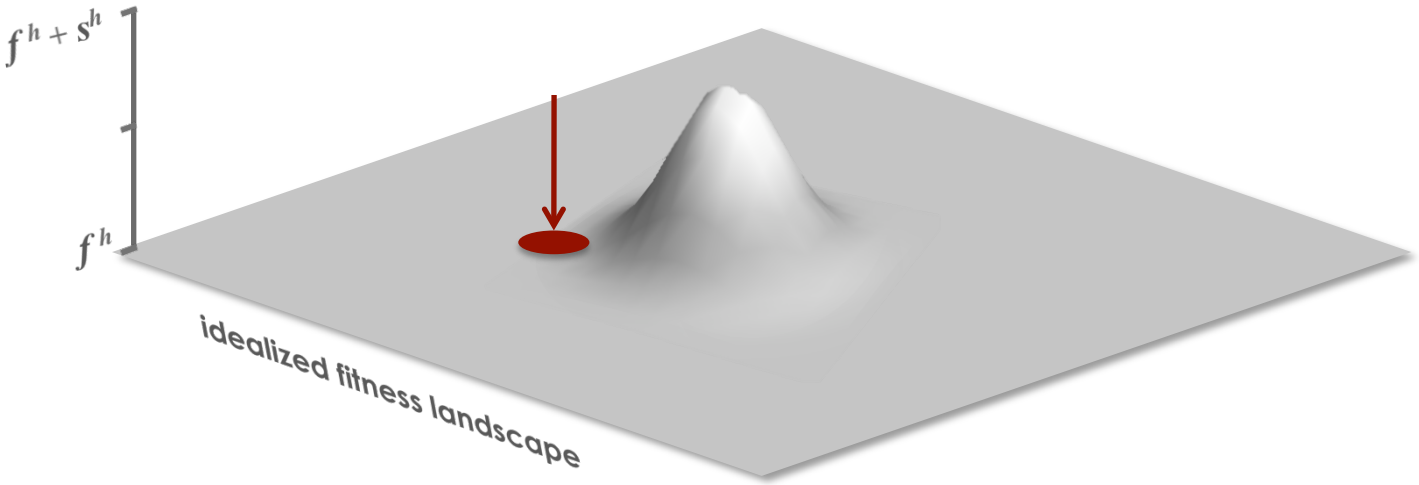

**population:** at fitness peak

**fitness peak**: stationary

**FFTNS:** keeps population at peak

# adaptive peak shift: evolution of novel function

sub-optimal function in a novel environment




**population:** lower fitness

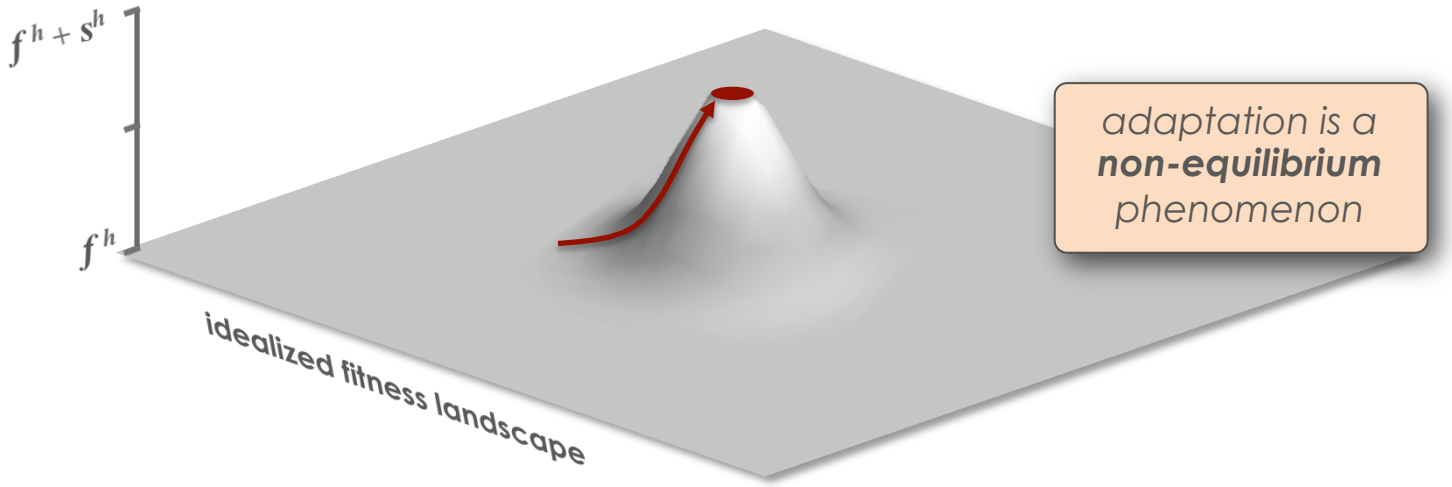
**fitness peak**: moving

**FFTNS:** increase population mean fitness

(non-stationary process)

# adaptive peak shift: evolution of novel function

**episodic adaptive evolution** of a novel function




**population:** returns to peak

**fitness peak**: stabilized

**FFTNS:** increases population mean fitness until at peak

# adaptive peak shift: MutSelES model

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Research

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**Molecular evolution**

## How to calculate the non-synonymous to synonymous rate ratio of protein-coding genes under the Fisher–Wright mutation–selection framework

Mario dos Reis

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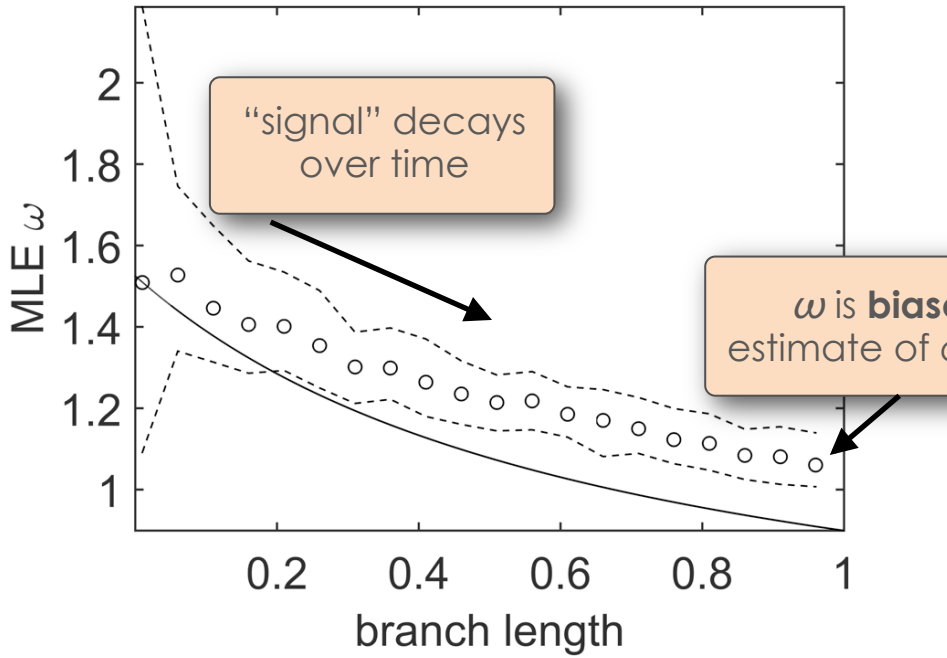
First principles of population genetics are used to obtain formulae relating the non-synonymous to synonymous substitution rate ratio to the selection coefficients acting at codon sites in protein-coding genes. Two theoretical cases are discussed and two examples from real data (a chloroplast gene and a virus polymerase) are given. The formulae give much insight into the dynamics of non-synonymous substitutions and may inform the development of methods to detect adaptive evolution.

### 4. The non-synonymous rate during adaptive evolution

# adaptive peak shift: MutSelES




**generating process:**

MutSelES

expectation = $dN^h/dS^h$

symbol = ——

**fitted model:**

model M0

inference = MLE $\omega$

symbol = O

**conclusion :** episodic models "work" because w>1 is a consequence of a system moving towards a new fitness peak.

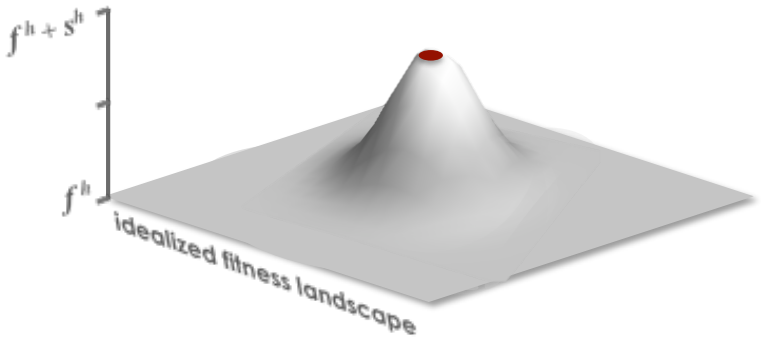
**conclusion :** episodic models "work" because they are sensitive to non-stationary behavior

# Scenario 3: non-adaptive evolution

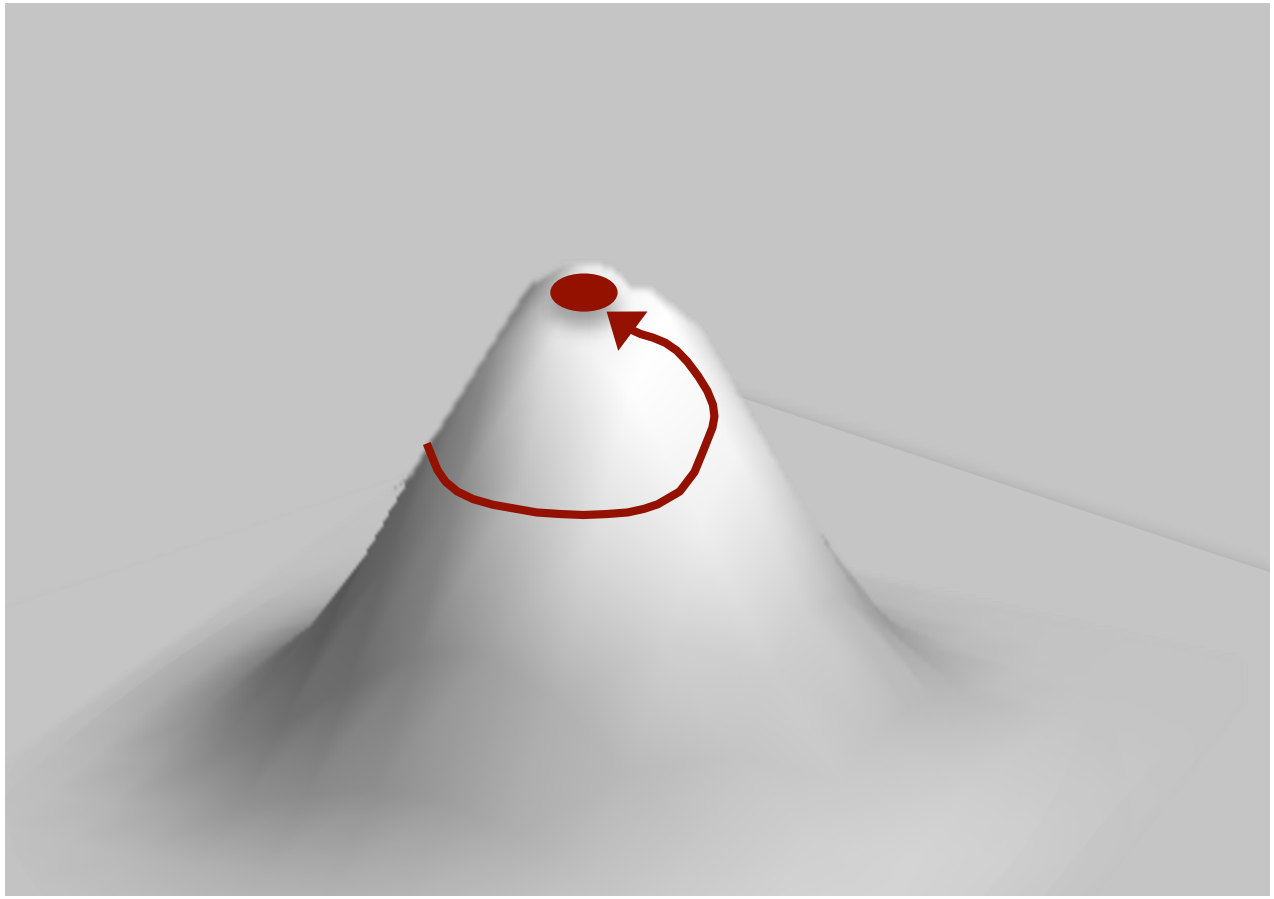
**3. fitness coefficients are constant (fixed-peak)**

Spielman and Wilke (2015)

- *dN/dS* must be ≤1 when fitness coefficients are fixed.
- positive selection is not possible on a stationary fitness peak

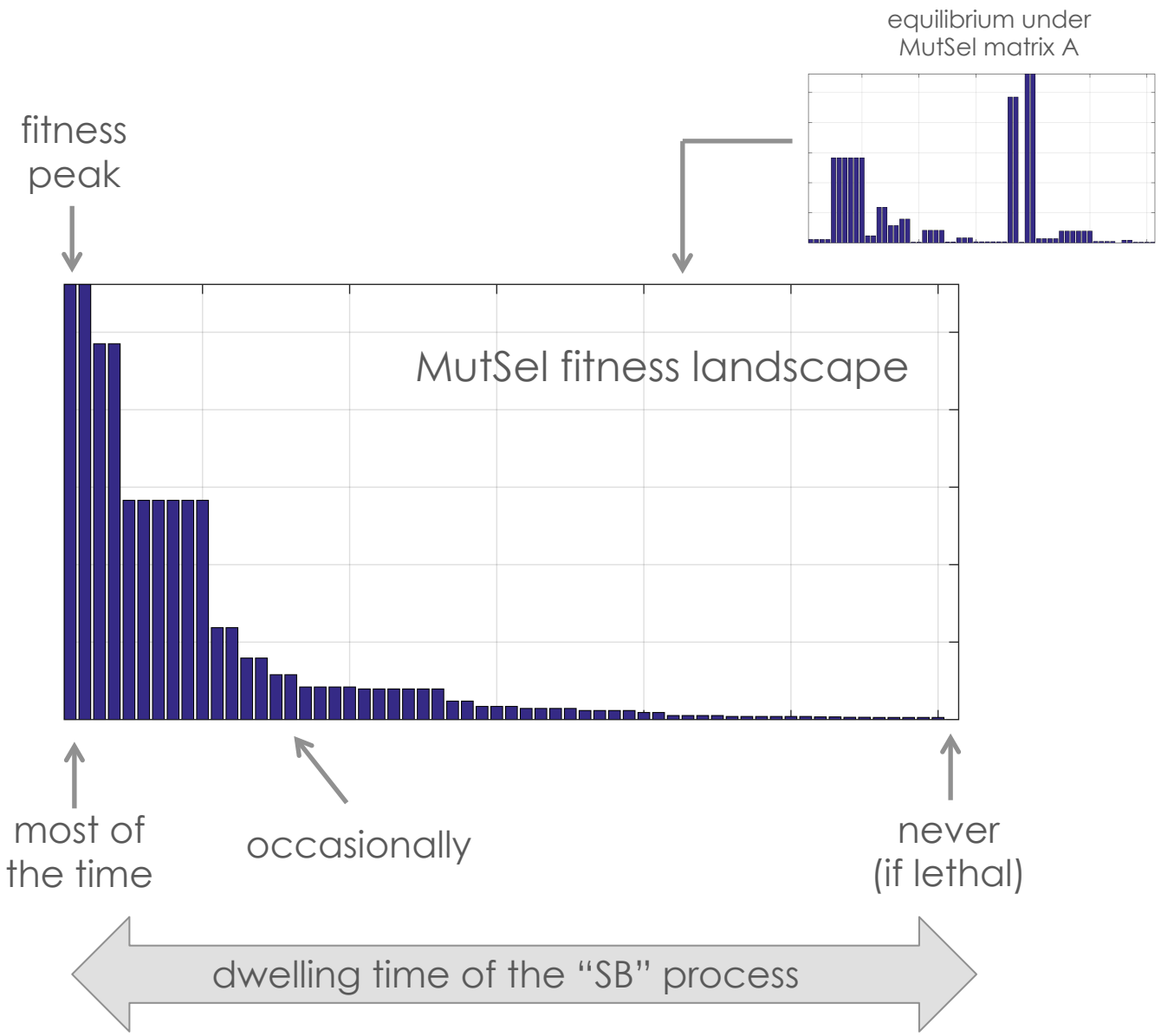


# shifting balance: movement around peak

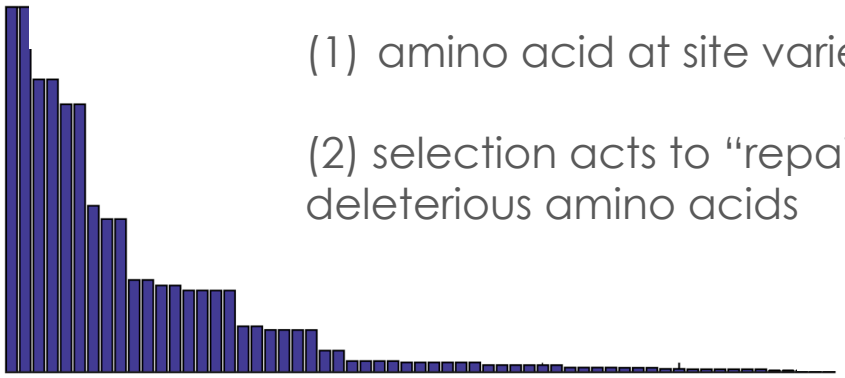


**mutation** and **drift** can move a pop. off a fitness peak

# shifting balance: the MutSel landscape



# shifting balance: positive selection on a MutSel landscape



(1) amino acid at site varies over time

(2) selection acts to "repair" shifts to deleterious amino acids

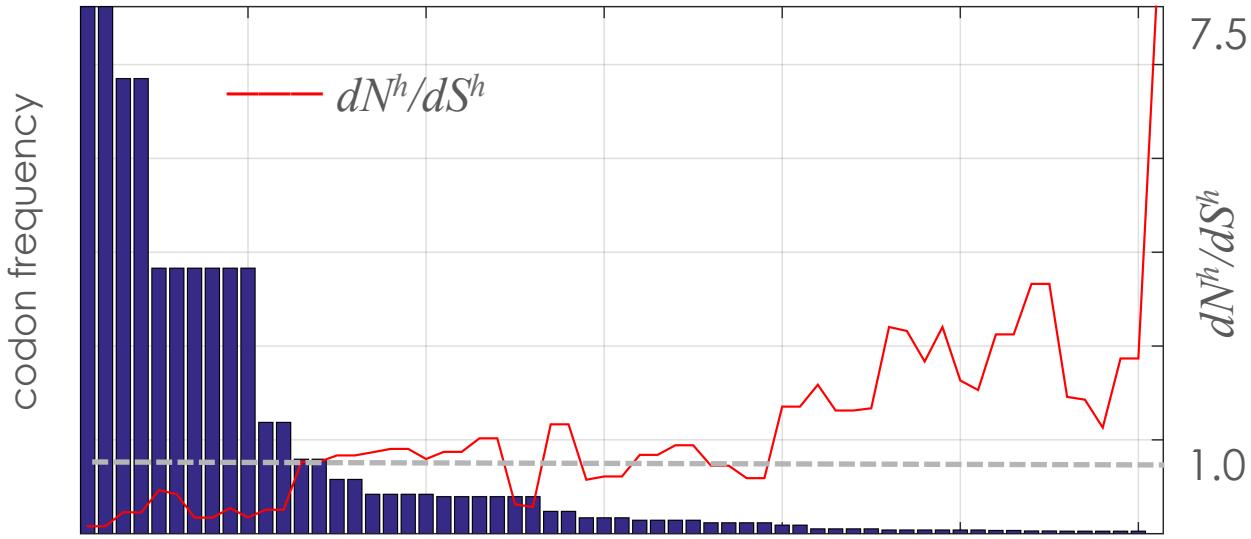
EXPECTED PROPORTION OF MUTATIONS FIXED BY SELECTION

$$p_+^h = \frac{\sum_{(i,j)} \pi_i^h \left( A_{ij}^h - \mu_i \right) I_+}{\sum_{i \neq j} \pi_i^h A_{ij}^h}$$

**conclusion:** $p_+ > 0$ as long as number of viable amino acids > 1 at a site

# shifting balance: the MutSel landscape

$dN^h/dS^h$ depends on the current amino acid

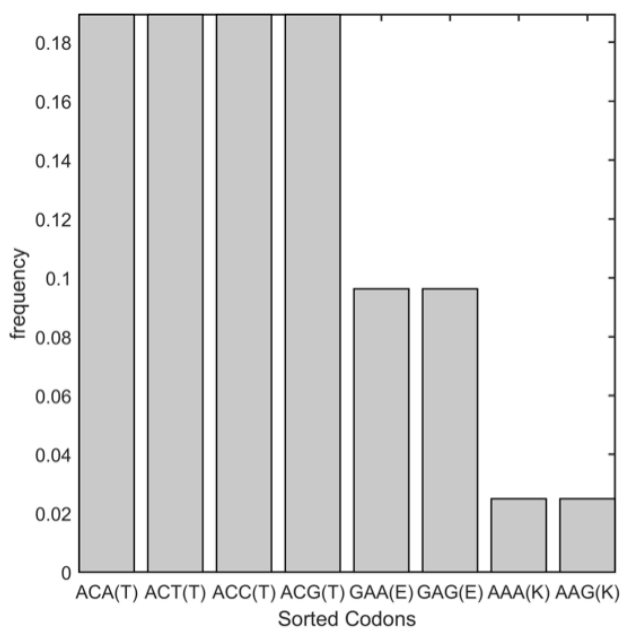



temporal average $dN^h/dS$ = 0.61

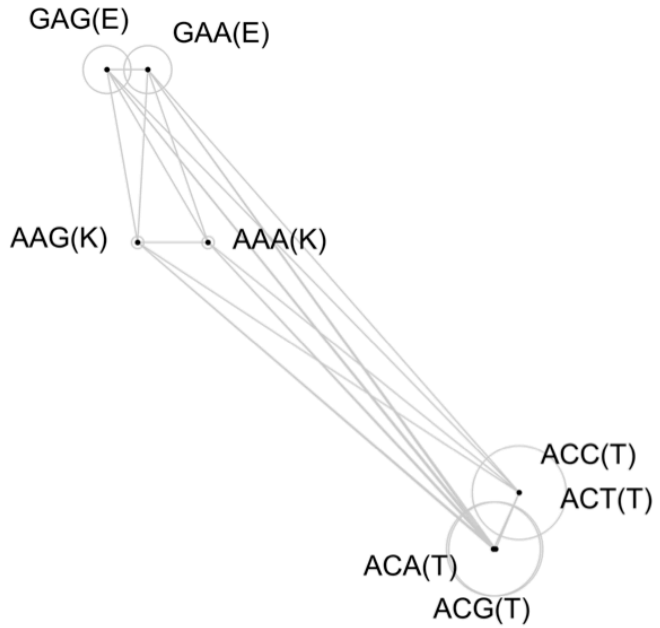
**conclusion:** positive selection operates on a stationary fitness peak in the same way as when there is an adaptive peak shift

# landscapes have unique structures

MutSel landscape




McCandlish landscape

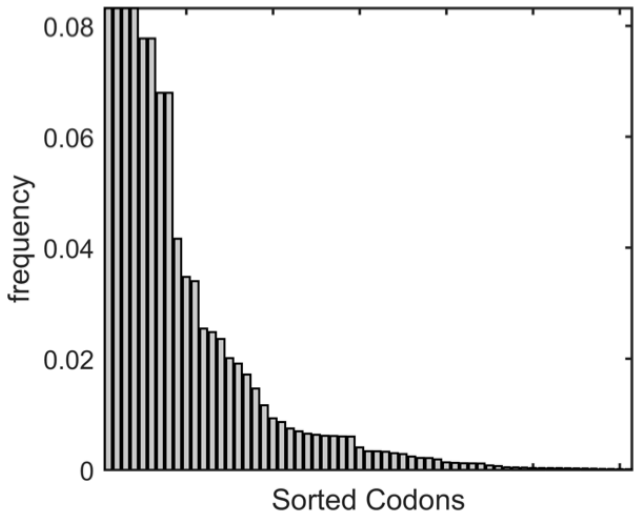



**conclusion:** A population can get to a sub-optimal codon (E) by drift and reside there for some time (b/c moving between T and E requires changes ≥ 2 codons).

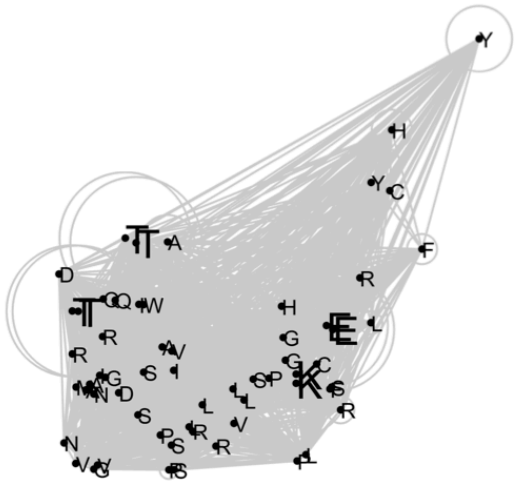
# landscape structure depends on N

**same site... 10x decrease in *N* ($f^h$ have not changed!)**

MutSel landscape




McCandlish landscape

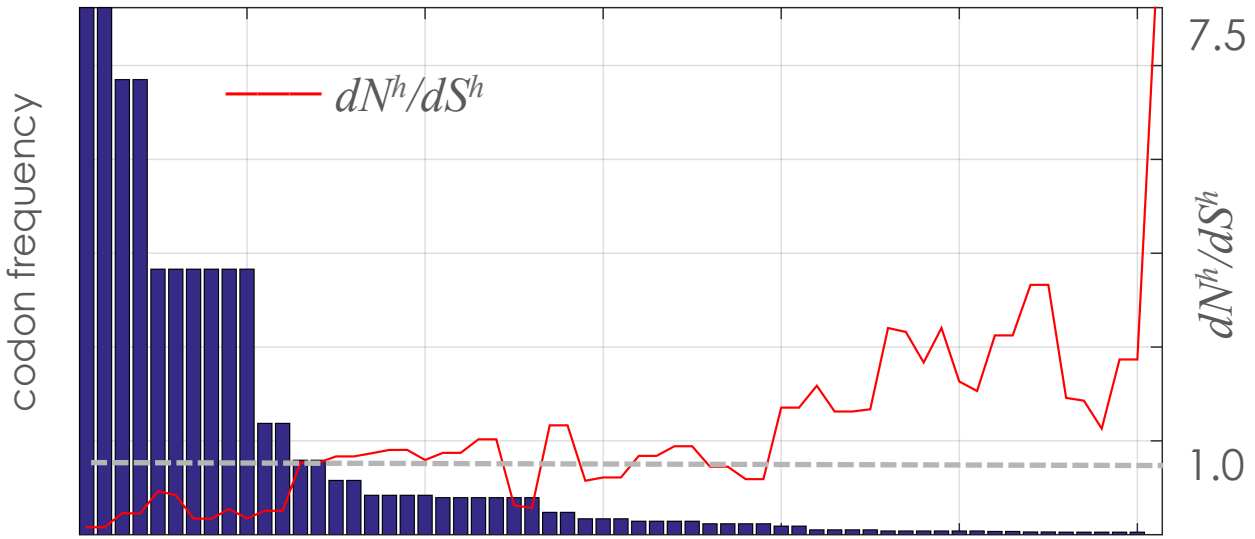


**conclusion:** decreasing N changes:

i. the "space" for shifting balance
ii. mean dN/dS
iii. equilibrium frequencies

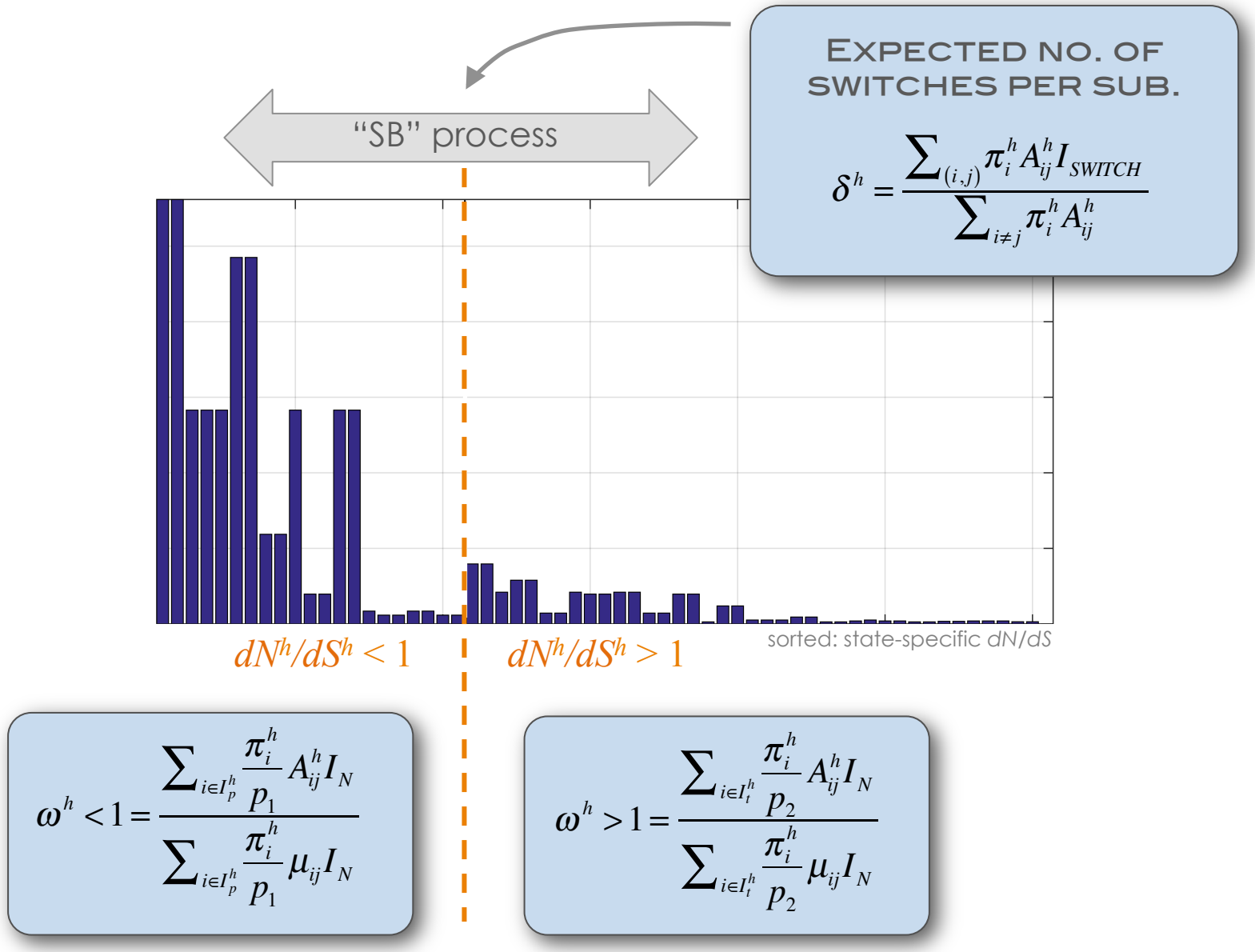
# shifting balance: the MutSel landscape

$dN^h/dS^h$ depends on the current amino acid




temporal average $dN^h/dS$ = 0.61

# shifting balance: a mechanistic model



# shifting balance: a mechanistic model


**landscapes:**

250 $f^{h}$

σ: {0.0001, 0.001, 0.01}

$N$ = 1000

| | high | moderate | low |
|---|---|---|---|
| median switching rate ($\delta$) | 0.45 | 0.25 | <0.01 |
| expected probability of a site being in the "tail" of the landscape ($p_{w>1}$) | high (>20%) | moderate (1%-25%) | very low (<0.1%) |
| Expected ***dN/dS*** in the "tail" of the landscape | ~ 1.1 | 1-3 | >>1 |
| Expected ***dN/dS*** near the "peak" of the landscape | ~ 0.95 | <0.4 | <0.01 |
| **rate of evolution (i.e., "type of site")** | **"fast"** | **"informative"** | **"conserved"** |

This **"signal"** is detectable with covarion and branch-site codon models!

**recall**: no adaptive evolution in this case (stationary fitness peak)!!!

## summary

- standard codon models (single $\omega$) assume frequency dependent selection, which yields a persistent dN/dS > 1
- episodic adaptive evolution leads to transient dN/dS > 1
- phenomenological codon models assume a stationary evolutionary process; adaptive evolution is non-stationary
- estimates of $\omega$ for episodic adaptive evolution are upwardly biased because adaptive evolution is non-stationary
- protein evolution on a static fitness landscape has temporal dynamics that include positive selection
- MutSel landscapes can be complex and a site can reside at a sub-optimal state for extended periods of time
- rate variation among sites reflects the interplay between mutation, drift, and selection (i.e., shifting balance dynamics)