

# A Brief Tour of Some Models of Nucleotide Substitution

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Université de Lyon

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# Outline

## I. A brief summary of Continuous-Time Markov chains (CTMCs)

The scale parameter

## II. Stochastic models of nucleotide substitution

What's the deal with time reversibility

Meet the GTR family

## III. Accommodating among-site heterogeneity in the substitution process

Among-site variation in substitution rates

Among-site variation in substitution process

## IV. Accommodating heterogeneity in the substitution process along the tree

# Stochastic Mechanisms of Character Change

Continuous-time Markov chains

*Why are they called like that ?*

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*Stationary frequencies:* the long-term probability of observing the chain in state  $j$

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<https://rpubs.com/boussau/scaleSubstRateMatrix>

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- sites are independent

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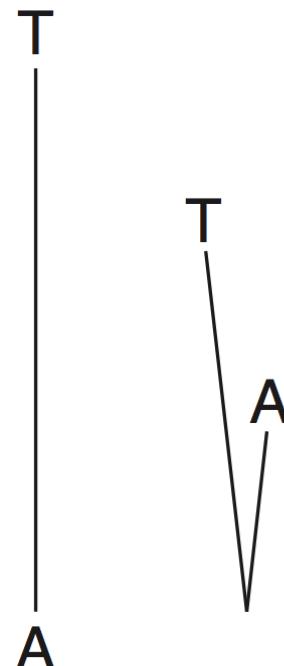
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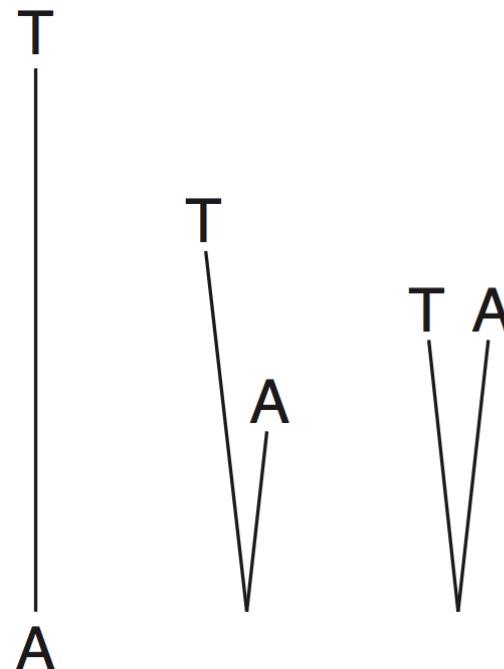
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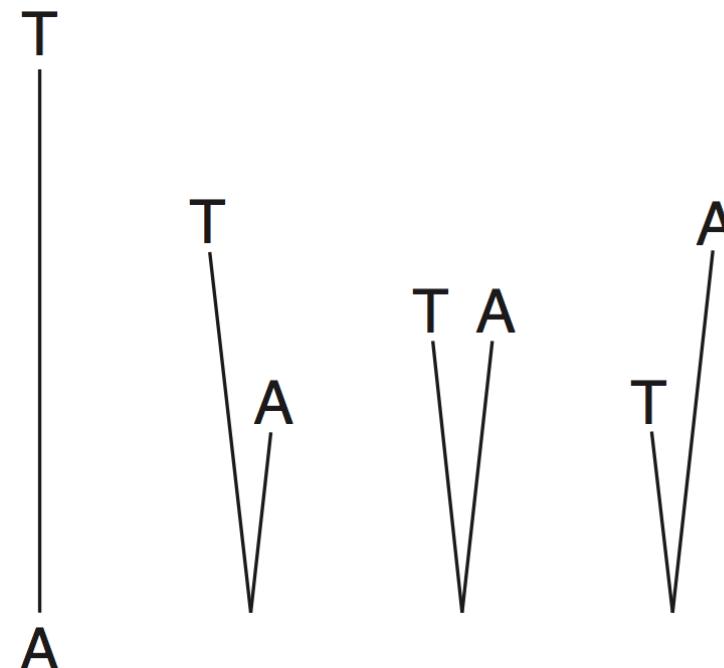
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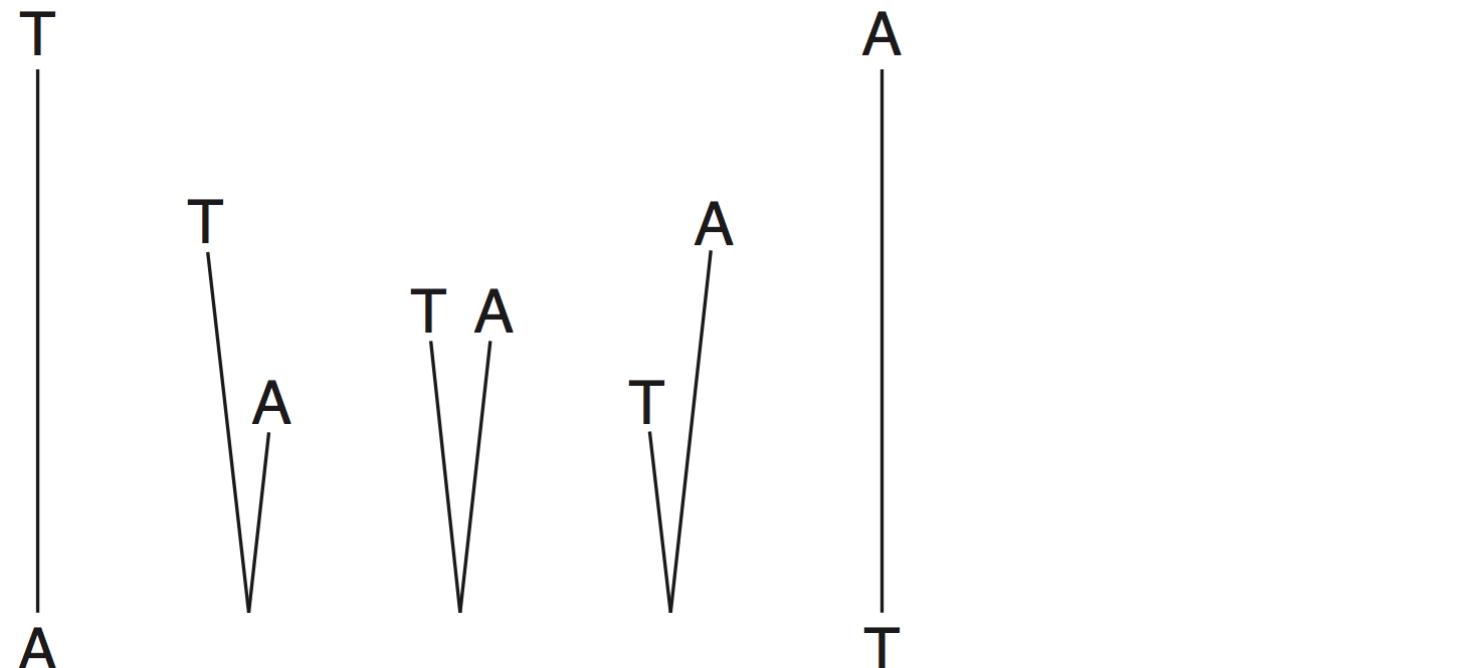
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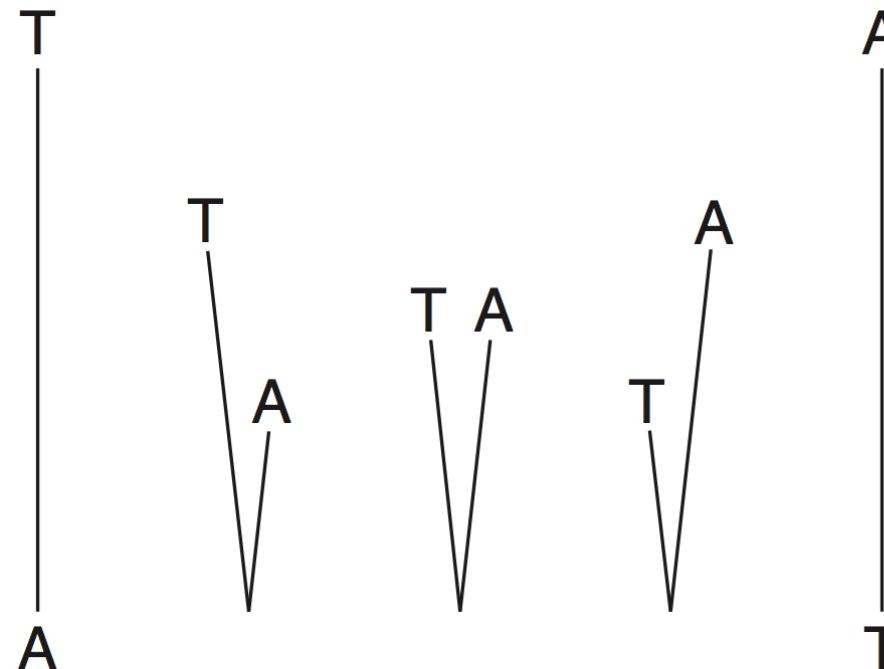
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*(One can still use the same algorithms for exploring tree space with non-reversible models of sequence evolution, but some extra care is needed (Boussau and Gouy 2006)*

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The **relative rates** allow for possible biases in the instantaneous rates of change between each pair of states,  $r_{ij}$

The **stationary frequencies** are in the columns of the matrix, reflecting the fact that the instantaneous rate of change to state  $j$  depends on its stationary frequency,  $\pi_j$

# Stochastic Models of Nucleotide Substitution

## Anatomy of General Time Reversible models

$$\mathbf{Q} = q_{ij} = \begin{pmatrix} - & \mu a \pi_C & \mu b \pi_G & \mu c \pi_T \\ \mu a \pi_A & - & \mu d \pi_G & \mu e \pi_T \\ \mu b \pi_A & \mu d \pi_C & - & \mu f \pi_T \\ \mu c \pi_A & \mu e \pi_C & \mu f \pi_G & - \end{pmatrix}$$

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The **stationary frequencies** are in the columns of the matrix, reflecting the fact that the instantaneous rate of change to state  $i$  depends on its stationary frequency,  $\pi_j$

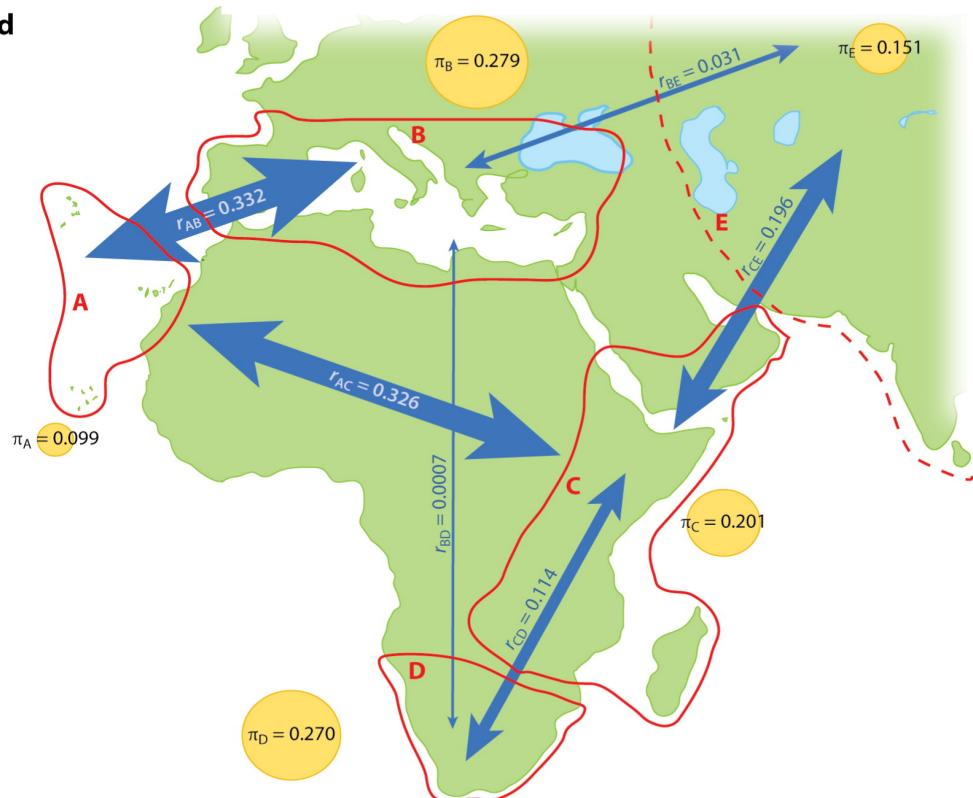
Recall that the average rate of substitution is scaled to be one:  $\mu = - \sum_i \pi_i q_{ii}$

# Stochastic Models of Nucleotide Substitution

*A phylogeographic intuition on relative rates and stationary frequencies*

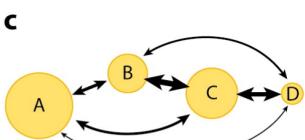
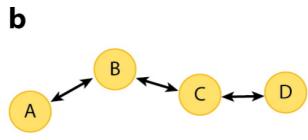
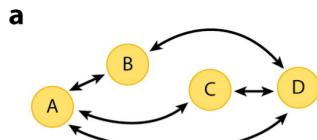
Ronquist and Sanmartin used a GTR model to study migrations of plants between parts of the old world.

d



# Stochastic Models of Nucleotide Substitution

*A phylogeographic intuition on relative rates and stationary frequencies*

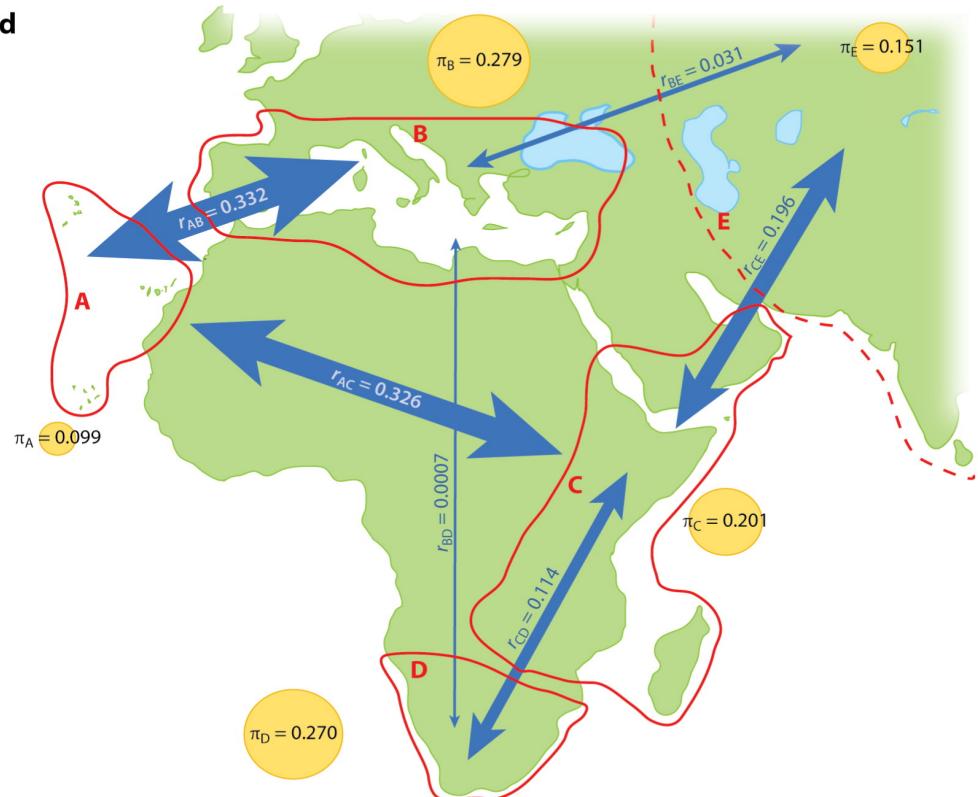


	[A]	[B]	[C]	[D]
[A]	—	$\mu$	$\mu$	$\mu$
[B]	$\mu$	—	$\mu$	$\mu$
[C]	$\mu$	$\mu$	—	$\mu$
[D]	$\mu$	$\mu$	$\mu$	—

	[A]	[B]	[C]	[D]
[A]	—	$\mu$	0	0
[B]	$\mu$	—	$\mu$	0
[C]	0	$\mu$	—	$\mu$
[D]	0	0	$\mu$	—

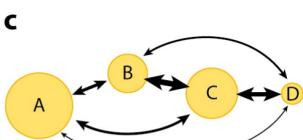
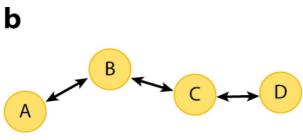
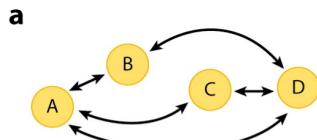
	[A]	[B]	[C]	[D]
[A]	—	$\pi_B r_{AB}$	$\pi_C r_{AC}$	$\pi_D r_{AD}$
[B]	$\pi_A r_{AB}$	—	$\pi_C r_{BC}$	$\pi_D r_{BD}$
[C]	$\pi_A r_{AC}$	$\pi_B r_{BC}$	—	$\pi_D r_{CD}$
[D]	$\pi_A r_{AD}$	$\pi_B r_{BD}$	$\pi_C r_{CD}$	—

Ronquist and Sanmartin used a GTR model to study migrations of plants between parts of the old world.



# Stochastic Models of Nucleotide Substitution

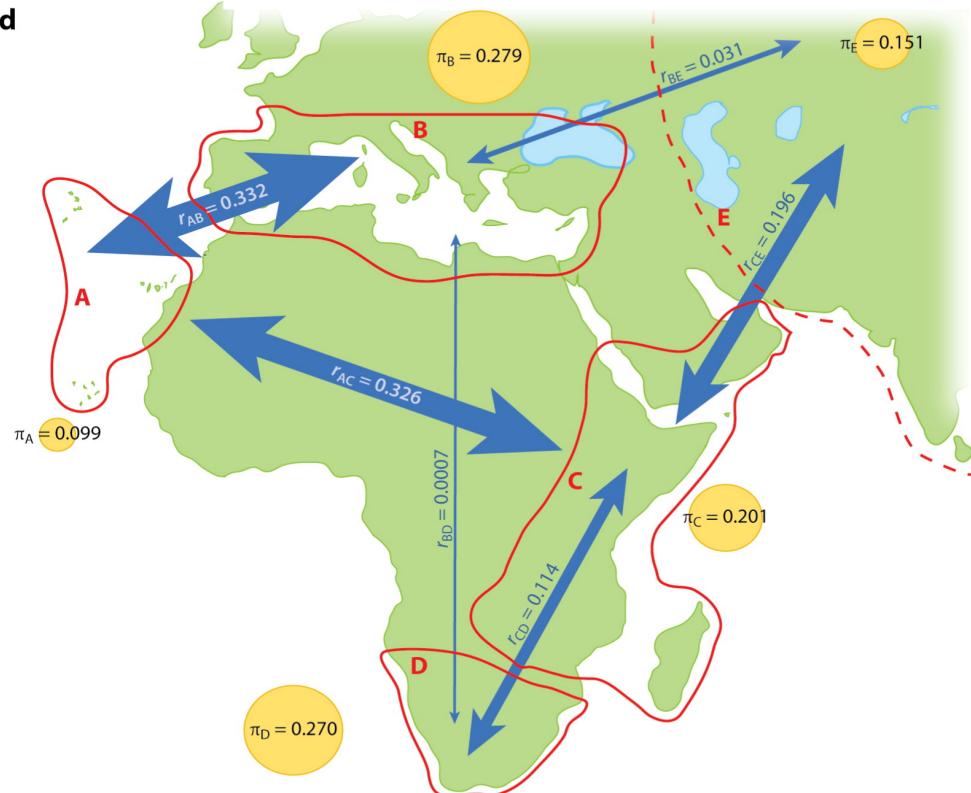
*A phylogeographic intuition on relative rates and stationary frequencies*



	[A]	[B]	[C]	[D]
[A]	—	$\mu$	$\mu$	$\mu$
[B]	$\mu$	—	$\mu$	$\mu$
[C]	$\mu$	$\mu$	—	$\mu$
[D]	$\mu$	$\mu$	$\mu$	—

	[A]	[B]	[C]	[D]
[A]	—	$\mu$	0	0
[B]	$\mu$	—	$\mu$	0
[C]	0	$\mu$	—	$\mu$
[D]	0	0	$\mu$	—

	[A]	[B]	[C]	[D]
[A]	—	$\pi_B r_{AB}$	$\pi_C r_{AC}$	$\pi_D r_{AD}$
[B]	$\pi_A r_{AB}$	—	$\pi_C r_{BC}$	$\pi_D r_{BD}$
[C]	$\pi_A r_{AC}$	$\pi_B r_{BC}$	—	$\pi_D r_{CD}$
[D]	$\pi_A r_{AD}$	$\pi_B r_{BD}$	$\pi_C r_{CD}$	—



Ronquist and Sanmartin used a GTR model to study migrations of plants between parts of the old world.

Exchangeabilities correspond to the intensities of biotic exchange (thickness of arrows)

Equilibrium frequencies correspond to the carrying capacities of the regions

# Stochastic Models of Nucleotide Substitution

The Jukes and Cantor, 1969 (JC69) substitution model

$$\mathbf{Q} = q_{ij} = \begin{pmatrix} - & \mu a \pi_C & \mu b \pi_G & \mu c \pi_T \\ \mu a \pi_A & - & \mu d \pi_G & \mu e \pi_T \\ \mu b \pi_A & \mu d \pi_C & - & \mu f \pi_T \\ \mu c \pi_A & \mu e \pi_C & \mu f \pi_G & - \end{pmatrix}$$

Relative rates of change between each pair of states  $i$  and  $j$ ,  $r_{ij}$ , are assumed to be equal, therefore:  $a = b = c = d = e = f$

# Stochastic Models of Nucleotide Substitution

The Jukes and Cantor, 1969 (JC69) substitution model

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# Stochastic Models of Nucleotide Substitution

The Jukes and Cantor, 1969 (JC69) substitution model

$$\mathbf{Q} = q_{ij} = \begin{pmatrix} - & \mu 1/4 & \mu 1/4 & \mu 1/4 \\ \mu 1/4 & - & \mu 1/4 & \mu 1/4 \\ \mu 1/4 & \mu 1/4 & - & \mu 1/4 \\ \mu 1/4 & \mu 1/4 & \mu 1/4 & - \end{pmatrix}$$

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How many free parameters are there in the JC69 substitution model?

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$$\mathbf{Q} = q_{ij} = \begin{pmatrix} - & \mu 1/4 & \mu 1/4 & \mu 1/4 \\ \mu 1/4 & - & \mu 1/4 & \mu 1/4 \\ \mu 1/4 & \mu 1/4 & - & \mu 1/4 \\ \mu 1/4 & \mu 1/4 & \mu 1/4 & - \end{pmatrix}$$

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0 !

# Stochastic Models of Nucleotide Substitution

The Jukes and Cantor, 1969 (JC69) substitution model

$$\mathbf{Q} = q_{ij} = \begin{pmatrix} - & \mu 1/4 & \mu 1/4 & \mu 1/4 \\ \mu 1/4 & - & \mu 1/4 & \mu 1/4 \\ \mu 1/4 & \mu 1/4 & - & \mu 1/4 \\ \mu 1/4 & \mu 1/4 & \mu 1/4 & - \end{pmatrix}$$

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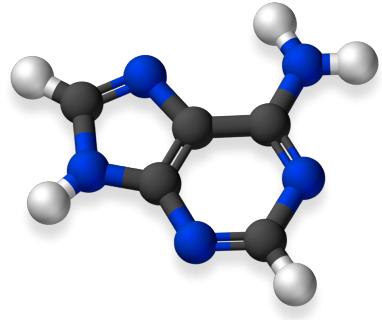
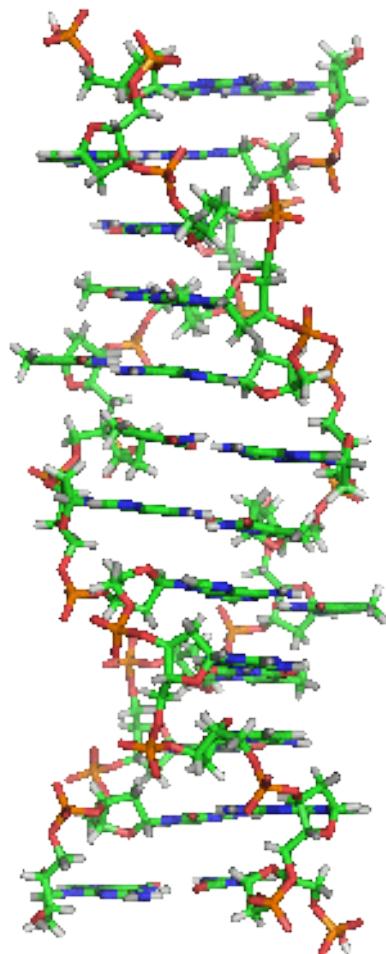
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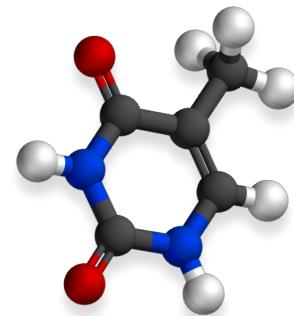
# Stochastic Models of Nucleotide Substitution

Biology motivates the extension of models

DNA

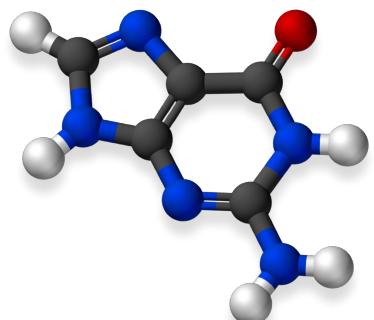


Adenine

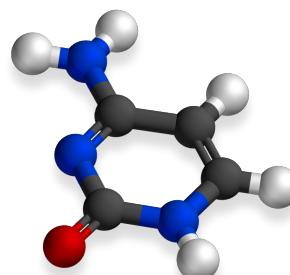


Thymine

Guanine

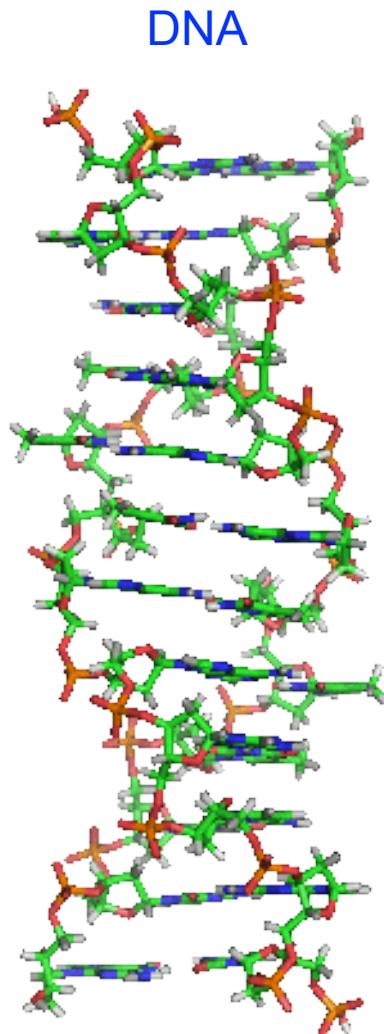


Cytosine

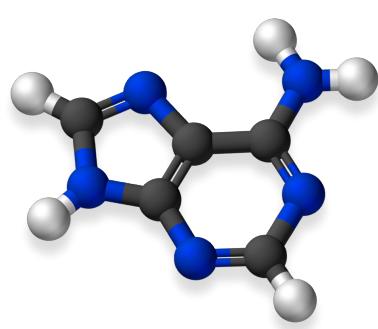


# Stochastic Models of Nucleotide Substitution

Biology motivates the extension of models

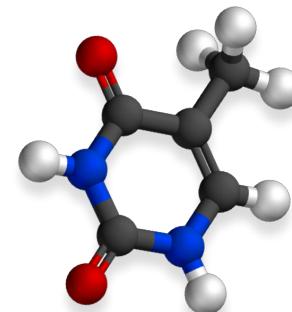


Purines



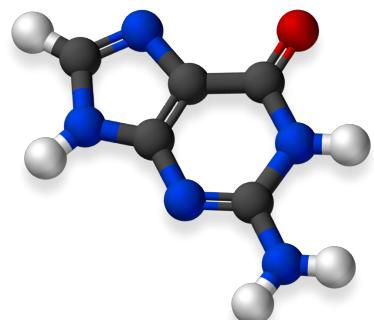
Adenine

Pyrimidines

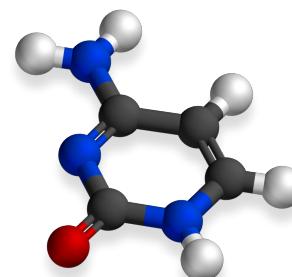


Thymine

Guanine

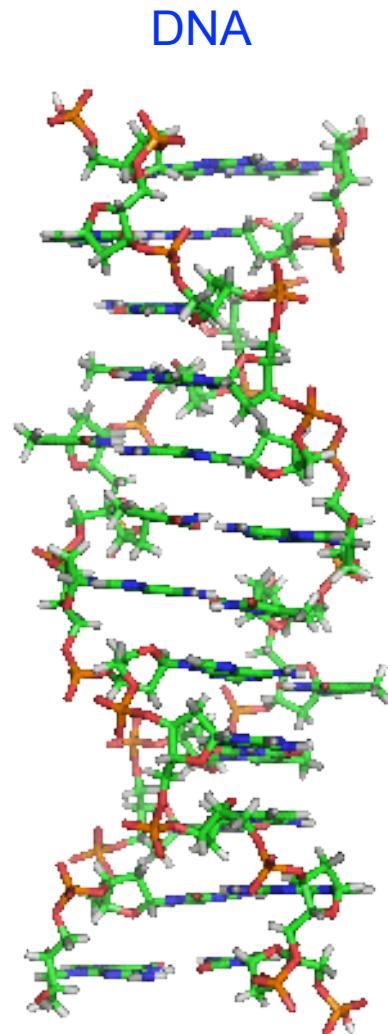


Cytosine

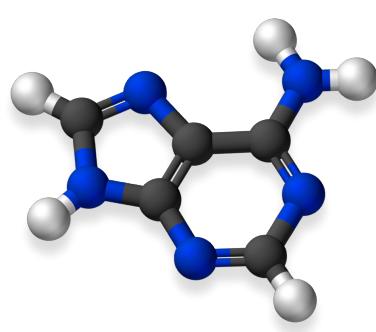


# Stochastic Models of Nucleotide Substitution

Biology motivates the extension of models

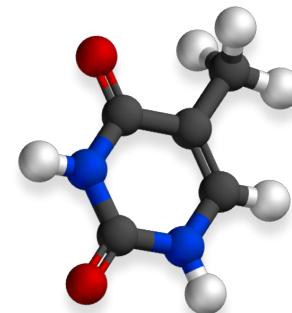


Purines



Adenine

Pyrimidines

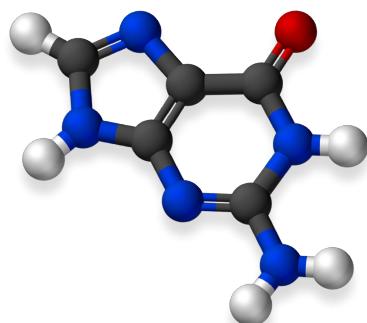


Thymine

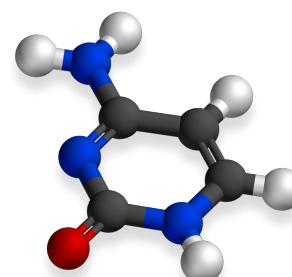
transition  
substitutions



Guanine

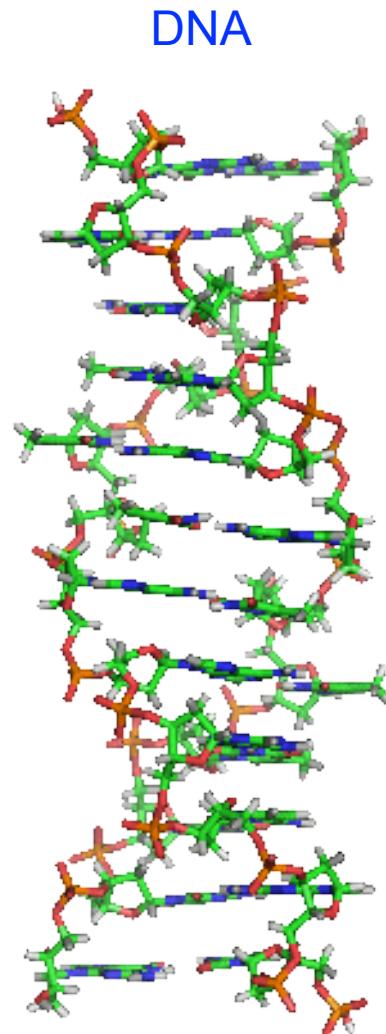


Cytosine

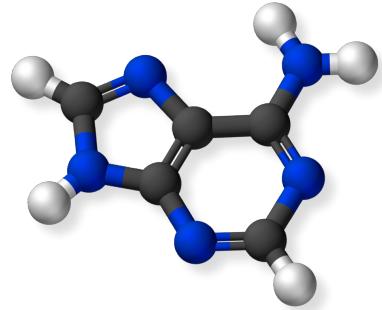


# Stochastic Models of Nucleotide Substitution

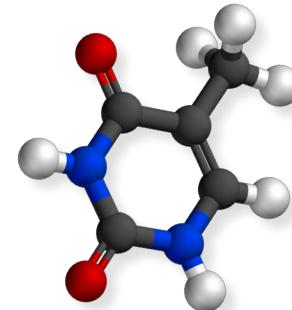
Biology motivates the extension of models



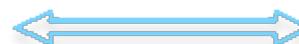
Purines



Pyrimidines

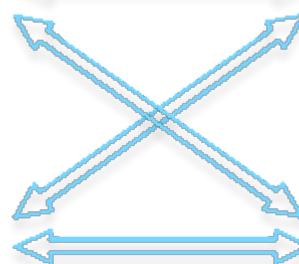


Adenine

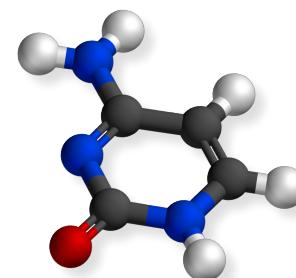
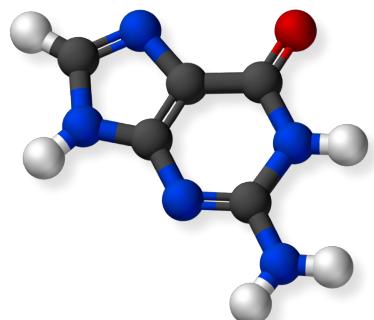


Thymine

Guanine



Cytosine

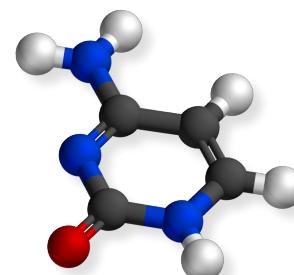
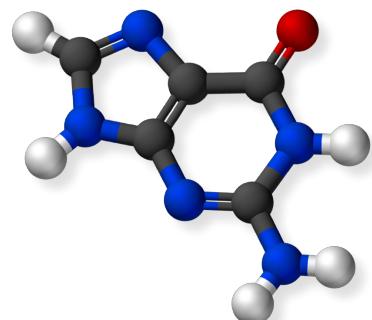
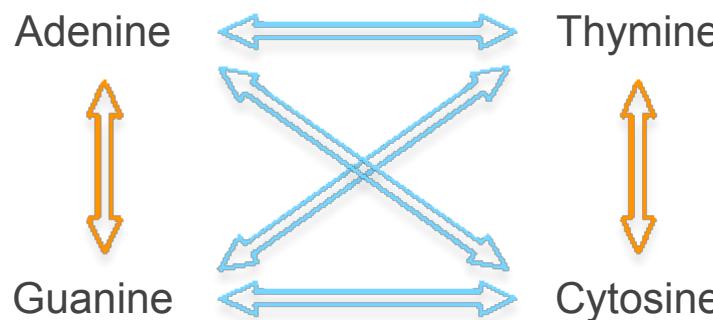
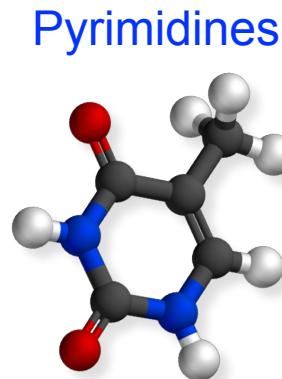
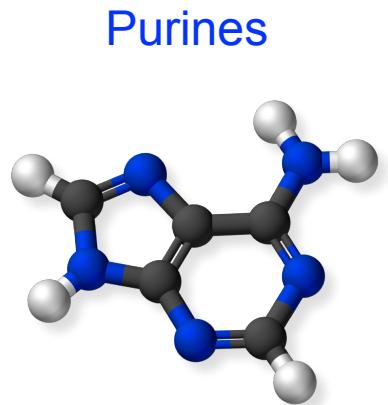
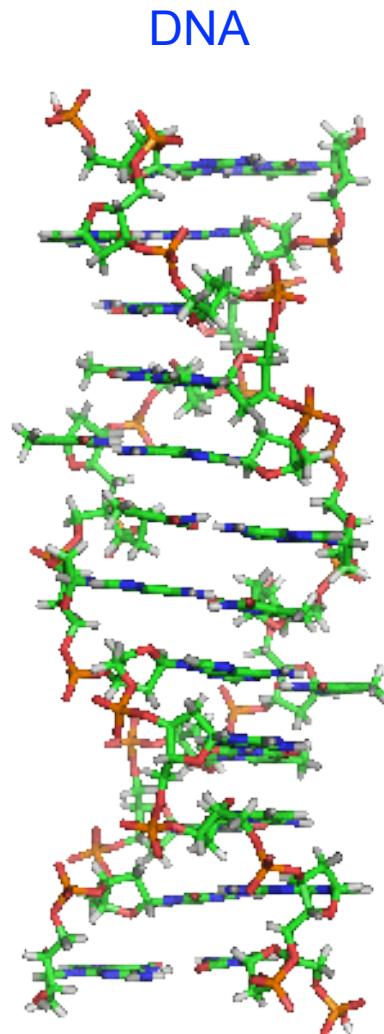


transversion  
substitutions

# Stochastic Models of Nucleotide Substitution

Biology motivates the extension of models

The molecular structure makes transitions more probable than transversions



transitions  
>  
transversions

# Stochastic Models of Nucleotide Substitution

The Kimura, 1980 (K80) substitution model

$$\mathbf{Q} = q_{ij} = \begin{pmatrix} - & \mu a 1/4 & \mu b 1/4 & \mu c 1/4 \\ \mu a 1/4 & - & \mu d 1/4 & \mu e 1/4 \\ \mu b 1/4 & \mu d 1/4 & - & \mu f 1/4 \\ \mu c 1/4 & \mu e 1/4 & \mu f 1/4 & - \end{pmatrix}$$

The stationary frequencies of all states are still assumed to be equal

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The **stationary frequencies** of all states are still assumed to be equal

The **relative rates** accommodate possible bias in the instantaneous rates of transition and transversion substitutions

Purine      Pyrimidine  
A            T

G            C

# Stochastic Models of Nucleotide Substitution

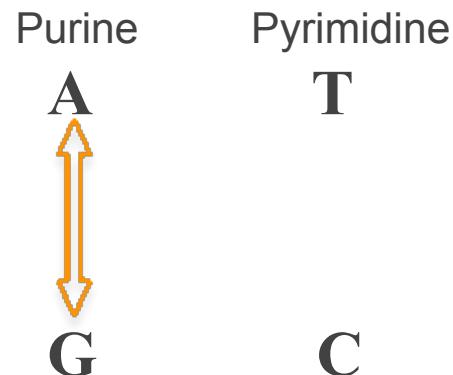
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$$b = r_{AG}$$



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The Kimura, 1980 (K80) substitution model

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The **stationary frequencies** of all states are still assumed to be equal

The **relative rates** accommodate possible bias in the instantaneous rates of transition and transversion substitutions

$$b = r_{AG}$$

$$e = r_{CT}$$

Purine



Pyrimidine



# Stochastic Models of Nucleotide Substitution

The Kimura, 1980 (K80) substitution model

$$\mathbf{Q} = q_{ij} = \begin{pmatrix} - & \mu a 1/4 & \mu b 1/4 & \mu c 1/4 \\ \mu a 1/4 & - & \mu d 1/4 & \mu e 1/4 \\ \mu b 1/4 & \mu d 1/4 & - & \mu f 1/4 \\ \mu c 1/4 & \mu e 1/4 & \mu f 1/4 & - \end{pmatrix}$$

The **stationary frequencies** of all states are still assumed to be equal

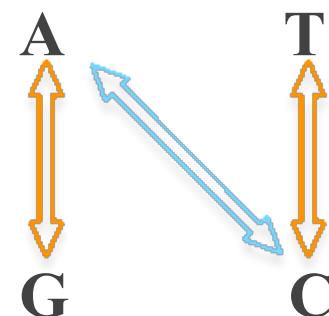
The **relative rates** accommodate possible bias in the instantaneous rates of transition and transversion substitutions

$$b = r_{AG}$$

$$e = r_{CT}$$

$$a = r_{AC}$$

Purine      Pyrimidine



# Stochastic Models of Nucleotide Substitution

The Kimura, 1980 (K80) substitution model

$$\mathbf{Q} = q_{ij} = \begin{pmatrix} - & \mu a 1/4 & \mu b 1/4 & \mu c 1/4 \\ \mu a 1/4 & - & \mu d 1/4 & \mu e 1/4 \\ \mu b 1/4 & \mu d 1/4 & - & \mu f 1/4 \\ \mu c 1/4 & \mu e 1/4 & \mu f 1/4 & - \end{pmatrix}$$

The **stationary frequencies** of all states are still assumed to be equal

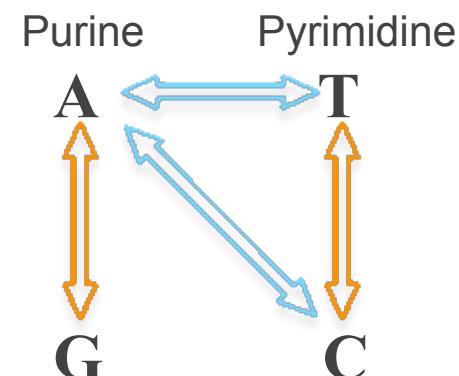
The **relative rates** accommodate possible bias in the instantaneous rates of transition and transversion substitutions

$$b = r_{AG}$$

$$e = r_{CT}$$

$$a = r_{AC}$$

$$c = r_{AT}$$



# Stochastic Models of Nucleotide Substitution

The Kimura, 1980 (K80) substitution model

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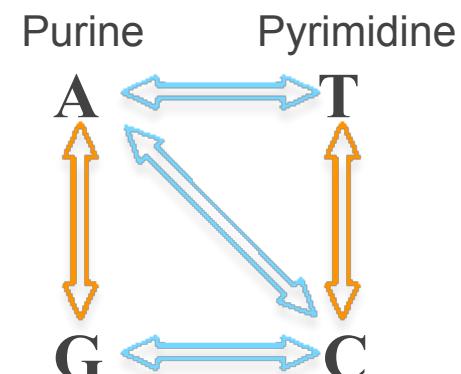
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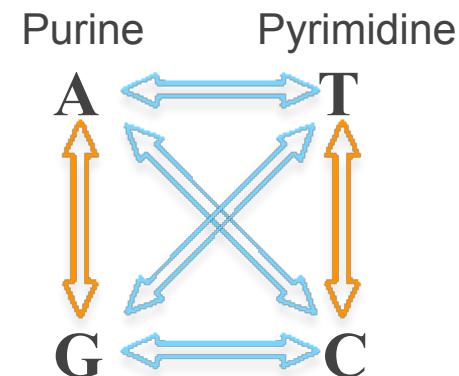
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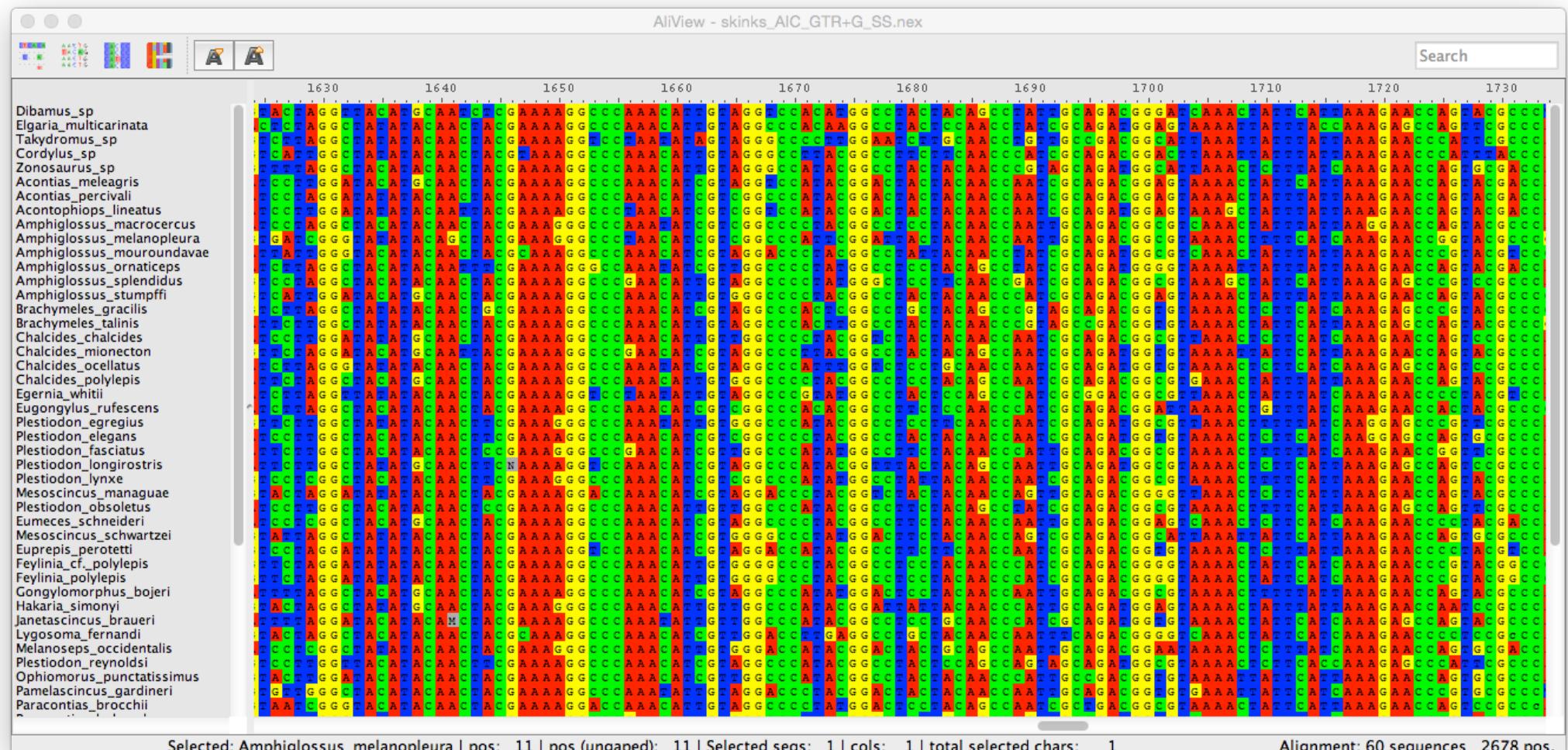
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Biology motivates the extension of models



$$A = 49,708 \div 151,015 = 32.9\%$$

$$G = 25,162 \div 151,015 = 16.7\%$$

$$A \neq C \neq G \neq T \neq 0.25$$

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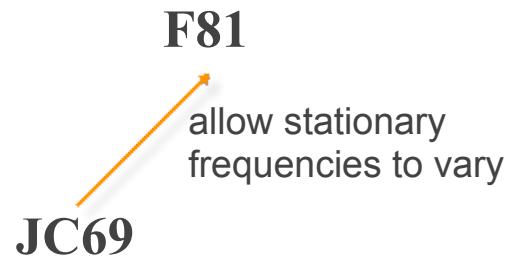
Members of the GTR substitution model family are hierarchically related

## JC69

We can move from a simpler to a more general model by relaxing a constraint

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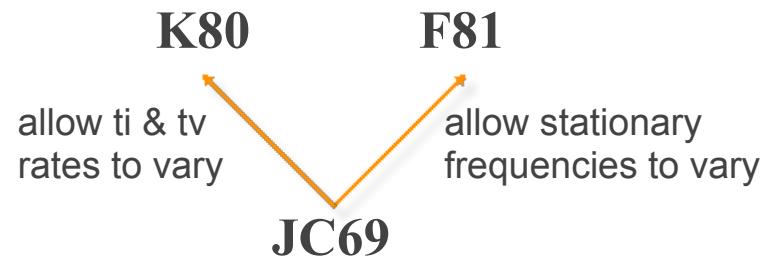
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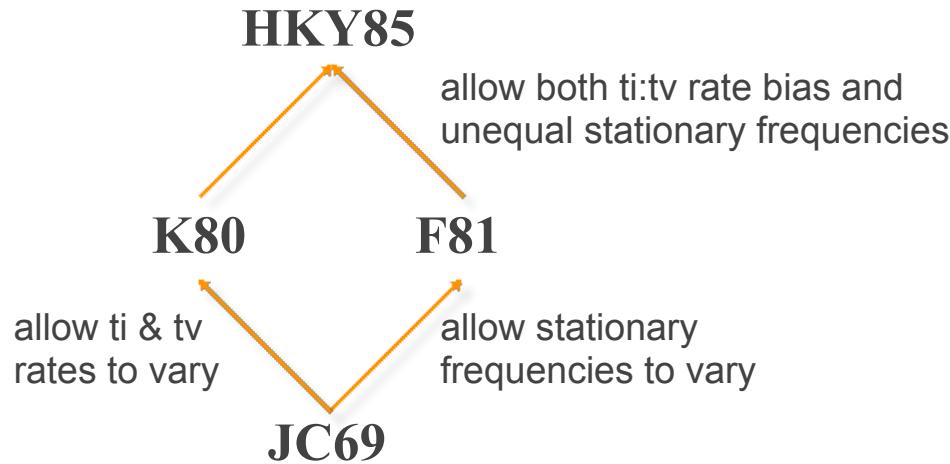
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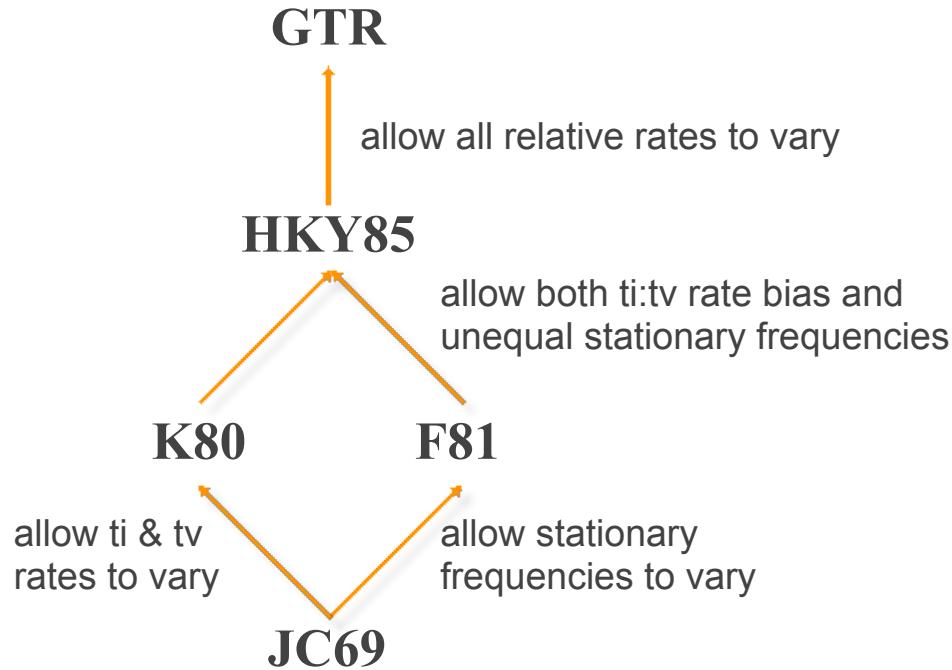
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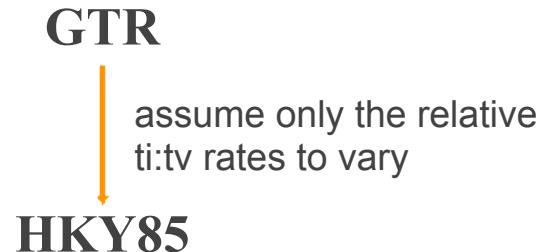
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# Stochastic Models of Nucleotide Substitution

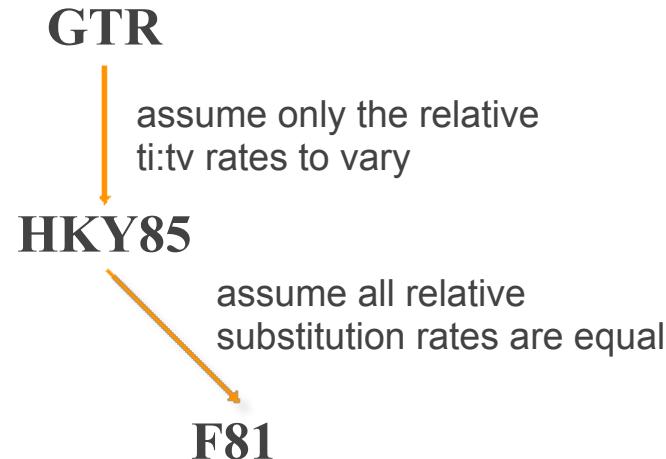
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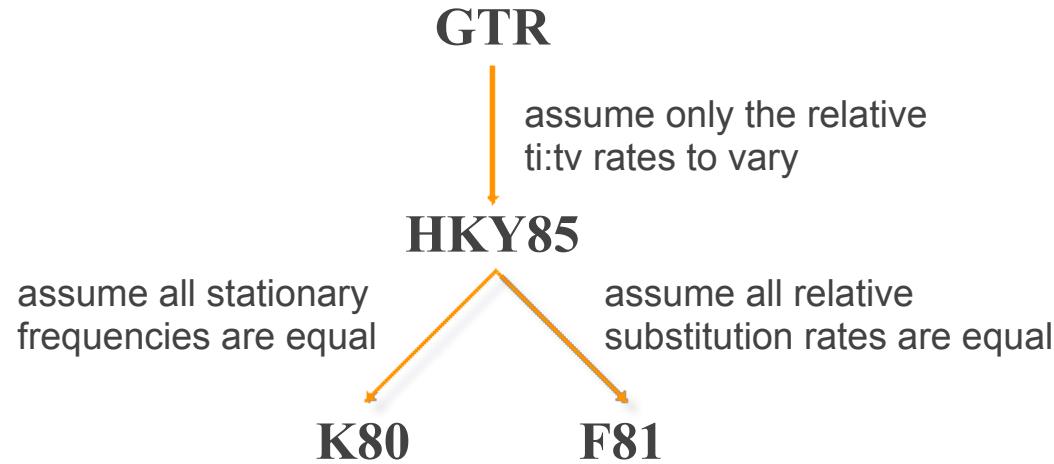
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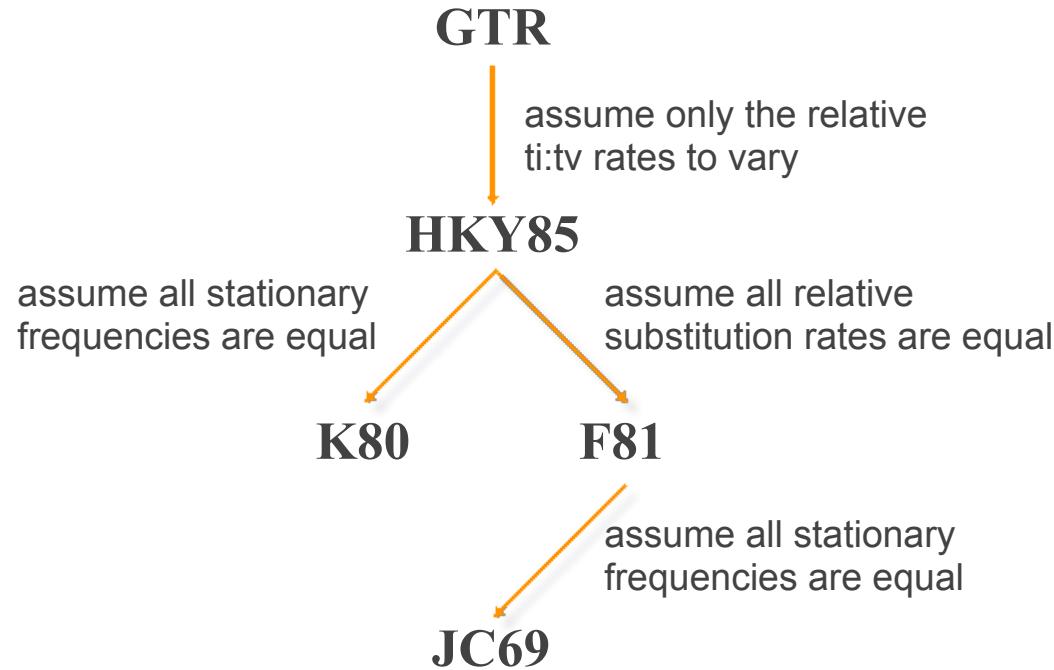
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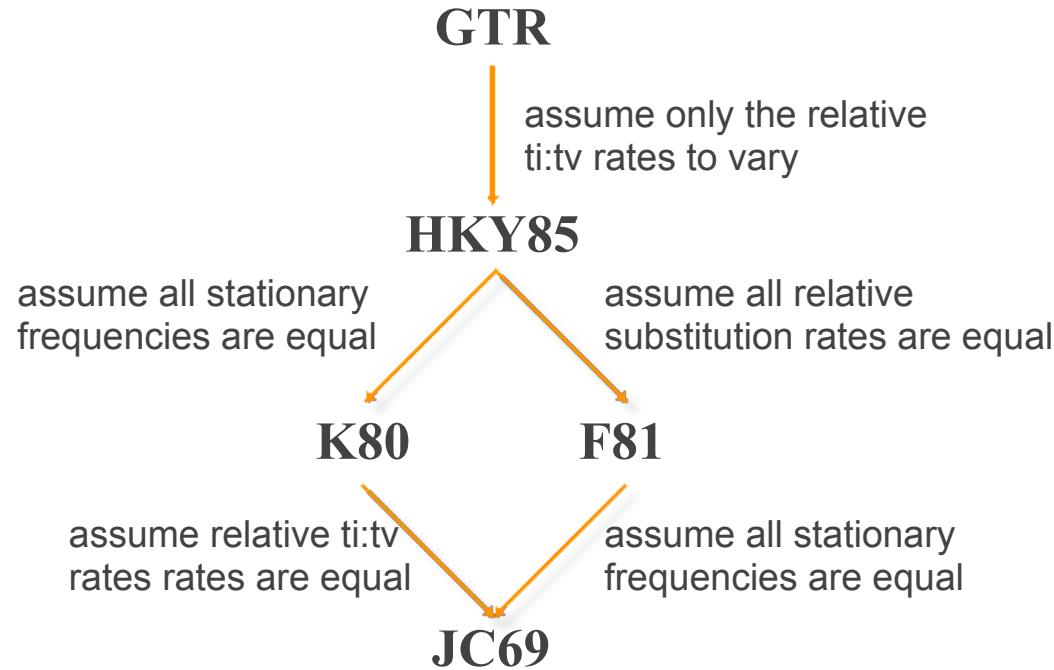
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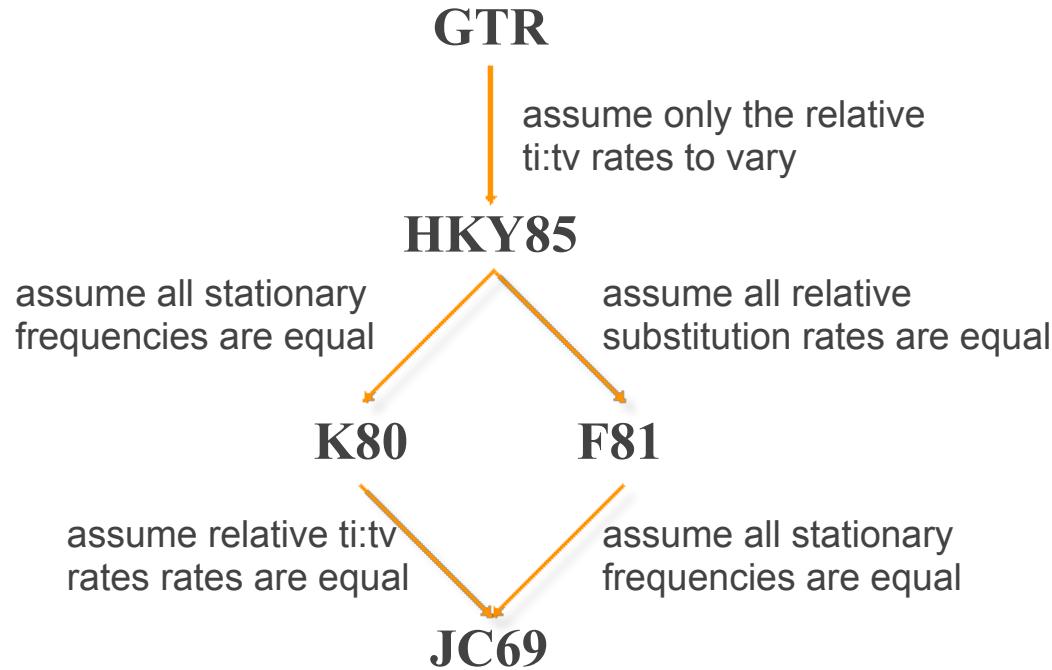
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# Stochastic Models of Nucleotide Substitution

Members of the GTR substitution model family are hierarchically related



We can move from a more general model to a simpler model by imposing a constraint  
The differences between models allow us to test hypotheses (to learn) about our data

# Stochastic Models of Nucleotide Substitution

*All the members of the GTR model family, focusing on relative rates*

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Many of those models are never used in practice, because they do not correspond to a biologically plausible hypothesis.

# Stochastic Models of Nucleotide Substitution

Limitations of the GTR model family:

Homogeneity along the sequence and along the tree

- If the process were homogeneous along the sequence: all sites would be similar in their ACGT composition, and in the number of substitutions they have undergone
- If the process were homogeneous along the tree, the sequences would all be similar in their ACGT composition

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Failure to account for heterogeneity along the tree and along the sequence can result in erroneous tree topologies, incorrect inferences of selection, etc.

# Outline

I. A brief summary of Continuous-Time Markov chains (CTMCs)

The scale parameter

II. Stochastic models of nucleotide substitution

What's the deal with time reversibility

Meet the GTR family

**III. Accommodating among-site heterogeneity in the substitution process**

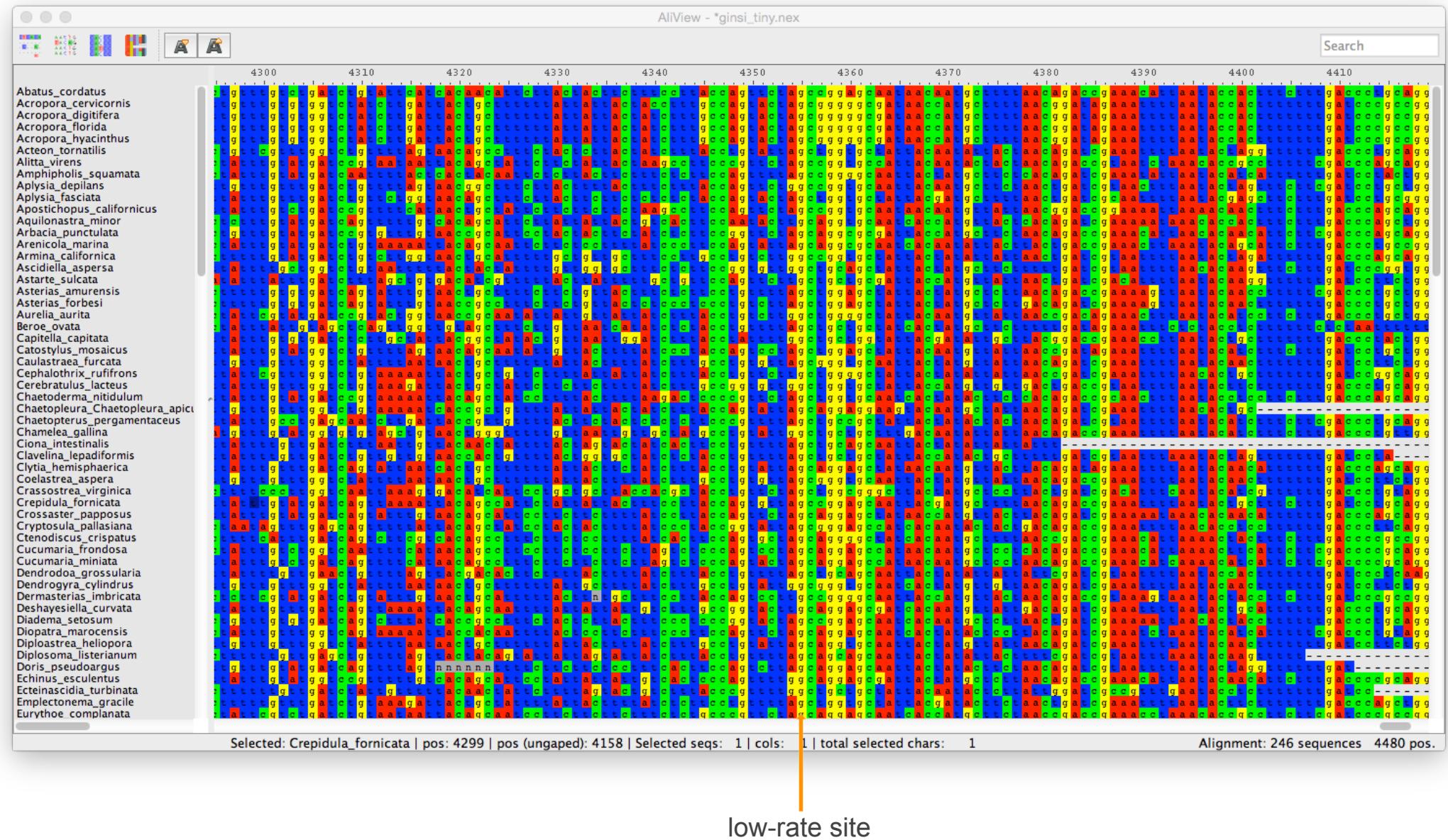
Among-site variation in substitution rates

Among-site variation in substitution process

**IV. Accommodating heterogeneity in the substitution process along the tree**

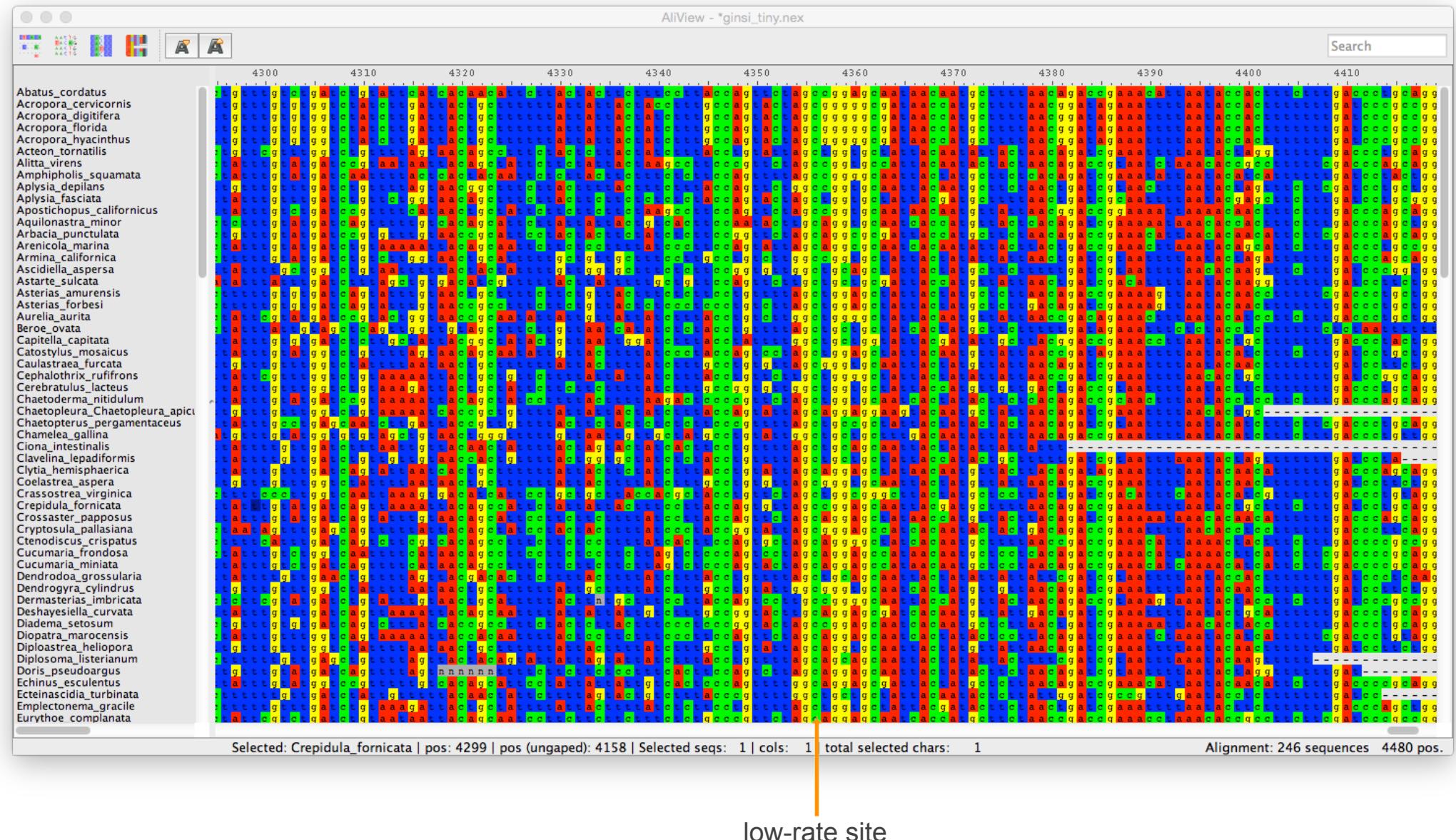
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Standard models assume that the substitution rate is constant across sites



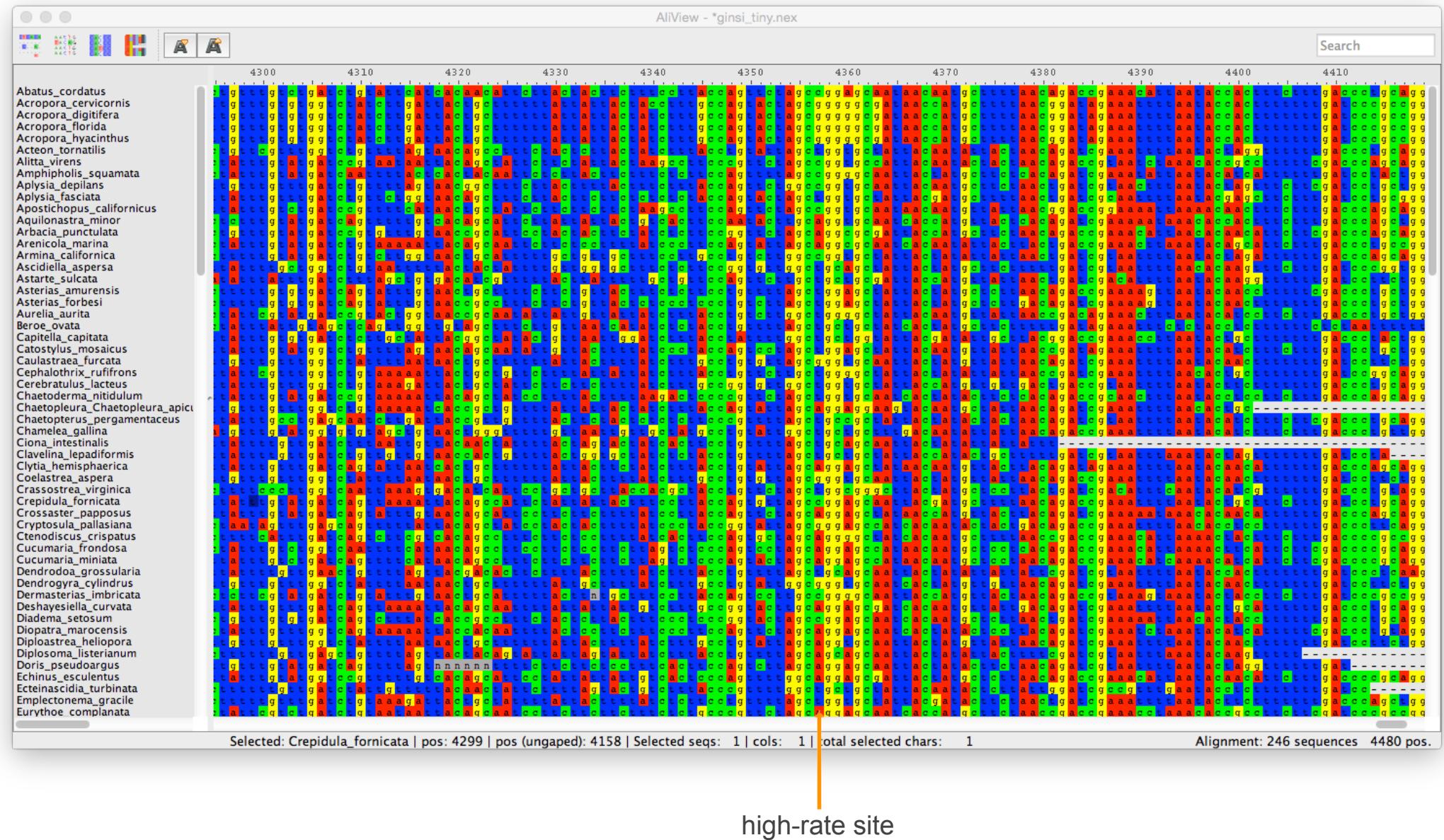
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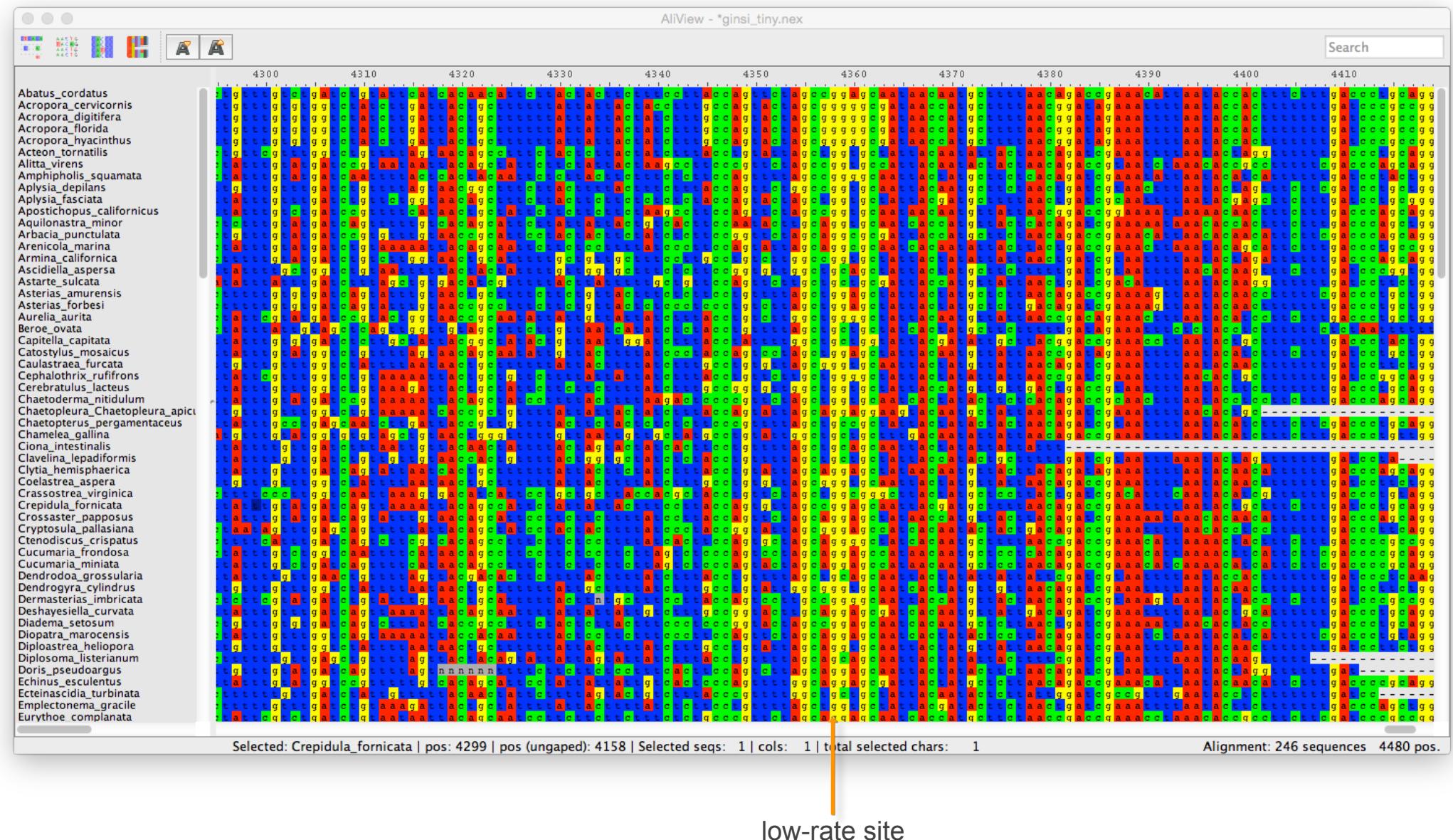
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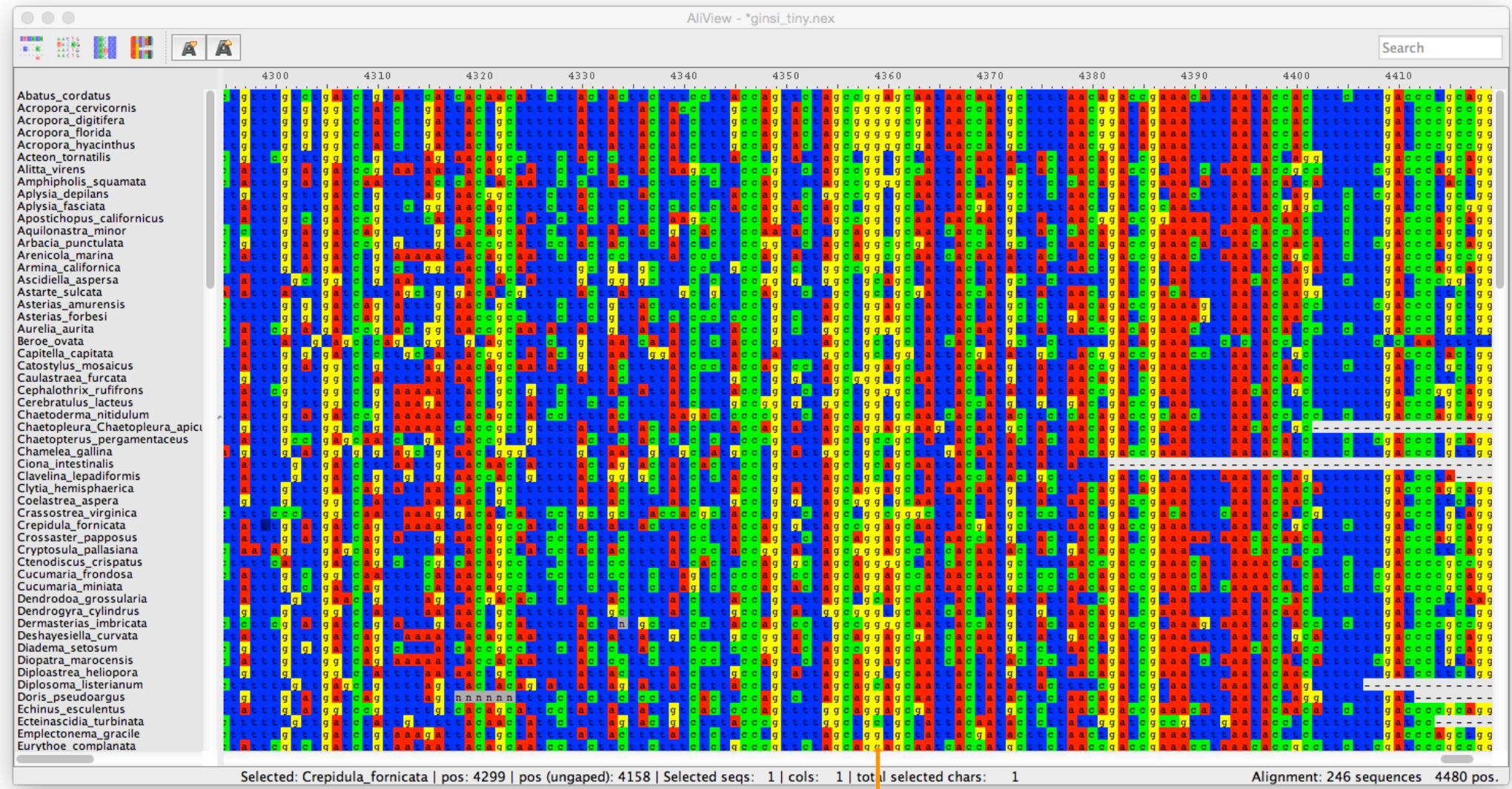
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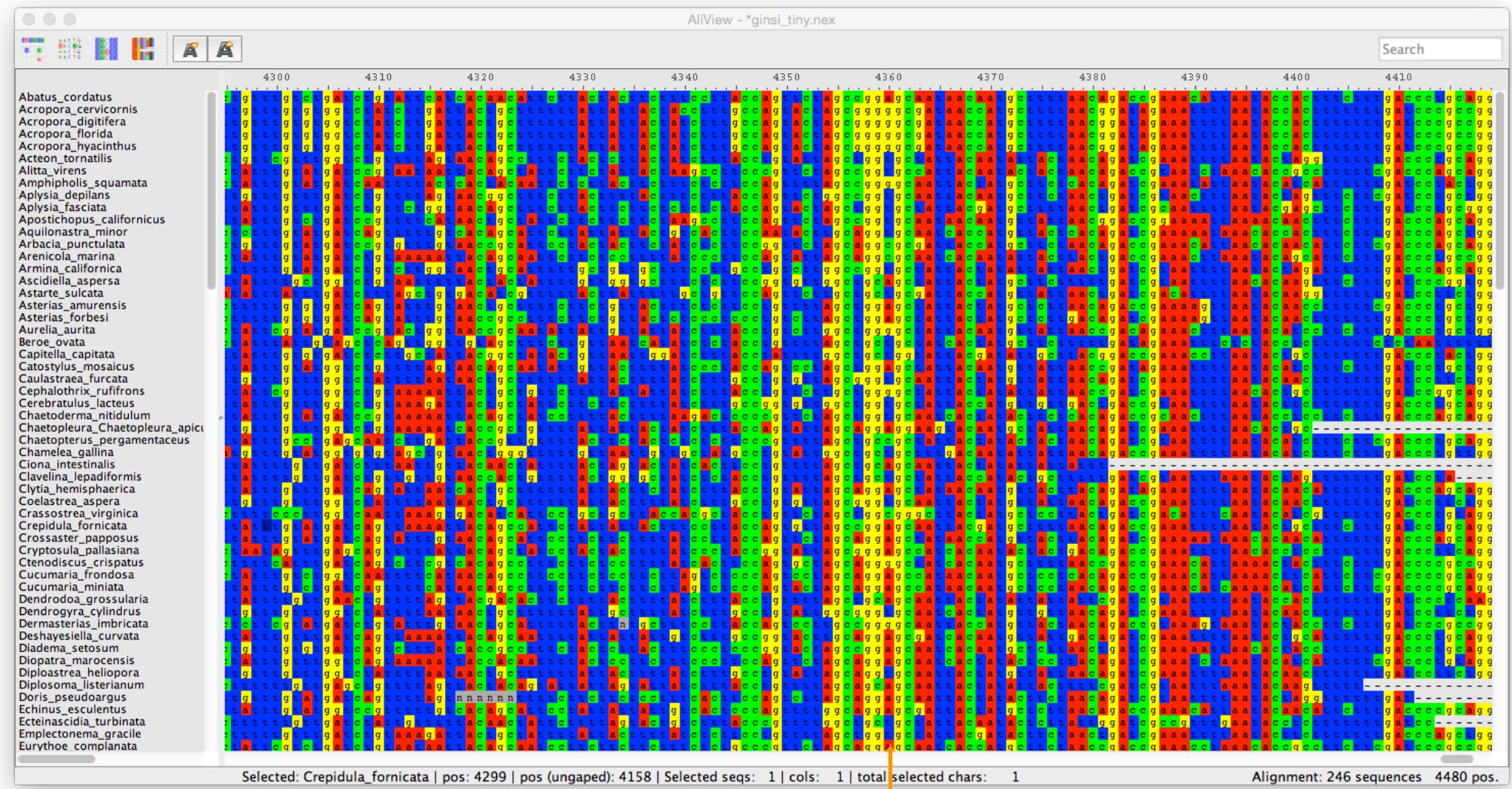
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## high-rate site

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The substitution rates may differ between sites at different codon positions of protein-coding genes

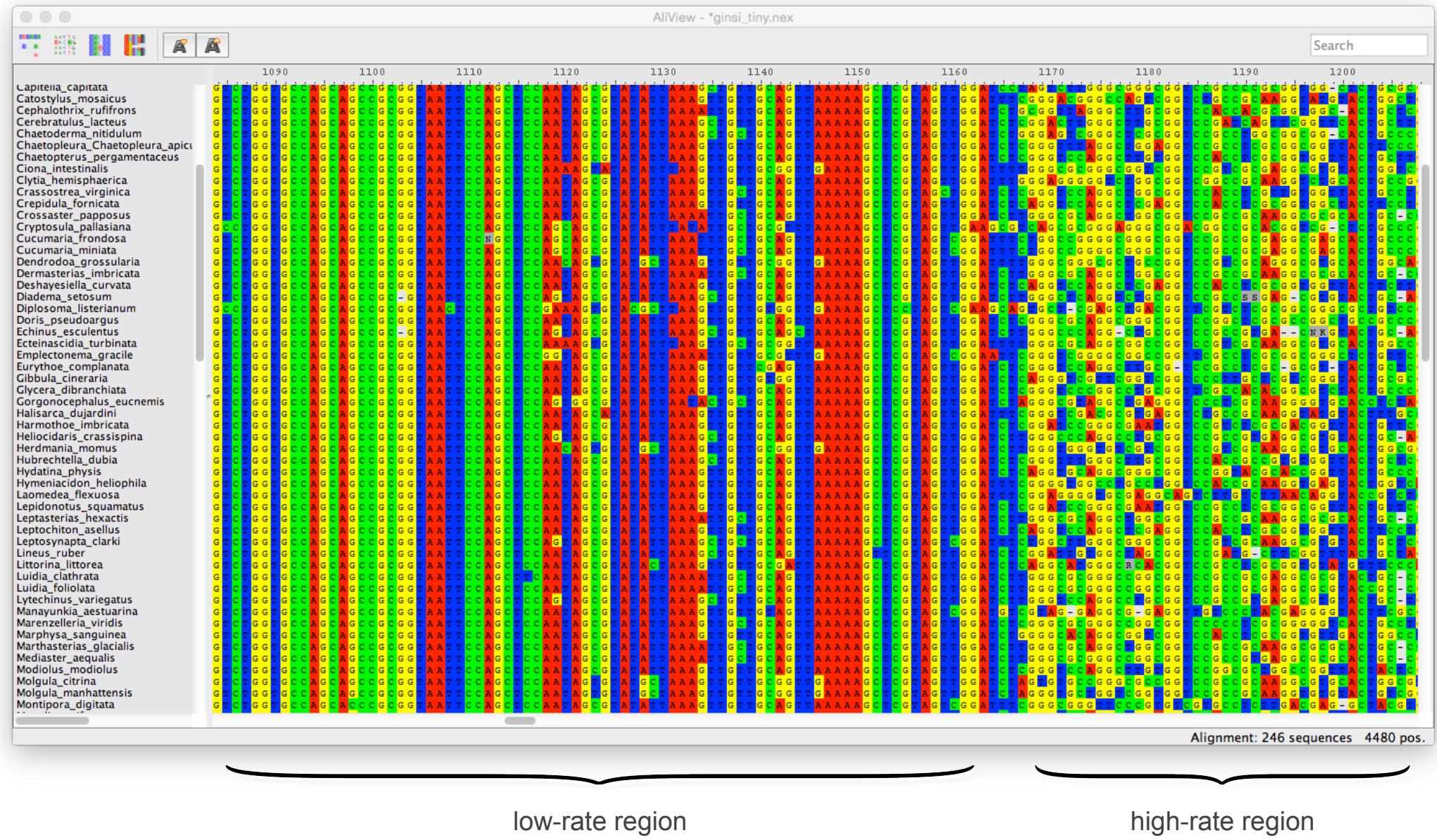
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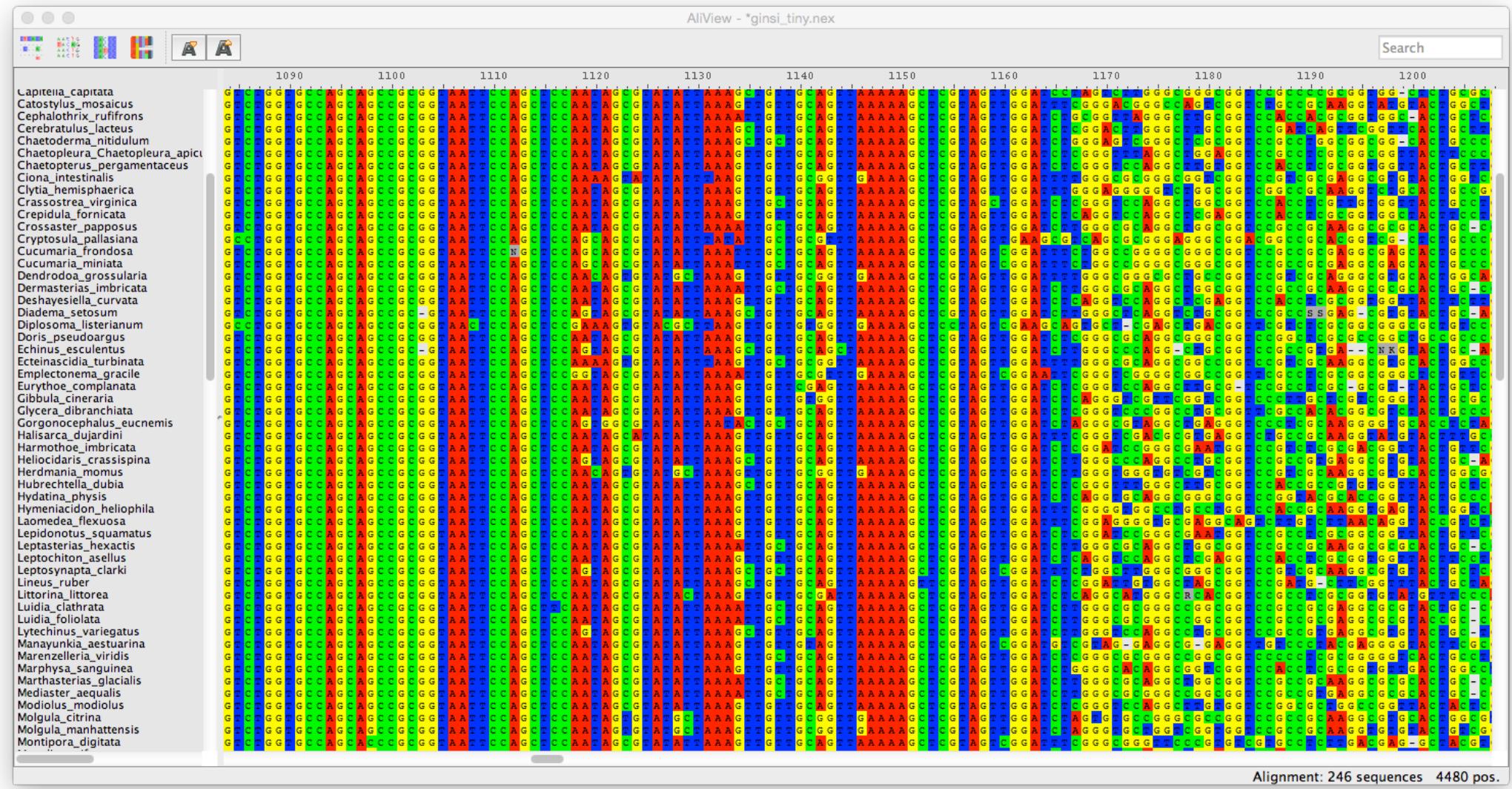
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The substitution rates may differ between stem and loop regions of ribosomal RNA genes

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- biased Gene conversion
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Under simulation, failure to accommodate ASRV can cause biased estimates of:

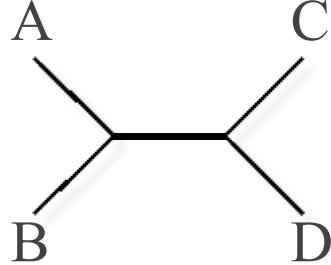
- tree topology
- branch lengths
- other parameters of the substitution model

# Accommodating Among Site Rate Variation

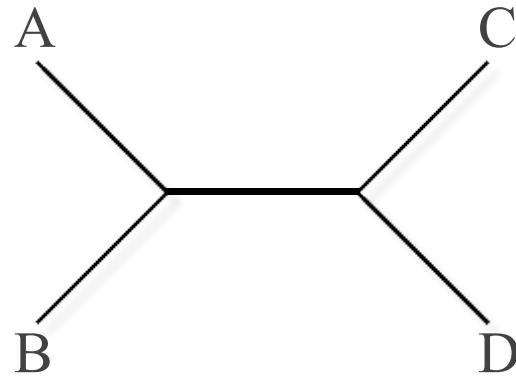
Biology motivates the extension of models

Substitution rates are reflected in the branch lengths of the tree

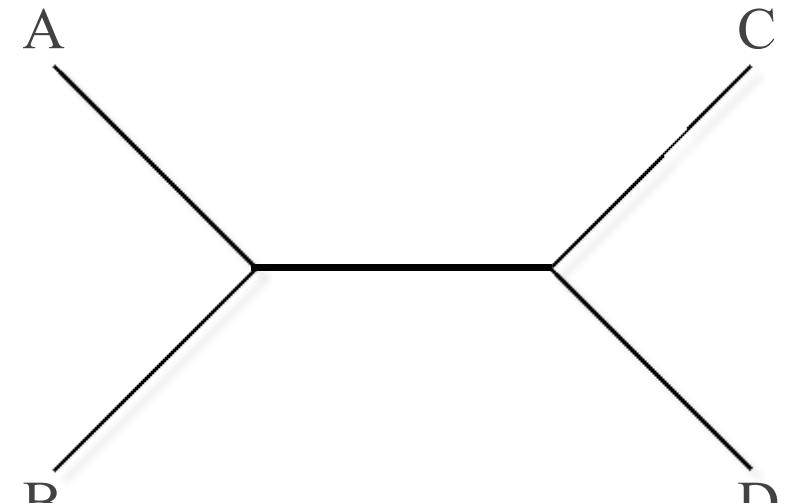
- the relative rate at a site proportionately stretches or compresses the branch lengths



low-rate site



intermediate-rate site



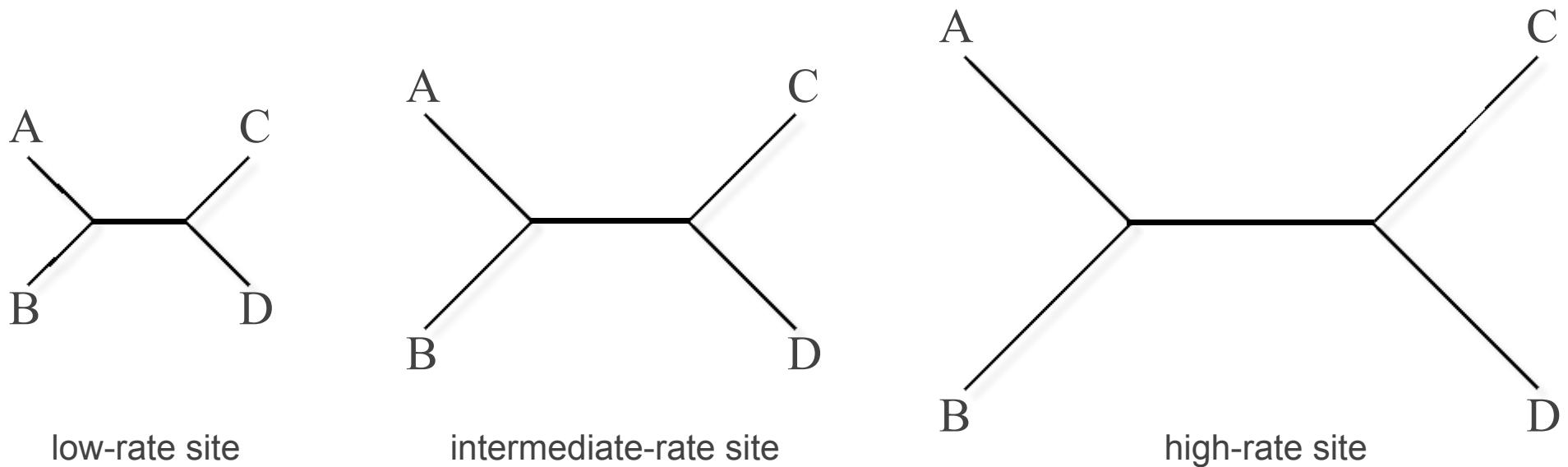
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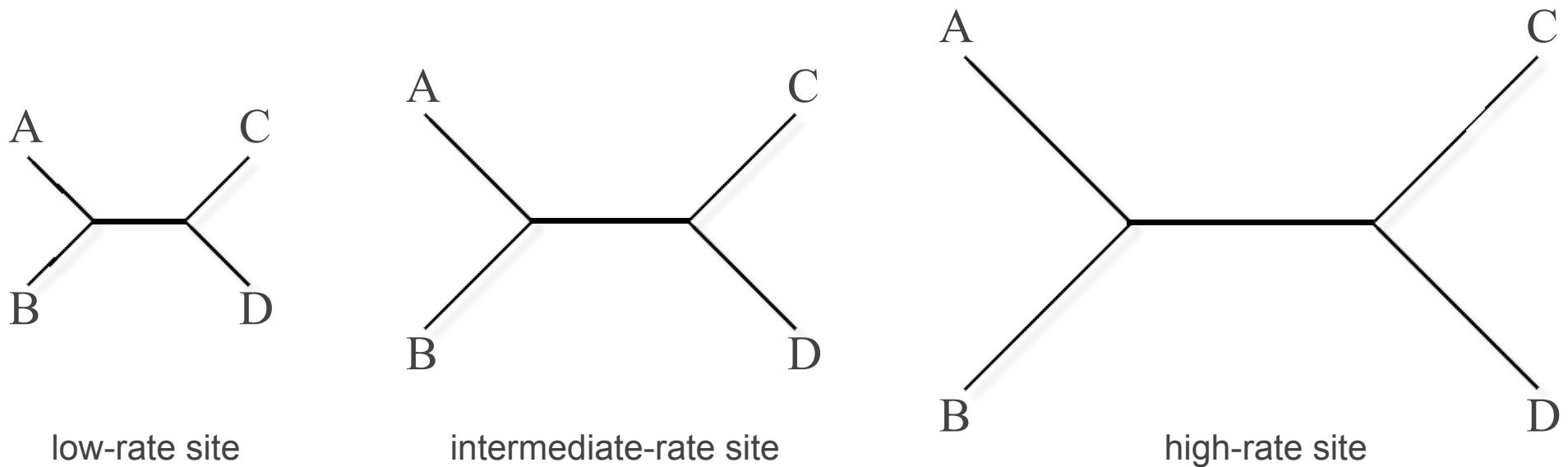
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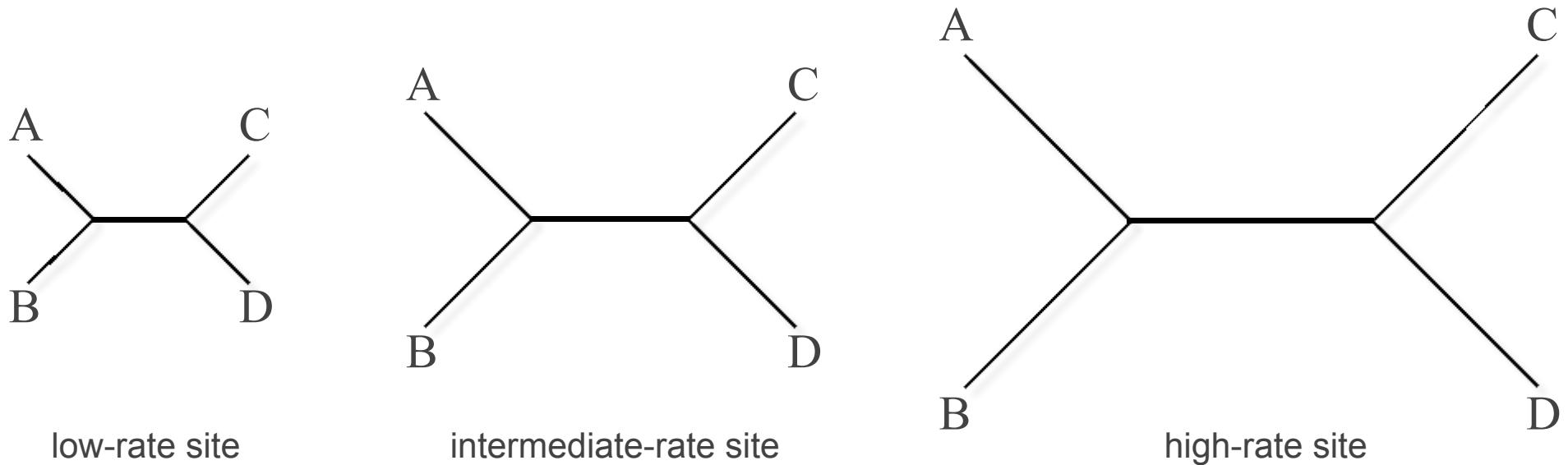
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We can accommodate ASRV by incorporating relative substitution-rate multipliers

- the relative-rate multipliers are constrained to have a mean rate of one
- the relative rate of a site can be assigned deterministically or treated as a random variable

# Accommodating Among Site Rate Variation

## The Site-Specific (+SS) or free rate model of ASRV

The 'base' substitution model (a member of the GTR family) is extended to accommodate ASRV (e.g., HKY+SS)

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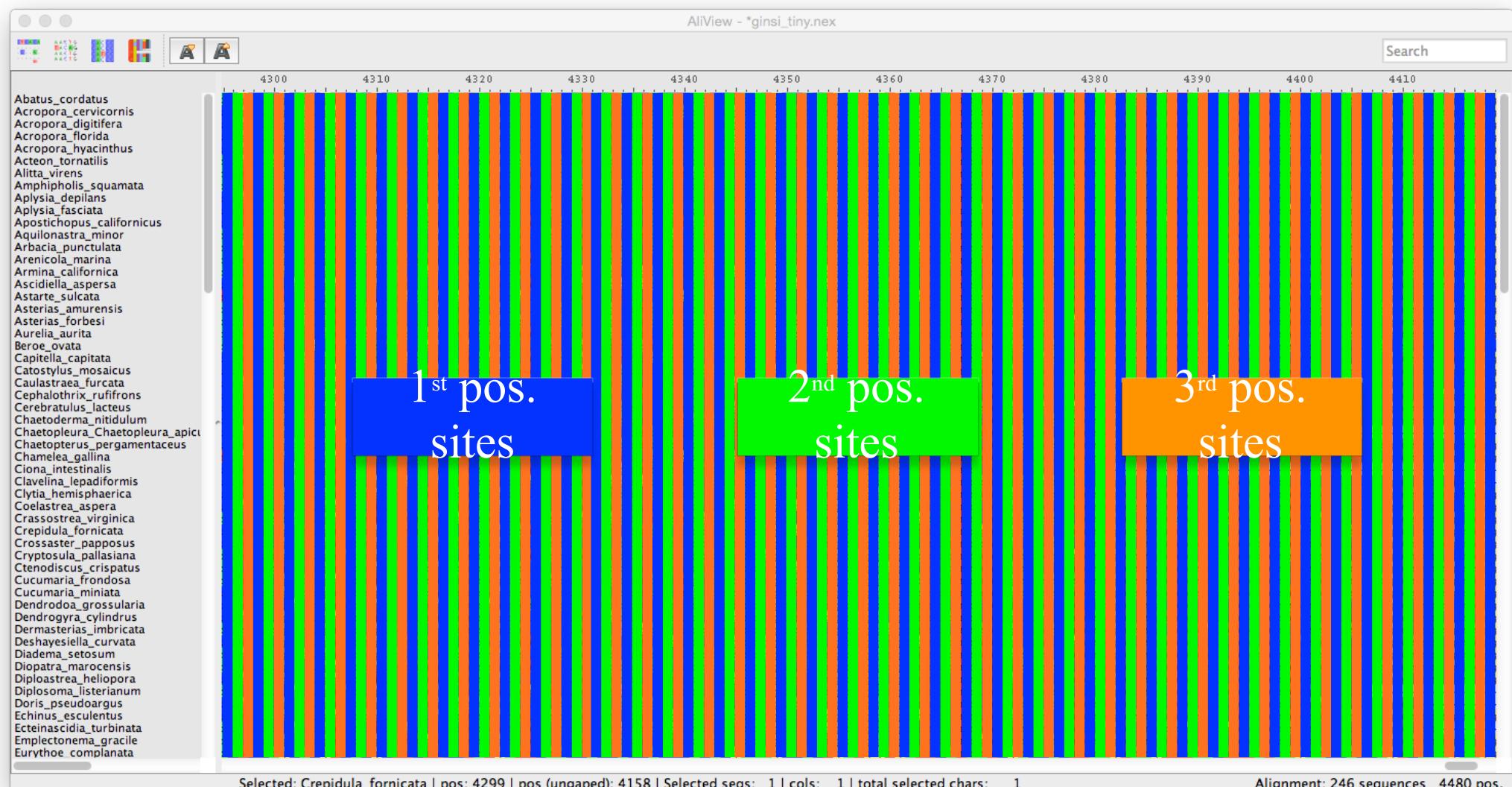
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- three rate categories for protein-coding genes (one for each codon position)

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A site-specific model for protein-coding genes might have three rate categories, with sites in each codon position assigned to each of the three relative-rate categories

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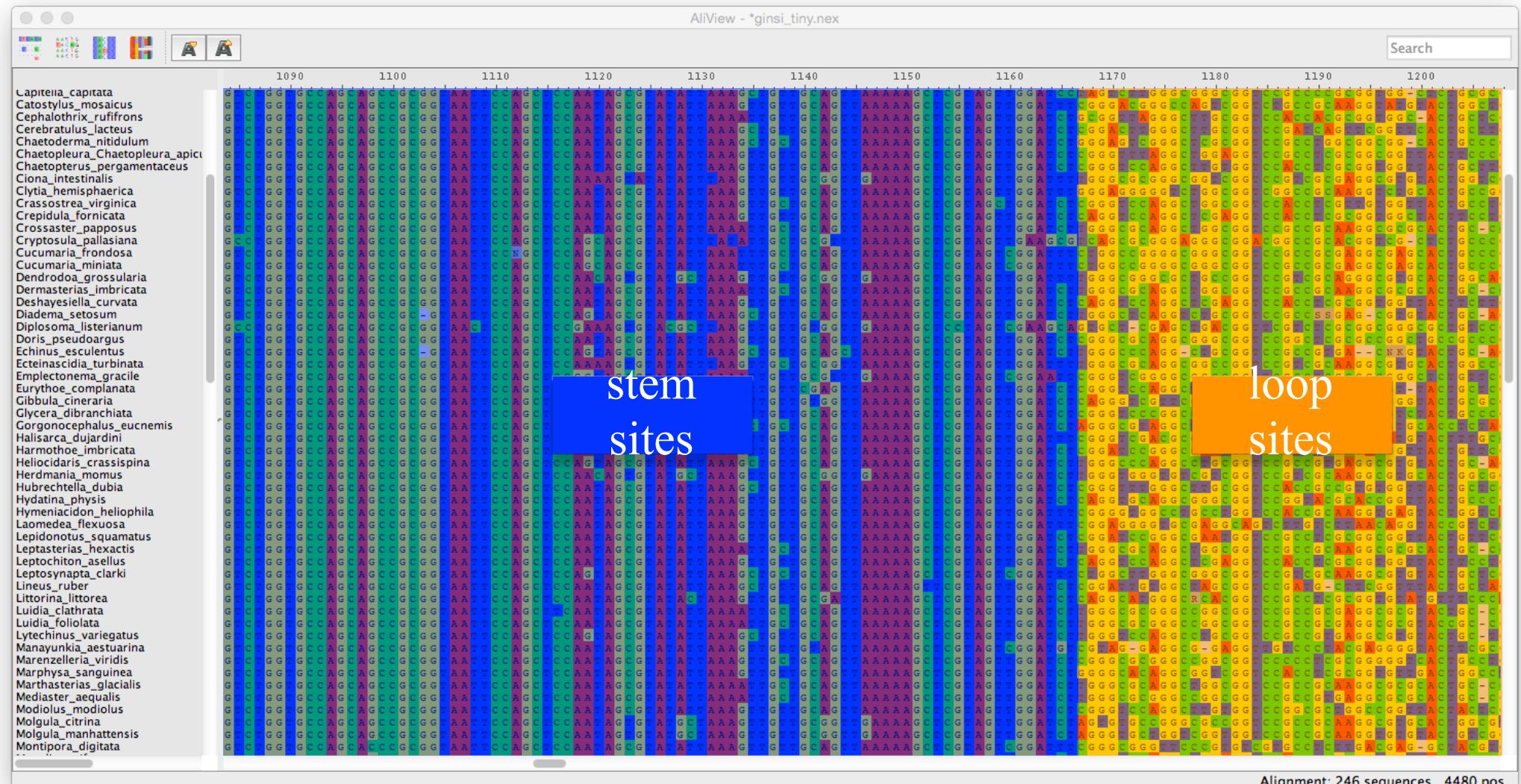
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A site-specific model for ribosomal genes might have two rate categories, with stem sites in one and loop sites in the other relative-rate category

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For a model with  $k$  rate categories, we estimate  $(k-1)$  relative-rate multipliers

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- two rate categories for ribosomal genes (one each for stem and loop regions)

All  $n_i$  sites within a given rate category are subject to the same rate multiplier,  $r_i$

For a model with  $k$  rate categories, we estimate  $(k - 1)$  relative-rate multipliers

The relative-rate multipliers are constrained to have a mean rate of 1.0.

# Accommodating Among Site Rate Variation

## The Proportion of Invariable Sites (+I) model of ASRV



The substitution process may be 'off' at some sites (but note that an invariant site ≠ invariable site)

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The likelihood of site  $i$  is then integrated over the two possible rate multipliers:

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Therefore, the pruning algorithm is iterated twice for each site:

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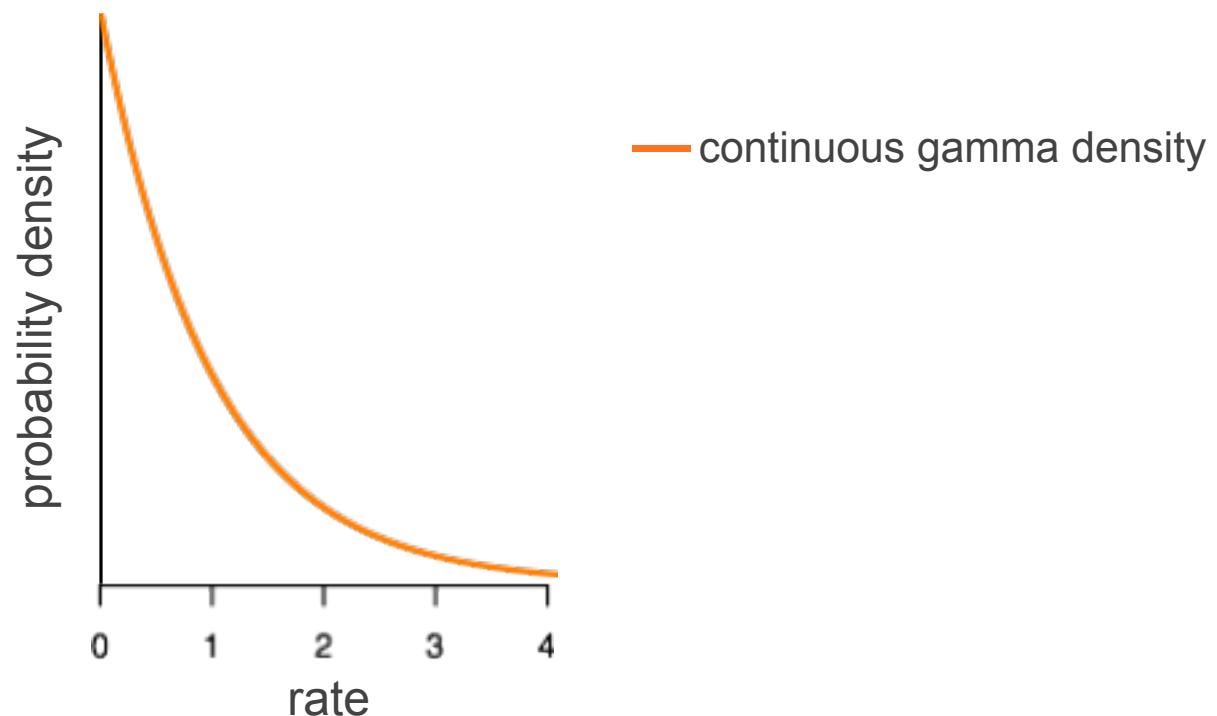
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- so, operationally, the gamma distribution involves the single shape parameter,  $\alpha$

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The gamma distribution provides a flexible means of accommodating ASRV

We constrain the mean of the gamma distribution to have a mean of one:  $\alpha = \beta$



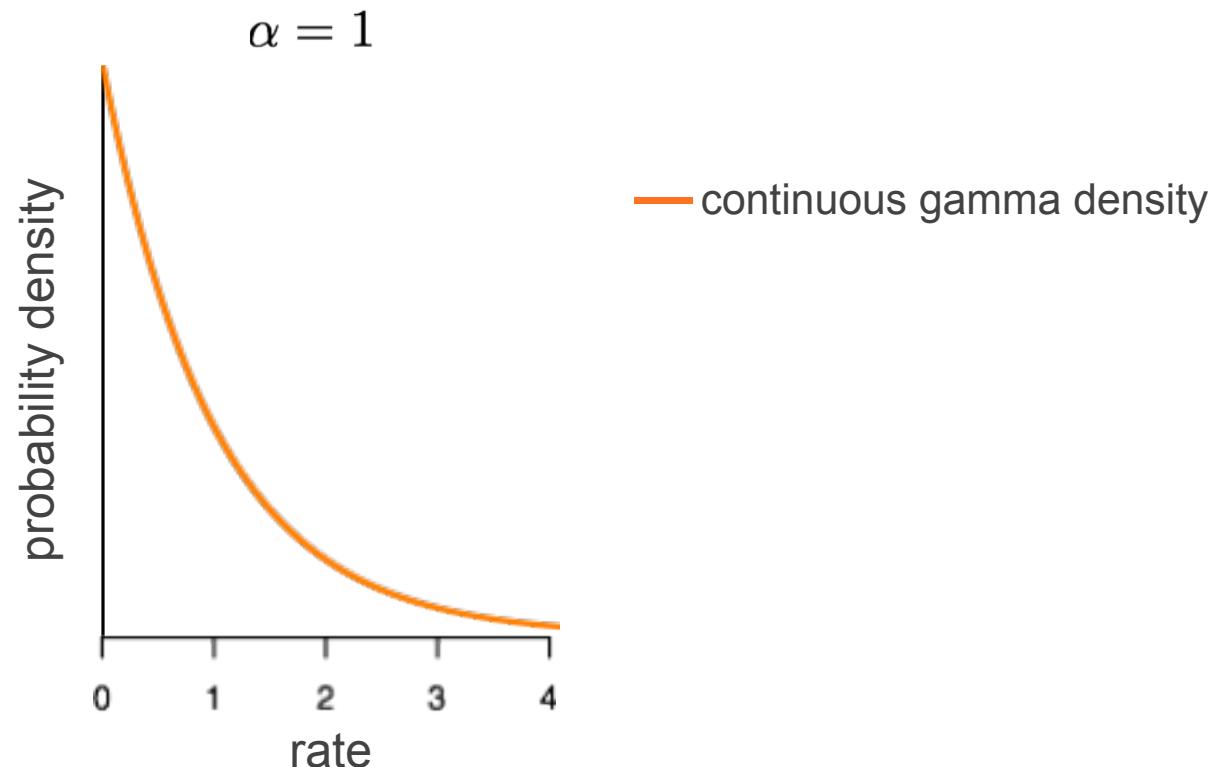
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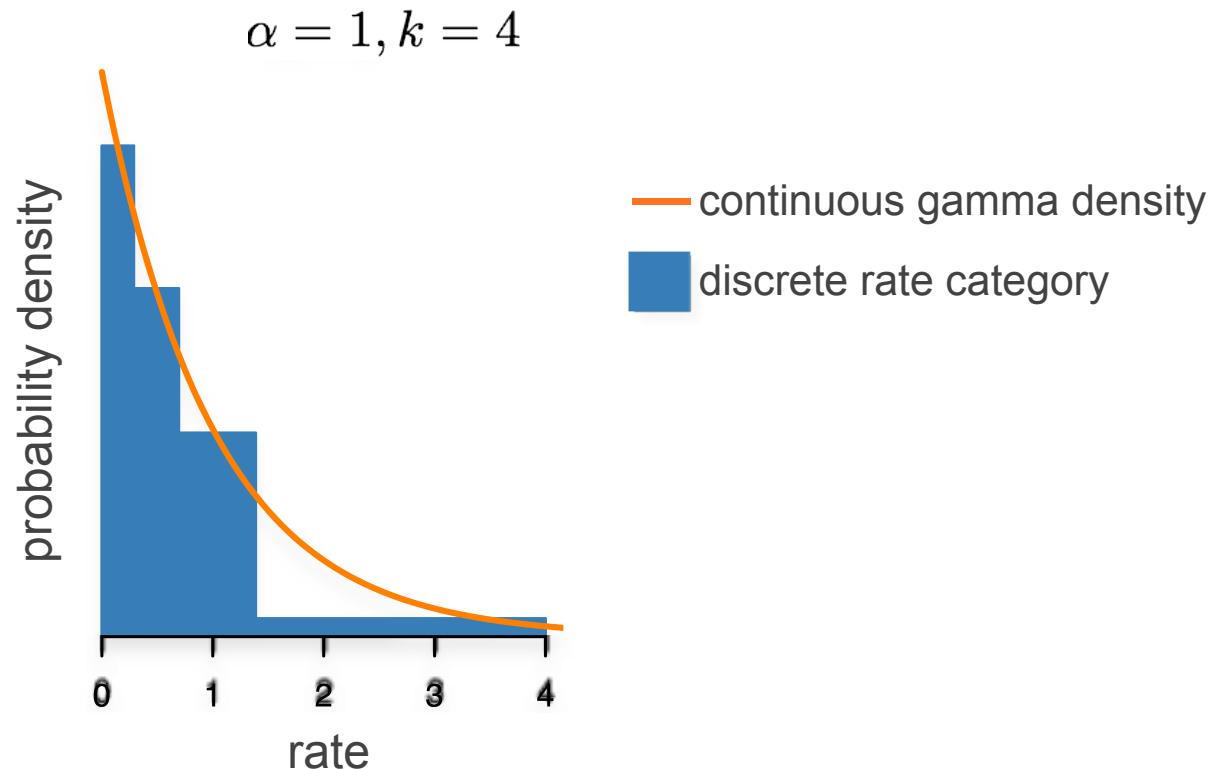


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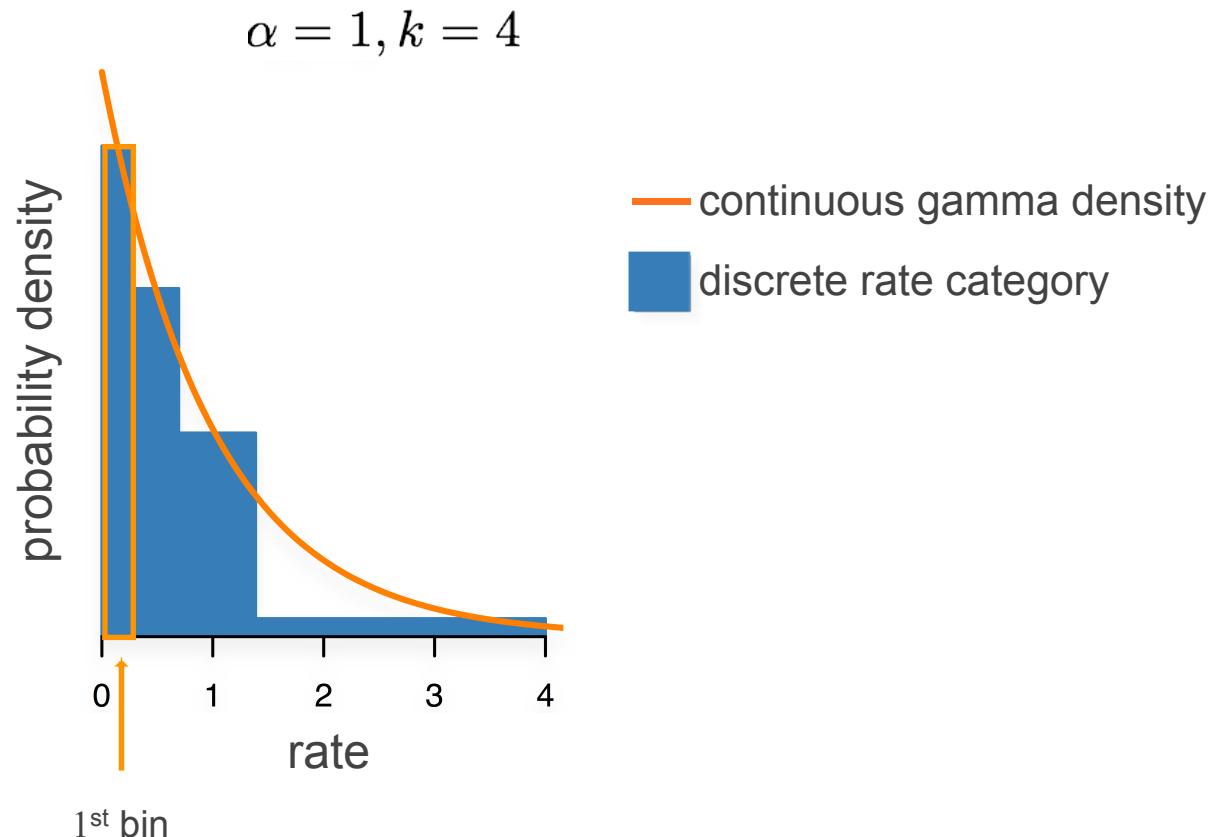
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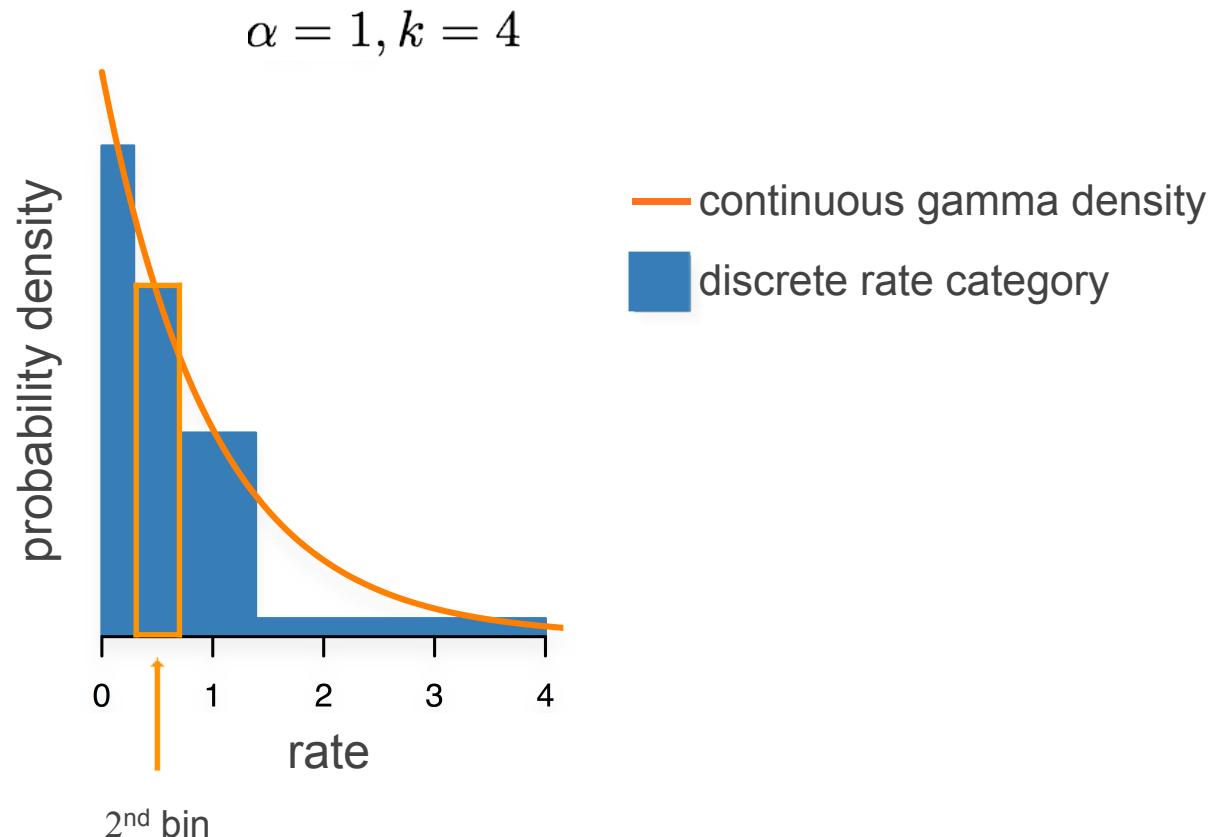
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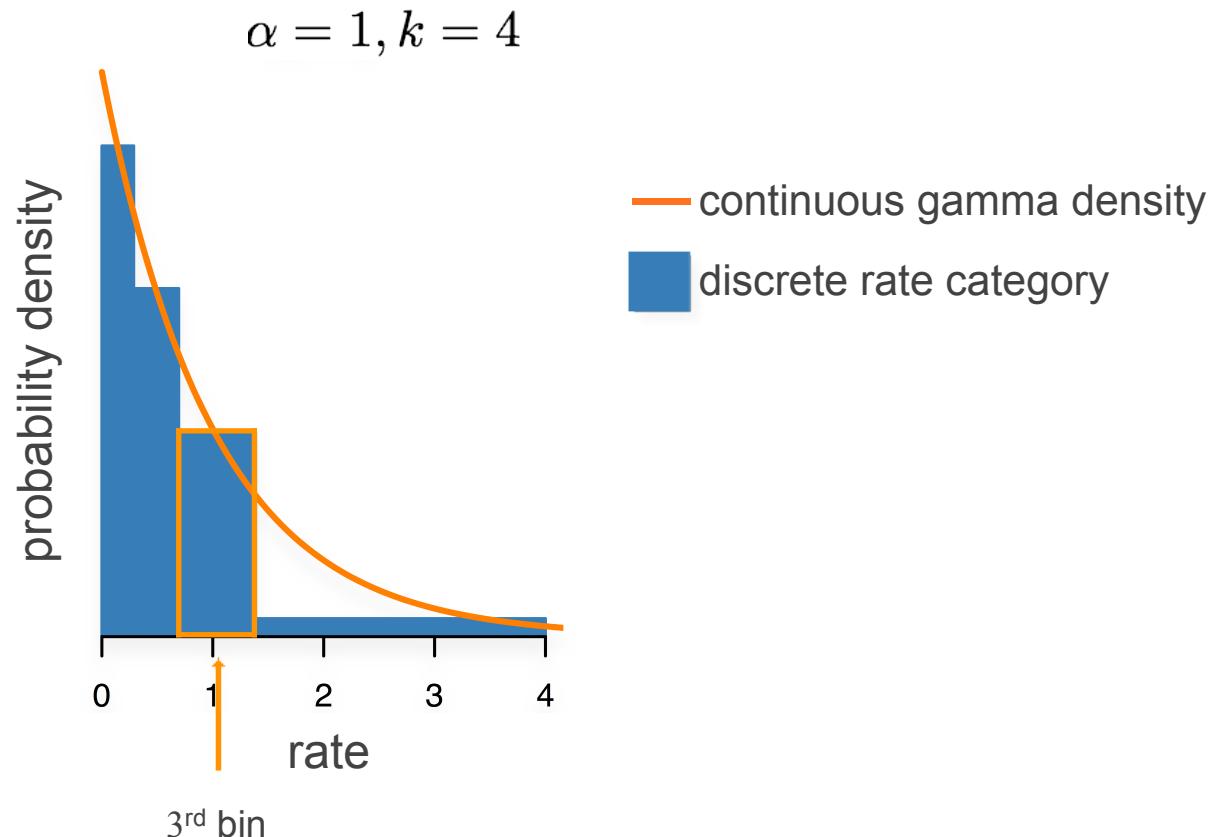
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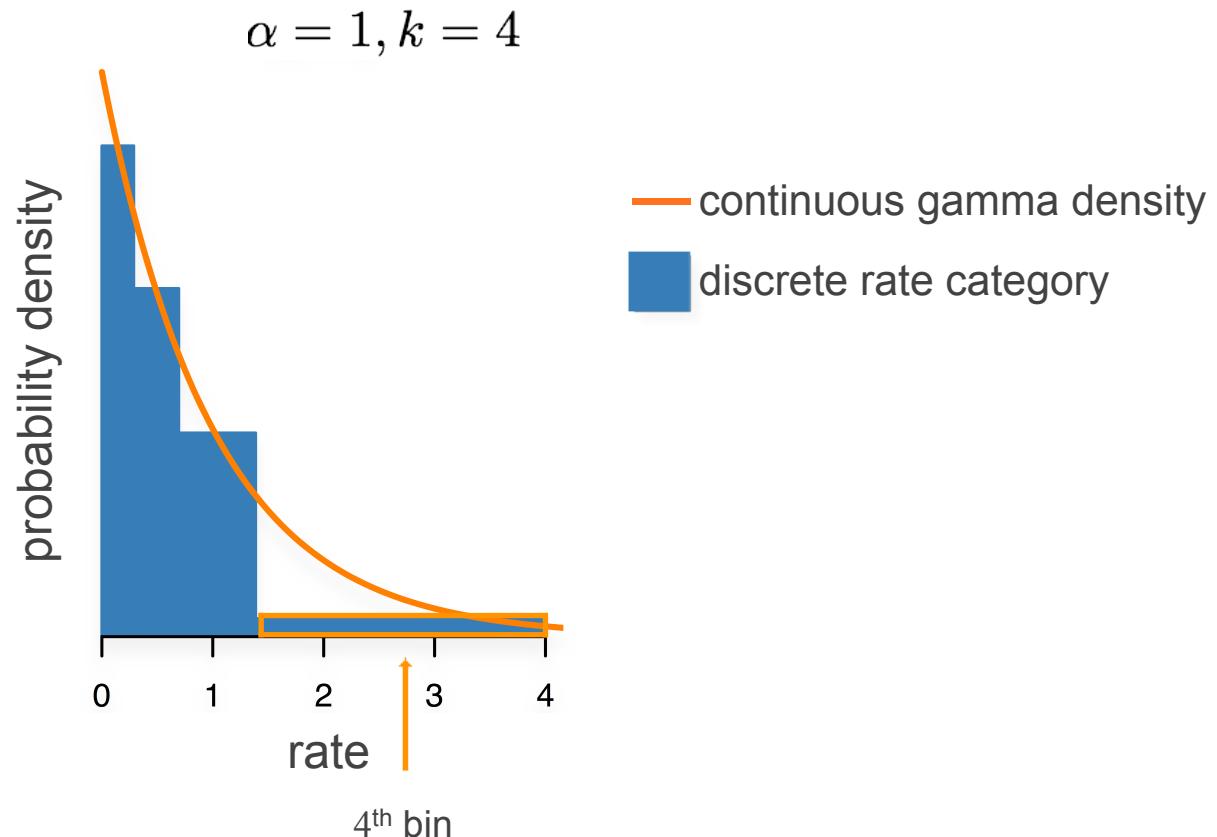
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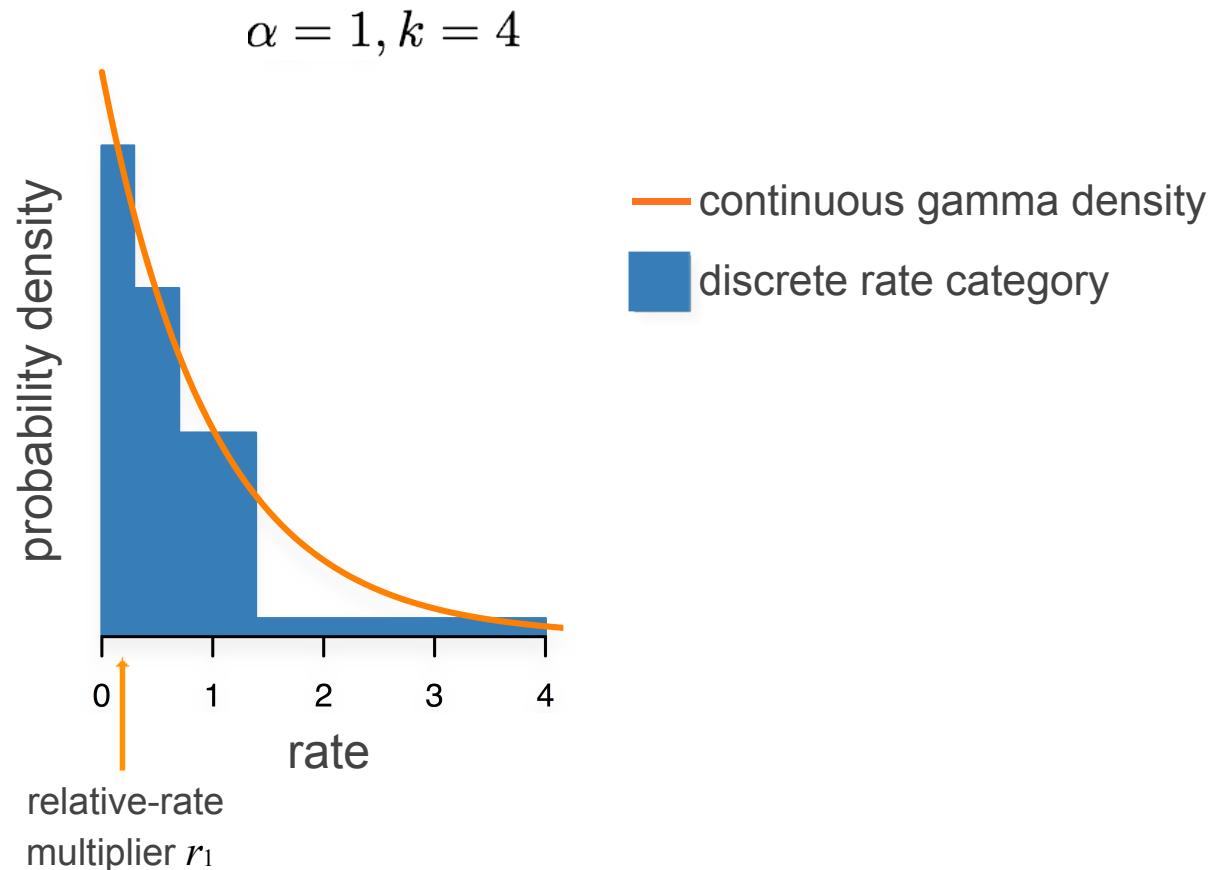
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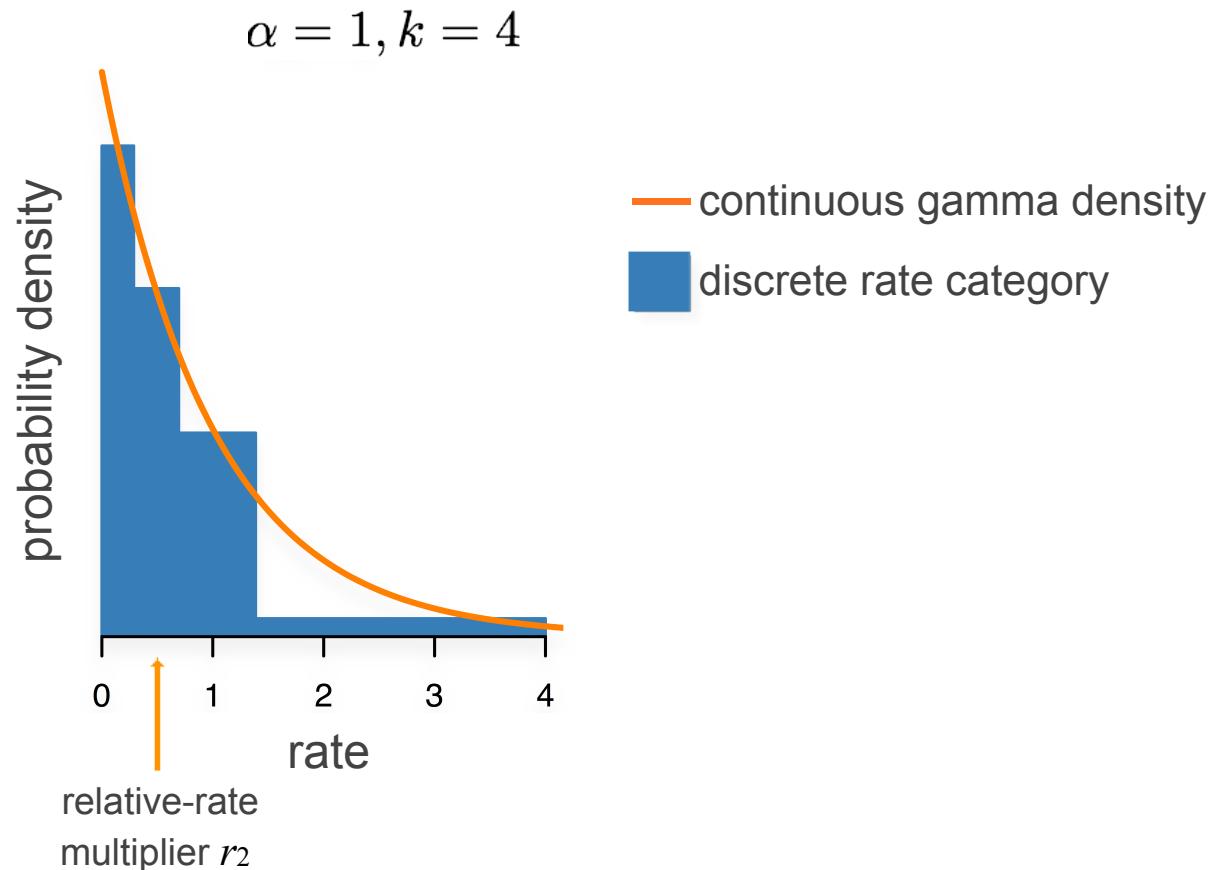
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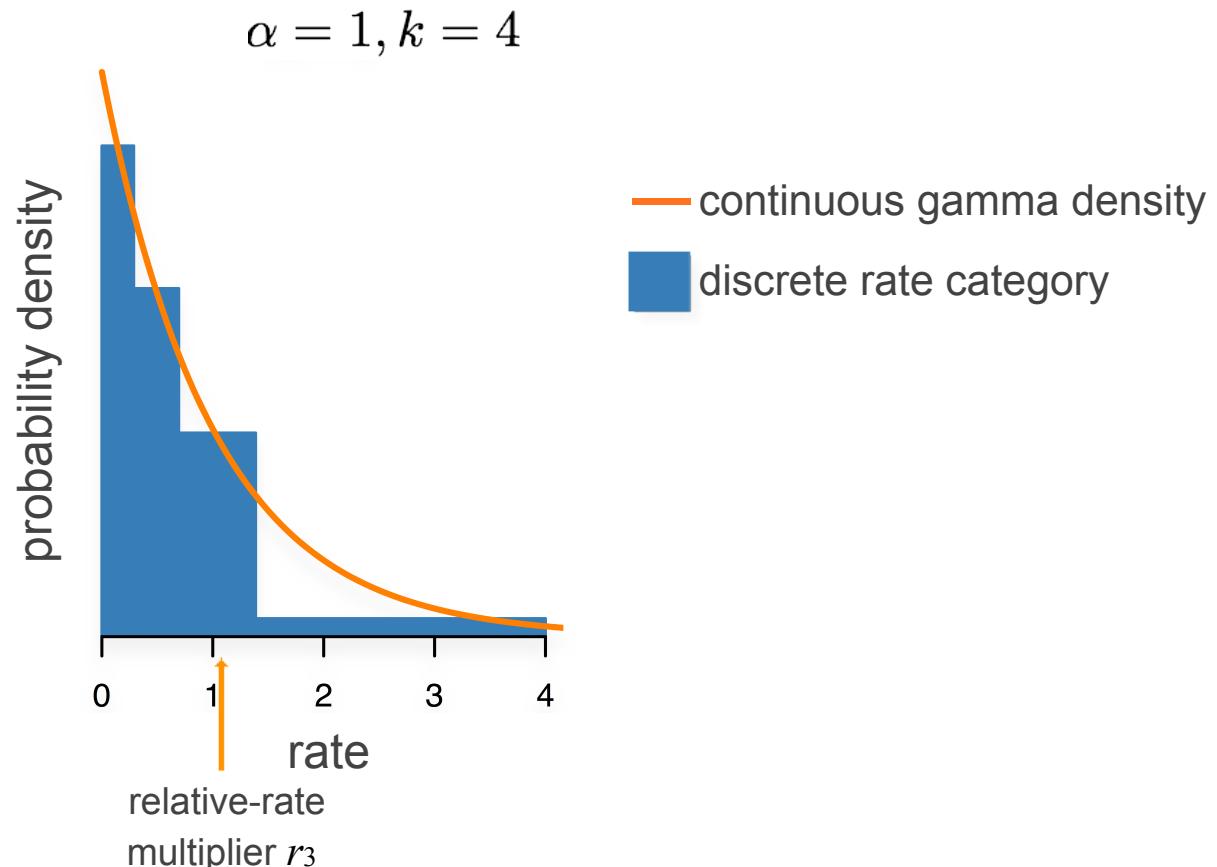
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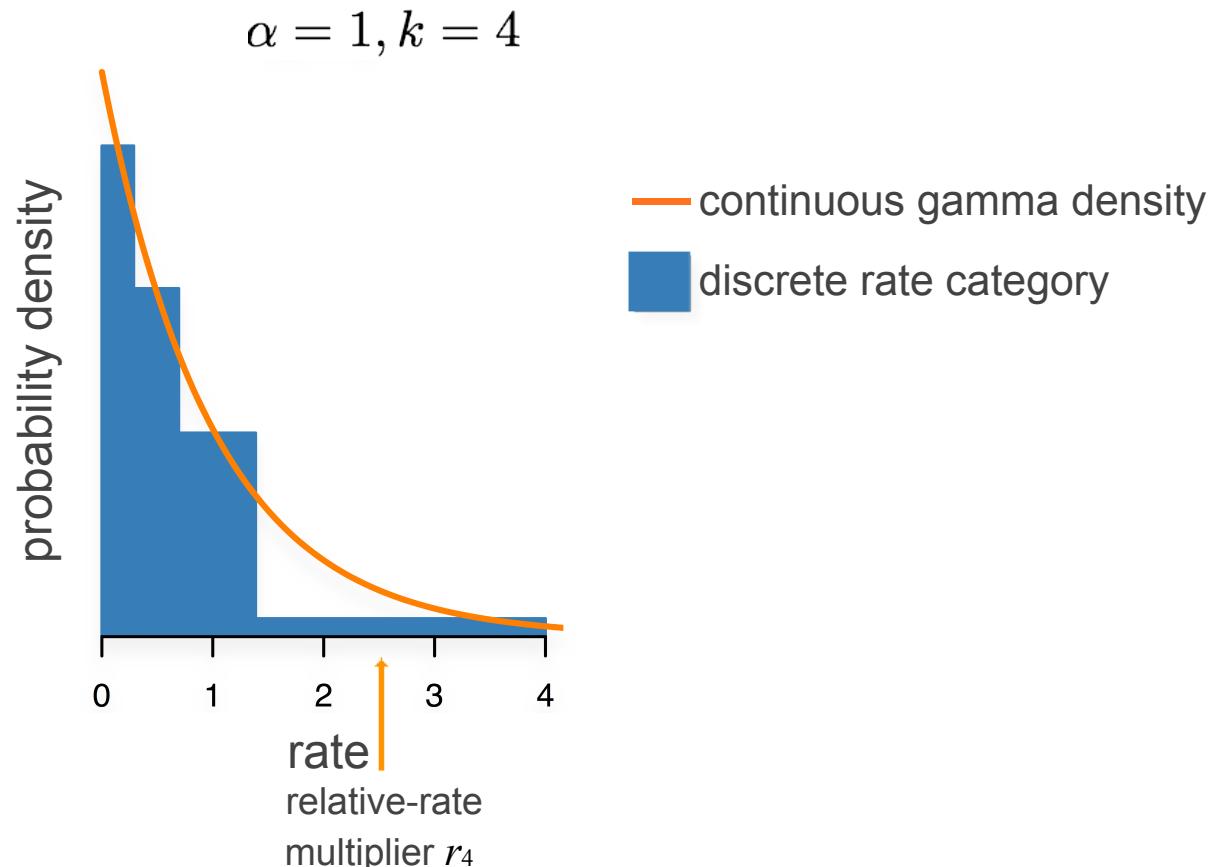
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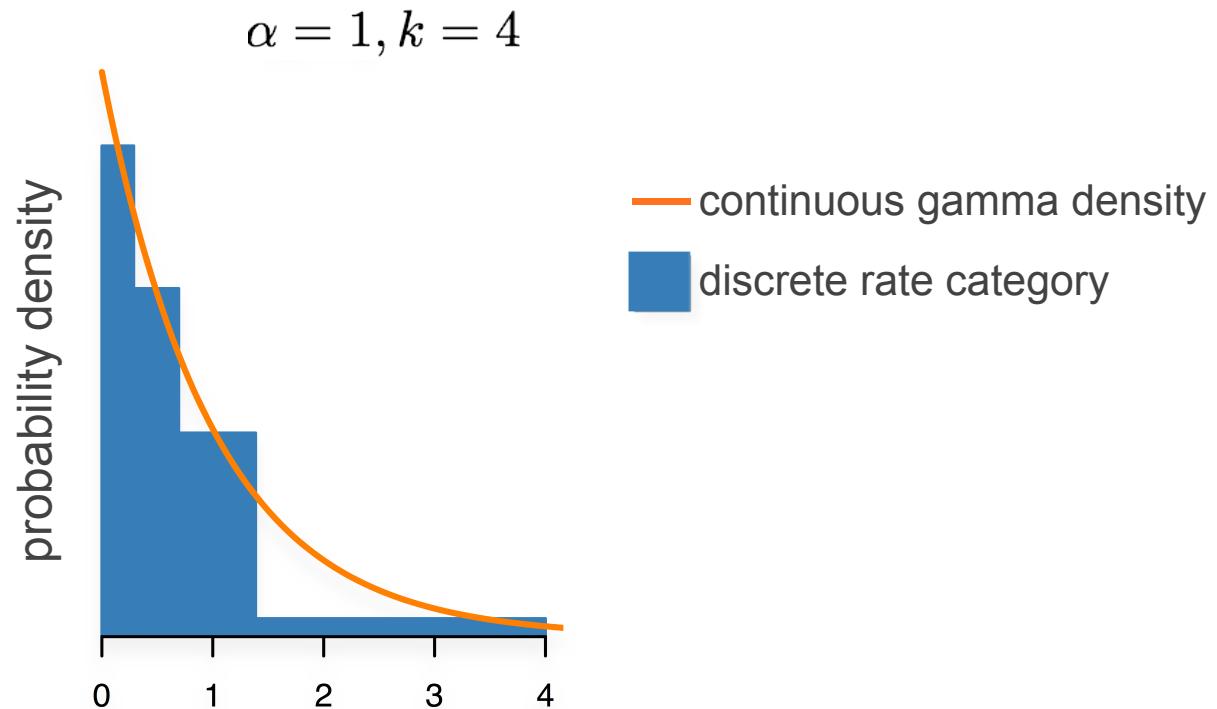
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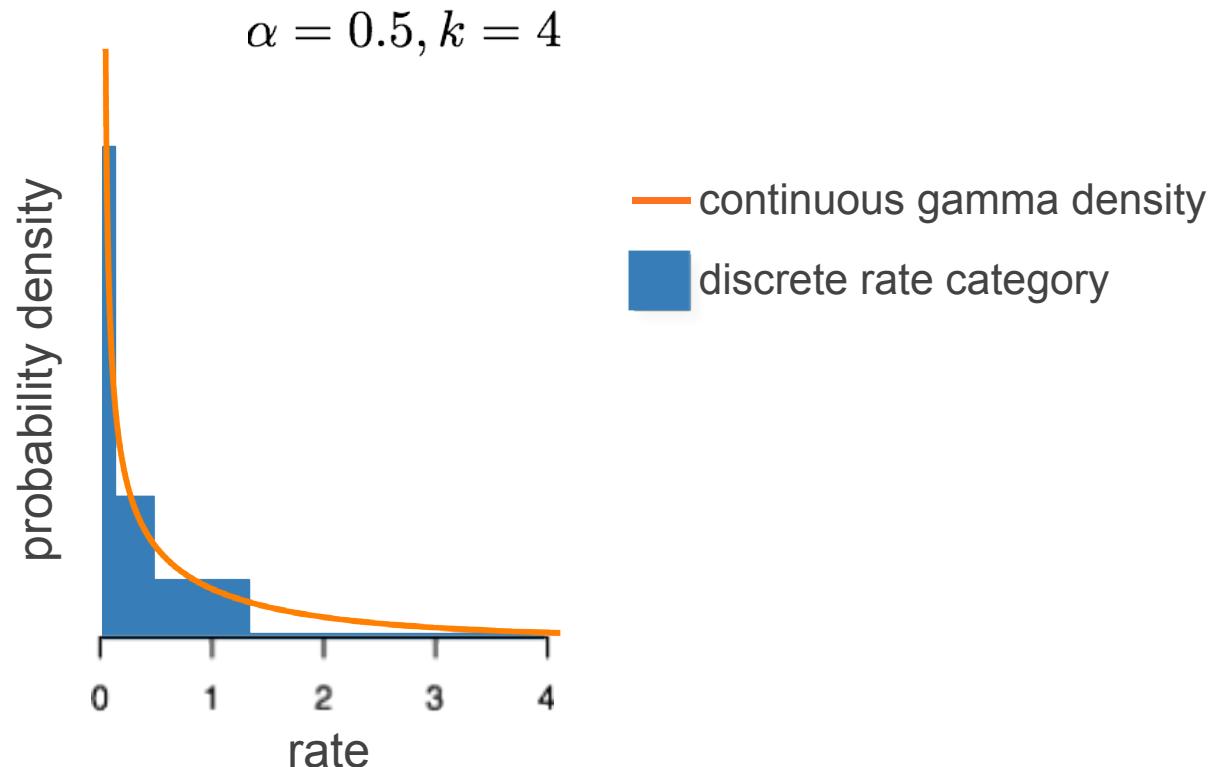
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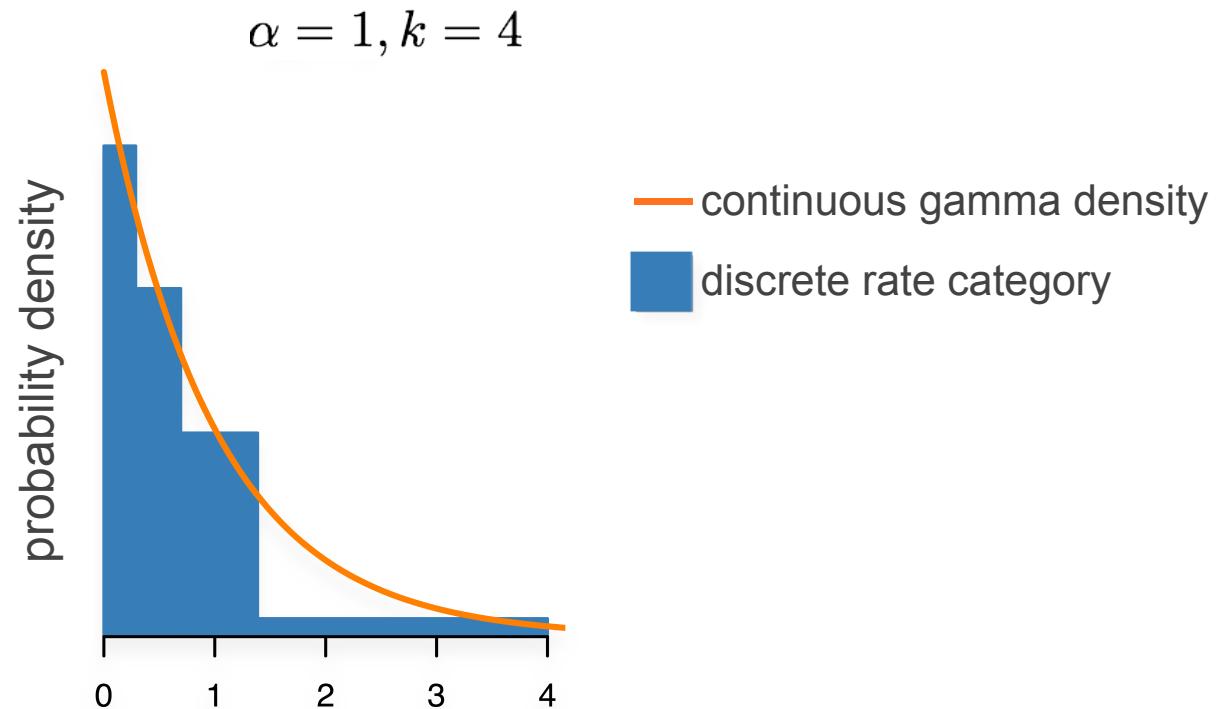
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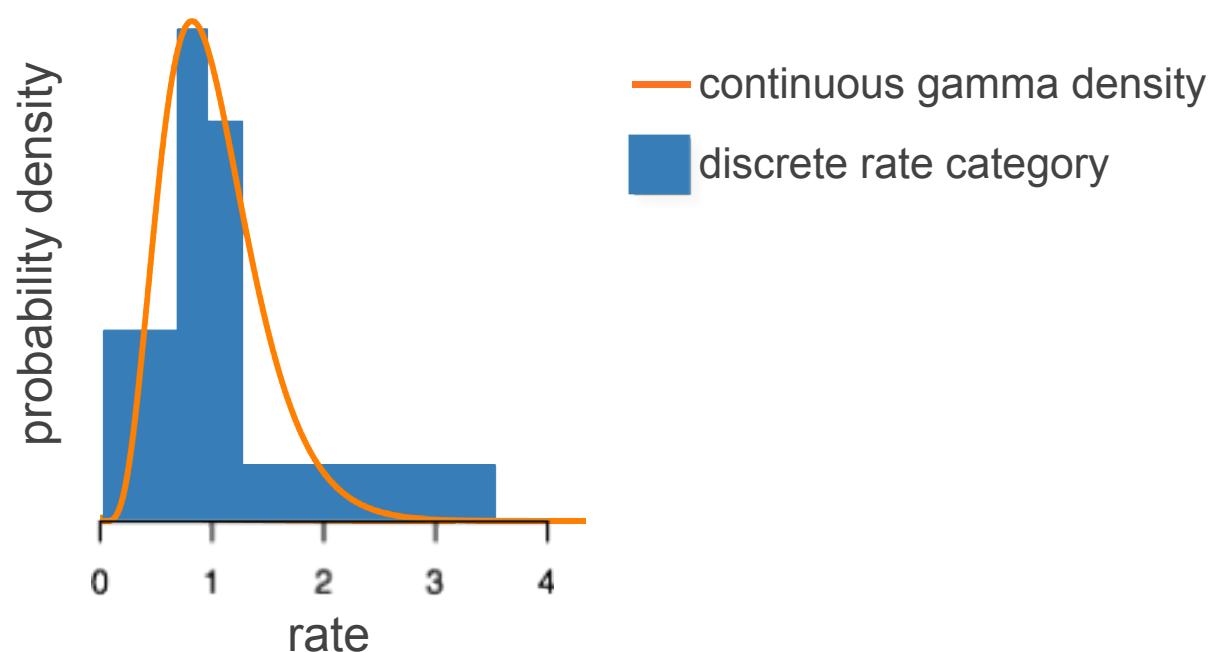
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$$\alpha = 5, k = 4$$



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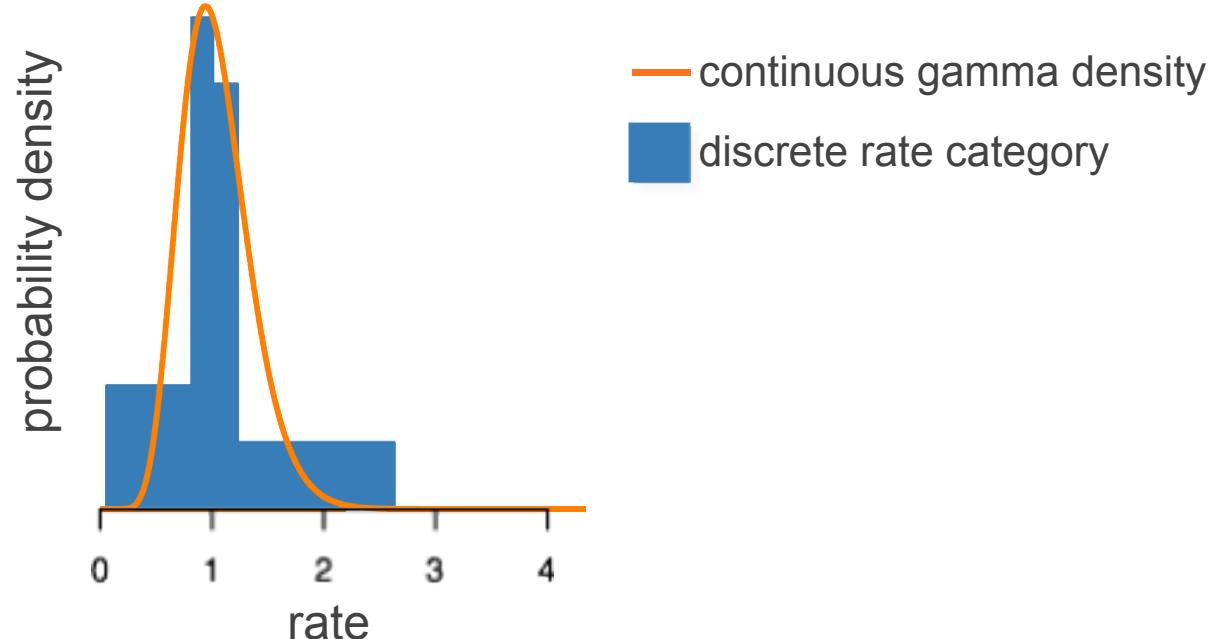
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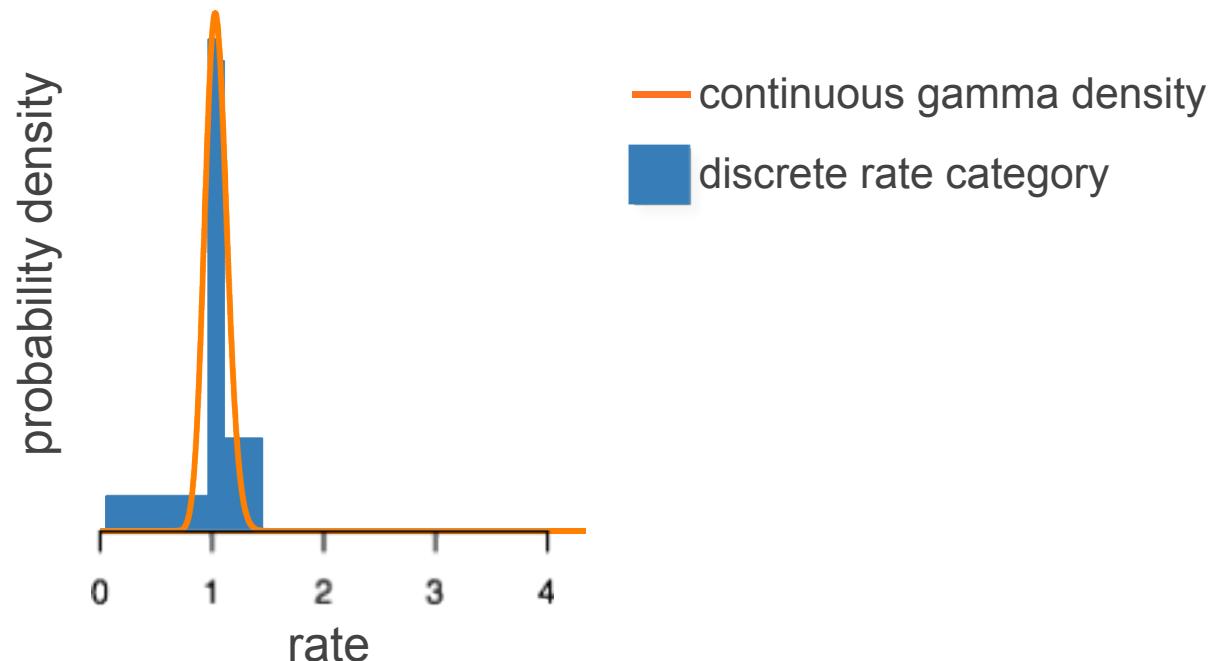
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Therefore, the pruning algorithm is iterated  $k$  times for each site:

- where the site rate is multiplied by the relative rate,  $r_j$ , for each of the  $k$  bins
- the discrete gamma model therefore incurs a  $k$ -fold increase in computational burden

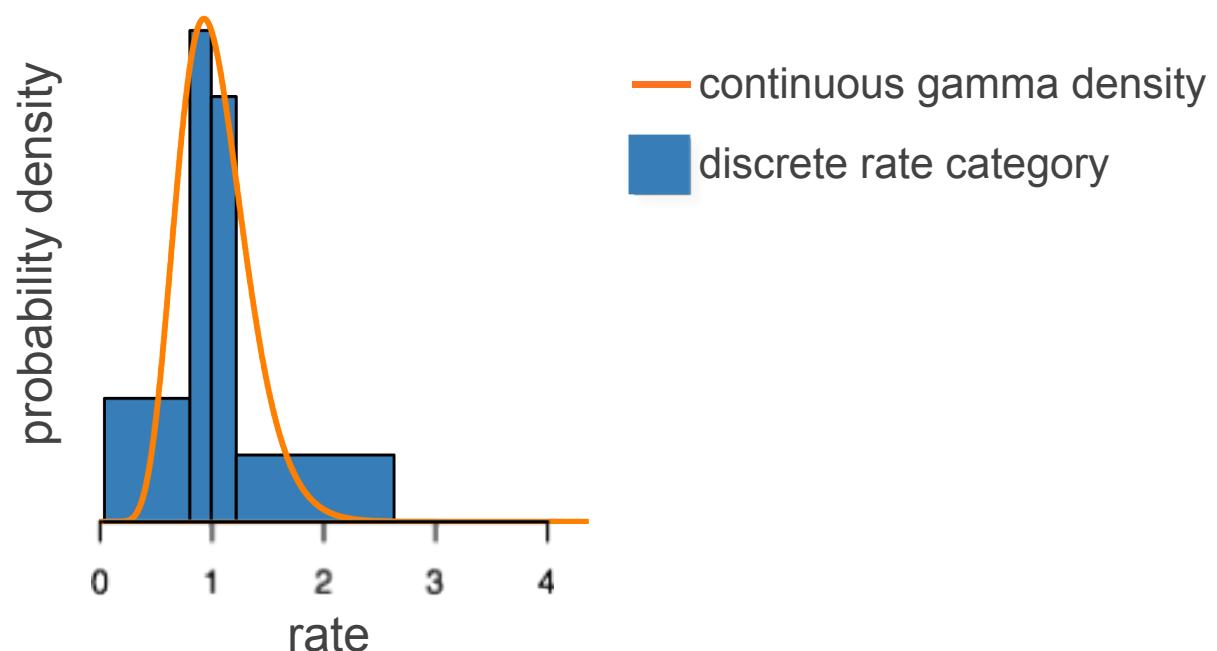
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## The Discrete Gamma Distribution (+G) model of ASRV

The gamma distribution is discretized into  $k$  discrete bins

- there are  $k$  relative-rate multipliers; corresponding to the mean or median rate of each bin
- the approximation of the continuous gamma improves with increasing  $k$ , but so does the computational burden

$$\alpha = 10, k = 4$$



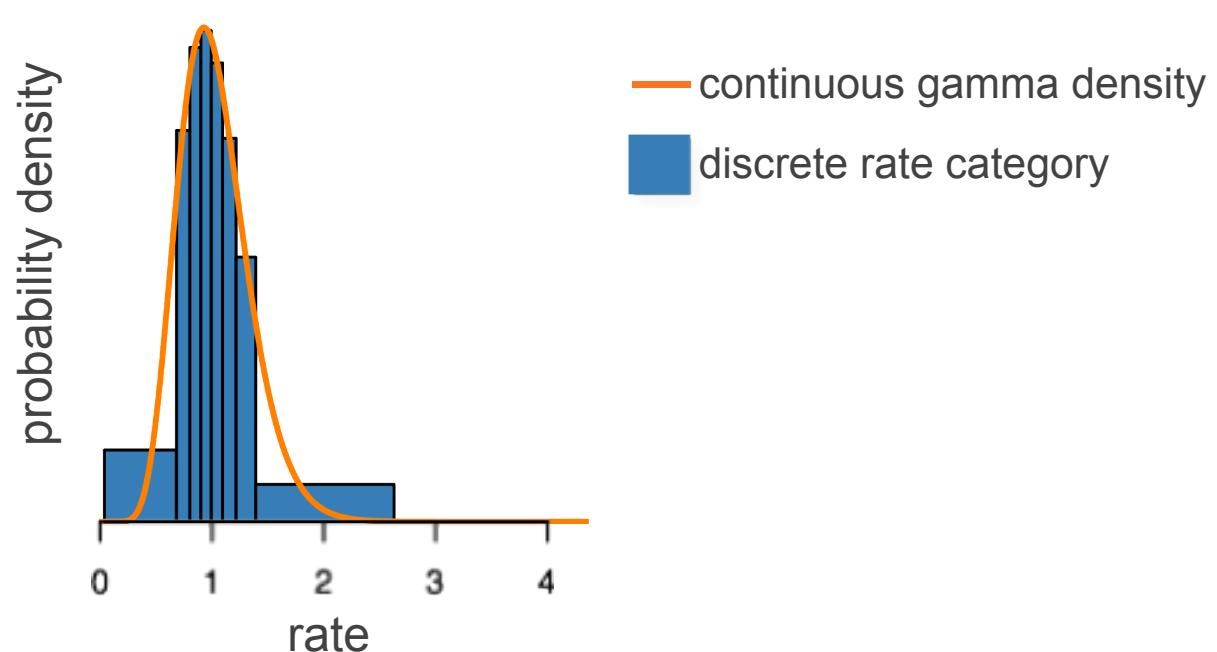
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$$\alpha = 10, k = 8$$



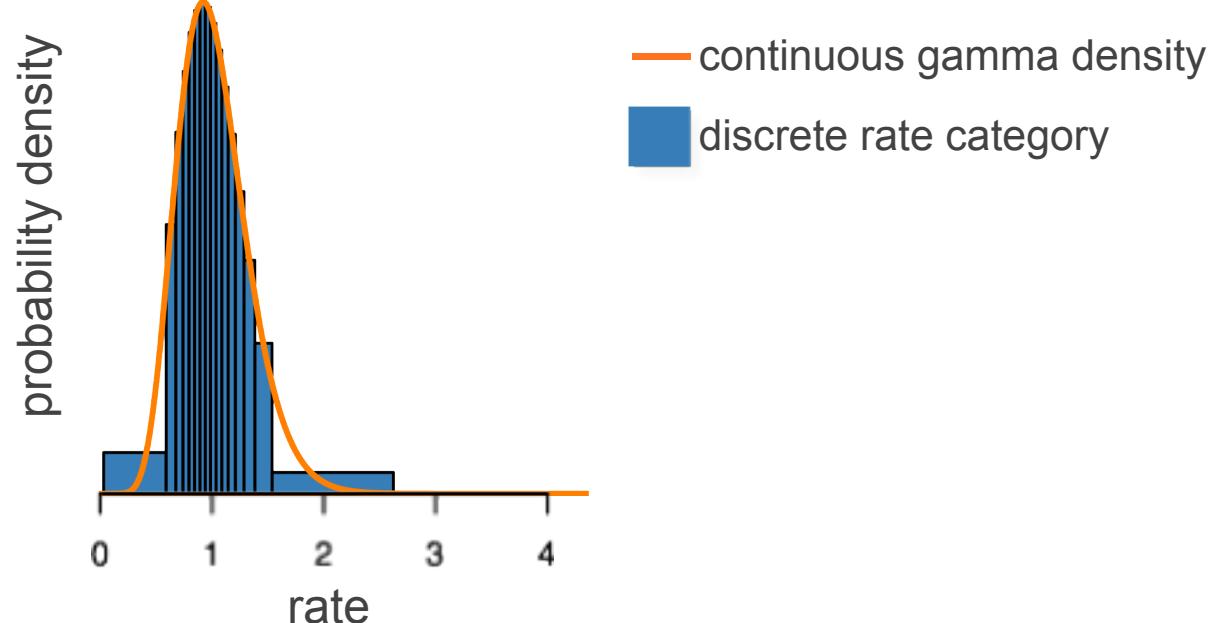
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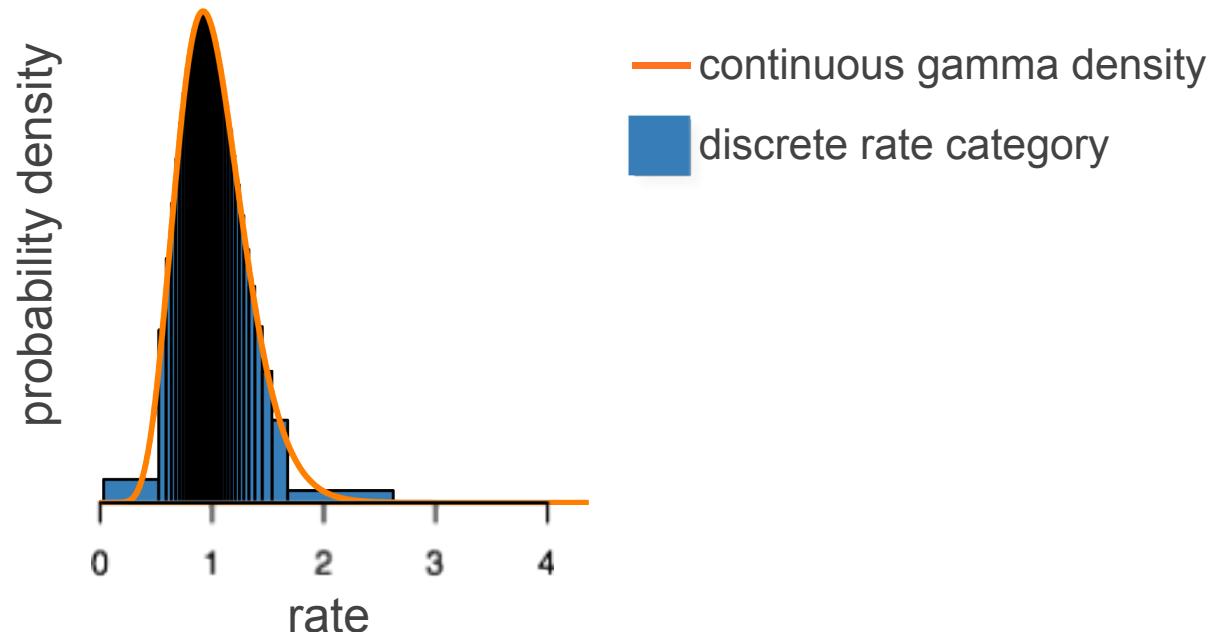
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$$\alpha = 10, k = 32$$



# Accommodating Among Site Rate Variation

## Mixture models for accommodating ASRV

Site rates can be modeled as a mixture of the individual ASRV models (SS, I, and G):

# Accommodating Among Site Rate Variation

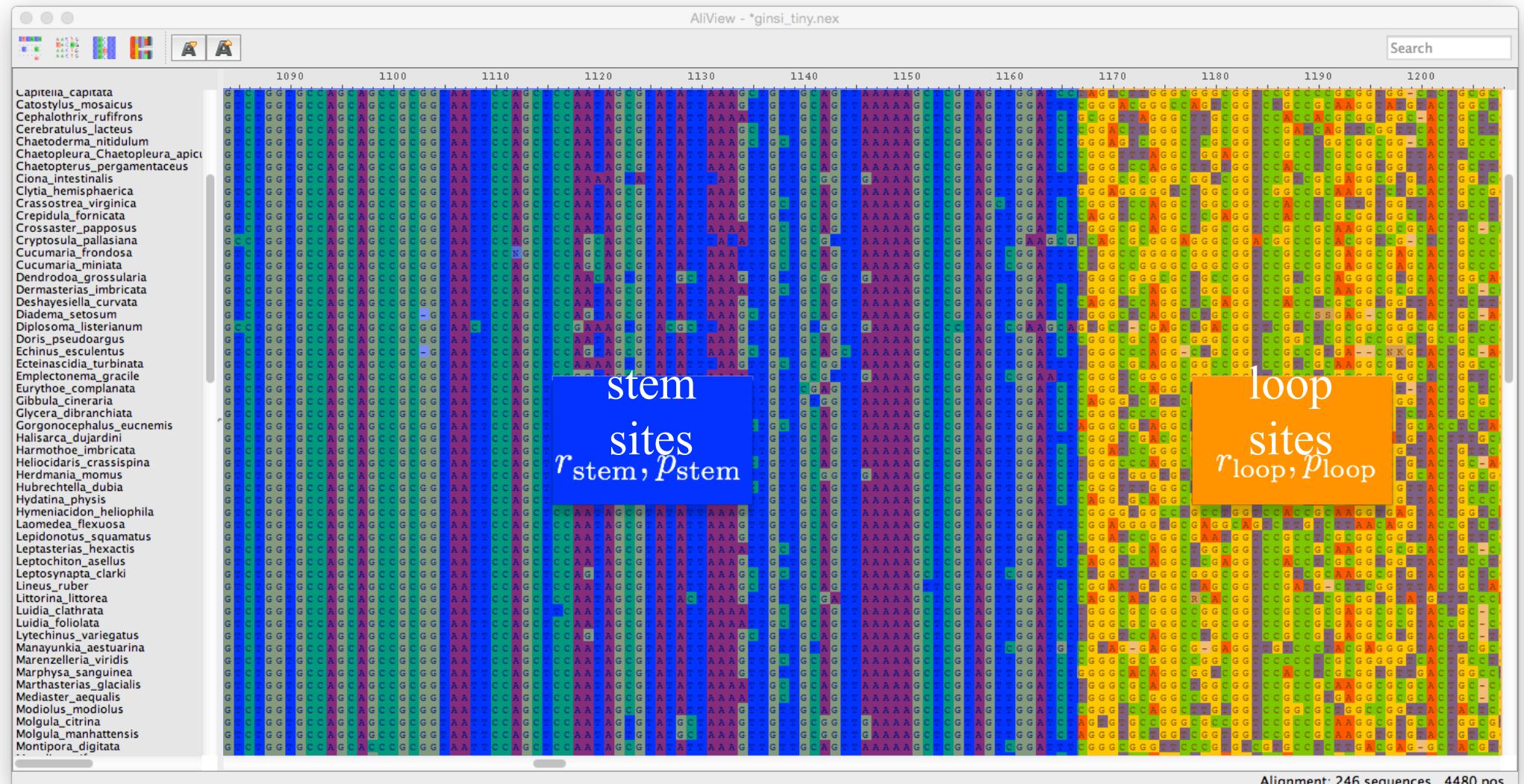
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Mixture models for accommodating ASRV



Each pre-specified subset of sites has an overall relative-rate multiplier, and the rate of each site within each category is modeled as proportion of invariable sites model

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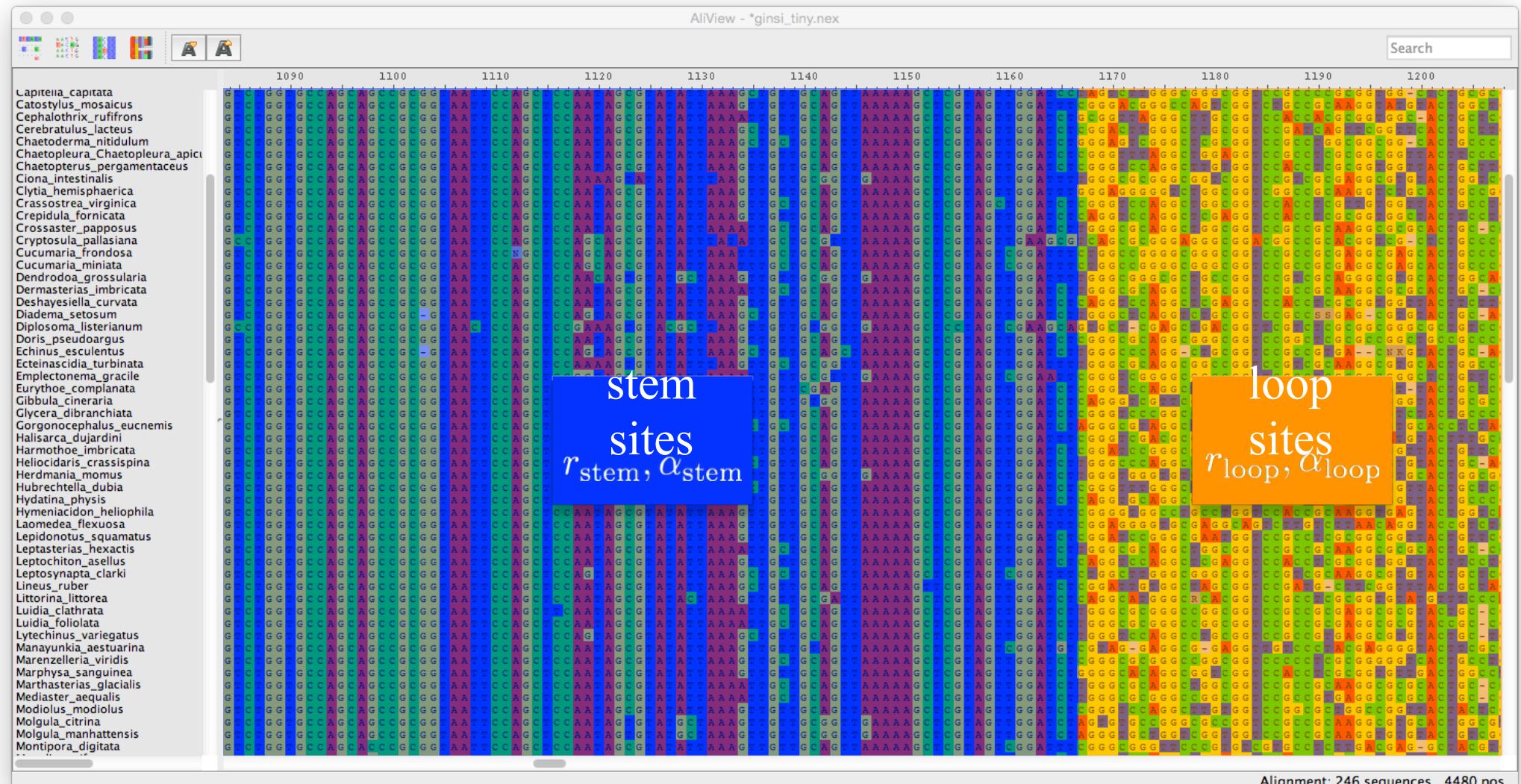
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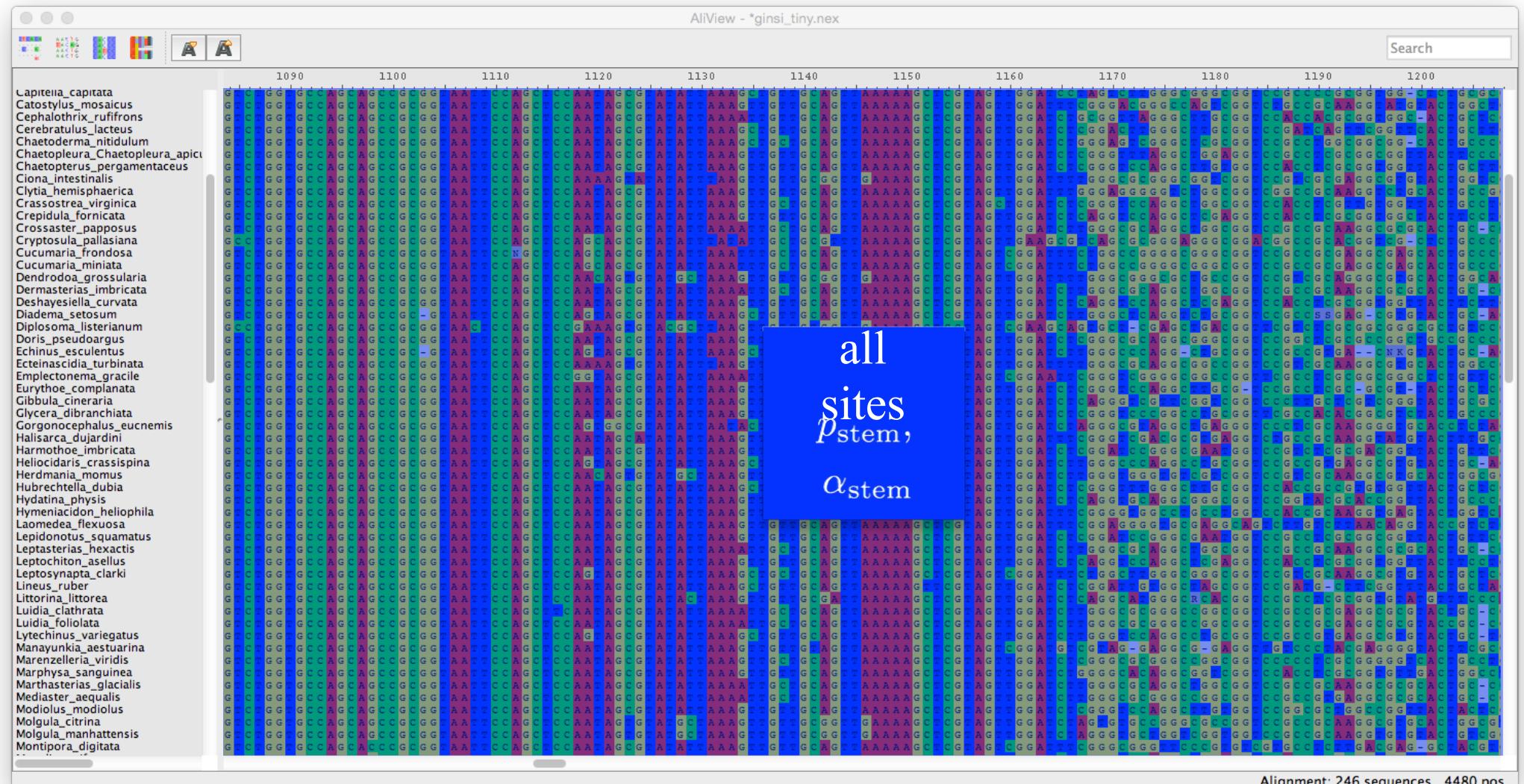
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# Accommodating Among Site Rate Variation

## Mixture models for accommodating ASRV



The rate of each site is modeled as a random variable drawn from a mixture of the discrete-gamma and proportion of invariable sites

# Accommodating Among Site Rate Variation

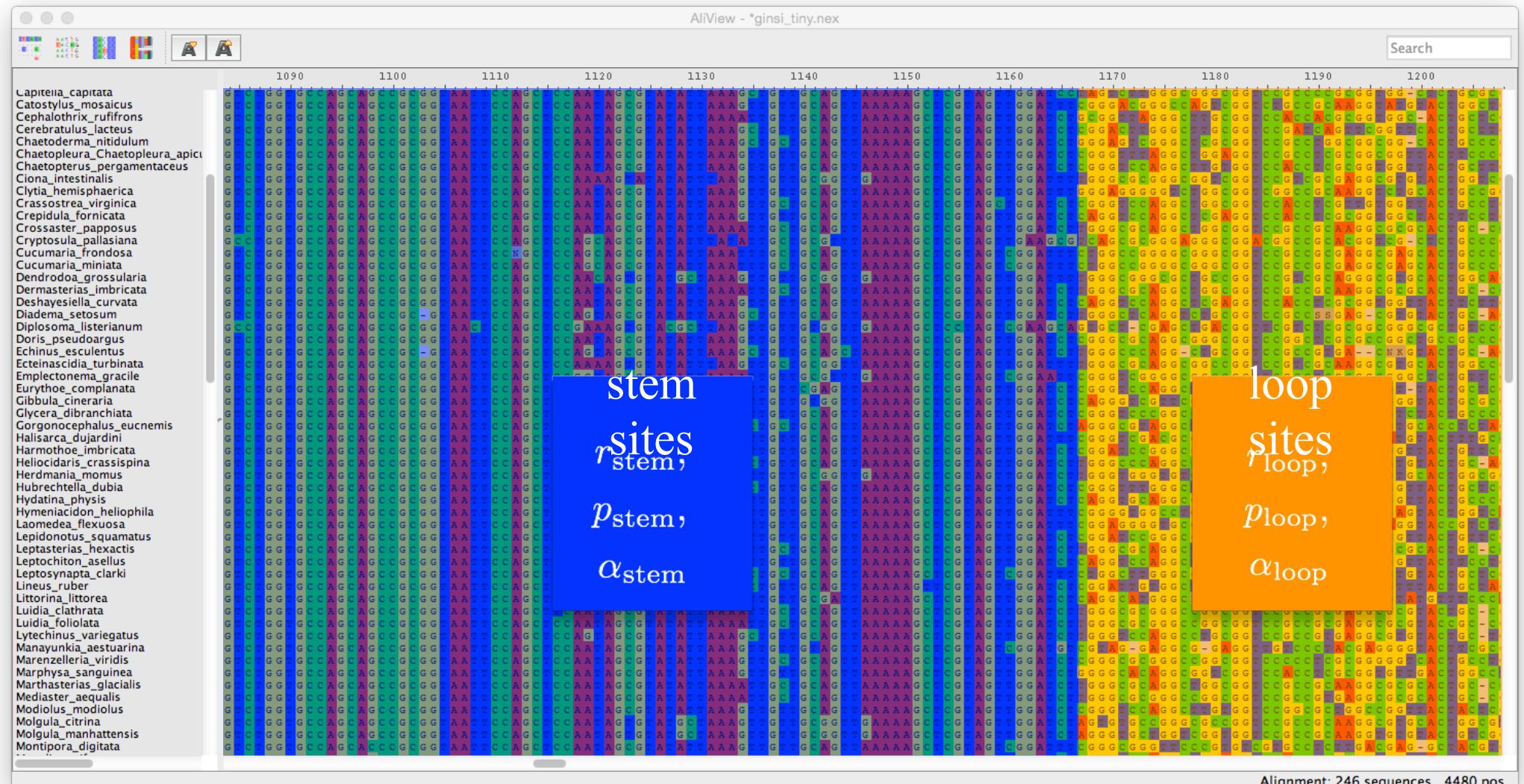
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- as a mixture of all three models (+SS+I+G)

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- as a mixture of all three models (+SS+I+G)

Mixtures of I+G can make optimization or sampling difficult :

- under this mixture model, there is an infinite number of parameter values for which the data are equally likely to be observed; e.g.,

# Accommodating Among Site Rate Variation

## Mixture models for accommodating ASRV

Site rates can be model as a mixture of the individual ASRV models (SS, I, and G):

- as a mixture of site-specific and proportion of invariable sites (+SS+I)
- as a mixture of site-specific and discrete-gamma distributed rates (+SS+G)
- as a mixture of proportion of invariable sites and discrete-gamma distributed rates (+I+G)
- as a mixture of all three models (+SS+I+G)

Mixtures of I+G can make optimization or sampling difficult :

- under this mixture model, there is an infinite number of parameter values for which the data are equally likely to be observed; e.g.,
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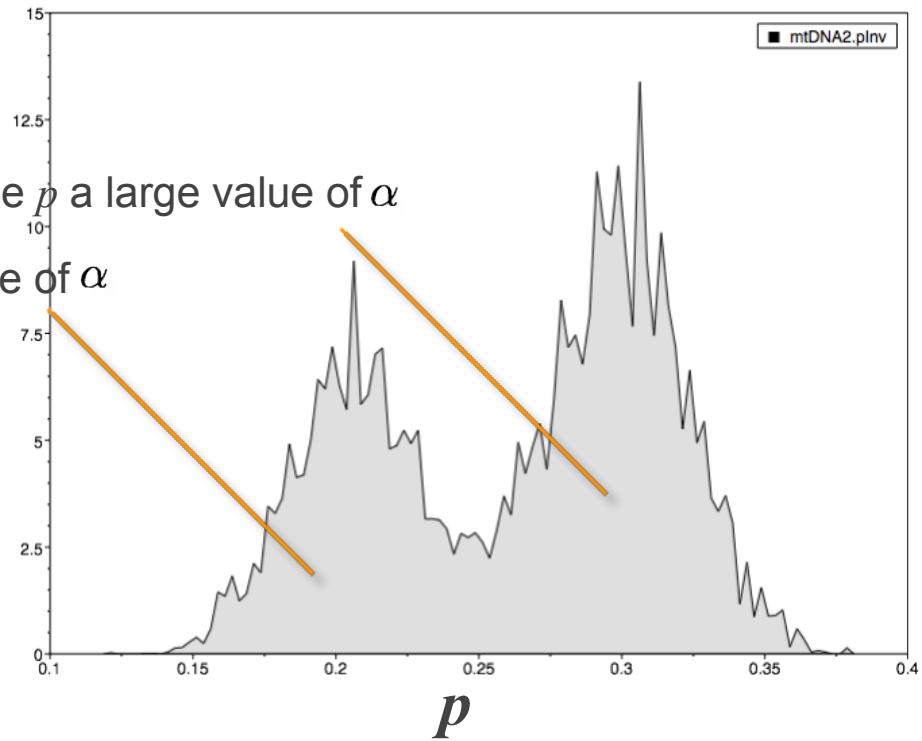
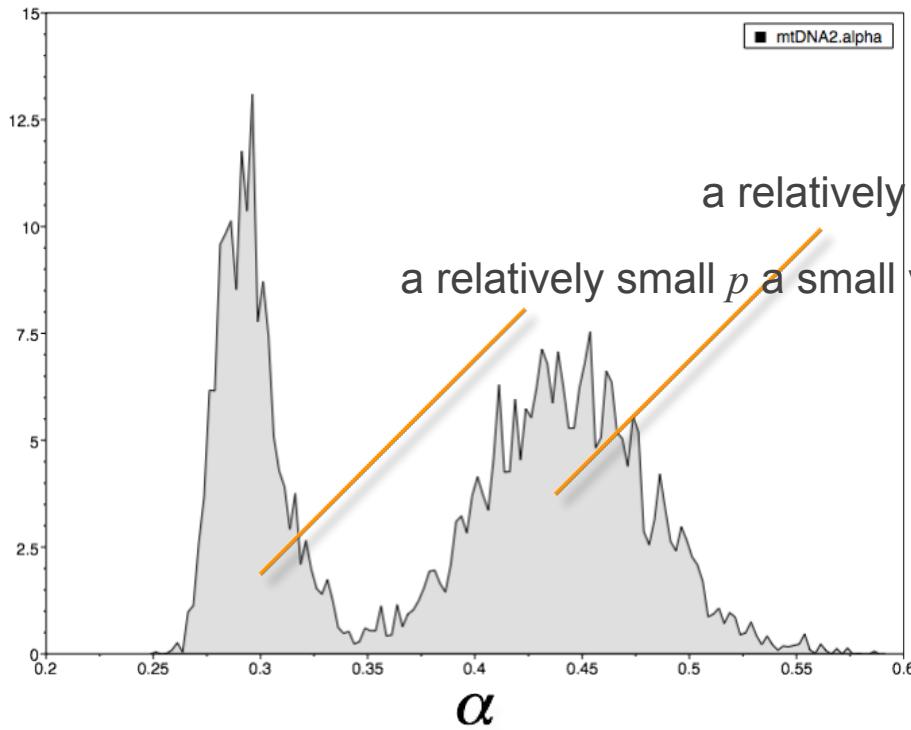
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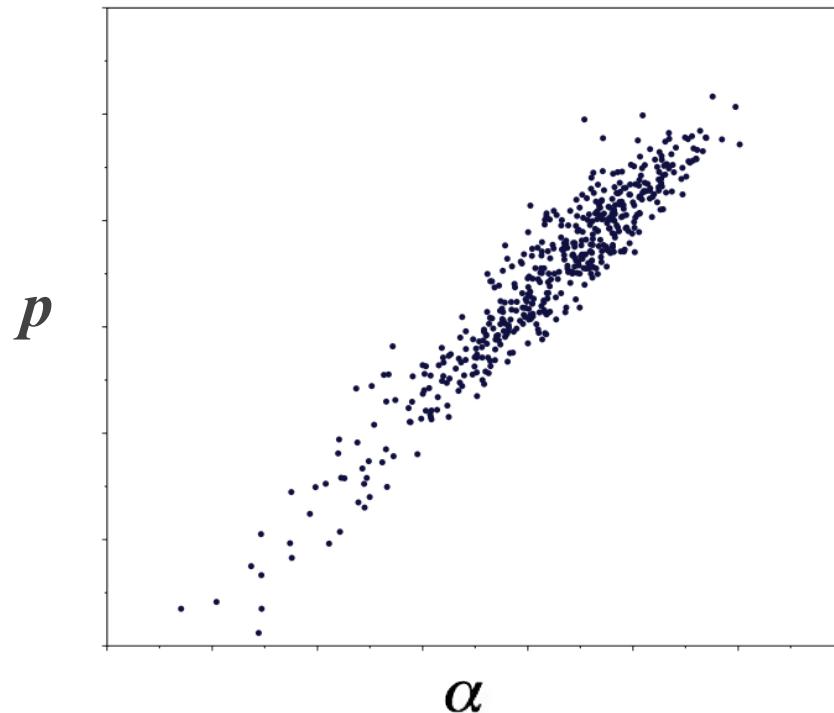
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These parameter interactions may make convergence difficult.

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We can identify parameter interactions by plotting their joint posterior probability distribution  
(see Bayesian MCMC presentations!)

# Accommodating Among Site Rate Variation

## Why do we model ASRV?

ASRV can be due to a variety of processes (mutation, bGC, selection, epistatic interactions...).

ASRV models do not help us understand the data, they help us deal with its complexities to study another aspect of the data.

We model ASRV in this way because we do not use a ***mechanistic*** model of the processes creating ASRV.

ASRV is a ***phenomenological*** model.

# Outline

I. A brief summary of Continuous-Time Markov chains (CTMCs)

The scale parameter

II. Stochastic models of nucleotide substitution

What's the deal with time reversibility

Meet the GTR family

**III. Accommodating among-site heterogeneity in the substitution process**

Among-site variation in substitution rates

Among-site variation in substitution process

**IV. Accommodating heterogeneity in the substitution process along the tree**

# Accommodating Among Site Process Heterogeneity

The substitution process may vary qualitatively across the alignment



Alignments may be composed of (subsets of) sites from different:

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- stem/loop regions of ribosomal genes

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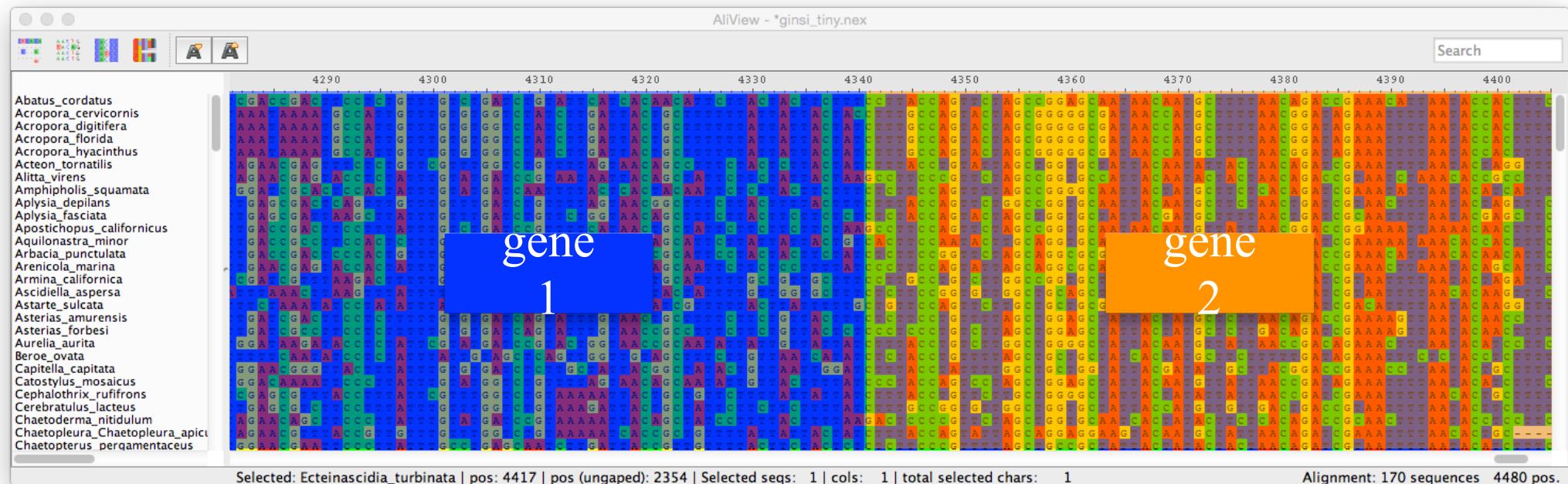


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- stationary frequencies ( $\pi_i$ )
- relative rates ( $a-f$ )
- the nature/degree of ASRV ( $p, \alpha$ )

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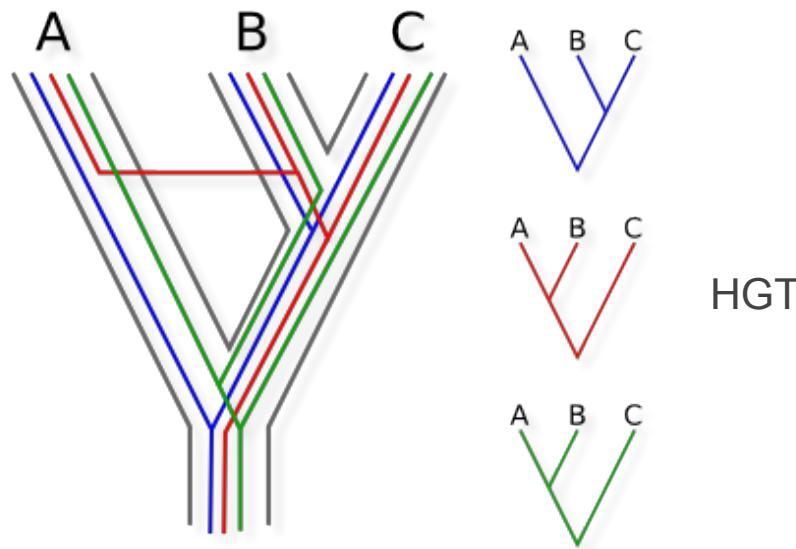
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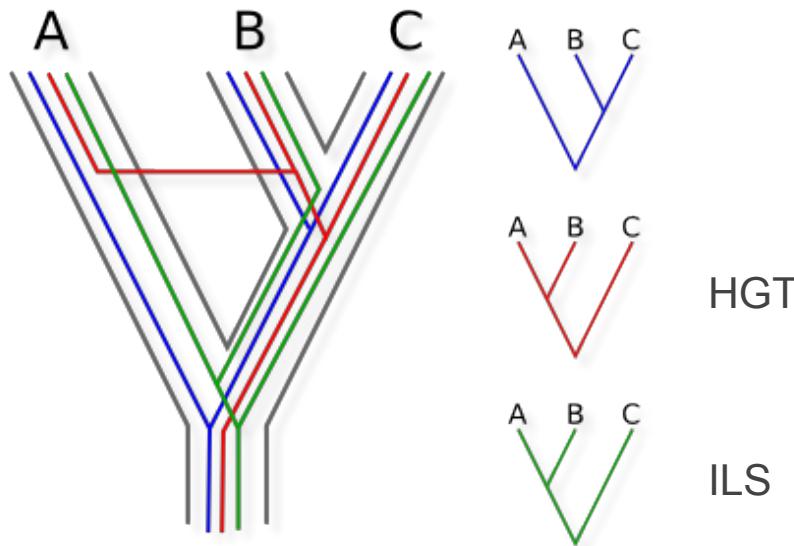
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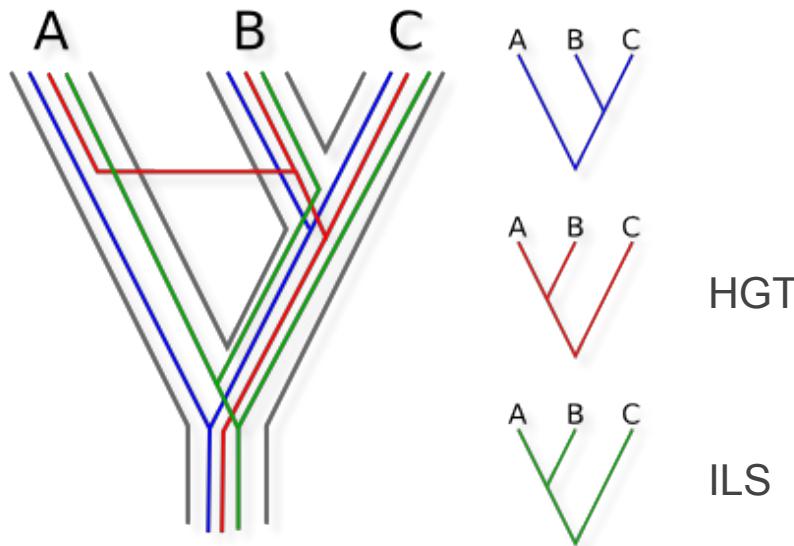
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- deep coalescence (incomplete lineage sorting)

There are 'species-tree' methods that allow the tree topology to vary across sites



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- branch lengths
- divergence times
- other substitution-model parameters

# Accommodating Among Site Process Heterogeneity

2 approaches

Partition model : we assign sites to groups of parameters

Mixture model : we don't assign sites, but integrate over several groups of parameters

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Partition model approach for modeling ASPH

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## Partition model approach for modeling ASPH

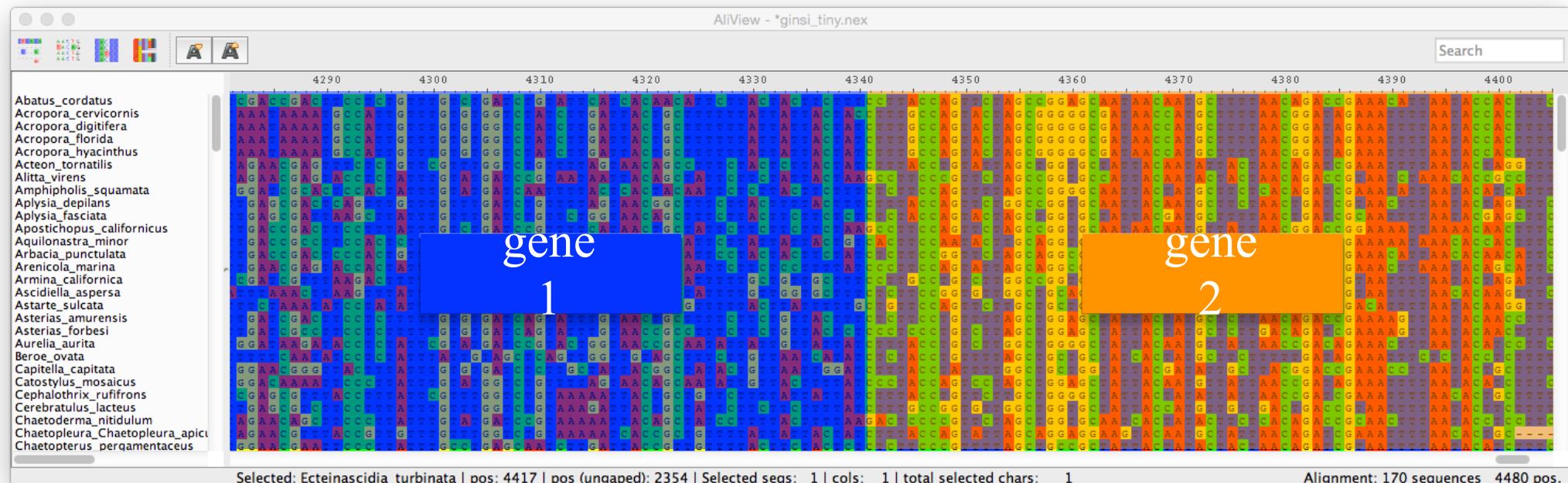
The basic idea is to assign (subsets of) sites to independent substitution models

The number of data subsets and the assignment of sites to subsets is assumed

- the number of partitions and assignment of subsets is informed by our biological knowledge
- a substitution model is specified for each data subset

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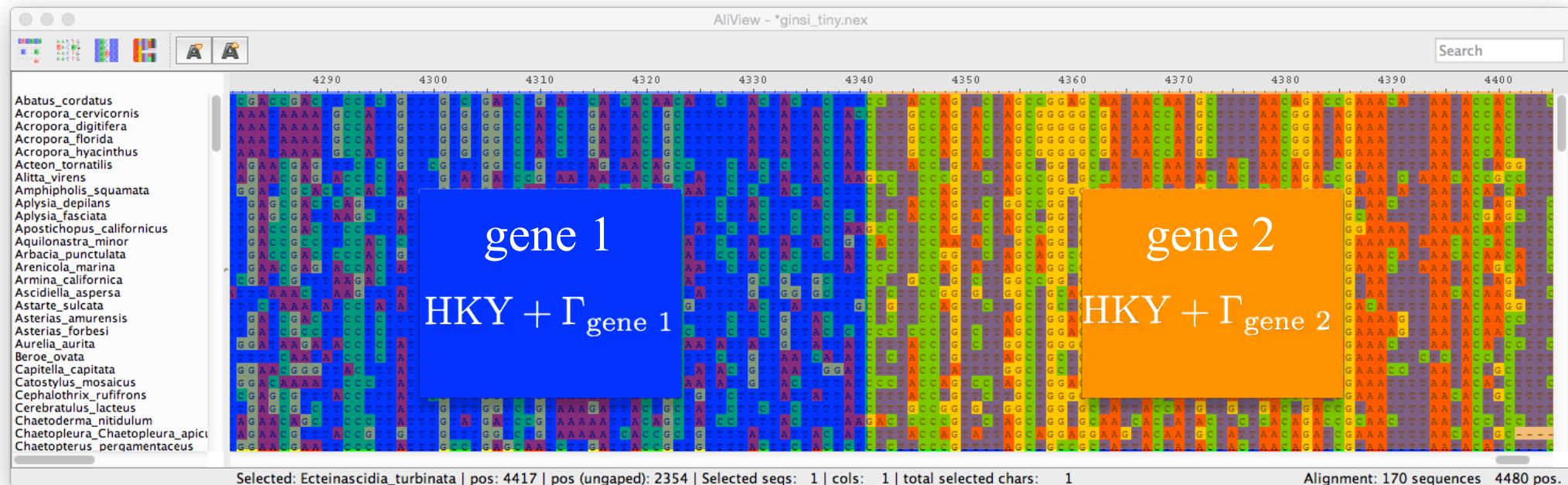
Partition model approach for modeling ASPH



Define two or more data subsets that are likely to capture substitution process heterogeneity

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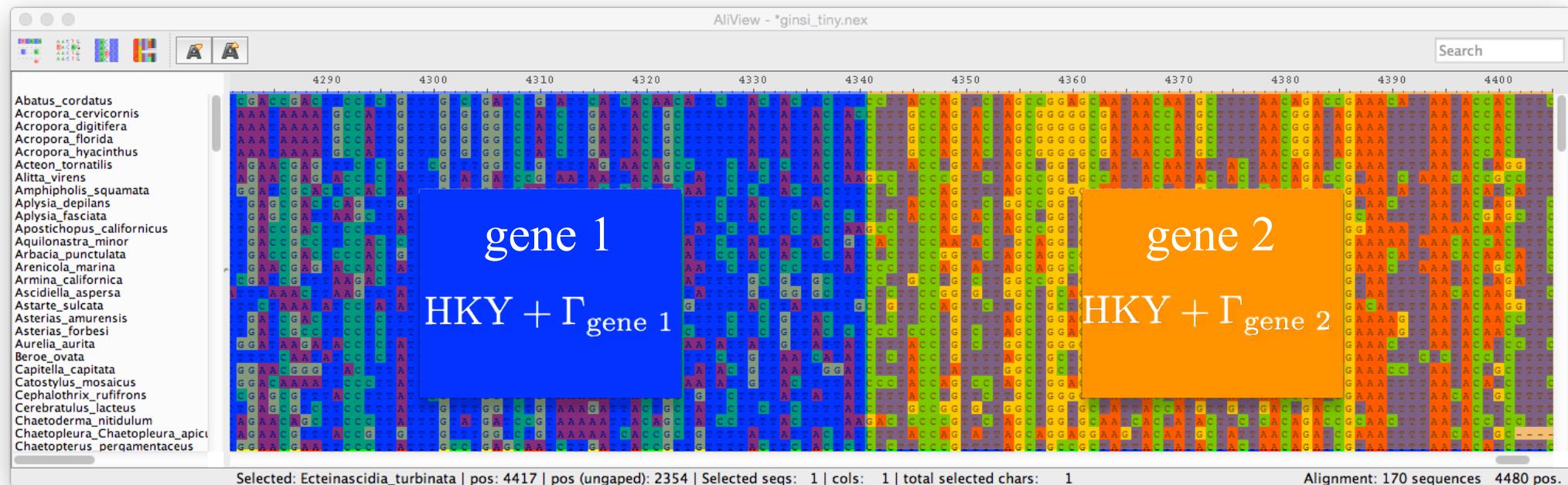


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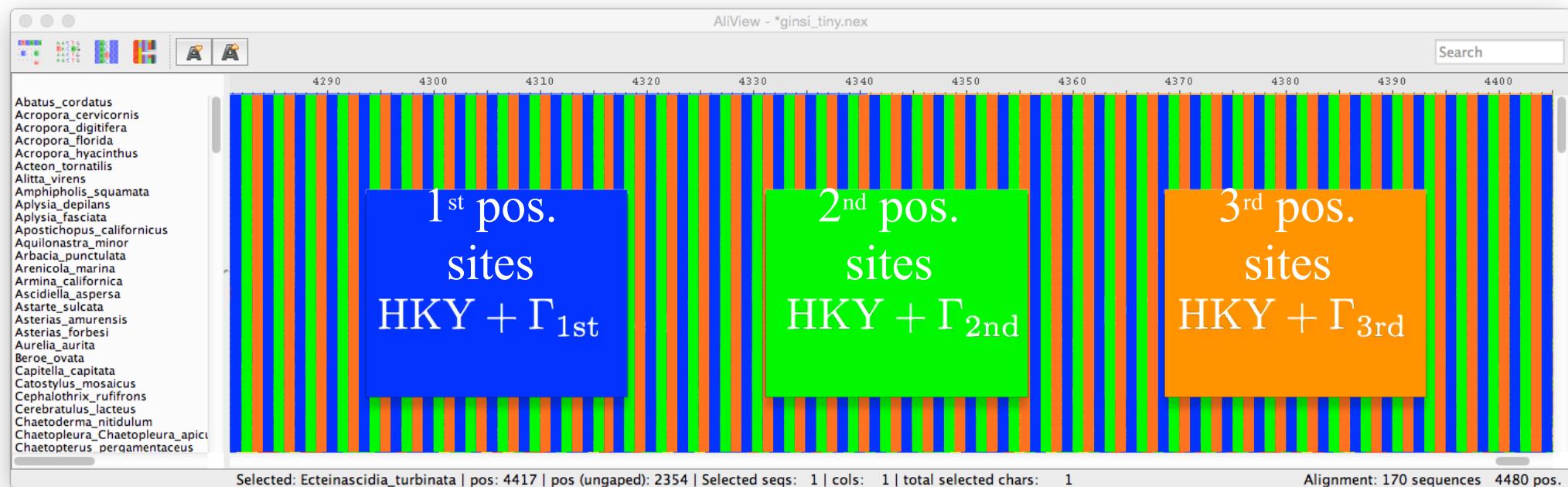
Define two or more data subsets that are likely to capture substitution process heterogeneity

Specify a substitution model for each pre-specified data subset

Estimate parameters of each model from sites in the corresponding data subset

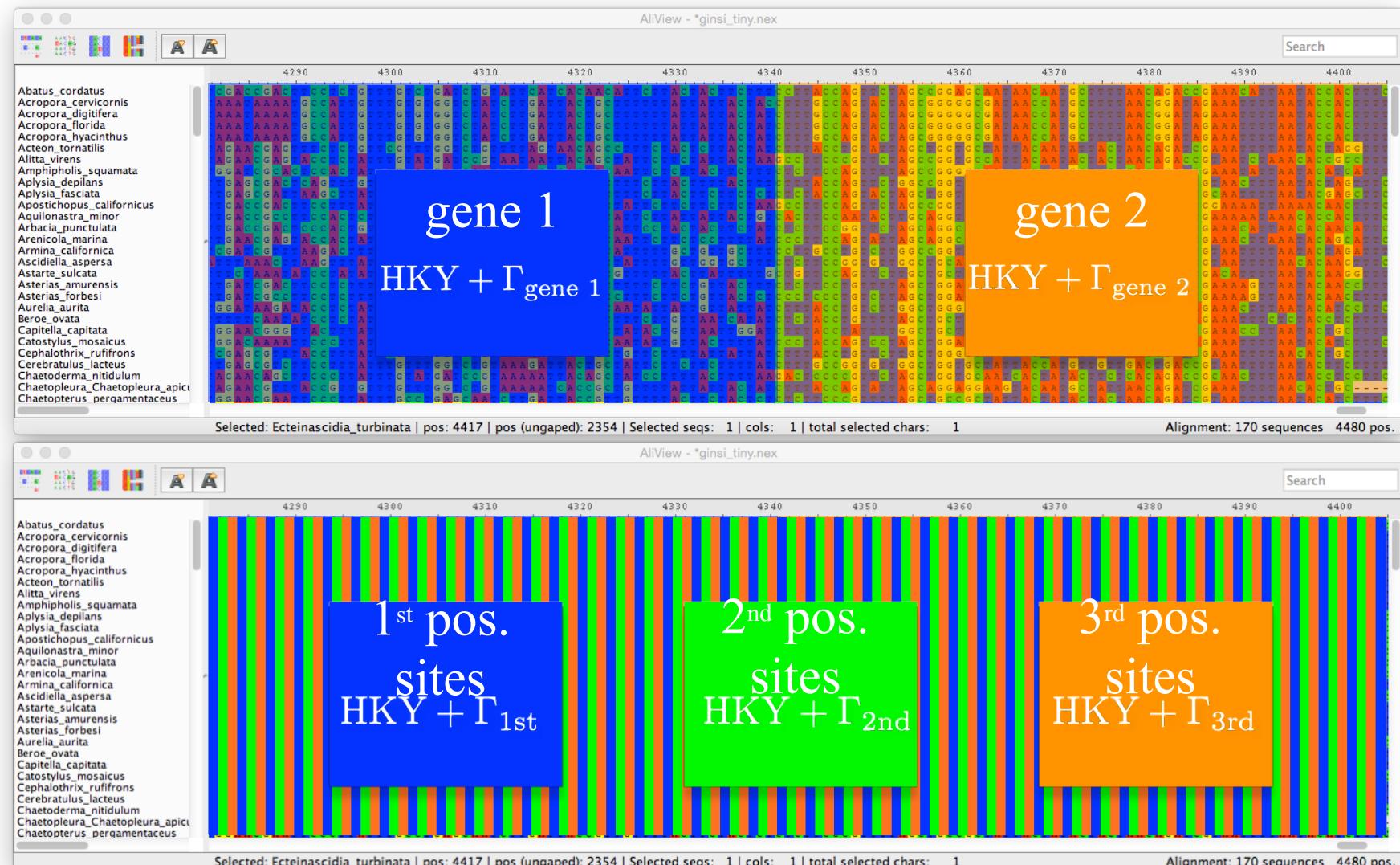
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Partition model approach for modeling ASPH



We can then compare the fit of the competing mixed-models to the data

# Accommodating Among Site Process Heterogeneity

## Mixture model approach for modeling ASPH

For instance, the CAT model (Lartillot and Philippe, 2004).

Similar to the discrete Gamma to model ASRH, at each site we *sum* over different parameter values.

Here, we model heterogeneity in the stationary frequencies, in an amino acid model.

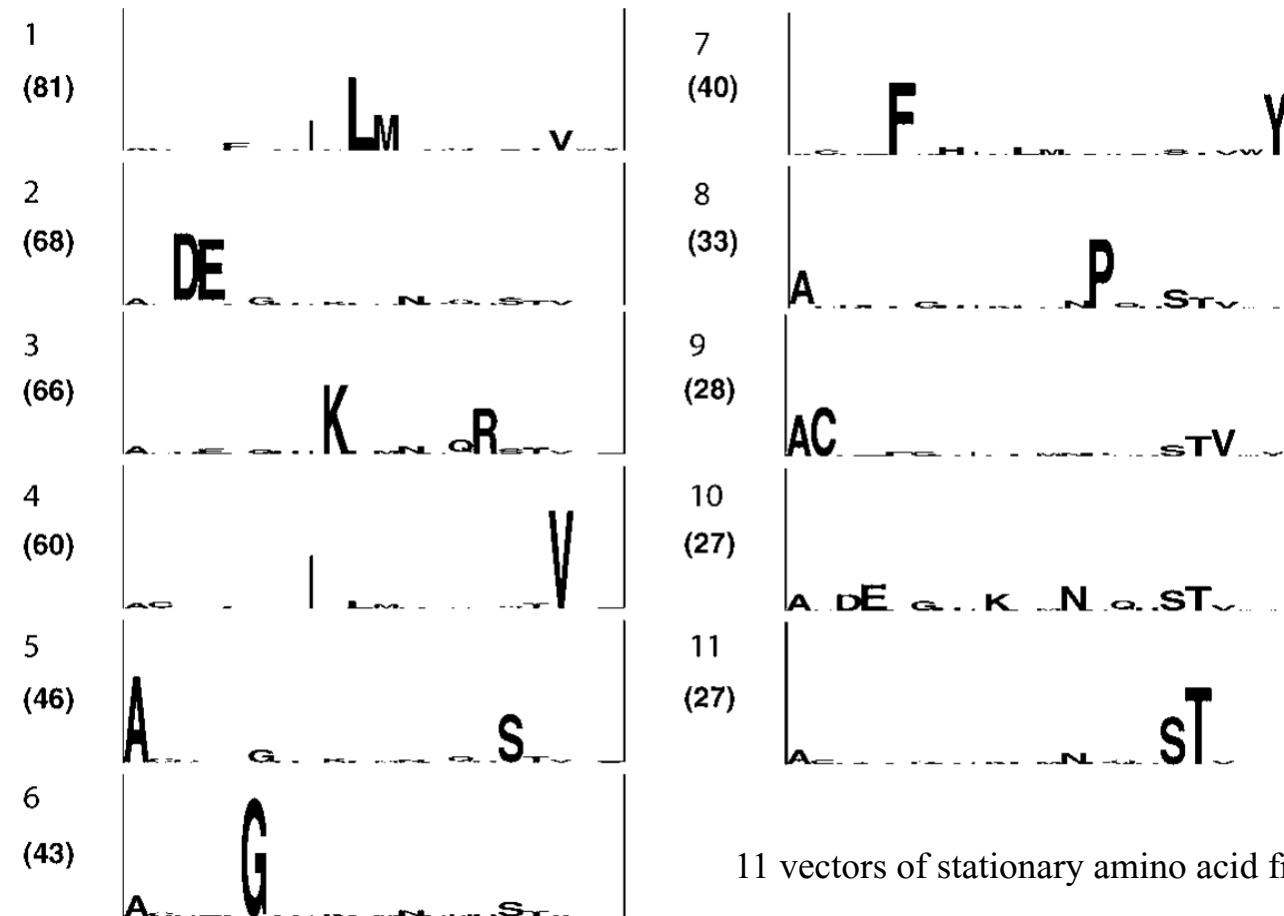
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11 vectors of stationary amino acid frequencies estimated from an alignment

of eukaryotic elongation factor 2 sequences (30 sequences, no gaps, 627 sites)

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# The Deinococcus-Thermus phylum and the effect of rRNA composition on phylogenetic tree construction.

Weisburg WG, Giovannoni SJ, Woese CR.

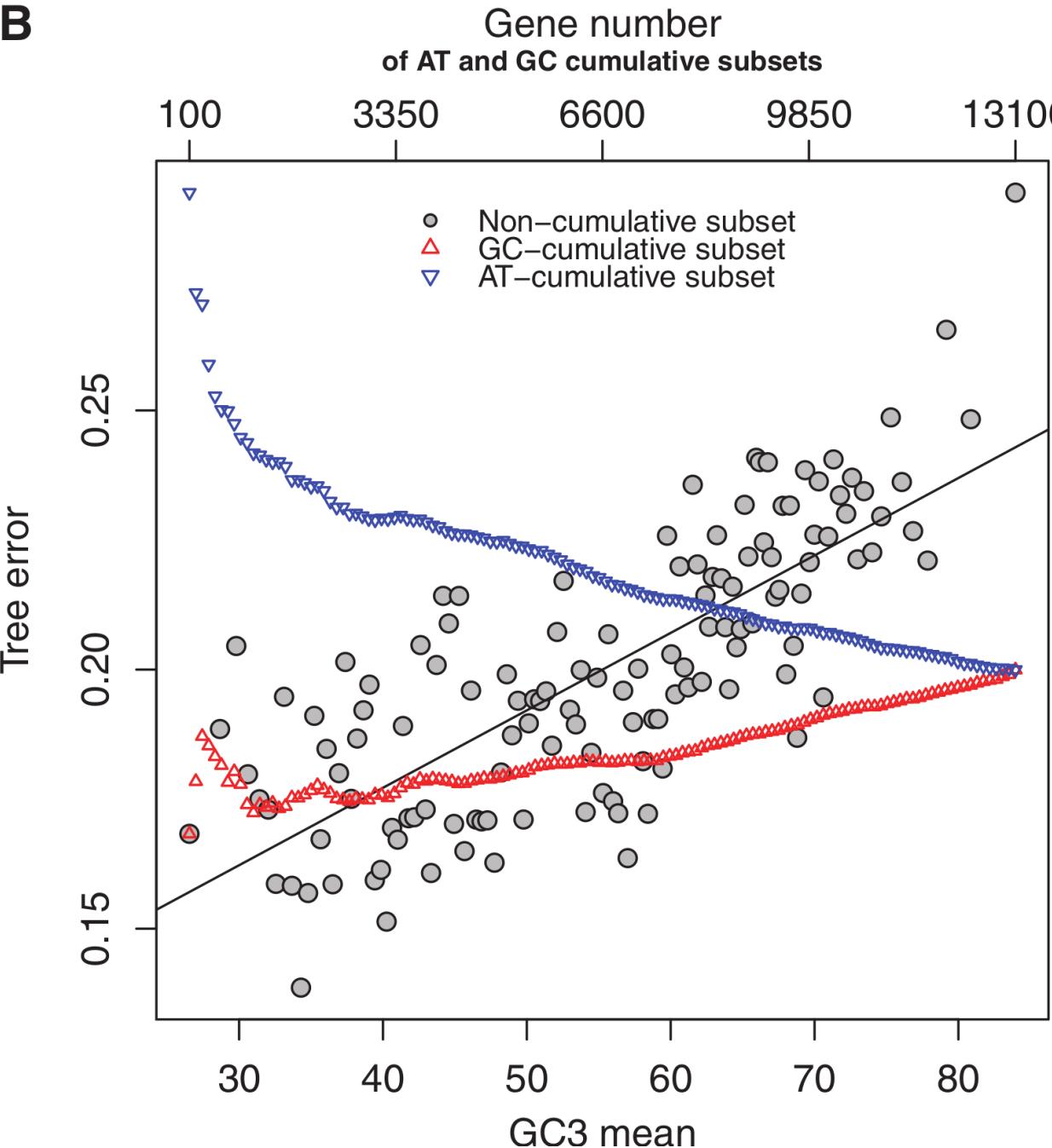
Syst Appl Microbiol. 1989;11:128-34.

sel=0	293	380
Aquifex	CTCCCCCTCGGGTAACGGGATGCGCACCGTAATGCATCCCGATGCCGATAGGCACCCCGCAGGC	CCGGCAGGTCTCGGAGAAGCAGC
Thermotoga	GGGCTGCCTGGTGTTCGGATGGTCACCGTGGCTCATCCGAATACCAGGTGGGGCGTAGAGAGACCGCGTGACGTATCGCGGGTGGCGT	
Thermus	GCGTTGCCTGGGGCTCCCATTGGAACCGTGGGACGTGGGATGCTCAGGAACGGTGGAGAGTGGTTCCGACAGGCACCGGGATCGAGC	
Deinococcus	GCGTTGATATTAACTGGTTTGAGACTCGAGTGACTGGATTGGATGTTACCTCTGAGATAACTCTGCGGTACCAAGAAATCGAAG	
Rickettsia	ATGCTGTTAGTAATTGGAAGGGCGTTCAATTCTTCAAATAACTAATAAGTGTATAGGATGATTCTATAATTATTAGAGGTGGGT	

"The (partial) sequence of *T. aquaticus* rRNA appears relatively close to those of other thermophilic eubacteria. [...] However, this closeness does not reflect a true evolutionary closeness; rather it is due to a "thermophilic convergence", the result of unusually high G+C composition in the rRNAs of thermophilic bacteria. Unless such compositional biases are taken into account, the branching order and root of phylogenetic trees can be incorrectly inferred."

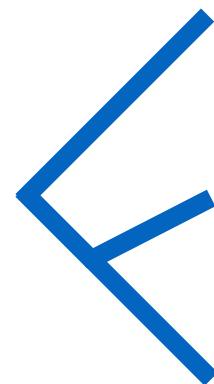
# The impact of compositional heterogeneity on mammalian phylogeny

B



- 131 sets of 100 genes ordered from low to high GC
- In GC rich gene families, GC content varies widely between genes
- GC rich genes have trees with more difference to the true tree

# Homogeneous models



Commonly used models inherit from GTR:

$$Q = \begin{pmatrix} -(\alpha\pi_C + \beta\pi_A + \gamma\pi_G) & \alpha\pi_C & \beta\pi_A & \gamma\pi_G \\ \alpha\pi_T & -(\alpha\pi_T + \delta\pi_A + \epsilon\pi_G) & \delta\pi_A & \epsilon\pi_G \\ \beta\pi_T & \delta\pi_C & -(\beta\pi_T + \delta\pi_C + \eta\pi_G) & \eta\pi_G \\ \gamma\pi_T & \epsilon\pi_C & \eta\pi_A & -(\gamma\pi_T + \epsilon\pi_C + \eta\pi_A) \end{pmatrix}$$

Where  $\Pi = (\pi_T, \pi_C, \pi_A, \pi_G)$  is the set of ***equilibrium*** frequencies

When a single matrix is used over a phylogeny, one assumes that sequences all tend towards

$$\Pi = (\pi_T, \pi_C, \pi_A, \pi_G)$$

*Does not fit many data sets*

# Software explicitly handling compositional heterogeneity

- Paml (Z. Yang)
- nhml (N. Galtier)
- nhPhyML (B. Boussau)
- bppML (J. Dutheil, L. Gueguen, B. Boussau)
- p4 (P. Foster)
- Hal-Has (V. Jayaswal)
- PhyloBayes ? (N. Lartillot)
- *not* PhyML, IQTree, RaXml, Garli, mrBayes, Beast(\*)...

# Mixtures of GTR matrices

Used for:

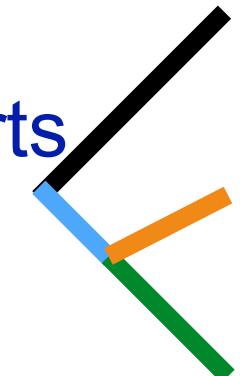
- model fitting (Jayaswal et al., 2011; Jayaswal et al., 2014; Dutheil et al., 2012)
- topology search (Boussau et al. 2006)

*Problem: lack of closure (Sumner et al. 2012)*

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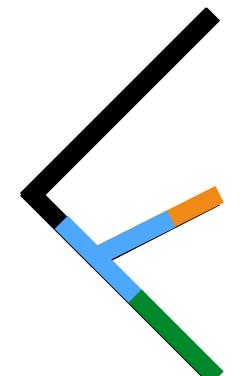
Changes at nodes:

- ➊  $n$  branches ->  $n$  matrices: Yang and Roberts 1995, Galtier and Gouy 1998, Boussau 2006, Heaps et al., 2014
- ➋  $n$  branches ->  $k < n$  matrices: Foster 2004



Changes along branches:

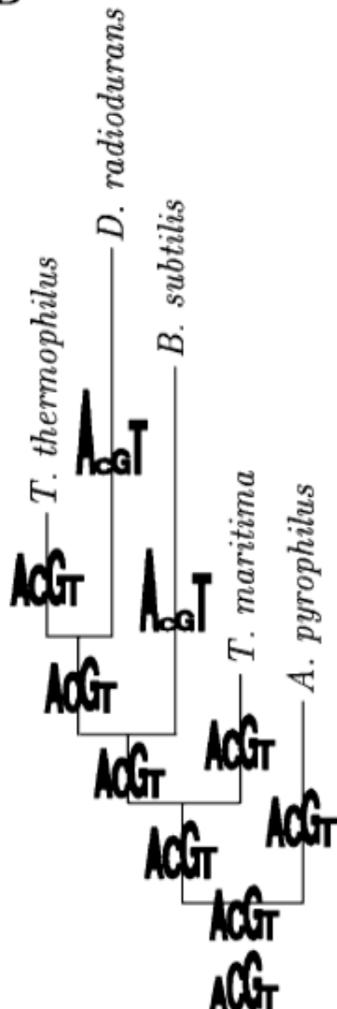
- ➌ Blanquart and Lartillot 2006, 2008



# Blanquart and Lartillot 2006

Bayesian MCMC sampling of histories of breakpoints between equilibrium frequencies along the phylogeny, and of the equilibrium frequencies themselves

B



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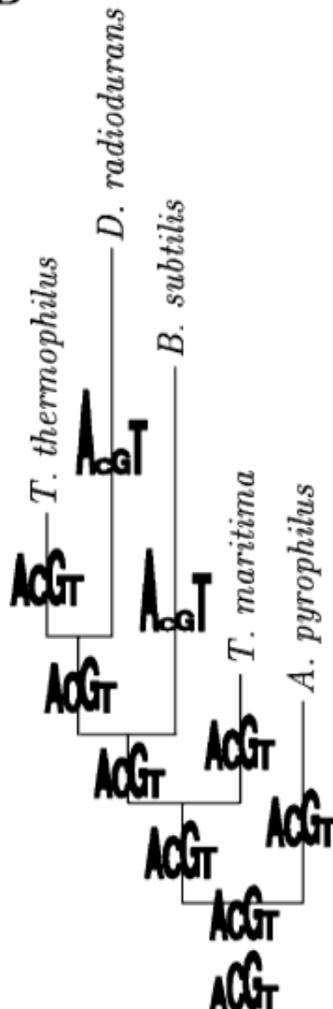
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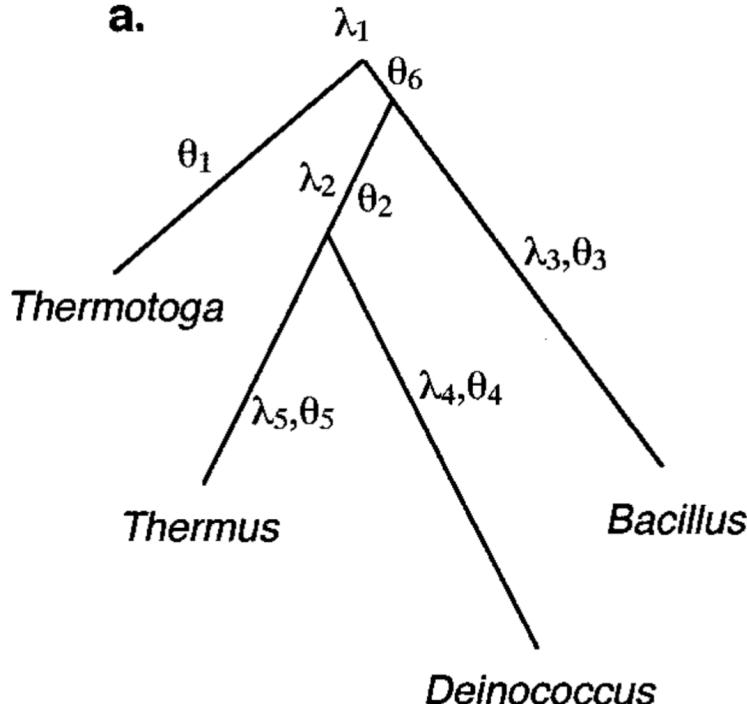
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*Problem: does not scale very well*

# Galtier and Gouy 1998

## ML estimation of branch-wise GC equilibrium frequencies

a.



b.

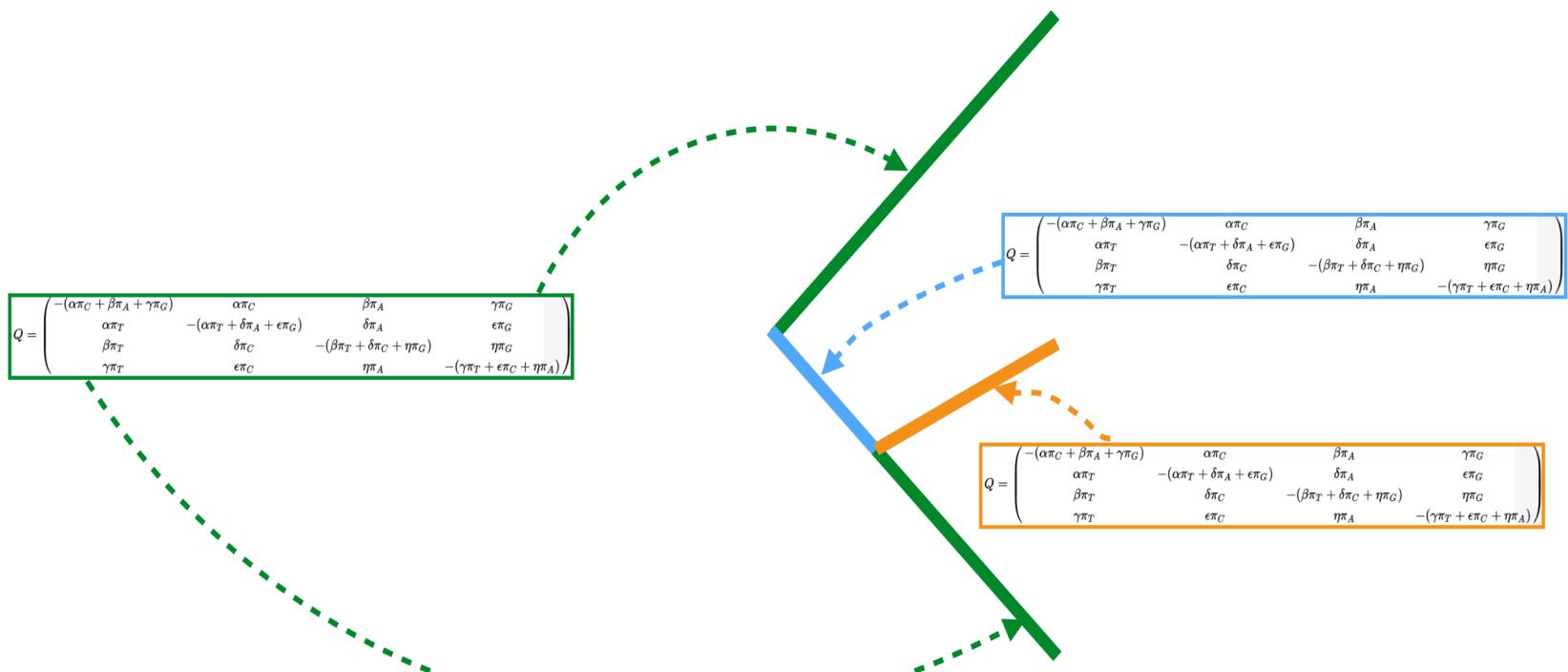
	estimate	s.e.
$\kappa$	2.073	0.201
$\phi$	0.962	0.136
$\omega$	61.8%	1.5%
$\lambda_1$	0.097	0.012
$\lambda_2$	0.042	0.008
$\lambda_3$	0.111	0.012
$\lambda_4$	0.118	0.013
$\lambda_5$	0.067	0.010
$\theta_1$	81.4%	5.0%
$\theta_2$	69.7%	8.2%
$\theta_3$	28.6%	4.4%
$\theta_4$	28.3%	4.2%
$\theta_5$	71.4%	5.7%
$\theta_6$	100%	15.1%

$$Q = \begin{pmatrix} -(\alpha\tau_C + \beta\tau_A + \gamma\tau_D) & \alpha\tau_C & \beta\tau_A & \gamma\tau_D \\ \alpha\tau_T & -(\alpha\tau_T + \beta\tau_A + \gamma\tau_D) & \beta\tau_A & \gamma\tau_D \\ \beta\tau_T & \beta\tau_A & -(\beta\tau_T + \beta\tau_A + \gamma\tau_D) & \gamma\tau_D \\ \gamma\tau_T & \gamma\tau_D & \gamma\tau_D & -(\gamma\tau_T + \gamma\tau_C + \gamma\tau_A) \end{pmatrix}$$

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## Bayesian MCMC estimation of a limited set of equilibrium frequencies

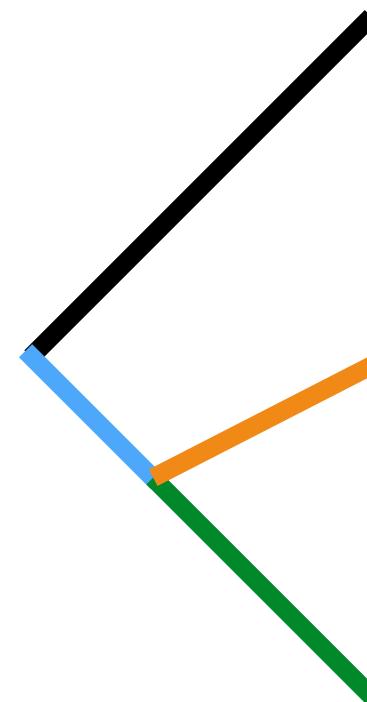


# Heaps 2014

Bayesian MCMC estimation

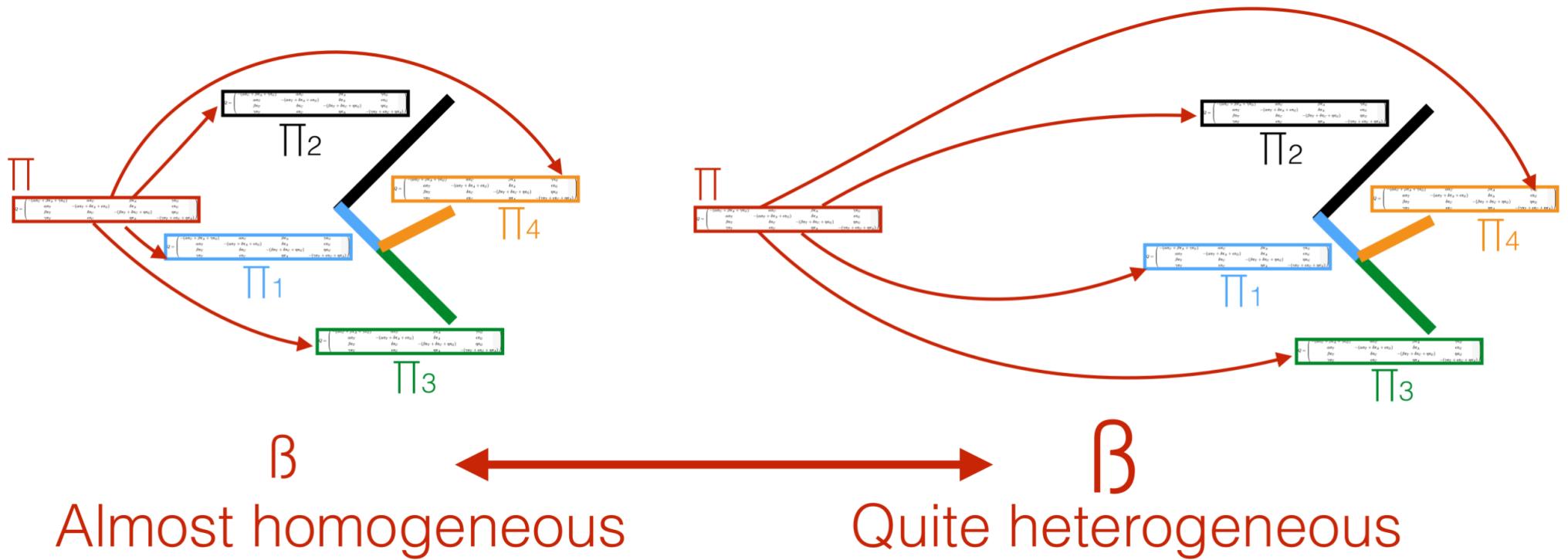
2 different models:

- ➊ a hierarchical model
- ➋ a correlated model



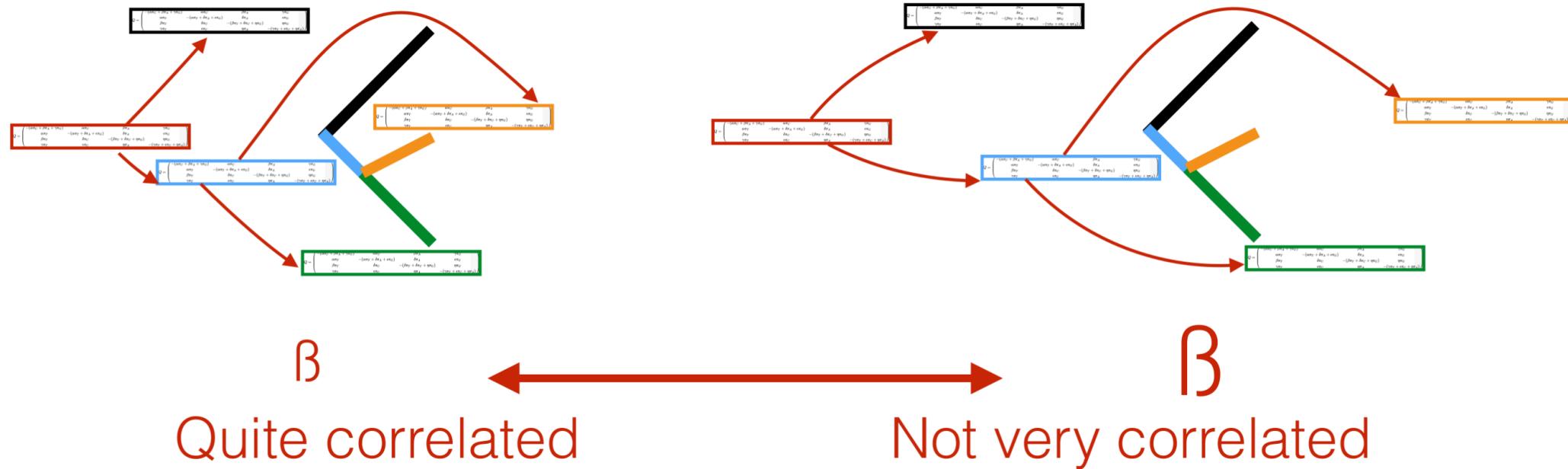
# Heaps 2014: Hierarchical model

- One central vector  $\Pi$
- Each branch  $i$  has its own vector  $\Pi_i$  in the neighbourhood of  $\Pi$



# Heaps 2014: Correlated model

- One ancestral vector  $\Pi$
- Each branch  $i$  has its own vector  $\Pi_i$  in the neighbourhood of its parent vector  $\Pi_{pi}$



# Using models of compositional heterogeneity

- Not implemented in the most widely used software packages (except revBayes)
- Have not been used very often
- Have been used for ancestral sequence reconstruction
- Have rarely been combined with models of process heterogeneity across sites

# Outline

## I. A brief summary of Continuous-Time Markov chains (CTMCs)

The scale parameter

## II. Stochastic models of nucleotide substitution

What's the deal with time reversibility

Meet the GTR family

## III. Accommodating among-site heterogeneity in the substitution process

Among-site variation in substitution rates

Among-site variation in substitution process

## IV. Accommodating heterogeneity in the substitution process along the tree

### Many things we have not addressed :

- Heterogeneity in rates of evolution across the tree (Tuffley and Steel 1998 ; Galtier 2001)
- Correlated evolution of traits and sequences (e.g. Tamuri et al. 2009 ; Poujol and Lartillot 2010 ; Bielejec 2014...)
- Non-independence between sites (e.g. Schöniger and von Haeseler (1994), Robinson et al. 2003, Meyer et al. 2019...)

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*See Jeff's talk !*

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