A Brief Tour of Some Models of Nucleotide Substitution

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Stochastic Mechanisms of Character Change

Continuous-time Markov models

describe the stochastic process by which traits (nucleotides) evolve over the tree

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

Scaling the Instantaneous Rate Matrix

What is the scale of the instantaneous rates?

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This is achieved by scaling the instantaneous-rate matrix by the weighted average of substitution rates:

$$i \neq j \qquad \mu = \sum_i \sum_j \pi_i q_{ij}$$

or equivalently:

$$\mu = -\sum_i \pi_i q_{ii}$$

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$i \neq j$ $\quad \mu = \sum_i \sum_j \pi_i q_{ij}$ weighted sum of off-diagonal rates

or equivalently:

$\mu = -\sum_i \pi_i q_{ii}$ negative weighted sum of diagonal rates

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We then multiply each element in the instantaneous-rate matrix by the scalar $1/\mu$

Scaling the Instantaneous Rate Matrix

Let's check the scaling of our hypothetical rate matrix

The instantaneous-rate matrix...

$$\mathbf{Q} = \{q_{ij}\} = \begin{pmatrix} -1.916 & 0.541 & 0.787 & 0.588 \\ 0.148 & -1.069 & 0.415 & 0.506 \\ 0.286 & 0.170 & -0.591 & 0.135 \\ 0.525 & 0.236 & 0.594 & -1.355 \end{pmatrix}$$

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Stationary frequencies...

$$\mathbf{P}(100.0) = \begin{array}{c} \begin{matrix} \pi_A & \pi_C & \pi_G & \pi_T \end{matrix} \\ \begin{pmatrix} 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \end{pmatrix} \end{array}$$

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probability of starting in A

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probability of starting in A

overall rate of change away from A

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probability of starting in C

overall rate of change away from C

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probability of starting in G

overall rate of change away from G

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probability of starting in T

overall rate of change away from T

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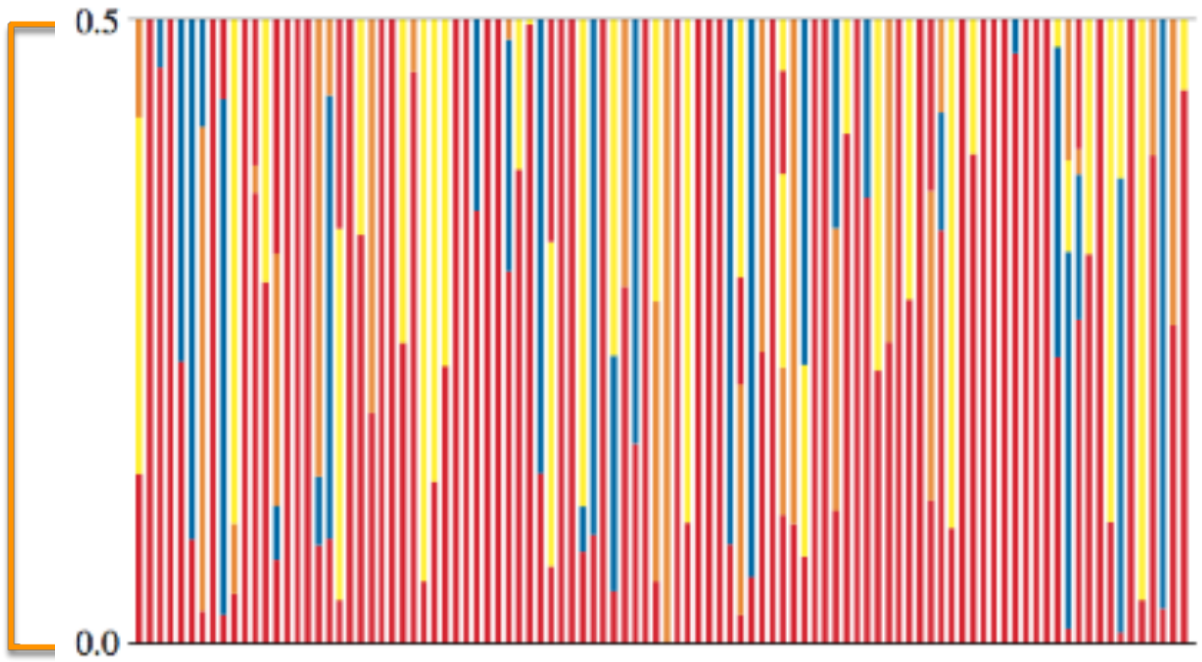
$$-(0.138 \times -1.916 + 0.188 \times -1.069 + 0.495 \times -0.591 + 0.179 \times -1.355) = 1$$

The average substitution rate in our instantaneous-rate matrix is therefore 1!

Scaling the Instantaneous Rate Matrix

Can we correctly estimate the true branch length used in our simulation?

The true branch length was $\nu = 0.5$



For simulations starting in A, the average number of changes was $z = 0.788$

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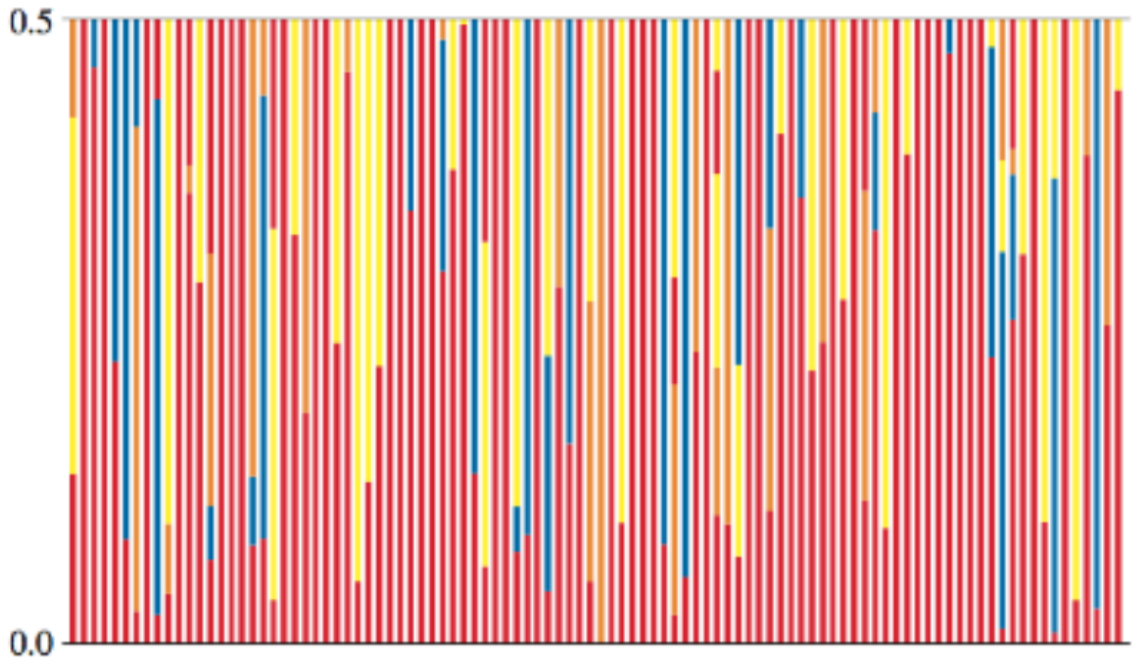
We compute the average number of changes for each starting state, z



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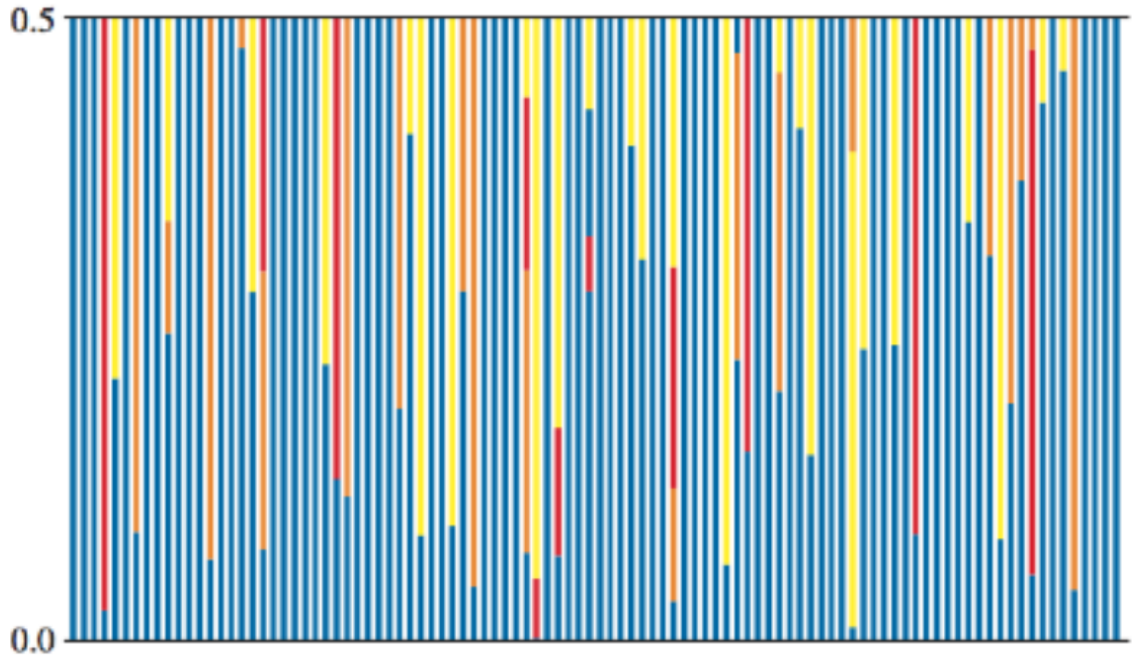

For simulations starting in C, the average number of changes was $z = 0.541$

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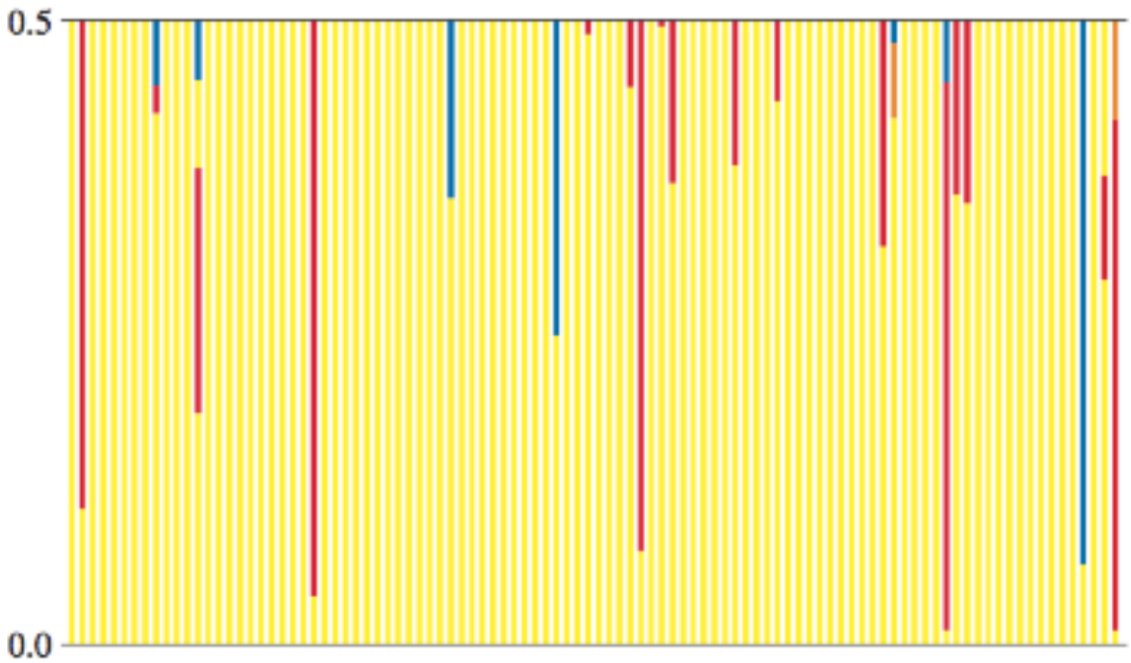

For simulations starting in G, the average number of changes was $z =$ 0.352

Scaling the Instantaneous Rate Matrix

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The true branch length was $\nu = 0.5$

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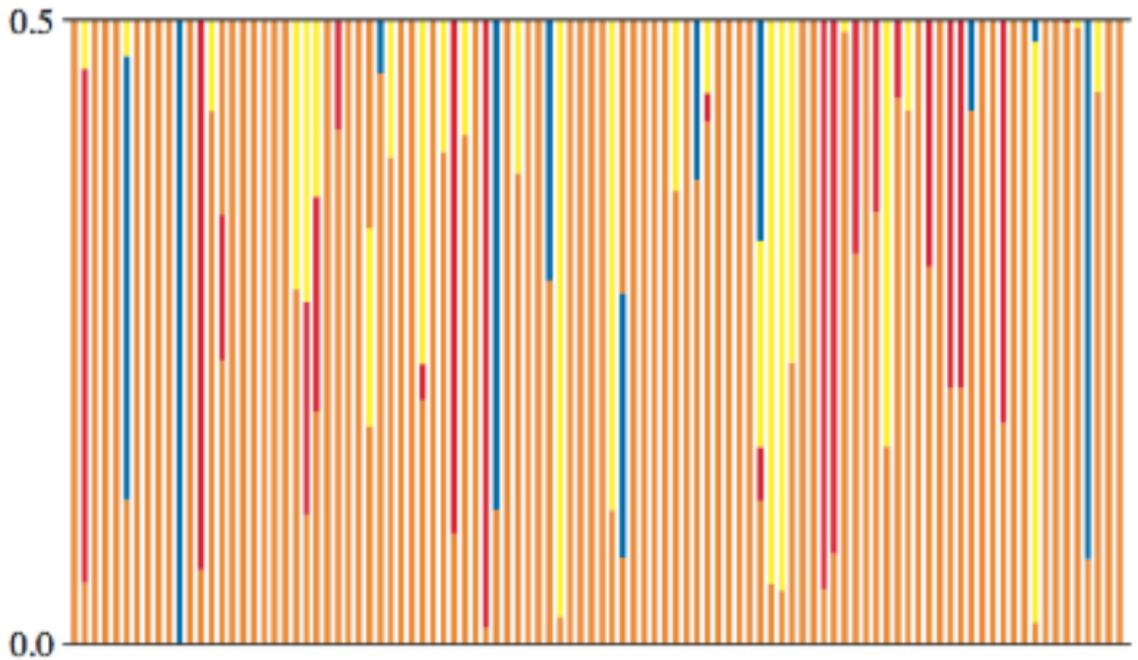

For simulations starting in T, the average number of changes was $z =$ 0.643

Scaling the Instantaneous Rate Matrix

Can we correctly estimate the true branch length used in our simulation?

The weighted sum of the average (expected) number of changes for all four states when the average of the $\mathbf{Q}$ matrix is 1...

i	π_i
A	0.138
C	0.188
G	0.495
T	0.179

probability of each starting state

Scaling the Instantaneous Rate Matrix

Can we correctly estimate the true branch length used in our simulation?

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i	π_i	z_i
A	0.138	0.788
C	0.188	0.541
G	0.495	0.352
T	0.179	0.643

average number of changes away from each state

Scaling the Instantaneous Rate Matrix

Can we correctly estimate the true branch length used in our simulation?

The weighted sum of the average (expected) number of changes for all four states when the average of the $\mathbf{Q}$ matrix is 1...

i	π_i	z_i	$\pi_i z_i$
A	0.138	0.788	0.109
C	0.188	0.541	0.102
G	0.495	0.352	0.174
T	0.179	0.643	0.155

product of $\pi_i z_i$ for each state

Scaling the Instantaneous Rate Matrix

Can we correctly estimate the true branch length used in our simulation?

The weighted sum of the average (expected) number of changes for all four states when the average of the $\mathbf{Q}$ matrix is 1...

i	π_i	z_i	$\pi_i z_i$
A	0.138	0.788	0.109
C	0.188	0.541	0.102
G	0.495	0.352	0.174
T	0.179	0.643	0.155
			0.500 ← sum of terms for all states

Scaling the Instantaneous Rate Matrix

Can we correctly estimate the true branch length used in our simulation?

The weighted sum of the average (expected) number of changes for all four states when the average of the **Q** matrix is 1...

i	π_i	z_i	$\pi_i z_i$
A	0.138	0.788	0.109
C	0.188	0.541	0.102
G	0.495	0.352	0.174
T	0.179	0.643	0.155
			0.500

i.e., the true branch length, in units of expected (average) number of substitutions per site!

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T	0.179	0.643	0.155
			0.500

i.e., the true branch length, in units of expected (average) number of substitutions per site!

Scaling the instantaneous-rate matrix such that the average substitution rate is 1 therefore allows us to interpret the branch lengths, ν, in terms of the expected (average) number of substitutions per site.

Scaling the Instantaneous Rate Matrix

Can we correctly estimate the true branch length used in our simulation?

The weighted sum of the average (expected) number of changes for all four states when the average of the $\mathbf{Q}$ matrix is 2...

i	π_i	z_i	$\pi_i z_i$
A	0.138	1.576	0.218
C	0.188	1.082	0.204
G	0.495	0.704	0.348
T	0.179	1.286	0.230
			1.000

i.e., the branch length, in units of expected number of substitutions per site is 2 x the true value!

Scaling the Instantaneous Rate Matrix

Can we correctly estimate the true branch length used in our simulation?

The weighted sum of the average (expected) number of changes for all four states when the average of the $\mathbf{Q}$ matrix is 2...

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			1.000

i.e., the branch length, in units of expected number of substitutions per site is 2 x the true value!

Scaling the instantaneous-rate matrix such that the average substitution rate is 2 would require that we divide the estimated branch lengths by 2 in order to interpret the branch lengths, ν, in terms of the expected (average) number of substitutions per site.

Outline

I. A brief review of Continuous-Time Markov models

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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General Time Reversible models of nucleotide substitution

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- the nature of the substitution process is constant across sites

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General Time Reversible models of nucleotide substitution

This family of CTMC models makes several simplifying assumptions:

- the rate of the substitution process is constant across sites
- the nature of the substitution process is constant across sites
- sites are independent

Time Reversibility

Most continuous-time Markov models assume time reversibility

The probability of a sequence of states visited forward in time is equal to the series of states visited in the reverse order

$$\pi_j p_{ji}(t) = \pi_i p_{ij}(t)$$

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probability of starting state j

probability of ending in state i given starting state j and running over duration t

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probability of starting state i

probability of ending in state j given starting state i and running over duration t

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Consider two rate matrices:

time irreversible

$$\mathbf{Q}_1 = \begin{pmatrix} -1.918 & 0.127 & 1.670 & 0.121 \\ 0.093 & -1.031 & 0.334 & 0.604 \\ 0.463 & 0.127 & -0.711 & 0.121 \\ 0.093 & 0.634 & 0.334 & -1.061 \end{pmatrix}$$

time reversible

$$\mathbf{Q}_2 = \begin{pmatrix} -1.916 & 0.541 & 0.787 & 0.588 \\ 0.148 & -1.069 & 0.415 & 0.506 \\ 0.286 & 0.170 & -0.591 & 0.135 \\ 0.525 & 0.236 & 0.594 & -1.355 \end{pmatrix}$$

Time Reversibility

Most continuous-time Markov models assume time reversibility

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time irreversible: $\mathbf{Q}_1$ 0.0166716

time reversible: $\mathbf{Q}_2$ 0.0045155

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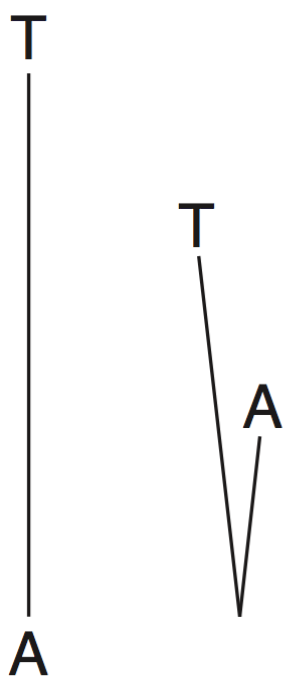

time irreversible:	$\mathbf{Q}_1$	0.0166716	0.0172425
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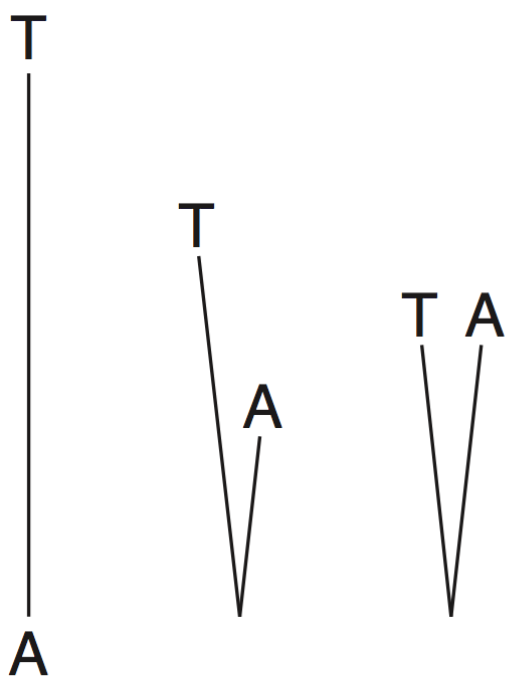

time irreversible:	$\mathbf{Q}_1$	0.0166716	0.0172425	0.0175681
time reversible:	$\mathbf{Q}_2$	0.0045155	0.0045155	0.0045155

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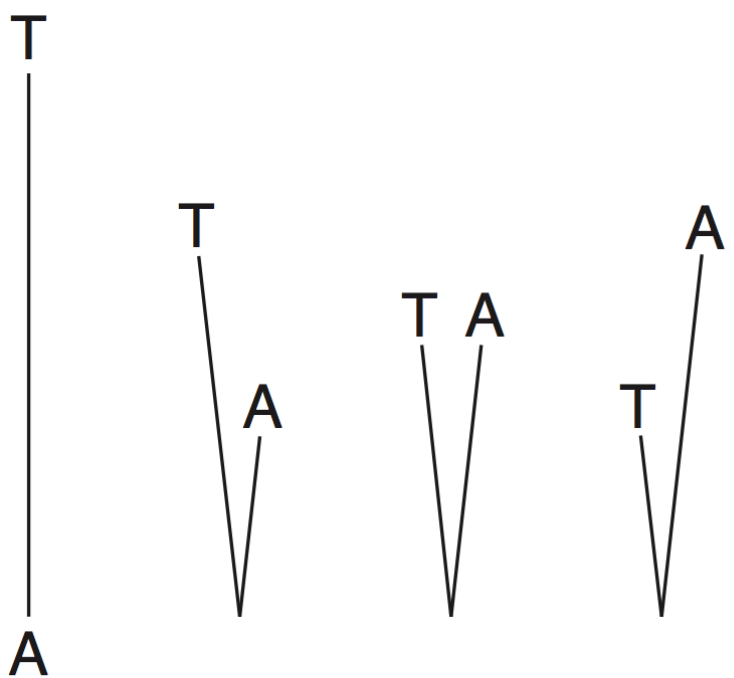

time irreversible:	$\mathbf{Q}_1$	0.0166716	0.0172425	0.0175681	0.0179176
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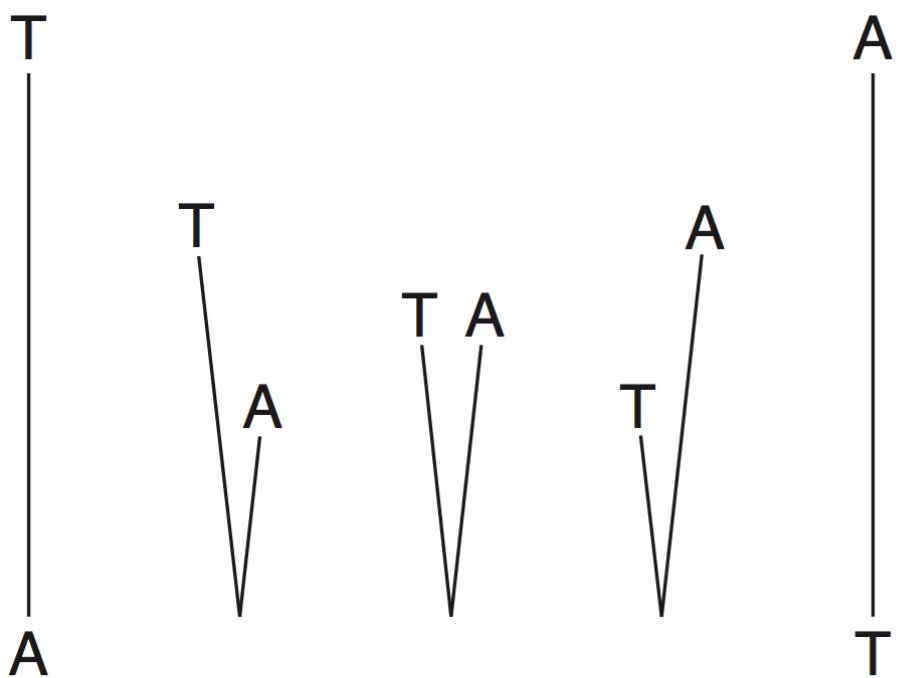

time irreversible: $\mathbf{Q}_1$	0.0166716	0.0172425	0.0175681	0.0179176	0.0186808
time reversible: $\mathbf{Q}_2$	0.0045155	0.0045155	0.0045155	0.0045155	0.0045155

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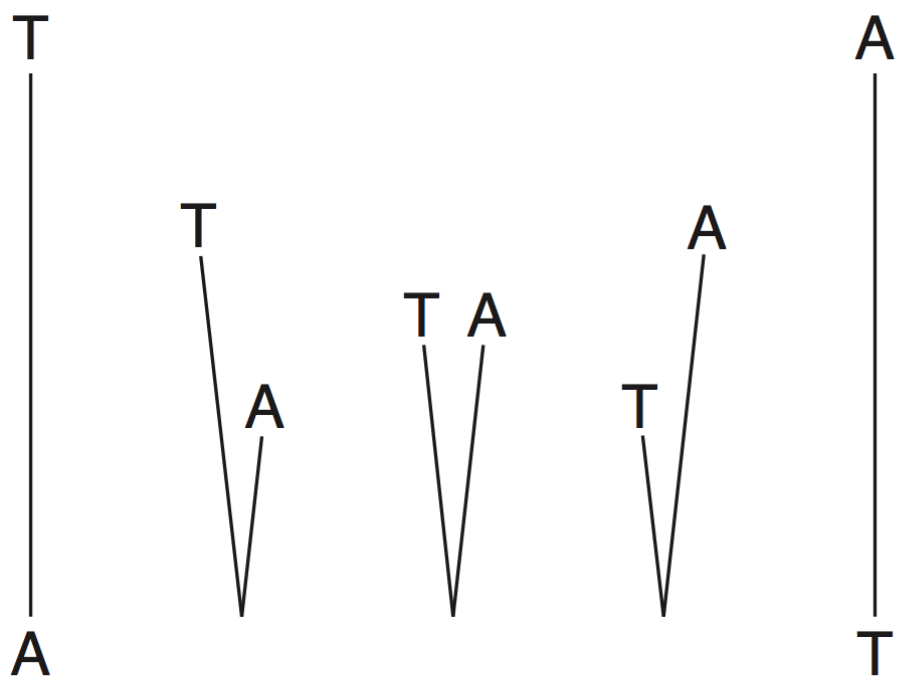

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Time Reversibility

Most continuous-time Markov models assume time reversibility

The probability of a sequence of states visited forward in time is equal to the series of states visited in the reverse order

$$\pi_j p_{ji}(t) = \pi_i p_{ij}(t)$$

Time-reversible models allow an unrooted tree to be rooted anywhere without changing the probability of the data

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This allows us to perform inference under unrooted trees, which simplifies the space of trees that we have to evaluate, and the algorithms used to compute the likelihood

(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)

Outline

I. A brief review of Continuous-Time Markov models

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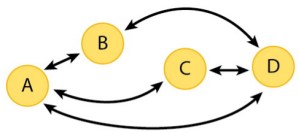
Recall that the average rate of substitution is scaled to be one: $\mu = -\sum_i \pi_i q_{ii}$

Stochastic Models of Nucleotide Substitution

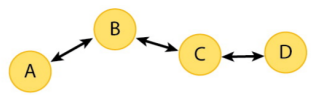
A phylogeographic intuition on relative rates and stationary frequencies

a



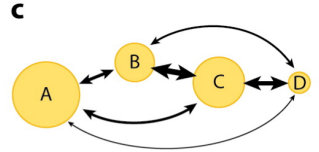
	[A]	[B]	[C]	[D]
[A]	—	μ	μ	μ
[B]	μ	—	μ	μ
[C]	μ	μ	—	μ
[D]	μ	μ	μ	—

b



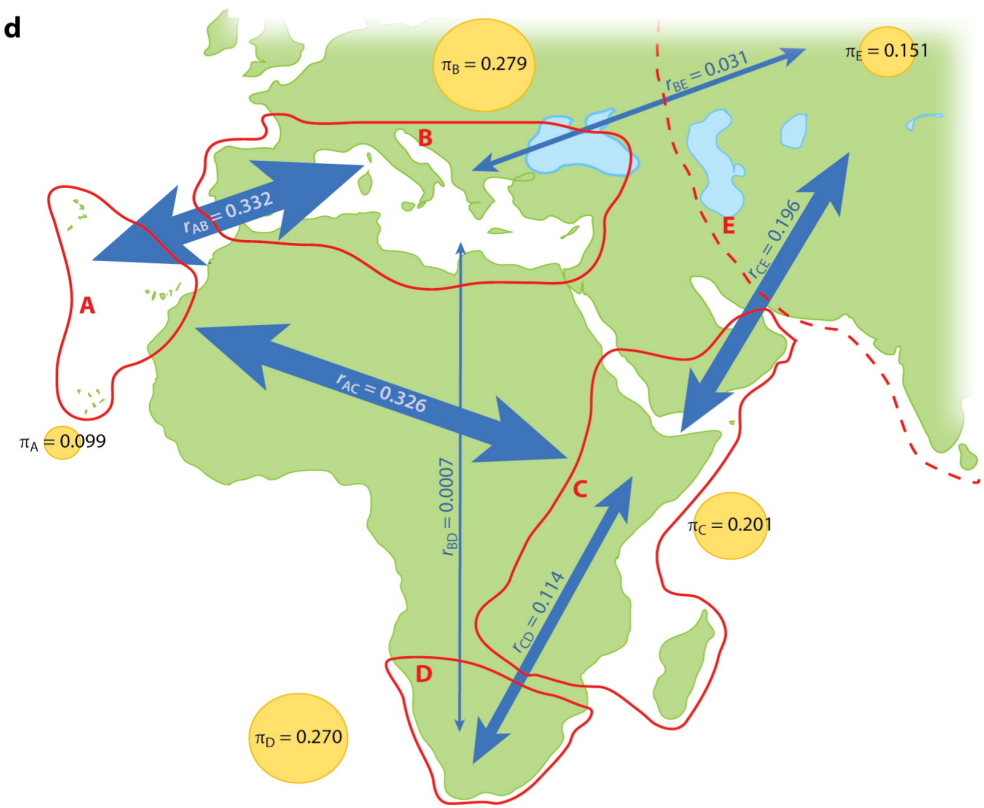
	[A]	[B]	[C]	[D]
[A]	—	μ	0	0
[B]	μ	—	μ	0
[C]	0	μ	—	μ
[D]	0	0	μ	—

c



	[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]	$\pi_A r_{AD}$	$\pi_B r_{BD}$	$\pi_C r_{CD}$	—

d



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

Ronquist F, Sanmartín I. 2011.
Annu. Rev. Ecol. Evol. Syst. 42:441–64

Stochastic Models of Nucleotide Substitution

The Jukes and Cantor, 1969 (JC69) substitution model

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

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Stochastic Models of Nucleotide Substitution

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$$\mathbf{Q} = q_{ij} = \begin{pmatrix} - & \mu\pi_C & \mu\pi_G & \mu\pi_T \\ \mu\pi_A & - & \mu\pi_G & \mu\pi_T \\ \mu\pi_A & \mu\pi_C & - & \mu\pi_T \\ \mu\pi_A & \mu\pi_C & \mu\pi_G & - \end{pmatrix}$$

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

The stationary frequencies of each state are assumed to be equal, therefore: $\pi_A = \pi_C = \pi_G = \pi_T = 1/4$

Stochastic Models of Nucleotide Substitution

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A free parameter is a parameter that is free to vary (it is estimated from the data)

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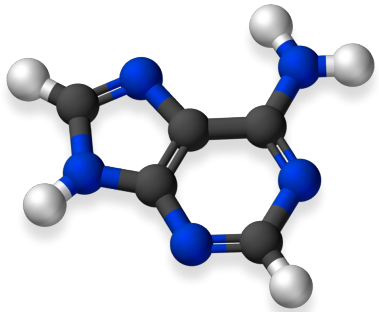
Stochastic Models of Nucleotide Substitution

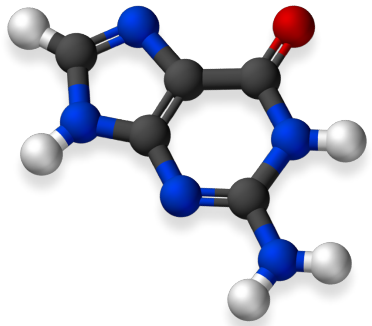
Biology motivates the extension of models

DNA

Purines

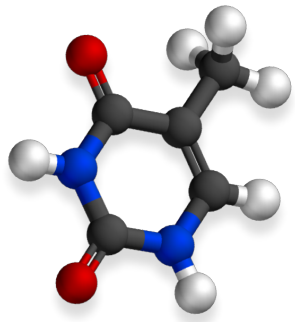


Adenine



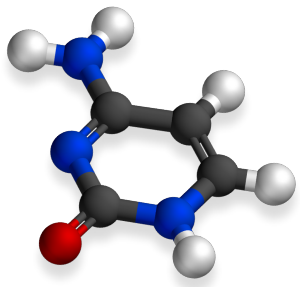
Guanine

Pyrimidines



Thymine

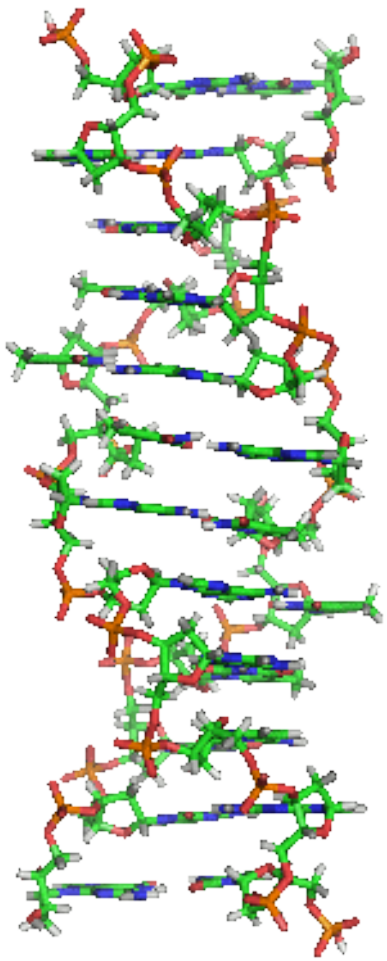
Cytosine



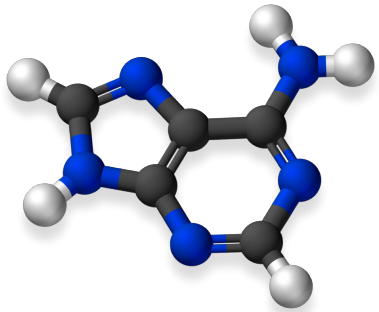
Stochastic Models of Nucleotide Substitution

Biology motivates the extension of models

DNA

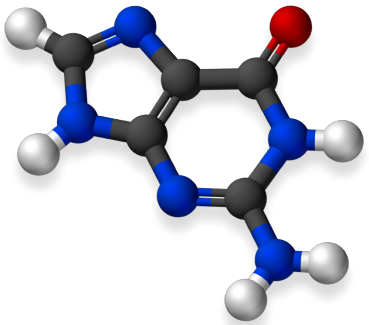


Purines

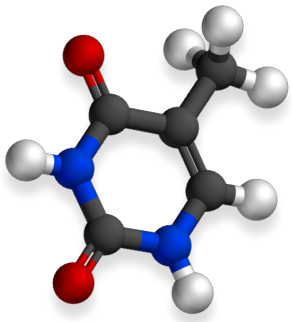


Adenine

Guanine

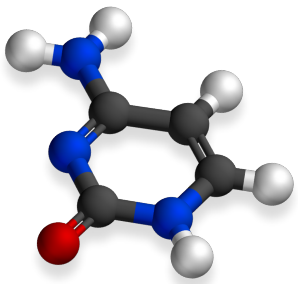


Pyrimidines



Thymine

Cytosine

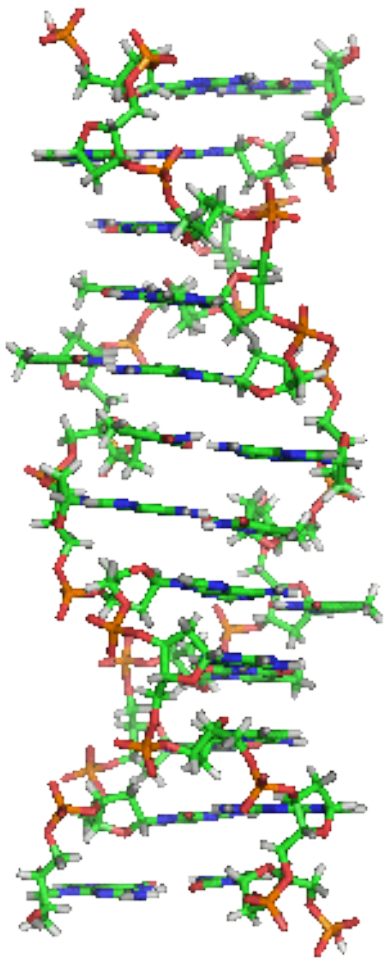


transition
substitutions

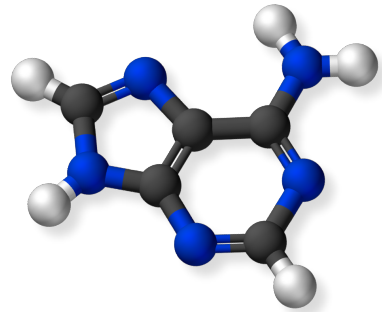
Stochastic Models of Nucleotide Substitution

Biology motivates the extension of models

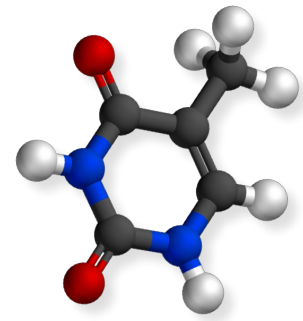
DNA



Purines



Pyrimidines

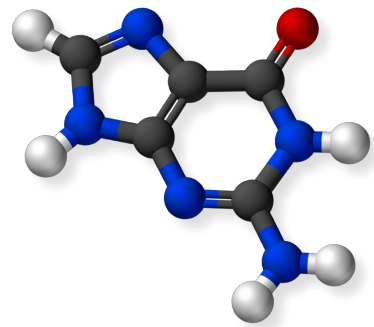


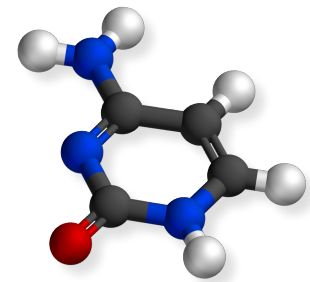
Adenine

Thymine

Guanine

Cytosine





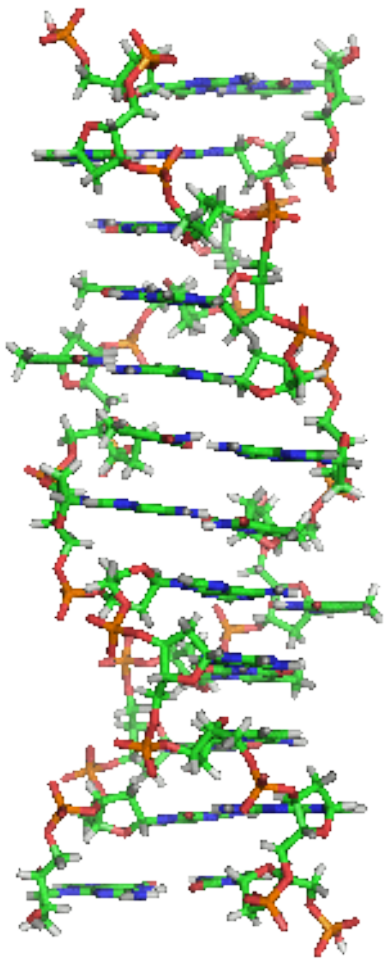
transversion
substitutions

Stochastic Models of Nucleotide Substitution

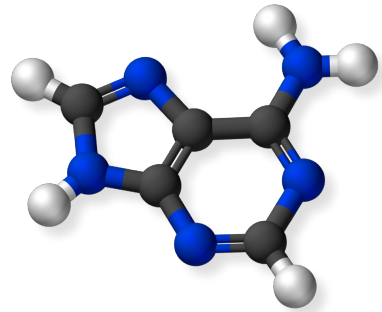
Biology motivates the extension of models

The molecular structure makes transitions more probable than transversions

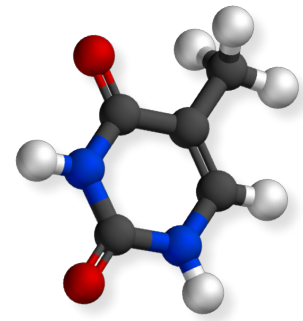
DNA

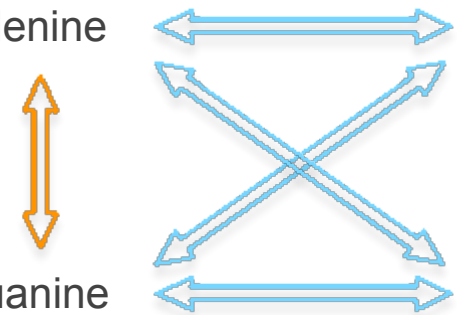


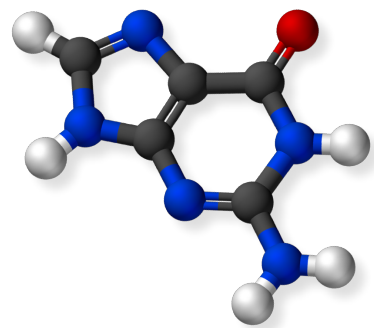
Purines

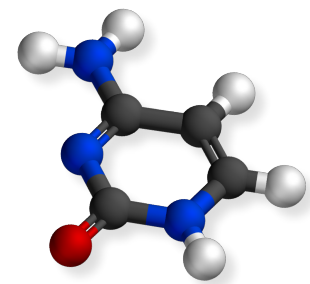


Pyrimidines









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

Purine Pyrimidine

A **T**

G **C**

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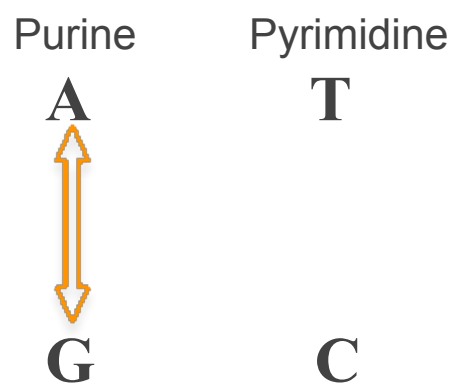
$$b = r_{AG}$$



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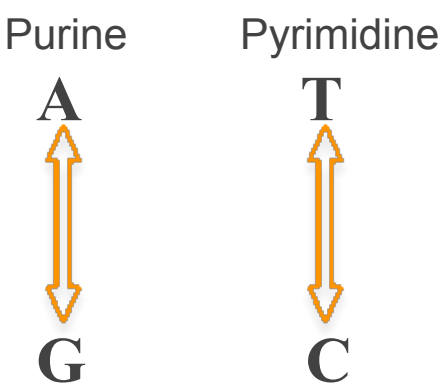
$$b = r_{AG}$$

$$e = r_{CT}$$



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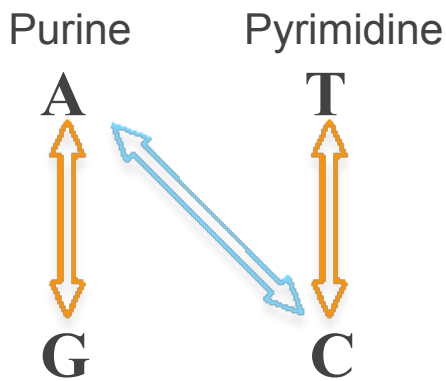
The stationary frequencies of all states are still assumed to be equal

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

$$b = r_{AG}$$
$$e = r_{CT}$$
$$a = r_{AC}$$



Stochastic Models of Nucleotide Substitution

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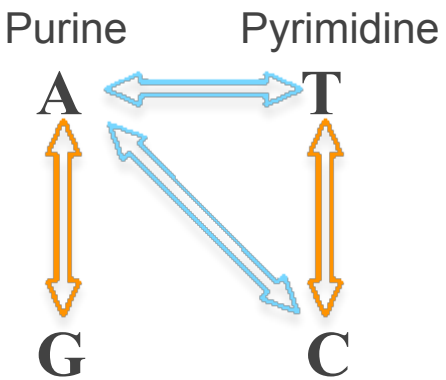
$$b = r_{AG}$$
$$e = r_{CT}$$
$$a = r_{AC}$$
$$c = r_{AT}$$



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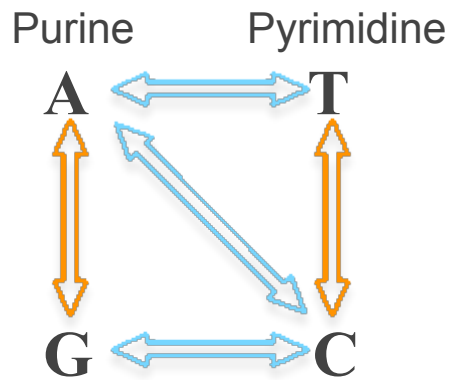
$$a = r_{AC}$$
$$c = r_{AT}$$
$$d = r_{CG}$$



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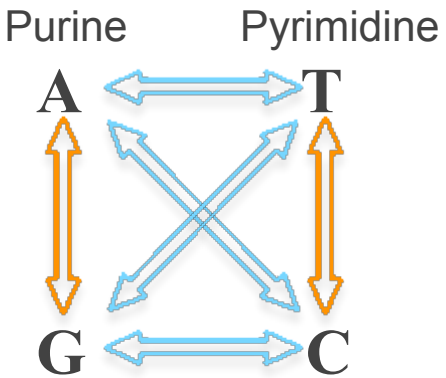
The relative rates accommodate possible bias in the instantaneous rates of transition and transversion substitutions

$$b = r_{AG}$$
$$e = r_{CT}$$
$$a = r_{AC}$$
$$c = r_{AT}$$
$$d = r_{CG}$$
$$f = r_{GT}$$



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

Under this model, all transition substitutions are assumed to have the same rate ($b = e$) and all transversion substitutions are assumed to have the same rate ($a = c = d = f$)

Stochastic Models of Nucleotide Substitution

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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

Under this model, all transition substitutions are assumed to have the same rate ($b = e$) and all transversion substitutions are assumed to have the same rate ($a = c = d = f$) BUT we allow for a possible bias in the relative rate of transitions and transversions by introducing a new parameter, κ:

$$\kappa = \frac{r_{\text{transition}}}{r_{\text{transversion}}}$$

Stochastic Models of Nucleotide Substitution

The Kimura, 1980 (K80) substitution model

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

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

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

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How many free parameters are there in the K80 substitution model?

Stochastic Models of Nucleotide Substitution

Biology motivates the extension of models

$\mathbf{A} = 49{,}708 \div 151{,}015 = 32.9\%$ $\mathbf{G} = 25{,}162 \div 151{,}015 = 16.7\%$ $\mathbf{A} \neq \mathbf{C} \neq \mathbf{G} \neq \mathbf{T} \neq 0.25$

$\mathbf{C} = 41{,}073 \div 151{,}015 = 27.2\%$ $\mathbf{T} = 34{,}972 \div 151{,}015 = 23.2\%$

Stochastic Models of Nucleotide Substitution

The Felsenstein, 1981 (F81) substitution model

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

Like the JC69 model, all relative rates are assumed to be equal, therefore: $a = b = c = d = e = f$

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How many free parameters are there in the F81 substitution model?

Stochastic Models of Nucleotide Substitution

The Hasegawa, Kishino, Yano, 1985 (HKY85) substitution model

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

Combines features of the K80 and F81 substitution models

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Like the K80 model, all transitions are assumed to have the same rate ($b = e$)
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and accommodates a possible bias in the transition/transversion rate ratio, κ

Stochastic Models of Nucleotide Substitution

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How many free parameters are there in the HKY85 substitution model?

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Stochastic Models of Nucleotide Substitution

The General Time Reversible (GTR) substitution model

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

Allows all six relative substitution rates $(a - f)$ to vary

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Stochastic Models of Nucleotide Substitution

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

Stochastic Models of Nucleotide Substitution

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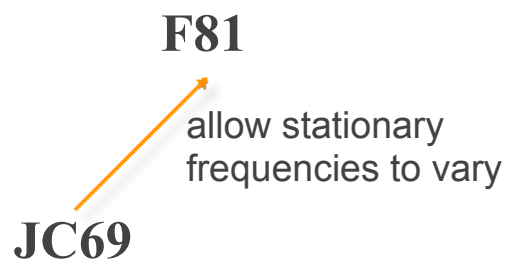

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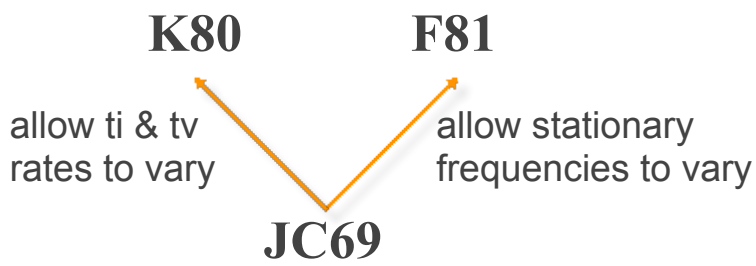

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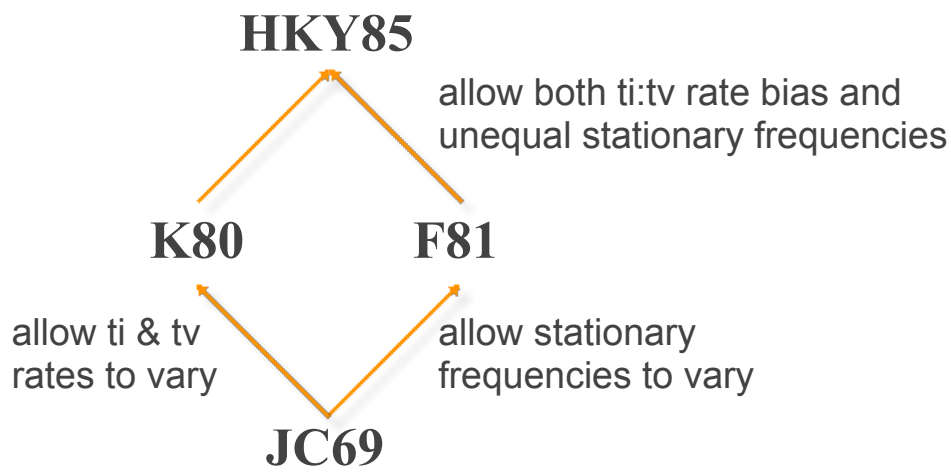

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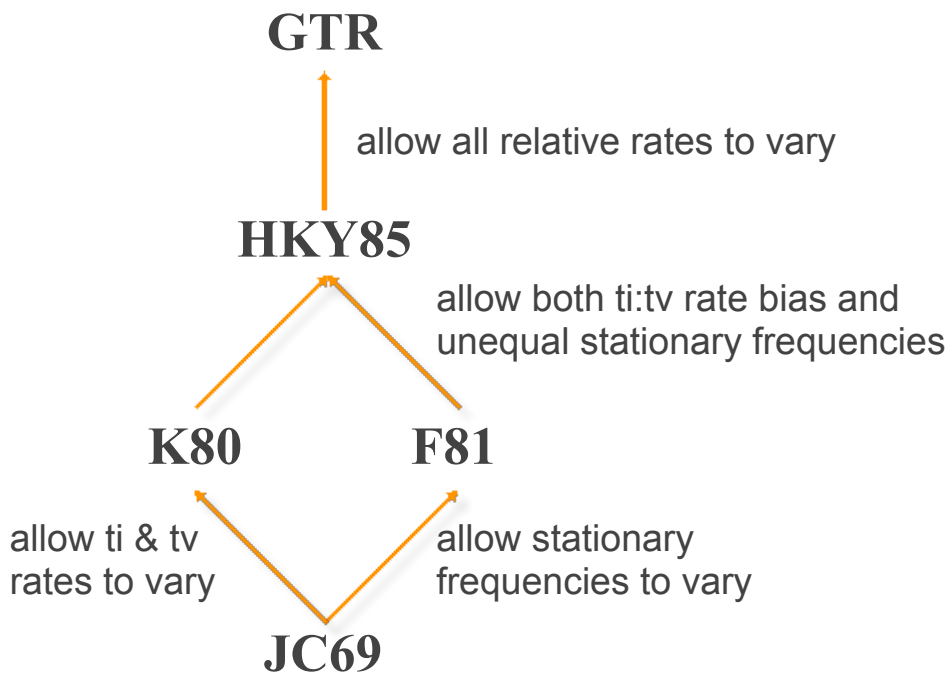

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Stochastic Models of Nucleotide Substitution

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GTR

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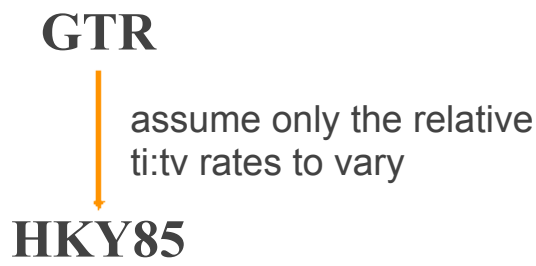

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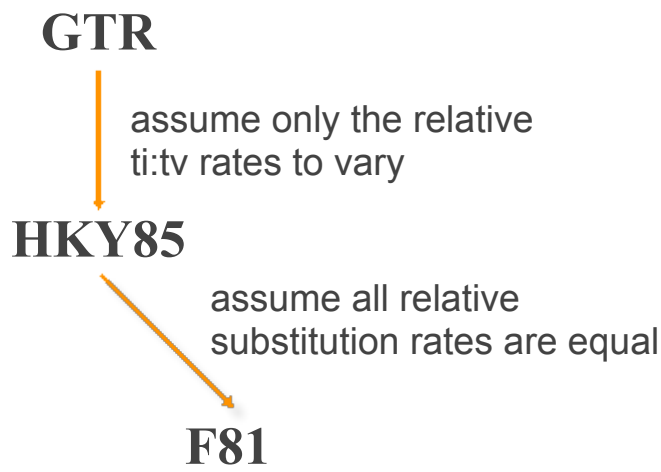

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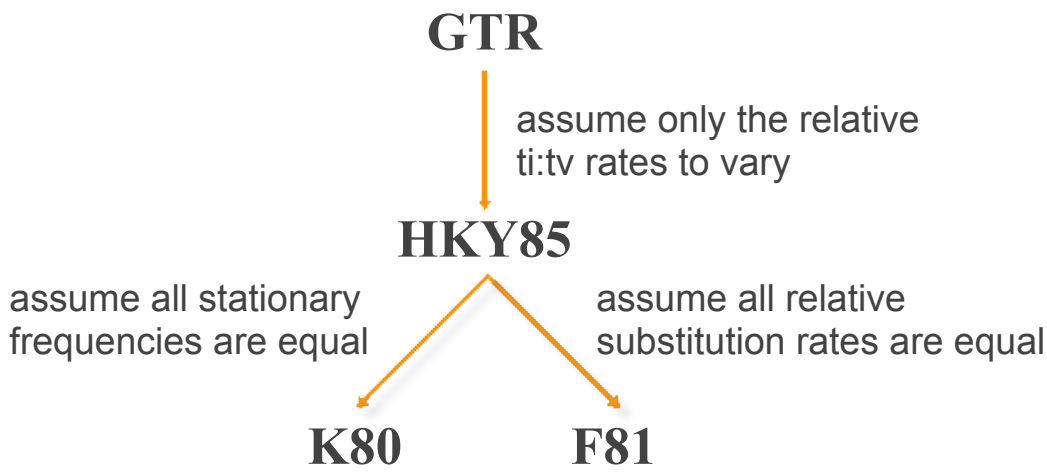

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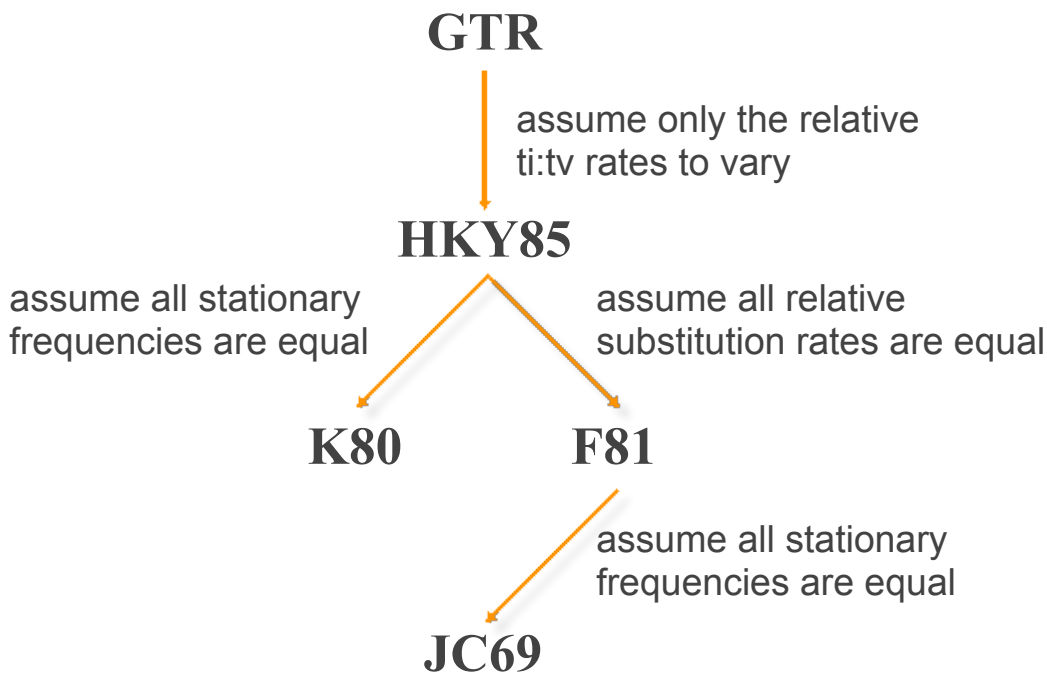

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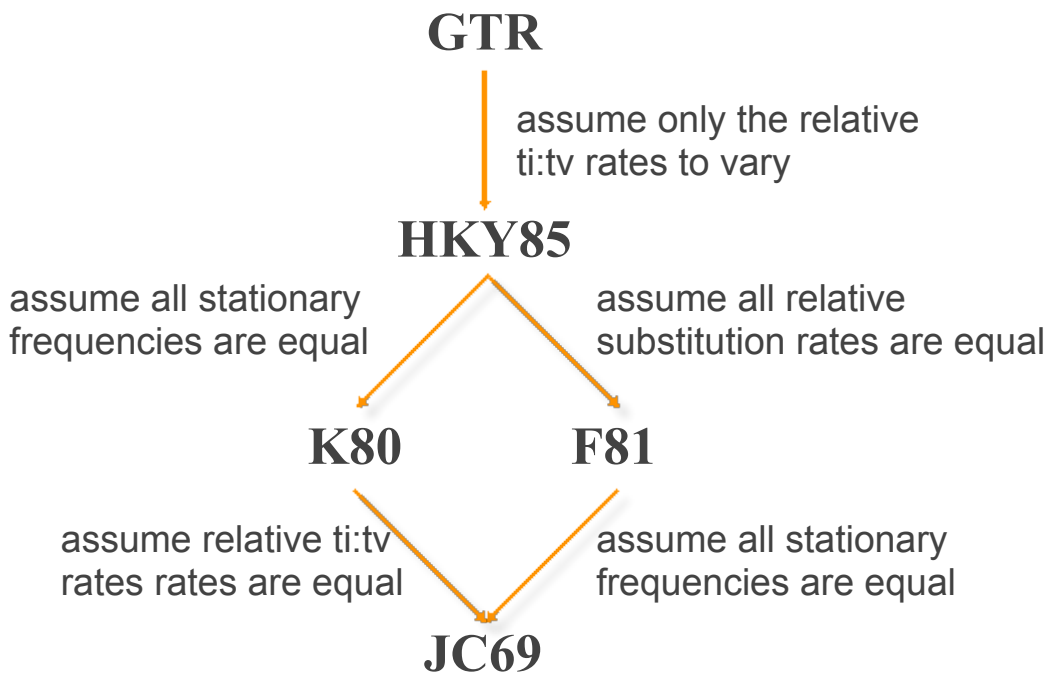

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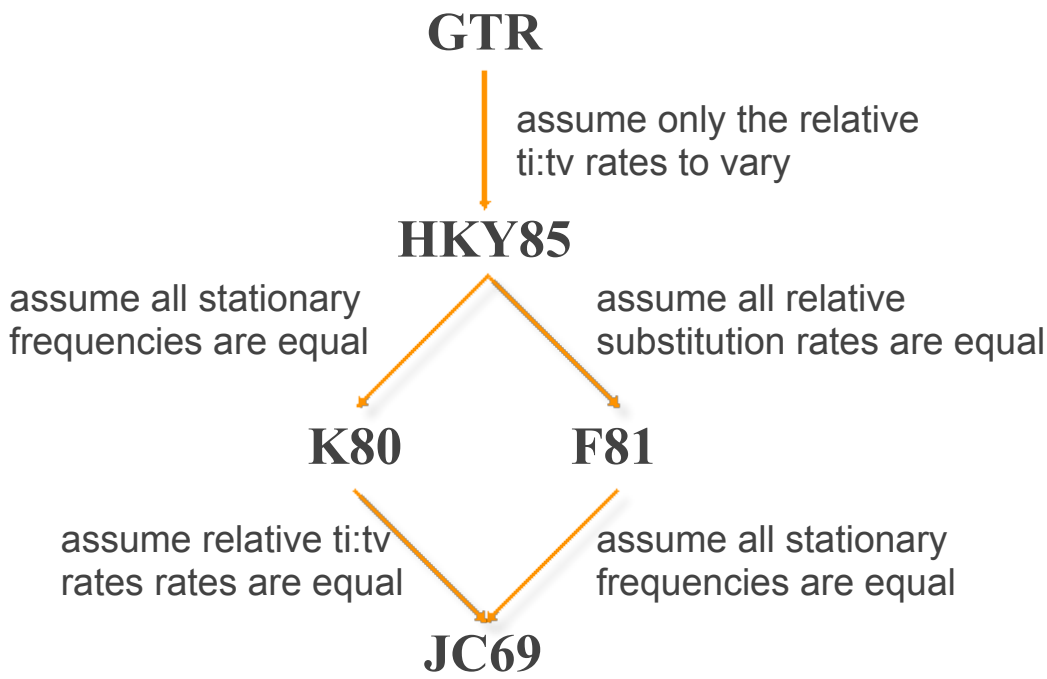

We can move from a more general model to a simpler model by imposing a constraint

The differences between models allow us to test hypotheses (to learn) about our data

Stochastic Models of Nucleotide Substitution

How many members of the GTR model family are there?

K	Models				
1	$M_1 = 111111$				
2	$M_2 = 122222$	$M_3 = 121111$	$M_4 = 112111$	$M_5 = 111211$	$M_6 = 111121$
	$M_7 = 111112$	$M_8 = 112222$	$M_9 = 121222$	$M_{10} = 122122$	$M_{11} = 122212$
	$M_{12} = 122221$	$M_{13} = 122111$	$M_{14} = 121211$	$M_{15} = 121121$	$M_{16} = 121112$
	$M_{17} = 112211$	$M_{18} = 112121$	$M_{19} = 112112$	$M_{20} = 111221$	$M_{21} = 111212$
	$M_{22} = 111122$	$M_{23} = 111222$	$M_{24} = 112122$	$M_{25} = 112212$	$M_{26} = 112221$
	$M_{27} = 121122$	$M_{28} = 121212$	$M_{29} = 121221$	$M_{30} = 122112$	$M_{31} = 122121$
	$M_{32} = 122211$				
3	$M_{33} = 123333$	$M_{34} = 123222$	$M_{35} = 122322$	$M_{36} = 122232$	$M_{37} = 122223$
	$M_{38} = 123111$	$M_{39} = 121311$	$M_{40} = 121131$	$M_{41} = 121113$	$M_{42} = 112311$
	$M_{43} = 112131$	$M_{44} = 112113$	$M_{45} = 111231$	$M_{46} = 111213$	$M_{47} = 111123$
	$M_{48} = 122333$	$M_{49} = 123233$	$M_{50} = 123323$	$M_{51} = 123332$	$M_{52} = 123322$
	$M_{53} = 123232$	$M_{54} = 123223$	$M_{55} = 122332$	$M_{56} = 122323$	$M_{57} = 122233$
	$M_{58} = 121333$	$M_{59} = 123133$	$M_{60} = 123313$	$M_{61} = 123331$	$M_{62} = 112333$
	$M_{63} = 112322$	$M_{64} = 112232$	$M_{65} = 112223$	$M_{66} = 123122$	$M_{67} = 123212$
	$M_{68} = 123221$	$M_{69} = 121322$	$M_{70} = 121232$	$M_{71} = 121223$	$M_{72} = 122312$
	$M_{73} = 122321$	$M_{74} = 122132$	$M_{75} = 122123$	$M_{76} = 122231$	$M_{77} = 122213$
	$M_{78} = 123311$	$M_{79} = 123131$	$M_{80} = 123113$	$M_{81} = 121331$	$M_{82} = 121313$
	$M_{83} = 121133$	$M_{84} = 123211$	$M_{85} = 123121$	$M_{86} = 123112$	$M_{87} = 122311$
	$M_{88} = 122131$	$M_{89} = 122113$	$M_{90} = 121321$	$M_{91} = 121312$	$M_{92} = 121231$
	$M_{93} = 121213$	$M_{94} = 121132$	$M_{95} = 121123$	$M_{96} = 112331$	$M_{97} = 112313$
	$M_{98} = 112133$	$M_{99} = 112321$	$M_{100} = 112312$	$M_{101} = 112231$	$M_{102} = 112213$
	$M_{103} = 112132$	$M_{104} = 112123$	$M_{105} = 111233$	$M_{106} = 111232$	$M_{107} = 111223$
	$M_{108} = 112233$	$M_{109} = 112323$	$M_{110} = 112332$	$M_{111} = 121233$	$M_{112} = 121323$
	$M_{113} = 121332$	$M_{114} = 122133$	$M_{115} = 122313$	$M_{116} = 122331$	$M_{117} = 123123$
	$M_{118} = 123132$	$M_{119} = 123213$	$M_{120} = 123231$	$M_{121} = 123312$	$M_{122} = 123321$
4	$M_{123} = 123444$	$M_{124} = 123433$	$M_{125} = 123343$	$M_{126} = 123334$	$M_{127} = 123422$
	$M_{128} = 123242$	$M_{129} = 123224$	$M_{130} = 122342$	$M_{131} = 122324$	$M_{132} = 122234$
	$M_{133} = 123411$	$M_{134} = 123141$	$M_{135} = 123114$	$M_{136} = 121341$	$M_{137} = 121314$
	$M_{138} = 121134$	$M_{139} = 112341$	$M_{140} = 112314$	$M_{141} = 112134$	$M_{142} = 111234$
	$M_{143} = 123344$	$M_{144} = 123434$	$M_{145} = 123443$	$M_{146} = 123244$	$M_{147} = 123424$
	$M_{148} = 123442$	$M_{149} = 122344$	$M_{150} = 122343$	$M_{151} = 122334$	$M_{152} = 123423$
	$M_{153} = 123432$	$M_{154} = 123243$	$M_{155} = 123234$	$M_{156} = 123342$	$M_{157} = 123324$
	$M_{158} = 123144$	$M_{159} = 123414$	$M_{160} = 123441$	$M_{161} = 121344$	$M_{162} = 121343$
	$M_{163} = 121334$	$M_{164} = 123413$	$M_{165} = 123431$	$M_{166} = 123143$	$M_{167} = 123134$
	$M_{168} = 123341$	$M_{169} = 123314$	$M_{170} = 112344$	$M_{171} = 112343$	$M_{172} = 112334$
	$M_{173} = 112342$	$M_{174} = 112324$	$M_{175} = 112234$	$M_{176} = 123412$	$M_{177} = 123421$
	$M_{178} = 123142$	$M_{179} = 123124$	$M_{180} = 123241$	$M_{181} = 123214$	$M_{182} = 121342$
	$M_{183} = 121324$	$M_{184} = 121234$	$M_{185} = 122341$	$M_{186} = 122314$	$M_{187} = 122134$
5	$M_{188} = 123455$	$M_{189} = 123454$	$M_{190} = 123445$	$M_{191} = 123453$	$M_{192} = 123435$
	$M_{193} = 123345$	$M_{194} = 123452$	$M_{195} = 123425$	$M_{196} = 123245$	$M_{197} = 122345$
	$M_{198} = 123451$	$M_{199} = 123415$	$M_{200} = 123145$	$M_{201} = 121345$	$M_{202} = 112345$
6	$M_{203} = 123456$				

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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- If the process were homogeneous along the tree, the sequences would all be similar in their ACGT composition

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 review of Continuous-Time Markov models

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

low-rate site

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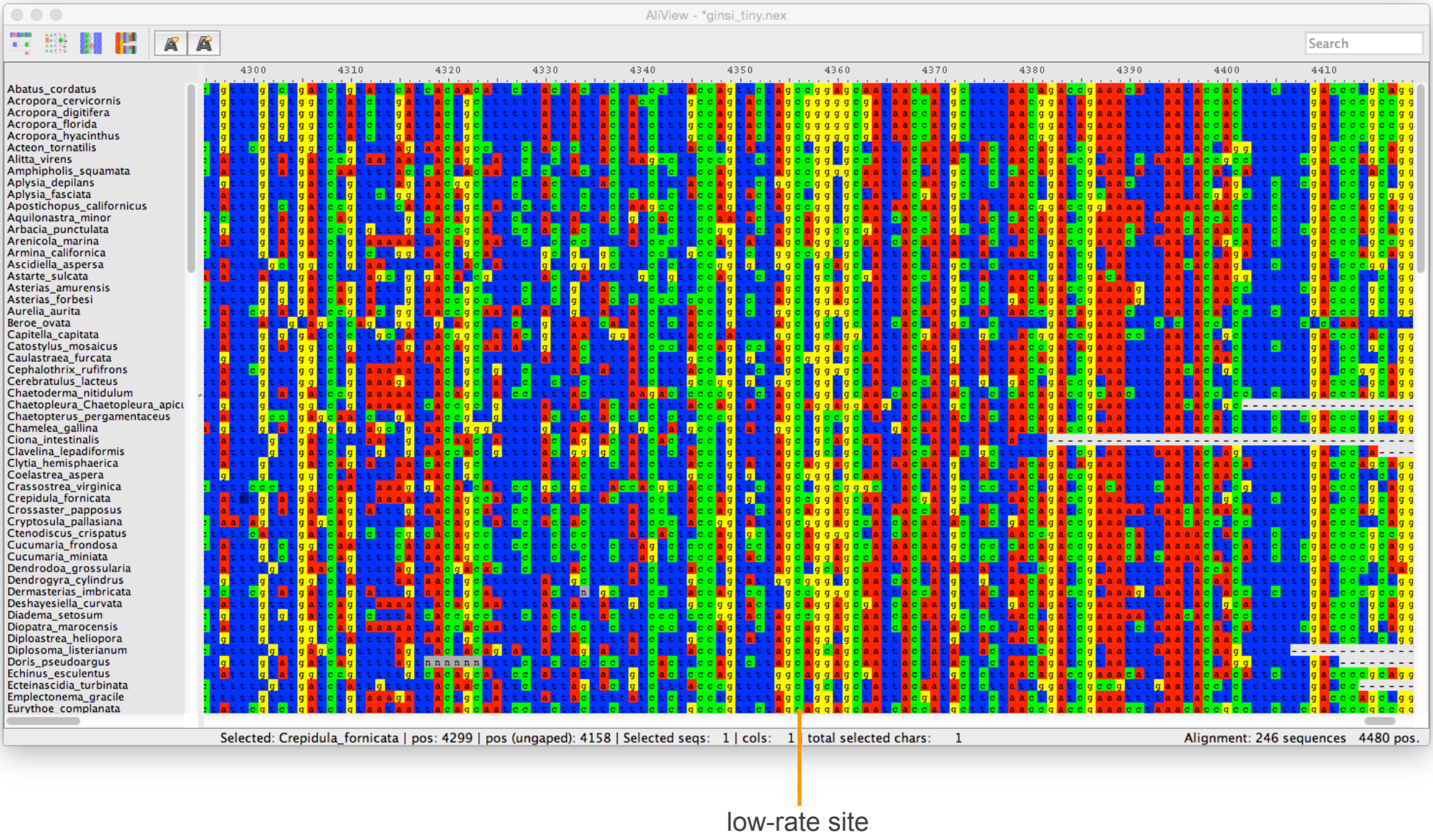

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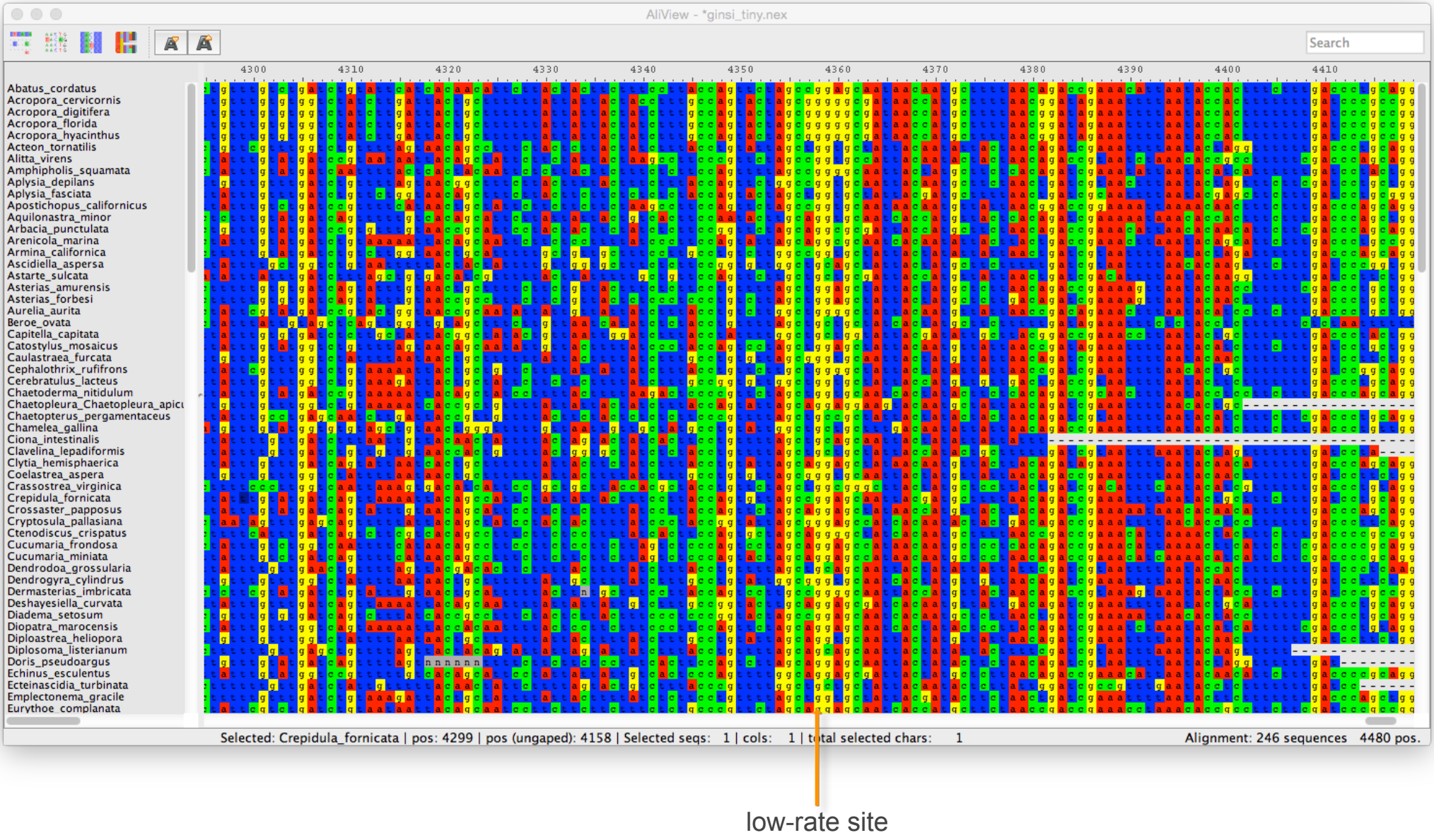

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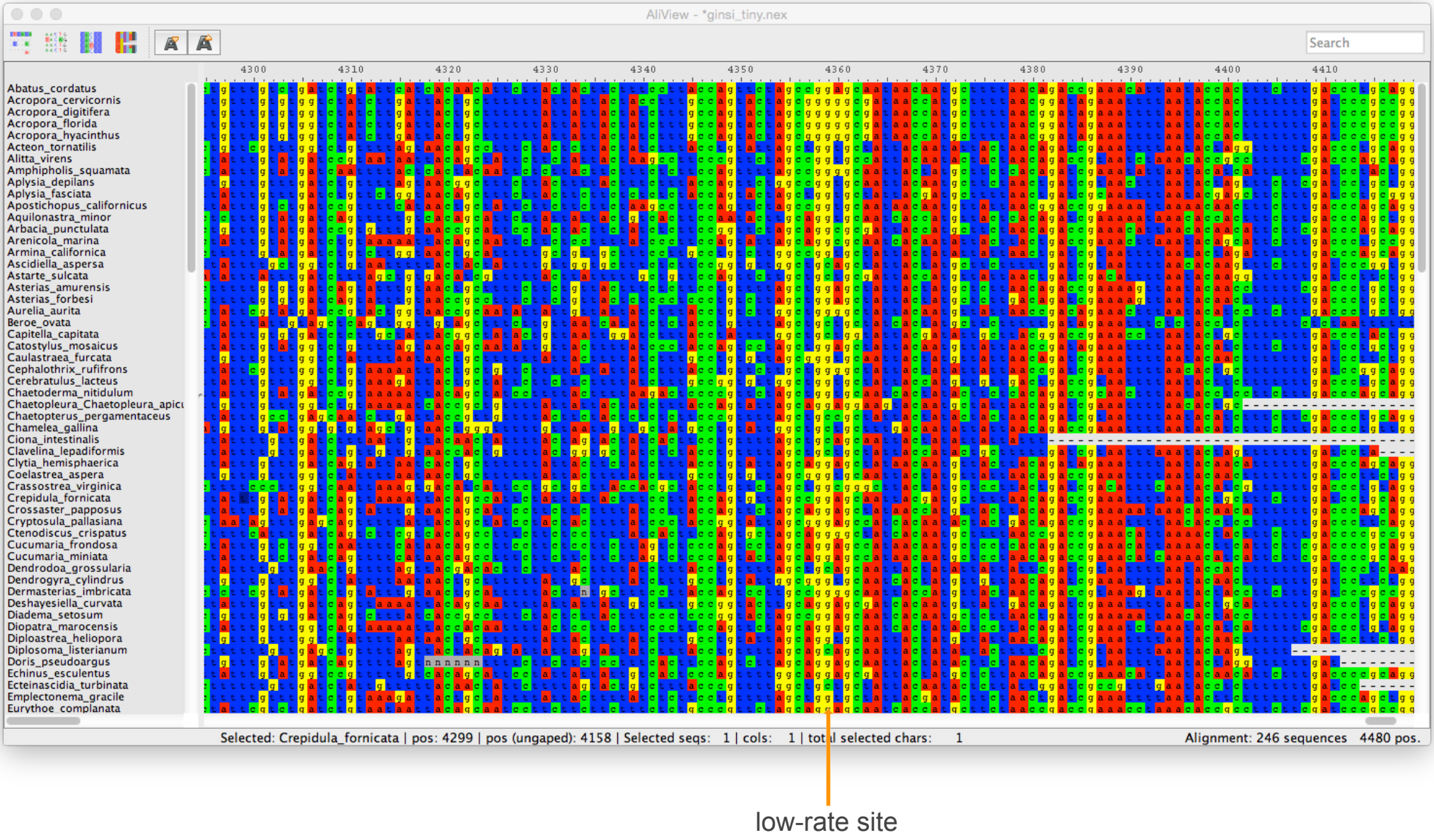

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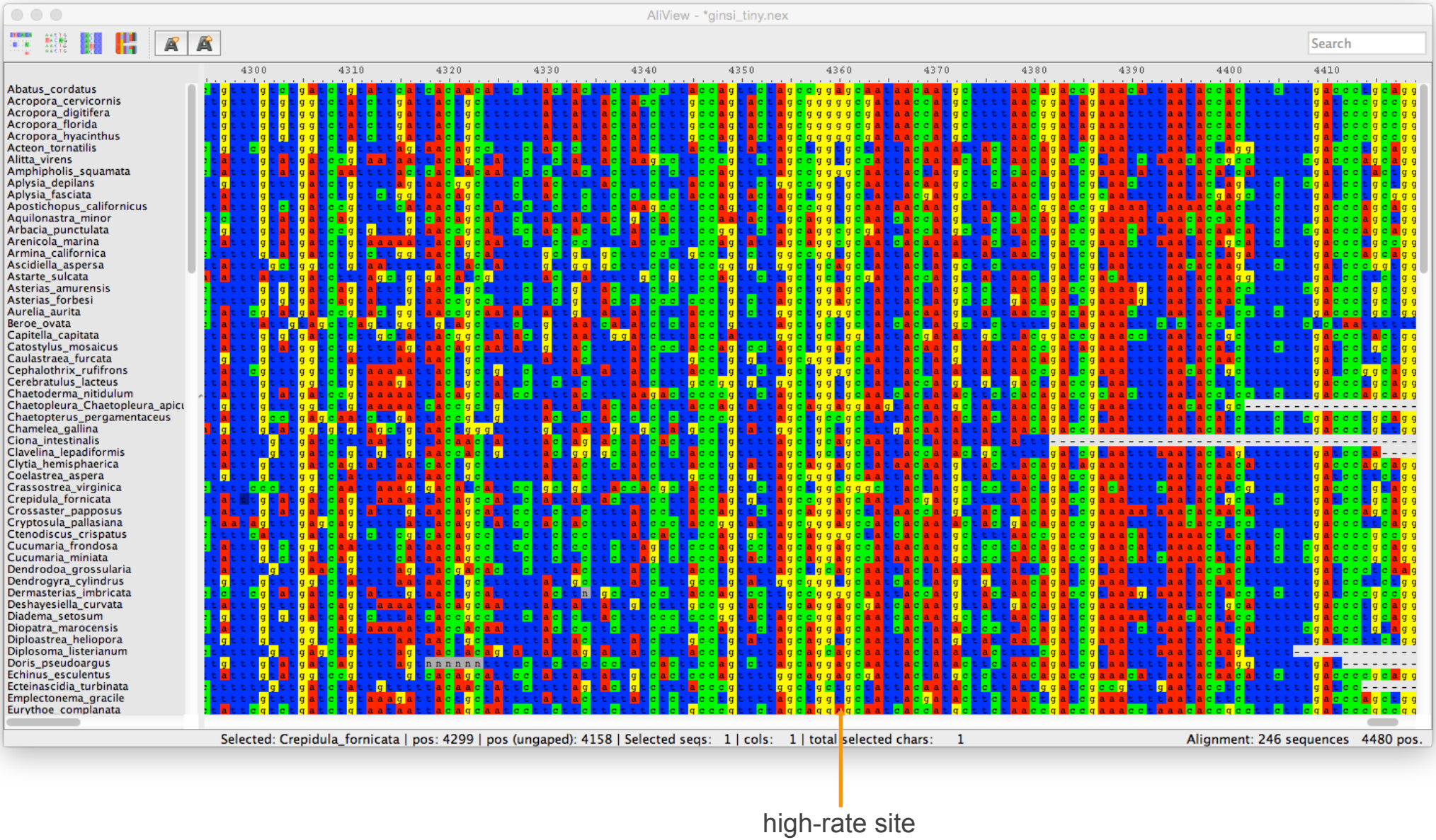

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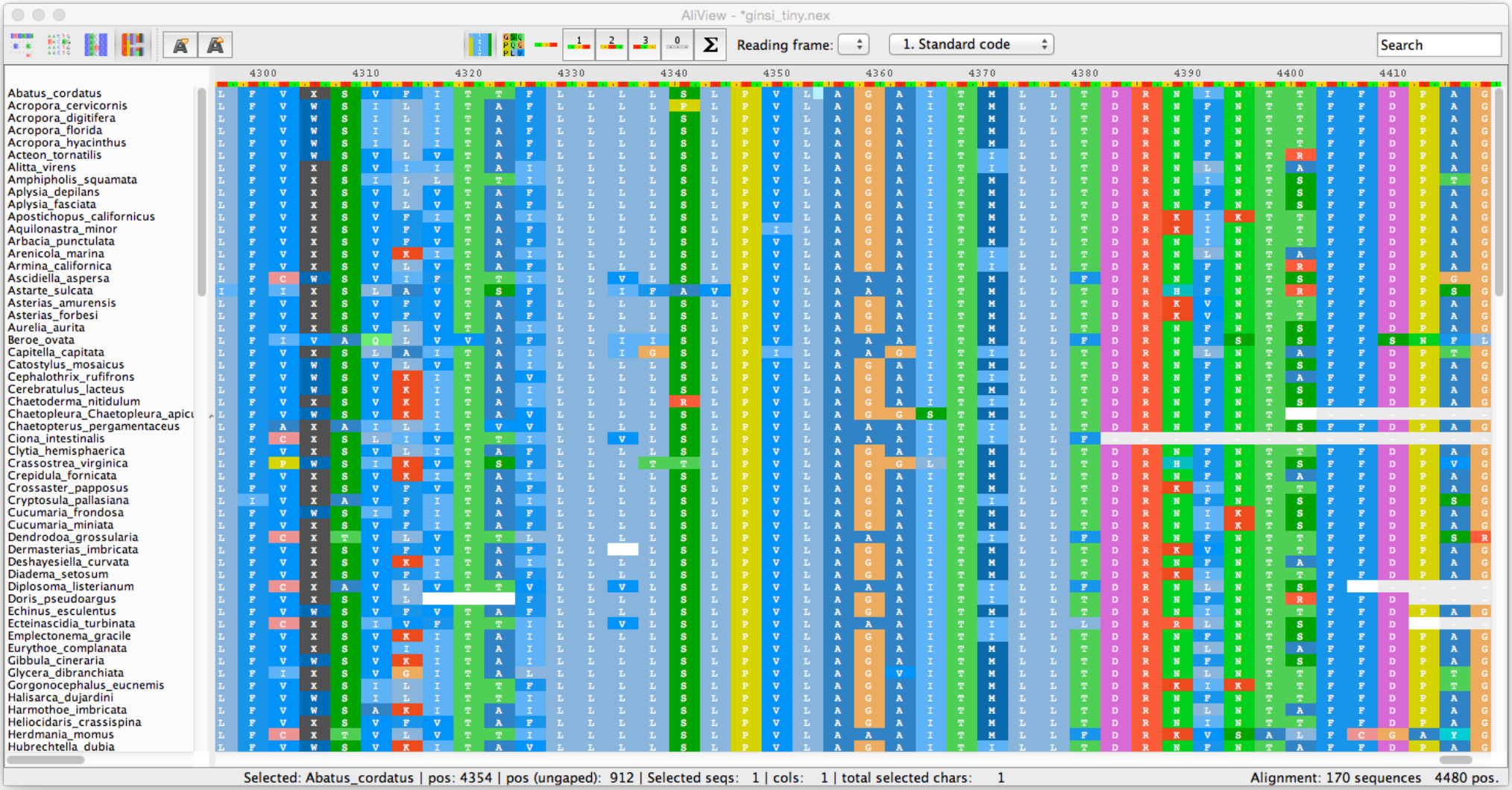

The substitution rates may differ between sites at different codon positions of protein-coding genes

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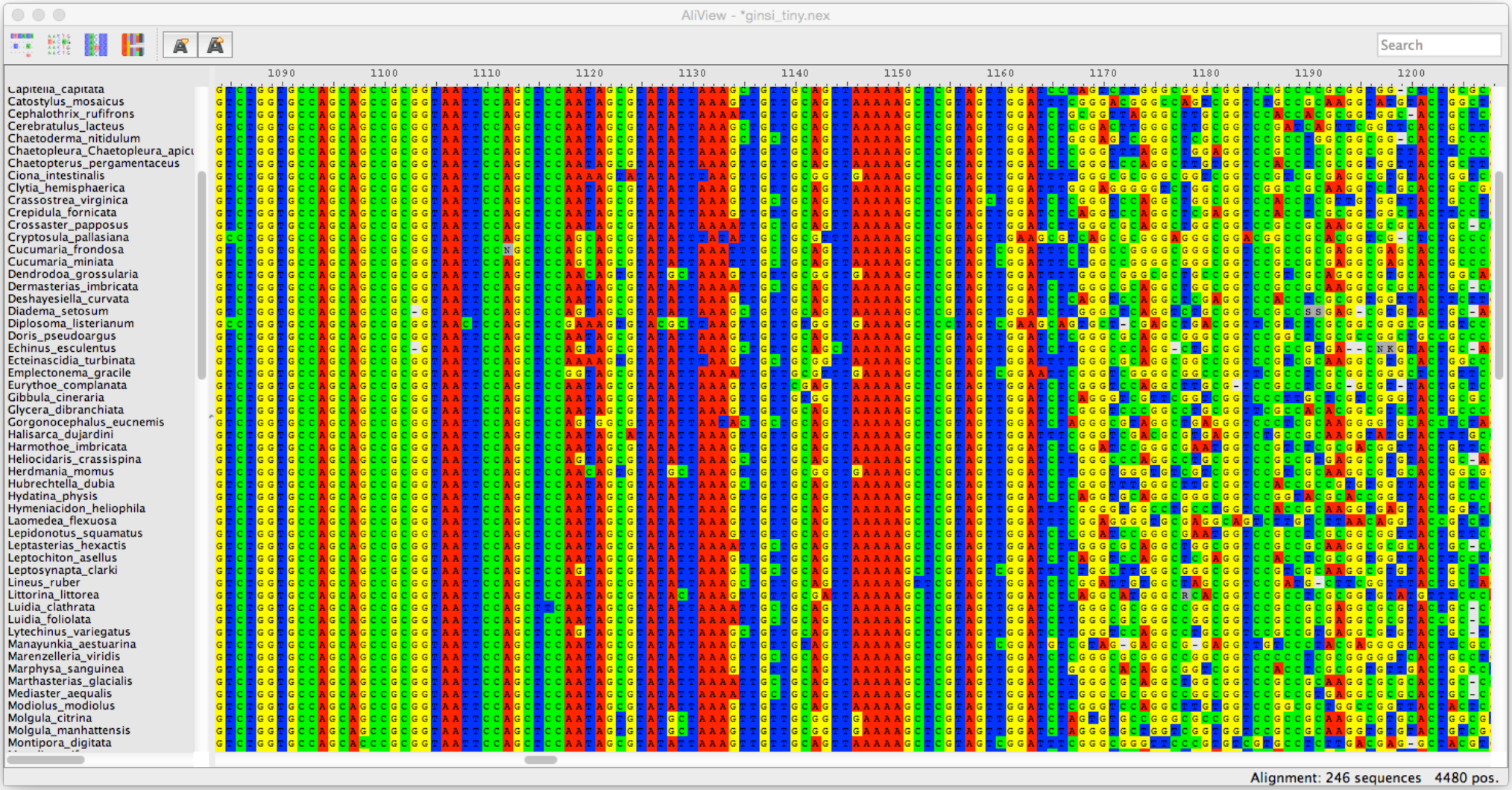

low-rate region

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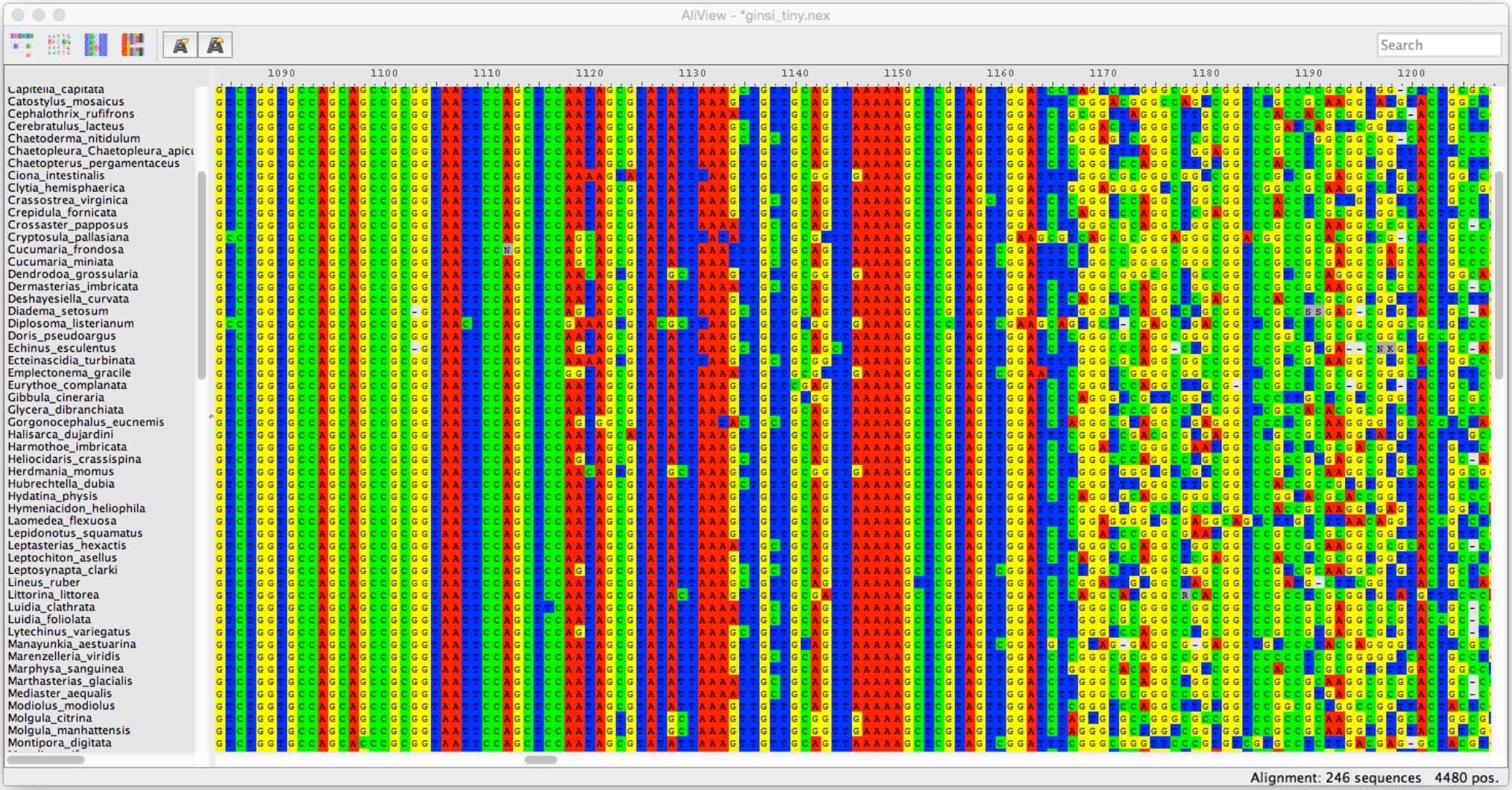

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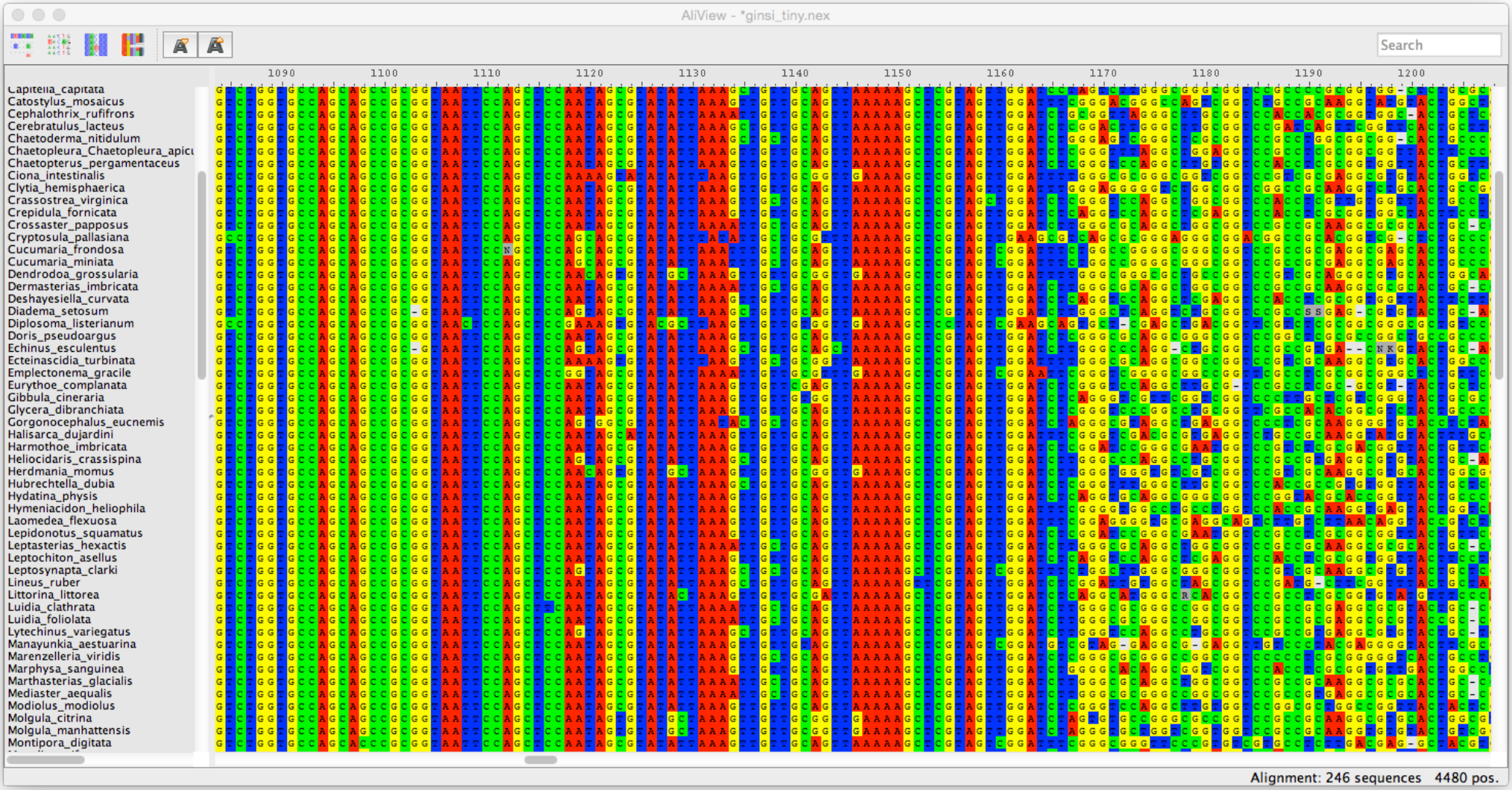

stem region

loop region

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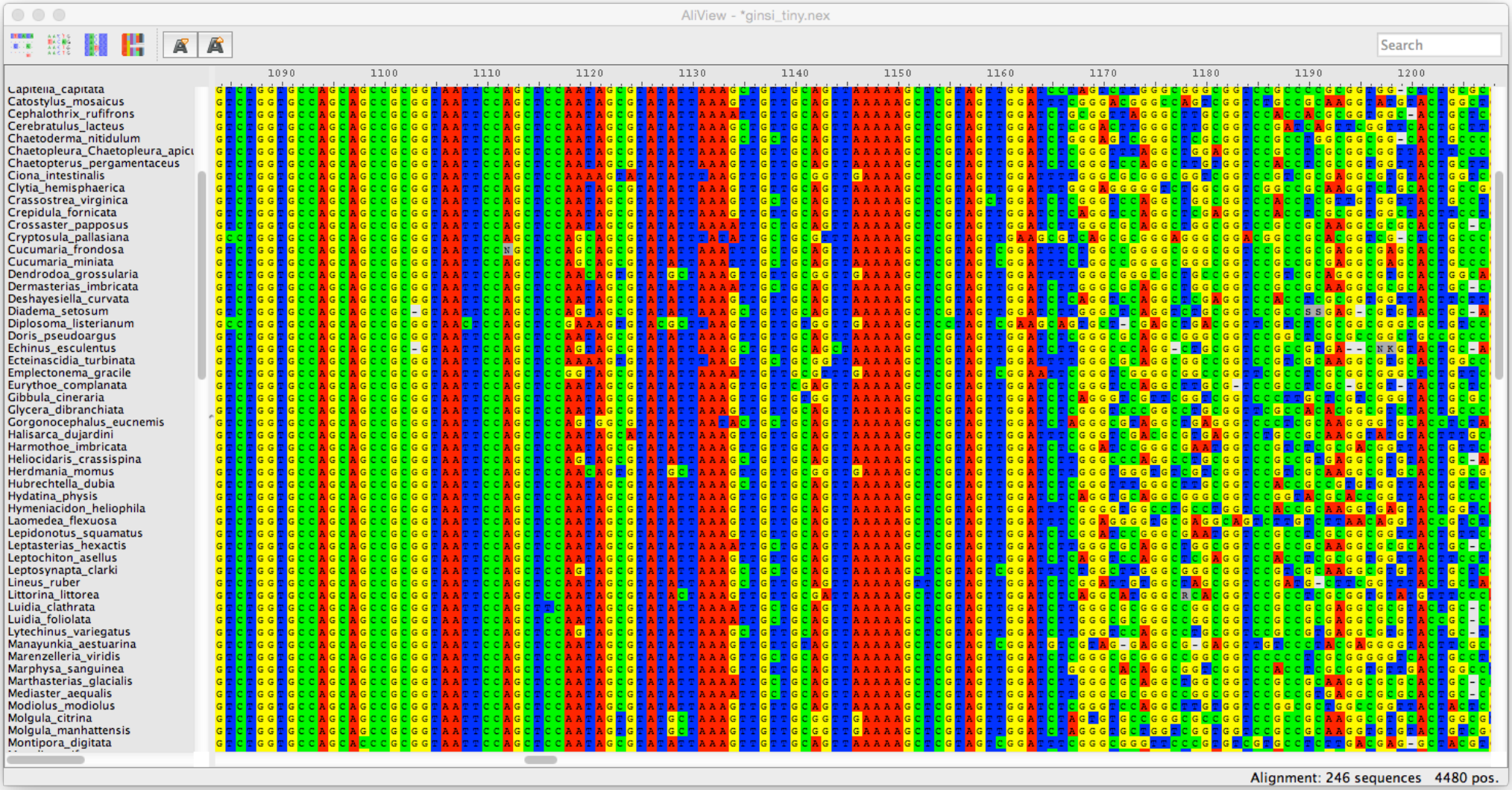

The substitution rates may differ between stem and loop regions of ribosomal RNA genes

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Variation in substitution rates across sites is a prevalent feature of empirical datasets

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Substitution rates may vary across sites because of:

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- biased Gene conversion
- differences in functional constraints

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

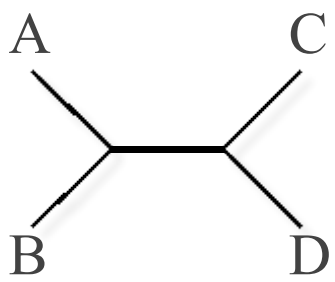
- tree topology
- branch lengths
- other parameters of the substitution model

Accommodating Among Site Rate Variation

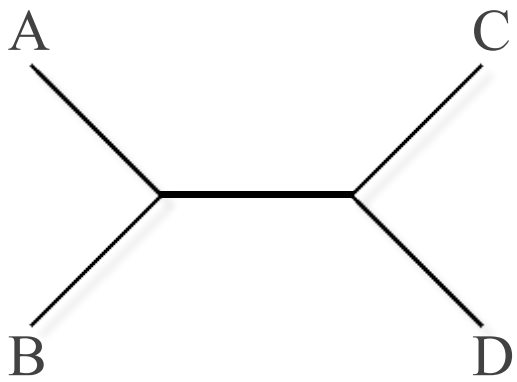
Biology motivates the extension of models

Substitution rates are reflected in the branch lengths of the tree

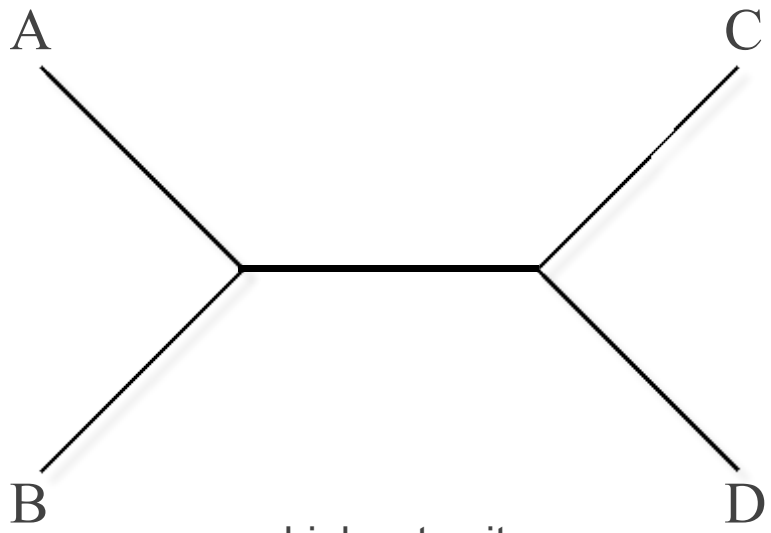
- the relative rate at a site proportionately stretches or compresses the branch lengths



low-rate site



intermediate-rate site



high-rate site

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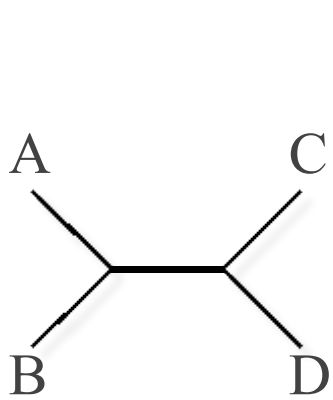

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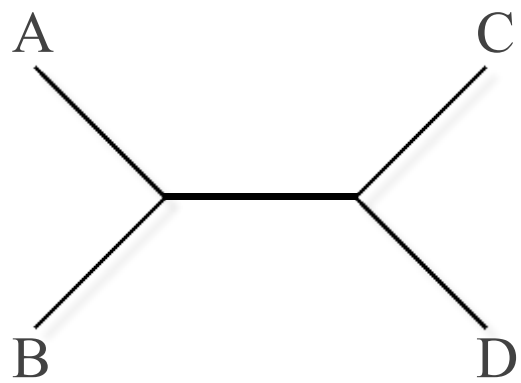

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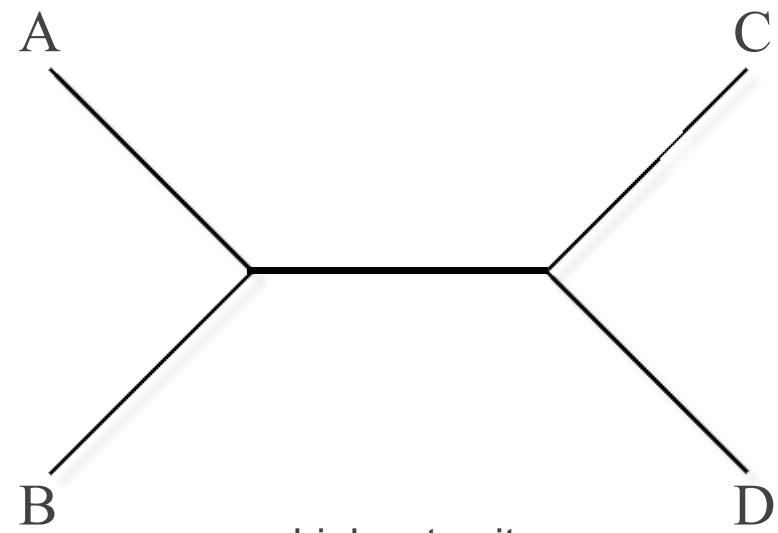

high-rate site

We can accommodate ASRV by incorporating relative substitution-rate multipliers

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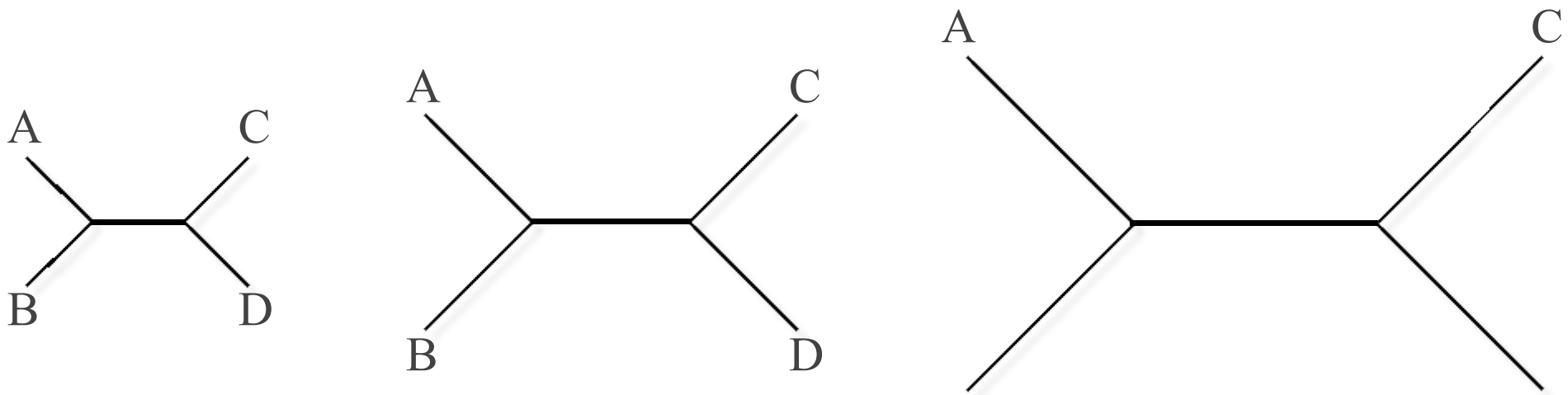

low-rate site intermediate-rate site high-rate site

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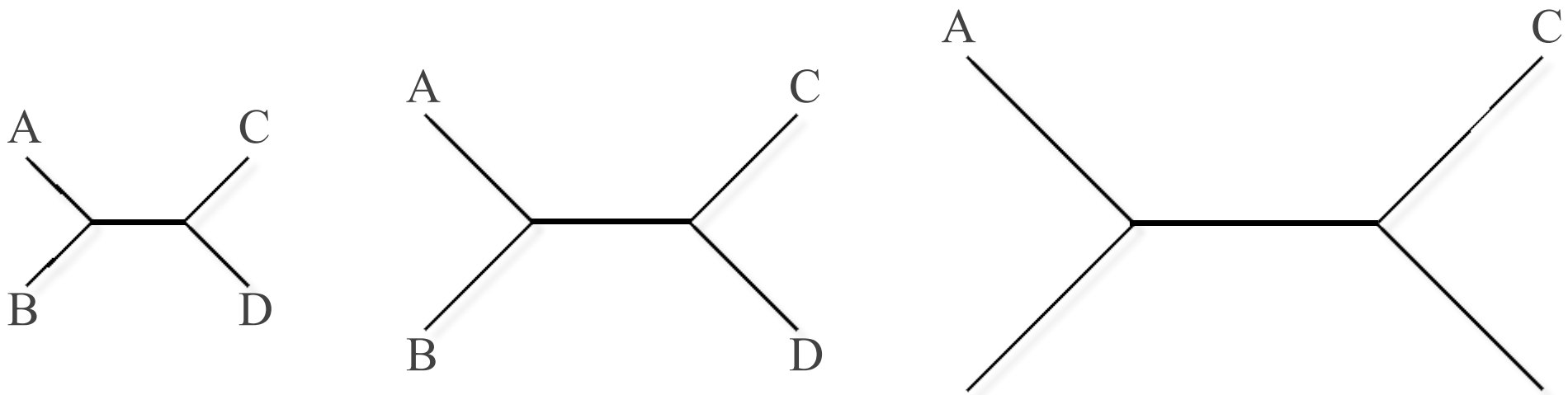

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- the relative-rate multipliers are constrained to have a mean rate of one
- the relative rate of a site can be assigned deterministically or treated as a random variable

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

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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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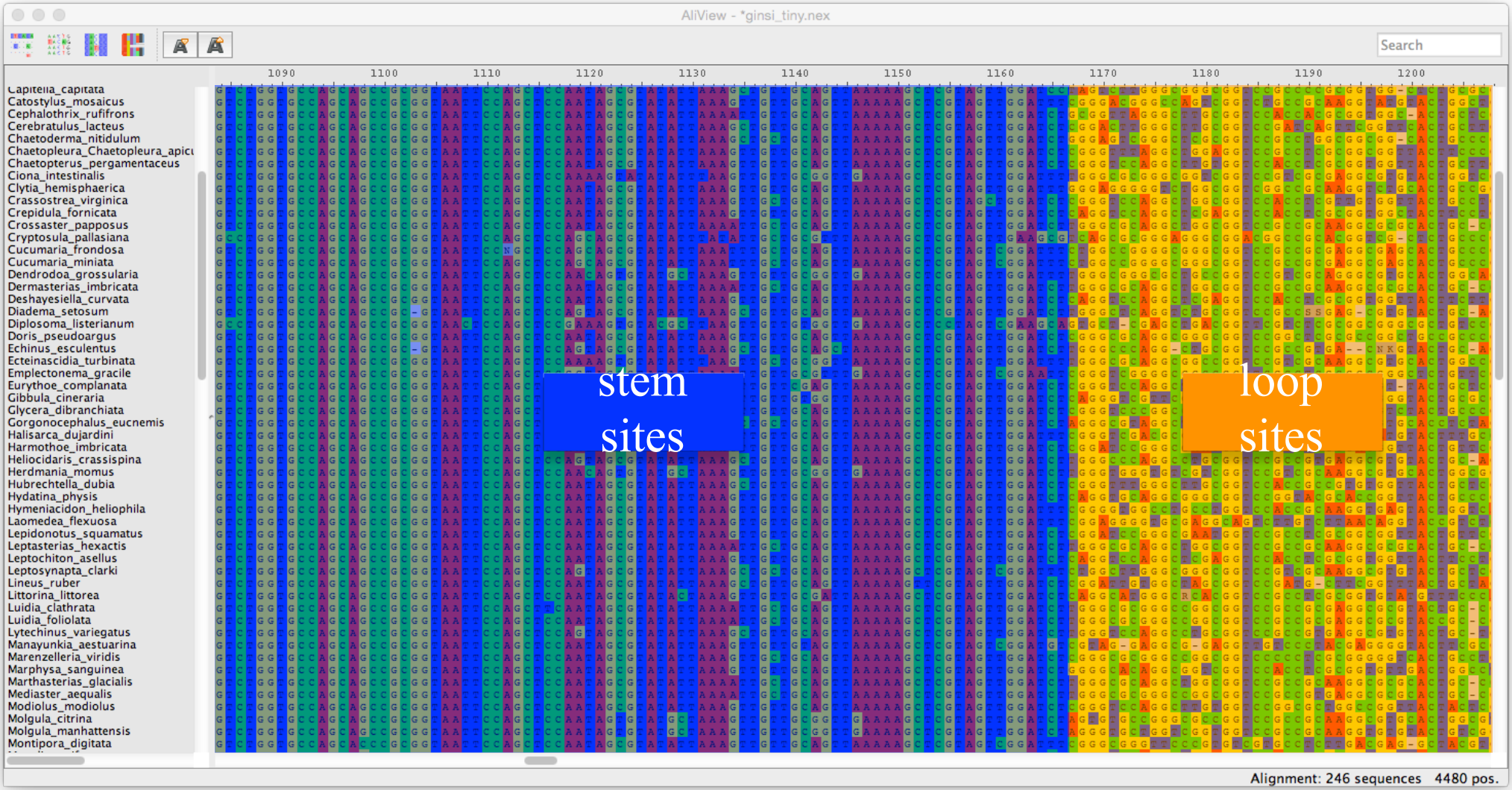

A site-specific model for ribosomal genes might have two rate categories, with stem sites in one and loop sites in the other relative-rate category

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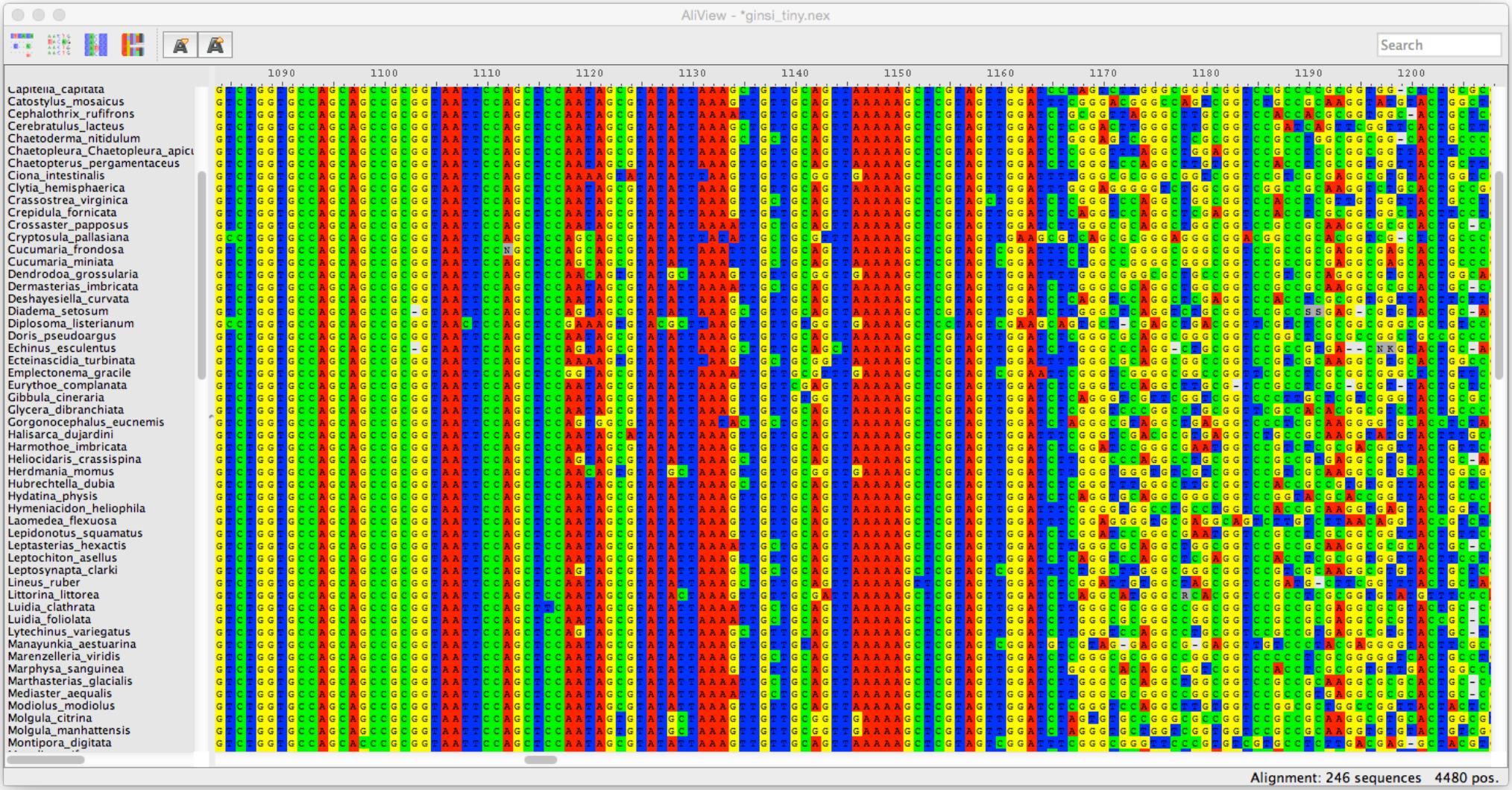
Accommodating Among Site Rate Variation

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:

$$L(x_i \mid \theta, p) = \underbrace{p \times L(x_i \mid \theta, r_{\text{off}})}_{\text{likelihood when process is 'off'}} + \underbrace{(1-p)L(x_i \mid \theta, r_{\text{on}})}_{\text{likelihood when process is 'on'}}$$

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- the mean of the gamma distribution is α/β
- we constrain the mean of the gamma distribution to have a mean of one: $\alpha = \beta$

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The rate of a site is a random variable drawn from a discrete gamma distribution:

- the gamma distribution has two parameters: the shape parameter, α and the scale parameter, β
- the mean of the gamma distribution is α/β
- we constrain the mean of the gamma distribution to have a mean of one: $\alpha = \beta$
- so, operationally, the gamma distribution involves the single shape parameter, α

Accommodating Among Site Rate Variation

The Discrete Gamma Distribution (+G) model of ASRV

The gamma distribution provides a flexible means of accommodating ASRV

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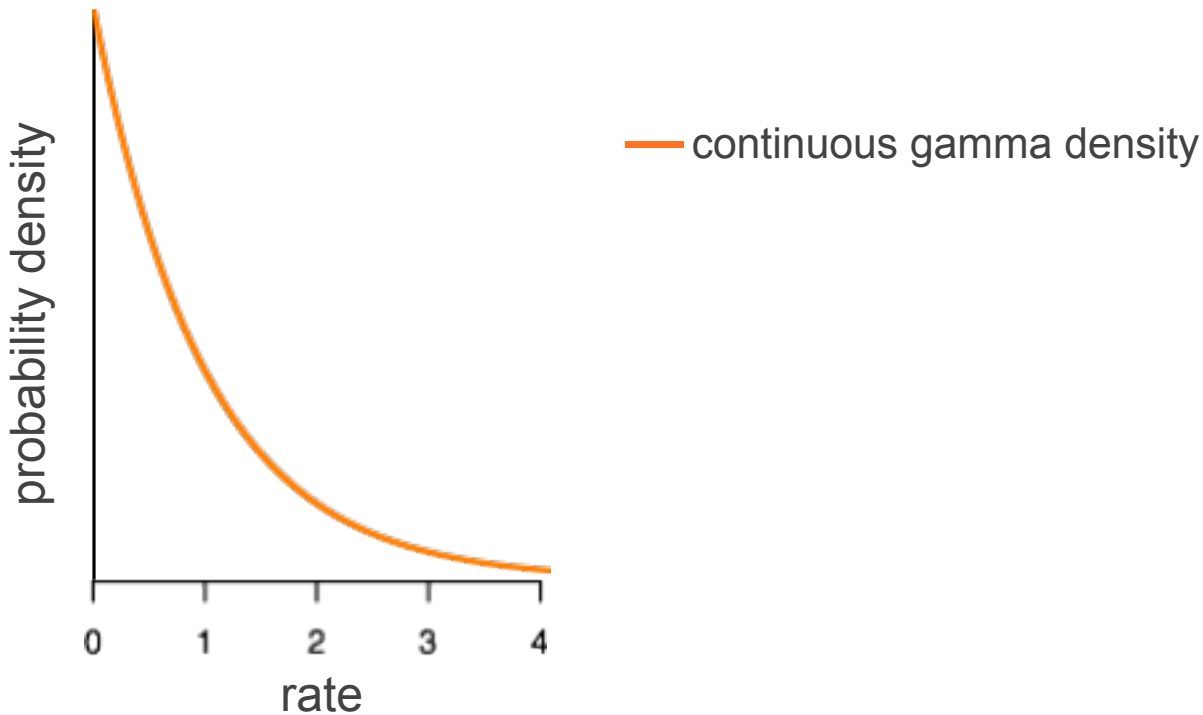

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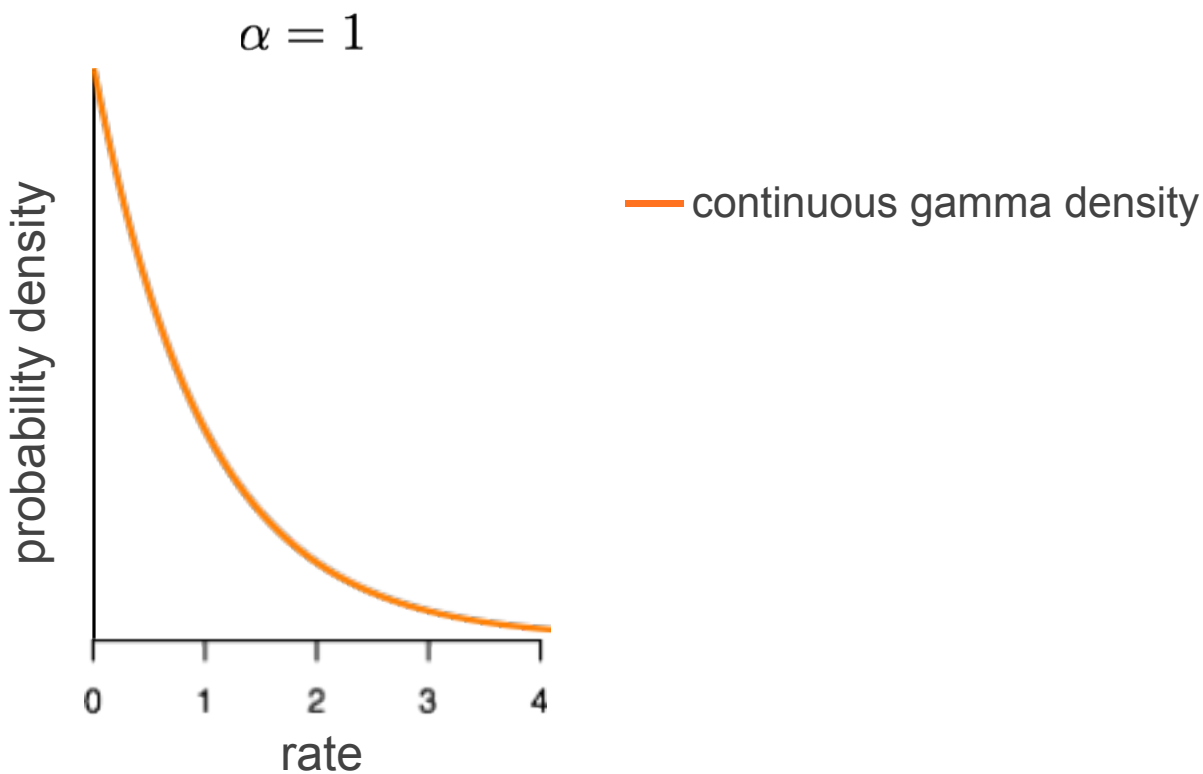

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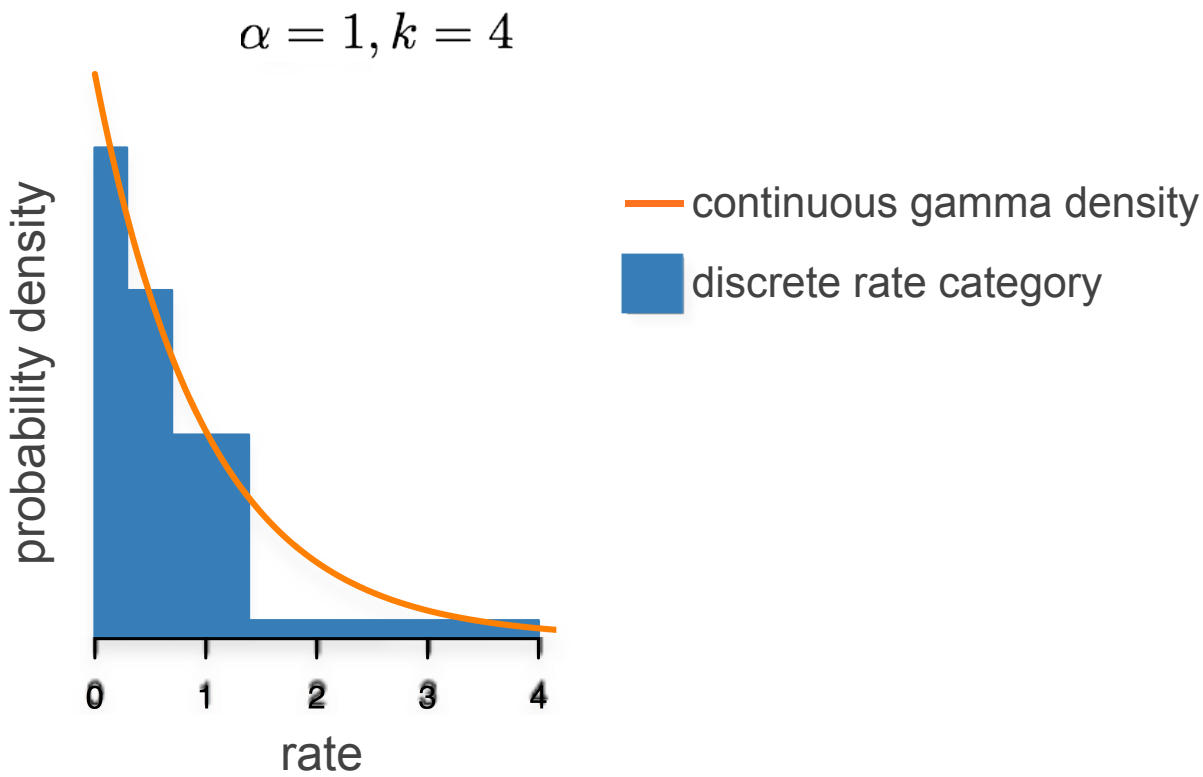

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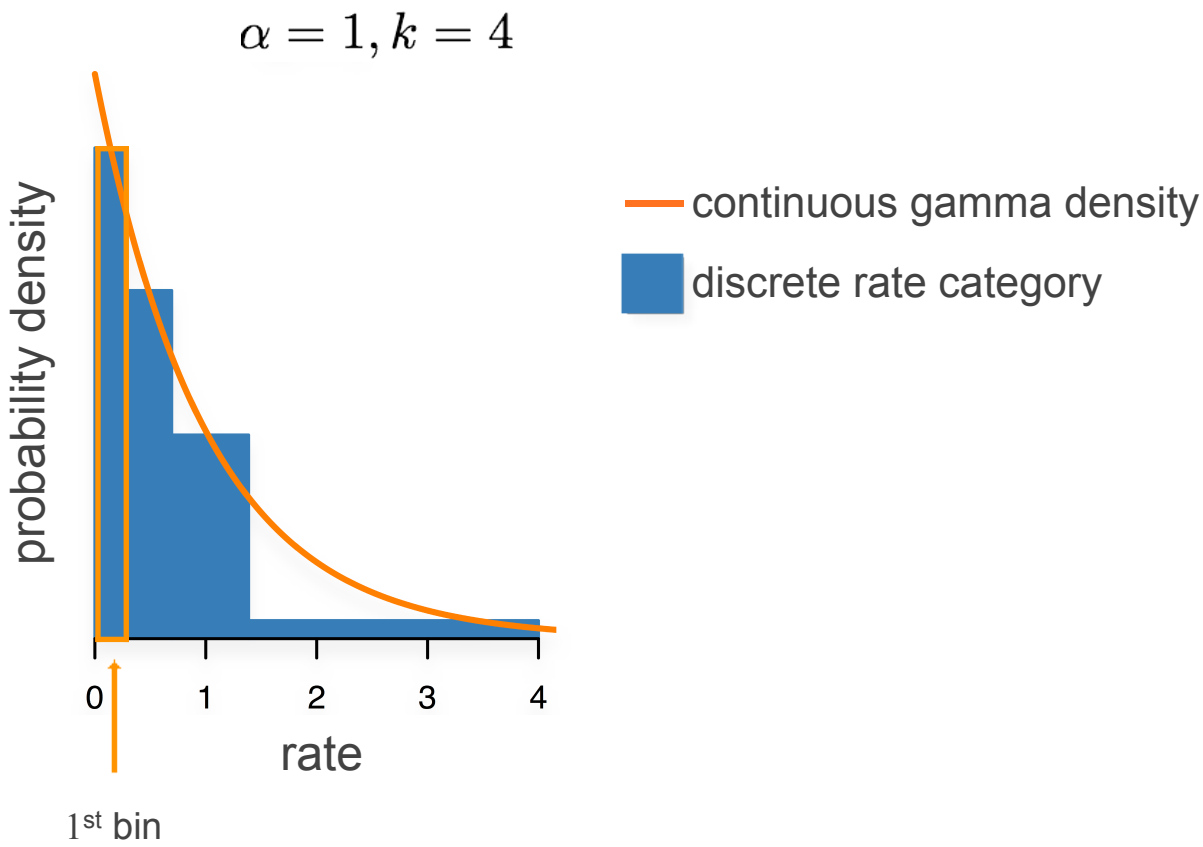

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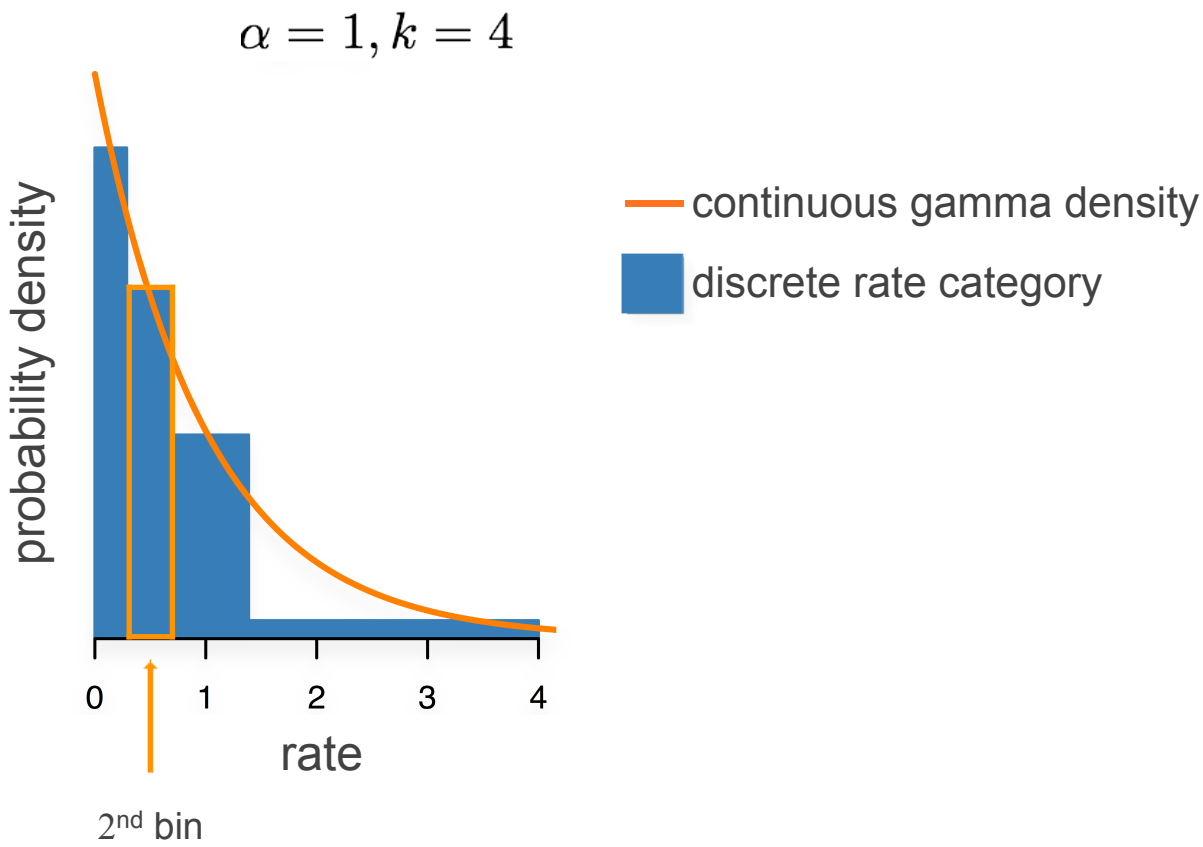

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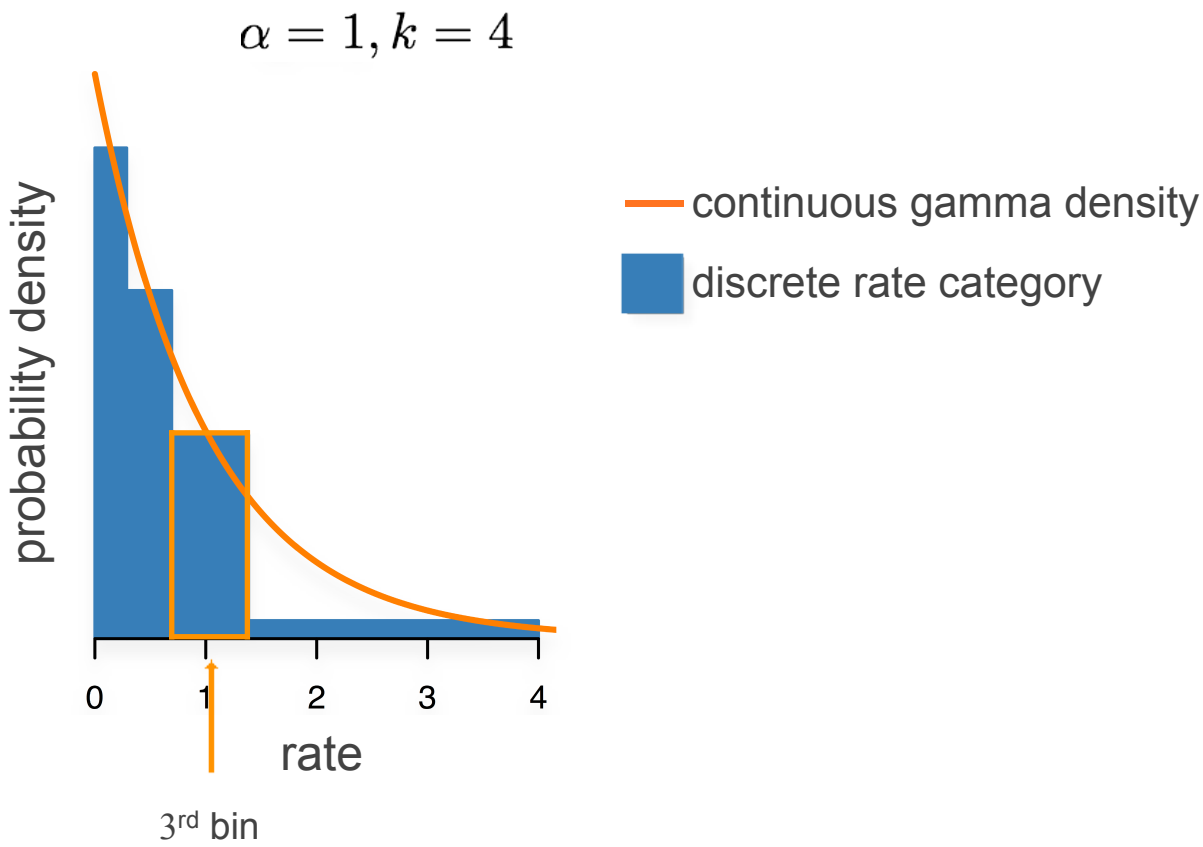

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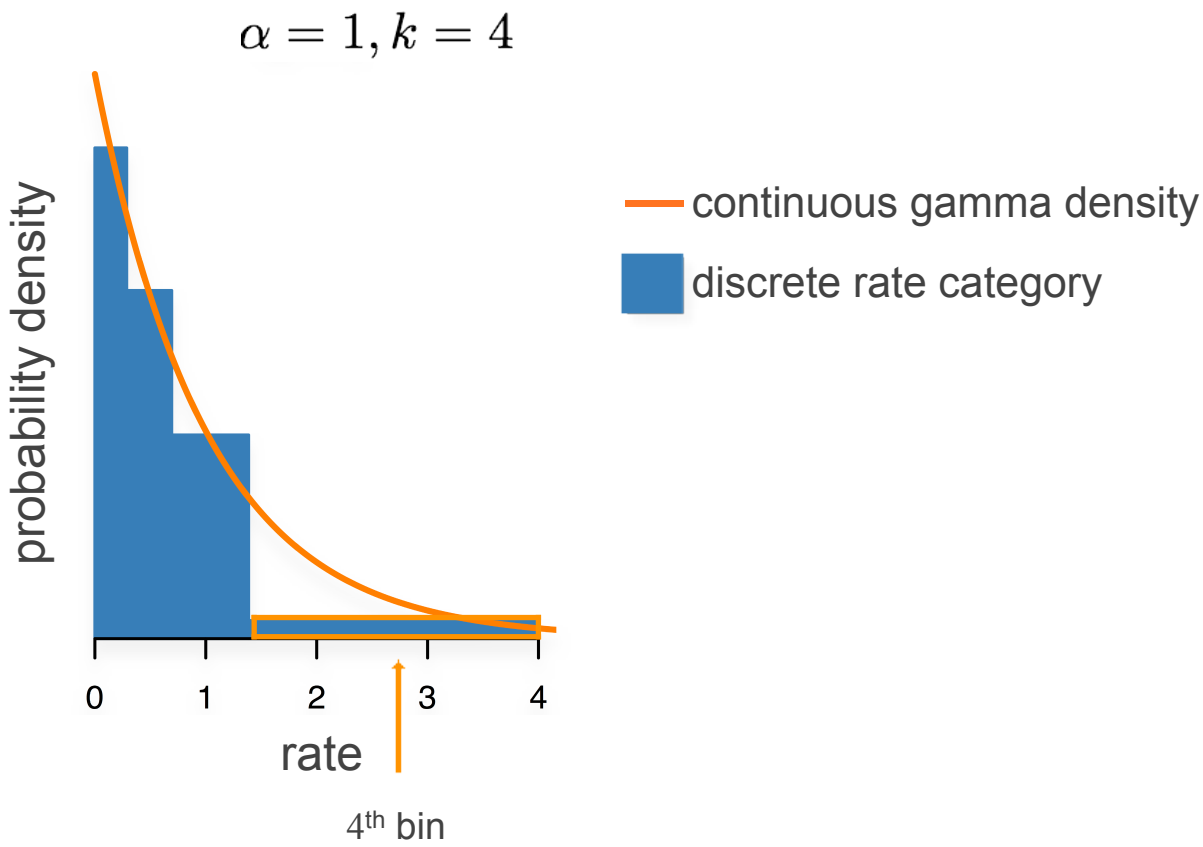

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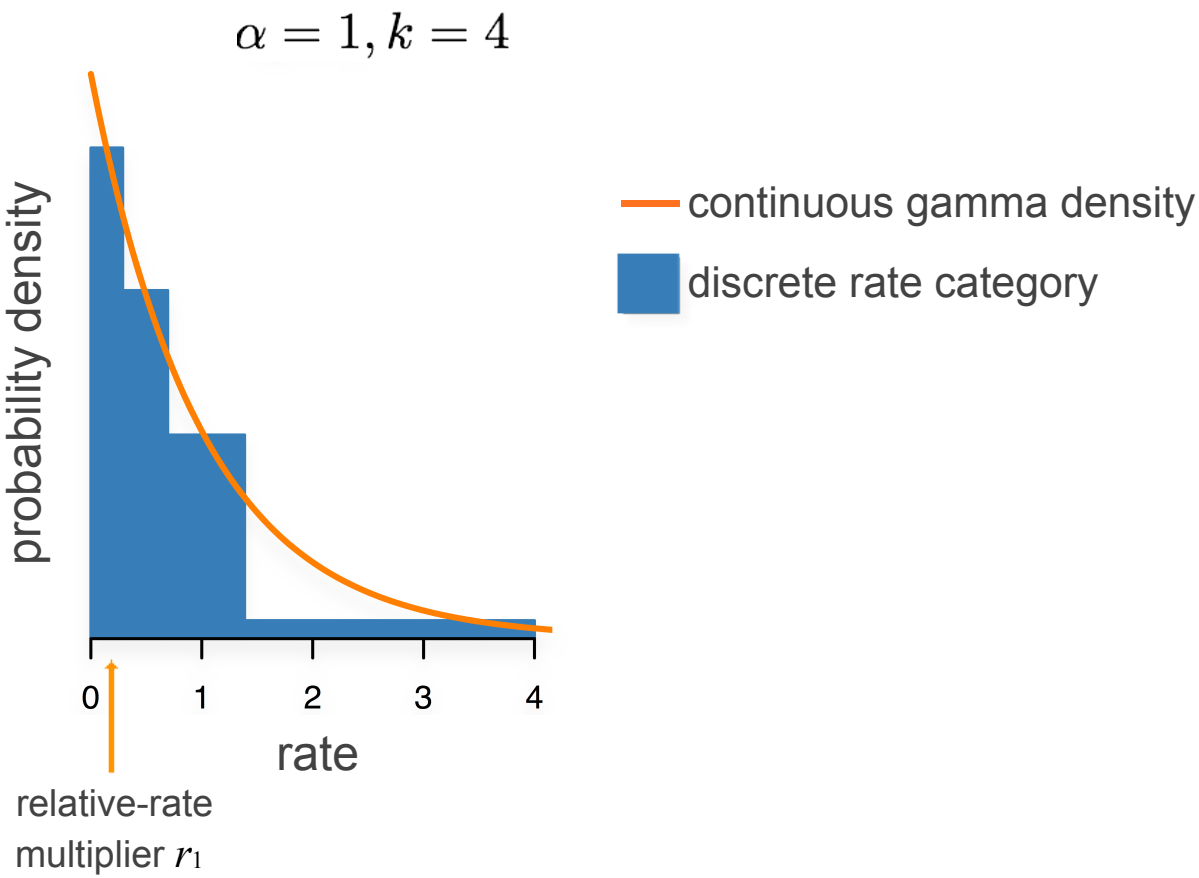

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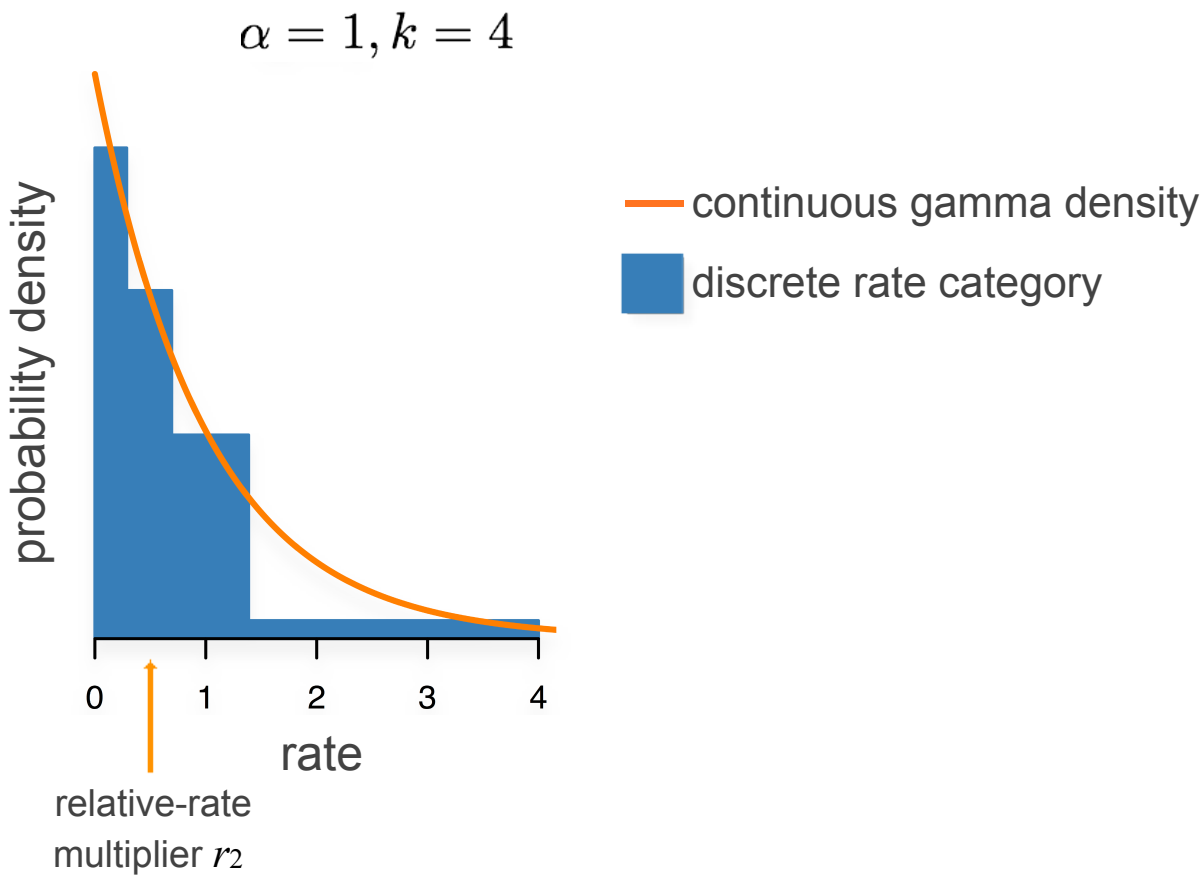

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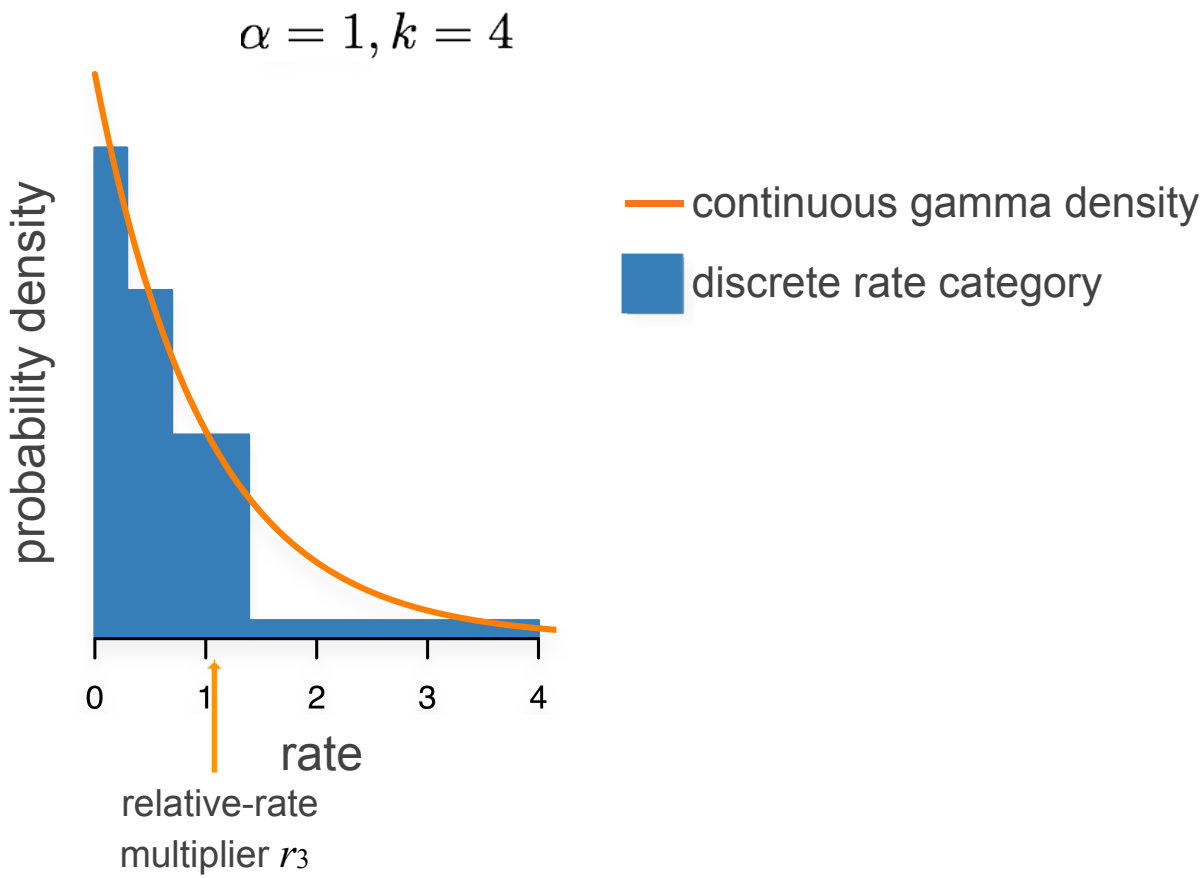

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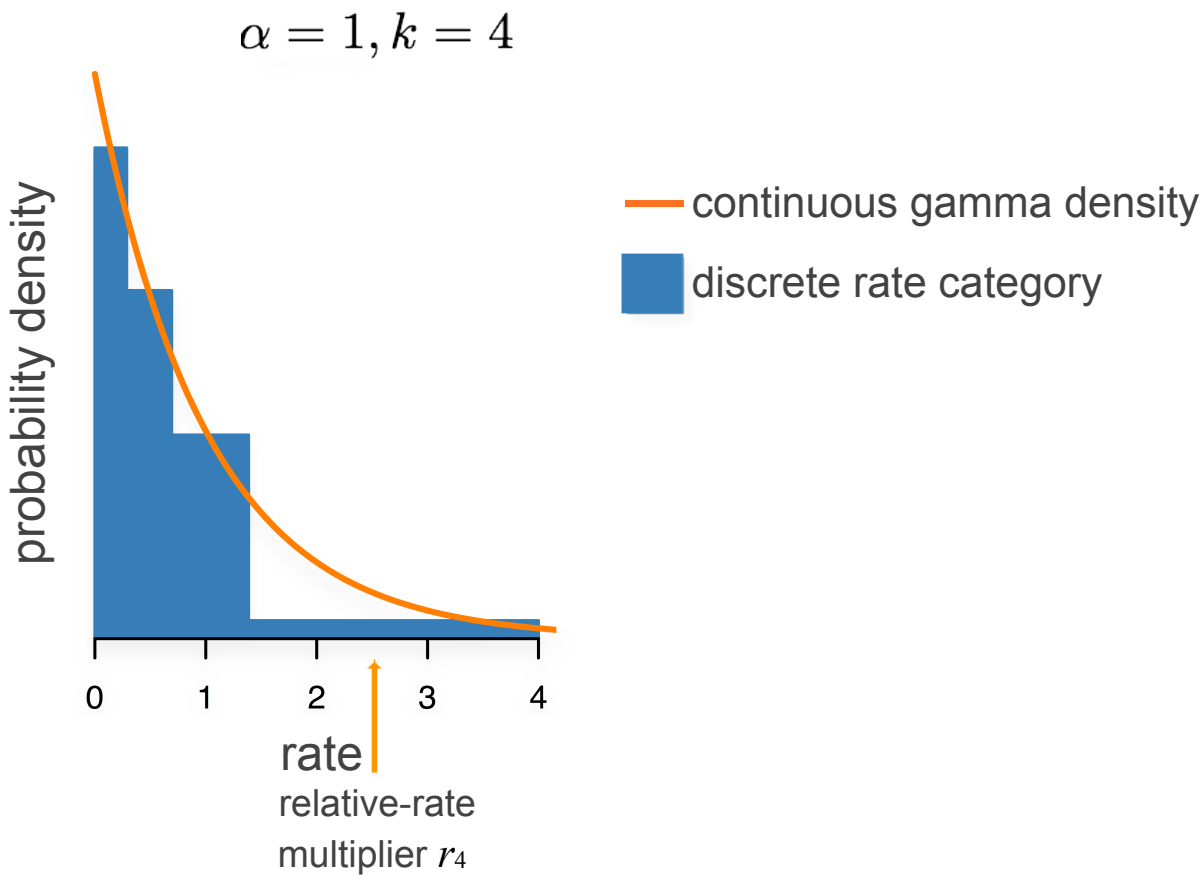

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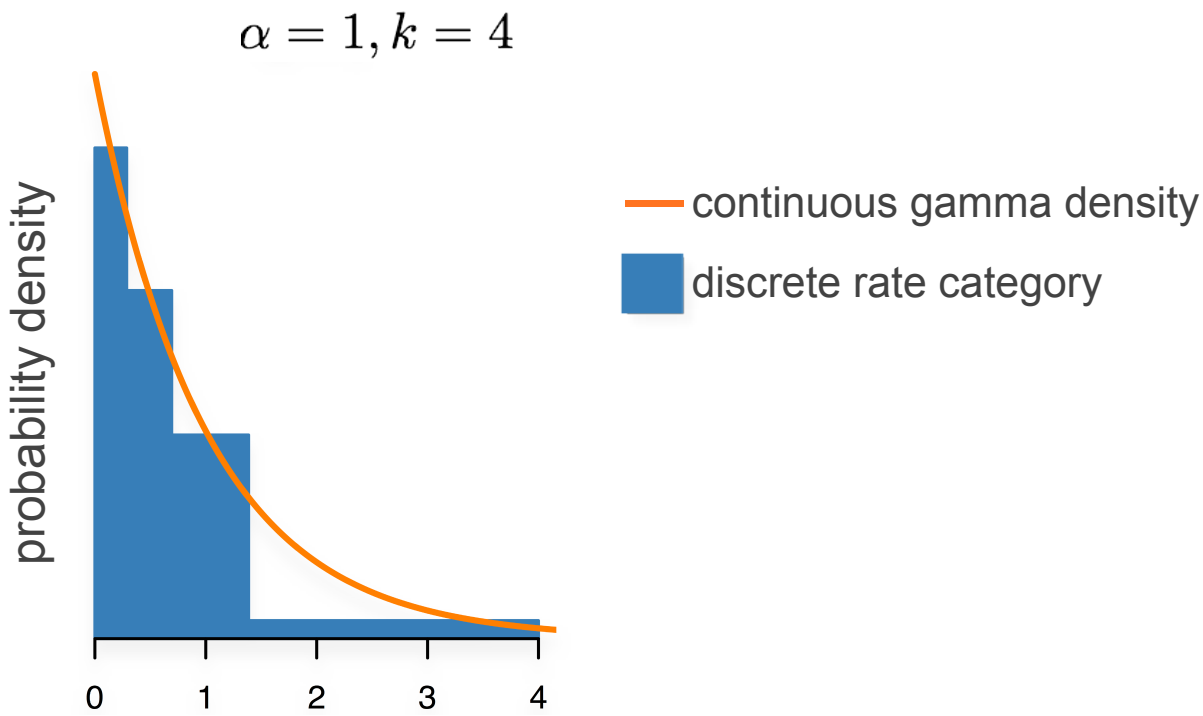

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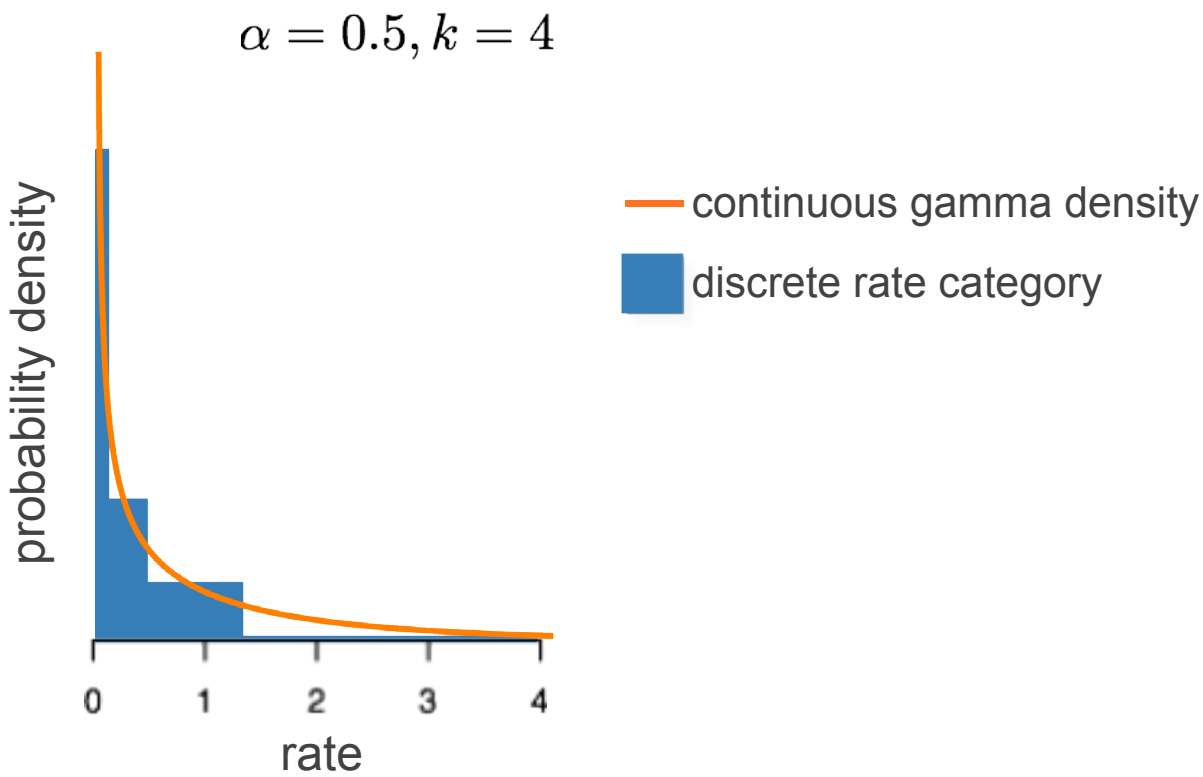

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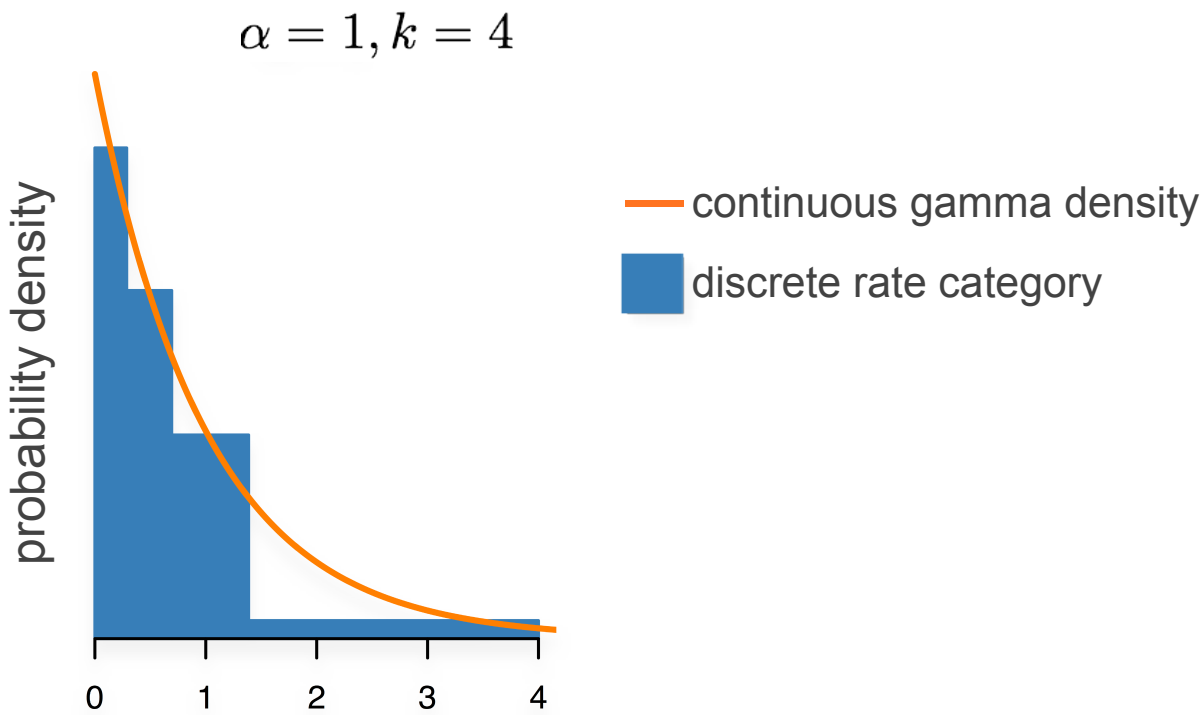

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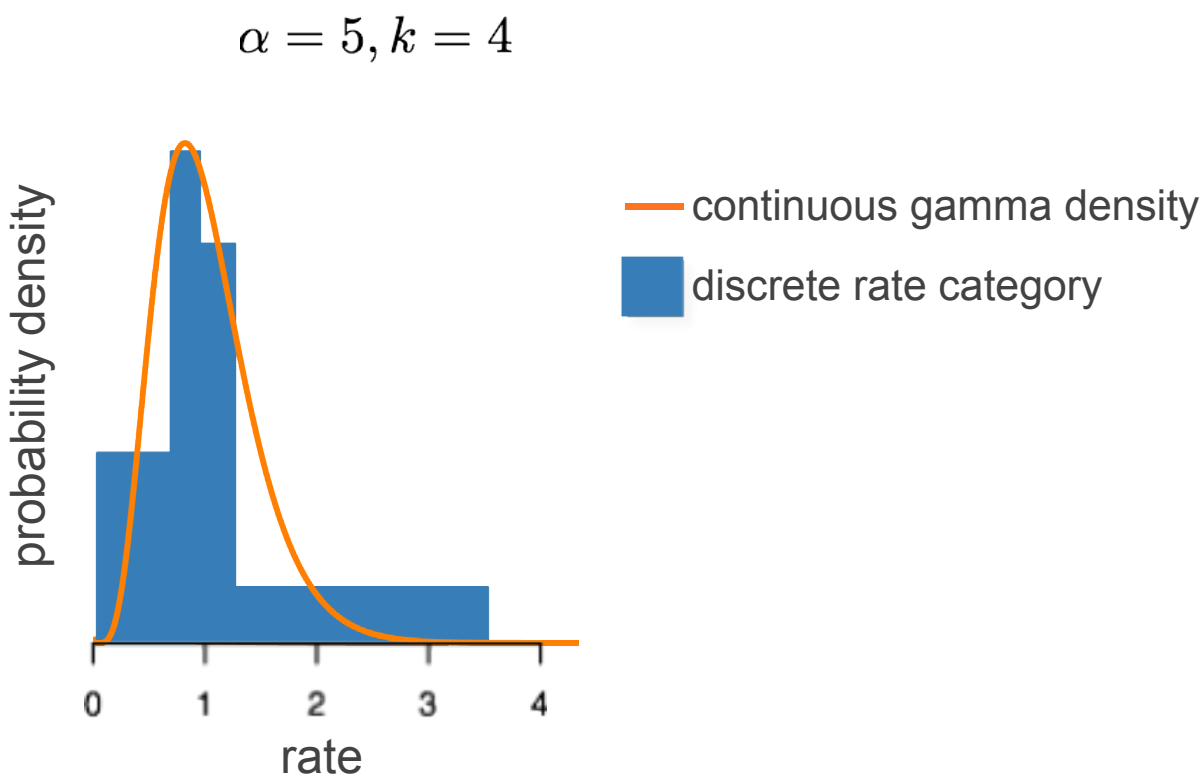

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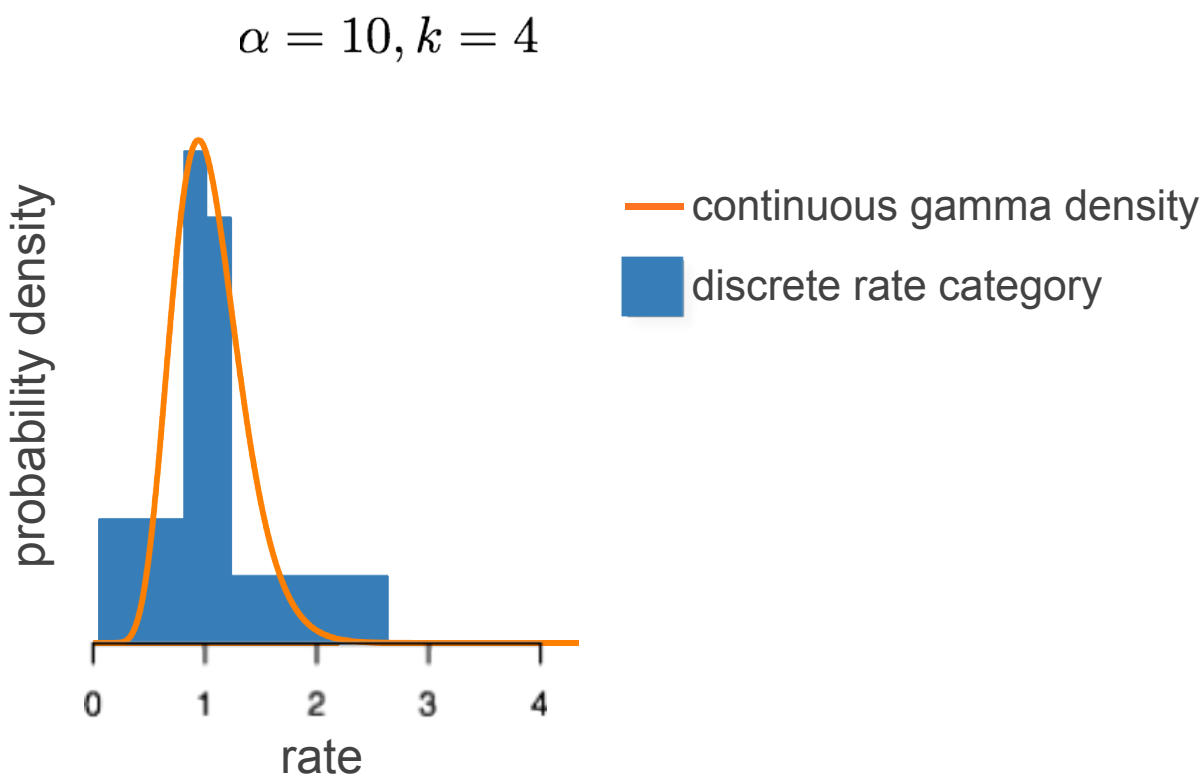

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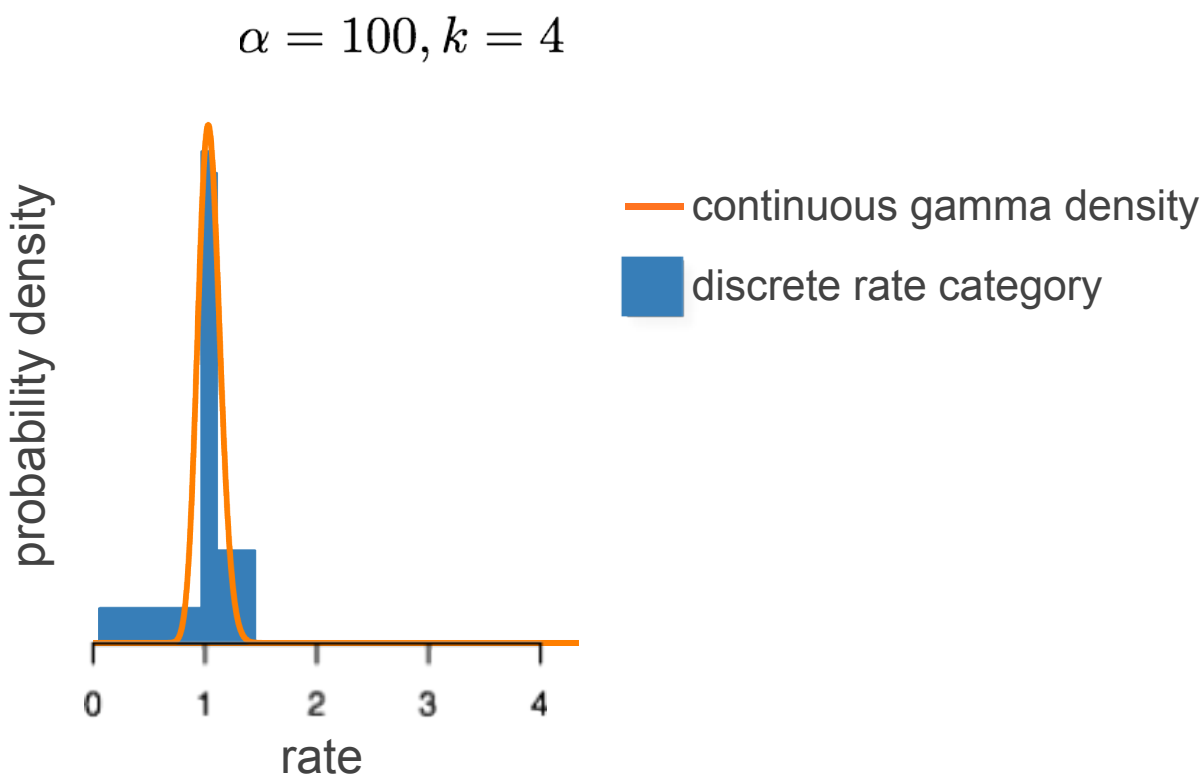

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$$L(x_i \mid \theta, \alpha) = \sum_{j=1}^{k} f(x_i \mid \theta, r_j)$$

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- the discrete gamma model therefore incurs a k-fold increase in computational burden

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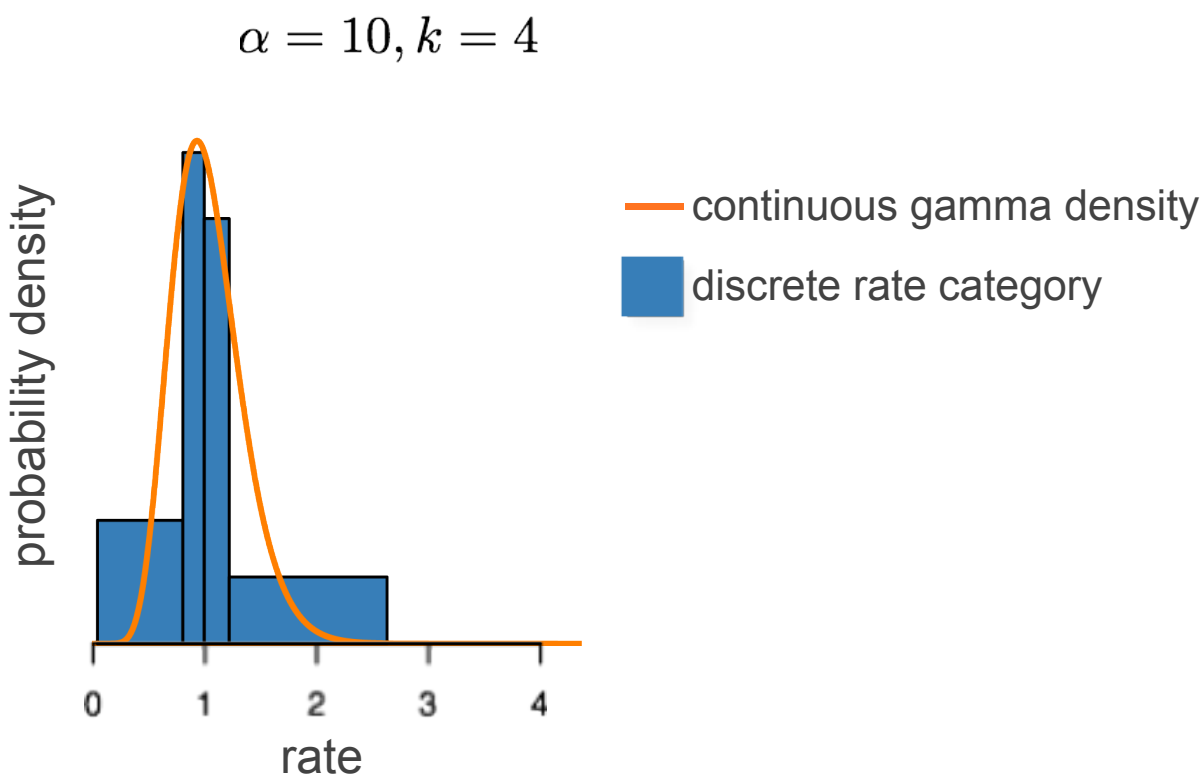
- there are k relative-rate multipliers; corresponding to the mean or median rate of each bin
- the approximation of the continuous gamma improves with increasing k, but so does the computational burden



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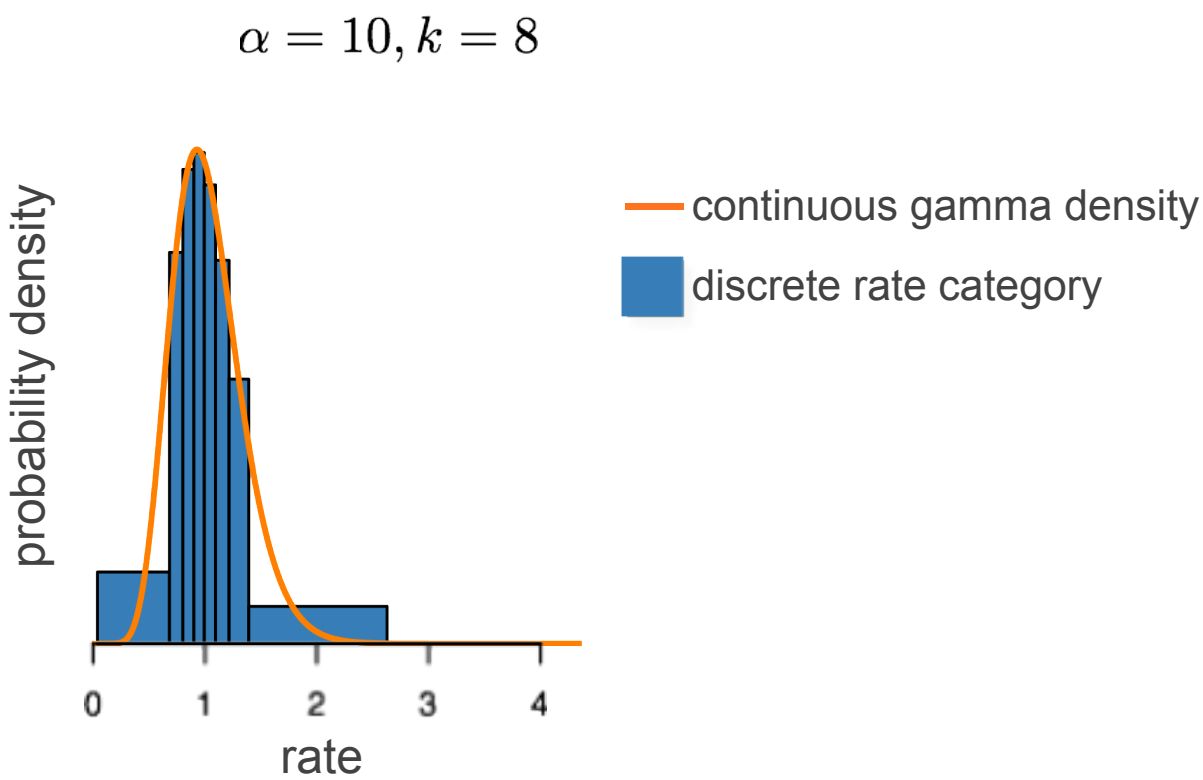

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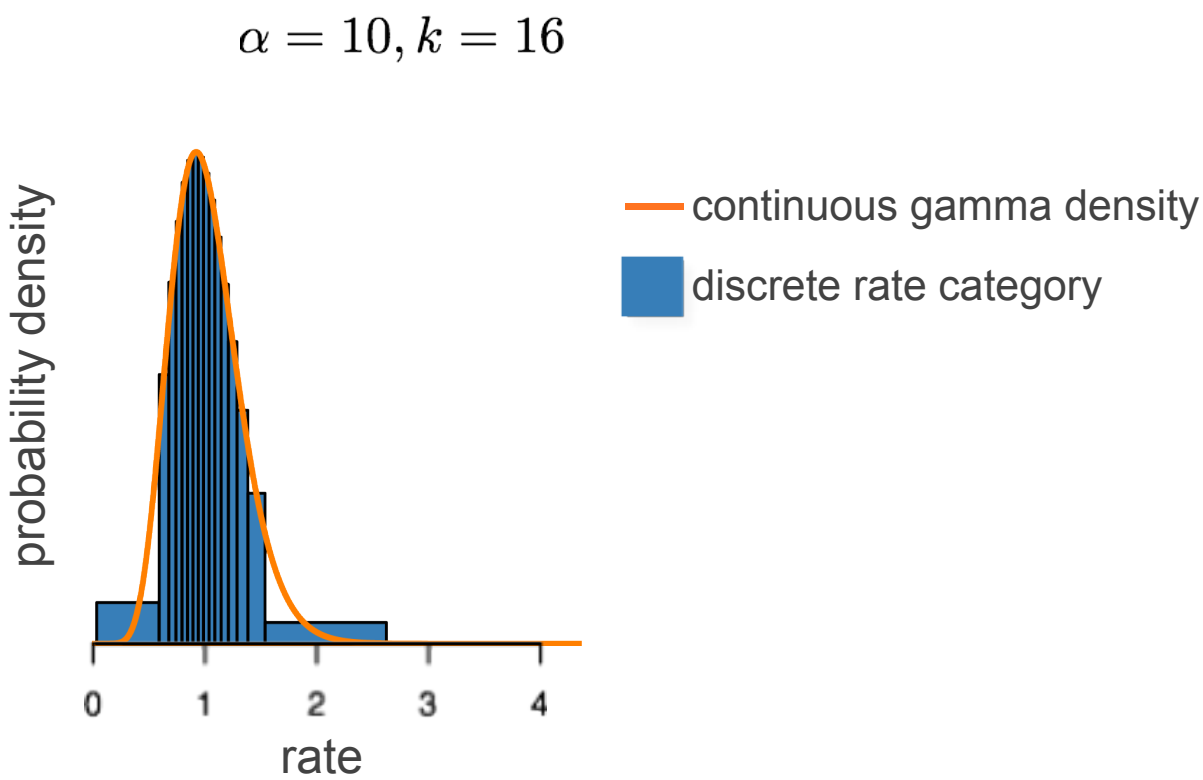

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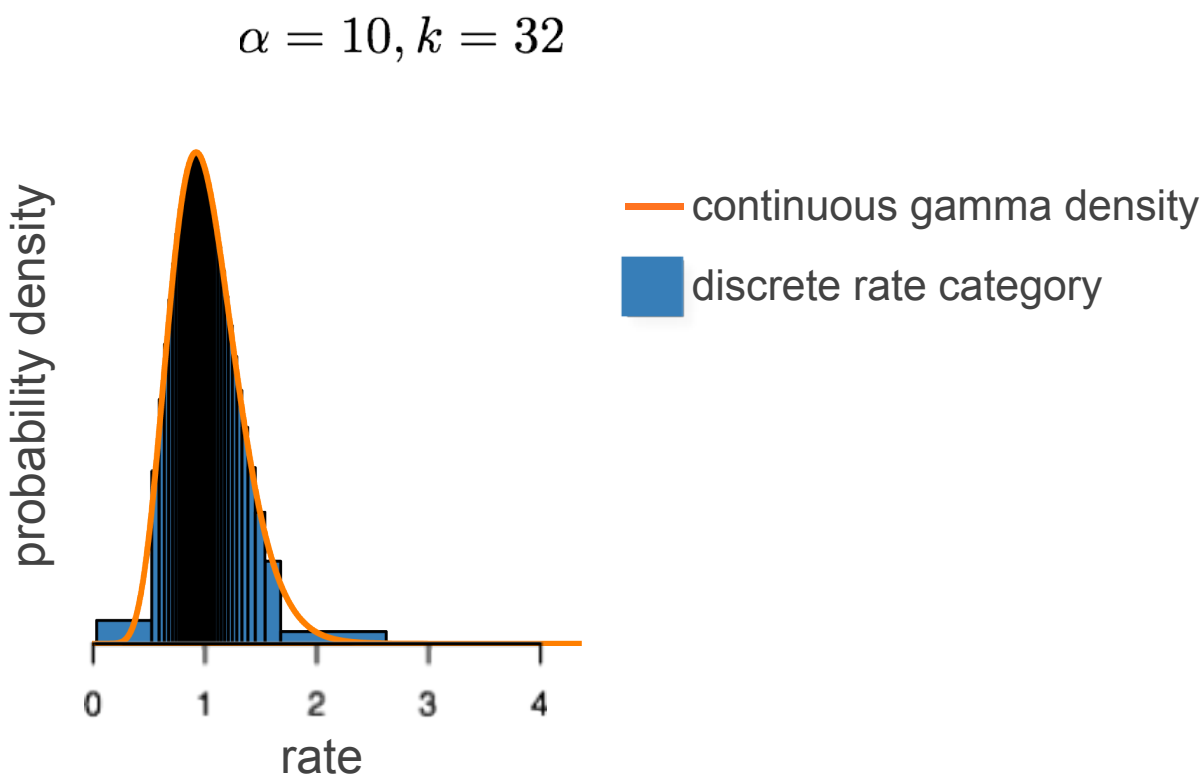

Accommodating Among Site Rate Variation

Mixture models for accommodating ASRV

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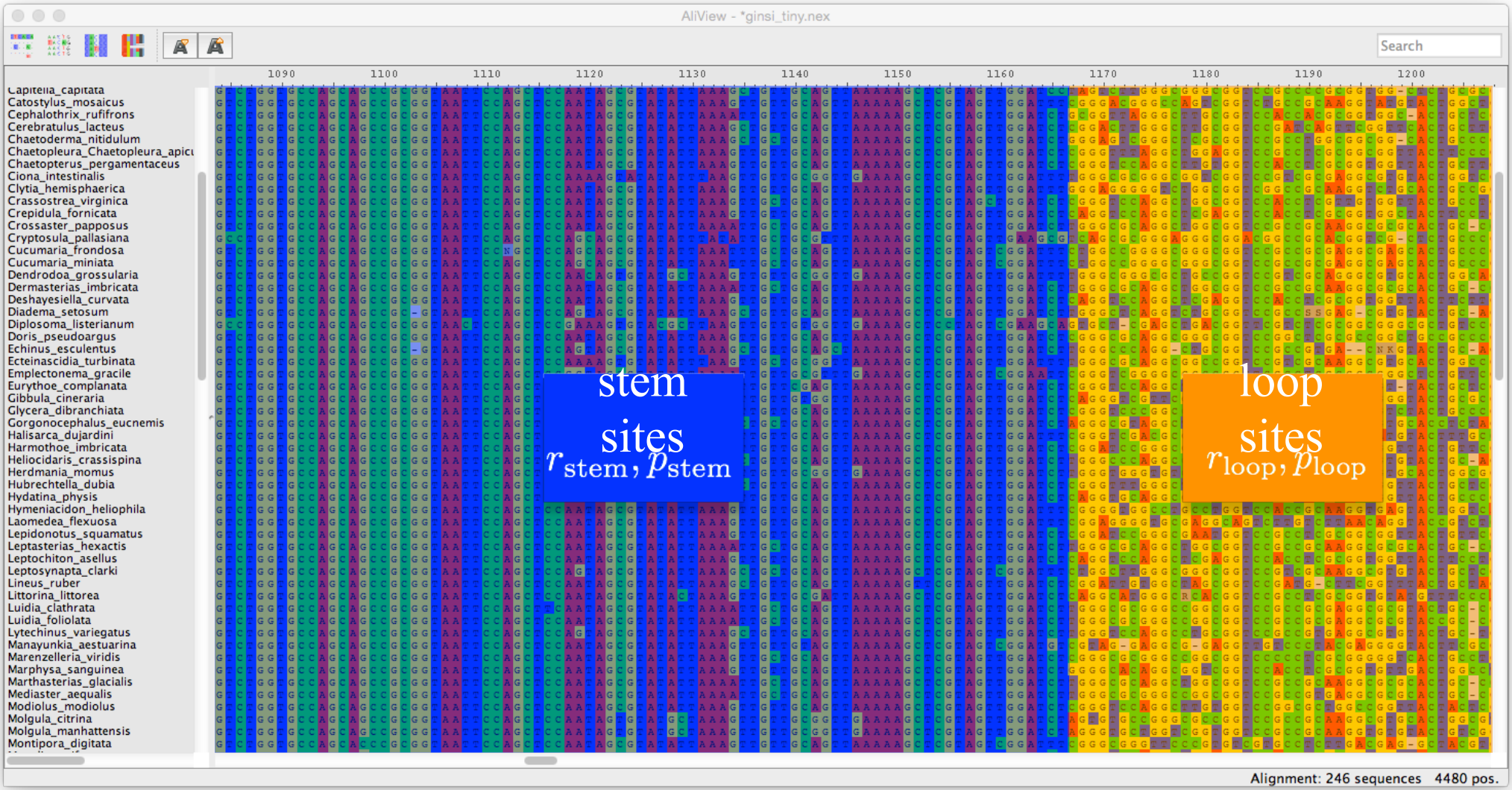

Each pre-specified subset of sites has an overall relative-rate multiplier, and the rate of each site *within* each category is modeled as proportion of invariable sites model

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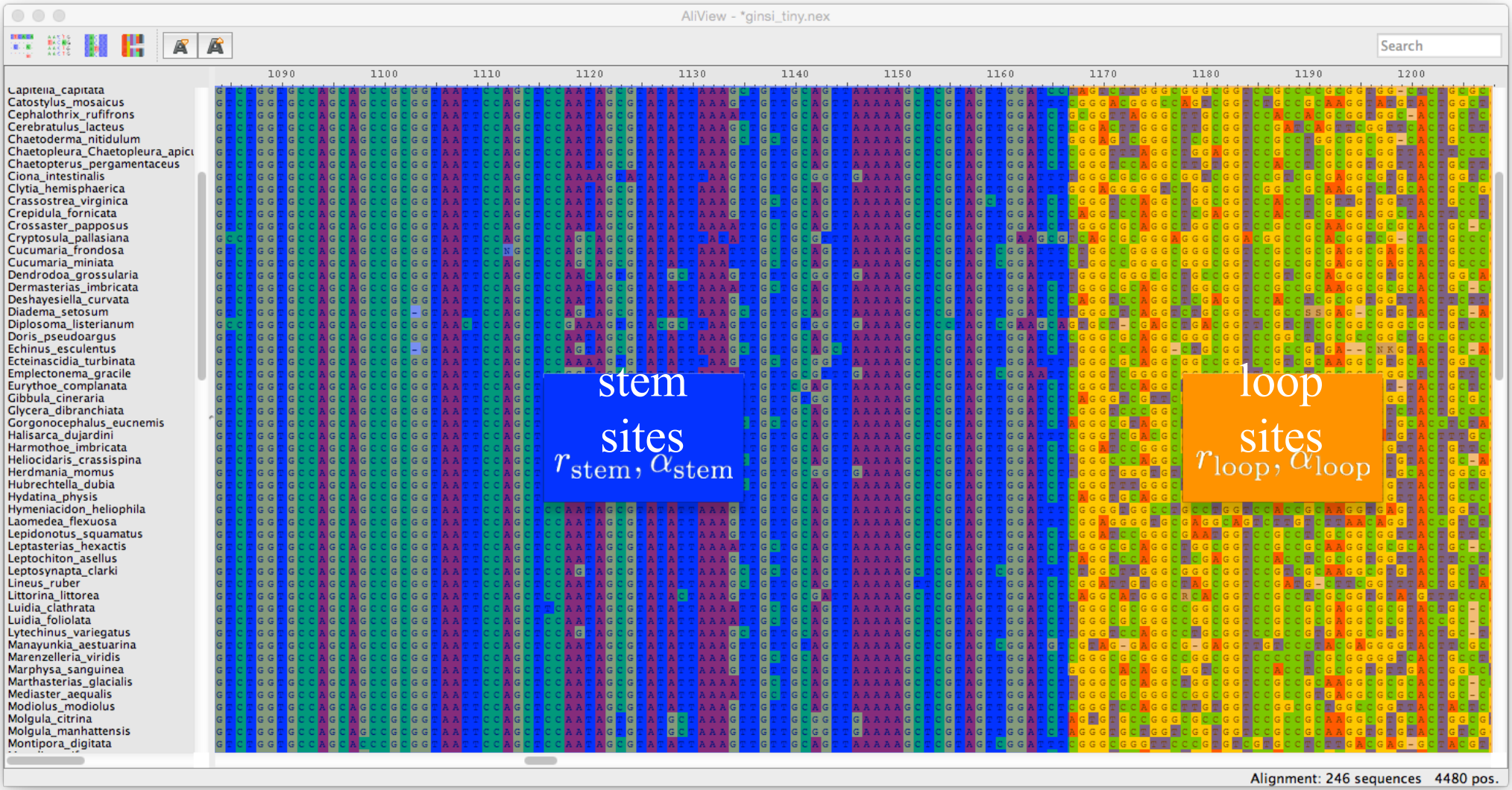

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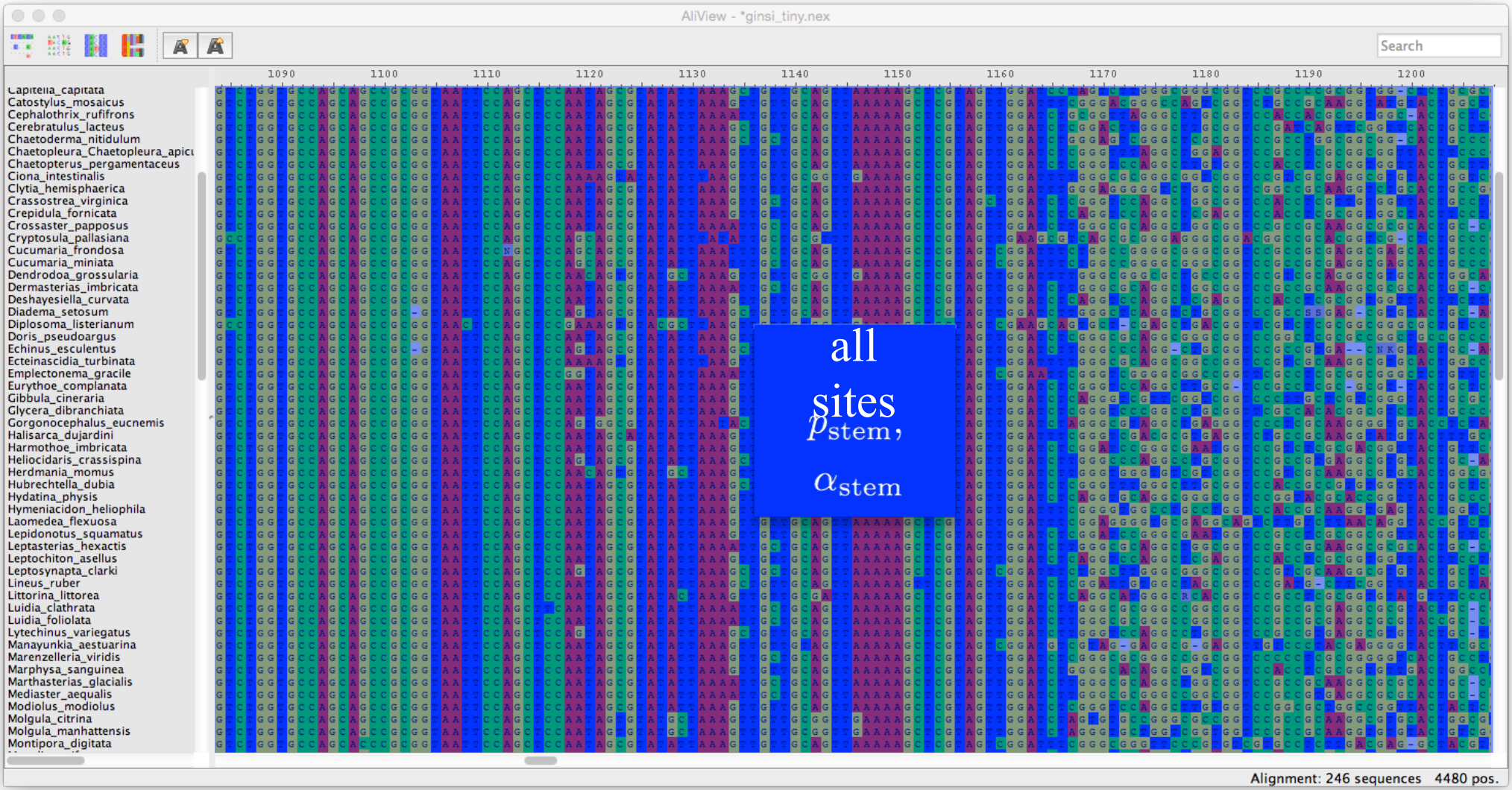

The rate of each site is modeled as a random variable drawn from a mixture of the discrete-gamma and proportion of invariable sites

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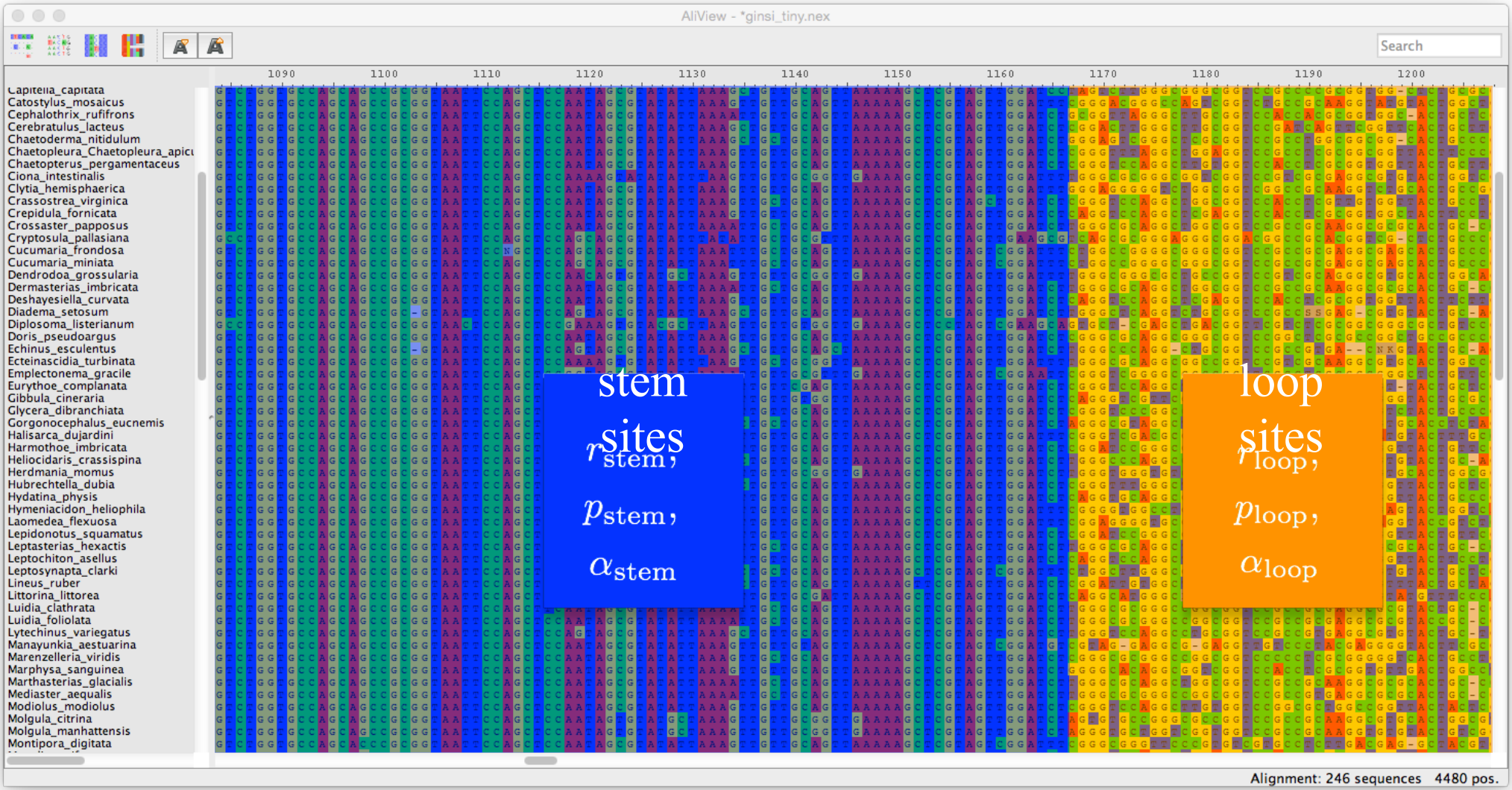

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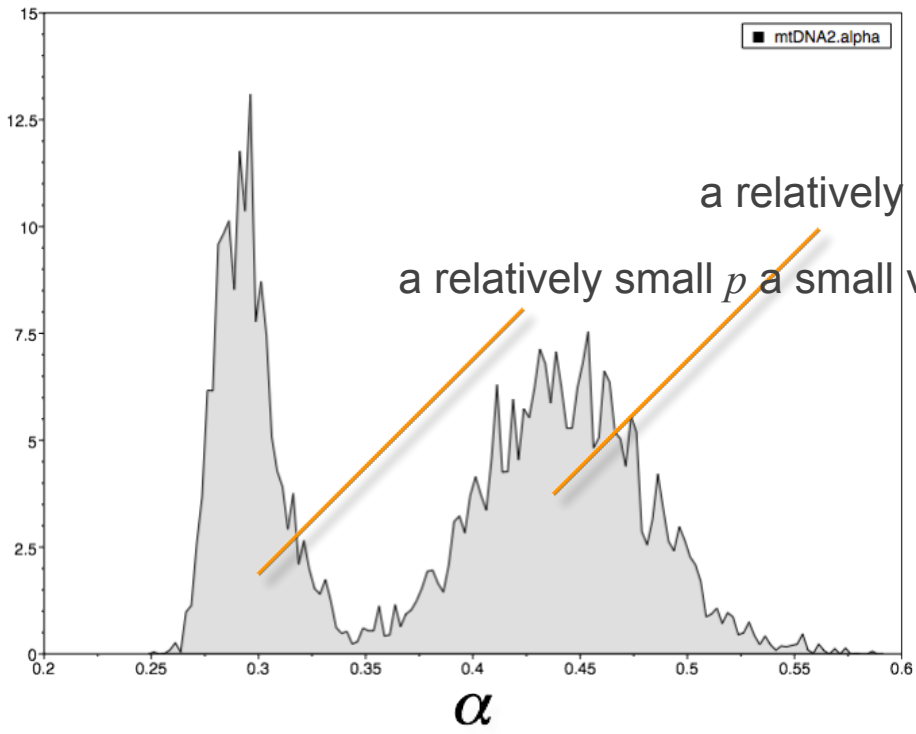
Mixture models of (I+G) for accommodating ASRV may be non-identifiable



a relatively small p a small value of α

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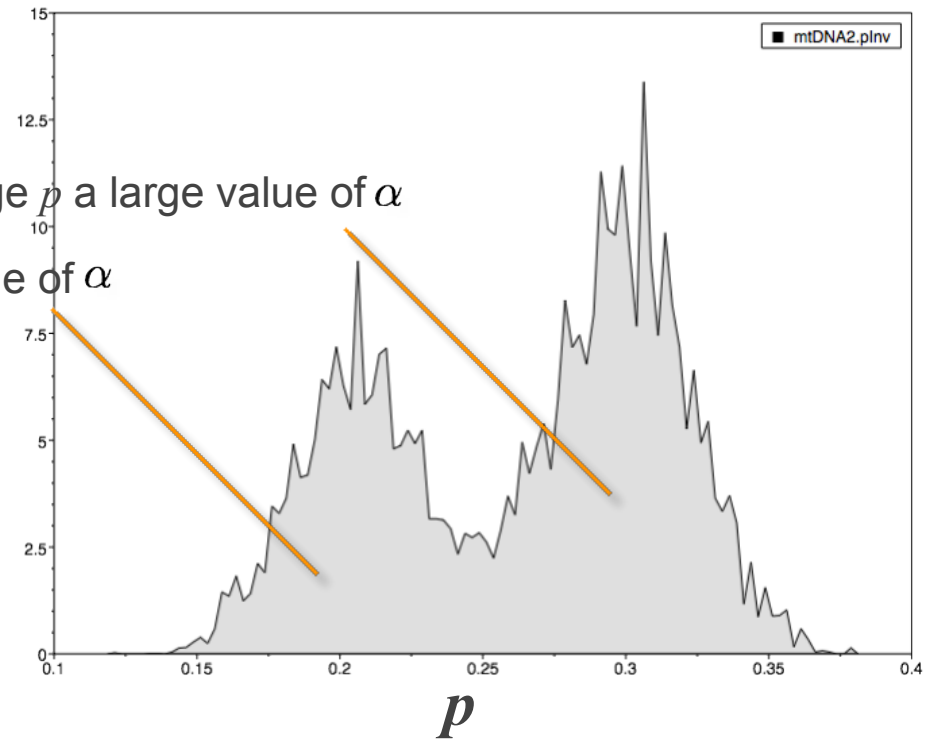

These parameter interactions may cause pathologies that impact estimates of other model parameters, and make convergence difficult.

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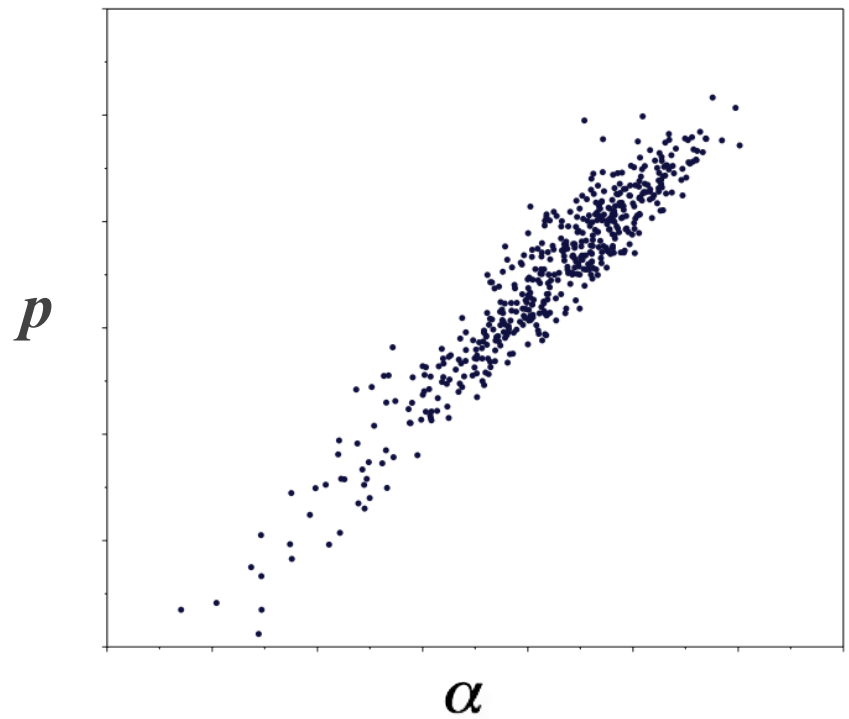

We can identify parameter interactions by plotting their joint posterior probability distribution (see Bayesian MCMC presentations!)

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

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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

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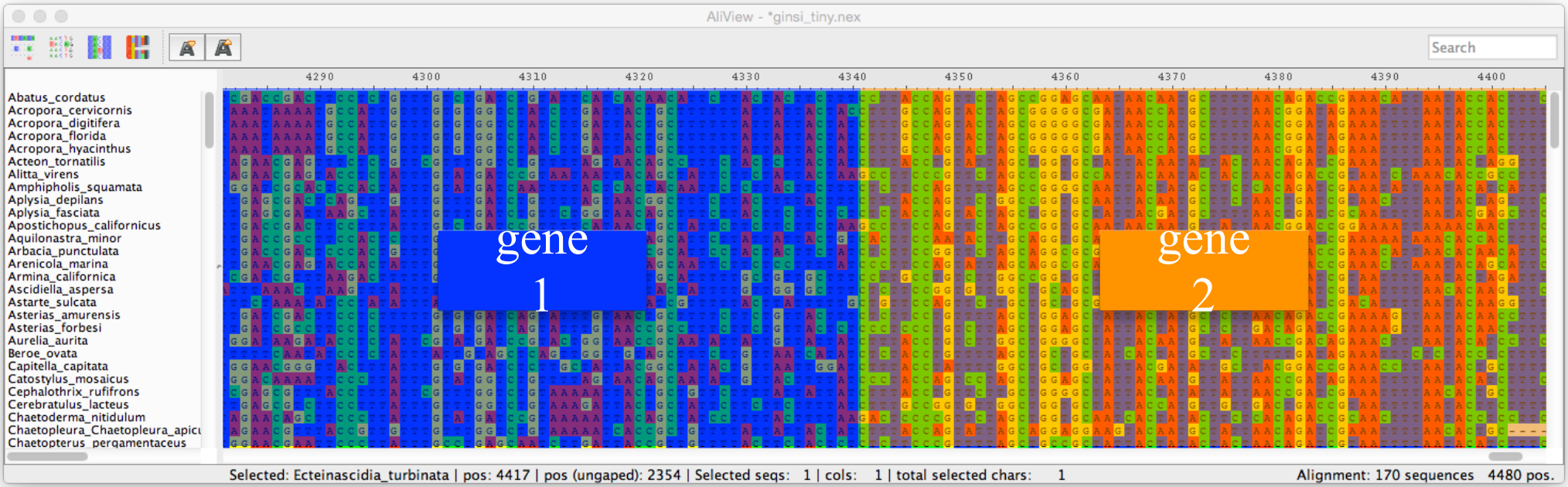
Accommodating Among Site Process Heterogeneity

The substitution process may vary qualitatively across the alignment



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

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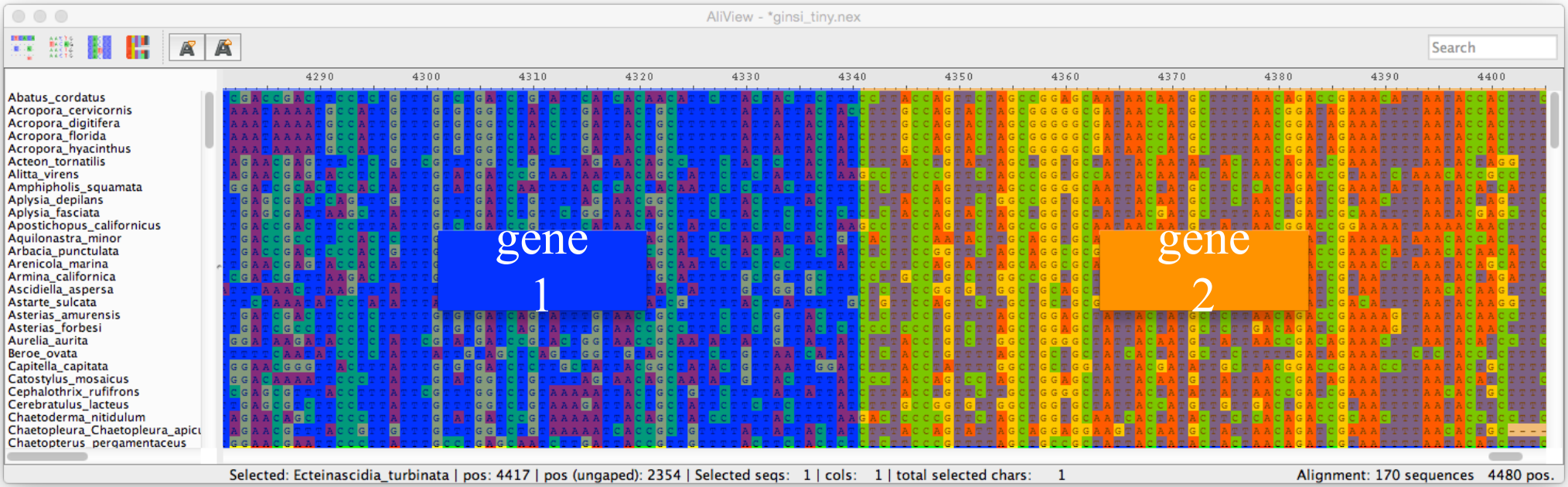

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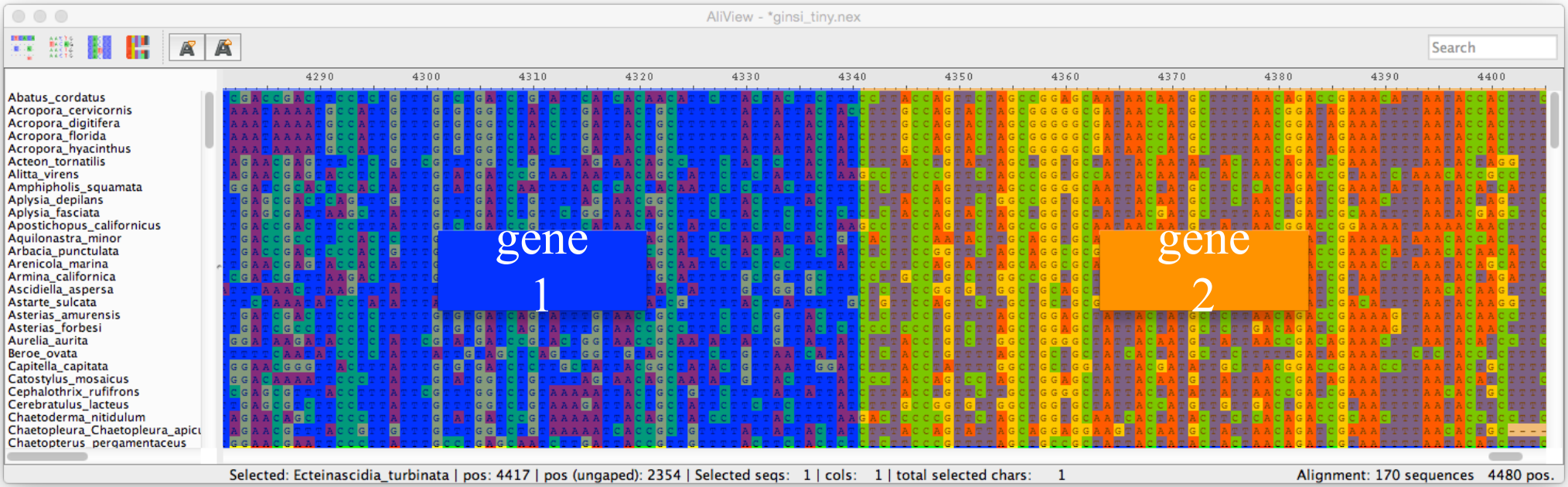

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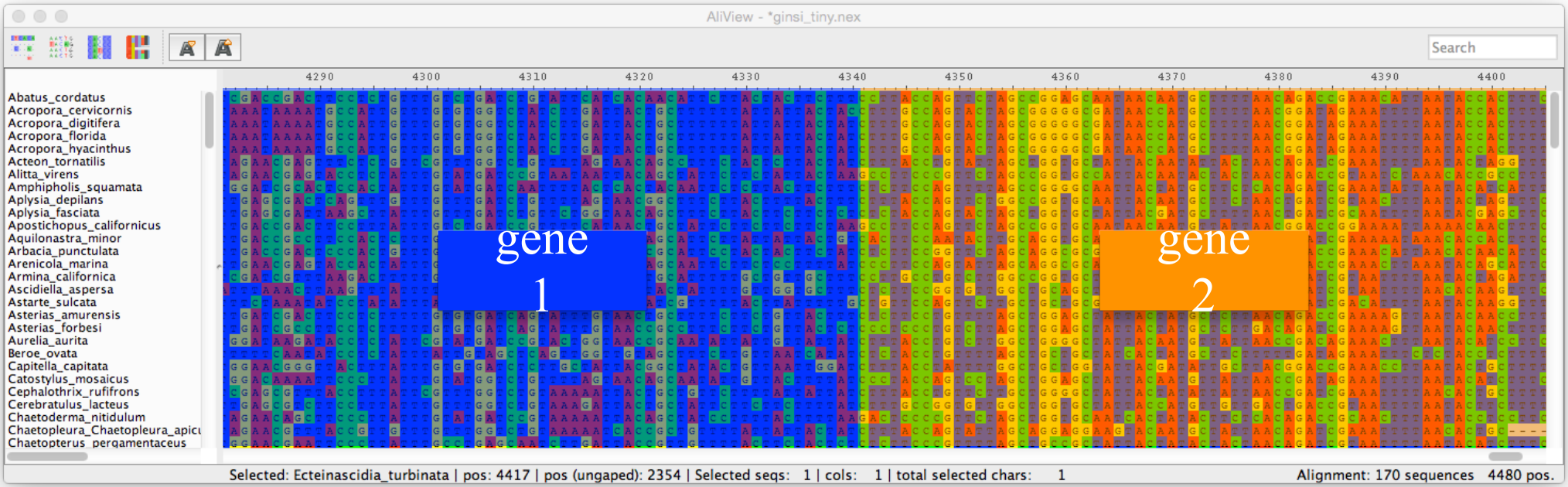

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- stem/loop regions of ribosomal genes

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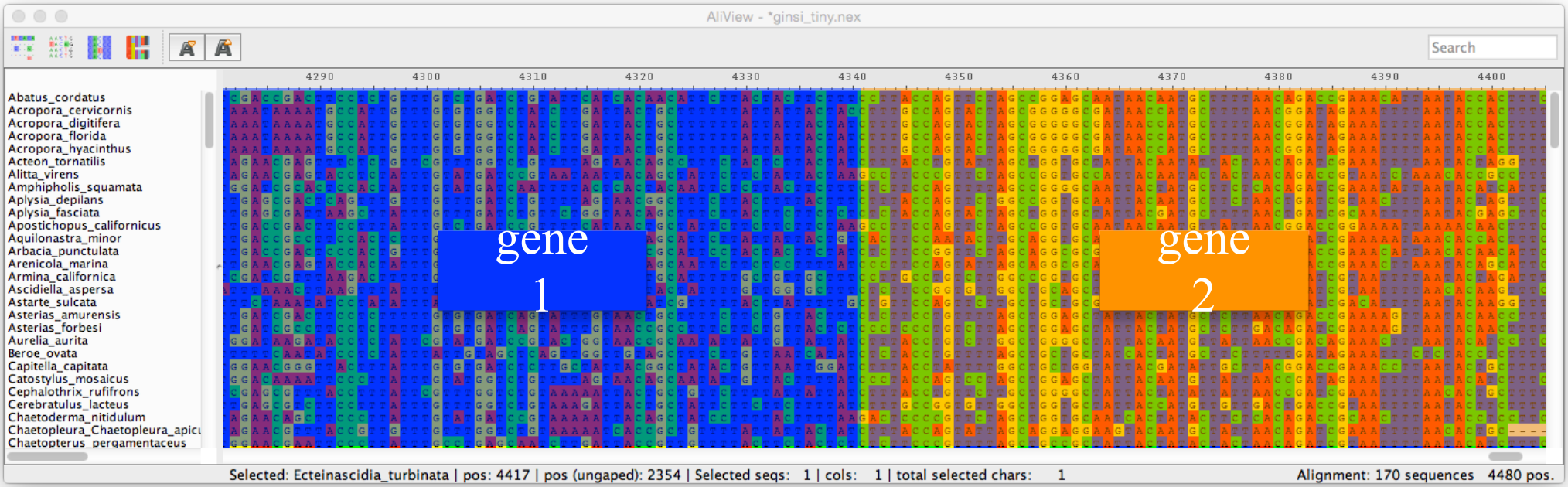

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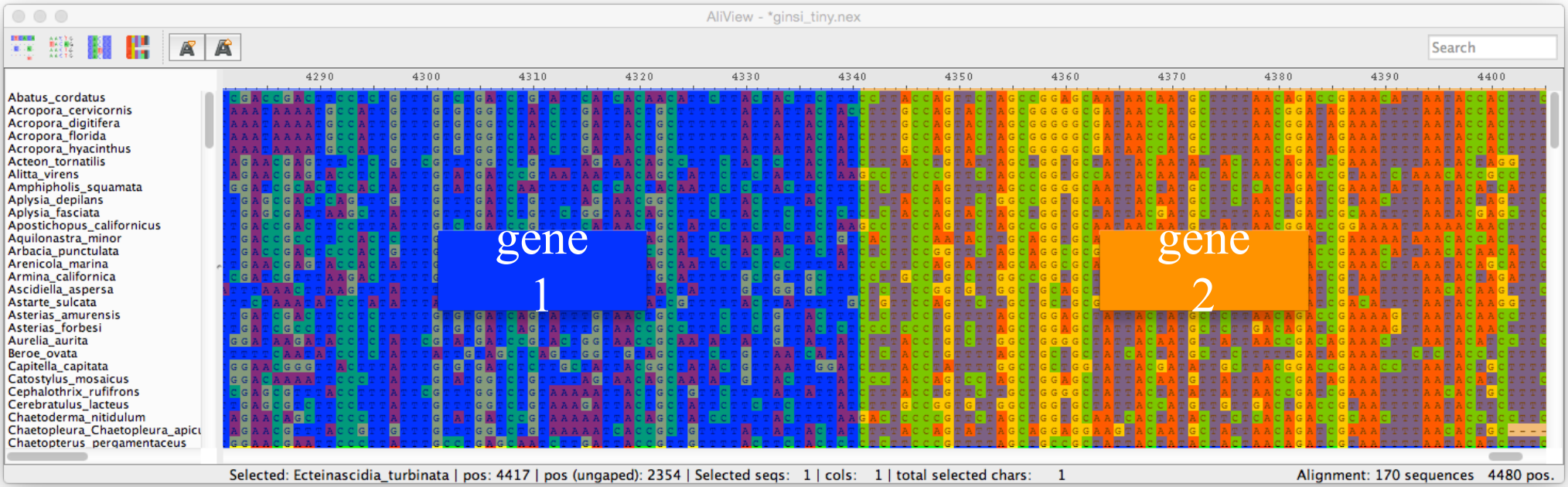

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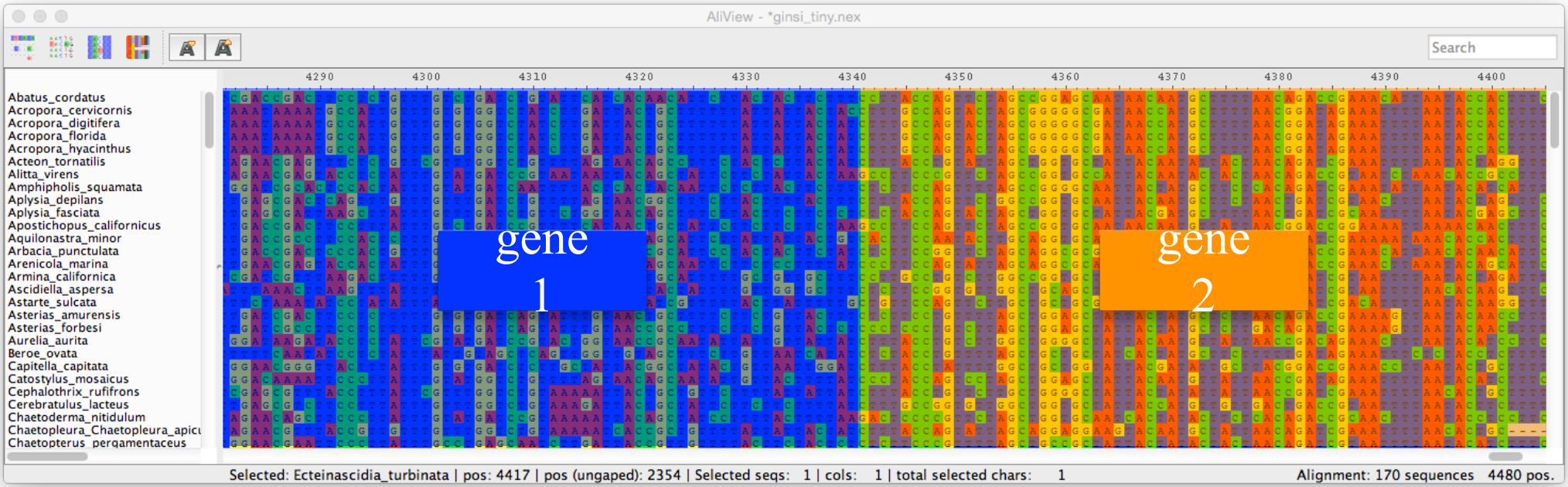

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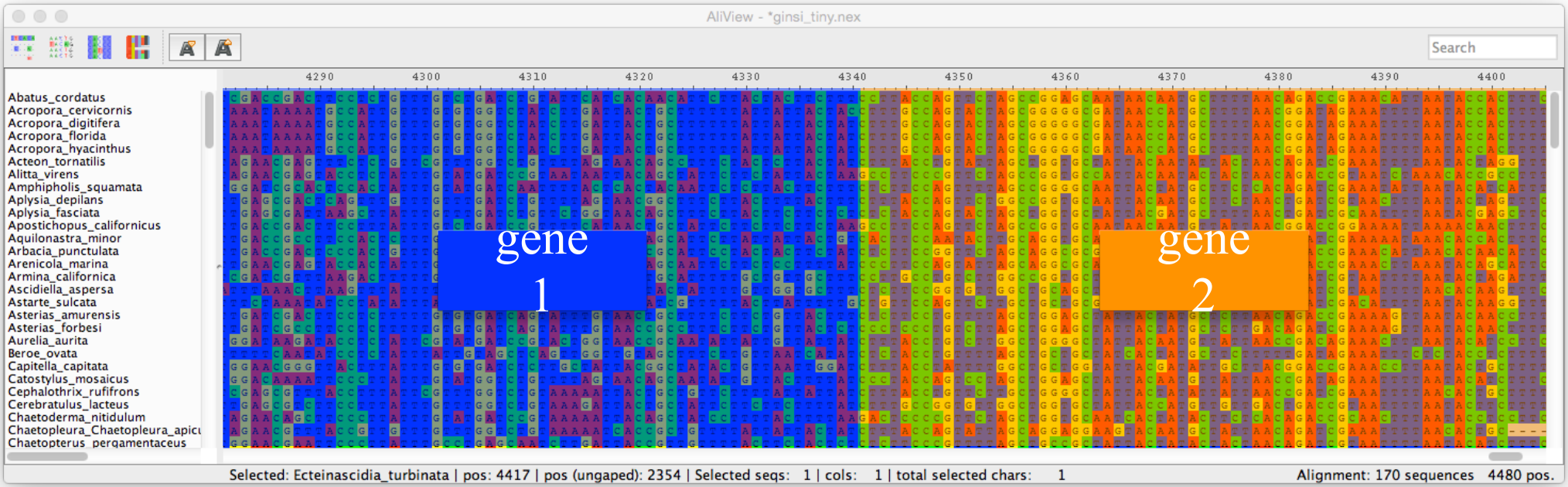

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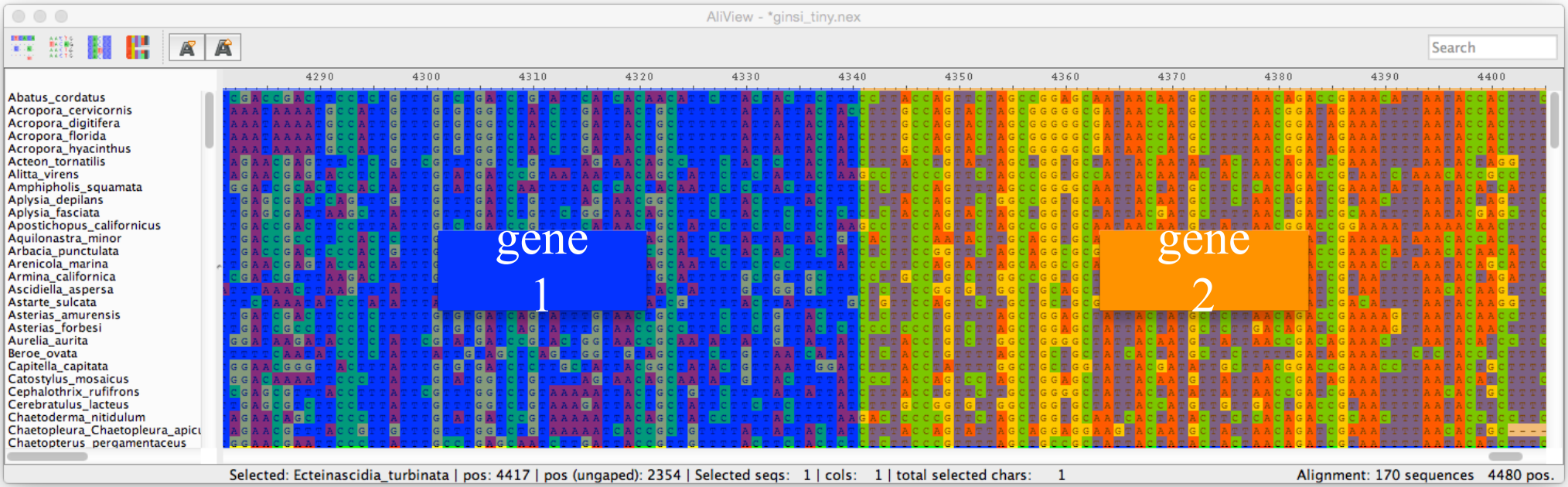

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- relative rates (a–f)
- the nature/degree of ASRV (p, α)

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Biology motivates the extension of models

Variation in substitution process across sites is a prevalent feature of empirical datasets

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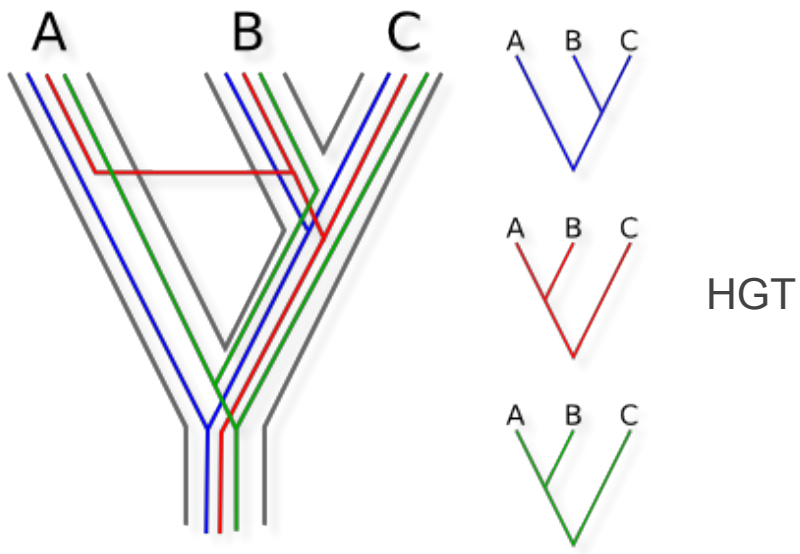

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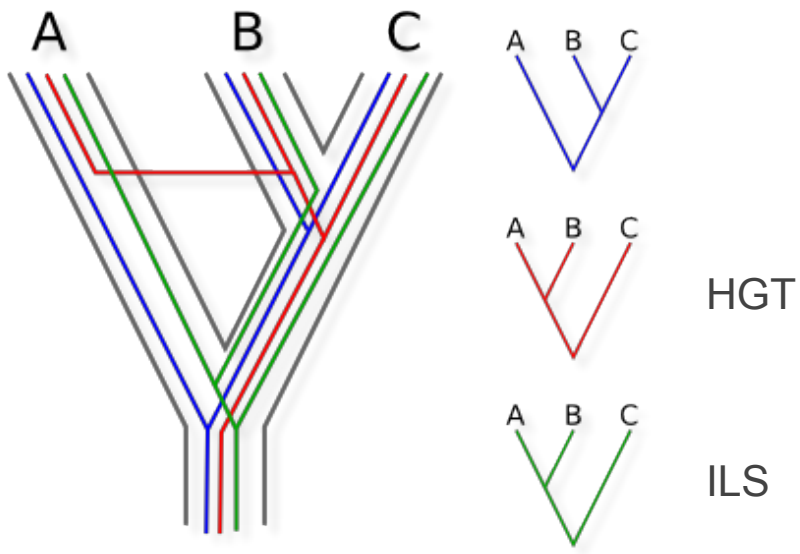

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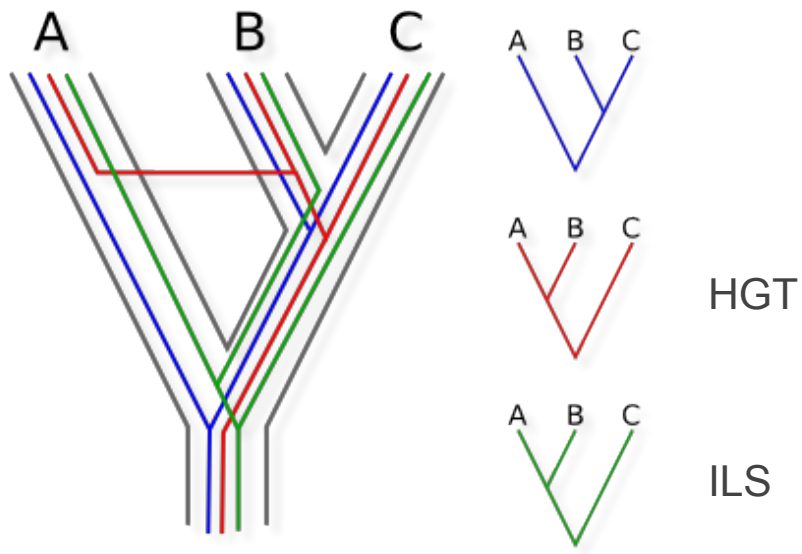
There are 'species-tree' methods that allow the tree topology to vary across sites



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Under simulation, failure to accommodate substitution process heterogeneity can cause biased estimates of:

- tree topology and nodal support
- 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

Accommodating Among Site Process Heterogeneity

Partition model approach for modeling ASPH

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

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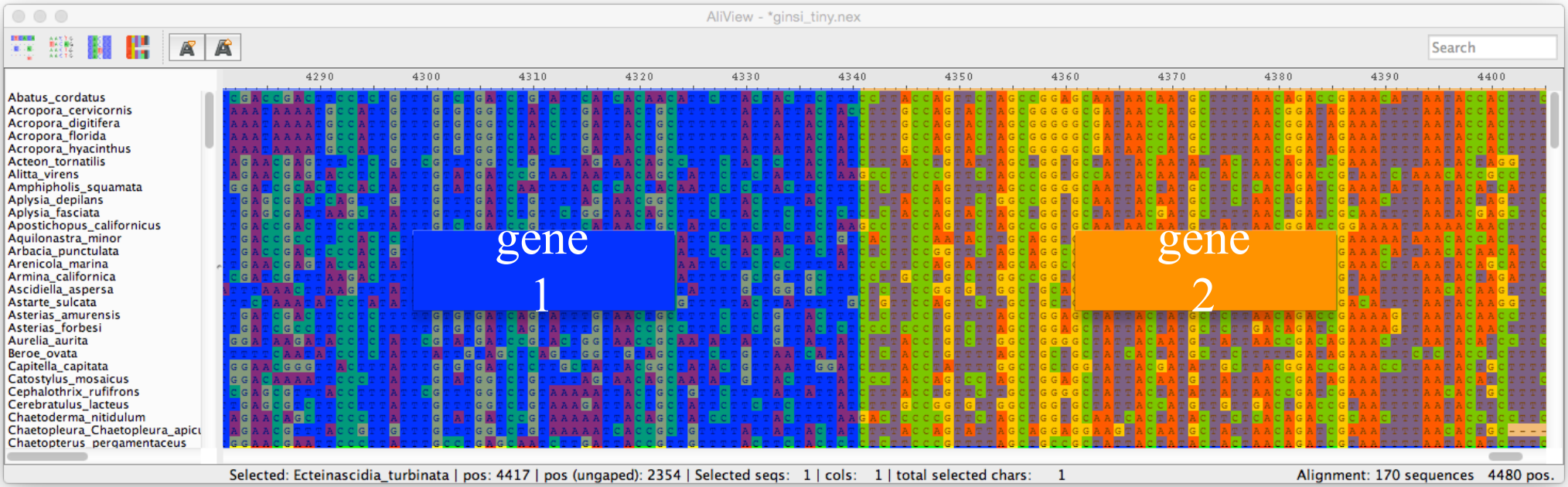

Define two or more data subsets that are likely to capture substitution process heterogeneity

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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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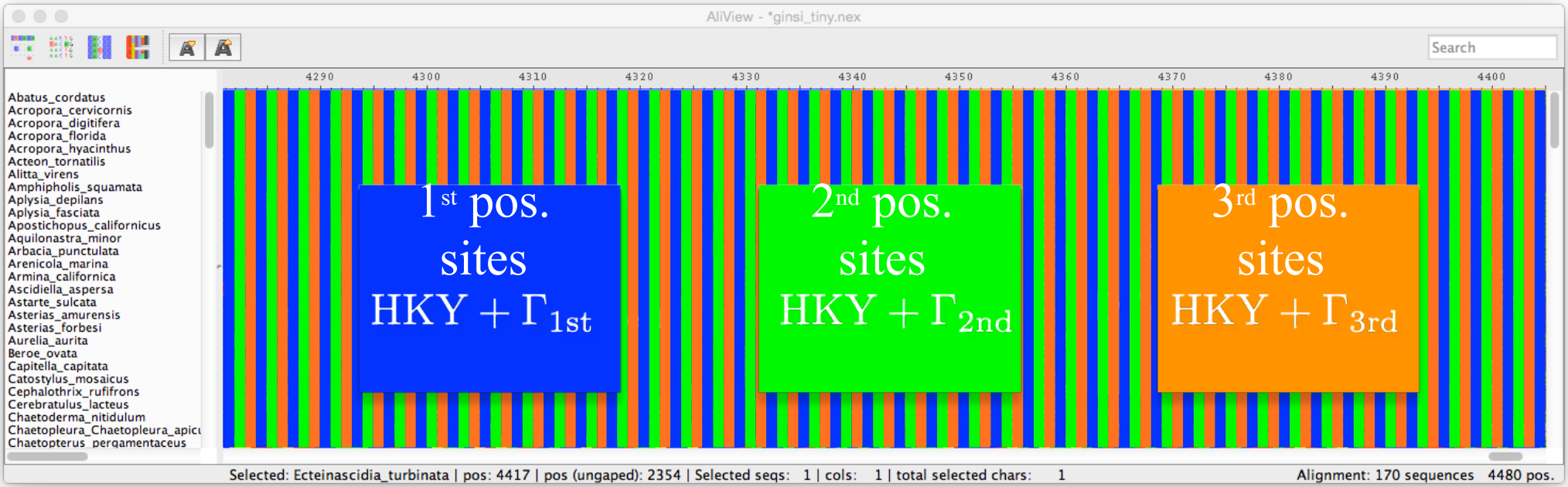
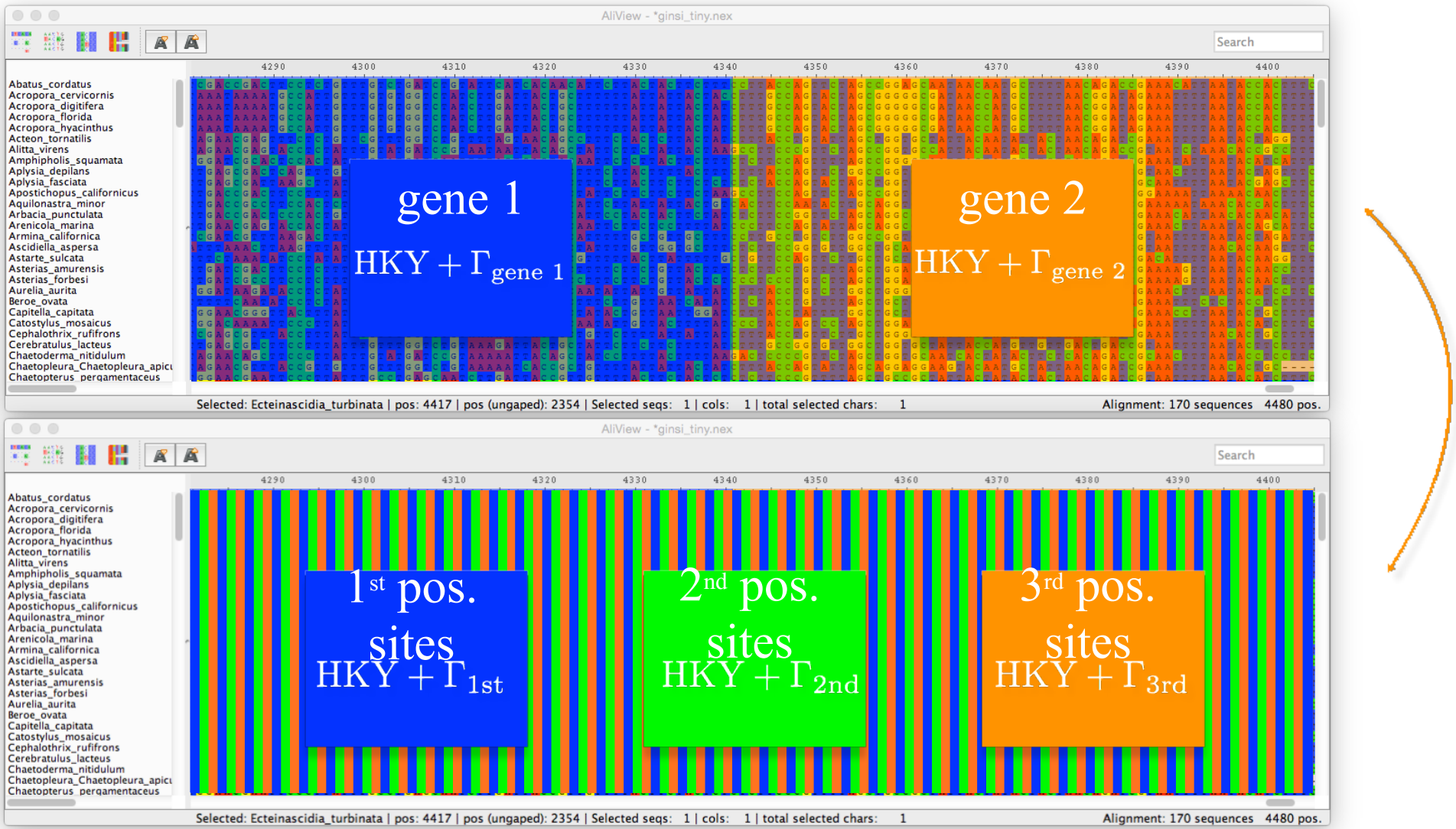


Alternative mixed-models are possible: for instance, the CAT model in Phylobayes (Lartillot et al.)

Accommodating Among Site Process Heterogeneity

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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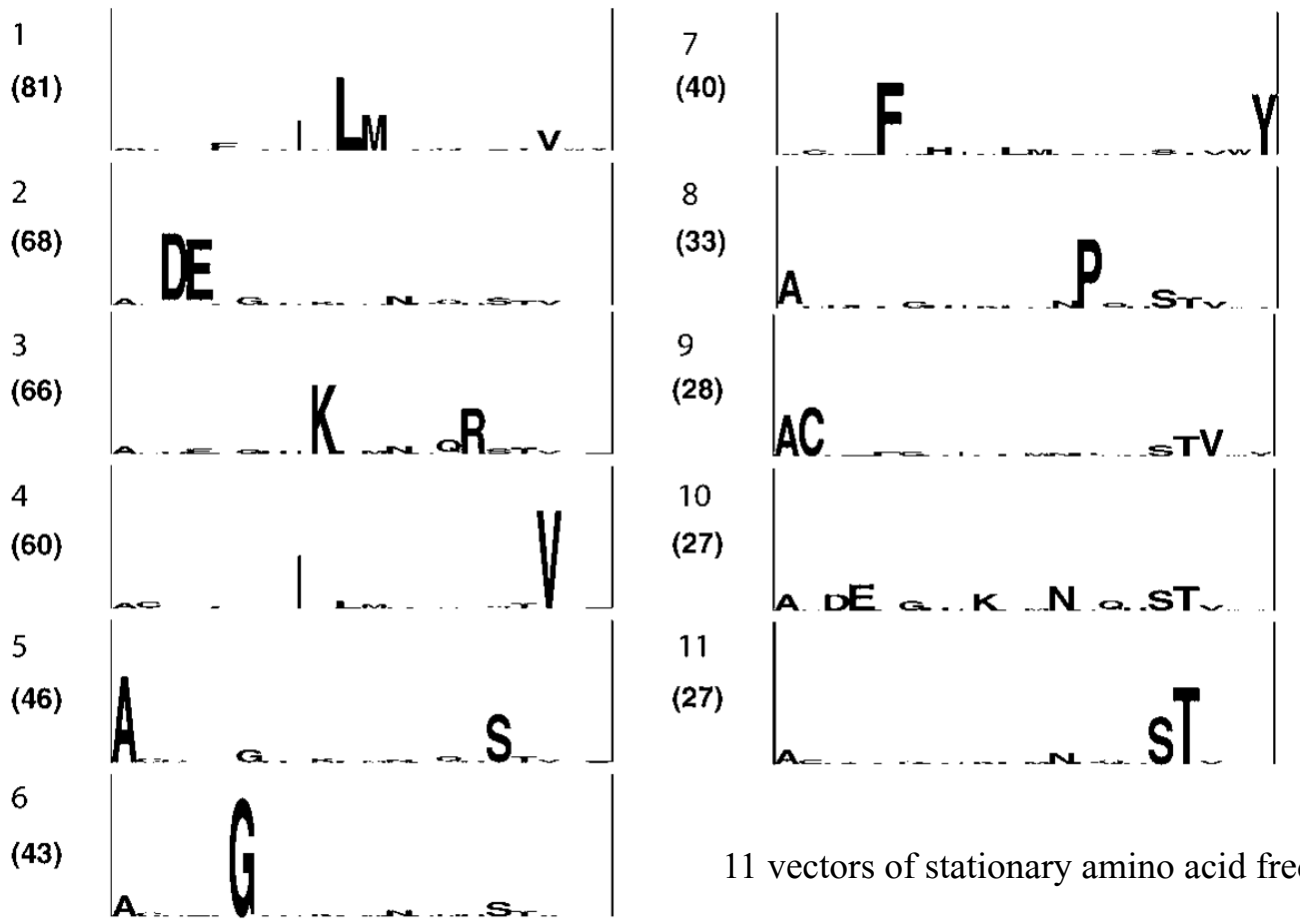

11 vectors of stationary amino acid frequencies estimated from an alignment

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

Outline

I. A brief review of Continuous-Time Markov models

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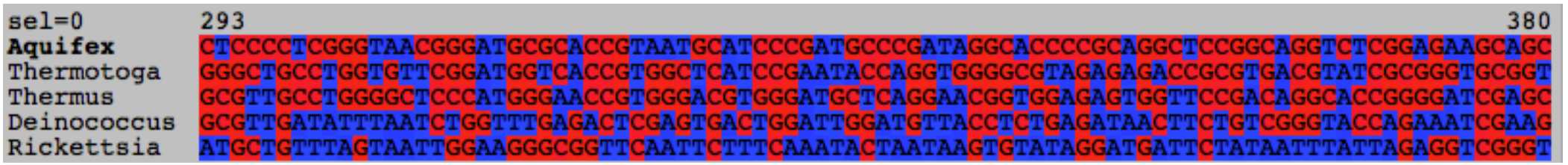
The Deinococcus-Thermus phylum and the effect of rRNA composition on phylogenetic tree construction.

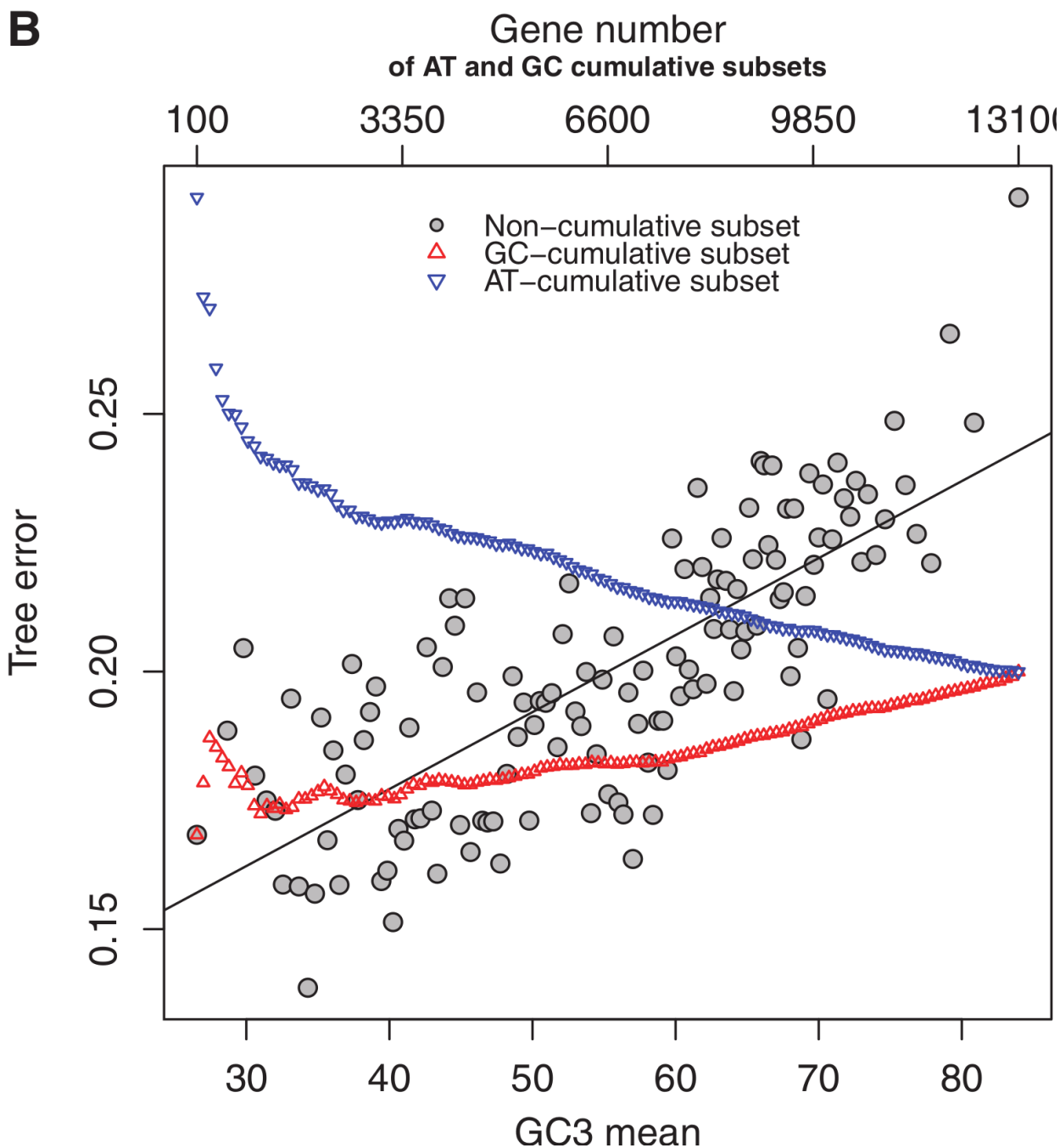
Weisburg WG, Giovannoni SJ, Woese CR.

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



“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.”

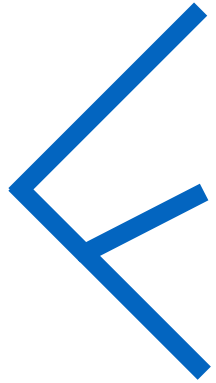
The impact of compositional heterogeneity on mammalian phylogeny



- 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

Romiguier et al., MBE 2013

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)

Mixtures of GTR matrices

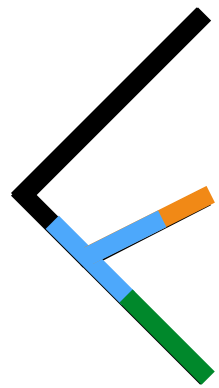
Changes at nodes:

- *n* branches -> *n* matrices: Yang and Roberts 1995, Galtier and Gouy 1998, Boussau 2006, Heaps et al., 2014

- *n* branches -> *k*<*n* matrices: Foster 2004

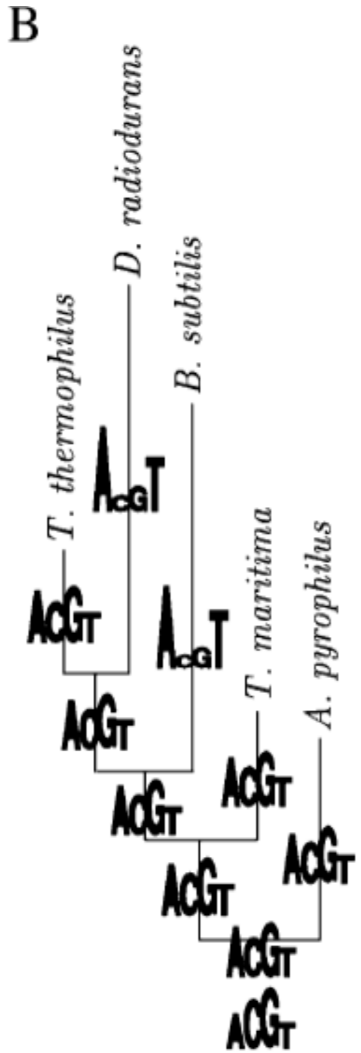
Changes along branches:

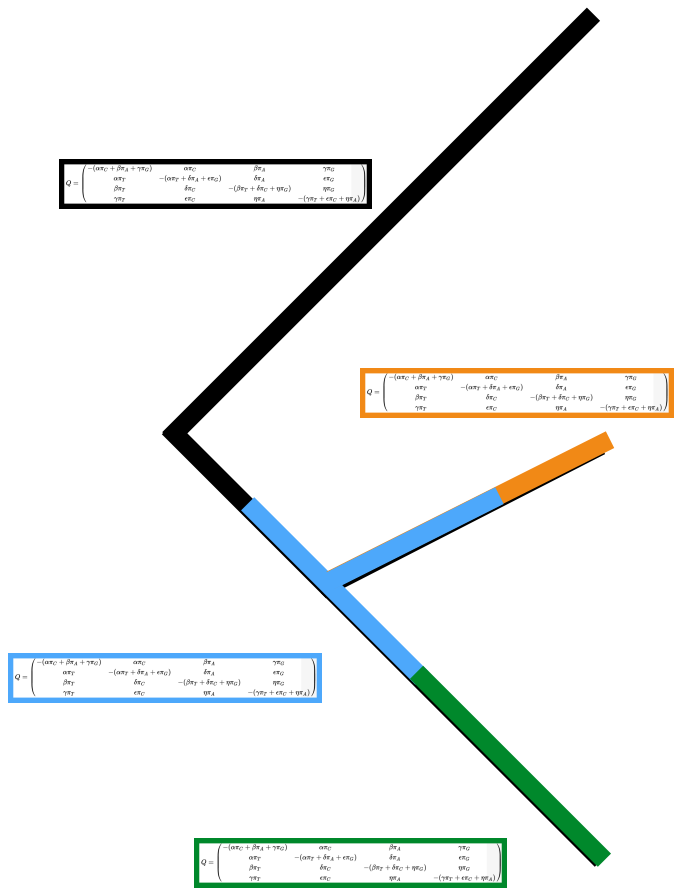
- Blanquart and Lartillot 2006, 2008



Blanquart and Lartillot 2006

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





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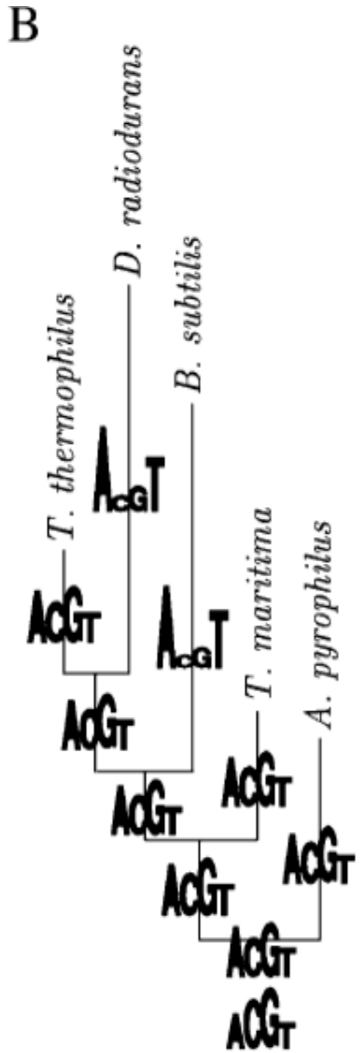
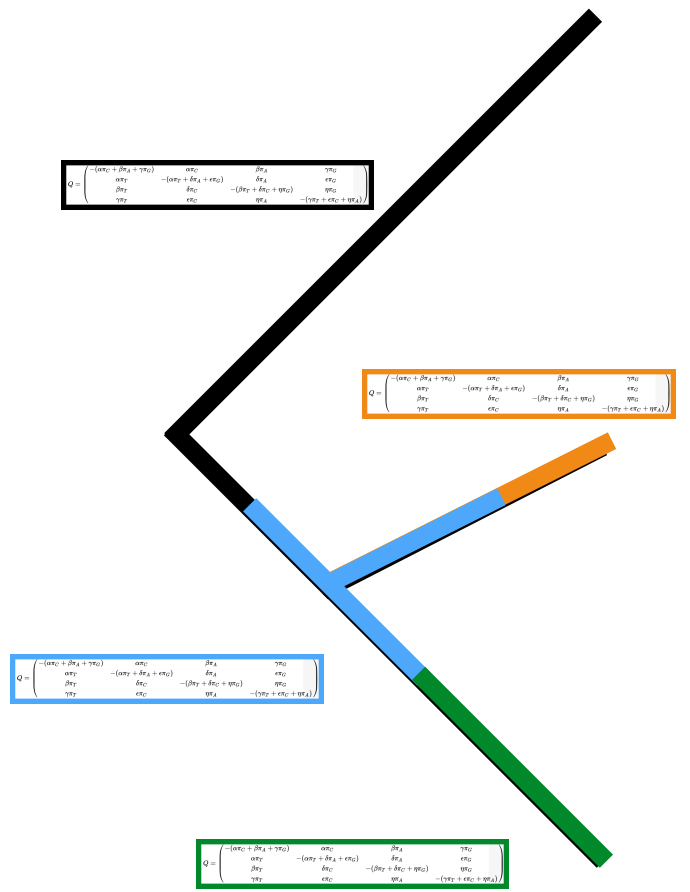


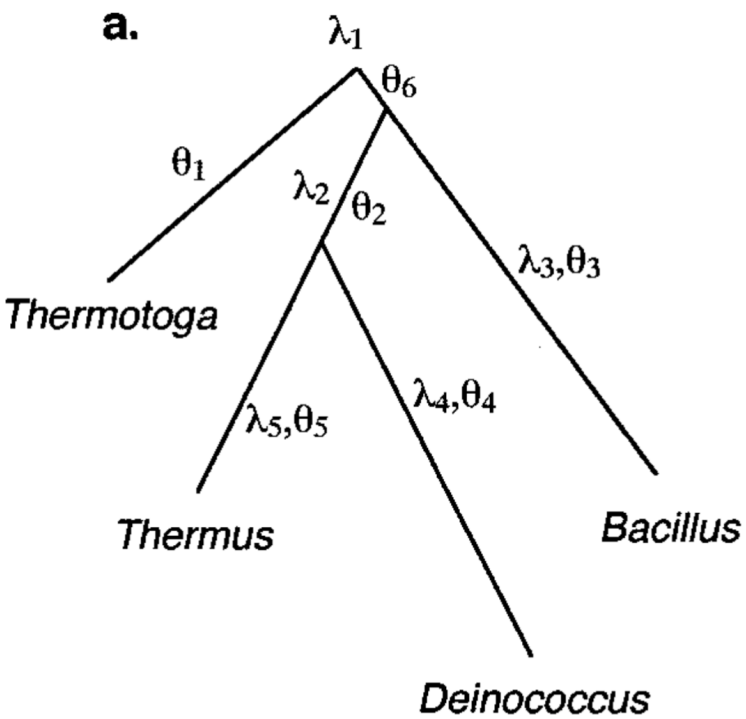


Problem: does not scale very well

Galtier and Gouy 1998

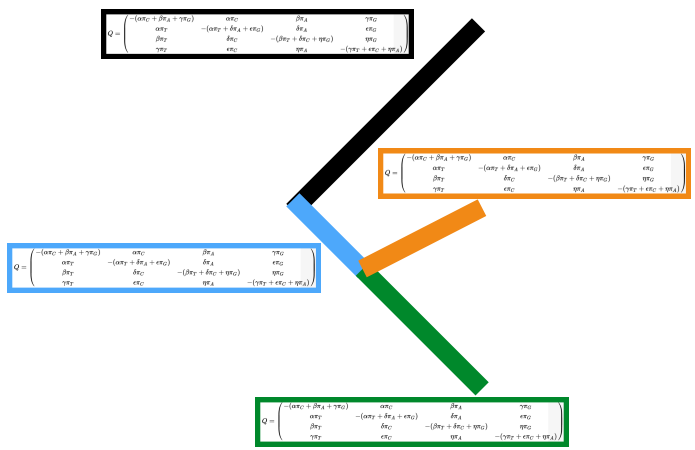
ML estimation of branch-wise GC equilibrium frequencies

a.



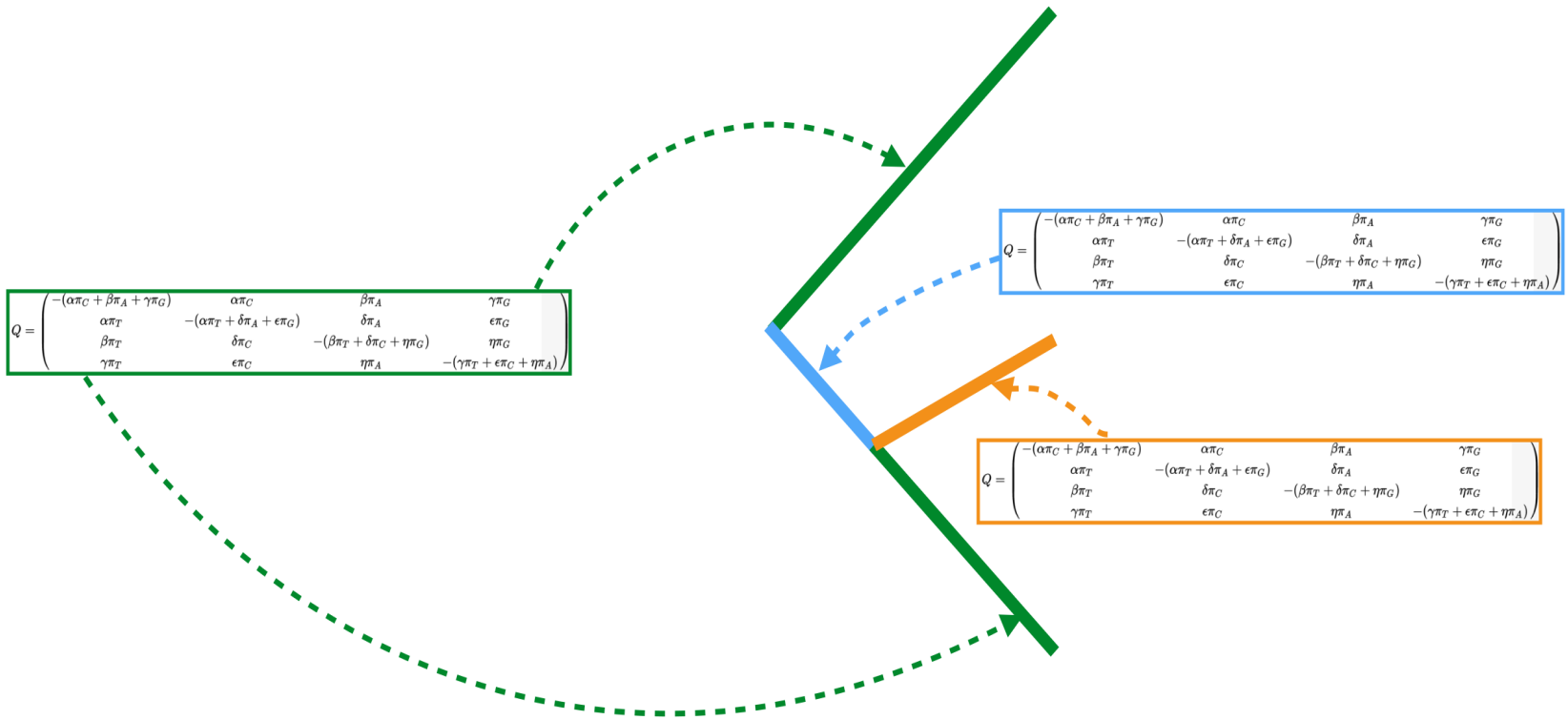
b.

	estimate	s.e.
κ	2.073	0.201
ϕ	0.962	0.136
ω	61.8%	1.5%
λ_1	0.097	0.012
λ_2	0.042	0.008
λ_3	0.111	0.012
λ_4	0.118	0.013
λ_5	0.067	0.010
θ_1	81.4%	5,0%
θ_2	69.7%	8.2%
θ_3	28.6%	4.4%
θ_4	28.3%	4.2%
θ_5	71.4%	5.7%
θ_6	100%	15.1%



Foster 2004

Bayesian MCMC estimation of a limited set of equilibrium frequencies

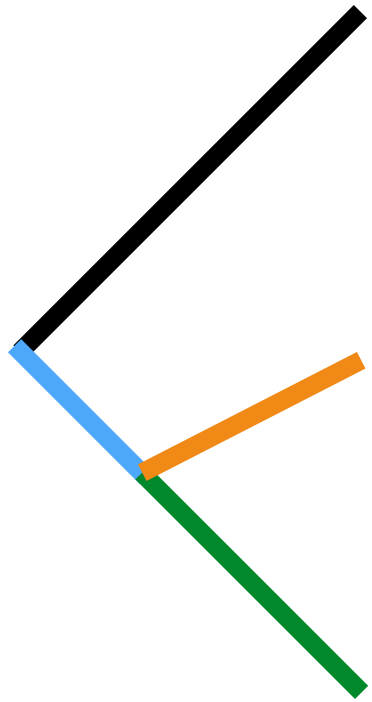


Heaps 2014

Bayesian MCMC estimation

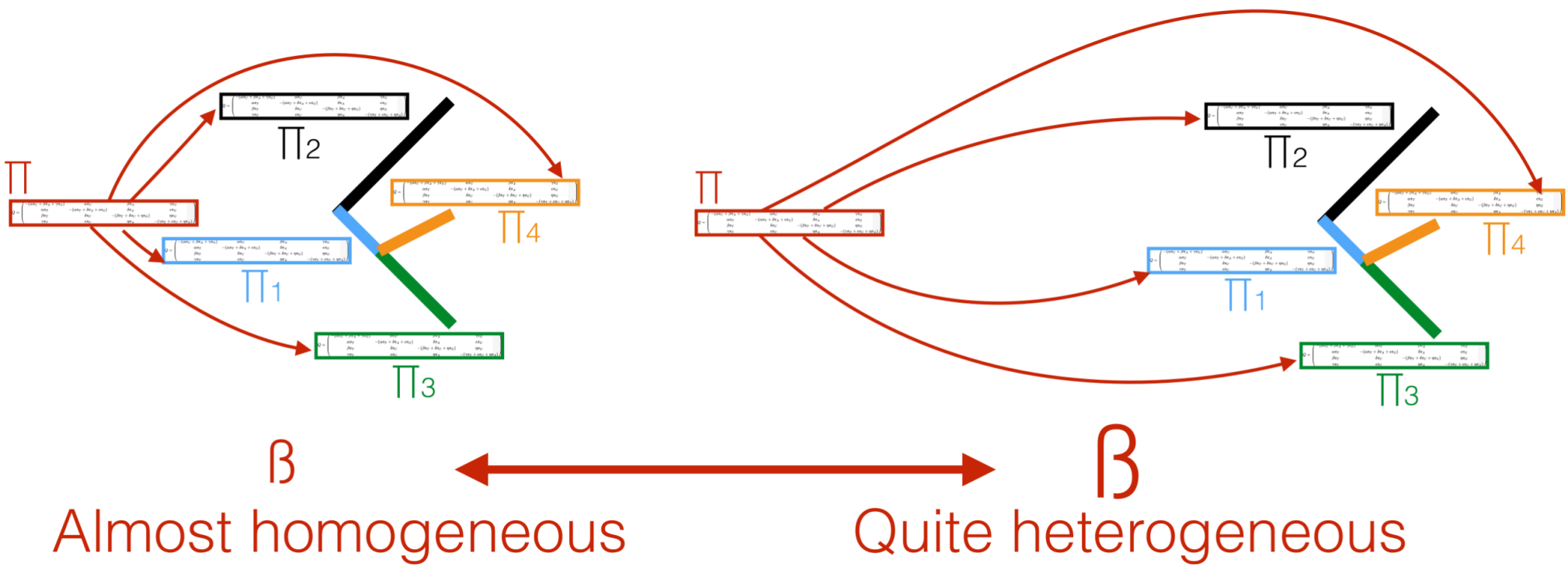
2 different models:

- a hierarchical model
- a correlated model



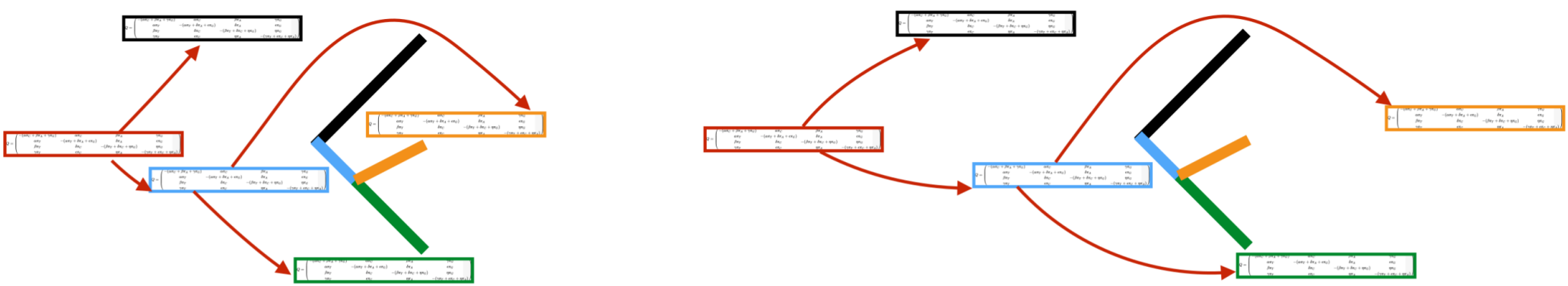
Heaps 2014: Hierarchical model

- One central vector Π
- Each branch i has its own vector Π_i in the neighbourhood of Π



Heaps 2014: Correlated model

- One ancestral vector $\prod$
- Each branch i has its own vector $\prod_i$ in the neighbourhood of its parent vector $\prod_{pi}$



ß

Quite correlated

ß

Not very correlated

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 review of Continuous-Time Markov models

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...)
- ...

See Jeff's talk !