

Introduction to modelling sequence evolution

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@bastounette



Who am I?

- CNRS researcher at LBBE in Lyon, France
- Interested in methods for sequence and genome evolution, and in their application
- Keywords: gene tree-species tree, phylogenetic reconstruction (neural networks recently), site- and branch-heterogeneous models of sequence evolution, genome-phenotype associations

Cave oratorem

- There is a reason why the day off is in the middle of the “Phylogeny reconstruction methods” session



This course

- A lot of the good stuff was borrowed from Brian Moore's slides



(<http://phylolab.org/>)

- The bad stuff is mine

Why modelling sequence evolution?

Generic statistical paradigm

- Question about some part of the world
- Model of how this part of the world works
- Collect data
- Estimate parameters of the model that allow answering the question

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Example

- Is my coin fair?
- Repeated throws=independent identically distributed *Bernoulli* draws
- Throw coin N times
- Estimate probability of heads

Why modelling sequence evolution?

Generic statistical paradigm

- Question about some part of the world
- Model of how this part of the world works
- Collect data
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Phylogeny example

- Are transitions as probable as transversions in rodents?
- Sites of alignment=independent identically distributed Markov chains running along a phylogeny
- Sequence rodents
- Estimate transition/transversion ratio

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Aims and outline

Understand the main ideas underlying models of sequence evolution










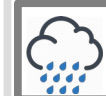




















- To do so, we will:
 - Introduce important probability notions
 - Play with models of character evolution through simulations
- Briefly present some of the main models of nucleotide evolution

Useful probability concepts

- Conditional probabilities
- Independence/intersection
- Union
- Bayes theorem
- Common distributions that will be useful in this talk:
 - Bernoulli
 - Binomial
 - Poisson
 - Exponential































Crash course in probability

Record of various events during 10 days

Days	1	2	3	4	5	6	7	8	9	10
Weather in Lyon										
Laundry dry										
Beyonce singing										

Crash course in probability










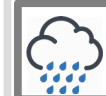




















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$P(\text{rainy}) = ?$

Crash course in probability










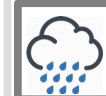




















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










$$P(\text{rainy}) = 0.5$$

$$P(\text{sunny}) = 1 - P(\text{rainy}) = 0.5$$

$$P(\text{dry laundry}) = 0.6$$

Crash course in probability

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










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




















$$P(\text{dry laundry} | \text{sunny}) = 0.8$$

$$P(\text{dry laundry} | \text{rainy}) = 0.4$$

Conditional probability: $P(A|B)$

Crash course in probability































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




















$$P(\text{dry laundry} | \text{rainy}) = 0.4$$

$$P(\text{Beyonce singing}) = 0.4$$

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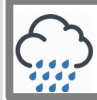


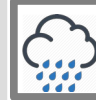




















The events “Beyonce singing” and “sunny” are independent

$$P(\text{Beyonce singing}) = 0.4$$

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























$$P(\text{dry laundry} | \text{sunny}) = 0.8$$

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The events “dry laundry” and “sunny” are NOT independent

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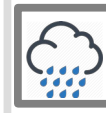




















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$$\begin{aligned}P(\text{dry laundry}) &= P(\text{dry laundry}|\text{sunny}) \times P(\text{sunny}) \\&\quad + P(\text{dry laundry}|\text{rainy}) \times P(\text{rainy}) \\&= 0.8 \times 0.5 + 0.4 \times 0.5 = 0.6\end{aligned}$$

Bayes formula

$$P(A|B) = \frac{P(A \wedge B)}{P(B)} = \frac{P(B \wedge A)}{P(B)}$$

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

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$$P(\text{sunny} | \text{dry laundry}) = \frac{P(\text{dry laundry} | \text{sunny}) P(\text{sunny})}{P(\text{dry laundry})}$$

Useful distributions

- *Discrete distributions (values in $\{0,1\}$, $\{0,1,2,\dots\}$):*
 - **Bernoulli:** coin flip: $P(X=1)=p$; $P(X=0)=1-p$

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$$Pr(k; n, p) = \Pr(X = k) = \binom{n}{k} p^k (1 - p)^{n-k}$$

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$$P(k \text{ events in interval}) = e^{-\lambda} \frac{\lambda^k}{k!}$$

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$$P(k \text{ events in interval}) = e^{-\lambda} \frac{\lambda^k}{k!}$$

- *Continuous distributions (values in \mathbb{R} , $[0,1]...$):*

- **Exponential:** Time between events in a Poisson process: how much time between two meteorites with diameter $> 1\text{m}$:

$$f(x; \lambda) = \begin{cases} \lambda e^{-\lambda x} & x \geq 0, \\ 0 & x < 0. \end{cases}$$

More on waiting times in Poisson processes

Waiting times in a Poisson process

Some rare, discrete event that occurs at a constant rate in continuous time is described by a Poisson process



Siméon Poisson (1821)

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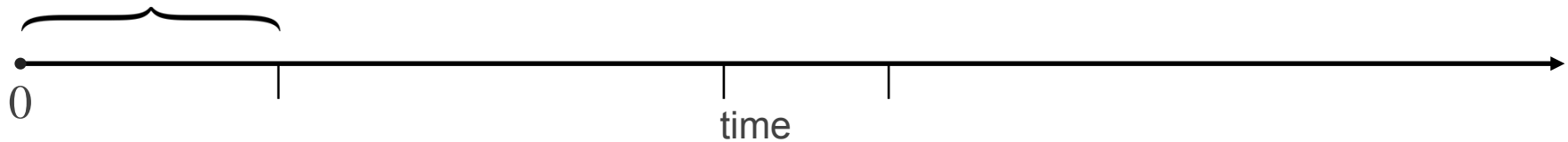
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The waiting (sojourn) time for the first event



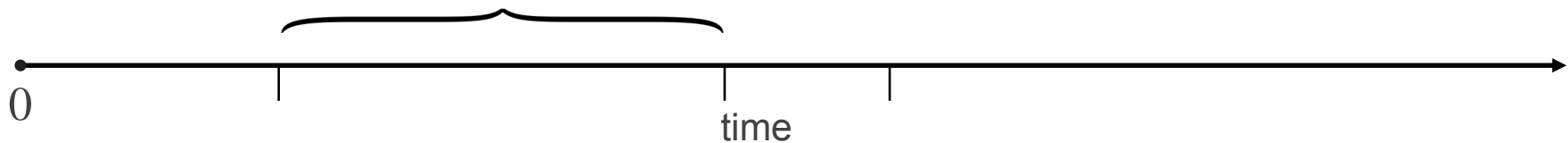
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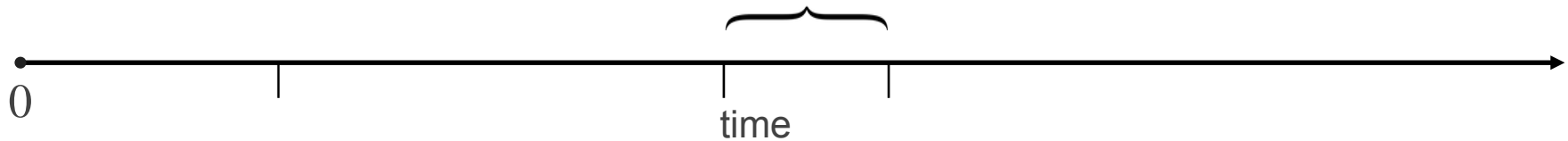
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These events occur with a rate λ

The waiting (sojourn) time for the third event



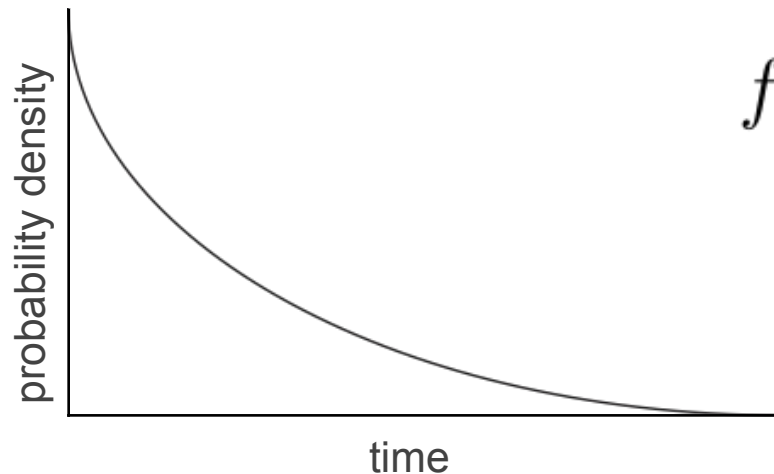
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Waiting times in a Poisson process

Some rare, discrete event that occurs at a constant rate in continuous time is described by a Poisson process

These events occur with a rate λ

The waiting (sojourn) times are exponentially distributed random variables



$$f(t) = \lambda e^{-\lambda t}$$

Aims and outline

Understand the main ideas underlying models of sequence evolution

- To do so, we will:
 - Introduce important probability notions
 - Play with models of character evolution through simulations
- Briefly present some of the main models of nucleotide evolution

Why are we interested in simulations?

- Simulating data forces us to think in terms of a generating process
- By comparing true to simulated data, we can get a sense of how realistic our model is
- Simulations are also central to a lot of inferential problems:
 - Validation of inference methods
 - Posterior predictive tests
 - Approximate Bayesian Computation (ABC)
 - ...

Why are we interested in simulations?

- Simulating data forces us to think in terms of a generating process
- By comparing true to simulated data, we can get a sense of how realistic our model is

Assumption:

If I can simulate my data set, I understand my data set.

- Approximate Bayesian Computation (ABC)
- ...

Stochastic Models of Nucleotide Substitution

Species

Sequence data

Species I

GCG--CACCGGCGCAGTCA

Species II

GCGTTCA--GGCG--GTCA

Species III

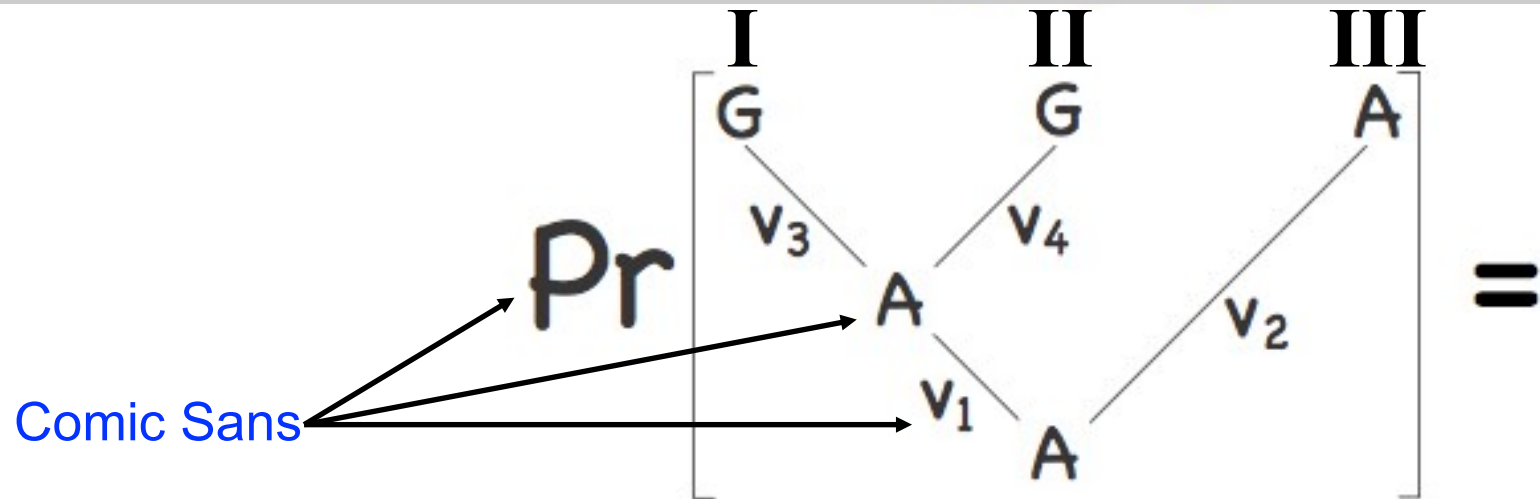
ACGTTACCGGCGCAGTCA

How do we compute the likelihood of a site pattern?

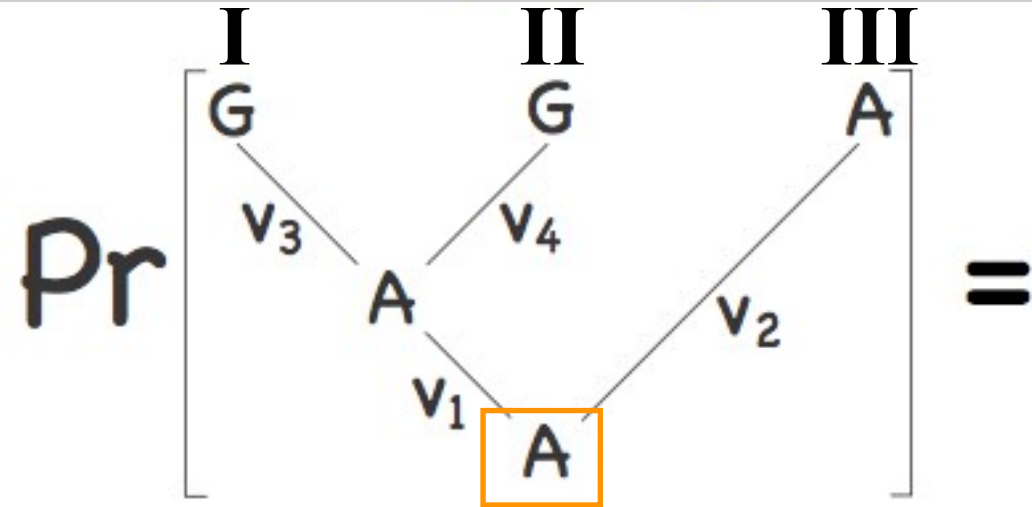
First, we'll see how we compute the likelihood of a site history.

To do that, we'll use simulations.

Stochastic Models of Nucleotide Substitution

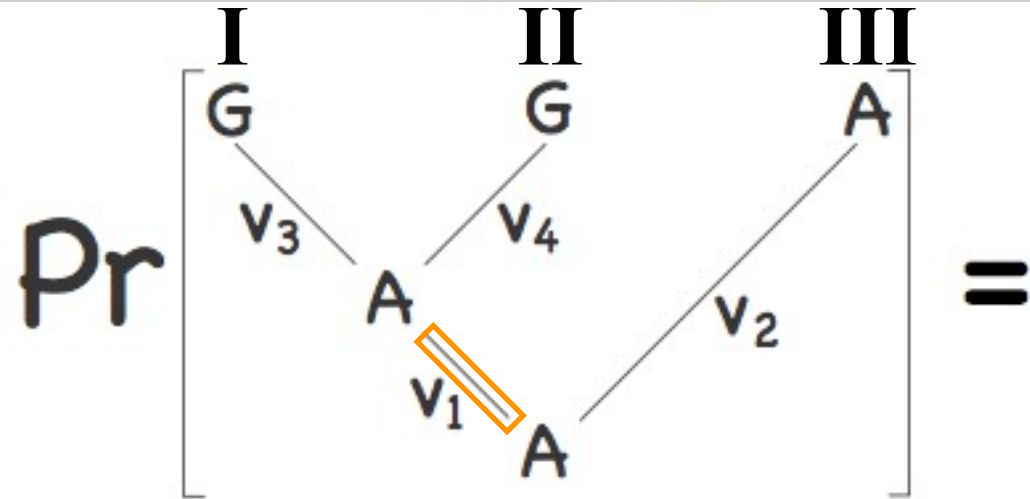


Stochastic Models of Nucleotide Substitution



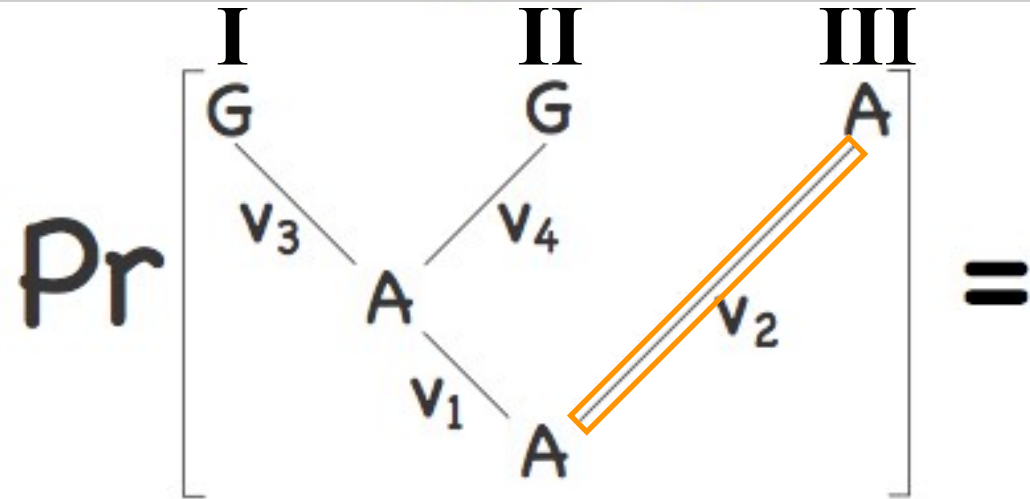
π_A

Stochastic Models of Nucleotide Substitution



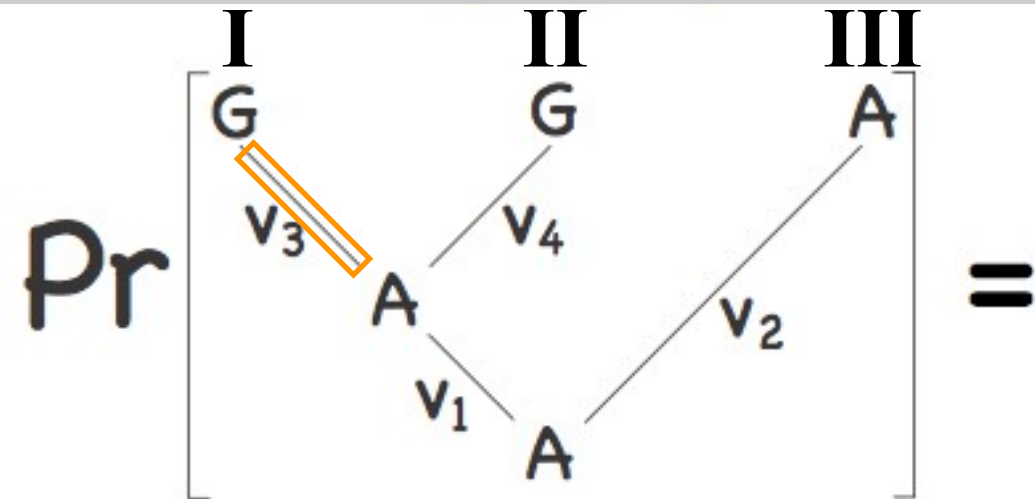
$$\pi_A \times p_{AA}(v_1)$$

Stochastic Models of Nucleotide Substitution



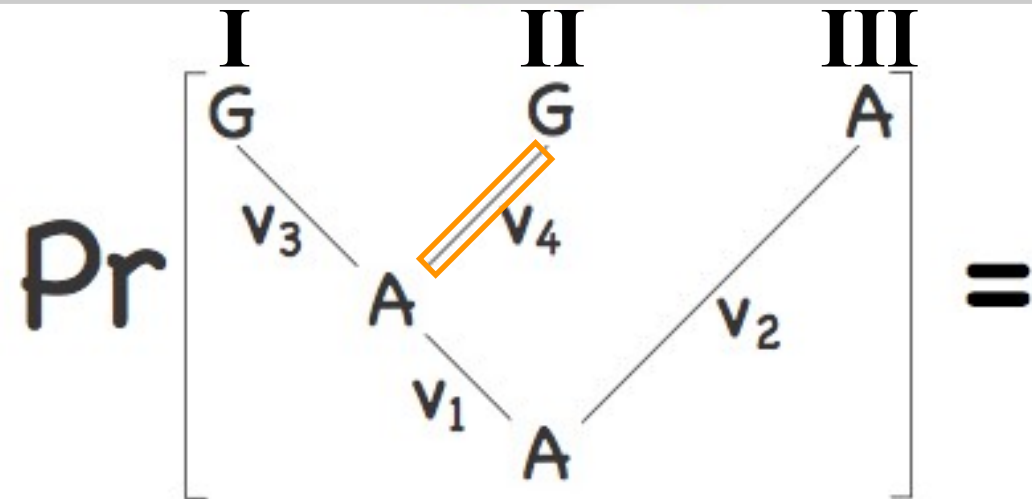
$$\pi_A \times p_{AA}(v_1) \times p_{AA}(v_2)$$

Stochastic Models of Nucleotide Substitution



$$\pi_A \times p_{AA}(v_1) \times p_{AA}(v_2) \times p_{AG}(v_3)$$

Stochastic Models of Nucleotide Substitution



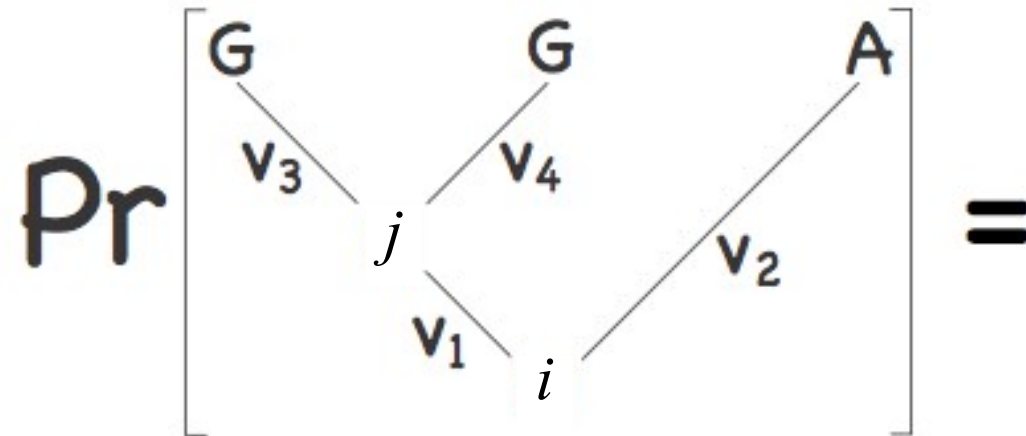
$$\pi_A \times p_{AA}(v_1) \times p_{AA}(v_2) \times p_{AG}(v_3) \times p_{AG}(v_4)$$

Stochastic Models of Nucleotide Substitution

$$\Pr \left[\begin{array}{c} \text{G} \quad \text{G} \quad \text{A} \\ \quad \swarrow \quad \searrow \quad \nearrow \\ \quad \text{v}_3 \quad \text{v}_4 \quad \text{v}_2 \\ \quad \quad j \quad \quad \quad i \\ \quad \quad \swarrow \quad \searrow \\ \quad \quad \text{v}_1 \end{array} \right] =$$

$$\pi_i \times p_{ij}(v_1) \times p_{iA}(v_2) \times p_{jG}(v_3) \times p_{jG}(v_4)$$

Stochastic Models of Nucleotide Substitution

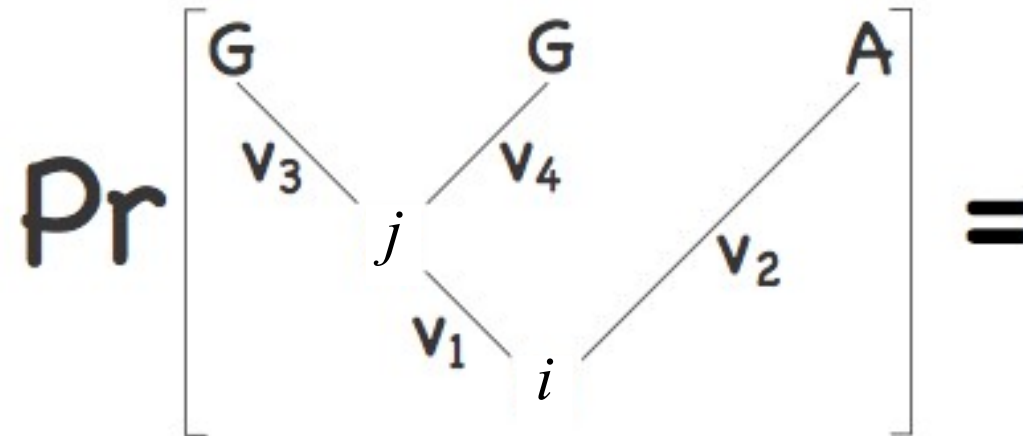


$$\pi_i \times p_{ij}(v_1) \times p_{iA}(v_2) \times p_{jG}(v_3) \times p_{jG}(v_4)$$

π_i Stationary frequencies

$p_{ij}(v)$ Transition probabilities

Stochastic Models of Nucleotide Substitution



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$p_{ij}(v)$ Stochastic Models of Nucleotide Substitution

Continuous-time Markov Chains (CTMC)

Evolution of discrete traits (e.g., substitution models, morphological models)

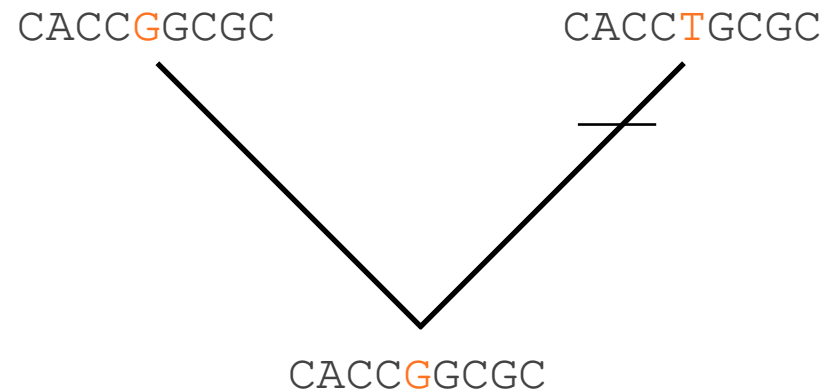
We will introduce:

- ***Substitution rates***
- ***Substitution probabilities***
- ***Stationary frequencies***

$p_{ij}(v)$ Stochastic Models of Nucleotide Substitution

Models describe changes in the nucleotide sites at the species level

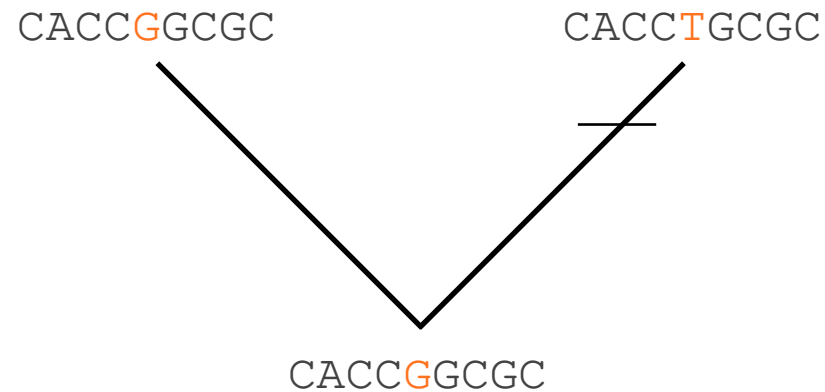
We are (generally) not trying to model the dynamics of allele frequencies in populations



$p_{ij}(v)$ Stochastic Models of Nucleotide Substitution

Models describe changes in the nucleotide sites at the species level

We are (generally) not trying to model the dynamics of allele frequencies in populations



We are modeling the process of **nucleotide substitution**, which describes the outcome of the mutation and fixation processes within populations

$p_{ij}(v)$ Stochastic Models of Nucleotide Substitution

Continuous-time Markov Models

Character change (nucleotide substitution) is modeled as a continuous-time Markov chain (CTMC)

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Continuous-time Markov Models

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Stochastic model in which the next state of the chain depends only on the current state

$p_{ij}(v)$ Stochastic Models of Nucleotide Substitution

Continuous-time Markov Models

Character change (nucleotide substitution) is modeled as a continuous-time Markov chain (CTMC)

Stochastic model in which the next state of the chain depends only on the current state

The model is central to model-based inference

Even if the parameters of the substitution model are not of direct interest, they are nevertheless critical to estimation of the focal model parameters

$$p_{ij}(v)$$

The Instantaneous-Rate Matrix

A Continuous-time Markov model is defined by a matrix of substitution rates

A table that specifies the rates of all possible changes between states.

$$p_{ij}(v)$$

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A hypothetical instantaneous-rate matrix

		To			
From	A	A	C	G	T
	A	−1.916	0.541	0.787	0.588
	C	0.148	−1.069	0.415	0.506
	G	0.286	0.170	−0.591	0.135
	T	0.525	0.236	0.594	−1.355

This table of rates specifies the instantaneous rate of change between states.

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This table of rates specifies the instantaneous rate of change between states.

The rates are in terms of the expected number of substitutions per site.

$$p_{ij}(v)$$

The Instantaneous-Rate Matrix

A Continuous-time Markov model is defined by a matrix of substitution rates

A table that specifies the rates of all possible changes between states.

A hypothetical instantaneous-rate matrix

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From		A	C	G	T
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$p_{ij}(v)$ A Mechanistic Interpretation of the Rate Matrix

A hypothetical instantaneous-rate matrix

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$$\sum P_{ij} = 1.0$$

Developing Intuition for CTMCs: A Monte Carlo Simulation Experiment

What the heck is Monte Carlo Simulation?

We generate a number of **replicate outcomes** (we will perform multiple trials)

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Developing Intuition for CTMCs: A Monte Carlo Simulation Experiment

What the heck is Monte Carlo Simulation?

We generate a number of **replicate outcomes** (we will perform multiple trials)
of a **stochastic process** (our replicate experiments involve randomness)
under a **fully specified model** (with specific values for all model parameters)

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation

We will assume that we have a **fully specified phylogenetic model**:

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation

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there is a single branch (the tree 'topology')

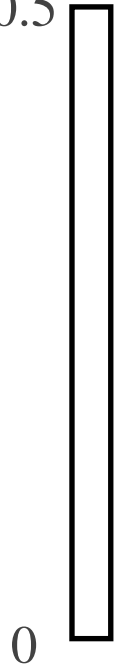


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A simple Monte Carlo Simulation

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- 0.5 there is a single branch (the tree 'topology')
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A simple Monte Carlo Simulation

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- 0.5
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 - the instantaneous-rate matrix is known
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What is the matrix of substitution probabilities over our branch of length 0.5?

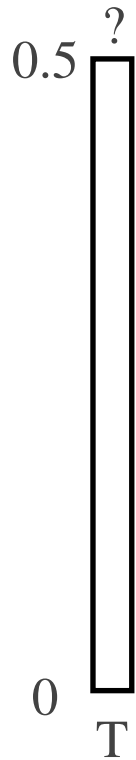
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A simple Monte Carlo Simulation

We will use a random-number generator to mimic the **stochastic process**

A Mechanistic Interpretation of the Rate Matrix

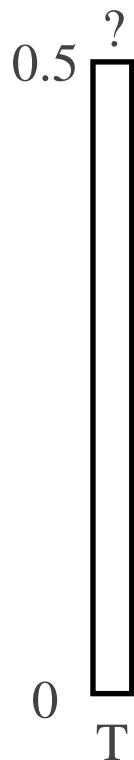
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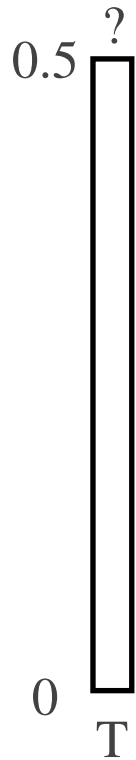


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Rate of leaving the current state, $T = 1.355$

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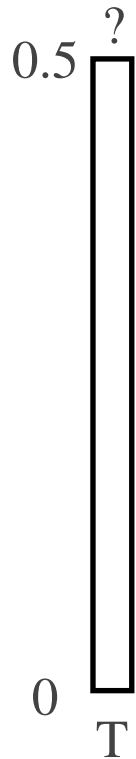
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Probability of changing to A:

$$P(T \rightarrow A) = q_{TA} / -q_{TT} = 0.525 / 1.355 = 0.387$$

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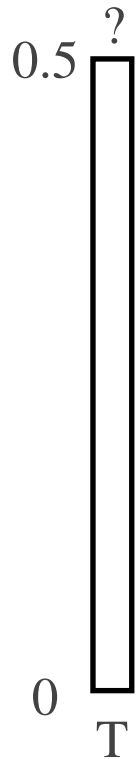
Probability of changing to C:

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$$P(T \rightarrow C) = q_{TC} / -q_{TT} = 0.236 / 1.355 = 0.174$$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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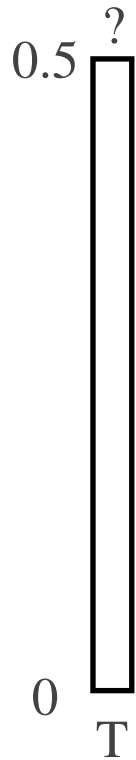
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A Mechanistic Interpretation of the Rate Matrix

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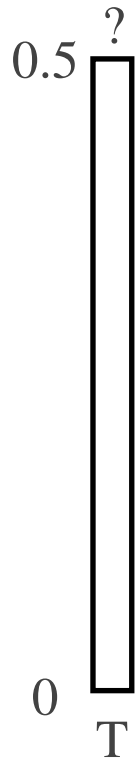


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Generate an exponentially distributed waiting time, x :

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



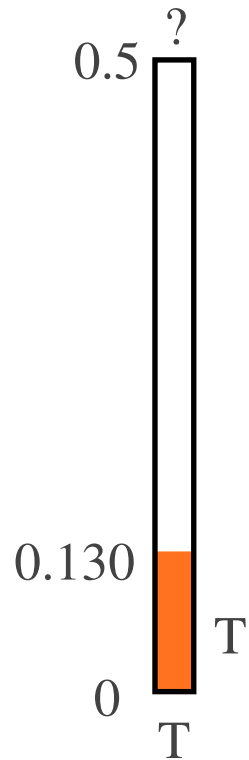
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A simple Monte Carlo Simulation



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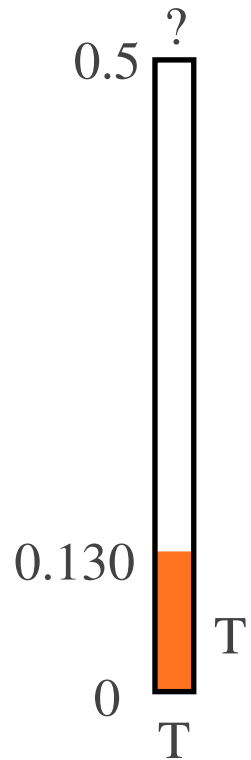
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A simple Monte Carlo Simulation



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Probabilities of substitution events in state T:

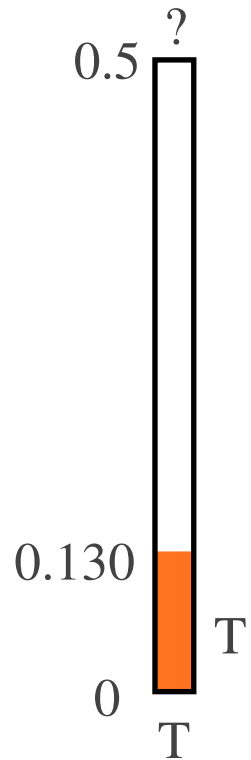
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Specify a set of intervals:

intervals

$P(T \rightarrow A) = 0.387$

$0 - 0.387$

(choose A)

$P(T \rightarrow C) = 0.174$

$0.387 - 0.561$

(choose C)

$P(T \rightarrow G) = 0.438$

$0.561 - 1$

(choose G)

Aside: Making Decisions within Random Numbers

Only the width of the bins matters, not their order

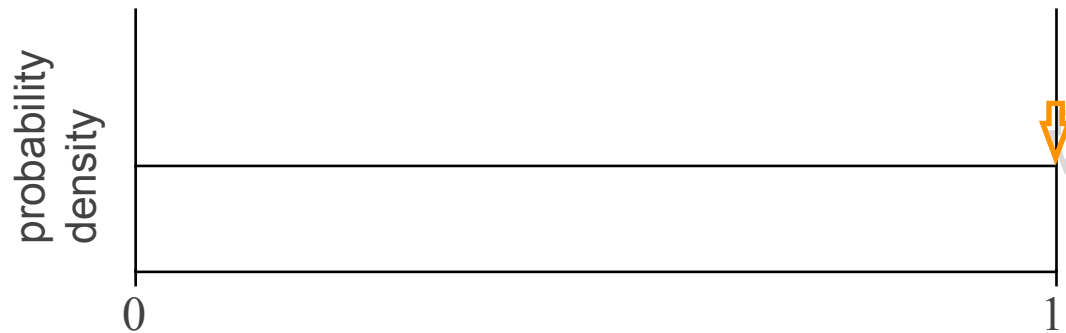
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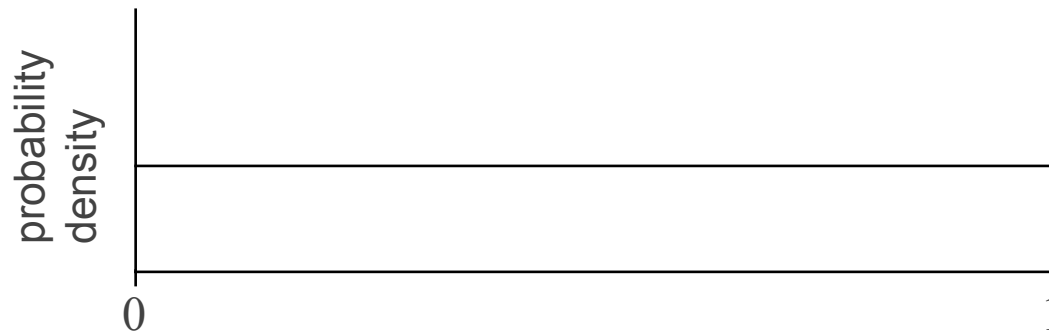
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Probability of outcomes:

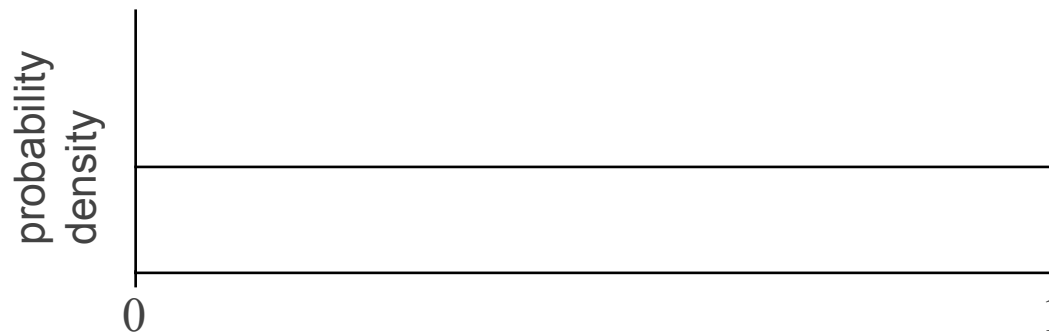
$$P(\text{option A}) = 0.6$$

$$P(\text{option B}) = 0.4$$

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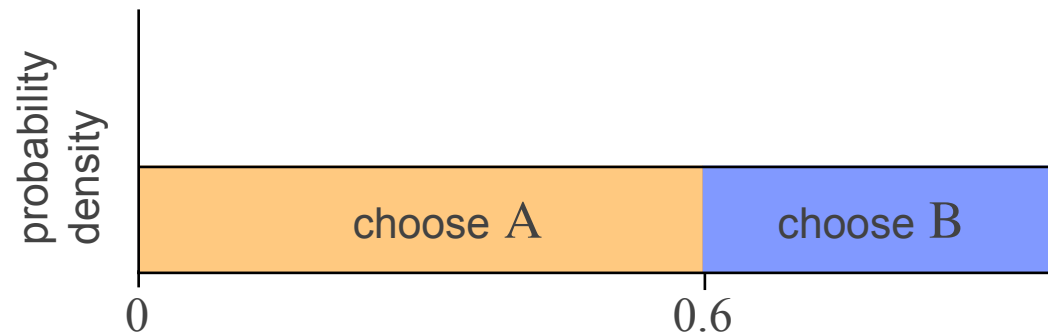
We can choose randomly (according to their probabilities) by specifying these intervals...

Probability of outcomes:	intervals	
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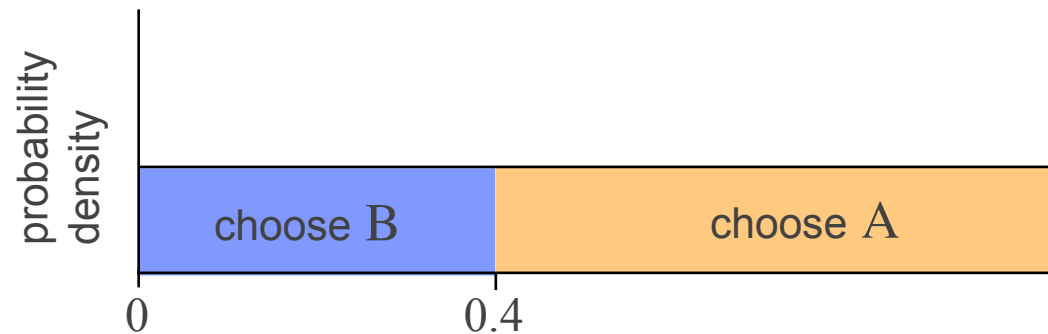
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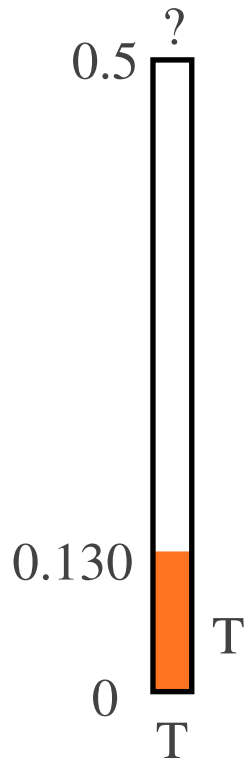
$$P(\text{option B}) = 0.4$$

Or equivalently by specifying these intervals...

Probability of outcomes:	intervals	
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Generate an exponentially distributed waiting time, x :

rate when process is in T: $\lambda = 1.355$

Draw x : $x \sim \text{dnExponential}(1.355) : x = 0.130$

Specify a set of intervals:

intervals

$P(T \rightarrow A) = 0.387$

$0 - 0.387$ (choose A)

$P(T \rightarrow C) = 0.174$

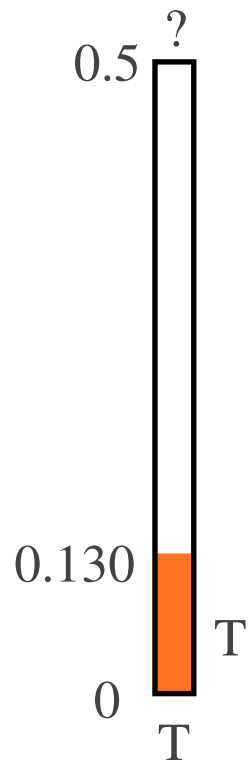
$0.387 - 0.561$ (choose C)

$P(T \rightarrow G) = 0.438$

$0.561 - 1$ (choose G)

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

Generate an exponentially distributed waiting time, x :

rate when process is in T: $\lambda = 1.355$

Draw x : $x \sim \text{dnExponential}(1.355) : x = 0.130$

Specify a set of intervals:

intervals

$P(T \rightarrow A) = 0.387$ $0 - 0.387$ (choose A)

$P(T \rightarrow C) = 0.174$ $0.387 - 0.561$ (choose C)

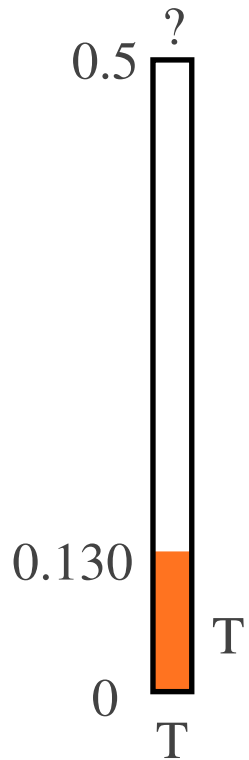
$P(T \rightarrow G) = 0.438$ $0.561 - 1$ (choose G)

Draw a uniformly distributed number, u , to select substitution event:

$u \sim \text{dnUniform}(0, 1) : u = 0.446$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

Generate an exponentially distributed waiting time, x :

rate when process is in T: $\lambda = 1.355$

Draw x : $x \sim \text{dnExponential}(1.355) : x = 0.130$

Specify a set of intervals:

intervals

$P(T \rightarrow A) = 0.387$

$0 - 0.387$ (choose A)

$P(T \rightarrow C) = 0.174$

0.387 – 0.561 (choose C)

$P(T \rightarrow G) = 0.438$

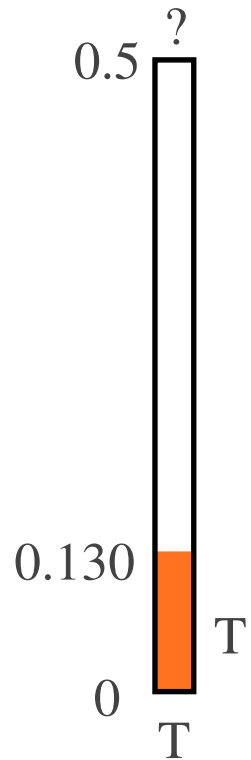
$0.561 - 1$ (choose G)

Draw a uniformly distributed number, u , to select substitution event:

$u \sim \text{dnUniform}(0, 1) : u = 0.446$

A Mechanistic Interpretation of the Rate Matrix

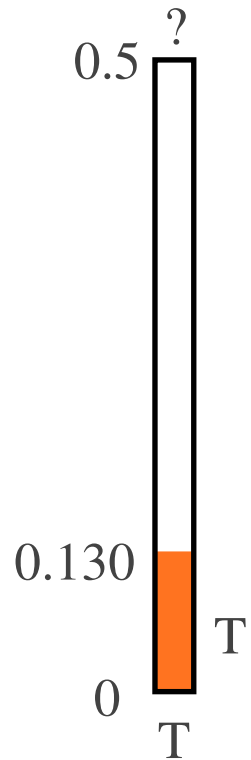
A simple Monte Carlo Simulation



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

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



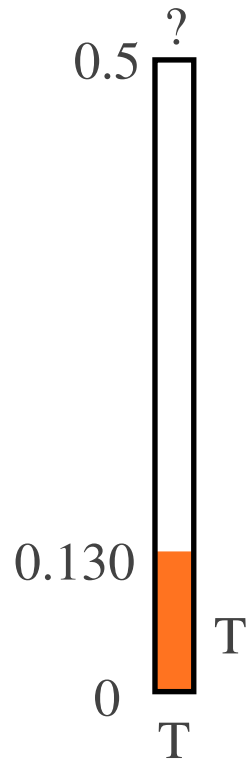
$$\mathbf{Q} = \{q_{ij}\} = \begin{pmatrix} -1.916 & 0.541 & 0.787 & 0.588 \\ 0.148 & -1.069 & 0.415 & 0.506 \\ 0.286 & 0.170 & -0.591 & 0.135 \\ 0.525 & 0.236 & 0.594 & -1.355 \end{pmatrix}$$

Generate waiting time to next event:

Rate when process in state C: $-q_{cc} = \lambda = 1.069$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

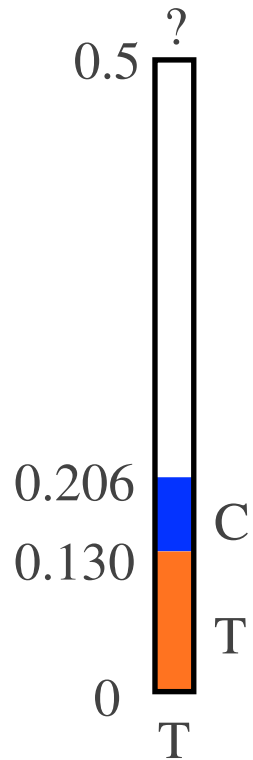
Generate waiting time to next event:

Rate when process in state C: $-q_{cc} = \lambda = 1.069$

Draw x : $x \sim \text{dnExponential}(1.069) : x = 0.076$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

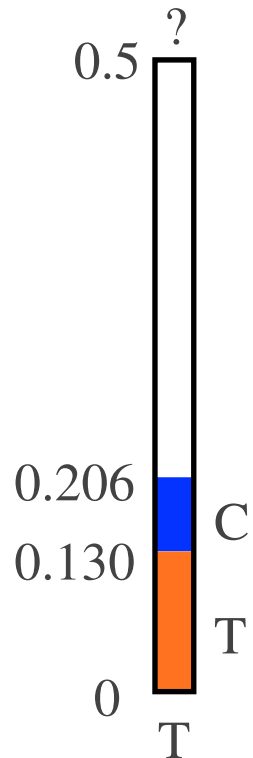
Generate waiting time to next event:

Rate when process in state C: $-q_{cc} = \lambda = 1.069$

Draw x: $x \sim \text{dnExponential}(1.069) : x = 0.076$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

Generate waiting time to next event:

Rate when process in state C: $-q_{cc} = \lambda = 1.069$

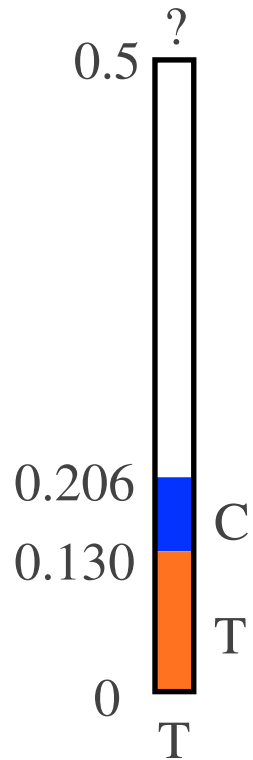
Draw x : $x \sim \text{dnExponential}(1.069) : x = 0.076$

Substitution probabilities in state C:

$$P(C \rightarrow A) = q_{ca} / -q_{cc} = 0.148 / 1.069 = 0.138$$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

Generate waiting time to next event:

Rate when process in state C: $-q_{cc} = \lambda = 1.069$

Draw x: $x \sim \text{dnExponential}(1.069) : x = 0.076$

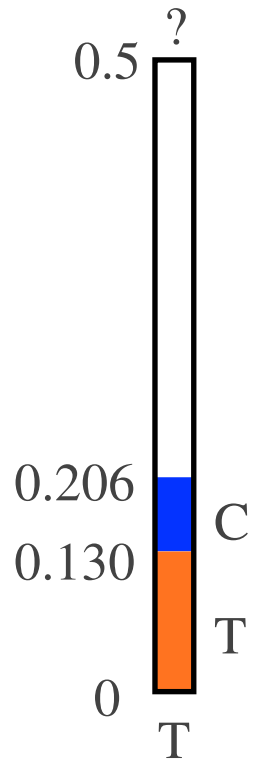
Substitution probabilities in state C:

$$P(C \rightarrow A) = q_{ca} / -q_{cc} = 0.148 / 1.069 = 0.138$$

$$P(C \rightarrow G) = q_{cg} / -q_{cc} = 0.415 / 1.069 = 0.388$$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

Generate waiting time to next event:

Rate when process in state C: $-q_{cc} = \lambda = 1.069$

Draw x: $x \sim \text{dnExponential}(1.069) : x = 0.076$

Substitution probabilities in state C:

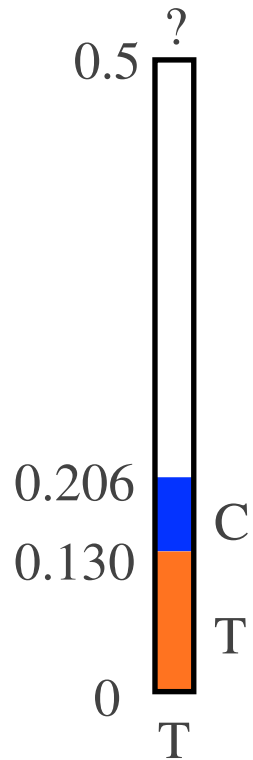
$$P(C \rightarrow A) = q_{ca} / -q_{cc} = 0.148 / 1.069 = 0.138$$

$$P(C \rightarrow G) = q_{cg} / -q_{cc} = 0.415 / 1.069 = 0.388$$

$$P(C \rightarrow T) = q_{ct} / -q_{cc} = 0.506 / 1.069 = 0.474$$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

Generate waiting time to next event:

Rate when process in state C: $-q_{cc} = \lambda = 1.069$

Draw x: $x \sim \text{dnExponential}(1.069) : x = 0.076$

Specify a set of intervals:

intervals

$$P(C \rightarrow A) = 0.138$$

$$0 - 0.138$$

(choose A)

$$P(C \rightarrow G) = 0.388$$

$$0.138 - 0.526$$

(choose G)

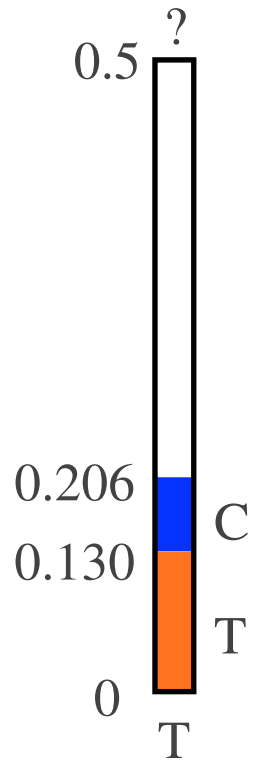
$$P(C \rightarrow T) = 0.474$$

$$0.526 - 1$$

(choose T)

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

Generate waiting time to next event:

Rate when process in state C: $-q_{cc} = \lambda = 1.069$

Draw x : $x \sim \text{dnExponential}(1.069) : x = 0.076$

Specify a set of intervals: intervals

$P(C \rightarrow A) = 0.138$ $0 - 0.138$ (choose A)

$P(C \rightarrow G) = 0.388$ $0.138 - 0.526$ (choose G)

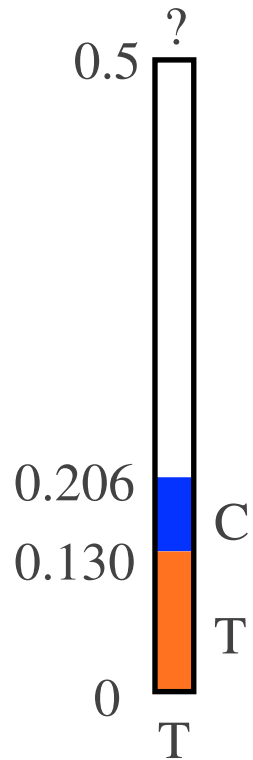
$P(C \rightarrow T) = 0.474$ $0.526 - 1$ (choose T)

Draw a uniformly distributed number, u , to select substitution event:

$u \sim \text{dnUniform}(0, 1) : u = 0.317$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

Generate waiting time to next event:

Rate when process in state C: $-q_{cc} = \lambda = 1.069$

Draw x : $x \sim \text{dnExponential}(1.069) : x = 0.076$

Specify a set of intervals:

$P(C \rightarrow A) = 0.138$

$P(C \rightarrow G) = 0.388$

$P(C \rightarrow T) = 0.474$

intervals

$0 - 0.138$

$0.138 - 0.526$

$0.526 - 1$

(choose A)

(choose G)

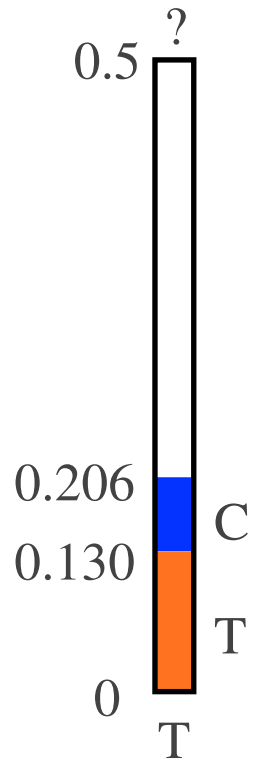
(choose T)

Draw a uniformly distributed number, u , to select substitution event:

$u \sim \text{dnUniform}(0, 1) : u = 0.317$

A Mechanistic Interpretation of the Rate Matrix

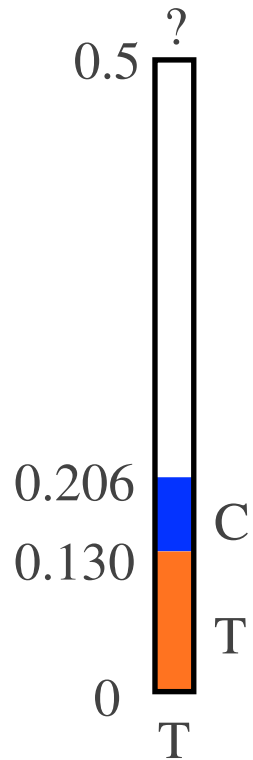
A simple Monte Carlo Simulation



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

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



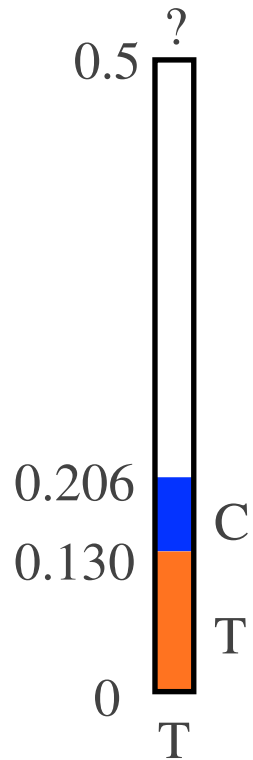
$$\mathbf{Q} = \{q_{ij}\} = \begin{pmatrix} -1.916 & 0.541 & 0.787 & 0.588 \\ 0.148 & -1.069 & 0.415 & 0.506 \\ 0.286 & 0.170 & -0.591 & 0.135 \\ 0.525 & 0.236 & 0.594 & -1.355 \end{pmatrix}$$

Generate waiting time to next event:

Rate when process in state G: $-q_{GG} = \lambda = 0.591$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

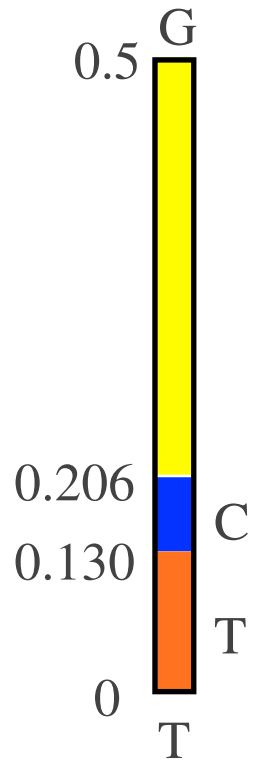
Generate waiting time to next event:

Rate when process in state G: $-q_{GG} = \lambda = 0.591$

Draw x: $x \sim \text{dnExponential}(1.069) : x = 1.820$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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

Generate waiting time to next event:

Rate when process in state G: $-q_{GG} = \lambda = 0.591$

Draw x: $x \sim \text{dnExponential}(1.069) : x = 1.820$

$1.820 > 0.5 - 0.206 \rightarrow \textit{Terminate simulation (in state G)}$

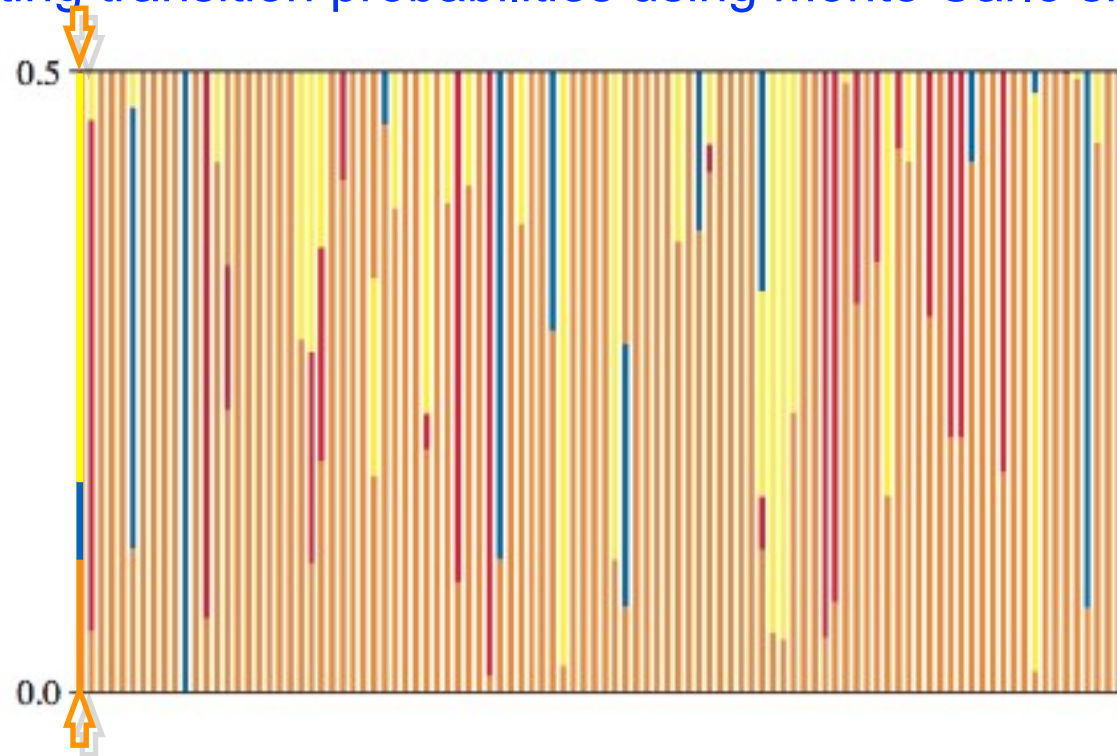
Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

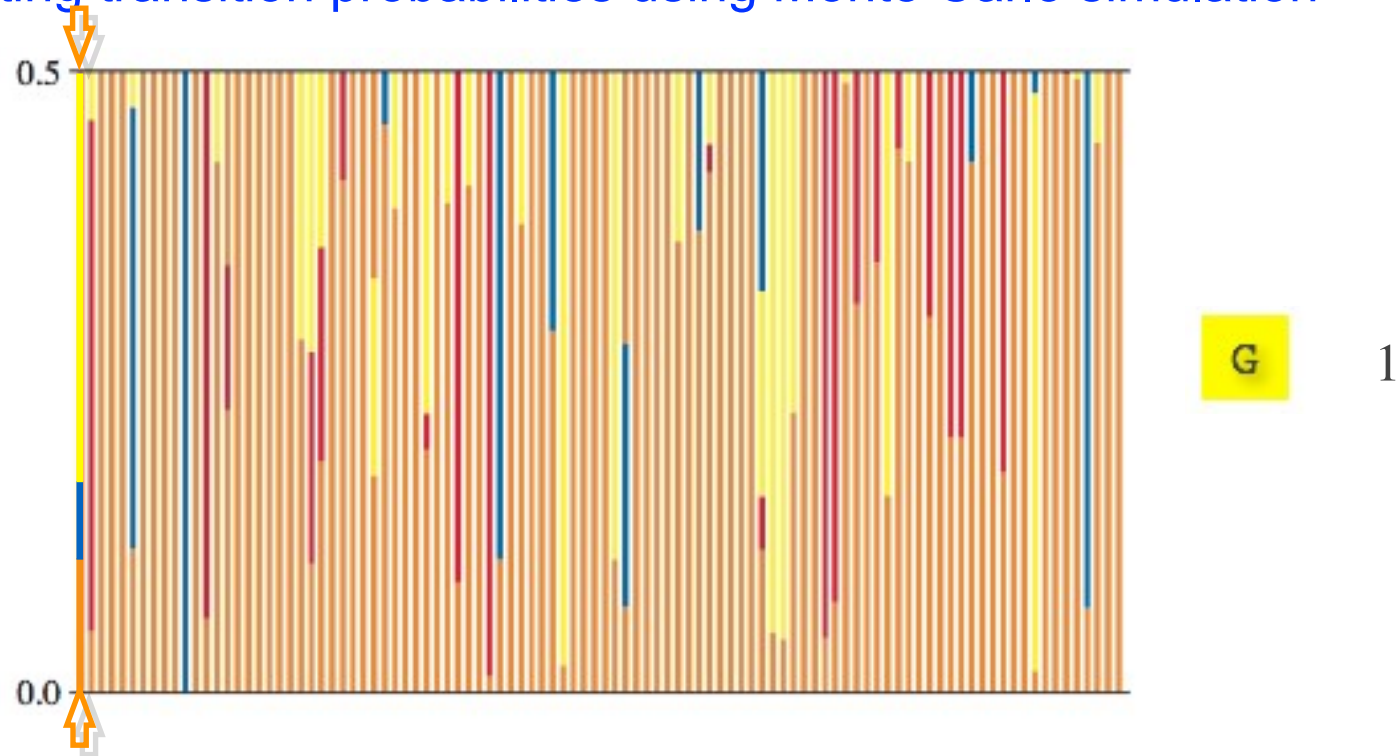


$T \rightarrow C \rightarrow G$

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

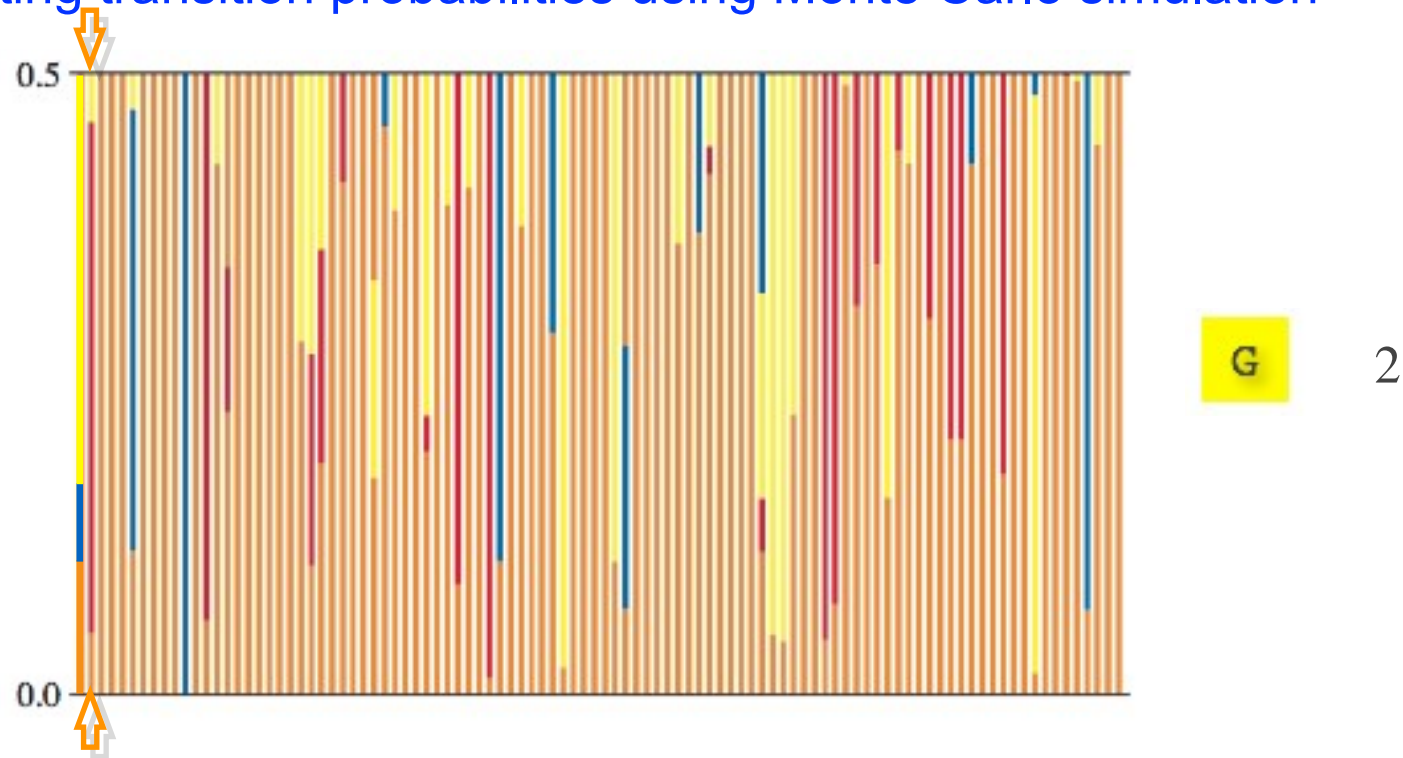


$T \rightarrow C \rightarrow G$

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

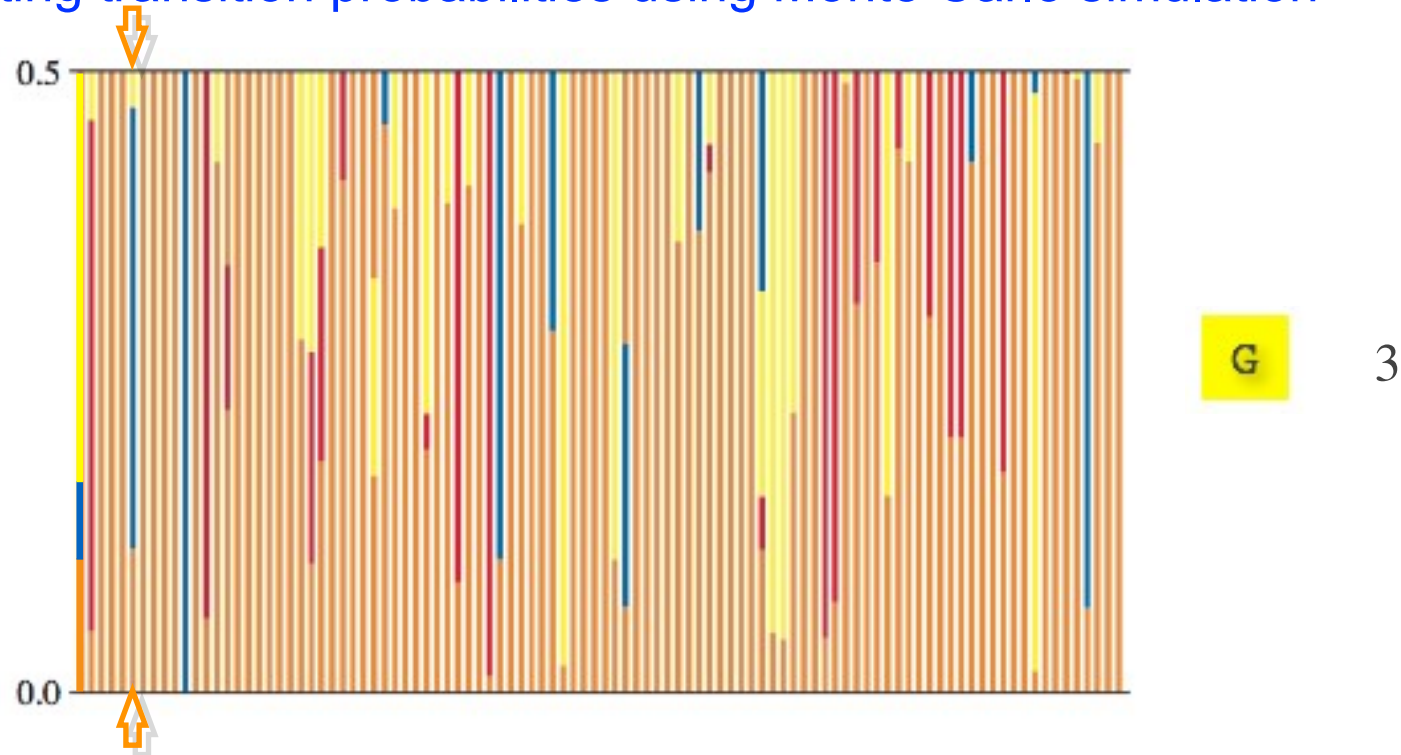


$T \rightarrow A \rightarrow G$

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

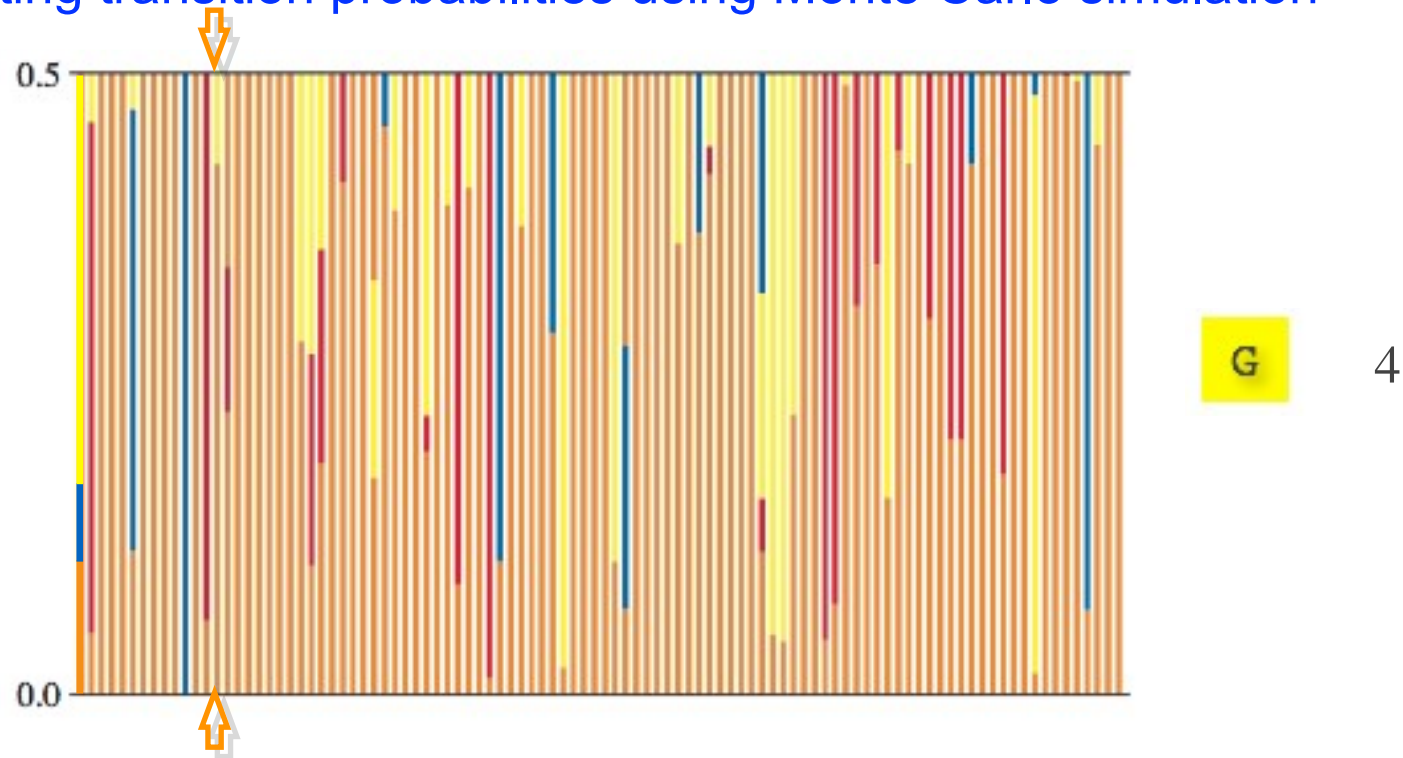


$T \rightarrow C \rightarrow G$

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



$T \rightarrow G$

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

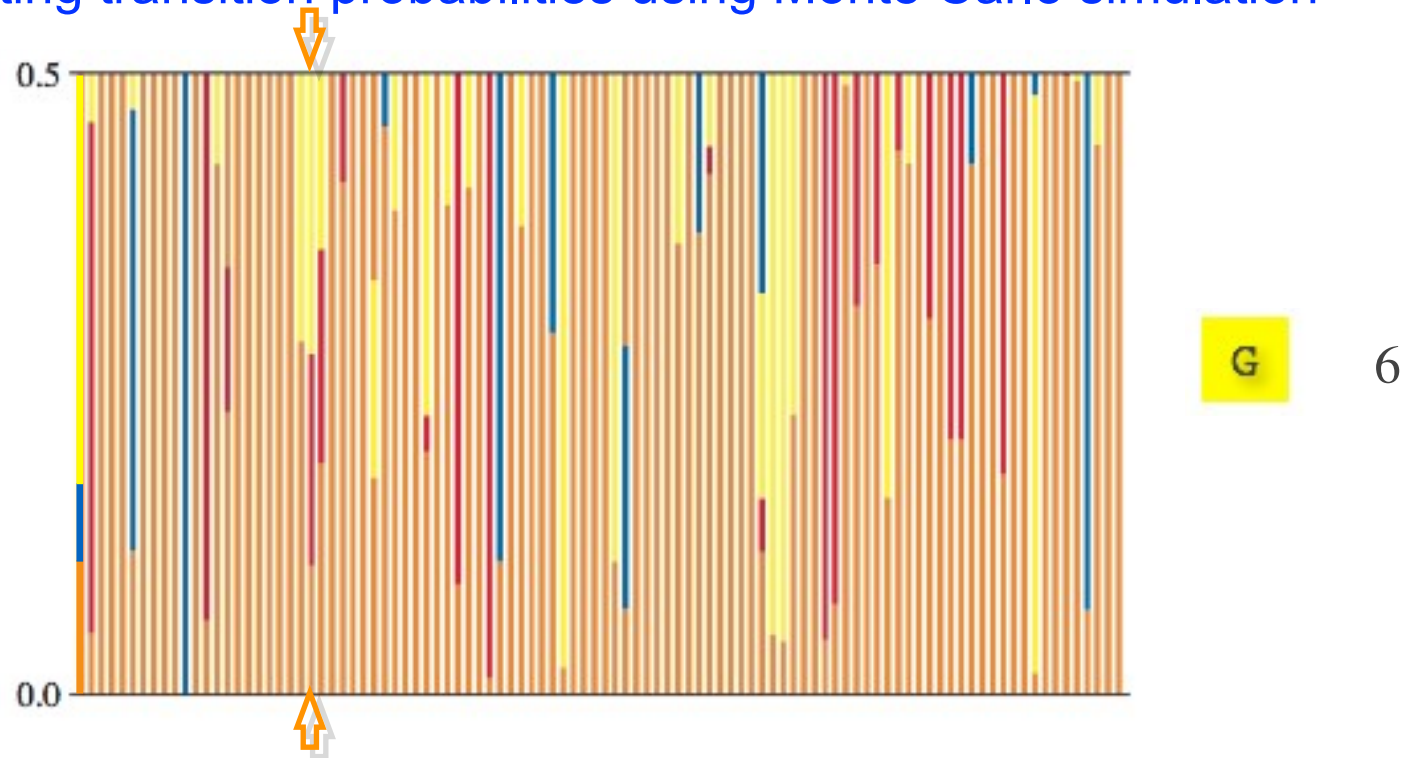


$T \rightarrow G$

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

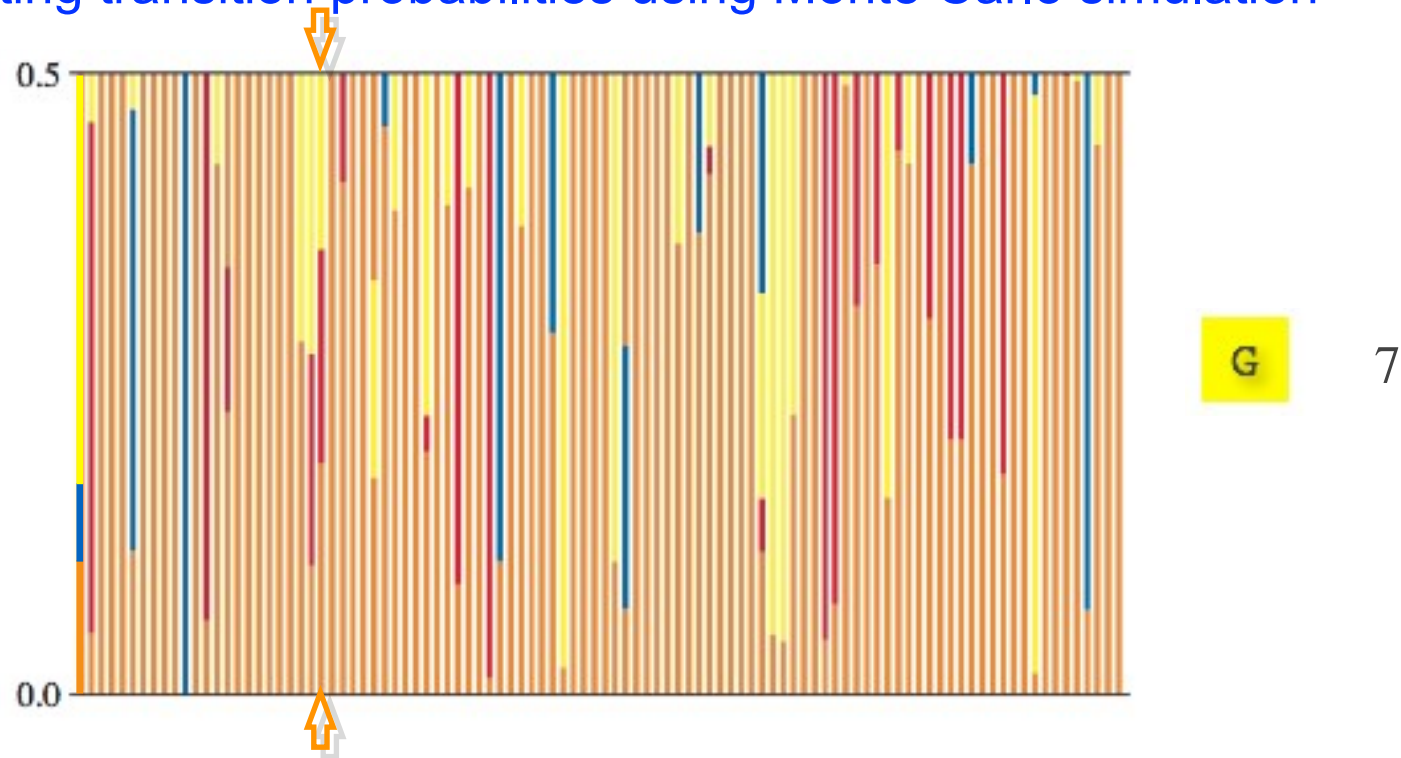


$T \rightarrow A \rightarrow G$

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

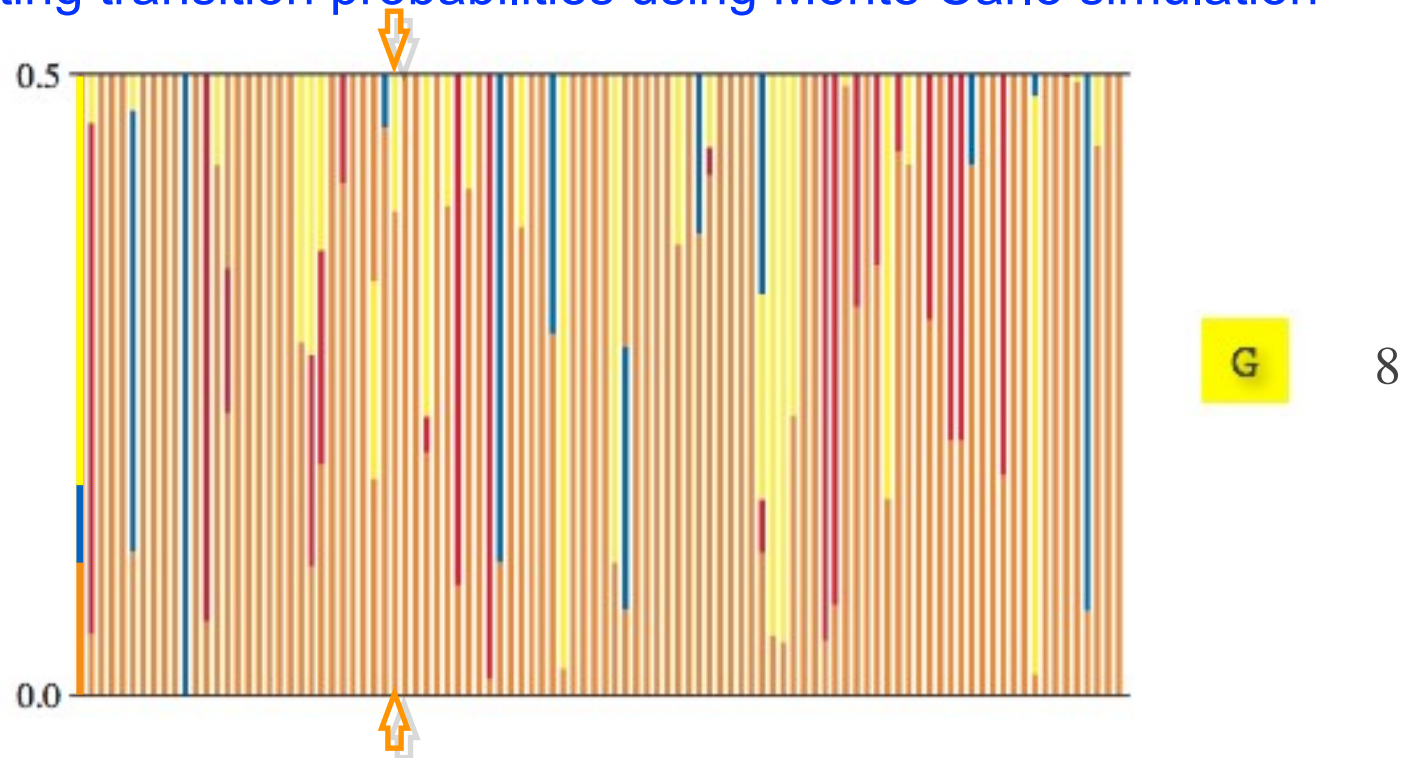


$T \rightarrow A \rightarrow G$

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

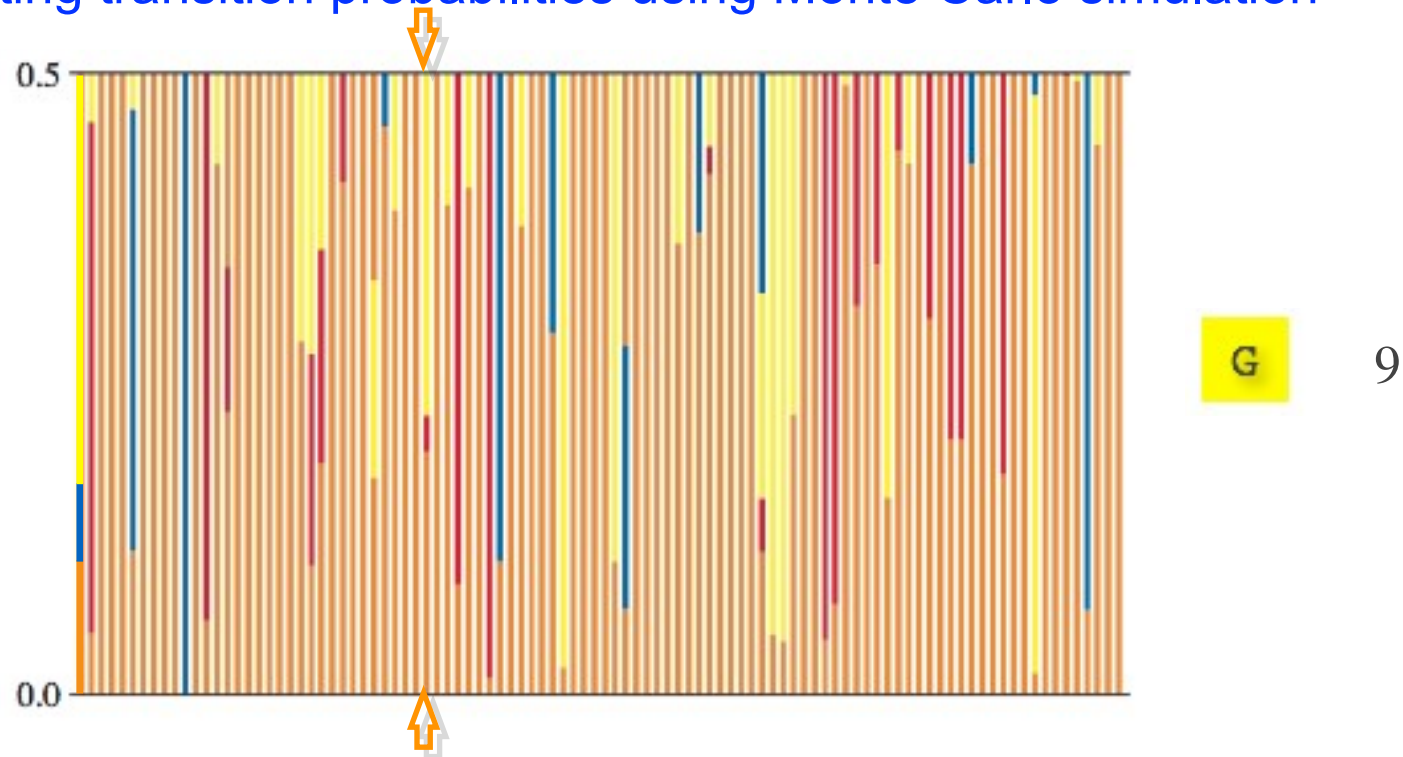


$T \rightarrow G$

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

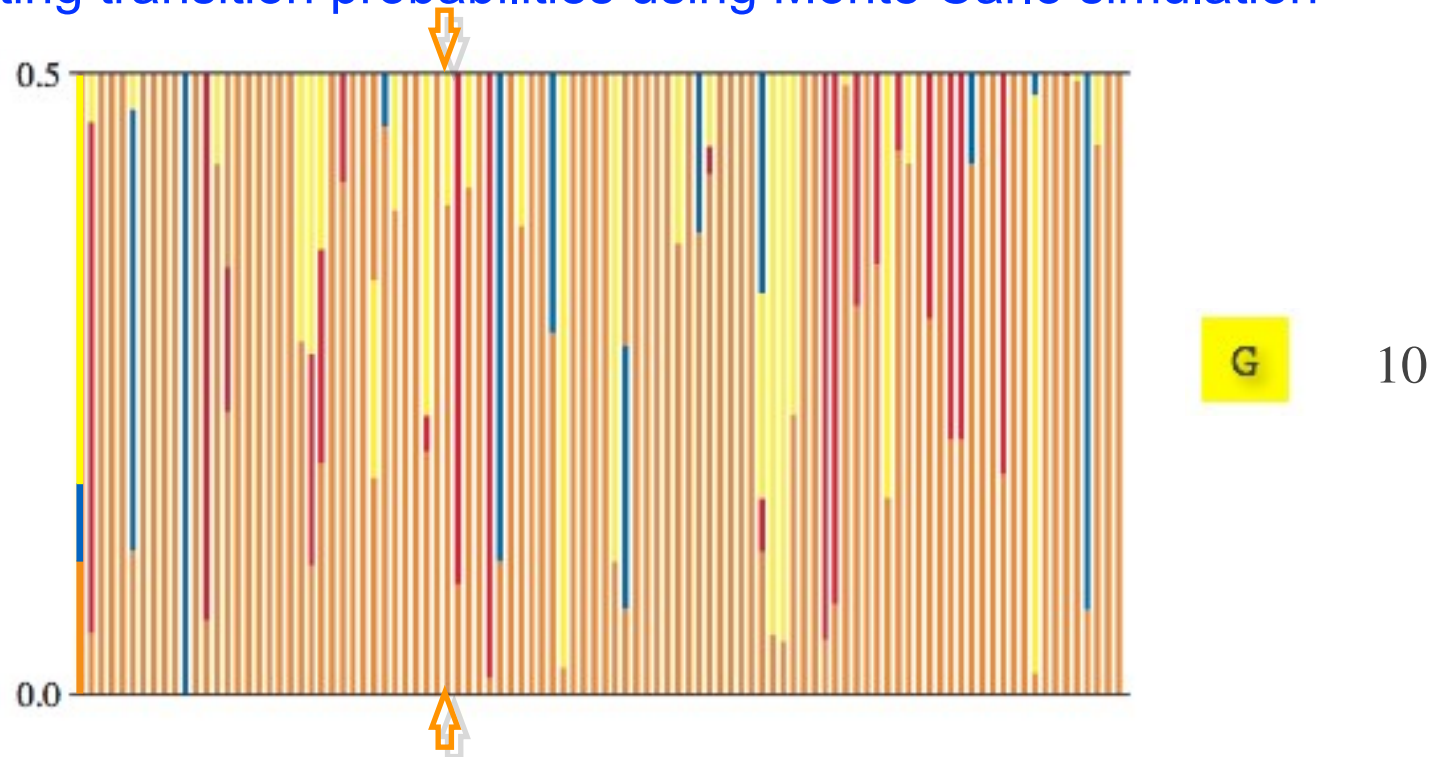


$T \rightarrow G$

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

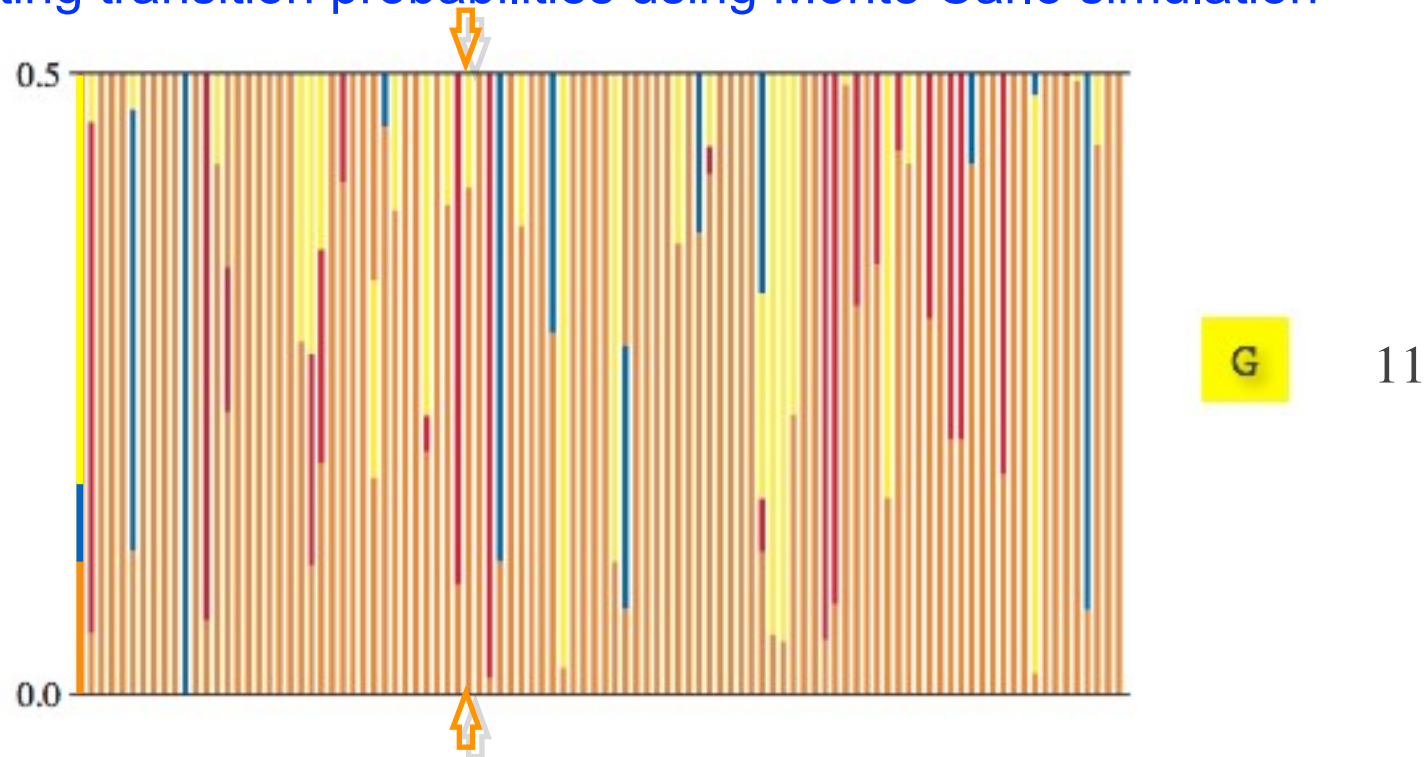


$T \rightarrow G$

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

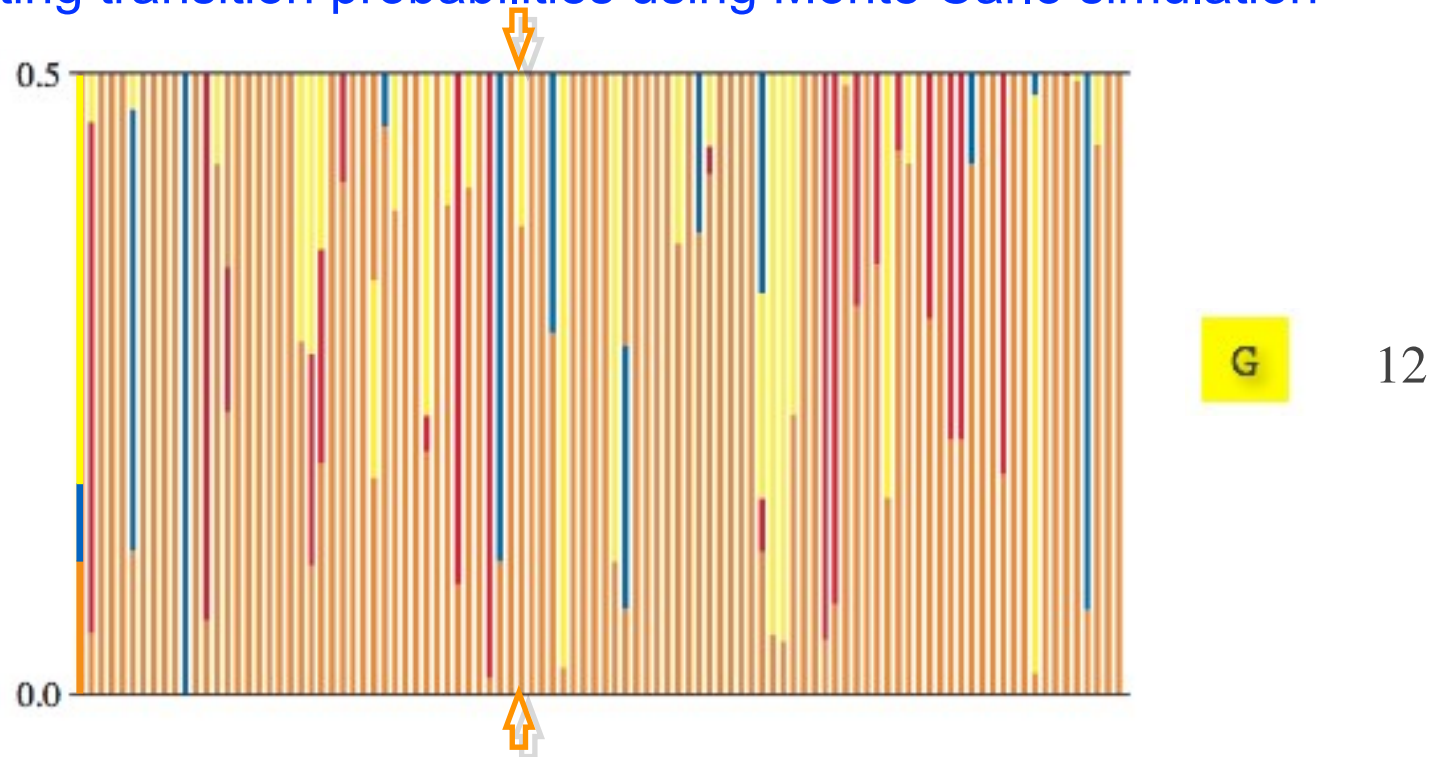


$T \rightarrow G$

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

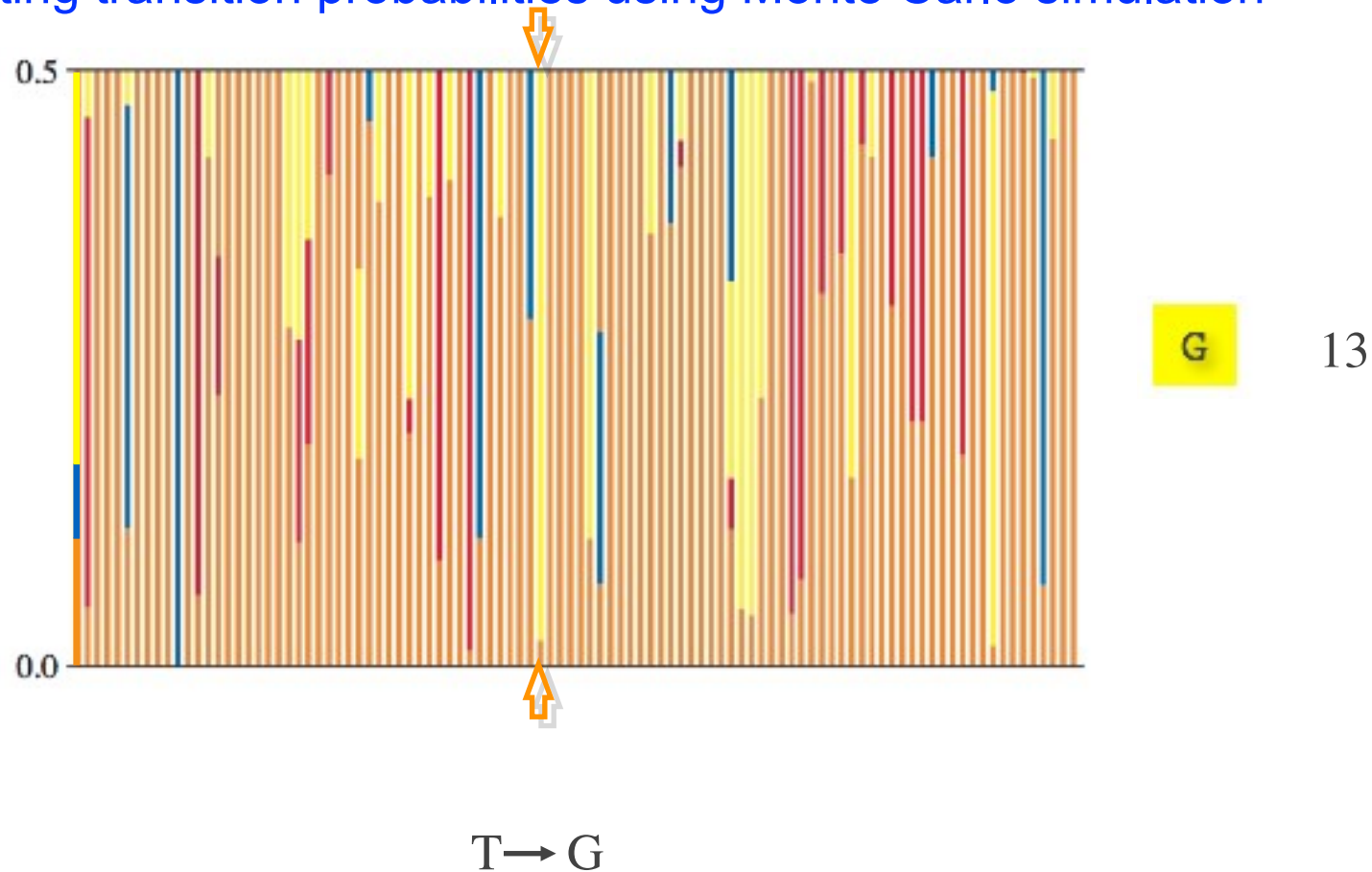


$T \rightarrow G$

Ended in G with one change

Transition Probabilities of a CTMC

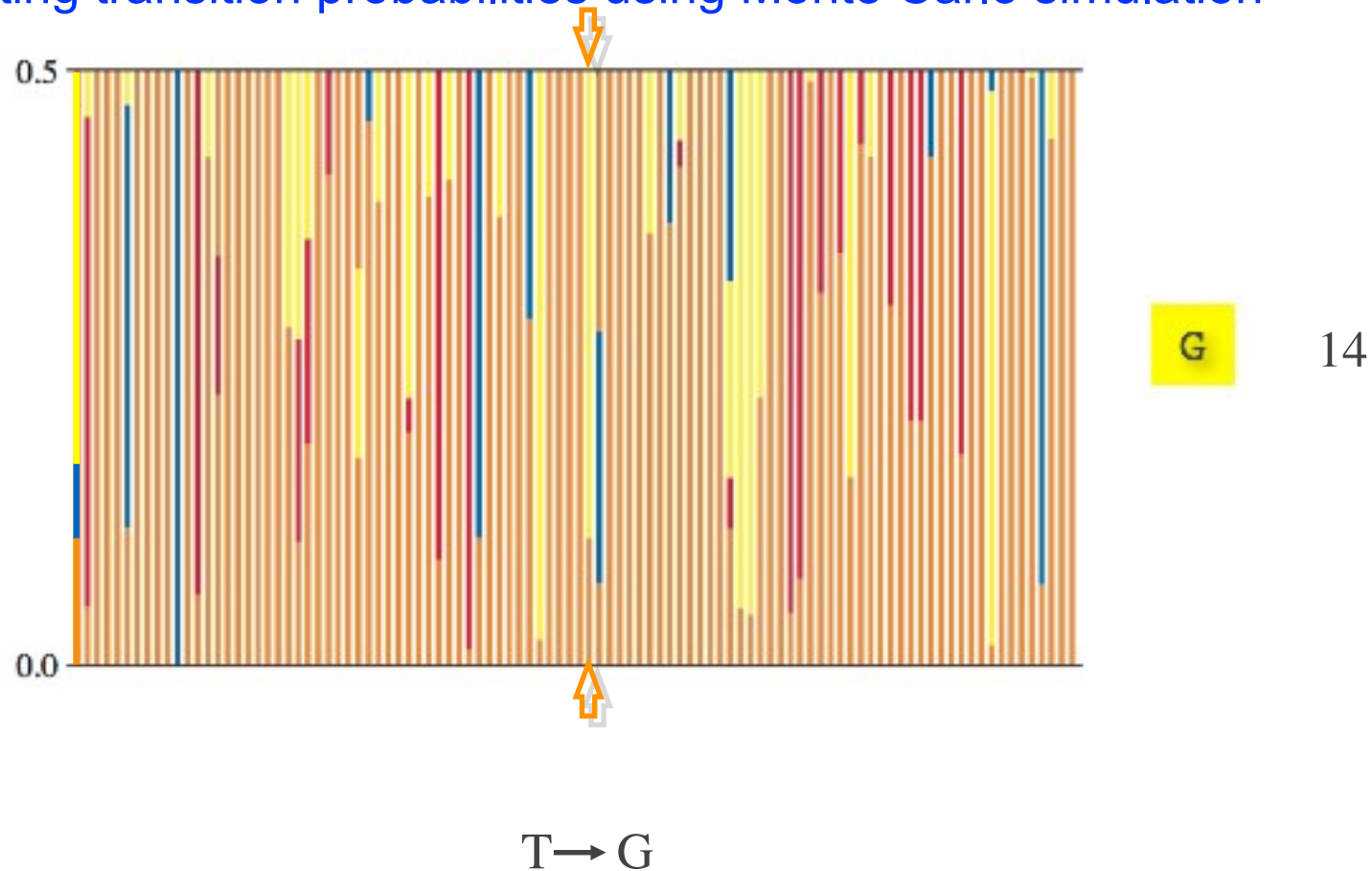
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

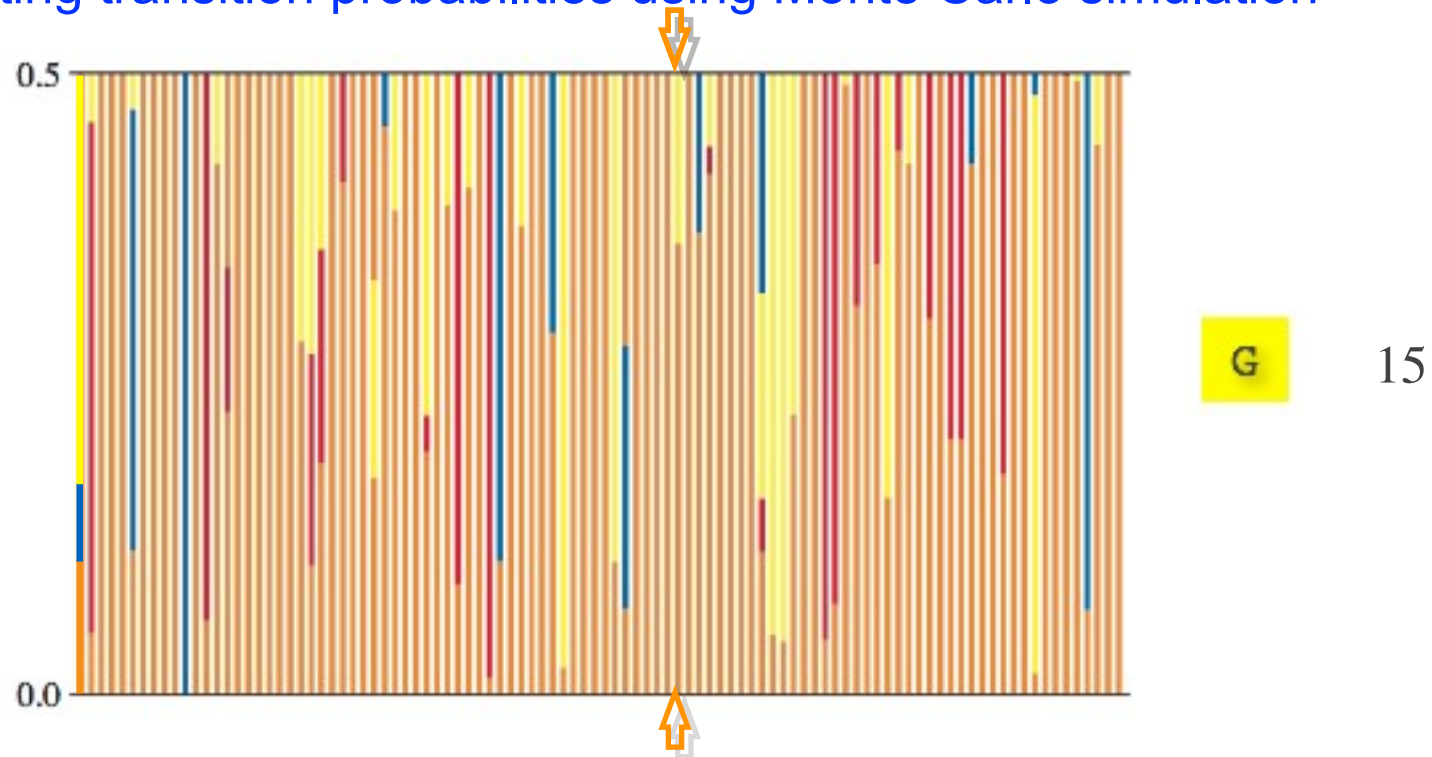
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

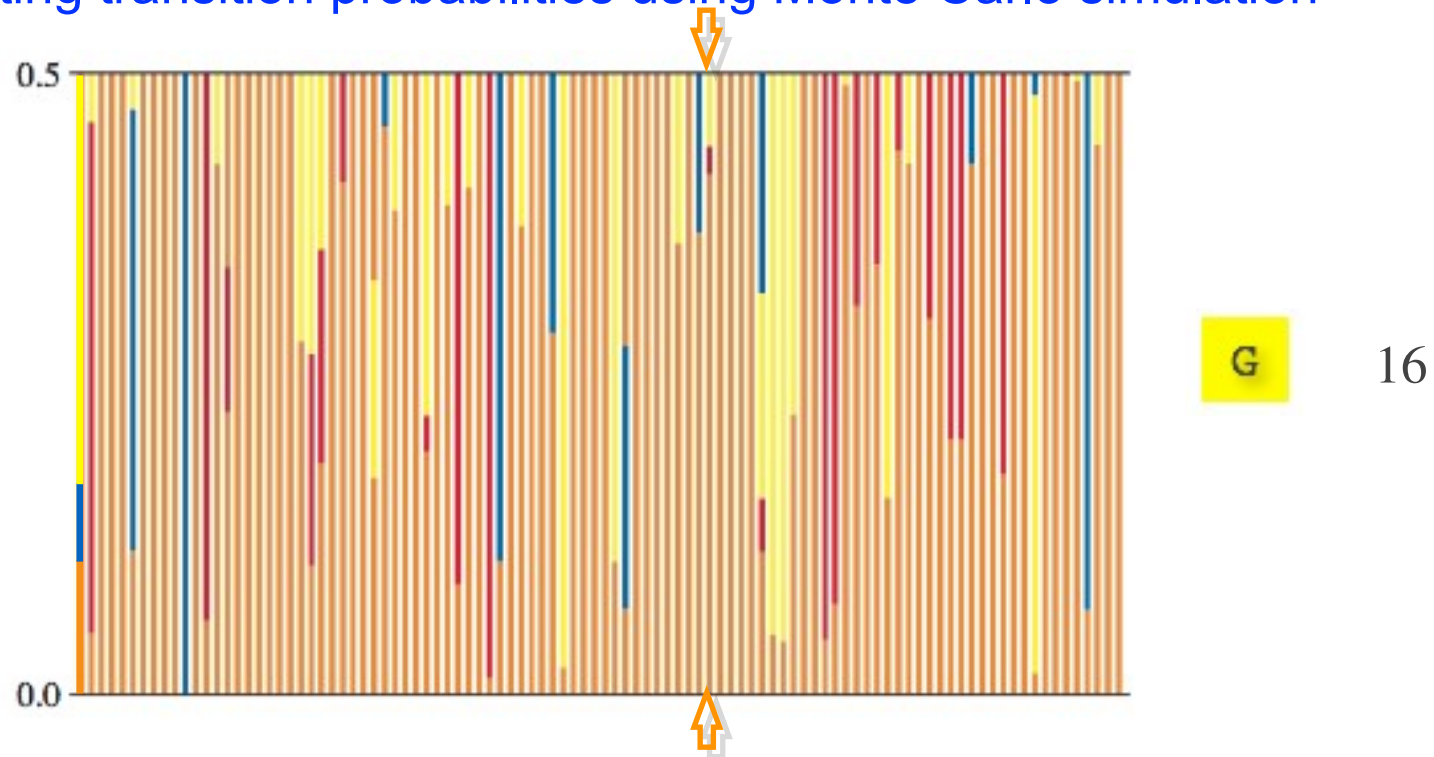
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

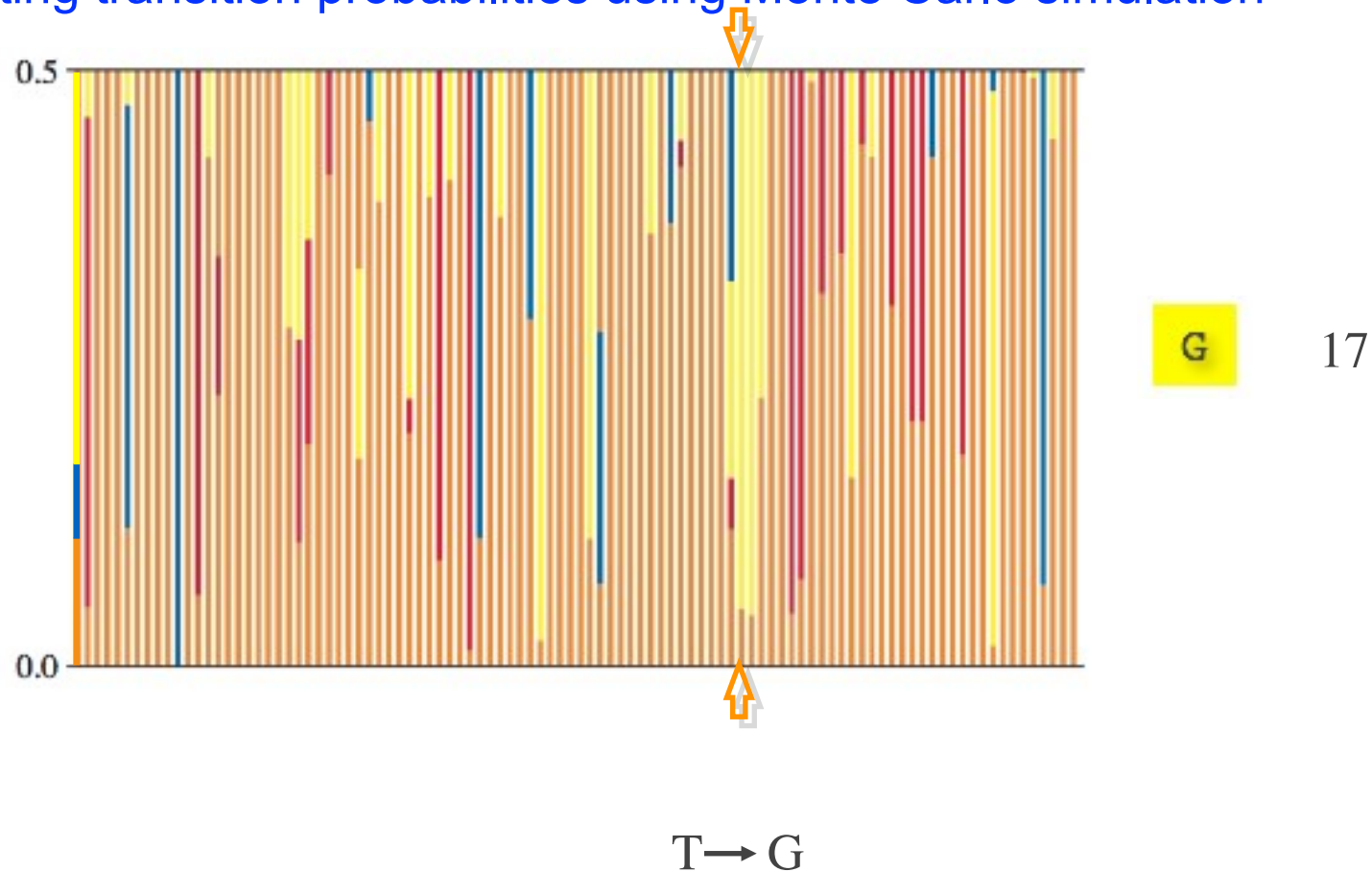


$T \rightarrow A \rightarrow G$

Ended in G with two changes

Transition Probabilities of a CTMC

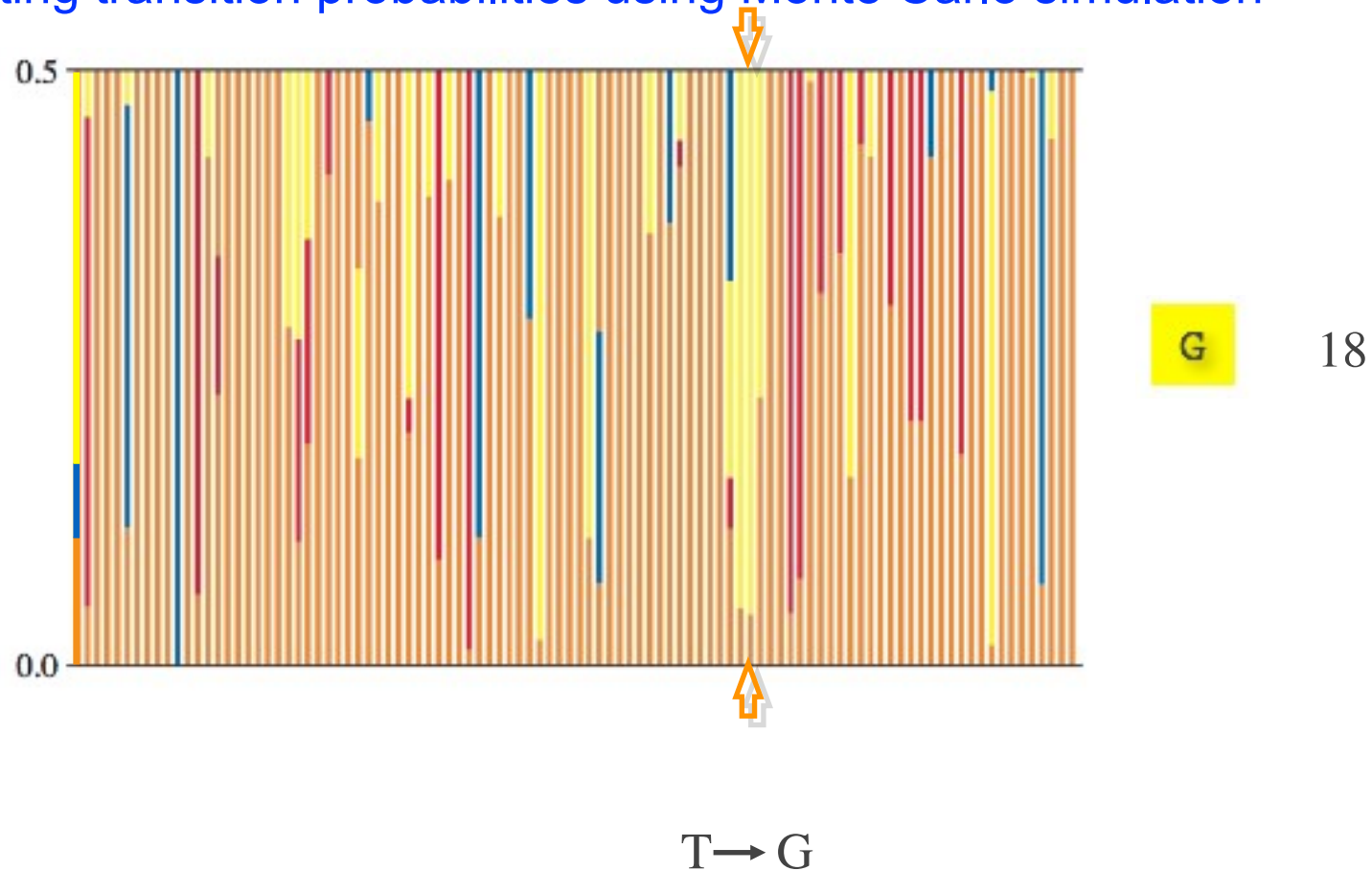
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

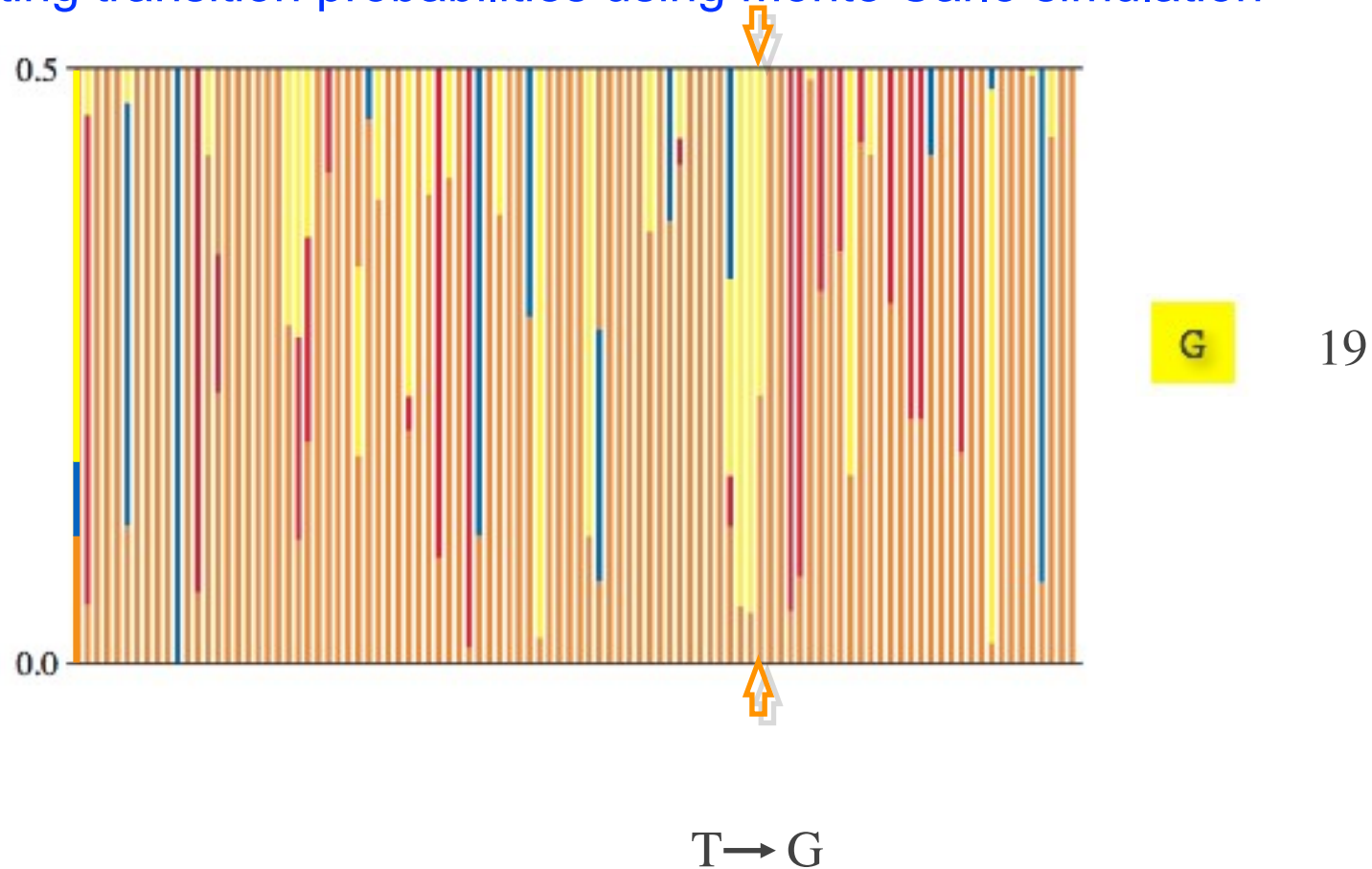
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

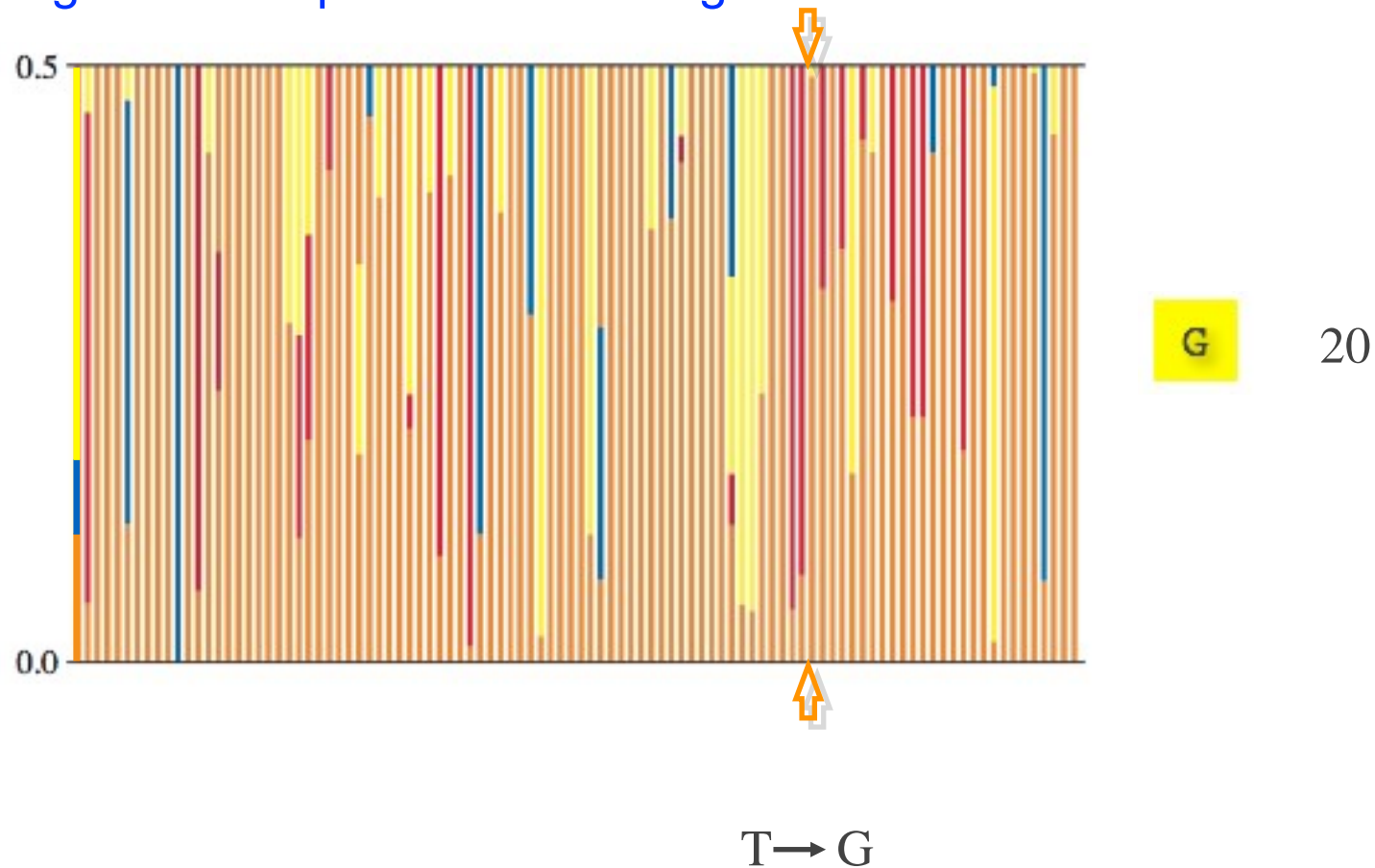
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

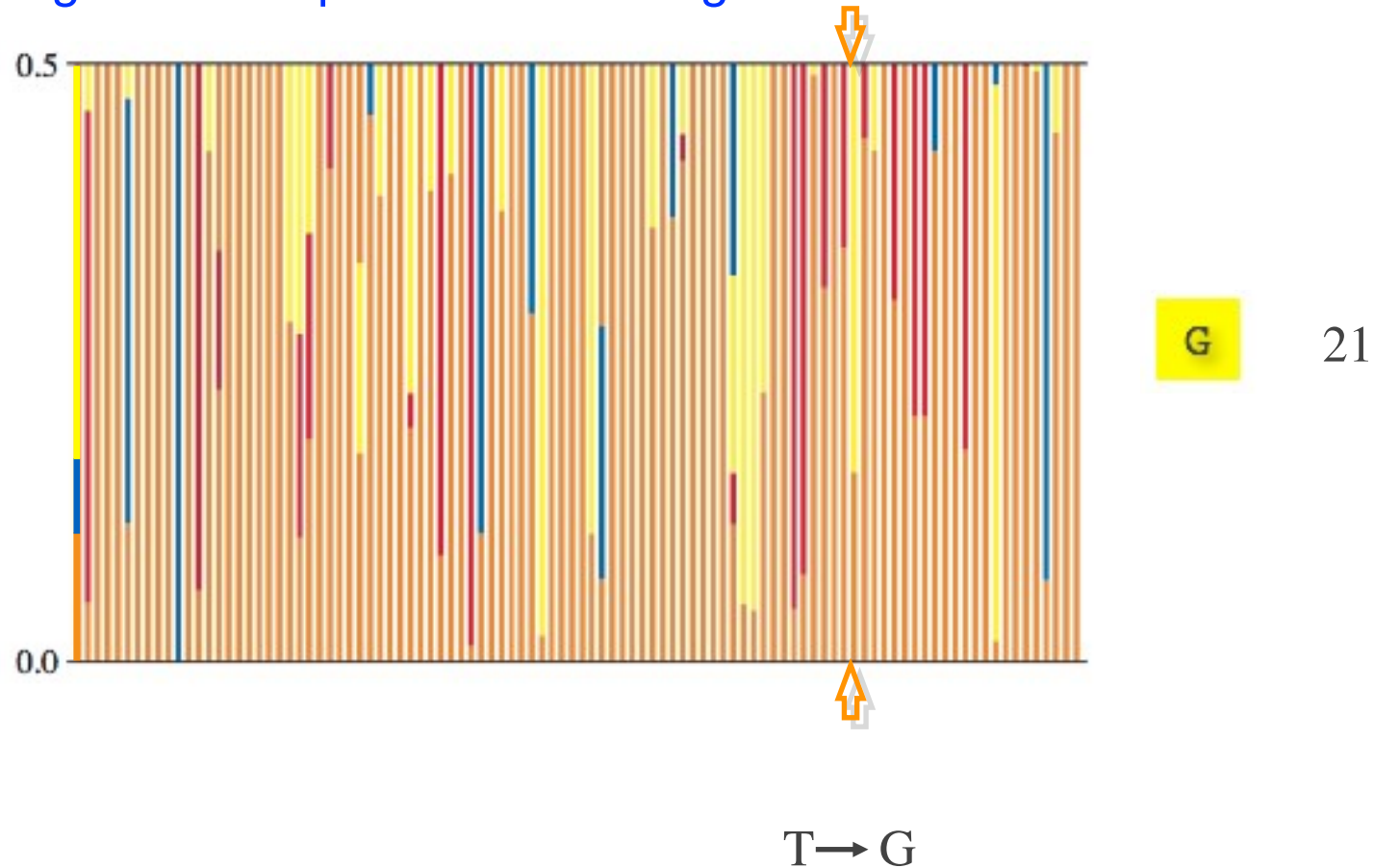
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

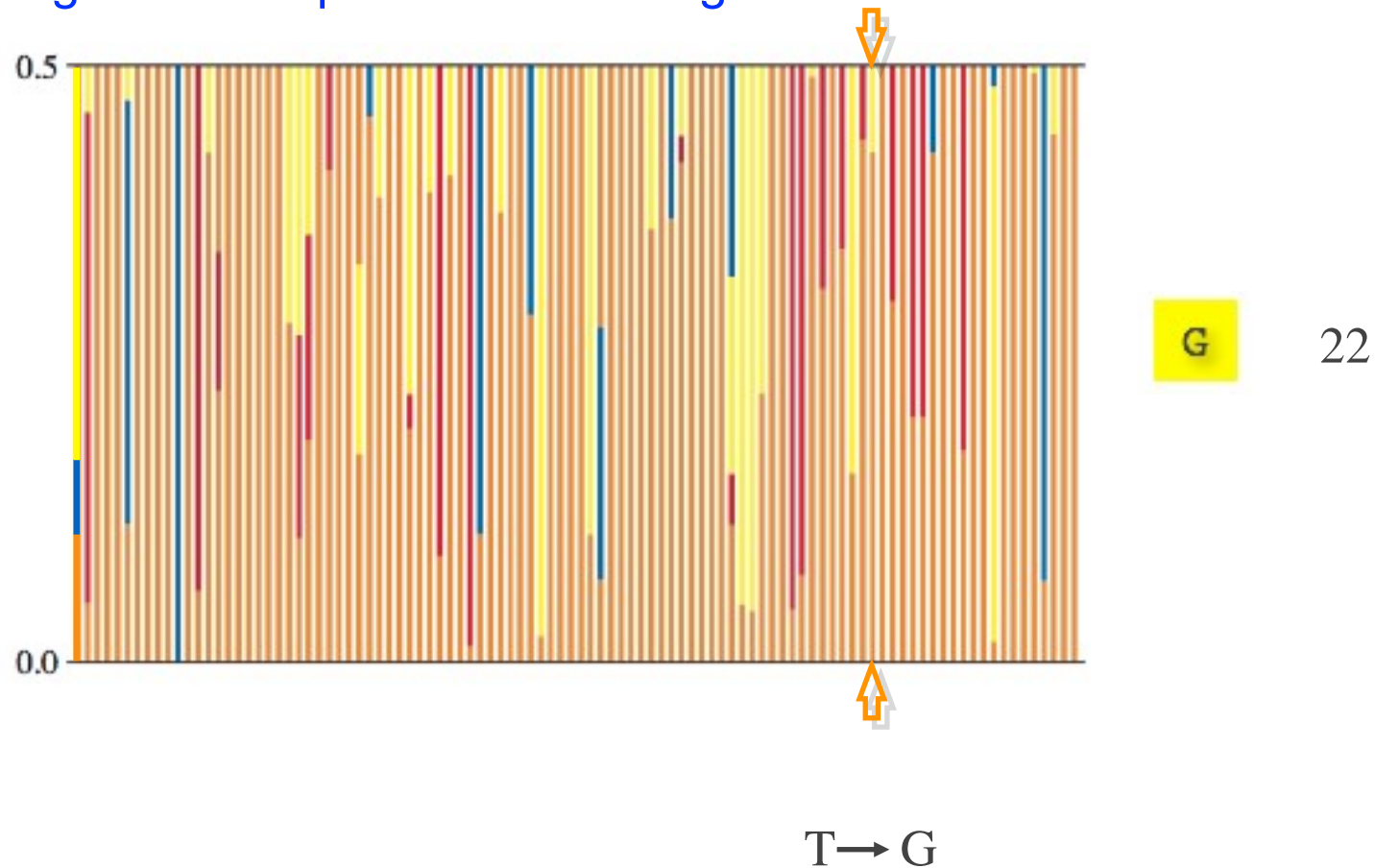
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

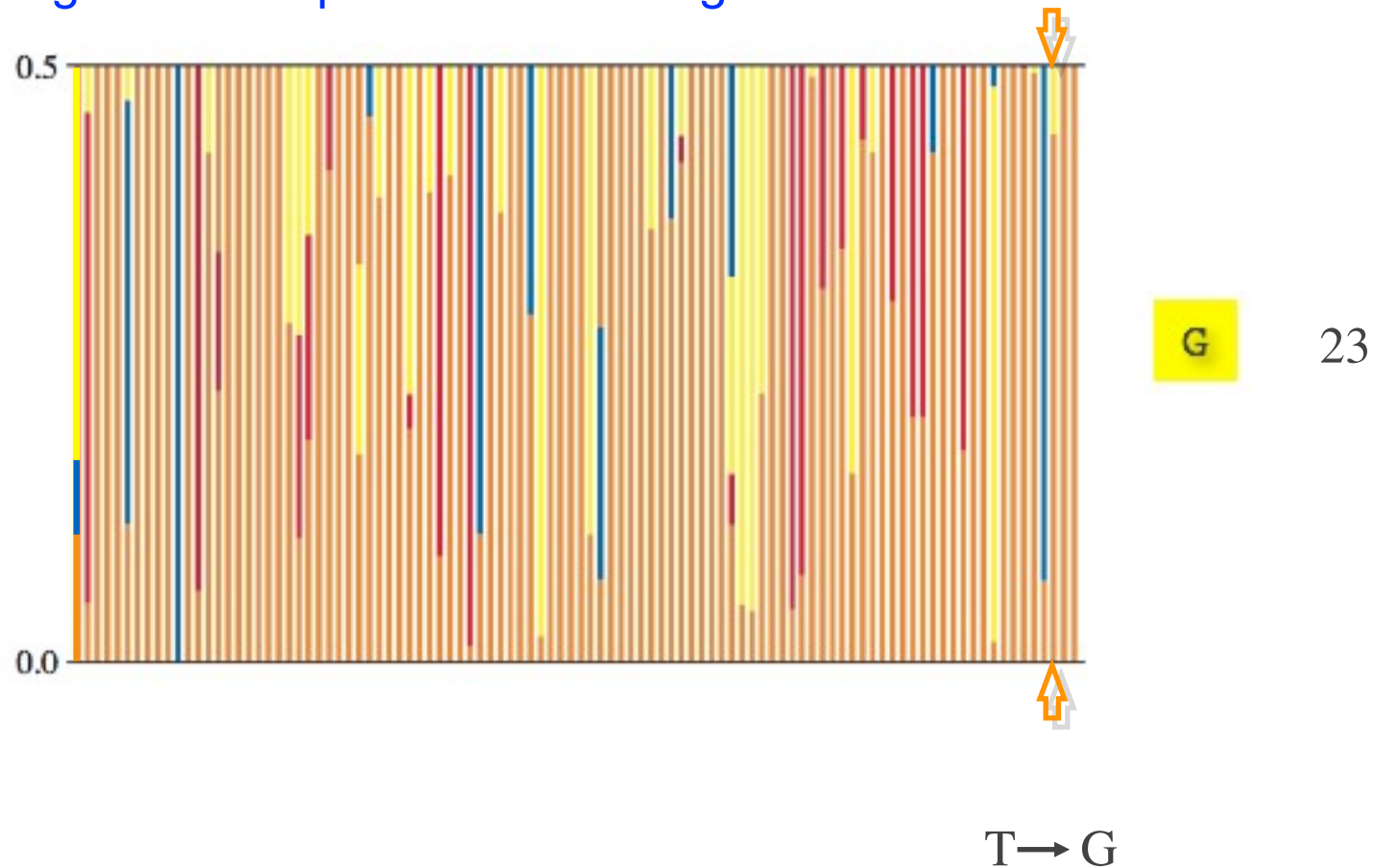
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

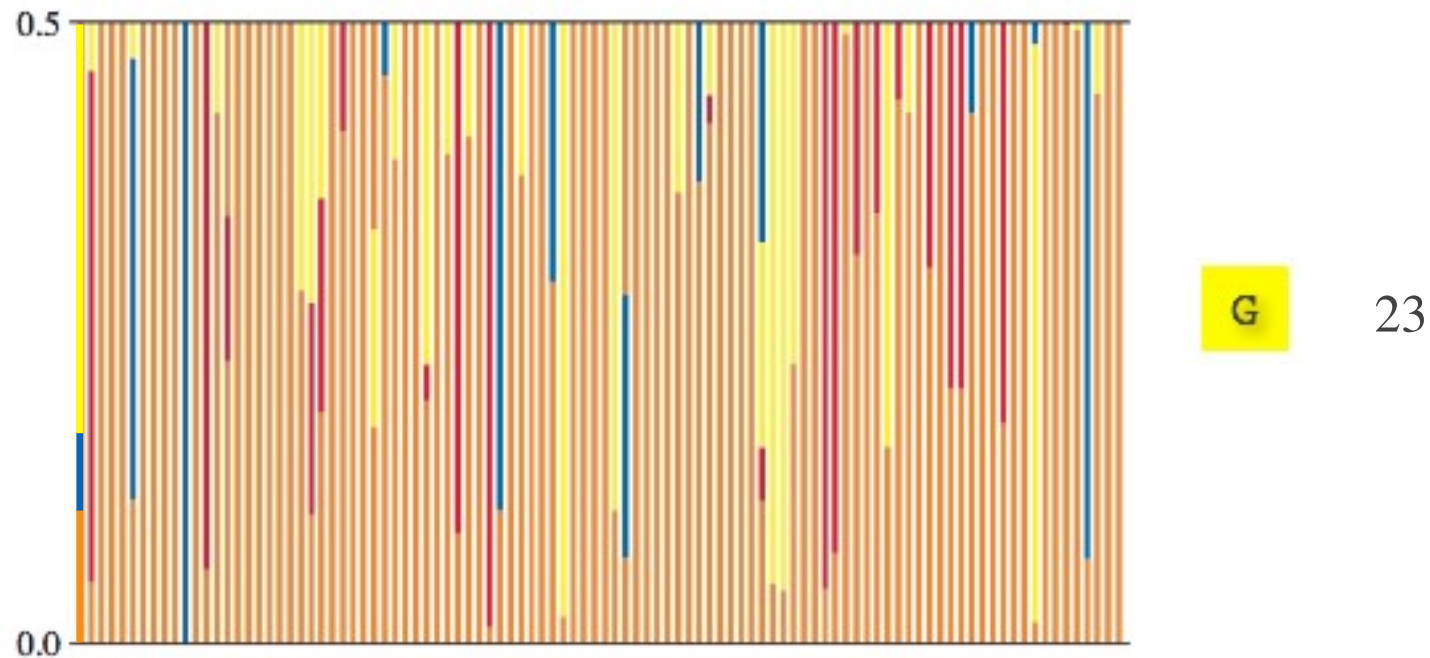
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

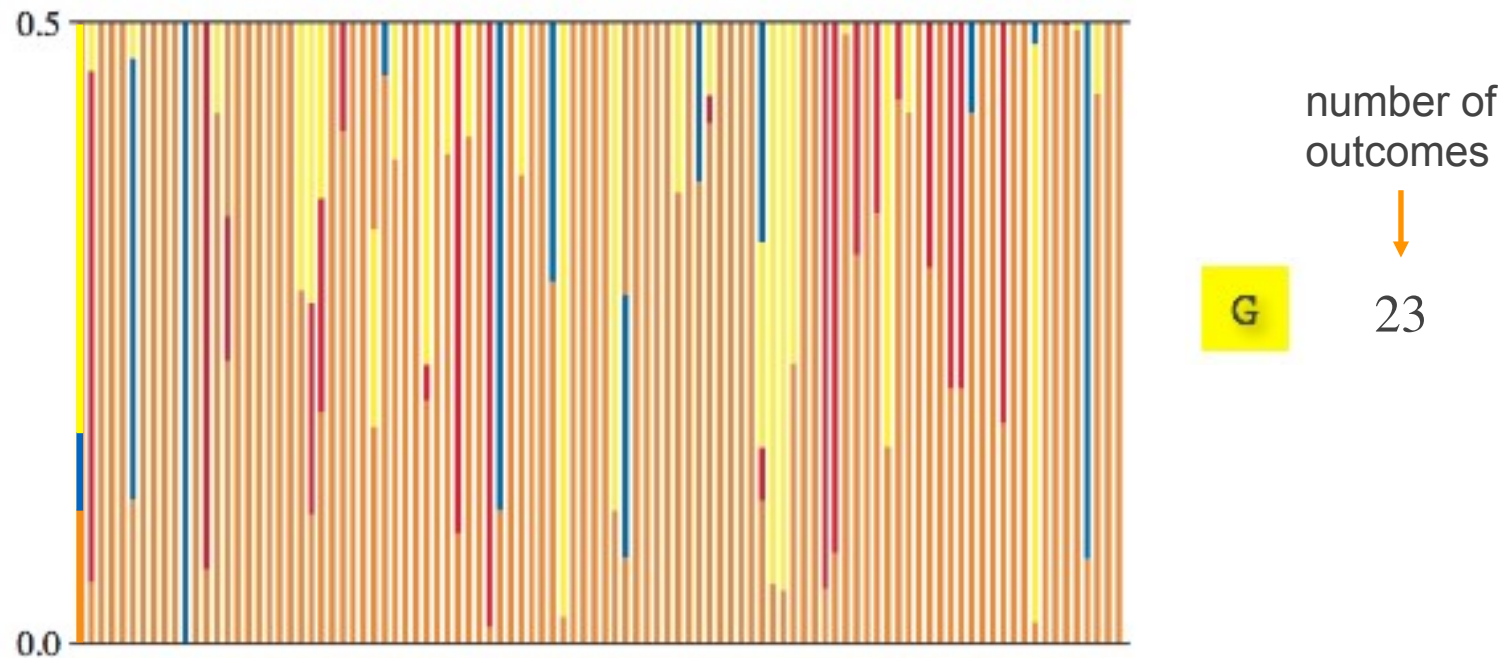
Estimating transition probabilities using Monte Carlo simulation



What is the probability that the process ends in G given that we started in T (and given the other parameters of the model)?

Transition Probabilities of a CTMC

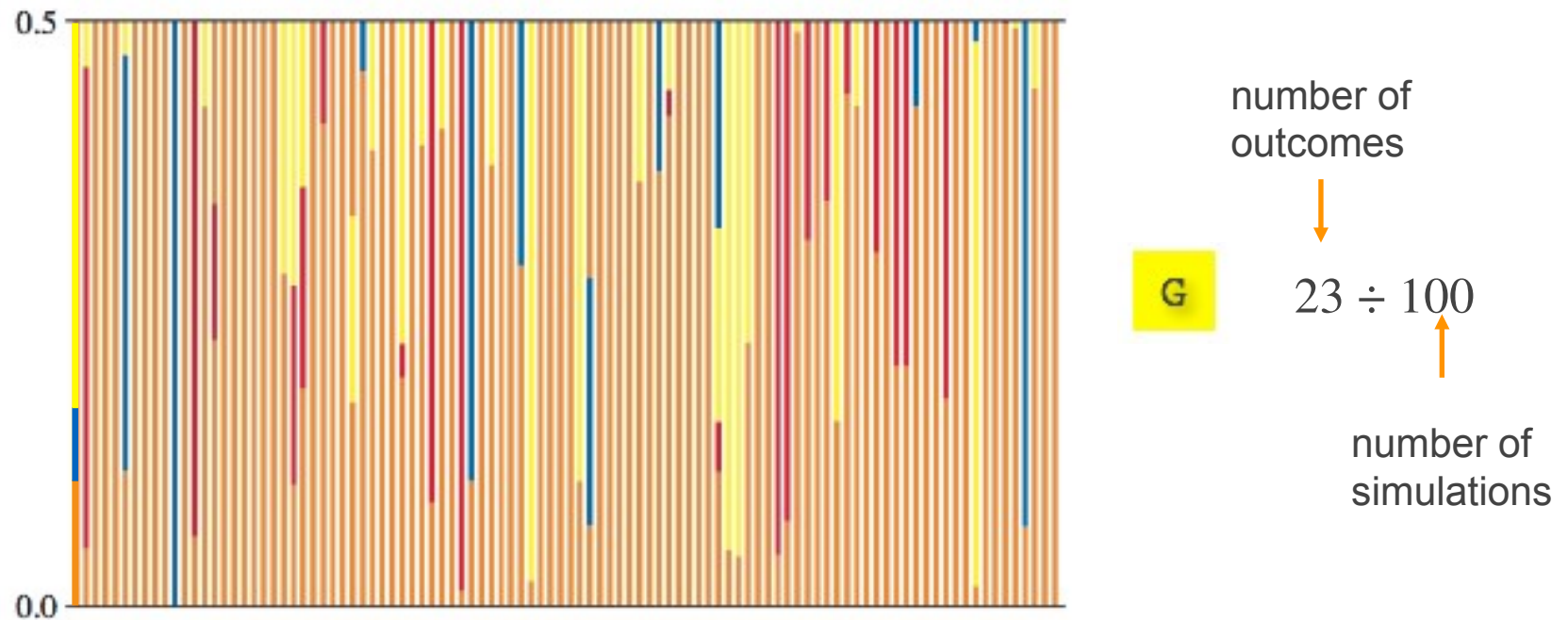
Estimating transition probabilities using Monte Carlo simulation



What is the probability that the process ends in G given that we started in T (and given the other parameters of the model)?

Transition Probabilities of a CTMC

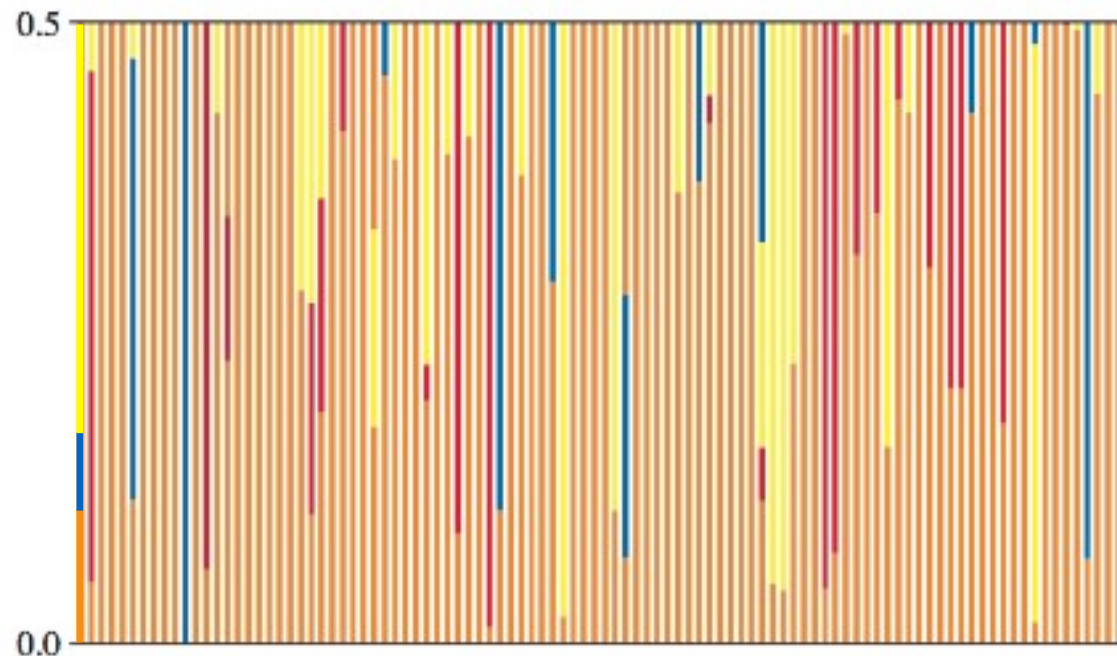
Estimating transition probabilities using Monte Carlo simulation



What is the probability that the process ends in G given that we started in T (and given the other parameters of the model)?

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



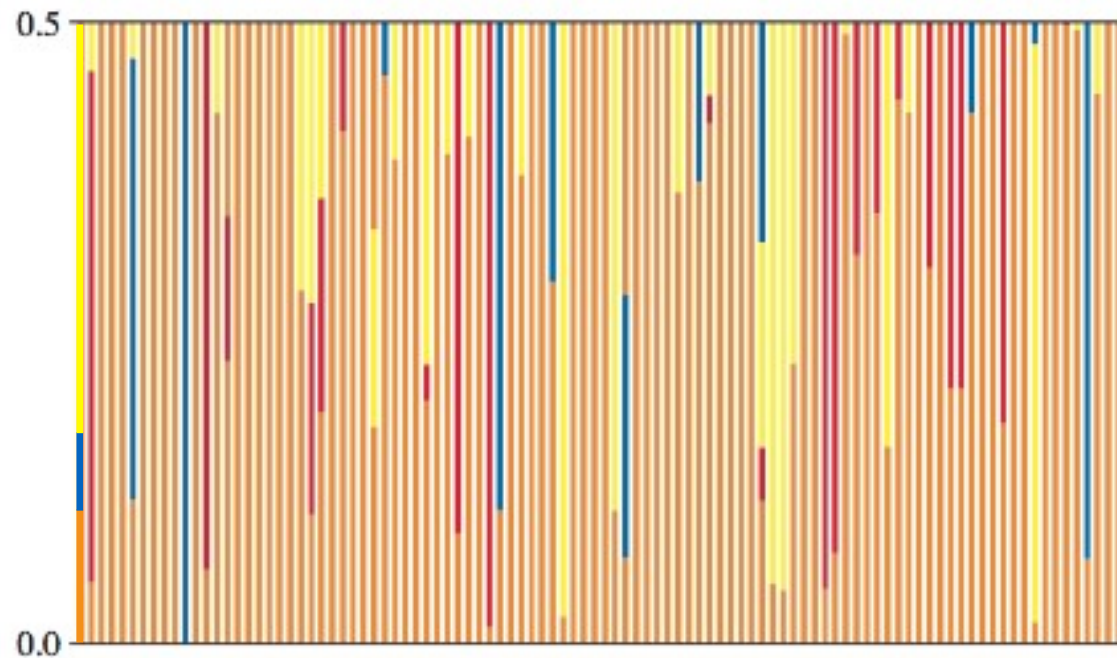
number of
outcomes
↓
G $23 \div 100$
↑
number of
simulations

		To			
		A	C	G	T
From	A				
	C				
	G				
	T			0.23	

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number of
outcomes

$$23 \div 100$$

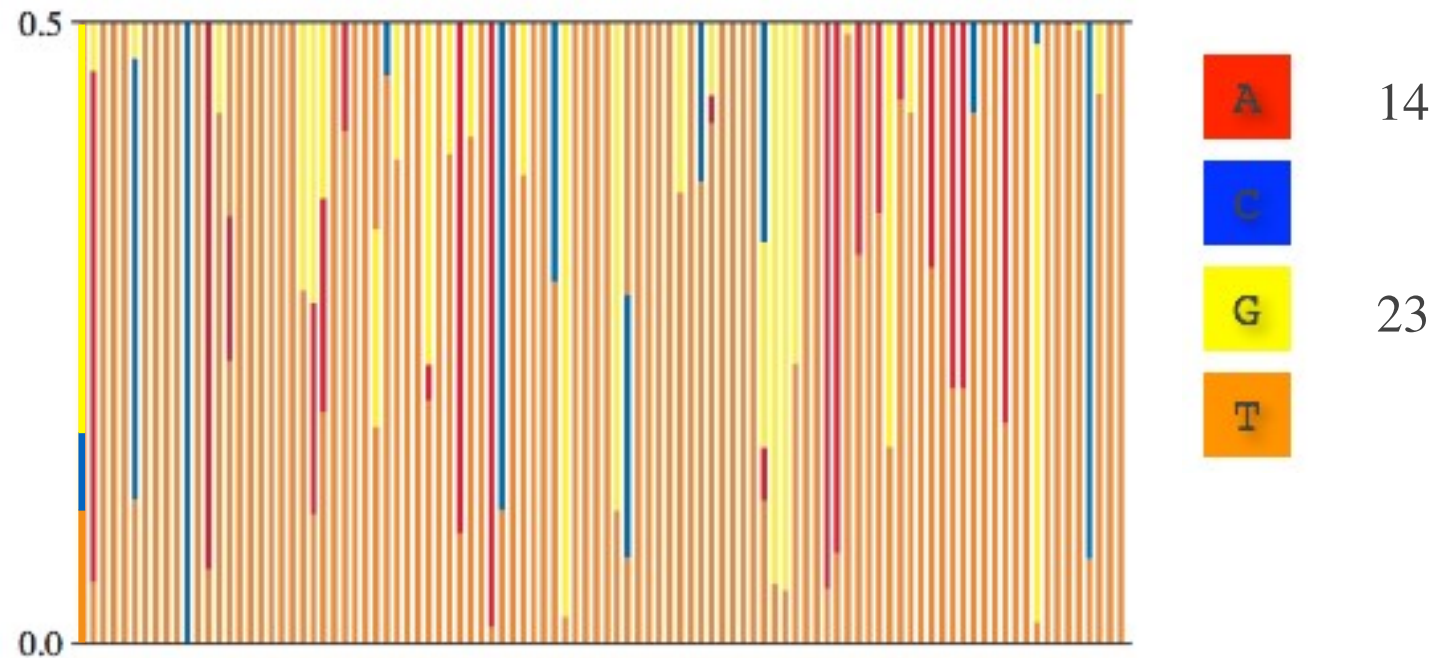
number of
simulations

		To			
		A	C	G	T
From	A				
	C				
	G				
	T			0.23	

This 'transition probability' reflects all possible histories that start in T and end in G (*i.e.*, histories with different numbers and/or positions of changes)

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

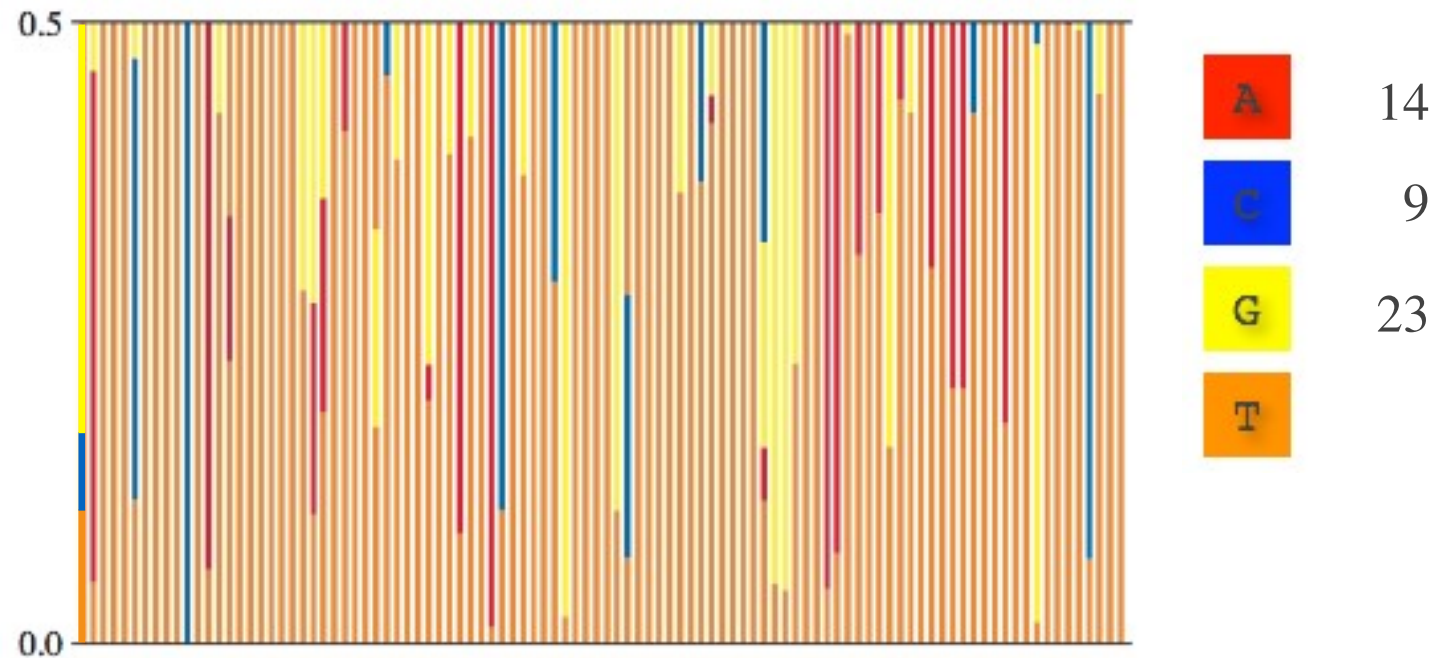


		To			
		A	C	G	T
From	A				
	C				
	G				
	T	0.14		0.23	

We can repeat this process for the other end states...

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

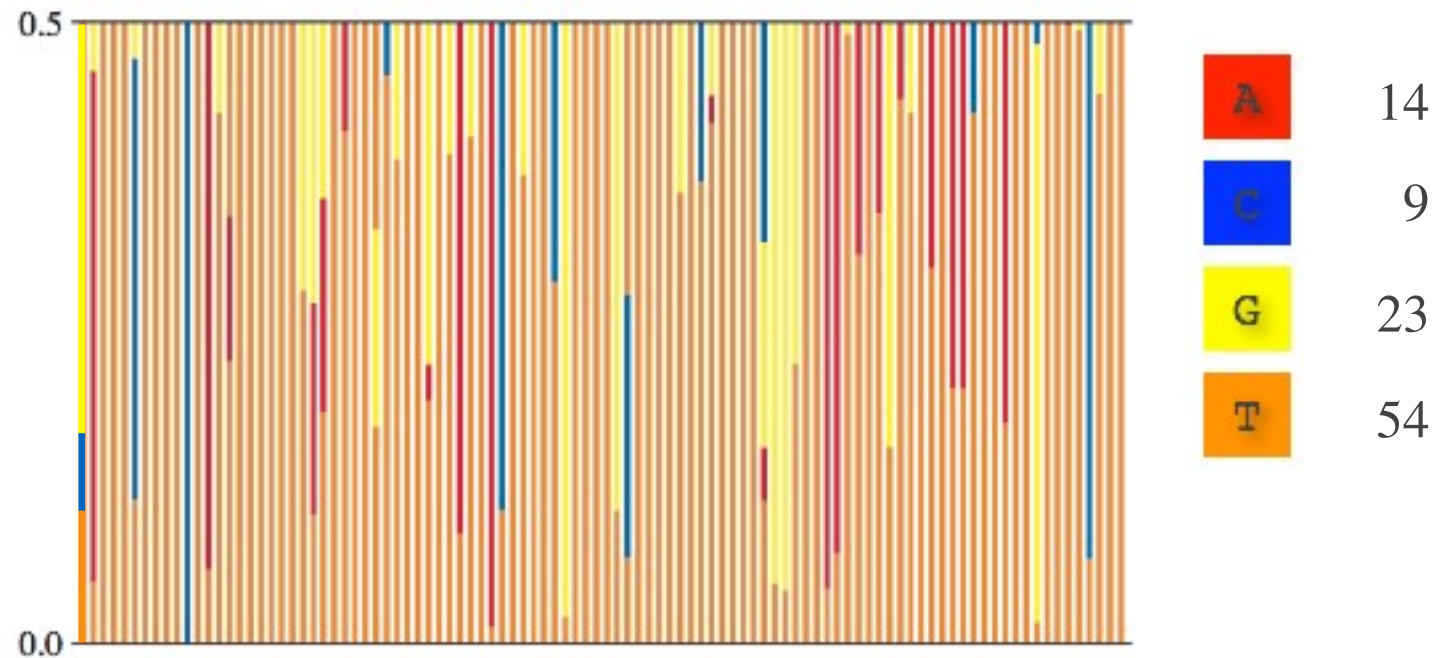


		To			
		A	C	G	T
From	A				
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	G				
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Transition Probabilities of a CTMC

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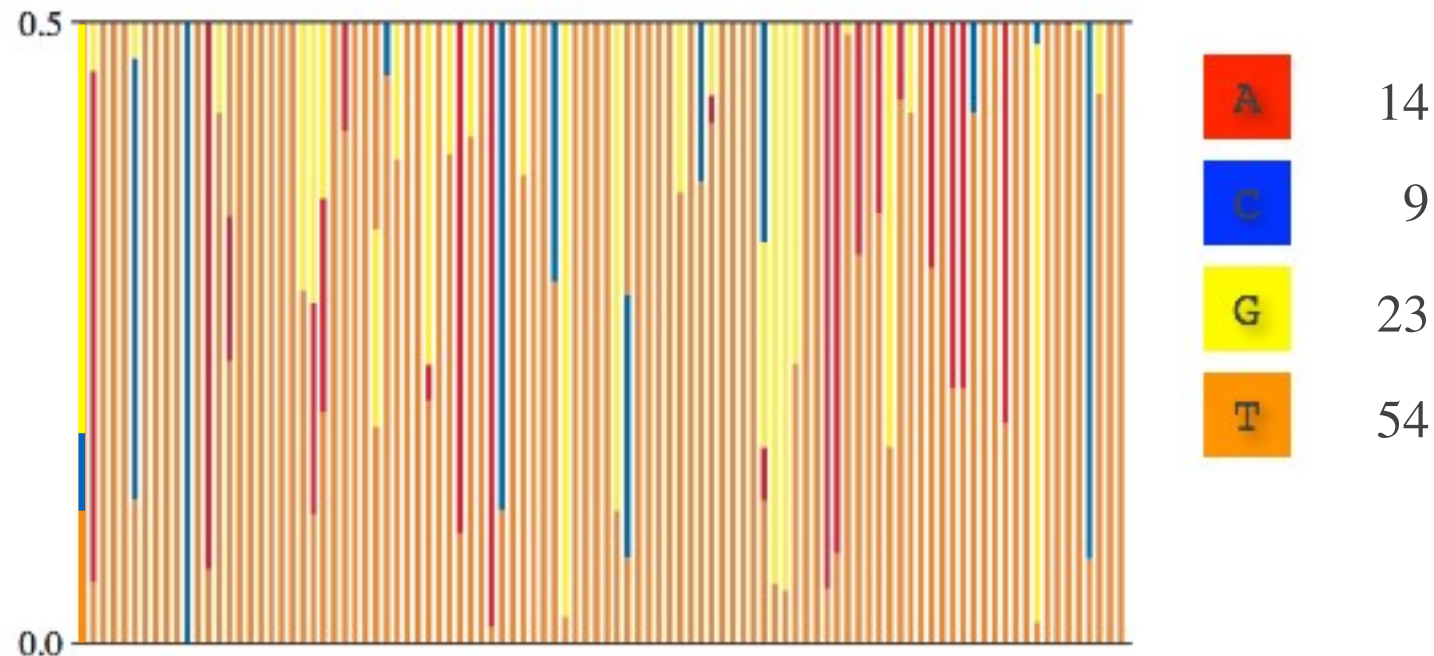


		To			
		A	C	G	T
From	A				
	C				
	G				
	T	0.14	0.09	0.23	0.54

We can repeat this process for the other end states...

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



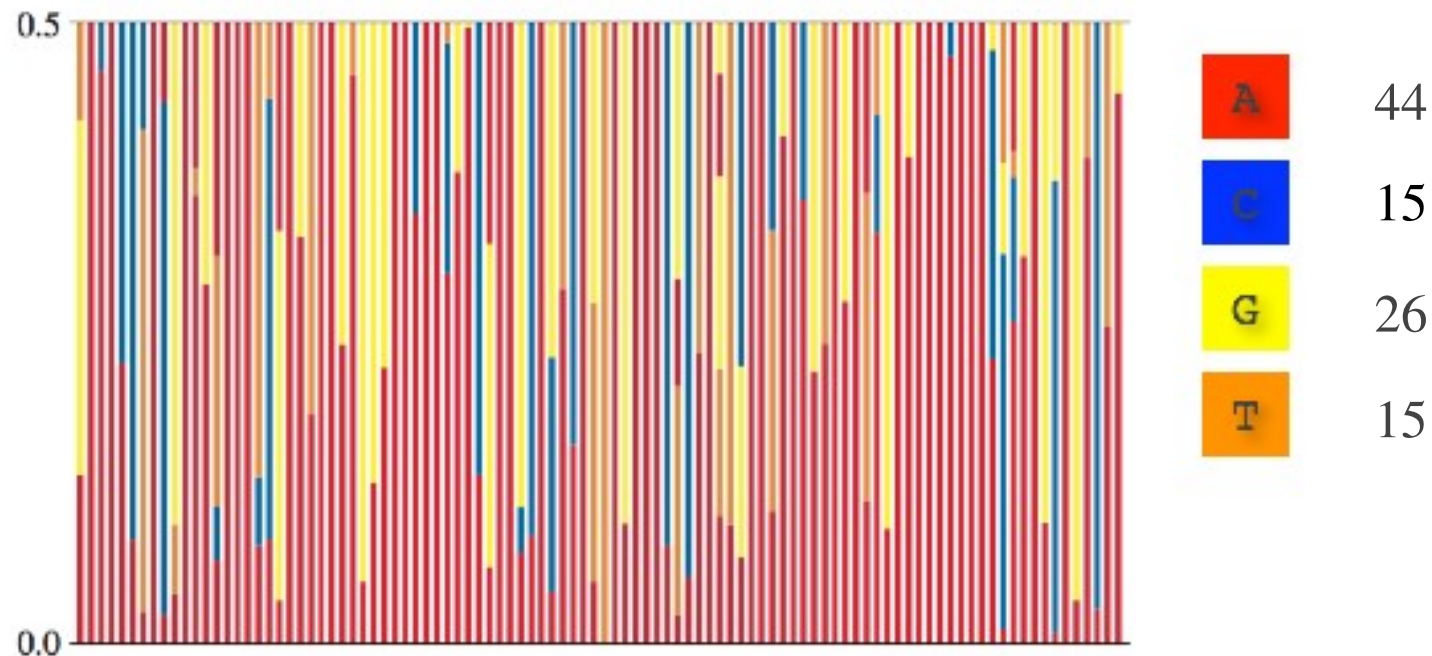
		To			
		A	C	G	T
From	A				
	C				
	G				
	T	0.14	0.09	0.23	0.54

$0.14 + 0.09 + 0.23 + 0.54 = 1$

Note that each row of the transition-probability matrix sums to 1
(*c.f.*, the Law of Total Probability).

Transition Probabilities of a CTMC

Realizations of 100 replicate simulations starting in state A

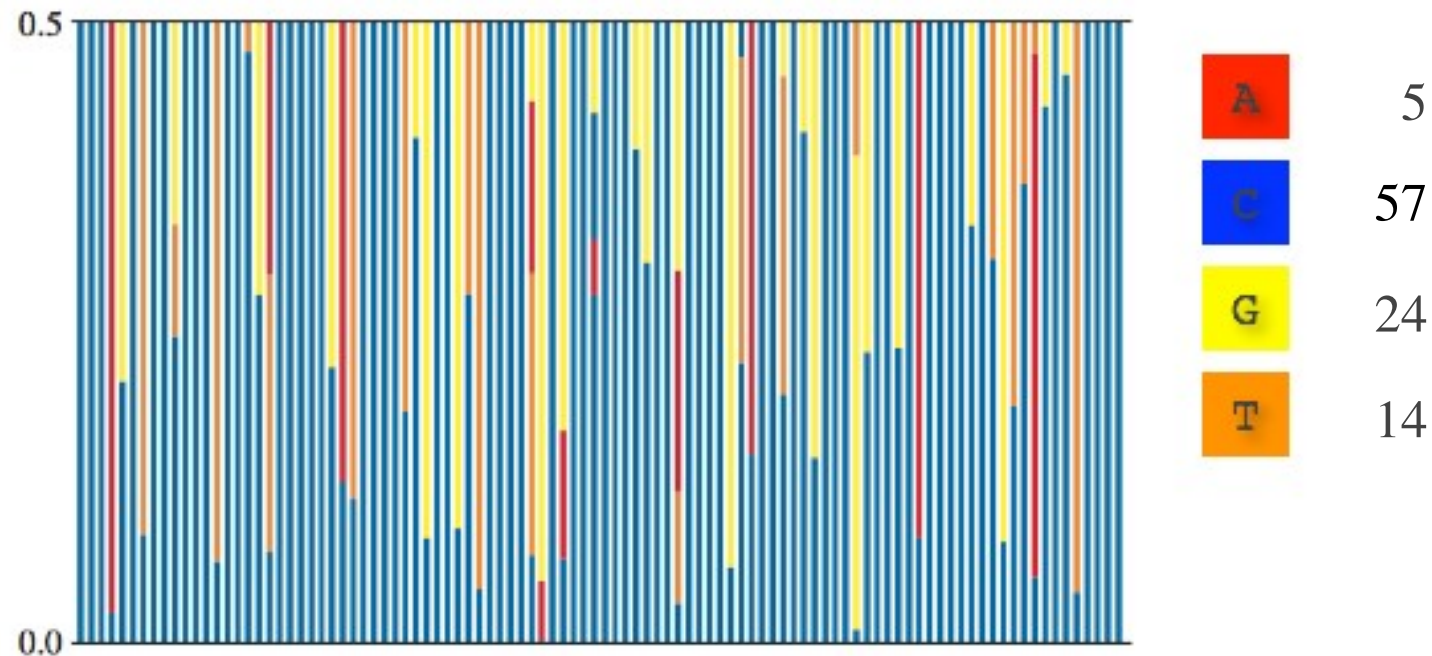


		To			
		A	C	G	T
From	A	0.44	0.15	0.26	0.15
	C				
	G				
	T	0.14	0.09	0.23	0.54

We can perform new Monte Carlo simulations that start in A to fill out the corresponding row of the transition-probability matrix.

Transition Probabilities of a CTMC

Realizations of 100 replicate simulations starting in state C

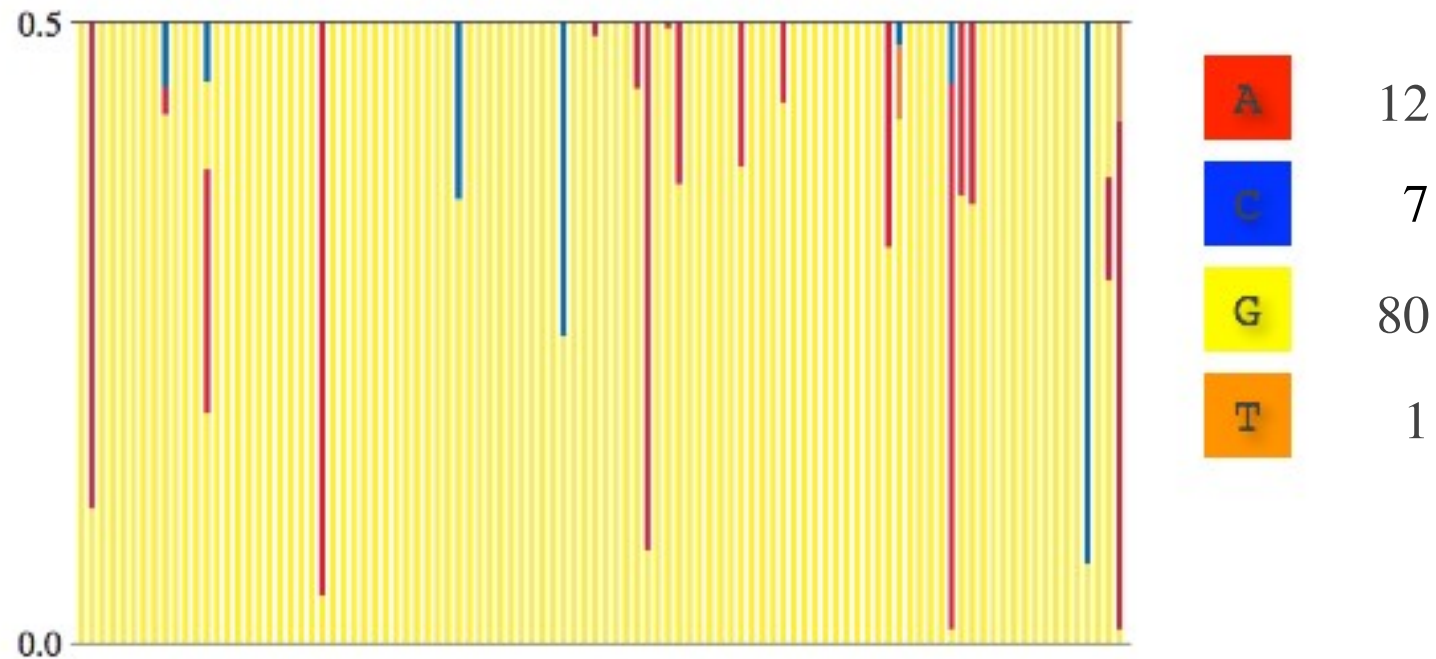


		To			
		A	C	G	T
From	A	0.44	0.15	0.26	0.15
	C	0.05	0.57	0.24	0.14
	G				
	T	0.14	0.09	0.23	0.54

And then for simulations that start in C ...

Transition Probabilities of a CTMC

Realizations of 100 replicate simulations starting in state G



		To			
		A	C	G	T
From	A	0.44	0.15	0.26	0.15
	C	0.05	0.57	0.24	0.14
	G	0.12	0.07	0.80	0.01
	T	0.14	0.09	0.23	0.54

And finally for simulations that start in G.

Transition Probabilities of a CTMC

Accuracy of Monte Carlo approximation depends on the number of replicates

100 replicates

From		To			
		A	C	G	T
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100,000 replicates

From		To			
		A	C	G	T
	A	0.42119	0.15365	0.26361	0.16155
	C	0.06209	0.60811	0.17602	0.15378
	G	0.08834	0.07241	0.77796	0.06129
	T	0.13534	0.09411	0.22724	0.54331

Transition Probabilities of a CTMC

Analytical solutions for the transition probabilities: matrix exponentiation

Monte Carlo simulation is computationally expensive and unnecessary, as the transition probabilities can be solved 'analytically'

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The transition probability matrix, \mathbf{P} , can be solved by exponentiating the product of the instantaneous-rate matrix, \mathbf{Q} , and the branch length, ν : $\mathbf{P}(\nu) = e^{\mathbf{Q}\nu}$

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The exact solution for the transition probability matrix for our instantaneous-rate matrix and branch length (0.5) is:

$$\mathbf{P}(\nu) = \{p_{ij}(\nu)\} = \begin{pmatrix} 0.422927 & 0.153118 & 0.263330 & 0.160625 \\ 0.062896 & 0.609068 & 0.175153 & 0.152883 \\ 0.087566 & 0.071950 & 0.778271 & 0.062212 \\ 0.134967 & 0.093601 & 0.226962 & 0.544470 \end{pmatrix}$$

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Compare with approximate solution (based on 100,000 replicates)

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		A	C	G	T
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Nineteen Dubious Ways to Compute the Exponential of a Matrix, Twenty-Five Years Later*

Cleve Moler[†]
Charles Van Loan[‡]

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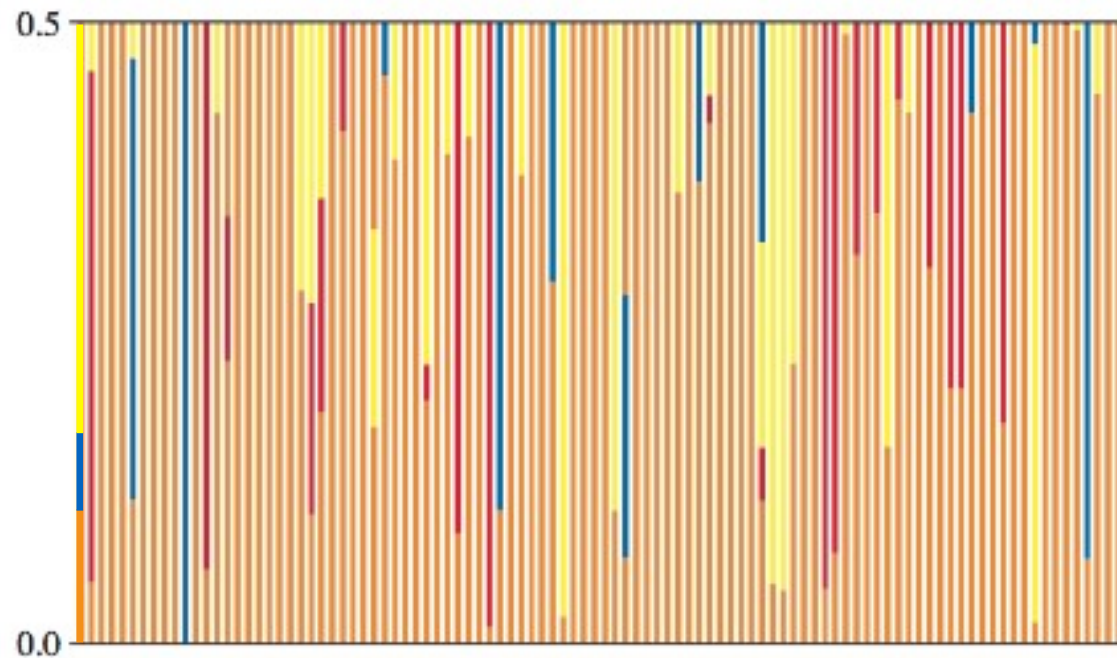
Transition Probabilities of a CTMC

An aside about transition probabilities

Transition probabilities account for all possible histories that a CTMC can end in a particular state, given a particular starting state (and fully specified model)

Transition Probabilities of a CTMC

Reminder:



number of
outcomes

$$23 \div 100$$

number of
simulations

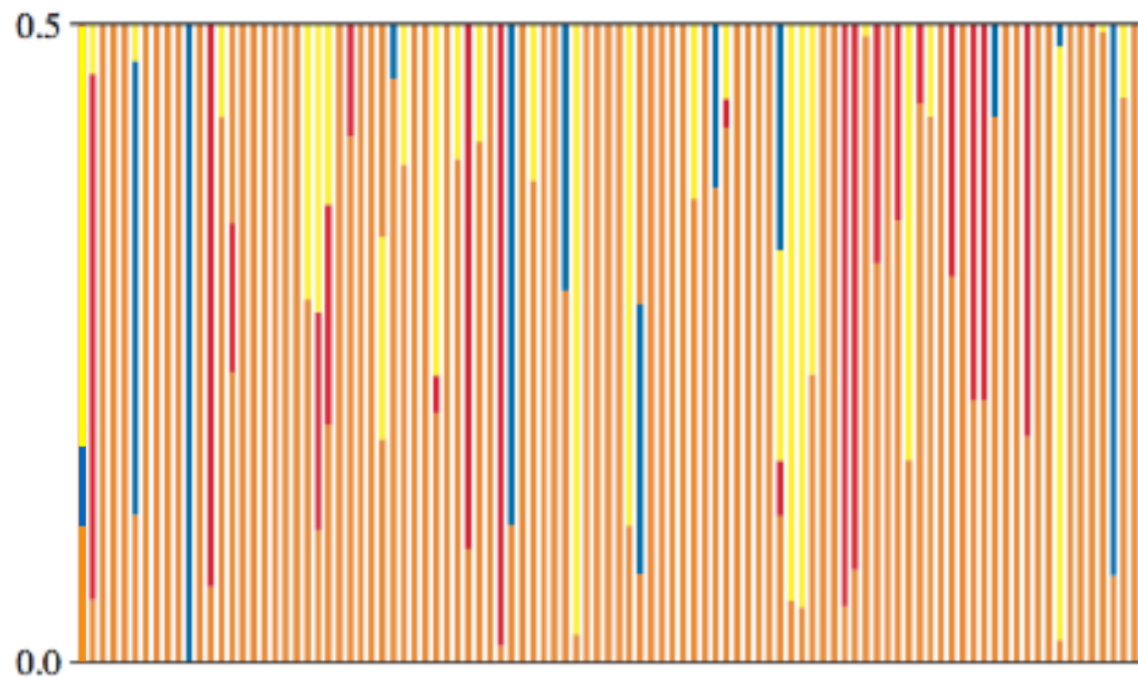
		To			
		A	C	G	T
From	A				
	C				
	G				
	T			0.23	

Transition Probabilities of a CTMC

An aside about transition probabilities

Transition probabilities account for all possible histories that a CTMC can end in a particular state, given a particular starting state (and fully specified model)

Transition probabilities play a key role in computing the likelihood, as they avoid the need to condition on a particular history of character change (nucleotide substitution)



π_i

Stationary Frequencies of a CTMC

Transition probabilities

The probability of observing state j conditioned on starting in state i and running the process over a branch of length ν ; *i.e.*, $p_{ij}(\nu)$

Can be estimated by Monte Carlo simulation or matrix exponentiation, $P(\nu) = e^{Q\nu}$

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The long-term probability of observing the process in state j

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Our hypothetical rate matrix:

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

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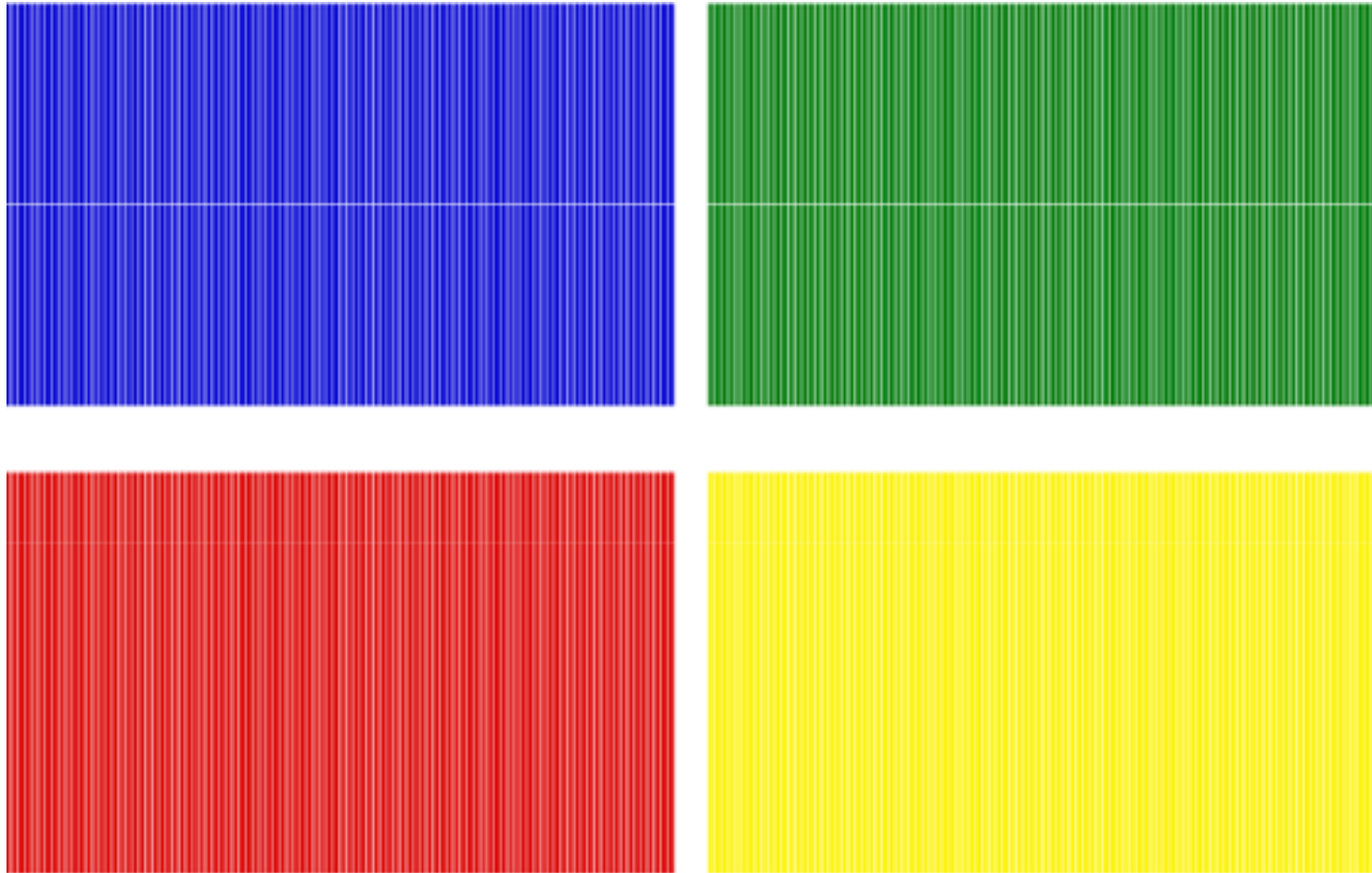
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Transition probabilities over a branch of length $\nu = 0.0$:

$$\mathbf{P}(0.0) = \begin{pmatrix} 1.000 & 0.000 & 0.000 & 0.000 \\ 0.000 & 1.000 & 0.000 & 0.000 \\ 0.000 & 0.000 & 1.000 & 0.000 \\ 0.000 & 0.000 & 0.000 & 1.000 \end{pmatrix}$$

π_i

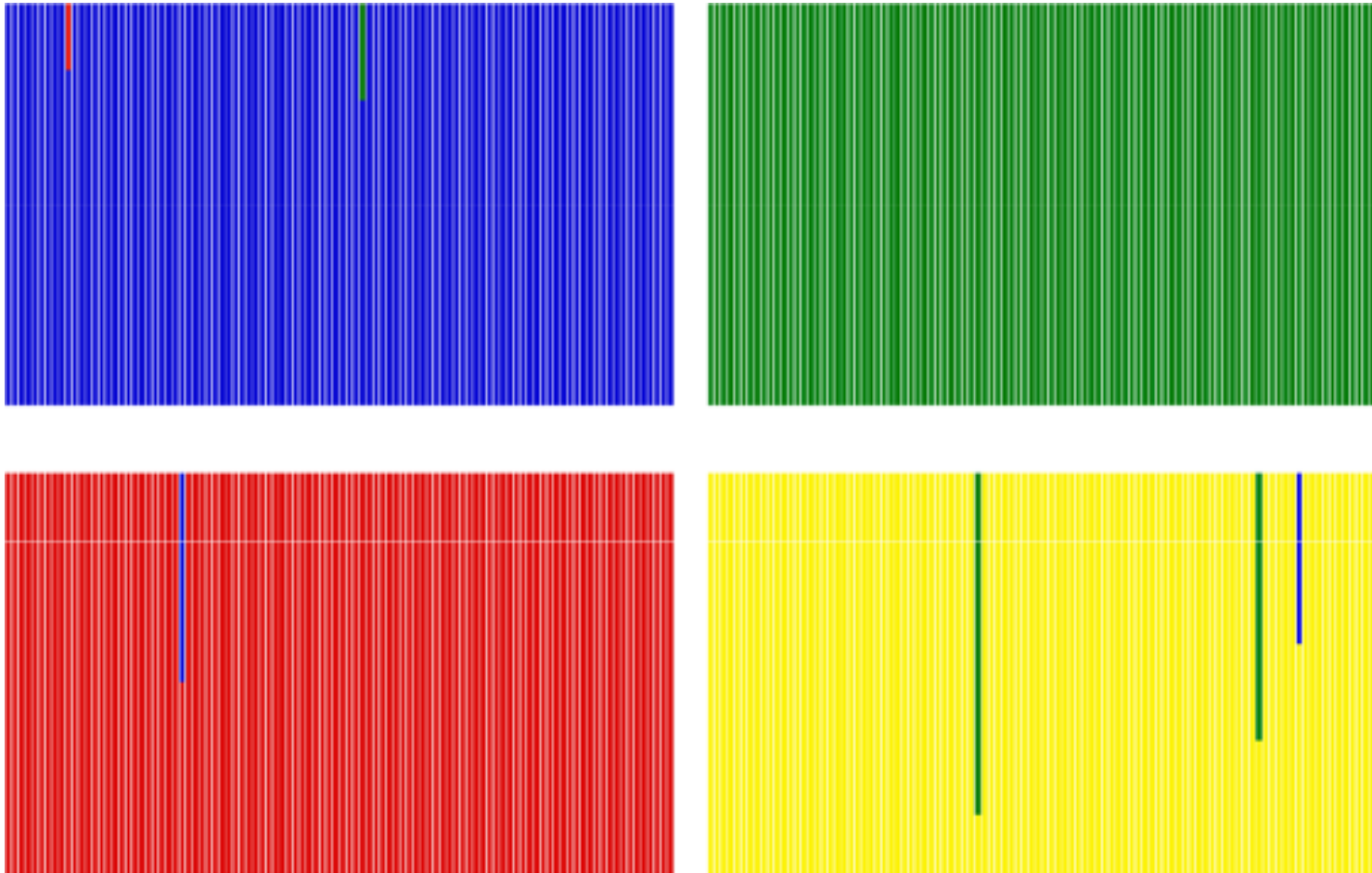
Stationary Frequencies of a CTMC



$$\mathbf{P}(0.0) = \begin{pmatrix} 1.000 & 0.000 & 0.000 & 0.000 \\ 0.000 & 1.000 & 0.000 & 0.000 \\ 0.000 & 0.000 & 1.000 & 0.000 \\ 0.000 & 0.000 & 0.000 & 1.000 \end{pmatrix}$$

π_i

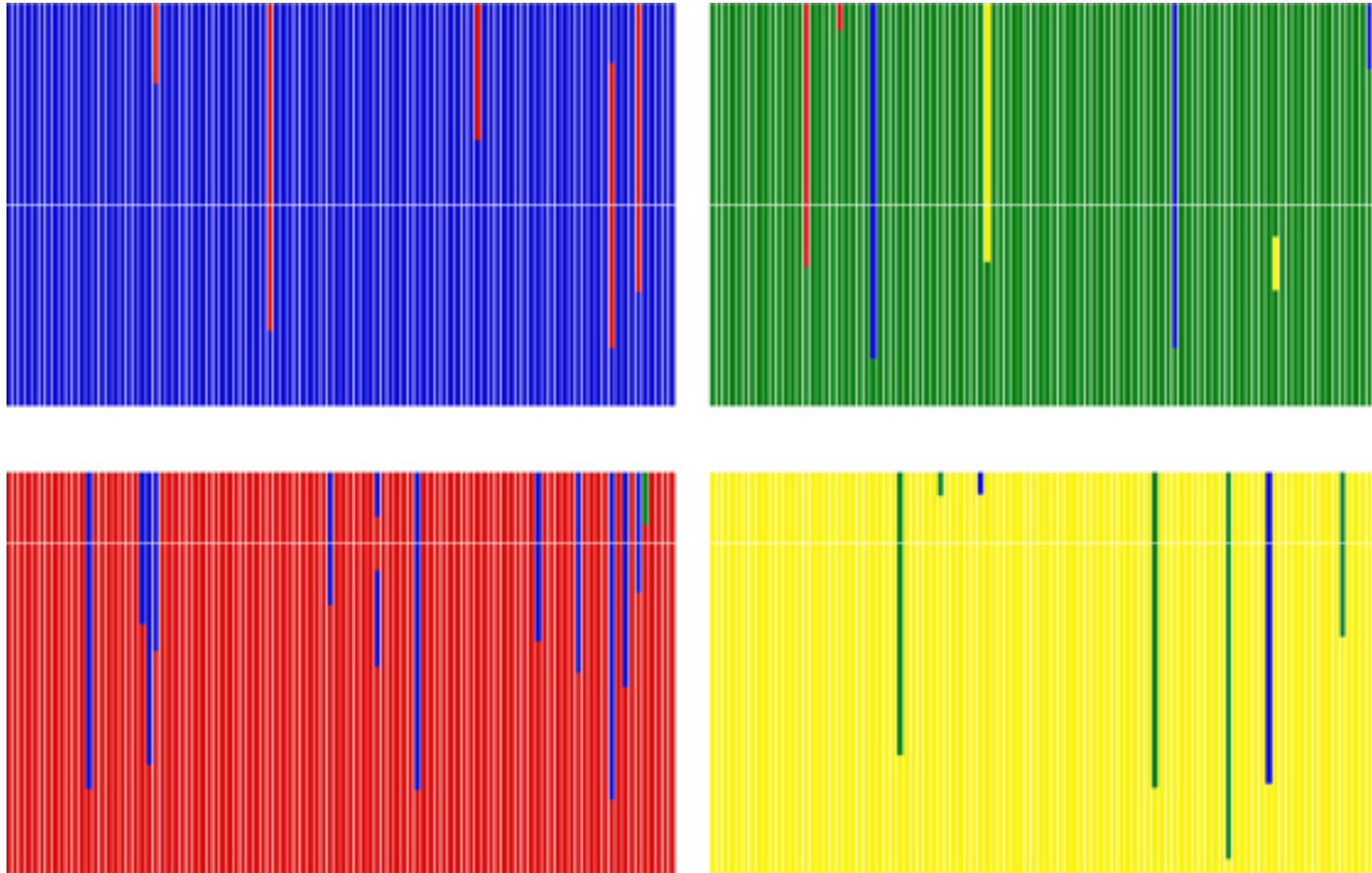
Stationary Frequencies of a CTMC



$$\mathbf{P}(0.01) = \begin{pmatrix} 0.981 & 0.005 & 0.008 & 0.006 \\ 0.001 & 0.989 & 0.004 & 0.005 \\ 0.003 & 0.002 & 0.994 & 0.001 \\ 0.005 & 0.002 & 0.006 & 0.986 \end{pmatrix}$$

π_i

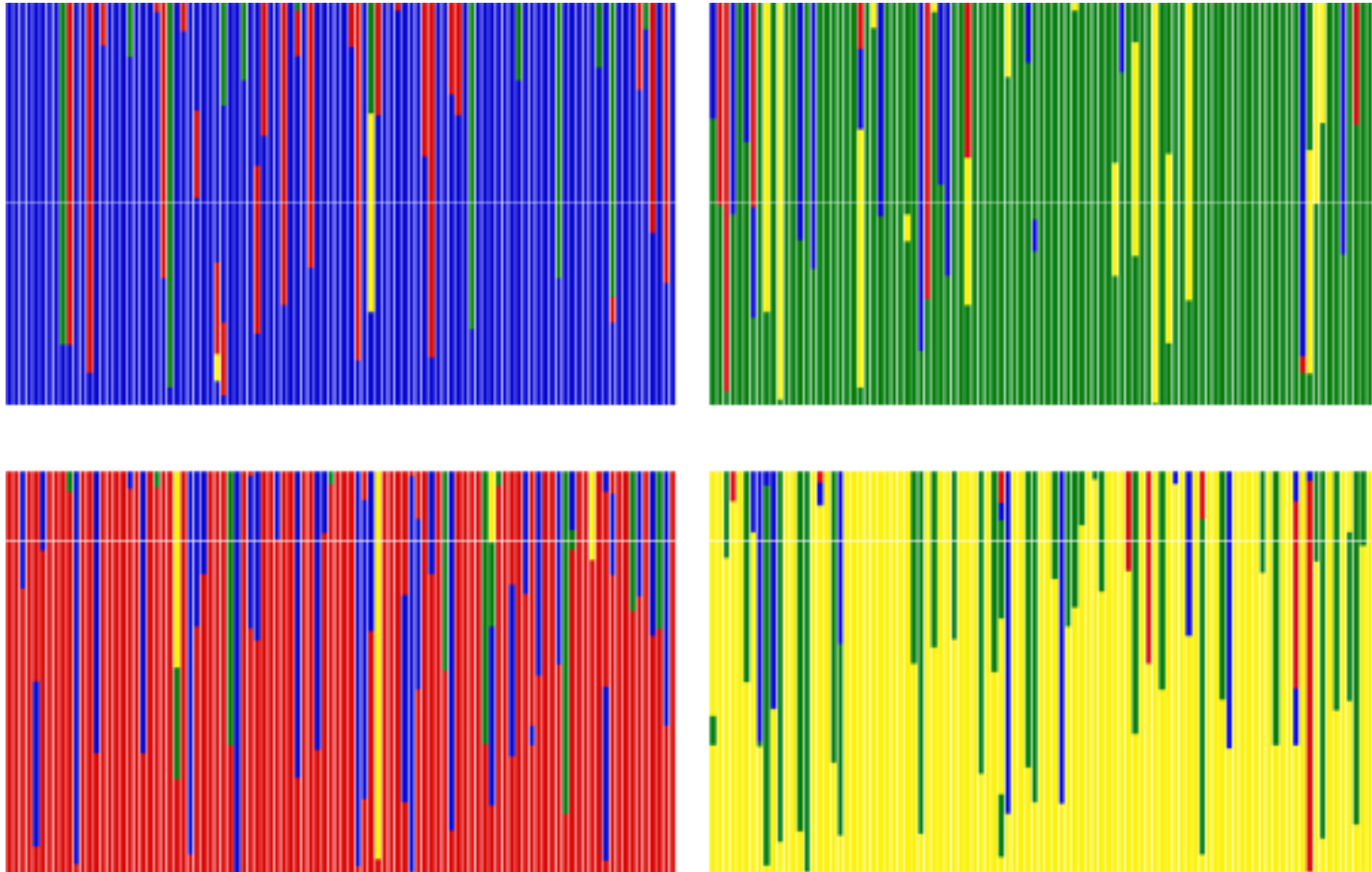
Stationary Frequencies of a CTMC



$$\mathbf{P}(0.10) = \begin{pmatrix} 0.828 & 0.048 & 0.072 & 0.052 \\ 0.014 & 0.900 & 0.040 & 0.046 \\ 0.026 & 0.017 & 0.944 & 0.013 \\ 0.046 & 0.023 & 0.056 & 0.876 \end{pmatrix}$$

π_i

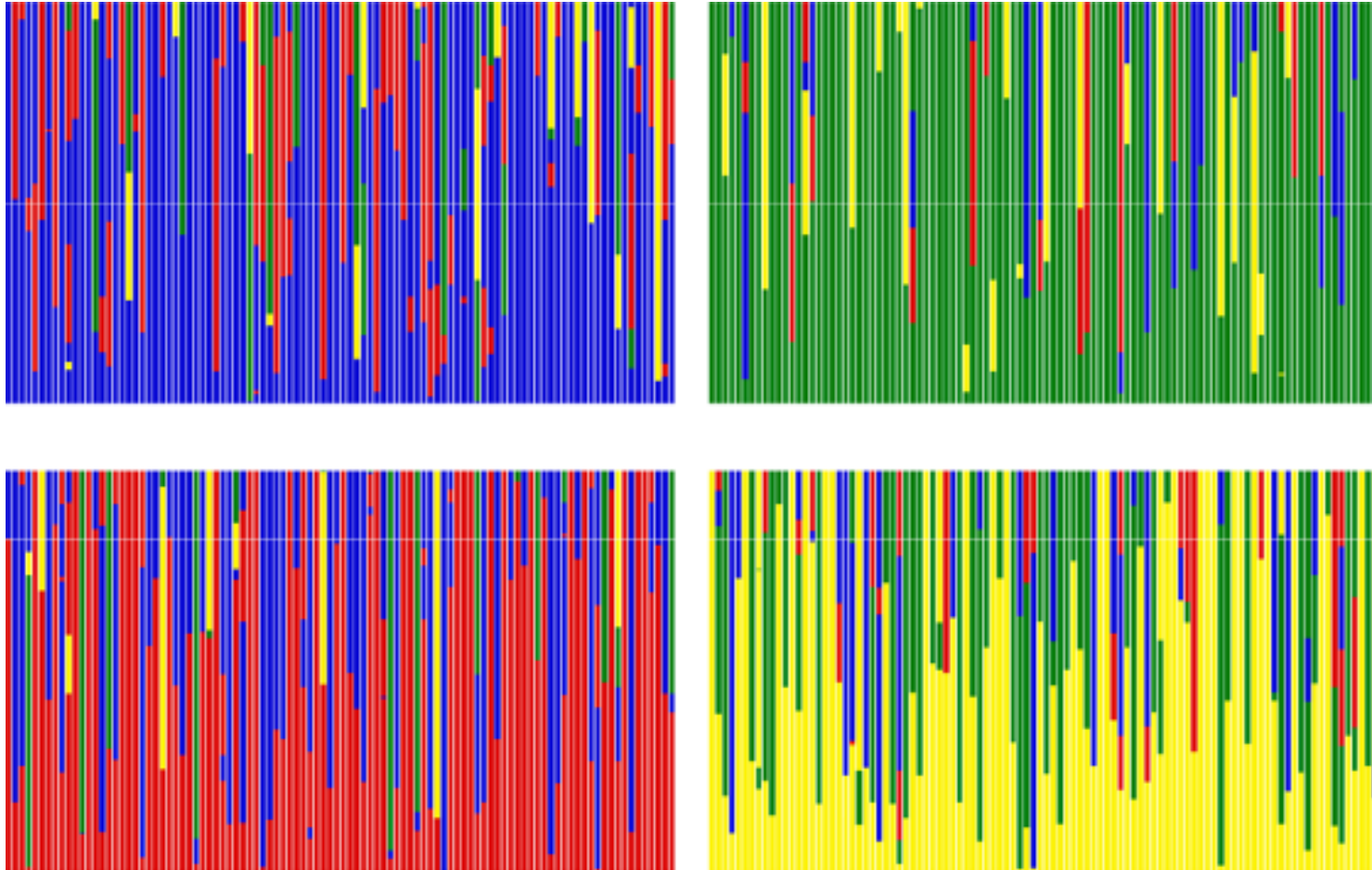
Stationary Frequencies of a CTMC



$$\mathbf{P}(0.50) = \begin{pmatrix} 0.423 & 0.153 & 0.263 & 0.161 \\ 0.063 & 0.609 & 0.175 & 0.153 \\ 0.088 & 0.072 & 0.778 & 0.062 \\ 0.135 & 0.094 & 0.227 & 0.544 \end{pmatrix}$$

π_i

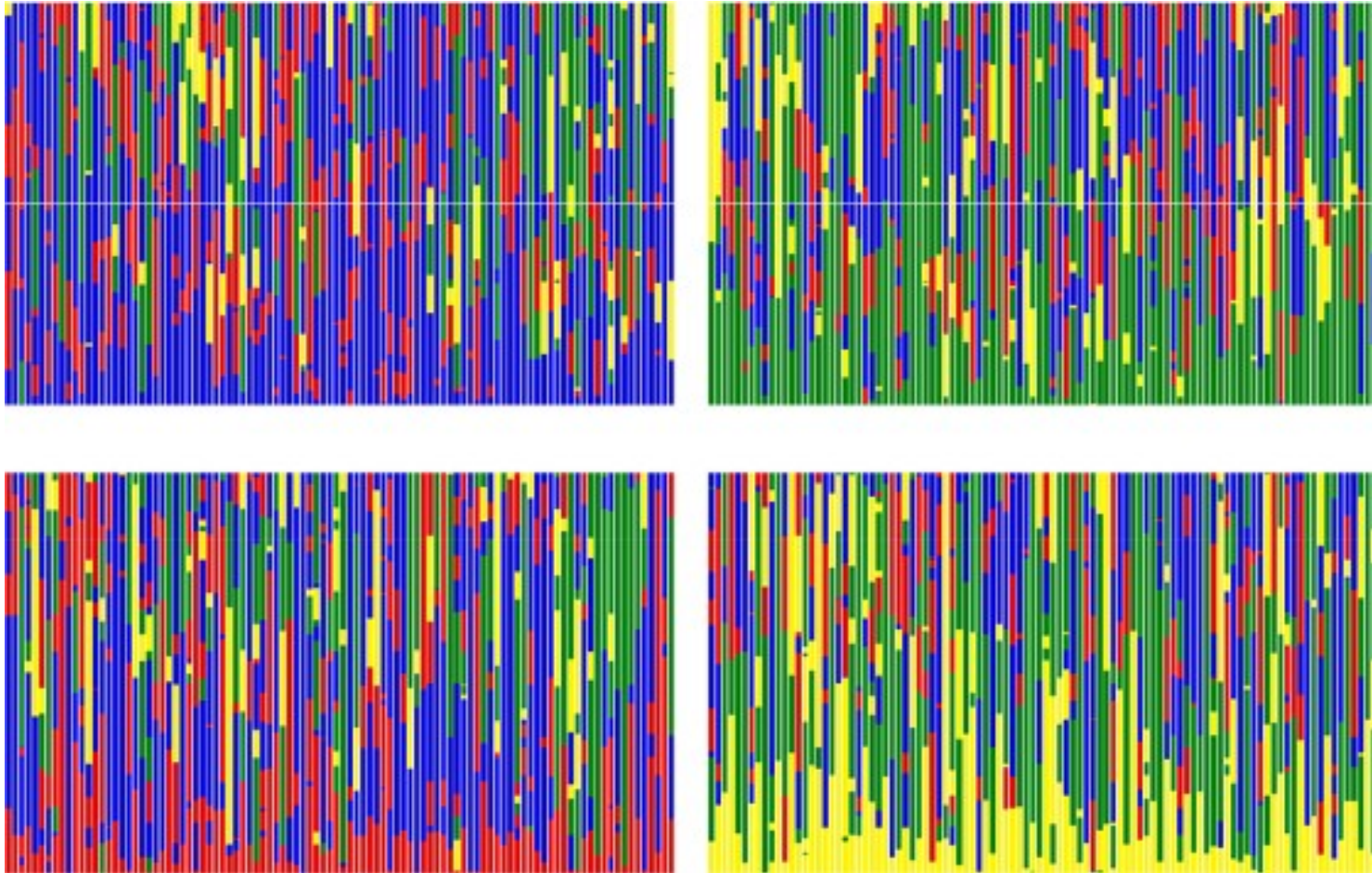
Stationary Frequencies of a CTMC



$$\mathbf{P}(1.0) = \begin{pmatrix} 0.233 & 0.192 & 0.379 & 0.195 \\ 0.101 & 0.408 & 0.295 & 0.197 \\ 0.118 & 0.119 & 0.655 & 0.107 \\ 0.156 & 0.145 & 0.352 & 0.347 \end{pmatrix}$$

π_i

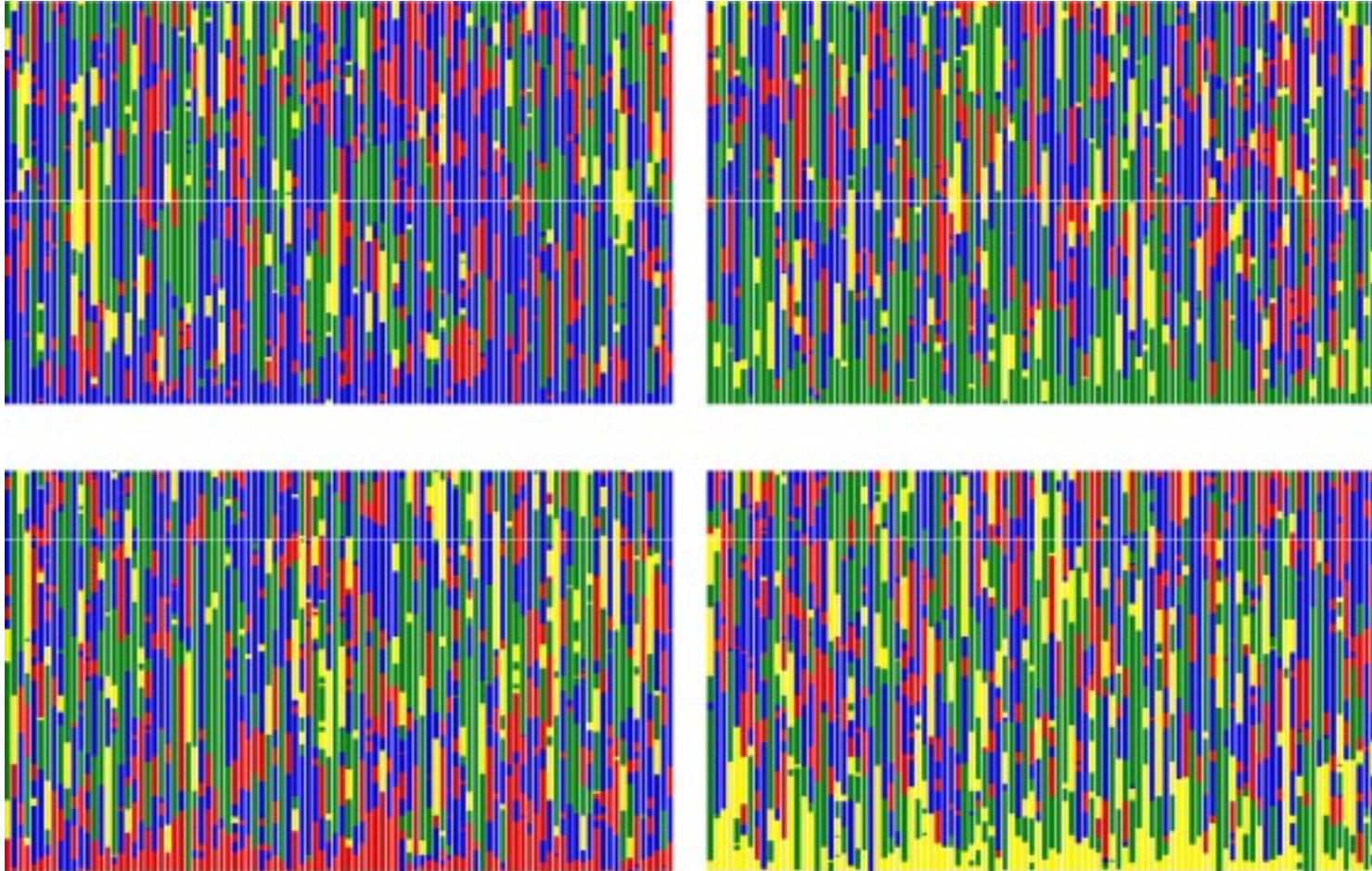
Stationary Frequencies of a CTMC



$$\mathbf{P}(5.0) = \begin{pmatrix} 0.138 & 0.188 & 0.494 & 0.180 \\ 0.138 & 0.190 & 0.492 & 0.181 \\ 0.137 & 0.187 & 0.497 & 0.178 \\ 0.138 & 0.188 & 0.494 & 0.180 \end{pmatrix}$$

π_i

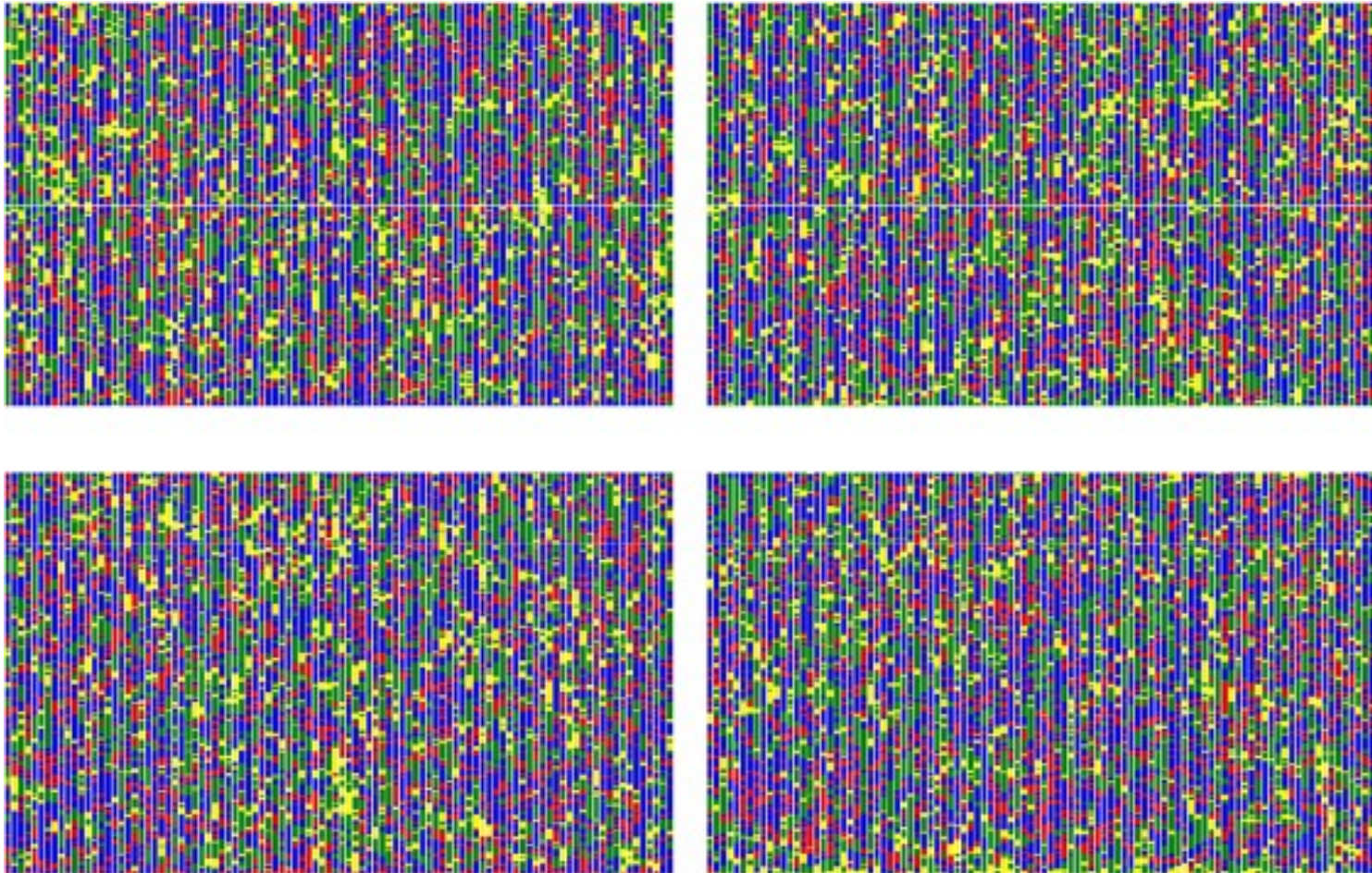
Stationary Frequencies of a CTMC



$$\mathbf{P}(10.0) = \begin{pmatrix} 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \end{pmatrix}$$

π_i

Stationary Frequencies of a CTMC



$$\mathbf{P}(100.0) = \begin{pmatrix} 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \end{pmatrix}$$

π_i

Stationary Frequencies of a CTMC

Stationary frequencies

The probability of observing the process in a particular state j after a long (infinite) period of time

π_i

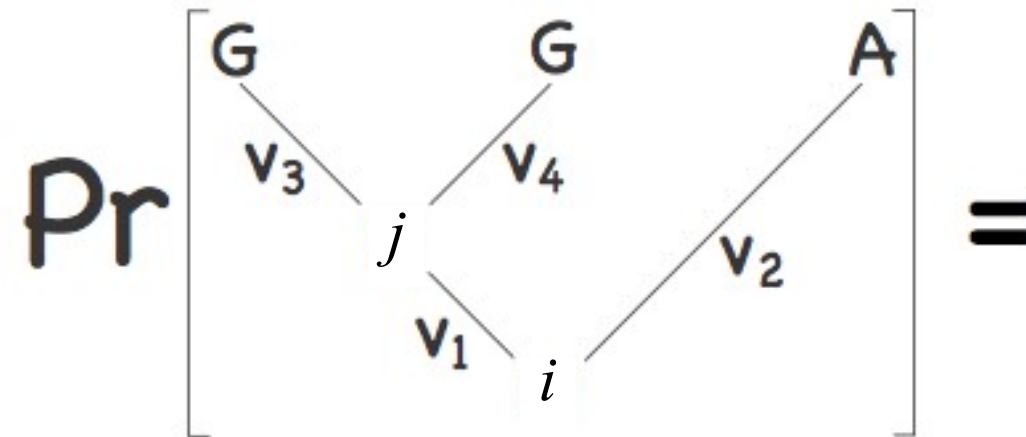
Stationary Frequencies of a CTMC

Stationary frequencies

The probability of observing the process in a particular state j after a long (infinite) period of time

When the continuous time Markov chain is at stationarity, the stochastic process has 'forgotten' the starting state: the process ends in a given state with the same probability, regardless of the starting state

Now we can compute the likelihood of a site history



$$\pi_i \times p_{ij}(v_1) \times p_{iA}(v_2) \times p_{jG}(v_3) \times p_{jG}(v_4)$$

π_i Stationary frequencies

$p_{ij}(v)$ Transition probabilities

What do we get if we sum over all site histories?

$$\Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ A \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ C \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ G \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ T \end{array} \right] +$$

$$\Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ A \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ C \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ G \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ T \end{array} \right] +$$

$$\Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ G \\ \diagup \quad \diagdown \\ A \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ G \\ \diagup \quad \diagdown \\ C \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ G \\ \diagup \quad \diagdown \\ G \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ G \\ \diagup \quad \diagdown \\ T \end{array} \right] +$$

$$\Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ T \\ \diagup \quad \diagdown \\ A \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ T \\ \diagup \quad \diagdown \\ C \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ T \\ \diagup \quad \diagdown \\ G \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ T \\ \diagup \quad \diagdown \\ T \end{array} \right]$$

$$= \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ \quad \quad \diagup \quad \diagdown \end{array} \right]$$

What do we get if we sum over all site histories?

$$\Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ A \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ C \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ G \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ T \end{array} \right] +$$

$$\Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ A \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ C \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ G \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ T \end{array} \right] +$$

$$\Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ G \\ \diagup \quad \diagdown \\ A \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ G \\ \diagup \quad \diagdown \\ C \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ G \\ \diagup \quad \diagdown \\ G \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ G \\ \diagup \quad \diagdown \\ T \end{array} \right] +$$

$$\Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ T \\ \diagup \quad \diagdown \\ A \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ T \\ \diagup \quad \diagdown \\ C \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ T \\ \diagup \quad \diagdown \\ G \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ T \\ \diagup \quad \diagdown \\ T \end{array} \right]$$

$$= \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ \quad \quad \diagup \quad \diagdown \\ \quad \quad \quad \quad \diagup \quad \diagdown \end{array} \right] = P(\text{GGA} | \text{tree, branch lengths, } Q)$$

What do we get if we sum over all site histories?

$$\Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ A \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ C \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ G \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ A \\ \diagup \quad \diagdown \\ T \end{array} \right] +$$

$$\Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ A \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ C \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ G \end{array} \right] + \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ C \\ \diagup \quad \diagdown \\ T \end{array} \right] +$$

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$$= \Pr \left[\begin{array}{c} G \quad G \quad A \\ \diagdown \quad \diagup \\ \quad \quad \diagup \quad \diagdown \\ \quad \quad \quad \quad \diagup \quad \diagdown \end{array} \right] = P(\text{GGA} | \text{tree, branch lengths, } Q)$$

This is the likelihood of site pattern (GGA)

Models 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

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Instantaneous-rate matrix, \mathbf{Q} , and the transition probability matrix, \mathbf{P}

The instantaneous rate matrix describes the probability of change between each state in an infinitesimal time interval, $q_{ij}(\partial t)$

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

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The transition probability matrix, \mathbf{P} , gives the probability of observing state j given state i after a branch of length ν

$\mathbf{P}(\nu) = \{p_{ij}(\nu)\}$

Are we clear on what are:

- ***Substitution rates***
- ***Substitution probabilities***
- ***Stationary frequencies***

?

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the transition probabilities integrate over all possible histories by which an initial state i can give rise to an end state j over branch length ν

Aims and outline

Understand the main ideas underlying models of sequence evolution

- To do so, we will:
 - Introduce important probability notions
 - Play with models of character evolution through simulations
- Briefly present some of the main models of nucleotide evolution

Time-reversible substitution models

Rate matrix

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

Substitution models

Rate matrix

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

Jukes and
Cantor 1969

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

0 free parameter (1 if we do not impose one substitution per unit time)

Kimura 1980

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

1 transition/transversion ratio : 1 free parameter

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

1 transition/transversion ratio
4 equilibrium frequencies:
4 free parameters

Substitution models

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0 free parameter (1 if we do not impose one substitution per unit time)

1 transition/transversion ratio : 1 free parameter

1 transition/transversion ratio
4 equilibrium frequencies:
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All those are particular cases of the GTR model

General Time Reversible model of substitution

Rate matrix

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

Lanave et al. 1984; Tavaré, 1986

4 **stationary frequencies**: 3 parameters

6 **exchangeability parameters**: 5 parameters (if we impose one substitution per unit time)

Summary on CTMCs

- We use CTMCs to model character evolution
- Given an instantaneous rate matrix, we can compute substitution probabilities on a branch with an arbitrary length
- We can combine these computations to compute the likelihood of a site history
- We can sum over site histories to get the likelihood of a site pattern
- The GTR family provides examples of reversible instantaneous rate matrices