Introduction to modelling sequence evolution

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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

https://en.wikipedia.org/wiki/Beware_of_the_dog

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

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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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- *Sites of alignment=independent identically distributed Markov chains running along a phylogeny*
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Aims and outline

Understand the main ideas underlying models of sequence evolution

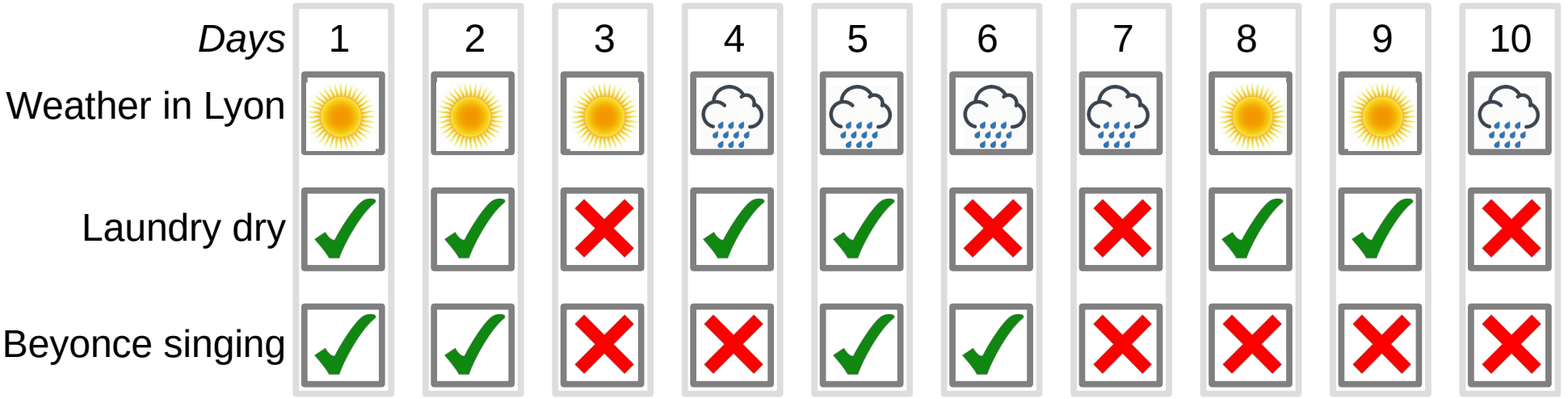
- To do so, we will:
  - Introduce important probability notions
  - Play with models of character evolution through simulations
- Briefly present some of the main models of nucleotide evolution

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



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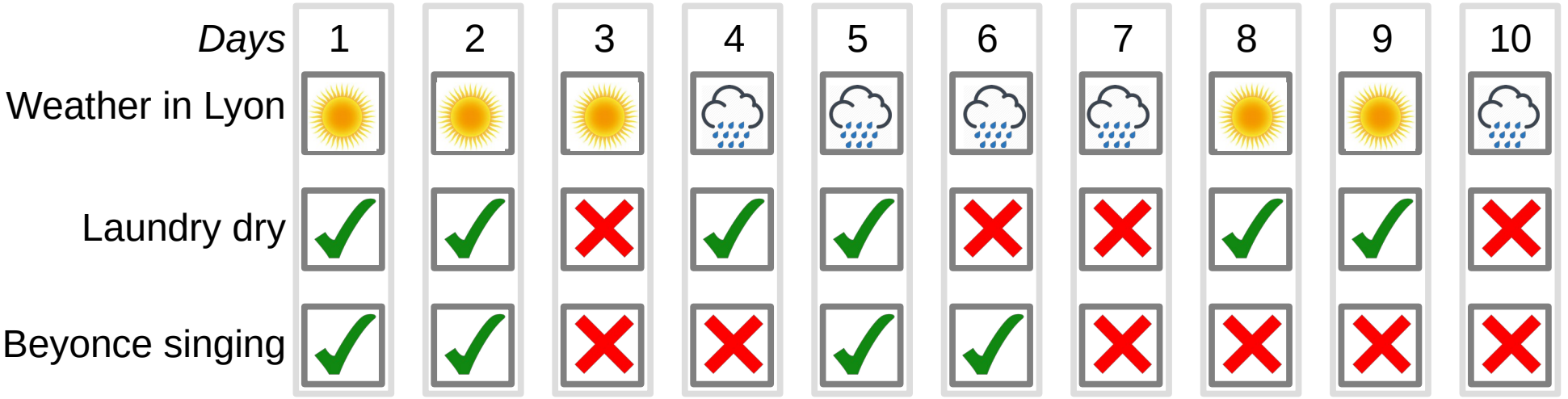

$P(rainy) = ?$

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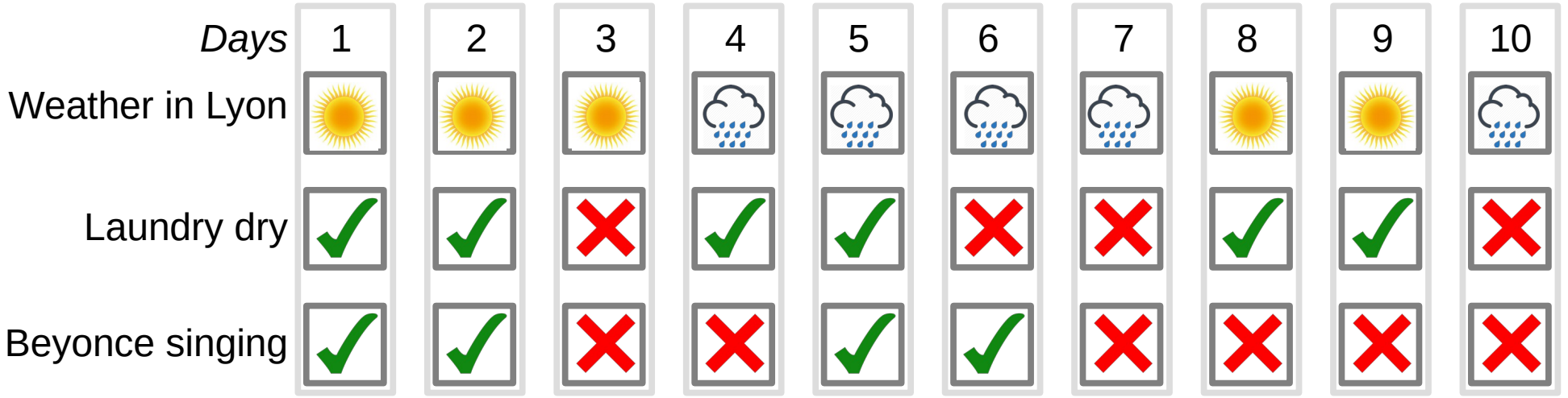

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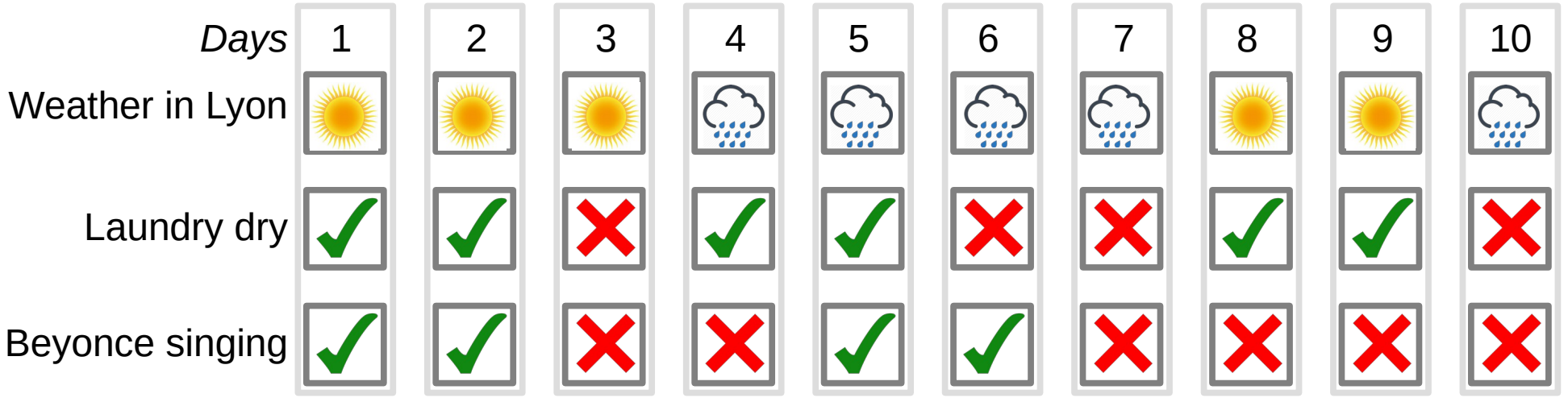

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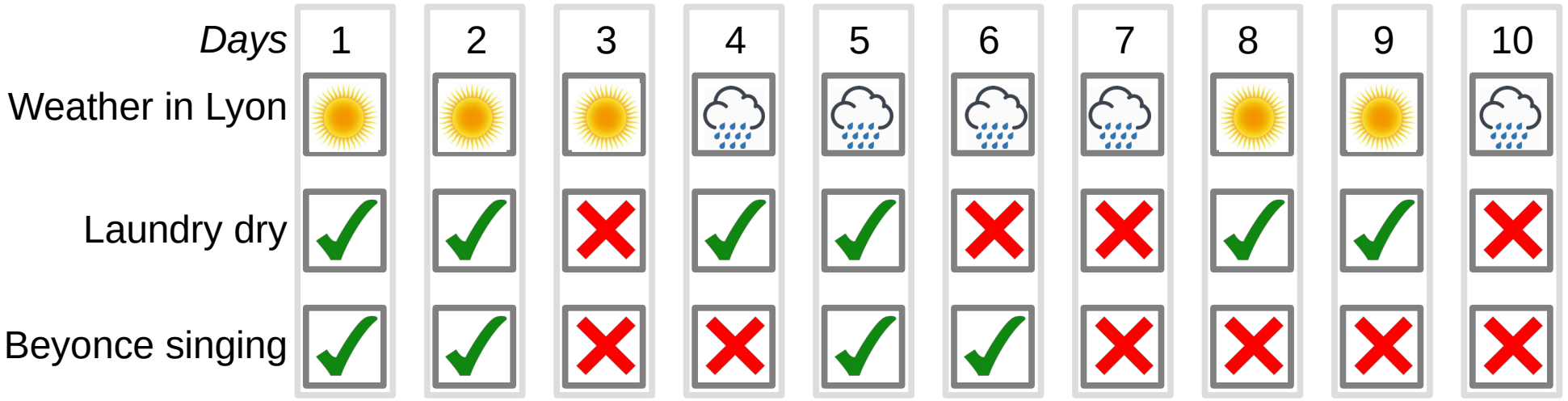

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$P(dry\ laundry | sunny) = ?$

$P(dry\ laundry | rainy) = ?$

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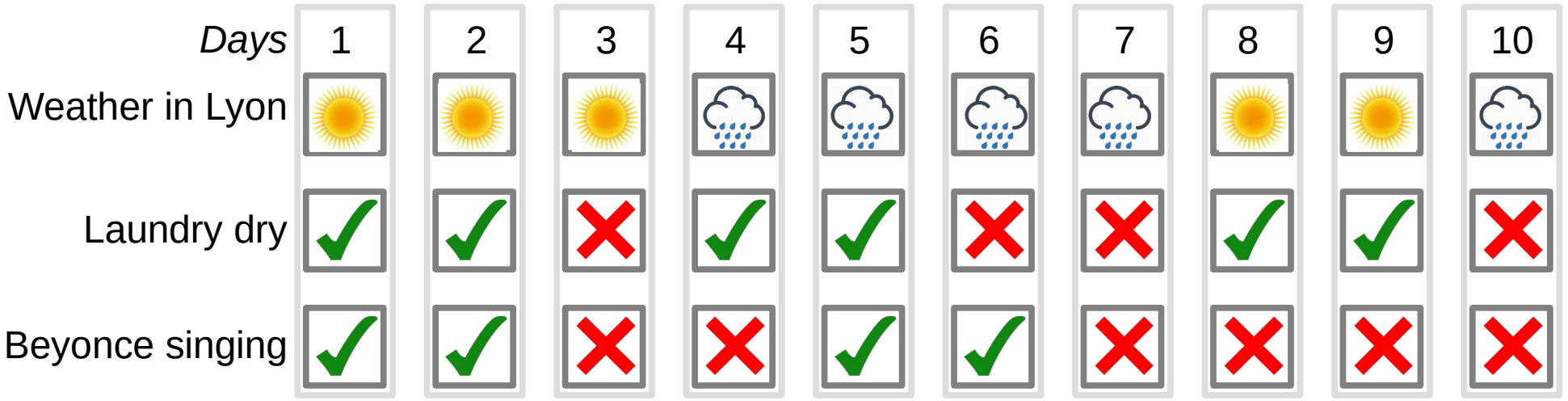

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$P(dry\,laundry|rainy)=0.4$

Conditional probability: P(A|B)

Crash course in probability

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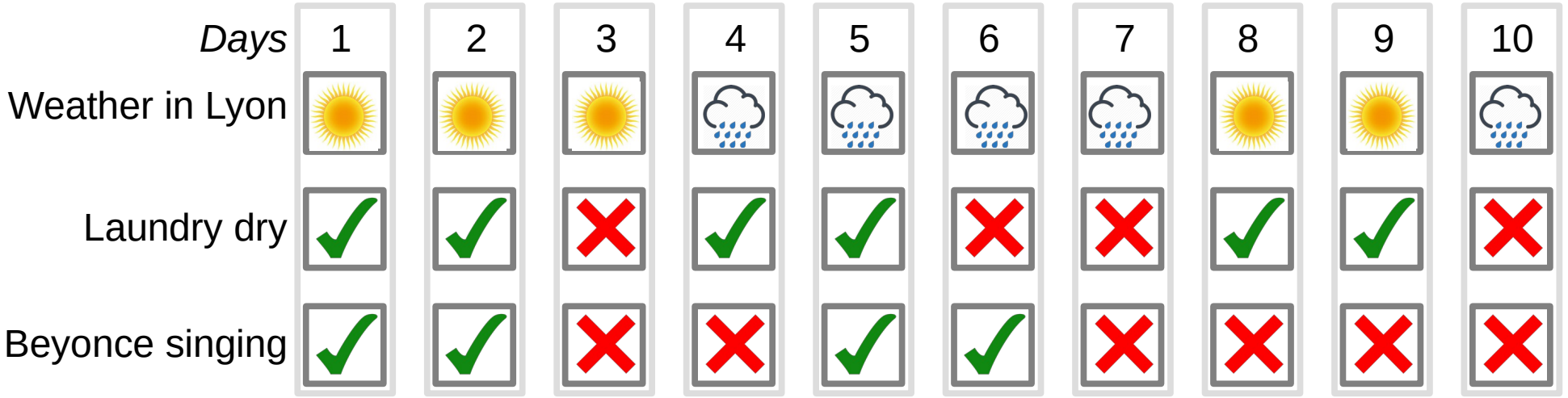

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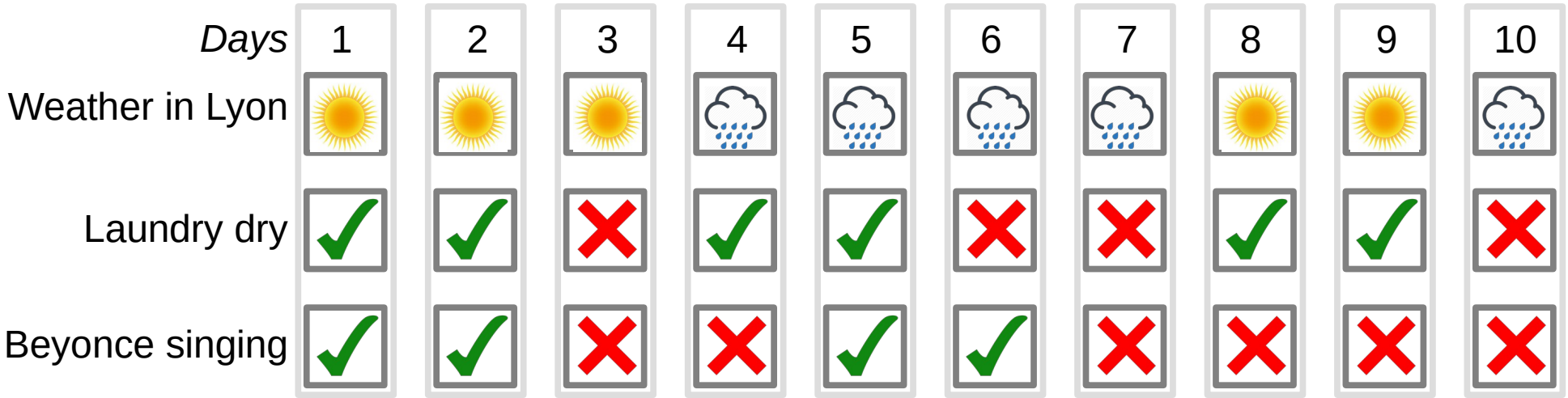

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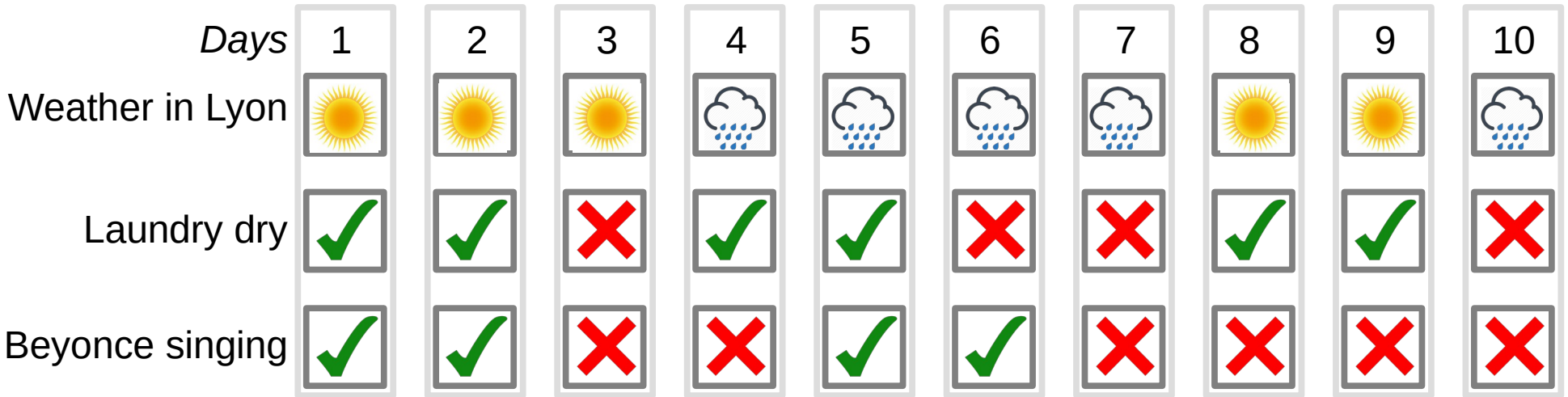

$P(rainy)=0.5 \qquad P(sunny)=1-P(rainy)=0.5$

The events "Beyonce singing" and "sunny" are independent

$P(Beyonce\ singing)=0.4$

$P(Beyonce\ singing)=P(Beyonce\ singing|rainy)=P(Beyonce\ singing|sunny)^{20}=0.4$

Crash course in probability

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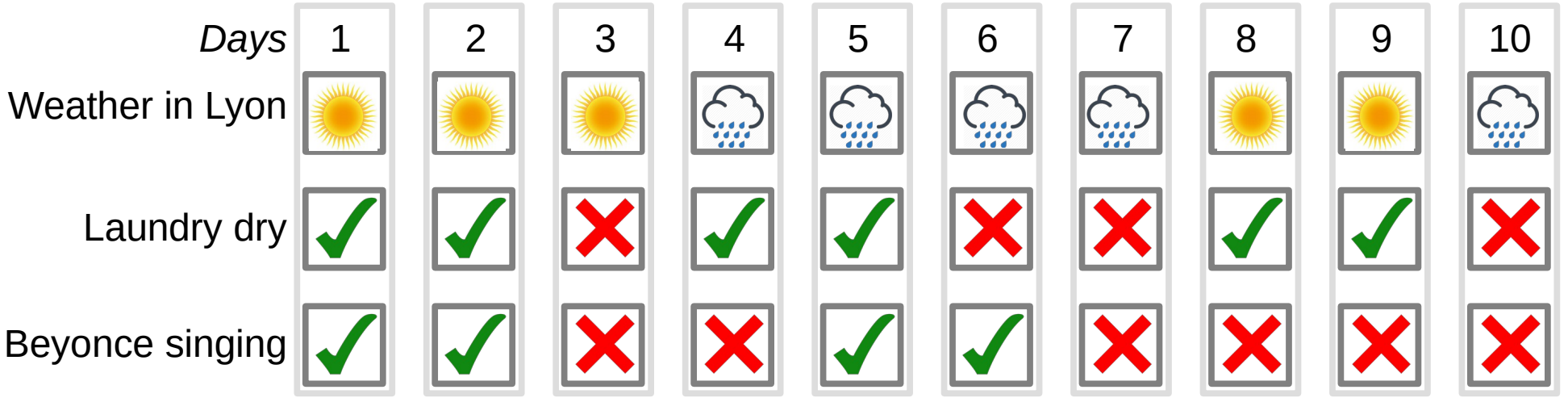

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The events "dry laundry" and "sunny" are NOT independent

Crash course in probability

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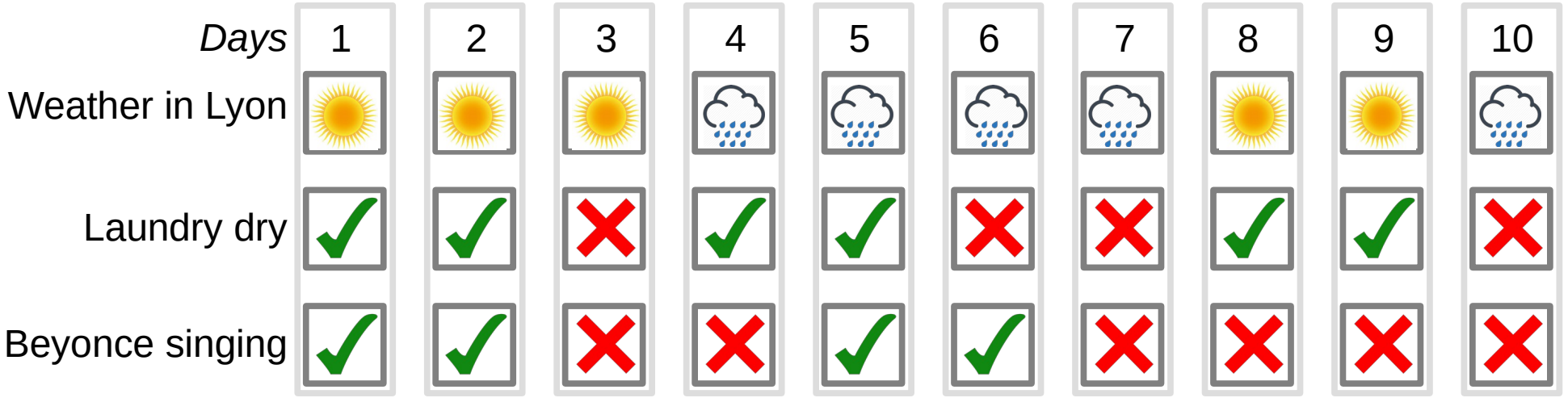


$$P(rainy) = 0.5 \qquad P(sunny) = 1 - P(rainy) = 0.5 \qquad P(dry\ laundry) = 0.6$$

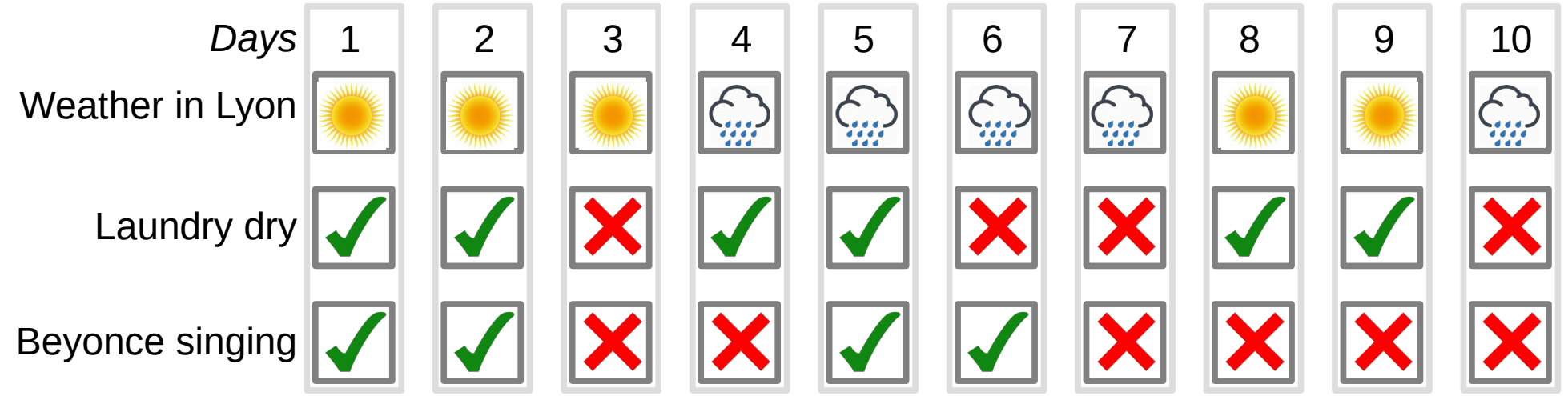
$$P(dry\ laundry \mid sunny) = 0.8 \qquad P(dry\ laundry \mid rainy) = 0.4$$

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

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

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

Useful distributions

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

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- *Continuous distributions (values in $\mathbb{R}$, [0,1]...):*
  - **Exponential**: Time between events in a Poisson process: how much time between two meteorites with diameter >1m:

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

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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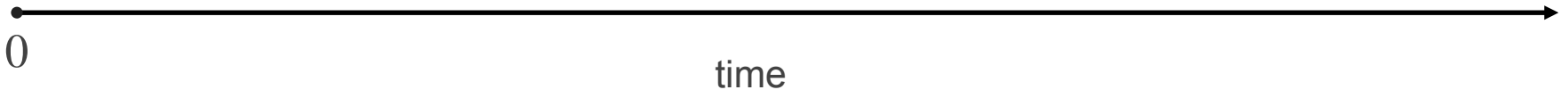

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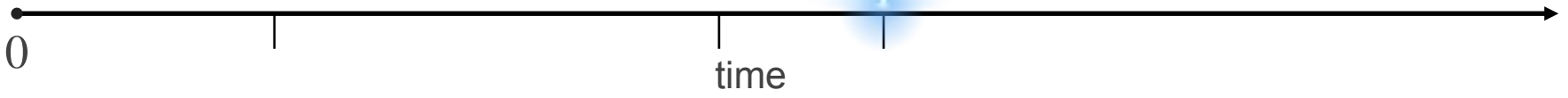

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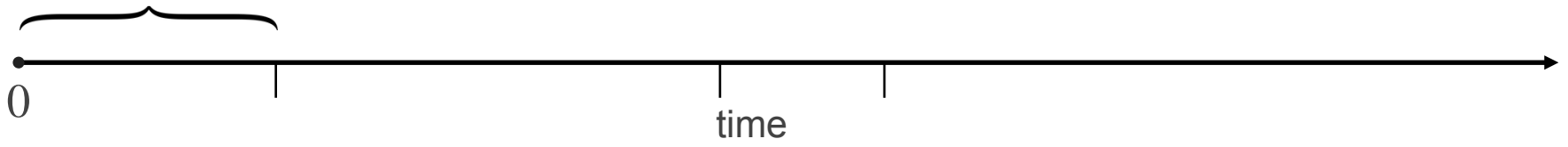
The waiting (sojourn) time for the first event



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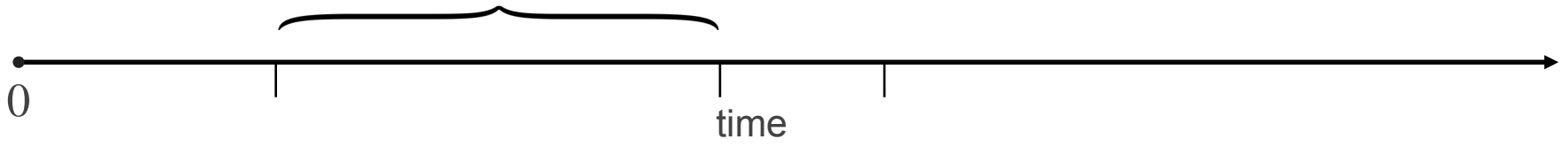
The waiting (sojourn) time for the second event



More on waiting times in Poisson processes

Waiting times in a Poisson process

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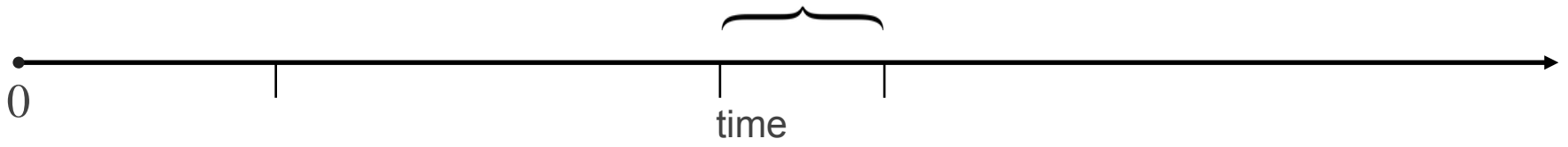
The waiting (sojourn) time for the third event



More on waiting times in Poisson processes

Waiting times in a Poisson process

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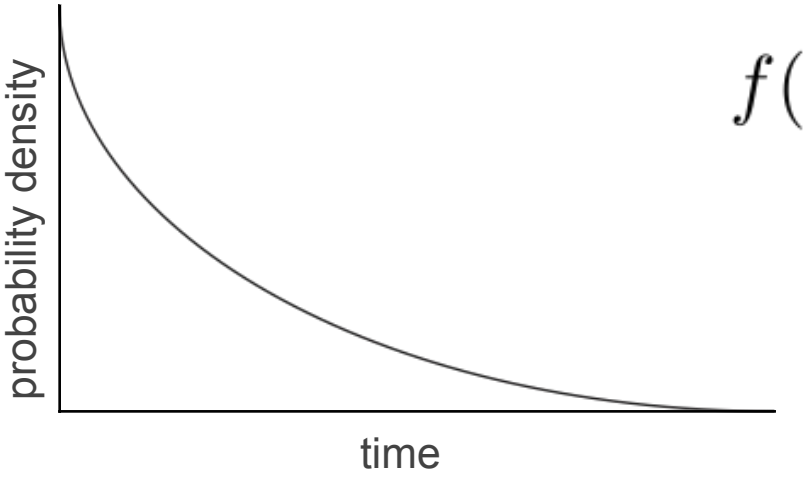
The waiting (sojourn) times are exponentially distributed random variables



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

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

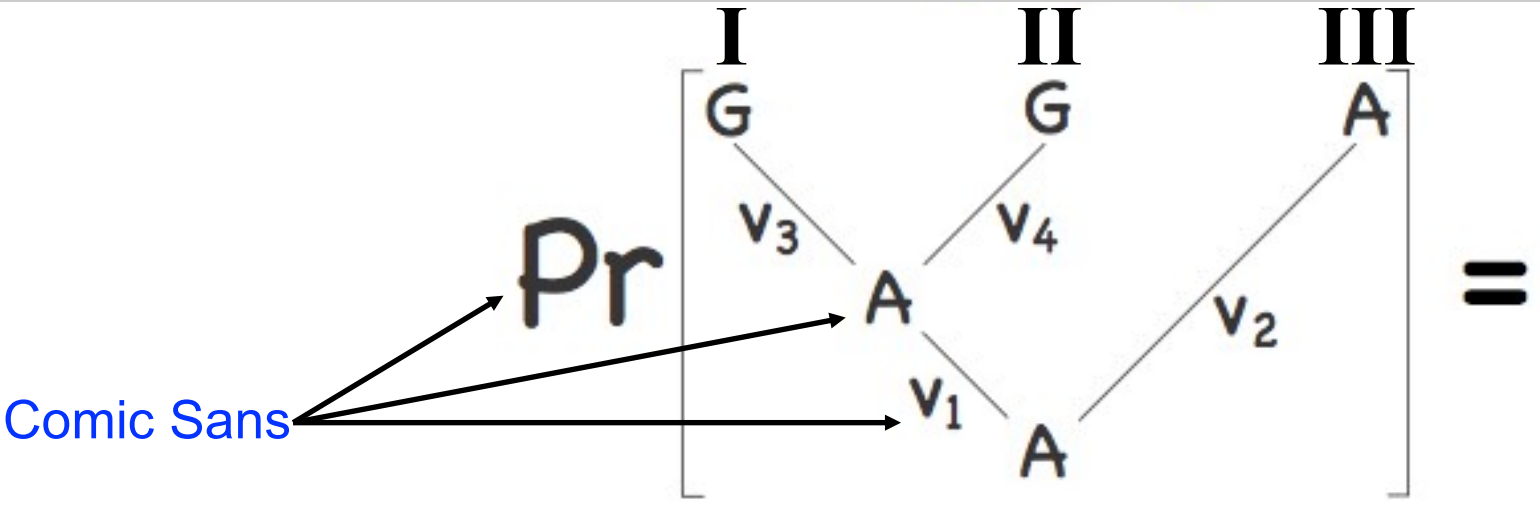
Species	Sequence data
Species I	GCG--CACCGGCGCAGTCA....
Species II	GCGTTCA--GGCG--GTCA....
Species III	ACGTTCACCGGCGCAGTCA....

How do we compute the likelihood of a site pattern?

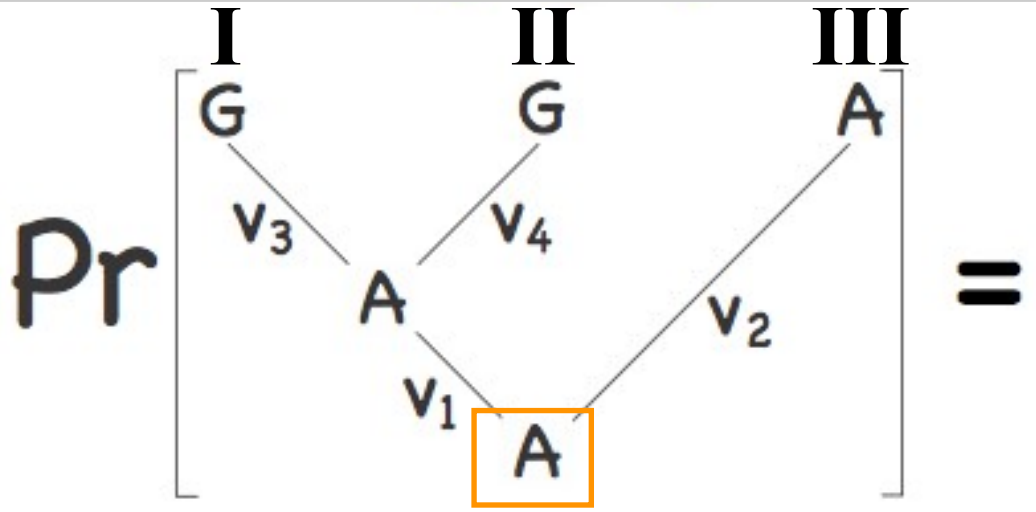
First, we'll see how we compute the likelihood of a site history.

To do that, we'll use simulations.

Stochastic Models of Nucleotide Substitution

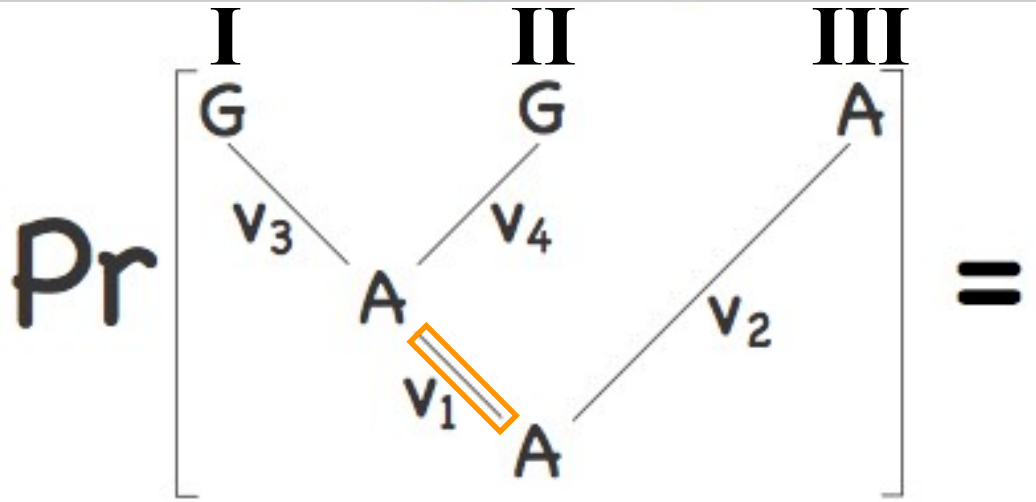


Stochastic Models of Nucleotide Substitution



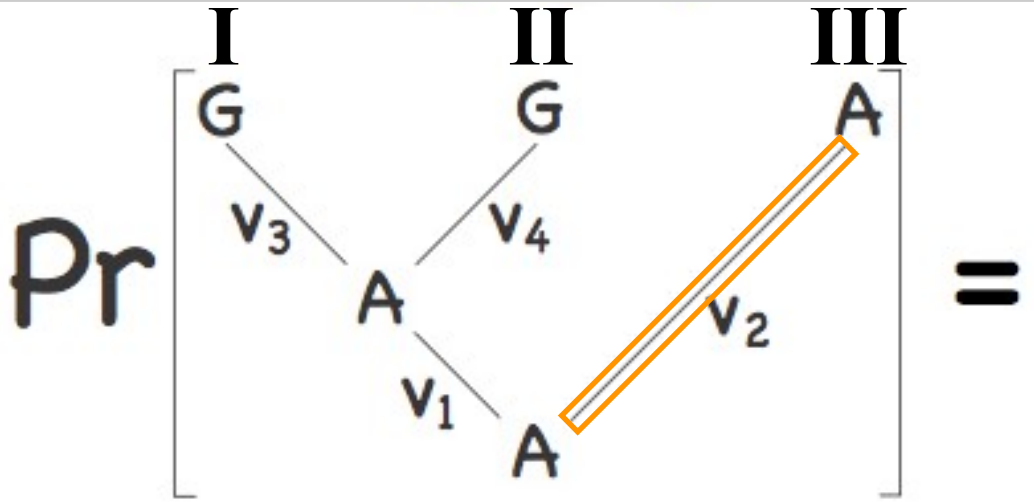
π_A

Stochastic Models of Nucleotide Substitution



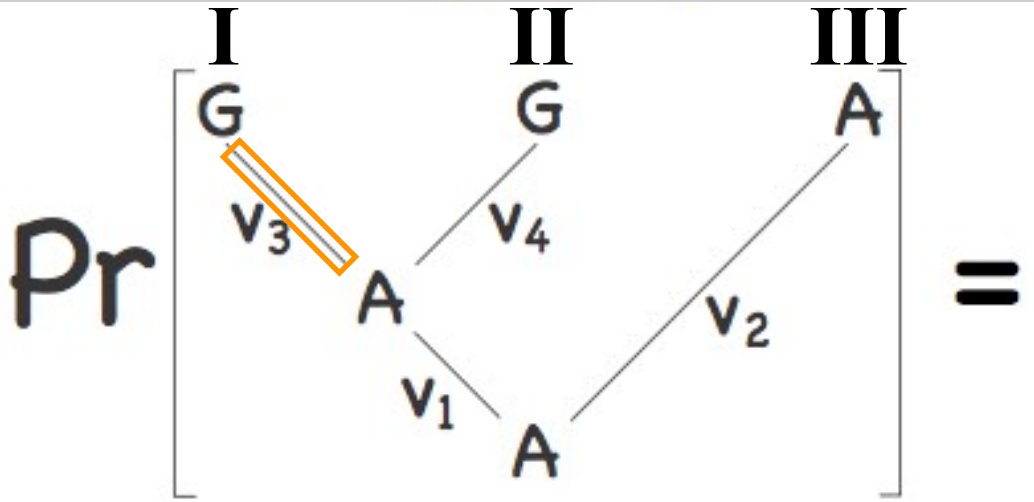
$$\pi_A \times p_{AA}(v_1)$$

Stochastic Models of Nucleotide Substitution



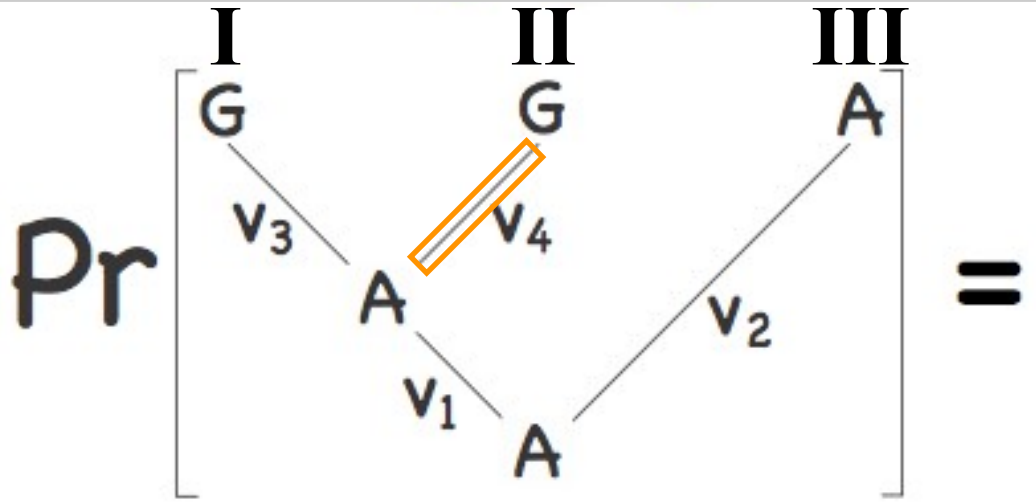
$$\pi_A \times p_{AA}(v_1) \times p_{AA}(v_2)$$

Stochastic Models of Nucleotide Substitution



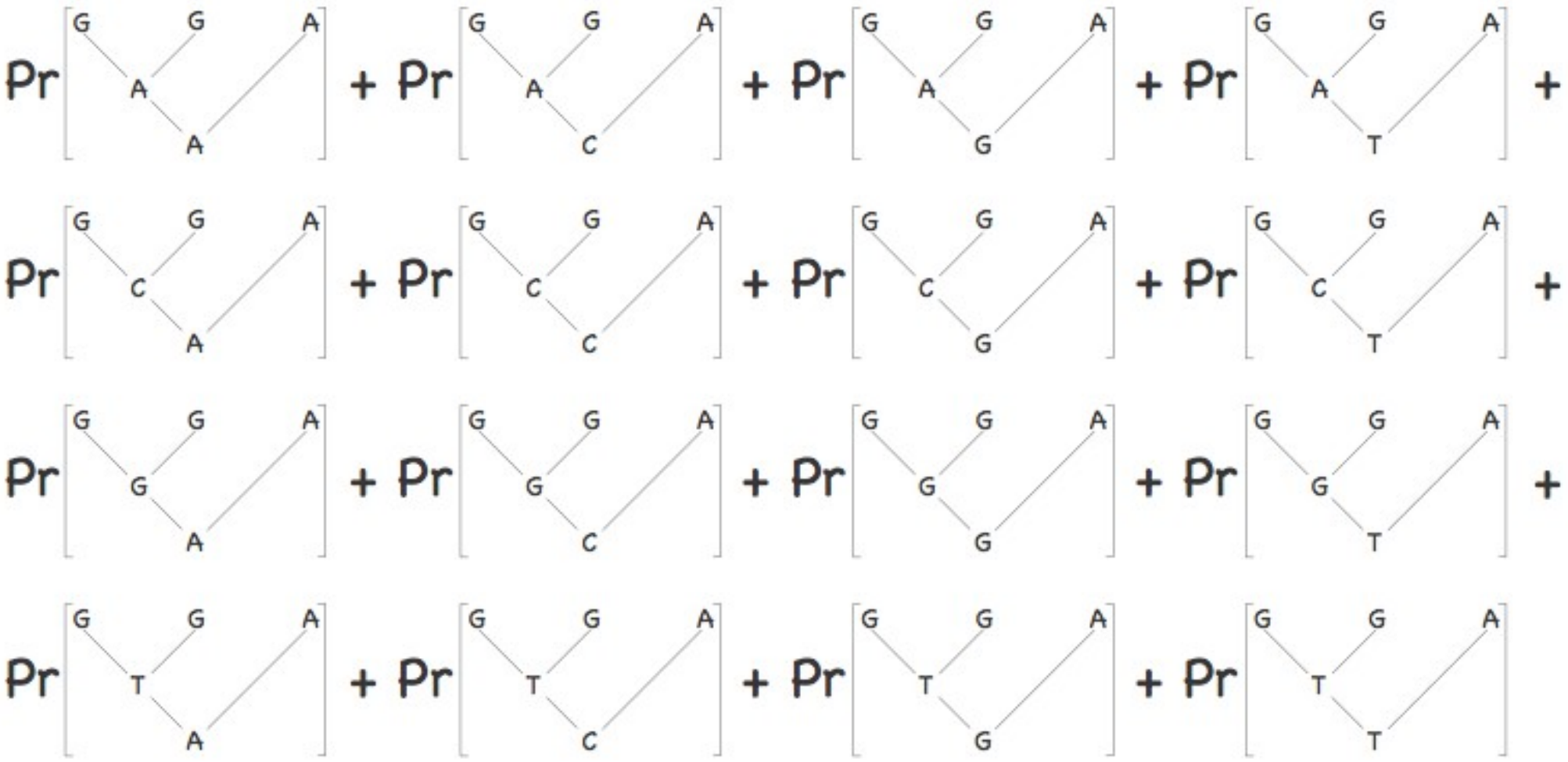
$$\pi_A \times p_{AA}(v_1) \times p_{AA}(v_2) \times p_{AG}(v_3)$$

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



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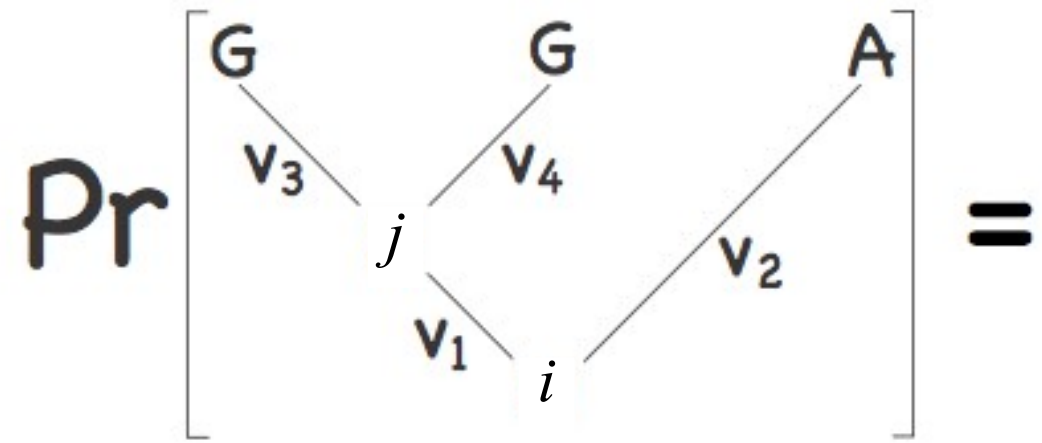
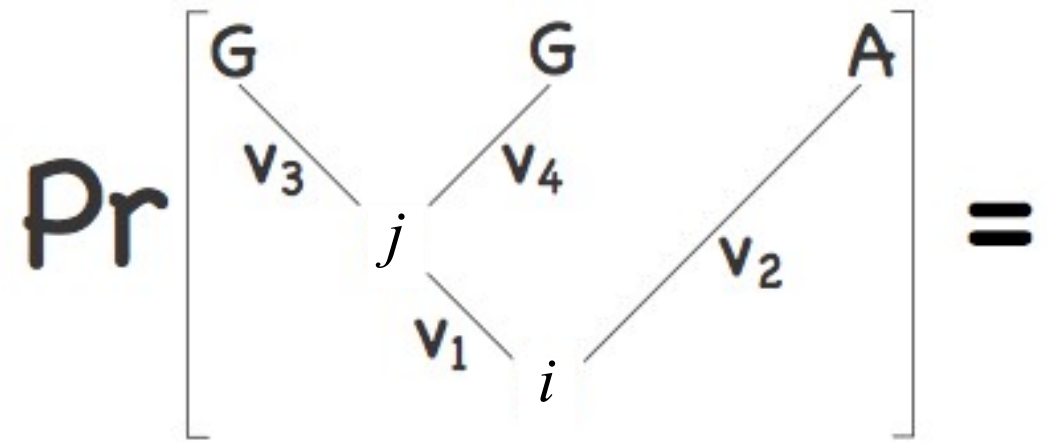


$$\pi_i \times p_{ij}(v_1) \times p_{iA}(v_2) \times p_{jG}(v_3) \times p_{jG}(v_4)$$

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

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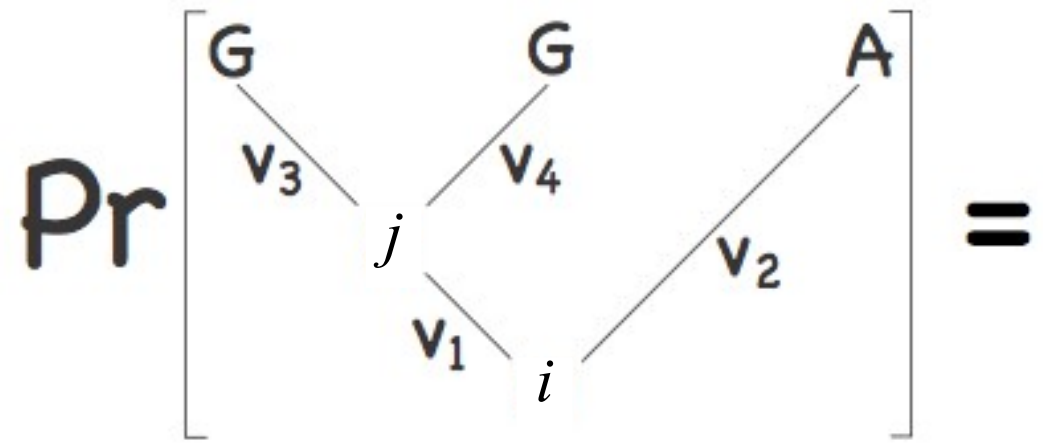


$$\pi_i \times p_{ij}(v_1) \times p_{iA}(v_2) \times p_{jG}(v_3) \times p_{jG}(v_4)$$

π_i	Stationary frequencies
$p_{ij}(v)$	Transition probabilities

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

Continuous-time Markov Chains (CTMC)

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

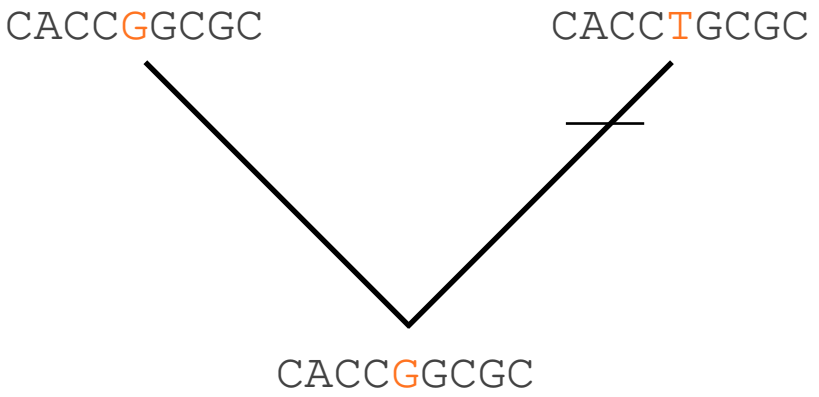
We will introduce:

- ***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



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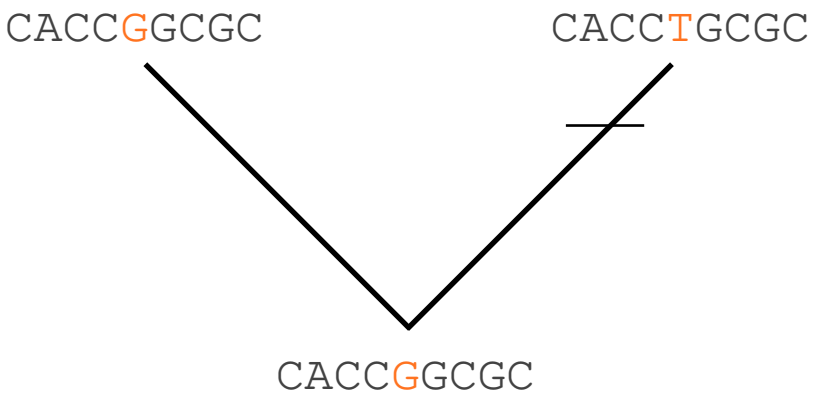

We are modeling the process of **nucleotide substitution**, which describes the outcome of the mutation and fixation processes within populations

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

Continuous-time Markov Models

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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.

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	C	0.148	−1.069	0.415	0.506
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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)

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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**:

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

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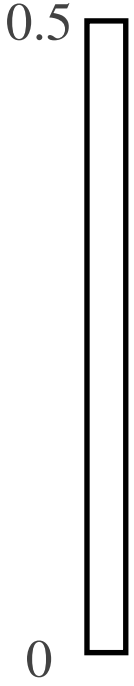

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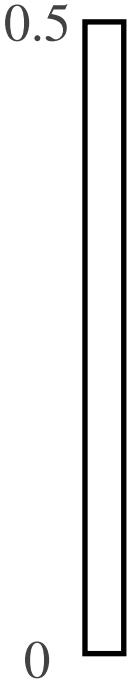

there is a single branch (the tree 'topology')
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the instantaneous-rate matrix is known

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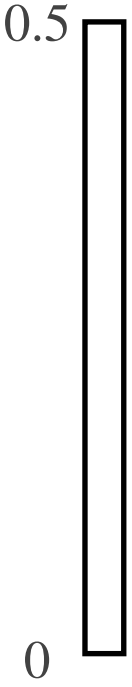

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What is the matrix of substitution probabilities over our branch of length 0.5?

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

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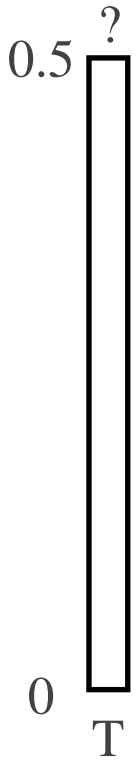

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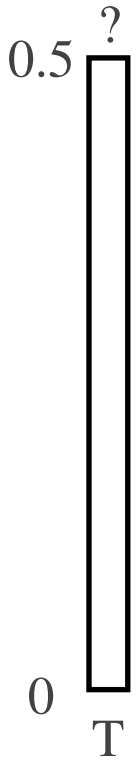

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Rate of leaving the current state, T = 1.355

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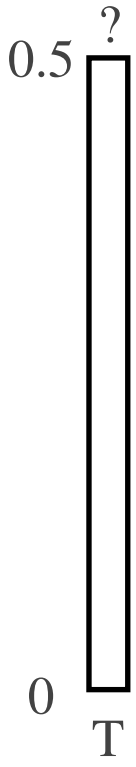

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Probability of changing to A:

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

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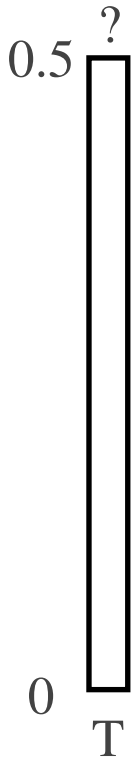

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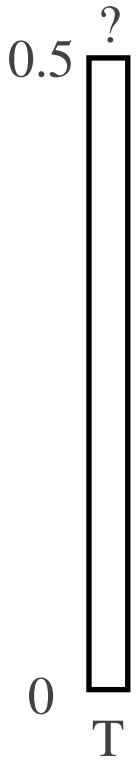
A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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A Mechanistic Interpretation of the Rate Matrix

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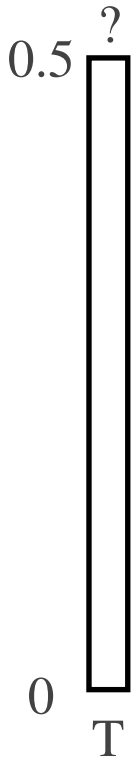

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Generate an exponentially distributed waiting time, x:

A Mechanistic Interpretation of the Rate Matrix

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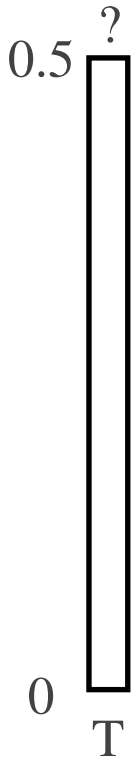

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Generate an exponentially distributed waiting time, x:

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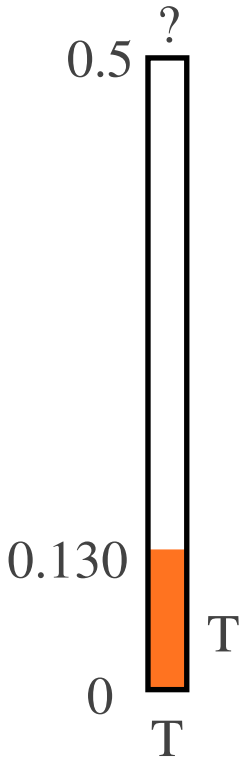

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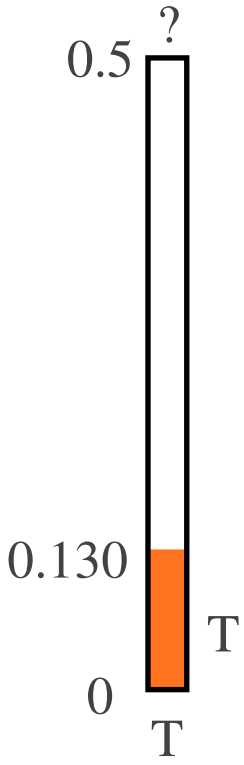
Draw x: `x~dnExponential(1.355)` : x = 0.130

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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Probabilities of substitution events in state T:

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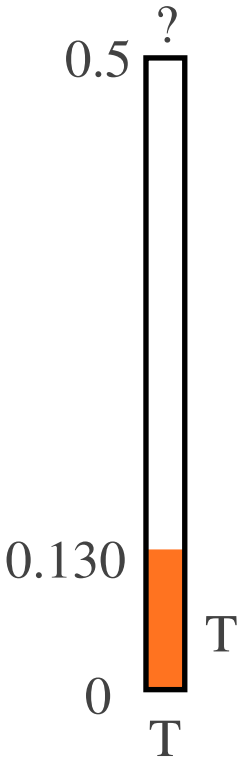
A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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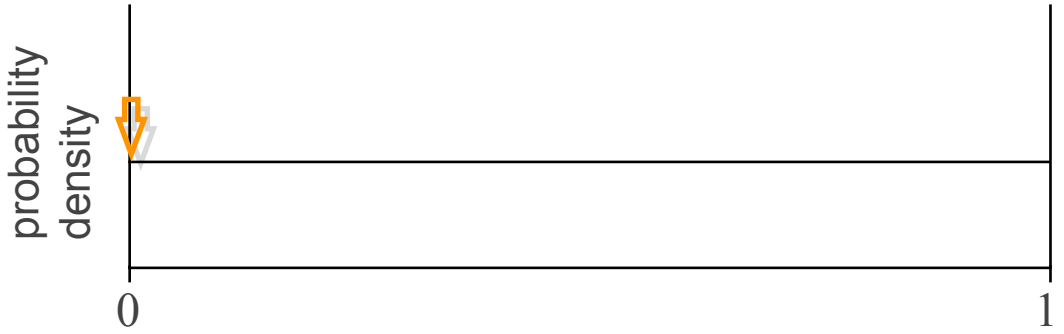
Specify a set of intervals:

	intervals	
P(T->A) = 0.387	0 – 0.387	(choose A)
P(T->C) = 0.174	0.387 – 0.561	(choose C)
P(T->G) = 0.438	0.561 – 1	(choose G)

Aside: Making Decisions within Random Numbers

Only the width of the bins matters, not their order

Our uniform$(0,1)$ random number will take any value between 0 and 1 with equal probability (by definition)



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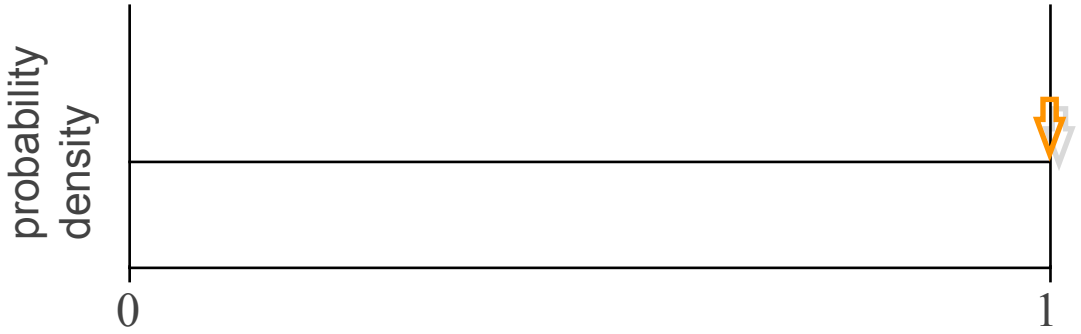

Aside: Making Decisions within Random Numbers

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Imagine that there are two possible outcomes, A and B, which occur with probabilities:

Probability of outcomes:

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

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

Aside: Making Decisions within Random Numbers

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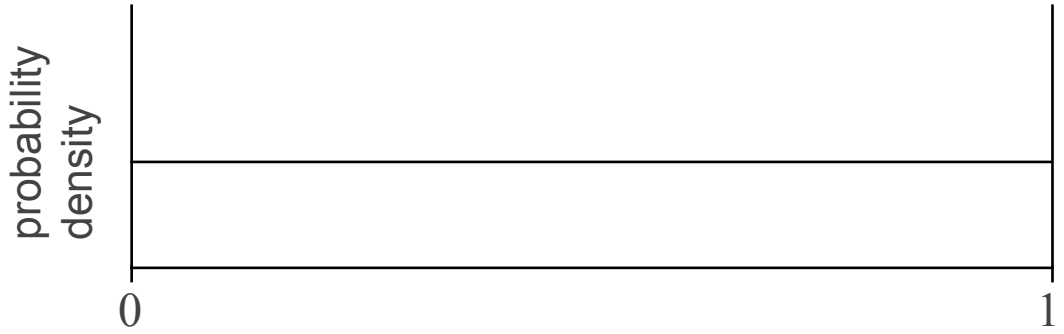

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$$\mathrm{P}(\text{option B}) = 0.4$$

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

Probability of outcomes:	intervals	
$\mathrm{P}(\text{option A}) = 0.6$	$0.0 - 0.6$	(choose A)
$\mathrm{P}(\text{option B}) = 0.4$	$0.6 - 1.0$	(choose B)

Aside: Making Decisions within Random Numbers

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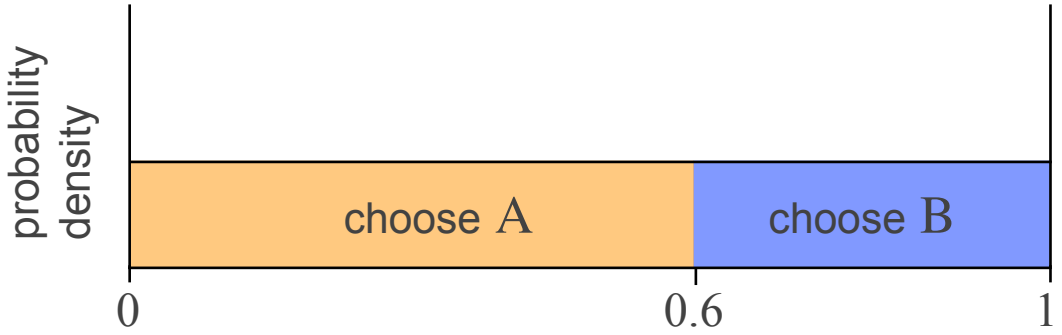
Our uniform$(0,1)$ random number will take any value between 0 and 1 with equal probability (by definition)



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Aside: Making Decisions within Random Numbers

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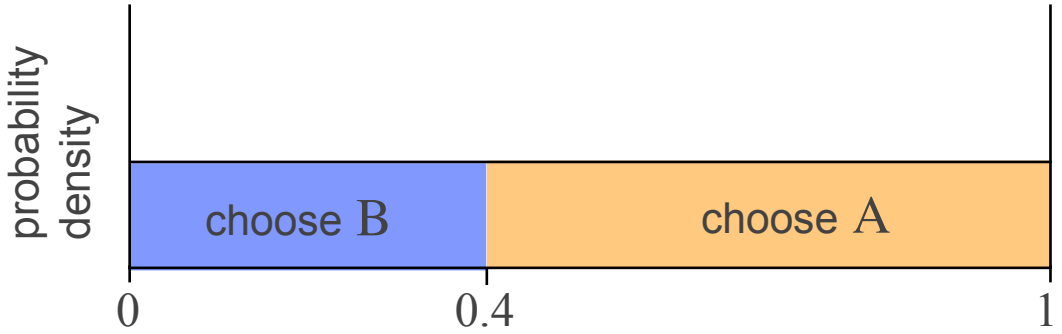


Imagine that there are two possible outcomes, A and B, which occur with probabilities:

Probability of outcomes:

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

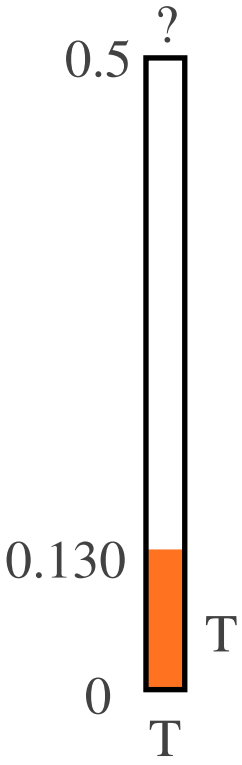
$$P(\text{option B}) = 0.4$$

Or equivalently by specifying these intervals…

Probability of outcomes:	intervals	
$P(\text{option A}) = 0.6$	$0.4 - 1.0$	(choose A)
$P(\text{option B}) = 0.4$	$0.0 - 0.6$	(choose B)

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 an exponentially distributed waiting time, x:

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

Draw x: `x~dnExponential(1.355)` : x = 0.130

Specify a set of intervals:

	intervals	
P(T->A) = 0.387	0 – 0.387	(choose A)
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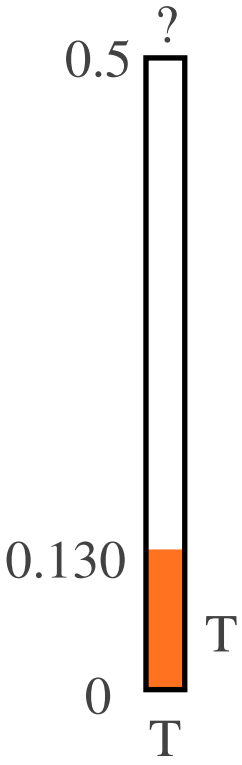
A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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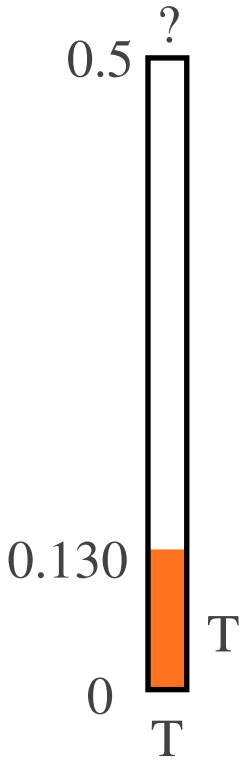
P(T->A) = 0.387	0 – 0.387	(choose A)
P(T->C) = 0.174	0.387 – 0.561	(choose C)
P(T->G) = 0.438	0.561 – 1	(choose G)

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

`u~dnUniform(0,1)` : u=0.446

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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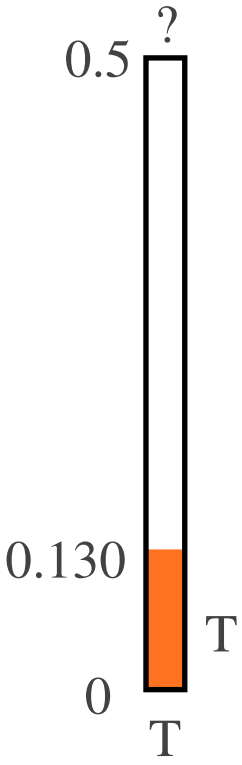
A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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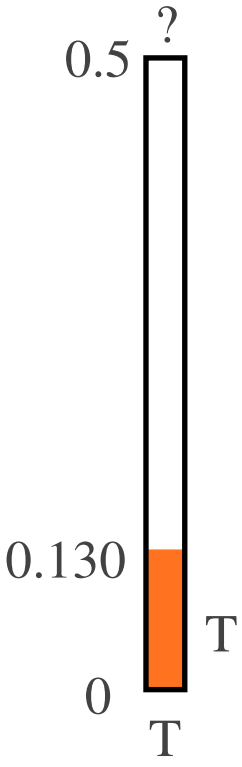
A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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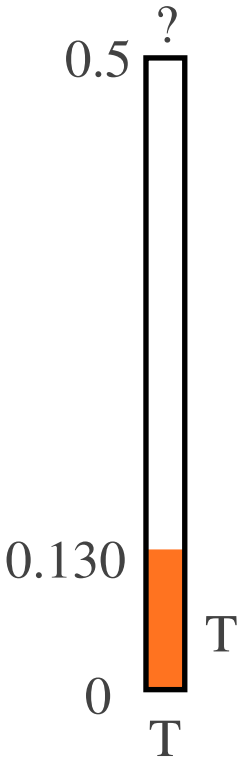
Generate waiting time to next event:

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

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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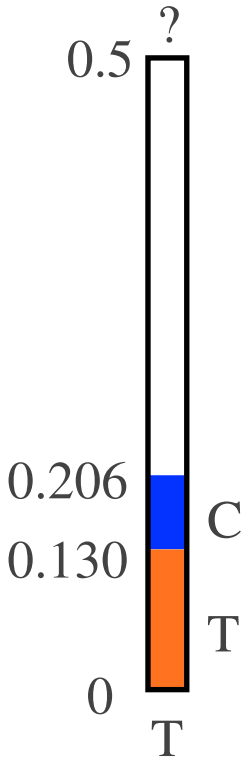
Generate waiting time to next event:

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

Draw x: `x~dnExponential(1.069)` : x = 0.076

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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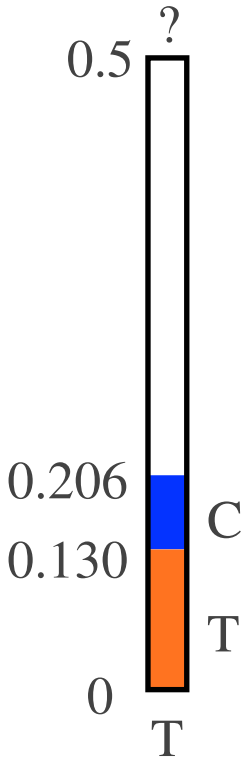
A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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Generate waiting time to next event:

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

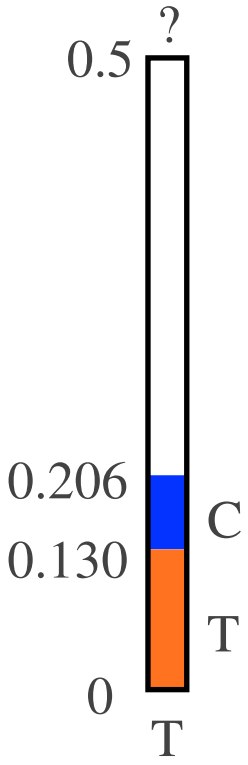
Draw x: `x~dnExponential(1.069)` : x = 0.076

Substitution probabilities in state C:

$$\text{P(C->A)} = q_{CA} / -q_{cc} = 0.148 \mid 1.069 = 0.138$$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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Generate waiting time to next event:

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

Draw x: `x~dnExponential(1.069)` : x = 0.076

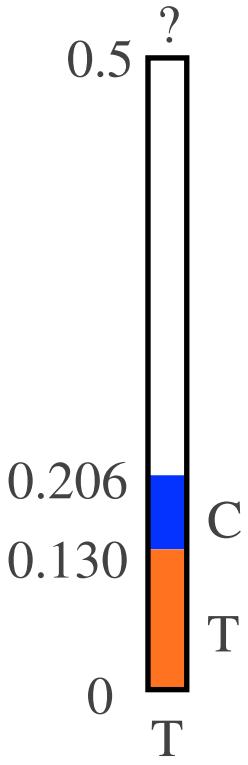
Substitution probabilities in state C:

$$P(C\text{->}A) = q_{CA}/-q_{CC} = 0.148 \mid 1.069 = 0.138$$

$$P(C\text{->}G) = q_{CG}/-q_{CC} = 0.415 \mid 1.069 = 0.388$$

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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Generate waiting time to next event:

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

Draw x: `x~dnExponential(1.069)` : x = 0.076

Substitution probabilities in state C:

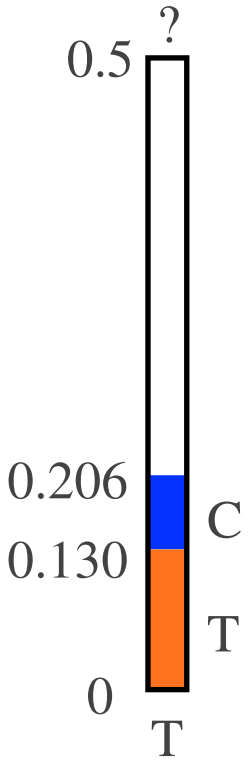
$$P(C\text{->}A) = q_{CA}/-q_{CC} = 0.148 \mid 1.069 = 0.138$$

$$P(C\text{->}G) = q_{CG}/-q_{CC} = 0.415 \mid 1.069 = 0.388$$

$$P(C\text{->}T) = q_{CT}/-q_{CC} = 0.506 \mid 1.069 = 0.474$$

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: $-q_{cc} = \lambda = 1.069$

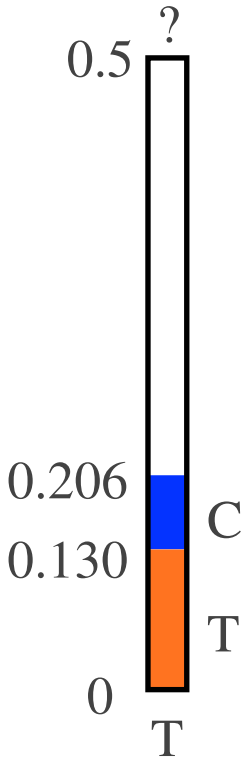
Draw x: `x~dnExponential(1.069)` : x = 0.076

Specify a set of intervals:

	intervals	
P(C->A) = 0.138	0 – 0.138	(choose A)
P(C->G) = 0.388	0.138 – 0.526	(choose G)
P(C->T) = 0.474	0.526 – 1	(choose T)

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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Generate waiting time to next event:

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

Draw x: `x~dnExponential(1.069)` : x = 0.076

Specify a set of intervals:

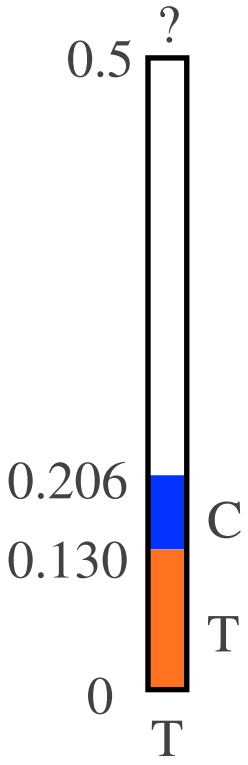
	intervals	
P(C->A) = 0.138	0 – 0.138	(choose A)
P(C->G) = 0.388	0.138 – 0.526	(choose G)
P(C->T) = 0.474	0.526 – 1	(choose T)

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

`u~dnUniform(0,1)` : u=0.317

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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Generate waiting time to next event:

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

Draw x: `x~dnExponential(1.069)` : x = 0.076

Specify a set of intervals:

	intervals	
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P(C->G) = 0.388	0.138 – 0.526	(choose G)
P(C->T) = 0.474	0.526 – 1	(choose T)

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

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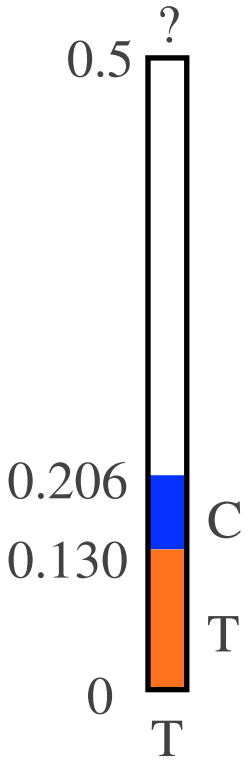
A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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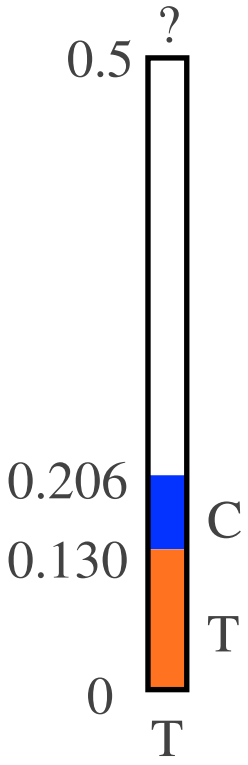
A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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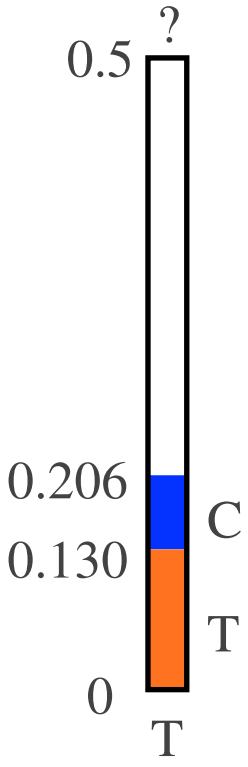
Generate waiting time to next event:

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

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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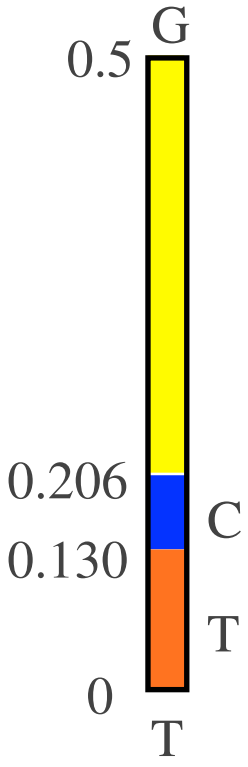
Generate waiting time to next event:

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

Draw x: `x~dnExponential(1.069)` : x = 1.820

A Mechanistic Interpretation of the Rate Matrix

A simple Monte Carlo Simulation



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Generate waiting time to next event:

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

Draw x: `x~dnExponential(1.069)` : x = 1.820

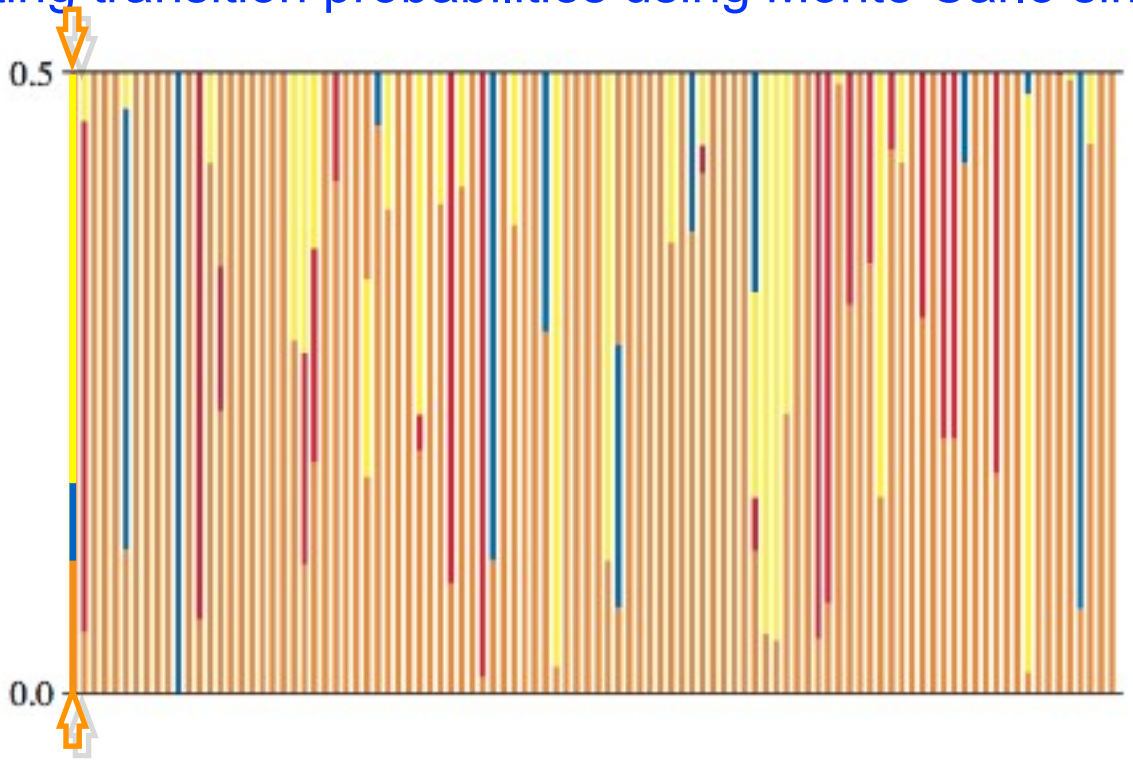
1.820 > 0.5-0.206 → *Terminate simulation (in state G)*

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

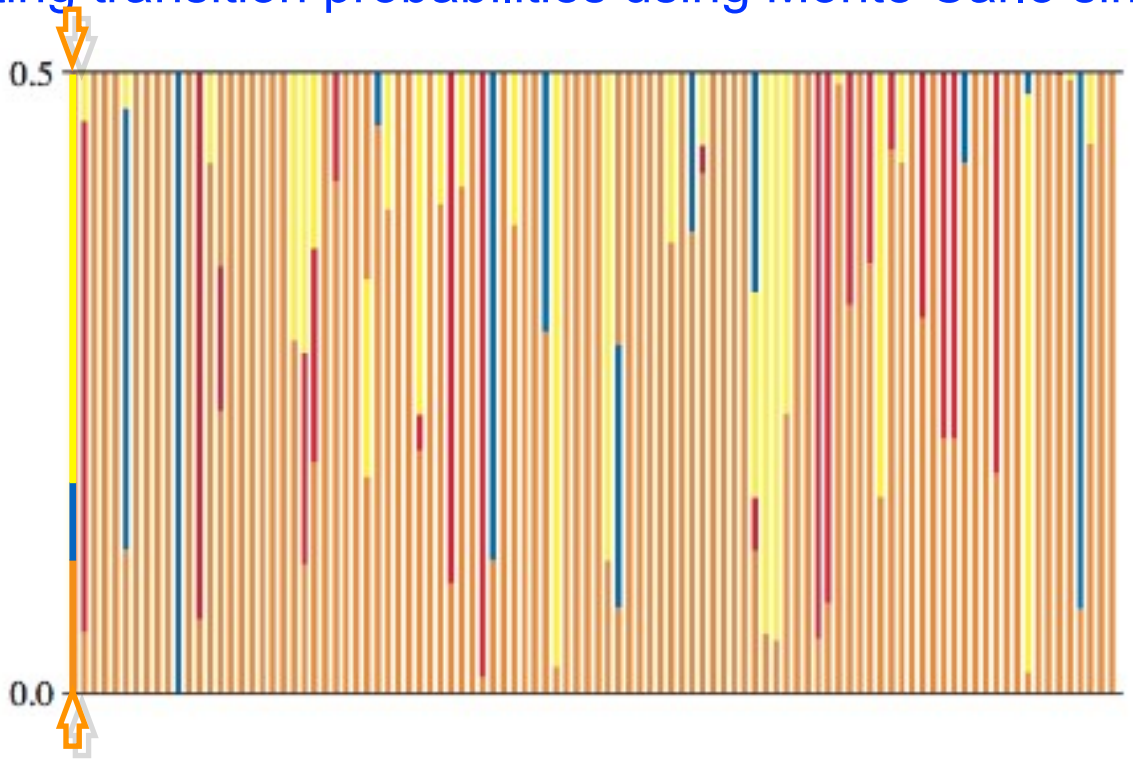


T→ C→ G

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



T→ C→ G

Ended in G with two changes

Transition Probabilities of a CTMC

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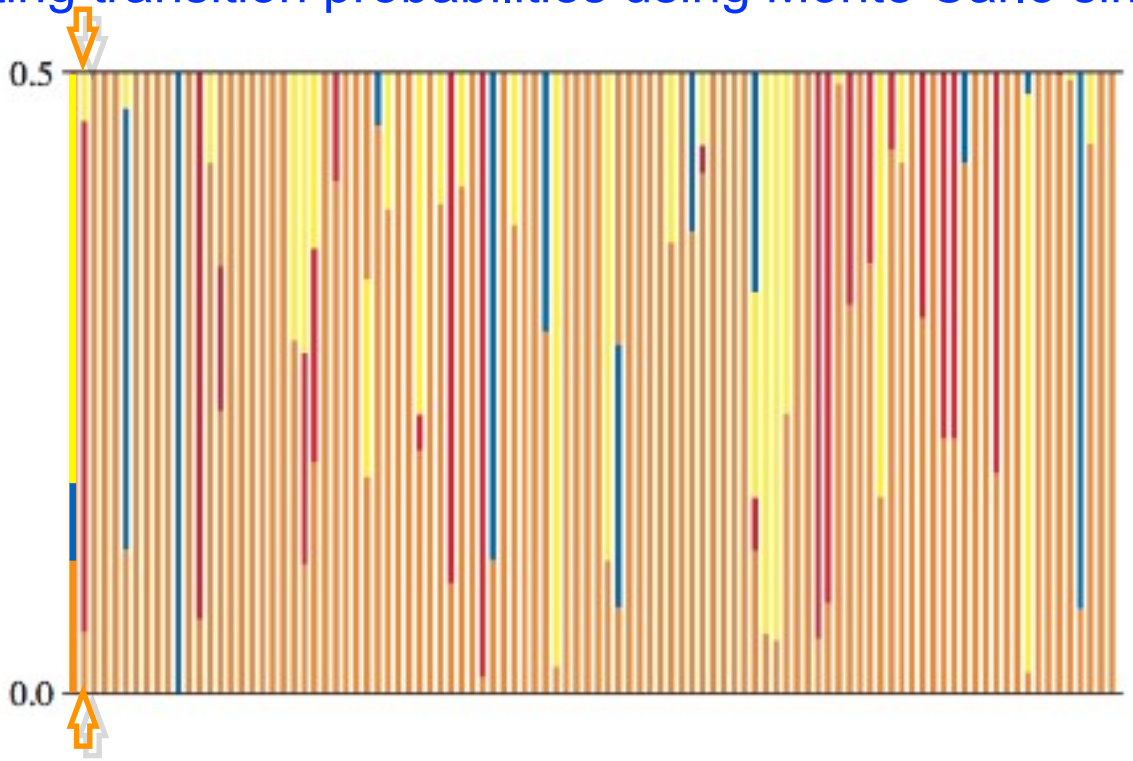


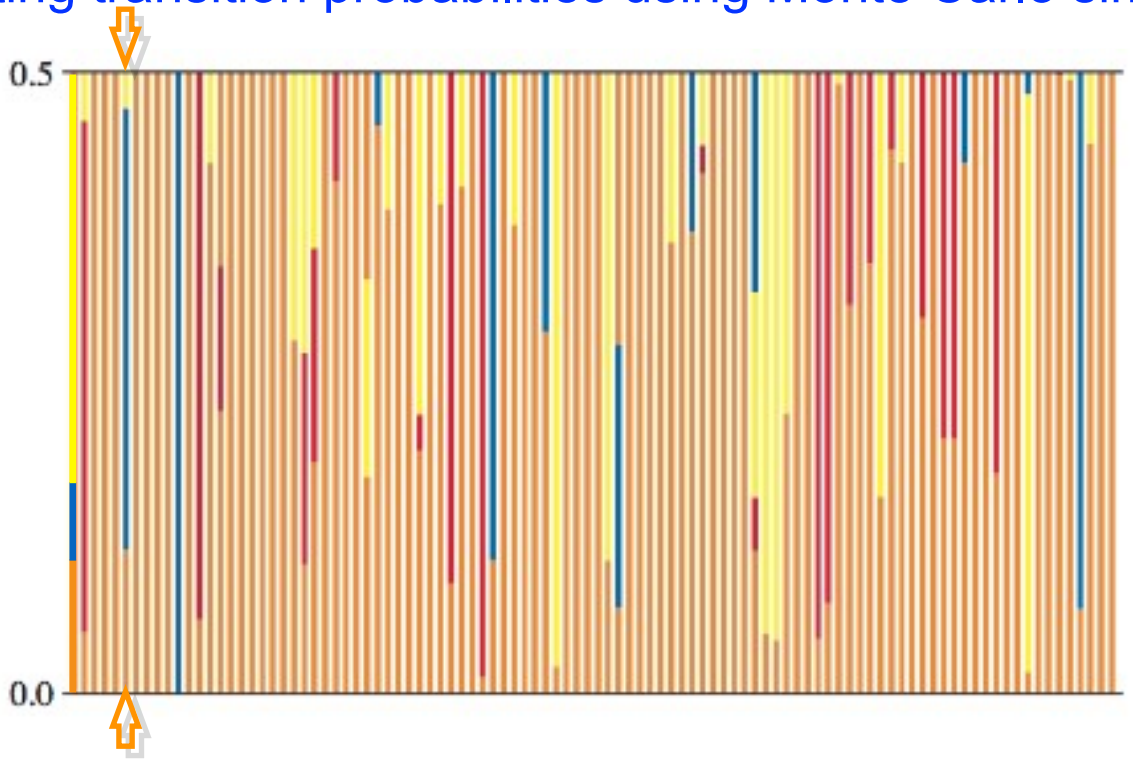
G 2

T → A → G

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



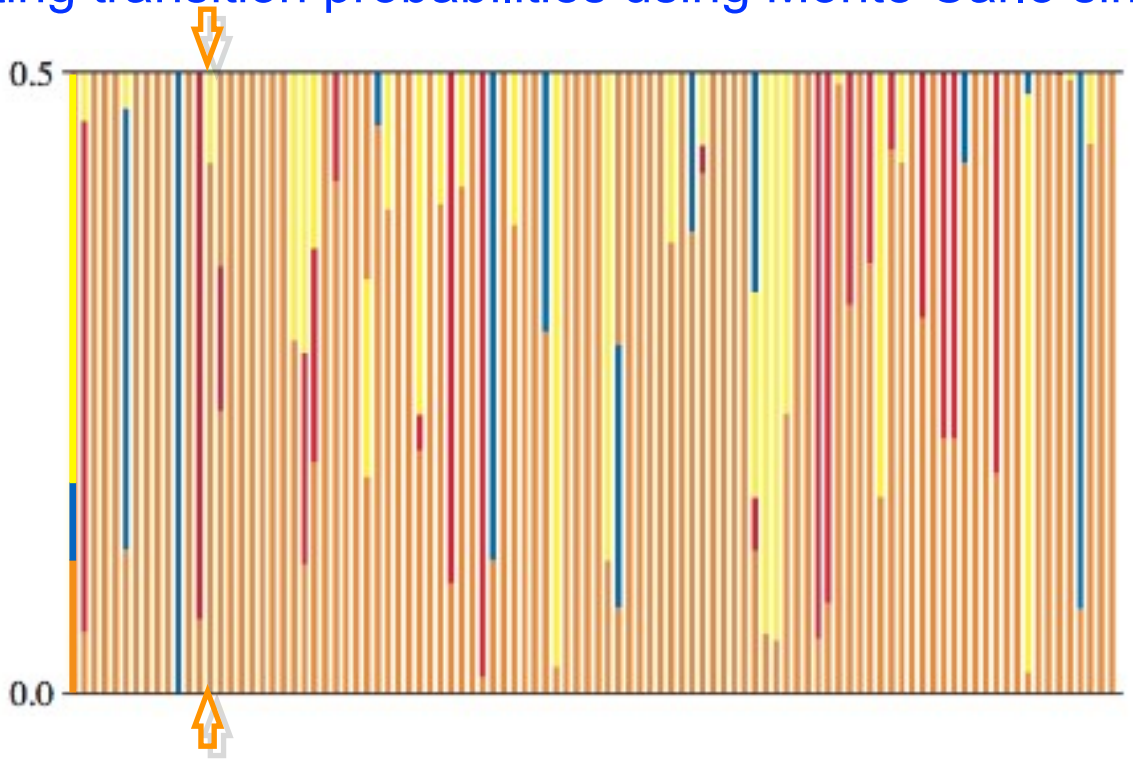
G 3

T → C → G

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



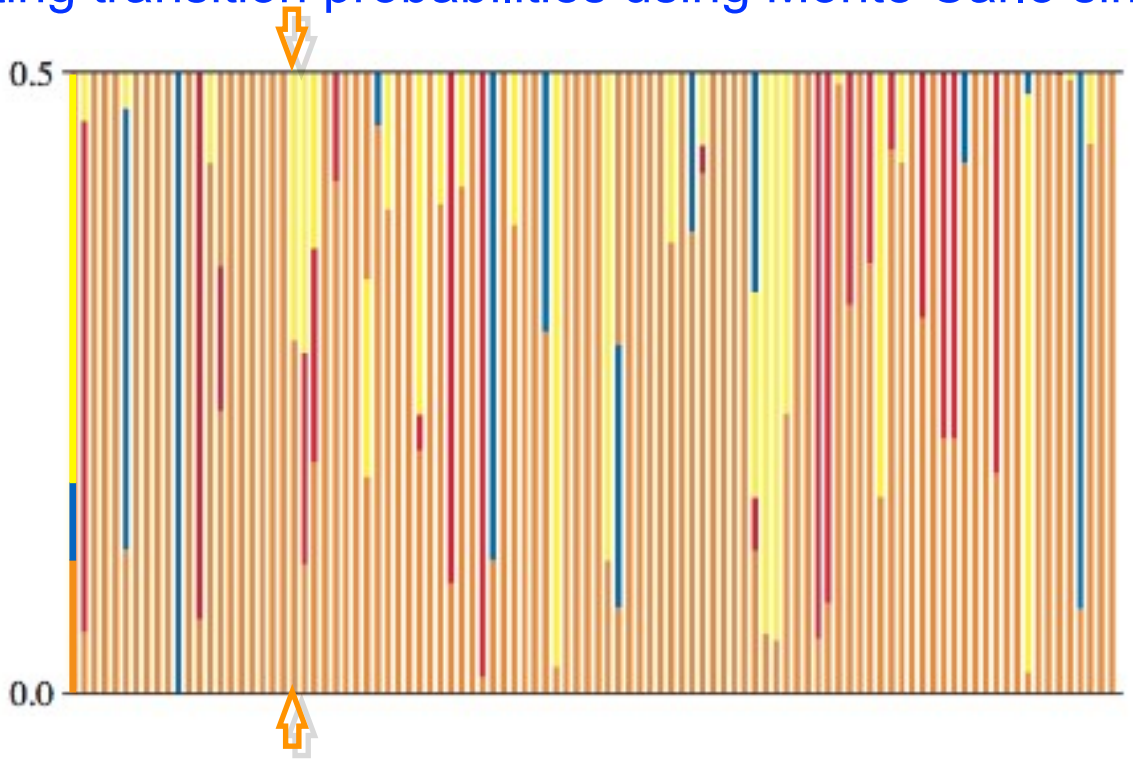
G 4

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



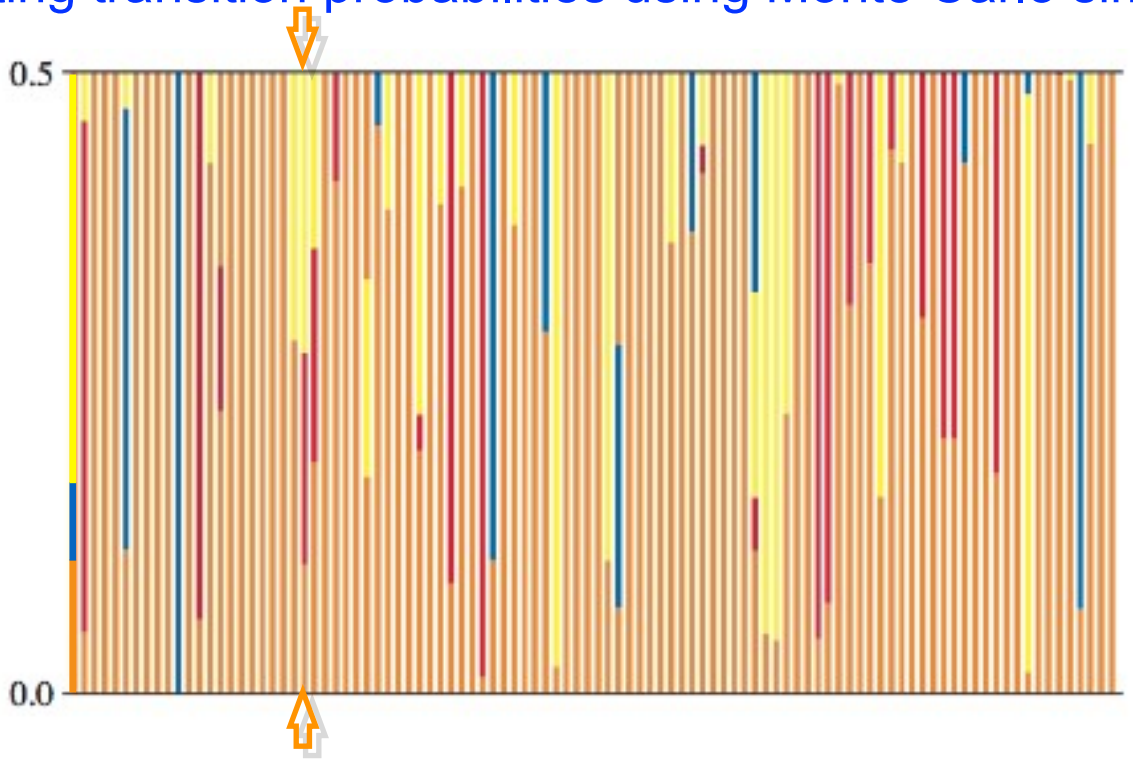
G 5

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



G

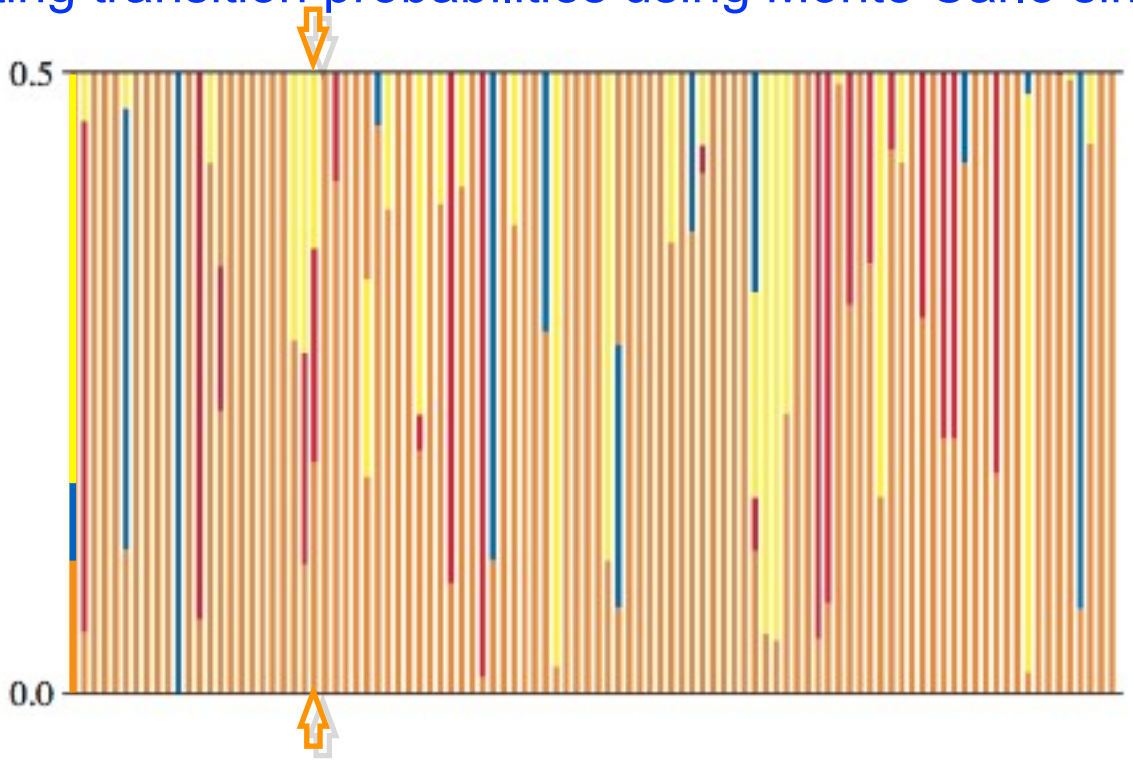
6

T → A → G

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



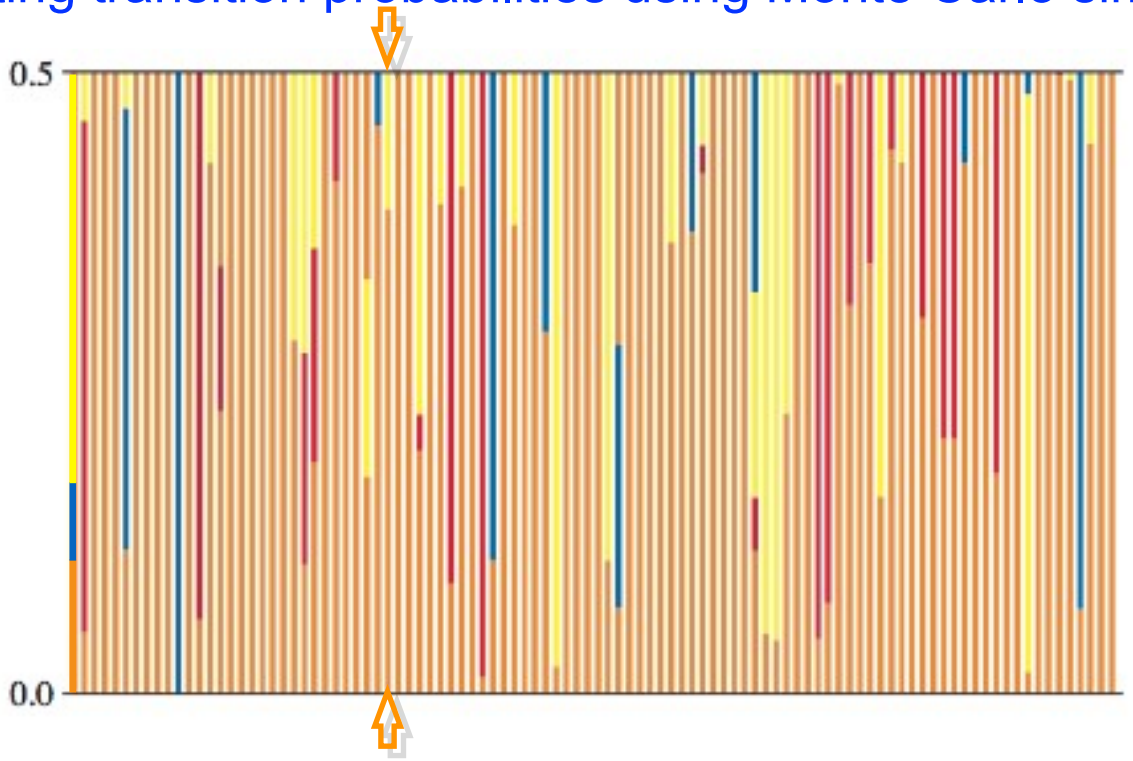
G 7

T → A → G

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



G

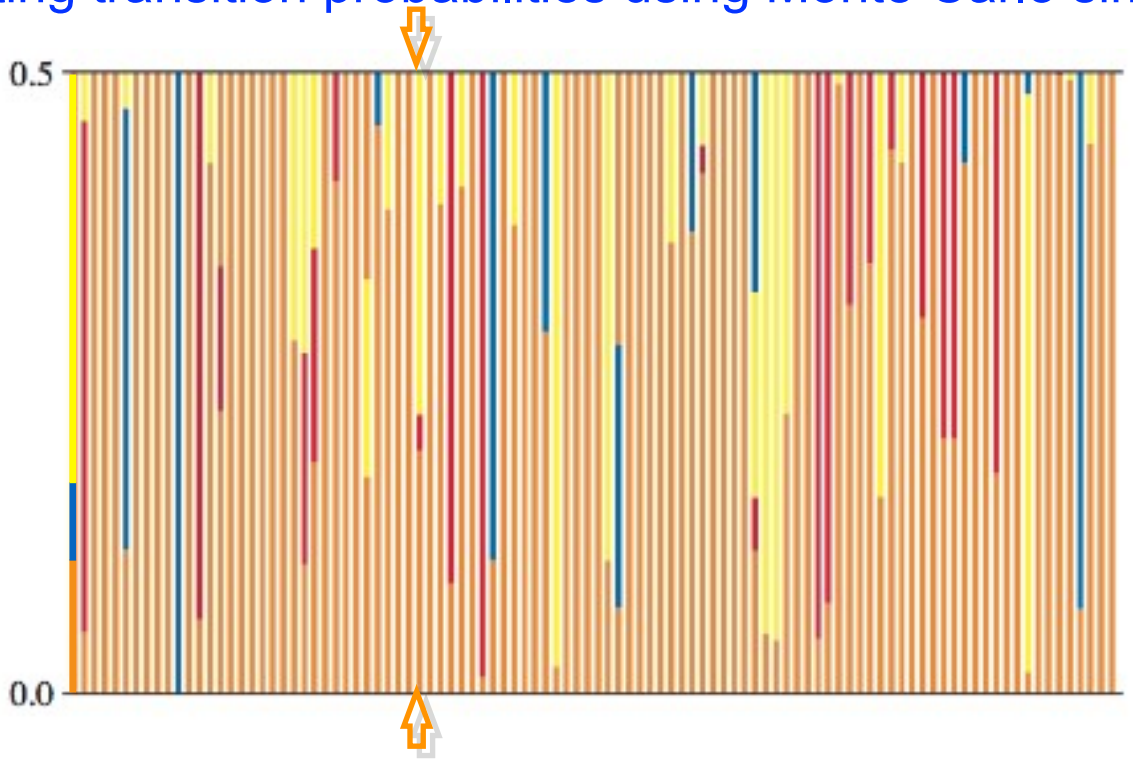
8

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



G

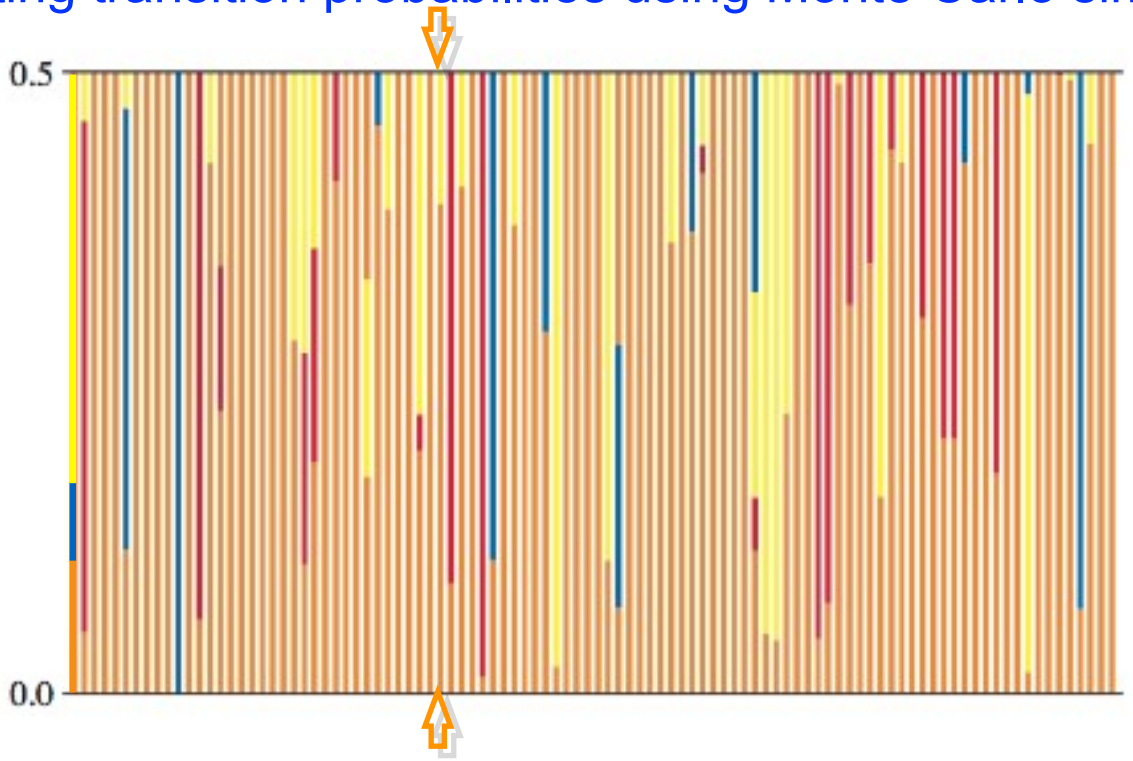
9

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



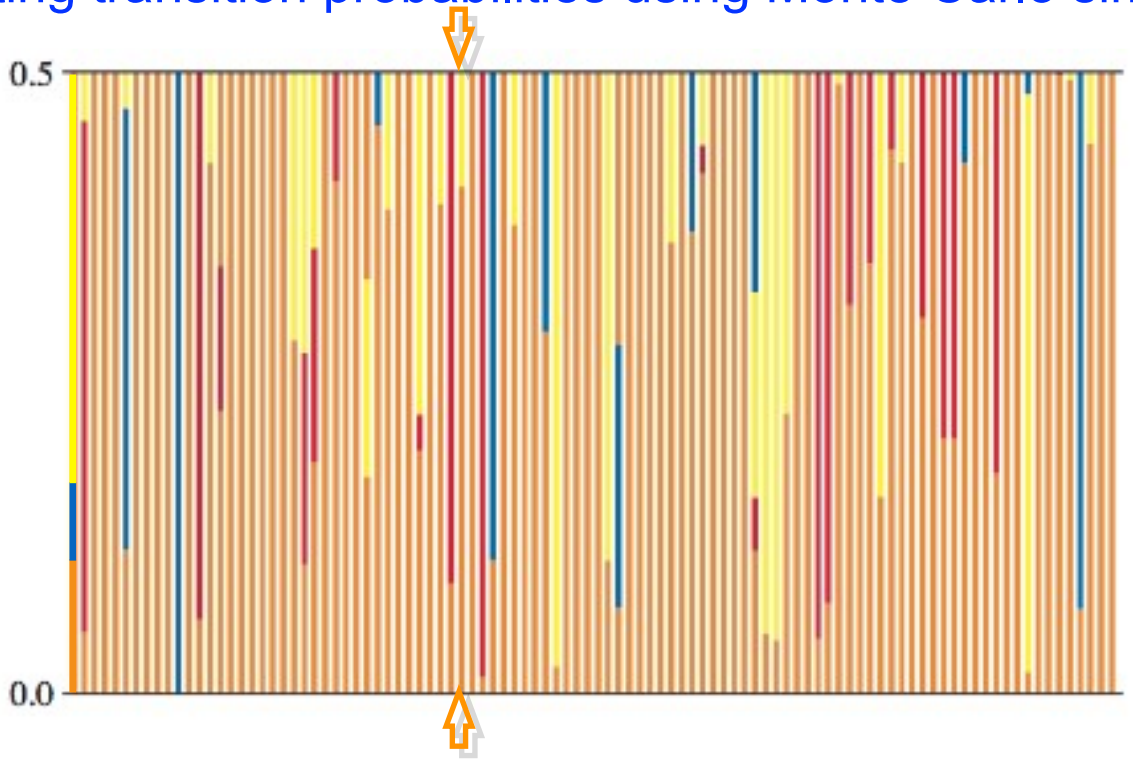
G 10

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



G

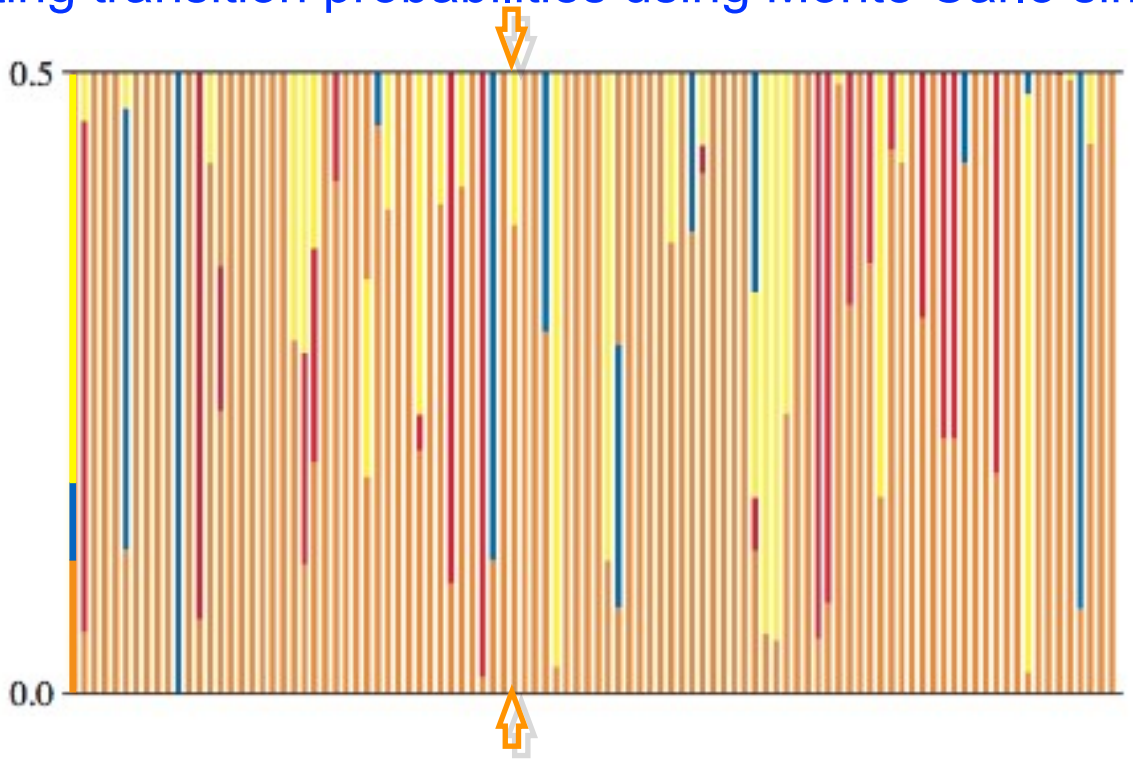
11

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



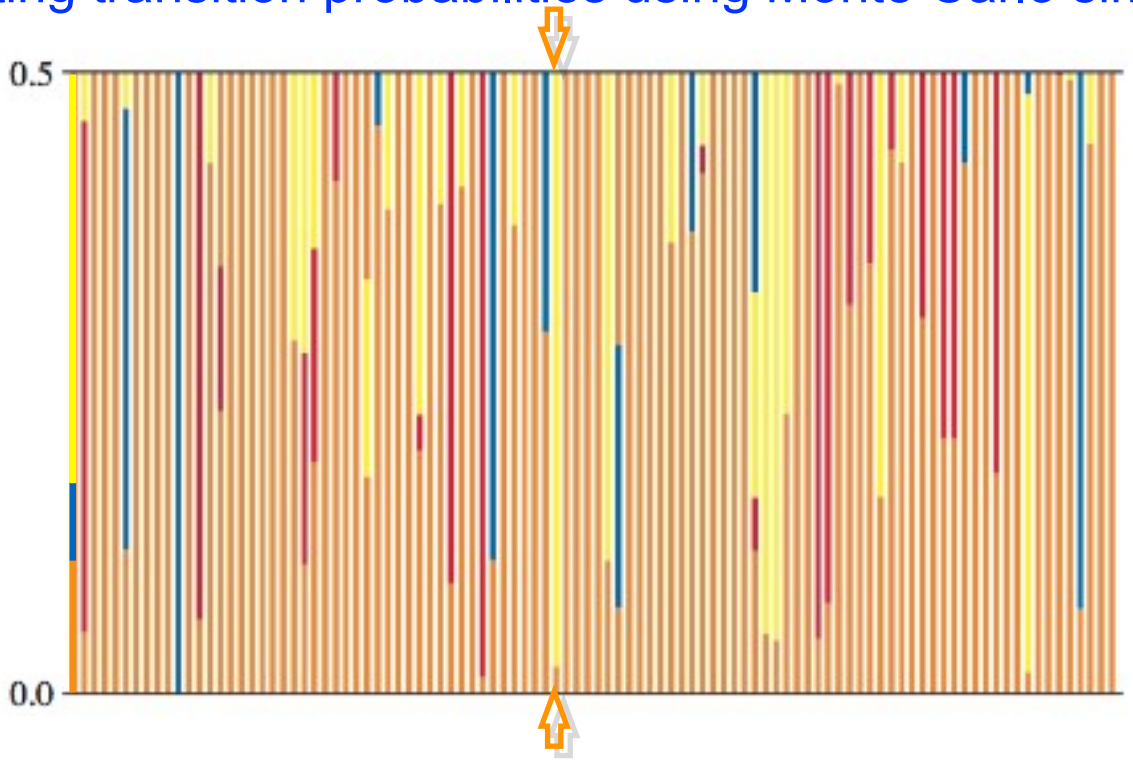
G 12

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



G

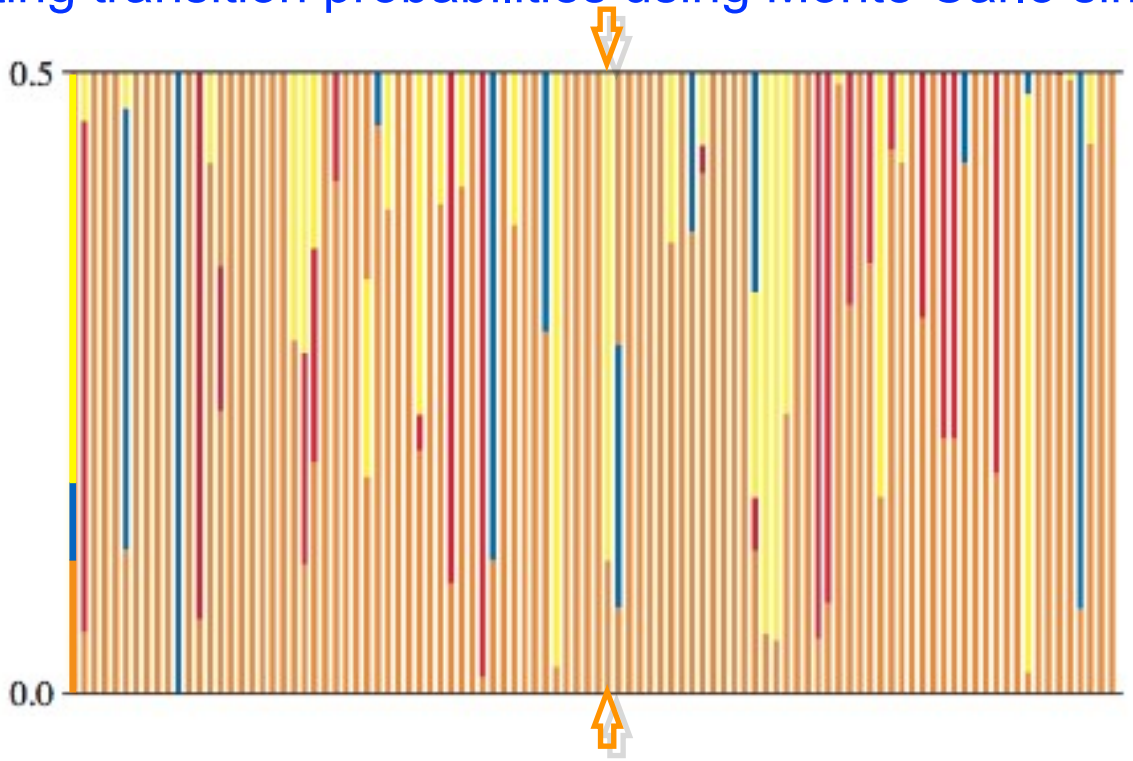
13

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



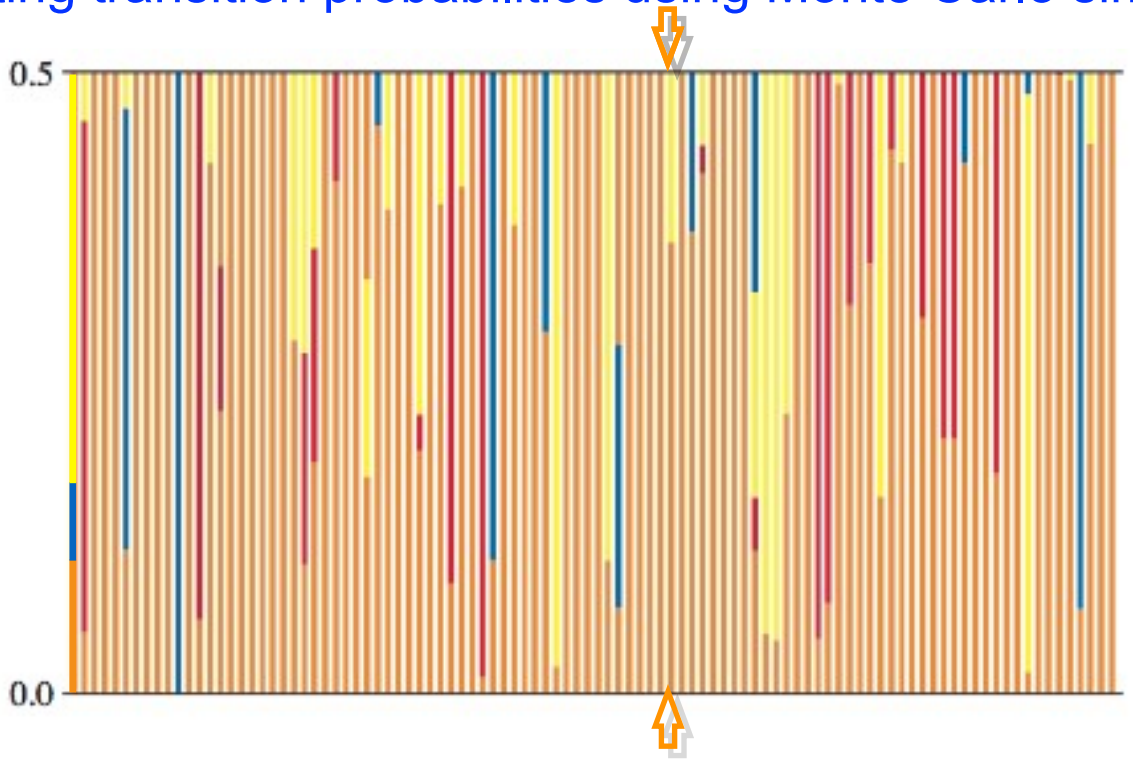
G

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



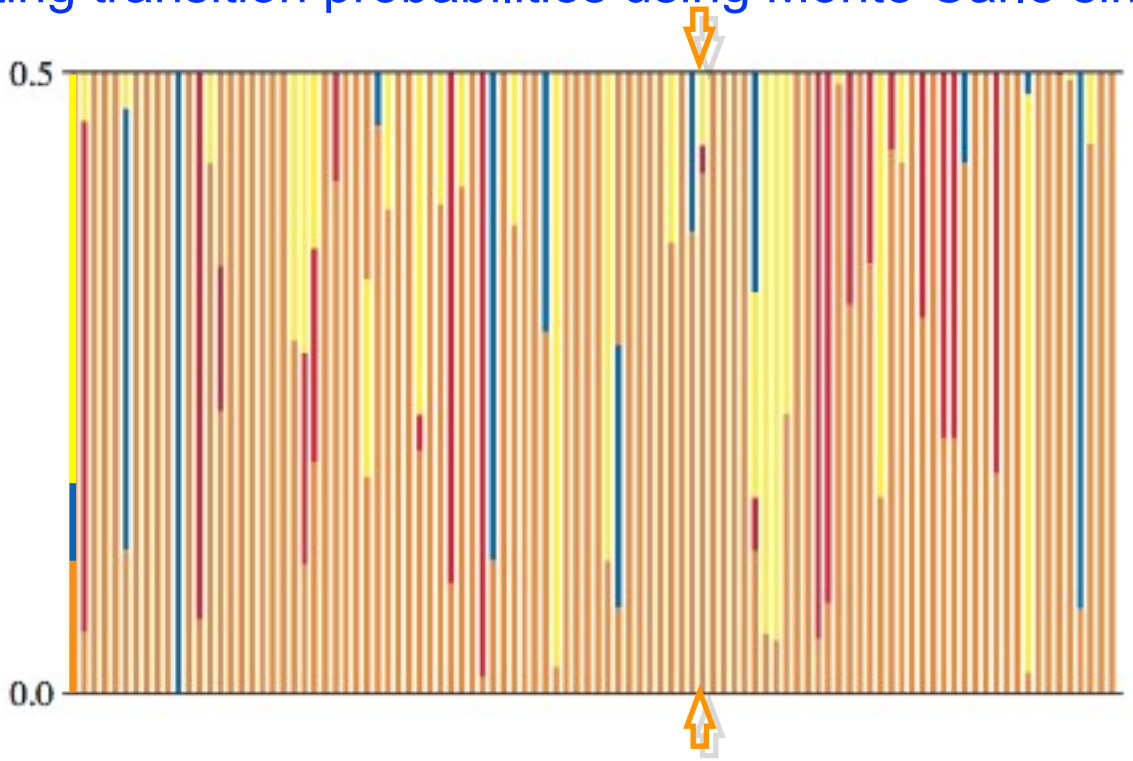
G

15

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



G

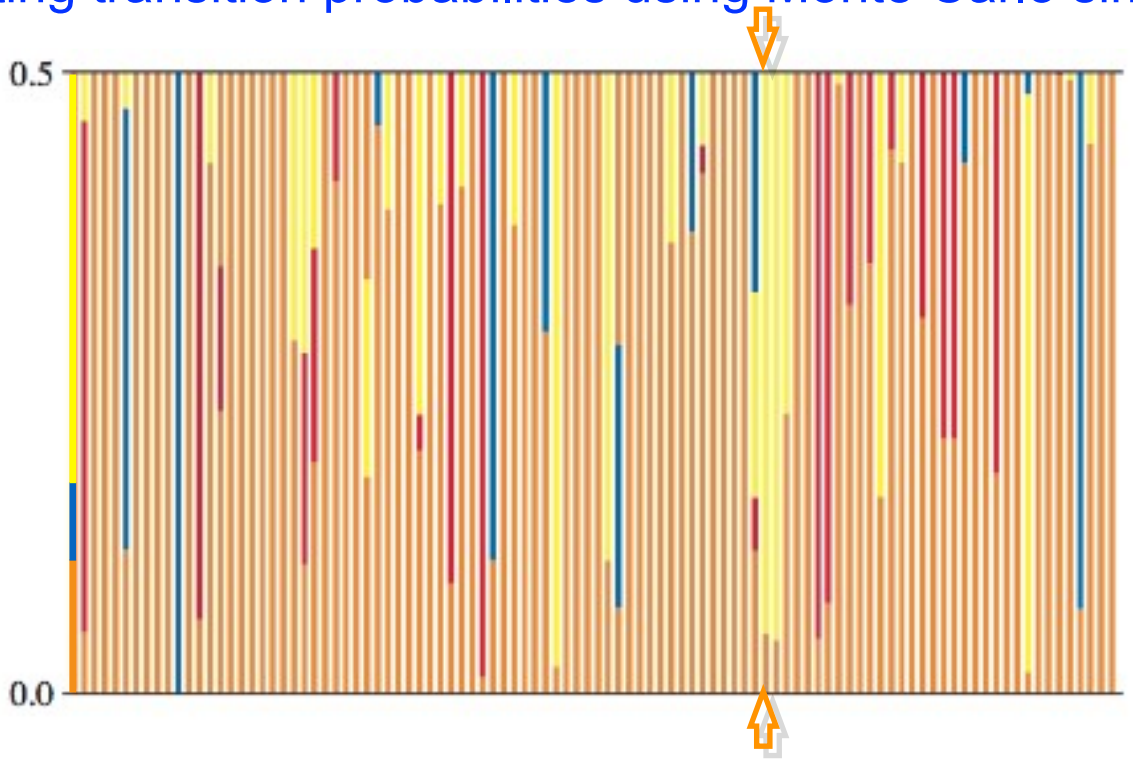
16

T → A → G

Ended in G with two changes

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



G

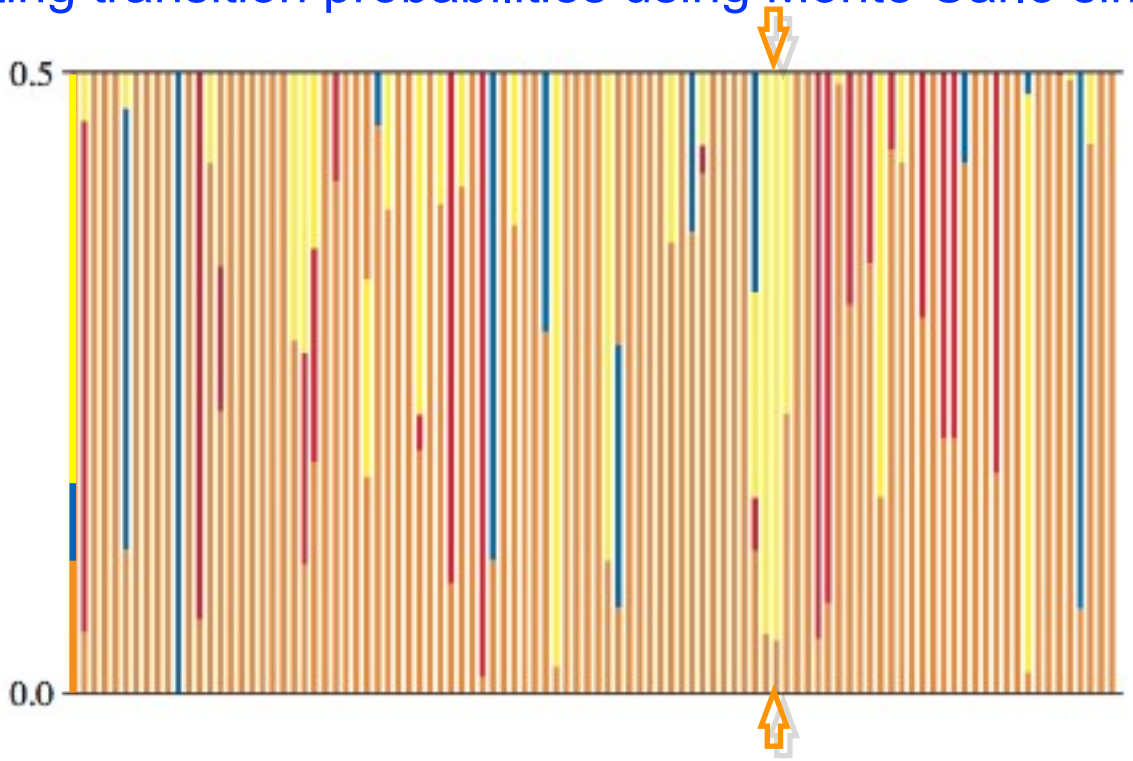
17

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



G

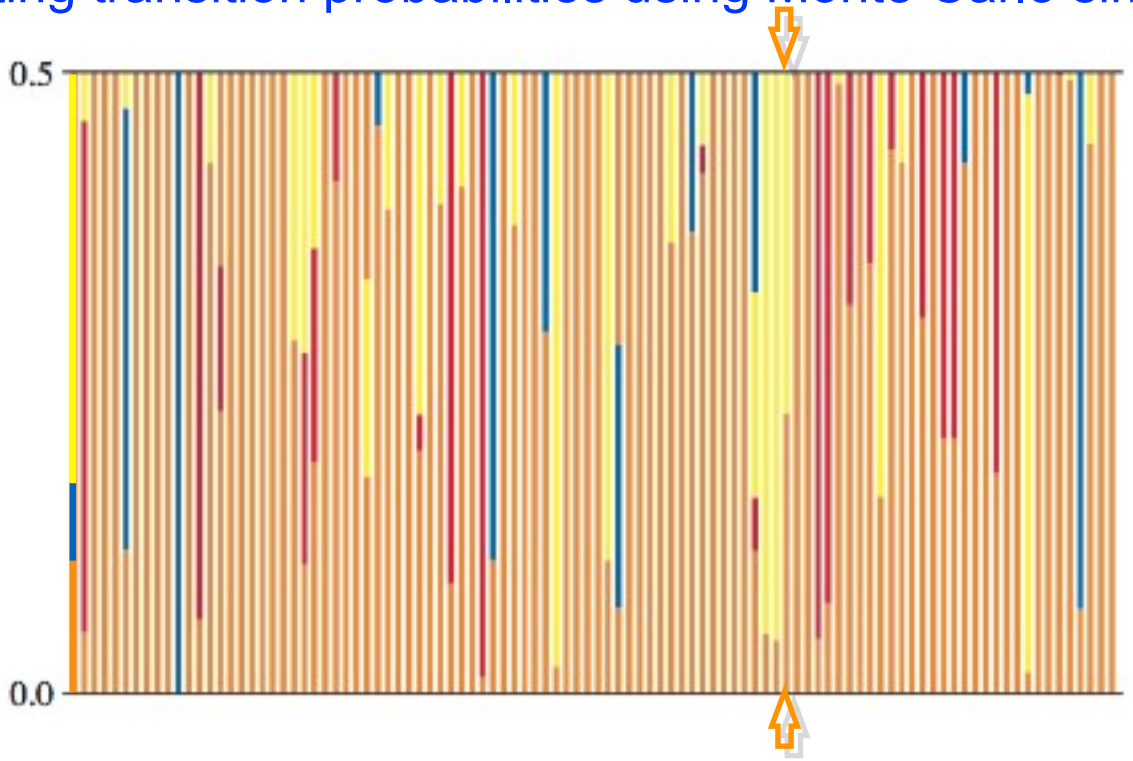
18

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



G

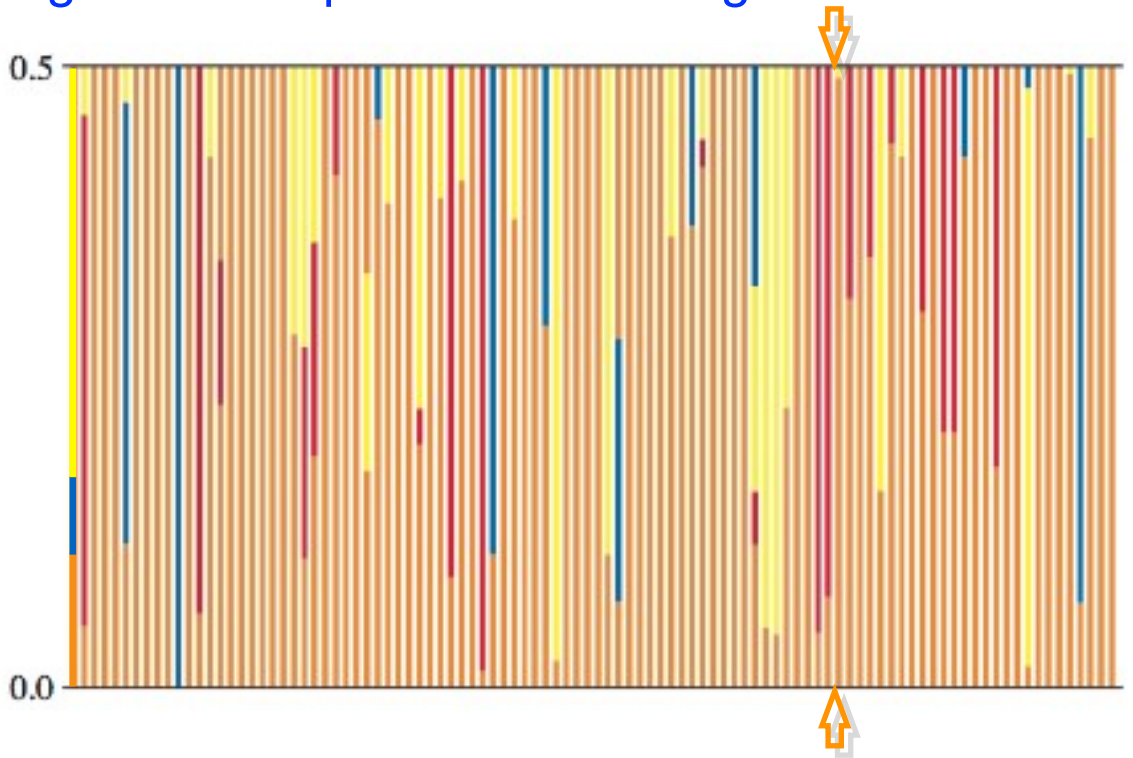
19

T → G

Ended in G with one change

Transition Probabilities of a CTMC

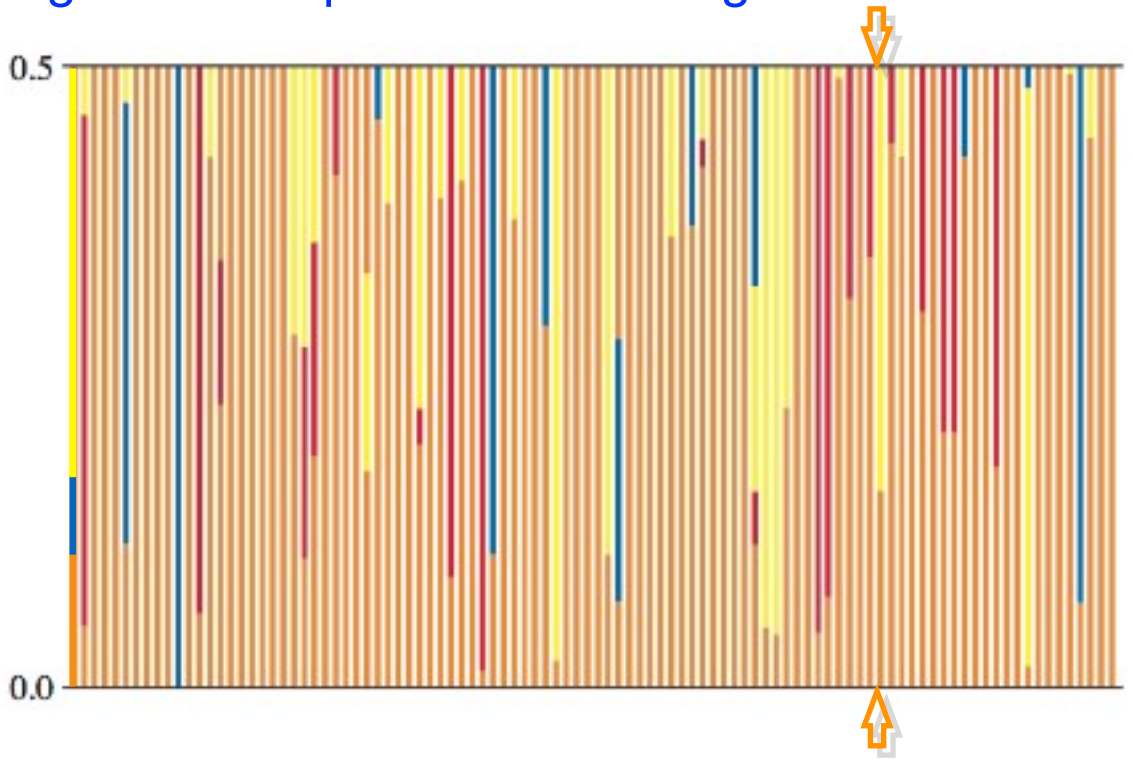
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



G

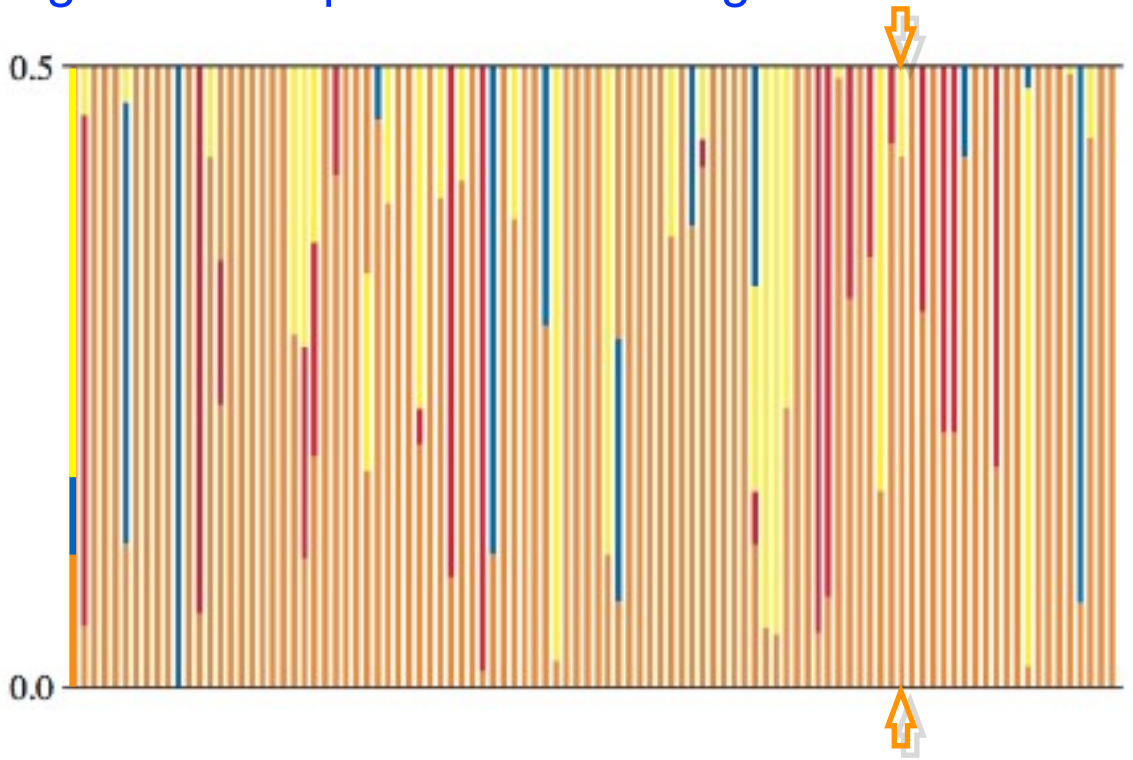
21

T → G

Ended in G with one change

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation



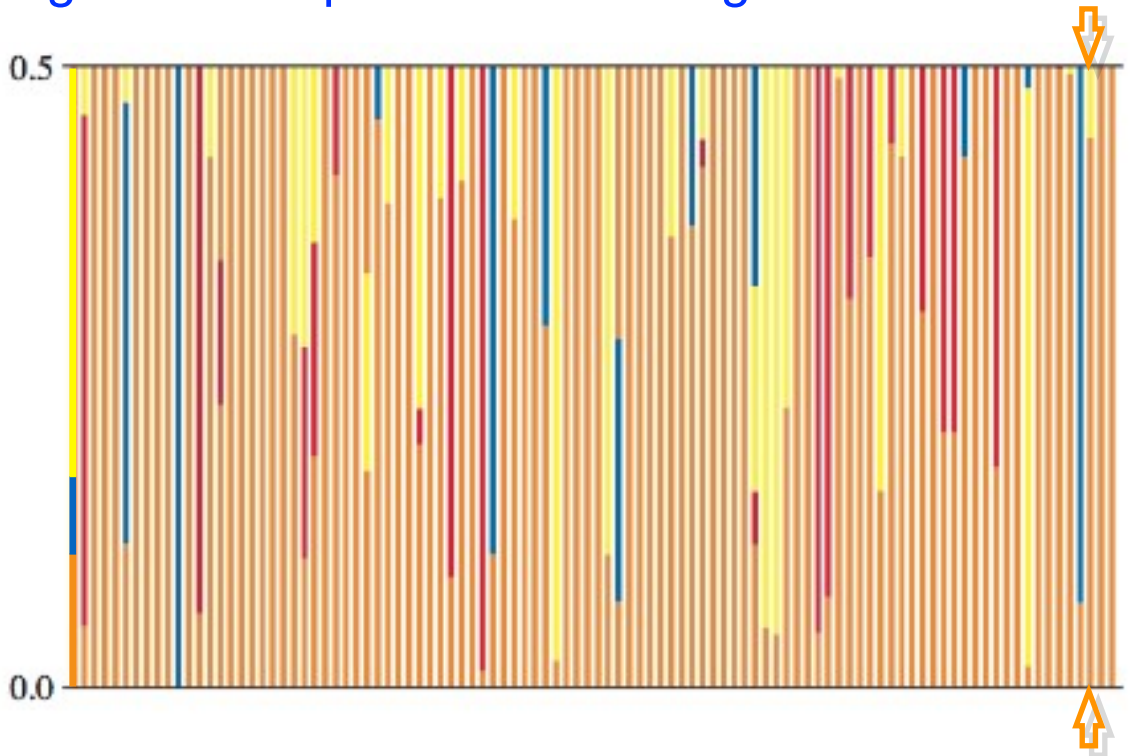
G 22

T → G

Ended in G with one change

Transition Probabilities of a CTMC

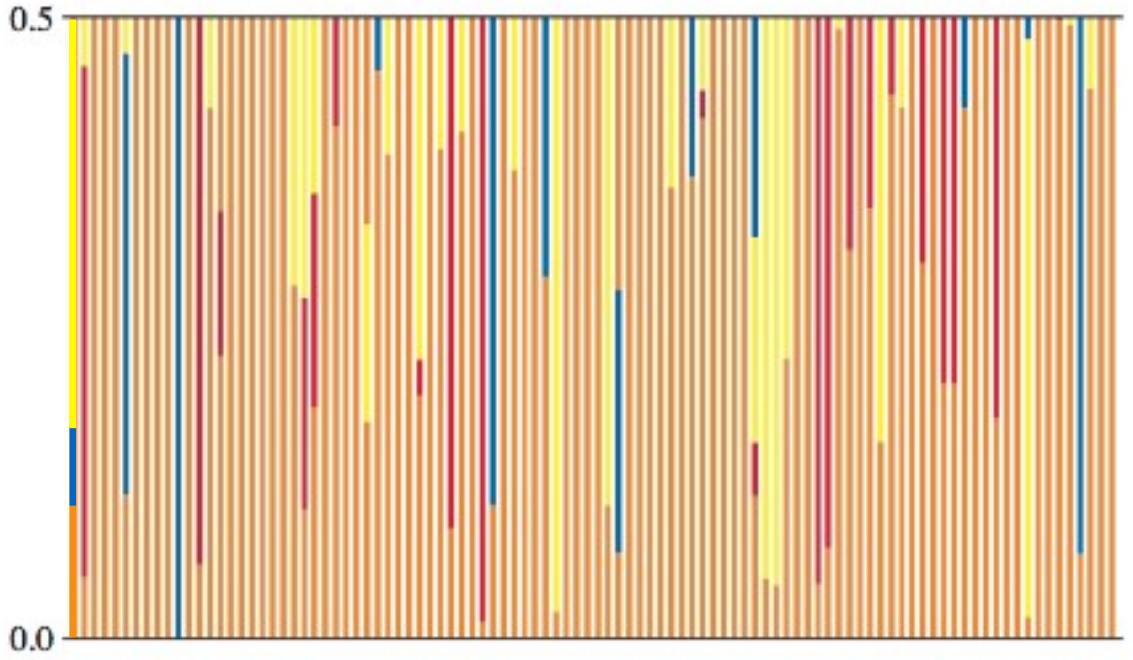
Estimating transition probabilities using Monte Carlo simulation



Ended in G with one change

Transition Probabilities of a CTMC

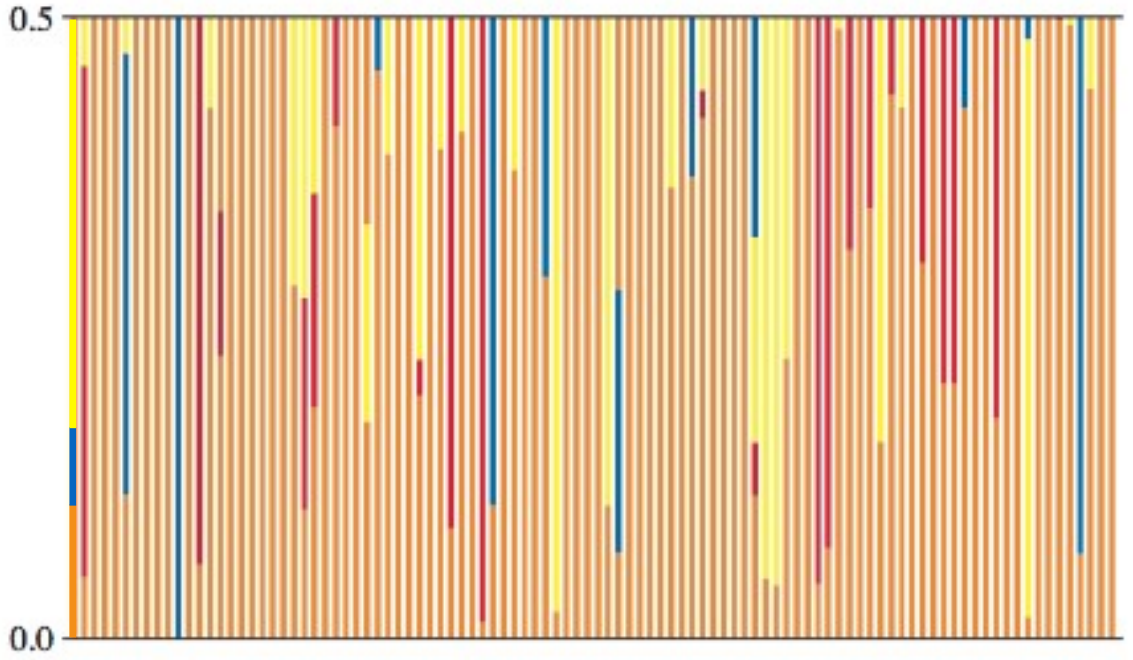
Estimating transition probabilities using Monte Carlo simulation



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



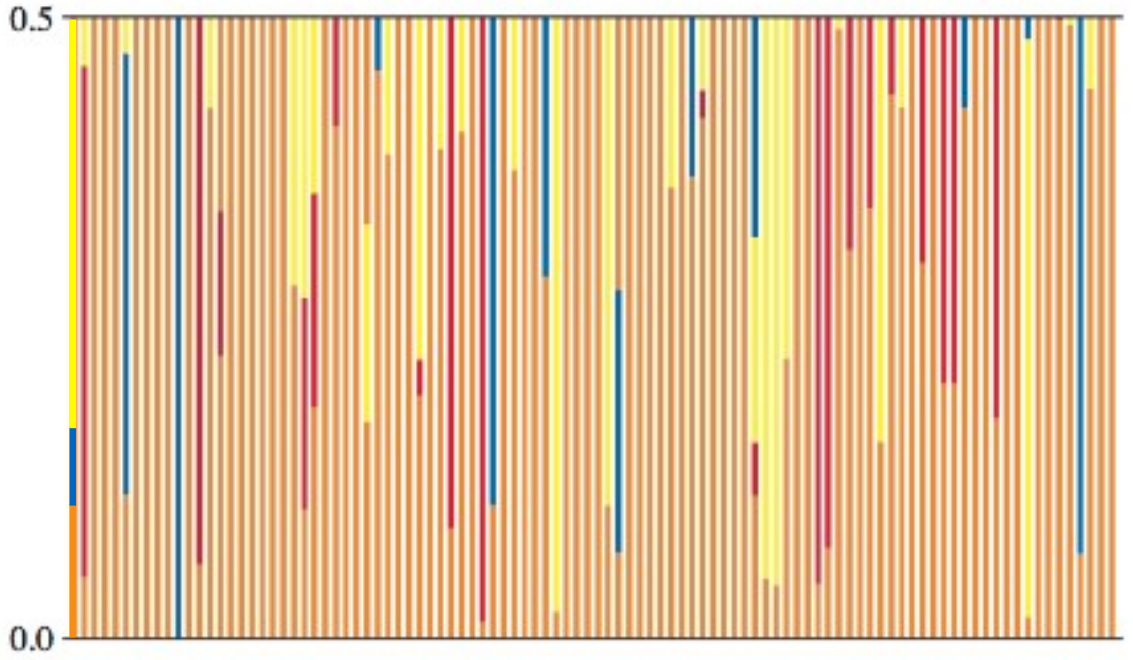
number of outcomes

G 23

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



G

number of outcomes

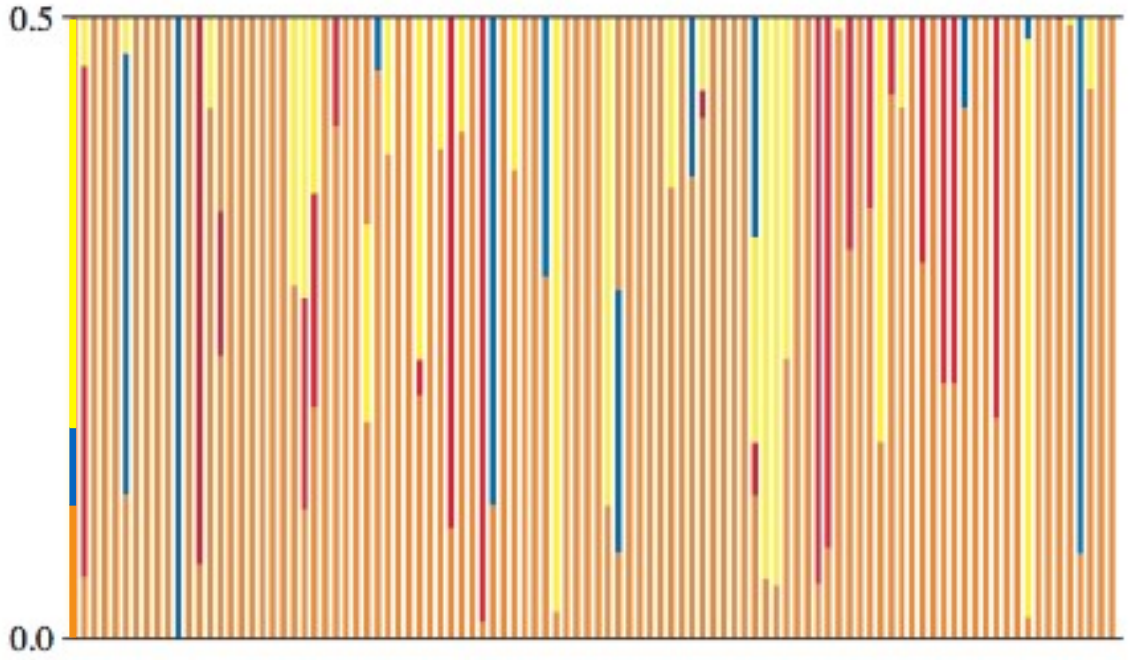
$23 \div 100$

number of simulations

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

$23 \div 100$

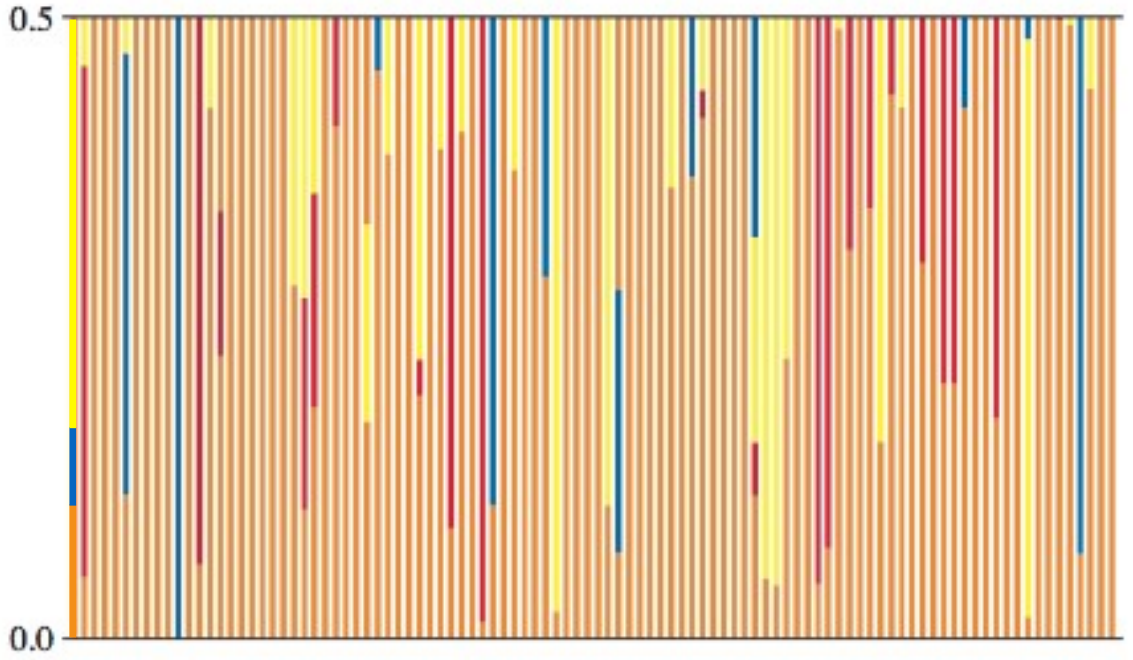
number of simulations

		To			
		A	C	G	T
From	A				
	C				
	G				
	T			0.23	

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



G

number of outcomes

$23 \div 100$

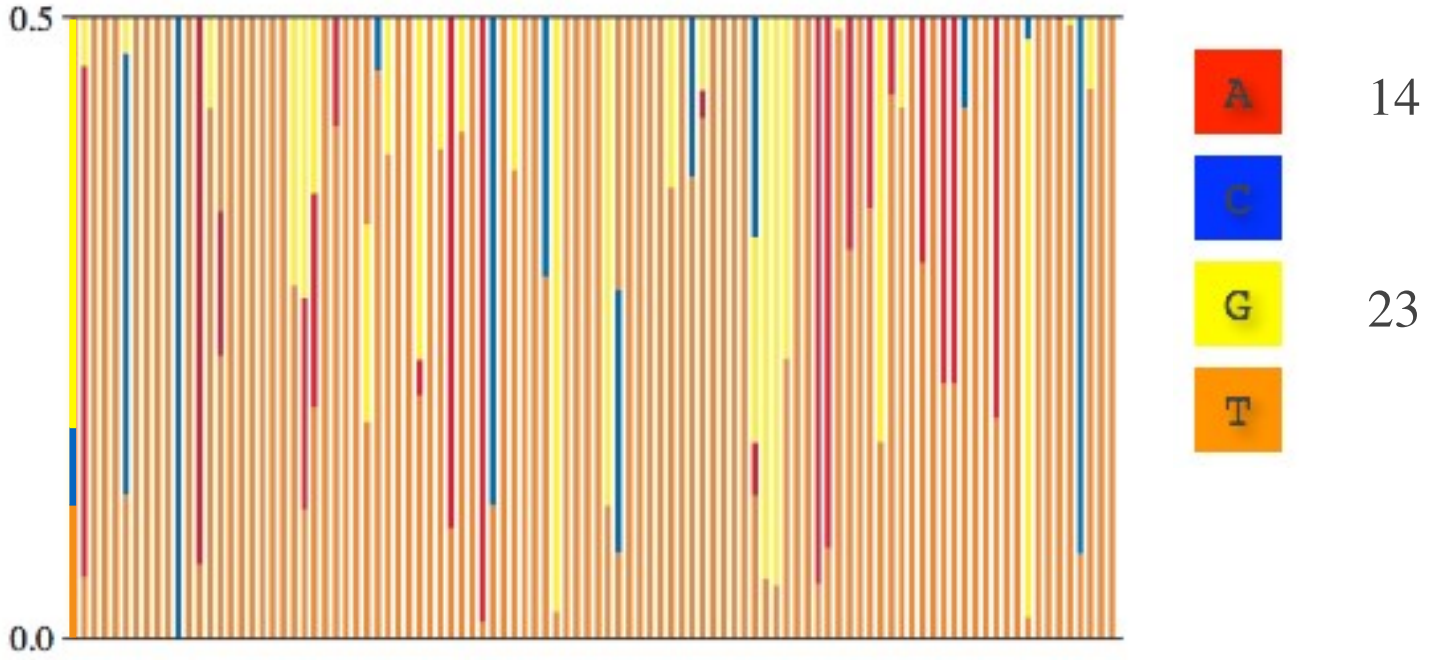
number of simulations

		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

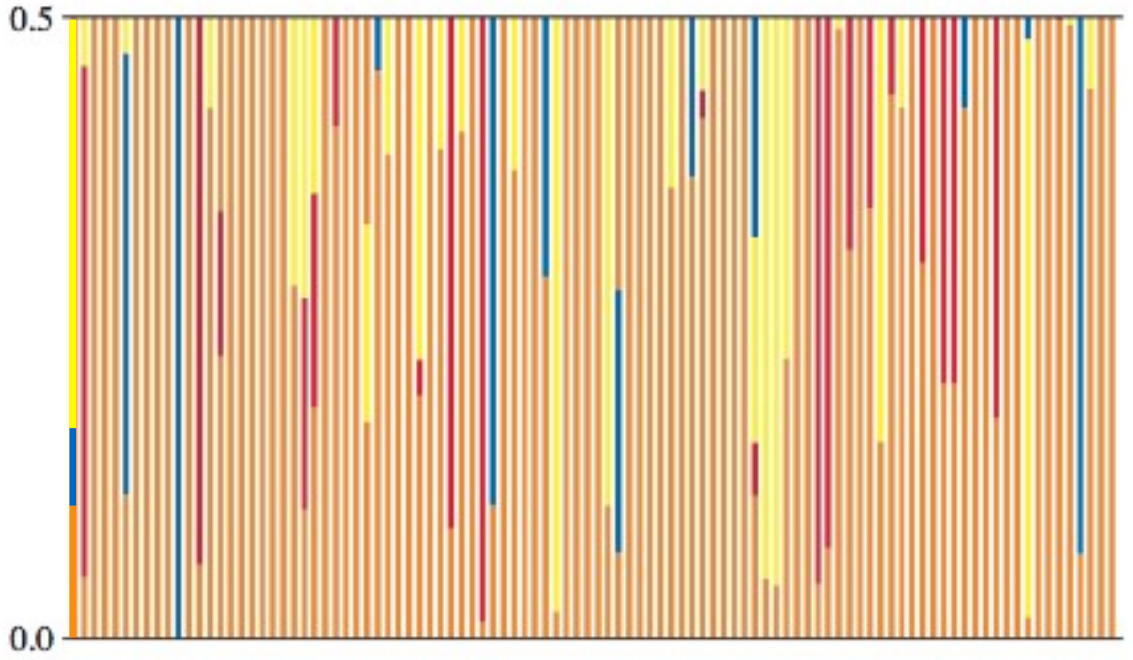


		To A	C	G	T
From	A				
	C				
	G				
	T	0.14		0.23	

We can repeat this process for the other end states…

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

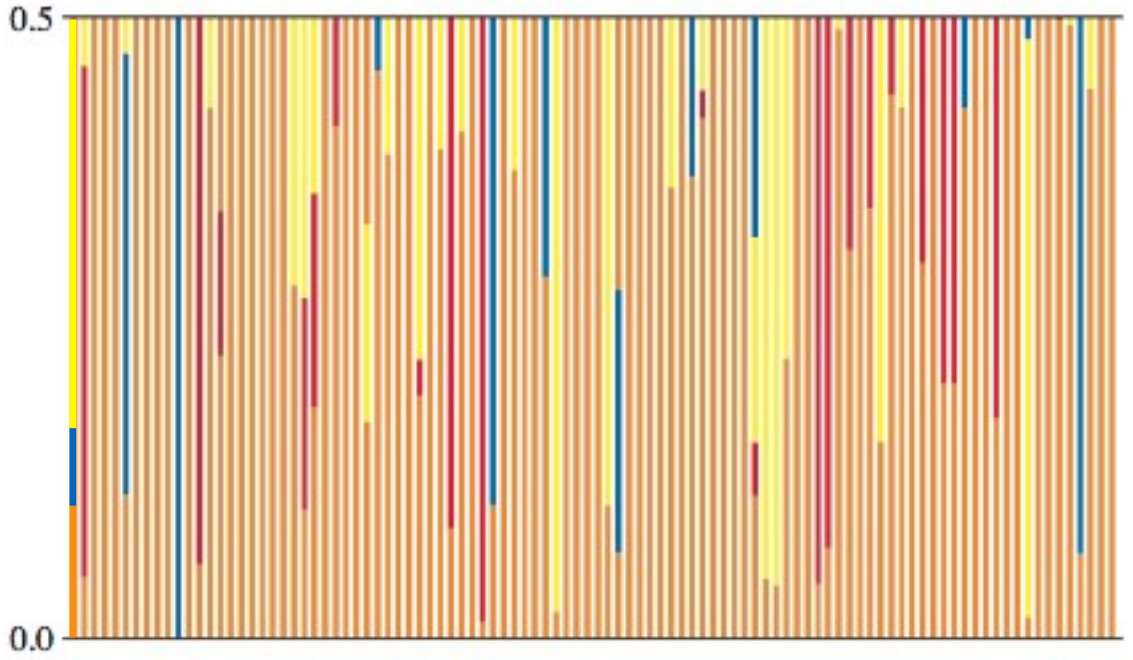


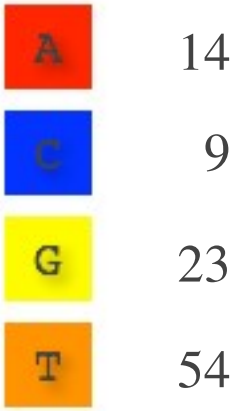
		To A	C	G	T
From	A				
	C				
	G				
	T	0.14	0.09	0.23	

We can repeat this process for the other end states…

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation





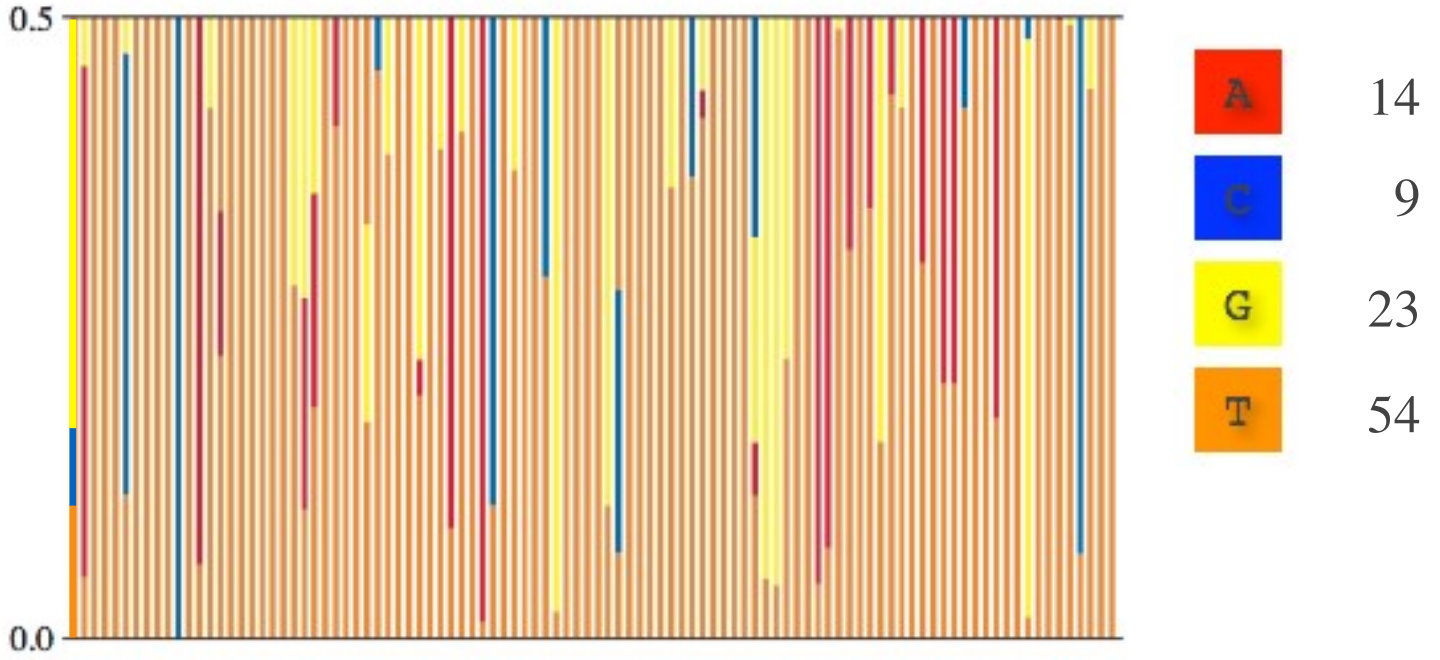
		To A	C	G	T
From	A				
	C				
	G				
	T	0.14	0.09	0.23	0.54

14
9
23
54

We can repeat this process for the other end states…

Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation

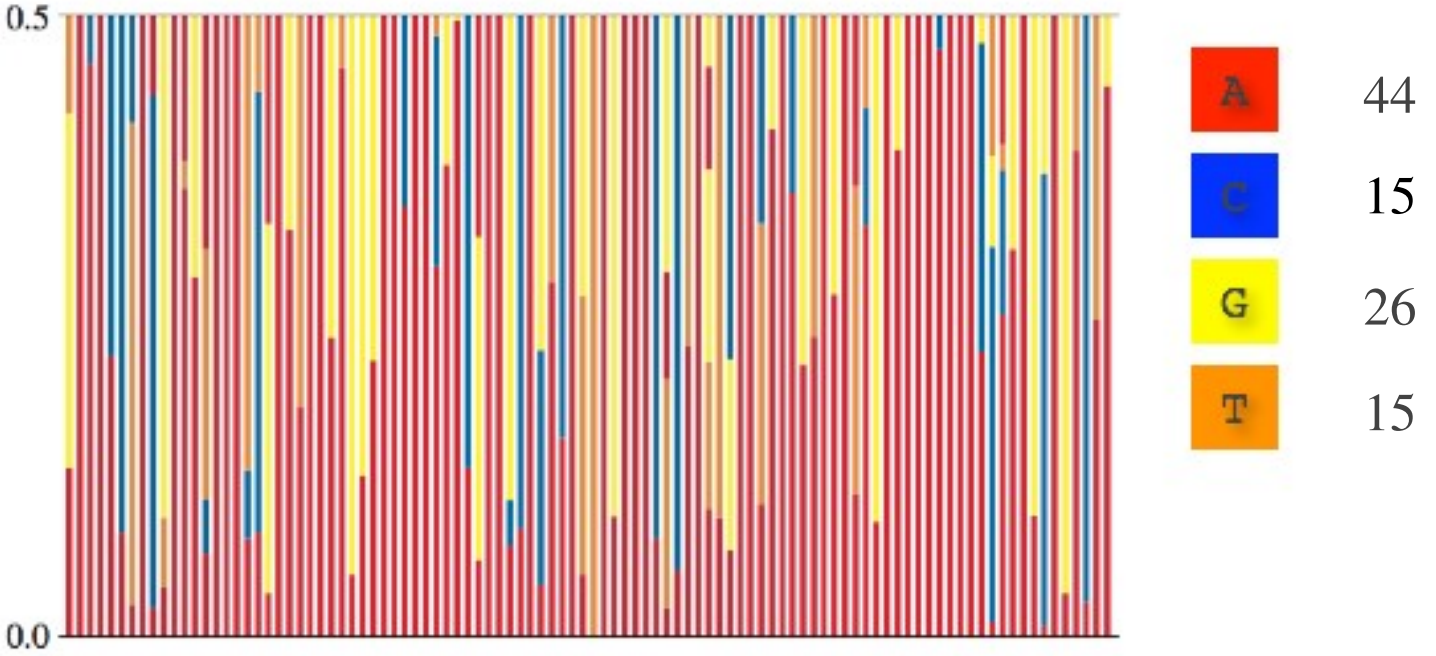


		To A	C	G	T
From	A				
	C				
	G				
	T	0.14	+ 0.09	+ 0.23	+ 0.54 = 1

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

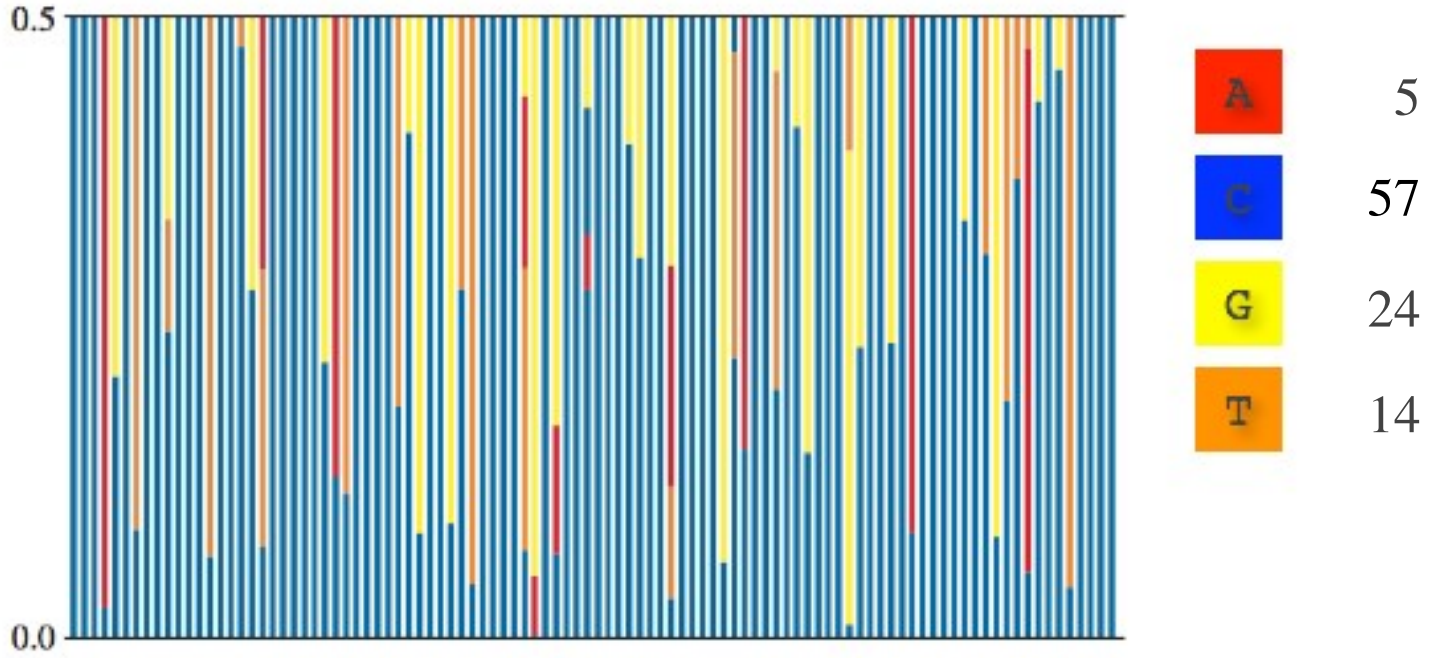


		To A	C	G	T
From	A	0.44	0.15	0.26	0.15
	C				
	G				
	T	0.14	0.09	0.23	0.54

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

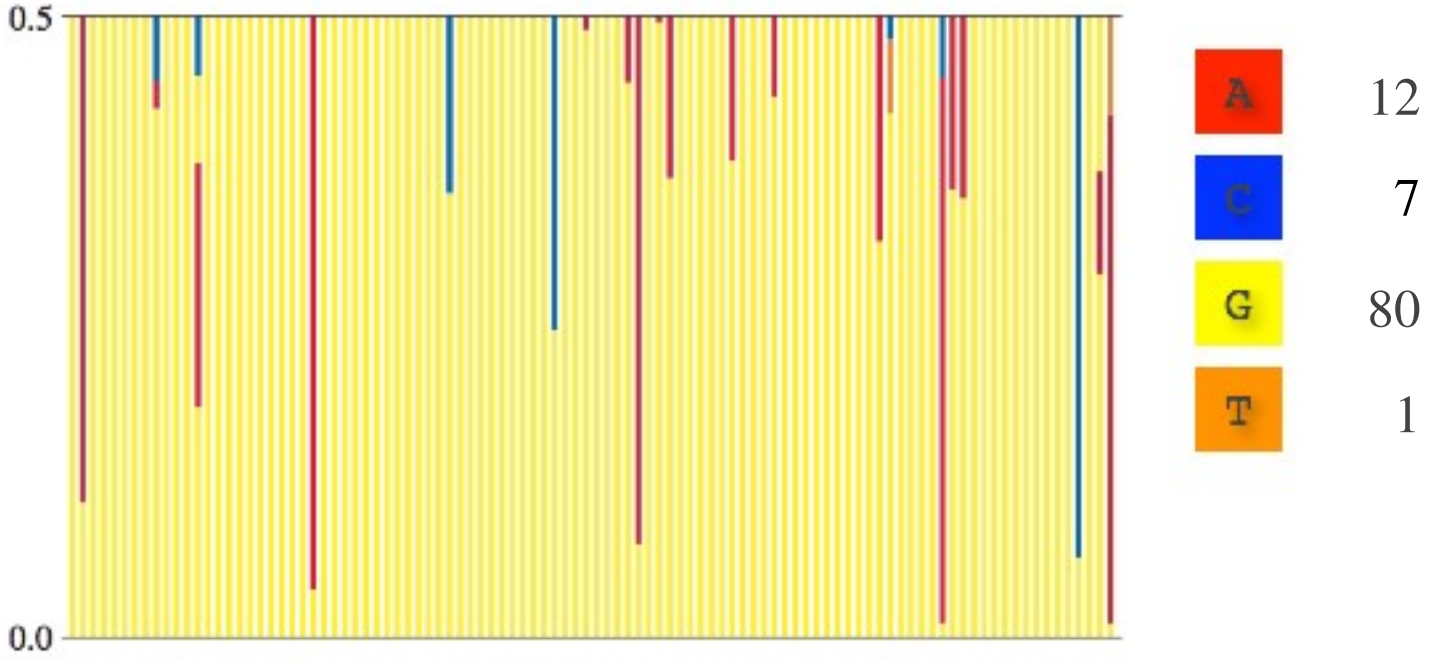


		To A	C	G	T
From	A	0.44	0.15	0.26	0.15
	C	0.05	0.57	0.24	0.14
	G				
	T	0.14	0.09	0.23	0.54

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

		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

Transition Probabilities of a CTMC

Accuracy of Monte Carlo approximation depends on the number of replicates

100 replicates

		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

100,000 replicates

		To A	C	G	T
From	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'

Transition Probabilities of a CTMC

Analytical solutions for the transition probabilities: matrix exponentiation

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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, v: $\mathbf{P}(v) = e^{\mathbf{Q}v}$

Transition Probabilities of a CTMC

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

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

Transition Probabilities of a CTMC

Analytical solutions for the transition probabilities: matrix exponentiation

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

		To A	C	G	T
From	A	0.42119	0.15365	0.26361	0.16155
	C	0.06209	0.60811	0.17602	0.15378
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Transition Probabilities of a CTMC

Analytical solutions for the transition probabilities: matrix exponentiation

Monte Carlo simulation is computationally expensive and unnecessary, as the

SIAM REVIEW
Vol. 45, No. 1, pp. 3–000

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

Cleve Moler†
Charles Van Loan‡

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	G	0.08834	0.07241	0.77796	0.06129
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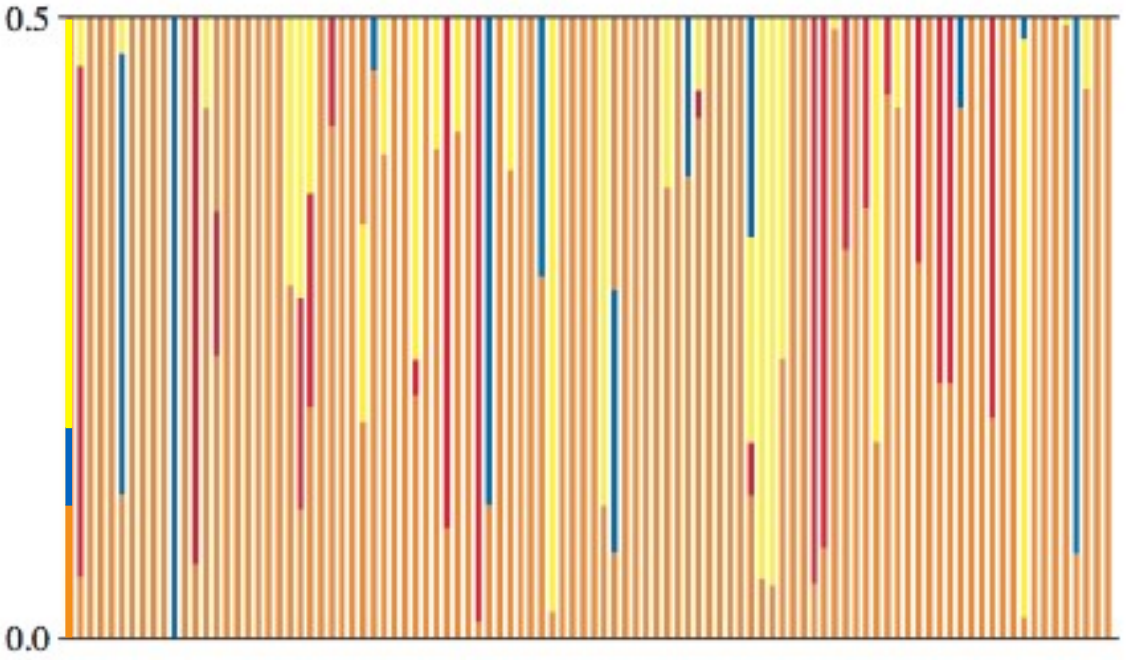
Transition Probabilities of a CTMC

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

G

$23 \div 100$

number of simulations

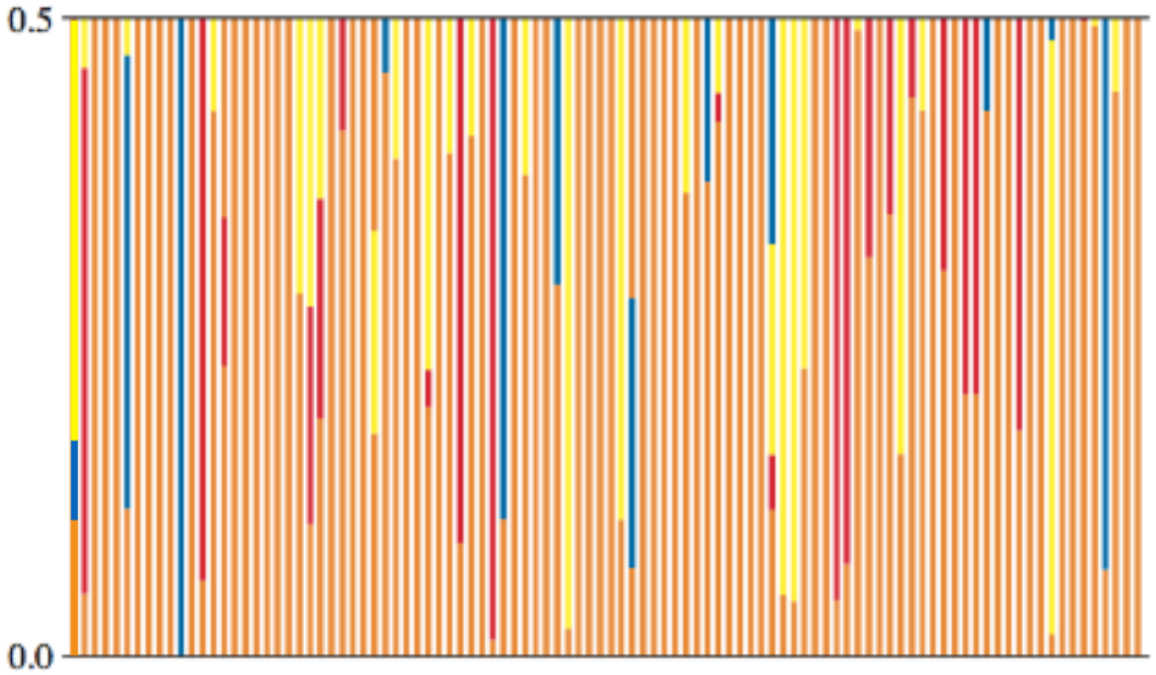
		To A	C	G	T
From	A				
	C				
	G				
	T			0.23	

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 v; *i.e.*, $p_{ij}(v)$

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

π_i

Stationary Frequencies of a CTMC

Transition probabilities

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

Stationary frequencies

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

π_i

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Transition probabilities over a branch of length $v = 0.0$:

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

π_i

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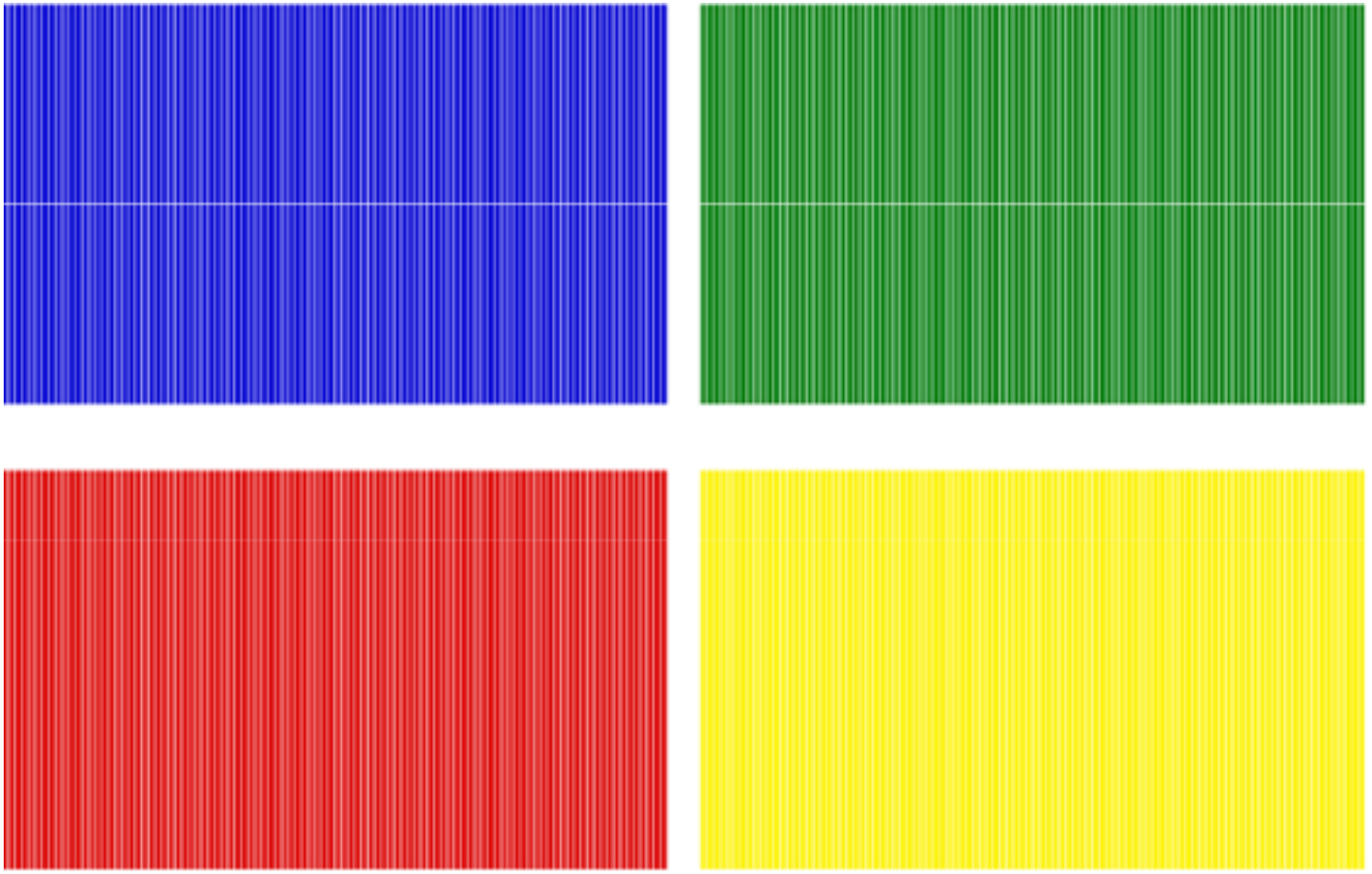

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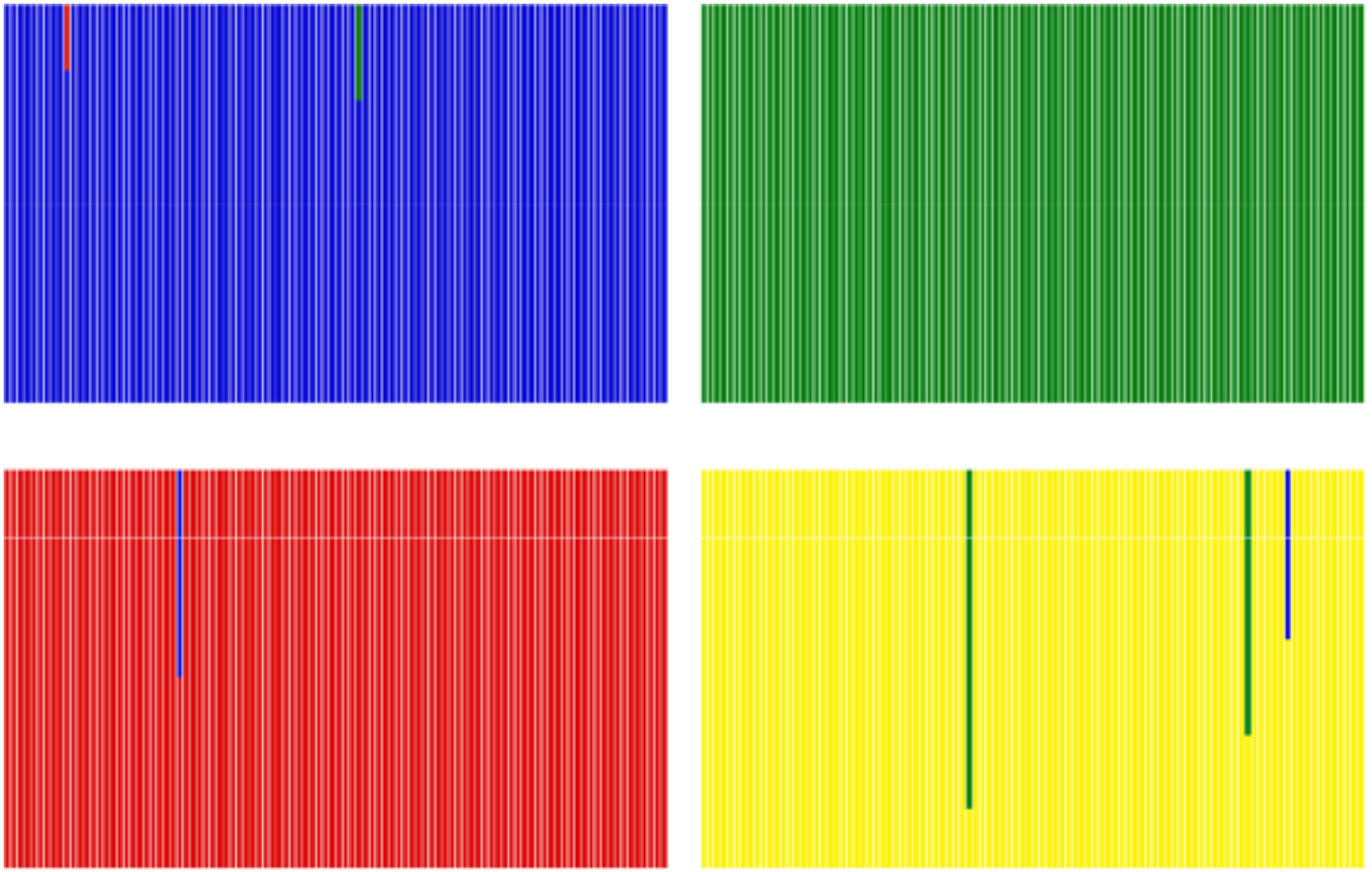
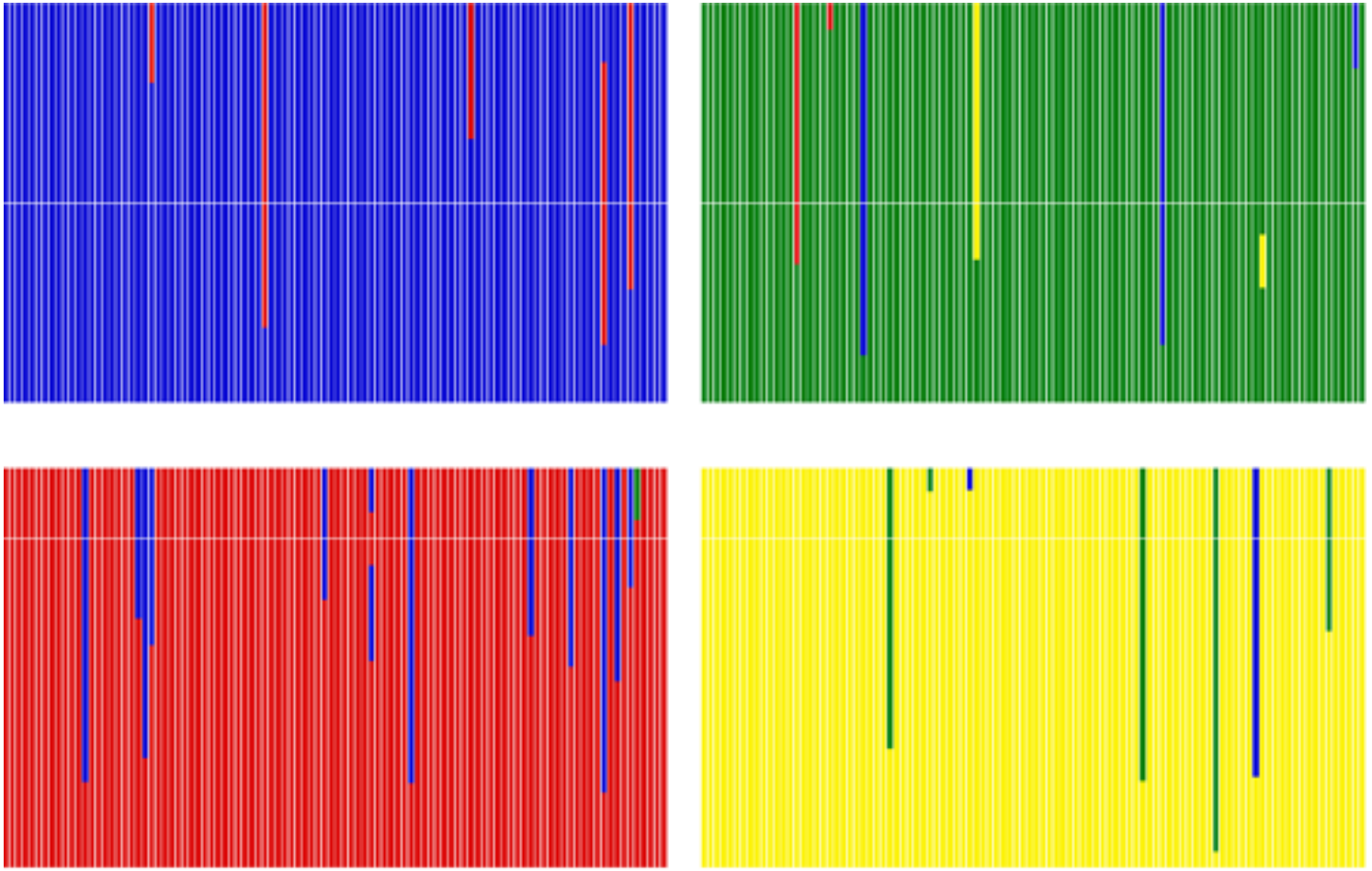


$$\mathbf{P}(0.01) = \begin{pmatrix} 0.981 & 0.005 & 0.008 & 0.006 \\ 0.001 & 0.989 & 0.004 & 0.005 \\ 0.003 & 0.002 & 0.994 & 0.001 \\ 0.005 & 0.002 & 0.006 & 0.986 \end{pmatrix}$$

π_i

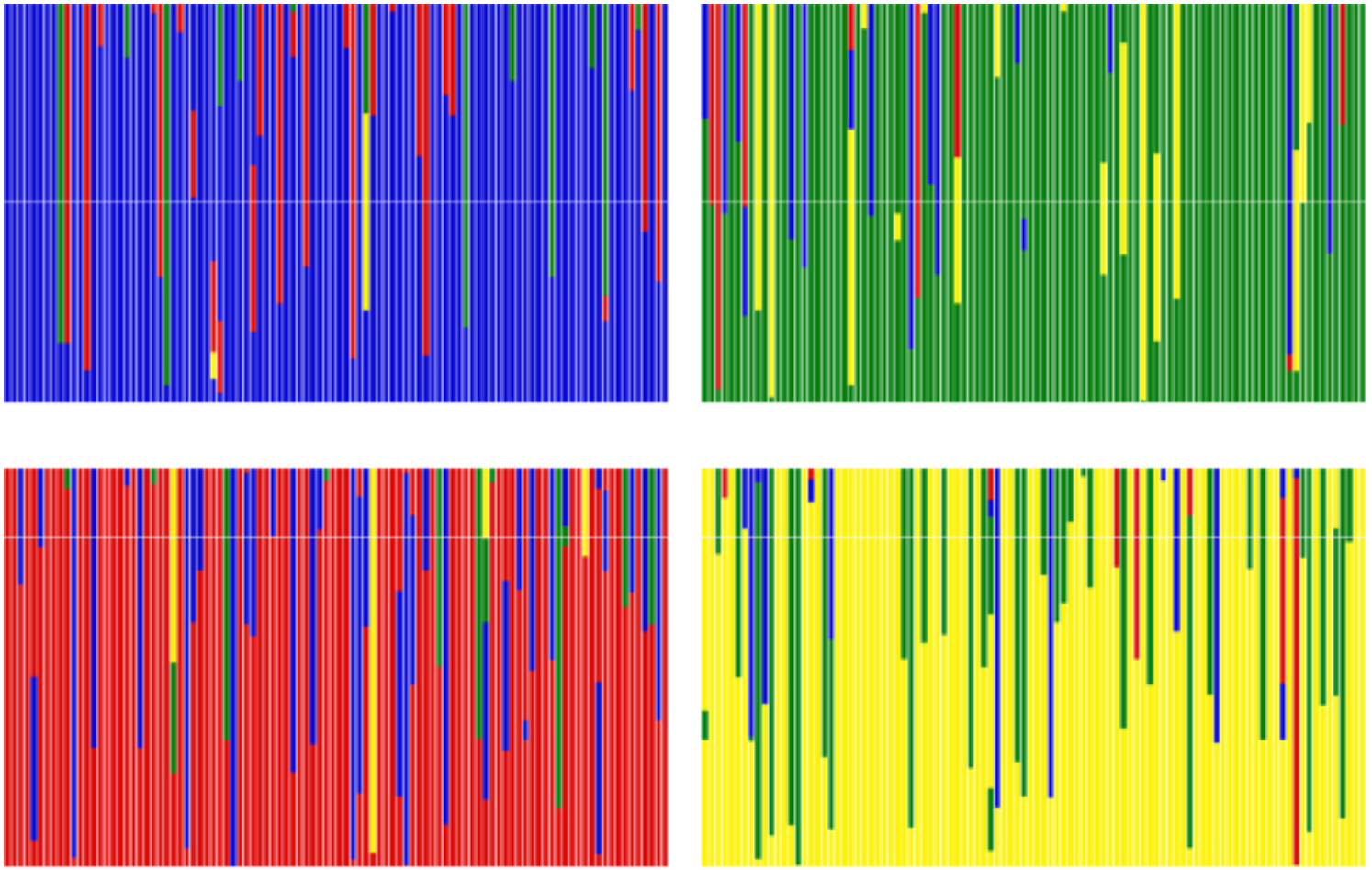
Stationary Frequencies of a CTMC



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

π_i

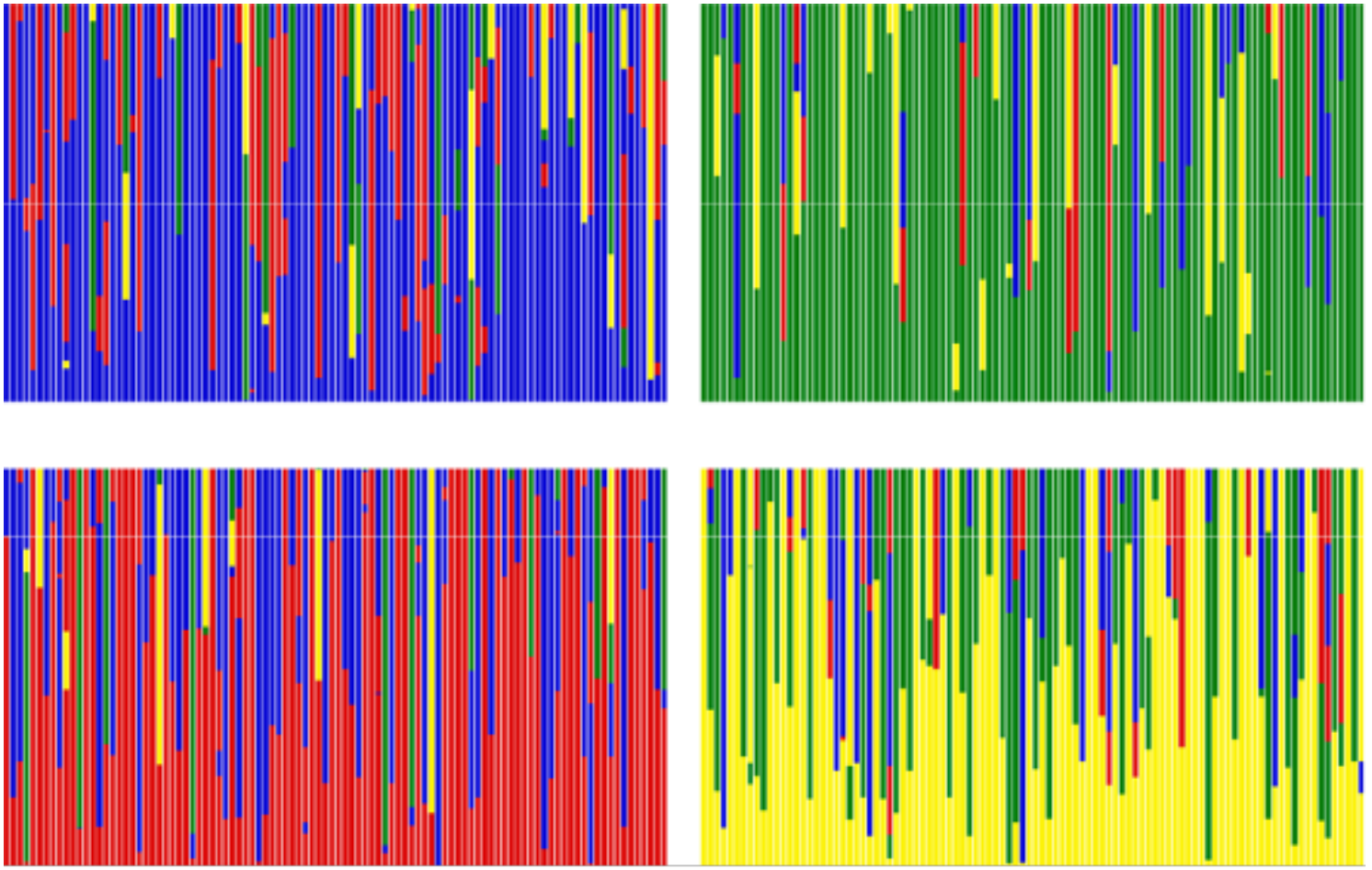
Stationary Frequencies of a CTMC



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

π_i

Stationary Frequencies of a CTMC



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

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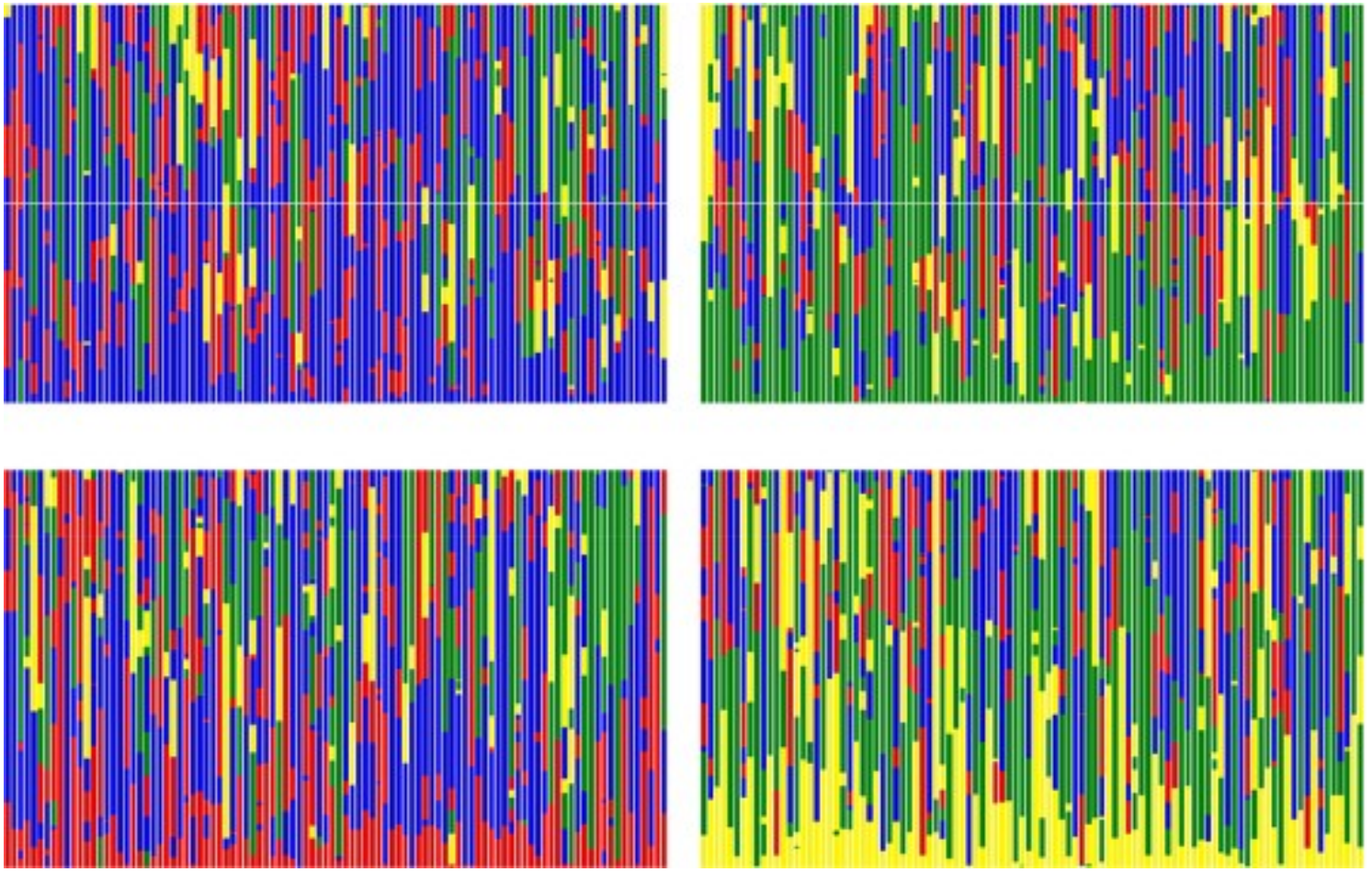

$$\mathbf{P}(5.0) = \begin{pmatrix} 0.138 & 0.188 & 0.494 & 0.180 \\ 0.138 & 0.190 & 0.492 & 0.181 \\ 0.137 & 0.187 & 0.497 & 0.178 \\ 0.138 & 0.188 & 0.494 & 0.180 \end{pmatrix}$$

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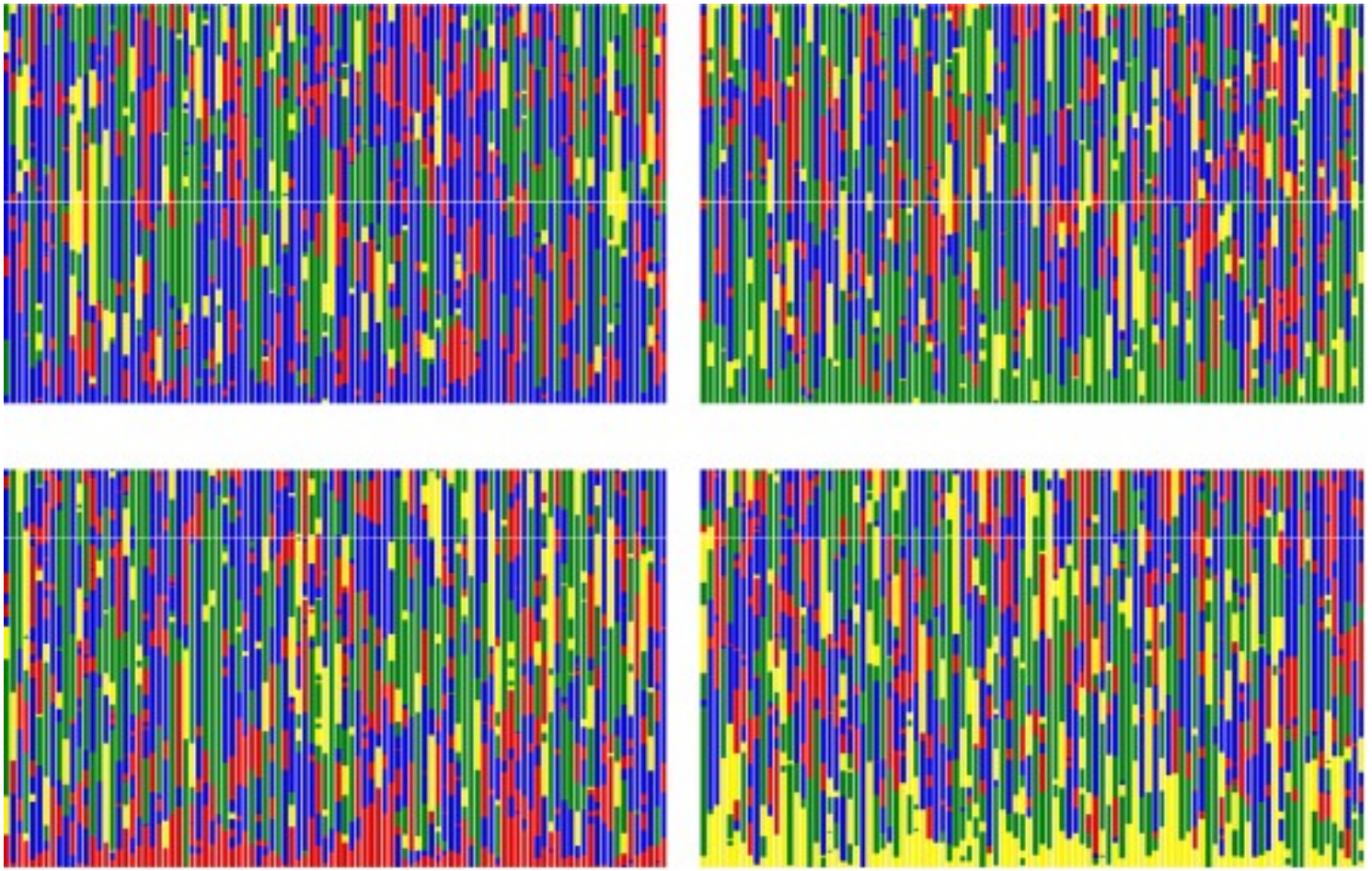

$$\mathbf{P}(10.0) = \begin{pmatrix} 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \end{pmatrix}$$

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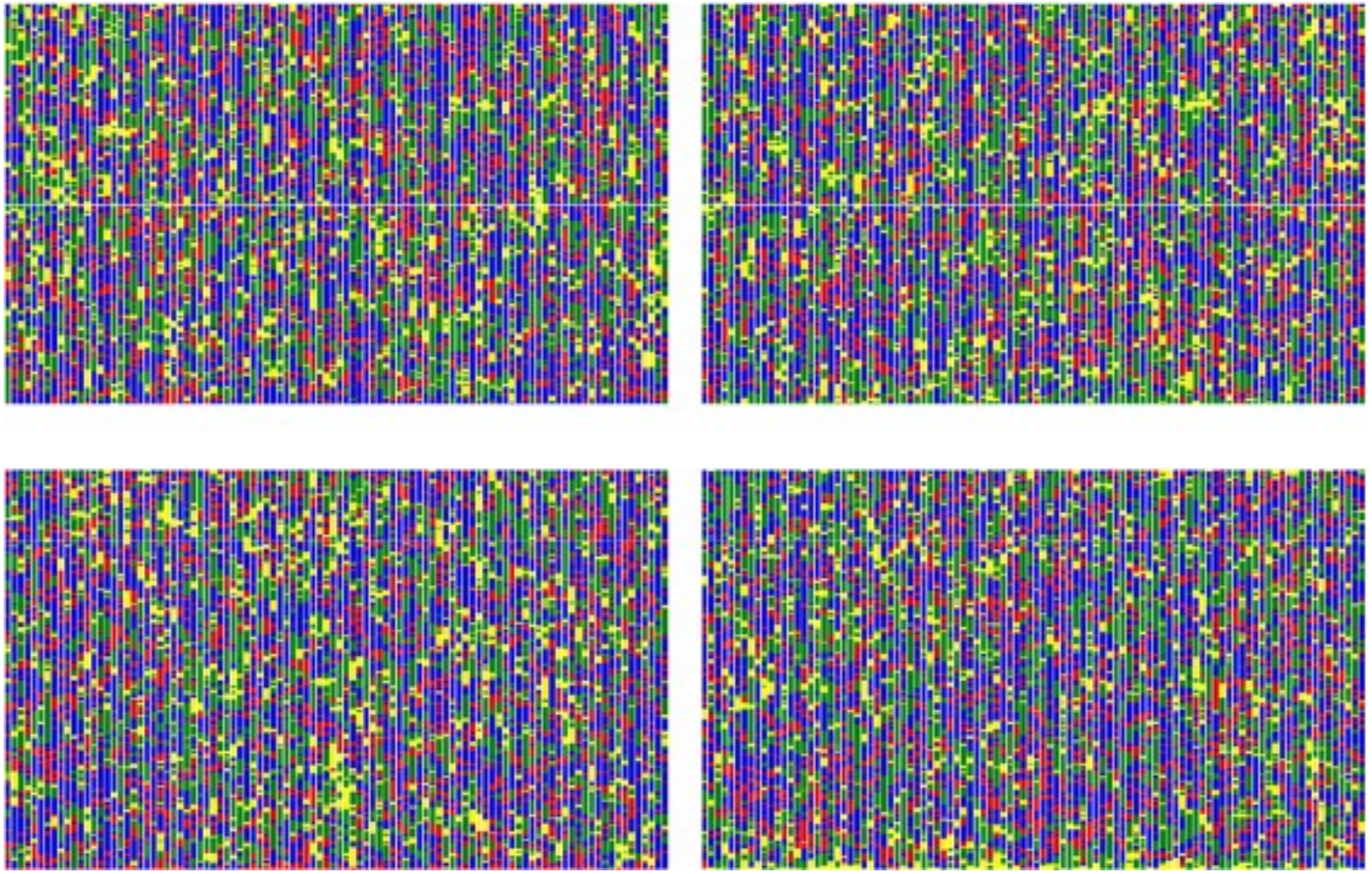

$$\mathbf{P}(100.0) = \begin{pmatrix} 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \end{pmatrix}$$

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

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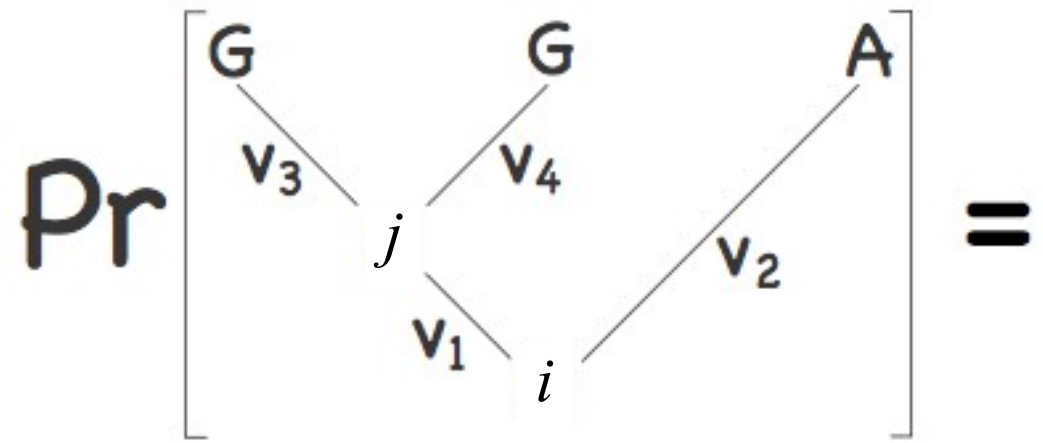
When the continuous time Markov chain is at stationarity, the stochastic process has 'forgotten' the starting state: the process ends in a given state with the same probability, regardless of the starting state

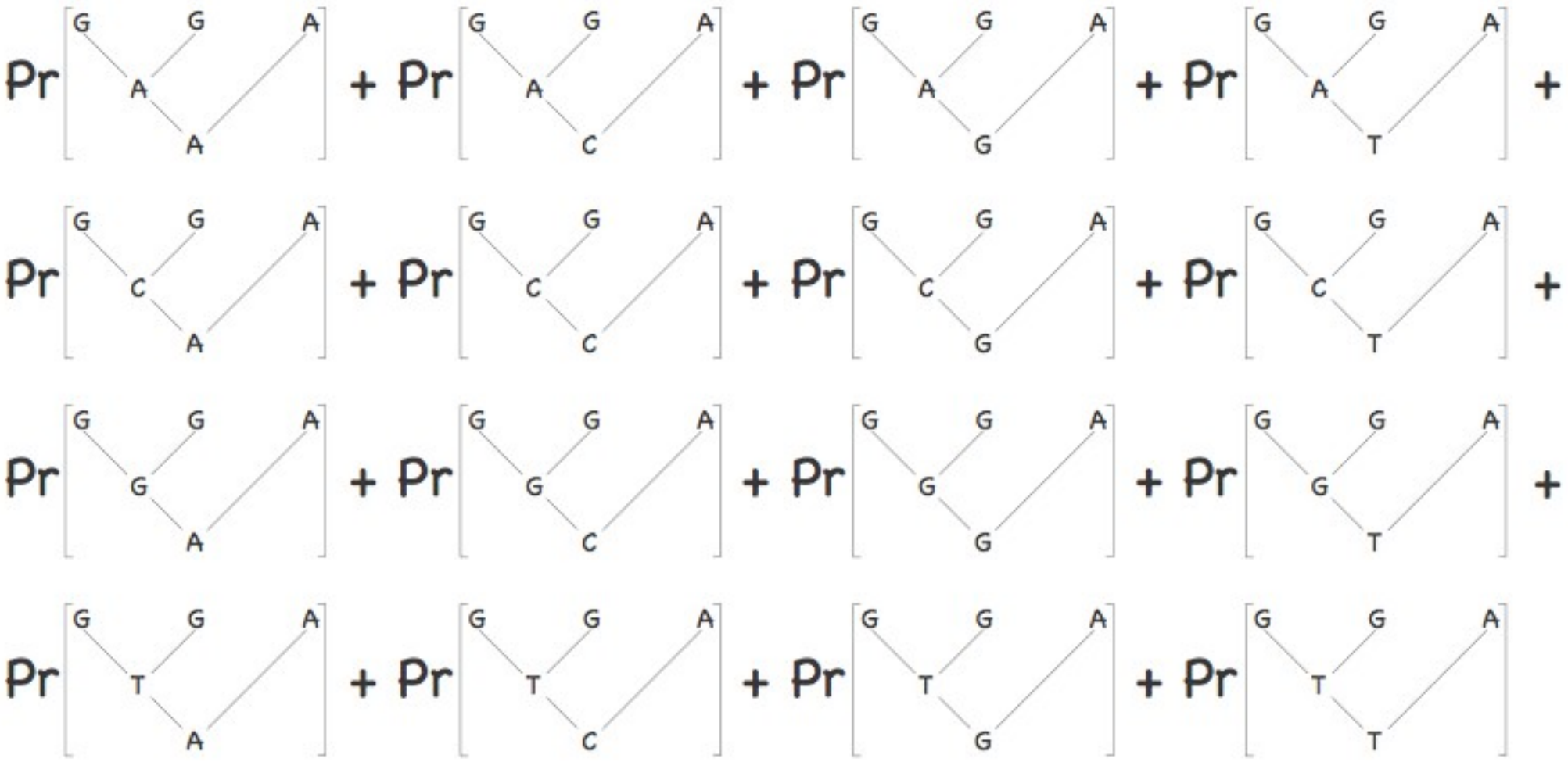
Now we can compute the likelihood of a site history



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

π_i	Stationary frequencies
$p_{ij}(v)$	Transition probabilities

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



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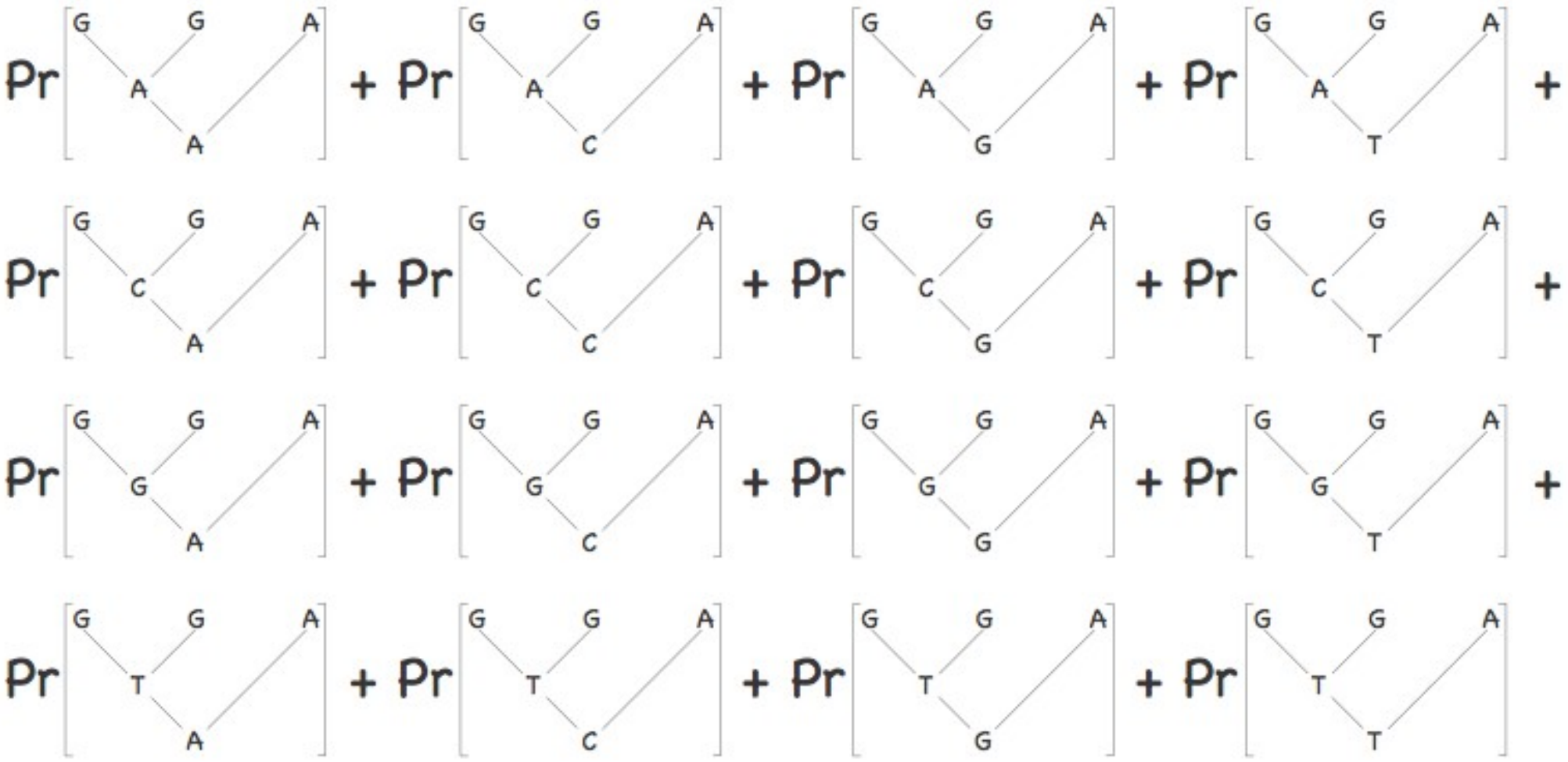
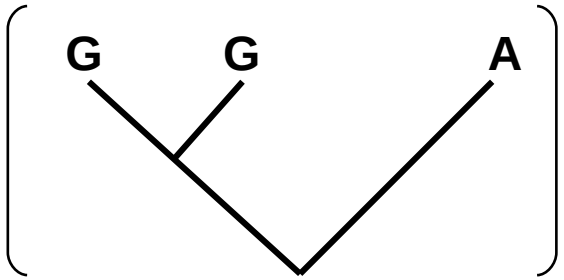


= Pr 

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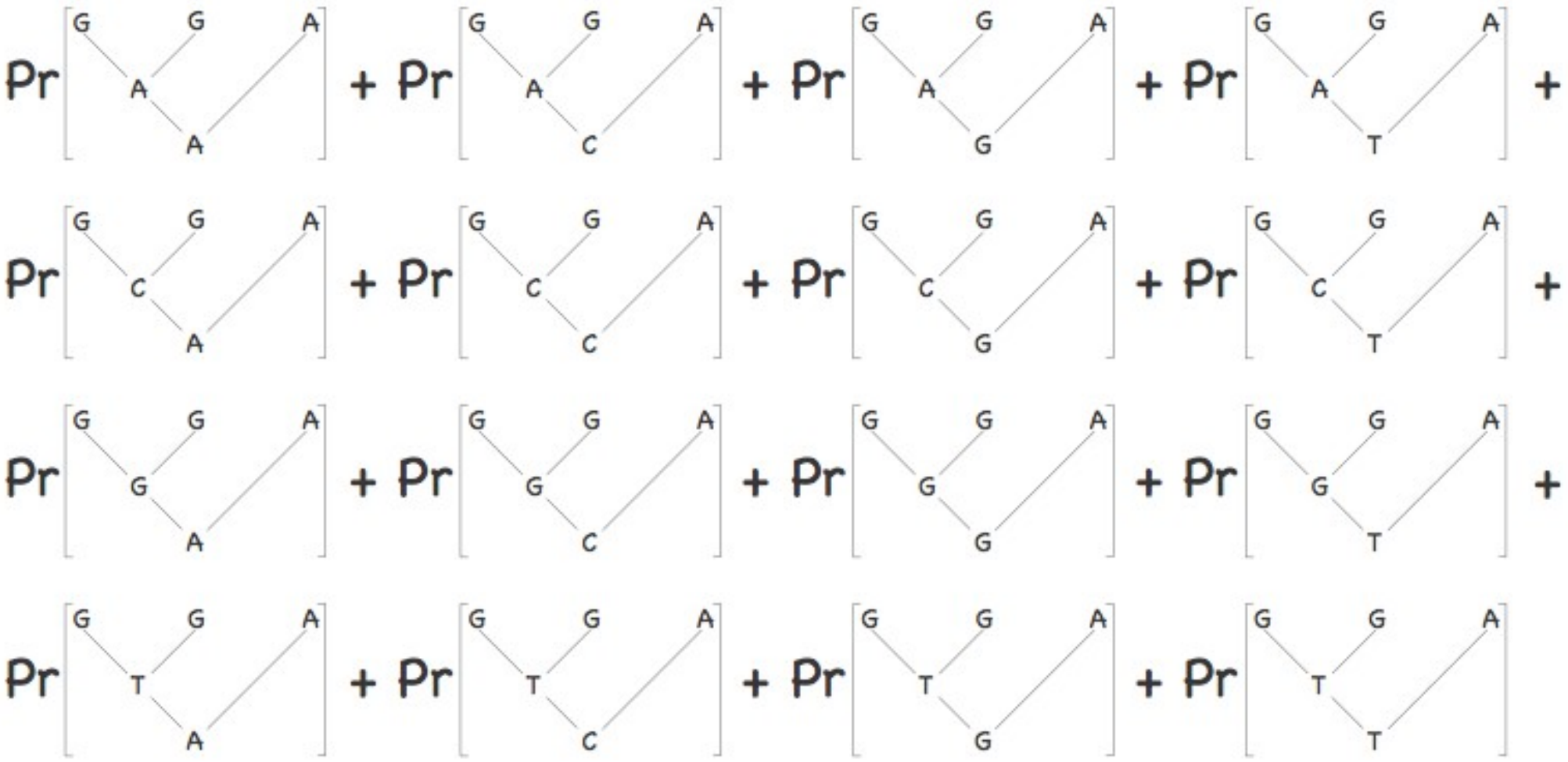

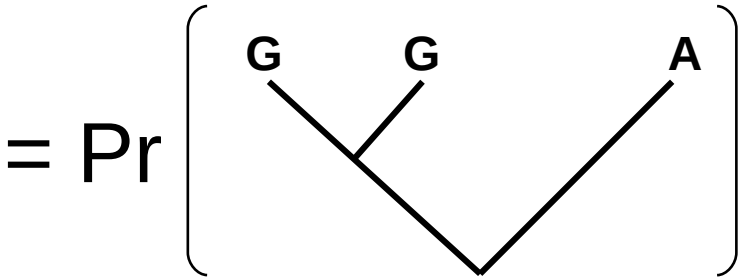

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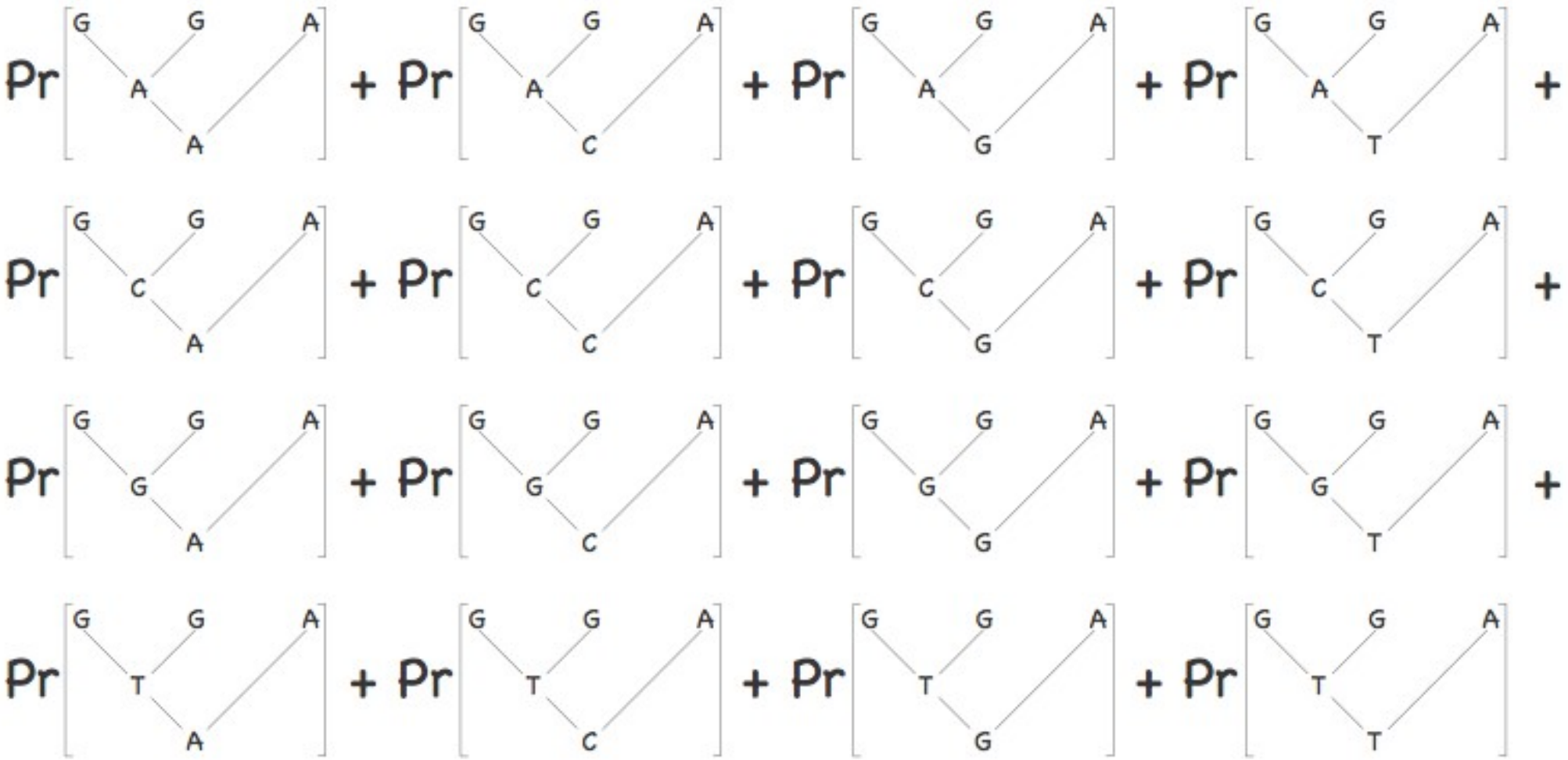
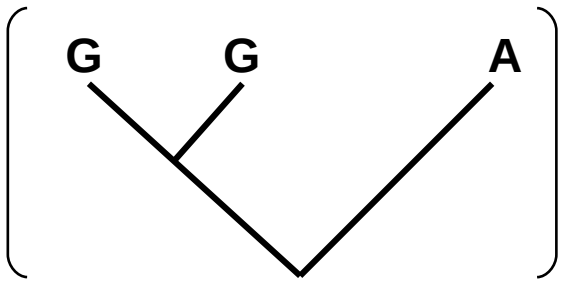


= Pr 

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This is the likelihood of site pattern (GGA)

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Continuous-time Markov models

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

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

Are we clear on what are:

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

?

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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

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

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Jukes and Cantor 1969

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

Kimura 1980

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1 transition/transversion ratio : 1 free parameter

Hasegawa, Kishino, Yano 1985

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

Substitution models

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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

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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