# 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

# 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
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- Are transitions as probable as transversions in rodents?
- *Sites of alignment=independent identically distributed Markov chains running along a phylogeny*
- Sequence rodents
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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 | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ | ✗ |
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$$P(rainy) = ?$$

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

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

***Conditional probability: P(A|B)***

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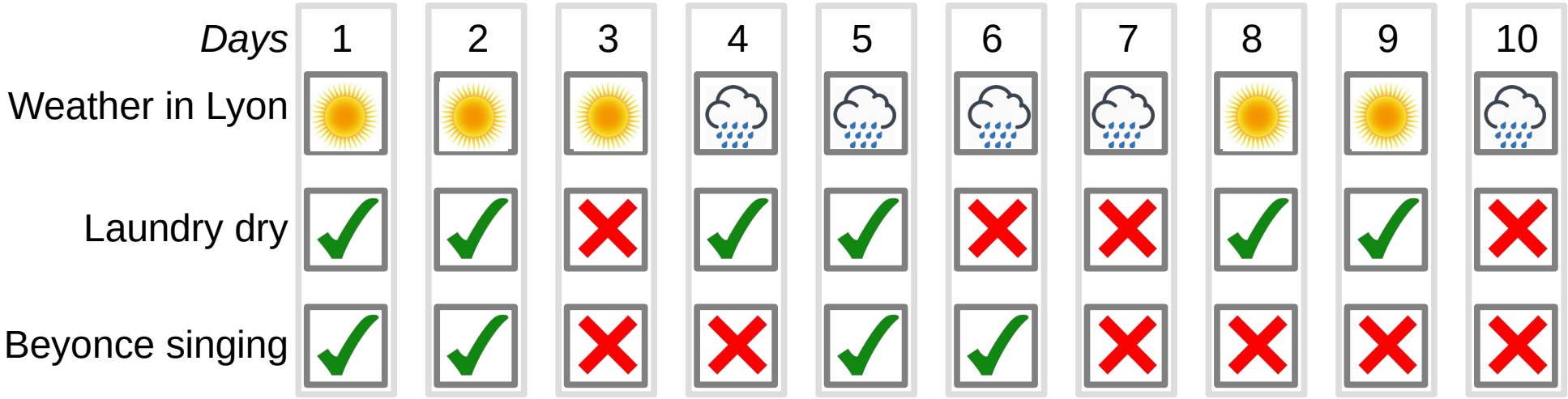


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$$P(rainy)=0.5 \qquad P(sunny)=1-P(rainy)=0.5$$

***The events "Beyonce singing" and "sunny" are <u>independent</u>***

$$P(Beyonce\ singing)=0.4$$

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***The events "dry laundry" and "sunny" are <u>NOT independent</u>***

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

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

# 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

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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

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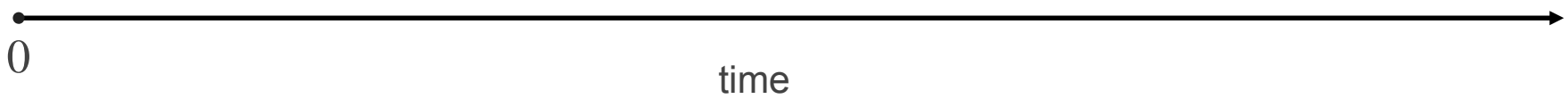

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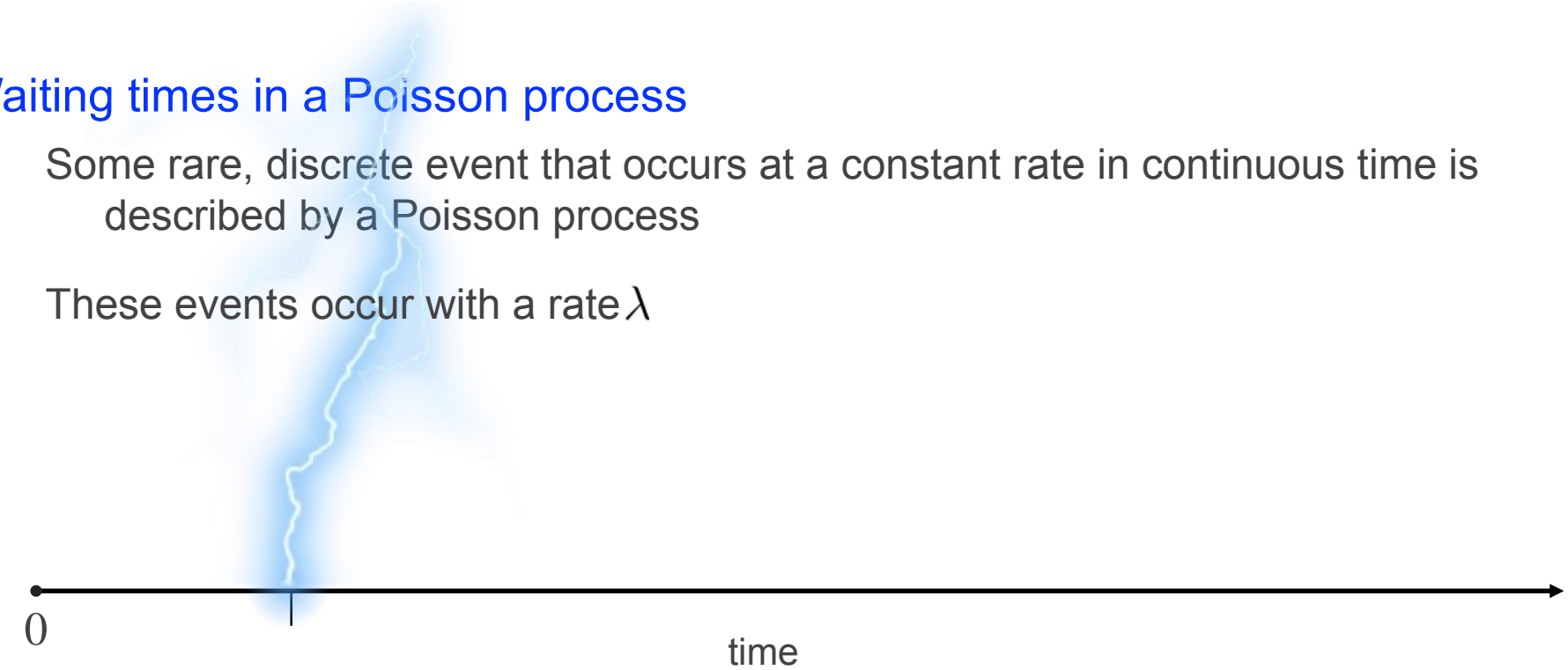

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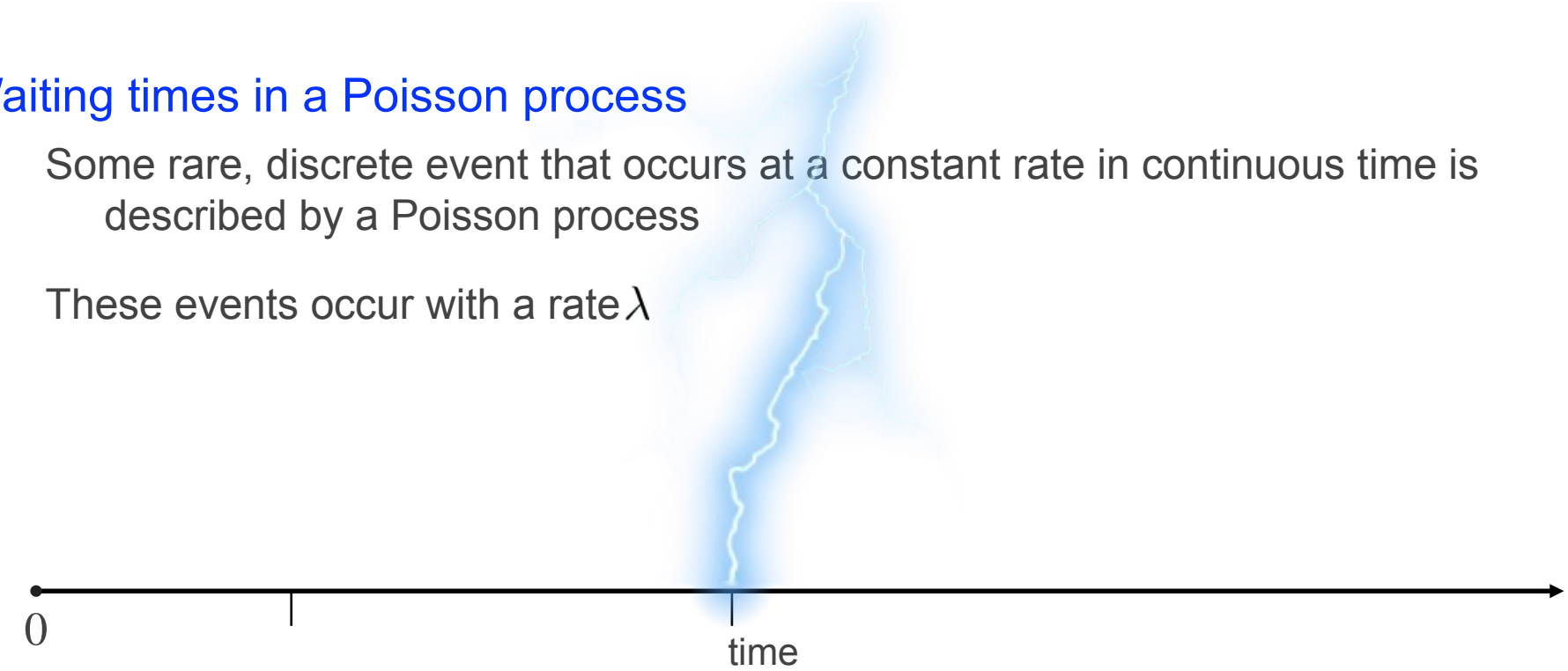

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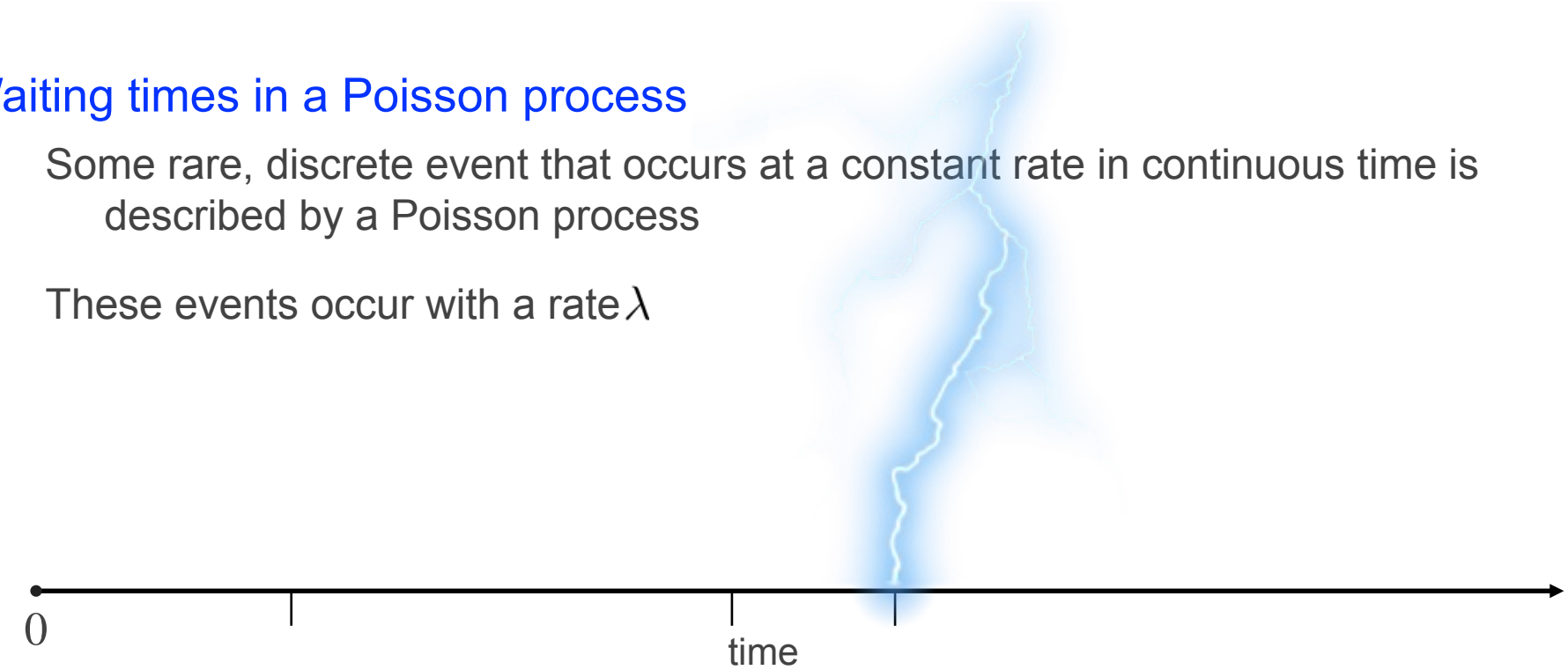

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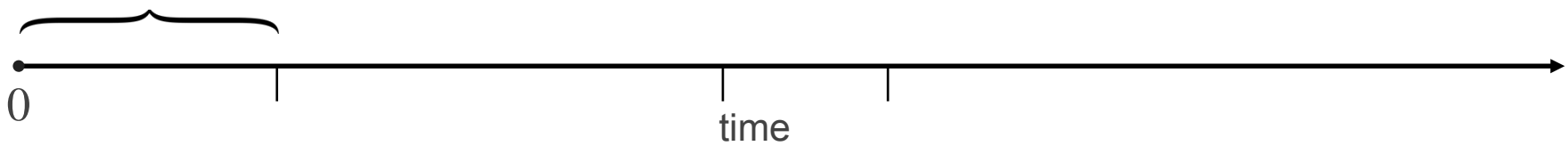
The waiting (sojourn) time for the first event



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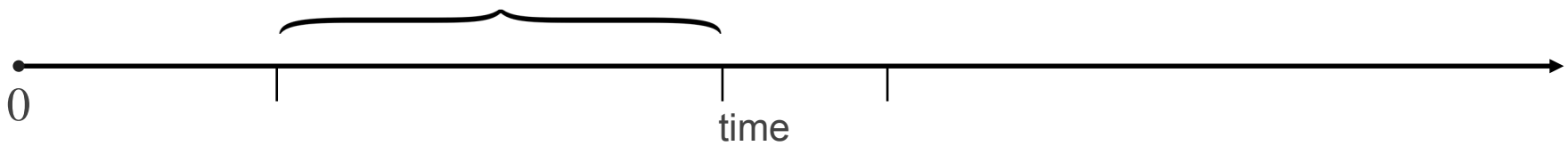
The waiting (sojourn) time for the second event



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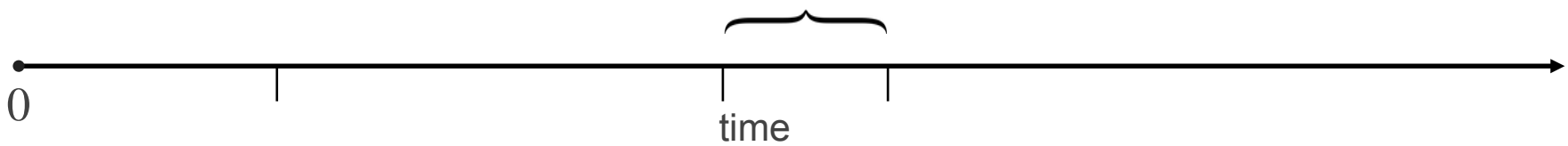
The waiting (sojourn) time for the third event



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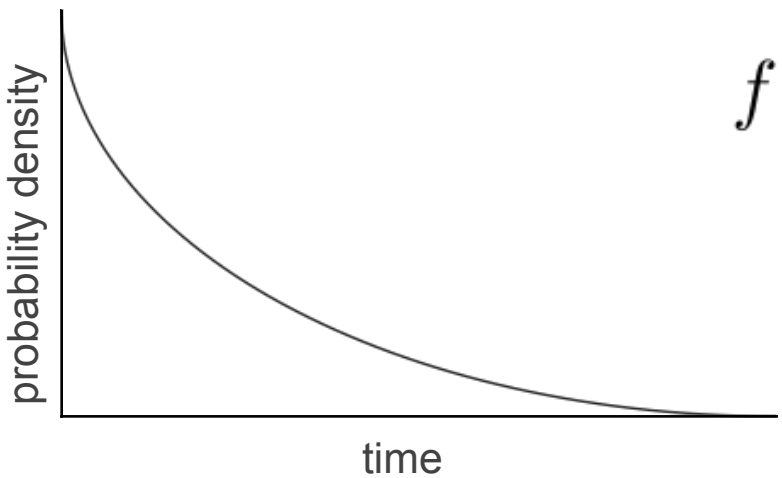
The waiting (sojourn) times are exponentially distributed random variables




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

# 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?

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**Assumption:**

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

  - Approximate Bayesian Computation (ABC)
  - ...

# Stochastic Models of Nucleotide Substitution

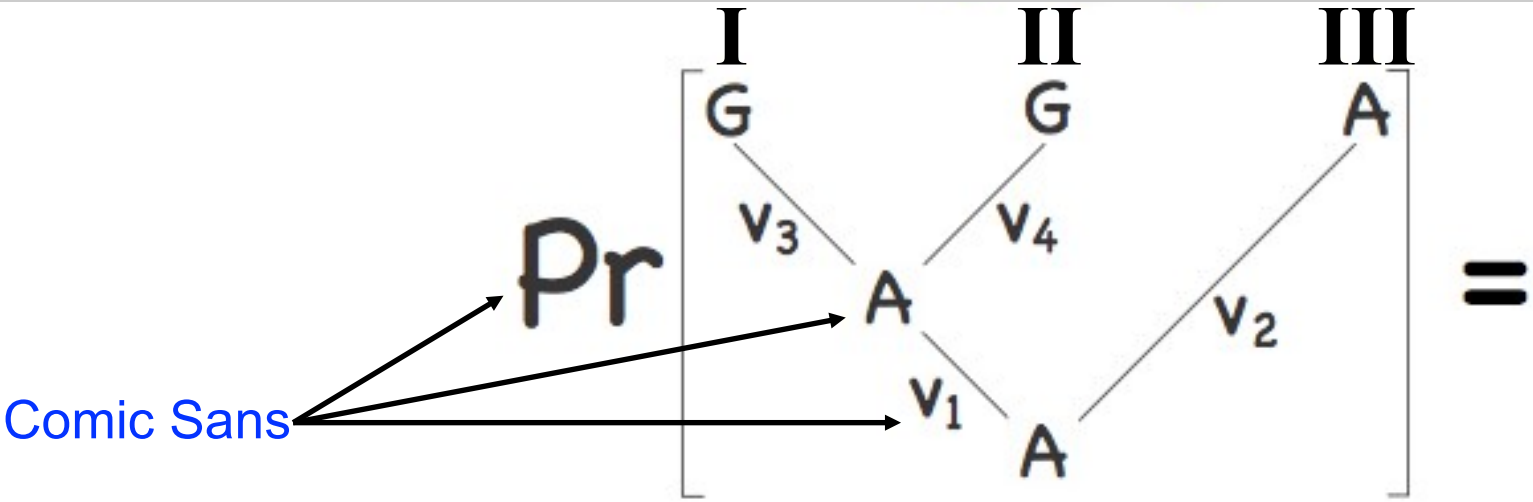
| Species | Sequence data |
|---|---|
| **Species I** | GCG--CACCGGCGCAGTCA.... |
| **Species II** | GCGTTCA--GGCG--GTCA.... |
| **Species III** | ACGTTCACCGGCGCAGTCA.... |

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



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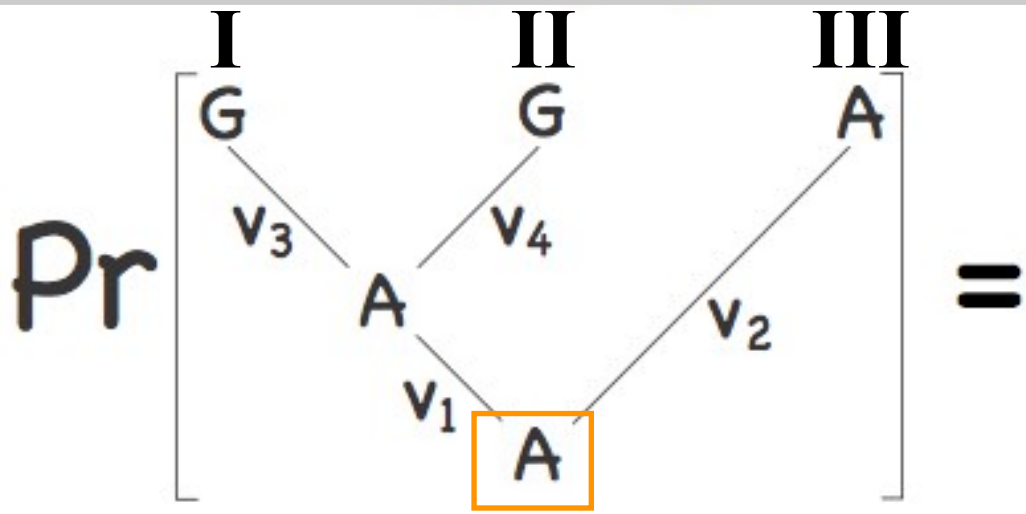


$\pi_A$

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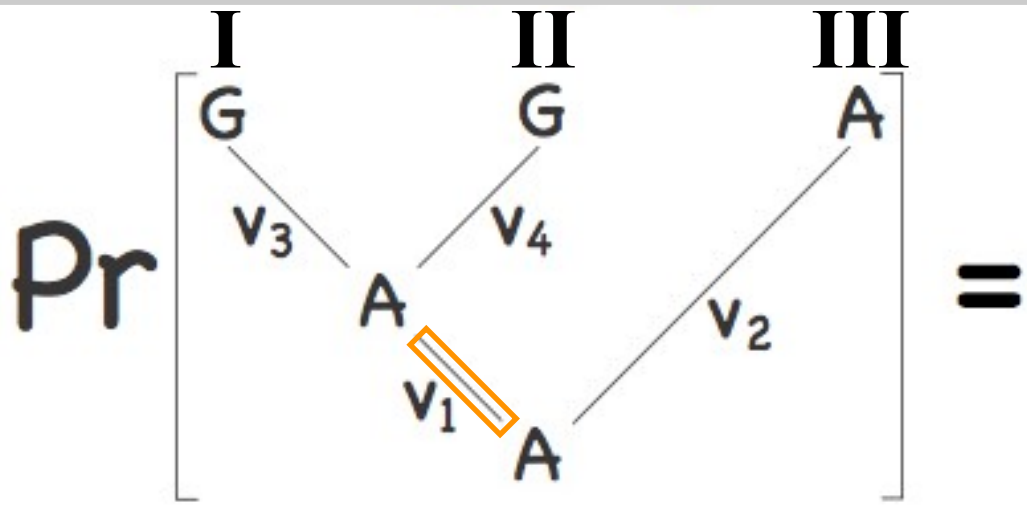


$$\pi_A \times p_{AA}(v_1)$$

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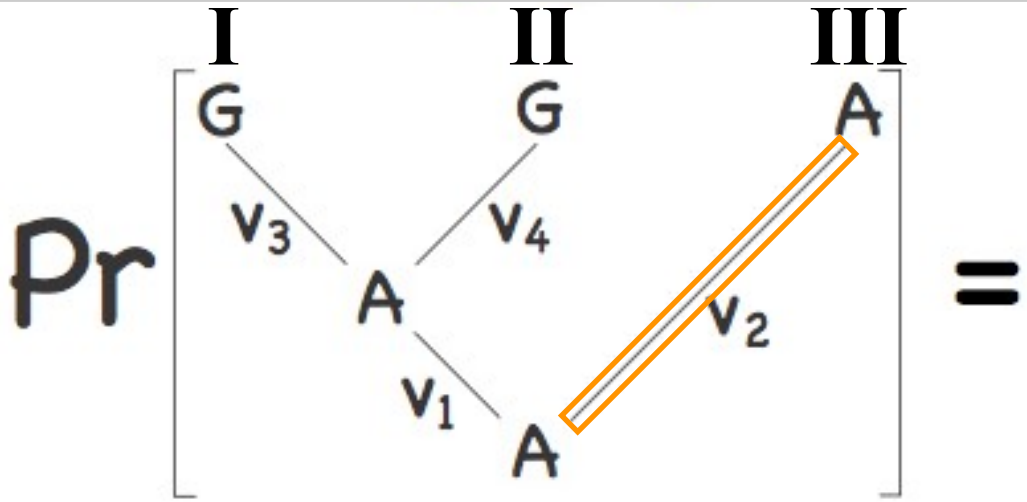


$$\pi_A \times p_{AA}(v_1) \times p_{AA}(v_2)$$

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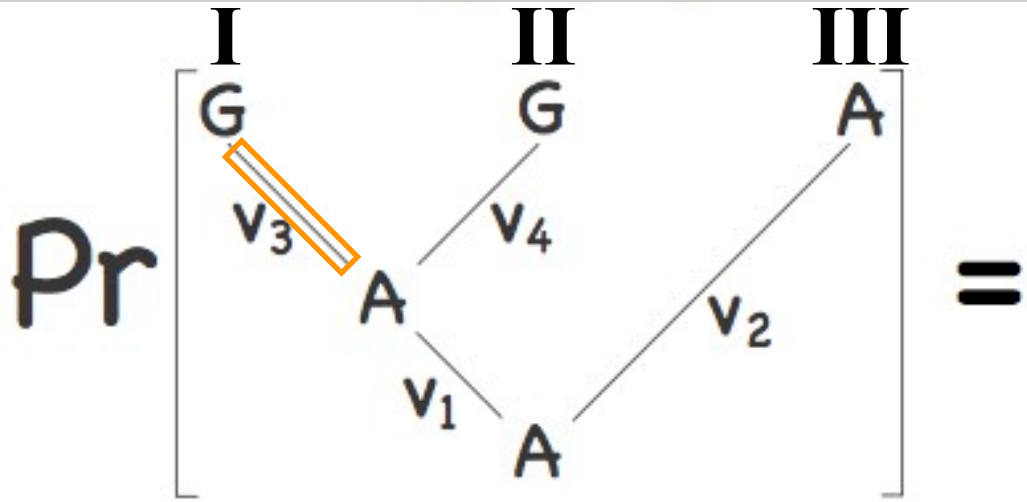


$$\pi_A \times p_{AA}(v_1) \times p_{AA}(v_2) \times p_{AG}(v_3)$$

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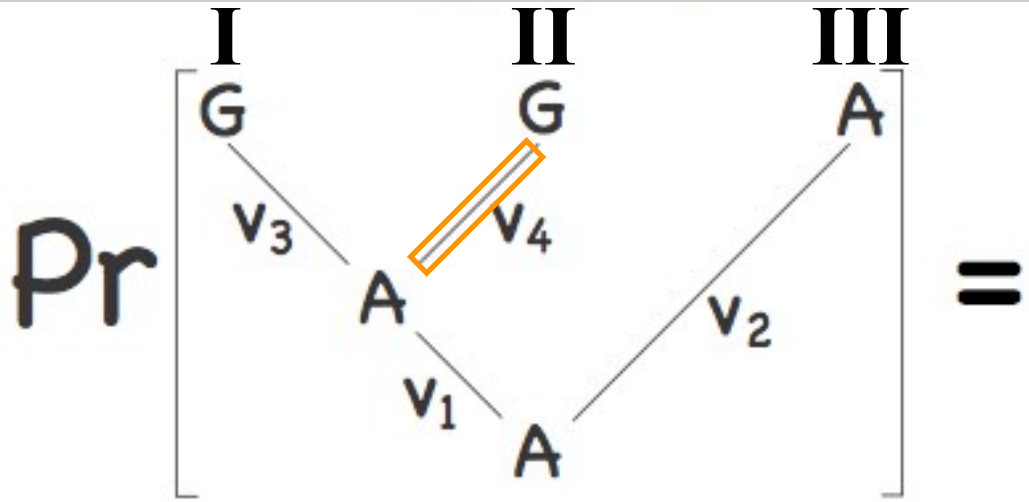


$$\pi_A \times p_{AA}(v_1) \times p_{AA}(v_2) \times p_{AG}(v_3) \times p_{AG}(v_4)$$

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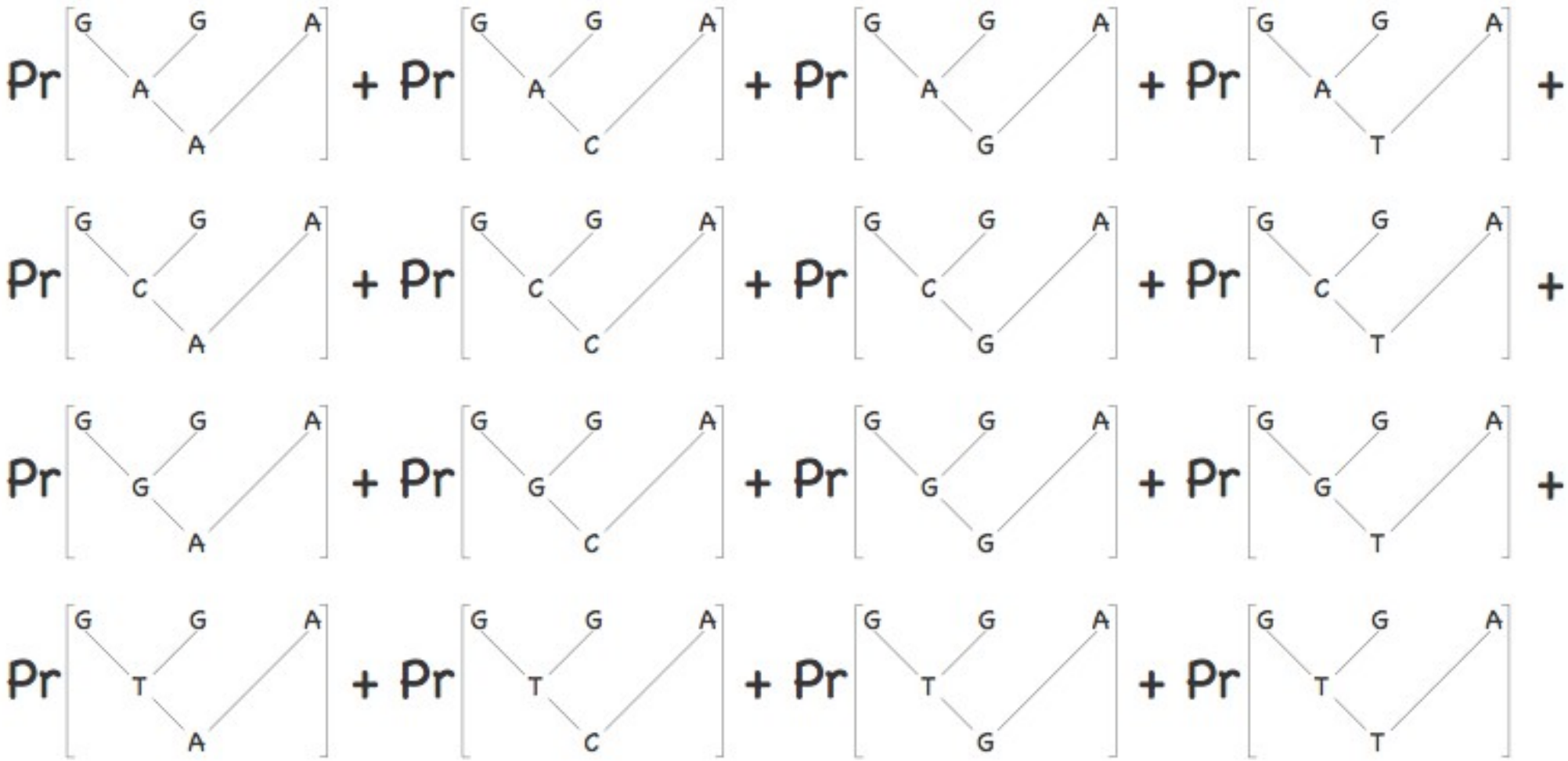

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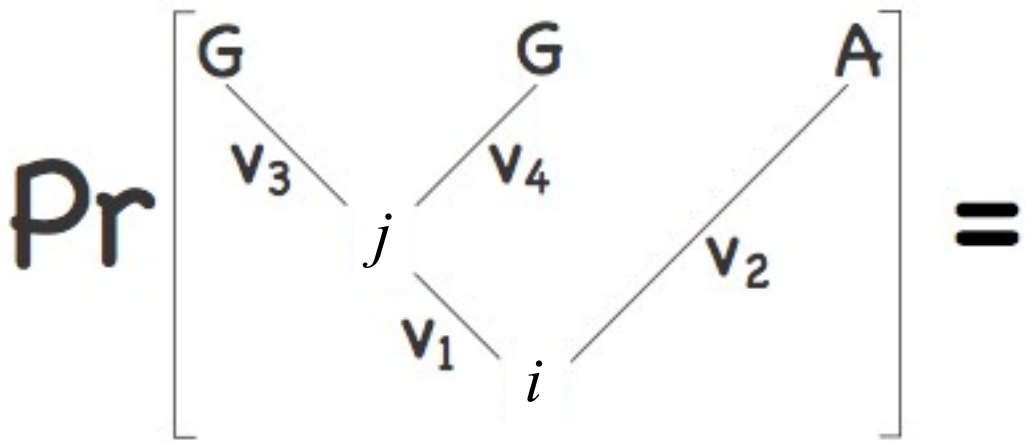


$$\pi_i \times p_{ij}(v_1) \times p_{iA}(v_2) \times p_{jG}(v_3) \times p_{jG}(v_4)$$

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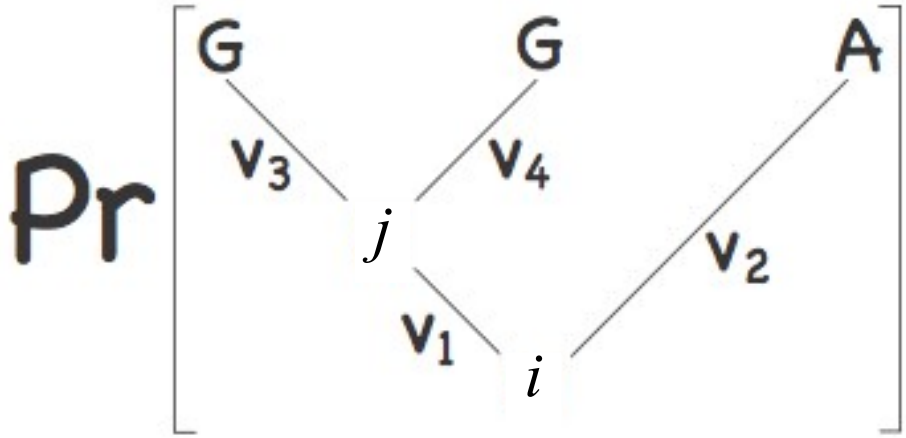
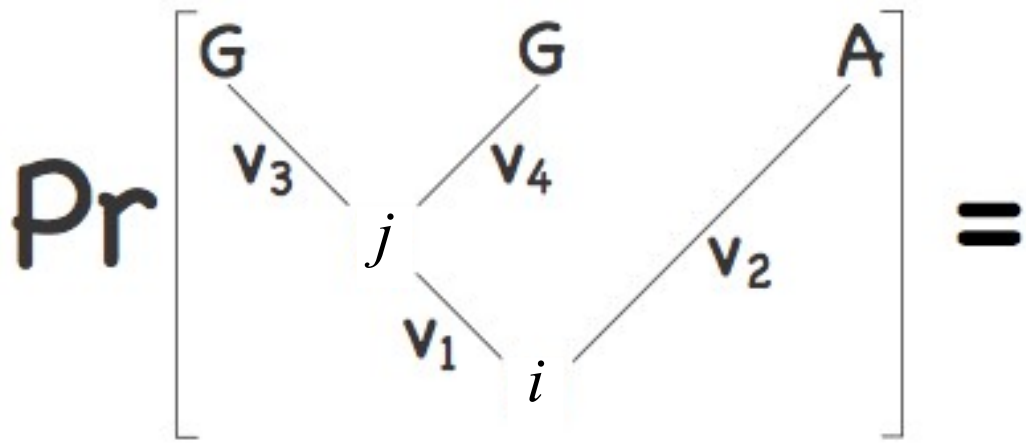



$$\pi_i \times p_{ij}(v_1) \times p_{iA}(v_2) \times p_{jG}(v_3) \times p_{jG}(v_4)$$

| | |
|---|---|
| $\pi_i$ | Stationary frequencies |
| $p_{ij}(v)$ | Transition probabilities |

# Stochastic Models of Nucleotide Substitution




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

| | |
|---|---|
| $\pi_i$ | 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)

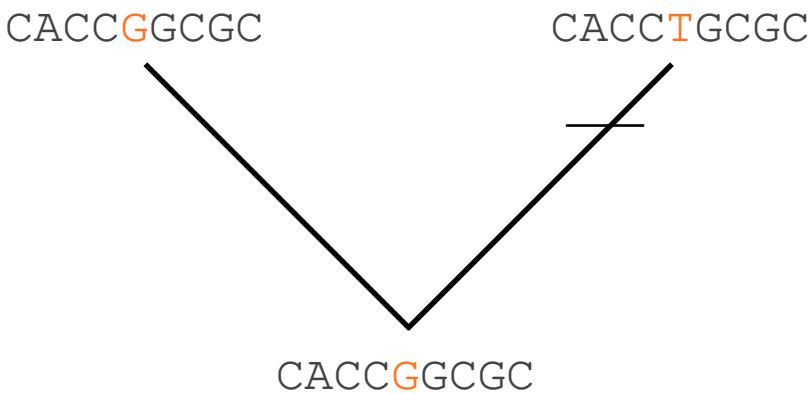
***We will introduce:***

- ***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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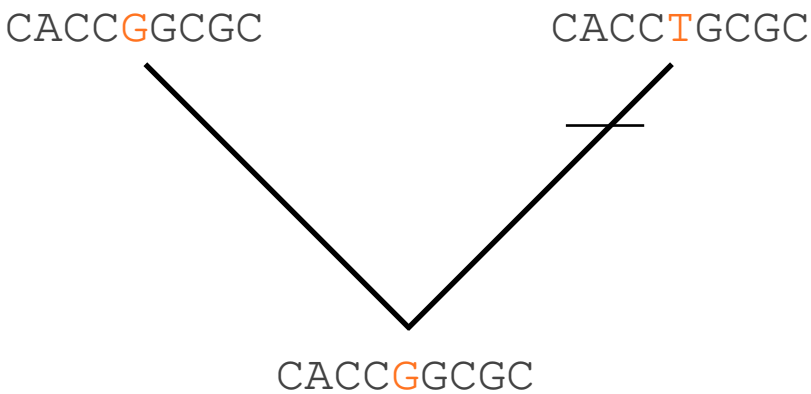


We are modeling the process of **nucleotide substitution**, which describes the outcome of the mutation and fixation processes within populations

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- 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.

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A hypothetical instantaneous-rate matrix

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|---|---|---|---|---|---|
| | | A | C | G | T |
| From | 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 |
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The rows of the table must sum to zero.

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# A Mechanistic Interpretation of the Rate Matrix

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

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

# 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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## 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**:

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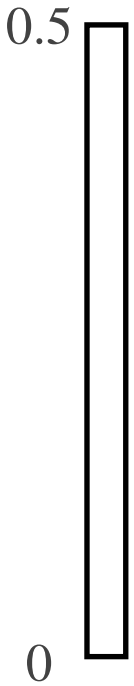


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0.5

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the instantaneous-rate matrix is known

0

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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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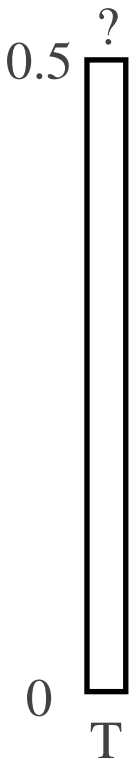


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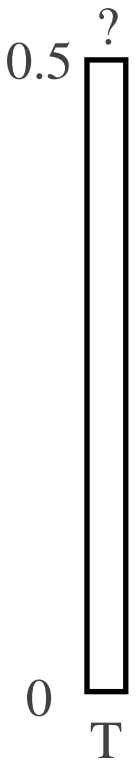


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Rate of leaving the current state, $T = 1.355$

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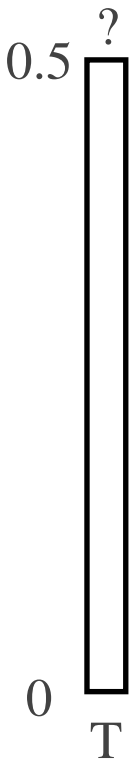


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Probability of changing to A:

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

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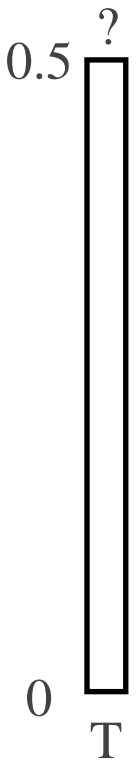


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Probability of changing to C:

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

$$P(T\text{->}C) = q_{TC} / -q_{TT} = 0.236 \;|\; 1.355 = 0.174$$

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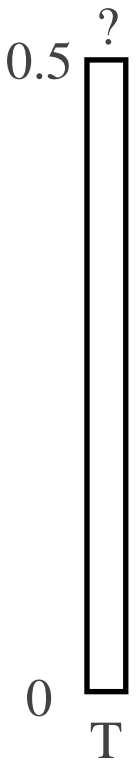


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Probability of changing to G:

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

$$P(T\text{->}C) = q_{TC}/-q_{TT} = 0.236 \;|\; 1.355 = 0.174$$

$$P(T\text{->}G) = q_{TG}/-q_{TT} = 0.594 \;|\; 1.355 = 0.438$$

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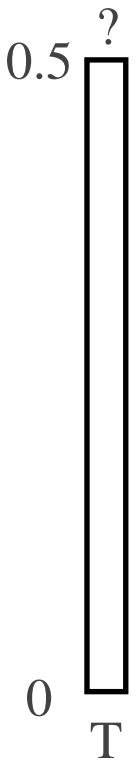


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Generate an exponentially distributed waiting time, $x$:

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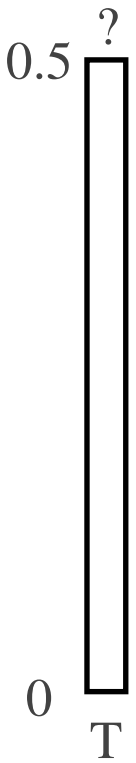


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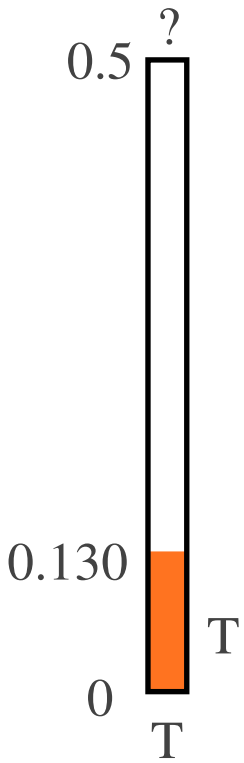


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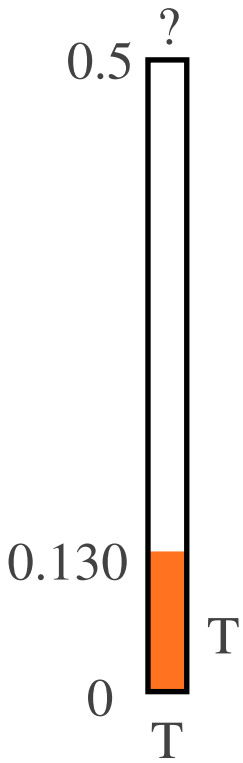
rate when process is in T: $\lambda = 1.355$

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

# 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

Probabilities of substitution events in state T:

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

$$P(T\text{->}C) = q_{TC}/-q_{TT} = 0.236 \;|\; 1.355 = 0.174$$

$$P(T\text{->}G) = q_{TG}/-q_{TT} = 0.594 \;|\; 1.355 = 0.438$$

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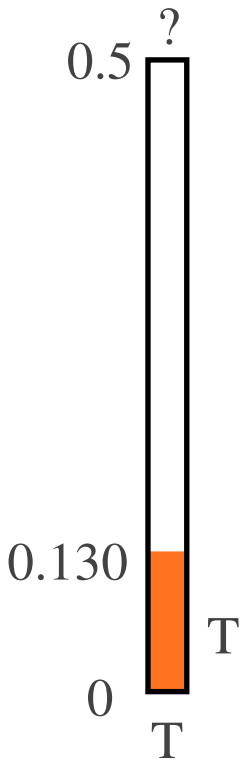


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Generate an exponentially distributed waiting time, $x$:

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

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

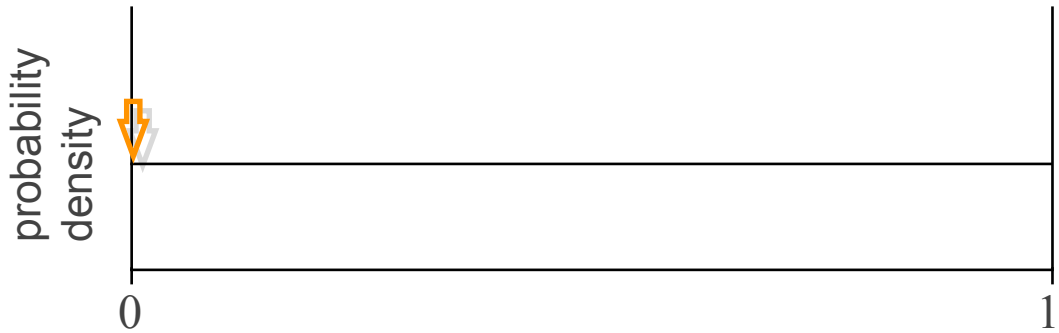
Specify a set of intervals:

| | intervals | |
|---|---|---|
| P(T->A) = 0.387 | 0 – 0.387 | (choose A) |
| 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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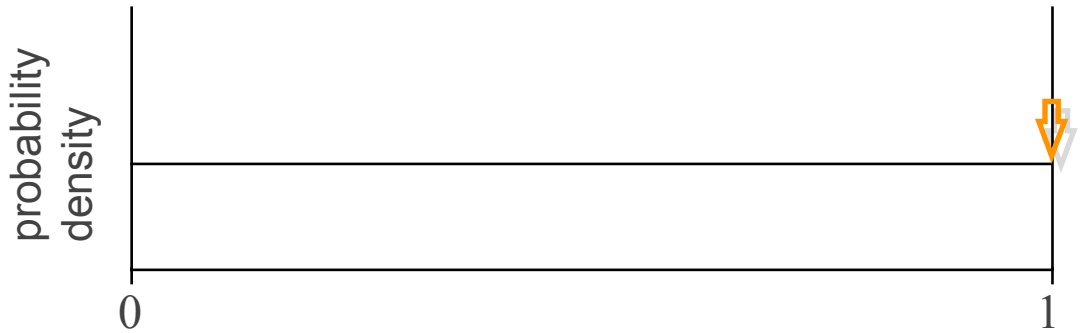

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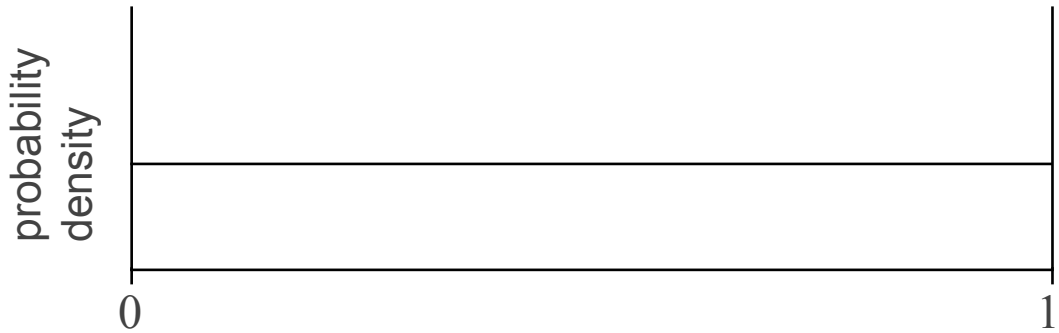


Imagine that there are two possible outcomes, $\mathrm{A}$ and $\mathrm{B}$, which occur with probabilities:

Probability of outcomes:

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

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

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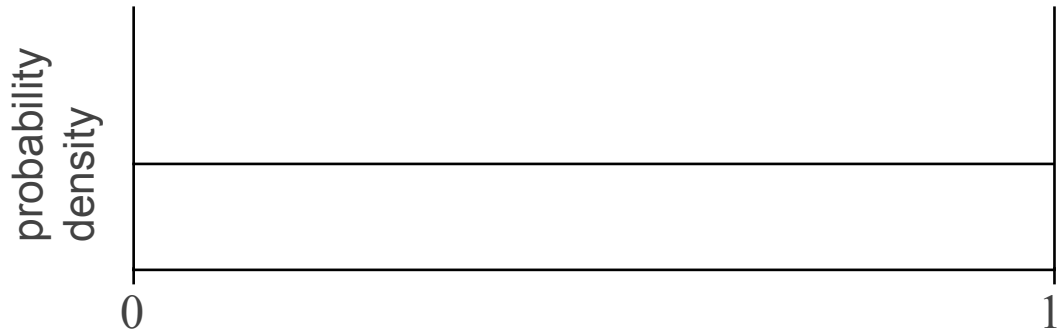


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We can choose randomly (according to their probabilities) by specifying these intervals…

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

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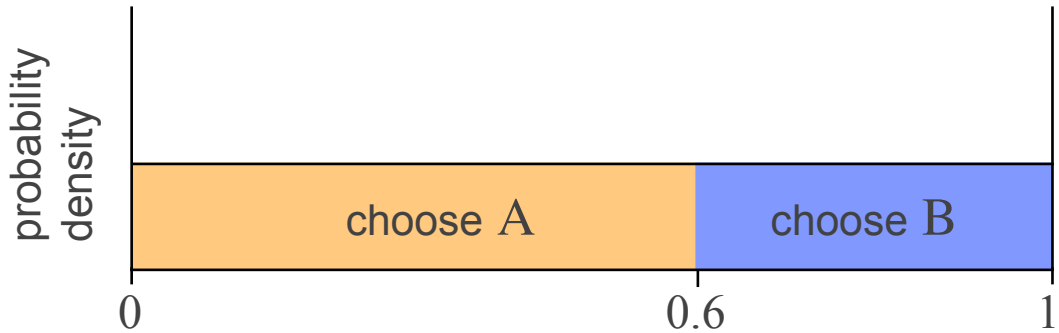


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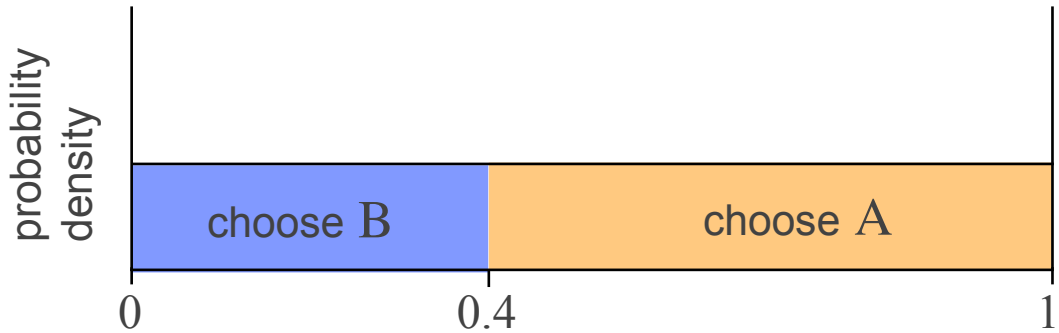


Imagine that there are two possible outcomes, $\mathrm{A}$ and $\mathrm{B}$, which occur with probabilities:

Probability of outcomes:

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

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

Or equivalently by specifying these intervals…

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

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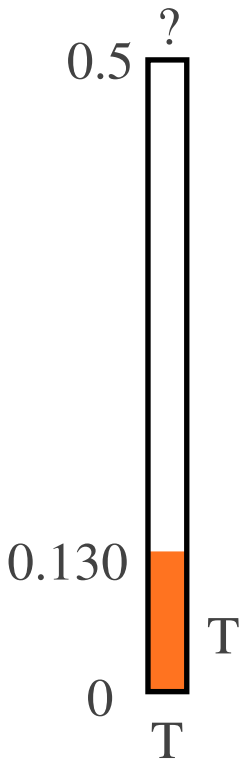


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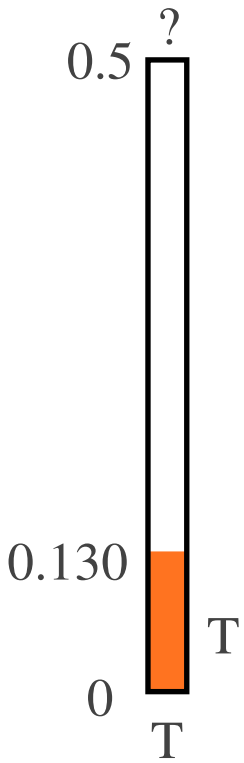


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Draw a uniformly distributed number, $u$, to select substitution event:
`u~dnUniform(0,1)` : u=0.446

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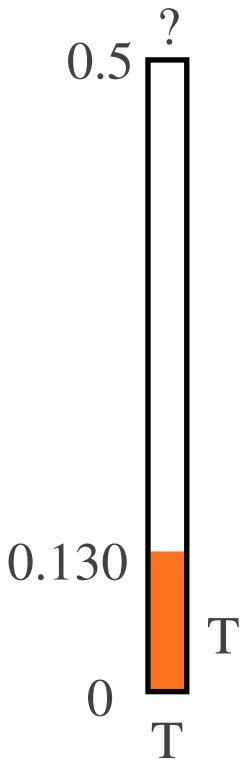


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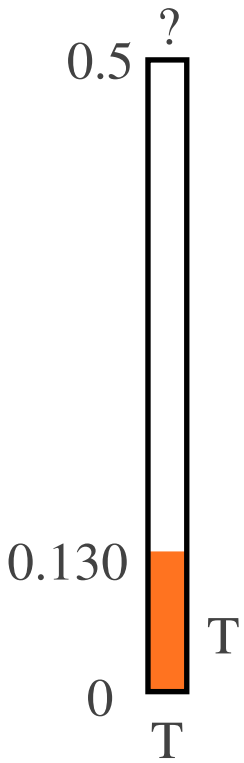


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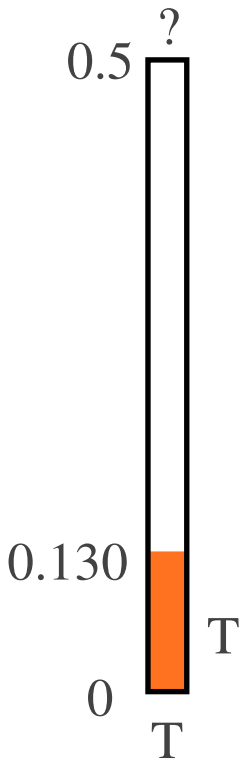


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Rate when process in state C: $-q_{cc} = \lambda = 1.069$

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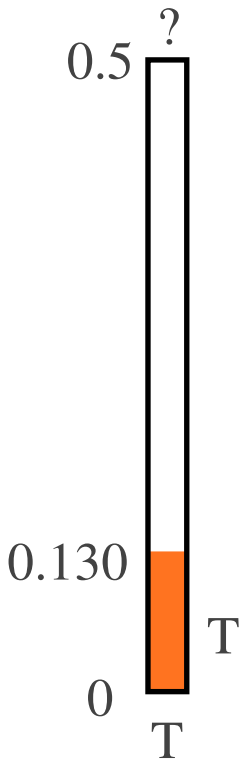


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Draw x: `x~dnExponential(1.069)` : x = 0.076

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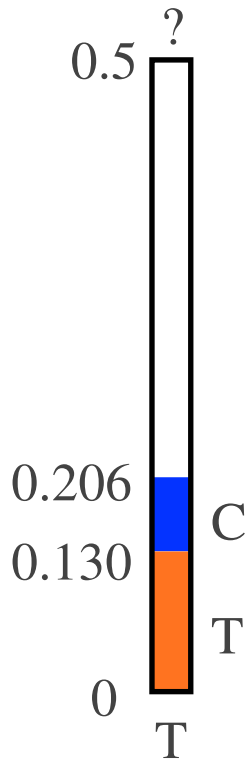


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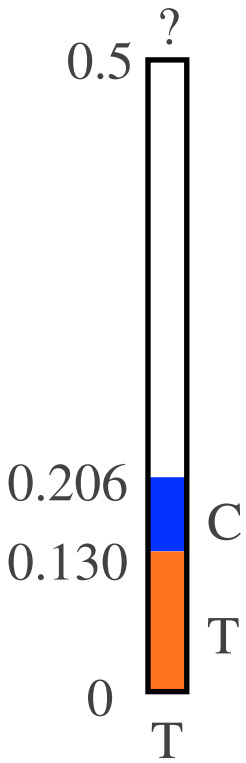


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Substitution probabilities in state C:

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

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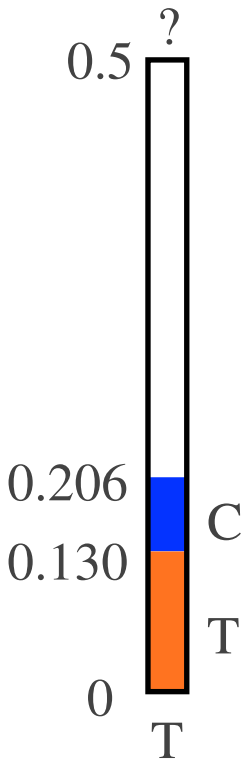


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Substitution probabilities in state C:

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

$$P(C\text{->}G) = q_{CG}/-q_{cc} = 0.415 \;|\; 1.069 = 0.388$$

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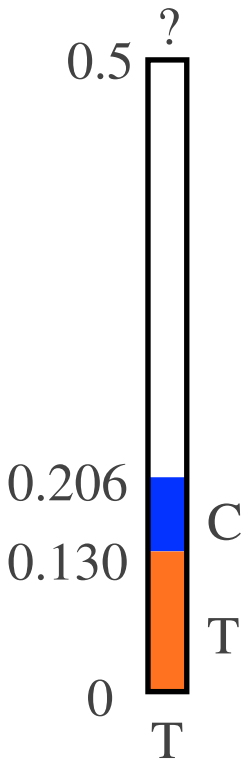


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$$P(C\text{->}T) = q_{CT}/-q_{cc} = 0.506 \;|\; 1.069 = 0.474$$

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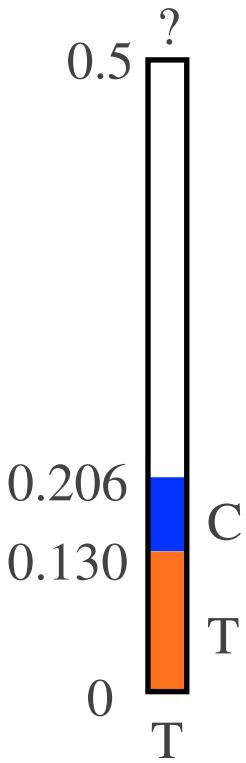


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Draw x: `x~dnExponential(1.069)` : x = 0.076

| 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) |

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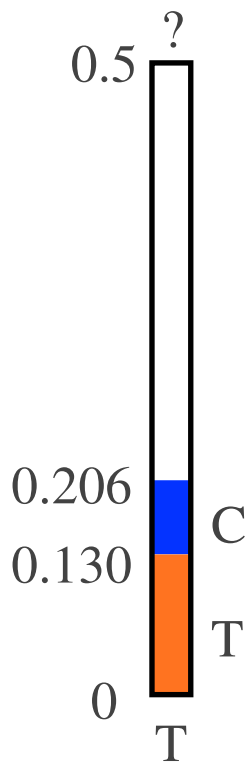


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Draw a uniformly distributed number, $u$, to select substitution event:
`u~dnUniform(0,1)` : u=0.317

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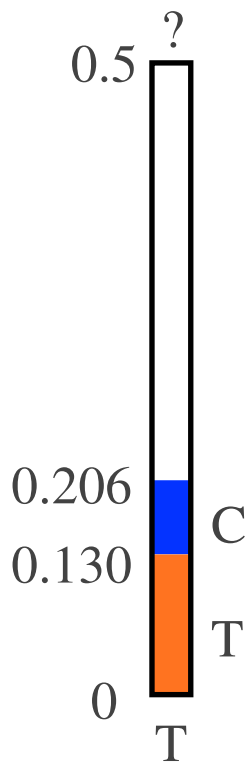
## A simple Monte Carlo Simulation

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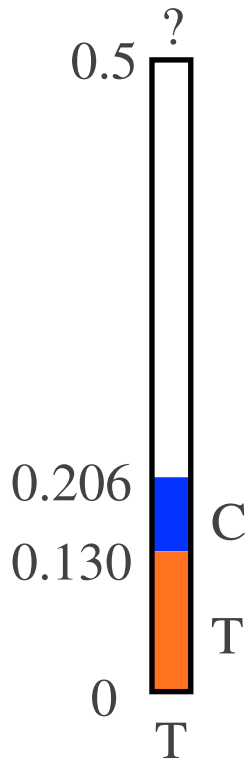


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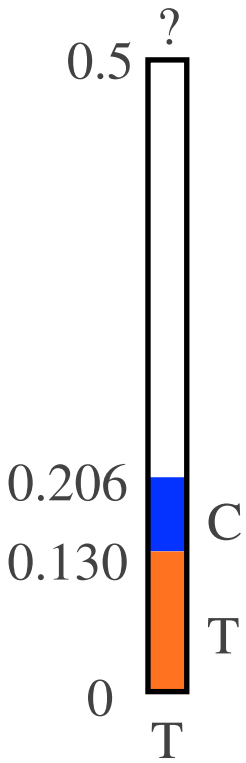


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Generate waiting time to next event:

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

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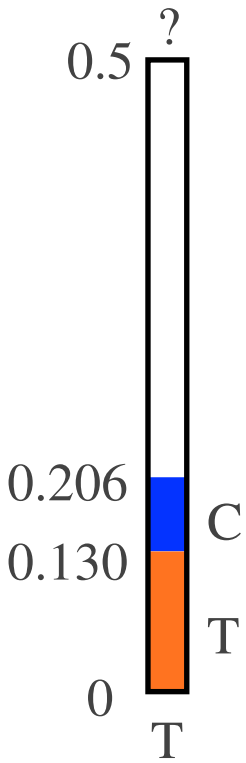


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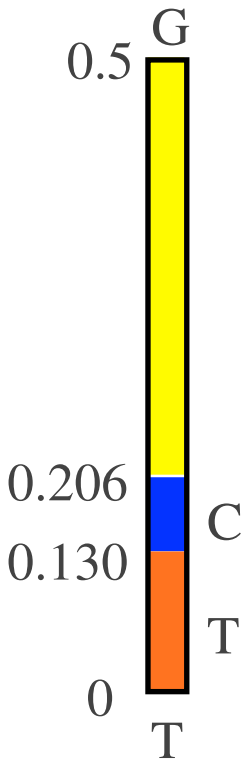
# A Mechanistic Interpretation of the Rate Matrix

## 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: $-q_{GG} = \lambda = 0.591$

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

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T → C → G

Ended in G with two changes

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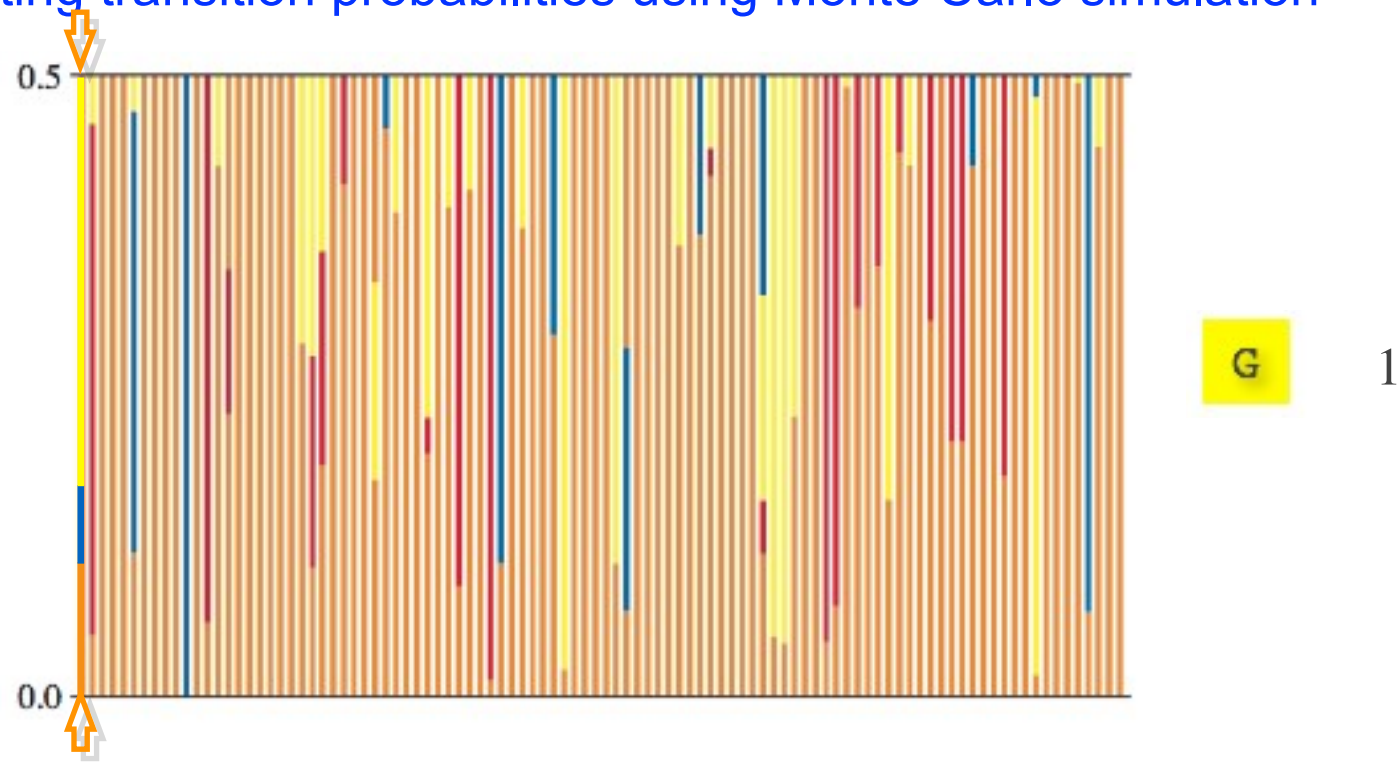


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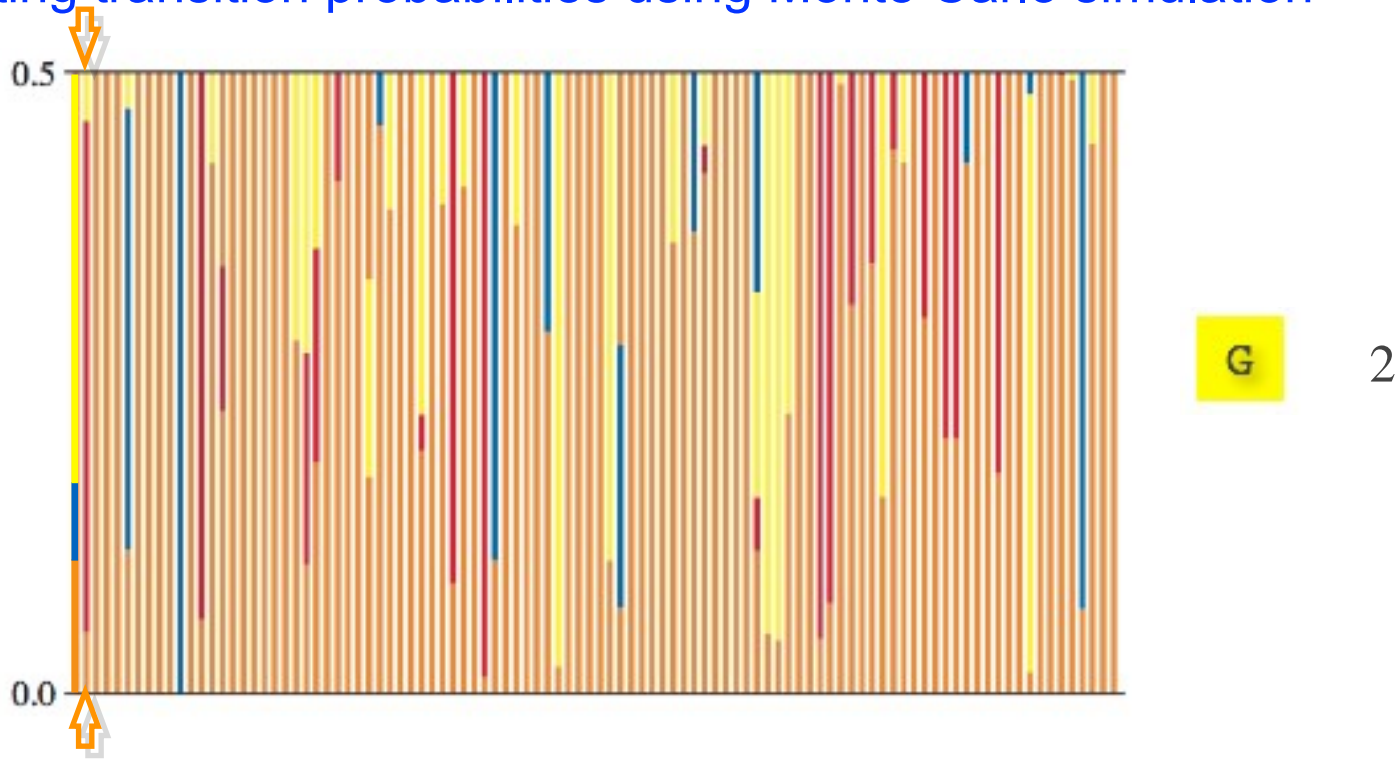


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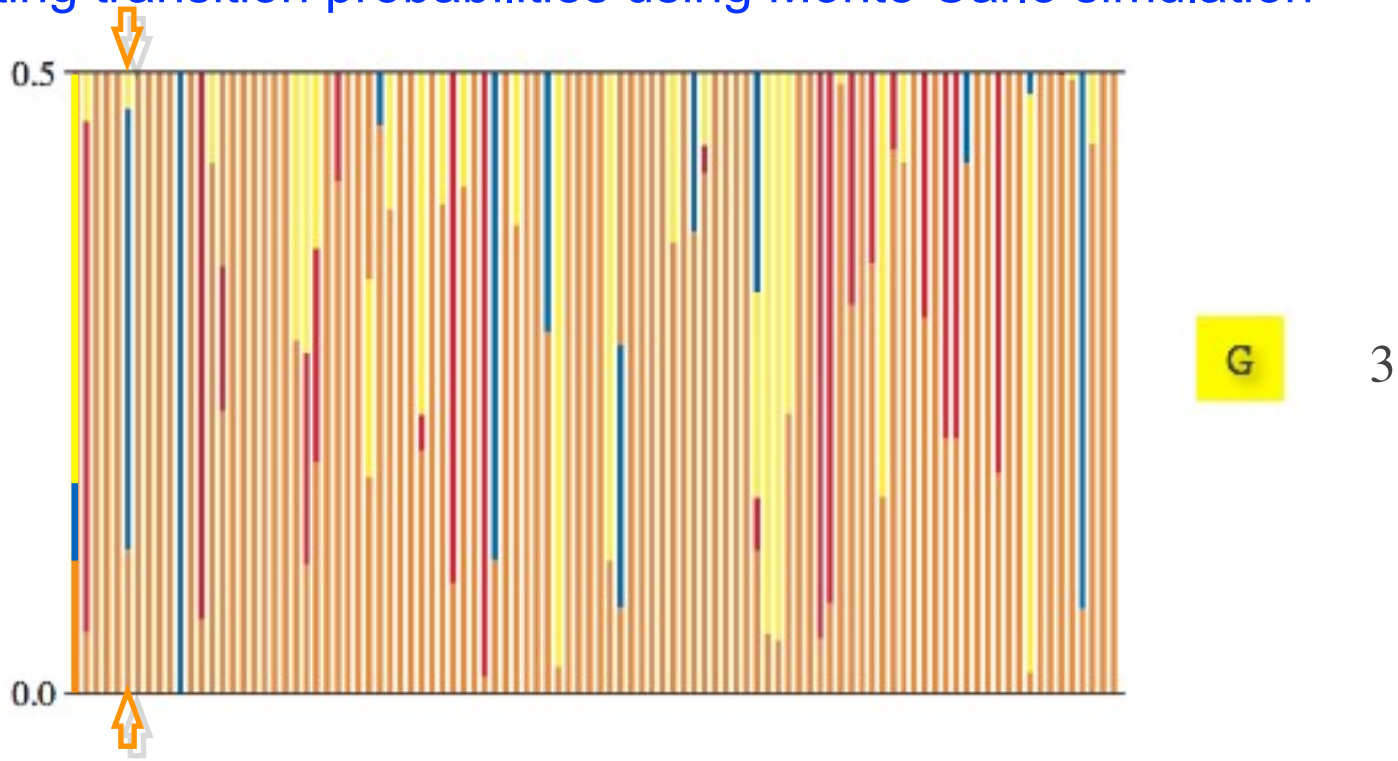


T → C → G

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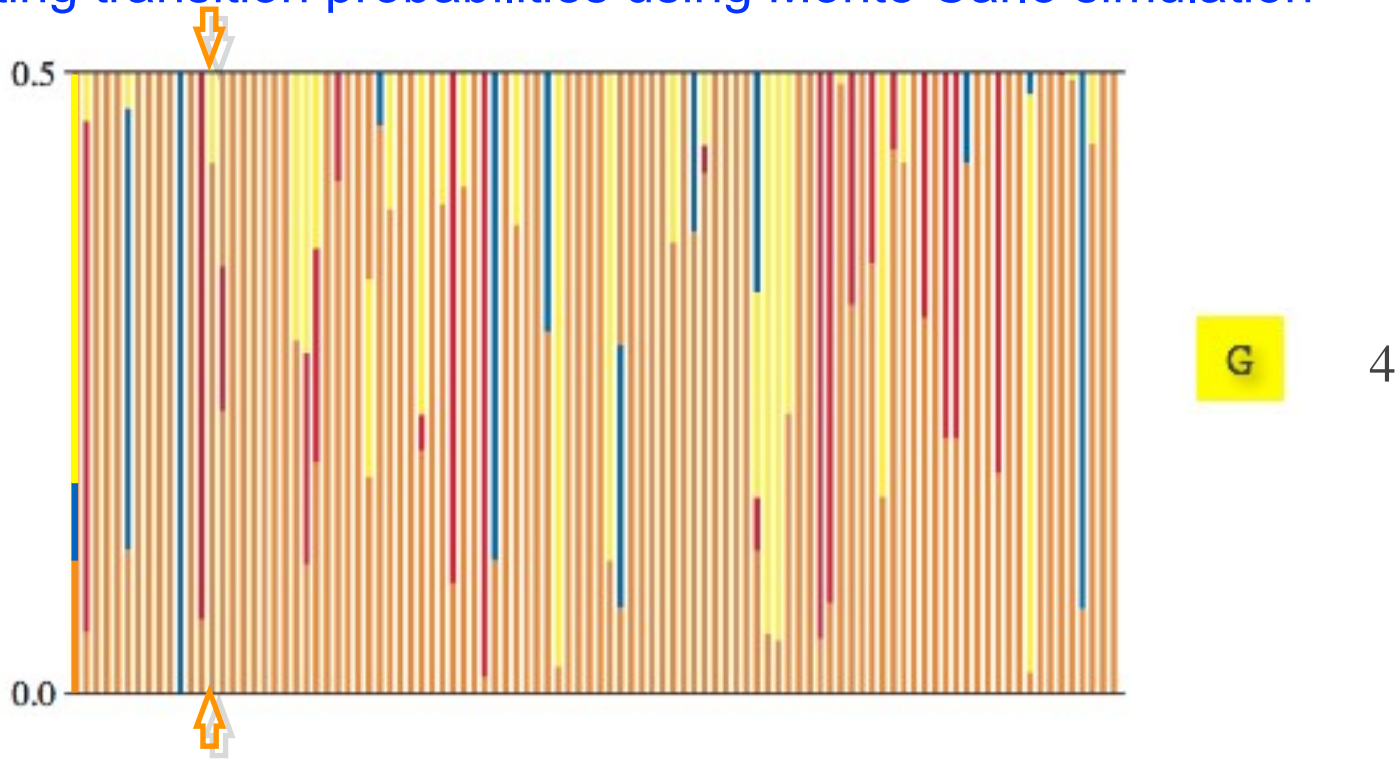


T→ G

Ended in G with one change

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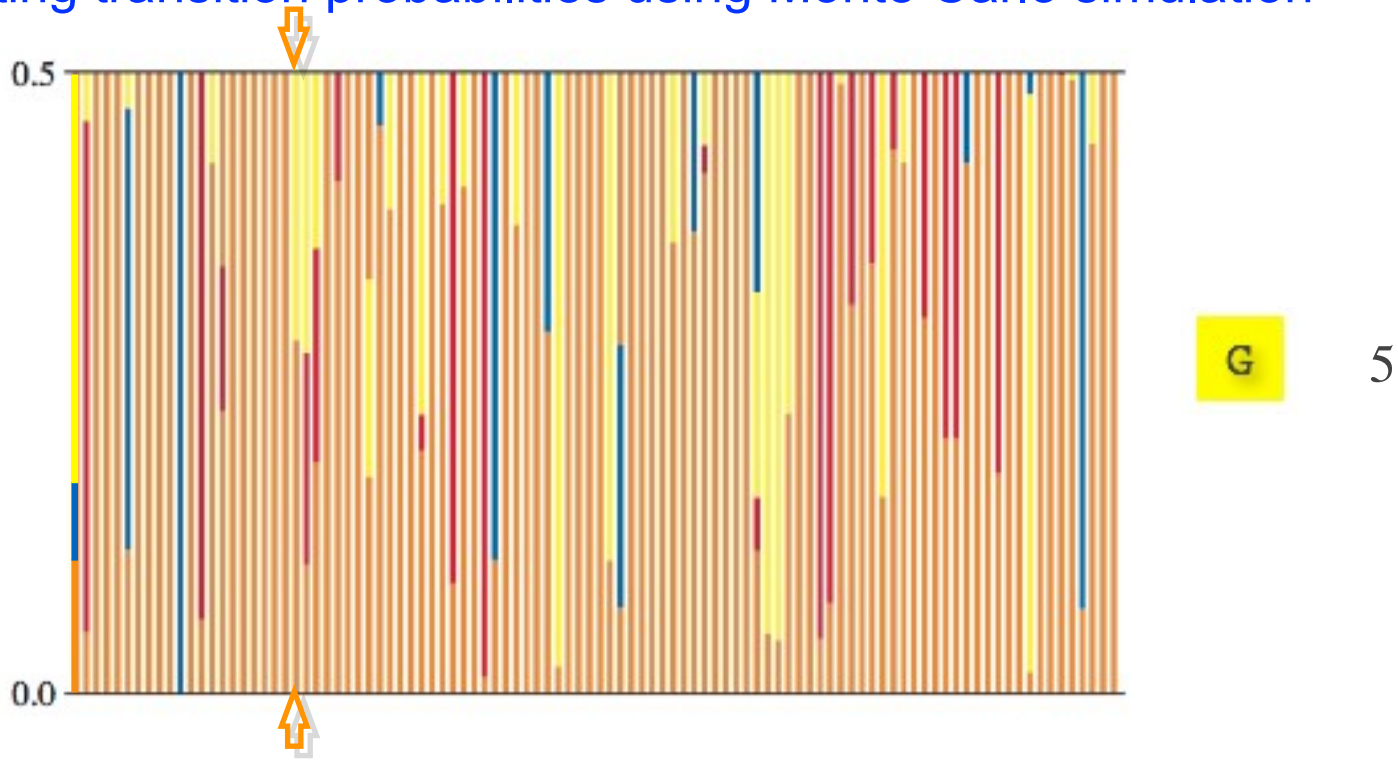


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Ended in G with one change

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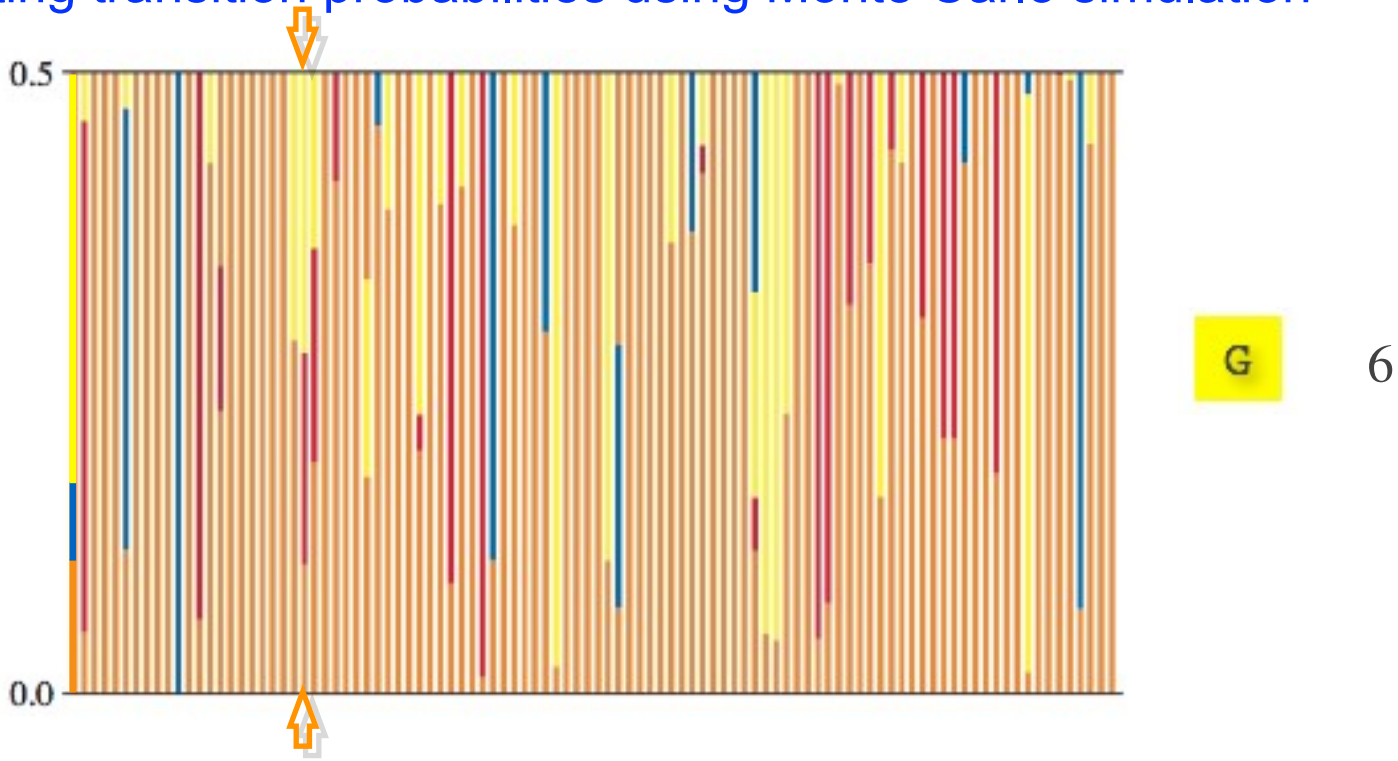


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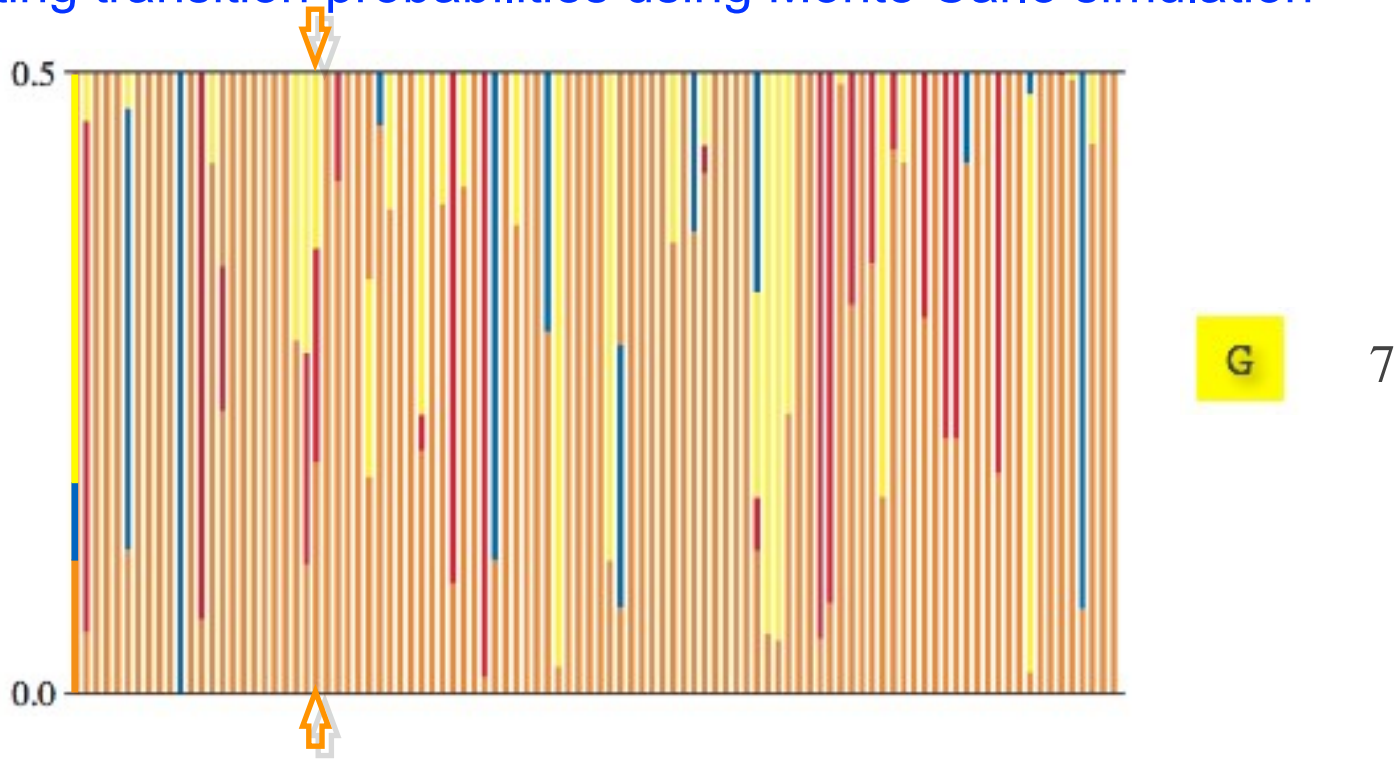


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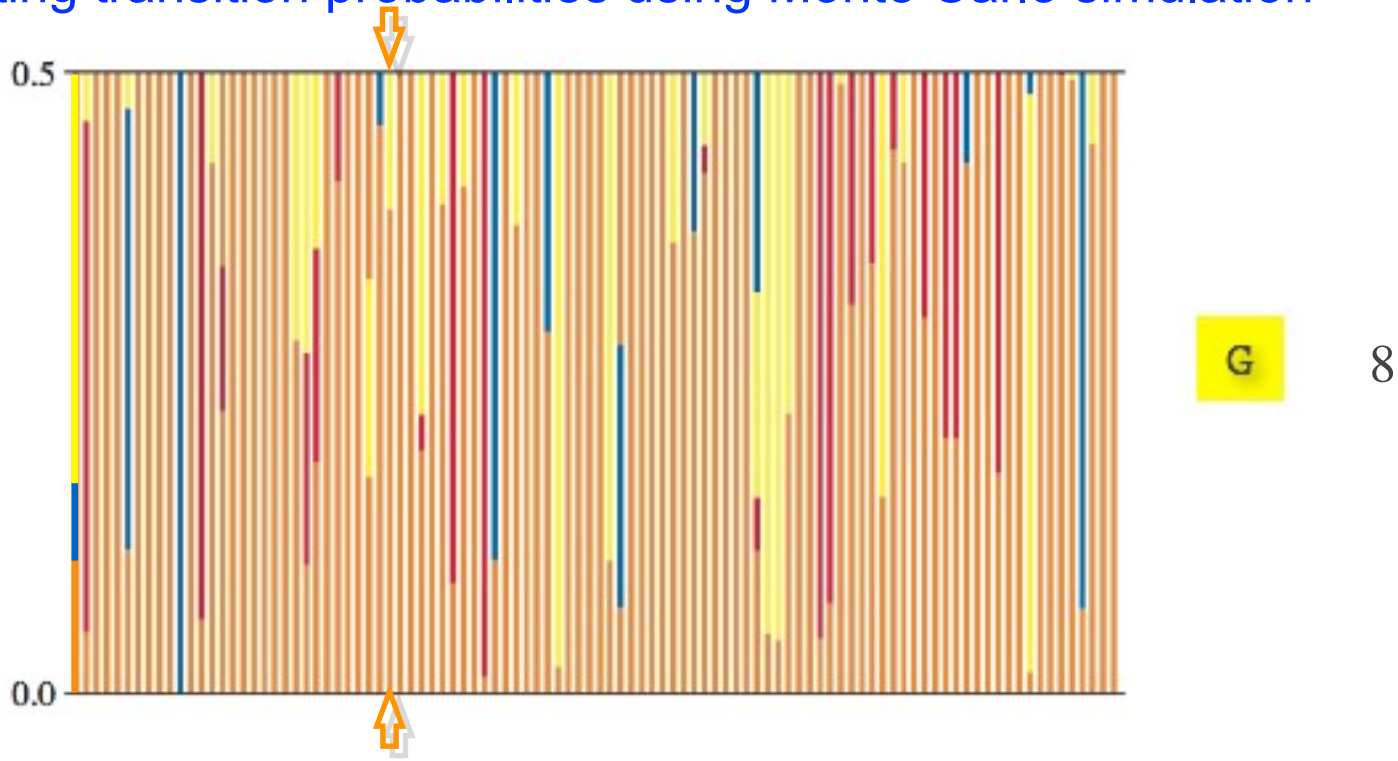


T→ G

Ended in G with one change

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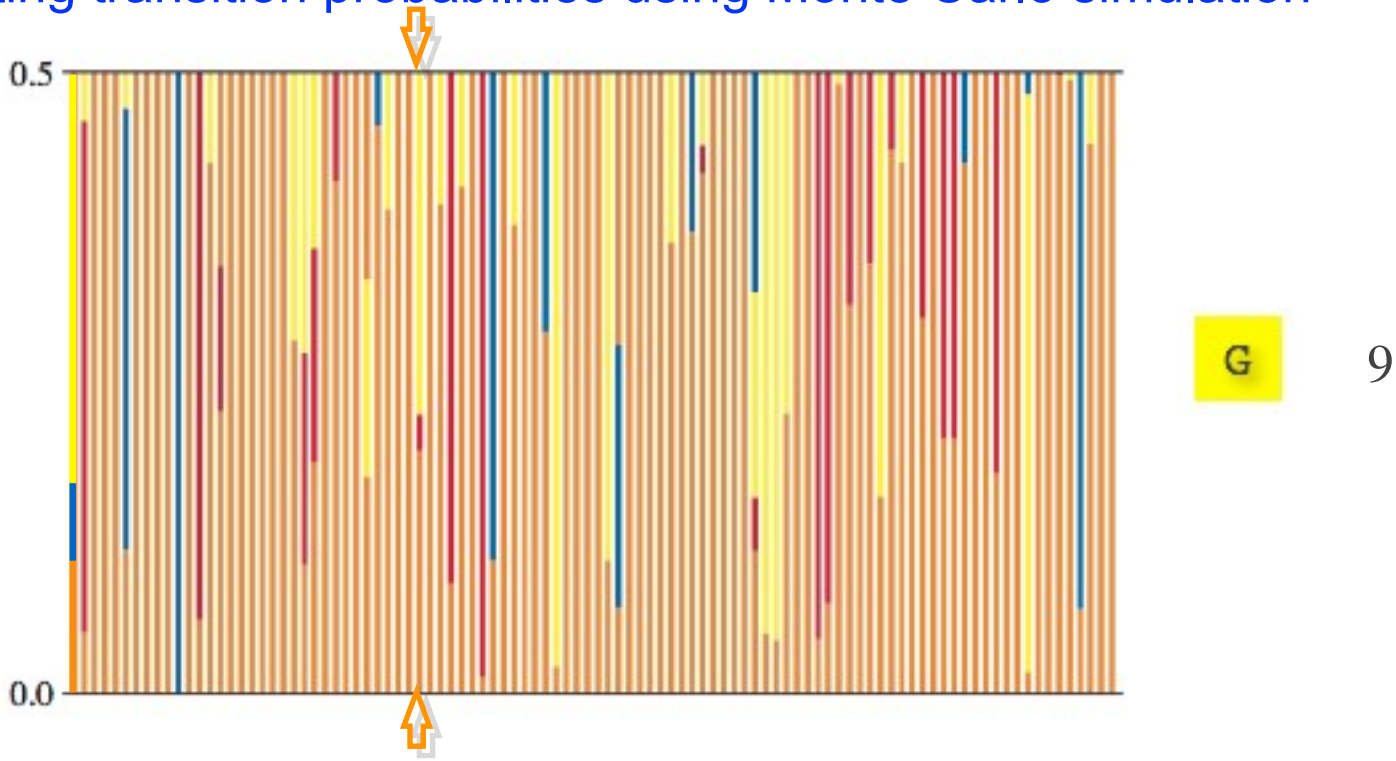


9

T→ G

Ended in G with one change

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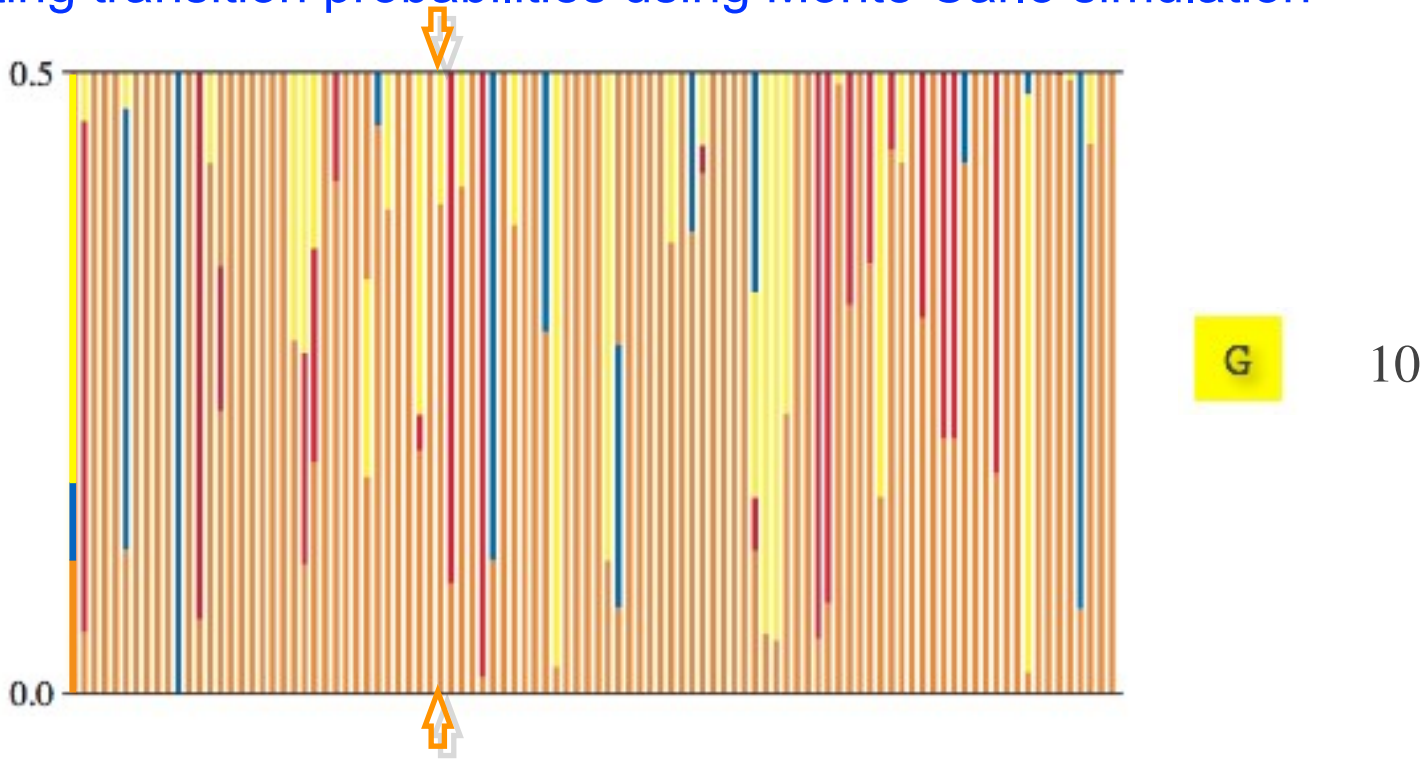


T→ G

Ended in G with one change

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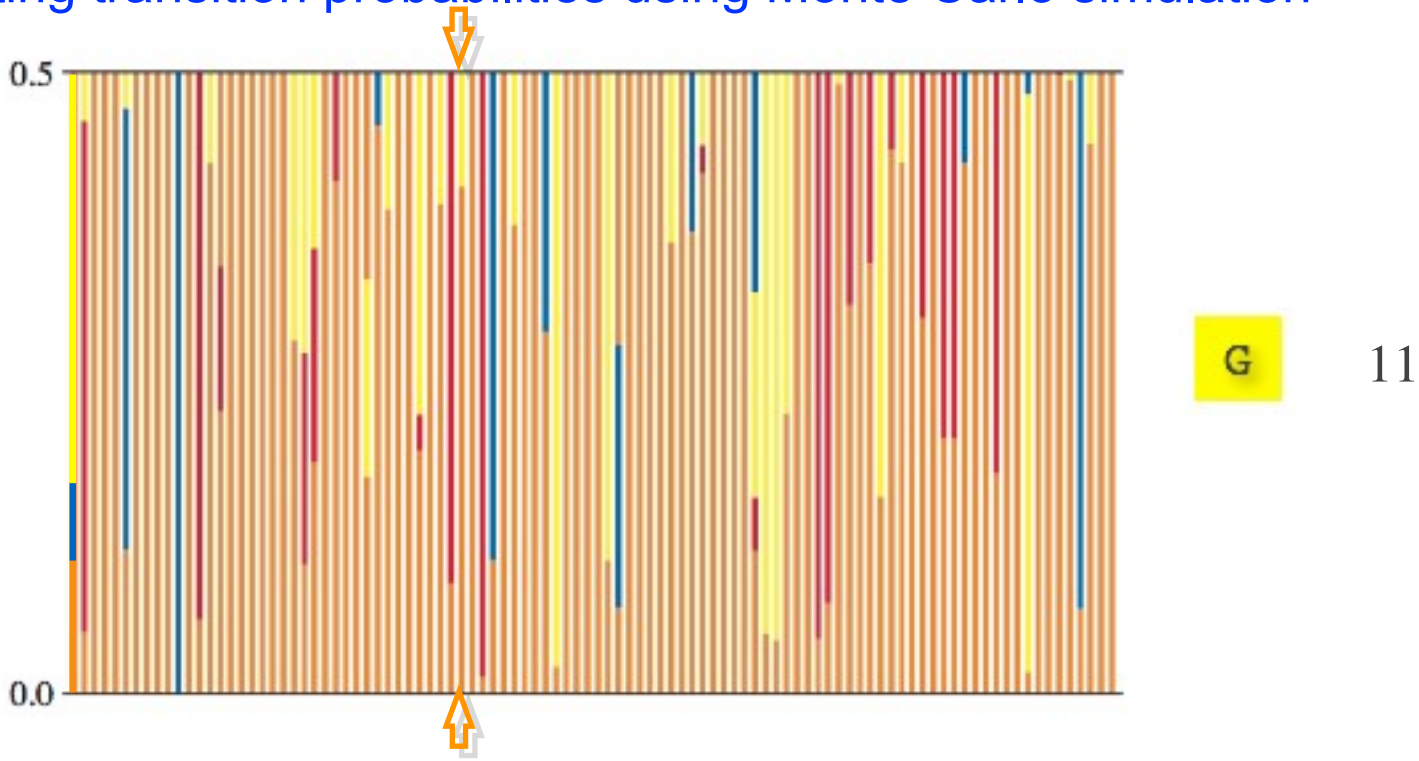


T→G

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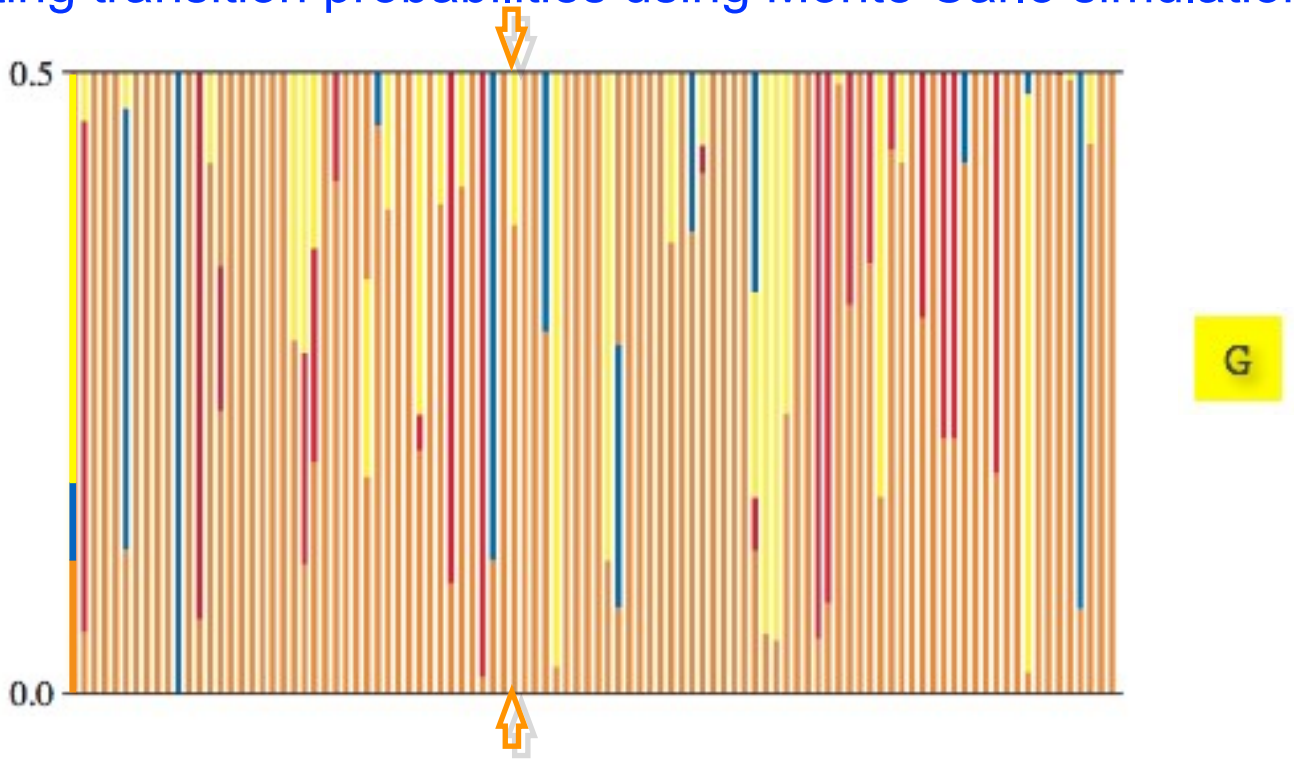


G

12

T→ G

Ended in G with one change

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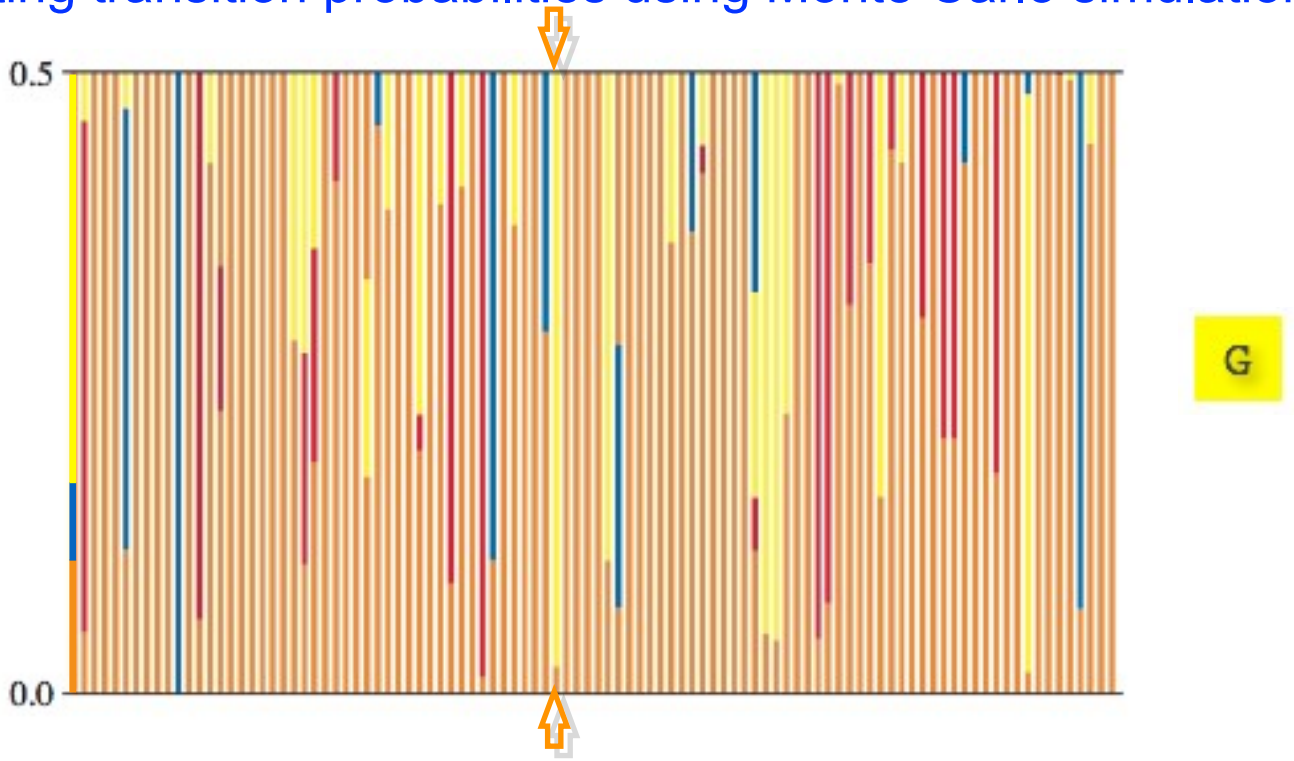
Estimating transition probabilities using Monte Carlo simulation




G

13

T→G

Ended in G with one change

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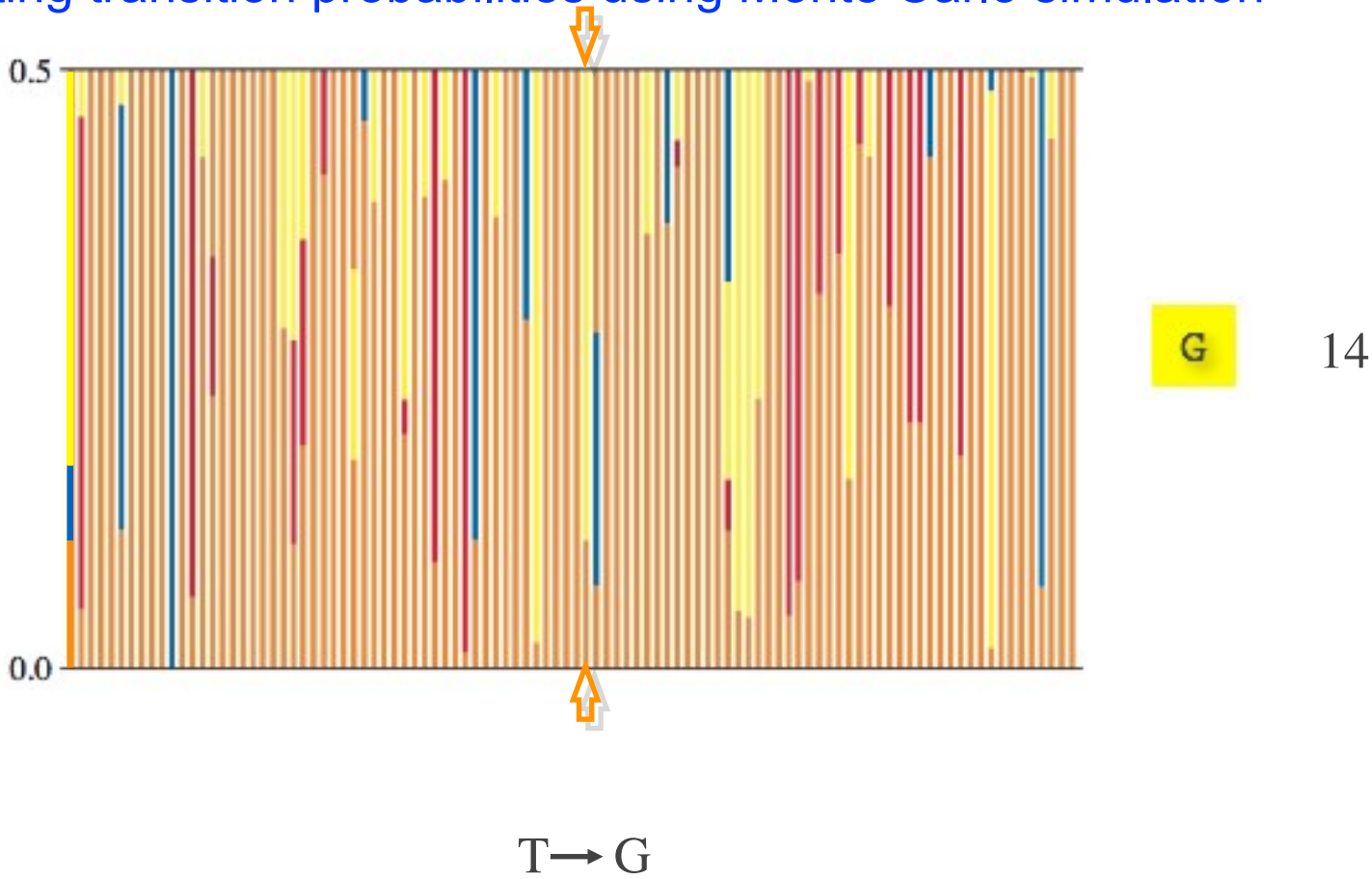
Estimating transition probabilities using Monte Carlo simulation

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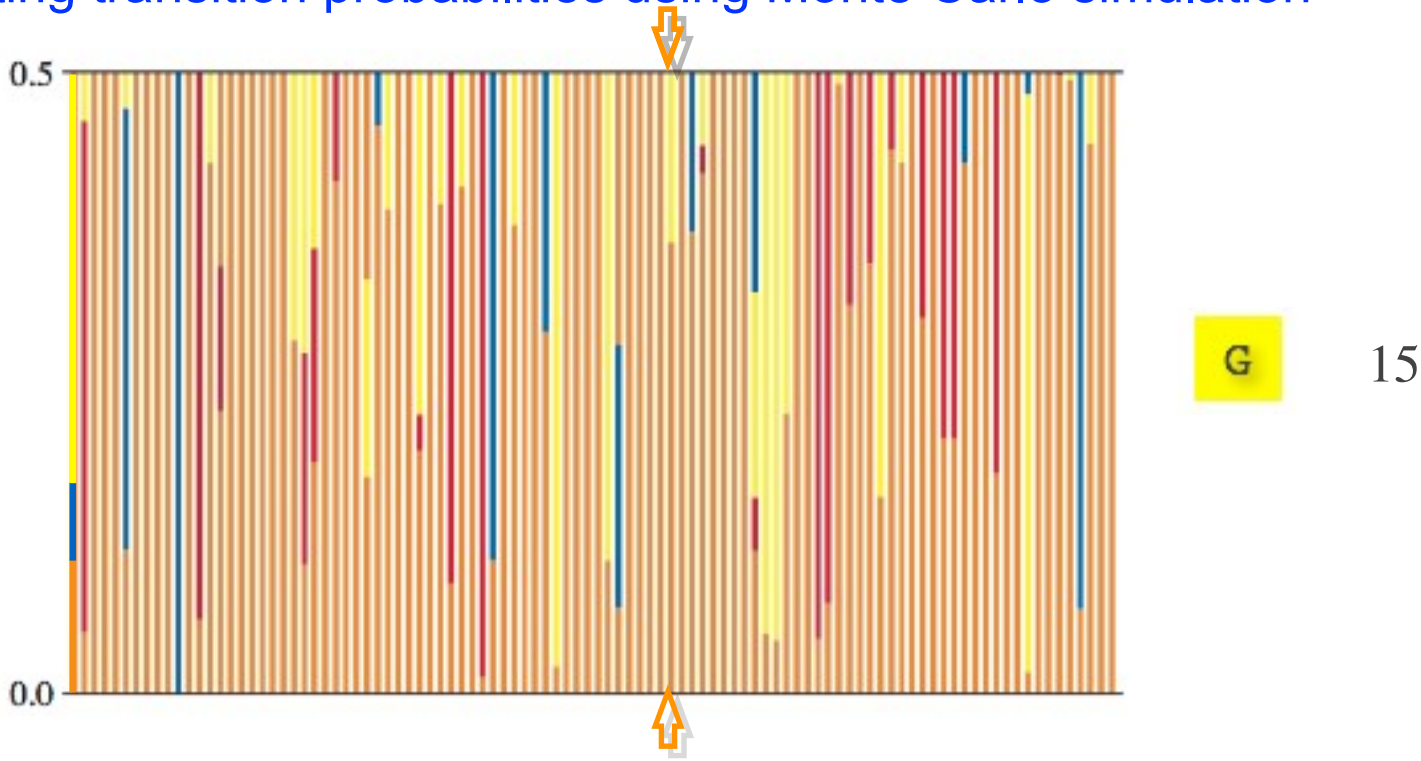


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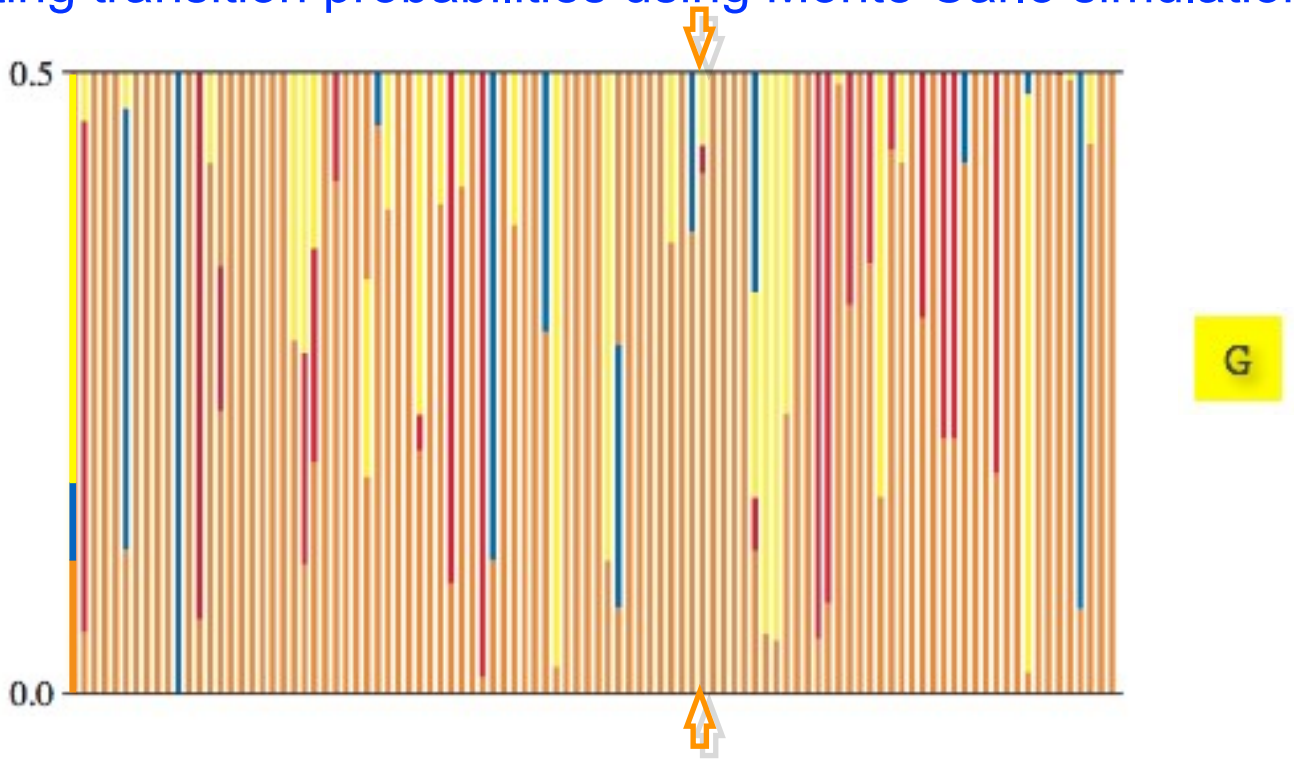


16

T → A → G

Ended in G with two changes

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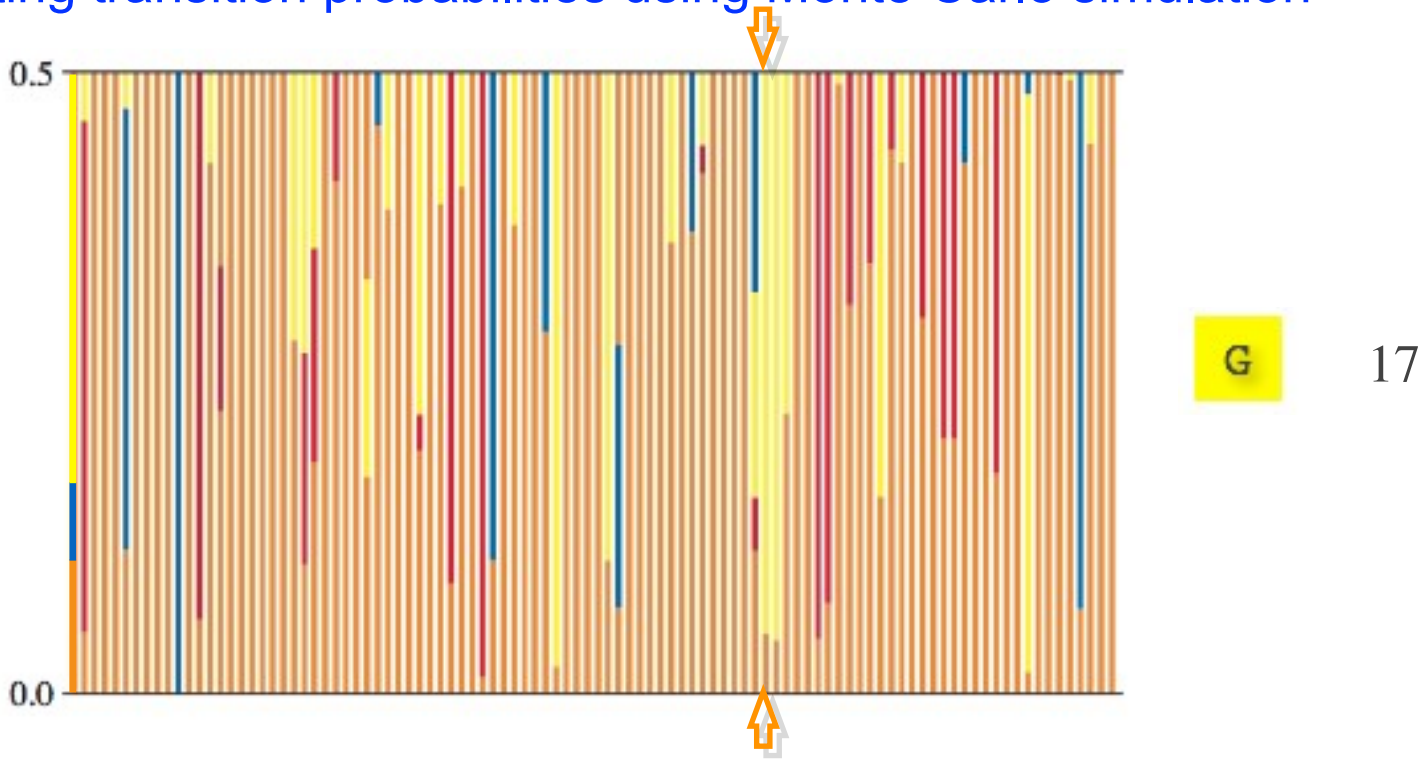
Estimating transition probabilities using Monte Carlo simulation




T→G

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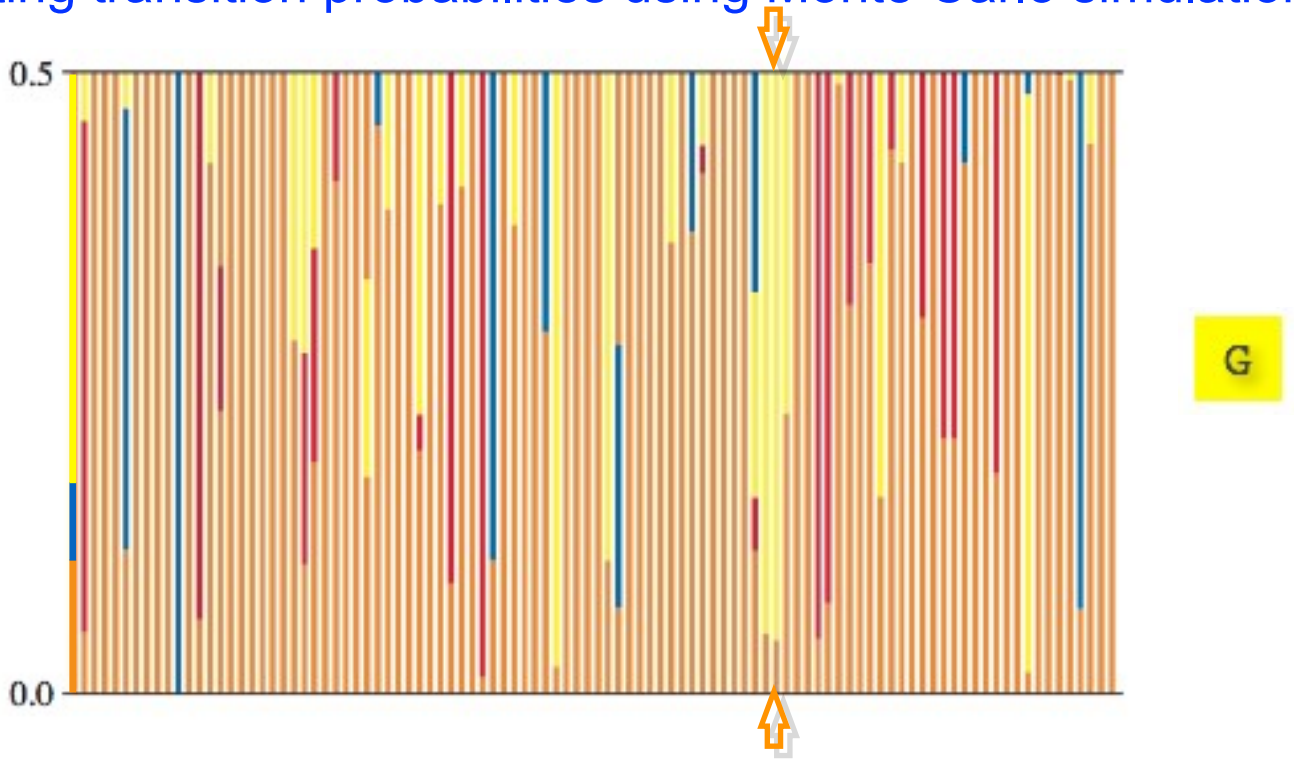


G

18

T→ G

Ended in G with one change

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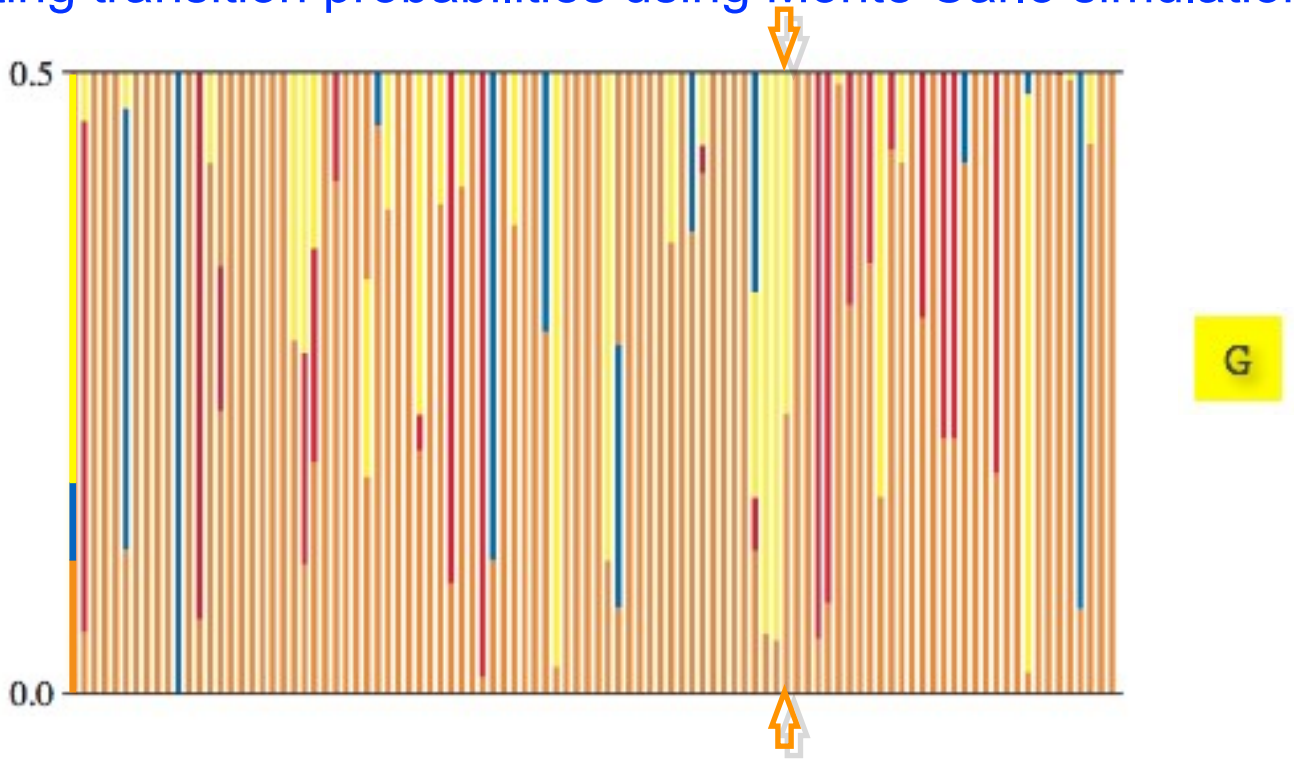


G

19

T→G

Ended in G with one change

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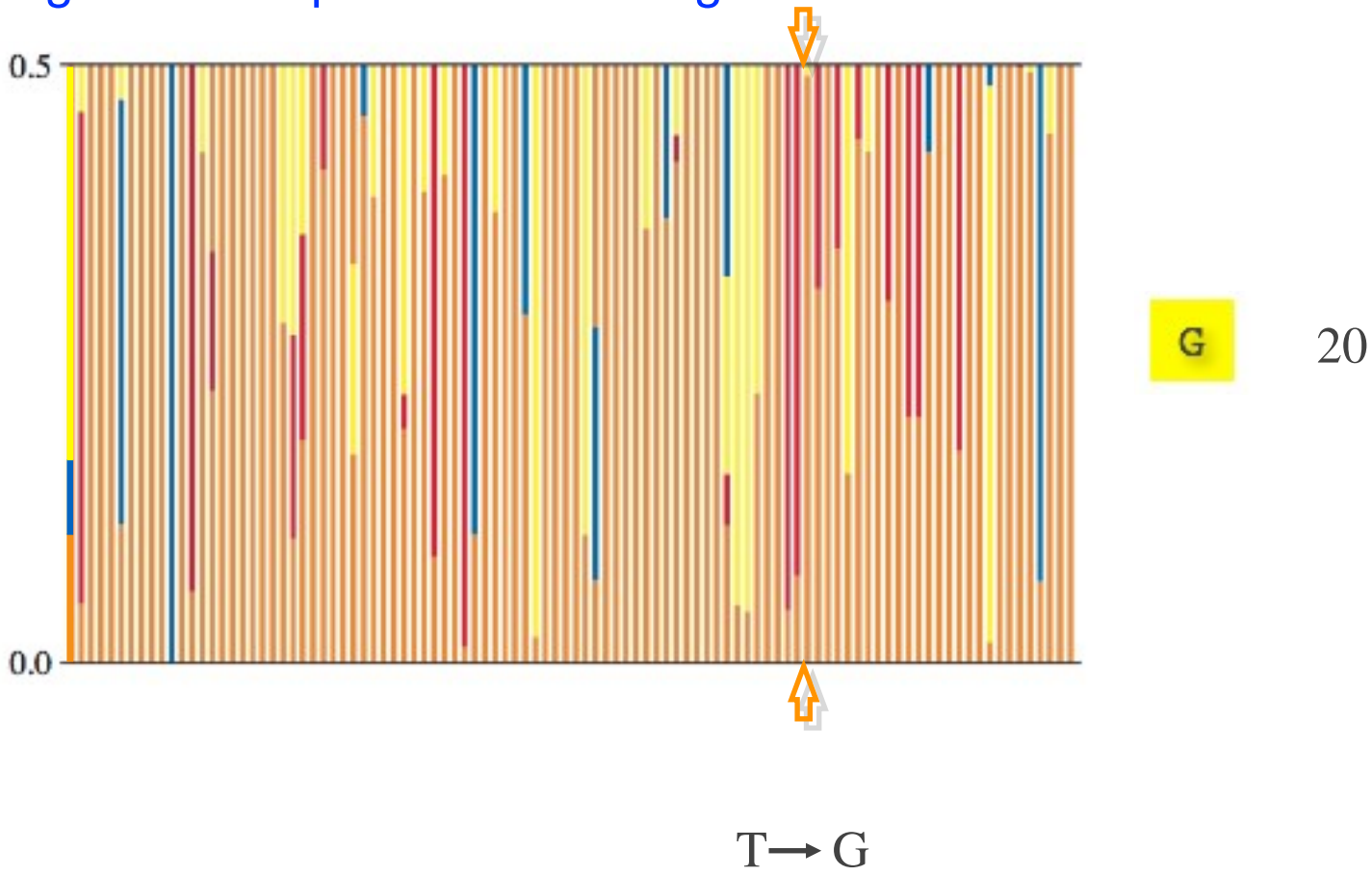


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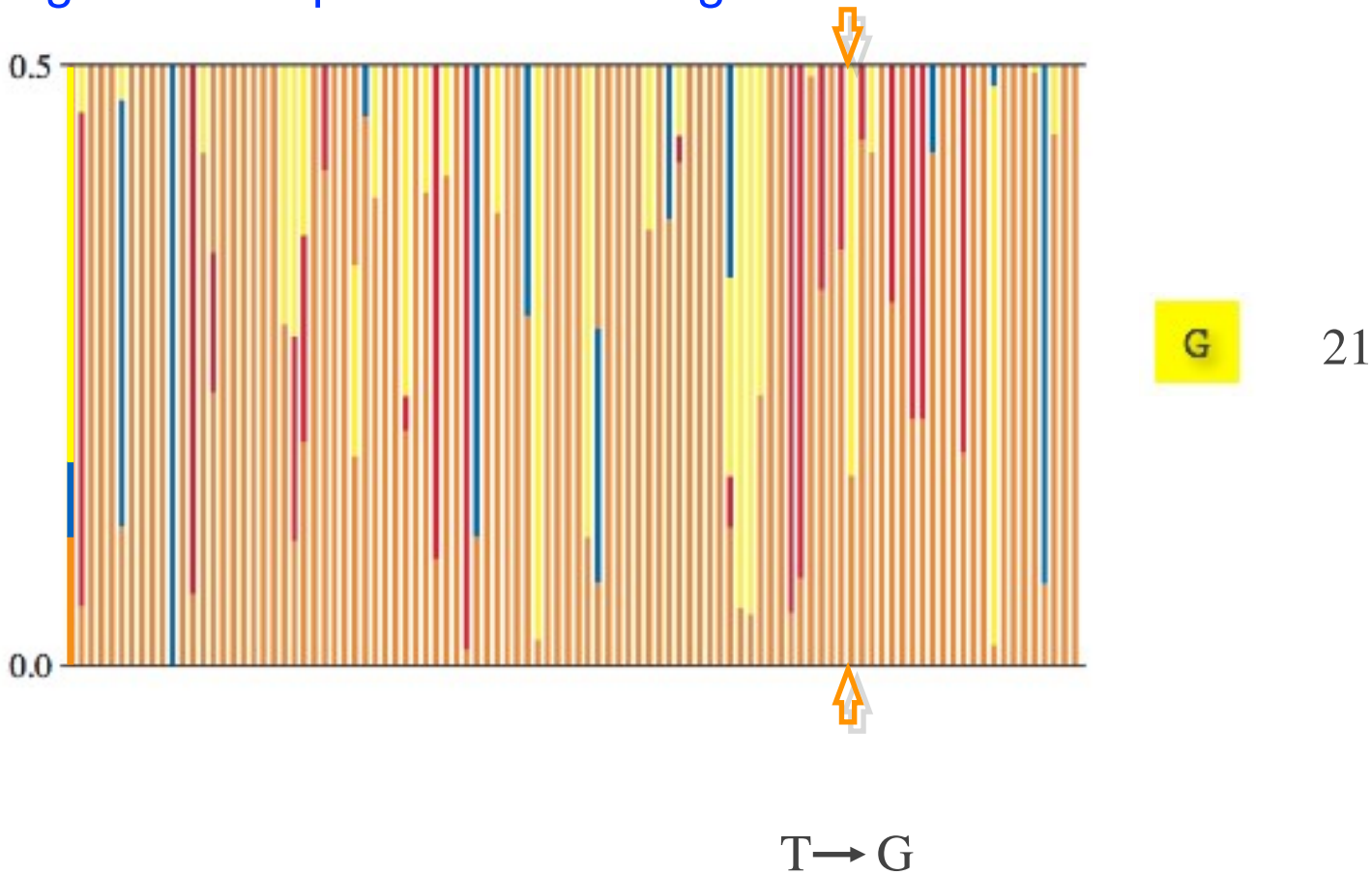


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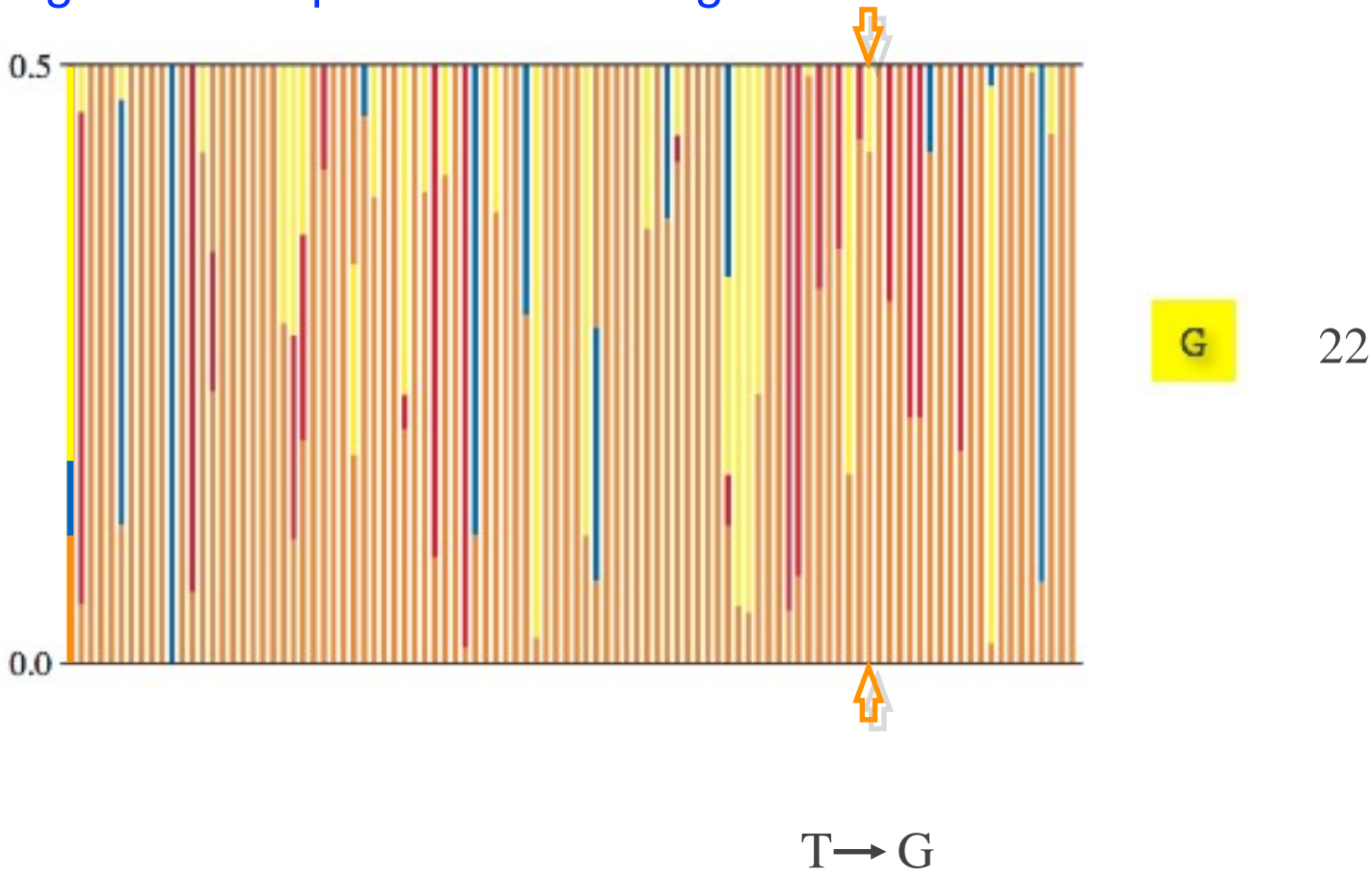


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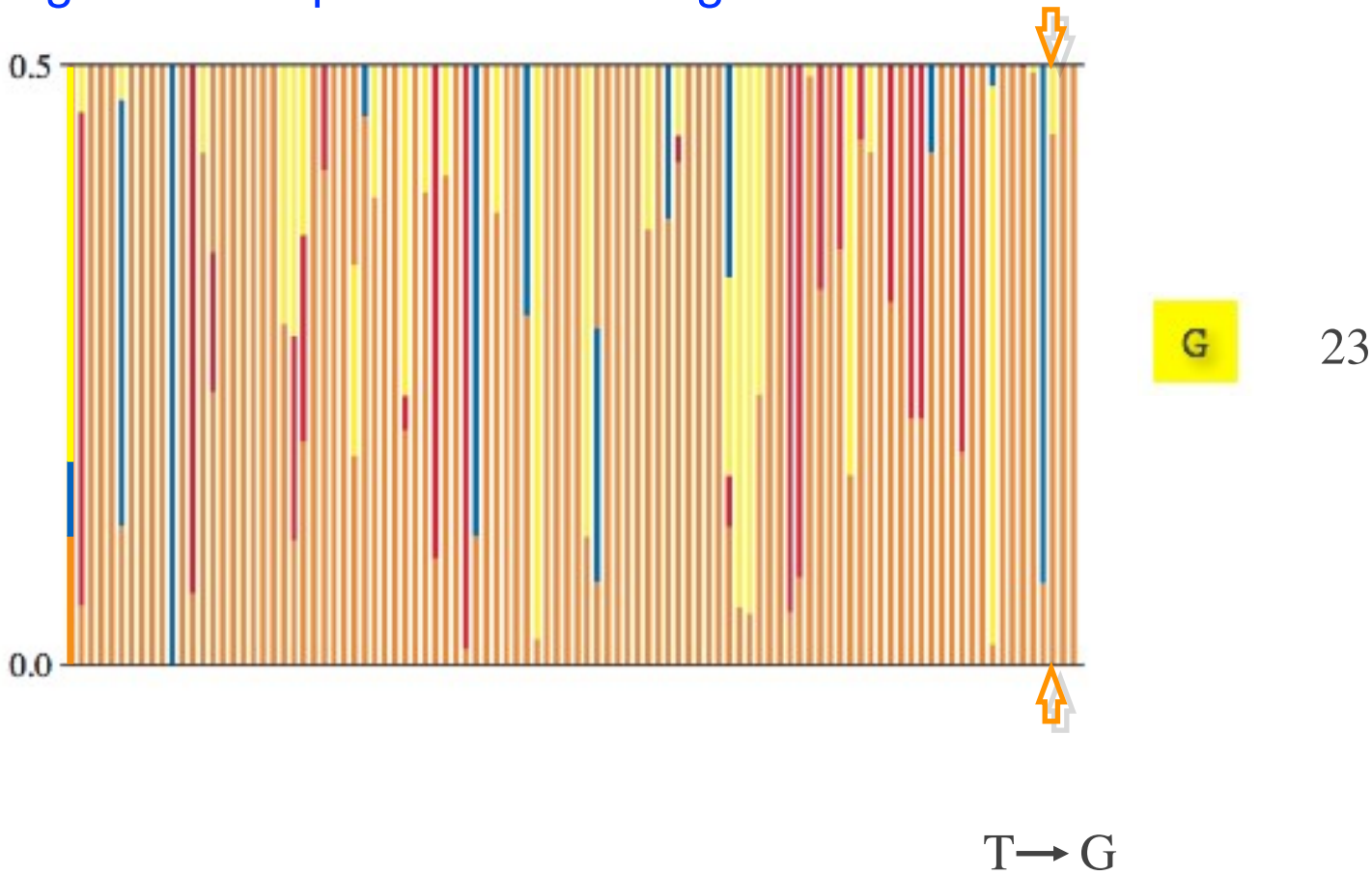


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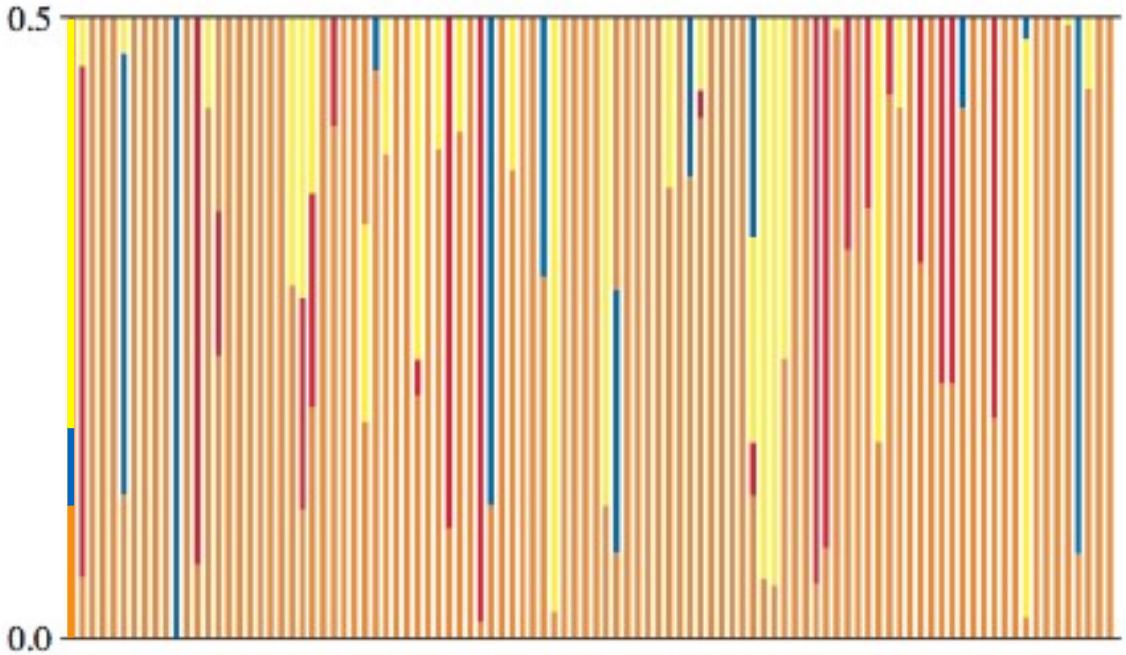
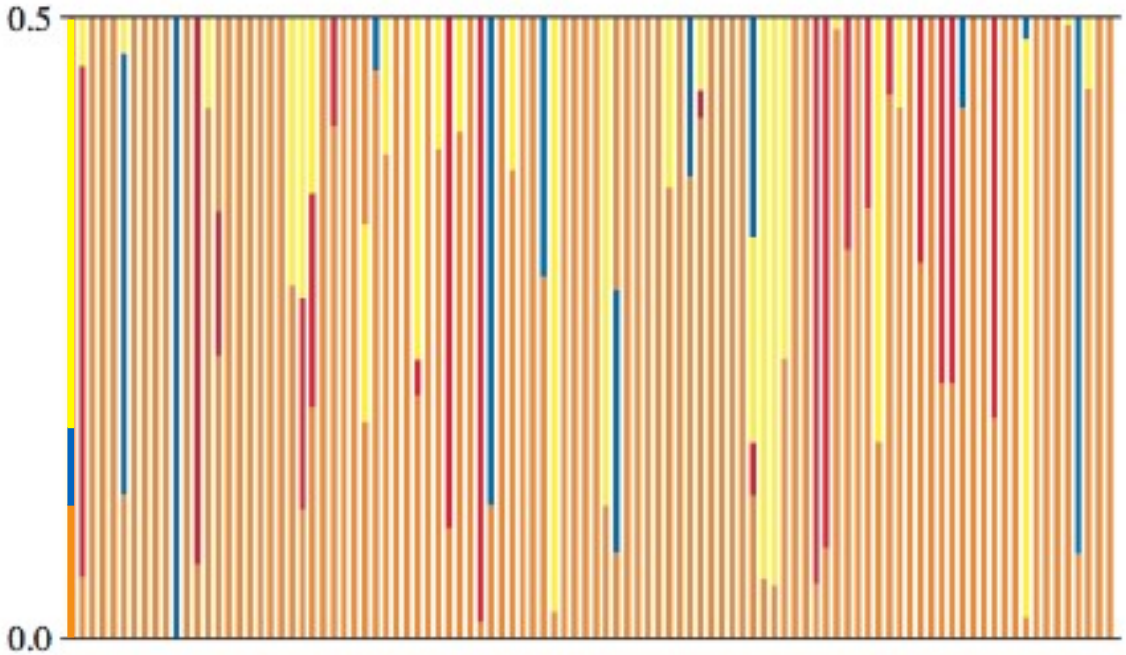



G 23

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




number of outcomes

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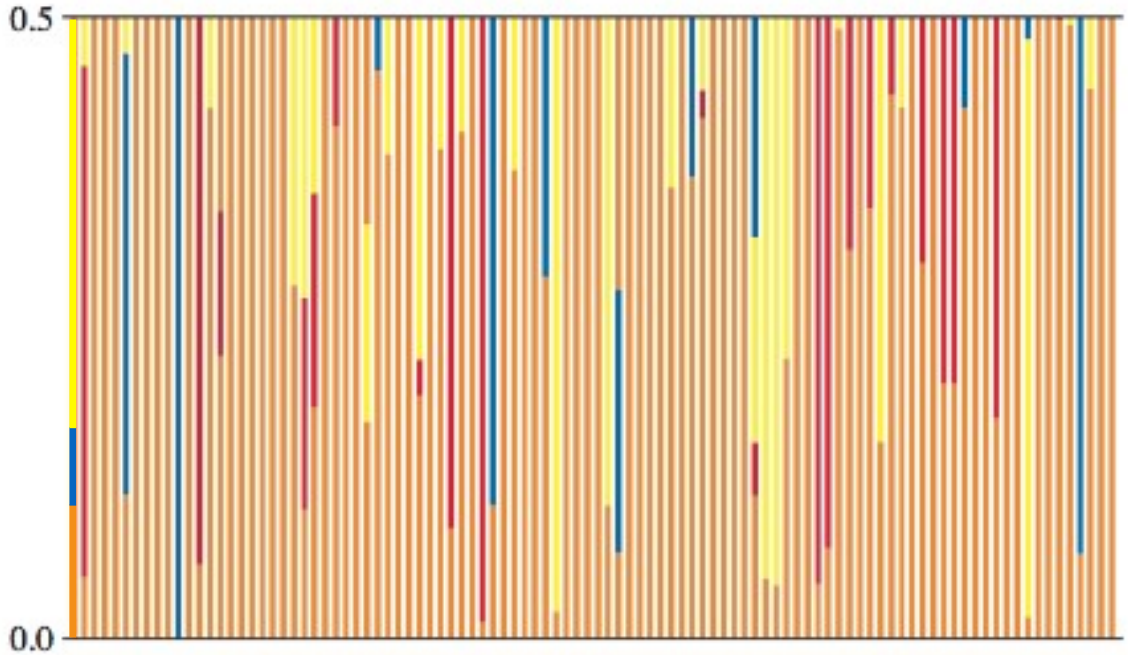



G

number of outcomes

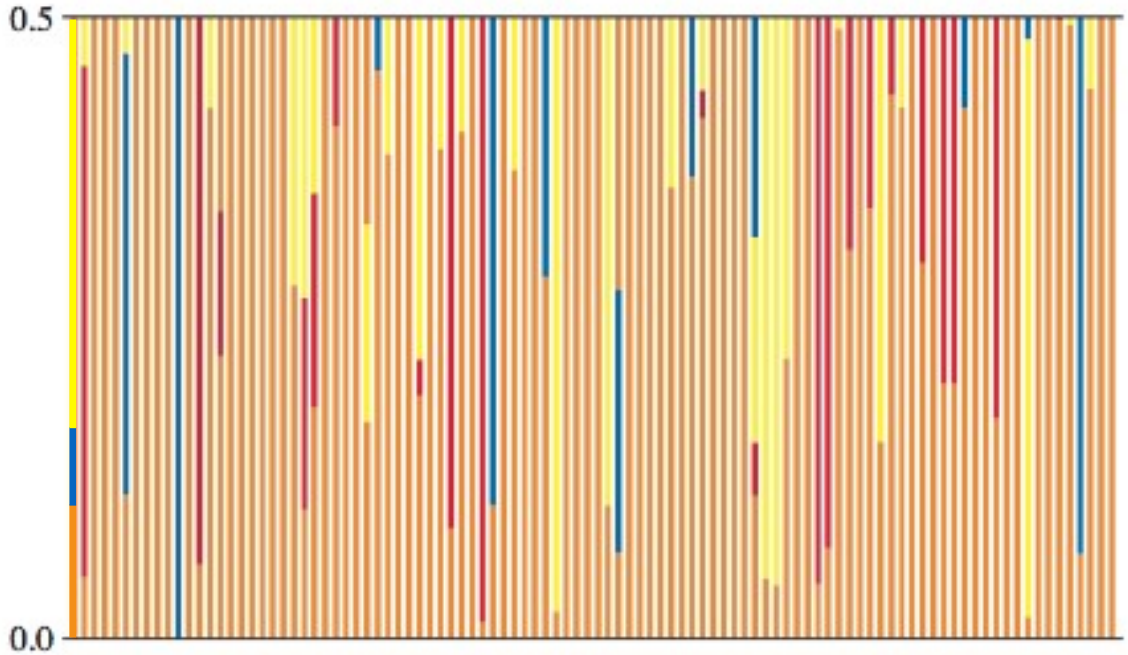
$23 \div 100$

number of simulations

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

# Transition Probabilities of a CTMC

Estimating transition probabilities using Monte Carlo simulation




G

number of outcomes

$$23 \div 100$$

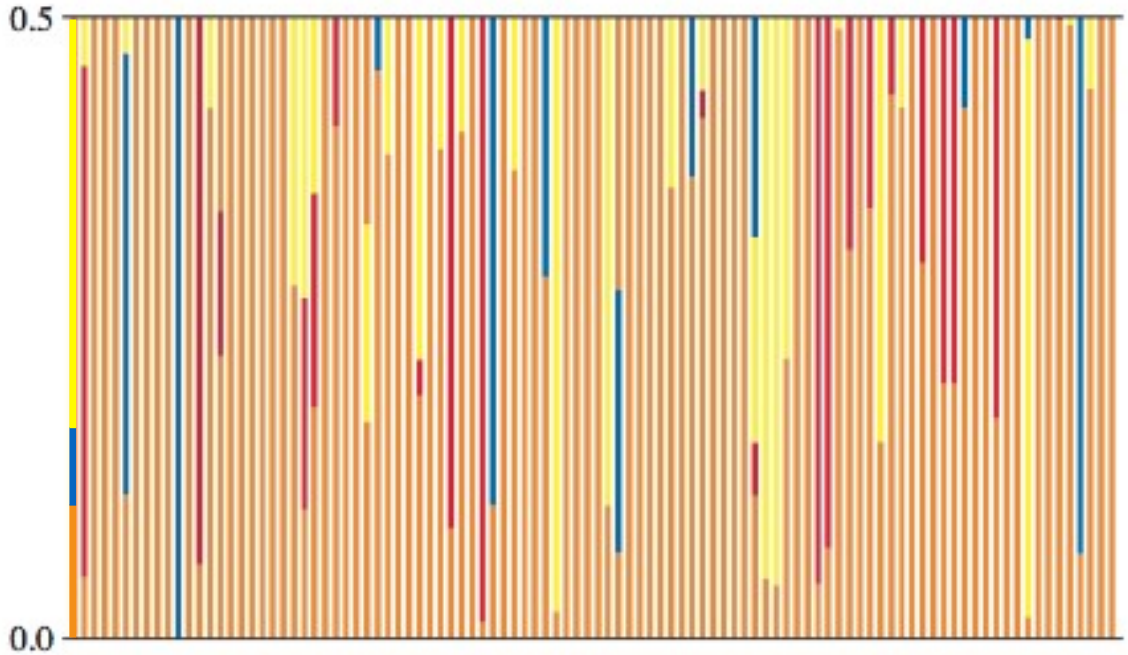
number of simulations

| | | To | | | |
|---|---|---|---|---|---|
| | | A | C | G | T |
| From | A | | | | |
| | C | | | | |
| | G | | | | |
| | T | | | 0.23 | |

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

$23 \div 100$

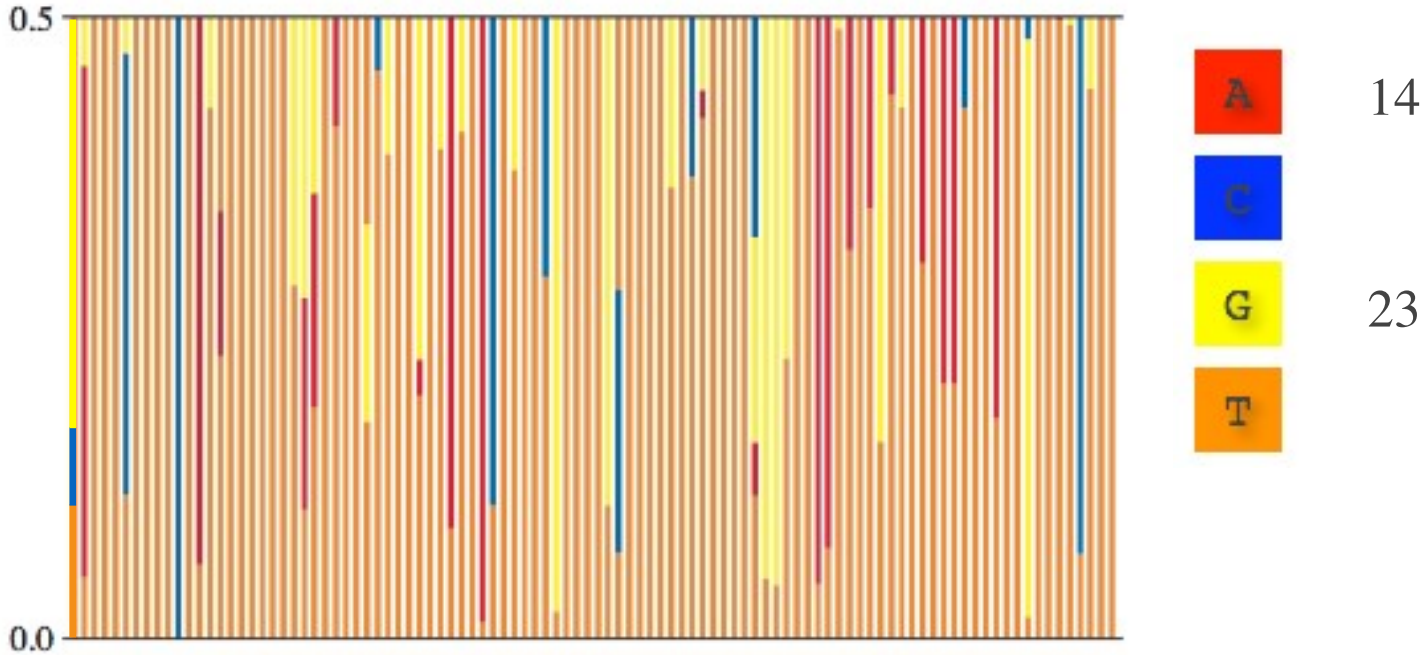
number of simulations

| | | 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…

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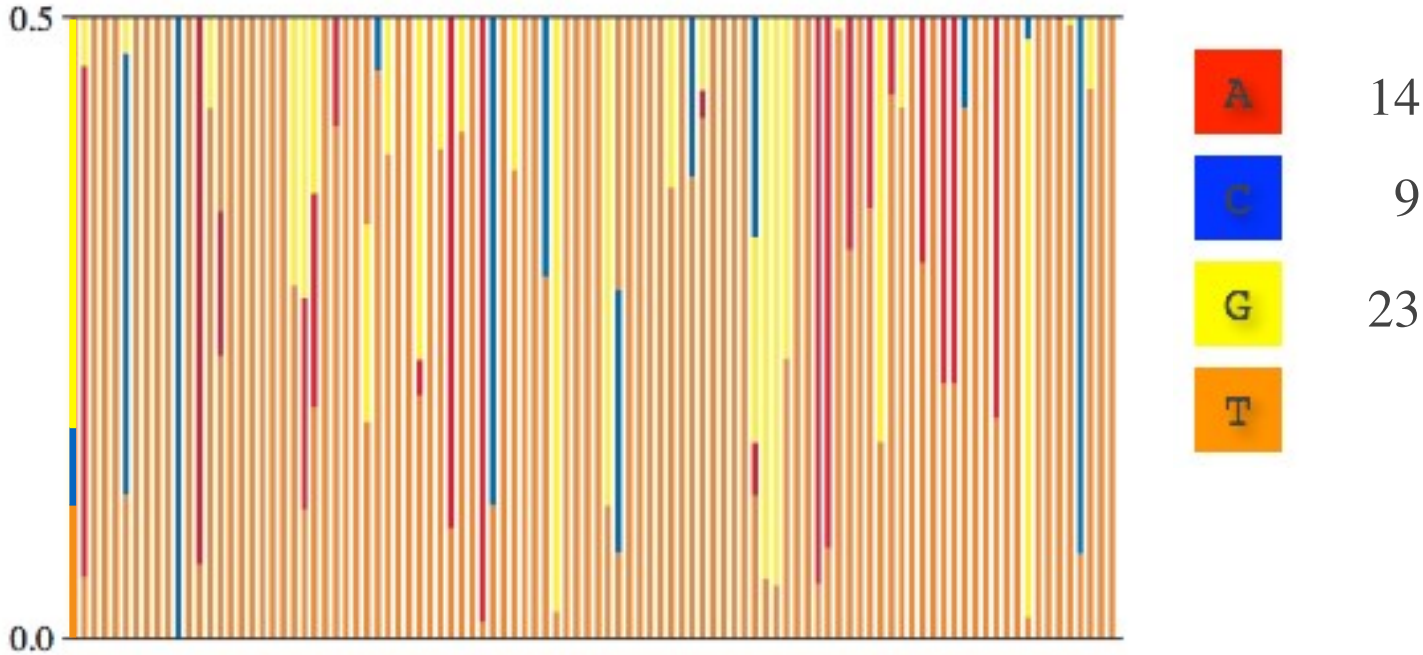
Estimating transition probabilities using Monte Carlo simulation




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

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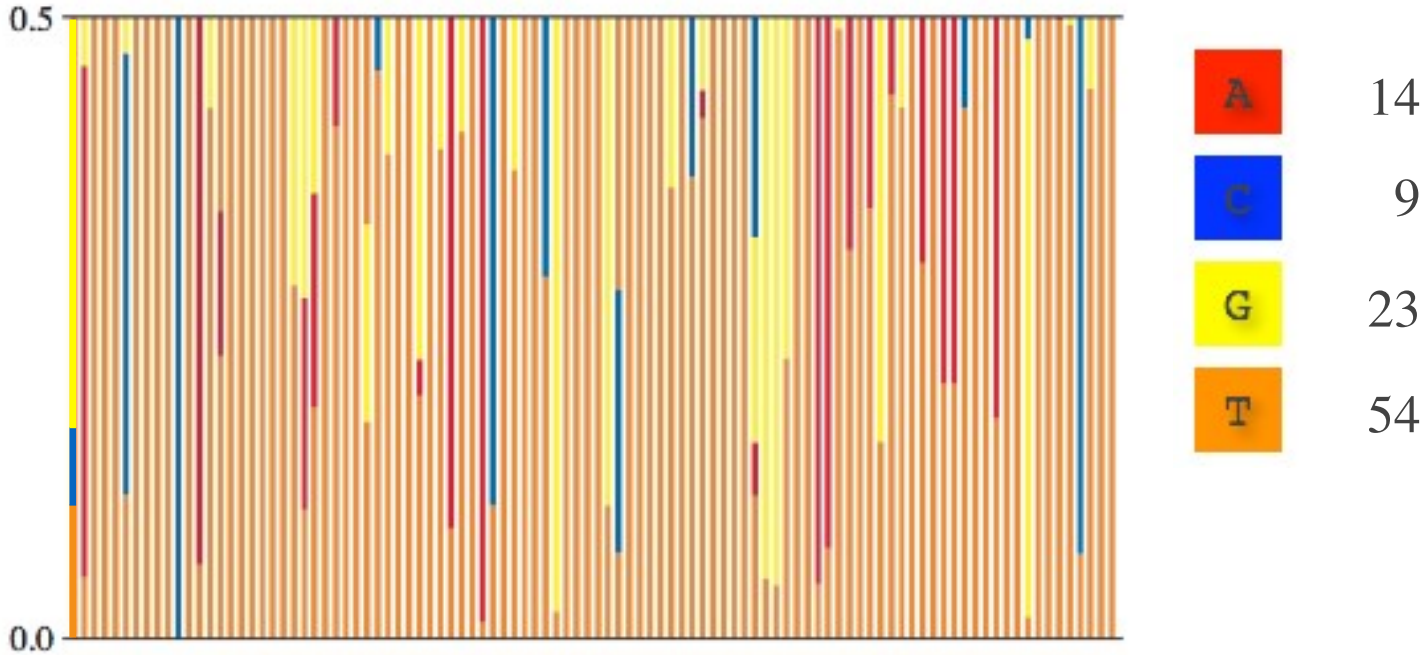
Estimating transition probabilities using Monte Carlo simulation




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

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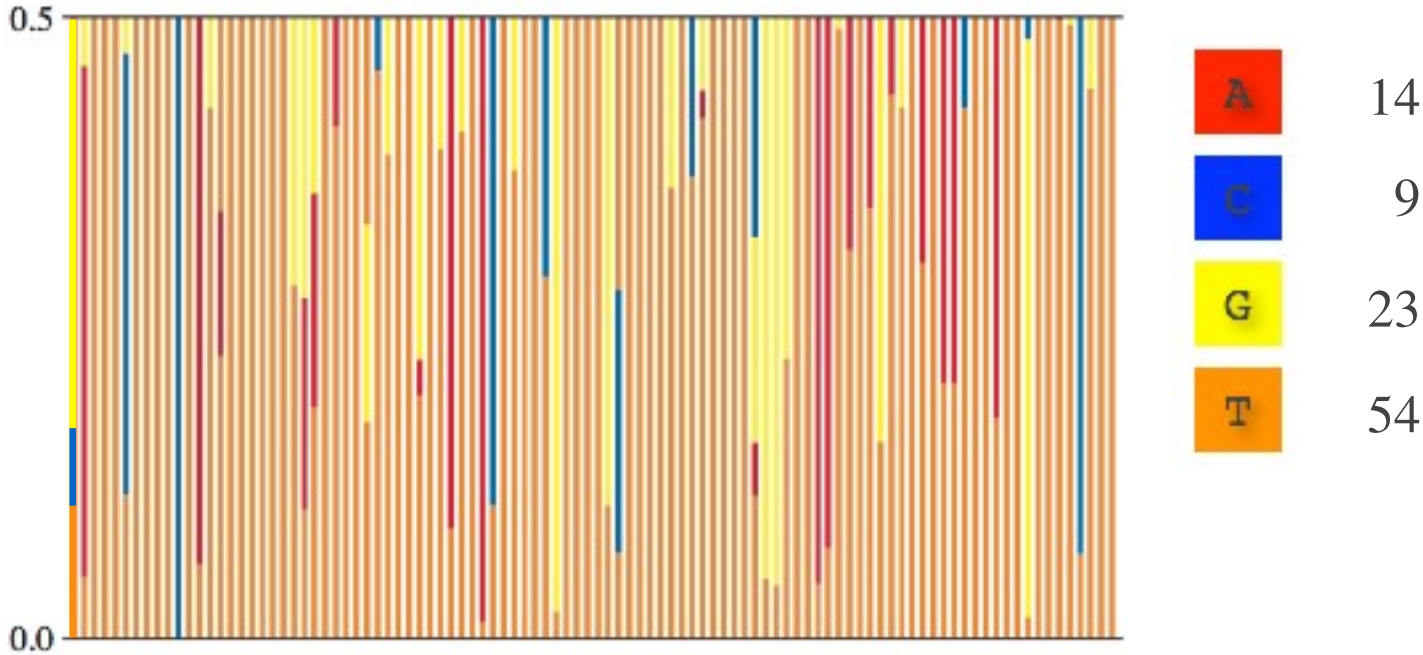
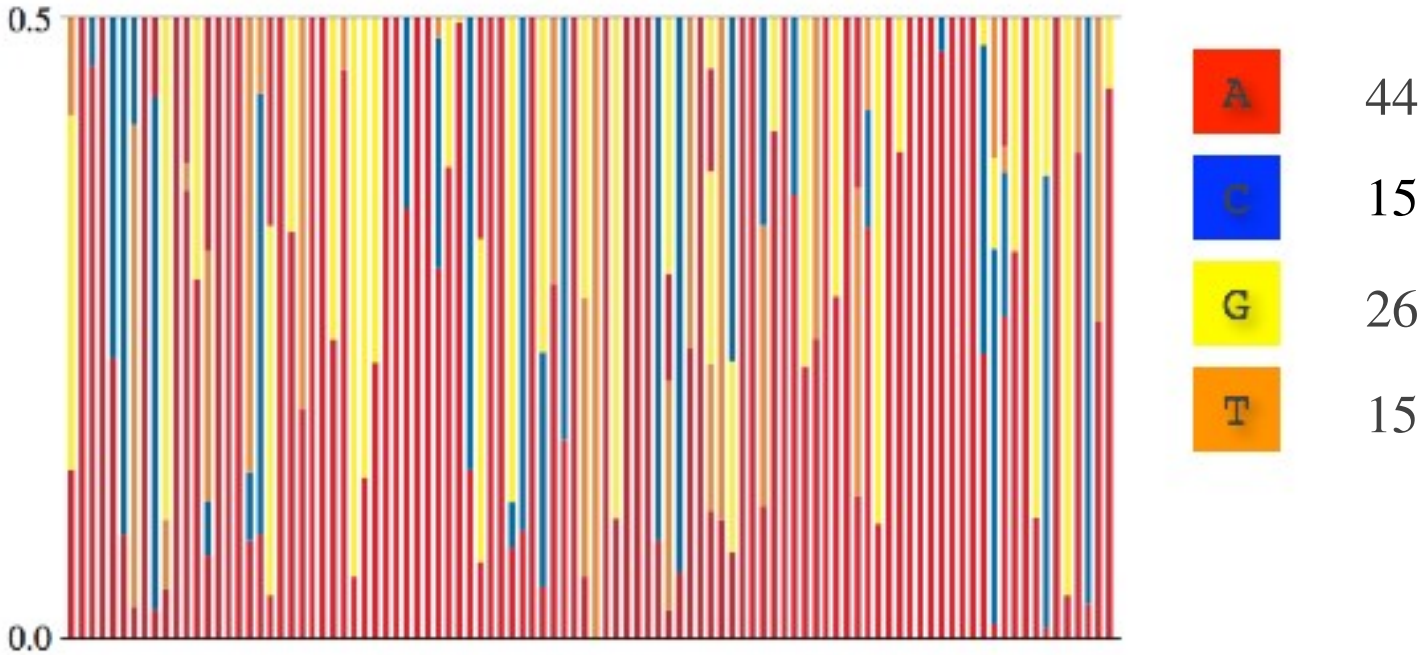



| | | To | | | |
|---|---|---|---|---|---|
| | | A | C | G | T |
| From | A | | | | |
| | C | | | | |
| | G | | | | |
| | T | 0.14 + | 0.09 + | 0.23 + | 0.54 = 1 |

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

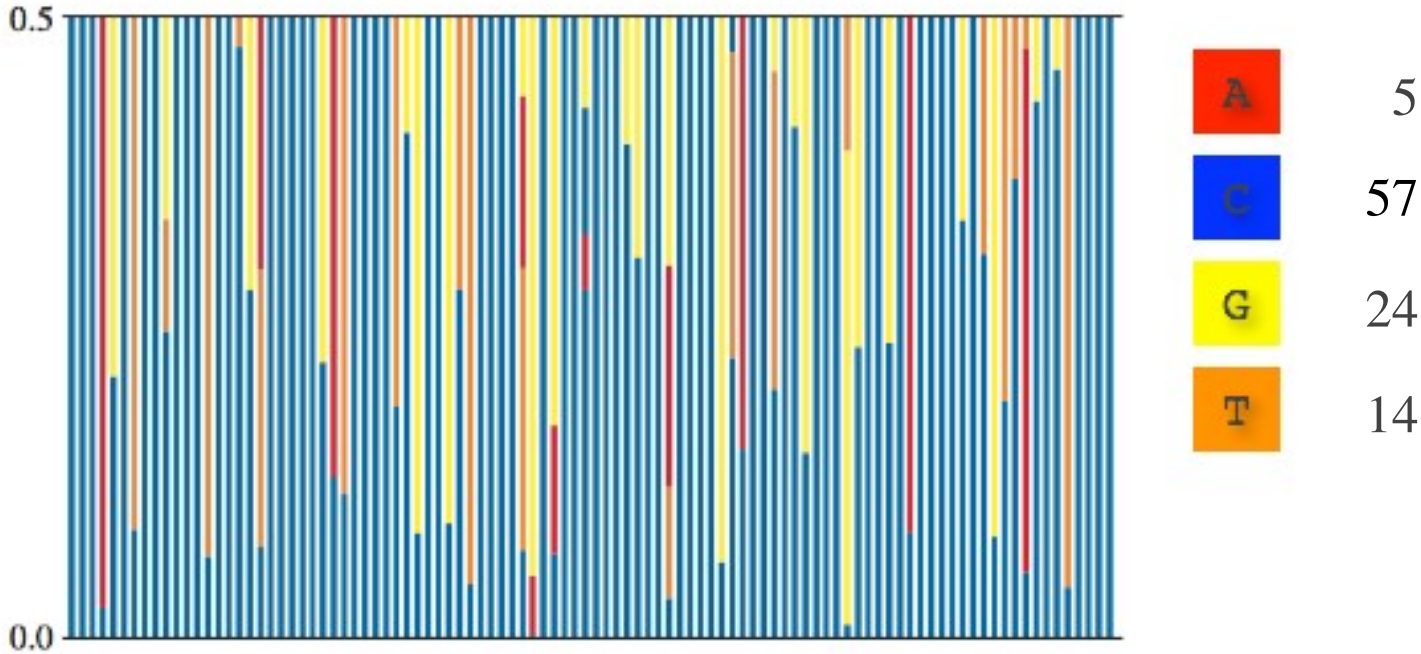



| | | To | | | |
|---|---|---|---|---|---|
| | | A | C | G | T |
| From | A | 0.44 | 0.15 | 0.26 | 0.15 |
| | C | | | | |
| | G | | | | |
| | T | 0.14 | 0.09 | 0.23 | 0.54 |

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

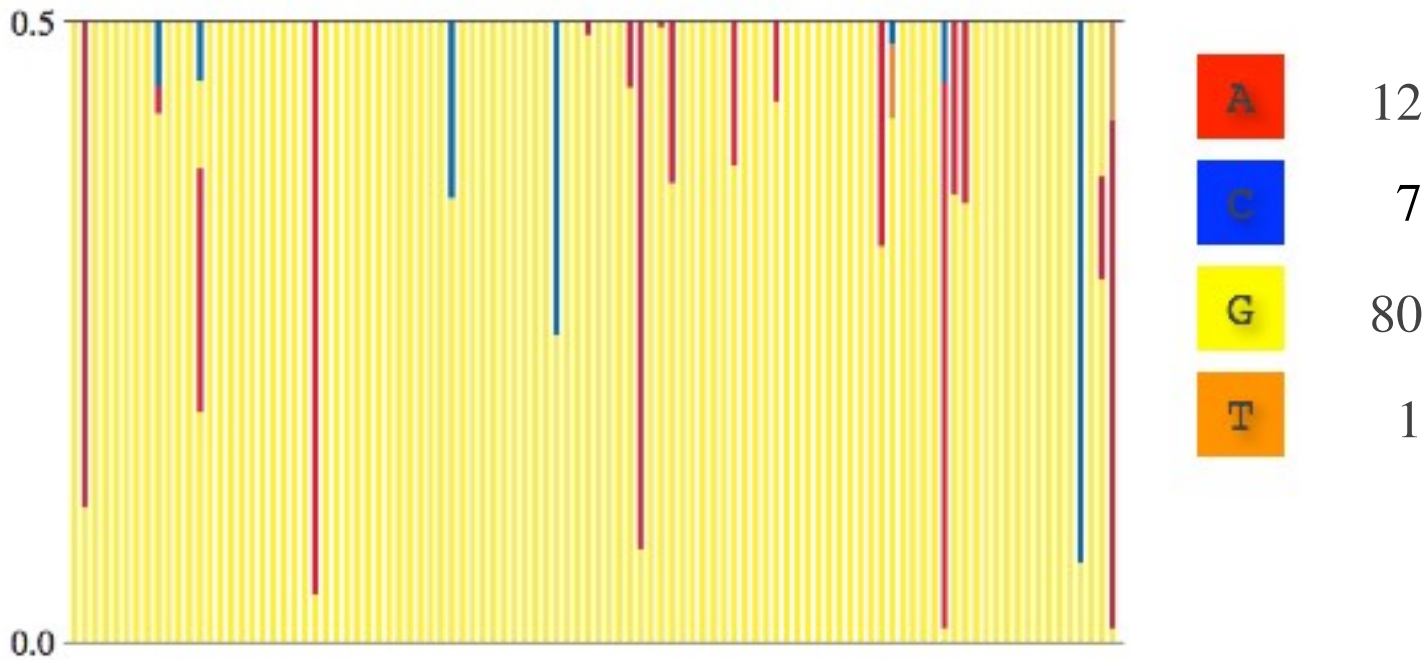



| | | To | | | |
|---|---|---|---|---|---|
| | | A | C | G | T |
| From | A | 0.44 | 0.15 | 0.26 | 0.15 |
| | C | 0.05 | 0.57 | 0.24 | 0.14 |
| | G | | | | |
| | T | 0.14 | 0.09 | 0.23 | 0.54 |

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 |
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|---|---|---|---|---|---|
| | | 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'

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

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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)

| | | 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

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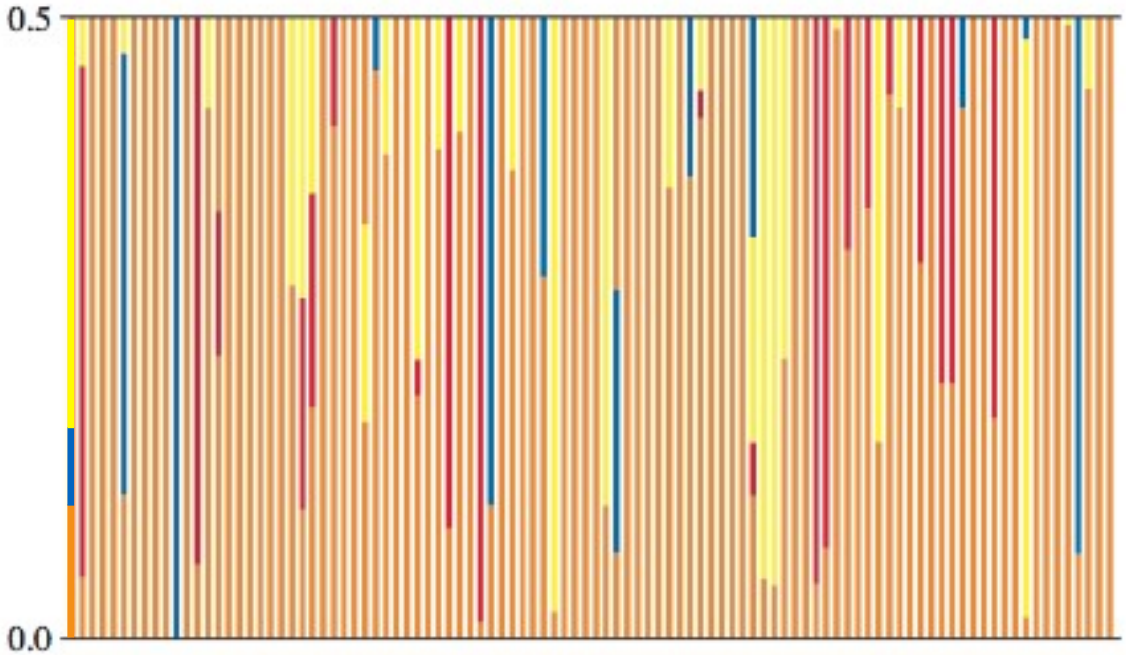
Transition probabilities account for all possible histories that a CTMC can end in a particular state, given a particular starting state (and fully specified model)

# Transition Probabilities of a CTMC

Reminder:




G

number of outcomes

$$23 \div 100$$

number of simulations

| | | To | | | |
|---|---|---|---|---|---|
| | | A | C | G | T |
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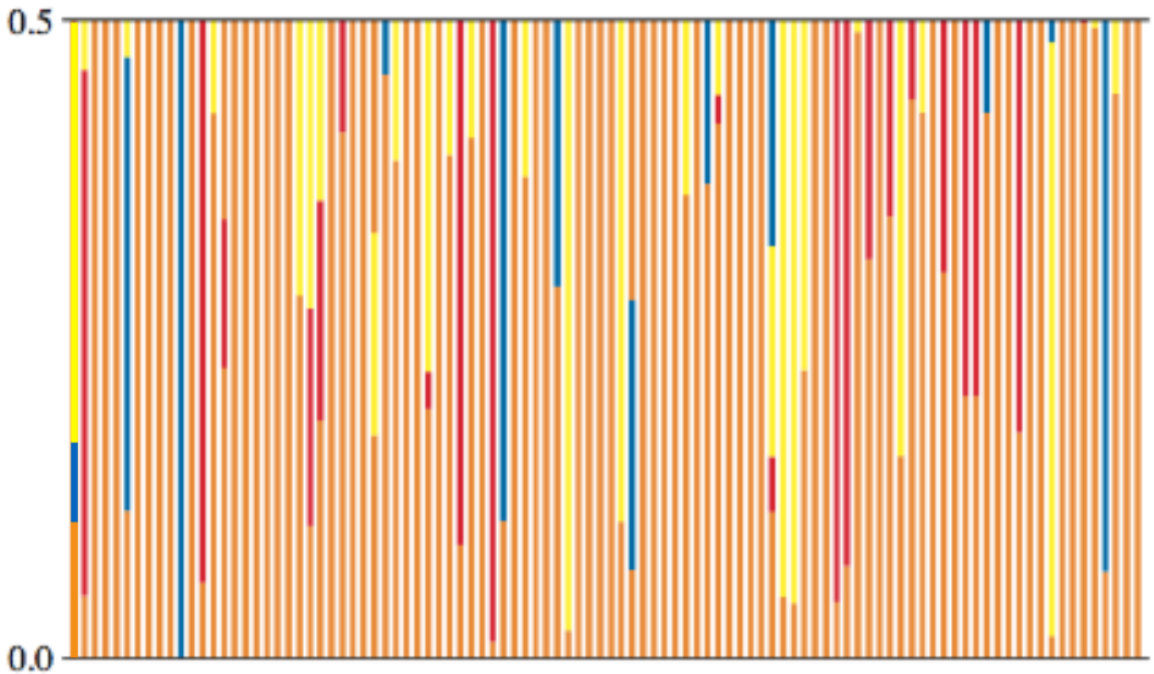
Transition probabilities account for all possible histories that a CTMC can end in a particular state, given a particular starting state (and fully specified model)

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)



$\pi_i$

# Stationary Frequencies of a CTMC

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

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

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

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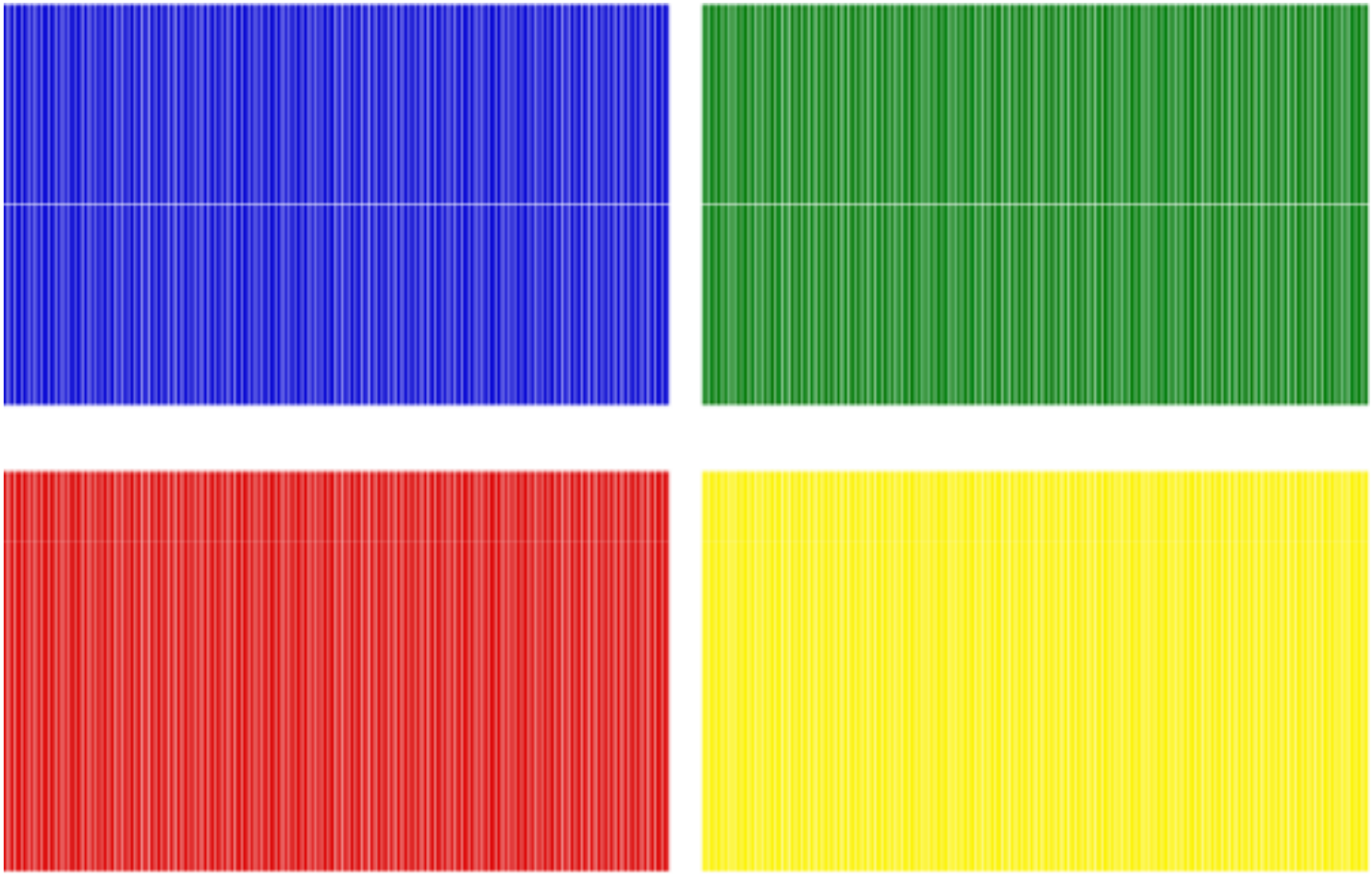

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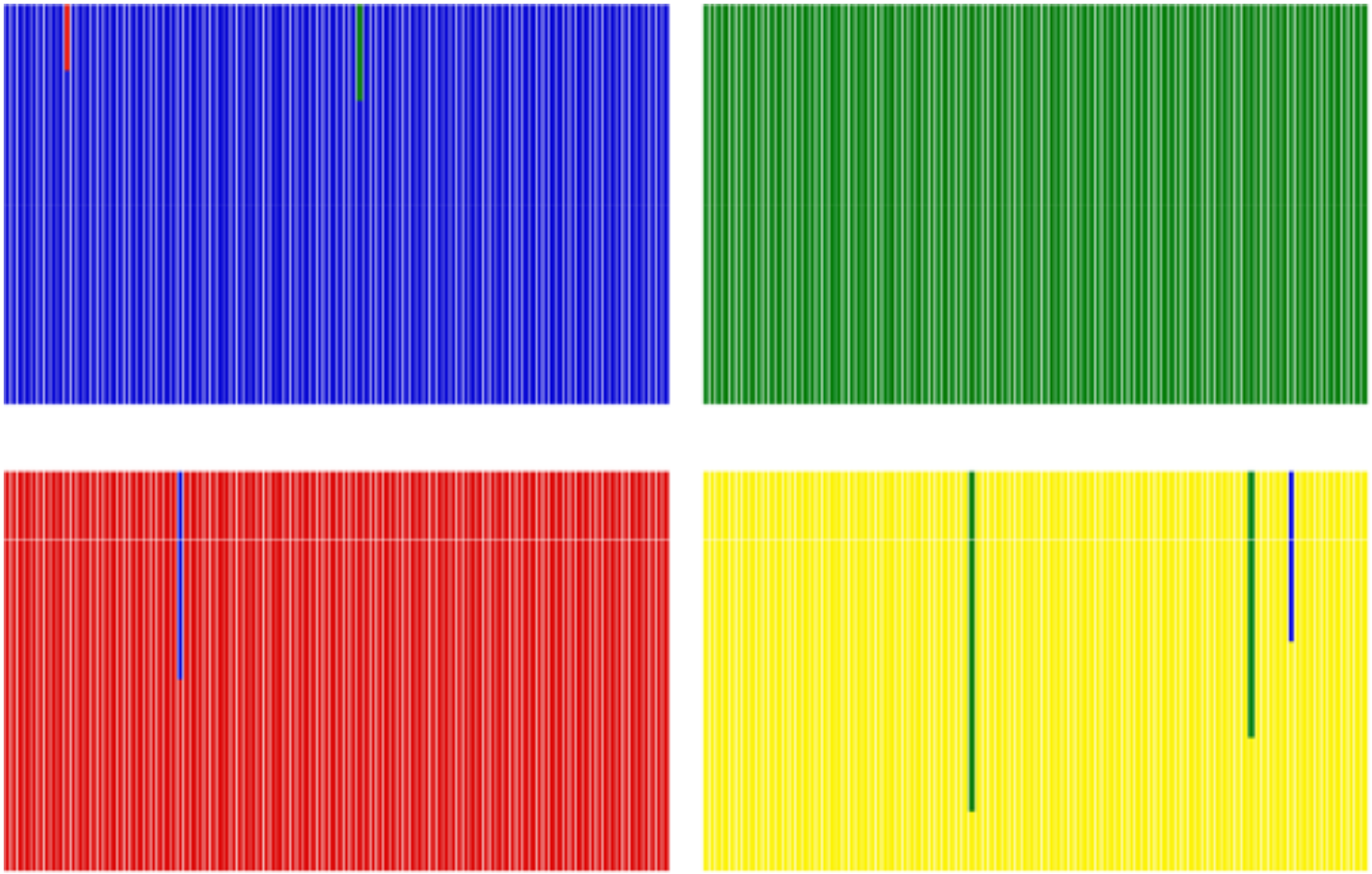

$$\mathbf{P}(0.01) = \begin{pmatrix} 0.981 & 0.005 & 0.008 & 0.006 \\ 0.001 & 0.989 & 0.004 & 0.005 \\ 0.003 & 0.002 & 0.994 & 0.001 \\ 0.005 & 0.002 & 0.006 & 0.986 \end{pmatrix}$$

$\pi_i$

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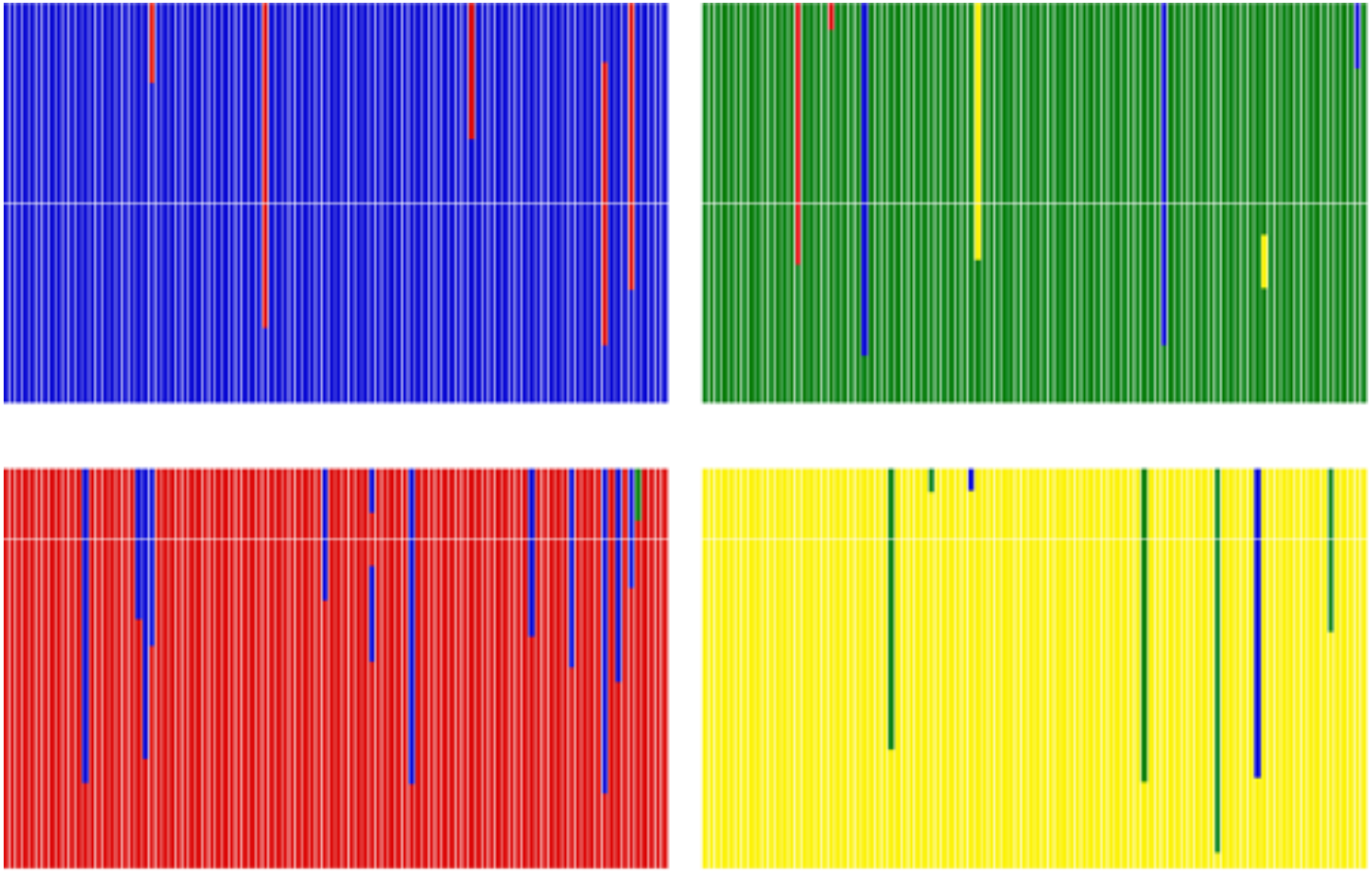

$$\mathbf{P}(0.10) = \begin{pmatrix} 0.828 & 0.048 & 0.072 & 0.052 \\ 0.014 & 0.900 & 0.040 & 0.046 \\ 0.026 & 0.017 & 0.944 & 0.013 \\ 0.046 & 0.023 & 0.056 & 0.876 \end{pmatrix}$$

$\pi_i$

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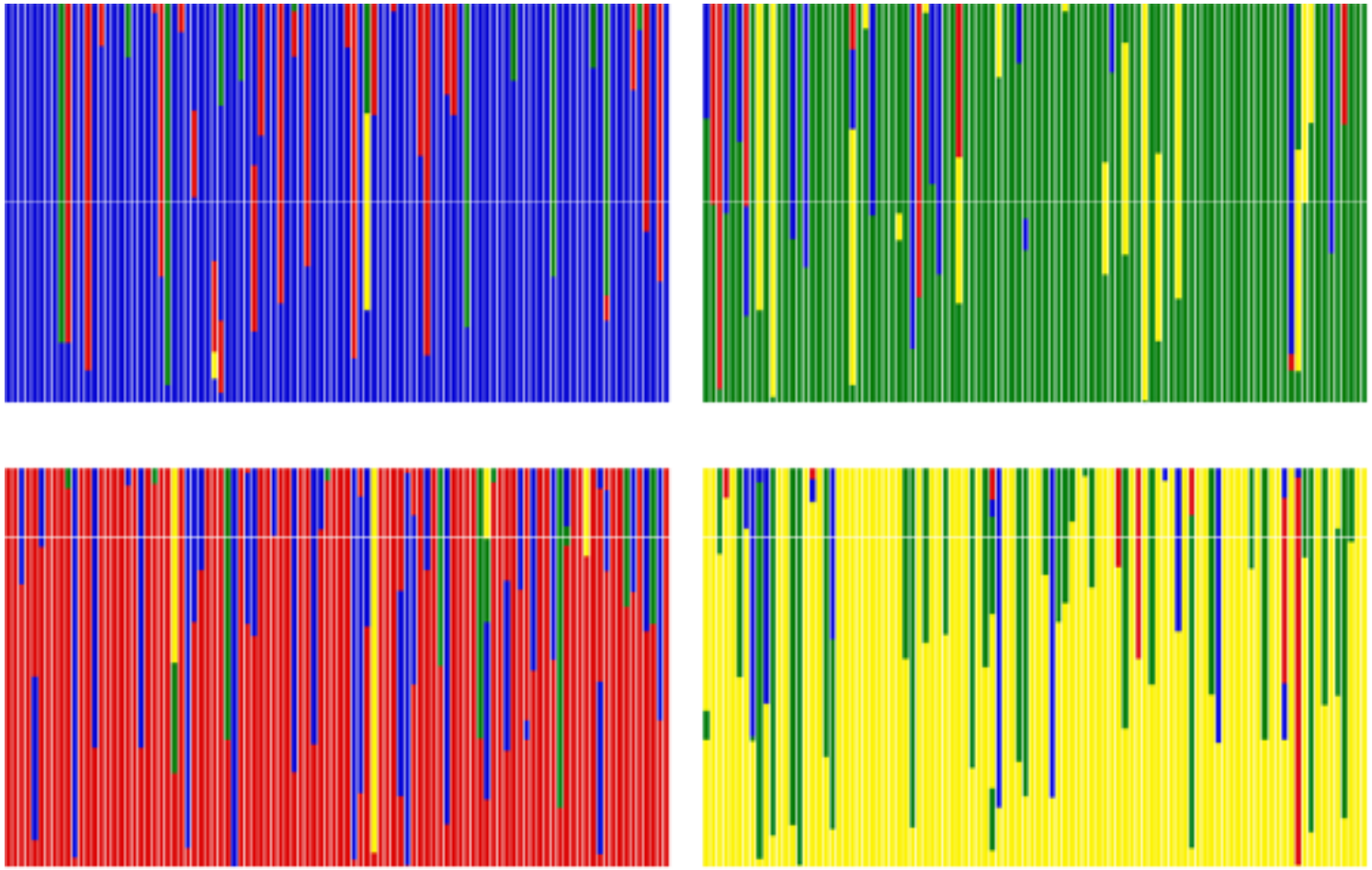

$$\mathbf{P}(0.50) = \begin{pmatrix} 0.423 & 0.153 & 0.263 & 0.161 \\ 0.063 & 0.609 & 0.175 & 0.153 \\ 0.088 & 0.072 & 0.778 & 0.062 \\ 0.135 & 0.094 & 0.227 & 0.544 \end{pmatrix}$$

$\pi_i$

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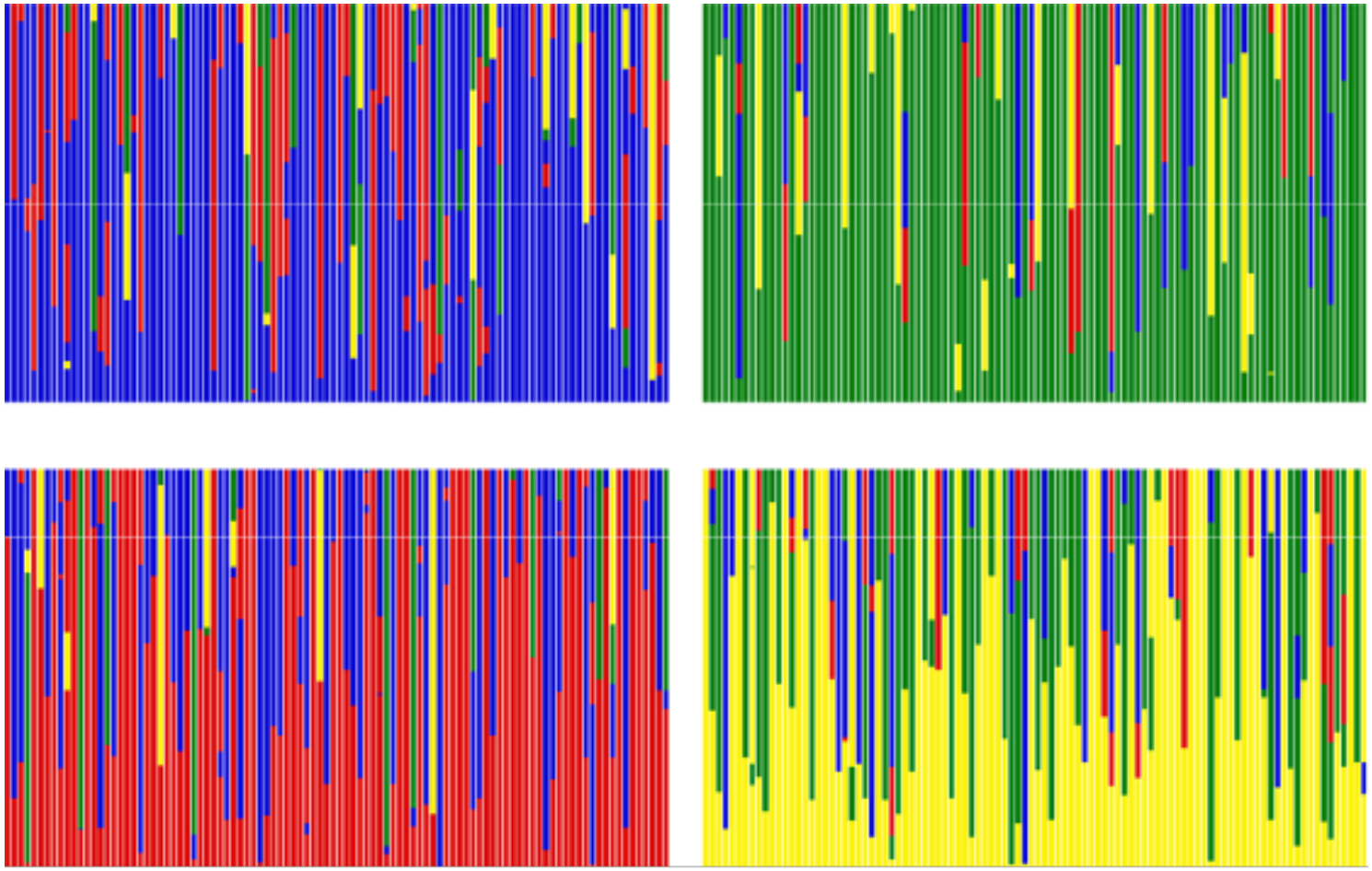

$$\mathbf{P}(1.0) = \begin{pmatrix} 0.233 & 0.192 & 0.379 & 0.195 \\ 0.101 & 0.408 & 0.295 & 0.197 \\ 0.118 & 0.119 & 0.655 & 0.107 \\ 0.156 & 0.145 & 0.352 & 0.347 \end{pmatrix}$$

$\pi_i$

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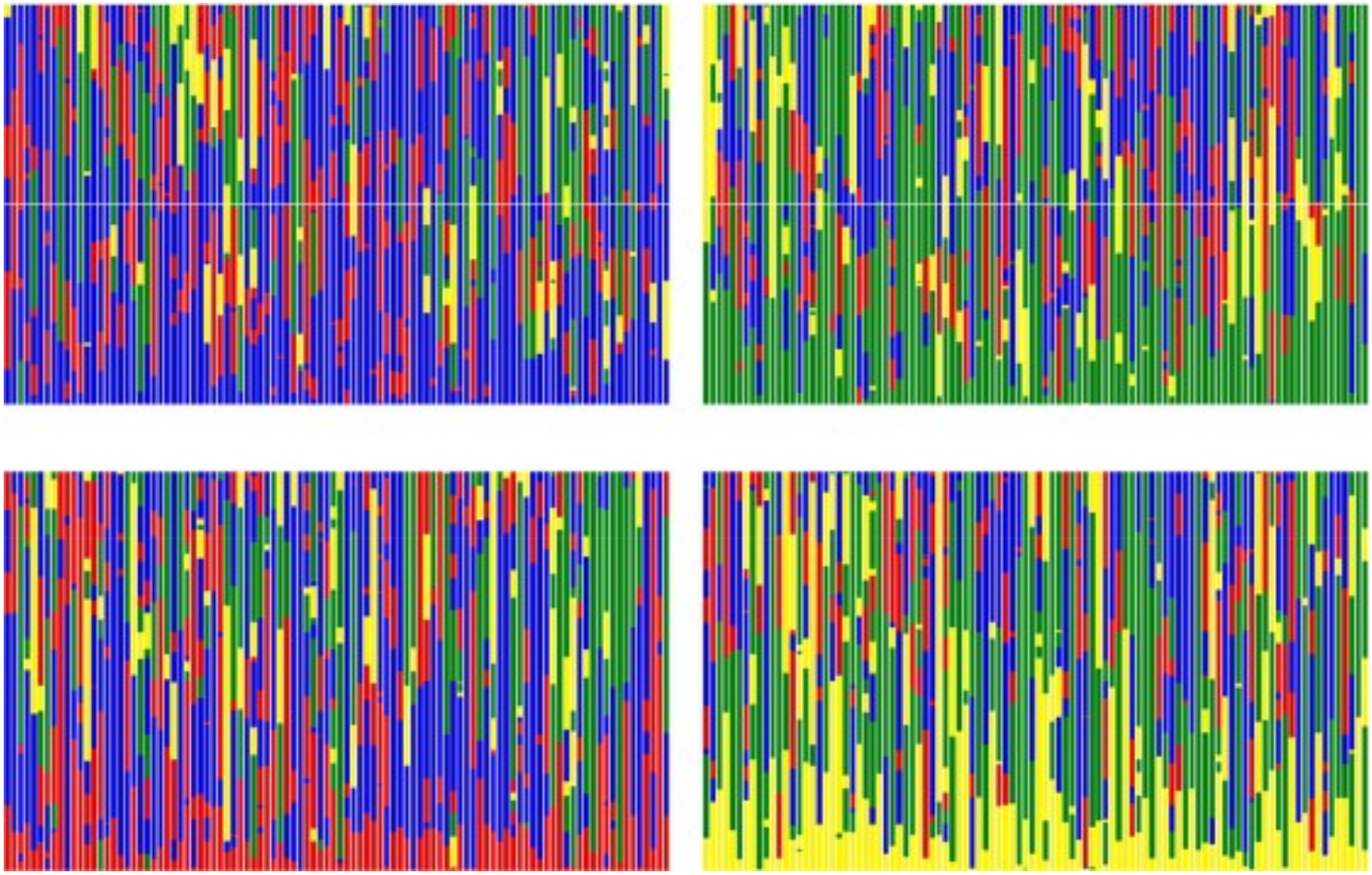

$$\mathbf{P}(5.0) = \begin{pmatrix} 0.138 & 0.188 & 0.494 & 0.180 \\ 0.138 & 0.190 & 0.492 & 0.181 \\ 0.137 & 0.187 & 0.497 & 0.178 \\ 0.138 & 0.188 & 0.494 & 0.180 \end{pmatrix}$$

$\pi_i$

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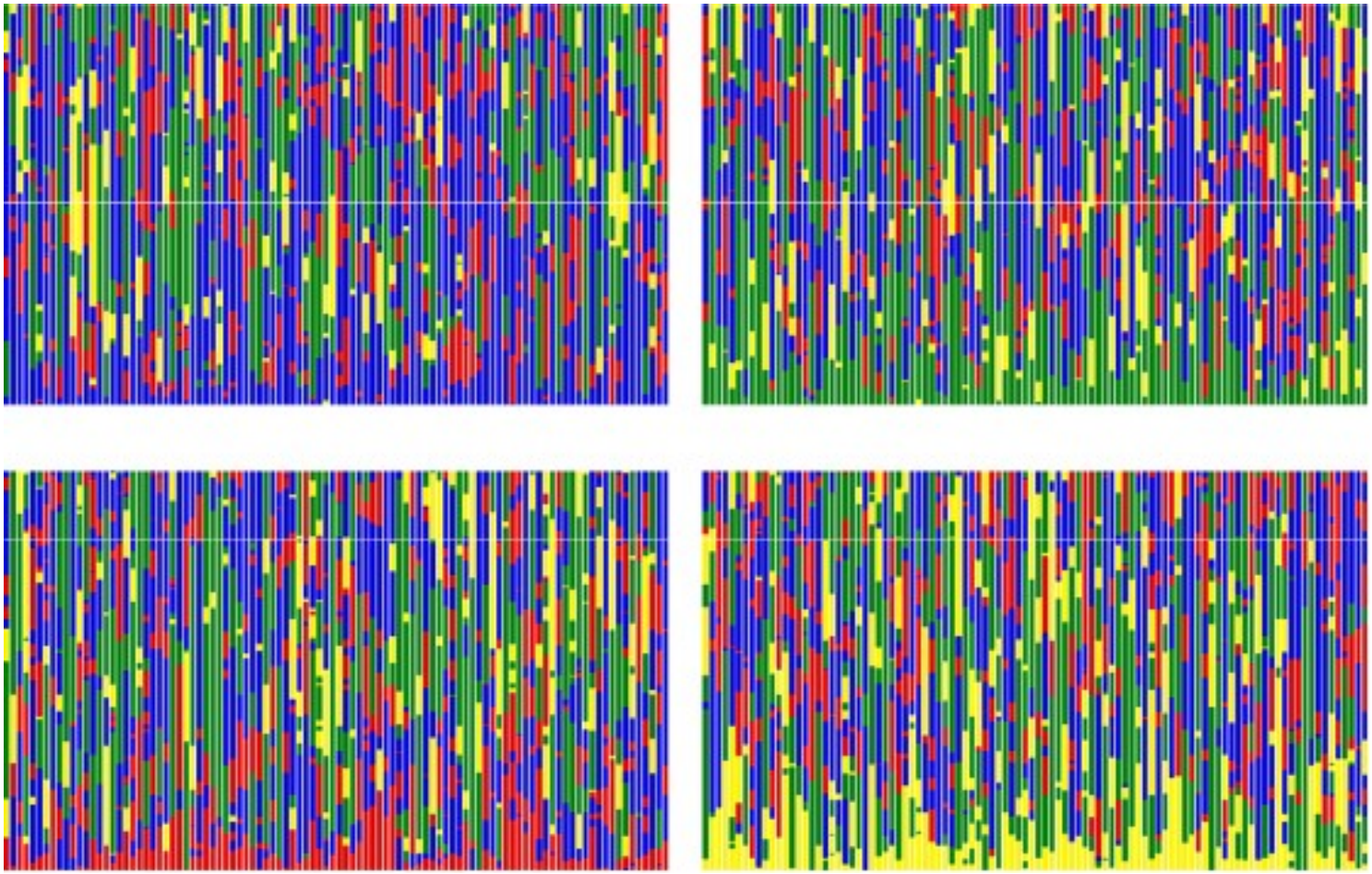

$$\mathbf{P}(10.0) = \begin{pmatrix} 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \end{pmatrix}$$

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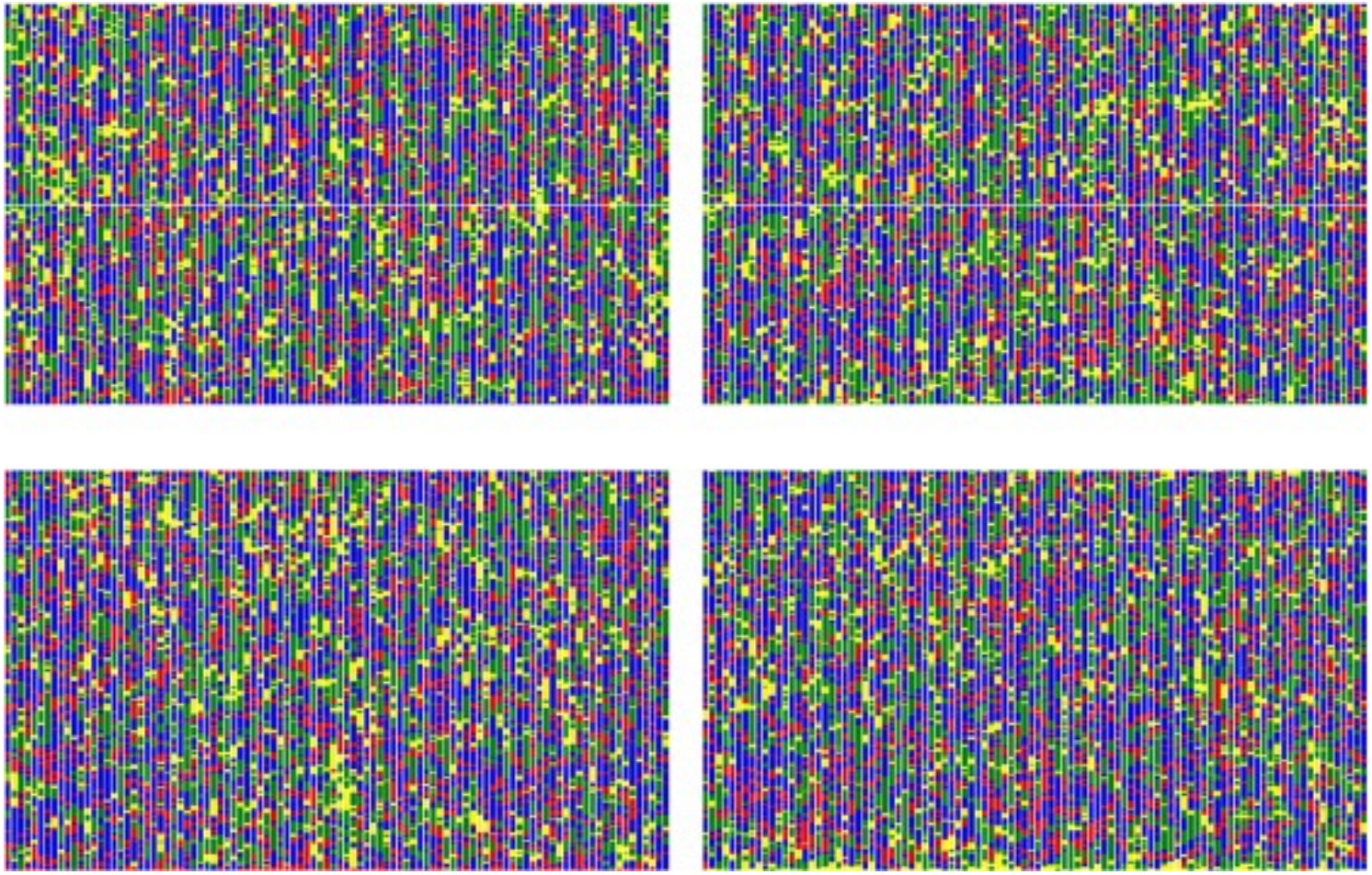

$$\mathbf{P}(100.0) = \begin{pmatrix} 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \\ 0.138 & 0.188 & 0.495 & 0.179 \end{pmatrix}$$

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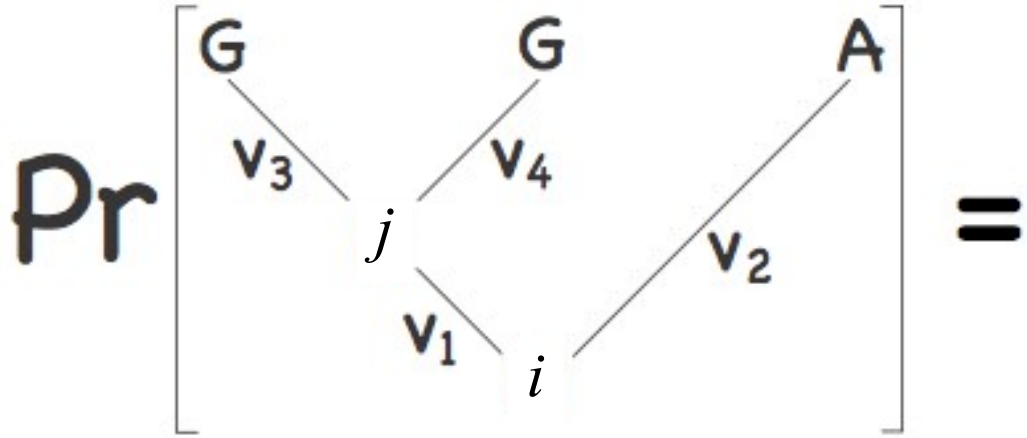
When the continuous time Markov chain is at stationarity, the stochastic process has 'forgotten' the starting state: the process ends in a given state with the same probability, regardless of the starting state

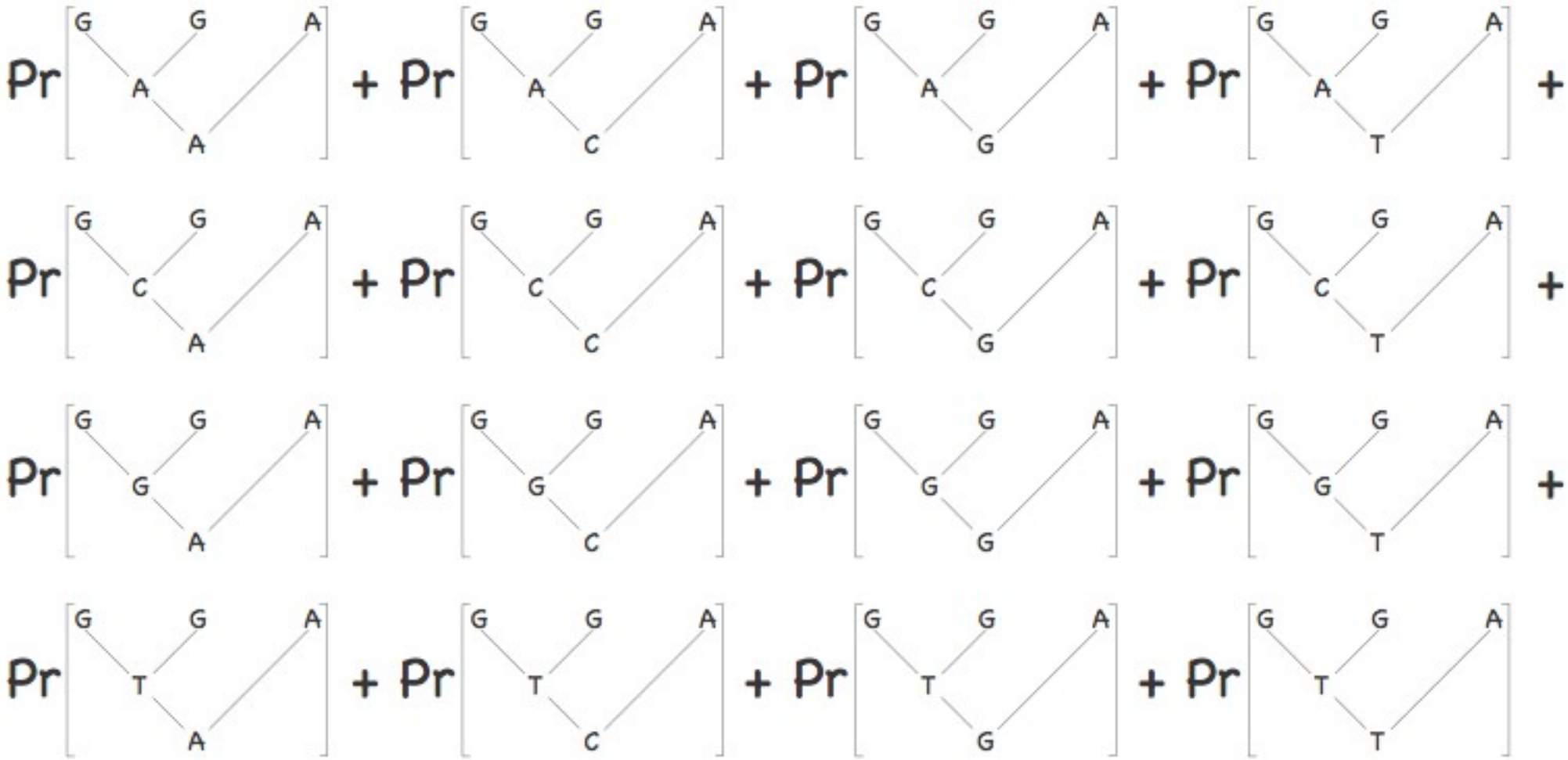
# Now we can compute the likelihood of a site history




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

| | |
|---|---|
| $\pi_i$ | Stationary frequencies |
| $p_{ij}(v)$ | Transition probabilities |

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



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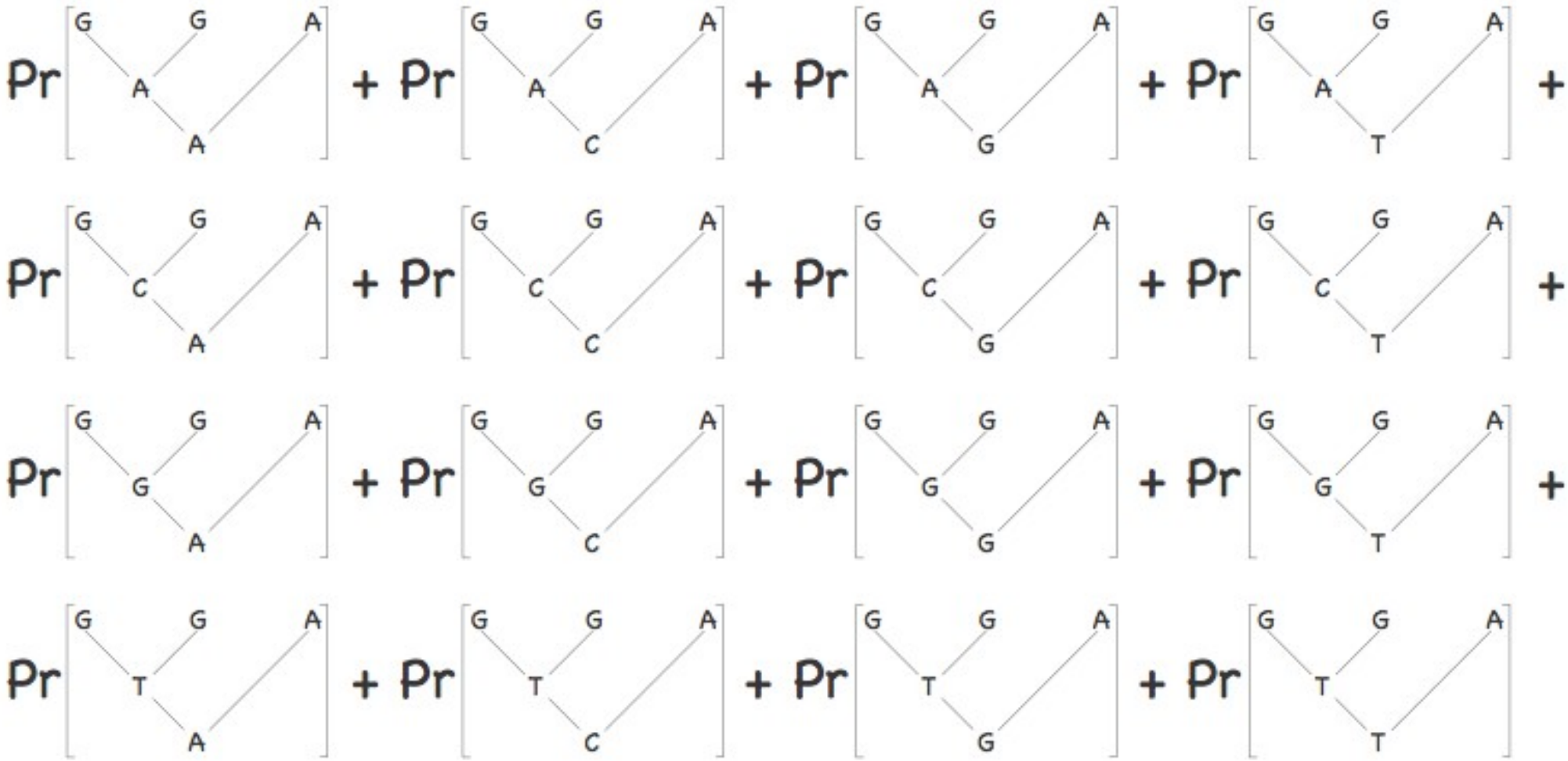
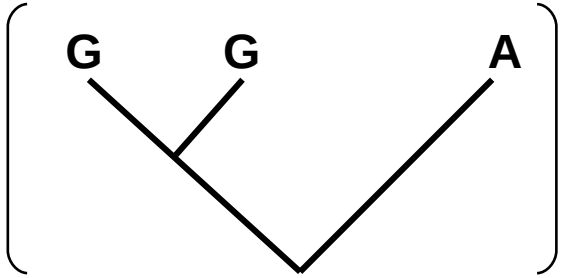



= Pr



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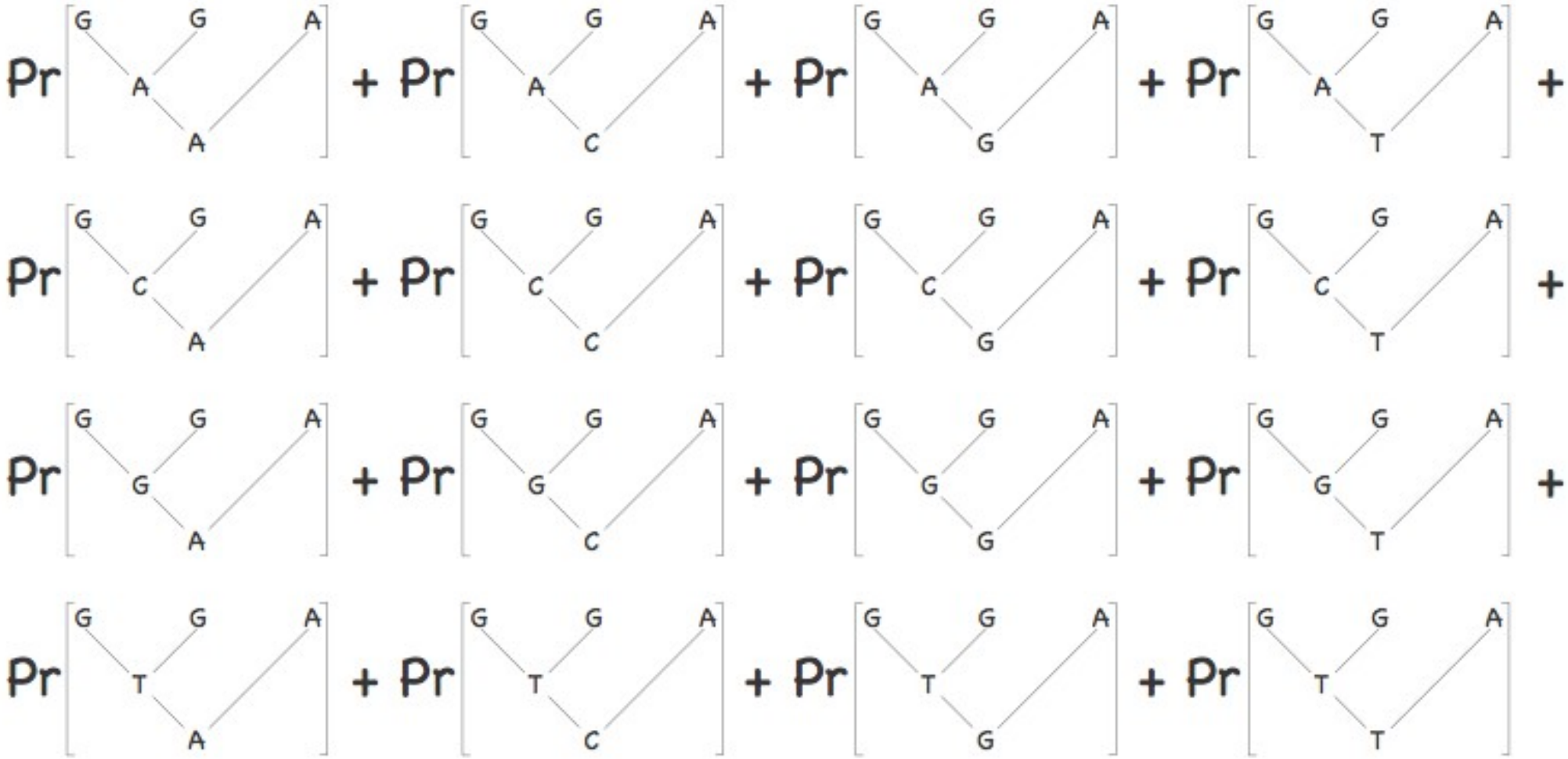
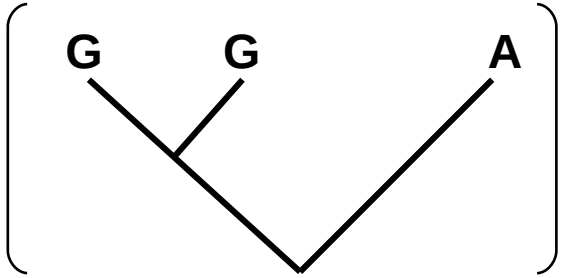



= Pr 

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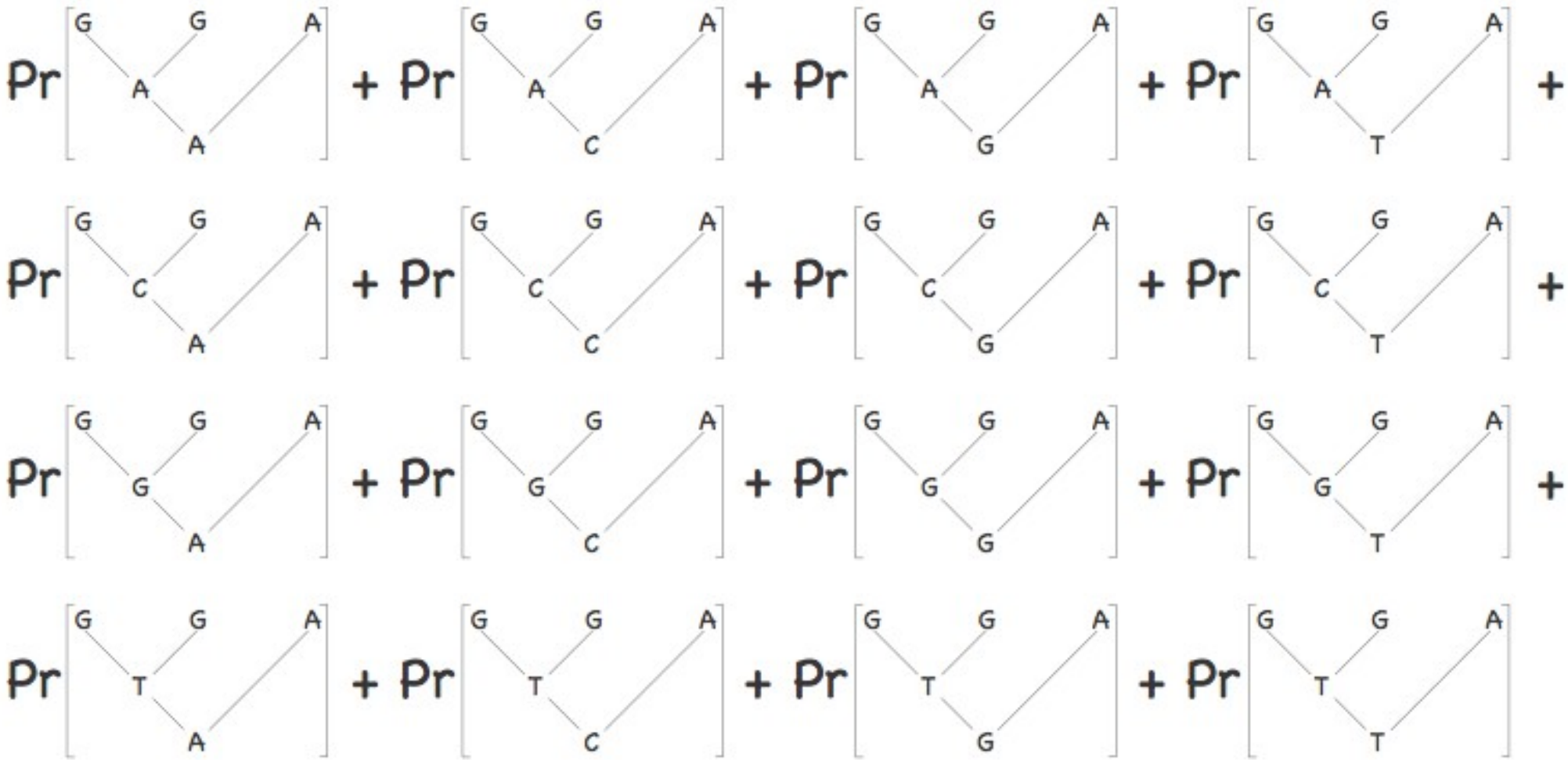
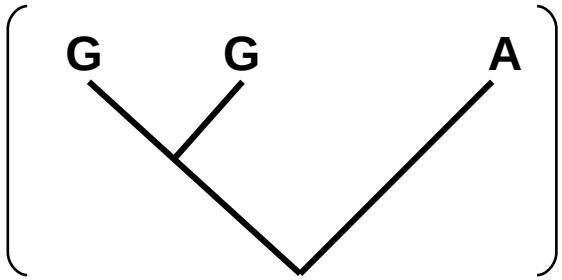



= Pr 

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

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

***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

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

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, Yano 1985

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

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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

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