Today

- Markov chains
  - Review
  - Stationary distributions
- Models of sequence evolution
  - Nucleotide substitution models
  - (Amino acids in about 2 weeks)

Box 2: Summary of Markov chain notation

A Markov chain has *states* E_1, E_1, ..., E_s corresponding to the range of the associated random variable.

$\varphi_j(t)$ is the probability that the chain is in state E_j at time t. The vector $\varphi(t) = (\varphi_1(t), \ldots \varphi_s(t))$ is the *state probability distribution* at time t.

$\pi = \varphi(0)$ is the *initial state probability distribution.*

P is the *transition probability matrix.* P_{jk} gives the probability of making a transition to state E_k at time $t+1$, given that the chain was in state E_j at time t. The rows of this matrix sum to one: $\sum_k P_{jk} = 1$.

The state probability distribution at time $t+1$ is given by $\varphi(t+1) = \varphi(t) \cdot P$. The probability of being in state E_k at $t+1$ is

$$\varphi_k(t+1) = \sum_j \varphi_j(t) P_{jk}$$

The *Markov property* states that Markov chains are memoryless. The probability that the chain is in state E_k at time $t+1$, depends only on $\varphi(t)$ and is independent of $\varphi(t-1), \varphi(t-2), \varphi(t-3) \ldots$

Markov chain properties

In this course, we consider *finite, discrete, time-homogeneous* Markov chains:

- Number of states *finite*
- Independent variable is *discrete*
- *Time homogeneous:* The transmission matrix does not change over time.

that are

- *irreducible:* every state may be reached from every other state
- *aperiodic:*
  There is no state that can only be visited multiples of m time steps, where m > 1

Questions to ask about steady state behavior:

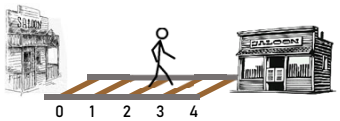
- Does the Markov chain have a *stationary distribution,* φ^*, such that
  $$\varphi^* = \varphi^* P \ ?$$
- If so, is it *unique*?
- Does the Markov chain have a *limiting distribution*? That is, a solution to
  $$Q = \lim_{n \to \infty} P^n \ ?$$

If so

$$Q = \begin{bmatrix} \varphi_1^* & \cdots & \varphi_s^* \\ \vdots & \ddots & \vdots \\ \varphi_1^* & \cdots & \varphi_s^* \end{bmatrix}$$

where $\varphi_1^* \ldots \varphi_s^*$ is the limiting and stationary disribution.

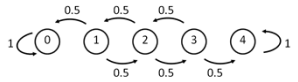
Random walk with *absorbing* boundaries



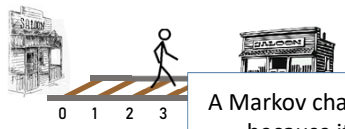
$$P = \begin{array}{c} \\ E_0 \\ E_1 \\ E_2 \\ E_3 \\ E_4 \end{array} \begin{array}{c} \begin{array}{ccccc} E_0 & E_1 & E_2 & E_3 & E_4 \end{array} \\ \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 \\ 0 & \frac{1}{2} & 0 & \frac{1}{2} & 0 \\ 0 & 0 & \frac{1}{2} & 0 & \frac{1}{2} \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix} \end{array}$$

Every time the clock ticks,
the drunk takes one step
- to the left with prob 0.5
- to the right with prob 0.5

If the drunk reaches State E_1 or E_4, the drunk enters the bar and stays there



Random walk with *absorbing* boundaries



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A Markov chain is not *irreducible* because it has absorbing boundaries

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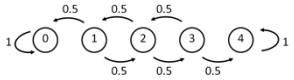
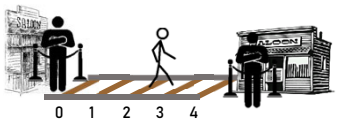
If the drunk reaches State E_1 or E_4, the drunk enters the bar and stays there



Random walk with *reflecting* boundaries



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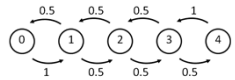
Every time the clock ticks,
the drunk takes one step
- to the left with prob 0.5
- to the right with prob 0.5

E_1, E_2, E_3

If the drunk enters State E_0 (E_4), the drunk reverses direction and enters E_1 (E_3) at the next tick



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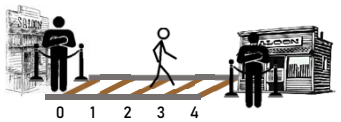
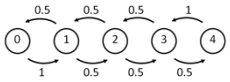
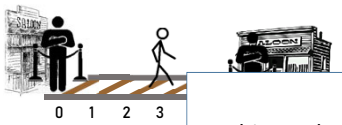




Random walk with *reflecting* boundaries



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This Markov chain is periodic

Every time the clock ticks,
the drunk takes one ste
- to the left with prob 0.5
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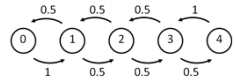
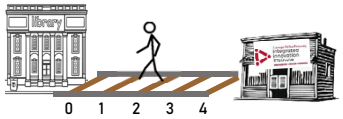
If the drunk enters State E_0 (E_4), the drunk reverses direction and enters E_1 (E_3) at the next tick



A third random walk



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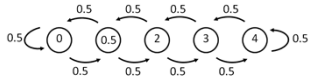
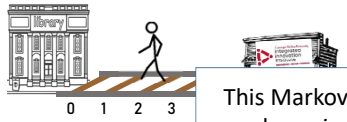
Every time the clock ticks, the drunk takes one step
- to the left with prob 0.5
- to the right with prob 0.5

If the drunk enters State E_0 (E_4), the drunk
- rests with prob 0.5
- reverses direction and enters E_1 (E_3) with prob 0.5



A third random walk

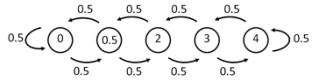


This Markov chain is *irreducible* and *aperiodic.* It has a unique stationary distribution.

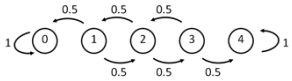
$$P = \begin{array}{c} \\ E_0 \\ E_1 \\ E_2 \\ \\ \end{array} \begin{array}{c} \begin{array}{ccccc} E_0 & E_1 & E_2 & E_3 & E_4 \end{array} \\ \begin{bmatrix} \frac{1}{2} & \frac{1}{2} & 0 & 0 & 0 \\ \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 \\ 0 & \frac{1}{2} & 0 & \frac{1}{2} & 0 \\ 0 & 0 & \frac{1}{2} & 0 & \frac{1}{2} \\ 0 & 0 & 0 & \frac{1}{2} & \frac{1}{2} \end{bmatrix} \end{array}$$

Every time the clock ticks,
- to the left with prob
- to the right with prob 0.5

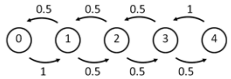
If the drunk enters State E_0 (E_4), the drunk
- rests with prob 0.5
- reverses direction and enters E_1 (E_3) with prob 0.5



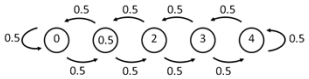
Random walk with *absorbing* boundaries
- Not irreducible because it has absorbing boundaries
- Does not have a *unique stationary distribution.*



Random walk with *reflecting* boundaries
- This Markov chain is *periodic*
- It has a *unique stationary distribution.*
- It does not have a *limiting distribution*



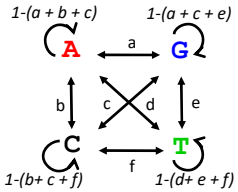
Random walk with neither absorbing nor *reflecting* boundaries
- This Markov chain has a *unique stationary distribution.*
- It has a *limiting distribution* which is the same as the *stationary distribution.*



Today

- Announcements
- Markov chains
  - Review
  - Stationary distributions
- **Models of sequence evolution**
  - **Nucleotide substitution models**
  - (Amino acids in about 2 weeks)

Properties of DNA substitution models



- State space: {E_1 = A, E_2 = G, E_3 = C, E_4 = T}
- States are fully connected
- Transition probabilities:
  substitution frequencies (*a, b, c, d* ...)
- Implicitly also specifies stationary base frequencies: $\varphi^* = (p_A, p_G, p_C, p_T)$

GACTAGCTAGACATAGCTAGACAGATACGAAGATACGAACTAGCTAGACATATTACATATAC

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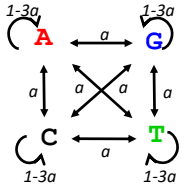
Jukes-Cantor model (1969)



p(A)=0.25
p(G)=0.25
p(C)=0.25
p(T)=0.25

Assumptions:

- All substitutions have equal probability
- Base frequencies are equal

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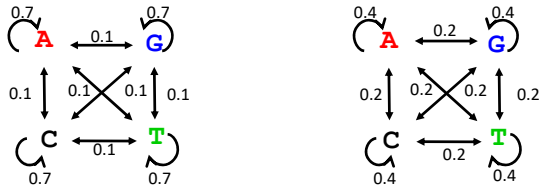
Two Jukes Cantor models with different rates

All Jukes Cantor models have a single rate parameter, *a*, $0 \le a \le 1/3$
Different instances of the JC model can have different rates. Rates are typically learned from data



The model on the right changes twice as fast as the model on the left.
In both models, all substitutions are equally probable

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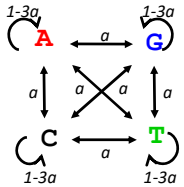
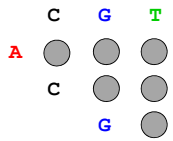
Three representations of the Jukes Cantor model





	A	C	G	T
A	*1-3a*	*a*	*a*	*a*
C	*a*	*1-3a*	*a*	*a*
G	*a*	*a*	*1-3a*	*a*
T	*a*	*a*	*a*	*1-3a*

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More nucleotide substitution models

Jukes Cantor
- Uniform substitution probabilities
- Uniform base frequencies

Substitution models can be extended by allowing
- different substitution probabilities for different base pairs
- non-uniform base frequencies

or both

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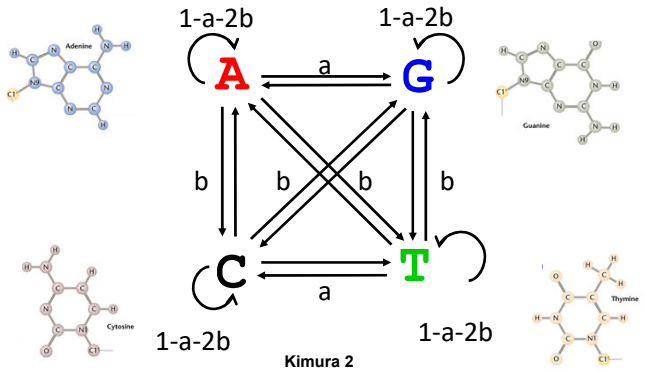
A more complex model
different probabilities for transitions and transversions



Kimura 2 parameter

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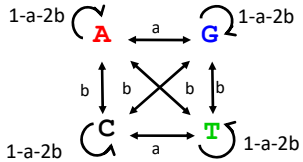
Kimura 2 parameter model (K2P) (1980)



*p(**A**)=0.25*
*p(**G**)=0.25*
*p(**C**)=0.25*
*p(**T**)=0.25*

- Transitions and transversions have different probabilities
- Base frequencies are equal

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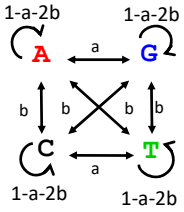
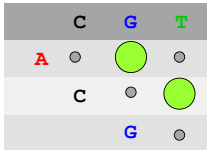
Three representations of the Kimura 2-parameter model





	A	C	G	T
A	1-a-2b	b	a	b
C	b	1-a-2b	b	a
G	a	b	1-a-2b	b
T	b	a	b	1-a-2b

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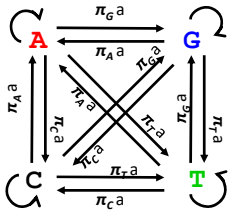
Felsenstein (1981)



$p(A)=\pi_A$
$p(G)=\pi_G$
$p(C)=\pi_C$
$p(T)=\pi_T$

- All substitutions have equal probability
- Unequal base frequencies $p(A)\neq p(G) \neq p(C) \neq p(T)$

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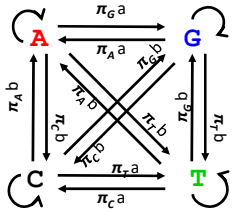
Hasegawa, Kishino & Yano (HKY) (1985)



$p(A)=\pi_A$
$p(G)=\pi_G$
$p(C)=\pi_C$
$p(T)=\pi_T$

- Transitions and transversions have different probabilities
- Unequal base frequencies $p(A)\neq p(G) \neq p(C) \neq p(T)$

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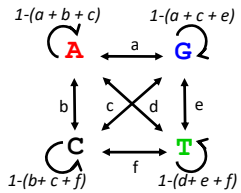
General Time Reversible model



- All six pairs have different substitution frequencies
- Unequal base frequencies $p(A)\neq p(G) \neq p(C) \neq p(T)$

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