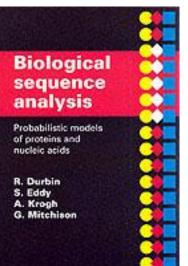
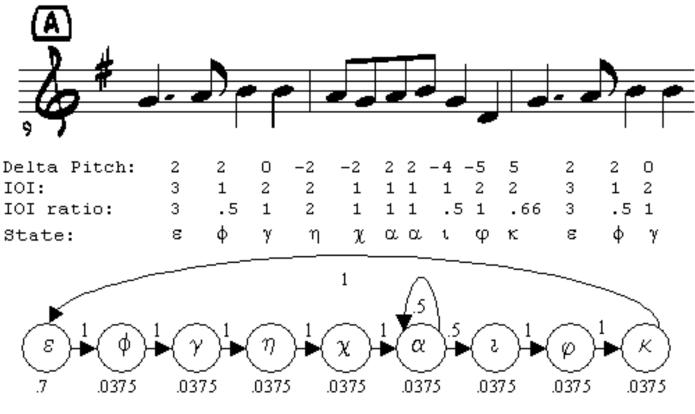
# Hidden Markov Models

based on chapters from the book Durbin, Eddy, Krogh and Mitchison Biological Sequence Analysis via Shamir's lecture notes



### music recognition

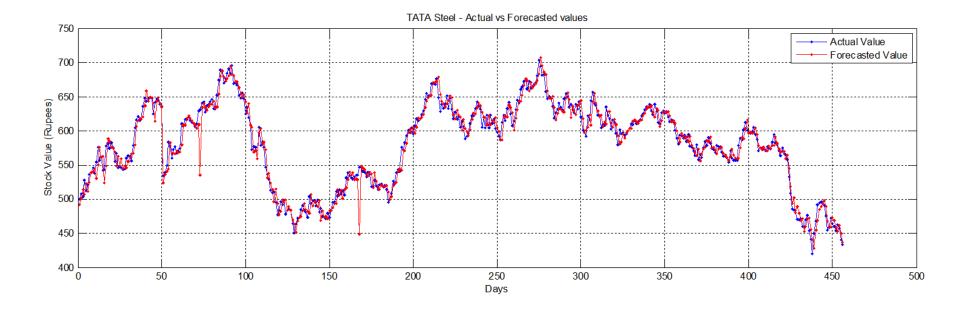


deal with variations in

- pitch
- timing
- timbre

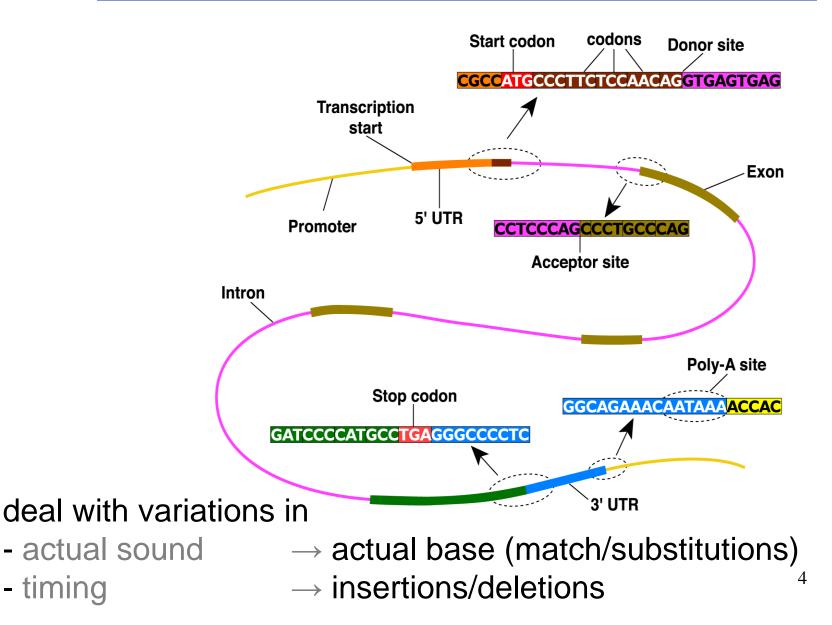
. . .

## **Stock Market Prediction**



- Actual Value versus Forcasted Value for Tata Steel in Rupees over the period 5-9 2009 – 23-9 2011.
- Variations of value over time.
- From: A. Gupta, B. Dhingra, Stock Market Prediction Using Hidden Markov Models, 2011.

# application: gene finding



# **Basic Questions**

Given:

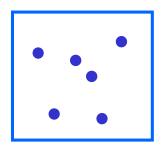
- A sequence of "observations"
- A probabilistic model of our "domain"

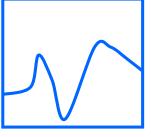
Questions:

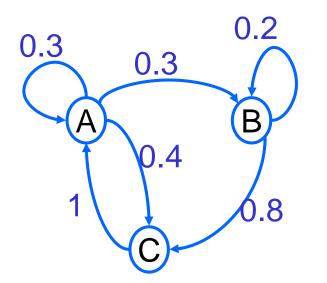
- Does the given sequence belong to a certain family?
  - Markov chains
  - Hidden Markov Models (HMMs)
- Can we say something about the internal structure of the sequence? (indirect observations)
  - Hidden Markov Models (HMMs)

# Introduction Markov Chain Model

#### Discrete vs Continuous







#### **Characteristics**

- Discrete time
- Discrete space
- No state History
  - Present state only
- States and transitions

#### **Notations:**

P(X)P(X,Y)P(X|Y)

probability for event X event X and event Y event X given event Y

### Definition of Markov Chain Model

- A Markov chain<sup>[1]</sup> model is defined by
  - a set of states
    - some states emit symbols
    - other states (e.g., the begin state) are silent
  - a set of transitions with associated probabilities
    - the transitions emanating from a given state define a distribution over the possible next states (i.e., all positive, and sum equals 1)

[1] Марков А. А., Распространение закона больших чисел на величины, зависящие друг от друга. — Известия физико-математического общества при Казанском университете. — 2-я серия. — Том 15. (1906) — С. 135—156



#### Markov Model M = (Q,P,T), with

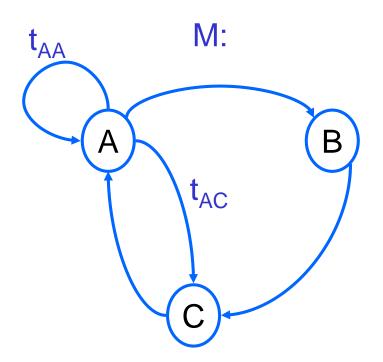
- Q the set of states
- P the set of initial probabilities p<sub>x</sub> for each state x in Q
- $T = (t_{xy})$  the transition probabilities matrix/graph, with  $t_{xy}$  the probability of the transition from state x to state y.

This is a first order Markov Model: no history is modeled

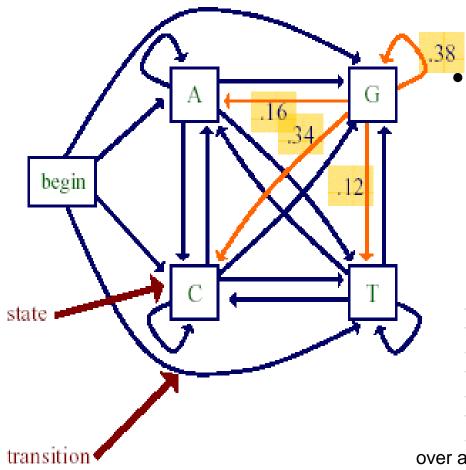
An observation X is a sequence of states:  $X = x_1 x_2 \dots x_n$ 

The probability of an observation X given the model M is equal to:

 $P(X|M) = p_{x_1} t_{x_1 x_2} t_{x_2 x_3} \dots t_{x_{n-1} x_n} = p_{x_1} \cdot \prod_{i=2}^n t_{x_{i-1} x_i}$ 



### A Markov Chain Model Example

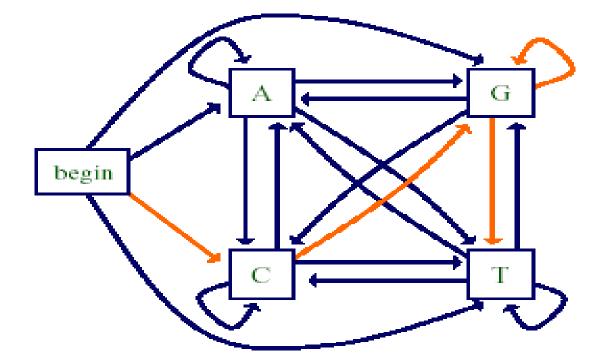


- Transition probabilities
  - $Pr(x_i = a | x_{i-1} = g) = 0.16$
  - $\Pr(x_i = c | x_{i-1} = g) = 0.34$
  - $Pr(x_i = g | x_{i-1} = g) = 0.38$
  - $\Pr(x_i = t | x_{i-1} = g) = 0.12$

$$\sum \Pr(x_i \mid x_{i-1} = g) = 1$$

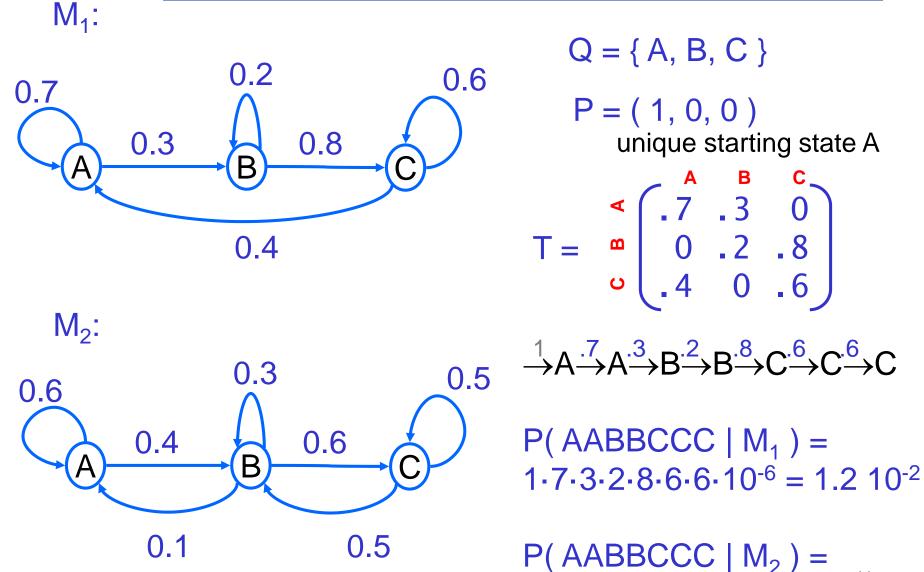
over all neighbors  $x_i$ 

#### The Probability of a Sequence for a Markov Chain Model



#### Pr(CGGT)=Pr(C)Pr(G|C)Pr(G|G)Pr(T|G)

### Markov Chains: Another Example



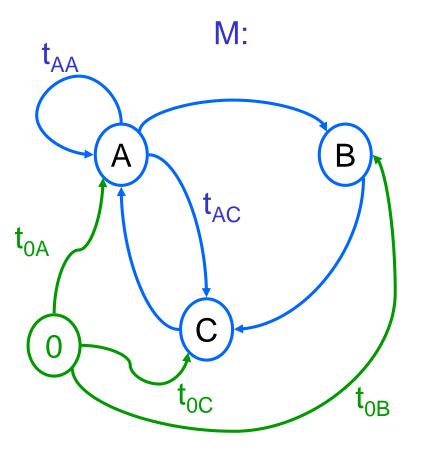
 $P(AABBCCC | M_2) =$ 1.6.4.3.6.5.5.10<sup>-6</sup> = 1.1<sup>11</sup>10<sup>-2</sup> Given some sequence *x* of length *L*, we can ask: How probable is the sequence *x* given our model *M*?

• For any probabilistic model of sequences, we can write this probability as

$$Pr(x) = Pr(x_L x_{L-1}...x_1)$$
  
= Pr(x<sub>L</sub> | x<sub>L-1</sub>...x<sub>1</sub>) Pr(x<sub>L-1</sub> | x<sub>L-2</sub>...x<sub>1</sub>)... Pr(x<sub>1</sub>)

• key property of a (1<sup>st</sup> order) Markov chain: the probability of each  $x_i$  depends only on the value of  $X_{i-1}$  Pr(x) = Pr( $x_L | x_{L-1}$ ) Pr( $x_{L-1} | x_{L-2}$ )... Pr( $x_2 | x_1$ ) Pr( $x_1$ ) = Pr( $x_1$ ) $\prod_{i=2}^{L}$  Pr( $x_i | x_{i-1}$ )

# Markov Model: Underflow Problem



 $t_{0x} = p_x$ 

- initial state x<sub>0</sub> fixed
   ~ initial probabilities
- final state [not depicted]

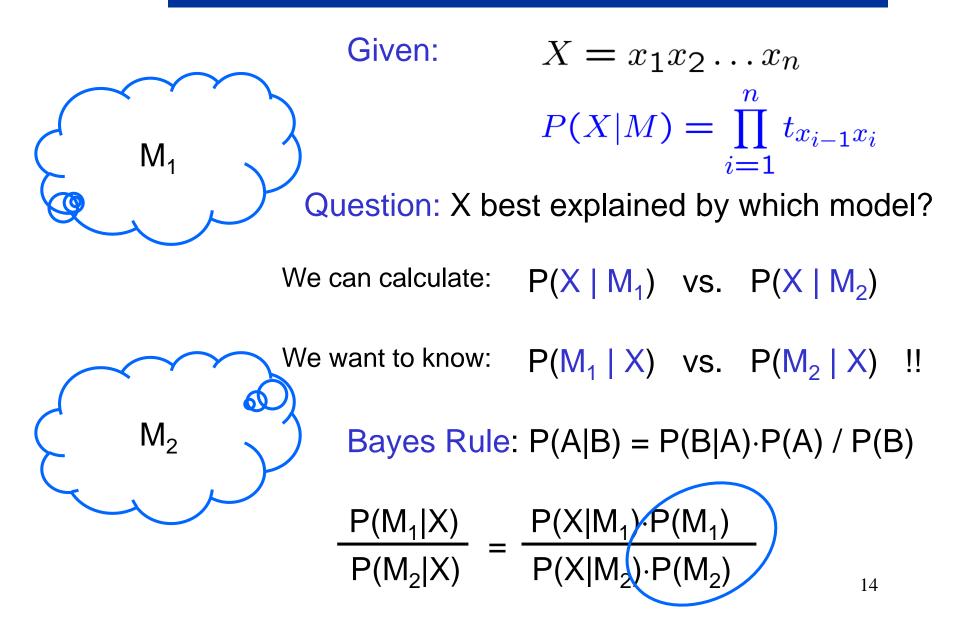
$$X = x_1 x_2 \dots x_n$$

$$P(X|M) = \prod_{i=1}^{n} t_{x_{i-1}x_i}$$

small values: underflow

$$\log P(X|M) = \sum_{i=1}^{n} \log t_{x_{i-1}x_i}$$

### Markov Model: Comparing Models





#### bases are not random

#### Motivation for Markov Models in Computational Biology

- There are many cases in which we would like to represent the statistical regularities of some *class of sequences* 
  - genes
  - various regulatory sites in DNA (e.g., where RNA polymerase and transcription factors bind)
  - proteins in a given family
- Markov models are well suited to this type of task

#### Markov Chain: An Example Application

- CpG islands
  - CG di-nucleotides are *rarer* in eukaryotic genomes than expected given the marginal probabilities of C and G
  - but the regions upstream of genes (reading is from 5' to 3') are
     richer in CG di-nucleotides than elsewhere so called CpG islands
  - useful evidence for finding genes
- Application: Predict CpG islands with Markov chains
  - a Markov chain to represent CpG islands
  - a Markov chain to represent the rest of the genome

# Markov Chains for Discrimination

- Suppose we want to distinguish CpG islands from other sequence regions
- Given sequences from CpG islands, and sequences from other regions, we can construct
  - a model to represent CpG islands
  - a null model to represent the other regions
- We can then score a test sequence X by:

$$score(X) = \log \frac{\Pr(X \mid CpGModel)}{\Pr(X \mid nullModel)}$$

### Markov Chains for Discrimination

Why can we use the scoring function:

$$score(X) = \log \frac{\Pr(X \mid CpGModel)}{\Pr(X \mid nullModel)}$$

• According to Bayes' rule we have:

$$Pr(CpG \mid X) = \frac{Pr(X \mid CpG) Pr(CpG)}{Pr(X)}$$
$$Pr(null \mid X) = \frac{Pr(X \mid null) Pr(null)}{Pr(X)}$$

• If we are not taking into account prior probabilities (Pr(CpG) and Pr(null)) of the two classes, then from Bayes' rule it is clear that we just need to compare Pr(X|CpG) and Pr(X|null) as is done in our scoring function score().

#### Markov Chain Application: CpG islands

observed frequencies	island	+ A C G T	0.171 0.161	0.368 0.339	G 0.426 0.274 0.375 0.384	0.188 0.125	
A	non island	– A C G T	0.322 0.248	0.298 0.246	G 0.285 0.078 0.298 0.292	0.302 0.208	
G	CG	In general consecutive CG pairs $CG \rightarrow CG$ are rare, although 'islands' Occur in signal (e.g.) promotor regions.					

#### basic questions

- observation: DNA sequence
- model 1: CpG islands
- model 2: non-islands

 does this sequence belong to a certain family? Markov chains is this a CpG island (or not)?

 can we say something about the internal structure? Markov Chains: windowing where are the CpG islands?

## application: CpG islands

+ A C G T
A 0.180 0.274 0.426 0.120
C 0.171 0.368 0.274 0.188
G 0.161 0.339 0.375 0.125

T 0.079 0.355 0.384 0.182

A C G T
A 0.300 0.205 0.285 0.210
C 0.322 0.298 0.078 0.302
G 0.248 0.246 0.298 0.208
T 0.177 0.239 0.292 0.292

island

non island

score

X = ACGT

$$\frac{P(X| \text{ island})}{P(X| \text{ non})} = \frac{\prod_{i=1}^{n} t_{x_{i-1}x_{i}}^{+}}{\prod_{i=1}^{n} t_{x_{i-1}x_{i}}^{-}}$$

A->C C->G G->T

Note: A score > 1 is an Indication of a CpG island.

$$\frac{0.274 \cdot 0.274 \cdot 0.125}{0.205 \cdot 0.078 \cdot 0.208} = 2.82$$

# application: CpG islands

LLR = Log-Likelihood Ratio

$$\log(t_{xy}^+/t_{xy}^-)$$

'bits'  $(\log_2)$ 

LLR A C G T  
A -0.74 0.42 0.58 -0.80  
C -0.91 0.30 1.81 -0.69  
G -0.62 0.46 0.33 -0.73  
T -1.17 0.57 0.39 -0.68  

$$log_2(0.274/0.078) = 1.81$$

log-score (log<sub>2</sub>)

$$\log \frac{P(X|\text{ island})}{P(X|\text{ non})} = \log \frac{\prod_{i=1}^{n} t_{x_{i-1}x_{i}}^{+}}{\prod_{i=1}^{n} t_{x_{i-1}x_{i}}^{-}} = \sum_{i=1}^{n} \log(\frac{t_{x_{i-1}x_{i}}^{+}}{t_{x_{i-1}x_{i}}^{-}})$$

Α

С

G

Т

X = ACGT

$$\log_2 \frac{0.274 \cdot 0.274 \cdot 0.125}{0.205 \cdot 0.078 \cdot 0.208} = 0.42 + 1.81 - 0.73 = 1.50_{23}$$

# CpG Log-Likelihood Ratio

LLR(ACGT) = 
$$0.42+1.81-0.73 = 1.50$$
 (0.37 'bits' per base)  
 $1.5/4 = 0.375$ 

is a (short) sequence a CpG island ? compare with observed data (normalized for length)
where (in long sequence) are CpG islands ?

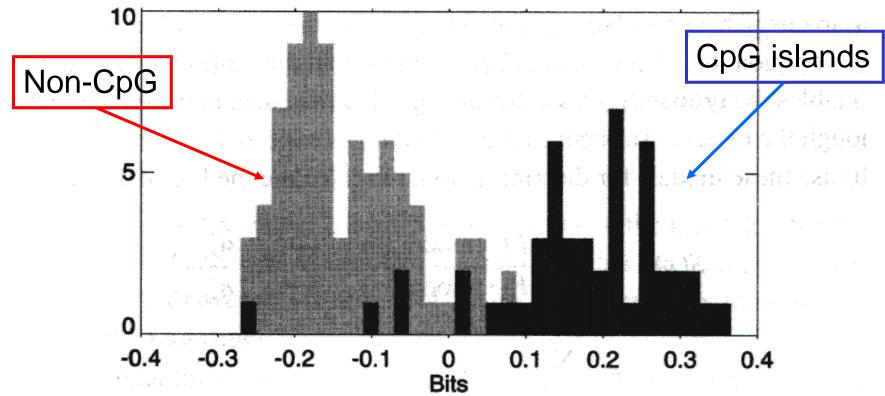
first approach: sliding window

 $\log(t_{xy}^+/t_{xy}^-)$ 

• ! What would be the length of window?

#### empirical data

#### • is a (short) sequence a CpG island ? compare with observed data (normalized for length)



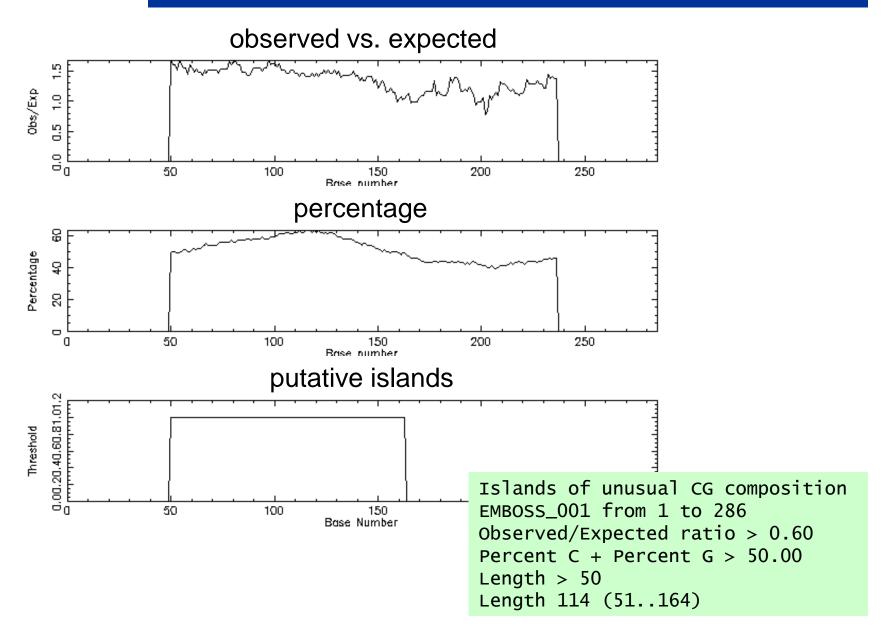
**Figure 3.2** The histogram of the length-normalised scores for all the sequences. CpG islands are shown with dark grey and non-CpG with light grey.

#### where (in long sequence) are CpG islands ? first approach: *sliding window*

# CpGplot

EMBL	-EBI Bioinformatics I	nstitute			Get Nucleotide	sequences 💌 for				
EBI Home About	t EBI Research	Services	Toolbox SEQ	Databas		ads Submissio				
<ul> <li>Help Index</li> <li>General Help</li> <li>Formats</li> <li>Gaps</li> <li>Matrix</li> <li>References</li> <li>CpGPlot Islands Help</li> </ul>	such regions are frequently switch	d to be associa attern are know rich areas, and of isochores, wo ompositionally urtitioned in a si	CpG pattern is im ated with genes v wn as CpG island d <u>cpgreport</u> to rep ery long stretche correlated with th mall number of fa	ds. port all CpG rich es of DNA that he coding 'amilies that						
	Program	Window Sep	Obs/Exp	MinPC Leng		Complement				
	Enter or Paste ACC CTC TAC ACC TAC	Enter or Paste a nucleic acid Sequence (at least 100bp) in any format:								
	Upload a file:		Blac	leren		Run Reset				





#### Some Notes on: Higher Order Markov Chains

- The Markov property specifies that the probability of a state depends only on the probability of the previous state
- But we can build more "memory" into our states by using a higher order Markov model
- In an n-th order Markov model

$$\Pr(x_i \mid x_{i-1}, x_{i-2}, ..., x_1) = \Pr(x_i \mid x_{i-1}, ..., x_{i-n})$$

The probability of the current state depends on the previous n states.

#### Selecting the Order of a Markov Chain Model

- But the number of parameters we need to estimate for an n-th order Markov model grows exponentially with the order
  - for modeling DNA we need  $O(4^{n+1})$  parameters (# of state transitions) for an n-th order model
- The higher the order, the less reliable we can expect our parameter estimates to be
  - estimating the parameters of a 2<sup>nd</sup> order Markov chain from the complete genome of E. Coli (5.44 x 10<sup>6</sup> bases), we would see each (length 3) word ~ 85.000 times on average (divide by 4<sup>3</sup>)
  - estimating the parameters of a 9<sup>th</sup> order chain, we would see each (length 10) word ~ 5 times on average (divide by 4<sup>10</sup> ~ 10<sup>6</sup>)

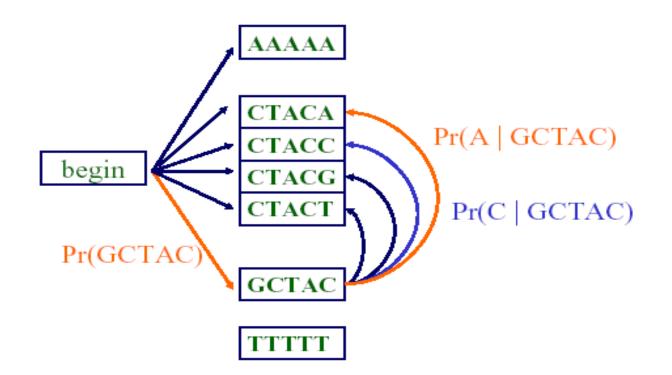
## Higher Order Markov Chains

- An n-th order Markov chain over some alphabet A is equivalent to a first order Markov chain over the alphabet of n-tuples: A<sup>n</sup>
- Example: a 2<sup>nd</sup> order Markov model for DNA can be treated as a 1<sup>st</sup> order Markov model over alphabet

AA, AC, AG, AT CA, CC, CG, CT GA, GC, GG, GT TA, TC, TG, TT

Transition probabilities: P(A|AA), P(A|AC), etc.

#### A Fifth Order Markov Chain Equivalent

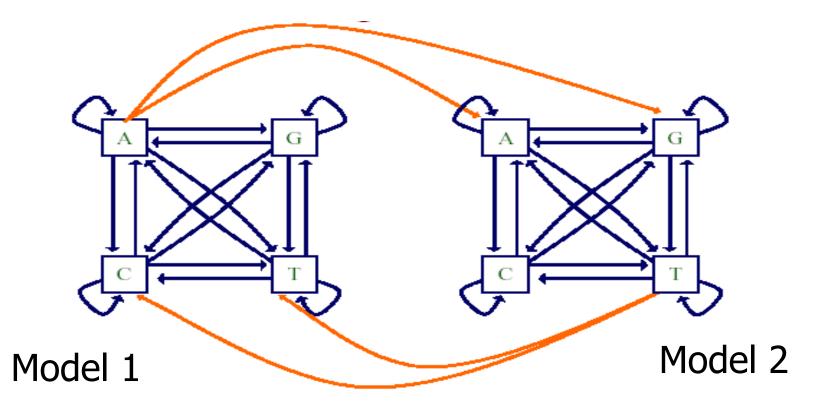


Pr(GCTACA)=Pr(GCTAC)Pr(A|GCTAC)

#### Where (in long sequence) are CpG islands?

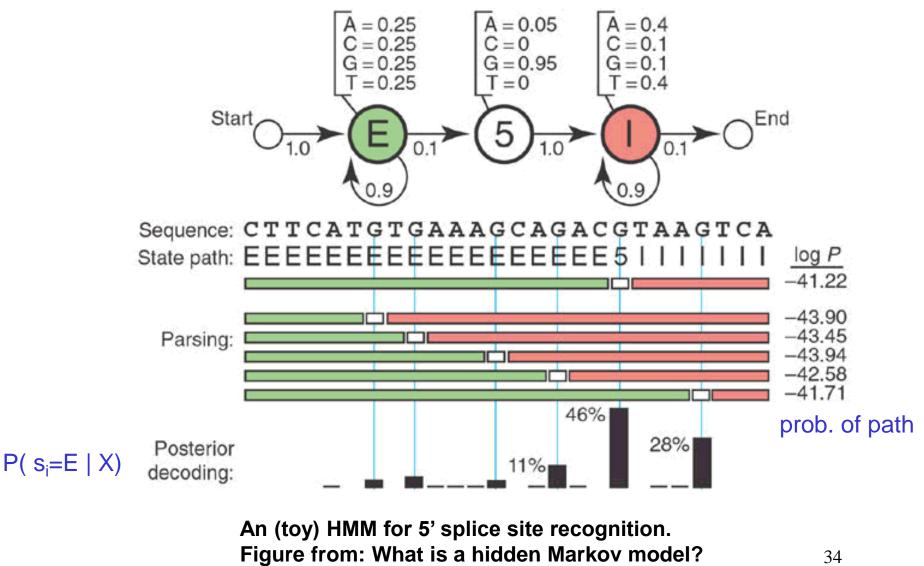
- first approach: Markov Chains + windowing
- second approach: *hidden Markov model*

#### Hidden Markov Model: A Simple HMM



Given observed sequence AGGCT, which state emits which item?

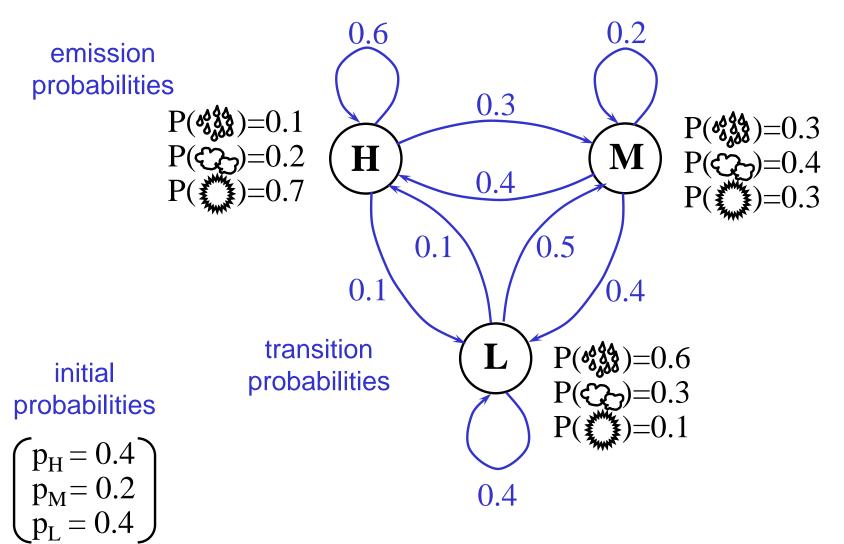
#### Another example: Eddy (2004)



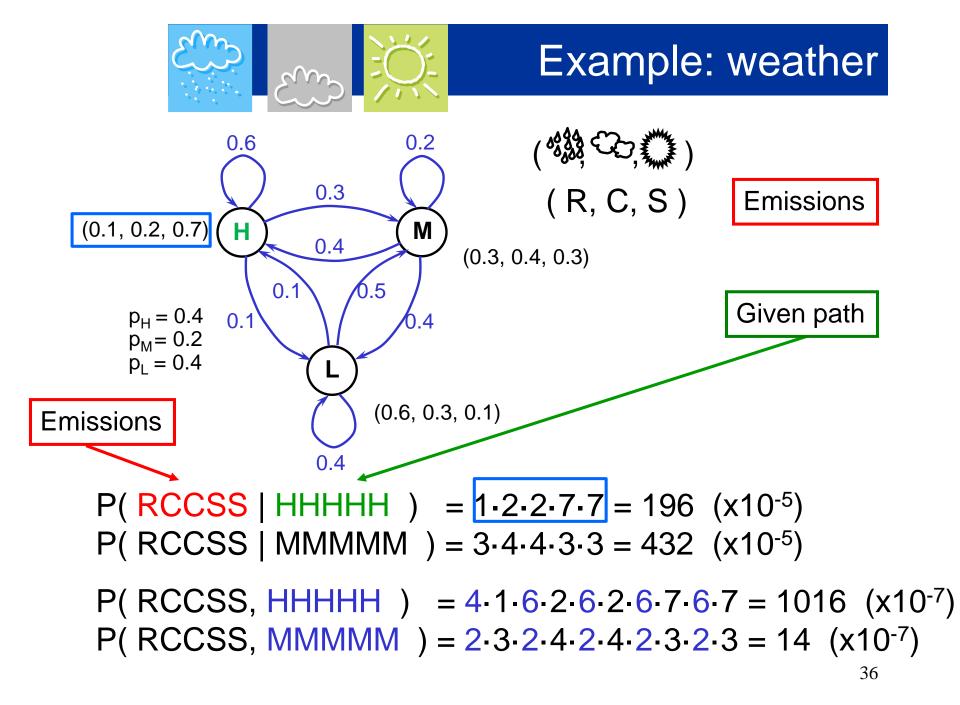
Sean R Eddy. Nature Biotechnology 22, 1315 - 1316 (2004)



#### Example: weather



observed weather vs. pressure



# hidden Markov model

what we see e<sub>Ax</sub>,  $\mathbf{e}_{\mathsf{Ay}}$ t<sub>AA</sub> B t<sub>AC</sub>

underlying process

**model**  $M = (\Sigma, Q, T)$ 

- states Q
- transition probabilities  $t_{pq}$ ,  $p,q \in Q$

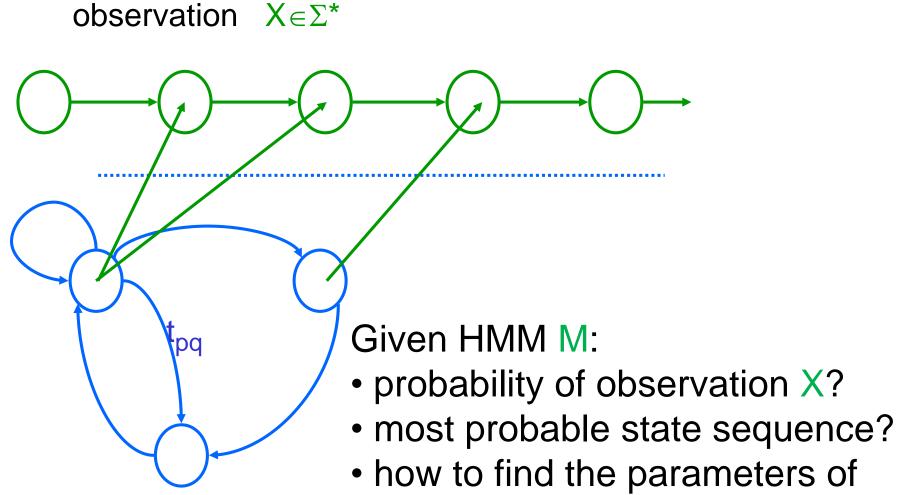
**observation**  $X = x_1 x_2 \dots x_n \in \Sigma^*$ observe states *indirectly* 'hidden' • emission probabilities

 $e_{px}, p \in Q, x \in \Sigma$   $e_p(x)$ 

#### probability

observation given the model ? there may be *many* state seq's

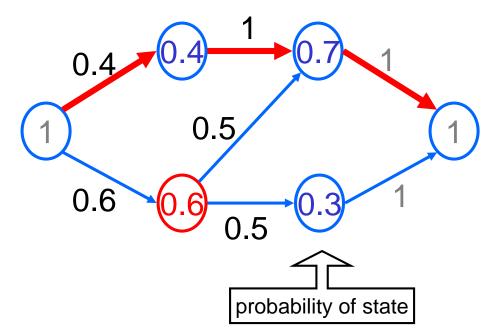
### HMM main questions



the model M? training

# probability ... !

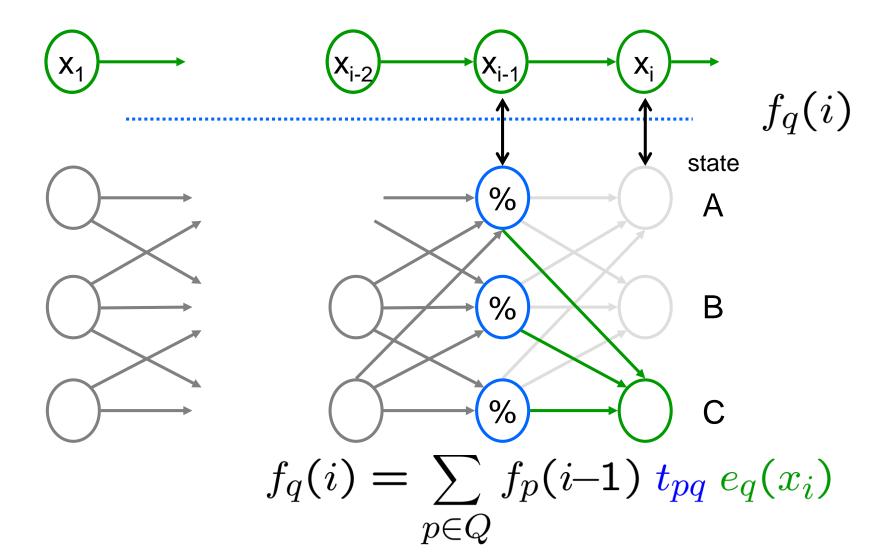
Given sequence X: most probable state vs. optimal path



 \* most probable state (over all state sequences) posterior decoding using forward & backward probabilities
 \* most probable path (= single state sequence) Viterbi

### probability of observation X

dynamic programming: probability ending in state q emitting symbol  $x_i$ 



### probability of observation X

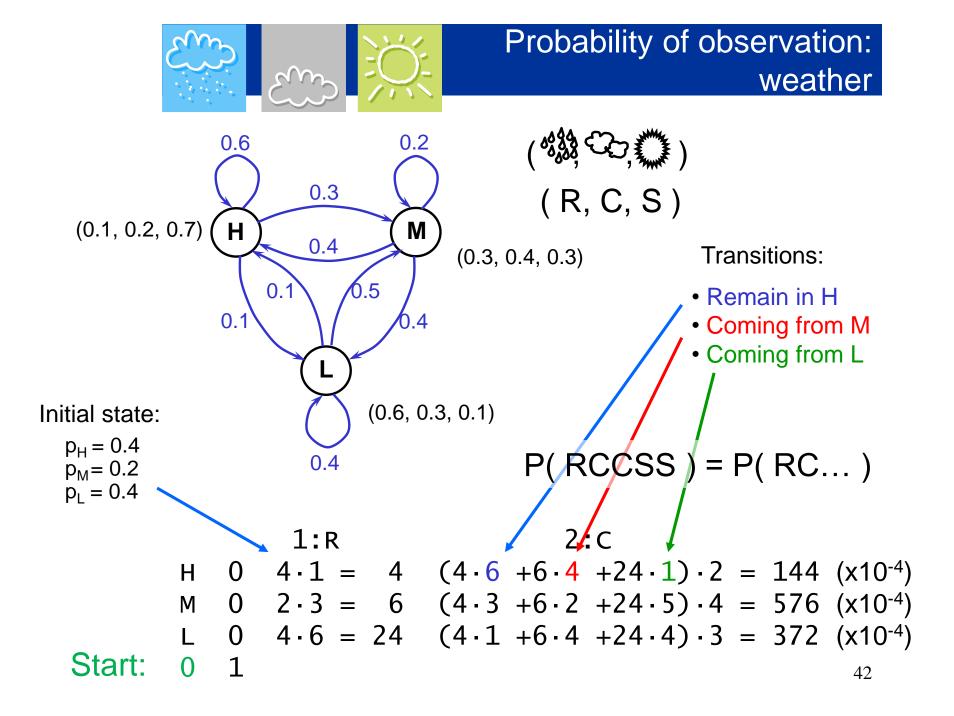
probability observing  $x_1, \ldots, x_i$  and ending in state *q*:

$$f_q(i) = P(x_1 \dots x_i, \pi_i = q)$$

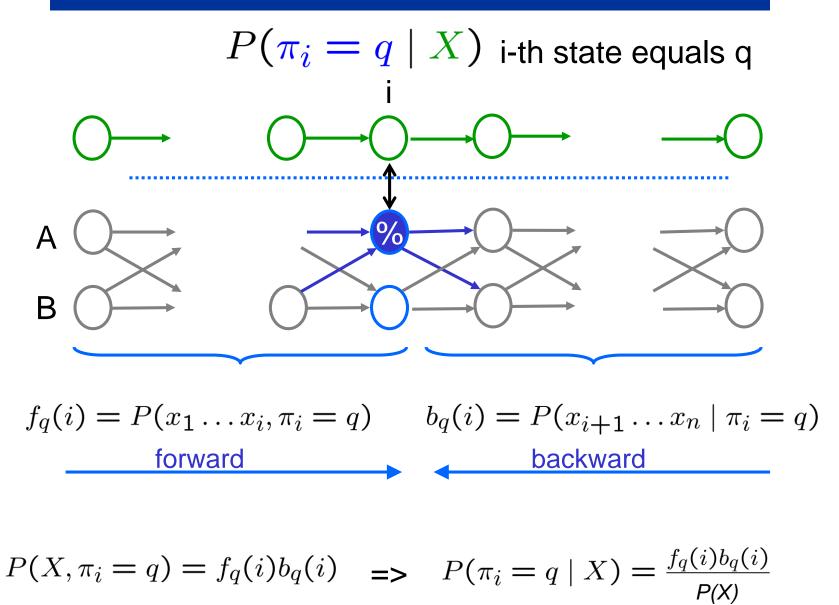
$$f_q(i) = \sum_{p \in Q} f_p(i-1) t_{pq} e_q(x_i)$$

'forward' probability

$$P(X) = \sum_{p \in Q} f_p(n) t_{p*}$$
 \* = end-state

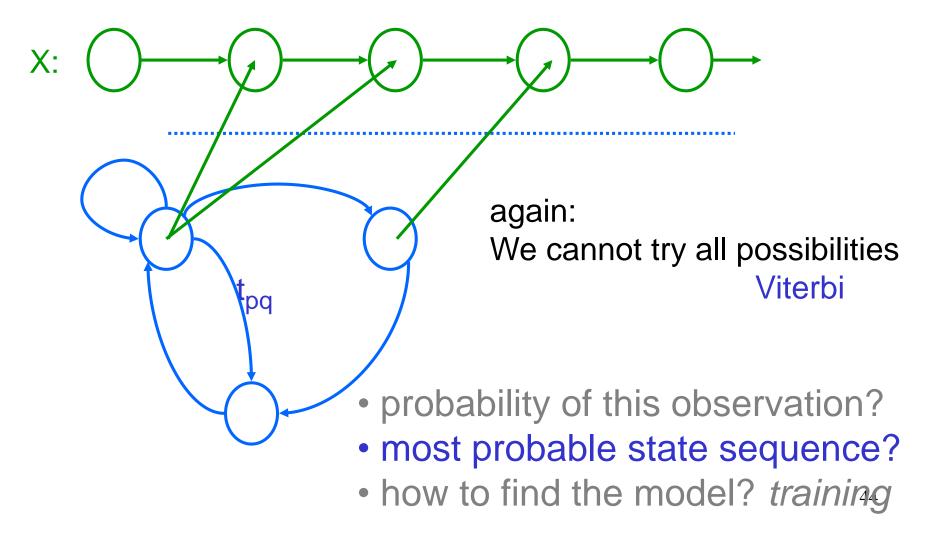


### posterior decoding



### HMM main questions

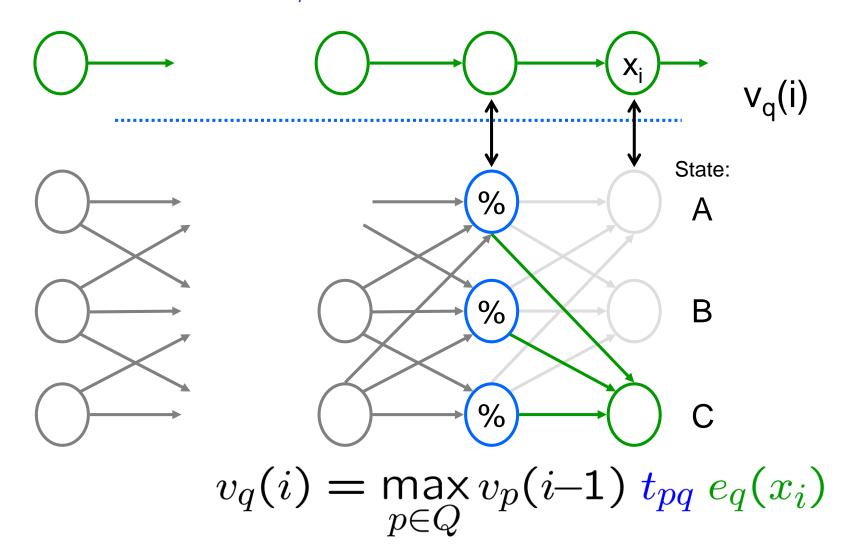
#### observation $X \in \Sigma^* \Rightarrow$ most probable state sequence



### Viterbi algorithm

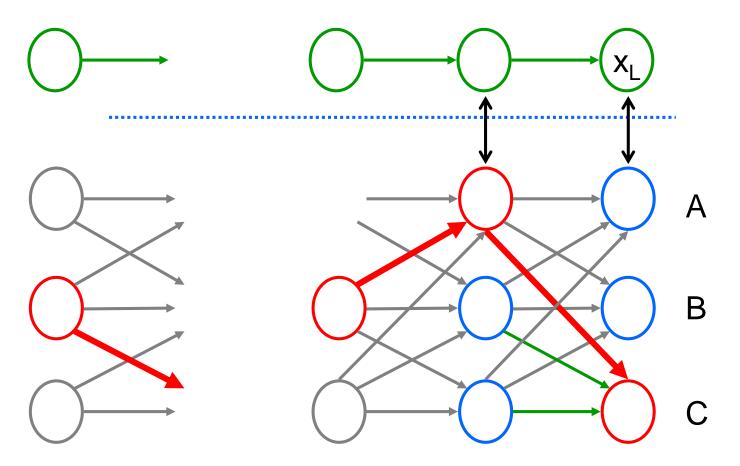
most probable state sequence for observation X

(1) dynamic programming:  $v_q(i)$  probability ending in state q and emitting  $x_i$ 

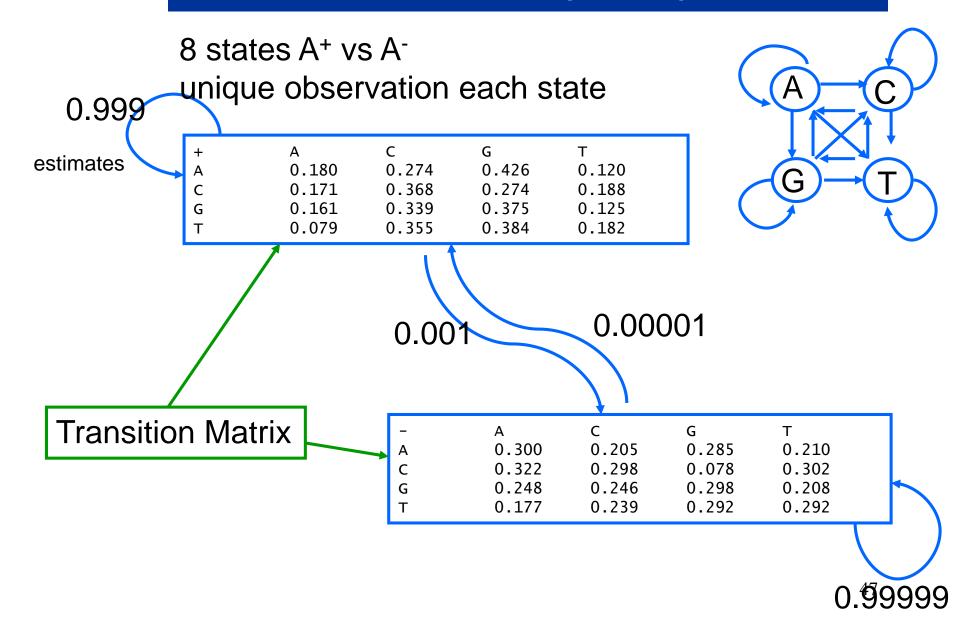


### Viterbi algorithm

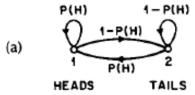
(2) *traceback*: most probable state sequence start with final maximum



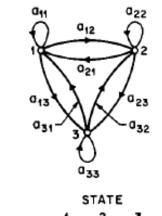
### HMM Example: CpG islands



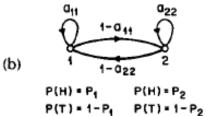
### HMM for Hidden Coin Tossing



0 = HHTTHTHHHTTH... S = 1 1 2 2 1 2 1 1 2 2 1 ...



0 = HHTTHTHHTTH... S = 31233112313...

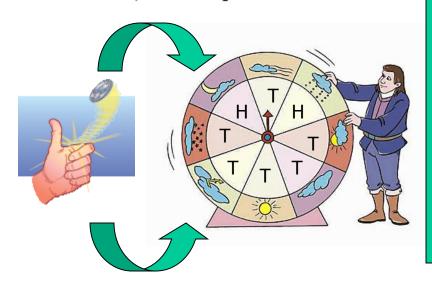


0 = HHTTHTHHTTH... S = 2 1 1 2 2 2 1 2 2 1 2 ...

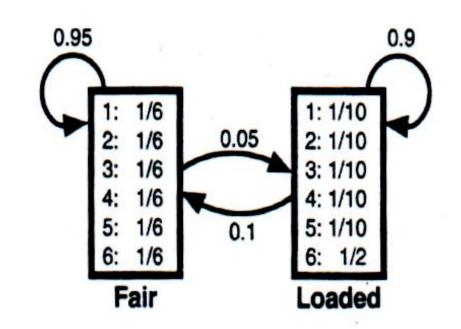
(c)

Fig. 2. Three possible Markov models which can account for the results of hidden coin tossing experiments. (a) 1-coin model. (b) 2-coins model. (c) 3-coins model.

ннттнтннттн



### dishonest casino dealer





### dishonest casino dealer

Rolls	315116246446644245321131631164152133625144543631656626566666
Die	FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi	FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Rolls	6511664531326512456366646316366631623264552352666666625151631
Die	LLLLLFFFFFFFFFFFFFFLLLLLLLLLLLLFFFFLLLLL
Viterbi	LLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Rolls	222555441666566563564324364131513465146353411126414626253356
Die	FFFFFFFFLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFF
Viterbi	FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Rolls	366163666466232534413661661163252562462255265252266435353336
Die	LLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi	LLLLLLLLLLFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Rolls	233121625364414432335163243633665562466662632666612355245242
Die	FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF
Viterbi	FFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFFF

#### 

Compare to:

#### 

### Sketch: Parameter estimation

training sequences  $X^{(i)}$ optimize score  $\prod_{i=1}^{n} P(X^{(i)} | \Theta)$  for model  $\Theta$ .

Markov Chain: state sequences known

- count transitions pq
- count emissions b in p

$$egin{array}{l} A_{pq}\ E_p(b) \end{array}$$

divide by

- total transitions in p
- emissions in q

Laplace correction

### Baum-Welch

HMM: state sequences unknown

### **Baum-Welch training**

based on model expected number of transitions, emissions build new (better) model & iterate

$$P(\pi_i = p, \pi_{i+1} = q \mid X, \Theta) = \frac{f_p(i) \cdot t_{pq} \cdot e_q(x_{i+1}) \cdot b_q(i+1)}{P(X)}$$

- *A<sub>pq</sub>* sum over all training sequences X sum over all positions i
- $E_p(b)$  sum over all training sequences X sum over all positions i with x<sub>i</sub>=b

### Baum-Welch training

#### concerns:

- guaranteed to converge target score, not ⊖
- unstable solutions !
- local maximum

#### tips:

- repeat for several initial  $\Theta$
- start with meaningful  $\Theta$

# Viterbi training (sketch):

- determine optimal paths
- re-compute as if paths are known
- score may decrease!

L.R. Rabiner, A Tutorial on Hidden Markov Models and Selected Applications in Speech Recognition,Proceeding of the IEEE, Vol. 77, No. 22, February 1989.

Krogh, I. Saira Mian, D. Haussler, A Hidden Markov Model that finds genes in E. coli DNA, Nucleid Acids Research, Vol. 22 (1994), pp 4768-4778

Furthermore:

R. Hassan, A combination of hidden Markov model and fuzzy model for stock market forecasting, Neurocomputing archive, Vol. 72, Issue 16-18, pp 3439-3446, October 2009.