Hidden Markov Models

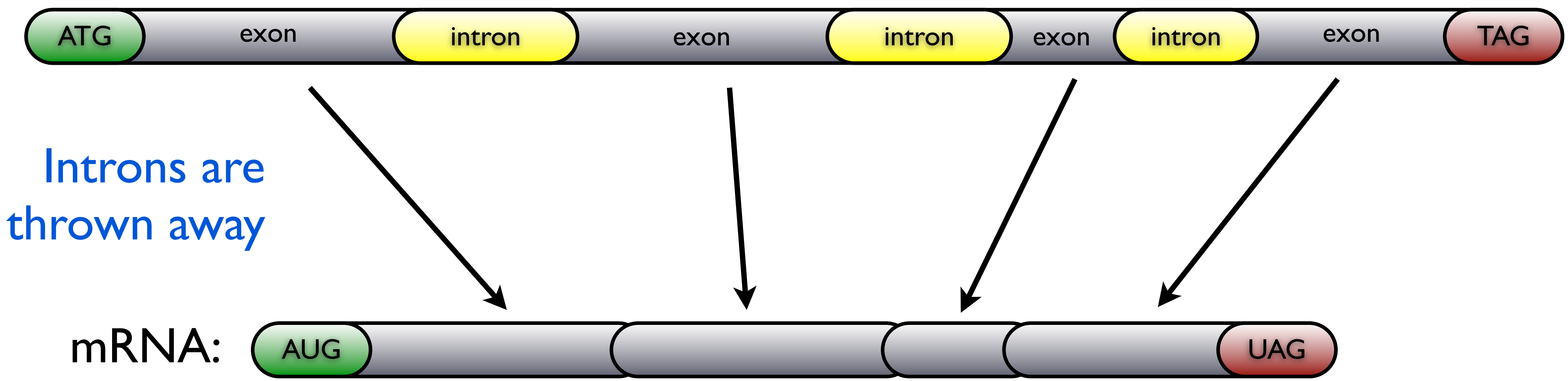
CMSC 423

Based on Chapter 11 of Jones & Pevzner, *An Introduction to Bioinformatics Algorithms*

Eukaryotic Genes & Exon Splicing

Prokaryotic (bacterial) genes look like this:

Eukaryotic genes usually look like this:



Exons are concatenated together

This spliced RNA is what is translated into a protein.

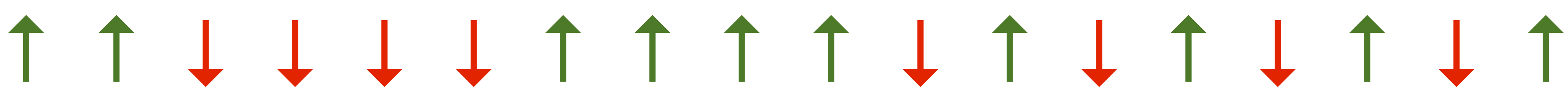
Checking a Casino

Fair coin:
Pr(Heads) = 0.5

Biased coin:
Pr(Heads) = 0.75

?

Suppose either a fair or biased coin was used to generate a sequence of heads & tails. But we don't know which type of coin was actual used.

Heads/Tails: 

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Heads/Tails: ↑ ↑ ↓ ↓ ↓ ↓ ↑ ↑ ↑ ↑ ↓ ↑ ↓ ↑ ↓ ↑ ↓ ↑

Checking a Casino

Fair coin:
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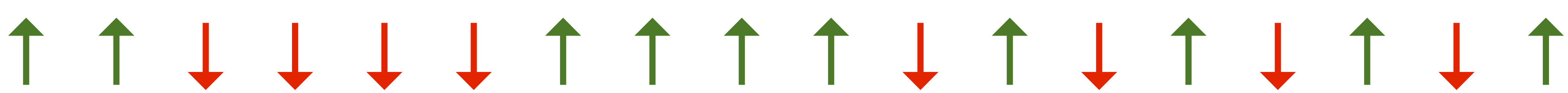
Suppose either a fair or biased coin was used to generate a sequence of heads & tails. But we don't know which type of coin was actual used.

Heads/Tails:



How could we guess which coin was more likely?

Compute the Probability of the Observed Sequence

Fair coin: Pr(Heads) = 0.5
Biased coin: Pr(Heads) = 0.75

X =	↑	↑	↓	↓	↓	↓	↑
Pr(x | Fair) =	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Pr(x | Biased) =	0.75	0.75	0.25	0.25	0.25	0.25	0.75

Compute the Probability of the Observed Sequence

Fair coin: Pr(Heads) = 0.5
Biased coin: Pr(Heads) = 0.75

X = ↑ ↑ ↓ ↓ ↓ ↓ ↑

Pr(x | Fair) = 0.5 × 0.5 × 0.5 × 0.5 × 0.5 × 0.5 × 0.5 $= 0.5^7 = 0.0078125$

Pr(x | Biased) = 0.75 × 0.75 × 0.25 × 0.25 × 0.25 × 0.25 × 0.75 = 0.001647949

Compute the Probability of the Observed Sequence

Fair coin: Pr(Heads) = 0.5
Biased coin: Pr(Heads) = 0.75

X = ↑ ↑ ↓ ↓ ↓ ↓ ↑

$\Pr(x \mid \text{Fair}) = 0.5 \times 0.5 \times 0.5 \times 0.5 \times 0.5 \times 0.5 \times 0.5 \quad = 0.5^7 = 0.0078125$

$\Pr(x \mid \text{Biased}) = 0.75 \times 0.75 \times 0.25 \times 0.25 \times 0.25 \times 0.25 \times 0.75 \quad = 0.001647949$

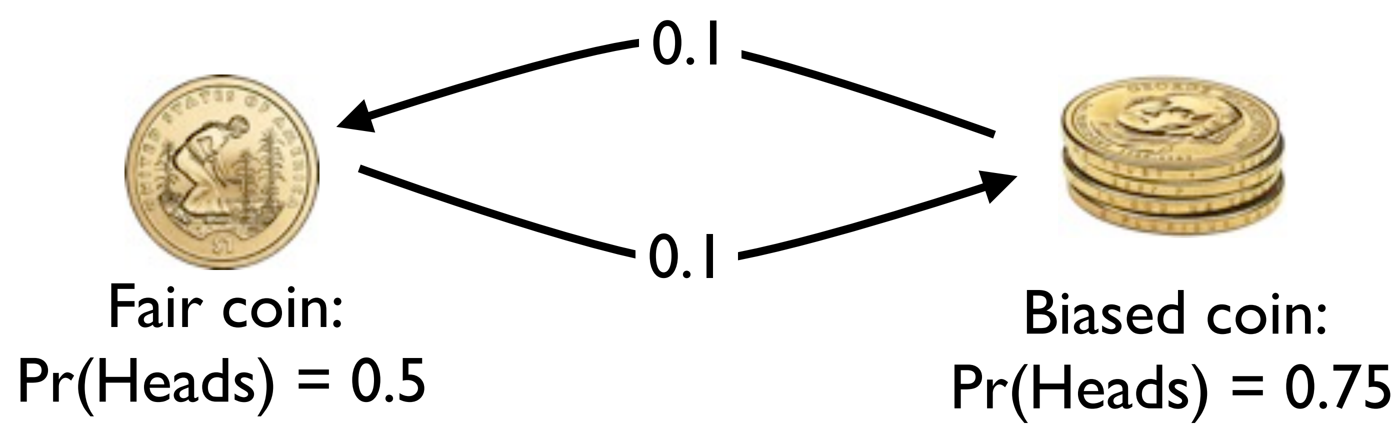
The *log-odds score*:

$$\log_2 \frac{\Pr(x \mid \text{Fair})}{\Pr(x \mid \text{Biased})} = \log_2 \frac{0.0078}{0.0016} = 2.245$$

> 0. Hence "Fair" is a better guess.

What if the casino switches coins?

Fair coin: Pr(Heads) = 0.5
Biased coin: Pr(Heads) = 0.75
Probability of switching coins = 0.1



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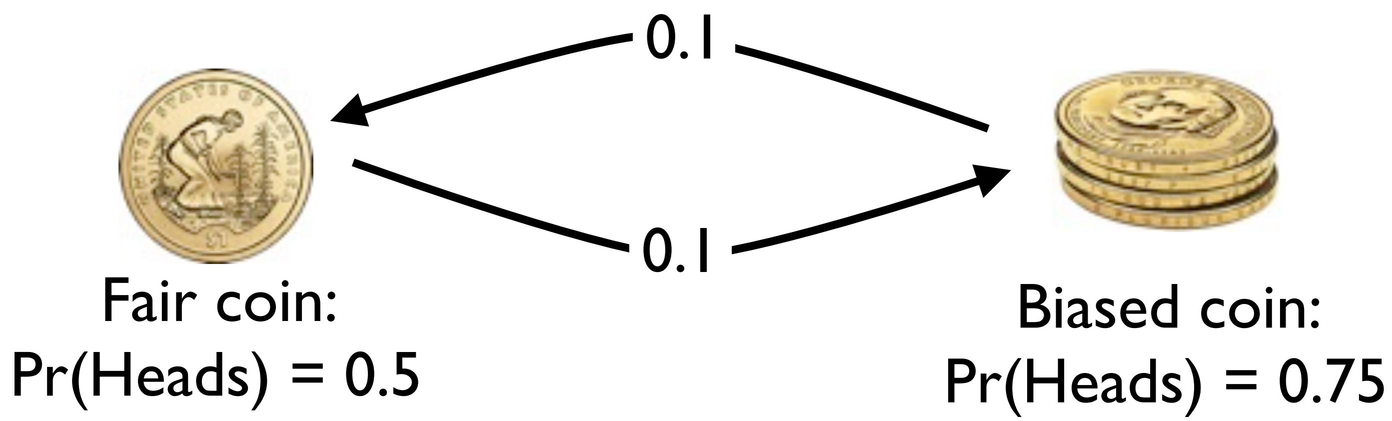

How can we compute the probability of the entire sequence?

What if the casino switches coins?

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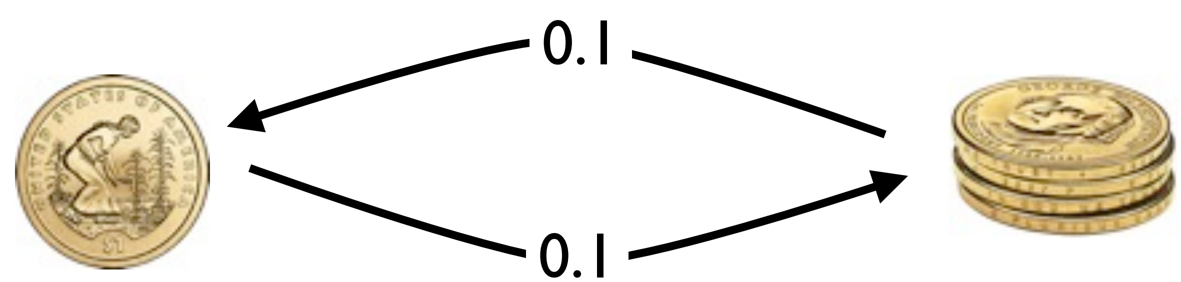

Fair coin:
Pr(Heads) = 0.5

Biased coin:
Pr(Heads) = 0.75

How can we compute the probability of the entire sequence?

How could we guess which coin was more likely **at each position**?

What does this have to do with biology?

atg gat ggg agc aga tca gat cag atc agg gac gat aga cga tag tga

What does this have to do with biology?

Before:

How likely is it that this sequence was generated by a fair coin?
Which parts were generated by a biased coin?

atg gat ggg agc aga tca gat cag atc agg gac gat aga cga tag tga

What does this have to do with biology?

Before:

How likely is it that this sequence was generated by a fair coin?

Which parts were generated by a biased coin?

Now:

How likely is it that this is a gene?

Which parts are the start, middle and end?

atg gat ggg agc aga tca gat cag atc agg gac gat aga cga tag tga

What does this have to do with biology?

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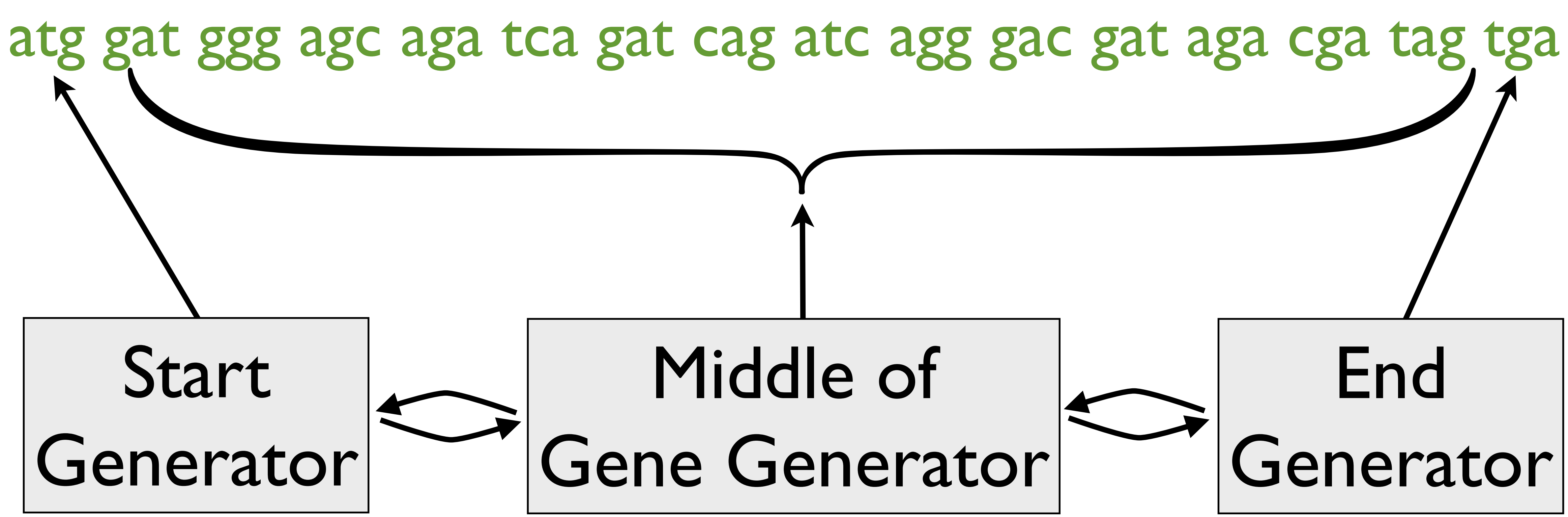
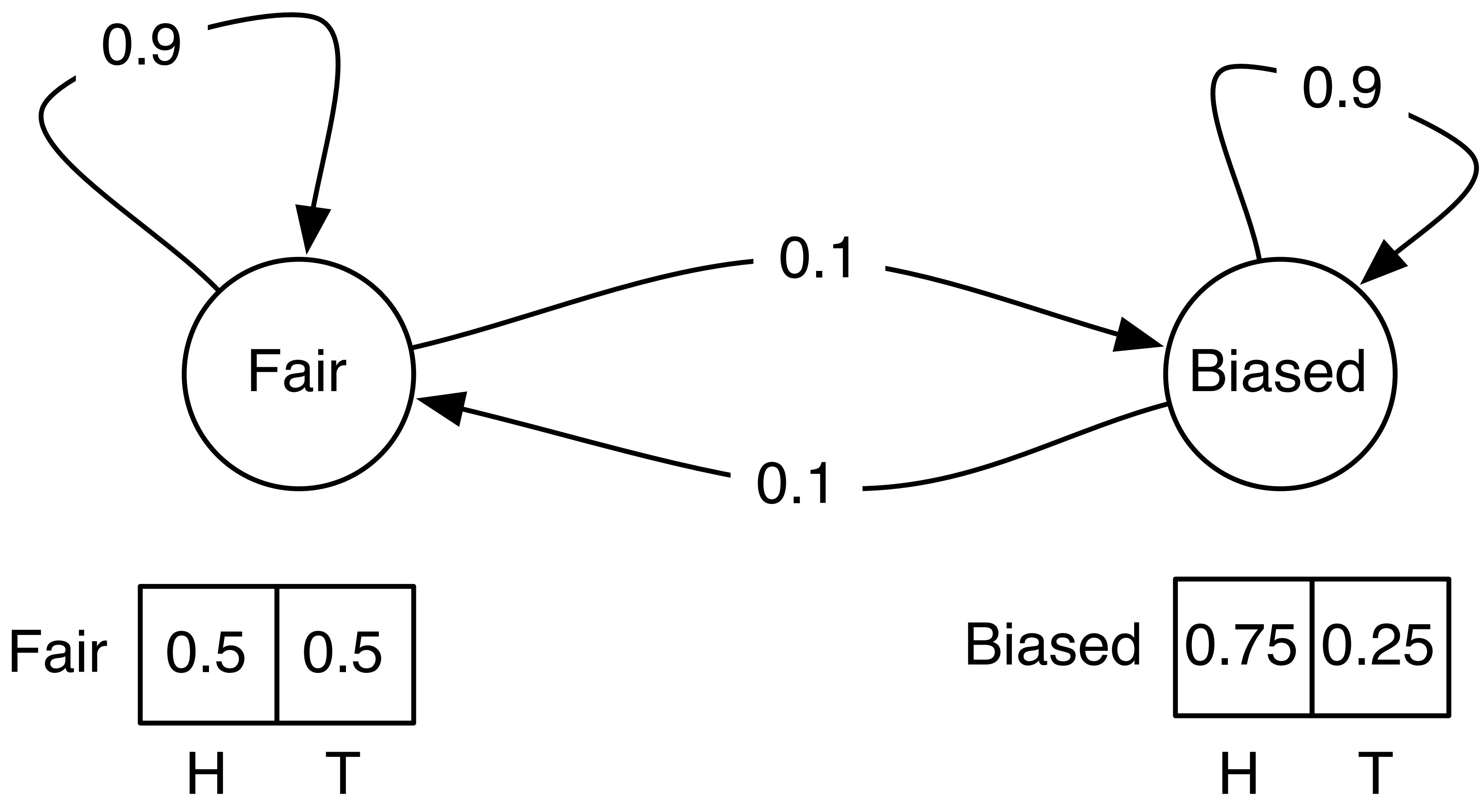


Hidden Markov Model (HMM)

Fair coin: Pr(Heads) = 0.5
Biased coin: Pr(Heads) = 0.75
Probability of switching coins = 0.1



Formal Definition of a HMM

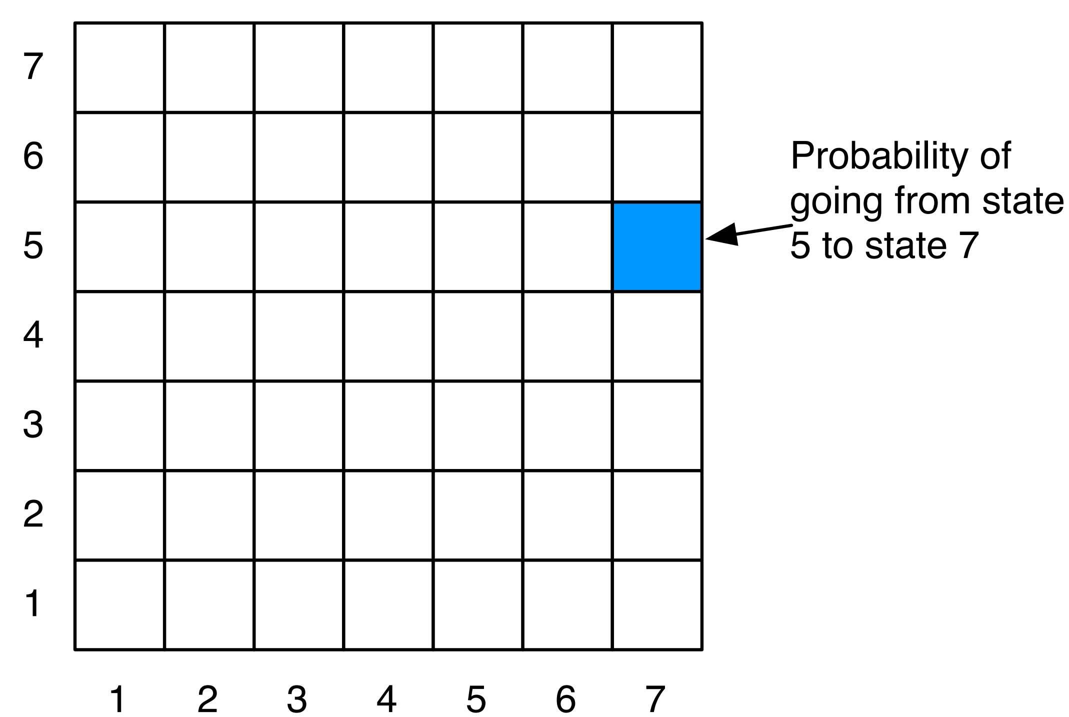
∑ = alphabet of symbols.

Q = set of states.

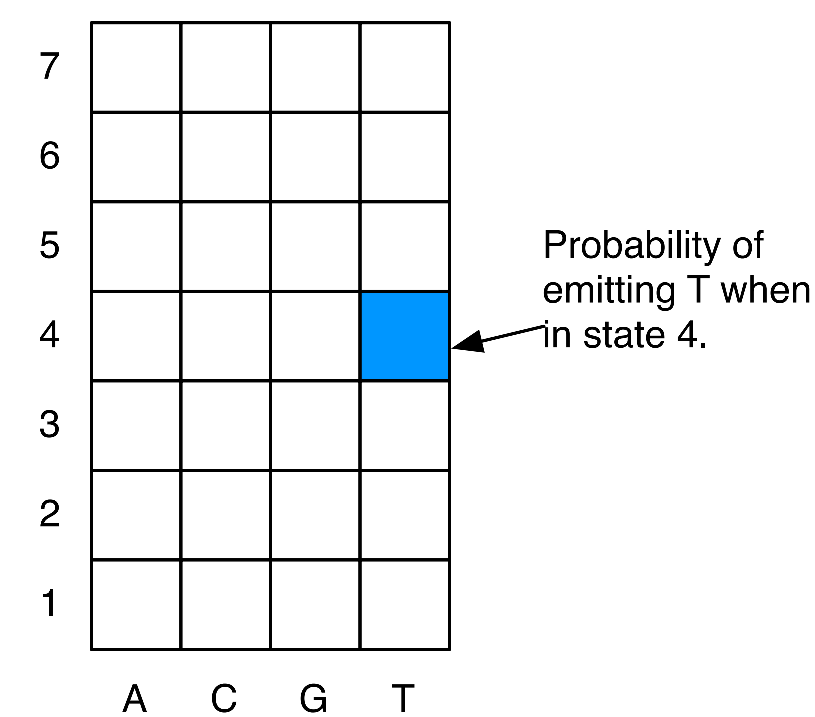
A = an |Q| x |Q| matrix where entry (k,l) is the probability of moving from state k to state l.

E = a |Q| x |∑| matrix, where entry (k,b) is the probability of emitting b when in state k.

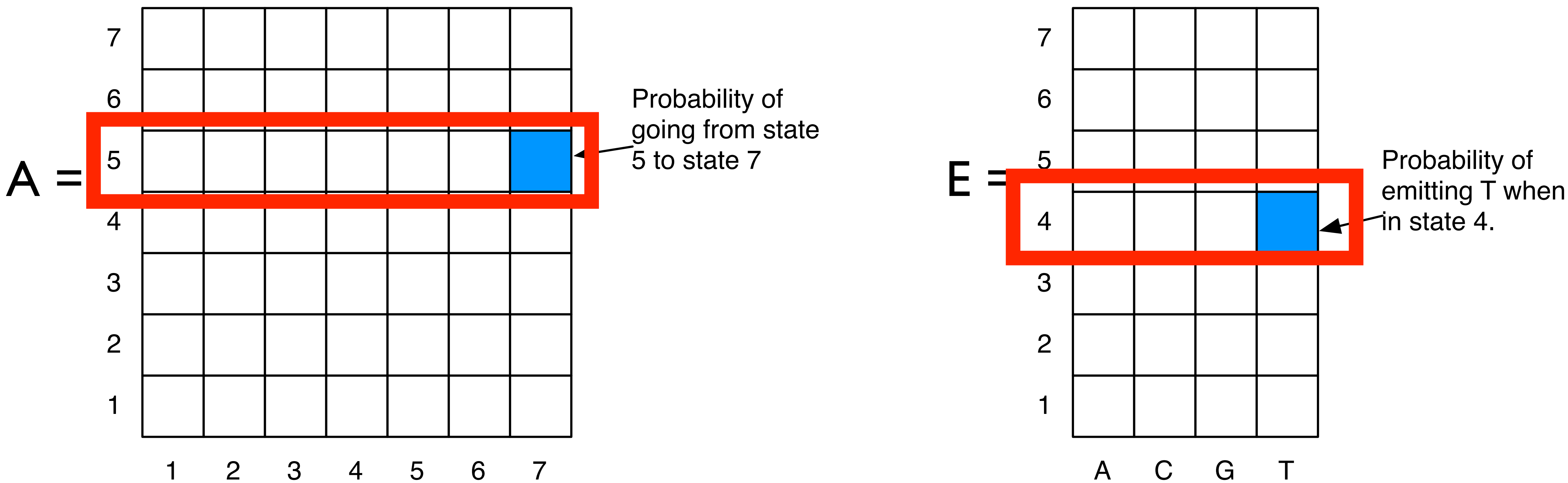
A =



E =

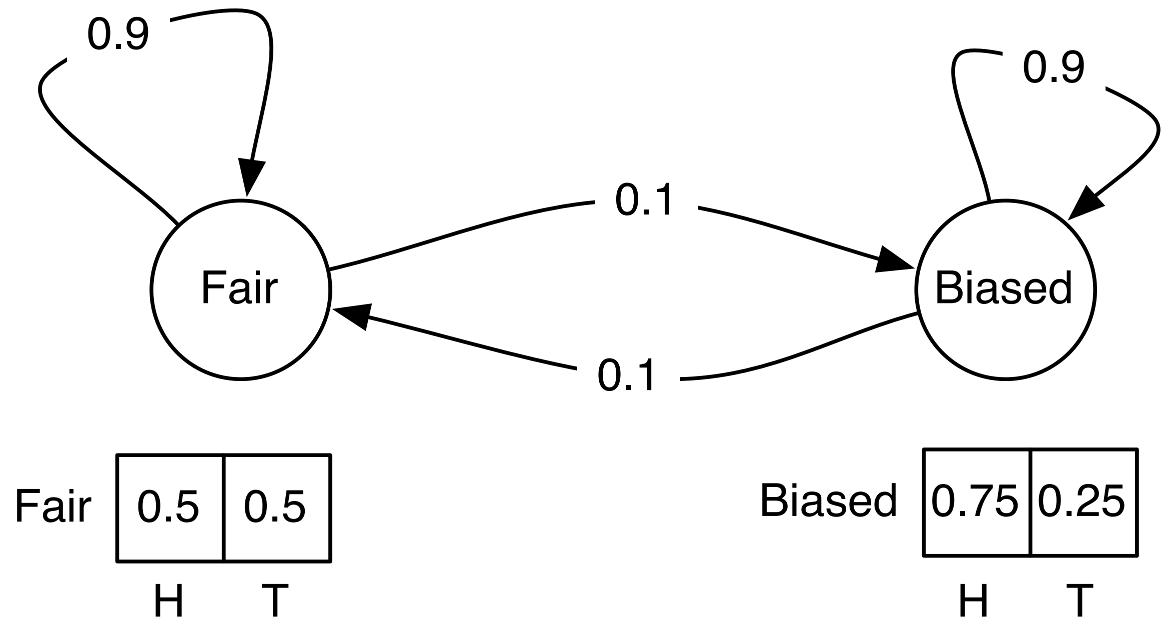


Constraints on A and E



Sum of the # in each row must be 1.

Computing Probabilities Given Path



x =	↓	↑	↓	↑	↑	↑	↓	↑	↑	↓
π =	F	F	F	B	B	B	B	F	F	F
$\Pr(x_i \mid \pi_i)$ =	0.5	0.5	0.5	0.75	0.75	0.75	0.25	0.5	0.5	0.5
$\Pr(\pi_i \rightarrow \pi_{i+1})$ =	0.1	0.9	0.9	0.1	0.9	0.9	0.9	0.1	0.1	0.1

The Decoding Problem

Given x and π, we can compute:

- $\Pr(x \mid \pi)$: product of $\Pr(x_i \mid \pi_i)$
- $\Pr(\pi)$: product of $\Pr(\pi_i \to \pi_{i+1})$
- $\Pr(x, \pi)$: product of all the $\Pr(x_i \mid \pi_i)$ and $\Pr(\pi_i \to \pi_{i+1})$

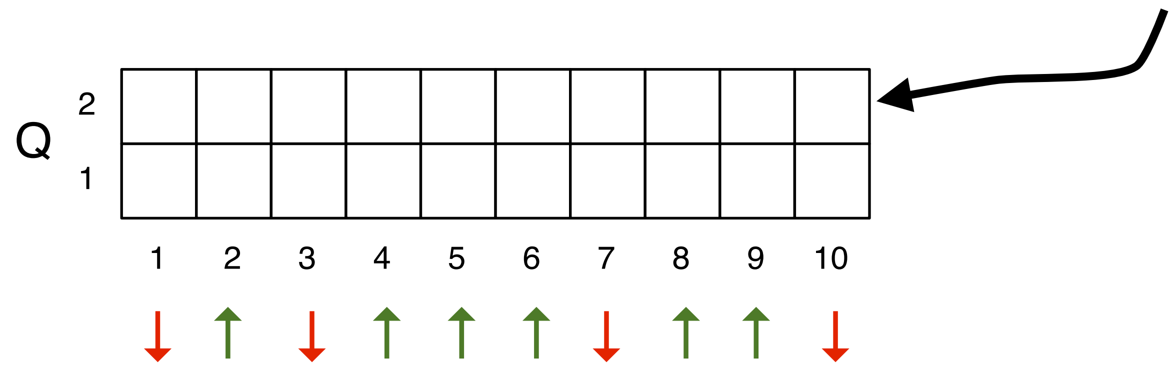
$$\Pr(x, \pi) = \Pr(\pi_0 \to \pi_1) \prod_{i=1}^{n} \Pr(x_i \mid \pi_i) \Pr(\pi_i \to \pi_{i+1})$$

But they are "hidden" Markov models because π is unknown.

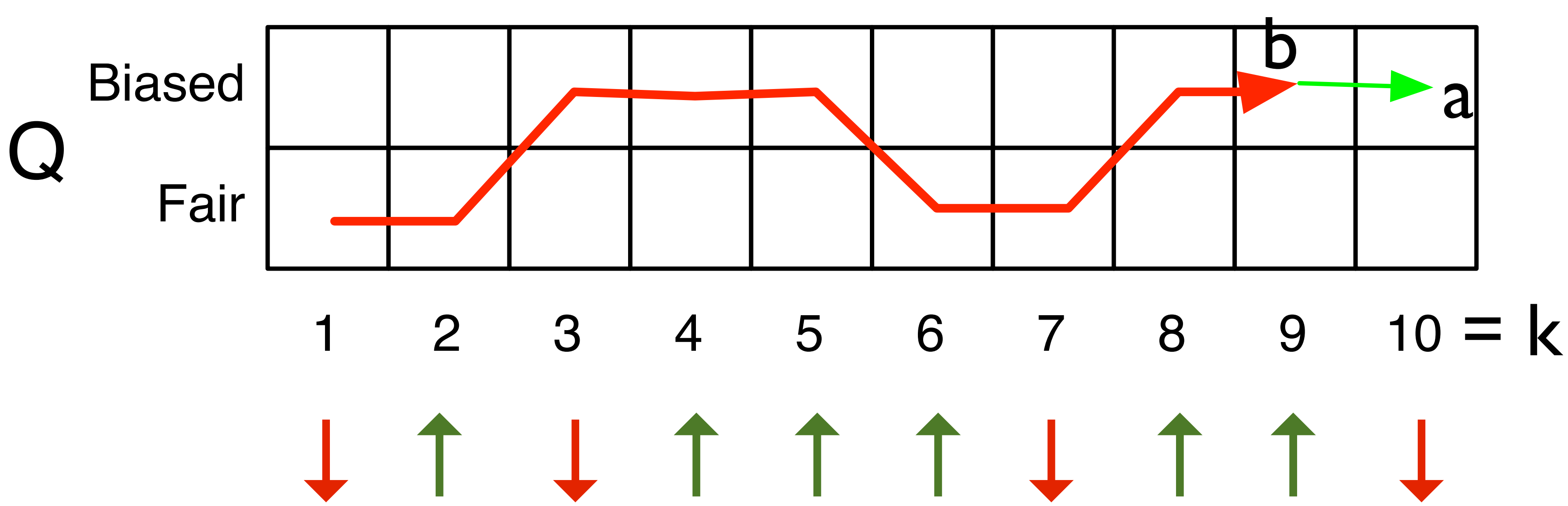
Decoding Problem: Given a sequence $x_1x_2x_3...x_n$ generated by an HMM (Σ, Q, A, E), find a path π that maximizes $\Pr(x, \pi)$.

The Viterbi Algorithm to Find Best Path

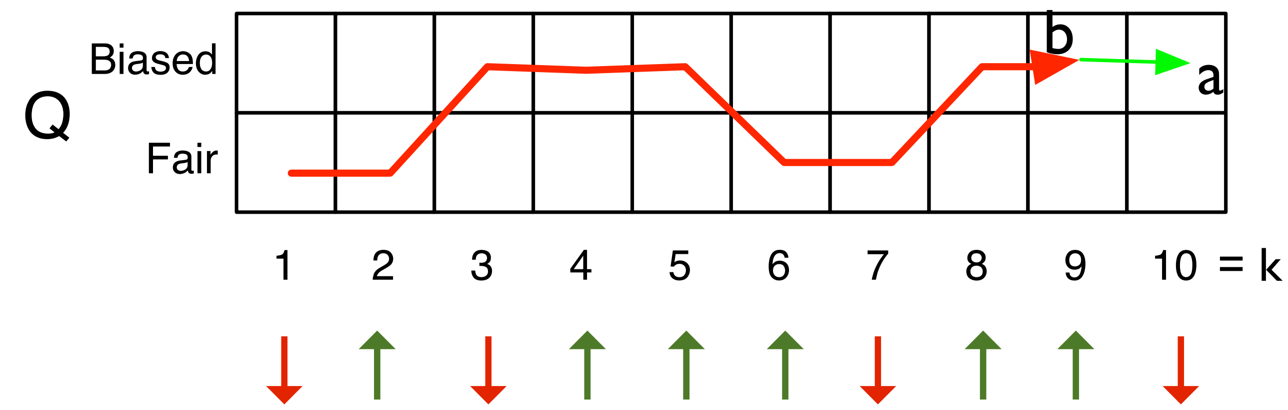
A[a, k] := the probability of the **best** path for $x_1 \ldots x_k$ that ends at state a.



A[a, k] = the path for $x_1 \ldots x_{k-1}$ that goes to some state *b* times cost of a transition from b to i, and then to output x_k from state a.



Viterbi DP Recurrence



$$A[a,k] = \max_{b \in Q} \{A[b, k-1] \times \Pr(b \to a) \times \Pr(x_k \mid \pi_k = a)\}$$

Over all possible previous states.

Best path for $x_1..x_k$ ending in state b

Probability of transitioning from state b to state a

Probability of outputting x_k given that the kth state is a.

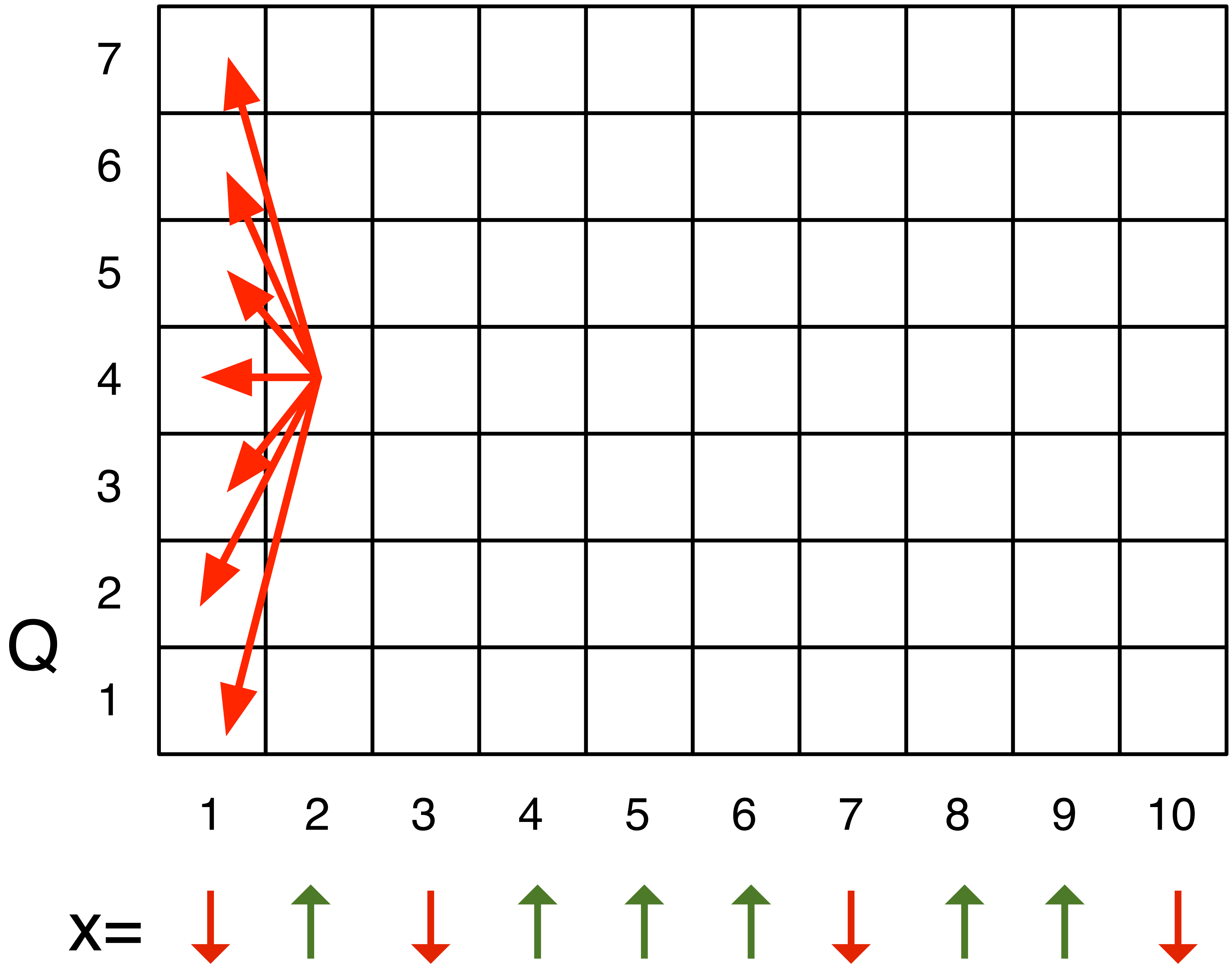
Base case:

$$A[a,1] = \Pr(\pi_1 = a) \times \Pr(x_1 \mid \pi_1 = a)$$

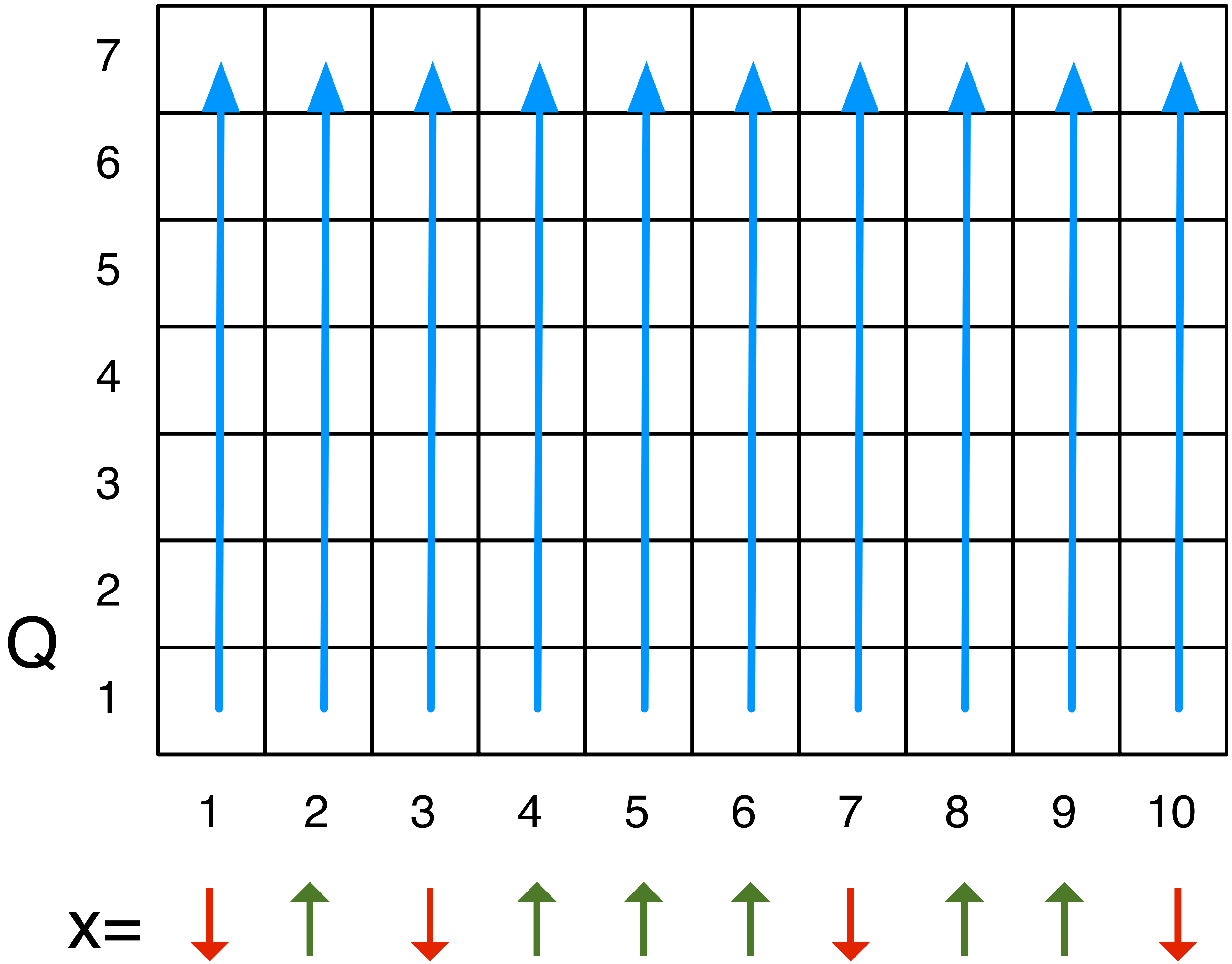
Probability that the first state is a

Probability of emitting x_1 given the first state is a.

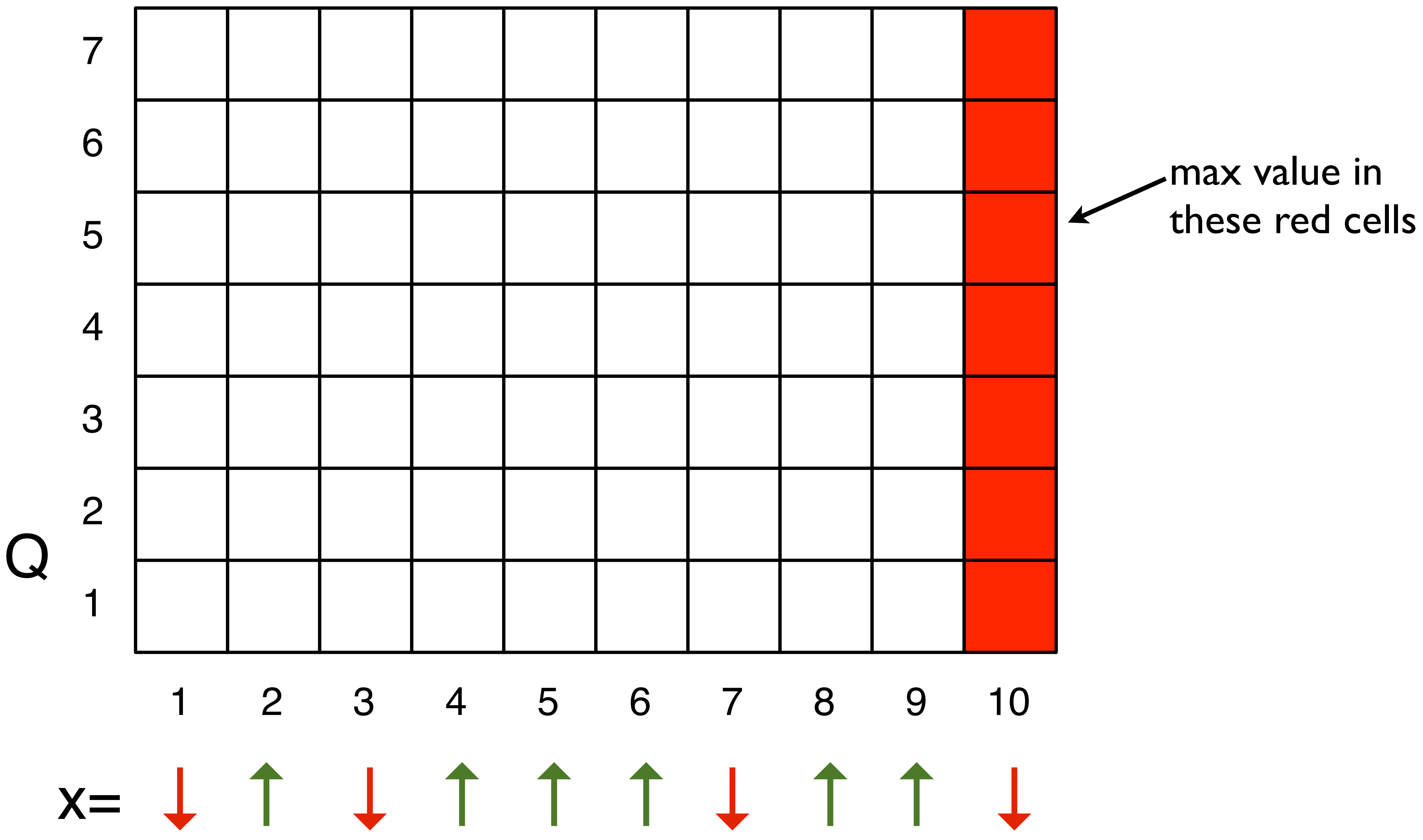
Which Cells Do We Depend On?



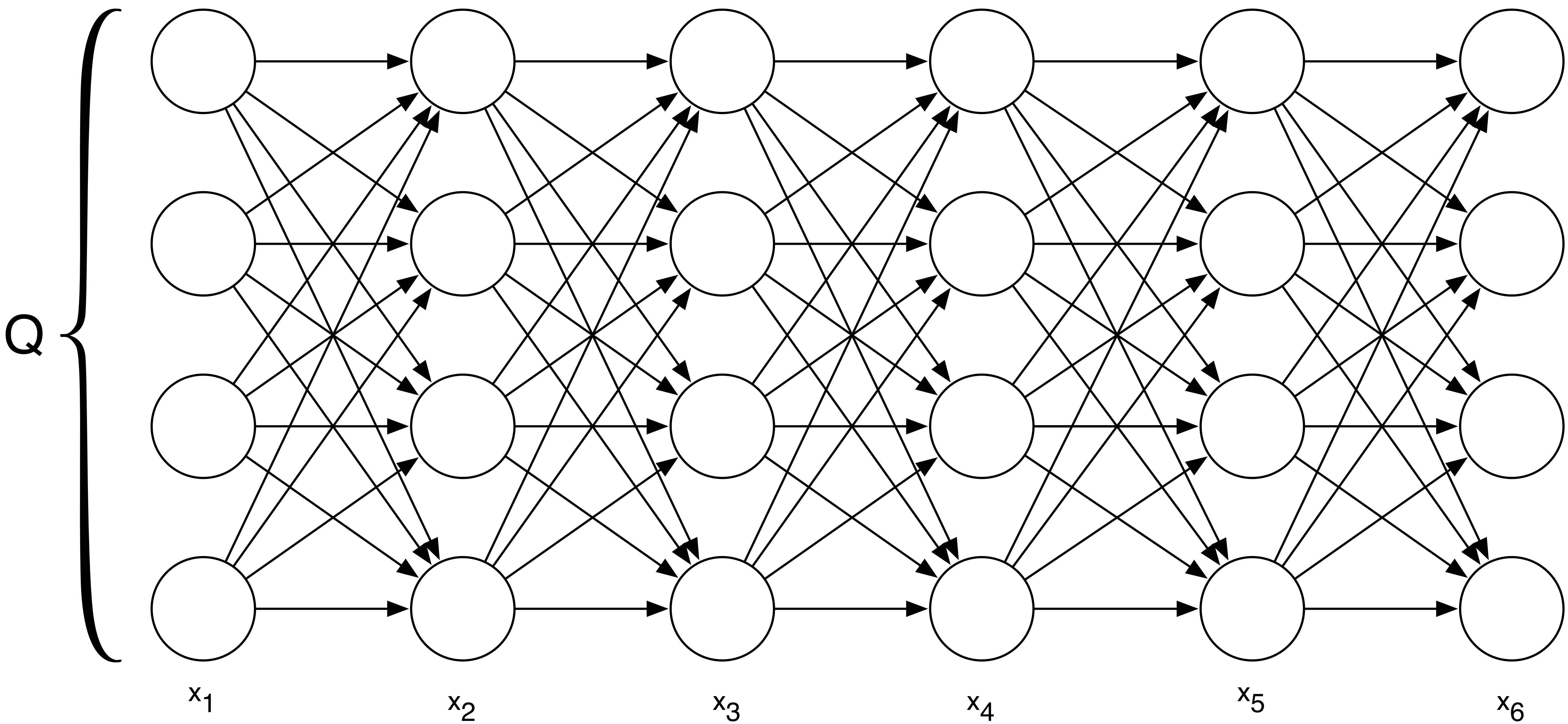
Order to Fill in the Matrix:



Where's the answer?



Graph View of Viterbi



Running Time

- # of subproblems = $O(n|Q|)$, where n is the length of the sequence.
- Time to solve a subproblem = $O(|Q|)$
- Total running time: $O(n|Q|^2)$

Using Logs

Typically, we take the log of the probabilities to avoid multiplying a lot of terms:

$$\begin{aligned}
\log(A[a,k]) &= \max_{b \in Q} \{\log(A[b,k-1] \times \Pr(b \to a) \times \Pr(x_k \mid \pi_k = a))\} \\
&= \max_{b \in Q} \{\log(A[b,k-1]) + \log(\Pr(b \to a)) + \log(\Pr(x_k \mid \pi_k = a))\}
\end{aligned}$$

Remember: $\log(ab) = \log(a) + \log(b)$

Why do we want to avoid multiplying lots of terms?

Using Logs

Typically, we take the log of the probabilities to avoid multiplying a lot of terms:

$$\log(A[a,k]) = \max_{b \in Q} \{\log(A[b,k-1] \times \Pr(b \to a) \times \Pr(x_k \mid \pi_k = a))\}$$
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Remember: $\log(ab) = \log(a) + \log(b)$

Why do we want to avoid multiplying lots of terms?

Multiplying leads to very small numbers:
0.1 x 0.1 x 0.1 x 0.1 x 0.1 = 0.00001
This can lead to underflow.
Taking logs and adding keeps numbers bigger.

Estimating HMM Parameters

$(x^{(1)},\pi^{(1)}) =$ $x_1^{(1)} x_2^{(1)} x_3^{(1)} x_4^{(1)} x_5^{(1)} \ldots x_n^{(1)}$
$\pi_1^{(1)} \pi_2^{(1)} \pi_3^{(1)} \pi_4^{(1)} \pi_5^{(1)} \ldots \pi_n^{(1)}$

$(x^{(2)},\pi^{(2)}) =$ $x_1^{(2)} x_2^{(2)} x_3^{(2)} x_4^{(2)} x_5^{(2)} \ldots x_n^{(2)}$
$\pi_1^{(2)} \pi_2^{(2)} \pi_3^{(2)} \pi_4^{(2)} \pi_5^{(2)} \ldots \pi_n^{(2)}$

Training examples where outputs and paths are known.

\# of times transition *a* → *b* is observed.

$$\Pr(a \to b) = \frac{A_{ab}}{\sum_{q \in Q} A_{aq}}$$

\# of times *x* was observed to be output from state *a*.

$$\Pr(x \mid a) = \frac{E_{xa}}{\sum_{x \in \Sigma} E_{xq}}$$

Pseudocounts

of times transition *a* → *b* is observed.

$$\Pr(a \to b) = \frac{A_{ab}}{\sum_{q \in Q} A_{aq}}$$

# of times *x* was observed to be output from state *a*.

$$\Pr(x \mid a) = \frac{E_{xa}}{\sum_{x \in \Sigma} E_{xq}}$$

What if a transition or emission is never observed in the training data?
⇒ 0 probability

Meaning that if we observe an example with that transition or emission in the real world, we will give it 0 probability.

But it's unlikely that our training set will be large enough to observe *every* possible transition.

Hence: we take A_{ab} = (#times a → b was observed) + 1 ← "pseudocount"
Similarly for E_{xa}.

Viterbi Training

- **Problem**: typically, in the real would we only have examples of the output x, and we don't know the paths π.

Viterbi Training Algorithm:

1. Choose a random set of parameters.
2. Repeat:
   1. Find the best paths.
   2. Use those paths to estimate new parameters.

This is an local search algorithm.

It's also an example of a "Gibbs sampling" style algorithm.

The Baum-Welch algorithm is similar, but doesn't commit to a single best path for each example.

Some probabilities we are interested in

What is the probability of observing a string *x* under the assumed HMM?

$$\Pr(x) = \sum_{\pi} \Pr(x, \pi)$$

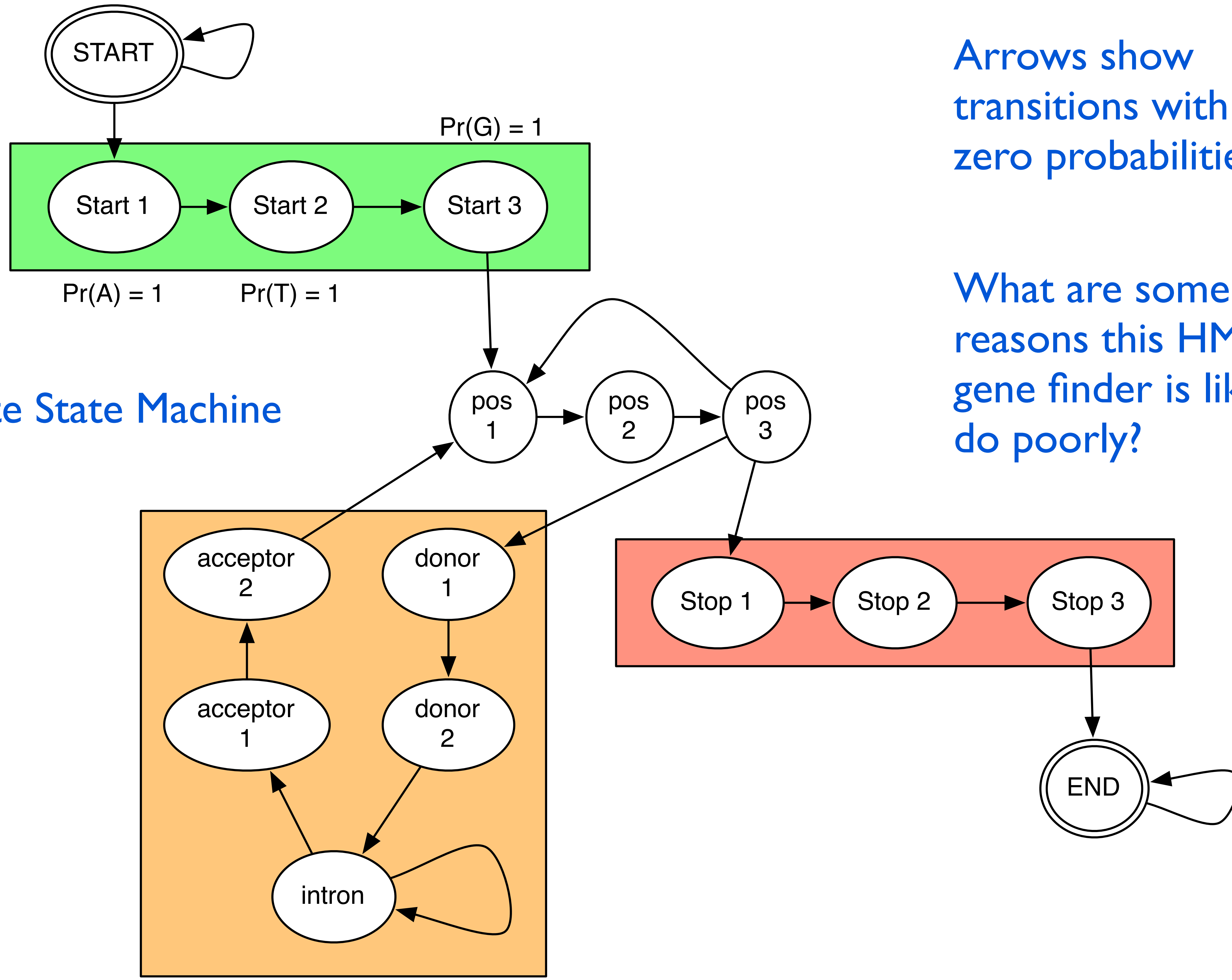
What is the probability of observing *x* using a path where the ith state is *a*?

$$\Pr(x, \pi_i = a) = \sum_{\pi : \pi_i = a} \Pr(x, \pi)$$

What is the probability that the ith state is *a*?

$$\Pr(\pi_i = a | x) = \frac{\Pr(x, \pi_i = a)}{\Pr(x)}$$

A (Bad) Eukaryotic Gene Finder



Finite State Machine

Arrows show transitions with non-zero probabilities

What are some reasons this HMM gene finder is likely to do poorly?

Bad Eukaryotic Gene Finder

Why is it so bad?

- The positions in the codons are treated independently: the probability of emitting a base can't depend on which previous base was emitted.

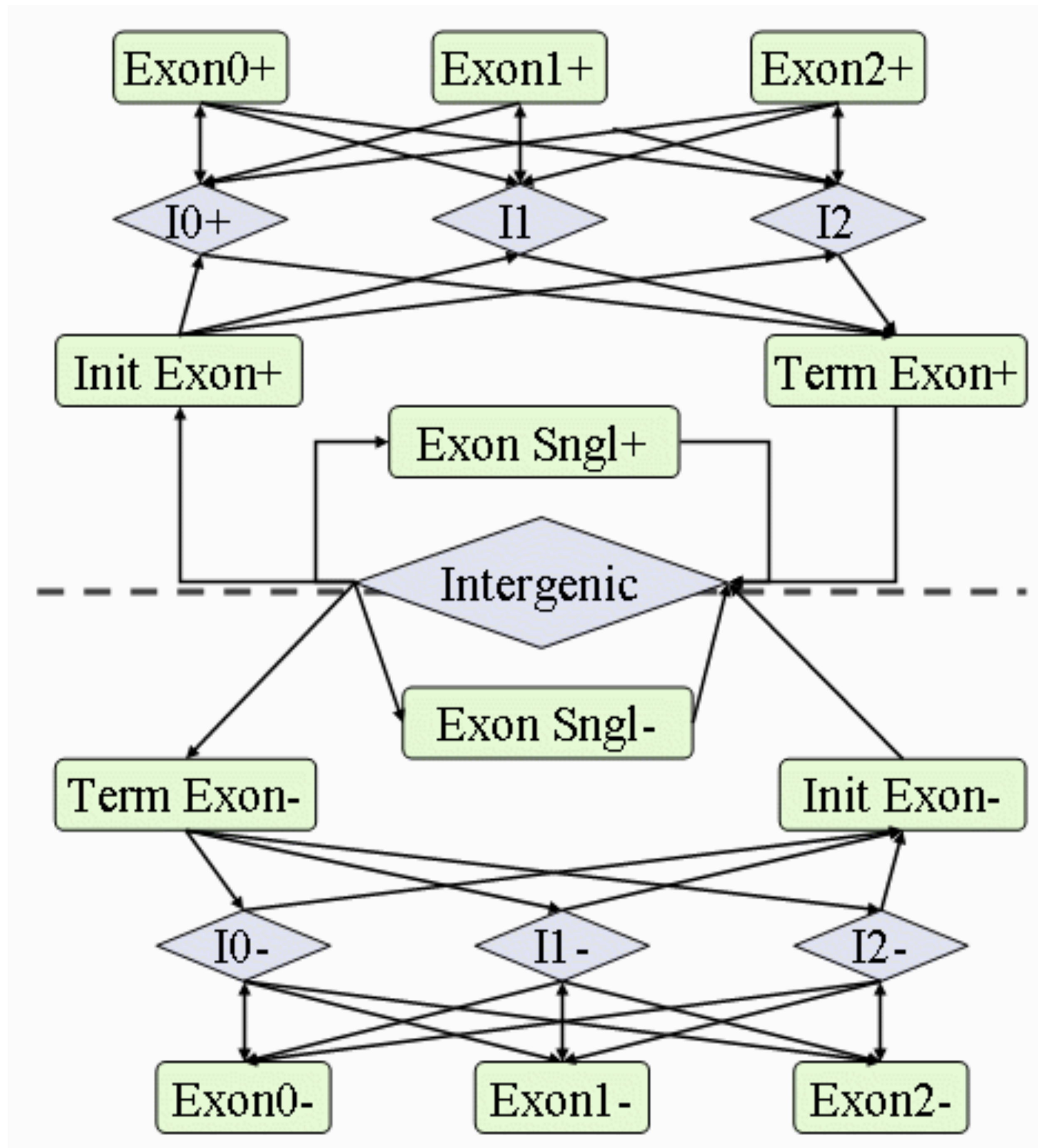
- Only one strand of the DNA is considered at once.

- Length distributions of introns and exons are not considered.

An Generalized HMM-based Gene Finder

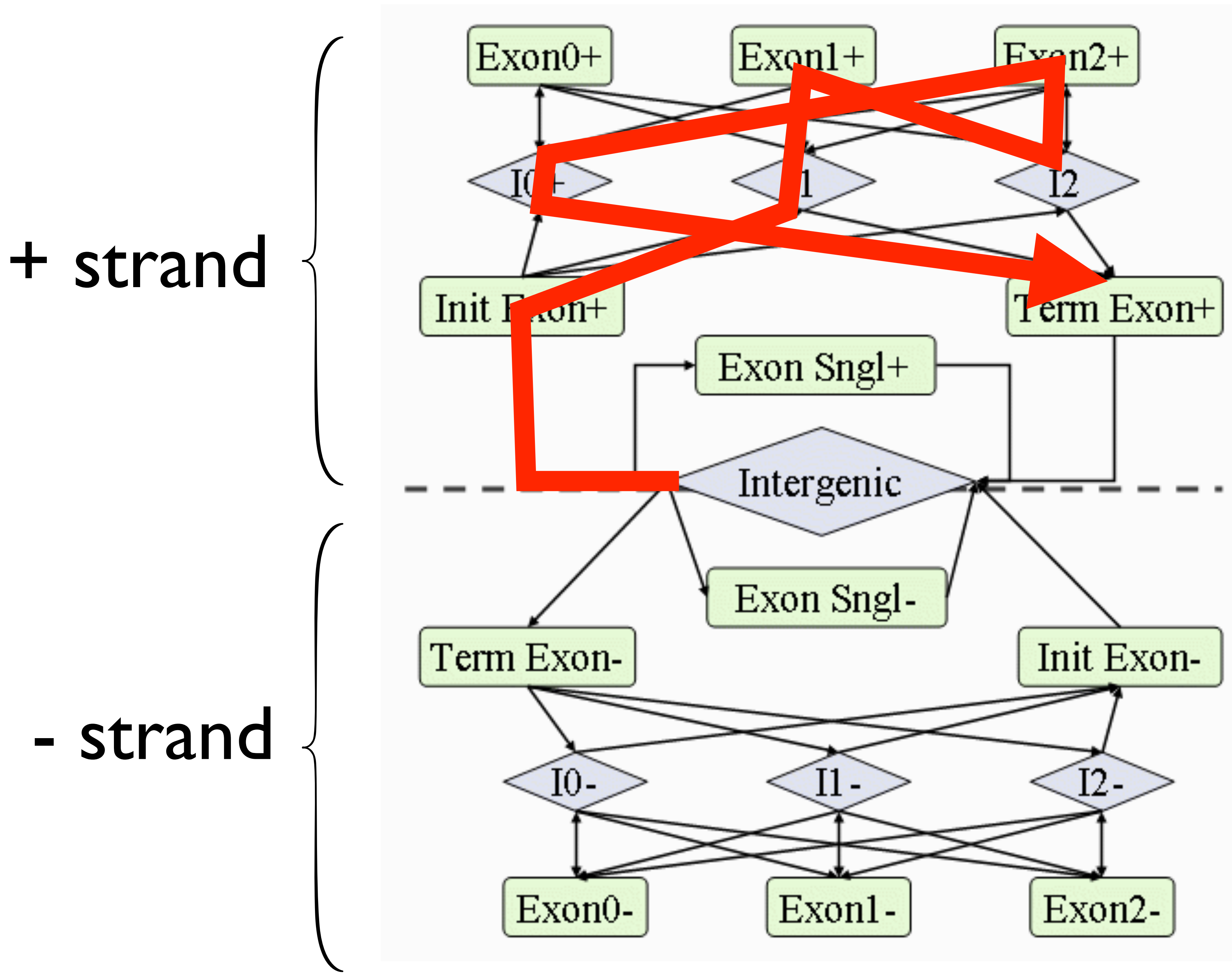
+ strand

- strand



GlimmerHMM model

An Generalized HMM-based Gene Finder



GlimmerHMM model

Generalized HMMs

- Each state can emit a *sequence* of symbols.
- In the diagram on the previous slide, each state emitted a *complete gene feature* (e.g. an entire exon):

$$\max_{\pi} \prod_{i=1}^{n} \underbrace{\Pr(x_i \ldots x_{i+d_i} \mid \pi_i, d_i)}_{\text{Probability of emitting the string of length } d_i.} \overbrace{\Pr(d_i \mid \pi_i)}^{\text{Probability that the state will emit } d_i \text{ symbols.}} \underbrace{\Pr(\pi_i \to \pi_{i+1})}_{\text{Probability of transitioning to the next state}}$$

Generalized HMMs

- Each state can emit a *sequence* of symbols.
- In the diagram on the previous slide, each state emitted a *complete gene feature* (e.g. an entire exon):

Probability that the state will emit d_i symbols.

$$\max_{\pi} \prod_{i=1}^{n} \underbrace{\Pr(x_i \ldots x_{i+d_i} \mid \pi_i, d_i)} \overbrace{\Pr(d_i \mid \pi_i)} \underbrace{\Pr(\pi_i \to \pi_{i+1})}$$

Probability of emitting the string of length d_i.

Probability of transitioning to the next state

This probability could itself be computed by an HMM or a Markov chain, etc.

GlimmerHMM Performance

% of predicted in-gene nucleotides that are correct

% of predicted exons that are true exons.

	Nuc Sens	Nuc Prec	Nuc Accur	Exon Sens	Exon Prec	Exact Genes	Size of test set
D.rerio	93%	78%	86%	77%	69%	24%	549 genes
C.elegans	96%	95%	96%	82%	81%	42%	1886 genes
Arabidopsis	97%	99%	98%	84%	89%	60%	809 genes
Cryptococcus	96%	99%	98%	86%	88%	53%	350 genes
Coccidioides	99%	99%	99%	84%	86%	60%	503 genes
Brugia	93%	98%	95%	78%	83%	25%	477 genes

% of true gene nucleotides that GlimmerHMM predicts as part of genes.

% of true exons that GlimmerHMM found.

% of genes perfectly found

Compare with GENSCAN

- On 963 human genes:

	Nuc Sens	Nuc Prec	Nuc Acc	Exon Sens	Exon Prec	Exon Acc	Exact Genes
GlimmerHMM	86%	72%	79%	72%	62%	67%	17%
Genscan	86%	68%	77%	69%	60%	65%	13%

- Note that overall accuracy is pretty low.

The Forward Algorithm

How do we compute this:

$$\Pr(x, \pi_k = a) = \Pr(x_1, \ldots, x_i, \pi_i = a) \Pr(x_{i+1}, \ldots, x_n \mid \pi_i = a)$$

Recall the recurrence to compute **best** path for $x_1 \ldots x_k$ that ends at state a:

$$A[a,k] = \max_{b \in Q} \{A[b,k-1] \times \Pr(b \to a) \times \Pr(x_k \mid \pi_k = a)\}$$

We can compute the probability of emitting $x_1, \ldots, x_k$ using **some** path that ends in *a*:

$$F[a,k] = \sum_{b \in Q} F[b,k-1] \times \Pr(b \to a) \times \Pr(x_k \mid \pi_k = a)$$

The Forward Algorithm

How do we compute this:

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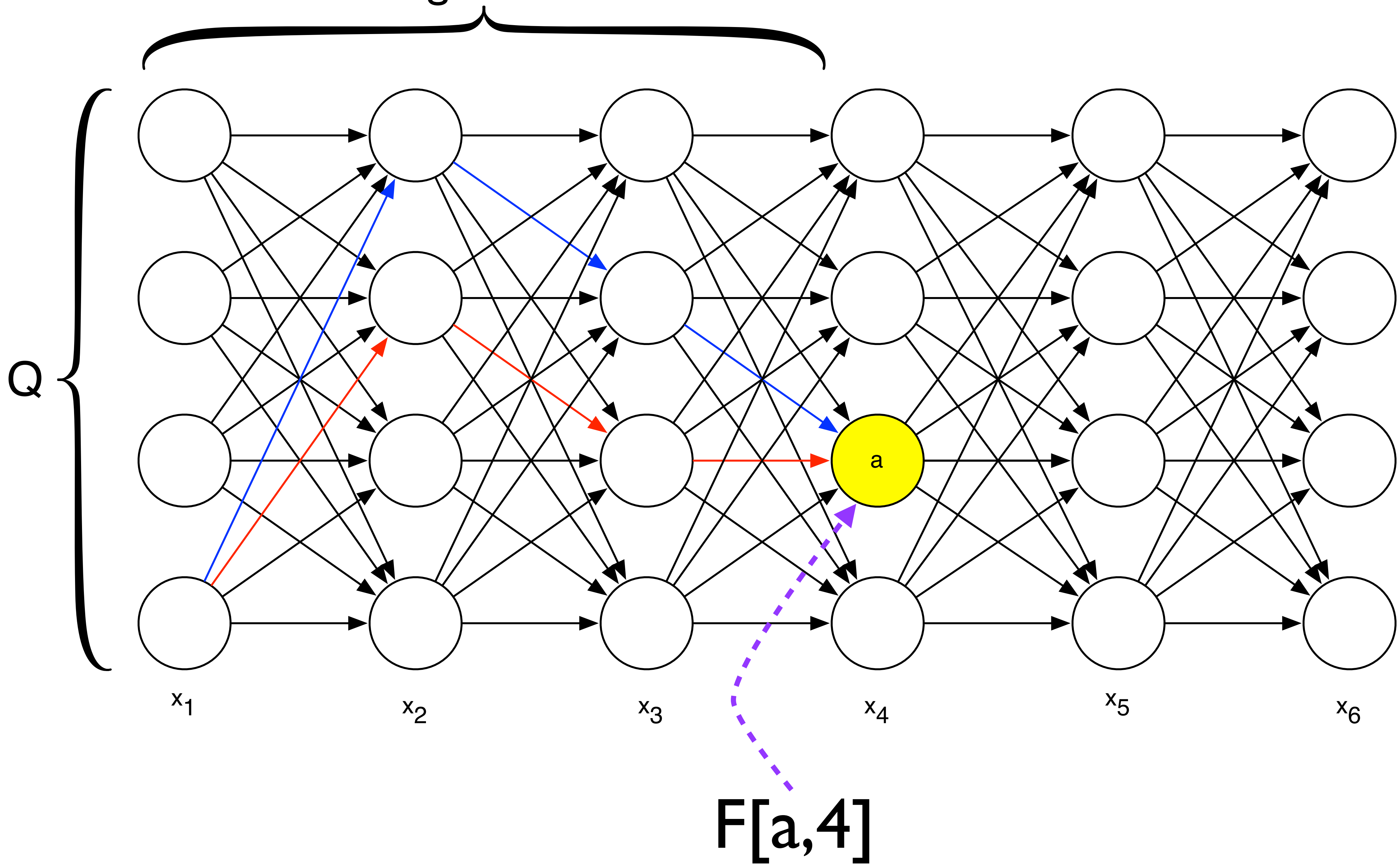
$$F[a, k] = \sum_{b \in Q} F[b, k-1] \times \Pr(b \to a) \times \Pr(x_k \mid \pi_k = a)$$

The Forward Algorithm

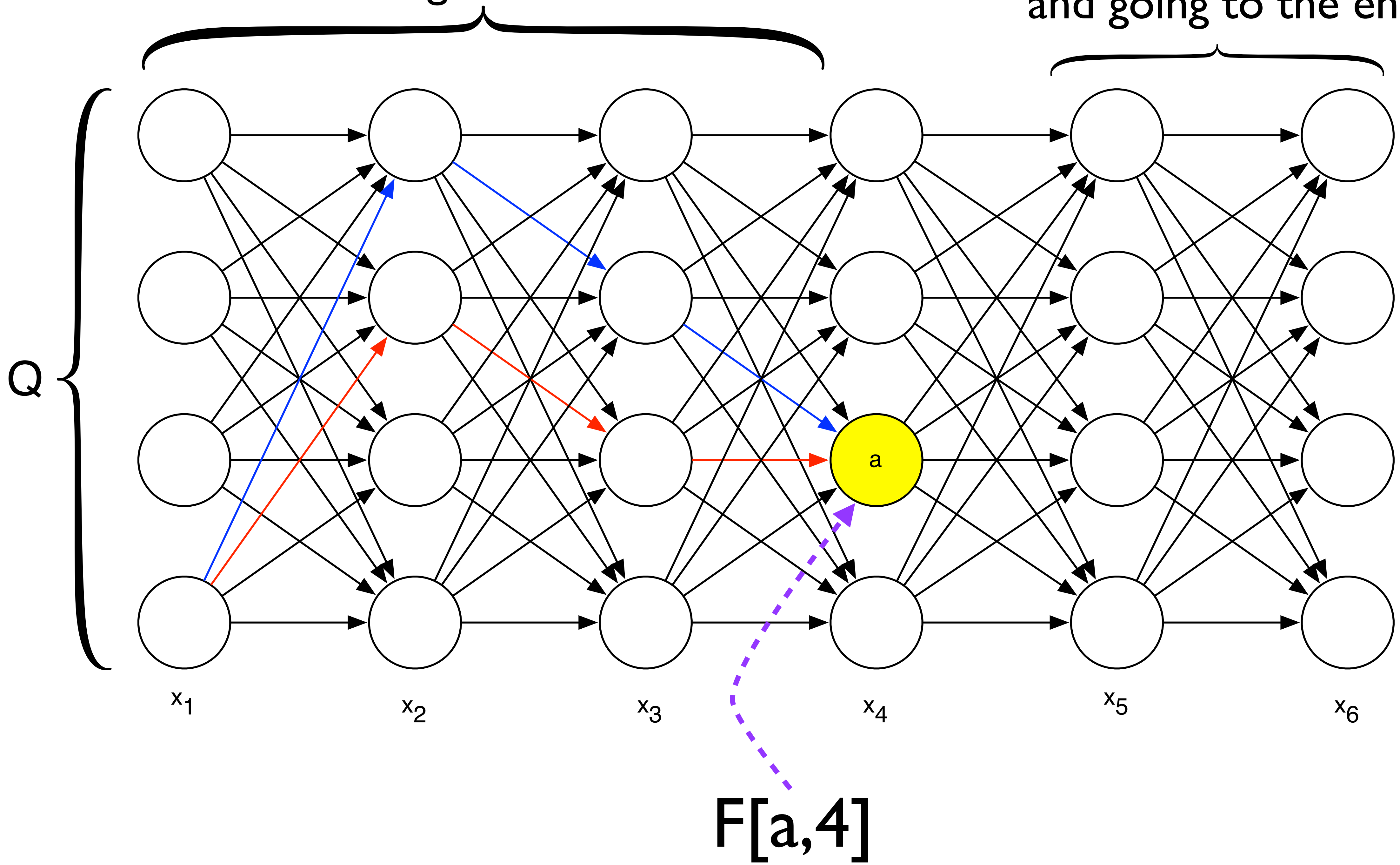
Computes the total probability of all the paths of length *k* ending in state *a*.



The Forward Algorithm

Computes the total probability of all the paths of length *k* ending in state *a*.

Still need to compute the probability of paths leaving *a* and going to the end.



The Backward Algorithm

The same idea as the forward algorithm, we just start from the *end* of the input string and work towards the beginning:

B[a,k] = "the probability of generating string $x_{k+1},\ldots,x_n$ starting from state b"

$$B[a,k] = \sum_{b \in Q} \underbrace{B[b,k+1]}_{\text{Prob for } x_{k+1}..x_n \text{ starting in state } b} \times \underbrace{\Pr(a \to b)}_{\text{Probability going from state } a \text{ to } b} \times \underbrace{\Pr(x_{k+1} \mid \pi_{k+1} = b)}_{\text{Probability of emitting } x_{k+1} \text{ given that the next state is b.}}$$

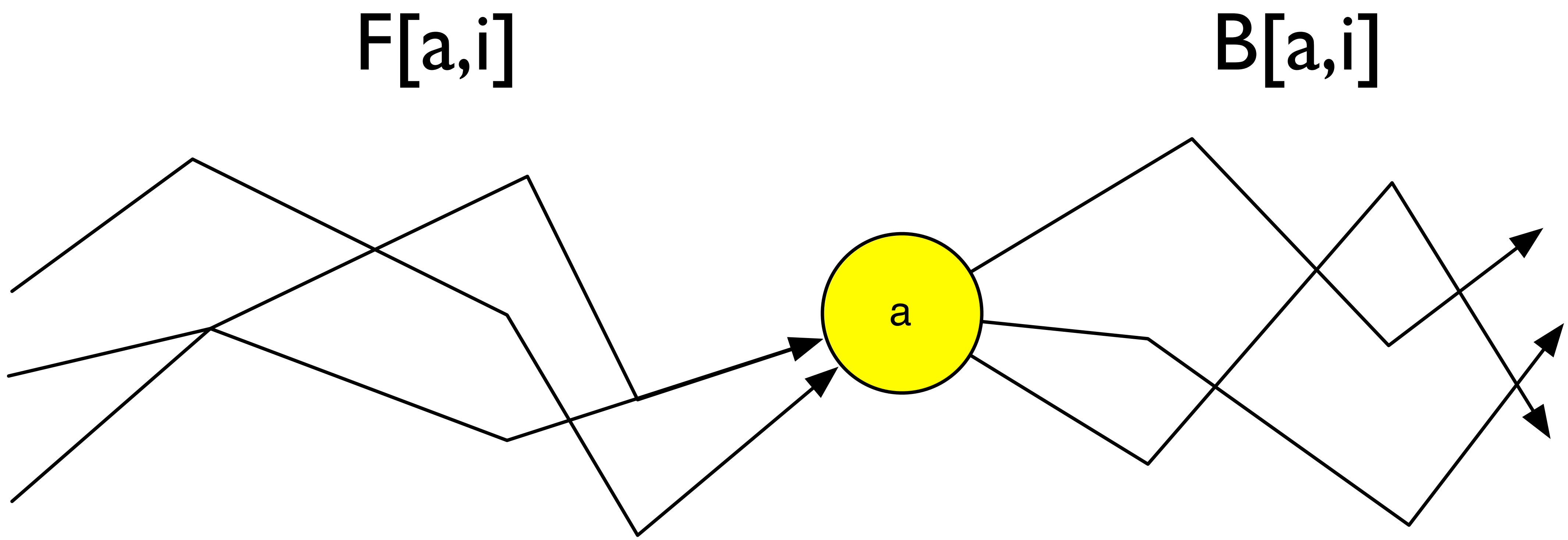
Prob for $x_{k+1}..x_n$ starting in state *b*

Probability going from state *a* to *b*

Probability of emitting x_{k+1} given that the next state is b.

The Forward-Backward Algorithm

$$\Pr(\pi_i = a \mid x) = \frac{\Pr(x, \pi_i = k)}{\Pr(x)} = \frac{F[a,i] \cdot B[a,i]}{\Pr(x)}$$



Recap

- Hidden Markov Model (HMM) model the generation of strings.
- They are governed by a string alphabet (Σ), a set of states (Q), a set of transition probabilities A, and a set of emission probabilities for each state (E).
- Given a string and an HMM, we can compute:
  - The most probable path the HMM took to generate the string (Viterbi).
  - The probability that the HMM was in a particular state at a given step (forward-backward algorithm).
- Algorithms are based on dynamic programming.
- *Finding* good parameters is a much harder problem.
  The Baum-Welch algorithm is an oft-used heuristic algorithm.