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6.047 / 6.878 Computational Biology: Genomes, Networks, Evolution
Fall 2008

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Modeling Biological Sequence and Hidden Markov Models

(part II - The algorithms)

Challenges in Computational Biology

4 Genome Assembly

9 Regulatory motif discovery

6 **Gene Finding**

DNA

2 Sequence alignment

14 Comparative Genomics

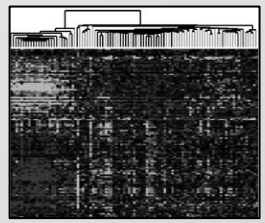
10 Evolutionary Theory

TCATGCTAT
TCGTGATAA
TGAGGATAT
TTATCATAT
TTATGATTT

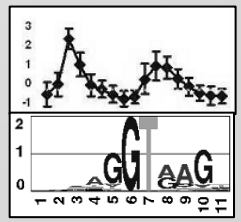
3 Database search

5 Gene expression analysis

RNA transcript

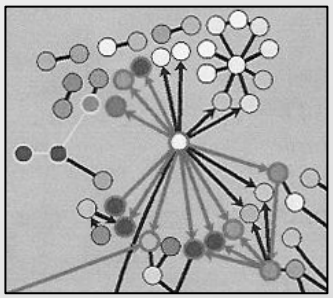


4 Cluster discovery



9 Gibbs sampling

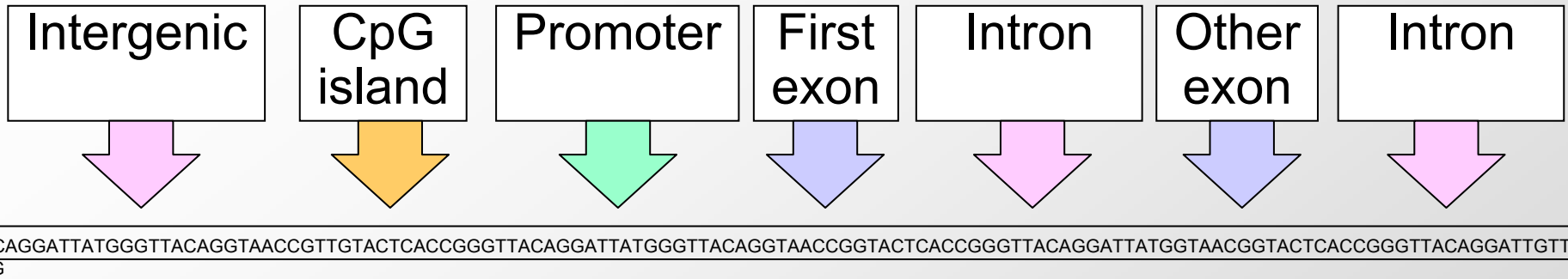
11 Protein network analysis



12 Regulatory network inference

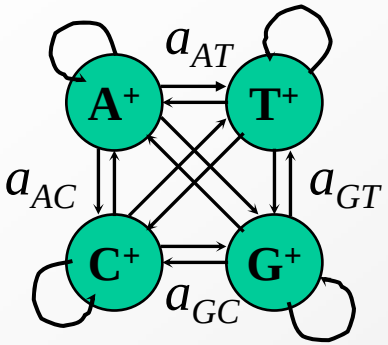
13 Emerging network properties

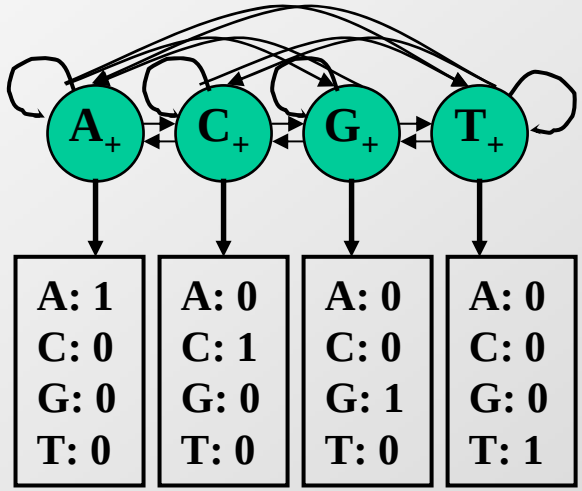
Modeling biological sequences



- Ability to **generate** DNA sequences of a certain ***type***
  - Not exact alignment to previously known gene
  - Preserving ‘properties’ of **type**, not identical sequence
- Ability to **recognize** DNA sequences of a certain type
  - What (hidden) state is most likely to have generated observations
  - Find set of states and transitions that generated a long sequence
- Ability to **learn** distinguishing characteristics of each type
  - Training our generative models on large datasets
  - Learn to classify unlabelled data

Markov Chains & Hidden Markov Models





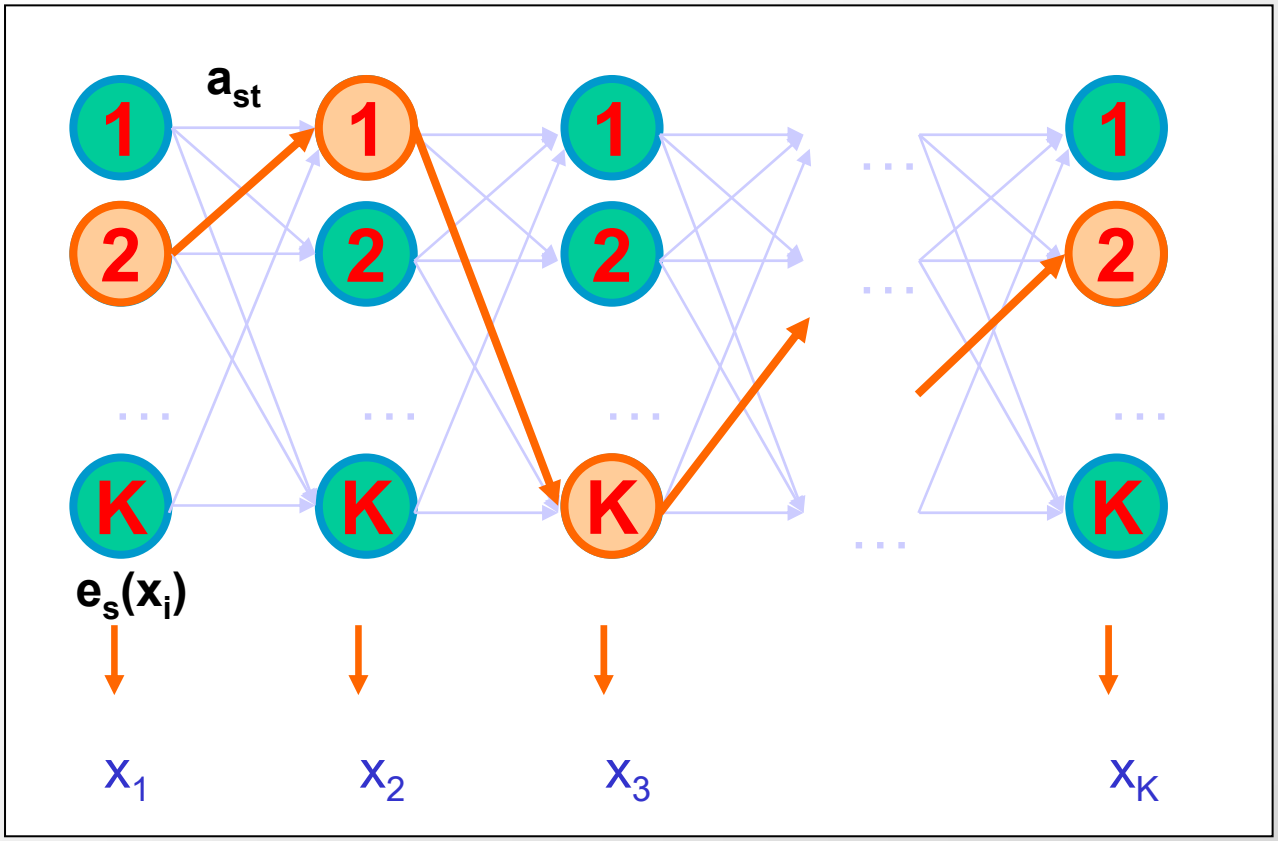
- Markov Chain
  - Q: states
  - p: initial state probabilities
  - A: transition probabilities

- HMM
  - Q: states
  - V: observations
  - p: initial state probabilities
  - A: transition probabilities
  - E: emission probabilities

HMM nomenclature

π is the (hidden) path

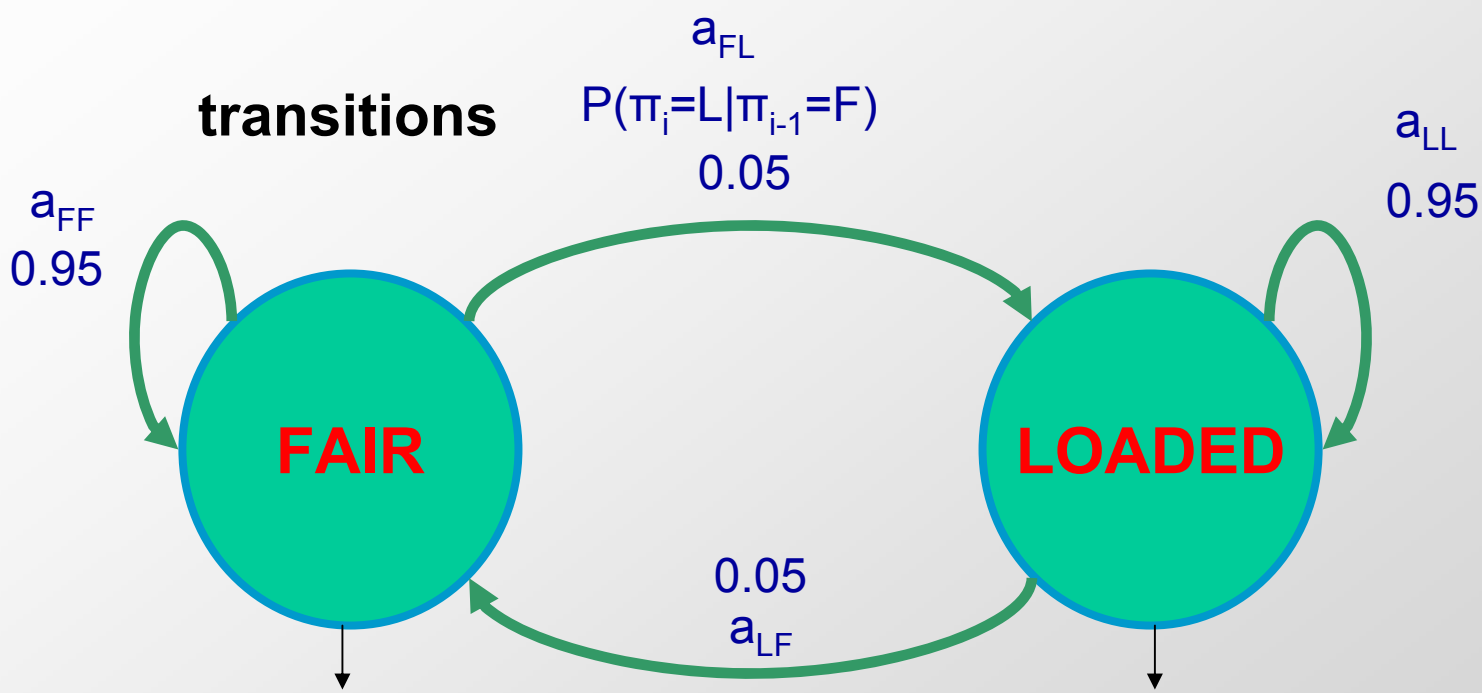
x is the (observed) sequence



- Find path π^* that maximizes total joint probability P[x, π]
  - $P(x,\pi) = a_{0\pi_1} * \prod_i e_{\pi_i}(x_i) \times a_{\pi_i\pi_{i+1}}$

start emission transition

HMM for the dishonest casino model

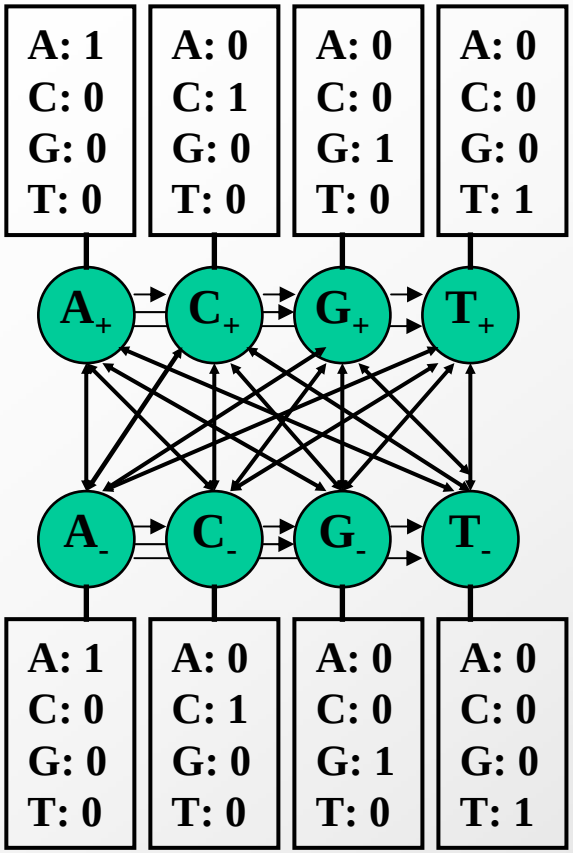


emissions

$e_F(1) = \mathbf{P(x_i=1|\pi_i=F)=1/6}$
$e_F(2) = 1/6$
$e_F(3) = 1/6$
$e_F(4) = 1/6$
$e_F(5) = 1/6$
$e_F(6) = 1/6$

$e_L(1) = \mathbf{P(x_i=1|\pi_i=L)} = 1/10$
$e_L(2) = 1/10$
$e_L(3) = 1/10$
$e_L(4) = 1/10$
$e_L(5) = 1/10$
$e_L(6) = 1/2$

HMM for CpG islands



- Build a single model that combines both Markov chains:
  - **'+' states**: A_+, C_+, G_+, T_+
    - Emit symbols: A, C, G, T in CpG islands
  - **'-' states**: A_-, C_-, G_-, T_-
    - Emit symbols: A, C, G, T in non-islands
- Emission probabilities distinct for the '+' and the '-' states
  - Infer most likely set of states, giving rise to observed emissions

➔ 'Paint' the sequence with + and - states

Question: Why do we need so many states?

In the Dishonest Casino we only had 2 states: Fair / Loaded

Why do we need 8 states here: 4 CpG+ / 4 CpG- ?

➔ Encode 'memory' of previous state: count nucleotide transitions!

The main questions on HMMs

PARSING

1. **Scoring** = Joint probability of a sequence and a path, given the model
   - GIVEN a HMM M, a path π, and a sequence x,
   - FIND Prob[x, π | M]
   - ➔ "Running the model", simply multiply emission and transition probabilities
   - ➔ Application: "all fair" vs. "all loaded" comparisons
2. **Decoding** = parsing a sequence into the optimal series of hidden states
   - GIVEN a HMM M, and a sequence x,
   - FIND the sequence π^* of states that maximizes P[x, π | M]
   - ➔ Viterbi algorithm, dynamic programming, max score over all paths, trace pointers find path

SCORING

3. **Model evaluation** = total probability of a sequence, summed across all paths
   - GIVEN a HMM M, a sequence x
   - FIND the total probability P[x | M] summed across all paths
   - ➔ Forward algorithm, sum score over all paths (same result as backward)
4. **State likelihood** = total prob that emission x_i came from state k, across all paths
   - GIVEN a HMM M, a sequence x
   - FIND the total probability P[π_i = k | x, M)
   - ➔ Posterior decoding: run forward & backward algorithms to & from state π_l =k

LEARNING

5. **Supervised learning** = optimize parameters of a model given training data
   - GIVEN a HMM M, with unspecified transition/emission probs., labeled sequence x,
   - FIND parameters θ = (e_i, a_{ij}) that maximize P[x | θ]
   - ➔ Simply count frequency of each emission and transition observed in the training data
6. **Unsupervised learning** = optimize parameters of a model given training data
   - GIVEN a HMM M, with unspecified transition/emission probs., unlabeled sequence x,
   - FIND parameters θ = (e_i, a_{ij}) that maximize P[x | θ]
   - ➔ Viterbi training: guess parameters, find optimal Viterbi path (#2), update parameters (#5), iterate
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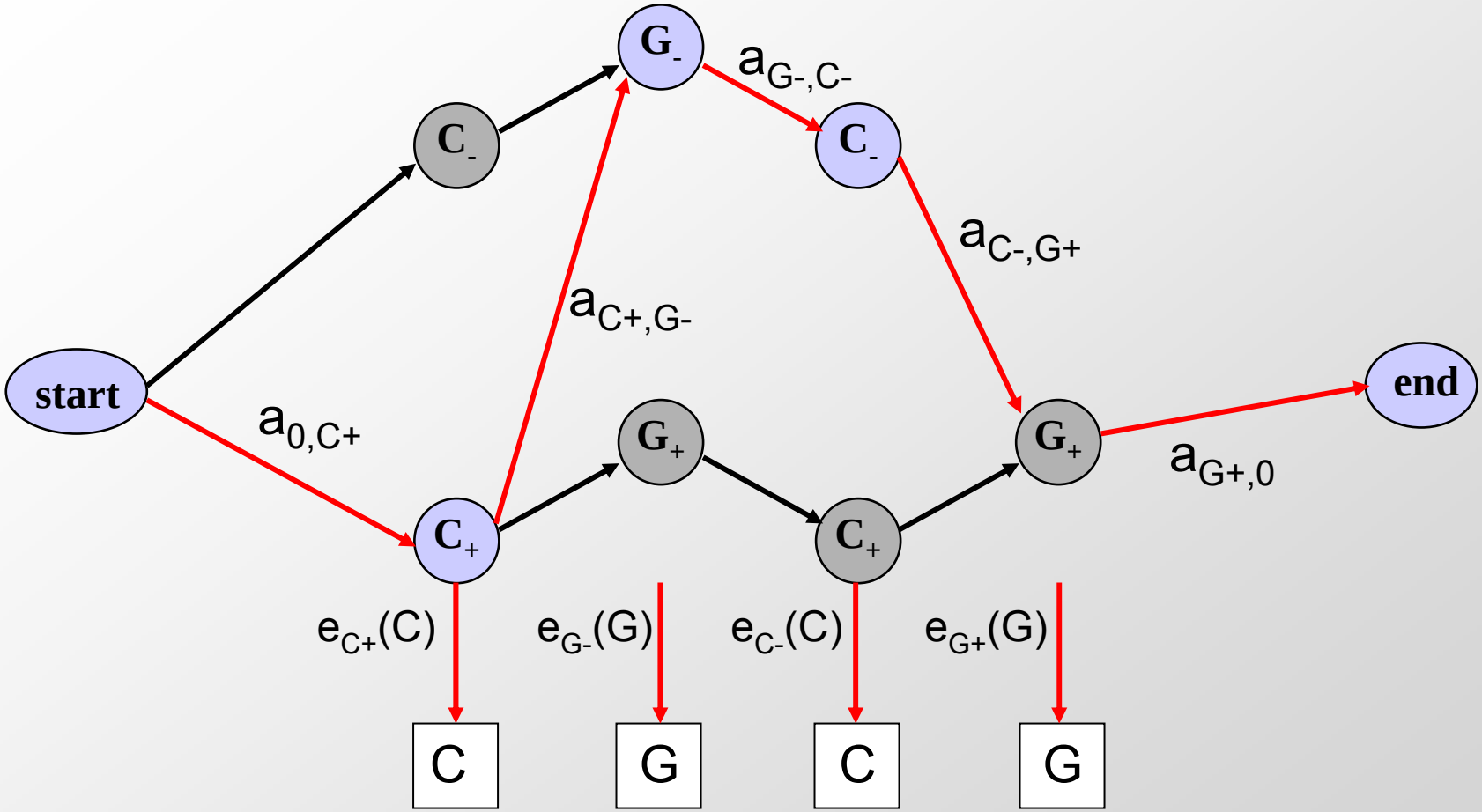
1. Scoring

Multiply emissions, transitions

1. Scoring



- $P(\boldsymbol{p},\boldsymbol{x}) = (a_{0,C+} * 1) * (a_{C+,G-} * 1) * (a_{G-,C-} * 1) * (a_{C-,G+} * 1) * (a_{G+,0})$

Probability of given path p & observations x

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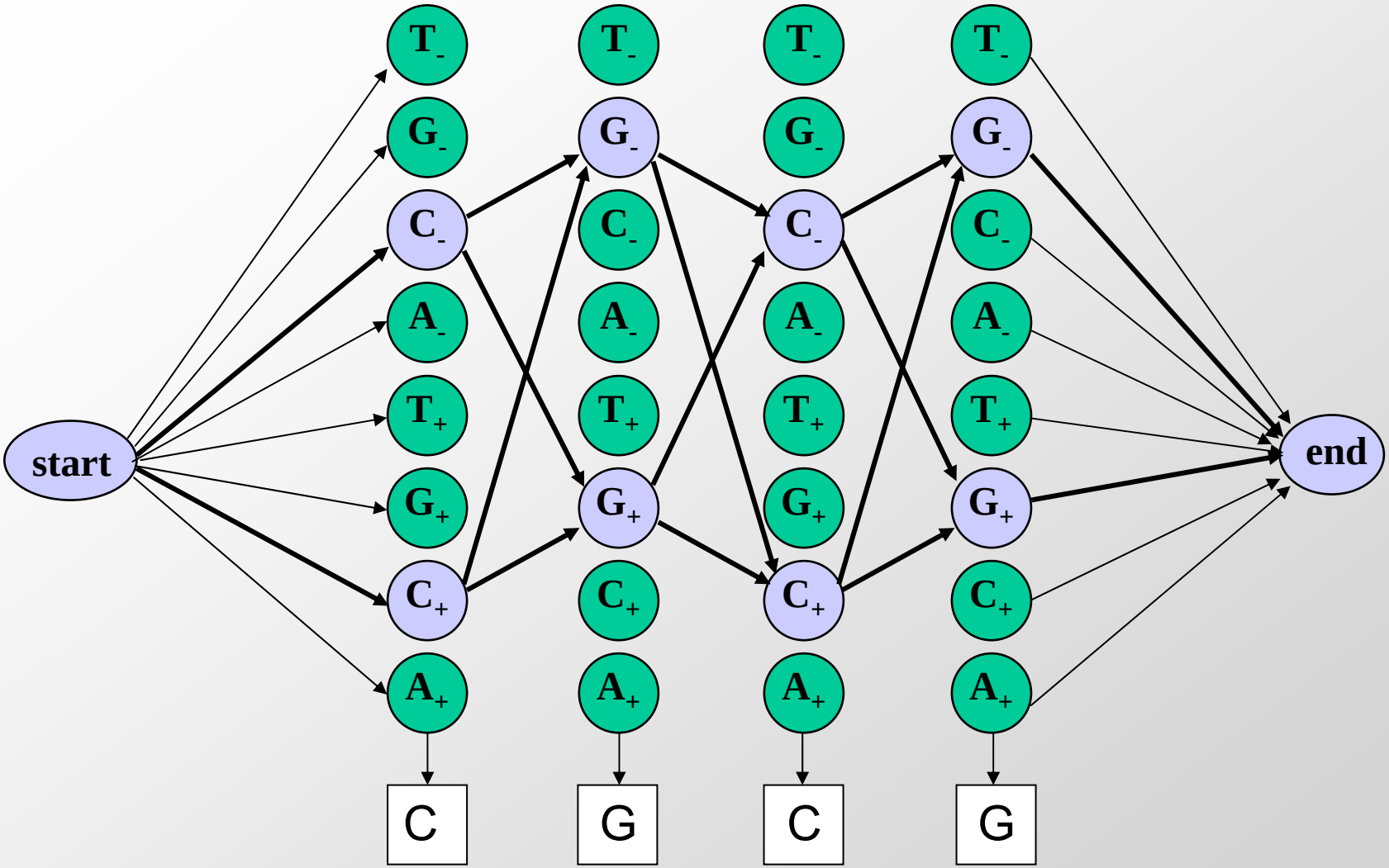
2. Decoding:
How can we find the most likely path?

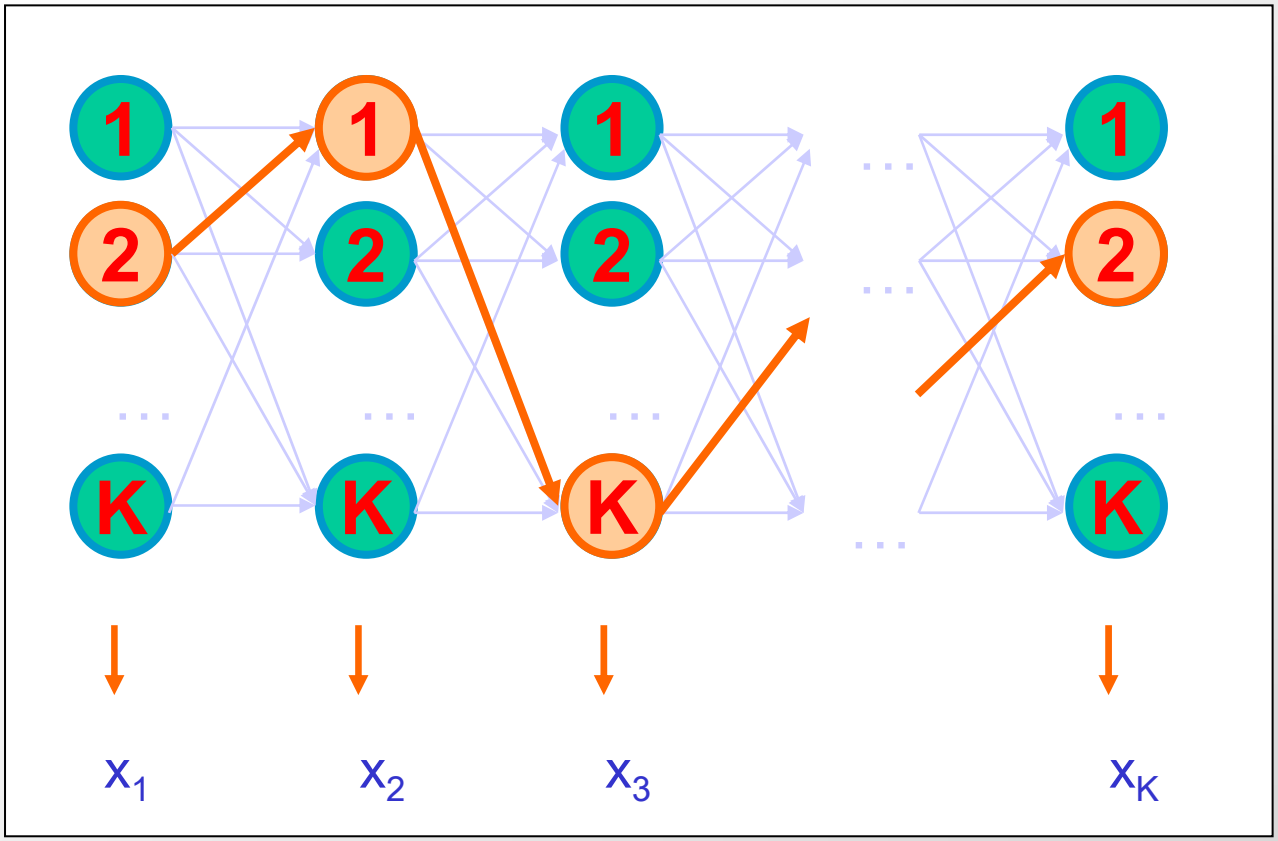
Viterbi algorithm

Finding most likely state path



- Given the observed emissions, what was the path?

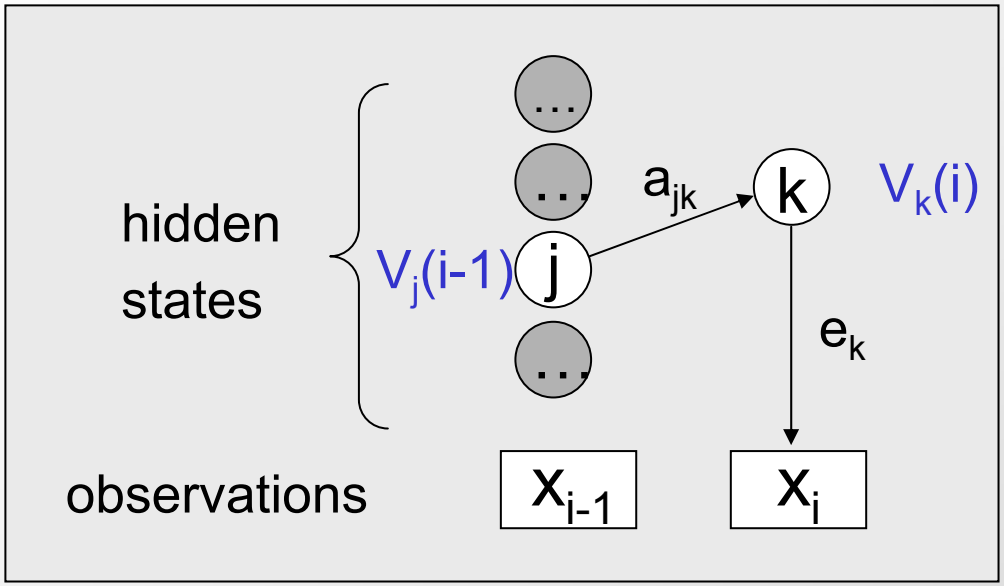
Finding the most likely path



- Find path π^* that maximizes total joint probability P[x, π]
  - $P(x,\pi) = a_{0\pi_1} * \prod_i e_{\pi_i}(x_i) \times a_{\pi_i \pi_{i+1}}$

start emission transition

Calculate maximum P(x,π) recursively



- Assume we know V_j for the previous time step (i-1)
- Calculate $V_k(i) = e_k(x_i) * \max_j (V_j(i-1) \times a_{jk})$

current max

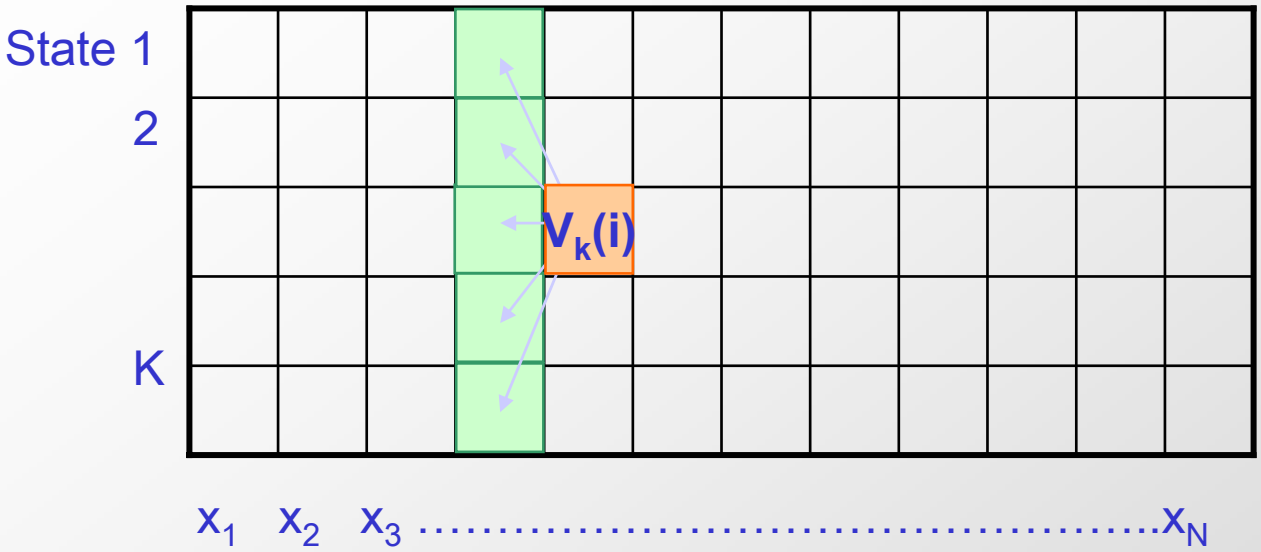
this emission

max ending in state j at step i

Transition from state j

all possible previous states j

The Viterbi Algorithm



Input: x = x1……xN

Initialization:

$V_0(0)=1$, $V_k(0) = 0$, for all $k > 0$

Iteration:

$V_k(i) = e_K(x_i) \times \max_j a_{jk} V_j(i-1)$

Termination:

$P(x, \pi^*) = \max_k V_k(N)$

Traceback:

Follow max pointers back

In practice:

Use log scores for computation

Running time and space:

Time: $O(K^2N)$

Space: $O(KN)$

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PARSING

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   - GIVEN a HMM M, a sequence x
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   - ➔ Posterior decoding: run forward & backward algorithms to & from state π_i =k

SCORING

5. **Supervised learning** = optimize parameters of a model given training data
   - GIVEN a HMM M, with unspecified transition/emission probs., labeled sequence x,
   - FIND parameters θ = (Ei, Aij) that maximize P[x | θ]
   - ➔ Simply count frequency of each emission and transition observed in the training data
6. **Unsupervised learning** = optimize parameters of a model given training data
   - GIVEN a HMM M, with unspecified transition/emission probs., unlabeled sequence x,
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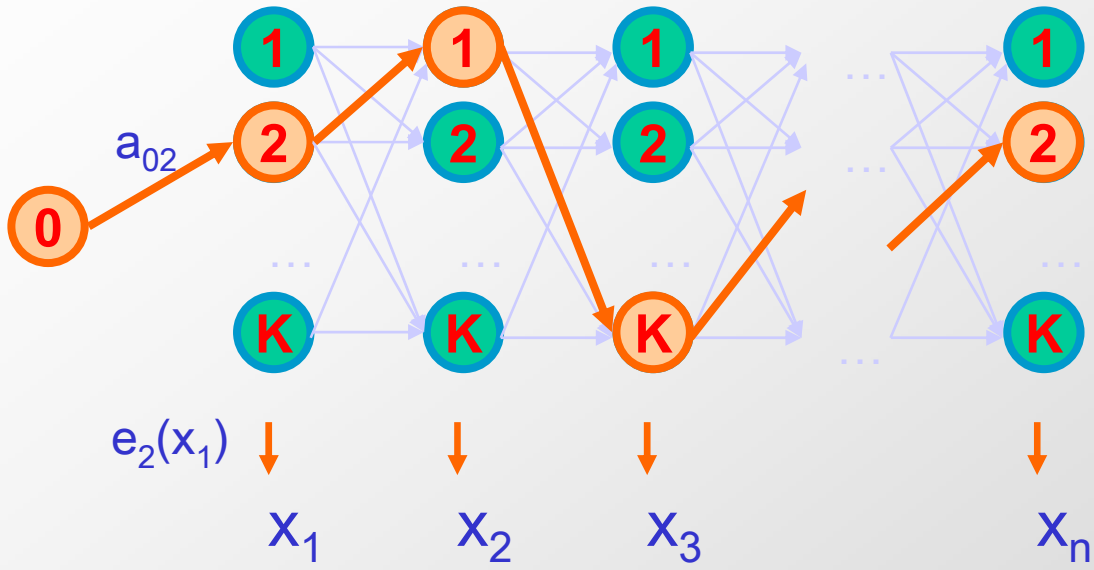
   - ➔ Viterbi training: guess parameters, find optimal Viterbi path (#2), update parameters (#5), iterate
   - ➔ Baum-Welch training: guess, sum over all emissions/transitions (#4), update (#5), iterate

LEARNING

3. Model evaluation: Total P(x|M), summed over all paths

Forward algorithm

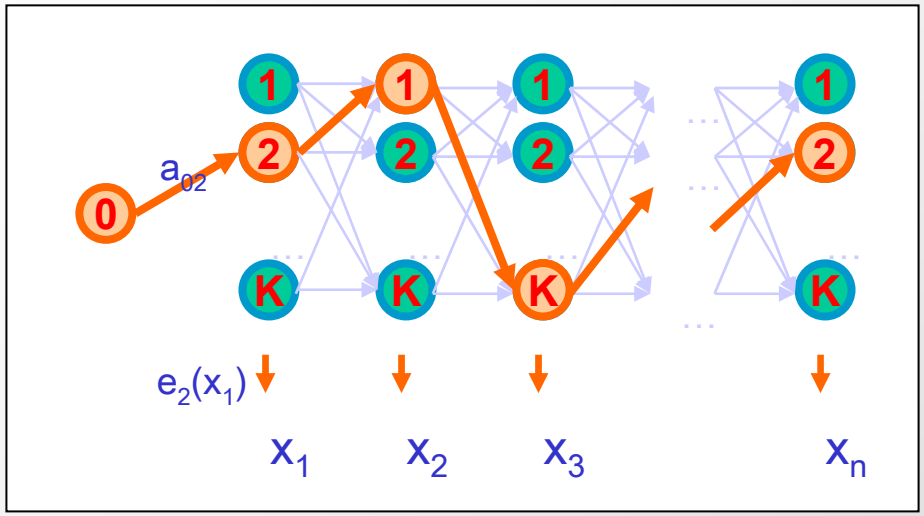
Simple: Given the model, generate some sequence x



Given a HMM, we can generate a sequence of length n as follows:

1. Start at state π_1 according to prob $a_{0\pi 1}$
2. Emit letter x_1 according to prob $e_{\pi 1}(x_1)$
3. Go to state π_2 according to prob $a_{\pi 1 \pi 2}$
4. … until emitting x_n

Complex: Given x, was it generated by the model?



Given a sequence x,
What is the probability that x was generated by the model (using any path)?

– $P(x) = \sum_{\pi} P(x,\pi)$

- Challenge: exponential number of paths

- (cheap) alternative:
  – Calculate probability over maximum (Viterbi) path π*
- (real) solution
  – Calculate sum iteratively using dynamic programming

The Forward Algorithm – derivation

Define the forward probability:

$$f_l(i) = P(x_1 \ldots x_i, \pi_i = l)$$

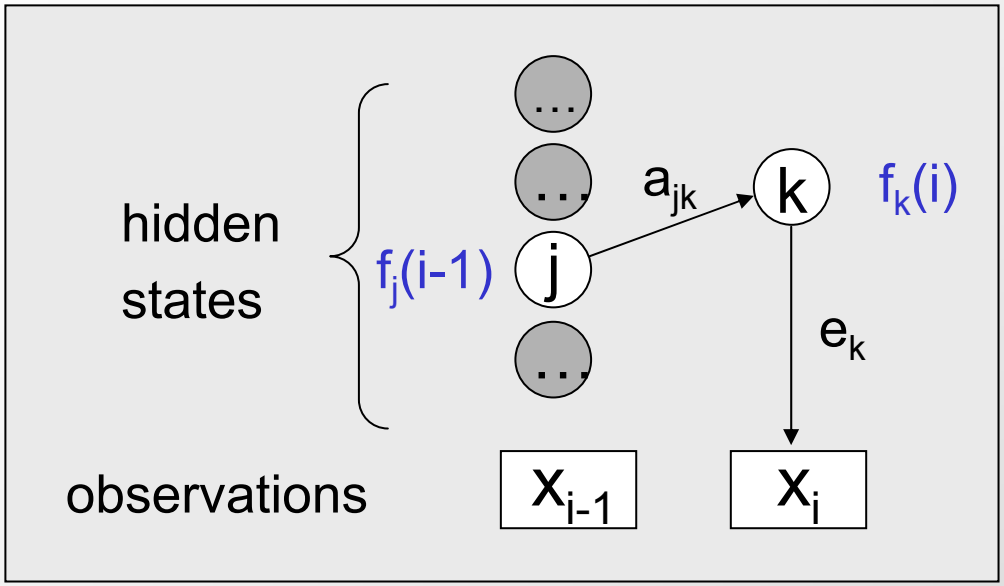
$$= \sum_{\pi 1 \ldots \pi i-1} P(x_1 \ldots x_{i-1}, \pi_1, \ldots, \pi_{i-2}, \pi_{i-1}, \pi_i = l)\, e_l(x_i)$$

$$= \sum_k \boxed{\sum_{\pi 1 \ldots \pi i-2} P(x_1 \ldots x_{i-1}, \pi_1, \ldots, \pi_{i-2}, \pi_{i-1} = k)}\, a_{kl}\, e_l(x_i)$$

$$= \sum_k \boxed{f_k(i-1)}\, a_{kl}\, e_l(x_i)$$

$$= e_l(x_i) \sum_k \boxed{f_k(i-1)}\, a_{kl}$$

Calculate total probability $\Sigma_\pi P(x,\pi)$ recursively



- Assume we know f_j for the previous time step (i-1)
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current max

this emission

sum ending in state j at step i

transition from state j

every possible previous state j

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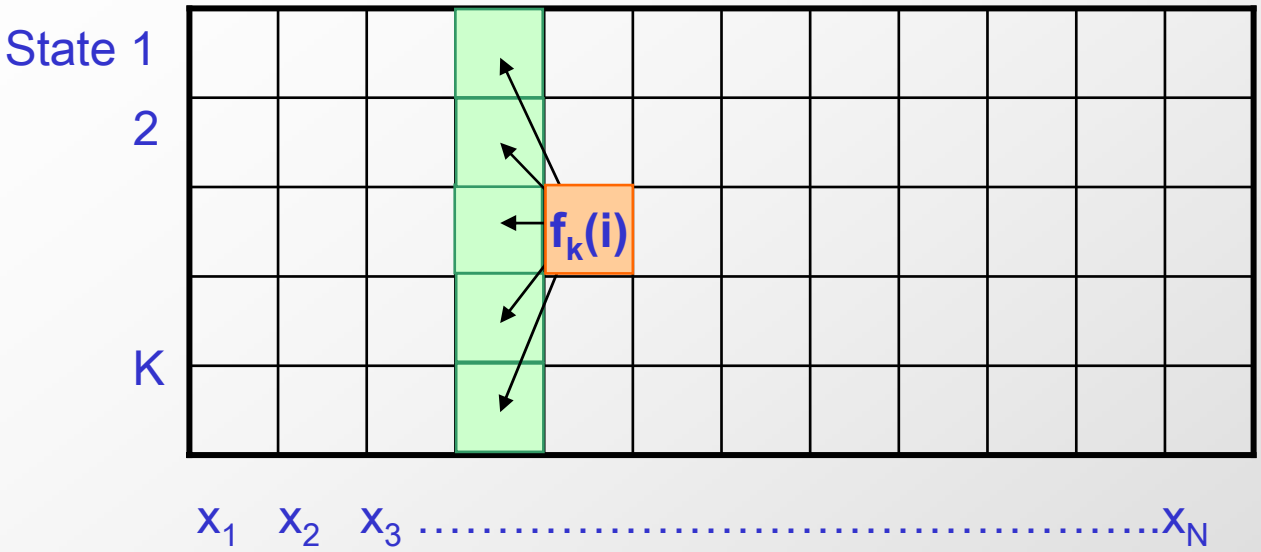

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Iteration:

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Termination:

$P(x, \pi^*) = \text{sum}_k\ f_k(N)$

In practice:

Sum of log scores is difficult

→ approximate exp(1+p+q)

→ scaling of probabilities

Running time and space:

Time: $O(K^2N)$

Space: $O(KN)$

Summary

- Generative model
  - Hidden states
  - Observed sequence
- 'Running' the model
  - Generate a random sequence
- Observing a sequence
  - What is the most likely path generating it?
    - Viterbi algorithm
  - What is the total probability generating it?
    - Sum probabilities over all paths
    - Forward algorithm
- Next: Classification
  - What is the probability that "CGGTACG" came from CpG+ ?

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4. State likelihood

Find the likelihood an emission x_i is generated by a state

Calculate $P(\pi_7 = \texttt{CpG+} \mid x_7 = G)$

- With no knowledge (no characters)
  - $P(\pi_i = k)$ = most likely state (**prior**)
  - Time spent in markov chain states

- With very little knowledge (just that character)
  - $P(\pi_i = k \mid x_i = G) = (\text{prior}) * (\text{most likely emission})$
  - Emission probabilities adjusted for time spent

- With knowledge of entire sequence (all characters)
  - $P(\pi_i = k \mid x = \text{AGCGCG…GATTATCGTCGTA})$
  - Sum over all paths that emit 'G' at position 7

  ➔ **Posterior** decoding

Motivation for the Backward Algorithm

We want to compute

$P(\pi_i = k \mid x)$, the probability distribution on the i^{th} position, given x

We start by computing

$$P(\pi_i = k, x) = P(x_1 \ldots x_i, \pi_i = k, x_{i+1} \ldots x_N)$$
$$= P(x_1 \ldots x_i, \pi_i = k)\, P(x_{i+1} \ldots x_N \mid x_1 \ldots x_i, \pi_i = k)$$
$$= P(x_1 \ldots x_i, \pi_i = k)\, P(x_{i+1} \ldots x_N \mid \pi_i = k)$$

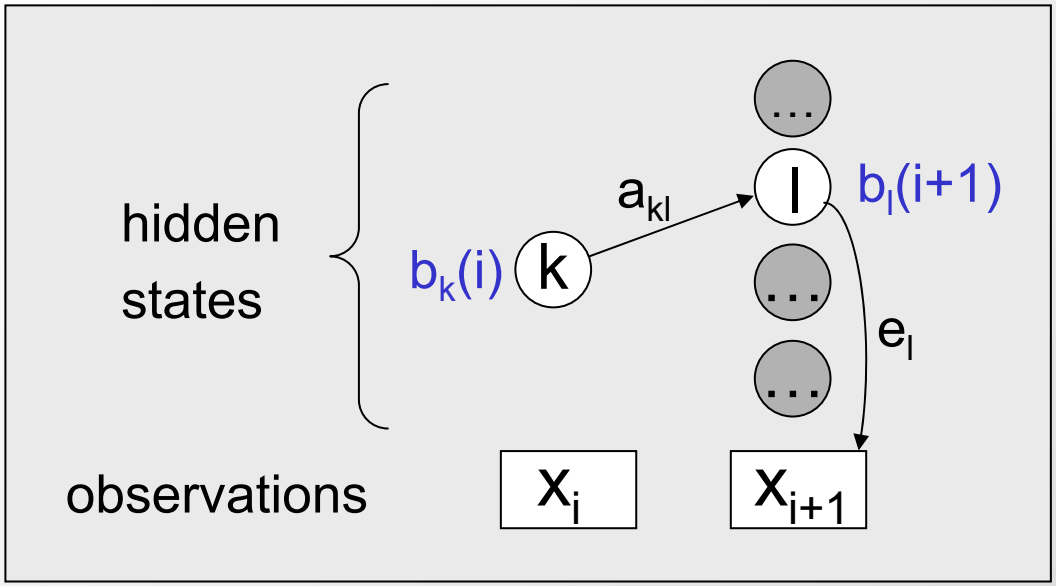
Forward, $f_k(i)$ Backward, $b_k(i)$

The Backward Algorithm – derivation

Define the backward probability:

$$
\begin{aligned}
b_k(i) &= P(x_{i+1} \ldots x_N \mid \pi_i = k) \\
&= \Sigma_{\pi i+1 \ldots \pi N} P(x_{i+1}, x_{i+2}, \ldots, x_N, \pi_{i+1}, \ldots, \pi_N \mid \pi_i = k) \\
&= \Sigma_l \Sigma_{\pi i+1 \ldots \pi N} P(x_{i+1}, x_{i+2}, \ldots, x_N, \pi_{i+1} = l, \pi_{i+2}, \ldots, \pi_N \mid \pi_i = k) \\
&= \Sigma_l e_l(x_{i+1}) a_{kl} \boxed{\Sigma_{\pi i+1 \ldots \pi N} P(x_{i+2}, \ldots, x_N, \pi_{i+2}, \ldots, \pi_N \mid \pi_{i+1} = l)} \\
&= \Sigma_l e_l(x_{i+1}) a_{kl} \boxed{b_l(i+1)}
\end{aligned}
$$

Calculate total end probability recursively



- Assume we know b_l for the next time step (i+1)
- Calculate $b_k(i)$ = sum_l ($e_l(x_{i+1})$ × a_{kl} × $b_l(i+1)$)

$b_k(i)$: current max

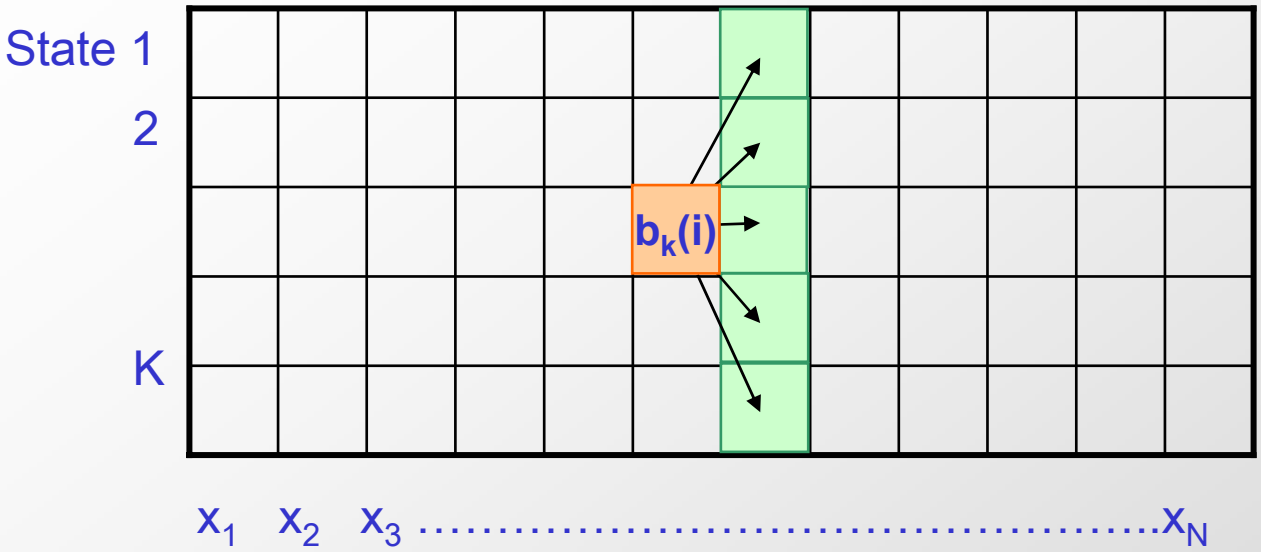
$e_l(x_{i+1})$: next emission

a_{kl}: transition to next state

$b_l(i+1)$: prob sum from state l to end

sum over all possible next states

The Backward Algorithm



Input: x = x1……xN

Initialization:

$b_k(N) = a_{k0}$, for all k

Iteration:

$b_k(i) = \Sigma_l\, e_l(x_{i+1})\, a_{kl}\, b_l(i+1)$

Termination:

$P(x) = \Sigma_l\, a_{0l}\, e_l(x_1)\, b_l(1)$

In practice:

Sum of log scores is difficult

→ approximate exp(1+p+q)

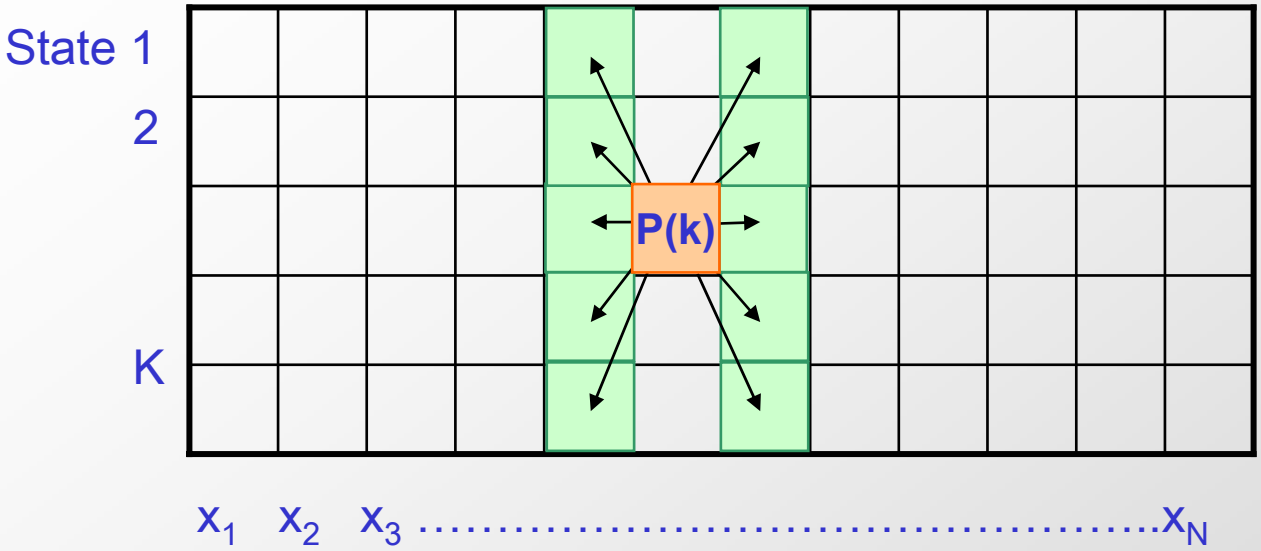
→ scaling of probabilities

Running time and space:

Time: $O(K^2N)$

Space: $O(KN)$

Putting it all together: Posterior decoding



- $P(k) = P(\pi_i = k \mid x) = f_k(i) * b_k(i) / P(x)$
  - Probability that i^{th} state is k, given all emissions x
- Posterior decoding
  - Define most likely state for every of sequence x
  - $\hat{\pi}_i = \text{argmax}_k \, P(\pi_i = k \mid x)$
- Posterior decoding 'path' $\hat{\pi}_i$
  - For classification, more informative than Viterbi path π^*
    - More refined measure of "which hidden states" generated x
  - However, it may give an invalid sequence of states
    - Not all j→k transitions may be possible

Summary

- Generative model
  - Hidden states
  - Observed sequence
- 'Running' the model
  - Generate a random sequence
- Observing a sequence
  - What is the most likely path generating it?
    - Viterbi algorithm
  - What is the total probability generating it?
    - Sum probabilities over all paths
    - Forward algorithm
- Classification
  - What is the probability that "CGGTACG" came from CpG+ ?
    - Forward + backward algorithm
  - What is the most probable state for every position
    - Posterior decoding

The main questions on HMMs

PARSING

1. **Scoring** = Joint probability of a sequence and a path, given the model
   - GIVEN a HMM M, a path π, and a sequence x,
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SCORING

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LEARNING

5. **Supervised learning** = optimize parameters of a model given training data
   - GIVEN a HMM M, with unspecified transition/emission probs., labeled sequence x,
   - FIND parameters θ = (Ei, Aij) that maximize P[x | θ]
   - ➔ Simply count frequency of each emission and transition observed in the training data
6. **Unsupervised learning** = optimize parameters of a model given training data
   - GIVEN a HMM M, with unspecified transition/emission probs., unlabeled sequence x,
   - FIND parameters θ = (Ei, Aij) that maximize P[x | θ]
   - ➔ Viterbi training: guess parameters, find optimal Viterbi path (#2), update parameters (#5), iterate
   - ➔ Baum-Welch training: guess, sum over all emissions/transitions (#4), update (#5), iterate

5: Supervised learning

Estimate model parameters
based on **labeled** training data

Two learning scenarios

Case 1. Estimation when the "right answer" is known

Examples:

GIVEN: a genomic region $x = x_1 \ldots x_{1,000,000}$ where we have good (experimental) annotations of the CpG islands

GIVEN: the casino player allows us to observe him one evening, as he changes dice and produces 10,000 rolls

Case 2. Estimation when the "right answer" is unknown

Examples:

GIVEN: the porcupine genome; we don't know how frequent are the CpG islands there, neither do we know their composition

GIVEN: 10,000 rolls of the casino player, but we don't see when he changes dice

QUESTION: Update the parameters θ of the model to maximize $P(x|\theta)$

Case 1. When the right answer is known

Given $x = x_1 \ldots x_N$
for which the true $\pi = \pi_1 \ldots \pi_N$ is known,

Define:

A_{kl} = # times $k \rightarrow l$ transition occurs in π
$E_k(b)$ = # times state k in π emits b in x

We can show that the maximum likelihood parameters θ are:

$$a_{kl} = \frac{A_{kl}}{\sum_i A_{ki}} \qquad e_k(b) = \frac{E_k(b)}{\sum_c E_k(c)}$$

Case 1. When the right answer is known

Intuition: When we know the underlying states,
Best estimate is the average frequency of
transitions & emissions that occur in the training data

Drawback:

Given little data, there may be **overfitting**:
$P(x|\theta)$ is maximized, but θ is unreasonable
0 probabilities – VERY BAD

Example:

Given 10 casino rolls, we observe

x = 2, 1, 5, 6, 1, 2, 3, 6, 2, 3
π = F, F, F, F, F, F, F, F, F, F

Then:

$a_{FF} = 1$; $a_{FL} = 0$
$e_F(1) = e_F(3) = .2$;
$e_F(2) = .3$; $e_F(4) = 0$; $e_F(5) = e_F(6) = .1$

Pseudocounts

Solution for small training sets:

Add pseudocounts

A_{kl} = # times k$\rightarrow$l transition occurs in π + r_{kl}

$E_k(b)$ = # times state k in π emits b in x + $r_k(b)$

r_{kl}, $r_k(b)$ are pseudocounts representing our prior belief

Larger pseudocounts $\Rightarrow$ Strong priof belief

Small pseudocounts (ε < 1): just to avoid 0 probabilities

Pseudocounts

Example: dishonest casino

We will observe player for one day, 500 rolls

Reasonable pseudocounts:

$r_{0F} = r_{0L} = r_{F0} = r_{L0} = 1;$

$r_{FL} = r_{LF} = r_{FF} = r_{LL} = 1;$

$r_F(1) = r_F(2) = \ldots = r_F(6) = 20$ (strong belief fair is fair)

$r_F(1) = r_F(2) = \ldots = r_F(6) = 5$ (wait and see for loaded)

Above #s pretty arbitrary – assigning priors is an art

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6: Unsupervised learning

Estimate model parameters
based on **unlabeled** training data

Learning case 2. When the right answer is unknown

We don't know the true A_{kl}, $E_k(b)$

Idea:

- We estimate our "best guess" on what A_{kl}, $E_k(b)$ are
- We update the parameters of the model, based on our guess
- We repeat

Case 2. When the right answer is unknown

Starting with our best guess of a model M, parameters θ:

Given $x = x_1 \ldots x_N$

for which the true $\pi = \pi_1 \ldots \pi_N$ is unknown,

We can get to a provably more likely parameter set θ

Principle: EXPECTATION MAXIMIZATION

1. Estimate A_{kl}, $E_k(b)$ in the training data
2. Update θ according to A_{kl}, $E_k(b)$
3. Repeat 1 & 2, until convergence

Estimating new parameters

To estimate $\mathbf{A_{kl}}$:

At each position i of sequence x,

Find probability transition k→l is used:

$$P(\pi_i = k, \pi_{i+1} = l \mid x) = [1/P(x)] \times P(\pi_i = k, \pi_{i+1} = l, x_1 \ldots x_N) = Q/P(x)$$

where
$$\begin{aligned} Q &= P(x_1 \ldots x_i, \pi_i = k, \pi_{i+1} = l, x_{i+1} \ldots x_N) = \\ &= P(\pi_{i+1} = l, x_{i+1} \ldots x_N \mid \pi_i = k)\, P(x_1 \ldots x_i, \pi_i = k) = \\ &= P(\pi_{i+1} = l, x_{i+1} x_{i+2} \ldots x_N \mid \pi_i = k)\, f_k(i) = \\ &= P(x_{i+2} \ldots x_N \mid \pi_{i+1} = l)\, P(x_{i+1} \mid \pi_{i+1} = l)\, P(\pi_{i+1} = l \mid \pi_i = k)\, f_k(i) = \\ &= b_l(i+1)\, e_l(x_{i+1})\, a_{kl}\, f_k(i) \end{aligned}$$

So:
$$\mathbf{P(\pi_i = k, \pi_{i+1} = l \mid x, \theta) = \frac{f_k(i)\, a_{kl}\, e_l(x_{i+1})\, b_l(i+1)}{P(x \mid \theta)}}$$

(For one such transition, at time step i→i+1)

Estimating new parameters

(Sum over all k→l transitions, at any time step i)

So,

$$A_{kl} = \sum_i P(\pi_i = k, \pi_{i+1} = l \mid x, \theta) = \sum_i \frac{f_k(i)\, a_{kl}\, e_l(x_{i+1})\, b_l(i+1)}{P(x \mid \theta)}$$

Similarly,

$$E_k(b) = [1/P(x)] \sum_{\{i \mid xi = b\}} f_k(i)\, b_k(i)$$

Estimating new parameters

(Sum over all training seqs, all k→l transitions, all time steps i)

If we have several training sequences, $x^1, \ldots, x^M$, each of length N,

$$A_{kl} = \sum_x \sum_i P(\pi_i = k, \pi_{i+1} = l \mid x, \theta) = \sum_x \sum_i \frac{f_k(i)\, a_{kl}\, e_l(x_{i+1})\, b_l(i+1)}{P(x \mid \theta)}$$

Similarly,

$$E_k(b) = \sum_x (1/P(x)) \sum_{\{i \mid x^i = b\}} f_k(i)\, b_k(i)$$

The Baum-Welch Algorithm

Initialization:

Pick the best-guess for model parameters

(or arbitrary)

Iteration:

1. Forward
2. Backward
3. Calculate A_{kl}, $E_k(b)$
4. Calculate new model parameters a_{kl}, $e_k(b)$
5. Calculate new log-likelihood $P(x \mid \theta)$

GUARANTEED TO BE HIGHER BY EXPECTATION-MAXIMIZATION

Until $P(x \mid \theta)$ does not change much

The Baum-Welch Algorithm – comments

Time Complexity:

iterations $\times$ $O(K^2N)$

- Guaranteed to increase the log likelihood of the model

$P(\theta \mid x) = P(x, \theta) / P(x) = P(x \mid \theta) / (P(x) P(\theta))$

- Not guaranteed to find globally best parameters

Converges to local optimum, depending on initial conditions

- Too many parameters / too large model: Overtraining

Alternative: Viterbi Training

Initialization: Same

Iteration:

1. Perform Viterbi, to find π^*
2. Calculate A_{kl}, $E_k(b)$ according to π^* + pseudocounts
3. Calculate the new parameters a_{kl}, $e_k(b)$

Until convergence

Notes:

- Convergence is guaranteed – Why?
- Does not maximize $P(x \mid \theta)$
- In general, worse performance than Baum-Welch

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The main questions on HMMs: Pop quiz

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What have we learned ?

- Generative model
  - Hidden states / Observed sequence
- 'Running' the model
  - Generate a random sequence
- Observing a sequence
  - What is the most likely path generating it?
    - Viterbi algorithm
  - What is the total probability generating it?
    - Sum probabilities over all paths
    - Forward algorithm
- Classification
  - What is the probability that "CGGTACG" came from CpG+ ?
    - Forward + backward algorithm
  - What is the most probable state for every position
    - Posterior decoding
- Training
  - Estimating parameters of the HMM
  - When state sequence is known
    - Simply compute maximum likelihood A and E
  - When state sequence is not known
    - Baum-Welch: Iterative estimation of all paths / frequencies
    - Viterbi training: Iterative estimation of best path / frequencies