Hidden Markov Models

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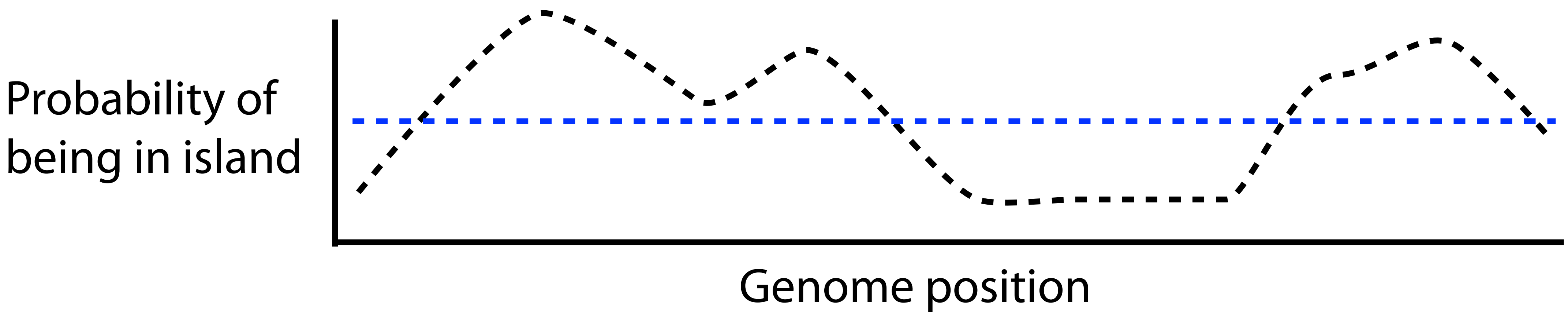
Sequence models

Can we use Markov chains to pick out CpG islands from the rest of the genome?

Markov chain assigns a score to a string; doesn't naturally give a "running" score across a long sequence

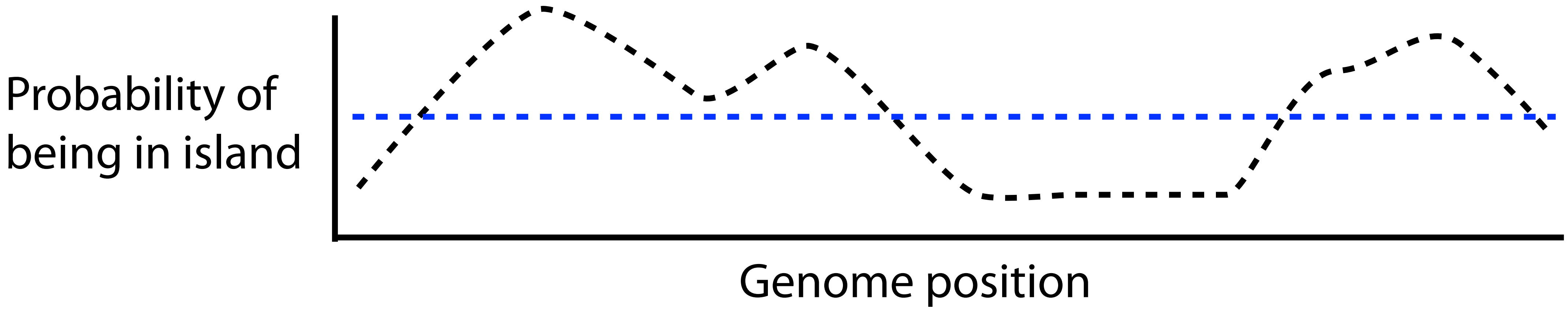


We could use a *sliding window*

(a) Pick window size *w*, (b) score every *w*-mer using Markov chains, (c) use a cutoff to find islands

Smoothing before (c) might also be a good idea

Sequence models



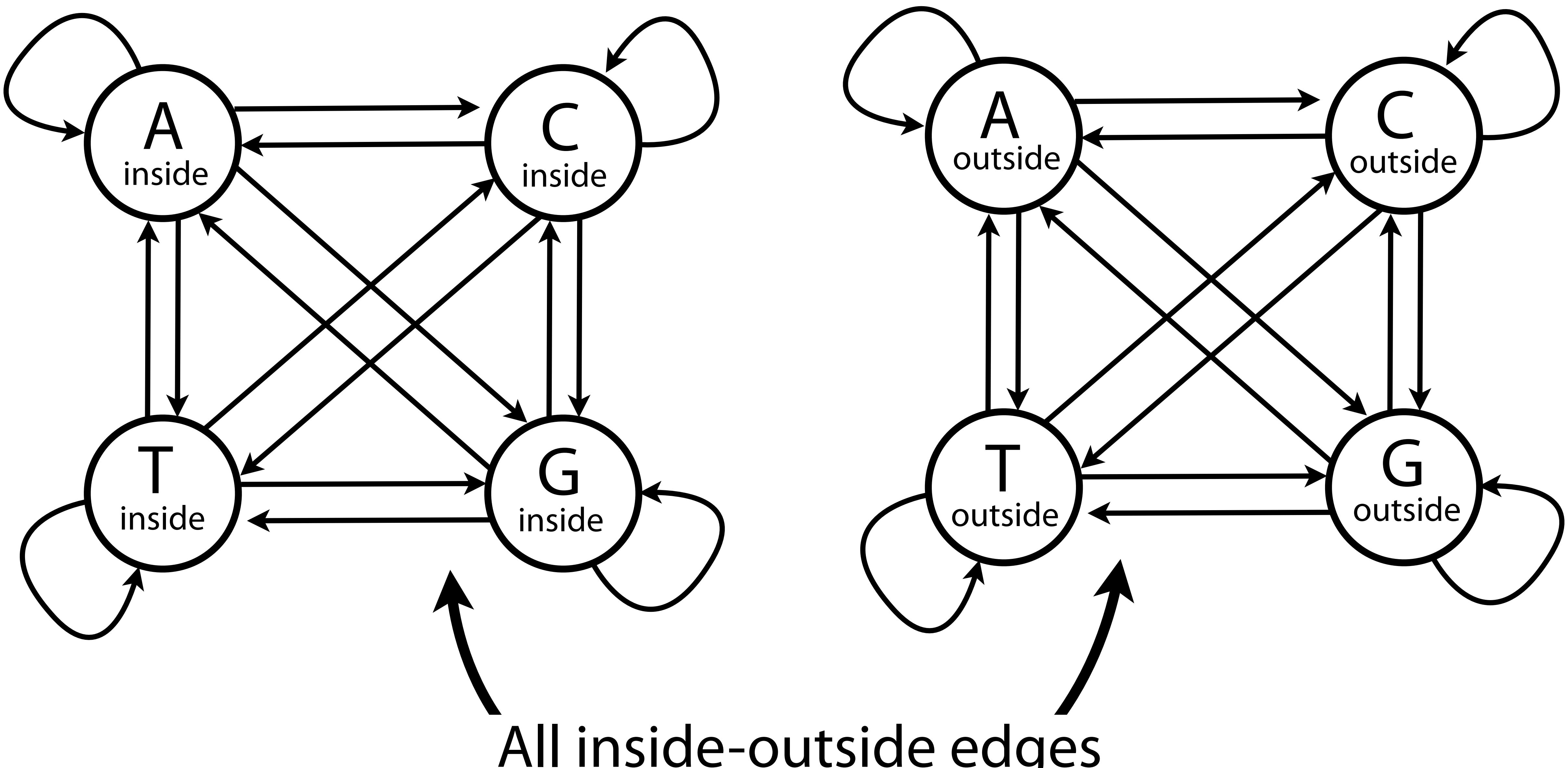
Choosing *w* involves an assumption about how long the islands are

- If *w* is too large, we'll miss small islands
- If *w* is too small, we'll get many small islands where perhaps we should see fewer larger ones

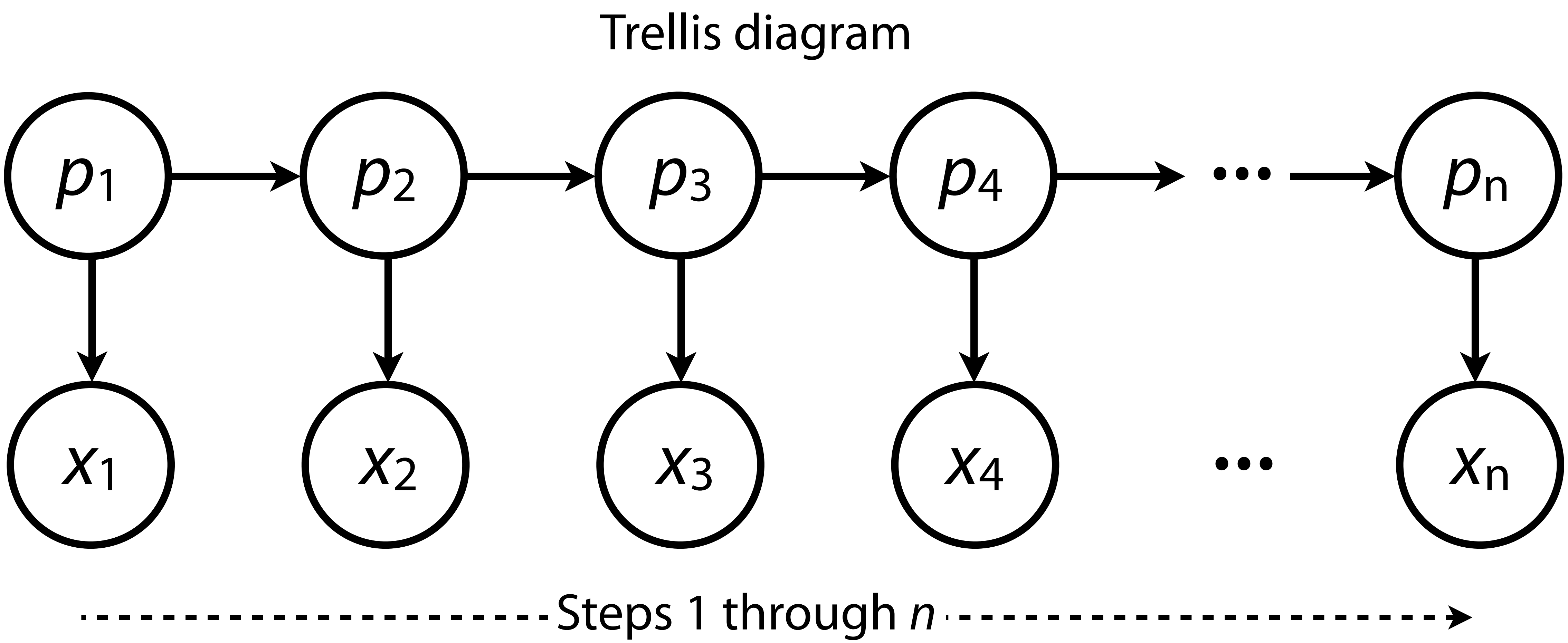
In a sense, we want to switch *between Markov chains* when entering or exiting a CpG island

Sequence models

Something like this:



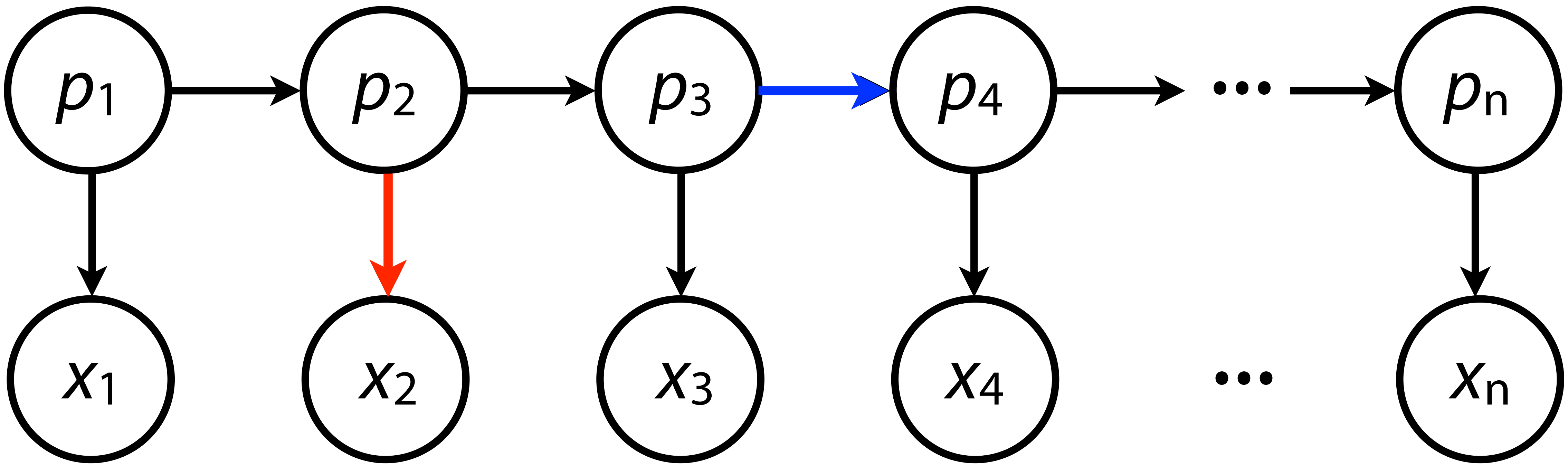
Hidden Markov Model



$p = \{ p_1, p_2, ..., p_n \}$ is a sequence of *states* (AKA a *path*). Each p_i takes a value from set Q. We ***do not*** observe p.

$x = \{ x_1, x_2, ..., x_n \}$ is a sequence of *emissions*. Each x_i takes a value from set Σ. We ***do*** observe x.

Hidden Markov Model



Like for Markov chains, edges capture conditional independence:

x_2 is conditionally independent of everything else given p_2

p_4 is conditionally independent of everything else given p_3

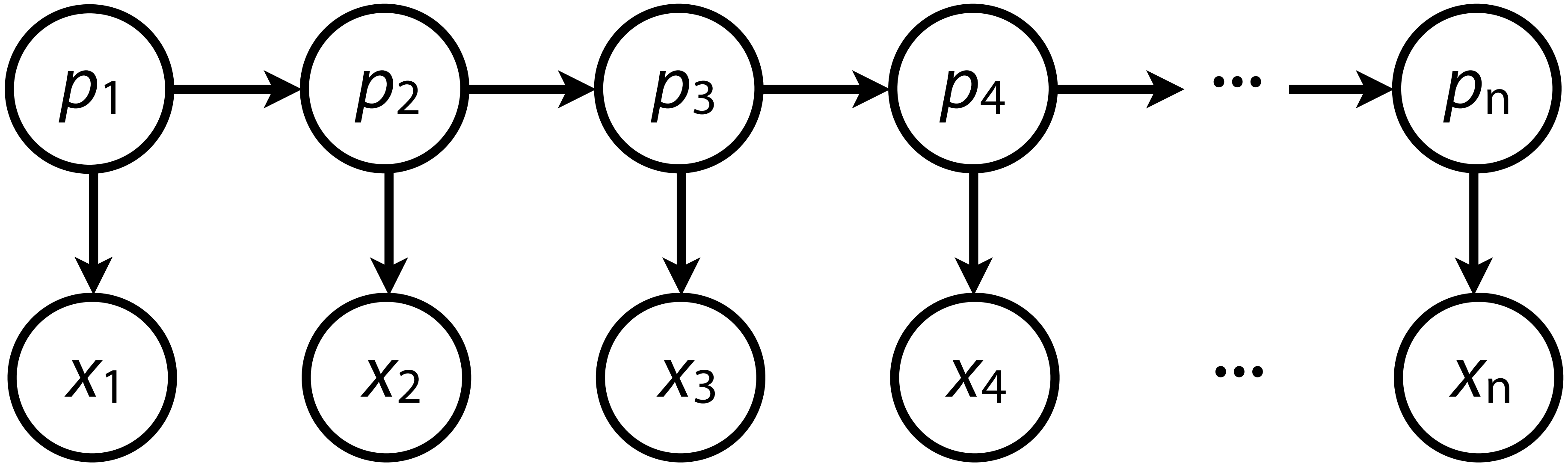
Probability of being in a particular state at step *i* is known once we know what state we were in at step *i*-1. Probability of seeing a particular emission at step *i* is known once we know what state we were in at step *i*.

Hidden Markov Model

Example: occasionally dishonest casino

Dealer repeatedly flips a coin. Sometimes the coin is *fair*, with P(heads) = 0.5, sometimes it's *loaded*, with P(heads) = 0.8. Dealer occasionally switches coins, invisibly to you.

How does this map to an HMM?



Hidden Markov Model

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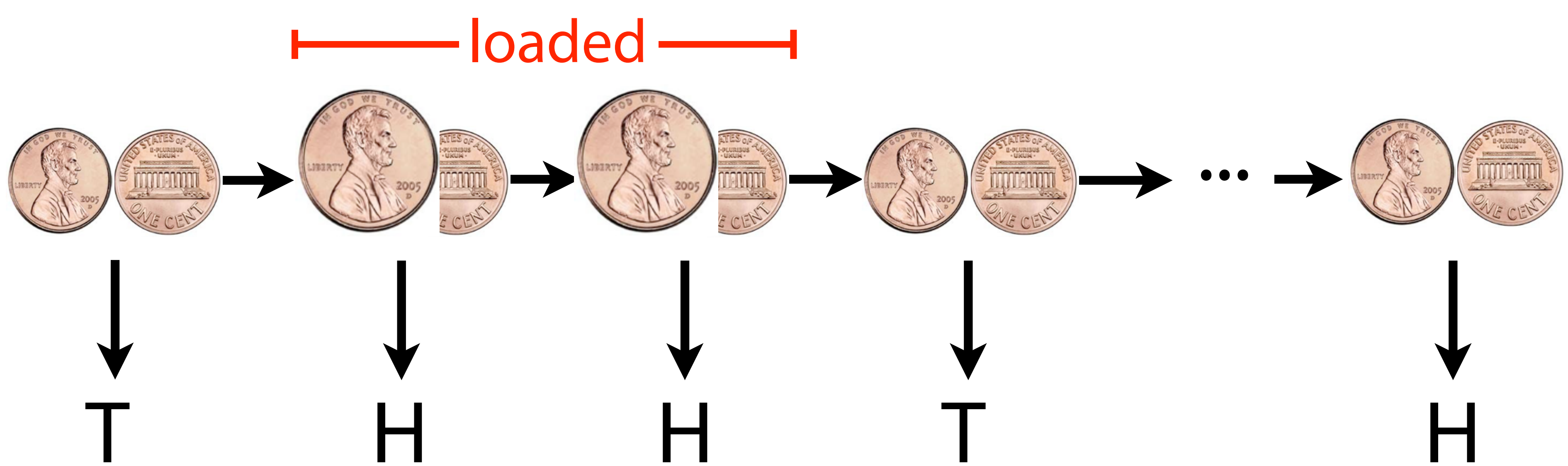

Emissions encode flip outcomes (observed), states encode loadedness (hidden)

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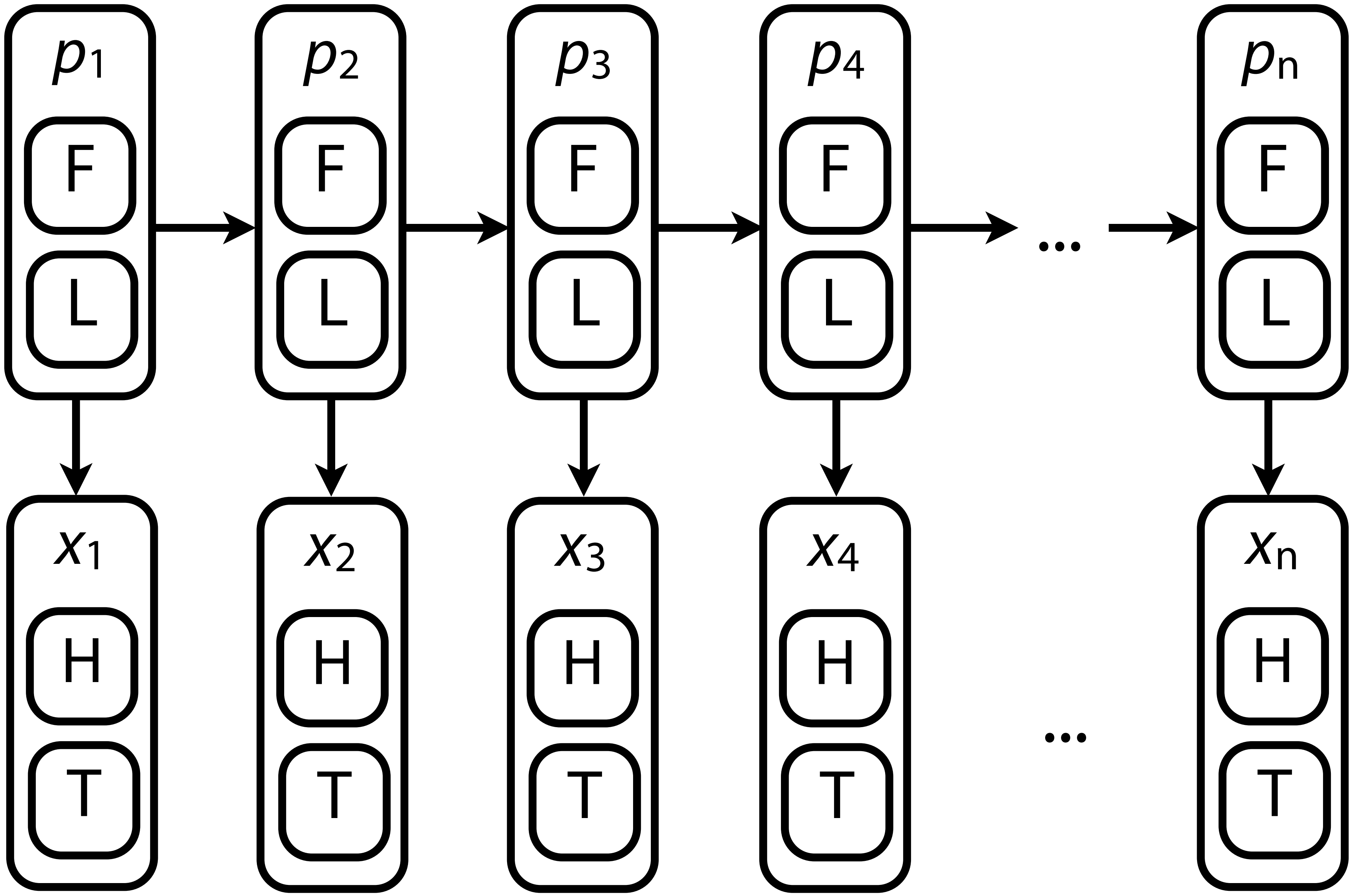
Hidden Markov Model

States encode which coin is used

F = fair
L = loaded



Emissions encode flip outcomes

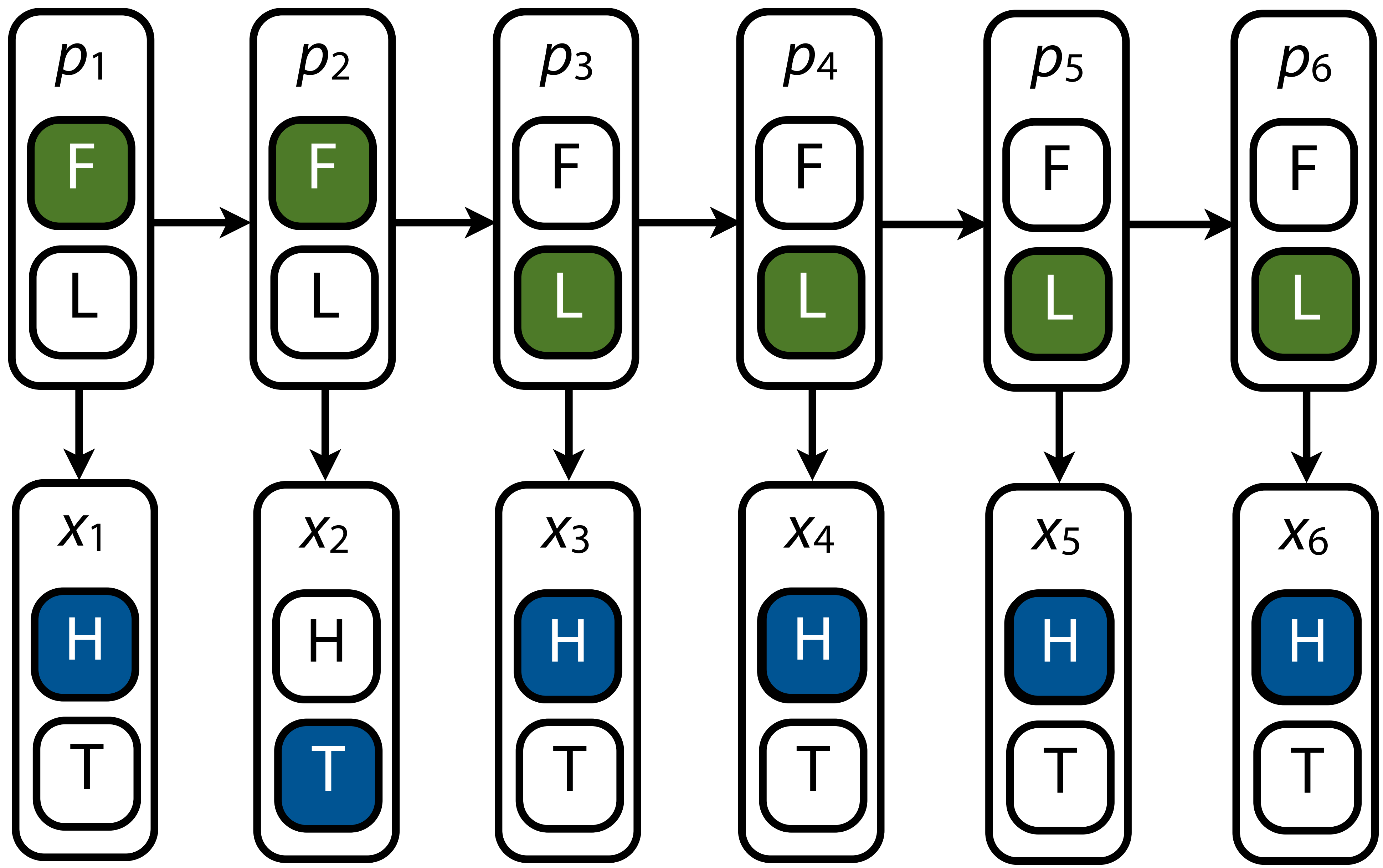
H = heads
T = tails

Hidden Markov Model

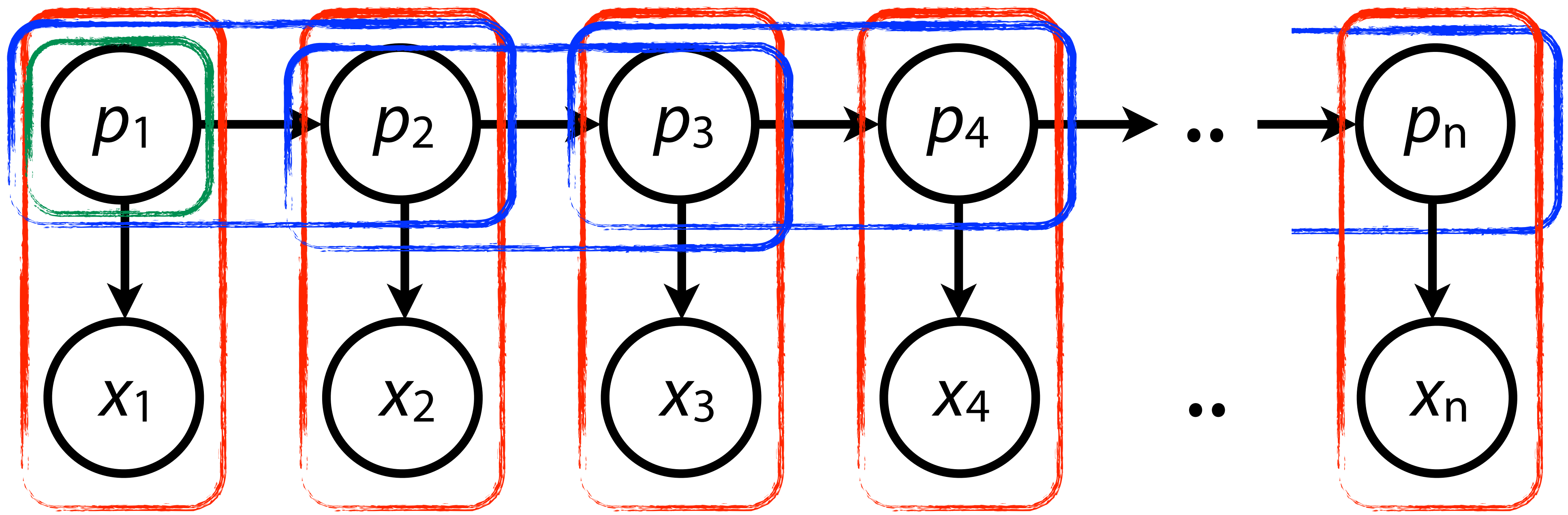
Example with six coin flips:

$p = \text{FFLLLL}$

$x = \text{HTHHHH}$



Hidden Markov Model



$$P(p_1, p_2, \ldots, p_n, x_1, x_2, \ldots, x_n) = \prod_{k=1}^{n} P(x_k \mid p_k) \prod_{k=2}^{n} P(p_k \mid p_{k-1})\, P(p_1)$$

$|Q| \times |\Sigma|$ emission matrix E encodes $P(x_i \mid p_i)$s $E[p_i, x_i] = P(x_i \mid p_i)$

$|Q| \times |Q|$ transition matrix A encodes $P(p_i \mid p_{i-1})$s $A[p_{i-1}, p_i] = P(p_i \mid p_{i-1})$

$|Q|$ array I encodes initial probabilities of each state $I[p_i] = P(p_1)$

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Hidden Markov Model

Dealer repeatedly flips a coin. Coin is sometimes *fair*, with P(heads) = 0.5, sometimes *loaded*, with P(heads) = 0.8. Dealer occasionally switches coins, invisibly to you.

After each flip, dealer switches coins with probability 0.4

A:

	F	L
F	0.6	0.4
L	0.4	0.6

E:

	H	T
F	0.5	0.5
L	0.8	0.2

$|Q| \times |\Sigma|$ emission matrix E encodes $P(x_i \mid p_i)$s $\quad E[p_i, x_i] = P(x_i \mid p_i)$

$|Q| \times |Q|$ transition matrix A encodes $P(p_i \mid p_{i-1})$s $\quad A[p_{i-1}, p_i] = P(p_i \mid p_{i-1})$

Hidden Markov Model

A	F	L
F	0.6	0.4
L	0.4	0.6

E	H	T
F	0.5	0.5
L	0.8	0.2

Given A & E (right), what is the joint probability of $\boldsymbol{p}$ & $\boldsymbol{x}$?

$\boldsymbol{p}$	F	F	F	L	L	L	F	F	F	F	F
$\boldsymbol{x}$	T	H	T	H	H	H	T	H	T	T	H
P(x_i | p_i)	0.5	0.5	0.5	0.8	0.8	0.8	0.5	0.5	0.5	0.5	0.5
P(p_i | p_{i-1})	-	0.6	0.6	0.4	0.6	0.6	0.4	0.6	0.6	0.6	0.6

If P(p_1 = F) = 0.5, then joint probability = $0.5^9\ 0.8^3\ 0.6^8\ 0.4^2$ = 0.0000026874

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Hidden Markov Model

Given flips, can we say when the dealer was using the loaded coin?

We want to find p^*, the most likely path given the emissions.

$$p^* = \underset{p}{\operatorname{argmax}}\, \mathrm{P}(\, p \mid x\,) \;\; = \underset{p}{\operatorname{argmax}}\, \mathrm{P}(\, p, x\,)$$

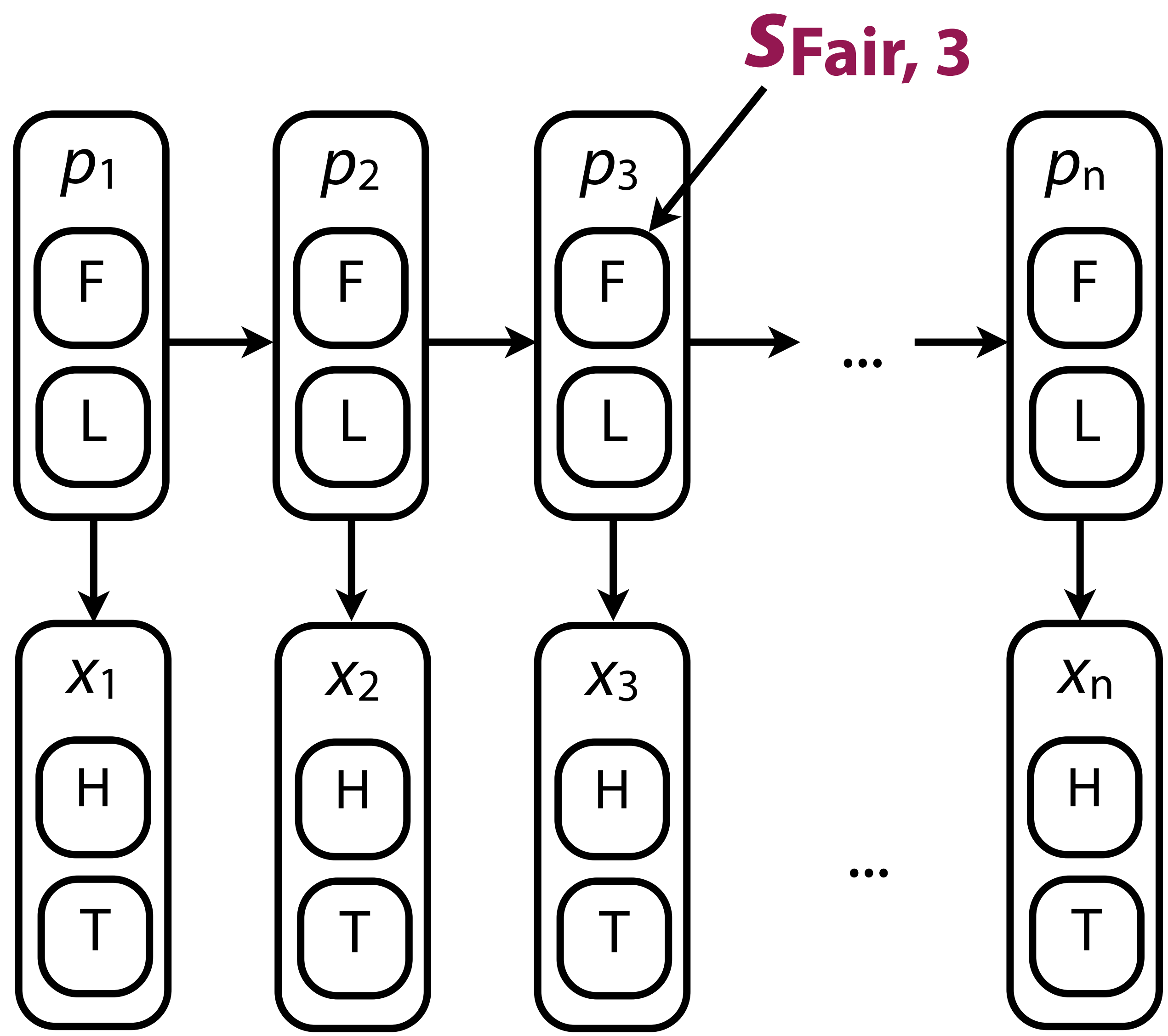
This is *decoding*. *Viterbi* is a common decoding algorithm.

Hidden Markov Model: Viterbi algorithm

Bottom-up dynamic programming

$s_{k,\,i}$ = score of the most likely path up to step *i* with p_i = k

Start at step 1, calculate successively longer $s_{k,\,i}$'s



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Hidden Markov Model: Viterbi algorithm

Given transition matrix *A* and emission matrix *E* (right), what is the most probable path *p* for the following *x*?

Initial probabilities of F/L are 0.5

A	F	L
F	0.6	0.4
L	0.4	0.6

E	H	T
F	0.5	0.5
L	0.8	0.2

p	?	?	?	?	?	?	?	?	?	?	?
x	T	H	T	H	H	H	T	H	T	T	H
$s_{\text{Fair}, i}$	0.25	?	?	?	?	?	?	?	?	?	?
$s_{\text{Loaded}, i}$	0.1	?	?	?	?	?	?	?	?	?	?

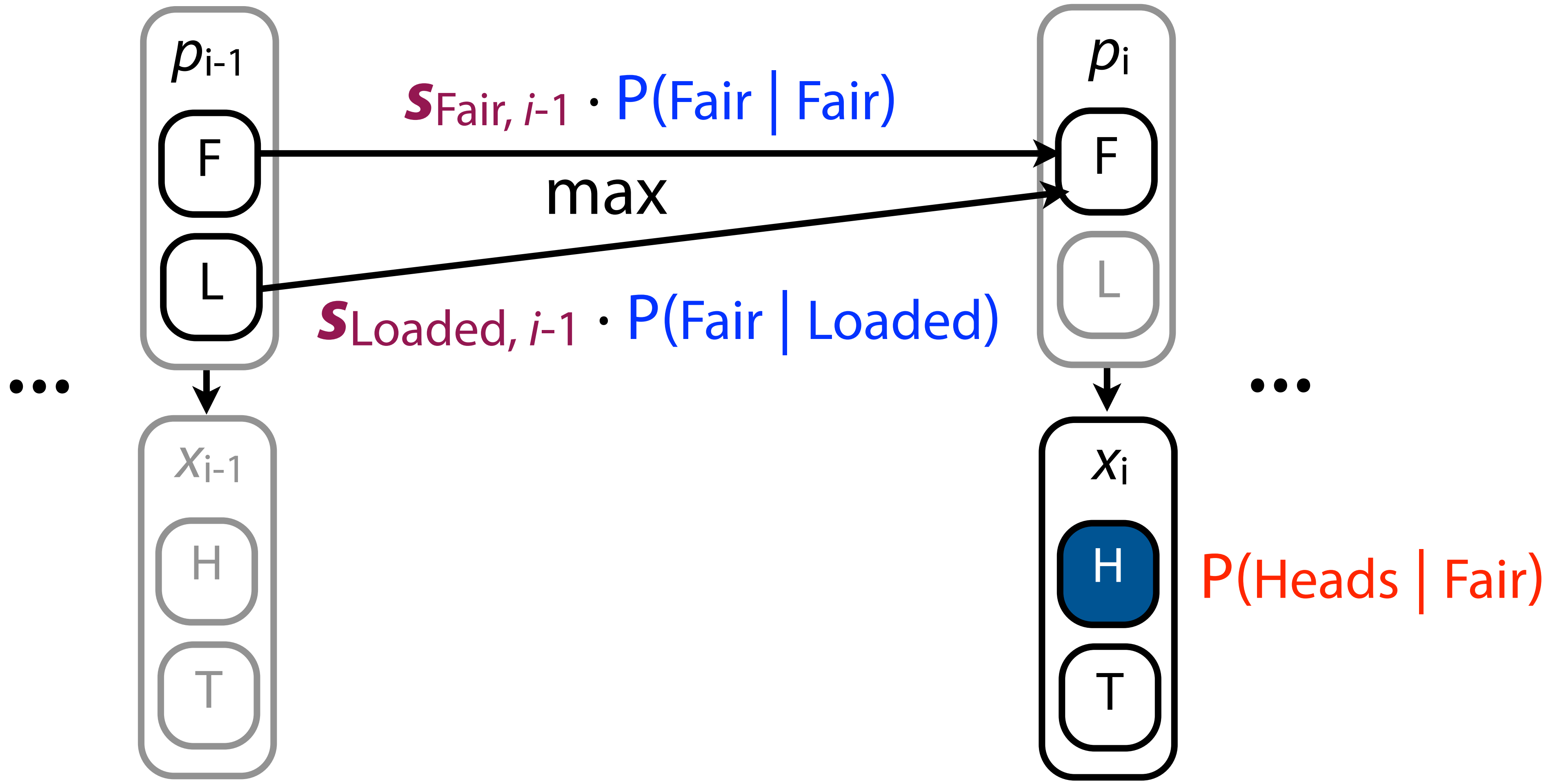
Viterbi fills in all the question marks

Hidden Markov Model: Viterbi algorithm

$$s_{Fair,i} = P(\text{Heads} \mid \text{Fair}) \cdot \max_{k \in \{\text{Fair, Loaded}\}} \{ s_{k,i-1} \cdot P(\text{Fair} \mid k) \}$$

Emission prob

Transition prob



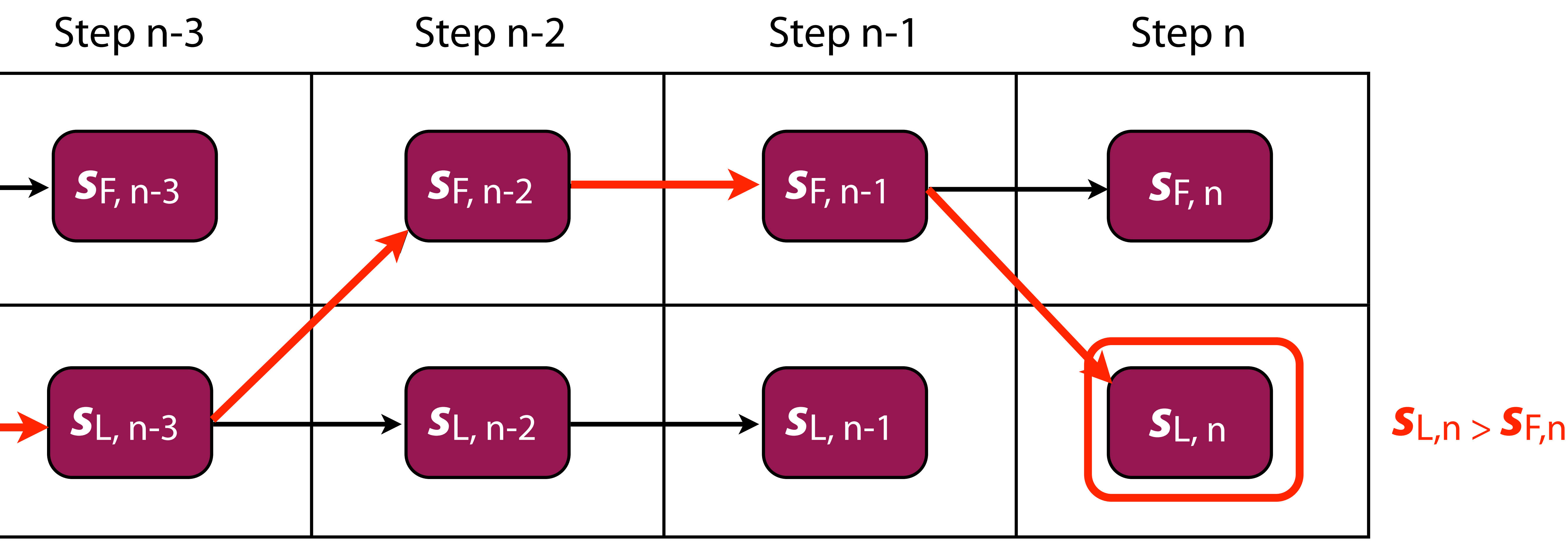
Hidden Markov Model: Viterbi algorithm

	Step 1	Step 2	Step 3	Step 4	...
x	**T**	**H**	**T**	**H**	
$S_{F,i}$	$p(T\|F) = 0.5$ $p(F) = 0.5$ $S_{F,1} = 0.5^2$	$p(H\|F) = 0.5$ max: $p(F\|F) = 0.6$ $0.5^3 \cdot 0.6$ $p(F\|L) = 0.4$ $0.2 \cdot 0.4 \cdot 0.5^2$ F wins max $S_{F,2} = 0.5^3 \cdot 0.6$	$p(T\|F) = 0.5$ max: $p(F\|F) = 0.6$ $0.5^4 \cdot 0.6^2$ $p(F\|L) = 0.4$ $0.2 \cdot 0.4 \cdot 0.5^2 \cdot 0.6 \cdot 0.8$ F wins max $S_{F,3} = 0.5^4 \cdot 0.6^2$	etc	
$S_{L,i}$	$p(T\|L) = 0.2$ $p(L) = 0.5$ $S_{L,1} = 0.2 \cdot 0.5$	$p(H\|L) = 0.8$ max: $p(L\|F) = 0.4$ $0.4 \cdot 0.5^2 \cdot 0.8$ $p(L\|L) = 0.6$ $0.2 \cdot 0.5 \cdot 0.6 \cdot 0.8$ F wins max $S_{L,2} = 0.4 \cdot 0.5^2 \cdot 0.8$	etc	etc	

Hidden Markov Model: Viterbi algorithm

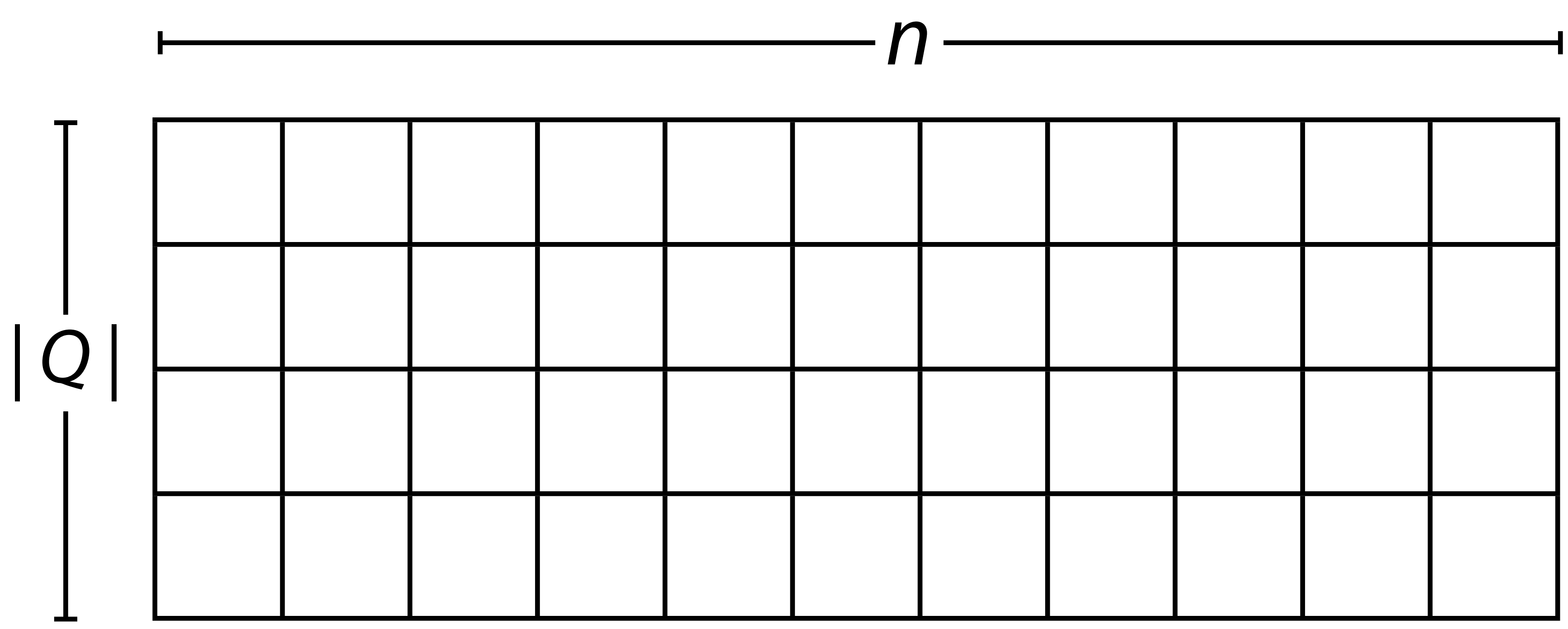
Pick state in step *n* with highest score; *backtrace* for most likely path

Backtrace according to which state *k* "won" the max in:



Hidden Markov Model: Viterbi algorithm

How much work did we do, given Q is the set of states and n is the length of the sequence?



\# $s_{k,i}$ values to calculate $= n \cdot |Q|$, each involves max over $|Q|$ products

$O(n \cdot |Q|^2)$

Matrix A has $|Q|^2$ elements, E has $|Q||\Sigma|$ elements, I has $|Q|$ elements

Hidden Markov Model: Implementation

```python
def viterbi(self, x):
    ''' Given sequence of emissions, return the most probable path
        along with its joint probability. '''
    x = map(self.smap.get, x) # turn emission characters into ids
    nrow, ncol = len(self.Q), len(x)
    mat   = numpy.zeros(shape=(nrow, ncol), dtype=float) # prob
    matTb = numpy.zeros(shape=(nrow, ncol), dtype=int)   # backtrace
    # Fill in first column
    for i in xrange(0, nrow):
        mat[i, 0] = self.E[i, x[0]] * self.I[i]
    # Fill in rest of prob and Tb tables
    for j in xrange(1, ncol):
        for i in xrange(0, nrow):
            ep = self.E[i, x[j]]
            mx, mxi = mat[0, j-1] * self.A[0, i] * ep, 0
            for i2 in xrange(1, nrow):
                pr = mat[i2, j-1] * self.A[i2, i] * ep
                if pr > mx:
                    mx, mxi = pr, i2
            mat[i, j], matTb[i, j] = mx, mxi
    # Find final state with maximal probability
    omx, omxi = mat[0, ncol-1], 0
    for i in xrange(1, nrow):
        if mat[i, ncol-1] > omx:
            omx, omxi = mat[i, ncol-1], i
    # Backtrace
    i, p = omxi, [omxi]
    for j in xrange(ncol-1, 0, -1):
        i = matTb[i, j]
        p.append(i)
    p = ''.join(map(lambda x: self.Q[x], p[::-1]))
    return omx, p # Return probability and path
```

`mat` holds the $s_{k,i}$'s

`matTb` holds traceback info

`self.E` holds emission probs

`self.A` holds transition probs

`self.I` holds initial probs

Calculate $s_{k,i}$'s

Find maximal $s_{k,n}$

Backtrace

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Hidden Markov Model: Viterbi algorithm

```
>>> hmm = HMM({"FF":0.6, "FL":0.4, "LF":0.4, "LL":0.6},
...           {"FH":0.5, "FT":0.5, "LH":0.8, "LT":0.2},
...           {"F":0.5, "L":0.5})
>>> prob, _ = hmm.viterbi("THTHHHTHTTH")
>>> print prob
2.86654464e-06
>>> prob, _ = hmm.viterbi("THTHHHTHTTH" * 100)
>>> print prob
0.0
```

Repeat string 100 times

Occasionally dishonest casino setup

What happened? Underflow!

Python example: http://nbviewer.ipython.org/7460513

Hidden Markov Model: Viterbi algorithm

```
>>> hmm = HMM({"FF":0.6, "FL":0.4, "LF":0.4, "LL":0.6},
...           {"FH":0.5, "FT":0.5, "LH":0.8, "LT":0.2},
...           {"F":0.5, "L":0.5})
>>> prob, _ = hmm.viterbi("THTHHHTHTTH")
>>> print prob
2.86654464e-06
>>> prob, _ = hmm.viterbi("THTHHHTHTTH" * 100)
>>> print prob
0.0
>>> logprob, _ = hmm.viterbiL("THTHHHTHTTH" * 100)
>>> print logprob
-1824.4030071946879
```

Repeat string 100 times

log-space Viterbi

When multiplying many numbers in (0, 1], we quickly approach the smallest number representable in a machine word. Past that we have *underflow* and processor rounds down to 0.

Switch to log space. Multiplies become adds.

Python example: http://nbviewer.ipython.org/7460513

Hidden Markov Model: Implementation

log-space version

```
def viterbiL(self, x):
    ''' Given sequence of emissions, return the most probable path
        along with log2 of its joint probability. '''
    x = map(self.smap.get, x) # turn emission characters into ids
    nrow, ncol = len(self.Q), len(x)
    mat   = numpy.zeros(shape=(nrow, ncol), dtype=float) # prob
    matTb = numpy.zeros(shape=(nrow, ncol), dtype=int)   # backtrace
    # Fill in first column
    for i in xrange(0, nrow):
        mat[i, 0] = self.Elog[i, x[0]] + self.Ilog[i]   *
    # Fill in rest of log prob and Tb tables
    for j in xrange(1, ncol):
        for i in xrange(0, nrow):
            ep = self.Elog[i, x[j]]                          *
            mx, mxi = mat[0, j-1] + self.Alog[0, i] + ep, 0    *
            for i2 in xrange(1, nrow):
                pr = mat[i2, j-1] + self.Alog[i2, i] + ep    *
                if pr > mx:
                    mx, mxi = pr, i2
            mat[i, j], matTb[i, j] = mx, mxi
    # Find final state with maximal log probability
    omx, omxi = mat[0, ncol-1], 0
    for i in xrange(1, nrow):
        if mat[i, ncol-1] > omx:
            omx, omxi = mat[i, ncol-1], i
    # Backtrace
    i, p = omxi, [omxi]
    for j in xrange(ncol-1, 0, -1):
        i = matTb[i, j]
        p.append(i)
    p = ''.join(map(lambda x: self.Q[x], p[::-1]))
    return omx, p # Return log probability and path
```

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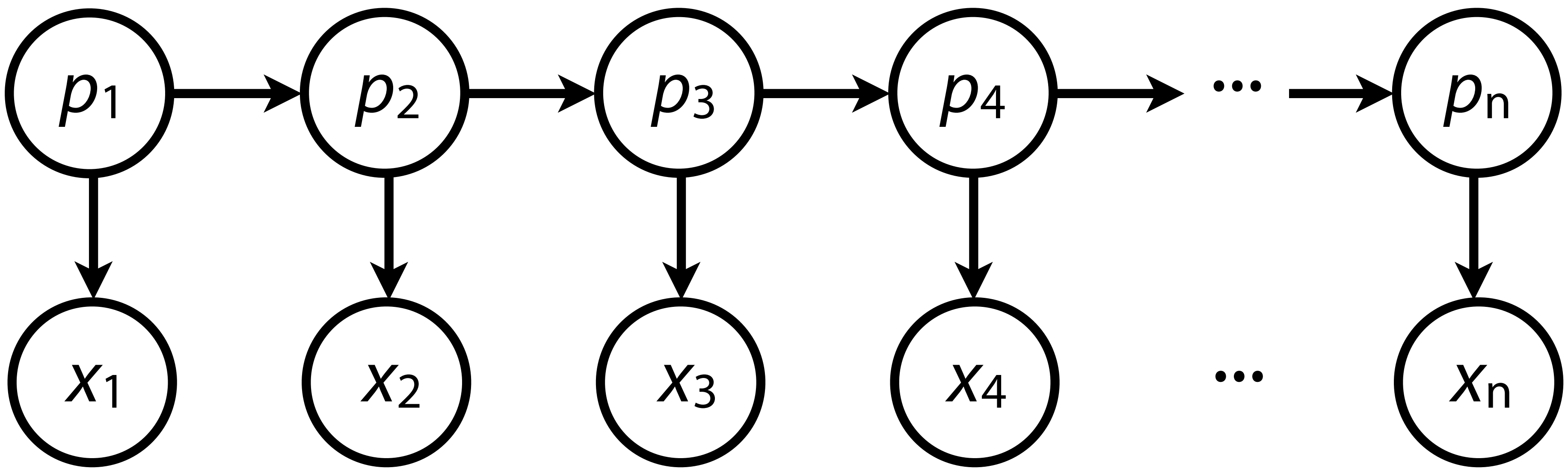
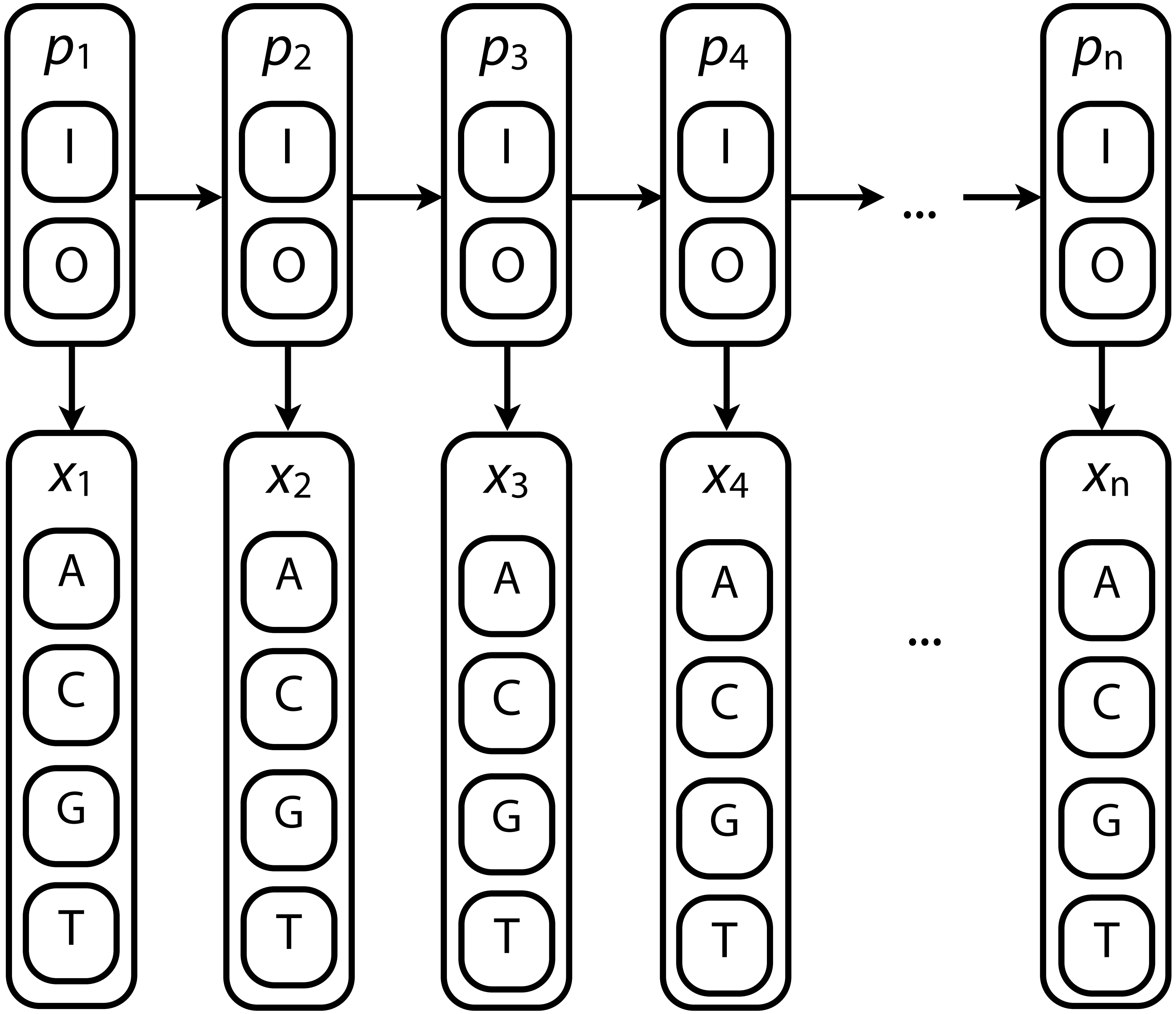
Hidden Markov Model

Task: design an HMM for finding CpG islands?



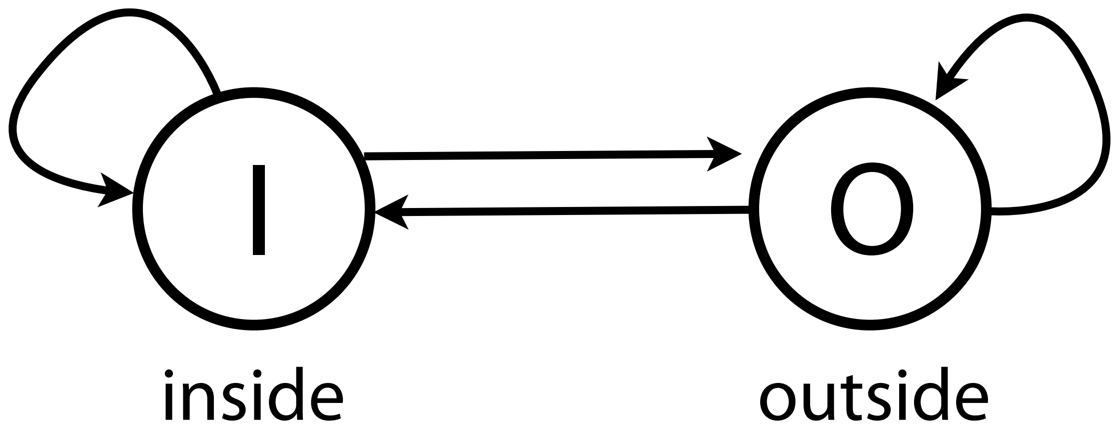
Hidden Markov Model

Idea 1: Q = { inside, outside }, Σ = { A, C, G, T }



Hidden Markov Model

Idea 1: $Q = \{$ inside, outside $\}$, $\Sigma = \{$ A, C, G, T $\}$



A	I	O
I		
O		

Transition matrix

Estimate as fraction of positions where we transition from inside to outside

E	A	C	G	T
I				
O				

Emission matrix

Estimate as fraction of nucleotides inside islands that are C

Hidden Markov Model

Example 1 using HMM idea 1:

A	I	O
I	0.8	0.2
O	0.2	0.8

E	A	C	G	T
I	0.1	0.4	0.4	0.1
O	0.25	0.25	0.25	0.25

x: ATATATACGCGCGCGCGCGCGATATATATATATA

p: OOOOOOOIIIIIIIIIIIIIIOOOOOOOOOOOOO

(from Viterbi)

Python example: http://nbviewer.ipython.org/7460513

Hidden Markov Model

Example 2 using HMM idea 1:

A	I	O
I	0.8	0.2
O	0.2	0.8

E	A	C	G	T
I	0.1	0.4	0.4	0.1
O	0.25	0.25	0.25	0.25

x: ATATCGCGCGCGATATATCGCGCGCGATATATAT

p: 0000IIIIIIII000000IIIIIIII00000000

(from Viterbi)

Python example: http://nbviewer.ipython.org/7460513

Hidden Markov Model

Example 3 using HMM idea 1:

A	I	O
I	0.8	0.2
O	0.2	0.8

E	A	C	G	T
I	0.1	0.4	0.4	0.1
O	0.25	0.25	0.25	0.25

x: ATATATACCCCCCCCCCCCCCATATATATATATA

p: 0000000IIIIIIIIIIIIII0000000000000

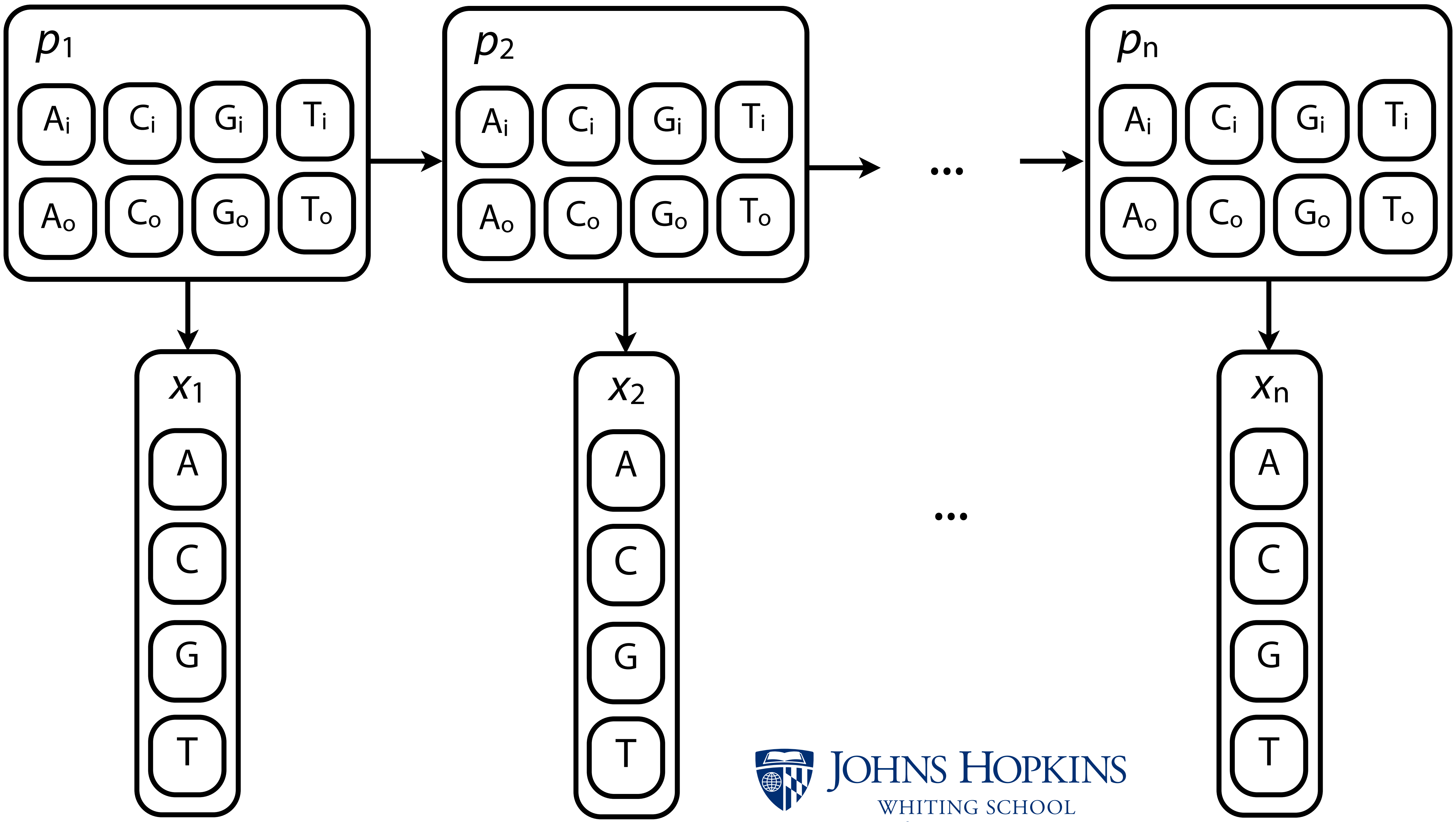
(from Viterbi)

Oops - not a CpG island!

Python example: http://nbviewer.ipython.org/7460513

Hidden Markov Model

Idea 2: $Q = \{ A_i, C_i, G_i, T_i, A_o, C_o, G_o, T_o \}$, $\Sigma = \{ A, C, G, T \}$



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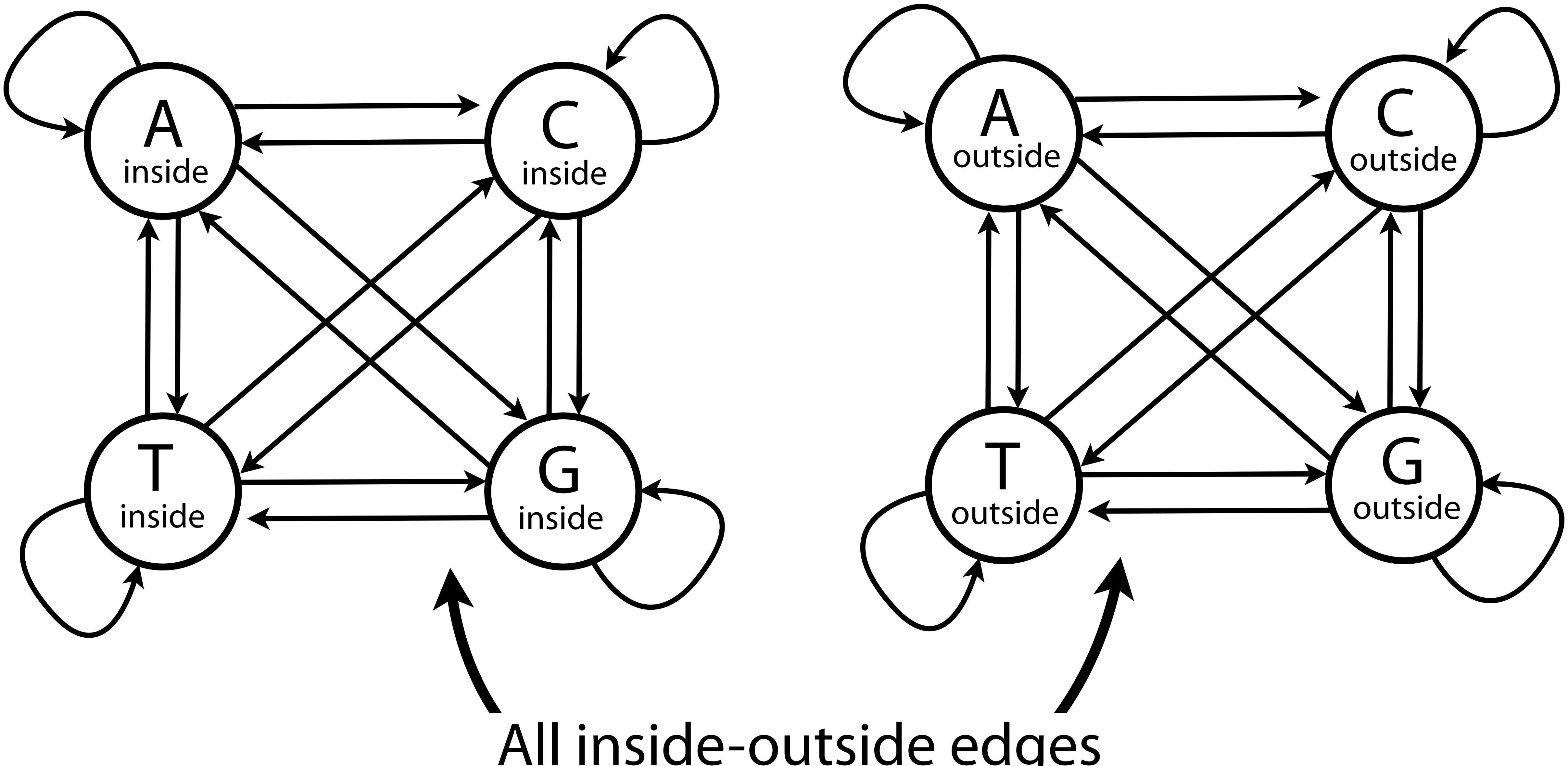
Hidden Markov Model

Idea 2: $Q = \{ A_i, C_i, G_i, T_i, A_o, C_o, G_o, T_o \}$, $\Sigma = \{ A, C, G, T \}$



Hidden Markov Model

Idea 2: $Q = \{ A_i, C_i, G_i, T_i, A_o, C_o, G_o, T_o \}$, $\Sigma = \{ A, C, G, T \}$

A	A_i	C_i	G_i	T_i	A_o	C_o	G_o	T_o
A_i								
C_i								
G_i								
T_i								
A_o								
C_o								
G_o								
T_o								

Estimate $P(C_i \mid T_i)$ as fraction of all dinucleotides where first is an inside T, second is an inside C

E	A	C	G	T
A_i	1	0	0	0
C_i	0	1	0	0
G_i	0	0	1	0
T_i	0	0	0	1
A_o	1	0	0	0
C_o	0	1	0	0
G_o	0	0	1	0
T_o	0	0	0	1

Hidden Markov Model

Actual trained transition matrix A:

```
A:
[[  1.85152516e-01   2.75974026e-01   4.00289017e-01   1.37026750e-01
    3.19045117e-04   3.19045117e-04   6.38090233e-04   2.81510397e-04]
 [  1.89303979e-01   3.58523577e-01   2.52868527e-01   1.97836007e-01
    4.28792308e-04   5.72766368e-04   3.75584503e-05   4.28792308e-04]
 [  1.72369088e-01   3.29501650e-01   3.55446538e-01   1.40829292e-01
    3.39848138e-04   4.94038497e-04   7.64658311e-04   2.54886104e-04]
 [  9.38783432e-02   3.40823149e-01   3.75970400e-01   1.86949063e-01
    2.56686367e-04   5.57197235e-04   1.05804868e-03   5.07112091e-04]
 [  0.00000000e+00   3.78291020e-05   0.00000000e+00   0.00000000e+00
    2.94813496e-01   1.94641138e-01   2.86962055e-01   2.23545482e-01]
 [  0.00000000e+00   7.57154865e-05   0.00000000e+00   0.00000000e+00
    3.26811872e-01   2.94079570e-01   6.17258712e-02   3.17306971e-01]
 [  0.00000000e+00   5.73810399e-05   0.00000000e+00   0.00000000e+00
    2.57133507e-01   2.33483327e-01   2.94234944e-01   2.15090841e-01]
 [  0.00000000e+00   3.11417347e-05   0.00000000e+00   0.00000000e+00
    1.79565378e-01   2.32469115e-01   2.94623408e-01   2.93310958e-01]]
```

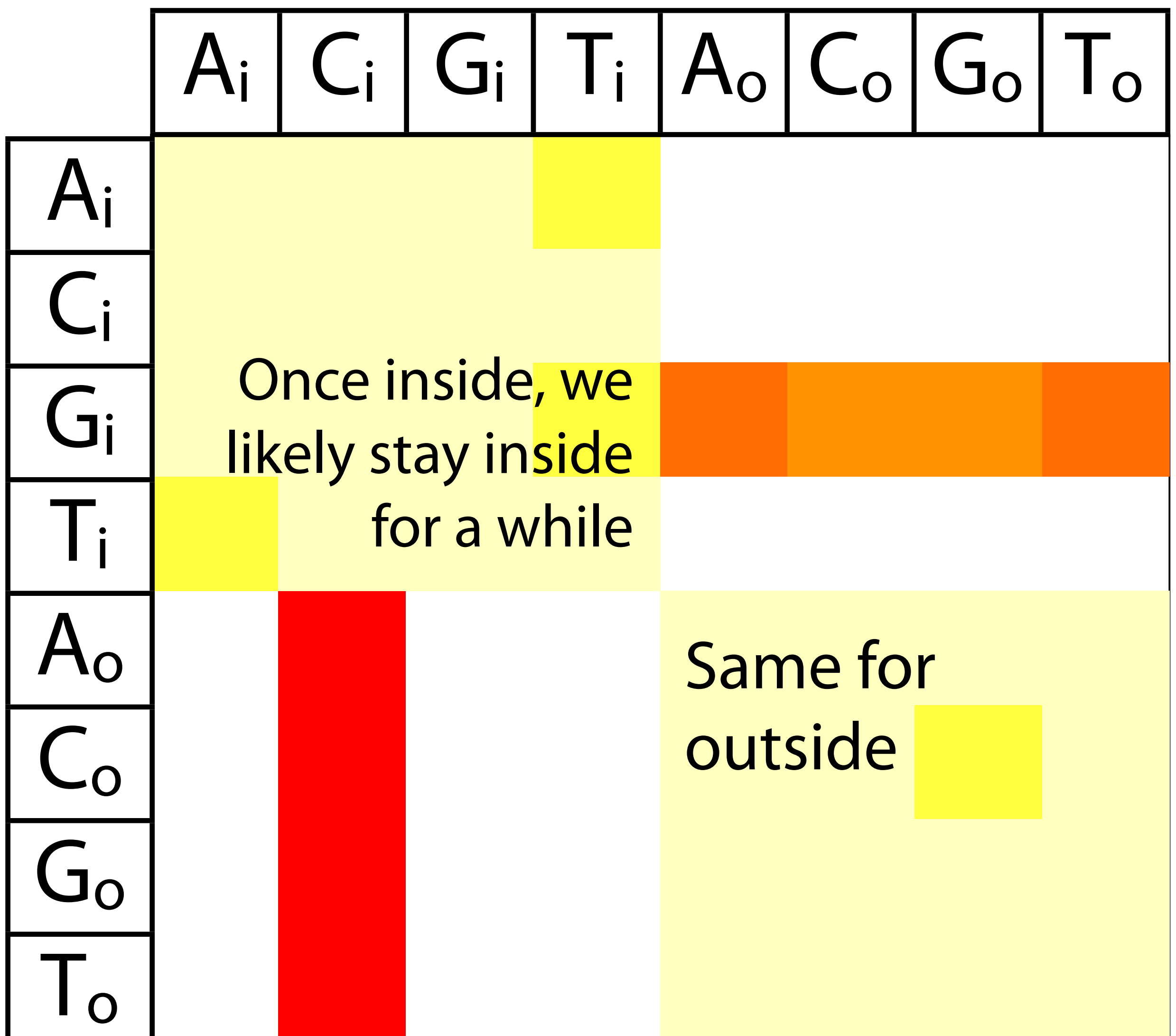
Hidden Markov Model

Actual trained transition matrix A:

Red & orange: low probability

Yellow: high probability

White: probability = 0



← CpG islands end with G (in fact, they end with CG)

↖ CpG islands start with C (in fact, they start with CG)

Hidden Markov Model

Viterbi result; lowercase = *outside*, uppercase = *inside*:

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atatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatat
atatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatat
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atatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatat
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Hidden Markov Model

Viterbi result; lowercase = *outside*, uppercase = *inside*:

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atatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatat
atatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatat
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atatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatatat
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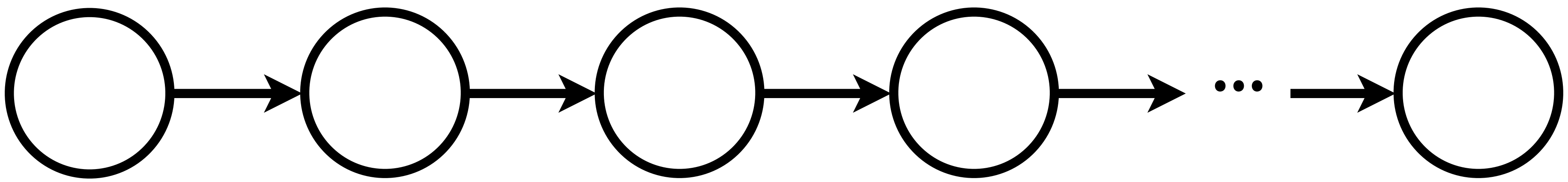
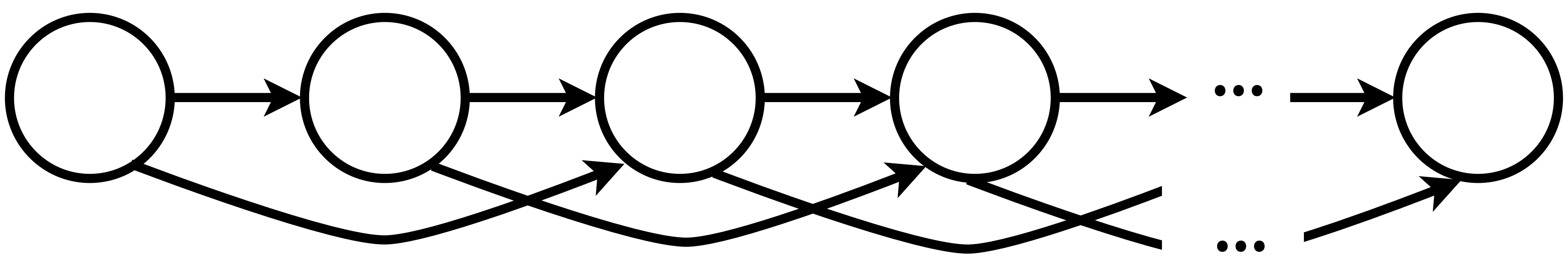
Hidden Markov Model

Many of the Markov chains and HMMs we've discussed are *first order,* but we can also design models of higher orders

First-order Markov chain:

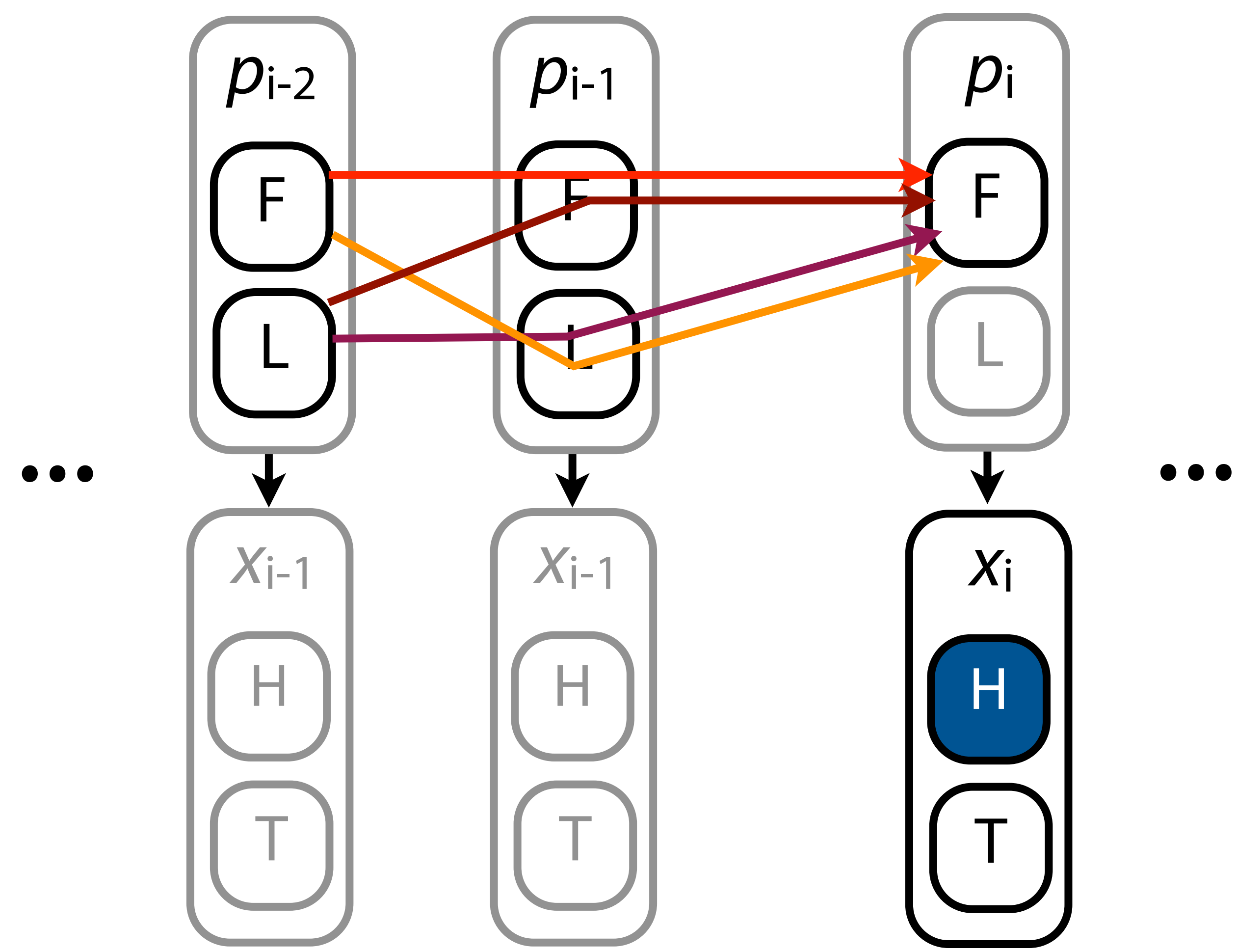


Second-order Markov chain:



Hidden Markov Model

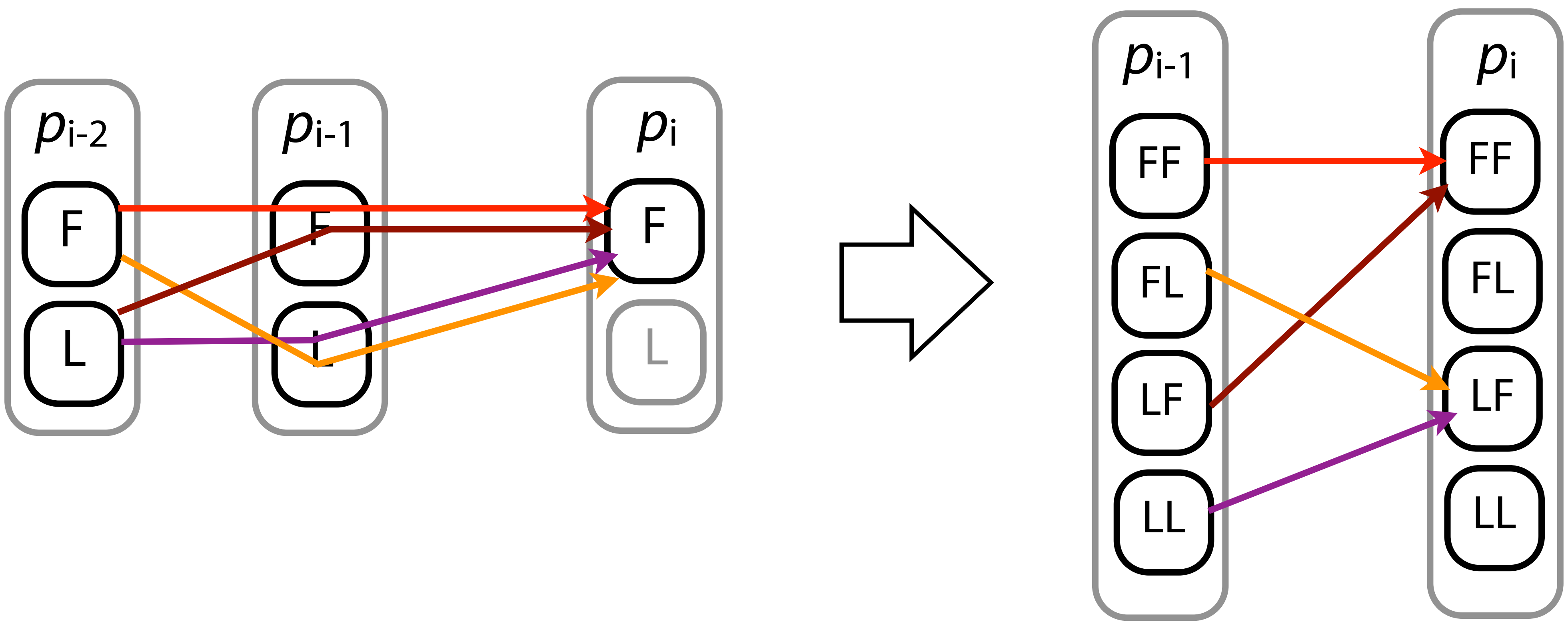
For higher-order HMMs, Viterbi $s_{k,i}$ no longer depends on just the previous state assignment



Can sidestep the issue by expanding the state space...

Hidden Markov Model

Now *one* state encodes the last *two* "loadedness"es of the coin



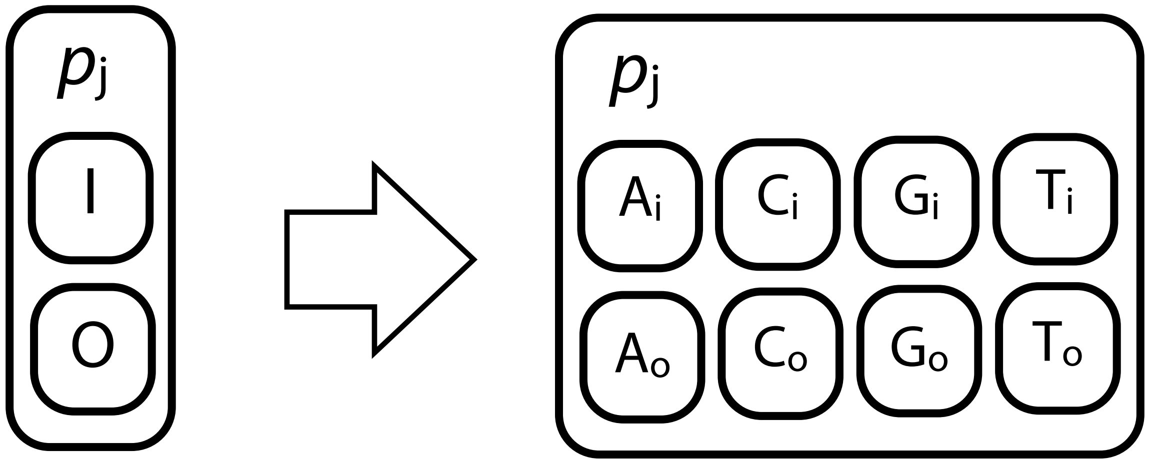
$Q = \{ \mathrm{F}, \mathrm{L} \}$

$Q = \{ \mathrm{F}, \mathrm{L} \} \times \{ \mathrm{F}, \mathrm{L} \}$

After expanding, usual Viterbi works fine.

Hidden Markov Model

We also expanded the state space here:



$Q = \{ \mathrm{I}, \mathrm{O} \}$ $\qquad$ $Q = \{ \mathrm{I}, \mathrm{O} \} \times \{ \mathrm{A}, \mathrm{C}, \mathrm{G}, \mathrm{T} \}$