Hidden Markov Model

HMM

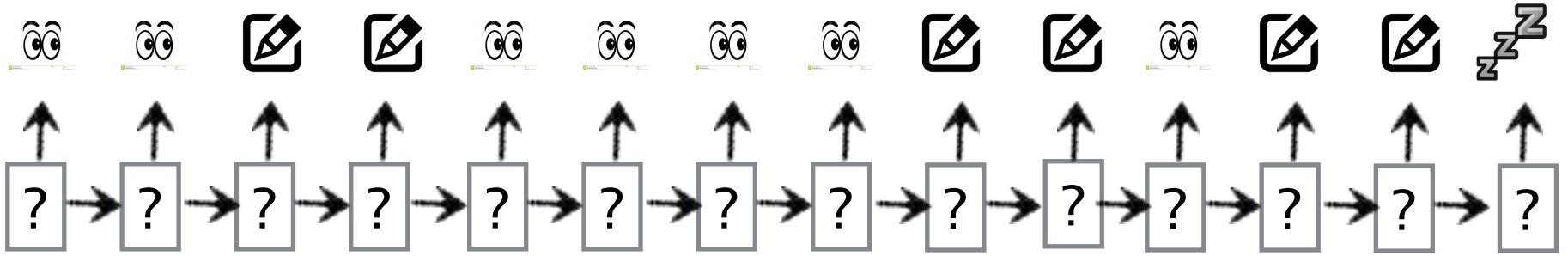
- Hidden Markov model was first invented in speech recognition. But are widely used in many other areas including bioinformatics.
- An automata that has “hidden states”. At each time point, it emits a symbol, and change a state with certain probability.
- We want to derive the hidden states by the emitted symbols.

Classroom example

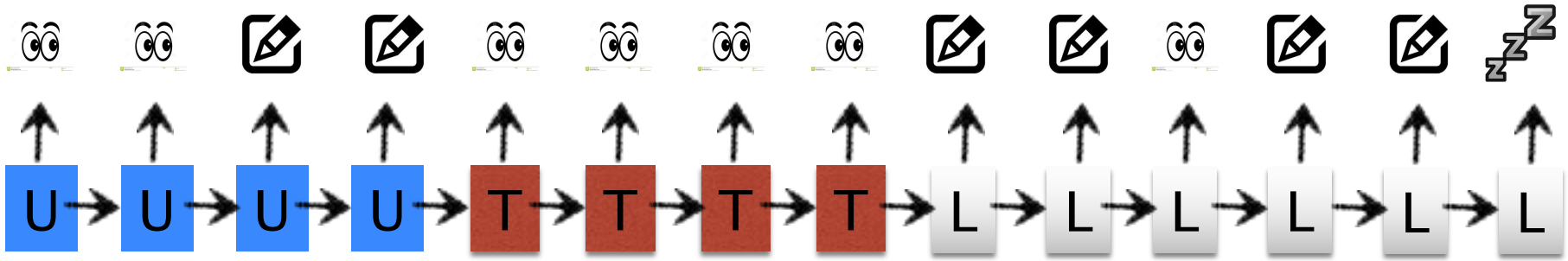
- Think of a student in classroom.
- At any minute, a student is in one of 3 hidden *states* that I try to figure out:
  - U: understands
  - T: does not understand but tries to understand
  - L: is lost completely and does not try to understand
- Meanwhile, the student emits one of 3 *symbols* that I can observe
  - Look at me
  - Write/Type
  - Sleep

Classroom Example

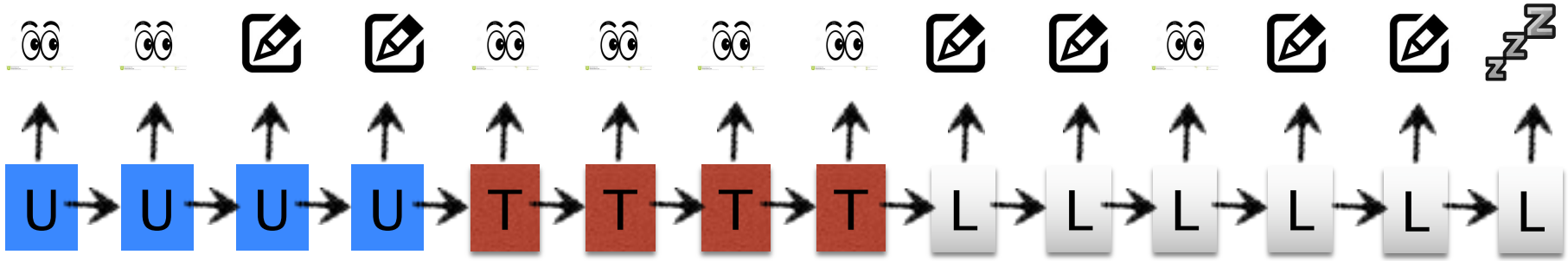
- Now suppose I see a student's behavior is the following in the past several minutes. What is his internal states at each minute?



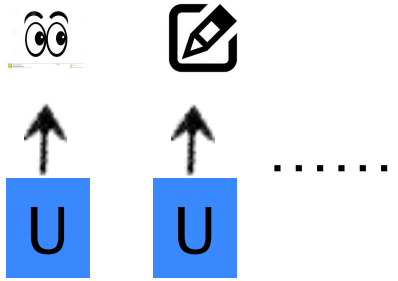
Classroom Example



Classroom Example



Emissions



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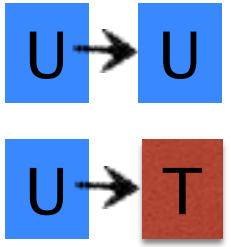
Transitions



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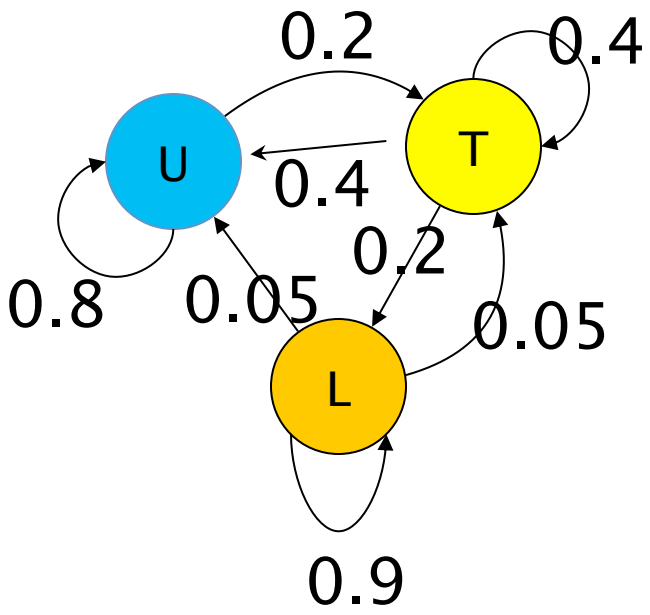
Typically, HMM assumes that emission probability depends only on current state; and current state only depends on previous state.
We want to find the most likely path of states given the symbols (observations).

Classroom Example



U: Understands
T: Tries to understand
L: Lost completely

(T) Transition matrix

	U	T	L
U	0.8	0.2	0
T	0.4	0.4	0.2
L	0.05	0.05	0.9

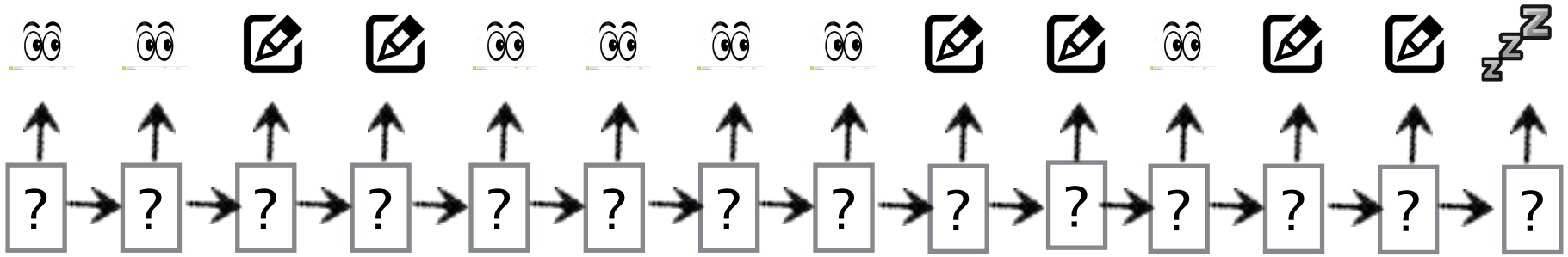
(E) Emission matrix

	Look	Write	Sleep
U	0.6	0.35	0.05
T	0.9	0.1	0
L	0.1	0.6	0.3

Classroom Example

- $S=S_1S_2\ldots S_n$: sequence of symbols;
- $P=P_1P_2\ldots P_n$: path of states.
- We want to maximize Pr(P|S) = Pr(P,S) / Pr(S).
- Therefore, we want to maximize

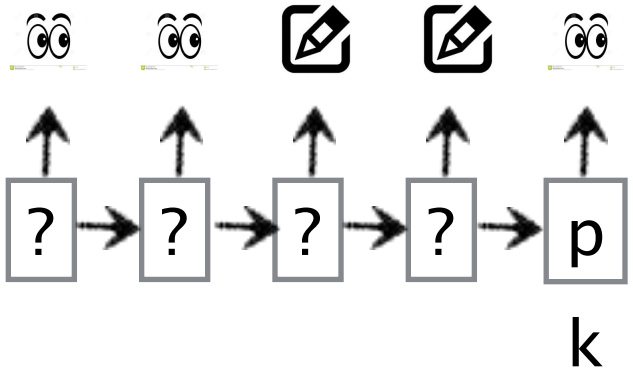
$$\Pr(P,S)=\prod_i \Pr(P_i \mid P_{i-1})\Pr(S_i \mid P_i)$$



* Note: To deal with the first state, we can define $\Pr(P_1|P_0)=1$ in above formula.

Solving HMM

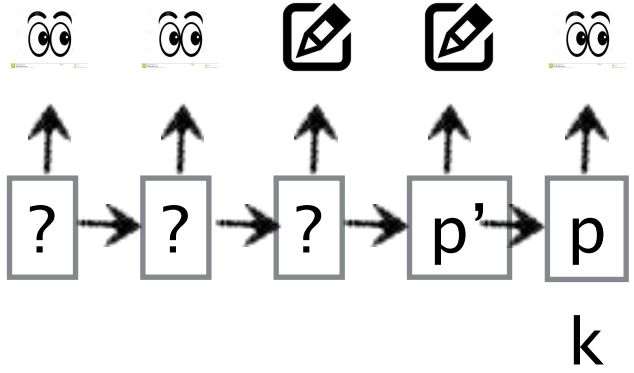
- We use dynamic programming again. Define D[k,p] be the maximum probability achieved by first k states given that the last state is p.



- Then $\max_p$ D[n,p] is the maximum probability achieved by the complete path, which is what we want to compute.
- It is not hard to obtain a recurrence Relation:

$$D[k,p] = \max_{P[1..k];P[k]=p} \prod_{1 \le i \le k} T[P_{i-1}, P_i] E[P_i, S_i]$$

Solving HMM



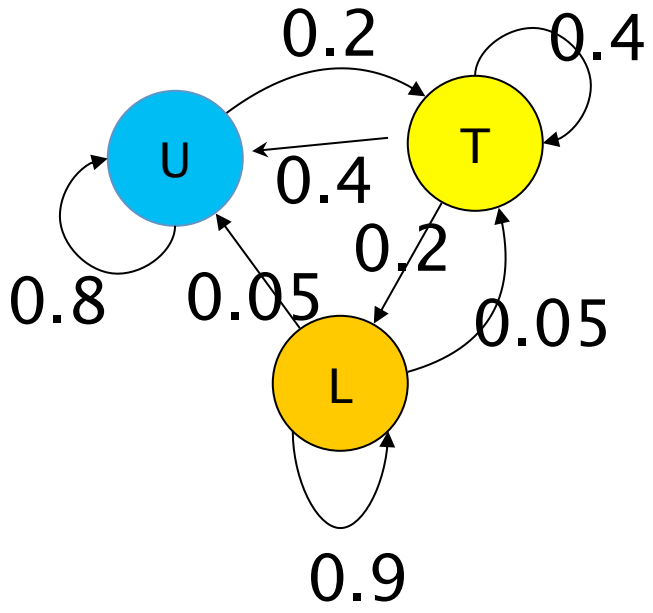
$$D[k,p] = \max_{p'} D[k-1,p'] \Pr(p|p') \Pr(S_i|p)$$

k

Solving HMM

- The algorithm:
- Input: $S = S_1 S_2 \ldots S_n$
- Output: $P = P_1 P_2 \ldots P_n$
- 1. for every state p, let $D[1,p] = \Pr(S_1|p)$.
- 2. for k from 2 to n,
- 2.1 for every state p,
- 2.1.1 let $D[k,p] = \max_{p'} D[k-1,p'] \Pr(p|p') \Pr(S_i|p)$
- 3. backtrace to compute the optimal path.

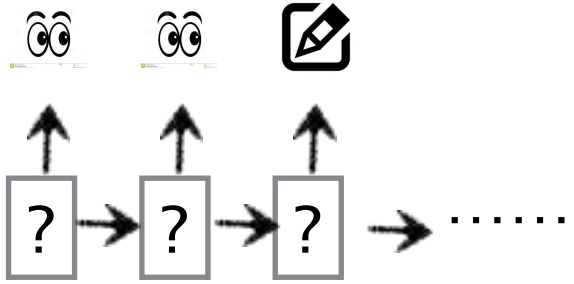
Example



(E) emission matrix

	Look	Write	Sleep
Understand	0.6	0.35	0.05
Try	0.9	0.1	0
Lost	0.1	0.6	0.3

$$D[k,p] = \max_{p'} D[k-1,p'] \Pr(p|p') \Pr(S_i|p)$$

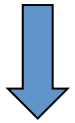


0.6		
0.9		
0.1		

Notes

- Do not multiply
  - because soon the numbers become so small that the double precision will give you value 0.
  - Do a logarithm and use additions instead.

$$D[k,p] = \max_{p'} D[k-1,p'] \Pr(p|p') \Pr(S_i|p)$$



$$\log D[k,p] = \max_{p'} (\log D[k-1,p'] + \log \Pr(p|p') + \log \Pr(S_i|p))$$

Parameter Estimation

- All of our computation depends on the transition probabilities and emission probabilities. How do we estimate these parameters?

Parameter Estimation

- If we have an annotated sequence with both symbols and states, then these can be trained by counting.
- If we do not, then we can start with a reasonable guess of the parameters and annotate the sequence.
- Then we use the annotation to train a new set of probabilities. Repeat until converge.
- There is some guarantee to the convergence. But does not guarantee this will converge to the right solution.

Pseudocounts

- If the training data include no cases of a particular emission from a particular state, then its probability will be 0 in this model.
- That's no good.
- So we add pseudocounts to make the probabilities not zero when an event should be able to happen.

Higher Order HMM

- Think again the classroom example:

U: Understands
T: Tries to understand
L: Lost

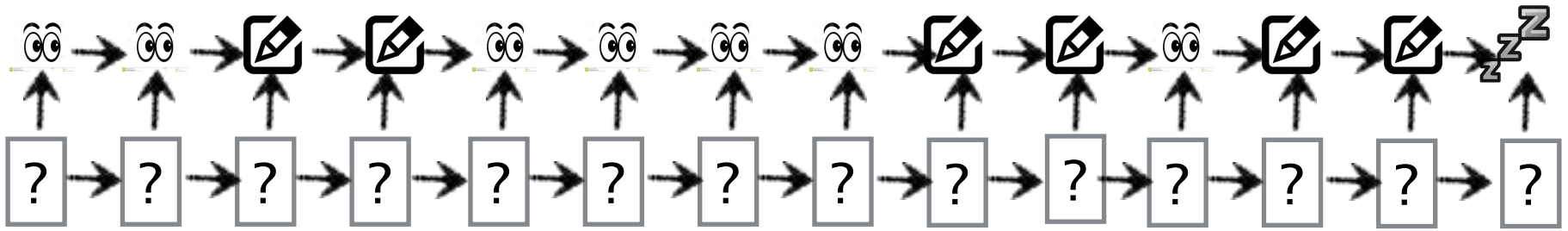
(E) Emission matrix

	Look	Write	Sleep
U	0.6	0.35	0.05
T	0.9	0.1	0
L	0.1	0.6	0.3

- The emission of a symbol should not only depend on current state, but sometimes also the previous symbol.
  - E.g. Sleeping at previous moment leads to a higher probability of sleeping now.

1st Order HMM

- To accommodate the correlation between the adjacent symbols, the emission matrix needs to be expanded.
- The emission matrix becomes $Pr(S_i | P_i, S_{i-1})$.



1st Order HMM

- Before

$$\Pr(P,S) = \prod_i \Pr(P_i \mid P_{i-1}) \Pr(S_i \mid P_i)$$

- Now

$$\Pr(P,S) = \prod_i \Pr(P_i \mid P_{i-1}) \Pr(S_i \mid P_i, S_{i-1})$$

- To find the path P to maximize, we let D[k,p] be the maximum probability obtained by the first k states ending at p. We can obtain the following recurrence relation similarly as before.

$$D[k,p] = \max_{p'} D[k-1,p'] \Pr(p|p') \Pr(S_i|p, S_{i-1})$$

- We can still do dynamic programming.

Higher Order HMM

- To generalize, we can let the current emission depend on the current state, and previous k symbols.
- Then this is called the k-th order HMM.
- Solving such a HMM is similar as before. Running time not changed.
- The only difficulty is the parameter training because the emission matrix has many more parameters for larger k.

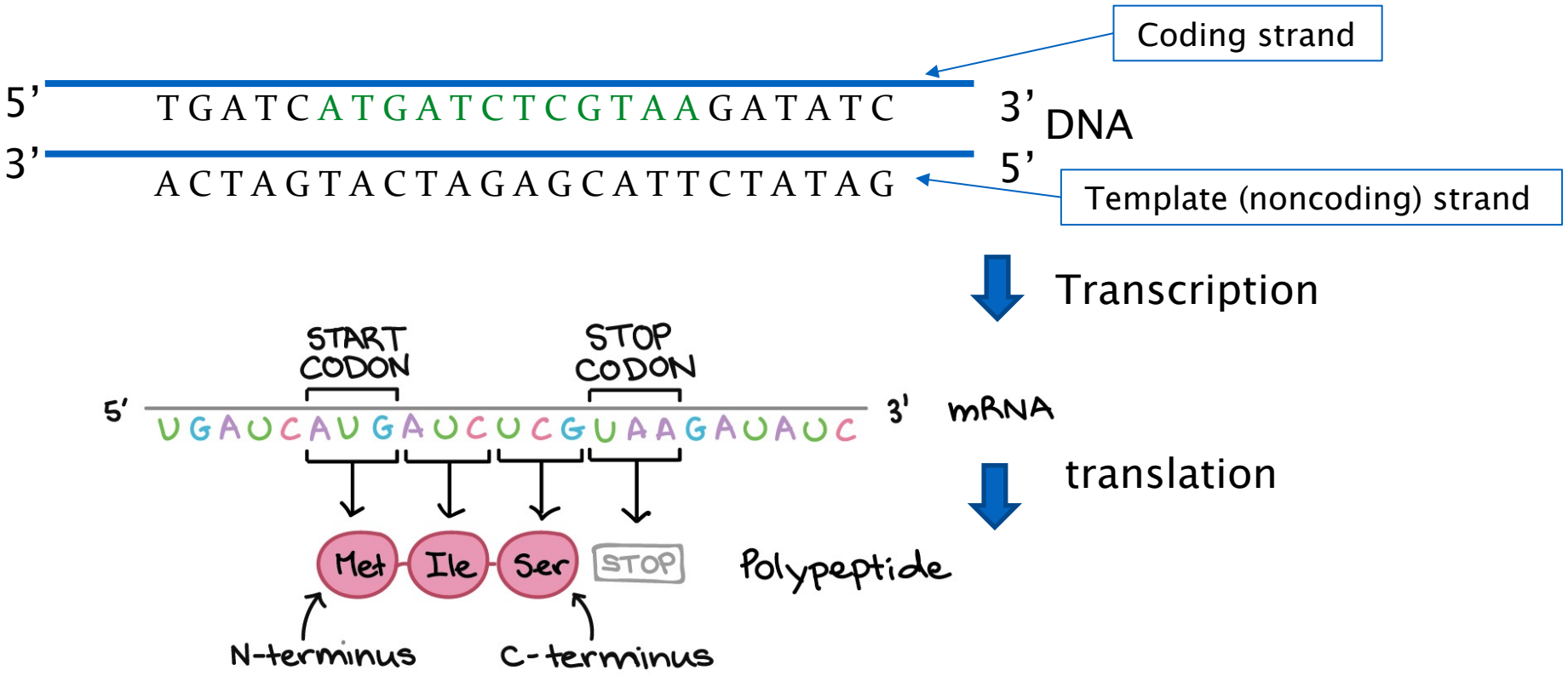
Prokaryote Gene Finding

- The **prokaryotes** (pronounced /proʊˈkæriəʊts/; singular **prokaryote** /proʊˈkæriət/) are a group of organisms that lack a cell nucleus (= karyon).
  - The opposite is the eukaryotes.
- Most of prokaryotes are unicellular.
- Prokaryote genes do not have introns. So their genes is a linear structure.

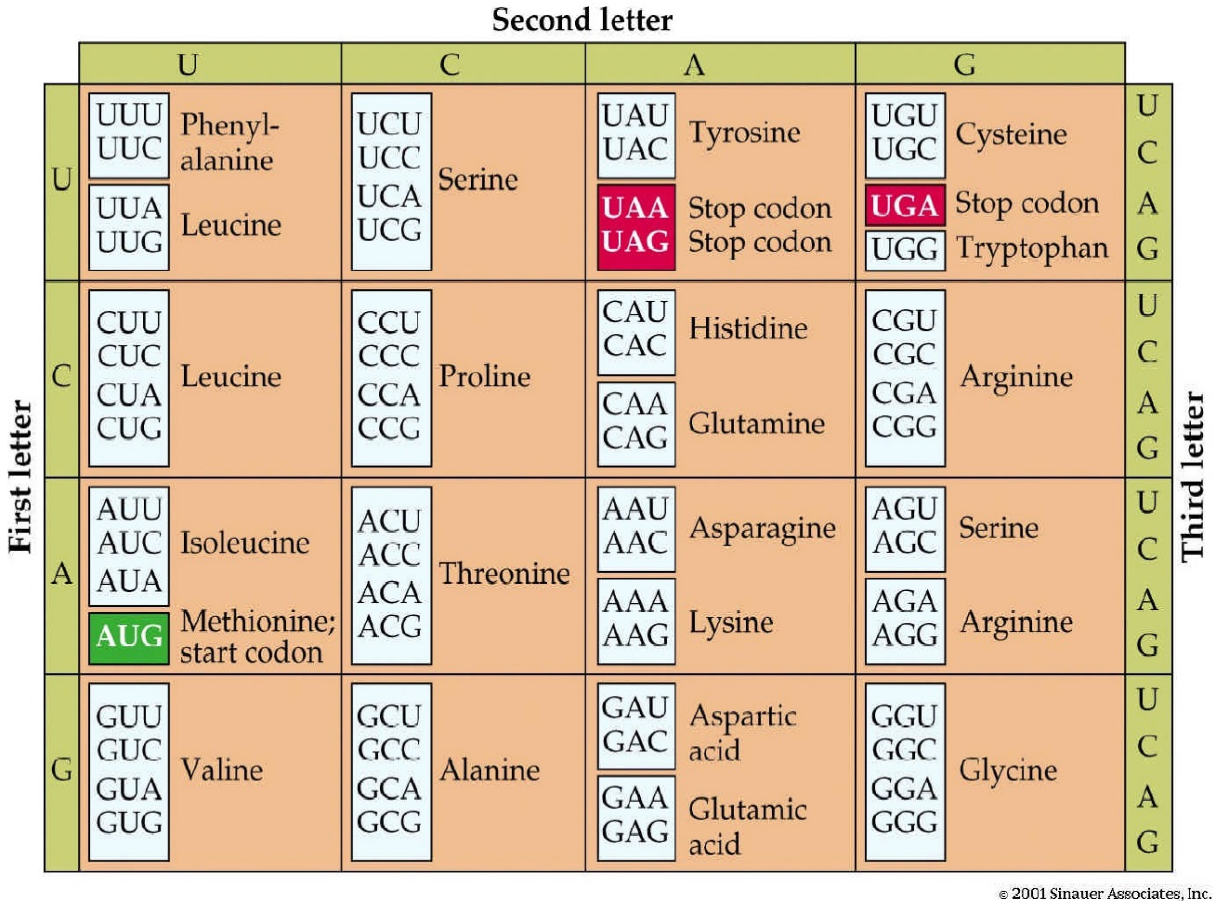
Intron video:

http://www.youtube.com/watch?v=o0BQJbLNYSg

From Gene to Protein (in *Prokaryotes*)



Genetic code



codons

ATT ATC ATA I

CTT CTC CTA CTG H

CAA CAG S

ATG G

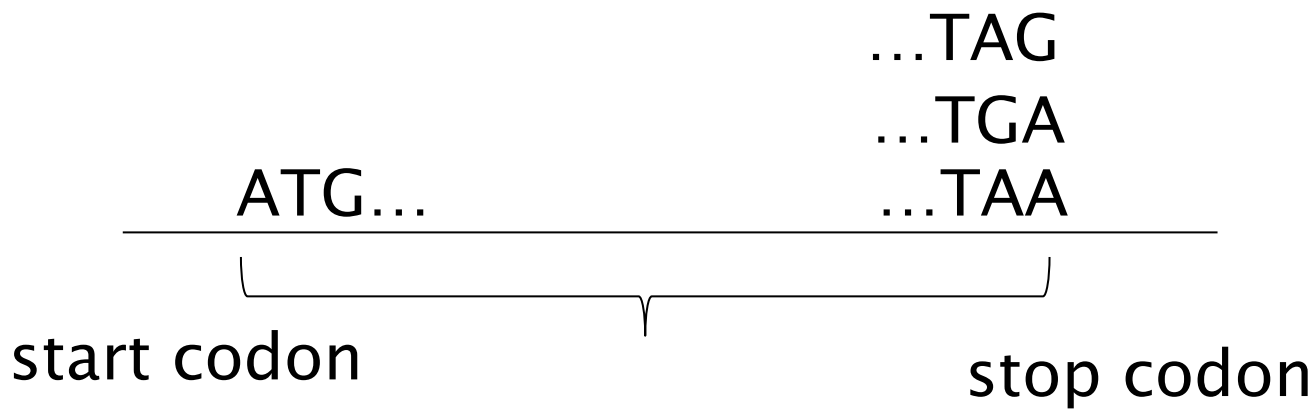
GTT GTC GTA GTG G

GAA GAG G

23

A Trivial Gene Finder

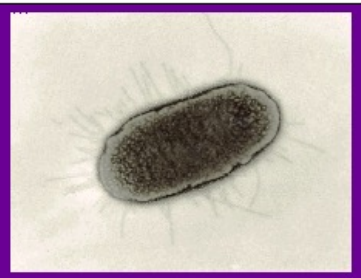
- Open Reading Frame (ORF) is a substring that
  - starts with a start codon
  - ends with a stop codon
  - no stop codon in the middle
- If ORF is long, then likely it is a gene or a part of a gene.
- Why?



Codon bias

- A codon XYZ occurs with different frequencies in coding regions and non-coding regions
  - different amino acids have different freq.
  - Diff. codons for the same amino acid have diff. freq.
  - In random regions approx. p(X)*p(Y)*p(Z)

Codon Bias Tables
(% of codons used for each residue)



Amino Acid	Codon		
Gly	GGG	2	25
Gly	GGA	0	25
Gly	GGU	59	16
Gly	GGC	39	34

http://www.kazusa.or.jp/codon/

Escherichia coli O157:H7 EDL933 **[gbbct]: 5347 CDS's (1611503 codons)**

fields: [triplet] [frequency: **per thousand**] ([number])

UUU 22.2(35846)	UCU 8.7(14013)	UAU 16.5(26648)	UGU 5.2(8458)
UUC 15.9(25565)	UCC 8.9(14420)	UAC 12.3(19766)	UGC 6.4(10285)
UUA 13.8(22316)	UCA 8.1(13117)	UAA 2.0(3163)	UGA 1.1(1751)
UUG 13.0(20904)	UCG 8.8(14220)	UAG 0.3(435)	UGG 15.3(24656)
CUU 11.4(18366)	CCU 7.2(11657)	CAU 12.8(20631)	CGU 20.2(32590)
CUC 10.5(16869)	CCC 5.6(8961)	CAC 9.4(15116)	CGC 20.8(33547)
CUA 3.9(6257)	CCA 8.4(13507)	CAA 14.7(23703)	CGA 3.8(6166)
CUG 51.1(82300)	CCG 22.4(36178)	CAG 29.4(47324)	CGG 6.2(9955)
AUU 29.7(47838)	ACU 9.1(14639)	AAU 19.2(30864)	AGU 9.4(15123)
AUC 23.9(38504)	ACC 22.8(36724)	AAC 21.7(34907)	AGC 16.0(25800)
AUA 5.5(8835)	ACA 8.1(13030)	AAA 34.0(54723)	AGA 2.9(4656)
AUG 27.2(43846)	ACG 15.0(24122)	AAG 11.0(17729)	AGG 1.8(2915)
GUU 18.1(29200)	GCU 15.4(24855)	GAU 32.8(52914)	GGU 24.2(38983)
GUC 14.8(23870)	GCC 25.2(40571)	GAC 19.2(30953)	GGC 28.1(45226)
GUA 10.9(17561)	GCA 20.7(33343)	GAA 39.3(63339)	GGA 8.9(14286)
GUG 26.2(42261)	GCG 32.3(52091)	GAG 18.7(30158)	GGG 11.8(18947)

Coding GC 51.50% 1st letter GC 58.44% 2nd letter GC 40.88% 3rd letter GC 55.17%

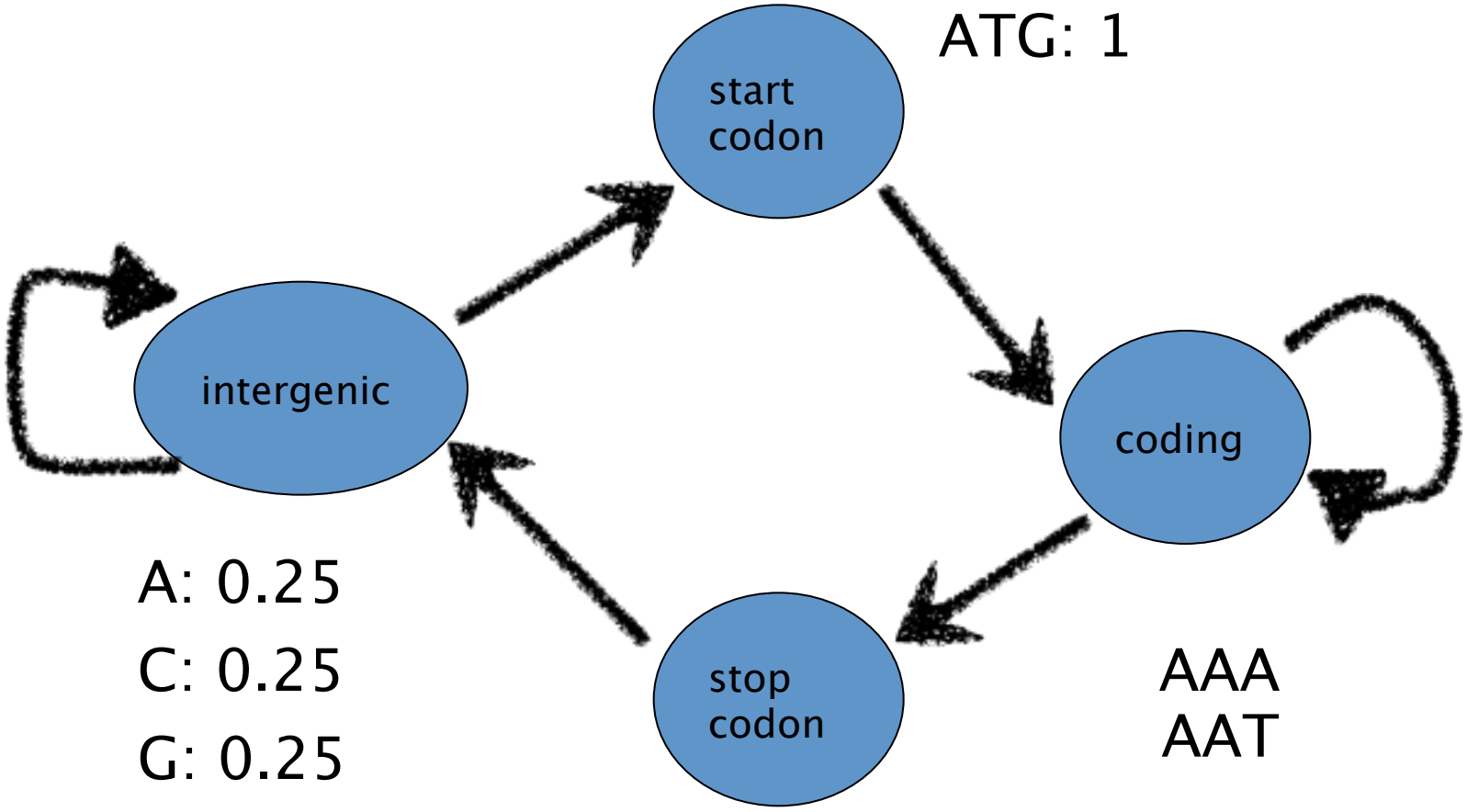
A Better Gene Finder

- We can use the log likelihood ratio score to evaluate each ORF. Each codon XYZ contributes score
- $\log \frac{P(XYZ)}{P(X)P(Y)P(Z)}$
- An ORF is predicted as a gene if the sum of codon score is above a threshold.
- This is better. But it does not catch the correlation between adjacent codons.

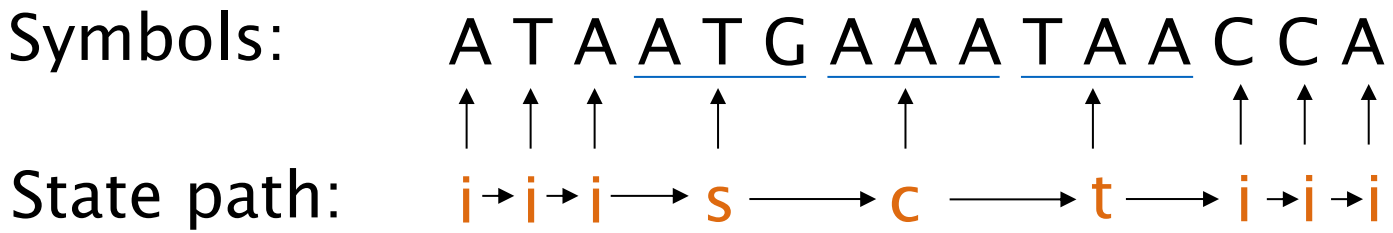
HMM

- We have used HMM in the classroom example to catch correlations between adjacent events.
- This can be used to model gene prediction.
- For example:
  - Symbols: Nucleotide bases.
  - States: start codon, stop codon, coding, non-coding (intergenic).

Prokaryote gene finding HMM



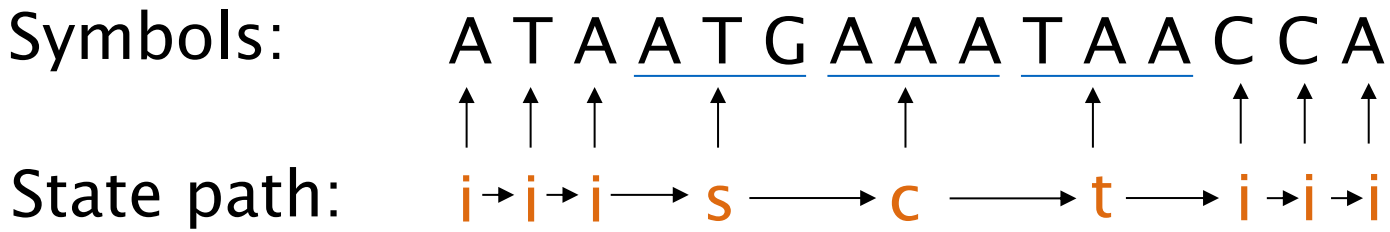
Gene Prediction as HMM



start codon
coding
intergenic
stop codon

- Annotated the sequence with most probable path of states. This provides a reasonable answer to gene prediction.
- A difference here: emission is not fixed length. But this does not forbid us from solving it with dynamic programming.

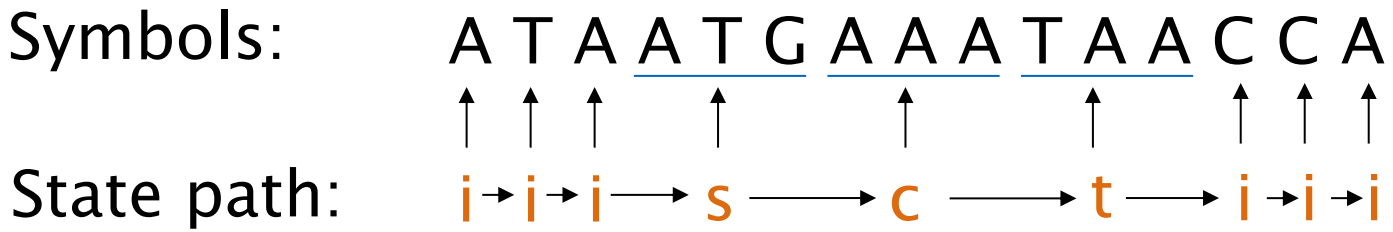
Dynamic Programming



start codon
coding
intergenic
stop codon

- Define D[k,p] be the max probability achieved by first k symbols for a path with the last state being p.

Recurrence Relation



start codon
coding
intergenic
stop codon

For p=intergenic

$$D[k,p] = D[k-1,p']\Pr(p|p')\Pr(S_k|p)$$

For p=start, coding, or stop

$$D[k,p] = D[k-3,p']\Pr(p|p')\Pr(S_{k-2}S_{k-1}S_k|p)$$

Dynamic Programming

- Once the recurrence relation is obtained. It is straightforward to work out a dynamic programming algorithm.

Easy enough to implement?

- This is very easy to implement.
- If desired, one can also use a higher-order HMM.
- Parameter training must be done carefully.

Gene Prediction

- Besides the codon bias that can be captured by HMM, there are other signals in a gene structure that can be employed by a gene prediction program.
  - E.g. the promoter of a gene is a region of DNA sequence located near the start codon.

```
 <-- upstream                                                    downstream -->
5'-XXXXPPPPPPXXXXXXXXXPPPPPPXXXXGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGXXXX-3'
       -35            -10       Gene to be translated
```

Promoters

```
 <-- upstream                                                                    downstream -->
5'-XXXXPPPPPPXXXXXXXXXPPPPPPXXXXGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGXXXX-3'
       -35             -10       Gene to be translated
```

-10:	**T**	**A**	**T**	**A**	**A**	**T**
	77%	**76%**	**60%**	**61%**	**56%**	**82%**
-35:	**T**	**T**	**G**	**A**	**C**	**A**
	69%	**79%**	**61%**	**56%**	**54%**	**54%**

- These rules are only approximately correct.
- The presence of promoters allow a very high transcription rate.
- Exercise: How to assign a score to the promoter.

Summary

- HMM is a general model to predict some hidden states by examining emitted symbols.
- HMM can be used in gene prediction to harvest the codon bias and adjacent codon correlation.
- Gene prediction can use more information about the gene structure than codon bias.
- We only talked about prokaryote gene prediction. Eukaryote gene prediction is harder because of introns.