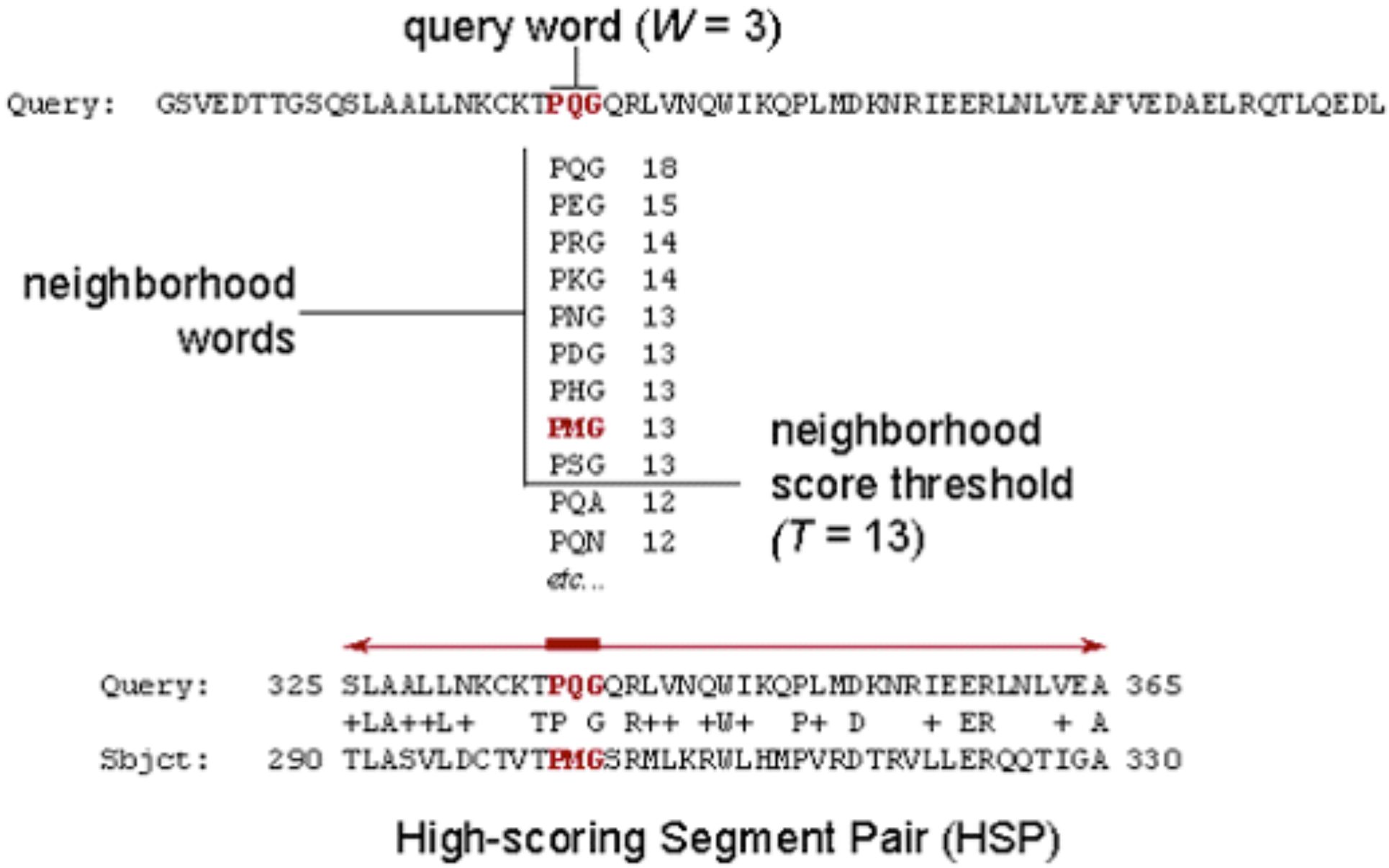
If you learn just one thing Bioinformatics just learn this:

Basic Local Alignment Search Tool (BLAST)

BLAST programs

blastp: protein

blastn: DNA


query word (W = 3)
Query: GSVEDTTGSQSLAALLNKCKTPQGQRLVNQWIKQPLMDKNRIEERLNLVEAFVEDAELRQTLQEDL
neighborhood words
PQG 18
PEG 15
PRG 14
PKG 14
PNG 13
PDG 13
PHG 13
PMG 13
PSG 13
PQA 12
PQN 12
etc...
neighborhood score threshold (T = 13)
Query: 325 SLAALLNKCKTPQGQRLVNQWIKQPLMDKNRIEERLNLVEA 365
+LA++L+ TP G R++ +W+ P+ D + ER + A
Sbjct: 290 TLASVLDCTVTPMGSRMLKRWLHMPVRDTRVLLERQQTIGA 330
High-scoring Segment Pair (HSP)

E-value

$$E \approx 1 - e^{-p(S \geq x)D}$$

Where,

x = a score cutoff

D = database size

p = P-value

Example BLAST output

http://www-bimas.cit.nih.gov/blastinfo/blastexample.html

BLOSUM62

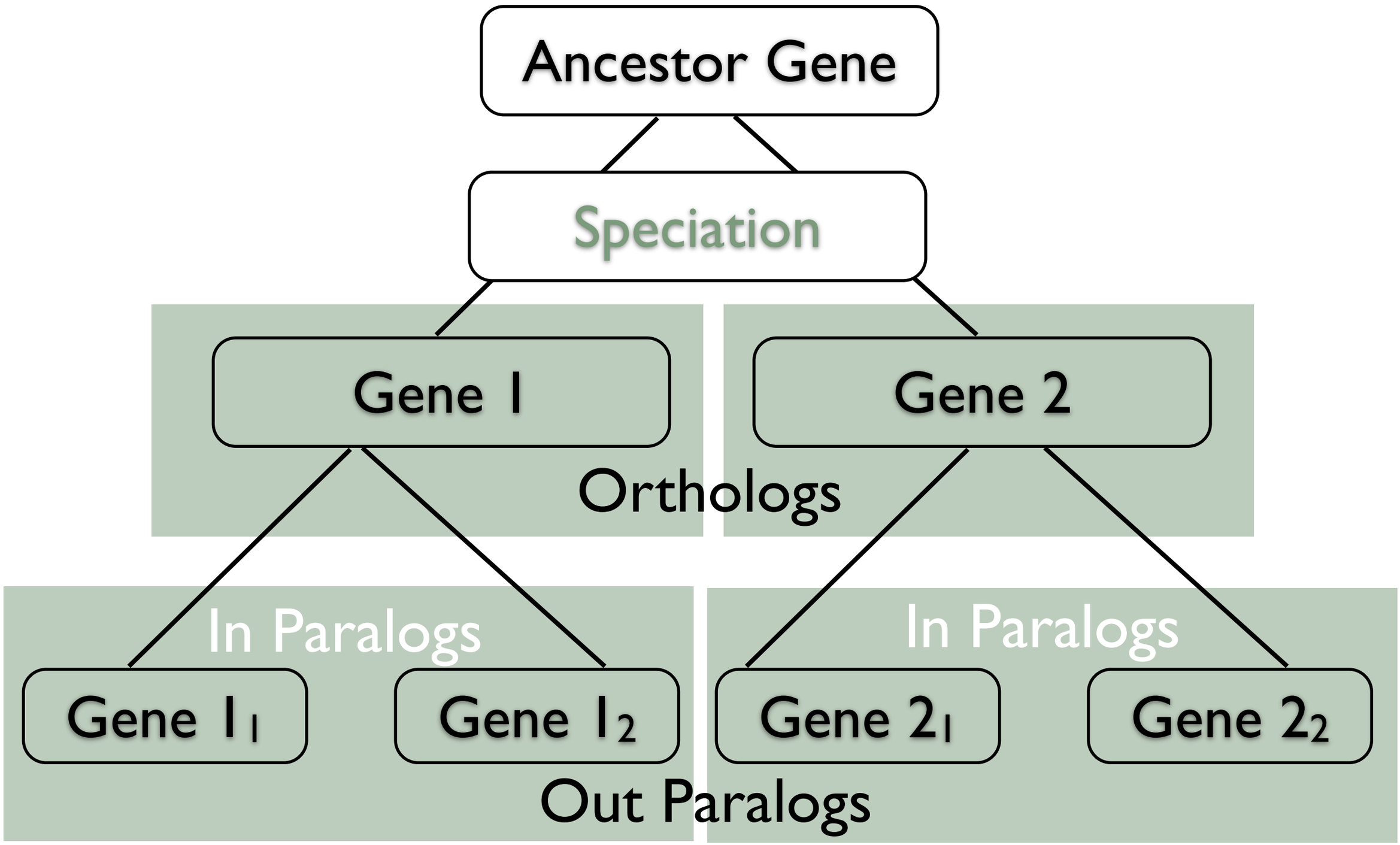
```
#  Matrix made by matblas from blosum62.iij
#  * column uses minimum score
#  BLOSUM Clustered Scoring Matrix in 1/2 Bit Units
#  Blocks Database = /data/blocks_5.0/blocks.dat
#  Cluster Percentage: >= 62
#  Entropy =   0.6979, Expected =  -0.5209
   A  R  N  D  C  Q  E  G  H  I  L  K  M  F  P  S  T  W  Y  V  B  Z  X  *
A  4 -1 -2 -2  0 -1 -1  0 -2 -1 -1 -1 -1 -2 -1  1  0 -3 -2  0 -2 -1  0 -4
R -1  5  0 -2 -3  1  0 -2  0 -3 -2  2 -1 -3 -2 -1 -1 -3 -2 -3 -1  0 -1 -4
N -2  0  6  1 -3  0  0  0  1 -3 -3  0 -2 -3 -2  1  0 -4 -2 -3  3  0 -1 -4
D -2 -2  1  6 -3  0  2 -1 -1 -3 -4 -1 -3 -3 -1  0 -1 -4 -3 -3  4  1 -1 -4
C  0 -3 -3 -3  9 -3 -4 -3 -3 -1 -1 -3 -1 -2 -3 -1 -1 -2 -2 -1 -3 -3 -2 -4
Q -1  1  0  0 -3  5  2 -2  0 -3 -2  1  0 -3 -1  0 -1 -2 -1 -2  0  3 -1 -4
E -1  0  0  2 -4  2  5 -2  0 -3 -3  1 -2 -3 -1  0 -1 -3 -2 -2  1  4 -1 -4
G  0 -2  0 -1 -3 -2 -2  6 -2 -4 -4 -2 -3 -3 -2  0 -2 -2 -3 -3 -1 -2 -1 -4
H -2  0  1 -1 -3  0  0 -2  8 -3 -3 -1 -2 -1 -2 -1 -2 -2  2 -3  0  0 -1 -4
I -1 -3 -3 -3 -1 -3 -3 -4 -3  4  2 -3  1  0 -3 -2 -1 -3 -1  3 -3 -3 -1 -4
L -1 -2 -3 -4 -1 -2 -3 -4 -3  2  4 -2  2  0 -3 -2 -1 -2 -1  1 -4 -3 -1 -4
K -1  2  0 -1 -3  1  1 -2 -1 -3 -2  5 -1 -3 -1  0 -1 -3 -2 -2  0  1 -1 -4
M -1 -1 -2 -3 -1  0 -2 -3 -2  1  2 -1  5  0 -2 -1 -1 -1 -1  1 -3 -1 -1 -4
F -2 -3 -3 -3 -2 -3 -3 -3 -1  0  0 -3  0  6 -4 -2 -2  1  3 -1 -3 -3 -1 -4
P -1 -2 -2 -1 -3 -1 -1 -2 -2 -3 -3 -1 -2 -4  7 -1 -1 -4 -3 -2 -2 -1 -2 -4
S  1 -1  1  0 -1  0  0  0 -1 -2 -2  0 -1 -2 -1  4  1 -3 -2 -2  0  0  0 -4
T  0 -1  0 -1 -1 -1 -1 -2 -2 -1 -1 -1 -1 -2 -1  1  5 -2 -2  0 -1 -1  0 -4
W -3 -3 -4 -4 -2 -2 -3 -2 -2 -3 -2 -3 -1  1 -4 -3 -2 11  2 -3 -4 -3 -2 -4
Y -2 -2 -2 -3 -2 -1 -2 -3  2 -1 -1 -2 -1  3 -3 -2 -2  2  7 -1 -3 -2 -1 -4
V  0 -3 -3 -3 -1 -2 -2 -3 -3  3  1 -2  1 -1 -2 -2  0 -3 -1  4 -3 -2 -1 -4
B -2 -1  3  4 -3  0  1 -1  0 -3 -4  0 -3 -3 -2  0 -1 -4 -3 -3  4  1 -1 -4
Z -1  0  0  1 -3  3  4 -2  0 -3 -3  1 -1 -3 -1  0 -1 -3 -2 -2  1  4 -1 -4
X  0 -1 -1 -1 -2 -1 -1 -1 -1 -1 -1 -1 -1 -1 -2  0  0 -2 -1 -1 -1 -1 -1 -4
* -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4 -4  1
```

Find the score of PQG matching PQG using BLOSUM62

Homologs

Genes related by evolution.

Orthologs


Ancestor Gene
Speciation
Gene 1
Gene 2
Orthologs
In Paralogs
In Paralogs
Gene 1_1
Gene 1_2
Gene 2_1
Gene 2_2
Out Paralogs

Fitch W. (1970). "Distinguishing homologous from analogous proteins". *Syst Zool* **19** (2): 99–113.

DISTINGUISHING HOMOLOGOUS FROM ANALOGOUS PROTEINS

WALTER M. FITCH

Abstract

Fitch, W. M. (Dept. Physiological Chem., U. Wisconsin, Madison 53706) 1970. Distinguishing homologous from analogous proteins. Syst. Zool., 19:99–113.—This work provides a means by which it is possible to determine whether two groups of related proteins have a common ancestor or are of independent origin. A set of 16 random amino acid sequences were shown to be unrelated by this method. A set of 16 real but presumably unrelated proteins gave a similar result. A set of 24 model proteins which was composed of two independently evolving groups, converging toward the same chemical goal, was correctly shown to be convergently related, with the probability that the result was due to chance being $<10^{-28}$. A set of 24 cytochromes composed of 5 fungi and 19 metazoans was shown to be divergently related, with the probability that the result was due to chance being $< 10^{-5}$. A process was described which leads to the absolute minimum of nucleotide replacements required to account for the divergent descent of a set of genes given a particular topology for the tree depicting their ancestral relations. It was also shown that the convergent processes could realistically lead to amino acid sequences which would produce positive tests for relatedness, not only by a chemical criterion, but by a genetic (nucleotide sequence) criterion as well. Finally, a realistic case is indicated where truly homologous traits, behaving in a perfectly expectable way, may nevertheless lead to a ludicrous phylogeny.

The demonstration that two proteins are related has been attempted using two different criteria. One criterion is to show that their chemical structures are very similar. An early example of this approach was the observation of the relatedness of the oxygen carrying proteins, myoglobin and hemoglobin (Watson and Kendrew, 1961). More recent is the relatedness of two enzymes in carbohydrate metabolism, lysozyme and alpha-lactalbumin (Brew, Vanaman and Hill, 1967). The other criterion is to show that underlying genetic structures of the proteins are more alike than one would expect by chance. This is now possible because our knowledge of the genetic code permits us to determine how many nucleotide positions, at the minimum, must differ in the genes encoding the two presumptively homologous proteins. One then compares the answer obtained to the number of differences one would expect for unrelated proteins. An example of this approach is the observation of the relatedness of plant and bacterial ferredoxins (Matsubara, Jukes and Cantor, 1969) for which added evidence has been produced (Fitch, 1970a). But regardless of the approach, the impulse, too powerful to resist, is to conclude that a particular pair of proteins had a common genic ancestor if they meet whichever criterion the observer uses.

Now two proteins may appear similar because they descend with *di*vergence from a common ancestral gene (i.e., are homologous in a time-honoured meaning dating back at the least to Darwin's *Origin of Species*) or because they descend with *con*vergence from separate ancestral genes (i.e., are analogous). And, if a common genic ancestor is to be the conclusion, a genetic criterion should be superior to a chemical criterion. This is because analogous gene products, although they have no common ancestor, do serve similar functions and may well be expected to have similar chemical structures and thereby be confused with homologous gene products. This danger can only be increased by using a chemical, as opposed to a genetic, criterion.

Ortholog determination

Fundamental for comparative genomics

Open problem

No clear winner

Special Issue: Orthology and Applications

Volume 12 Issue 5 September 2011

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Ortholog determination

Sequence similarity based clustering

Tree based

Hybrid approach

Sequence similarity

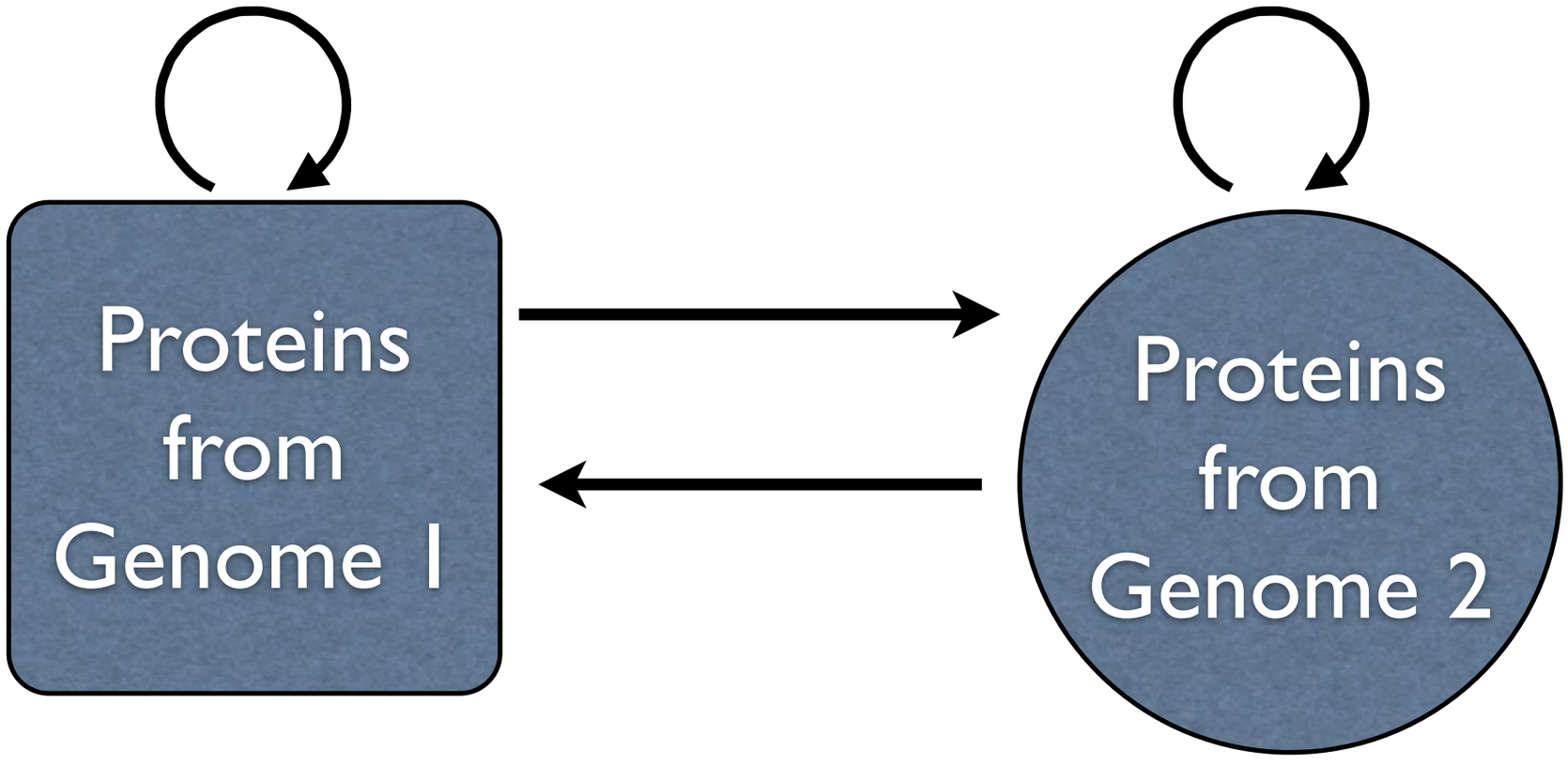
Pioneered by "COG"

Reciprocal Best Hit (usually BLAST)

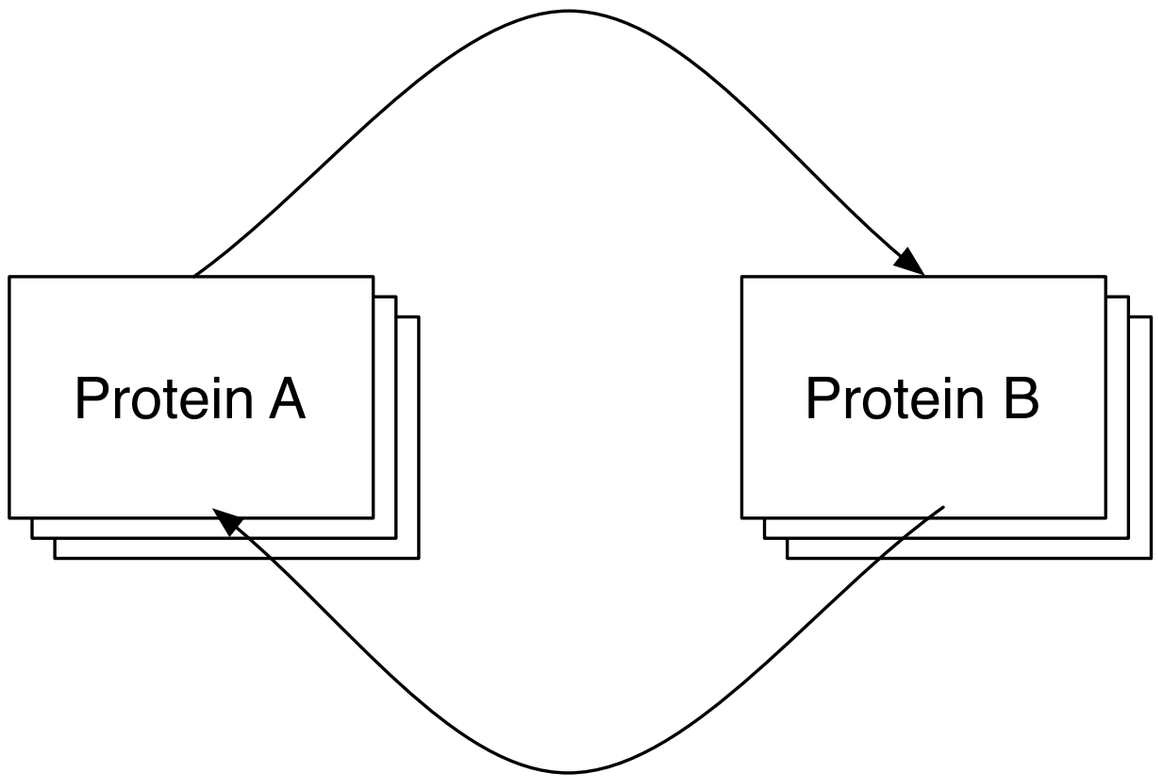
Additional clustering on top of RBH (OrthoMCL)

Numerous databases: COG, eggNOC, OrthoMCL, InParanoid...

All vs All BLAST



Reciprocal Best BLAST Hit



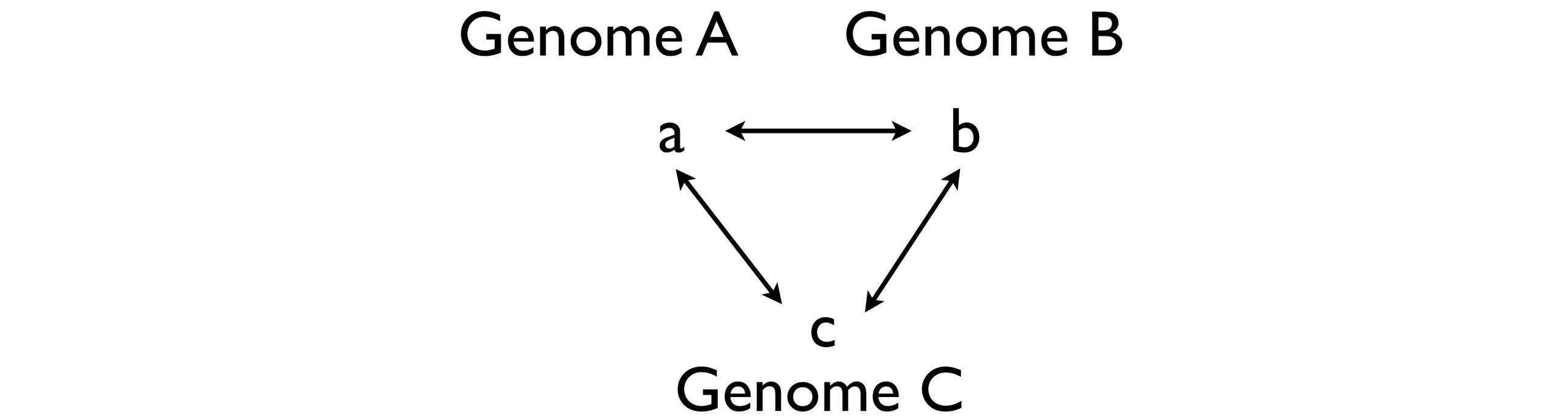
Orthologs

Nothing to do with function!

Homology vs Homoplasy

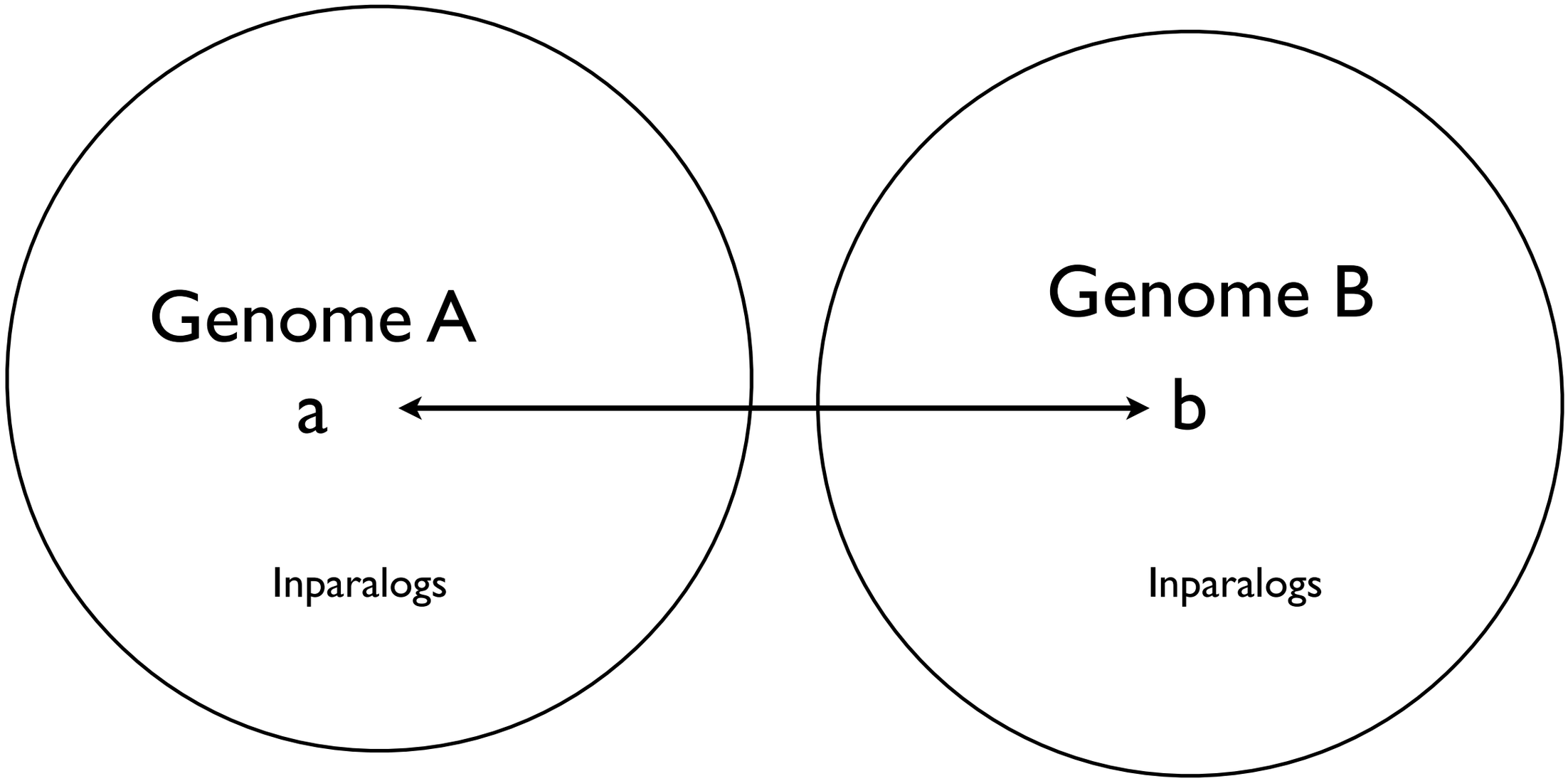
Cluster of orthlogous groups (COG)

http://www.ncbi.nlm.nih.gov/COG/



InParanoid

http://inparanoid.sbc.su.se/cgi-bin/index.cgi



Download BLAST

ftp://ftp.ncbi.nih.gov/blast/executables/release/2.2.25/

Creating a BLAST DB from a multifasta file

```
formatdb -i multifasta
```

BLASTP

```
blastall -i input.fas -d dbname
         -o outputfile
```

Position Specific Scoring Matrix (PSSM)

	1	2	3	4
Seq1	A	G	G	A
Seq2	A	G	G	G
Seq3	A	A	C	A
Seq4	A	A	C	G

$$p_{ca} = (n_{ca} + b_{ca}) \,/\, (N_c + B_c)$$

Nca = real count

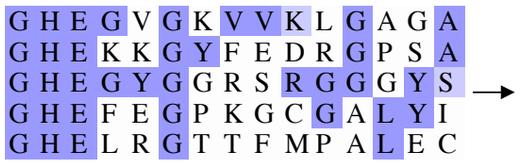
bca = pseudo count

Nc = total real count

Bc = total pseudo count

- Column 1: $f'_{A,1} = \frac{0+1}{5+20} = 0.04$, $f'_{G,1} = \frac{5+1}{5+20} = 0.24$, ...
- Column 2: $f'_{A,2} = \frac{0+1}{5+20} = 0.04$, $f'_{H,2} = \frac{5+1}{5+20} = 0.24$, ...
- ...
- Column 15: $f'_{A,15} = \frac{2+1}{5+20} = 0.12$, $f'_{C,15} = \frac{1+1}{5+20} = 0.08$, ...

A *PSSM* is based on the *frequencies* of each residue in a specific position of a multiple alignment.



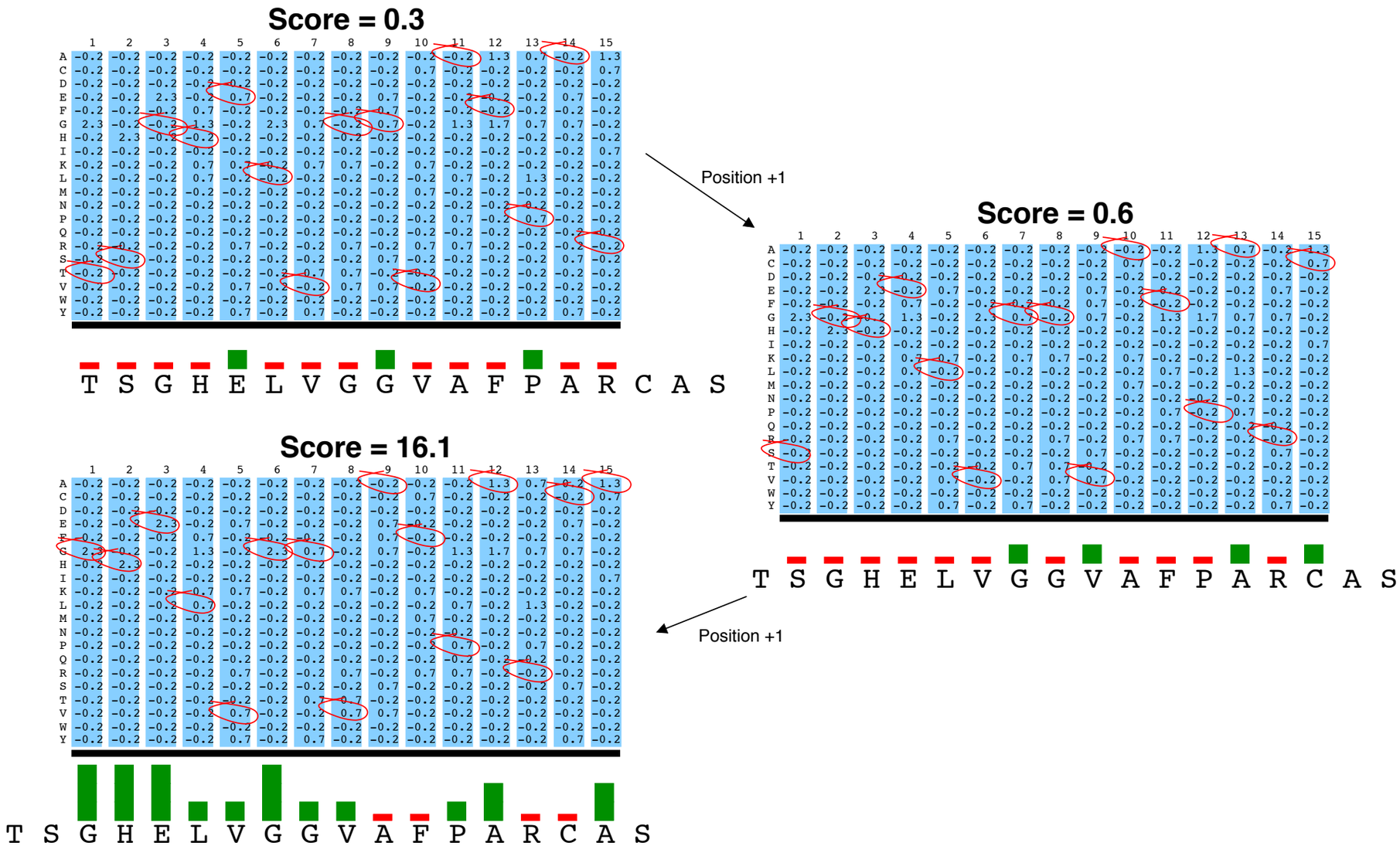
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
A	0	0	0	0	0	0	0	0	0	0	0	2	1	0	2
C	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
D	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
E	0	0	5	0	1	0	0	0	1	0	0	0	0	1	0
F	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0
G	5	0	0	2	0	5	1	0	1	0	2	3	1	1	0
H	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0
I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
K	0	0	0	1	1	0	1	1	0	1	0	0	0	0	0
L	0	0	0	1	0	0	0	0	0	0	1	0	2	0	0
M	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0
Q	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R	0	0	0	0	1	0	0	1	0	1	1	0	0	0	0
S	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0
T	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0
V	0	0	0	0	1	0	0	1	1	0	0	0	0	0	0
W	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Y	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0

- Column 1: $f_{A,1} = \frac{0}{5} = 0$, $f_{G,1} = \frac{5}{5} = 1$, ...
- Column 2: $f_{A,2} = \frac{0}{5} = 0$, $f_{H,2} = \frac{5}{5} = 1$, ...
- ...
- Column 15: $f_{A,15} = \frac{2}{5} = 0.4$, $f_{C,15} = \frac{1}{5} = 0.2$, ...

$$Score_{ij} = log(\frac{f'_{ij}}{q_i})$$

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
A	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	1.3	0.7	-0.2	1.3
C	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	0.7	-0.2	-0.2	-0.2	-0.2	0.7
D	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2
E	-0.2	-0.2	2.3	-0.2	0.7	-0.2	-0.2	-0.2	0.7	-0.2	-0.2	-0.2	-0.2	0.7	-0.2
F	-0.2	-0.2	-0.2	0.7	-0.2	-0.2	-0.2	-0.2	0.7	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2
G	2.3	-0.2	-0.2	1.3	-0.2	2.3	0.7	-0.2	0.7	-0.2	1.3	1.7	0.7	0.7	-0.2
H	-0.2	2.3	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2
I	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	0.7
K	-0.2	-0.2	-0.2	0.7	0.7	-0.2	0.7	0.7	-0.2	0.7	-0.2	-0.2	-0.2	-0.2	-0.2
L	-0.2	-0.2	-0.2	0.7	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	0.7	-0.2	1.3	-0.2	-0.2
M	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	0.7	-0.2	-0.2	-0.2	-0.2	-0.2
N	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2
P	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	0.7	-0.2	0.7	-0.2	-0.2
Q	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2
R	-0.2	-0.2	-0.2	-0.2	0.7	-0.2	-0.2	0.7	-0.2	0.7	0.7	-0.2	-0.2	-0.2	-0.2
S	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	0.7	-0.2	-0.2	-0.2	-0.2	0.7	-0.2
T	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	0.7	0.7	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2
V	-0.2	-0.2	-0.2	-0.2	0.7	-0.2	-0.2	0.7	0.7	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2
W	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2
Y	-0.2	-0.2	-0.2	-0.2	0.7	-0.2	0.7	-0.2	-0.2	-0.2	-0.2	-0.2	-0.2	0.7	-0.2

- At every position, a PSSM score is calculated by summing the scores of all columns;
- The highest scoring position is reported.



- modeling positional dependencies
- recognizing pattern instances with indels
- modeling variable length patterns
- detecting boundaries

PSSM search

rpsblast can be used to search a PSSM.

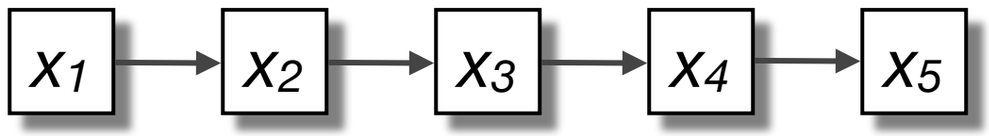
NCBI Conserved Domain Database (CDD) is a collection of PSSMs.

Markov process

No state information

Memoryless

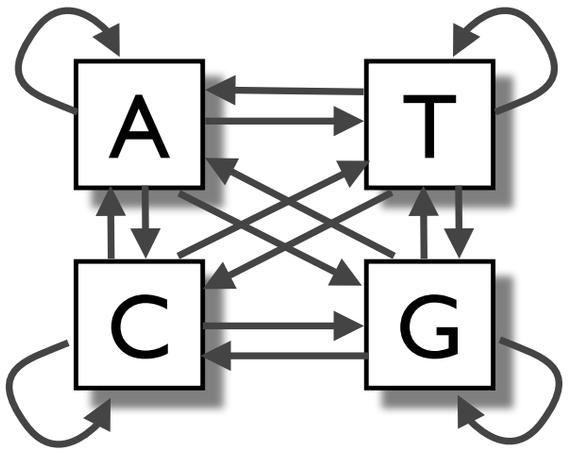
Markov Chains



$$p(x_1, x_2, x_3, \ldots) = p(x_1)\, p(x_2 | x_1)\, p(x_3 | x_2)\, p(x_4 | x_3) \ldots$$

Markov Chains are memory less:
probability of a state depends only on the previous state

Markov chains are defined as a state diagram



A Markov chain is defined by:

- a finite set of ***states***, $S_1, S_2 \ldots S_N$
- a set of ***transition probabilities***: $a_{ij} = P(q_{t+1}=S_j|q_t=S_i)$
- *and* an ***initial state probability distribution***, $\boldsymbol{\pi}_i = P(q_0=S_i)$

Markov chains example

Observed sequence: x = **abaaababbaa**

Model:

transition probabilities

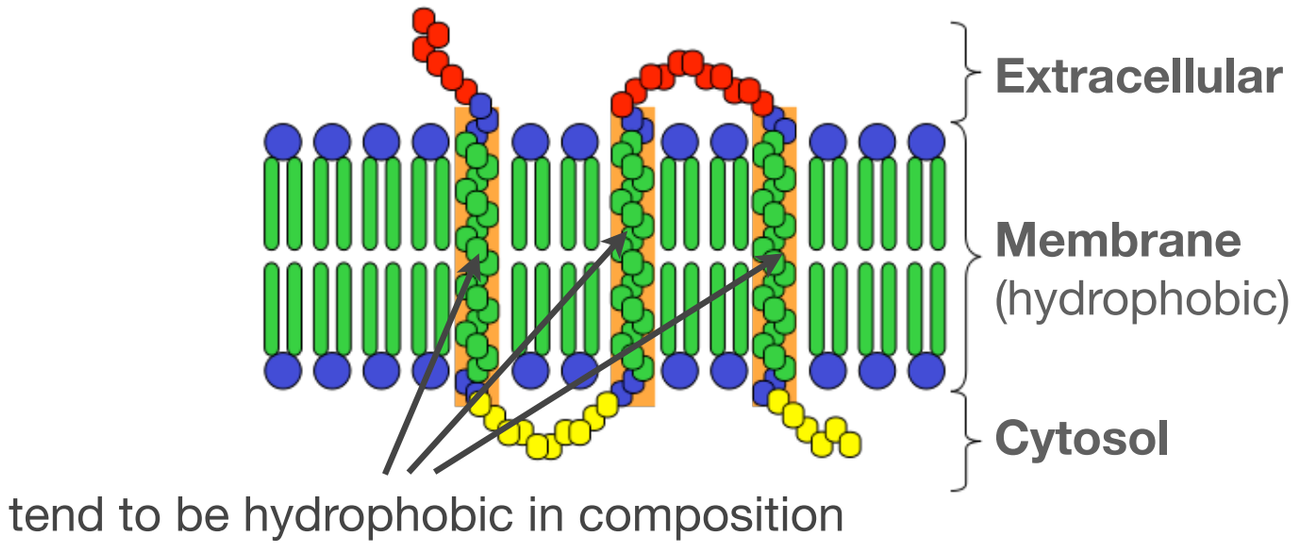
Prev *i*	Next *j*	Prob a_{ij}
a	a	0.7
a	b	0.3
b	a	0.5
b	b	0.5

initial state probability distribution

Start probs	π_i	a 0.5
		b 0.5

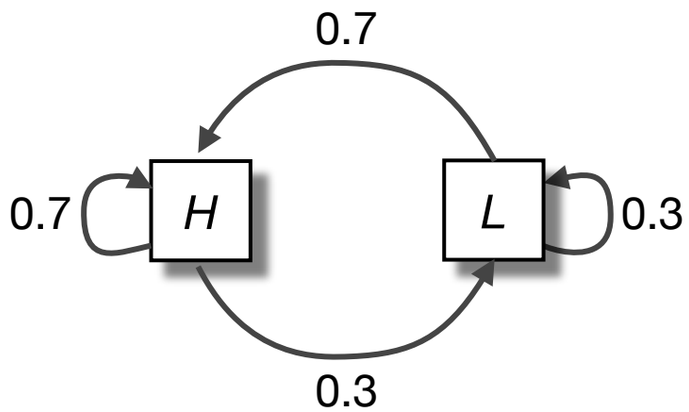
P(x) = 0.5 x 0.3 x 0.5 x 0.7 x 0.7 x 0.3 x 0.5 x 0.3 x 0.5 x 0.5 x 0.7

Markov chain example

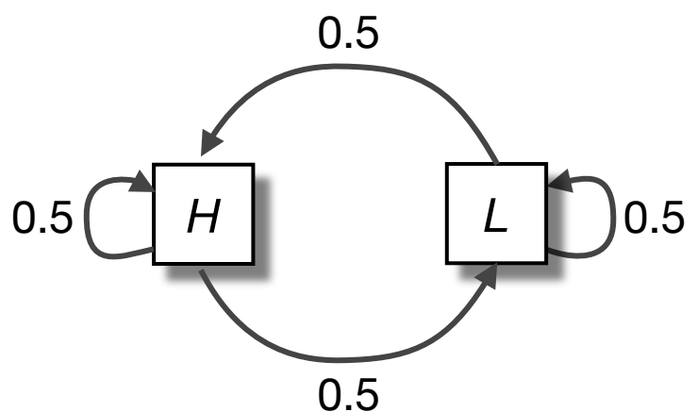


Question: Is sequence **HHLHH** a transmembrane protein?

transmembrane model



null model



Transmembrane (TM)

- $\pi(H) = 0.6$, $\pi(L) = 0.4$

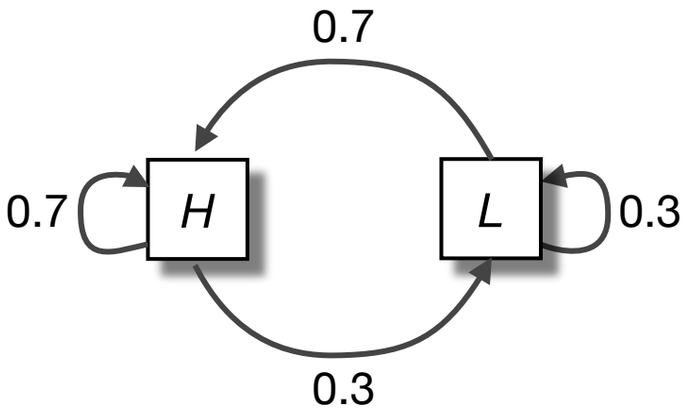
Extracellular/cytosolic (E/C)

- $\pi(H) = 0.5$, $\pi(L) = 0.5$

$$\frac{P(\text{HHLHH} \mid \text{TM})}{P(\text{HHLHH} \mid \text{EC})} = \frac{0.6 \times 0.7 \times 0.7 \times 0.3 \times 0.7 \times 0.7}{0.5 \times 0.5 \times 0.5 \times 0.5 \times 0.5 \times 0.5} = \frac{0.043}{0.016} = 2.69$$

In other words, it is more than twice as likely that **HHLHH** is a transmembrane sequence. The log-odds score is: $\log_2(2.69) = 1.43$

Markov chain Parameter estimation



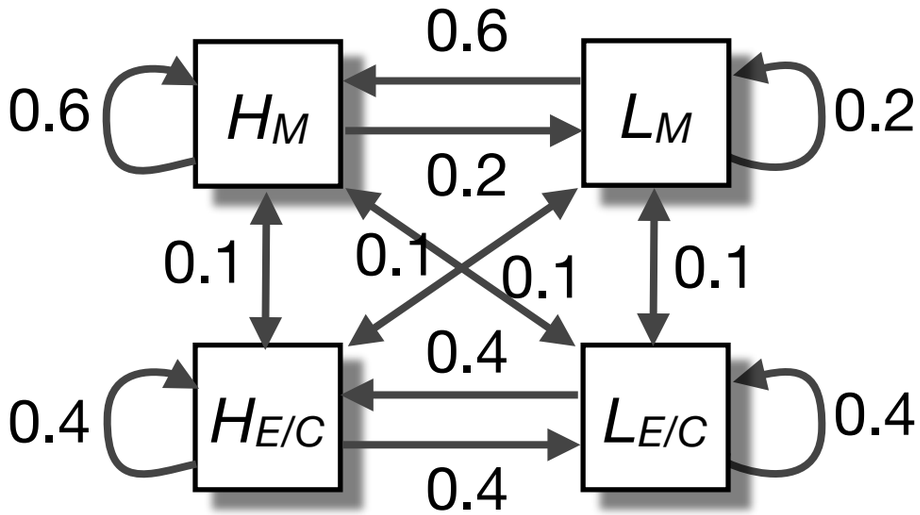
π(H) = # of sequences that begin with H, normalized by the total # of training sequences

- π(H) = 0.6, π(L) = 0.4

HHHLLHHHLLLLHLHLLHLLLHLHHHL
HHHLHHLHLLLLLLHHHHLLLHHHHHL
HH . . . (A_{HL} = 12, A_{H^*} = 40)

$$a_{HL} = \frac{A_{HL}}{\sum_i A_{Hi}} \qquad \frac{\text{\#HL pairs}}{\text{\# H* pairs}} \qquad \frac{12}{40}$$

HMM:
Given a sequence of H and L find the transmembrane region



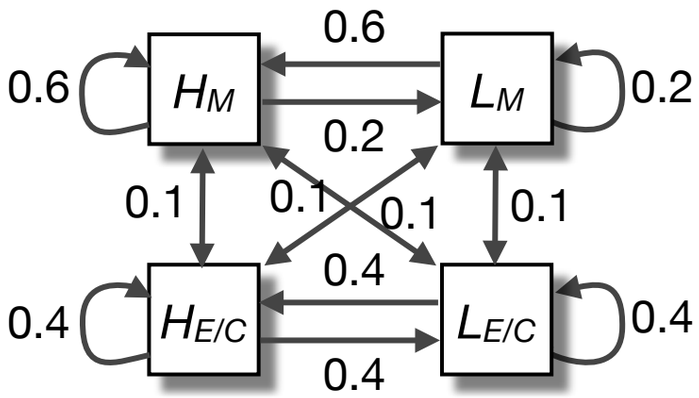
In our new model, there are multiple states that could account for each part of the observed sequence

i.e. we don't know which state emitted a given symbol from knowledge of the sequence and the structure of the model

- This is the *hidden* part of the problem

For our HMM

- Given HLLH..., we must infer the most probable state sequence
- This HMM state sequence will yield the boundaries between likely TM and E/C regions




```
HM, LM, LM, HM
HM, LM, LM, HE/C
HM, LM, LH/C, HM
HM, LM, LH/C, HE/C
HM, LE/C, LM, HM
HM, LE/C, LM, HE/C
HM, LE/C, LH/C, HM,
HM, LE/C, LH/C, HE/C,
HE/C, LM, LM, HM
HE/C, LM, LM, HE/C
HE/C, LM, LH/C, HM
HE/C, LM, LH/C, HE/C
HE/C, LE/C, LM, HM
HE/C, LE/C, LM, HE/C
HE/C, LE/C, LH/CM, HM
HE/C, LE/C, LH/CM, HE/C
```

Markov Chains

- States: $S_1, S_2 \ldots S_N$
- Initial probabilities: π_i
- Transition probabilities: a_{ij}

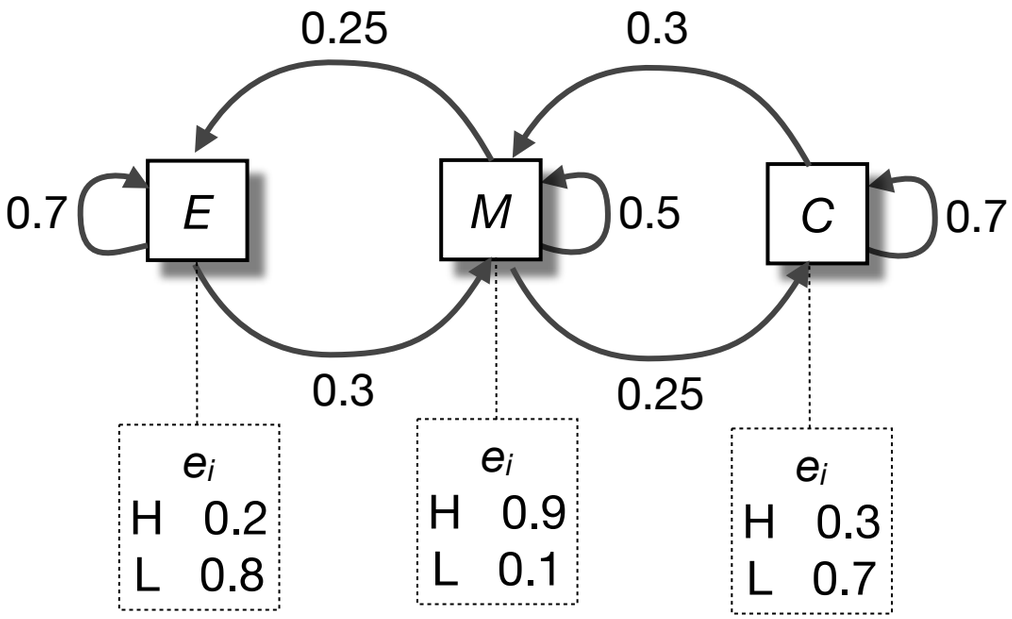
One-to-one correspondence between states and symbols

Hidden Markov Models

- States: $S_1, S_2 \ldots S_N$
- Initial probabilities: π_i
- Transition probabilities: a_{ij}
- **Alphabet** of emitted symbols, **Σ**
- **Emission probabilities**: $e_i(a)$ probability state *i* emits symbol *a*

Symbol may be emitted by more than one state

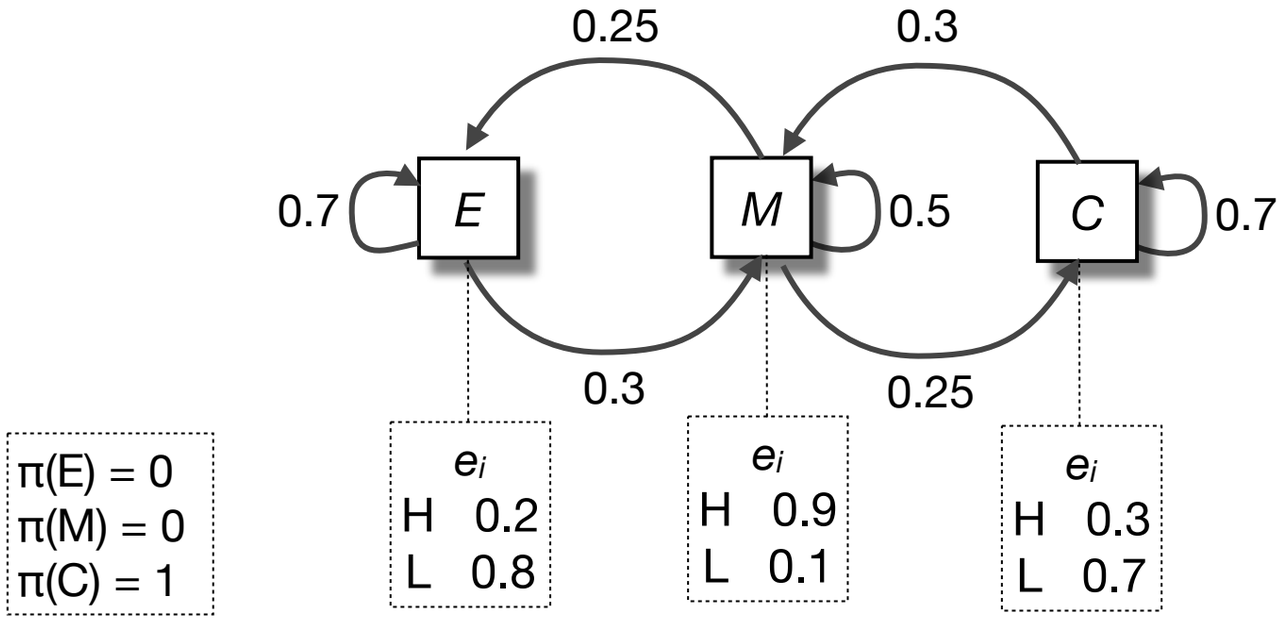
Similarly, a state can emit more than one symbol



$$a_{ij} = \begin{bmatrix} 0.7 & 0.3 & 0 \\ 0.25 & 0.5 & 0.25 \\ 0 & 0.3 & 0.7 \end{bmatrix}$$

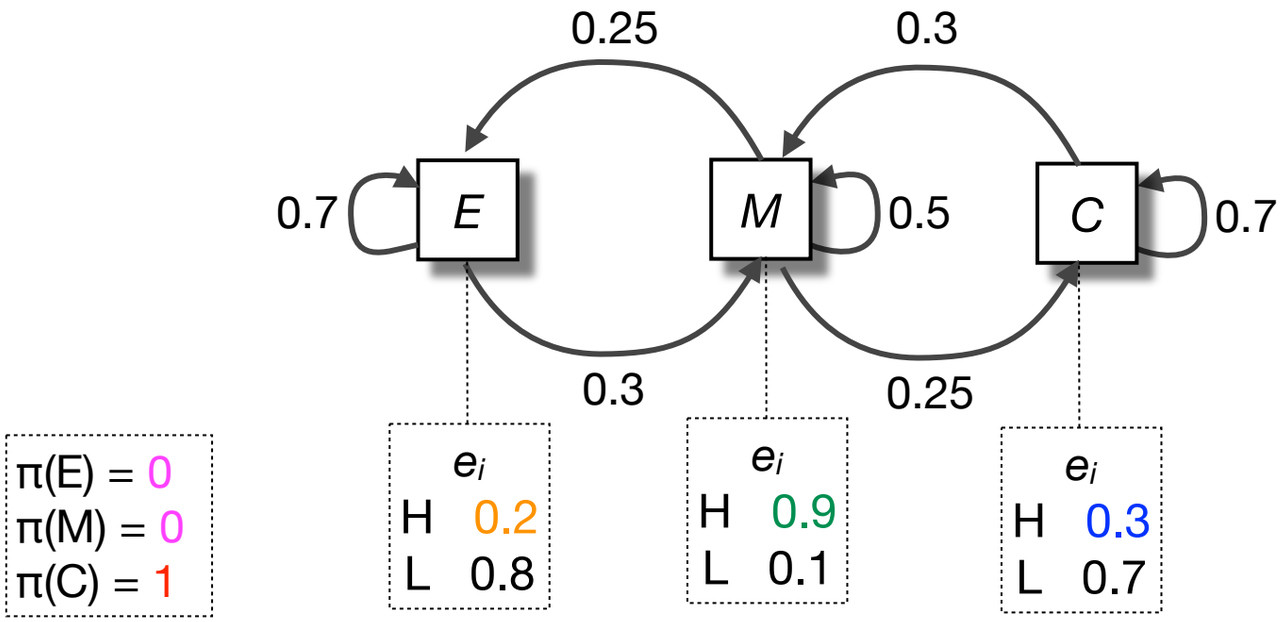
	E	*M*	*C*
π_i	0	0	1
$e_i(H)$	0.2	0.9	0.3
$e_i(L)$	0.8	0.1	0.7

$$a_{ij} = \frac{A_{ij}}{\sum_{j'} A_{ij'}} \qquad e_i(x) = \frac{E_i(x)}{\sum_{x}^{'} E_i(x')}$$



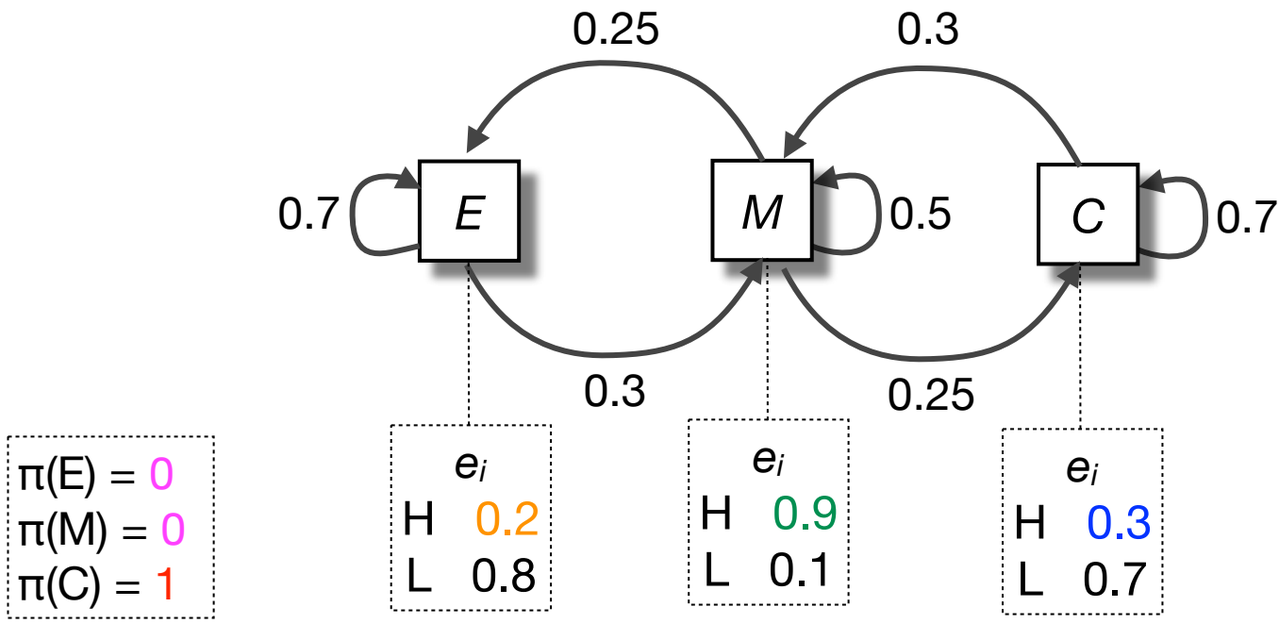
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E					
M					
C					
START					



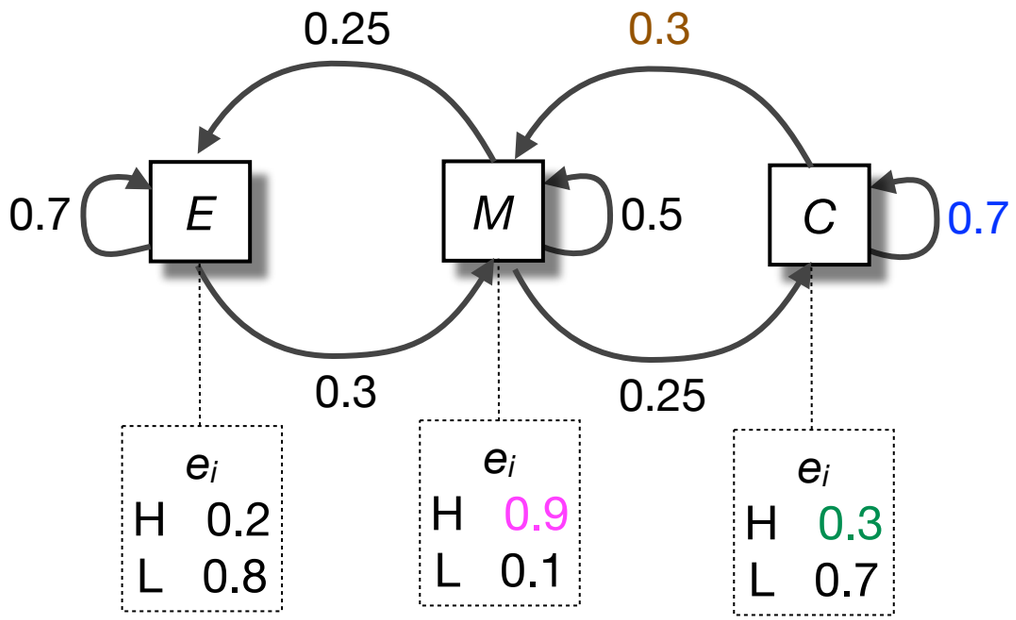
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0×0.2 =0				
M	0×0.9 =0				
C	1×0.3 =0.3				
START					



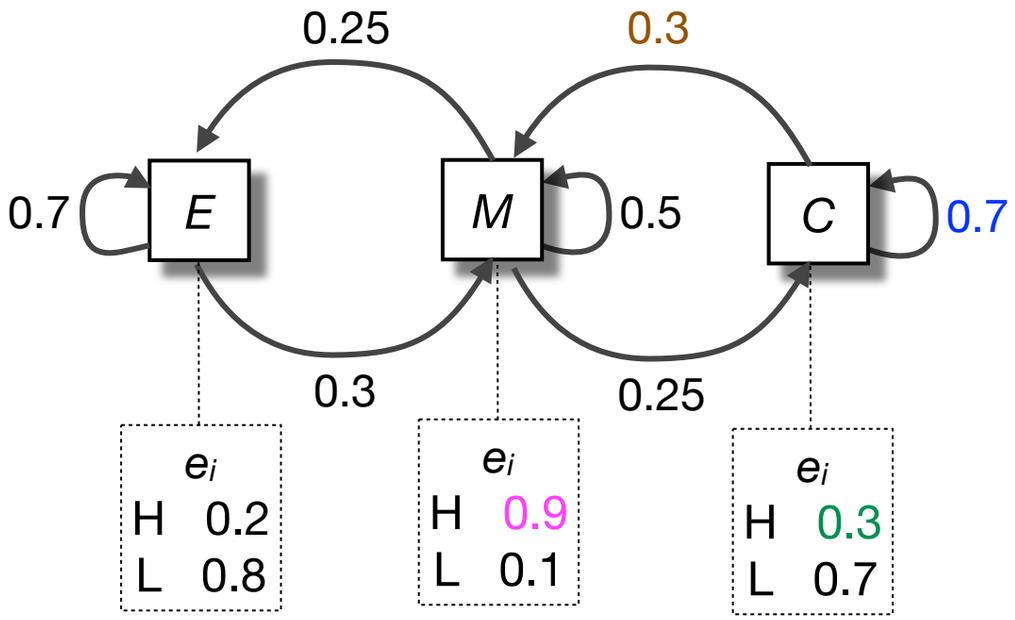
Query Sequence

States	H	H	L	L	H
E	0x0.2 =0				
M	0x0.9 =0				
C	1x0.3 =0.3				
START					



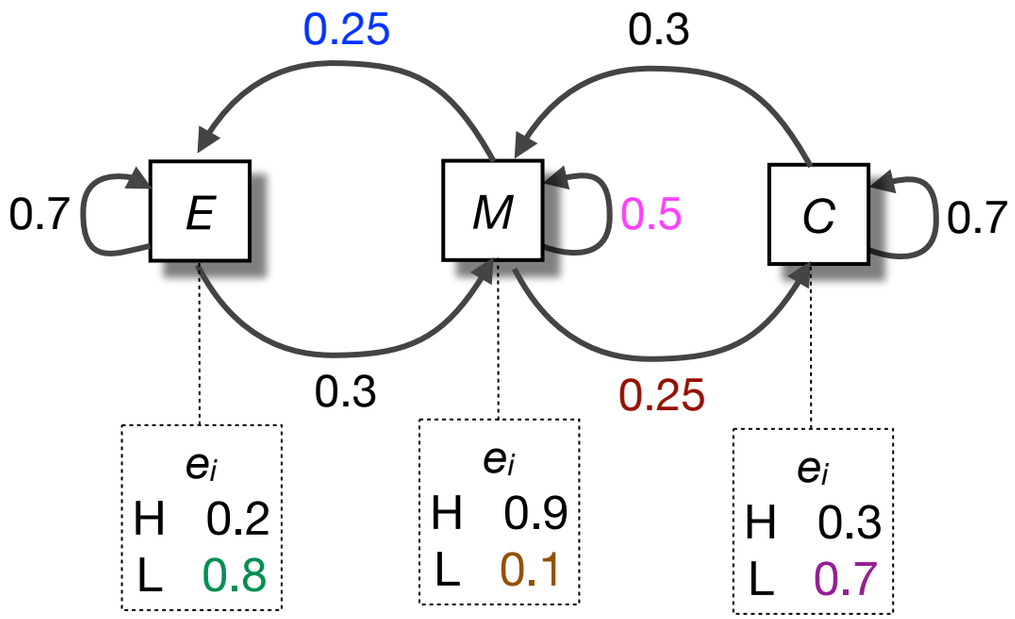
Query Sequence

States	H	H	L	L	H
E	0x0.2 =0	-			
M	0x0.9 =0	0.3x0.9x0.3 =0.081			
C	1x0.3 =0.3	0.7x0.3x0.3 =0.063			
START					



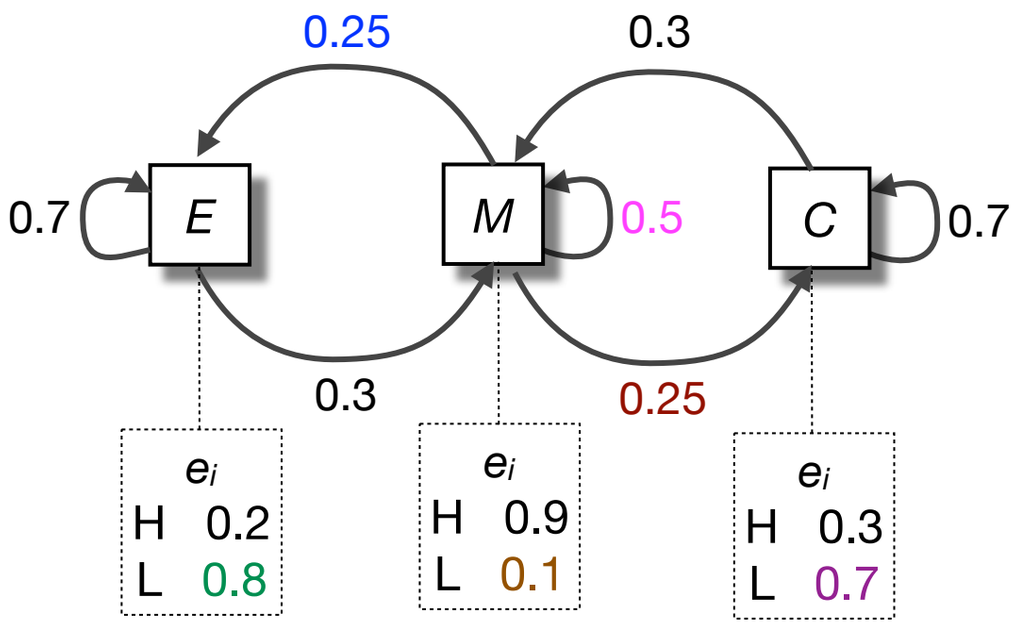
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-			
M	0x0.9 =0	0.3x0.9x0.3 =0.081			
C	1x0.3 =0.3	0.7x0.3x0.3 =0.063			
START					



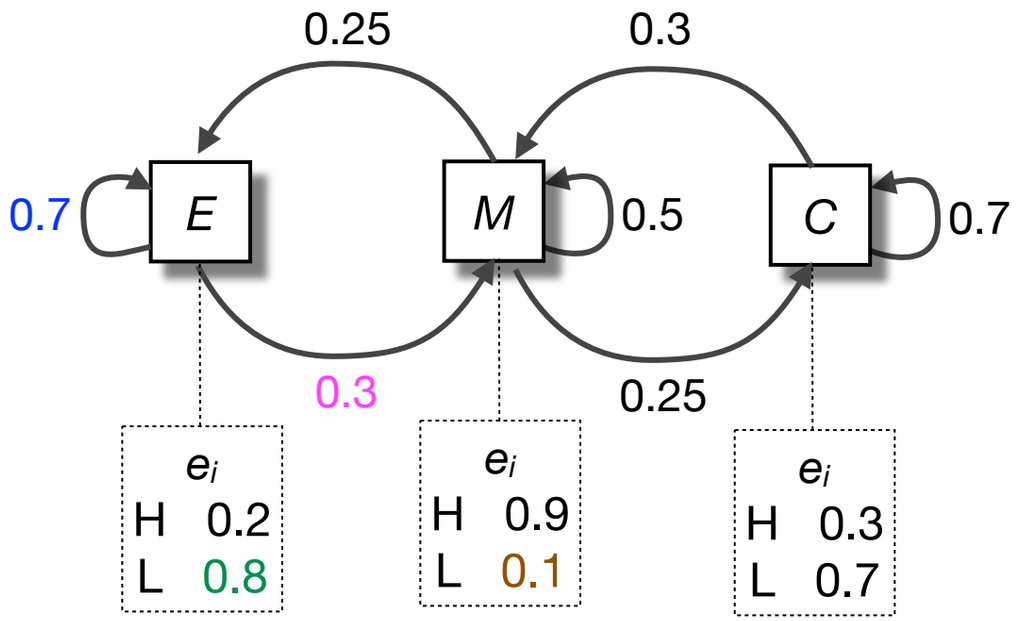
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016		
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04		
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014		
START					



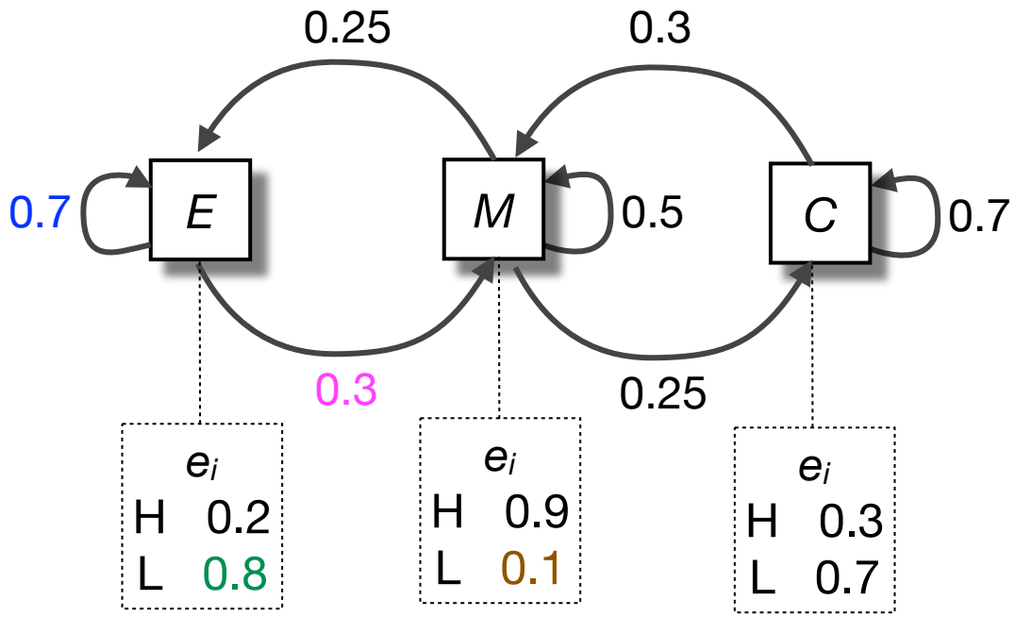
Query Sequence

States	H	H	L	L	H
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016		
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04		
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014		
START					



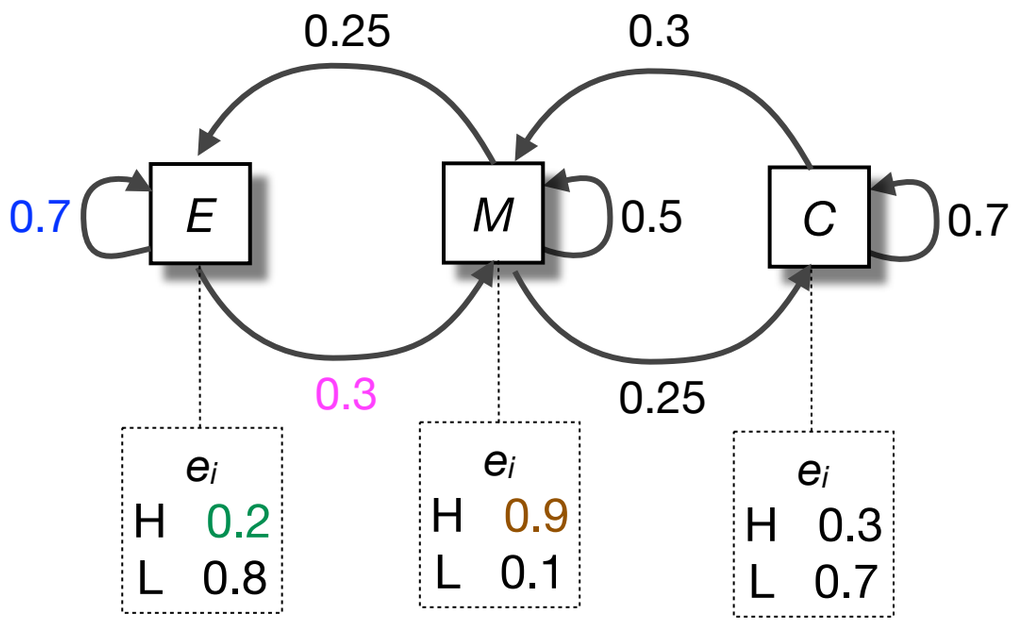
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016	0.7x0.8x0.016 =0.009	
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04	0.3x0.1x0.016 =0.0005	
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014	-	
START					



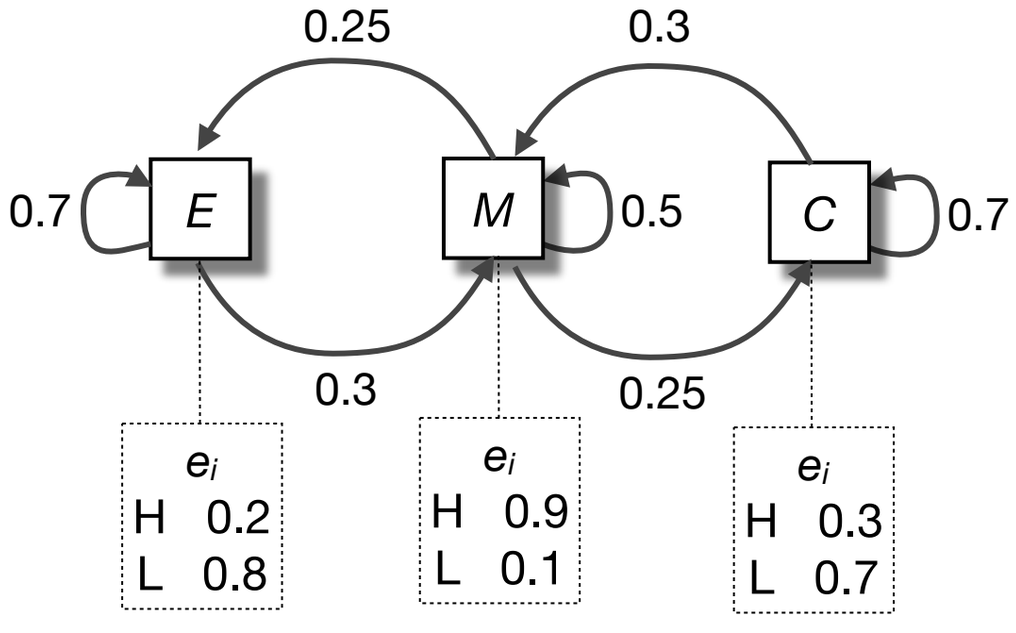
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016	0.7x0.8x0.016 =0.009	
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04	0.3x0.1x0.016 =0.0005	
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014	-	
START					



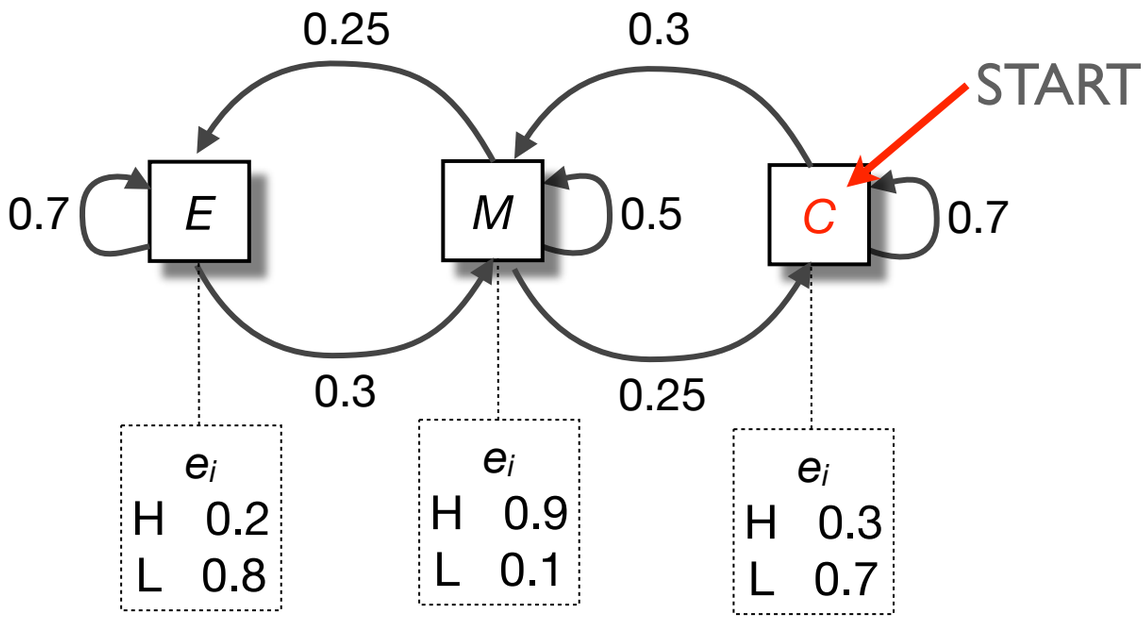
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016	0.7x0.8x0.016 =0.009	0.7x0.2x0.009 =0.001
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04	0.3x0.1x0.016 =0.0005	0.3x0.9x0.009 =0.002
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014	-	-
START					



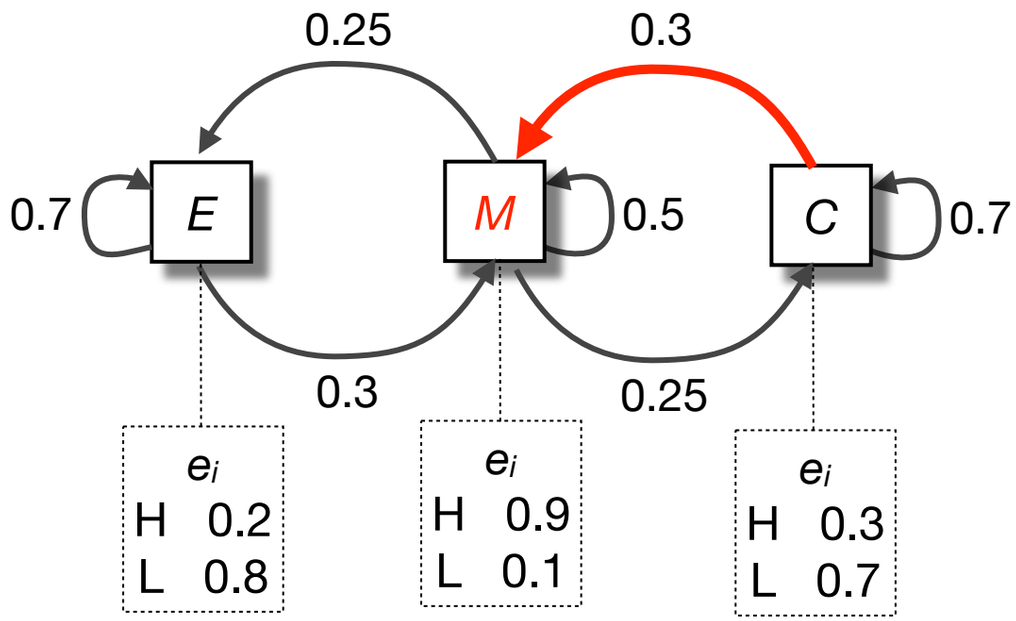
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016	0.7x0.8x0.016 =0.009	0.7x0.2x0.009 =0.001
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04	0.3x0.1x0.016 =0.0005	0.3x0.9x0.009 =0.002
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014	-	-
START					



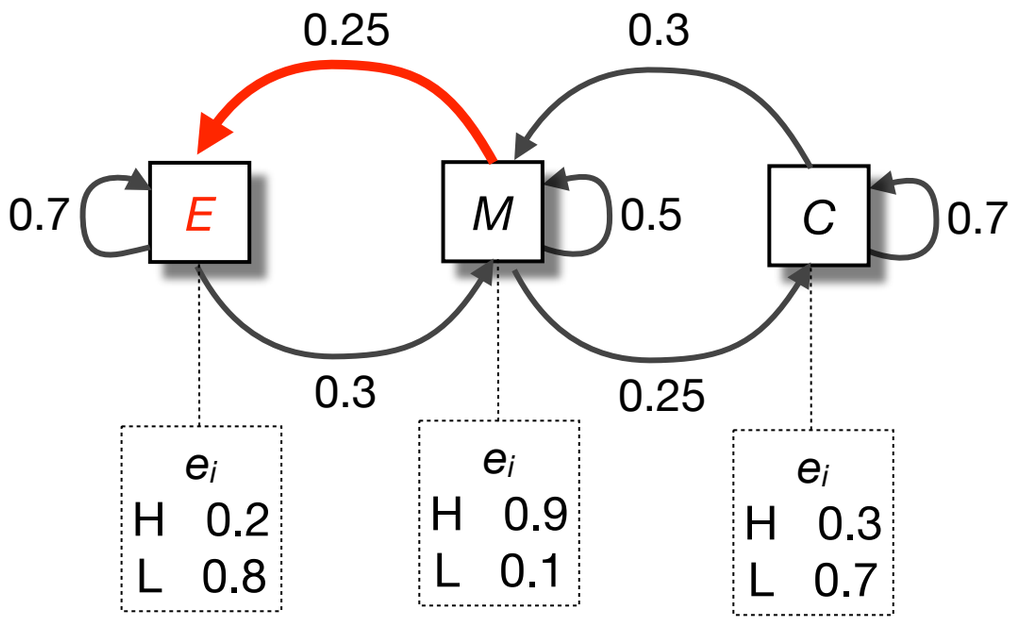
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016	0.7x0.8x0.016 =0.009	0.7x0.2x0.009 =0.001
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04	0.3x0.1x0.016 =0.0005	0.3x0.9x0.009 =0.002
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014	-	-
START	C				



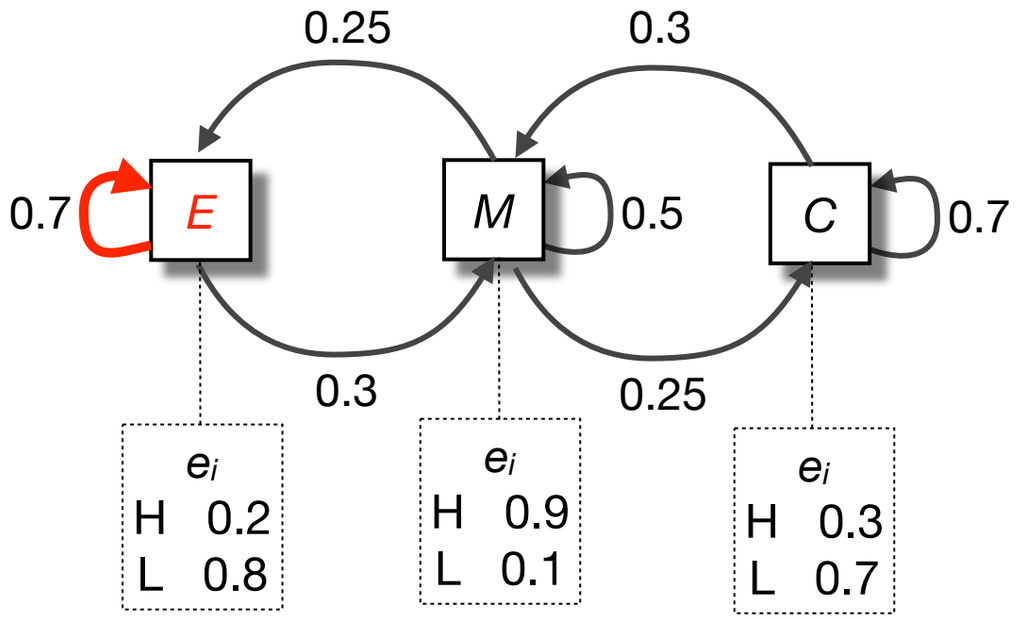
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016	0.7x0.8x0.016 =0.009	0.7x0.2x0.009 =0.001
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04	0.3x0.1x0.016 =0.0005	0.3x0.9x0.009 =0.002
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014	-	-
START	C	M			



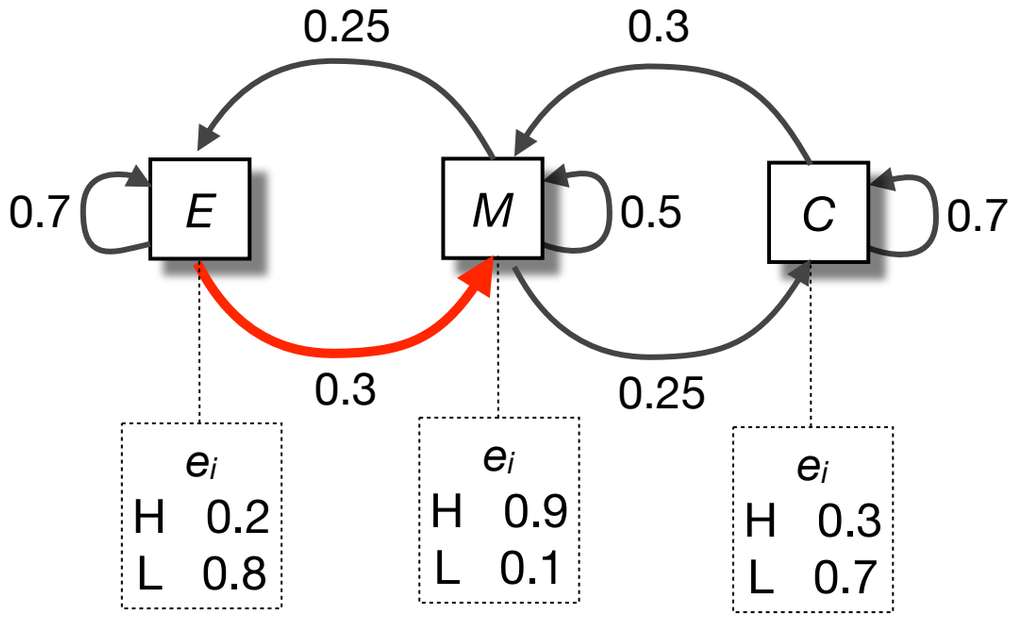
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016	0.7x0.8x0.016 =0.009	0.7x0.2x0.009 =0.001
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04	0.3x0.1x0.016 =0.0005	0.3x0.9x0.009 =0.002
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014	-	-
START	C	M	E		



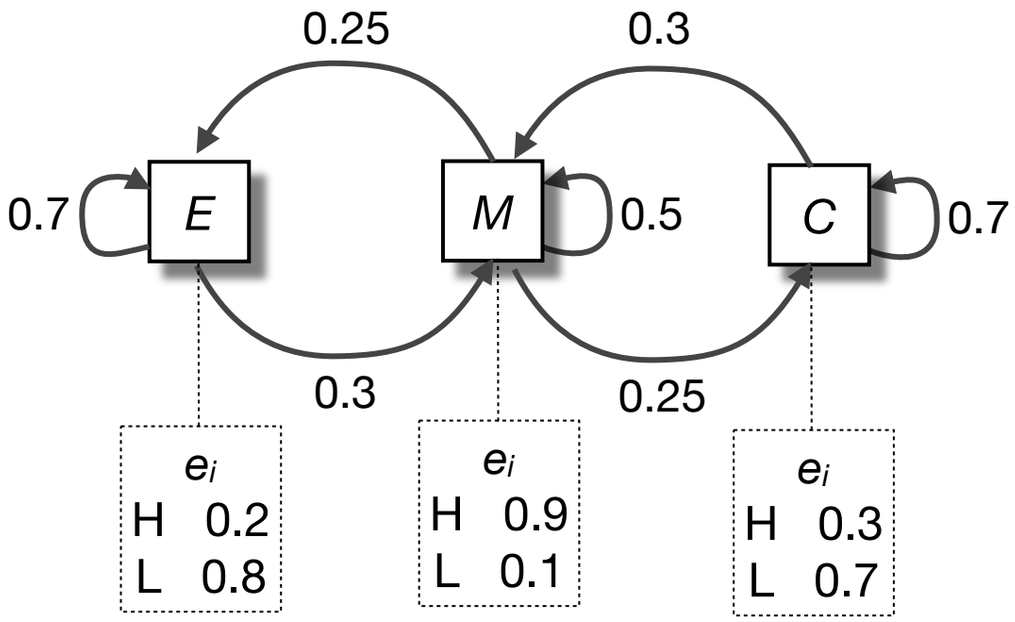
Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016	0.7x0.8x0.016 =0.009	0.7x0.2x0.009 =0.001
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04	0.3x0.1x0.016 =0.0005	0.3x0.9x0.009 =0.002
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014	-	-
START	C	M	E	E	



Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016	0.7x0.8x0.016 =0.009	0.7x0.2x0.009 =0.001
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04	0.3x0.1x0.016 =0.0005	0.3x0.9x0.009 =0.002
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014	-	-
START	C	M	E	E	M

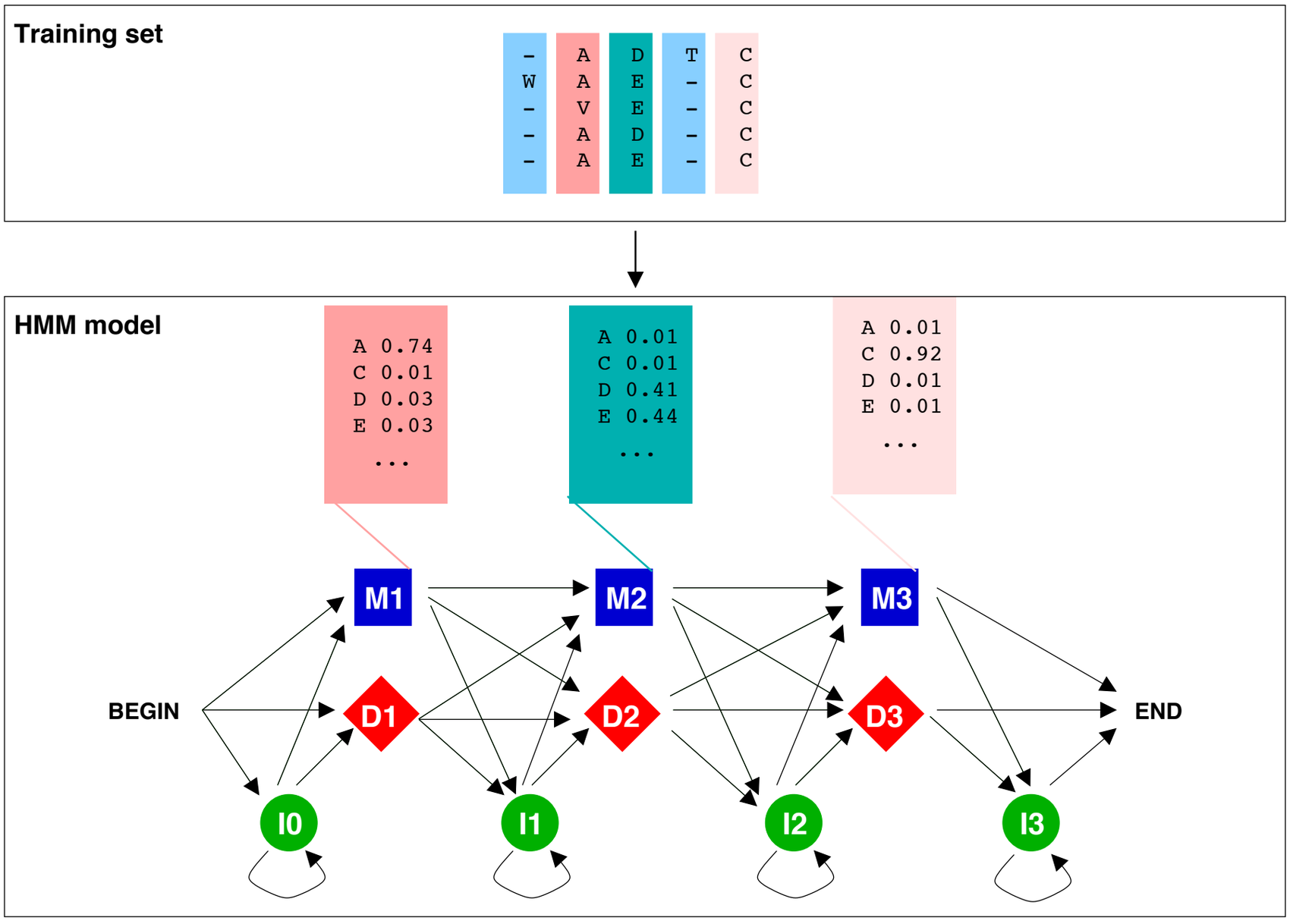


Query Sequence

States	**H**	**H**	**L**	**L**	**H**
E	0x0.2 =0	-	0.25x0.8x0.081 =0.016	0.7x0.8x0.016 =0.009	0.7x0.2x0.009 =0.001
M	0x0.9 =0	0.3x0.9x0.3 =0.081	0.5x0.1x0.081 =0.04	0.3x0.1x0.016 =0.0005	0.3x0.9x0.009 =0.002
C	1x0.3 =0.3	0.7x0.3.0.3 =0.063	0.25x0.7x0.081 =0.014	-	-
START	C	M	E	E	M

Most Probable State Sequence

Viterbi Algorithm


Training set
- W - - -
A A V A A
D E E D E
T - - - -
C C C C C
HMM model
A 0.74
C 0.01
D 0.03
E 0.03
...
A 0.01
C 0.01
D 0.41
E 0.44
...
A 0.01
C 0.92
D 0.01
E 0.01
...
M1
M2
M3
BEGIN
D1
D2
D3
END
I0
I1
I2
I3

Hidden Markov Model

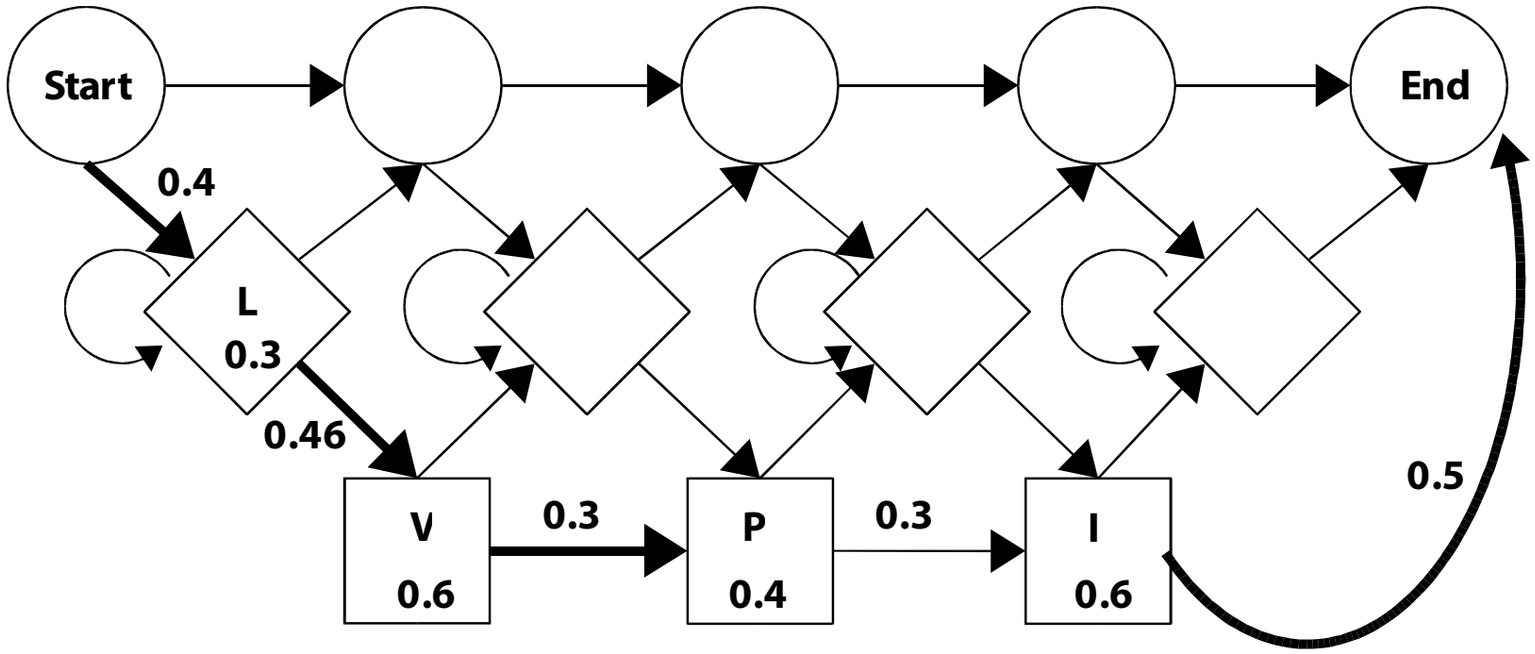


Figure 6: A possible hidden Markov model of protein LVPI. The numbers in the box indicates the emission probabilities and numbers next to arrows indicate transition probabilities. The probability of the protein LVPI is show in bold.

HMMER3

http://hmmer.janelia.org

cd ~/Desktop/h<tab>

cd binaries

sudo cp * /usr/bin/

Creating a HMM model of p53

Align:

```
muscle -stable -in infile -out outfile
```

Create HMM:

```
hmmbuild --informat afa p53.hmm
outfile
```

Search human genome:

```
hmmsearch -o hits.txt p53.hmm
human.faa
```

HMMER result

```
# hmmsearch :: search profile(s) against a sequence database
# HMMER 3.0 (March 2010); http://hmmer.org/
# Copyright (C) 2010 Howard Hughes Medical Institute.
# Freely distributed under the GNU General Public License (GPLv3).
# - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
# query HMM file:                  PF00870.hmm
# target sequence database:        PF00870_full_length_sequences-1.fasta
# output directed to file:         result.out
# - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

Query:       PF00870  [M=612]
Scores for complete sequences (score includes all domains):
   --- full sequence ---   --- best 1 domain ---    -#dom-
    E-value  score  bias    E-value  score  bias    exp  N  Sequence     Description
    ------- ------ -----    ------- ------ -----   ---- --  --------     -----------
      6e-226  746.2  22.8   7.3e-226  745.9  15.8    1.0  1  P63_MOUSE    (O88898)
    7.7e-226  745.8  21.8   9.7e-226  745.5  15.1    1.0  1  P63_RAT      (Q9JJP6)
    1.7e-225  744.7   4.7   3.5e-225  743.6   3.2    1.5  1  P73_HUMAN    (O15350)
    1.6e-224  741.5  23.2     2e-224  741.2  16.1    1.0  1  P63_HUMAN    (Q9H3D4)
      2e-223  737.9  20.5   2.2e-223  737.7  14.2    1.0  1  Q3UVI3_MOUSE (Q3UVI3)
    1.5e-222  735.0   3.4   4.3e-222  733.4   2.3    1.6  1  P73_CERAE    (Q9XSK8)
    2.1e-222  734.5  20.2   2.3e-222  734.3  14.0    1.0  1  Q5CZX0_MOUSE (Q5CZX0)
    2.1e-221  731.1  34.0   2.4e-221  731.0  23.6    1.0  1  C4Q601_SCHMA (C4Q601)
```

PFAM readymade HMM library