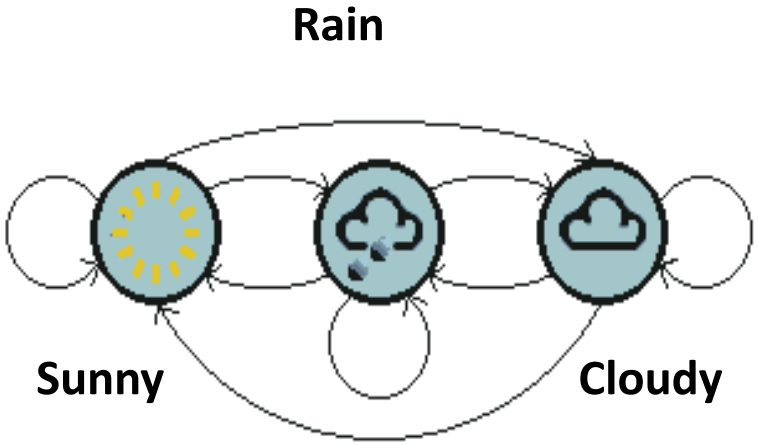
Hidden Markov Models, HMM's

Objectives

- Introduce Hidden Markov models and understand that they are just weight matrices with gaps
- How to construct an HMM
- How to "align/score" sequences to HMM's
  - Viterbi decoding
  - Forward decoding
  - Backward decoding
  - Posterior Decoding
- Use and construct Profile HMM
  - HMMer

Markov Chains



weather today

weather yesterday	Sun	Cloud	Rain
Sun	0.5	0.25	0.25
Cloud	0.375	0.125	0.375
Rain	0.125	0.625	0.375

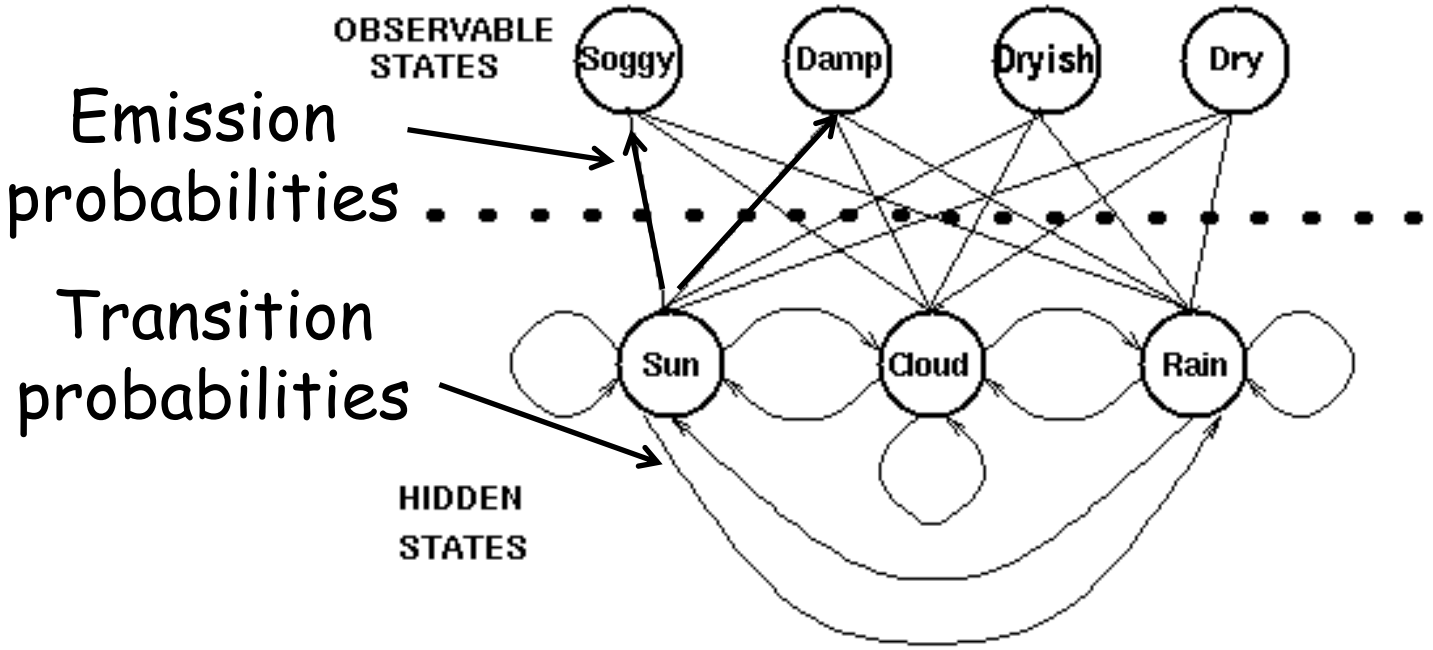
States : Three states - sunny, cloudy, rainy.

State transition matrix : The probability of the weather given the previous day's weather.

Sun	Cloud	Rain
1.0	0.0	0.0

Initial Distribution : Defining the probability of the system being in each of the states at time 0.

Hidden Markov Models



Hidden states : the (TRUE) states of a system that may be described by a Markov process (e.g., the weather).

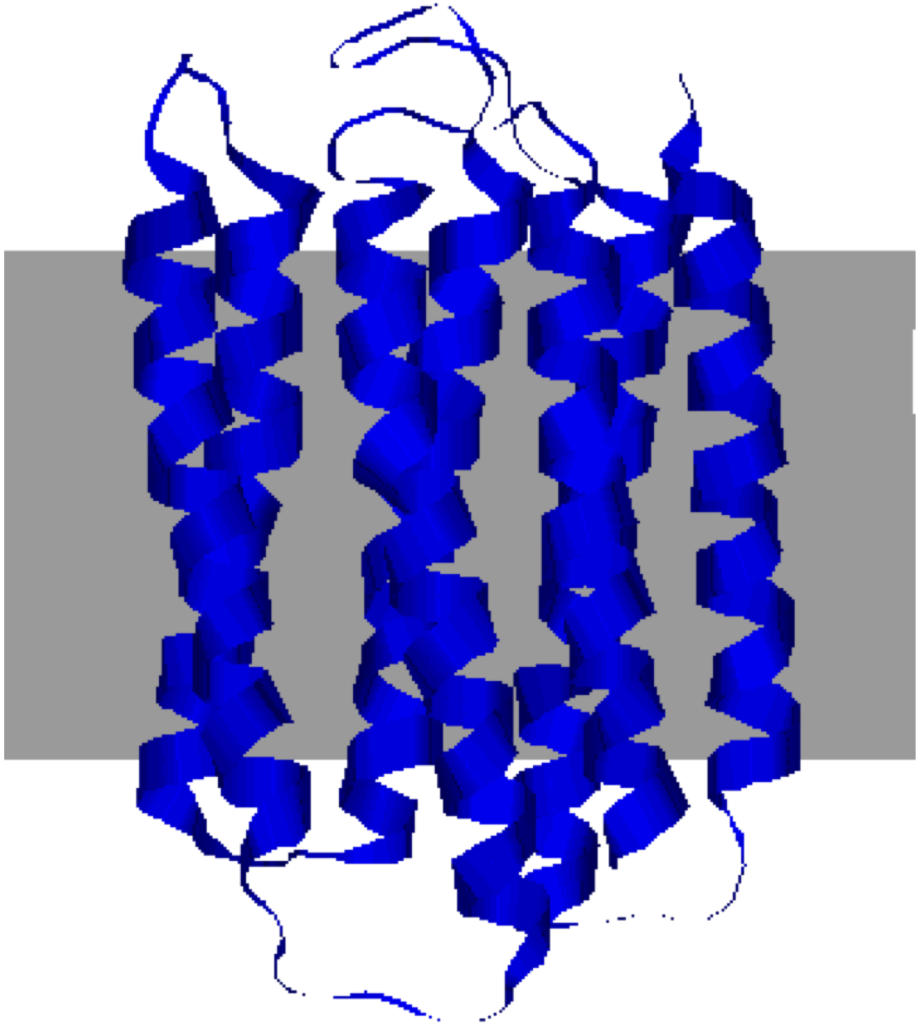
Observable states : the states of the process that are `visible' (e.g., seaweed dampness).

TMHMM (trans-membrane HMM)
(Sonnhammer, von Heijne, and Krogh)

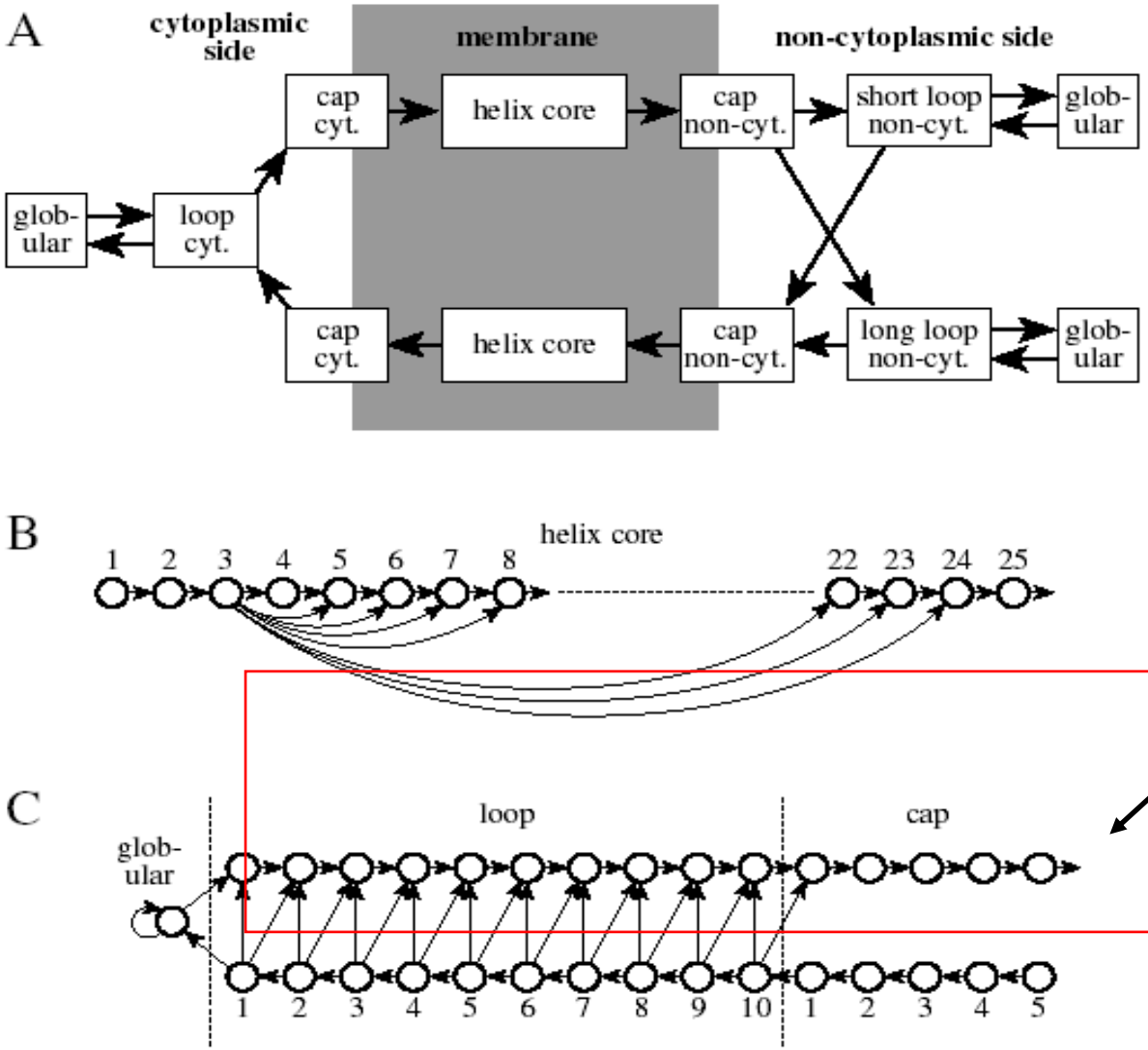
Extra cellular

Trans membrane

Intra cellular



TMHMM (trans-membrane HMM) (Sonnhammer, von Heijne, and Krogh)



Model TM length distribution.
Power of HMM.
Difficult in alignment.

ALLYVDWQILPVIL

Weight matrix construction

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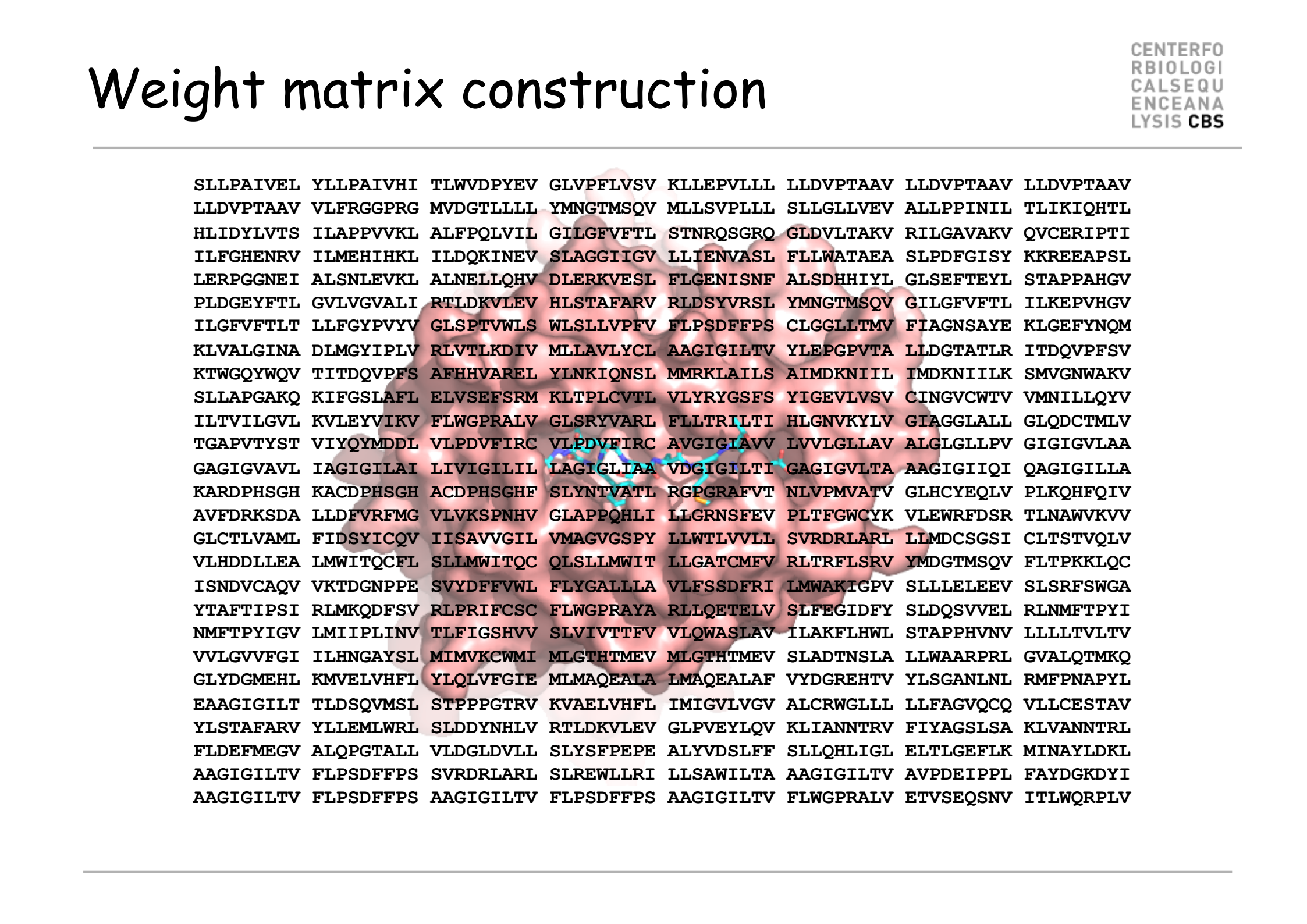

SLLPAIVEL YLLPAIVHI TLWVDPYEV GLVPFLVSV KLLEPVLLL LLDVPTAAV LLDVPTAAV LLDVPTAAV
LLDVPTAAV VLFRGGPRG MVDGTLLLL YMNGTMSQV MLLSVPLLL SLLGLLVEV ALLPPINIL TLIKIQHTL
HLIDYLVTS ILAPPVVKL ALFPQLVIL GILGFVFTL STNRQSGRQ GLDVLTAKV RILGAVAKV QVCERIPTI
ILFGHENRV ILMEHIHKL ILDQKINEV SLAGGIIGV LLIENVASL FLLWATAEA SLPDFGISY KKREEAPSL
LERPGGNEI ALSNLEVKL ALNELLQHV DLERKVESL FLGENISNF ALSDHHIYL GLSEFTEYL STAPPAHGV
PLDGEYFTL GVLVGVALI RTLDKVLEV HLSTAFARV RLDSYVRSL YMNGTMSQV GILGFVFTL ILKEPVHGV
ILGFVFTLT LLFGYPVYV GLSPTVWLS WLSLLVPFV FLPSDFFPS CLGGLLTMV FIAGNSAYE KLGEFYNQM
KLVALGINA DLMGYIPLV RLVTLKDIV MLLAVLYCL AAGIGILTV YLEPGPVTA LLDGTATLR ITDQVPFSV
KTWGQYWQV TITDQVPFS AFHHVAREL YLNKIQNSL MMRKLAILS AIMDKNIIL IMDKNIILK SMVGNWAKV
SLLAPGAKQ KIFGSLAFL ELVSEFSRM KLTPLCVTL VLYRYGSFS YIGEVLVSV CINGVCWTV VMNILLQYV
ILTVILGVL KVLEYVIKV FLWGPRALV GLSRYVARL FLLTRILTI HLGNVKYLV GIAGGLALL GLQDCTMLV
TGAPVTYST VIYQYMDDL VLPDVFIRC VLPDVFIRC AVGIGIAVV LVVLGLLAV ALGLGLLPV GIGIGVLAA
GAGIGVAVL IAGIGILAI LIVIGILIL LAGIGLIAA VDGIGILTI GAGIGVLTA AAGIGIIQI QAGIGILLA
KARDPHSGH KACDPHSGH ACDPHSGHF SLYNTVATL RGPGRAFVT NLVPMVATV GLHCYEQLV PLKQHFQIV
AVFDRKSDA LLDFVRFMG VLVKSPNHV GLAPPQHLI LLGRNSFEV PLTFGWCYK VLEWRFDSR TLNAWVKVV
GLCTLVAML FIDSYICQV IISAVVGIL VMAGVGSPY LLWTLVVLL SVRDRLARL LLMDCSGSI CLTSTVQLV
VLHDDLLEA LMWITQCFL SLLMWITQC QLSLLMWIT LLGATCMFV RLTRFLSRV YMDGTMSQV FLTPKKLQC
ISNDVCAQV VKTDGNPPE SVYDFFVWL FLYGALLLA VLFSSDFRI LMWAKIGPV SLLLELEEV SLSRFSWGA
YTAFTIPSI RLMKQDFSV RLPRIFCSC FLWGPRAYA RLLQETELV SLFEGIDFY SLDQSVVEL RLNMFTPYI
NMFTPYIGV LMIIPLINV TLFIGSHVV SLVIVTTFV VLQWASLAV ILAKFLHWL STAPPHVNV LLLLTVLTV
VVLGVVFGI ILHNGAYSL MIMVKCWMI MLGTHTMEV MLGTHTMEV SLADTNSLA LLWAARPRL GVALQTMKQ
GLYDGMEHL KMVELVHFL YLQLVFGIE MLMAQEALA LMAQEALAF VYDGREHTV YLSGANLNL RMFPNAPYL
EAAGIGILT TLDSQVMSL STPPPGTRV KVAELVHFL IMIGVLVGV ALCRWGLLL LLFAGVQCQ VLLCESTAV
YLSTAFARV YLLEMLWRL SLDDYNHLV RTLDKVLEV GLPVEYLQV KLIANNTRV FIYAGSLSA KLVANNTRL
FLDEFMEGV ALQPGTALL VLDGLDVLL SLYSFPEPE ALYVDSLFF SLLQHLIGL ELTLGEFLK MINAYLDKL
AAGIGILTV FLPSDFFPS SVRDRLARL SLREWLLRI LLSAWILTA AAGIGILTV AVPDEIPPL FAYDGKDYI
AAGIGILTV FLPSDFFPS AAGIGILTV FLPSDFFPS AAGIGILTV FLWGPRALV ETVSEQSNV ITLWQRPLV

PSSM construction

- Calculate amino acid frequencies at each position using
  - Sequence weighting
  - Pseudo counts
- Define background model
  - Use background amino acids frequencies
- PSSM is

$$S(a_i) = \log \frac{p(a_i)}{q(a)}$$

More on scoring

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
1	0.6	0.4	-3.5	-2.4	-0.4	-1.9	-2.7	0.3	-1.1	1.0	0.3	0.0	1.4	1.2	-2.7	1.4	-1.2	-2.0	1.1	0.7
2	-1.6	-6.6	-6.5	-5.4	-2.5	-4.0	-4.7	-3.7	-6.3	1.0	5.1	-3.7	3.1	-4.2	-4.3	-4.2	-0.2	-5.9	-3.8	0.4
3	0.2	-1.3	0.1	1.5	0.0	-1.8	-3.3	0.4	0.5	-1.0	0.3	-2.5	1.2	1.0	-0.1	-0.3	-0.5	3.4	1.6	0.0
4	-0.1	-0.1	-2.0	2.0	-1.6	0.5	0.8	2.0	-3.3	0.1	-1.7	-1.0	-2.2	-1.6	1.7	-0.6	-0.2	1.3	-6.8	-0.7
5	-1.6	-0.1	0.1	-2.2	-1.2	0.4	-0.5	1.9	1.2	-2.2	-0.5	-1.3	-2.2	1.7	1.2	-2.5	-0.1	1.7	1.5	1.0
6	-0.7	-1.4	-1.0	-2.3	1.1	-1.3	-1.4	-0.2	-1.0	1.8	0.8	-1.9	0.2	1.0	-0.4	-0.6	0.4	-0.5	-0.0	2.1
7	1.1	-3.8	-0.2	-1.3	1.3	-0.3	-1.3	-1.4	2.1	0.6	0.7	-5.0	1.1	0.9	1.3	-0.5	-0.9	2.9	-0.4	0.5
8	-2.2	1.0	-0.8	-2.9	-1.4	0.4	0.1	-0.4	0.2	-0.0	1.1	-0.5	-0.5	0.7	-0.3	0.8	0.8	-0.7	1.3	-1.1
9	-0.2	-3.5	-6.1	-4.5	0.7	-0.8	-2.5	-4.0	-2.6	0.9	2.8	-3.0	-1.8	-1.4	-6.2	-1.9	-1.6	-4.9	-1.6	4.5

$$S = \sum_i S(a_i)$$

$$S = \sum_i \log \frac{p(a_i)}{q(a_i)}$$

$$S = \log \left(\frac{\prod_i p(a_i)}{\prod_i q(a_i)} \right)$$

Probability of observation given Model

Probability of observation given Prior (background)

$$S = \log \left(\frac{P(a \mid M)}{P(a \mid B)} \right)$$

Hidden Markov Models

- Weight matrices do not deal with insertions and deletions
- In alignments, this is done in an ad-hoc manner by optimization of the two gap penalties for first gap and gap extension
- HMM is a natural framework where insertions/deletions are dealt with explicitly

Multiple sequence alignment
Learning from evolution

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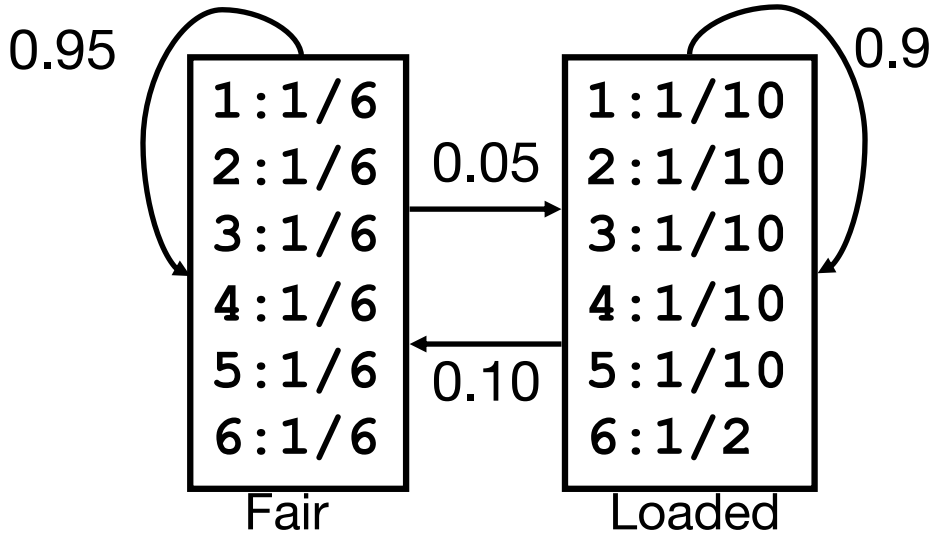
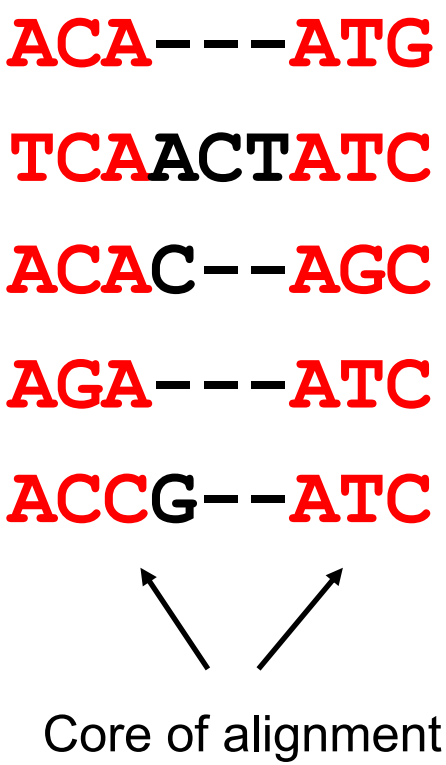
Why hidden?

The unfair casino: Loaded die p(6) = 0.5; switch fair to load:0.05; switch load to fair: 0.1

- Model generates numbers
  - 312453666641
- Does not tell which die was used
- Alignment (decoding) can give the most probable solution/path (Viterbi)
  - FFFFFFLLLLLL
- Or most probable set of states
  - FFFFFFLLLLLL

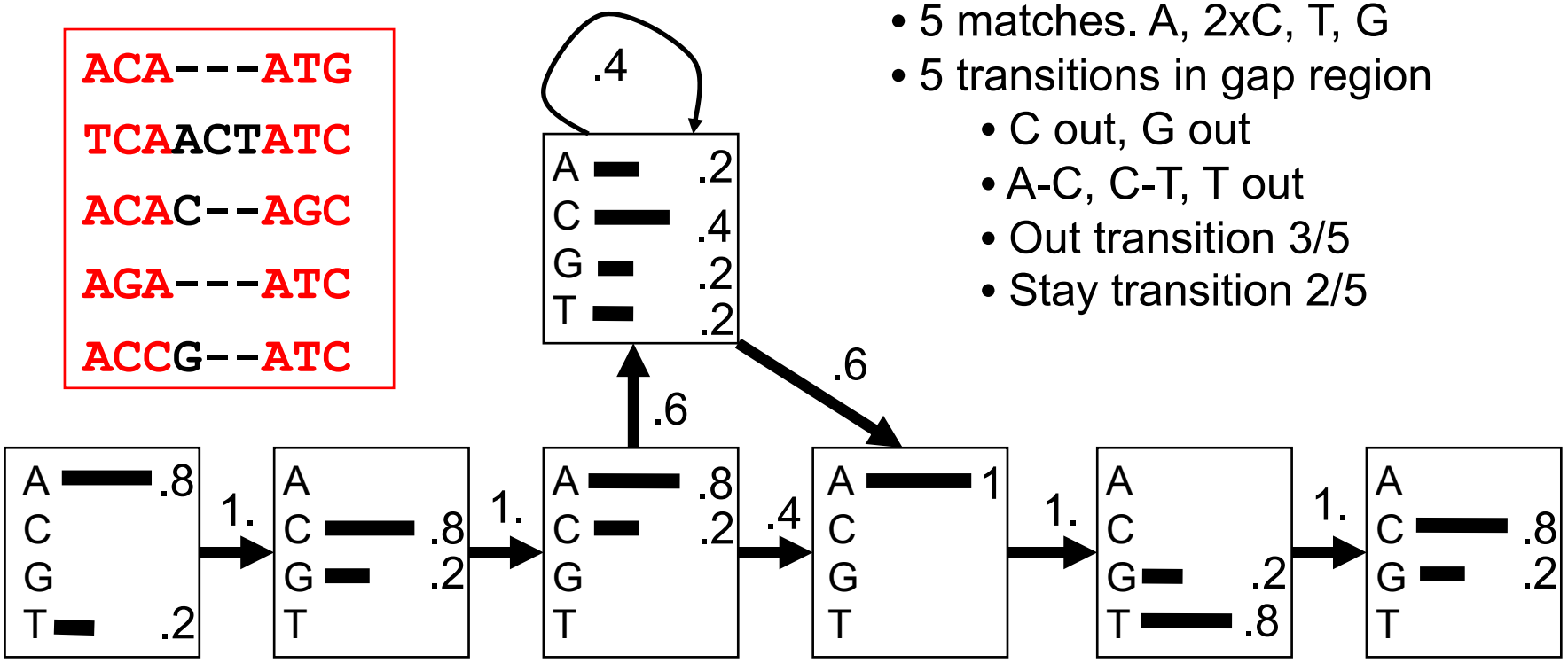


HMM (a simple example)



- Example from A. Krogh
- Core region defines the number of states in the HMM (red)
- Insertion and deletion statistics are derived from the non-core part of the alignment (black)

HMM construction (supervised learning)



- 5 matches. A, 2xC, T, G
- 5 transitions in gap region
  - C out, G out
  - A-C, C-T, T out
  - Out transition 3/5
  - Stay transition 2/5

ACA---ATG 0.8x1x0.8x1x0.8x0.4x1x1x0.8x1x0.2 = 3.3×10^{-2}

Scoring a sequence to an HMM

ACA---ATG 0.8x1x0.8x1x0.8x0.4x1x0.8x1x0.2 = 3.3×10^{-2}

TCAACTATC 0.2x1x0.8x1x0.8x0.6x0.2x0.4x0.4x0.4x0.2x0.6x1x1x0.8x1x0.8 = 0.0075×10^{-2}

ACAC--AGC = 1.2×10^{-2}

Consensus:

ACAC--ATC = 4.7×10^{-2}, **ACA---ATC** = 13.1×10^{-2}

Exceptional:

TGCT--AGG = 0.0023×10^{-2}

Align sequence to HMM - Null model

- Score depends strongly on length
- Null model is a random model. For length L the score is 0.25^L
- Log-odds score for sequence S
- Log(P(S)/0.25^L)
- Positive score means more likely than Null model
- **This is just like we did for PSSM log(p/q)!**

```
ACA---ATG = 4.9
TCAACTATC = 3.0
ACAC--AGC = 5.3
AGA---ATC = 4.9
ACCG--ATC = 4.6
Consensus:
ACAC--ATC = 6.7
ACA---ATC = 6.3
Exceptional:
TGCT--AGG = -0.97
```

Note!

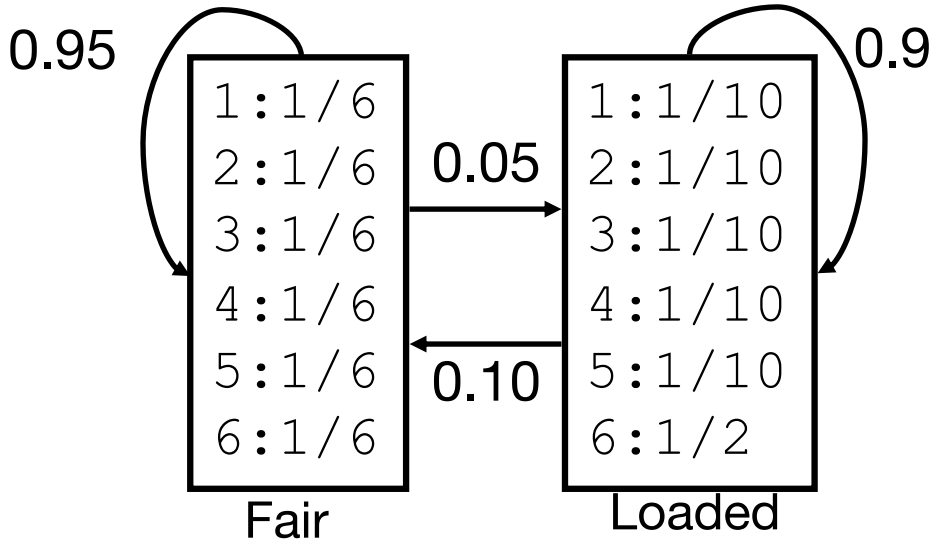
Aligning a sequence to an HMM

- Find the path through the HMM states that has the highest probability
  - For alignment, we found the path through the scoring matrix that had the highest sum of scores
- The number of possible paths rapidly gets very large making brute force search infeasible
  - Just like checking all path for alignment did not work
- Use dynamic programming
  - The Viterbi algorithm does the job

The Viterbi algorithm

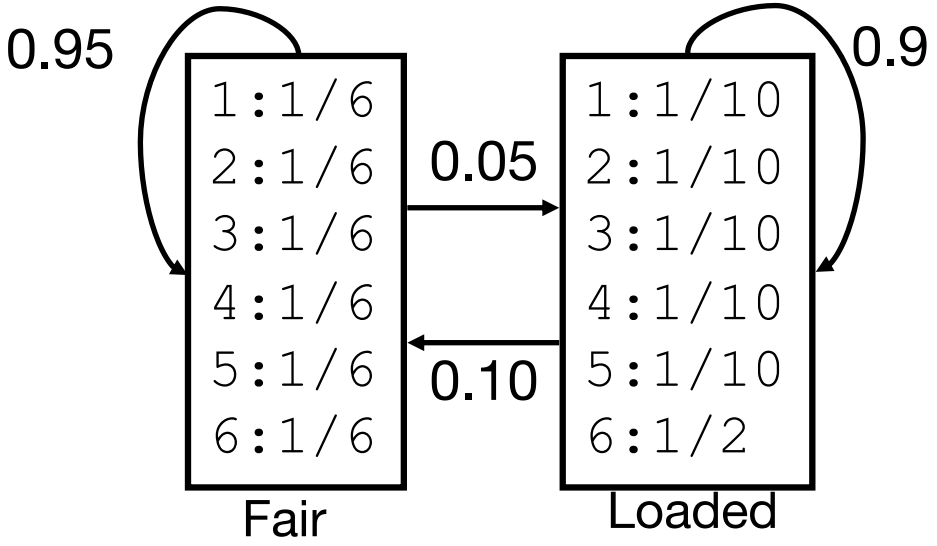
The unfair casino: Loaded dice p(6) = 0.5; switch fair to load:0.05; switch load to fair: 0.1

- Model generates numbers
  - 312453666641



Model decoding (Viterbi)

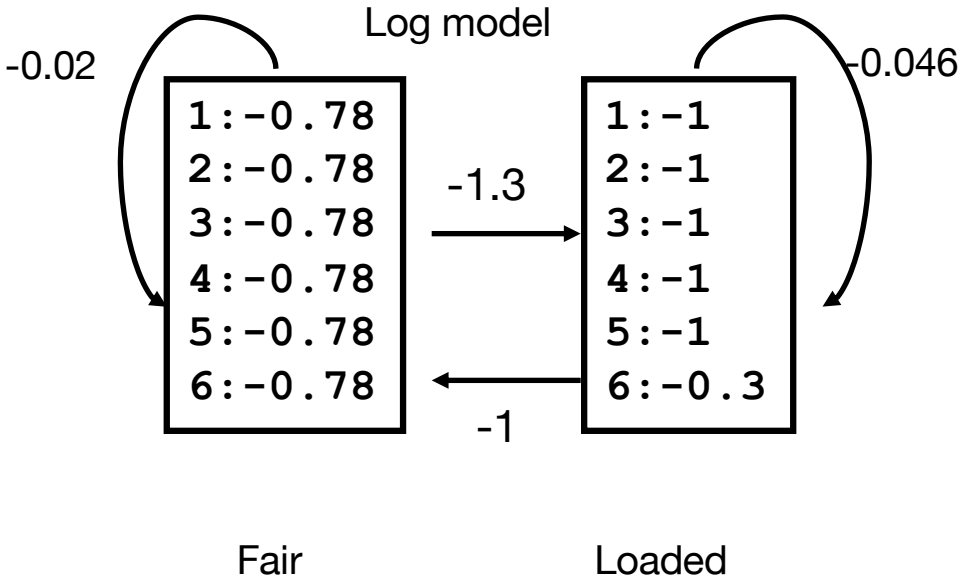
- Example: 566. What was the most likely series of dice used to generate this output?
- Use Brute force




```
FFF = 0.5*0.167*0.95*0.167*0.95*0.167 = 0.0021
FFL = 0.5*0.167*0.95*0.167*0.05*0.5 = 0.00333
FLF = 0.5*0.167*0.05*0.5*0.1*0.167 = 0.000035
FLL = 0.5*0.167*0.05*0.5*0.9*0.5 = 0.00094
LFF = 0.5*0.1*0.1*0.167*0.95*0.167 = 0.00013
LFL = 0.5*0.1*0.1*0.167*0.05*0.5 = 0.000021
LLF = 0.5*0.1*0.9*0.5*0.1*0.167 = 0.00038
LLL = 0.5*0.1*0.9*0.5*0.9*0.5 = 0.0101
```

Or in log space

- Example: 566. What was the most likely series of dice used to generate this output?

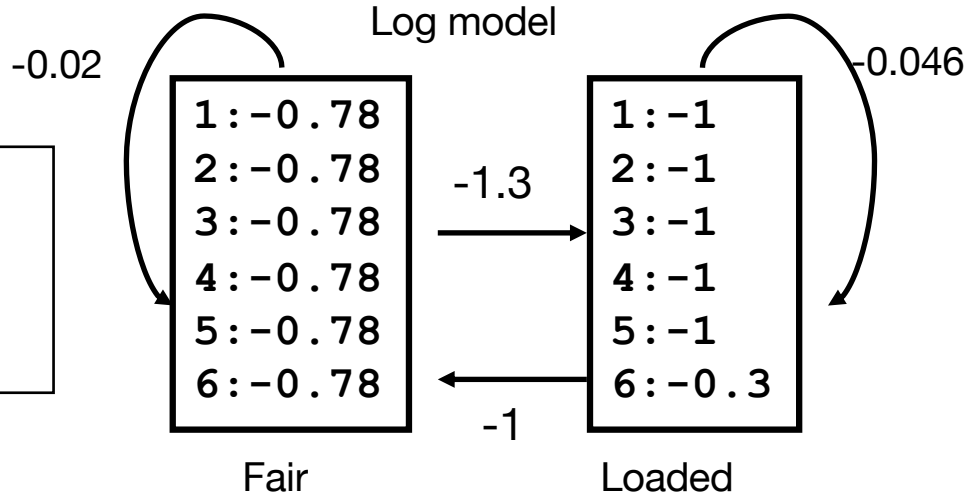



```
Log(P(LLL|M)) = log(0.5*0.1*0.9*0.5*0.9*0.5) = log(0.0101)
                                    or
Log(P(LLL|M)) = log(0.5)+log(0.1)+log(0.9)+log(0.5)+log(0.9)+log(0.5)
              = -0.3 -1 -0.046 -0.3 -0.046 -0.3 = -1.99
```

Model decoding (Viterbi)

- Example: 566611234. What was the most likely series of dice used to generate this output?

```
F = 0.5*0.167
log(F) = log(0.5) + log(0.167) = -1.08
L = 0.5*0.1
log(L) = log(0.5) + log(0.1) = -1.30
```

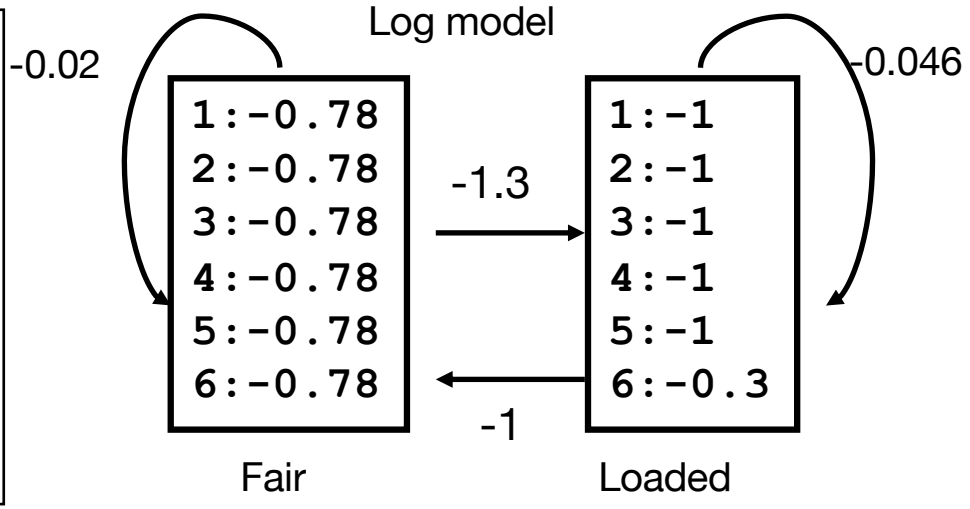


	5	6	6	6	1	1	2	3	4
F	-1.08								
L	-1.30								

Model decoding (Viterbi)

- Example: 566611234. What was the most likely series of dice used to generate this output?

```
FF = 0.5*0.167*0.95*0.167
Log(FF) = -0.30 -0.78 - 0.02 -0.78 = -1.88
LF = 0.5*0.1*0.1*0.167
Log(LF) = -0.30 -1 -1 -0.78 = -3.08
FL = 0.5*0.167*0.05*0.5
Log(FL) = -0.30 -0.78 - 1.30 -0.30 = -2.68
LL = 0.5*0.1*0.9*0.5
Log(LL) = -0.30 -1 -0.046 -0.3 = -1.65
```



	5	6	6	6	1	1	2	3	4
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Model decoding (Viterbi)

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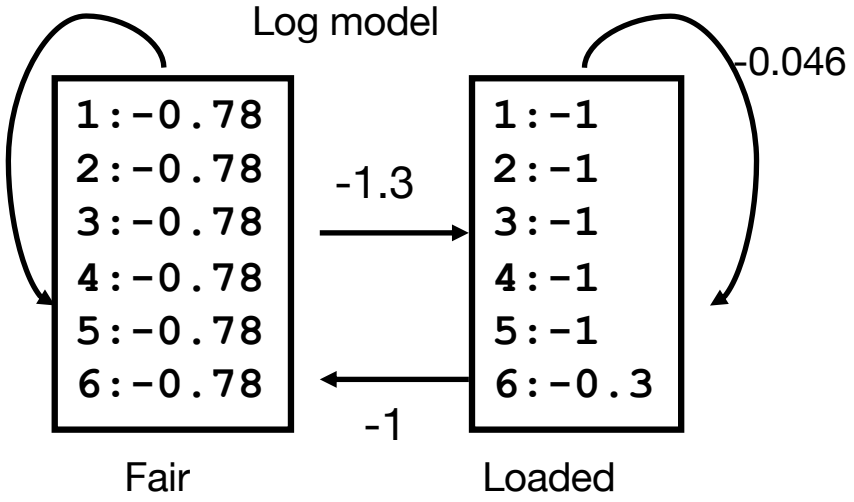
FL = 0.5*0.167*0.05*0.5
Log(FL) = -0.30 -0.78 - 1.30 -0.30 = -2.68
LL = 0.5*0.1*0.9*0.5
Log(LL) = -0.30 -1 -0.046 -0.3 = -1.65
```

-0.02



	5	6	6	6	1	1	2	3	4
F	-1.08	-1.88							
L	-1.30	-1.65							

Model decoding (Viterbi)

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RBIOLOGI
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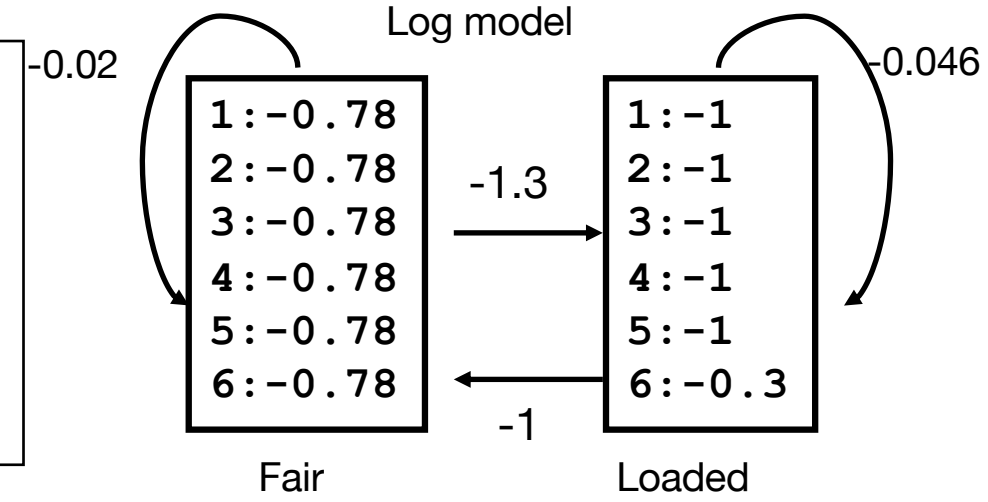
LYSIS CBS

- Example: 566611234. What was the most likely series of dice used to generate this output?

```
FFF = 0.5*0.167*0.95*0.167*0.95*0.167 = 0.0021
FLF = 0.5*0.167*0.05*0.5*0.1*0.167 = 0.000035
LFF = 0.5*0.1*0.1*0.167*0.95*0.167 = 0.00013
LLF = 0.5*0.1*0.9*0.5*0.1*0.167 = 0.00038
FLL = 0.5*0.167*0.05*0.5*0.9*0.5 = 0.00094
FFL = 0.5*0.167*0.95*0.167*0.05*0.5 = 0.00333
LFL = 0.5*0.1*0.1*0.167*0.05*0.5 = 0.000021
LLL = 0.5*0.1*0.9*0.5*0.9*0.5 = 0.0101
```



	5	6	6	6	1	1	2	3	4
F	-1.08	-1.88							
L	-1.30	-1.65							

Model decoding (Viterbi)

- Example: 566611234. What was the most likely series of dice used to generate this output?

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FFF = 0.5*0.167*0.95*0.167*0.95*0.167 = 0.0021
Log(P(FFF))=-2.68
LLL = 0.5*0.1*0.9*0.5*0.9*0.5 = 0.0101
Log(P(LLL))=-1.99
```

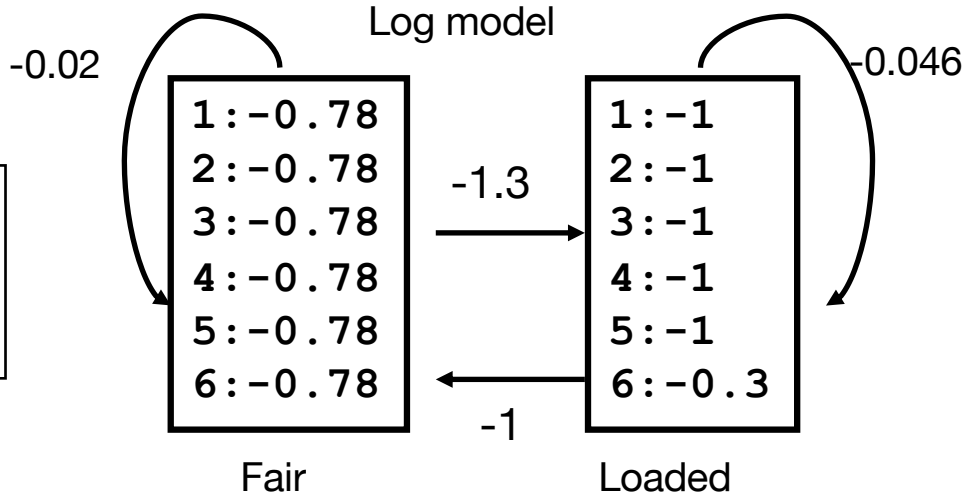

	5	6	6	6	1	1	2	3	4
F	-1.08	-1.88	-2.68						
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Model decoding (Viterbi)

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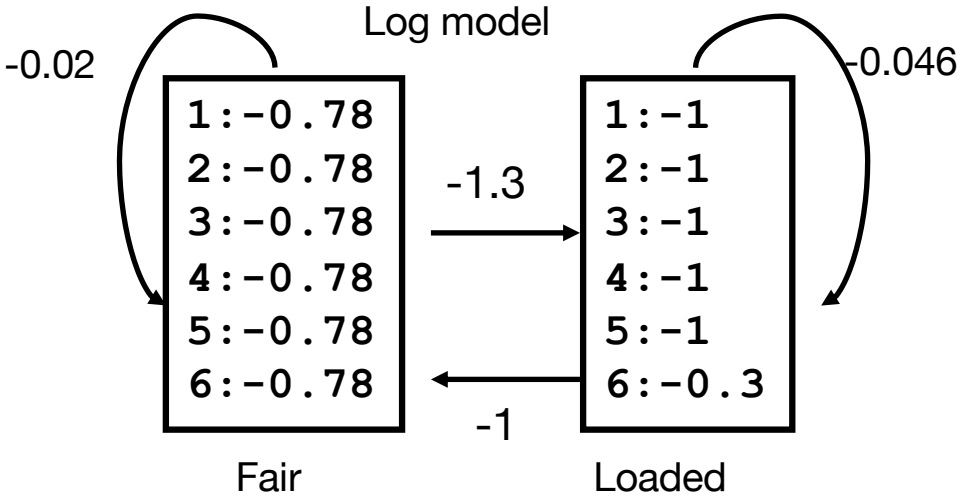


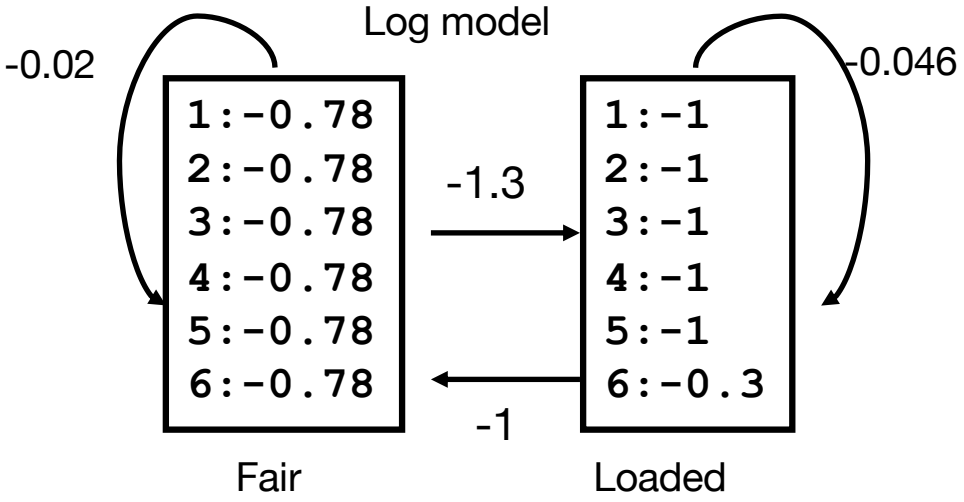
	5	6	6	6	1	1	2	3	4
F	-1.08	-1.88	-2.68						
L	-1.30	-1.65	-1.99						

Model decoding (Viterbi)

- Example: 566611234. What was the most likely series of dice used to generate this output?

$$-0.78 - 0.02 - 2.68 = -3.48$$

$$-0.78 - 1 - 1.99 = -3.77$$



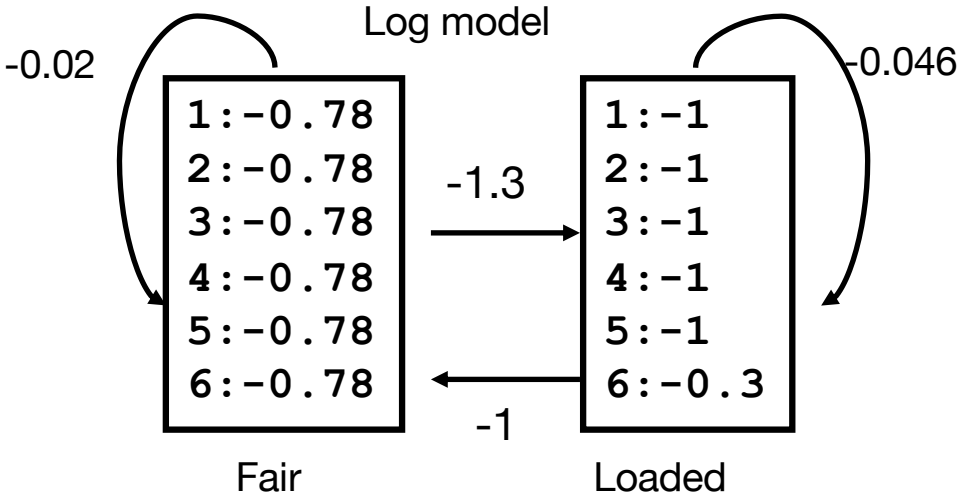
	5	6	6	6	1	1	2	3	4
F	-1.08	-1.88	-2.68						
L	-1.30	-1.65	-1.99						

Model decoding (Viterbi)

- Example: 566611234. What was the most likely series of dice used to generate this output?

$$-0.78 - 0.02 - 2.68 = -3.48$$

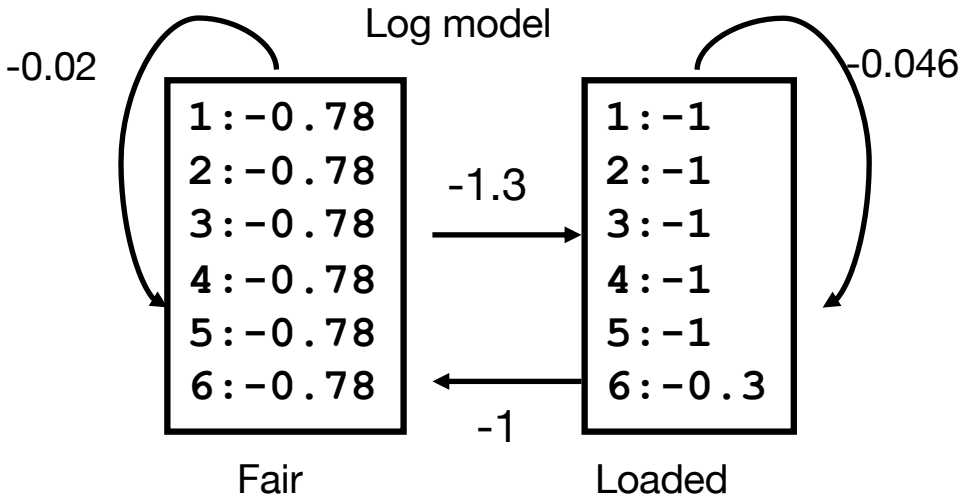
$$-0.78 - 1 - 1.99 = -3.77$$



	5	6	6	6	1	1	2	3	4
F	-1.08	-1.88	-2.68	-3.48					
L	-1.30	-1.65	-1.99						

Model decoding (Viterbi)

- Now we can formalize the algorithm!



$$P_l(i+1) = p_l(i+1) \bullet \max_k(P_k(i) \bullet a_{kl}) \quad or$$

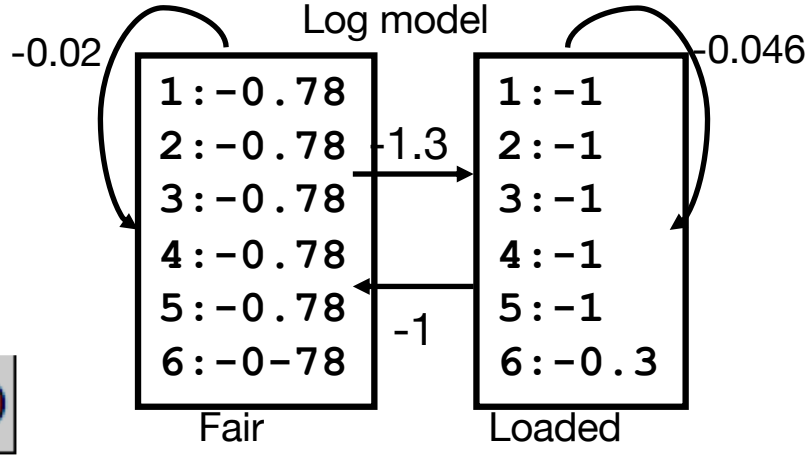
$$\log(P_l(i+1) = \log(p_l(i+1)) + \max_k(\log(P_k(i) + \log(a_{kl}))$$

New match Old max score Transition

Model decoding (Viterbi). Can you do it?

- Example: 566611234. What was the mots likely series of dice used to generate this output?
- Fill out the table using the Viterbi recursive algorithm
  - Add the arrows for backtracking
- Find the optimal path

$$\log(P_l(i+1) = \log(p_l(i+1)) + \max_k(\log(P_k(i) + \log(a_{kl}))$$



	5	6	6	6	1	1	2	3	4
F	-1.08	-1.88	-2.68	-3.48					
L	-1.30	-1.65	-1.99						

Model decoding (Viterbi). Can you do it?

- Example: 566611234. What was the mots likely series of dice used to generate this output?
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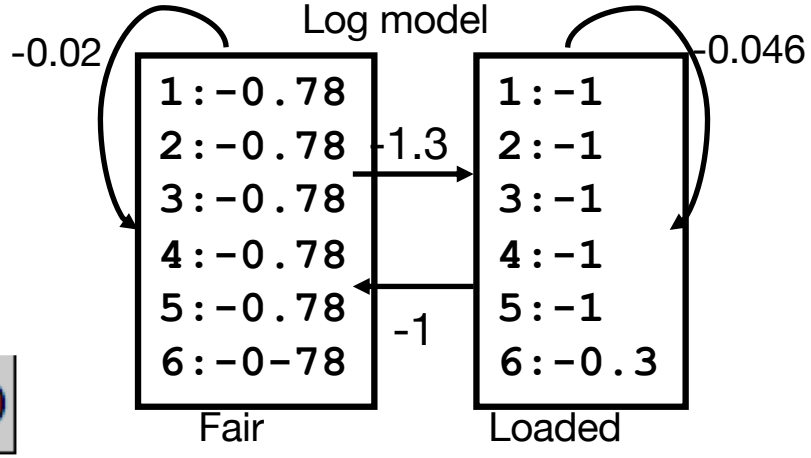


$$\log(P_l(i+1) = \log(p_l(i+1)) + \max_k(\log(P_k(i) + \log(a_{kl}))$$

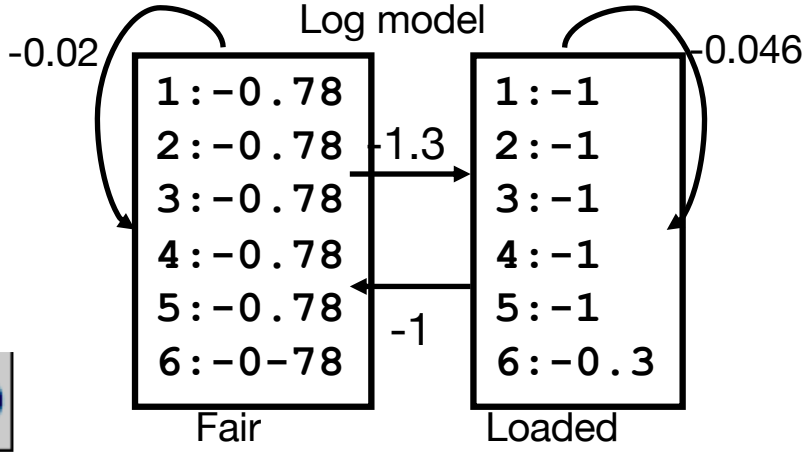
-0.78 + max((-2.68 – 0.02, -1.99 – 1)

	5	6	6	6	1	1	2	3	4
F	-1.08	-1.88	-2.68	-3.48					
L	-1.30	-1.65	-1.99						

Model decoding (Viterbi). Can you do it?

- Example: 566611234. What was the most likely series of dice used to generate this output?
- Fill out the table using the Viterbi recursive algorithm
  - Add the arrows for backtracking
- Find the optimal path

$$\log(P_l(i+1) = \log(p_l(i+1)) + \max_k(\log(P_k(i) + \log(a_{kl}))$$



	5	6	6	6	1	1	2	3	4
F	-1.08	-1.88	-2.68	-3.48		-4.92		-6.53	
L	-1.30	-1.65	-1.99		-3.39			-6.52	

Model decoding (Viterbi). Can you do it?

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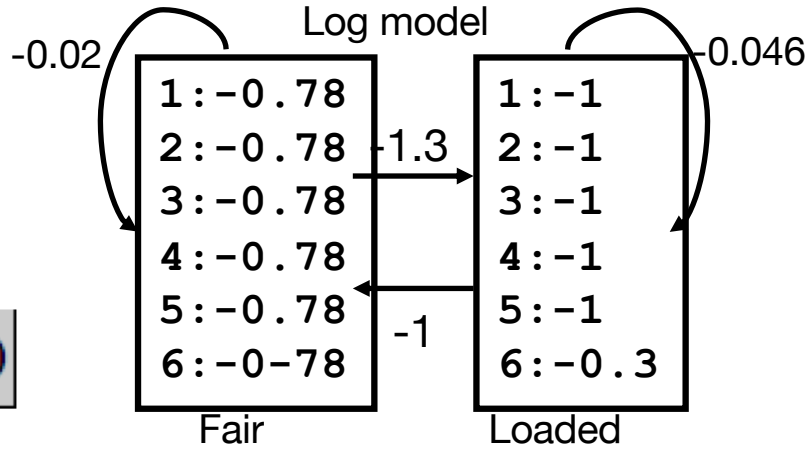
- Example: 566611234. What was the most lilely series of dice used to generate this output?
- Fill out the table using the Viterbi recursive algorithm
  - Add the arrows for backtracking
- Find the optimal path

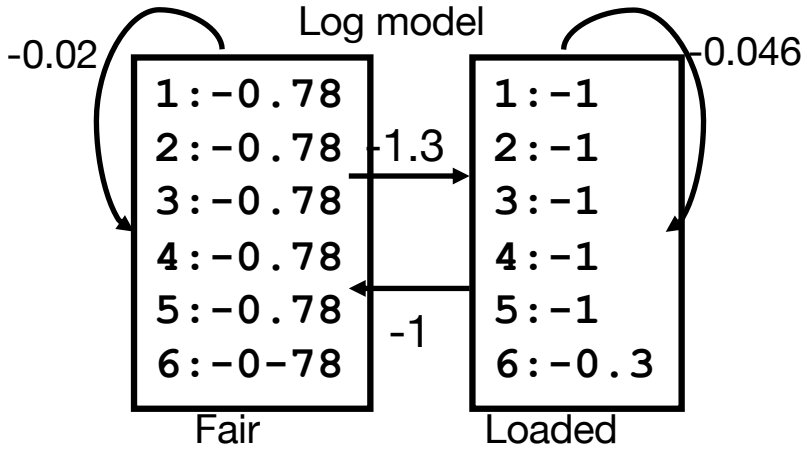
$$\log(P_l(i+1) = \log(p_l(i+1)) + \max_k(\log(P_k(i) + \log(a_{kl}))$$



	5	6	6	6	1	1	2	3	4
F	-1.08	-1.88	-2.68	-3.48	-4.12	-4.92	5.73	-6.53	-7.33
L	-1.30	-1.65	-1.99	-2.34	-3.39	-4.44	-5.48	-6.52	-7.57

Model decoding (Viterbi). Can you do it?

- Example: 566611234. What was the most likely series of dice used to generate this output?
- The most likely path is
  - LLLLFFFFF



	5	6	6	6	1	1	2	3	4
F	-1.08	-1.88	-2.68	-3.48	-4.12	-4.92	5.73	-6.53	-7.33
L	-1.30	-1.65	-1.99	-2.34	-3.39	-4.32	-5.48	-6.52	-7.57

Model decoding (Viterbi).

- What happens if you have three dice?

	5	6	6	6	1	1	2	3	4
F	-1.0								
L1	-1.2								
L2	-1.3								

$$\log(P_l(i+1) = \log(p_l(i+1)) + \max_k(\log(P_k(i) + \log(a_{kl}))$$

And if you have a trans-membrane model

- What is the most likely path (alignment) of a protein sequence to the model

	D	G	V	L	I	M	A	D	Q
iC	-1.0								
M	-1.2								
xC	-1.3								

$$\log(P_l(i+1) = \log(p_l(i+1)) + \max_k(\log(P_k(i) + \log(a_{kl}))$$

HMM's and weight matrices

- In the case of un-gapped alignments HMM's become simple weight matrices
- To achieve high performance, the emission frequencies are estimated using the techniques of
  - Sequence weighting
  - Pseudo counts

Profile HMM's

- Alignments based on conventional scoring matrices (BLOSUM62) scores all positions in a sequence in an equal manner
- Some positions are highly conserved, some are highly variable (more than what is described in the BLOSUM matrix)
- Profile HMM's are ideal suited to describe such position specific variations

Sequence profiles

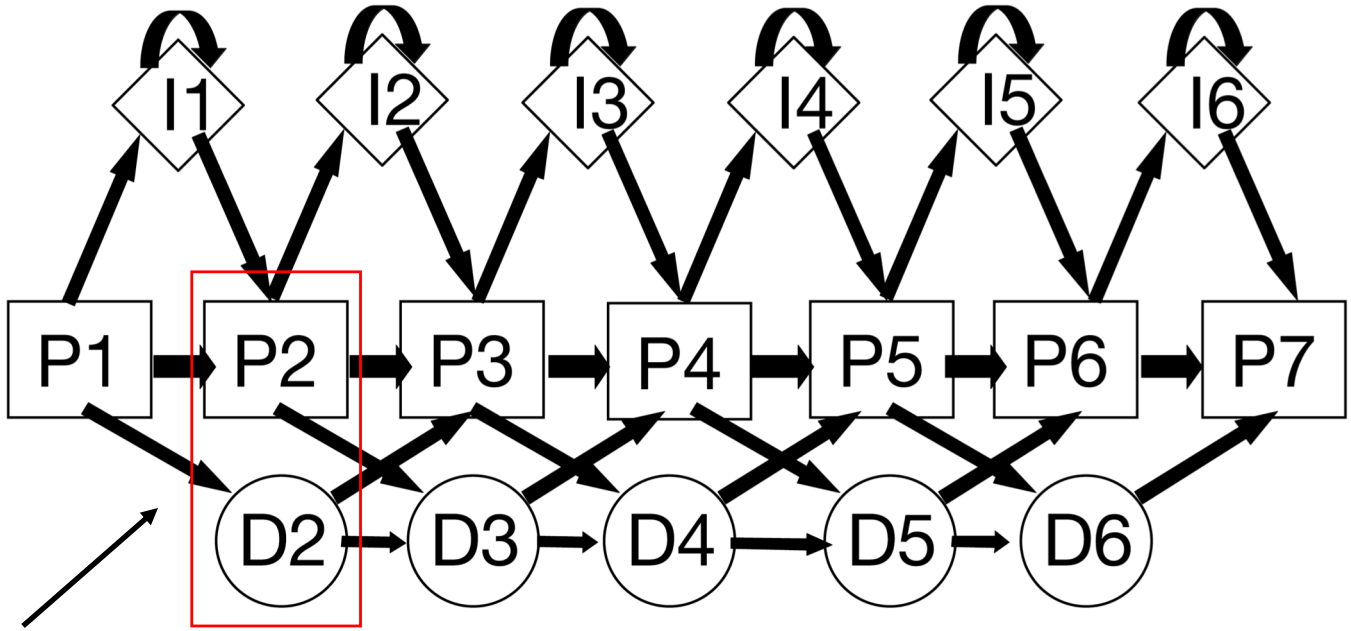
Matching any thing
but G => large
negative score

Any thing can match

HMM vs. alignment

- Detailed description of core
  - Conserved/variable positions
- Price for insertions/deletions varies at different locations in sequence
- These features cannot be captured in conventional alignments

Profile HMM's



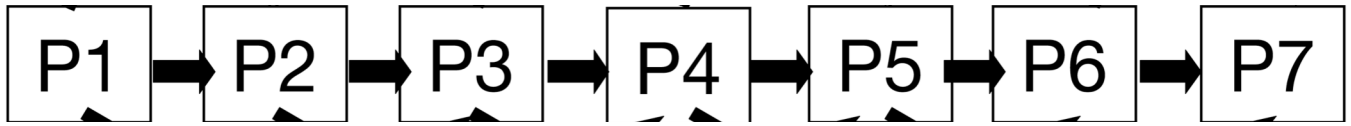
All P/D pairs must be visited once

$L_1 - Y_2A_3V_4R_5 - I_6$

$P_1D_2P_3P_4I_4P_5D_6P_7$

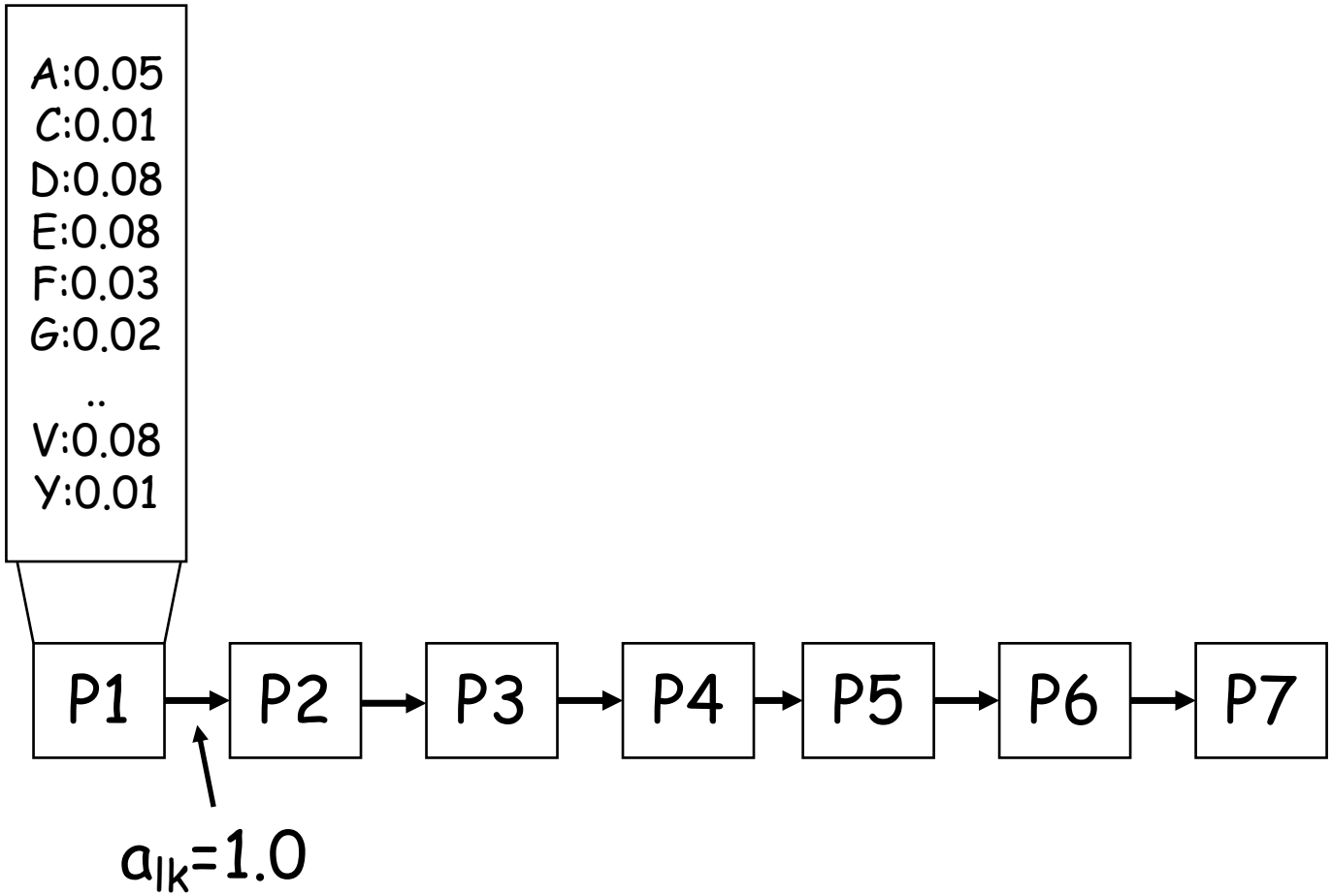
Profile HMM

- Un-gapped profile HMM is just a sequence profile



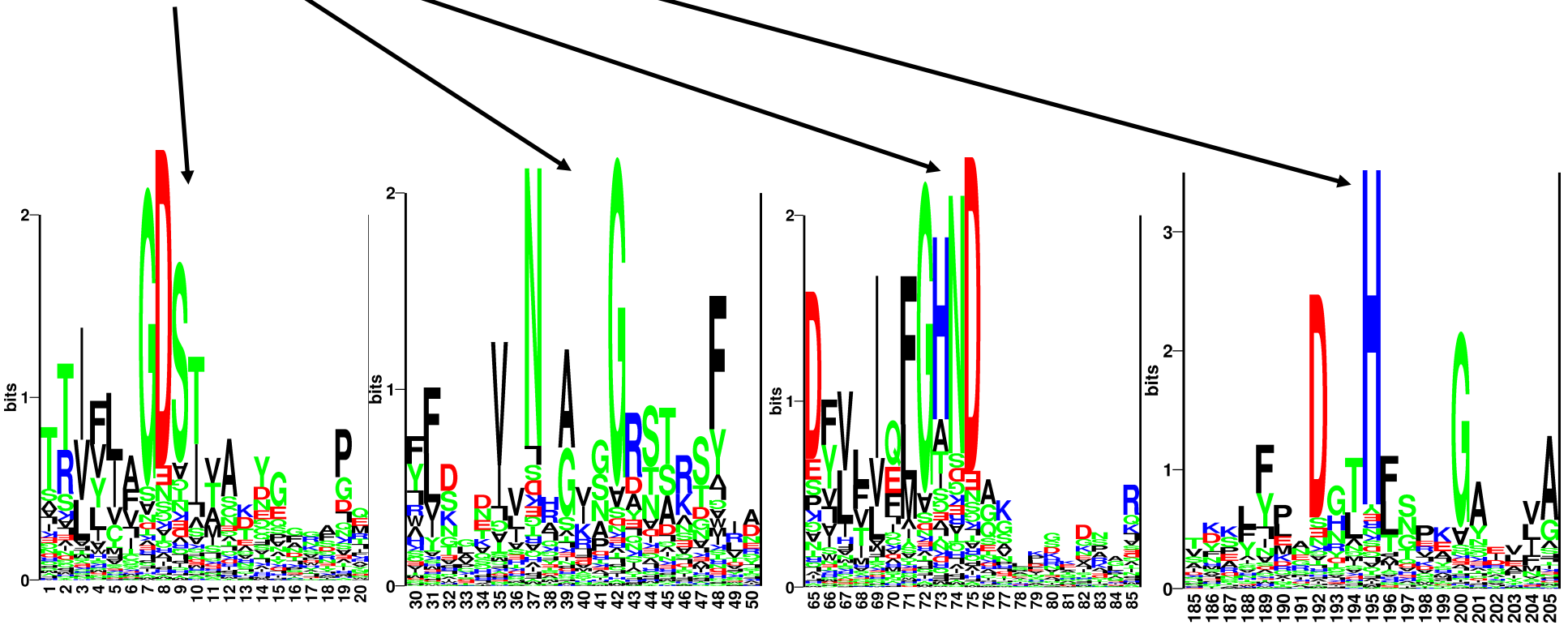
Profile HMM

- Un-gapped profile HMM is just a sequence profile



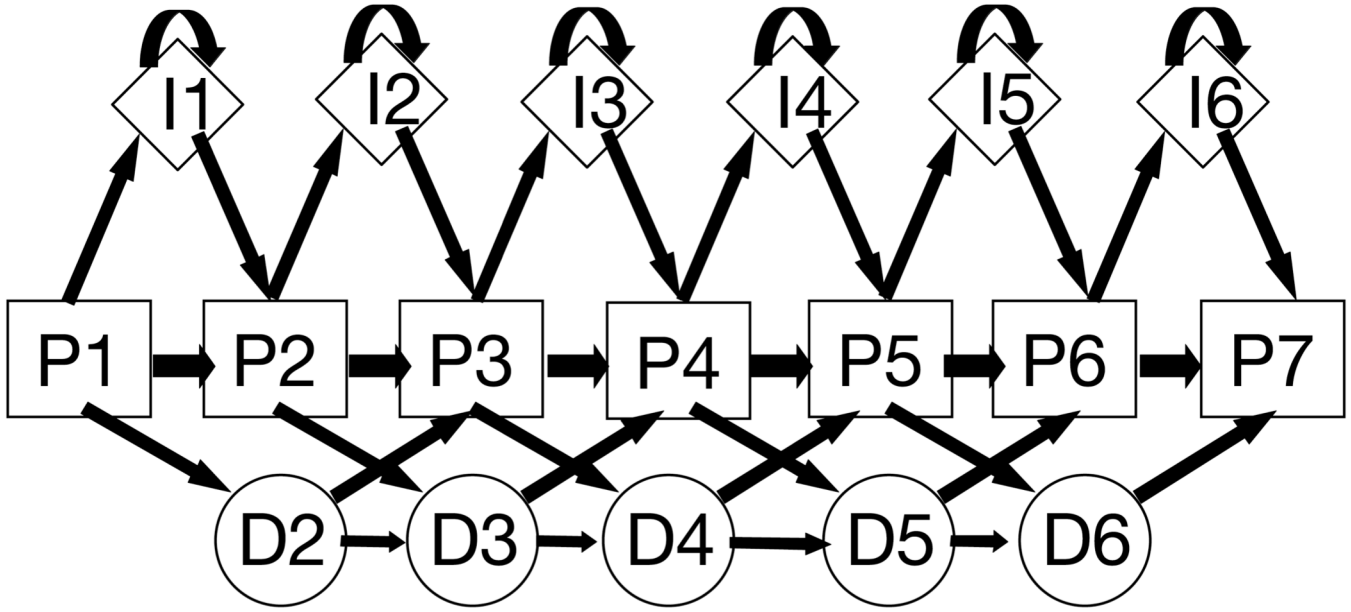
Example. Where is the active site?

- Sequence profiles might show you where to look!
- The active site could be around
  - S9, G42, N74, and H195



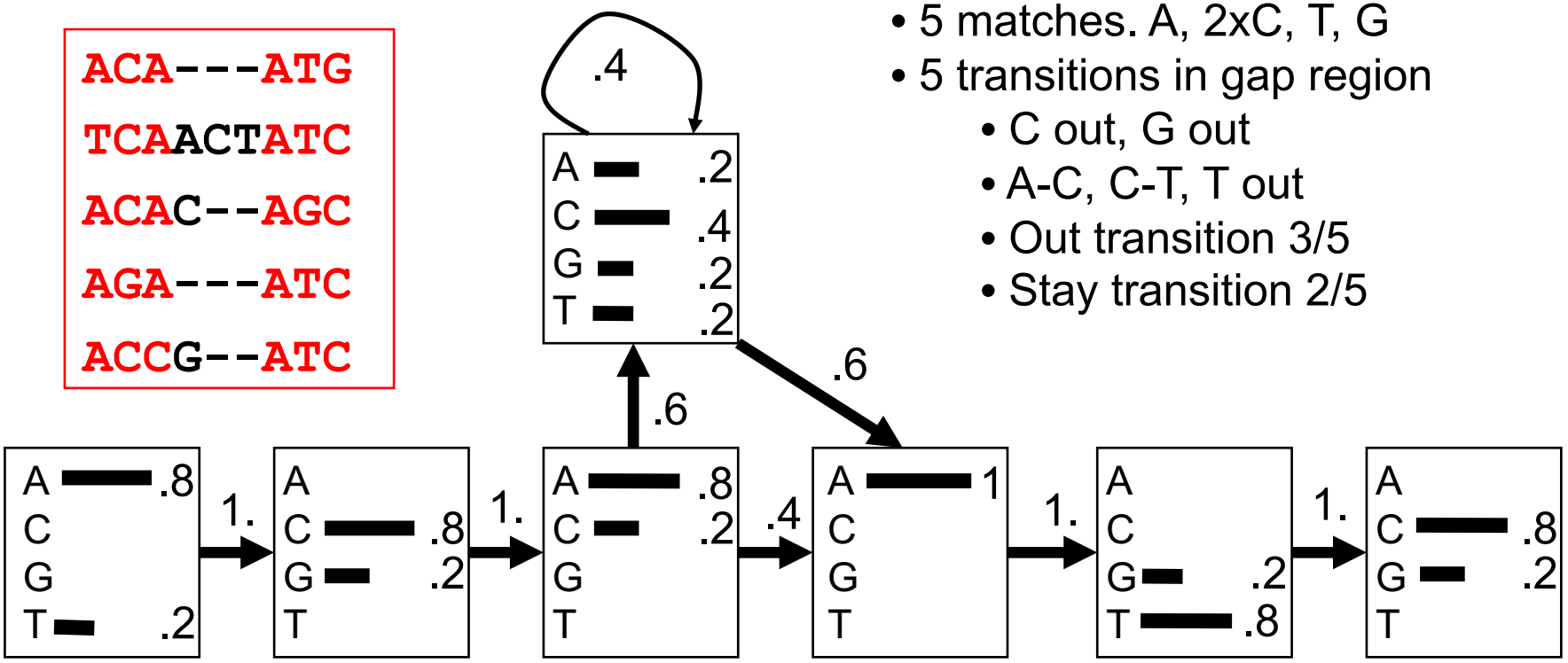
Profile HMM

- Profile HMM (deletions and insertions)



Profile HMM (deletions and insertions)

HMM construction (supervised learning)



- 5 matches. A, 2xC, T, G
- 5 transitions in gap region
  - C out, G out
  - A-C, C-T, T out
  - Out transition 3/5
  - Stay transition 2/5

ACA---ATG 0.8x1x0.8x1x0.8x0.4x1x1x0.8x1x0.2 = 3.3×10^{-2}

The HMMer program

- HMMer is a open source program suite for profile HMM for biological sequence analysis
- Used to make the Pfam database of protein families
  - http://pfam.sanger.ac.uk/

A HMMer example

- Example from the CASP8 competition
- What is the best PDB template for building a model for the sequence T0391

```
>T0391 rieske ferredoxin, mouse, 157 residues
SDPEISEQDEEKKKYTSVCVGREEDIRKSERMTAVVHDREVVIFYHKGEYHAMDIRCYHS
GGPLHLGEIEDFNGQSCIVCPWHKYKITLATGEGLYQSINPKDPSAKPKWCSKGVKQRIH
TVKVDNGNIYVTLSKEPFKCDSDYYATGEFKVIQSSS
```

A HMMer example

- What is the best PDB template for building a model for the sequence T0391
- Use Blast
  - No hits
- Use Psi-Blast
  - No hits
- Use Hmmer

A HMMer example

- Use Hmmer
  - Make multiple alignment using Blast
  - Make model using
    - hmmbuild
    - hmmcalibrate
  - Find PDB template using
    - hmmsearch

A HMMer example

- Make multiple alignment using Blast

  blastpgp -j 3 -e 0.001 -m 6 -i T0391.fsa -d sp -b 10000000 -v 10000000 > T0391.fsa.blastout

- Make Stockholm format

```
# STOCKHOLM 1.0
QUERY DPEISEQDEEKKKYTSVCVGREEDIRKS-ERMTAVVHD-RE--V-V-IF--Y-H-KGE-Y
Q8K2P6 DPEISEQDEEKKKYTSVCVGREEDIRKS-ERMTAVVHD-RE--V-V-IF--Y-H-KGE-Y
Q8TAC1 ----SAQDPEKREYSSVCVGREDDIKKS-ERMTAVVHD-RE--V-V-IF--Y-H-KGE-Y
```

- Build HMM

  hmmbuild T0391.hmm T0391.fsa.blastout.sto

- (Calibrate HMM (to estimate correct p-values)

  hmmcalibrate T0391.hmm) In older version of HMMER

- Search for templates in PDB

  hmmsearch T0391.hmm pdb > T0391.out

A HMMer example

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Sequence	Description	Score	E-value	N
2E4Q.A	mol:aa ELECTRON TRANSPORT	163.7	6.7e-45	1
2E4P.B	mol:aa ELECTRON TRANSPORT	163.7	6.7e-45	1
2E4P.A	mol:aa ELECTRON TRANSPORT	163.7	6.7e-45	1
2E4Q.C	mol:aa ELECTRON TRANSPORT	163.7	6.7e-45	1
2YVJ.B	mol:aa OXIDOREDUCTASE/ELECTRON TRANSPORT	163.7	6.7e-45	1
1FQT.A	mol:aa OXIDOREDUCTASE	160.9	4.5e-44	1
1FQT.B	mol:aa OXIDOREDUCTASE	160.9	4.5e-44	1
2QPZ.A	mol:aa METAL BINDING PROTEIN	137.3	5.6e-37	1
2Q3W.A	mol:aa ELECTRON TRANSPORT	116.2	1.3e-30	1
1VM9.A	mol:aa ELECTRON TRANSPORT	116.2	1.3e-30	1

Validation. CE structural alignment

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```
CE 2E4Q A 3D89 A (run on IRIX machines at CBS)

Structure Alignment Calculator, version 1.01, last modified: May 25,
   2000.

CE Algorithm, version 1.00, 1998.

Chain 1: /usr/cbs/bio/src/ce_distr/data.cbs/pdb2e4q.ent:A (Size=109)
Chain 2: /usr/cbs/bio/src/ce_distr/data.cbs/pdb3d89.ent:A (Size=157)

Alignment length = 101 Rmsd = 2.03A Z-Score = 5.5 Gaps = 20(19.8%)
   CPU = 1s Sequence identities = 18.1%

Chain 1:    2 TFTKACSVDEVPPGEALQVSHDAQKVAIFNVDGEFFATQDQCTHGEWSLSEGGYLDG----DVVECSLHM
Chain 2:   16 TSVCVGREEDIRKSERMTAVVHDREVVIFYHKGEYHAMDIRCYHSGGPLH-LGEIEDFNGQSCIVCPWHK

Chain 1:   68 GKFCVRTGKVKS-----PPPC---------EPLKVYPIRIEGRDVLVDFSRAALH
Chain 2:   85 YKITLATGEGLYQSINPKDPSAKPKWCSKGVKQRIHTVKVDNGNIYVTL-SKEPF
```

HMM packages

- HMMER (http://hmmer.wustl.edu/)
  - S.R. Eddy, WashU St. Louis. Freely available.
- SAM (http://www.cse.ucsc.edu/research/compbio/sam.html)
  - R. Hughey, K. Karplus, A. Krogh, D. Haussler and others, UC Santa Cruz. Freely available to academia, nominal license fee for commercial users.
- META-MEME (http://metameme.sdsc.edu/)
  - William Noble Grundy, UC San Diego. Freely available. Combines features of PSSM search and profile HMM search.
- NET-ID, HMMpro (http://www.netid.com/html/hmmpro.html)
  - Freely available to academia, nominal license fee for commercial users.
  - Allows HMM architecture construction.

- EasyGibbs (http://www.cbs.dtu.dk/biotools/EasyGibbs/)
  - Webserver for Gibbs sampling of proteins sequences