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AACCCTAACCCTAACCCTAACCCCTAACCCTA
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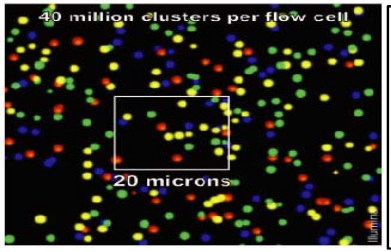

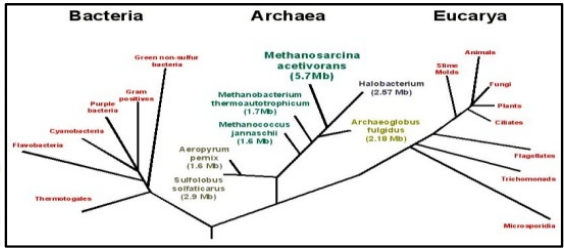

Markov Model

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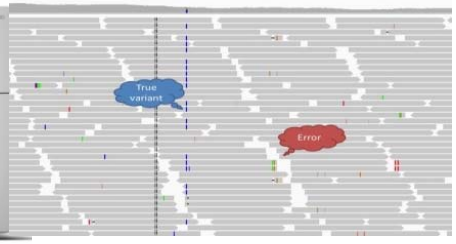

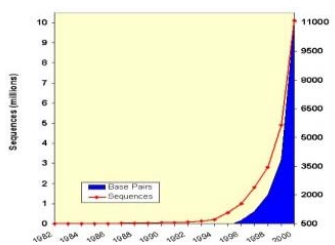

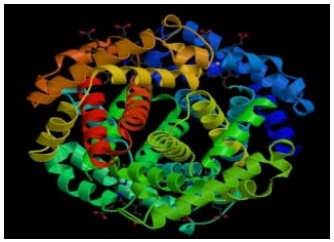

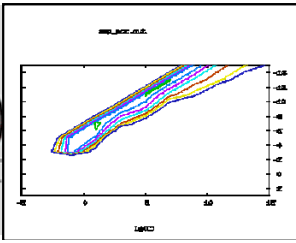

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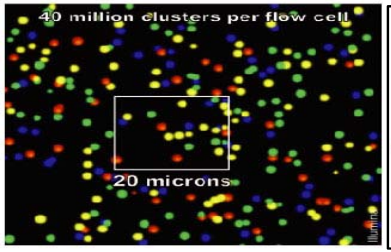

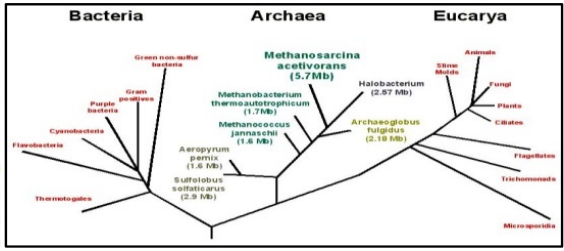

Unit 2:
Hidden Markov Model

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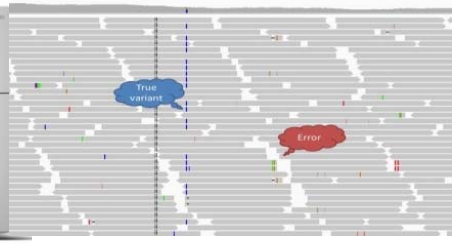
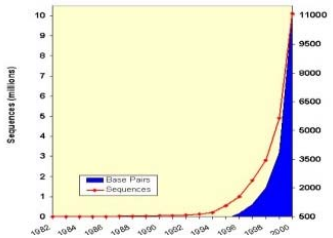
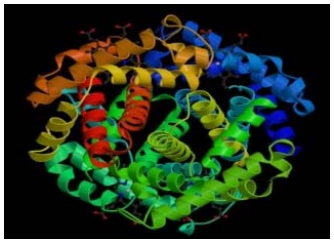
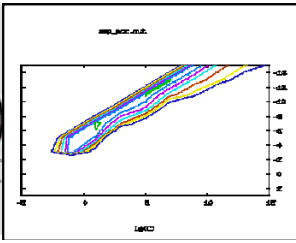


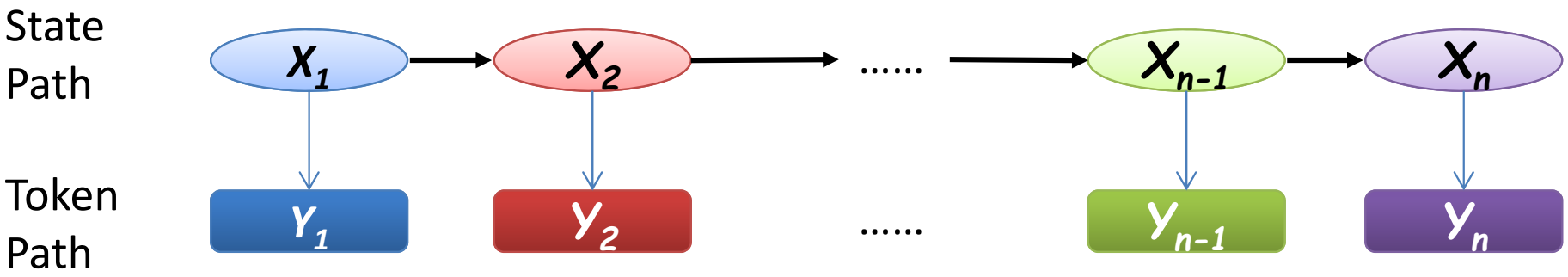






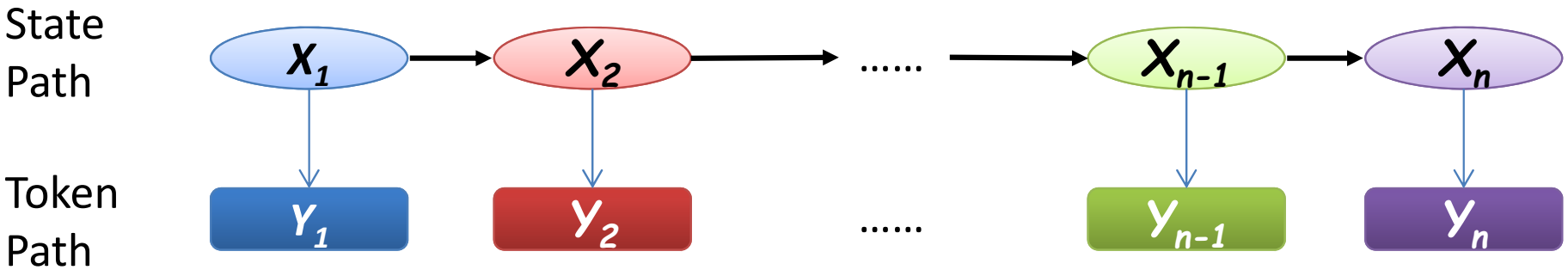
Hidden Markov Model

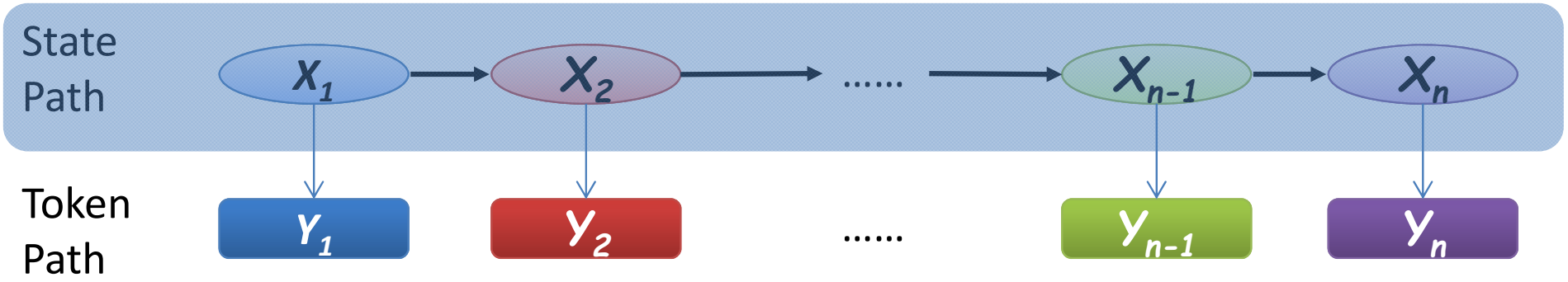
The observable symbols ("tokens", y(t)) are generated according to their corresponding states (x(t)).



Hidden Markov Model (HMM)

- In addition to State Transition Probability, each state of HMM has a probability distribution over the possible output tokens (Emission Probability).
- Thus, a HMM is consist of two strings of information.
  - The state path
  - The token path (emitted sequence).

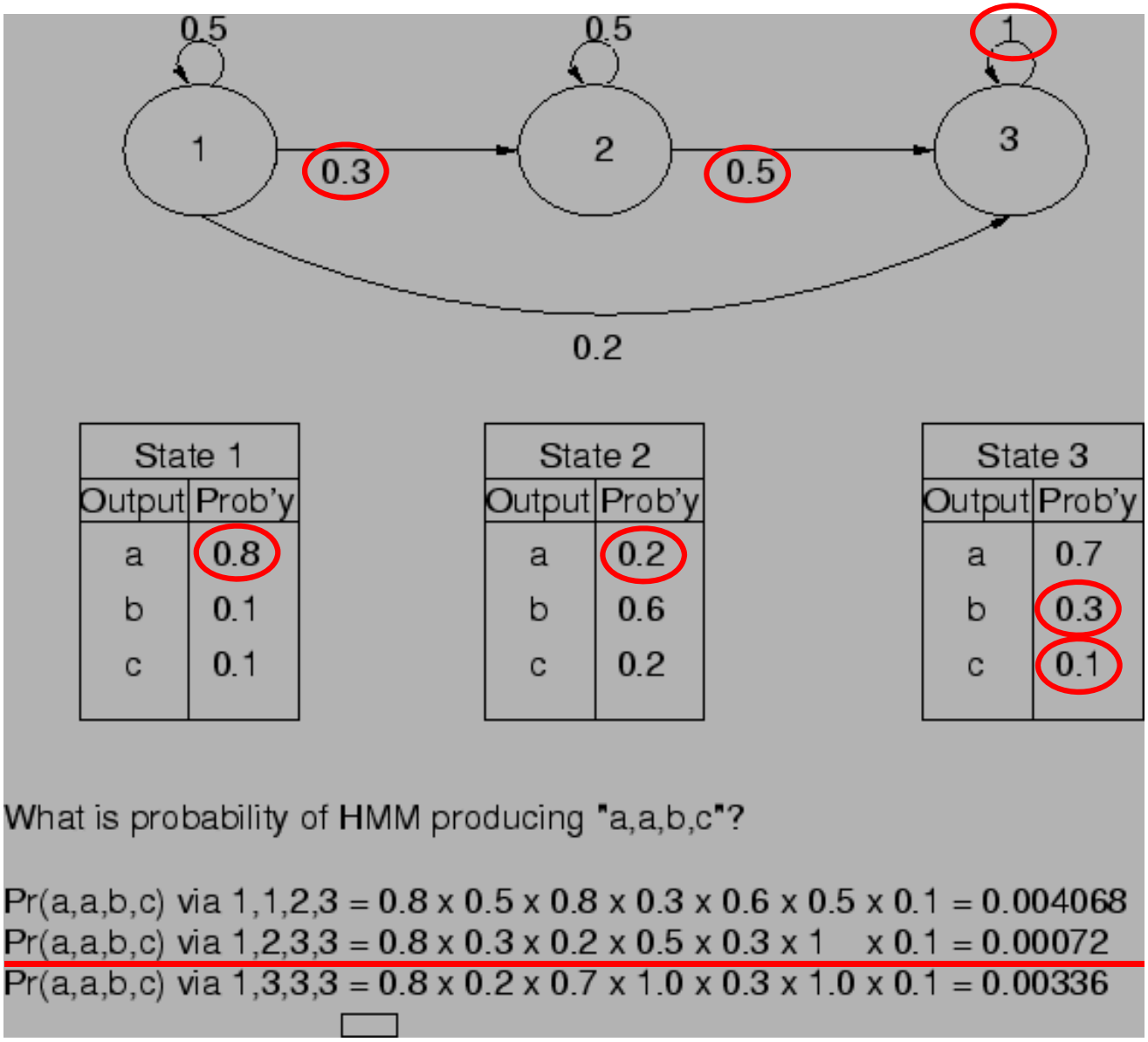




- But the state path is not directly visible
- Instead, we have to infer the underling state path, based on the observable token path.

Transition Probability

Emission Probability



(Figure source: http://www.cse.unsw.edu.au/~waleed/phd/html/node34.html)

Given a HMM, a sequence of tokens could be generated as following:

- When we “visit” a state, we emit a token from the state's emission probability distribution.
- Then, we choose which state to visit next, according to the state's transition probability distribution.

Transition Probability

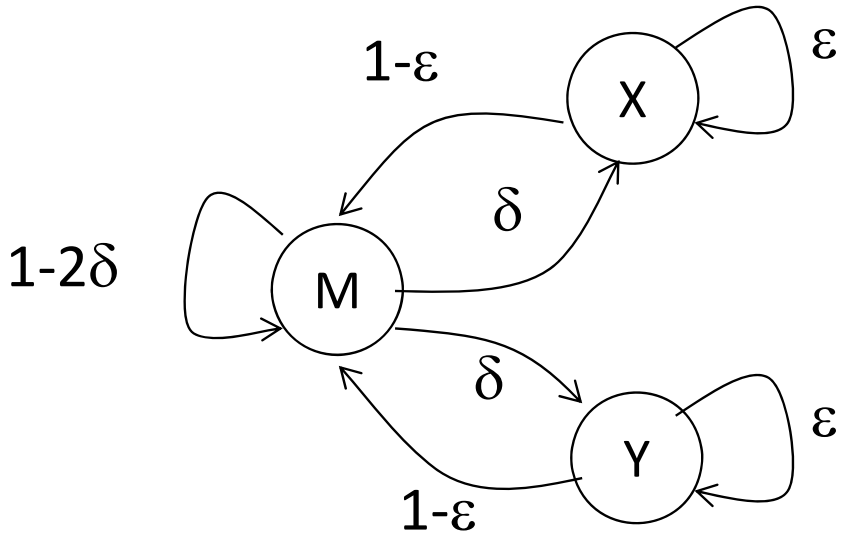
$$a_{kl} = P(x_t = S_l \mid x_{t-1} = S_k)$$

Emission Probability

$$e_k(b) = P(y_i = b \mid x_i = S_k)$$

$$P(X, Y) = \prod_{i=1}^{L} (e_{x_i}(y_i) * a_{x_i x_{i+1}})$$

M	*Match (**not necessarily identical**)*
X	*Insert* at sequence X (delete at sequence Y)
Y	*Insert* at sequence Y (delete at sequence X)

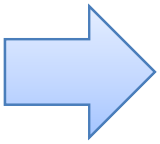


δ	Gap open
ε	Gap Extension

Transition Probability

	M	X	Y
M	1-2δ	δ	δ
X	1-ε	ε	0
Y	1-ε	0	0

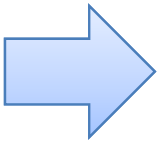
	SS	SC	ST	SP	…	WW
Match						



S
T

p_{ab}

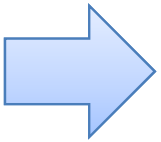
	C	S	…	W
X insertion				



S
-

q_a

	C	S	…	W
Y insertion				



-
T

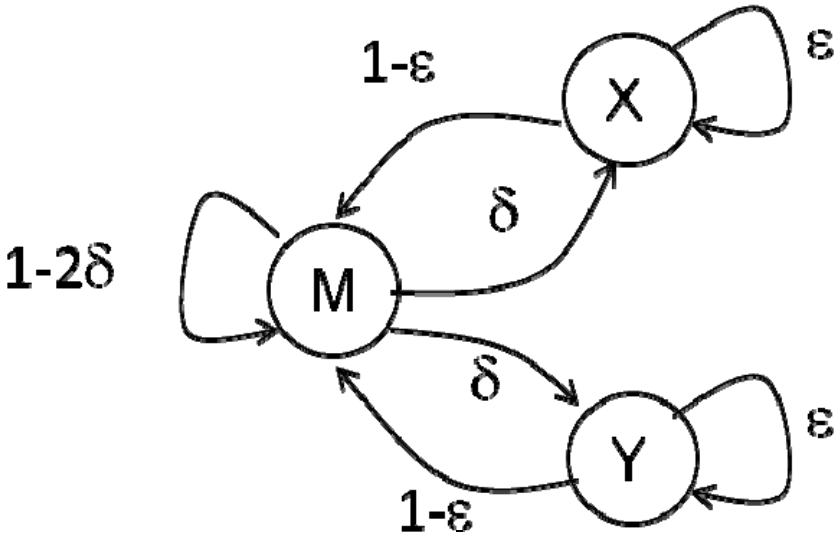
q_a

Sequence alignment with HMM

- Each "token" of the HMM is an aligned pair of two residues (M state), or of a residue and a gap (X or Y state).
  - Transition and emission probabilities define the probability of each aligned pair of sequences.

- Based on the HMM, each alignment of two sequences can be assigned with a probability
  - Given two input sequences, we look for an alignment with the maximum probability.

$$\arg\max_{ali}(P(S1, S2, ali))$$



- P_M (i,j) is the probability of the best alignment between $x_{1...i}$ and $y_{1...j}$, given ***x*$_i$ aligned to *y*$_j$**
- P_X (i,j) is the probability of the best alignment between $x_{1...i}$ and $y_{1...j}$, given ***x*$_i$ aligned to *a gap***
- P_Y (i,j) is the probability of the best alignment between $x_{1...i}$ and $y_{1...j}$, given ***y*$_j$ aligned to *a gap***

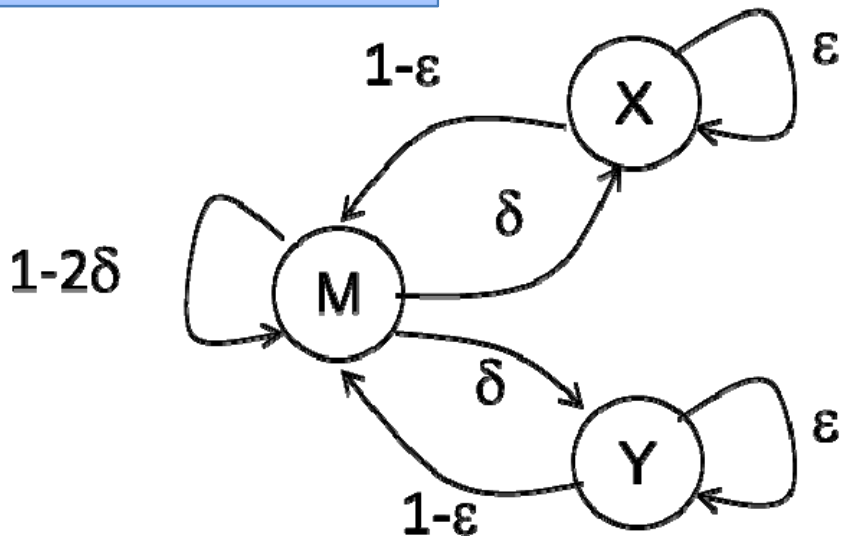
$$P_M(i,j) = p_{x_i y_j} \max \begin{pmatrix} (1-2\delta)P_M(i-1,j-1) \\ (1-\varepsilon)P_X(i-1,j-1) \\ (1-\varepsilon)P_Y(i-1,j-1) \end{pmatrix}$$

$$P_X(i,j) = q_{x_i} \max \begin{pmatrix} \delta P_M(i-1,j) \\ \varepsilon P_X(i-1,j) \end{pmatrix}$$

$$P_Y(i,j) = q_{y_j} \max \begin{pmatrix} \delta P_M(i,j-1) \\ \varepsilon P_Y(i,j-1) \end{pmatrix}$$

$$P(X,Y,ali) = \max(P_M(n,m), P_X(n,m), P_Y(n,m))$$

Transition Probability



	M	X	Y
M	1-2δ	δ	δ
X	1-ε	ε	0
Y	1-ε	0	0

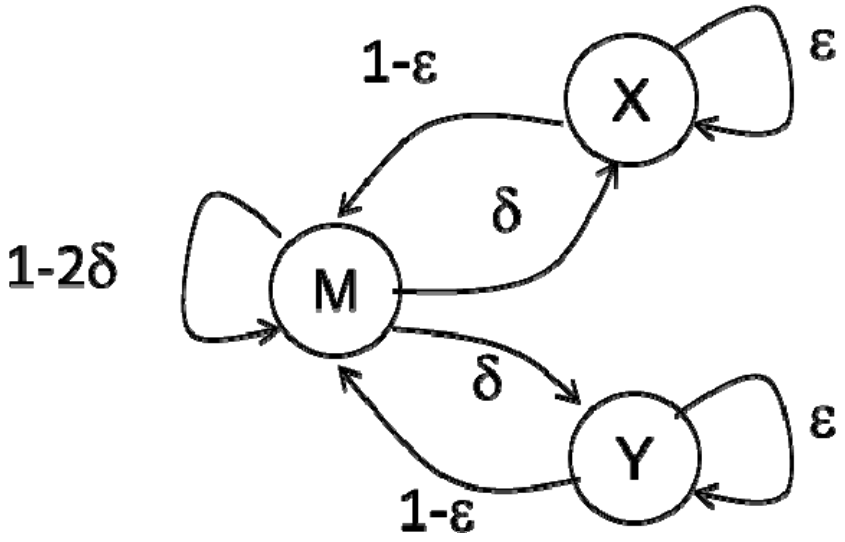
Emission Probability

	SS	SC	ST	SP	…	WW
Match						

	C	S	…	W
X insertion				

	C	S	…	W
Y insertion				

Probabilistic interpretation



	SS	SC	ST	SP	…	WW
Match						

ORIGINAL AMINO ACID

REPLACEMENT AMINO ACID	A Ala	R Arg	N Asn	D Asp	C Cys	Q Gln	E Glu	G Gly	H His	I Ile	L Leu	K Lys	M Met	F Phe	P Pro	S Ser	T Thr	W Trp	Y Tyr	V Val
A Ala	9867	2	9	10	3	8	17	21	2	6	4	2	6	2	22	35	32	0	2	18
R Arg	1	9913	1	0	1	10	0	0	10	3	1	19	4	1	4	6	1	8	0	1
N Asn	4	1	9822	36	0	4	6	6	21	3	1	13	0	1	2	20	9	1	4	1
D Asp	6	0	42	9859	0	6	53	6	4	1	0	3	0	0	1	5	3	0	0	1
C Cys	1	1	0	0	9973	0	0	0	1	1	0	0	0	0	1	5	1	0	3	2
Q Gln	3	9	4	5	0	9876	27	1	23	1	3	6	4	0	6	2	2	0	0	1
E Glu	10	0	7	56	0	35	9865	4	2	3	1	4	1	0	3	4	2	0	1	2
G Gly	21	1	12	11	1	3	7	9935	1	0	1	2	1	1	3	21	3	0	0	5
H His	1	8	18	3	1	20	1	0	9912	0	1	1	0	2	3	1	1	1	4	1
I Ile	2	2	3	1	2	1	2	0	0	9872	9	2	12	7	0	1	7	0	1	33
L Leu	3	1	3	0	0	6	1	1	4	22	9947	2	45	13	3	1	3	4	2	15
K Lys	2	37	25	6	0	12	7	2	2	4	1	9926	20	0	3	8	11	0	1	1
M Met	1	1	0	0	0	2	0	0	0	5	8	4	9874	1	0	1	2	0	0	4
F Phe	1	1	1	0	0	0	0	1	2	8	6	0	4	9946	0	2	1	3	28	0
P Pro	13	5	2	1	1	8	3	2	5	1	2	2	1	1	9926	12	4	0	0	2
S Ser	28	11	34	7	11	4	6	16	2	2	1	7	4	3	17	9840	38	5	2	2
T Thr	22	2	13	4	1	3	2	2	1	11	2	8	6	1	5	32	9871	0	2	9
W Trp	0	2	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	9976	1	0
Y Tyr	1	0	3	0	3	0	1	0	4	1	1	0	0	21	0	1	1	2	9945	
V Val	13	2	1	1	3	2	2	3	3	57	11	1	17	1	3	2	10	0	[illegible]	9901

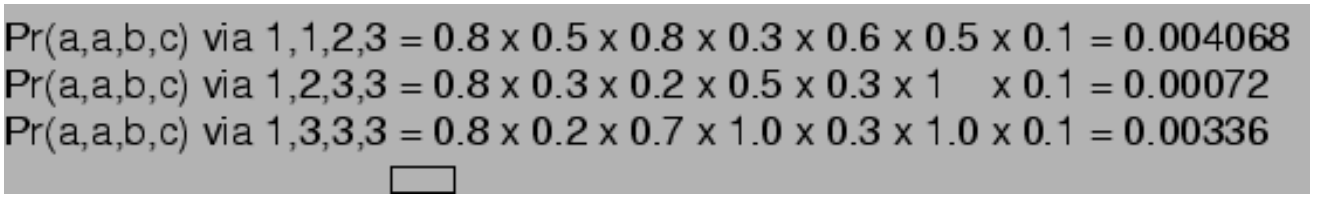
(Dayhoff 1978)

Probabilistic inference

For example, to calculate the probability that a given pair of sequences are related by *any* (unspecified) alignment

- Or, what's the best likelihood we can expect for given two sequences?

Given the nature of HMM, many different state paths can give rise to the same token sequence



(Figure source: http://www.cse.unsw.edu.au/~waleed/phd/html/node34.html)

So we can simply sum up them together to get the ***full probability of a given token sequence***

$$P(X,Y) = \sum_{ali} P(X,Y,ali)$$

$$P_M(i,j) = p_{x_i y_j} \max \begin{pmatrix} (1-2\delta)P_M(i-1,j-1) \\ (1-\varepsilon)P_X(i-1,j-1) \\ (1-\varepsilon)P_Y(i-1,j-1) \end{pmatrix}$$

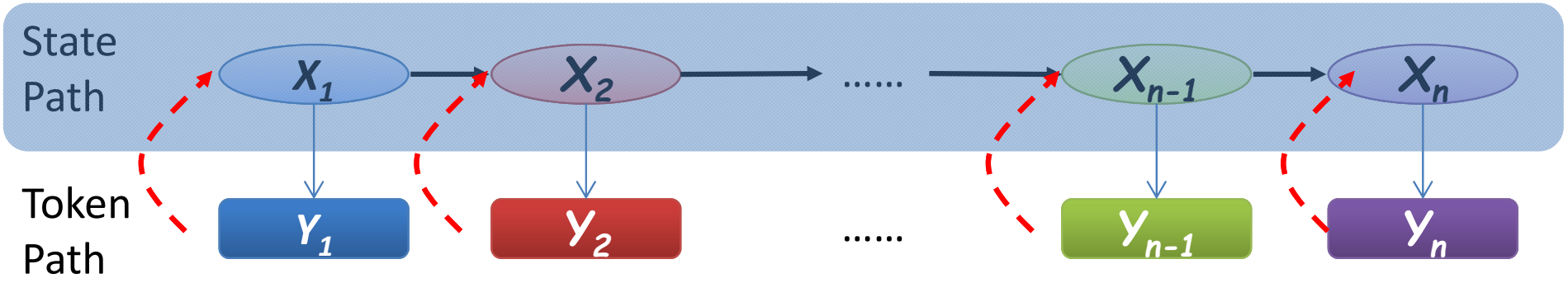
$$P_X(i,j) = q_{x_i} \max \begin{pmatrix} \delta P_M(i-1,j) \\ \varepsilon P_X(i-1,j) \end{pmatrix}$$

$$P_Y(i,j) = q_{y_j} \max \begin{pmatrix} \delta P_M(i,j-1) \\ \varepsilon P_Y(i,j-1) \end{pmatrix}$$

$$\Rightarrow \begin{cases} P_M(i,j) = p_{x_i y_j} \times [(1-2\delta)P_M(i-1,j-1) \\ \quad + (1-\varepsilon)P_X(i-1,j-1) \\ \quad + (1-\varepsilon)P_Y(i-1,j-1)] \\ P_X(i,j) = q_{x_i} \times [\delta P_M(i-1,j) \\ \quad + \varepsilon P_X(i-1,j)] \\ P_Y(i,j) = q_{y_j} \times [\delta P_M(i,j-1) \\ \quad + \varepsilon P_Y(i,j-1)] \end{cases}$$

$$P(X,Y,ali) = \max(P_M(n,m), P_X(n,m), P_Y(n,m))$$

$$\Rightarrow P(X,Y) = P_M(n,m) + P_X(n,m) + P_Y(n,m)$$



Hidden Markov Model: as a predictor

Summary Questions

- Could you name a few Markov Chain and Hidden Markov Model?

- Did we construct the global alignment or local alignment in this Unit? Explain.

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