Hidden Markov Models

Laboratory of Bioinformatics I
Module 2

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Formal Definition

A HMM is a stochastic generator of sequences characterized by:

- *N* states
- A set of transition probabilities between two states $\{a_{kj}\}$

  $a_{kj} = P(\pi(i) = j \mid \pi(i-1) = k)$
- A set of starting probabilities $\{a_{0k}\}$

  $a_{0k} = P(\pi(1) = k)$
- A set of ending probabilities $\{a_{k0}\}$

  $a_{k0} = P(\pi(i) = \mathrm{END} \mid \pi(i-1) = k)$
- An alphabet ***C*** with *M* characters.
- A set of emission probabilities for each state $\{e_k(c)\}$

  $e_k(c) = P(s^i = c \mid \pi(i) = k)$
- Constraints:

$$\Sigma_k \; a_{0k} = 1$$

$$a_{k0} + \Sigma_j \; a_{kj} = 1 \qquad \forall k$$

$$\Sigma_{c \in C} \; e_k(c) = 1 \qquad \forall k$$

s: sequence, **π**: path through the states

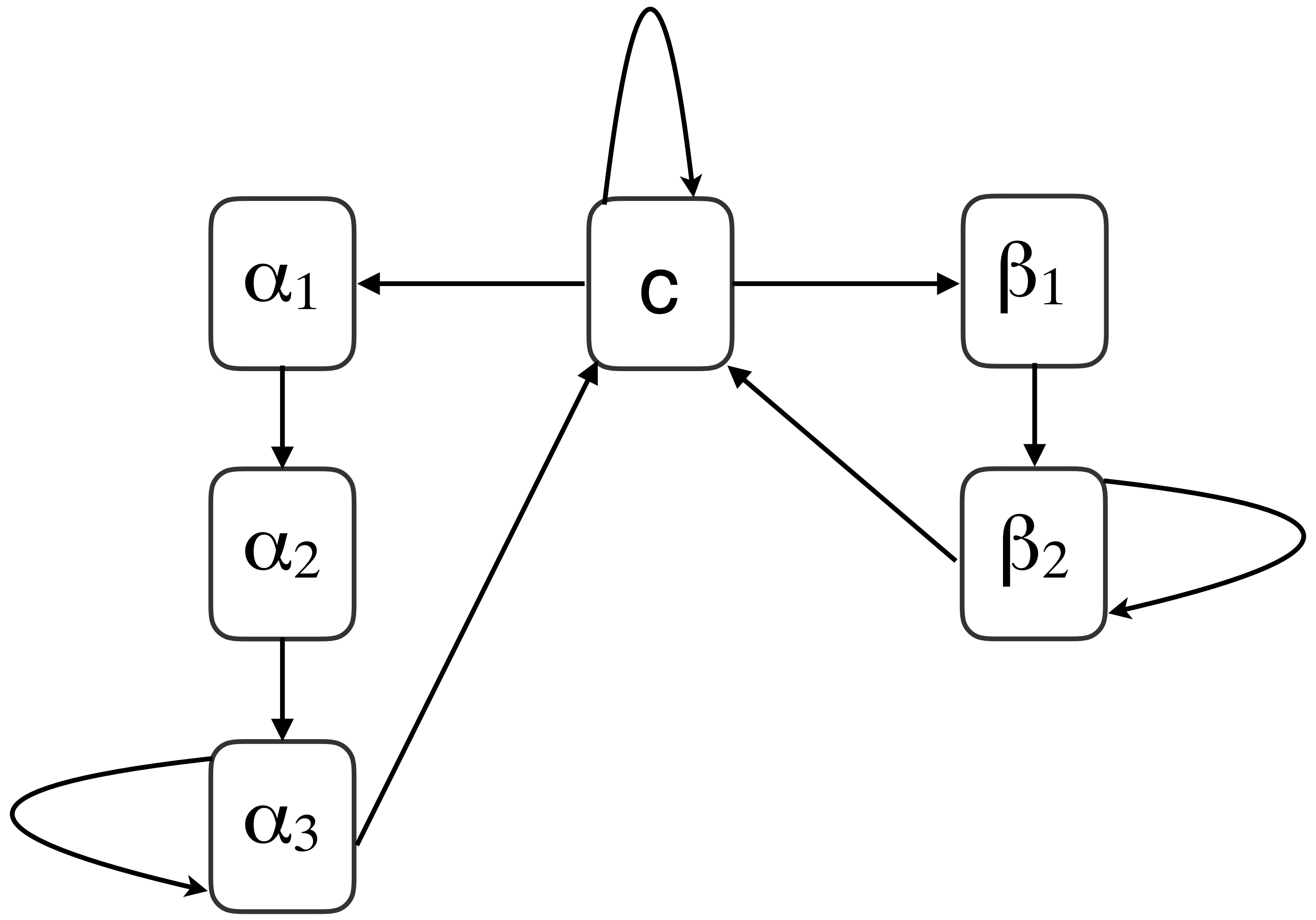
Hidden Markov Models

HMMs interpret an observable sequence (residue sequence or DNA/RNA sequence) as «generated» by an underlying (hidden) process.

Transition topology and probabilities define a global grammar

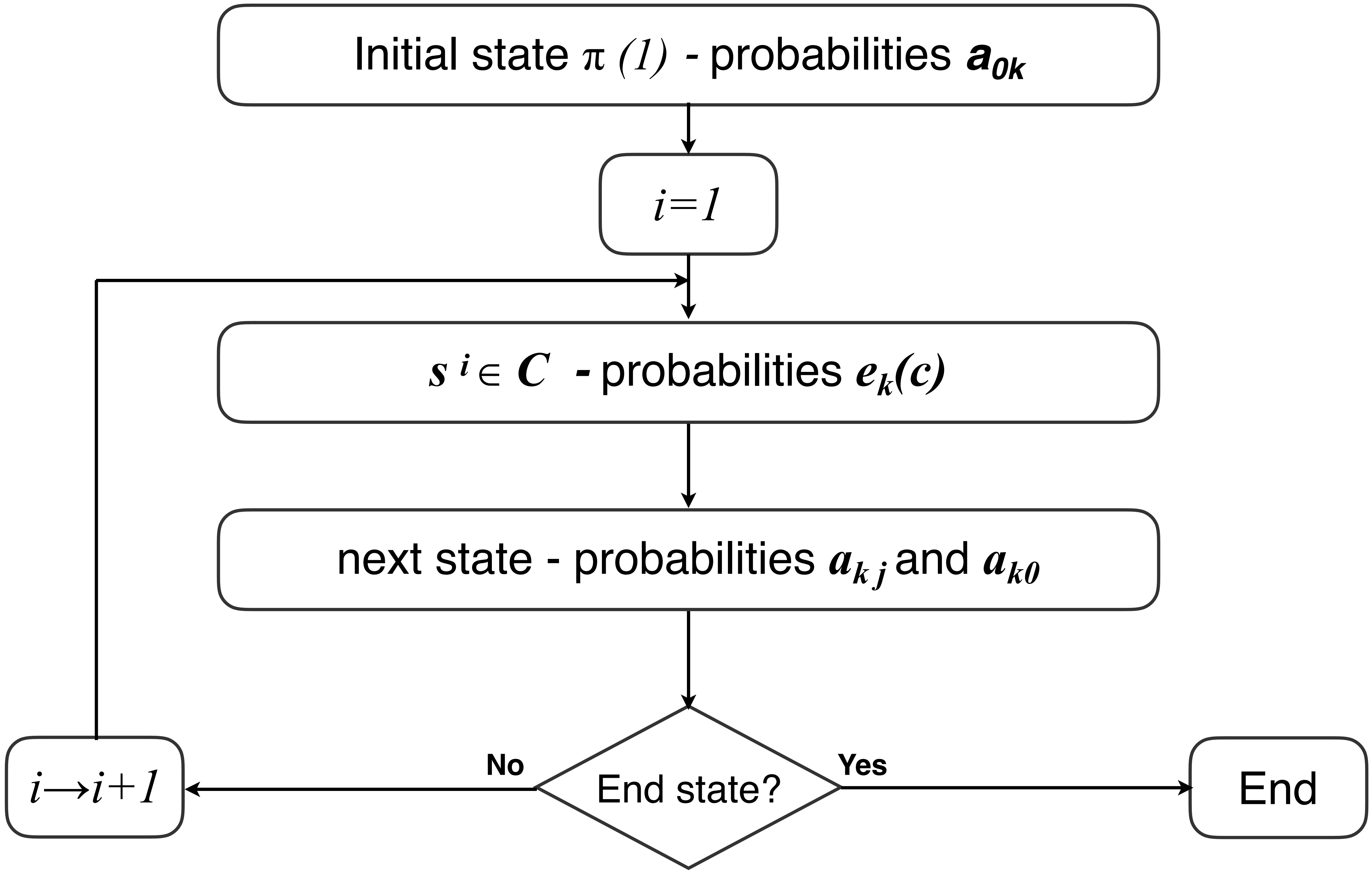
Emission probabilities cast the propensity of observable symbols in each state

Secondary Structure


$$\begin{tikzcd}
\alpha_1 \arrow[d] & c \arrow[l] \arrow[r] \arrow[loop above] & \beta_1 \arrow[d] \\
\alpha_2 \arrow[d] & & \beta_2 \arrow[ul] \arrow[loop right] \\
\alpha_3 \arrow[uur] \arrow[loop left] & &
\end{tikzcd}$$

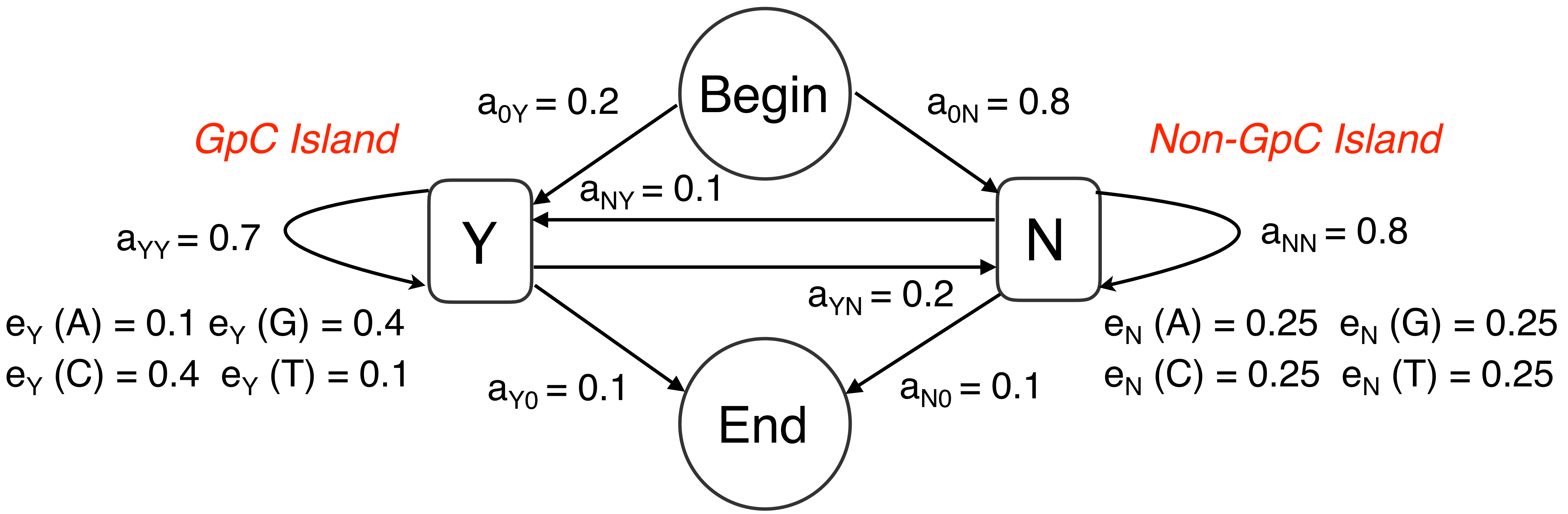
S	A	L	K	M	N	Y	T	R	E	I	M	V	A	S	N	Q	s: sequence
c	α_1	α_2	α_3	α_3	α_3	α_3	c	c	c	c	β_1	β_2	β_2	β_2	c	c	π: path
c	α	α	α	α	α	α	c	c	c	c	β	β	β	β	c	c	$Y(\pi)$: labels

Generating HMM Sequence


Initial state π *(1)* - probabilities $\boldsymbol{a_{0k}}$
$i=1$
$\boldsymbol{s}^{\,i} \in \boldsymbol{C}$ - probabilities $\boldsymbol{e_k(c)}$
next state - probabilities $\boldsymbol{a_{kj}}$ and $\boldsymbol{a_{k0}}$
End state?
No
Yes
$i \rightarrow i+1$
End

GpC Islands Model

Probability of a sequence s with a given path π



s :	A	G	C	G	C	G	T	A	A	T	C	T	G
π :	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N

Emission: $0.1 \times 0.4 \times 0.4 \times 0.4 \times 0.4 \times 0.4 \times 0.1 \times 0.25 \times 0.25 \times 0.25 \times 0.25 \times 0.25 \times 0.25$

Transition: $0.2 \times 0.7 \times 0.7 \times 0.7 \times 0.7 \times 0.7 \times 0.7 \times 0.2 \times 0.8 \times 0.8 \times 0.8 \times 0.8 \times 0.8 \times 0.1$

Joint Probability

Calculate the joint probability of the sequence (s) ad the path (π) given the model (M)

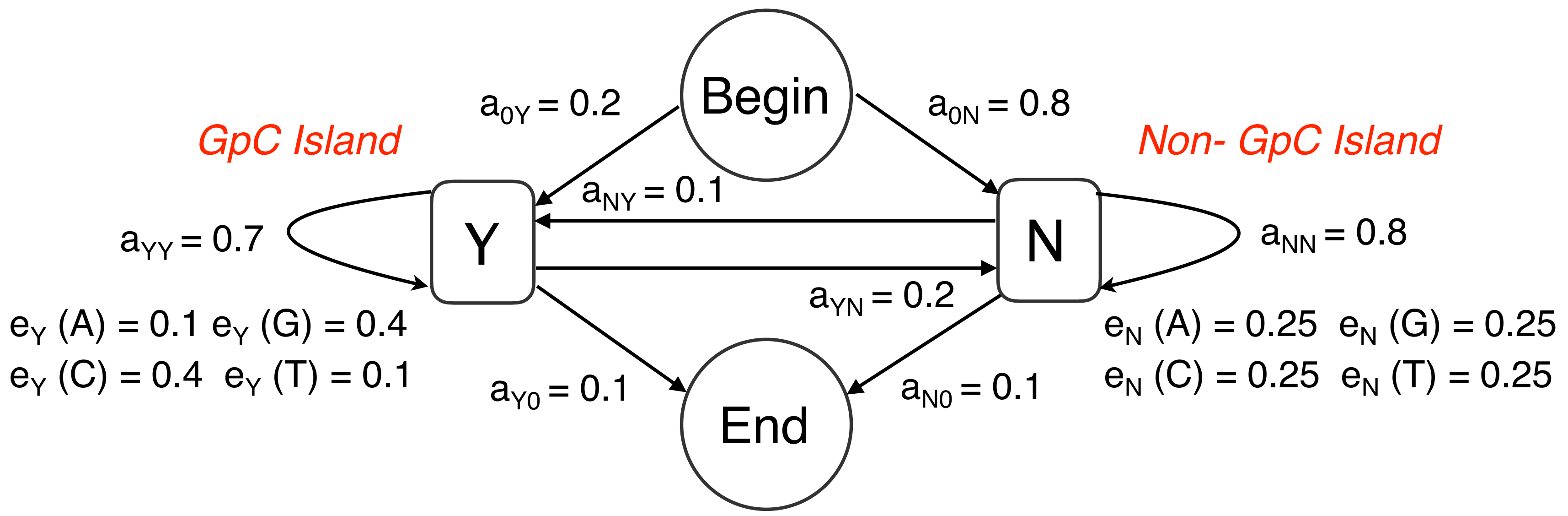
$$P(s,\pi \mid M) = P(s \mid \pi, M) \cdot P(\pi \mid M)$$

$$P(\pi \mid M) = a_{0\pi(1)} \cdot \prod_{i=2}^{T} a_{\pi(i-1)\pi(i)} \cdot a_{\pi(T)0}$$

$$P(s \mid \pi, M) = \prod_{i=1}^{T} e_{\pi(i)}(s^{i})$$

$$P(s,\pi \mid M) = a_{\pi(T)0} \cdot \prod_{i=1}^{T} a_{\pi(i-1)\pi(i)} \cdot e_{\pi(i)}(s^{i})$$

Sequence Probability



$$P(s \mid M) = \Sigma_\pi P(s, \pi \mid M)$$

2^{13} different paths

Summing over all the path will give the probability of having the sequence

s:	A	G	C	G	C	G	T	A	A	T	C	T	G
π_1:	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
π_2:	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
π_3:	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
π_4:	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
π_5:	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y

Forward Algorithm

On the basis of preceding observations the computation of P(s I M) can be decomposed in simplest problems

For each state k and each position i in the sequence, we compute:

$$F_k(i) = \mathrm{P}(\, s^1 s^2 s^3 \ldots\ldots s^{\,i},\ \pi\,(i) = k \mid M)$$

Initialization: $F_{BEGIN}\,(0) = 1 \qquad F_i\,(0) = 0 \qquad \forall\ \ i \neq \mathrm{BEGIN}$

Recurrence: $F_l\,(\,i{+}1) = \mathrm{P}(\, s^1 s^2 \ldots s^{\,i} s^{\,i+1},\ \pi\,(i+1) = l\,)\ =$

$$= \Sigma_k\, \mathrm{P}(\, s^1 s^2 \ldots s^{\,i},\ \pi\,(i) = k\,) \cdot \mathrm{a}_{\,k\,l} \cdot \mathrm{e}_{\,l}(\, s^{\,i+1}\,) =$$

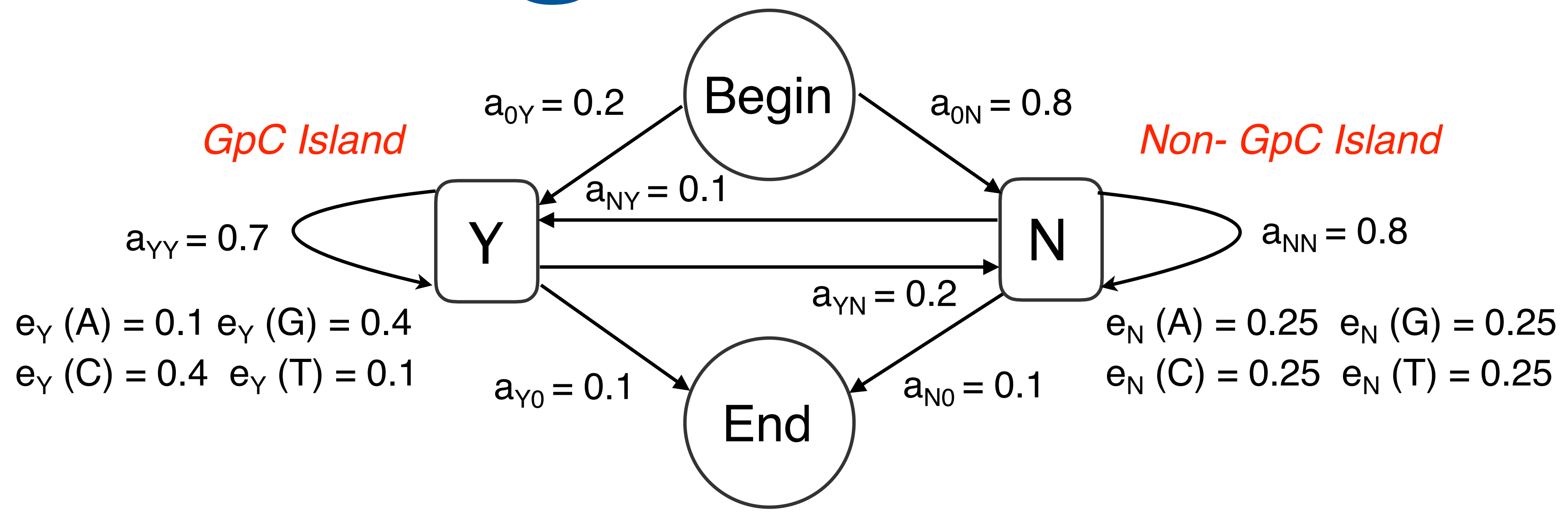
$$= \mathrm{e}_{\,l}(\, s^{\,i+1}\,) \cdot \Sigma_k F_k\ (\,i\,) \cdot \mathrm{a}_{\,k\,l}$$

Termination: $\mathrm{P}(\,s\,) = \mathrm{P}(\, s^1 s^2 s^3 \ldots\ldots s^{\,T},\ \pi\,(T+1) = END\,) =$

$$= \Sigma_k\, \mathrm{P}(\, s^1 s^2 \ldots s^{\,T},\ \pi\,(T) = k\,) \cdot \mathrm{a}_{\,k0}$$

$$=\ \Sigma_k\, F_k\,(\,T\,) \cdot \mathrm{a}_{\,k\,0}$$

Forward Algorithm: Example



S: ATGCG *Initialization*: $F_{BEGIN}(0) = 1 \; F_i(0) = 0 \; \forall \; i \neq \text{BEGIN}$

Recurrence: $F_l(i+1) = e_l(s^i) \cdot \Sigma_k F_k(i) \cdot a_{kl}$ *Termination*: $P(s) = \Sigma_k F_k(T) \cdot a_{k0}$

	-	A	T	G	C	G	-
Begin	1	0	0	0	0	0	0
Y	0	0.2x0.1	2e-2x0.7x0.1+ +0.2x0.1x0.1= =3.4e-3	3.4e-3x0.7x0.4+ +4.1e-2x0.1x0.4= =2.59e-3	2.59e-3x0.7x0.4+ +8.37e-3x0.1x0.4= =1.06056e-3	1.06056e-3x0.7x0.4+ +1.8036e-3x0.1x0.4= =3.691008e-4	
N	0	0.8x0.25	2e-2x0.2x0.25+ +0.2x0.8x0.25= =4.1e-2	3.4e-3x0.2x0.25+ +4.1e-2x0.8x0.25= =8.37e-3	2.592e-3x0.2x0.25+ +8.37e-3x0.8x0.25= =1.8036e-3	1.06056e-3x0.2x0.25+ +1.8036e-3x0.8x0.25= =4.13748e-4	
End	0	0	0	0	0	0	3.69e-4x0.1+ +4.13e-4x0.1= =7.82e-5

Backward Algorithm

Similar to the Forward algorithm: it computes P(s I M), reconstructing the sequence from the end

For each state k and each position i in the sequence, we compute:

$$B_k(i) = \mathrm{P}(\, s^{\,i+1} s^{\,i+2} s^{\,i+3} \ldots\ldots s^{\,T} \mid \pi\,(i) = k\,)$$

Initialization: $B_k\,(T) = \mathrm{P}(\pi\,(T{+}1) = \mathrm{END} \mid \pi\,(T) = k\,) = \mathrm{a}_{k0}$

Recurrence: $B_l(\,i\text{-}1) = \mathrm{P}(s^{\,i} s^{\,i+1} \ldots s^{\,T} \mid \pi\,(i - 1) = l\,) \;=$

$$= \Sigma_k\, \mathrm{P}(s^{\,i+1} s^{\,i+2} \ldots s^{\,T} \mid \pi\,(i) = k) \cdot \mathrm{a}_{\,l\,k} \cdot \mathrm{e}_{\,k}(s^{\,i}) =$$

$$= \Sigma_k\, B_k\,(\,i\,) \cdot \mathrm{e}_{\,k}(\,s^{\,i}\,) \cdot \mathrm{a}_{\,l\,k}$$

Termination: $\mathrm{P}(\,s\,) = \mathrm{P}(\,s^1 s^2 s^3 \ldots\ldots s^{\,T} \mid \pi\,(0) = BEGIN\,) =$

$$= \Sigma_k\, \mathrm{P}(\,s^2 \ldots s^{\,T} \mid \pi\,(1) = k\,) \cdot \mathrm{a}_{\,0\,k} \cdot \mathrm{e}_{\,k}(\,s^{\,1}\,) =$$

$$= \Sigma_k\, B_k\,(\,1\,) \cdot \mathrm{a}_{\,0k} \cdot \mathrm{e}_{\,k}(\,s^{\,1}\,)$$

Computational Complexity

Naïf method

$$P(s \mid M) = \Sigma_\pi P(s, \pi \mid M)$$

There are N^T possible paths.

Each path requires about $2 \cdot T$ operations.

The time for the computation is $O(T \cdot N^T)$

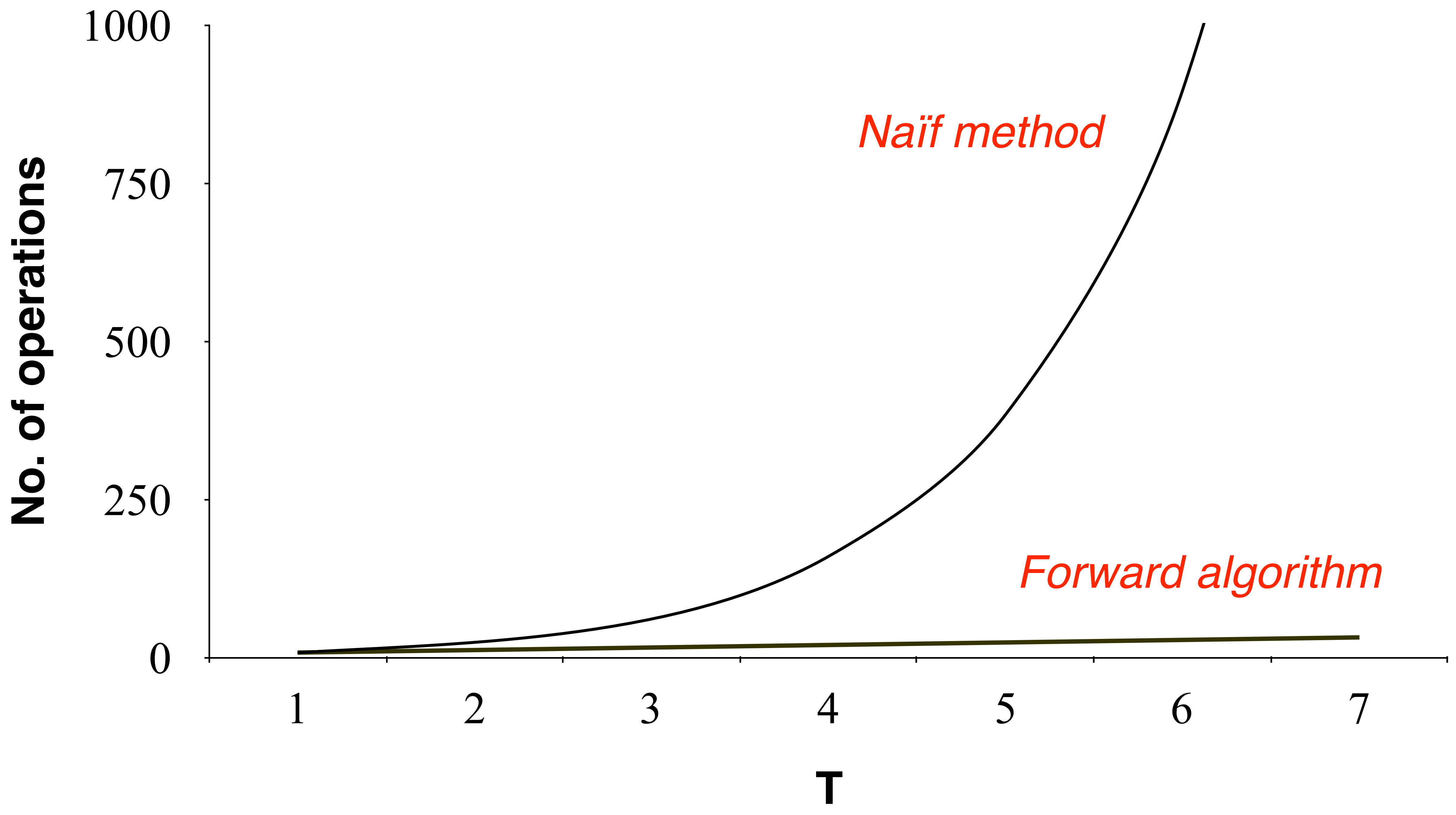
Forward Algorithm

T positions, N values for each position

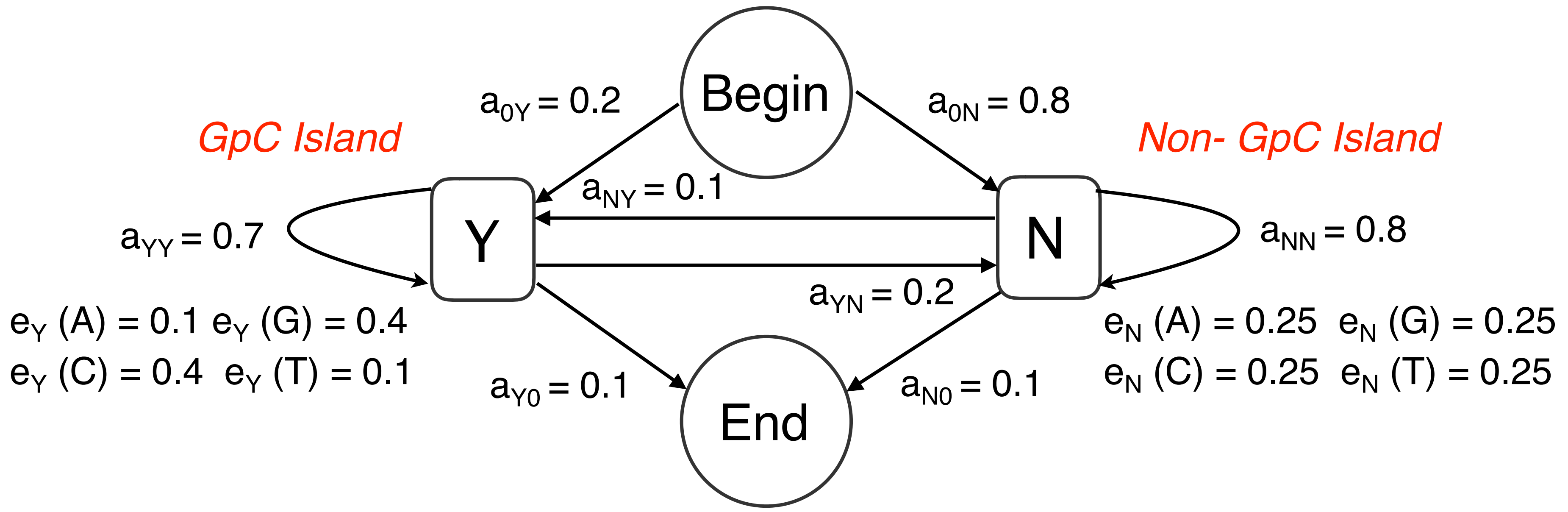
Each element requires about $2 \cdot N$ product and **1** sum

The time for the computation is $O(T \cdot N^2)$

Complexity Plot



Hidden Paths



$$\pi^* = \operatorname{argmax}_\pi [\, P(\pi \mid s, M)\,] = \operatorname{argmax}_\pi [\, P(\pi, s \mid M)\,]$$

2^{13} different paths
Viterbi path: path that gives the best joint probability

s :	A	G	C	G	C	G	T	A	A	T	C	T	G
π_1:	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
π_2:	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
π_3:	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
π_4:	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
π_5:	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y

Searching the Hidden Path

Viterbi decoding
Among all the possible path, choose the path π^* that maximizes the $P(\pi \mid s, M)$

$$\pi^* = \text{argmax}_{\pi} [\, P(\pi \mid s, M) \,] = \text{argmax}_{\pi} [\, P(\pi , s \mid M) \,]$$

A Posteriori decoding
For each position choose the state $\underline{\pi}\,(i)$:

$$\underline{\pi}\,(i) = \text{argmax}_{k} [\, P(\pi\,(i) = k \mid s, M) \,]$$

The contribution to this probability derives from all the paths that go through the state *k* at position *i.*

The A posteriori path can be a non-sense path (it may not be a legitimate path if some transitions are not permitted in the model)

Viterbi Algorithm

$\pi^* = \text{argmax}_{\pi} [\, P(\pi, s \mid M) \,]$

The computation of $P(s,\pi^* \mid M)$ can be decomposed in simplest problems

Let $V_k(i)$ be the probability of the most probable path for generating the subsequence $s^1 s^2 s^3 \ldots\ldots s^i$ ending in the state *k* at iteration *i.*

Initialization: $V_{BEGIN}(0) = 1 \qquad V_i(0) = 0 \qquad \forall\ i \neq \text{BEGIN}$

Recurrence: $V_l(i+1) = e_l(s^{i+1}) \cdot \text{Max}_k (V_k(i) \cdot a_{kl})$

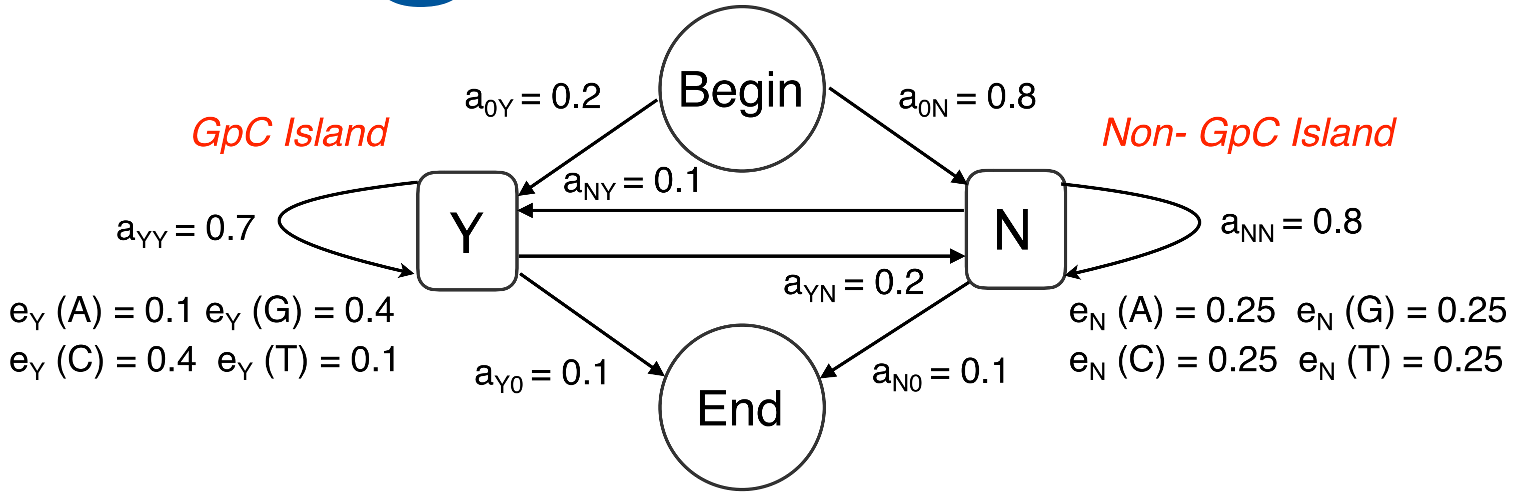
$\text{ptr}_i(l) = \text{argmax}_k (V_k(i) \cdot a_{kl})$

Termination: $P(s, \pi^*) = \text{Max}_k (V_k(T) \cdot a_{k0})$

$\pi^*(T) = \text{argmax}_k (V_k(T) \cdot a_{k0})$

Traceback: $\pi^*(i-1) = \text{ptr}_i(\pi^*(i))$

Viterbi Algorithm: Example



S: ATGCG *Initialization*: $V_{BEGIN}(0) = 1$ $V_i(0) = 0 \; \forall \; i \neq \mathrm{BEGIN}$

Recurrence: $V_l(\mathrm{i}) = \mathrm{e}_l(s^{\mathrm{i}}) \cdot \mathrm{Max}_k(V_k(\mathrm{i}-1) \cdot \mathrm{a}_{kl})$ — $ptr_i(l) = argmax_k(V_k(i-1) \cdot a_{kl})$

Termination: $\mathrm{P}(s, \pi^*) = \mathrm{Max}_k(V_k(T) \cdot \mathrm{a}_{k0})$ — $\pi^*(T) = argmax_k(V_k(T) \cdot a_{k0})$

Traceback: $\pi^*(i-1) = \mathrm{ptr}_i(\pi^*(i))$

	-	A	T	G	C	G	-
Begin	1	0	0	0	0	0	0
Y	0	0.2x0.1= =2e-2 ptr=Begin	Max(2e-2x0.7x0.1; 0.2x0.1x0.1) 2e-3; ptr=N	Max(2e-3x0.7x0.4; 1.6e-2x0.1x0.4) 6.4e-4; ptr=**N**	Max(6.4e-4x0.7x0.4; 3.2e-4x0.1x0.4) 1.79e-4; ptr=**Y**	Max(1.79e-4x0.7x0.4; 6.4e-5x0.1x0.4) 5.02e-5; ptr=**Y**	
N	0	0.8x0.25= =0.2 ptr=Begin	Max(2e-2x0.2x0.25; 0.2x0.8x0.25) 1.6e-2; ptr=**N**	Max(2e-3x0.2x0.25; 1.6e-2x0.8x0.25) 3.2e-4; ptr=N	Max(6.4e-4x0.2x0.25; 3.2e-4x0.8x0.25) 6.4e-5; ptr=N	Max(1.79e-4x0.2x0.25 ;6.4e-5x0.8x0.25) 1.28e-5; ptr=N	
End	0	0	0	0	0	0	Max(5.01e-5x0.1; 1.28e-5x0.1) 5.02e-6; ptr=**Y**

A Posteriori Decoding

For each position choose the state $\underline{\pi}(t)$:

$$\underline{\pi}(i) = \operatorname{argmax}_k [\, \mathrm{P}(\pi(i) = k \mid s, M)\,]$$

How to compute $\mathrm{P}(\pi(i) = k \mid s, M)$ for any state *k* and any position *i*?

$$P(\pi(i) = k \mid s, M) = \frac{P(\pi(i) = k, s \mid M)}{P(s \mid M)}$$

$$P(\pi(i) = k, s \mid M) = P(s^1 s^2 \ldots s^i, \pi(i) = k \mid M) \cdot P(s^{i+1}, s^{1+2}, \ldots s^T \mid \pi(i) = k, M) =$$

$$= F_k(i) \cdot B_k(i)$$

Elements of the Forward and Backward matrices

$$P(\pi(i) = k \mid s, M) = \frac{F_k(i) \cdot B_k(i)}{P(s \mid M)}$$

Computed with Forward or Backward algorithm termination steps

Exercise

Using the BLAST tool at Uniprot, retrieve all the SwissProt sequences that are similar with an E-value <0,001 to the Rhodopseudomonas cytochrome C (P00091) .

Download the sequences in Fasta format and align with ClustalW, Muscle or T-Coffee

Analyse the conserved positions in the alignments

Repeat with the Arabidopsis (Q93VA3) and the human (P99999) sequences

Compare the results, an in particular the pattern of conserved residues