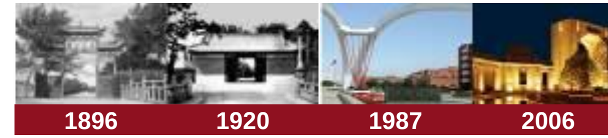
Course organization

- **Introduction (Week 1-2)**
  - Course introduction
  - A brief introduction to molecular biology
  - A brief introduction to sequence comparison
- **Part I: Algorithms for Sequence Analysis (Week 3 - 8)**
  - Chapter 1-3, Models and theories
    - » Probability theory and Statistics (Week 3)
    - » Algorithm complexity analysis (Week 4)
    - » Classic algorithms (Week 5)
  - Chapter 4. Sequence alignment (week 6)
  - Chapter 5. Hidden Markov Models (week 7）
  - Chapter 6. Multiple sequence alignment (week 8)
- **Part II: Algorithms for Network Biology (Week 9 - 16)**
  - Chapter 7. Omics landscape (week 9)
  - Chapter 8. Microarrays, Clustering and Classification (week 10)
  - Chapter 9. Computational Interpretation of Proteomics (week 11)
  - Chapter 10. Network and Pathways (week 12,13)
  - Chapter 11. Introduction to Bayesian Analysis (week 14,15)
  - Chapter 12. Bayesian networks (week 16)



Chapter 5
Hidden Markov Models
（隐马尔科夫模型）

Chaochun Wei

Spring 2018

Contents

- **Reading materials**
- **Introduction to Hidden Markov Model**
  - **Markov chains**
  - **Hidden Markov Models**
  - **Three problems of HMMs**
    - Calculate the probability from observations and the model
    - Parameter estimation for HMMs

Reading

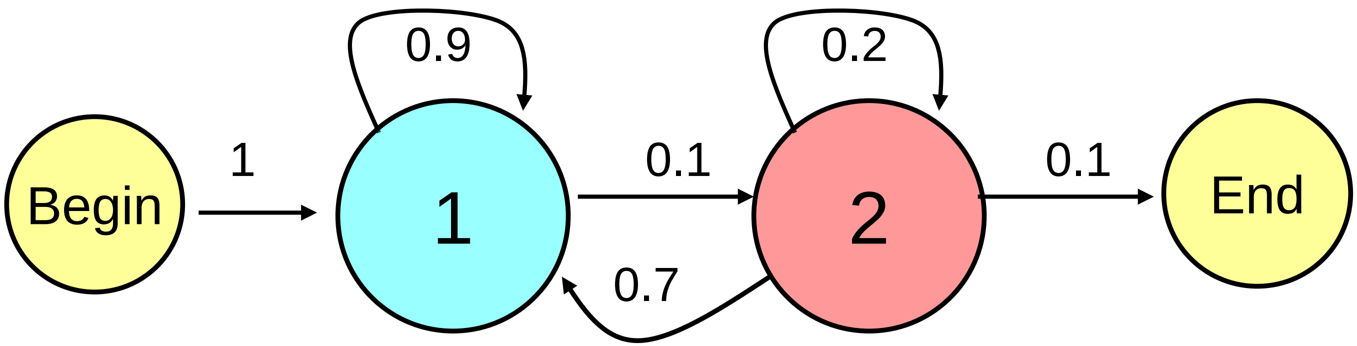
- Rabiner, L.(1989) A Tutorial on Hidden Markov Models and Selected Applications in Speech Recognition. Proceedings of the IEEE, 77 (2) 257-286
- Rabiner, L., and Juang, Biing-Hwang, (1993), Fundamentals of Speech Recognition, Prentice Hall.

Markov chain: a process that the current state depends on at most a limited number of previous states

- Weather
  - Sunny, Rain, Rain, Sunny, Cloudy, Cloudy,….
- Stock market index
  - Up, up, down, down, down, up, up, up, ….
- Girl/boy friend’s mood
  - High, low, low, high, high, high, …
- Genome sequence
  - ATGTTAGATATAACAGATAA
- Flip coins
  - HTTTHHHHHH

Hidden Markov Model

HMM for two biased coins flipping



$$e_1(H)=0.8, e_1(T)=0.2, e_2(H)=0.3, e_2(T)=0.7$$

TTHHTTHTTTTTHTHHHHHTHTH **Observed sequence x**

11221111122221111112222 **Hidden state sequence** π

$$\pi^* = \arg\max_{\pi} P(x,\pi)$$

Hidden Markov Model

- **Elements of an HMM (N, M, A, E, Init)**

1. **N: number of states in the model**
   - $S=\{S_1, S_2, \ldots, S_N\}$, and the state at time t is q_t.
2. **M: alphabet size (the number of observation symbols)**
   - $V=\{v_1, v_2, \ldots, v_M\}$
3. **A: state transition probability distribution**
   - $A=\{a_{ij}\}$, where $a_{ij}=P[q_{t+1}=S_j|q_t=S_i]$, $1 \leq i,j \leq N$
4. **E: emission probability**
   - $E=\{e_j(k)\}$ (observation symbols probability distribution in state j), where $e_j(k)=P[v_k \text{ at } t \mid q_t = S_j\}$, $1 \leq j \leq N$, $1 \leq k \leq M$
5. **Init: initial state probability, π_i**
   - Init=$\{\pi_i\}$, where $\pi_i = P[q_1=S_i]$, $1 \leq i \leq N$.

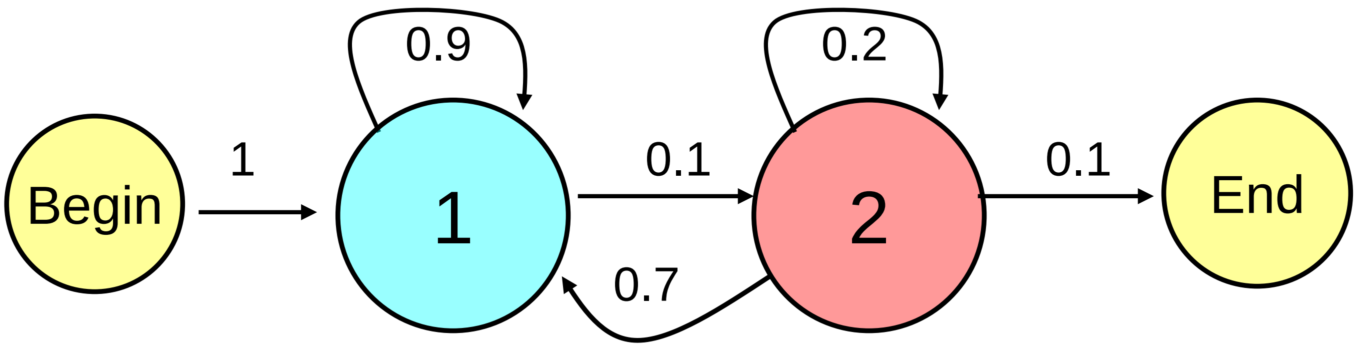
HMM is a generative model

- HMM can be used as a generator to produce an observation sequence $O=O_1O_2\ldots O_T$, where each O_t is one of the symbols from V, and T is the number of observations in the sequence.

1. Choose an initial state $q_1=S_i$ according to Init;
2. Set $t=1$;
3. Choose $O_t=v_k$ according to $e_i(k)$ (the symbol probability distribution in state S_i);
4. Transit to a new state $q_{t+1}=S_j$ according to a_{ij};
5. Set $t=t+1$; return to step 3 if $t<T$; otherwise terminate the procedure.

HMM is a generative model

HMM for two biased coins flipping



$$e_1(H) = 0.8,\ e_1(T) = 0.2,\ e_2(H) = 0.3,\ e_2(T) = 0.7$$

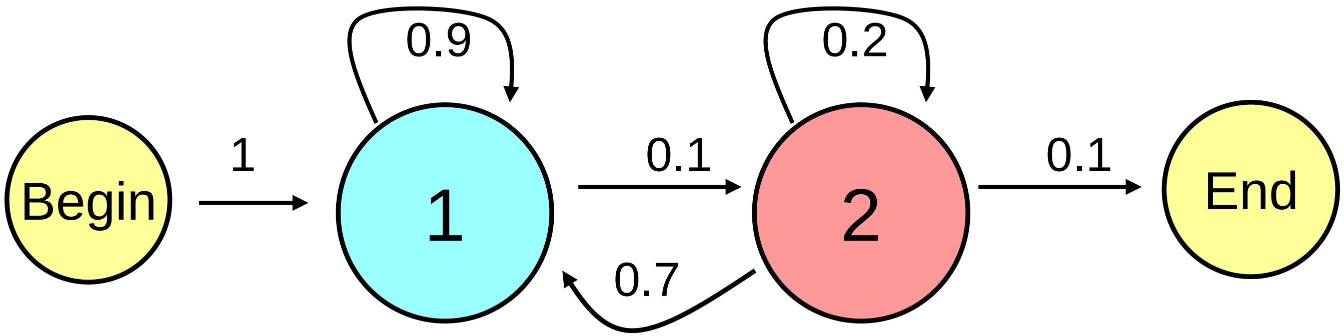
TTHHTTHTTTTTHTHHHHHTHTH **Observed sequence x**

11221111122221111112222 **Hidden state sequence** π

$$P(x, \pi \mid \lambda) = Init_{\pi_0} * e_{\pi_0}(x(0)) * \prod_{0 \le i \le T-1} (a_{\pi_i \pi_{i+1}} e_{\pi_{i+1}}(x(i)))$$

HMM is a generative model

HMM for two biased coins flipping



$$e_1(H)=0.8, e_1(T)=0.2, e_2(H)=0.3, e_2(T)=0.7$$

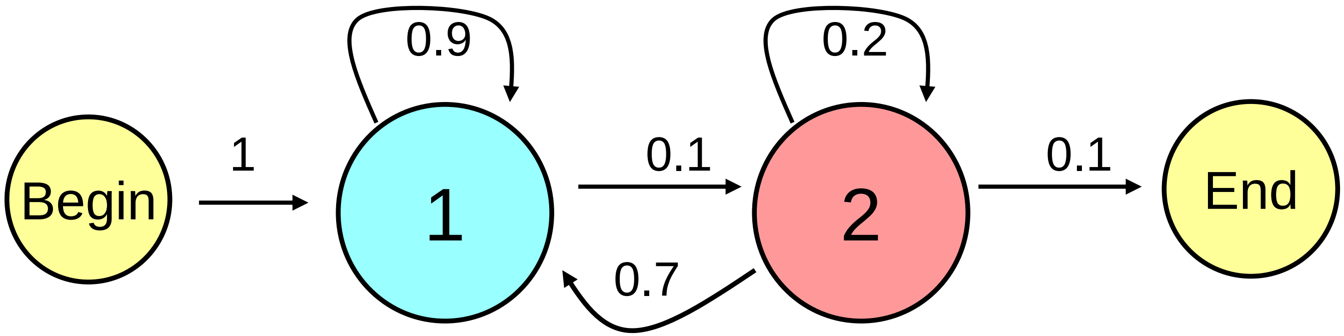
TTHHT **Observed sequence x**

11221 **Hidden state sequence** π

$$P(x, \pi \mid \lambda) = ?$$

HMM is a generative model

HMM for two biased coins flipping



$$e_1(H)=0.8, e_1(T)=0.2, e_2(H)=0.3, e_2(T)=0.7$$

TTHHT **Observed sequence x**

11221 **Hidden state sequence** π

$$P(x,\pi\mid\lambda)=Init_{\pi_0} * e_{\pi_0}(x(0)) * \prod_{0\le i\le T}(a_{\pi_i\pi_{i+1}} e_{\pi_{i+1}}(x(i))$$

$$=1*e_1(T)*(a_{11}e_1(T))*(a_{12}e_2(\mathrm{H}))*(a_{22}e_2(\mathrm{H}))*(a_{21}e_1(T))$$

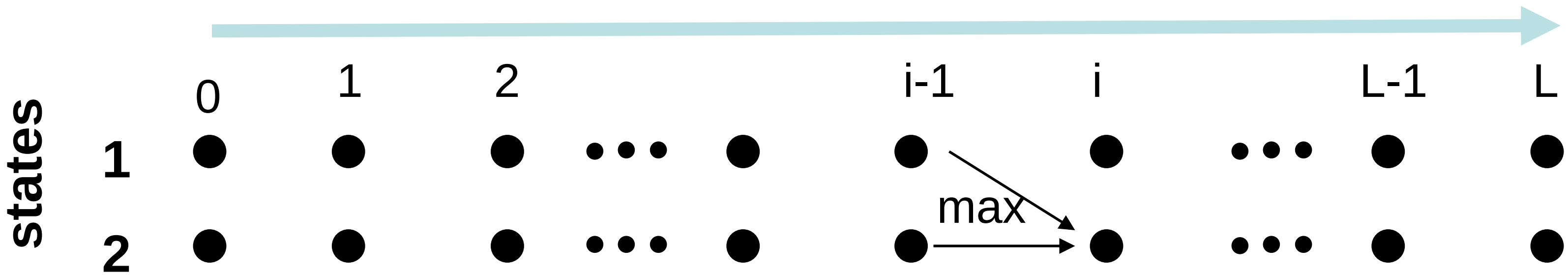
$$=1*0.2*(0.9*0.2)*(0.1*0.3)*(0.2*0.3)*(0.7*0.2)$$

Hidden Markov Model

- **HMM：λ={N, M, A, E, Init} or λ= {A, E, Init}**

- **Three basic problems for HMMs**
  - **Problem 1: Given the observation sequence $O=O_1O_2\ldots O_T$, and a model λ={A, E, Init}, how to compute P(O| λ), the probability of the observation sequence given the model?**
  - **Problem 2: Given the observation sequence $O=O_1O_2\ldots O_T$, and a model λ={A, E, Init}, how to choose a corresponding state sequence $Q=q_1q_2\ldots q_T$, which is optimal in some meaningful sense..**
  - **Problem 3: how to estimate model parameters λ={A, E, Init} to maximize P(O| λ).**

Most Probable Path and Viterbi Algorithm



Let $f_j(i) = \max_{\{\pi_0,\ldots,\pi_{i-1}\}} (\Pr(x_0,\ldots,x_{i-1},x_i,\pi_0,\ldots,\pi_{i-1},\pi_i = j))$

Initialization (j=1…N) $f_j(0) = \pi_j e_j(x_0)$

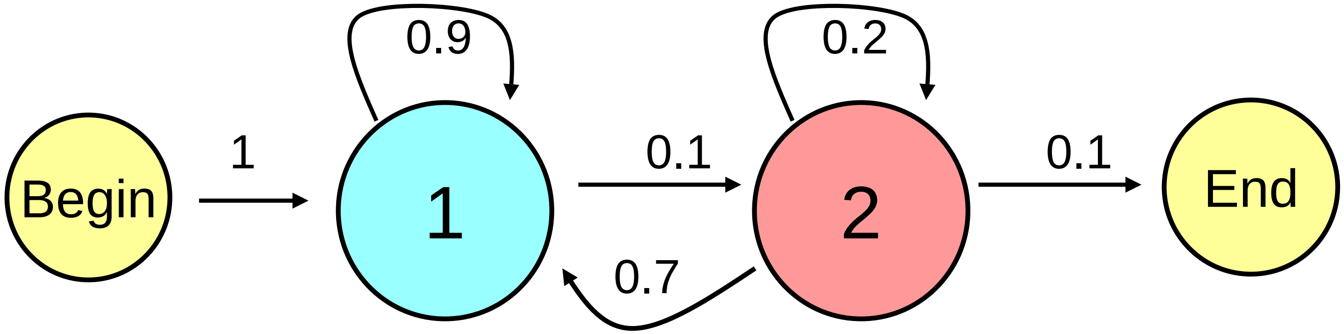
Recursion (i=1…L) $f_j(i) = e_j(x_i)\max_k (f_k(i-1)a_{kj});$

$ptr_j(i) = \arg\max_k (f_k(i-1)a_{kj}).$

Time complexity $O(N^2 L)$ space complexity $O(NL)$

Solution to problem 2: prob of best state sequence

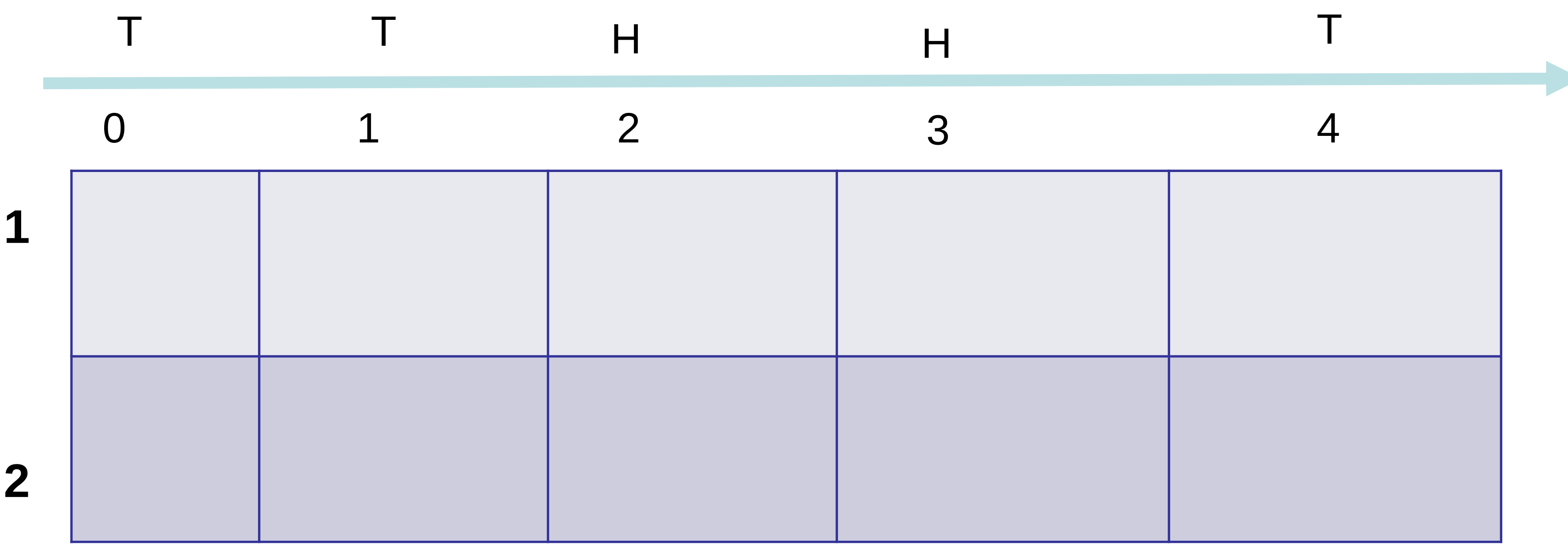
Viterbi for the HMM for two biased coins flipping



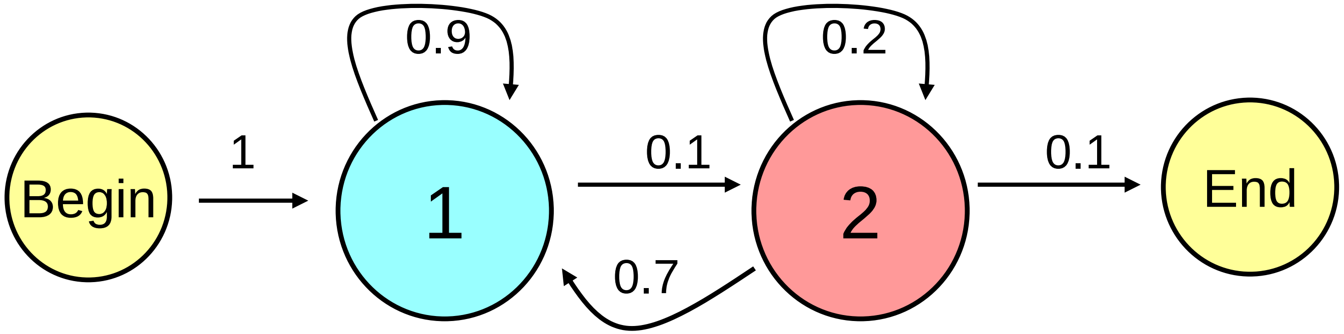
$$e_1(H) = 0.8, e_1(T) = 0.2, e_2(H) = 0.3, e_2(T) = 0.7$$

TTHHT **Observed sequence x**

11221 **Hidden state sequence** π



Viterbi for the HMM for two biased coins flipping



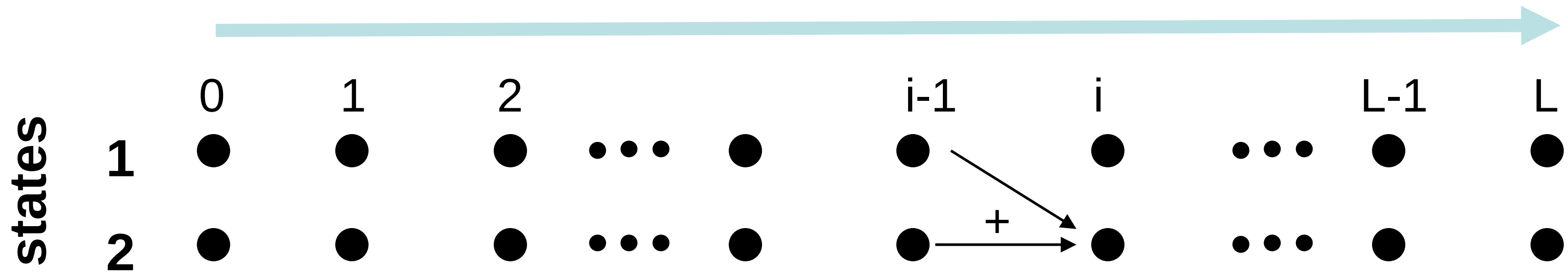
$$e_1(H)=0.8, e_1(T)=0.2, e_2(H)=0.3, e_2(T)=0.7$$

TTHHT **Observed sequence x**

11221 **Hidden state sequence** π

	T	T	H	H	T
	0	1	2	3	4
1	**0.2**	**Max0.2*(0.9 *0.2, 0) = 0.036**	**max0.8*(0.036*0.9, 0.014*0.7) = 0.0259**	**Max 0.8 * (0.0259*0.9, 0.0108*0.7) = 0.018662**	**=max0.2*(0.018662*0.9, 0.000777*0.7) = 0.003359**
2	0	Max0.7*(0.2 * 0.1, 0) = 0.014	Max0.3*(0.036*0.1, 0.014*0.2) = 0.0108	Max0.3(0.0259*0.1, 0.0108*0.2) = 0.000777	=max0.3(0.018662*0.1, 0.000777*0.7) = 0.0005599

Probability of All the Possible Paths and Forward Algorithm



Let $f_j(i) = \Pr(x_0, \ldots, x_i, \pi_i = j)$

Initialization (j=1…N) $f_j(0) = \pi_j e_j(x_0)$

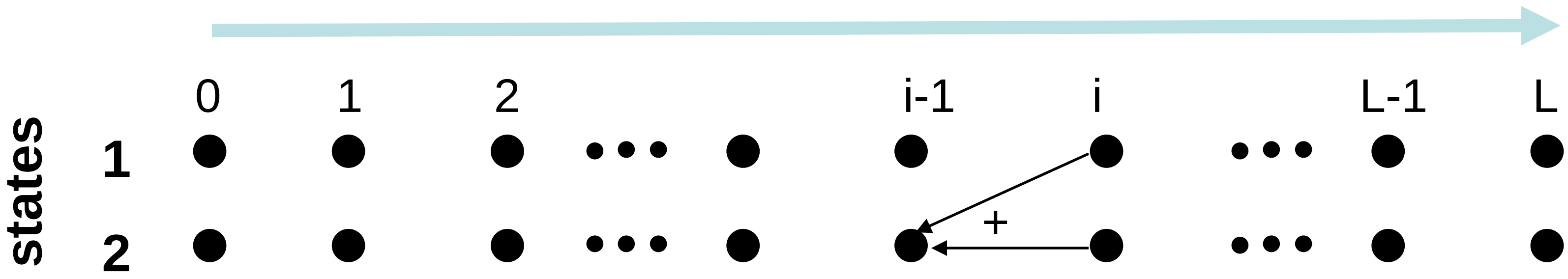
Recursion (i=1…L;

j = 1, .., N) $f_j(i) = e_j(x_i) \sum_k (f_k(i-1) a_{kj})$

Probability of all the probable paths $P(x) = \sum_\pi P(x, \pi) = \sum_k f_k(L)$

Solution to problem 1: prob of observation

Backward Algorithm



Let $b_j(i) = \Pr(x_{i+1}, x_{i+2}..., x_L, \pi_i = j)$

Initialization (j=1…N) $b_j(L) = 1$

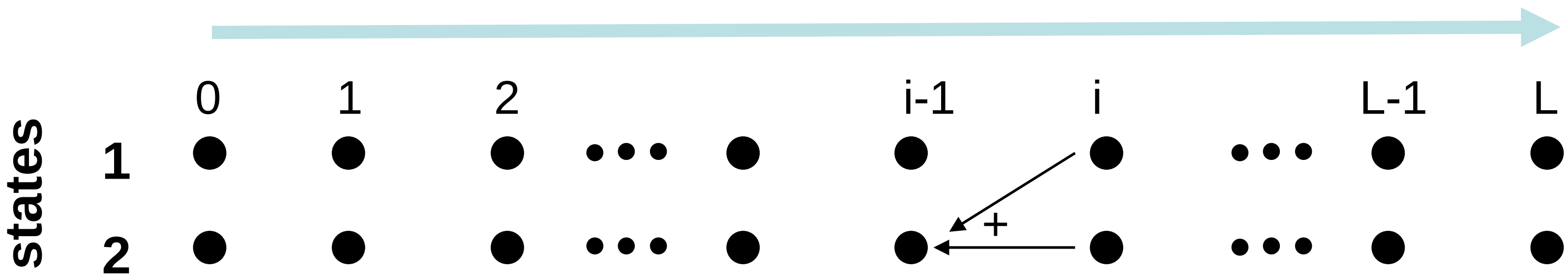
Recursion (i=L-1, L-2, …, 0, j=1, …, N)

$$b_j(i) = \sum_k (a_{jk} e_k(x_{i+1})) b_k(i+1)$$

Probability of all the probable paths

$$P(x) = \sum_\pi P(x,\pi) = \sum_k b_k(0)$$

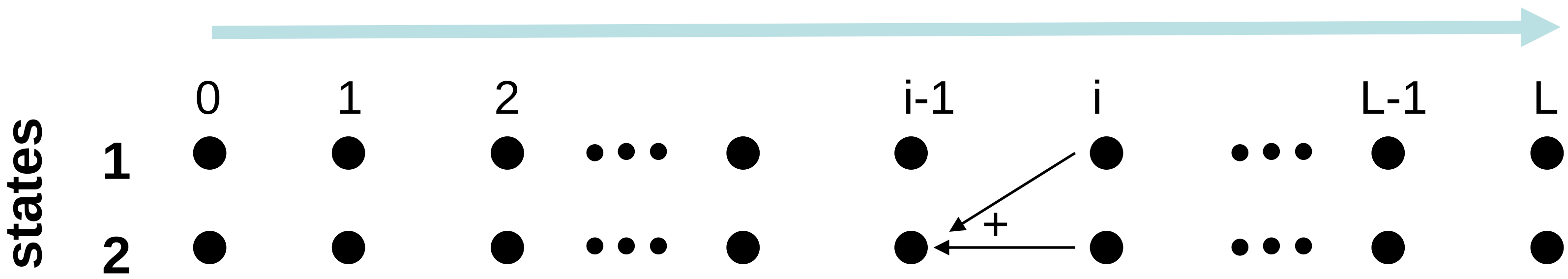
Decoding with Posterior Probability



Posterior Probability

$$P(\pi_i = k \mid x) = \frac{P(\pi_i = k, x)}{P(x)}$$

Decoding with Posterior Probability



Posterior Probability

$$P(\pi_i = k \mid x) = \frac{P(\pi_i = k, x)}{P(x)}$$

$$= \frac{f_k(i) * b_k(i)}{\sum_k (f_k(i) * b_k(i))}$$

Problem 3: Optimize the model parameters from the observation

- HMM： λ={A, E, Init}
- With annotations
  - Maximum likely-hood ratio
- Without annotations
  - Baum-Welch algorithm (EM algorithm)

Baum-Welch algorithm (estimate model parameters)

- Goal：given the observation sequence data set, estimate the model parameter λ to maximize $P(O|\lambda)$.
- Algorithm:

1. initialize the model λ_0,

2. calculate the new model λ based on λ_0 and the observation sequences

3. stop training if $\log P(X|\lambda) - \log(P(X|\lambda_0)) < Delta$

4. otherwise, let $\lambda_0 = \lambda$, and go to step 2.

Baum-Welch method (EM method)

- **HMM：λ={A, B, Init}, Without annotations**

Let $\xi_t(i,j) = P(\pi_t = i, \pi_{t+1} = j \mid x, \lambda)$

then $\xi_t(i,j) = \dfrac{f_i(t)a_{ij}e_j(x_{t+1})b_j(t+1)}{\sum_i^N \sum_j^N (f_i(t)a_{ij}e_j(x_{t+1})b_j(t+1))}$

Let $\gamma_t(i) = \sum_{j=1}^{N} \xi_t(i,j)$

then $\sum_{t=0}^{L} \gamma_t(i)$ = expected number of transitions from S_i

$\sum_{t=0}^{L} \xi_t(i,j)$ = expected number of transition S_i to S_j

Baum-Welch method (EM method) (2)

- **HMM： λ={A, B, Init}, Without annotations**

Then, $\overline{Init_i} =$ expected frequency in S_i at time 0 = $\gamma_0(i)$

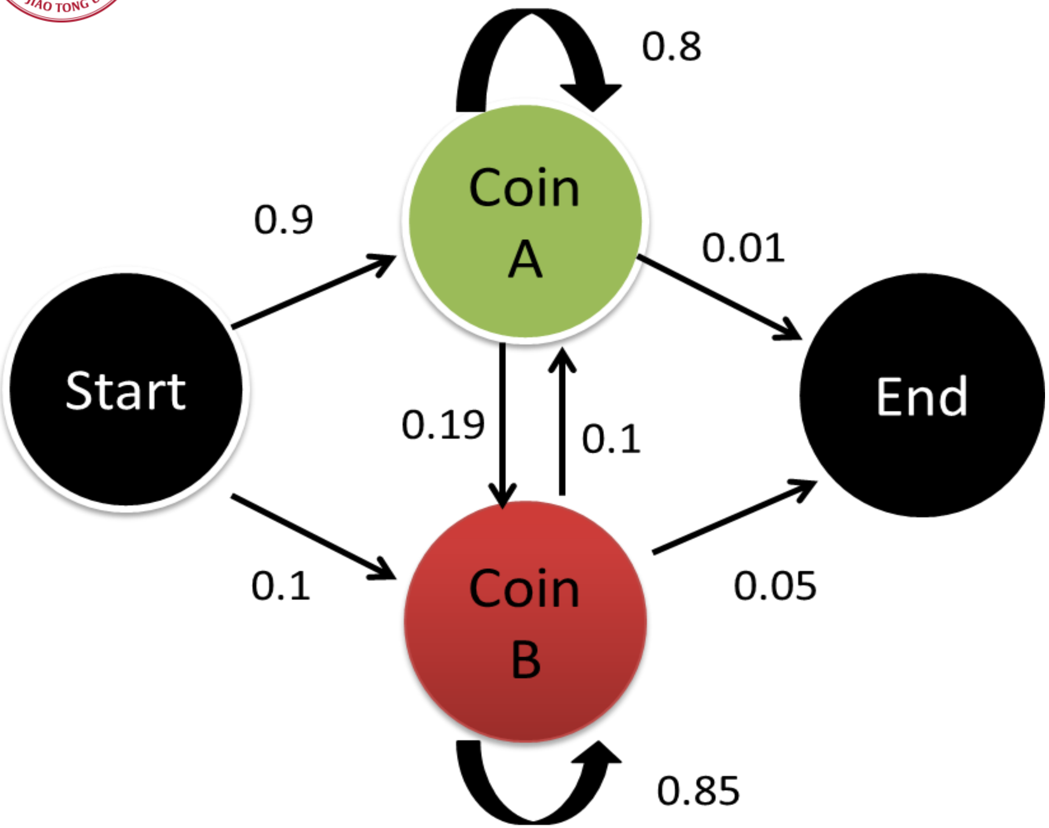
$$\bar{a}_{i,j} = \frac{expected \quad number \quad of \quad tranistions \quad from \quad S_i \quad to \quad S_j}{expected \quad number \quad of \quad tranistions \quad from \quad S_i}$$

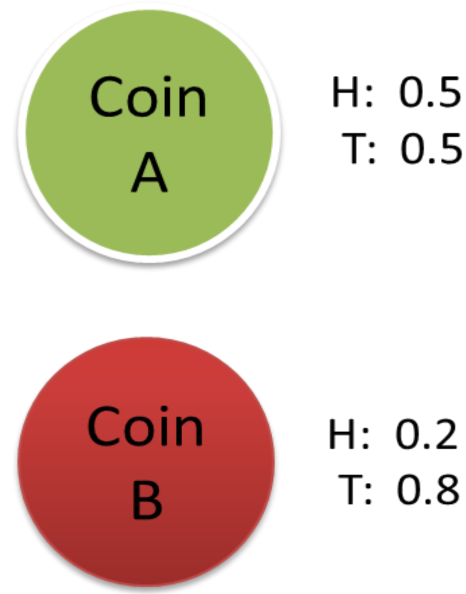
$$= \frac{\sum_{t=0}^{L} \xi_t(i,j)}{\sum_{t=0}^{L} \gamma_t(i)}$$

$$\bar{e}_i(k) = \frac{expected \quad number \quad of \quad times \quad in \quad state \quad j \quad and\,oberving \quad symbol \quad v_k}{expected \quad number \quad of \quad times \quad in \quad state \quad j}$$

$$= \frac{\sum_{\substack{t=0 \\ s.t.x_t=v_k}}^{L} \gamma_t(i)}{\sum_{t=0}^{L} \gamma_t(i)}$$

One more example: Flipping two coins



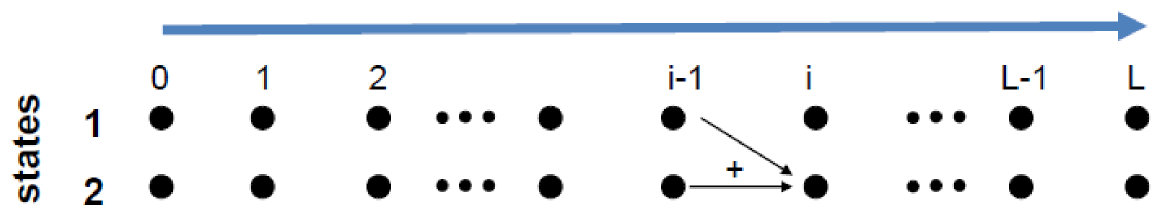


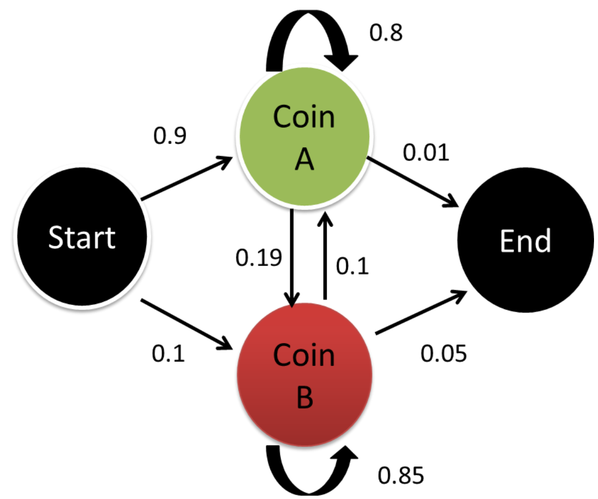
- **O= HHTHHTTTHT, P(O|λ)=?**

Problem 1: Given the observation sequence $O=O_1O_2...O_T$, and a model λ={A, B, Init}, how to compute P(O| λ), the probability of the observation sequence given the model?

Forward Algorithms

	H	H	T	H	H	T	T	T	H	T	End
A	0.45	0.181	0.07342	0.03144	0.01306	0.05371	0.02345	0.00111	5.817e-4	2.580e-4	2.423e-5
B	0.02	0.0205	0.04145	0.00983	0.00286	0.00394	0.00349	0.00273	5.067e-4	4.329e-4	



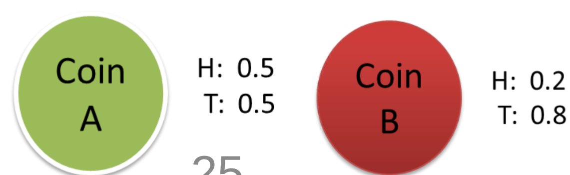


Let $f_j(i) = \Pr(x_0, \ldots, x_i, \pi_i = j)$

Initialization (j=1…N) $f_j(0) = \pi_j e_j(x_0)$

Recursion (i=1…L; j = 1, .., N) $f_j(i) = e_j(x_i) \sum_k (f_k(i-1) a_{kj})$

Probability of all the probable paths $P(x) = \sum_\pi P(x, \pi) = \sum_k f_k(L)$



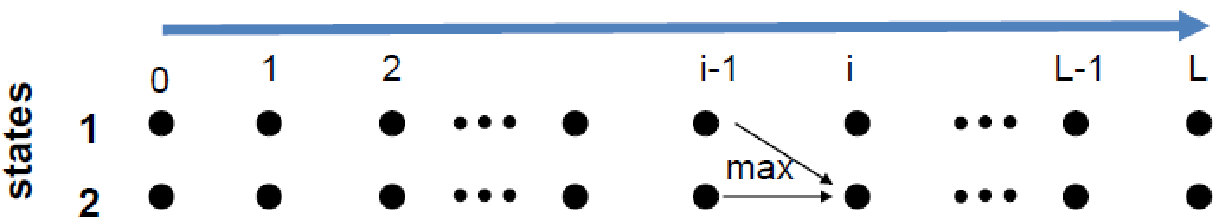
- **O= HHTHHTTTHT**
- **argmax(P(O, Q, λ))**

Problem 2: Given the observation sequence $O=O_1O_2 \ldots O_T$, and a model $\lambda=\{A, B, Init\}$, how to choose a corresponding state sequence $Q=q_1q_2 \ldots q_T$, which is optimal in some meaningful sense..

Viterbi Algorithms

A -> A -> A -> A -> A -> B -> B -> B -> B -> B

	H	H	T	H	H	T	T	T	H	T	End
A	0.45	0.18	0.072	0.0288	0.0115	0.0046	1.843e-3	7.372e-4	2.949e-4	1.180e-4	4.680e-6
B	0.02	0.0171	0.0274	4.652e-3	1.109e-3	1.751e-3	1.191e-3	8.097e-4	1.376e-4	9.360e-5	



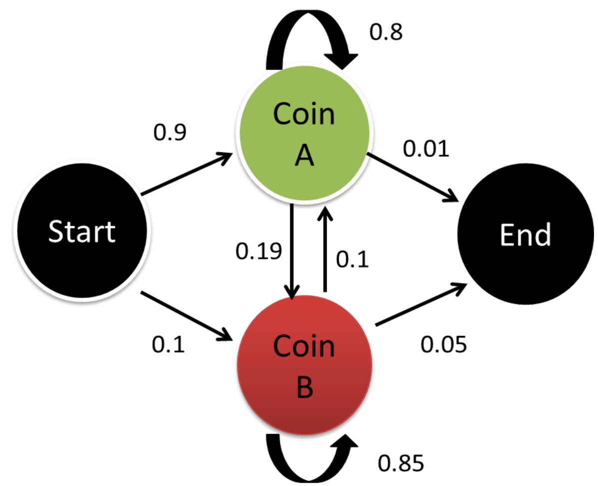
Let $f_j(i) = \max_{\{\pi_0,\ldots,\pi_{i-1}\}} (\Pr(x_0,\ldots,x_{i-1},x_i,\pi_0,\ldots,\pi_{i-1},\pi_i = j))$

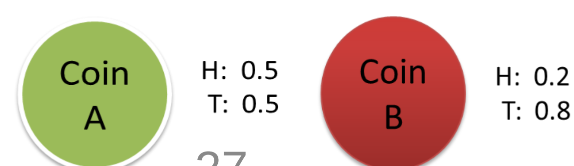
Initialization (j=1…N) $f_j(0) = \pi_j e_j(x_0)$

Recursion (i=1…L)

$$f_j(i) = e_j(x_i)\max_k (f_k(i-1)a_{kj});$$

$$ptr_j(i) = \arg\max_k (f_k(i-1)a_{kj}).$$

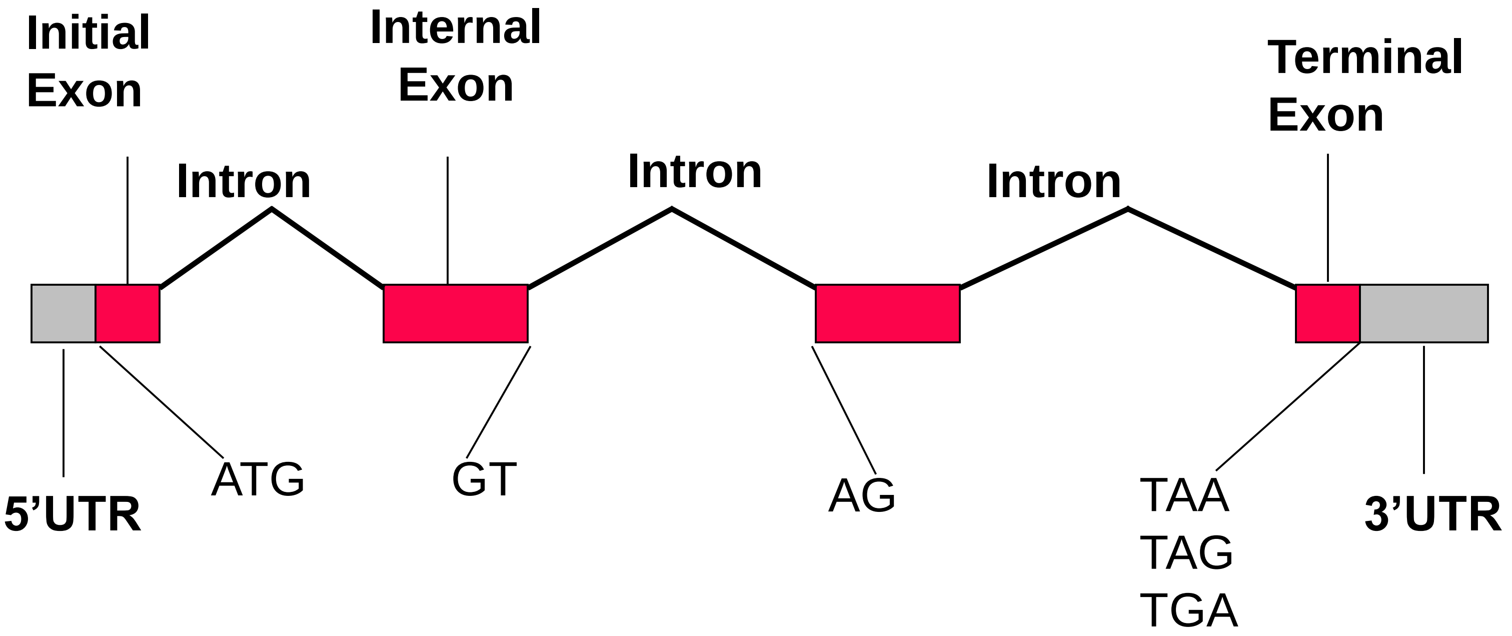




Problem 3. Model parameter estimation

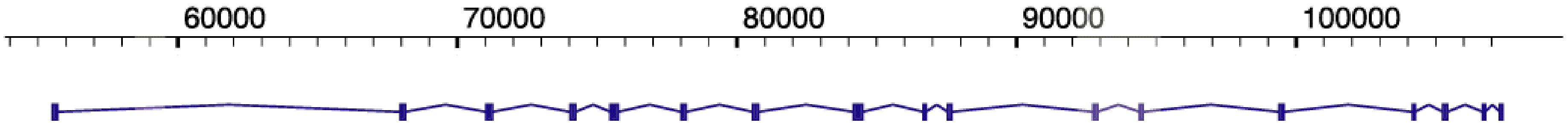
- See
  - Rabiner, L.(1989) A Tutorial on Hidden Markov Models and Selected Applications in Speech Recognition. Proceedings of the IEEE, 77 (2) 257-286
  - Rabiner, L., and Juang, Biing-Hwang, (1993), Fundamentals of Speech Recognition, Prentice Hall.

Gene Structure prediction with HMM



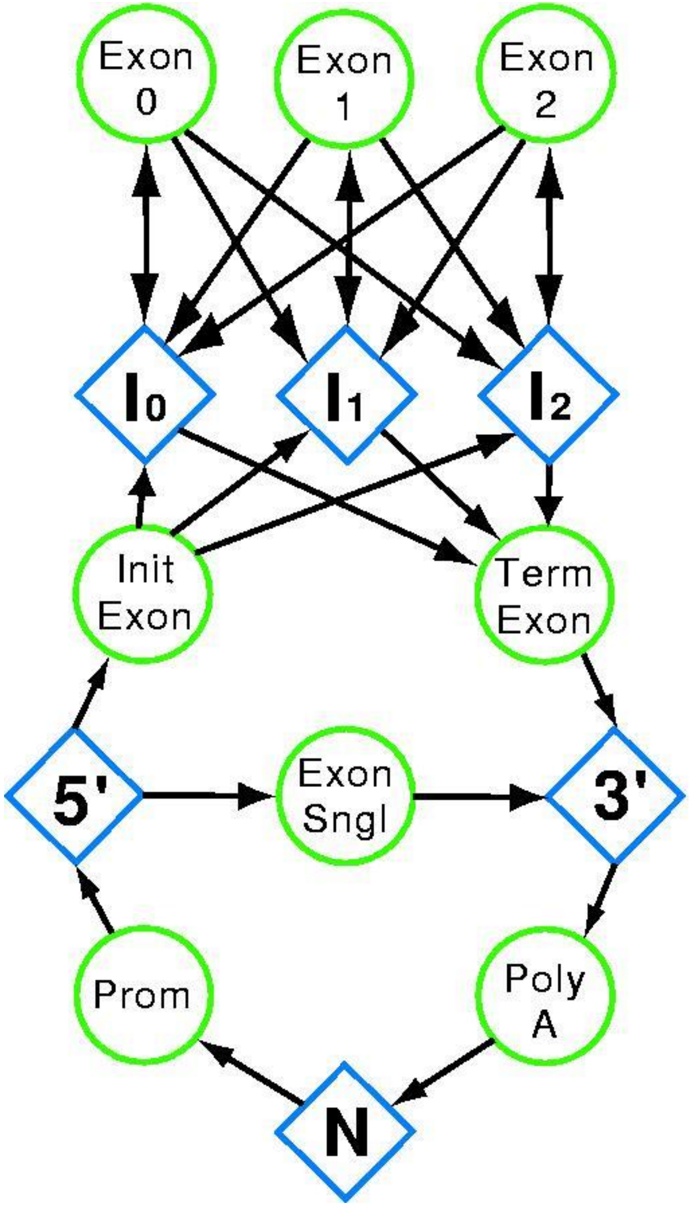
A gene is a highly structured region of DNA, it is a functional unit of inheritance.

A Typical Human Gene Structure



Gene Prediction Model

- HMM (27 states)
- Each state
  - For a gene structure
- State-specific models (Generalized HMM)
  - Length distribution
  - Sequence content



Another example: Pair HMM for local alignment