生物信息学：导论与方法
Bioinformatics: Introduction and Methods

生物信息学：导论与方法

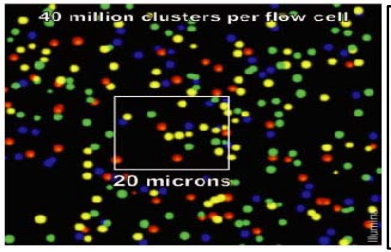
Bioinformatics: Introduction and Methods

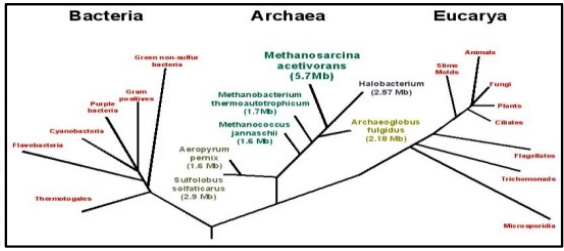
北京大学生物信息学中心 高歌、魏丽萍

Ge Gao & Liping Wei

Center for Bioinformatics, Peking University

TAACCCTAACCCTAACCCTAACCCTAACCCTA
CCTAACCCTAACCCTAACCCTAACCCTAACCC
CCCTAACCCCTAACCCTAACCCTAACCCTAAC
AACCCTAACCCTAACCCTAACCCCTAACCCTA
ACCCTAACCCCAACCCCAACCCCAACCCCAAC
CTACCCTAACCCTAACCCTAACCCTAACCCTA
ACCCTAACCCTAACCCTAACCCCTAACCCTAA



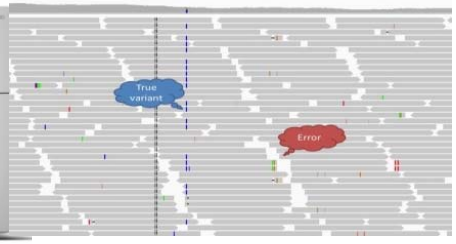


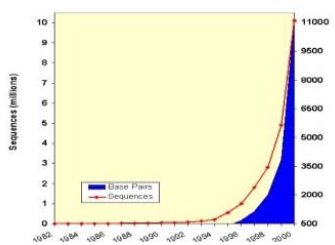
Markov Model

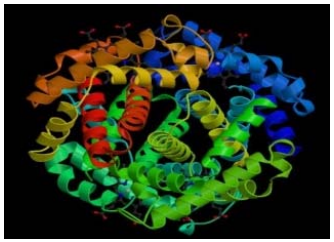
北京大学生物信息学中心 高歌

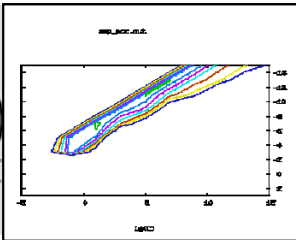
Ge Gao, Ph.D.

Center for Bioinformatics, Peking University

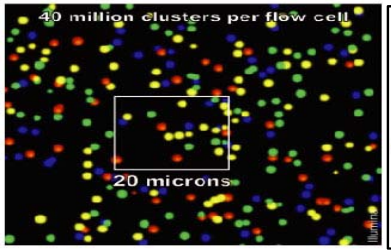


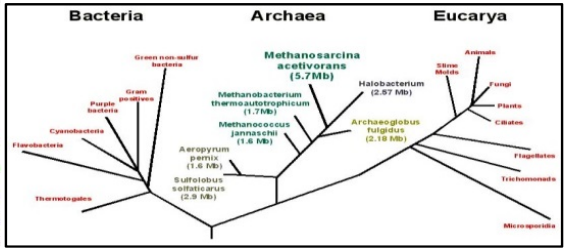






TAACCCTAACCCTAACCCTAACCCTAACCCTA
CCTAACCCTAACCCTAACCCTAACCCTAACCC
CCCTAACCCCTAACCCTAACCCTAACCCTAAC
AACCCTAACCCTAACCCTAACCCCTAACCCTA
ACCCTAACCCCAACCCCAACCCCAACCCCAAC
CTACCCTAACCCTAACCCTAACCCTAACCCTA
ACCCTAACCCTAACCCTAACCCCTAACCCTAA



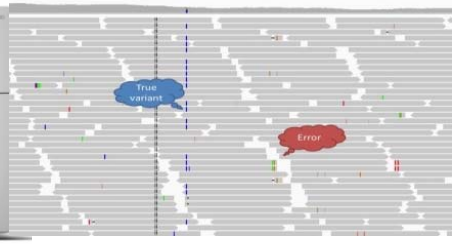


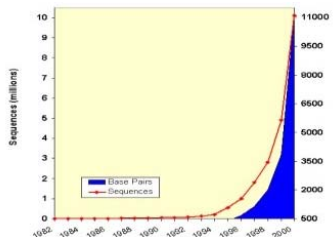
Unit 1:
From States to Markov Chain

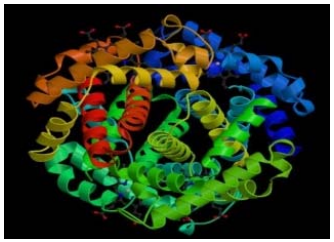
北京大学生物信息学中心 高歌

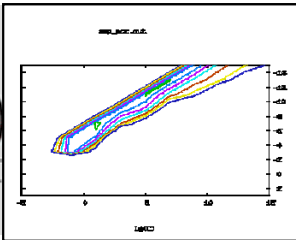
Ge Gao, Ph.D.

Center for Bioinformatics, Peking University







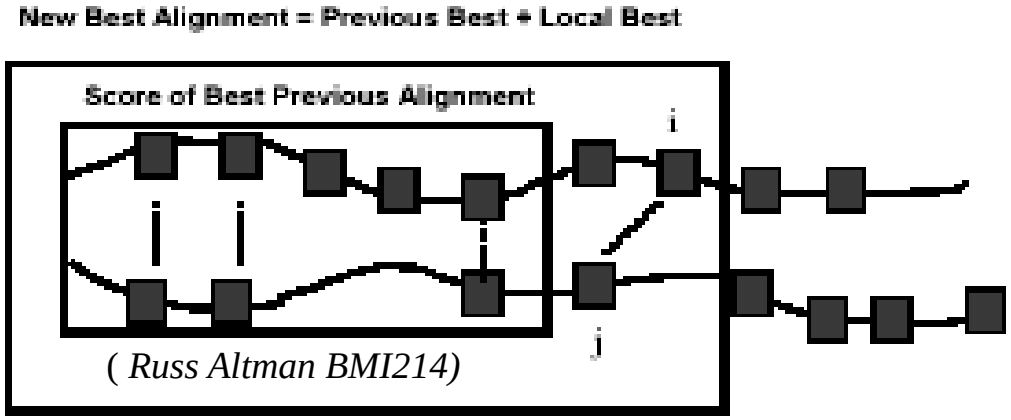


Affine gap penalty: opening a gap receives a score of d; extending a gap receives a score of e.

Penalty = d + (n-1)* e

```
#=======================================
#
# Aligned_sequences: 2
# 1: HBA_HUMAN
# 2: HBB_HUMAN
# Matrix: EBLOSUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
#
# Length: 149
# Identity:      65/149 (43.6%)
# Similarity:    90/149 (60.4%)
# Gaps:           9/149 ( 6.0%)
# Score: 292.5
#
#
#=======================================

HBA_HUMAN          1 MV-LSPADKTNVKAAWGKVGAHAGEYGAEALERMFLSFPTTKTYFPHF-D     48
                     || |:|.:|:.|.|.||||  :..|.|.|||.|:.:.:|.|:.:|..| |
HBB_HUMAN          1 MVHLTPEEKSAVTALWGKV--NVDEVGGEALGRLLVVYPWTQRFFESFGD     48

HBA_HUMAN         49 LS-----HGSAQVKGHGKKVADALTNAVAHVDDMPNALSALSDLHAHKLR     93
                     ||     .|:.:||.|||||..|.::.:||:|::....:.||:||..||.
HBB_HUMAN         49 LSTPDAVMGNPKVKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLH     98

HBA_HUMAN         94 VDPVNFKLLSHCLLVTLAAHLPAEFTPAVHASLDKFLASVSTVLTSKYR    142
                     |||.||:||.:.|:..||.|...||||.|.|:..|.:|.|:..|..||.
HBB_HUMAN         99 VDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH    147
```

Alignment as (a series of) state(s)



		A	A	G
	0	-5		
A		2	-3	
G				-1
C				-6

L S P -

\- T P E

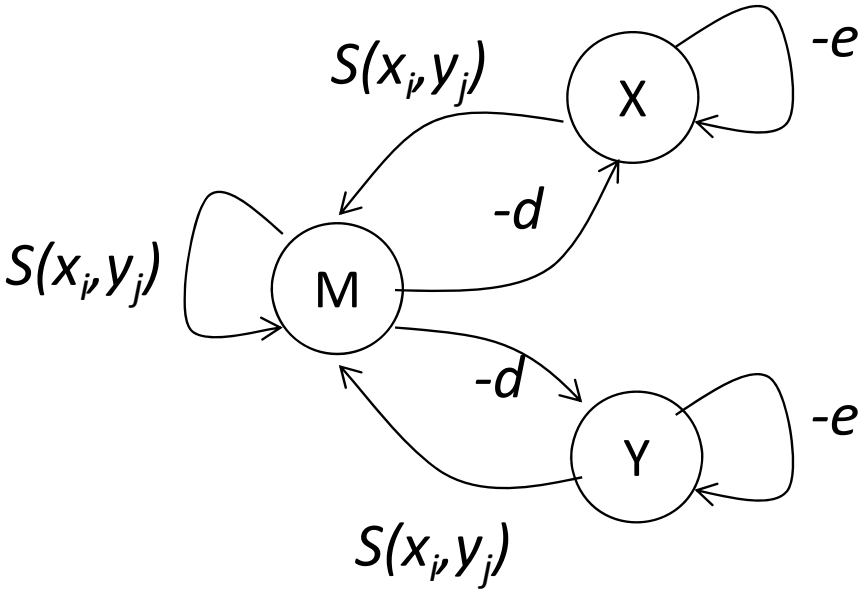
X M M Y

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

A A G -

A - G C

M X M Y

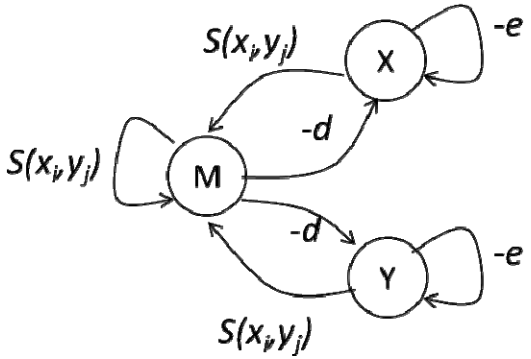


M	*Match (**not necessarily identical**)*
X	*Insert* at sequence X (delete at sequence Y)
Y	*Insert* at sequence Y (delete at sequence X)

d	Gap open
e	Gap Extension

- M (i,j) is the score of the best alignment between $x_{1...i}$ and $y_{1...j}$, given $\boldsymbol{x_i}$ **aligned to** $\boldsymbol{y_j}$
- X (i,j) is the score of the best alignment between $x_{1...i}$ and $y_{1...j}$, given $\boldsymbol{x_i}$ **aligned to *a gap***
- Y (i,j) is the score of the best alignment between $x_{1...i}$ and $y_{1...j}$, given $\boldsymbol{y_j}$ **aligned to *a gap***

$$M(i,\ j) = \max \begin{cases} M(i-1,\ j-1) + s(x_i, y_j) \\ X(i-1,\ j-1) + s(x_i, y_j) \\ Y(i-1,\ j-1) + s(x_i, y_j) \end{cases}$$



$$X(i,\ j) = \max \begin{cases} M(i-1,\ j) - d \\ X(i-1,\ j) - e \end{cases}$$

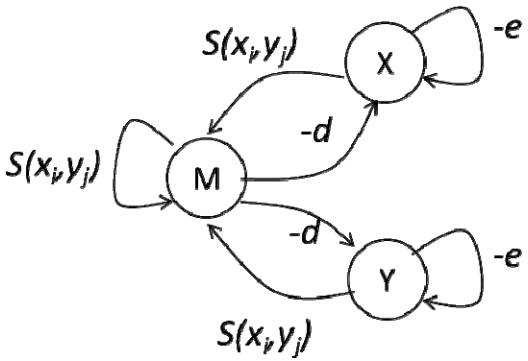
$$Y(i,\ j) = \max \begin{cases} M(i,\ j-1) - d \\ Y(i,\ j-1) - e \end{cases}$$

x_i aligned to y_j

$$M(i, j) = \max \begin{cases} M(i-1, j-1) + s(x_i, y_j) & \text{after a match} \\ X(i-1, j-1) + s(x_i, y_j) \\ Y(i-1, j-1) + s(x_i, y_j) \end{cases} \text{after a gap}$$

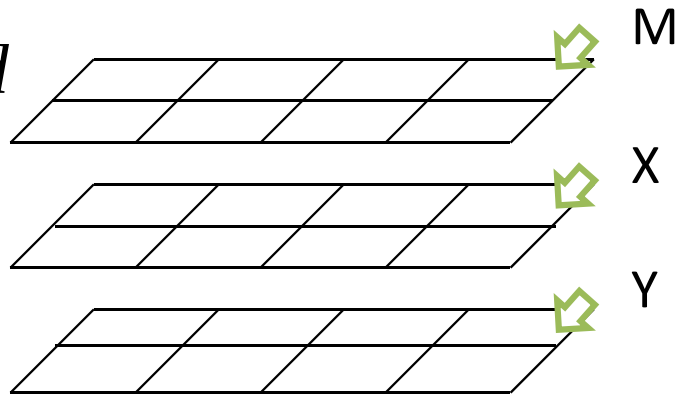
x_i aligned to *a gap*

$$X(i, j) = \max \begin{cases} M(i-1, j) - d \\ X(i-1, j) - e \end{cases}$$



y_j aligned to *a gap*

$$Y(i, j) = \max \begin{cases} M(i, j-1) - d \\ Y(i, j-1) - e \end{cases}$$



Andrei Andreyevich Markov (1856~1922)

The Mathematics Genealogy Project

Ph.D. University of St. Petersburg 1884

Dissertation: *On Some Applications of Algebraic Continuous Fractions*

Advisor: Pafnuty Chebyshev

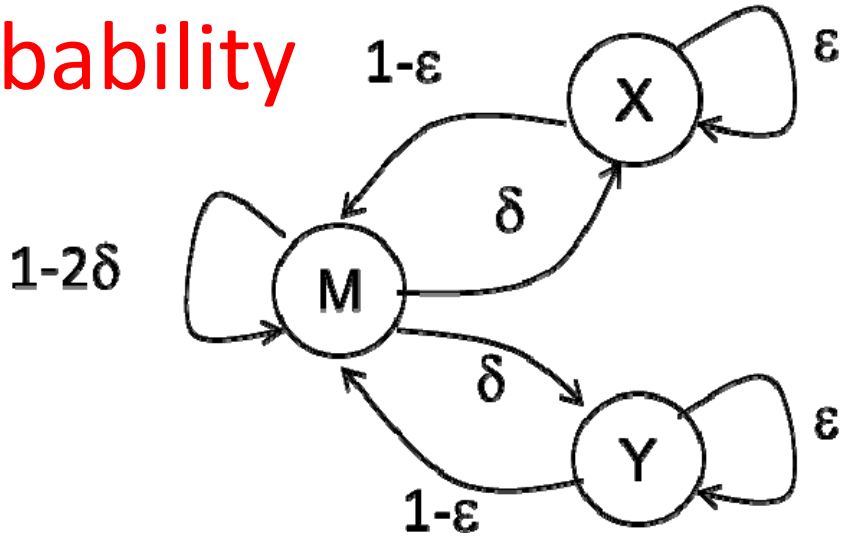
Student(s):
Click here to see the students listed in chronological order.

Name	School	Year	Descendants
Abram Besicovitch	University of St. Petersburg	1912	34
Nikolai Gunter	University of St. Petersburg	1915	124
Jacob Tamarkin	University of St. Petersburg	1917	778
Georgy Voronoy	University of St. Petersburg	1897	2100

According to our current on-line database, Andrei Markov has 4 students and 3039 descendants.

Markov Chain

- A Markov chain describes a discrete stochastic process at successive times. The transitions from one state to any of all states, including itself, are governed by a probability distribution.



Markov Chain

- $P(x_t \mid x_1 \ldots x_{t-1}) = P(x_i \mid x_{t-m} \ldots x_{t-1})$
  - $X_t = f(X_{t-1}, X_{t-2}, \ldots X_{t-m})$

- A chain of random variables in which the next one depends (only) on the current one
  - $P(x_t \mid x_1 \ldots x_{t-1}) = P(x_i \mid x_{t-1})$

Transition Probability

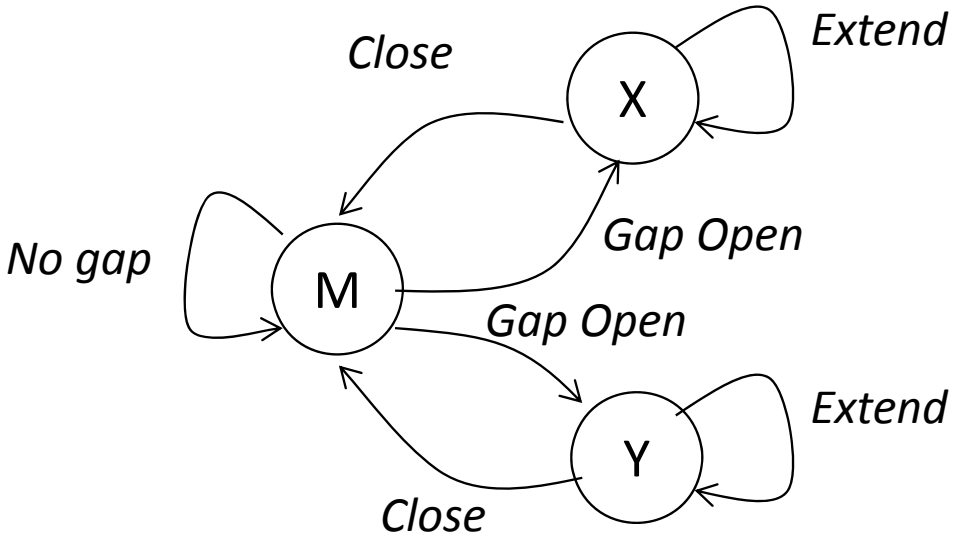
$$a_{kl} = P(X_t = S_l \mid X_{t-1} = S_k)$$

$$a_{lk} = P(X_t = S_k \mid X_{t-1} = S_l)$$

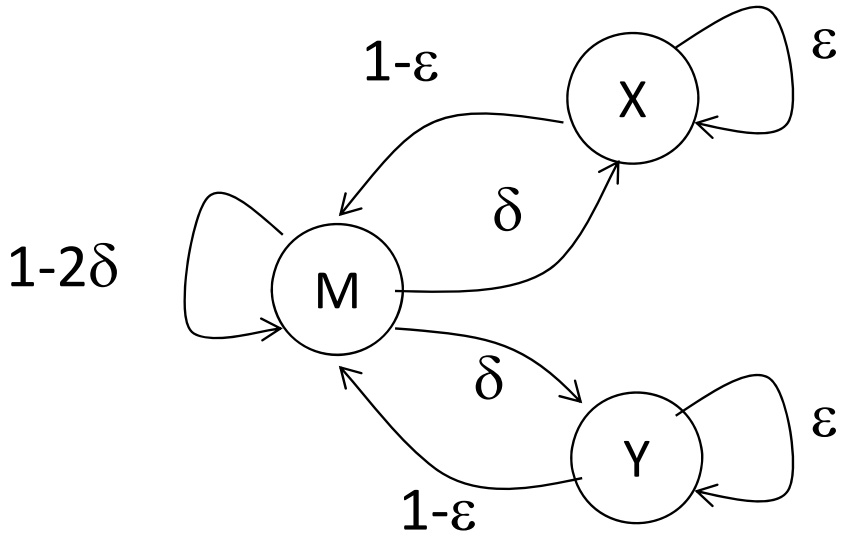
	S_1	…	S_k	…	S_l	…	S_n
S_1							
…							
S_k					a_{kl}		
…							
S_l			a_{lk}				
…							
S_n							

Affine gap penalty: opening a gap receives a score of d; extending a gap receives a score of e.

Penalty = d + (n-1)* e



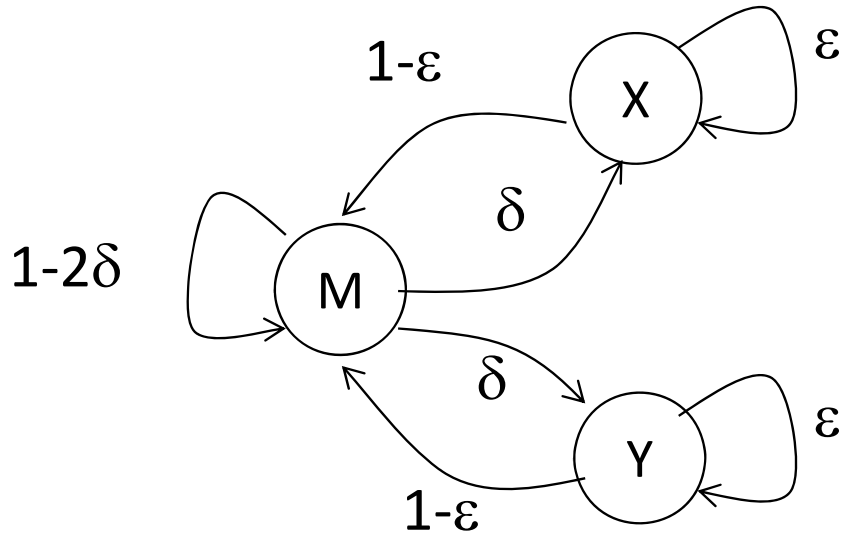

```
#=======================================
#
# Aligned_sequences: 2
# 1: HBA_HUMAN
# 2: HBB_HUMAN
# Matrix: EBLOSUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
#
# Length: 149
# Identity:      65/149 (43.6%)
# Similarity:    90/149 (60.4%)
# Gaps:           9/149 ( 6.0%)
# Score: 292.5
#
#
#=======================================

HBA_HUMAN         1 MV-LSPADKTNVKAAWGKVGAHAGEYGAEALERMFLSFPTTKTYFPHF-D     48
                    || |:|.:|:.|.|.||||  :..|.|.|||.|:.:.:|.|:.:|..| |
HBB_HUMAN         1 MVHLTPEEKSAVTALWGKV--NVDEVGGEALGRLLVVYPWTQRFFESFGD     48

HBA_HUMAN        49 LS-----HGSAQVKGHGKKVADALTNAVAHVDDMPNALSALSDLHAHKLR     93
                    ||     .|:.:||.|||||..|.::.:||:|::...:.||:||..||.
HBB_HUMAN        49 LSTPDAVMGNPKVKAHGKKVLGAFSDGLAHLDNLKGTFATLSELHCDKLH     98

HBA_HUMAN        94 VDPVNFKLLSHCLLVTLAAHLPAEFTPAVHASLDKFLASVSTVLTSKYR    142
                    |||.||:||.:.|:..||.|...|||.|.|:..|.:|.|:..|..||.
HBB_HUMAN        99 VDPENFRLLGNVLVCVLAHHFGKEFTPPVQAAYQKVVAGVANALAHKYH    147
```



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

	M	X	Y
M	1-2δ	δ	δ
X	1-ε	ε	0
Y	1-ε	0	0



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

L S P -
- T P E ➡ *X M M Y*

$$P(XMMY) = a_{XM} a_{MM} a_{MY}$$
$$= (1-\varepsilon)(1-2\delta)\delta$$

	M	X	Y
M	1-2δ	δ	δ
X	1-ε	ε	0
Y	1-ε	0	0

Summary Questions

- There isn’t direct transition between X and Y in our model, do you think it’s reasonable? Explain your answer.

- Is it possible to have global alignment based on the rephrased Markov Chain-based model? Explain your answer.

生物信息学：导论与方法
Bioinformatics: Introduction and Methods