CS 466
Introduction to Bioinformatics

Lecture 21

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Nov 12, 2021

Outline

- Hidden Markov Models: Viterbi algorithm

Reading:

- Jones and Pevzner: Chapters 11.1-11.3
- Lecture notes

CpG Islands

Question: Given four nucleotides $\Sigma = \{A, T, C, G\}$, what is the probability of observing dinucleotide CG?

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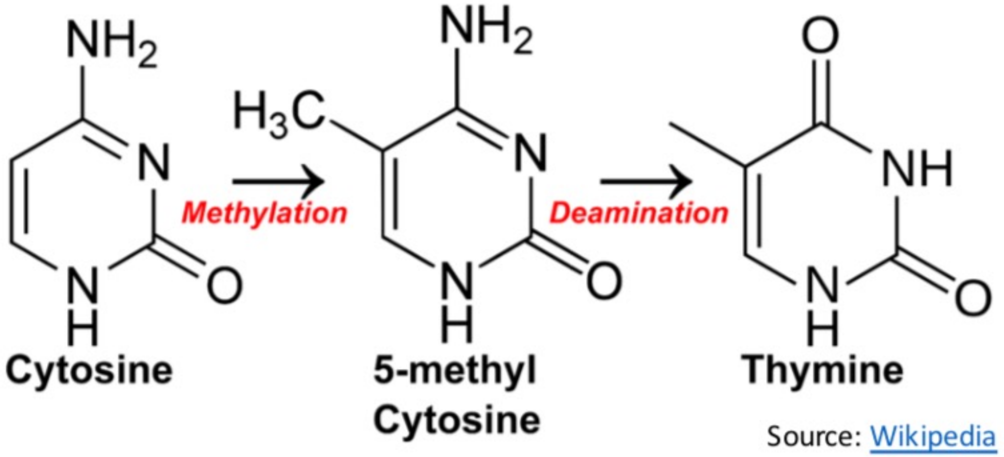


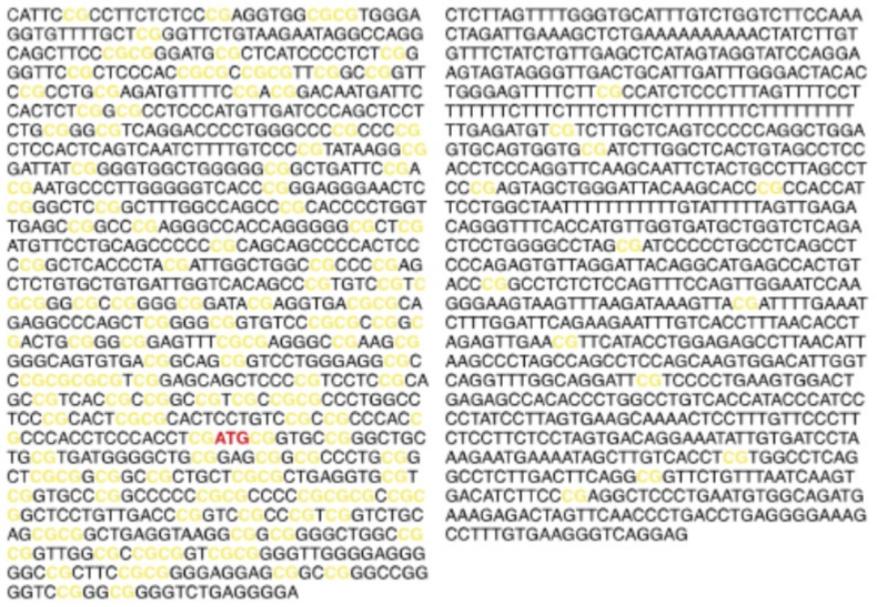
Source: Wikipedia

CG → *C*G* → *TG*

CG is least observed dinucleotide as C is easily methylated and has tendency to mutate into a T afterwards

CpG Islands

- Methylation is suppressed around promoter regions of genes in a genome. So CG appears at relatively high frequency within these CpG island.
- Finding CpG islands in a genome is an important problem for annotating genes and regulatory regions.



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CTCCACTCAGTCAATCTTTTGTCCCCGTATAAGGCG
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CAGGTTTGGCAGGATTCGTCCCCTGAAGTGGACT
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CTCCTTCTCCTAGTGACAGGAAATATTGTGATCCTA
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GCCTCTTGACTTCAGGCGGTTCTGTTTAATCAAGT
GACATCTTCCCGAGGCTCCCTGAATGTGGCAGATG
AAAGAGACTAGTTCAACCCTGACCTGAGGGGAAAG
CCTTTGTGAAGGGTCAGGAG
```

Left: CpG sites at 1/10 nucleotides, constituting a CpG island. The sample is of a gene-promoter, the highlighted ATG consitutes the start codon.
Right: CpG sites present at every 1/100 nucleotides, consituting a more normal example of the genome, or a region of the genome that is commonly methylated.

Source: Wikipedia

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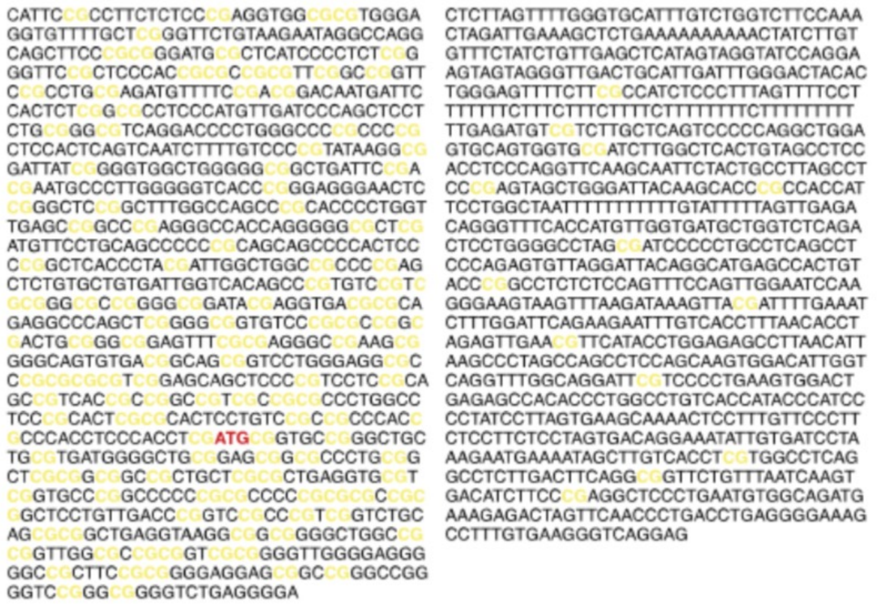

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GGTTCCGCTCCCACCGCGCCGCGTTCGGCCGGTT
CCGCCTGCGAGATGTTTTCCGACGGACAATGATTC
CACTCTCGGCGCCTCCCATGTTGATCCCAGCTCCT
CTGCGGGCGTCAGGACCCCTGGGCCCCGCCCCG
CTCCACTCAGTCAATCTTTTGTCCCCGTATAAGGCG
GATTATCGGGGTGGCTGGGGGCGGCTGATTCCGA
CGAATGCCCTTGGGGGTCACCCGGGAGGGAACTC
CGGGCTCCGGCTTTGGCCAGCCCGCACCCCTGGT
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GAGGCCCAGCTCGGGGCGGTGTCCCGCGCCGGC
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GGTCCGGGCGGGGTCTGAGGGGA

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CCCGAGTAGCTGGGATTACAAGCACCCGCCACCAT
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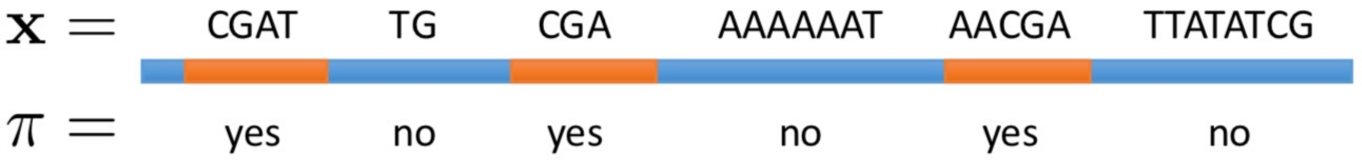
Source: Wikipedia

Input: DNA sequence $\mathbf{x} = x_1 x_2 \ldots x_n$

Output: $\pi : \{1, \ldots, n\} \rightarrow \{\text{yes}, \text{no}\}$



Question: How do we identify CpG islands?

A Related Problem: Fair Bet Casino

- Game is to flip coins, two outcomes:

Head or **T**ail

- Two coins: **F**air and **B**iased

$$\Pr(H \mid F) = \Pr(T \mid F) = 1/2$$
$$\Pr(H \mid B) = 3/4, \Pr(T \mid B) = 1/4$$

- The crooked dealer changes between Fair and Biased coins with probability 10%

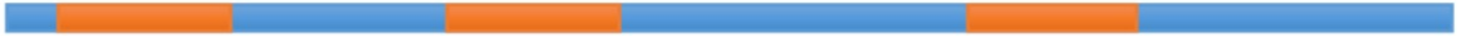
CpG Islands and Fair Bet Casino

CG Islands

Input: DNA sequence $\mathbf{x} = x_1 x_2 \ldots x_n$ where $x_i \in \{A, T, C, G\}$

Output: $\pi : \{1, \ldots, n\} \rightarrow \{\text{yes}, \text{no}\}$

$\mathbf{x} =$ CGAT TG CGA AAAAAAT AACGA TTATATCG



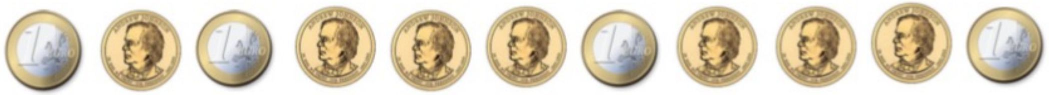
$\pi =$ yes no yes no yes no

Fair Bet Casino

Input: Coin flips $\mathbf{x} = x_1 x_2 \ldots x_n$ where $x_i \in \{H, T\}$

Output: $\pi : \{1, \ldots, n\} \rightarrow \{F, B\}$

$\mathbf{x} =$



$\pi =$ F F F B B B B B F F F

$\pi' =$ F F F B B B F F F F F

Question: Given **x**, what is more likely: **π** or **π**′?

Markov Model $\mathcal{M} = (Q, A)$

- Set of states *Q*
  - Markov property:

$$\Pr(Q_i = q_i \mid Q_1 = q_1, \ldots, Q_{i-1} = q_{i-1}) = \Pr(Q_i = q_i \mid Q_{i-1} = q_{i-1})$$

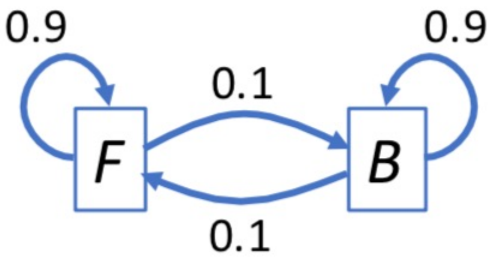
- Transition probabilities $A = [a_{ij}]$ on pairs of states
  - Rows sum to 1

Andrey Markov (source: Wikipedia)

Fair Bet Casino

$Q = \{F, B\}$

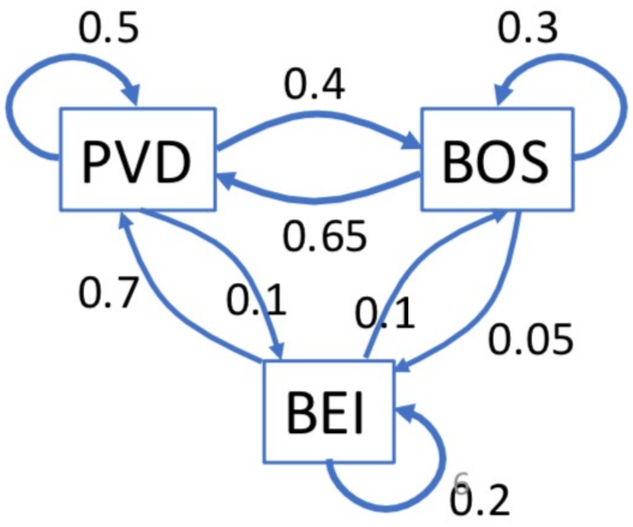
$$A = \begin{pmatrix} 0.9 & 0.1 \\ 0.1 & 0.9 \end{pmatrix}$$



Where is the professor?

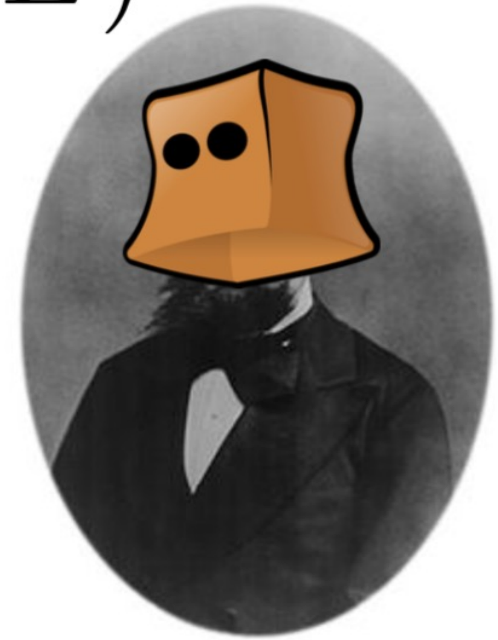
$Q = \{\text{Providence}, \text{Boston}, \text{Beijing}\}$

$$A = \begin{pmatrix} 0.5 & 0.4 & 0.1 \\ 0.65 & 0.3 & 0.05 \\ 0.7 & 0.1 & 0.2 \end{pmatrix}$$



Hidden Markov Model $\mathcal{M} = (Q, A, \Sigma, E)$

- Set of *hidden* states Q
  - Markov property
- Transition probabilities $A = [a_{ij}]$ on pairs of states
- Set of *emitted* symbols Σ
- Emission probabilities $E = [e_{ik}]$ on state-symbol pairs



Andrey Markov

<u>Two decisions:</u>

1. What symbol should I emit?
   [emission probabilities *E*]
2. What state should I move to next?
   [transition probabilities *A*]

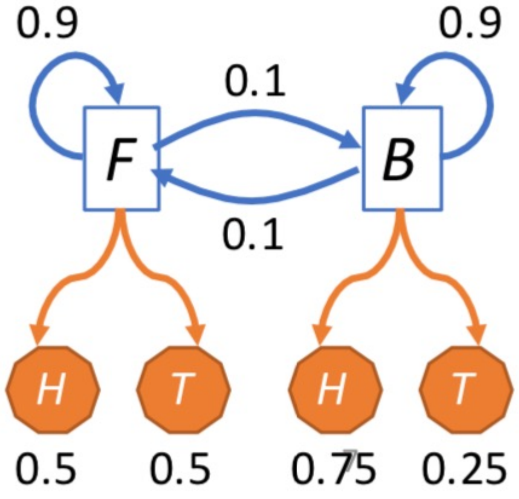
Fair Bet Casino

$$Q = \{F, B\}$$

$$A = \begin{array}{ccc} F & B & \\ 0.9 & 0.1 & F \\ 0.1 & 0.9 & B \end{array}$$

$$\Sigma = \{H, T\}$$

$$E = \begin{array}{ccc} H & T & \\ 0.5 & 0.5 & F \\ 0.75 & 0.25 & B \end{array}$$



Three Questions

Question 1:
What is the most probable path $\boldsymbol{\pi}^*$ that generated observations $\mathbf{x}$?

Question 2:
What is probability of observations $\mathbf{x}$ generated by any path $\boldsymbol{\pi}$?

Question 3:
What is the probability of observation x_i generated by state s?

Three Questions

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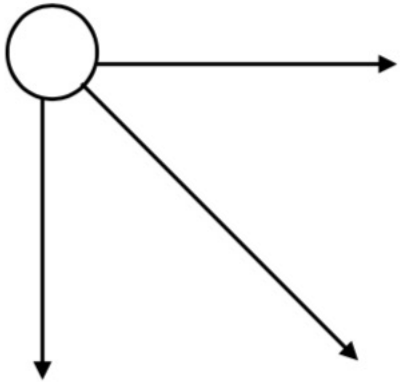
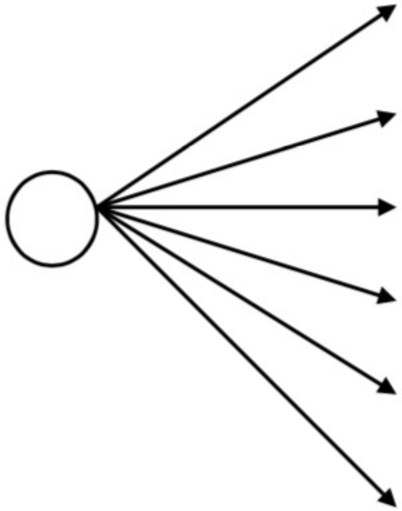
Joint Probability

Recurrence

Alignment vs. Decoding Problem



Valid directions in the *alignment problem.*



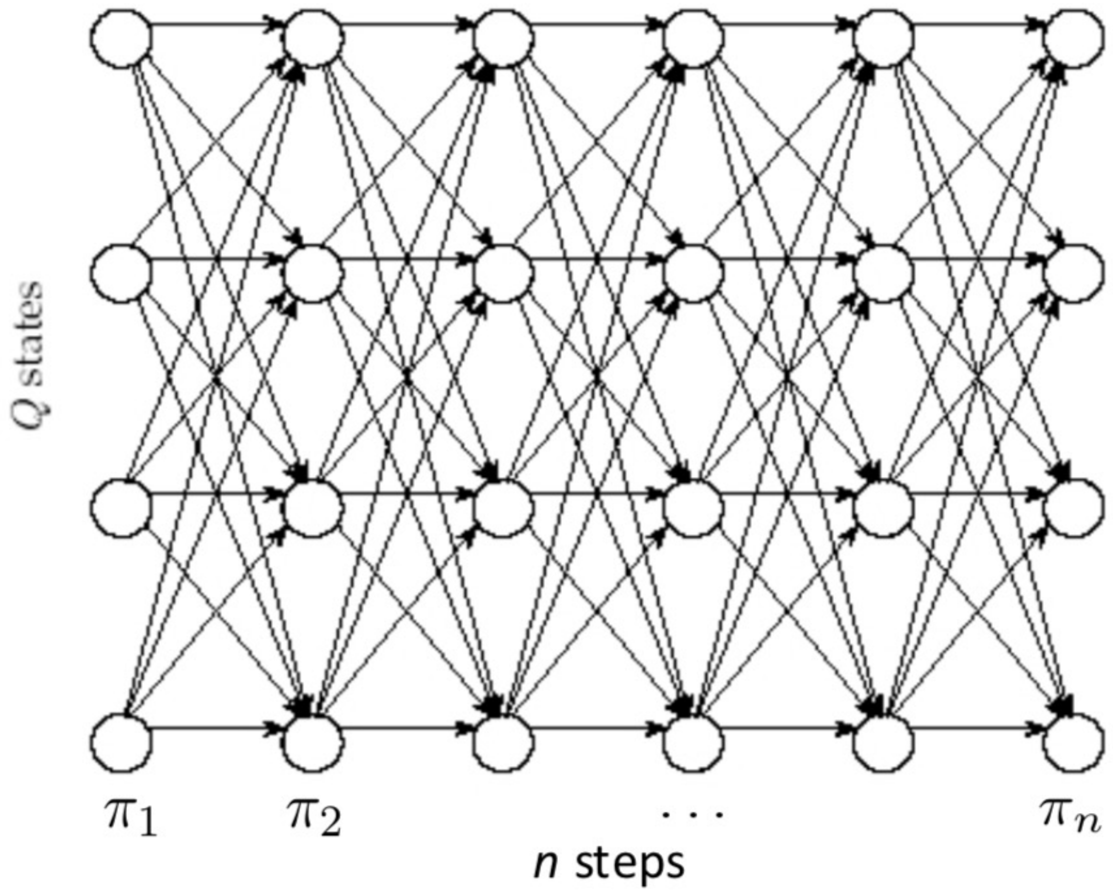
Valid directions in the *decoding problem.*

Viterbi Algorithm

- Finds path π^* with maximum $\Pr(\mathbf{x}, \pi^*)$

- Dynamic Programming algorithm

- Runs in $O(\#\text{edges}) = O(n|Q|^2)$



Viterbi Algorithm – Numerical Issues

Value of products can become extremely small, leading to underflow

$$v[s,i] = \begin{cases} a_{0,s} \cdot e_{s,x_1}, & \text{if } i = 1, \\ e_{s,x_i} \max_{t \in Q}\{v[t,i-1]a_{t,s}\}, & \text{if } i > 1. \end{cases}$$

Viterbi Algorithm – Numerical Issues

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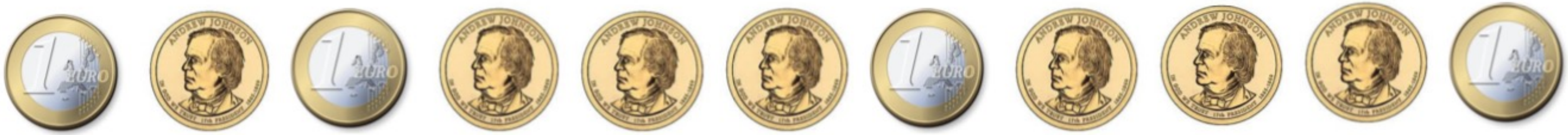
Use logarithms!

$$\log(v[s,i]) = \begin{cases} \log(a_{0,s}) + \log(e_{s,x_1}), & \text{if } i = 1, \\ \log(e_{s,x_i}) + \max_{t \in Q}\{\log(v[t,i-1]) + \log(a_{t,s})\}, & \text{if } i > 1. \end{cases}$$

Fair Bet Casino: Example

$\mathbf{x} =$ 

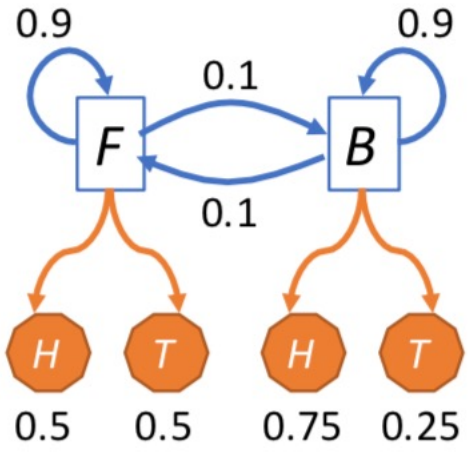
	0	1 (T)	2 (H)	3 (T)	4 (H)	5 (H)	6 (H)	7 (T)	8 (H)	9 (H)	10 (H)	11 (T)
F												
B												

$Q = \{F, B\}$

$$A = \begin{array}{cc} \begin{matrix} F & B \end{matrix} & \\ \begin{pmatrix} 0.9 & 0.1 \\ 0.1 & 0.9 \end{pmatrix} & \begin{matrix} F \\ B \end{matrix} \end{array}$$

$\Sigma = \{H, T\}$

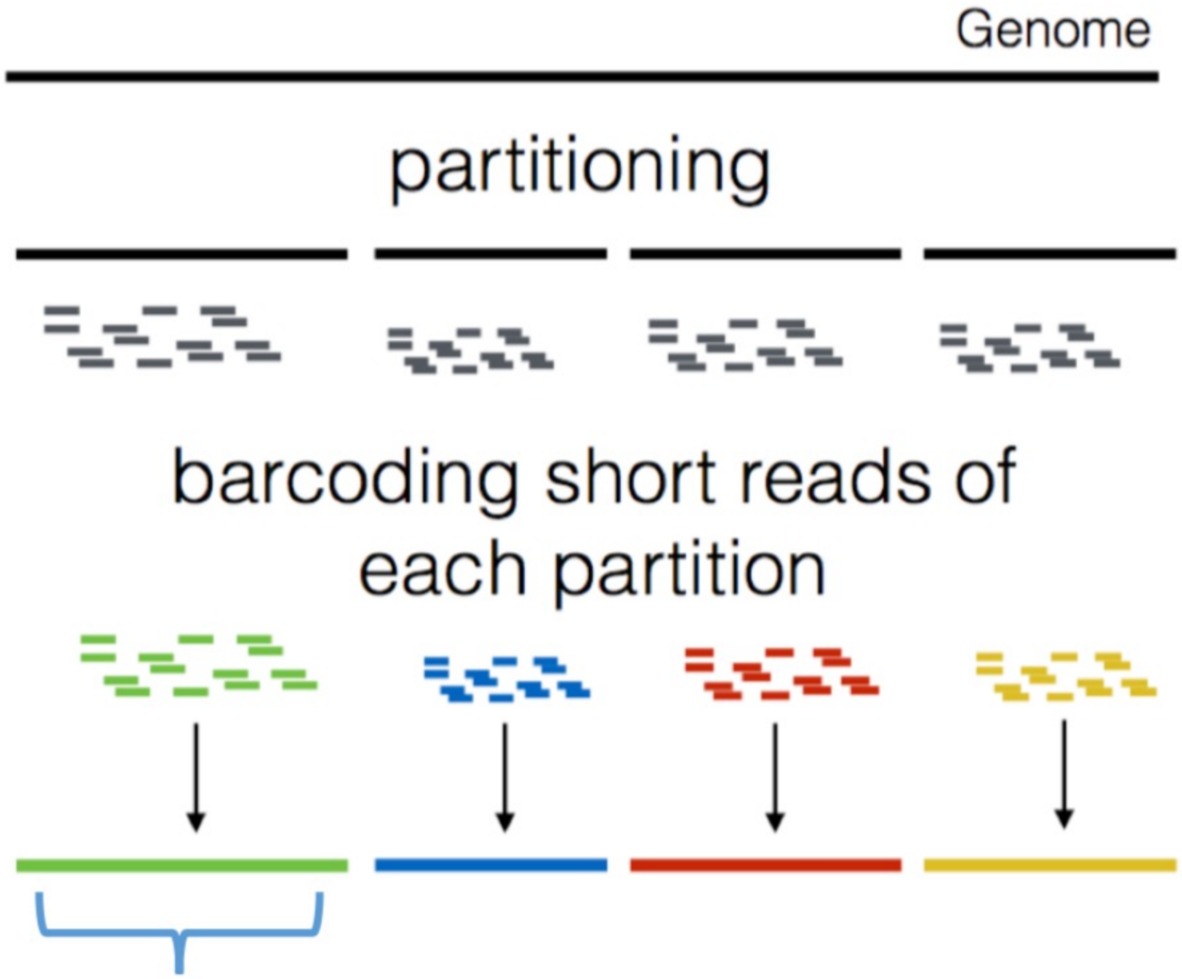
$$E = \begin{array}{cc} \begin{matrix} H & T \end{matrix} & \\ \begin{pmatrix} 0.5 & 0.5 \\ 0.75 & 0.25 \end{pmatrix} & \begin{matrix} F \\ B \end{matrix} \end{array}$$



$$v[s,i] = \begin{cases} a_{0,s} \cdot e_{s,x_1}, & \text{if } i = 1, \\ e_{s,x_i} \max_{t \in Q} \{v[t, i-1] a_{t,s}\}, & \text{if } i > 1. \end{cases}$$

10X Genomics: Synthetic Long Reads

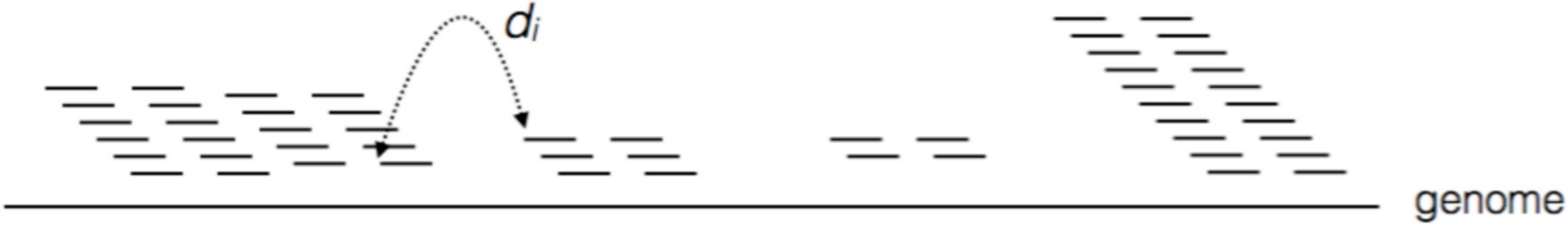
Genome indexing by partitioning and molecular barcoding



50-75 molecules per droplet

~50 kb, coverage ~0.1X

$R_j=\{r_i \mid \forall\, i,\ r_i \text{ contains barcode } j\}$: Paired-reads possessing barcode ***j***



Sort linked-reads and calculate distances between them

$$D_j=[d_i \mid \forall\, i,\ d_i : \text{distance between } r_i \text{ and } r_{i+1},\ r_i < r_{i+1}]$$

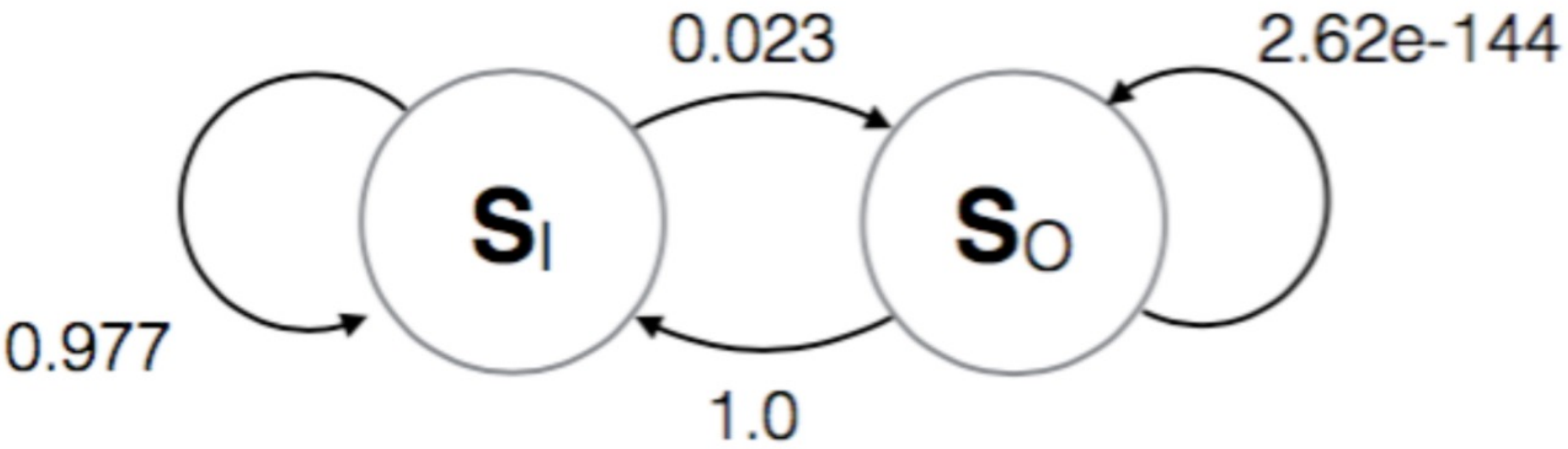
Define distances d_i as intra- or inter- long molecules

$$\Sigma_i = [d_1,\ d_2,\ d_3,\ \ldots\ d_{500},\ d_{501},\ d_{502},\ \ldots\ d_{1001},\ d_{1002},\ d_{1003},\ \ldots]$$

$$Q_j = [\ \mathrm{I},\ \ \mathrm{I},\ \ \mathrm{I},\ \ldots,\ \mathrm{I},\ \ \mathrm{O},\ \ \mathrm{I},\ \ldots,\ \ \mathrm{I},\ \ \mathrm{O},\ \ \mathrm{I},\ \ldots.\ ]$$

I: intra long molecule, O: inter long molecules

HMM

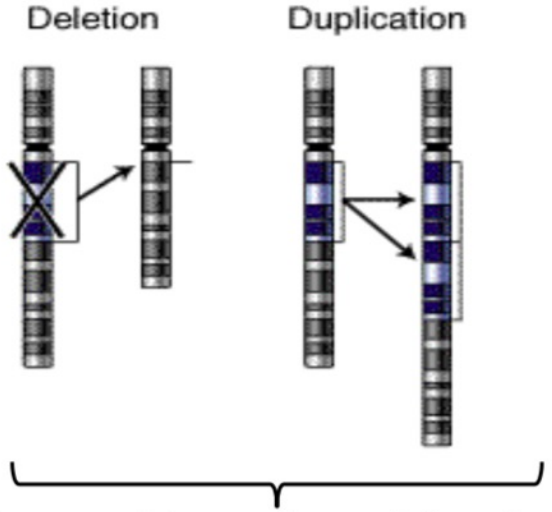


$$\Sigma_i = [d_1, d_2, d_3, \ldots d_{500}, d_{501}, d_{502}, \ldots d_{1001}, d_{1002}, d_{1003}, \ldots]$$

$$Q_j = [\underbrace{I, I, I, \ldots, I,}_{\ell_{j1}} O, \underbrace{I, \ldots, I,}_{\ell_{j2}} O, \underbrace{I,}_{\ell_{j3}} \ldots]$$

I: intra long molecule, O: inter long molecules

Copy Number Variation

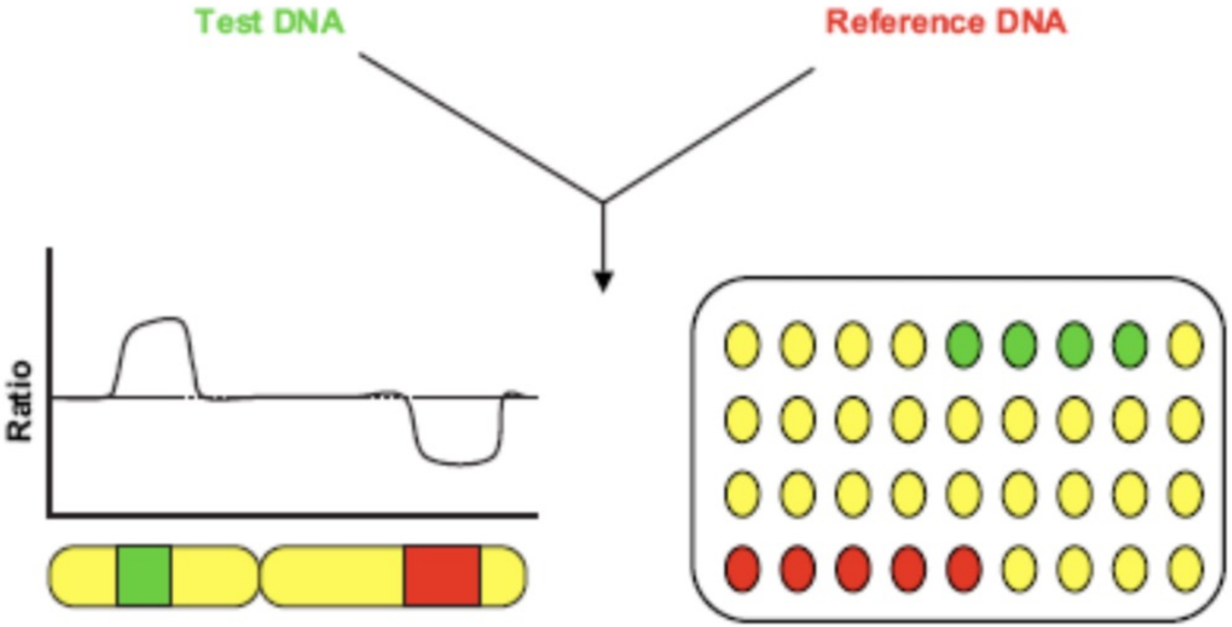


Copy Number Variants

- Different individuals may have different number of copies of segments of genome.
- These variants are associated with various diseases: autism, schizophrenia, cancer

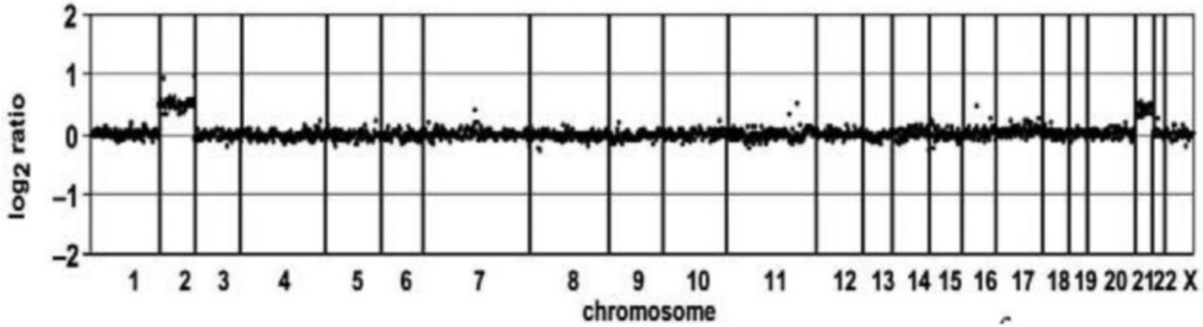
Measuring Copy Number Variants

Comparative Genomic Hybridization (CGH)

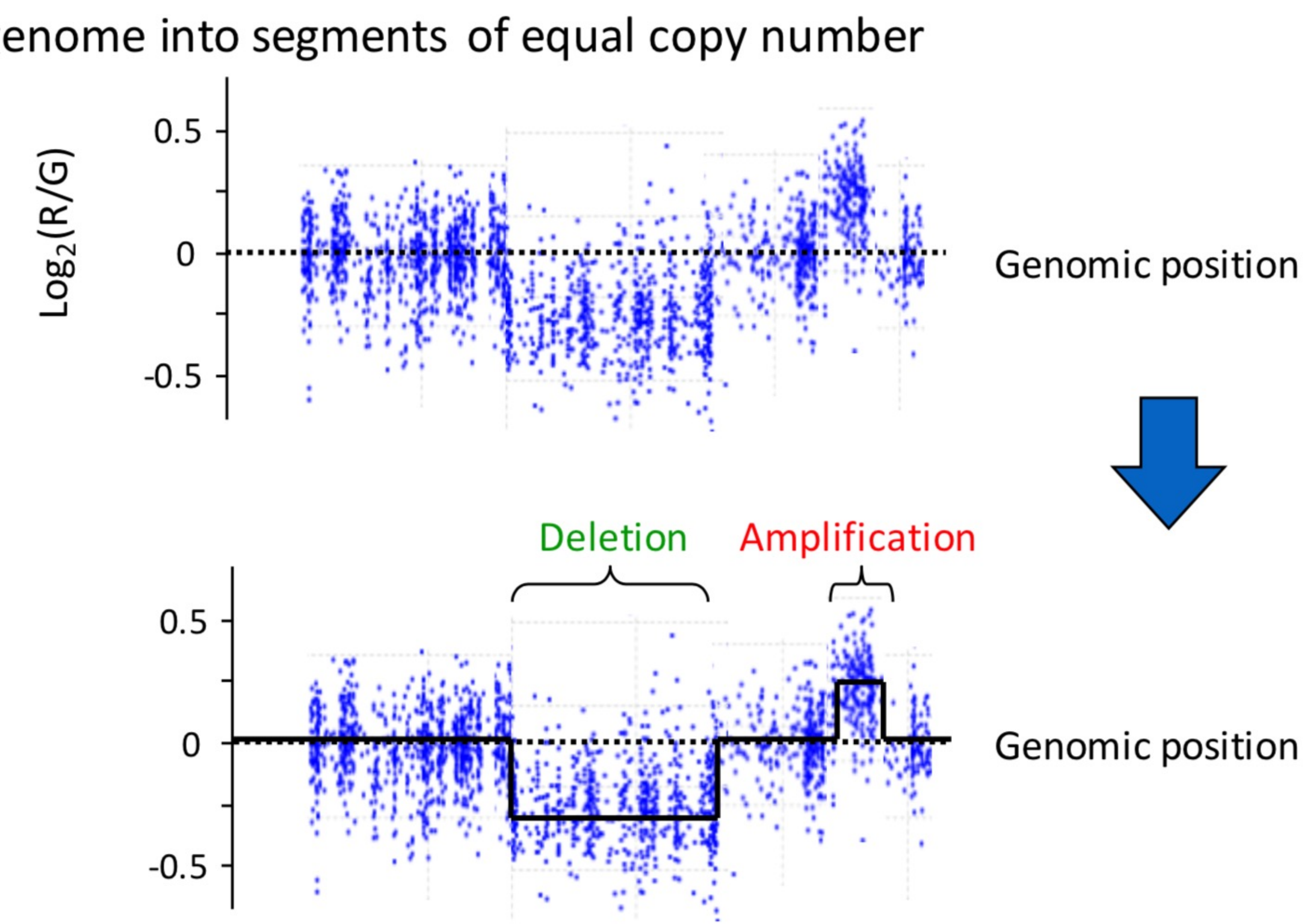


Chromosome CGH provides "cytogenetic" resolution ~ 10 Mb

Resolution of array CGH depends on spacing and length of clones

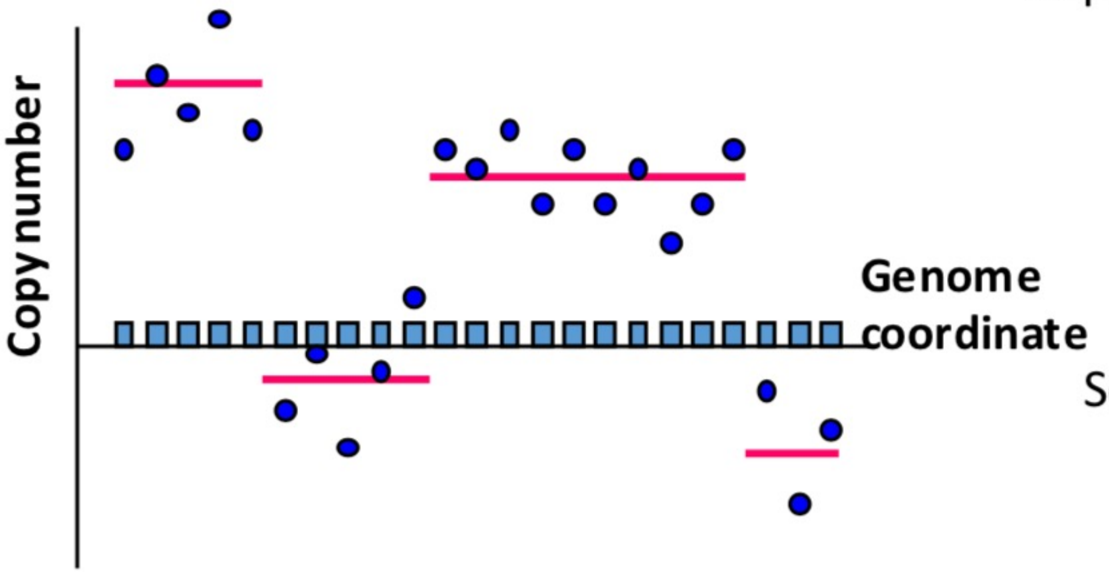


Segmentation and Copy Number Calling



Segmentation and Copy Number Calling

Divide genome into segments of equal copy number



Input: $X_i = \log_2 T_i / R_i$, clone i = 1, …, N

Output: Assignment $s(i) \in \{S_1, \ldots, S_K\}$ where S_i represent *copy number states*

Summary

- Markov property – Current state depends only on previous state
- Hidden Markov Models: states are not given only emitted symbols
- Viterbi algorithm: Find the most likely sequence of states given a set of observations

Reading:

- Jones and Pevzner: Chapters 11.1-11.3
- Lecture notes