582670 Algorithms for Bioinformatics

Lecture 2: Exhaustive search and motif finding

4.9.2014

These slides are based on previous years' slides by
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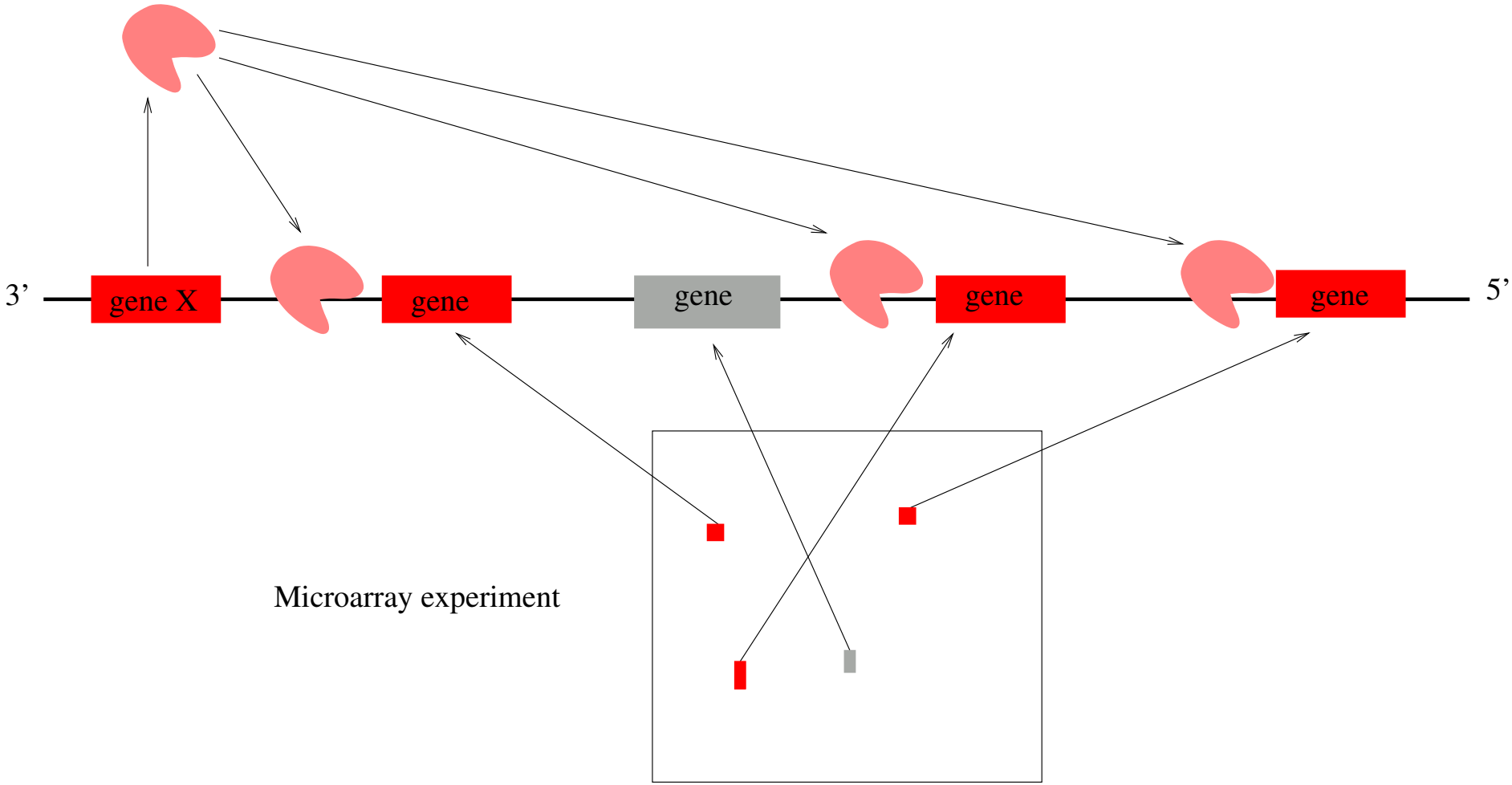
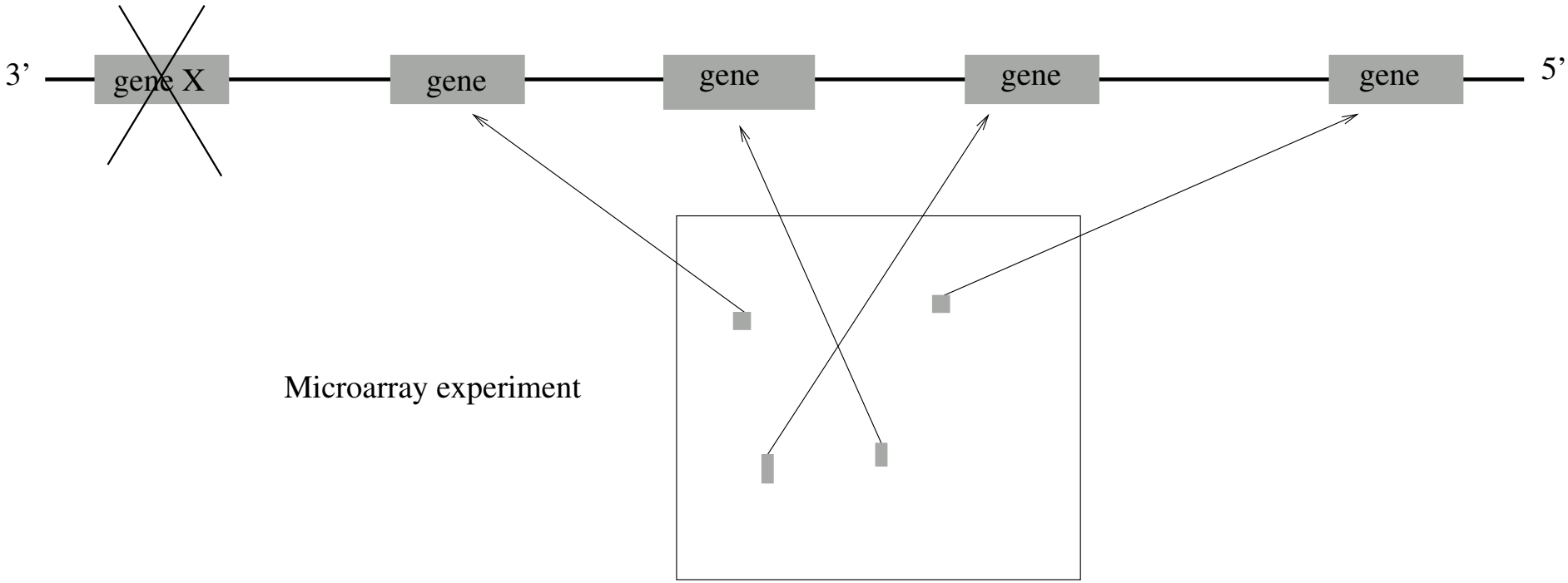
These slides use material from `http://bix.ucsd.edu/bioalgorithms/slides.php`

Outline

Biological Motivation



Biological Motivation (cont'd)



Gene Regulation

- Microarray experiments can be used to measure gene activity
- A gene can be knocked out to see what effect that has on gene activity
- An experiment can show that when one gene (gene X) is knocked out, 20 other genes stop being expressed.
- How can one gene have such a drastic effect?

Regulatory Proteins

- Gene X encodes a regulatory protein, a.k.a. a transcription factor (TF)
- The 20 unexpressed genes rely on gene X's TF to induce transcription
- A single TF may regulate multiple genes

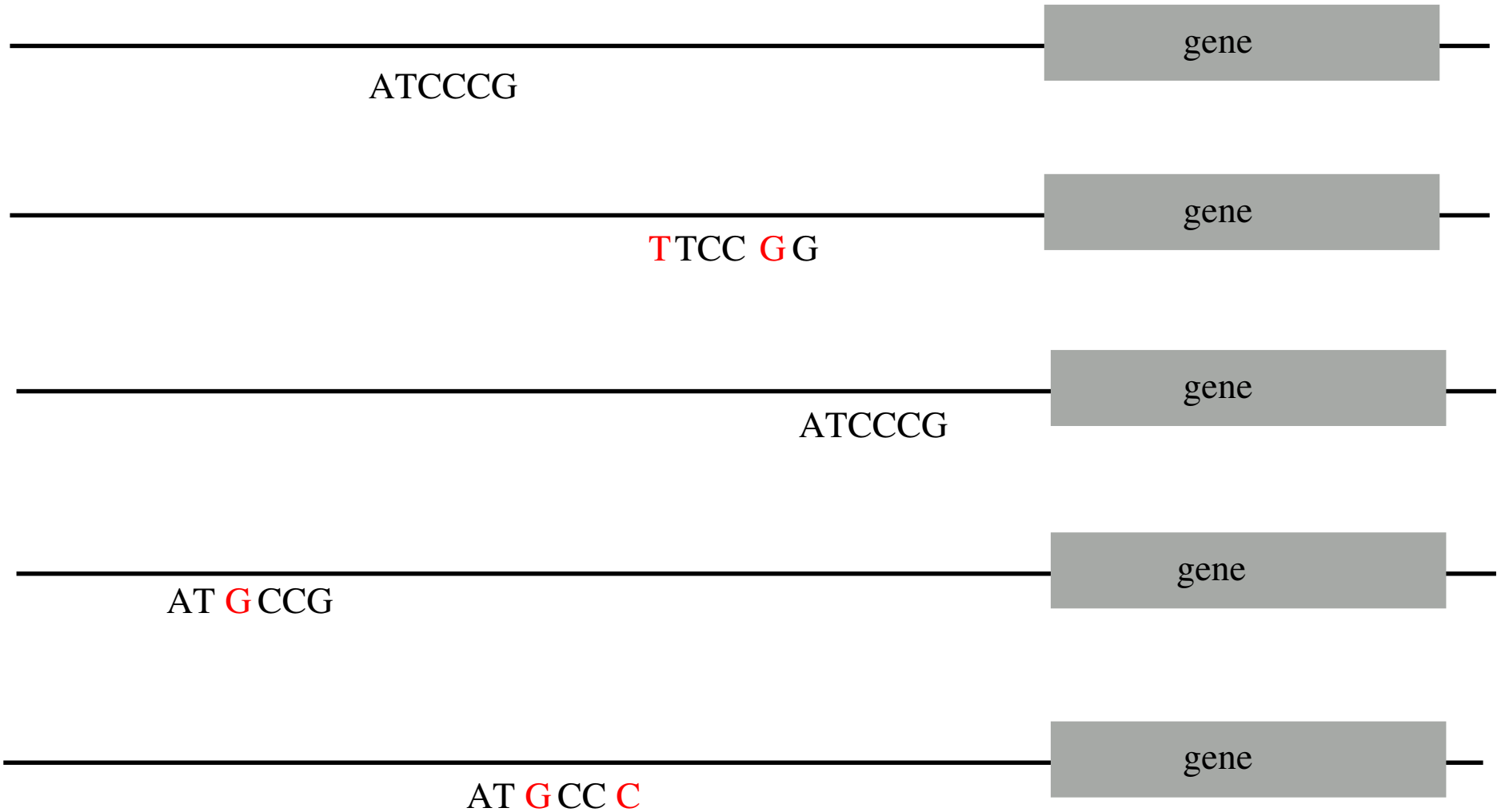
Regulatory Regions

- Every gene contains a regulatory region (RR) typically stretching 100-1000 bp upstream of the transcriptional start site
- Located within the RR are the Transcription Factor Binding Sites (TFBS), also known as motifs, specific for a given transcription factor
- TFs influence gene expression by binding to a specific location in the respective gene's regulatory region - TFBS

Transcription Factor Binding Sites

- A TFBS can be located anywhere within the regulatory region
- TFBS may vary slightly across different regulatory regions since non-essential bases could mutate

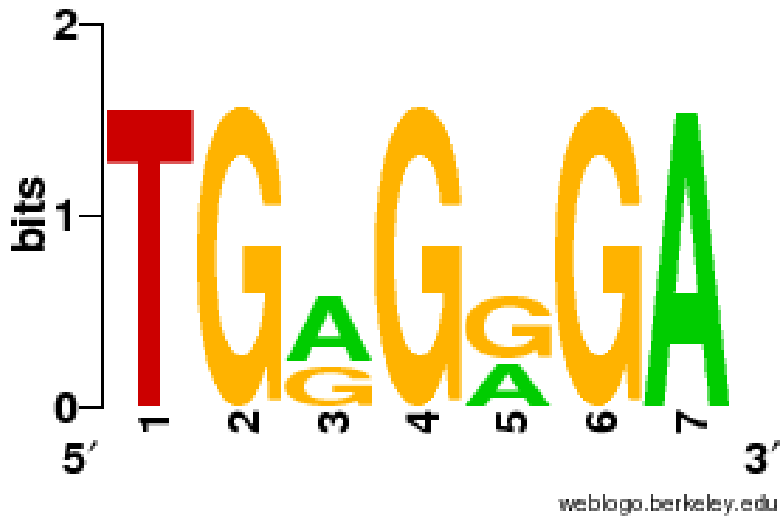
Motifs and Transcriptional Starting Sites



Motif Logo

- Motifs can mutate on non important bases
- The five motifs in five different genes have mutations in positions 3 and 5
- Representations called motif logos illustrate the conserved and variable regions of a motif

TGGGGGA
TGAGAGA
TGGGGGA
TGAGAGA
TGAGGGA



Identifying Motifs

- Genes are turned on or off by regulatory proteins
- These proteins bind to upstream regulatory regions of genes to either attract or block an RNA polymerase
- Regulatory protein (TF) binds to a short DNA sequence called a motif (TFBS)
- So finding the same motif in multiple genes' regulatory regions suggests a regulatory relationship among those genes

Identifying Motifs: Complications

- We do not know the motif sequence
- We do not know where it is located relative to the gene's start
- Motifs can differ slightly from one gene to the next
- How to discern it from "random" motifs?

Outline

Random Sample

atgaccgggatactgataccgtatttggcctaggcgtacacattagataaacgtatgaagtacgttagactcggcgccgcc

acccctatttttgagcagatttagtgacctggaaaaaaaatttgagtacaaaactttccgaatactgggcataaggtac

tgagtatccctgggatgacttttgggaacactatagtgctctcccgatttttgaatatgtaggatcattcgccagggtccg

gctgagaattggatgaccttgtaagtgttttccacgcaatcgcgaaccaacgcggacccaaaggcaagaccgataaaggag

tccctttgcggtaatgtgccgggaggctggttacgtagggaagccctaacggacttaatggcccacttagtccacttata

gtcaatcatgttcttgtgaatggatttttaactgagggcatagaccgcttggcgcacccaaattcagtgtgggcgagcgca

cggttttggcccttgttagaggcccccgtactgatggaaactttcaattatgagagagctaatctatcgcgtgcgtgttca

aacttgagttggtttcgaaaatgctctggggcacatacaagaggagtcttccttatcagttaatgctgtatgacactatgt

ttggcccattggctaaaagcccaacttgacaaatggaagatagaatccttgcatttcaacgtatgccgaaccgaaagggaa

ctggtgagcaacgacagattcttacgtgcattagctcgcttccggggatctaatagcacgaagcttctgggtactgatagc

Implanting Motif AAAAAAAAGGGGGGG

atgaccgggatactgatAAAAAAAAGGGGGGGggcgtacacattagataaacgtatgaagtacgttagactcggcgccgcc

acccctatttttgagcagatttagtgacctggaaaaaaaatttgagtacaaaacttttccgaataAAAAAAAAGGGGGGG

tgagtatccctgggatgacttAAAAAAAAGGGGGGGtgctctcccgatttttgaatatgtaggatcattcgccagggtccg

gctgagaattggatgAAAAAAAAGGGGGGGtccacgcaatcgcgaaccaacgcggacccaaaggcaagaccgataaaggag

tccctttgcggtaatgtgccgggaggctggttacgtagggaagccctaacggacttaatAAAAAAAAGGGGGGGcttata

gtcaatcatgttcttgtgaatggatttAAAAAAAAGGGGGGGgaccgcttggcgcacccaaattcagtgtgggcgagcgca

cggttttggcccttgttagaggcccccgtAAAAAAAAGGGGGGGcaattatgagagagctaatctatcgcgtgcgtgttca

aacttgagttAAAAAAAAGGGGGGGctggggcacatacaagaggagtcttccttatcagttaatgctgtatgacactatgt

ttggcccattggctaaaagcccaacttgacaaatggaagatagaatccttgcatAAAAAAAAGGGGGGGaccgaaagggaa

ctggtgagcaacgacagattcttacgtgcattagctcgcttccggggatctaatagcacgaagcttAAAAAAAAGGGGGGG

Where is the implanted motif?

atgaccgggatactgataaaaaaaaggggggggcgtacacattagataaacgtatgaagtacgttagactcggcgccgcc

acccctatttttgagcagatttagtgacctggaaaaaaaatttgagtacaaaactttccgaataaaaaaaaggggggg

tgagtatccctgggatgacttaaaaaaaaggggggtgctctcccgattttgaatatgtaggatcattcgccagggtccg

gctgagaattggatgaaaaaaaaggggggtccacgcaatcgcgaaccaacgcggacccaaaggcaagaccgataaaggag

tccctttgcggtaatgtgccgggaggctggttacgtagggaagccctaacggacttaataaaaaaaaggggggcttata

gtcaatcatgttcttgtgaatggatttaaaaaaaaggggggggaccgcttggcgcacccaaattcagtgtgggcgagcgca

cggttttggcccttgttagaggcccccgtaaaaaaaaggggggcaattatgagagagctaatctatcgcgtgcgtgttca

aacttgagttaaaaaaaaggggggctggggcacatacaagaggagtcttccttatcagttaatgctgtatgacactatgt

ttggcccattggctaaaagcccaacttgacaaatggaagatagaatccttgcataaaaaaaaggggggggaccgaaagggaa

ctggtgagcaacgacagattcttacgtgcattagctcgcttccggggatctaatagcacgaagcttaaaaaaaaggggggg

Implanting Motif AAAAAAAAGGGGGGG with four mutations

atgaccgggatactgat**AgAAgAAAGGttGGG**ggcgtacacattagataaacgtatgaagtacgttagactcggcgccgcc

acccctatttttgagcagatttagtgacctggaaaaaaaatttgagtacaaaacttttccgaata**cAAtAAAAcGGcGGG**

tgagtatccctgggatgactt**AAAAtAAtGGaGtGG**tgctctcccgattttgaatatgtaggatcattcgccagggtccg

gctgagaattggatg**cAAAAAAAGGGattG**tccacgcaatcgcgaaccaacgcggacccaaaggcaagaccgataaaggag

tccctttgcggtaatgtgccgggaggctggttacgtagggaagccctaacggacttaat**AtAAtAAAGGaaGGG**cttata

gtcaatcatgttcttgtgaatggattt**AAcAAtAAGGGctGG**gaccgcttggcgcacccaaattcagtgtgggcgagcgca

cggttttggcccttgttagaggcccccgt**AtAAAcAAGGaGGGc**caattatgagagagctaatctatcgcgtgcgtgttca

aacttgagtt**AAAAAAtAGGGaGcc**ctggggcacatacaagaggagtcttccttatcagttaatgctgtatgacactatgt

ttggcccattggctaaaagcccaacttgacaaatggaagatagaatccttgcat**ActAAAAAGGaGcGG**accgaaagggaa

ctggtgagcaacgacagattcttacgtgcattagctcgcttccggggatctaatagcacgaagctt**ActAAAAAGGaGcGG**

Where is the implanted motif???

atgaccgggatactgatagaagaaaggttgggggcgtacacattagataaacgtatgaagtacgttagactcggcgccgcc

acccctatttttgagcagatttagtgacctggaaaaaaaatttgagtacaaaactttccgaatacaataaaacggcggg

tgagtatccctgggatgacttaaaataatggagtggtgctctcccgatttttgaatatgtaggatcattcgccagggtccg

gctgagaattggatgcaaaaaaagggattgtccacgcaatcgcgaaccaacgcggacccaaaggcaagaccgataaaggag

tccctttgcggtaatgtgccgggaggctggttacgtagggaagccctaacggacttaatataataaaggaagggcttata

gtcaatcatgttcttgtgaatggatttaacaataagggctgggaccgcttggcgcacccaaattcagtgtgggcgagcgca

cggttttggcccttgttagaggcccccgtataaacaaggagggccaattatgagagagctaatctatcgcgtgcgtgttca

aacttgagttaaaaaatagggagccctggggcacatacaagaggagtcttccttatcagttaatgctgtatgacactatgt

ttggcccattggctaaaagcccaacttgacaaatggaagatagaatccttgcatactaaaaaggagcggaccgaaagggaa

ctggtgagcaacgacagattcttacgtgcattagctcgcttccggggatctaatagcacgaagcttactaaaaaggagcgg

Why finding (15,4)-motifs is hard?

atgaccgggatactgatAgAAgAAAGGttGGGggcgtacacattagataaacgtatgaagtacgttagactcggcgccgcc

acccctatttttgagcagatttagtgacctggaaaaaaaatttgagtacaaaacttttccgaatacAAtAAAAcGGcGGG

tgagtatccctgggatgacttAAAAtAAtGGaGtGGtgctctcccgattttgaatatgtaggatcattcgccagggtccg

gctgagaattggatgcAAAAAAAGGGattGtccacgcaatcgcgaaccaacgcggacccaaaggcaagaccgataaaggag

tccctttgcggtaatgtgccgggaggctggttacgtagggaagccctaacggacttaatAtAAtAAAGGaaGGGcttata

gtcaatcatgttcttgtgaatggatttAAcAAtAAGGGctGGgaccgcttggcgcacccaaattcagtgtgggcgagcgca

cggttttggcccttgttagaggcccccgtAtAAAcAAGGaGGGccaattatgagagagctaatctatcgcgtgcgtgttca

aacttgagttAAAAAAtAGGGaGccctggggcacatacaagaggagtcttccttatcagttaatgctgtatgacactatgt

ttggcccattggctaaaagcccaacttgacaaatggaagatagaatccttgcatActAAAAAGGaGcGGaccgaaagggaa

ctggtgagcaacgacagattcttacgtgcattagctcgcttccggggatctaatagcacgaagcttActAAAAAGGaGcGG

Aligning two first occurrences of the motif

AgAAgAAAGGttGGG
..|..|||.|..|||
cAAtAAAAcGGcGGG

The Implanted Motif Problem

Finding a motif in a sample of

- 20 random sequences (e.g. 600 nt long)
- Each sequence containing an implanted pattern of length 15 at random position
- Each pattern appearing with 4 random mismatches as (15,4)-motif

Outline

The Motif Finding Problem

- Given a random sample of DNA sequences:

```
cctgatagacgctatctggctatccacgtacgtaggtcctctgtgcgaatctatgcgtttccaaccat
agtactggtgtacatttgatacgtacgtacaccggcaacctgaaacaaacgctcagaaccagaagtgc
aaacgtacgtgcaccctctttcttcgtggctctggccaacgagggctgatgtataagacgaaaatttt
agcctccgatgtaagtcatagctgtaactattacctgccacccctattacatcttacgtacgtataca
ctgttatacaacgcgtcatggcggggtatgcgttttggtcgtcgtacgctcgatcgttaacgtacgtc
```

- Find the pattern that is implanted in each of the individual sequences, namely, the motif

The Motif Finding Problem

- Given a random sample of DNA sequences:

```
cctgatagacgctatctggctatccacgtacgtaggtcctctgtgcgaatctatgcgtttccaaccat
agtactggtgtacatttgatacgtacgtacaccggcaacctgaaacaaacgctcagaaccagaagtgc
aaacgtacgtgcaccctctttcttcgtggctctggccaacgagggctgatgtataagacgaaaatttt
agcctccgatgtaagtcatagctgtaactattacctgccacccctattacatcttacgtacgtataca
ctgttatacaacgcgtcatggcggggtatgcgttttggtcgtcgtacgctcgatcgttaacgtacgtc
```

- Find the pattern that is implanted in each of the individual sequences, namely, the motif
- Additional information:
  - The hidden sequence is of length 8
  - The pattern is not exactly the same in each sequence because random point mutations may occur in the sequences

The Motif Finding Problem (cont'd)

The patterns revealed with no mutations:

cctgatagacgctatctggctatccacgtacgtaggtcctctgtgcgaatctatgcgtttccaaccat

agtactggtgtacatttgatacgtacgtacaccggcaacctgaaacaaacgctcagaaccagaagtgc

aaacgtacgtgcaccctctttcttcgtggctctggccaacgagggctgatgtataagacgaaaatttt

agcctccgatgtaagtcatagctgtaactattacctgccacccctattacatcttacgtacgtataca

ctgttatacaacgcgtcatggcggggtatgcgttttggtcgtcgtacgctcgatcgttaacgtacgtc

$\Longrightarrow$ Consensus String: acgtacgt

The Motif Finding Problem (cont'd)

The patterns revealed with 2 mutations:

cctgatagacgctatctggctatccaGgtacTtaggtcctctgtgcgaatctatgcgtttccaaccat

agtactggtgtacatttgatCcAtacgtacaccggcaacctgaaacaaacgctcagaaccagaagtgc

aaacgtTAgtgcaccctctttcttcgtggctctggccaacgagggctgatgtataagacgaaaatttt

agcctccgatgtaagtcatagctgtaactattacctgccacccctattacatcttacgtCcAtataca

ctgttatacaacgcgtcatggcggggtatgcgttttggtcgtcgtacgctcgatcgttaCcgtacgGc

The Motif Finding Problem (cont'd)

The patterns revealed with 2 mutations:

cctgatagacgctatctggctatccaGgtacTtaggtcctctgtgcgaatctatgcgtttccaaccat

agtactggtgtacatttgatCcAtacgtacaccggcaacctgaaacaaacgctcagaaccagaagtgc

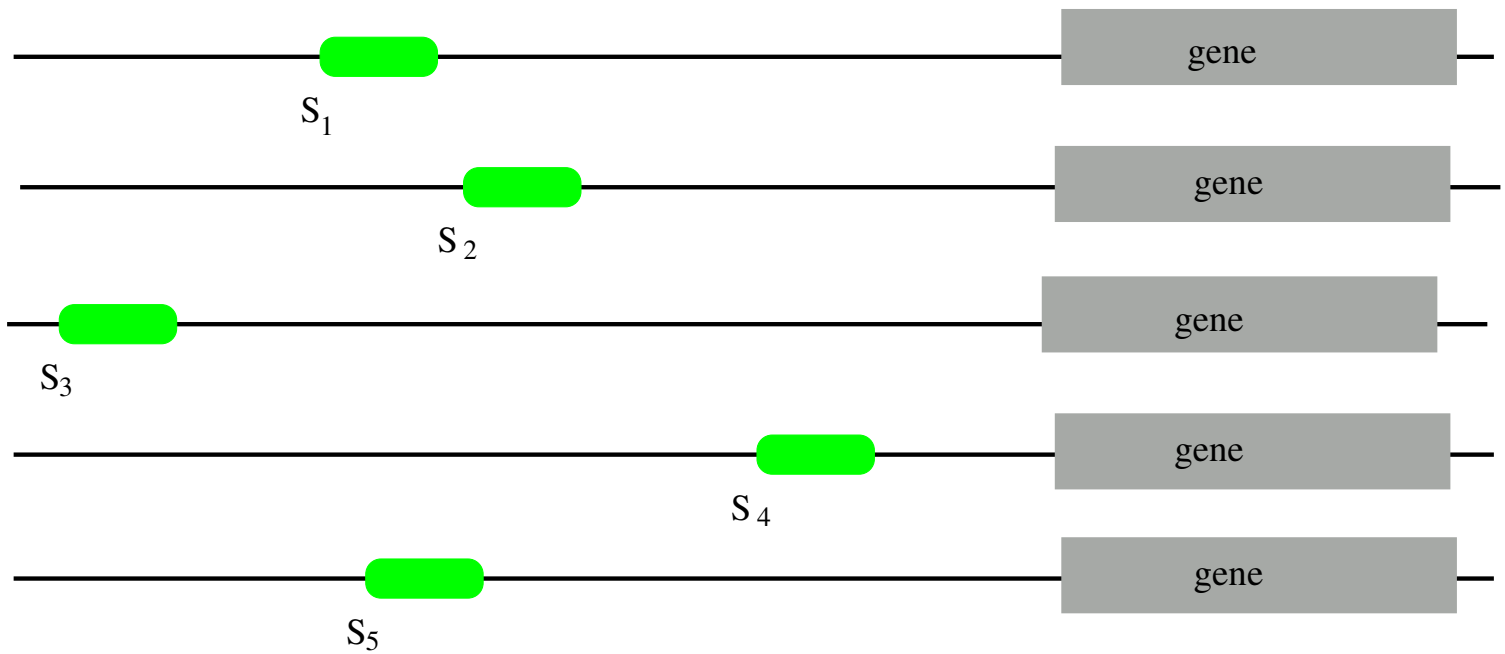
aaacgtTAgtgcaccctctttcttcgtggctctggccaacgagggctgatgtataagacgaaaatttt

agcctccgatgtaagtcatagctgtaactattacctgccacccctattacatcttacgtCcAtataca

ctgttatacaacgcgtcatggcggggtatgcgttttggtcgtcgtacgctcgatcgttaCcgtacgGc

Defining Motifs

- To define a motif, let's say we know where the motif starts in each sequnce
- The motif start positions in their sequences are $\mathbf{s} = (s_1, s_2, s_3, \ldots, s_t)$



Motifs: Profile and Consensus

Alignment

a	G	g	t	a	c	T	t
C	c	A	t	a	c	g	t
a	c	g	t	T	A	g	t
a	c	g	t	C	c	A	t
C	c	g	t	a	c	g	G

Profile

A	3	0	1	0	3	1	1	0
C	2	4	0	0	1	4	0	0
G	0	1	4	0	0	0	3	1
T	0	0	0	5	1	0	1	4

Consensus A C G T A C G T

- Line up the patterns by their start indexes

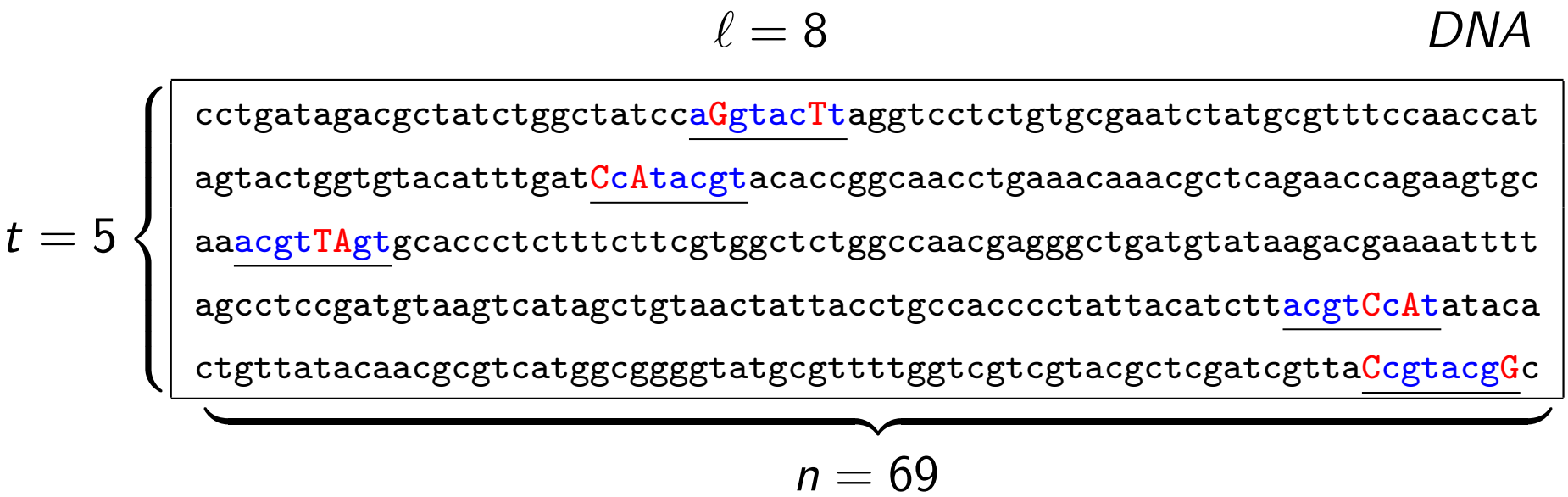
$$\mathbf{s} = (s_1, s_2, s_3, \ldots, s_t)$$

- Construct matrix profile with frequencies of each nucleotide in columns
- Consensus nucleotide in each position has the highest score in column

Some Term Definitions

- t: number of sample DNA sequences
- n: length of each DNA sequence
- DNA: sample of DNA sequences ($t \times n$ array)
  - $DNA[i]$ denotes the i:th DNA sequence
  - $DNA[i][j \ldots j']$ denotes substring $T[j \ldots j']$ where $T = DNA[i]$
- ℓ: length of the motif (ℓ-mer)
- s_i: starting position of an ℓ-mer in sequence i
- $\mathbf{s} = (s_1, s_2, \ldots, s_t)$: array of motif's starting positions

Parameters



$$\mathbf{s} = \{s_1 = 26, s_2 = 21, s_3 = 3, s_4 = 56, s_5 = 60\}$$

Scoring Motifs

- Given $\mathbf{s} = (s_1, \ldots, s_t)$ and *DNA*:

$$Score(s, DNA) = \sum_{j=1}^{\ell} \max_{c \in \{A,C,G,T\}} count(c, j)$$

where $count(c, j)$ gives the number of times symbol c equals $DNA[i][s_i + j - 1]$, that is,

$$count(c, j) = \left| \{ i | DNA[i][s_i + j - 1] = c, i \in [1, t] \} \right|.$$

ℓ

	a	G	g	t	a	c	T	t
	C	c	A	t	a	c	g	t
	a	c	g	t	T	A	g	t
	a	c	g	t	C	c	A	t
	C	c	g	t	a	c	g	G

t

A	3	0	1	0	3	1	1	0
C	2	4	0	0	1	4	0	0
G	0	1	4	0	0	0	3	1
T	0	0	0	5	1	0	1	4

Consensus A C G T A C G T

Score 3+4+4+5+3+4+3+4=30

The Motif Finding Problem

- If starting positions $\mathbf{s} = (s_1, s_2, \ldots, s_t)$ are given, finding consensus is easy even with mutations in the sequences because we can simply construct the profile to find the motif (consensus)
- But... the starting positions $\mathbf{s}$ are usually not given.
  How can we find the "best" profile matrix?

The Motif Finding Problem: Formulation

- Goal: Given a set of DNA sequences, find a set of ℓ-mers, one from each sequence, that maximizes the consensus score.
- Input: A $t \times n$ matrix DNA, and ℓ, the length of the pattern to find
- Output: An array of t starting positions $\mathbf{s} = (s_1, s_2, \ldots, s_t)$ maximizing $Score(\mathbf{s}, DNA)$

The Motif Finding Problem: Brute Force Solution

- Compute the scores for each possible combination of starting positions $\mathbf{s}$
- The best score will determine the best profile and the consensus pattern in DNA
- The goal is to maximize $Score(\mathbf{s}, DNA)$ by varying the starting positions s_i, where

$$s_i \in [1, \ldots, n - \ell + 1]$$

$$i \in [1, \ldots, t]$$

BruteForceMotifSearch

BruteForceMotifSearch(DNA, t, n, ℓ)

1: $bestScore \leftarrow 0$
2: **for** each $\mathbf{s} = (s_1, s_2, \ldots, s_t)$ from $(1, 1, \ldots, 1)$ to $(n - \ell + 1, \ldots, n - \ell + 1)$ **do**
3: **if** $Score(\mathbf{s}, DNA) > bestScore$ **then**
4: $bestScore \leftarrow score(\mathbf{s}, DNA)$
5: $bestMotif \leftarrow (s_1, s_2, \ldots, s_t)$
6: **return** $bestMotif$

Running Time of BruteForceMotifSearch

- Varying $(n - \ell + 1)$ position in each of t sequences, we get $(n - \ell + 1)^t$ sets of starting positions
- For each set of starting positions, computing the scoring function requires ℓt operations, so complexity is

$$\ell t(n - \ell + 1)^t = O(\ell t n^t)$$

- E.g. for $t = 8, n = 1000, \ell = 10$ we must perform approximately 10^{20} computations – it will take millions of years

The Median String Problem

- Given a set of t DNA sequences find a pattern that appears in all t sequences with the minimum number of mutations
- This pattern will be the motif

Hamming Distance

- The Hamming distance $d_H(v, w)$ is the number of nucleotide pairs that do not match when v and w are aligned
- For example:

$$d_H(\mathrm{AAAAAA}, \mathrm{ACAAAC}) = 2$$

Total Distance: Example

- Given $v =$ "acgtacgt" and **s**:

acgtacgt $\rightarrow d_H(v, x) = 1$
cctgatagacgctatctggctatccacgtacAtaggtcctctgtgcgaatctatgcgtttccaaccat
acgtacgt $\rightarrow d_H(v, x) = 0$
agtactggtgtacatttgatacgtacgtacaccggcaacctgaaacaaacgctcagaaccagaagtgc
acgtacgt $\rightarrow d_H(v, x) = 2$
aaaAgtCcgtgcaccctctttcttcgtggctctggccaacgagggctgatgtataagacgaaaatttt
$d_H(v, x) = 0 \leftarrow$ acgtacgt
agcctccgatgtaagtcatagctgtaactattacctgccacccctattacatcttacgtacgtataca
$d_H(v, x) = 1 \leftarrow$ acgtacgt
ctgttatacaacgcgtcatggcggggtatgcgttttggtcgtcgtacgctcgatcgttaacgtaGgtc

- $TotalDistance(v, DNA) = 1 + 0 + 2 + 0 + 1 = 4$

Total Distance: Definition

- For each DNA sequence i, compute all $d_H(v, x)$, where x is an ℓ-mer with starting position s_i $(1 \leq s_i \leq n - \ell + 1)$
- Find minimum of $d_H(v, x)$ among all ℓ-mers in sequence i
- $\mathit{TotalDistance}(v, \mathit{DNA})$ is the sum of the minimum Hamming distances for each DNA sequence i

$$\mathit{TotalDistance}(v, \mathit{DNA}) = \sum_{i \in [1,t]} \min_{s_i \in [1, m-\ell+1]} d_H(v, \mathit{DNA}[i][s_i, \ldots, s_i + \ell - 1])$$

The Median String Problem: Formulation

- Goal: Given a set of DNA sequences, find a median string
- Input: a $t \times n$ matrix DNA, and ℓ, the length of the pattern to find
- Output: A string v of ℓ nucleotides that minimizes $TotalDistance(v, DNA)$ over all strings of that length

Median String Search Algorithm

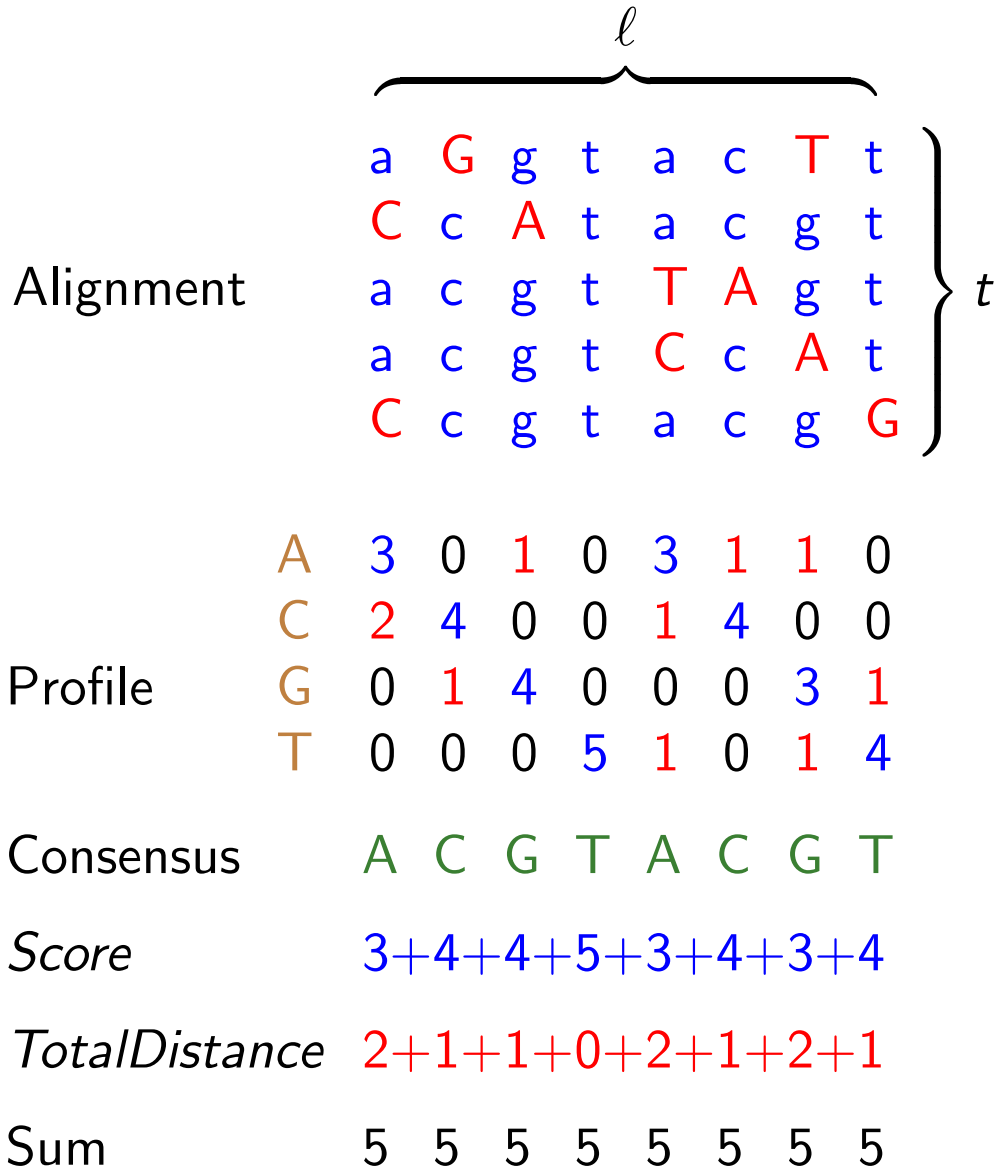
MedianStringSearch(DNA, t, n, ℓ)

```
1: bestWord ← AAA...A
2: bestDistance ← ∞
3: for each ℓ-mer v from AAA...A to TTT...T do
4:     if TotalDistance(v, DNA) < bestDistance then
5:         bestDistance ← TotalDistance(v, DNA)
6:         bestWord ← v
7: return bestWord
```

Motif Finding Problem = Median String Problem

- *Motif Finding* is a maximization problem while *Median String* is a minimization problem
- However, *Motif Finding* and *Median String* problems are computationally equivalent
- We need to show that minimizing *TotalDistance* is equivalent to maximizing *Score*

We are looking for the same thing



- At any column i

  $Score_i + TotalDistance_i = t$

- ℓ columns $\Longrightarrow$

  $Score + TotalDistance = \ell \cdot t$

- Rearranging:

  $Score = \ell \cdot t - TotalDistance$

- $\ell \cdot t$ is constant so the minimization of the right side is equivalent to the maximization of the left side

Motif Finding Problem vs Median String Problem

- Why bother reformulating the Motif Finding problem into the Median String problem?
  - The Motif Finding problem needs to examine all the combinations for **s**
    $\Longrightarrow$ Total running time $O(\ell t n^t)$
  - The Median String problem needs to examine all 4^ℓ combinations for v
    $\Longrightarrow$ Total running time $O(\ell t n 4^\ell)$

Outline

Motif Finding: Improving the Running Time

Recall the BruteForceMotifSearch:

BruteForceMotifSearch(DNA, t, n, ℓ)

1: $bestScore \leftarrow 0$
2: **for** each $\mathbf{s} = (s_1, s_2, \ldots, s_t)$ from $(1, 1, \ldots 1)$ to $(n - \ell + 1, \ldots n - \ell + 1)$ **do**
3: **if** $Score(\mathbf{s}, DNA) > bestScore$ **then**
4: $bestScore \leftarrow score(\mathbf{s}, DNA)$
5: $bestMotif \leftarrow (s_1, s_2, \ldots, s_t)$
6: **return** $bestMotif$

Structuring the Search

- How can we perform the line

  for each $\mathbf{s} = (s_1, s_2, \ldots, s_t)$ from $(1, 1, \ldots 1)$ to $(n - \ell + 1, \ldots n - \ell + 1)$ **do**

- We need a method for efficiently structuring and navigating the many possible motifs
- This is not very different from exploring all t-digit numbers

Median String: Improving the Running Time

Recall the MedianStringSearch:

MedianStringSearch(DNA, t, n, ℓ)

```
1: bestWord ← AAA...A
2: bestDistance ← ∞
3: for each ℓ-mer v from AAA...A to TTT...T do
4:     if TotalDistance(v, DNA) < bestDistance then
5:         bestDistance ← TotalDistance(v, DNA)
6:         bestWord ← v
7: return bestWord
```

Structuring the Search

- How can we perform the line

  for each ℓ-mer v from `AAA...A` to `TTT...T` **do**

- We need a method for efficiently structuring and navigating all 4^ℓ possible ℓ-mers
- This is not very different from exploring all ℓ-digit numbers (in base 4):

$$\overbrace{\texttt{AA...AA}}^{\ell}$$
$$\texttt{AA...AC}$$
$$\texttt{AA...AG}$$
$$\texttt{AA...AT}$$
$$\vdots$$
$$\texttt{TT...TT}$$

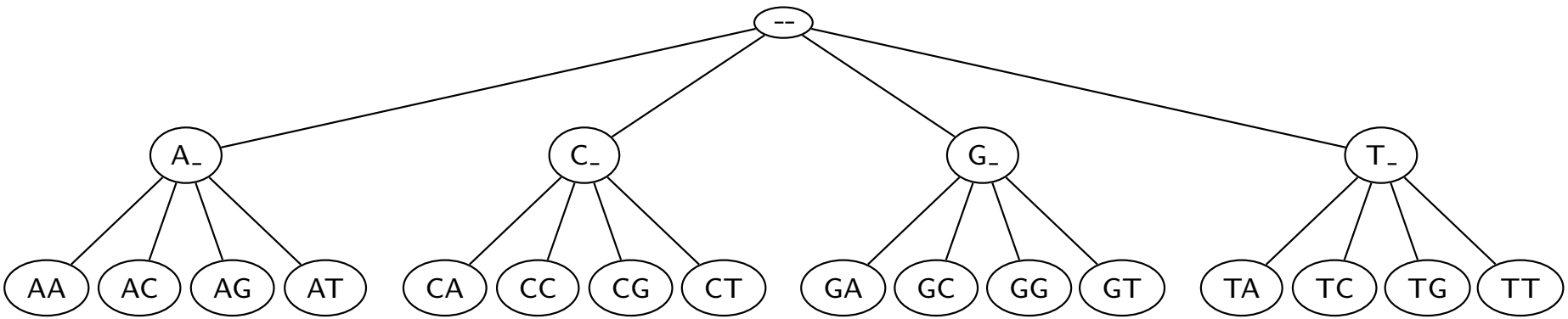
Alternative Representation of the Search Space

- Let $\texttt{A} = 1$, $\texttt{C} = 2$, $\texttt{G} = 3$, $\texttt{T} = 4$
- Then the sequences from $\texttt{AA...A}$ to $\texttt{TT...T}$ become:

$$\overbrace{\texttt{11...11}}^{\ell}$$
$$\texttt{11...12}$$
$$\texttt{11...13}$$
$$\texttt{11...14}$$
$$\vdots$$
$$\texttt{44...44}$$

- Notice that the sequences above simply list all ℓ-digit numbers in base 4 using digits 1, 2, 3, and 4

Search Tree



Analyzing Search Trees

- Characteristics of search trees
  - The sequences are contained in its leaves
  - The parent of a node is the prefix of its children
- How can we move through the tree?

Analyzing Search Trees

- Characteristics of search trees
  - The sequences are contained in its leaves
  - The parent of a node is the prefix of its children
- How can we move through the tree?
- Four common moves in a search tree that we are about to explore:
  - Move to next leaf
  - Visit all the leaves
  - Visit next node
  - Bypass the children of a node

Visit the Next Leaf

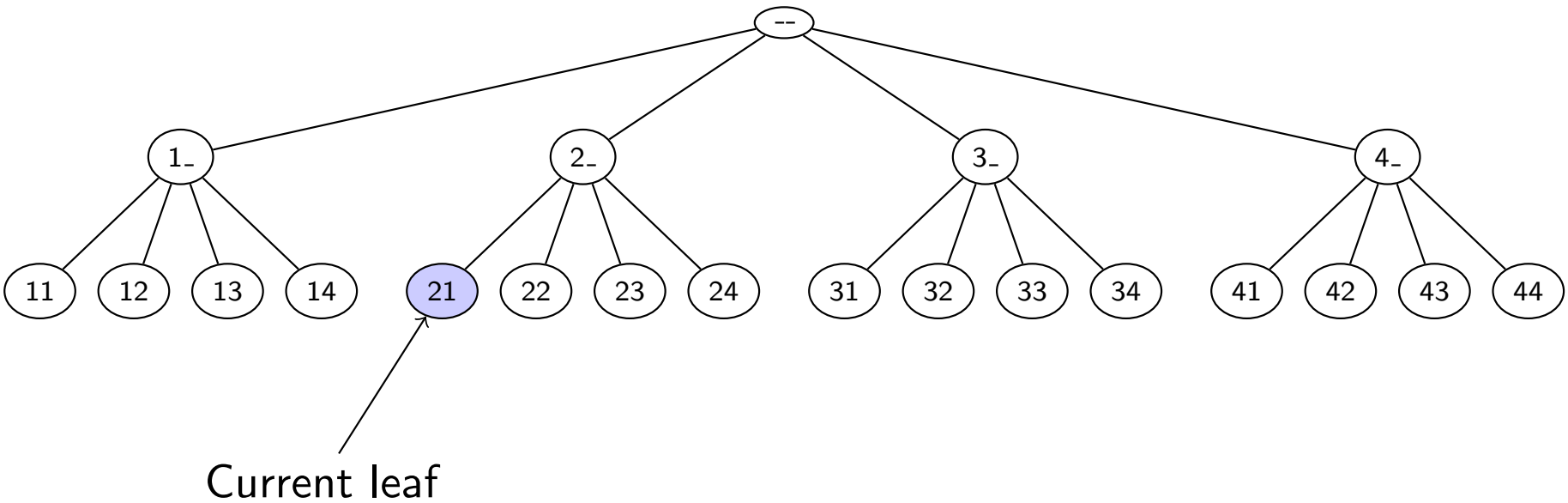
Given a current leaf a, we need to compute the next leaf:

NextLeaf(a, L, k)

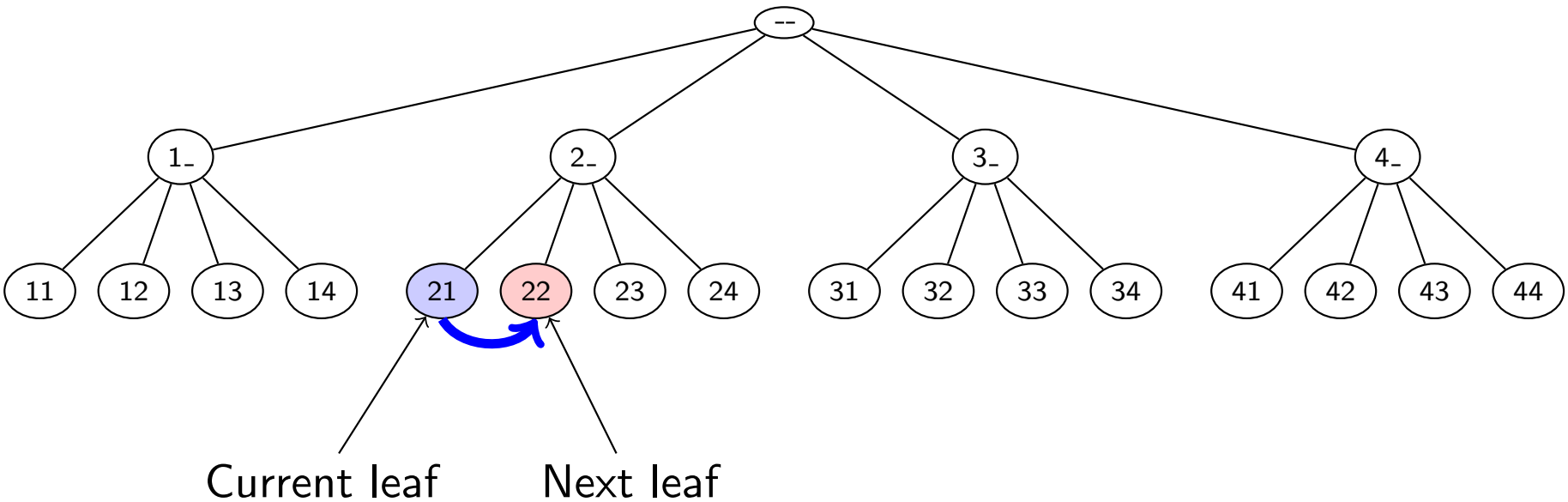
1: **for** $i \leftarrow L$ to 1 **do**
2: **if** $a_i < k$ **then**
3: $a_i \leftarrow a_i + 1$
4: **return** a
5: $a_i \leftarrow 1$
6: **return** a

- Arguments:
  - a: the array of digits
  - L: length of the array
  - k: max digit value
- The algorithm is common addition in radix k:
  - Increment the least significant digit
  - "Carry the one" to the next digit position when the digit is at maximal value

NextLeaf: Example



NextLeaf: Example



Visit All Leaves

Print all permutations in ascending order:

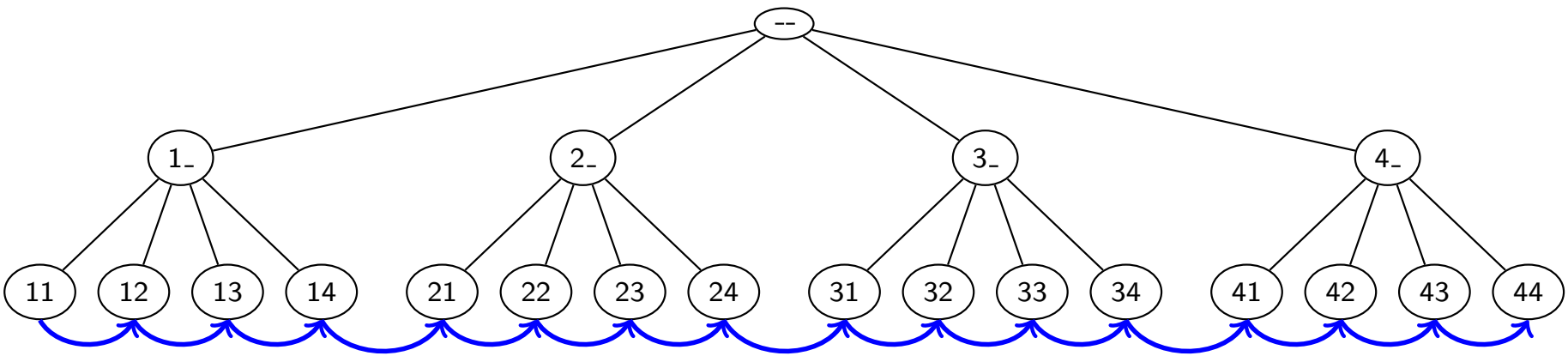
AllLeaves(L, k)

1: $a \leftarrow (1, ..., 1)$
2: **while** forever **do**
3: output a
4: $a \leftarrow \mathrm{NextLeaf}(a, L, k)$
5: **if** $a = (1, 1, ..., 1)$ **then**
6: **return**

- L: length of the sequence
- k: max digit value
- a: array of digits

Visit All Leaves: Example

Moving through all the leaves in order:



Depth First Search

- The previous slides showed how to search leaves
- How about searching all vertices of the tree?
- We can do this with a *depth first* search

Visit the Next Vertex

Given a current vertex a, we need to compute the next vertex:

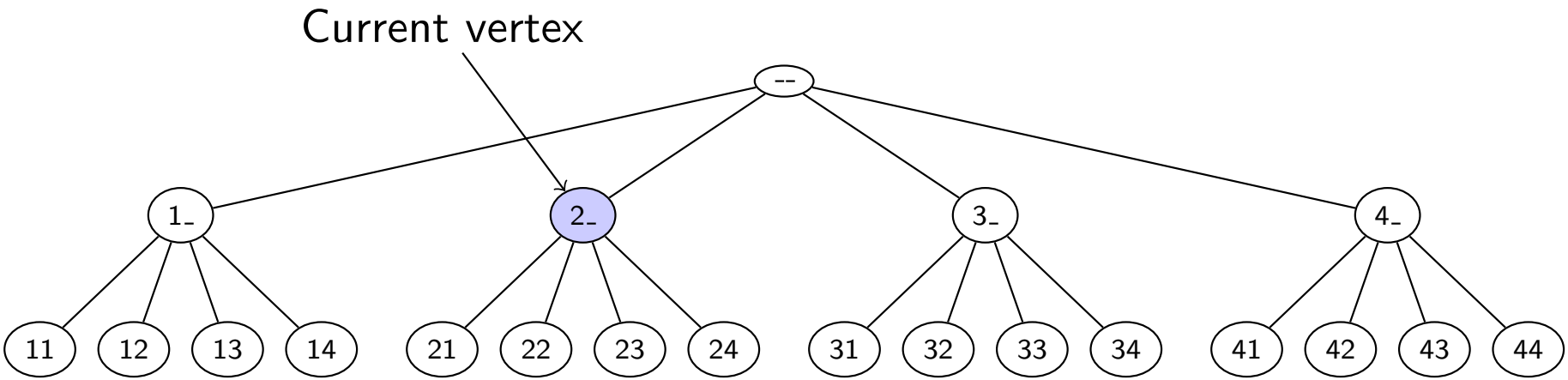
NextVertex(a, i, L, k)

1: **if** $i < L$ **then**
2: $\quad a_{i+1} \leftarrow 1$
3: $\quad$ **return** $(a, i+1)$
4: **else**
5: $\quad$ **for** $j \leftarrow L$ to 1 **do**
6: $\quad\quad$ **if** $a_j < k$ **then**
7: $\quad\quad\quad a_j \leftarrow a_j + 1$
8: $\quad\quad\quad$ **return** (a, j)
9: **return** $(a, 0)$

- Arguments:
  - a: the array of digits
  - i: prefix length
  - L: length of the array
  - k: max digit value
- The algorithm returns a prefix which is represented by digits in the array a and the prefix length

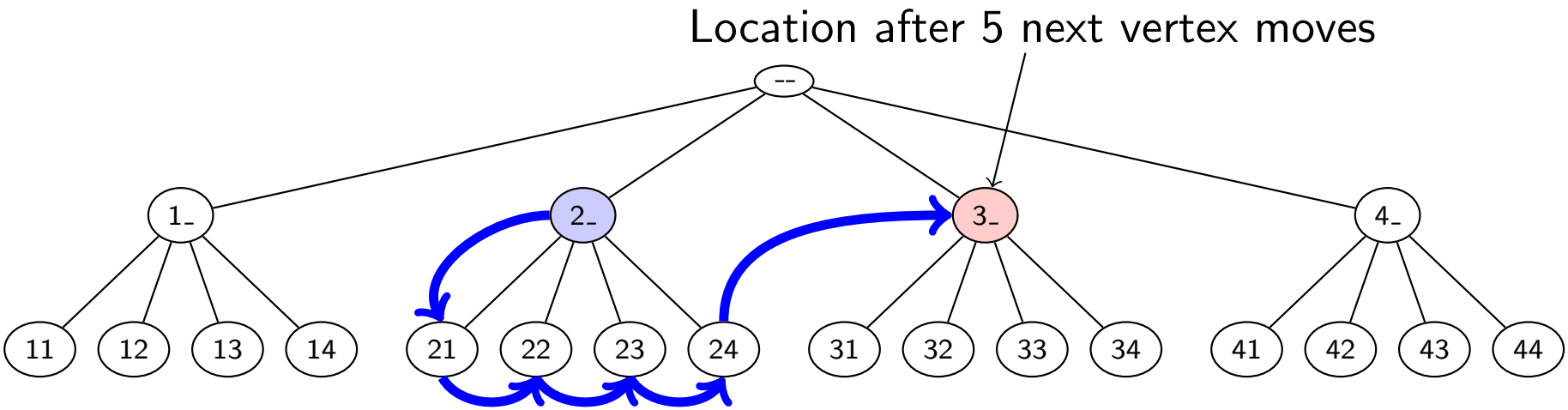
NextVertex: Example

Moving to the next vertices:



NextVertex: Example

Moving to the next vertices:



Bypass Move

Given a prefix (internal vertex), find next vertex after skipping all its children

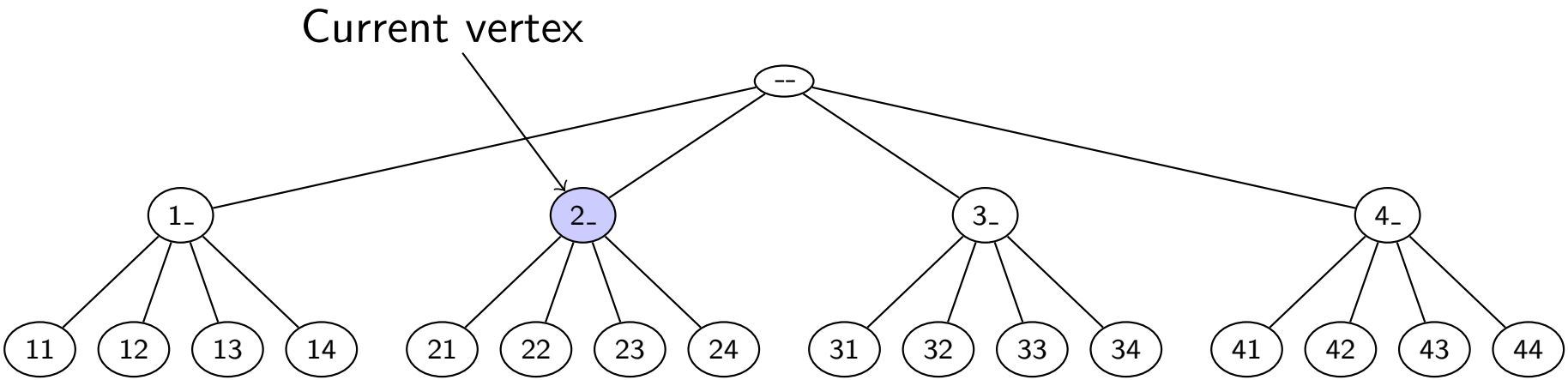
Bypass(a, i, L, k):

1: **for** $j \leftarrow i$ to 1 **do**
2: **if** $a_j < k$ **then**
3: $a_j \leftarrow a_j + 1$
4: **return** (a, j)
5: **return** $(a, 0)$

- a: array of digits
- i: prefix length
- L: maximum length
- k: max digit value

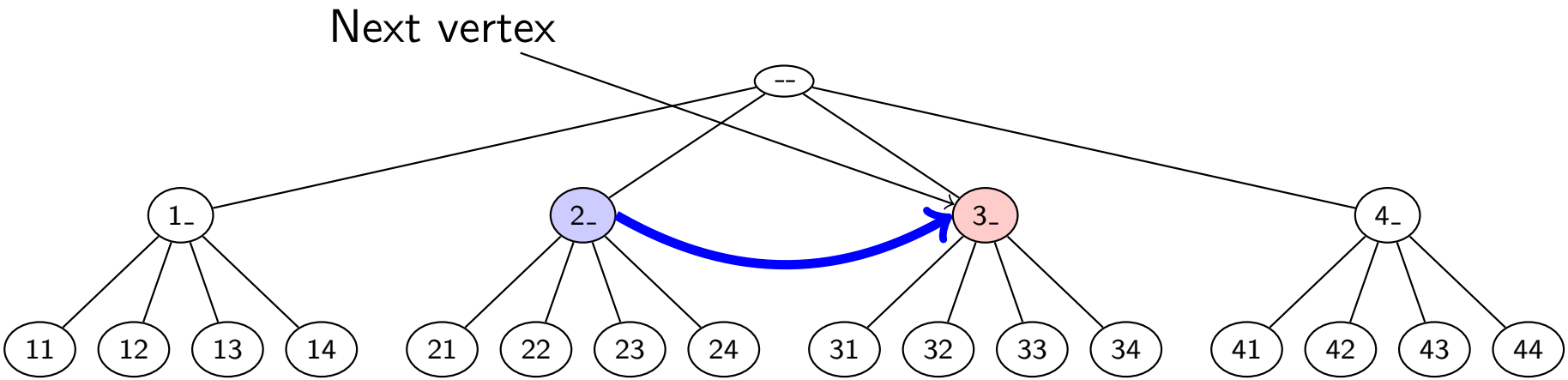
Bypass Move: Example

Bypassing descendants of "2-"



Bypass Move: Example

Bypassing descendants of "2-"



Outline

Brute Force Search Again

Now that we have a method for navigating the tree, let's look again at BruteForceMotifSearch.

BruteForceMotifSearchAgain(DNA, t, n, ℓ)

```
1: s ← (1, 1, ..., 1)
2: bestScore ← score(s, DNA)
3: while forever do
4:     s ← NextLeaf(s, t, n − ℓ + 1)
5:     if Score(s, DNA) > bestScore then
6:         bestScore ← score(s, DNA)
7:         bestMotif ← (s_1, s_2, ..., s_t)
8:     if s = (1, 1, ..., 1) then
9:         return bestMotif
```

Can We Do Better?

- Sets of $\mathbf{s} = (s_1, s_2, \ldots, s_t)$ may have a weak profile for the first i positions $(s_1, s_2, \ldots, s_i)$
- Every row of the alignment may add at most ℓ to *Score*
- Define $Score(s, i, DNA)$ to be the score involving only the i first rows of the alignment matrix

$$Score(s, i, DNA) = \sum_{j=1}^{\ell} \max_{c \in \{A,C,G,T\}} count_i(c, j)$$

where $count_i(c, j)$ gives the number of times nucleotide c occurs in column j int the first i rows of the alignment matrix

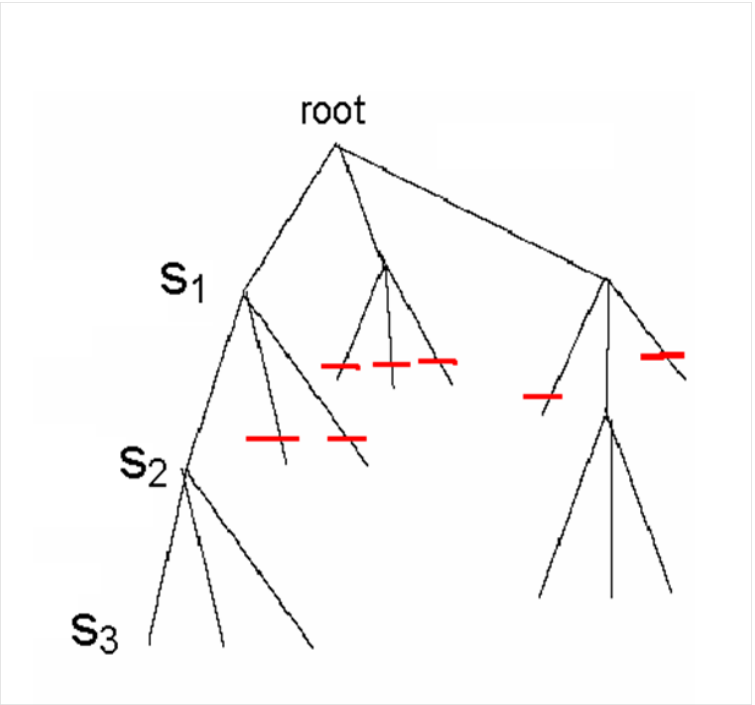
- Optimism: if all remaining $(t - i)$ positions $(s_{i+1}, \ldots, s_t)$ add

$$(t - i) \cdot \ell \text{ to } Score(s, i, DNA)$$

- If $Score(s, i, DNA) + (t - i) \cdot \ell < BestScore$, it makes no sense to search in vertices of the current subtree $\Longrightarrow$ Use ByPass()!

Branch and Bound Algorithm for Motif Search

- Since each level of the tree goes deeper into the search, discarding a prefix discards all following branches
- This saves us from looking at $(n - \ell + 1)^{t-i}$ leaves
  - Use NextVertex() and ByPass() to navigate the tree



Pseudocode for Branch and Bound Motif Search

BranchAndBoundMotifSearch(DNA, t, n, ℓ)

$s \leftarrow (1, 1, \ldots, 1)$
$bestScore \leftarrow 0$
$i \leftarrow 1$
while $i > 0$ **do**
  if $i < t$ **then**
    $optimisticScore \leftarrow Score(s, i, DNA) + (t - i) \cdot \ell$
    if $optimisticScore < bestScore$ **then**
      $(s, i) \leftarrow \text{Bypass}(s, i, n - \ell + 1)$
    else
      $(s, i) \leftarrow \text{NextVertex}(s, i, t, n - \ell + 1)$
  else
    if $Score(\mathbf{s}, DNA) > bestScore$ **then**
      $bestScore \leftarrow score(\mathbf{s}, DNA)$
      $bestMotif \leftarrow (s_1, s_2, \ldots, s_t)$
    $(s, i) \leftarrow \text{NextVertex}(s, i, t, n - \ell + 1)$
return $bestMotif$

Median String Search Improvements

- Recall the computational differences between motif search and median string search
  - The Motif Finding Problem needs to examine all $(n - \ell + 1)^t$ combinations for $\mathbf{s}$
  - The Median String Problem needs to examine 4^ℓ combinations of v. This number is relatively small
- We want to use median string algorithm with the Branch and Bound trick!

Branch and Bound Algorithm for Median String Search

- Note that if the total distance for a prefix is greater that that for the best word so far:

$$TotalDistance(prefix, DNA) > BestDistance$$

  there is no use exploring the remaining part of the word
- We can eliminate that branch and ByPass exploring it further

Bounded Median String Search

BranchAndBoundMedianStringSearch(DNA, t, n, ℓ)

```
1:  v ← (1, ..., 1) # recall that 1=A, 2=C, 3=G, 4=T
2:  bestWord ← AAA...A
3:  bestDistance ← ∞
4:  i = 1
5:  while i > 0 do
6:      if i < ℓ then
7:          prefix ← string corresponding to the first i nucleotides of v
8:          optimisticDistance ← TotalDistance(prefix, DNA)
9:          if optimisticDistance > bestDistance then
10:             (v, i) ← ByPass(v, i, ℓ, 4)
11:         else
12:             (v, i) ← NextVertex(v, i, ℓ, 4)
13:     else
14:         word ← nucleotide string corresponding to v
15:         if TotalDistance(word, DNA) < bestDistance then
16:             bestDistance ← TotalDistance(word, DNA)
17:             bestWord ← word
18:         (v, i) ← NextVertex(v, i, ℓ, 4)
19: return bestWord
```

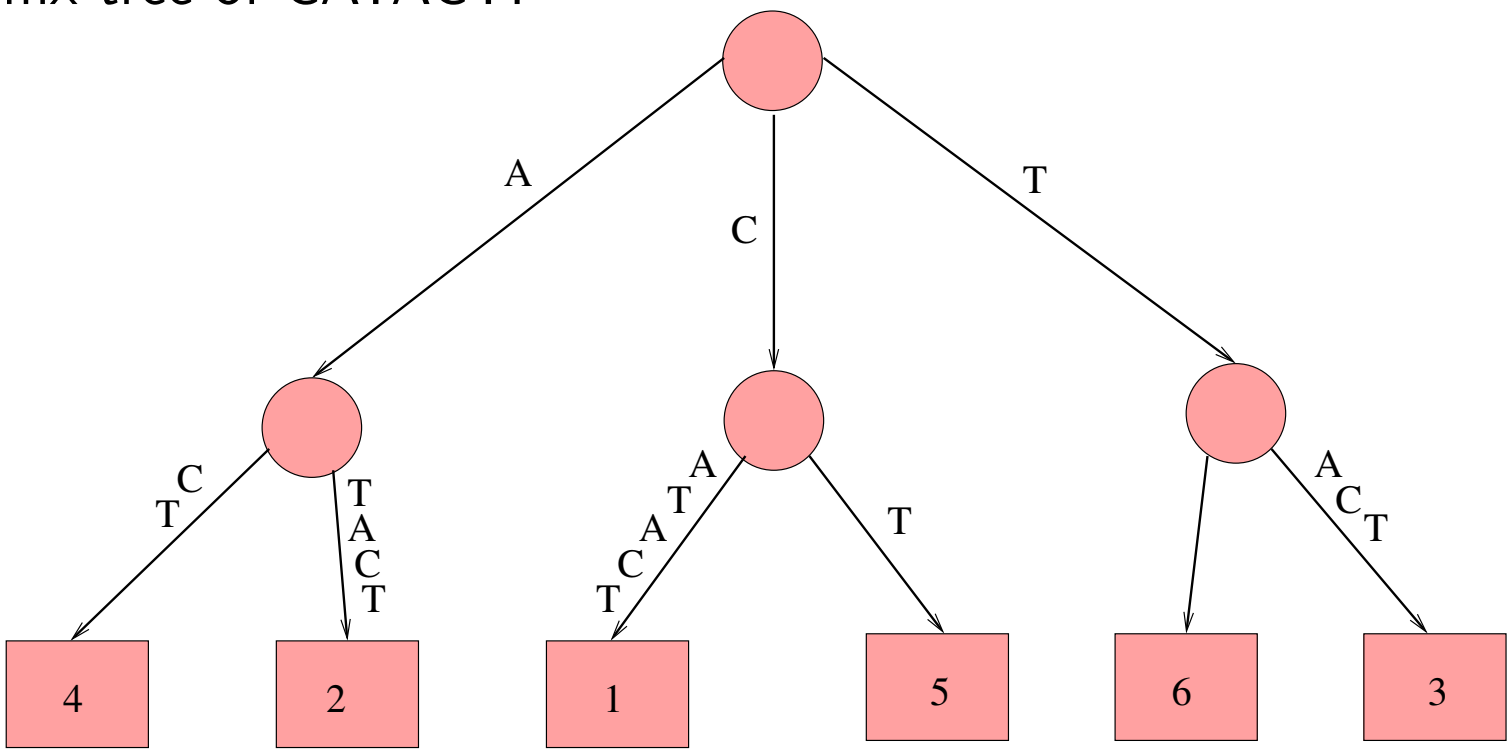
Some Motif Finding Programs

- CONSENSUS (*Hertz, Stromo (1989)*)
- GibbsDNA (*Lawrence et al (1993)*)
- MEME (*Bailey, Elkan (1995)*)
- Weeder (*Pavesi, Mauri, Pesole (2001)*)
- RandomProjections (*Buhler, Tompa (2002)*)
- MULTIPROFILER (*Keich, Pevzner (2002)*)
- MITRA (*Eskin, Pevzner (2002)*)
- Pattern Branching (*Price, Pevzner (2003)*)

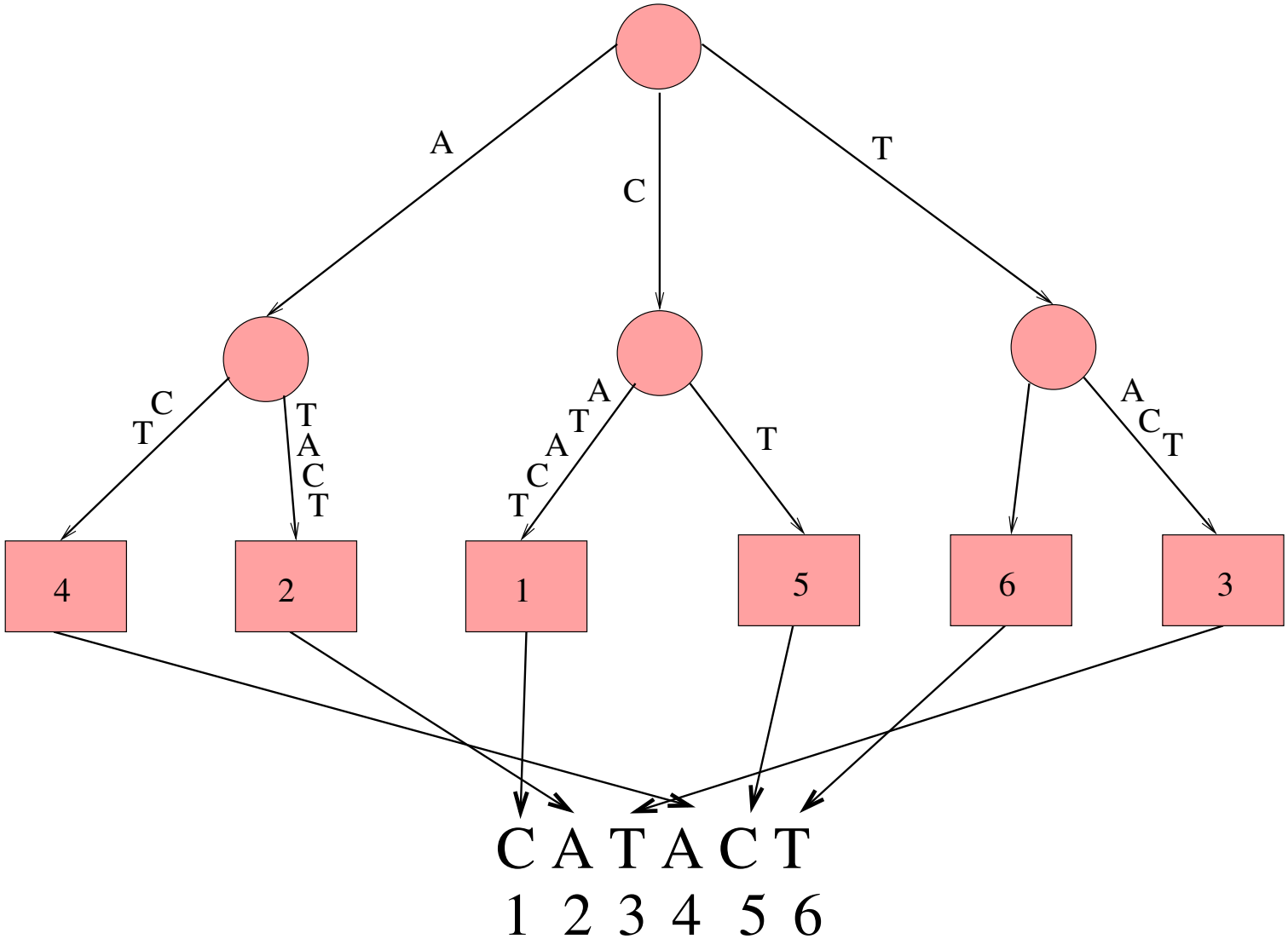
Outline

Weeder: Suffix Tree -Based Approach

- Suffix tree is a compressed keyword trie of all suffixes of a sequence
- E.g. suffixes of sequence CATACT are CATACT, ATACT, TACT, ACT, CT, T.
- Suffix tree of CATACT:

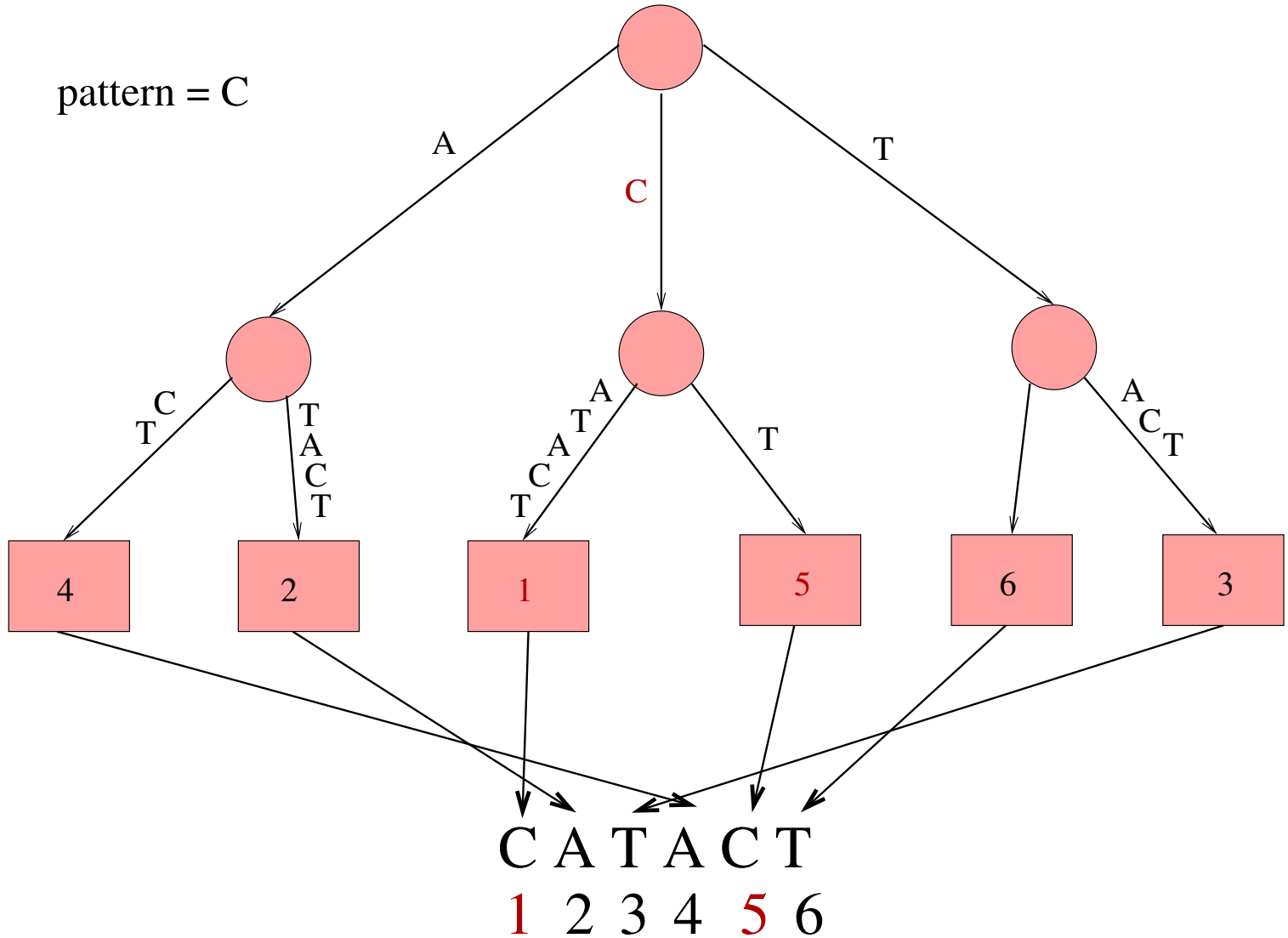


Suffix Tree

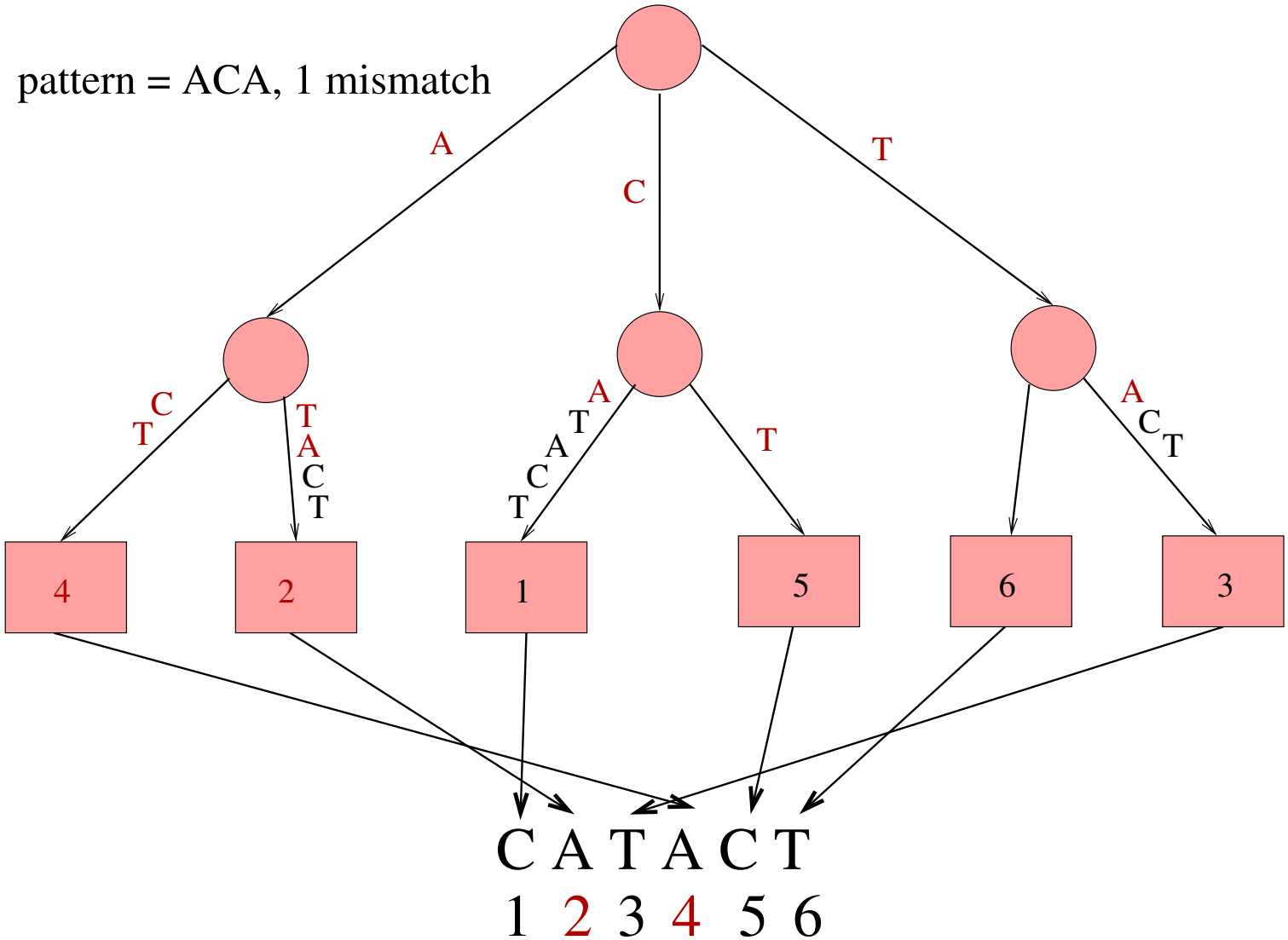


$\Longrightarrow$ 58093 String Processsing Algorithms (5 cr), period II

Exact Search on Suffix Tree



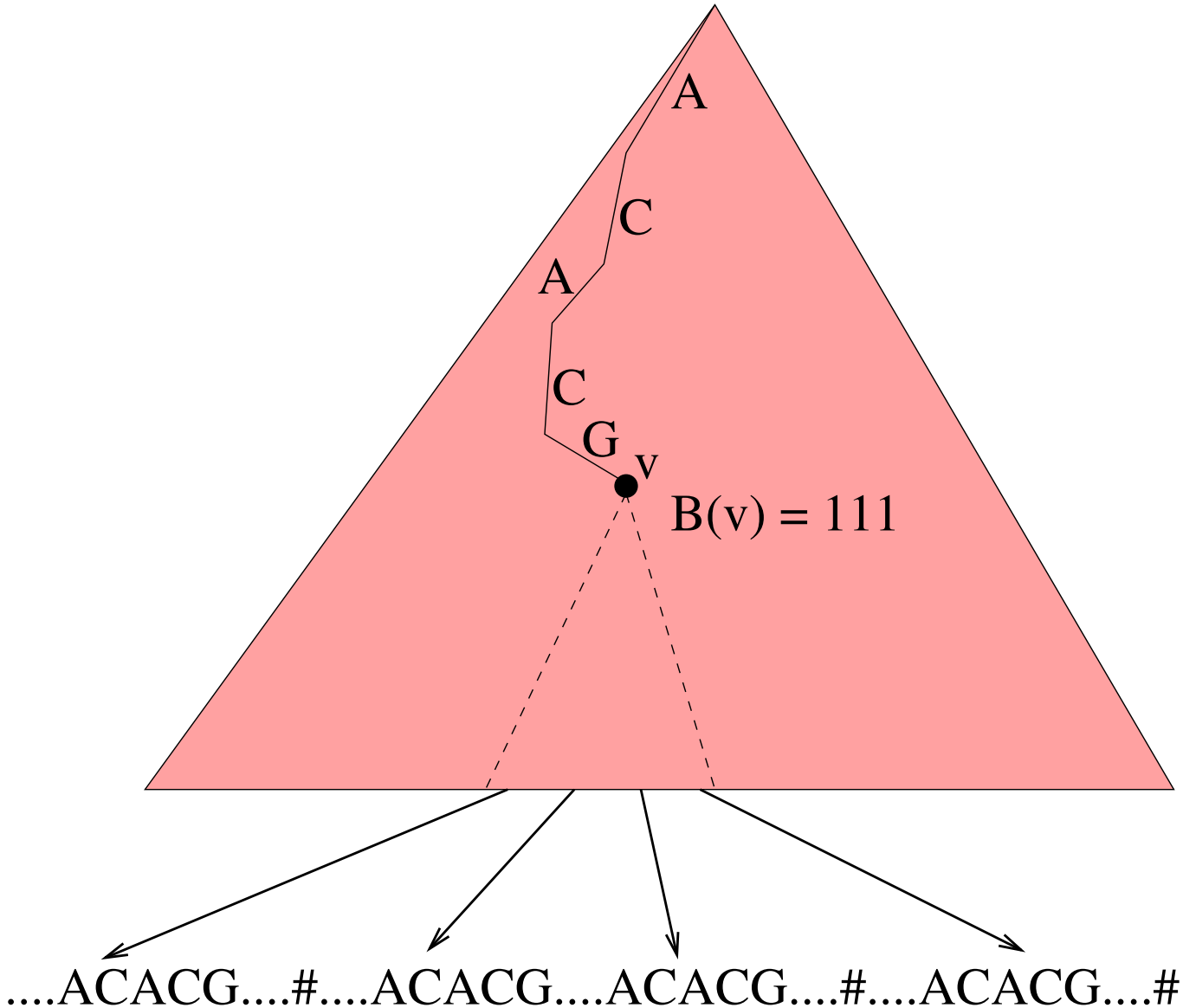
Backtracking on Suffix Tree



Suffix Tree and Exact Motif Finding

- Concatenate the rows of the $t \times n$ matrix DNA into a string S, inserting an endmarker $\#$ between the rows
- Build suffix tree T of S and for each node v store a bitvector $B(v)[1, t]$ such that $B(v)[i] = 1$ iff any suffix starting from row t is in the subtree of v.
- Let $v(s)$ denote an internal node of T such that the path from the root to the incoming edge of $v(s)$ spells s.
- String s is an *exact motif* if $B(v(s))[i] = 1$ for all i.

Suffix Tree and Exact Motif Finding



Weeder: a Suffix Tree -Based Approach

- Weeder extends the exact motif finding algorithm to approximate motifs
- Backtracking plugged in
- Some heuristics to avoid too extensive branching

Outline

Study Group Assignments: Group 1 (Lastnames A-L)

- Read Sections 4.1-4.3 (partial digest problem) from the course book *before* coming to the study group meeting
- Solve Problem 4.2 (page 119) *at* study group and use the solution to explain the material to the other groups:
  - Consider partial digest

$$L = \{1, 1, 1, 2, 2, 3, 3, 3, 4, 4, 5, 5, 6, 6, 6, 9, 9, 10, 11, 12, 15\}$$

  - Solve the Partial Digest problem for L (i.e. find X such that $\Delta X = L$).

Study Group Assignments: Group 2 (Lastnames M-R)

- Read the following article before coming to the study group:

  Alvis Brazma, Inge Jonassen, Jaak Vilo, and Esko Ukkonen. Predicting Gene Regulatory Elements in Silico on a Genomic Scale. *Genome Res.* 1998. 8: 1202-1215.
  `http://genome.cshlp.org/content/8/11/1202.full`

  Read especially section METHODS.

- At study group, discuss the approach, and draw a pattern trie for some small example input.

Study Group Assignments: Group 3 (Lastnames S-Z)

- Read the following article before coming to the study group:

  Pavesi G, Mauri G, Pesole G. An algorithm for finding signals of unknown length in DNA sequences. *Bioinformatics*, 2001, 17(Suppl 1):S207-S214.

  `http://bioinformatics.oxfordjournals.org/content/17/suppl_1/S207.full.pdf`

- At study group, summarize the message of the article and share the message to other groups.