Lecture 23: Randomized Algorithms

Chapter 12

Randomized Algorithms

- Randomized algorithms incorporate random, rather than deterministic, decisions
- Commonly used in situations where no exact and/or fast algorithm is known
- Main advantage is that no input can reliably produce worst-case results because the algorithm runs differently each time.

Select

- **Select(L, k)** finds the kth smallest element in L
- Select(L,1) find the smallest…
  - Well known O(n) algorithm

```
minv = HUGE
for v in L:
    if (v < minv):
        minv = v
```

- Select(L, len(L)/2) find the median…
  - How?
  - median = sorted(L)[len(L)/2] → O(n logn)
- Can we find medians, or 1st quartiles in O(n)?

Select Recursion

- **Select(L, k)** finds the kth smallest element in **L**
  - Select an element *m* from unsorted list **L** and partition L the array into two smaller lists:

    $\mathbf{L}_{lo}$ - elements smaller than *m*

    and

    $\mathbf{L}_{hi}$ - elements larger than *m*.

- If len($\mathbf{L}_{lo}$) > k then

  Select($\mathbf{L}_{lo}$, k)

- else if k > len($\mathbf{L}_{lo}$) + 1 then

  Select($\mathbf{L}_{hi}$, k - len($\mathbf{L}_{lo}$) - 1)

- else *m* is the kth smallest element

Example of Select(L, 5)

Given an array: **L** = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9 }

<u>Step 1</u>: Choose the first element as *m*

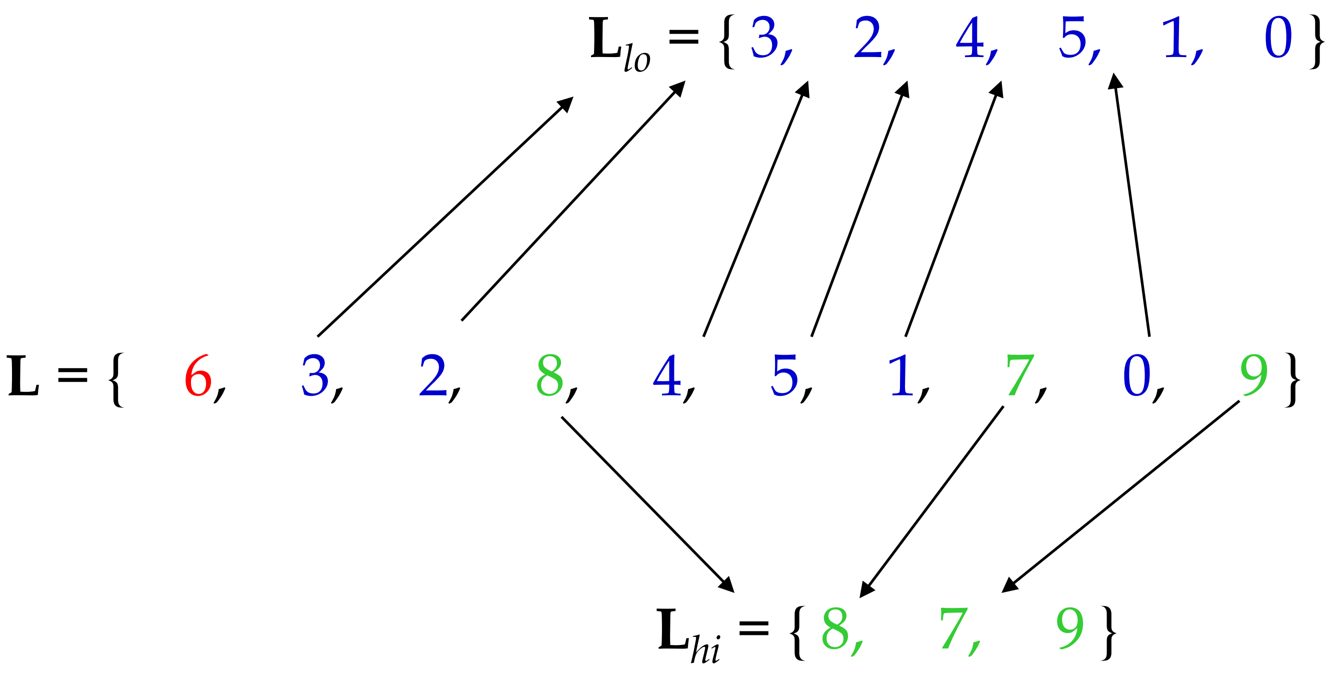
L = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9 }

$\uparrow$

Our Selection

Example of Select(cont’d)

Step 2: Split the array into $\mathbf{L}_{\text{lo}}$ and $\mathbf{L}_{\text{hi}}$



L_lo = { 3, 2, 4, 5, 1, 0 }
L = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9 }
L_hi = { 8, 7, 9 }

Example of Select(cont'd)

Step 3: Recursively call Select on either $\mathbf{L}_{lo}$ or $\mathbf{L}_{hi}$ until len($\mathbf{L}_{lo}$) = k, then return *m*.

len(L_{lo}) > k = 5 → Select({ 3, 2, 4, 5, 1, 0 }, 5)

m = 3

L_{lo} = { 2, 1, 0 } L_{hi} = { 4, 5 }

k = 5 > len(L_{lo}) +1 → Select({4, 5 }, 5 - 3 - 1)

m = 4

L_{lo} = { empty }, L_{hi} = { 5 }

k = 1 == len(L_{lo}) + 1 → return 4

Select Code

```
def select(L, k):
    value = L[0]
    Llo = [t for t in data if t < value]
    Lhi = [t for t in data if t > value]
    below = len(Llo) + 1
    if (k < len(Llo)):
        return select(Llo, k)
    elif (k > below):
        return select(Lhi, k - below)
    else:
        return value
```

Select Analysis with Good Splits

- Runtime depends on our selection of *m*:

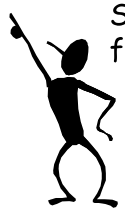
  - A good selection will split **L** evenly such that

  $|\mathbf{L}_{lo}| = |\mathbf{L}_{hi}| = |\mathbf{L}|/2$

  - The recurrence relation is:

  $$T(n) = T(n/2)$$

  - $n + n/2 + n/4 + n/8 + n/16 + \ldots = 2n \rightarrow O(n)$



Same as search for minimum

Select Analysis with Bad Splits

However, a poor selection will split **L** unevenly and in the worst case, all elements will be greater or less than *m* so that one Sublist is full and the other is empty.

For a poor selection, the recurrence relation is

$$T(n) = T(n-1)$$

In this case, the runtime is O(n^2).

Our dilemma:

O(n) or O(n^2),

depending on the list… or O(n log n) independent of it

Select Analysis (cont'd)

- Select seems risky compared to sort
- To improve Select, we need to choose *m* to give good 'splits'
- It can be proven that to achieve O(*n*) running time, we don't need a perfect splits, just reasonably good ones.
- In fact, if both subarrays are at least of size *n/4*, then running time will be O(*n*).
- This implies that half of the choices of *m* make good splitters.

A Randomized Approach

- To improve Select, ***randomly*** select *m*.
- Since half of the elements will be good splitters, if we choose *m* at random we will get a 50% chance that *m* will be a good choice.
- This approach will make sure that no matter what input is received, the expected running time is small.

Randomized Select

```
def randomizedSelect(L, k):
    value = random.choice(L)
    Llo = [t for t in data if t < value]
    Lhi = [t for t in data if t > value]
    below = len(Llo) + 1
    if (k < len(Llo)):
        return randomizedSelect(Llo, k)
    elif (k > below):
        return randomizedSelect(Lhi, k-below)
    else:
        return value
```

RandomizedSelect Analysis

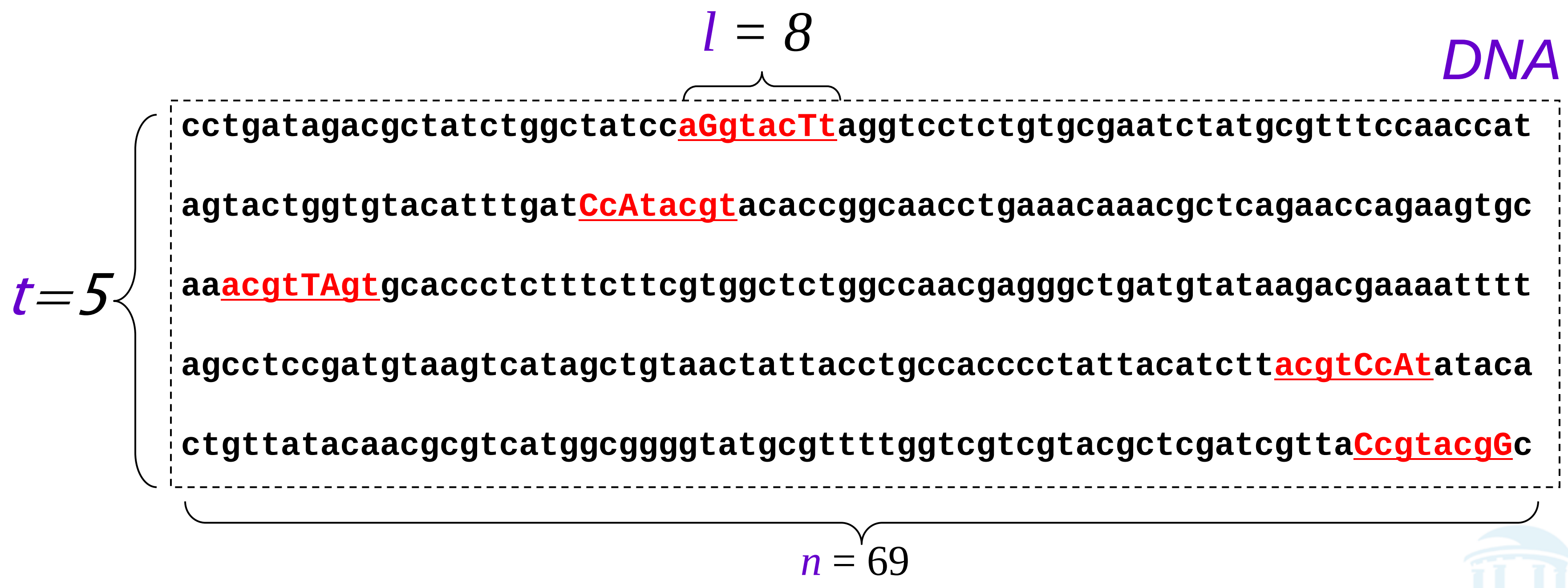
- Worst case runtime: O(n^2)
- ***Expected runtime***: O(n).
- Expected runtime is a good measure of the performance of randomized algorithms, often more informative than worst case runtimes.
- Worst case runtimes are rarely repeated
- RandomizedSelect always returns the correct answer, which offers a way to classify Randomized Algorithms.

Two Types of Randomized Algorithms

- **Las Vegas Algorithms** – always produce the correct solution (i.e. randomizedSelect), but may exceed expected time bound with small probability
- **Monte Carlo Algorithms** – do not always return the correct solution (but typically meet a worst case boudn)
- Las Vegas Algorithms are always preferred, but not always easy to come by.

The Motif Finding Problem

Motif Finding Problem: Given a list of *t* sequences each of length *n*, find the "best" pattern of length *l* that appears in each of the *t* sequences.



```
cctgatagacgctatctggctatccaGgtacTtaggtcctctgtgcgaatctatgcgtttccaaccat
agtactggtgtacatttgatCcAtacgtacaccggcaacctgaaacaaacgctcagaaccagaagtgc
aaacgtTAgtgcaccctctttcttcgtggctctggccaacgagggctgatgtataagacgaaaatttt
agcctccgatgtaagtcatagctgtaactattacctgccacccctattacatcttacgtCcAtataca
ctgttatacaacgcgtcatggcggggtatgcgttttggtcgtcgtacgctcgatcgttaCcgtacgGc
```

A New Motif Finding Approach

- **Motif Finding Problem**: Given a list of *t* sequences each of length *n*, find the "best" pattern of length *l* that appears in each of the *t* sequences.
- **Previously:** we solved the Motif Finding Problem using a Branch and Bound or a Greedy technique.
- **Now**: **randomly** select possible locations and find a way to greedily change those locations until we converge to the hidden motif.

Profiles Revisited

- Let **s** = (s_1,…,s_t) be the starting positions for *l*-mers in our *t* sequences.
- The substrings corresponding to these starting positions will form:

  - *t* x *l* ***alignment matrix***

  - 4 x *l* ***profile matrix****

$$\left.\overbrace{\begin{array}{cccccccc} \mathtt{a} & \mathtt{G} & \mathtt{g} & \mathtt{t} & \mathtt{a} & \mathtt{c} & \mathtt{T} & \mathtt{t} \\ \mathtt{C} & \mathtt{c} & \mathtt{A} & \mathtt{t} & \mathtt{a} & \mathtt{c} & \mathtt{g} & \mathtt{t} \\ \mathtt{a} & \mathtt{c} & \mathtt{g} & \mathtt{t} & \mathtt{T} & \mathtt{A} & \mathtt{g} & \mathtt{t} \\ \mathtt{a} & \mathtt{c} & \mathtt{g} & \mathtt{t} & \mathtt{C} & \mathtt{c} & \mathtt{A} & \mathtt{t} \\ \mathtt{C} & \mathtt{c} & \mathtt{g} & \mathtt{t} & \mathtt{a} & \mathtt{c} & \mathtt{g} & \mathtt{G} \end{array}}^{l}\right\}t$$

$$\begin{array}{c|cccccccc} \mathtt{A} & 0.6 & 0.0 & 0.2 & 0.0 & 0.6 & 0.2 & 0.2 & 0.0 \\ \mathtt{C} & 0.4 & 0.8 & 0.0 & 0.0 & 0.2 & 0.8 & 0.0 & 0.0 \\ \mathtt{G} & 0.0 & 0.2 & 0.8 & 0.0 & 0.0 & 0.0 & 0.6 & 0.2 \\ \mathtt{T} & 0.0 & 0.0 & 0.0 & 1.0 & 0.2 & 0.0 & 0.2 & 0.8 \end{array}\left.\vphantom{\begin{array}{c}A\\C\\G\\T\end{array}}\right\}4$$

```
X     a   c   g   t   a   c   g   t
```

```
P(X|profile)=0.6*0.8*0.8*1.0*0.6*0.8*0.6*0.8 = 0.0885
```

* Note that we now define the profile matrix in terms of frequency, not counts as in Lecture 5.

Scoring Strings with a Profile

- Let l-mer **a** = $a_1, a_2, a_3, \dots a_l$
- P(**a** | **P**) is defined as the probability that an l-mer **a** was created by the Profile **P**.
- If **a** is very similar to the consensus string of **P** then P(**a** | **P**) will be high
- If **a** is very different, then P(**a** | **P**) will be low.

$$Prob(\mathbf{a} \mid \mathbf{P}) = \prod_{i=1}^{l} p(a_i, i)$$

Scoring Strings with a Profile (cont'd)

Given a profile: **P** =

A	1/2	7/8	3/8	0	1/8	0
C	1/8	0	1/2	5/8	3/8	0
T	1/8	1/8	0	0	1/4	7/8
G	1/4	0	1/8	3/8	1/4	1/8

The probability of the consensus string:

Prob(**aaacct**|**P**) = ???

Scoring Strings with a Profile (cont'd)

Given a profile: **P** =

A	**1/2**	**7/8**	**3/8**	0	1/8	0
C	1/8	0	1/2	**5/8**	**3/8**	0
T	1/8	1/8	0	0	1/4	**7/8**
G	1/4	0	1/8	3/8	1/4	1/8

The probability of the consensus string:

Prob(**aaacct**|**P**) = 1/2 x 7/8 x 3/8 x 5/8 x 3/8 x 7/8 = .033646

Scoring Strings with a Profile (cont'd)

Given a profile: **P** =

A	**1/2**	7/8	**3/8**	0	**1/8**	0
C	1/8	0	1/2	**5/8**	3/8	0
T	1/8	**1/8**	0	0	1/4	7/8
G	1/4	0	1/8	3/8	1/4	**1/8**

The probability of the consensus string:

Prob(**aaacct|P**) = 1/2 x 7/8 x 3/8 x 5/8 x 3/8 x 7/8 = .033646

Probability of a different string:

Prob(**atacag|P**) = 1/2 x 1/8 x 3/8 x 5/8 x 1/8 x 1/8 = .001602

P-Most Probable *l*-mer

- Define the **P**-most probable *l*-mer from a sequence as an *l*-mer in that sequence which has the highest probability of being created from the profile **P**.

P =

A	1/2	7/8	3/8	0	1/8	0
C	1/8	0	1/2	5/8	3/8	0
T	1/8	1/8	0	0	1/4	7/8
G	1/4	0	1/8	3/8	1/4	1/8

Given a sequence = ctataaaccttacatc, find the P-most probable *l*-mer

P-Most Probable *l*-mer (cont'd)

A	1/2	7/8	3/8	0	1/8	0
C	1/8	0	1/2	5/8	3/8	0
T	1/8	1/8	0	0	1/4	7/8
G	1/4	0	1/8	3/8	1/4	1/8

Find the *Prob*(**a**|**P**) of every possible 6-mer:

First try: **c t a t a a a c c t t a c a t c**

Second try: **c t a t a a a c c t t a c a t c**

Third try: **c t a t a a a c c t t a c a t c**

-Continue this process to evaluate every possible 6-mer

P-Most Probable *l*-mer (cont'd)

Compute *prob*(**a**|**P**) for every possible 6-mer:

String, Highlighted in Red	Calculations	*prob*(**a** | **P**)
ctataaaccttacat	1/8 x 1/8 x 3/8 x 0 x 1/8 x 0	0
ctataaaccttacat	1/2 x 7/8 x 0 x 0 x 1/8 x 0	0
ctataaaccttacat	1/2 x 1/8 x 3/8 x 0 x 1/8 x 0	0
ctataaaccttacat	1/8 x 7/8 x 3/8 x 0 x 3/8 x 0	0
ctataaaccttacat	1/2 x 7/8 x 3/8 x 5/8 x 3/8 x 7/8	.0336
ctataaaccttacat	1/2 x 7/8 x 1/2 x 5/8 x 1/4 x 7/8	.0299
ctataaaccttacat	1/2 x 0 x 1/2 x 0 1/4 x 0	0
ctataaaccttacat	1/8 x 0 x 0 x 0 x 0 x 1/8 x 0	0
ctataaaccttacat	1/8 x 1/8 x 0 x 0 x 3/8 x 0	0
ctataaaccttacat	1/8 x 1/8 x 3/8 x 5/8 x 1/8 x 7/8	.0004

P-Most Probable *l*-mer (cont'd)

P-Most Probable 6-mer in the sequence is aaacct:

String, Highlighted in Red	Calculations	*Prob*(**a** | **P**)
ctataaaccttacat	1/8 x 1/8 x 3/8 x 0 x 1/8 x 0	0
ctataaaccttacat	1/2 x 7/8 x 0 x 0 x 1/8 x 0	0
ctataaaccttacat	1/2 x 1/8 x 3/8 x 0 x 1/8 x 0	0
ctataaaccttacat	1/8 x 7/8 x 3/8 x 0 x 3/8 x 0	0
ctataaaccttacat	**1/2 x 7/8 x 3/8 x 5/8 x 3/8 x 7/8**	**.0336**
ctataaaccttacat	1/2 x 7/8 x 1/2 x 5/8 x 1/4 x 7/8	.0299
ctataaaccttacat	1/2 x 0 x 1/2 x 0 1/4 x 0	0
ctataaaccttacat	1/8 x 0 x 0 x 0 x 0 x 1/8 x 0	0
ctataaaccttacat	1/8 x 1/8 x 0 x 0 x 3/8 x 0	0
ctataaaccttacat	1/8 x 1/8 x 3/8 x 5/8 x 1/8 x 7/8	.0004

P-Most Probable *l*-mer (cont'd)

aaacct is the **P**-most probable 6-mer in:

ctataaaccttacatc

because *Prob*(**aaacct|P**) = .0336 is greater than the *Prob*(**a|P**) of any other 6-mer in the sequence.

Dealing with Zeroes

- In our toy example *prob*(**a** | **P**)=0 in many cases. In practice, there will be enough sequences so that the number of elements in the profile with a frequency of zero is small.
- To avoid many entries with *prob*(**a** | **P**)=0, there exist techniques to equate zero to a very small number so that one zero does not make the entire probability of a string zero (assigning a *prior* probability, we will not address these techniques here).

P-Most Probable *l*-mers in Many Sequences

- Find the **P**-most probable *l*-mer in each of the "t" sequences.

P=

A	1/2	7/8	3/8	0	1/8	0
C	1/8	0	1/2	5/8	3/8	0
T	1/8	1/8	0	0	1/4	7/8
G	1/4	0	1/8	3/8	1/4	1/8

ctataaacgttacatc

atagcgattcgactg

cagcccagaaccct

cggtataccttacatc

tgcattcaatagctta

tatcctttccactcac

ctccaaatcctttaca

ggtcatcctttatcct

P-Most Probable *l*-mers in Many Sequences (cont'd)

1	a	a	a	c	g	t
2	a	t	a	g	c	g
3	a	a	c	c	c	t
4	g	a	a	c	c	t
5	a	t	a	g	c	t
6	g	a	c	c	t	g
7	a	t	c	c	t	t
8	t	a	c	c	t	t
A	5/8	5/8	4/8	0	0	0
C	0	0	4/8	6/8	4/8	0
T	1/8	3/8	0	0	3/8	6/8
G	2/8	0	0	2/8	1/8	2/8

```
ctataaacgttacatc
atagcgattcgactg
cagcccagaaccct
cggtgaaccttacatc
tgcattcaatagctta
tgtcctgtccactcac
ctccaaatcctttaca
ggtctacctttatcct
```

P-Most Probable *l*-mers form a new profile

Comparing New and Old Profiles

1	a	a	a	c	g	t
2	a	t	a	g	c	g
3	a	a	c	c	c	t
4	g	a	a	c	c	t
5	a	t	a	g	c	t
6	g	a	c	c	t	g
7	a	t	c	c	t	t
8	t	a	c	c	t	t
A	5/8	5/8	4/8	0	0	0
C	0	0	4/8	6/8	4/8	0
T	1/8	3/8	0	0	3/8	6/8
G	2/8	0	0	2/8	1/8	2/8

A	1/2	7/8	3/8	0	1/8	0
C	1/8	0	1/2	5/8	3/8	0
T	1/8	1/8	0	0	1/4	7/8
G	1/4	0	1/8	3/8	1/4	1/8

Red – frequency increased, Blue – frequency decreased

Greedy Profile Motif Search

Use P-Most probable *l*-mers to adjust start positions until we reach a "best" profile; this is the motif.

1) Select random starting positions.
2) Create a profile **P** from the substrings at these starting positions.
3) Find the **P**-most probable *l*-mer **a** in each sequence and change the starting position to the starting position of **a**.
4) Compute a new profile based on the new starting positions after each iteration and proceed until we cannot increase the score anymore.

GreedyProfileMotifSearch Algorithm

```
1.  GreedyProfileMotifSearch(DNA, t, n, l )
2.      Randomly select starting positions s=(s_1,…,s_t) from DNA
3.      bestScore ← 0
4.      while Score(s, DNA) > bestScore
5.         form profile P from s
6.         bestScore ← Score(s, DNA)
7.         for  i ← 1  to  t
8.             Find a P-most probable l-mer a from the ith sequence
9.             s_i ← starting position of a
10.     return bestScore
```

GreedyProfileMotifSearch Analysis

- Since we choose starting positions randomly, there is little chance that our guess will be close to an optimal motif, meaning it will take a very long time to find the optimal motif.
- It is unlikely that the random starting positions will lead us to the correct solution at all.
- In practice, this algorithm is run many times with the hope that random starting positions will be close to the optimum solution simply by chance.

Gibbs Sampling

- GreedyProfileMotifSearch is probably not the best way to find motifs.
- However, we can improve the algorithm by introducing **Gibbs Sampling**, an iterative procedure that discards one *l*-mer after each iteration and replaces it with a new one.
- Gibbs Sampling proceeds more slowly and chooses new *l*-mers at random increasing the odds that it will converge to the correct solution.

How Gibbs Sampling Works

1) Randomly choose starting positions **s** = (s_1,...,s_t) and form the set of *l*-mers associated with these starting positions.
2) Randomly choose one of the *t* sequences.
3) Create a profile **P** from the other *t* -1 sequences.
4) For each position in the removed sequence, calculate the probability that the *l*-mer starting at that position was generated by **P**.
5) Choose a new starting position for the removed sequence at random based on the probabilities calculated in step 4.
6) Repeat steps 2-5 until there is no improvement

Gibbs Sampling: an Example

Input:

t = 5 sequences, motif length l = 8

```
1.  GTAAACAATATTTATAGC
2.  AAAATTTACCTCGCAAGG
3.  CCGTACTGTCAAGCGTGG
4.  TGAGTAAACGACGTCCCA
5.  TACTTAACACCCTGTCAA
```

Gibbs Sampling: an Example

1) Randomly choose starting positions, $\boldsymbol{s}=(s_1,s_2,s_3,s_4,s_5)$ in the 5 sequences:

$s_1=7$	`GTAAACAATATTTATAGC`
$s_2=11$	`AAAATTTACCTTAGAAGG`
$s_3=9$	`CCGTACTGTCAAGCGTGG`
$s_4=4$	`TGAGTAAACGACGTCCCA`
$s_5=1$	`TACTTAACACCCTGTCAA`

Gibbs Sampling: an Example

2) Choose one of the sequences at random:

Sequence 2: AAAATTTACCTTAGAAGG

$s_1=7$ GTAAACAATATTTATAGC

$s_2=11$ AAAATTTACCTTAGAAGG

$s_3=9$ CCGTACTGTCAAGCGTGG

$s_4=4$ TGAGTAAACGACGTCCCA

$s_5=1$ TACTTAACACCCTGTCAA

Gibbs Sampling: an Example

2) Choose one of the sequences at random:

Sequence 2: AAAATTTACCTTAGAAGG

```
s1=7      GTAAACAATATTTATAGC

s3=9    CCGTACTGTCAAGCGTGG
s4=4         TGAGTAAACGACGTCCCA
s5=1    TACTTAACACCCTGTCAA
```

Gibbs Sampling: an Example

3) Create profile ***P*** from *l*-mers in remaining 4 sequences:

1	A	A	T	A	T	T	T	A
3	T	C	A	A	G	C	G	T
4	G	T	A	A	A	C	G	A
5	T	A	C	T	T	A	A	C
A	1/4	2/4	2/4	3/4	1/4	1/4	1/4	2/4
C	0	1/4	1/4	0	0	2/4	0	1/4
T	2/4	1/4	1/4	1/4	2/4	1/4	1/4	1/4
G	1/4	0	0	0	1/4	0	3/4	0
Consensus String	T	A	A	A	T	C	G	A

Gibbs Sampling: an Example

4) Calculate the $prob(\boldsymbol{a} \mid \boldsymbol{P})$ for every possible 8-mer in the removed sequence:

Strings Highlighted in Red	*prob*(**a** | **P**)
AAAATTTACCTTAGAAGG	.000732
AAAATTTACCTTAGAAGG	.000122
AAAATTTACCTTAGAAGG	0
AAAATTTACCTTAGAAGG	0
AAAATTTACCTTAGAAGG	0
AAAATTTACCTTAGAAGG	0
AAAATTTACCTTAGAAGG	0
AAAATTTACCTTAGAAGG	.000183
AAAATTTACCTTAGAAGG	0
AAAATTTACCTTAGAAGG	0
AAAATTTACCTTAGAAGG	0

Gibbs Sampling: an Example

5) Create a distribution of probabilities of *l*-mers $prob(\boldsymbol{a} \mid \boldsymbol{P})$, and randomly select a new starting position based on this distribution.

A) To create this distribution, divide each probability $prob(\boldsymbol{a} \mid \boldsymbol{P})$ by the total:

Starting Position 1: *prob*(AAAATTTA | P) = .706

Starting Position 2: *prob*(AAATTTAC | P) = .118

Starting Position 8: *prob*(ACCTTAGA | P) = .176

Gibbs Sampling: an Example

B) Select a new starting position at random according to computed distribution:

P(selecting starting position 1):	.706
P(selecting starting position 2):	.118
P(selecting starting position 8):	.176

```
t = random.random()
if (t < .706):
    # use position 1
elif (t < (.706 + .118)):
    # use position 2
else:
    # use position 8
```

Gibbs Sampling: an Example

Assume we select the substring with the highest probability – then we are left with the following new substrings and starting positions.

$s_1=7$	GTAAACAATATTTATAGC
$s_2=1$	AAAATTTACCTCGCAAGG
$s_3=9$	CCGTACTGTCAAGCGTGG
$s_4=5$	TGAGTAATCGACGTCCCA
$s_5=1$	TACTTCACACCCTGTCAA

Gibbs Sampling: an Example

6) We iterate the procedure again with the above starting positions until we cannot improve the score any more.

Gibbs Sampler in Practice

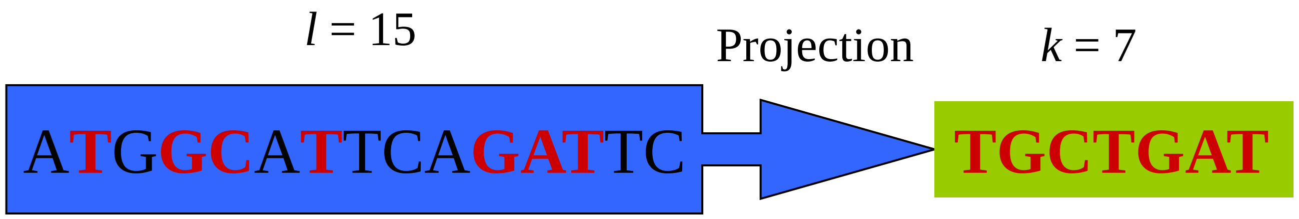
- Gibbs sampling needs to be modified when applied to samples with biased distributions of nucleotides (*relative entropy* approach).
- Gibbs sampling often converges to locally optimal motifs rather than globally optimal motifs.
- Must be run with many randomly chosen seeds to achieve good results.

Another Randomized Approach

- **Random Projection Algorithm** is a different way to solve the Motif Finding Problem.
- **Guiding principle:** Instances of a motif agree at a subset of positions.
- However, it is unclear how to find these "non-mutated" positions.
- To bypass the effect of mutations within a motif, we randomly select a subset of positions in the pattern creating a **projection** of the pattern.
- Search for that projection in a hope that the selected positions are not affected by mutations in most instances of the motif.

Projections

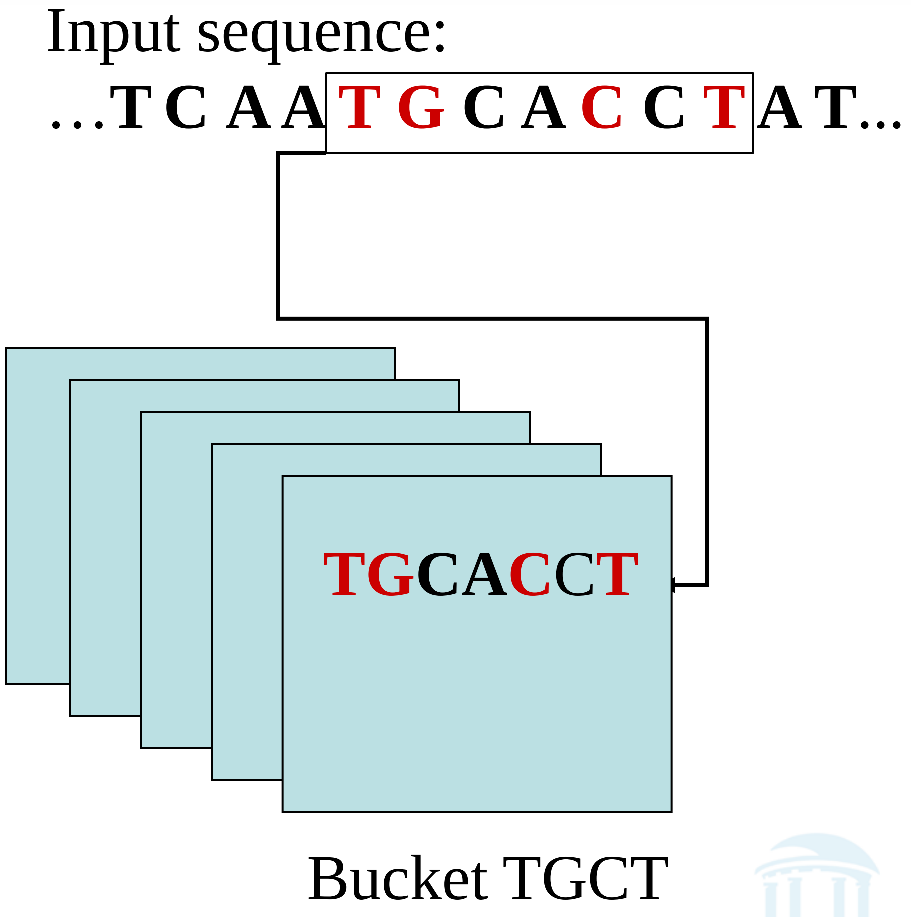
- Choose *k* positions in string of length *l*.
- Concatenate nucleotides at chosen *k* positions to form *k*-tuple.
- This can be viewed as a projection of *l*-dimensional space onto *k*-dimensional subspace.



Projection = (2, 4, 5, 7, 11, 12, 13)

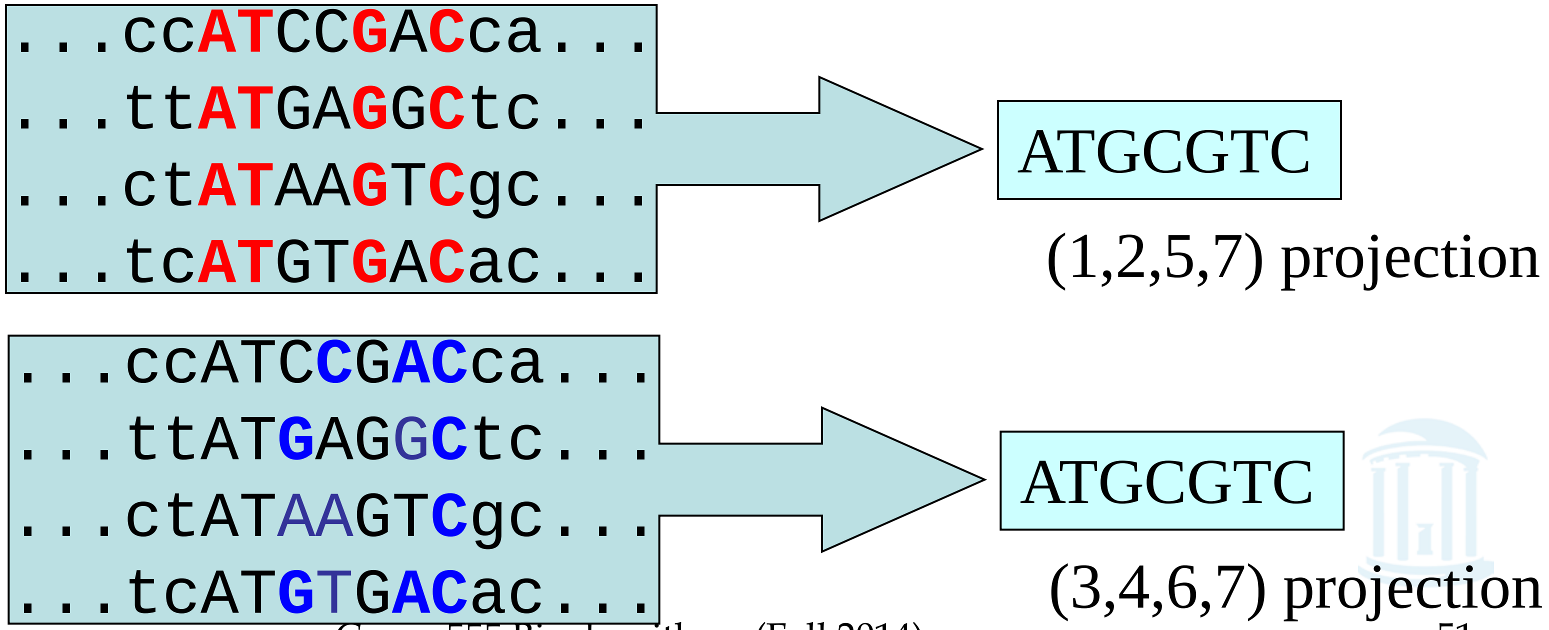
Random Projections Algorithm

- Select *k* out of *l* positions uniformly at random.
- For each *l*-tuple in input sequences, hash into buckets based on the *k* selected positions.
- Recover motif from ***enriched*** buckets that contain many *l*-tuples with at least one from each sequence.



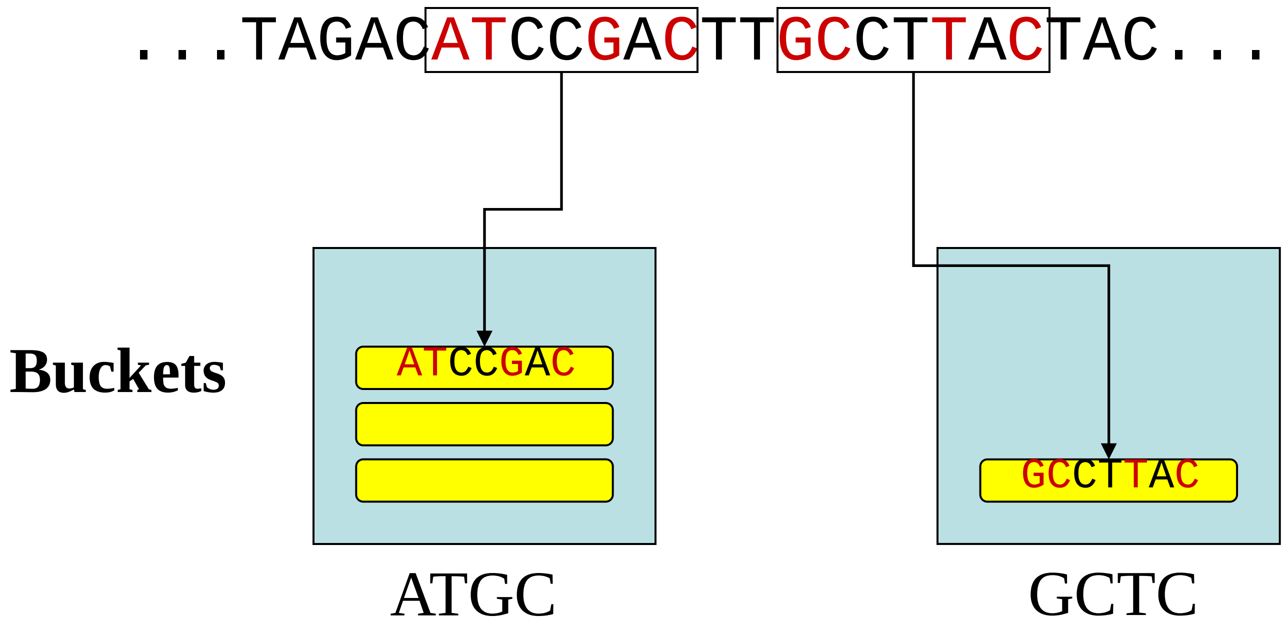
Random Projections Algorithm (cont'd)

- Some projections will fail to detect motifs but if we try many of them the probability that one of the buckets fills increases.
- In the example below, the bucket **GC*AC is "bad" while the bucket AT**G*C is "good"



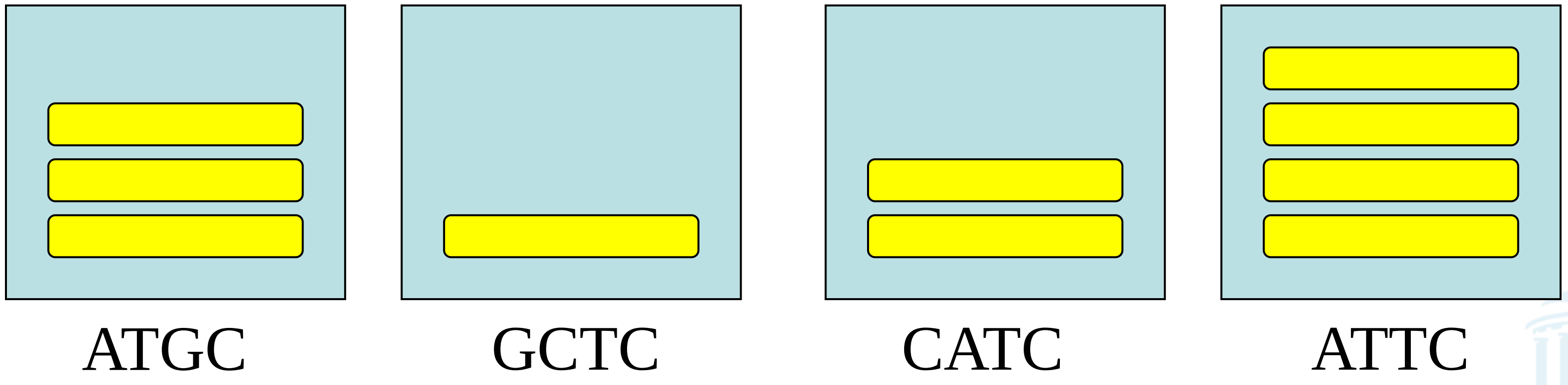
Example

- $l = 7$ (motif size) , $k = 4$ (projection size)
- Choose projection (1,2,5,7)



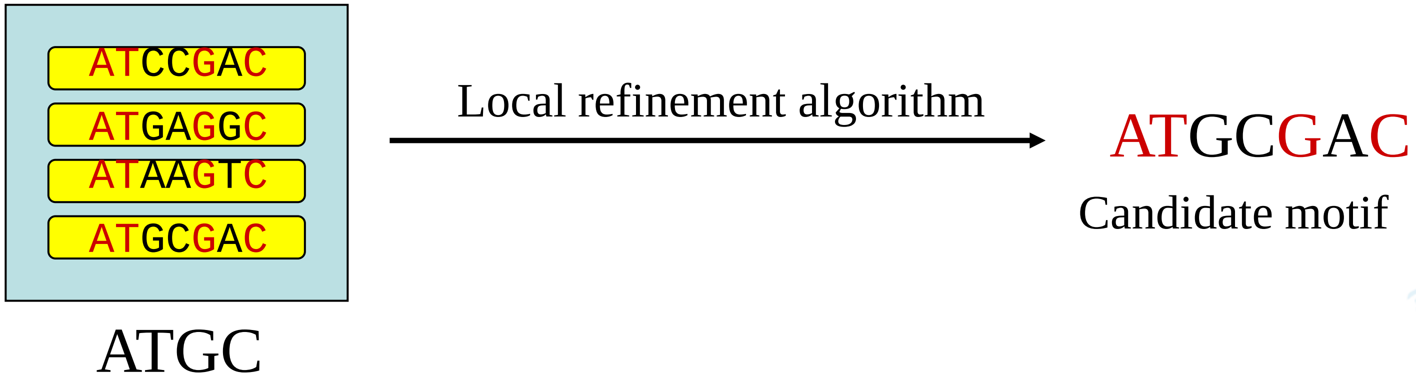
Hashing and Buckets

- Hash function *h(x)* obtained from *k* positions of projection.
- Buckets are labeled by values of *h(x)*.
- *Enriched buckets*: contain more than *s* *l*-tuples, for some parameter *s* with representatives from all sequences



Motif Refinement

- How do we recover the motif from the sequences in enriched buckets?
- *k* nucleotides are exact matches, (hash key of bucket).
- Use information in other *l*-*k* positions as starting point for local refinement scheme, e.g. Gibbs sampler.



Synergy between Random Projection and Gibbs Sampler

- Random Projection is a procedure for finding good starting points: every enriched bucket is a potential starting point.
- Feeding these starting points into existing algorithms (like Gibbs sampler) provides good local search in vicinity of every starting point.
- These algorithms work particularly well for "good" starting points.

Building Profiles from Buckets

ATCCGAC

ATGAGGC

ATAAGTC

ATGTGAC

ATGC

$$
\begin{array}{c|ccccccc|}
A & 1 & 0 & .25 & .50 & 0 & .50 & 0 \\
C & 0 & 0 & .25 & .25 & 0 & 0 & 1 \\
G & 0 & 0 & .50 & 0 & 1 & .25 & 0 \\
T & 0 & 1 & 0 & .25 & 0 & .25 & 0
\end{array}
$$

Profile P

Gibbs sampler

Refined profile P*

Motif Refinement

- For each bucket *h* containing more than *s* sequences, form profile **P(***h***)**

- Use Gibbs sampler algorithm with starting point **P(***h***)** to obtain refined profile **P***

Random Projection Algorithm

A Single Iteration:

- Choose a random *k*-projection.
- Hash each *l*-mer *x* in input sequence into bucket labeled by *h*(x)
- From each enriched bucket (e.g., a bucket with more than *s* sequences), form profile **P** and perform Gibbs sampler motif refinement
- Candidate motif is best found by selecting the best motif among refinements of all enriched buckets.

Choosing Projection Size

- Projection size *k*

  - choose *k* small enough so that several motif instances hash to the same bucket.

    $$k << l, \qquad l/2 < k < l - const$$

  - choose *k* large enough to avoid contamination by spurious *l*-mers:

    $$4^k >> t\,(n - l + 1)$$