Randomized Algorithms and Motif Finding

Outline

- Randomized QuickSort
- Randomized Algorithms
- Greedy Profile Motif Search
- Gibbs Sampler
- Random Projections

Randomized Algorithms

- Randomized algorithms make random rather than deterministic decisions.
- The main advantage is that no input can reliably produce worst-case results because the algorithm runs differently each time.
- These algorithms are commonly used in situations where no exact and fast algorithm is known.

Introduction to QuickSort

- **QuickSort** is a simple and efficient approach to sorting:
- Select an element *m* from unsorted array **c** and divide the array into two subarrays:

  $\mathbf{c}_{small}$ - elements smaller than *m* and

  $\mathbf{c}_{large}$ - elements larger than *m*.
- Recursively sort the subarrays and combine them together in sorted array $\mathbf{c}_{sorted}$

Example of QuickSort

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

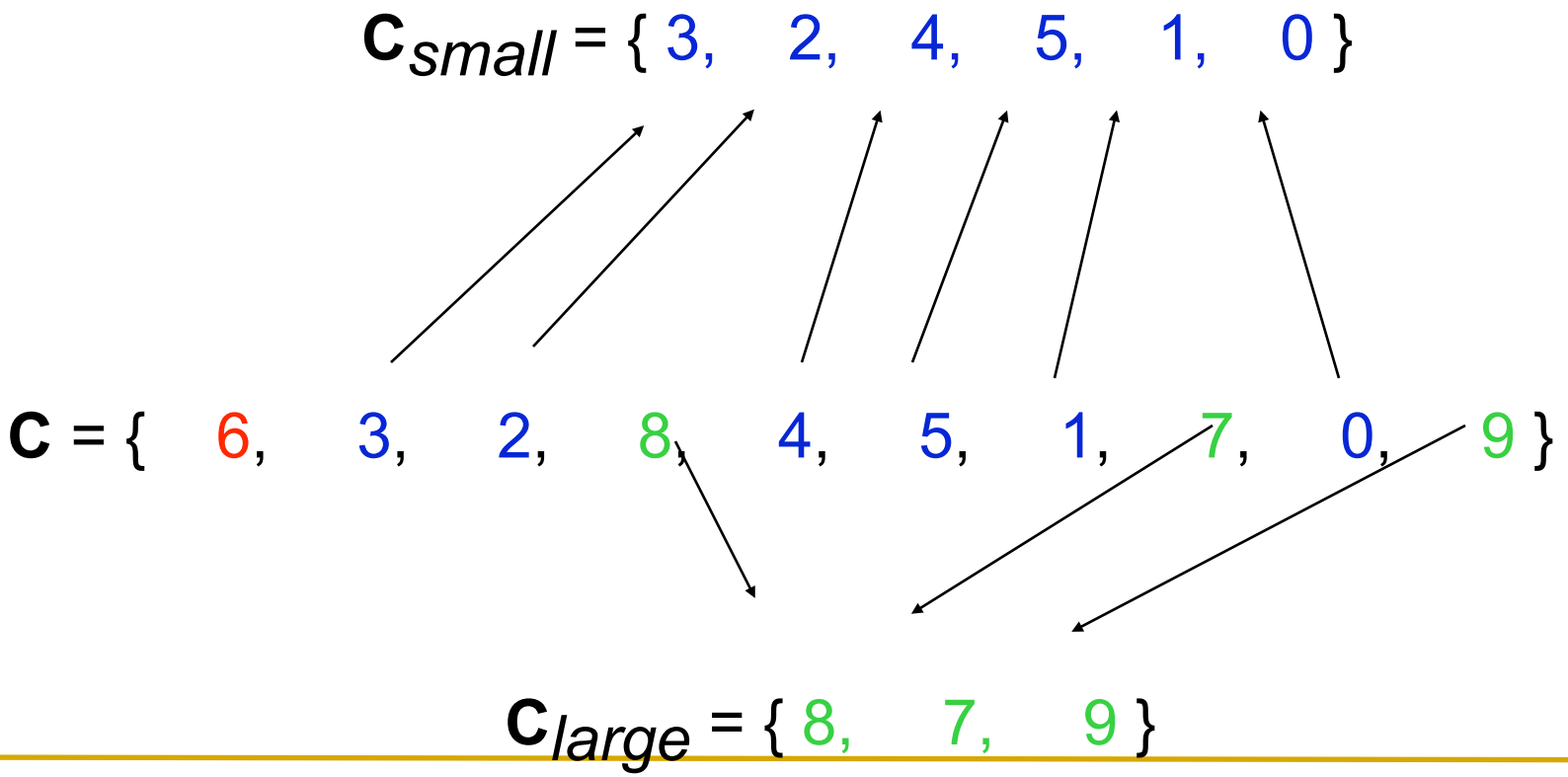
Step 1: Choose the first element as *m*

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

Our Selection

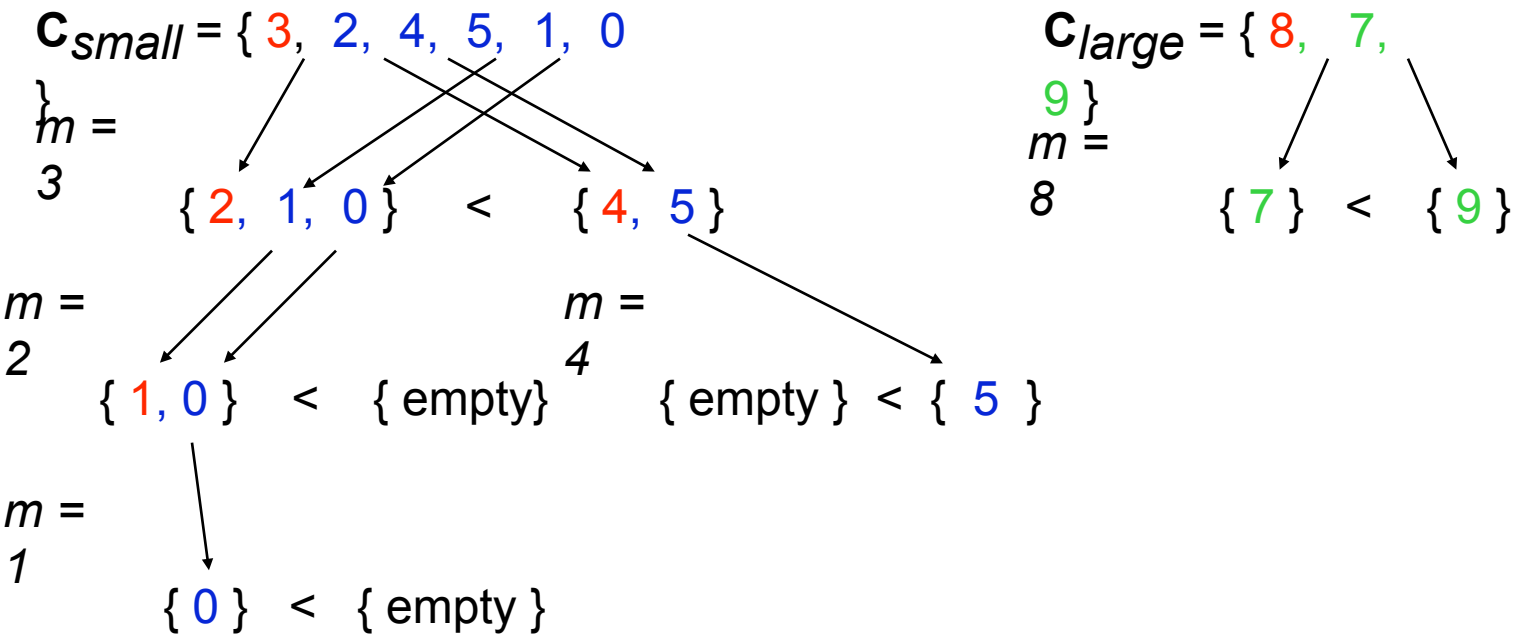
Example of QuickSort (cont'd)

Step 2: Split the array into $\mathbf{c}_{small}$ and $\mathbf{c}_{large}$



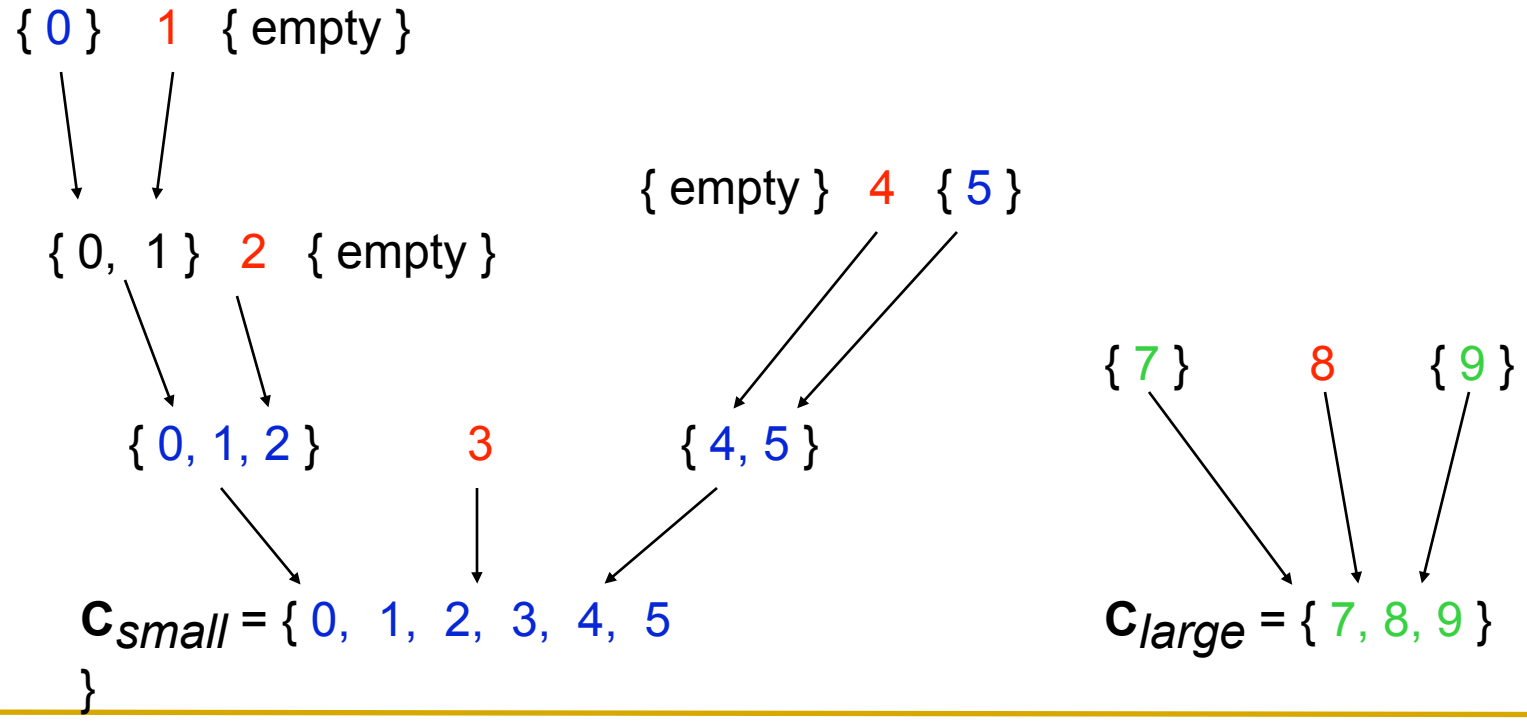
Example of QuickSort (cont'd)

Step 3: Recursively do the same thing to $\mathbf{c}_{small}$ and $\mathbf{c}_{large}$ until each subarray has only one element or is empty.



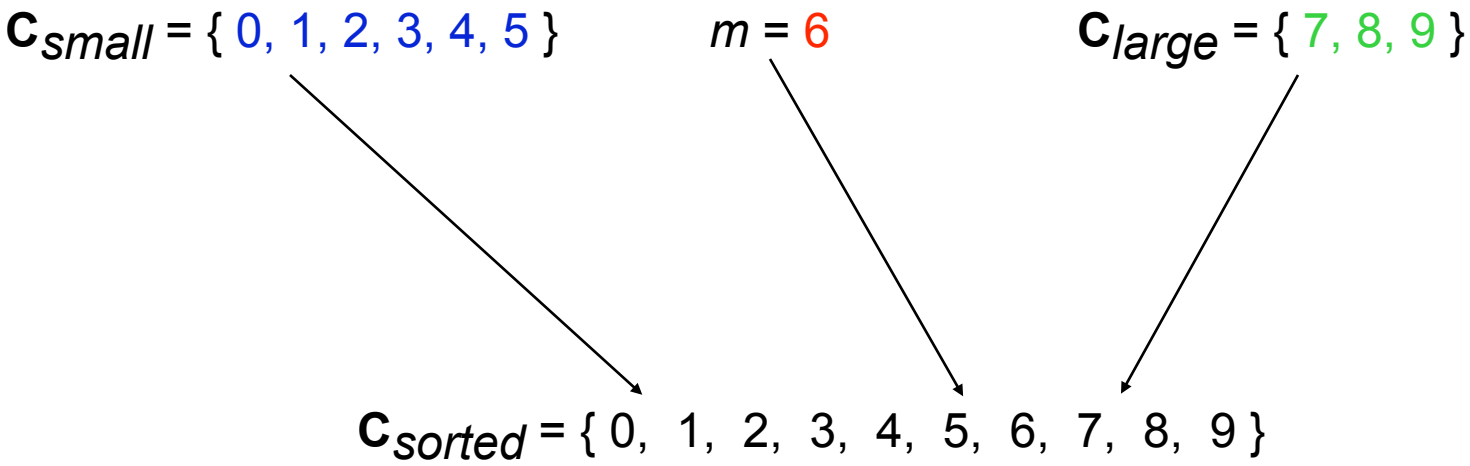
Example of QuickSort (cont'd)

Step 4: Combine the two arrays with *m* working back out of the recursion and as we build together the sorted array.



Example of QuickSort (cont'd)

Finally we can assemble $\mathbf{c}_{small}$ and $\mathbf{c}_{large}$ with our original choice of m, creating the sorted array.



The QuickSort Algorithm

1. QuickSort(c)
2. if c consists of a single element
3. return c
4. *m* ß c_1
5. Determine the set of elements c_{small} smaller than *m*
6. Determine the set of elements c_{large} larger than *m*
7. QuickSort(c_{small})
8. QuickSort(c_{large})
9. Combine c_{small}, *m*, and c_{large} into a single array, c_{sorted}
10. return c_{sorted}

QuickSort Analysis: Optimistic Outlook

- Runtime is based on our selection of *m*:

  -A good selection will split **c** evenly such that $|\mathbf{c}_{small}| = |\mathbf{c}_{large}|$, then the runtime is O(*n* log *n*).

  -For a good selection, the recurrence relation is:

$$T(n) = 2T(n/2) + const \cdot n$$

The time it takes to sort two smaller arrays of size *n*/2

Time it takes to split the array into 2 parts where *const* is a positive constant

QuickSort Analysis: Pessimistic Outlook

However, a poor selection will split **c** unevenly and in the worst case, all elements will be greater or less than *m* so that one subarray is full and the other is empty. In this case, the runtime is $O(n^2)$.

For a poor selection, the recurrence relation is:

$$T(n) = T(n-1) + const \cdot n$$

The time it takes to sort one array containing *n*-1 elements

Time it takes to split the array into 2 parts where *const* is a positive constant

QuickSort Analysis (cont'd)

- QuickSort seems like an ineffecient MergeSort
- To improve QuickSort, we need to choose *m* to be a good 'splitter.'
- It can be proven that to achieve O(*n*log*n*) running time, we don't need a perfect split, just reasonably good one. In fact, if both subarrays are at least of size *n/4*, then running time will be O(*n* log *n*).
- This implies that half of the choices of *m* make good splitters.

A Randomized Approach

- To improve QuickSort, ***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.

The RandomizedQuickSort Algorithm

1. RandomizedQuickSort(c)
2. if c consists of a single element
3. return c
4. Choose element *m* uniformly at random from c
5. Determine the set of elements c_{small} smaller than *m*
6. Determine the set of elements c_{large} larger than *m*
7. RandomizedQuickSort(c_{small})
8. RandomizedQuickSort(c_{large})
9. Combine c_{small}, *m*, and c_{large} into a single array, c_{sorted}
10. return c_{sorted}

**Lines Highlighted in red indicate the differences between QuickSort and and RandomizedQuickSort*

RandomizedQuickSort Analysis

- Worst case runtime: $O(m^2)$
- ***Expected runtime***: $O(m \log m)$.
- Expected runtime is a good measure of the performance of randomized algorithms, often more informative than worst case runtimes.
- RandomizedQuickSort will always return the correct answer, which offers a way to classify Randomized Algorithms.

Two Types of Randomized Algorithms

- **Las Vegas Algorithms** – always produce the correct solution (ie. RandomizedQuickSort)
- **Monte Carlo Algorithms** – do not always return the correct solution.
- Las Vegas Algorithms are always preferred, but they are often hard 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.

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 have converged to the hidden motif.

Profiles Revisited

- Let **s**=(s_1,...,s_t) be the set of starting positions for *l*-mers in our *t* sequences.
- The substrings corresponding to these starting positions will form:
  - *t* x *l* ***alignment matrix*** and
  - 4 x *l* ***profile matrix**** **P**.

*We make a special note that the profile matrix will be defined in terms of the frequency of letters, and not as the count of letters.

Scoring Strings with a Profile

- *Prob*(**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 *Prob*(**a**|**P**) will be high
- If **a** is very different, then *Prob*(**a**|**P**) will be low.

$$Prob(\mathbf{a}|\mathbf{P}) = \prod_{i=1}^{n} p_{a_i, i}$$

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 (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 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

ggtctaccttttatcct

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 descreased

Greedy Profile Motif Search

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

3) Select random starting positions.
4) Create a profile **P** from the substrings at these starting positions.
5) Find the **P**-most probable *l*-mer **a** in each sequence and change the starting position to the starting position of **a**.
6) 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=(s1,…,st) from DNA
3.   bestScore ß 0
4.   while Score(s, DNA) > bestScore
5.         Form profile P from s
6.     bestScore ß Score(s, DNA)
7.     for   i ß 1  to  t
8.           Find a P-most probable l-mer a from the i^th sequence
9.           si ß 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, ***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

s_1=7	GTAAACAATATTTATAGC
s_3=9	CCGTACTGTCAAGCGTGG
s_4=4	TGAGTAAACGACGTCCCA
s_5=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*(***a***|***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*(***a***|***P***), and randomly select a new starting position based on this distribution.

a) To create this distribution, divide each probability *prob*(***a***|***P***) by the lowest probability:

Starting Position 1: *prob(* AAAATTTA | P) = .000732 / .000122 = 6

Starting Position 2: *prob(* AAATTTAC | P) = .000122 / .000122 = 1

Starting Position 8: *prob(* ACCTTAGA | P) = .000183 / .000122 = 1.5

Ratio = 6 : 1 : 1.5

Turning Ratios into Probabilities

b) Define probabilities of starting positions according to computed ratios

Probability (Selecting Starting Position 1): 6/(6+1+1.5)= 0.706

Probability (Selecting Starting Position 2): 1/(6+1+1.5)= 0.118

Probability (Selecting Starting Position 8): 1.5/(6+1+1.5)=0.176

Gibbs Sampling: an Example

c) Select the start position according to computed ratios:

P(selecting starting position 1): .706

P(selecting starting position 2): .118

P(selecting starting position 8): .176

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

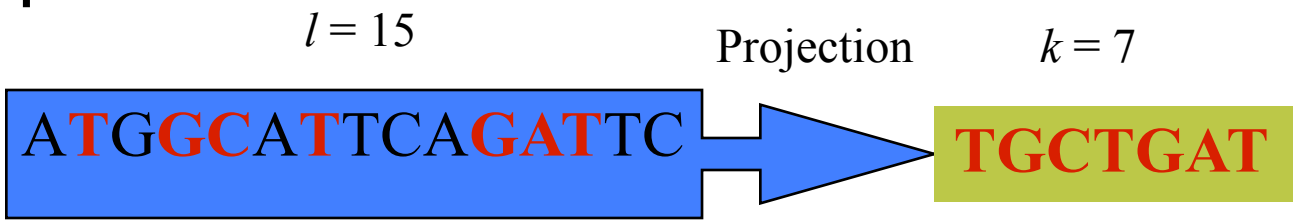
- Gibbs sampling needs to be modified when applied to samples with unequal distributions of nucleotides (*relative entropy* approach*).*
- Gibbs sampling often converges to locally optimal motifs rather than globally optimal motifs.
- Needs to be run with many randomly chosen seeds to achieve good results.

Another Randomized Approach

- **Random Projection Algorithm** is a different way to solve the Motif Finding Problem.
- **Guiding principle:** Some instances of a motif agree on 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

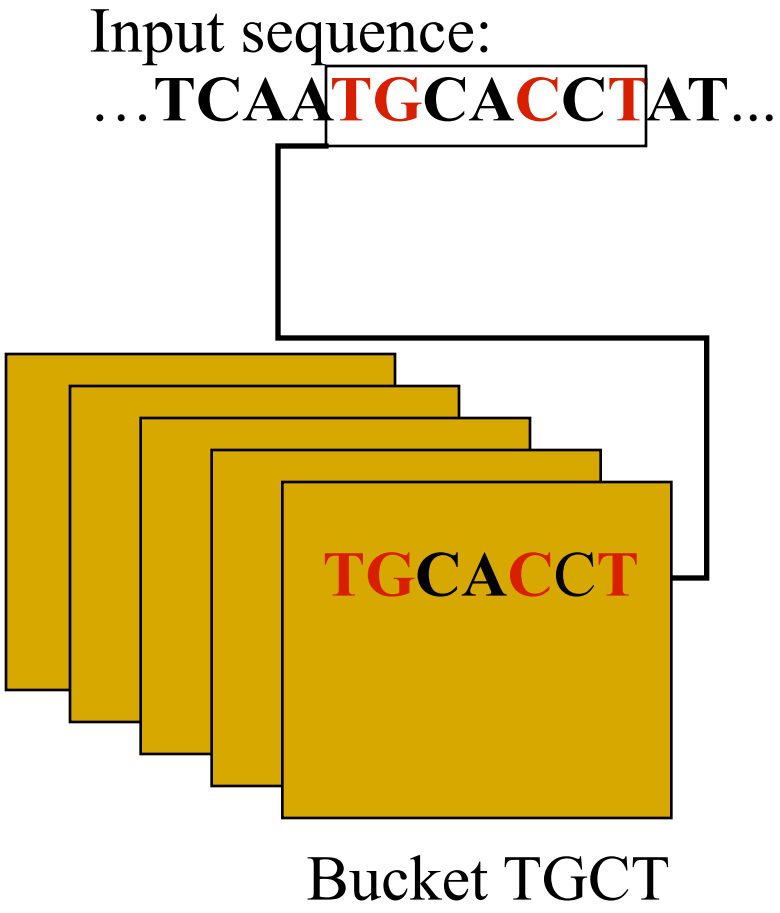
- Choose *k* positions in string of length *l*.
- Concatenate nucleotides at chosen *k* positions to form *k*-tuple.
- This can be viewed as a projection of *l*-dimensional space onto *k*-dimensional subspace.



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

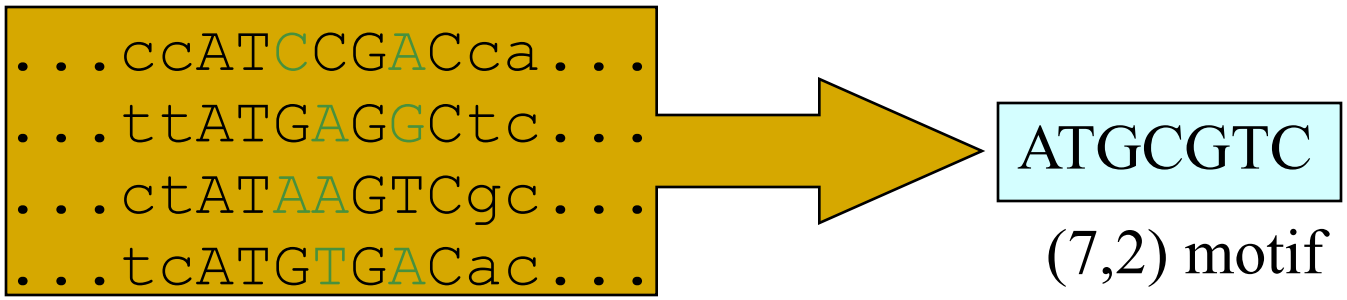
Random Projections Algorithm

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



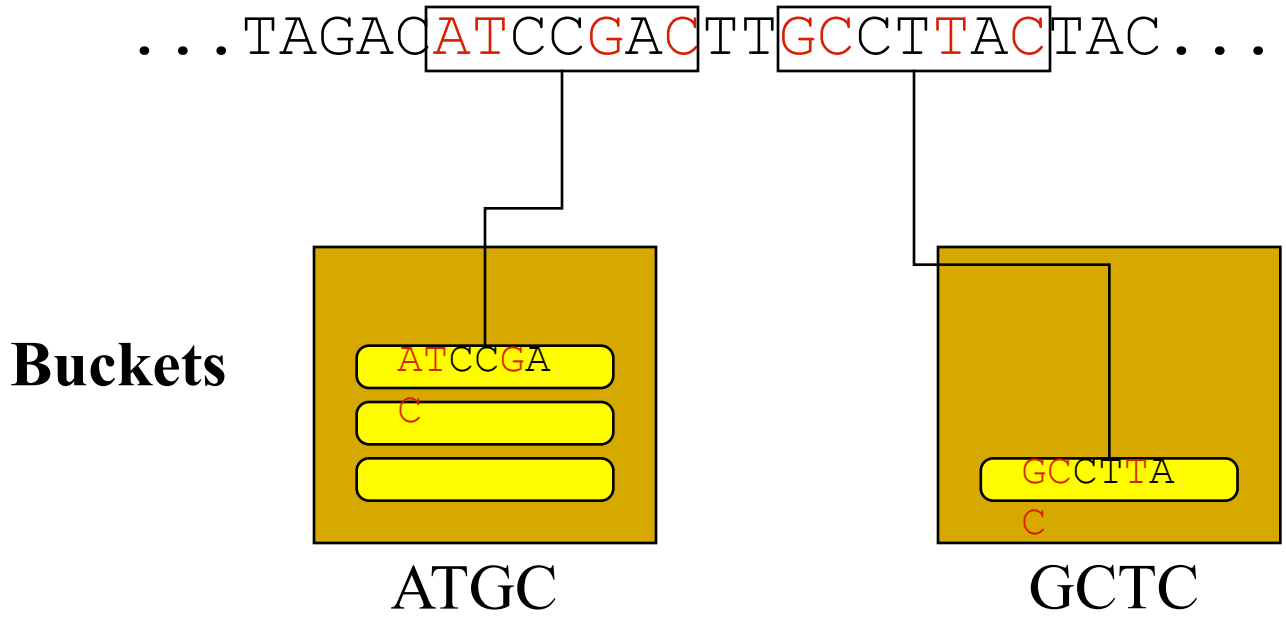
Random Projections Algorithm (cont'd)

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



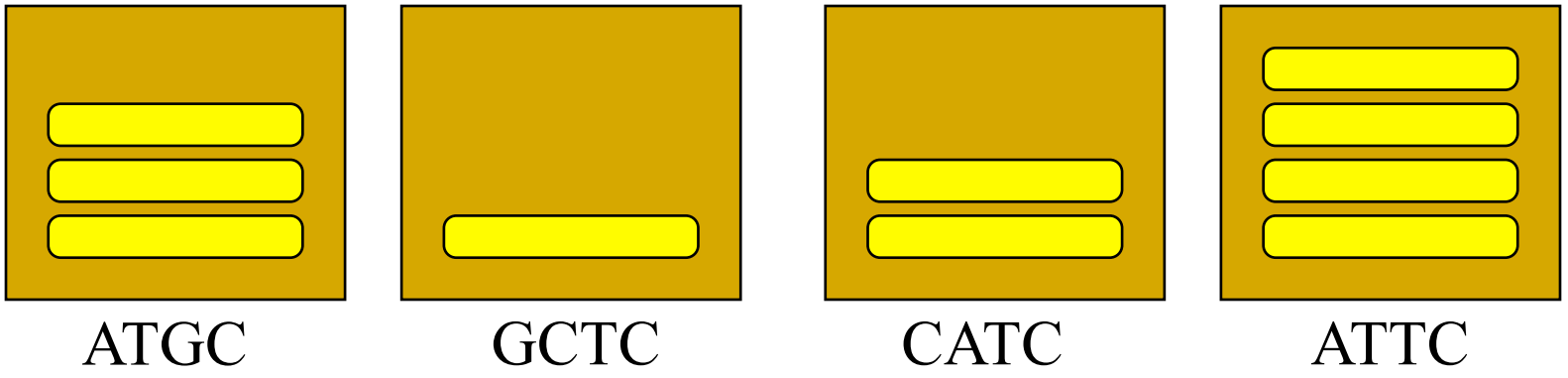
Example

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



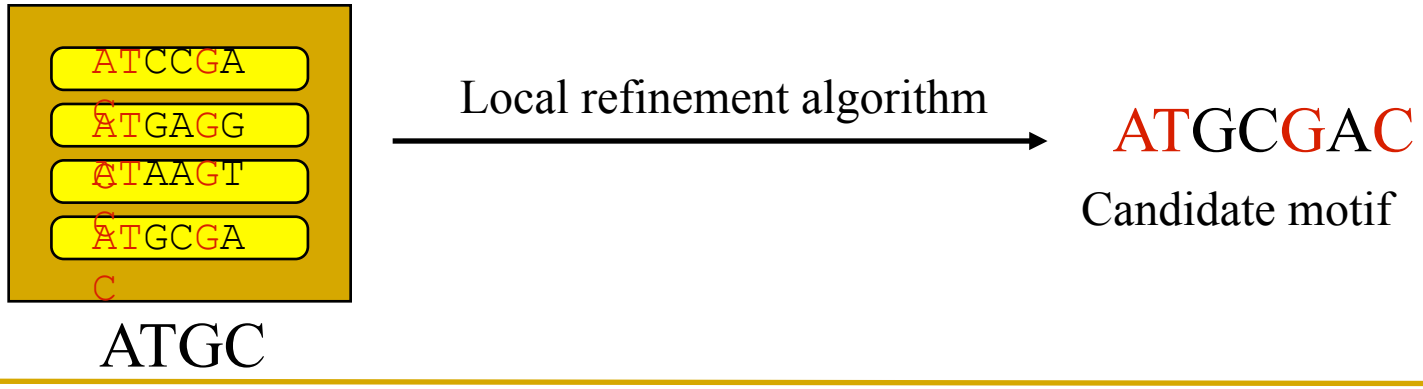
Hashing and Buckets

- 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.*



Motif Refinement

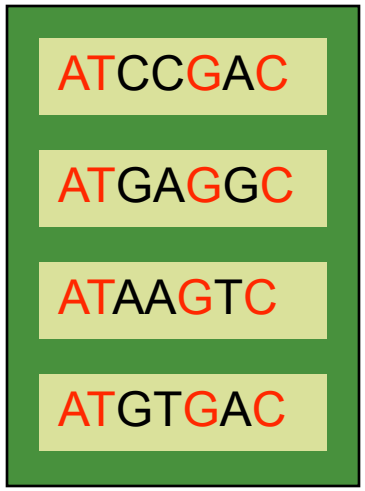
- How do we recover the motif from the sequences in the enriched buckets?
- *k* nucleotides are from hash value of bucket.
- Use information in other *l*-*k* positions as starting point for local refinement scheme, e.g. Gibbs sampler.



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



ATGC

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

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.

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

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

How Many Iterations?

- *Planted bucket* : bucket with hash value $h(\boldsymbol{M})$, where $\boldsymbol{M}$ is the motif.
- Choose m = number of iterations, such that

Pr(planted bucket contains at least s sequences in at least one of m iterations) =0.95

- Probability is readily computable since iterations form a sequence of independent Bernoulli trials

Expectation Maximization (EM)

- $S = \{ x(1),\ldots x(t)\}$: set of input sequences
- Given: A probabilistic motif model W(Q) depending on unknown parameters Q, and a background probability distribution P.
- Find value Q_{max} that maximizes likelihood ratio:

$$\frac{\Pr(S \mid W(Q_{max}), P)}{\Pr(S \mid P)}$$

- EM is local optimization scheme. Requires starting value Q_0.

EM Motif Refinement (cont'd)

- For each input sequence, x(*i*), return *l*-tuple *y* (*i*) which maximizes likelihood ratio:

$$\frac{\Pr(\, y(i) \mid \mathbf{W}(Q_{h}^{*}))}{\Pr(\, y(i) \mid P)}$$

-T = { *y*(1), *y*(2),…,*y*(*t*) }

-C(T) = consensus string