Randomized Algorithms and Motif Finding

Outline

1. Randomized QuickSort
2. Randomized Algorithms
3. Greedy Profile Motif Search
4. Gibbs Sampler
5. Random Projections

Section 1: Randomized QuickSort

Randomized Algorithms

- **Randomized Algorithm**: Makes 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.
  1. Select an element m from unsorted array $\mathbf{c}$ and divide the array into two subarrays:

     $\mathbf{c}_{small}$ = elements smaller than m

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

QuickSort: Example

- Given an array: $\boldsymbol{c} = \{ 6, 3, 2, 8, 4, 5, 1, 7, 0, 9\}$

- **Step 1:** Choose the first element as *m*

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

QuickSort: Example

- Given an array: $\boldsymbol{c}$ = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9}
- **Step 2:** Split the array into $\boldsymbol{c}_{\text{small}}$ and $\boldsymbol{c}_{\text{large}}$ based on m.

$\boldsymbol{c}_{\text{small}} = \{ \}$

$\boldsymbol{c}_{\text{large}} = \{ \}$

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

QuickSort: Example

- Given an array: $\boldsymbol{c}$ = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9}
- **Step 2:** Split the array into $\boldsymbol{c}_{\text{small}}$ and $\boldsymbol{c}_{\text{large}}$ based on m.

$\boldsymbol{c}_{\text{small}}$ = { 3 }

$\boldsymbol{c}_{\text{large}}$ = { }

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

QuickSort: Example

- Given an array: $\boldsymbol{c}$ = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9}
- **Step 2:** Split the array into $\boldsymbol{c}_{\text{small}}$ and $\boldsymbol{c}_{\text{large}}$ based on *m*.

$\boldsymbol{c}_{\text{small}}$ = { 3, 2 }

$\boldsymbol{c}_{\text{large}}$ = { }

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

QuickSort: Example

- Given an array: $\boldsymbol{c} = \{ 6, 3, 2, 8, 4, 5, 1, 7, 0, 9\}$

- **Step 2:** Split the array into $\boldsymbol{c}_{\text{small}}$ and $\boldsymbol{c}_{\text{large}}$ based on m.

$\boldsymbol{c}_{\text{small}} = \{ 3, 2 \}$

$\boldsymbol{c}_{\text{large}} = \{ 8 \}$

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

QuickSort: Example

- Given an array: $\boldsymbol{c}$ = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9}
- **Step 2:** Split the array into $\boldsymbol{c}_{\text{small}}$ and $\boldsymbol{c}_{\text{large}}$ based on m.

$\boldsymbol{c}_{\text{small}}$ = { 3, 2, 4 }

$\boldsymbol{c}_{\text{large}}$ = { 8 }

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

QuickSort: Example

- Given an array: $\boldsymbol{c}$ = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9}
- **Step 2:** Split the array into $\boldsymbol{c}_{\text{small}}$ and $\boldsymbol{c}_{\text{large}}$ based on m.

$\boldsymbol{c}_{\text{small}}$ = { 3, 2, 4, 5 } $\boldsymbol{c}_{\text{large}}$ = { 8 }

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

QuickSort: Example

- Given an array: $\boldsymbol{c}$ = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9}

- **Step 2:** Split the array into $\boldsymbol{c}_{\text{small}}$ and $\boldsymbol{c}_{\text{large}}$ based on m.

$\boldsymbol{c}_{\text{small}}$ = { 3, 2, 4, 5, 1 }

$\boldsymbol{c}_{\text{large}}$ = { 8 }

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

QuickSort: Example

- Given an array: $\boldsymbol{c}$ = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9}
- **Step 2:** Split the array into $\boldsymbol{c}_{\text{small}}$ and $\boldsymbol{c}_{\text{large}}$ based on m.

$\boldsymbol{c}_{\text{small}}$ = { 3, 2, 4, 5, 1 }

$\boldsymbol{c}_{\text{large}}$ = { 8, 7 }

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

QuickSort: Example

- Given an array: $\boldsymbol{c}$ = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9}

- **Step 2:** Split the array into $\boldsymbol{c}_{\text{small}}$ and $\boldsymbol{c}_{\text{large}}$ based on *m*.

$\boldsymbol{c}_{\text{small}}$ = { 3, 2, 4, 5, 1, 0 }

$\boldsymbol{c}_{\text{large}}$ = { 8, 7 }

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

QuickSort: Example

- Given an array: $\boldsymbol{c}$ = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9}
- **Step 2:** Split the array into $\boldsymbol{c}_{\text{small}}$ and $\boldsymbol{c}_{\text{large}}$ based on m.

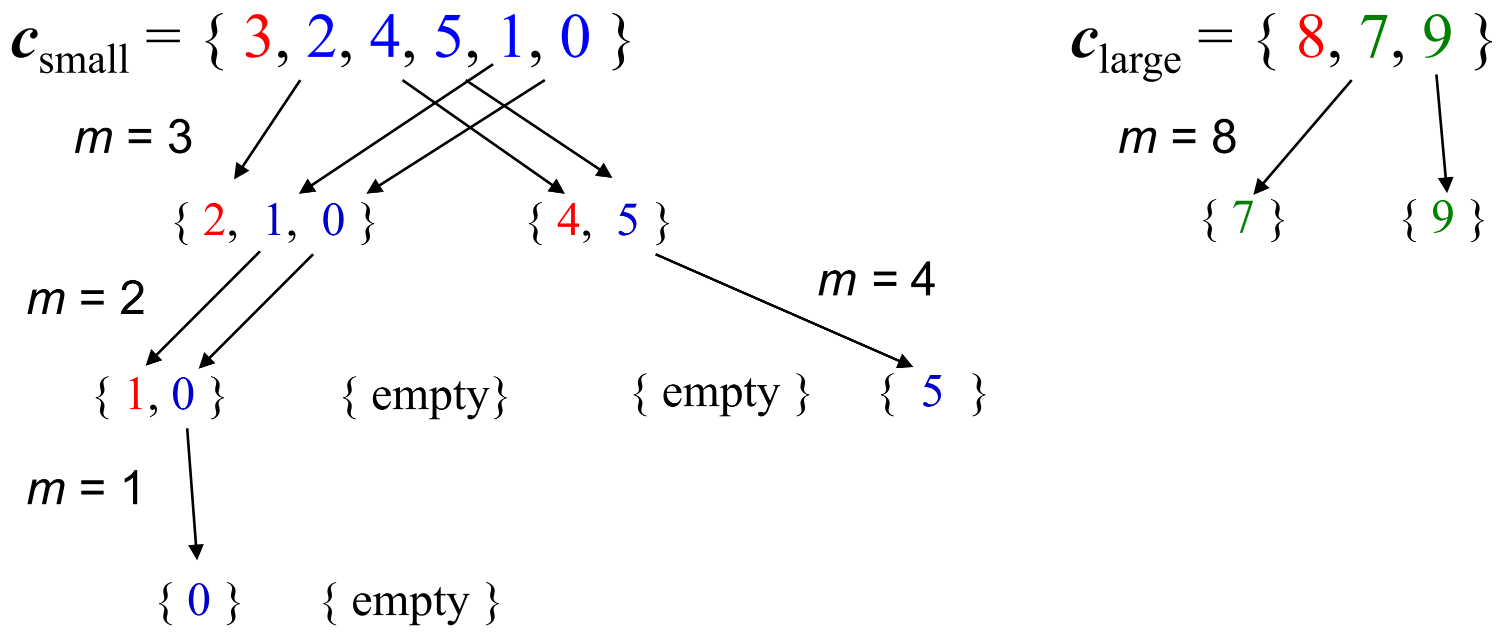
$\boldsymbol{c}_{\text{small}}$ = { 3, 2, 4, 5, 1, 0 }

$\boldsymbol{c}_{\text{large}}$ = { 8, 7, 9 }

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

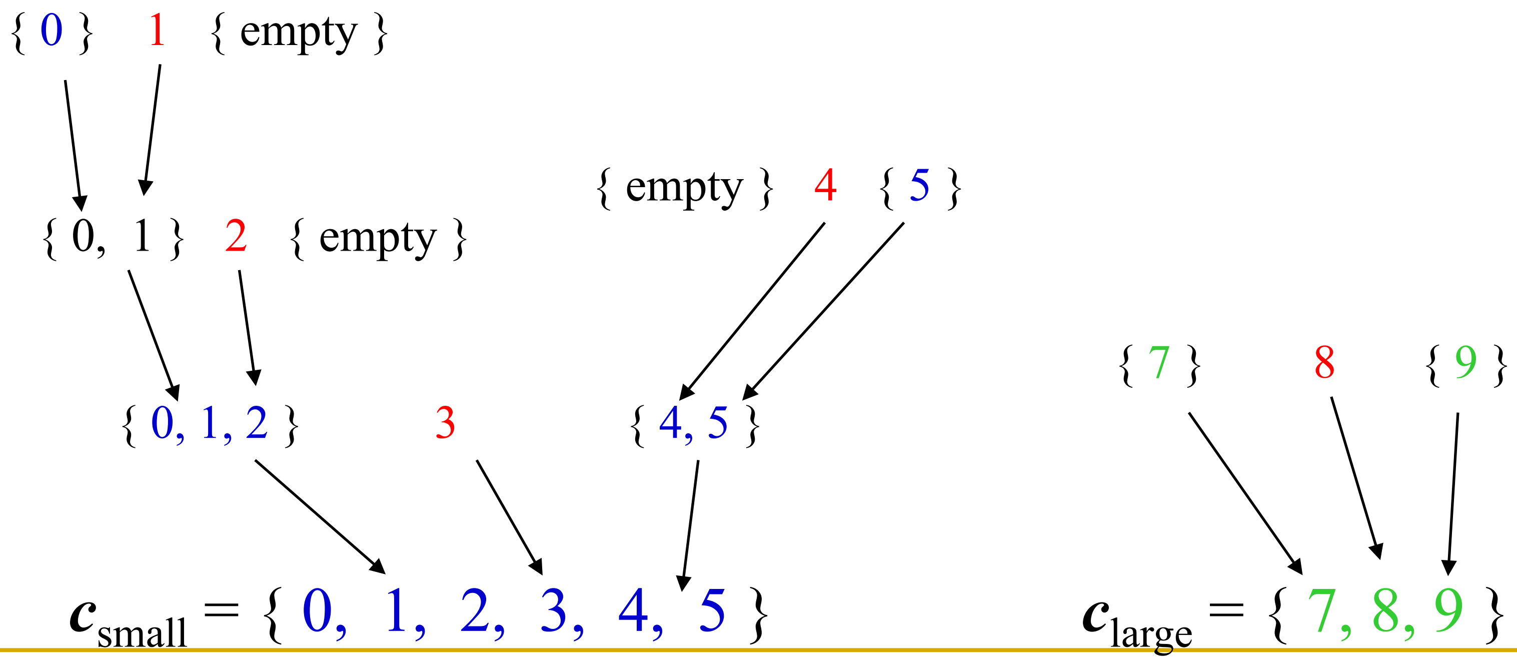
QuickSort: Example

- Given an array: $\boldsymbol{c}$ = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9}
- **Step 3:** Recursively do the same thing to c_{small} and $\mathbf{c}_{large}$ until each subarray has only one element or is empty.



QuickSort: Example

- Given an array: $\boldsymbol{c}$ = { 6, 3, 2, 8, 4, 5, 1, 7, 0, 9}
- **Step 4:** Combine the two arrays with *m* working back out of the recursion as we build together the sorted array.



QuickSort: Example

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

$$\begin{tikzcd}
\boldsymbol{c}_{\text{small}} = \{\, 0, 1, 2, 3, 4, 5 \,\} \arrow[dr] & m = 6 \arrow[d] & \boldsymbol{c}_{\text{large}} = \{\, 7, 8, 9 \,\} \arrow[dl] \\
 & \boldsymbol{c}_{\text{sorted}} = \{\, 0,\ 1,\ 2,\ 3,\ 4,\ 5,\ 6,\ 7,\ 8,\ 9 \,\} &
\end{tikzcd}$$

The QuickSort Algorithm

```
1.  QuickSort($c$)
2.  if $c$ consists of a single element
3.      return $c$
4.  $m \leftarrow c_1$
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 so that $|\mathbf{c}_{small}| = |\mathbf{c}_{large}|$.
  - For a sequence of good selections, the recurrence relation is:

$$T(n) = \underbrace{2T\left(\frac{n}{2}\right)}_{\text{The time it takes to sort two smaller arrays of size } n/2} + \underbrace{\text{constant} \cdot n}_{\text{Time it takes to split the array into 2 parts}}$$

  - In this case, the solution of the recurrence gives a runtime of O(n log n).

QuickSort Analysis: Pessimistic Outlook

- However, a poor selection of m will split $\boldsymbol{c}$ 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.

- For a sequence of poor selection, the recurrence relation is:

$$T(n) = \underbrace{T(n-1)}_{\text{The time it takes to sort one array containing } n\text{-1 elements}} + \underbrace{\text{constant} \cdot n}_{\text{Time it takes to split the array into 2 parts where const is a positive constant}}$$

- In this case, the solution of the recurrence gives runtime O(n^2).

QuickSort Analysis

- 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 a reasonably good one. In fact, if both subarrays are at least of size *n*/4, then the running time will be O(*n* log *n*).
- This implies that half of the choices of *m* make good splitters.

Section 2: Randomized Algorithms

A Randomized Approach to QuickSort

- To improve QuickSort, *randomly* select *m*.
- Since half of the elements will be good splitters, if we choose *m* at random we will have 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 in red indicate the differences between QuickSort 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; it is often more informative than worst case runtimes.
- RandomizedQuickSort will always return the correct answer, which offers us a way to classify Randomized Algorithms.

Two Types of Randomized Algorithms

1. **Las Vegas Algorithm**: Always produces the correct solution (ie. RandomizedQuickSort)

2. **Monte Carlo Algorithm**: Does not always return the correct solution.

- Good Las Vegas Algorithms are always preferred, but they are often hard to come by.

Section 3: Greedy Profile Motif Search

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 an Exhaustive Search 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 $\mathbf{s}=(s_1,\ldots,s_t)$ 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*
  - 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

- Pr(***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 Pr(***a*** | ***P***) will be high.
- If ***a*** is very different, then Pr(***a*** | ***P***) will be low.
- Formula for Pr(***a*** | ***P***):

$$\Pr\left(a \mid P\right) = \prod_{i=1}^{n} P_{a_i\,,\,i}$$

Scoring Strings with a Profile

- 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:
  - Pr(**AAACCT** | ***P***) = ???

Scoring Strings with a Profile

- 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:
  - Pr(**AAACCT** | ***P***) = 1/2 x 7/8 x 3/8 x 5/8 x 3/8 x 7/8 = 0.033646

Scoring Strings with a Profile

- 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:
  - Pr(**AAACCT** | ***P***) = 1/2 x 7/8 x 3/8 x 5/8 x 3/8 x 7/8 = 0.033646
- The probability of a different string:
  - Pr(**ATACAG** | ***P***) = 1/2 x 1/8 x 3/8 x 5/8 x 1/8 x 1/8 = 0.001602

P-Most Probable *l*-mer

- Define the ***P***-most probable *l*-mer from a sequence as the *l*-mer contained in that sequence which has the highest probability of being generated by 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

- **Example**: Given a sequence = CTATAAACCTTACATC, find the P-most probable *l*-mer.

P-Most Probable *l*-mer

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

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

- First Try: **C T A T A A A C C 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 6-mer.

P-Most Probable *l*-mer

- Compute Pr(***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

- The *P*-Most Probable 6-mer in the sequence is thus 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

Dealing with Zeroes

- In our toy example Pr(***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 Pr(***a*** | ***P***) = 0, there exist techniques to equate zero to a very small number so that having one zero in the profile matrix 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

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

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

Comparing New and Old Profiles

- Red = frequency increased, Blue – frequency decreased

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

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 actually unlikely that the random starting positions will lead us to the correct solution at all.

- Therefore this is a *Monte Carlo* algorithm.

- In practice, this algorithm is run many times with the hope that random starting positions will be close to the optimal solution simply by chance.

Section 4: Gibbs Sampler

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.

Gibbs Sampling Algorithm

1. Randomly choose starting positions **s** = ($s_1,\dots,s_t$) 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: Example

- **Input**: $t = 5$ sequences, motif length $l = 8$
  1. GTAAACAATATTTATAGC
  2. AAAATTTACCTCGCAAGG
  3. CCGTACTGTCAAGCGTGG
  4. TGAGTAAACGACGTCCCA
  5. TACTTAACACCCTGTCAA

Gibbs Sampling: Example

1. Randomly choose starting positions, $\mathbf{s} = (s_1, s_2, s_3, s_4, s_5)$ 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: Example

2. Choose one of the sequences at random

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

Gibbs Sampling: Example

2. Choose one of the sequences at random: **Sequence 2**

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

Gibbs Sampling: 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: Example

4. Calculate Pr(***a*** | ***P***) for every possible 8-mer in the removed sequence:

Strings Highlighted in Red	Pr(***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: Example

5. Create a distribution of probabilities of *l*-mers Pr(***a*** | ***P***), and randomly select a new starting position based on this distribution.
   - To create this distribution, divide each probability Pr(***a*** | ***P***) by the lowest probability:

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

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

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

- Ratio = 6 : 1 : 1.5

Turning Ratios into Probabilities

- Define probabilities of starting positions according to the computed ratios.

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

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

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

- Select the start position probabilistically based on these ratios.

Gibbs Sampling: 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: Example

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

Gibbs Sampling 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.

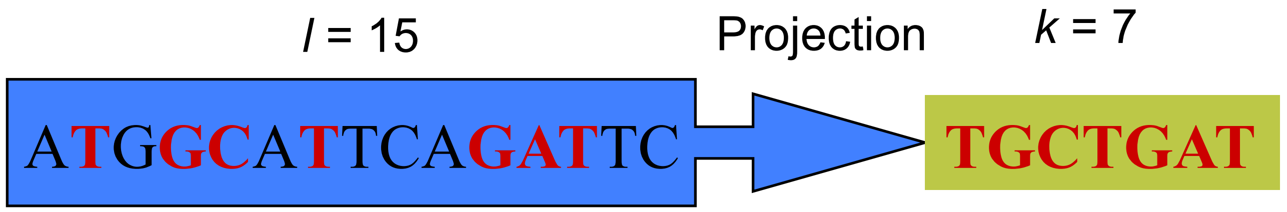
Section 5: Random Projections

Another Randomized Approach

- The **Random Projection Algorithm** is an alternative 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 patter,n creating a **projection** of the pattern.
- We then search for the projection in a hope that the selected positions are not affected by mutations in most instances of the motif.

Projections: Formation

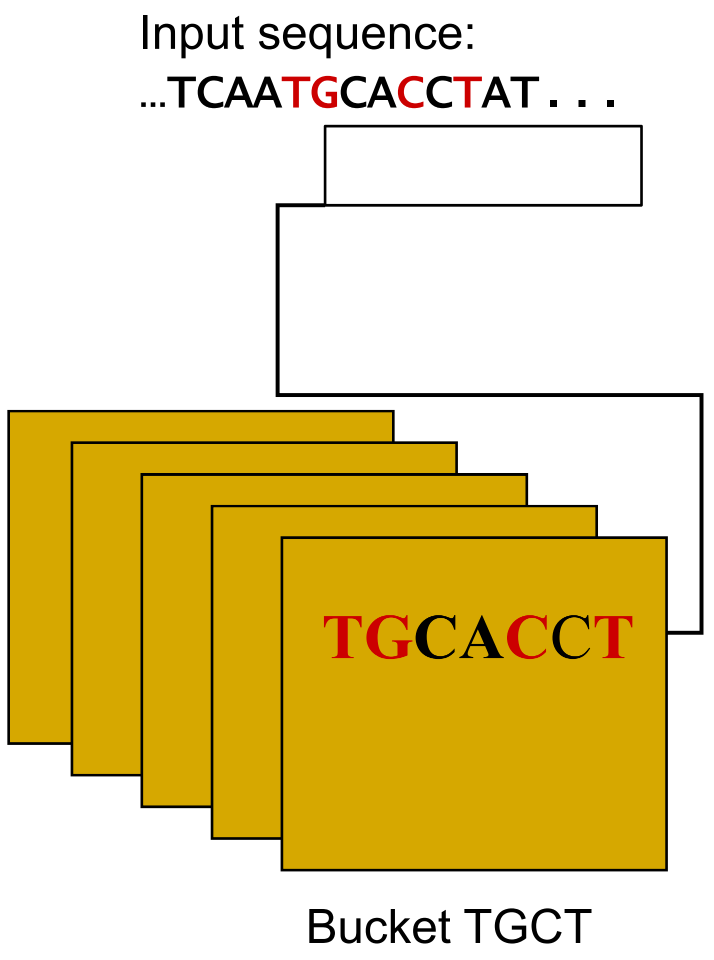
- Choose k positions in a string of length l.
- Concatenate nucleotides at the chosen k positions to form a k-tuple.
- This can be viewed as a projection of l-dimensional space onto k-dimensional subspace.



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

Random Projections Algorithm

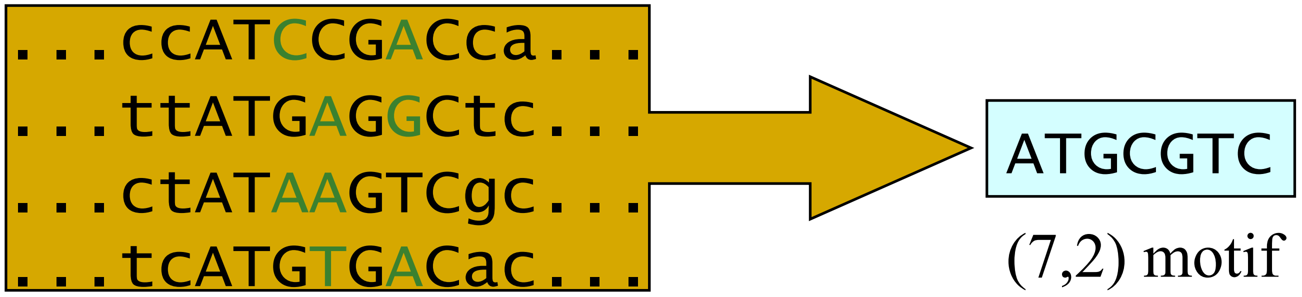
- Select *k* out of *l* positions uniformly at random.
- For each *l*-tuple in input sequences, hash into bucket based on letters at *k* selected positions.
- Recover motif from *enriched* bucket that contains many *l*-tuples.



Random Projections Algorithm

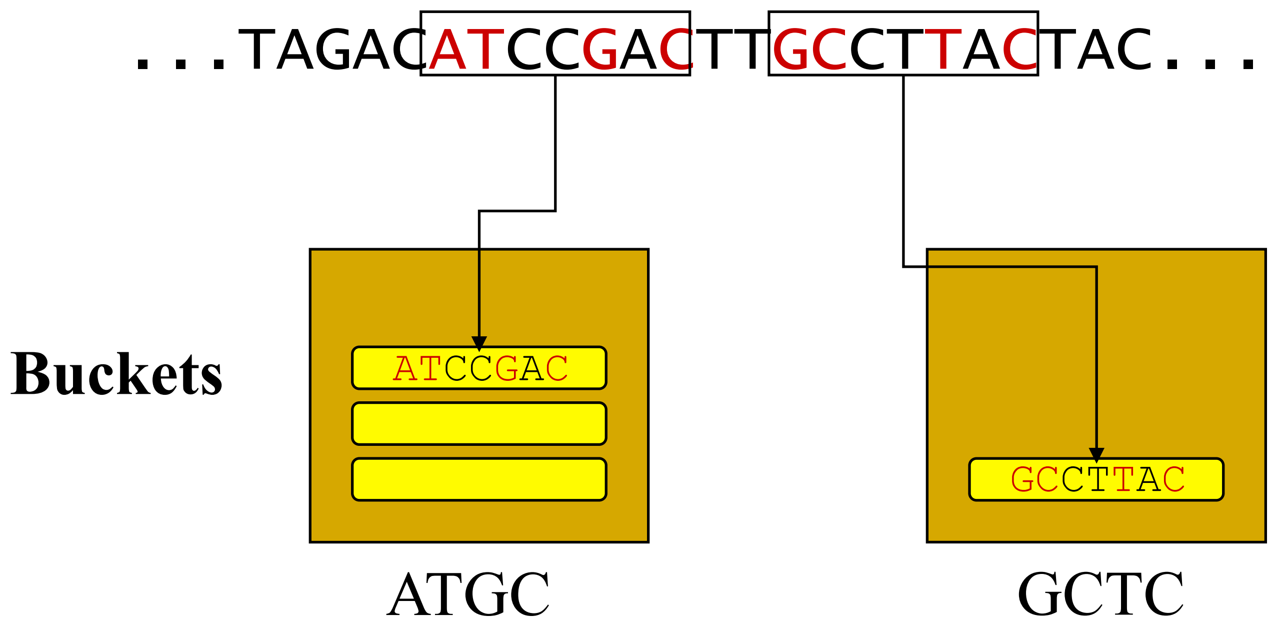
- Some projections will fail to detect motifs but if we try many of them the probability that one of the buckets fills in is increasing.

- In the example below, the bucket **GC*AC is "bad" while the bucket AT**G*C is "good"



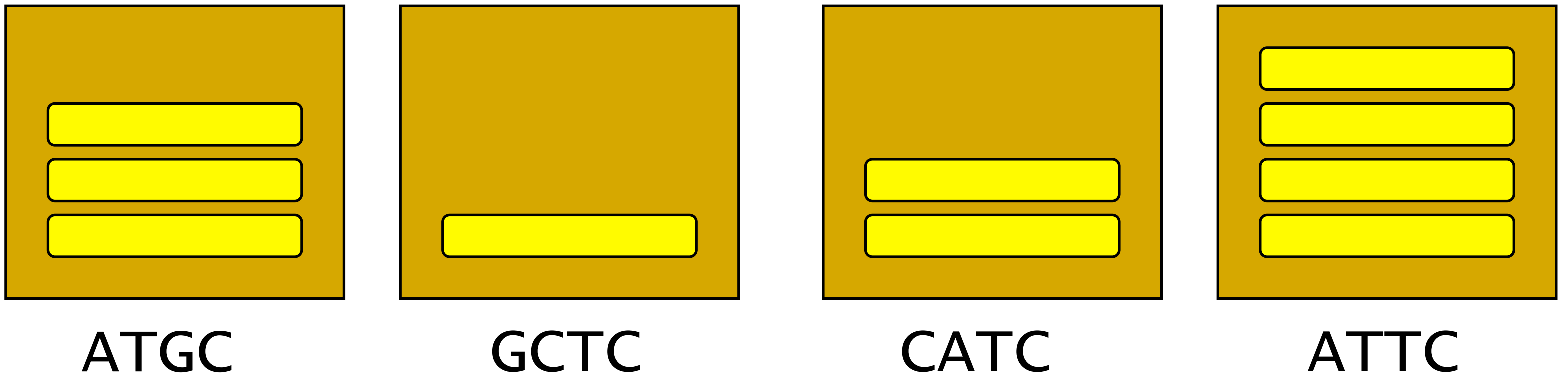
Random Projections Algorithm: Example

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



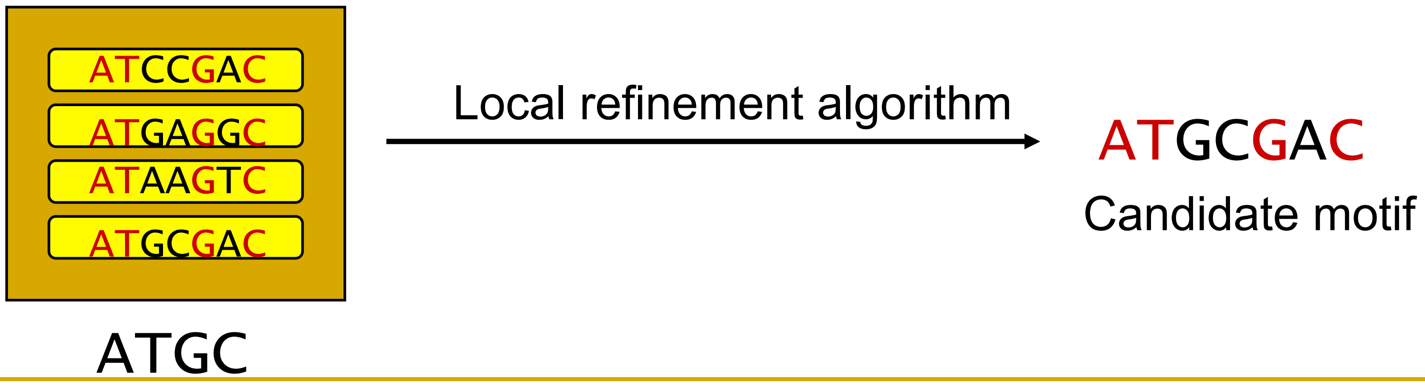
Hashing and Buckets

- Hash function $h(x)$ is obtained from k positions of projection.
- Buckets are labeled by values of $h(x)$.
- **Enriched Buckets**: Contain more than s l-tuples, for some decided upon 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.



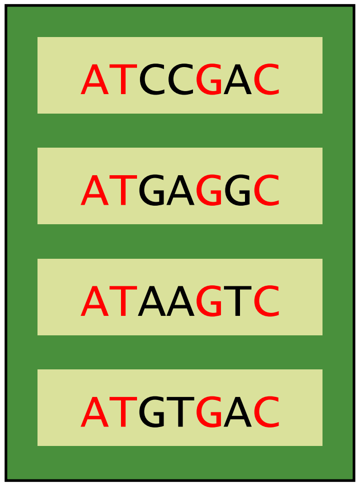
Synergy Between Random Projection and Gibbs

- 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 a good local search in vicinity of every starting point.

- These algorithms work particularly well for “good” starting points.

Building Profiles from Buckets



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

- 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
- This 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(✈) depending on unknown parameters ✈, and a background probability distribution P.

- Find value ✈ $_{\max}$ that maximizes the likelihood ratio:

$$\frac{\Pr\left(S \mid W(\Theta_{\max}), P\right)}{\Pr\left(S \mid P\right)}$$

- EM is local optimization scheme. Requires starting value ✈$_0$.

EM Motif Refinement

- For each input sequence x(i), return l-tuple $y(i)$ which maximizes likelihood ratio:
  - T = { $y(1), y(2),\ldots,y(t)$ }
  - C(T) = consensus string

$$\frac{\Pr\left(y(i) \mid W\left(\Theta_h^*\right)\right)}{\Pr\left(y(i) \mid P\right)}$$