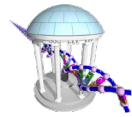


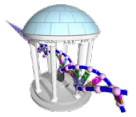
Comp 555 - BioAlgorithms - Spring 2021



- Recall from last time that the Brute Force approach for finding a common 10-mer motif common to 10 sequences of length 80 bases was going to take up roughly 30,000 years
- Today we'll consider alternative and non-obvious approaches for solving this problem
- We will trade one old man (us) for another (an Oracle)

THERE WILL BE A PYTHON/JUPYTER CRASH COURSE NEXT TUESDAY NIGHT, JAN 28, FROM 5:00PM-6:30PM.

Finding TFBS Motifs in our Lifetime



Recall from last lecture

The following set of 10 sequences have an embedded noisy motif, *TAGATCCGAA*.

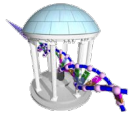
```
1 tagtggctcttttgagtgTAGATCTGAAgggaaagtatttccaccagttcggggtcacccagcagggcagggtgacttaat
2 cgcgactcggcgctcacagttatcgcacgtttagacaaaacggagtTGGATCCGAAactggagtttaatcggagtcctt
3 gttacttgtgagcctgggTAGACCCGAAatataattggttgctgcatagcggagctgacatacagagtaggggaaatgctg
4 aacatcaggcctttgattaacaatttaagcacgTAAATCCGAAttgacctgatgacaatacggaacatgccggctccggg
5 accaccggataggctgcttatTAGGTCCAAAaggtagtatcgtaataatggctcagccatgtcaatgtgcggcattccac
6 TAGATTCGAAtcgatcgtgtttctccctctgtgggttaacgaggggtccgaccttgctcgcgatgtgccgaacttgtacc
7 gaaatggttcgggtgcgatatcaggccgttctcttaacttggcgggtCAGATCCGAAcgtctctggaggggtcgtgcgta
8 atgtatactagacattctaacgctcgttattggcggagaccatttgtccactacaagaggctactgtgTAGATCCGTA
9 ttcttacacccttcttTAGATCCAAAcctgttggcgccatcttcttttcgagtccttgtacctccatttgcctgatgac
10 ctacctatgtaaaacaacatctactaacgtagtccggctcttctctgatctgccctaacctacaggTCGATCCGAAattcg
```

```
TAGATCTGAA
TGGATCCGAA
TAGACCCGAA
TAAATCCGAA
TAGGTCCAAA
TAGATTCGAA
CAGATCCGAA
TAGATCCGTA
TAGATCCAAA
TCGATCCGAA
```

9+9+9+9+9
+8+9+9+8+10 = 89

Some notes:

1. There are no exact matches
2. The consensus motif gives a good score



Consensus Scoring Function

- We developed an $O(k)$ consensus scoring function to address noise (inexact matches)
- But, we need to apply it an exponential number, $O(N^M)$ of times!
- Here's the scoring function...

```
In [8]: ▶ def Score(s, DNA, k):
        """
        compute the consensus SCORE of a given k-mer
        alignment given offsets into each DNA string.
        s = list of starting indices, 1-based, 0 means ignore
        DNA = list of nucleotide strings
        k = Target Motif length
        """
        score = 0
        for i in range(k):
            # loop over string positions
            cnt = dict(zip("acgt", (0,0,0,0)))
            for j, sval in enumerate(s):
                # loop over DNA strands
                base = DNA[j][sval+i]
                cnt[base] += 1
            score += max(cnt.values())
        return score
```

And here's the Score we're looking for...



```
In [9]: ▶ seqApprox = [  
    'tagtggcttttgagtgtagatctgaagggaaagtatttccaccagttcggggtcaccagcagggcagggtgacttaat',  
    'cgcgactcggcgctcacagttatcgcacgtttagacaaaacggagttggatccgaaactggagtttaatcggagtcctt',  
    'gttacttgtgagcctggttagaccgaaatataaattggtggctgcatagcggagctgacatacagtaggggaaatgct',  
    'aacatcaggctttgattaacaatttaagcacgtaaatccgaattgacctgatgacaatacggaacatgccggctccggg',  
    'accaccggataggctgcttattaggtccaaaaggtagtatcgaataatggctcagccatgtcaatgtgcggcattccac',  
    'tagattcgaatcgatcgtgttttccctctgtgggttaacgaggggtccgacctgctcgcgatgtccgaacttgtacc',  
    'gaaatggttcggtgcgatatcaggccgttctcttaacttggcgggtgcagatccgaacgtctctggaggggtcgtgcgcta',  
    'atgtatactagacattctaacgctcgcttattggcggagaccatttgcctcactacaagaggctactgtgtagatccgta',  
    'ttcttacacccttcttagatccaaacctgttggcgccatctcttttcgagtccttgacctccatttgctctgatgac',  
    'ctacctatgtaaaacaacatctactaacgtagtcgggtcttctctgatctgcctaacctacaggtcgatccgaaattcg']
```

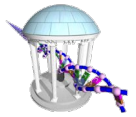
```
In [10]: ▶ print(Score([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], seqApprox, 10))
```

89

```
In [12]: ▶ %timeit Score([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], seqApprox, 10)
```

26.2 μ s \pm 437 ns per loop (mean \pm std. dev. of 7 runs, 10000 loops each)

So even at a blazing 40μ s we'll need many lifetimes to compute the 70^{10} scores



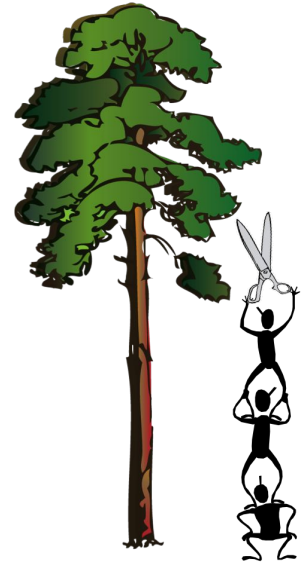
Pruning Trees

- One method for reducing the computational cost of a search algorithm is to prune the space of permutations that could not possibly lead to a better answer than the current best answer.
- Pruning decisions are based on solutions to subproblems that appear early on and offer no hope
- How does this apply to our Motif finding problem?
- Consider any permutation of offsets that begins with the indices [25, 63, 10, 43,]. Just based on the first 4 indices the largest possible score is $17 + (6 \cdot 10) = 77$, which assumes that all 6 remaining strings match perfectly at all 10 positions.

DNA[0][25:35]	a	a	g	g	g	a	a	a	g	t	
DNA[1][63:73]	g	t	t	t	a	a	t	c	g	g	
DNA[2][10:20]	a	g	c	c	t	g	g	t	t	a	
DNA[3][43:53]	t	t	g	a	c	c	t	g	a	t	

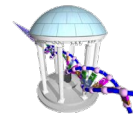
Profile	a	[2,	1,	0,	1,	1,	2,	1,	1,	1,	1]
	c	[0,	0,	1,	1,	1,	1,	0,	1,	0,	0]
	g	[1,	1,	2,	1,	1,	1,	1,	1,	2,	1]
	t	[1,	2,	1,	1,	1,	0,	2,	1,	1,	2]
		[2,	2,	2,	1,	1,	2,	2,	1,	2,	2]

Score = 17



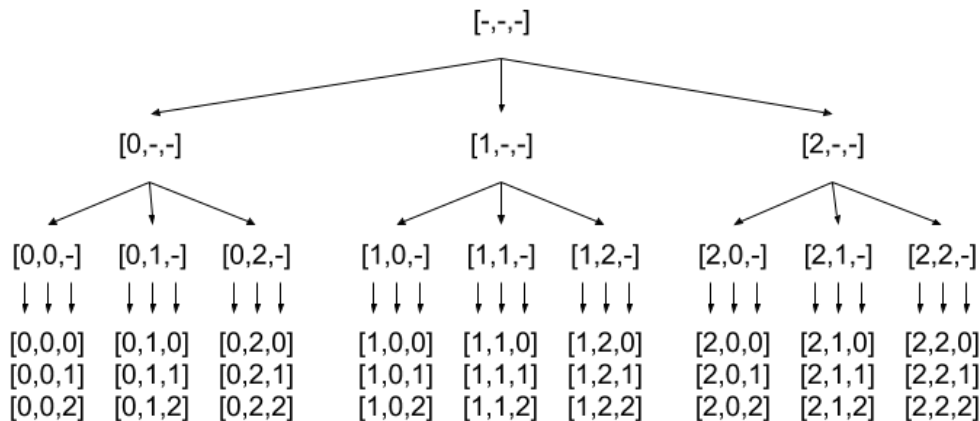
If the best answer so far is 79, there is no need to consider the 70^6 offset permutations that start with these 4 indices.

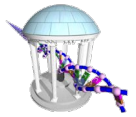
Search Trees



- Our standard method for enumerating permutations can be considered as a traversal of leaf nodes in a search tree
- Suppose after checking the first few offsets we can determine that any score of children nodes could not beat the best score seen so far?

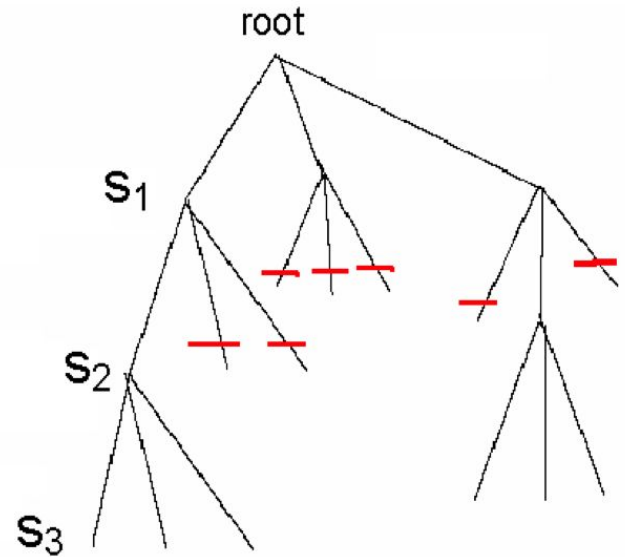
Search tree of the Cartesian product
 $(0,1,2) \times (0,1,2) \times (0,1,2)$



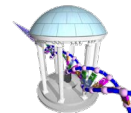


Branch-and-Bound Motif Search

- Since each level of the tree goes deeper into search, discarding a prefix discards all following branches
- This saves us from looking at $(N-k+1)^{M-\text{depth}}$ leaves
- Note our enumeration of tree-branches is depth-first
- We'll formulate of trimming algorithm as a recursive algorithm



Recursive Exploration of a Search Tree



```
In [17]: ▶ bestAlignment = []
prunedPaths = 0

def exploreMotifs(DNA, k, path, bestScore):
    """ Search for a k-length motif in the list of DNA sequences by exploring
        all paths in a search tree. Each call extends path by one. Once the
        path reaches the number of DNA strings a score is computed. """
    global bestAlignment, prunedPaths
    depth = len(path)
    M = len(DNA)
    if (depth == M):          # here we have an index in all M sequences
        s = Score(path, DNA, k)
        if (s > bestScore):
            bestAlignment = [p for p in path]
            return s
        else:
            return bestScore
    else:
        # Let's consider if an optimistic best score can beat the best score so far
        if (depth > 1):
            OptimisticScore = k*(M-depth) + Score(path, DNA, k)
        else:
            OptimisticScore = k*M
        if (OptimisticScore < bestScore):
            prunedPaths = prunedPaths + 1
            return bestScore
        else:
            for s in range(len(DNA[depth])-k+1):
                newPath = tuple([i for i in path] + [s])
                bestScore = exploreMotifs(DNA, k, newPath, bestScore)
            return bestScore
```


Let's try it



```
In [18]: ▶ def BranchAndBoundMotifSearch(DNA, k):  
    """ Finds a k-length motif within a list of DNA sequences"""  
    global bestAlignment, prunedPaths  
    bestAlignment = []  
    prunedPaths = 0  
    bestScore = 0  
    bestScore = exploreMotifs(DNA, k, [], bestScore)  
    print(bestAlignment, bestScore, prunedPaths)  
  
%time BranchAndBoundMotifSearch(seqApprox[0:6], 10)  
  
[17, 47, 18, 33, 21, 0] 53 8615931  
CPU times: user 3min 17s, sys: 0 ns, total: 3min 17s  
Wall time: 3min 17s
```

Recall that last time it took almost 13 mins to search the first 4 sequences.

Here we took nearly $\frac{1}{4}$ of that to search 6 sequences.

Observations



- For our problem instance, Branch-and-Bound Motif finding is significantly faster
 - It found a motif in the first 6 strings in less time than the Brute Force approach found a solution in the first 4 strings
 - More than $70^2 \approx 5000$ times faster
 - It did so by trimming more than 8 Million paths
 - Trimming added extra calls to Score (no worse than doubling the worst-case number of calls), but ended up saving even more hopeless calls along longer paths.
 - In practice, Branch-and-Bound, significantly improves average performance
- Does this improve the worst-case performance from $O(kN^M)$?
 - What if all of our motifs were found at the end of each DNA string?
 - How do we avoid these worse case data sets?
 - Randomize the search-tree traversal order



We need a new approach



- Enumerating every possible permutation of motif positions is still not getting us the speed we want.
- Let's try another tried-and-tested approach to algorithm design, mixing up the problem
 - Suppose that some Oracle could tell us *what* the motif is...
 - How long would it take us to find its position in each string?
 - We could compute the Hamming Distance from our given motif to the k-mer at every position in each DNA sequence and keep track of the smallest distance and its position on each string.
 - These positions are our best guess of where the motif can be found on each string
- Let's call this approach *scanning-and-scoring* to find a given motif.



Scanning-and-Scoring a Motif



```
In [30]: ▶ def ScanAndScoreMotif(DNA, motif):
totalDist = 0
bestAlignment = []
k = len(motif)
for seq in DNA:
    minHammingDist = k+1
    for s in range(len(seq)-k+1):
        HammingDist = sum([1 for i in range(k) if motif[i] != seq[s+i]])
        if (HammingDist < minHammingDist):
            bestS = s
            minHammingDist = HammingDist
    bestAlignment.append(bestS)
    totalDist += minHammingDist
return bestAlignment, totalDist
```

```
In [31]: ▶ print(ScanAndScoreMotif(seqApprox, "tagatccgaa"))
%timeit ScanAndScoreMotif(seqApprox, "tagatccgaa")
```

```
[[17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11)
```

```
1.09 ms ± 16.2 µs per loop (mean ± std. dev. of 7 runs, 1000 loops each)
```

Wow, we can test over 900 motifs per second!



Scan-and-Score Motif Performance

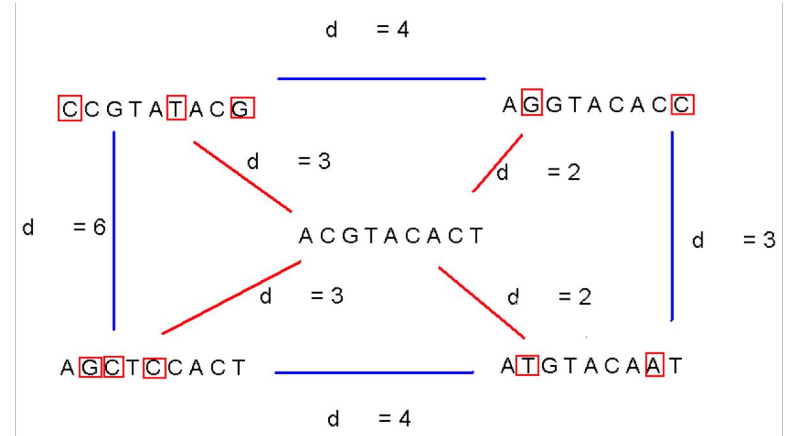
- There are $M(N-k+1)$ positions to test the motif, and each test requires k tests.

So each scan is $O(MNk)$

- So where where do we get candidate motifs?
- Can we try all of them?
 - There are $4^{10} = 1048576$ in our example.
 - 1048576 motifs $\times 1.09$ mS ≈ 19 mins
 - Not fast, but much less than a lifetime
 - $O(4^k MNk)$ vs. $O(N^M k)$

- This approach is called a **Median String Motif Search**

- Recall from last Lecture that a string that minimizes Hamming distance is like finding a *middle* or *median* string that is closer to all instances than the instances are to each other.



Let's do it!



```
In [37]: ▶ import itertools

def MedianStringMotifSearch(DNA, k):
    """ Consider all possible 4**k motifs"""
    bestAlignment = []
    minHammingDist = k*len(DNA)
    kmer = ''
    for pattern in itertools.product('acgt', repeat=k):
        motif = ''.join(pattern)
        align, dist = ScanAndScoreMotif(DNA, motif)
        if (dist < minHammingDist):
            bestAlignment = [p for p in align]
            minHammingDist = dist
            kmer = motif
    return bestAlignment, minHammingDist, kmer

%time MedianStringMotifSearch(seqApprox,10)
```

```
CPU times: user 18min 40s, sys: 0 ns, total: 18min 40s
Wall time: 18min 40s
```

```
Out[37]: ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')
```

The right answer in under 20 mins! Much less than a lifetime.

Notes on Median String Motif Search



- Similarities between finding and alignment with minimal Hamming Distance and maximizing a Motif's consensus score.
- In fact, if instead of counting mismatches as in the code fragment:

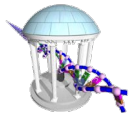
```
HammingDist = sum([1 for i in range(k) if motif[i] != seq[s+i]])
```

we had counted matches

```
Matches = sum([1 for i in range(k) if motif[i] == seq[s+i]])
```

and found the maximum(TotalMatches) instead of the min(TotalHammingDistance) we would be using the same measure as Score().

- Thus, we expect MedianStringMotifSearch() to give the same answer as either BruteForceMotifSearch() or BranchAndBoundMotifSearch().
- However, the 4^k term raises some concerns. If k were instead 20, then we'd have to Scan-and-Score more than 10^{12} times. Another not-in-a-lifetime algorithm
- We can also apply the Branch-and-Bound approach to the Median string method, but, as before it would only improve the average case.



Other ways to guess the motif?

- If we knew that the motif that we are looking for was "contained" somewhere in our DNA sequences we could test the $(N-k+1)M$ motifs from our DNA, giving a $O(N^2M^2)$ algorithm.

```
tagtggctcttttgagtgtagatctgaagggaaagtatttccaccagttcggggtcaccagcagggcagggtgacttaat
cgcgactcggcgcctcacagttatcgcacgcttttagaccaaaccggagttggatccgaaactggagtttaacggagtcctt
gttacttgtgagcctggtttagaccgaaatataattgttggctgcatagcggagctgacatacagtaggggaaatgcgt
aacatcaggcctttgattaaacaatttaagcacgTAGATCCGAAttgacctgatgacaatacggaaacatgccggctccggg
accaccggataggctgcttattaggtccaaaaggtagtatcgtataatggctcagccatgtcaatgtgcggcatccac
tagattcgaatcgatcgtgtttctccctctgtggggttaacgaggggtccgaccttgctcgcattgtgccgaacttgtacc
gaaatggttcggtgcgatatcaggccgttctcttaacttggcgggtgcagatccgaacgtctctggaggggtcgtgcgcta
atgtatactagacattctaacgctcgttattggcggagaccatttgcctcactacaagaggctactgtgtagatccgta
ttcttaccccttcttagatccaaacctgttggcgcacctctcttttcgagtccttgaacctcatttgcctgatgac
ctacctatgtaaaacaacatctactaacgtagctccggcttttctgatctgccctaacctacaggtcgatccgaaattcg
```

- Unfortunately, as you may recall, our motif does not actually appear in our data.
- Let's not be discouraged and try it anyway

Let's consider only Motifs seen in the DNA



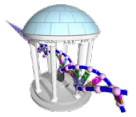
```
In [39]: ▶ def ContainedMotifSearch(DNA,k):
          """ Consider only motifs from the given DNA sequences"""
          motifSet = set()
          for seq in DNA:
              for i in range(len(seq)-k+1):
                  motifSet.add(seq[i:i+k])
          print("%d Motifs in our set" % len(motifSet))
          bestAlignment = []
          minHammingDist = k*len(DNA)
          kmer = ''
          for motif in motifSet:
              align, dist = ScanAndScoreMotif(DNA, motif)
              if (dist < minHammingDist):
                  bestAlignment = [s for s in align]
                  minHammingDist = dist
                  kmer = motif
          return bestAlignment, minHammingDist, kmer

          %time ContainedMotifSearch(seqApprox,10)
```

```
709 Motifs in our set
CPU times: user 771 ms, sys: 0 ns, total: 771 ms
Wall time: 769 ms
```

```
Out[39]: ([17, 31, 18, 33, 21, 0, 46, 70, 16, 65], 17, 'tagatccaaa')
```

Not exactly the motif we wanted (off by a 'g'), [17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatcc**g**aa', but it was fast!



Insights from the consensus score matrix

If we call `Score([17, 31, 18, 33, 21, 0, 46, 70, 16, 65], seqApprox, 10)`

The only different offset value.



DNA[0][17:27]	t	a	g	a	t	c	t	g	a	a
DNA[1][31:41]	t	a	g	a	c	c	a	a	a	a
DNA[2][18:28]	t	a	g	a	c	c	c	g	a	a
DNA[3][33:43]	t	a	a	a	t	c	c	g	a	a
DNA[4][21:31]	t	a	g	g	t	c	c	a	a	a
DNA[5][0:10]	t	a	g	a	t	t	c	g	a	a
DNA[6][46:56]	c	a	g	a	t	c	c	g	a	a
DNA[7][70:80]	t	a	g	a	t	c	c	g	t	a
DNA[8][16:26]	t	a	g	a	t	c	c	a	a	a
DNA[9][65:75]	t	c	g	a	t	c	c	g	a	a

This is the "contained" string. Had to be here. Why?



a	[0, 9, 1, 9, 0, 0, 1, 3, 9,10]								
c	[1, 1, 0, 0, 2, 9, 8, 0, 0, 0]								
g	[0, 0, 9, 1, 0, 0, 0, 7, 0, 0]								
t	[9, 0, 0, 0, 8, 1, 1, 0, 1, 0]								
Consensus	[9, 9, 9, 9, 8, 9, 8, 7, 9,10]								
t	a	g	a	t	c	c	g	a	a

Score = 87
Our motif!

Any Ideas?

Contained-Consensus Motif Search



```
In [42]: ▶ def Consensus(s, DNA, k):
          """ compute the consensus k-Motif of an alignment given offsets into each DNA string.
              s = list of starting indices, 1-based, 0 means ignore, DNA = list of nucleotide strings,
              k = Target Motif length """
          consensus = ''
          for i in range(k):
              # loop over string positions
              cnt = dict(zip("acgt", (0,0,0,0)))
              for j, sval in enumerate(s):
                  # loop over DNA strands
                  base = DNA[j][sval+i]
                  cnt[base] += 1
              consensus += max(cnt.items(), key=lambda tup: tup[1])[0]
          return consensus

          def ContainedConsensusMotifSearch(DNA,k):
              bestAlignment, minHammingDist, kmer = ContainedMotifSearch(DNA,k)
              motif = Consensus(bestAlignment,DNA,k)
              newAlignment, HammingDist = ScanAndScoreMotif(DNA, motif)
              return newAlignment, HammingDist, motif

          %time ContainedConsensusMotifSearch(seqApprox,10)
```

The consensus motif's hamming distance can be no more than the "contained" string's. Why?

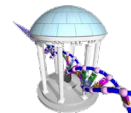


```
709 Motifs in our set
CPU times: user 770 ms, sys: 0 ns, total: 770 ms
Wall time: 767 ms
```

```
Out[42]: ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')
```

Look for a "contained" motif, and then do one last scoring pass with the consensus motif. That was fast!

Dad, are we there yet?



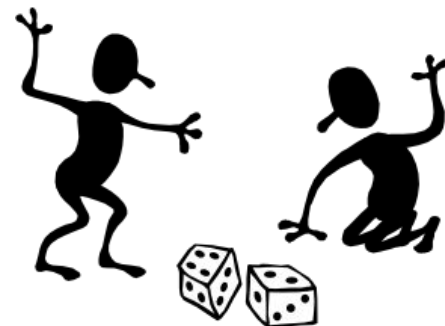
- We got the answer that we were looking for, **but**
- How can we be sure it will always give the correct answer?
 - Our other methods (branch and bound & median search) were exhaustive, they examined every possibility
 - This method considers only a subset of possible solutions, and picks the best one in a greedy fashion
 - What if there had been ties among the candidate motifs?
 - What if the consensus score (87% matches) had been lower
 - Would we, should we, be satisfied?
- It's one thing to be greedy, and another to be both *greedy* and *biased*
 - Our method is greedy in that it considers only the best contained motif, greedy methods are subject to falling into **local minimums**
 - Since we consider only subsequences as motifs we introduce bias
- Recall that Consensus can generate motifs not seen in our data



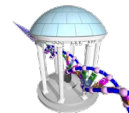
A randomized approach to motif finding



- One way to avoid *bias* and local minima is to introduce randomness
- We can generate candidate motifs from our data by treating the set of all possible offsets as a distribution
 - Likely motif candidates from this distribution are those generated by **Consensus**
 - Consensus strings can then be tested using **Scan-and-Score** and these alignments lead to new consensus strings
 - Eventually, we should converge to some local minimal answer
- To avoid finding a **local minimum**, we try several random starts, and search for the best score amongst all these starts.
- A randomized algorithm **does not guarantee an optimal solution**. Instead it promises a good/plausible answer on average, and one that is not susceptible to a worse-case data sets as our greedy/biased method was.



A Randomized Motif Search



In [56]: `import random`

```
def RandomizedMotifSearch(DNA, k):  
    """ Searches for a k-length motif that appears  
    in all given DNA sequences. It begins with a  
    random set of candidate consensus motifs  
    derived from the data. It refines the motif  
    until a true consensus emerges."""  
  
    # Seed with motifs from random alignments  
    motifSet = set()  
    for i in range(500):  
        randomAlignment = [random.randint(0, len(DNA[j])-k) for j in range(len(DNA))]  
        motif = Consensus(randomAlignment, DNA, k)  
        motifSet.add(motif)  
  
    bestAlignment = []  
    minHammingDist = k*len(DNA)  
    kmer = ''  
    testSet = motifSet.copy()  
    while len(testSet) > 0:  
        print(len(motifSet), end=', ')  
        nextSet = set()  
        for motif in testSet:  
            align, dist = ScanAndScoreMotif(DNA, motif)  
            # add new motifs based on these alignments  
            newMotif = Consensus(align, DNA, k)  
            if (newMotif not in motifSet):  
                nextSet.add(newMotif)  
            if (dist < minHammingDist):  
                bestAlignment = [s for s in align]  
                minHammingDist = dist  
                kmer = motif  
        testSet = nextSet.copy()  
        motifSet = motifSet | nextSet  
    return bestAlignment, minHammingDist, kmer
```

Creates 500 random "offset" vectors, finds their consensus motif, and uses these 500 as candidate k-mers.



Score each candidate and see if its offsets lead to a new motif candidate. If so add it to the next set to be considered.



This set union keeps track of all the k-mers we've considered.



Let's try it



```
In [57]: ▶ %time RandomizedMotifSearch(seqApprox,10)
```

```
500, 771, 866, 883, 889, 890, CPU times: user 1.03 s, sys: 4.01 ms, total: 1.04 s  
Wall time: 1.03 s
```

```
Out[57]: ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')
```

Randomized algorithms need to be run multiple times to insure a stable solution

```
In [58]: ▶ for i in range(10):  
           print(RandomizedMotifSearch(seqApprox,10))
```

```
499, 774, 861, 876, 878, ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')  
500, 768, 843, 863, 869, ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')  
500, 743, 823, 843, 845, ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')  
500, 756, 832, 844, 845, ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')  
500, 745, 826, 844, 850, ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')  
500, 776, 852, 870, 873, 874, ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')  
500, 762, 857, 878, 880, ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')  
500, 753, 822, 839, 844, 845, ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')  
500, 764, 845, 865, 867, 868, ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')  
500, 749, 825, 839, 841, ([17, 47, 18, 33, 21, 0, 46, 70, 16, 65], 11, 'tagatccgaa')
```

Lessons Learned



- We can find Motifs in our lifetime
 - Practical exhaustive search algorithm for small k , MedianStringMotifSearch()
 - Practical fast algorithm RandomizedMotifSearch(DNA, k)
- Three algorithm design approaches "Branch-and-Bound", "Greedy", and "Randomized"
- Reversing the objective, guessing an answer, and validating it (Needs good guesses).
- The power of randomness
 - Not susceptible to worse case data
 - Avoids local minimums that plague some greedy algorithms

