CSE 4065
Computational Genomics

Programming
Assignment #2

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Randomized Motif Search

```
RandomizedMotifSearch(Dna, k, t)
    randomly select k-mers Motifs = (Motif1, …, Motift) in each string from Dna
    BestMotifs ← Motifs
    while forever
        Profile ← Profile(Motifs)
        Motifs ← Motifs(Profile, Dna)
        if Score(Motifs) < Score(BestMotifs)
            BestMotifs ← Motifs
        else
            return BestMotifs
```

Randomized algorithms may be nonintuitive because they lack the control of traditional algorithms. Some randomized algorithms are Las Vegas algorithms, which deliver solutions that are guaranteed to be exact, even though they rely on making random decisions. Yet most randomized algorithms, including the motif finding algorithms that we will consider, is Monte Carlo algorithms. These algorithms are not guaranteed to return exact solutions, but they do quickly find approximate solutions. Because of their speed, they can be run many times, allowing us to choose the best approximation from thousands of runs.

In general, we can begin from a collection of randomly chosen k-mers Motifs in Dna, construct PROFILE(Motifs), and use this profile to generate a new collection of k-mers:

MOTIFS(PROFILE(Motifs), Dna)

Our hope is that MOTIFS(PROFILE(Motifs), Dna) has a better score than the original collection of k-mers Motifs. We can then form the profile matrix of these k-mers,

PROFILE(MOTIFS(PROFILE(Motifs), Dna)),

and use it to form the most probable k-mers,

MOTIFS(PROFILE(MOTIFS(PROFILE(Motifs), Dna)), Dna).

We can continue to iterate…

... PROFILE(MOTIFS(PROFILE(MOTIFS(PROFILE(Motifs), Dna)), Dna)) ...

for as long as the score of the constructed motifs keeps improving, which is exactly what Randomized Motif Search does. To implement this algorithm, we will need to randomly select the initial collection of k-mers that form the motif matrix Motifs. To do so, we will need a random number generator.

Since a single run of Randomized Motif Search may generate a rather poor set of motifs, bioinformaticians usually run this algorithm thousands of times. On each run, they begin from a new randomly selected set of k-mers, selecting the best set of k-mers found in all these runs.

Gibbs Sampler

```
GibbsSampler(Dna, k, t, N)
    randomly select k-mers Motifs = (Motif1, …, Motift) in each string from Dna
    BestMotifs ← Motifs
    for j ← 1 to N
        i ← Random(t)
        Profile ← profile matrix constructed from all strings in Motifs except for Motifi
        Motifi ← Profile-randomly generated k-mer in the i-th sequence
        if Score(Motifs) < Score(BestMotifs)
            BestMotifs ← Motifs
    return BestMotifs
```

Like Randomized Motif Search, Gibbs Sampler starts with randomly chosen k-mers in each of t DNA sequences, but it makes a random rather than a deterministic choice at each iteration. It uses randomly selected k-mers Motifs = ($Motif_1$, …, $Motif_t$) to come up with another (hopefully better scoring) set of k-mers. In contrast with Randomized Motif Search, which deterministically defines new motifs as:

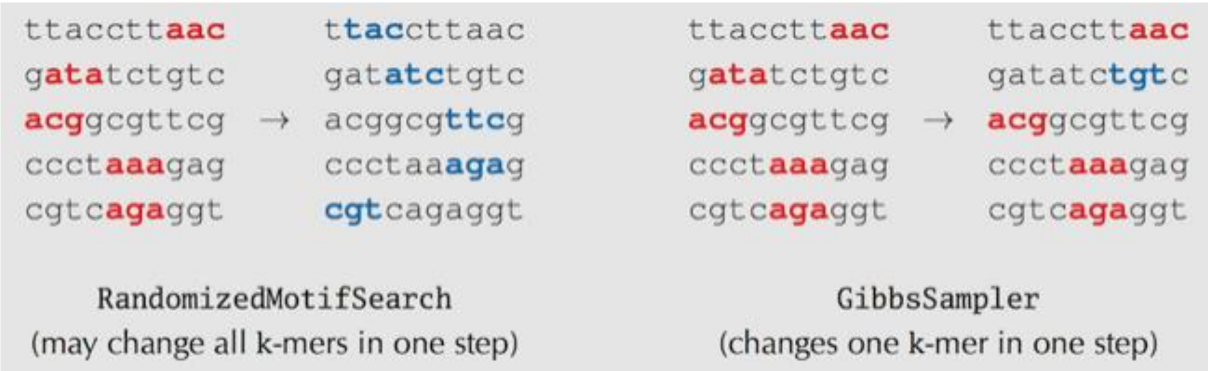
MOTIFS (PROFILE (Motifs), Dna)

Gibbs Sampler randomly selects an integer i between 1 and t and then randomly changes a single k-mer Motif. To describe how Gibbs Sampler updates Motifs, we will need a slightly more advanced random number generator. Given a probability distribution (p_1, ... , p_n), this random number generator, denoted RANDOM(p_1, ... , p_n), models an n-sided biased die and returns integer i with probability p_i.

Although Gibbs Sampler performs well in many cases, it may converge to a suboptimal solution, particularly for difficult search problems with elusive motifs. A local optimum is a solution that is optimal within a small neighbouring set of solutions, which is in contrast to a global optimum, or the optimal solution among all possible solutions. Since Gibbs Sampler explores just a small subset of solutions, it may “get stuck” in a local optimum. For this reason, similarly to Randomized Motif Search, it should be run many times with the hope that one of these runs will produce the best-scoring.

Comparison Between Randomized Motif Search and Gibbs Sampler

1. Randomized Motif Search may change all t strings in Motifs in a single iteration. This strategy may prove reckless, since some correct motifs may potentially be discarded at the next iteration. Gibbs Sampler is a more cautious iterative algorithm that discards a single k-mer from the current set of motifs at each iteration and decides to either keep it or replace it with a new one. This algorithm thus moves with more caution in the space of all motifs, as illustrated below:



2. Randomized motif search can be run for a larger number of iterations to discover better and better motifs. It can also find good solutions for larger values of k.
3. Gibbs Sampler continue until the score of the algorithms no longer improve. For example, we check our score every 50 iterations. If it seems like that the score remains the same for the last 50 iterations, then the algorithm stops to run.

Outputs of the Algorithms for Different k Values

Consensus(Motifs)

- When k = 9

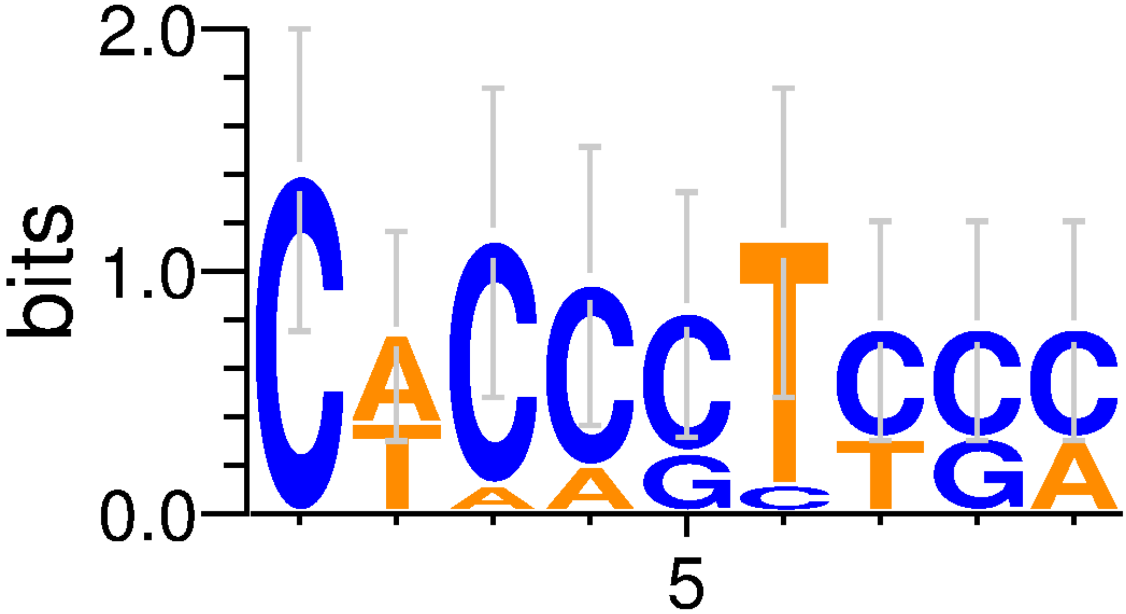


Figure 1: Consensus(Motifs) of Randomized Motif Search

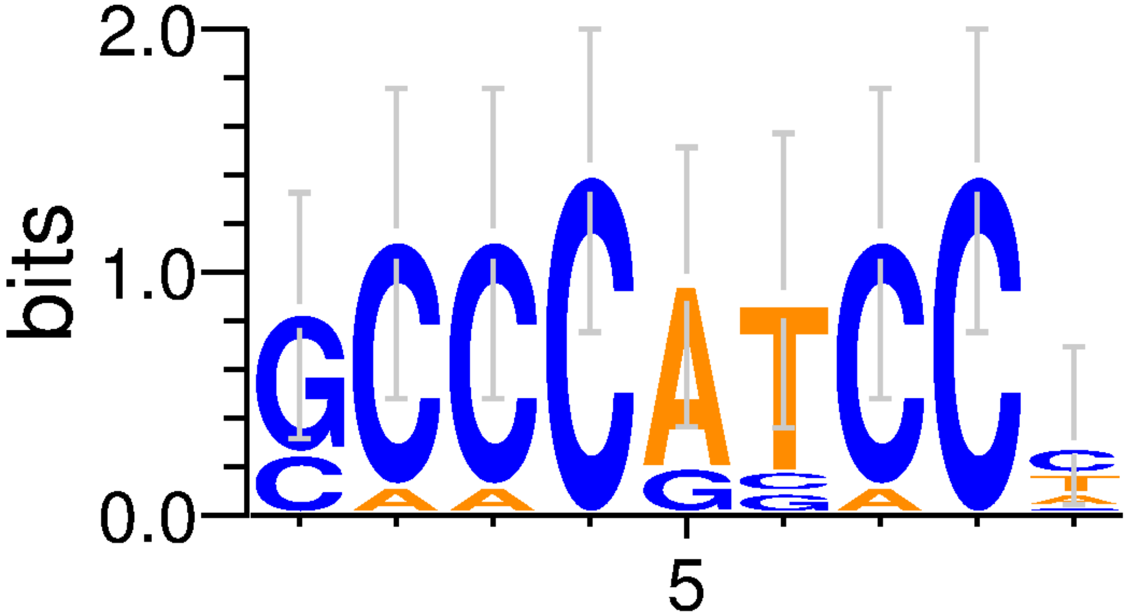


Figure 2: Consensus(Motifs) of Gibbs Sampler

- When k = 10

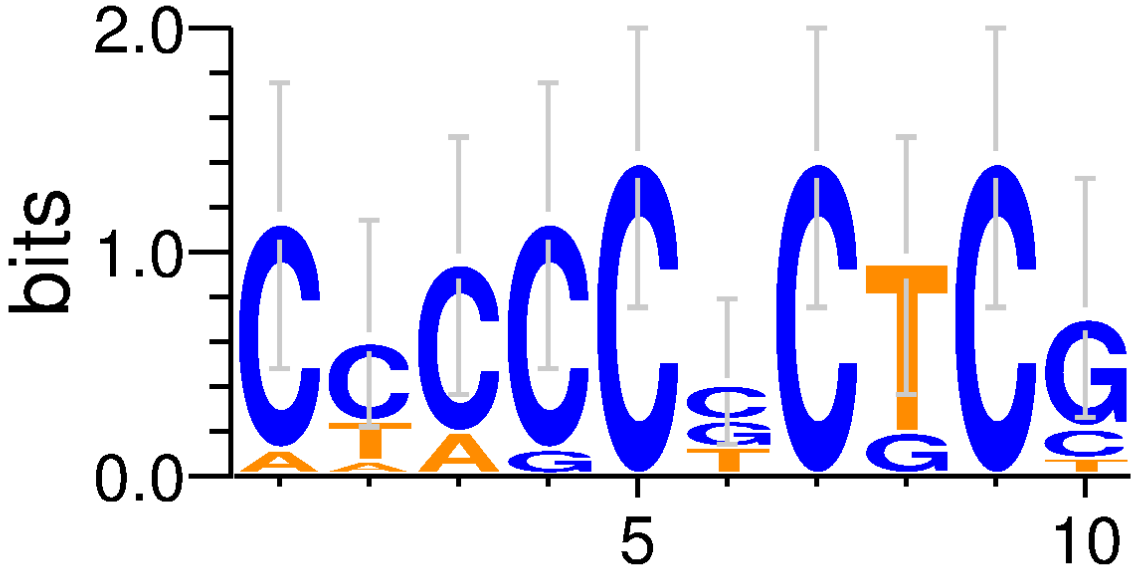


Figure 3: Consensus(Motifs) of Randomized Motif Search

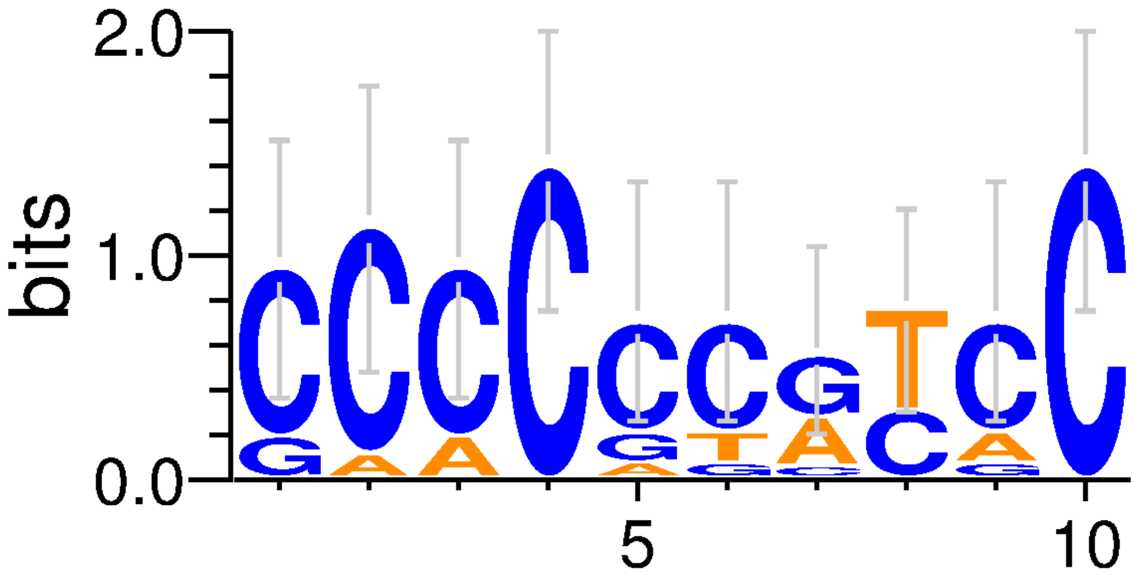


Figure 4: Consensus(Motifs) of Gibbs Sampler

- When k = 11

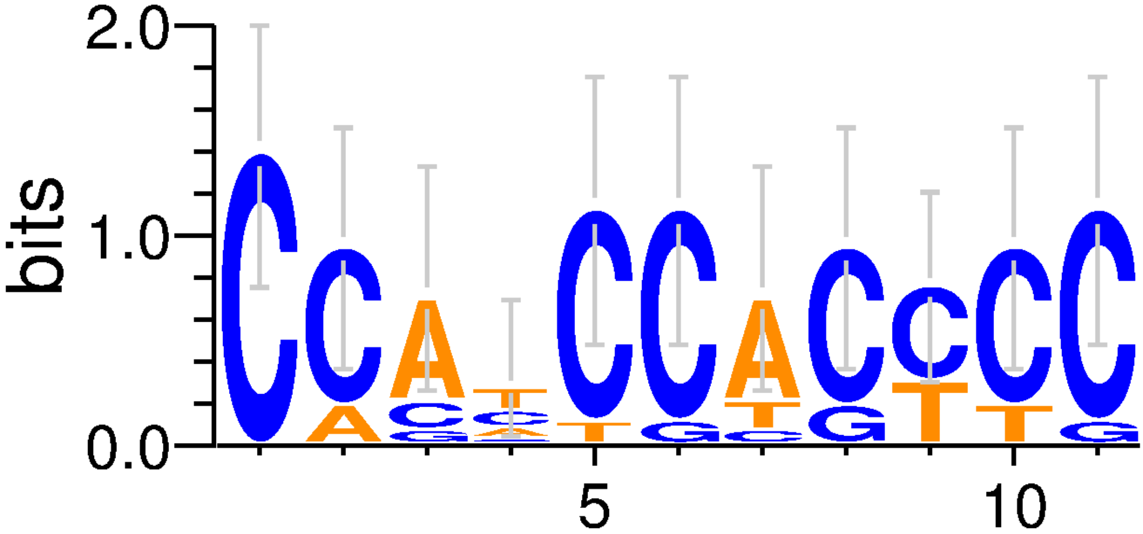


Figure 5: Consensus(Motifs) of Randomized Motif Search

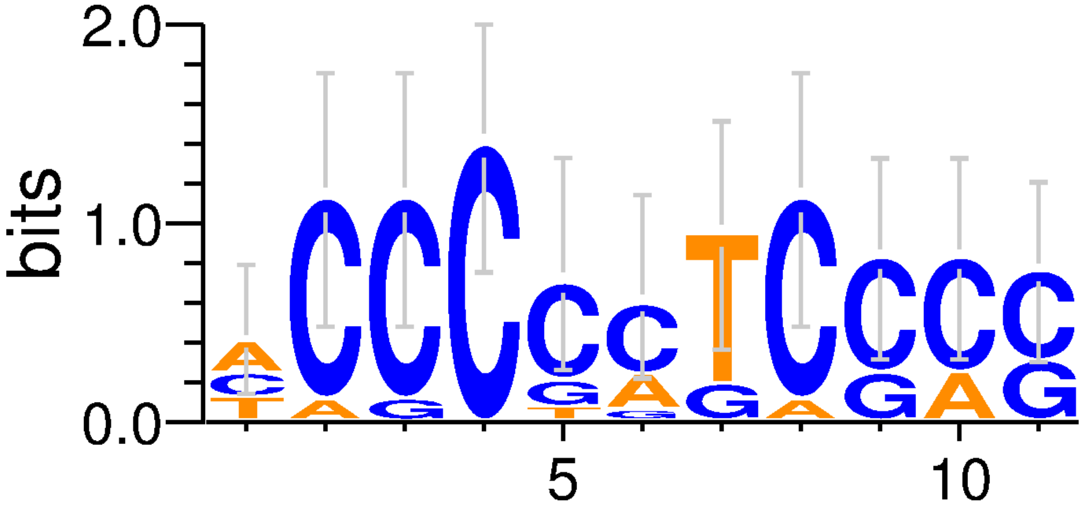
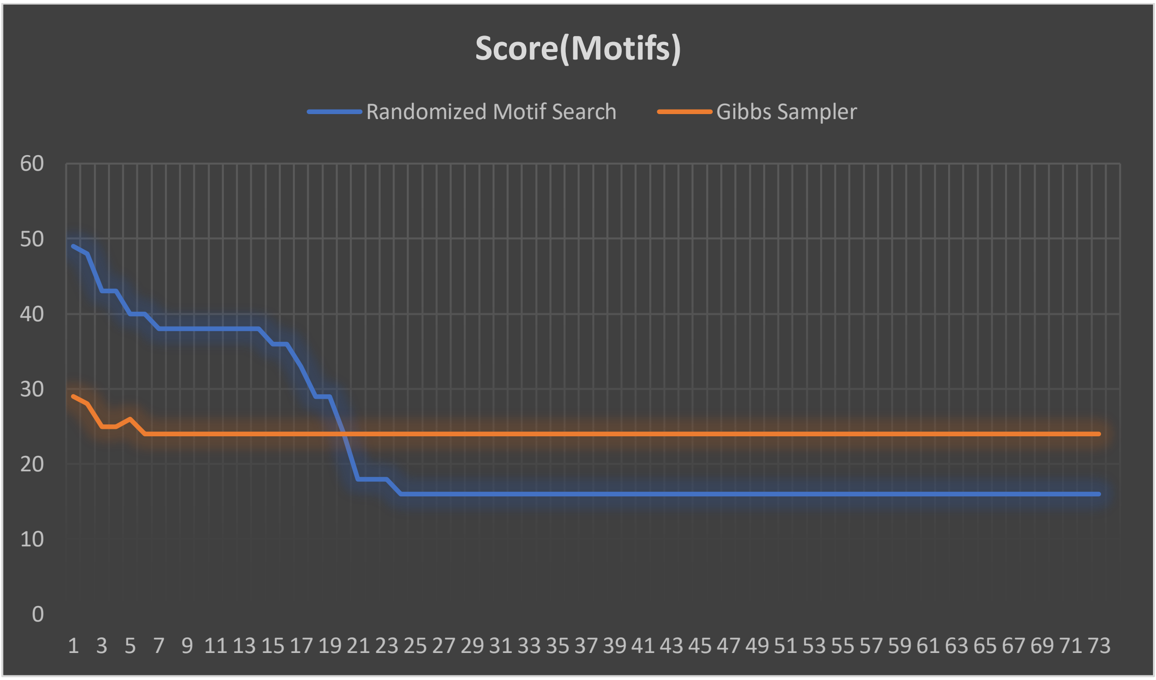


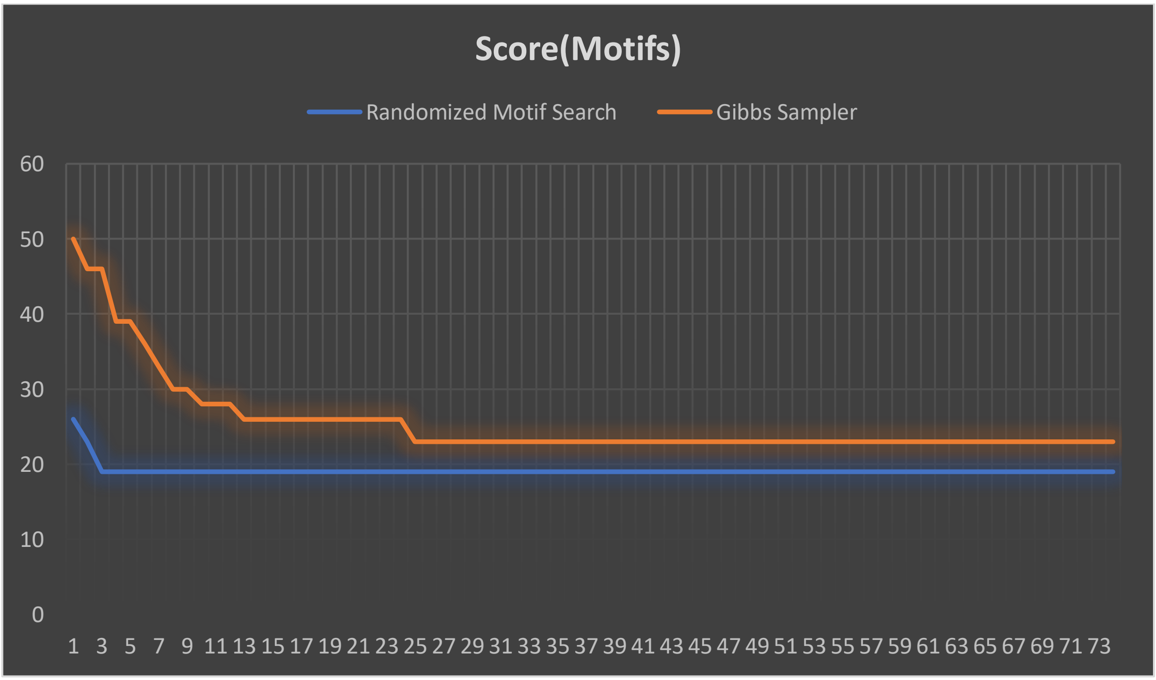
Figure 6: Consensus(Motifs) of Gibbs Sampler

Score(Motifs) Graphs

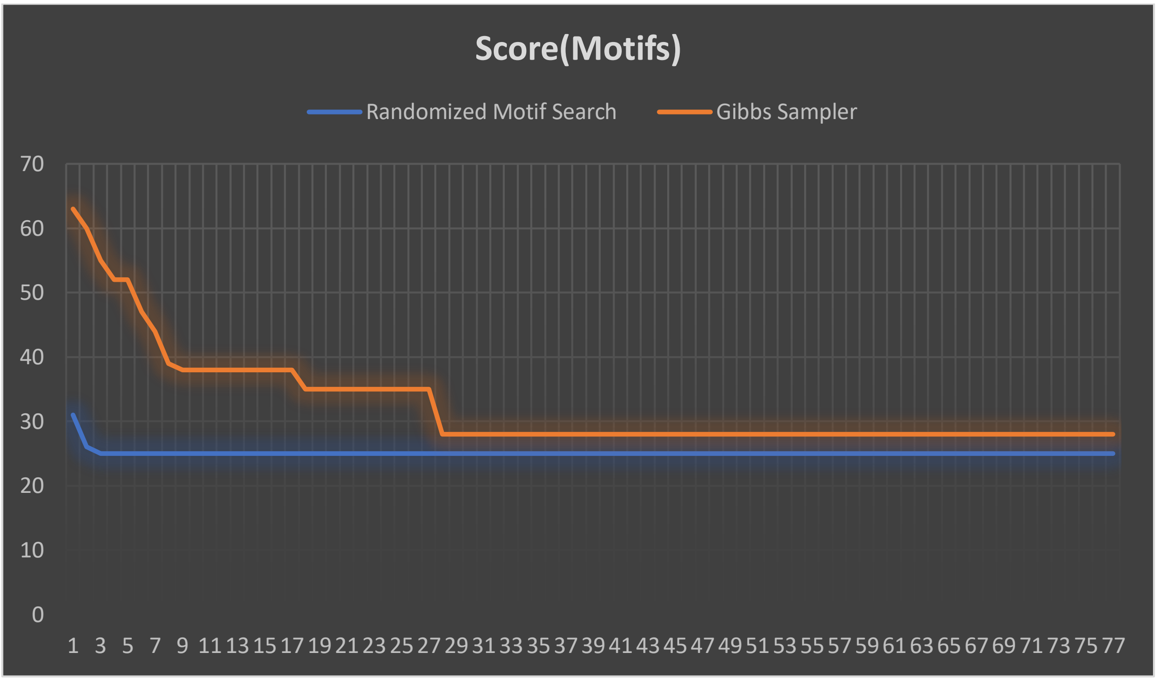
- k = 9



- k = 10



- k = 11



Conclusion

Capturing a single implanted motif is often insufficient to steer Randomized Motif Search to an optimal solution. Therefore, since the number of starting positions of k-mers is huge, the strategy of randomly selecting motifs is often not successful. The chance that these randomly selected k-mers will be able to guide us to the optimal solution is relatively small.

Although Gibbs Sampler performs well in many cases, it may converge to a suboptimal solution, particularly for difficult search problems.

Gibbs Sampler explores just a small subset of solutions, it may get stuck in a local optimum

Gibbs Sampler should be run many times with the hope that one of these runs will produce the best-scoring motifs.