Statistically Significant Strings are Related to Regulatory Elements in the Promoter Regions of *Saccharomyces cerevisiae*

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Abstract

Finding out statistically significant words in DNA and protein sequences forms the basis for many genetic studies. By applying the maximal entropy principle, we give one systematic way to study the nonrandom occurrence of words in DNA or protein sequences. Through comparison with experimental results, it was shown that patterns of regulatory binding sites in *Saccharomyces cerevisiae*(yeast) genomes tend to occur significantly in the promoter regions. We studied two correlated gene family of yeast. The method successfully extracts the binding sites verified by experiments in each family. Many putative regulatory sites in the upstream regions are proposed. The study also suggested that some regulatory sites are active in both directions, while others show directional preference.

1 Introduction.

It is attractive, but not unexpected, that DNA and protein sequences deviate remarkably from random sequences \(\mathbb{1}\). According to information theory, random sequences carry minimal information (maximal entropy) \(\mathbb{2}\), while the total information of life is assumed to be in DNA and protein sequences. As a result, investigation on the non-randomness of DNA and amino acid sequences would be the focus of Bioinformatics.

To find out nonrandom occurrence of words (short strings) in non-coding DNA sequences is interesting because a large portion of regulatory elements of eukaryotes usually are words of
limit length in the non-coding sequences (for example, about 10 bases, while the core part is about 5 bases [3]). subjected to functional constraints, the patterns of regulatory elements are expected to deviate from random occurrence.

In this paper, by applying the Maximal Entropy Principle (MEP), we develop one way to investigate the nonrandom occurrence of words in DNA sequences. Each word is given one significance index which quantifies the nonrandomness occurrence of the word. The method is then applied to study the promoter regions of *Saccharomyces cerevisiae* (*yeast*). [4] We compare the theoretical result with experiments in two ways. In the first way, the promoter database of *yeast* (SCPD) [5] was analysed. It was found that, statistically, overrepresented words are more easily encountered in the database. The second way is to study the promoters of coregulated gene families. The experimentally found binding sites were successfully extracted, and more putative binding sites are suggested.

In the following the method will be developed in details, and in the third section the method will be applied to study the promoter regions of *yeast*.

2 Treat the nonrandomness of DNA sequences via Maximal Entropy Principle.

The idea comes from a simple observation. Take a long DNA sequence as an example. Given only the (normalized) frequencies of $A, C, G, T$ ($P_A, P_C, P_G, P_T$), one would expected that the frequencies 2-tuples have the form

\[ P_{c_1c_2}^0 = P_{c_1} \times P_{c_2} \]  

Here $c_1$ and $c_2$ are one of the four bases $A, C, G, T$.

Comparison between the measured frequency $P_{c_1c_2}$ and the expected value $P_{c_1c_2}^0$ reveals the statistical significance of $c_1c_2$ in the sequence.

To generalize the above idea, one encounters the problem to predict the frequencies of $k+1$-tuples from the frequencies of $k$-tuples when $k > 1$. A reasonable definition can then be used to evaluate the statistical significance of words longer than two bases.

The following is an attempt to answer this problem. In the treatment, when the composition of a $k$-tuple is concerned, the word will be written as $c_1c_2\cdots c_{k-1}c_k$. However when only the length $k$ of the word is relevant, it will be given in the form of $w^k$. A combinatorial form may also be used. For example, $w^kc (cw^k)$ is the word obtained by adding a letter $c$ to the right (left) of $w^k$. The measured and expected frequencies of $w^k$ in the sequence will be written as $P_{w^k}$ and $P_{w^k}^0$, respectively.
There are a total of $4^k$ $k$-tuples. For prediction the Maximal Entropy Principle (MEP) is a preferred choice. According to modern genetics, the driving force for nucleotide sequence evolution is, on one hand, random mutations of bases that maximize the entropy, and, on the other hand, the natural selection which subjects the maximization of entropy to certain constraints. Therefore, DNA sequence analysis shows intrinsic correlation to the MEP. One brief introduction (which is necessary for our use) to MEP will be given below. More details can be found in e.g. [3].

Suppose that $\{P_i, i = 0, 1, 2, \cdots \}$ is a discrete distribution. An information entropy can be defined on it [2]:

$$S = \sum_i P_i \ln P_i.$$  \tag{2}

Usually $\{P_i\}$ satisfies some constraints:

$$F_j(\{P_i\}) = 0, \quad j = 1, 2, \ldots, M.$$  \tag{3}

Here $M$ is the number of constraints. Define a target function:

$$H = S + \sum_{j=1}^{M} \lambda_j F_j(\{P_i\}),$$  \tag{4}

$\lambda_j$ being Largrange factors. MEP states that the distribution minimizing the target function $H$ is the most reasonable distribution satisfying constraints (3). This, however, does not state that $\{P_i\}$ is the only distribution satisfying (3).

The MEP now can be applied to study the problem raised above. The entropy function here is:

$$S = \sum_i P_{0w^{k+1}(i)} \ln P_{0w^{k+1}(i)},$$

where $i$ is an index used to distinguish $k$-tuples from each other. (In order to get the index of a word, the following maps were used: $A$ to 0, $C$ to 1, $G$ to 2, and $T$ to 3. The original word is thus mapped to a string containing only 0,1,2 and 3. The string is then considered as quaternary number. After being transformed to decimal, the number is used as the index of the word.)

Constraints in the present problem is:

$$P_{w^k(i)} = \sum_c P_{0w^k(i)c},$$

$$P_{w^k(i)} = \sum_c P_{c w^k(i)},$$

$$i = 0, 1, 2, \cdots, 4^k - 1.$$  \tag{5}
$P^0_{w^{k+1}}$ is the frequency needs to be predicted and $P_{w^k}$ is the frequency already known. There is a total of $2 \times 4^k$ constraints. It is possible that these constraints are linearly related, so that the number of effective constraints is smaller than $2 \times 4^k$. This, however, does not alterate the result.

The solution can be obtained:

$$P^0_{c_1c_2 \cdots c_{k+1}} = \frac{P_{c_1c_2 \cdots c_k} \times P_{c_{2}c_3 \cdots c_{k+1}}}{P_{c_2c_3 \cdots c_k}}.$$  \hspace{1cm} (6)

When $k=1$, the solution reduces to the intuitively result, eq. (1).

The above treatment is from $k$-tuples to $k + 1$-tuples. As a generic scheme, the MEP can also be applied to predict the frequencies of $k + 2$-tuples, $k + 3$-tuples and so on, based on the frequency of $k$-tuples. Actually, one can get the result by repeatedly applying eq. (6). For example:

$$P^0_{c_1c_2 \cdots c_{k+1}c_{k+2}} = \frac{P^0_{c_1c_2 \cdots c_{k+1}} \times P^0_{c_2c_3 \cdots c_{k+2}}}{P_{c_2c_3 \cdots c_{k+1}}} = \frac{P_{c_1c_2 \cdots c_k} \times P_{c_2c_3 \cdots c_{k+1}} \times P_{c_3c_4 \cdots c_{k+2}}}{P_{c_2c_3 \cdots c_k} \times P_{c_3c_4 \cdots c_{k+1}}}.$$  \hspace{1cm} (7)

Thus, when one refers to the expected frequency of a certain word of length $k$, the knowledge that the prediction is based on must be pointed out.

With the frequencies of longer words, one can always obtain the frequencies of shorter ones. On the other hand, the expected frequencies of longer words, eq. (6), is predicted from the frequencies of shorter words, with no more information added. Therefore, the deviation of the measured frequencies from the expected ones gives new information emerges only in the frequencies of the longer words. In order to use this part of information, we refer to the following significance index

$$I_{w^k} = \frac{P_{w^k} - P^0_{w^k}}{\sqrt{P^0_{w^k}}}. \hspace{1cm} (8)$$

The indexes of $k$-tuples form a vector of $4^k$ dimension.

It should be pointed out that the simple solution eq. (6) results from the constraints, eq. (5). Although there are many ways to write down the prediction [7, 8], the Maximal Entropy Principle ensure that, submitted to these constraints, the solution eq. (6) is the best one. However, one can consider more constraints. Expect for the continuous words, spaced patterns can also be involved in the above statistical treatment [8]. As an example, consider the spaced word $c_1c_2$, where $c_1$ and $c_2$ are certain bases and the base between them is not relevant. One more constraint

$$P_{c_1c_2} = \sum_c P_{c_1cc_2}$$
can be added to the frequencies of 3-tuples, and the statistical significance of the spaced words can also be evaluated. The MEP, as a general framework, is still applicable, but there will be no simple explicit solution as eq.(3).

3 The relationship between regulatory elements and statistically significant words in the yeast promoter regions.

With the accumulation of huge amount of genome sequences, analysis of the regulatory regions becomes urgent, because they govern the regulation of gene expression. Finding out the regulatory sites in Eukaryotes genomes is especially difficult, largely because of their strong variance. This, however, gives the chance for statistical methods to play an important role in binding sites prediction.

The regulatory elements are functionally constrained and are often shared by many genes. As a result, the sites are expected to be significantly represented. Based on this belief, the method developed above is expected to be applicable in finding regulatory sites in the promoter regions of yeast. We employ two ways to check this point.

In the first way, as just an illustration of the effectiveness of the MEP treatment, a data set including all the promoters of yeast will be used to perform the statistical evaluation. The promoter regions refer, according to Zhang [3], to the upstream region of 500 bases long. From the sequence set the word frequencies are obtained and $I_{w^k}, k = 2, \cdots, 8$, are calculated according to eq.(6) and eq.(8). (to obtain $I_{w^k}, P_{w^k}$ is predicted based on the frequency of k-1-tuples.) For comparison the index $I_{w^k}, k = 2, \cdots, 8,$ of words in the coding regions (CDSs) of yeast were also calculated.

To compare the significance index of words with experimentally verified regulatory elements, a strongly statistically characterized method was pursued. The promoter database of yeast collected by Zhou et al. [5] was used as targets. One word is called to hit the target if it covers a known regulatory element or part of the element. In this way, each word will be checked against all the elements in the database. We want to see if the total hits of words show correlation with the significance index.

Fig.1 shows the ratio of the average hits of words whose significance index are larger than a certain cutoff (5.0, 3.0, or 2.0) to the average hits of all the $k$-tuples. Some properties of significance index in the promoter regions are revealed. First, for all the cutoff value shown in fig.1, the ratios are always larger than 1. Second, when the words are longer than 4 bases, the average hits increase with the increase of cutoff. Furthermore, the ratio also increases with the

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increase of word length. As a comparison, Fig.1 shows that the ratio of hits does not depend on significance index in the CDS regions.

To see the dependence of hits on significance index further, words are divided into groups according to their significance index values. In each group the hits were averaged. See table 1, and Fig.2 which is based upon the data in Table.1 but shown as a more audio-visual illustration. The dependence of hits on significance index shown in Fig.1 is seen again. Furthermore, the average hits are not the monotonic function of significance index in the promoter regions. For words with both positively and negatively large significance index in the promoter regions, the average hits are larger than those of words whose significance index is around zero. Again no dependence of average hits on significance index in CDS regions is observed in Table.1 and Fig.2.

That words with large negative significant index in the promoter regions also show higher affinity to binding sites deserves more consideration. One account is that although some regulatory elements, such as those involved in the expression of housekeeping genes, are expected to be overrepresented since large amount of the genes are needed, others that control the expression of some essential but restrictedly needed genes, are expected to be underrepresented to avoid inappropriate translation. However, more convincing explanation exists: if a word, e.g., wA, has high positive index, then some of wC, wG, wT are expected to have negative index. This can be seen from the following example. While the index of TATA is 16.3, that of TATAA is -12.2. Actually, both have much high counts in the sequences and both are variance of binding site of the same transcriptional factor.

For universally existing regulatory elements, as expected, the significance index in the promoter regions are much high. One example is the poly(A/T) stretches. As given above, the significance index of TATA is 16.3. Also the significance index of TATATA, 8.1, is high. As another example, the significance index of the core of CAAT-box, CAAT, is 8.95. However, in order to develop an algorithm for regulatory elements prediction, more subtle consideration must be involved. First, genes are needed to be classified into families to improve the compositional bias of the sequences. Furthermore, more complicated usage of the information given by significance index should be considered, because, according to eq.(7), the expected frequency of k-mers can be defined in $k-1$ ways, i.e., based on the frequency of 1, 2, · · · , $k-1$-mers, respectively. For each definition the significance index can be obtained. On considering the statistical property of words in the sequences, each of these indexes would give useful information. We choose two coregulated gene family to further test our method.

The coregulated genes of yeast metabolism have been widely studied, and these datasets provide ideal material to test the methods for binding sites prediction. Two families of coregulated
genes, GCN and TUP, were shown in table 2. Detailed information on them can be found in [9].

For each family, the frequencies of 6-tuples in the promoter regions were first collected. The expected frequencies them were predicted in five ways, which are based on the frequencies of bases, 2-tuples, 3-tuples, 4-tuples, 5-tuples, respectively. In stead of \( I_{w_k} \), a simpler significance index \( P_{w_k}/P_{0,w_k} \) was used. In our study only the single strand of promoter sequences is considered. This is different from that of [9]. They count the number of each words in both strands. In this way there are only 2080 distinct oligonucleotides, while the number in ours is \( 4^6 = 4096 \).

Table 3 shows the words that possess no less than 3 among the 5 significance index larger than 3. There are 13 such words for GCN family, and 23 for TUP family. In table 3 several words tend to cluster together to form a longer pattern. Generally speaking, the clusters can be expanded by involving words with slightly lower significance.

In both families, 6-tuples corresponding to regulatory binding sites found by experimental analysis are observed in table 3. See the first cluster of words for GCN family and the first and the second clusters for TUP family. Most of these words also show high statistical significance in the analysis of [9]. Some words predicted by [9] but not verified by experiments are also observed in table 3 (significant words shared by [9] and the present analysis are shown in bold in table 3). However, our analysis also found many significant words which do not show as highly significant scores according to [9].

Two clusters of words for TUP families is noteworthy (see the first and the second clusters in table 3). The first cluster includes GTGGGG, AGGGGC, ACGGGC, TGGGGT, and GGGGTA, and the second cluster involves TACCCC, ACCCCG, CCCCCG, and CCCCAC. Between them GTGGGG and CCCCAC, GGGGTA and TACCCC are reverse complements. The two clusters both correspond to the binding sites of transcription factor Mig1p (Zn finger), but seen from different strands. This may imply that the binding sites of Mig1p are active in both orientation. This property, however, was not found for the binding sites of Gcn4p (see table 3). For example, when the cutoff of significance index is reduced to 1.3 (now 46 words satisfy the criterion), the cluster of TGACTC and GACTCA expands to involve another 4 members: CGATGA, GATGAC, ATGACT, and GTGACT; while only one of inverse complements of them, GAGTCA, also has 3 index larger than 1.3. Among the 46 words, it can only be clustered with another words GGAGTC. Thus, the binding sites of Gcn4p seem to be active preferentially in one direction.

Among the available methods of binding sites prediction, ours is similar to that of [9] in that both work by defining expected frequencies of words. the difference is that our method defines the expected frequencies on the statistical stproperties of the sequences themselves, while [9]
more or less heuristically defines the word frequencies of whole non-coding sequences as the expected value. It is thus expected that our method is more precise and gives more unbiased result.

An alternative method developed by Li et al. [10], gives more subtle consideration on the statistical feature of DNA sequences. In their model, the sequence is considered as a text without interwords delimiters. They apply maximal likelihood consideration to recover the words, which they consider as possible binding site candidates. But the computation is far more complex to get meaningful result.

More methods to detect unknown elements within functionally related sequences are available (for a review, see [11]), most of which, such as the consensus [12] and the Gibbs sampler [13], are based upon well defined biological models. The type of signals that can be detected are generally limited; it is difficult for them to detect multiple signals. But these methods are able to detect much larger patterns with high precision. The present method can be used to detect multiple elements, but the pattern it can find is short.

It is also a widely explored problem in biology to compare the noncoding and coding regions of DNA sequences [14, 15, 16]. The MEP treatment gives one systematic way to study the statistical differences between coding and noncoding regions. In table 1 it is shown that significance index in CDS regions distribute much more stretchy than that of the promoter regions. The contrast keeps for all the word lengths we studied (up to 8 bases). This reveals that CDS regions are in a more nonrandom state. Two factors may help to interpret this phenomenon. First, the mutation rate of CDS regions is much lower than that of the promoter regions [15]. Secondly, the code usage in CDS region is universal and definite, while in the promoter regions the length of regulatory elements differ from each other and the regulatory elements may differ strongly from the consensus sequences.

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Figure 1: The ratio of average hits ($H$) of words above certain cutoff of significance index to the average hits ($H_0$) of all the words of same length. The $H_0$(word length) are 405(2), 94.4(3), 21.7(4), 4.92(5), 1.10(6), 0.241(7), 0.0528(8).

Figure 2: The dependence of average hits of 6-tuples on their average significance index. The data in this figure are shown as a more audio-visual illustration of the 6-tuple data in Table 1.
Table 1: The dependence of average hits on the significance index $I_w = \frac{P_w - P_0}{\sqrt{P_0 w}}$. The values shown in the hits volume are averaged over the hits of the points (words) included in the significance index range shown in the $I_w$ column.

| $I_w$ | Points | Hits | $I_w$ | Points | Hits | $I_w$ | Points | Hits | $I_w$ | Points | Hits |
|-------|--------|------|-------|--------|------|-------|--------|------|-------|--------|------|
| -15,-9 | 9 | 7.33 | -29,-12 | 16 | 5.50 | -11,-6 | 10 | 2.10 | -15,-9 | 12 | 1.17 |
| -9,-7 | 12 | 4.75 | -12,-10 | 12 | 4.33 | -6,-4 | 15 | 1.40 | -9,-7 | 15 | 0.60 |
| -7,-5 | 16 | 4.00 | -10,-9 | 12 | 5.67 | -4,-3 | 28 | 1.79 | -7,-6 | 30 | 1.40 |
| -5,-4 | 22 | 3.50 | -9,-8 | 14 | 5.14 | -3,-2 | 161 | 1.04 | -6,-5 | 95 | 0.78 |
| -4,-3 | 29 | 4.31 | -8,-7 | 23 | 4.87 | -2,-1 | 716 | 0.976 | -5,-4 | 102 | 0.98 |
| -3,-2 | 91 | 4.02 | -7,-6 | 40 | 5.38 | -1,-0 | 1137 | 0.997 | -4,-3 | 202 | 1.15 |
| -2,-1 | 158 | 4.03 | -6,-5 | 44 | 4.34 | 0,1 | 1169 | 1.05 | -3,-2 | 334 | 1.10 |
| -1,0 | 182 | 4.46 | -5,-4 | 46 | 5.41 | 1,2 | 593 | 1.27 | -2,-1 | 563 | 1.07 |
| 0,1 | 198 | 5.02 | -4,-3 | 63 | 5.27 | 2,3 | 178 | 1.51 | -1,0 | 738 | 1.09 |
| 1,2 | 134 | 5.58 | -3,-2 | 74 | 5.34 | 3,4 | 52 | 1.28 | 0,1 | 750 | 1.04 |
| 2,3 | 77 | 5.25 | -2,-1 | 79 | 4.52 | 4,5 | 19 | 1.68 | 1,2 | 570 | 1.09 |
| 3,4 | 47 | 6.55 | -1,0 | 94 | 5.53 | 5,6 | 11 | 2.18 | 2,3 | 345 | 1.24 |
| 4,6 | 21 | 7.09 | 0,1 | 101 | 4.58 | 6,13 | 12 | 3.17 | 3,4 | 117 | 1.07 |
| 6,8 | 13 | 6.15 | 1,2 | 83 | 4.16 | 4,5 | 94 | 1.29 | 4,5 | 94 | 1.29 |
| 8,10 | 10 | 7.40 | 2,3 | 59 | 5.47 | 5,6 | 64 | 1.17 | 6,7 | 21 | 1.23 |
| 10,19 | 9 | 10.22 | 3,4 | 60 | 4.60 | 6,7 | 18 | 1.00 | 7,9 | 16 | 1.44 |
| 4,5 | 48 | 4.70 | 5,6 | 38 | 4.08 | 7,9 | 16 | 1.00 | 9,10 | 13 | 5.46 |
| 6,7 | 27 | 4.19 | 7,8 | 25 | 4.80 | 8,9 | 19 | 6.84 | 10,12 | 12 | 4.42 |
| 8,9 | 19 | 6.84 | 9,10 | 13 | 5.46 | 10,12 | 12 | 4.42 | 12,20 | 19 | 5.21 |
Table 2: The coregulated gene family GCN and TUP, and criterion for them being clustered.

| Family | Genes | Shared regulatory property | References |
|--------|-------|---------------------------|------------|
| GCN    | ARG1, ARG3, ARG4, ARG8, ARO3, ARO4, ARO7, CPA1, CPA2, GLN1, HIS1, HIS2, HIS3, HIS4, HIS5, HOM2, HOM3, HOM6, ILV1, ILV2, ILV5, LEU1, LEU2, LEU3, LEU4, LYS1, LYS2, LYS5, LYS9, MES1, MET14, MET3, MET6, TRP2, TRP3, TRP4, TRP5, THR1 | General amino acid control; genes activated by Gcn4p. | Hinnebusch [17] |
| TUP    | FSP2, YNR073C, YOL157C, HXT15, SUC2, YNR071C, YDR533C, YEL070W, RNR2, YER067W, CWP1, YGR243W, YDR043C, YER096W, HXT6, YLR327C, YJL171C, YGR138C, HXT4, GSY1, YOR389W, MAL31, YML131W, RCK1 | All genes which are both derepressed by a factor larger than 4 when TUP1 is deleted, and induced by a factor larger than during the diauxic shift | DeRisi et al. [18] |
Table 3: Highly overrepresented words in promoter regions of GCN and TUP family. For each family, the 6-tuples with no less than 3 among the 5 significance index larger than 3 are indicated. The words also appear in table 2 of [9] as significant patterns are highlighted in bold. Words are clustered according to their similarity. \( \text{sig}(i) \) is the value of \( P_{w^6} / P_{w^6}^0 \) with \( P_{w^6}^0 \) being the frequency of 6-tuple \( w^6 \) predicted based on the frequencied of i-tuples.

| Family | Sequences | analysis result on 6-tuples | sites previously characterized |
|--------|-----------|-----------------------------|-------------------------------|
|        | counts    | \( \text{sig}(1) \) | \( \text{sig}(2) \) | \( \text{sig}(3) \) | \( \text{sig}(4) \) | \( \text{sig}(5) \) | Consensus | binding factors |
| GCN    | TGACTC    | 29  | 4.47 | 4.61 | 4.16 | 2.93 | 1.39 | RRTGACTCTTT | Gcn4p (bZip) |
|        | GACTCA    | 21  | 3.28 | 3.30 | 3.25 | 3.24 | 1.39 |
|        | CCGGTT    | 12  | 3.18 | 3.38 | 3.47 | 2.07 | 1.50 |
|        | CCGGCT    | 6   | 2.77 | 3.27 | 3.29 | 3.01 | 1.70 |
|        | GGGCGG    | 5   | 4.02 | 3.10 | 2.93 | 3.66 | 1.68 |
|        | CCGCAG    | 16  | 4.35 | 3.45 | 3.12 | 1.99 | 1.69 |
|        | CAGCGG    | 12  | 5.61 | 4.95 | 4.63 | 2.28 | 1.55 |
|        | CCGCTG    | 12  | 4.99 | 4.60 | 3.51 | 2.18 | 1.36 |
|        | CCCCCC    | 7   | 3.71 | 3.88 | 3.15 | 2.10 | 1.84 |
|        | CCTGCC    | 10  | 3.75 | 3.15 | 3.22 | 1.94 | 1.55 |
|        | GTGCCA    | 14  | 3.76 | 3.35 | 3.06 | 2.23 | 1.37 |
|        | GGTGCT    | 10  | 3.26 | 3.73 | 3.14 | 2.19 | 1.53 |
| TUP    | GGGGGC    | 9   | 6.67 | 5.23 | 3.76 | 3.27 | 1.47 | KANWWWWATSYYGGGGW | Mig1p (Zn finger) |
|        | AGGGGC    | 10  | 6.77 | 3.90 | 3.65 | 2.64 | 1.64 |
|        | ACGGGG    | 7   | 4.49 | 3.57 | 3.23 | 2.62 | 1.97 |
|        | TGGGCT    | 9   | 4.10 | 3.21 | 3.14 | 3.39 | 1.37 |
|        | GGGGTA    | 10  | 4.39 | 4.29 | 3.52 | 2.89 | 1.58 |
|        | TACCCC    | 16  | 5.67 | 5.73 | 4.22 | 2.52 | 1.32 |
|        | ACCCCG    | 11  | 6.34 | 5.24 | 5.15 | 3.27 | 1.39 |
|        | CCCCAG    | 8   | 7.37 | 4.68 | 3.60 | 2.31 | 1.33 |
|        | CCCCAC    | 12  | 6.55 | 5.05 | 3.49 | 2.27 | 1.36 |
|        | ACGAGG    | 11  | 4.66 | 3.79 | 3.12 | 1.70 | 1.44 |
|        | GGTTGG    | 9   | 4.10 | 4.27 | 3.41 | 2.21 | 1.31 |
|        | CTCGAG    | 8   | 3.15 | 4.00 | 4.42 | 2.22 | 1.17 |
|        | TCGAGG    | 9   | 3.75 | 3.88 | 4.38 | 2.15 | 1.73 |
|        | GCCGAG    | 7   | 4.74 | 4.07 | 3.20 | 1.84 | 1.35 |
|        | CGGAGA    | 10  | 4.02 | 4.17 | 3.05 | 1.97 | 1.69 |
|        | CTGCTA    | 10  | 2.42 | 3.23 | 4.28 | 3.21 | 1.90 |
|        | GTGCTT    | 17  | 6.95 | 6.81 | 4.86 | 3.34 | 1.71 |
|        | TGCCAC    | 10  | 3.74 | 3.38 | 3.02 | 1.74 | 1.51 |
|        | GCCCGG    | 4   | 4.10 | 3.12 | 3.13 | 3.23 | 2.67 |
|        | GCAACG    | 9   | 3.43 | 2.88 | 3.12 | 3.13 | 1.37 |
|        | GCACGG    | 8   | 5.13 | 4.66 | 3.12 | 2.58 | 1.66 |
|        | CAGTGG    | 8   | 3.33 | 3.48 | 3.01 | 1.90 | 1.61 |
|        | CGCGAT    | 7   | 2.76 | 3.48 | 4.12 | 3.68 | 2.083 |

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