Nucleosome sliding mechanism based on the potential energy of sequence

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Abstract. Nucleosome sliding and nucleosome digestion are two main ways for regulating gene transcription. We constructed three characteristic parameters (CP) based on the information of CG0, CG1 and CG2 motifs, and used these parameters to analyze the sliding trend of −1 and +1 nucleosomes around TSS of genes with NFR in yeast. The CP distribution was used to describe the features of nucleosome sequences, and the slope of fit line of CP distribution curve was used to represent the potential energy of nucleosome sequences. Results show that nucleosome sliding trend could be reflected by CG0 and CG2 CP distributions, and CG0 CP distribution has a good correlation with nucleosome sliding trend. In addition, the sliding trend of nucleosomes is different in various expression level genes. For high expression gene, sliding trend of −1 nucleosome is weaker and that of +1 nucleosome is stronger.

Key words: Sliding trend — Transcription regulation — Sequence characteristic — k-mer — CG dinucleotide

Abbreviations: CG0, subset of 8-mer motif that contains no CG dinucleotide; CG1, subset of 8-mer motif that contains only one CG dinucleotide; CG2, subset of 8-mer motif that contains two or more CG dinucleotide; CP, characteristic parameter of a given sequence; NFR, nucleosome-free region; RF, relative frequency of m-mer (m < 8) in a given 8-mer set; RMN, relative motif number; TSS, transcription start site.

Introduction

k-mer, as an important frequency-based algorithm, is widely used in computational genomics. Because of its fast and efficient advantages, many k-mer-based approaches have been developed and used in similarity analyses (Blaisdell 1986; Sims et al. 2009; Huang et al. 2011; Yu 2013; Wen et al. 2014). For some special k-mer motifs, they could be used as signature signals to predict CpG islands (Yang et al. 2012; Mohamed Hashim et al. 2015), promotors (Li et al. 2006; Lin et al. 2011, 2014), noncoding RNA (Feng et al. 2016), DNA binding sites (Badis et al. 2009; Liu et al. 2012; Liu et al. 2015), and nucleosome positioning (Segal et al. 2009; Guo et al. 2014). k-mer has also been involved in probe design (Fofanov et al. 2004), repeat sequence annotation (Kurtz et al. 2008), genome assembly (Compeau et al. 2011), epigenetic analysis (Quante et al. 2016), and drug design (Chou 2015). In addition, based on k-mer, information entropy can be further calculated, and which has been used in biological computational analysis (Meng et al. 2017). k-mer spectra of whole genome sequences are a visualization approach to reveal the genomic features. It has been found that frequency distributions of k-mers 8 ≤ k ≤ 10 is basically in agreement with that of k-mer 5 ≤ k ≤ 15 (Das et al. 2007), and 8-mer spectra are multimodal in human and mouse, but unimodal in bacteria (Stacey et al. 2003). G+C content and CpG suppression are thought to contribute to the multimodal (Chor et al. 2009). Our previous study has also found that multimodal of 8-mer spectrum is only closely related to
the amount of CG dinucleotide in 8-mer motif, in analyzed model organism genomes, the spectra of only CG2, CG1, and CG0 subsets form independent unimodal distributions. The functions of 8-mer sets containing different amounts of CG dinucleotide are different, CG1 motifs are related to the nucleosome-binding and CG2 motifs are related to the modular units of CpG islands (Zheng et al. 2017).

In eukaryotic cells, DNA is highly packaged into nucleosomes, arrays, and a nucleosome core particle comprises 146/147 base pairs of DNA wrapped around an octamer of histone proteins (Luger et al. 1997; Zhu et al. 2016). Nucleosome positioning is very important for transcription regulation (Jiang et al. 2009; Bai et al. 2010; Radman-Livaja et al. 2010). It is generally recognized that there are two well-positioned nucleosomes around TSS (transcription start site), and a nucleosome-free region (NFR) on the upstream of the TSS (Struhl et al. 2013; Lieleg et al. 2015). However, not all genes have the typical nucleosome organization (Kornberg et al. 1988; Becker 2014). Kubik et al. (2015) have pointed out that, in yeast, about 40% promoters have narrower NFR, and the formation of wider NFR in these promoters depends on the digestion of the “fragile” −1 nucleosome. For the “stable” −1 nucleosome promoters, the transcription regulation is mainly depended on the sliding of nucleosome. It has been proved that chromatin-remodeling complex is related to the sliding of nucleosome (Gangaraju et al. 2007; Zhou et al. 2016; Sinha et al. 2017), and sequence also has an effect on nucleosome sliding (McKnight et al. 2016; Niina et al. 2017; Brandani et al. 2018; Guoqing Liu et al. 2018). Here, we constructed three characteristic parameters based on the information of 8-mer sets containing different amounts of CG dinucleotide, and used these parameters to analyze the relations between sequence potential energy and nucleosome sliding trend.

Materials and Methods

Data sources

Nucleosome positioning data of Saccharomyces cerevisiae (unique map) were accessed from Brogaard et al. (2012). The reference genome sequence and gene annotation information of Saccharomyces cerevisiae were obtained from UCSC (SAC2 version) (http://genome.ucsc.edu/). The experimental data of gene expression levels were obtained from Holstege et al. (1998).

k-mer of genomic sequence

k-mer could be described as follows: supposing there is a genomic sequence S with length L, ‘N1, N2,...,Nj’, where $N_j \in \{A,T,C,G\}$. A string of consecutive k nucleotides within genetic sequence S is called a k-mer. The k-mers appearing in a sequence can be enumerated by using a sliding window of length k, shifting one base each time from position 1 to $L - k + 1$, until the entire sequence has been scanned. Given any k, there will be $4^k$ different possible permutations.  

Relative motif number of 8-mers

According to the definition of k-mer, for a given DNA sequence with length L, all of the 8-mer frequencies could be counted. The relative motif number (RMN) of the 8-mers with frequency i could be calculated by the following equation:

$$RMN = \frac{N_i}{4^8}$$  \hspace{1cm} (1)

$N_i$ is the number of the 8-mers with frequency i. The distribution of RMN also called as the 8-mer spectrum.

Relative frequency of m-mer in 8-mers

The relative frequency (RF) of m-mer (m < 8) in a given 8-mer set is defined as follows:

$$RF = \frac{4^m}{(8-m+1)} \sum_{j=1}^{L_k} \frac{H_j}{\sum_{j=1}^{L_k} H_j}$$ \hspace{1cm} (2)

where $L_k$ is the number of the k-th 8-mer set, $H_j$ is the frequency of the j-th 8-mer in the k-th 8-mer set, $N_j$ represents the occurrence number of the i-th m-mer in the j-th 8-mer, and RF = 1 denotes that the i-th m-mer appears randomly.

Characteristic parameter

CP value is used to represent the characteristic parameter of a given sequence. CP is defined by the following equation:

$$CP = \frac{1}{N} \sum_{i=1}^{N} RF_i$$  \hspace{1cm} (3)

where i is the i-th m-mer and N is the total number of m-mers in a given sequence. $RF_i$ is the relative frequency after the i-th m-mer in the given sequence is assigned by m-mer RF in a given 8-mer subset. The CP value represents the average abundance of m-mers in the given sequence. In our analysis, m = 3.

Results

Two types of nucleosome distribution modes around TSS

Based on the single-base pair resolution map of nucleosome positions given by Brogaard et al. (2012) we analyzed the
nucleosome distribution around TSS of yeast genes. The nucleosome located at TSS or nearest to the TSS is defined as +1 nucleosome, and the first nucleosome on the upstream of +1 nucleosome is defined as −1 nucleosome (Teves et al. 2014), and the distances between nucleosome dyad and TSS were calculated. Results show that not all genes have an obvious nucleosome free region on the upstream of TSS (Fig. 1). About 2/3 genes have a traditional nucleosome distribution pattern, and a longer interval appears between −1 and +1 nucleosome. These genes are called NFR genes. Meanwhile, about 1/3 genes have a different nucleosome distribution pattern. There is no NFR on the upstream of TSS, and the distance between −1 and +1 nucleosome dyad is much shorter than the average. These genes are called non-NFR genes. In Kubik’s research, they have given a reasonable explanation through analyzing the stability of −1 nucleosome, and thought that the transcription regulation in non-NFR genes depends on the digestion of −1 nucleosome, and in NFR genes depends on the sliding of −1 and +1 nucleosome (Kubik et al. 2015). Sequence preference is an important factor in nucleosome positioning, and the difference of nucleosome stability could also be reflected in the interaction between histone and DNA. In our study, we made further analysis about these two transcription regulation mechanisms by the information content of −1 and +1 nucleosome sequences.

We separately analyzed −1 and +1 nucleosome sequences of NFR genes and non-NFR genes by 3 characteristic parameters constructed by the information of 8-mer set of CG0, CG1 and CG2, and the CP distribution was used to describe the characteristic of nucleosome sequences. Results show that (Fig. 2), no matter which parameter was used, the CP distributions of +1 nucleosome sequences have no obvious differences between NFR genes and non-NFR genes, but CP distributions of −1 nucleosome sequences are different. For the CP distributions obtained by the information of CG1 set, only the CP distribution of −1 nucleosome sequence in non-NFR genes deviates obviously from that of all nucleosome sequences. Our previous research showed that the CG1 motif was the important positioning signal for nucleosome (Zheng et al. 2017), so this deviation could reflect the instability of −1 nucleosome in non-NFR genes to some extent. For the CP distributions obtained by the information of CG0 set, in NFR genes, the downstream of CP distribution of −1 nucleosome shows an increasing trend, so the CP distribution line of −1 nucleosome is tilted. In non-NFR genes, either the downstream or the upstream of CP distribution of −1 nucleosome shows an increasing trend, so the CP distribution line of −1 nucleosome is acinic. For the CP distributions obtained by the information of CG2 set, the CP distribution of −1 nucleosome shows a decreasing trend in NFR genes, but not in non-NFR genes. In NFR genes, we thought that transcription regulation should depend on the slide of −1 and +1 nucleosome, and the slide of nucleosomes must be closely related to the sequence construction. In our

**Figure 1.** Two types of nucleosome distributions around TSS. A. Nucleosome distributions around TSS in NFR genes. B. Nucleosome distributions around TSS in non-NFR genes. C. Schematic diagram of the most probable position of nucleosomes in NFR genes. D. Schematic diagram of the most probable position of nucleosomes in non-NFR genes. NFR, nucleosome-free region; TSS, transcription start site.
previous study, it has been shown that CG1 motifs are associated with nucleosome positioning. The distribution of CG1 motifs in nucleosome sequences has the balanced and symmetrical characteristic, and this characteristic could be used to predict the nucleosome positioning. However, the distribution characteristics of CG1 motifs have no difference between special nucleosomes (−1 and +1 nucleosome) and normal nucleosomes. Oppositely, the distribution characteristics of CG0 and CG2 motifs have difference between special nucleosomes and normal nucleosomes, so the potential energy of sequence reflected by the CP distribution obtained by the information of CG0 and CG2 sets could be an appropriate parameter to describe the sliding trend of nucleosome.

Potential energy of nucleosome sequences with different length of NFR

For discussing the correlation between the potential energy of sequence and the sliding trend of nucleosome, we analyzed −1 and +1 nucleosome sequences with different length of intervals in NFR genes by the CP distribution obtained by the information of CG0 and CG2 sets. NFR genes were divided into 3 groups: (1) when the distance between −1 and +1 nucleosome dyad is shorter than 217 bp (or the length of NFR is shorter than 70 bp), these genes were called short NFR genes (S-NFR); (2) when the distance between −1 and +1 nucleosome dyad is between 217 bp and 287 bp (or the length of NFR is between 70 bp and 140 bp), these genes were called middle NFR genes (M-NFR); (3) when the distance between −1 and +1 nucleosome dyad is longer than 287 bp (or the length of NFR is longer than 140 bp), these genes were called long NFR genes (L-NFR). The CP distributions of −1 and +1 nucleosomes in each group of NFR genes obtained by the information of CG0 and CG2 sets are shown in Fig. 3A–D. The main characteristics of −1 and +1 nucleosome sequences in 3 groups of genes have not changed. Though it shows some differences, the correlation between the potential energy of sequence and the sliding trend of nucleosome could not be described directly. In physics, potential energy curve is often used to describe the change of potential energy with relative position. In this study, we introduced the idea of potential energy curve and expected it to describe the relation between nucleosome sliding tendency and position of sequence. To visualize this relation, the linear fitting analysis was applied in these distribution curves, and the slope of the fit line was used to represent the difference of the potential energy of sequences (Fig. 3E–H). In CG0 linear fitting analysis, −1 and +1 nucleosomes both show a reasonable relation between potential energy of sequence and sliding trend of nucleosome. With the decrease of the interval between −1 and +1 nucleosomes, the absolute values of the slope of the fit line of −1 and +1 nucleosome increase. It is appropriate that the −1 and +1 nucleosomes with shorter interval need more sliding trend to facilitate transcription initiation. So CG0 CP distribution could well reflect the sliding trend of nucleosome. The slope of fit line obtained by CG2 could not show a reasonable relation between potential energy of sequence and sliding trend of nucleosome, because the
amount of CG2 motif is so small that it has no universality. However, the CG2 motif also affects nucleosome sliding in some case, and this affection is just the opposite to that of CG0 motif. Totally, the potential energy of sequences reflected by CG0 CP distribution is the most appropriate to describe the nucleosome sliding trend.

**Potential energy of nucleosome sequences with different gene expression level**

Further, the −1 and +1 nucleosome sequences in NFR genes with different expression levels were analyzed by CG0 CP distributions. NFR genes were divided into 3 groups according to gene expression level: (1) genes with expression values less than 1 mRNA/h were called low expression genes; (2) genes with expression values among 1–4 mRNA/h were called middle expression genes; (3) genes with expression values higher than 4 mRNA/h were called high expression genes. The CG0 CP distributions of −1 and +1 nucleosomes in each group of NFR genes are shown in Fig. 4A, B, and the fit lines of distribution curves are shown in Fig. 4C, D. For −1 nucleosome, the slope of fit line of middle expression genes is the highest, and that of high expression genes is the lowest. This phenomenon is reasonable, because the statistical distance between −1 and +1 nucleosome in high expression genes is obviously higher than those in other two groups of genes, and the distances in other two groups of genes are similar (Fig. 4). In high expression genes, the length of NFR is sufficient, so the −1 nucleosome has a weak sliding trend. The potential energy of −1 nucleosome sequences in middle expression level genes is different from that in low expression level genes, which indicates that the −1 nucleosome with stronger sliding trend would be more beneficial to gene transcription. For +1 nucleosome, the absolute value of the slope of fit line of high expression genes is obviously higher (about 50% higher) than those in other two groups of genes. For most of yeast genes, +1 nucleosome occupies the TSS. The sliding of +1 nucleosome is for exposing TSS, and not only for extending NFR. So the stronger sliding trend of +1 nucleosome in high expression genes is necessary.

**Discussion**

The position of nucleosomes in the genome is dynamic. The functions of nucleosomes in different positions in the genome are different. −1 and +1 nucleosomes, as two special nucleosomes, are closely related to transcription regulation, and the nucleosome sliding is an important way of regulation. The nucleosome sliding mechanism is complex, and it is regulated by many factors, such as chromatin-remodeling
complex and sequence matter. Sequence preference determines nucleosome positioning, and it also affects the stability of nucleosomes. However, not all sequence motifs are related to the nucleosome sliding. Our results show that the usage of CG1 motifs is always equalizing, and these motifs should determine the stability of nucleosomes but not sliding. CG0 and CG2 motifs both reflect the changes of potential energy of nucleosome sequence, but the correlation between potential energy and sliding trend obtained by CG2 motifs is poor. This may be attributed to the small amount of CG2 motifs. The CP constructed by the information of CG0 motifs is the most appropriate parameter to describe the sliding trend of nucleosomes. Because of our previous study has found that multimodal of 8-mer spectrum is only closely related to the amount of CG dinucleotide, we paid more attention on CG dinucleotide. Therefore, we can't yet conclude that CG determines nucleosome sliding. The potential energy of sequences reveals the nucleosome sliding mechanism. The sliding trend of −1 and +1 nucleosomes is mainly determined by the length of NFR. The longer the NFR is, the weaker the trend will be. For middle and low expression genes, the higher expression level genes have a stronger sliding trend of −1 nucleosome. For high expression level genes, it only needs the strong sliding trend of +1 nucleosome to expose TSS.

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Conflict of interest. The authors declare no competing financial interests.

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Figure 4. The CG0 CP distributions and fit lines of −1 and +1 nucleosome sequences in NFR genes with different expression levels. The blue line represents nucleosomes in low expression level genes. The red line represents nucleosomes in middle expression level genes. The green line represents nucleosomes in high expression level genes. k value represents the slope of the fit line. A. and B. The CG0 CP distributions of −1 and +1 nucleosome sequences. C. and D. The fit lines of CP distribution curves. For abbreviations, see Fig. 2. (See online version for color figure.)
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