

## Sequence analysis

# Prediction of nucleosome positioning by the incorporation of frequencies and distributions of three different nucleotide segment lengths into a general pseudo k-tuple nucleotide composition

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Associate Editor: Dr. John Hancock

## Abstract

**Motivation:** Nucleosome positioning plays important roles in many eukaryotic intranuclear processes, such as transcriptional regulation and chromatin structure formation. The investigations of nucleosome positioning rules provide a deeper understanding of these intracellular processes.

**Results:** Nucleosome positioning prediction was performed using a model consisting of 3 types of variables characterizing a DNA sequence—the number of 5-nucleotide sequences, the number of 3-nucleotide combinations in 1 period of a helix, and mono- and di-nucleotide distributions in DNA fragments. Using recently proposed stringent benchmark datasets with low biases for *Saccharomyces cerevisiae*, *Homo sapiens*, *Caenorhabditis elegans*, and *Drosophila melanogaster*, the present model was shown to have a better prediction performance than the recently proposed predictors. This model was able to display the common and organism-dependent factors that affect nucleosome forming and inhibiting sequences as well. Therefore, the predictors developed here can accurately predict nucleosome positioning and help determine the key factors influencing this process.

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**Supplementary information:** Supplementary data are available at *Bioinformatics* online.

## 1 Introduction

Nucleosomes are the basic units of eukaryotic chromatin, and each one is formed by 147 DNA base pair (bp) sequences wrapped tightly around a histone octamer. The precise nucleosome formation and its inhibitory effects on promoters (Tirosh et al., 2008; Choi et al., 2009; Jiang et al., 2009), enhancers (McPherson et al., 1996; He et al., 2010; Andreu-Vieyra et al., 2011; Maston et al., 2012), and insulators (Bi et al., 2004; Takagi et al., 2012) play crucial roles in the precise regulation of transcription (West et al., 2014). The precise nucleosome positioning

facilitates DNA replication, DNA repair, and RNA splicing (Yasuda et al., 2005; Schwartz et al., 2009; Berbenetz et al., 2010; Chen et al., 2010; Chen et al., 2014a). Therefore, the elucidation of nucleosome positioning steps may allow an in-depth understanding of various biological processes.

Recently, high-resolution genome-wide nucleosome maps were obtained for several model organisms (Segal et al., 2006; Lee et al., 2007; Schones et al., 2008; Mavrich et al., 2008a; Mavrich et al., 2008b). In contrast to this, the determinant factors of the nucleosome positioning remained unclear. However, with the increase in the availability of high-quality experimental datasets, various computational

methods and tools for the prediction of nucleosome positioning were proposed (reviewed in Teif, 2015), providing valuable insights and allowing the mechanisms determining nucleosome positioning to be unveiled. Furthermore, the construction of the accurate predictors can lead to the possibility of the analysis of single nucleotide polymorphism (SNP) and gene mutation effects on this process.

Many of these predictors were constructed based on the information about the frequencies and distributions of the combinations of polynucleotide sequences as feature vectors (Segal et al., 2006; Ioshikhes et al., 2006; Kaplan et al., 2009; Field et al., 2008; Peckham et al., 2007; Ogawa et al., 2010; Zhang et al., 2012; Yi et al., 2012; Struhl et al., 2013). Sequence-dependent mechanical properties, such as sequence-dependent geometry and DNA fragment flexibility, were also considered for the characterization of nucleosome forming and inhibiting sequences (Goñi et al., 2008; Yuan et al., 2008; Tolstorukov et al., 2008; Nikolaou et al., 2010; Stolz et al., 2010; Chen et al., 2012a; Guo et al., 2014; Freeman et al., 2014; Isami et al., 2015; Chen et al., 2015; Tahir et al., 2016). Furthermore, a powerful web-server called Pse-in-One (Liu et al., 2015a) was developed, where all existing feature vectors for DNA/RNA and protein/peptide sequences can be generated (see references cited in Chen et al., 2015), together with the generation of the feature vectors for the sequences defined by users themselves.

For human (*Homo sapiens*), worm (*Caenorhabditis elegans*), and fly (*Drosophila melanogaster*) genomes, Guo et al. (Guo et al., 2014) constructed the stringent benchmark datasets of nucleosome forming and inhibiting sequences with low similarities, in order to examine the performance of nucleosome position predictors. Additionally, predictors iNuc-PseKNC and iNuc-PseSTNC (we call iNuc-Pse predictors) were proposed, and they were shown to have better success rates in the prediction of nucleosome positioning than any of the previously developed predictors (Guo et al., 2014; Tahir et al., 2016). Furthermore, for yeast (*Saccharomyces cerevisiae*) genomes, Chen et al. (Chen et al., 2015) constructed a stringent benchmark dataset using the same methodology as Guo et al. (Guo et al., 2014), and predicted the nucleosome positioning in yeast genome based on the deformation energies of DNA fragments.

In order for iNuc-Pse predictors to show the best prediction performance for nucleosome positioning in different organisms, different sets of parameter values must be used (Guo et al., 2014; Tahir et al., 2016). The sequence predicted as the nucleosome forming sequence in one organism may be predicted as the nucleosome inhibiting sequence in another organism. This shows that the function of any given DNA sequence in assisting or inhibiting nucleosome formation depends on the investigated organism. However, no key factors and criteria affecting this process could be elucidated using this predictor, because iNuc-Pse predictors are based on Support Vector Machine (SVM). Additionally, based on these datasets, some common short motif nucleosome forming and inhibiting sequences were found (Giancarlo et al., 2015). However, the nucleosome positioning cannot be predicted sufficiently well using only these motives.

In this study, a novel nucleosome positioning predictor was developed based on the linear regression model, consisting of 3 types of variables with different fragment length scales—the number of 5-nucleotide sequences, the number of 3-nucleotide combinations in 1 period of helix, and mono- and di-nucleotides distributions in whole DNA fragments. This predictor exhibited better prediction performance than the recently developed iNuc-Pse predictors for the same benchmark datasets of human and fly genomes and displayed common and organism-dependent key factors of nucleosome positioning explicitly.

A series of recent publications (Lin et al., 2014; Qiu et al., 2014; Liu et al., 2016; Xiao et al., 2015; Jia et al., 2015; Jia et al., 2016; Qiu et al., 2016a) demonstrated, in compliance with Chou's 5-step rule (Chou, 2011), that, in order to establish a useful sequence-based statistical predictor for a biological system, the following five guidelines should be observed: (a) how to construct or select a valid benchmark dataset to train and test the predictor; (b) how to represent the biological sequence samples by catching their key features associated with the target to be predicted; (c) how to introduce or develop a powerful algorithm to operate the prediction; (d) how to properly perform cross-validation tests to objectively evaluate the anticipated accuracy; and (e) how to establish a user-friendly web-server for the predictor that is accessible to the public. Below, these steps are further explained.

## 2 MATERIAL AND METHODS

### 2.1 Benchmark datasets of nucleosome forming and inhibiting sequences

The stringent benchmark datasets of nucleosome forming and inhibiting sequences with low biases constructed by Guo et al. (Guo et al., 2014) and Chen et al. (Chen et al., 2015) were used for the evaluation of the performance of the proposed predictor. These datasets involved human (*H. sapiens*: 2273 forming sequences and 2300 inhibiting sequences of 147 bp), worm (*C. elegans*: 2567 forming sequences and 2608 inhibiting sequences of 147 bp), fly (*D. melanogaster*: 2900 forming sequences and 2850 inhibiting sequences of 147 bp) (Guo et al., 2014), and yeast (*S. cerevisiae*: 1880 forming sequences and 1740 inhibiting sequences of 150 bp) (Chen et al., 2015).

In these datasets, none of the sequences has > 80% pairwise sequence identity with any other sequence. Note that the benchmark datasets used in previous studies were expected to contain many redundant, highly similar sequences, and these biased datasets lacked statistical representativeness (Chou, 2011), and the predictors may have yielded misleading results if trained and tested using these biased datasets. Therefore, only the low-biased datasets, proposed by Guo et al. (Guo et al., 2014) and Chen et al. (Chen et al., 2015) were employed in this study.

### 2.2 Model predicting nucleosome positioning 1: 3-length scales model

In order to predict whether a given 147-bp DNA sequence of human, worm, and fly genomes is involved in the formation or the inhibition of formation of nucleosome, the model included 3 types of variables: i) the number of 5-nucleotide sequences, ii) the number of 3-nucleotide combinations in one period of a double helix, and iii) mono- and di-nucleotide distributions in DNA fragments. The model was named 3 length scales (3LS), and it belongs to a class of general PseKNC based predictors (Guo et al., 2014; Liu et al., 2015a).

The model is described by the following equations:

$$Q_{seq} = Q_0 + \sum_i \{ M(i | A \text{ or } T) S_{seq}^1(i | A \text{ or } T) + \sum_{Di} D(i | Di-seq \text{ or } Di-seq^*) S_{seq}^2(i | Di-seq \text{ or } Di-seq^*) \} + \sum_{Tri} \sum_{0 < j < k < 11} T(0, j, k, = 3-nuc \text{ or } 0, k-j, k, = 3-nuc^*) \times S_{seq}^3(0, j, k, = 3-nuc \text{ or } 0, k-j, k, = 3-nuc^*) + \sum_{Pent} P(5-seq \text{ or } 5-seq^*) S_{seq}^5(5-seq \text{ or } 5-seq^*), \quad (1)$$

$$S_{seq}^1(i | A \text{ or } T) = \log_2(N_{seq}^1(i | A \text{ or } T) + 1), \quad (2)$$

$$S_{seq}^2(i' | Di-seq \text{ or } Di-seq^*) = \log_2(N_{seq}^2(i' | Di-seq \text{ or } Di-seq^*) + 1), \quad (3)$$

$$S_{seq}^3(0, j, k, = 3-nuc \text{ or } 0, k-j, k, = 3-nuc^*) = \log_2(N_{seq}^3(0, j, k, = 3-nuc \text{ or } 0, k-j, k, = 3-nuc^*) + 1), \quad (4)$$

and

$$S_{\text{seq}}^5(5\text{-seq or } 5\text{-seq}^*) = \log_2(N_{\text{seq}}^5(5\text{-seq or } 5\text{-seq}^*) + 1). \quad (5)$$

Here,  $Q_{\text{seq}}$  is defined as a value of a given sequence, and when  $Q > Q_c = 0.5$ , this sequence was considered a nucleosome forming sequence, while it was predicted as an inhibiting sequence otherwise.  $N_{\text{seq}}^1$ ,  $N_{\text{seq}}^2$ ,  $N_{\text{seq}}^3$ , and  $N_{\text{seq}}^5$  are defined as follows:

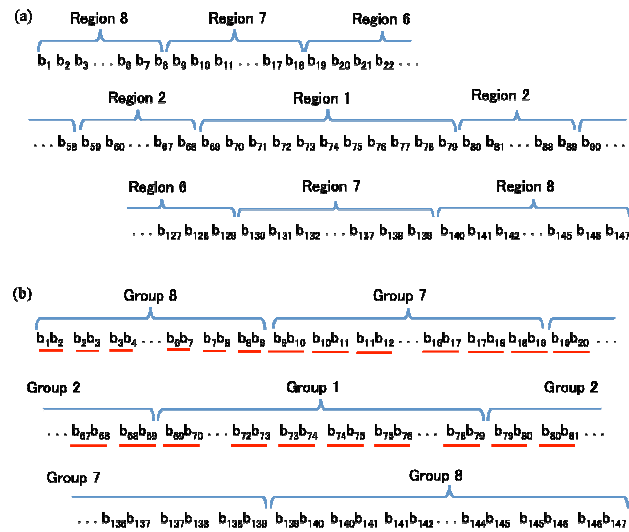
$N_{\text{seq}}^1(i' | A \text{ or } T)$  defines the number of adenine (A) or thymine (T) nucleotides in  $i$ -th region of the given DNA sequence. Here, region 1 occupies the central 11 bp fragment of the given 147-bp DNA, the regions for  $1 < i < 8$  occupy 2 10-bp fragments (20 bp) at  $(i-1)$ -th nearest neighbor of first region, and 8-th region occupies the remaining 16-bp fragment (Fig. 1(a)).

$N_{\text{seq}}^2(i' | \text{Di-seq or Di-seq}^*)$  defines the sum of the number of each type of successive dinucleotide sequence and its complementary sequence, named Di-seq and Di-seq<sup>\*</sup>, in the  $i'$ -th group of the dinucleotide series of a given DNA sequence. Here, first group consists of 10 dinucleotides at the central region of a given 146-dinucleotide series,  $i'$ -th groups for  $1 < i' < 8$  consist of 20 dinucleotides between  $(5 \pm (10 \times (i'-2) + 1))$ -th to  $(5 \pm 10 \times (i'-1))$ -th dinucleotide from the center of a given 146 dinucleotide series, and 8-th group contains the remaining 16 dinucleotides (Fig. 1(b)).

$N_{\text{seq}}^3(0, j, k, = 3\text{-nuc or } 0, k - j, k, = 3\text{-nuc}^*)$  defines the sum of the number of each type of combination of 3-nucleotide set (3-nuc) that consists of a nucleotide, the second nucleotide located downstream at the distance  $j$ , and the third nucleotide located at the distance  $k$  in downstream sequence ( $j < k$ ), together with the number of the complementary nucleotide combinations (3-nuc<sup>\*</sup>) in the given DNA sequence. Here,  $5 < k < 11$  cases were considered.

$N_{\text{seq}}^5(5\text{-seq or } 5\text{-seq}^*)$  defines the sum of the number of each type of successive 5-nucleotide sequence (5-seq) and that of the complementary sequence (5-seq<sup>\*</sup>) in the given DNA sequence.

The coefficients  $M()$ ,  $D()$ ,  $T()$ , and  $P()$  provide the weight of the contributions of  $S_{\text{seq}}^1()$ ,  $S_{\text{seq}}^2()$ ,  $S_{\text{seq}}^3()$ , and  $S_{\text{seq}}^5()$  to  $Q_{\text{seq}}$  and  $Q_0$  as a constant value. They are organism-dependent values, which reveal the common and organism-specific characteristics of nucleosome forming and inhibiting sequences.



**Figure 1.** Nucleotide regions and groups analyzed in each 147-bp DNA sequence. (a) Each nucleotide belongs to a specific region. (b) Each dinucleotide pair belongs to a specific group.  $b_n$  indicates the  $n$ -th base of nucleotide, and dinucleotide pairs are underlined red.

### 2.3 Variable selection in 3LS model

In order to obtain high prediction performances, the 3LS model should contain only the appropriate variables of  $S_{\text{seq}}^1()$ ,  $S_{\text{seq}}^2()$ ,  $S_{\text{seq}}^3()$ , and  $S_{\text{seq}}^5()$ . The coefficients  $M()$ ,  $D()$ ,  $T()$ , and  $P()$  of the appropriate variables should be given as finite values, while the values of redundant variables should be given as zero. The appropriate variables were chosen by the stepwise forward selection method (Efroymson, 1960). Here, in order to avoid multicollinearity (Farrar et al., 1967), the variance inflation factors of all chosen variables were kept below 10 (10.5 for fly genomes, since the prediction performance of the model increased drastically in comparison with the case when 10.0 was used) (O'Brien, 2007). The model consists of the linear combination of  $S_{\text{seq}}^1()$ ,  $S_{\text{seq}}^2()$ ,  $S_{\text{seq}}^3()$ , and  $S_{\text{seq}}^5()$ , instead of that of  $N_{\text{seq}}^1()$ ,  $N_{\text{seq}}^2()$ ,  $N_{\text{seq}}^3()$ , and  $N_{\text{seq}}^5()$ , since this allows a better prediction performance.

### 2.4 Model predicting nucleosome positioning 2: Tri-nucleotide sequence model

For the prediction of nucleosome positioning, a simpler model than 3LS, named Tri-nucleotide sequence (TNS) model was introduced:

$$Q_{\text{seq}} = Q_0 + \sum_{\text{tri}} R(3\text{-seq or } 3\text{-seq}^*) N_{\text{seq}}^T(3\text{-seq or } 3\text{-seq}^*),$$

where  $N_{\text{seq}}^T(3\text{-seq or } 3\text{-seq}^*)$  is defined by the sum of the number of each type of successive 3-nucleotide sequence and that of the complementary sequence in a given DNA sequence. The coefficient  $R()$  provide the weight of the contributions of  $N_{\text{seq}}^T()$  to  $Q_{\text{seq}}$  and  $Q_0$  as a constant value. This simple model allows a very high accuracy of the nucleosome positioning prediction for yeast genome.

### 2.5 Evaluations of the quality of prediction

The prediction quality of the present model was evaluated using the jackknife test (Lachenbruch et al., 1968) and Relative Operating Characteristic (ROC) curve. These methods were generally employed for the evaluation of the quality of several previously developed predictors (Chen et al., 2012b; Chen et al., 2013; Chen and Li, 2013; Chou et al., 2012; Esmaeili et al., 2010; Gupta et al., 2013; Mei, 2012; Mohabatkari et al., 2012; Mohabatkari et al., 2013) and iNuc-Pse predictors (Guo et al., 2014; Tahir et al., 2016).

Here,  $N^+$ ,  $N^-$ ,  $N^+$ , and  $N^-$  were defined as the total number of nucleosome forming sequences, nucleosome inhibiting sequences, nucleosome forming sequences incorrectly predicted as nucleosome inhibiting sequences, and nucleosome inhibiting sequences incorrectly predicted as nucleosome forming sequences. Using the jackknife test, the following metrics were obtained:

$$Sn = 1 - N^+/N^+$$

$$Sp = 1 - N^-/N^-$$

$$Acc = 1 - (N^+ + N^-)/(N^+ + N^-)$$

$$MCC = \{1 - (N^+/N^+ + N^-/N^-)\} / \{(1 + (N^+ - N^-)/N^+)(1 + (N^- - N^-)/N^-)\}^{1/2}$$

where  $Sn$ ,  $Sp$ ,  $Acc$ , and  $MCC$  stand for sensitivity, specificity, accuracy, and Mathew's correlation coefficient, respectively. Note that  $Sn$  and  $(1 - Sp)$  represent true positive rate (TPR) and false positive rate (FPR), respectively. The conventional formulations of the four metrics are not quite intuitive and it may be difficult for many experimental scientists to understand them, particularly  $MCC$ . Fortunately, the more intuitive expressions, presented in this paper, can be derived using the symbols

defined in a signal peptide study (Chou, 2001), and elaborated in other studies (Chen et al., 2013; Xu et al., 2013).

The ROC curve can be obtained as the trajectory of TPR-FPR two-dimensional surface for the change in  $Q_c$ . The area surrounded by TPR = 0, FPR = 0, and ROC curve, called AUROC, was used to estimate the performances of predictors, where AUROC = 0.5 is equivalent to a random prediction, and AUROC = 1 indicates perfect prediction.

Note that the following three cross-validation methods are often used to examine the effectiveness of a predictor in practical applications: independent dataset test, subsampling test, and jackknife test (Chou et al., 1995). However, of the three, the jackknife test is deemed the least arbitrary one (most objective) that can always yield a unique result for a given benchmark dataset (Chou, 2011), and therefore, it has been increasingly used for the investigations of the accuracy of various predictors (e.g., Dehzangi et al., 2015; Kabir et al., 2016; and references cited in Chou, 2011). Accordingly, the jackknife test was also adopted here for the examination of the quality of the present predictor.

## 2.6 Construction of nucleosome positioning predictor

Based on the 3LS and TNS models, the nucleosome positioning predictors for each organism were constructed. The predictors for human, worm, and fly genomes were assumed to consist of the appropriately chosen variables. The coefficients of these chosen variables were determined by the multiple regression analysis, using benchmark datasets for each organism, and the explanatory variables were given by the chosen  $S^1_{seq}()$ ,  $S^2_{seq}()$ ,  $S^3_{seq}()$ , and  $S^5_{seq}()$  for 3LS model, and  $N^T_{seq}()$  for TNS model, and the objective variables were given as 1 for nucleosome forming sequences and 0 otherwise.

# 3 RESULTS

## 3.1 Variable selection for 3LS model using human, worm, and fly sequences

Variables  $S^1_{seq}()$ ,  $S^2_{seq}()$ ,  $S^3_{seq}()$ , and  $S^5_{seq}()$ , involved in the construction of the nucleosome positioning predictors in 3LS model were chosen by stepwise forward selection method. Here, 403, 392, and 325 variables were chosen for human, worm, and fly genomes, respectively (Supplementary Table S1).

**Table 1.** The prediction quality of 3LS model-based predictor measured using jackknife tests. Values in brackets are those obtained using iNuc-PseKNC<sup>(a)</sup> and iNuc-PseSTNC<sup>(b)</sup>

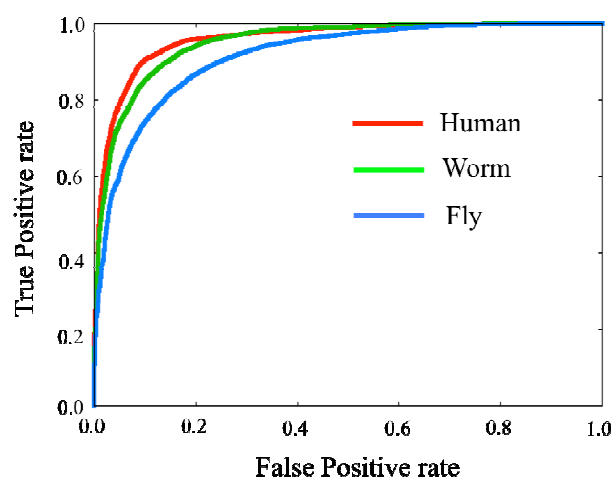
	Human	Worm	Fly
ACC	0.9001 (0.8627 <sup>a</sup> , 0.8760 <sup>b</sup> )	0.8786 (0.8690 <sup>a</sup> , 0.8862 <sup>b</sup> )	0.8341 (0.7997 <sup>a</sup> , 0.8167 <sup>b</sup> )
Sn	0.9169 (0.8786 <sup>a</sup> , 0.8931 <sup>b</sup> )	0.8654 (0.9030 <sup>a</sup> , 0.9162 <sup>b</sup> )	0.8407 (0.7831 <sup>a</sup> , 0.7976 <sup>b</sup> )
Sp	0.8835 (0.8470 <sup>a</sup> , 0.8591 <sup>b</sup> )	0.8921 (0.8355 <sup>a</sup> , 0.8666 <sup>b</sup> )	0.8274 (0.8165 <sup>a</sup> , 0.8361 <sup>b</sup> )
MCC	0.8006 (0.73 <sup>a</sup> , 0.75 <sup>b</sup> )	0.7576 (0.74 <sup>a</sup> , 0.77 <sup>b</sup> )	0.6682 (0.60 <sup>a</sup> , 0.63 <sup>b</sup> )

\* Sn, sensitivity; Sp, specificity; Acc, accuracy; MCC, Mathew's correlation coefficient.

## 3.2 Prediction quality for human, worm, and fly genomes

Using the jackknife cross-validation tests, Sn, Sp, ACC, and MCC of 3LS model based predictor were evaluated for human, worm, and fly genome benchmark datasets (Table 1). The obtained ACCs of the investigated predictor for these datasets ( $\approx 0.9001$ ,  $\approx 0.8786$ , and  $\approx$

$0.8341$ , respectively) were shown to be higher than those obtained by iNuc-PseKNC (Guo et al., 2014) for all organisms, and higher than those obtained by iNuc-PseSTNC (Tahir et al., 2016) for human and fly genomes. The higher AUROC values were obtained as well ( $\approx 0.9588$ ,  $\approx 0.9505$ , and  $\approx 0.9147$  for human, worm, and fly datasets, respectively), compared with those obtained by iNuc-PseKNC ( $\approx 0.925$ ,  $\approx 0.935$ , and  $\approx 0.874$ ) (Guo et al., 2014) (Fig. 2). Thus, we expected that 3LS model-based predictor with appropriate coefficients (Supplementary Table S2(a)) can predict the nucleosome positioning more accurately than the recent iNuc-Pse predictors for human and fly genomes.



**Figure 2.** ROC curves obtained with the jackknife tests using human, worm, and fly genome datasets.

## 3.3 TNS model for yeast genome

The quality of TNS model-based predictor was expected to be lower than that of 3LS model based. ACCs of TNS model were shown to be  $\approx 0.8167$ ,  $\approx 0.8394$ , and  $\approx 0.7082$  for human, worm, and fly genomes, respectively. However, TNS model based predictor exhibited perfect nucleosome positioning prediction (ACC = 1.0) for the benchmark yeast genome dataset, presented in Chen *et al.* (Chen et al., 2015). For the same benchmark dataset, the predictor based on DNA deformation energy (Chen et al., 2015) had ACC of  $\approx 0.981$ . Moreover, we confirmed that the predictor based on the nearest neighbor algorithm (Yi et al., 2012) had ACC of  $\approx 0.9906$  for the same benchmark dataset. These predictors can perform sufficiently well in predicting nucleosome positioning for yeast genome. However, we expected that TNS model-based predictor with appropriate coefficients (Supplementary Table S2(b)) is able to predict the nucleosome positioning more precisely than these recent predictors.

# 4 DISCUSSION

3LS model-based predictor can predict nucleosome positioning in human and fly genomes more accurately than the recently proposed nucleosome position predictors can. Additionally, the predictor defined here can display the details of organism-dependent key factors for the determination of nucleosome forming and inhibiting sequences.

The chosen  $S^1_{seq}()$ ,  $S^2_{seq}()$ ,  $S^3_{seq}()$ , and  $S^5_{seq}()$  in 3LS model differed greatly between human, worm, and fly genomes (Supplementary Table S1). This indicates there are many organism-dependent differences in the features contributing to the nucleosome formation. The coefficients of these variables,  $M()$ ,  $D()$ ,  $T()$ , and  $P()$ , and constant value  $Q_0$ ,

obtained by multiple regression analysis, clearly showed organism-dependent specificities (Supplementary Table S2). These differences are presented in the following examples:

I) In 3LS models of these genomes that contained common variables, their coefficients' signs often differed between the organisms.

II) There were only 6 variables with the same signs of their coefficients between these organisms, and these were:

$T(0, 1, 6, = CTT \text{ or } 0, 5, 6, = AAG) > 0$ ,

$T(0, 1, 10, = TTG \text{ or } 0, 9, 10, = CAA) > 0$ ,

$P(TTTTT \text{ or } AAAAA) < 0$ ,

$P(GCTTC \text{ or } GAAGC) > 0$ ,

$P(GTGTC \text{ or } GACAC) > 0$ , and

$P(GGATC \text{ or } GATCC) > 0$

Poly(dA-dT) sequences, such as AAAAA sequence, are known as physically rigid sequences (Nelson et al., 1987; Brunkner et al., 1995; Packer et al., 2000). Therefore, the sequences containing these motives inhibit the nucleosome formation in the genomes of several organisms, which was confirmed by experimental evidence and the use of different nucleosome positioning predictors (Kunkel et al., 1981; Bi et al., 2004; Yi et al., 2012; Giancarlo et al., 2015), which is consistent with the results presented here. The sequences with high GC content were reported to have a nucleosome-forming tendency (Tillo et al., 2009). However, considering the results of the recent studies, 30-50% nucleotides found in the nucleosome forming sequences are A or T nucleotides located at the appropriate positions (Satchwell et al., 1986; Ohshima 2001; Ioshikhes et al., 2006; Segal et al., 2006; Ogawa et al., 2010; Giancarlo et al., 2015), which seems to agree with the results obtained in this study.

III) When only the 6 variables described above were chosen in 3LS model based predictor, ACCs for human, worm, and fly genomes were  $ACC \approx 0.7525$ ,  $\approx 0.7716$ , and  $0.6438$ , respectively, which is much lower than the values obtained using the model with suitable variables. However, even when these variables were removed from the 3LS model based predictor with suitable variables, the decrease in ACCs for human, worm, and fly genomes was not considerable, and the obtained ACC values were  $\approx 0.8974$ ,  $\approx 0.8730$ , and  $\approx 0.8290$ , respectively. This indicates that the organism-specific sequence patterns dominantly contribute to the determination of nucleosome forming abilities.

IV) The weight of the contribution of the set  $S^3_{seq}(0, j, k, = 3\text{-nuc or } 0, k - j, k, = 3\text{-nuc}^*)$  for each  $k$  is defined as  $W_k = [\text{Number of chosen } S^3_{seq}(0, j, k, = 3\text{-nuc or } 0, k - j, k, = 3\text{-nuc}^*)] / [\text{Number of chosen variables}]$  (Table 2). The obtained  $W_k$  values were different for different organisms, for example  $W_5 \sim 0.074$ ,  $0.112$ ,  $0.080$  ( $k = 5$  as the smallest  $k$ ) and  $W_{10} \sim 0.159$ ,  $0.115$ ,  $0.151$  ( $k = 10$  as the largest  $k$ ) were obtained for human, worm, and fly genomes, respectively. This indicates that the length scale of nucleotide combinations required for the characterization of nucleosome forming sequences depends on the organism analyzed.

V) The weight of the contribution of the set  $S^2_{seq}(i' | \text{Di-seq or Di-seq}^*)$  near and far from the center of sequence (dyad position) was defined as  $W_{near} = [\text{Number of chosen } S^2_{seq}(i' = 1 \sim 5 | \text{Di-seq or Di-seq}^*)] / [\text{Number of chosen variables}]$  and  $W_{far} = [\text{Number of chosen } S^2_{seq}(i' = 6 \sim 8 | \text{Di-seq or Di-seq}^*)] / [\text{Number of chosen variables}]$  (Table 2).  $W_{near}$  values were similar values in the datasets for the 3 investigated organisms. The values of  $W_{far}$ ,  $\approx 0.027$ ,  $0.015$ , and  $0.006$ , were obtained for human, worm, and fly genomes, respectively, where  $W_{far}$  for fly was shown to be  $\sim 1/2$  of that for worm and  $\sim 1/4$  for human. This suggests that the contribution of the sequences far from the dyad position to the nucleosome formation depends on the organism type.

Using the TNS model-based predictor, the obtained ACC values of nucleosome position predictions for human, worm, and fly genomes

were much lower than those obtained using 3LS model-based predictor. while  $ACC = 1$  was obtained for yeast genome. This clearly demonstrates organism-dependent characteristics of nucleosome forming and inhibiting sequences, showing that the nucleosome positioning is much more easily predicted in yeast than in higher organisms.

**Table 2.** Weights of the contributions of  $S^3_{seq}(0, j, k, = 3\text{-nuc or } 0, k - j, k, = 3\text{-nuc}^*)$  for each  $k$  ( $W_k$ ) and  $S^2_{seq}(i' | \text{Di-seq or Di-seq}^*)$  for the positions near and far from the dyad position ( $W_{near}$  and  $W_{far}$ ).

	Human	Worm	Fly
$W_5$	0.074441687	0.112244898	0.08
$W_6$	0.094292804	0.068877551	0.089230769
$W_7$	0.069478908	0.073979592	0.098461538
$W_8$	0.11662531	0.114795918	0.083076923
$W_9$	0.1191067	0.135204082	0.12
$W_{10}$	0.158808933	0.114795918	0.150769231
$W_{near}$	0.027295285	0.025510204	0.027692308
$W_{far}$	0.027295285	0.015306122	0.006153846

The predictors developed here can predict nucleosome positioning in human, fly, and yeast genomes with higher accuracy than the recently proposed predictors and can determine the key factors influencing this positioning in human, worm, fly, and yeast genomes. In contrast to the recently proposed iNuc-Pse predictors, 3LS model-based predictor developed in this study is based on the following sequence properties as well: i) Combinations of nucleotides located further away than those considered by iNuc-Pse predictors; ii) More detailed distributions of A, T, and dinucleotide sequences in a DNA fragment than those in iNuc-Pse predictors. These properties most likely contribute to the exhibited improved performance of the predictor proposed here in comparison with the iNuc-Pse predictors.

However, the variable selections and the formalization of the model can be improved, and further modifications are needed for this predictor to perform better than the recent ones. Recent studies suggested that sequence-dependent geometry and flexibility of each DNA fragment may play important roles in the determination of its nucleosome forming ability (Goñi et al., 2008; Yuan et al., 2008; Tolstorukov et al., 2008; Nikolaou et al., 2010; Stolz et al., 2010; Chen et al., 2012a; Guo et al., 2014; Freeman et al., 2014; Chen et al., 2015; Isami et al., 2015). Furthermore, the nucleosome forming ability of each sequence may change with intracellular and environmental conditions (McPherson et al., 1996; He et al., 2010; Andreu-Vieyra et al., 2011; Maston et al., 2012; Zhang et al., 2012; Struhl et al., 2013). Because of this, the predictors should be modified in the future by considering these physical and chemical influences.

Additionally, as demonstrated in a series of recent publications (e.g., Chen et al., 2014b; Lin et al., 2014; Jia et al., 2015; Liu et al., 2015b; Chen et al., 2016; Qiu et al., 2016b), during the development of new prediction methods, user-friendly and publicly accessible web-servers can significantly enhance the impacts of these tools (Chou, 2015). Therefore, the future efforts will include providing a web-server for the use of the prediction method presented here.

## Acknowledgements

The author is grateful to N. Sakamoto, S. Isami, T. Kameda, H. Nishimori, H. Yanagihara, and H. Wakaki for their fruitful discussion.



## Funding

This work was partially supported by the Japan Agency for Medical Research and Development (AMED); and the Grant-in-Aid for Scientific Research on Innovative Areas “Initiative for High-Dimensional Data-Driven Science through Deepening of Sparse Modeling” [grant numbers 4503, 26120525] of MEXT of Japan.

*Conflict of Interest:* None declared.

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