A Fast Algorithm for Exonic Regions Prediction in DNA Sequences

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A B S T R A C T

The main purpose of this paper is to introduce a fast method for gene prediction in DNA sequences based on the period-3 property in exons. First, the symbolic DNA sequences were converted to digital signal using the electron ion interaction potential method. Then, to reduce the effect of background noise in the period-3 spectrum, we used the discrete wavelet transform at three levels and applied it on the input digital signal. Finally, the Goertzel algorithm was used to extract period-3 components in the filtered DNA sequence. The proposed algorithm leads to decrease the computational complexity and hence, increases the speed of the process. Detection of small size exons in DNA sequences, exactly, is another advantage of the algorithm. The proposed algorithm ability in exon prediction was compared with several existing methods at the nucleotide level using: (i) specificity - sensitivity values; (ii) receiver operating curves (ROC); and (iii) area under ROC curve. Simulation results confirmed that the proposed method can be used as a promising tool for exon prediction in DNA sequences.

Key words: Algorithm, DNA sequence, discrete wavelet transform, Exon, Goertzel, protein coding region, signal processing

INTRODUCTION

Deoxyribonucleic Acid (DNA) is of the most important chemical compounds in living cells, bacteria, and some viruses. It is composed of four types of different nucleotides, namely adenine (A), cytosine (C), guanine (G), and thymine (T). However, only some specific areas of the DNA molecule, which called as genes, carry the coding information for protein synthesis. In eukaryotic cells, the DNA is divided into genes and inter-genic spaces. Genes are further divided into exon and intron, which is shown in Figure 1. Genes are responsible for protein synthesis; therefore, they are called protein-coding regions because they carry the necessary information for protein coding. Protein-coding regions exhibit a period-3 behavior due to the codon bias involved in the translation process. This phenomenon caused background noise, which leads to more difficult of exon finding in DNA sequences.

Nowadays, there are many digital signal processing (DSP) methods presented in literatures to identify the protein coding regions and also reduce the background noise in DNA sequences, which are based on Fourier spectral. In Tiwari et al.[8] Fourier transform is used for this purpose. In this way, a fixed-length window is selected and moved on the numerical sequence. Then, the exonic regions are determined by calculating the power spectrum. In our previous work,[9] the notch filter with the central frequency of 2π/3 was used in order to remove the background noise. First, the DNA sequence is passed through a notch filter and then a sliding windowed discrete Fourier transform (DFT) is applied on the filtered sequence. In Saberkari et al.[10] a windowless technique based on the Z-curve was implemented to identify gene islands in total DNA sequence which called cumulative GC-Profile method. The main characteristic of this method is that the resolution of the algorithm output in displaying the genomic GC content is high since no sliding window is used, but the computational complexity of this method is also high. In Deng et al.[11] an appropriate method is proposed to predict the protein regions by combining the DFT and continues wavelet transform (CWT). CWT leads to eliminate the high frequency noise and, therefore, improves the accuracy of the prediction. In Datta et al.[12] a new algorithm is proposed based on Fourier transform using Bartlett window to suppress the non-exonic regions. In Akhtar et al.[13] the time domain algorithms have been used to determine the coding regions in DNA sequences. Adaptive filters[14] are one of the best tools for prediction tasks. In Baoshan et al.[15,16] two adaptive filtering approaches based on Kalman filter and least mean squares (LMS) are proposed for human gene identification. However, the major problem with LMS is that...
the convergence behavior of the algorithm is slow, which leads to high computational complexity. A parametric method based on autoregressive (AR) model proposed in Chakravarthy et al.,[17] for spectral estimation. The AR model has the advantage over the DFT that it works with smaller window sizes and, thus, shorter sequences.

In this paper, a fast method based on DWT and Goertzel algorithm is proposed to determine the location of exons in DNA sequences. The proposed algorithm improves the accuracy of the prediction, especially in detection of the small size exons. The rest of the paper is organized as follows: Section II describes the proposed algorithm in details. The evaluation criteria at nucleonic level are expressed in Section III. Section IV shows simulation results using Genbank database. Finally, Section V concludes the experiments and algorithms.

THE PROPOSED ALGORITHM

Figure 2 shows block diagram of the proposed algorithm to identify protein coding regions. The main steps of the algorithm are as follows that will be discussed in more details in this section.

- Numerical mapping of DNA sequence using EIIP method,
- Using DWT to remove the noise from the numerical sequence,
- Choosing Blackman window with the length 351 and sliding it on the filtered sequence, and
- Using Goertzel algorithm to extract the period-3 components.

DNA Numerical Representation

Converting the DNA sequences into digital signals[18,19] opens the possibility to apply signal processing methods for analyzing genomic data and reveals features of chromosomes. The genomic signal approach has already proven its potential in revealing large scale features of DNA sequences maintained over distance of 10^6-10^8 base pairs, including both coding and non-coding regions, at the scale of whole genomes or chromosomes.[20-22]
EIIP\cite{24}. In VOSS technique, the background noise is more dominant because the magnitude for each base is the same (i.e. 1 represents the presence of the nucleotide and 0 for its absence). The Z-curve technique is a 3-D curve for representing the DNA sequence. In this method, the dimension is reduced by projecting each 3-D curve into x-y axes, which leads to more computational complexity. In this paper, we have used EIIP method to convert DNA sequence into numerical signal. This approach allows DNA representations with either one or four sequence (s). It can be noticed that the EIIP representation has a different magnitude for each base and the distances among them are unequal. In this method, the electron-ion-interaction potential associated with each nucleotide is used for mapping of the DNA sequence. The EIIP values for the nucleotides are: A = 0.1260, G = 0.0806, T = 0.1335, C = 0.1340\cite{24}.

**Using Discrete Wavelet Transform to Reduce the High Frequency Noise**

In this paper, DWT is applied on the input numerical sequence to remove the high frequency noise and hence, improve the accuracy of the algorithm for exonic region identification. In DWT, the signal is passed first through the high and low pass filters, then by down-sampling the filtered signal, samples are divided into two signals; high frequency samples (detail signals) and low frequency ones (approximation signals). The DNA numerical signal, \(x[n]\), is passed first through the high pass filter, \(g[n]\), then through the low pass filter, \(h[n]\). So, we have:

\[
\begin{align*}
    s_{\text{high}}[k] &= \sum_n x[n], g[2k - n] \\
    s_{\text{low}}[k] &= \sum_n x[n], h[2k - n]
\end{align*}
\]

Figure 3 shows our user-friendly package designed to analyze DNA sequences. This tool has been designed by our research group on genomic signal processing at Sahand University of Technology, Tabriz, Iran and consists of two main parts: The graphic display and the DSP tools for analyzing the DNA sequences. The graphic display allows the user to view the structure record either as a graphic or as a text record in txt formats. Also, it can be useful to search option for special patterns in the sequences (for example, start and stop codons in DNA sequences). The DSP tools are applying to DNA sequences in order to spectral analysis.

Briefly, there are some advantages for this tool as mentioned below:

- Loading of any DNA sequences
- Genomic sequence representation
- Conversion of the genomic sequence into digital values by EIIP or binary methods
- Search option for special patterns in the sequence

Figure 4a and b show the result of applying DWT algorithm on the sequence F56F11.4. The power spectrum of the signal is smoothed by removing the high frequency components. Hence, the noise effect is decreased, which leads to improve the accuracy of identification task.

**Choosing Blackman Window and Sliding it on the Estimated Sequence**

In DNA sequence analysis, it is important to make the window size sufficiently large. In this paper, like many other researches such as Tiwari \textit{et al.}\cite{8} and Akhtar \textit{et al.}\cite{13}, we have taken the window length equal to 351. Since there are very few intron-containing genes in these sequences, open reading frames (ORFs) of length less than 300 bp are not frequently encountered. A window length in the range of 250-400 gives the similar results. The windows of length less than 250 increase the noise level resulting in unacceptable statistics, while those greater than 400 tend to miss the ORFs due to numerous overlaps\cite{8}.

In the proposed algorithm, we have employed a Blackman window to segment the filtered sequence. The Blackman window gives high weight to the codon positions residing in center of window and much less weight to the codons near the window boundaries. Hence, the noise cancelling level in Blackman window is higher than the other windows. The impulse response of the FIR windows is depicted in Figure 5. As can be seen, Blackman window has the highest amount of attenuation between the other windows. So, the background noise is more suppressed by Blackman window.

**Goertzel Algorithm**

The Goertzel algorithm is a digital signal processing technique that provides a means for efficient evaluation of individual terms of DFT, thus making it useful in
The Goertzel filter is composed of a recursive part and a non-recursive part [Figure 6]. The DFT coefficients are obtained as the output of the system after $N$ iterations which $N$ is the input signal length. The recursive part is a second-order IIR filter (resonator) with a direct form structure. The resonant frequency of the first stage filter is set at equally spaced frequency points; that is, $\omega_k = \frac{2\pi k}{N}$ (This value is chosen $\frac{2\pi}{3}$ in this work to extract the period-3 components, exactly). The second stage filter can be observed to be an FIR filter, since its calculations do not use of the previous values of the output. In fact, we only compute the recursive part of the filter at every sample update and the non-recursive part is computed only after the $N^{th}$ time instant when the Fourier coefficients are to be determined.\textsuperscript{28}

The major advantage of Goertzel algorithm is its ability to reduce the computational complexity relative to other existence methods such as DFT. This algorithm requires $N$ real multiplications and a single complex multiplication to compute a sample. However, DFT and decimation in time FFT require $N^2$ and $N \log_2 N$ complex multiplications, respectively.\textsuperscript{28}

**EVALUATION CRITERIA AT NUCLEOTIDE LEVEL**

In order to compare accuracy of the different methods for protein coding regions detection, the evaluation is done at nucleotide level. For this purpose, we introduce some parameters that are listed as follows:

**Figure 4:** Applying DWT to the numerical sequence. (a) High frequency components of level 3 DWT decomposition (detail signal). (b) Low frequency components of level 3 DWT decomposition (approximation signal)

**Figure 5:** Comparison of the different FIR windows and their frequency impulse responses

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certain practical application, such as dual-tone multi frequency (DTMF) signals,\textsuperscript{25} digital multi frequency (MF) receiver,\textsuperscript{26} and in a very small aperture terminal (VSAT) satellite communication system.\textsuperscript{27}
Sensitivity, Specificity, and Precision

These parameters are defined as follow according to [13] and [29]:

\[
S_n = \frac{TP}{TP + FN},
\]

\[
S_p = \frac{TP}{TP + FP},
\]

\[
P = \frac{TP + TN}{TP + FP + TN + FN}
\]

where true positive (TP) is the number of coding nucleotides correctly predicted as coding, false negative (FN) is the number of coding nucleotides predicted as non-coding. Similarly, true negative (TN) is the number of non-coding nucleotides correctly predicted as non-coding, and false positive (FP) is the number of non-coding nucleotides predicted as coding.

Receiver Operating Characteristic Curves

The receiver operating characteristic (ROC) curves were developed in the 1950s as a tool for evaluating prediction techniques based on their performance [30]. An ROC curve explores the effects on TP and FP as the position of an arbitrary decision threshold is varied. The ROC curve can be approximated using an exponential model as follow:

\[
y = \alpha \left( 1 - e^{-\beta_1 \sqrt{x} + \beta_2 x} \right) \]

(3)

where \( \alpha, \beta_1, \) and \( \beta_2 \) can be determined by minimizing the error function:

\[
E(p) = \sum_{i=1}^{N} \left[ \alpha - \left( 1 - e^{-\beta_1 \sqrt{x_i} + \beta_2 x_i} \right) - y_i \right]^2
\]

(4)

where \( p = [\alpha, \beta_1, \beta_2] \) and \( \{x_i, y_i\} \) are points in the ROC plane.

Area Under the ROC Curve

This parameter is also a good indicator of the overall performance of an exon-location technique. The greater the AUC leads to the better performance of the tested algorithm [29].

SIMULATION RESULTS

In order to demonstrate the performance of the methods, we apply them on four gene sequences: F56F11.4, AF009962, AF019074.1, and AJ223321 from GenBank database [32]. The gene sequence F56F11.4 (GenBank No. AF099922) is on chromosome III of Caenorhabditis elegans. C. elegans is a free living nematode, about 1 mm in length, which lives in temperate soil environment. It has five distinct exons, relative to nucleotide position 7021 according to the NCBI database. These regions are 3156-3267, 4756-5085, 6342-6605, 7693-7872, and 9483-9833 [32]. AF009962 is the accession number for single exon, which has one coding region at position 3934-4581. The gene sequence AF019074.1 has the length of 6350, which has three distinct exons, 3101-3187, 3761-4574, and 5832-6007. AJ223321.1 is in the HMR195 dataset. This database consists of 195 mammalian sequences with exactly one complete either single-exon or multi-exon gene. All sequences contain exactly one gene, which starts with the ‘ATG’ initial codon and ends with a stop codon (TAA, TAG, or TGA). There is one coding region existed in AJ223321.1 gene sequence, which its location is 1196-2764. All mentioned sequences are converted to numerical sequences using EIIP method.

In this paper, to compare the performance of the proposed algorithm and other tested methods, we used the parameters \( S_n, S_p, \) and \( P \), which were described in section III. Amounts of these parameters achieved from equation (2). The amounts of TP, FP, TN, and FN are calculated by changing threshold level in range of 0 and 1 with small steps according Figure 7. In this Figure, the value of threshold is 0.161. It can be observed in Figure 7 that if the decision threshold is very high, then there will be almost no false positives, but it won’t be really identified many true positives either.

In this paper, to evaluate the performance of the proposed algorithm, DFT [8] and Multi-Stage filter (MS) [33] methods are implemented. Figures 8-11a and b show results of implementation of these methods and the proposed algorithm in identifying protein coding regions in four gene sequences explained above. As can be seen, the accuracy of the DFT method for protein coding regions estimation is not high due to the noise associated with the original signal. However, the MS filter resulted a good spectral component compared to DFT and reduced the computational complexity. Also, the non-coding regions are relatively suppressed in it, but this method cannot recognize the small size exonic regions. As shown in Figures 8-11c, the large amount of noise is removed in the proposed method due to applying...
Figure 7: Parameters for exon-intron separation problem

Figure 8: Results of the algorithms for identification of the exonic regions on the gene sequence F56F11.4: (a) DFT, (b) MS-filter, and (c) Proposed algorithm
the DWT, and small size of exons (for example, first exon in F56F11.4 gene sequence) can be identified because of using the Goertzel algorithm.

Table 1 shows the estimated exons by methods DFT, MS filter, and the proposed algorithm compared with the locations of exons in a sample gene sequence F56F11.4 from NCBI database. As can be seen, the proposed algorithm result is better than the other methods because of using the Goertzel algorithm. In Table 2, the number of false positive nucleotides, specificity, and precision for specified sensitivities are presented for the proposed and the other tested methods. According to this table, the proposed algorithm has the minimum nucleotides incorrectly identified as exons in all four gene sequences. For example, in F56F11.4, at the sensitivity of 0.5, the

Figure 9: Results of the algorithms for identification of the exonic regions on the gene sequence AF009962: (a) DFT, (b) MS-filter, and (c) Proposed algorithm

Figure 10: Results of the algorithms for identification of the exonic regions on the gene sequence AF019074.1: (a) DFT, (b) MS-filter, and (c) Proposed algorithm
number of false positives in the proposed method is 18 bp, while this quantity for MS filter and DFT are 1052 and 1183, respectively. Also, the proposed algorithm shows relative improvement of 11.1% and 12.5% over the MS filter and DFT methods, respectively, in terms of the precision measure in the same gene sequence. Similar results of the proposed algorithm are apparent for the other three gene sequences, which are shown in Table 2.
To compare the computational efficiencies of the proposed algorithm and other tested methods, the average CPU time is computed over 1000 runs of the techniques for the four gene sequences. Note that all of the implemented algorithms were run on a PC with a 1.6 GHz processor (Intel (R) Pentium (R) M processor) and 2 GB of RAM. Table 3 summarizes results of the average CPU times. It is observed that the proposed algorithm has improved the average CPU time by the factors of 65.9, 28.7, 23.5, and 16.2 relative to the next-best performing method, DFT in F56F11.4, AF009962, AF019074.1, and AJ223321.1 gene sequences, respectively.

Finally, Figures 12-15 illustrate the ROC’s of the algorithms. It is obvious that the proposed algorithm has the highest value of its parameter over the other methods. By way of illustration, the area under the ROC curve is improved by the factors of 1.36, 1.84, 1.38, and 1.83 over the DFT and 2, 1.82, 1.56, and 1.25 over the MS filter methods in F56F11.4, AF009962, AF019074.1, and AJ223321.1 gene sequences, respectively. This implies that the proposed algorithm is superior to the other methods for identifying exonic gene regions.

**CONCLUSION**

Gene identification is a complicated problem, and the detection of the period-3 patterns is a first step towards
gene and exon prediction. Due to the complex nature of the gene identification problem, we usually need a powerful model that can effectively represent the characteristics of protein-coding regions. Many different DSP techniques have been successfully applied for the identification task, but still improvement in this direction is needed. In this paper, a fast model-independent algorithm is presented for exon detection in DNA sequences. First, EIIP method is used to convert the symbolic sequence into digital signal. Then, we applied discrete wavelet transform to reduce the correlation between the numerical data and, therefore, reduce the high frequency noise. Finally, the Goertzel algorithm was applied to the filtered sequence for the period-3 detection. The proposed algorithm minimizes the number of nucleotides incorrectly predicted as coding regions, which leads to increase the specificity. Also, area under the ROC curve is improved in the proposed algorithm over the other methods. The main advantage of the proposed algorithm is its high speed characteristic, which leads to less run process.

REFERENCES

BIOGRAPHIES

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