

Susceptibility Gene Prediction in Hereditary Disease Retinoblastoma

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Abstract— Nowadays Bioinformatics, proteomics and Genomics are the most intriguing sciences to understand the human genome and diseases. Several hereditary genetic diseases like Retinoblastoma involve a sequence of complex interactions between multiple biological processes. With this paper, genetic similarities were found within a selected group of patient's DNA sequences through the use of signal processing tools. DNA, RNA and protein sequences have similarities in structure and function of the gene with their location. In this paper, we introduce a novel method using scoring matrix and wavelet windowing, for the integrative gene prediction. The proposed methods not only integrate multiple genomic data but can be used to predict gene location, gene mutation and genetic disorder from the multi-block genomic data. The performance was assessed by simulation.

Keywords— Gene, scoring matrix, WWM.

I. INTRODUCTION

Retinoblastoma is a malignant cancer of the increasing retinal cells caused in the majority cases by mutations in both copies of the RB1 gene. The RB1 gene is a tumor suppressor gene, located on the genetic material, chromosome 13q14 and is the first cloned human cancer gene. The gene codes for the tumor suppressor protein pRB, which by binding to the transcription factor E2F, inhibits the cell from entering the S-phase during mitosis. Latest facts about retinoblastoma suggests that post-mitotic cone precursors are uniquely sensitive to pRB depletion and may be the cells in which retinoblastoma originates. The occurrence and viability of retinoblastic cells may be more complex than suggested by simple loss of function of the RB1 alleles. Hereditary retinoblastoma demonstrate close relation of the gene for this cancer with genetic locus for esterase D. Data are presented here in support of the hypothesis that at least one disease, the retinoblastoma observed in children is caused by two mutational events.



Fig.1: Healthy eye



Fig.2: Retinoblastoma affected eye

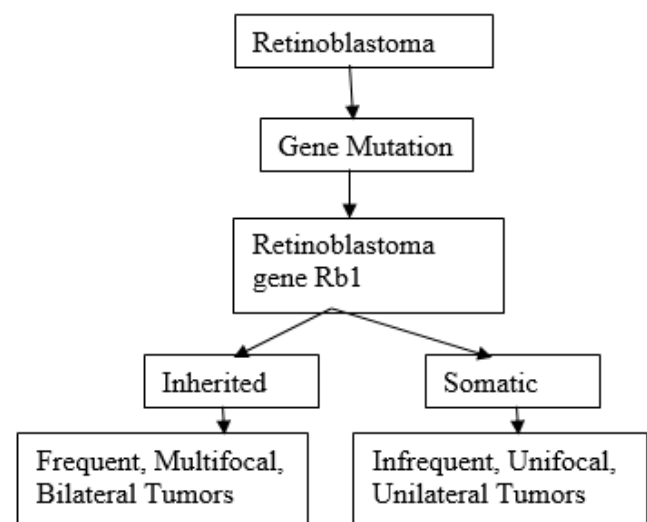


Fig.3: Flow graph of gene mutation in Eye

In 5% of retinoblastoma cases with germline mutations the ancestor history is positive. The risk for developing bilateral and multifocal retinoblastoma is high and the age of inception is around 15 months. The mean number of tumors is about 5 in the two eyes. The offspring of a parent with bilateral retinoblastoma have a 50% probability of developing a tumor and 50% possibility of inheriting the germline mutant allele. Reduced reentrance of 10 to 15% lowers the estimated occurrence of disease from 50% to 25%. Individuals who have mutations in both alleles somatically do not have a mutation in their germ cells and therefore usually transfer no tumor risk to their offspring.

II. DNA SEQUENCE

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are consisting of a nucleobases, a pentose sugar and a phosphate group. DNA nucleobases are Cytosine (C), Guanine (G), Adenine (A) and Thymine (T) and RNA nucleobases are Cytosine (C), Guanine (G), Adenine (A) and Uracil (U)^[1]. In recent years huge databases available for genetic information as open source which lead to a huge progress in bioinformatics; if a genetic sequences are known then this information could be a very important in early disease diagnosis, drug discovery for it.^[2] It leads to Biological sequence alignment a field of Bioinformatics and Computational Biology. It's aim analyzing similarities between DNA, RNA or protein sequences, to predict the genetic relationship between organisms and structural or functional relationships.

Each segment in DNA is called a gene. Genes control the protein synthesis and regulate most of the activities inside a living organism. All the genetic information is copied when a cell divides. When a change occurs in the base sequence of a DNA strand, it is called a mutation. These mutations can lead to diseases or the death of a cell.

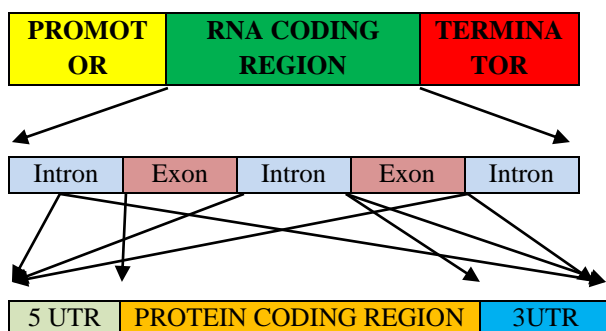


Fig.4: Gene structure

The numerical representation of DNA sequences becomes very essential as almost all DSP techniques require two parts: mapping the symbolic sequence into a numeric and calculating a kind of transform of the resultant numeric series [2]. Most of the numerical representations associate one numerical value to one position in the sequence using numerical values related to each nucleotide and, finally, reveal the existence or the nonexistence of a certain nucleotide in a specific position [3]. Another approach could be to include information about the number and type of repeated nucleotides to generate only one numerical value for each DNA subsequence which may be associated with a recur. This representation needs a mapping algorithm which use distances to determine similar subsequences and then evaluate a consensus sequence for these subsequences to generate candidates.

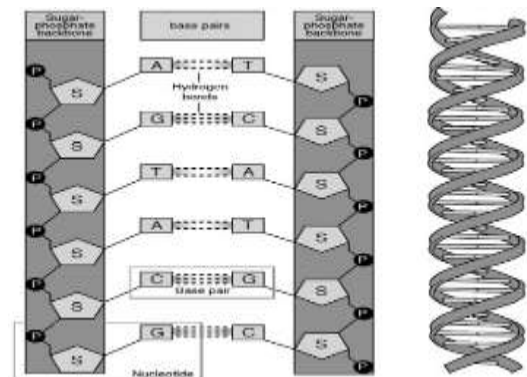


Fig.5: DNA Helical Structure

III. GENE PREDICTION

Gene Prediction refers to detect the locations of the protein-coding regions of genes in a lengthy DNA sequence. Signal processing techniques offer a huge guarantee in analyzing genomic data because of its digital nature. Signal processing analysis of bio-molecular sequences is stalled by their representation as strings of alphabet characters.

Table.1: Genetic code

	T(U)	C	A	G
T(U)	TTT Phe (F) TTC Phe TTA Leu (L) TTG Leu	TCT Ser (S) TCC Ser TCA Ser TCG Ser	TAT Tyr (Y) TAC Tyr TAA Ter TAG Ter	TGT Cys (C) TGC Cys TGA Ter TGG Trp (W)
C	CTT Leu (L) CTC Leu CTA Leu CTG Leu	CCT Pro (P) CCC Pro CCA Pro CCG Pro	CAT His (H) CAC His CAA Gln (Q) CAG Gln	CGT Arg (R) CGC Arg CGA Arg CGG Arg
A	ATT Ile (I) ATC Ile ATA Ile ATG Met (M)	ACT Thr (T) ACC Thr ACA Thr ACG Thr	AAT Asn (N) AAC Asn AAA Lys (K) AAG Lys	AGT Ser (S) AGC Ser AGA Arg (R) AGG Arg
G	GTT Val (V) GTC Val GTA Val GTG Val	GCT Ala (A) GCC Ala GCA Ala GCG Ala	GAT Asp (D) GAC Asp GAA Glu (E) GAG Glu	GGT Gly (G) GGC Gly GGA Gly GGG Gly

IV. NUMERICAL REPRESENTATION

The arithmetical depiction of a DNA sequence is given as a chain of integers derived from a unique graphical representation of the regular hereditary code. This numerical representation is appropriate for the quantitative analysis of the sequences.

4.1 LD matrix

LD matrix is used to calculate linkage disequilibrium values. "composite" for LD composite measure, "r" for R coefficient (by EM algorithm), "dprime" for D', and "corr" for correlation coefficient. The method "corr" is equivalent to "composite", when SNP genotypes are coded as: 0 – BB, 1 – AB, 2 – AA. Matrix elements adjacent to the main diagonal represent the extent of the line segments producing the line.

4.2 Transition matrix

Transition matrix is used for transitions from one kind of base to another. For a given DNA sequence 's' it can construct a 4×4 matrix $A = (t_{ij})$, where t_{ij} means the number of times a given base being succeeded by another in the sequence. A is called the transition frequency matrix of s. We can construct a matrix $P = (P_{ij})$ by dividing each element by the total of all entries in A. Such a matrix represents the relative frequency of all the possible types of transitions, and is called the transition proportion matrix of s. The initial mapping of DNA to binary which represents DNA with four binary indicator sequences showing the presence '1' and absence '0' of the relevant nucleotides at locations 'n'.

4.3 Complex representation

The complex representation is based on the assumption that coefficients of the four 3-D tetrahedron vectors representing each DNA letter are either +1 or -1. The dimensionality of the resultant bipolar representation can be condensed to two.

V. DSP TECHNIQUES

A. DFT

Fourier transform is used to detect the likely coding regions in DNA sequences, by computing the amplitude profile of this spectral component which is a sharp peak at frequency $f = 1/3$ in the power spectrum. The strength of the peak depends obviously on the repetition of gene. This gives relatively good results but it is dependent on DNA sequence and thus requires computation before processing of the mapping scheme for gene prediction. The DNA sequence to be generated from a white random process through an all

pole system and thus used Auto-Regressive modeling to replace Fourier analysis for exon prediction.

B. STFT

In non-stationary signals, The Short Time Fourier Transform (STFT) is an algorithm frequently used for the DFT-based spectral analysis. In the STFT, the time signal is divided into short segments and a DFT is calculated for each one of these segments. Spectrogram, a three dimensional graph called is obtained by plotting the squared magnitude of the DFT coefficients as a function of time.

C. DWT

The Discrete Wavelet Transform is a mathematical tool that can be used very effectively for non-stationary signal analysis. The DWT, for which an algorithm called Fast Wavelet Transforms (FWT) allows a very efficient calculation. Methods based on a modified Gabor-wavelet transform (MGWT) for the identification of protein coding regions also exists.

VI. WAVELET WINDOW METHOD

A Wavelet Transform Modulus Maxima (WTMM) is defined as a point (x_0, t_0) such that

$$|W_{x_0, t}| \leq |W_{x_0, t_0}|$$

when t belongs to either a right or the left neighbourhood of t_0 , and

$$|W_{x_0, t}| \leq |W_{x_0, t_0}|$$

when t belongs to the other side of the neighbourhood of t_0 . We describe maxima line, any connected curve in the scale space (x, t) along which all points are WTMM.

VII. RESULTS AND DISCUSSIONS

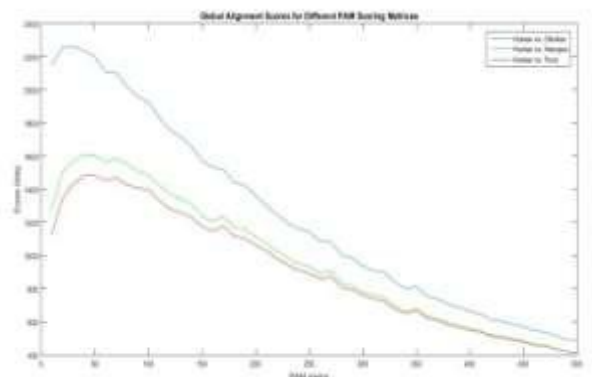


Fig.1: Best of DNA seq

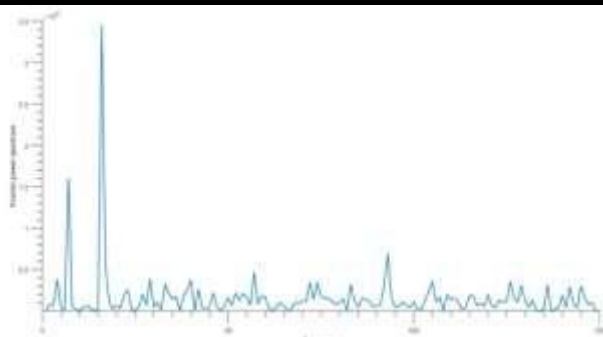


Fig.2: Fourier spectrum of DNA sequence

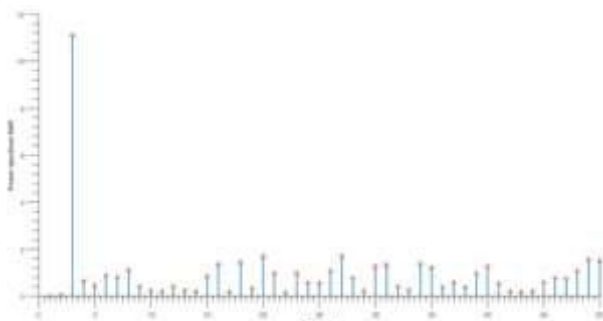


Fig.3: Power spectrum SNR of DNA sequence using WWM



Fig.4: Spectrum analysis of normal and abnormal DNA sequence

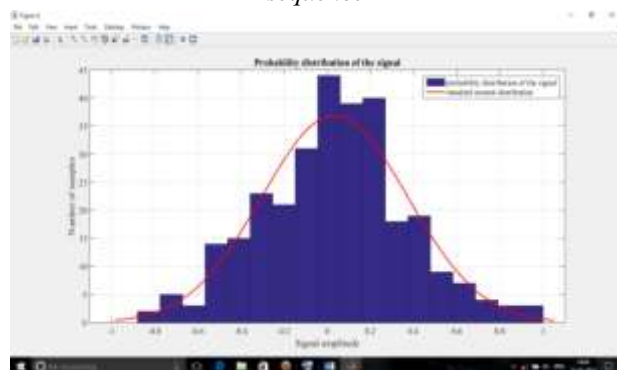


Fig.5: PDF of given sequence

VIII. CONCLUSION

In this work, a new analyzing wavelet window and scoring matrix method for the prediction of protein coding regions has been proposed. The wavelet window method can be applied to predict different coding regions of different lengths. The selection of the value of the window length has always been a problem in DSP based methods as it has an effect on the gene prediction. Future work can focus on integrating this technique to refine the predicted location of gene and protein coding regions.

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