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An immunoinformatics based approach to identify and design the synthetic peptide vaccine for Loiasis

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ABSTRACT

The causative agent 'Loa loa" responsible for the "Loiasis" (African eye worm).The deerflies is the intermediate host for the parasitic worm transmission to the human through the repetitive bites. The protein cytochrome c oxidase subunit III (COX3) of the Loiasis (Loa loa) is a 259 amino acid residue with 251 nonamers. In this assay we predicted the binding affinity of COX3 protein , we found the high affinity TAP Transporter peptide regions as 73-YDYRMFNQG(Score:8.644),102-DSSLCSLTW(Score:8.62),66-VSGQYSFYD(Score:8.62),36-SMGCFFSIF(Score:8.6),126-IGINGMASL(Score:8.594),155-FNCEVFLLI(Score:8.58),104-SLCSLTWLG(Score:8.562),161-LLICIFIGS(Score:8.555),123-PDYIGINGM(Score:8.543),21-GFGILGIDV(Score:8.503).We also predicted the SVM based MHC-IAb peptide regions,12-EYSYYPLMF(optimalscore:0.836),52-YVSFLWLKD(optimalscore:0.596),56-LWLKDVMLE(optimal score:0.588),220-IKLFNFNWY(optimal score:0.567); MHC-IAd peptide regions, 168-GSFFLCFQF(optimal score:0.721),38-GCFFSIFIC(optimalscore:0.717),127-GINGMASLF(optimalscore:0.658),23-GILGIDVSL(optimal score:0.605); MHC-IAg7 peptide regions, 26-GIDVSLALF(optimal score:1.309),77-MFNQGFRLF(optimal score:1.305),49-YIIYVSFLW(optimal score :1.289),126-IGINGMASL(optimal score:1.286);MHC-RT1.B peptide regions,223-FNFNWYHTQ(optimal score:0.645),136-LMMNSQLLK(optimal score:0.606),77-MFNQGFRLF(optimal score:0.548),84-LFLFSELAL(optimal score :0.513) which represented predicted binders from cytochrome c oxidase subunit III (COX3)of the Loiasis (Loa loa). We can assume that even these predicted small antigenic peptide fragment can induce the immune response against the whole antigen .On the basis of this finding the subunit and synthetic peptide vaccines can be developed.

Keywords*–*Loiasis; Loa loa; Epitopes; Antigenic peptides; MHC-Binders; TapPred; PSSM; SVM; Nonamers; cytochrome c oxidase subunit III (mitochondrion)

I. INTRODUCTION

"Loiasis" commonly known as African eye worm and causative agent is "*Loa loa*", [1-3] a parasitic worm which is transmitted through the intermediate host of the genus Chrysops through the repetitive bites of the deerflies, well known mango flies or mangrove flies [4] .Usually this parasite breed in the high –canipied raint forest region of the West and central Africa .The symptoms of this infection is Calabar swellings which is a itchy swellings (local angioedema). This infection remains asymptomatic for several months in many individual .The non- painful swelling appears in any parts of the body more commonly near joints. The detection of this infection is found in the blood test which shows high eosinophils count, which is mostly known to associate with the parasitic infections.

Recognition of *Loa loa* infections has become more important in Africa because the presence of infection has limited programs to control or eliminate onchocerciasis and lymphatic filariasis. This infection is non-contagious. The intermediate host that is Chrysops becomes infectious when they bit and suck the blood of infected person. The mangrove flies usually attracted by the people movement and wood fires smoke .The occurrence of these flies were also seen in those area where the rubber plantation are in practice . The worm can be surgically removed in order to provide immediate relief but this not the full proof elimination techniques because worm can be localized in other parts of body also. The medical practitioners usually provide the medication to kill the worm and eliminated from the infected individuals such as diethylcarbamazine, or DEC. The worm killing through medication is not the safe way of treatment because there is small risk of the serious side effect which is associated with the worm killing. The health practitioner before selecting the treatment method to treat the patient they do test so that they can provide safe treatment to the infected person. The precaution measures are bring into this practice to avoid the infection such as wearing long pants and long-sleeved shirts and avoid the smoke of wood fires. Due to increasing travel and the migration of people from the endemic countries of West Africa to Europe and the USA, there are possible emergences of loiasis [5]. *Loa loa* macrofilariasis in the eyelid is also reported in India [6].

II. MATERIALS AND METHODS

II(a). Protein sequence analysis

The antigenic protein sequence of cytochrome c oxidase subunit III (mitochondrion) of parasite *Loa loa* was analyzed to study the antigenicity, solvent accessible regions and MHC class peptide binding, which allows potential drug targets to identify active sites against parasitic infection.

II(B). Prediction of antigenicity

Prediction of antigenicity program predicts those segments from antigenic protein that are likely to be antigenic by eliciting an antibody response. Antigenic epitopes are determined using the Gomase [7], Hopp and Woods, Welling, Parker, B-EpiPred Server and Kolaskar and Tongaonkar antigenicity methods [8-13].

II(c) . Prediction of protein secondary structure

The important concepts in secondary structure prediction are identified as: residue conformational propensities, sequence edge effects, moments of hydrophobicity, position of insertions and Deletions in aligned homologous sequence, moments of conservation, auto-correlation, residue ratios, secondary structure feedback effects, and filtering [14].

II(d). Finding the location in solvent accessible regions

Finding the location in solvent accessible regions in protein, type of plot determines the hydrophobic and hydrophilic scales and it is utilized for prediction. This may be useful in predicting membrane spanning domains, potential antigenic sites and regions that are likely exposed on the protein surface [15-35]

II(e) Prediction of MHC binding peptide

The MHC peptide binding is predicted using neural network strained on C terminals of known epitopes. In analysis predicted MHC peptide binding is a log-transformed value related to the IC50 values in nM units. MHC2Pred predicts peptide binders to MHCI and MHCII molecules from protein sequences or sequence alignments using Position Specific Scoring Matrices (PSSMs). Support Vector Machine (SVM) based method for prediction of promiscuous MHC class II binding peptides. The average accuracy of SVM based method for 42 alleles is ~80%. For development of MHC binder, an elegant machine learning technique SVM has been used. SVM has been trained on the binary input of single amino acid sequence. In addition, we predicts those MHCI ligands whose C-terminal end is likely to be the result of proteosomal cleavage [36-46].

III. RESULT AND INTERPRETATION

A antigenic sequence cytochrome c oxidase subunit III (mitochondrion) is 259 aa residues long as MFLKFRKFHKMEYSYYPLMFGFGILGIDVSLALFMSMGCFFSIFICLLYIIYVSFLWLKDVMLEDVSGQY SFYDYRMFNQGFRLFLFSELALFFSIFWTYLDSSLCSLTWLGGVWSPLGILSPDYIGINGMASLFLMMNS QLLKYSRRYLCLNKFNCEVFLLICIFIGSFFLCFQFYEYNNNCFVMNDSIYGNVFYVGTGLHGSHVFVG VCFLIINLFRIKLFNFNWYHTQSYDMSIDYWRFLEWMWGIMFCLLYIWGA

III.A. Prediction of antigenic peptides

In these methods we found the antigenic determinants by finding the area of greatest local hydrophilicity. The Hopp-Woods scale was designed to predict the locations of antigenic determinants in a protein, assuming that the antigenic determinants would be exposed on the surface of the protein and thus would be located in hydrophilic regions (Figure:1).

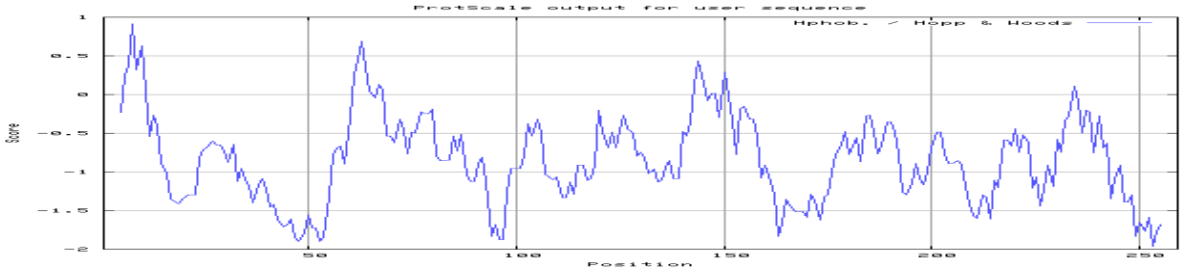

Figure 1: Hydrophobicity plot of Hopp and Woods (1981) of cytochrome c oxidase subunit III. At the Position:8 the peak is found highest with Score: 0.911 (max) and sequence is 5-FRKFHKM-11], whereas at the Position: 253, the peak is found lower with Score: -1.967 (min).

Its values are derived from the transfer free energies for amino acid side chains between ethanol and water. Welling antigenicity plot gives value as the log of the quotient between percentage in a sample of known antigenic regions and percentage in average proteins (Figure 2).

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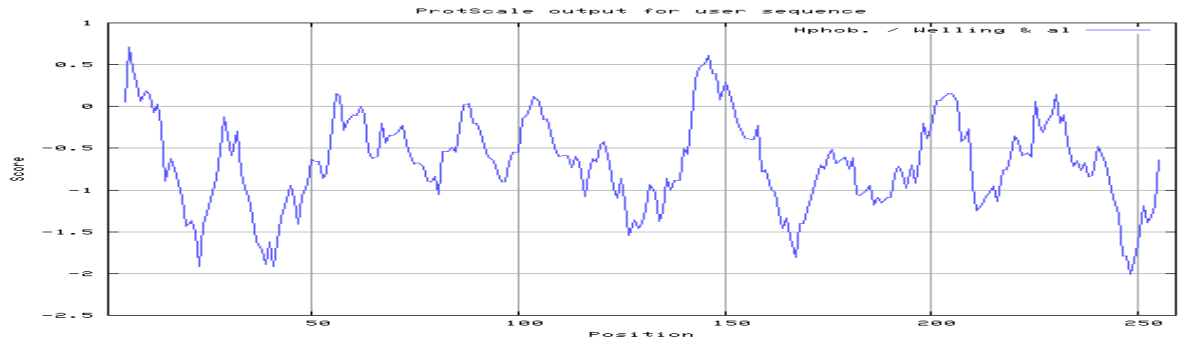
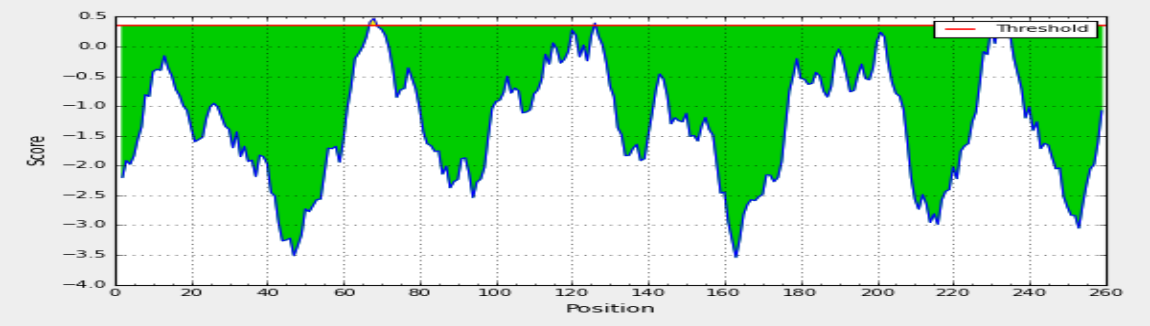


Figure 2: Hydrophobicity plot of Welling et al. (1985) of cytochrome c oxidase subunit III. The highest Score: 0.711 (max) is obtained at Position: 6 with sequence 3-LKFRKFH-9 and min score (Score: -2.007) found Position: 248

We also study B-EpiPred Server(Figure3 & Table 1), Kolaskar and Tongaonkar ntigenicity methods(Figure 4 & Table 2), Parker (Figure 5& Table 3)and the predicted antigenic fragments can bind to MHC molecule is the first bottlenecks in vaccine design (Figure 3- 5).



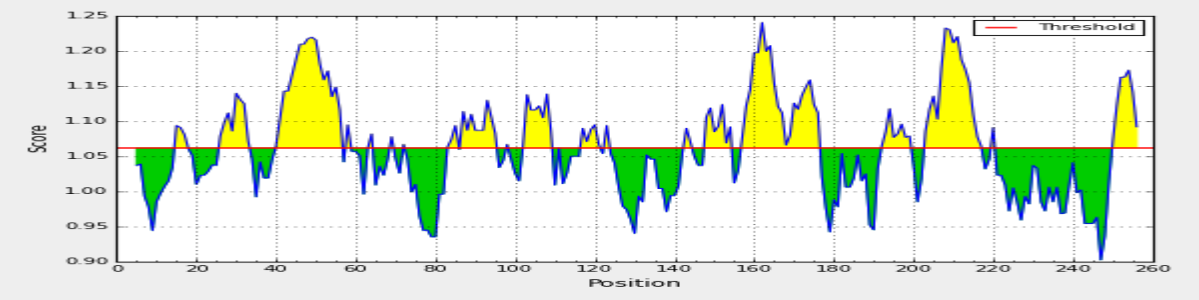
Average: -1.318 ; **Minimum:** -3.542; **Maximum:** 0.474

Figure3: B-cell epitopes are the sites of molecules that are recognized by antibodies of the immune system of the cytochrome c oxidase subunit III.

Predicted peptides:

No.	Start	End	Peptide	Length
1	67	68	SG	2
2	126	126	I	1
3	232	232	S	1
4	234	234	D	1

Table 1: B-cell predicted peptides of the cytochrome c oxidase subunit III.



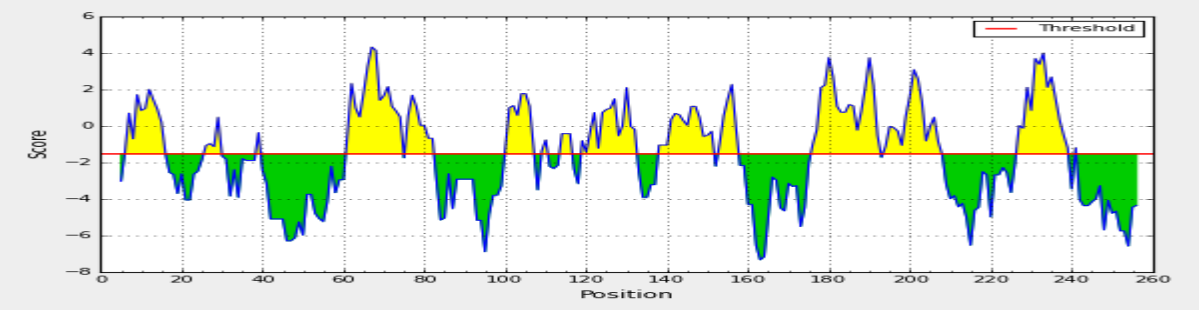
Average: 1.062 **Minimum:** 0.902 **Maximum:** 1.241

Figure 4: Kolaskar and Tongaonkar antigenicity are the sites of molecules that are recognized by antibodies of the immune system for the cytochrome c oxidase subunit III.

Predicted residue scores:

Position	Residue	Start	End	Peptide	Score
162	**L**	159	165	VFLLICI	1.241
208	**V**	205	211	HVFVGVC	1.233
209	**G**	206	212	VFVGVCF	1.231

Table 2: Kolaskar and Tongaonkar antigenicity predicted peptides for the cytochrome c oxidase subunit III.



Average: -1.533 **Minimum:** -7.343 **Maximum:** 4.343

Figure 5: Hydrophobicity plot of HPLC / Parker et al. (1986) of cytochrome c oxidase subunit III.

Predicted residue scores:

Position	Residue	Start	End	Peptide	Score
67	**S**	64	70	EDVSGQY	4.343
68	**G**	65	71	DVSGQYS	4.157

Table 3: Hydrophobicity plot of HPLC / Parker et al. (1986) predicted peptide for cytochrome c oxidase subunit III.

III.B Secondary alignment

The Robson and Garnier method predicted the secondary structure of the cytochrome c oxidase subunit III. Each residue is assigned values for alpha helix, beta sheet, turns and coils using a window of 7 residues (Figure 6). Using these information parameters, the likelihood of a given residue assuming each of the four possible conformations alpha, beta, reverse turn, or coils calculated, and the conformation with the largest likelihood is assigned to the residue.

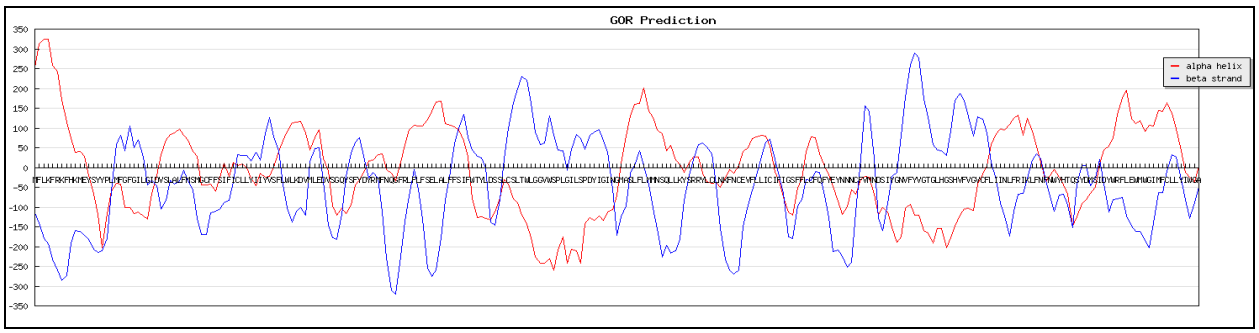


Figure 6: Secondary structure GOR plot of the cytochrome c oxidase subunit III

III.C Solvent accessible regions

Solvent accessible scales for delineating hydrophobic and hydrophilic characteristics of amino acids and scales are developed for predicting potential antigenic sites of globular proteins, which are likely to be rich in charged and polar residues. It was shown that a cytochrome c oxidase subunit III is hydrophobic in nature and contains segments.

III.D Prediction of MHC binding peptides

These MHC binding peptides are sufficient for eliciting the desired immune response. The prediction is based on cascade support vector machine, using sequence and properties of the amino acids. The correlation coefficient of 0.88 was obtained by using jack-knife validation test. In this test, we found the MHCI and MHCII binding regions (Tables 4and 5). MHC molecules are cell surface glycoproteins, which take active part in host immune reactions and involvement of MHC class-I and MHC II in response to almost all antigens. In this assay we predicted the binding affinity of cytochrome c oxidase subunit III having 259 amino acids, which shows different nonamers (Tables 4 and 5). For development of MHC binder prediction method, an elegant machine learning technique support vector machine (SVM) has been used. SVM has been trained on the binary input of single amino acid sequence. In this assay we predicted the binding affinity of cytochrome c oxidase subunit III having 259 amino acids, which shows 251nonamers. Small peptide regions found as High affinity TAP Transporter peptide regions as, 73-YDYRMFNQG(Score:8.644),102-DSSLCSLTW(Score:8.62),66-VSGQYSFYD(Score:8.62),36-SMGCFFSIF(Score:8.6),126-IGINGMASL(Score:8.594),155-FNCEVFLLI(Score: 8.58),104-SLCSLTWLG(Score:8.562),161-LLICIFIGS(Score:8.555),123-PDYIGINGM(Score:8.543),21-GFGILGIDV(Score:8.503).

Peptide Rank	Start Position	Sequence	Score	Predicted Affinity
1	73	YDYRMFNQG	8.644	High
2	102	DSSLCSLTW	8.62	High
3	66	VSGQYSFYD	8.62	High
4	36	SMGCFFSIF	8.6	High
5	126	IGINGMASL	8.594	High
6	155	FNCEVFLLI	8.58	High
7	104	SLCSLTWLG	8.562	High
8	161	LLICIFIGS	8.555	High
9	123	PDYIGINGM	8.543	High
10	21	GFGILGIDV	8.503	High

*Optimal Score for given MHC binder in Mouse

Table 4: TAP Peptide binders of cytochrome c oxidase subunit III.

Prediction method	Rank	Sequence	Residue No.	Peptide Score
ALLELE I-Ab	1	EYSYYPLMF	12	0.836
ALLELE I-Ab	2	YVSFLWLKD	52	0.596
ALLELE I-Ab	3	LWLKDVMLE	56	0.588
ALLELE I-Ab	4	IKLFNFNWY	220	0.567
ALLELE I-Ad	1	GSFFLCFQF	168	0.721
ALLELE I-Ad	2	GCFFSIFIC	38	0.717
ALLELE I-Ad	3	GINGMASLF	127	0.658
ALLELE I-Ad	4	GILGIDVSL	23	0.605
ALLELE I-Ag7	1	GIDVSLALF	26	1.309
ALLELE I-Ag7	2	MFNQGFRLF	77	1.305
ALLELE I-Ag7	3	YIIYVSFLW	49	1.289
ALLELE I-Ag7	4	IGINGMASL	126	1.286
ALLELE RT1.B	1	FNFNWYHTQ	223	0.645
ALLELE RT1.B	2	LMMNSQLLK	136	0.606
ALLELE RT1.B	3	MFNQGFRLF	77	0.548
ALLELE RT1.B	4	LFLFSELAL	84	0.513

*Optimal Score for given MHC II peptide binder in Mouse

Table 5: Peptide binders to MHCII molecules of cytochrome c oxidase subunit III.

We also predicted the SVM based MHC-IAb peptide regions, 12-EYSYYPLMF(optimalscore:0.836),52-YVSFLWLKD(optimalscore:0.596),56-LWLKDVMLE(optimal score:0.588),220-IKLFNFNWY(optimal score:0.567); MHC-IAd peptide regions, 168-GSFFLCFQF(optimal score:0.721),38-GCFFSIFIC(optimal score:0.717),127-GINGMASLF(optimal score: 0.658),23-GILGIDVSL(optimal score:0.605); MHC-IAg7 peptide regions, 26-GIDVSLALF(optimal score:1.309),77-MFNQGFRLF(optimal score:1.305),49-YIIYVSFLW(optimal score :1.289),126-IGINGMASL(optimal score:1.286); MHC-RT1.B peptide regions,223-FNFNWYHTQ(optimal score:0.645),136-LMMNSQLLK(optimal score:0.606),77-MFNQGFRLF(optimal score:0.548),84-LFLFSELAL(optimal score :0.513) which represent the predicted peptide binders from cytochrome C oxidase III from *Loa loa* (table:5).The predicted binding affinity is normalized by the 1% fractal. The MHC peptide binding is predicted using the neural networks trained on c terminal of known epitopes. In analysis predicted MHC –peptide binding is log-transformed value related to the IC50 values in nM units. These MHC binding peptides are sufficient for eliciting the desired immune response. Predicted MHC binding regions in an antigen sequence and there are directly associated with immune reactions, in analysis we found the MHCII binding region.

IV. DISCUSSION AND CONCLUSION

Gomase method, B-EpiPred Server, Hopp and Woods, Welling, Parker, Kolaskar and Tongaonkar antigenicity scales were designed to predict the locations of antigenic determinants in cytochrome c oxidase subunit III. Protein shows beta sheets regions, which are high antigenic response than helical region of this peptide and shows highly antigenicity (Figure 1-5). We also found the Sweet hydrophobicity, Kyte & Doolittle hydrophobicity, Abraham & Leo, Bull & Breese hydrophobicity, Guy, Miyazawa hydrophobicity, Roseman hydrophobicity, Cowan HPLC pH7.5 hydrophobicity, Rose hydrophobicity, Eisenberg hydrophobicity, Manavalan hydrophobicity, Black hydrophobicity, Fauchere hydrophobicity, Janin hydrophobicity, Rao & Argos hydrophobicity, Wolfenden hydrophobicity, Wilson HPLC hydrophobicity, Cowan HPLC pH-3.4, Tanford hydrophobicity, Rf mobility hydrophobicity and Chothia hydrophobicity scales, Theses scales are essentially a hydrophilic index, with a polar residues assigned negative values (Figures 7-27). In this assay we predicted the binding affinity of cytochrome c oxidase subunit III having 259 amino acids, which shows 251 nonamers. Small peptide regions found as, 73-YDYRMFNQG (Score:8.644),102-DSSLCSLTW(Score:8.62), 66-VSGQYSFYD(Score:8.62), 36-SMGCFFSIF (Score:8.6), 126-IGINGMASL(Score:8.594), 155-FNCEVFLLI(Score:8.58), 104-SLCSLTWLG(Score:8.562), 161-LLICIFIGS(Score:8.555), 123-PDYIGINGM(Score:8.543), 21-GFGILGIDV(Score:8.503). Adducts of MHC and peptide complexes are the ligands for T cell receptors (TCR) (Table 1). MHC molecules are cell surface glycoproteins, which take active part in host immune reactions and involvement of MHC class-I and MHC II in response to almost all antigens (Table 5). Kolaskar and Tongaonkar antigenicity are the sites of molecules that are recognized by antibodies of the immune system for the cytochrome c oxidase subunit III, analysis shows epitopes present in the cytochrome c oxidase subunit III the desired immune response. The region of maximal hydrophilicity is likely to be an antigenic site, having hydrophobic characteristics, because C-terminal regions of cytochrome c oxidase subunit III is solvent accessible and unstructured, antibodies against those regions are also likely to recognize the native

protein. For the prediction of antigenic determinant site of cytochrome c oxidase subunit III, we got eighteen antigenic determinant sites in the sequence. The SVM based MHCII-IAb peptide regions12-EYSYYPLMF(optimalscore:0.836),52-YVSFLWLKD (optimalscore:0.596), 56-LWLKDVMLE (optimal score:0.588), 220-IKLFNFNWY(optimal score:0.567); MHC-IAd peptide regions, 168-GSFFLCFQF (optimal score:0.721), 38-GCFFSIFIC (optimal score:0.717), 127-GINGMASLF(optimal score:0.658),23-GILGIDVSL(optimal score:0.605); MHC-IAg7 peptide regions, 26-GIDVSLALF(optimal score:1.309),77-MFNQGFRLF(optimalscore:1.305),49-YIIYVSFLW(optimalscore:1.289), 126-IGINGMASL (optimal score:1.286) ; MHC-RT1.B peptide regions, 223-FNFNWYHTQ(optimal score:0.645),136-LMMNSQLLK(optimal score:0.606),77-MFNQGFRLF(optimal score:0.548),84-LFLFSELAL(optimal score :0.513) (Table-5). Which is a larger percentage of their atoms are directly involved in binding as compared to larger molecules.

V. FUTURE PERSPECTIVES

This method will be useful in cellular immunology, Vaccine design, immunodiagnostics, immunotherapeutics and molecular understanding of autoimmune susceptibility. cytochrome c oxidase subunit III sequence involved multiple antigenic components to direct and empower the immune system to protect the host from the infection. MHC molecules are cell surface proteins, which take active part in host immune reactions and involvement of MHC class in response to almost all antigens and it give effects on specific sites. Predicted MHC binding regions acts like red flags for antigen specific and generate immune response against the parent antigen. So, a small fragment of antigen can induce immune response against whole antigen. The method integrates prediction of peptide MHC class binding; proteosomal C terminal cleavage and TAP transport efficiency. This theme is implemented in designing subunit and synthetic peptide vaccines.

Figures List :

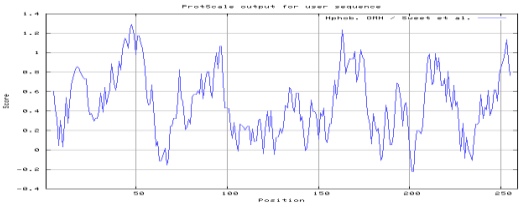


Figure7:Hydrophobicity Sweet et al., plot

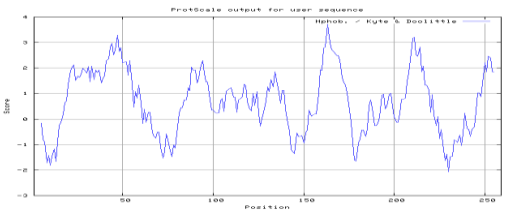


Figure 8: Hydrophobicity plot of Kyte and Doolittle (1982)

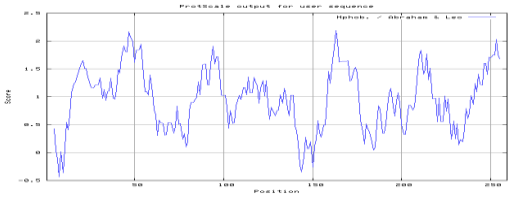


Figure9: Hydrophobicity plot of Abraham and Leo(1987)

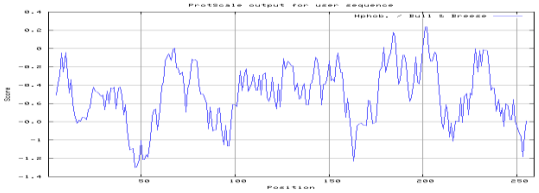


Figure10: Hydrophobicity plot of Bull and Breese (1974)

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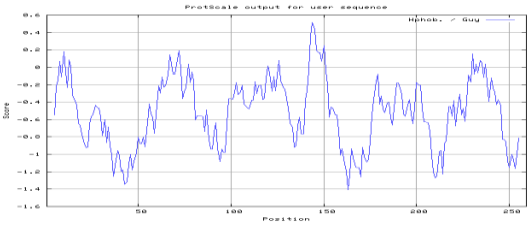

Figure 11: Hydrophobicity plot of Guy (1985)

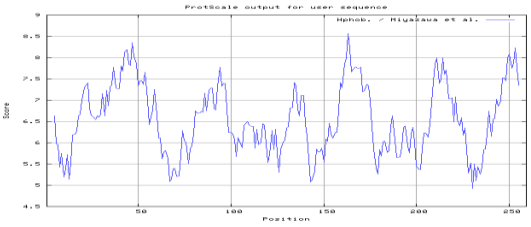

Figure 12: Hydrophobicity plot of Miyazawa, et al (1985)

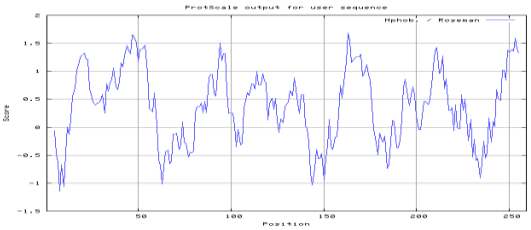

Figure 13: Hydrophobicity plot of Roseman (1988)

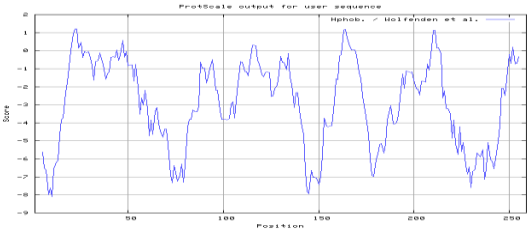

Figure 14: Hydrophobicity plot of Wolfenden et al. (1981)

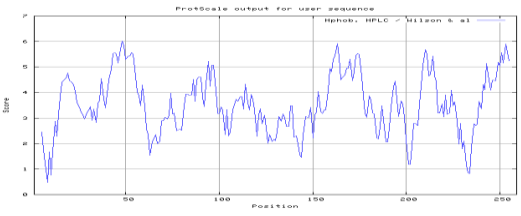

Figure 15: Hydrophobicity Wilson et al. (1981) plot

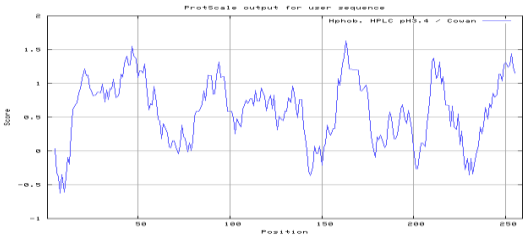

Figure 16: Hydrophobicity Cowan (1990) plot

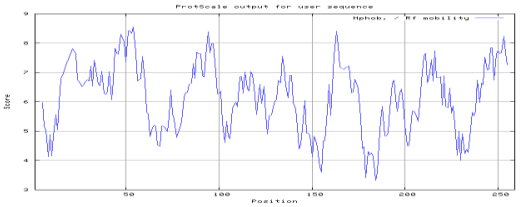

Figure 17: Hydrophobicity plot of Rf mobility

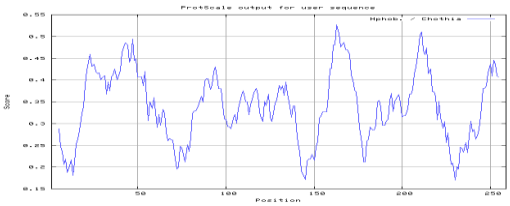

Figure 18: Hydrophobicity plot of Chothia (1976)

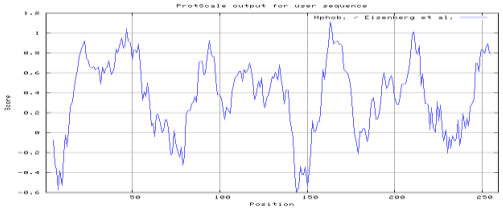

Figure19: Hydrophobicity plot of Eisenberg et al. (1984)

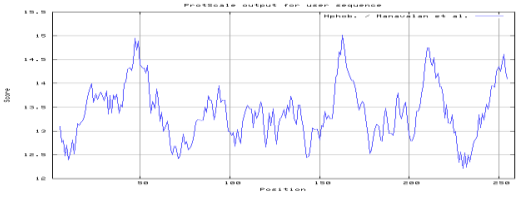

Figure 20: Hydrophobicity plot of Manavalan, et al (1978)

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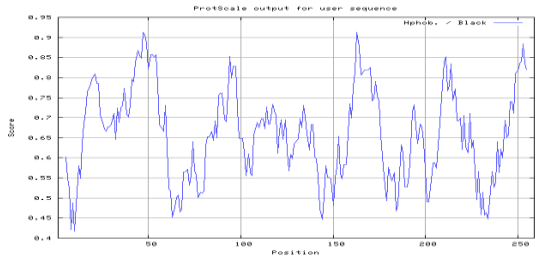

Figure 21: Hydrophobicity plot of Black (1991)

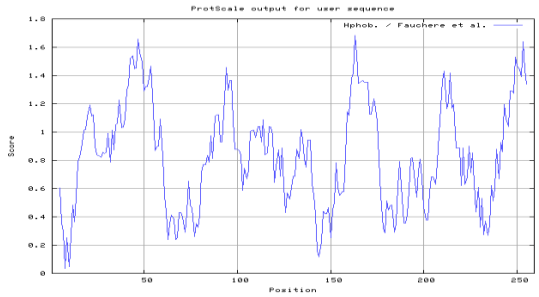

Figure 22: Hydrophobicity plot of Fauchere, et al (1983)

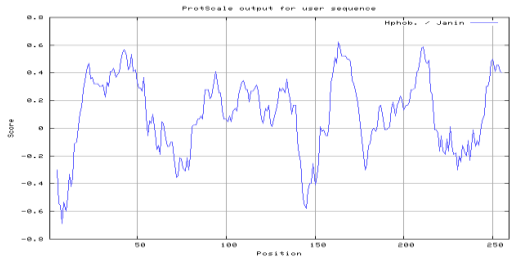

Figure 23: Hydrophobicity plot of Janin (1979)

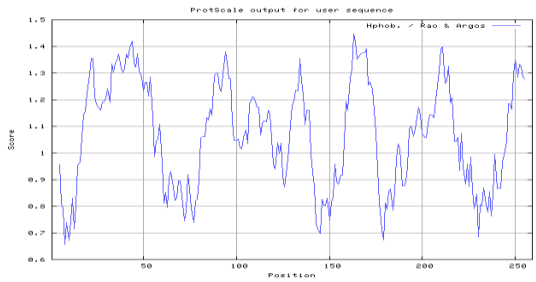

Figure 24: Hydrophobicity plot of Rao and Argos (1986)

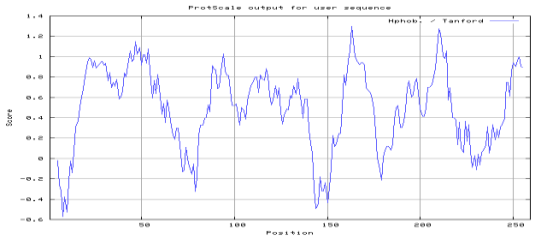

Figure 25: Hydrophobicity plot of Tanford (1962)

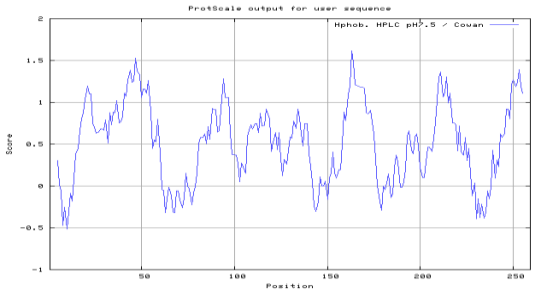

Figure 26: Hydrophobicity Cowan (1990) plot of HPLC pH7.5

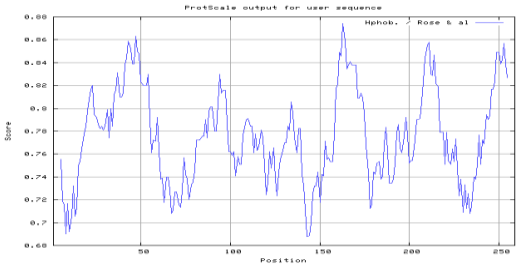

Figure 27: Hydrophobicity plot of Rose et al. (1985)

Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

1. MHC-Major Histocompatibility Complex
2. PSSM- Position-Specific Scoring Matrix
3. SVM- Support vector machine
4. NCBI: National Center for Biotechnology Information
5. TAP : Transporter Associated with Antigen Processing

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