European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 07, Issue 07, 2020

Application Of Hmm-Viterbi Model For Identification Of Epitopic Signature Within Screened Protein-Antigens Of Hepatitis C Virus

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ABSTRACT: Antigenic drift in epitopic part of a virus, especially for Hepatitis C Virus is a well-known fact. However, this problem can be overcome due to the fact that the epitopes are dispersed amongst a few proteins that are already filtered out by researchers. Minor changes or variation in the sequential structure of this protein group results in amendment of their epitope structures which ultimately renders any vaccine or drug ineffective against the target organism. Therefore the problem is reduced to first revisiting the identification steps of altered sequences of these 10 proteins which is quite achievable experimentally and secondly identification of epitopic part out of these altered peptide sequences. Hidden Markov models (HMMs) have been comprehensively deployed in analysis of bio-molecular sequences. The work presented in this paper deals with the recognition step of epitopes through probabilistic machine learning model Viterbi of HMM and achieved significantly high efficiency towards this direction. As a consequence, a considerably high precision was obtained for T-cell based linear epitope recognition.

Keywords- Machine Learning, HMM, ANN, Epitope, Hidden Layer, Vaccine,

1 INTRODUCTION

1.1 A Subsection Sample

Prevention has always been the best option when it comes to dealing with viral and bacterial diseases. It is also more cost effective as compared to disease treatment [29]. The most effective method of disease prevention is vaccination. Vaccination is a method of stimulating immune response by deliberately introducing antigens in the body. The vaccines thus introduced are mostly inactivated pathogens of a given disease. Thus, a vaccine is immunogenic, not pathogenic. Vaccines are usually designed against epitopes. A Peptide-epitope is that part of a protein based-antigen recognized by immune-system. It is the specific antigenic part to which an antibody binds. Hence, they are suitable vaccine candidates. Nowadays, a new concept of a peptide-based vaccine has been increasingly popular over the last few years. The

initial step for applying computation to vaccine improvement comprised on discerning epitopes that induce immune response from the one's that does not. The part of antigen, which stimulates T-cell response are known as T-cell epitopes. T-cell epitopes elucidated as linear stretches of less than 10 successive amino acid residues [1]. But, it has been remarkably notified by scientists that expanding amino-acid length-span often out-turn in to greater than prior to immunogenic effectiveness [1]. It's presently conventional that epitopes are coupled cooperatively on fissure for binding present at the Major histocompatibility complexes Class I and II proteins. This close fit takes place among the side chains present on the R-group chains of epitope and the binding domains existing in the Major histocompatibility complexes exposures [4–6]. Based on this understanding, a vast number of designs for portraying T-cell epitopes had recognized and employed to build up tools to quickly identify alleged T-cell epitopes [3, 7, 8]. NetCTLpan server is deployed to foresee CTL epitopes for arrangements of protein and by utilizing ANN(Artificial Neural Networks) [9]. This procedure has been updated which incorporate the new discharged MHC allele from the chronicles of IMGT/HLA and IPD-MHC (for non-human primates just as pig). Forecasts through this technique are made distinctly for 8-11mer peptides, as the majority of the HLA allelic-peptides gain a fixed option for interacting 9mers [9]. ProPred1 is a server that predicts MHC Class-II restricting locale in an antigen grouping by methods for quantitative grids [10]. In the following examination, a deliberate exertion is made in order to precisely foresee MHC class I controlled T cell epitopes for countless MHC class I alleles. In any case, a quantitative lattice/matrices based plan (QM) was created for 47 MHC class I alleles which have at the base 15 folios. A subsequent counterfeit neural system based method (ANN) was developed for 30 from 47 MHC allelic proteins having at least 40 folios. ANN is a model which mimics natural neural networks [25]. It strives to achieve human-like thinking in machines [26], i.e. problems solving by learning and parallel processing [27]. The learning phase is known as the training phase of the neural net [28]. Amalgamation of these ANN and QM-based forecast methods for 30 alleles enhanced the precision of guess by 6%, as compared to individual methods. Normal correctness of hybrid scheme for 30 MHC alleles is 92.8% [11]. The SVMHC server additionally permits estimation for MHC Class-I just as Class-II restricting peptides, paying little heed to of the truth that the most wide extension is for MHC Class-II (51 alleles). Valuable graphical outcome exhibited through this method constantly countenance for effortless recognition for putative epitopes. SVMHC avails for the matrices which are designed by the TEPITOPE software [12]. The already well established tools for epitopes prediction are based on databases such as SYFPEITHI, MHCBN, LANL, IEDB, etc. which contain known epitopes. The epitope identification tools thus stated is applicable to most of the pathogens including HCV. The Hepatitis C virus attacks the liver and scars it [23]. It is a major hazard, both in general population as well as in hospitals, particularly in Haemo Dialysis units [24].

New procedures for recognition of T-cell epitopes are very expensive and time-span intensive. To take care of this limitation of experimental methods in the past, quite a lot of models have been developed to predict linear T-cell epitopes. The IEDB Analysis Resource database (http://www.iedb.org/) uses NetMHCpan as forecast technique since 2011. This scheme generates a quantitative guess of the likeness of any peptide-MHC class I contact [13]. NetMHC software predicts peptide binding to a number of diverse HLA alleles by means of ANNs. The training technique associated with the server is one of the best available, and has been worn to guess probable MHC-binding peptides in a sequence of pathogen viral proteomes including HIV, Influenza and SARS, consequential in an average of 75-80% confirmed MHC binders [14]. BEPPE (Binding Epitope Prediction from Protein Energetic), an assistance that

provides a index of epitope stretches which are putative and associated BLAST searches aligned with complete human proteome as present in UniProt. This service can be engaged for biophysical process learning at the base of the immune identification. It can also be used for immunological purposes, such as designing of biomarkers in a rational manner and also identifying the targets for vaccine discovery, diagnostics and therapeutics [15]. Recently Paul et al developed an web server, TepiTool. It is component of the Immune Epitope Database (IEDB). The purpose of this tool is to provide a number of guess algorithms for binding of top MHCs of number of species; such as humans, chimpanzees, bovines, macaques, gorillas, pigs, and mice [16]. It is tricky to make antibodies against viral epitopes, because they are quiet dynamic in nature and change their structures upon coming under attack from the immune system. Upon such a change, the antibodies can no longer recognize the binding site on epitope, and thus the virus escapes the immune system and proliferates. Researchers have come out with some advanced methods and tools for the prediction of vaccine candidates but there is always a question mark on medical acceptability of these methods. The dynamic nature of viral epitopes can be computationally predicted by the use of a stochastic model which describes a chain of events based on probability of preceding events [21][22]. One such robust model is known as the Hidden Markov Model (HMM). Hence, machine learning approach can be used quite extensively to take care of this problem with various combinations including artificial neural networks, Hidden Markov Models and Support vector machine in addition to the selection of diverse features. In this work, after trying all these options we could achieve an acceptable accuracy with hidden Markov Model for epitope prediction.

In this study, we have extracted verified epitopes from IEDB database; we refined the total available dataset on the basis of linearity and availability of starting and ending position. Finally we have derived a dataset of 1426 T-cell epitopes and 3256 non epitopes from IEDB [17]. We crafted distinct HMM structures on these rational sets for discerning T-cell peptides from non-epitope stretches.

2 METHODOLOGY

2.1 Collection and depiction of information:

We initiated extraction experimentally validated 1426 epitopes and 3255 non-epitopes with starting and ending positions available from Immune epitope database IEDB in October [17]. Epitopes varies from 6 to 31amino acid residues and non-epitopes varies from 4 to 43 amino acid residues. The epitope data is divided into 4 categories namely: positive, positive-high, positive intermediate and positive low with 1332, 23, 8 and 63 epitopes. We have calculated the length of each epitope and non-epitope with the help of position values shown in Table. 1. We have shown the length wise division of epitopes and non-epitopes in Fig. 1.

Table 1. Efficiency considering all learning models data.

Model S No	**Sequence No**		**Training efficiency**	**Empirical error**	**Test efficiency**	**True Error**	**Average test Efficiency (%)**
	Training	**Testing**					
1	4, 5, 6, 7, 8, 9, 10	1, 2, 3	85.7395	0.1426	98.5255	0.0147	**90.0998**
2	5, 6, 7, 8, 9, 10, 1	2, 3, 4	86.8839	0.1312	96.7585	0.0324	
3	6, 7, 8, 9, 10, 1, 2	3, 4, 5	88.6824	0.1132	89.7356	0.1026	
4	7, 8, 9, 10,	4,	86.7143	0.1329	93.9627	0.0604	

	1, 2, 3	5, 6					
5	8, 9, 10, 1, 2, 3, 4	5, 6, 7	86.3442	0.1366	94.9002	0.0510	
6	9, 10, 1, 2, 3, 4, 5	6, 7, 8	83.8257	0.1617	100.0000	0.0000	
7	10, 1, 2, 3, 4, 5, 6	7, 8, 9	89.8132	0.1019	86.2385	0.1376	
8	1, 2, 3, 4, 5, 6, 7	8, 9, 10	96.1404	0.0386	79.4005	0.2060	
9	2, 3, 4, 5, 6, 7, 8	9, 10, 1	96.2942	0.0371	78.2114	0.2179	
10	3, 4, 5, 6, 7, 8, 9	10, 1, 2	91.6053	0.0839	83.2649	0.1674	

2.2 Mathematical and Algorithmic description

All the computational works were done by for the most part composing MATLAB (R2014b) codes and insignificantly utilizing standard MATLAB library capacities. Viterbi learning model of Hidden Markov Model was employed as grade for predicting peptide candidates against each of the residue within the test protein sequences. For computation of model parameters, initial probability, transition probability and emission probability, standard protocol described in [18] was followed. 10 fold cross-validations were used for validating the results.

2.3 Statistical Approaches

HMM: It is a statistical representation that can be utilized to depict evolution of visible events that depend on inner factors, which are not observable straightaway. The observed occurrence is denoted as a `symbol' and the hidden factor which is underlying the observation is denoted as a `state'. There are two processes of stochastic nature in HMM, an unseen process consisting of hidden states and a detectable process comprising of observable signs. A Markov chain is structured by the hidden states, and the distribution of likelihood of the observed sign depends on underlying situation [18]. Modeling interpretation in these two layers, one visible and the other one is invisible, is very helpful in separating epitopes from non epitopic regions. Here we have trained Hidden Markov Model (HMM) on linear epitopes.

VAPNIK–CHERVONENKIS INEQUALITY: The hypothesis is an outline of computational learning assumption, which strives to make clear the learning procedure from a view point of statistics. The VC is a result in learning theory that allows us to control the generalization error [19].

CONTEXT BASED MODIFICATION: The major dissimilarity between a HMM which is context sensitive and a conventional HMM is that that the former one can use fraction of the earlier period emissions, called the `context', to fine-tune certain possible future states' probabilities. Such contextual information, when used, is quite valuable in unfolding long-range correlations between signs, and this dependency on context increases the HMM's explanatory potential significantly [20].

3. RESULT AND DISCUSSION

The T-cell epitopes were analyzed to be aware of their distinctiveness. At first, disposition of T-cell peptides were length wise examined. As spoke to in Fig 1, most of the epitopes are of 5–16 amino corrosive length. Following stage was to perceive the tendency of deposits in T-

cell epitopes. This was finished by producing a two-example logo plot utilizing 9-mer epitope (upper board) and non-epitope (lower board), as given in Fig 2.It can be observed that in comparison to the non-epitope region, there is a prominent incidence of exterior residue in the epitope section which is also flexible in nature. Adding up, a high inclination of Glycine residue was observed in the epitope section, which may be accountable for bend formation, or flexibility in the epitope regions. We used these characteristics to train HMM. We computed accuracies with HMM along with VC and context base logic. Accuracy of HMM considering all learning models is given in table 1, accuracy after applying VC inequality is given in table 2, accuracy after applying VC inequality and context based logic is given in table 3. Acceptance of model is explained in table 4. Immune cells play vital role in preventing the infections as well as targeting the cancer cells. It is observed M2 macrophages to support cancer cell growth but it has beneficial effects in successful pregnancy [30]. Novel drug delivery strategies have been found successful in treating the infections as well as cancers and it is well discussed in lung cancer therapy by Sharma et al. (2019)[31]. Various in sillico studies and other studies have been performed on hepatitis-C virus and useful informations have been gathered for vaccine production and other aspects against these viruses [32-37].

Table 2. Efficiency considering all learning models data after applying VC inequality

Model S No	Sequence No		Training efficiency	Empirical error	Test efficiency	True Error	Average test Efficiency (%)
	Training	Testing					
1	4, 5, 6, 7, 8, 9, 10	1, 2, 3	85.7395	0.1426	98.5255	0.0147	**94.0927 (after Applying VC inequality)**
2	5, 6, 7, 8, 9, 10, 1	2, 3, 4	86.8839	0.1312	96.7585	0.0324	
3	6, 7, 8, 9, 10, 1, 2	3, 4, 5	88.6824	0.1132	89.4246	0.1058	
4	7, 8, 9, 10, 1, 2, 3	4, 5, 6	86.7143	0.1329	93.6334	0.0637	
5	8, 9, 10, 1, 2, 3, 4	5, 6, 7	86.3442	0.1366	94.5676	0.0543	
6	9, 10, 1, 2, 3, 4, 5	6, 7, 8	83.8257	0.1617	99.8943	0.0011	
7	10, 1, 2, 3, 4, 5, 6	7, 8, 9	89.8132	0.1019	85.8453	0.1415	

Table 3. Efficiency after applying VC inequality and context based logic

Model S No	Sequence No		Training efficiency	Empirical error	Test efficiency	True Error	Average test Efficiency (%)
	Training	Testing					
1	4, 5, 6, 7, 8, 9, 10	1, 2, 3	85.7395	0.1426	98.5255	0.0147	**94.3030 (after Applying VC inequality with context based)**
2	5, 6, 7, 8, 9, 10, 1	2, 3, 4	86.8839	0.1312	96.7585	0.0324	
3	6, 7, 8, 9, 10, 1, 2	3, 4, 5	88.6824	0.1132	89.7356	0.1026	
4	7, 8, 9, 10, 1, 2, 3	4, 5, 6	86.7143	0.1329	93.9627	0.0604	
5	8, 9, 10, 1, 2, 3, 4	5, 6, 7	86.3442	0.1366	94.9002	0.0510	
6	9, 10, 1, 2, 3, 4, 5	6, 7, 8	83.8257	0.1617	100.0000	0.0000	
7	10, 1, 2, 3, 4, 5, 6	7, 8, 9	89.8132	0.1019	86.2385	0.1376	

Table 4. VC inequality considering eta = 0.1

Model S No	Sequence No		H	vc term	Training efficiency	Empirical error	Test efficiency	True Error	Model acceptance
	Training	Testing							
1	4, 5, 6, 7, 8, 9, 10	1, 2, 3	0.69	0.0	85.7395	0.1426	98.5255	0.01	yes
2	5, 6, 7, 8, 9, 10, 1	2, 3, 4	0.69	0.0	86.8839	0.1312	96.7585	0.03	yes
3	6, 7, 8, 9, 10, 1, 2	3, 4, 5	0.69	0.0	88.6824	0.1132	89.7356	0.10	yes
4	7, 8, 9, 10, 1, 2, 3	4, 5, 6	0.69	0.0	86.7143	0.1329	93.9627	0.06	yes
5	8, 9, 10, 1, 2, 3, 4	5, 6, 7	0.69	0.0	86.3442	0.1366	94.9002	0.05	yes

6	9, 10, 1, 2, 3, 4, 5	6, 7, 8	0.69	0.0	83.8257	0.1617	100.000	0.00	yes
7	10, 1, 2, 3, 4, 5, 6	7, 8, 9	0.69	0.0	89.8132	0.1019	86.2385	0.13	yes
8	1, 2, 3, 4, 5, 6, 7	8, 9,	0.69	0.0	96.1404	0.0386	79.4005	0.20	No
9	2, 3, 4, 5, 6, 7, 8	9, 10,	0.69	0.0	96.2942	0.0371	78.2114	0.21	No
10	3, 4, 5, 6, 7, 8, 9	10, 1,	0.69	0.0	91.6053	0.0839	83.2649	0.16	No

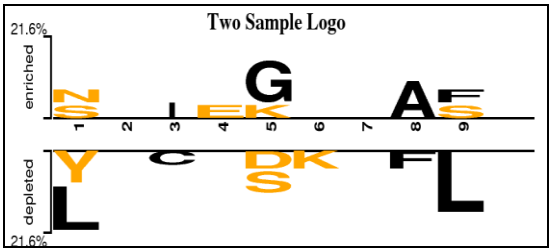

Fig. 2 2 sample Logo demonstrating domination of exterior available amino acids in T-cell peptides. Black and yellow colour residues indicate to surface non-available and available amino acids correspondingly.

4. CONCLUSION

Hidden Markov models have turned out to be very popular tools for analysis of biological sequence. Considering dependency among emissions seems reasonable and leads to some improvement in the prediction accuracy of epitopes. Towards this effort, linear epitopes based on T cell were recognized with improved accuracy. In this direction, our preliminary literature review discovered that the existing level of accuracy tended to attain saturation and was not adequate medically. Accuracy deficit remain a major setback despite presence of a wide selection of properties of small sequences of peptides representing these epitopes. Hidden Markov models offer a robust statistical support for modeling and classifying protein stretches in to epitopic and non-epitopic regions. We anticipate that their biological significance as well as their applicability range will develop only in future.

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