

# BiodMHC: an online server for the prediction of MHC class II-peptide binding affinity

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Received for publication 1 December 2008; revised 8 January 2009; accepted 21 January 2009

## Abstract

Effective identification of major histocompatibility complex (MHC) molecules restricted peptides is a critical step in discovering immune epitopes. Although many online servers have been built to predict class II MHC-peptide binding affinity, they have been trained on different datasets, and thus fail in providing a unified comparison of various methods. In this paper, we present our implementation of seven popular predictive methods, namely SMM-align, ARB, SVR-pairwise, Gibbs sampler, ProPred, LP-top2, and MHCpred, on a single web server named BiodMHC (<http://biod.whu.edu.cn/BiodMHC/index.html>, the software is available upon request). Using a standard measure of AUC (Area Under the receiver operating characteristic Curves), we compare these methods by means of not only cross validation but also prediction on independent test datasets. We find that SMM-align, ProPred, SVR-pairwise, ARB, and Gibbs sampler are the five best-performing methods. For the binding affinity prediction of class II MHC-peptide, BiodMHC provides a convenient online platform for researchers to obtain binding information simultaneously using various methods.

**Keywords:** MHC II; MHC-peptide binding predictions; web server

## Introduction

Major histocompatibility complex (MHC) molecules bind short peptides derived from antigens and present them on the surface for inspection by the T-cell receptor (Parham, 2005). The underlying molecular mechanisms of this selectivity are still indistinct, but one crucial factor is that the amino acids in the antigen peptide and the MHC binding pocket are complementary (Yewdell and Bennink,

1999). Based on the distinct roles in immune systems, MHC molecules can be classified into MHC class I molecules and MHC class II molecules. MHC class I molecules present short endogenous peptides to CD8 cytotoxic T lymphocytes (CTL), whereas MHC class II molecules present peptides from exogenous resources to CD4 helper T cells. Successful identification of MHC restricted peptides undoubtedly accelerates the time-consuming process of vaccine design and production.

The prediction of MHC class II peptide binding affinity is more difficult than that of MHC class I peptide (Peters et al., 2006; Zhu et al., 2006; Wang et al., 2008). This is mainly due to the high flexibility in the position of the binding core of MHC class II binding peptides. From the

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structural point of view, the binding groove of MHC class I molecules closed at both ends make the binding core length-fixed, which is usually around 9 residues. The binding groove of MHC class II molecules, however, is open at both ends and peptides are generally longer than those that bind to MHC class I molecules, which are typically 9 to 25 residues. Moreover, a recent study speculates that binding may not be completely deterministic, as the same peptide may have multiple possible binding cores (Tong et al., 2006). In addition, several studies indicate that the binding core is not the only factor, because residues outside of the binding groove (flanking residues) also influence the binding ability (Carson et al., 1997). All of these make it very complicated to predict the binding affinity of MHC class II-peptide, leading to the prediction performance far from satisfaction (Wang et al., 2008).

In spite of high complexities, there are many popular tools for the binding prediction of MHC class II-peptide, such as NetMHCII (Nielsen et al., 2007), ARB (Bui et al., 2005), Gibbs sampler (Nielsen et al., 2004), ProPred (Sturniolo et al., 1999), LP-top2 (Murugan and Dai, 2005), and MHCpred (Guan et al., 2003). Several classical algorithms on the binding prediction of MHC-peptide provided in the tools are Stabilization matrix alignment (SMM-align) (Nielsen et al., 2007), LP (Linear Programming), PLS (Partial Least Squares), Gibbs sampling, and SVM (Support Vector Machine). All these tools validate the algorithms on different datasets, thereby failing in providing a uniform comparison. In order to provide a convenient platform for researchers, we implement the prediction models of these popular methods on the same dataset.

## Materials and methods

### Data

Two datasets are used in this paper. The first dataset is available at <http://www.cbs.dtu.dk/suppl/immunology/NetMHCII.php> (Nielsen et al., 2007). This dataset consists of 14 HLA-DR alleles including 9 HLA-DR supertypes, and 3 mouse H2-IA alleles (Table 1). The second dataset was downloaded from [http://mchbindingpredictions.immuneepitope.org/MHCII/\(Wang et al., 2008\)](http://mchbindingpredictions.immuneepitope.org/MHCII/(Wang et al., 2008)), which includes 14 HLA-DR alleles and 2 mouse H2 alleles (Table 2). A threshold of 500 nM in binding affinity is set to classify peptides into binders and non-binders. Similar to the work by Nielsen and his colleagues (Nielsen et al., 2007), the binding affinity is transformed using  $\log_{50k}$ . That is, for

Table 1  
An overview of the IEDB dataset

Type	Allele	Binder	Non-binders	Total
Mouse H2	I-Ab	43	33	76
	I-Ad	56	286	342
	I-As	35	91	126
Human HLA	DRB1-0101	921	282	1,203
	DRB1-0301	65	409	474
	DRB1-0401	209	248	457
	DRB1-0404	74	94	168
	DRB1-0405	88	83	171
	DRB1-0701	125	185	310
	DRB1-0802	58	116	174
	DRB1-0901	47	70	117
	DRB1-1101	95	264	359
	DRB1-1302	101	78	179
	DRB1-1501	188	177	365
	DRB3-0101	3	99	102
DRB4-0101	74	107	181	
DRB5-0101	112	231	343	

Table 2  
An overview of the Sette dataset

Type	Allele	Binder	Non-binders	Total
Mouse H2	I-Ab	107	393	500
	I-Ed	14	25	39
Human HLA	DRB1-0101	2,579	1,303	3,882
	DRB1-0301	209	293	502
	DRB1-0401	286	226	512
	DRB1-0404	286	163	449
	DRB1-0405	338	119	457
	DRB1-0701	358	147	505
	DRB1-0802	90	155	245
	DRB1-0901	209	203	412
	DRB1-1101	317	203	520
	DRB1-1302	83	206	289
	DRB1-1501	252	268	520
	DRB3-0101	70	350	420
DRB4-0101	123	122	245	
DRB5-0101	356	164	520	

a peptide with binding affinity of  $aff$ , its transformed value is  $1 - \log_{50k}(aff)$ . Based on this formula, a peptide whose transformed value is no less than 0.426 is classified as a binder. Additionally, if the affinity value of a peptide is greater than 50,000 nM, its value is then assigned to be zero after the transformation. In this paper, we name the two

datasets as the IEDB dataset and the Sette dataset, respectively. As shown in Table 3, there is very little overlapping in peptides between IEDB and Sette for the same MHC allele.

Table 3  
Overlaps between the IEDB dataset and Sette dataset in each allele

Type	Allele	IEDB dataset	Sette dataset	Overlaps	
Mouse H2	I-Ab	76	500	0	
	DRB1-0101	1,203	3,882	1	
	DRB1-0301	474	502	1	
	DRB1-0401	457	512	1	
	DRB1-0404	168	449	0	
	DRB1-0405	171	457	0	
	DRB1-0701	310	505	1	
	Human HLA	DRB1-0802	174	245	0
		DRB1-0901	117	412	0
		DRB1-1101	359	520	1
DRB1-1302		179	289	0	
DRB1-1501		365	520	1	
DRB3-0101		102	420	0	
DRB4-0101		181	245	0	
DRB5-0101		343	520	0	

### Server interface

The server is a JSP project under Apache 5.0 running on the Linux system. The interface is simple and easy to use. After entering the sequence(s) of a protein antigen, users can select an MHC allele and a prediction method (Fig. 1). Different methods may have various outputs, and the annotation in result pages will give the users enough information on measuring the binding affinity (Fig. 2).

### Prediction methods

#### SMM-align

The stabilization matrix alignment (SMM-align) is a novel matrix-based method that considers the flanking residues outside of binding grooves. The basic idea of this method is to find a weight matrix that optimally reproduces the measured IC50 values for each peptide in the training set (Swets, 1988; Nielsen et al., 2007) and incorporates the Gibbs sampler (Nielsen et al., 2004) method. By considering the flanking peptide residues, the SMM-align method tends to improve the performance compared with other score matrix-based methods. In this paper, the SMM-align method is implemented in the same way as

Fig. 1. The input interface of BiodMHC.

**BiodMHC MHC-II binding prediction online service**

**Method**  
ARB

**Specification**  
The Average Relative Binding (ARB) matrix method introduced by Huynh-Hoa et al. (Bui et al., 2005) has made a favorable performance in both MHC I and MHCII (Wang et al., 2008). Compared with other popular methods, ARB matrix method is constructed in a lower complexity which makes it advantaged in dealing with large dataset.  
The peptide is a binder when the predicted score is > the threshold .

Number	Sequence	Score	Threshold
1	VDAQGTLISKIFKLGGRDSRS	1.168	1.3
2	LGALGTGVVYNHLTPLRDWA	1.255	1.3
3	CGKYLFWAVRKLKLTPIA	1.267	1.3
4	QLQPSLQGTGSEELRSLY	1.159	1.3
5	RQANFLGKIWFPSKGR	1.154	1.3
6	YILLKKILSSRFNQIM	1.299	1.3
7	VYSVFLYLYTFYFTIN	1.235	1.3
8	VQHVVVKSALLADKF	1.329	1.3

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Fig. 2. The output interface of BiodMHC.

described (Nielsen et al., 2007). There is also a public service called NetMHCII using the SMM-align, which is available at <http://www.cbs.dtu.dk/services/NetMHCII/>.

#### ARB

The Average relative binding (ARB) matrix method (Bui et al., 2005) has achieved a favorable performance in predicting both MHC I (Peters et al., 2006) and MHC II (Wang et al., 2008). The matrix is estimated as:

$$w_{i,a} = 10^{P_{i,a} - Q_{i,a}}$$

In the above equation,  $i$  is a position in the 9-mer binding core and  $a$  is an amino acid.  $P_{i,a}$  is the geometric average value of binding affinity (IC50) of peptides that contain the residue at position  $i$  with amino acid  $a$ .  $Q_{i,a}$  is the same value of the rest peptides. The score of a nine-residue core sequence is calculated by:

$$S = \left( \prod_{i=1}^9 w_{i,a} \right)^{-\frac{1}{9}}$$

The maximum value of  $S$  among all nine substrings is assigned as the score of the whole peptide. An iterative procedure finds the finest 9-mer binding cores of all the peptides with the best agreement between the predicted values (score) and the true values (IC50).

#### SVR-pairwise

Motivated by the fact that the structure or function of an

unknown protein can be inferred from the sequence similarity with one or more proteins whose structures or functions are already known, we propose an approach to represent proteins using the similarity scores of pairwise sequences. Based on the existing research of protein homology prediction using SVM-pairwise (Liao and Noble, 2003), we introduce SVR-pairwise for the binding affinity prediction of MHC II-peptide. The method is implemented as follows. First, we transform each peptide into a fixed-length vector. In this step, each peptide in the training set is compared against all peptides in the same training set including itself one by one. The dimension of the vector representing this peptide is equal to the number of the peptides in the training set. The Smith-waterman algorithm is used for pairwise comparison in this step. Second, we construct an SVR model from the training data. Here we introduce LIBSVM (<http://www.csie.ntu.edu.tw/~cjlin/libsvm/>) which is an open package that provides both SVC and SVR to train the model from the training data. Third, we predict the binding affinities of each input peptide. Through the pairwise comparison with the peptides in the training set, each peptide in the test dataset can be transformed into an  $n$ -dimensional vector where  $n$  is the number of peptides in the corresponding training set. Using this vector as the input, the SVR model can predict the binding affinity of the input peptide.

#### Gibbs sampler

We implement the Gibbs sampler prediction method

based on Nielsen and his colleagues' work (Nielsen et al., 2004). We first use Gibbs sampling to find the binding core of all positive peptides ( $IC_{50} < 500$  nM) and then input those sequences into hmmer downloaded from <http://hmmer.janelia.org/>. Finally, the score of a new peptide can be obtained by hmsearch contained in hmmer. In the Gibbs sampler method, only the sequences of binding peptides are used in building the model.

### ProPred

According to the theory presented by Sturniolo et al. (1999), the pocket profiles of HLA-DR can be described quantitatively *via* the interactions of all natural amino acids with given pockets, which are called as "binding pocket profile". Such pocket profiles are usually independent of the remaining HLA-DR groove. This means that a relatively small number of pocket profiles can be assigned to a large number of HLA-DR alleles *via* sequence comparison. In this way, we introduce the virtual matrices (can be downloaded from <http://www.imtech.res.in/raghava/PROPPRED/page4>) to score peptides through the nonapeptide sliding-window.

### LP-top2

We implement a LP model that distinguishes disjoint sets in the 180-dimensional real space  $R^n$ , in which one point denotes a sliding-nonapeptide-window. For solving the LP problem, we score each nonapeptide in positive training sequences using function  $f(x) = w^T x + b$  after obtaining a weight vector  $w$  and value  $b$ . Nonapeptides with negative scores are moved to the negative set. We keep sliding-nonapeptide-windows that obtain the two highest positive scores in a peptide. In order to predict the peptides in the test set, our training process with LP modeling is then executed again to form the final LP function  $f(x)$  as described above. More details can be found in Merugan and Dai (2005).

### MHCPred

The partial least squares (PLS) method was first developed in the 1960's by Herman Wold as an econometric technique (Henseler and Kaplan, 2004). PLS analysis is a multivariate statistical technique that compares multiple response variables with multiple explanatory variables. It can deal with deficiency in data such as the small size of datasets, missing values, and multicollinearity, which cannot be resolved by the ordinary least squares (OLS) regression. PLS has been employed by an online server to predict MHC-peptide binding (<http://www.Jenner.ac.uk/>

MHCPred/). However, it has only three MHC class II alleles. In contrast, here we employ PLS and Gibbs sampling to construct training models on the NetMHC2 dataset for all MHC class II alleles. In particular, Gibbs sampler is used to find the binding core of training datasets. We construct training models as Doytchinova and Flower did (Doytchinova and Flower, 2003). As for prediction, we compute the score of each possible nonapeptide in a peptide and choose the maximal one as the predicted score of the peptide.

## Results

Our experiment includes two parts: 1) construct a prediction model on the IEDB dataset and evaluate its performance using 5-fold cross validation. We made use of the same partition of the IEDB dataset as that used in SMM-align (Nielsen et al., 2007); 2) after training the model with the whole IEDB dataset, we evaluate the model performance on an independent test dataset of the Sette dataset. For a fair comparison, the small overlap with IEDB in the Sette dataset was removed before evaluation. Using the AUC value, we evaluate the prediction performance of each model. The AUC value is equal to the area under the receiver operating the characteristic (ROC) curve, which plots sensitivity against 1-specificity. Sensitivity is the rate of correctly classified positive instances, while specificity refers to the rate of correctly classified negative instances. The value of AUC measures the classifier's ability of discriminating positive instances from negative instances. This value usually ranges from 0.5 to 1, where 1 is the perfect distinguishing ability and 0.5 represents the worst one because of almost random prediction. We report the experimental results on IEDB and Sette datasets in Table 4 and Table 5, respectively. Due to the limitation of space, the top-five performances among all seven models are presented in the two tables. For each allele, we further highlight the AUC value of the best model in bold face.

As shown in Table 4 and Table 5, we can make the following observations: first, the best-performing model for both datasets is the SMM-align method, followed by ProPred, SVR-pairwise, ARB, and Gibbs sampler. In the 5-fold cross validation experiments on the IEDB dataset, the SMM-align has achieved an AUC average value of 0.78, ProPred of 0.74, and SVR-pairwise of 0.72. In addition, performing the experiments on the Sette dataset, the SMM-align has achieved an AUC average value of 0.73,

Table 4  
Performance comparisons of different models on the IEDB dataset using 5-fold cross-validations

Type	Allele	AUC				
		SMM-align	ProPred	SVR-pairwise	ARB	Gibbs sampler
Mouse H2	I-Ab	<b>0.91</b>		0.78	0.82	0.83
	I-Ad	<b>0.82</b>		0.70	0.66	0.68
	I-As	<b>0.90</b>		0.75	0.80	0.75
Human HLA	DRB1-0101	<b>0.72</b>	0.65	0.71	0.66	0.61
	DRB1-0301	<b>0.77</b>	0.72	0.66	0.67	0.70
	DRB1-0401	<b>0.76</b>	0.75	0.69	0.65	0.70
	DRB1-0404	0.79	<b>0.83</b>	0.71	0.70	0.68
	DRB1-0405	0.74	<b>0.79</b>	0.66	0.72	0.63
	DRB1-0701	0.79	0.76	0.67	0.71	0.68
	DRB1-0802	0.76	0.77	<b>0.85</b>	0.67	0.71
	DRB1-0901	<b>0.78</b>		0.64	0.55	0.64
	DRB1-1101	0.73	0.71	<b>0.76</b>	0.65	0.66
	DRB1-1302	<b>0.82</b>	0.72	0.80	0.79	0.79
	DRB1-1501	0.74	0.72	<b>0.76</b>	0.70	0.68
	DRB4-0101	0.74		0.71	<b>0.76</b>	0.67
	DRB5-0101	0.66	0.66	<b>0.69</b>	0.66	0.62
	Maximum	0.91	0.83	0.85	0.82	0.83
	Minimum	0.66	0.65	0.64	0.55	0.61
Average	0.78	0.74	0.72	0.70	0.70	

For each allele, the highest AUC is highlighted in bold face.

Table 5  
Performance comparisons of different models on the Sette dataset by training the prediction model on the IEDB dataset

Type	Allele	Model				
		SMM	ProPred	SVR-pairwise	ARB	Gibbs sampler
Mouse H2	I-Ab	<b>0.75</b>		0.71	0.61	0.65
	I-Ad	–		–	–	–
	I-As	–		–	–	–
Human HLA	DRB1-0101	<b>0.77</b>	0.74	<b>0.77</b>	0.70	0.72
	DRB1-0301	<b>0.69</b>	0.65	0.61	0.58	0.53
	DRB1-0401	0.68	<b>0.69</b>	0.64	0.65	0.58
	DRB1-0404	0.75	<b>0.79</b>	0.64	0.68	0.70
	DRB1-0405	0.69	<b>0.75</b>	0.55	0.58	0.62
	DRB1-0701	<b>0.78</b>	<b>0.78</b>	0.70	0.64	0.68
	DRB1-0802	0.75	0.77	<b>0.79</b>	0.66	0.69
	DRB1-0901	<b>0.66</b>		0.57	0.60	0.60
	DRB1-1101	<b>0.81</b>	0.80	0.70	0.68	0.66
	DRB1-1302	<b>0.69</b>	0.58	0.68	0.65	0.67
	DRB1-1501	<b>0.74</b>	0.72	0.65	0.66	0.61
	DRB4-0101	0.71		<b>0.72</b>	<b>0.72</b>	0.68
	DRB5-0101	0.75	<b>0.79</b>	0.67	0.70	0.74
	Maximum	0.81	0.80	0.79	0.72	0.74
	Minimum	0.66	0.58	0.55	0.58	0.53
Average	0.73	0.73	0.67	0.65	0.65	

For each allele, the highest AUC is highlighted in bold face.

ProPred of 0.73, and SVR-pairwise of 0.67 using the model trained on the IEDB dataset.

Second, except for ProPred, the performances of all other models decrease significantly when these models are applied to the Sette dataset other than to cross validation of the IEDB dataset. For example, the AUC value of SMM-align decreases from 0.78 to 0.73, and the one of SVR-pairwise decreases from 0.72 to 0.67. This reflects a common fact in the application of machine learning techniques. Since the distribution of test datasets may differ from that of training data, the model learned from training data may overfit the training data. The performance of the model would therefore decrease significantly on unseen test data. Here only the ProPred model performs almost equally well on both datasets. This is because ProPred is trained by the quantitative peptide binding profiles and the structure information of each MHC allele, which are independent from the two datasets (Sturniolo et al., 1999).

Third, the best-performing method for different alleles varies considerably from case to case. Although the SMM-align method achieves the highest AUC average score, it is not the best-performing model for all alleles. For example, in the IEDB dataset, ProPred obtains the highest AUC score on DRB1-0404 and DRB1-0405, SVR-pairwise on DRB1-0802, DRB1-1101, DRB1-1501 and DRB5-0101, and ARB on DRB4-0101. On the other hand, in the Sette dataset, ProPred achieves the highest AUC on DRB1-0401, DRB1-0404, DRB1-0405, DRB1-0701 and DRB5-0101, SVR-pairwise on DRB1-0101, DRB1-0802 and DRB4-0101, and ARB on DRB4-0101.

## Discussion

The prediction of binding affinity of MHC II-peptide is crucial to the development of computer-aided vaccine design. As many online tools for MHC class II peptide binding prediction have been developed, such as NetMHCII, ARB (Bui et al., 2005), and ProPred (Sturniolo et al., 1999), it is important to identify satisfactory prediction models that can help biologists to make a choice. Although Wang and colleagues (Wang et al., 2008) compared several popular models by making predictions on the Sette dataset, each model was trained on distinct training datasets, and thus the result would be biased. With all models (except for ProPred that uses the virtual matrix directly) being trained with the same dataset, here we provide a uniform platform that is able to evaluate the performance of different prediction methods. In addition, the evaluation uses

internal cross validation, as well as independent test datasets. We also implemented a new model called SVR-pairwise, which incorporates the pairwise alignment into SVR for the binding affinity prediction. Experimental results have shown that the best prediction model is SMM-align, followed by ProPred, SVR-pairwise, ARB, and Gibbs sampler.

In this study, the AUC average value that has been achieved by the best model of SMM-align is around 0.75 for predicting binding affinity of MHC II peptide. In contrast, for MHC I peptide binding prediction, the AUC average value achieved by one of the best models, SMM (Peters and Sette, 2005), is higher than 0.85 (Peters et al., 2006). It is obvious that there is a large gap between MHC I peptide and MHC II peptide on the performances of their binding prediction. One important reason for this is that the length variation in MHC II binding peptides makes it difficult to predict the binding core. Improving the performance of MHC II peptide binding prediction thus becomes a challenging problem in immunological bioinformatics. Our experimental results shed light on how to enhance the prediction performance. First, the steady and good prediction capacity of ProPred demonstrates the importance of utilizing structure information of MHC molecules. Most existing methods use only sequence information of binding peptides for prediction. We speculate that the performance can be further improved by incorporating the structure information of MHC alleles. Additionally, we can combine different prediction models for improving the performance by means of the ensemble method. As demonstrated in the experiment, the best prediction model varies from case to case. Ensemble learning works very well when the component models are diverse and accurate (Duda et al., 2001; Polikar, 2006). In our case, the variation of the best prediction model and close performance of top models provide a substantial basis for adopting ensemble learning methods. Our future works will integrate more methods relating to MHC class II prediction into our web server, and update the existing models when new data are available.

## Acknowledgements

This work was supported by the National Nature Science Foundation of China (No. 60773010) and the Shanghai Committee of Science and Technology, China (No. 08DZ2271800 and 09DZ2272800). We would like to thank Mr. Hongbiao Liu for his earnest guidance and Mr. Yi Xiong for his enthusiastic help in constructing the web server.

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