



## Editorial

# Machine learning competition in immunology – Prediction of HLA class I binding peptides

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## 1. Introduction

Experimental studies of immune system and related applications such as characterization of immune responses against pathogens, vaccine design, or optimization of therapies are combinatorially complex, time-consuming and expensive. The main methods for large-scale identification of T-cell epitopes from pathogens or cancer proteomes involve either reverse immunology or high-throughput mass spectrometry (HTMS). Reverse immunology approaches involve pre-screening of proteomes by computational algorithms, followed by experimental validation of selected targets (Mora et al., 2006; De Groot et al., 2008; Larsen et al., 2010). HTMS involves HLA typing, immunoaffinity chromatography of HLA molecules, HLA extraction, and chromatography combined with tandem mass spectrometry, followed by the application of computational algorithms for peptide characterization (Bassani-Sternberg et al., 2010). Hundreds of naturally processed HLA class I associated peptides have been identified in individual studies using HTMS in normal (Escobar et al., 2008), cancer (Antwi et al., 2009; Bassani-Sternberg et al., 2010), autoimmunity-related (Ben Dror et al., 2010), and infected samples (Wahl et al., 2010).

Computational algorithms are essential steps in high-throughput identification of T-cell epitope candidates using both reverse immunology and HTMS approaches. Peptide binding to MHC molecules is the single most selective step in defining T cell epitope and the accuracy of computational algorithms for prediction of peptide binding, therefore, determines the accuracy of the overall method. Computational predictions of peptide binding to HLA, both class I and class II, use a variety of algorithms ranging from binding motifs to advanced machine learning techniques (Brusic et al., 2004; Lafuente and Reche, 2009) and standards for their

assessments have been developed. The assessments of computational servers that predict peptide binding to several common HLA class I alleles have been performed by different groups (see Peters et al., 2006; Lin et al., 2008; Gowthaman et al., 2010). Some of these models were reported to be highly accurate while others need improvement.

## 2. The competition

Computational methods offer key support for collection, processing, and analysis of high-throughput data in immunology. This issue of the Journal of Immunological Methods focuses on machine learning aspects of high-throughput methods for identification of T cell epitopes. Here we report the results of machine learning competition where the target was to benchmark the performance of computational methods of peptide binding to three HLA class I molecules, HLA-A\*01:01, –A\*02:01, and B\*07:02, using newly generated sets of 9-mer and 10-mer peptides. The competition aims were: (a) Compare two classical benchmark methods to a selection of existing and novel methods to assess the ability to improve prediction accuracy and (2) Assess the accuracy of predicting 9-mers as well as 10-mers for these alleles. There were 20 contestants, including both existing and newly developed methods. For new contestants, the pre-processed training data were available from the DFMRLI web site (Zhang et al., 2011-a this issue) and also from other public sources such as IEDB, SYFPEITHI, MHCPEP, ANTIJEN, and MHCBN (Vita et al., 2010; Schuler et al., 2007; Brusic et al., 1998; Toseland et al., 2005; Lata et al., 2009). The target data are described in Rock et al. (2011-this issue) and the selection of alleles was limited by this study. These target data include 144 binders and 651 non-binders (9-mers) as well as 86 binders and 487 non-binders (10-mers) (Table 1). The competition was held in conjunction with the 19th International Conference on Artificial Neural Networks, held on 14–17 September 2009, Limassol, Cyprus.

The experimental measurement of peptide binding was identified using iTopia system (Wulf et al., 2009). The performance of 20 prediction systems in the competition and two benchmark predictors BIMAS ([www.bimas.cit.nih.gov/molbio/hla\\_bind/](http://www.bimas.cit.nih.gov/molbio/hla_bind/); Parker et al., 1994) and SYFPEITHI ([www.](http://www.)

**Table 1**

The number of test peptides in each studied group.

	9-mers		10-mers	
	Binder	Non-binder	Binder	Non-binder
A*01:01	25	240	14	177
A*02:01	76	189	62	129
B*07:02	43	222	10	181
Total	144	651	86	487

syfpeithi.de, Schuler et al., 2007) was compared with experimental results. The predictive performance was assessed in accordance to criteria defined in Lin et al.(2008), where classification into binders and non-binders was performed, followed by prediction of binding affinity. Briefly, methods were assessed both on classification accuracy – predicting binders vs. non-binders, and on overall ranking, as measured by correlation coefficients between actual and predicted binding affinities. Methods were ranked both for six individual prediction tasks (i.e. predicting 9-mer and 10-mer binders for all three studied alleles) and for overall performance, measured by ranking the average performance of each predictor for six individual tasks.

The classification performance problem (see Table 2) – prediction of binders vs. non-binders – indicated that 15 (75%) of predictors and both benchmark predictors showed excellent performance in classification of HLA-A\*01:01 9-mer binders. Nineteen (95%) predictors and both benchmark predictors showed excellent performance in prediction of HLA-A\*02:01 9-mer binders. 16 (80%) of the predictors and

**Table 2**

The prediction systems assessment for classification into binders and non-binders using the area under the ROC curve (see Lin et al., 2008; Swets, 1988). The respective values of  $A_{ROC} > 0.9$ ,  $0.8 < A_{ROC} < 0.9$ , and  $A_{ROC} < 0.8$  indicate excellent, moderate, and poor classification performance. The best performing predictors are indicated by shaded fields.

	Area under the ROC curve ( $A_{ROC}$ )					
	A*01:01 9mer	A*02:01 9mer	B*07:02 9mer	A*01:01 10mer	A*02:01 10mer	B*07:02 10mer
BIMAS	0.91	<b>0.99</b>	<b>0.92</b>	<b>0.92</b>	<b>0.99</b>	<b>0.85</b>
SYFPEITHI	<b>0.92</b>	0.98	0.72	0.69	0.96	0.82
Bunsen	0.94	<b>0.99</b>	0.94	0.88	0.98	0.89
FragS	0.77	0.93	0.90	0.92	0.93	0.86
FudanCS	0.95	<b>0.99</b>	<b>0.95</b>	<b>0.95</b>	<b>0.99</b>	<b>0.88</b>
H00001	<b>0.97</b>	<b>0.99</b>	<b>0.96</b>	0.96	0.99	0.90
hnp	0.95	0.98	0.95	0.89	0.98	<b>0.97</b>
I00001	0.96	<b>0.99</b>	<b>0.95</b>	0.97	0.98	0.89
imaginary1	0.96	<b>0.99</b>	<b>0.96</b>	0.81	0.41	0.73
imaginary2	0.91	0.94	0.94	0.98	0.98	0.95
imaginary3	0.96	<b>0.99</b>	<b>0.96</b>	0.95	0.95	0.89
lpp729	0.91	<b>0.99</b>	0.91	0.81	0.94	0.83
MHChackers1	0.46	0.58	0.52	0.53	0.51	0.53
N00001	0.96	<b>0.99</b>	<b>0.95</b>	<b>0.99</b>	<b>0.99</b>	0.94
N00002	0.96	<b>0.99</b>	<b>0.96</b>	<b>0.98</b>	<b>0.99</b>	<b>0.97</b>
N00003	0.96	<b>0.99</b>	<b>0.96</b>	<b>0.99</b>	<b>0.99</b>	0.95
P00001	0.93	<b>0.99</b>	0.92	0.95	0.98	0.91
PepMHC-I	0.88	<b>0.99</b>	0.94	0.85	<b>1.00</b>	0.89
SBS	0.93	<b>0.99</b>	0.95	0.73	0.97	0.89
St+	0.86	0.91	0.90	0.92	0.83	0.83
SuperMHC	0.90	0.98	0.94	0.92	0.97	0.87
SuperMHCR	0.92	0.98	0.94	0.74	0.91	0.87
Maximum value	0.97	0.99	0.96	0.99	1.00	0.97

both benchmark predictors showed excellent performance in prediction of HLA-B\*07:02 9-mer binders. 11 (50%) predictors and one benchmark predictor showed excellent performance in prediction of HLA-A\*01:01 10-mer binders. 13 (65%) predictors and both benchmark predictors showed excellent performance in prediction of HLA-A\*02:01 10-mer binders. Only 6 (30%) predictors and no benchmark predictors showed excellent performance in prediction of HLA-B\*07:02 10-mer binders. The number of predictors that showed better performance than benchmark servers were twelve (A\*01:01 9-mers), none (A\*02:01 9-mers), fifteen (B\*07:02 9-mers), eight (A\*01:01 10-mers), one (A\*02:01 10-mers), and sixteen (B\*07:02 10-mers). In addition 13 and 4 predictors, respectively, predicted equally well as benchmark predictors in classification of A\*02:01 9-mers and 10-mers. In summary, the existing benchmark predictors (BIMAS and SYFPEITHI) showed excellent classification performance for HLA-A\*02:01, for both 9-mer and 10-mer peptides. The majority of modern predictors showed equal or improved predictions as compared to the benchmark performance. Modern predictors showed marked improvements over classification performance for A\*01:01 and B\*07:02. The  $A_{ROC}$  values of best predictors range from 0.96 to 1.00 showing nearly perfect classification performance (Table 3). The results show that the leading modern predictors have improved prediction performance relative to the benchmark predictors. The greatest improvement was shown for HLA-B\*07:02 10-mers. The analysis of prediction of binding affinity results (Table 4) shows that predictor performance, measured by correlation coefficient, ranges from  $r = 0.663$  to  $r = 0.931$ . This represents a marked improvement over the performance of benchmark methods ( $r = 0.455$  to  $r = 0.775$ ).

**Table 3**

Average classification performance of each predictor. The best prediction results are shaded.

	Rank		Rank		Rank	
	AVE	AVE	AVE 9-mers	AVE 9-mers	AVE 10-mers	AVE 10-mers
BIMAS	0.93	(12)	0.94	(14)	0.92	(11)
SYFPEITHI	0.85	(19)	0.87	(19)	0.82	(19)
Bunsen	0.94	11	0.96	8	0.92	11
FragS	0.89	16	0.87	19	0.90	14
FudanCS	0.95	6	0.96	8	0.94	9
H00001	0.96	4	0.97	1	0.95	5
hnp	0.95	6	0.96	8	0.95	5
I00001	0.96	4	0.97	1	0.95	5
imaginary1	0.81	19	<b>0.97</b>	1	0.65	19
imaginary2	0.95	6	0.93	17	0.97	3
imaginary3	0.95	6	<b>0.97</b>	1	0.93	10
lpp729	0.90	15	0.94	14	0.86	15
MHChackers1	0.52	20	0.52	20	0.52	20
N00001	0.97	2	<b>0.97</b>	1	0.97	3
N00002	<b>0.98</b>	1	0.97	1	<b>0.98</b>	1
N00003	0.97	2	<b>0.97</b>	1	<b>0.98</b>	1
P00001	0.95	6	0.95	12	0.95	5
PepMHC-I	0.93	12	0.94	14	0.91	13
SBS	0.91	14	0.96	8	0.86	15
St+	0.88	18	0.89	18	0.86	15
SuperMHC	0.93	12	0.94	14	0.92	11
SuperMHCR	0.89	16	0.95	12	0.84	18
Maximum value	0.98		0.97		0.98	

**Table 4**

Prediction of binding affinity performance for competitors and benchmark predictors.

	CORRELATION COEFFICIENT						Average
	A0101 9mer	A0201 9mer	B0702 9mer	A0101 10mer	A0201 10mer	B0702 10mer	
<b>BIMAS</b>	0.293	0.448	<b>0.513</b>	<b>0.455</b>	0.496	<b>0.576</b>	0.464
<b>SYFPEITHI</b>	<b>0.553</b>	<b>0.775</b>	0.324	0.174	<b>0.750</b>	0.453	0.505
<b>Bunsen</b>	0.609	0.848	0.688	0.408	0.855	0.526	0.656
<b>FragS</b>	0.384	0.642	0.539	0.490	0.697	0.447	0.533
<b>FudanCS</b>	0.377	0.675	0.492	0.267	0.535	0.314	0.443
<b>H00001</b>	0.406	0.706	0.555	0.332	0.641	0.353	0.499
<b>hnp</b>	0.632	0.900	0.728	0.448	0.803	0.514	0.671
<b>I00001</b>	0.541	0.773	0.626	0.498	0.810	0.442	0.615
<b>imaginary1</b>	0.739	0.888	0.764	0.454	0.196	0.216	0.543
<b>imaginary2</b>	0.557	0.826	0.656	0.603	0.818	0.567	0.671
<b>imaginary3</b>	0.193	0.311	0.232	0.376	0.718	0.299	0.355
<b>lpp729</b>	0.471	0.856	0.542	0.307	0.733	0.437	0.558
<b>MHChackers1</b>	0.016	0.153	0.031	0.054	0.015	0.001	0.045
<b>N00001</b>	0.766	0.931	0.784	0.761	0.930	0.603	0.796
<b>N00002</b>	0.731	0.916	0.785	0.749	0.924	0.663	0.795
<b>N00003</b>	0.757	0.925	0.790	0.761	0.929	0.64	0.800
<b>P00001</b>	0.509	0.844	0.622	0.525	0.851	0.536	0.648
<b>PepMHC-I</b>	0.476	0.773	0.638	0.389	0.857	0.415	0.591
<b>SBS</b>	0.592	0.826	0.675	0.514	0.786	0.53	0.654
<b>St+</b>	0.494	0.454	0.565	0.681	0.498	0.258	0.492
<b>SuperMHC</b>	0.552	0.873	0.69	0.516	0.795	0.466	0.649
<b>SuperMHC-R</b>	0.605	0.905	0.700	0.293	0.669	0.459	0.605
<b>Maximum value</b>	0.766	0.931	0.790	0.761	0.930	0.663	0.800

The purpose of this competition was to stimulate the development of improved methods in the field, engage more contributors from the machine learning community, and define new benchmarks in the field. The best performing methods are described elsewhere in this issue. The best classifier for A\*01:01 9-mers H00001 is described in (Hu et al., 2011-this issue), the best classifier for A\*02:01 10-mers PepMHC-I in (Vider-Shalit and Louzoun, 2011-this issue). The overall winner N00003 (NetMHCcons), see Table 4, together with N00001 (netMHC) and N00002 (netMHCpan) are described in (Lundegaard et al., 2011-this issue). An additional application of N00002 is described in (Zhang et al., 2011-b this issue). Other well-performing predictors are also described: I00001 (Kim et al., 2011-this issue), and imaginary1-3 (Huang and Jovic, 2011-this issue). Previous benchmark predictors, BIMAS and SYFPEITHI showed surprisingly robust performance that has only recently been surpassed due to availability of much larger data sets.

### 3. Conclusion

This competition clearly established new benchmarks in the field of HLA binding prediction. The results are consistent with previous comparison results (Lin et al., 2008; Gowthaman et al., 2010) where similar performance of best predictors was reported. Further improvements in the field should focus in expanding the range of HLA alleles that have excellent predictive models as well as inclusion and benchmarking of predictors for 8-mers, 10-mers, and 11-mers. In particular, attention should be focused on alleles that have not been well characterized experimentally, both

to assess the ability of novel prediction methods to generalize to these alleles, and also to expand the available binding data for these alleles. In addition, there is a need for predictors for classification of naturally processed peptides that will significantly reduce the number of binders that are readily identified in binding assays, but are functionally irrelevant. This will be achieved by combining existing data with new data generated by HTMS with existing set and definition of patterns that define naturally processed peptides. We must note, however that because of the selection bias, the target data for this competition tend to favor high-affinity binders. Because of this issue the prediction results are suitable for comparison of predictor performance, but may represent an overestimate of accuracy if applied to *in silico* scanning of complete proteins or proteomes.

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