

Research article

Types of inter-atomic interactions at the MHC-peptide interface: Identifying commonality from accumulated data

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Abstract

Background: Quantitative information on the types of inter-atomic interactions at the MHC-peptide interface will provide insights to backbone/sidechain atom preference during binding. Qualitative descriptions of such interactions in each complex have been documented by protein crystallographers. However, no comprehensive report is available to account for the common types of inter-atomic interactions in a set of MHC-peptide complexes characterized by variation in MHC allele and peptide sequence. The available x-ray crystallography data for these complexes in the Protein Databank (PDB) provides an opportunity to identify the prevalent types of such interactions at the binding interface.

Results: We calculated the percentage distributions of four types of interactions at varying inter-atomic distances. The mean percentage distribution for these interactions and their standard deviation about the mean distribution is presented. The prevalence of SS and SB interactions at the MHC-peptide interface is shown in this study. SB is clearly dominant at an inter-atomic distance of 3Å.

Conclusion: The prevalently dominant SB interactions at the interface suggest the importance of peptide backbone conformation during MHC-peptide binding. Currently, available algorithms are developed for protein sidechain prediction upon fixed backbone template. This study shows the preference of backbone atoms in MHC-peptide binding and hence emphasizes the need for accurate peptide backbone prediction in quantitative MHC-peptide binding calculations.

Background

The established associations between the highly polymorphic MHC loci and several human diseases have elucidat-

ed the possible genetic basis of their predisposition. [1,2] From a classical approach of mapping an MHC allele with a particular disease, the focus has shifted to determine the

specific peptides presented to MHC molecules with clearly defined sequences. Different MHC alleles recognize different peptides and the binding probabilities of natural and non-natural peptide ligands to MHC molecules are non-static. [3] The current challenge is to screen the sequences for candidate MHC ligands or tissue specific disease-inducing peptides as relevant T-cell epitopes. Identification of T-cell epitopes associated with a particular disease can lead to the development of potential peptide vaccines. [4] Such epitopes also find application in tetramer staining as powerful immuno-markers for estimating antigen specific T cells during pathogenesis. [5] Establishing MHC binding differences to mHags (minor histocompatibility antigen peptides) will guide the interpretation of HA-1 related GvHD (Graft vs Host Disease) data in the context of different MHC alleles. [6,7] However, additional parameters describing the mechanism of peptide processing, peptide transport, loading of peptide to MHC molecules and presentation of MHC-peptide complexes for inspection by T cells are crucial in epitope selection. [8,9]

The successful sampling of short peptides from a pool of viral or bacterial protein sequences using MHC-peptide binding prediction programs depends on the accuracy of their algorithms. A number of computational methods have been developed for the prediction of MHC-peptide binding [10–26]. Using data from allele specific binding experiments – sequence binding motif analysis [10]; weight matrices [11–13], ANN [14–16], HMM [17] and iterative stepwise discriminant meta-algorithm [18] have been applied for predictions. These algorithms have been used to predict peptide binding to very few MHC molecules because binding data is not available for many alleles. Protein threading [19–22] and side-chain packing [23–26] techniques have been applied in molecular mechanics based MHC-peptide binding predictions. The molecular mechanics based binding prediction approach can be extrapolated to a wide range of MHC molecules defined by sequence nomenclature. The prediction of peptide binding to MHC molecules is described as a two-fold problem, the first being protein folding [27] and the second molecular interactions. [28–30] The problem of packing sidechains using a near native backbone has been solved. [27] Generating peptide backbones sufficiently close to the native backbone to allow packing algorithms is still a challenge. [31] Hence, methods for predicting backbone conformation are not as developed as that for sidechains.

Data for a number of A*0201, A*6801, B*0801, B*2705, B*3501, B*5301, H-2K^B, H-2D^B, H-2D^D, H-2L^D, DR1, DR2, DR3, DR4, I-A^D MHC-peptide crystal complexes are available in the PDB. A comprehensive report mapping MHC sequences with X-ray crystal structures and relative binding strength is available. [32] Recently, Cano and Fan

conceptualized peptide binding to MHC by algebraic and geometric frameworks using structural data. [33] All MHC alleles have more than 70% sequence identity with known MHC structures. [25] This allows structure prediction for the known 1,500 HLA sequences [34] using known templates. [25] Currently, accurate prediction of peptide structures in the MHC groove is not reliable due to the limited availability of peptide backbone templates and the shortcomings in the existing peptide backbone prediction methods. Using independent procedures, Schuler et al., [21,22] and Rognan et al. [23] have demonstrated a method for peptide backbone selection and showed a reasonable improvement in the MHC-peptide binding prediction. [21–23] An accurate prediction of the peptide structure in the groove can be achieved through the appropriate selection of backbone templates for threading or side chain packing. The critical nature of the backbone conformation that affects MHC-peptide binding will be interesting to investigate. The nature of inter-atomic interactions at the MHC-peptide interface has been studied for individual complexes by protein crystallographers. However, there is no comprehensive report available describing the common types of interactions in a set of MHC-peptide complexes characterized by MHC allele variation and peptide sequence diversity. The objective of this study is to find which types of inter-atomic interactions contribute more in defining the binding between peptides and MHC molecules.

Results

The available data in the PDB are redundant and hence we created a non-redundant set from those entries with the best resolution for the related structural complexes having identical sequence information. The non-redundant dataset consists of twenty-eight class I MHC-Peptide complexes and ten class II MHC-peptide complexes. All the complexes chosen for the study are characterized by variation in sequences constituting the MHC-peptide complexes. The binding of MHC and peptide can be described using inter-atomic interactions based on backbone and sidechain atom preference at their interface.

We calculated the percentage prominence for each of the four types of interactions (BB, SS, BS and SB) at the interface of these complexes (Figures 1 and 2). The backbone or sidechain atom preference at the interface induced by MHC-peptide sequence variation is estimated by calculating the mean percentage for each type in the dataset (Figures 3 and 4). The preferences for the interaction types are found to be similar between complexes but not identical (Figures 1 and 2). Therefore, we calculated the standard deviation about the mean percentage preference for each of the interaction types in both the data sets (Figures 5 and 6).

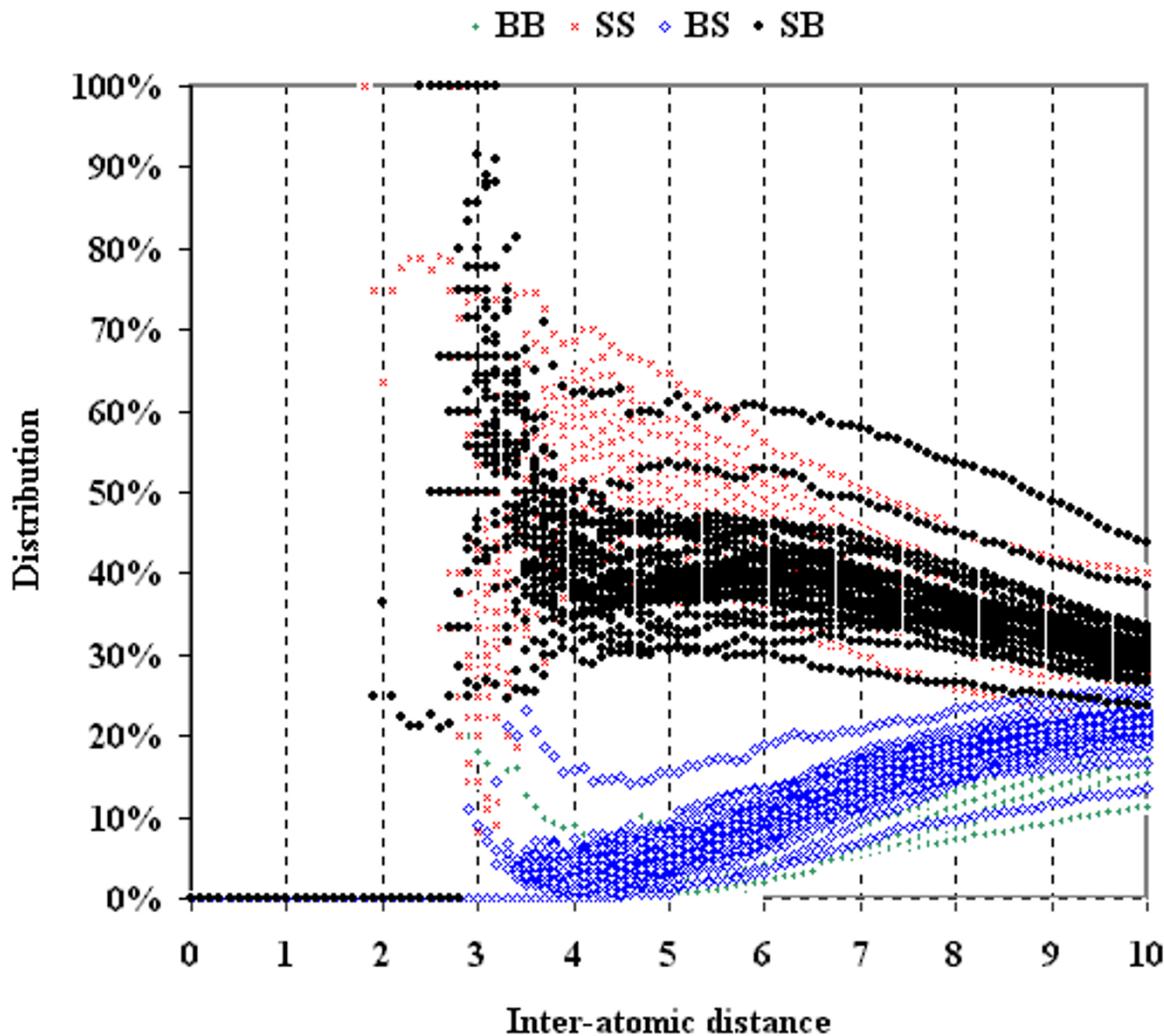


Figure 1
 Percentage distribution of the four interaction types at the interface of class I MHC-peptide complexes. Inter-atomic distances are expressed in Å units.

SS and SB interactions are prevalent compared to the other two types (Figures 3 and 4). This observation is true for both class I and class II MHC-peptide complexes. SB interactions are prevalent than SS interactions at 3Å cut-off distance in these molecules. From 3.5–6Å SS interactions dominate over SB interactions in class I complexes. At inter-atomic distances greater than 6Å, SS and SB interactions are just as prevalent. However, SB interactions are relatively dominant over SS in class II complexes.

SS and SB interactions are influenced by MHC sequence polymorphism and peptide sequence diversity. The mean

percentage distribution is maximum at an inter-atomic distance of 3Å for SS and SB interactions (Figures 3 and 4). However, the distribution of standard deviation remains at a maximum for inter-atomic distance ranges of 2–3Å in both the classes of MHC-peptide complexes (Figures 5 and 6). The standard deviation for SB type interactions is the highest in these complexes and this explains the sequence induced variation in peptide backbone/MHC sidechain atom preference during MHC-peptide binding. The sequence induced deviation for inter-atomic interactions is also observed for SS in class I complexes. It is interesting to note that the presence of BB and BS

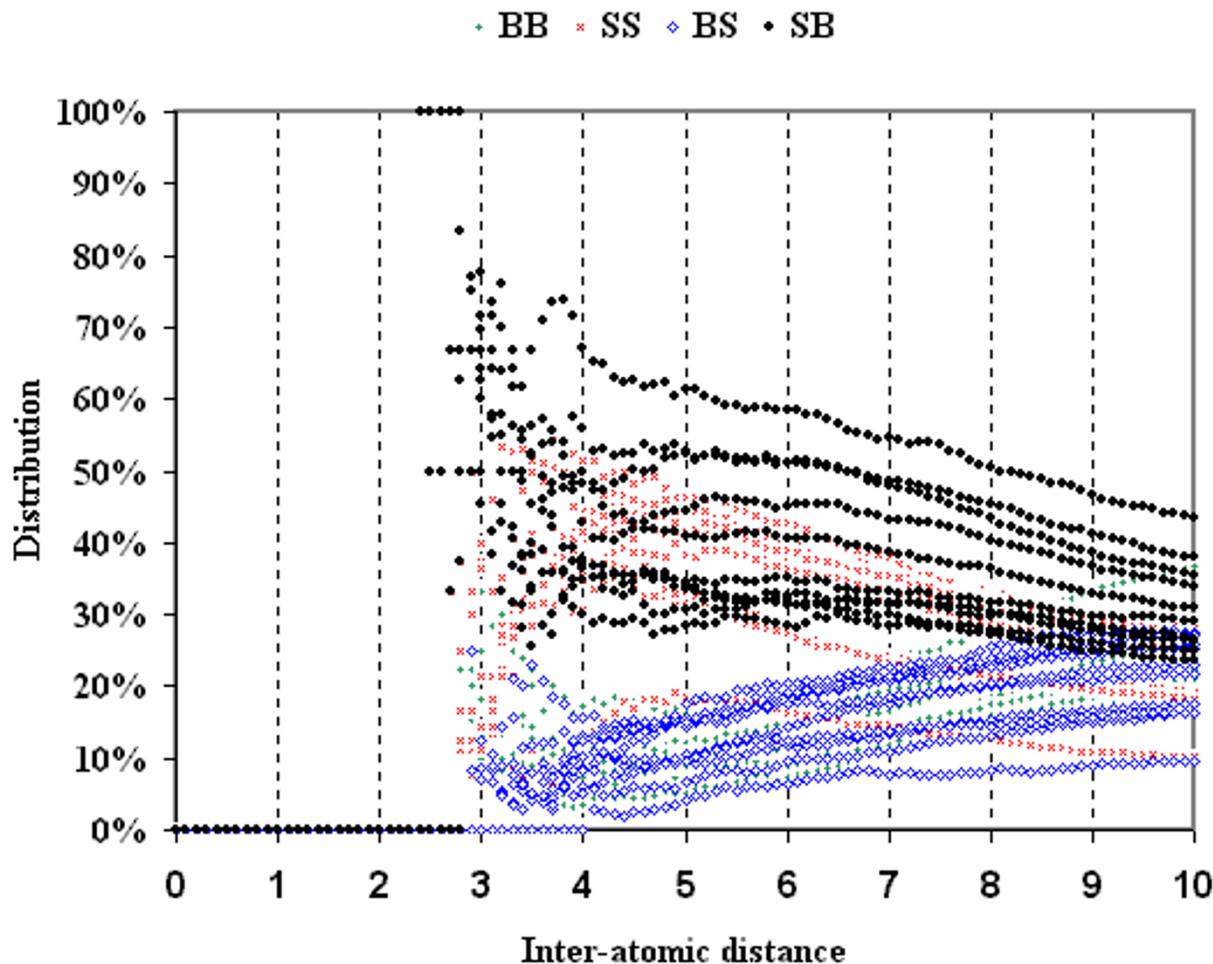


Figure 2
Percentage distribution of the four interaction types at the interface of class I MHC-peptide complexes. Inter-atomic distances are expressed in Å units.

interactions in these complexes is limited compared to the other two types and the standard deviation is also minimal (Figures 3 and 4). Our results explain the consistent prevalence of SS and SB interactions at the MHC-peptide interface.

Discussion

The differential binding of peptides to diverse MHC molecules during cell-mediated immune response has been fairly established using MHC-peptide structural data obtained by X-ray crystallography. [32,35,38] The available biochemical binding data obtained by kinetic studies [36,37] complements the structural explanation for MHC-peptide binding. [32,35,38] The structural similarity be-

tween known MHC alleles allows for side-chain prediction procedures to be carried out for other MHC molecules using available structural templates. [25,39] However, model building of a user defined peptide sequence in the groove using sidechain packing techniques requires reliable backbone templates. The prediction of allele specific peptide structures depends on the selection of peptide backbone from a template library. [21] The root mean square deviation for peptide backbone atoms (N, C α , C and O) lies within 2.1Å among structure groups based on allele specificity and peptide length. [21] Thus, it is possible to select the most appropriate peptide backbone template for predicting the structure of a user defined peptide sequence in the groove. In this approach,

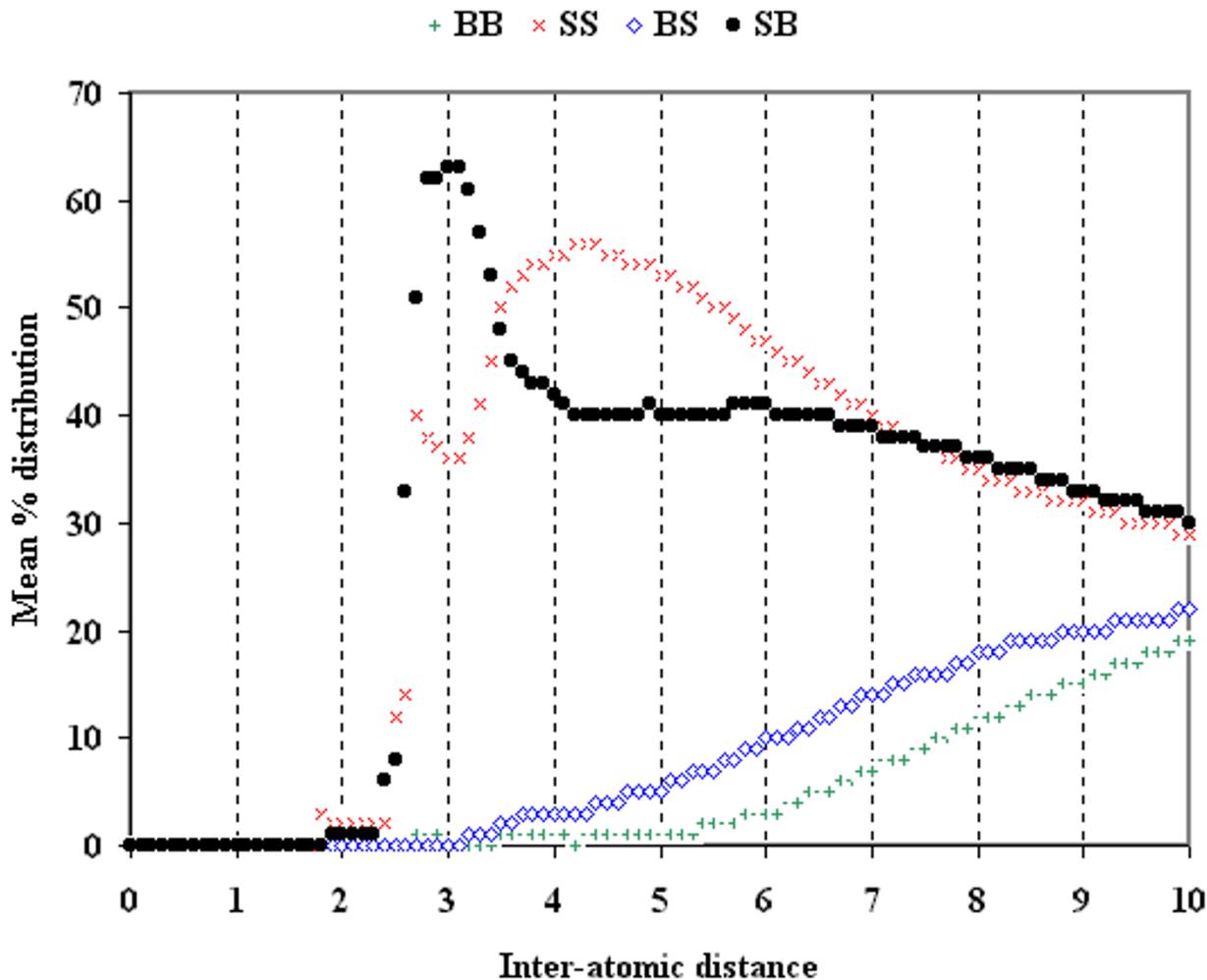


Figure 3
 Mean percentage distribution of the four interaction types in class I MHC-peptide complexes. Inter-atomic distances are expressed in Å units.

the peptide structure in the groove is constructed by threading and its compatibility to bind is evaluated by statistical pair-wise potentials. [21,22] These pair-wise potential tables emphasize either hydrophobic [40,41] or hydrophilic interactions [42] at the interface. The efficient prediction of peptide side-chain conformations in the groove has been shown mainly due to van der Waals contribution. [21] An independent study used a simple and fast free energy function (Fresno) to predict the binding free energies of peptides to class I MHC proteins. [23] This was based on the explicit treatment of ligand desolvation and unfavorable MHC protein-peptide contacts. A similar binding/non-binding grouping scheme was based on vdWC and SEHPR. [25] Despite sufficient knowledge on

the chemical nature of molecular interactions very little is known about the common interaction types for MHC-peptide complexes. Here, we present the distribution of four types of inter-atomic interactions between MHC and peptide. SS and SB interactions are commonly found at the interface of these complexes. This implies that the backbone atoms in the MHC molecules play a secondary role in the binding of the peptide; it is the interaction between the sidechain atoms in the MHC molecules with both side-chain and backbone atoms in the peptide what determines the binding. Success in peptides designed to bind in the MHC groove has been achieved by carefully dissecting side chain interactions and placing appropriate flexible residues at key positions in the peptide. Hence, SS

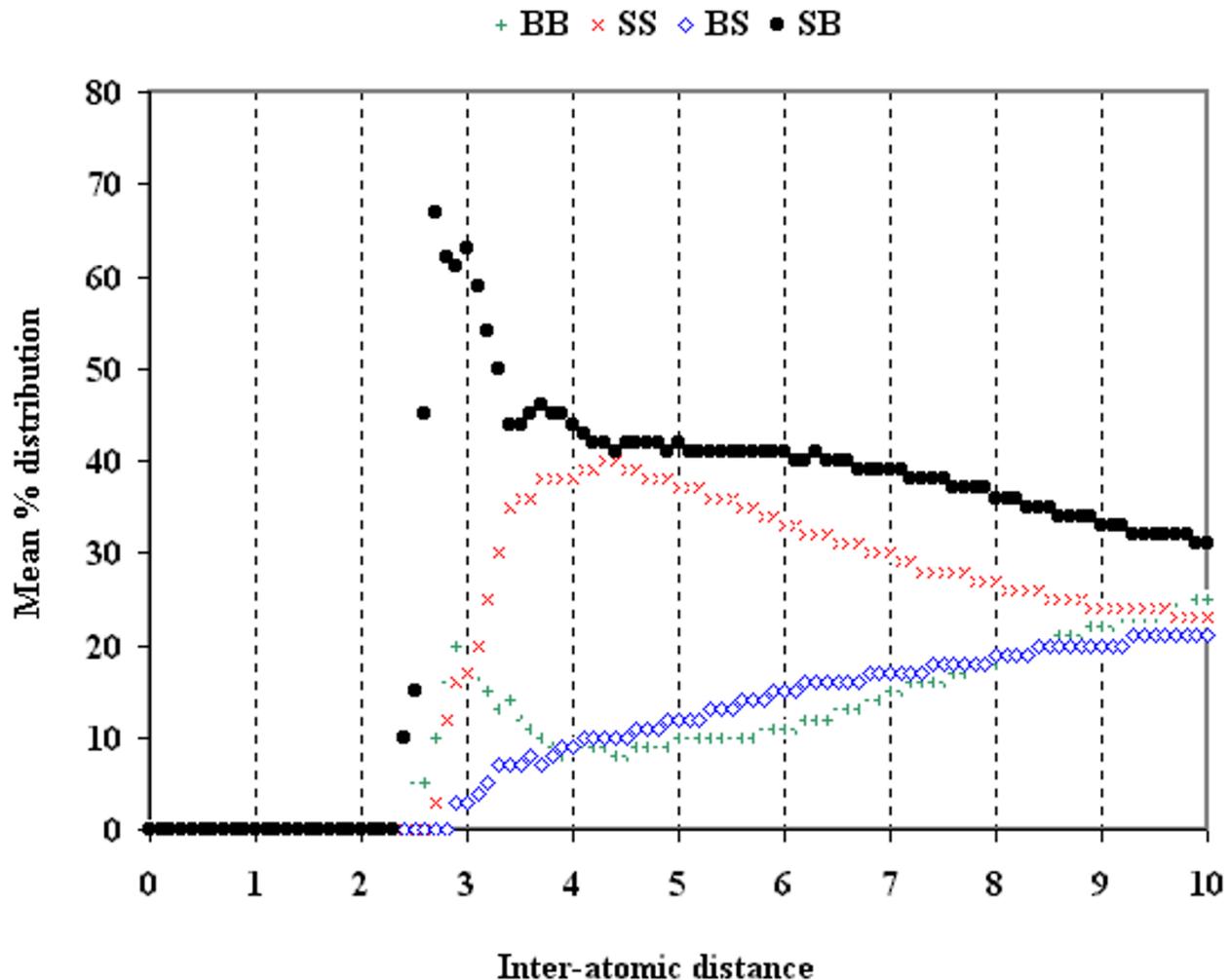


Figure 4
Mean percentage distribution of the four interaction types in class II MHC-peptide complexes. Inter-atomic distances are expressed in Å units.

interactions are crucial for proper anchoring of short peptides within the groove. The SB interactions might facilitate an induced fit of the peptide during entry into the groove. The backbone conformation adopted by the peptide in the groove is important for maintaining the predominantly common SB interactions. Specific interactions by peptide sidechain atoms inside the groove may force its backbone to adopt a suitable conformation for maximal interactions with the receptor atoms.

Conclusions

The current challenge in MHC-peptide binding prediction is twofold: (1) accurate prediction of peptide backbone conformation for subsequent sidechain packing (2) accu-

rate estimation of function by such predictions for quantitative MHC-peptide binding studies. Much of our earlier understanding on protein-ligand interactions is based on the steric factors, electrostatic contributions, hydrophobicity, hydrogen-bond donor or acceptor capability. Our results show the prevalence of backbone or sidechain atom preference at the MHC-peptide interface characterized by varying sequence composition. The prevalence of SB interactions in these complexes suggests the importance of peptide backbone conformation during MHC-peptide binding. The currently available protein structure prediction algorithms are well developed for protein sidechain packing upon fixed backbone templates. This study shows the prevalence of backbone atoms in MHC-

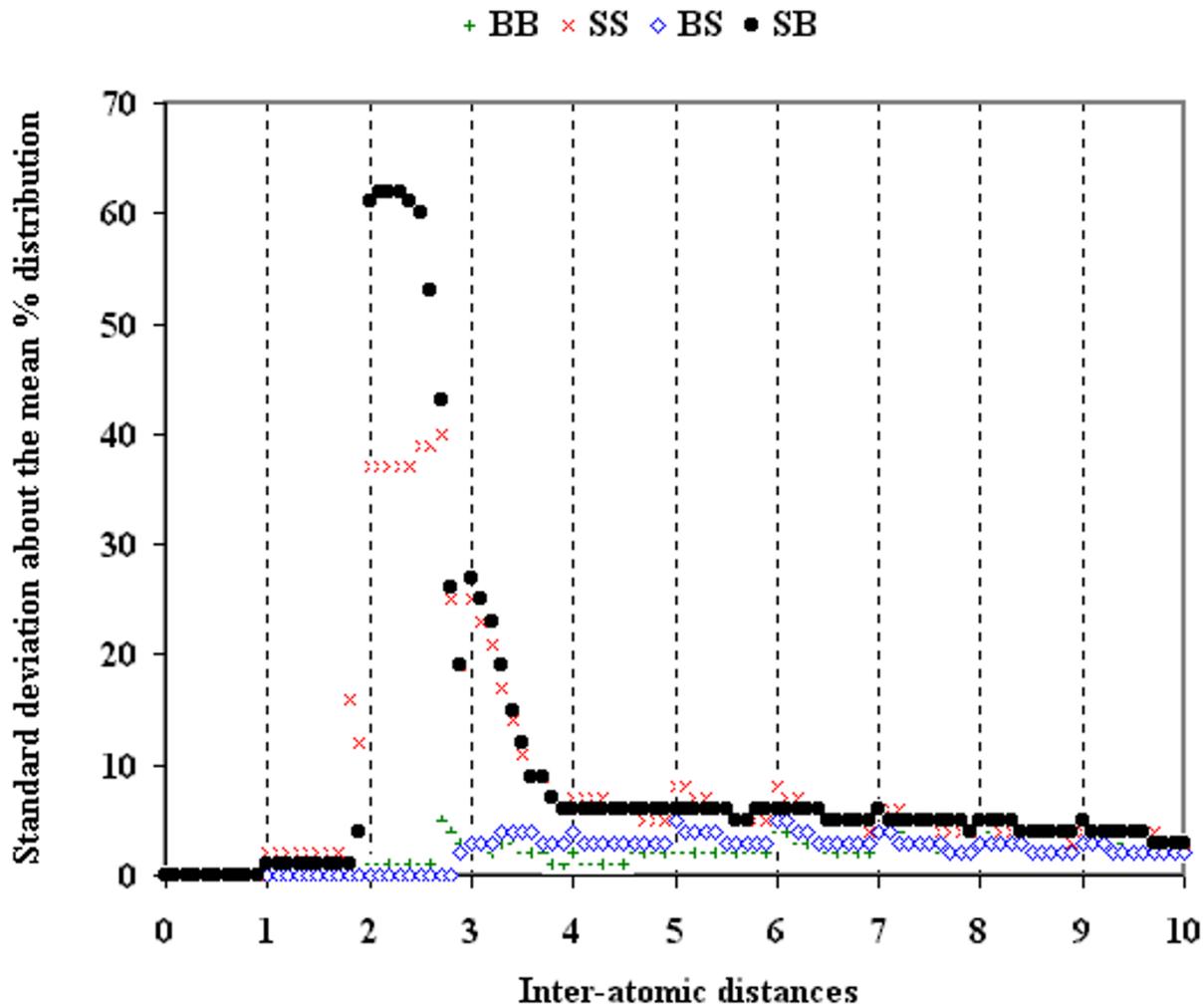


Figure 5
Standard deviation about the mean percentage distribution of the four interaction types in class I MHC-peptide complexes. Inter-atomic distances are expressed in Å units.

peptide binding and hence highlights the need for accurate peptide backbone prediction in quantitative MHC-peptide binding estimation using molecular mechanics calculations. Development of an efficient energy function for the accurate prediction of both backbone and side-chain conformations followed by an effective MHC-peptide interaction function will help to quantify the differences in peptide binding caused by MHC polymorphism and peptide diversity. It should be noted that the conclusions reached in this article are based on the available crystal data. Additional data will be required to confirm the proposed hypothesis. If the efficiency of MHC-peptide binding prediction is carefully assessed for routine application then identification of T-cell epitopes from se-

quence information will become easier. Apart from peptide MHC specificity many other important parameters that describe cellular mechanisms such as enzyme-mediated antigen processing, peptide transport, loading of peptides to MHC molecules and the phenomenon of TCR repertoires have to be identified and incorporated into the prediction framework.

Methods and materials

MHC-peptide X-ray crystal data

X-ray crystal data for MHC-peptide complexes are retrieved from Protein Databank (PDB) ([www.rcsb.org/pdb/]). If more than one entry described an identical combination of MHC and peptide sequence information

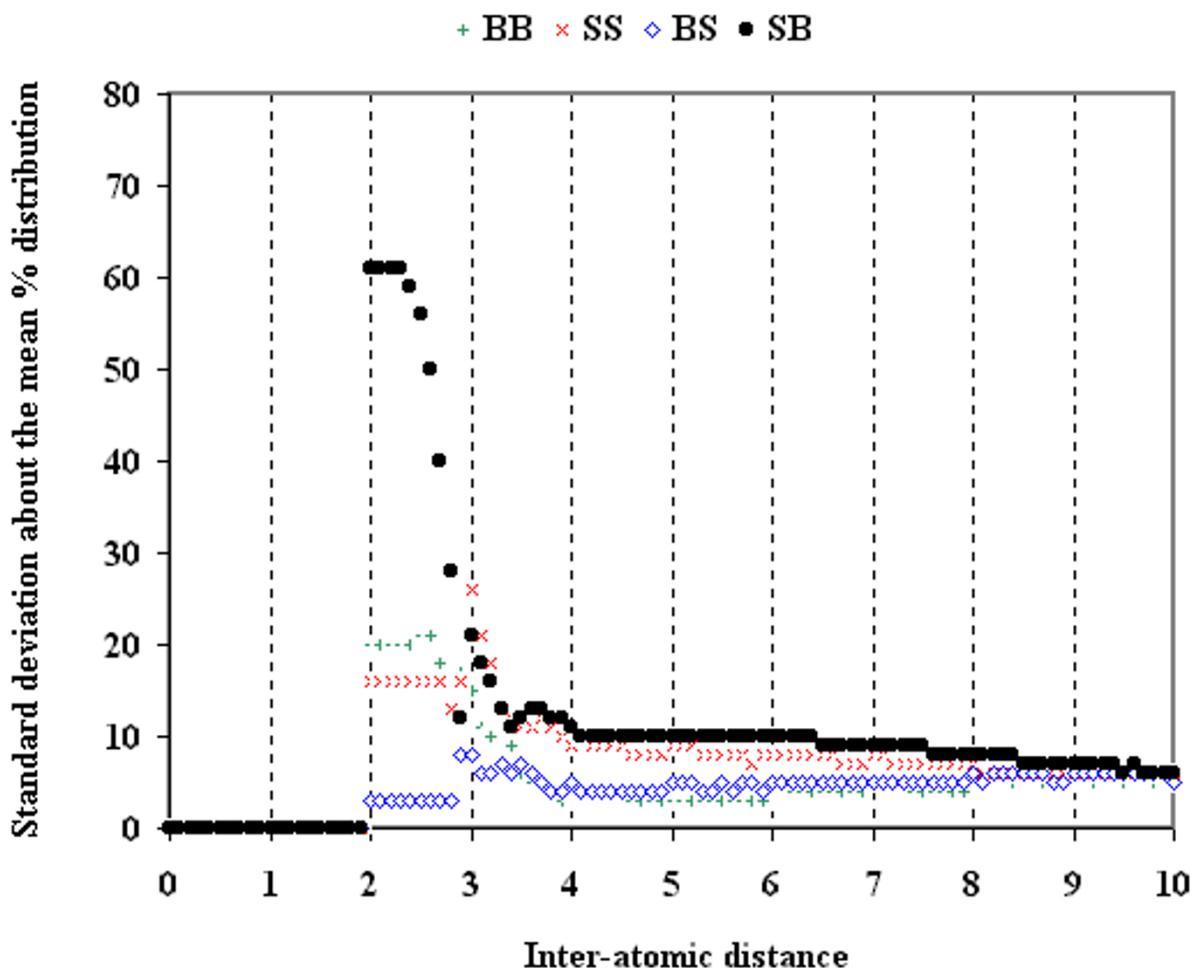


Figure 6
Standard deviation about the mean percentage distribution of the four interaction types in class II MHC-peptide complexes. Inter-atomic distances are expressed in Å units.

we selected the entry with the best atomic resolution (Å). We identified 28 non-redundant class I MHC-peptide complexes (Table 1) and 10 non-redundant class II MHC-peptide complexes (Table 2). The two sets of crystal complexes are examined for the different types of inter-atomic interactions at the interface.

Data analysis

Inter-atomic interactions at the MHC-peptide Interface

The interactions between MHC and peptide are studied by measuring the distance between each atom in the MHC and each atom in the peptide. An atom in a MHC residue or a peptide residue is considered to be involved in MHC-peptide binding if the distance between any atom of the

peptide and any atom of the MHC is less than or equal to x (Å). The value of x is varied from 0.0 to 10.0 (Å) at increments of 0.1 (Å). The total number of inter-atomic interactions at every value of x is grouped into four different types based on backbone and sidechain atom preference between MHC and peptide. Four types of inter-atomic interactions namely, BB (backbone MHC – backbone peptide), SS (sidechain MHC – sidechain peptide), BS (backbone MHC – sidechain peptide) and SB (sidechain MHC – backbone peptide) characterize the MHC-peptide interface based on backbone and sidechain atom preference.

Table 1: Class I MHC-peptide complexes in the protein databank

MHC source	PDB code	MHC alleles	Redundant peptide set	Non redundant peptide set	Peptide length	Peptide source	Resolution (Å)
Human	IHHJ	A*0201	ILKEPVHGV	ILKEPVHGV	9	Synthetic	2.50
Human	IAKJ	A*0201	Ilkepvhgv		9	HIV-1 RT	2.65
Human	IHHK	A*0201	LLFGYPVYV	LLFGYPVYV	9	Synthetic	2.50
Human	IAO7	A*0201	llfgypvyv		9	HTLV-1 Tax	2.60
Human	IBD2	A*0201	llfgypvyv		9	HTLV-1 Tax	2.50
Human	IB0G	A*0201	ALWGFPPVL	ALWGFPPVL	9	Human-peptide P1049	2.60
Human	IHHG	A*0201	TLTSCNTSV	TLTSCNTSV	9	HIV-1 gp 120	2.60
Human	IHHI	A*0201	GILGFVFTL	GILGFVFTL	9	Synthetic	2.50
Human	IB0R	A*0201	gilgfvftcde		9	Influenza matrix	2.90
Human	2CLR	A*0201	MLLSVPLLLG	MLLSVPLLLG	10	Synthetic	2.00
Human	IHHH	A*0201	FLPSDFPPSV	FLPSDFPPSV	10	HBV nucleocapsid	3.00
Human	ITMC	A*6801	EVAPPEYHRK	EVAPPEYHRK	10	Synthetic	2.30
Human	IAGB	B*0801	GGRKKYKL	GGRKKYKL	8	HIV-1 gag	2.20
Human	IAGC	B*0801	GGKKKYQL	GGKKKYQL	8	HIV-1 gag	2.10
Human	IAGD	B*0801	GGKKKYKL	GGKKKYKL	8	HIV-1 gag	2.05
Human	IAGE	B*0801	GGRKKYRL	GGRKKYRL	8	HIV-1 gag	2.30
Human	IAGF	B*0801	GGKKRYKL	GGKKRYKL	8	HIV-1 gag	2.20
Human	IHSA	B*2705	ARAAAAAAA	ARAAAAAAA	9	-	2.10
Human	IA1N	B*3501	VPLRPMTY	VPLRPMTY	8	HIV-1 nef	2.00
Human	IA9E	B*3501	LPPLDITPY	LPPLDITPY	9	EBV-Ebna3c	2.50
Human	IA9B	B*3501	lpplditpy		9	EBNA-3C	3.20
Human	IA1M	B*5301	TPYDINQML	TPYDINQML	9	HIV-2 gag	2.30
Human	IA1O	B*5301	KPIVQYDNF	KPIVQYDNF	9	HIV-1 nef	2.30
Murine	I0SZ	H-2K ^B	RGYLYQGL	RGYLYQGL	8	Vsv-nucleoprotein	2.10
Murine	2VAB	H-2K ^B	RGYVYQGL	RGYVYQGL	8	SV nucleoprotein	2.50
Murine	1KBG	H-2K ^B	RGYVY _u GL		8	Synthetic	2.20
Murine	1VAC	H-2K ^B	SIINFEKL	SIINFEKL	8	Ovalbumin	2.50
Murine	1VAD	H-2K ^B	SRDHSRTPM	SRDHSRTPM	9	Yeast α -glucosidase	2.50
Murine	2VAA	H-2K ^B	FAPGNYPAL	FAPGNYPAL	9	Vsv nucleoprotein	2.30
Murine	1BZ9	H-2D ^B	FAPGVFPYM	FAPGVFPYM	9	Peptide P1027	2.80
Murine	1CE6	H-2D ^B	FAPGNYPAL	FAPGNYPAL	9	SV nucleoprotein	2.90
Murine	1QLF	H-2D ^B	FAPSNYPAL	FAPSNYPAL	9	SV-nucleoprotein	2.65
Murine	1BII	H-2D ^D	RGPGRFVTI	RGPGRFVTI	10	HIV-1 P ₁₈₋₁₁₀	2.40
Murine	1LDP	H-2L ^D	APAAAAAAM	APAAAAAAM	9	Natural peptide	3.10

References: IHHG, IHHH, IHHI, IHHJ and IHHK [43]; IAKJ [44]; IAO7 [45]; IBD2 [46]; B0G, 1BZ9 [47]; 1B0R [48]; 2CLR [49]; ITMC [50]; IAGB, IAGC, IAGD, IAGE and IAGF [51]; IHSA [52]; IA1N [53]; IA9E, IA9B [54]; IA1M, IA1O [55]; I0SZ [56]; 2VAA, 2VAB [57]; 1KBG [58]; 1VAC, 1VAD [59]; 1CE6, 1QLF [60]; 1BII [61]; 1LDP [62].

Table 2: Class II MHC-Peptide complexes in the protein databank

MHC source	PDB code	MHC allele	Peptide sequence	Peptide length	Peptide source	Resolution (Å)
Human	IFV1	DR2	NPVVHFFKNIVTPRTPPPSQ	20	Myelin basic protein	1.90
Human	IAQD	DR1	VGSWRFRLRGYHQYA	15	Endogenous peptide	2.45
Human	IBX2	DR2	ENPVVHFFKNIVTPR	15	HMBP	2.60
Human	IA6A	DR3	PVSKMRMATPLLMQA	15	CLIP fragment	2.75
Human	IDLH	DR1	PKYVKQNTLKLAT	13	Influenza virus	2.80
Human	ISEB	DR1	AAAAAAAAAAAAA	13	Endogenous peptide	2.70
Human	IFYT	DR1	PKYVKQNTLKLAT	13	Influenza HA antigen peptide	2.60
Human	2SEB	DR4	AYMRADAAAGGA	12	Collagen II	2.50
Murine	1IAO	I-A ^D	RGISQAVHAAHAEI	14	Egg ovalbumin	2.60
Murine	2IAD	I-A ^D	GHATQGVTAASSHE	14	Influenza hemagglutinin	2.40

References: IFV1 [63]; IAQD [64]; IBX2 [65]; IA6A [66]; IDLH [67]; ISEB [68]; IFYT [69]; 2SEB [70]; 1IAO, 2IAD [71].

Percentage distribution for the interaction types

Percentage distribution for the interaction types is defined as the percentage of each interaction type over all interactions for a given inter-atomic distance.

List of abbreviations

ANN = artificial neural network

BB = backbone MHC – backbone peptide

BS = backbone MHC – sidechain peptide

EBNA = Epstein Barr nuclear antigen

EBV = Epstein Barr virus

GvHD = graft vs host disease

HA = hemagglutinin

HBV = hepatitis B virus

HIV = human immunodeficiency virus

HMBP = human myelin basic protein

HMM = hidden Markov model

HTLV = human T lymphotropic virus

mHag = minor histocompatibility antigen

MHC = major histocompatibility complex

PDB = protein databank

vdWC = van der Waals Clash

RT = reverse transcriptase

SB = sidechain MHC – backbone peptide

SEHPR = solvent exposed hydrophobic peptide residues

SS = sidechain MHC – sidechain peptide

SV = Sendai virus

Vsv = vesicular stomatitis virus

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References

- Eckels DD: **MHC: function and implication on vaccine development.** *Vox Sang (Suppl. 2)* 2000, **78**:265-267
- McDevitt HO: **Discovering the role of the major histocompatibility complex in the immune response.** *Annu Rev Immunol* 2000, **18**:1-17
- Rammensee HG, Friede T, Stevanovic S: **HC ligands and peptide motifs: first listing.** *Immunogenetics* 1995, **41**:178-228
- Buus S: **Description and prediction of peptide-MHC binding: the 'human MHC project'** *Curr Opin Immunol* 1999, **11**:209-213
- Altman JD, Moss PAH, Goulder PJR, Barouch DH, McHeyzer-Williams MG, Bell JI, McMichael AJ, Davis MM: **Phenotypic analysis of antigen-specific T lymphocytes.** *Science* 1996, **274**:94-96
- Den Haan JM, Meadows LM, Wang W, Pool J, Blokland E, Bishop TL, Reinhardus C, Shabanowitz J, Offringa R, Hunt DF, Engelhard VH, Goulmy E: **The minor histocompatibility antigen HA-I: A diallelic gene with a single amino acid polymorphism.** *Science* 1998, **279**:1054-1057
- Ren EC, Kanguane P, Kolatkar P, Lin MT, Tseng LH, Hansen JA: **Molecular modeling of the minor histocompatibility antigen HA-I peptides binding to HLA-A alleles.** *Tissue Antigens* 2000, **55**:24-30
- Corradin G, Demotz S: **Peptide-MHC complexes assembled following multiple pathways: an opportunity for the design of vaccines and therapeutic molecules.** *Hum Immunol* 1997, **54**:137-47
- Uebel S, Tampe R: **Specificity of the proteasome and the TAP transporter.** *Curr Opin Immunol* 1999, **11**:203-208
- Sette A, Buus S, Appella E, Smith JA, Chesnut R, Miles C, Colon SM, Grey HM: **Prediction of major histocompatibility complex binding regions of protein antigens by sequence pattern analysis.** *Proc Natl Acad Sci* 1989, **86**:3296-3300
- Parker KC, Shields M, DiBriano M, Brooks A, Coligan JE: **Peptide binding to MHC class I molecules: implications for antigenic peptide prediction.** *Immunol Res* 1995, **14**:34-57
- Schafer JR, Jesdale BM, George JA, Kouttab NM, De Groot AS: **Prediction of well-conserved HIV-1 ligands using a matrix-based algorithm, EpiMatrix.** *Vaccine* 1998, **16**:1880-1884
- Udaka K, Wiesmuller KH, Kienle S, Jung G, Tamamura H, Yamagishi H, Okumura K, Walden P, Suto T, Kawasaki T: **An automated prediction of MHC class I-binding peptides based on positional scanning with peptide libraries.** *Immunogenetics* 2000, **51**:816-828
- Adams HP, Koziol J: **A Prediction of binding to MHC class I molecules.** *J Immunol Methods* 1995, **185**:181-190
- Honeyman MC, Brusica V, Stone NL, Harrison LC: **Neural network-based prediction of candidate T-cell epitopes.** *Nat. Biotechnol.* 1998, **16**:966-969
- Brusica V, Rudy G, Honeyman G, Hammer J, Harrison L: **Prediction of MHC class II-binding peptides using an evolutionary algorithm and artificial neural network.** *Bioinformatics* 1998, **14**:121-130
- Mamitsuka H: **Predicting peptides that bind to MHC molecules using supervised learning of hidden Markov models.** *Proteins: Structure Function and Genetics.* 1998, **33**:460-474
- Mallios RR: **Predicting class II MHC/peptide multi-level binding with an iterative stepwise discriminant analysis meta-algorithm.** *Bioinformatics* 2001, **17**:942-948
- Altuvia Y, Schueler O, Margalit H: **Ranking potential binding peptides to MHC molecules by a computational threading approach.** *J Mol Biol* 1995, **249**:244-250
- Altuvia Y, Sette A, Sidney J, Southwood S, Margalit H: **A structure-based algorithm to predict potential binding peptides to MHC molecules with hydrophobic binding pockets.** *Hum Immunol* 1997, **58**:1-11
- Schueler-Furman O, Elber R, Margalit H: **Knowledge-based structure prediction of MHC class I bound peptides: a study of 23 complexes.** *Fold Des* 1998, **3**:549-564
- Schueler-Furman O, Altuvia Y, Sette A, Margalit H: **Structure-based prediction of binding peptides to MHC class I molecules: application to a broad range of MHC alleles.** *Protein Sci* 2000, **9**:1838-1846
- Rognan D, Lauemoller SL, Holm A, Buus S, Tschinke V: **Predicting binding affinities of protein ligands from three-dimensional models: application to peptide binding to class I major histocompatibility proteins.** *J Med Chem* 1999, **42**:4650-4658

24. Lee C, McConnell HM: **A general model of invariant chain association with class II major histocompatibility complex proteins.** *Proc Natl Acad Sci* 1995, **92**:8269-8273
25. Kanguane P, Sakharkar MK, Lim KS, Hao H, Lin K, Ren EC, Kolatkar PR: **Knowledge based grouping of modeled HLA peptide complexes.** *Hum Immunol* 2000, **61**:460-466
26. Doytchinova IA, Flower DR: **Toward the quantitative prediction of t-cell epitopes: comfa and comsia studies of peptides with affinity for the class I MHC molecule hla-a0201.** *J Med Chem* 2001, **44**:3572-3581
27. Levitt M, Gerstein M, Huang E, Subbiah S, Tsai J: **Protein folding: the endgame.** *Annu Rev Biochem* 1997, **66**:549-579
28. Jones S, Thornton JM: **Principles of protein-protein interactions.** *Proc Natl Acad Sci* 1996, **93**:13-20
29. Jones S, Marin A, Thornton JM: **Protein domain interfaces: characterization and comparison with oligomeric protein interfaces.** *Protein Eng* 2000, **13**:77-82
30. Conte LL, Chothia C, Janin J: **The atomic structure of protein-protein recognition sites.** *J Mol Biol* 1999, **285**:2177-98
31. Pillardy J, Czaplewski C, Liwo A, Lee J, Ripoll DR, Kazmierkiewicz R, Oldziej S, Wedemeyer WJ, Gibson KD, Arnautova YA, Saunders J, Ye YJ, Scheraga HA: **Recent improvements in prediction of protein structure by global optimization of a potential energy function.** *Proc Natl Acad Sci*, **98**:2329-2333
32. Kanguane P, Sakharkar MK, Kolatkar PR, Ren EC: **Towards the MHC-Peptide Combinatorics,** *Hum Immunol* 2001, **62**:539-556
33. Cano P, Fan B: **A geometric and algebraic view of MHC-peptide complexes and their binding properties.** *BMC Struct Biol* 2001, **1**:2
34. Robinson J, Waller MJ, Parham P, Bodmer JG, Marsh SGE: **IMGT/HLA Database – a sequence database for the human major histocompatibility complex.** *Nucleic Acids Research* 2001, **29**:210-213
35. Zhang C, Anderson A, DeLisi C: **Structural principles that govern the peptide binding motifs of class I MHC molecules.** *J Mol Biol* 1998, **281**:929-947
36. Joshi RV, Zarutskie JA, Stern LJ: **A three step kinetic mechanism for peptide binding to MHC class II proteins.** *Biochemistry* 2000, **39**:3751-3762
37. Kasson PM, Rabinowitz JD, Schmitt L, Davis MM, McConnell HM: **Kinetics of peptide binding to the class II MHC protein I-Ek.** *Biochemistry* 2000, **39**:1048-1058
38. Batalia MA, Collins EJ: **Peptide binding by class I and class II MHC molecules.** *Biopolymers* 1997, **43**:281-302
39. Chung SY, Subbiah S: **How similar must a template protein be for homology modeling by side-chain packing methods?** *Pac Symp Biocomput* 1996, 126-141
40. Miyazawa S, Jernigan RL: **Estimation of effective inter residue contact energies from protein crystal structures quasi-chemical approximation.** *Macromolecules* 1985, **18**:534-552
41. Miyazawa S, Jernigan RL: **Residue-residue potentials with a favorable contact pair term and an unfavorable high packing density term, for simulation and threading.** *J Mol Biol* 1996, **256**:623-644
42. Betancourt MR, Thirumalai D: **Pair potentials for protein folding: choice of reference states and sensitivity of predicted native states to variations in the interaction schemes.** *Protein Sci* 1999, **8**:361-369
43. Madden DR, Garboczi DN, Wiley DC: **The antigenic identity of peptide-MHC complexes: a comparison of the conformations of five viral peptides presented by HLA-A2.** *Cell* 1993, **75**:693-708
44. Gao GF, Tormo J, Gerth UC, Wyer JR, McMichael AJ, Stuart DI, Bell JI, Jones EY, Jakobsen BK: **Crystal structure of the complex between human CD8 alpha (alpha) and HLA-A2.** *Nature* 1997, **387**:630-634
45. Garboczi DN, Ghosh P, Utz U, Fan QR, Biddison WE, Wiley DC: **Structure of the complex between human T-cell receptor, viral peptide and HLA-A2.** *Nature* 1996, **384**:134-141
46. Ding YH, Smith KJ, Garboczi DN, Utz U, Biddison WE, Wiley DC: **Two human T cell receptors bind in a similar diagonal mode to the HLA-A2/Tax peptide complex using different TCR amino acids.** *Immunity* 1998, **8**:403-411
47. Zhao R, Loftus DJ, Appella E, Collins EJ: **Structural evidence of T cell xeno-reactivity in the absence of molecular mimicry.** *J Exp Med* 1999, **189**:359-370
48. Bouvier M, Guo HC, Smith KJ, Wiley DC: **Crystal structures of HLA-A*0201 complexed with antigenic peptides with either the amino or carboxyl-terminal group substituted by a methyl group.** *Proteins* 1998, **33**:97-106
49. Collins EJ, Garboczi DN, Wiley DC: **Three-dimensional structure of a peptide extending from one end of a class I MHC binding site.** *Nature* 1994, **371**:626-629
50. Collins EJ, Garboczi DN, Karpusas MN, Wiley DC: **The three-dimensional structure of a class I major histocompatibility complex molecule missing the alpha 3 domain of the heavy chain.** *Proc Natl Acad Sci* 1995, **92**:1218-1221
51. Reid SW, McAdam S, Smith KJ, Klenerman P, O'Callaghan CA, Harlos K, Jakobsen BK, McMichael AJ, Bell JI, Stuart DI, Jones EY: **Antagonist HIV-1 Gag peptides induce structural changes in HLA B8.** *J Exp Med* 1996, **184**:2279-2286
52. Madden DR, Gorga JC, Strominger JL, Wiley DC: **The three-dimensional structure of HLA-B27 at 2.1 Å resolution suggests a general mechanism for tight peptide binding to MHC.** *Cell* 1992, **70**:1035-1048
53. Smith KJ, Reid SW, Stuart DI, McMichael AJ, Jones EY, Bell JI: **An altered position of the alpha 2 helix of MHC class I is revealed by the crystal structure of HLA-B*3501.** *Immunity* 1996, **4**:203-213
54. Messen R, Orth P, Ziegler A, Saenger W: **Decamer like conformation of a nona-peptide bound to HLA-B*3501 due to non-standard positioning of the C terminus.** *J Mol Biol* 1999, **285**:645-653
55. Smith KJ, Reid SW, Harlos K, McMichael AJ, Stuart DI, Bell JI, Jones EY: **Bound water structure and polymorphic amino acids act together to allow the binding of different peptides to MHC class I HLA-B53.** *Immunity* 1996, **4**:215-228
56. Ghendler Y, Teng MK, Liu JH, Witte T, Liu J, Kim KS, Kern P, Chang HC, Wang JH, Reinherz EL: **Differential thymic selection outcomes stimulated by focal structural alteration in peptide/major histocompatibility complex ligands.** *Proc Natl Acad Sci* 1998, **95**:10061-10066
57. Fremont DH, Matsumura M, Stura EA, Peterson PA, Wilson IA: **Crystal structures of two viral peptides in complex with murine MHC class I H-2Kb.** *Science* 1992, **257**:919-927
58. Speir JA, Abdel-Motal UM, Jondal M, Wilson IA: **Crystal structure of an MHC class I presented glycopeptide that generates carbohydrate-specific CTL.** *Immunity* 1999, **10**:51-61
59. Fremont DH, Stura EA, Matsumura M, Peterson PA, Wilson IA: **Crystal structure of an H-2Kb-ovalbumin peptide complex reveals the interplay of primary and secondary anchor positions in the major histocompatibility complex binding groove.** *Proc Natl Acad Sci* 1995, **92**:2479-2483
60. Glithero A, Tormo J, Haurum JS, Arsequell G, Valencia G, Edwards J, Springer S, Townsend A, Pao YL, Wormald M, Dwek RA, Jones EY, Elliott T: **Crystal structures of two H-2Db/glycopeptide complexes suggest a molecular basis for CTL cross-reactivity.** *Immunity* 1999, **10**:63-74
61. Achour A, Persson K, Harris RA, Sundback J, Sentman CL, Lindqvist Y, Schneider G, Karre K: **The crystal structure of H-2Dd MHC class I complexed with the HIV-1-derived peptide P18-110 at 2.4 Å resolution: implications for T cell and NK cell recognition.** *Immunity* 1998, **9**:199-208
62. Speir JA, Garcia KC, Brunmark A, Degano M, Peterson PA, Teyton L, Wilson IA: **Structural basis of 2C TCR allorecognition of H-2Ld peptide complexes.** *Immunity* 1998, **8**:553-562
63. Li Y, Li H, Martin R, Mariuzza AR: **Structural Basis for the Binding of an Immunodominant Peptide from Myelin Basic Protein in Different Registers by Two Hla-Dr2 Alleles** *J Mol Biol* 2000, **304**:177-188
64. Murthy VL, Stern LJ: **The class II MHC protein HLA-DR1 in complex with an endogenous peptide: implications for the structural basis of the specificity of peptide binding.** *Structure* 1997, **5**:1385-1396
65. Smith KJ, Pyrdol J, Gauthier L, Wiley DC, Wucherpfennig KW: **Crystal structure of HLA-DR2 (DRA* DRB1*1501) complexed with a peptide from human myelin basic protein.** *J Exp Med* 2001, **188**:1511-1520
66. Ghosh P, Amaya M, Mellins E, Wiley DC: **The structure of an intermediate in class II MHC maturation: CLIP bound to HLA-DR3.** *Nature* 1995, **378**:457-462

67. Stern LJ, Brown JH, Jardetzky TS, Gorga JC, Urban RG, Strominger JL, Wiley DC: **Crystal structure of the human class II MHC protein HLA-DR1 complexed with an influenza virus peptide.** *Nature* 1994, **368**:215-221
68. Jardetzky TS, Brown JH, Gorga JC, Stern LJ, Urban RG, Chi YI, Stauffer C, Strominger JL, Wiley DC: **Three-dimensional structure of a human class II histocompatibility molecule complexed with superantigen.** *Nature* 1994, **368**:711-718
69. Hennecke J, Carfi A, Wiley DC: **Structure of a Covalently Stabilized Complex of a Human Ab-T Cell Receptor, Influenza Ha Peptide and Mhc Class II Molecule, Hla-Dr1** *Embo J* 2000, **19**:5611-5624
70. Dessen A, Lawrence CM, Cupo S, Zaller DM, Wiley DC: **X-ray crystal structure of HLA-DR4 (DRA* DRB1*0401) complexed with a peptide from human collagen II.** *Immunity* 0101, **7**:473-481
71. Scott CA, Peterson PA, Teyton L, Wilson IA: **Crystal structures of two I-Ad-peptide complexes reveal that high affinity can be achieved without large anchor residues.** *Immunity* **8**:319-329

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