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Exploring peptide/MHC detachment processes using hierarchical natural move Monte Carlo

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Abstract

Motivation: The binding between a peptide and a major histocompatibility complex (MHC) is one of the most important processes for the induction of an adaptive immune response. Many algorithms have been developed to predict peptide/MHC (pMHC) binding. However, no approach has yet been able to give structural insight into how peptides detach from the MHC.

Results: In this study, we used a combination of coarse graining, hierarchical natural move Monte Carlo and stochastic conformational optimization to explore the detachment processes of 32 different peptides from HLA-A*02:01. We performed 100 independent repeats of each stochastic simulation and found that the presence of experimentally known anchor amino acids affects the detachment trajectories of our peptides. Comparison with experimental binding affinity data indicates the reliability of our approach (area under the receiver operating characteristic curve 0.85). We also compared to a 1000 ns molecular dynamics simulation of a non-binding peptide (AAKTPVIV) and HLA-A*02:01. Even in this simulation, the longest published for pMHC, the peptide does not fully detach. Our approach is orders of magnitude faster and as such allows us to explore pMHC detachment processes in a way not possible with all-atom molecular dynamics simulations.

Availability and implementation: The source code is freely available for download at http://www.cs.ox.ac.uk/mosaics/.

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 Introduction

Presentation of protein fragments on the surface of antigen-presenting cells is a fundamental part of the human immune system. In virus-infected cells, proteosomes degrade viral proteins into peptides. These peptides are then transported via the transporter associated with antigen processing into the lumen of the endoplasmic reticulum where the peptides are loaded on major histocompatibility complex (MHC) class I molecules. These peptide/MHC (pMHC) complexes are then presented on the surface of antigen-presenting cells to the T-cell receptors (TCR) of T cells (Rudolph et al., 2006). The linkage between MHC, peptide and TCR determines if an immune reaction is triggered against this peptide (van der Merwe and Dushek, 2011). Only if the binding affinity between peptide and MHC is strong enough, a peptide can be presented to TCR and a productive immune response against this peptide can take place. A wide range of pMHC binding affinity prediction methods have been developed (reviewed in Knapp et al., 2009; Zhang et al., 2012b). Sequence-based methods usually achieve high accuracy if sufficient training data are available. Structure-based methods are often worse at predicting binding affinity but give insight into the binding mode of the peptide (compare Knapp et al., 2009; Zhang et al., 2012b). Prediction methods
based on molecular dynamics (MD) simulation attempt to not only predict the binding affinity and binding mode but also the dynamics of a peptide bound inside the MHC binding groove (Knapp et al., 2015). However, no all-atom MD simulation has so far been able to give insight into the structural detachment process of a peptide from an MHC. This is likely to be due to the immense resource consumption that standard MD would take to map out the conformational space of pMHC detachment.

There are a large number of methods that have the potential to enhance sampling of structural simulations over standard MD. These include coarse graining at different levels [e.g. bond length constraints (Mazur, 1998), increased masses (Feenstra et al., 1999), virtual sites (Hess et al., 2008), $n$-bead models (Minary and Levitt, 2008) or the movement of rigid protein segments (Sim et al., 2012)], biased force methods [e.g. metadynamics (Leone et al., 2010), steered MD (Bayas et al., 2003; Cuendet et al., 2011; Kosztin et al., 1999) or umbrella sampling (Torrie and Valleau, 1977)], replica exchange MD (Bernardi et al., 2015), Monte Carlo simulations or alchemistic methods (Spiwok et al., 2014). While these methods have been employed successfully for several ligand/receptor interactions, they have so far not been used to study pMHC detachment. Therefore, to date, neither experiments nor simulations have provided structural information on potential peptide detachment pathways from MHC.

In this study, we gain structural insight into the process of peptide detachment from the MHC HLA-A*02:01 by identifying a large number of low energy conformational states along the detachment pathway. Instead of all-atom MD, we use a simplified protein representation combined with generalized collective degrees of freedom and repeated simulated annealing. These three steps use already established methods: First, we coarse grain our all-atom model by using a 3-point-based amino acid representation (Minary and Levitt, 2008) and a knowledge-based statistical potential (Minary and Levitt, 2008). Second, we use hierarchical natural move Monte Carlo (HNMMC) (Sim et al., 2012) to control the degrees of freedom. Third, we use temperature modulation (Zhang et al., 2012a) to efficiently sample the energy landscape. On the basis of this protocol, we are for the first time able to give a comprehensive structural insight into the detachment processes of peptides from MHCs.

2 Methods

All-atom MD simulations are often hampered by two obstacles: the large number of degrees of freedom and the complexity of the energy function. In this study, we address these challenges by the combination of coarse graining, HNMMC and temperature annealing accelerated conformational optimization.

2.1 Coarse-grained protein model and force field

The all-atom pMHC structures were converted into 3-point representations (Minary and Levitt, 2008) using gro2mat (Dien et al., 2014). In this representation, an amino acid is modelled by the $\alpha$-carbon and carbonyl oxygen backbone atoms as well as a point at the centre of the side chain.

The previously established (Minary and Levitt, 2008) 3-point knowledge-based potential was used for the simulations. A coarse-grained potential can in principal allow atoms to approach closer than the excluded volume. To ensure that our small peptides did not approach the protein surface too closely, we uniformly scaled all pair interaction energies by the continuous non-linear function:

$$s(r) = \begin{cases} s_0 + (1 - s_0) \left(\frac{r}{r_0}\right)^6 & \text{if } r < r_0 \\ 1.0 & \text{if } r \geq r_0 \end{cases}$$

Where $r_0 = 0.7 \text{ nm}$ represents approximately the size of a large amino acid and $s_0 = 0.15$ was chosen, so that all peptides can escape deep energy minima. All pair interactions over 0.7 nm are identical to the established knowledge-based potential (Minary and Levitt, 2008).

2.2 Hierarchical natural move Monte Carlo

We follow the previously described HNMMC methodology (Sim et al., 2012), which has been used in combination with the above coarse-grained model (Zhang et al., 2012a) and is implemented in the software package MOSAICS. Natural moves are degrees of freedom that describe the collective motion of groups of residues (called regions). In proteins, this could be the movement of a stable secondary structure element such as an $\alpha$-helix or $\beta$-sheet. Regions can additionally be grouped together and thereby form super-regions. In our study, we grouped the MHC into seven regions (Fig. 1; schematically in Supplementary Appendix Fig. S1). Both helices can move independently from the rest of the MHC and are flexible in themselves around the evolutionary conserved kinks (Wilman et al., 2014) position in the middle of the helices. Also the peptide can be moved as a whole as well as in sub-regions. This decomposition enables all essential motions of the pMHC while keeping the number of degrees of freedom to a (necessary) minimum. In our Markov chain Monte Carlo (MCMC) simulation, each region as well as super-region (e.g. the two regions of one MHC helix) is propagated independently along three translational and three rotational degrees of freedom. The resulting chain breaks are resolved by an efficient stochastic chain-closure algorithm (Minary and Levitt, 2010).

![Fig. 1. Structure of the pMHC complex HLA-A*02:01 based on PDB accession code 3PWN. The peptide is bound above the $\beta$-sheet floor and flanked by two kinked $\alpha$-helices. The decomposition of the pMHC complex into regions as used in this study is illustrated with transparent surfaces. White: MHC $\beta$-floor; red: peptide; orange: whole MHC helices; magenta: MHC regions broken by kinks. For clarity, the $\alpha$3 region and the $\beta$2-microglobulin are not shown](image)
2.3 Temperature modulation
In structural simulations, higher temperature allows for more flexibility, while a lower temperature hampers flexibility. In this study, we used repeated simulated annealing, which allows the rapid search for an ensemble of energetically favourable structural states along the peptide detachment process. It has been implemented by using a temperature modulation protocol (Zhang et al., 2012a) as described by the function

\[ T_k = A \cdot \sin \left( \frac{2\pi k}{\Omega} \right) + s + A \]

Where \( A \) is the amplitude of the temperature modulation, \( k \) the MCMC step counter, \( \Omega \) is the number of steps per period and \( s \) is used to shift the minimum temperature. Similar to previous applications (Zhang et al., 2012a), this conformational optimization protocol enabled the efficient exploration of important energy minima and corresponding pMHC conformations. In this study, we used \( A = 600 \) (Kelvin), \( k = 100 000 \), \( \Omega = 5000 \) and \( s = 0 \) (Kelvin).

2.4 Preparation of the pMHC dataset
We used the MHC allele HLA-A*02:01 as it is among the most frequent MHC alleles in humans. To ensure that we did not use an outlier HLA-A*02:01 structure for our study, we extracted the 10 X-ray structures of HLA-A*02:01 with the highest resolutions from the protein data bank (PDB) (Berman et al., 2000) and validated their amino acid sequence against the IMGT/HLA database (Robinson et al., 2013). We then selected PDB-accession code 3PWN as it represents an average HLA-A*02:01 structure.

Thirty-two peptides with experimentally determined binding affinities were selected from Ishizuka et al. (2009) (Supplementary Appendix Table SI). We chose all peptides from the same study as this makes it likely that the measurements are comparable in rank order. These peptides were chosen to cover the whole range of observed experimental binding affinities. We chose a dataset with experimental IC50 values as those are available in abundance [e.g. from the Immune Epitope Data Base (IEDB) (Vita et al., 2010)] and therefore used for benchmarking most pMHC binding affinity predictors.

SCWRL (Krivov et al., 2009) and the peptX (Knapp et al., 2011b) framework were used to model the 32 peptides of Ishizuka et al. (2009) into the MHC binding groove of PDB accession code 3PWN. This has been shown to be the most appropriate approach for altered pMHC modelling (Knapp et al., 2008).

2.5 Performed simulations
Initial test HNMMC simulations were run for 500 000 steps. These simulations showed that detachment usually takes place within 100 000 MCMC steps (Fig. 2A). Therefore, we ran the simulations of all 32 modelled pMHC complexes for 100 000 steps using the above-described HNMMC protocol. We repeated each simulation 100 times using different random seeds.

For comparison, we performed a 1000-ns standard MD simulation of the same pMHC (Fig. 2B). To date, this is the longest reported MD simulation of pMHC and took about 247 h using 128 cores. The runtime of this single MD simulation corresponds roughly to the overall runtime of all (\( n = 3200 \)) HNMMC simulations (100 independent simulations for 32 different peptide sequences) of this project (Fig. 2C). There is a high degree of similarity between the first 25 000 frames of the HNMMC detachment process and the MD simulation (compare Fig. 2A and B). Both simulations start their detachment process by an up and down flapping of peptide’s C-terminal end. However, during 1000 ns of MD, only this partial detachment can be observed (Fig. 2B). Thus, our HNMMC-based protocol is capable of accelerating calculations for pMHC detachment processes by several orders of magnitude.

3.2 Putative peptide detachment pathways
Having demonstrated that the methodology is able to simulate peptide detachment and that the results show agreement with classical methods, we then simulated 32 different peptides and repeated each simulation 100 times with different random initial seeds to initiate stochastically different trajectories.

The average peptide detachment pathway, grouped by experimentally known binder and non-binder, is illustrated in Figure 3A. X-ray structures show that peptides bind in the MHC groove in a slightly bent configuration. This allows for a closer proximity between the peptide ends and the MHC binding groove than between the peptide middle and the MHC binding groove. All 32 peptides have an initial distance between peptide and MHC floor of 1.31 nm for the peptide C-terminal (C1peptide to C28MHC) and 1.08 nm and 1.09 nm for the peptide N- and C-terminal ends (C1peptide to C399MHC and C29peptide to C1117MHC, respectively) (Fig. 3A). The peptides do not start their detachment process from our HNMMC protocol, important conformational states for the partial peptide detachment process of this peptide can be located within 25 000 steps. These states imply that this peptide starts to detach C-terminally. All relevant conformational states for the full detachment are detected after 100 000 steps (arrow in Fig. 2A). This corresponds to approximately 2.5 h of simulation time on a standard desktop machine (all 500 000 steps took about 13 h).

For comparison, we performed a 1000-ns MD simulation of the same pMHC (Fig. 2B). To date, this is the longest reported MD simulation of pMHC and took about 247 h using 128 cores. The runtime of this single MD simulation corresponds roughly to the overall runtime of all (\( n = 3200 \)) HNMMC simulations (100 independent simulations for 32 different peptide sequences) of this project (Fig. 2C). There is a high degree of similarity between the first 25 000 frames of the HNMMC detachment process and the MD simulation (compare Fig. 2A and B). Both simulations start their detachment process by an up and down flapping of peptide’s C-terminal end. However, during 1000 ns of MD, only this partial detachment can be observed (Fig. 2B). Thus, our HNMMC-based protocol is capable of accelerating calculations for pMHC detachment processes by several orders of magnitude.

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![Fig. 2. Simulated detachment process of AAAKTPVIV from HLA-A*02:01. (A) Equally distributed snapshots of the 500 000 HNMMC simulation steps. This simulation took about 13 h on a single core of an Intel i7-3770 3.40 GHz CPU. (B) Equally distributed snapshots of a 1000 ns MD simulation. The simulation took about 247 h using 128 Xeon cores at 2.0 GHz of the Oxford Advanced Research Computing facility. (C) Runtime comparison between our HNMMC simulations and a single MD simulation. The 1000 ns MD simulation has about the same runtime demand as all the HNMMC simulations (\( n = 3200 \)) of our study combined.](image-url)
the middle but from the N- or C-terminal end or from all peptide positions at the same time (Fig. 3B). After only 20,000 steps, the middle distance tends to become the shortest distance. The peptides generally do not show a preference for an N- or C-terminal start of the detachment process from HLA-A*02:01 (Fig. 3A), but individual peptides do have preferences for N- or C-terminal detachment (Fig. 3C–E and Supplementary Appendix Fig. S2).

Two mechanisms, which we never observed, are detachments starting from the peptide middle by either bending the ends inwards or bending the ends outwards (Fig. 3B, lowest panel).

3.3 The relationship between MHC anchor residues and peptide detachment pathways

The idea that certain residues are more important than others for MHC binding is called the anchor residue concept (Rammensee et al., 1999). We investigated the relation between known anchor residues and the detachment pathways of our peptides. We extracted all experimentally tested HLA-A*02:01 peptides from the IEDB. In Supplementary Appendix Figure 4, we show the frequency of residues for binders and non-binders. This shows that binders have a preference for the hydrophobic residues L, M or I at peptide position 2 and V, L or I at peptide position nine. These residues are in agreement with the preferred anchors listed in the SYFPEITHI database (Rammensee et al., 1999).

The presence or absence of these residues influences the detachment trajectories of the peptides. For example, the experimentally known binder FLIDLAFLI has anchor residue L at position 2 and anchor residue I at position 9 which keeps the peptide stable in the MHC binding groove. Middle column: peptides most frequently start their detachment N- or C-terminally and in rare cases simultaneously from both sides. A detachment process starting from the middle or by bending the ends inversely was never observed. Right column: full detachment of the peptide is reached. (D) Stable binding between FLIDLAFLI and MHC due to matching anchor residues at peptide positions two and nine. (E) Detachment pathway of the peptide WIKTISKR from MHC. Peptide position two is a matching anchor residue. (E) Detachment pathway of the peptide RQQLEDIFM from MHC. This peptide contains no matching anchor residues. For (C–E), the average distance over 100 replicas is shown. The dotted lines indicate the standard error of the mean over the 100 replicas. Values above 3 nm were considered as full detachment and therefore set to 3 nm. The detachment trajectories of all peptides are shown in Supplementary Appendix Figure S2.

3.4 Experimental binding affinity and peptide detachment

The accuracy of our HNMMC approach in discriminating between experimentally known MHC binders and non-binders gives an indication of the reliability of our proposed detachment trajectories. Non-binders should have larger distances to the MHC binding groove than binders i.e. they are likely to detach more quickly. We tested this by comparing the average distance over all replicas of a peptide against its experimentally known binding affinity. This test yields an area under the receiver operating characteristic curve (AROC) of 0.85 (Fig. 4A) and Pearson correlation coefficient of 0.67 (Supplementary Appendix Fig. S4). Furthermore, the difference between the pMHC-distances of all binders and all non-binders is significant (Fig. 4B).

Single simulations might be misleading because the conformational exploration could be trapped in one or few local minima. The use of multiple replica simulations is usually more reliable. To test whether this is the case for our pMHC detachment simulations, we performed a boot-strapping analysis using the 100 replicas per peptide. We investigated how the results would change if fewer replicas are taken into account. We randomly chose n (taking the values 1 to 100) replicas out of our 100 replicas with repetition. We calculated the AROC against experimental data. We repeated this 5000 times for each n and calculated the standard deviation between the 5000 AROC values. Each point in Figure 5A is the standard deviation over the 5000 AROC values. If only one replica is used, the standard deviation is 0.08 and the AROCs stretch between 0.53 (close to complete randomness) and 0.91 (close to perfect
TCR/pMHC structures (Dunbar et al., 2012). This shows that current standard MD simulations are not giving insight into the pMHC detachment processes with high accuracy and reliability if at least 25, or empty MHC binding grooves (Rupp et al., 2012; Knapp et al., 2011; Yaneva et al., 2012) are used. More systematic analysis is needed for reliable conclusions. This is in agreement with recent studies that showed that the comparison between few MD simulations with different initial seeds per pMHC. On the basis of a boot strapping analysis, we found that about 25–50 replicas are necessary for reliable binding free energy prediction of HIV drugs to HIV-1 Protease (Wright et al., 2014) and peptides to MHC (Wan et al., 2015).

5 Conclusion
In this study, we showed that HNMMC is able to give insight into the peptide detachment process from MHC. For the first time, we were able to analyse peptide detachment trajectories and thereby provide new views of the MHC structural landscape.

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