
Partial Dissociation of Antigenic Peptides from MHC I – Linking NMR Data to Microstates Observed in MD Simulations

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Abstract

Major Histocompatibility Complex I (MHC I) is one of the key players in adaptive immunity. Expressed on the surface of all nucleated cells, it displays sample antigenic peptides from the cytosol to patrolling cytotoxic T-cells that can thus identify and kill malignantly transformed and virally infected cells.

Although several crystal structures of MHC I in complex with an antigenic peptide (pMHC I) have been solved, the structural dynamics of pMHC I at the cell surface remain largely elusive. According to a recent NMR study on HLA-B*35:01 (Yanaka et al., *J. Biol. Chem.*, 2014), pMHC I complexes can adopt a minor state in which the antigenic peptide is bound tightly to MHC I and a major state in which the peptide is bound more loosely. In unbiased MD simulations of the pMHC I studied by Yanaka et al., the peptide N-terminus dissociated from the MHC I binding groove during a few hundred nanoseconds. This finding suggests that pMHC I with completely bound peptide may correspond to the proposed minor state, whereas pMHC I with partially dissociated peptide may constitute the major state.

To underpin this, the potential of mean force (PMF) along the distance between the anchor residue of the peptide N-terminus and its binding partner in the MHC I binding groove has been calculated. The resulting free energy differences can be compared to values derived from the published NMR data. Preliminary results from umbrella sampling (1 microsecond of MD simulation per umbrella window) suggest that pMHC I in which the peptide N-terminus has dissociated from MHC I are lowest in free energy. Contrarily, Hamiltonian replica exchange simulations (2 x 2 microseconds), in which the effective temperature of the MHC I binding groove and the antigenic peptide is increased, predict pMHC I with completely bound peptide to be the global minimum of the free energy. This seemingly contradicting difference is discussed and further elucidated.

Keywords: Major Histocompatibility Complex I (MHC I), molecular dynamics (MD), enhanced sampling, umbrella sampling, replica exchange

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Augmented Reality and Virtual Reality tools for visualization of Molecular Dynamics simulations

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Abstract

The design of new advances in the field of computational simulations and visualization tools provide new opportunities to optimize the design of supramolecular entities at structural level. Different examples carried out recently in our research group will be presented, such as the development of a mapping algorithm to map Coarse-grained and all-atoms structures,[1] or Molecular Dynamics results showing the power of combining experimental and computational methods in the field of lipid membranes and peptide nanopores.[2-3]

Furthermore, several tools developed by the MD.USE Innovative Solutions, based on state-of-the art technologies such as Molecular Dynamics (MD), Virtual Reality (VR) and Augmented Reality (AR) will be presented. It is possible now to travel along complex molecular systems looking at them from different perspectives, orientations and positions in a fully immersive way. The visualization of molecular structures, such as cyclodextrins, in 360o and VR allow users immersing into an amazing experience. The creation of images in AR is now possible, opening the door to a new era in the way of presenting scientific papers or posters.

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I. Louzao et al. *J. J. Mat. Chem. B.* 5, (2017), 4426.

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Keywords: Molecular Dynamics, Coarse Grained, AR, VR

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Less is more: Coarse-grained integrative modelling of large biomolecular assemblies with HADDOCK

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Abstract

Predicting the 3D structure of protein interactions remains a challenge in the field of computational structural biology. This is in part due to difficulties in sampling the complex energy landscape of multiple interacting flexible polypeptide chains. Coarse-graining approaches, which reduce the number of degrees of freedom of the system, help address this limitation by smoothing the energy landscape, allowing an easier identification of the global energy minimum. They also accelerate the calculations, allowing to model larger assemblies. Here, we present the implementation of the MARTINI coarse-grained force field for proteins into HADDOCK, our integrative modelling platform. Docking and refinement are performed at the coarse-grained level and the resulting models are then converted back to atomistic resolution through a distance restraint-guided morphing procedure. Our protocol, tested on the largest complexes of the protein docking benchmark 5, shows an overall ~ 7 -fold speed increase compared to standard all-atom calculations, while maintaining a similar accuracy and yielding substantially more near-native solutions. To showcase the potential of our method, we performed simultaneous 7 body docking to model the KaiC-KaiB complex, integrating mutagenesis and hydrogen/deuterium exchange data from mass spectrometry with symmetry restraints, and validated the resulting models against a recently published cryo-EM structure.

Keywords: protein, protein interactions, HADDOCK, coarse, grain, docking

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Modeling structural and mechanical properties of recurrent RNA motifs

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Abstract

Recurrent RNA internal loops, such as C-loops [1] and kink-turns [2], are highly conserved key structural and functional elements in the ribosome, which are also being used as building blocks in artificial nanostructures. While their geometry has been partially characterized, their mechanical properties remain to be investigated.

We propose a method to evaluate global structure and elasticity of the internal loops [1]. A-RNA helices flanking the motif are modeled as rigid bodies. Their relative rotation and displacement dictated by the motif are described by a set of six interhelical coordinates. The deformation energy is assumed to be a general quadratic function of the given interhelical coordinates. The model parameters are inferred from atomistic molecular dynamics simulations of isolated motifs.

C-loops show high twist as reported earlier, but also introduce modest bending and lateral displacement of the flanking helices. Bending and displacement are nearly isotropic and the overall stiffness is similar to control A-RNA helix. Kink-turns, on the other hand, exhibit sharp bend and displacement shows relatively high anisotropy. In general, Kink-turns are almost two times more flexible than C-loops and A-RNA helices.

Our results can help to better understand the function of C-loops and kink-turns in the ribosome and can enable one to choose optimally stiff loop for use in nanostructures [1]. The approach can be extended to more complex structural motifs.

T. Drsata, K. Reblova, I. Besseova, J. Sponer and F. Lankas, *J. Chem. Theory Comput.* 13 3359 (2017)

K. Reblova, J.E Sponer, N. Spackova, I. Besseova and J. Sponer, *J. Phys. Chem. B* 115 13897 (2011)

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Structural Refinement of Small Ribosomal Subunit Using Self-Guided Langevin Dynamics

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Abstract

A central process in all living beings is protein synthesis which involves the ribosome machinery, transfer RNA, messenger RNA and various protein factors. [1] The main difficulty in understanding the translation of proteins is a lack of structural and dynamical information. However, with the advances in X-ray crystallography and cryo-EM microscopy, it is possible to obtain some insights and static snapshots of the translation process. Our work is focused on translation initiation, which is a rate-limiting step. The experimental Mechulam/Schmitt group in our department have derived a detailed structural model of the small ribosomal subunit (the 30S) of *Pyrococcus abyssi*. We are using molecular dynamics (MD) to study its structure, flexibility and function. The low-resolution experimental structure is being refined using a Molecular Dynamics Flexible Fitting method [2] implemented in Charmm, with the Self-Guided Langevin Dynamics method for enhanced sampling [3]. During the MD, the structure is constrained to stay within the cryo-EM electron density map. Since ribosomal complexes are extremely large, the solvent is described implicitly. We will describe results from our first simulations.

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Keywords: ribosome, structural refinement, MDFF, SGLD, molecular dynamics, implicit solvent

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Temperature Dependence of DNA Structure

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Abstract

It is well known that the three-dimensional structure of DNA varies with temperature. In a recent work, our group studied the temperature dependence of DNA twist and demonstrated strong quantitative agreement between magnetic tweezer experiments and molecular dynamics simulations. However, precise quantification of the temperature-dependent global conformational characteristics that occur remains incomplete. Thus, in this work, we investigate the relationships between the global shape of the DNA double helix and both other local coordinate changes and backbone torsion angle substates. As the data source, we used atomic-resolution molecular dynamics simulations with the explicit inclusion of water and ions in the range of 7–47 °C. 3DNA software was used to extract time series of DNA local coordinates from the simulated data. MATLAB analysis showed that all global conformational characteristics changed almost linearly with temperature. Decomposition of the overall thermal changes to contributions from the local base pairs revealed that the global shape of DNA was dependent on changes in the structure of the individual substates rather than on changes in the population of the backbone substates.

Keywords: conformational characteristics of DNA, molecular dynamics simulations, temperature dependence

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