Developing native contacts-based dissipative particle dynamics framework for modeling enzymes

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Dissipative particle dynamics (DPD) is a mesoscale approach that utilizes soft repulsive interactions between the beads representing clusters of atoms[1-3], thus permitting the use of a significantly larger time step between successive iterations. Developing a realistic model requires an accurate coarse-graining of atomistic representation into DPD beads. We will use the contact map obtained from the crystal structure and our complementary molecular dynamics simulations to develop an accurate DPD representation of enzymes. Fig. 1a shows our preliminary studies on mapping a lysozyme using its crystal structure into a suitable DPD representation. The DPD beads are shown in grey and are superimposed with the native crystal structure of the enzyme. Each amino acid is represented with one to three DPD beads depending on its size (for example, Glycine, with an effective volume of 60 $Å^3$, is represented by a single bead). We are developing a framework to accurately identify interaction parameters between DPD beads within the enzyme and between the enzyme beads and water. We scale the interaction parameters between the enzyme beads and water based on the hydropathy scale of amino acids. Further, we focus on developing an algorithm on assigning the interactions between the enzyme's DPD beads based on native contacts. Based on the principle of minimum frustration, the native contacts are known to play major role in folding mechanism.[4] Herein, two amino acids are considered to be in contact if the distance between the alpha carbons, C_α , is less than 7 Å and the residues are at least three or more sequence positions apart.[5-7] Contact map (Fig. 1b) serves both as a representation of a protein structure and as an energy fingerprint of protein conformation.[8] The contact map summarizes amino acid interactions and introduces an instructive visual representation of the secondary structures. For example, alpha helices appear as relatively thick bands along the main diagonal,

since they involve contacts between one amino acid and its four successors. Antiparallel (or parallel) β-strands give rise to a set of residues which are in contact and appear as lines of contacts perpendicular (or parallel) to the main diagonal. We compute contact maps from both the crystal (native) structure and from our DPD representation with selected DPD interaction parameters and point out to the routs to optimizing these parameters to achieve a closest match between the DPD and native contact maps. In essence, we aim to develop a native contacts-based DPD approach for modeling enzymes and evaluate advantages and limitations of this approach. While current work focuses on initial steps towards this goal, ultimately achieving this task is expected to have transformative influence on modeling a variety of stimuli-responsive biomaterials incorporating multiple enzymes and polymer chains. DPD framework would also allow one to introduce reactions between multiple moieties in a straightforward manner.

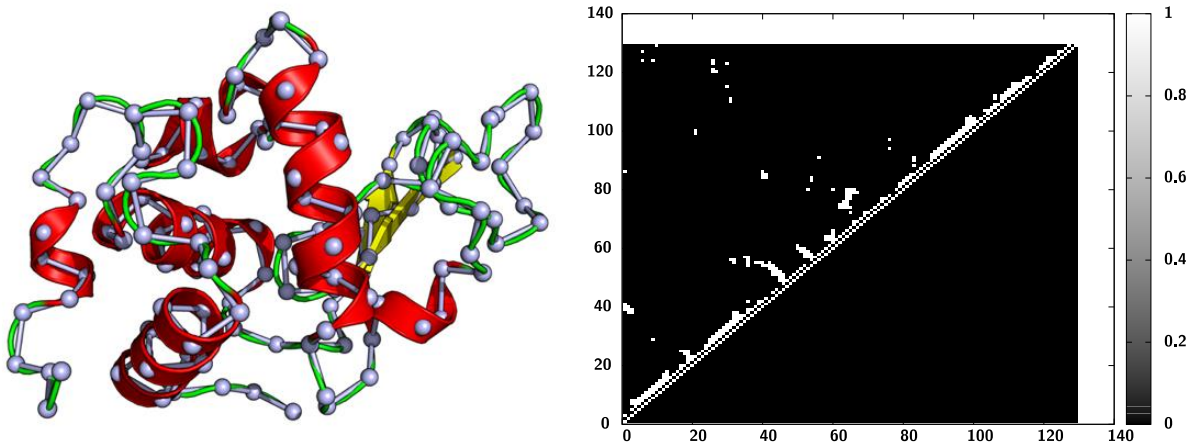

Fig 1. (a) Cartoon representation of 3TXJ enzyme. Helices and sheets are represented by the red and yellow, respectively. C_α position for each amino acid are shown as a bead, which represents the initial position for DPD simulations. (b) the native contact map for 3TXJ crystal structure. The white dots are the contacts.

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