sequence similarity and chain H of 1BTH possesses only about 36% sequence similarity. The sequence similarity among other chains of these interactions is very low except two identical chains P in 1BTH and I in 2PTC. Overall, there are no two pairs of interactions whose sequence similarity is larger than 40%. That is, there is no pair sequence redundancy in these six non-obligate interactions. The details of these sequence similarities are provided in Table 8. The computational steps for determining the sequence similarity between two sequence pairs can be found in Methods.

The 3D structures of this DWE biclique in the six different PDB protein complexes are displayed and compared in Figure 1. The 3D shape of these structures looks highly similar to each other with a common lock-and-key topology [24]. Since this stable topology is repetitive in six non-obligate interactions, it is worthy of further investigation to see whether this group of residues in this biclique is closely related to or involved in the above mentioned protein functions.

Another interesting question is: which residues in this DWE biclique are energetically outstanding. Lys in the sequence position 15 of chain I in 2PTC is a wet-lab confirmed hot spot residue with an extremely high energy (10 kcal/mol) according to ASEdb (Alanine Scanning Energetics database) [6]. This may suggest that the Lys residue is also a hot spot residue in the other 5 interacting chain pairs.

B. Residue Composition of the DWE Bicliques for the Three Types of Protein Interfaces

The residue composition of protein binding interfaces or binding sites has been intensively studied previously [8,15–18,25]. The composition of residues and residue pairs in DWE bicliques are studied by the current work in order to understand whether protein binding hot spots change their residue composition under the constraint of ‘double water exclusion’ hypothesis. We focus on the preference and tendency of residues to the specific types of interactions, as well as the preference and tendency of residue pairs. We would like to note that the composition of residues and their pairs in unique bicliques may be more interesting than that in DWE bicliques. But our investigation shows that there is no signifi-