Title:	A study on structural conservation of intra-chain domain-domain interfaces: learning for modeling interfaces
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Abstract:	A protein domain is considered as a modular conserved region of protein sequence or compact region of tertiary structure that serves as an evolutionary/functional unit of protein. Domains combine to form multidomain protein, which can facilitate complex biological functions. Analyses of many genomes have shown that only a limited repertoire of domain combinations is observed in genomes. The structural analyses of multidomain proteins have been largely focused on characterizing domain orientation. However, most of these have not analyzed domain-domain interfaces or explored their structural relatedness. In thesis work, we have comprehensively and systematically investigated the conservation of intra-chain domain interfaces in multidomain proteins from closely to distantly or completely unrelated domains. This study can facilitate accurate modeling of interfaces in multidomain proteins. In order to characterize intra-chain domain interfaces (DDI), we first compared various approaches to define domain interfaces. Thus, defined domain interfaces were compared with protein-protein interaction interfaces (PPIs) in terms of physicochemical features, amino acid propensity and secondary structure content. The study showed that domain-domain interface size is relatively smaller than protein interfaces. Despite this, interfaces of domains and proteins are similar in almost all analyzed features such as hydrophobicity, average number of hydrogen bonds and secondary structures. We examined the extent of domain interface conservation in multiple structures of a multidomain protein. This showed that in general domain interfaces are conserved (average interfacial rmsd ~1.3Å) for most proteins. The variation in domain interface is found due to interaction with ligand/DNA/RNA. Further, we compared domain interface conservation among domains sharing a level of structural relatedness as defined in structural domain database CATH. The interface similarity as assessed by IS-score, showed closely related domains conserve interfaces with mean IS- score of 0.7. However, distantly related domain-domain interfaces show variable conservation, which could arise because of functional constraints. Extending this study, we have analyzed structural degeneracy of interfaces by structurally aligning intra-chain domain interfaces of unrelated domains. Their interface alignment showed that for most interfaces (~76%) structural matching interfaces having similar C-alpha geometry and contact pattern despite that aligned domain pairs are unrelated. Moreover, the mean interface similarity score (~0.3) is more than random interface suggesting these are statistically significant alignments. Next, we characterized the structural space of DDI using graph theory, which showed this is highly connected network of interfaces. The degeneracy of interfaces is because of limited possible ways of packing secondary structures and flat interfaces. An important application of these observations of DDIs is identifying near native interfaces to improve the modeling of multidomain proteins. We applied similarity of interfaces to identify near native domain interfaces on rigid body docked complexes of domains. The interface similarity score could identify native like interfaces from a pool of very closely related docked poses. The improvement in the method was achieved by including geometrical constraints and protein globularity, which resulted in the enrichment of native solution to 90% in top 20 docked poses. Thus, this could be useful in modelling multidomain protein structures.
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