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Modeling protein-peptide interactions using protein fragments: fitting the pieces?

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An estimated 15-40% of all interactions in the cell are mediated through protein-peptide interactions [1,2] meaning that, at the most extreme, nearly every protein is affected either directly or indirectly by peptide-binding events.

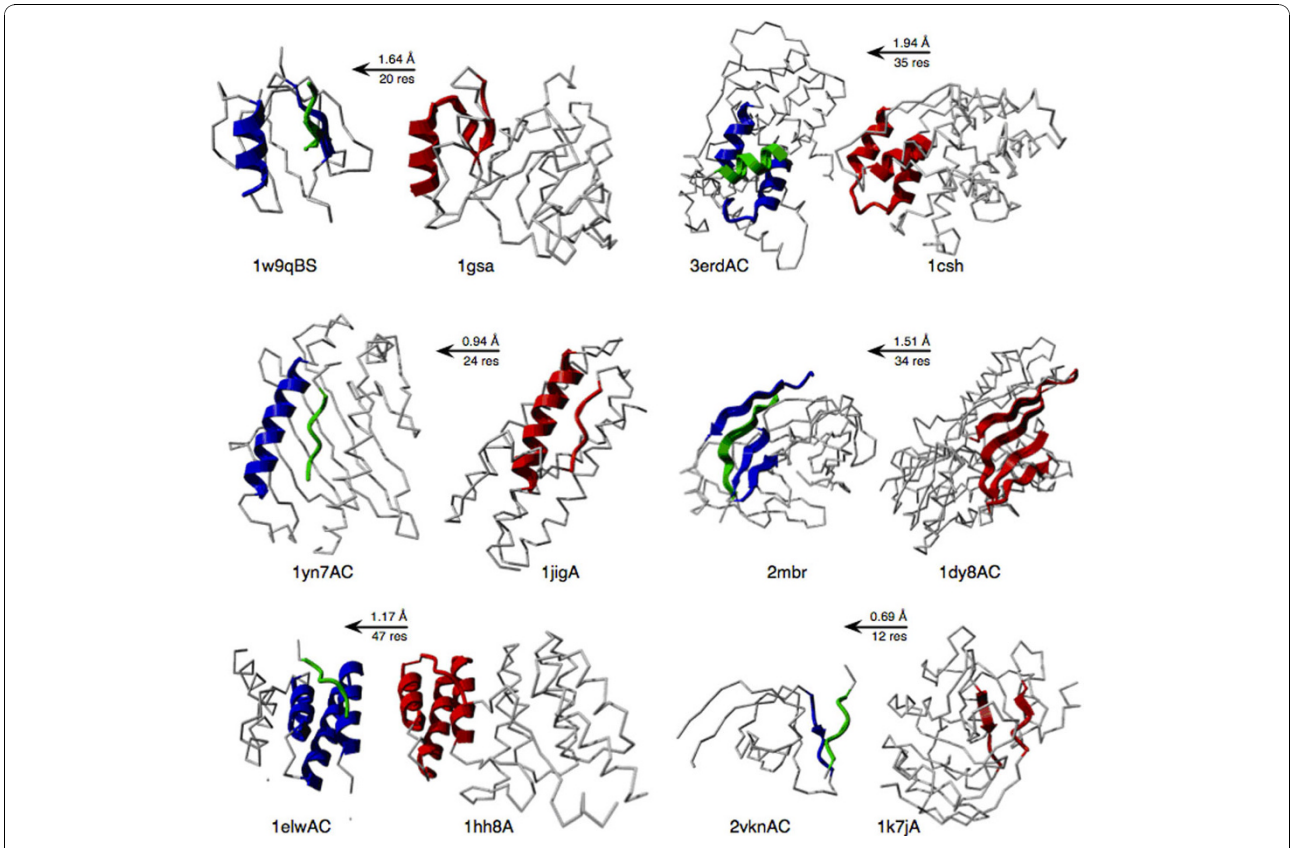

Figure 1 Relation between intermolecular protein-peptide interface architectures (blue for receptor, green for peptide ligand) and intramolecular protein architectures from our database of monomeric proteins, BriX (red) [4].

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We compared the modes of interaction between protein-peptide interfaces and those observed within monomeric proteins and found surprisingly little differences [3]. Over 65% of 731 protein-peptide interfaces could be reconstructed within 1 Å RMSD using solely fragment interactions occurring in monomeric proteins, using our fragment database BriX containing over 1000 non-redundant protein structures [4]. Interestingly, more than 80% of interacting fragments used in reconstructing a protein-peptide binding site were obtained from monomeric proteins of an entirely different structural classification, with an average sequence identity below 15%. Nevertheless, geometric properties perfectly match the interaction patterns observed within monomeric proteins (see Figure 1), suggesting that our fragment interaction approach might provide an alternative to homology modelling.

We show the usefulness of our method by redesigning the interaction scaffold of nine protein-peptide complexes, for which five of the peptides can be modelled to within 1 Å RMSD of the original peptide position.

These data suggest that the wealth of structural data on monomeric proteins could be harvested to model protein-peptide interactions and, more importantly, that sequence homology is no prerequisite. In addition, we have made our dataset of 505 non-redundant protein-peptide complexes from 1431 entries in the PDB available at http://pepx.switchlab.org [5] and the BriX database at http://brix.crg.es [6].

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