IntGeom: A Server for the Calculation of the Interaction Geometry between Planar Groups in Proteins

Arumay Pal[1], Rajasri Bhattacharyya[1,2,3], Maitrayee Dasgupta[1,2], Saptarshi Mandal[1] and Pinak Chakrabarti[1,2,*]

[1]Department of Biochemistry
[2]Bioinformatics Centre, Bose Institute, P-1/12 CIT Scheme VIIM, Calcutta 700 054, India

[3]Present address: Department of Experimental Medicine and Biotechnology,
Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

*Corresponding author: Pinak Chakrabarti, Bioinformatics Centre,
Bose Institute, P-1/12 CIT Scheme VIIM, Calcutta 700 054, India
Fax: +91-33-2355-3886; Tel: +91-33-2355-0256; E-mail: pinak@boseinst.ernet.in

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Abstract

   IntGeom is a server for the calculation of the relative orientation between any two planar groups in protein side chains. IntGeom1 considers ten planar groups, while IntGeom2 is meant for studying the contact between a S-containing group and an aromatic residue. When the interaction is between two aromatic residues or involving an aromatic ring with Pro or Arg or an amide side chain, the occurrence of any C–H···π (N–H···π) interaction is also studied. All contacts between any two of the above types of residues juxtaposed on the protein structure can be displayed. The software is available at: http://www.boseinst.ernet.in/resources/bioinfo/stag.html.

Introduction

   Whereas hydrophobic interaction is the main contributing factor to the stability of the protein fold, the specificity of the folding process depends on many directional interactions, notably hydrogen bonding (Dill, 1990; Zhou et al., 2001). However, many non-conventional interactions such as C-H···π or C-H···O interactions are directional, and can thus contribute to the uniqueness of a particular local structural motif and to the binding of substrates/cofactors to proteins (Burley and Petsko, 1988; Wahl and Sundaralingam, 1997; Weiss et al., 2001). A residue, such as Pro, which is notionally assumed to engage aromatic side chains through hydrophobic forces, can indeed form C-H···π interactions, and it is found that the relative orientations of the rings that favor these interactions outnumber those that cannot sustain

these stereospecific interactions (Bhattacharyya and Chakrabarti, 2003). Likewise, the proper juxtaposition of molecular orbitals is important in the selection of the orientation of sulfur-containing group of Cys or Met relative to aromatic or carbonyl groups (Pal and Chakrabarti, 1998; Pal and Chakrabarti, 2001; Bhattacharyya et al., 2004). Although there is a non-randomness in the packing of any two residues, indicating thereby that some specific orientations are energetically favorable or provide more efficient mode of packing (Mitchell et al., 1997; Brocchieri and Karlin, 1994; Chakrabarti and Bhattacharyya, 2007), a software for the calculation of interaction geometry is not generally available. Servers, such as NCI, identifies non-canonical interactions in protein structures (Babu, 2003), whereas PIC iden-

tifies residue pairs showing different types of interactions (Tina et al., 2007), but these do not calculate the relative orientations between the planar groups, for which purpose a server, IntGeom, has been developed and is presented here.

Results and Discussion

Description of the software

The software can be accessed at http://www.boseinst.ernet.in/resources/bioinfo/stag.html. There are two separate servers, IntGeom1, for the calculation of the relative orientation when the planar part of the side chains of ten residues (Phe, Tyr, His, Trp, Pro, Asp, Glu, Asn, Gln and Arg) are within a limiting distance (default, 4.5 Å), and IntGeom2, which considers the interaction of the S atom (of free or disulfide-bonded Cys residues and Met) with four aromatic residues.

On reading a coordinates file in the PDB (Berman et al., 2000) format, IntGeom1 provides a 10 x 10 triangular matrix showing the number of contacts between all possible pairs of residues (Fig. 1A). The number given here is twice the number of independent pair, as for any X-Y contact the geometry is calculated both for Y relative to X and vice versa. On clicking a number, the geometry for all the contacts for the corresponding residue types is calculated (Fig. 1C). The atoms used to define the planar moieties and the various geometric parameters are discussed in the HELP file. The relative orientation between two planar groups is given by the interplanar angle, P and θ, which is the angle between the line joining the centroid of the 2nd residue to that of the first and the normal to the latter. Schematic representations and the designation of the canonical geometries at the nine grid elements (into which the 0-90° ranges of P and θ are divided) are shown in Fig. 1B, following the published convention (Samanta et al., 1999; Bhattacharyya et al., 2002, 2003; Bhattacharyya and Chakrabarti, 2003). In Fig. 1C, the orientation of the second residue is shown schematically relative to the first (or the central residue, marked in darker color). If the geometric conditions (Bhattacharyya and Chakrabarti, 2003) are satisfied, the presence of a C/N-H···π interaction (involving the two aromatic residues or an aromatic residue with proline or arginine or an amide side chain) is marked in the table (note that the C/N-H group is located on the first residue). The hydrogen atoms needed for these are fixed stereochemically using REDUCE (Word et al., 1999). Jmol can be used (with a Java enabled browser or Java Runtime Environment, available at www.java.com) to display the interacting side chains of a particular type of residue pair against the backbone of the whole structure.

While the geometry of aromatic-aromatic interactions has attracted considerable attention over the years (Singh and Thornton, 1985; Burley and Petsko, 1988; Bhattacharyya et al., 2002), it is only recently that there has been realization that the disulfide group (involving cystine and Met residues) can have preferred orientations relative to aromatic planes (Pal and Chakrabarti, 2001; Bhattacharyya et al., 2004), which can be found out using IntGeom2. When a S atom is within a cut-off distance (default, 4.3 Å) from an aromatic plane, the interplanar angle (with the plane defined by S with its two bonded neighbors), P and θ, the angle between line joining S to the centroid of the aromatic ring and the normal to it, are calculated. The schematic representation of the relative orientation indicated by these two parameters, along with the values of other distances and angles, are tabulated (Fig. 1D). When the S atom belongs to a free Cys, only the angle θ is calculated, and the S atom is assumed to be on the face of the aromatic ring if θ is in the range 0 to 45°, or the edge, when $\theta > 45°$.

Comparison to other servers

A web server, CHpredict exists for the prediction of the occurrence of weak hydrogen bond interactions, such as C-H···π or C-H···O, but involving the main-chain C$^{\alpha}$-H group only (Kaur and Raghava, 2006). Similarly, the server, AR_NHPred deals with the prediction of interaction between the backbone NH group and the aromatic side chain (Kaur and Raghava, 2004). Unlike NCI that identifies all weak hydrogen bond interactions in three-dimensional structure of a protein (Babu, 2003), the server presented here deals with the planar residues only and compute the relative geometry of the interacting pairs. Some of these geometries may be congenial for the formation of C/N-H···π interaction, if one of the moieties is an aromatic side chain. The server also considers the interaction between a sulfur-containing residue and an aromatic side chain, something that is not dealt with by any other available software. Aromatic residues are abundant in interfaces formed by protein-protein interactions and various interactions involving these are assumed to confer the strength of binding (Saha et al., 2007). If a PDB file of a complex is given as input to IntGeom, the interactions occurring across the interface can be identified by noting the different chain IDs of the interacting pair.
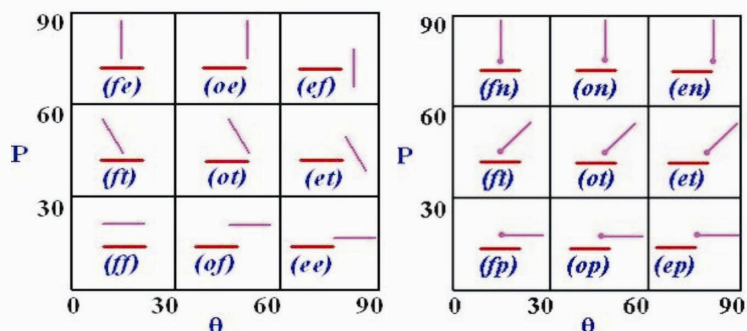
Conclusion and Perspectives

A web server is presented that can elucidate the geometry of interactions between various planar side chains in protein structures that should be useful in understanding the protein conformation and the stability of interactions between polypeptide chains. It can also be used in designing protein

A

B

C

Residue 1	Residue 2	Shortest Contact	Centroid-Centroid Distance	P	Theta	XHPI [X=C/N]	Relative Orientation
4 P HIS	79 B TRP	CE1 CD1 3.2	4.6	89	82	CHPI	(ef)
4 P HIS	2 P TRP	CD2 CH2 3.8	6.5	73	58		(oe)

D

Cys Residues	Interacting		Shortest Contact		Centroid-SG Distance	Angle		P	Theta	Relative Orientation
	Cys	Aromatic	From SG	From SG'		CB-SG-Centroid	SG'-SG-Centroid			
16 A 36 A	36 A	38 A TRP	NE1 3.7	CD1 5.6	4.9 6.6	117.7	139.0	88	52	(on)
22 A 46 A	22 A	21 A TYR	CD2 4.2	CE2 4.0	5.4 5.0	96.4	68.4	63	67	(en)
22 A 46 A	46 A	21 A TYR	CE2 4.0	CD2 4.2	5.0 5.4	163.6	89.6	40	61	(et)

Figure 1: Examples of results. (A) The number of interacting residue-pairs for the PDB file, 1RST. (B) Nine standard geometrical orientations spanning the 90° range of P and θ, the left one for IntGeom1 and the right, for IntGeom2. While the centroid of the interacting ring is used for the calculation of the orientation relative to the central residue (in thicker line) in the former, it is the S atom (dot) in the latter. As such, the designations of the idealized geometries are different in the two diagrams (Bhattacharyya et al., 2004). Partial output of different geometrical parameters (C) for the His-Trp pair in 1RST and (D) cystine-aromatic pair in the PDB file, 1AHO.

engineering experiments to increase protein stability. For example, it has been observed that the edge of a His residue, when directed towards the π electron cloud (i.e., the face) of an aromatic ring, results in an increase in the stability of the protein (Bhattacharyya et al., 2002). Based on the results of IntGeom one can select suitable candidates for mutation to arrive at such an interacting set of pairs. Additionally, it is known that the disulfide bonds are susceptible to cleavage when protein crystals are exposed to synchrotron radiation during data collection in Xray crystallography (Weik et al., 2000). One can study if there is any correlation between the degree of susceptibility of different disulfide bridges and the geometry of interaction with the aromatic residues in their environment.

Acknowledgements

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