

SBION: A Program for Analyses of Salt-Bridges from Multiple Structure Files

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Received February 11, 2014; Revised February 24, 2014; Accepted February 25, 2014; Published March 19, 2014

Abstract:

Salt-bridge and network salt-bridge are specific electrostatic interactions that contribute to the overall stability of proteins. In hierarchical protein folding model, these interactions play crucial role in nucleation process. The advent and growth of protein structure database and its availability in public domain made an urgent need for context dependent rapid analysis of salt-bridges. While these analyses on single protein is cumbersome and time-consuming, batch analyses need efficient software for rapid topological scan of a large number of protein for extracting details on (i) fraction of salt-bridge residues (acidic and basic). (ii) Chain specific intra-molecular salt-bridges, (iii) inter-molecular salt-bridges (protein-protein interactions) in all possible binary combinations (iv) network salt-bridges and (v) secondary structure distribution of salt-bridge residues. To the best of our knowledge, such efficient software is not available in public domain. At this juncture, we have developed a program i.e. SBION which can perform all the above mentioned computations for any number of protein with any number of chain at any given distance of ion-pair. It is highly efficient, fast, error-free and user friendly. Finally we would say that our SBION indeed possesses potential for applications in the field of structural and comparative bioinformatics studies.

Availability: SBION is freely available for non-commercial/academic institutions on formal request to the corresponding author (akbanerjee@biotech.buruniv.ac.in).

Keywords: salt-bridges, stability, proteins, software, program, network salt bridges.

Background:

The stability of a protein results from a delicate balance between opposing forces. Salt-bridges are bonds between oppositely charged side chain atoms of acidic (acceptor atoms) and basic (donor atoms) residues that are within 4Å distance [1]. Under cellular pH conditions, these side chains in proteins remain ionized and thus form salt-bridges. It can form in 1:1, 1:2, 1:3 etc ratios. The first type is known as monomeric (**Figure 1: I-A**) and others are network type salt-bridges (**Figure 1: I-B**).

Salt-bridge forming residues can either be in secondary (sheet and helix) or in coil structures of which more in the former indicates that they are evolutionarily conserved. Both in experimental and theoretical scenario, it has been entertained that salt bridges are mostly stabilizing and specific in nature [2, 3, 4]. Salt-bridges play crucial role in protein-protein interactions (**Figure 1: I-C**), molecular recognition, allosteric regulation, domain motions. Extremophilic proteins make

special use of these interactions for maintenance of stability in their robust environments [4, 5].

At this point it is worth raising the question as to how many of the database-protein-structures are computationally approach for the above purpose. The question is relevant as currently there are about sixty thousand (till 4th Feb, 2014) high resolution (<2.5Å) crystal structures in the protein database to extract massive information on salt-bridges and to find their involvement in relation to the above issues. Such computation would also be useful for determining “structural classification of protein” (SCOP) based pattern of salt-bridges and to develop pattern specific scoring functions. The paucity of such results might have stemmed from the fact of lack of efficient software

that could analyze a large number of structures in a single run for output with all relevant details. Mention may be made of the fact that while interface [6], plug-in [7] and web based [8] computation of salt-bridges are possible; some produce erroneous results [6] or lack of complete details [6, 7] and others are limited by the speed of internet [8]. Moreover, none of this program provides information on network salt-bridge, secondary structure and residue specific analysis. In this end our development i.e. SBION potentially overcome most of the above limitations. Not only salt-bridge but also ion-pair of any distance can be computed for any number of protein with any number of chain. Taken together it could be said that our SBION is unique and first of its kind.

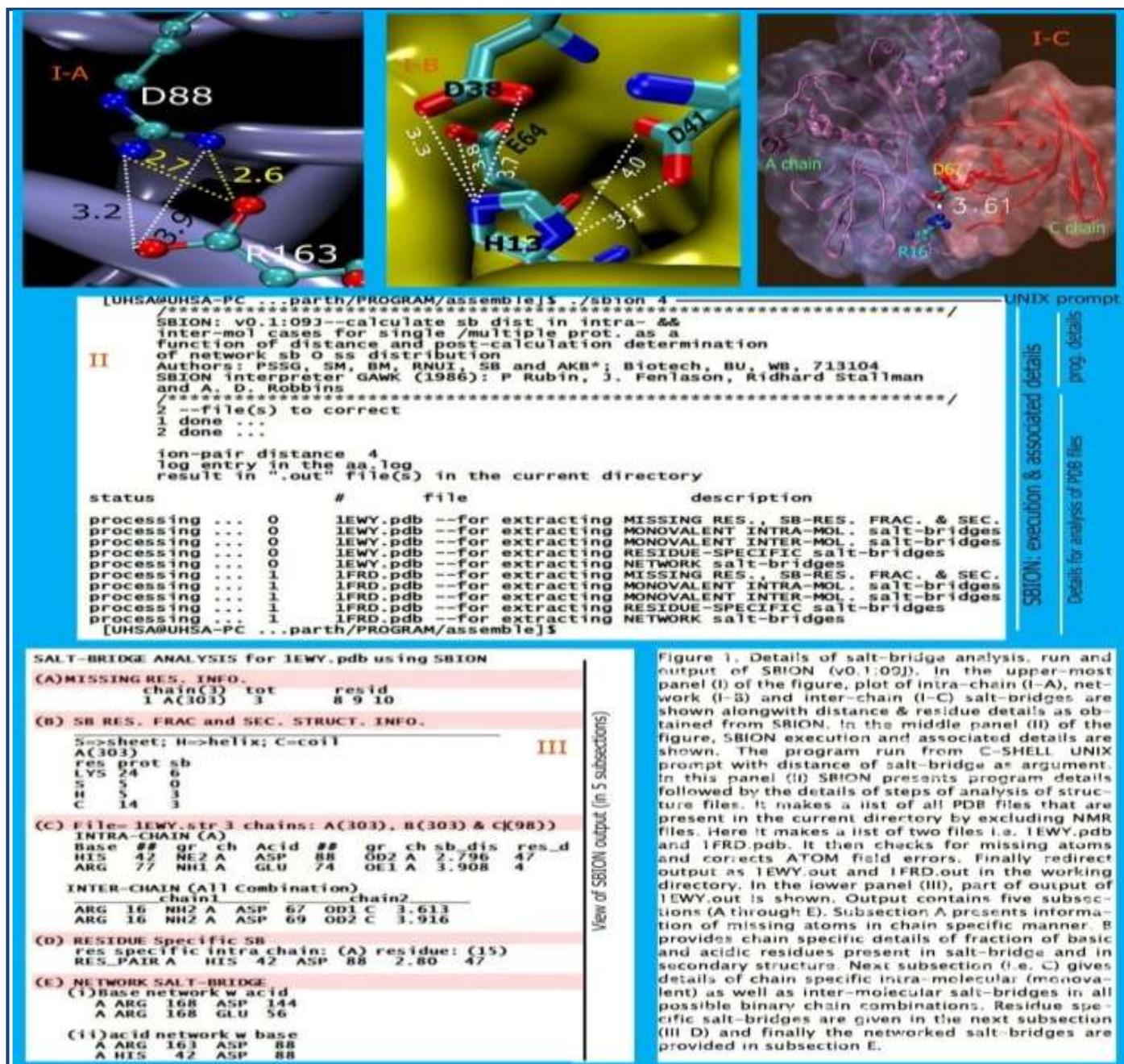


Figure 1: Details of SBION extracted salt-bridge analysis (panel-I: A, B & C), response during run (panel-II) and output in subsections (panel-III).

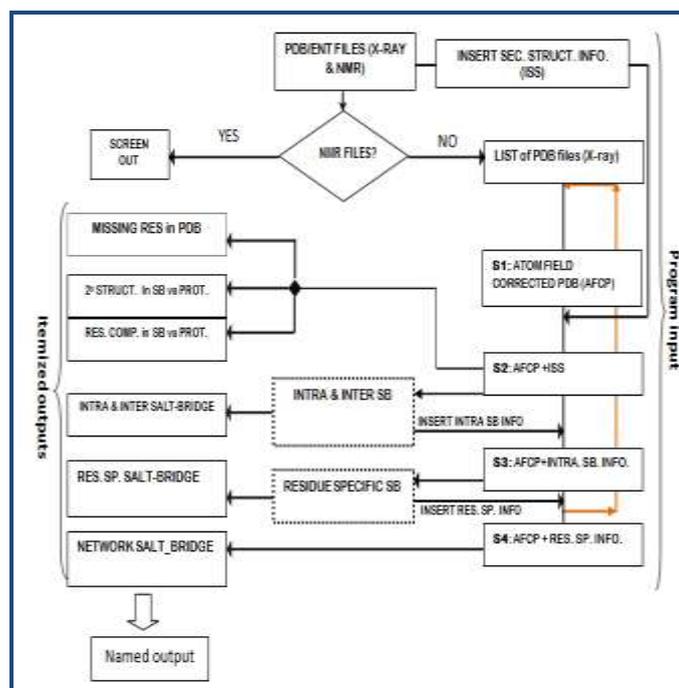


Figure 2: Flowchart for topology scanning procedure by SBION

Methodology:

SBION works in C-Shell UNIX environment and is interpreted by GAWK programming language. A detailed flow-chart of its functioning is shown below (Figure 2). First it makes a list of all crystal structure files that are present in the working directory and process one at a time in stage wise manner (four stages e.g. S1, S2, S3 and S4). The program extracts itemized results for preparing compact, named output per input file. Upon completion, it loops back to next PDB for named output as above and so on.

Program input:

Users need to place all protein structures (X-ray/NMR: PDB/ENT files) in a directory and run SBION from UNIX prompt providing salt-bridge distance (Figure 1: panel II). The program uses crystal structure files as input by screening out NMR files (Figure 2), if they exist in the working directory.

Program output:

All named outputs (Figure 2) will be in the same working directory. SBION writes one output per PDB/ENT file in itemized manner (Figure 1: panel III). In first section of output file it gives missing atoms information, if any are there in the structure files (III: A). Then it describes details on secondary structure and residue composition (III: B). In next section, it provides intra molecular (monovalent) and inter-molecular salt bridges (III: C). Finally details on residue specific and networked salt-bridges are presented (III: D & E).

Caveats and future development:

Program is written in GAWK (interactive) language which can preferably run in any C shell UNIX prompt including CYGWIN and also be made work in B shell LINUX and WINDOWS environment. We are developing web interface to integrate SBION and other tools such as PHYSICO [9] developed in our lab, within a unique web service.

Acknowledgement:

We thankfully acknowledge the computational facility Laboratory of the Department of Biotechnology, The University of Burdwan.

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Edited by P Kanguane

Citation: Gupta *et al.* *Bioinformatics* 10(3): 164-166 (2014)

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