ADSBET2: Automated Determination of Salt-Bridge Energy-Terms version 2

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Abstract:
Component (bridge: ΔΔG_\text{brd}, background: ΔΔG_\text{prot}, desolvation: ΔΔG_\text{dsolv}) and net (ΔΔG_{\text{net}}) energy-terms of salt-bridge-structure (SBS) are auto-generated by the program ADSBET that makes use of general purpose Adaptive Poison Boltzmann Solver (APBS) method. While the procedure reports gross energy terms (\text{Kcal Mol}^{-1}), report on bond-multiplicity corrected normalized energy-terms (\text{Kcal Mol}^{-1} \text{Bond}^{-1}) along with their accessibility (ASA) in monomer, isolated-SBS (ISBS) and networked-SBS (NSBS) format would be very useful for statistical comparison among SBSs and understanding their location in protein structure. In this end, ADSBET2 potentially incorporates these features along with additional model for side-chain. Gross and normalized energy-terms are redirected in monomer, ISBS and NSBS format along with their ASA informations. It works on any number of SBSs for any number of structure files present in a database. Taken together, ADSBET2 has been suitable for statistical analyses of SBSs energetics and finds applications in protein engineering and structural bioinformatics.

Availability: ADSBET2 is freely available at http://sourceforge.net/projects/ADSBET2/ for all users.

Keywords: Energy terms, Networked, Isolated, Salt Bridge, ASA, Kcal Mol^{-1} Bond^{-1}

Background:
Salt-bridge, electrostatic interactions between partial charges of side-chain of acidic and basic residues, plays crucial role in stability and packing of protein. It is more so for proteins adapted in extreme environments [1]. Use of general purpose integrators of Poison Boltzmann Equation such as open-source Adaptive Poison Boltzmann Solver (APBS) [2] is the only means over experimental pKa or double-mutational cycle methods [3] to compute overall components (i.e. bridge-energy: ΔΔG_\text{brd}, background-energy: ΔΔG_\text{prot}, desolvation-energy: ΔΔG_\text{dsolv}) and net-energy (ΔΔG_{\text{net}}) terms of SBS [4, 5]. However, relative to other applications of the solver, computation of energy-terms of SBS is highly labor intensive that includes determination of protein-specific a] and residue specific salt bridges or ion-pairs [6, 7], b] grid-points, c] grid center and d] hydrophobic-isosteres-mediated mutation-files (five per SBS) from original protein-charge-radius (PQR) file [8] prior computation. Further in post-computation scenario, great deals of manual involvement are also necessary to obtain i] energy-terms from reaction field energies and relevant choice of partial atomic charges [9] and ii] side-chains-specific accessibility of SBS. While ADSBET [10] performs all these pre and post-run computations, it has few short-comings. Firstly it does not report bond multiplicity corrected normalized energy-terms (\text{EnergyBond}^{-1} \text{SBS}^{-1}) in monomer, ISBS and NSBS format which would be necessary for comparison among SBSs.
present in a database. While, for example, comparable net energy-terms for ISBS (in S1 and S2 of Figure 1: FII) are E1 and E2/2 and that for NSBS (in N1 and N2 of Figure 1: FII) are (E3+E4) and (E5/2+E6/2) respectively, ADSBET only reports E1, E2, E3, E4, E5 and E6 in monomer format. Secondly it does not inform side-chain model-specific accessibility [10] which would be crucial for understanding surface and core location of SBS [5, 6] (Figure 1: p). Finally as far as models for side-chains of interacting partner of SBS are concerned, only a less popular model (i.e. MDL-1) is available in ADSBET [10] (Figure 1). In this context, ADSBET2 potentially includes all these features along with popular additional model of side chain (i.e. MDL-2). When opted, it reports side-chain ASA by the use of either of three alternative methods.

Figure 1: Model-based side-chains (FII), different SBS (FII) and flow-chart (FIII) for ADSBET2. MDL-1 and MDL-2 are used in model-1 and model-2 respectively. S1 (energy E1) and N1 (energy E3 and E4) are single-bonded isolated and networked SBS. S2 (energy E2) and N2 (energy E5 and E6) are multiple-bonded isolated and networked SBS. P shows core and surface location of SBS. In FIII, N-A and U-A are acidic side-chains in folded and unfolded state of protein respectively. Additional features in ADSBET2 over its earlier version are shown in green color.
Method of computation of $\Delta G_{\text{bind}}, \Delta G_{\text{prot}}, \Delta G_{\text{dissolv}}$, and $\Delta G_{\text{net}}$ remains similar as earlier [10]. Detailed methods also precede analytical result of each item of outputs. Normalized energy-terms of each monomeric SBS are obtained by dividing these terms by their bond-multiplicity (Figure 1: FII, S2, and N2). When opted, accessibility (hence surface and core location) of SBS is computed. Overall and normalized energy-terms for NSBS are obtained by summing energy-terms of all monomeric cases having either a common acidic (A-NSBS: FII N1) or basic (B-NSBS: FII N2) partner in a SBS (thus forming dimer, trimer etc.). Apart from MDL-1 of ADSBET [10], ADSBET2 utilizes additional most-popular model for side chains i.e. MDL-2 (Figure 1: Fl). Operational details of the program includes following sequence of events: a) make list of x-ray files in PDB format (Figure 1: FIII), b) uptake user’s parameters from command line, c) extract atomic SBS and then convert them into residue-specific SBS, d) select model of side-chain, e) select accessibility mode and method, f) Generate force-field dependent PQR-file and protein-specific APBS-parameters (such as dume, gcent, grid-points, ionic-strength and pH), g) generate 5 relevant mutated-POR-files per SBS, h) prepare input-file for APBS using user, default, generated parameters and mutated PQRs, i) run APBS, j) redirect output and k) repeat the process for other SBSs and PDBs.

Program input
Poison Boltzmann Equation solvers (such as APBS) require multi-parameters input for generation of reaction field energy [2]. Thus, apart from PDB-files in the working directory users need to input parameters (Figure 1: FIII: User Input) such as model for side-chain (F1), ASA method, grid-spacing, pH, mobile ion concentration (in Molar), dielectric constant of protein, salt-bridge or ion-pair distance and force-field. Protein specific parameters (such as dume, gcent and grid-points) are auto-generated by the program and other parameters are used as default (Figure 1: FIII: Default pars) if not mentioned otherwise.

Program output
Details of SBS-energetics and accessibility for any number of SBS in any number of PDBs are redirected into two different named-outputs. Unlike ADSBET [10], ADSBET2 redirects most relevant model-based additional output (Figure 1: FIII: Green color parts) on overall and normalized energetics in monomer, ISBS and NSBS format along with their core and surface location informations (Figure 2).

Caveats and future development:
The program which is interpreted by AWK programming language is tested to run in the OS: CYGWIN (32 bit). We further are working to develop GUI-based version of the program.

Conclusion:
ADSBET2, interpreted by AWK programming language, produces model-based overall and normalized SBS-energetics in monomer, ISBS and NSBS formats along with their accessibility information for any member of X-ray structure files with any number of SBSs in them. These results are useful for statistical comparison of SBS-energetics of candidate salt-bridges or ion-pairs present in a database.

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