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The Star STING server: a multiplatform environment for protein structure analysis

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ABSTRACT. Star STING is the latest version of the STING suite of programs and corresponding database. We report on five important aspects of this package that have acquired some new characteristics, designed to add key advantages to the whole suite: 1) availability for most popular platforms and browsers, 2) introduction of the STING_DB quality assessment, 3) improvement in algorithms for calculation of three STING parameters, 4) introduction of five new STING modules, and 5) expansion of the existing modules. Star STING is freely accessible at: http://sms.cbi.cnptia.embrapa.br/SMS/, http://trantor.bioc.columbia.edu/SMS,

http://www.es.embnet.org/SMS/, http://gibk26.bse.kyutech.ac.jp/SMS/ and http://www.ar.embnet.org/SMS.

Key words: Protein structure analysis, Per-residue structure descriptors, Topology similarity, Structure summaries

INTRODUCTION

STING, a multiplatform environment for protein structure analysis, continues to build on what is considered its main asset: a principal database (DB) of per-residue-reported descriptors (available for display both numerically and graphically) for either the public protein data base (PDB) (Berman et al., 2004) or local files. Since its first appearance in 1998, STING has undergone seven major updates (Neshich et al., 2003, 2004, 2005a,b; Higa et al.,2004) with ever increasing integration of data describing the protein sequences, structure, function, and stability. We describe some new features available in the Star STING suite.

PLATFORM AND BROWSER COMPATIBILITY

A dual protein structure viewer capability was introduced in Star STING, with options for using either Jmol or Chime. The former makes STING compatible with major platforms and browsers.

STING_DB QUALITY ASSESSMENT

The STING_DB is regularly updated in synchrony with the PDB updates (once a week). All the STING_DB parameters are calculated immediately upon receiving the newly deposited structures. However, some parameters might not be successfully processed while updating STING_DB and calculating parameters in high-throughput mode. Hence, there was an immediate demand for introducing a module for checking the quality of the STING_DB. The STING_DB Quality Assessment (STING_DB QA) is an answer to this particular demand. With this new module, a user can perform tracking of the PDB files that contain insufficient information clarity for a specific structure descriptor calculation. Also, the overall quality of the STING_DB is now much easier to check, setting this STING version apart from most of the other (similar) products in this area (Galperin, 2006).

ALGORITHM IMPROVEMENTS

Three of the STING_DB per-residue-reported structure descriptors: Order of Cross-Link, Order of Cross-Presence as well as Evolutionary Pressure, were re-calculated, using new default input parameter settings for the corresponding programs. The cross-links were re-defined in STING; we previously defined them as the contacts (any type from possible five classes)

established among residues that are far apart in the protein primary sequence, but are close in its 3-D folding. Only a single occurrence is counted for the Order of Cross-Link, even though several contacts could be identified, starting from the central amino acid, which can make more than one contact, and each of these can be established with a different amino acid belonging to the same stretch of probing sequence size [15, 20 and 30 residues long]. We introduced an additional restriction in Star STING, so that the occurrence of the contact is only counted for the order of cross-link if the target residues are also 15, 20 or 30 amino acids (respectively) apart in a primary sequence. As a result, we have fewer occurrences of identified cross-links. This further emphasizes the importance of those that remain.

We have also used a new Rate4Site algorithm for calculating the Evolutionary Pressure parameter. The new version of this algorithm was used with the following default input values: no branch length optimization for phylogenetic trees and 10 discrete "Gamma categories" (Mayrose et al., 2004). This algorithm configuration allowed us to obtain the best balance between accuracy of reported data and running time on available CPUs, which in turn will allow us to make more frequent STING_DB updates.

NEW MODULES FOR COMPLEX PROTEIN STRUCTURE ANALYSIS

Five new STING modules were introduced: I. Multiple Structures - Single Parameter 2-D plot for comparing a chosen parameter among several structures (Figure 1, inset H); II. STING_TGZ for obtaining encapsulated STING_DB parameters for up to five public PDB files at the same time; III. Contact Distance Map for simultaneous visualization of the five classes of contacts for all amino acids of a chosen structure; IV. TopSiMap for evaluating the topology similarity among any two structures, based on the contact pattern (Figure 1, inset E), and V. Protein Contacts Difference, which generates an easy-to-grasp HTML table listing contact differences among any two structures (Figure 1, inset F).

GENERAL IMPROVEMENTS

In Star STING we improved: 1) The procedure for selecting the structure parameter ranges in [Java]Protein Dossier while searching for those amino acids that satisfy particular conditions. Most importantly, the parameter ranges could now be saved and transferred from one STING session to the other, greatly facilitating the process of selection. 2) In addition, the STING Report module was expanded with new module images, including MolScript (Kraulis, 1991) presentation of the amino acid whose characteristics are particularly targeted (Figure 1, inset C). 3) At the opening of STING, a user is now presented with a third window: "At-a-glance Structure/File Characteristics" (Figure 1, inset G), offering general information on this specific PDB entry, facilitating analysis by displaying some background information, summaries about the structure and the "Highlights" - the list of residues with some structural descriptors occupying an outstanding position among the others (Figure 1, inset I).

FUTURE DEVELOPMENTS

The Star STING and STING_DB are already being expanded: two new parameters will be added in Blue Star STING (protein-ligand contacts and co-evolving amino acids). The

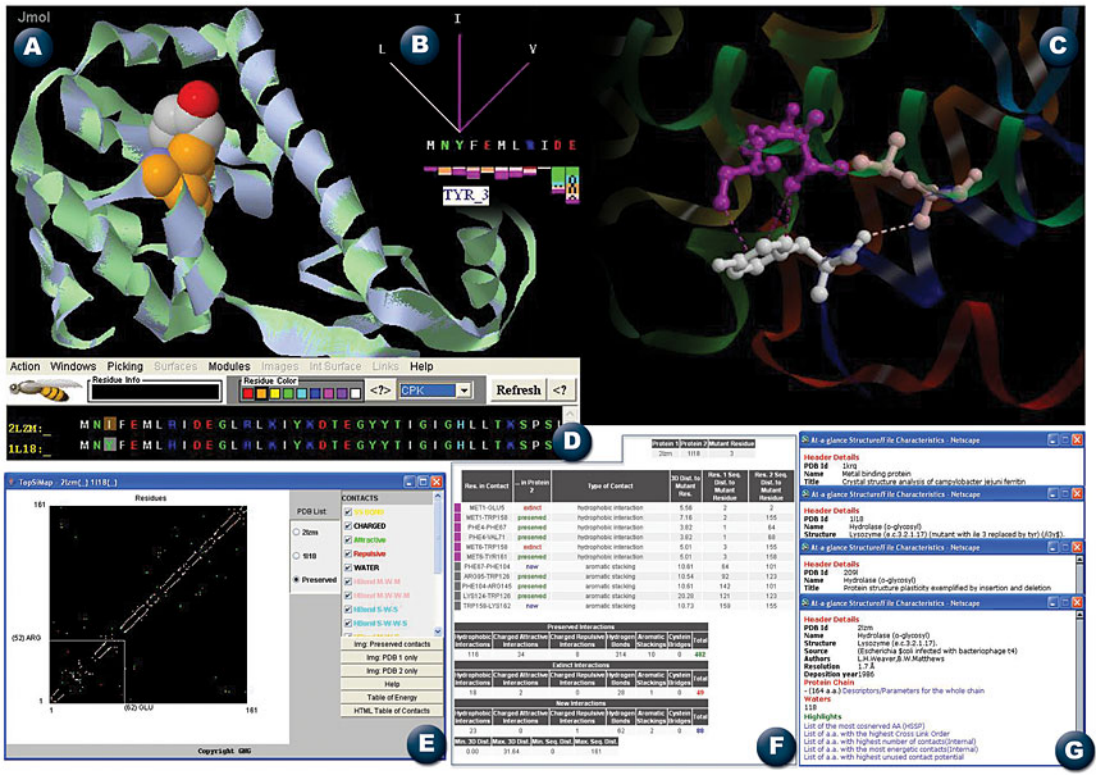

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Figure 1. A screenshot montage of the Star STING modules output. **A.** Sting uses Jmol as a structure graphics viewer; here we show the output generated by the TopSiMap module: the two proteins are structurally aligned: 2LZM.pdb and 1L18.pdb. These two structures were taken as representatives of a wild-type protein and a single-residue mutant. The mutation occurred at position 3 of the sequence (inset D), where isoleucine residue (yellow) was substituted by tyrosine (white). **B** and **C.** Two different views of the contacts established between the TYR_3 and its neighboring residues: the STING Graphical Contacts presentation and the STING Report MolScript 3-D presentation, respectively. **D.** The STING Sequence window showing the two aligned sequences and emphasizing position 3 (corresponding colors are used both in the Jmol and Sequence Windows). **E.** The TopSiMap output showing only preserved contacts in both structures: 2LZM.pdb and 1L18.pdb. **F.** The Protein Contacts Difference HTML table, showing the full list of preserved, extinct and new contacts identified, while comparing the wild-type structure with the structure of the mutant (2LZM.pdb and 1L18.pdb, respectively). This table can also show the distance both in sequence and in 3-D, of the contacts listed, from the mutation point; this is an interesting feature, showing that widespread changes may occur even at the other end of the protein relative to the site of mutation. **G.** The "At-a-Glance Structure/File Characteristics" window showing a resumed report about the PDB files and about the structure itself, from three lysozyme structures (2LZM.pdb, 1L18.pdb and 209L.pdb) and one ferritin (1KRQ.pdb). The "Highlights" portion of this report (shown at inset I) tabulates "the 10 most/highest/lowest" residues, such as: conserved, number of contacts, number of unused contacts, cross-link order, and energy of contacts. **H.** The Multiple Structures - Single Parameter (MSSP) output. The upper inset demonstrates the "Electrostatic potential at the molecular surface" reported in per-residue fashion for the same four structures listed in inset I. The first three are lysozymes (white, red and blue curves), while the yellow curve belongs to the ferritin molecule. The MSSP module makes it easy to quickly grasp the differences among the lysozymes on one hand and the ferritin (in terms of the chosen structural parameter), on the other. The bottom inset shows the parameter "Distance from the N-terminal" (reporting Cα - Cα distances in Å) for the same four structures. Again, the difference among two types of proteins is clearly observed. **I.** The "Highlights" from the STING "At-a-Glance Structure/File Characteristics" window, shown for the 2LZM.pdb file.

Blue Star STING will have the following new modules: 1) 3-D Java Protein Interface Viewer, 2) 2-D Interface Maps, 3) Multiple Parameter 3-D Plot, 4) Sting Enzyme Classification, 5) Protein Ligand Contacts, 6) Topologs 100, 7) Topologs Astral 40, and 8) AA Co-evolution. All

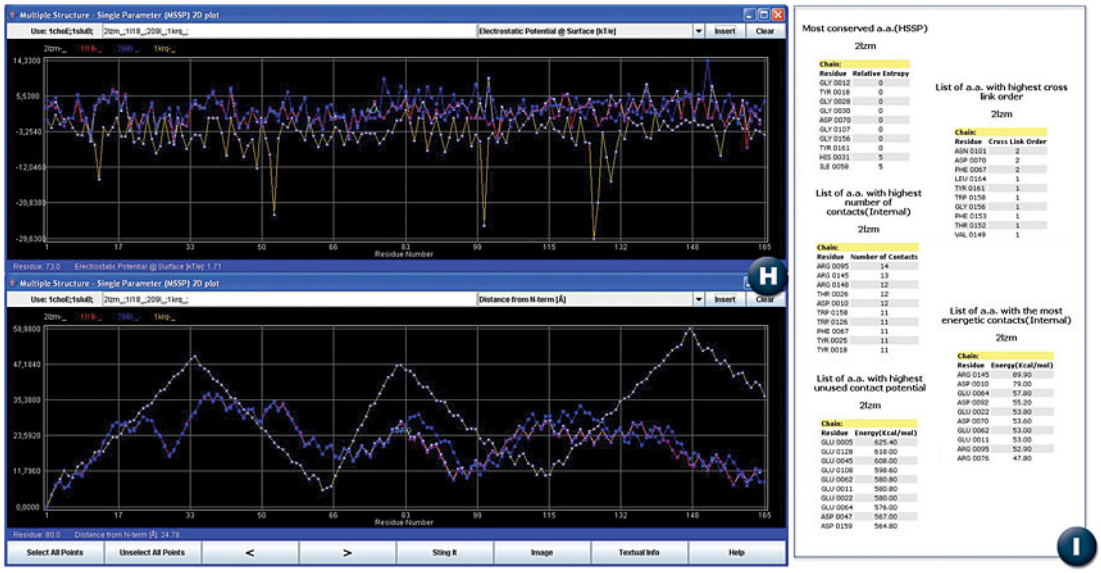

Figure 1. Continued.

these new modules will further advance the capabilities of the STING environment toward ever more complex studies and analyses of protein structure.

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