BRAGI: linking and visualization of database information in a 3D viewer and modeling tool

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ABSTRACT
Summary: BRAGI is a well-established package for viewing and modeling of three-dimensional (3D) structures of biological macromolecules. A new version of BRAGI has been developed that is supported on Windows, Linux and SGI. The user interface has been rewritten to give the standard ‘look and feel’ of the chosen operating system and to provide a more intuitive, easier usage. A large number of new features have been added. Information from public databases such as SWISS-PROT, InterPro, DALI and OMIM can be displayed in the 3D viewer. Structures can be searched for homologous sequences using the NCBI BLAST server.
Availability: Freeware, licensed: http://bragi.gbf.de/
Contact: Reichelt@gbf.de
Supplementary Information: http://bragi.gbf.de/gallery

INTRODUCTION
BRAGI (Schomburg and Reichelt, 1988) is one of the first computer programs optimized for the display and modification of protein and nucleic acid structures. Combined with force field analysis it is a highly valuable tool for the design of new proteins based on known structures. Linking information of public databases, such as SWISS-PROT, InterPro, DALI and OMIM to three-dimensional (3D) structures considerably increases the power of BRAGI as a tool to analyze the known and to predict the unknown 3D structures based on homologous 3D structures.

FEATURES
The new version of BRAGI has the ‘look and feel’ known from other current programs. Coordinate data can be opened (.pdb, .ent, as well as .mmCIF files) or directly imported from the Protein Data Bank (PDB) (Berman et al., 2002). Pull-down menus, keys and mouse buttons support give an intuitive handling of numerous features, e.g. to manipulate and visualize structures, and to obtain structure-inherent and -external information in separate windows. The use of the right mouse button gives quick access to various menu functions, e.g. to manipulate the representation of atoms, residues and chains. All movements of 3D structures follow the mouse pointer and BRAGI can move a set of molecules relative to each other, the first step in ‘docking’. Amino acid or nucleotide sequences for all chains can be selected from a separate window. All information is linked to the 3D viewer whenever possible. A ‘hierarchy structured window’ provides information on all loaded structures in a tree view (Fig. 1). Video sequences and figures of ‘publication quality’ can be saved in different formats, e.g. .avi, .gif, .bmp, .jpeg or .png. An interface to POV-Ray (POV-Ray, 1991–2002) provides the possibility to generate high-resolution pictures. Free text and markers, such as arrows or boxes, can be placed in the image. BRAGI has a built-in scripting language with a set of more than 70 basic commands.

The 3D structures stored in the PDB were correlated with different external information from public databases (Dieterich et al., 2004). For all PDB structures mentioned in the SWISS-PROT database (Boeckmann et al., 2003, Cn3D: http://www.ncbi.nlm.nih.gov/Structure/CN3D/cn3d.shtml) we linked data from the feature table of SWISS-PROT entries to the corresponding PDB chain sequence. The chain amino acid sequences were scanned against a local version of InterProScan (Zdobnov and Apweiler, 2001). To detect amino acid residues related to known diseases in humans, we also linked data from OMIM (McKusick-Nathans, 2000, http://www.ncbi.nlm.nih.gov/omim/) to the PDB entries (Fig. 2). All these functional annotations can be loaded, features selected and viewed in the 3D viewer.

BRAGI offers all necessary tools to predict protein structures based on known 3D structures, to replace as well as to insert and to delete residues in a protein structure (Desmet et al., 1997). The insertion of residues is supported by the use of an internal loop-database (Lessel and Schomburg, 1999; Wohlfahrt et al., 2002; Fechteler et al., 1995). Furthermore, BRAGI allows a sequence-based BLAST search on all sequences deposited in the PDB (default search database) via the NCBI BLAST server. The visualization of conserved regions between proteins in a separate ‘alignment’ window optimizes the process of modelling of protein structures.

The fold analysis of new structures is supported by the DALI database. DALI (Heger and Holm, 2000) provides a multiple alignment of structural homologues of a query structure. BRAGI submits the coordinates to the DALI server, receives the response and then offers all alignments for seamless download and automatic 3D alignment.

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To closely follow an ongoing molecular dynamics run, BRAGI reads atomic coordinates from an AMBER force field analysis. To watch an active run, BRAGI will read in the trajectories of a running AMBER job and visualize them all or show one snapshot after another.

**DISCUSSION AND CONCLUSION**

BRAGI includes several novel additions that are useful in the structural analysis of macromolecules. Although some of the newly included features are not original, the integration of public databases in a tool for visualization, animation and editing of macromolecules is unique. A short comparison follows.

Cn3D is a helper application for web browsers that allows the viewing of 3D structures from NCBI’s Entrez retrieval service. SRS3D (O’Donoghue et al., 2004) is a viewer for annotations found in the SRS system. Both are limited in their graphic capabilities and are not suited for modification of biomolecules and use only their own databases. Links to public databases are available, e.g. in DeepView—The Swiss-PdbViewer (Schwede et al., 2003).

Fig. 1. Screenshot of a session with BRAGI. The protein structure ‘Hemoglobin (1CBM)’ is entered by the user. In the ‘Tree View’ listing some atoms and residues are selected – orange lines – and highlighted in the 3D viewer in yellow ball and sticks respectively wireframe.

Searches in SWISS-PROT and ExPDB, BLAST or a local database of PROSITE are implemented, but not integrated in a comparable way.

Other publicly available powerful 3D tools such as PyMOL (DeLano, 2002, http://www.pymol.org), UCSF Chimera (Huang et al., 1996), VMD (Humphrey et al., 1996) or YASARA (Krieger et al., 2003) currently do not provide the visualization of information available from various public databases, a precondition for a better understanding of protein function. The visualization possibilities are comparable to those of BRAGI. One can use lines, solid bonds (sticks), CPK, cartoons tubes, ribbons and many more to highlight interesting parts of molecules. RASMOL (Bernstein, 2000) is a frequently used viewer for all kinds of molecules included in nearly all Linux distributions. RASMOL does not use modern hardware for graphics display. In contrast to these programs BRAGI is fully menu driven, hence there is no need to use a command language to select parts of the molecule for a special display mode. Even movies are created using the graphic interface. For advanced users BRAGI provides a built-in command language.

The combination of a proven modelling and visualization tool, as established in BRAGI, and the linkage and integration of information

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<td>W 15, Amado acid Volume 227.8, Heli BA</td>
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Fig. 2. Screenshot of a session with BRAGI. The protein structure ‘Hemoglobin (1CBM)’ is entered by the user. In the ‘Human Mutation Databases’ window containing all known mutation of this structure from OMIM one mutation PHE122LEU (No. 317) – jointly responsible for sickle cell anemia – is selected. This PHE residue in highlighted in the 3D viewer and marked with an arrow.

from public databases harbours an enormous simplification for the analysis of protein structures and rational protein design.

REFERENCES


McKusick-Nathans, V.A. (2000) Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, Online Mendelian Inheritance in Man, OMIM (TM).


