BIOINFORMATICS APPLICATIONS NOTE Vol. 27 no. 12 2011, pages 1711–1712
doi:10.1093/bioinformatics/btr254

Structural bioinformatics

Advance Access publication April 19, 2011

A graphical interface for the FoldX forcefield

Joost Van Durme[1], Javier Delgado[2], Francois Stricher[2], Luis Serrano[2,3,*], Joost Schymkowitz[1,*] and Frederic Rousseau[1,*]

[1]VIB Switch Laboratory, Vrije Universiteit Brussel, Pleinlaan 2, 1050 Brussels, Belgium, [2]EMBL/CRG Systems Biology Research Unit, Centre for Genomic Regulation (CRG), UPF, C/Dr. Aiguader, 88, 08003 and [3]Intitució Catalana de Recerca I Estudis Avançats (ICREA), Barcelona, Spain.

Associate Editor: Anna Tramontano

ABSTRACT

Summary: A graphical user interface for the FoldX protein design program has been developed as a plugin for the YASARA molecular graphics suite. The most prominent FoldX commands such as free energy difference upon mutagenesis and interaction energy calculations can now be run entirely via a windowed menu system and the results are immediately shown on screen.

Availability and Implementation: The plugin is written in Python and is freely available for download at http://foldxyasara.switchlab.org/ and supported on Linux, MacOSX and MS Windows.

Contact: frederic.rousseau@switch.vib-vub.be; joost.schymkowitz@switch.vib-vub.be; luis.serrano@crg.es

Received on February 7, 2011; revised on March 18, 2011; accepted on April 9, 2011

1 INTRODUCTION

The empirical forcefield FoldX (Guerois *et al.*, 2002; Schymkowitz *et al.*, 2005) was developed for the rapid evaluation of the effect of mutations on the stability, folding and dynamics of proteins and nucleic acids (Alibes *et al.*, 2010; Bershtein *et al.*, 2006; Rakoczy *et al.*, 2011). FoldX is normally run from the command line with userprovided configuration files. To increase the usability, many core functionalities of FoldX have now become available through a complete graphics interface as a plugin for the YASARA (Krieger *et al.*, 2002) molecular viewer.

2 IMPLEMENTATION AND REQUIRED SOFTWARE

The plugin is written in Python, is platform-independent and requires YASARA, FoldX and Python. The free stage of YASARA (View) can be downloaded at http://www.yasara.org. FoldX is free for non-commercial purposes from http://foldx.crg.es and Python is by default installed on MacOSX and Linux machines. MS Windows users can get Python from http://www.python.org. Installing the plugin adds a new dropdown 'FoldX' menu in the main 'Analyze' menu (Fig. 1). A selection of FoldX commands is also available through the YASARA atom- and residue-context menus.

*To whom correspondence should be addressed.

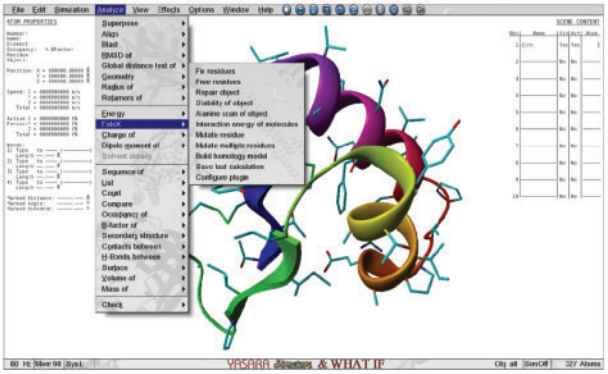

Fig. 1. FoldX interface in YASARA. The FoldX dropdown menu is part of the Analyze main menu and lists the currently implemented FoldX commands.

3 DOCUMENTATION

Documentation is provided at http://foldxyasara.switchlab.org/. The website offers regular plugin updates, step-by-step installation instructions, tutorials and a detailed PDF user manual.

4 THE FOLDX MENU ITEMS

Fix and free residues: FoldX optimizes residue side chain rotamers during an energy minimization or a mutagenesis task. The 'Fix' option allows the user to select residues that, for a specific reason, should not be moved during these tasks. The 'Free' option unfixes previously fixed residues.

Repair object: a YASARA object is a collection of molecules, normally a loaded PDB file. The 'Repair' command starts a FoldX energy minimization (RepairPDB) by optimizing the amino acid side chains to get a lower free energy of the protein by removing Vander Waals clashes and bad contacts. The minimized structure is loaded as a new YASARA object and superposed with the original structure. Any energy calculation with FoldX requires the structure to be minimized in advance to obtain reliable results.

Stability of object: the FoldX 'Stability' command calculates the free energy of unfolding (ΔG). This is the difference in free energy between the folded and the unfolded states. All energies resulting from the plugin are expressed in kcal/mol.

Alanine scan of object: 'Alanine scan' mutates every residue in an object to alanine and calculates the energy difference for each

mutation. This allows a rapid evaluation of the influence of single residues on the structure stability of large structures. The users should be aware that this command does not move the neighboring side chains, and therefore the changes in free energy reflect the maximum overestimation by FoldX. Residues that need further investigation after an alanine scan should ideally be re-evaluated with the more computationally intensive 'Mutate residue' command (see below) to obtain the most accurate results.

Interaction energy of molecules: this option executes the FoldX 'AnalyseComplex' command to determine the interaction energy between two selections of molecules. This command also lists the residues at the interface of the selected molecules in the YASARA console.

Mutate residue: mutates one residue to one or more new residues, using the FoldX 'BuildModel' command. Five selection menus are presented: (i) residue selection menu to select the residue to mutate; (ii) checkbox menu to enable 'RepairPDB' prior to mutagenesis, calculate stability change and interaction energy change upon mutation; (iii) residue selection menu to choose the desired replacement residue(s); (iv) options menu to enable or disable the optimization of neighbouring side chains around the mutation site, zoom in on mutation site, show new or disrupted hydrogen bonds and Vander Waals clashes; and (v) options menu for FoldX specific settings: number of runs, temperature, pH, ionic strength and Vander Waals penalty.

Each mutant will load as a new YASARA object superposed on the original structure. The free energy difference report is printed in the YASARA console and to a tab-delimited text file (see below). It should be noted that FoldX only modifies residue side chains and not the protein backbone.

Mutate multiple residues: the 'Mutate multiple residues' command allows the user to make double, triple, etc. mutations in a single structure, including energy calculations. The main differences with the 'Mutate residue' command are the possibility to select multiple residues in the residue selection menu and a new menu called 'New amino acids' to specify the replacing residues as a contiguous amino acid sequence in one letter code. This command can be of great interest to predict the additive effect of multiple mutations as has been shown previously (Bershtein *et al.*, 2006).

Build homology model: this command acts in the same way as Mutate multiple residues, except for the user input format. The latter is designed to specify more than just a few residues, which is often the case when building a homology model. This command shows two new menus compared to the 'Mutate multiple residues' command: (i) object selection menu to select the model template structure; and (ii) alignment file selection menu: the alignment file is a plain text file containing two lines: one representing the sequence of the template protein and one representing the target model sequence. The final model is loaded as a new YASARA object and superposed on the template structure.

Save last calculation: the user is presented the choice to save all files or just the FOLDXSUMMARY.out file. This tab-delimited file contains free energies, as obtained during the requested calculation, and can be readily imported in any spreadsheet program. If the user chooses to save all files, this will include FoldX configuration files that can be re-used to run FoldX from the command line if needed.

5 SUMMARY

Realistic free energy predictions using a graphical front-end have been shown to be very successful in attracting a large userbase to solve biological problems (Cooper *et al.*, 2010). The graphical interface for FoldX eliminates manual writing of configuration files and using the command line interpreter. All requirements to use the plugin are free of charge for non-commercial purposes and it is expected that the plugin will attract non-experienced computer users to perform complex energy calculations with FoldX at the touch of a button.

Funding: Fonds Wetenschappelijk Onderzoek—Vlaanderen (FWOTM443 to J.V.D.); the EU project Prospects; UnicellSys.

Conflict of Interest: none declared.

REFERENCES

Alibes,A. *et al.* (2010) Using protein design algorithms to understand the molecular basis of disease caused by protein–DNA interactions: the Pax6 example. *Nucleic Acids Res.*, **38**, 7422–7431.

Bershtein,S. *et al.* (2006) Robustness–epistasis link shapes the fitness landscape of a randomly drifting protein. *Nature*, **444**, 929–932.

Cooper,S. *et al.* (2010) Predicting protein structures with a multiplayer online game. *Nature*, **466**, 756–760.

Guerois,R. *et al.* (2002) Predicting changes in the stability of proteins and protein complexes: a study of more than 1000 mutations. *J. Mol. Biol.*, **320**, 369–387.

Krieger,E. *et al.* (2002) Increasing the precision of comparative models with YASARA NOVA–a self-parameterizing force field. *Proteins*, **47**, 393–402.

Rakoczy,E.P. *et al.* (2011) Analysis of disease-linked rhodopsin mutations based on structure, function, and protein stability calculations. *J. Mol. Biol.*, **405**, 584–606.

Schymkowitz,J. *et al.* (2005) The FoldX web server: an online force field. *Nucleic Acids Res.*, **33**, W382–W388.