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Applications Note

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FoldX 5.0: working with RNA, small molecules and a new graphical interface

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Abstract

Summary: A new version of FoldX, whose main new features allows running classic FoldX commands on structures containing RNA molecules and includes a module that allows parametrization of ligands or small molecules (ParamX) that were not previously recognized in old versions, has been released. An extended FoldX graphical user interface has also being developed (available as a python plugin for the YASARA molecular viewer) allowing user-friendly parametrization of new custom user molecules encoded using JSON format.
Availability and implementation: http://foldxsuite.crg.eu/
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1 Introduction

The FoldX toolsuite (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. Parametrization of DNA bases by using template atoms taken from amino acids (Nadra *et al.*, 2011) has been shown to correctly predict energetic changes (Alibés *et al.*, 2010; Redondo *et al.*, 2008). An important limitation of the FoldX toolsuite was that it only recognized a limited set of molecules and that the introduction of new molecules required a complex update of many different tables that could not be done by the user. In FoldX 5.0, the user has now the possibility of introducing new molecules either using the existing parameters or by parameterizing them FoldX 4.0 could recognize and mutate DNA but not RNA. As an example, we have thus parameterized and included RNA bases as mutable residues so that the user can mutate them and determine the associated energy changes. Finally, to facilitate the introduction of new small molecules, we have updated the graphical user interface (GUI).

2 Implementation and requirements

FoldX 5.0 was written in C++, and has been compiled as a universal and portable binary file for each of the three main platforms (Windows, Linux and Mac OS) and for Raspberry PI. It has a user-friendly boost (https://www.boost.org) command line interface (CLI) and an update of the FoldX-Yasara plugin (Van Durme *et al.*, 2011), including a new Yasara dropdown menu for parametrization of molecules. This plugin is written in Python and is adapted to the new CLI, so it is not compatible with FoldX version 3.6 or earlier. The FoldX executable has two dependencies, a rotamer library file (rotabase.txt) and an optional folder (molecules) with one file per user-parametrized molecule. The free academic version of the binary file, the new Yasara plugin and the dependencies can all be downloaded at http://foldxsuite.crg.es. The molecules folder contains the parameters for RNA nucleotides, among others, in JSON format and is also the location where new molecules parameterized by the user (either with the new Yasara plugin or manually) have to be placed. Installing the plugin adds a new dropdown 'Foldx Molecule

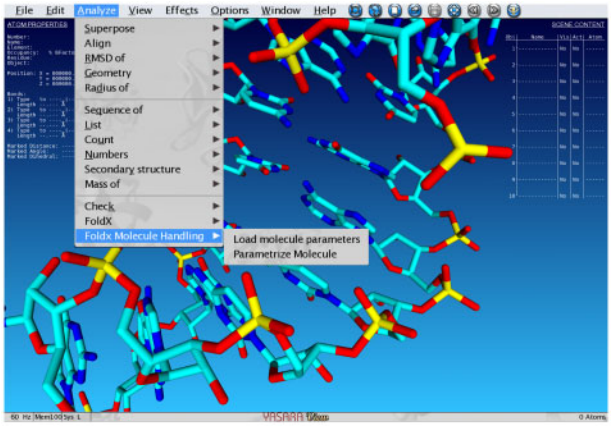

Fig. 1. The parametrization engine ParamX: New molecules can be parametrized either from scratch or by the use of template atoms

Handling' menu in the main 'Analyze' menu (Fig. 1) . A manual of the parameter set to define is available on the website.

3 New features of FoldX and its GUI

This new version of FoldX contains an update of already-existing commands as well as a new one termed *RnaScan*, which mutates every RNA nucleotide to the four bases (A, C, G, U) in a systematic fashion, produces a PDB for each mutation and outputs interaction ΔΔG upon mutation in Kcal/mol. In order to work with RNA, the *RepairPDB, BuildModel, AnalyseComplex* and *Stability all described* commands require the use of the parameter *complexWithRNA=true*.

A validation case of the RNA parameterization is the PDB 1a9n, crystal structure of the spliceosomal U2B″-U2A′ protein complex bound to a fragment of U2 small nuclear RNA. In the original paper (Price *et al.*, 1998) is mentioned that the spliceosomal complex U2B″ through small changes accomplish better specificity of binding with RNA than the U2A′ complex. After repairing the structure and running the *AnalyseComplex* command for the proper chains (Q-B for U2B″ and R-D for U2A′) we can observe an interaction energy difference of ∼6 kcal/mol (−6.85 kcal/mol for U2B″ and −0.77 kcal/mol for U2A'). Another example is provided in the *RNAScan* command description within the web manual for the PDB 5zq0.

The FoldX-Yasara plugin also has a new menu entry called 'Foldx Molecule Handling', which allows the user to parametrize novel molecules either from scratch by adding all required parameters ('Parametrize Molecule' submenu entry), or by using parameters from atoms that are already parameterized ('Load Molecule Parameters' submenu entry). The JSON format of the newly parametrized molecules slightly reduces the time of a FoldX 5.0 run versus a FoldX 4.0 run (by around 0.5 s). The coordinates of a desired molecule in PDB format are the departure point of a graphical parametrization. User-parametrized new molecules will only be considered for energy calculation commands (Stability and AnalyseComplex) and not for commands that require mutational capabilities. Command outputs are the same as for previous FoldX versions and are explained in the documentation.

4 Documentation

Documentation is available at http://foldxsuite.crg.eu/. The website contains a full description of new or updated FoldX 5.0 commands and parameters, step-by-step installation instructions, tutorials, and a detailed PDF user manual for the new Yasara plugin.

5 Summary

Novel functionalities have been added to the FoldX toolsuite to enable users to work with any kind of molecule. Template-based parameterization has been successfully carried out using previous versions of FoldX for DNA molecules and other molecules such as ATP and GTP etc. RNA has now been added to the list of available molecules. Unlike RNA, other new molecules parametrized by the user will be seen by FoldX as free ligands and not as mutable residues. The graphical parametrization interface eliminates the need for manual writing of parameter files (JSON format). An automatic parameterizer and the possibility to mutate other molecules (non-standard amino acids and nucleotides) or to include rotational bonds in small molecules are the goals for future versions of FoldX. All requirements to use FoldX and the plugin are free of charge for non-commercial purposes.

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