BIOINFORMATICS APPLICATIONS NOTE Vol. 27 no. 17 2011, pages 2441–2442
doi:10.1093/bioinformatics/btr400

Structural bioinformatics

Advance Access publication July 4, 2011

ModeRNA server: an online tool for modeling RNA 3D structures

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Associate Editor: Ivo Hofacker

ABSTRACT

Summary: The diverse functional roles of non-coding RNA molecules are determined by their underlying structure. ModeRNA server is an online tool for RNA 3D structure modeling by the comparative approach, based on a template RNA structure and a user-defined target-template sequence alignment. It offers an option to search for potential templates, given the target sequence. The server also provides tools for analyzing, editing and formatting of RNA structure files. It facilitates the use of the ModeRNA software and offers new options in comparison to the standalone program.

Availability and implementation: ModeRNA server was implemented using the Python language and the Django web framework. It is freely available at http://iimcb.genesilico.pl/modernaserver.

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Received on April 21, 2011; revised on June 16, 2011; accepted on June 20, 2011

1 INTRODUCTION

Non-coding RNAs have important catalytic and regulatory functions in organisms from all domains of life. The high costs and numerous obstacles in nucleic acid structure determination prompted the development of *in silico* RNA modeling methods, in analogy to similar efforts in the protein structure modeling field (Rother *et al*., 2011a). One successful approach is comparative modeling, based on the experimental observation that in evolutionarily related RNAs, 3D structure is typically more conserved than sequence (Capriotti and Marti-Renom, 2010). We have recently developed ModeRNA, a standalone tool for RNA 3D structure prediction based on the comparative modeling approach (Rother *et al*., 2011b). Here, we present a web server, which considerably extends the functionality of our original method.

2 USAGE OF THE MODERNA SERVER

The ModeRNA server enables three main functionalities: searching the Protein Data Bank for a suitable RNA structure to be used as a modeling template, analyzing/editing/formatting the structure, and building a model for a target sequence, based on its alignment to the template (Fig. 1):

Template identification: in order to create a model according to the comparative approach, the user has to provide a template (a known RNA structure in the PDB format), and an alignment between the sequence to be modeled (the target) and the template. The original ModeRNA method did not support any method for identification of potential templates. ModeRNA server can be queried with a target RNA sequence, and employs ParAlign (Rognes, 2001) to identify families of related sequences in the RfamSeq10 database (Gardner *et al*., 2009) that possess structurally characterized representatives. For each identified family, the server returns a covariance model derived from the Rfam multiple sequence alignment and pairwise sequence alignments of the target with the tentative templates (with resolution ≤ 2.5 Å) obtained with Infernal (Nawrocki *et al*., 2009). This simple procedure does not guarantee that the template or the target-template alignment are correct, but provides the user with a convenient starting point for further analyses, e.g. manual refinement.

Analyzing and editing the structure: ModeRNA server can recognize several common variations of the PDB format and supports reformatting of the structure files. This facilitates interoperability with other tools for RNA structure analysis. It also provides a number of simple geometry checks that can be used to test both template and model structures for the possible presence of unusual bond lengths, flat and torsion angles and interatomic clashes. ModeRNA server can remove water, ions and ligands, add missing phosphate groups, renumber residues and standardize the atom names to those used by the PDB (which may be a necessary step for template preparation). Straightforward changes such as addition or removal of post-transcriptional modifications or single residue substitutions can be introduced. Finally, the server outputs the sequence and secondary structure of the RNA structure analyzed.

Template-based modeling: ModeRNA server can be used as a front-end to produce a model of the RNA using the ModeRNA method in its 'basic' mode (without extensive scripting). It copies coordinates of identical residues from the template, replaces substituted residues with those from the target, models insertions and deletions using fragments from a database, and edits post-transcriptional modifications, according to the alignment. A detailed description of the ModeRNA workflow has been published (Rother *et al*., 2011b). The similarity of the template and target structures (resulting from their evolutionary conservation and conditions of structure determination) and the accuracy of sequence alignment are the major determinants of model quality. Typically, target-template alignments have to be checked and curated manually. For wrong

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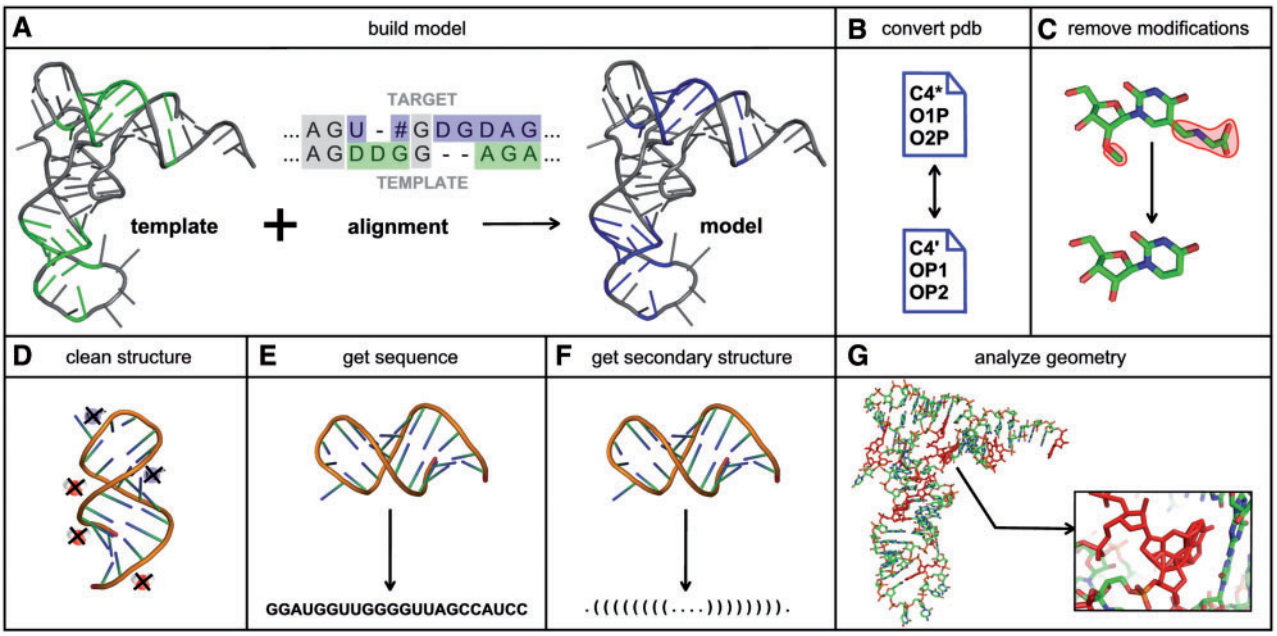

Fig. 1. Usage examples of the ModeRNA server: (**A**) building a model of $tRNA^{Thr}$ based on a template (PDB code 1QF6) and a pairwise alignment; (**B**) conversion between 'old' and 'remediated' ribose and phosphate nomenclature in a PDB file; (**C**) replacing a modified nucleotide (5-carboxymethylaminomethyl-2-*O*-methyluridine) with a standard uridine; (**D**) removal of water and ions; (**E**) reading the sequence from a structure (PDB code 2KD8); (**F**) parsing secondary structure information from a tertiary structure (1F1T); (**G**) analyzing clashes, bond lengths and angles in a model.

templates and wrong alignments ModeRNA will always produce wrong models, which can be actually a useful feature, e.g. for generation of structural decoys.

For targets with unknown structure, the accuracy of the model is unknown. We recommend to evaluate the likelihood of model correctness by using independent scoring functions, e.g. the recently developed RASP potential (Capriotti *et al.*, 2011), and (whenever possible) by critical assessment with respect to agreement with experimental data.

3 IMPLEMENTATION

ModeRNA server was implemented using the Django web framework (http://www.djangoproject.com/) and the Python programming language (http://www.python.org/). The results are displayed on a separate page using the Jmol applet to show 3D models (http://www.jmol.org/). The VARNA applet (http://varna.lri.fr/) is used to show secondary structures. All results are kept on the server, currently without time limits.

4 DISCUSSION

ModeRNA server is an important extension of the standalone application for RNA template-based 3D structure modeling, as it enables the use of ModeRNA by users with limited computer skills. The major added value of the server is the availability of a template search tool, and tools for preparation of template and alignment files. One should be aware that the server does not cover the full range of functions included in the standalone program, e.g. multi-template modeling. For detailed discussions of possibilities, limitations and alternative programs for homology and *ab initio* modeling of RNA, see (Rother *et al.*, 2011a,b). However, for straightforward model building from a template structure and alignment, especially when the template and target are highly similar, ModeRNA server is an ideal solution.

ACKNOWLEDGEMENTS

We are grateful to all our colleagues involved in testing the ModeRNA server.

Funding: This work was supported by the Foundation for Polish Science (FNP)(TEAM/2009-4/2 to J.M.B.). K.M. and T.P. were additionally supported by the Polish Ministry of Science and Higher Education (N301072640 and N301035539, respectively); K.R. was additionally supported by the German Academic Exchange Service (D/09/42768); J.M.B. was additionally supported by the European Research Council (RNA+P=123D) and the FNP ('Ideas for Poland' fellowship).

Conflict of Interest: none declared.

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