SimbiosNews

BY JOY P. KU, PhD, DIRECTOR OF DISSEMINATION FOR SIMBIOS

Solving the 3-D RNA Structure Puzzle with NAST

For proteins, structure information leads to an understanding of function. The same turns out to be true for ribozymes, ribosomal RNAs, and some other recently discovered RNAs. But mapping out that three-dimensional (3-D) structure isn't always possible experimentally and structures that are obtained are often incomplete. The Nucleic Acid Simulation Tool (NAST) helps solve the 3-D puzzle, using what's known about a given RNA to generate a large number of plausible 3-D structures in a fully automatic way. In addition to advancing basic biology, such structural information could also potentially aid in the design of new RNAs—for example, as gene therapy tools.

"NAST is a powerful tool for exploring possible conformations of an RNA given a particular set of constraints," says **Alain Laederach, PhD**, a research scientist at the Wadsworth Center in New York and an assistant professor in the School of Biomedical Sciences at SUNY Albany. Laederach was one of the original developers of NAST.

Rather than model all the atoms in the RNA molecule, NAST uses what is called coarse-graining—it groups atoms together and represents them as a single particle. This means fewer computations are required so more results can be generated in a given time period.

But such a simplified system isn't accurately described by classical equations of physics. "We've lost a lot of information and can't use real physics because we no longer have real atoms," says **Magdalena Jonikas**, a graduate student in bioengineering at Stanford University and the lead developer of NAST. "So we built our own physics about how particles interact."

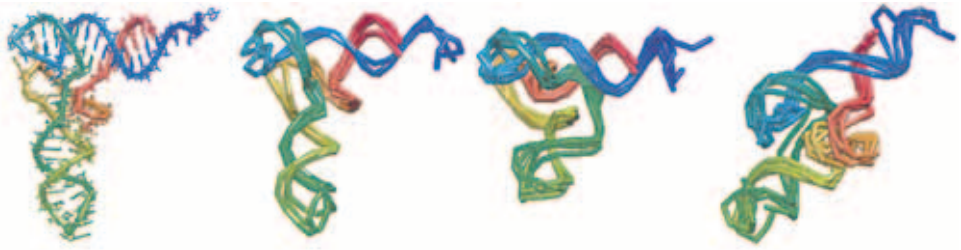
The NAST physics is based on the structural properties of coarse-grained representations of two ribosomal RNAs with known structures. That information was used to design an energy-based function that can produce realistic 3-D structures—helical parts of the molecule are identified and turned into helices, while non-helical portions are modeled after an average piece of ribosomal RNA.

Validation tests with NAST showed the average error for a prediction varied from 8-16 Angstroms, depending on the RNA and the available experimental data.

These results are encouraging, says **Nikolay Dokholyan, PhD**, an associate professor in biochemistry and biophysics at the University of North Carolina at Chapel Hill and the project lead for Discrete Molecular Dynamics (DMD), which has goals similar to NAST. "Predicting RNA structure is a very difficult task, perhaps more difficult than proteins."

NAST could also be useful for capturing snapshots of the RNA in motion, says Dokholyan. "RNA molecules can be quite dynamic and it would be important to have clusters of structures that show up during the lifetime of these RNA molecules. And in this case, NAST would do great."

"NAST is probably the best RNA structure prediction system based on molecular dynamics that's been published so far," says **Francois Major, PhD**, a principal investigator at the Institute for Research in Immunology and Cancer at the University of Montreal and project leader of MC-Fold and MC-Sym pipeline, an all-atoms approach for structure prediction. "If I had to use one such system today, I would use NAST." □



NAST generates a large number of 3-D structures that satisfy user-provided constraints. The image above shows the known crystal structure of a yeast tRNA and three subsets of five similar structures generated by NAST without reliance on crystal structure data. Reprinted from Coarse-grained modeling of large RNA molecules with knowledge-based potentials and structural filters, M. Jonikas et al., RNA, 2009, 15:189-199.

What You Need to Use NAST

NAST only needs information about the order of the A, U, G, C bases that make up RNA (the primary sequence) and the 2D map of the RNA, which shows how the bases pair up when the RNA folds back on itself (the secondary structure). Long-range tertiary interactions between bases can also be incorporated. NAST can be freely downloaded from http://simtk.org/home/nast.

Simbios (http://simbios.stanford.edu) is the National Center for Biomedical Computing located at Stanford University.