

Played by humans, scored by nature, online game helps unravel secrets of RNA

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Many video games boast life-like graphics and realistic game play, but have no connection with reality. A new online game developed by Carnegie Mellon University and Stanford University researchers, however, finally shatters the virtual wall.

The game, called EteRNA (<http://eterna.cmu.edu>) harnesses game play to uncover principles for designing [molecules](#) of RNA, which biologists believe may be the key regulator of everything that happens in living cells. But the game doesn't end with the highest computer score. Rather, players are scored and ranked based on how well their virtual designs can be rendered as real, physical molecules. Each week's top designs are synthesized in a biochemistry laboratory so researchers can see if the resulting molecules fold themselves into the three-dimensional shapes predicted by computer models.

"Putting a ball through a hoop or drawing a better poker hand is the way we're used to winning games, but in EteRNA you score when the molecule you've designed can assemble itself," said Adrien Treuille, an assistant professor of computer science at Carnegie Mellon, who leads the EteRNA project with Rhiju Das, an assistant professor of biochemistry at Stanford. "Nature provides the final score — and nature is one tough umpire."

Because EteRNA is crowdsourcing the scientific method — enlisting non-experts to uncover still-mysterious RNA design principles — it is essential that scoring be rigorous.

"Nature confounds even our best computer models," said Jeehyung Lee, a computer science Ph.D. student at Carnegie Mellon who led the game's development. "We knew that if we were to truly tap the wisdom of crowds, our game would have to expose players to every aspect of the scientific process: design, yes, but also experimentation, analysis of results and incorporation of those results into future designs."

The complex, three-dimensional shape of an RNA molecule is critical to its function. The goal of the EteRNA project is to design RNA knots, polyhedra and other shapes never seen before.

"We want to understand how RNA folds in a test tube and eventually in viruses and living cells," Das said. "We also want to create a toolkit of basic building blocks that could be used to construct sensors, therapeutic agents and tiny machines."

By synthesizing a design generated by game play, researchers will learn quickly whether the resulting molecule folds into the predicted shape, or something close to it, or if it even folds at all. Even designs that are not synthesized will be scored by nature, in that their scores will be based on the performance of similar designs previously synthesized.

"These experiments are the first-line strategy for validating a design and a crucial part of the scientific method," said Das, whose lab at Stanford synthesizes the molecules. "This makes EteRNA similar to what goes on in my lab on a daily basis: You make a prediction, do an experiment, make adjustments and start again." Initially, Das' lab is synthesizing eight designs each week, but is ramping up to synthesize about 100 a week.

RNA, or ribonucleic acid, long has been recognized as a messenger for genetic information, yet its role usually was overshadowed by DNA, which encodes genes, and by proteins, which do the work of the cell. But

biologists now suspect RNA plays a much broader role as the regulator of cells, acting much like the operating system of a computer. Understanding RNA design could prove useful for treating or controlling such diseases as HIV, for creating RNA-based sensors and even for building computers out of RNA.

The game employs state-of-the-art simulation software that players use to generate designs. It includes training exercises and challenge puzzles for honing skills, as well as challenges for designing molecules that will be synthesized.

In its use of game play to generate results of scientific interest, EteRNA is similar to other online games such as Foldit, an online protein-folding game that Treuille helped create while at the University of Washington. In fact, Treuille and Das met when they sat at adjacent desks in the Washington biochemistry lab of David Baker, where Treuille was working on Foldit and Das was studying RNA and protein folding and occasionally offering advice.

Both men recognized that the lack of real-world feedback was a limitation of these games. They realized an RNA design game could solve this problem because RNA, unlike many biological molecules, can be readily synthesized in a matter of hours.

RNA consists of long, double strands of four bases — adenine, guanine, cytosine and uracil — with the shape determined by the sequence of the bases. The rules controlling shape are relatively simple, but the sheer size of the molecules greatly complicates the design process.

"We've already found it's better not to use regularly repeating sequences of bases because they prove unstable," Treuille said, based on play by beta testers. "We're trying to build things that work in nature, and nature favors solutions that are robust."

The [game](#) is integrated with Facebook, so players can post accomplishments to their Facebook wall automatically and can create groups that talk about play and compete with each other.

The first challenges are relatively simple, arbitrary shapes, Das said, but will soon begin to incorporate designs of scientific relevance, such as [RNA](#) switches that could be used to sense and respond to other molecules in living cells.

Ultimately, players may end up creating designs and making discoveries of their own. "They're already beginning to act like a scientific community," Treuille said. "One player solved a puzzle that a widely used algorithm could not. Another player has written a strategy guide that proposes an algorithm for solving design problems that is different and simpler than anything in the scientific literature."

Provided by Carnegie Mellon University

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