



CROWDSOURCING

## Online Video Game Plugs Players Into Remote-Controlled Biochemistry Lab

Crowdsourcing is the latest research rage—Kickstarter to raise funding, screen savers that number-crunch, and games to find patterns in data—but most efforts have been confined to the virtual lab of the Internet. In a new twist, researchers have now crowdsourced their experiments by connecting players of a video game to an actual biochemistry lab. The game, called EteRNA, allows players to remotely carry out real experiments to verify their predictions of how RNA molecules fold. The first big result: a study published this week in the *Proceedings of the National Academy of Sciences*, bearing the names of more than 37,000 authors—only 10 of them professional scientists. “It’s pretty amazing stuff,” says Erik Winfree, a biophysicist at the California Institute of Technology in Pasadena.

Some see EteRNA as a sign of the future for science, not only for crowdsourcing citizen scientists but also for giving them remote access to a real lab. “Cloud biochemistry,” as some call it, isn’t just inevitable, Winfree says: It’s already here. DNA sequencing, gene expression testing, and many biochemical assays are already outsourced to remote companies, and any “wet lab” experiment that can be automated will be automated, he says. “Then the scientists can focus on the non-boring part of their work.”

EteRNA grew out of an online video game called Foldit. Created in 2008 by a team led by David Baker and Zoran Popović, a molecular biologist and computer scientist, respectively, at the University of Washington, Seattle, Foldit focuses on predicting the shape into which a string of amino acids

will fold. By tweaking virtual strings, Foldit players can surpass the accuracy of the fastest computers in the world at predicting the structure of certain proteins. Two members of the Foldit team, Adrien Treuille and Rhiju Das, conceived of EteRNA back in 2009. “The idea was to make a version of Foldit for RNA,” says Treuille, who is now based at Carnegie Mellon University in Pittsburgh, Pennsylvania. Treuille’s doctoral student Jeehyung Lee developed the needed software, but then Das persuaded them to take it a giant step further: hooking players up directly to a real-world, robot-controlled biochemistry lab. After all, RNA can be synthesized and its folded-up structure determined far more cheaply and rapidly than a protein can.

Lee went back to the drawing board, redesigning the game so that it had not only a molecular design interface like Foldit, but also a laboratory interface for designing RNA sequences for synthesis, keeping track of hypotheses for RNA folding rules, and analyzing data to revise those hypotheses. By 2010, Lee had a prototype game ready for testing. Das had the RNA wet lab ready to go at Stanford University in Palo Alto, California, where he is now a professor. All they lacked were players.

A message to the Foldit community attracted a few hundred players. Then in early 2011, *The New York Times* wrote about EteRNA and tens of thousands of players flooded in.

The game comes with a detailed tutorial and a series of puzzles involving known RNA structures. Only after winning 10,000 points do you unlock the ability to join

**Game on!** EteRNA players win points by submitting experiments to a real lab and using the data.

EteRNA’s research team. There the goal is to design RNA sequences that will fold into a target structure. Each week, eight sequences are chosen by vote and sent to Stanford for synthesis and structure determination. The data that come back reveal how well the sequences’ true structures matched their targets. That way, Treuille says, “reality keeps score.” The players use that feedback to tweak a set of hypotheses: design rules for determining how an RNA sequence will fold.

Two years and hundreds of RNA structures later, the players of EteRNA have proven themselves to be a potent research team. Of the 37,000 who played, about 1000 graduated to participating in the lab for the study published today. (EteRNA now has 133,000 players, 4000 of them doing research.) They generated 40 new rules for RNA folding. For example, at the junctions between different parts of the RNA structure—such as between a loop and an arm—the players discovered that it is far more stable if enriched with guanines and cytosines, the strongest bonding of the RNA base pairs. To see how well those rules describe reality, the humans then competed toe to toe against computers in a new series of RNA structure challenges. The researchers distilled the humans’ 40 rules into an algorithm called EteRNA Bot.

The human players still came out on top, solving structures more accurately than the standard software 99% of the time. The algorithmic version of their rules also outperformed the standard software, but only 95% of the time, showing that the crowdsourced human RNA-folding know-how has not been completely captured yet. The next step, Lee says, is to make the wet lab completely robotic. It still requires humans to operate some of the steps between the input of player RNA sequences and the data output.

EteRNA’s approach won’t work for every kind of science, says Shawn Douglas, a biomolecular engineer at the University of California, San Francisco, because a problem has to be “amenable to game-ification.” But he’s optimistic that there will be many more to come. “Many areas of biological research have reached a level of complexity that the mental bandwidth of the individual researcher has become a bottleneck,” Douglas says. EteRNA proves that “there are tens of thousands of people around the world with surplus mental bandwidth and the desire to participate in scientific problem solving.” The trick is to design a good game.

—JOHN BOHANNON