Now coming to your iPhone: App that shows 2-D structure of thousands of RNA molecules

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(PhysOrg.com) -- For the first time, it's possible to experimentally capture a global snapshot of the conformation of thousands of RNA molecules in a cell. The finding is important because this scrappy little sister of DNA has recently been shown to be much more complex than previously thought.

"There's an app for that." To a cadre of scientists, the familiar phrase will soon mean they can enter a specific RNA from baker's yeast into their iPhone and see a depiction of its two-dimensional structure - thanks to a new technology developed by scientists at Stanford University.

The application is cool, but it's just window dressing for the real advance: For the first time, it's possible to experimentally capture a global snapshot of the conformation of thousands of RNA molecules in a cell. The finding is important because this scrappy little sister of DNA has recently been shown to be much more complex than previously thought.

"We used to think of RNA as just a long, floppy string that delivers instructions from DNA to the protein-assembly points in the cell," said associate professor of dermatology Howard Chang, MD, PhD. "But now we're learning that often the molecule's structure - and not just its sequence of nucleotide letters - determines its function. So we set out to develop a method that can map the structure of all the RNA in a cell."

Chang, who was selected last year as a Howard Hughes Medical Institute

Early Career Scientist, and Eran Segal, PhD, of the Weizmann Institute of Science in Israel, are the senior authors of the research, which will be published Sept. 2 in *Nature*. Michael Kertesz, PhD, previously at the Weizmann Institute and currently a postdoctoral scholar in Stanford's Department of Bioengineering, and Stanford graduate student Yue Wan are co-first authors.

For years, RNA was known only for its role in shuttling information in the form of nucleotide sequences from the DNA in a cell's nucleus to the protein factories in the cytoplasm. Now we know that RNAs control many aspects of gene regulation and function.

In comparison to DNA - a relatively inflexible, double strand of paired nucleotides that spiral around one another in a helix formation - RNA is a veritable circus contortionist. It can fold back on itself to form stem and loop structures, and these structures can bind to one another in pseudoknots, which can twist around and ... well, you get the idea. Until now, the only way to know what shape a particular RNA molecule preferred was to conduct a laborious series of experiments focused on just that molecule. But the effort was necessary to fully understand what it might be doing in the cell.

The researchers capitalized on the recent development of deep-sequencing techniques that allow scientists to simultaneously sequence millions of nucleotide fragments for their analysis. They treated the pool of more than 3,000 protein-encoding RNA molecules from Saccharomyces cerevisiae, also known as baker's yeast, with structure-specific enzymes (one cleaves only single-stranded nucleotides at specific sequences and while another cleaves only double-stranded, or paired, RNA sequences). They then sequenced the fragments and pieced together the structure of each RNA molecule in a process they call "parallel analysis of RNA structure" or PARS.

"It's now possible to look at RNA structure much more quickly and comprehensively," said Chang. "Now we can see patterns that were not previously evident, and begin to categorize RNAs by structure rather than sequence."

Some of the patterns they identified were surprising. The researchers found that regions of RNA that encode specific instructions for protein tend to have more secondary structure than do other regions, and that it is possible to identify the beginning, middle and end of an RNA transcript simply by analyzing its structure. Finally, they found that RNA molecules that had similar functions often have similar structures - perhaps to better direct them to specific locations within the cell.

The researchers tested their technique on baker's yeast because it is a well-studied organism with a relatively limited number of RNA molecules in action at any one time (about 3,000 vs. 10,000 in humans). But they plan to tackle other organisms soon, and to expand their analysis to include regulatory RNAs that don't carry protein-building instructions.

"There's so much more information to be discovered," said Chang. "This is just a snapshot of RNAs in isolation. But we can leverage this information for biological insight into how RNA structures may change under different conditions. There are levels of complexity that we're only just beginning to understand."

The researchers are also developing a searchable website (genie.weizmann.ac.il/pubs/PARS10/index.html) with their data. And then there's that iPhone application. "Now you can use your phone to look up structures and pull up RNA sequences," said Chang.

Provided by Stanford University Medical Center