3-D structure and indeed often drive the most interesting geometries such as loops, bulges, and twists.

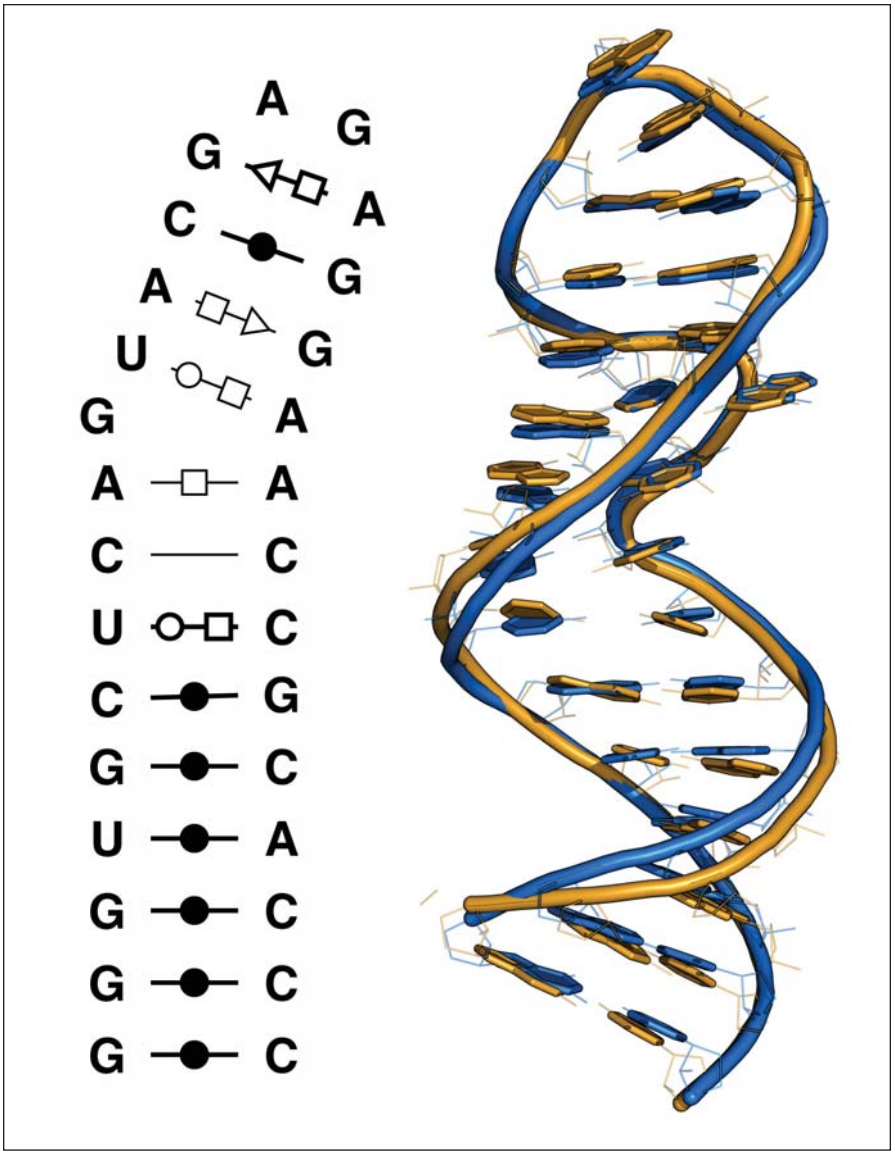
To better predict non-canonical pairings, Major and Parisien identified 19 regular, repeated small motifs (mostly 3 to 5 nucleotides) in solved RNA structures. They call these the RNA structural alphabet or "nucleotide cyclic motifs" (NCMs). The most common "letter" (or NCM) consists of two Watson-Crick base pairs stacked on top of each other; a bunch of these together form a basic helix. But many of the other NCMs are defined by non-Watson-Crick base pairs. One example is a four-nucleotide loop with a G-A pair at the bottom.

To determine the 3-D structure of a given RNA primary sequence, Major and Parisien feed it through two programs: MC-Fold and MC-Sym. MC-Fold enumerates all possible base pairings (including non-canonicals) and all possible arrangements of NCMs. It then picks the most probable arrangement based on statistical data from solved RNA structures. Next, MC-Sym translates the NCMs directly into 3-D structures. The pipeline is available as a web service (http://www.major.iric.ca/MC-Pipeline/). Currently, accuracy is limited to sequences of fewer than 75 base pairs—unless experimental or multiple-sequence data are incorporated into the program, Major says.

As a test case, Major and Parisien folded several precursor microRNAs (with previously unknown structures). Such molecules would be expected to share a common structural element for binding to the enzyme Dicer, which processes them into functional microRNAs. The result: despite different primary sequences as well as non-canonical base pairs and bulges, the pre-microRNAs all folded into double helices.

"That's a pretty powerful result," comments **Philip Bevilacqua, PhD**, professor of chemistry at Penn State University. "I think this method is going to be of practical benefit to the RNA community," he says. "This has the potential for enormous impact, and hopefully it will get fulfilled."

—By Kristin Sainani, PhD

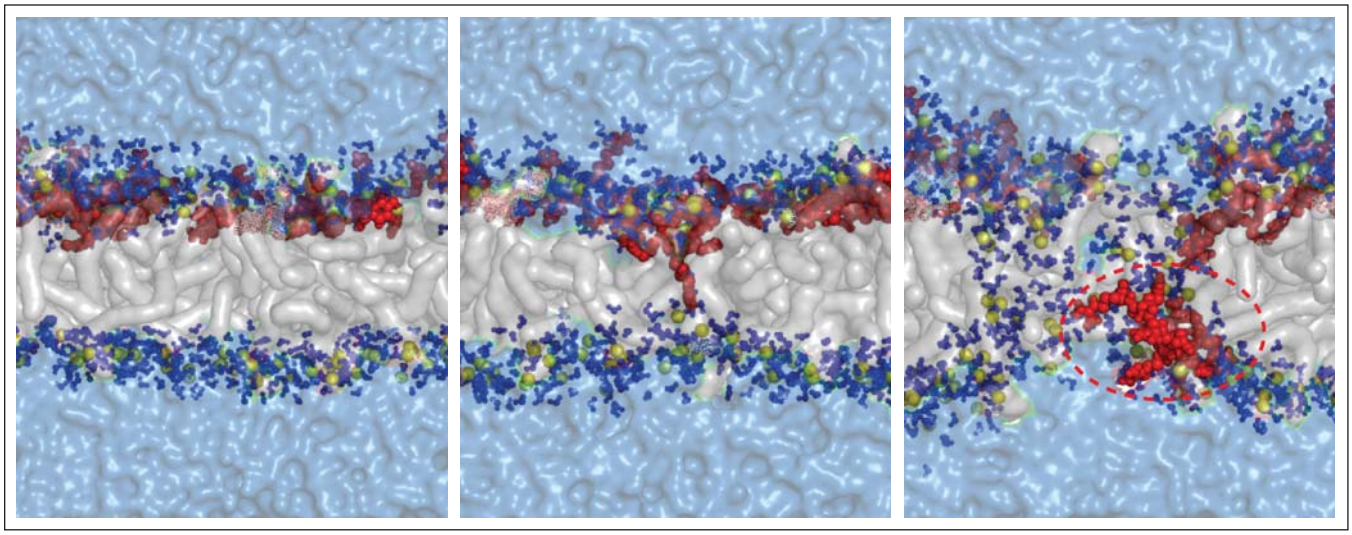


Predicted 2D and 3D structures of an RNA loop (Sarcin/Ricin loop from rat ribosomal RNA). Left: Watson-Crick (black dots) and non-Watson-Crick base pairs predicted by MC-Fold. Right: predicted 3D structure (blue) superimposed on the experimentally determined structure (gold). Courtesy of Francois Major and Mark Parisien.

Trojan Peptide

A powerful snippet of protein called the Tat peptide ferries itself across cell membranes dragging just about anything it's attached to along with it. How it accomplishes this feat has been a puzzle for a decade. Now, computational simulations offer a detailed picture of how the string of eleven amino acids cajoles the membrane's lipid bilayer into doing most of the work.

"I was expecting that the peptide would act like a snake going through a hole," says **Angel Garcia, PhD**, professor of biocomputation and bioinformatics at Rensselaer Polytechnic Institute, who helped design the simulations. Yet his laboratory's simulations suggest that instead of the snake doing all the work, it is as if the ground makes space for the snake to pass. "I wasn't expecting the lipids to change so drastically," he adds.



At left, four Tat peptides (red) cluster on one side of a lipid bilayer (white) attracted to the phosphate groups (yellow). As the Tat peptide reaches toward phosphate groups on the opposite side (middle), the bilayer thins enough for a chain of water molecules (blue) and the peptide to pass through the membrane (right). Courtesy of Angel Garcia. Reprinted from **Proceedings of the National Academy of Sciences** *104:52 (2007).*

"Once you see it, of course, it could not be any other way." The work was published in *Proceedings of the National Academy of Sciences* in December 2007.

The Tat peptide, discovered on an HIV protein, is part of a potent group of cell-penetrating peptides sometimes called Trojan horse peptides. They haul drugs, proteins or DNA right across the lipid bilayer and into the cell. The myriad uses of such peptides in both therapy and research are not hard to imagine. But how these highly charged, water-loving bits of protein so readily cross the waterless middle of the lipid bilayer has evaded answer for years.

Garcia and postdoctoral fellow **Henry Herce, PhD**, decided to apply the power of a new computer center at RPI to conduct molecular dynamics simulations of the Tat peptide as it approaches and crosses a lipid bilayer.

Over and over again, the simulations reveal how the peptide induces a change in the bilayer. Because six of the eleven amino acids in Tat are arginine, a relatively large, positively charged amino acid, researchers knew that Tat would be strongly attracted to the lipid bilayer with its blanket of negatively charged phosphates. But Garcia did not expect that phosphates on both sides of the bilayer—not just on Tat's side—would align to help neutralize Tat's charge. The more peptides added to the mix, the greater the influence on the opposite side of the bilayer. As the arginine side chains and distant phosphate groups move toward each other, the bilayer thins until it creates a hole lined with phosphate groups, letting a small chain of water and the peptide pass through.

"The idea that the bilayer is 'thinned,' thereby allowing the cationic TAT to touch anionic phosphate head groups on both sides of the membrane was utterly unexpected," says **Steven Dowdy, PhD**, a Howard Hughes investigator and professor of cellular and molecular medicine at the University of California, San Diego. Dowdy says the information from Garcia's computational work will inspire experimental testing of the mechanism. And, he says, it could be very helpful in designing enhanced peptides with increased potential to deliver drugs or DNA where researchers want them.

—By Louisa Dalton

Window into Microbial Behavior

We know they are there, but most microbial denizens of deep oceans, sea floor vents, even our own intestines, remain a mystery. Because most microbes won't grow in the lab, researchers have few clues to their communal activities. With better gene sequencing and computational ability, researchers now sample genes from whole communities to assemble the "metagenome"—a picture of the genes driving metabolic processes important to growth and survival in a given environment.

In a new study, researchers found remarkable diversity in how microbes function in each of nine distinct biomes. Indeed the bacterial and viral genomes from each biome had distinguishing metabolic profiles. And viral genomes—which researchers expected would be similar across environments—were just as different as the bacteria.

It turns out that there's a surprisingly extensive genetics arms race going on between bacteria and the viruses (called phages) that infect them, says **Rob Edwards, PhD**, assistant professor in the Computational Sciences Research Center at San Diego State University. Viruses are actively shuffling their host bacteria's DNA. "We didn't know (just) how much DNA the viruses move around," Edwards says. In fact, it happens so often that, he believes, the viruses likely profit from moving pieces of DNA that are beneficial to the bacteria.

Edwards and his collaborators from San Diego State University, Argonne National Laboratory and around the world reached these conclusions by comparing nearly 15 million sequences from