Nanocomputers Inside Our Bodies: Understanding How the Ribosome Decodes Genetic Information

Kevin Y. Sanbonmatsu, T-10

The ribosome is a giant molecular complex central to all living things and ancient in evolutionary terms. Its job is to read genes and synthesize the proteins that the genes code for. It is analogous to a computer's CPU in the sense that it is able to perform a complex 'look-up table' operation, reading sequences based on the 4-letter alphabet used by DNA and RNA, and converting these sequences into new sequences written in a 20-letter alphabet (i.e., the amino acid sequences which constitute proteins). It accomplishes this feat with a suite of adapter molecules called transfer RNAs, which were first predicted to exist by Francis Crick, codiscoverer of the DNA double helix structure. The ribosome is, in fact, a nanoscale computer and is very much analogous to the 'CPU' of the cell. The ribosome is so fundamental to life that many portions of this molecular machine are identical in every organism ever sequenced. These 100% evolutionarily conserved portions are called universal bases.

We have simulated the key step by which the ribosome decodes genes using the Advanced Simulation and Computing Q Machine. Until now, only static snapshot structures of the ribosome have been available. Limitations in time resolution and spatial resolution make it impossible to image the ribosome in motion in atomic detail. However, large-scale supercomputers make it possible to simulate the movement of the ribosome between these experimentally determined snapshots. We have used these supercomputers to determine how the transfer RNA molecule moves inside the ribosome, enabling it to decode genes [1]. We have identified a corridor inside the ribosome that the transfer RNA must pass through for the decoding to occur. This corridor happens to be constructed almost entirely of universal bases, implying that it is evolutionarily ancient. The corridor represents a new region of the ribosome containing a slew of potential new antibiotic targets. We have also shown that the transfer RNA must be flexible in two places for this movement to occur, suggesting that the transfer RNA plays an even more active role in decoding than previously thought. Recent developments are leading researchers to conclude that the transfer RNA played a role equally important to the ribosome in the development of protein synthesis, a key step in the origin of life on Earth.

The simulation method also presents a proof-of-principle for locating potential antibiotic targets on large molecular complexes. Antibiotic drugs are less than 1/1000th the size of the ribosome but have the ability to diffuse into the most critical sites of this huge molecular factory and grind the inner workings to a halt like a 'monkey wrench.' The simulation maps out where, exactly, we expect the transfer RNA to rub against the ribosome, giving us the best places to insert the molecular monkey wrench if we want to take out the ribosomes of harmful bacteria such as anthrax. Because the ribosomes are analogous to the CPU of the bacteria, taking out the ribosomes results in rapid cell death of the bacteria.

For more information contact Kevin Sanbonmatsu at kys@lanl.gov.

[1] K.Y. Sanbonmatsu, et al., *Proc. Nat. Acad. Sci.* **102** (44), 15854 (November 1, 2005).

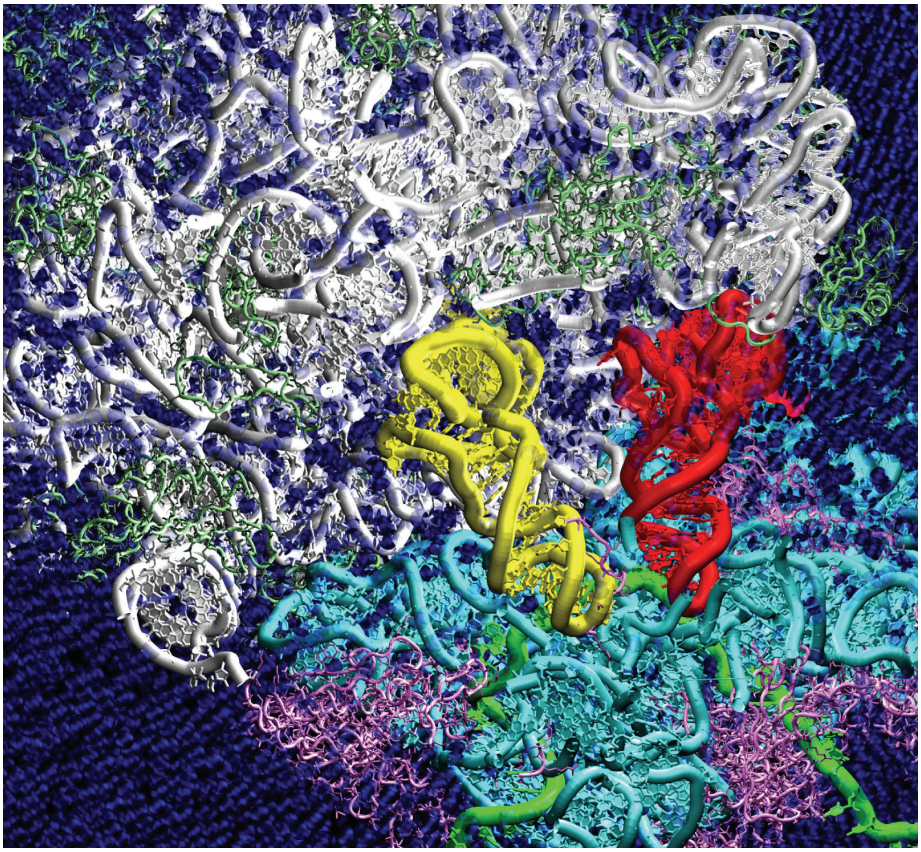

Fig. 1.
The ribosome is a living factory, the essential element within cells that creates proteins by decoding each protein type's specific recipe that is stored within messenger RNA. Ribosomes are a fundamental model for future nanomachines, producing the protein building blocks of all living tissue.