Understanding the mechanical biology of life's bonds

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(PhysOrg.com) -- When he was 10 years old, Julio Fernandez took a correspondence course in electronics and earned a certificate for putting together a doorbell. Today, the Columbia professor of biological sciences builds and takes apart proteins, the building blocks of the body which, when they bond improperly, may cause disease.

Traditionally, scientists study proteins in a test tube, a method that Fernandez believes does not offer an accurate enough picture of complex body biochemistry. “In a test tube how would you know what’s happening to something that requires mechanical force to extend and relax?” he says, referring to the stretching and contracting that happens to proteins when they bond with one another in the body. “You have to study proteins and biological molecules in an environment as close to their native condition as possible.”

To that end, Fernandez has spent his career developing a new field—mechanical biology—to understand organic substances with tools from physics, engineering and computer science. His team in the Northwest Corner building builds its own equipment, engineers its own proteins and writes its own computer programs to analyze the data. Though the students each have academic specialties, many have picked up expertise on the job in other disciplines.

In a paper published in the October edition of *Nature Chemistry*, Fernandez’s team made the first direct observation of how disulfide bonds reshuffle within a protein. Disulfide bonds play a central role in

controlling the elasticity of tissues. They used an atomic force microscope, a device developed by physicists in the 1980s to study items such as computer chips at the nanoscale, but adapted by his team to examine biological substances.

“Think of a protein as a rope tied up in a knot that is held together by a disulfide bond,” explains Pallav Kosuri, a Ph.D. student on Fernandez’s team. “Someone breaks the disulfide bond and the knot can now unfurl. We’re watching knots unfurl in a single protein molecule.” The team placed proteins on the examining surface of the atomic force microscope, which is fitted with a sensitive tip that is more than a thousand times sharper than the thickness of a human hair. The tip is attached to the protein, and a laser is used to record the exact position of the tip as the knot unfurls—or when the protein bonds reshuffle.

Disulfide bonds occur in nearly 30 percent of proteins; because they’re so prevalent, scientists believe their interactions may be clues to unraveling a broad range of illnesses, from infectious disease to cancer. Viruses, for example, interact with human cells through proteins that contain disulfide bonds. Marfan Syndrome is a disorder in which fibrillin, a disulfide-bonded protein in connective tissue, malfunctions. Symptoms may include extraordinarily stretchy skin, and in heart tissue, a faulty elasticity that can affect healthy blood flow.

As a physics student at the University of Chile, Fernandez met a group of neuroscientists from Los Angeles studying a squid native to the shores of that South American country. They lured Fernandez to the UCLA School of Medicine, where he received his Ph.D. in physiology and was a post-doctoral research fellow. Following appointments at the Max Planck Institute, the University of Pennsylvania’s School of Medicine and the Mayo Foundation, Fernandez came to Columbia in 2002.

His lab is currently at work studying how muscle elasticity works.

They’re also trying to understand the elasticity of the main receptor implicated in HIV infection—another protein with disulfide bonds. “We’re trying to revolutionize protein biochemistry from the point of view of mechanical forces,” he says.

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