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TIME

Monday, Aug. 20, 2001

Molecular Mechanics: Protein Wizard

By Unmesh Kher

A living cell bustles with molecular activity. Lilliputian protein motors ferry goods and services. Enzymes curl and unfurl. Even on its calmest days, the DNA double-helix twists, unwinds and wiggles like a loopy spring.

Breaking this molecular hullabaloo into its elemental physical forces is Carlos Bustamante's specialty. Bustamante, 50, a Howard Hughes Medical Institute investigator at the University of California, Berkeley, came to the U.S. from Peru 26 years ago as a Fulbright scholar. In the early 1990s, while at the University of Oregon, he and his colleagues tacked one end of a DNA molecule to a magnetic bead and measured its elasticity by tugging at the bead with magnets. A stroke of genius, no doubt, but to what end? "We didn't quite know how to answer that question at the time," admits Bustamante. "We did it because nobody had done it before. And it was fun."

Good thing they did. The experiment established that large molecules could be mechanically manipulated. "Until recently," says Robert Tjian, Bustamante's colleague at Berkeley, "we all studied complex molecular machines as populations--what we call bucket biochemistry." The approach has its uses, but it reveals little about how the machines work or what forces they can generate.

Using an atomic force microscope and a quaint gadget called the laser tweezer, Bustamante found a way around such limits. The microscope reads the topography of molecules by trailing a fine needle over their surfaces--much as a phonograph reads the grooves of a record. Coat the needle with an appropriate chemical, however, and you convert it into a grapple for manipulating molecules. Laser tweezers, meanwhile, trap molecules and particles in a tightly focused beam of light. Move the beam and you move the object.

Bustamante had refined his techniques sufficiently by 1997 to grasp a single protein and, applying forces only a trillionth as strong as those the earth exerts on an apple, pull it apart like molecular Velcro. Why bother? To study how proteins and nucleic acids fold into their complex structures. That's a matter of considerable interest to drug designers, who tailor molecules to monkey-wrench the proteins that make us sick.

But Bustamante isn't just interested in tearing molecules apart. Last year he applied the lessons he learned in the early 1990s to describe, step by step, how a lone enzyme copies a DNA sequence into RNA. Even identical enzymes, he found, often work differently--some dawdle and abandon their duties, while others go about their business with a bluster. Routine biochemistry would have glossed over such details. "Carlos," says Tjian, "has taken us to the next level."

It is the frisson of such discoveries that motivates Bustamante. "Being a scientist means living on the borderline between your competence and your incompetence," he says. "If you always feel competent, you aren't doing your job."

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