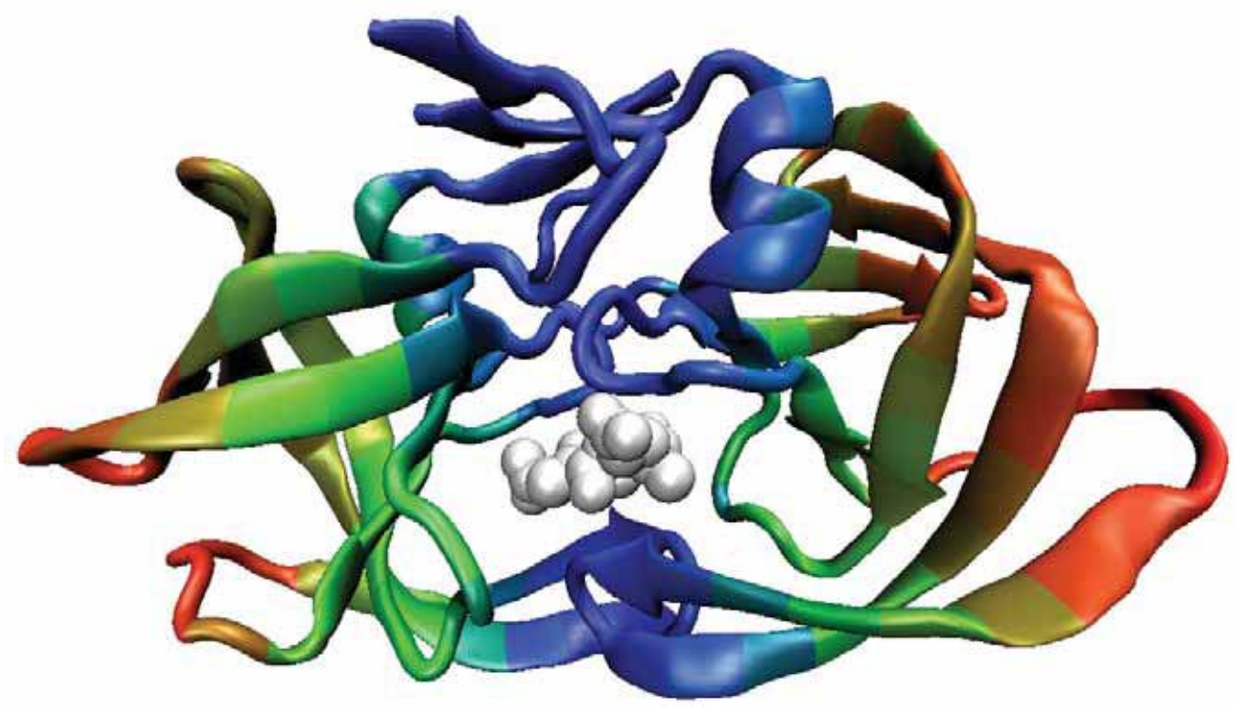

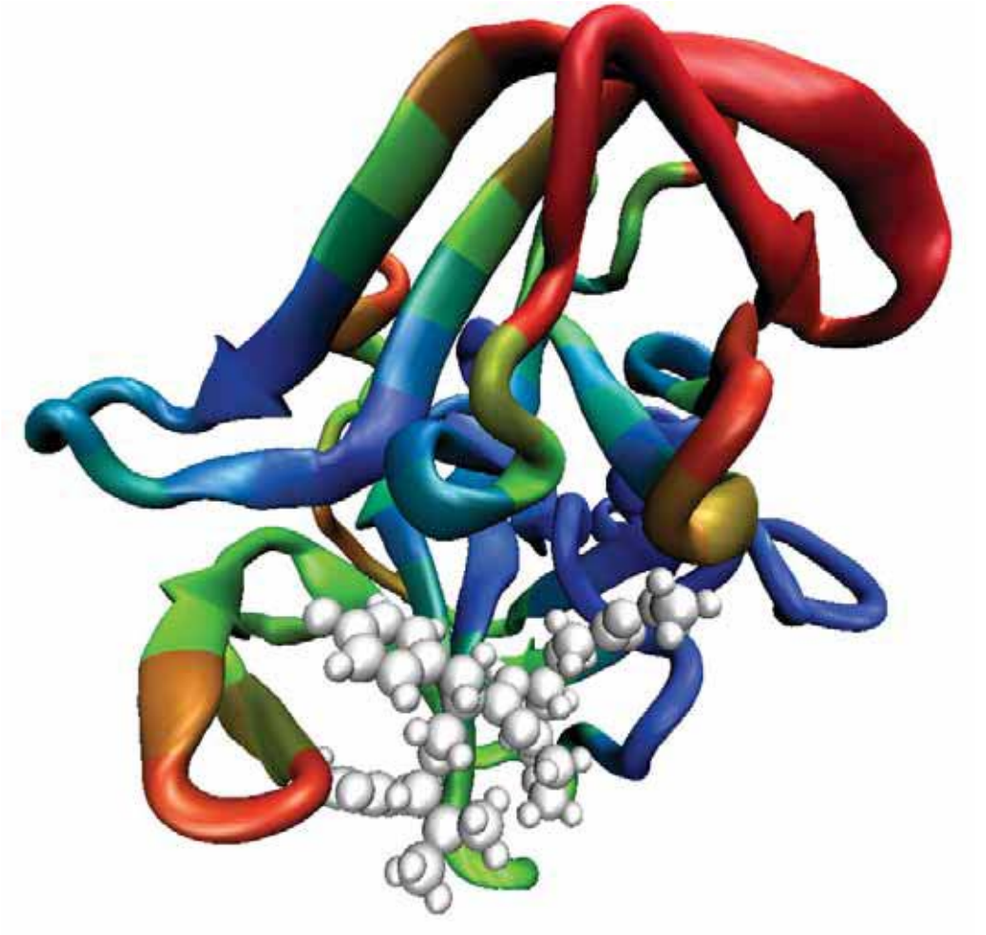

Ivet Bahar and Lee-Wei Yang made the connection between the architecture and stability of proteins and their function. Both figures here show the propensity of enzymes to bind ligands at highly stable regions. TOP: This HIV-1 protease is color coded by its ability to change structurally. Blue represents the most stable region. A binding molecule sits in the blue area at the bottom of the image—that's where the reaction that accounts for the protein activity occurs. BOTTOM: Similar features are illustrated for another enzyme (type 2 rhinovirus 3c protease) bound to an inhibitor (white).

COURTESY LEE-WEI YANG

IN SHAPE

RESEARCHERS SEEK LINK BETWEEN FORM AND FUNCTION | BY SHARON TREGASKIS

In 1913, biochemist Maud Menten—who would later spend four decades on the University of Pittsburgh School of Medicine faculty—copublished the Michaelis-Menten equation for predicting the rate of chemical reactions spurred by enzymes. Before the equation became standard, the pace at which any particular reaction might occur was a mystery. Even the most sophisticated scholars were stumped when it came to anticipating the speed at which the body's various biochemical feedback loops operated, and drug development was largely a game of chance.

In the intervening decades, the understanding of proteins and their functions has grown exponentially. Advanced imaging techniques reveal the molecular twists and turns of proteins, while the increasing speed and sophistication of computer processing allow for analysis of massive amounts of data. Yet, a clear conception of the relationship between a protein's chemical function and its shape has remained elusive. According to Pitt's Ivet Bahar, that means the basic science behind drug development really hasn't evolved much since Menten's day.

"Most drug discoveries are made through a kind of trial and error," says Bahar, the chair of the Department of Computational Biology, who is also a professor of molecular genetics and biochemistry.

"There are libraries of compounds that are screened against proteins to see which ones produce an effect."

A more rational—and effective—approach, she suggests, would allow researchers to identify optimal drug candidates in advance of experimentation, anticipating the molecular reactions they might initiate. Such capacity would save vast quantities of time and money.

But that means understanding both the rate at which any given reaction will proceed and how the structure of a particular enzyme influences its interactions.

Bahar, a PhD in chemistry, has dedicated her career to crafting sophisticated computer simulations that reveal the connection between form and function.

"Michaelis-Menten is useful and still widely used in experimental data," says Bahar, "but it doesn't provide a molecular understanding of what's happening."

In a June 2005 paper in the journal *Structure*, Bahar and postdoctoral research associate Lee-Wei Yang published their analyses of a set of two dozen proteins, examining both the chemical properties and physical dynamics of each.

"When we analyzed a whole bunch of proteins and identified their mechanical key regions—forget the chemistry, look at the mechanics—we identified key regions that act as a hinge," says Bahar.

Those hinge regions tended to be near the places where chemical reactions took place.

In the same issue of *Structure*, University of Wisconsin, Madison, biochemists Dimitry Kondrashov and George Phillips noted that the Pitt findings added a new dimension to the field of protein dynamics and would likely ease the job of solving protein structures.

The findings led Bahar and postdoctoral research associate Dror Tobi to investigate how chemical interactions between proteins relate to the shapes of increasingly complex macromolecules, such as immunoreceptors and muscle filaments.

Previously, scientists imagined proteins bound as interlocking rigid structures, much like a gate latch snapping down.

Bahar and Tobi's findings, published in the December *Proceedings of the National Academy of Sciences*, suggest that the architecture of a single protein—in its unbound state—provides clues as to where and how it will ultimately couple with other molecules.

Their studies suggest a more flexible coming together than the gate-latch model. Remember the popular Transformers toys from the '80s with multiple hinges and joints? They were two or three toys in one. (Like the "prehistoric pterodactyl" that became an "evil robot with snap-out attack blades.") Proteins also possess an "ensemble of conformations," says Bahar. One form best suits any given biological function, she explains, and binding stabilizes that particular shape.

As the name suggests, research in Bahar's department relies heavily on sophisticated algorithms and detailed computer coding. But the underlying conceptual framework takes precedence.

"First, we need to understand the fundamental phenomenon," she says. ■

DATA PLEASE

The Howard Hughes Medical Institute has honored the School of Medicine's new doctoral program in computational biology with a $1 million grant to develop a course to give students hands-on training in wet labs. More than 130 institutions across the country contended for the awards, intended to bolster interdisciplinary efforts. Ten programs received funding.

"There's a real necessity for closely coordinating experimental and computational approaches," says program codirector Ivet Bahar, who chairs Pitt's Department of Computational Biology.

She notes students can do *in silico* (her term for computational) studies to assess what might be eliminated from an experimental task. "That saves time and funds," she says. "On the other hand, computational biologists need data—all of our calculations are based on a repository of experimental results." —*ST*