Computer Simulation, Lab Synthesis Sift Through Universe of Possible Molecules for the Best

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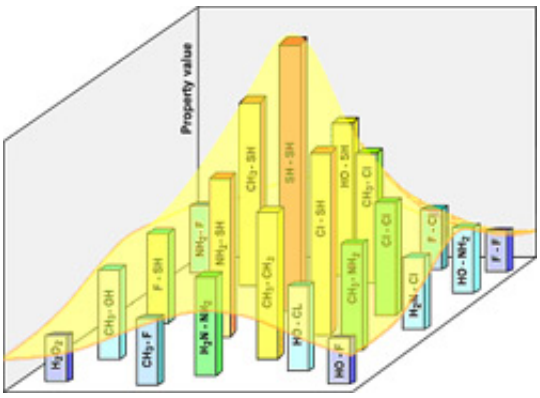

Computer visualization shows how different chemical building blocks can be ranked (vertical bars) for fulfillment a certain property, then "cloaked" with a yellow-colored surface to allow researchers to find the "mountaintop" for that trait.

Duke University theoretical chemists are investigating a new computer method that could help scientists identify the best molecules for drugs, electronic devices or an array of other uses. Their method would address the "daunting" fact that "that there aren't enough atoms in the universe to make all the reasonable-sized molecules that could be made," said Duke chemistry professor David Beratan.

In an article published in the Friday, Feb. 17, 2006 online issue of the

Journal of the American Chemical Society (JACS), Beratan, fellow chemistry professor Weitao Yang and two post doctoral associates proposed a computer-assisted way to find novel and superior materials.

Their technique -- for which they are seeking a patent and recently received renewed federal exploratory funding -- focuses on a certain universal property of molecules. This property, called a "linear combination of atomic potentials" (LCAP), is applicable to all molecules.

LCAP, whose use in simulating and characterizing molecular behavior was pioneered by Yang's research team at Duke, accounts for energy relationships between electrons and associated nuclei in the atoms making up all possible molecules.

The JACS article's authors wrote that using LCAP would enable targeted searches for the best molecules exhibiting various key chemical or physical properties. Those searches would quickly sort through all the possible molecular building blocks assembled within a computer-calculated "space" containing the multitude of possible molecules, according to the researchers. The best, or "optimal," candidates for a given use would emerge through a computed process of accepting or rejecting various building block combinations.

The mathematics of this process can also be envisioned graphically as bringing order to a huge jumbled surface that represents the properties of all possible molecules, Beratan and Yang said. On the more-ordered landscape their calculations allow the best choices to extend above the rest, like the computer equivalent of the perfectly symmetrical Mt.Fuji.

"So for one such application, the 'peak' might be the perfect drug from the standpoint of binding to a protein, Beratan explained. "Down in the 'basin' would be other molecules that are average to poor from the

standpoint of that application. And for each application there would be a different Mt.Fuji at a different location in this space," he said.

"The purposeful design of molecules with optimized properties is daunting because the number of accessible stable candidate molecules is immense," wrote Beratan, fellow chemistry professor Yang and research associates Mingliang Wang and Xiangqian Hu in the JACS paper.

"Each molecule is unique in structure and properties, and no set of continuous variables categorizes properties in the molecular space," their research paper said. "We introduce an approach that ‘smooths out’ the chemical properties in the space of discrete target structures and thus facilitate property optimization."

In their JACS paper, the Duke researchers wrote that LCAP "continuously links all possible molecules." As a result, it could be used "as a scheme to build up libraries of chemical potential functions that can be 'snapped together' to build the analytically exact electron-nuclear attraction potential for a whole molecule to put together from the chemical groups."

Beratan will also describe the work in a presentation at about 3:30 p.m. on Tuesday, March 28, 2006, in Room B304 of the GeorgiaWorldCongressCenter during a national meeting of the American Chemical Society in Atlanta. That talk will be part of a symposium organized by Yang.

The research is supported by a Defense Advance Research Project Agency (DARPA) "grand challenge" initiative seeking radically new approaches to speed searches for the most favorable chemical compounds, Beratan and Yang said.

Initial Phase I funding by the Defense Advanced Research Projects

Agency (DARPA) enabled the researchers to demonstrate the technique's feasibility. Phase II funding, to begin in March 2006, will support further exploratory computational work as well as laboratory syntheses to verify theory. If successful, those pilot efforts could lead to new kinds of devices that use light and electricity for telecommunications, they said.

Candidate top molecules that Beratan's and Yang's theoretical group identifies through simulation will be synthesized in the laboratory of collaborators at the University of Pennsylvania. Investigators at the University of Leuven in Belgium will then evaluate those materials' characteristics.

According to Beratan, present-day "rational" discovery processes that identify new molecules by making small structural changes to previous ones can get "lost" in the huge space of molecular possibilities.

"For instance, all the current molecules related to aspirin may be in one place, while all the Tylenol-like molecules are in a separate cluster," he said. "Meanwhile, maybe the best possible drug of that type may be undiscovered somewhere else with a chemistry that's quantitatively different from known molecules.

"If we just make small chemical modifications to known themes, we'll never discover that molecule."

Source: Duke University