UW team builds artificial enzymes

In what's been called a landmark breakthrough, scientists at the University of Washington have designed and built two artificial enzymes that could "green up" the production of plastics, drugs, textiles and a wide range of other goods.

By Sandi Doughton
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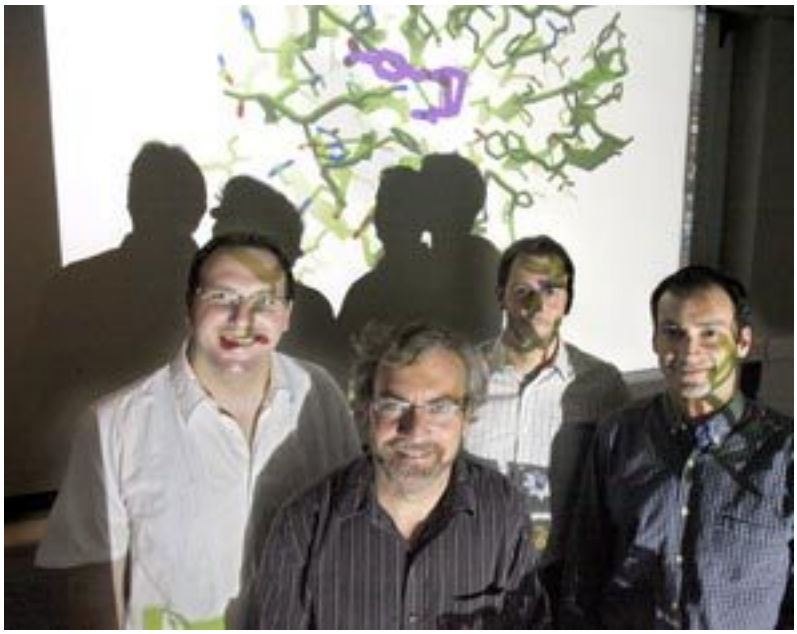

UW graduate student Justin Siegel, pictured left along with professor Forrest Michael, professor Michael Gelb and post-doctor fellow Alexandre Zanghellini, have designed and built an enzyme from the ground up. Using a computer program, they sorted through more than 10 billion possible combinations for the design which could prove useful in a wide range of industrial applications.

Information

Arzeda: www.arzeda.com/

index.php/home

Rosetta@home:

http://boinc.bakerlab.org/rosetta

Foldit, a computer game that allows users to build their own proteins:

http://fold.it/portal

From manufacturing tires to churning out pharmaceuticals, industrial-scale chemistry can be a nasty business. Stews of ingredients are pressurized, boiled and laced with solvents and toxic metal catalysts to drive the reactions that yield useful products.

Nature takes a gentler approach, marshaling armies of enzymes to produce the things living cells need to keep them humming.

Now, scientists at the University of Washington have followed nature's lead to design and build two artificial enzymes that could "green up" the production of plastics, drugs, textiles and a wide range of other goods.

To accomplish their feat, the team sorted through more than 10 billion billion possible molecular combinations, and logged nearly 100,000 hours of computer time. No one had ever created such complicated enzymes from scratch.

"It's a landmark," said Emory University chemistry professor Stefan Lutz, who was not involved in the project. "People shouldn't expect to find this sitting on the chemist's shelf tomorrow ... but it demonstrates that we are, in principle, capable of designing such complex systems."

Published Friday in the journal Science, the work comes from the lab of David Baker, a pioneer in puzzling out the three-dimensional structure of enzymes and other proteins. Baker and his colleagues are applying their breakthrough approaches to development of an AIDS vaccine, flu-fighting drugs and microbes that "eat" greenhouse gases from cars and industry and turn them back into fuel.

"We want to use these tools we've developed ... to re-engineer biology to do things that are useful to us," said graduate student Justin Siegel, a lead author of the study, which also involved scientists at several other research centers.

Baker and some of his colleagues created a spinoff company, Arzeda

Corp., to commercialize the enzymes they develop, including the ones reported this week.

In living creatures, enzymes speed up chemical reactions crucial to digestion, muscle contraction, drug metabolism and most other key functions. But there are no naturally occurring enzymes that catalyze the chemical reaction the UW team decided to tackle.

The reaction, which earned its discoverers a Nobel Prize in chemistry, is a mainstay of manufacturing. It fuses two smaller molecules to yield a building block for everything from nylon to morphine.

The three other enzymes Baker and his team previously designed are simpler, acting like scissors to snip things apart.

"It's a much more challenging task to design something that brings two pieces together, in the right precision, in order for the chemistry to take place," Lutz said.

To appreciate the difficulty, think of an enzyme as a hand, he explained. The chemicals being joined have to fit snugly in the palm, in exactly the right configuration, or the reaction won't work.

That's why the shape of the enzyme is crucial.

Every protein, enzymes included, is little more than a chain of compounds called amino acids, strung together like beads. Blueprints for the chains are coded in DNA.

But as soon as they're produced, proteins fold into complex shapes that allow them to perform their designated tasks. Improperly folded proteins can lead to diseases like Alzheimer's and mad cow.

The UW scientists, led by Siegel and former graduate student Alexandre Zanghellini, used a computer program called Rosetta to evaluate the mind-boggling number of possible configurations for their artificial enzyme.

More than 300,000 science-lovers have signed up for a version of the computer program called Rosetta@home, which allows them to devote spare computer time to similar projects.

Intuition is still an important part of the process, especially after the possibilities are narrowed to a manageable number, Zanghellini said.

"You have to understand how an enzyme works."

The scientists winnowed the field down to a million candidates, then to 84 finalists. Each was synthesized and tested in the lab.

Two worked.

And they worked at room temperature, without the need for noxious chemicals used by industry.

"We believe that starting with this method, we can develop new enzymes for "green chemistry," said Zanghellini, who now works for Arzeda, the spinoff company.

But the artificial enzymes were almost a million times slower at catalyzing reactions than natural enzymes, Baker cautioned.

The team is tweaking them now to improve their performance.

"We're only at a very early stage here in terms of what we can really do," Baker said. "The future could be huge, but we're not at the future yet."

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