Foldit gamers improve protein design through crowdsourcing

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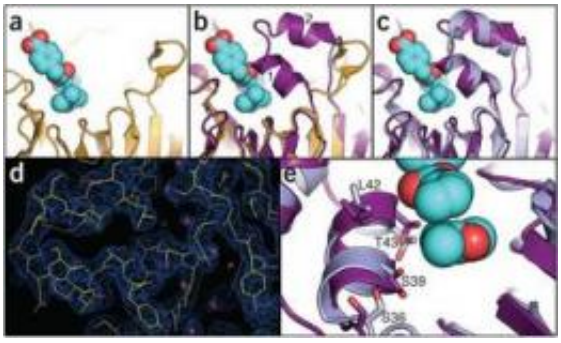

Image: *Nature Biotechnology* (2012) doi:10.1038/nbt.2109

(PhysOrg.com) -- Gamers on Foldit have succeeded in improving the catalyst abilities of an enzyme, making it 18-fold more active than the original version. The idea is the brainchild of University of Washington scientist Zoran Popovic who is director of the Center for Game Science, and biochemist David Baker. Together they have created the Foldit site which is a video game application that allows players to work with protein design, rather than shooting virtual aliens. By giving players a basic concept to work with and a box of tools, the team has created a means for crowd sourcing protein design. Those that come up with the most efficient way to fold an enzyme get the most points.

Proteins are made up of long chains of amino acids which wind up in various shapes due to the chemical properties of each link in the chain.

Eventually three dimensional shapes emerge, sort of like balloon animals, and the shape a protein takes determines the activity that it performs. One activity that some proteins, such as enzymes provide, is acting as a catalyst for chemical reactions. Researchers are always interested in finding better catalysts because the better they are the more money can be saved in manufacturing costs of materials that come about as a result of chemical reactions.

In earlier versions of the Foldit game, players were simply given existing proteins to play with and asked to find the minimal energy state for them by folding them in optimum ways, this latest version has gone much farther by giving players the opportunity to come up with a whole new protein design.

To create the new design, gamers were given a simple beginning structure and some basic ideas about the goal of the new protein, in this case to serve as a better catalyst for a class of Diels-Alder reactions, which are used to synthesize many commercial products. After offering some ideas such as remodeling certain sections to make them behave in certain ways, the gamers went to work folding the proteins using the tools at hand.

The first go-round proved mostly futile, with few gamers coming up with good improvements. To improve the results, the team took the best foldings from the first round and fed them back into the game allowing gamers to improve on them. This time, the crowd proved quite adept at coming up with a much improved enzyme; they succeeded in designing a new catalyst that was a hundred times more active than prior designs.

Unfortunately, the new protein isn't really useful though because the chemical reaction that it's used for doesn't have any purpose except to serve as a proof of concept. That will change very soon though. The current protein the gamers are working on is an improvement on a

protein inhibitor to block the spread of the virus responsible for the 1918 flu pandemic.

More information: Increased Diels-Alderase activity through backbone remodeling guided by Foldit players, *Nature Biotechnology* (2012) doi:10.1038/nbt.2109

Abstract

Computational enzyme design holds promise for the production of renewable fuels, drugs and chemicals. De novo enzyme design has generated catalysts for several reactions, but with lower catalytic efficiencies than naturally occurring enzymes. Here we report the use of game-driven crowdsourcing to enhance the activity of a computationally designed enzyme through the functional remodeling of its structure. Players of the online game Foldit5, 6 were challenged to remodel the backbone of a computationally designed bimolecular Diels-Alderase3 to enable additional interactions with substrates. Several iterations of design and characterization generated a 24-residue helix-turn-helix motif, including a 13-residue insertion, that increased enzyme activity >18-fold. X-ray crystallography showed that the large insertion adopts a helix-turn-helix structure positioned as in the Foldit model. These results demonstrate that human creativity can extend beyond the macroscopic challenges encountered in everyday life to molecular-scale design problems.