Fundamental discovery casts enzymes in new light

November 8 2011

Just as a breeze causes leaves, branches and ultimately the tree to move, enzymes moving at the molecular level perform hundreds of chemical processes that have a ripple effect necessary for life. Protein complexes are often viewed as static entities with their biological functions understood in terms of direct interactions, but that isn't the case, as emphasized in a paper published November 8 in the online, open-access journal *PLoS Biology*. The work shows that the amount of flexibility in a protein may itself be an important feature of enzyme function.

"Our discovery is allowing us to perhaps find the knobs that we can use to improve the catalytic rate of enzymes and perform a host of functions more efficiently," said author Pratul Agarwal, from Oak Ridge National Laboratory.

Making this discovery possible was ORNL's supercomputer, Jaguar, which allowed Agarwal and co-author Arvind Ramanathan to investigate a large number of enzymes at the atomic scale. The researchers found that enzymes have similar flexibility features that are entirely preserved from the smallest living organism—bacteria—to complex life forms, including humans.

"If something is important for function, then it will be present in the protein performing the same function across different species," Agarwal said. "For example, regardless of which company makes a car, they all have wheels and brakes." Similarly, scientists have known for decades that certain aspects of protein sequence and some structural features of

the enzyme are also preserved because of their important function. Agarwal and Ramanathan now believe the same is true for enzyme flexibility: it's conserved, independent of sequence and structure.

"The importance of the structure of enzymes has been known for more than 100 years, but only recently have we started to understand that the internal motions may be the missing piece of the puzzle to understand how enzymes work," Agarwal said. "If we think of the tree as the model, the protein moves at the molecular level with the side-chain and residues being the leaves and the protein backbone being the entire stem."

This research builds on previous work in which Agarwal identified a network of protein vibrations in the enzyme Cyclphilin A, which is involved in many biological reactions, including the AIDS-causing virus HIV-1.

While Agarwal sees this research perhaps leading to medicines able to target hard to cure diseases such as AIDS, he is also excited about its energy applications, specifically in the area of cellulosic ethanol. Highly efficient enzymes could bring down the cost of biofuels, making them a more attractive option.

More information: Ramanathan A, Agarwal PK (2011) Evolutionarily Conserved Linkage between Enzyme Fold, Flexibility, and Catalysis. PLoS Biol 9(11): e1001193. doi:10.1371/journal.pbio.1001193

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