Computational chemistry draws for the first time the 'interactive cartographic map' of enzymes during chemical reactions

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Knowing how enzymes work is key to control the chemical processes involving these biological macromolecules that have countless applications in the fields of medicine and industry. Computational chemistry has enabled to draw for the first time the enzymes "cartographic map" during the catalysis process, including the moment when they are at the point of maximum energy on the way from reactants to products that takes only a femtosecond (the quadrillionth of a second).

This map is also interactive in the sense that it relates the changes experienced by the molecule with the movements of the protein that contains it. The study conducted by researchers at the Universitat Jaume I and the University of Valencia has been published in the prestigious *Nature Chemistry* journal, which has published only 27 articles with involvement of Spanish scientists to date.

Simulating catalysis processes through supercomputers has enabled to know how the enzyme evolves during the process. "If we compare it with a cartographic map, we would have on one axis a coordinate that represents the molecule that is being transformed, and what is being represented on the other axis is what changes the protein that houses and modifies this molecule. If we combine these data, we can make a quantitative estimate of the flexibility of the protein, how much it deforms itself, how much energy you need to deform that protein to

generate the reaction that you want, etc.", said Vicent Moliner, coordinator of the Computational Biochemistry Group at the UJI that has developed the project in collaboration with the Environmental Effects Research Group at the University of Valencia led by Iñaki Tuñón. The research has also involved José Javier Ruiz and Sergio Martí at the UJI, and Rafael García-Meseguer at the UV.

To date, we could get information about the initial and final structure of the protein, but we did not know how it was in the transition state, the so-called "maximum power point", which marks the highest level of the barrier to pass from one point to another. "Knowing how the protein evolves as the reaction takes place means going one step further, because the protein or certain amino acids of the protein are also participating synchronously with breaking and bond formation during this process that is being catalyzed", explains Moliner. Coinciding with the 60th anniversary of the first documented climb of Mount Everest, the professor of Physical Chemistry at the UJI establishes a parallel with the mountain: if you want to go from one valley to another, you have to know the highest point through which you have to cross. "In the valleys the situation is stable, these molecules are stable and can be studied with experimental techniques (nuclear magnetic resonance, X-ray diffraction, etc.), but those molecules at the point of maximum energy, at the highest point, are there for a short time, and they have not been able to be studied so far. If you know how high the barrier is and how it is, then you can manage it, try to lower it or even find an alternative path".

Enzymes are catalysts which enable to occur at high speed a chemical reaction that usually proceeds at a very low speed. Under normal environmental conditions, it would be even virtually impossible to take place. In industry, high temperatures or high pressures are used to cause these reactions, and that implies high energy costs and environmental impact. Biotechnology enables to develop biocatalysts that produce these reactions more economically, efficiently and sustainably. "If we are able

to synthesize a catalyst to cause reactions that require high temperatures or pressures in natural conditions at room temperature, it would be a major economic and energetic saving", notes the researcher.

In living organisms, enzymes enable to go from one point to another along a much easier path. "With reactions that occur in living organisms in minutes or seconds, it would take the time equivalent to the life of the Earth, billions of years, without enzymes", he states. In the medical field, the development of new catalysts and inhibitors that block the action of these enzymes are key. "For example, chemotherapy blocks the enzymes that favour the reproduction of malignant cells, but with significant side effects. A better knowledge of enzymes may enable to block them in a more selective and efficient way", stresses Miller.

The aim of the Computational Biochemistry Research Group at the Universitat Jaume I is going further to better understand enzymes and catalysis processes because, as Moliner says, "if you know how they work, you are in a unique position to control the majority of chemical processes".

More information: García-Meseguer, R. et al. Studying the role of protein dynamics in an SN2 enzyme reaction using free-energy surfaces and solvent coordinates, *Nature Chemistry* 5, 566–571 (2013). doi:10.1038/nchem.1660

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