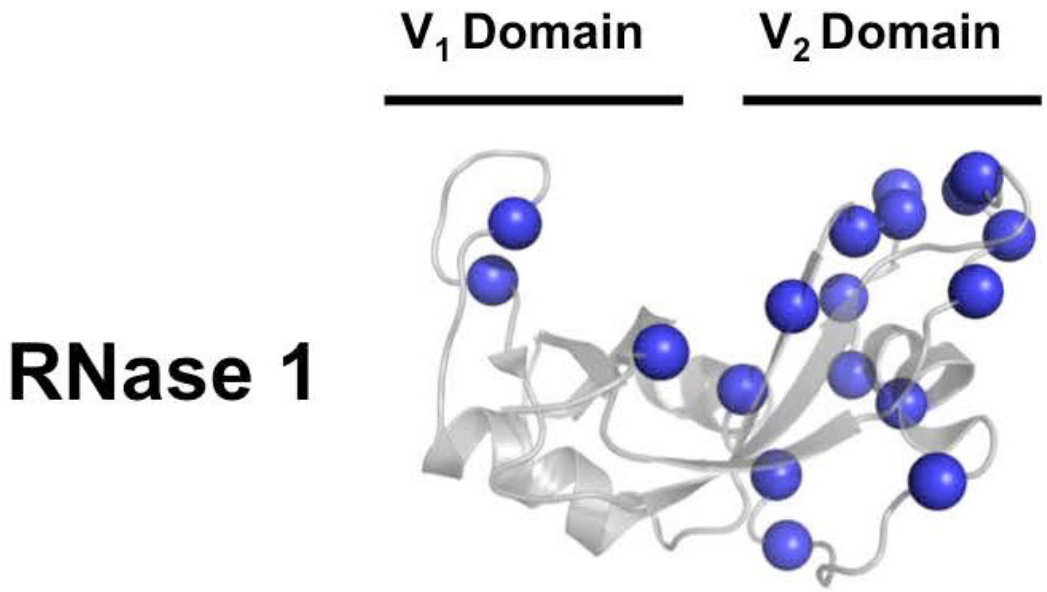
The subtle dance of atoms influences enzyme activity

December 10 2015, by Stéphanie Thibault



Infinitesimal fluctuations occurring on the milli- and even nano-second time scales within the three-dimensional structure of enzymes may be one of the keys to explaining protein function. Professor Nicolas Doucet's team at INRS has demonstrated that even when certain amino acids are far from the active site of an enzyme, a change in their flexibility and atomic fluctuations can significantly impact enzyme

activity. This phenomenon, which has been underestimated up to now, could explain certain protein engineering failures and help improve the way synthetic functional enzymes are designed.

Enzymes are nanomachines that are exceptionally efficient at catalyzing a chemical reaction. They play a role in all cellular mechanisms. Like all proteins, they are made up of amino acid chains that are folded and assembled in a very precise 3D structure. Some enzymes, like ribonuclease A, are so efficient that they catalyze the transformation of chemical molecules thousands of times per second.

In this study, Donald Gagné, a researcher in Professor Doucet's lab holding a PhD in biology from INRS, analyzed the impact of removing a methyl group located near a loop distant from the reaction site of ribonuclease A—a very slight change that presumably would have no effect. The mutation does not perturb the 3D structure of the enzyme. However, it did result in a four-fold reduction in the affinity of ribonuclease A for nucleotides (molecules to which it must bind to carry out its function). How is this possible?

Using crystallography techniques and nuclear magnetic resonance to examine the enzyme at atomic resolution, Donald Gagné compared normal ribonuclease A with the mutated enzyme. He observed that when ribonuclease A is modified, the nucleotides do not position themselves correctly and have a harder time binding to the active site. It appears that this repositioning is due to an increase in enzyme fluctuations caused by the elimination of this distant methyl group, which we can picture as creating vibrations that spread through the enzyme structure all the way to the site of catalysis.

This demonstration of the importance of enzyme dynamics could change our understanding of protein and enzyme mechanisms. While it remains a challenge to measure fluctuations at this atomic scale, researchers have

studied the three-dimensional structure of proteins to understand how they function. Despite the staggering complexity of this phenomenon, we now know that proteins are increasingly regulated by the subtle dance of their atoms.

More information: Donald Gagné et al. Perturbation of the Conformational Dynamics of an Active-Site Loop Alters Enzyme Activity, *Structure* (2015). DOI: 10.1016/j.str.2015.10.011

Provided by Institut national de la recherche scientifique