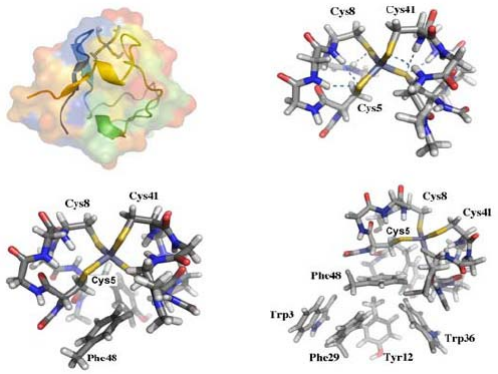
Structural element and center of activity

Zinc is focus of integrated studies to understand metalloprotein structure and function

Predictive models for metalloproteins are gaining accuracy because of integrated research using supercomputing and nuclear magnetic resonance spectrometry capabilities housed at the Department of Energy's EMSL. In a series of studies to relate metal-center protein environments to structure and function, a research team from EMSL and Pacific Northwest National Laboratory is using EMSL's NWChem computational chemistry software and NMR spectroscopy to derive a molecular theory that describes the electronic environment of the metal-amino acid motif, zinc coordinated to four cysteines. This motif was once thought to only play a structural role, but is now known to play a reactive role as well, for example, facilitating DNA repair.



Structure of the zinc- and cysteine-containing region of Pyrococcus furiosis *rubredoxin determined with different computational chemistry models.*

In previous experiments, the research team used model proteins containing the zinc-cysteine motif to find a level of theory adequate to predict NMR results (*Journal of the American Chemical Society*, 129[29]:9192-9200). In the new phase of their studies described here, the team refined their model using a real-world example: zinc-substituted rubredoxin derived from the thermophile, *Pyrococcus furiosis*. Rubredoxins play a role in electron transfer–an important regulatory mechanism in biological systems. In zinc-substituted rubredoxin, the iron center of rubredoxin's active site is substituted with zinc, serving as a system of study for a zinc-cysteine site with only a structural role. To predict NMR data in this real-world scenario, computational theory requires a combination of quantum mechanics and molecular mechanics. In comparison to the level of computational theory required to describe the model proteins in previous studies, anisotropic shielding must be more heavily accounted for–in other words, NMR spectra peak characteristics measured at the zinc site are more dependent on the electron densities and the point of view of the observer for rubredoxin. In future studies, similar sites with reactive roles will be compared.

Scientific impact: Refining molecular theory using experimental data furthers researchers' understanding about the metal environment in structural and reactive sites of proteins, gaining strides in EMSL's focus to predict biological functions from molecular and chemical data.

Societal impact: Many critical biological functions, including DNA repair, depend on proteins with reactive metal centers. Understanding the structure of these proteins at the molecular level gives researchers insight into how those proteins carry out their very important jobs.

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