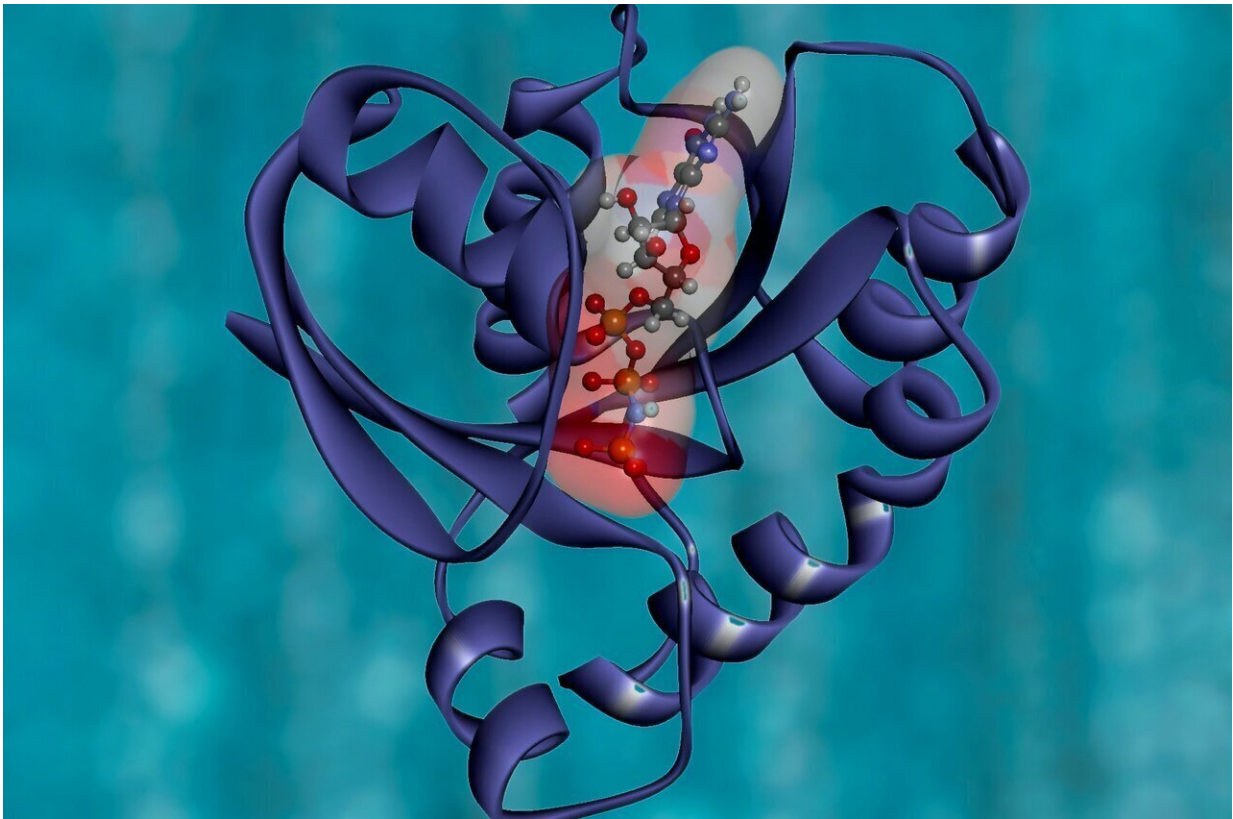


Computational protein design utilizes unnatural amino acids

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Proteins are the molecular machines that make all living things hum. They stop deadly infections, heal cells, capture energy from the sun and so much more.

Proteins are built by stringing together chemical building blocks called amino acids, according to instructions in an organism's genome. These strings then "fold up" based on the chemical forces between the amino acids, forming the complex three-dimensional structures needed to perform specific jobs

Fluorescent proteins have revolutionized our ability to study [biological systems](#). Despite a wealth of fluorescence tools, some fundamental biological processes—like the interactions between proteins and metabolites—remain difficult to study.

Assistant Professor Jeremy Mills and his group in Arizona State University's School of Molecular Sciences and the Center for Molecular Design and Biomimetics in the Biodesign Institute have just published their research in the journal *Biochemistry* and present a novel solution to this problem.

Specifically, they use a fluorescent amino acid that is not found in nature to generate a number of new [fluorescent proteins](#) whose light-emitting properties change when they interact with biotin, a compound that is very important in a number of metabolic processes.

"An important aspect of this study is that atomic-level pictures of many of these new proteins were generated that provide a great deal of information about how the binding of biotin changes the fluorescence properties of the proteins," Mills said. "This information lays a foundation for the development of new fluorescent proteins that will help further the legacy that fluorescent proteins have already forged in the study of biological systems."

"The [protein](#) studies of Jeremy Mills are typified by outstanding scholarship and a relentless commitment to making critical advances that will benefit science and society at large," said Tijana Rajh, director of

the School of Molecular Sciences.

This study involved a huge amount of work, including designing protein constructs and experiments, and purifying and crystalizing the proteins in order to collect the diffraction data. The data will be used in future studies aimed at the rational design of fluorescent, protein-based sensors of small molecule binding or dissociation.

This work was funded by a grant from the National Institutes of Health (NIH). The Research Project Grant (R01) is the original and historically oldest grant mechanism used by NIH. The focus of the grant is to develop novel fluorescent, protein-based tools that will be broadly applicable to the study of biological systems in ways that would be very difficult to achieve using existing fluorescent proteins.

Although nature has been building proteins for more than three billion years, the number of possible proteins is astronomical: There are more ways of assembling 100 amino acids than there are atoms in the universe. For years, scientists have tried to predict the shapes protein molecules should assume based on their [amino acids](#)—with limited success. The current study is a significant step toward understanding how to harness the power of proteins to help guide future efforts to rationally design new fluorescent sensors.

Mills is also passionate about bringing his enjoyment of science to the local community. He attributes a great deal of his love of research to participation in science fairs at the local and international levels while in high school. He serves as a judge at the Arizona Science and Engineering Fair and the International Science and Engineering Fair when possible. He also frequently demonstrates the use of the protein folding software Foldit to the public and has even developed lessons that are aimed at lay audiences that use Foldit as their foundation.

More information: Patrick R. Gleason et al, Structural Origins of Altered Spectroscopic Properties upon Ligand Binding in Proteins Containing a Fluorescent Noncanonical Amino Acid, *Biochemistry* (2021). [DOI: 10.1021/acs.biochem.1c00291](https://doi.org/10.1021/acs.biochem.1c00291)

Provided by Arizona State University

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