

General Strategy to Guide Biochemical Investigation of Protein Function

Distinctive Approach:

We address a central challenge of the genomic era - the widening gap between the number of sequenced proteins and the number that can be studied experimentally – with a completely general strategy. Our central premise is that abundant amino acid sequence data can be strategically mined to guide hands-on experimentation, yielding broadly applicable insights from limited but efficient laboratory work. We exploit sequence alignments of a given domain to: 1) identify variable residues of likely functional importance via coevolutionary coupling followed by experimental validation, 2) select physiologically relevant substitutions for experimental testing based on natural amino acid abundance at functionally important positions, which reduces experimental complexity by orders of magnitude, and 3) reveal distinct functional classes within a domain using clustering and dimensionality reduction techniques.

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\$7.4M in direct costs from NIH (27 years) and NSF (3 years)

Research Topics:

- As a proof of principle to develop and improve our general strategy, we elucidate molecular mechanisms and other fundamental properties of signaling proteins that regulate bacterial physiology, pathogenesis, and antibiotic resistance.
- The results will enhance ability to predict and manipulate properties of bacterial two-component systems for practical uses, including synthetic biology, biotechnology, and design of new antimicrobial agents.

Experimental Techniques:

- Affinity purification of tagged proteins.
- Stopped-flow measurement of enzyme kinetics with fluorescence spectroscopy.
- ^{32}P radioisotopes to characterize phosphotransfer reactions.
- X-ray crystallography.

Keywords:

- signal transduction, protein phosphorylation, two-component regulatory systems, sensor kinases, response regulators, receiver domains

Publications & Recognitions:

- [Link to my publications](#)
- Fellow, American Academy of Microbiology
- Chair, Board of Directors, Bacterial Locomotion & Signal Transduction, Inc. 2011-2026