Ackert Hall, Room 120
Wednesday, April 2, 2025
4:00 P.M.

Coffee and Cookies
Chalmers Hall Atrium
3:30 P.M.

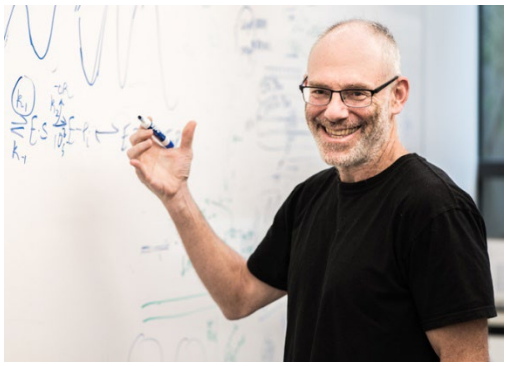
Biochemistry & Molecular Biophysics

Hageman Lecture in Agricultural Biochemistry

From structure–function to ensemble–function: A new paradigm for quantitative understanding of protein function

Daniel Herschlag

Department of Biochemistry
Stanford University



We have moved beyond traditional structure-function relationships to develop ensemble-function studies. Conformational ensembles encode states and their probabilities, thereby providing a means to access the free energies that define biological interactions and function. While serine proteases are often used as examples in biochemistry textbooks to illustrate enzyme catalysis, it remained unclear how their active sites accelerate the peptide bond cleavage reaction.

Conformational ensembles built from >1000 serine protease structures revealed atomic-level changes across their reaction states. By comparing the enzymatic and solution reaction, we identified molecular features that provide catalysis and quantified their energetic contributions to catalysis. Serine proteases precisely position their reactants in destabilized conformers, creating a downhill energetic gradient that selectively favors the motions required for reaction while limiting off-pathway conformational states. The same catalytic features have repeatedly evolved in proteases and additional enzymes across multiple distinct structural folds. Our ensemble-function analyses revealed previously unknown catalytic mechanisms, provided quantitative models based on simple physical and chemical principles, and identified motifs recurrent in nature that may inspire enzyme design. The ensemble-function approach can be used broadly to evaluate the fundamental origins of binding and catalysis, allostery, and molecular machines.