Enzyme Dynamics: Consensus and Controversy

Amnon Kohen

A vigorous contemporary debate spotlights the role of protein dynamics in enzyme catalysis [1-7]. By the end of the day, the controversy goes down to statements that obviously do not agree with each other, such as "enzyme dynamics do (or do not) contribute to catalysis". However, as the researchers studying this issue come from very different fields (kinetics, spectroscopy, theory, computer simulations, etc.) it is important to distinguish between "semantic disagreements" resulting from different terminologies, and matters of scientific merit (i.e., how enzymes work). Below I try to clarify points of agreement that sometimes go unrecognized, and sharpen the disagreements on matters of merit.

While there is a broad consensus that enzymes dynamically change their conformations upon binding of ligands and substrates ("induced-fit"), different views and approaches invoke different roles for motion in catalysis. Several key issues seem to be included in the consensus, e.g. enzymatic functions require a broad range of protein, ligand, and solvent motions at various time scales (seconds to femtoseconds); and proteins in solution, including globular enzymes in complex with their reactants (substrates), occupy a diverse conformational space, where only some of these conformations lead to the catalyzed chemistry.

So where is the controversy? First, several leading experimentalists have implied (mostly based on the relationship between NMR relaxation dynamics and enzyme kinetic parameters) that enzyme dynamics are directly coupled to the catalyzed chemical step [5,8-10]. The claim that the relationship between the measured dynamics and the kinetic parameters indicate coupling between the protein motions and the catalyzed chemical conversion is problematic for H-transfer reaction, as the time scales of the two phenomena are very different. The C-H cleavage event, which occurs on picoseconds to femtosecond timescales, is so much faster than the measured motions, which occur at millisecond to nanosecond timescales, that the motions appear rigid within the life time of the reactive state, thus prohibiting direct coupling. Consequently, it appears that the conclusions from the experimental studies in references 5 and 8 stretched beyond what the data could support when it comes to demonstrating direct coupling between the motion and the chemistry. While this point is almost certainly true for H-transfer reactions (as H-tunneling is very fast), it might not be a problem for isomerization reactions which may certainly true for H-transfer reactions (as H-tunneling is very fast), between the motion and the chemistry. While this point is almost...
fact that the uncatalyzed reaction was not studied. This issue led to some literature that argued for substantial controversy, which again is probably semantic rather than substantive. Probably more attention to words on the one hand, and more willingness to assume that loose language does not indicate bad faith or stupidity on the other hand, could better focus the discussion and advance the field.

In summary, part of the apparent controversy regarding the role of dynamics in catalysis is indeed substantive and requires further investigation by both experimentalists and theoreticians. This part includes pico-femtosecond dynamics across the system that might be non-statistically coupled to the catalyzed chemistry, and comparison to non-enzymatic reactions. Other parts of the controversy are likely semantic, where closer interactions between the communities addressing these problems could mediate and focus that debate. This part includes all models that do not assume non-statistical dynamics and focus on the catalyzed enzymatic reaction. The last type of debate is not always scientifically productive as both “schools” actually see eye to eye on the nature of the catalyzed chemistry. What’s next? To the best of my knowledge no current experimental data directly examine the role of non-statistical dynamics in enzymatic catalysis. Studies aiming at this question could have high impact in the future. Also, closer comparisons of the physical nature of the same chemical transformation in an enzyme and in solution would address the role of various physical features in catalysis.

References

3. Glowacki DR, Harvey JN, Mulholland AJ (2012) Taking Ockham’s razor to eye to eye on the nature of the catalyzed chemistry. What’s next? To the best of my knowledge no current experimental data directly examine the role of non-statistical dynamics in enzymatic catalysis. Studies aiming at this question could have high impact in the future. Also, closer comparisons of the physical nature of the same chemical transformation in an enzyme and in solution would address the role of various physical features in catalysis.

Author Affiliation

1Department of Chemistry, University of Iowa, USA

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