Of polemics and progress

Disagreements are common in science and can lead to better understanding, but must be handled carefully.

People disagree; it's a fact of life. How dull would our existence be if everything was black and white, and we always had the same opinions? What would we talk about? There would be no discussion of art because we would all be at home painting the same picture; there would be no politics because we would already agree on what the best policies were — and science? It would be unrecognizable.

Science is, in essence, the pursuit of 'truths', but not all seemingly valid hypotheses are accepted as such. The only way to separate science fact from science fiction is to have people point out limitations in any given experiment or suggest alternative explanations for the acquired data. This theme has been an intrinsic part of science since the inception of formal experimentation; hypotheses are made, data are gathered, and a logical explanation is put forward. Colleagues are then free to propose their own hypotheses, and gather their own data — the cycle begins again. From the laws of planetary motion, to the wave–particle nature of light, and through to the recent suggestion of lifeforms that incorporate arsenic into their DNA[1], disagreements born of critical thinking have played a central role in answering important scientific questions.

In this spirit we have two Perspective articles[2,3] in this issue that take differing views on the significance that structural dynamics have on the reactivity of enzymes. It is a debate that has been building over the past decade[4,5] and centres on the possibility that the motions of enzymes could amplify the contribution that quantum mechanical tunnelling makes to their activity.

The fact that the conformational movements of proteins can be integral to their function is broadly accepted. They can be important to ligand binding and release, and in allowing access to a given active site through large-scale loop–lid movements. The debate arises when discussing the reaction step that the enzyme catalyses, the all-important transition from reactant to product. At this point, how important are the fast structural fluctuations of the protein, motions such as vibrations? Can they significantly promote a reaction or can enzyme reactivity be accounted for with a model based on transition-state theory, which does not consider such individual atomic motions?

A Perspective article from Sam Hay and Nigel Scrutton highlights[2] the evidence in favour of such promoting motions. They suggest that catalysis can be enhanced by the coupling of vibrational motion to the reaction co-ordinate — 'pushing' the reactants into a position that effectively compresses the reaction barrier and therefore enhances tunnelling in hydrogen-transfer reactions. The evidence for this is indirect, something that Scrutton and Hay acknowledge. However, they believe that support from the unusual temperature dependencies of primary kinetic isotope effect experiments, and the consistency seen between such experimental results and various theoretical models, is compelling.

An alternative view comes from David Glowacki, Jeremy Harvey and Adrian Mulholland, who take 'Ockham's razor' to the problem[3]. They discuss various aspects of transition-state theory relevant to protein tunnelling dynamics and suggest a model within this framework, which enables them to conclude that one does not have to consider such dynamics to reproduce experimental results. Rather, a multidimensional energy landscape model that invokes at least two enzyme–substrate conformers with different reactivities is all that is required.

These Perspectives[2,3] and recent contrary results[6,7] suggest that this debate is not likely to subside in the near future. The one thing that is agreed on, however, is that more direct experimental evidence is required if a significant role for enzyme dynamics is to be wholly accepted.

Protein dynamics is far from the only topic in science in which there are fundamentally different views taken by those actively studying it. And although such differences in opinion can be stimulating and drive advances in the field, they can also have the opposite effect, creating issues that impede progress. For example, rifts can form between scientists who are working to answer the same questions; direct collaboration becomes more difficult, and even discussions at conferences can become awkward and unhelpful.

The publication of articles in divided research fields can be very problematic for all involved: authors, referees and certainly editors. The benefits, and indeed the purpose, of peer review can be undermined by authors who create long lists of excluded reviewers and by referees who are either hypercritical or overly positive. Editors can find themselves in a situation where their initial choice of referees could dictate the fate of an article because of the chosen referees' 'allegiances'.

Although editors normally honour requests to exclude potential referees, in some cases, to ensure that a paper is competently refereed, this is not possible. To help editors in making such decisions, authors should provide details explaining why they have asked for a potential referee to be excluded; simply stating that there is a 'conflict of interest' is not enough in controversial fields. Rather than suggesting sympathetic referees and excluding those who are known to hold a counter opinion, perhaps it is more appropriate in such fields to provide a brief history of the controversy and a list of those who you feel may have preconceived ideas on a given topic. The editors could therefore be upfront with referees when asking for their advice and would also be in a far better position to interpret their reports. Similarly, referees could help the editor by providing some background on the controversy and their opinion on how this might influence referees' reports.

Even when fundamentally disagreeing, referees should try to judge the technical aspects of research articles on controversial topics, and should thoroughly explain their subjective opinions on a paper's possible significance. Such topics inevitably generate alternative interpretations of the same data, and without enough evidence to conclusively prove one over another, referees should not recommend the rejection of technically sound, well-analysed data simply because the author's interpretation is incongruous with their own.

All practitioners of the scientific method know that disagreements can occur, but human foibles must not be allowed to hamper the communication of competently acquired results. Although progress in the study of enzyme dynamics has not been smooth, it is a relatively new field and further research is certainly needed if a consensus of opinion is to be reached. For now, we shall leave it to the reader to make their own mind up. ❒

References

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