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EDITORIAL

Speculation, Simulation and Common Sense

In the context of financial markets 'speculation' is a well understood word. Speculators attempt to guess trends in short term price fluctuations of specific shares, hoping to buy at a low price, while selling at a higher price. Good guesses yield profits, while the penalties for bad guesses are clear. In science, 'speculation' is a word that is not always respectable. Referees and editors are often quick to dismiss unsupported conjectures and hypotheses as 'speculative'.

Indeed the words 'conjecture', 'hypothesis' and 'theory' can often be used in curious ways in writing about science. An untestable 'hypothesis' or one that requires an impossible investment of time, money and technology is hardly helpful to the progress of science. Almost by definition science is advanced by testable hypotheses. Speculation in science is often an attempt to expand and enlarge understanding of fields, that have grown by interpretation of well established bodies of facts. Hard evidence is needed in science before a 'hypothesis' graduates to the level of an accepted idea. When a broad conceptual framework is established, the words 'theory' and 'law' enter scientific discourse. Newton's Laws of Motion and Einstein's Theory of Relativity are familiar examples. The Darwinian synthesis, which forms the conceptual underpinning of biology has at various times during its evolution been referred to as a 'hypothesis' and a 'theory'. The word 'conjecture' is common in mathematics, where I suspect the word 'hypothesis' has no place. Words and their usage can be fascinating, sometimes revealing interesting insights into different fields and their practitioners.

I was drawn to this discussion of words by a recent essay entitled 'Predicting Molecules – More Realism Please!' (Hoffmann, R., Schleyer, P. von R. and Schaefer III, H. F., *Angew Chem. Int. Ed. Engl.*, 2008, **47**, 7164). The authors, all eminent computational chemists, seem worried about the word 'stability', which is used to argue for the existence of strange, new molecules predicted by theoretical chemistry, empowered in recent times by powerful computers and even more by readily available suites of programs, which permit a remarkable range of properties to be calculated. Most outsiders to the field of chemistry (and I suspect a significant number of insiders) believe that chemistry was, is and must remain an experimental science. There is surely a greater joy in finding an unexpected molecule as a reaction product or in a natural mixture (although the former may dismay a purposeful synthetic chemist), than in conjuring up 'hypothetical' molecules on a computer screen. Despite the joys of experiment, the inroads of 'theoreticians' and 'speculators' into chemistry have been broad and deep. To Hoffmann *et al.* the fact, that 'the body of computations of molecules for which there is as yet no experimental evidence is growing very rapidly', is 'simply wonderful'. The authors note these predictions are a 'marker of the reliability of theory' and indeed they are. These computational exercises are suggested to be 'sociologically' valuable 'in creating a tense and fruitful balance between theory and synthesis in chemistry'. It is the word 'stability' and its usage in the literature of computational chemistry that seems to leave the authors mildly concerned. For Indians today the word 'stability' seems particularly important with respect to governments after elections. Parliamentary majorities determine stability. Coalitions can often be metastable. In the world of molecules there are significantly different interpretations of the term 'stability' when viewed from the somewhat distinct standpoints of thermodynamics and kinetics. Unfortunately as Hoffmann *et al.* point out 'in our minds and in everyday discourse, stability in the thermodynamic sense merges with stability in the kinetic persistence sense'. For substances which can occupy a large 'structure space' there are minima of energy into which a molecule can descend. The deepest is, of course, the most 'stable' state, in accordance with thermodynamics. On occasion molecules fall into other wells, but are prevented from escape by energetically insurmountable walls, literally incarcerated in a 'kinetic trap'. These are the 'metastable' states. A political analogy would be the stability of a government that lacks a parliamentary majority but survives nevertheless for considerable periods of time. Hoffmann *et al.* note that it would be difficult to 'get jewelers to call their diamonds metastable', an allusion to the lower thermodynamic 'stability' of this glamorous form of carbon, as compared to its more common counterpart. Hoffmann *et al.* suggest that computational chemists who speculate on the existence of novel molecular species should use the common English words 'viable' and 'fleeting'. The former

would be applicable to persistent species, which survive under normal laboratory conditions. The latter would describe transitory species that are trapped under special conditions or are observable in unusual circumstances, like interstellar space. The authors acknowledge that 'experimental communities are inherently skeptical of the claims of theoreticians' and hope that a more circumspect claim for 'stability' of newly predicted species may be helpful in enhancing the credibility of computational chemistry. Their appeal for realism is engagingly phrased: 'A degree of realism in what is calculated would help allay the skepticism of experimentalists. And such realism is also consistent with the strain of humility which characterizes any honest spiritual activity. Such as science.' Since computer 'simulations' are now a part of everyday research in chemistry, both theoreticians and experimentalists alike should read the essay by Hoffmann *et al.*

There are many areas of science where speculative (sometimes wildly so) theories abound. The 'origins of life' area and the attendant problem of the origin of molecular asymmetry (chirality) in biology are fertile fields for speculators. Curiously, a recent essay on this area attracted my attention largely because of its wonderfully provocative title: ' "If Pigs Could Fly" Chemistry: A Tutorial on the Principle of Microscopic Reversibility' (Blackmond, D. G., *Angew Chem. Int. Ed. Engl.*, 2009, **48**, 2). The speculators on the issue of how life originated (or more precisely the evolution of biological molecules and catalytic cycles) on earth are divided into two distinct camps; the 'geneticists' who believe in a primordial 'RNA world' and the 'metabolists' who 'believe that complex transformations characteristic of enzymes might have occurred prior to the evolution of informational molecules'. Blackmond notes that the 'tension' that exists in this area is reminiscent of Hoffmann *et al.*'s characterization of the 'tense and fruitful balance between theory and synthesis in chemistry'. Having quoted from Lewis Carroll in my last column, I was drawn inevitably to the phrase 'if pigs could fly chemistry' in the title of Blackmond's essay. This has been borrowed from the conclusions of an essay on 'The Implausibility of Metabolic Cycles on the Prebiotic Earth' by the late Leslie Orgel, a leading figure in the 'origins of life' area (*PLOS Biol.*, 2008, **6**, e18). Orgel, who in Blackmond's words 'sat in the geneticists camp' had a cautious view of theories that attempt to explain life's origin. In concluding his essay, that was published after his death, he suggested that 'solutions offered by supporters of geneticist or metabolist scenarios that are dependent on "if pigs could fly" hypothetical chemistry are unlikely to help'. The allusion here is to a famous exchange in *Alice's Adventures in Wonderland*, which is reproduced in Blackmond's essay: ' " I've a right to think" said Alice sharply, for she was beginning to feel a little worried. "Just about as much right," said the Duchess, "as pigs have to fly" '.

The Blackmond essay deals with hypothetical reaction schemes that are advanced to explain the origins of homochirality in nature. The author argues that 'models based on hypothetical reactions with no experimental corroboration have been shown to be in violation of a fundamental chemical principle', namely that of microscopic reversibility of chemical reaction at equilibrium. The origins of chirality and life have been the subject of much fanciful speculation. 'Hypothetical chemistry' may indeed be on much more treacherous ground than 'computational chemistry', but both Hoffmann *et al.* and Blackmond make strong pleas for common sense. In discussing 'significant figures in theoretical calculations' and the oft used terms of 'accuracy' and 'precision' the authors note that 'it's pretty much common sense. As is science'. Blackmond endorses this view noting 'that the reporting of non-experimentally corroborated conclusions carries with it a special responsibility ... and that common sense can be a practical aid'. Reaction schemes that attempt to rationalize the evolution of homochirality from an initially symmetric (racemic) world often postulate unusual behaviour. Blackmond suggests that 'common sense should guide the search for experimental systems exhibiting such behaviour; todate the balance between experiment and prediction has been more tense and fruitful.'

There is undoubtedly a need for speculation and hypotheses in science. It is sometimes fashionable to dismiss some areas of experimental research by arguing that they are not 'hypothesis driven'. There is still some merit in observation and careful cataloguing in many fields of science. An excessive reliance on deceptively sophisticated computational approaches in chemistry can be misleading. I cannot resist borrowing the last lines of Blackmond's essay—'As the Cheshire cat said to Alice: "If you don't know where you are going, any road will take you there." '

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