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## **Historical *What Ifs* and Counterfactual Science**

In his otherwise perfunctory and uninspiring introduction to the book "What Might Have Been", the right wing historian Andrew Roberts makes an intriguing and potential contentious statement about science and its incommensurable incompatibility with the counterfactual approach to history. This book details with alternative outcomes to famous - and not so famous - historical events: what might have happened if Charles I had won the English Civil War or if Margaret Thatcher had been killed by the Brighton Bomb or had Al Gore won the Presidential election. Such *What If* books are currently, and steadily, increasing in number, feeding off the present day appetite for history and mood for speculation. Roberts makes a point that scientific invention, or rather the lack of it, does not make for a good *What If*. He questions the historical imperative for scientific discovery, citing Newton and Archimedes in the process, arguing that gravity and the displacement of mass still operate even if we do not understand them as concepts. Apart from demonstrating his own profound lack of understanding of the detail implicit in the history of science, it also demonstrates his equally profound ignorance of the nature of science itself, though it would, perhaps, be asking much of a prize-winning Oxford historian to lower his exalted mind to the commonplace of science. In passing, one may note that earlier in his introduction Roberts cites the help technical innovations in the design of the Spitfire gave Britain in maintaining a degree of air superiority as a key counterfactual moment in World War II. Still we are all allowed a degree of inconsistency, are we not?

What Roberts clearly does not understand is the degree to which science is a strongly matrix process, involving both foot-soldiers and generals, not simply the product of individual, occasional acts of genius. Newton, ranked alongside Aristotle and Einstein, was undoubtedly one of the greatest scientists and greatest thinkers to have ever lived, yet his insights were not the product solely of his own mind and imagination. No, Newton, like all scientists great and small, based his work, at least in part, on the work of others. Likewise, profound as his work was, it still required the work of others - many others - to bring it fully to fruition. All science is like this, needing the work of the many to bring fame to the few. Where would the Alpha Males - and increasingly the Alpha Females - who dominate the academic and industrial jungles be without the myriad of industrious lesser mortals, thrall to their burgeoning personalities and egregious egos.

Science is driven from without as much as it is driven from within. Arguably the two greatest periods of innovation of recent centuries, the Industrial Revolution and the Second World War, saw remarkable and rapid advances, one driven by unprecedented commercial opportunity and the other by an overwhelming need to thwart dark forces. Although one must set this against an unbroken, if punctuated, background of scientific development stretching back into antiquity, nonetheless these were years when the nature of the world was redefined. Yet it was not that people of the time were fundamentally cleverer or fundamentally more inventive than people of any other time - there is little evidence of significant changes in brain volume during the last 40,000 years - nor even that they were better educated. Indeed, many of the greatest innovators of the Industrial Revolution were almost totally uneducated in the traditional sense. Yet the times in which Richard Arkwright and Abraham Derby lived were different. The opportunity and the freedom was there, the capacity to create and exploit, in a way that the modern world, with all its up-beat talk and supposed entrepreneurial culture, does not support. Worse still other eras, and particularly Antiquity, with its ossified hierarchical societies and slave-based economies; they had no economic imperative driving scientific or technical innovation. This is why, perhaps, we had no industrial revolution in the Roman era exploiting Hellenistic science; why Hero of Alexandria's steam engine remained a toy or the *Parthian Battery* and *Antikythera mechanism* are still poorly understood mysteries.

Science, as any student of Thomas Kuhn, author of *The Structure of Scientific Revolutions*, will tell you, has, of course, its own counterfactuals. These are implicit in the science we do and the science we learn about. As the apostle Paul said, *we see through a glass darkly*: all our knowledge is partial and incomplete and biased and subjective. This is true of science, as it is true of history or, indeed, of anything else. We deal in theories and ideas which are simply wrong, not from ignorance or stupidity but because we have, if you like, not yet peeled away enough layers of the onion to reveal the truth, if there is such a thing as truth. Newtonian mechanics is, for example, an incomplete explanation of the world, giving way to bigger, better theories encompassing more and more observations. This leads physicists to believe that they are ever closer to a theory of everything, yet science has hardly begun to properly observe the world around us; our understanding of biology and the solid state is still woefully naïve, and altogether too dirty and complex to trouble the minds of ambitious theoretical physicists. Will such a search for a theory of everything ever reach fulfilment? I, for one, doubt it but I am happy to let history be the judge of that.

- Darren Flower, Chairman

## The Modelling Review Award 2004

It's not too late to submit your entries for the Modelling Review Award 2004, but the closing date for entries, 30th September 2004, is rapidly approaching. As we told you in the last Newsletter, judging will take place during October, with winners notified towards the end of the year.

### A reminder of the rules...

- Entries must be no longer than 3000 words and submitted before 30th September 2004. Pictures/figures are encouraged. Entries must have industrial relevance.
- Entries must be submitted in electronic (pdf) format. They will be published on the CD 'as is' with no editing.
- Authors agree that their papers are available for publication to other group members, e.g. that there are no pre-existing copyright restrictions that would inhibit such distribution.
- Each entry must be from one individual, with clear references to any collaborators (including their contact details). Please remember to include your own contact details too! And if your details are likely to change (for example if you are a student who will be moving elsewhere next year) keep us posted on your changes
- Entries should state which commercial or academic simulation products were used, or whether self-written codes were employed.
- All work must have been completed with the last 12 months and not have been published previously in this form

All entries should be sent to the MMG Treasurer, **Dr John Kendrick, 13 Castle Close, Middleton-St-George, Darlington DL2 1DE**. If you want to submit them by e-mail, send them to [john@kendrick.me.uk](mailto:john@kendrick.me.uk).

## Molecular Modelling 4 Chemists

Do you have friends, especially those working in industry, who would benefit from knowing about modelling and how it can be applied to help them solve their problems? Help to spread the word and increase the understanding of modelling in industry, by pointing them in the direction of Molecular Modelling 4 Chemists. This 3-day course bills itself as "a practical training course covering the basics of molecular modelling and informatics" and spans areas from biological modelling to catalysis. Worked examples and case studies will help with:

1. understanding how modelling supports modern product development
2. using some modelling tools in practice and interpret results
3. showing how these tools and techniques complement experimental studies

Lecturers include John Kendrick, Jerry Winter, David Willock, Massimo Mella and Jamie Platts. The course is organised under the auspices of the Royal Society of Chemistry, and will be held at the University of Cardiff from 20-22 September 2004. For full details, visit [www.rsc.org/industry](http://www.rsc.org/industry), or else follow the short-cut [www.rsc.org/mm4](http://www.rsc.org/mm4). Samantha Bradley at the RSC ([BradleyS@rsc.org](mailto:BradleyS@rsc.org)) can also get further details for you and your fellow converts. Come on, get some of your friends interested in what you do for a living! Closing date is September 1<sup>st</sup>.

## Cutting Edge Approaches to Drug Design 2004

*Adrian Stevens and Darren Flower report on the latest in the annual series of one-day meetings. This year's meeting was held at the SCI in London, on 24 March. It attracted over 65 attendees, who wanted to take stock of the impact of computational technologies on drug design and discovery.*

The keynote lecture was delivered by Dr Peter Goodfellow (GlaxoSmithKline). His subject - the delivery of new drugs to market. He pointed out that the past five years' record levels of investment have not resulted in a comparable rise in the number of drugs within the pharmaceutical pipeline. He outlined GSK's attempts to deliver a long term strategic solution to this shortfall. By fundamentally reorganising its research business, GSK has made key investments in three areas: genomics, genetics and automation. They gamble that by combining an automated approach with the cloning and screening of all tractable target classes in the genome, the delivery of new chemical entities (NCEs) to the market can be increased significantly.

One challenge that is impacted by GSK's new strategy - managing the emerging data mountain - was discussed by GSK's Dr Stephen Pickett. Far from increasing the number of hits, Pickett showed that the size and signal-to-noise problems associated with high throughput screening could actually mask real hits buried in the noise and sheer volume of data. New strategies have been developed at GSK to meet their ambition of screening the whole druggable genome. Clustering the screening hits on the basis of corresponding chemotypes, and interactive data analysis methods, have been developed and rolled out. In addition, the issue of maintaining quality and confidence in the same collections had to be addressed in parallel with the increases in throughput. 'Pure and Sure' is the motto at GSK, with every compound in the million-compound collection having been characterised and analysed.

Looking at the other end of the drug pipeline, Bob Docherty of Pfizer (and MMG Committee member) discussed the impact of computing on formulation. The conversion of a pharmacologically active NCE into a medicine demands a detailed understanding of the materials science of all its crystal forms. Docherty showed how computational approached, like the analysis of hydrogen bonding patterns in small-molecule crystals, can be applied successfully to enable modelling of characteristics from the microscopic to the macroscopic level, demonstrating how *in silico* tools (such as calculations of crystal packing energy) can be used to help target experimentation.

Professor David Fell of Oxford Brookes University discussed how the computer modelling of biological pathways may transform our appreciation of drug action. He explained how deviations in IC<sub>50</sub> are dominated by the systemic response of a metabolic or signalling

pathway, compromising our naïve understanding of how drugs influence higher order biology from the level of the pathway through the cell and organ to the whole organism. Modelling the systemic response to an inhibitor is fundamental to a proper understanding of the action of that inhibitor, and requires complete characterisation of a signalling or metabolic pathway. The implications of this research are profound, especially at a time when the pharmaceutical industry is beginning to grapple with multifactorial disease.

Looking at the *in vivo* fate of a drug, Dr Andy Davis of AstraZeneca reviewed strategies for modelling ADMET in the light of the 'fail fast, fail early' philosophy that is currently adopted across the Pharma industry. With enormous numbers of compounds in early-stage discovery, truly accurate *in silico* approaches are a latter-day holy grail. Two strategies are in use: modelling large diverse collections (Global Models) and modelling small homogeneous sets (Local Models). Since accuracy is often improved when constraining predictions within the same congeneric series, David questioned whether future development should continue to expand chemotype-based approaches. Given the diversity of early-stage screens, though, at least an order of magnitude more data are required.

Often in drug development, a lead series is found to have one or more undesirable characteristics that prevent its development to a NCE. Dr Andy Vinter (Cresset BioMolecular Discovery) asked how might it be possible to move between structural classes while retaining biological activity? He reasoned that the key to this challenge is the successful modelling of surface and field characteristics, rather than structures. To explore this, Vinter illustrated the novel XEDS fieldprints system using the results of a collaboration with the James Black Foundation. One and a half million compounds were screened virtually against a target receptor. 88 matches were subsequently screened, giving four that were active at concentrations of less than 1  $\mu$ M and a further 27 compounds that were active at concentrations less than 10  $\mu$ M. All current molecular mechanics approaches rely on atom-centred charges, and Vinter questions whether it is possible that 'castles have been built on the sand' of flawed approximations.

In a wry and witty talk, Dr Michael Bodkin of Eli Lilly looked at the issue of improving communication between computational and medicinal chemists. The greatest successes in this area involve the use of web-based point-and-click interfaces to the burgeoning variety of different modelling software, like that for protein docking and the automatic enumeration and filtering of combinatorial libraries. Such systems have gained increasing popularity across the industry, yielding significant improvements in the understanding and usefulness of computation. Bodkin mused that this must be a two-way road: one of the next challenges should be to ensure that the computational chemist maintains ownership of compound suggestions, whether they prove to be active or not.

Dr Philip Dean of *de novo* Pharmaceuticals rounded off the day, with a review of the 'industrialisation of drug design'. Referencing Stuart Schreiber's recent article in *Drug Delivery Technology* (9, 7 April 2004, p299), Dean questioned whether industry is willing to accept that the number of drugable targets is very limited, even after completion of the genome project. If computational tools can evolve to manage active sites and to be coupled flexibly with *de novo* tools of improved quality, it might just be possible to test these hypotheses!

Once again, the meeting provided a well-structured and timely review of rapidly changing trends within the pharmaceutical industry. Although it coincided with the SciPharm meeting in Edinburgh, the excellent turnout from both industry and academia demonstrated that CEAtDD remains a pre-eminent event in the annual conference calendar.

## Cutting Edge Approaches to Drug Development

On 26-27 April, the RSC Molecular Modelling Group, together with the new Institute of Pharmaceutical Innovation at the University of Bradford, hosted a meeting on "Cutting Edge Approaches to Drug Development" (note our cunning adaptation of the well-established Cutting Edge brand!) held at the IPI.

The role of computational chemistry has long been clear in drug discovery. However, its use in drug development is still (no pun intended) under development. There are areas where computational chemistry and molecular simulation have made significant impacts - especially in the area of understanding crystal (poly)morphology. However, integrating the various modelling techniques across the size and time scales involved is still an ambitious project. It was particularly significant that the meeting was being held at the Institute of Pharmaceutical Innovation, which will be offering computational modelling services across the size scale from molecules to finished products and processes.

With Frank Leusen of the IPI in the Chair, the meeting was opened by Professor Peter York, one of the driving forces in establishing the IPI. He welcomed the delegates, outlining the role of the IPI and its mission. Then, Dr Steve Wicks of Pfizer gave a talk with the intriguing title "Feeding the Celestial Fire". In this he highlighted the 'fiendishly expensive' cost of full drug development, stressing that industry has a strong desire to settle on the solid form as soon as possible, and hot to change it, since changes are most expensive in the later stages. For 100 discovery approaches, giving about 7 million compounds to screen, only one product can be expected. Dr Darren Flower of the Edward Jenner Institute for Vaccine Research, who also is Chairman of the MMG, then presented his talk "I've discovered the molecule. What's your problem?" which completed our scene-setting by outlining the issues involved in drug discovery, the challenges of working as a computational chemist in the discovery field, and the attention that the 'discovery' computational chemist gives to the relationship between discovery and development. He highlighted that often, chemists view the results from simulations as reality; computational chemists know that it's just a model. Uptake of the technique depends on a number of factors too - the age of the user (with older users being more sceptical about computers) and the in-house culture, since some companies have an activity just because others do.

After lunch, the next talk on "Molecules making choices - from solutions to crystals" was given by Professor Roger Davey of UMIST. He introduced us to the phenomenon of polymorphism, and how it is influenced by changes in crystallisation conditions. Illustrated by several examples, he showed that polymorphism may be controlled by steering crystal nucleation through our understanding of solid state and solution chemistry. Professor Allan Myerson of the Illinois Institute of Technology, Chicago, USA, enlightened us on "Novel methods for the control of crystal size, shape and solid form". He presented the latest results of the laser-induced nucleation experiments pioneered in his group. This approach not only speeds up nucleation and leads to larger crystals in comparison to spontaneous nucleation, but by polarising the laser pulse it is also possible to crystallise specific polymorphs. In the second part of his talk, he discussed the results of crystallisation experiments studying the nucleation and growth of crystals on substrate surfaces resulting in different polymorphs and morphologies depending on the choice of substrate.

Focusing again on the area of molecules and crystals, Professor Angelo Gavezzotti from the University of Milan, Italy, told us about "The crystalline state of organic compounds: what a computer can do for you". He first gave an overview of the thermodynamic and kinetic considerations in crystal modelling, leading to a critical review of the calculation of intermolecular interactions by the traditional atom-atom potential. Using the crystal structure prediction of caffeine as an example, he then introduced a novel method of calculating lattice energies very accurately: the PIXEL approach in which a molecule is represented by some 10,000 pixels of electron density. Then, moving up the size scale, Professor Hans Fraaije from the University of Leiden, the Netherlands, spoke on "Cutting edge mesoscopic modelling for drug delivery", concentrating especially on the applications of his Mesodyn program in the area of 'soft solids'.

He presented exciting results of a series of simulations, predicting the properties and behaviour of systems over time and length scales that are far beyond the scope of atomistic simulation methods. This wrapped up the formal session of an interesting and thought-provoking first day. But it wasn't over yet - we then had a poster session (complete with drinks and nibbles) in the IPI, before making our way to Nawaab for the conference dinner. After all, the conference was held in Bradford, curry capital of the UK - so it was the logical choice.

On the second day, chaired by Liz Colbourn of Intelligensys, Dr Jamshed Anwar of King's College London gave a very clear explanation of "Applications of molecular simulation in drug delivery and formulation", concentrating especially on the information that can be obtained from molecular dynamics. This was followed by Peter York's "Predictive drug product design and processing - pipedream or realistic goal?". The conclusion was that it was at this stage a bit of both! but that we can expect more and more to see it as a realistic goal. Professor Ray Rowe, of AstraZeneca and the PROFITS Group at Bradford, then gave an overview of "Recent advances in computer-aided formulation", covering the full gamut from expert systems to data mining techniques to simulations. These were put in an industrial context, with an overview of which companies were using various techniques for specific applications. Dr David Barlow of King's College London gave a very lucid overview of neural networks as part of his talk on "Applications of artificial neural networks in drug formulation and development", giving full details on several application areas. This complemented the overview given earlier by Ray Rowe, and showed clearly that these techniques are very valuable for developing models of complex systems like drug formulations.

Moving up the size scales, Dr James Elliott from Cambridge discussed "Multi-scale modelling of powder compaction: from granules to tablets". Although much of the focus was on the smaller size scales, his talk indicated the promise of being able to bridge the gap between molecular and macroscopic properties. Finally, Professor Jonathan Seville of Birmingham gave an overview of "Structure in products and processes: computational methods and their validation". The meeting was wrapped up by Bob Docherty from Pfizer, who summarized some of the key issues raised in the meeting and then invited a 'panel' of the speakers to contribute their views on some of the contentious issues. The overall conclusion was that these techniques can be applied to drug development, but that communications between modellers at the different size scales, and between modellers and experimentalists, will be essential to make real progress.

A questionnaire was distributed to participants, who overwhelmingly ranked the meeting very high in terms of its scientific calibre. The only complaint was about the Bradford weather - unfortunately, something we couldn't do much about! This meeting was generously sponsored by Pfizer, AstraZeneca, Bristol-Myers Squibb and the Angela and Tony Fish Bequest Fund of the Royal Society of Chemistry. Yorkshire Forward provided additional funding and publicity for the meeting. We are grateful to all our sponsors for ensuring that this event was a resounding success.

- Liz Colbourn and Frank Leusen

## Report on the Young Materials Modellers' Forum

Following last year's successful event the Young Material Modellers Forum was held at Daresbury Laboratories on May 27<sup>th</sup>. Some 22 young scientists gathered together to give presentations and posters about their work. The standard of the scientific work was very high and demonstrated a wide range of applicability from new algorithms for molecular dynamic calculations, to the calculation of the energetics of screw dislocations in zeolite A, to the origins and modelling of stick-slip processes in nano-indentation devices.

It was difficult to choose between the oral presentations but in the end the prize for the best talk was given to Leandro Liborio of Queen's University Belfast. Leandro presented work on first principles modelling of the surfaces of SrTiO<sub>3</sub>. Various possible models for the surface reconstruction of the (001) surface were compared using a combination of total energy surface energy calculations and a method for estimating the surface free energy as a function of the oxygen partial pressure and temperature.

It was even more difficult to choose a winning poster and in the end the organisers compromised by awarding two prizes for the best poster presentation. One of these went to Katie Finch, from Manchester, who presented molecular mechanics calculations of the effect of calcium on the barite crystal morphology. The other poster prize was presented to Miguel Mora-Fonz, from University College London, who was using density functional calculations to understand the nucleation and growth of silicate species. In particular, the roles that pH and solvation have to play in the stability of charged species and the relative stability of rings and chains of low oligomers of silicates.

Our thanks go to Daresbury Laboratory who has been so helpful in providing us with the facilities. We would also like to thank our sponsors, CCP5, Unilever and Accelrys, and Steve Maginn whose entertaining chairmanship ensured the meeting ran smoothly. Finally we would like to thank Neil Allan who put in so much work in organising the meeting and who provided the Dalek that kept the meeting to time. (Editor's Note: It's amazing what the threat to 'exterminate, exterminate' can do!)

- John Kendrick

## Diary Dates- Upcoming Meetings

**19 October 2004 - Young Bioinformaticians' Forum**, to be held at the Said Business School, Oxford. This meeting (like last year's) is being organised jointly with the Oxford Bioinformatics Forum. Contact [ybf@bioinformaticsforumuk.net](mailto:ybf@bioinformaticsforumuk.net) or Dr Darren Flower ([Darren.Flower@jenner.ac.uk](mailto:Darren.Flower@jenner.ac.uk)) if you are interested in or attending the meeting. No registration fee is associated with this meeting.

**3 December 2004 - Young Modellers' Forum 2004**, to be held at the English Heritage Lecture Theatre (formerly Scientific Societies Lecture Theatre) London. For more details see <http://www.mgms.org/diary.htm>, or contact Dr Steve Maginn ([smaginn@chemcomp.com](mailto:smaginn@chemcomp.com)). This meeting is jointly organised between the MMG and the Molecular Modelling and Graphics Society.