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From diatomics to drugs and dividends

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Abstract

The path from diatomic molecule spectroscopy to molecular modelling and drug discovery is described, along with aspects of the commercialisation of research. It is a history tightly coupled with the advances in computers over the past 50 years, but with a future full of opportunity.

Keywords: Computational chemistry; Drug discovery; Grid computing; Commercialisation

1. Introduction

My career, like that of so many people, is a testament to the 'cock-up' theory of history. Although it is possible with hindsight to discern some sort of plan and to ascribe wise decisions about significant changes in direction, in fact chance has been the major factor.

The birthdate of 1 October 1939 meant missing compulsory military service by a single day and coming to Oxford as a student 2 years earlier than anticipated. Starting research in 1961 determined that I was part of the first generation of scientists to use computers as opposed to the pioneers who had developed them. The subsequent 50 years have been strongly coupled to hardware advances.

In the early 1960s the UK computer industry was second to none, and at Oxford having a Ferranti Mercury put us in a strong position. In particular the crystallographers guided by Dorothy Hodgkin did wonderful and Nobel Prize winning studies. Chemists were a little way behind, but in the Physical Chemistry Laboratory Ken Lawley did some very early Monte Carlo work and I, working on diatomic molecule spectroscopy as a student of Richard Barrow, stumbled into trying to use the machine, described by one of my senior colleagues as 'far too complex for a chemist ever to use'.

2. Diatomics

My first research was a study of the spectrum of diatomic chlorine where one of the points of interest was the variation of the dissociation energies of the halogens. The heavier members of the series hold together at greater interatomic distances than one might expect. This led me to try to calculate the potential curves using the Rydberg–Klein–Rees method [1]. This involves computing a couple of integrals of the form:

$$f(U) = \frac{1}{2\pi(2\mu)^{1/2}} \int_0^{I'} \frac{\mathrm{d}I}{\{U - E(I,K)\}^{1/2}}, \qquad g(U) = \frac{1}{2\pi(2\mu)^{1/2}} \int_0^{I'} \frac{(\partial E/\partial K)\,\mathrm{d}I}{\{U - E(I,K)\}^{1/2}}$$

where $f = (1/2)(r_{max} - r_{min})$, $g = (1/2)((1/r_{max}) - (1/r_{min}))$, $I = h(v + (1/2))$, $K = (h^2/8\pi^2\mu)J(J+1)$.

My 'breakthrough' was to realise that with a computer, any integral can be evaluated numerically and all the complex and in some cases incorrect analytical solutions could be avoided [2]. Computers looked like a good idea.

Intending initially to go to Harvard to work with Bill Klemperer, I took a deviation and spent a year's post-doctoral spell with Carl Moser in Paris to learn how to do *ab initio* calculations on diatomics using the software originally by Bob Nesbet of IBM and improved by Dick Stevens. What I could bring to the party was a knowledge of good spectroscopic questions which *ab initio* calculations might help solve.

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Table 1
Spin–orbit coupling constants

	Calculated (cm^{-1})	Observed (cm^{-1})
BeH	2.3	2.14
CH	30.4	28.0
OH	141.4	139.7
SH	362.0	382.4

Together with Georges Verhaegen we settled the nature of the ground state of BeO which in principle could be either a triplet or a singlet. To do this we did the first open-shell calculations of excited electronic states as opposed to using virtual orbitals [3].

An even more intriguing problem was the nature of the first excited states of molecules like BeF and MgF. Here there is no doubt that they are $^2\Pi$ states, but calculation suggests that they should be so-called 'regular' with the 1/2 component closer to the ground state than the 3/2 sub-level, but the experimental spin–orbit coupling constant has the wrong sign for that to be true.

To resolve this dilemma, together with Timothy Walker, one of my first graduate students, we calculated, for the first time, diatomic spin–orbit coupling constants [4,5]. The results as Table 1 shows were impressive.

This still however did not explain the anomaly in the alkaline earth halide molecules. To resolve that we were pushed into calculating the so-called Λ-doubling constants which are off-diagonal spin–orbit coupling matrix elements [6].

$$P = 4\sum \frac{\langle {}^2\Pi|\mathrm{H}_{80}|^2\Sigma\rangle\langle {}^2\Pi|B(\mathrm{L}^+ + \mathrm{L}^-)|^2\Sigma\rangle}{E_\pi - E_\Sigma}$$

and

$$q = 2\sum \frac{\langle {}^2\Pi|B(\mathrm{L}^+ + \mathrm{L}^-)|^2\Sigma\rangle^2}{E_\pi - E_\Sigma}$$

Yet again these calculations, performed using perturbation theory, were amazingly accurate and encouraged us to try to calculate the Λ-splitting in CH. This, in the 1960s, was a very important problem as molecules were starting to be discovered in interstellar space. First was OH seen from its Λ-doubling spectrum, but CH could not be found even though it had to be the precursor of the many organic species being discovered. We made a prediction which proved to be better than the terrestrial experiment (Table 2): a real triumph for theory [7].

By the late 1960s I was then something of an expert on *ab initio* calculations, and even published a book on the topic [7], but only experienced with diatomic molecules.

Table 2
Off-diagonal spin–orbit coupling

	Splitting in CH (MHz)
Terrestrial experiment	3374 ± 20
Astronomical experiment	3335.47 ± 0.01
Calculation	3311

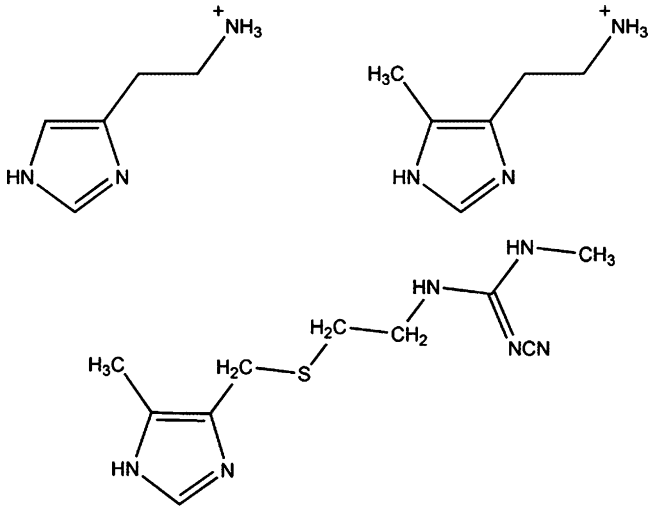

Fig. 1. The histamine monocation: the 4-methyl compound and cimetidine.

3. Drugs

The jump to drugs and applying computers to problems in molecular pharmacology was again unplanned. Out of the blue in 1968 I received a letter from Anthony Roe of Smith Kline and French asking me my opinion about a paper which computed the conformational energy of histamine (Fig. 1).

Not surprisingly, since histamine is a 1:2 disubstituted ethane the calculations indicated that there are two stable conformers, the trans and gauche (or more properly antiperiplanar and synclinal conformers). It went on to hypothesize that the then known distinct pharmacological actions could be mediated by one conformer for the H1 activity and the other for H2, acid secretion in the gut. Finding inhibitors of H2 activity was the research topic of Jim (now Sir James) Black and his team, with Robin Ganellin leading the medicinal chemistry. That problem drew me into a collaboration which both fascinated me and changed the direction of my own research. Trying to understand why 4-methyl histamine is an H2 agonist but does not affect the H1 receptor led to work on essential conformations for activity [8].

The idea of using theoretical chemistry to help discover biologically active molecules was sufficiently outrageous for it to be necessary to write a book on the topic, and hence the publication in 1977 of *Quantum Pharmacology* [9]. This was written in part because the outline won a prize from the publishers, Butterworth, that helped finance a sabbatical at Stanford and Berkeley.

The real spurt in research activity in the area came in the early 1980s when colour graphics was introduced. I believe that we were the first to publish the description of the work as 'computer-aided molecular design' in 1983 when we published what were probably the first colour graphic molecular displays (Fig. 2) [10], obtained from a black and white screen by shooting part of the figure through a red filter and the other part through a blue one, after rewinding the film.

Colour enabled non-specialists to see what was going on in enzymes and provided a real boost to the subject. I well

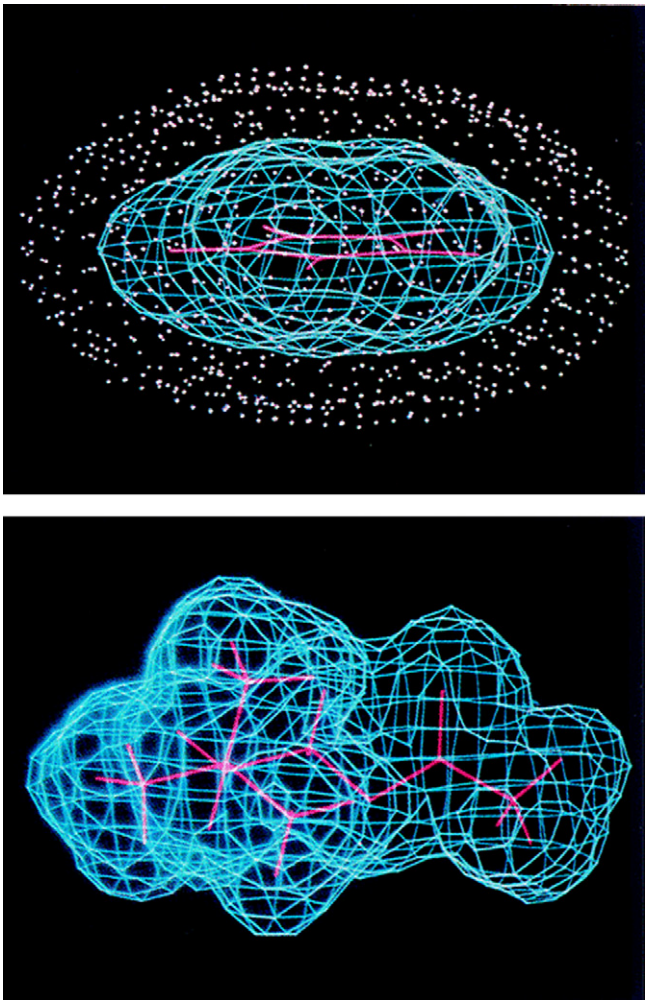

Fig. 2. The first coloured molecular graphics pictures. Reprinted from Richards and Mangold [10b], with permission from Elsevier.

remember a Damascus-like conversion of Jack Baldwin who got really excited about the mechanism of cytochrome P450 as a result of watching Garrett Morris at work in my lab [11].

One problem was this: at that time, it was enormously expensive to publish coloured plates. This then was the raison d'être for the Molecular Graphics Society, of which I was part of the founding committee along with David White, Andy Vinter, Frank Blaney and Peter Murray-Rust, but driven by Andy Morffew who edited the first few numbers of our new journal until I took over the editorship, which I did during the period 1984–1996.

The contributions from my group to the subject covered a wide range, but one recurrent feature has been the topic of molecular similarity. This we popularized, and extended to cover electrostatic field and shape as well as electron density [12]. Andy Good and Edward Hodgkin were responsible for the use of Gaussians, which greatly simplify these calculations, and this is now incorporated into many standard packages.

In the late 1980s, free energy perturbation techniques were introduced, and Chris Reynolds, Paul King and Jon Essex were particularly successful in exploiting that idea [13]. I think that the work on computed redox potentials, with its implication for bioreductive drugs, was particularly striking, and similarly the computation of partition coefficients with their relevance to drug transport [14].

Like so many other groups we became involved in protein structure prediction [15] by homology methods and had real success with the cytokines, work started by Paul Bamborough who used the sequence matching program CAMELEON written by Garrett Morris that was one of the first bioinformatics tools. Adrian Mulholland opened the vein of studies on enzyme mechanisms, a field in which he now plays a major role [16].

With Sung-Sau So we were among the first to apply neural networks [17] and developed our new structure–activity tool SOMFA [18].

Most recently, sparked by Daniel Robinson, we have tried to exploit pattern recognition techniques in the area of molecular design. Successful outcomes have included molecular alignment [19] and the finding of binding sites on proteins of known structure. This I believe will become an even more important type of problem as synchrotron sources spew out more and more protein crystal structures. The use of this by Guy Grant and Meir Glick to find the sensitive binding spot in the anthrax toxin, which could serve as a target site for a drug, was particularly satisfying [20].

Once the target site is known, then virtual screening becomes a possibility. This was the basis of our almost embarrassingly successful screensaver project [21]. The first phase was done in collaboration with Keith Davies, and has made possible the screening of billions of small drug-like molecules against a protein target in a matter of days. Started in 2001 we have had 3.5 million PCs working for us in over 200 countries, yielding over 450,000 years of computer time. This is a system for this type of study which is about three times as powerful as the world's fastest supercomputer.

In one case, phosphatase (protein-tyrosine-phosphatase 1B), some hundreds of the predicted hits have been synthesized and tested and about 10% of the compounds proved active: good by industry standards.

Currently we are pushing this type of work forward on two fronts. Dan Butler is improving and extending the small molecule database, and Pedro Ballester has devised an ultrafast method to compare shapes of molecules, capable of answering questions about shape similarities in billions of compounds in minutes.

Many of these applications have obvious commercial implications and indeed have produced financial dividends both for companies and for the University of Oxford.

4. Dividends

It may be unusual in a scientific paper to discuss the extent of commercial return from research, but particularly in the current funding environment, the success of our research in terms of dividends needs to be appreciated.

The Oxford Chemistry Department has provided for the central University some £80 million: £40 million in actual cash; about £20 million in unrealised value in quoted

companies, and a similar sum as a reasonable fair value estimate for its holdings in as yet unquoted companies. This return all comes from spin-out companies and as yet nothing from royalties.

The first spin-out company from the University in which it held equity was Oxford Molecular, founded by me and Tony Marchington with the credit for its success being almost wholly due to Tony. The company was founded in 1989 with £350,000 of venture capital and the University being given 30% of the equity for the intellectual property: software written in my group by David Ricketts, Garrett Morris and Kate Burt. It grew rapidly, opening offices in Paris and Palo Alto in 1992, and having a successful IPO on the London Stock Exchange in 1994. The company made a string of acquisitions, including seven in the USA, so that at its height it became valued at £450 million, only to lose its way and eventually be sold in two parts for considerably less. Nevertheless, the University benefited to the tune of £10 million and the model was repeated in other successful ventures.

With that background, when in 1997 I became Chairman of the Department of Chemistry and needed a new building, it was to that world I looked for financial support. We succeeded in building a new research laboratory costing some £62 million without the University having to make any financial contribution. The novel feature of that funding was the deal we made with the City of London institution, Beeson-Gregory. They provided £20 million up front, in return for half of the University share in any spin-out companies from the Department for 15 years. Typically the equity split in spin-outs is 30% to the funders; 20% kept for management; 25% to the University for the intellectual property, and 25% to the academic researcher or researchers. Thus the academic is not affected by the deal, and once a company is formed the University and Beeson-Gregory would have identical interest.

The model has been outstandingly successful for all parties. Beeson-Gregory merged with Evolution Group to set up a separate company, IP2IPO Ltd., to make similar deals with other universities. That company, now IP Group Plc, a London Stock Exchange main board company, has partnerships with 10 universities and has created over 40 new companies. From the Oxford Chemistry Department have come 11 new companies, 2 of which have floated on the Alternative Investment Market (AIM) and have a combine market capitalisation of over £40 million.

Amongst the recent Oxford Chemistry spin-outs, the majority are in the biomedical, pharmaceutical area. One of these is Inhibox Ltd., the company derived from the screensaver project. That company owns the intellectual property in terms of these predicted hits. The equity which would have gone to me in this case was given to the National Foundation for Cancer Research, who have been long-term funders of my research. It did not seem right to benefit financially from the generosity of the millions who provided their computer time, but in this way any profit will be ploughed back into cancer research.

This novel method of funding was described by *The Financial Times* as ''the way universities should be financed in the future''. That may be an exaggeration, but there is little doubt that it is to the advantage of both universities and researchers if this type of opportunity is born in mind, although quite wrong were it to determine the nature and direction of research.

Table 3
Co-workers of W. Graham Richards

John Horsley	Mary Anne Cordeiro
Tim Walker	Joanne Taylor
Anthony Hall	Christine Walmsley
Reg Hinkley	SUNG-SAU SO
Alistir Todd	SANJAY SANGHANI
Jim Port	STEVE GARLAND
John Raftery	Ankash Nandra
Peter Scott	Nia Neville
Les Farnell	ANABEL TODD
Les Clyne	CHARLOTTE DEAN
Bob Hammersley	
ELIZABETH COLBOURN	Jane Hammond
Ian Wilson	Jennifer Wallis
Stephen Moore	Gaynor Leggate
TONY MARCHINGTON	Susan West
Chet Chung	PAUL FINN
DAVID COOPER	JOHN WILKIE
VALERIE SACKWILD	
Alda de Sousa	SUK PING SO
Robert Elliott	JILL GREADY
Sandra Robins	Harit Trivedi
NEIL STUTCHBURY	Roger Humphries
CHRIS NAYLOR	George Jaroskiewcz
Ruth Holmes	Alistair Cuthbertson
Saira Mian	CHRIS REYNOLDS
Pippa Bowen-Jenkins	IAN HAWORTH
DAVE RICKETTS	GUY GRANT
EDWARD HODGKIN	Barry Hardy
ANDREW SMELLIE	JEFF ROTHMAN
Paul King	PAUL LYNE
CATHERINE BURT	ROMANO KROEMER
GARRETT MORRIS	ANA CASTRO
JONATHAN ESSEX	PETER WINN
GRAHAM WORTH	AARON DINER
Richard Gilbert	XABIER LOPEZ
Paul Boscott	MEIR GLICK
ADRIAN ELCOCK	Juan Adelentado
ANDY GOOD	MASSOUD MAHMOUDIAN
ADRIAN MULHOLLAND	VIJAY COMBAR
PAUL BAMBOROUGH	AKIRA NAKAYAMA
DAVID LOWIS	MYRNA GIL
ALAN ROBINSON	VERNON CHENEY
James Bradley	FEDERICO GAGO
Tom Barlow	CRISTINA MENZIANI
STEPHEN DOUGHTY	GYORGY FERENCZY
Ivy Boey	Amatz Meyer
Martin Parretti	MARIA RAMOS
DANIEL ROBINSON	Carl Schwalbe
PETER VARNAI	Alon Seri-Levy
Owen Walsh	Sakaya Shinomoto
STEWART ADCOCK	Justin Caravalla
BEN WEBB	ANDERSON COSER GAUDIO
MAYA TOPF	TONY HOPFINGER
BIRGIT ALBRECHT	DAVE WINKLER
BEN ALLEN	MILAN REMKO
DAVE HUGGINS	PERRY KAYE
CHRIS BAKER	ESTHER LONSO
	MARTIN EGLI
Brian Hill	MILAN REMKO

5. Conclusion

Starting out as a diatomic molecule spectroscopist hardly seemed an obvious precursor to research in drug discovery and even less as a way to creating companies. As always in research, not having too clear a plan as to where one is going is wise. Ideally one needs a research group, in my case over 40 years averaging about a dozen able people. In that way I have been particularly fortunate. I have supported some 60 graduate students and over 150 Part II chemists. In future I will work with visitors and post-doctoral workers. In Table 3 I list those co-workers, with those still active in the world of modelling in capitals. It is to these people that I owe so much and would like to thank them and especially the organisers of this meeting, Guy Grant and Frank Blaney.

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References

[1] (a) R. Rydberg, Graphical representation of some band spectral data, Z. Phys. 73 (1931) 376–385;
(b) O. Klein, On the calculation of potential curves for diatomic molecules with the aid of spectroscopic term values, Z. Phys. 76 (1932) 226–236;
(c) A.G.L. Rees, The calculation of potential-energy curves from band-spectroscopic data, Proc. Phys. Soc. 59 (1947) 998–1008.

[2] W.G. Richards, R.F. Barrow, The calculation of potential curves from spectroscopic data, Proc. Phys. Soc. 83 (1964) 1045–1049.

[3] (a) G. Verhaegen, W.G. Richards, The valence levels of BeO, J. Chem. Phys. 45 (1966) 1828–1833;
(b) W.G. Richards, G. Verhaegen, C.M. Moser, The low-lying energy levels of MgO, J. Chem. Phys. 45 (1966) 3226–3230.

[4] T.E.H. Walker, W.G. Richards, The nature of the first excited electronic state in MgF, J. Phys. B: Proc. Phys. Soc. 1 (1968) 1061–1065.

[5] (a) T.E.H. Walker, W.G. Richards, Ab initio computation of spin-orbit coupling constants in diatomic molecules, Phys. Symp. Faraday Soc. 2 (1968) 64–68;
(b) T.E.H. Walker, W.G. Richards, Calculation of spin–orbit coupling constants in diatomic molecules, Phys. Rev. 177 (1969) 100–101.

[6] (a) T.E.H. Walker, W.G. Richards, The assignment of molecular orbital configurations on the basis of Λ-type doubling, J. Phys. B 3 (1970) 271–279;
(b) J.A. Hall, R.K. Hinkley, T.E.H. Walker, W.G. Richards, Λ doubling in 2Π states of diatomic molecules, J. Phys B 5 (1972) 204–212;
(c) R.K. Hinkley, T.E.H. Walker, W.G. Richards, The variation of Λ doubling with rotational quantum number BeH and BeD, J. Phys. B 5 (1972) 2016–2024;
(d) R.K. Hinkley, T.E. Walker, W.G. Richards, On the e.p.r. spectrum of vibrationally excited hydroxyl radicals, Proc. R. Soc. Lond. A331 (1973) 553–560.

[7] W.G. Richards, J.A. Horsley, Ab initio Molecular Orbital Calculations for Chemists, Clarendon Press, Oxford, 1970.

[8] (a) C.R. Ganellin, E.S. Pepper, G.N.J. Port, W.G. Richards, Conformation of histamine derivatives. 1. Application of molecular orbital calculations and nuclear magnetic resonance spectroscopy, J. Med. Chem. 16 (1973) 610–616;
(b) C.R. Ganellin, G.N.J. Port, W.G. Richards, Conformation of histamine derivatives. 2. Molecular orbital calculations of preferred conformations in relation to dual receptor activity, J. Med. Chem. 16 (1973) 616–620;
(c) L. Farnell, W.G. Richards, C.R. Ganellin, Calculation of conformational free energy of histamine, J. Theor. Biol. 43 (1974) 389–392.

[9] W.G. Richards, Quantum Pharmacology, Butterworths, London, 1977.

[10] (a) W.G. Richards, V. Sackwild, Computer graphics in drug research, Chem. Brit. 18 (1982) 635–636;
(b) W.G. Richards, L. Mangold, Computer-aided molecular design, Endeavour, New Series 7 (1983) 2–4.

[11] J.E. Baldwin, G.M. Morris, W.G. Richards, Electron transport in cytochromes P-450 by covalent switching, Proc. R. Soc. Lond. B 245 (1991) 43–51.

[12] (a) T.W. Barlow, W.G. Richards, A novel representation of protein structures, J. Mol. Graph. 13 (1995) 373–376;
(b) T.W. Barlow, W.G. Richards, A one-dimensional representation of protein structure, J. Mol. Graph. 14 (1996) 232–234;
(c) D.D. Robinson, T.W. Barlow, W.G. Richards, Reduced dimensional representations of molecular structure, J. Chem. Inf. Comput. Sci. 37 (1997) 939–942;
(d) D.D. Robinson, T.W. Barlow, W.G. Richards, The utilization of reduced dimensional representations of molecular structure for rapid molecular similarity calculations, J. Chem. Inf. Comput. Sci. 37 (1997) 943–950;
(e) T.W. Barlow, W.G. Richards, Reduced molecular representations and their role in protein structure prediction, J. Mol. Struct. (Theochem.) 398 (1997) 483–487.

[13] (a) C.A. Reynolds, P.M. King, W.G. Richards, Computed redox potentials and the design of bioreductive agents, Nature 334 (1988) 80–82;
(b) C.A. Reynolds, P.M. King, W.G. Richards, Accurate redox potentials from theoretical calculations: methyl-substituted benzoquinones, J. Chem. Soc. Chem. Commun. 21 (1988) 1434–1436.

[14] J.W. Essex, C.A. Reynolds, W.G. Richards, Theoretical determination of partition coefficients, J. Am. Chem. Soc. 114 (1992) 3634–3639.

[15] (a) P. Bamborough, G.H. Grant, C.J.R. Hedgecock, S.P. West, W.G. Richards, A computer model of the interleukin-4 receptor complex, Proteins: Struct. Funct. Genet. 17 (1993) 11–19;
(b) P. Bamborough, C.J.R. Hedgecock, W.G. Richards, The interleukin-2 and interleukin-4 receptors studied by molecular modelling, Structure 2 (1994) 839–851;
(c) P. Bamborough, D. Duncan, W.G. Richards, Predictive modelling of the 3-D structure of interleukin-13, Protein Eng. 7 (1994) 1077–1082;
(d) P.D. Lyne, P. Bamborough, D. Duncan, W.G. Richards, Molecular modeling of the GM-CSF and IL-3 receptor complexes, Protein Sci. 4 (1995) 2223–2233;
(e) J.A. Caravella, P.D. Lyne, W.G.A. Richards, partial model of the erythropoietin receptor complex, Proteins: Struct. Funct. Genet. 24 (1996) 394–401;
(f) R.T. Kroemer, W.G. Richards, Helical cytokines and signal transduction: a computational approach, Chem. Des. Automat. News 11 (1996) 1–12;
(g) R.T. Kroemer, W.G. Richards, Homology modeling study of the human interleukin-7 receptor complex, Protein Eng. 9 (1996) 1135–1142;
(h) C.M. Deane, R.T. Kroemer, W.G. Richards, A structural model of the human thrombopoietin complex, J. Mol. Graph. Model. 15 (1997) 170–178;
(i) R.T. Kroemer, R. Kröncke, J. Gerdes, W.G. Richards, Comparison of the 3D models of four different human IL-7 isoforms with human and murine IL-7, Protein Eng. 11 (1998) 31–40.

[16] (a) A.J. Mulholland, G.H. Grant, W.G. Richards, Computer modelling of enzyme catalysed reaction mechanisms, Protein Eng. 6 (1993) 133–147;
(b) A.J. Mulholland, W.G. Richards, Acetyl-CoA enolization in citrate synthase: a quantum mechanical/molecular mechanical (QM/MM) study, Proteins: Struct. Funct. Genet. 27 (1997) 9–25;
(c) A.J. Mulholland, W.G. Richards, Modeling enzyme reaction intermediates and transition states: citrate synthase, J. Phys. Chem. B 102 (1998) 6635–6646;

(d) P. Varnai, W.G. Richards, P.D. Lyne, Modelling the catalytic reaction in human aldose reductase, Proteins: Struct. Funct. Genet. 37 (1999) 218–227;
(e) M. Topf, P. Varnai, W.G. Richards, Quantum mechanical/molecular mechanical study of three stationary points along the deacylation step of the catalytic mechanism of elastase, Theor. Chem. Acc. 106 (2001) 146–151;
(f) M. Topf, P. Varnai, C.J. Schofield, W.G. Richards, Molecular dynamics simulations of the acyl-enzyme and the tetrahedral intermediate in the deacylation step of serine proteases, Proteins: Struct. Funct. Genet. 47 (2002) 357–369;
(g) M. Topf, P. Varnai, W.G. Richards, Ab initio QM/MM dynamics simulation of the tetrahedral intermediate of serine proteases: insights into the active site hydrogen-bonding network, J. Am. Chem. Soc. 124 (2002) 14780–14788.

[17] S.-S. So, W.G. Richards, Application of neural networks: quantitative structure–activity relationships of the derivatives of 2,4-diamino (substituted-benzyl) pyrimidines as DHFR inhibitors, J. Med. Chem. 35 (1992) 3201–3207.

[18] D.D. Robinson, P.J. Winn, P.D. Lyne, W.G. Richards, Self-organizing molecular field analysis (SOMFA): a tool for structure–activity studies, J. Med. Chem. 42 (1999) 573–583.

[19] (a) D.D. Robinson, P.D. Lyne, W.G. Richards, Alignment of 3D-structures by the method of 2D-projections, J. Chem. Inf. Comput. Sci. 39 (1999) 594–600;
(b) D.D. Robinson, P.D. Lyne, W.G. Richards, Partial molecular alignment via local structure analysis, J. Chem. Inf. Comput. Sci. 40 (2000) 503–512.

[20] (a) M. Glick, D.D. Robinson, G.H. Grant, W.G. Richards, Identification of ligand binding sites on proteins using a multi-scale approach, J. Am. Chem. Soc. 124 (2002) 2337–2344;
(b) M. Glick, G.H. Grant, W.G. Richards, Docking of flexible molecules using multiscale ligand representations, J. Med. Chem. 45 (2002) 4639–4646.

[21] W.G. Richards, Virtual screening using GRID computing: the screensaver project, Nat. Rev. Drug Discov. 1 (2002) 551–555.