Institution: University of Birmingham

Unit of Assessment: UoA 8 - Chemistry

Title of case study: MOLPRO – A Quantum Chemistry Package

1. Summary of the impact (indicative maximum 100 words)

Work at Birmingham by Peter Knowles and Fred Manby on improving the efficiency of calculating integrals for so-called *ab initio* calculations, widely used in computational chemistry, has led to a novel, fast algorithm for the accurate calculation of molecular energies and structures. It contains a level of theory, known as MP2, widely used in modelling by industry (pharmaceutical and chemical) as well as in academia. The new local approximation of the method, DF-LMP2, was developed at Birmingham and implemented in the MOLPRO package that has been sold worldwide, generating economic impact. A major attraction of the package is that MOLPRO can do a range of calculations efficiently, MP2 being one of them.

2. Underpinning research

MOLPRO is a complete system of *ab initio* programs for molecular electronic structure calculations. As distinct from other commonly used quantum chemistry packages, the emphasis is on highly accurate computations, with extensive treatment of the electron correlation problem.

MP2 (Møller–Plesset perturbation theory to second order) is widely used to include "dynamic correlation" in the calculation of molecular energies, which needs to be performed for accurate results. The standard methods scale poorly so can only be applied to small molecules. At Birmingham, Manby (funded by a Royal Society Fellowship) and Knowles developed density-fitting methods suitable for Hartree-Fock and Kohn-Sham (density functional theory, DFT) calculations. Two papers were published together on this work (Manby and Knowles PRL (01) 87: 163001, [Ref 1] Manby, Knowles and Lloyd JCP (01) 115: 9144 [Ref 2]) as well as a paper on automatic code generation in DFT [Ref 3].

In 2001, Manby left for the University of Bristol and continued this work together with Knowles at Birmingham. They then combined it with so-called linear scaling methods that are efficient for calculating the wavefunctions of large molecules and this led to the DF-LMP2 method (Werner, Manby and Knowles JCP (03) 118: 8149. [Ref 4]). This work facilitates an approach for the modelling of larger molecules using accurate *ab initio* or quantum mechanical (QM) methodologies that can then be coupled with faster, but generally less accurate, molecular mechanical (MM) methodologies. The significance of this paper can be seen by it having >300 citations. The work was implemented in MOLPRO 2003 when it was hosted and licensed from the University of Birmingham and is an integral part of the MOLPRO package (see Section 4). The evidence for the continuing academic importance of this DF-LMP2 work (detailed in Ref 4) and its role in the MOLPRO package is evidenced by recent papers and review articles on the use of computational models to study large biological molecules:

Banas *et al* in a review on RNA catalysis in *Methods* (2009), 49, 202-216 state: *"...Another, very different and so far less popular approximation is local treatment of orbitals; for example, MP2 method with this local approximation is abbreviated as LMP2 (see, e.g. Ref [4]). Methods based on local treatment of orbitals are efficient for very large molecules*…."

Aldulaijan *et al* in studies on peptide binding interactions in *Journal of Molecular Graphics and Modelling* (2010), 29, 240 state: "….*Density fitted, local MP2 (DF-LMP2) makes use of the local nature of electron correlation to further reduce the computational resources required for MP2 calculations.[Ref 4] Importantly for the study of non-covalent interactions, this also effectively eliminates basis set superposition error (BSSE), thereby removing the need for potentially expensive counterpoise corrections*…."

A seminal review on *QM/MM Methods for Biomolecular Systems* by Senn and Thiel in *Angew. Chem. Int. Ed.* (2009), 48, 1198 states: '…*The recent development (refs including Ref 4] of linear-scaling local correlation methods (e.g., LMP2, LCCSD) has significantly extended the size of systems that can be treated with such methods, up to several tens of atoms. The superior accuracy of high-level ab initio methods can now therefore also be exploited for biomolecular QM/MM studies, certainly at the level of energy calculations at fixed geometry (i.e., single points)..."*

In 2003, Knowles left Birmingham for Cardiff University. By that time MOLPRO was already established as a licensed programme, with income having generated ca. £250k for the university between 1996 and 2003. The licensing arrangements for MOLPRO as a semi-commercial program were transferred to Cardiff upon Knowles' departure. Theoretical and computational chemistry continues to be a strength at Birmingham, now led by the groups of Johnston, Winn and Worth, with Worth and Winn current users of MOLPRO.

In 2012, an overview of the current MOLPRO package by Knowles, Manby and co-workers was published [Ref 5]. For further details on MOLPRO, see: http://www.molpro.net

As a measure of its continuing importance, the EPSRC UK National Service for Computational Chemistry Software (NSCCS) lists MOLPRO as one of 12 pieces of software that are quantum chemistry programs, with it being one of the leading choices for general purpose calculations of this type (MOs, energies, structures, etc.).

3. References to the research (indicative maximum of six references)

Papers published by the Birmingham team:

[Ref 1]. Poisson equation in the Kohn-Sham Coulomb problem. Manby, F. R.; Knowles, P. J.; PHYSICAL REVIEW LETTERS, **2001**, *87*, 163001. DOI: 10.1103/PhysRevLett.87.163001.
(40 citations)

[Ref. 2]. The Poisson equation in density fitting for the Kohn-Sham Coulomb problem. Manby, F. R.; Knowles, P. J.; Lloyd, A. W.; JOURNAL OF CHEMICAL PHYSICS, **2001**, *115*, 9144-9148. DOI: 10.1063/1.1414370.
(60 citations)

[Ref 3]. Automatic code generation in density functional theory. Strange, R.; Manby, F. R.; Knowles, P. J.; COMPUT PHYS COMMUN, **2001**, *136*, 310–318. DOI: 10.1016/S0010-4655(01)00148-5.
(11 citations)

[Ref 4]. Fast linear scaling second-order Moller-Plesset perturbation theory (MP2) using local and density fitting approximations. Werner, H. J.; Manby, F. R.; Knowles, P. J.; JOURNAL OF CHEMICAL PHYSICS, **2003**, *118*, 8149-8160. DOI: 10.1063/1.1564816.
(311 citations)

A recent review article on MOLPRO that cites Birmingham work:
[Ref 5]. Molpro: a general-purpose quantum chemistry program package. Werner, H-J; Knowles, P. J.; Knizia, G.; Manby, F. R.; Schutz, M.; WILEY INTERDISCIPLINARY REVIEWS: COMPUTATIONAL MOLECULAR SCIENCE, **2012**, *2*, 242–253.
(86 citations)

Grants:
Fred Manby: Royal Society Fellowship, 2000-2008. This was awarded to Manby while he was in Birmingham and he took it to Bristol when he moved there in April 2001.

EU – Research Training Network: THEONET II - *Theoretical Studies of Electronic and Dynamical Processes in Molecules and Clusters* (HPRN-CT-1999-00005) 2000-2004. This successful RTN, involving 11 research groups in nine countries, including the University of Birmingham from the UK, was funded by the European Commission and was aimed at extending the successes of first-principle computational chemistry. As outlined in the article by the coordinator P. Rosmos in *Molecular Physics*, 2004, 102, 2165–2166, it directly supported the training of a number of post-doctoral researchers and published more than 300 research papers.

References 1, 2 and 4 best reflect the quality of the underpinning research. A recent review from Cardiff (ref 5) cites the Birmingham ref 4 as being important for the current programme.

4. Details of the impact

The impact from MOLPRO in the REF window has been primarily economic and can be quantified through sales of MOLPRO to academia and industry throughout the REF window, as follows (data provided by Cardiff University): **£1,783,714** (January 2008 – July 2013). The main contributors to the economic impact are academic users but just over 10% have been commercial users and companies, contributing **£203,480**, as of 31 July 2013. These include organisations such as Cilag AG (a Swiss pharmaceutical firm), BASF, Hitachi, Nissan Chemical Industries, DE Shaw Research (a computational biochemistry research company) and Schrodinger (a software company).

Evidence for the impact of MOLPRO on facilitating research by commercial users includes that from BASF. BASF conducts research into fields such as theoretical chemical modelling as part of its ongoing product development process, which requires a high-performance computing (HPC) platform. A Group Leader in Quantum Chemistry at BASF and current user of MOLPRO states:

"*MOLPRO and in particular its capability for very accurate computations on large molecules, has become a valuable tool for estimating thermochemical and kinetic data for substances and reactions involved in our development of new materials and processes*."

Further evidence of the importance of MOLPRO to BASF comes from a 2009 INTEL document describing a project in which MOLPRO, as a "key application", was test run on an INTEL Xeon processor 5500 series, with the new platform driving improvements in time performance of the program.

Furthermore, a user at DE Shaw Research, has written the following related to their work on drug design:

"*The issue of force field accuracy is even more critical in our work on problems of drug design,*

which require a very accurate description of protein-small molecule interactions. Here we are taking the approach of developing new force fields from scratch, adding force field components to account for polarization, charge penetration, and other physical effects not typically included in existing biomolecular models. We have used MOLPRO extensively to generate the data necessary for fitting these more complex biomolecular and small molecule force fields. The wide variety of methods available in, and performance and flexibility of, the MOLPRO software make it key to our force field development efforts in general, and to the development of improved force fields for small molecules in particular. We expect these projects - in which MOLPRO plays an important role - to help foster collaborations with industry in the area of drug development."

The role of the Birmingham-based research to this impact is shown by its important contribution to the current MOLPRO package, as evidenced as follows:

(i) UoB research [Refs 1, 3 and 4] being highlighted in the recent review article on Molpro [Ref 5], in particular DF-LMP2, which is used to "*speed up the treatment of exchange, using localized orbitals, and local subsets of fitting functions for each orbital product. In large molecules, this can significantly increase efficiency without much affecting accuracy*".

(ii) UoB research being cited in the current version of the Molpro manual (see www.molpro.net) where it is written: "…*The heart of the program consists of the multiconfiguration SCF, multireference CI, and coupled cluster routines, and these are accompanied by a full set of supporting features. The package comprises…. local density fitting methods, as described in [Ref 4]…*". Also it is written: *"…Depending on which programs are used, the following references should be cited….Density fitting methods: DFT, Poisson fitting: [Ref 2]… DF-MP2, DF-LMP2: [Ref 4]…"*

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Corroborating email from Peter Knowles stating the current income from Molpro in the REF window, dated 4th April 2013.
2. Corroborating emails and spreadsheet from administrator at Cardiff University detailing contribution from non-academic licence holders
3. Molpro users manual, Version 2012.1
4. Corroborating email from Principal Scientist, Group Leader Quantum Chemistry, BASF, Ludwigshafen, Germany, dated 8th October 2013 and commercial document from INTEL, *Blueprint for High Performance.*
5. Corroborating email from DE Shaw Research, dated 11th October 2013

Copies of all these sources are held by the University