Institution: University College London (UCL)

Unit of Assessment: 8 – Chemistry

Title of case study: Abraham solvation parameter approach benefiting the chemical industries

1. Summary of the impact

The Abraham solvation parameter approach developed at UCL has become integral to the work carried out by drug discovery teams at [text removed for publication] and other major pharmaceutical companies, as well as research and development groups at international chemical companies including Syngenta and [text removed for publication]. It enables chemists to predict physicochemical and biochemical properties of chemicals, including drugs and agrochemicals, rapidly and efficiently, without the need to conduct time-consuming experiments. The method helps drug discovery teams to identify and optimise the most promising compounds, and often results in fewer compounds being made before a candidate is selected, saving time and resources. The approach has been integrated into software used for drug discovery [text removed for publication].

2. Underpinning research

Solvation processes have been a subject of interest for many decades, because dramatic changes in reaction rates can be observed in different solvents. The Abraham solvation parameter approach uses linear free energy relationships (LFERs) to describe solvent–solute interactions. It revolves around a set of Abraham descriptors, which characterise the solute and are part of the LFERs. The approach enables systems and solutes to be characterised using multiple linear regression analysis, and in turn predicts solvation properties (such as logP) without the need for an actual experiment. The Abraham approach was first developed within the Department of Chemistry at UCL before the REF research period; however, its application by and subsequent impact on the pharmaceutical, agri-chemical and chemical industries in recent years are underpinned by the department's establishment of the approach and continued work in this area since 1993.

Since 1993, the Abraham group at UCL has published more than 300 papers in peer-reviewed journals, detailing the underlying research, application of the method and numerous enhancements to the approach. Key findings documented in these publications include a method (developed together with the Science Development Group at Glaxo Wellcome R&D) for calculating Abraham descriptors from molecular fragment structures [1], which allows drug discovery teams to rapidly assess the solvation properties of drug candidates that have not yet been synthesised; an extension of the Abraham approach to allow for ionic solutes, since many drug candidate molecules are ionised [2]; and the determination (in work conducted with researchers from Glaxo Wellcome, Roche Products and Cardiff University) of solvation equations (LFERs) that characterise important biological processes for drug delivery, such as skin permeation, blood-brain distribution, and intestinal absorption [3], allowing drug discovery teams to predict these properties for drug candidates rapidly.

In the late 1990s, this UCL group also collaborated with teams at Glaxo Wellcome Medicines Research Centre [4] and Pfizer's Central Research Division [5] to develop high-throughput reversed-phase high-performance liquid chromatography (RP-HPLC) methods for determining lipophilicity (expressed as the chromatographic hydrophobicity index, CHI, and ElogP/ElogD respectively), an important property in drug discovery. These methods were developed to replace the time-consuming traditional determination of lipophilicity from a measurement of the partition of molecules in the octanol–water system. Advantages of these newer methods include increased accuracy and rapid measurements. The Abraham solvation parameter approach was crucial in validating and refining these faster methods, and was used to confirm that both CHI and ElogP encode the same information as other measures of lipophilicity. Further work, in the early 2000s – again in collaboration with Glaxo Wellcome – led to the development of biomimetic HPLC systems that measure human serum albumin binding (HSA) and immobilised artificial membrane interaction (CHI IAM) [6], enabling chemists to easily assess a drug candidate's protein binding and membrane affinity – both important properties for drug discovery.

In 2004, the Abraham group concluded that for processes that entail transfer of a solute from one

phase to another, no more than five or six solute descriptors are required to provide a reasonably accurate analysis of a given process [7]. This work has been cited over 300 times since, contributing to the development of *ab initio* and empirical software for predicting solvation energies and profiling of chemicals used for a number of applications. In summary, this UCL research group and its collaborators have made significant progress in defining transport-related or dependent processes for a diverse set of chemicals, utilising only a few descriptors.

Key UCL researchers: Michael Abraham (Honorary Reader 1994-2002; Honorary Professor 2002-present) and the following Postdoctoral Research Fellows: Chau My Du (1996-1998), James Platts (1997-1999), Andreas Zissimos (2000-2003) and Yuan Zhao (1999-2001 and 2003-2006).

3. References to the research

[1] Estimation of molecular linear free energy relation descriptors using a group contribution approach, J.A. Platts, D. Butina, M.H. Abraham and A. Hersey, *J. Chem. Inf. Comput. Sci.*, 39, 835-845 (1999) doi:10.1021/ci980339t

[2] Determination of solvation descriptors for ionic species: Hydrogen bond acidity and basicity, M.H. Abraham and Y.H. Zhao, *J. Org. Chem.*, 69, 4677-4685 (2004) doi:10.1021/jo049766y

[3] Evaluation of human intestinal absorption data and subsequent derivation of a quantitative structure—activity relationship (QSAR) with the Abraham descriptors, Y.H. Zhao, J. Le, M.H. Abraham, A. Hersey, P.J. Eddershaw, C.N. Luscombe, D. Boutina, G. Beck, B. Sherborne, I. Cooper and J.A. Platts, *J. Pharm. Sci.*, 90, 749-784 (2001) doi:10.1002/jps.1031

[4] Rapid gradient RP-HPLC method for lipophilicity determination: A solvation equation based comparison with isocratic methods, C. My Du, K. Valko, C. Bevan, D. Reynolds and M.H. Abraham, *Anal. Chem.*, 70, 4228-4234 (1998) doi:10.1021/ac980435t

[5] ElogP_{oct}: A tool for lipophilicity determination in drug discovery, F. Lombardo, M.Y. Shalaeva, K.A. Tupper, F. Gao and M.H. Abraham, *J. Med. Chem.*, 43, 2922-2928 (2000) doi:10/cfqkpq

[6] Rapid-gradient HPLC method for measuring drug interactions with immobilized artificial membrane: Comparison with other lipophilicity measures, K. Valko, C. My Du, C.D. Bevan, D.P. Reynolds and M.H. Abraham, *J. Pharm. Sci.*, 89, 1085-1096 (2000) – PDF available on request

[7] Determination of sets of solute descriptors from chromatographic measurements, M.H. Abraham, A. Ibrahim and A.M. Zissimos, *J. Chromatogr. A*, 1037, 29-47 (2004) doi:10/bzn5hz

References [1], [2] and [3] best indicate the quality of the underpinning research.

4. Details of the impact

The Abraham solvation model is a well-known and well-used equation for the description of relationships between structure and both physicochemical and biochemical properties, which can be applied to biological, chromatographic and environmental partition systems. As such, Abraham descriptors and the Abraham solvation parameter approach are widely used in the chemical industries, where they provide a rapid and efficient way to compare and characterise partition systems and solutes, and allow the determination of unknown properties of solutes without conducting an actual experiment or even synthesising the molecule. In the pharmaceutical industry, the model is used for predicting the pharmacokinetics (absorption, distribution, metabolism, excretion, and toxicity; or ADMET) of chemical agents, which is vital in determining their performance and pharmacological activity as drugs. Meanwhile, agri-businesses use the method to create bioavailability profiles for agrochemicals, which informs not only on efficacy but also the fate of the chemicals in terms of environmental risk assessment.

In recent years, commercial, open source and “in-house” computational modelling software has been developed and made available to users worldwide based upon the Abraham solvation model, in order to provide a framework with which to analyse, rationalise and quantify problems such as solubility and partitioning. For example, the Absolv software is used by chemists to calculate various solvation-associated properties from equations (LFERs) involving transfer from the gas phase to a condensed phase or between different condensed phases, and to carry out structure-based prediction of the solvation parameters required for those calculations [A]. Absolv was first commercialised by Sirius, then later by Pharma Algorithms, who in 2009 partnered with

ACD/Labs; in 2011, the latter launched the "Percepta Platform", which includes the Absolv prediction module. From a commercial perspective, Absolv has been, and continues to be, a very important component in ADMET and physicochemical property prediction. As such, Percepta is recognised as a core component of the drug discovery toolkit and is highly valued by research institutions and industrial groups worldwide [A]. In many drug discovery teams at multinational pharmaceutical companies – [text removed for publication] – the use of such software, and thus the Abraham model, has become a fundamental part of the way that they understand and optimise drug candidate solubility and partitioning. It has also become fundamental to how they establish vital parameters for determining whether a candidate can be formulated and delivered in sufficient quantities to be effective as a drug. The alternative approach is simply calculating the number of hydrogen-bond donor and acceptor groups and the size of the molecules, which often gives inferior information to the Abraham approach. The useful information provided by the Abraham approach means that scientists need to make fewer compounds before a candidate is selected and do not often make the wrong compounds [text removed for publication].

[text removed for publication]

In 2010, a team from Pfizer developed an *in silico* model of rat biliary excretion – an important property in drug discovery – with the help of the Abraham approach [D]. When Sanofi sought an improvement in the solubility of the main compound used in an oncology program in 2008, commercial software proved unsatisfactory at predicting more soluble compounds; however, the team was able to build their own local models using Abraham descriptors. The model built at pH = 4 was a success, achieving an 82% correct prediction rate of the solubility [text removed for publication] [E]. The results obtained from the work in these and other examples have made a significant contribution to internal research at pharmaceutical companies and have helped to streamline discovery efforts over the last five years.

Outside of the pharmaceutical industry, physical chemists supporting Syngenta, one of the world's leading bioscience companies, measure a diverse range of organic/water partition coefficients to enable the experimental determination of Abraham descriptors and prediction of difficult-to-measure properties such as water/air, soil/water and plant-related partitioning processes from LFERs. A significant benefit of this work to Syngenta is that it offers its scientists an alternative way of thinking about and addressing chemical design issues related to expression of activity and environmental fate for agrochemicals, beyond conventional physical chemical properties [F].

[text removed for publication]

The RP-HPLC methods for determining lipophilicity expressed as CHI and *E*log*P*/*E*log*D*, which were co-developed at UCL, are now in routine use within drug discovery at [text removed for publication], Pfizer, Merck and other drug discovery companies. These techniques allow scientists to measure more quickly and accurately the lipophilicities of potential drug candidates, which helps them assess whether the candidates would be suitable for use *in vivo*. The high-throughput HPLC methods are also useful when scientists wish to modify the lipophilicity (alongside other physicochemical properties) of drug candidates systematically in order to optimise a series and find the most promising compound to progress to further testing. Most uses of the methods are confidential; however, there are a few published examples that demonstrate how this method has helped drug discovery teams to optimise series of compounds. These include novel GPR119 agonists (for a potential treatment for type 2 diabetes) in 2011 and ghrelin receptor agonists (for the relief of symptoms of gastroparesis in both type 1 and type 2 diabetes) in 2012 by drug discovery teams at Pfizer [H]; and novel cannabinoid CB2 receptor agonists and novel TRPV1 antagonists (both investigated as potential treatments of pain) in 2011 by teams at Merck and MSD respectively [I].

Additionally, the biomimetic HPLC systems are also now in use at GSK [text removed for publication] and other companies. They provide scientists with fast and automated methods for modelling the membrane interaction and protein binding of drug candidates. Again, most uses are confidential; however, a few examples of impacts on drug discovery programs have been published. These include the use of the CHI IAM and HSA biomimetic systems, as well as CHI, by a GSK team in 2012 in a successful attempt to find novel antimicrobially inactive anti-inflammatory macrolides; and the use of the two biomimetic systems by a Novartis team in 2011

to confirm the superior physicochemical properties of the useful 2-amino-5-*tert*-butylpyridine fragment compared to the currently used fragment [J].

5. Sources to corroborate the impact

[A] Supporting statement from Academic Account Manager at ACD/Labs, and a particular example cited on the ACD/Labs website: http://www.acdlabs.com/download/docs/poster_absolv_syngenta.pdf – corroborates the use and value of the Absolv software. The statement is available on request.

[text removed for publication]

[D] Structure-pharmacokinetic relationship of *in vivo* rat biliary excretion, Y. Chen et al., *Biopharm. Drug Dispos.*, 31, 82-90 (2010) doi:10/bppvcq – corroborates the use of the Abraham approach in the development of the *in silico* model at Pfizer.

[E] Supporting statement from a scientist in the Molecular Modeling Team, Sanofi – corroborates that Sanofi built a successful local model using Abraham descriptors. Available on request.

[F] Supporting statement from former (left in August 2012) Senior Physical Chemistry Consultant at Syngenta – corroborates the impact of the Abraham approach on agrochemical research at Syngenta. Available on request.

[text removed for publication]

[H] V. Mascitti et al., *Bioorg. Med. Chem. Lett.*, 21, 1306-1309 (2011) doi:10/b4ss3x; and D.W. Kung et al., *Bioorg. Med. Chem. Lett.*, 22, 4281-4287 (2012) doi:10/pvd – corroborate Pfizer's use of the ElogP/ElogD method to optimise series of compounds.

[I] M. van der Stelt et al., *J. Med. Chem.*, 54, 7350-7362 (2011) doi:10/ckp8z7; and P. Ratcliffe et al., *Bioorg. Med. Chem. Lett.*, 21, 2559-2563 (2011) doi:10/dgzvkj – corroborate Merck and MSD's use of the ElogP/ElogD method to optimise series of compounds.

[J] M. Bosnar et al., *J. Med. Chem.*, 55, 6111-6123 (2012) doi:10/pvg; and C.G. Thomson et al., *Bioorg. Med. Chem. Lett.*, 21, 4281-4283 (2012) doi:10/fwts42 – corroborate GSK and Novartis' use of CHI IAM and HSA biomimetic systems.