Institution: University of Oxford

Unit of Assessment: 8 Chemistry

Title of case study: UOA08-09: Computational chemistry to facilitate drug development

1. Summary of the impact

Since 2008, pioneering contributions to the field of computational chemistry for drug discovery have been made by InhibOx Ltd., a spin-out company based on the research of Graham Richards and co-workers at the University of Oxford. InhibOx launched Scopius, the world's largest searchable virtual database of small-molecules (>112 million compounds) and pioneered the use of cloud computing for large-scale molecular modelling. The key impact for customers of InhibOx has been the reduced costs in identifying molecular leads for new drugs. InhibOx's work has helped to open up early stages of drug development to smaller companies; 75% of InhibOx's clients are SMEs. Since 2008, InhibOx has received £ 2.8M in income and investment.

2. Underpinning research

A common problem in small-molecule drug discovery is identifying useful hits and leads. Researchers have a difficult task in selecting compounds with therapeutic potential from the billions of possible starting points. Improving the selection of which molecules to work with is a key part of improving return on investment from early stage R&D spend, especially for SME companies. Computer-based screening is a potentially valuable tool for predicting which molecules warrant further investigation. Drug companies hold internal databases which may hold tens of millions of real or virtual molecules; however:

- they are often narrowly concentrated around that company's areas of expertise;
- it can take 2-3 weeks to search the database (depending on computer power available) to predict whether a molecule has potential for binding to a particular target;
- developing a database in house is a specialised task and may be too expensive for small organisations (typically requiring two full-time staff for 5 years, or around £400,000).

With these limitations in mind, in 2001, a project known as Screensaver Lifesaver led by Graham Richards set out to build a database of millions of drug-like molecules. The database has two sections: CSPACE, all molecules available commercially and VSPACE, virtual molecules but with known synthetic route. Software developed by the Richards group used the idle processing power of volunteers' computers around the globe to screen molecules and assess whether they are candidate inhibitors of human proteins for cancer treatment. The concept was simple: ruling out molecules that were unlikely to be pharmaceutically beneficial meant that resources could be efficiently concentrated on a smaller number of more promising molecules. Screensaver Lifesaver was an early example of a computational chemistry project of this kind and remains the largest such experiment ever conducted. It was very successful, with over 3.5 million personal computers in more than 200 countries used to screen 3.5 billion separate molecules for their inhibitory potential. The project produced a wealth of potential cancer drug leads for 12 target proteins and, importantly, revealed for the first time the viability of virtual screening using a grid of PCs [1]. Screensaver Lifesaver led directly to the spin-out of the company InhibOx Ltd in late 2001, based on the Richards-group research.

Subsequent research focused on improving effectiveness in searching the billions of *virtually accessible* compounds. In particular, this focused on enabling searches with virtual molecules which 'look like' known drug candidates (e.g. a natural drug or an existing commercial synthetic compound). The Richards Group made two important advances:

- Novel ultrafast computing techniques were needed to help whittle down the millions of molecular options more quickly. Techniques were developed to search databases efficiently for molecules of similar shape [2, 3]. In particular they used an approach based on the moments of distance distributions which improved the speed of molecular-shape recognition by at least 3 orders of magnitude. A prospective screening application of the method to identify novel inhibitors of arylamine N-acetyltransferases had a 40% hit rate (ie. active above a critical limit) and was amongst the most cited articles in the Journal of the Royal Society Interface in 2010 [4]. In order to be useful as an antagonist or agonist of a target, a small molecule must bind to a specific site on the target. The method for

identification of this site was the subject of a patent granted to Richards in 2007 [5].

- Virtual screening requires the search procedure to group molecules with strong resemblances in terms of electrostatics and lipophilicity as well as shape. In 2010 - 2011 the Richards Group developed and published innovative solutions to this problem [6]. At the time, the most widely-used methods for this type of virtual screening involved a molecular alignment step that was computationally intensive and thus provided a constraint on the size of database that could be searched. The new methods developed an alignment-free approach that was orders of magnitude faster, while maintaining accuracy. By introducing partial charge information as a 4th dimension the electrostatics was handled very efficiently.

These key advances, together with additional developments at InhibOx allowing chirality to be incorporated into molecular similarity searching (i.e. distinguishing enantiomers), made it possible to perform extremely fast searches of a database of billions of compounds for molecular similarity incorporating shape, chirality, electrostatics and lipophilicity, all critical components when determining potential drug molecules.

Richards was a member of the academic staff at Oxford University until his retirement in Dec 2007; the research was continued in the UOA by two University-employed post-doctoral researchers, Ballester and Moretti, in collaboration with Richards (at InhibOx since 2008).

3. References to the research

Asterisked outputs denote best indicators of quality; University of Oxford authors are underlined.

1. *Richards, W. G., Virtual screening using grid computing: the screensaver project. Nature Reviews Drug Discovery, 1 (7), 551-5, 2002. DOI:10.1038/nrd841. *The article describes how massively distributed computing using screensavers has allowed databases of billions of compounds to be screened against protein targets in a matter of days.*
2. Ballester, P. J.; Richards, W. G., Ultrafast shape recognition for similarity search in molecular databases. Proceedings of the Royal Society A: Mathematical Physical and Engineering Sciences 463 (2081), 1307-1321, 2007. DOI: 10.1098/rspa.2007.1823
3. Ballester, P. J.; Finn, P. W.; Richards, W. G., Ultrafast shape recognition: Evaluating a new ligand-based virtual screening technology. Journal of Molecular Graphics & Modelling 27 (7), 836-845, 2009. DOI: 10.1016/j.jmgm.2009.01.001
4. *Ballester, P. J.; Westwood, I.; Laurieri, N.; Sim, E., Richards, W.G. Prospective virtual screening with Ultrafast Shape Recognition: the identification of novel inhibitors of arylamine N-acetyltransferases. Journal of the Royal Society Interface 7 (43), 335-342, 2010. DOI: 10.1098/rsif.2009.0170. *A virtual screening technique (USR) is described based on ligand-receptor shape complementarity and is applied to discover a novel inhibitor by screening almost 700 million molecular conformers*.
5. Richards, W. G., Patent no 03700921.4-2201-GB0300241 (2007); Method for binding site identification using a multi-scale approach. https://www.google.com/patents/EP1468392B1
6. *Armstrong, M. S.; Morris, G. M.; Finn, P. W.; Sharma, R.; Moretti, L.; Cooper, R. I.; Richards, W. G., ElectroShape: fast molecular similarity calculations incorporating shape, chirality and electrostatics. Journal of Computer Aided Molecular Design 24 (9), 789-801, 2010. DOI: 10.1007/s10822-010-9374-0. *The paper describes a novel ligand-based virtual screening method that combines shape and electrostatic information into a single unified framework*.

4. Details of the impact

Since 2008, InhibOx Ltd. has made important contributions to computational chemistry in the field of drug discovery. Taking advantage of cloud computing techniques, the natural successor to Screensaver Lifesaver, to increase the scale and speed of its virtual screening methods, InhibOx has helped to drive down costs of searching for leads in a way that has enabled much smaller companies to enter the field of drug development. InhibOx's key product is the drug database Scopius.

After spin-out in 2001, Isis Innovation Ltd. (the technology transfer arm of the University of Oxford)

exclusively licensed the software technology developed by the Richards group to InhibOx. From 2004 to 2008, a new round of investment enabled InhibOx to develop initial versions of the Scopius database and novel software methods, informed by the lessons learned regarding the issues of large scale database construction obtained with Screensaver; in this period the level of commercial activity was minimal. At the start of 2008, Scopius consisted of approximately 3 million molecules; by the end of the assessment period it contained >112 million molecules, making it the world's largest high-quality database of candidate compounds, either commercially available or synthesisable in a few steps. InhibOx has also produced an array of more focused databases for specialist applications. Since 2008, InhibOx has used ElectroShape, the ultrafast technique invented by the Richards Group which incorporates chiral shape recognition, to further develop the search software. InhibOx's CEO states that "*InhibOx has developed a comprehensive array of computer-aided drug design technologies that helped to advance real-world commercial drug discovery projects. The contribution of Richards has been fundamental to this achievement both through the development of new science and his experience in bridging the gap between basic and applied research.*" [7]

Rather than developing a software product to sell, InhibOx has focussed on running targeted database searches for customers, producing lists of potential molecules that they can use as drug leads. This has had a particular impact for SMEs. In some fields of drug discovery, it can cost billions to bring a drug to market, including an estimated £ 400,000 for a company to build its own molecule database in order to find the right molecules to experiment with, and typically >£ 50M - 100M to develop compounds suitable for use in clinical trials. These high costs have hindered the pre-clinical trial phases of drug development, restricting them to very large, well-financed companies. InhibOx has enabled increased competition in early-stage drug R&D by making compound searching more affordable for SMEs; a target search of molecules using Scopius costs around £ 20,000 – a fraction of what it would cost a small company to build its own database. InhibOx's client base demonstrates the way in which it has helped to open up early-stage development to smaller companies: 75% of its clients are SMEs, e.g. DormaTarg, Mission Therapeutics, Lauras and Cephalon, and 25% are corporates, e.g. Bristol Myers Squibb and Colgate Palmolive. This reflects and supports a shift in the way the market operates; big pharma will in some cases buy drug leads from small companies rather than develop leads themselves. Lauras' Vice President for R&D commented that InhibOx has *helped redesign the company's drug targeting programmes and suggested new lines of derivatisation that have delivered compounds with the properties they wanted* [8]. Likewise DormaTarg worked with InhibOx on *in silico* screening, testing several of the hits predicted by InhibOx, and finding that several showed the kind of novel activity they were seeking [9].

In 2010 InhibOx designed a programme to develop Tumour Necrosis Factor-α Converting Enzyme inhibitors for inflammatory disease starting from a non-selective weak lead molecule. Using InhibOx structure-based design technology and project management expertise, a cost-effective semi-virtual discovery project delivered a novel compound series and optimised a lead candidate requiring the synthesis of only 33 compounds within a 6-month timescale. The series (based on bicyclosulfonyl acid compounds) was patented by InhibOx [10], and the programme was sold in December 2010 to a large EU-based pharmaceutical company. This is an example of InhibOx providing the initial screening of compounds that are now being taken forward in further research.

More recently InhibOx has taken advantage of the experience developed in its pioneering use of cloud computing for large-scale molecular modelling. The availability of new and powerful cloud computing services which can be leveraged on demand has enabled InhibOx to provide large-scale virtual screening throughput at low cost for specific purposes. In 2012, the company created a corporate virtual library for a major corporation based on their available chemistry. The result contained over 28 million drug-like molecules and was completed in just over 4 days using cloud computing facilities from Amazon Web Services (AWS). The computational cluster constructed would have ranked the project in the Top 500 Supercomputers, with a speed to 240 TFlop/s.; constructing this level of hardware infrastructure in-house would have cost InhibOx around $ 200k, so the use of AWS led to considerable cost savings. This work was highlighted in a case study on the AWS web site [11]. Company expertise in this area is reflected in a recent review by InhibOx

authors analysing the applications of cloud computing to molecular modelling [12].

InhibOx has made a conscious decision to remain focussed and concentrate on core areas of expertise, a strategy which has helped it to weather the upheaval in the pharmaceutical industry while many larger biotechs have gone out of business. It has maintained steady business during the impact period; income and investment since 2008 has totalled around £ 2.8M, including sales revenue of £ 250,000 in 2012. It is an export-led company with 60% of sales in the US, 25% in Europe and 15% within the UK [7]. Since 2008, it has established an additional office in Princeton, USA and since 2010 developed commercial partnerships with the Cambridge Crystallographic Data Centre, Intelligensys, COSMIC Discoveries and Molport [13]. These companies provide complementary expertise in virtual screening, computer-aided drug discovery and chemical compound manufacture. The Scientific Director of Intelligensys has outlined the benefits to them (and to drug discovery generally) of the partnership: '*We have seen, over many years, too many seemingly promising lead compounds fail to make it through preclinical tests. This has been expensive to the industry and is largely avoidable. This collaboration is delivering the capability to stem these losses and deliver much more cost-effective drug discovery as a result*.' [14].

InhibOx's innovation, underpinned by the Richards' Group work, has led to it being selected as a partner on several high-profile EU projects such as a recent FP7 framework grant worth € 1M to InhibOx [15], and its innovation/international excellence was recognised in May 2011 with InhibOx being short listed for the prestigious Red Herring 100 Award - a mark of distinction for identifying promising new companies and entrepreneurs. Red Herring is a global media company with a focus on technology innovation [16].

5. Sources to corroborate the impact

7. The CEO of InhibOx can corroborate the benefits to the company of the Richards Group research, details relating to the Scopius database, and income, investment and sales figures.
8. http://www.inhibox.com/node/23
   Quote on the InhibOx website from the VP for R&D at Lauras AS, corroborating the fact that InhibOx's *in silico* screening has helped Lauras advance its drug discovery pipeline.
9. http://www.inhibox.com/dormatarg-endorses-inhibox
   Quote on the InhibOx website from the President and CSO of DormaTarg, Inc., corroborating the fact that InhibOx's *in silico* screening has helped DormaTarg's drug discovery programme.
10. http://www.google.com/patents/US20100311741
    Patent number PCT/GB2008/001683 relating to the TACE inhibitor work at InhibOx.
11. http://aws.amazon.com/solutions/case-studies/inhibox/ InhibOx case study on the AWS website, corroborating creation of a corporate virtual library using cloud computing.
12. The emerging role of cloud computing in molecular modelling. Ebejer JP, Fulle S, Morris GM, Finn PW. J Mol Graph Model. 44:177-87 (2013). Review with InhibOx authors analysing the applications of cloud computing to molecular modelling, corroborating InhibOx's expertise in this area. http://www.sciencedirect.com/science/article/pii/S1093326313001137
13. http://www.inhibox.com/commercial-partners
    InhibOx webpage confirming commercial partners.
14. http://www.inhibox.com/inhibox-intelligensys-partnership
    Quote on the InhibOx website from the Scientific Director of Intelligensys, corroborating the benefits to them of the partnership with InhibOx.
15. http://www.inhibox.com/node/92
    23 July 2013 announcement on the InhibOx website, confirming the FP7 framework grant.
16. http://www.redherring.com/events/red-herring-europe/2011-red-herring-europe-finalists/
    Red Herring website, confirming InhibOx as a 2011 finalist for the Red Herring 100 Award.