Institution: Newcastle University

Unit of Assessment: 11 Computer Science and Informatics

Title of case study: Novel computational approaches to discover medicines

1. Summary of the impact

New computational analysis methods have been developed to make drug discovery and toxicological analysis much more efficient. These methods have been patented (UK, EU, US) and are employed in e-Therapeutics Plc, a computational drug discovery spin-off company of the University. The company, introduced to the Alternative Investment Market of the London Stock Exchange in 2007, is now the eighth largest company (by market capitalisation - £92.7M (26/6/2013)) in the pharma/biotech sector. The underlying technologies derive from network analysis and workflow research at the University. The company has an anti-cancer drug (ETS2101) in phase I clinical trials in the UK and the US, and an anti-depression drug (ETS6103) planned to enter phase IIb clinical trial shortly. The beneficiaries of this research are e-Therapeutics directly, other drug companies, and ultimately patients.

2. Underpinning research

The case study rests on contributions to *network analysis and application* led by Peter Andras, and to *workflow development* led by Anil Wipat. Through collaboration with the Faculty of Medical Sciences at Newcastle University, the research was applied to the field of n*etwork pharmacology*. The key computer science researchers are given below. Andras and Wipat are the lead authors on the respective papers.

Andras, P. (*Lecturer/Reader in Complex Systems: 2002-present*)
Research associates:
Idowu, O. C. (*2003-2005*), Lynden, S. J. (*2003-2004*) & Periorellis, P. (*2000-2004*)

Wipat, A. *(Lecturer/Reader/Professor of Integrative Bioinformatics: 2001- present)*
Lee, P. A. (*Professor/ Emeritus Professor, Computing Science: 1986-2013*)
Lord, P. *(Lecturer, Computing Science: 2005 - present)*
Wilkinson, D. *(Lecturer/ Senior Lecturer/ Professor of Stochastic Modelling: 1996 - present)*
Research Associates:
Flanagan, K. (*2006-present*); Pocock, M. (*2005-2010*); Sun, Y. (*2003-2006*); Wiele, J. (*2009-2011*); Worthington, J. T. (*2005-2006*)

Network algorithms

Complex networks, whether biological or artificial, can be classified on the basis of their structure which is important as it can influence the robustness of the underlying system (one important aspect, for example, is the pattern of distribution of connections between nodes).The networks that control processes in health and disease are scale-free networks most of whose nodes can be bypassed but with a few nodes that receive many connections and make the whole network vulnerable when they are disrupted. Within the *eXSys* project [G1], Andras, working with colleagues, developed and applied algorithms to analyse the structure of the network of protein interactions of parasitic bacteria and healthy and diseased host cells [P1, P2, P4]. The algorithms were applied to the identification of known protein targets of antibiotics but in the context of their involvement in key structural elements of the graphs that represent bacterial cells as protein interaction networks (e.g. penicillin-binding proteins as bottlenecks, ribosomal proteins as hubs). Further algorithms are then used to identify an optimal set of points to target and disrupt the disease process. Finally, an existing drug candidate that interacts selectively with the target proteins is chosen. These algorithms are embodied in a workflow, also developed during the research, to create a pipeline for candidate evaluation. e-Therapeutics, a university spin-out, was

established to commercialise these developments.

Workflow

Wipat and colleagues worked with e-Therapeutics under a *KTP* project [G2], the *MicroBase* project [G3] and the *SABRE Ondex* project [G4]. Microbase is a high throughput analysis system that exploits highly parallel grid and cloud environments for complex and computational intensive bioinformatics tasks. The system was used to automatically carry out "all-against-all" protein sequence similarity comparisons to help build the protein interaction networks, and to produce predictions about likely novel antibiotic targets in bacteria for the discovery of the new targets. The Microbase system was one of the first bioinformatics pipelines to facilitate a rapid all-against-all comparison of large numbers protein sequences on the Grid [P4]. This system was successfully deployed and the resulting protein sequence similarity data was used to develop e-Therapeutics networks.

Wipat and colleagues also developed integrated networks for e-Therapeutics within the Ondex project (http://www.ondex.org/) from 2008-2009 leading to a joint journal publication [P3]. Multiple data sources were used to produce individual graphs which were then combined to produce a complex graph, providing a richer view of a drug, its properties and its interactions. The Ondex system is one of the few systems that can perform a full graph-based analysis with sufficient semantic rigour to allow computational reasoning for new drug targets. Ondex was installed in the company and its employees trained to use it.

3. References to the research

[P1] Idowu, O.C., Lynden, S.J., Young, M. P. and Andras, P. (2004). "*Bacillus subtilis Protein Interaction Network Analysis".* In Proceedings of IEEE Computational Systems Bioinformatics Conference, pp. 623-625.

[P2] Periorellis, P., Idowu, O.C., Lynden, S. J., Young, M. P., Andras, P. (2004). "*Dealing with complex networks of protein interactions: A security measure*". In Proceedings of 9th IEEE International Conference on Engineering of Complex Systems (ICECCS), pp.29-36. (UK Patent GB 2,411,268;) [*Key ref.]

[P3] Cockell, S. J., Weile, J., Lord, P., Wipat, C., Andriychenko, D., Pocock, M., Wilkinson, D., Young, M. P. and Wipat, A. (2010). "*An integrated dataset for in silico drug discovery*". Journal of Integrative Bioinformatics, 7(3): 116. [*Key ref.]

[P4] Sun, Y., Wipat, A., Pocock, M., Lee, P. A., Flanagan, K. and Worthington, J. T. (2007). "*Exploring microbial genome sequences to identify protein families on the grid*". IEEE Transactions on Information Technology in Biomedicine, 11(4) pp. 435-442. [*Key ref.]

Key Research Grants:

[G1] EPSRC *eXSys project*, 01/01/2003 - 01/01/2005, £179,680. PI: Watson, Co-I: Andras, Young

[G2] *KTP project*, 01/01/2006 – 30/06/2006, £60,000. Andras, Wipat.

[G3] *Development of a Data Base for Microbial Genome Comparison (MicroBase)* [11/3/2003 - 13/5/2007] £166,696. PI: Wipat.

[G4] BBSRC BBS/B/13640, BB/F006039/1 *SABRE ONDEX,* 01/04/08 - 31/10/11, £625,164. PI: Wipat.

4. Details of the impact

The productivity of research and development spending by the pharmaceutical industry has fallen dramatically over recent decades, and it may be that the existing method of reductionist drug discovery – identifying one 'target' protein and then finding a drug that binds to it – is not suitable for treating complex diseases such as depression and Alzheimer's disease. This reduction in output has triggered the pharmaceutical industry to seek to *reposition* existing (or somewhat modified) drugs using a network pharmacology approach [E1]. Industry analysts have commented favourably on this new way of finding medicines. In addition, new drugs based on new chemistry

are extremely expensive to develop (recent figures from the Office of Health Economics estimate an average cost of £1.2 billion [E2]), many taking 10-15 years to reach the market. Most candidates fail before or during clinical trials, a huge burden for the companies concerned.

The *repositioning* approach to discovering new treatments aims to find new uses for drugs already on the market or for drug candidates for which there is substantial safety data, obviating the requirement for many of the pre-approval tests required of completely new therapeutic compounds, since the compound has already been validated as safe for its original purpose. A number of such compounds have been identified providentially, but *network pharmacology* provides a systematic approach to identify new targets and diseases for existing drugs and to identify drugs that are more effective when used in combination than when either is used individually. The research from Newcastle University's School of Computing Science has been applied to this field and underpins this case study.

Route to impact

In 2002 Malcolm Young and Peter Andras founded e-Therapeutics (www.etherapeutics.co.uk), a medicines discovery company spun out from their research at Newcastle University. The company's new and unique approach, which involves network pharmacology, is protected by six patents that contain more than 200 separate claims of invention and granted in Europe and the USA [E3].

A key feature of the company's method is that it finds the crucial few proteins that must be targeted to disrupt the disease process; it therefore follows that a drug candidate which interacts selectively with those target proteins must be identified. The company initially sought candidates from among known molecules, using its approach to identify those suitable for 'repositioning' into the disease in question. Such molecules often have safety data that can support rapid progress into clinical trials and typically have well-characterised interactions with human proteins.

In September 2011 the Wall Street Journal published an article titled "*Drugs that are as smart as our diseases"* [E4] in which the limitations of the old approaches to drug discovery and the merits of e-Therapeutics' implementation of network pharmacology are described.

Drugs in clinical trials

Two drugs, both re-positioned, are currently being evaluated in clinical trials. The company's anti-cancer drug candidate, ETS2101, is in phase I clinical trials [E5] in the US and UK. ETS2101 is dexanabinol, a compound that was thought to have a neuroprotective function after brain injury, but that was shown in a phase III trial to be safe but ineffective for this indication (Maas et al., Lancet Neurology 2006. PMID: 1636102). Network modelling predicted an anti-apoptotic action. One trial involves patients with primary or secondary brain cancer (started June 2012; key data on safety and dosing expected Q4 2013) and the other involves patients with solid tumours (started September 2012; key data expected Q1 2014) [E5]. By May 2013, a total of 17 patients had been treated in the two phase I trials. No patient had experienced serious adverse events related to treatment (although one patient experienced severe fatigue after dosing and continued on a lower dose). One patient with oesophageal cancer had experienced an objective anti-tumour response.

The second drug candidate, ETS6103, is a generic drug with an established safety profile. A controlled phase IIa trial of ETS6103 for an anti-depressant indication, which ended in January 2009, demonstrated encouraging results when the drug was compared with a marketed tricyclic anti-depressant: "*significantly and consistently reduced depression scores in all patients during the 12-week treatment period*" [E6]. A larger phase IIb trial is expected to start shortly [E7].

The company

e-Therapeutics has grown substantially since it was founded in 2002. It was listed on the Alternative Investment Market (AIM) of the London Stock Exchange (LSE) in November 2007, and with a market capitalisation of £37.3 million at flotation it has become a significant presence in the UK marketplace with a current (26/06/2013) valuation of £92.7 million [E8]. In May 2013, e-Therapeutics became the eighth largest company by market capitalisation in the pharmaceutical /

biotechnology sector on the AIM [E9]. In the context of UK university spin-outs, e-Therapeutics ranks favourably. The 2010/11 UK Higher Education Business Community and Interaction Survey showed that there were just over 1000 active spin-outs in which HEIs had equity stakes that year and that the average external investment was of the order of £0.7 million per company [E10]. In contrast, e-Therapeutics raised £18 million in February 2011 and another £40 million in February/March 2013 via share issues [E10]. The major investors are Invesco (49.8%) and Aviva (16.2%) [E10].

Twenty highly skilled people are employed by e-Therapeutics across two sites in the UK, the Network Pharmacology Centre in Oxfordshire (opened in February 2012) and the company's facility in Newcastle. Since 2008, research and development spending has totalled more than £11.3 million. Money raised from recent share issues is expected to sustain employment and high levels of research spending through 2017 [E11].

Young (CEO, e-Therapeutics) has acknowledged the key contributions of Andras and Wipat, and noted that Newcastle University Research has *"positioned e-Therapeutics as the world leader in the new science of network pharmacology drug discovery"* [E12].

5. Sources to corroborate the impact

[E1] Hopkins AL (2008). Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol* 4(11):682–90

[E2] Mestre-Ferrandiz, J., Sussex, J. and Towse, A. (2012) *The R&D Cost of a New Medicine*. London: Office of Health Economics. http://www.ohe.org/publications/article/the-rd-cost-of-a-new-medicine-124.cfm

[E3] Patents assigned to e-Therapeutics: EP1968237, EP2028792, EP2157734, EP2154824; US8301391, US7768942, US7990878. Available from www.google.com/patents

[E5] Wall Street Journal (September 2011): Drugs that are as smart as our diseases. http://online.wsj.com/article/SB10001424053111904265504576567070931547618.html

[E6] Company update on progress of ETS2101 cancer trials, (2012). http://www.etherapeutics.co.uk/userfiles/file/ets2101_trials_update_dec_2012_final_181212.pdf

[E7] Company-reported results of the completed phase IIa trial of ETS6103, (2009). http://www.etherapeutics.co.uk/userfiles/file/e-Therapeutics%20antidepressant%20trial%20announcement_FINAL.pdf

[E7] Company plan for phase IIb trial of ETS6103 http://www.etherapeutics.co.uk/index.php?option=com_content&view=article&id=3&Itemid=5

[E8] London Stock Exchange: financial information on e-Therapeutics http://www.londonstockexchange.com/exchange/prices-and-markets/stocks/summary/company-summary.html?fourWayKey=GB00B2823H99GBGBXAIM

[E9] London Stock Exchange: AIM index statistics (May 2013). http://www.londonstockexchange.com/statistics/historic/aim/may-2013.xls

[E10] HEFCE HE-BCI (2010-11). Section B UK sector figures for spin-off and start-up activity. http://www.hefce.ac.uk/media/hefce/content/pubs/2013/201311/Annex%20A%20Summary%20data%20-%20UK.xls. (Table 4d)

[E11] e-Therapeutics annual report and accounts (May 2013). http://www.etherapeutics.co.uk/userfiles/file/e-therapeutics_plc_annual_report_and_accounts_2013_final.pdf

[E12] Corroboration from CEO e-Therapeutics