The advantages of outsourcing computational chemistry

With the increasing pressure to drive efficiencies in the drug discovery process, innovative approaches using computational chemistry are delivering proven results, particularly in the areas of lead identification and optimisation. However, maintaining an in-house team is often a luxury and there is an increasing trend to outsource computational chemistry in order to benefit from the advantages it delivers in terms of insight into the biological activity and interactions of molecules across a range of target classes, enabling the identification of new candidates that would otherwise have been overlooked.

Computational chemistry is the process of modelling chemistry *in silico*. It uses the principles and equations of physical and theoretical chemistry to provide solutions to problems that either cannot be solved or can be solved faster than using traditional experiments. Key to the success of any computational chemistry experiment is the relationship between the real experiment and the computer models so that the results are trusted by the scientists in the lab.

"In drug discovery, agrochemical discovery and, increasingly, in bulk chemicals, computational chemistry is used to predict the physical properties and most importantly the biological activity of compounds before they are synthesised or biologically analysed," says Martin Slater, director of consulting at Cresset BioMolecular Discovery. "Using the computer in this way saves many hours of lab time or in the case of HTS, millions of dollars in wet screening costs.

"In performing these tasks, computational chemists rely on the accuracy of the computer algorithms and approaches to provide reliable results," he continues. "Unfortunately, the methods that are used often fall short of the accuracy that would revolutionise the discovery process and hence wet chemistry has to take over. Whilst the ideal of designing one molecule in silico that then becomes the drug is a long way off, new computational methods such as those invented by Cresset are making a significant impact on the discovery process."

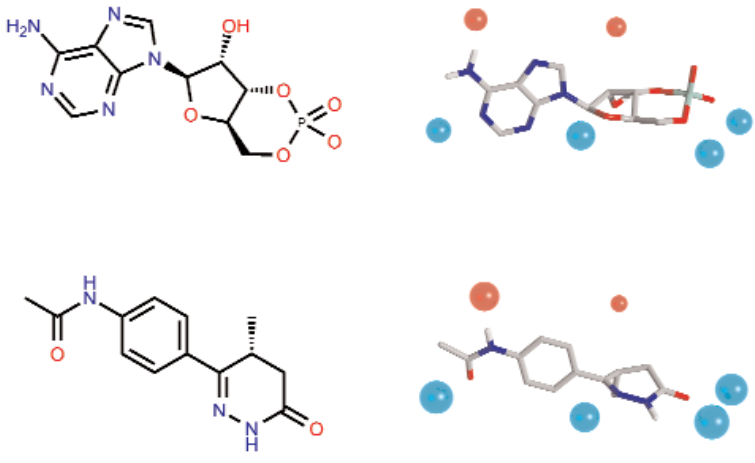
Slater says that where computational chemistry has really made a mark in practical drug discovery is in the combinatorial and high throughput screening explosion from the past two decades, in which it has become necessary to be able to process millions of molecules that are the feedstock of modern drug discovery:

"This would simply not be possible to do without a new branch of computational chemistry now known as 'cheminformatics'. What Cresset specialises in is both very detailed molecular modelling analyses and also very high throughput cheminformatics approaches that are applicable to not only drug discovery but potentially to physical property prediction, catalyst design, toxicology prediction, flavours and fragrances, patent protection and protein modelling to mention but a few."

Modelling molecular interactions

Cresset's technology was developed from work initiated in the 1980s by Dr Andrew Vinter while working at pharmaceutical company Wellcome with Nobel laureate and inventor of Cimetidine and Propranolol, Sir James Black. Vinter sought new ways to describe the way that molecules interacted with one another. Over the next twenty years, he worked in collaboration with major pharmaceutical and biotech companies to develop computer algorithms to precisely model molecular interactions through generation of accurate molecular fields. This culminated in funding to form Cresset in 2002.

The company received seed funding from The Wellcome Trust to implement Vinter's core science in a virtual screening platform. The ability to use the computer to improve on or replace high throughput screening (HTS) held great promise, particularly for smaller companies that lacked the resources to implement the expensive HTS framework. Cresset began offering virtual screening



2D structures of structurally diverse bioisosteres both active at PDE3, cAMP (the natural substrate) and SKF93741.

The field patterns of the compounds reveal that they are biologically similar.

Fig 1. Closing the gap between chemistry and biology: two structurally diverse molecules with similar biological activity.

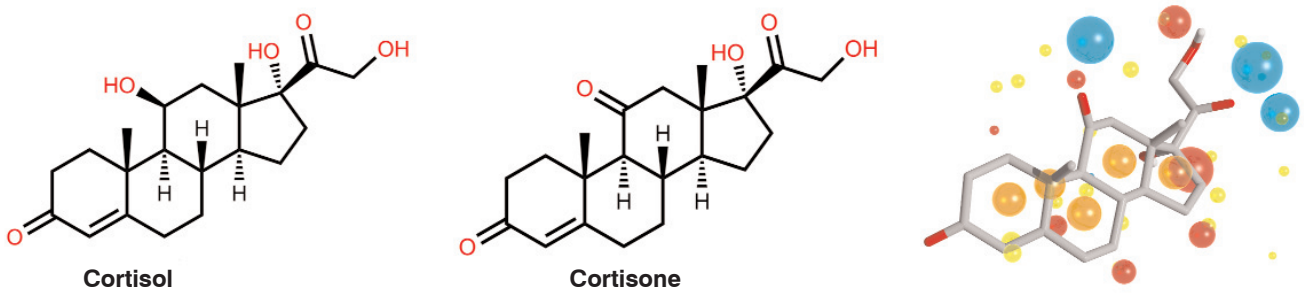


Fig 2. Molecular field of binding fragment (far right) from cortisol and cortisone.

project services in late 2002, using the feedback from users and customers to improve the software infrastructure leading to the launch of the software business in 2005. The recently expanded Cresset Consulting business unit remains an integral part of Cresset, influencing and validating new scientific methods and software algorithms.

Biological behaviour

Cresset's software uses its proprietary XED approach to describe molecules as they behave in a biological context. Expressed as 'field points', the company's descriptors highlight compounds as similar if they bind to the same biological target regardless of the two-dimensional structure (Fig 1).

"The field points encode the 'personality' of a molecule, the three-dimensional shape and electrostatic character that surround it," explains Slater. "Traditionally, this might have been described using a simplistic pharmacophore, the key elements that are needed for binding, and in this respect, Cresset's field points can be considered a pharmacophore. However, they are full of incisive detail and completely unlike those that have been used before.

"Working with Cresset's field technology gives a rich, informative view of each individual molecule," he continues. "Moreover, this view resonates with synthetic chemists whose methods for assembling molecules rely on thinking of molecules in terms of the electronic charateristics such as electron-rich or electron-poor. The result is a method that is both cutting-edge but also intuitive to the scientists who will employ the results. By comparing active molecules from diverse chemical series, Cresset users gain a deep understanding of the root causes of activity. With this knowledge they are empowered to design new molecules that go beyond the obvious iterations to be the best possible step forward for the project. For the business that has made the investment in Cresset, the result is motivated, highly productive scientists that deliver drug candidates with an excellent chance of success."

Cresset works on projects ranging through scaffold-hopping and ligand-based virtual screening, fragment replacement, fragment growth and SAR analysis including 3D QSAR using fields. Figure 2 illustrates one of the wide range of fields in which Cresset consultants have worked (see Case study below).

This is the first part of a two-part article. Part 2 will be published in the January/February 2013 issue of sp2 Inter-Active.

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Case study: Virtual screening with 11βHSD-1

The following Cresset client case study describes virtual screening with the enzyme 11β-hydroxysteroid dehydrogenase type 1(11βHSD-1) which resulted in diverse new leads.

The enzyme 11βHSD-1 is highly expressed in key metabolic tissues and has been linked with the control of visceral fat deposition. Cresset's consulting team was asked to generate new ideas for lead structures in this area, using the natural ligand as a starting point. The company's scientists used blazeV10 virtual screening software to find new active structures with diverse chemotypes.

11βHSD-1 was originally thought to predominate as an oxidase, converting cortisol to cortisone. However, it has been shown to act as a reductase in vivo for cortisone. This strongly suggests that the inhibition of 11βHSD-1 and the associated decrease of active cortisol could be important in the control of obesity, insulin-resistant diabetes and cognition.

The client wanted to generate new ideas for lead structures in this area, but had only the natural ligand as a starting point. In the absence of specific X-ray data, the Cresset team modelled the binding action of the steroids cortisol and cortisone. From this, they deduced the molecular field of the binding fragment (Fig 2) for use in Cresset's blazeV10.

Cresset's blazeV10 uses the shape and electrostatic character of ligands to rapidly search large chemical collections for molecules with similar properties. Using the molecular field pattern of the binding fragment, blazeV10 searched a database of millions of known structures to find compounds with a similar field pattern. Since ligand interactions are based on the shape and electrostatic character of molecules, compounds that share similar field patterns are likely to have similar biological activity, regardless of their chemical structure.

The results were ranked by field similarity to the seed structure and a list of the best 500 hits was submitted to the client. When tested, ten of these were active at $< 10\mu M$, one was active at 470nM and the best was active at 170nM.

On the basis of these results, further financing was granted to Cresset's client to develop the tetrazole chemotype. Independent patent filings were subsequently submitted for the benzfuranones and piperazines by other drug discovery companies. These patents and the subsequent appearance of many 11βHSD-1 X-ray crystal structures confirmed the validity of the original field binding pattern.