Outsourcing Computational Chemistry for Drug Discovery

PEER REVIEWED

The trend to outsource is making computational chemistry methods affordable and accessible for smaller research organisations. Dr Martin Slater, Director of Consulting Services at Cresset, outlines the scientific and business reasons for outsourcing this important drug discovery method.

Computational chemistry is a highly-skilled scientific field that has delivered proven results for drug discovery, particularly in the areas of lead identification and optimisation. Many companies maintain an in-house team or expert who can perform data analysis and carry out molecular modelling. Computational chemistry is an integrated part of many discovery pipelines, and is ideally placed to help medicinal chemists answer questions such as:

- Which compound should I make next?
- Which structures have the best chance of succeeding against this target?
- How can I best optimise this compound to reduce this side-effect?
- Given a choice of targets, which should I choose?
- How can I generate a back-up series for this project?
- Have I missed any potential hits from my data set?

However, maintaining an in-house team can be expensive. The overheads include recruiting and training expert staff, buying a range of software and making a significant investment in computational hardware. This can effectively price computational chemistry out of the market for some smaller drug discovery companies. It has led others to question how they can access this technology in a cost-effective way.

The Advantages of Outsourcing

The opportunity to outsource computational chemistry projects puts this technology firmly within the reach of any research organisation. Outsourcing carries many advantages, both for organisations with in-house computational chemistry, and those without.

The first and most obvious advantage is that by choosing to outsource rather than maintain an in-house team, you remove the overhead of buying and maintaining hardware and software and of recruiting and training users. Some computational methods, such as library design, may only be useful at the start of a new drug discovery project. It does not make sense to maintain in-house expertise for skills that are only used once or twice a year.

The word 'consultant' may conjure up negative connotations, but in scientific fields, a consultant really has to know their stuff. By choosing to outsource computational chemistry to consultants, you ensure that you are getting years of scientific experience, not only in your particular field, but across a range of protein targets and compound types. Confidentiality remains paramount, but expertise gained by constantly working on diverse compounds and targets brings fresh perspectives to your project that can be hard to gain in-house.

Outsourcing gives you just-in-time delivery with a single point of contact. By working with consultants, you are in control of how and when you receive the deliverables, and whether you would like extra work done when projects reveal unexpected results. Most consultants are open to the option of adding extra services. For example, as described in case study 1, you may wish to outsource not only the computational work, but also your procurement services for a particular project, ensuring you receive the compounds when you want them, while only dealing with a single vendor.

Outsourcing gives you access to a range of industry software. Most consultants will use the best-in-breed software, rather than sticking to software from just one vendor, even if the consulting services are provided by a software vendor.

An added advantage of choosing consulting services from a software vendor is that they can offer early access to methods that they have developed but not yet released as software. Qualitative models add value in situations where the 3D-QSAR cannot, as they do not depend upon the development of an equation to predict activity (Figure 1). The customer's dataset is processed to find molecules that describe critical features or excluded volumes. These are put into a model, which is then used visually to explain the observed SAR or computationally to score new designs or in virtual screening.

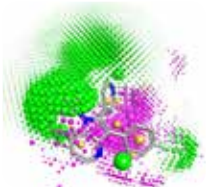

Figure 1: Consultants can add value by giving access to new methods that are still under development. In this case, a qualitative model has been created from ligand data alone, showing allowed (green) and disallowed (magenta) regions around a p38 ligand.

Popular Outsourcing Projects

Virtual screening is an effective means of switching chemical series to identify new intellectual property. Virtual screening can be ligand-based or protein-based, depending on the available information. In either case, a 3D model is developed of the desired properties of the ideal compound. This is used to search a database to come up with possible new chemotypes.

Ligand-based virtual screening is a very popular way to produce ideas for new projects in disease areas where very little information is available for the biological target.

Library design. Libraries of chemical compounds are the lifeblood of modern pharmaceutical discovery programmes. The quality of library design can determine a project's success or failure. Both molecular modelling and cheminformatics techniques are important for building a focused screening library with novel and diverse chemical structures [1].

Scaffold hopping. One of the best ways to discover new intellectual property is to perform scaffold hopping on known active compounds. Scaffold hopping is a useful technique during the discovery phase of a project when there are no starting points other than a complex natural product. The aim is to find new chemical structures with similar biological activity to the original by changing components of the

molecule. A related software capability called 'fragment replacement' explores changing one component of the active molecule at a time. Rather than searching for commercial compounds to purchase, fragment replacement provides ideas for new molecules that can be synthesised.

SAR data analysis. SAR analysis is an expert field, which is why many customers prefer an outsourced solution. Our scientists use a variety of techniques to study SAR. These range from simple ligand alignment to more involved methods such as 3D-QSAR, qualitative model development or activity cliff detection.

Choosing the Right Outsourcing Model

Outsourcing models vary, depending on customer requirements. Project-based work is very popular, in particular for virtual screening, compound library design and the analysis of SAR data. By contrast, some companies enter ongoing collaborations where consultant computational chemists work closely and iteratively with in-house medicinal chemists to add insight to their work on a daily basis. Collaborative working models, such as that described in case study 2, can often lead to the most productive results. The synergy between medicinal chemists and computational chemists adds a new dimension to their thinking and understanding, often with innovative and ultimately profitable results. From a billing point of view, consultants may charge a daily rate, or a project rate. Some vendors are so flexible that it is possible to buy a flexible bank of pre-paid service hours, valid for a fixed time period, usually the next 12 months. Project-based work may be narrowly defined, or can be more open-ended. For open-ended, collaborative projects it is vital to have clear and frequent communication between consultant and client regarding milestones, agreed review points, and deliverables. Most vendors will negotiate arrangements to suit the particular requirements, sometimes adding extra bespoke services, such as procurement, as described in case study 1.

Case Study 1: From Virtual Screening to Plated Compounds

The usual result from a computational chemistry project is a list of compounds to make or purchase. However, it can be helpful for consultants to go further and manage the customer's procurement process so that the result is plated, assay-ready compounds. A recent consulting project involved a customer who started the project with a known target. They had a number of published active compounds and were looking for some new chemistry for assays they had booked with a biology CRO. The virtual screening work resulted in recommendations for 250 screening compounds. For additional diversity, the consultants used Spark to do some bioisosteric replacements around the core of the known active compounds. These new bioisosteres were used for a further virtual screen that resulted in a further 50 compound recommendations. The customer chose to completely outsource the procurement of these compounds to the same consultants who had carried out the virtual screening project.

The procurement process was managed using a dedicated chemistry provider and specialist shipping agents. The compounds were bought from the various vendors, weighed, dissolved, plated and delivered to the biology CRO to be screened. The compound procurement for this project was multi-national, including the UK, Europe, Eastern Europe and the US. The final delivery was to a California-based biology CRO.

Case Study 2: A Collaborative Project Resulting in New Lead Molecules

The small molecule drug discovery company Senexis had developed a series of N-methylated peptides that block the aggregation of β-amyloid (Figure 2). They engaged consultants to work with them collaboratively to identify a novel series of drug-like, non-peptide small molecules that would produce the same effect. The consultants` field-based software was ideal for identifying the key properties of the peptides, providing the seed for a virtual screening experiment. The consultants identified several possible new chemotypes, which they sent to Senexis's chemists for review. Senexis embarked on a programme of medicinal chemistry and biological testing that resulted in two distinct chemotype sets. Working from these two chemotypes, the consultants used Forge to produce templates for four active structures (two from each set) to find the common field pattern across all of the conformations. From this they deduced the bioactive conformation and pharmacophore for activity.

Further searches using these more reliable field patterns from the bioactive conformations revealed more information and ideas for the Senexis chemists to work with. Their resulting lead molecules were SEN1269 and SEN1186 (Figure 3).

The collaborative nature of this consulting project resulted in new perspectives for the Senexis chemists, providing them with several possible leads and enabling them to make informed choices about which to pursue

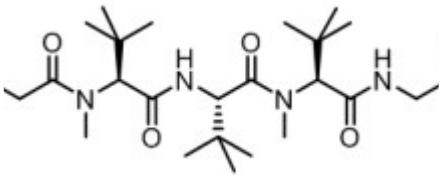

Figure 2: An example 'L-meptide' search molecule from Senexis Ltd., used by Cresset's consultants as the basis for finding non-peptide small molecules with similar activity.

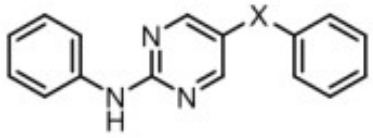

Figure 3: The core of SEN1269 and SEN1186, the lead molecules identified as the result of a collaborative outsourcing project between Senexis and Cresset.

References

1. Harris, Hill, Sheppard, Slater, Stouten, 'The Design and Application of Target-Focused Compound Libraries', Combinatorial Chemistry & High Throughput Screening, 2011, 14, 521-531 521.

Dr Martin Slater is Director of Consulting Services at Cresset. Cresset provides flexible scientific consulting and contract research solutions for a variety of organizations. The team uses Cresset's innovative field-based chemistry software, the XED molecular mechanics force field, as well as more traditional approaches. Cresset consultants have worked on over a hundred diverse consulting projects with many of the world's top pharmaceutical, biotech and agrochemical companies.
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