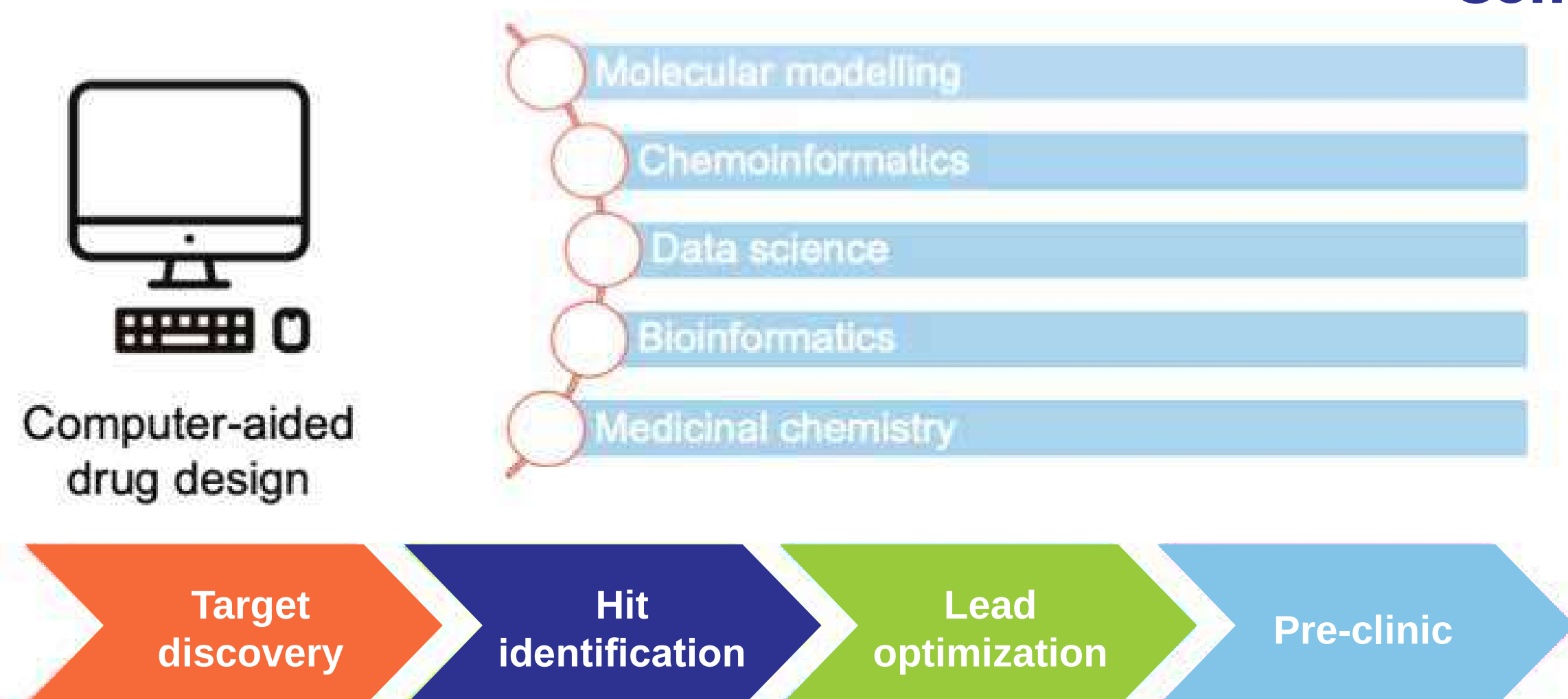


Computer-aided Drug Design at Charnwood Discovery

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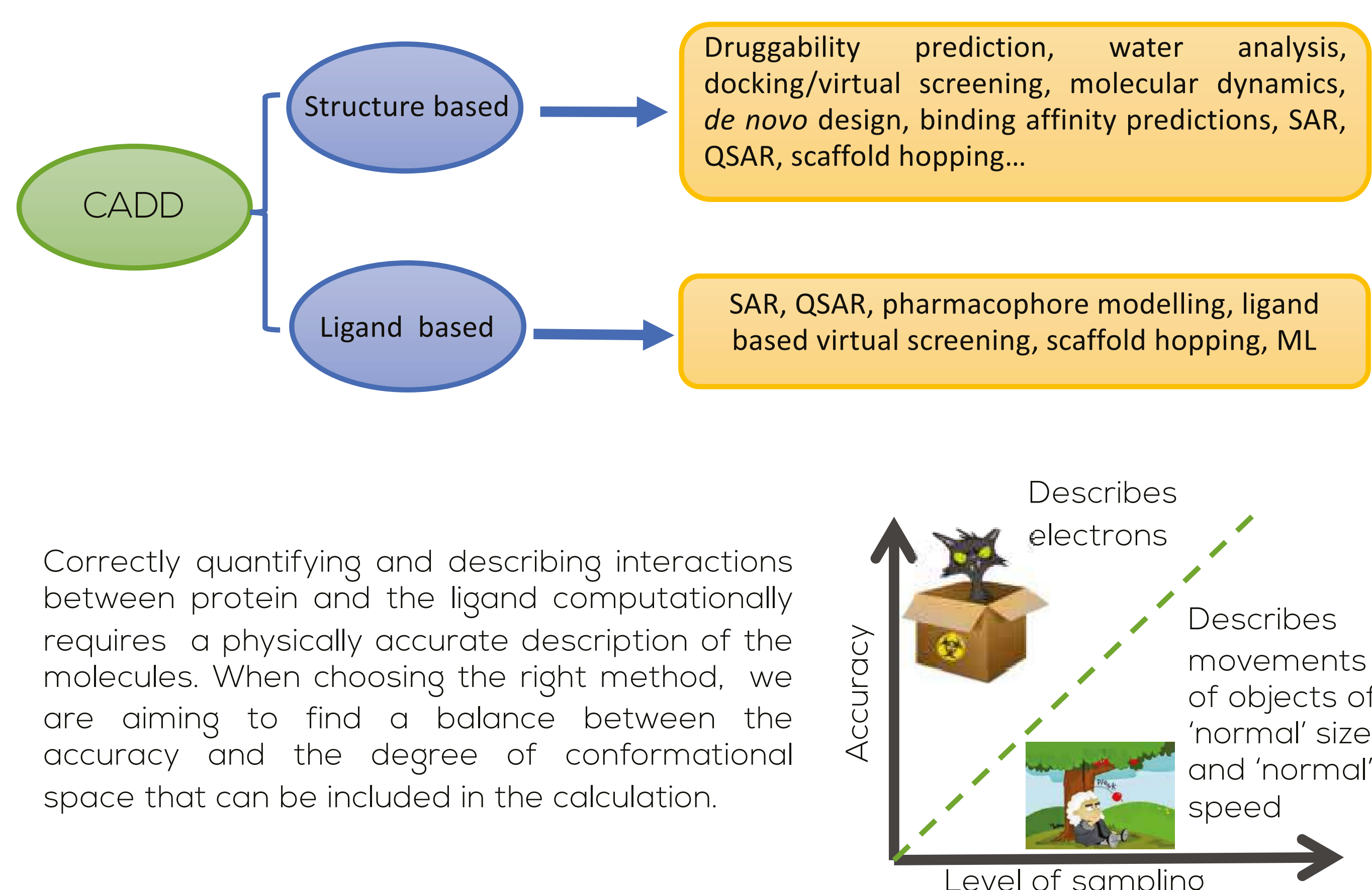
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Computer-aided Drug Design



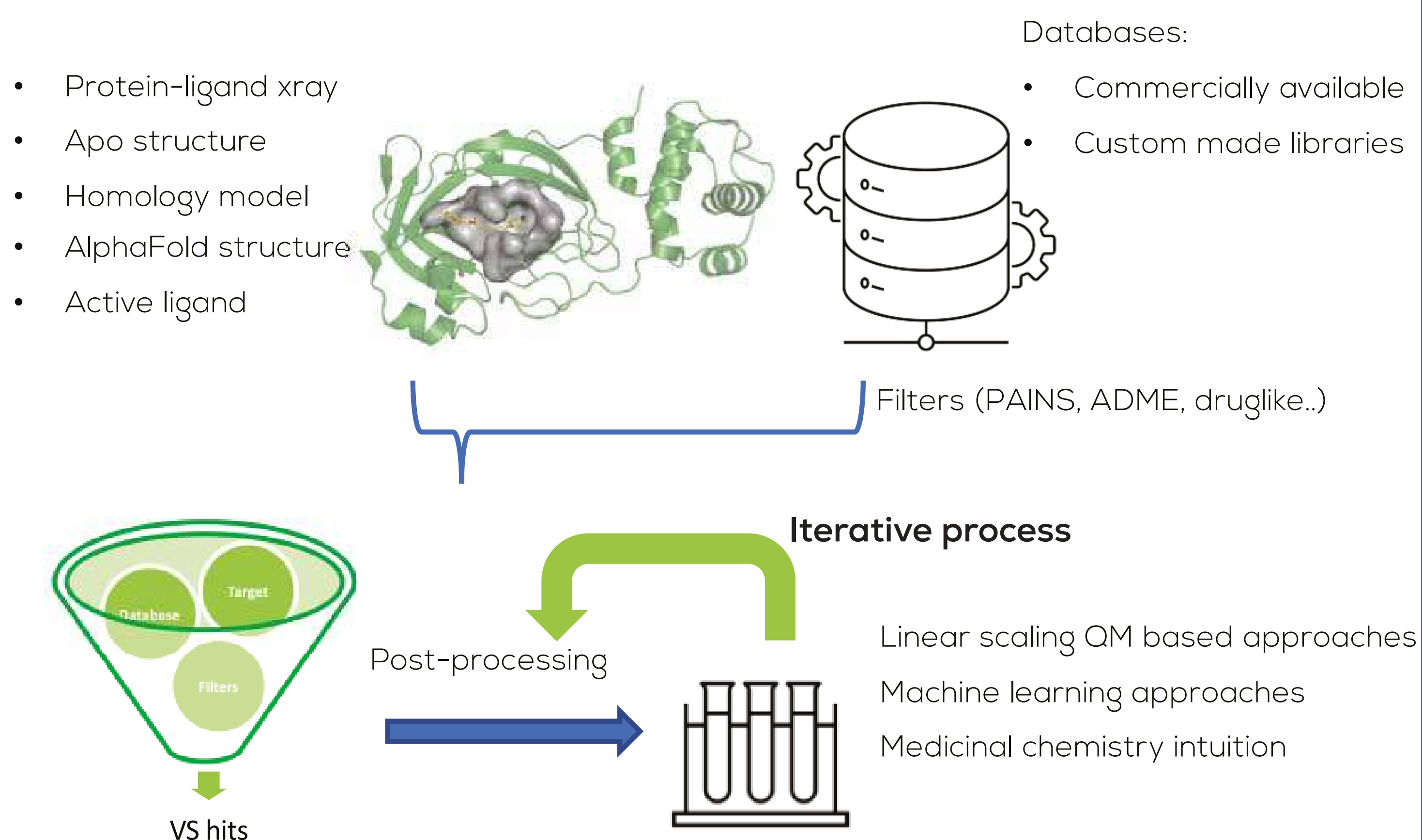
Computational chemistry can be described as chemistry performed using computers rather than chemicals. Much like the experiment, calculations can be applied in order to collect the data or simply as a way of looking at the unusual. Use of computer-aided drug design (CADD) in early phases of drug discovery pipeline helps expedite the whole process and minimize chances of failure in the later stages. Rational drug design relies on useful insights derived from structure-activity relationship, understanding the interactions between the hits and their target, and exploiting these insights when generating new ideas. Recent advances in machine learning (ML) techniques and artificial intelligence (AI) have greatly advanced how biological data is analyzed, presented and explained.

The Toolbox



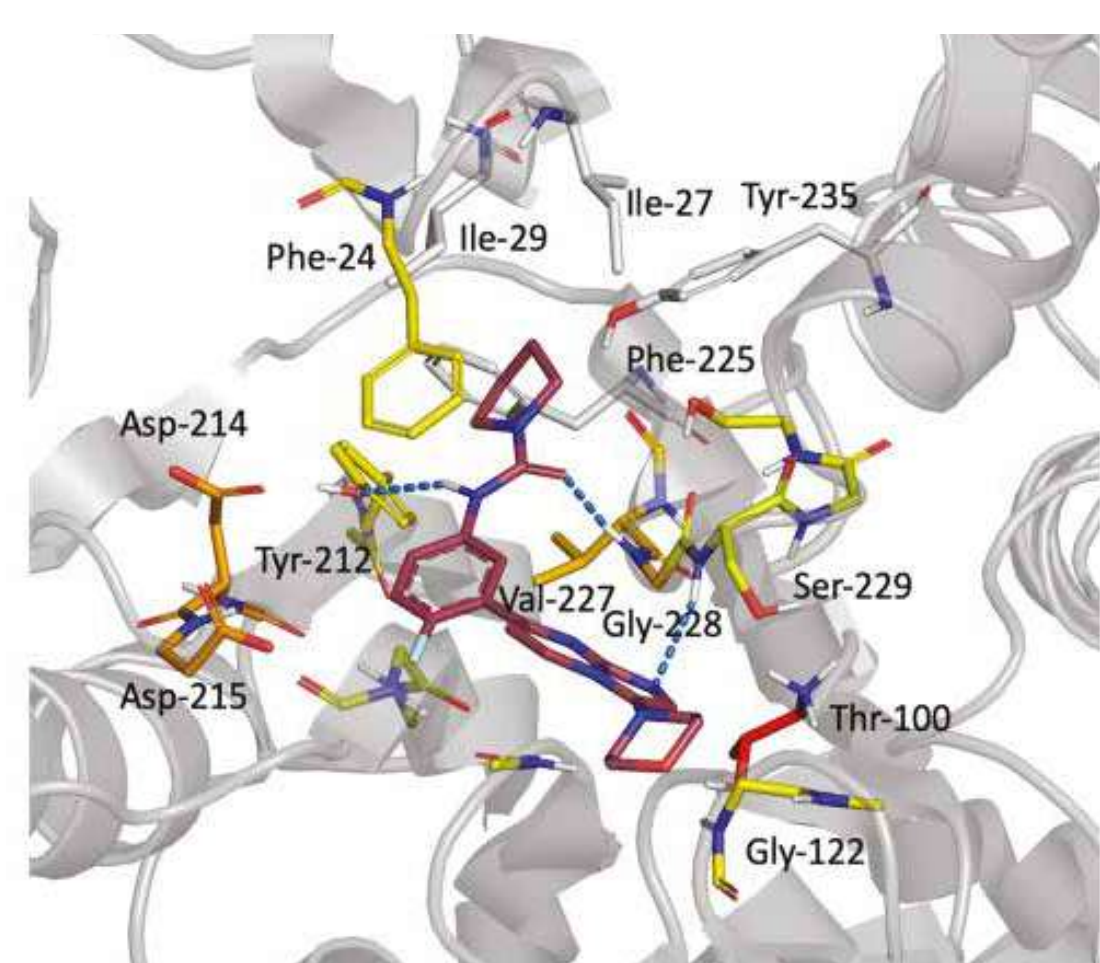
Correctly quantifying and describing interactions between protein and the ligand computationally requires a physically accurate description of the molecules. When choosing the right method, we are aiming to find a balance between the accuracy and the degree of conformational space that can be included in the calculation.

Virtual Screening Cascade



Post-processing of hits (virtual or HTS) is an iterative approach. By applying modern computational techniques, complex data is converted into highly visual, actionable insights, information rich 3D sessions, custom made interactive dashboards that are platform agnostic and easy to understand interactive plots. Drug discovery is highly multidisciplinary process, and requires researchers with different backgrounds and expertise to look at the same data. Experienced medicinal chemists will be able to quickly spot the interesting patterns amongst the chemical series, but also some of the features that have proven to be problematic in the past. It is essential that chemist examine the data as well as they are the ones with the most domain knowledge. It is therefore imperative to find the ways of incorporating this background knowledge and experience with the modern data science approaches.

QM in Drug Discovery



QM calculations can overcome many of the limitations imposed by molecular mechanics-based approaches (e.g. polarizations and charge fluctuation). Despite the greater accuracy, QM methods have not been routinely used in drug discovery due to the high computational costs required to deal with large biological systems.

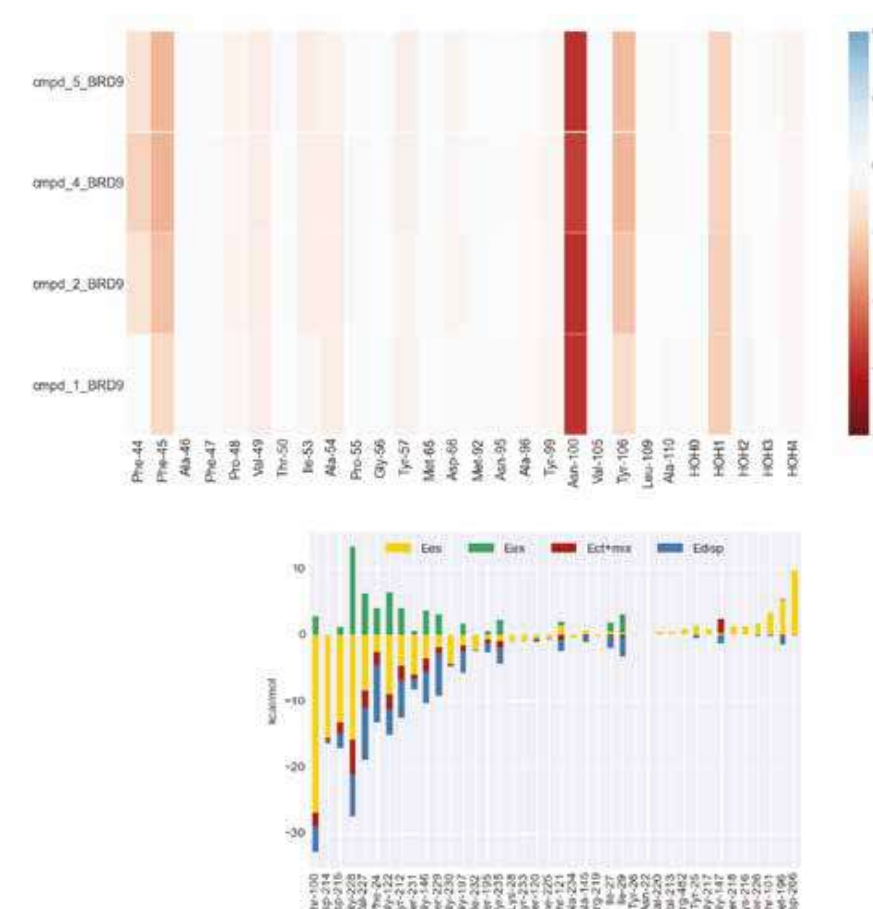
Recently, the development of fragment molecular orbital (FMO) methods have increased the computational speed of QM approaches. This is achieved by fragmenting the system into smaller parts, and deriving QM based pairwise interaction energies (PIE) between the fragment and the ligand. By combining the PIE of all the fragment-ligand pairs it is possible to derive the total interaction energy of a ligand with its biological target.

Binding Affinity Prediction

The combination of computed QM binding energies with measured or predicted logP values can provide usefully accurate predictions of protein-ligand binding energies [1].

Rationalising SAR

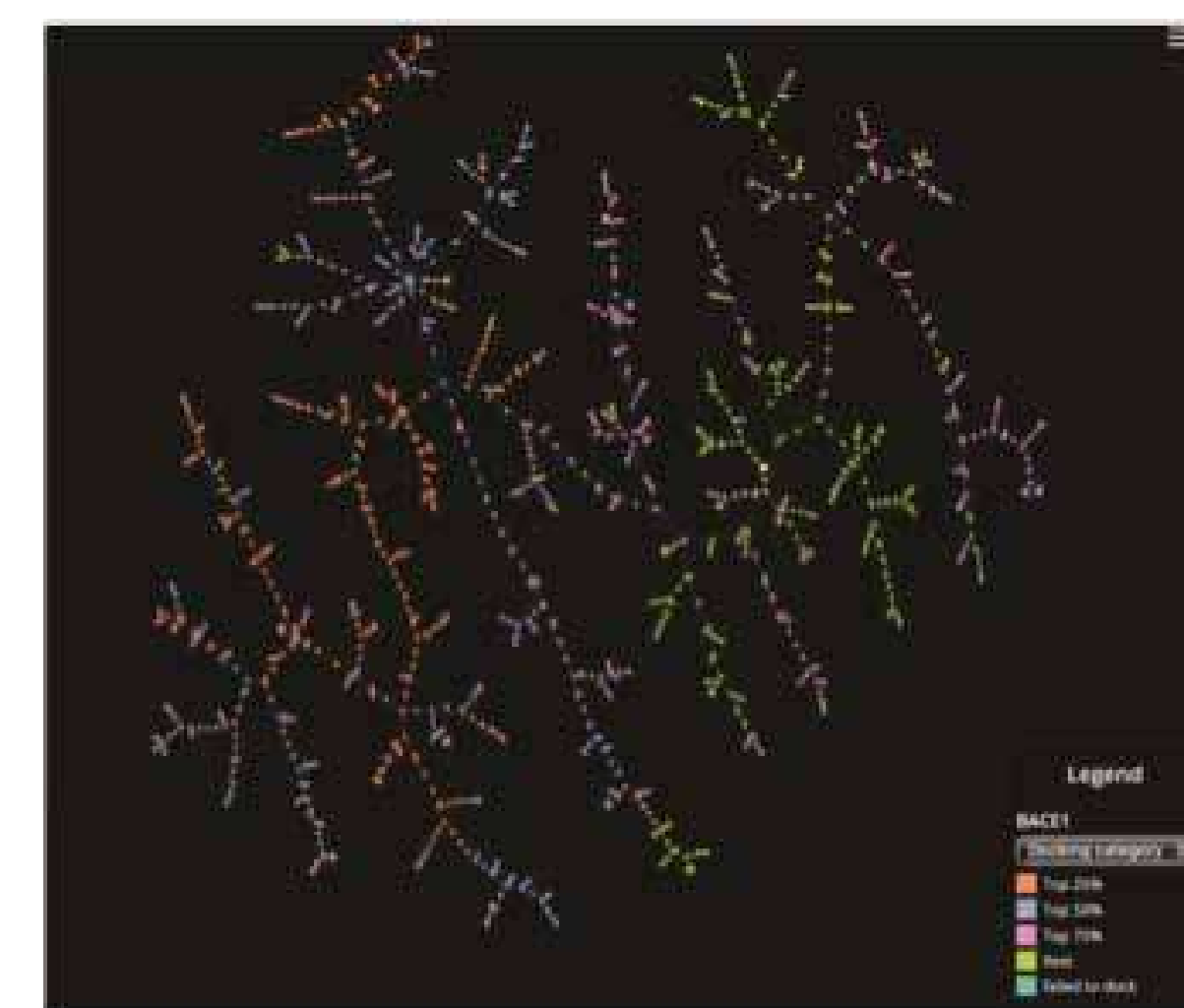
Going beyond 'visual inspection' and identifying nonintuitive interactions [2,3].



Machine Learning/AI

Visualizing **chemical space** and organizing chemical structures in a sensible way has been of interest to drug discovery research community for many years, but in practice, linking these findings back to medicinal chemists and turning data into valuable information has been a challenge.

Current ML/AI activities within the group are focused on effective navigation of chemical spaces, pragmatic exploration of ultra-large libraries such as Enamine REAL or WuXi GalaXi, and implementation of *de-novo* generative approaches.



Visualizing large multidimensional datasets as two dimensional minimum spanning trees (tmap)^[4]. Snapshot from a web-based interactive visualisations. BACE-1 embedding, colouring based on docking score bins.

Summary

Computational chemistry group at Charnwood Discovery can help drug discovery process in each of its phases by applying molecular modelling, chemoinformatics and data science techniques. The group has an extensive track record of building custom and creative solutions to different project needs, as well as applying industry standard solutions.

