3D Modelling for the Masses: A Universal Interface for Easy Access to Expertly Prepared 3D Models

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Introduction

Drug discovery is a challenging multi-parameter optimisation process, in which target potency, selectivity and a broad range of Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties must be simultaneously optimised.

Making computational tools that are accessible to all project decision-makers and guide this optimisation process, using all available data, is critical to quickly achieving a successful project outcome. Here we present an integrated, universal Pose Generation Interface which seamlessly links expertly-prepared docking and 3D alignment models with a comprehensive environment for data visualisation, analysis and predictive modelling, to automate routine compound assessment in docking and alignment models.

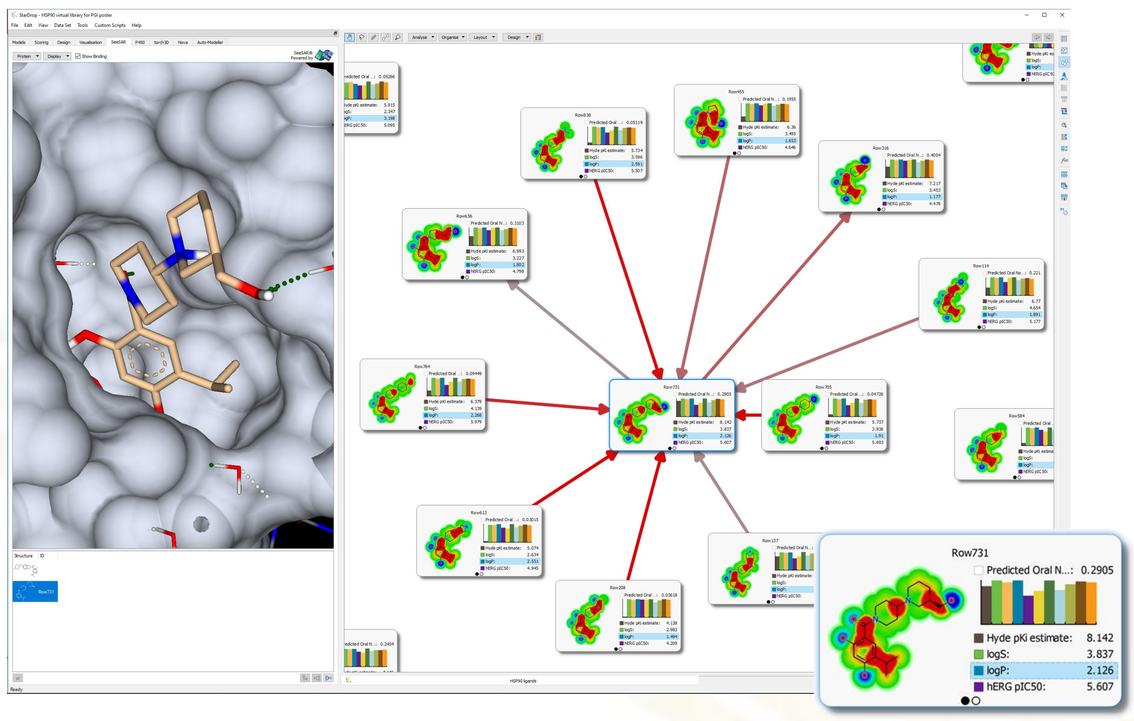

Figure 1. Visualisation of compound structures alongside associated 2D data allows trends and relationships (e.g. activity cliffs) to be quickly identified.

Current Workflow

Predictions based on 2-dimensional (2D) and 3-dimensional (3D) structures are typically generated in an arsenal of modelling tools, often restricted to expert computational scientists due to their complexity.

This leads to a decentralised approach, which detracts from efficient data analysis and compound prioritisation.

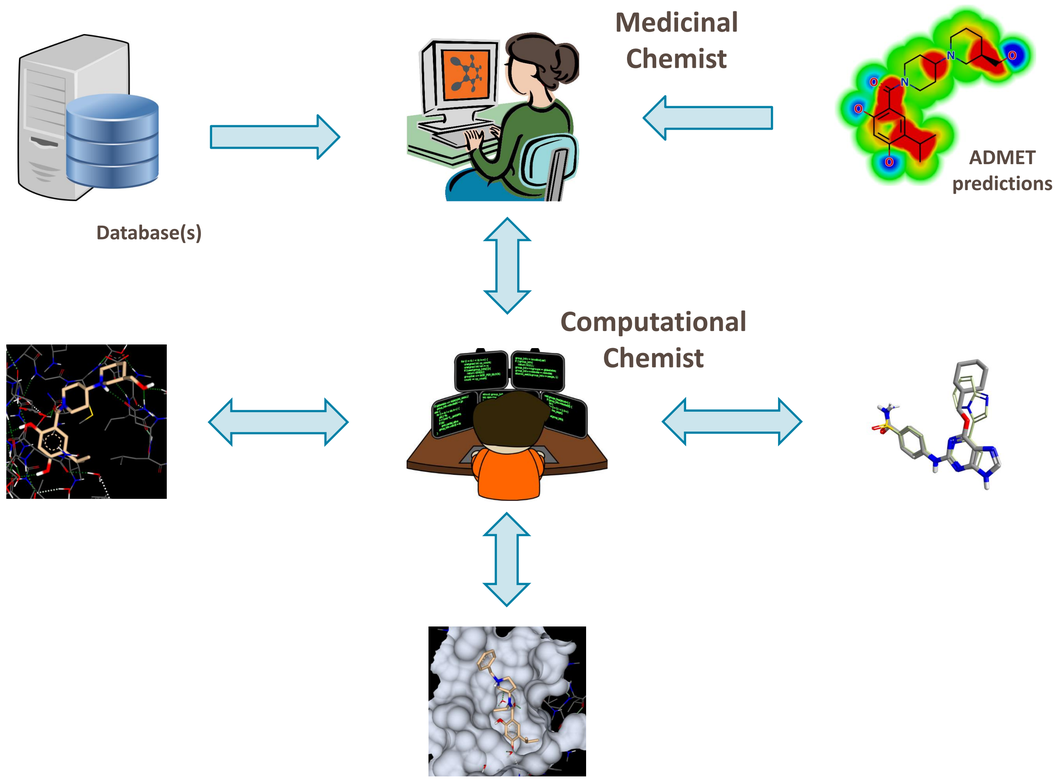

Figure 2. Typical drug discovery data analysis workflow.

Medicinal chemists waste time on inconvenient data export, import and merging and have to wait for feedback from computational analyses.

Computational chemists often run routine calculations, distracting from more scientifically challenging tasks, such as preparation and validation of protein docking models, where they can add most value.

This creates a barrier to rigorous assessment of new compound ideas prior to synthesis.

Pose Generation Interface

Our Pose Generation Interface links docking and 3D alignment models, from a variety of applications, with StarDrop™ [1].

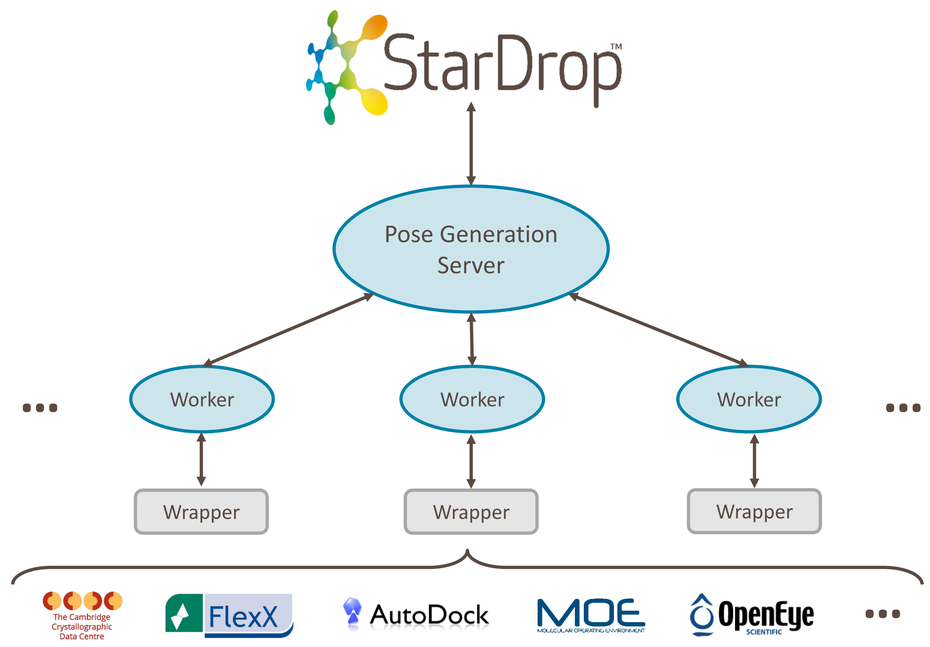

Figure 3. Data flow within the StarDrop™ Pose Generation Interface. Applications from the listed 3rd parties have available wrappers; more can be easily configured.

- Docking or 3D alignment models (Figure 3), developed by expert computational chemists, are published on a Pose Generation Server
- The server manages requests and distributes docking/alignment calculation to multiple workers or via an HPC queuing system, supporting multiple 3rd party platforms
- A Python wrapper encodes the platform-specific process to run the calculations and return the resulting 3D poses, scores and associated protein structures
- Medicinal chemists can see all available models and submit their compounds for analysis
- The poses and scores are automatically retrieved for analysis and visualisation in the context of the relevant protein conformation

Conclusions

This approach supports collaboration between computational and medicinal chemists, helping to share the results of 3D modelling studies with all decision makers. Scientists can quickly understand structure-activity relationships, identify potential liabilities and design new compounds with the highest chance of success.

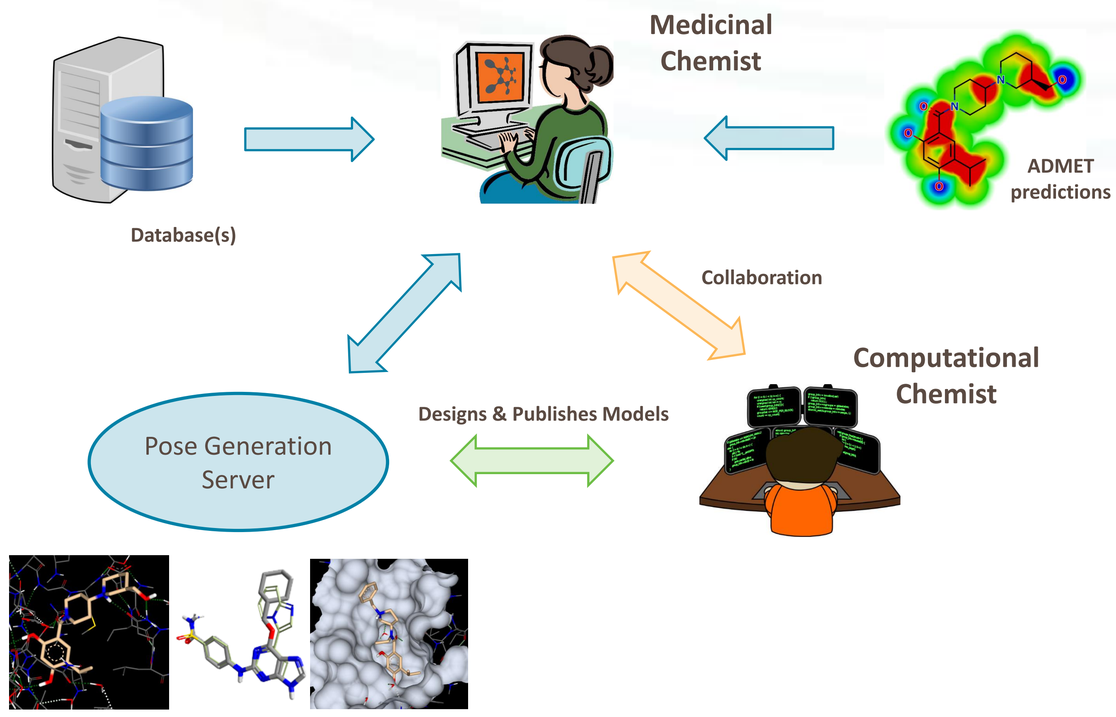

Figure 4. Improved workflow integrating all information for decision-makers.

Medicinal chemists can access all relevant data in one place and evaluate multiple iterations of designs on-the-fly, to prioritise those ideas which have the greatest likelihood of success. Inspection of the returned poses gives the medicinal chemist understanding of key binding interactions.

Computational chemists have greater opportunity to focus on expert computational design and model building, rather than routine docking, resulting in greater impact on project progression. Only the most relevant compounds undergo further expert computational evaluation.

[1] StarDrop v.6.4, Optibrium Ltd; http://www.optibrium.com/stardrop