Viruses present uniquely difficult challenges for pharmaceutical R&D. Not only do these pathogens tend to mutate rapidly, they also utilize much of our own molecular machinery to proliferate. Candidate treatments must therefore find a means to prevent viral replication without significantly impacting normal bodily function. Considering the dire need for effective treatment against many zoonotic diseases – especially in light of the COVID-19 outbreak in December 2019 – traditional drug discovery techniques are likely too slow to bring rapid relief to patients. To this end, many researchers are looking to drug repurposing, searching lists of treatments previously approved for other uses by various regulatory bodies, to source novel therapies for current or emerging pathogens quickly. This should ensure resulting treatments are relatively safe, as previous clinical trials have done much of the work to assess toxicity risk. But the question remains: which treatments should be tested first? BIOVIA Discovery Studio offers a range of \textit{in silico} techniques to virtually screen existing candidates for efficacy against viral targets, guiding drug repurposing projects and shortening the time to get treatments to the patients who need them most.
**IN SILICO VIRTUAL SCREENING**

Protein structure is critical to developing an understanding of its function and how it interacts with ligands. BIOVIA Discovery Studio offers a range of methods to generate protein structures, dock ligands, and develop pharmacophore models to rapidly screen approved therapies as novel antiviral medications.

**Homology Modeling**

In many cases, an experimentally-derived structure for a target protein may not be readily available. However, Discovery Studio provides a collection of techniques to generate a novel protein structure from homologues, providing the needed foundation for many virtual screening methodologies. With Discovery Studio, researchers can query the PDB using BLAST or PSI-BLAST to identify optimal template models based on sequence similarity and align these sequences to identify key structural motifs, such as potential binding sites. Homology models of the target protein can be generated via MODELER and refined with various CHARMm-based methods. Missing loops within the protein can be analyzed with the LOOPER algorithm, which builds and ranks various loop conformations, capturing nuanced details which can be critical to protein function. Lastly, various forcefield-based model refinements can be calculated such as protein ionization, residue pKs, side chain optimization and minimization.

![Figure 1: Superimposition of an initial model of the SARS-CoV-2 S protein (blue) and the cryo-EM structure (green).](image1)

**Docking**

Once a protein structure has been generated, researchers can dock various ligands to assess the key chemical interactions that influence binding behavior. Researchers can convert 2D molecular structures to 3D, evaluate various isomers and tautomers, explore various conformations, and generate molecular fingerprints to filter compound libraries. Discovery Studio also provides a range of methods to dock large and small numbers of compounds, from high throughput methods like LibDock to more intensive methods such as CDOCKER and ChiFlex/ChiRotor. Researchers can visualize various non-bond interactions to characterize binding modes and identify residues which mediate binding. Collections of bound ligands can also be scored to determine top performers for further refinement and subsequent study at the bench.

**Pharmacophore Development**

Pharmacophores, a 3D description of the key molecular features involved in protein-ligand interactions, can be used as a tool to rapidly estimate the potential for a drug compound to be repurposed as an antiviral therapeutic. Discovery Studio uses the CRTRLYST Pharmacophore Modeling and Analysis tools to identify key molecular features for pharmacophore generation and refinement. With this information, researchers can rapidly screen millions of potential compounds for potential treatments and predict their activity.

![Figure 2: Docking and key non-bonding interactions of a leading antiviral against SARS-CoV-2 main protease.](image2)
STATISTICAL AND MACHINE LEARNING-BASED TECHNIQUES

In instances where R&D is looking to directly tie chemical features directly to pharmacological outcomes such as IC\textsubscript{50}, researchers can generate quantitative structure-activity relationship (QSAR) models to predict the activity of new compounds. Models can be trained on a variety of physicochemical, topological, electronic, geometric and molecular fingerprint properties, including semi-empirical (BIOVIA Discovery Studio VAMP) and DFT (BIOVIA Discovery Studio DMoL\textsuperscript{3}) descriptors.

Teams can also leverage a variety of native validation tools to confirm the predictive power of new models throughout the training process. This also helps researchers expand the size and scope of their potential screening protocols, as QSAR models do not require protein structure data. These models, once developed and validated, can also be shared between teams, improving collaboration and accelerating discovery.

All of these techniques can help guide physical experimentation in the identification of novel therapeutic candidates for antivirals based on regulatory body-approved treatments. In addition, Discovery Studio provides a range of methods for small molecule and biologics lead design and optimization.

To learn more about these techniques, please visit 3ds.com/biovia