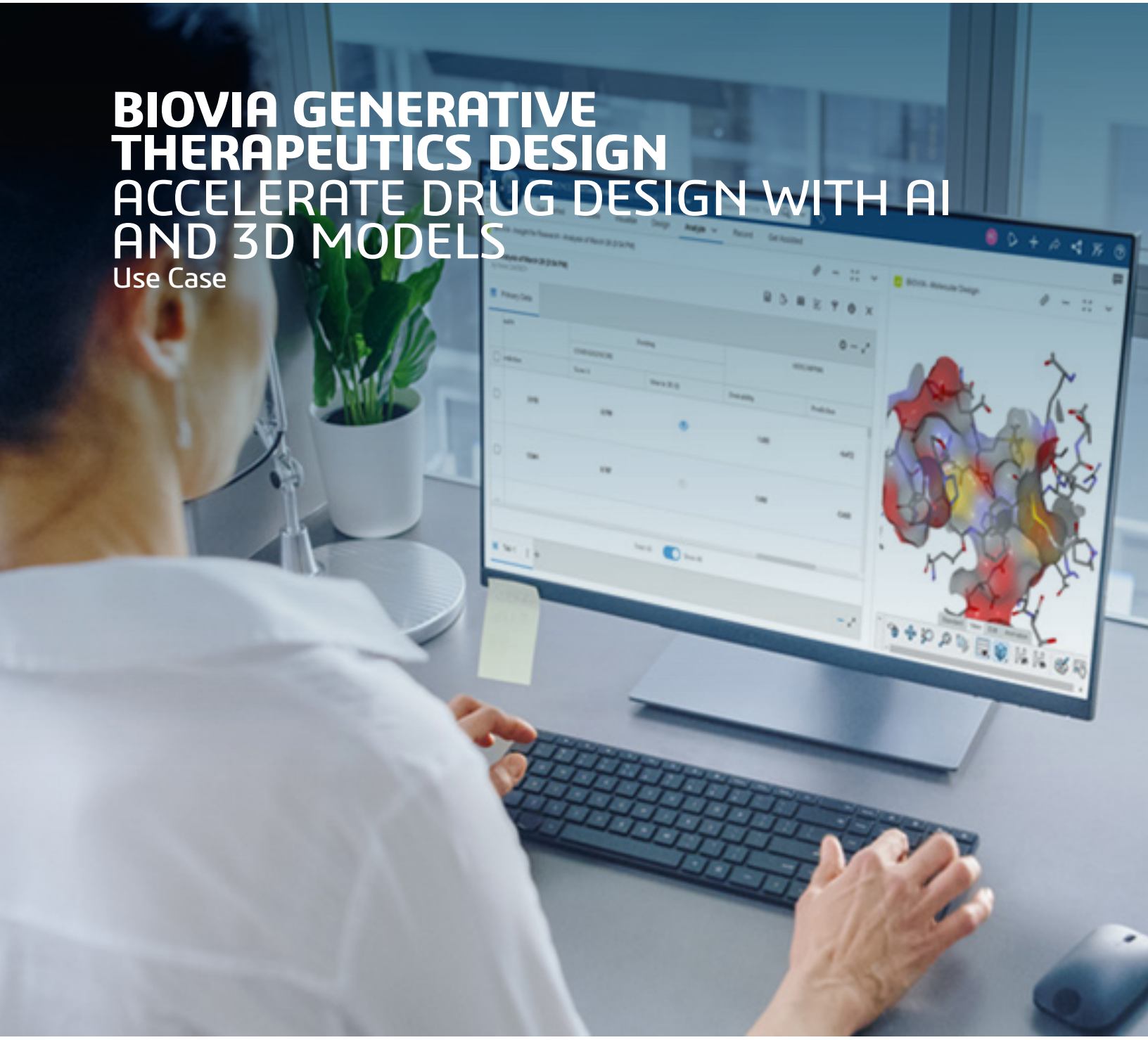
BIOVIA

3DEXPERIENCE®

BIOVIA GENERATIVE THERAPEUTICS DESIGN

ACCELERATE DRUG DESIGN WITH AI AND 3D MODELS

Use Case



DASSAULT SYSTEMES

Challenge:

- Small molecule drug discovery is time-consuming, tedious and costly
- Most AI/ML models work in 2D to optimize leads and they do not have the ability to incorporate 3D ligand-protein interaction information

Solution:

BIOVIA Generative Therapeutics Design using AI and pharmacophore modeling to generate lead compounds

Results:

- Re-identification of lead compounds in clinical development within months, along with 41 closely related compounds
- Generation of additional, novel chemical compounds with a hybrid 3D pharmacophore model

CUSTOMER:

This BIOVIA customer is a large, research-based bio-pharmaceutical company focused on the discovery, development, and commercialization of innovative medicines. The company is constantly exploring new frontiers in biomedical research and investing heavily in cutting-edge technologies that can unlock new therapeutic possibilities. Although, historically, the company has been very conventional in the drug discovery process, they recently started using artificial intelligence (AI) and machine learning (ML) to improve this process and were interested in the BIOVIA solutions.

CHALLENGES:

Small molecule drug discovery is an expensive process that takes time and effort. Because of the large and growing number of potential drug molecules, synthesizing and testing a representative field of candidates in the lab is rapidly becoming untenable, and this approach could completely miss promising molecules.

AI and ML methods can accelerate the process of drug design and optimization by exploring large parameter spaces and filtering large datasets down to molecules with the most promising properties and functionalities. However, using AI tools in-house still requires data scientists and computational biologists and/or chemists with the knowledge and understanding to apply these tools and generate meaningful results. Outsourcing drug discovery to companies that specialize in AI is an option, but it can be costly—not only the cost of the discovery itself, but also the licensing fees that AI companies often charge for the molecules that they generate, which can run into the tens of millions of dollars upfront. Nevertheless, it doesn't always work in favor of the pharmaceutical company seeking solutions.

This BIOVIA customer was very well-positioned by having a protein kinase inhibitor dataset as they looked into several AI-drive solutions for drug discovery. They found that most models they explored were impractical, ineffective or did not produce the desired outcomes. One factor the customer identified as a shortcoming was the inability to include the 3D information.

Most AI/ML models work in 2D to optimize leads, and they do not have the ability to incorporate 3D protein–ligand interaction information. Even 2D models with large amounts of input data sometimes fail to predict compounds beyond their training sets. Weakly predictive ML models are prone to error propagation, and they sometimes fail to weed out "hits" that are minor variations on known compounds. Few existing commercial software models have 3D capabilities, and such models are challenging to build without the expertise of a computational chemist or previous knowledge of the protein–ligand interface determined by X-ray crystallography or cryo-EM.

SOLUTION:

BIOVIA partnered with the company, providing software engineering and computational expertise in a pilot program. The cloud-based, AI-driven ideation tool, Generative Therapeutics Design (GTD) was tested on the company's in-house protein kinase inhibitor dataset to re-identify the lead drug candidates.

GTD's automation tools can save time on repetitive tasks like calculating properties and reviewing past data. New chemical structures can be generated and virtually tested using models built on in-house data, identifying structures that optimally fulfill a set of preselected characteristics. Molecular transformations generate a range of analogues of the input molecules. ML model-based property predictions, trained on experimental data, can be used to filter the resulting molecules and generate a set of optimal candidates. (Figure 1)

> "What BIOVIA is offering is a mature, cloud-based system for enhancing the power of drug design teams. It enables mixing of explicit chemical, physiochemical properties with 2D ML-models and 3D pharmacophore models to obtain useful suggestions at various stages of the drug discovery process."
>
> — Executive Director of Structural Biology and Chemistry Biopharma Company.

Users can then tailor the parameter controls in GTD by removing implausible structures and toxicophores, filtering unknown fragments, flagging preferences for molecular features, prioritizing specific physicochemical properties, prioritizing specific molecular characteristics, assessing likeness to existing drugs, and assessing binding potentials.

Furthermore, GTD allows the use of 3D structural models to explore the interactions between ligands and proteins, as well as typical docking and scoring steps to refine the search for an ideal candidate.

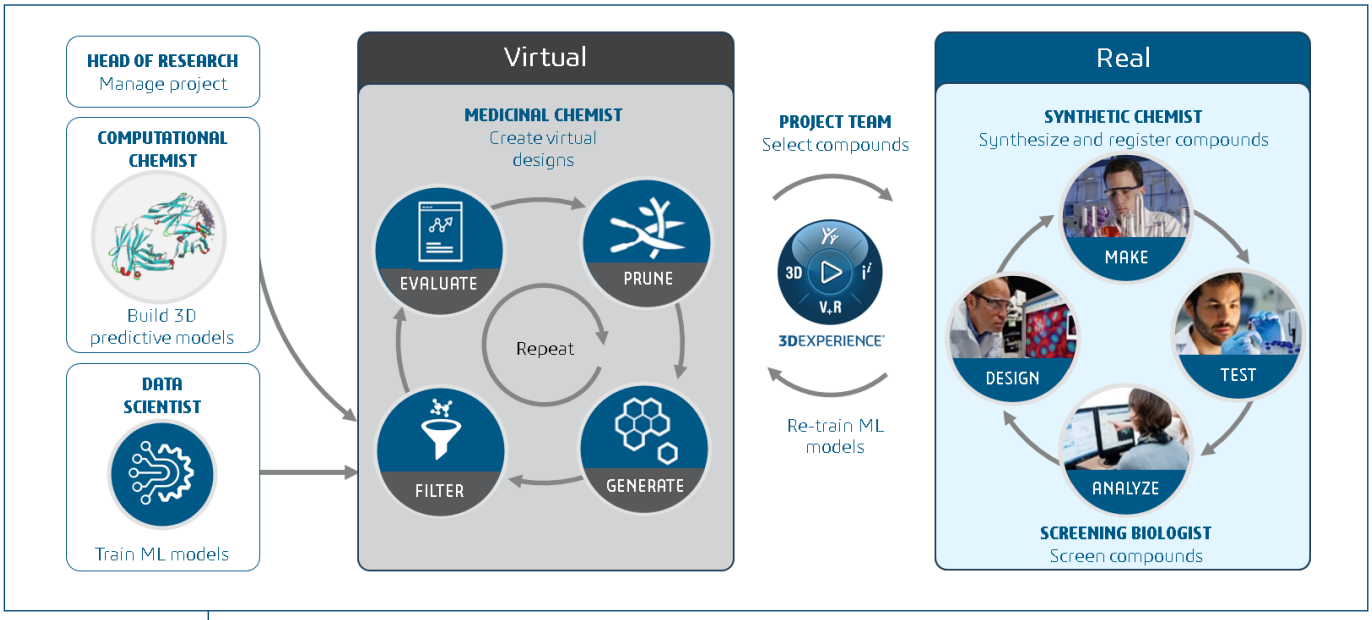


Figure 1. Virtual plus Real (V+R). The discovery process is multi-disciplinary, involving different departments and specialists. The Dassault Systèmes **3D**EXPERIENCE® platform optimizes both the speed and quality of these collaborative activities. Generative Therapeutics Design generates and optimizes new virtual molecules before submitting optimized leads to the lab and uses latest lab results in active learning cycle to retrain Machine Learning models.

RESULTS:

Using the company's data collected by medicinal chemists and biologists, GTD re-identified molecules that are now in clinical development and helped generate pre-qualified ideas to choose from, including molecules from unfamiliar chemical areas.

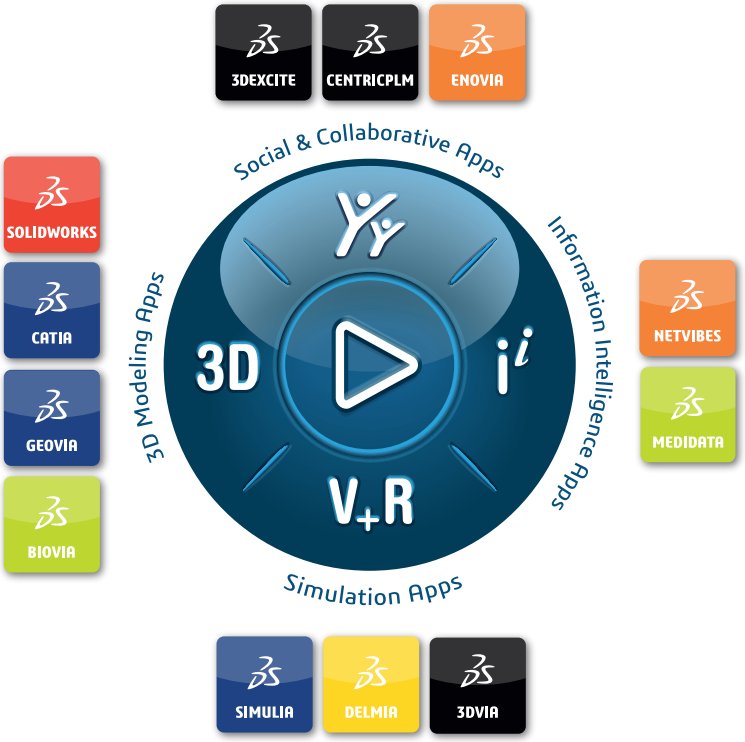
By using a 3D pharmacophore model of the binding site for the starting compound of the project, GTD was able to successfully identify a kinase inhibitor with the desired TPP along with 41 closely related compounds, after five iterations under optimized input conditions. BIOVIA used this pilot program to augment its ML models with robust 3D pharmacophore models of protein–ligand interactions, which was critical to enhance the quality of the molecules.

The project team then tested a diverse set of molecules against the 3D pharmacophore model, morphing one candidate into another (scaffold hopping). In a scaffold merging test, a hybrid 3D pharmacophore model was used to generate novel chemical compounds from known scaffolds. Starting with known input structures, GTD generated novel molecules with similar shapes and space-filling properties, and with plausible activity. These novel chemicals are slated for further evaluation.

These results demonstrate that although GTD can be implemented without the intervention of computational experts, the process can be optimized with expert input. The customer benefited from modeling experts who could build and optimally implement relevant 3D models when a robust dataset is used.

Overall, with the help of GTD, the company could identify viable clinical candidate structures within months, given the right inputs. This collaboration model not only allowed the BIOVIA customer to quickly tailor software solutions to their needs, but also enabled BIOVIA software consultants to improve their AI-driven drug discovery software for everyone, while using their expertise to rapidly enable new tools for this customer.

In regard to his experience with BIOVIA, the Executive Director of Structural Biology and Chemistry at the company said: "***What BIOVIA is offering is a mature, cloud-based system for enhancing the power of drug design teams. It is built on years of work at BIOVIA with Pipeline Pilot. It enables mixing of explicit chemical, physiochemical properties with 2D ML-models and 3D pharmacophore models to obtain useful suggestions at various stages of the drug discovery process. We also had a very good collaboration. It was phenomenal. We are looking forward to the next phase with BIOVIA.***"



Our **3D**EXPERIENCE® platform powers our brand applications, serving 11 industries, and provides a rich portfolio of industry solution experiences.

Dassault Systèmes, the **3D**EXPERIENCE Company, is a catalyst for human progress. We provide business and people with collaborative virtual environments to imagine sustainable innovations. By creating 'virtual experience twins' of the real world with our **3D**EXPERIENCE platform and applications, our customers push the boundaries of innovation, learning and production.

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