DASSAULT SYSTEMES

BIOVIA

BIOVIA PREDICTIVE SCIENCES AND BIOVIA DISCOVERY STUDIO

INTEGRATED PREDICTIVE SCIENCES SOLUTIONS TO ACCELERATE DRUG DISCOVERY AND INNOVATION

WHITE PAPER

The pharmaceutical industry is currently going through an unprecedented transformation that will certainly see further consolidations and, optimistically, the emergence of new disruptive business strategies that will drive increased value for stakeholders across the healthcare industry, especially for patients. Four market drivers are leading the charge: the rise of biologics, increase in government regulation, development of precision medicine, and digitalization of technology.

RISE OF BIOLOGICS

In recent years, pharmaceutical companies have been faced with the difficulty to discover and develop new therapeutics in order to alleviate pressures from blockbuster drugs going off patent and treat diseases with more complex mechanisms of action such as cancer. Many of these companies are increasing their efforts to remain competitive by shifting focus toward biologics drug discovery and development. Beyond pure business value such as premium pricing and higher competitive barriers to entry, biologics provide additional technological benefits such as improved binding specificity compared to small molecules. This has allowed organizations to target these more complex diseases more effectively than before, opening a new range of potential therapeutic areas for organizations to explore. However, while there are several areas of research and development workflow for biologics that are similar to small molecule drug discovery, the complexity of biologics development often requires more specialized processes and data analysis. Companies are thus being forced to actively remove bottlenecks while simultaneously incorporating novel workflows efficiently throughout the entire R&D value chain, especially in early discovery. Tools that help to process, understand, and manage high volume antibody sequence data and to rapidly customize workflows are becoming more necessary.

INCREASED GOVERNMENT REGULATION

The second important market driver is increased governmental regulation and scrutiny in many key target drug markets. These regulations have in part been introduced to improve healthcare quality and accountability, but they are increasingly also directed at containing rising drug costs for healthcare services. As healthcare systems steadily move from "fee-for-service" or volume-based models to "value" or outcome-based models, the burden will fall on the pharmaceutical industry to demonstrate added value relative to current standards of care. This will increase development costs due to more comprehensive comparative effectiveness reviews—e.g., comparing pharmaceutical vs. non-pharmaceutical therapeutic options—and more complex reporting to demonstrate this value.[1]

PRECISION MEDICINE

The third market driver, precision medicine, is, according to the National Institute of Health (NIH), "an emerging approach for disease prevention and treatment that takes into account individual variability in genes, environment, and lifestyle of each person."[2] This approach is in stark contrast to past drug development in which therapies for diseases were created for the "average" person, rather than on a case by case basis. An important factor in personalized medicine is the involvement of systems biology and the computational modeling of biological processes. This allows drug developers to take a much more holistic approach as opposed to the reductionist method of drug discovery and development used commonly in the past. The concept of data-driven treatments which incorporate the unique context of each patient will be an important factor for companies to adhere to when looking to create therapies that target and address disease mechanisms.

DIGITALIZED TECHNOLOGY

The fourth market driver is the digital information technology wave that is impacting how healthcare is viewed, managed and delivered today. Digitalization enables actionable data to improve delivery of care and enhance transparency for patients and other healthcare stakeholders. Today, digitalized tools are seeing increased adoption across the entire pharmaceutical R&D value chain, capturing data as it is generated in experiments, standardizing operations, and streamlining workflows. However, data is frequently stored in multiple locations, limiting its utility and dragging down operational efficiency for the organization at large. With the advent of novel technologies and techniques such as Big Data analytics, these disconnects are creating significant barriers to innovation for even the most forward thinking industry leaders. As a result, there is now greater awareness and reliance on technology designed to surmount these challenges. These technologies are increasingly mobile with new applications which allow healthcare providers to manage many of their professional activities using smartphones and tablets. Today's changing demographic and digitalization trends are increasing consumer-patient involvement in health care and making individual consumer-patients more responsible for managing and tracking their own health care.[3]

AN EXPANDED BUSINESS MODEL ACROSS THE CONTINUUM OF CARE

These four factors are driving a new economic business model that will transform the pharmaceutical industry and drive a new era of business growth. Pharmaceutical firms are moving more towards healthcare-oriented organizations as they collaborate with many different partners with interests that extend beyond just the medical solution. These partners include telecommunication and engineering companies for technology; patient communities and advocacy groups for services; and food and fitness businesses and associations for lifestyle approaches. The result will be the capability of delivering more complex, integrated solutions that can be tailored to the specific needs of a modern, more educated patient base.

The ability to manage structured and unstructured data of different types to generate new insights and outcomes constitutes a true competitive advantage for organizations that build more patient-centric and interactive information platforms. Integrated and interoperable informatics applications with advanced tools for identifying data trends and patterns can be used to develop more predictive and preventative approaches, especially when the generated knowledge can be harvested back into a unified, collaborative workflow ecosystem. This new R&D environment is moving the pharmaceutical industry into a new era of predictive sciences extending across the complete value chain of the continuum of care.

A NEW ERA OF PREDICTIVE SCIENCES ON A UNIFIED PLATFORM

This paradigm shift is directly impacting the way scientists can apply predictive solutions in life sciences R&D today. Indeed, predictive algorithms are now accurate enough to facilitate the resolution of a broad range of R&D challenges, enabling scientists to evaluate many more hypotheses more quickly than is possible with experimentation alone. In silico methodologies not only enhance the quality and speed of decision making, they also provide a less expensive and more scalable approach to improving R&D efficiency, especially when deployed with a holistic vision in mind.

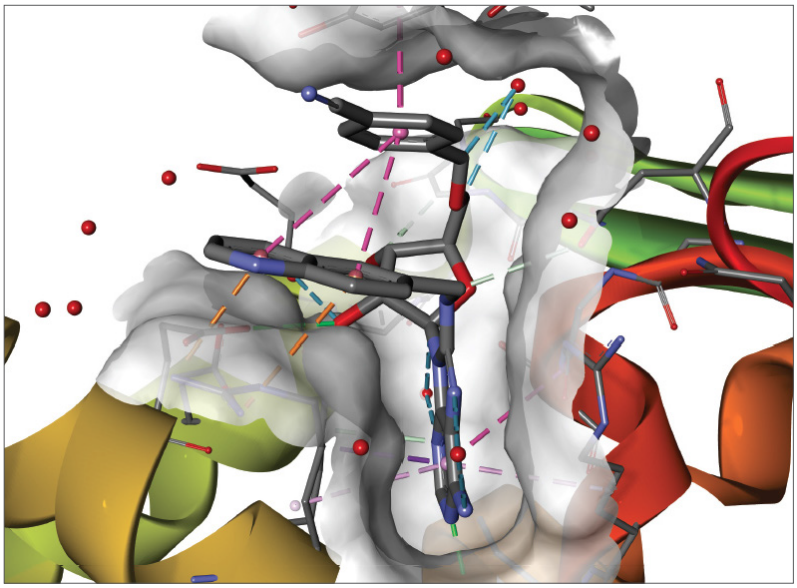

Figure 1:
Structure-based Design in BIOVIA Discovery Studio: 3D pocket views of a novel adenosine inhibitor bound inside the active site of the 70 kDa heat shock protein [PDB: 3FZM].

BIOVIA's predictive sciences capabilities can be easily integrated into the customer's R&D work flows, delivering a scientific decision support environment that reduces time and expense, improves quality, enhances collaboration and accelerates innovation in bringing new drugs to market.

Predictive workflows are typically multi-step involving model building, model validation and model consumption stages. These stages typically cross multiple scientific disciplines including computational specialists and scientists with little or no computational expertise. This can result in significant bottlenecks in the discovery process. BIOVIA's integrated predictive sciences solutions eliminate the pinch-points and errors resulting from manual data exchanges. Discovery teams can be more productive and make better informed decisions on drug design strategies because they are aligned with common discovery workflows. Furthermore, extending these tools on an organizational level enables project teams to share data and standardized analysis methods across the enterprise and among networked partners.

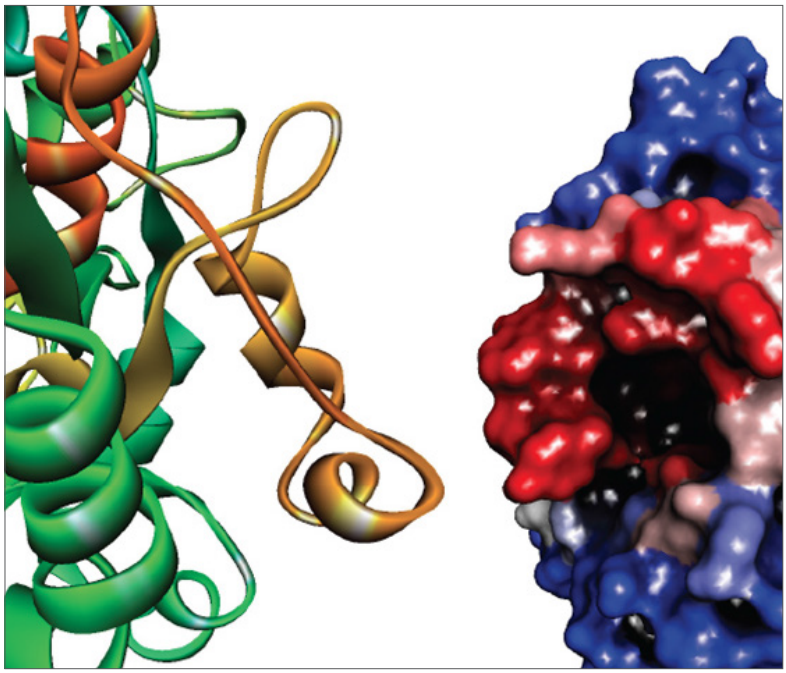

Figure 2:
Antibody Development in BIOVIA Discovery Studio: Solvent exposed surface on the fAb domain of an antibody, colored to show the predicted binding site 'hot-spot' (red) as calculated by the spatial aggregation propensity algorithm, Aggmap.

BIOVIA predictive sciences solutions enable the prediction of key physicochemical, biophysical and pharmacological end-points within shared workflows, enabling R&D scientists and project teams to:

- **Accelerate innovations and reduce dependence on experimentation:** Focus on molecules (small and biologics) most likely to possess favorable properties
- **Save time and expense:** Investigate and test hypotheses in silico prior to costly, time-consuming experimentation
- **Enhance quality:** Identify undesirable pharmacological and biological developability issues early in discovery before progression to development
- **Speed optimization:** Expend fewer cycles optimizing bioactivity and pharmacological profiles in discovery; accelerate projects to development with fewer resources consumed
- **Work consistently:** Leverage a uniform set of prediction tools across teams, partners and geographic locations
- **Integrate R&D solutions:** Align prediction tools with common R&D workflows; reduce time wasted on multiple copy-and-paste actions between disparate point solutions
- **Capture best practices in scientific innovation:** Identify and refine best research practices in a collaborative, open-platform framework

INTEGRATED PREDICTIVE SCIENCES SOLUTIONS

With the integrated predictive science solutions from BIOVIA, medicinal and computational chemists, molecular biologists, computational structural biologists and others can democratize their predictive science efforts and remove the bottlenecks in their workflows. These solutions provide the scientifically-aware capabilities scientists need to better leverage their existing knowledge and more confidently make data-driven decisions:

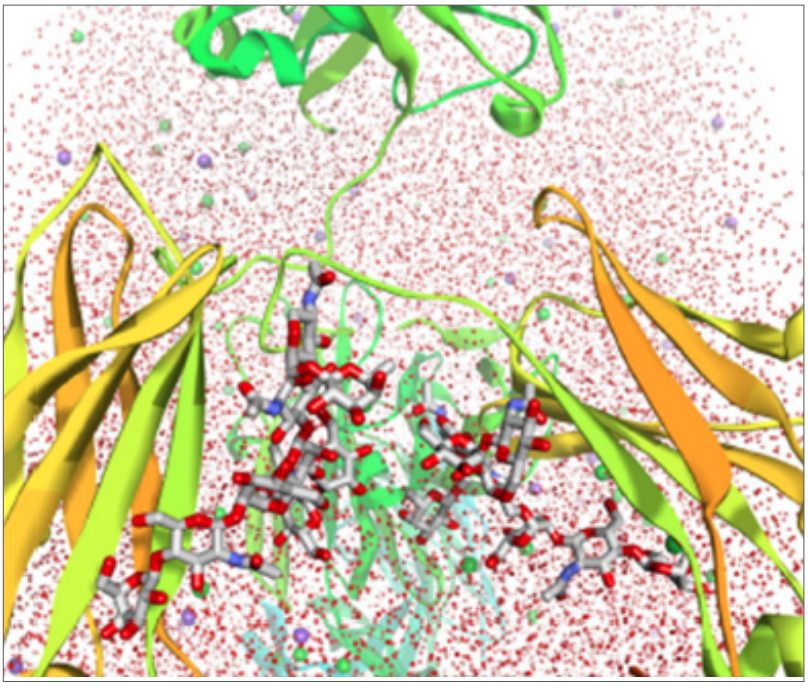

Figure 3:
BIOVIA Discovery Studio: Slice through an explicit water box, illustrating the oligosaccharide groups bound to the Fc domain of an IgG1 antibody.

- **BIOVIA Discovery Studio** – Accelerate life sciences investigation with a comprehensive portfolio of validated modeling and simulation tools for both small molecule and macromolecule-based drug design.
- **BIOVIA Materials Studio** – Support therapeutic delivery development with a collection of excipient modeling and simulation tools.

- **BIOVIA QSAR Workbench** – Automate the development, validation and deployment of predictive Quantitative Structure-Activity Relationship models to accelerate lead optimization.
- **BIOVIA Pipeline Pilot** – Rapidly create, test and publish scientific services that automate data analysis and enable scientists to rapidly explore, visualize and report results.
- **BIOVIA Component Collections** – Build, deploy and analyze complex scientific data types using BIOVIA Pipeline Pilot's discipline-specific functions to improve scientific processes and accelerate decisions.

BIOVIA DISCOVERY STUDIO: TAKING PREDICTIVE SCIENCES TO THE NEXT LEVEL

BIOVIA Discovery Studio offers a wide range of protein engineering tools including multiple-site mutation analysis and prediction of disulfide bridges. Aggregation Propensity and Developability Index calculations (among other tools) enable molecular biologists and protein/antibody design specialists to engineer stable and optimized novel biologics. Market-leading force field-based methods (e.g., Molecular Dynamics methods: CHARMm, NAMD) ensure that computational experts can also study the biophysical characteristics of solvated macromolecules on the nanosecond scale using state-of-the-art methodology.

Effective tools for analyzing, visualizing and interpreting receptor-ligand interactions are a core capability in structure-based drug design. Unique interaction visualization and analysis tools in BIOVIA Discovery Studio enable computational experts and medicinal chemists alike to design and optimize small molecule drugs using improved ligand-enumeration and scaffold-hopping work flows. These new technologies complement existing offerings in small molecule design including

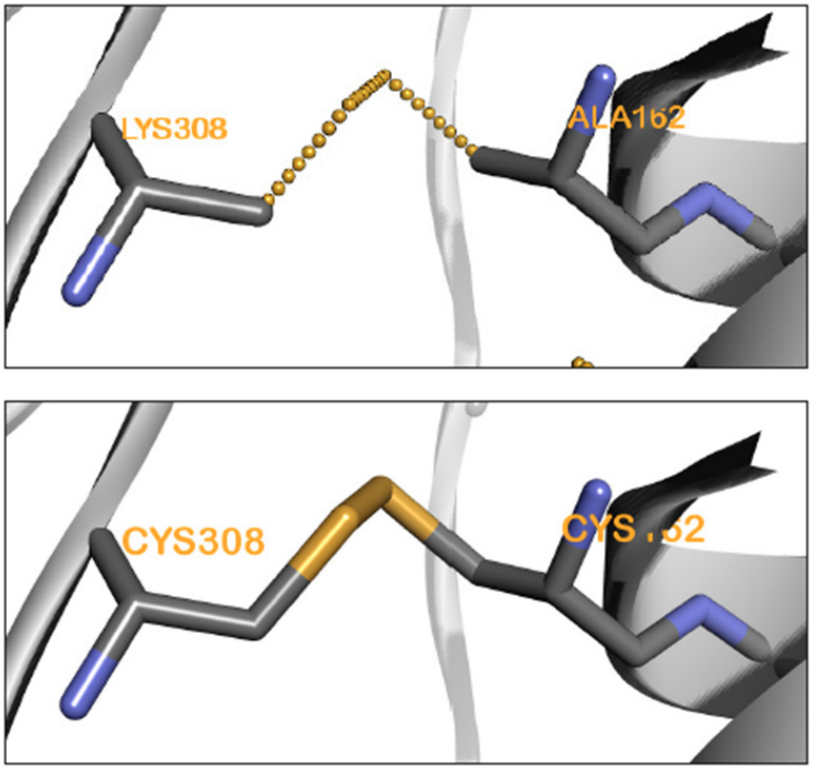

Figure 4:
BIOVIA Discovery Studio:
The predicted disulfide bridge with the top mobility score correctly matches the engineered position reported by Kim et al [Le Q.A.T, Joo J.C., Yoo Y.J., Kim Y.H., Biotech and Bioeng., 2012, 109(4), 867-76] in lipase B [PDB: 1TCA].

Ligand base (CATALYST) and Protein-based (GOLD, CDOCKER) virtual screening BIOVIA Discovery Studio QSAR and Library Design.

Built on BIOVIA Pipeline Pilot, BIOVIA Discovery Studio addresses both the science and the workflow requirements for project teams. Organizations can rapidly automate routine tasks, integrate with third-party applications and deploy "best practice" modeling methods enterprise-wide (and with networked external partners). The free BIOVIA Discovery Studio Visualizer enables interactive 3D visualizations, providing a collaborative environment for scientists to share and exchange data within project teams.

These capabilities uniquely position BIOVIA Discovery Studio—a key component of the BIOVIA predictive sciences offering for life science R&D scientists—as the most comprehensive, collaborative predictive solution for computational experts and project teams alike.

REFERENCES

1. Patient Protection and Affordable Care Act
2. https://syndication.nih.gov/multimedia/pmi/infographics/pmi-infographic.pdf
3. IBM, Healthcare 2015: Win-win or lose-lose?

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