USER STORY

Merrimack Pharmaceuticals Reduces Drug Discovery Time with MATLAB® and SimBiology

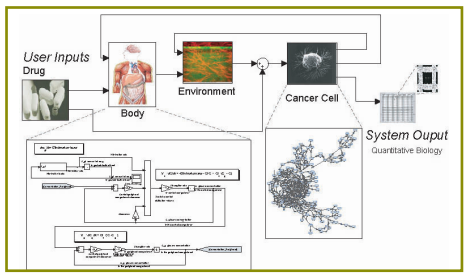
Historically, developing therapeutics to treat cancer has been challenging for pharmaceutical companies. Researchers have relied on time-consuming and costly experiments to determine which signal pathways spur uncontrolled cell growth, select the most effective mechanism to inhibit them, and then identify the patients that respond best to treatments.

Merrimack Pharmaceuticals has developed a more efficient approach to drug discovery—Network Biology—which applies computational modeling to high-throughput quantitative biology. Merrimack combines the disciplines of biology, engineering, and computational modeling to understand and design therapies. Researchers use MATLAB® and SimBiology as an integral part of their work.

"Many large pharmaceutical companies use mathematical modeling in their drug development process, but it is typically done by isolated teams," explains Birgit Schoeberl, Director of Network Biology at Merrimack. "We used MathWorks tools to fuse our quantitative biology expertise with our modeling expertise. The Network Biology platform promotes close interaction between modelers and experimentalists, enables us to analyze and simulate drug candidates using models, and streamlines the drug discovery process."

THE CHALLENGE

As a smaller pharmaceutical research company, Merrimack sought to develop a more rational drug discovery process to discover and develop breakthrough drugs with unparalleled efficiency. They saw the advantages of Model-Based Design in other engineering industries, and wanted to apply those same principles and technologies to biology.



Model-based drug design for an anticancer drug.

"In the automotive industry, you build models of your combustion and then optimize the engine to the car's design. There are similar optimizations in drug development," explains Schoeberl. "You may need to optimize antibodies to inhibit a given pathway most efficiently. Mathematical models can guide this optimization process."

Merrimack sought to combine the expertise of their biologists and modelers to pinpoint the most promising pathways, determine the optimal actions of inhibiting those pathways, and then identify patients for clinical trials. Since Merrimack's Network Biology platform uses protein arrays to gather massive quantitative data sets on parallel protein-protein interactions, they needed to translate this data into knowledge.

THE SOLUTION

Merrimack has adopted MathWorks tools to help foster and support the computational modeling piece of the Network Biology platform. Using MATLAB and SimBiology, Schoeberl and her colleagues built detailed computational models of the biochemical pathways in cancer and other diseases.

THE CHALLENGE

To develop cancer treatments based on inhibiting cell-signaling pathways that control cell growth

THE SOLUTION

Use MathWorks tools to model cell pathways, identify effective inhibition mechanisms, and focus lab experiments

THE RESULTS

- Drug discovery time cut by 80%
- Learning curve shortened
- Development platform integrated

> *Model-based drug design enables us to rapidly identify optimal pathway targets and determine the best approach. MathWorks tools are an essential part of this process. The models inform our decisions throughout drug development, enabling us to develop targeted therapeutics with higher efficacy and fewer side effects.*
>
> Birgit Schoeberl, Merrimack Pharmaceuticals

These models enable researchers to make more informed decisions throughout the drug discovery process. MathWorks tools support Merrimack's researchers at multiple stages.

In the earliest stages of a research program, Merrimack will generate large data sets to understand which networks are most critical to a specific disease or disease state. To help identify these networks from Merrimack's large data sets, researchers use the clustering algorithms in the Bioinformatics Toolbox.

Once a target network has been identified, researchers use SimBiology to build a mathematical model of the biochemical pathways. Merrimack's proprietary network models are highly data-driven and incorporate diverse data sets and information about the pathway and its components.

The team also uses SimBiology to assist in running simulations on the network and analyzing the signal dynamics that govern system behavior. These simulations help to determine the optimal therapeutic strategy to inhibit signal transduction along the pathway. Researchers assess the optimal target and how it may vary based on heterogeneity as well as the best therapeutic approach.

MATLAB and the Statistics Toolbox aid in analyzing animal experiments and pharmacokinetic modeling to find the optimal dosing and dosing strategy. As Merrimack's products enter the clinic, they will continue using their proprietary models to identify biomarkers that will help clinicians identify patients that are most likely to respond to the new drugs.

Merrimack is currently expanding the use of MathWorks tools beyond the core group of six researchers to a team of 30, including process development.

APPLICATION AREAS

- Algorithm development
- Computational biology
- Data analysis

PRODUCTS USED

- MATLAB
- SimBiology
- Bioinformatics Toolbox
- Statistics Toolbox

THE RESULTS

▪ **Drug discovery time cut by 80%.** "Relying on the fundamentals of our Network Biology platform and using MathWorks tools, a group of six researchers created seven drug candidates in fewer than three years," says Schoeberl. "Other approaches would have taken us four to five times longer, and the need for more experimentation would have increased our costs."

▪ **Learning curve shortened.** The graphical environment of the tools and MathWorks Training helped researchers to understand the programs. "The training was very helpful," notes Schoeberl. "We were all surprised at how user friendly the MATLAB development environment was and how much you can do without being a programmer. SimBiology also makes it much easier to communicate and share our models with other teams."

▪ **Development platform integrated.** "SimBiology is more flexible than other graphical tools because we can write and combine our own code with the models. It is also much easier to move data within MATLAB and SimBiology than between disparate tools," says Schoeberl. "We would have to acquire and learn three or four different software packages to complete the work we do with MathWorks tools."

To learn more about the Merrimack Pharmaceuticals, visit
www.merrimackpharma.com

www.mathworks.com

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