USER STORY

Roche Evaluates Drug Safety and Efficacy Using MathWorks Tools

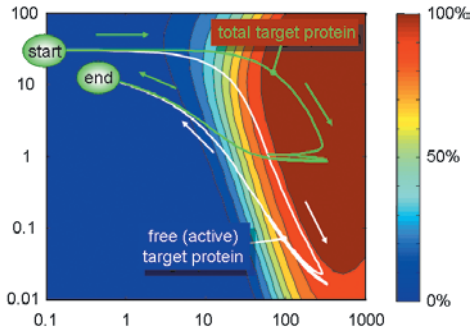
Pharmaceutical companies gain a substantial advantage when they can predict a drug's efficacy at the preclinical stage, reducing the failure rate in costly and time-consuming clinical trials.

Researchers at Roche use MathWorks tools to develop models that help predict the effect of new drugs on the body and the body's effect on the drug. These pharmacodynamic pharmacokinetic (PK/PD) models, when combined with models of organs, enable researchers to screen potential drug compounds, predict their efficacy and safety, and suggest optimal dosing regimens.

"Drug discovery today is still basically empirical," says Dr. Cristiano Migliorini, Project Leader SystemsX (Swiss Initiative on Systems Biology) at Roche. "Companies conduct multiple studies with different protocols, and it can take years to determine which drug regimen or drug cocktail is the best for a given patient population. At Roche, we use MathWorks tools to model the safety and efficacy of drugs and optimize dose scheduling, which greatly improves the efficiency of a drug's transition from preclinical to clinical trials."

THE CHALLENGE

"Researchers need to predict drug efficacy as early as possible from animal experiments," says Thierry Lavé, Global Head of Preclinical Modeling at Roche. "Modeling can be used to determining how fast the drug is cleared from the body, how safe the drug is, and how effective—which is often the most difficult characteristic to model."



MATLAB visualization used to predict the clearance rate of the target protein.

Roche needed to rapidly develop PK/PD and other biological models that use complex systems of ordinary differential equations (ODEs) and partial differential equations (PDEs). Through simulation, they would optimize critical parameters and determine the most effective dosing schedules for preclinical and early clinical trials.

THE SOLUTION

Working with MATLAB®, Optimization Toolbox, and Curve Fitting Toolbox, Roche researchers built both PK/PD and organ models for several initiatives, including tracking the effect of white blood cell maturation for an anticancer drug and monitoring the transport and accumulation of biologicals, such as antibodies, in tissues.

Because many anticancer drugs suppress the immune system and affect bone marrow, predicting the safety of specific dosing regimens is critical. The Roche team developed a PK/PD model that predicted the disposition of the drug from the body and its penetration to the target organs. They combined the general model with a detailed model of the target organ based on a complex set of ODEs and used Optimization Toolbox to determine safe dosing schedules.

THE CHALLENGE

To increase the efficacy and safety of clinical drug trials and accelerate drug discovery

THE SOLUTION

Use MathWorks tools to model drug interaction with human tissues and organs and optimize dosing regimens

THE RESULTS

- Months of effort saved
- Therapeutic profile redefined
- Clinical trial approval process streamlined

> *MATLAB® is vital in the development of specialized biological models at Roche. Using MathWorks tools to solve difficult ODE and ODE-PDE models, visualize results, and perform parameter optimization enables us to quickly isolate issues in the development of candidate drugs and to design the best experiments to tackle those issues.*
>
> Cristiano Migliorini, Roche

The model incorporates data from animal tests on the new drug and on a similar, existing drug, as well as publicly available data for the existing drug derived from human clinical trials. It can be used to estimate the efficacy of the new drug in humans and guide initiation of clinical trials. Curve Fitting Toolbox enabled Roche to find empirical functions that fit points in the experimental data and then use these complex functions in dynamic simulations.

On the second project, Roche used MATLAB to develop a physiologically-based model of an organ based on PDEs. This model enabled researchers to simulate fluid transport through the tissue and the distribution of the biological drug. By combining the organ model with a PK model of the peripheral system, it is possible to predict how much of the compound will accumulate in the organ, and once again to suggest an optimal dosing regimen in preclinical and clinical trials.

Roche researchers plan to use Simulink® to rapidly assemble and reuse sophisticated models of biological systems based on their MATLAB PK/PD and other models. They continue to use MATLAB to model new drugs and design preclinical and clinical studies.

THE RESULTS

- **Months of effort saved.** "Our MATLAB models helped us design the 'right' experiments," says Lavé. "As a result, Roche streamlined animal experiments and technical formulation of the compound. We avoided what would have been a risky development path, saving months of effort."
- **Therapeutic profile redefined.** Using MATLAB, we were able to integrate knowledge from heterogeneous sources to show that one drug compound occupied the target much longer than expected," says Hans Peter Grimm, Senior Scientist in the Preclinical Modeling group at Roche. "This information influences the design of further experiments, the selection of the dosing regimen, and the therapeutic profile."
- **Clinical trial approval process streamlined.** "We always support our requests to start clinical trials with our models of PK in combination with pharmacodynamic or safety end points," says Grimm. "MATLAB, with its unique combination of computational power, user-friendly development environment, graphical output of results, and data handling capabilities, has become one of the most powerful tool for this task."

To learn more about Roche, visit **www.roche.com**

APPLICATION AREAS

- Biotechnology, pharmaceutical, and medical
- Data analysis
- Algorithm development
- Modeling and simulation

PRODUCTS USED

- MATLAB®
- Simulink®
- Optimization Toolbox
- Curve Fitting Toolbox
- Statistics Toolbox

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