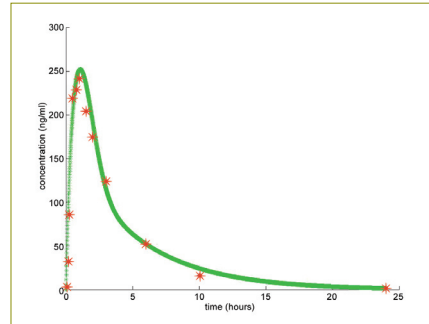


Novartis Accelerates Model Development Process with MathWorks Tools

How can a pharmaceutical company most accurately predict the efficacy of potential drugs and determine the most promising dosing regimens for humans before conducting clinical trials?

Researchers in the Modeling and Simulation group at Novartis use MathWorks products to develop simulations that help answer these difficult questions.

“MathWorks tools help us streamline the development process by enabling us to simulate dosing regimens before clinical trials,” says Brian Stoll, senior scientist at Novartis.



Comparison of experimental and model-predicted tissue concentration of Novartis drug as a function of time following oral administration.

To accomplish their goals, the group requires a flexible, integrated modeling environment to enable rapid simulation, optimization, and statistical analysis. This environment must provide easy access to a wide range of capabilities, including tools for symbolic math and ordinary differential equations.

THE SOLUTION

Novartis uses MATLAB® and Simulink® to create physiologically based pharmacokinetic (PBPK) models that describe the uptake and distribution of a drug given to animal species or humans over time.

They create these PBPK models using a system of ordinary differential equations, with an associated set of variables and parameters.

THE CHALLENGE

To facilitate and streamline the drug development process by combining the analysis of existing sparse experimental data with computational models

THE SOLUTION

Use MathWorks tools to model and simulate the interaction of biological systems and potential drug compounds

THE RESULTS

- Model development streamlined
- Productivity increased through model reuse and collaboration
- Tight deadlines met consistently

THE CHALLENGE

The Modeling and Simulation group at Novartis provides a wide range of services to researchers, including simulating biological systems using mathematical models to prioritize and select drug candidates and recommend dosage for clinical studies.

“We use models to make predictions in humans when we cannot do a direct measurement,” says Anna Georgieva, senior scientist at Novartis. “This is a way to incorporate existing data and guide clinical trials.”

The models typically include a set of known parameters, such as tissue volume and blood flow rate, and an unknown set, such as rate of absorption and partition coefficients. For Novartis, getting useful results depends on developing accurate models, finding values for unknown parameters, and estimating their uncertainty.

“For solving our systems of ordinary differential equations, the algorithms in MATLAB are more robust than other software packages I’ve used,” explains Stoll, who adds that Simulink simplifies the model development process and facilitates collaboration. “With Simulink, you can graphically organize the organs of the body physiologically. This makes it easier to explain what we’ve done to someone with expertise in biology.”

Finding values for the unknown parameters in PBPK models is a three-step process. First, the team generates predictions from the models using educated guesses for the unknown parameters. Next, they use the Genetic Algorithm and Direct Search Toolbox and the Optimization Toolbox to compare those predictions to experimentally measured data and find the best values for the parameters that describe the data. Once they find the best parameter values, they use the Statistics Toolbox to conduct parameter positivity and uncertainty analyses.

The Novartis team sees the role of MathWorks tools in the drug development process potentially expanding over the next few years.

“We have support for the integration of computational modeling into various aspects of the drug development process,” Stoll says. “The adaptability and versatility of MathWorks products are a definite advantage. These products enable us to address a wide range of challenges as they arise.”

APPLICATION AREAS

- Biotechnology, pharmaceutical, and medical
- Data analysis
- Simulation

PRODUCTS USED

- MATLAB
- Simulink
- Genetic Algorithm and Direct Search Toolbox
- Optimization Toolbox
- Statistics Toolbox

“Having a single, widely used package in our industry that has many capabilities for solving ordinary differential equations as well as optimization and statistical capabilities is quite valuable. That is why we use MathWorks tools.”

Anna Georgieva,
Novartis Pharmaceuticals Corporation

THE RESULTS

- **Model development streamlined.** “I compared the time required to develop a PBPK model using an advanced Fortran editor and debugger with the time required using Simulink,” explains Stoll. “In Simulink, the same model took approximately a third of the time to develop.”
- **Productivity increased through model reuse and collaboration.** “We can quickly customize our models to a particular compound or biological system by changing parameters,” says Stoll. “The wide use of MATLAB in our industry also facilitates collaboration with other researchers.”
- **Tight deadlines met consistently.** Novartis expects the Modeling and Simulation group to complete and optimize certain compound-specific models within two to three weeks. “After we create the model, a typical optimization run takes no more than a minute, so we can easily meet our deadlines using MATLAB,” Georgieva notes.

To learn more about Novartis, visit
www.novartis.com

www.mathworks.com