

Certara NLME

State of the Art Modeling Software for Today's PK/PD Scientists

Certara's NLME is the premier PK/PD modeling engine that powers Certara's industry-leading Phoenix[®] software, and is now available as a stand-alone software that can be driven by programming in R. In both implementations, NLME is user-friendly and easy-to-learn. Phoenix NLME is the most powerful non-linear mixed effect modeling engine available to scientists today and is used by 1,400 scientists, 18 of the top 20 pharmaceutical companies in the world, renowned academic institutes, and multiple regulatory agencies, including the US Food and Drug Administration (FDA).

NLME includes a full suite of algorithms for non-linear mixed effects models including QPREM, the most advanced expectation maximization algorithm available. In tested models, QPREM was found to be consistently the fastest to converge among EM methods, demonstrating the advantage of this approach¹.

Included Algorithms

Individual and Pooled Data Analysis	Population Analysis	
	Parametric Method	Non-parametric Method
<ul style="list-style-type: none"> • Naïve Pooled 	<ul style="list-style-type: none"> • FO • FOCE-LB • FOCE-ELS • IT2S-EM • Laplacian • AGQ • QPREM 	<ul style="list-style-type: none"> • Non-parametric Engine

Phoenix NLME

Built from the ground up on the Phoenix workbench architecture, Phoenix NLME enables users to focus on modeling, and not on the tools or coding required to implement the modeling. The result is more time for analysis and strategic decision-making. Plus, Phoenix NLME is the first PK/PD modeling software to be out-of-the-box grid-enabled, supporting remote parallel execution on compute platforms.

Most User-friendly PK/PD Software Available

Phoenix NLME uses a modern, intuitive graphical user interface (GUI) that provides a seamless transition between modeling ideas and modeling execution.

- Select from a complete library of built-in models or use the graphical model editor for quick customizations. In either case, the full model code is available using Phoenix Modeling Language (PML), a modern modeling language that is easy to read and understand.
- Informative diagnostic messages are provided during model building and execution to quickly and easily identify and remedy errors in a model. Phoenix NLME automatically produces the required diagnostic tables and plots, enabling instant evaluation of model results.
- Along with the Model Comparer tool, the model selection process can be automated with Run Options such as Covariate Search, Covariate Shotgun, and Scenarios.

Combining these innovative features for modeling with data preparation, data formatting, statistics, table, and plotting tools built into the Phoenix workbench makes Phoenix NLME a modern tool for today's PK/PD modeling scientist.

New Features and Enhancements in NLME

- Model delayed outcomes using the automated and fully integrated discrete and distributed delay functions
- Greater flexibility and broader applicability with the Visual Predictive Check function
- Significantly reduce model run times via parallelizing jobs on remote compute platforms
- Seamlessly pair Phoenix NLME with Certara's Compute Grid to accelerate model runs, affordably and without IT support

The power and flexibility of Phoenix NLME makes it suitable for many demanding PK/PD studies including:

- Translational modeling
- Extrapolating PK data from animals to humans
- Enabling sparse sampling strategies
- Predicting the pharmacodynamics in humans based on *in vitro* models
- Combining PK and PD data from multiple studies
- Enhancing study designs to minimize animal use

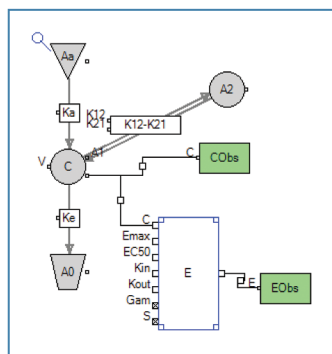
Powerful and Widely Used for Regulatory PK/PD Submissions

Phoenix NLME was developed for optimal performance and maximum flexibility. Both beginners and advanced users can leverage the power of NLME for PK/PD analysis. NLME has integrated support for parameter estimation, simulation, automated covariate searches, bootstrap parameter estimation, and visual predictive checks give a user the flexibility to conduct all phases of a PK/PD analysis with a single intuitive tool.

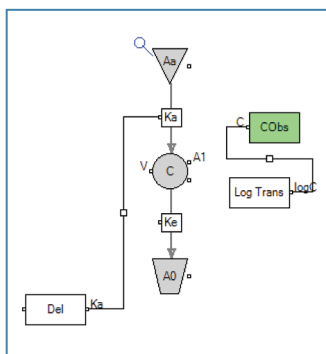
Guided Model Development

Phoenix NLME provides full 1-to-1 mapping between the development of an optimal modeling strategy and corresponding tools required to perform the analysis. Often the most difficult part of PK/PD modeling is building the right model for the study. Phoenix NLME makes that easy with a graphical model building interface called the Drug Model Explorer (DME) that can easily create custom models including multiple absorption or clearance pathways, parent-metabolite models, and complex exposure-response models. The DME also writes PML code for users, helping new users learn model coding. Combining these innovative features of the software with step-by-step examples and classroom/online training courses at Certara University makes Phoenix NLME easy to learn for beginners, self-guiding for novice modelers, and optimized for advanced users.

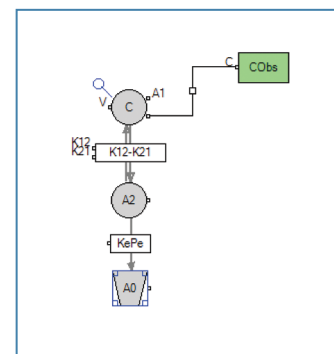
Custom Models Created by Drug Model Explorer



PK/PD Model with Emax Pharmacodynamics Response



PK Model with Modified Ka and Log-transformed Concentration Data

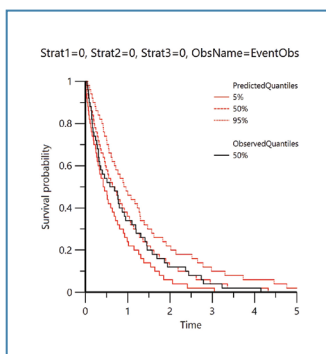


2-Compartment PK Model with Elimination from the Peripheral Compartment

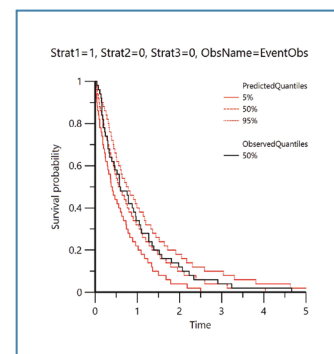
Visual Predictive Check

Visual Predictive Check (VPC) is a graphical comparison and analysis of observations and simulated predictions.² VPC in Phoenix NLME now provides broader applicability and flexibility for users. These enhanced functionalities include the ability to perform separate analyses for different data types such as continuous data, including Below Quantification Limit (BQL), and discrete observations such as categorical, single time-to-event, and count data. Other improvements include separate Visual Predictive Check and Simulation modes and VPC Stratification for categorical covariates.

Single Time-to-event with Stratification



Stratum Value 0



Stratum Value 1

Out-of-the-box Grid-enabled

One challenge of population PK/PD modeling is the need for computing power to solve complex models in a reasonable time frame to support drug development decisions. NLME features parallelization for almost all run modes, versus command line and manual execution, and the ability to run on powerful remote compute platforms, reducing run times from days to minutes.

NLME uses an algorithm that automatically maximizes the number of cores for each run to minimize run times without any user intervention. For example, a standard laptop computer has 4 CPUcores available for model fitting, but a grid configured with 100 cores will run an NLME job 25 times faster than the laptop computer. After sending a NLME job to the grid, the results are automatically downloaded when the job is finished. Users can disconnect and reconnect to running jobs and view interim run results to catch and fix any mistakes. NLME also enables a user to initiate an NLME job on a remote/parallel compute platform directly from the desktop application without the need to install NLME on the remote computer.

How Does Automatic Algorithm for NLME Parallelization Work?

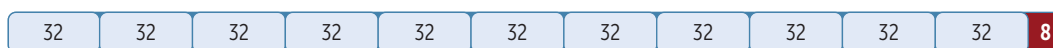
Example 1: Simple run with sort variable (360 cores, 400 subjects, 3 unique sort keys)

With 400 subjects and 3 unique sort keys using a 360-core grid, the automatic algorithm selects the optimal number of cores to maximize the use of all 360 cores.



Example 2: Log-likelihood Profiling (360 cores, 10 perturbations, 300 subjects and no sort keys)

The total number of models (n) equals (# perturbations + 1). The automatic algorithm runs 11 models in parallel with 32 cores each.



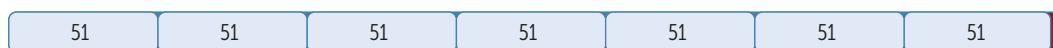
Example 3: Covariate Search Stepwise (360 cores, 8 covariate-parameter relationships, 300 subjects, 3 covariates in final model)

The algorithm calculates the optimal parallelization at each stage of addition and deletion.

Round 1: Baseline + 8 covariate models, forward addition



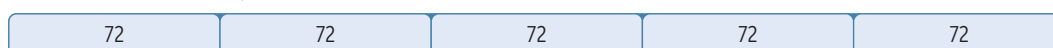
Round 2: 7 covariate models, forward addition



Round 3: 6 covariate models, forward addition



Round 4: 5 covariate models, forward addition



Round 5: 3 covariate models, backward deletion



Faster Model Runs with NLME Parallelization

- All run modes are parallelized on remote platforms, except Sim./Pred. Check
- Automatic algorithm uses the maximum number of cores for each run to minimize run times without any user intervention
- There are no additional license fees to access remote platforms to run NLME models; grid usage costs are separate
- Disconnect and reconnect to running jobs, and view interim run results to catch and fix any mistakes
- Settings for remote computational grids are included in the Preferences section of Phoenix

Cutting-edge Science

Phoenix NLME is the first PK/PD modeling engine to offer integration of discrete and distributed delay functions, eliminating the need to add complex lines of code. This methodology can be used to replace transit compartments, dual absorption models, effect compartment models, or even indirect response models, providing a more accurate evaluation of these models. The new delay functions greatly simplify modeling delayed outcomes, an important function in several therapeutic areas such as oncology, diabetes, and arthritis.^{3,4} A delay function can be added with a single Phoenix Modeling Language (PML) command, avoiding inefficient workarounds and approximations.^{5,6}

Interoperability

Phoenix NLME is interoperable with any PK/PD modeling paradigm. Phoenix also provides interoperability with software packages such as SAS®, R, SigmaPlot®, NONMEM®, PSN, Watson LIMS™, and more. This allows users to integrate specialized software tools into a Phoenix workflow to ensure compliance and data traceability. Phoenix NLME is designed to easily export analysis results for incorporation into PK/PD reports. Any plot, figure, or table can be exported to a Microsoft® Word document with a single click. Using the Phoenix Reporter tool, users can compile a series of plots, figures, and tables into a single Microsoft Word file with customized numbering and headers. This output can then be quickly and easily attached to a PK/PD report for communicating results internally and to regulatory agencies.

Compliance

PK/PD modeling requires users to follow regulations to ensure compliance with regulatory agencies around the world. Phoenix NLME does the compliance work for users. Each object includes a validation tab to confirm proper operation, a history tab that keeps an audit trail of any changes, and a settings output that records the settings used for analysis.

Leverage your Experience with Phoenix WinNonlin

Since it is built on the Phoenix workbench, Phoenix NLME leverages the same GUI that users rely on when using WinNonlin®. Combining Phoenix NLME with WinNonlin creates a comprehensive analysis package that can be used for optimal PK/PD modeling and simulation through all stages of drug development, including regulatory submission. The integrated tools for data processing, PK/PD modeling, post analysis statistics, table creation, and an integrated graphics engine create a single all-in-one collaboration workbench for scientists, reviewers, medical writers, and quality assurance team members.

Ready to Experience the Power of Phoenix NLME?

Contact us at sales@certara.com to learn how you can start using Phoenix NLME today.

References

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4. Koch G, Krzyzanski W, Pérez-Ruixo JJ, & Schopp J. (2014). Modeling of delays in PKPD: Classical approaches and a tutorial for delay differential equations. *J Pharmacokinetic Pharmacodyn*, 41, 291–318.
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6. Krzyzanski W, Hu S, & Dunlavy M. (2018). Evaluation of performance of distributed delay model for chemotherapy-induced myelosuppression. *J Pharmacokinetic Pharmacodyn*, 45, 329–337.

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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