

PECAN, a Shiny application for calculating confidence and prediction intervals for pharmacokinetic and pharmacodynamic models

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INTRODUCTION

BACKGROUND Confidence of model predictions is an important aspect for the utility of pharmacokinetic (PK) and pharmacodynamic (PD) models in the decision-making processes, e.g., for defining safety margins or selecting doses. Available fitting tools typically provide information about the confidence of the estimated model parameters, but information about the confidence around the primary result, e.g., the predicted concentration-time or exposure-response curve, is not available directly (Table 1).

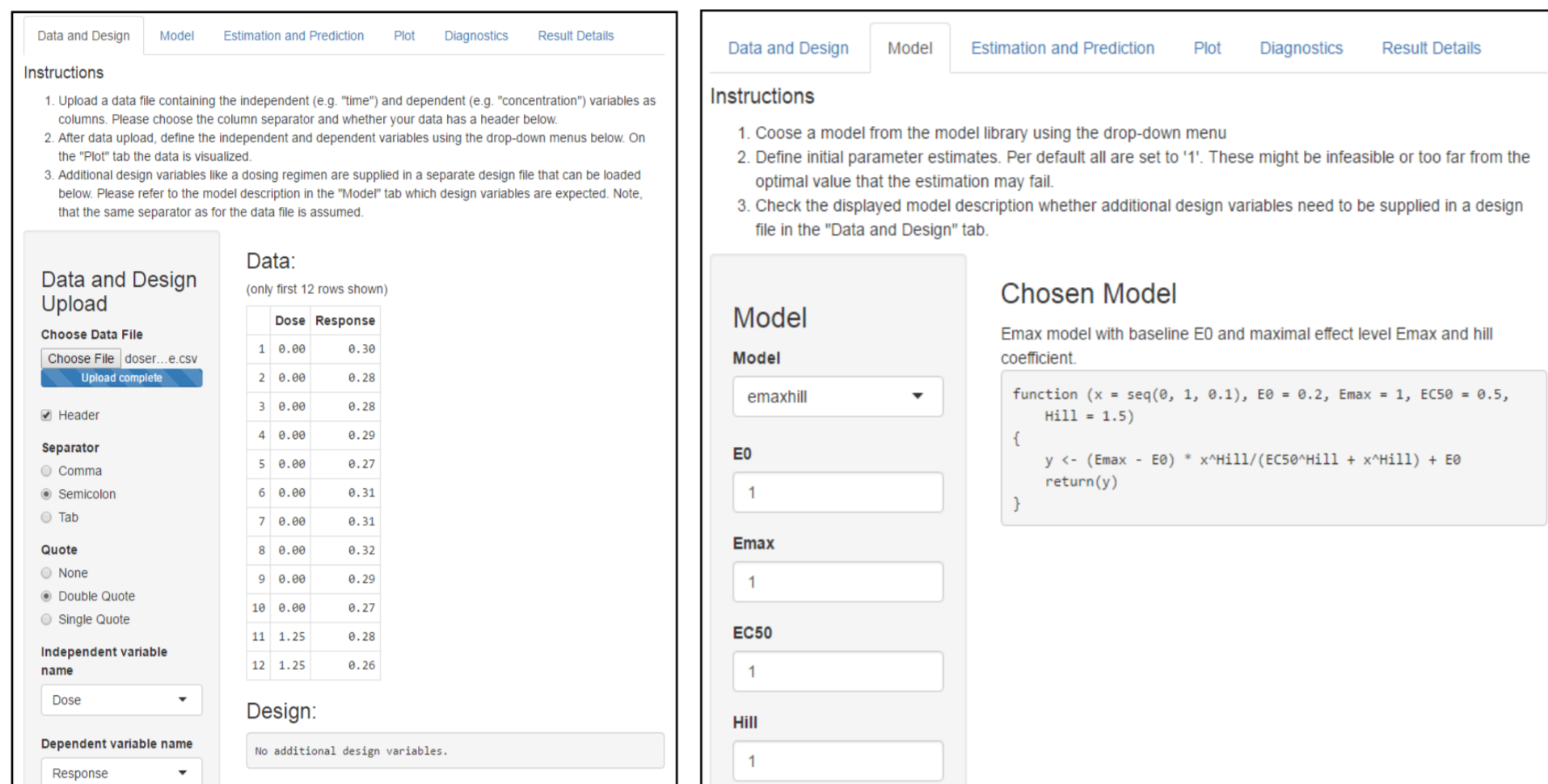
OBJECTIVE Implementation of a single-interface framework for data fitting, confidence and prediction interval derivation for typical PK and PD/PD functions with visualization of the results.

PECAN INTERFACE

Data upload and model selection

Datasets are uploaded on the “Data and Design” panel. The model is chosen from the model library (see Implementation section) and initial parameter values are defined on the “Model” panel (Figure 1).

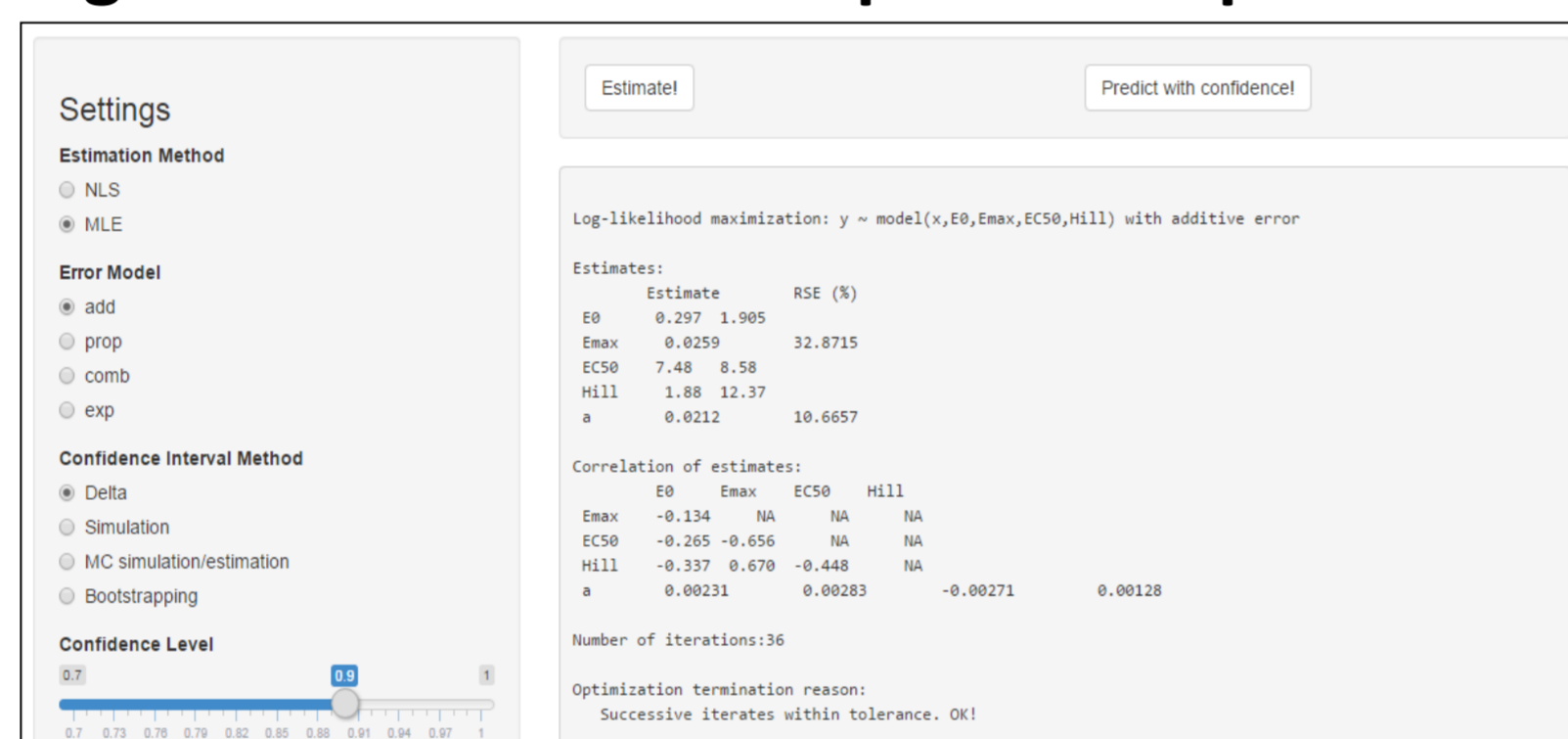
Figure 1: Data and Design (left) and Model panel (right)



Settings and estimated parameters

The estimation method, error model and confidence calculation method (see Methods) are defined on the “Estimation and Prediction” panel (Figure 2). Parameter estimation results are displayed.

Figure 2: Estimation and prediction panel



Result visualization

Predictions and their confidence intervals are visualized with the underlying data on the “Plot” panel (Figure 3).

Figure 3: Overlay of data and predictions

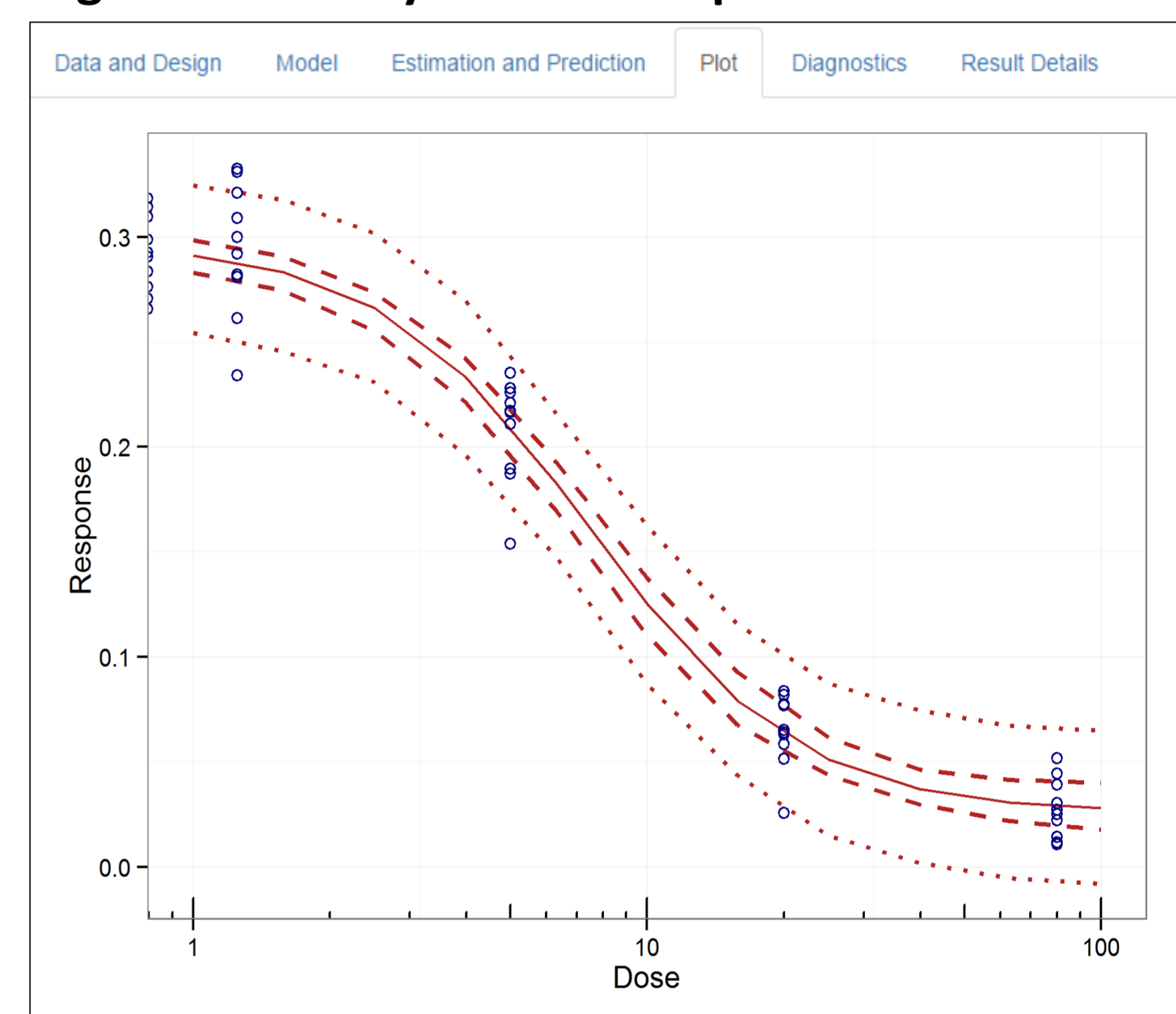
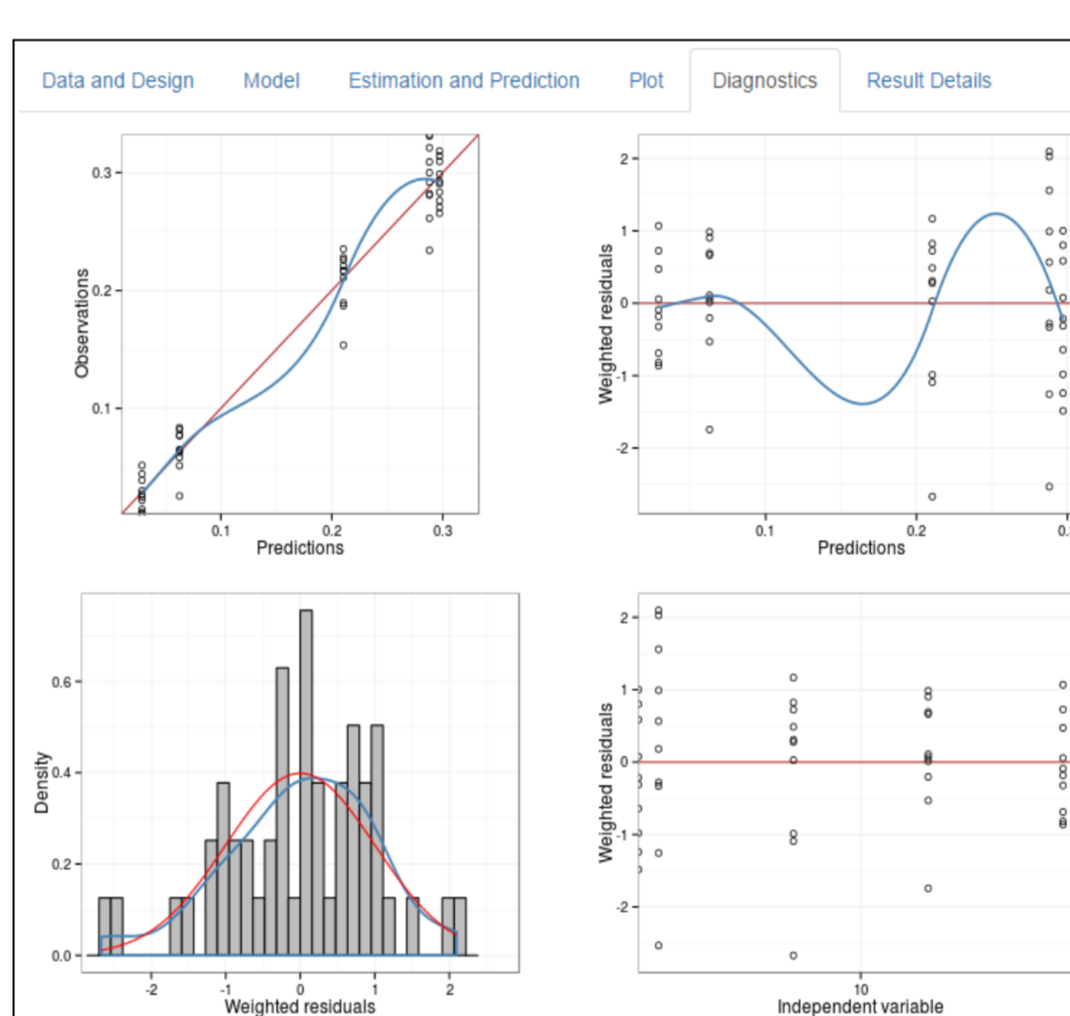


Figure 4: Diagnostic plots



Diagnostic plots can be inspected on the “Diagnostics” panel (Figure 4), including, observed vs. predicted values, distribution of residuals, and residuals vs. independent and dependent variable.

IMPLEMENTATION

Model library

Typical pharmacometric and pharmacodynamic models are implemented in the model library:

- E_{max} model with and without Hill coefficient
- 1- and 2-compartmental models following single oral or iv administration
- ADVAN style analytical solutions of 1- to 3-compartment models [1] allowing for flexible dosing regimens (defined in design file which must be uploaded in addition to the data)

Parameter estimation

Non-linear least squares (NLS) or maximum likelihood estimation (MLE) are implemented using the standard R functions “nls” and “nlm”.

An additive, proportional, combined (additive + proportional), or an exponential error can be applied when using MLE.

NLS is faster than MLE but limited to an additive error model. In this case, the standard deviation of the residuals is used as an estimator of the residual error.

Confidence interval calculation

The implemented CI calculation methods are listed and compared in Table 1.

Table 1: Implemented CI calculation methods

Method	Calculus
Delta method [2]	Prediction uncertainty based on parameter estimation errors and Jacobian matrix (approach derived by Taylor approximation).
Simulation	Simulations by sampling from the parameter estimate covariance matrix to derive prediction uncertainty.
MC simulation/estimation [3,4]	Re-estimation of parameters based on simulated datasets (while sampling from the parameter estimate covariance matrix). Simulations using the re-estimated parameters to derive prediction uncertainty.
Bootstrapping [3,4]	Re-estimation of parameters based on bootstrapped datasets. Simulations using the re-estimated parameters to derive prediction uncertainty.

RESULTS AND CONCLUSION

RESULTS PECAN, a Shiny application, combines models for pharmacometric applications and different methods into a single-interface framework, generalizing the concept of confidence and prediction intervals. PECAN demonstrates how PK and PK/PD model uncertainty can be derived in a standard programming language such as R. At the same time, the implementation as a Shiny application provides easy access for a broad audience. The user can choose between different methods for estimation and confidence calculation and error models. The Shiny application can be accessed at <https://carumcarvi.shinyapps.io/pecan/>.

CONCLUSION Visualization of model fit, confidence and prediction intervals allows judgment about the overall uncertainty of PK and PK/PD models: the uncertainty around the fitted model curve in contrast to only the individual model parameter estimates. This allows a direct visual assessment of the predicted relevant clinical outcome, e.g., the expected response of a future dose or the PK profile.

REFERENCES

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