A Scalable, Traceable and Integrated Tool for Large QSP Models Calibration

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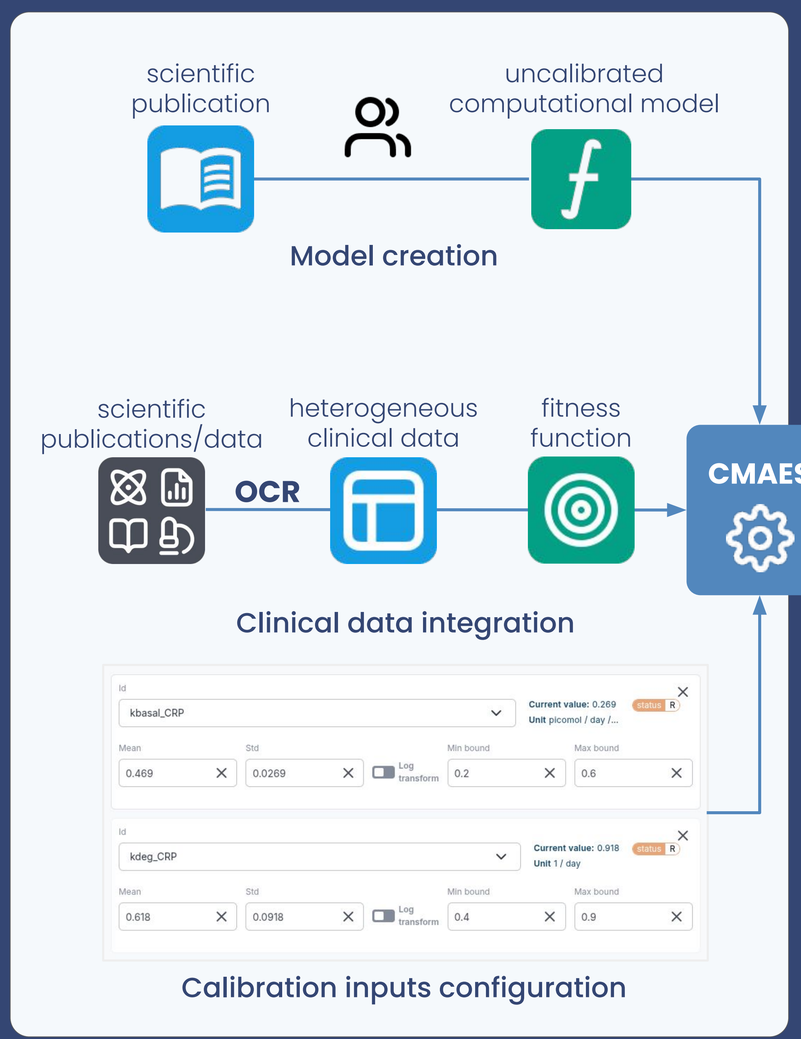
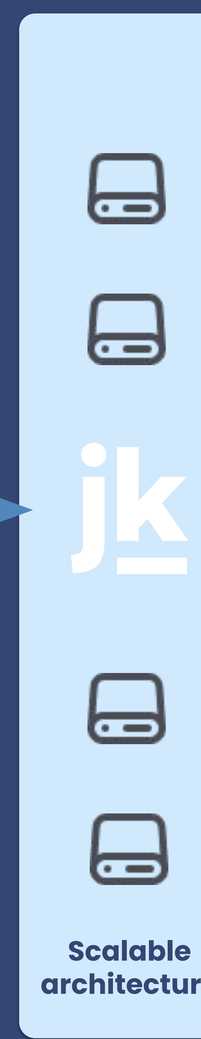
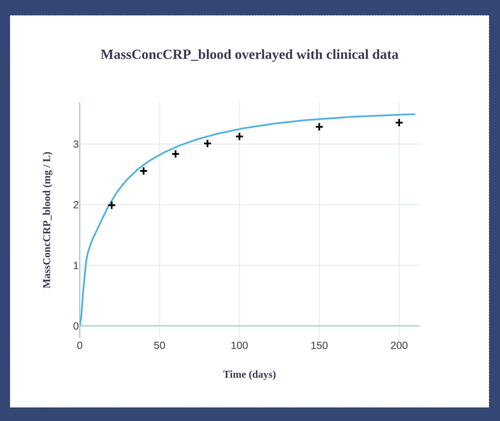
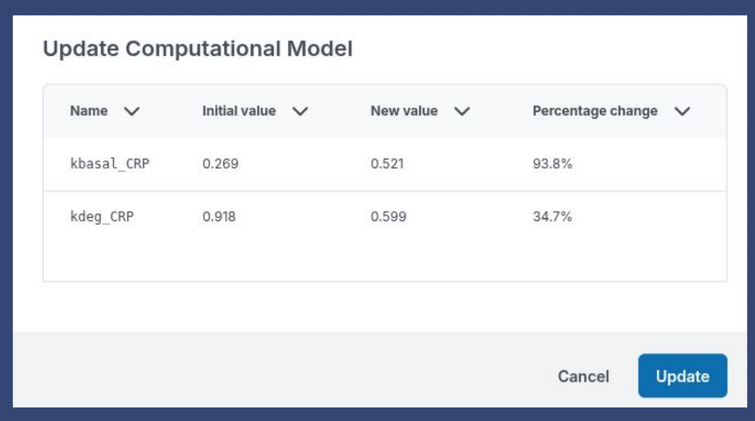
A streamlined workflow to **calibrate** QSP models, leveraging Jinkō's integrated **traceability** and **scalability**





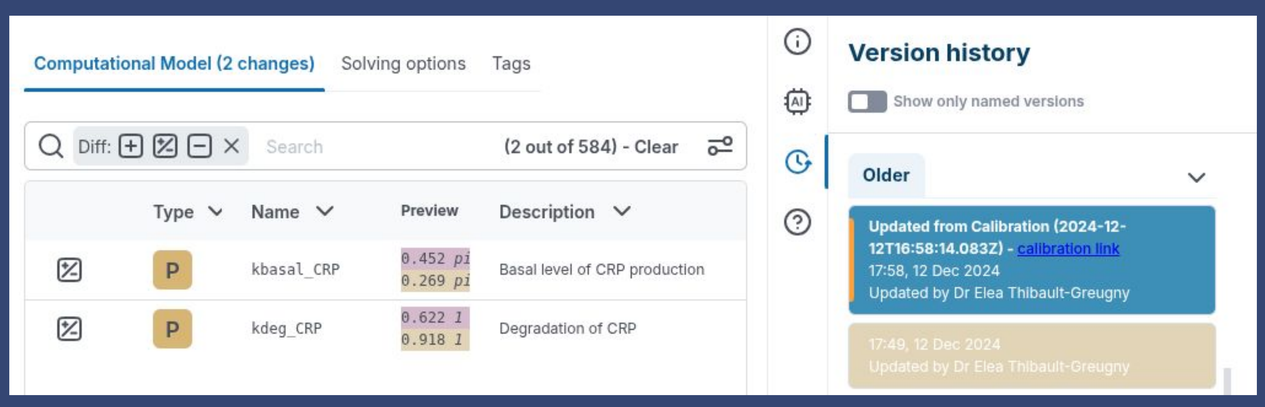


Results assessment



Seamless model update

Calibrated Computational model



Traceable and versioned changes

From heterogeneous clinical data to a calibrated model in a matter of minutes: produce reliable simulation results thanks to Jinkō's streamlined calibration workflow

BACKGROUND

Model calibration is a key step in producing reliable simulation results. In the context of large quantitative systems pharmacology (QSP) models, parameter estimation requires careful integration of diverse datasets, as well as an optimization strategy and a simulation architecture in line with the computational cost of model evaluation.

Jinkō [1] implements a streamlined workflow emphasizing traceability and scalability in order to efficiently fine tune large QSP models to reproduce clinical data.

METHODS

We have implemented in our system a workflow that encompasses the following steps.

- ➔ **Clinical Data Integration**: Extraction of relevant data from scientific publications into version-controlled data tables using Optical Character Recognition (OCR) [2], ensuring traceability to original sources.
- ➔ **Calibration Inputs Configuration**: Definition and configuration of the model parameters to estimate, including their scales and bounds, supported by sensible defaults to accommodate diverse datasets.
- ➔ **Fitness Function Definition**: Automatic generation of the calibration fitness function from data tables, with the option to incorporate advanced scoring metrics for nuanced calibration objectives.
- ➔ **Optimization Algorithm**: Efficient optimization of model parameters using the Covariance Matrix Adaptation Evolution Strategy (CMA-ES) [3], a state-of-the-art evolutionary algorithm adept at navigating complex cost functions in high-dimensional search spaces.
- ➔ **Scalability**: Augment the optimization strategy with advanced solving techniques from the Sundials suite [4], and efficient parallelism thanks to our system's cloud-based architecture, which allows us to simulate large models against extensive virtual populations on multiple protocol arms.
- ➔ **Results Assessment**: Quantitative and qualitative evaluations to validate the calibration outcomes, with visual overlays, access to the numerical distance between experimental and simulated data, and convergence metrics.
- ➔ **Model Update**: Seamless update of the model with calibrated parameters through a one-click process, creating a new versioned model instance for ongoing development.
- ➔ **Traceability and Collaboration**: Our system helps maintain traceability throughout the calibration process, from parameter adjustments to data sources, and supports collaborative efforts through multi-user editing and version control features.

RESULTS

Accelerated calibration cycles

The implementation of this workflow has demonstrated significantly accelerated calibration cycles, with the ability to iteratively refine models while maintaining a clear audit trail of changes.

Successful application of the workflow to large QSP models

Specifically, we have successfully applied this workflow to the calibration of **20** parameters from a QSP pruritus model comprising about **200** ordinary differential equations. Jinkō facilitated the import of **large and heterogeneous datasets** with a total of more than **50,000** model evaluations.

CONCLUSION

The proposed workflow offers a robust, user-friendly solution for aligning large QSP models with experimental data. By integrating advanced optimization algorithms, scalable simulation capabilities, and comprehensive traceability features, our system has allowed us to perform efficient and reproducible model calibrations, fostering greater confidence in simulation outcomes.

REFERENCES

[1] Jinkō: www.jinko.ai
[2] Shunji Mori, Hirobumi Nishida, and Hiromitsu Yamada. 1999. Optical character recognition. John Wiley & Sons, Inc., USA.
[3] Hansen N, Kern S (2004). Evaluating the CMA evolution strategy on multimodal test functions. In Xin Yao et al., editors, Parallel Problem Solving from Nature – PPSN VIII, pp. 282–291, Springer
[4] Hindmarsh, Alan C., et al. "SUNDIALS: Suite of nonlinear and differential/algebraic equation solvers." ACM Transactions on Mathematical Software (TOMS) 31.3 (2005): 363-396.