

¹ estim8 - An FMI-compliant Python toolbox for ² bioprocess modeling and parameter estimation

³ **Tobias Latour**  ¹, **Daniel Strohmeier**  ², **Michael Osthege**  ¹, **Wolfgang Wiechert**  ^{1,3}, and **Stephan Noack** 

⁵ **1** Institute for Bio- and Geosciences (IBG-1), Forschungszentrum Jülich GmbH, Jülich, Germany **2**

⁶ **Institute for Sustainable Hydrogen Economy (INW)**, Forschungszentrum Jülich GmbH, Jülich, Germany

⁷ **3** Computational Systems Biotechnology, RWTH Aachen University, Aachen, Germany

DOI: [10.xxxxxx/draft](https://doi.org/10.xxxxxx/draft)

Software

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Editor: [Rachel Kurchin](#) 

Submitted: 17 July 2025

Published: unpublished

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⁸ Summary

⁹ Modeling and simulation are indispensable tools for understanding the complex nature of biological systems and making the most of the information contained in experimental data. ¹⁰ Functional integration of quantitative measurement data and rigorous parameter estimation are essential for creating valid, predictive models. We present estim8, a Python package ¹¹ for FMI-compliant ODE and DAE (bio)process modeling and parameter estimation. It offers ¹² convenient handling of multiple experimental replicates coupled with highly scalable solutions ¹³ using federated simulation operations. The source code is available on [GitHub](#). The package ¹⁴ is unit-tested on Windows and Linux. Thorough documentation is available under <https://estim8.readthedocs.io> including various example notebooks.

Statement of Need

¹⁹ Mathematical modeling has become a pivotal tool in biotechnological research and industrial ²⁰ bioprocess development, supporting the analysis and interpretation of complex experimental data ²¹ ([Fischer, 2008](#); [Hartmann et al., 2022](#); [Noll & Henkel, 2020](#); [Ploch et al., 2019](#)). While ordinary ²² differential equations (ODEs) are commonly used to describe continuous biological systems, ²³ many biotechnological applications require differential algebraic equation (DAE) systems to ²⁴ handle discontinuities, discrete events, physical constraints, and embedded optimization criteria ²⁵ ([Ploch et al., 2020](#)).

²⁶ A crucial step in the modeling workflow is parameter estimation – or in layman's terms “fitting ²⁷ the model”. This step questions the theoretical understanding of the system under investigation ²⁸ using real data, ultimately leading to confirmation or falsification of the hypotheses put ²⁹ forward. Although several general-purpose software tools for model formulation, simulation ³⁰ and parameter estimation exist, they currently present various limitations for biotechnological ³¹ applications, particularly regarding DAE support, handling of experimental replicates, and ³² accessibility.

³³ To address these limitations, we present estim8: a Python-based toolbox for simulation and ³⁴ parameter estimation of dynamic models. It is built on the Functional Mock-up Interface (FMI) ³⁵ standard ([Modelica Association, 2023](#)) and employs metaheuristic algorithms for optimization ³⁶ problems. estim8 provides specialized functionality for biotechnological applications, particularly ³⁷ in handling experimental replicates. By supporting model definition and simulation export ³⁸ from various FMI-compliant third-party software, including the open source OpenModelica ³⁹ platform ([Fritzson et al., 2020](#)), estim8 enables comprehensive DAE support and convenient ⁴⁰ event handling.

41 State of the Field

42 Many established tools such as pyFOOMB ([Hemmerich et al., 2021](#)), COPASI ([Hoops et al.,](#)
43 [2006](#)), PyBioNetFit ([Mitra et al., 2019](#)), and Data2Dynamics ([Raue et al., 2015](#)) are limited
44 to ODE systems, leaving users without native support for the DAE formulations often required
45 in biotechnological process modeling. DAE Tools ([Nikolić, 2016](#)) and ModestPy ([K. Arendt,](#)
46 [2018](#)) support DAE systems but lack dedicated functionality for common biotechnological
47 workflows such as structured handling of experimental replicates across different conditions,
48 and therefore require substantial workarounds. The combination of AMICI ([Fröhlich et al.,](#)
49 [2021](#)) and pyPESTO ([Schälte et al., 2023](#)) offers high-performance sensitivity analysis, but
50 poses a relatively high entry barrier with respect to model formulation, making it less accessible
51 to domain experts without extensive computational background. estim8 combines FMI-based
52 DAE support, dedicated replicate handling, and an accessible Python interface to address these
53 gaps.

54 Workflow

55 The workflow in estim8 follows a structured approach to bioprocess modeling and parameter
56 estimation (Figure 1). Users start by developing mathematical models using third-party
57 software that supports the FMI standard, such as OpenModelica ([Fritzson et al., 2020](#)). This
58 open-source platform provides an interactive modeling environment with graphical features
59 and allows models to be exported as Functional Mock-up Units (FMUs), supporting both
60 CoSimulation and ModelExchange formats. Notably, models of the SBML ([Hucka et al., 2003](#))
61 standard can be translated to Modelica ([Maggioli et al., 2019](#)), further expanding the range of
62 modeling tools supported by estim8.

63 The exported FMU is then loaded into estim8 using the FmuModel class. The package
64 implements a structured data hierarchy where Experiment objects contain Measurement objects
65 with an associated error_model and an observation_mapping. A key feature of estim8
66 is its comprehensive handling of biological replicates, which are crucial for the statistical
67 quality of data from biological experiments ([Casler et al., 2015](#)). Based on a user-defined
68 ParameterMapping, common properties of replicates and different conditions between them can
69 be modeled by defining so-called global and local parameters. This concept utilizes redundant
70 information in the measurement data, thereby effectively reducing the number of parameters
71 to be estimated ([Helleckes et al., 2022; Hemmerich et al., 2021; Osthege & Helleckes, 2022](#)).

72 The core of estim8 is the Estimator class, which serves as a central hub for managing parameter
73 estimation tasks. This class stores all data entered by the user and provides functions for solving
74 optimization problems. In addition, identifiability analyses and uncertainty quantifications can
75 be performed using profile likelihood or Monte Carlo sampling. The visualization module
76 offers comprehensive visualization methods for analyzing simulation results, comparing model
77 predictions with experimental data, and evaluating parameter estimation results. A thorough
78 guideline is given by several example notebooks in our [documentation](#).

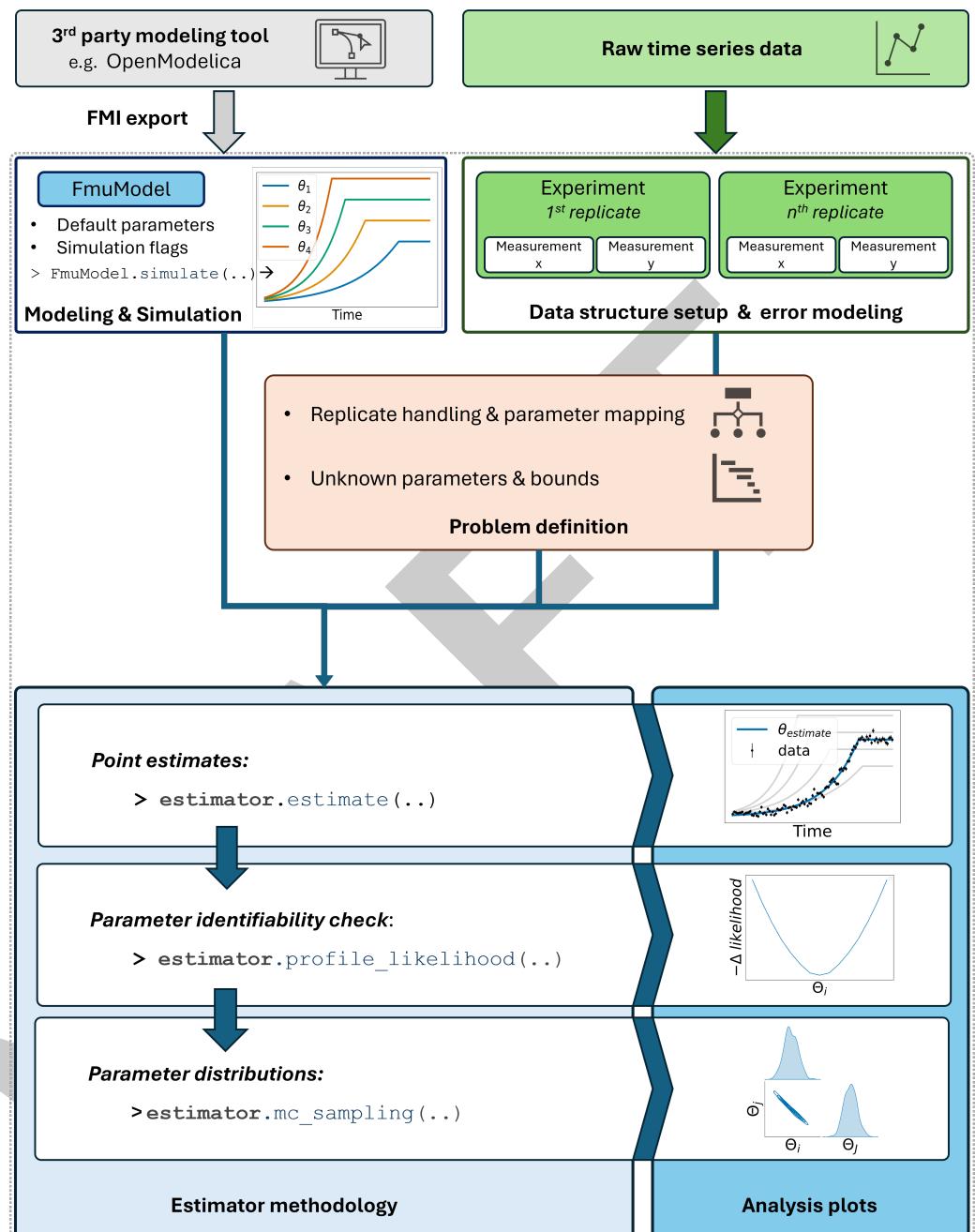


Figure 1: Schematic overview of the estim8 workflow.

Software Design

estim8 is an open-source Python package compatible and tested with Windows and Linux/Unix platforms. The modular, object-oriented architecture allows for easy expansion by new implementations, e.g. custom simulators or cost functions. At the very core, estim8 currently features interactive simulation of Functional Mock-up Units (FMUs) via the ModelExchange or CoSimulation interface in Python utilizing FMPy (Sommer, 2020). The embedded SciPy (Virtanen et al., 2020) and pygmo (Izzo & Dario, 2020) packages offer a variety of optimization algorithms that can be used for parameter estimation. Additionally, estim8 supports error propagation in measurement data and quantification of uncertainties in model predictions.

Scalability

Parameter estimation requires numerous simulation steps for evaluating a candidate solution θ by comparing the resulting model predictions to experimental data based on a statistical likelihood measure \mathcal{L} . This procedure – commonly referred to as *evaluation of the objective function* – is the time-determining step in most applications. Many population-based solvers therefore enable parallel evaluations of the objective function; the pygmo package in particular allows for highly parallelizable setups (grey parts of Figure 2).

However, the integration of experimental replicates significantly increases the number of simulations, as the objective function for a global parameter set θ_{global} is now a differentiable function resulting from the sum of replicate-specific (local) likelihood measures:

$$\mathcal{L}(\theta_{global} | y_{global}) = \sum_{i=1}^n \mathcal{L}(\theta_{local_i} | y_{local_i})$$

To this end, estim8 provides the option to use a so-called federated computing setup (Figure 2), which effectively introduces an additional parallelization layer. Using pytensor-federated ([Ostehege, 2023](#)), the computation of differentiable objective functions is distributed via gRPC streams to federated worker nodes which carry out the simulation tasks. The worker nodes can therefore be launched on different machines in a computer cluster. This allows for massive parallelization of computationally expensive model units.

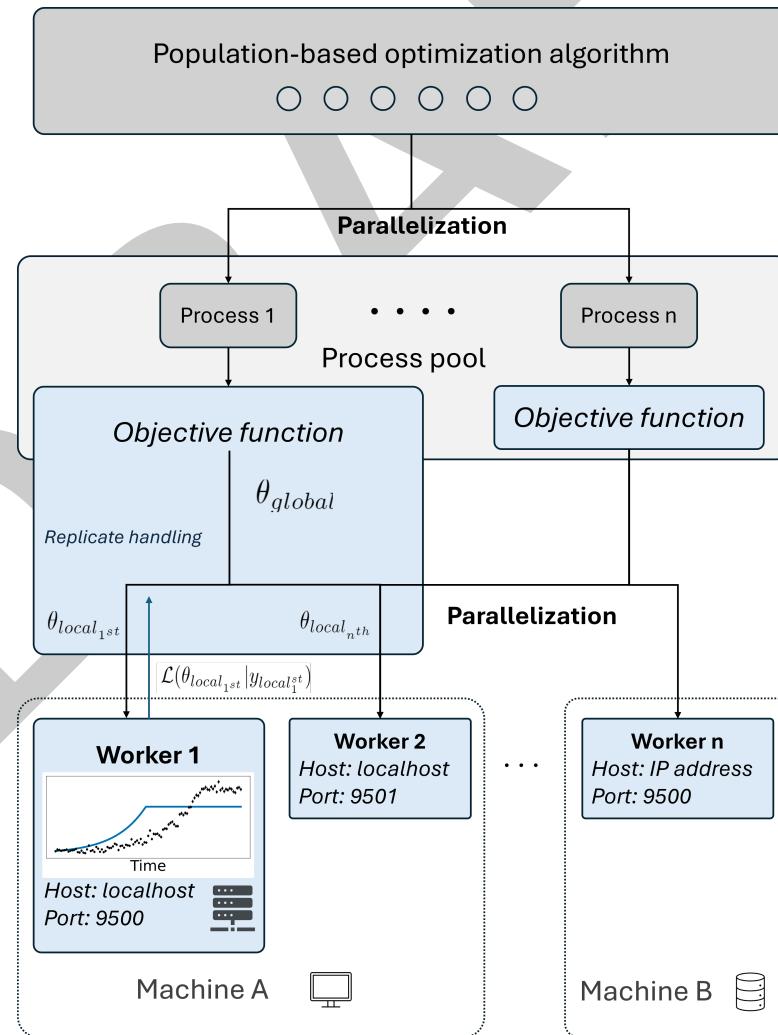


Figure 2: Federated computation setup for differentiable objective functions.

¹⁰⁸ Limitations

¹⁰⁹ Currently, estim8 does not incorporate gradient-based optimization algorithms, which could
¹¹⁰ enhance parameter estimation efficiency through parametric sensitivities (Villaverde et al.,
¹¹¹ 2018). This capability could be implemented once OpenModelica supports FMI 3.0 (Modelica
¹¹² Association, 2022), providing access to adjoint derivative functions, which are essential for
¹¹³ efficiently computing gradients in high-dimensional parameter spaces. Future developments
¹¹⁴ include the integration of Bayesian optimization methods from packages like PyMC (Abril-Pla
¹¹⁵ et al., 2023) and hopsy (Paul et al., 2024).

¹¹⁶ Research impact statement

¹¹⁷ estim8 introduces a streamlined bioprocess modeling workflow that makes rigorous hypothesis
¹¹⁸ testing accessible to domain experts without extensive computational background. By
¹¹⁹ combining accessible Python interfaces and FMI-compliant modeling software such as
¹²⁰ OpenModelica, estim8 allows researchers to focus on the scientific question rather than the
¹²¹ computational implementation. With comprehensive DAE support and tailored solutions
¹²² for handling experimental replicates — which are increasingly relevant in the context of
¹²³ laboratory automation — estim8 enables rapid iteration through cycles of model evaluation,
¹²⁴ fitting, and falsification. This lowers the barrier for model-based reasoning in biotechnological
¹²⁵ applications, supporting faster translation of experimental observations into quantitative
¹²⁶ process understanding.

¹²⁷ AI usage disclosure

¹²⁸ Claude 3.5 Sonnet was occasionally used during software development for drafting and refining
¹²⁹ implementation ideas. No AI-generated code was incorporated into the software. All design
¹³⁰ decisions, code editing and reviews were conducted by the researchers. The authorship of this
¹³¹ manuscript was conducted without the use of generative AI tools.

¹³² Author contributions

¹³³ estim8 was conceptualized by DS, SN and TL. Software developments were conducted by TL
¹³⁴ and DS, critical review of architecture decisions and contribution to the distributed computing
¹³⁵ setup by MO. The original draft was written by TL, editing and review was done by SN and
¹³⁶ MO. The work was supervised by SN and funding was acquired by SN and WW.

¹³⁷ Acknowledgements

¹³⁸ The authors thank Niels Hollmann and Marijke Rudolph for application tests on real-world
¹³⁹ problems as well as Mateo Herrera for checking and testing the example notebooks. Funding was
¹⁴⁰ received from the German Federal Ministry of Education and Research (BMBF) (grant number
¹⁴¹ 031B1134A) as part of the innovation lab “AutoBioTech” within the project “Modellregion,
¹⁴² BioRevierPLUS: BioökonomieREVIER Innovationscluster Biotechnologie & Kunststofftechnik”.

¹⁴³ Competing interests

¹⁴⁴ No competing interest is declared.

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