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

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Summary

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. Functional integration of quantitative measurement data and rigorous parameter estimation are essential for creating valid, predictive models. We present `estim8`, a Python package for FMI-compliant ODE and DAE (bio)process modeling and parameter estimation. It offers convenient handling of multiple experimental replicates coupled with highly scalable solutions using federated simulation operations. The source code is available on GitHub. The package is unit-tested on Windows and Linux. A thorough documentation is available under https://estim8.readthedocs.io including various example notebooks.

Statement of Need

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

A crucial step in the modeling workflow is parameter estimation – or in layman terms "fitting the model". This step questions the theoretical understanding of the system under invesigation using real data, ultimately leading to confirmation or falsification of the hypotheses put forward. Although several general-purpose software tools for model formulation, simulation and parameter estimation exist, they currently have some limitations: Many only support ODE systems (Hemmerich et al., 2021; Hoops et al., 2006; Mitra et al., 2019; Raue et al., 2015), require substantial workarounds for biological problems (K. Arendt, 2018; Nikolić, 2016), or depend on proprietary licenses such as MATLAB for DAE simulation (Fröhlich et al., 2021).

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

Implementation

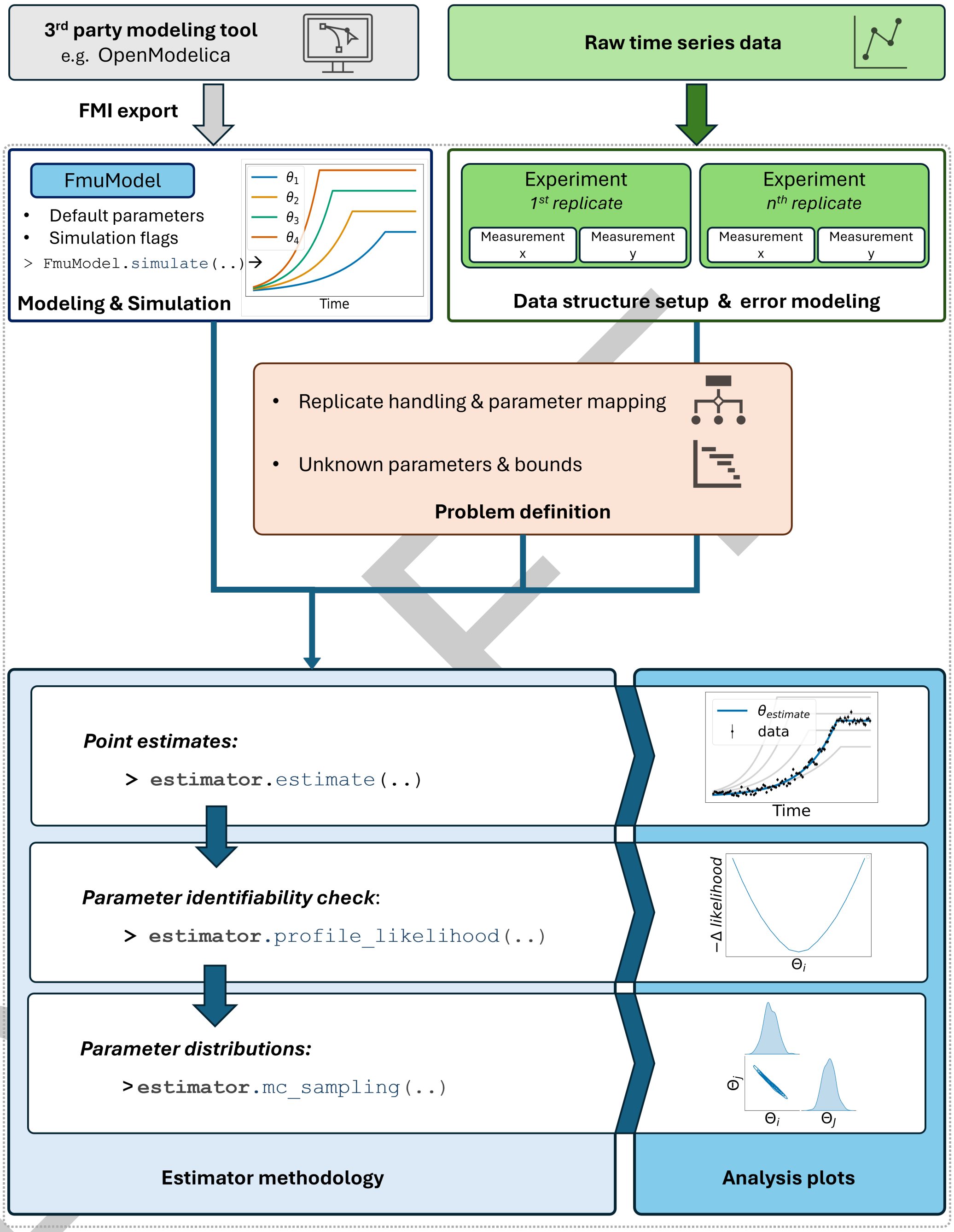
estim8 is an open source Python package compatible and tested with Windows and Linux/Unix platforms. The modular, object-oriented architecture allows for easy expansion by new implementations, like e.g. custom simulators or cost functions. At the very core, estim8 currently features interactive simulation 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, including error propagation in measurement data and quantification of uncertainties in model predictions.

Workflow

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

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

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



```
> FmuModel.simulate(..)
```

```
> estimator.estimate(..)
```

```
> estimator.profile_likelihood(..)
```

```
>estimator.mc_sampling(..)
```

Figure 1: Schematic overview of the `estim8` workflow.

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:

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

For this matter, `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.

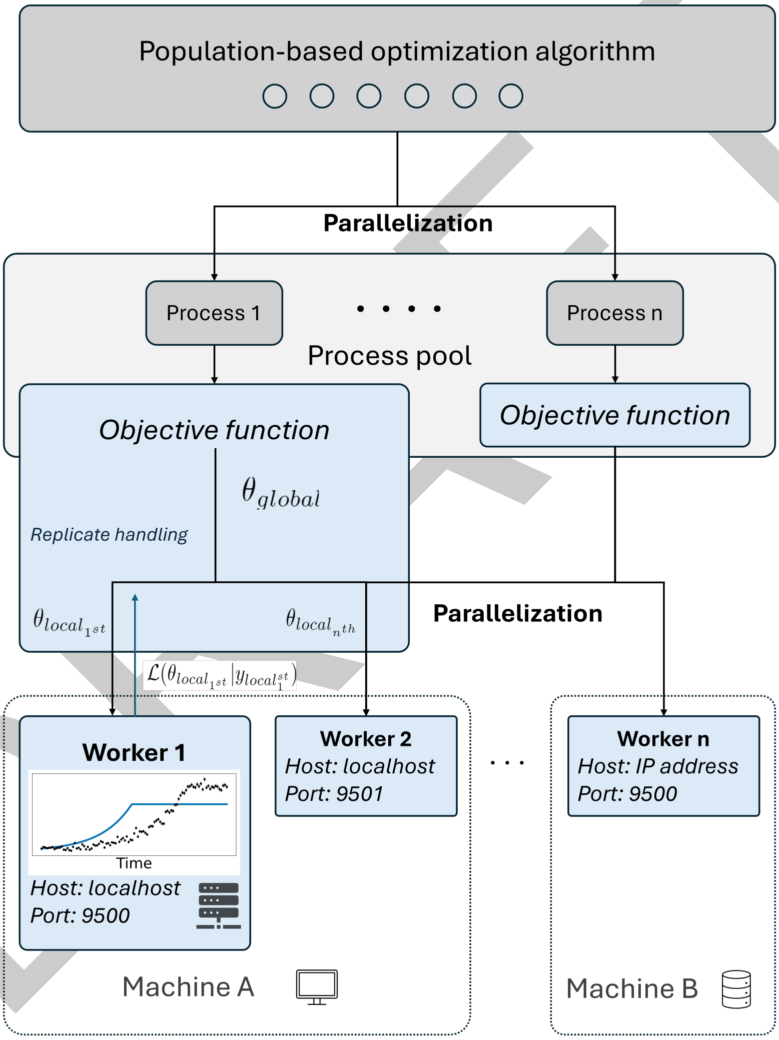


Figure 2: Federated computation setup for differentiable objective functions.

Limitations

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

Author contributions

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

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Competing interests

No competing interest is declared.

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