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Benchmarking parallel optimization methods in computational systems biology

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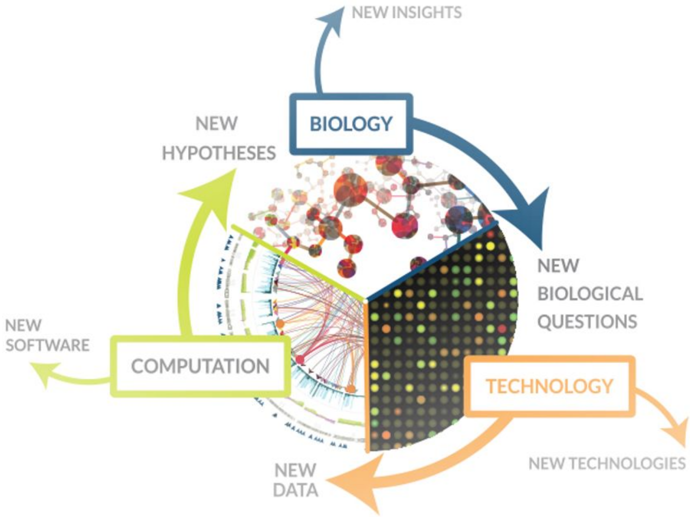
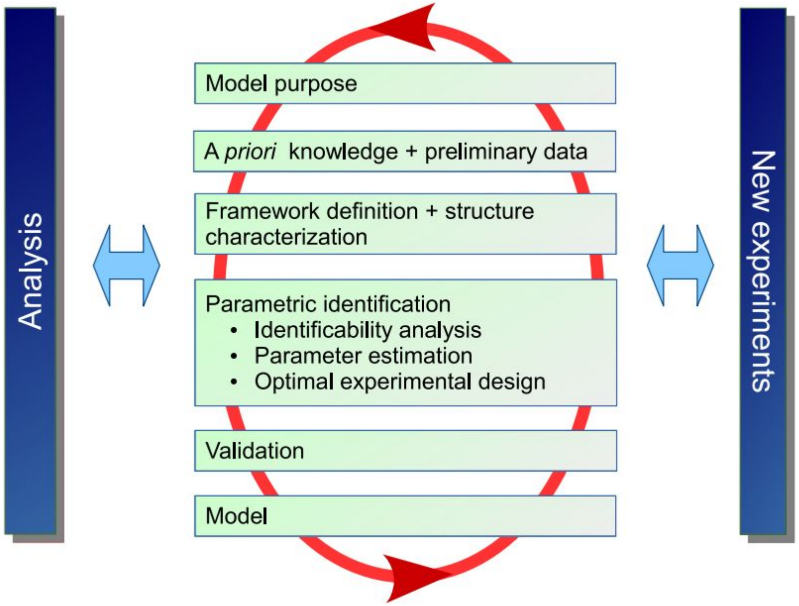
Large-scale dynamic models in systems biology

Systems Biology:

New knowledge about complex biological systems by combining:

- experimental data
- mathematical modeling
- advanced computational techniques





Analysis

Model purpose

A *priori* knowledge + preliminary data

Framework definition + structure characterization

Parametric identification
- Identificability analysis
- Parameter estimation
- Optimal experimental design

Validation

Model

New experiments

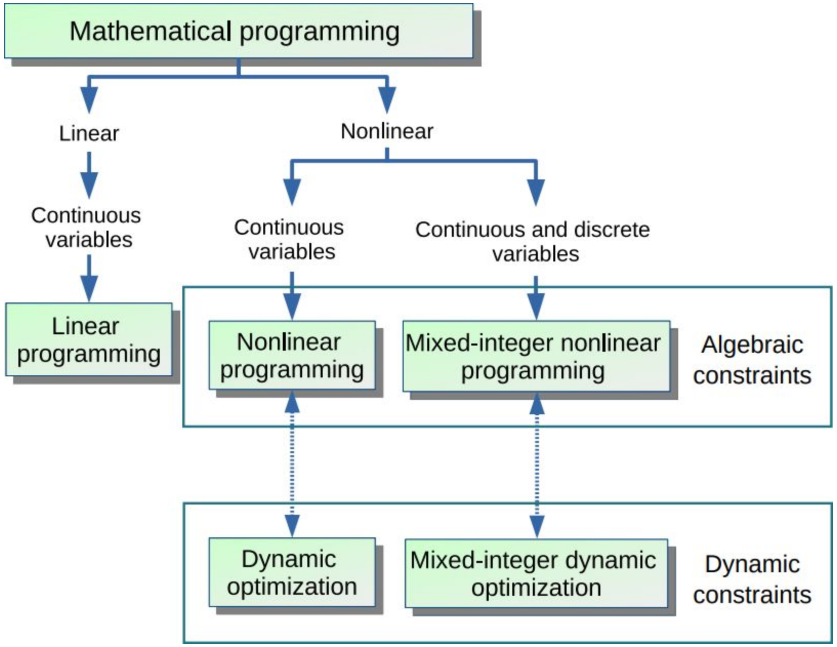
Model calibration or parameter estimation

They can be formulated as mathematical optimization problems:

- finding the parameters of a dynamic model that give the best fit to a set of time-series experimental data
- minimizing a cost function that measures the goodness of this fit

Class of optimization problems?

- RMSE
- NLP-DO
  - non-convex
  - bound constraints
  - multiple local optima
  - NP-hard
- Solvers
  - metaheuristics
  - multistart strategies
- HPC techniques



Mathematical programming

Linear

Nonlinear

Continuous variables

Continuous variables

Continuous and discrete variables

Linear programming

Nonlinear programming

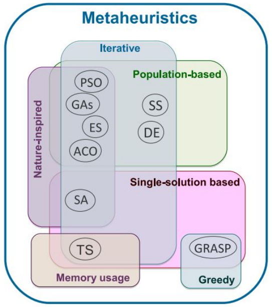
Mixed-integer nonlinear programming

Algebraic constraints

Dynamic optimization

Mixed-integer dynamic optimization

Dynamic constraints



Systematic comparison of optimizers

- Comparison of different solvers, executed on a parallel machine

- The main question we want to address: **Given a set of `P` problems and a set of `S` solvers, and given pre-specified parallel computational resources (`MP` machine processors and a budget of computational time, `T` hours), which are the most efficient and robust solvers?**

- **Efficient:** faster in getting the best solution

- **Robust:** able to solve most problems within the computational budget defined by `MP*T`

Parallel optimization methods

- **pyPESTO: Parameter EStimation TOolbox for python**

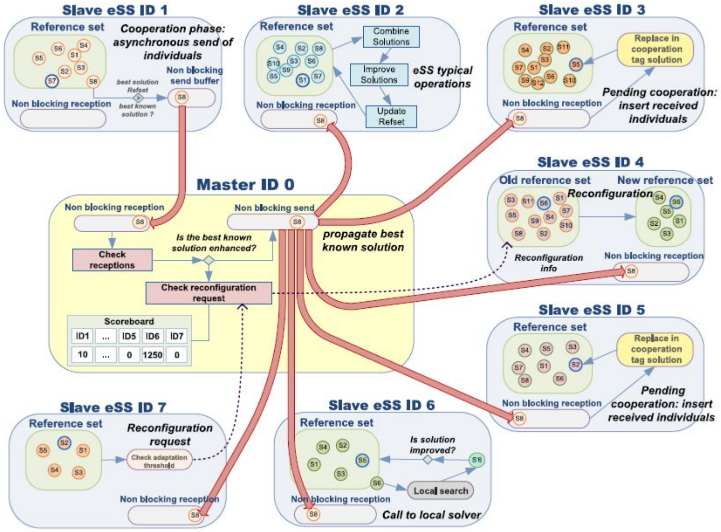
S. Leonard, D. Weindl, and J. Hasenauer (2021)."Efficient gradient-based parameter estimation for dynamic models using qualitative data. *Bioinformatics* 37. 23: 4493-4500.

- **parPE: parameter estimation for PEtab**

L. Schmiester, Y. Schälte, F. Fröhlich, J. Hasenauer, and D. Weindl. (2019) Efficient parameterization of large-scale dynamic models based on relative measurements. *Bioinformatics* 36, 594–602.

- **saCeSS: parameter estimation for PEtab**

D.R. Penas, P. González, J.A. Egea, R. Doallo, and J.R. Banga, (2017). Parameter estimation in large-scale systems biology models: a parallel and self-adaptive cooperative strategy. *BMC bioinformatics*, *18*(1), 1-24.



ID1	...	ID5	ID6	ID7
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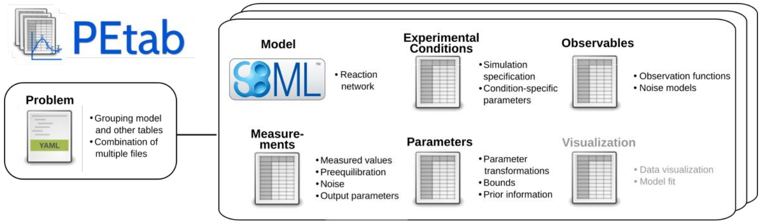
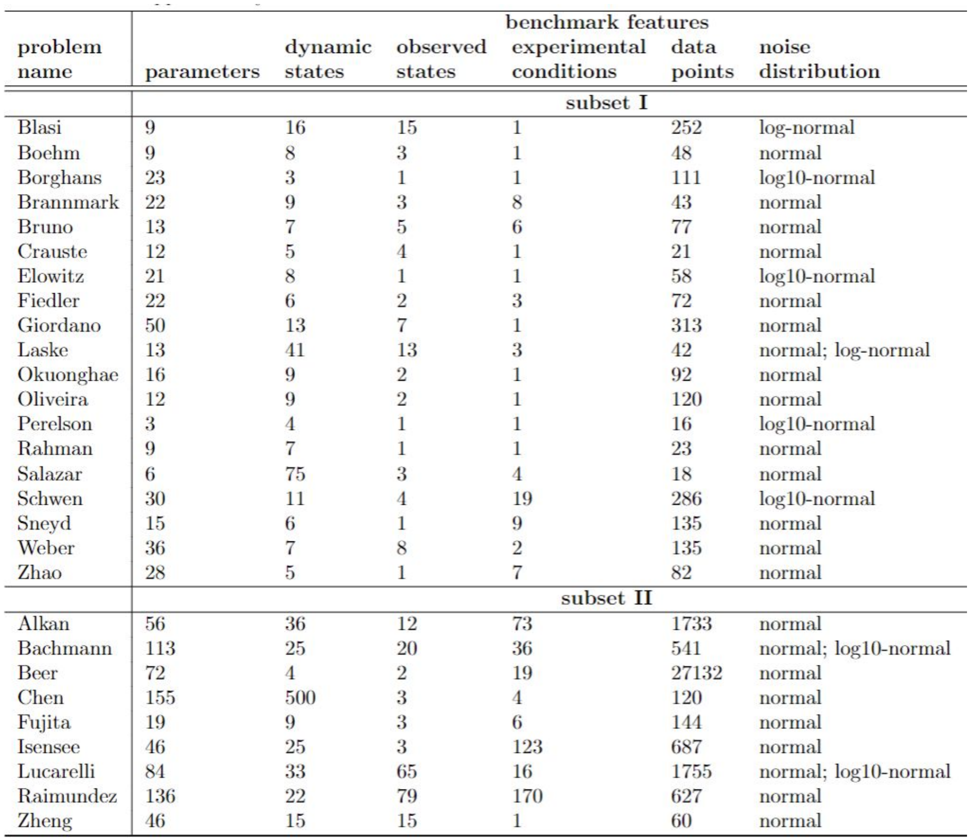
PEtab benchmarks considered

- **PEtab** - a data format for specifying parameter estimation problems in systems biology.





	benchmark features					
problem name	parameters	dynamic states	observed states	experimental conditions	data points	noise distribution
				subset I		
Blasi	9	16	15	1	252	log-normal
Boehm	9	8	3	1	48	normal
Borghans	23	3	1	1	111	log10-normal
Brannmark	22	9	3	8	43	normal
Bruno	13	7	5	6	77	normal
Crauste	12	5	4	1	21	normal
Elowitz	21	8	1	1	58	log10-normal
Fiedler	22	6	2	3	72	normal
Giordano	50	13	7	1	313	normal
Laske	13	41	13	3	42	normal; log-normal
Okuonghae	16	9	2	1	92	normal
Oliveira	12	9	2	1	120	normal
Perelson	3	4	1	1	16	log10-normal
Rahman	9	7	1	1	23	normal
Salazar	6	75	3	4	18	normal
Schwen	30	11	4	19	286	log10-normal
Sneyd	15	6	1	9	135	normal
Weber	36	7	8	2	135	normal
Zhao	28	5	1	7	82	normal
				subset II		
Alkan	56	36	12	73	1733	normal
Bachmann	113	25	20	36	541	normal; log10-normal
Beer	72	4	2	19	27132	normal
Chen	155	500	3	4	120	normal
Fujita	19	9	3	6	144	normal
Isensee	46	25	3	123	687	normal
Lucarelli	84	33	65	16	1755	normal; log10-normal
Raimundez	136	22	79	170	627	normal
Zheng	46	15	15	1	60	normal

- Benchmarks were divided in two subsets:
  - **I-easier**
    - **Processors:** 12.
    - **Execution time:** 3 hours.
  - **II-harder**
    - **Processors:** 24.
    - **Execution time:** 9 hours.

Comparison methodology & infrastructure

- We have tested 37 solvers:
  - 3 based on **SaCeSS** configurations
  - 1 using the parallel multistart implemented in **parPE+Ipopt**
  - 33 solvers using the parallel **pyPESTO** multistart method with different solvers

- Each solver was executed 10 times (jobs) for each problem

- All solvers were run in a parallel setup, we used the same number of parallel processors in each job.
- In adition, we used the same computational infrastructure (**Finisterrae III**), and the same **MPI** implementation (**openmpi 4.1.1**) and compilers (**gcc 10.1.0**)

Summary of results: the best solution achieved.

Solutions 0-1% (or larger) from best

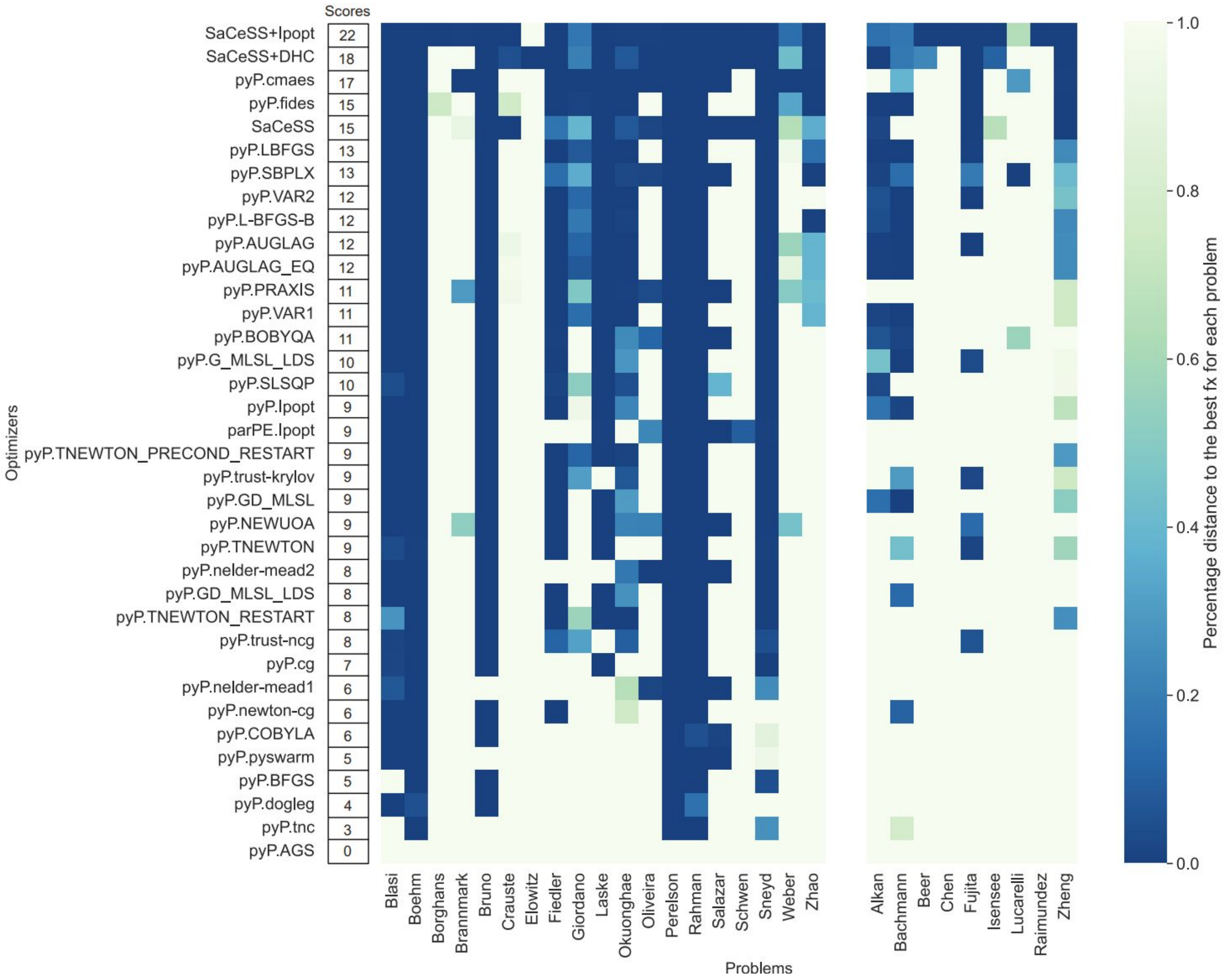
The heatmap with the percentage distance to the best fx for each solver and in each problem

Calculating distance of solver1 in problem P1:

distance_solver1 =

(best_cost_P1 - best_cost_solver1)

/ best_cost_P1 * 100



Conclusions

- Considering most problems solved (best or near-best solution achieved), **`SaCeSS+Ipopt`** is the winner

- **`SaCeSS+DHC`** and **`SaCeSS`** without local solver also have a good performance in terms of the best solution reached and robustness

- Multistart of **`fides`** and **`cmaes`** was competitive in some benchmarks, with a small dispersion in the results. An integration between **`SaCeSS+fides`** looks promising.

- Cooperative methods such as **`SaCeSS`** are a good alternative to solve complex problems in the **calibration of large-scale dynamic models in systems biology**

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