

Implementation and comparison of seven algorithms for automated model selection in Monolix: two simulation studies and eleven applications



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CONTEXT

- To build a population model of the dose–concentration relationship requires to define each of the following components:

Structural model features

Delay	Absorption	Distribution	Elimination	
			Pharmacokinetic (PK)	Target-Mediated Drug Disposition (TMDD)
No Delay	Zero order	1 cmt	Linear	Full
Lag Time	First order	2 cmt	Nonlinear	Irreversible binding
Transit cmt (TC)		3 cmt		Quasi equilibrium

Variability model features

Parameter model	Error model
Inter-individual variability (IIV)	Constant
No IIV	Proportional
	Combined

cmt: compartment

→ To improve efficiency and reproducibility of this process automated model selection approaches have been explored since 2006 [1]

- Decision Tree (DT)** [2, 3]: starting from one model, defining each feature sequentially (left to right in the table above)
- Genetic Algorithm (GA)** [1, 4–8]: starting from a pool of models/genes, iteratively mixing, crossing, mutating and selecting models
- Ant Colony Optimization (ACO)** [9]: starting from a pool of models/ants, sampling models using a transition **probability matrix (PM)** updated through the iterations
- Particle Swarm Optimization (PSO)** [7, 8]: starting from a pool of models/particles, sampling models with several local and one global **PM** updated through the iterations
- We implemented these algorithms in R 4.4.2 [10] using the Monolix Suite[11] and proposed and implemented three new automated model selection algorithms
 - Simulated Annealing (SA)**: starting from one model, sampling models from a **PM** updated through the iterations, with decreasing temperature
 - Tournament Algorithm (TA)**: starting from one model, sampling models from a **PM** updated through the iterations, with memory over the number of wins
 - Decision Tree 2 (DT2)**: second round of the DT algorithm starting from the model selected with **DT**

Objectives

- Comparison of these seven algorithms for selecting structural and/or variability model features in terms of speed and accuracy in two simulation studies
 - a simple PK model with a reduced search space (not accounting for IIV): 90 models
 - a TMDD model with a large search space (accounting for IIV): 230 400 models
- Application to eleven real datasets [12]

SIMULATION STUDY: PHARMACOKINETIC MODEL

Simulation settings

- One hundred datasets were simulated based on a population PK model of verapamil, a drug used as a calcium channel blocker against hypertension, angina, tachycardia [13]
- Design: 22 patients divided into two groups with sampling designs (0.25, 0.5, 1, 3.5, 9.5) and (0.5, 2, 5.5, 16, 24) hours
- Population PK model: lag time, first order absorption, 2 compartments, linear elimination and proportional error model

Algorithm settings

- All algorithms with the corrected Bayesian Information Criteria (BICc) as a cost function [14]
- Model parameters initialization: `pkpopini` function from the `Rsmix` R package [11]
- Model fit: Stochastic Approximation Expectation Maximization (SAEM), relative standard errors (RSE) via stochastic approximation, likelihood via importance sampling [11]

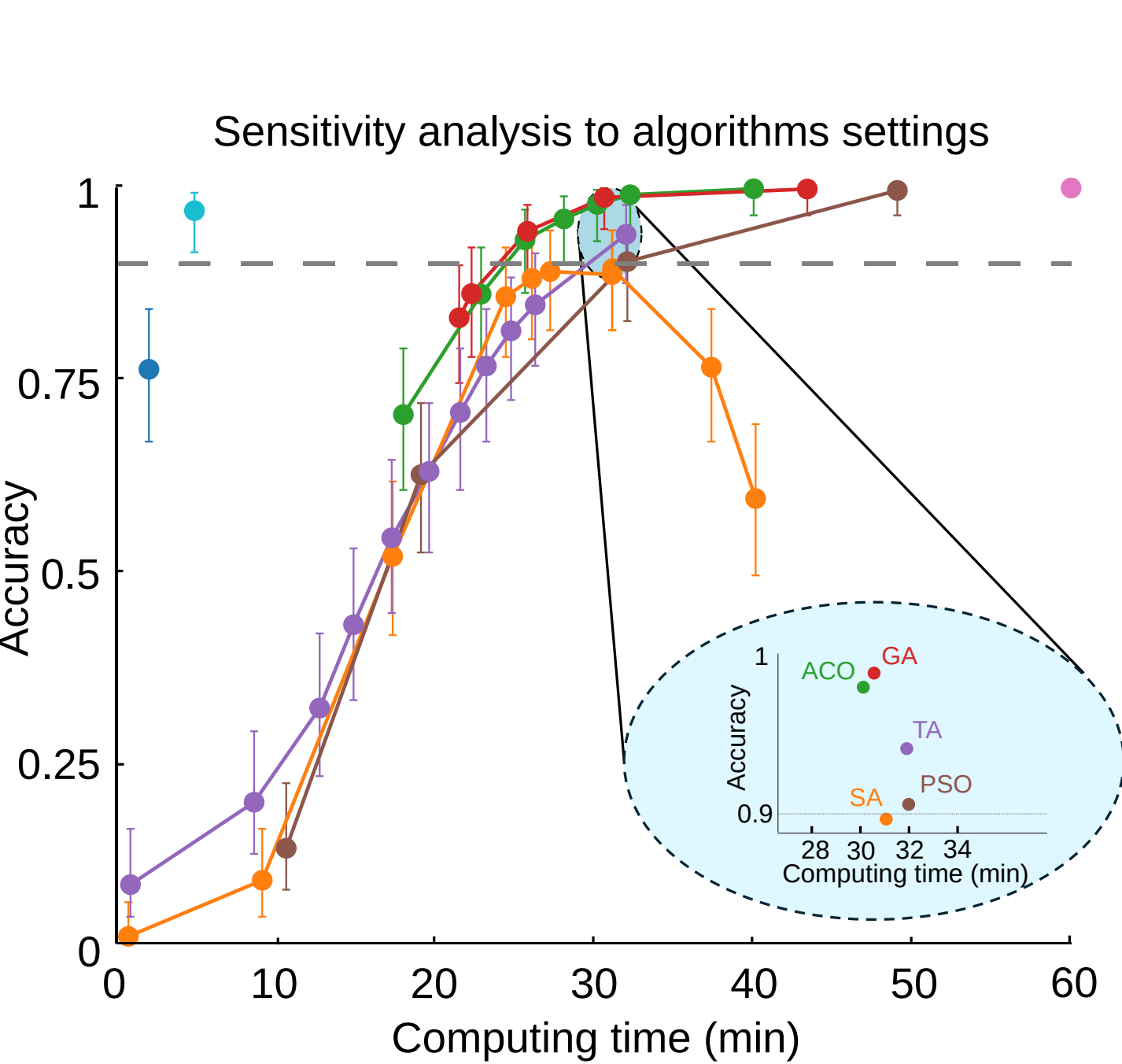
Evaluation

- Accuracy: proportion of datasets where the algorithm finds the same model as an **Exhaustive Search (ES)**
- Computing time
- Sensitivity analysis of algorithm settings: the temperature for **SA**, the mutation rate for **GA** and **PM** convergence related settings for **PSO**, **ACO** and **TA**
- Relative estimation errors (REEs) on individual area under the curve (AUC)

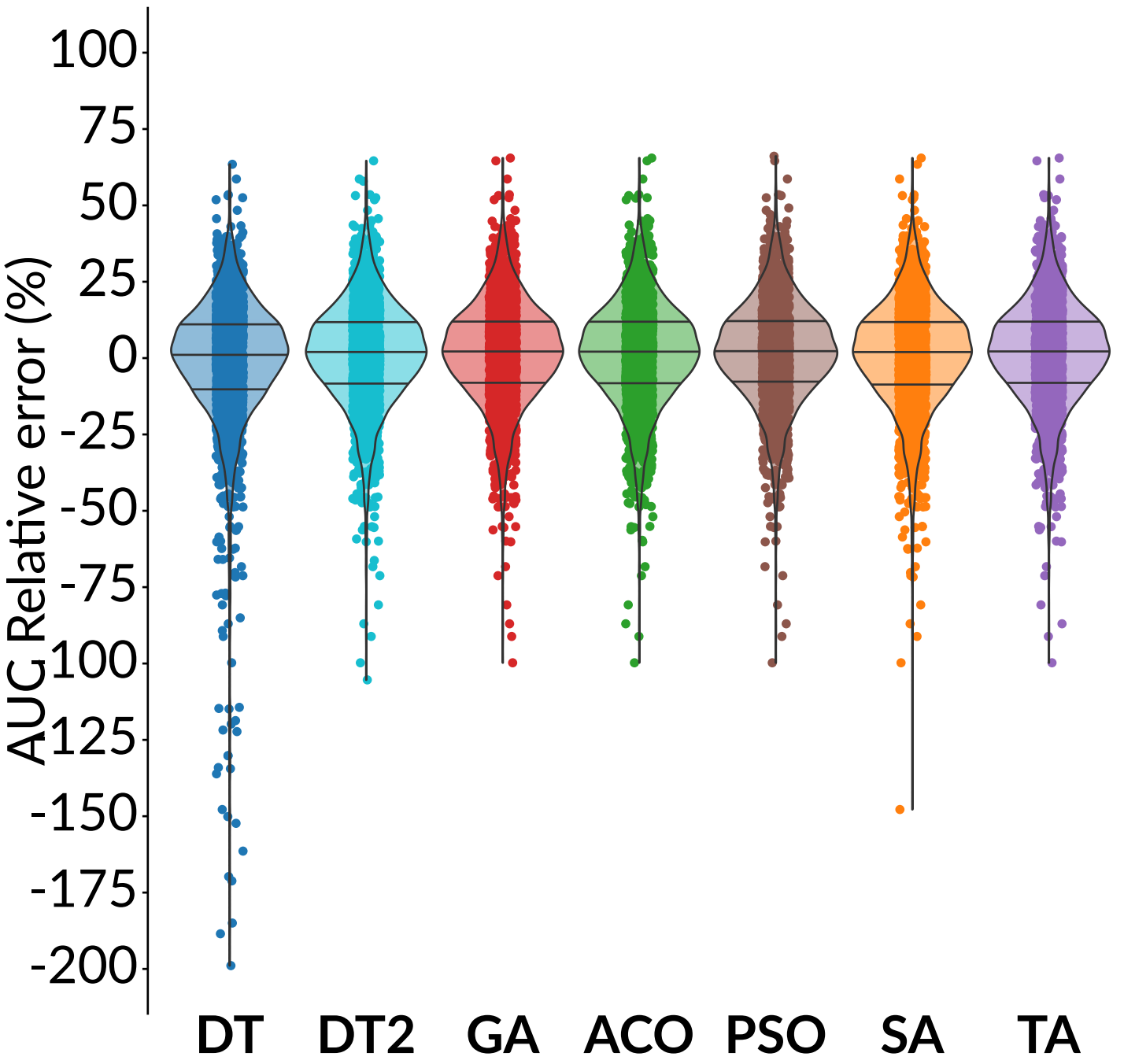
$$REE_i^{AUC} = \frac{\hat{AUC}_i - AUC_i^*}{AUC_i^*}$$

with $\hat{AUC}_i$ the AUC from the selected model and AUC_i^* from the simulated model of individual i

Results



- **SA**: non-monotonic relationship between computation time and accuracy
- **DT**: substantially faster but less accurate
- **PSO**, **ACO**, **GA**, **TA**: achieved 90% accuracy in just 30 minutes of runtime
- **DT2**: highly accurate and very fast



- Good AUC prediction of all algorithms except **DT**
- **DT2** performed best, ahead of **ACO**, **GA** and **TA**
- These algorithms were selected for the larger search space, except **GA** due to an implementation issue

SIMULATION STUDY: TARGET-MEDIATED DRUG DISPOSITION MODEL

Simulation settings

- One hundred datasets were simulated based on a population PK model of RG7652, a monoclonal antibody used against PCSK9 to lower cholesterol [15]
- Design: 18 patients divided into 3 dosing groups with 20 sampling times per patient
- Population TMDD model: lag time, first order absorption, 2 compartments, irreversible binding approximation and proportional error model for the total ligand concentration (Lt_{tot}) and the total receptor concentration (R_{tot})

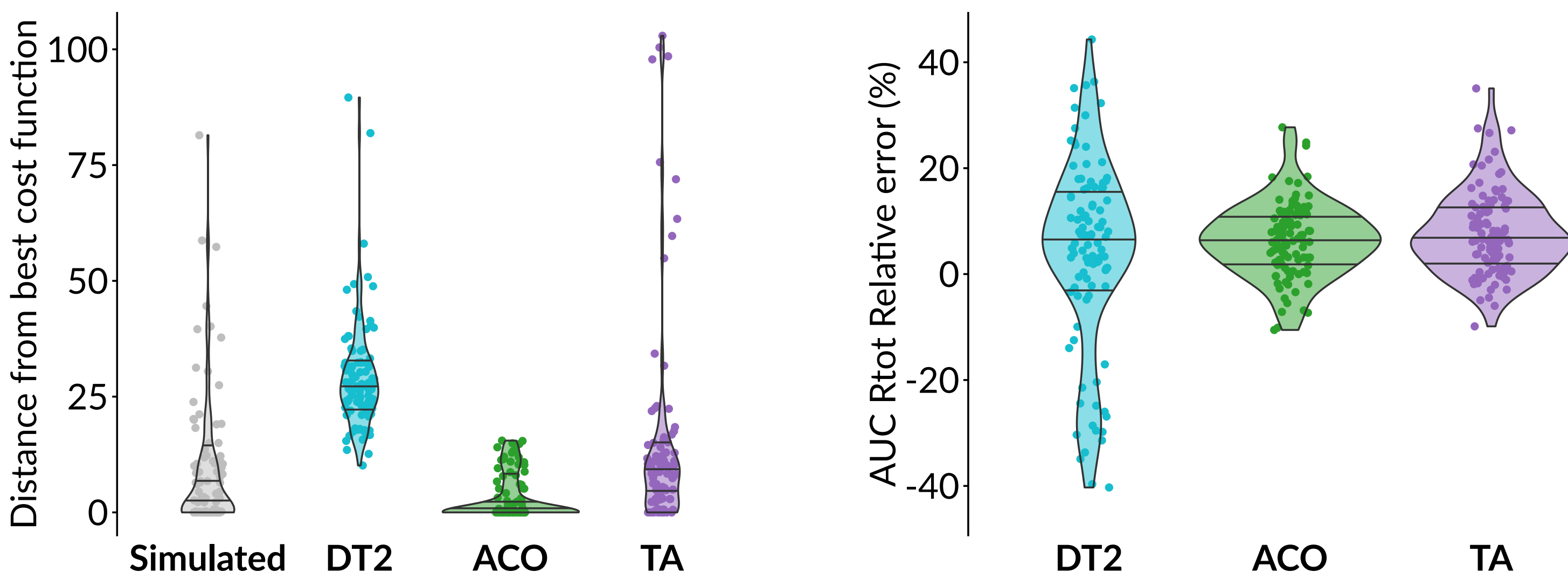
Algorithm settings

- DT2**, **ACO** and **TA** using a cost function $BICc + n_{RSE>50\%} \log(n_{tot})$, where $n_{RSE>50\%}$ is the number of parameters with an RSE above 50% and n_{tot} is the total number of observations
- Model parameters initialization: values fixed a priori
- Model fit: SAEM, RSEs via stochastic approximation, likelihood via importance sampling [11]

Evaluation

- Accuracy: distance from the best cost function value across all models tested by all algorithms
- Computing time
- REEs on individual AUCs

Results



- **DT2**: failed to find the best model and showed less precision in AUC prediction
- **TA**: less accurate than **ACO**, but faster
- **ACO**: very precise and robust

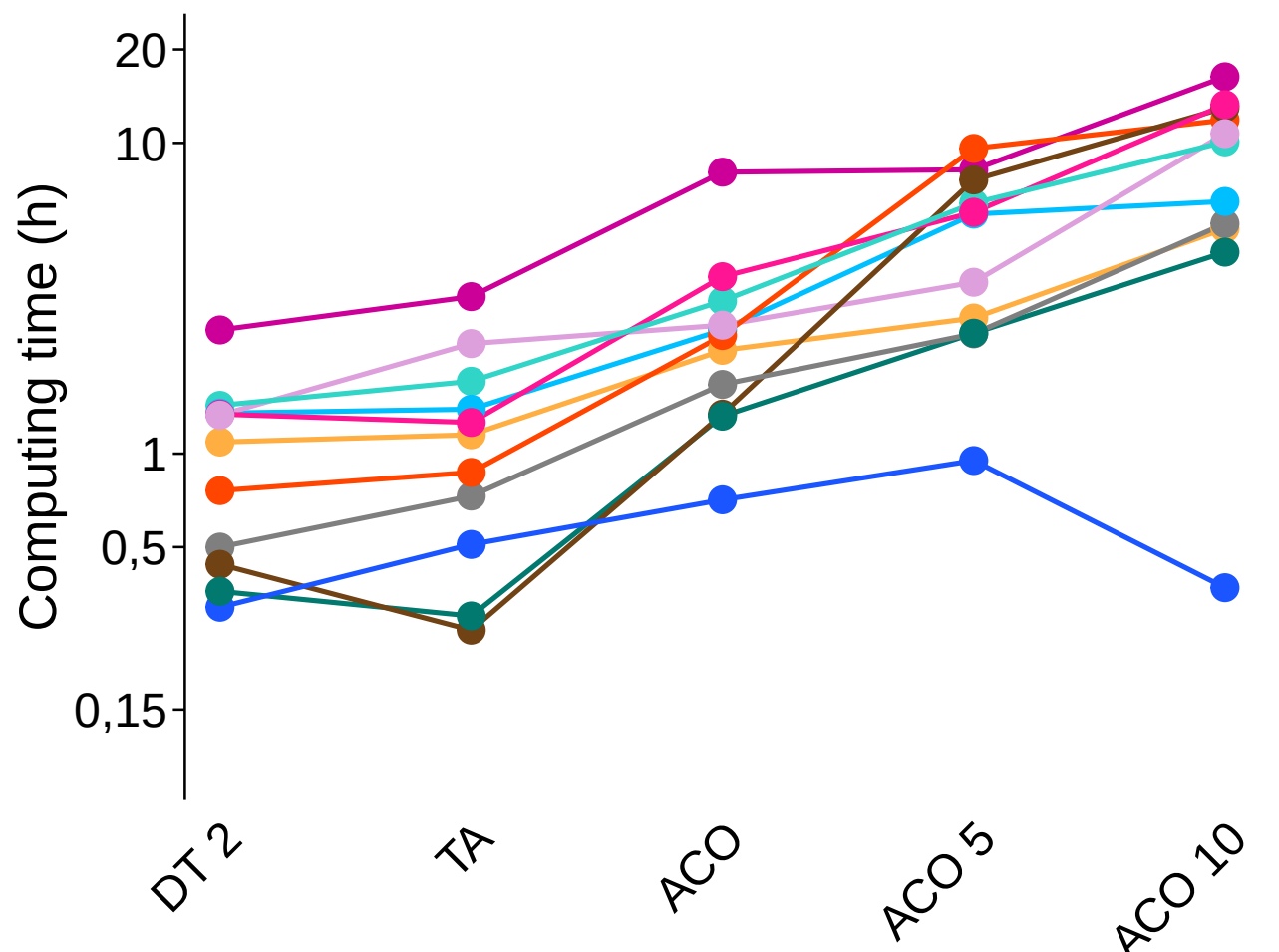
APPLICATION TO REAL DATASETS

Drug	Nb of subjects	Nb of observations	Administration	Model type	Search space
Dofetilide	22	330	Oral	PK	15 120
Warfarin	33	279	Oral	PK	15 120
Theophylline	12	132	Oral	PK	15 120
Verapamil	22	352	Oral	PK	15 120
Quinidine	21	316	Oral	PK	15 120
Quinidine Dihydrochloride	136	361	Oral	PK (no TC)	9 072
IgG1 mAb	12	232	Oral	PK (no TC)	9 072
Remifentanyl	28	393	Bolus	TMDD	6 000
Cisplatin	65	1992	Infusion	PK	756
Cisplatin	23	524	Infusion	PK	756
Tobramycin	97	322	Bolus	PK	756

Difference in BICc between the published and the selected model using the default number of chains – for **ACO** we explored increasing the number of chains to 5 and 10 (**ACO 5** and **ACO 10**):

Dataset	DT2	TA	ACO	ACO 5	ACO 10
Dofetilide	-15	-5	-20	-18	-18
Warfarin	-243	-235	-254	-242	-242
Theophylline	-64	-60	-64	-62	-64
Verapamil	-34	-35	-35	-34	-35
Quinidine	-36	-33	-34	-30	-38
Quinidine Dihydrochloride	-38	-38	-42	-42	-41
IgG1 mAb	-61	-61	-57	-61	-63
Remifentanyl	-11	-13	-11	-11	-17
Cisplatin	-52	-32	-47	-49	-59
Cisplatin	10	11	8	8	8
Tobramycin	2	-11	-23	-16	-23

Computing time per dataset and algorithm:



- In 10 out of 11 cases the algorithms found a better model than the published one
- **DT2** and **TA** are quite similar and **ACO** is much longer
- As the number of chains increases, the computing cost remains similar while the estimation becomes more stable with regard to parameter initialization

TAKE HOME MESSAGE

For small search spaces (up to 15 000 models), **DT2** performed best. For larger search spaces, **ACO** was the most precise and robust, but slower than **TA**. An R package implementing these algorithms is under development.

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