

Physiologically based Pharmacokinetic model implementations are different in available Software platforms and their choice can significantly influence the reproduction of results and related Regulatory and clinical decisions: Case of oral contraceptives

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Introduction

Physiologically Based Pharmacokinetic (PBPK) models are increasingly recognized for drug-drug interaction (DDI) assessment, with regulatory agencies like EMA and FDA endorsing their use. Although PBPK models are implemented across different commercial and open-source platforms, the influence of software choice on DDI simulation outcomes remains underexplored. This study compares two widely used tools, Simcyp and PK-Sim, to evaluate how platform differences can affect pharmacokinetic predictions. Understanding these impacts is crucial for developers and regulators to ensure robust platform qualification, support tool interchangeability, and guide reliable extrapolation of modeling results.

Methods

- **Software Versions:** Simcyp® V23 R2 / PK-Sim® V11.
- PBPK models incorporated three components:
 - Drug model (physicochemical properties)
 - System model (anatomical and physiological properties)
 - Population model (variability across individuals)
- **Approach:** Physicochemical and pharmacokinetic parameters were extracted from the literature for oral contraceptive and DDI perpetrators.
- **Population:** Healthy women, 18–45 years old.
- **Simulation Scenarios:**
 - Single administration of oral contraceptives.
 - Co-administration with CYP3A4 inhibitors (e.g., fluconazole) and inducers (e.g., carbamazepine).

	Simcyp	PK-Sim	Mean relative difference (%)
Population			
Definition of the population	Directly a population	Population based on an individual	
Drug model			
Number of absorption model	3	1	100
Number of compartments in the PBPK full model	12	19	45.16
Amount of enzymes			
CYP2B6	21.6 (pmol/mg)	39 (pmol/mg)	57.43
CYP3A5	103 (pmol/mg)	1 (pmol/mg)	196.15
CYP2C8	24 (pmol/mg)	64 (pmol/mg)	90.91
CYP2C19	4.4 (pmol/mg)	19 (pmol/mg)	124.79
CYP2A6	29.3 (pmol/mg)	68 (pmol/mg)	79.56
Extracellular water			
Brain	9.2 (%)	16.2 (%)	55.12
Skin	62.3 (%)	38.2 (%)	47.96
Intracellular water			
Adipose	3.9 (%)	0.89 (%)	125.68
Heart	44.5 (%)	24.8 (%)	56.85
Lung	46.3 (%)	23.8 (%)	64.19
Skin	9.47 (%)	27.6 (%)	97.81
Spleen	57.9 (%)	35.5 (%)	47.97
Neutral lipids			
Bone	7.4 (%)	1.74 (%)	123.85
Brain	5.1 (%)	3.91 (%)	26.42
Kidney	2.07 (%)	1.21 (%)	52.44
Liver	3.48 (%)	1.35 (%)	88.20
Lung	0.3 (%)	2.15 (%)	151.02
Skin	2.84 (%)	6.03 (%)	71.93
Spleen	2.01 (%)	0.71 (%)	95.59
Neutral phospholipids			
Bone	0.11 (%)	0.16 (%)	37.04
Brain	5.65 (%)	0.15 (%)	189.66
Heart	1.66 (%)	1.06 (%)	44.12
Kidney	1.62 (%)	2.4 (%)	38.81
Lung	0.9 (%)	1.23 (%)	30.99
Skin	1.11 (%)	0.44 (%)	86.45
Spleen	1.98 (%)	1.07 (%)	59.67
Volume of organs			
Bone	3.88 (L)	9.12 (L)	80.62
Lung	0.46 (L)	0.95 (L)	69.50
Pancreas	0.12 (L)	0.17 (L)	34.48
Organ blood flow			
Adipose (call fat in pksim)	20.37 (L/h)	30 (L/h)	38.24
Muscle	69.27 (L/h)	40.2 (L/h)	53.11
Values for phospholipid acid			
Heart	3.07 (mg/g)	2.25 (mg/g)	30.83
Kidney	2.48 (mg/g)	5.03 (mg/g)	67.91
Lung	0.5 (mg/g)	3.91 (mg/g)	154.65

Table 1: parameters with a mean relative difference of more than 25% between the two software packages. All the other parameters related to each of the section (amount of enzymes, extracellular water, intracellular water, neutral lipids, neutral phospholipids, volume of organs, organ blood flow, values for phospholipid acid) not included in this table have a mean relative difference of less than 25% and were considered acceptably similar.

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Objectives

The aim of this study is to assess the results and impact of implementing PBPK models in the Simcyp and PK-Sim software platforms for evaluating DDIs, using well-documented CYP3A4-related DDIs for oral contraceptives as case studies.

Results

- **Table 1** represents the differences between the two software platforms whose mean relative difference between the value of Simcyp and the value of PK-Sim is greater than 25%.
- The results after implementation of the analysis are shown in **Figures 1 and 2** and numerically in **Table 2**.
- The bioequivalence limits are between 0.8 and 1.25. This means that if the ratio of the maximum plasma concentration with interaction divided by the ratio of the maximum plasma concentration without interaction is outside these limits, the interaction should be considered clinically relevant.
- Based on the results, depending on the software, the interactions may or may not be considered clinically significant.
- For a reliable and reproducible regulatory assessment, it seems essential that scientific publications provide not only the parameter values, but also the software context and the modelling options chosen.

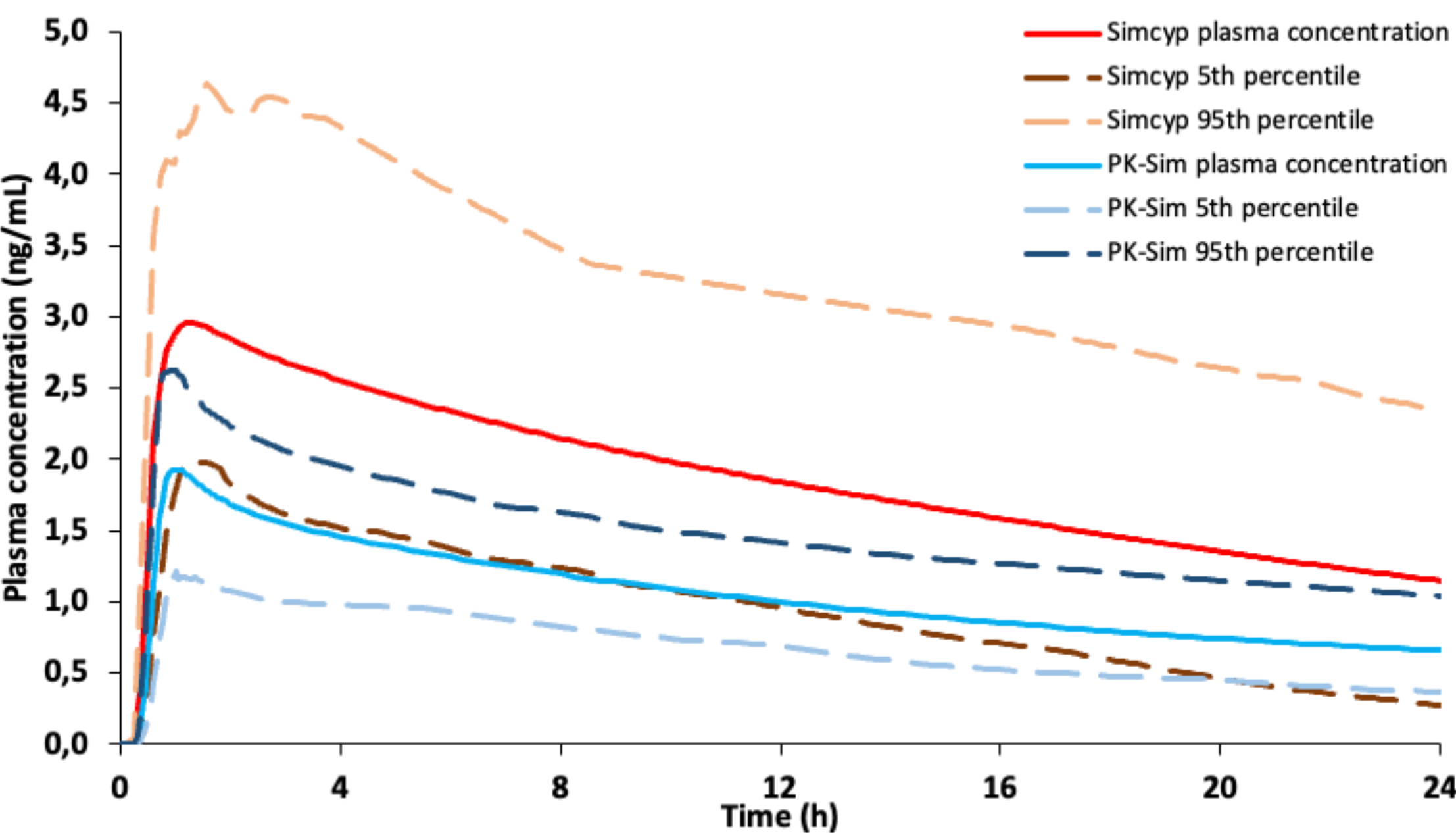


Figure 1: Plasma concentration of gestodene following concomitant oral administration of 0.075 mg of gestodene and 0.02 mg of ethinylestradiol. Plot shows predicted mean (solid lines) for the population (10 individuals x 10 trials) and 5:95 percentile (dashed lines).

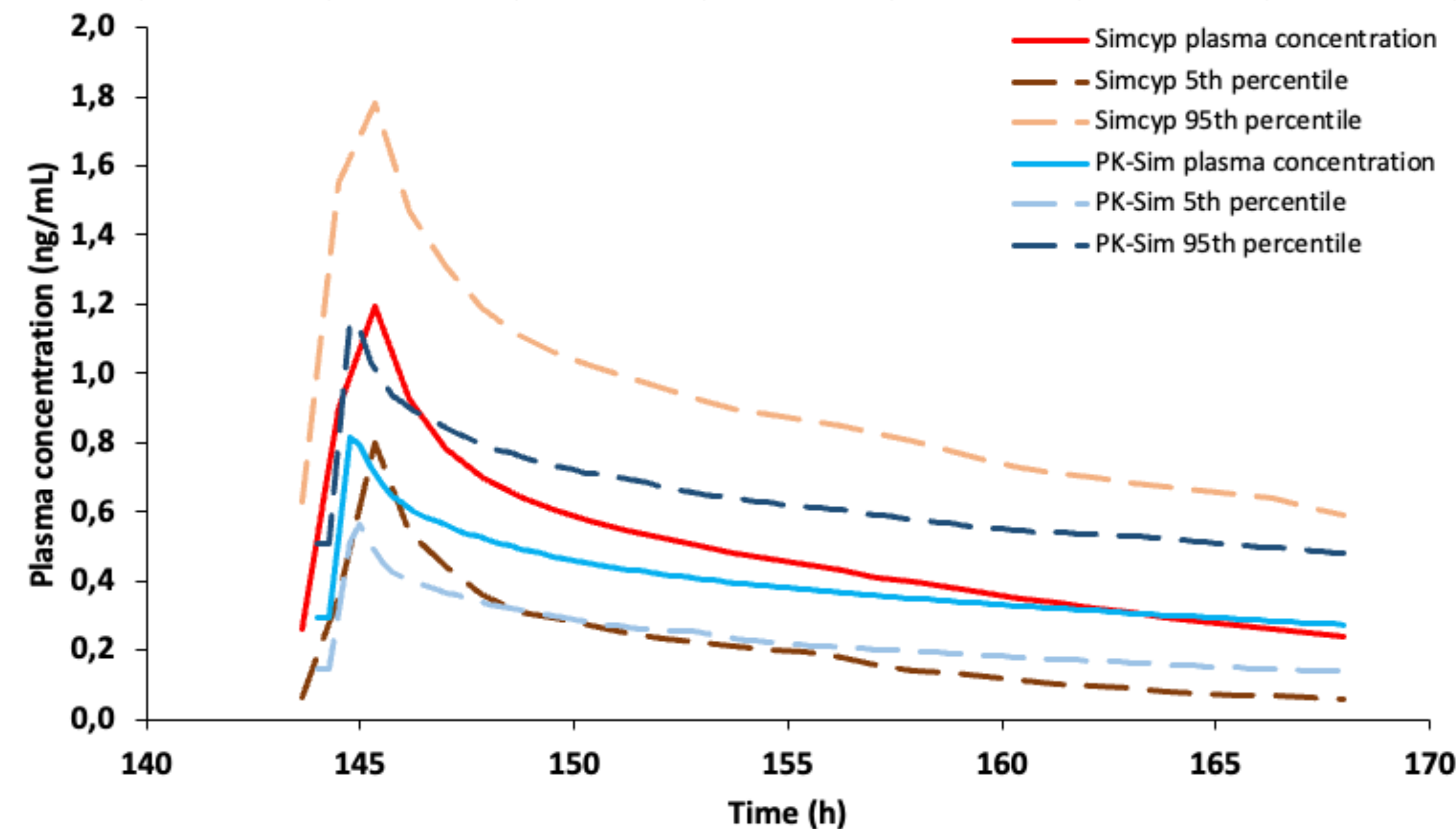


Figure 2: Plasma concentration of levonorgestrel following multiple oral doses of 0.1 mg of levonorgestrel with 0.03 mg of ethinylestradiol in the presence of 200 mg of carbamazepine (strong CYP3A4 inducer). Plot shows predicted mean (solid lines) for the population (10 individuals x 10 trials) and 5:95 percentile (dashed lines).

Case		Simcyp	Pk-Sim	Relative Difference
0.1 mg of GSD + 0.02 mg of EE	C _{max} (ng/mL)	3.20	1.93	49.52%
	AUC (ng*h/mL)	44.38	25.03	55.75%
0.1 mg of LNG + 0.03 mg of EE	C _{max} (ng/mL)	1.35	0.60	76.92%
	AUC (ng*h/mL)	10.84	6.81	45.68%
0.1 mg of LNG + 0.03 mg of EE + 200 mg of CBZ (for 7 days)	C _{max} ratio	0.81	0.61	28.17%
	AUC ratio	0.59	0.42	33.66%
	C _{max} after 7 days (ng/mL)	1.50	0.82	58.62%

Table 2: Numerical results corresponding to the graphs above, including the mean relative difference for each case. LNG= levonorgestrel, EE = ethinylestradiol, GSD=gestodene, CBZ = carbamazepine

Conclusion

Differences in PBPK platform implementation can hinder direct reproduction of modeling results across software. Even with closely matched parameters, the choice of platform can lead to divergent DDI predictions, potentially affecting regulatory decisions and patient outcomes. Each software should therefore be independently qualified. Results obtained with one platform should not be extrapolated to another, and studies must explicitly report the software version, parameters, and options used during simulations.