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PharmML & SO – Standards for Encoding Models and Results in Pharmacometrics and Quantitative Systems Pharmacology

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Introduction: New formats enabling the efficient exchange and integration of Pharmacometric and Quantitative System Pharmacology models across software tools have been defined and implemented as key elements of the DDMoRe interoperability platform [1]. Specifically, PharmML has been designed as the exchange medium for mathematical and statistical models [2, 3], and the Standard Output (SO) has been developed as a complementary component for storing typical output produced in a pharmacometric workflow. PharmML and SO, as essential elements of the DDMoRe interoperability platform, proved to be capable to handle complex modeling scenarios, and to facilitate model exchange and results storage across various tools.

Role of exchange formats

- Smooth and error-free transmission of models between tools.
- Use of complex workflows via standardised model and output definitions.
- Reproducibility of research.
- Easier reporting and bug tracking.



- Improved interaction with regulatory agencies regarding modeling and simulation.
- Development of new tools and methods.
- Expanding the community developing/applying pharmacometric models.
- Reuse of existing models, e.g. BioModels database of computational models of biological processes (SBML).

	Variability Model	Parameter Variability Residual Variability	Level	Parent Level			
Model Co Model Co Str Str Obs Obs	Parameter Model	Parameter					
		Population	Distril Ger	oution Ieral	ence		
		Individual	Structu Fixed/Ran Distri Ger	ured w. dom Effcts bution neral	ability Refere		
		Correlation Structure	Pair-wise Matrix		Uar		
	Covariate Model	Categorical/ Continuous	Interpolation (cont)				
			Transformation				
			Distri	bution			
			Assig	nment			
	Structural Model	Algebraic Eqs					
		PK Macros					
		ODE	Initial Condition				
		DDE	History				
	Observation Model	Continuous	Distri	oution	lef.		
			General		ar.F		
			Star	idard	Ŭ.	PMF	
		Discrete	Со	unt		PMF	
			Categorical Time-To-Event		PMF/Tra	Insition M	
					Hazard Ce	I/Survival ensoring	

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Figure 1: The role of PharmML/SO and their connection to the target tools.

PharmML

- Model definition, trial design and modelling steps \bullet storing tool-agnostic exchange format.
- Declarative structure allows it to play a role as an interoperability hub, a *lingua franca*, between tools used in pharmacometrics.

SCOPE

- Structural model defined as a system of ordinary differential equation (ODE), algebraic equations, PK macros & delay differential equations (DDE).
- Parameter model allowing for implementation of a \bullet wide variety of parameter models.
- Discrete/continuous covariates, and if required their \bullet transformation, distribution, interpolation features.
- Variability model (nested hierarchy) capable of expressing complex random error structures.



	NONMEM/MONOLIX Dataset		-	Mapping/ Transformation		Column/Target/ Category		
Frial esign		Interventions		Administrations		Bolus		
				Actions		Washout Variable Reset		
				Lookup Table				
				Individual Administrations		Dosing Time	Dose Amount	
	SIGN			Interventions-Combinations				
		Observations		Observation		Continuou	e Discroto	
	RIA			Indiv. Observation	าร			
				Lookup Table				
	XPLIC			Observations Combinations				
	Ē	Coupristoc		Covariate Mode	l			
		LUVANALES		Indiv. Covariates	v. Covariates			
		Occasions		Start/End Points	Start/End Points			
		Arms		ArmSize, DoseAmount/Times, Duration, Stage, NumberArms/Samples/Times, ObsTimes, Refs				
		Design Spaces	5	Reference to any design element with space definition				



- **Observation model** with flexible residual error model \bullet supporting untransformed or transformed continuous data.
- **Discrete data models** supports count, categorical, time-to-event data models with Markov dependencies.
- Trial design model with support for common design patterns, drug administration types and encoding of experimental data needed for typical simulation or estimation tasks, such as dosing, observations and covariates. Design spaces for Optimal Design.
- Hierarchical models/Bayesian inference definition \bullet via assignment of distributions to any model parameter.
- Typical modeling steps such as estimation, simulation, • design optimization/evaluation.



Figure 2: SO sections.

SO

- Tool-independent storage format for typical results of M&S analyses performed in DDMoRe target tools.
- Enables effective data flow across tasks to ensure optimal interactions among software tools and extends the modeling capabilities of the workflow.
- Facilitates information retrieval for post-processing and reporting, by allowing access to M&S results.

SCOPE

- Tool settings, raw results and task information sections carry the according information.
- Estimation section holds the results from MLE and

Figure 3: PharmML sections.

References

[1] Swat, MJ., Moodie S., Wimalaratne S., et al. (2015). Pharmacometrics Markup Language (PharmML) - Opening New Perspectives for Model Exchange in Drug Development, Vol. 4, Issue 6, 316–319. [2] Terranova, N. et al. (2016) Standard Output (SO) - Format Specification for Version 0.3.1. URL: ddmore.eu/projects/so-standard-output [3] Swat, MJ., Grenon P., Wimalaratne S. (2016). ProbOnto: ontology and knowledge base of probability distributions. Bioinformatics, 1-3, doi: 10.1093/bioinformatics/btw170.

GP1 NB2 FR1 EMG1 GP2 CAU1 NAK1 LOGU1 GP3 IGAM1 PARII1 NB5 GEOM LOGN6 SICS1 POI2 OL1 LOGN4 HN1 WDM1 SKN1 LOGN3 HS1 VM1 LOGL2 IGAU1 LOM1 LOGL1 LOGITN1 LAP1

Figure 4: Coverage of distributions in ProbOnto and target tools.

ProbOnto – knowledge base of probability distributions, featuring more than 100 uni- and multivariate distributions with their defining functions, characteristics, relationships and re-parameterization formulas [3]. Facilitates the encoding of distribution-based models, related functions and can be used for model annotation.

Bayesian inference analyses for population and individual parameters and their precision.

- Model Diagnostic section holds information required for model diagnostic plots - related to structural model, residual error specification and individual parameters.
- Simulation section stores results from simulation tasks, such as time course of observations, population and individual parameters, random effects, covariates and dosing records for each subject.
- Optimal Design section holds data following design evaluation or optimization steps, e.g. FIM, covariance matrix, parameter values, their precision, information about the adopted criteria and performed tests.

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