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).

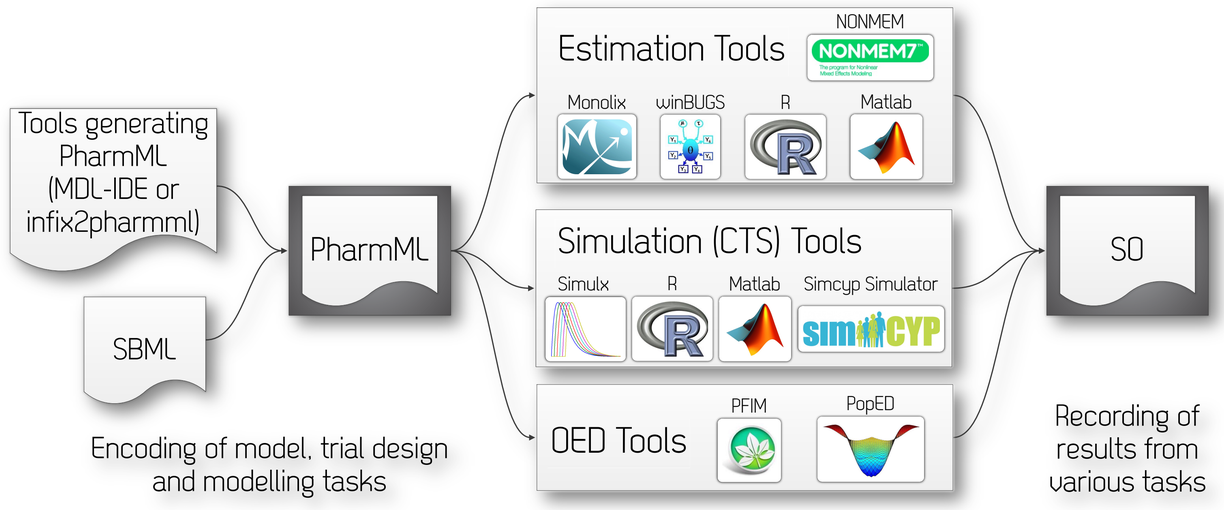

Figure 1: The role of PharmML/SO and their connection to the target tools.

PharmML

- **Model definition, trial design and modelling steps** 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 wide variety of parameter models.
- Discrete/continuous **covariates**, and if required their transformation, distribution, interpolation features.
- **Variability model** (nested hierarchy) capable of expressing complex random error structures.
- **Observation model** with flexible residual error model 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 via assignment of distributions to any model parameter.
- Typical **modeling steps** such as estimation, simulation, design optimization/evaluation.

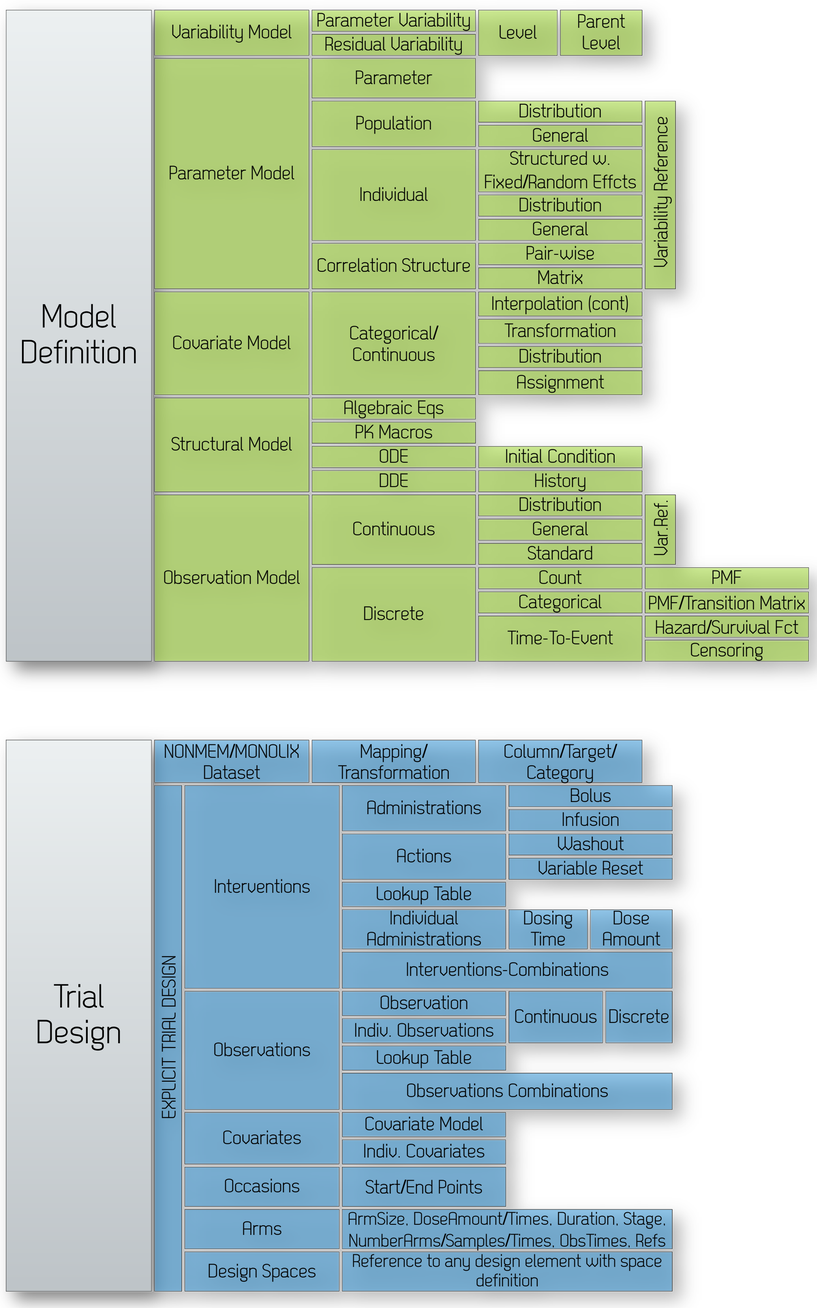

Figure 3: PharmML sections.

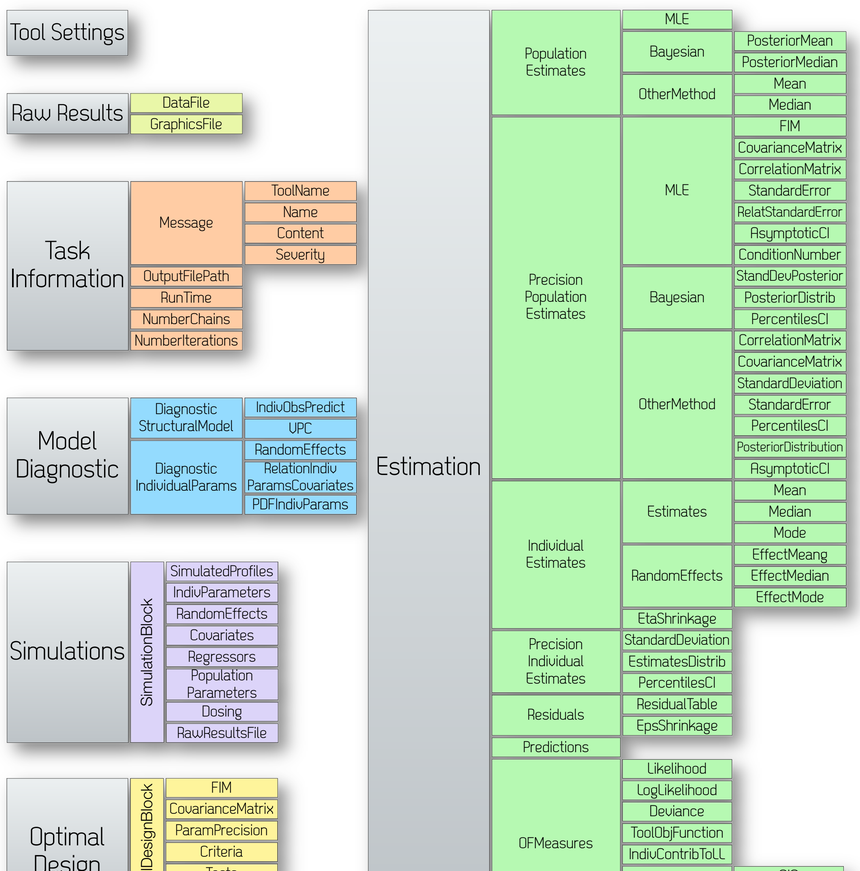

Figure 2: SO sections.

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 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.

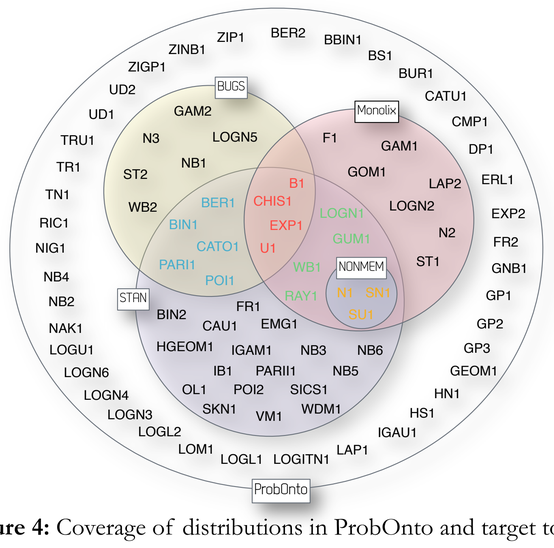

Figure 4: Coverage of distributions in ProbOnto and target tools.

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.

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.
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