Standardised Output (SO): flexible and tool-independent storage format of typical M&S results

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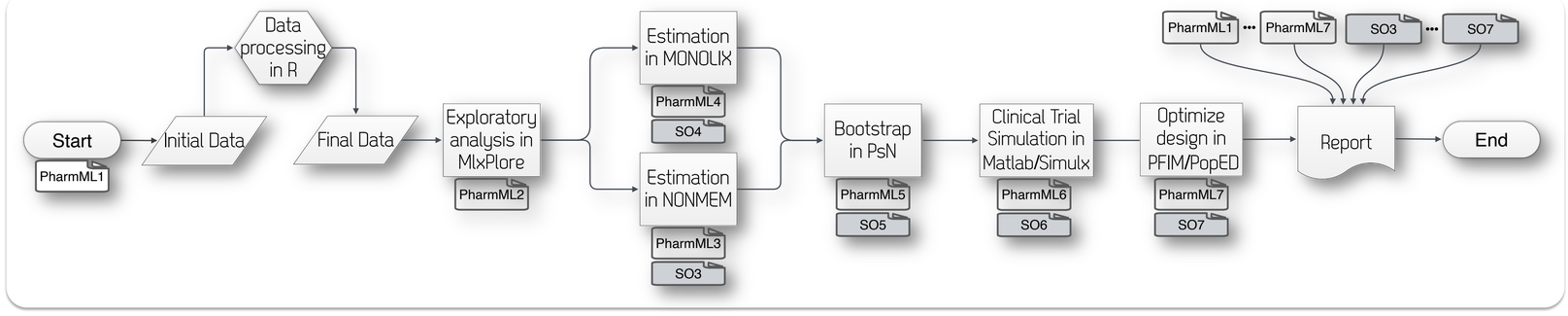
Introduction

Objectives

The definition and implementation of formats enabling a reliable exchange of pharmacometric models across software tools is one of the key goals for efficiently promoting collaborative drug and disease modelling and simulation (M&S) research. **PharmML**, one of the key DDMoRe interoperability platform elements, has been designed to play the role of the exchange medium for mathematical and statistical models [1]. Similarly, the Standardised Output (**SO**) has been developed as a complementary element, tool-independent format, for storing typical output produced in a pharmacometric workflow.

As a generic output model, SO aims at:

- providing a **flexible storage structure for typical results** of M&S analyses performed in any DDMoRe target tool;
- enabling **effective data flow across tasks** to ensure optimal interactions among software tools and, then, extend the modelling capabilities of the workflow;
- facilitating **information retrieval for post-processing and reporting**, by allowing immediate access to M&S results.

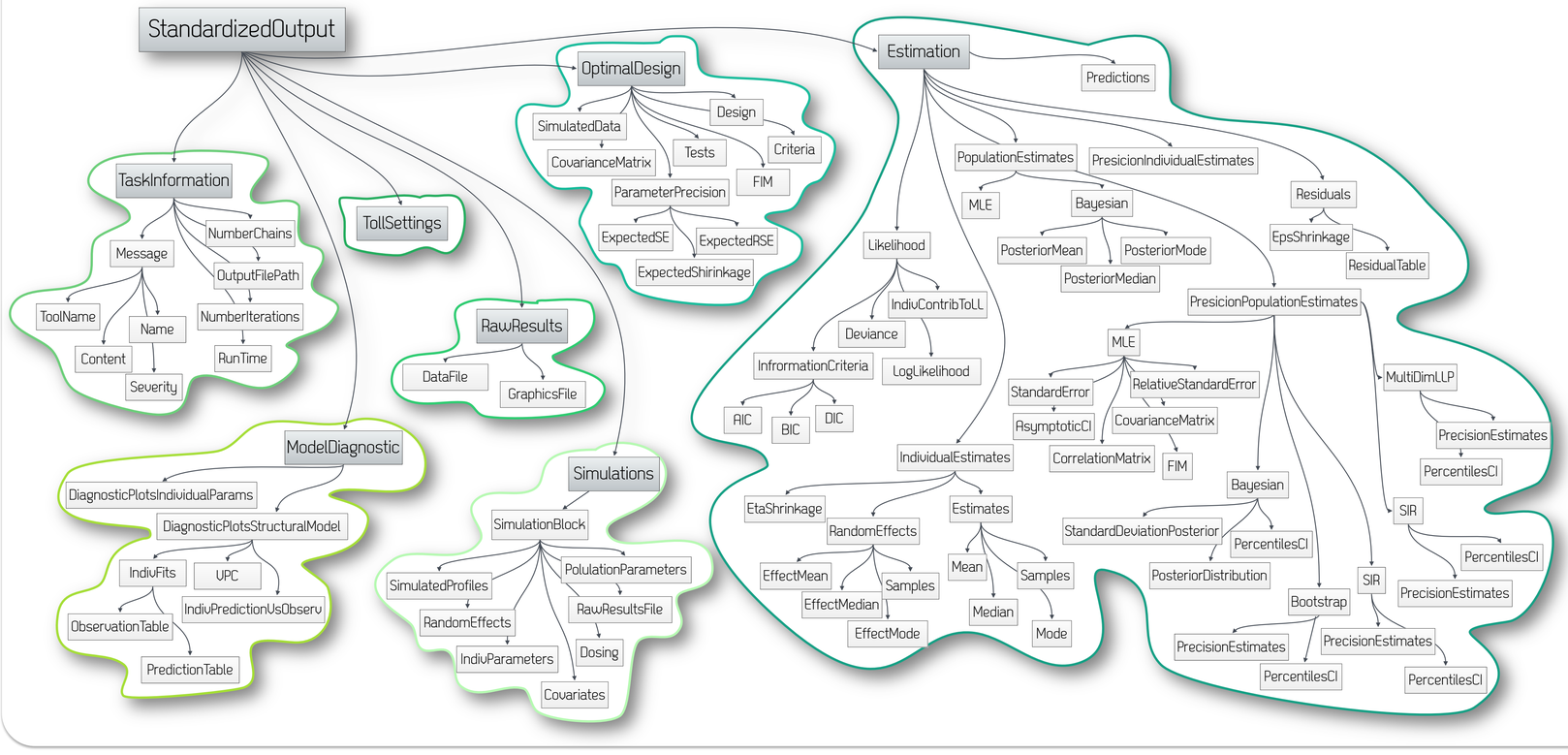


Effective workflow support – the key benefit coming from SO usage

SO Structure

SO consists of the following seven main sections:

- **Tool Settings** – storing the reference to any file containing the tool settings of a performed task.
- **Raw results** – placing references to original output files, both data and graphics, produced by any target tool.
- **Task Information** – holding the information about the modelling step execution.
- **Estimation** – storing typical output of interest resulting from an estimation task.
- **Model Diagnostic** – designed for storing information resulting from typical model diagnostic plots.
- **Simulation** – storing typical results produced in a simulation task.
- **Optimal Design** – storing results coming from a evaluation or optimization step.



Example 1: Population estimates

Typical output for parameter estimation. First the columns – here the names of population parameters – are specified. Then two options exist: either the results are stored inline or in an external data file.

```
<Estimation>
    <PopulationEstimates>
        <MLE>
            <Definition xmlns="http://www.pharmml.org/pharmml/0.6/Dataset">
                <Column columnId="POP_CL" columnType="popParameter" valueType="real" columnNum="1"/>
                <Column columnId="POP_V" columnType="popParameter" valueType="real" columnNum="2"/>
                <Column columnId="POP_KA" columnType="popParameter" valueType="real" columnNum="3"/>
                <Column columnId="POP_TLAG" columnType="popParameter" valueType="real" columnNum="4"/>
                <Column columnId="BETA_CL_WT" columnType="popParameter" valueType="real" columnNum="5"/>
                <Column columnId="BETA_V_WT" columnType="popParameter" valueType="real" columnNum="6"/>
                <Column columnId="PPV_CL" columnType="popParameter" valueType="real" columnNum="7"/>
                <Column columnId="PPV_V" columnType="popParameter" valueType="real" columnNum="8"/>
                <Column columnId="PPV_KA" columnType="popParameter" valueType="real" columnNum="9"/>
                <Column columnId="PPV_TLAG" columnType="popParameter" valueType="real" columnNum="10"/>
                <Column columnId="RUV_PROP" columnType="popParameter" valueType="real" columnNum="11"/>
                <Column columnId="RUV_ADD" columnType="popParameter" valueType="real" columnNum="12"/>
                <Column columnId="CORR_PPV_CL_V" columnType="popParameter" valueType="real" columnNum="13"/>
            </Definition>
            <Table xmlns="http://www.pharmml.org/pharmml/0.6/Dataset">
                <Row><ct:Real>0.93882</ct:Real><ct:Real>1.63219</ct:Real><ct:Real>8.10703</ct:Real>
                    <ct:Real>1</ct:Real><ct:Real>0.13426</ct:Real><ct:Real>0.75</ct:Real>
                    <ct:Real>0.54806</ct:Real><ct:Real>0.76833</ct:Real><ct:Real>0.13334</ct:Real>
                    <ct:Real>0.26875</ct:Real><ct:Real>0.16612</ct:Real><ct:Real>0.32349</ct:Real>
                    <ct:Real>0.07736</ct:Real>
                </Row>
            </Table>
            <!-- ALTERNATIVELY: external data reference
            <ds:ExternalFile oid="ext1">
                <ds:path>popEstimates.csv</ds:path>
            </ds:ExternalFile>-->
        </MLE>
```

Example 2: Optimal design

In an optimal design task, e.g. evaluation, relevant results such as the Fisher Information Matrix (FIM) and the covariance matrix are captured.

```
<OptimalDesign type="evaluation">
    <OptimalDesignBlock blockNumber="1">
        <FIM>                    <!-- 3x3 matrix for simplicity -->
            <ct:Matrix matrixType="Any">
                <ct:RowNames>
                    <ct:String>POP_CL</ct:String><ct:String>POP_V</ct:String><ct:String>POP_KA</ct:String>
                </ct:RowNames>
                <ct:MatrixRow>
                    <ct:Real>4.21e-05</ct:Real><ct:Real>2.36e-04</ct:Real><ct:Real>-0.000124</ct:Real>
                </ct:MatrixRow>
                <ct:MatrixRow>
                    <ct:Real>2.36e-04</ct:Real><ct:Real>4.95e-02</ct:Real><ct:Real>-0.006150</ct:Real>
                </ct:MatrixRow>
                <!-- omitted other matrix rows -->
            </ct:Matrix>
        </FIM>

        <CovarianceMatrix>               <!-- 3x3 matrix for simplicity -->
            <ct:Matrix matrixType="Any">
                <ct:RowNames>
                    <ct:String>POP_CL</ct:String><ct:String>POP_V</ct:String><ct:String>POP_KA</ct:String>
                </ct:RowNames>
                <ct:MatrixRow>
                    <ct:Real>4.21e-05</ct:Real><ct:Real>2.36e-04</ct:Real><ct:Real>-0.000124</ct:Real>
                </ct:MatrixRow>
                <ct:MatrixRow>
                    <ct:Real>2.36e-04</ct:Real><ct:Real>4.95e-02</ct:Real><ct:Real>-0.006150</ct:Real>
                </ct:MatrixRow>
                <!-- omitted other matrix rows -->
            </ct:Matrix>
        </CovarianceMatrix>
```

Target tool – SO connection: libSO & connectors

DDMoRe Target Tools

Simulx | PFIM | PopED | Monolix | winBUGS | NONMEM | Simcyp Simulator | PsN | R | Matlab

Target tool – PharmML connection: libPharmML & connectors

PharmML

Model Definition

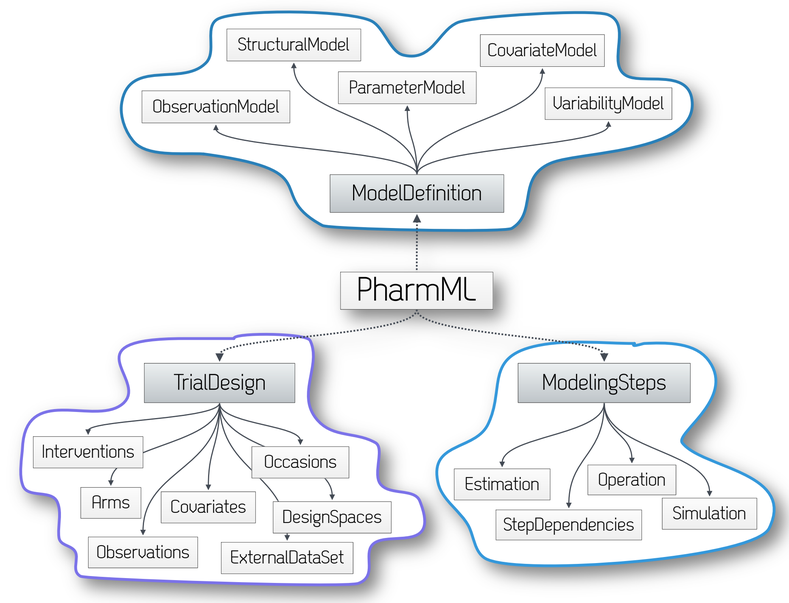
- **Variability Model** – allows to define any number of variability levels as a nested hierarchy.
- **Covariate Model** – describes the covariates, both continuous and discrete, their distribution, transformation and interpolation.
- **Parameter Model** – offers flexible structure to encode structured and equation type parameter models with any number of variability levels and covariates.
- **Structural Model** – prediction PK, PD or disease models can be formulated here as ODE, DDE or algebraic equations.
- **Observation Model** – model for continuous or discrete data models.

Trial Design

Specifies explicitly the structure of a clinical study, used for optimal design and simulations, as an alternative to a design sourced from a dataset.

Modelling Steps

The specification of how a mathematical model and the associated trial design can be used, e.g. for simulation, estimation or optimal design tasks.



Non-linear mixed effects model

The general NLME model for N subjects and n_i measurements per subject i reads as follows [2]

$$\underbrace{y_{ij}}_{\text{Experimental data}} = \underbrace{f(x_{ij},\psi_i)}_{\text{Model prediction}} + \underbrace{g(x_{ij},\psi_i,\xi)\,\epsilon_{ij}}_{\text{Residual error}}, \quad 1 \le i \le N,\ 1 \le j \le n_i$$

y_{ij} - j^{th} observation for subject i
f - structural model prediction
x_{ij} - regression variables
ψ_i - individual parameters
g - standard deviation of the residual error
ξ - parameters of the residual error
ϵ_{ij} - residual error

References

[1] Swat, MJ., Moodie S., Wimalaratne S., et al. (2015). Pharmacometrics Markup Language (PharmML) – Opening New Perspectives for Model Exchange in Drug Development, Accepted for publication in CPT:PSP.
[2] Lavielle, M. Mixed Effects Models for the Population Approach: Models, Tasks, Methods and Tools. Chapman & Hall/CRC Biostatistics Series. 2014.

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