Development and integration of the WinBUGS connector in the DDMoRe Interoperability Framework

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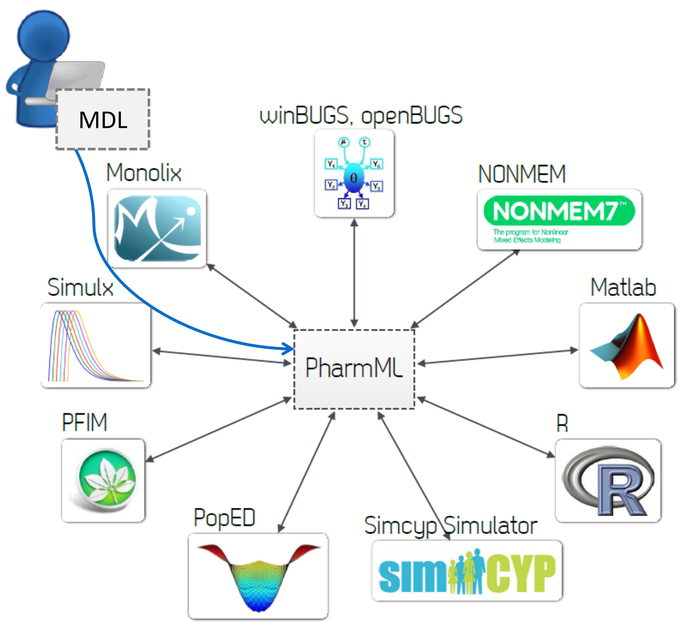
BACKGROUND AND OBJECTIVES.

The DDMoRe Interoperability Framework [1] is an integrated infrastructure to enable efficient exchange and integration of models across modelling languages and tools. This platform is built on the Pharmacometrics Markup Language (PharmML) [2], a tool-independent standard language for PK/PD model representation, designed to facilitate the translation and execution of user-specified models into target languages and tools. The objective of our work is to develop and test a connector integrating WinBUGS [3] in the DDMoRe Interoperability Framework. The connector allows the user to perform all the steps of a WinBUGS model execution: PharmML-to-WinBUGS model translation, WinBUGS run, generation and retrieval of the desired output.

DDMoRe Interoperability Framework: platform overview

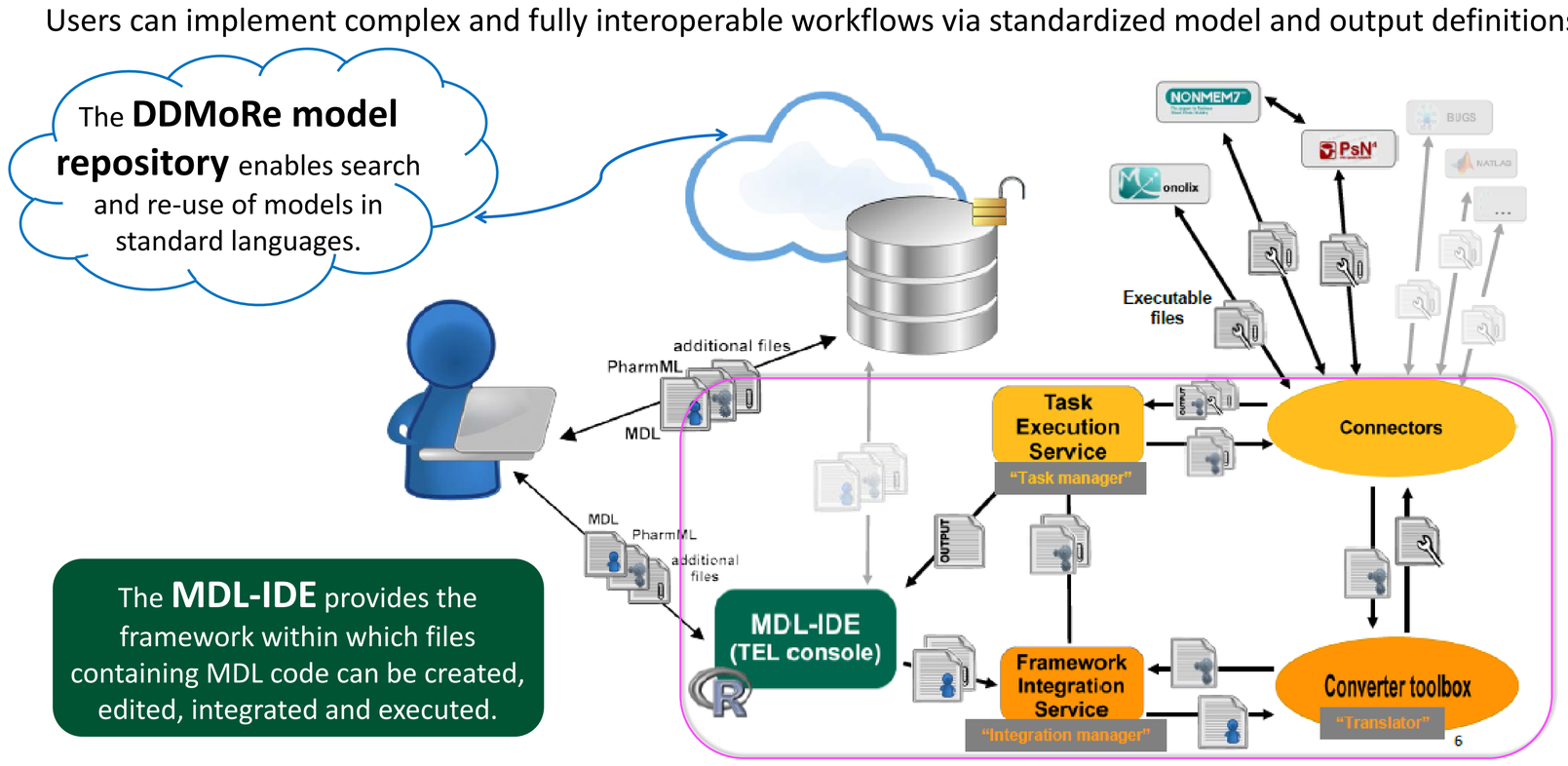
New model-specifying languages

A «user language» (MDL) and a «computer language» (PharmML).



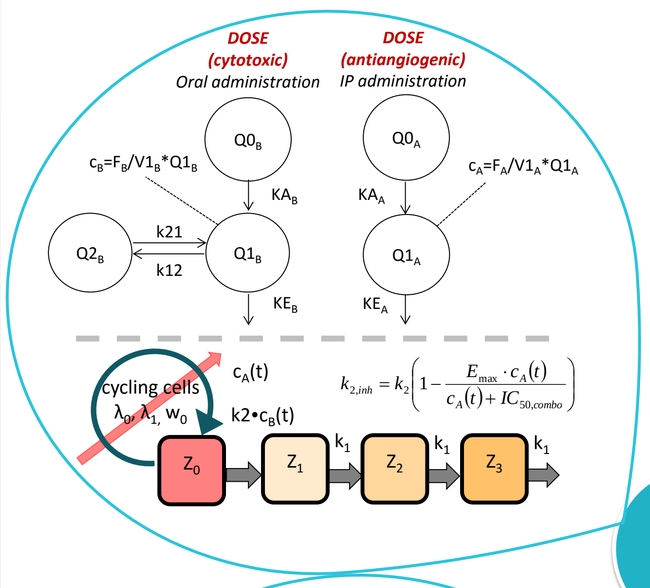
Environment for model retrieval, encoding and task execution

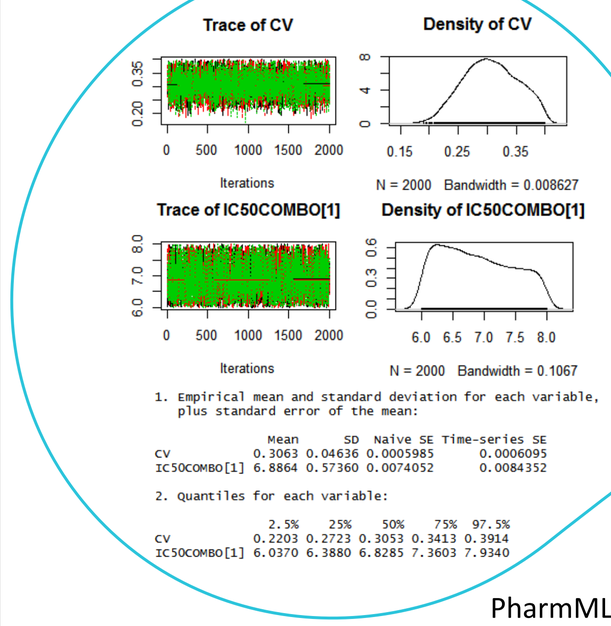
Users can implement complex and fully interoperable workflows via standardized model and output definitions.



Development of a WinBUGS connector

Workflow example: Perform a Bayesian estimation task for a PK-PD model (Rocchetti et al., 2013 [4]), available in the Model Repository (http://repository.ddmore.eu/model/DDMODEL00000008), describing the tumor growth inhibition of a combination therapy. Priors were added for the two model parameters $IC_{50,COMBO}$ and CV.



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1. Empirical mean and standard deviation for each variable,
   plus standard error of the mean:

                Mean      SD  Naive SE Time-series SE
CV            0.3063 0.04636 0.0005985      0.0006095
IC50COMBO[1] 6.8864 0.57360 0.0074052      0.0084352

2. Quantiles for each variable:

                2.5%    25%    50%    75%  97.5%
CV            0.2203 0.2723 0.3053 0.3413 0.3914
IC50COMBO[1] 6.0370 6.3880 6.8285 7.3603 7.9340
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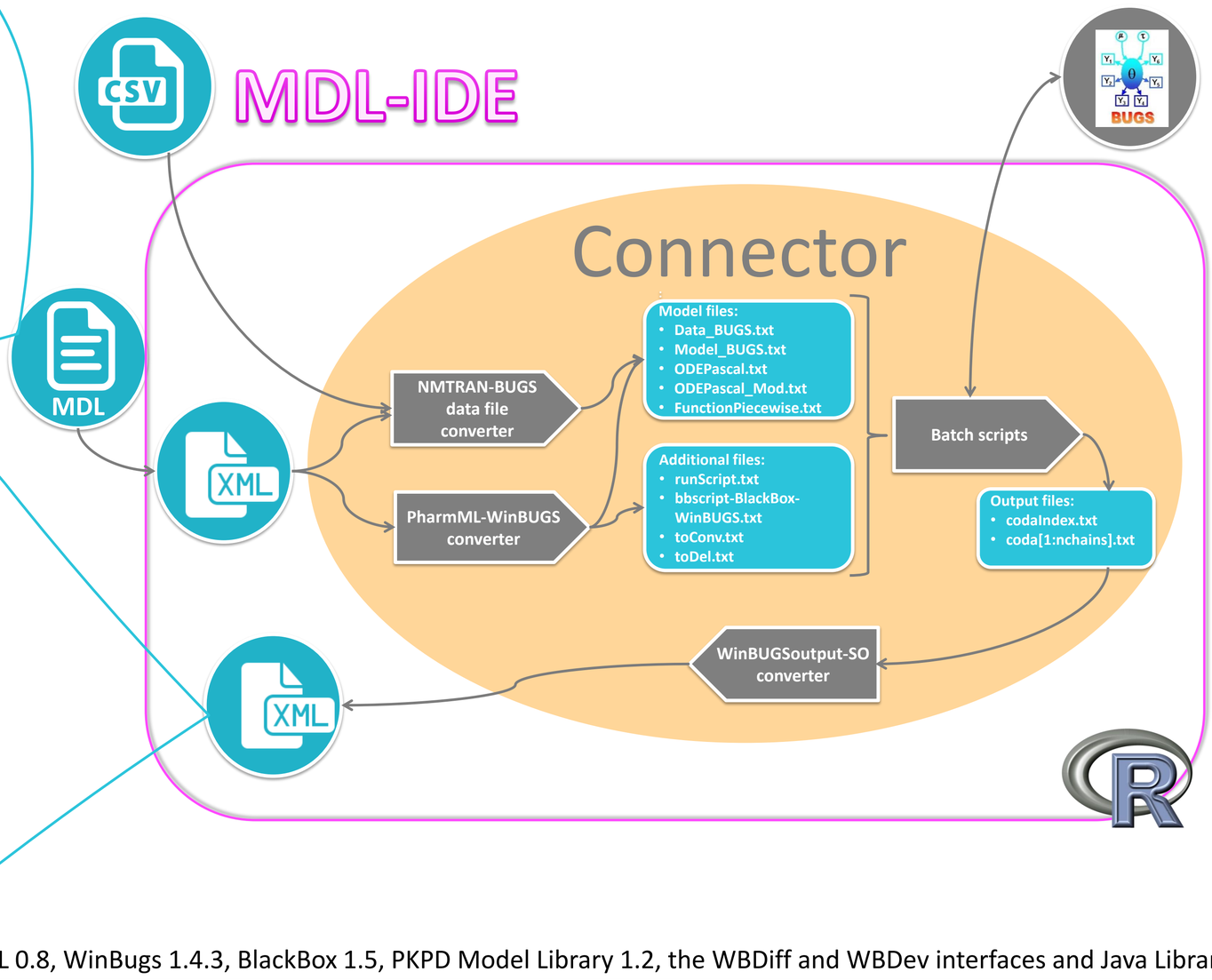

New tools:

- A Java-based **tool for standardized output (SO) file creation** was developed using lib-PharmML-SO [2].
- A **connector** via different shell scripts responsible for: preparing inputs, invoking the tool, monitoring the progress of the processing and retrieving results from execution.

Supported features:

- Single-subject and population models
- Algebraic equations model
- ODE models, solved via Pascal code using PKPD Library and WBDev, supporting multiple dosing
- **Models with multiple DVs (NEW)**
- Dose administration in multiple compartments
- NONMEM dataset including: AMT, RATE, CMT, EVID, MDV, ID, DV, DVID
- **Time-dependent categorical and continuous covariates (NEW)**
- **Piecewise functions(NEW)**
- **Correlation matrix (NEW)**
- **Prior distributions (NEW)**
- Estimation task

PharmML 0.8, WinBugs 1.4.3, BlackBox 1.5, PKPD Model Library 1.2, the WBDiff and WBDev interfaces and Java Libraries, previously described in [5], were used.

WHAT'S NEXT?

- ODE solving via WBDiff and inline *ode block*
- PK macros
- Simulation task
- Between-occasion variability
- Time to Event models
- Count and categorical data

REFERENCES.

[1] DDMoRe Interoperability Framework [http://www.ddmore.eu/product/interoperability-framework]
[2] Swat MJ et al. (2015). Pharmacometrics Markup Language (PharmML): Opening new perspectives for model exchange in drug development. CPT Pharmacometrics Syst. Pharmacol. 4, 316-319.
[3] Lunn DJ et al. (2000). WinBUGS - a Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing, 10:325-337.
[4] Rocchetti M et al. (2013). Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth after administration of an anti-angiogenic agent, bevacizumab, as single-agent and combination therapy in tumor xenografts. Cancer Chemother Pharmacol. 71(5):1147-57.
[5] Larizza C et al. (2015). Automatic translation of Bayesian pharmacometric models: the PharmML-to-WinBugs converter. PAGE 24 (2015) Abstr 3565 [www.page-meeting.org/?abstract=3565]