

Automatic translation of Bayesian pharmacometric models: the PharmML-to-WinBugs converter Cristiana Larizza¹, Lorenzo Pasotti², Enrica Mezzalana², Elisa Borella², Gareth Smith³, Paolo Magni²



Drug Disease Model Resources

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BACKGROUND. PharmML is a markup language for pharmacometric models description, under development by the DDMoRe consortium, that will enable the tool-independent formulation, exchange and integration of models and tasks [1]. The Modelling Description Language (MDL), also under development, is a human-readable standard language aimed to facilitate model writing and enable, via automatic translation, the generation of PharmML-encoded models that can be converted into the desired target language [2]. This work describes the efforts undertaken for the development of a PharmML-to-WinBugs converter, which will support Bayesian model estimation tasks in fully integrated interoperable workflows.

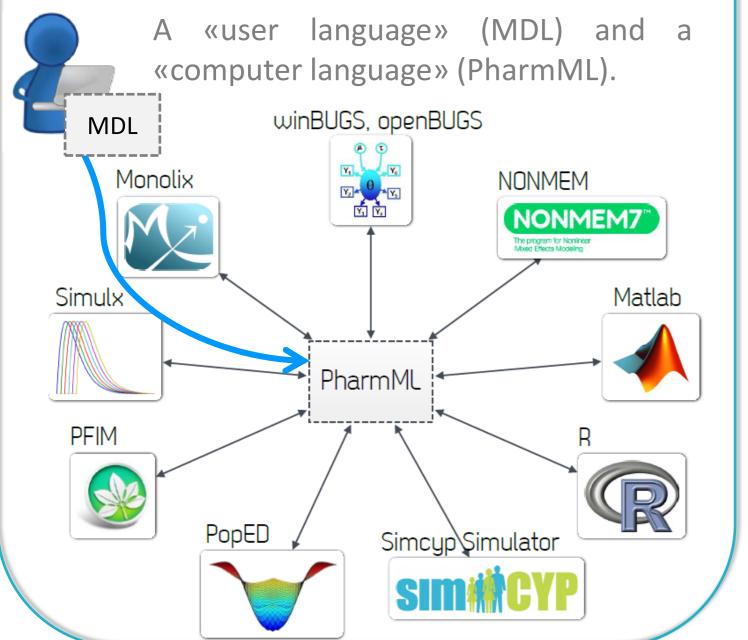
MATERIALS AND METHODS.

DDMoRe platform overview

New model-specifying languages

Standard workflow for pharmacometric analysis

Environment for model retrieval, encoding and task execution The DDMoRe model repository enables search and re-use of models in standard languages, while the MDL-IDE provides the framework within which files containing MDL code can be created, edited, integrated and executed.

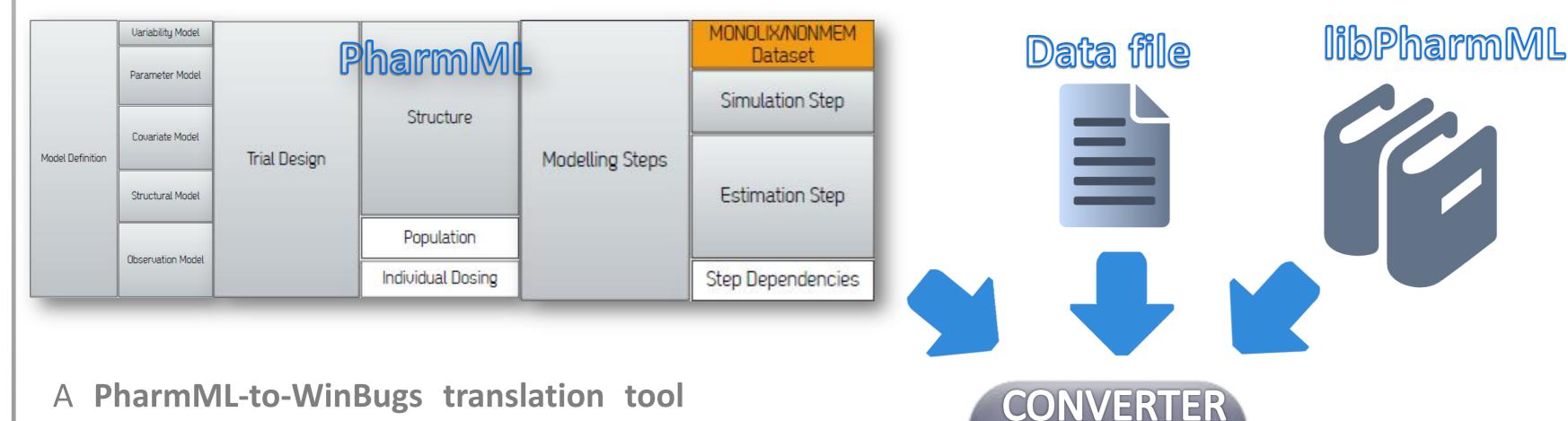


Users can implement complex and fully interoperable workflows via standardized model and output definitions.

End PharmML1 Start SO3 Ínitial Data, S07 Data Report rocessin PharmML1 Final Data PharmML Estimation in MONOLIX Optimize Clinical Trial Exploratory PharmML4 Bootstrap design in Simulation in analysis in SO4 in PsN MlxPlore PFIM/PopED Matlab**/**Simulx PharmML2 PharmML6 PharmML7 PharmML5 Estimation SO5 S07 SO6 in NONMEM PharmML3

Executable Execution Connectors MDL-IDE (TEL console) Converter toolbox

Development of a PharmML-to-WinBugs converter



Supported features:

- single-subject and population models
- algebraic and ordinary differential equations (ODEs)
- multiple Observation Models with additive Gaussian error
- time-varying continuous covariates

Individual Parameters and Observation

transformation of Covariates,

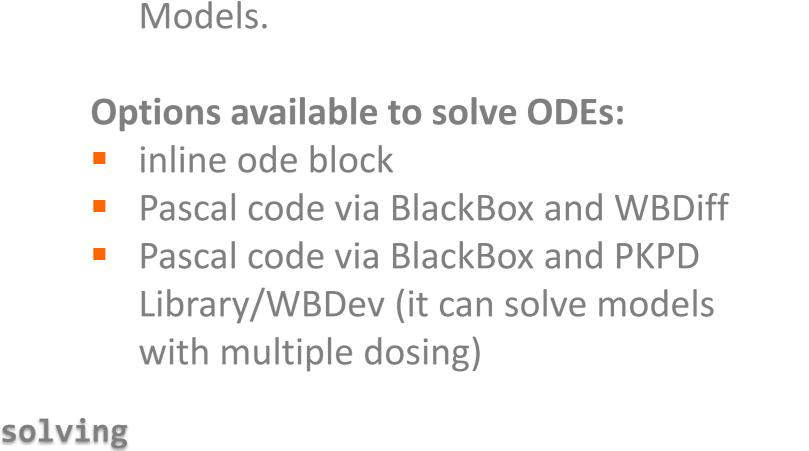
- A PharmML-to-WinBugs translation tool was developed via Java using:
- libPharmML to read/validate PharmML files
- libraries to generate an intermediate model representation.

A data conversion tool was developed via R to translate NONMEM-format data files into WinBugs input files, also considering the dataset structure defined in PharmML file.

PharmML 0.4, WinBugs 1.4.3, BlackBox 1.5, PKPD Model Library 1.2, and the WBDiff and WBDev interfaces were considered.

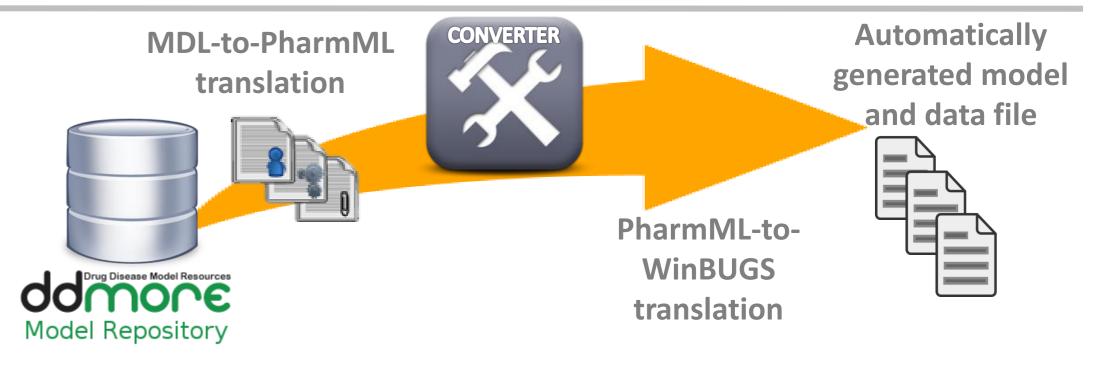
RESULTS.

- The converter was tested on about 100 ad-hoc encoded PharmML models of increasing complexity which span a wide range of PharmML language features.
- It was also tested on some PharmML files, obtained after automatic translation of MDL files available on the DDMoRe model repository.



Pascal file(s) for ODE solving Data file in WinBugs format WinBugs model file

lava



REFERENCES.

[1] Swat MJ, Wimalaratne S, Kristensen NR. PharmML 1.0 - An exchange standard for models in Pharmacometrics. Proceedings of the PAGE meeting (2014) June 10-13, Alicante, Spain.

FUTURE WORK.

- Connector
- Support for the remaining PharmML

[2] Harnisch L, Matthews I, Chard J, Karlsson MO. Drug and Disease Mode Resources: a consortium to

create standards and tools to enhance model-based drug development, CPT Pharmacometrics Syst





Prior distribution representation



