Drug Disease Model Resources

Newsletter

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EDITORIAL

Dear Reader,

With this newsletter we wish to provide a comprehensive summary of our activities in delivering a Modelling and Simulation framework and an associated Library of models to the broader user community.

Before the next issue of this newsletter, a public release of the model repository will have been created, and a preliminary set of models will have been implemented to enable the user to experience the functionality and content of this version of the DDMoRe Repository.

We are excited about the DDMoRe introductory workshop to be held during the 7th Noordwijkerhout Symposium on PK, PD and Systems Pharmacology, which will demonstrate our first implementation of the core features of the DDMoRe framework.

We would also like to welcome Takeda as a new EFPIA partner to the consortium. Takeda joins us as part of our successful ENSO (explore new scientific opportunities) application which will enable several new activities. One of these will be the creation of a model review process to evaluate contributions from partners in our key disease areas in the first instance. Ultimately though we wish to constitute an independent expert board whose remit will be to establish and maintain a robust model qualification process in order to create trust in both the content and reliability of models uploaded to the repository and establish credibility for future instances of the Drug and Disease Model Repository.

Given the time frame of this project, the initial definitions of MDL (human readable component), PharmML (machine executable component) were generated in parallel. Now, with the provision of various models in a series of cross translational exercises, integration issues arose in the current versions of both of these languages. The early release of the public instance of the OpenSource framework in one month will enable the user to assess how successful we have been in rectifying and harmonizing both of these language components.

The consortium members are acutely aware that despite the tangible progress on our goals there is a lot of work still outstanding which is required to be completed before the end of the project, in 2 years time. In order to maintain what DDMoRe has or will establish well into the future, the partners will continue the development of the library and framework in an open source context. Furthermore through another element of the successful ENSO application we plan to ensure sustainability through the creation of a “DDMoRe Foundation”, details of which will be communicated in a future newsletter.

We hope you enjoy reading about our advances.

Executive team DDMoRe

imi Innovative Medicines Initiative efpia

DDMoRe Repository

Mihai Glont

The DDMoRe Repository is storing and disseminating drug and disease models encoded in standard formats. Once publicly available, modellers can use the resource to effectively store, retrieve, search and share models plus the associated dataset and annotations.

Over the last year, the repository has been under active development, going from a set of blueprints and a prototype to adding the finishing touches in preparation for its first public release. Along the way, a number of development versions have been made available to the consortium members, resulting in valuable feedback being incorporated into the application.

Now, the repository has features that facilitate collaborative model development. A user-friendly wizard can be used to submit models and associated information to the repository. With a detailed model display and the preserved history of changes made when the model is updated, the user is able to track the model's development. By default, models are only accessible to the submitter, but can also be shared with other modellers. Comprehensive documentation is available on all pages of the DDMoRe Repository web site. For increased usability, a help button takes the user to the relevant section of the manual based on their current activity.

Refinements to the DDMoRe Repository will not stop when it goes public, as we already have a wish list for new features and improvements. Enhanced support for annotations, resulting in a richer model display and a more intelligent search, has a high priority. We also plan to develop a classification mechanism based on tags and complemented by facets. Adding to our own wish list, we welcome user feedback to help improving the DDMoRe Repository.

CNS Models

Paolo Magni

Models for central nervous system (CNS) diseases are selected for submission to the DDMoRe Repository on the basis of the DDMoRe partners' interest and of their high potential impact on drug development. Our selection ranges from basic models for drug disposition in the brain and placebo responses to complex models describing variability in composite scales for psychiatric diseases (e.g. schizophrenia), neurodegenerative diseases (e.g. Alzheimers, Parkinsons, multiple sclerosis) and cyclic disorders (e.g. epilepsy). Here, symptom frequency is used as a measure of clinical benefit and underlying pathophysiological conditions not formally included in the assessment of efficacy.

To finalize the first DDMoRe CNS model collection, a selection of the most important CNS models reported in literature was ranked on basis of their priority and impact. Four of them were encoded by using one of the existing modelling languages (3 in NM-TRAN and 1 in WINBUGS) and run using the suitable software environment. This first CNS model collection acts as a gold reference for the DDMoRe platform validation. We are encoding three models into the new Modelling Description Language (MDL) and Pharmacometrics Markup Language (PharmML), making them suitable to populate the DDMoRe Repository before its first public release and to be used during the CNS beginner course scheduled for mid July.

In parallel, several research activities have been started to develop new models and fill the gaps that were highlighted during the literature review. For example, item response theory was used to model ADAS-cog scores in the development of new therapeutic agents for Alzheimer's Disease, to model EDSS score in multiple sclerosis and PANSS score in schizophrenia.

MDL

Nick Holford

The Modelling Description Language (MDL) has been extended since the public release (November 2013) to include more flexible use of the data object with the ability to derive new data variables from an existing data set, a table description of supported 'use' and 'type' attributes and inclusion of named distributions with associated parameters. The Model Coding Language (MCL) specification has been re-written in many places in response to user comments to add more detail and explain more clearly what is required.

The updated MDL (March 2014) has been successfully used to implement and test 50 use cases and published model examples. The public release version of the MDL use Cases was used with the public version of the MDL Integrated Development Environment (IDE) to teach a train-the-trainer course on the MDL. The purpose of the course was to explain in detail the MDL structure, focussing mainly on the MCL, and to show how to use the MDL-IDE to edit MDL code. The teaching documents prepared for the train-the-trainer course will provide a good foundation for teachers to train students participating in the first on-site courses.

PharmML - Going Public

Maciej Swat

The lack of a common standard to smoothly exchange models between different software tools such as Monolix, NONMEM or BUGS has been a longstanding problem in the field of population PK/PD. The Pharmacometrics Markup Language (PharmML) is being developed to become such a standard. We have released the first public version of PharmML (November 2013) for encoding of models, associated tasks and their annotations. This version supports non-linear mixed effect models as used in analysis of continuous longitudinal population PK/PD data with:

- a structural model defined as a system of ordinary differential equations (ODE) and/or algebraic equations;
- a flexible parameter model allowing for implementation of virtually any parameter type used in the majority of models;
- discrete or continuous covariates;
- a nested hierarchical variability model capable of expressing very complex random error structures;
- an observation model with a flexible residual error model supporting untransformed or transformed data;
- a novel trial design model allowing for (1) definition of many common design and drug aministration types, (2) encoding of experimental data needed for typical simulation or estimation tasks, such as dosing, observations and covariates;
- defining typical modelling steps such as estimation or simulation.

The PharmML is under active development. Some features are still missing, for example discrete data models (e.g. models for count, categorical or time-to-event data), Bayesian inference method, delay or stochastic differential equations. Future releases will take care of these. For a detailed description and user feedback, please have a look at the specification documents and forum on our website ddmore.eu or pharmml.org.

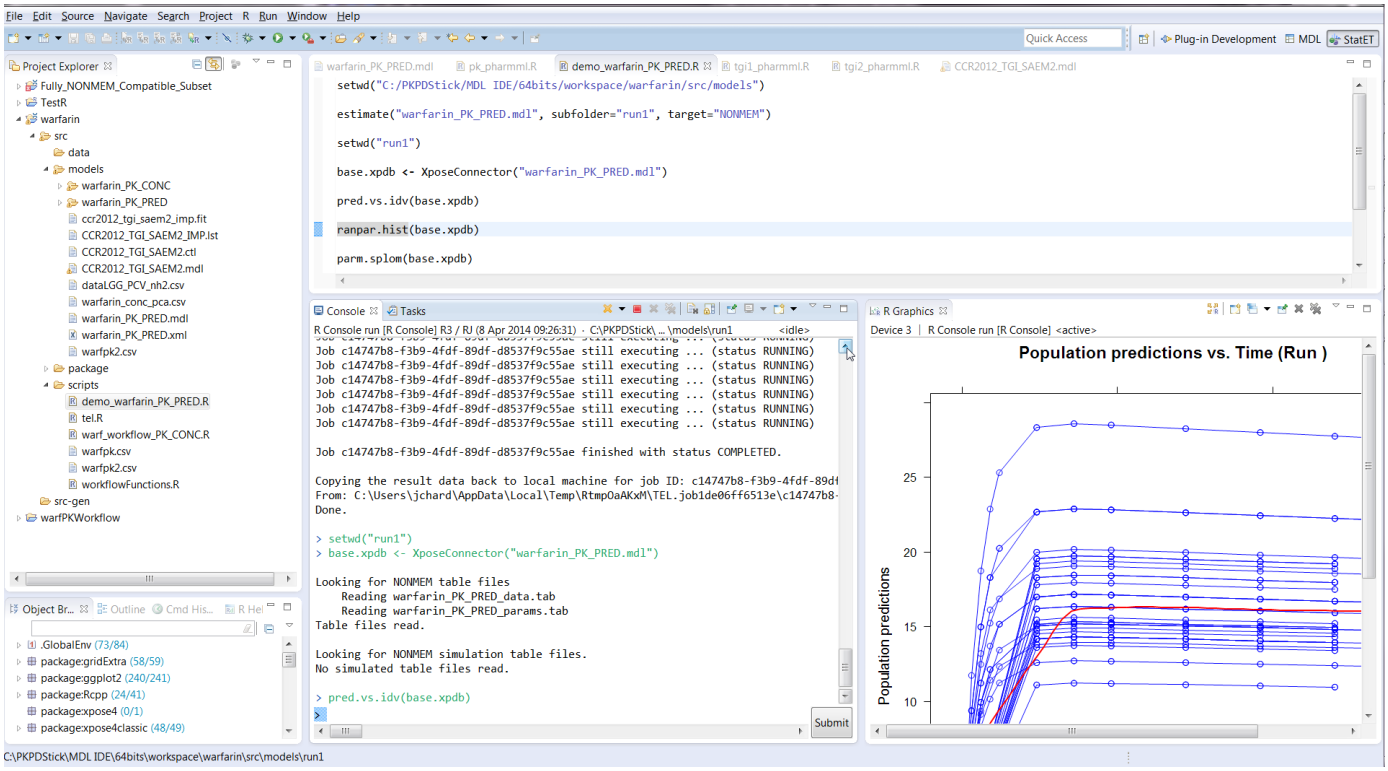
Framework

Natallia Kokash / Jonathan Chard

Since the release of the latest versions of the MDL and PharmML specifications, the MDL-IDE has seen an update to support the new language features. Classification of variables according to the full range of use attributes (id, idv, amt, etc. 25 types in total) is now supported. The MDL-IDE recognizes and validates all commonly- used distributions (Bernoulli, Beta, Binomial, etc.; about 30 types and their compositions). The current release also provides a more rigorous validation of user specifications. More specifically, matching between expected value types and actual types is now enabled for parameter and variable attributes in all blocks. Validation of function calls has been updated to recognize an extensive set of standard mathematical functions and to match function calls with their signatures. Validation of unit metrics is available.

We have taken a step forward to validate dynamically assembled MDL specifications by passing selected data, model and parameter objects to tasks specified in the task objects. Validation of task object properties is supported.

R has also been integrated into the MDL-IDE, which, allows the user to execute models via the TEL.



Screenshot DDMoRe MDL-IDE

STANDARDS

The publication of the PharmML specification has been the start of the translation effort both to PharmML and to our target tools. The MDL syntax has been revised to make the language compatible with PharmML and partial conversion of MDL specifications to PharmML is available for testing. The MDL to PharmML converter generates PharmML model definitions that are validated and displayed by the DDMoRe Repository.

Further downstream, translations from PharmML to NONMEM, Monolix and Matlab are under way, with success in all languages. The translator for NONMEM has been integrated into the task execution environment, which now supports local execution on a user's desktop. This will be of key importance for the training courses that are running later this year.

The coming months will see further development and improvements to these translations, and also extend the Task Execution Language (TEL) to allow the user to manipulate models in their development environment. Support for annotations will be added to the IDE, to allow the user to describe their work for the benefit of other modelling community members.

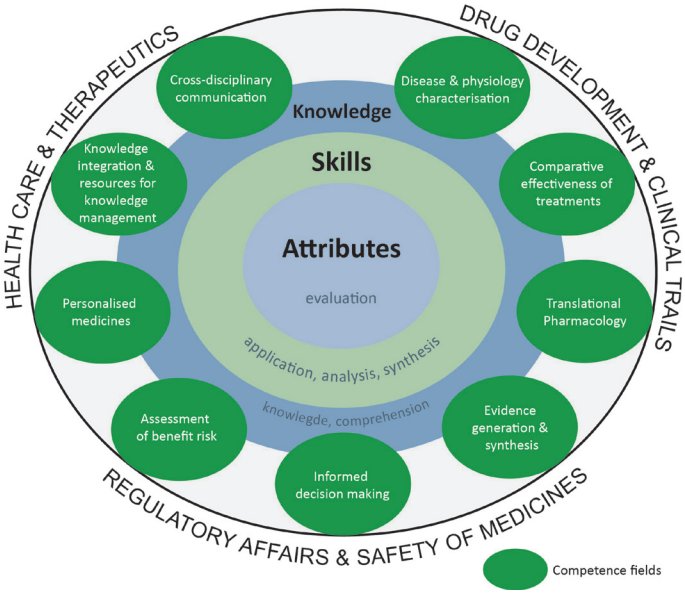
Education and Training

Thomas Leja / Charlotte Kloft

Drug Disease Modelling & Simulation (DDM&S) defines a paradigm for enabling knowledge integration and informed decision-making across all stages of pharmaceutical drug development and in therapeutic use of medicines. Despite the increasing impact of DDM&S, there is no consensus about knowledge, skills or attributes essential to perform activities in the context of DDM&S.

A recent survey identified gaps and challenges in DDM&S as perceived by the different stakeholders in academia, industry and health care [Vlasakakis 2013, CPT:PSP, 2:e40]. On the basis of these findings we have developed a Framework of Competencies to guide future strategic and implementation efforts in Education & Training. The proposed framework consists of the three main areas for DDM&S activities in R&D and therapeutic usage (i) drug development & clinical trials, (ii) regulatory affairs & safety of medicines, and (iii) health care & therapeutics. For these three areas, nine Competence Fields are proposed spanning from disease & physiology characterisation to cross-disciplinary communication. By combining the Competence Fields with Cognitive Complexity Levels (knowledge, skills, attributes) we have derived stakeholder-driven learning objectives, which are required for effective performance in DDM&S.

This Framework of Competences is at the core of the DDMoRe Education & Training program. Effective dissemination of the new standards being developed within DDMoRe will be supported with a set of on-site courses dedicated to 5 therapeutic areas incorporating the scientific, methodological, conceptual and decision-making components in DDM&S. The therapeutic areas include Central Nervous System Diseases, Diabetes, Infectious Diseases, Oncology and Safety. Based on defined learning outcomes, a '2+3 day course concept' has been developed comprising theoretical concepts as well as hands-on exercises in these specific therapeutic areas, implementing the new modelling standards (MDL/PharmML), repository, ontology and integrated interoperability platform. The first on-site training course will be given later in the year.



Survey on EFPIA Expectations

Marylore Chenel / Eunice Yuen

As we crossed the mid-point of the 5-year DDMoRe project, a survey was sent to members of all EFPIA project partners in October 2013. The aim of the survey was to measure satisfaction with the ongoing progress within individual work packages, and also to understand current expectations of the DDMoRe project end result.

There were 22 respondents to the anonymous survey with at least one response from each EFPIA partner. More than 80% of respondents are expecting a drug and disease model library and/or a framework integrating different pieces of software for use in M&S as end results of the project. Across the different work streams, respondents were generally satisfied with the completed tasks to date and the level of engagement from academia was generally viewed as the highest. The survey also highlighted the importance of fostering communications and sustaining the engagement of all partners to deliver the project successfully. Now an EFPIA working group is in place to ensure that this is maintained, with a follow-up survey planned in 2014.