Drug Disease Model Resources

ddmore

# Newsletter

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EDITORIAL

Dear Reader,

The DDMoRe initiative has reached the end of its second year, and it is now time to report on the significant advances we have made with some of our deliverables, especially those which will enter the public domain soon and hence might be of heightened interest to you.

In the first year, we explored requirements in various domains: modelling tools and skills, existing languages, standards, and ontologies. By surveying Pharma, Academics and Regulators on Model Based Drug Development (MBDD) approaches, we achieved a more complete picture on their needs and expectations to accomplish a more efficient, impactful, and sustainable implementation of Modelling & Simulation (M&S). With the second year coming to an end , we wish to give some specifics on what the framework implementation could look like, what efforts have been undertaken to arrive at standards for M&S, how thinking on structure and content of our model repository have progressed, and also some insights into our methodological and educational advances.

Many aspects of the project are described in more detail on the following pages, but of those reported in the previous newsletter, the Modelling Description Langauge (MDL) has been released early autumn 2012, in which most features of existing languages have been taken into account. The MDL now resembles a unified code base and is accompanied by a “Rosetta Stone” that showcases the translatability of models between languages.

To cover most relevant modelling features, we selected a battery of models for inclusion into our repository. Some diabetes models were discussed in the previous newsletter, in this edition advances on oncology models are discussed. Beyond publishing the models shortly on the first instance of the repository, these models led us to define Use Cases driving the syntax and semantic definition of the languages. These Use Cases also inform real world scenarios on workflows that will be implemented using the framework. Ensuring the modelling “code” is translatable and executable, the first release of our prototype will attempt to amalgamate the workflow elements and all relevant modelling exercise steps. It will use an early instance of our Markup Language (ML) and include a modelling editor as the primary user interface.

Towards autumn this year another public consultation is planned, the second advisory board meeting, which will allow key stakeholders to scrutinize DDMoRe again.

We hope you will enjoy reading this newsletter and our recently published perspective in CPT:PSP, www.nature.com/doifinder/10.1038/psp.2013.10. Feel free to visit our newly designed portal at www.ddmore.eu presenting all our publications and where output will appear once made public.

***Executive team DDMoRe***

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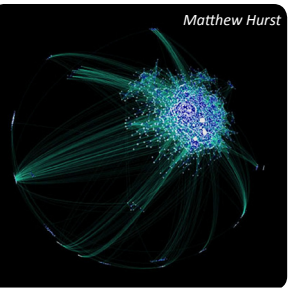
## From DDMoRe Library to Repository

*Mihai Glont*




The DDMoRe library started as a collection of models within the selected disease areas, but due to the extraordinary functionality added to this collection, DDMoRe will obtain a model repository. The DDMoRe model repository will support collaborative MBDD by providing a secured platform for knowledge exchange within DDMoRe and for selected information exchange with the wider pharmacometric modelling community. By offering efficient means of storing, searching, sharing, retrieving and simulating models, it will help scientists and pharmaceutical companies obtain answers to key questions in the drug discovery process.

A set of blueprints for the DDMoRe model repository has been created that describe the functionality of the resource and the way it can be used. These plans cover two important aspects: on one hand, the direct interaction between users and the DDMoRe model repository through the Web, on the other hand, we have specified how third-party software systems can collaborate with the model repository through message systems or web services. These blueprints, conceived with modularity, robustness and extensibility in mind, represent the backbone of the technical implementation of the platform.

This year a survey of model storage strategies will be performed within DDMoRe. In parallel the DDMoRe members will gain access to development versions of the repository, providing valuable feedback. This exercise will result in the first public prototype of the DDMoRe model repository to be expected in Q1 2014.

REPOSITORY

## Models for Oncology

*Benjamin Ribba*

As a consequence of the high attrition rate of anticancer drug molecules, the FDA has recently suggested to modernise the critical development path of drug development through extensive use of M&S. Modeling in oncology has a long history, starting in the 60's with the use of the Gompertz equation to model the growth of a cell colony in vitro. Since this time, several developed models have demonstrated relevance in aiding to better analyse efficacy and safety data in preclinical and clinical stages of anticancer drug development.

In 2004, an ordinary differential equation modelling formalism was proposed to describe both the time-course of tumour volume and the efficacy of major chemotherapy compounds in xenografted preclinical mice. On the clinical side, there were major achievements in the development of models for haematological toxicity in patients undergoing chemotherapy. More recently, several models were proposed to describe the time-course of tumour size in colorectal and lung cancer patients and to aid in the prediction of long-term clinical criteria such as overall survival.

It is the scope of the DDMoRe working group "models for oncology" to identify and highlight the most relevant models to be part of the future model repository. Moreover, as project year two finishes, the group has started developing new models in collaboration between academia, SMEs and pharmaceutical companies within the DDMoRe consortium. This focuses on the development of translational modelling methods from preclinical to clinical stages, from early clinical to late clinical stages, and on the improvement of current models to better integrate tumour morphological characteristics and advances in measurements of tumour size and activity.

## Rosetta Stone

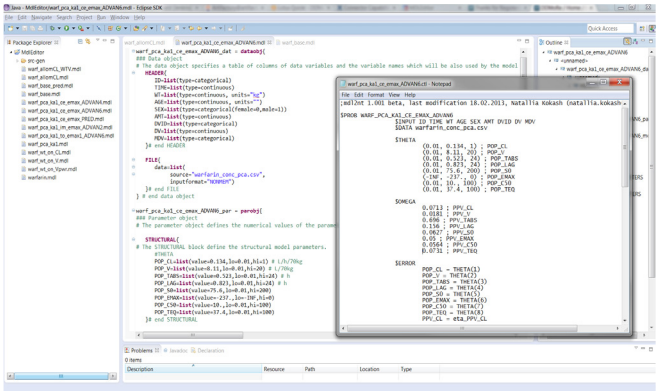
*Mike K Smith*

Within DDMoRe, we are working on producing a "Rosetta Stone" for each Use Case, which will present the Modelling Description Language (MDL) for the Use Case along with the corresponding NONMEM NM-TRAN, Monolix MLX-TRAN, WinBUGS, Phoenix PML equivalents. This will allow us to check that model features described in each language are captured appropriately by the MDL. It helps the translation process between the MDL and corresponding target languages as domain experts for each language are providing code for the Use Cases. We hope this will be a useful resource for the project team, for trainers in MDL and for users alike.

## Framework

*Jonathan Chard*

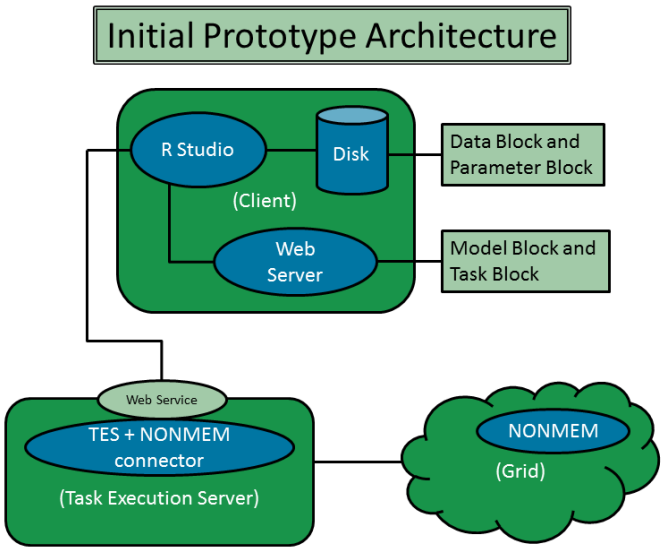
An initial prototype for the DDMoRe framework was demonstrated in December 2012 showing the end-to-end process of import, modification, execution and post-processing of NONMEM models.



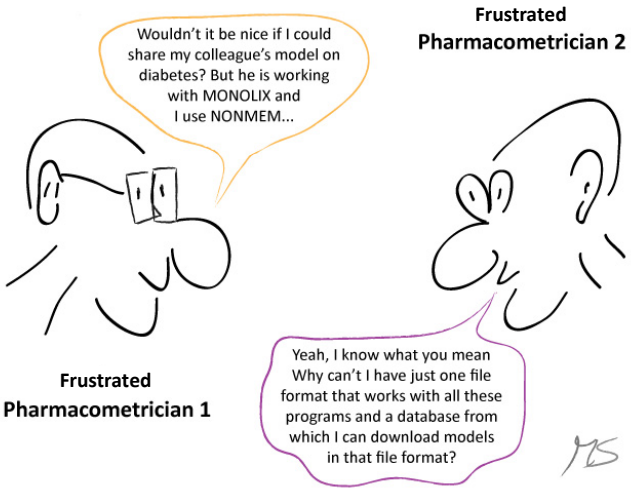
*Screenshot DDMoRe MDL editor*

The prototype was developed as an R package, as this offered a powerful rapid application development tool and the opportunity to reuse many packages already in existence. This R package is founded on data structures that are compatible with the modular concepts defined by the DDMoRe MDL specification, namely: Data, Parameters, Models, and Tasks. These objects can be created by importing a NONMEM control stream (or part of a NONMEM control stream), either from a local file, or from a model repository. A set of TEL commands has also been implemented in the R package, which enable new models to be assembled from these MDL concepts and allow the user to perform estimations or simulations.

The R package interacts with the Interoperability Framework via a web service to perform a parameter estimation or simulation. The Framework has been developed as an autonomous layer, utilising an extendable architecture based on connectors, which implement the bridge between the Framework and the supported 3rd-party tools. Connectors have been developed that execute NONMEM jobs and R scripts, allowing models assembled in the R environment to be executed asynchronously. When the execution is complete, the results can be imported into R and evaluated using existing packages such as RNMImport and Xpose. The R package and the Interoperability Framework are available from the SourceForge website at: https://sourceforge.net/projects/ddmore/




The next goal is to take what has been learned in the development of the R package into the next phase of the project – the creation of a bespoke UI (the MDL Editor) using Xtext. The MDL Editor will support native model development using the MDL, translation of the MDL model into MML, and utilise the same Interoperability Framework for job execution. It will then replace R Studio in the initial prototype architecture.




## The Frustrated Pharmacometrician?

*Stuart Moodie*

We could have added the caption: "Someone, somewhere must be trying to solve this problem!" Well fortunately they are, but before we go into that, let's look elsewhere: for in Systems Biology the problems our Frustrated Pharmacometricans complain of do not exist. Software tools exchange models using the Systems Biology Markup Language (SBML; www.sbml.org) and modellers don't worry about the content of an SBML file; they rely on the fact that when they exchange it between their favourite modelling tools it all just works!

How was this achieved? SBML was launched over a decade ago and it has evolved into a mature standard with wide acceptance. Crucial to its success has been an active community of tool developers and modellers who have supported and used it during that time. Equally important has been the provision of sophisticated software libraries that minimise the effort required by software providers to support what is a complex standard.

"So why are you telling me about Systems Biology? I thought DDMoRe was about Pharmacometrics?" It is. In DDMoRe we are developing an exchange file format, called the Pharmacometrics Markup Language or PharmML for short. It can describe virtually any pharmacometric model and will enable model exchange between NONMEM, MONOLIX, WinBUGS and related tools. We intend this to be a community standard nucleated around the members of the DDMoRe consortium. Our first release will be early 2013. To be followed by a software library (libPharmML) that will provide support for PharmML and will facilitate its adoption by modelling tools.

So for Frustrated Pharmacometricians there is hope. We in the DDMoRe project are working to make your life easier.

NEW TOOLS

## Survey on Optimal Design Tools

*France Mentré*

Methods and software tools for optimal design have been developed for a decade. Present tools do not yet allow optimization of adaptive designs, which are increasingly used and promising in drug development. Before developing this capacity we conducted the first survey of this kind among the ten EFPIA members of DDMoRe, to identify current practices, shortcomings and expectations.

This survey demonstrates that this new methodology has been quickly adopted within the industry and that optimal design using population PKPD models plays an important role in the pharmaceutical industry. The survey further highlights the expected improvements, in interoperability with the software and in statistical capabilities. A smooth workflow between estimation, evaluation and design will be facilitated on the DDMoRe platform.

High priority was given to further development of adaptive optimal design in NLMEM. As pharmacometrics has increased its scope beyond population PK, design tools for more complex models and for other types of data are now needed, especially discrete data. Academic groups are actively working on those topics and are sharing their results to translate progress into new software tools. Optimal design enriches clinical trial simulation, and both will work in collaboration to establish model-based drug development in the pharmaceutical industry

## Education & Training

*Charlotte Kloft*

An extensive Education & Training program has been recognised as a critical factor for delivering innovation, dissemination and management of knowledge in the context of Drug Disease Modelling & Simulation (DDM&S).

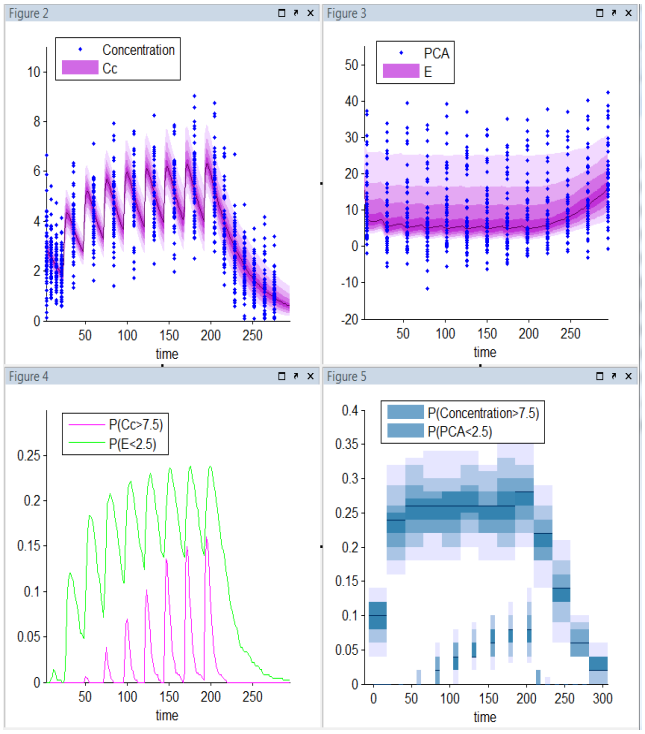
In order to obtain a comprehensive inventory of the skills and competences relevant to the DDMoRe project we have performed an extensive survey with different stakeholders being involved in DDM&S in academia, in pharmaceutical R&D in industry, or health care. The survey provides an overview of the current impact, benefits, weaknesses and potential hurdles as perceived by those different stakeholders and identifies both technical and conceptual requirements for effective knowledge integration and decision-making.

The insight and landscape gained from these results will form the basis for the development of a framework of competences for on-site and web-based Education & Training programs developed within DDMoRe. Within this program, besides the need for scientific training on an integrated and higher level of understanding of drugs, (diseased) systems characteristics and their interactions throughout the entire R&D process and therapeutic usage, the need for thorough understanding on how different professionals and stakeholders currently operate and what their competences are, should be addressed.

## Clinical Trial Simulator

*Marc Lavielle*

Version 2 of the CTS has been developed during the last year. The capabilities of this new version comprise of: 1) Flexible study designs used in Phase 2 of clinical drug development: parallel group studies, cross-over studies, complex treatments defined as a combination of different administrations, 2) Simulation of patients sampled form a joint distributions or using an external data file, 3) Simulation of exposure to the investigational drug and several types of drug effects related to drug exposure (continuous, categorical, count, time to event), 4) Graphics and statistical tests, 5) Automatic reporting.




*Screenshot Clinical Trial Simulator*

For those not familiar with the terminology we explain a few acronyms here: MBDD = model based drug development, M&S = Modelling and Simulation, ML = Markup Language, MDL = Modelling Description Language further terms are explained at: www.ddmore.eu/projects/glossary