Drug Disease Model Resources

ddmore

Newsletter

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EDITORIAL

Dear Reader,

Model Based Drug Development (MBDD) is now widely accepted as a vital approach in understanding patients' drug-related benefit and risk.

At key stages in the drug development programme, decision makers rely on the best rationale to select drug candidates, targets, trial designs, dose regimens, patient populations and suitable endpoint measures. A lack of informed decision making can have detrimental effects to patients, cause attrition of the wrong development program, and potentially induce huge financial losses.

Models enable us to integrate information from diverse sources collected during the preclinical and clinical drug development process to describe and predict the behaviour of complex diseases, biological systems and drug actions. We see Modelling and Simulation (M&S) as the core technology in MBDD, essential to performing such knowledge integration, providing through inference the quantitative basis for well informed decision making.

The current path to model based knowledge integration is hampered by a lack of common tools, languages and ontologies for M&S, with limited or time consuming access to stored information, creating unnecessary hurdles to exploit knowledge.

The DDMoRe consortium was founded early in 2011 by a group of enthusiastic EFPIA partners, academics and SMEs across Europe to address concerns to those who want to bring new medicines to patients in a safe, but also efficient manner. The consortium is developing a public drug and disease model library supported by an open source interoperability framework providing access to existing modelling tools and those of the future. This may be ambitious; however we wish the standards and tools developed to become the reference for future collaborative drug and disease M&S work, serving internal and external stakeholders, regulators, academics, and the pharmaceutical industry in better addressing the current bottlenecks in the drug development process.

Naturally, such an initiative can only show its potential, if it's accompanied early by a comprehensive training programme to influence the environment in a persistent way. Training will cover the methodological and technological aspects of the project, and model based training exercises will cover a number of drug-development scenarios across a variety of therapeutic areas.

As with all IMI projects, most of DDMoRe's outcomes will be made public; we've set up a portal at www.ddmore.eu and will update you by further newsletters twice a year. We are keen to engage with stakeholders and the public alike to allow them to explore, provide feedback and contribute to this initiative.

Enjoy reading!

imi Innovative Medicines Initiative

efpia

DDMoRe first year

The first year of this unique 5-year partnership was fruitful, with efforts focused on collecting and harmonizing requirements for the consortium deliverables. Major achievements were as follows:

- A collection of models, both existing and requiring development, were selected for their value in drug development in diabetes, oncology and other therapeutic areas;
- A model description language has been drafted bringing together the features of various model coding languages and is intended to be flexible, extensible, easy to code, understand and use;
- Specifications for a task execution language have been drafted connecting the users modelling aims, the immediate task of execution of a modelling related task and the overarching workflow within the framework;
- A prototype interoperability software platform was scoped to lay out an early implementation of the framework;
- Relevant markup languages were identified and evaluated to determine whether they could form part of the DDMoRe markup languages;
- Collaboration with CDISC has been established to ensure consistency with existing standards;
- Communication with the Ricordo team was started, to scope integration of a semantic toolbox within the framework; also a coordination with the IMI consortia OpenPHACTS and EHR4CR has been initiated, to ensure compatibility of the developed ontology and meta standards;
- Knowledge gaps in model selection, diagnostics, and the implementation of complex models were identified leading to a methodological development program;
- A prototype of a clinical trial simulation engine was developed initially also including sources for patient variability and models describing realistic trial scenarios;
- Surveys on optimal/adaptive design, and technical and conceptual requirements in Drug/Disease Modelling and Simulation (DD M&S), were conducted to highlight areas for improvements in trial design and related statistical methodologies and to identify opportunities for training and education purposes respectively.

PROGRESS

Model selection for the DDMoRe library

Drug and disease model library

A drug and disease model library is being created to store and promote the reusability of models and to provide support for education and training in the M&S area. Published PK, PD, PKPD, PBPK, statistical and SP/SB models covering differing phases of the drug development process will be initially available with new models in key therapeutic areas added over time. In each therapeutic disease area, the most relevant models available in the literature were identified. Gaps identified in model coverage across a therapeutic domain will direct new model development over the course of the project.

The flexibility and power of the DDMoRe library will be showcased by a range of "proof of concept" drug and disease models. Currently 20-30 existing models have been selected for incorporation and qualification of the modelling framework, and their value in informing drug development in a persistent way.

Spotlight on diabetes

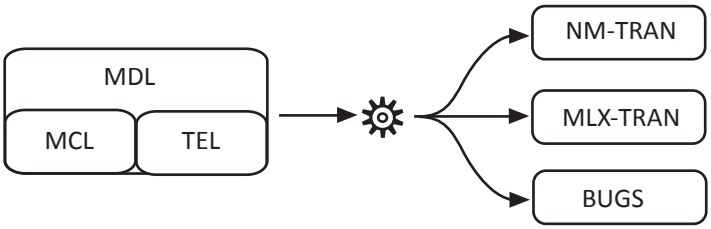
Modelling is relevant for drug development in several aspects. Models are used for testing drug efficacy and predicting future trials, thereby providing scenarios for guiding drug development on the basis of quantitative data. Glucose homeostasis models describe the interactions between glucose and insulin and have a long tradition in the field of modelling oral and intravenous glucose tolerance tests. Based on simulations from mechanism-based models, one can predict the reduction in glucose levels that would be observed after administering a new insulin formulation or a drug that enhances beta-cell function.

Another relevant use of models is the possibility to develop tools for reducing the length of clinical trials. HbA1c reflects average glucose levels and is generally observed over a 3-4 month time frame. This trial duration could be reduced by predicting HbA1c based on shorter observations and modelling.

DDMoRe has envisaged including in the model library a number of relevant diabetes models covering glucose disposal and insulin secretion, glucose homeostasis and HbA1c formation. New models will focus on three areas: new enhancements for glucose homeostasis modelling, improved prediction of HbA1c as a tool to shorten clinical trials, and models for predicting diabetic complications.

DDMoRe Framework

For the DDMoRe project to be successful, an integration platform must be developed that can incorporate modelling tools such as NONMEM, R and OpenBugs. Initially these tools will be used directly, but later there will be mechanisms to translate the new modelling language into the tool specific language (e.g. NM-TRAN). Once we support simple commands, we will incorporate a workflow engine that manages complex processes (e.g. simulation -> estimation -> post process). We will extend the framework to allow interactions with modelling ontology knowledge base server (OKB) that provides assistance with the annotation of models to facilitate sharing and reuse.



We identified a number of use cases that will exercise the main integration points of the framework, namely running an analysis workflow that will allow execution and manipulation of the following models: Warfarin PKPD, Alzheimer's dose finding, Tumour growth, and Diabetes therapy.

We have been working on the underlying infrastructure that will be used by the framework, namely:

- A distributed tool execution framework;
- Connectors within this framework initially for R, but soon for PsN and NONMEM;
- Rule-sets that define constraints on how the tools will be executed;
- Selection of a workflow engine that will initially be used to orchestrate the execution of a sequence of MDL blocks.

In the coming 6 months the consortium will start to implement the translators and executors that will allow the development of the identified use cases. We will develop a package in R that will permit model manipulation, and for this we need a format that we can use to marshal information from the workflow engine to R and NONMEM and back again. This will be done in collaboration with the language team responsible for the machine readable language.

FRAMEWORK

NEW TOOLS

The Model Description Language

MCL + TEL = MDL

The aim of the Model Description Language (MDL) is to provide a single, unified language which will capture the definition of models together with their parameter and data attributes irrespective of the target software for performing the modelling and simulation task. The MDL is split into a Model Coding Language (MCL) to describe quantitative models and a complementary Task Execution Language (TEL) to describe how the input from the MCL will be used to generate the desired output. The MCL will promote consistency in describing models across practitioners and will reduce rework and recoding in passing models between software platforms (which is common in current practice).

A specification for the MDL (MCL and TEL) has been delivered and reviewed. It is currently undergoing a second round of development to include additional features in the MCL description of models and to clearly define the scope of the TEL in relation to the upcoming prototype.

Use cases

Examples have been defined to show how the MDL can be used for solving PK, PKPD, tumour growth and time to event problems. A more complex use case involving meta-analysis, simulation and optimal design in the context of Alzheimer's disease progression is planned.

A tool for automatically translating NM-TRAN model control streams into MDL has been developed by Nick Holford and can be tested by the DDMoRe community at

http://www.ddmore.eu/nmtran-to-mdl.

New tools to facilitate Model Based Drug Development

DDMoRe will provide a platform that accommodates modelling tools designed to perform population style PKPD analyses to facilitate MBDD in the pharmaceutical industry. Going beyond the facilitation of interactions between existing software tools, the consortium will work on:

- The simulation of future studies to support development decisions leading to an optimal portfolio management. A prototype of a Clinical Trial Simulator (CTS) has been released and is undergoing dynamic development, with a next release in June 2012, incorporating models for dependent categorical and continuous covariates.
- The optimal design of future experiments or studies, increasing the probability of success, but also delivering results within a reasonable timeframe and predefined budget.
- New methodologies for parameter estimation in complex models, with an initial focus on complex drug input by means of depot and latent compartments.
- The evaluation of such mechanistic models. Early achievements include: visual diagnostics for time-to-event models, guidance for model building with correlated covariates, and new types of normalised prediction distribution errors.