Drug Disease Model Resources

Newsletter

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DDMoRe website:

www.ddmore.eu

Dear Reader,

How do pharmaceutical companies make smart choices about their R&D portfolio, and reduce the escalating costs of drug development? These are two of the key issues identified in PWC's most recent Pharma 2020 report. MID3[1] has been coined as the approach, which when consistently utilized addresses them. As DDMoRe approaches the final stage of the project, we are set to deliver an integrated collection of M&S[2] tools and processes that support MID3. There is a growing environment of partnership and collaboration in pharmaceutical R&D - seen in the work of organisations like IMI and C-Path, which rely for their success on improved knowledge management. DDMoRe's products are well positioned to improve the path on getting new medicines to patients, supporting the triple helix of industry, academia and health authorities.

The main focus over the last year has been on DDMoRe's core products - the Model Repository, the Interoperability Framework and on initiating Training and Education. As these work streams have progressed, the consortium has started to develop communication and implementation plans that are vital to ensure long-term adoption of the core products. Sustainability became a primary topic of our October Consortium Meeting. We learned from OpenPHACTS colleagues about the key factors needed for delivering a toolkit that can easily be adopted, maintained, and developed further. With the engagement of consultants from Roland Berger a detailed sustainability strategy is being laid out, and we are making good progress in establishing DDMoRe's translation from project to product.

As a result of participating in PAGE and ACoP meetings, DDMoRe has developed a set of communication materials including video testimonials from many team members. With the aim in mind to extend our collaborations and offer new partners an effective way of interaction, we established a process for engaging them as associated partners, which has already been picked up on by a number of third parties.

While developing our relations with health authorities and scientific journals as key stakeholders in regulatory decision making and knowledge exchange we had positive initial discussions with FDA and EMA representatives, as well as the editor of CPT:PSP. Also, the Model Review Group has drafted a process for qualifying models submitted to the Model Repository, addressing another important aspect in releasing a curated and shareable model repository.

DDMoRe has a complex, highly interconnected set of objectives. The progress in recent months has been exciting to see, as the theoretical discussions and early prototypes have developed into working products, ready to be tested in the wider M&S community. We know there is a lot of work still to be done to ensure a successful transition from project to product, but the consortium members have a clear vision of the goal and are focused on achieving it. We're looking forward to an exciting final season towards a successful project completion in 2016.

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1. Model-Informed Drug Discovery and Development
2. Modelling and Simulation

DDMoRe Repository

The DDMoRe model repository is a user-friendly platform enabling the global modelling community to store and share models used to describe the interaction of drugs and treated diseases. The public open-access repository, available (http://repository.ddmore.eu/) allows users to encode their models in a single format that can be converted seamlessly and executed in commonly used software packages. Since models are private by default, users can make iterative refinements until models are deemed suitable for publishing. A private model can be share with a restricted set of collaborators, which facilitates secure knowledge sharing.

The single format used to encode models in the DDMoRe repository – the Model Description Language (MDL) – facilitates model sharing and promotes knowledge building. The repository has been created for everyone involved in creating and using models to develop a drug, give recommendations about its use, evaluate drug registration or teach about therapeutic use.

The repository had its successful public release in October 2014 with 13 reference models in oncology (3), diabetes (5), CNS (2) and pharmacokinetics (3).

The second release is expected in June 2015 and will use information from external resources to build a smarter search and a more comprehensive model display. The final release during the DDMoRe project, expected in March 2016, will contain at least 50 models including reference models from literature, newly developed models, basic pharmacokinetics and pharmacodynamics models and an initial set of safety models.

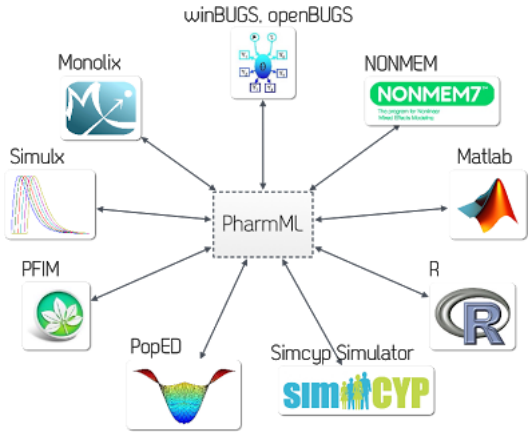
As the repository evolves from the DDMoRe project to become a long-term stable open platform (March-September 2016), it will provide a safe environment to host both public and private models, enabling collaboration to improve models, while preserving the full history (track changes). The platform content will also be indexed and fully searchable.

This repository is open to anyone involved in drug and disease modelling; DDMoRe members have provided a leading role in developing and implementing it. The modelling community is encouraged to test and take full advantage of this new platform by submitting their models and having them tested by others community members .

Interoperability Framework

The DDMoRe InterOperability Framework (IOF) enables modellers to obtain the benefit of all of the key software tools used within Pharmacometrics today, while only having to learn one modelling language. The IOF enables modellers to work more efficiently and produce higher quality analyses and reports than is currently possible.

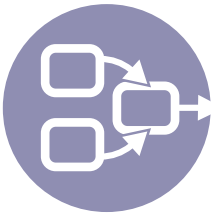
Increasing numbers of drug projects are run as multi-party collaborations, and the re-use and re-purposing of existing data sets is also rising. This drives the need for transcoding models from one software tool to another to accommodate the range of tools and techniques used by different organisations. The IOF will significantly reduce the time required to carry out transcoding, and at the same time eliminate the associated risk of coding errors.



A typical modelling exercise may involve switching between estimation and simulation a number of times; the IOF helps error-free switching and significantly reduces the time spent on each switch. This enables modellers to devote more time to preparing, running and interpreting their models, improving productivity in addition to the value of preserving quality.

An important major benefit of the IOF is that, being based on well-developed standards, it can drive improvements in quality and reliability by ensuring reproducibility of analysis results and report output. This is a vital factor in driving adoption and acceptance of model-based analyses by regulatory bodies, as results can be exchanged directly in the standardised formats used by the IOF, increasing trust and reducing review times for new drug applications.

A test version of the IOF was launched in February 2015, integrating NONMEM and Monolix for estimation, Xpose for model diagnostics, PsN for VPC and bootstrap, and Simulx for simulations. The next version is planned for the Summer 2015, integrating tools for Bayesian estimation and optimal design.



Pharmacometrics Workflow

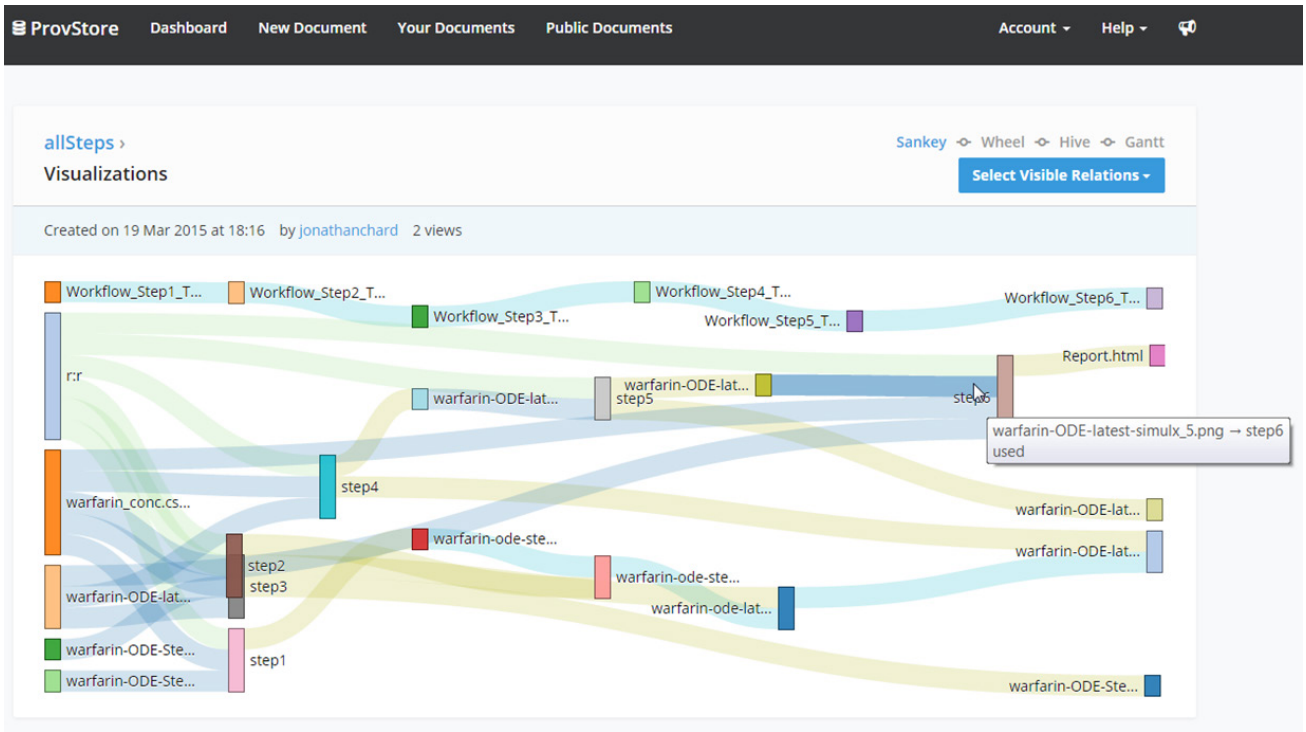
The overarching pharmacometrics workflow describes the path from an initial model to a final model, capturing which "branches" of the development "tree" are fruitful in describing the observed data and which are not. This workflow incorporates the sequence of tasks and dependencies within the process, and the knowledge required for the process to be of value.

A typical pharmacometric analysis consists of a sequence of tasks (task workflow) requiring the integration of different tools and analysis engines. The key steps are preparing for model development (data manipulation, setting initial estimates, defining task information), estimating parameters in the model, examining model diagnostics and collecting information to make inferences and decisions.

Each of these tasks has inputs (data, models, parameter values, task properties) and produces outputs (estimations, graphs, etc.), as well as a description of the sequence of events and dependencies between tasks, i.e. the outputs of one task forming the inputs of another.

The core value of DDMoRe's Pharmacometrics Workflow is in providing a standard for capturing the provenance of task outputs ("how was this output created?") and the process used to reach those outputs. ("how did we get to this model?"). This delivers a robust basis for ensuring reproducibility, enabling consistent, repeatable models and outputs to be shared and communicated clearly with others. For EFPIA members this is critical in ensuring compliance with regulatory expectations of a computer system producing material that may be part of a regulatory submission (FDA regulation 21 CFR Part 11).

The workflow group will provide a specification for provenance capture that will lay out the 'input-to-output' task workflow and the pharmacometrics knowledge management needed for describing a whole modelling and simulation exercise. The PROV-O ontology (http://www.w3.org/TR/prov-o/) is being assessed for this purpose. It is a W3C (World Wide Web Consortium) standard that captures the provenance and relationships between items, as well as audit trail information (who did what, when, how) required for the workflow environment. By using an existing standard we can take advantage of available tools for visualizing relationships, and 'future-proof' the tools developed by DDMoRe so they can easily be adopted and supported beyond the lifetime of the consortium.



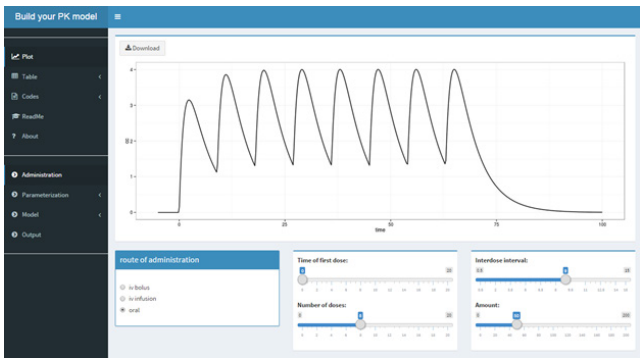
New modelling tools

Simulx is a function within the R package mlxR. Simulx allows one to simulate complex models for longitudinal data by interfacing the C++ MlxLibrary with R. Models can be implemented using either Mlxtran or PharmML. (http://simulx.webpopix.org/)

Version 2.2.0. of mlxR is now available and includes some new functions for the simulation and visualization of complex models:

- shinymlx creates interactive Shiny applications for longitudinal data,

- exposure computes the area under the curve, the maximum and minimum values of a function of time over an interval, or at steady state.



Several Shiny applications using Simulx have been selected to be part of a showcase on the Rstudio website: (http://www.rstudio.com/products/shiny/shiny-user-showcase/)

First public DDMoRe training

"Model-Informed Drug Development in Oncology (beginners)", the first public DDMoRe course, was run very successfully in Berlin, March 2015. Hereby, DDMoRe launched a series of comprehensive face-to-face courses designed to support adoption of the MID3 principles using the newly developed DDMoRe platform.

Twenty participants from 4 different fields in quantitative life-sciences representing 14 different institutions (10 external to DDMoRe) from 8 different countries took part in this first, public DDMoRe course, organised by Charlotte Kloft, Zinnia Parra-Guillén (Freie Universität Berlin) and Paolo Magni (Università di Pavia, Italy).

The course provided an opportunity to explore all key products and processes being delivered by DDMoRe, illustrated through practical applications using oncology models. It was delivered as a combination of training approaches, including seminars, guided demos, group discussions and hands-on sessions. The "2 + 3 day course concept" proved to be highly beneficial; it started with the DDMoRe-specific aspects on days 1 and 2, and then incorporated the new knowledge, skills and competencies in the therapeutic area on days 3 to 5. In addition, the course was enhanced by expert contributions from Inaki Troconiz (University of Navarra, Spain), and Pascal Girard and Nadia Terrranova (Merck Serono). Their workshop during the course showed how the DDMoRe platform can be integrated into pharmaceutical development to a request from regulatory authorities, using a "real pharma example".

The participants enjoyed the course, and found it very useful, with an average quality rating of 3.6 out of 4 (4 being 'very helpful' and 0 being 'not helpful at all'). Most importantly, participants also showed a high interest in the DDMoRe project and what it is delivering (3.4/4).

The next public course will focus on the CNS disease area, and will be held in Leiden, The Netherlands, 27-31 July. Followed by an oncology course in September. Subsequent courses on safety and infectious disease modelling will be held in 2016.

Participant's quote: "I was very happy to have attended the course, I gained insight in what DDMoRe offers and I also improved my M&S skills by using the MDL-IDE program"

Apply for the DDMoRe courses at www.ddmore.eu