A technology roadmap to support model based drug development

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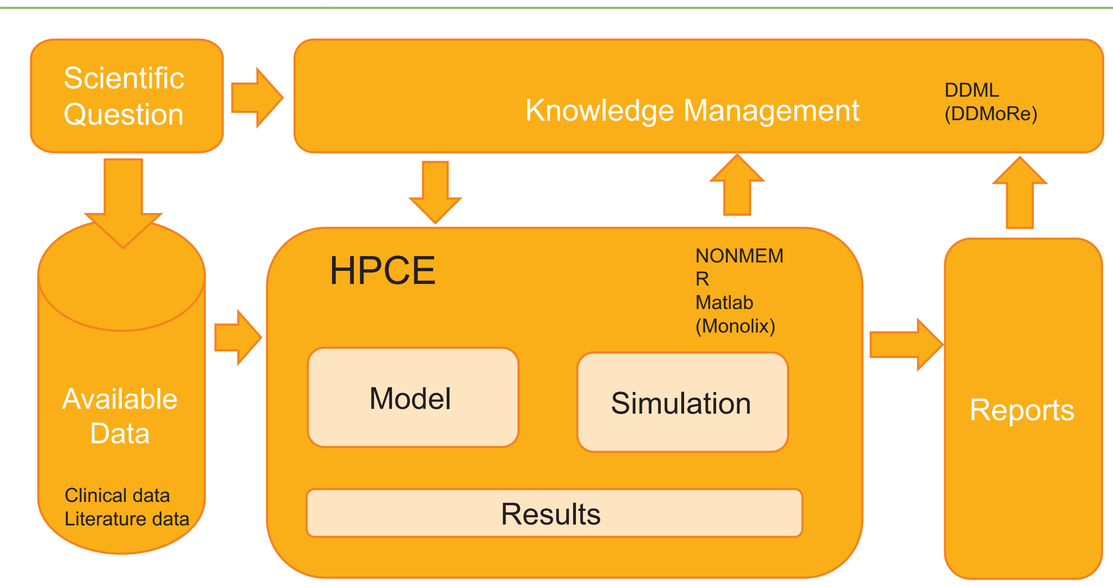
Objectives

- At Novartis, infrastructure has been put in place to provide the required computational power to support model based drug development[1]. We are now planning the next phase of development to automate activities and integrate systems from data sourcing to report generation.
- Modeling and simulation has become firmly established over the last decade in the pharmaceutical development sector of the industry with most organizations establishing modeling and simulation groups. To support these groups highly specialized computing services centered on high performance computing environment (HPCE) are needed to provide the required computational power but at the same time will stand up to regulatory scrutiny[1]. **Figure 1** shows our current landscape.

Figure 1. *Where we are today*



HPCE=High Performance Computing Environment; DDML=Drug Disease Model Library

- These computing resources need to integrate as much as possible into the general IT environment to efficiently manage resources and provide as much automation as possible.
- The purpose of this poster is to solicit feedback and discussion on how best to solve the challenges we all face in order to best support model-based drug development into the future.

Methods

The following approach was taken:

1) Identify the opportunities

2) Deliver the required technology

3) Knowledge Management

4) Review and improve

Raw computing power is the foundation on which modeling activities can be built, but, such power in itself is not sufficient. Additional capabilities are needed to help users (who have varying degrees of computing sophistication) in the following critical areas:

- The management of computer runs during model building and validation that are able to satisfy stringent Health Authority scrutiny.
- The production of documentation according to defined documentation standards.
- Promoting knowledge management approaches to encourage the extension and improvement of existing models rather then reinventing the wheel every time.

Results

Several areas of interest can be identified:

1) Emerging modeling algorithms

2) Workflow and Integration of tools into an end to end process

3) Knowledge management

1) Emerging modeling algorithms

Monolix and Nonmem7 both promise significant advances on what's available to us today for population analysis. NONMEM7 (http://www.iconplc.com/technology/products/nonmem/) has added Monte Carlo expectation-maximization and Markov Chain Monte Carlo Bayesian methods to its existing set of classical likelihood methods. The stochastic approximation methods in Monolix have received considerable attention[2]. Monolix is moving from the realm of academic research project to a more commercial focus with the foundation of Lixoft (www.lixoft.com) to provide a more industry ready version of Monolix that will run on a regular cluster and have the scripting capability required for reproducibility of results in a scientific regulatory environment.

2) Workflow and Integration of tools into an end to end process

In order to deliver the most productive working environment especially for the more routine modeling tasks, the use of workflow techniques to integrate the different steps involved for the user is considered as an important next step.

There are three main areas of interest here.

a) Run management to conduct a modeling activity

b) Usability – making it as easy as possible for the user to perform work

c) Documentation generation – the process of documenting what has been done.

a) Run management to conduct a modeling activity

Managing Nonmem modeling activities is notoriously difficult. At Novartis utilities have been constructed that simplify this process by automatically generating and managing batches of jobs and interrogating the Nonmem control stream and output to summarize and process the results. Other companies and academic institutions have also developed similar utilities. We have also validated our Perl Speaks Nonmem (PsN) installation to support Nonmem work[3]. Tools such as xpose (http://xpose.sourceforge.net/) and Pirana (http://www.pirana-software.com/) are currently being evaluated[4].

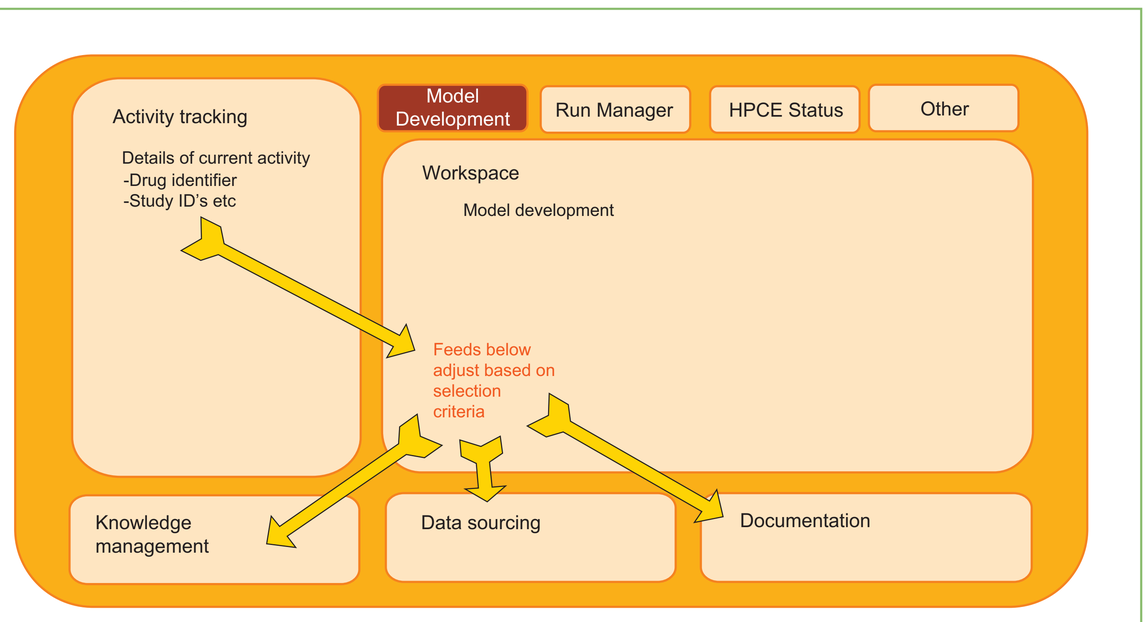
b) Usability

A major issue faced is the ease of using any system. Integrating all the different tools we use and generating the required documentation often involve excessive manual steps making training more difficult and increasing the risk of mistakes.

For this reason we have adopted two approaches. Firstly, providing an integrated user friendly desktop on our HPCE cluster and secondly, centralizing our processing on web-based tools as much as possible. The web-based approach means activities can be run and monitored from any Novartis computer without any additional software installation or dependence on any particular hardware, an iPad should work as well as in Intel PC or Linux workstation. We have implemented a classic LAMP* technology stack and integrated this with our cluster queue management to enable models to be run and output and results to be viewed and further processed from a web browser. This approach is still in its infancy but is showing promising results.

The long term vision is to integrate the different component systems to provide an integrated work environment (**Figure 2**).

Figure 2. *The long term vision – a unified integrated work environment*



c) Report generation

Working in a highly regulated industry requires documentation that conforms to the required standards for nearly all communications with health authorities. Routinely assembling these documents efficiently is a major opportunity to increase productivity. Currently, our most promising approach is the use of a documentation platform (developed with an external partner). This assembles modeling reports via templates and outputs from modeling runs into the Novartis document format. Once a template has been set up, the document can be instantly refreshed as often as necessary.

Going forward all steps in the regular work process will be linked and integrated to automate to as much as possible. Currently, we are developing an in-house data request tracker, for example, to manage our data sourcing and promote reuse of previously prepared data and/or sourcing programs.

3) Knowledge Management

It is time consuming and costly to invest time solving essentially similar modeling problems repeatedly. At Novartis we have implemented a Drug Disease Model Library (DDML) in association with an external provider to foster knowledge management and promote reuse, generalization and extension of models related to specific disease areas.

The Innovative Medicines Initiative (IMI), sponsored by the EU Commission endeavours to foster innovation within industry and academia within the EU by funding research and bringing together interested parties. In particular it aims to help smaller companies grow while at the same time industrializing the appropriate scientific advances. Novartis participates in several of the IMI projects but the Modeling and Simulation group is mainly active in the DDMoRe project. The latter seeks to provide industry-wide knowledge management similar to the Drug Disease Model Library discussed above.

Conclusions

- Technology and computing power are essential to the effective application of model-based drug development. High performance computing is now well established but there is still work to be done to integrate it in order to support model-based drug development with maximum efficiency. With continuing cost pressures and ever increasing demands for computing power the industry must come together to increase productivity cost effectively and deliver on the promise of model-based drug development. Can the industry and academia come together to deliver the best possible technology platform? If yes, then how?

*LAMP is an open source technology stack consisting of Linux, Apache, MySQL and PHP / Perl / Python (http://en.wikipedia.org/wiki/LAMP_(software bundle)).

This study was supported by Novartis Pharma AG, Basel, Switzerland.

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Poster presented at the Population Approach Group Europe (PAGE), June 7–10, 2010, Athens, Greece.