

A dedicated Programming Group working in a pharmaceutical Modeling & Simulation organization

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1. ABSTRACT

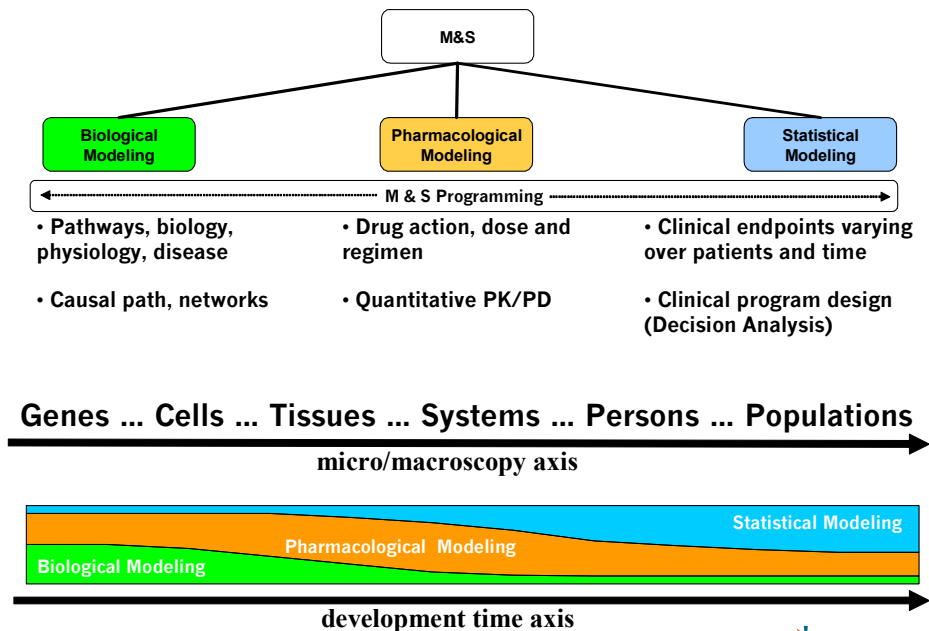
Modeling and Simulation (M&S) emerges as one of the tools which are advocated for new approaches to drug development. The presentation's objective is to raise awareness of the benefits and advantages of having programmers working in Modeling and Simulation.

2. INTRODUCTION

Modeling and Simulation at Novartis is active all along drug discovery and development, from Research, preclinical studies in animal and clinical trials in man. M&S consists of 4 subgroups: Biology, Pharmacology, Statistics and the Programming group. Programmers work in close collaboration with the 3 other modeling subgroups. A dedicated programming group that is integrated with the modeling group increases the efficiency of the modeler while ensuring reproducibility and quality

Graphic 1: Modeling and Simulation organization

Subgroups along the development axis



3. WHAT IS MODELING AND SIMULATION

Modeling and Simulation is not just done in Pharma industries. Modeling and Simulation has a long history of being applied in weather forecasting, engineering (plant design, product design), military (scenarios planning), energy, finance...

3.1 MODEL

A model is a mathematical relationship among relevant pieces of information. It's a conceptual tool for translating often complex, real-world subject matter into a simplified form (a mathematical model), generalizing detail ...⁽¹⁾ It allows us to summarize our information, data and assumptions into a form that can be used to probe alternate designs and outcomes⁽²⁾.

3.2 SIMULATION

During simulation the model is used to test new scenarios:

- To explore model properties (model structure, model parameters) and perform model qualification
- To estimate missing observations in the data and predict observations outside the scope of the data
- To examine the sensitivity of the model output to non-controllable inputs
- To explore situations that would be ethically, financially, or physically impossible, but provide valuable information
- To have an idea of what you don't know

3.3 EXAMPLES

Our colleague Nick Holford (Univ. of Auckland NZ) has designed an application mimicking the concentration of ethanol in blood, that you can download from:

http://www.health.auckland.ac.nz/pharmacology/staff/nholford/Ethanol_PKPD/Drink%20Me!.xls

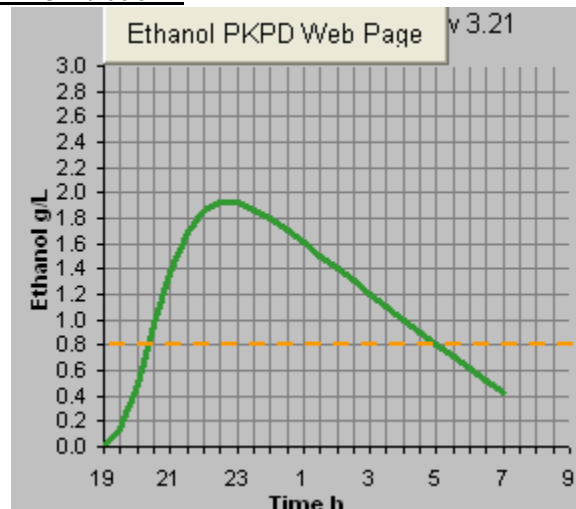
You can use the model and predict the ethanol concentration. Parameters are:

- Start drinking time
- Body weight
- Number of drinks
- Type of alcoholic beverage
- Fed or fasted
- Vomiting

Simulation1

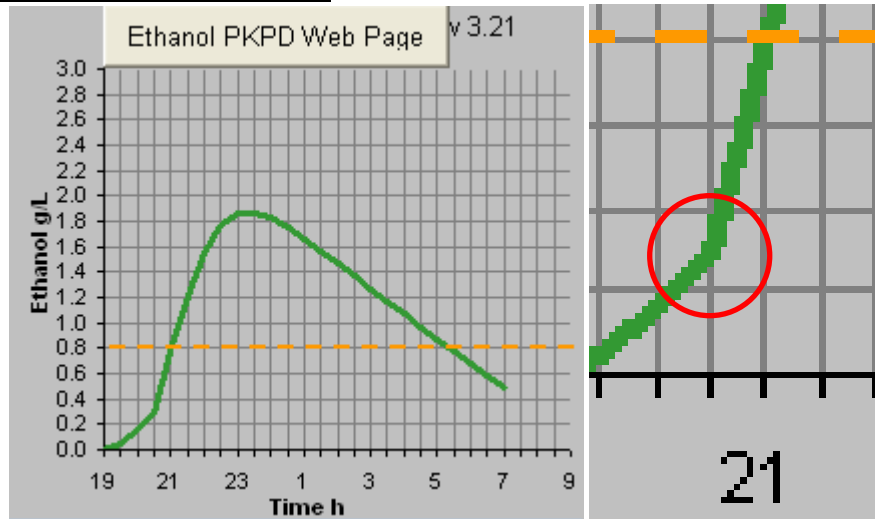
An 85 kg person starts drinking at 19:00 1 Pint of Steinlager. At 19:30, he drinks 2 additional Steinlager. At 20:00, he drinks 3 additional Steinlager. This patient achieves a blood alcohol concentration of 1.9g/L of ethanol at 22:45

Graphic 2: Ethanol simulation – simulation 1

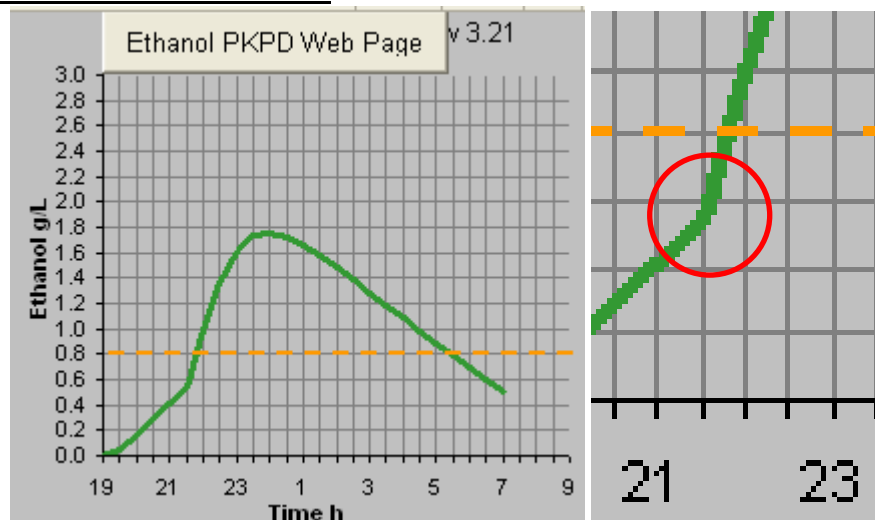


Simulation2

What about if the same patient eats at the same time as he drinks from 19:00 to 20:00? He reaches 1.85 g/L of ethanol at 23:15. From a graphical point of view, you'll notice that the shape of the curve changes when the patient stopped eating (red circle) – reflecting an increase in the rate of alcohol absorption.

Graphic 3: Ethanol simulation – simulation 2**Simulation3**

What about if the same patient ate a meal during 60 minutes after the last drink? The maximum ethanol concentration is 1.8 g/L at 24:00! The concentration increases slower compare to the fasted status. Like for the previous example, you'll notice that the shape of the curve changes when the patient stopped eating (red circle). Clearly food has an important impact on the ethanol concentration. In the first simulation, the patient reached 0.8g/L at 20:30. If the patient eats at the same time, the 0.8g/L limit is reached at 21:00, 21:45 in our last example.

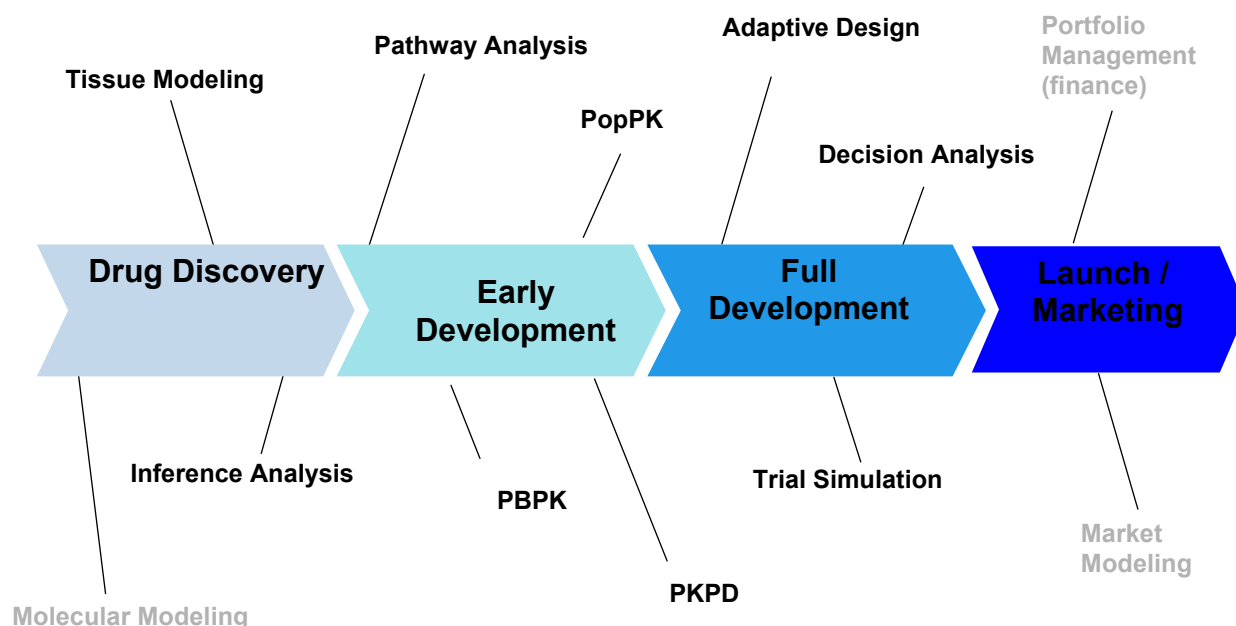
Graphic 4: Ethanol simulation – simulation 3

4. MODELING & SIMULATION AT NOVARTIS

The M&S Department at Novartis comprise a group of PhD and Masters level scientists, who work from Research to Health Authority Registration. Modeling and Simulation can help answer drug development questions such as:

- What is the best dose for the next study?
- Is there a risk that the compound is stopped in latter phase for safety reasons
- Can you identify the non-responder subgroup and explain us why they don't respond to the treatment in the same magnitude as other patients
-

Graphic 5: Modeling and Simulation activities



In 2001, the Modeling and Simulation group at Novartis had only one part-time programmer who supported the entire group of 17 modelers. The added value was recognized such that the M&S Programming subgroup has seen a sustained growth. It is today composed of 6 associates with mixed background and expertise, supporting about 35 modelers.

5. WHAT DO THE PROGRAMMERS DO IN MODELING AND SIMULATION AT NOVARTIS

5.1 DATA DELIVERY

To develop a model, you need data. Most modelers have the skills to format data, but don't have formal training in database programming so they are unable to efficiently extract and merge data into a suitable format for their use. The extraction and merging of data from disparate data sources (Pre-clinical, Clinical, Watson Lims, Legacy database, Biomarker database, Clinical database) to create a modeling database requires a knowledgeable database programmer. Modeling and Simulation programmers at Novartis extract the data, harmonize and pool them into a format suitable within SAS ® for the relevant modeling software (NONMEM®, Matlab®, S-Plus®, SAS®, Berkley Madonna®,). This activity is done in compliance with health authority and in-house pharmaceutical standard operating practices, in a validated audit trail environment.

5.2 QUALITY

The data processing activity is done in a validated audit trailed environment. If the modeling activity is of high criticality (e.g. a pivotal regulatory-type submission analysis), a second programmer might be requested to

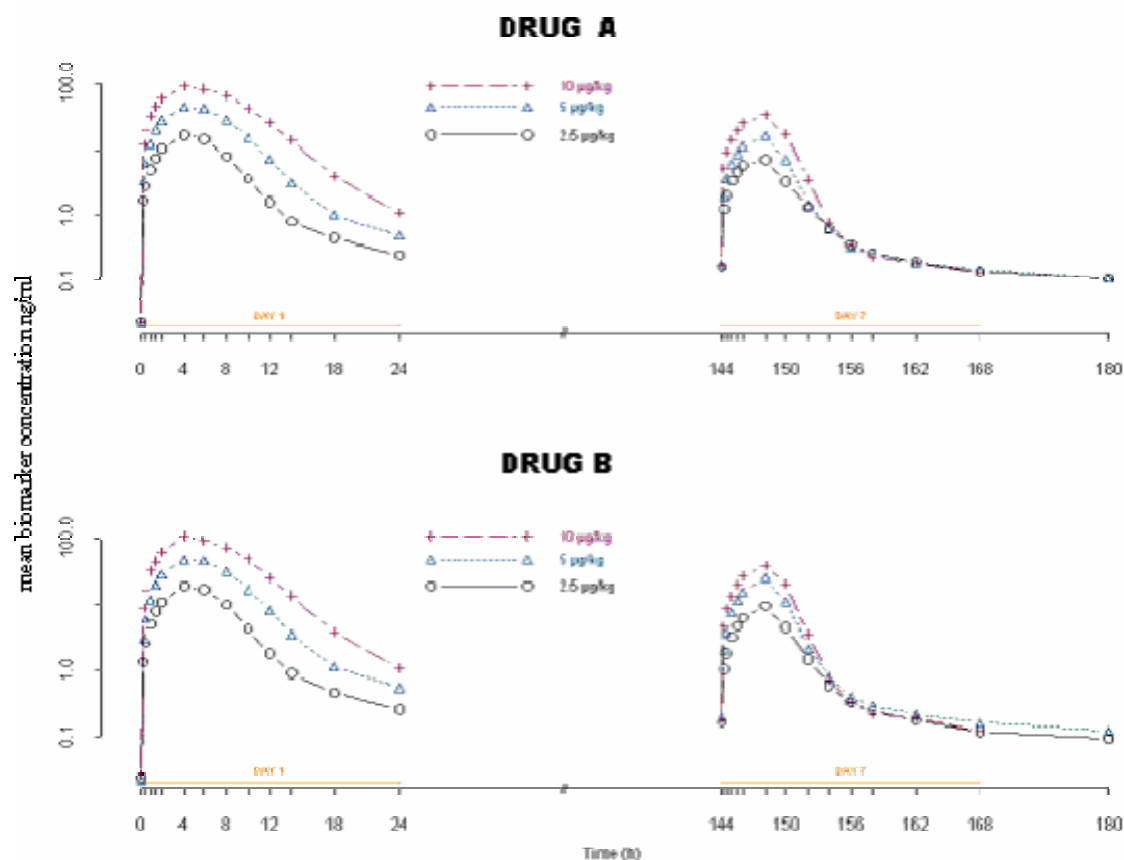
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independently re-do the work and compare it to guarantee high quality input data.

5.3 STATISTICAL ANALYSIS, MODELING ANALYSIS:

All programmers in the group hold at least a Masters degree in Statistics. Their role within M&S for some projects, also covers exploratory statistical analysis, production of graphics using SAS®, Matlab®, S-Plus® or R , preparation of computer code for some literature models or the conduct of modeling work in collaboration with an experienced modeler. The evolving role is supported by regular attendance at team meetings, ad-hoc discussions and trainings.

Graphic 6: Graphics examples



5.4 TRAINING

Programmers share their expertise in order to bring the modelers to the next step of the data manipulation tasks by providing internal SAS® courses based on modelers needs. They also train the modelers to properly use Novartis data repository system to become more efficient. We aim to deliver to the modelers one “big” dataset, and modelers would do the subsequent data manipulation and data extraction.

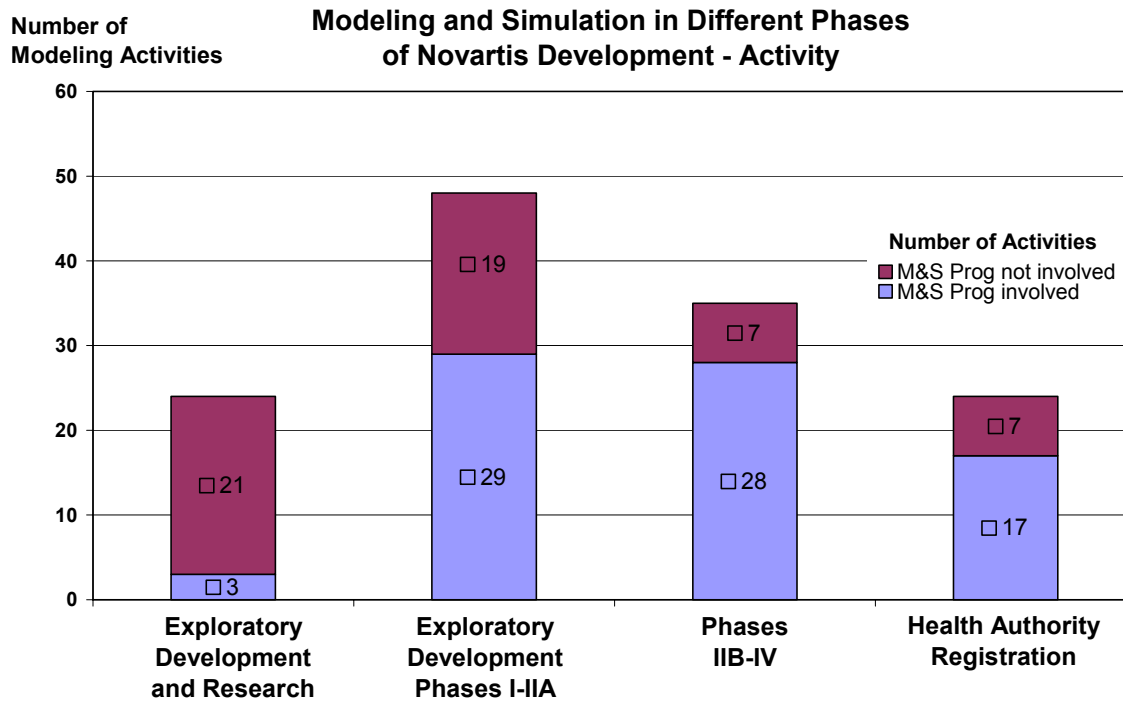
5.5 IT SUPPORT AND IMPROVEMENT

As modeling and simulation becomes a key component in drug development (3) (4), it is vital that hardware and software match our needs. Some global IT projects are currently on-going; M&S Prog is a business representative for the M&S group into all IT projects. The group tracks all software validation and facilitates some key software installation.

6. M&S PROGRAMMERS INVOLVEMENT

In 2006, M&S Prog was involved in nearly 60% of the projects, with a ratio of 1 programmer for 6 modelers. There was a higher focus on late phase projects due to the complexity on data generation and the need for regulatory rigor.

Graphic 7: M&S Prog activities in 2006



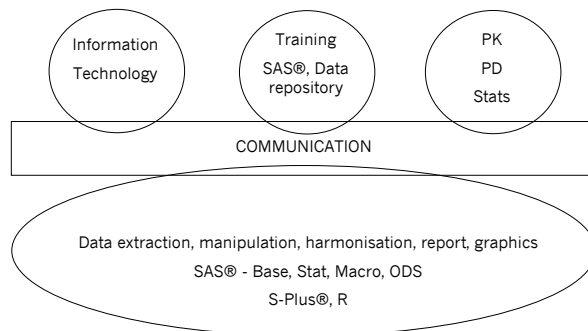
In 2007, M&S Prog is contributing to more projects +48% compared to 2006.

7. PROGRAMMERS SKILLS

A good programmer, within M&S, must have strong technical SAS® programming skills and experience in data handling. S/he must be open to changes, innovative and creative. S/he must be able to convert (sometimes vague and changing) modeling requests into a dataset specification. Communication between the modeler and the programmer must be good, the programmer must understand the modeler's needs, the modeler must understand possible data issues and discuss with the programmer actions to be taken.

Data extraction and manipulation are the key components. All programmers have at least a Masters-level statistics qualification, which allows them to conduct basic statistical analysis. Others have in addition an IT or biological sciences background, which allows them to do computational and modeling platform development work.

Graphic 8: M&S Programmer's skills



8. DIFFERENCES WITH A PHARMA STATISTICS DEPARTMENT PROGRAMMING GROUP

Programmers within M&S usually pool data across studies, whereas a programmer in a standard programming group will more often work at the study level, within a program.

By nature of the work, modeling and simulation is a data driven analysis. We're trying to answer a specific question from a clinical team. The dataset specification is a living document during the modeling work. We have to update the input datasets based on the modeling results. The changes can be minimum (example: add serum creatinine...) or much more complex and much more time consuming (example: add 3 additional phase II studies obtained from an external CRO that has different formats). A statistics department programming group used to follow pre-defined specifications.

A strong similarity for both groups is that they are transparent about what they are doing and follow good clinical practices.

8. CONCLUSION

Due to the diversity of talent in the group, we continue to expand the role of the programmers to do more statistical analyses and have recently commenced work on Population Pharmacokinetics analysis. The plan is to develop talented programmers into modelers, thereby providing a career ladder. A dedicated programming group can significantly improve the efficiency of a modeling and simulation organization within a pharmaceutical company.

Pharma industries are using more and more Modeling and Simulation. Modeling and Simulation has been recognized as a key component to improve the efficiency of drug development. Other Pharma companies start to adopt a similar structure, i.e. having some programmers dedicated to Modeling and Simulation. This represents exciting new career opportunities!

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