



KATHOLIEKE UNIVERSITEIT LEUVEN

Statistics Seminar

Joint organization by
ORSTAT, Faculty of Business and Economics and the Statistics Research Group,
Faculty of Science
Leuven Statistics Research Center

Dr. Luc Bijens

Biostatistics and programming Center of Excellence, JJPRD, Janssen Pharmaceutica

“Statistical innovation in pharmaceutical research”

Thursday March 25, 2010
12:00—13:00

Location: Room HOG 03.101, Naamsestraat 69, Leuven.
Supporting research project: GOA-project 2007/04

Abstract:

In this presentation a short report will be given about two innovative projects the statistics team of Janssen Pharmaceutica in Beerse has recently worked on. The first project is about the development of a statistical search engine for the screening of genes in microarray experiments and the second project is about the translation of pharmacokinetics of animals to that of humans. The first of the two projects was nominated for the Janssen business excellence award in 2008 in the category ‘innovation R&D’. The second pharmacokinetic project has only just started and was recently presented at the non-clinical statistics conference in Boston MA, USA in 2009.

The first project is about DNA microarray technology that measures hybridization of nucleic acids to complementary molecules attached to a solid surface, referred to as probes. For simplicity we call a set of probes a gene. This high-content genomic tool typically generates many measurements of which only a small subset is influenced by the treatment effect measured in the experiment. The aim of this kind of research is to find genes related to the treatment effects. In this project we developed a statistical method based on factor analysis (Hochreiter et al. 2006) that determines how a gene can be called informative or non-informative using probe level information. The underlying idea is that probes of an informative gene detect the mRNA transcript in a consistent way while probes of a non-informative gene are less correlated (Talloen et al. 2007). This gene selection approach outperforms currently available methods.

Consequently, by excluding many false positives, it offers a key solution to issues such as multiple testing and overfitting, the main problems in the analysis of highdimensional microarray data. It is therefore comparable to search engines that search the world wide web for information.

The second part of the presentation is about a meta-analytic approach to allometric scaling. To predict human pharmacokinetics (PK) such as the clearance and the plasma concentration profile of a new compound many animal based methods have been used in the past . Typically those methods are based on animal information of the compound of interest only (Mahmood 2005). This step is crucial in pharmaceutical development since it is used to estimate the starting dose for the first in man study. Among the currently used methods, allometric scaling is probably one of the oldest and simplest methods because it uses essentially body weight and brain weight to correct for species in the prediction of the human PK measures. The aim of this research project is to investigate the variability and uncertainty of the predictions of human clearance . The question is addressed in an applied way by using a combination of experimental data coming from 24 studies in six different species. The assumption that body weight can be used as a surrogate for animal species is key in the current methods. It also assumes that there is a general biological process that holds in mammal species such as mice, rats, rabbits, monkeys, dogs and man. Brain weight, life expectancy and a number of other corrections are often successfully used to fine tune the relationship between clearance and body weight. This research project investigates the variability that goes along with the current practice and suggests a meta-analytical approach to control for the variability. The new approach also establishes a model linking the animal data to human data in a way that has not been done before.