

## RECENT PHD THESES

### Université Catholique de Louvain (UCL)

Jullion Astrid. *Adaptive Bayesian P-splines models for fitting time-activity curves and estimating associated clinical parameters in Positron Emission Tomography and Pharmacokinetic study* (2008) – Promotor: Pr. Philippe Lambert (ULg).

In clinical experiments, the evolution of a product concentration in tissue over time is often under study. Different products and tissues may be considered. For instance, one could analyse the evolution of drug concentration in plasma over time, by performing successive blood sampling from the subjects participating to the clinical study. One could also observe the evolution of radioactivity uptakes in different regions of the brain during a PET scan (Positron Emission Tomography). The global objective of this thesis is the modelling of such evolutions, which will be called, generically, pharmacokinetic curves (PK curves).

Some clinical measures of interest are derived from PK curves. For instance, when analysing the evolution of drug concentration in plasma, PK parameters such as the area under the curve (AUC), the maximal concentration (C<sub>max</sub>) and the time at which it occurs (t<sub>max</sub>) are usually reported. In a PET study, one could measure Receptor Occupancy (RO) in some regions of the brain, i.e. the percentage of specific receptors to which the drug is bound. Such clinical measures may be badly estimated if the PK curves are noisy. Our objective is to provide statistical tools to get better estimations of the clinical measures of interest from appropriately smoothed PK curves.

Plenty of literature addresses the problem of PK curves fitting using parametric models. It usually relies on a compartmental approach to describe the kinetic of the product under study. The use of parametric models to fit PK curves can lead to problems in some specific cases. Firstly, the estimation procedures rely on algorithms which convergence can be hard to attain with sparse and/or noisy data. Secondly, it may be difficult to choose the adequate underlying compartmental model, especially when a new drug is under study and its kinetic is not well known.

The method that we advocate to fit such PK curves is based on Bayesian Penalized splines (P-splines): it provides good results both in terms of PK

curves fitting and clinical measures estimations. It avoids the difficult choice of a compartmental model and is more robust than parametric models to a small sample size or a low signal to noise ratio. Working in a Bayesian context provides several advantages: prior information can be injected, models can easily be generalized and extended to hierarchical settings, and uncertainty for associated clinical parameters are straightforwardly derived from credible intervals obtained by MCMC methods. These are major advantages over traditional frequentist approaches.