IAP PROJECT StUDyS

Université de Liège
– METHODOLOGICAL STATISTICS –

STATISTICS SEMINAR

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Bayesian MAP Estimation in Models with Random effects based on Ordinary Differential Equations applied to Treatment Monitoring in HIV

Models based on ordinary differential equations (ODE) are a widespread tool to describe dynamical system. In biomedical sciences, data within each subject can be sparse but information is often gained from between-subjects variability. This makes natural the use of mixed effect models to estimate population parameters. Moreover, random effects to take into account inter-individual variability open the perspective of treatment individualization based on ODE equilibrium properties.

Although maximum likelihood based approaches are a valuable option, both numerical and identifiability issues favor a Bayesian approach which can incorporate prior knowledge in a flexible way. However, the combination of difficulties coming from the ODE system and from the presence of random effects raises a major numerical challenge. Parameters estimation with classical MCMC chains are most of the time too long to run. Thus, we proposed an estimation method based on a normal approximation of the posterior. This can be obtained by computing the maximum of the posterior distribution (MAP) based on a quasi-Newton algorithm proposed by Guedj et al. [1]. This is implemented in an available program NIMROD (Normal approximation Inference in Models with Random effects based on Ordinary Differential equations).

Model fit and prediction abilities are illustrated on the ALBI clinical trial (n=150 untreated patients starting dual nucleosides therapy) [2] with a non-linear ODE model, the "Activated T-cell model". Then, we introduce how individual treatment monitoring and adaptation is possible based on the reproductive number R0 [3]. We propose a strategy to iteratively update in a Bayesian manner the treatment dose taking into account biomarkers dynamics, treatments and adherence. This would enable us to enhance the treatment by diminishing adverse effects without the definition of a cost function.

Tuesday, December 11, 2012 - 15h00 - Room S36 (Building B37)
Rue Grande Traverse 12, 4000 Liege (Parking P32-33)

References

1. J. Guedj, R. Thiébaut, and D. Commenges. Maximum likelihood estimation in dynamical models of HIV. *Biometrics*, 63(4) :1198-1206, 2007.
2. J.M. Molina, G. Chêne, F. Ferchal, V. Journot, I. Pellegrin, M.N. Sombardier, C. Rancinan, L. Cotte, I. Madelaine, T. Debord, et al. The ALBI trial : a randomized controlled trial comparing stavudine plus didanosine with zidovudine plus lamivudine and a regimen alternating both combinations in previously untreated patients infected with human immunodeficiency virus. *Journal of Infectious Diseases*, 180(2) :351, 1999.
3. M. Prague, D. Commenges, J. Drylewicz and R. Thiébaut. Treatment monitoring of HIV infected patients based on mechanistic models. *Biometrics* 68(3) : 902-911,2012.