**Objective**

- To assess the power of the stepwise-based procedure and HLAASSO for detecting Single Nucleotide Polymorphisms (SNP) effects on a pharmacokinetic parameter using NLMEM

**Context**

- Study of the DNA variations on genes coding for proteins involved in drug transport, metabolism, and effect in relation to the inter-individual variability in drug response
- Focus:
  - Selection of metabolic pathways during drug development
  - Individualized therapy
  - Integration of diversity in population genetics
- Statistical analyses
  - ANOVA-based protocol derived on known parameters
  - Selection of metabolic pathways during drug development
  - Individualized therapy
  - Integration of diversity in population genetics
  - Non-linear Mixed Effect models (NLMEM)

**Simulation study**

- A typical simulated dataset
- Structural and statistical model
  - Inspired from real study [4]
- Power = number of False positive
- True positive = number of True positive
- Power estimates and their 95% confidence interval versus the minor allele frequency (MAF) of the causal variant for both algorithms
- Figure 2: Power estimates and their 95% confidence interval versus the minor allele frequency (MAF) of the causal variant for both algorithms

**Results**

- Evaluation
  - 200 data sets simulated under H0 and H1
  - T = number of simulated data sets
  - P = number of PK model parameters
  - SNP = number of causal SNPs
  - TP = number of True positive
  - FP = number of False positive
  - SNPs uncorrelated to the causal variant

**Discussion**

- Similar power of the stepwise-based procedure and HLAASSO
- Reasonable number of false positives
- Important gain in computing time with HLAASSO
- On-going work
  - to increase the number of causal variants
  - to consider moderate to weak effects (gradient)

**References**