Incorporating genetic predictors within the SAEM algorithm

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Pharmacogenomics

- Personalized drug therapy[1]
  - High-throughput approach to identifying genetic determinants of drug response
  - lack of large-scale pharmacogenomic studies with adequate follow-up
- *Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products*[2]
  - large genetic arrays when no hypothesis on genetic origin
  - level of evidence similar to that required in drug-drug interaction
  - modelling and simulation to help in analysis and design

[1] Evans WE, Relling MV. Nature. 2004
[2] EMA/CHMP/37646/2009

Pharmacogenomic model

- Nonlinear mixed effects (NLME)

$$y_{ij} = f(\phi_i, t_{ij}) + \epsilon_{ij} \text{ , with } \epsilon_{ij} \sim N(0, \sigma^2)$$
$$\boldsymbol{\phi_i} = h\left(C_i\boldsymbol{\mu} + \boldsymbol{\eta_i}\right) \text{ , with } \boldsymbol{\eta_i} \sim N(0, \Omega)$$

$h(u) = e^u$ log-normal distribution

$\widehat{\boldsymbol{\theta}} = (\widehat{\boldsymbol{\mu}}, \widehat{\Omega}, \widehat{\sigma})$ $\quad$ $\mathbf{EBE_i} = Argmax_{\phi_i}\ p(\boldsymbol{\phi_i}|\boldsymbol{y_i}; \widehat{\boldsymbol{\theta}})$

Pharmacogenomic model

- Nonlinear mixed effects (NLME)
  - genetic variation: single nucleotide polymorphism, SNP

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  - linear regression on allele dosage $SNP = \{0, 1, 2\}$

$$\underset{\boldsymbol{\phi_i}}{\log CL_i} = \underset{C_i}{\begin{pmatrix} 1 & SNP_{1i} & \dots & SNP_{Nsi} \end{pmatrix}} \underset{\boldsymbol{\mu}}{\begin{pmatrix} \mu_{CL} \\ \beta_{CL,SNP_1} \\ \vdots \\ \beta_{CL,SNP_{Ns}} \end{pmatrix}} + \underset{\boldsymbol{\eta_i}}{\eta_{CLi}}$$

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  - number of SNPs, $N_s >> N$, number of subjects
  - varying in informativeness and correlated

Pharmacogenomic analysis

- Method 1: Modified stepwise procedure
  - commonly found in the literature
  - screening step adapted to account for genetic correlation
- Penalised regression
  - established in animal and plant genetics
  - Method 2: Lasso
  - Method 3: HLasso
    - developed for genome-wise association studies
    - higher effect size once included in the model
  - performed on EBE from base model

↪ computationally and statistically efficient[3]

↪ 2-stage approaches: SNP selection after model parameter estimation

[3] Bertrand J, Balding DJ. Pharmacogenet Genomics. 2013

Objectives

- To develop a method 4: integrated approach
  - to simultaneously estimate PK model parameters and genetic effects size
- To compare through a realistic simulation study:
  1. adapted stepwise procedure
  2. Lasso regression on EBE
  3. HLasso regression on EBE
  4. integrated approach

2-stage approaches

1. Stepwise procedure
   i. screening step, for each p^{th} model parameter per SNP
   $\widehat{\beta_{ps}} = argmin_{\beta_{ps}} \sum_i^N (\boldsymbol{EBE_{pi}} - \beta_{ps} \times SNP_{si})^2$
      - pruning on multiple significant SNPs with $r^2 \geq 0.8$
   ii. model inclusion and selection step
   ⟳ repeat i-ii until no more SNPs significant

2-stage approaches

1 Stepwise procedure

- i screening step, for each p^{th} model parameter per SNP
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  - pruning on multiple significant SNPs with $r^2 \geq 0.8$
- ii model inclusion and selection step
- ↻ repeat i-ii until no more SNPs significant

- Penalised regression, for each p^{th} model parameter
  $\widehat{\boldsymbol{\beta_p}} = argmin_{\boldsymbol{\beta_p}} \sum_i^N (\boldsymbol{EBE_{pi}} - \boldsymbol{\beta_p} \times \boldsymbol{SNP_i})^2 + P(\boldsymbol{\beta_p})$

2 Lasso, $P_{\xi}(\boldsymbol{\beta_p}) \approx$ double exponential prior on β_p

- ξ set by permutations to ensure a target family wise error rate (FWER)

3 HLasso, $P_{\lambda,\gamma}(\boldsymbol{\beta_p}) \approx$ normal exponential gamma prior on β_p

- λ set to 1, γ set by permutations

Integrated approach

- Simultaneous SNP selection and estimation of PK model parameters
  - HLasso at each iteration of the SAEM algorithm
- Maximization-step of $\boldsymbol{\mu}$ in SAEM

$\widehat{\boldsymbol{\mu}_{\boldsymbol{k+1}}} = argmin_{\boldsymbol{\mu}} \sum_{i=1}^{N} (\boldsymbol{s_{ik}} - C_i\boldsymbol{\mu})'\Omega^{-1}(\boldsymbol{s_{ik}} - C_i\boldsymbol{\mu})$

At iteration k

$\boldsymbol{\phi_{ik}}$ drawn from $p(.|\mathbf{y}; \boldsymbol{\theta_k})$

$\boldsymbol{s_{ik}} = \boldsymbol{s_{ik-1}} + \tau_k(\boldsymbol{\phi_{ik}} - \boldsymbol{s_{ik-1}})$

$\mu = (\mu_{Cl}, \mu_V, \beta_{Cl,1}, \ldots, \beta_{Cl,N_s})$

τ_k, a decreasing sequence of positive numbers

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  - call to `hlasso` program with $\boldsymbol{s_{ik}}$ as the response
  - λ set to 1, γ set using an asymptotic approximation
  - implemented in the `saemix` R package

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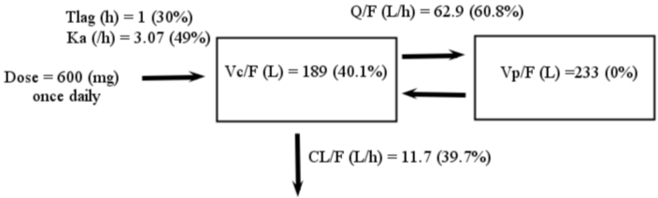
Pharmacokinetic settings

- Structural and statistical model
  - inspired from real study [4]



  - diagonal variance matrix of random effects
  - combined residual error model
- Phase II-like study design
  - 300 individuals with t= 0.5, 1.25, 2, 4, 9, 24

[4] Kappelhoff et al. Clinical pharmacokinetics, 2005

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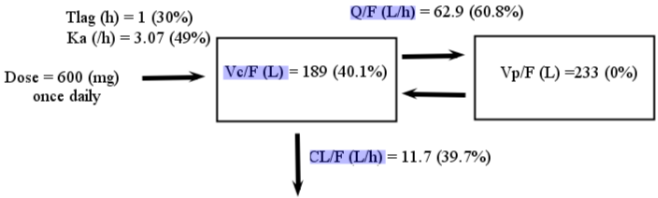

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Genetic settings

- Generation of genotypes using HAPGEN [5]
  - N_s=1227 snps on 171 genes from the DMET Chip [6]
  - 6 [1-56] snps per gene
  - HAPMAP caucasian reference haplotypes
- Alternative hypothesis H_1=presence of a genetic effect
  - 200 simulated data sets
  - 6 *unobserved* causal variants with allele frequency, p_s
    - decrease in log(CL/F) with allele dosage
    - varying genetic component of interindividual variability

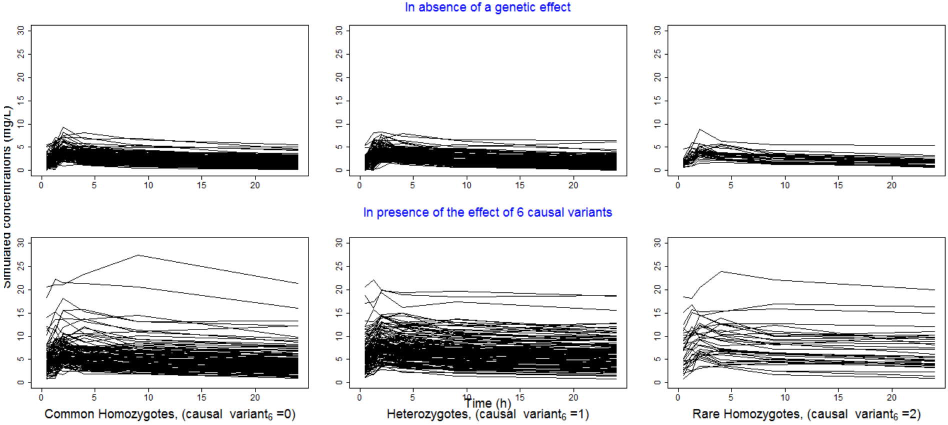
$$R_{Gs} = \frac{\beta_s^2 \times 2p_s(1-p_s)}{\beta_s^2 \times 2p_s(1-p_s) + \omega_{CL/F}^2} = (1,2,3,5,7,12)'\,\%$$

$$R_G = \sum_{s=1}^{6} R_{Gs} = 30\%$$

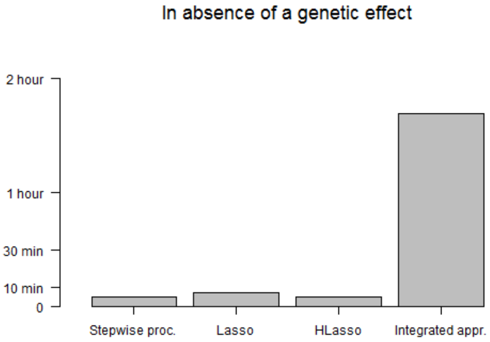
[5] Su et al. Bioinformatics, 2011

[6] Daly et al. Clinical Chemistry, 2007

A typical simulated dataset



Computing times



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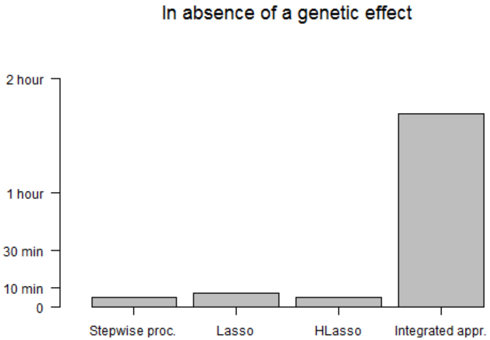

- Similar computing times for 2-stage approaches
- Integrated approach
  - HLasso run at each SAEM iteration

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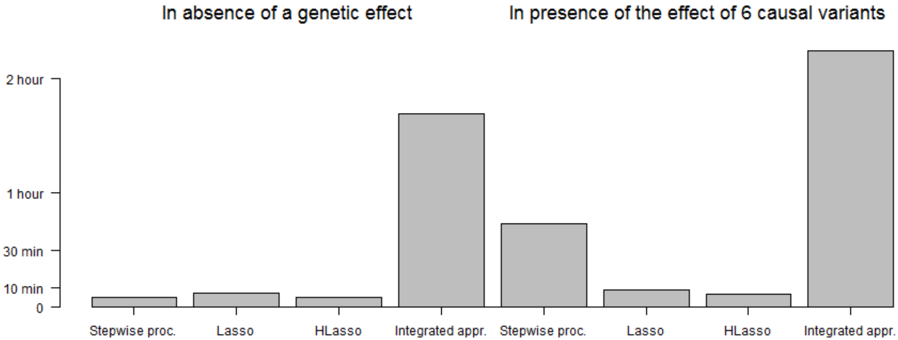

- Similar computing times for 2-stage approaches
- Integrated approach
  - HLasso run at each SAEM iteration
- Slight increase for all methods
- Stepwise proc.= 10 times longer run times under H_1

FWER and TP

	FWER(%)	TP	$FP_{CL/F}$	$FP_{Vc/F}$	$FP_{Q/F}$
Stepwise proc.	18.5	338 [302–374]	15 [7–23]	8 [2–14]	30 [19–41]
Lasso	18.5	311 [276–346]	12 [5–19]	18 [10–26]	11 [4–18]
HLasso	18	316 [281–351]	14 [7–21]	15 [7–23]	11 [4–18]
Integrated appr.	20	256 [225-287]	19 [10-28]	7 [2-12]	0

Family wise error rate, FWER= expected value of 20[14.5–25.5]%

True positive, TP=SNP in $r^2 \geq 0.05$ with causal variant; maximum, possible 1200

False positives, FP

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  - lower TP count

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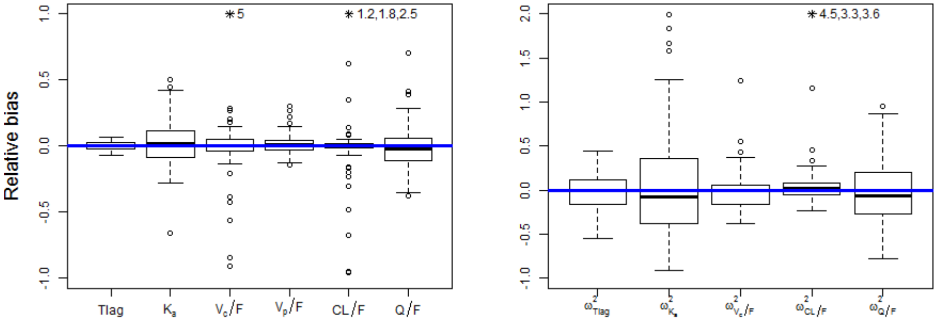
- Integrated approach
  - lower TP count
  - lower FP count on Vc/F and Q/F

Estimation performance

Integrated approach in absence of a genetic effect



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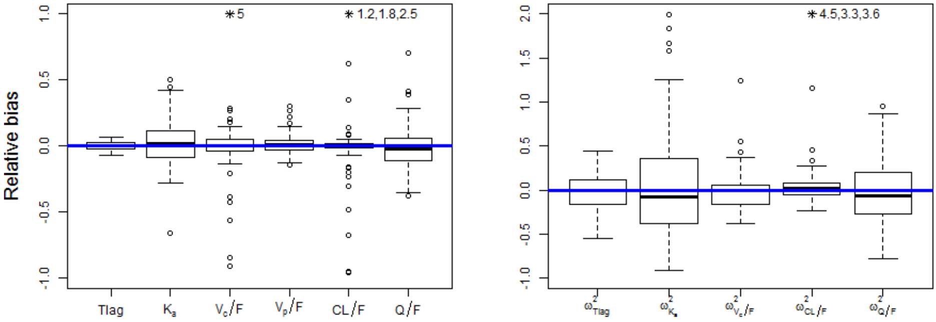
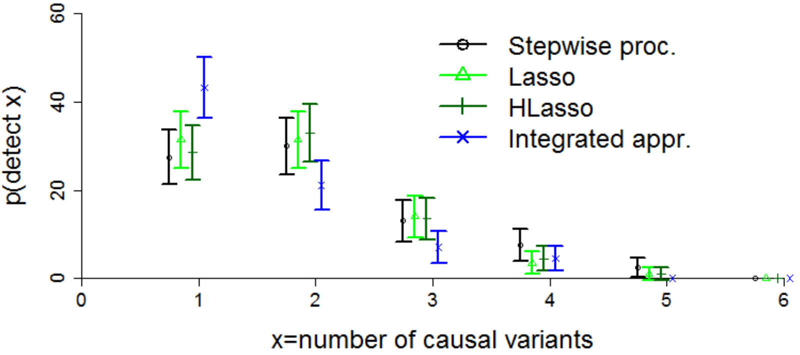


- Fixed effects
  - less than 3% Rbias and RRMSE from 3-15%
- Variances
  - less than 5% Rbias and RRMSE from 20-50%

Power to detect multiple variants



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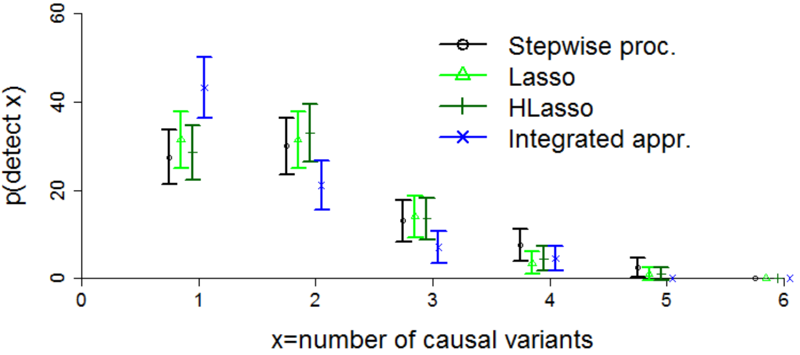

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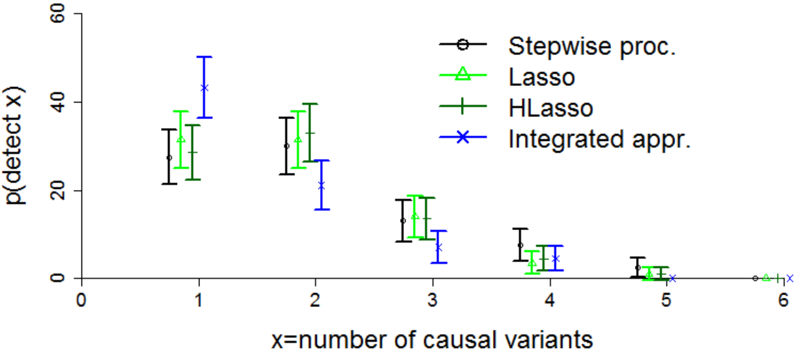

- None of the approaches select the 6 causal variants
- Integrated approach favours more parsimonious models

Discussion

- Realistic simulation study
  - feasability of combining large SNPs set and NLME model
  - chosen FWER of 20% to enable power comparisons
  - analyses for exploratory purposes
    - further functional studies required
- Integrated approach
  - \+ full model-based approach
  - \+ less false positives
  - – longer computing times
  - – less powerful to detect multiple SNPs
- Future works
  - influence of shape parameter
    - larger shape parameter → Lasso
  - full Bayesian approach

Acknowledgements

- `saemix` R package
  Dr Emmanuelle Comets
- UCL Genetics Institute
- London Pharmacometrics Interest Group

Asymptotic approximation to set γ

$$\frac{sign(\beta_p = 0^+)(2\lambda + 1)}{\gamma} \frac{D_{-(2\lambda+2)}\left(\frac{|\beta_p = 0^+|}{\gamma}\right)}{D_{-(2\lambda+1)}\left(\frac{|\beta_p = 0^+|}{\gamma}\right)} = \Phi^{-1}(1 - \alpha/2)\sqrt{\frac{N}{\delta_p}}$$

$\delta_p = \mathrm{VAR}(s_{p.k})/\omega_p^2$

reflects the design information

$\mathrm{VAR}(s_{p.k}) \ll \omega_p^2 \rightarrow$ increases penalisation

$\mathrm{VAR}(s_{p.k})$ derived using Batch means method