Bayesian approaches for pharmacogenetic models with JAGS and Stan

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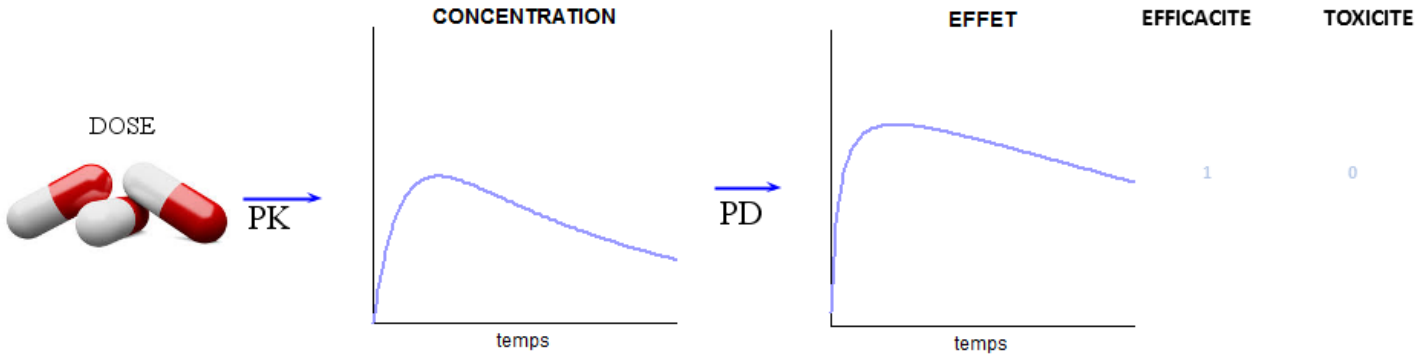
Pharmacological and genetic variability

- Clinical pharmacology: study the interaction between the organism and the drug
  - pharmacokinetics (PK) and pharmacodynamics (PD)



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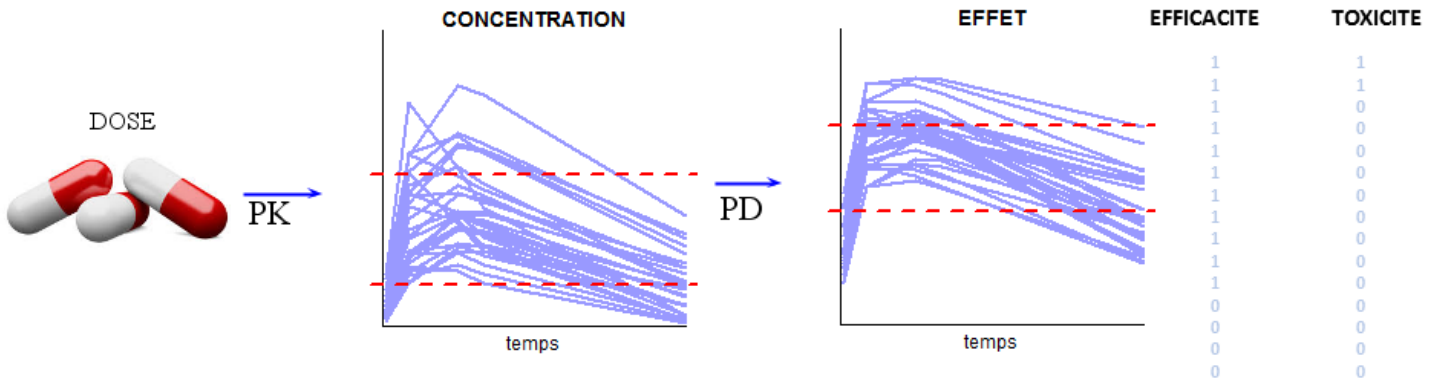

Pharmacological and genetic variability

- Clinical pharmacology: study the interaction between the organism and the drug and its variability
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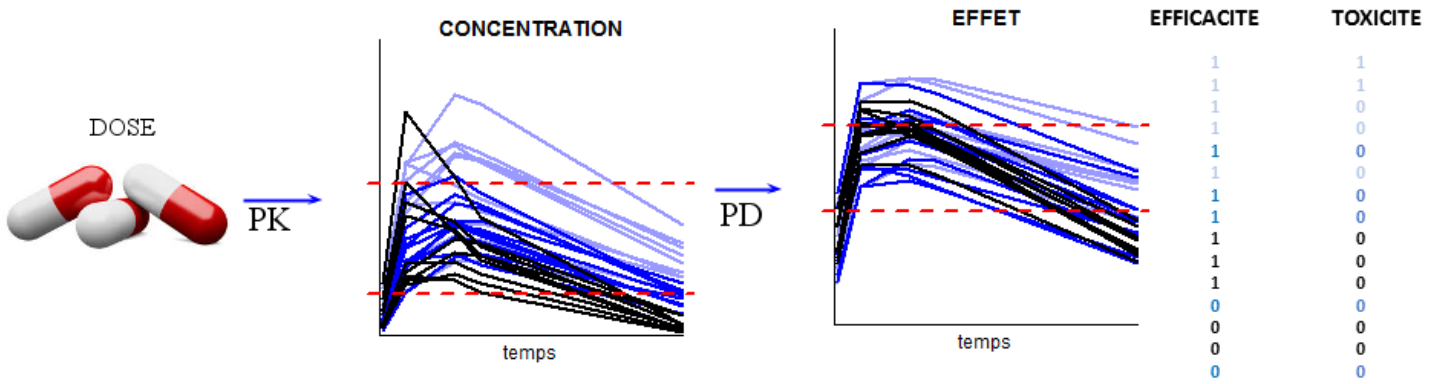
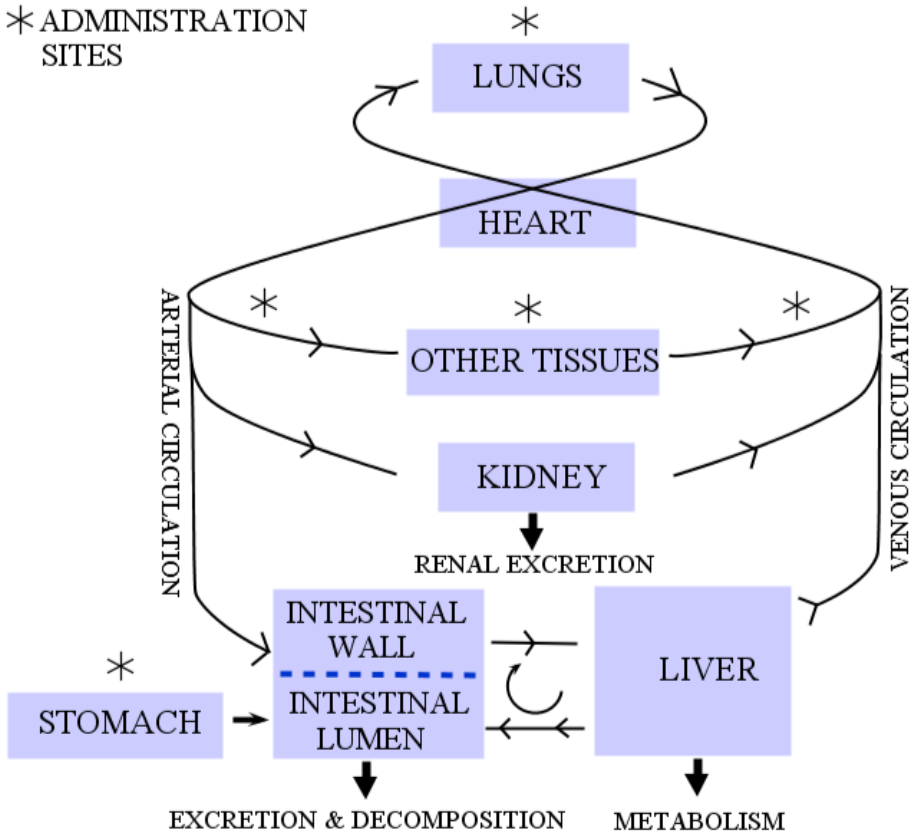


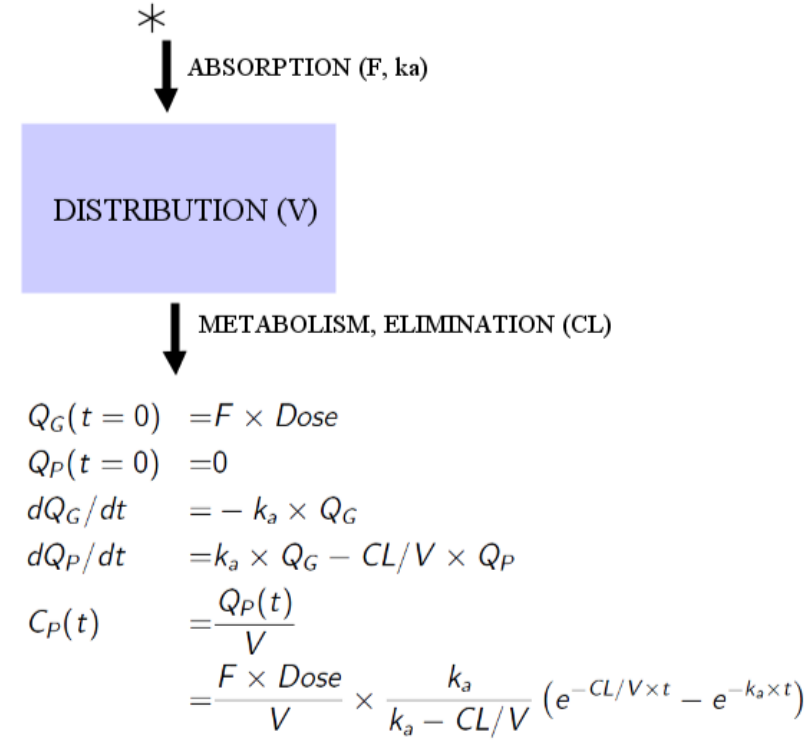
- Pharmacogenetics (PG): genetic part of the variability
  - stratified/precision medicine
  - genes coding for proteins involved in PK/PD processes
    - metabolism enzymes (CYP450, NAT)
    - single nucleotide polymorphism (SNP)

Methodological challenges in PGx

- PK/PD phenotype $\rightarrow$ not observed
  - data : plasma or insulin concentrations, ...

$\hookrightarrow$ dynamical model (nonlinear in its parameters)





$$
\begin{aligned}
Q_G(t=0) &= F \times Dose \\
Q_P(t=0) &= 0 \\
dQ_G/dt &= -k_a \times Q_G \\
dQ_P/dt &= k_a \times Q_G - CL/V \times Q_P \\
C_P(t) &= \frac{Q_P(t)}{V} \\
&= \frac{F \times Dose}{V} \times \frac{k_a}{k_a - CL/V}\left(e^{-CL/V \times t} - e^{-k_a \times t}\right)
\end{aligned}
$$

Methodological challenges in PGx

- PK/PD phenotype $\rightarrow$ not observed
  - data : plasma or insulin concentrations, ...

  $\hookrightarrow$ dynamical model (nonlinear in its parameters)

  $\hookrightarrow$ mixed effect models
    - all patients analyzed simultaneously
    - parameter decomposed in fixed and random effects

Example : $CL_i = \mu_{CL} + \eta_i$ with $\eta_i \sim N(0, \omega^2_{CL})$

Methodological challenges in PGx

- PK/PD phenotype $\rightarrow$ not observed
  - data : plasma or insulin concentrations, ...

  $\hookrightarrow$ dynamical model (nonlinear in its parameters)

  $\hookrightarrow$ mixed effect models
    - all patients analyzed simultaneously
    - parameter decomposed in fixed and random effects
    - covariates identification:

Example : $CL_i = \mu_{CL} + \beta \times SNP_i + \eta_i$ with $SNP = \{0, 1, 2\}$

Methodological challenges in PGx

- PK/PD phenotype $\rightarrow$ not observed
  - data : plasma or insulin concentrations, ...

  $\hookrightarrow$ dynamical model (nonlinear in its parameters)

  $\hookrightarrow$ mixed effect models
- Increased size of genetic data sets up to high throughput screening
  - dimensionality curse $N << p$

  $\hookrightarrow$ Stepwise procedure

  $\hookrightarrow$ Penalized regression

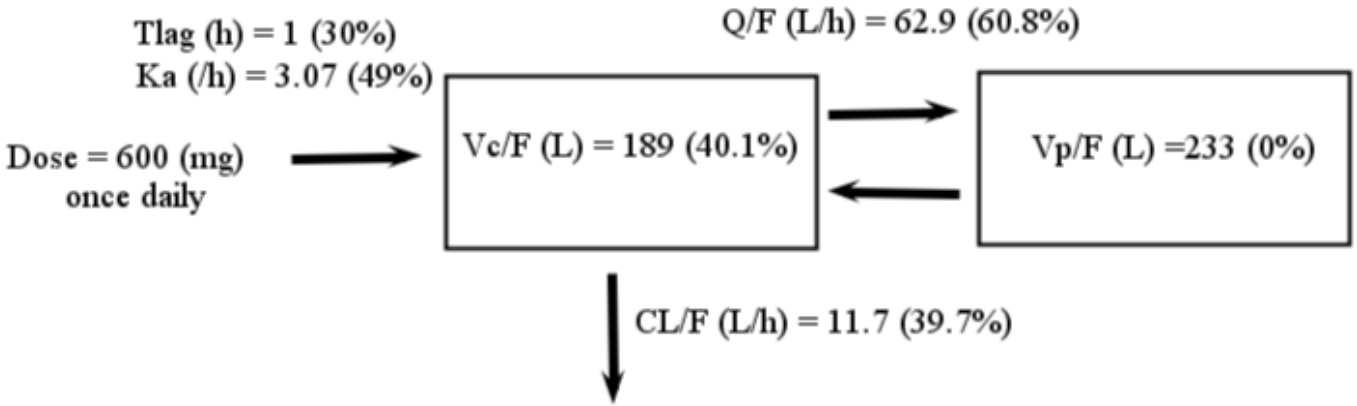
  $\hookrightarrow$ Bayesian variable selection

Objectives

- To evaluate, through a realistic simulation study, the performance to detect a pharmacogenetic association
  - stepwise procedure (Monolix software and lm R function)
  - penalized regression (saemix R package and hlasso program)
  - bayesian variable selection (R2jags)

Genetic and PK data

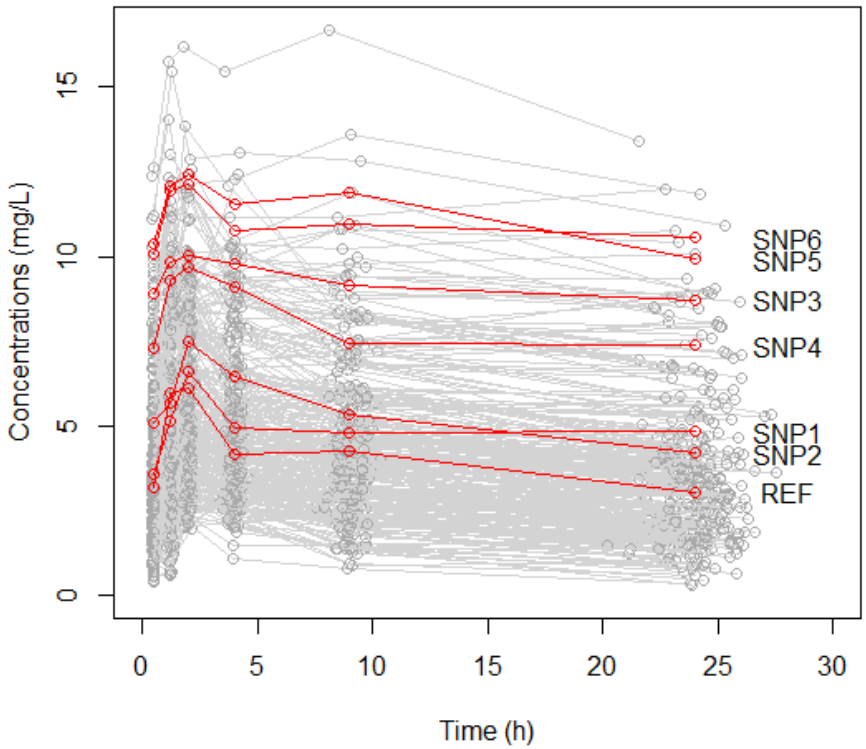
- Generation of genotypes using HAPGEN (Su et al. 2011)
  - N_s=1227 snps on 171 genes from the DMET Chip (Daly et al. 2007)
  - 6 [1-56] snps per gene
  - HAPMAP caucasian reference haplotypes
- Pharmacokinetic profiles inspired from real study (Kappelhoff et al. 2005)



  - phase II study: N=300/t=0.5, 1.25, 2, 4, 9, 24h
  - diagonal variance matrix of random effects
  - combined residual error model $g = \sigma_{inter} + \sigma_{prop} f(\phi_i, t_{ij})$

Pharmacogenetic effect

- 6 unobserved causal variants explaining 30% of the PK



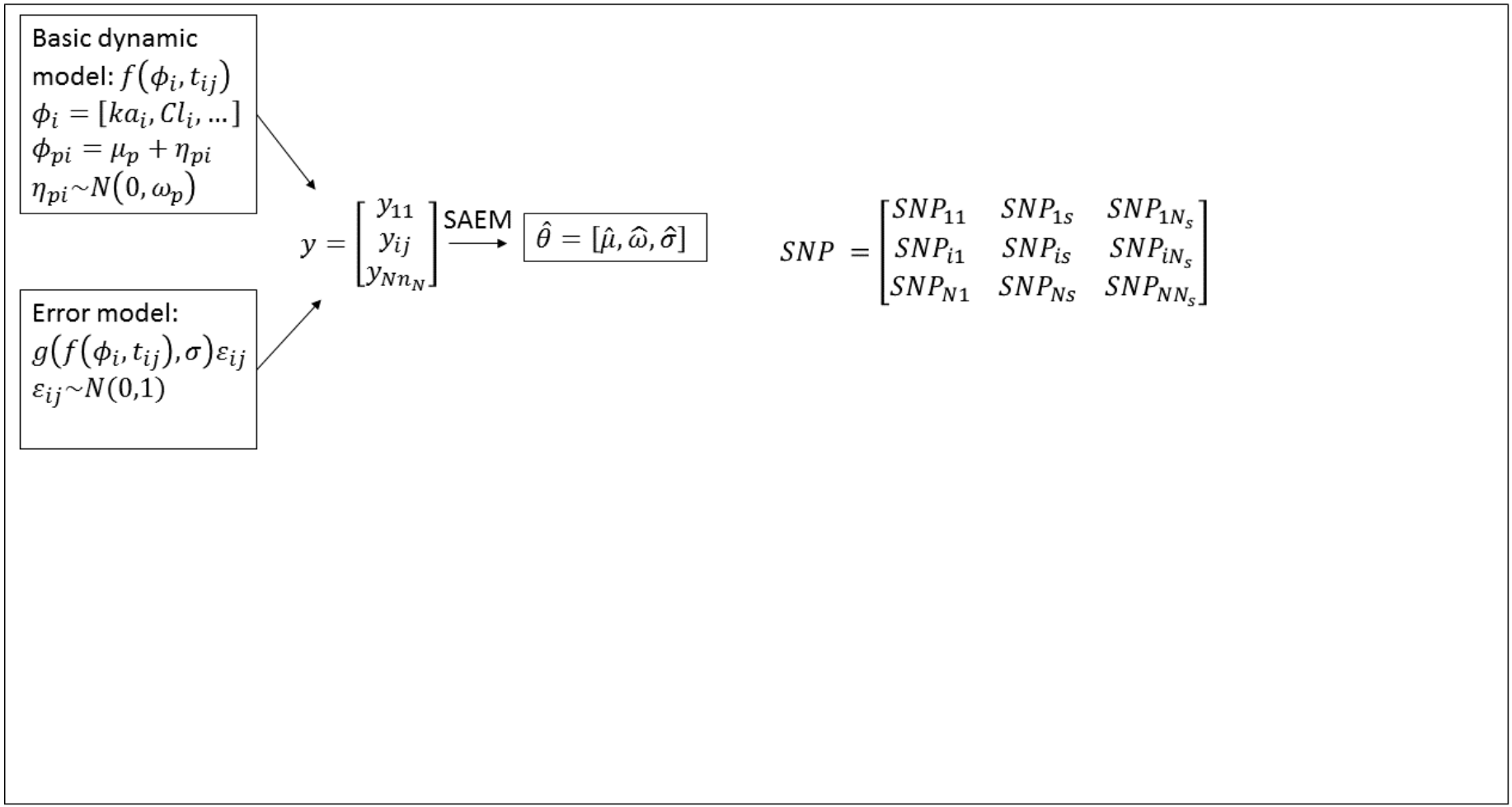
- $\log\ Cl_i = \log\ Cl + \sum_{s=1}^{6} \beta_{Cl_s} SNP_{s_i} + \eta_{Cl_i}$ with $SNP_{s_i} = 0, 1, 2$

Stepwise procedure (Lehr et al. 2010)

$$y = \begin{bmatrix} y_{11} \\ y_{ij} \\ y_{Nn_N} \end{bmatrix}$$

$$SNP = \begin{bmatrix} SNP_{11} & SNP_{1s} & SNP_{1N_s} \\ SNP_{i1} & SNP_{is} & SNP_{iN_s} \\ SNP_{N1} & SNP_{Ns} & SNP_{NN_s} \end{bmatrix}$$

Stepwise procedure (Lehr et al. 2010)



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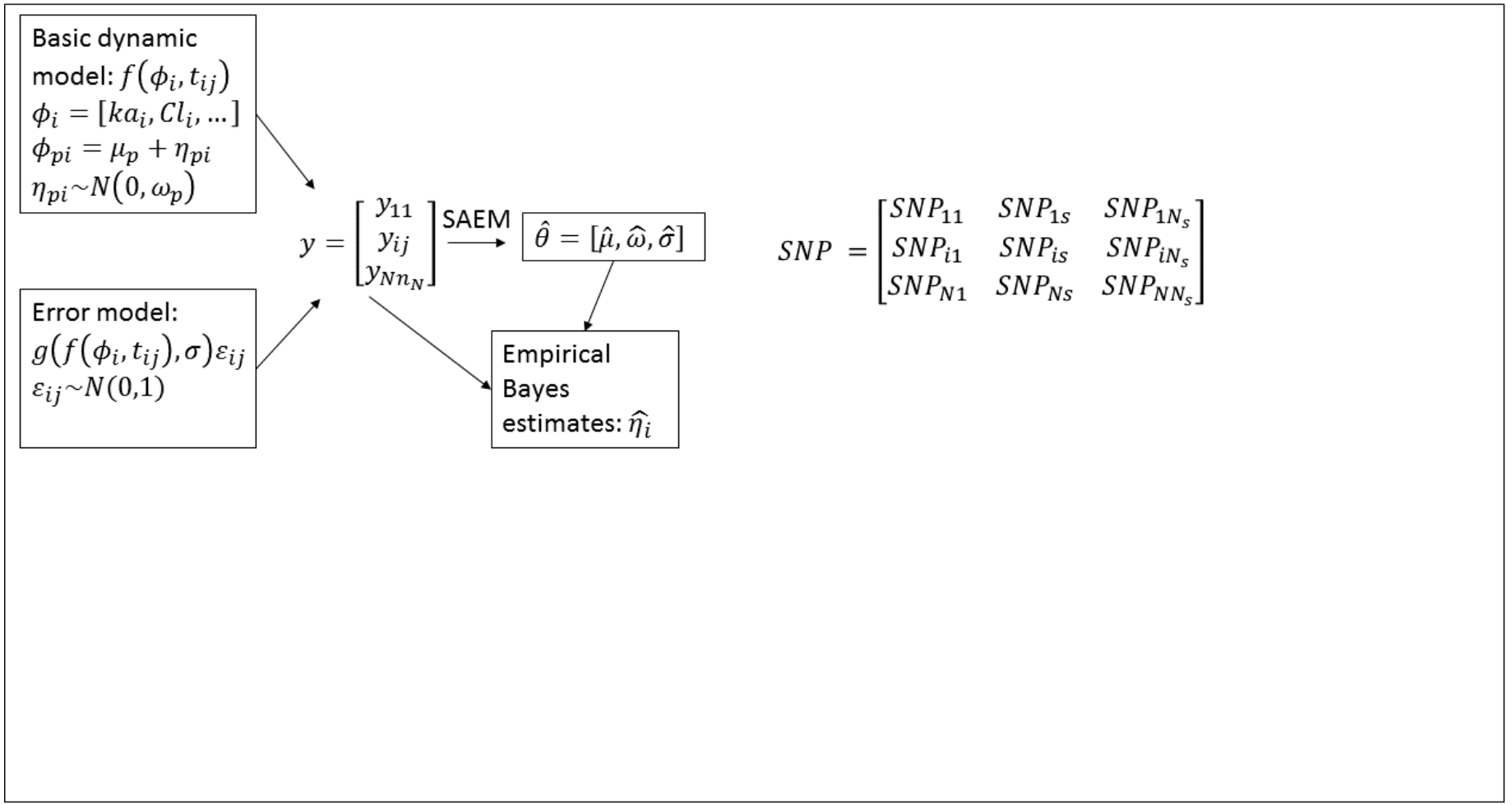

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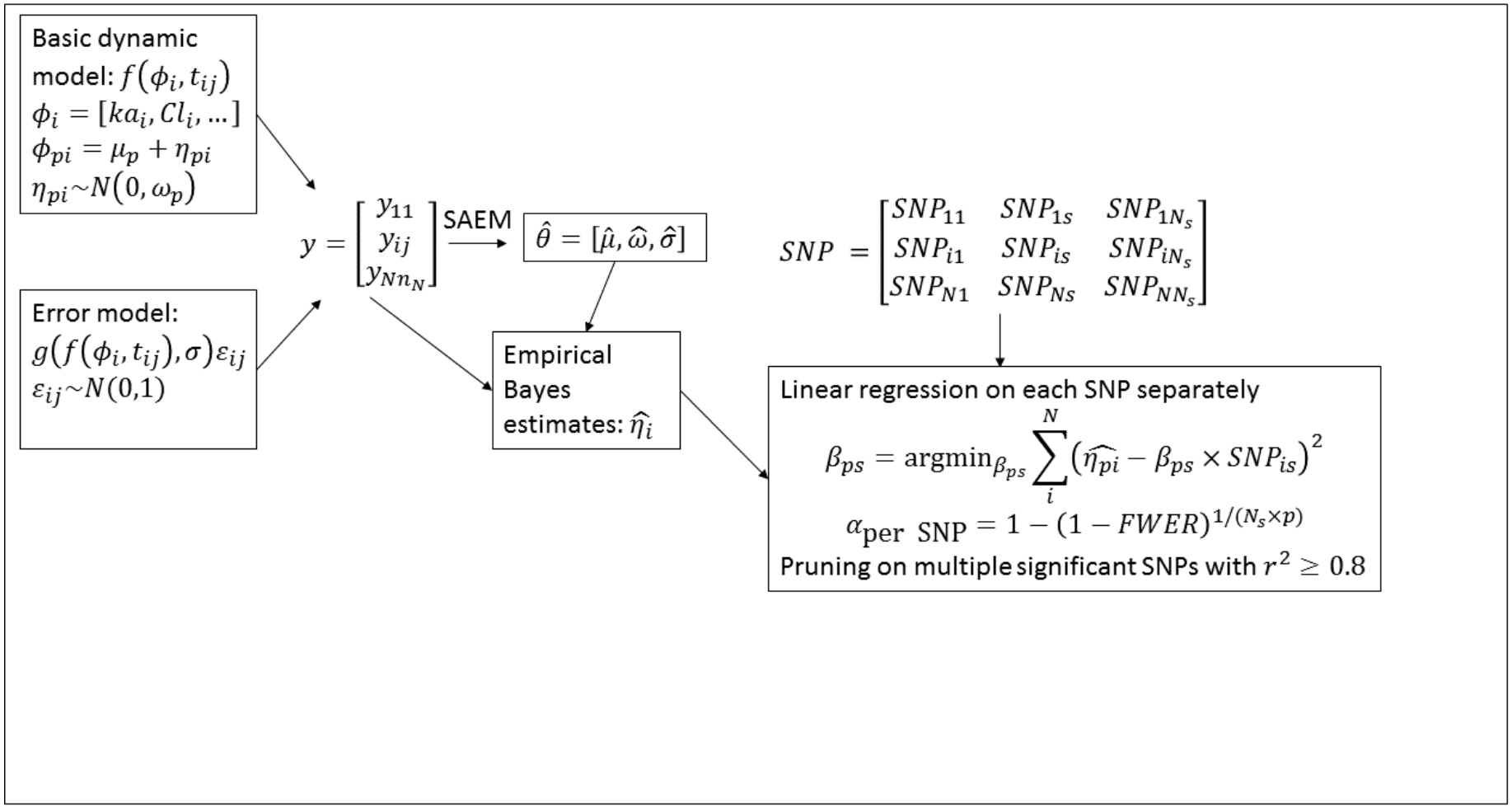

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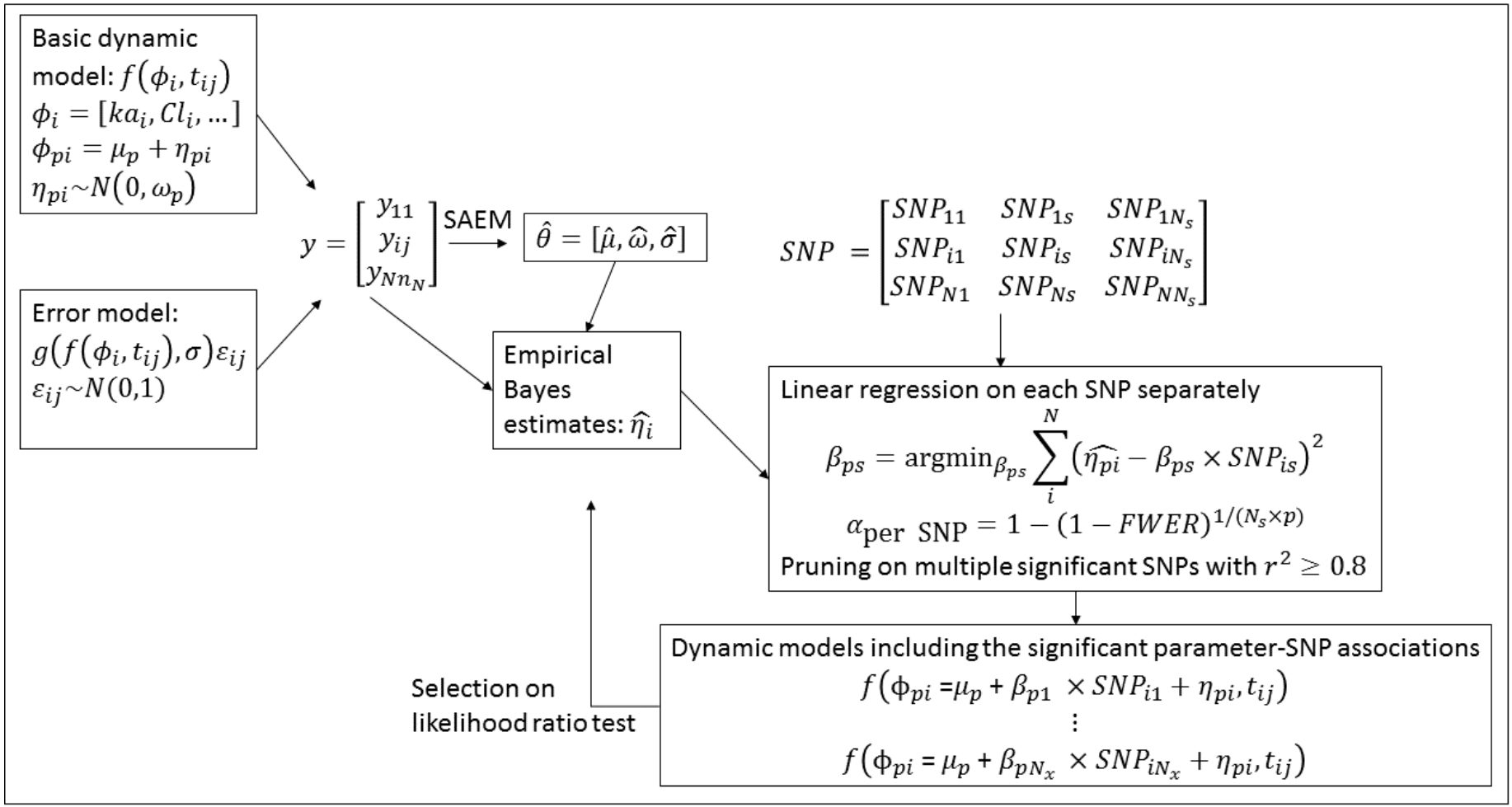

↪ SNP selection after estimation of model parameters

↪ SNP considered independently

Penalized regression (Bertrand et al. 2015)

$$y = \begin{bmatrix} y_{11} \\ y_{ij} \\ y_{Nn_N} \end{bmatrix} \qquad SNP = \begin{bmatrix} SNP_{11} & SNP_{1s} & SNP_{1N_s} \\ SNP_{i1} & SNP_{is} & SNP_{iN_s} \\ SNP_{N1} & SNP_{Ns} & SNP_{NN_s} \end{bmatrix}$$

Penalized regression (Bertrand et al. 2015)

Dynamic model including parameter-SNP associations:

$f(\phi_i = \mu + \beta \times SNP_i + \eta_i, t_{ij})$

$\eta_i \sim N(0, \Omega)$

Error model:

$g(f(\phi_i, t_{ij}), \sigma)\varepsilon_{ij}$

$\varepsilon_{ij} \sim N(0,1)$

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SAEM

Stochastic Approximation Expectation-step at iteration k

ϕ'_{ik} drawn from $p(.|y; \theta_k)$, Metropolis Hasting algorithm

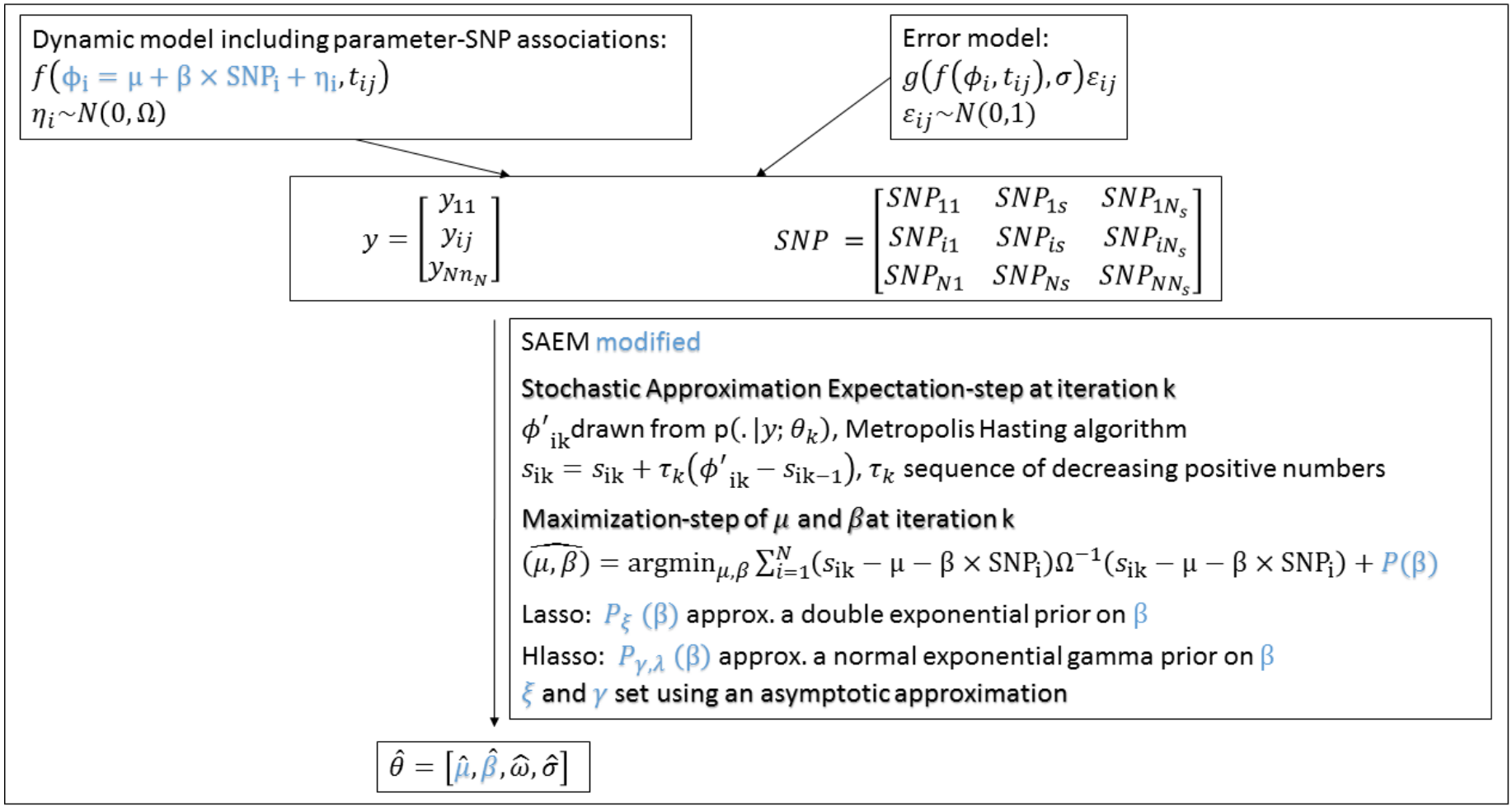
$s_{\mathrm{ik}} = s_{\mathrm{ik}} + \tau_k(\phi'_{\mathrm{ik}} - s_{\mathrm{ik-1}})$, τ_k sequence of decreasing positive numbers

Maximization-step of μ and β at iteration k

$(\widehat{\mu, \beta}) = \mathrm{argmin}_{\mu,\beta} \sum_{i=1}^{N} (s_{\mathrm{ik}} - \mu - \beta \times \mathrm{SNP_i}) \Omega^{-1} (s_{\mathrm{ik}} - \mu - \beta \times \mathrm{SNP_i})$

$\hat{\theta} = [\hat{\mu}, \hat{\beta}, \hat{\omega}, \hat{\sigma}]$

Penalized regression (Bertrand et al. 2015)



↪ Simultaneous SNP selection and estimation of model parameters

↪ All parameter-SNP associations considered simultaneously

Bayesian variable selection (Kuo & Mallick 1998)

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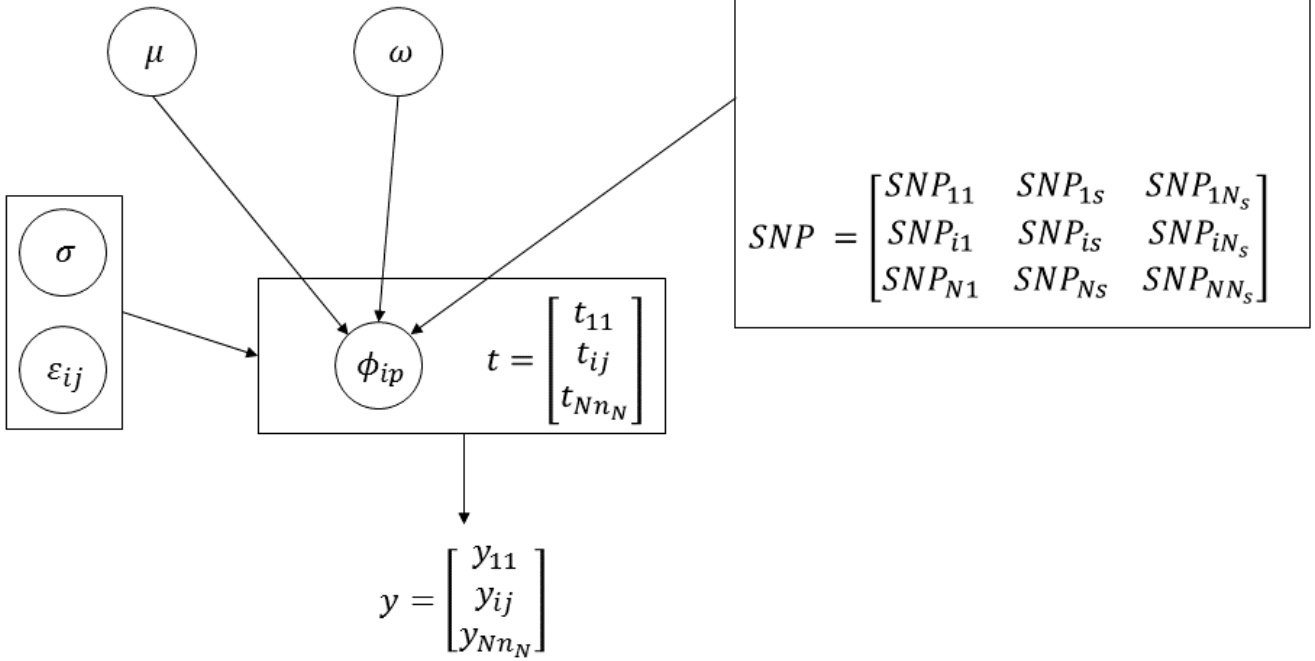

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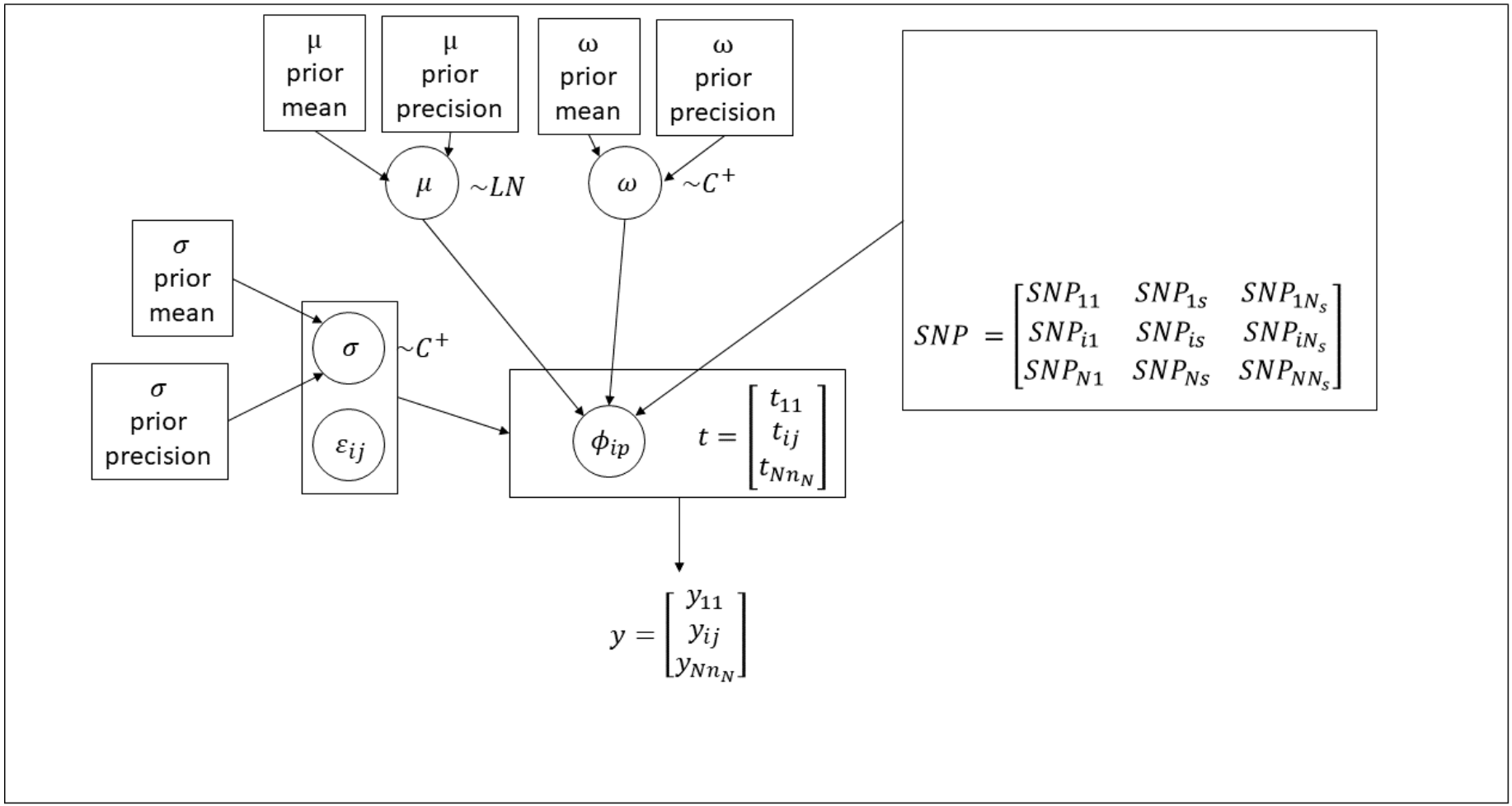

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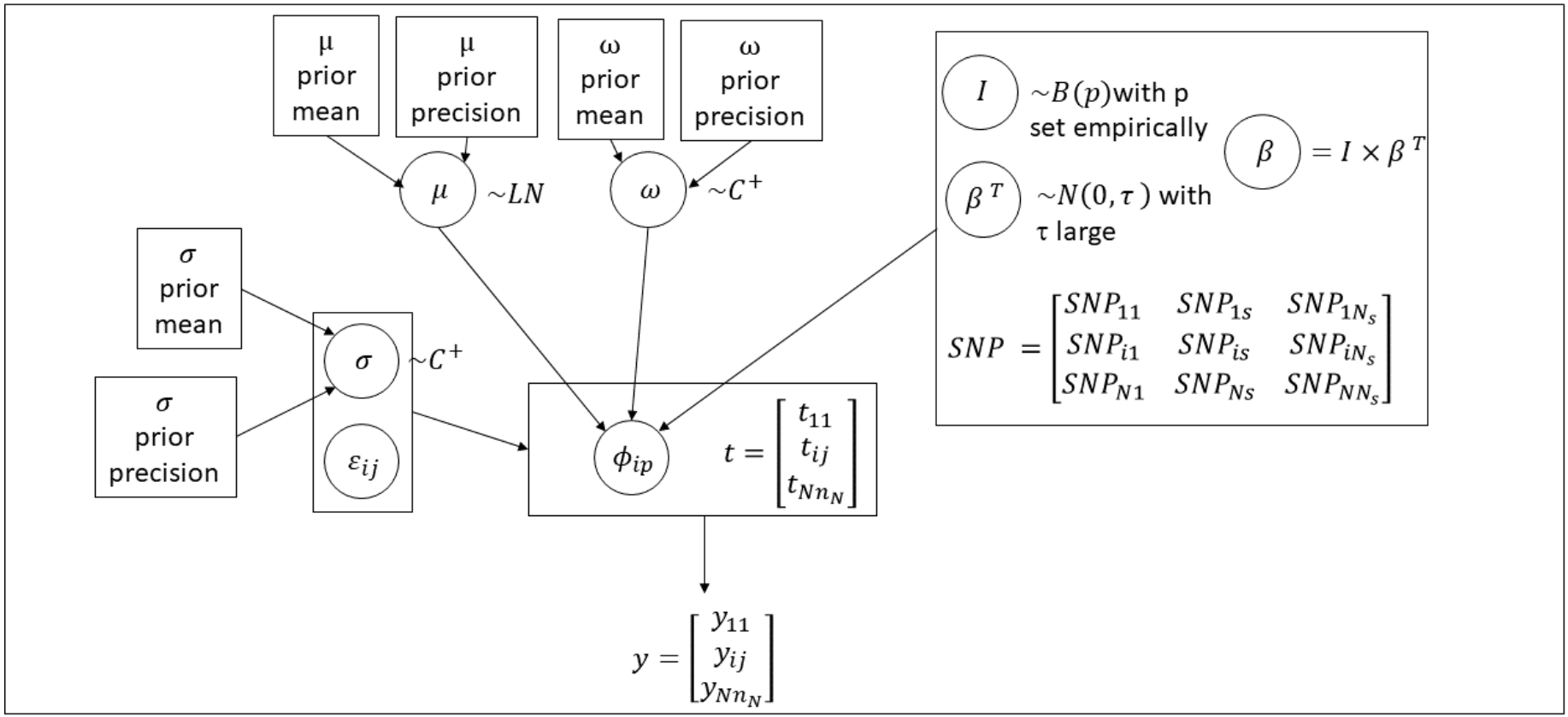

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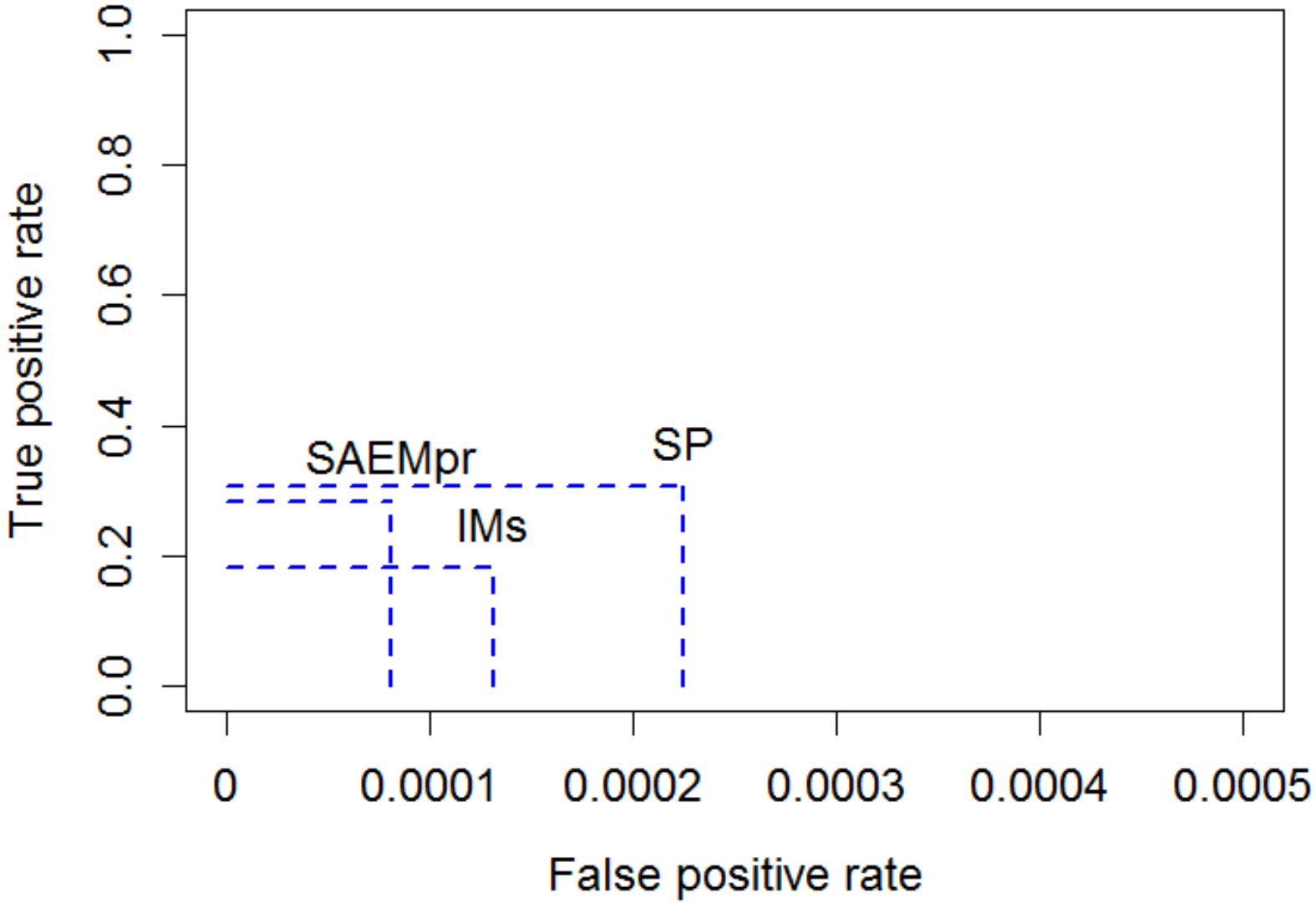
True and false positive rates



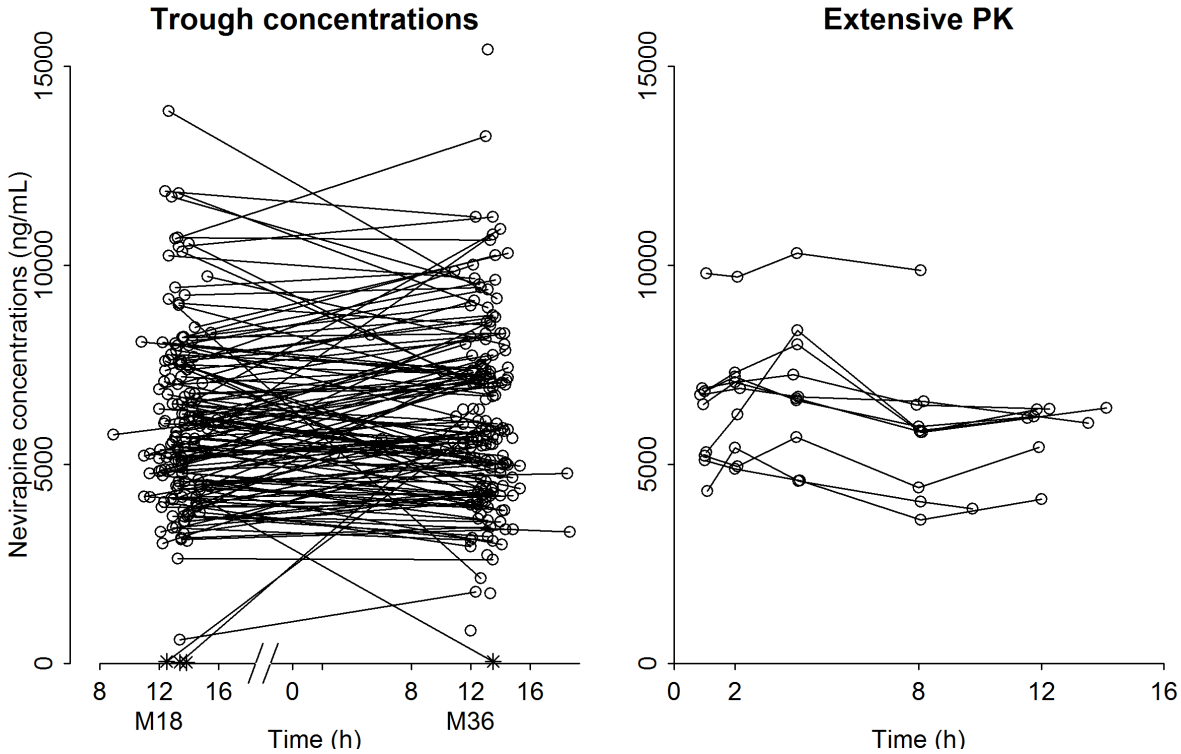
Computing times in hours - mean [range]

Stepwise procedure	**0.24 [0.06 - 1.09]**
Integrative appr.	**1.14[0.83 - 1.61]**
Bayesian appr.	**19.58 [11.51 - 23.12]**

Conclusions

- Feasibility of model-based PGx analyses on a real-case scenario
  - real need of increased sample size compared to classical drug development study designs
- Similar TPR between penalized regression and stepwise procedure
  - cost in computing time non-negligible
  - less so on larger data sets (not shown today)
  - better performance when multiple parameter-SNP associations (not shown today)
- Bayesian appr. performance not yet competitive
  - other indicator model selection (Gibbs variable selection, Stochastic search variable selection)
  - shrinkage priors (Laplacian, Horseshoe)
  - other MCMC algorithms (HMC in the rstan package)

PECAN ANRS 12154 (Dr AM Taburet and Prof D Haas)



- 129 patients on up to 3 occasions with 196 markers

Chromosome	3	7		19	
Gene	*NR1I2* (PXR)	ABCB1 (P-gp)	*CYP3A5*	*CYP3A4*	*CYP2A6*	*CYP2B6*
Number of markers	49	63	1	36	1	47

- 218 missing SNP with a maximum of 7 per subject

Analyses

- One compartment with 1st-order absorption and elimination
- Inter-individual and -occasion variability on CL/F
  - adjustment on CYP2B6 G516T (rs3745274)

1 Stepwise procedure
  - missing data removed

2 Indicator Model selection using `R2jags`
  - missing data imputed using observed allele frequency

2 Horseshoe shrinkage prior using `Rstan` (Piironen et al. 2017)

$$\beta_j|\lambda_j,\tau \sim N(0,\lambda_j^2\tau^2)$$
$$\lambda_j \sim C^+(0,1) \text{ and } \tau \sim C^+(0, p0/[(N_{SNP}-p0)\sqrt{N}])$$

  - missing data imputed to most common genotype

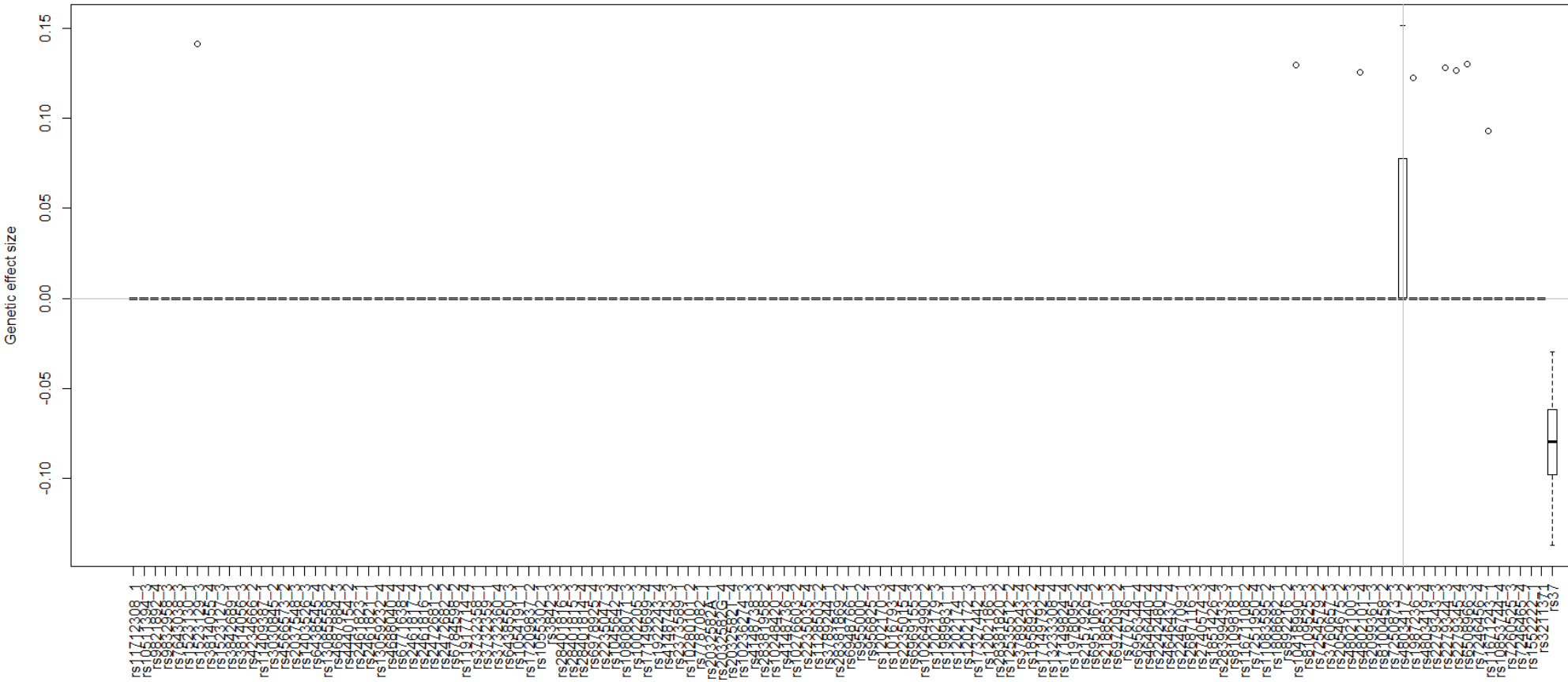
Stepwise procedure

Table 3 Multivariate linear regression for association between genetic variants and nevirapine clearance estimate

Variants	Gene	β	Statistic	P value
$n=129$ (all participants)				
rs3745274	*CYP2B6*	−1.606	−6.66	1.01×10^{-9}
rs2687116	*CYP3A4*	−1.913	−4.68	7.95×10^{-6}
rs2279343	*CYP2B6*	0.904	4.13	7.07×10^{-5}
rs7251950	*CYP2B6*	−0.499	−4.23	4.77×10^{-5}
$n=128$ (without outlier)[a]				
rs3745274	*CYP2B6*	−1.568	−7.66	6.78×10^{-12}
rs2279343	*CYP2B6*	0.835	4.50	1.66×10^{-5}
rs7251950	*CYP2B6*	−0.404	−4.01	1.09×10^{-4}
rs2032582A	*ABCB1*	0.456	3.60	4.73×10^{-4}

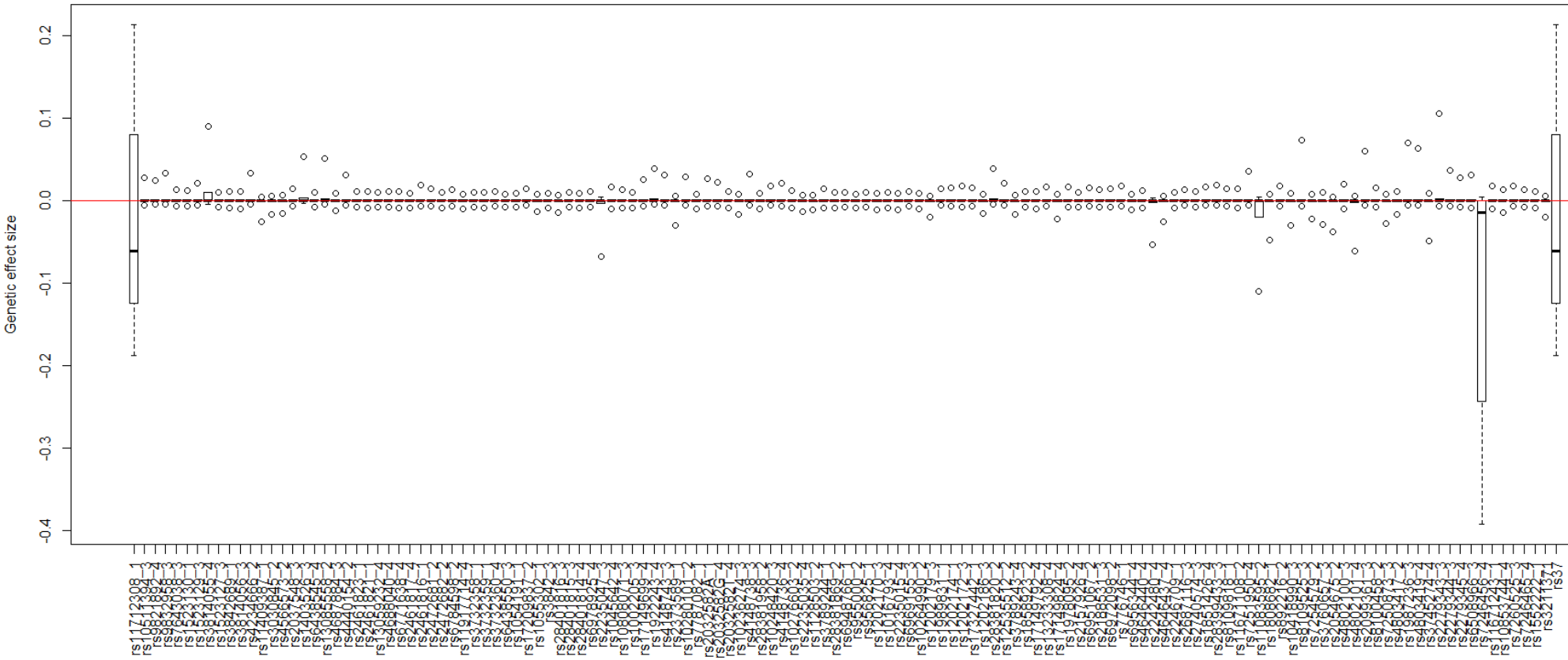
[a]Data from one individual outlier (extremely high) nevirapine clearance value were censored from this analysis.

Indicator model selection in R2jags



- n.chains=4, n.iter=5000, n.burnin=1000, n.thin=10
  $\text{Neff}_{CL/F} = 120$ / approx. 7 h

Horseshoe prior in Rstan



- n.chains=4, n.iter=1600, n.burnin=1600, n.thin=4
  Neff$_{CL/F}$ =1300 / approx. 1.5 h

Conclusions

- Similar model PK parameter estimates across methods
- No other snp associations, besides CYP2B6 G516T on CL/F, identified with Bayesian selection methods
- Rstan sampling marginally more efficient than R2jags
- Perspective
  - evaluate adaptive shrinkage in simulation study
  - application to HIV Swiss cohort and EARSII trial on diabetes data

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