Evaluation of methods in gene association studies: yet another case for Bayesian networks

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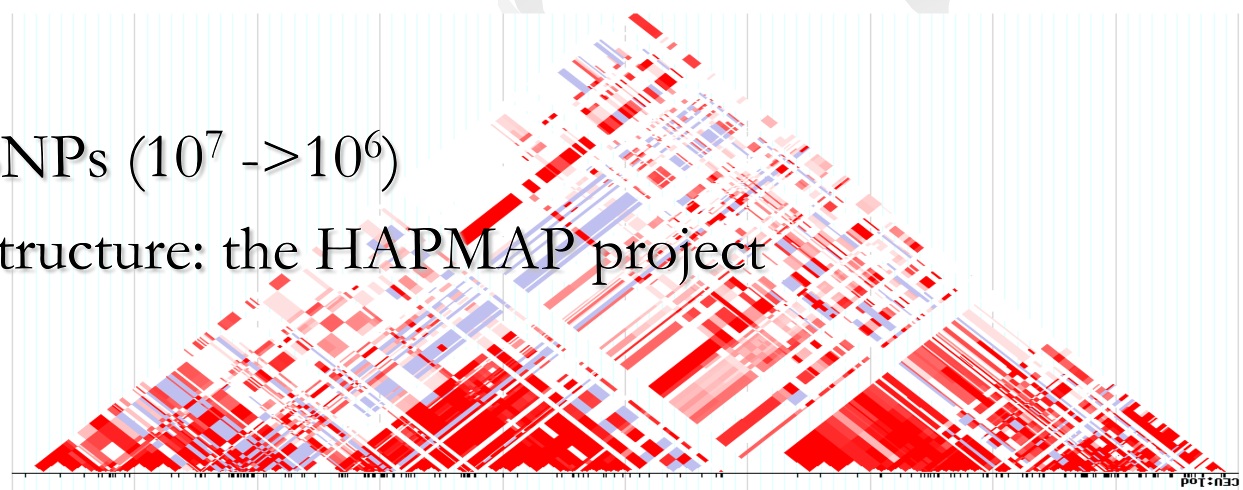
- Genetic association studies (GAS)
- A Bayesian approach to GAS
- Bayesian networks in GAS
- Evaluation of methods

Motivation: Exploring the variome

- Variome
  - Single-Nucleotide Polymorphisms (SNPs)
  - Copy-Number Variations (CNVs).
  - Genome rearrangements
  - Methylome

- SNPs
  - Number of SNPs (10^7 -> 10^6)
  - Correlation structure: the HAPMAP project



GAS phases

PGAS Data analysis → confirmations refutations

384x48 PGAS s_{11}	384x48 PGAS s_{12}	384x48 PGAS s_{13}

Study design → SNP datasets

GWAS Data analysis → candidate regions. genes

Genome wide association study (GWAS)

GAS Facts

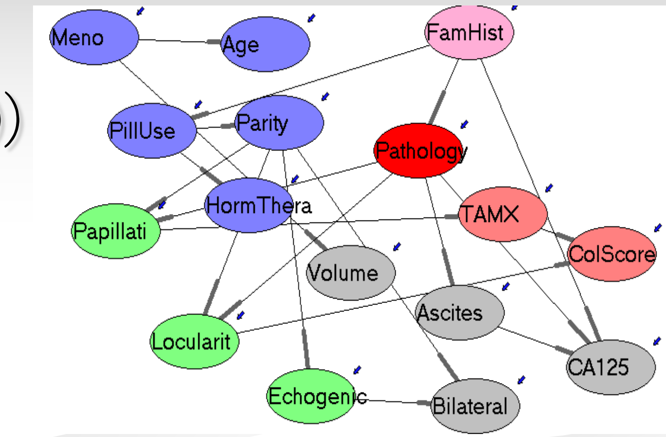
- Publications: ~40K
- SNPs on plate: 100K-2M
- Sample size: 30K
- Number of gene association studies
  - GWAS: ~100
  - PGAS-: ~10K
- Confirmed associations:
  - <1000
  - Small attributable risk
- Why?
  - Common disease – common variance hypothesis - **multifactorial diseases**, many weak interactions
  - Rare haplotype hypothesis (Minor allele freq. <1%)

Current challenge: the discovery of epistasis

- Statistical epistasis: non-linear interaction of genes
- The goal is the exploration of…
  - explanatory variables of the target variable(s)
  - the interaction of explanatory variables
- Genetic association concepts can be formalized (partially) as machine learning concepts and as Bayesian network concepts

The model class: Bayesian networks

- directed acyclic graph (DAG)
  - nodes – domain entities
  - edges – direct probabilistic relations
- conditional probability models P(X|Pa(X))
- interpretations:

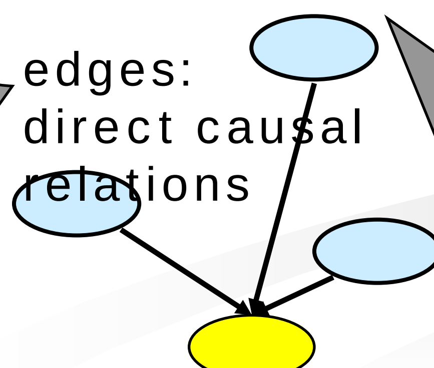


effective representation of the distribution

$$P(X_1,..X_N) = \prod_{i=1}^{N} P(X_i \mid Pa(X_i))$$

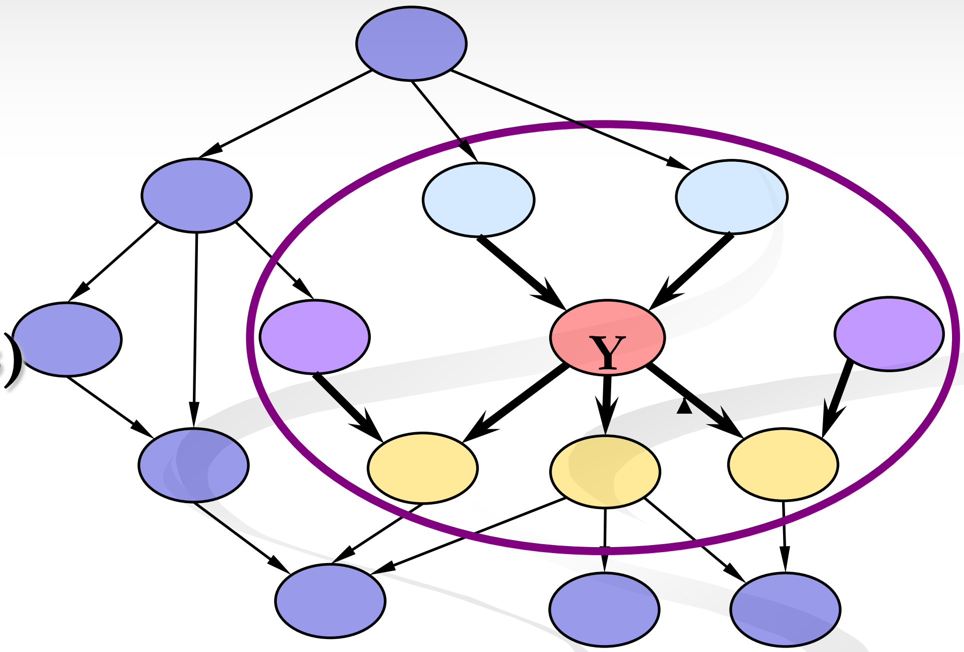
DAG structure: dependency map (d-separation)

edges: direct causal relations



Bayesian network features representing relevance

- **Markov Blanket (sub)Graphs (MBGs)**
  - (1) parents of the node
  - (2) its children
  - (3) parents of the children



- **Markov Blanket Sets (MBSs)**
  - the set of nodes which probabilistically isolate the target from the rest of the model
- **Markov Blanket Membership (MBM)**
  - pairwise relationship

GA-to-BN

- (model-based) pairwise association➔ Markov Blanket Memberhsips (MBM)
- Multivariate analysis ➔ Markov Blanket sets (MB)
- Multivariate analysis with interactions ➔ Markov Blanket Subgraphs (MBG)
- Causal relations/models ➔ Partially directed Bayesian network (PDAG)

- **Hierarchy**
  - DAG=>PDAG=>MBG=>MB=>MBM

Advantages of GA-to-BN - 1

- **Strong relevance - direct association:** Clear semantics and dedicated goal for the explicit. faithful representation of strongly relevant (e.g. non-transitive) relations
- **Graphical representation**: It offers better overview of the dependence-independence structure. e.g. about interactions and conditional relevance.
- **Multiple targets:** It inherently works for multiple targets.

Advantages of GA-to-BN – 2

- **Incomplete data:** It offers integrated management of incomplete data within Bayesian inference.
- **Causality:** Model-based causal interpretation of associations
- **Haplotype level:** Offers integrated approach to haplotype reconstruction and association analysis (assuming unphased genotype data)

Challenges of applying BNs in GAS

- High computational complexity
- High sample complexity ➔ Bayesian statistics

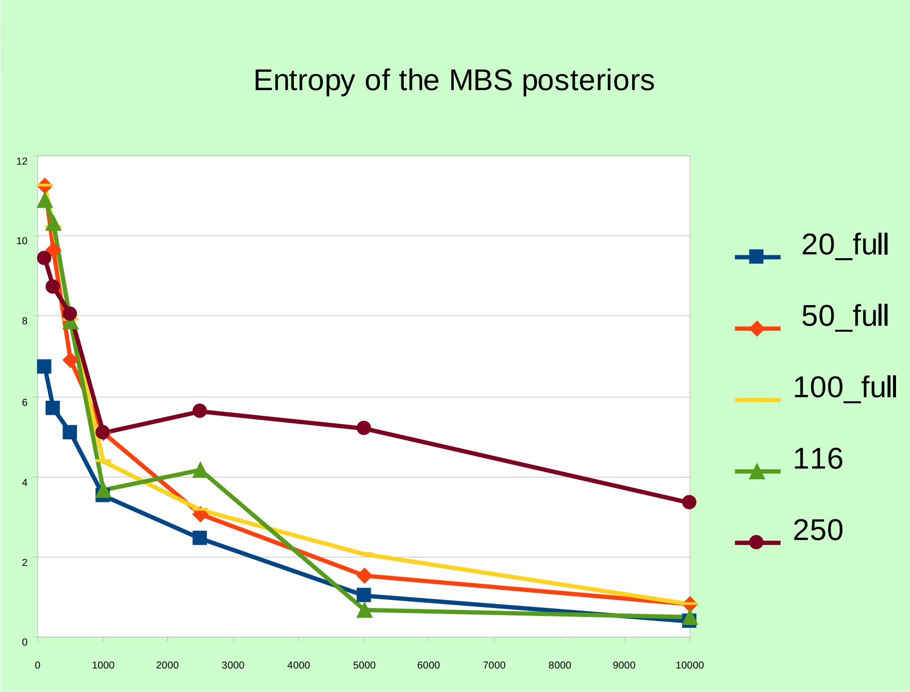
  ➔ Bayesian model averaging

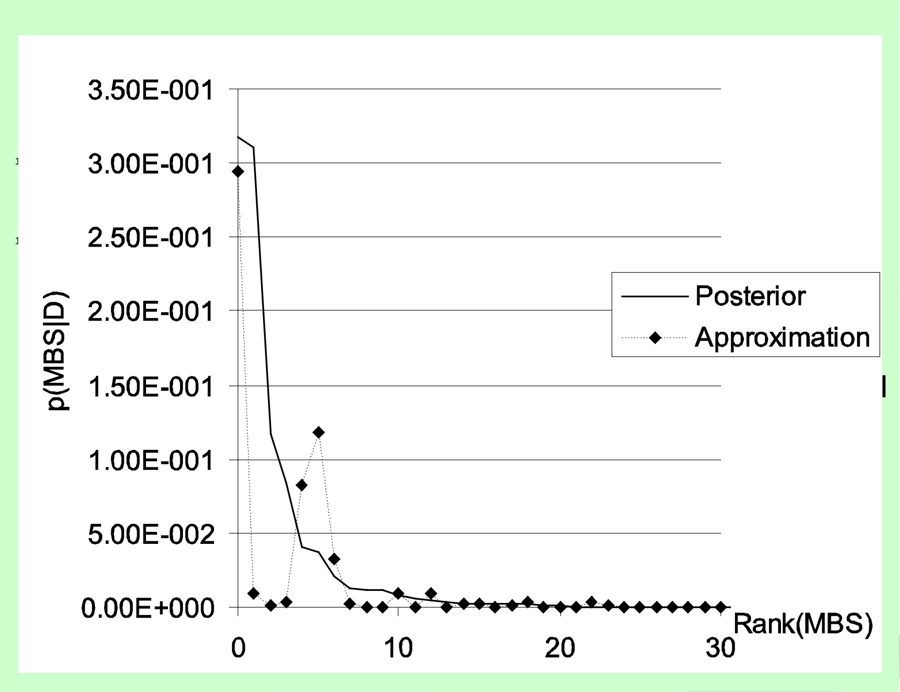
  ➔ Feature posterior

$$P(F = f) = \sum_{G:F^G = f} P(G)$$

- **Goal**: approximate the full-scale summation (integral)
- **A solution**: Metropolis coupled Markov chain Monte Carlo (MCMCMC)

Uncertainty in multivariate analysis





Advantages of the Bayesian framework

- **Automated correction for "multiple testing"**
  - The measure of uncertainty at a given level automatically indicates its applicability
- **Prior incorporation**: better prior incorporation both at parameter and structural levels.
- **Post fusion:** better semantics for the construction of meta probabilistic knowledge bases
- **Normative uncertainty for model properties** (cf. bootstrap)

The basis for comparison

Our approach is a model based exploration of the underlying structure

(note: multiple targets, causal and direct aspects)

$\neq$

Prediction of class labels

Comparison of GAS tools

Dedicated GAS tools

- BEAM
- BIMBAM
- SNPAssoc
- SNPMstat
- Powermarker

General purpose FSS tools

- MDR
- Causal Explorer

…

Application domain: The genomic background of asthna

- moderate number of clinical variables (in the range of 50)
- hundreds of genotypic SNP variables for each patient
- thousands of gene expression measurements

Asthma

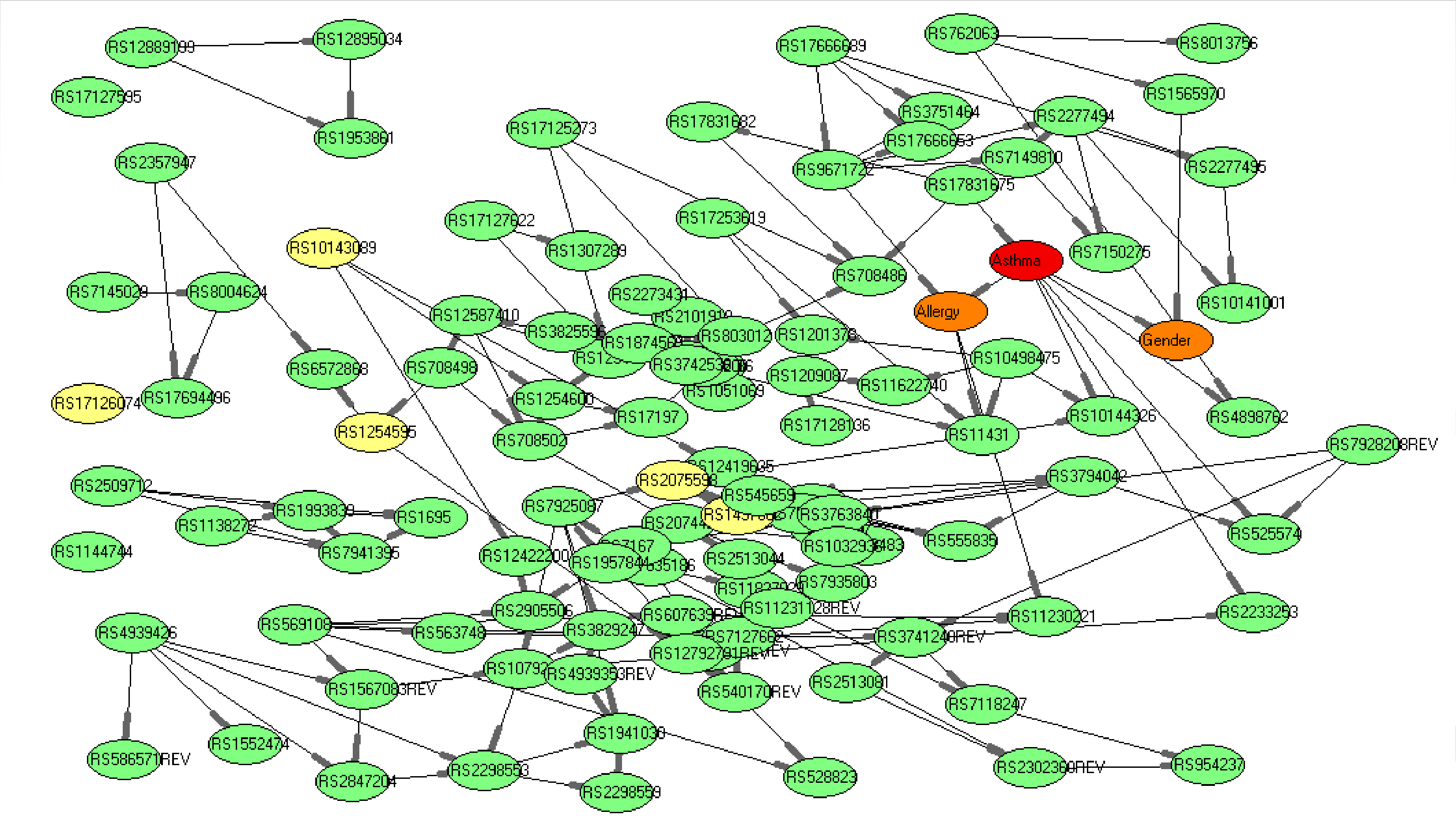
- Complex disease mechanism
- Half of the patients do not respond well to current treatments
- Unknown pathways in the asthmatic process

Evaluation on an artificial data set

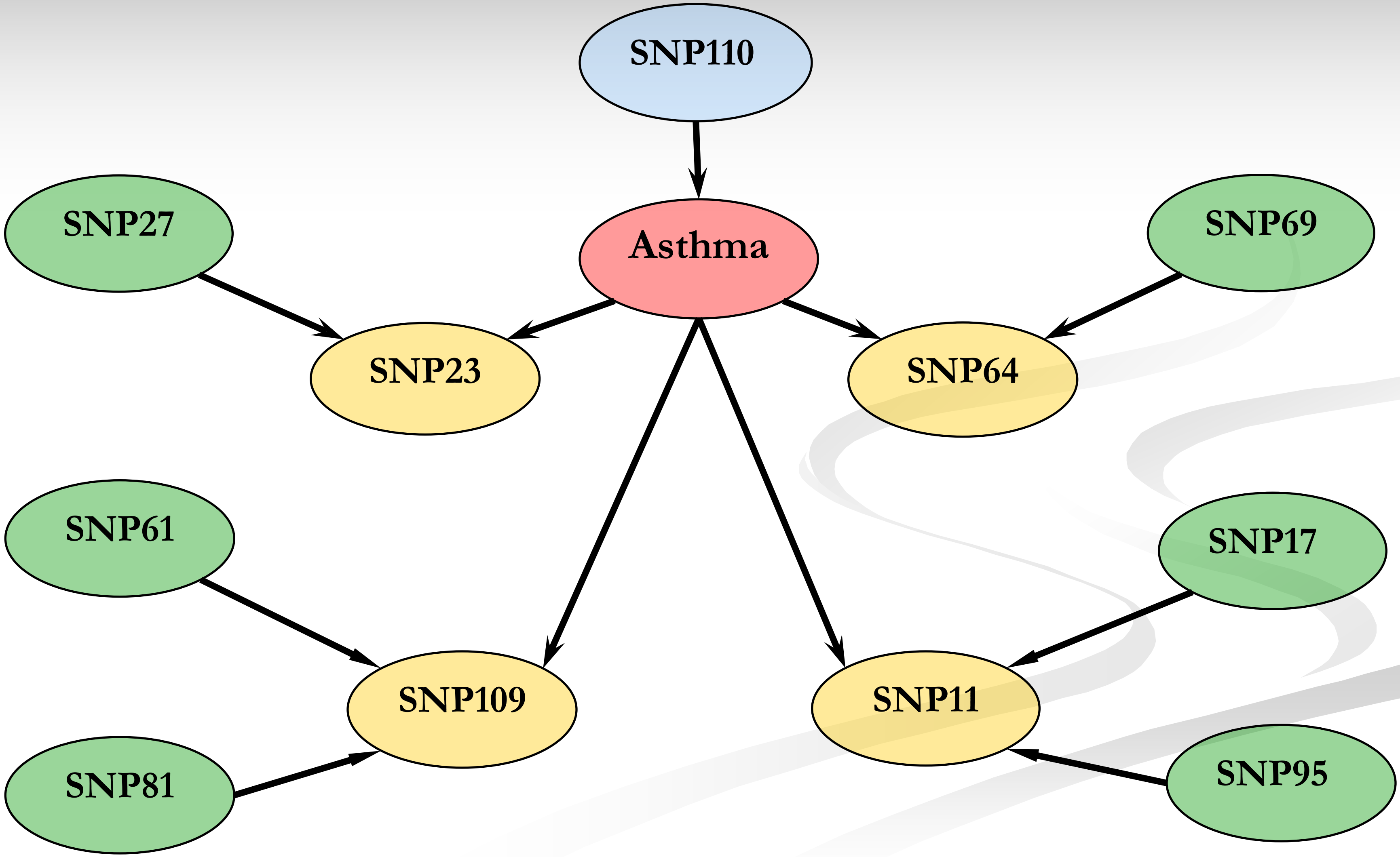
- Artificial model based on a real-world domain: the genomic background of asthma

- The real data set consists of:
  - 113 SNPs
  - 1117 samples

The reference model



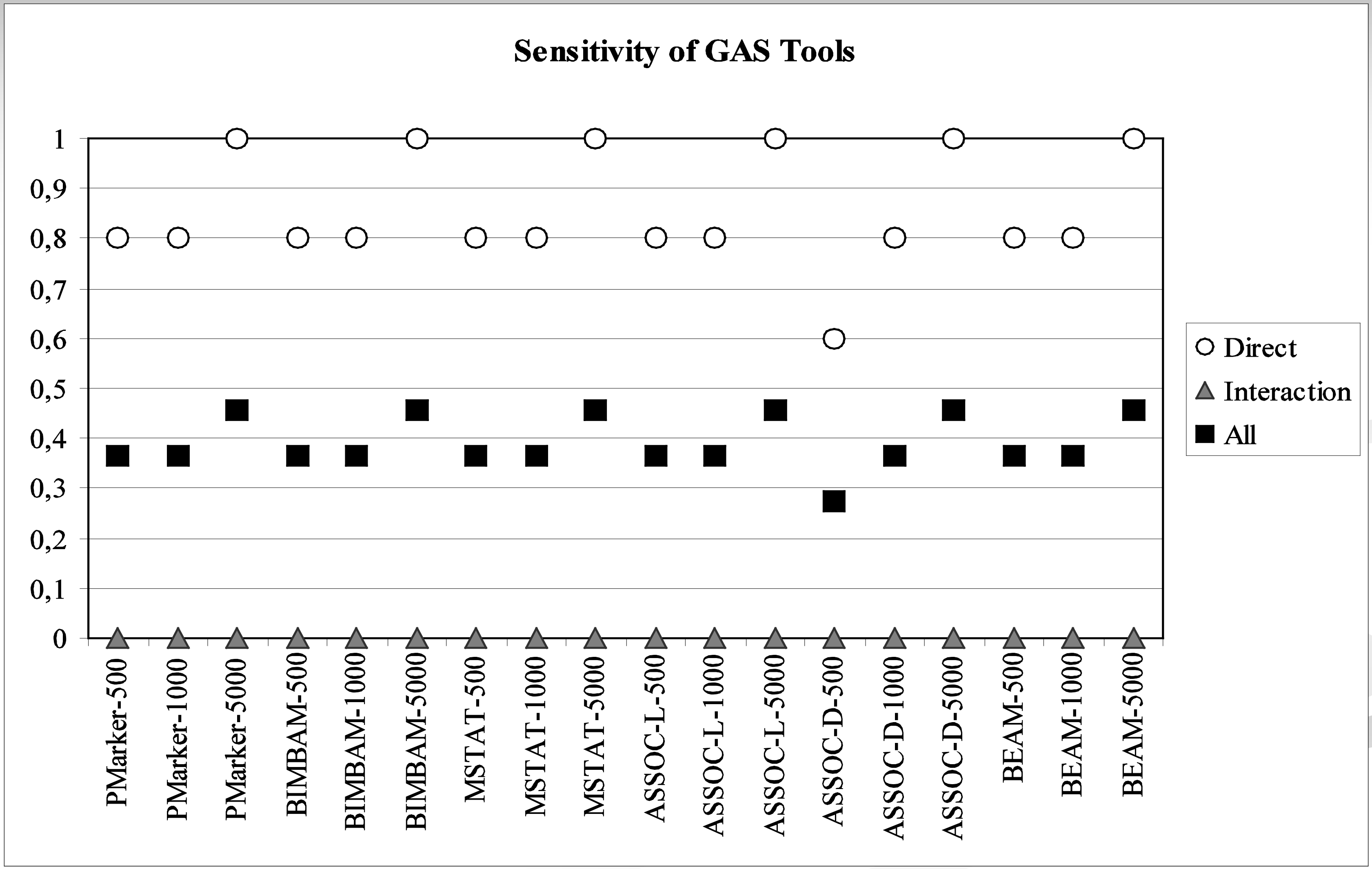
Reference MBG



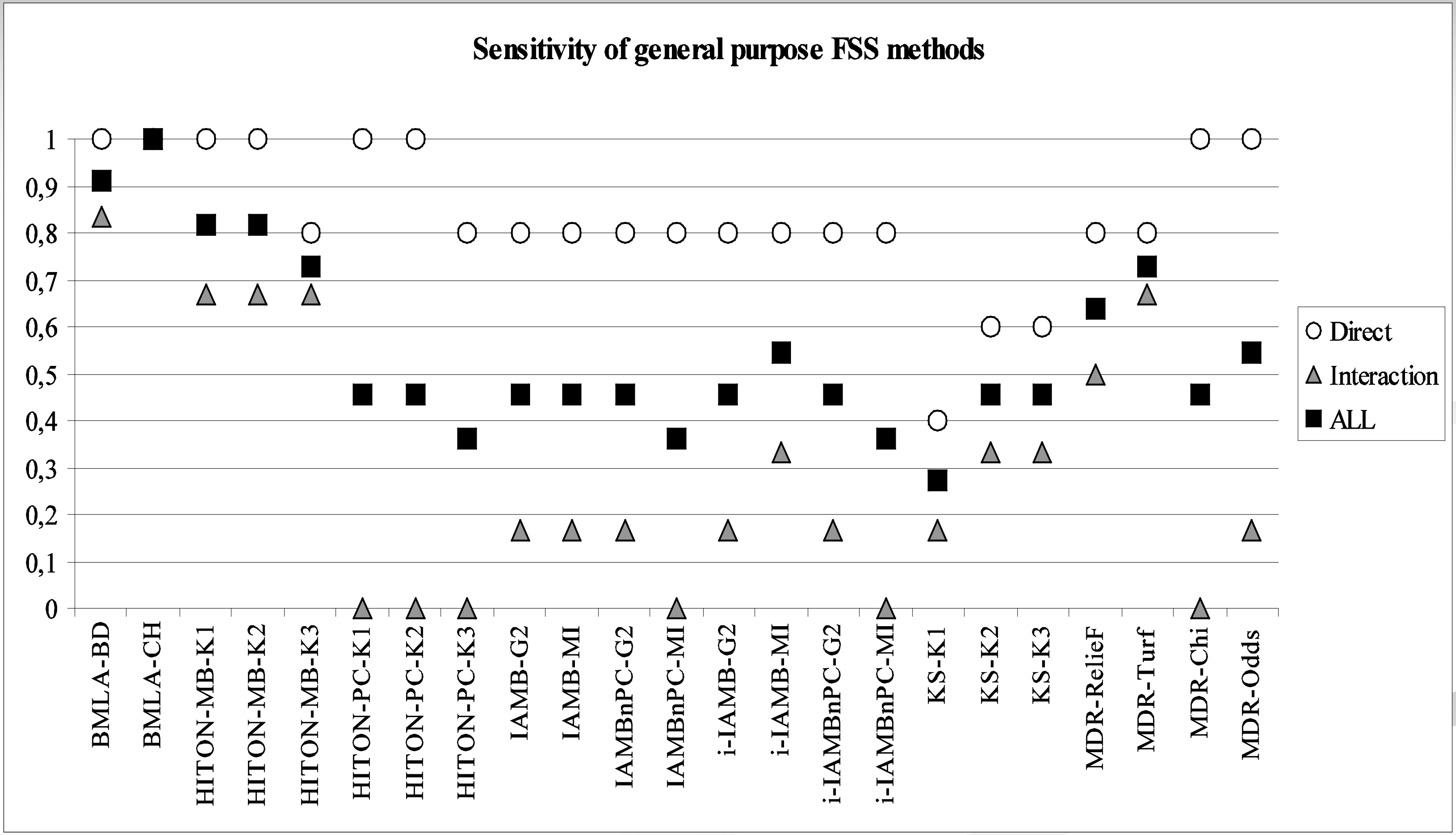
Results - 1

Software (Parameters)	Sensitivity	Specificity	Accuracy
BMLA (CH)	1	0.99	0.99115044
BMLA (BD)	0.92307692	1	0.99115044
HITON MB (k=1)	0.76923077	0.98	0.95575221
HITON MB (k=2)	0.76923077	0.99	0.96460177
HITON MB (k=3)	0.69230769	0.99	0.95575221
MDR – TurF	0.61538462	0.97	0.92920354
MDR – Relief	0.53846154	0.96	0.91150442
interIAMB (MI)	0.46153846	0.96	0.90265487

Results – 2.


Sensitivity of GAS Tools
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
PMarker-500
PMarker-1000
PMarker-5000
BIMBAM-500
BIMBAM-1000
BIMBAM-5000
MSTAT-500
MSTAT-1000
MSTAT-5000
ASSOC-L-500
ASSOC-L-1000
ASSOC-L-5000
ASSOC-D-500
ASSOC-D-1000
ASSOC-D-5000
BEAM-500
BEAM-1000
BEAM-5000
Direct
Interaction
All

Results – 3.



Sensitivity of general purpose FSS methods
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
BMLA-BD
BMLA-CH
HITON-MB-K1
HITON-MB-K2
HITON-MB-K3
HITON-PC-K1
HITON-PC-K2
HITON-PC-K3
IAMB-G2
IAMB-MI
IAMBnPC-G2
IAMBnPC-MI
i-IAMB-G2
i-IAMB-MI
i-IAMBnPC-G2
i-IAMBnPC-MI
KS-K1
KS-K2
KS-K3
MDR-RelieF
MDR-Turf
MDR-Chi
MDR-Odds
Direct
Interaction
ALL

Summary

- **General BN representation is feasible and gives superior performance for PGAS**
- **Bayesian statistics allows the quantification of applicability of BNs**
- Special extensions are necessary for
  - Multiple targets
  - Combined discovery of relevance and interactions (MBM, MBS, MBG)
  - Scalable multivariate analysis (k-MBS concept)
  - Feature aggregation

Antal et al.: A Bayesian View of Challenges in Feature Selection: Multilevel Analysis, Feature Aggregation, Multiple Targets, Redundancy and Interaction, JMLR Workshop and Conference Proceedings

Future work

- Specific local models (GA –specific local models)
- Integrated missing data management and GA analysis (cf. imputation)
- Noisy genotyping ➔ probabilistic data (see poster)
- Integrated haplotype reconstruction (see poster)
- Integrated study design and analysis (see poster)
- Scaling computation up to ~1000 variables