Predicting the functional consequences of amino acid polymorphisms using hierarchical Bayesian models

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- Protein structure and amino acid polymorphisms

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which folds spontaneously to a three-dimensional structure.

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  - introduces an hydrophobic patch on the surface of the molecule
  - major changes to its properties.
- Any nsSNP which disrupts structure is a strong candidate in disease/pharmacogenetic studies

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  - *structural* data: hydrophobicity, relative B factor, surface accessibility of native amino acid.
  - *sequence*-based data: conservation of native amino acid in table of multiple sequence alignment.

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- Lots of recent interest in this (Gunther *et al*, 2003; Stitziel *et al*, 2003; Wang and Moult, 2001; Terp *et al*, 2002; del Sol Mesa *et al*, 2003; Ng and Henikoff, 2002; Chasman and Adams, 2001; Sunyaev *et al*, 2000,2001; Saunders and Baker, 2002)

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- None of these use statistical models: we will build a probabilistic model for protein function.

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- We will train on the Lac repressor and validate on Lysozyme (and *vice-versa*).

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- *Lysozyme* molecule from T4 phage:
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  - Amino acids at 143 sites (out of 162) mutated to give a total of 1632 observations.

Predictive features used

Feature	*Description*
Accessibility	Solvent accessible area of native AA
Relative accessibility	Accessibility relative to maximum accessibility in training set
Relative phylogenetic entropy	Normalised phylogenetic entropy of native AA
Neighbourhood rel. phylogenetic entropy	Phylogenetic entropy of structural neighbourhood of native AA
Relative *B*-factor	Normalised *B*-factor of native AA
Neighbourhood relative *B*-factor	Normalised *B*-factor of structural neighbourhood of native AA
Unusual AA	Mutant AA is not in phylogenetic profile
Buried charge	Mutant is charged AA at buried site
Turn breaking	Mutant AA occurs at glycine or proline in a turn
Helix breaking	Mutant AA occurs in helical region and involves glycine or proline
Conserved	Native AA is at conserved position in phylogenetic profile

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Multivariate Adaptive Regression Splines

Extension of logistic regression, with logit$(p) = \eta$ where

$$\eta = \beta_0 + \sum_{k=1}^{K} \beta_k B_k(\mathbf{x})$$

with *basis functions* $B_k(\mathbf{x})$ defined as

$$B_k(\mathbf{x}) = \prod_{j=1}^{J_k} \left[s_{kj}(x_{w_{kj}} - t_{kj})\right]_+ \quad k = 1, \ldots, K$$

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The linear predictor of a MARS model is

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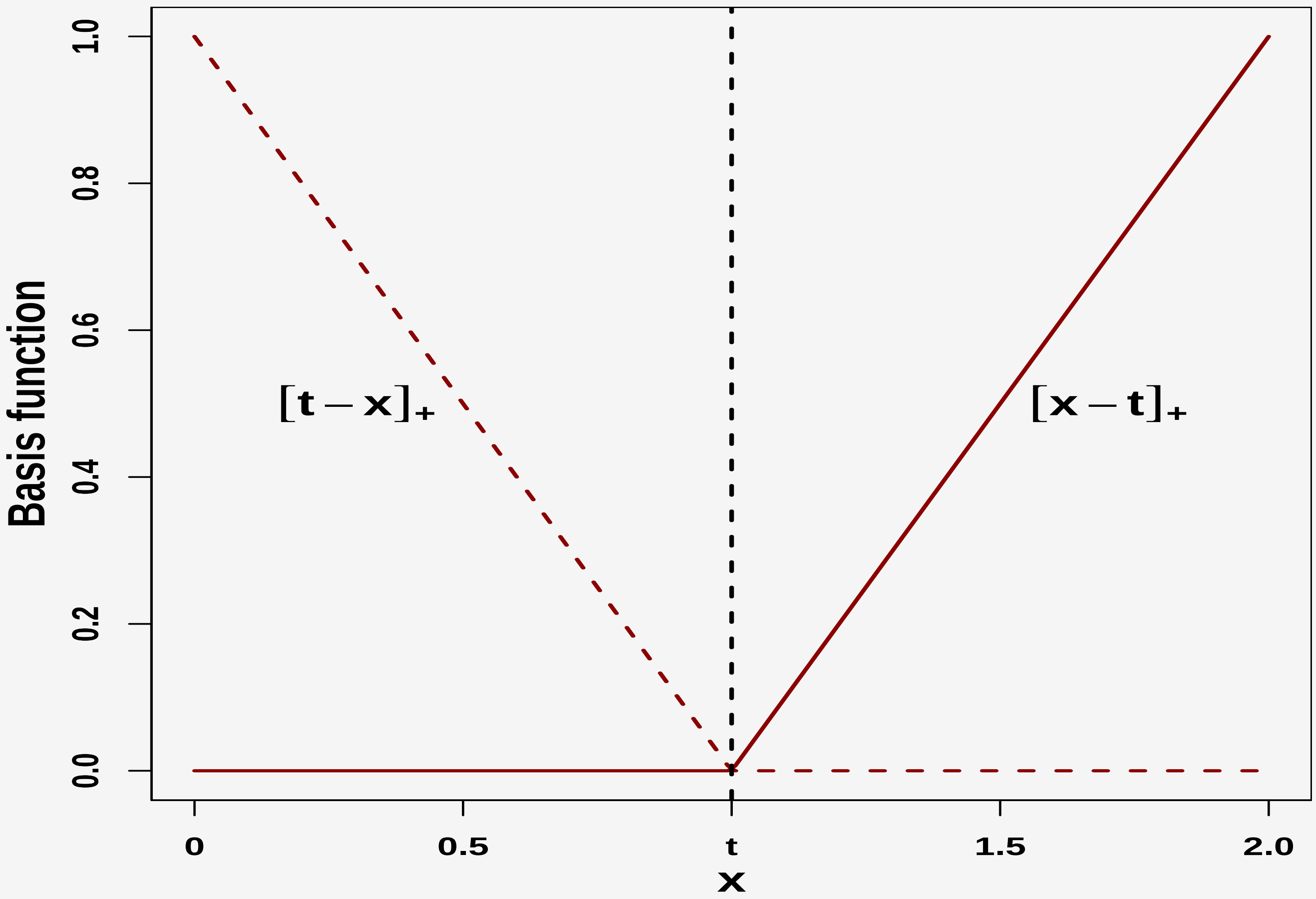

Example of MARS basis functions

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  - Uses Bayesian model averaging to make predictions
  - Fitted via MCMC

Hierarchical BMARS

- For amino acid site i and mutation m assume

$$p(y_{im} = 1|\boldsymbol{\beta}, \mathbf{x}_{im}, b_i) = \Phi\left(\beta_0 + \sum_{k=1}^{K} \beta_k B_k(\mathbf{x}_{im}) + b_i\right) = \Phi(\eta_{im}+b_i)$$

with $b_i \sim N(0, \sigma^2)$.

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- Reversible jump MCMC to add, delete or modify a basis function at each iteration.

Application to mutagenesis data

- Fitted values given by

$$\hat{y}_{new} = I\left[\frac{1}{N}\sum_{t=1}^{N}\Phi(\mathbf{B}^{(t)}(\mathbf{x}_{new})\boldsymbol{\beta}^{(t)}) > \alpha\right].$$

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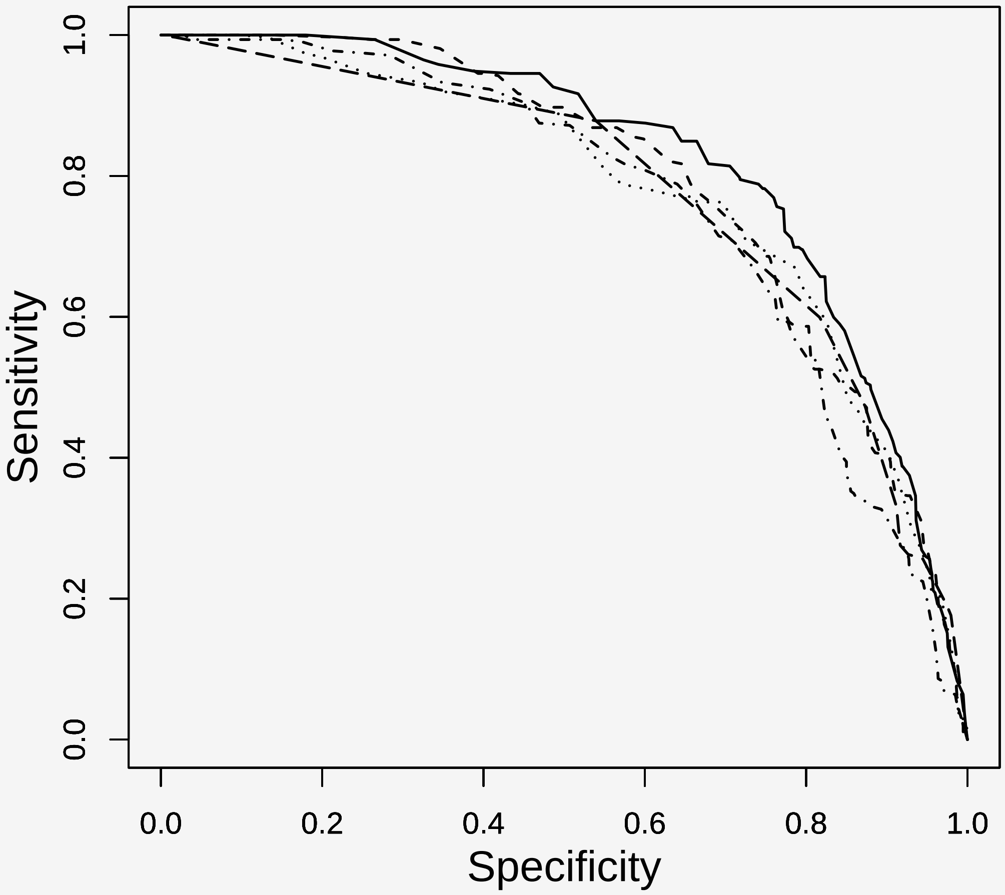
  - sensitivity: proportion of mutations affecting function correctly classified
  - specificity: proportion of mutations *not* affecting function correctly classified

Application to mutagenesis data

Train on Lac repressor/ Test on Lysozyme



— H-BMARS (0.82) - - BMARS (0.79) · · · MARS (0.78)

- · - SVM (0.76) – – Tree (0.77)

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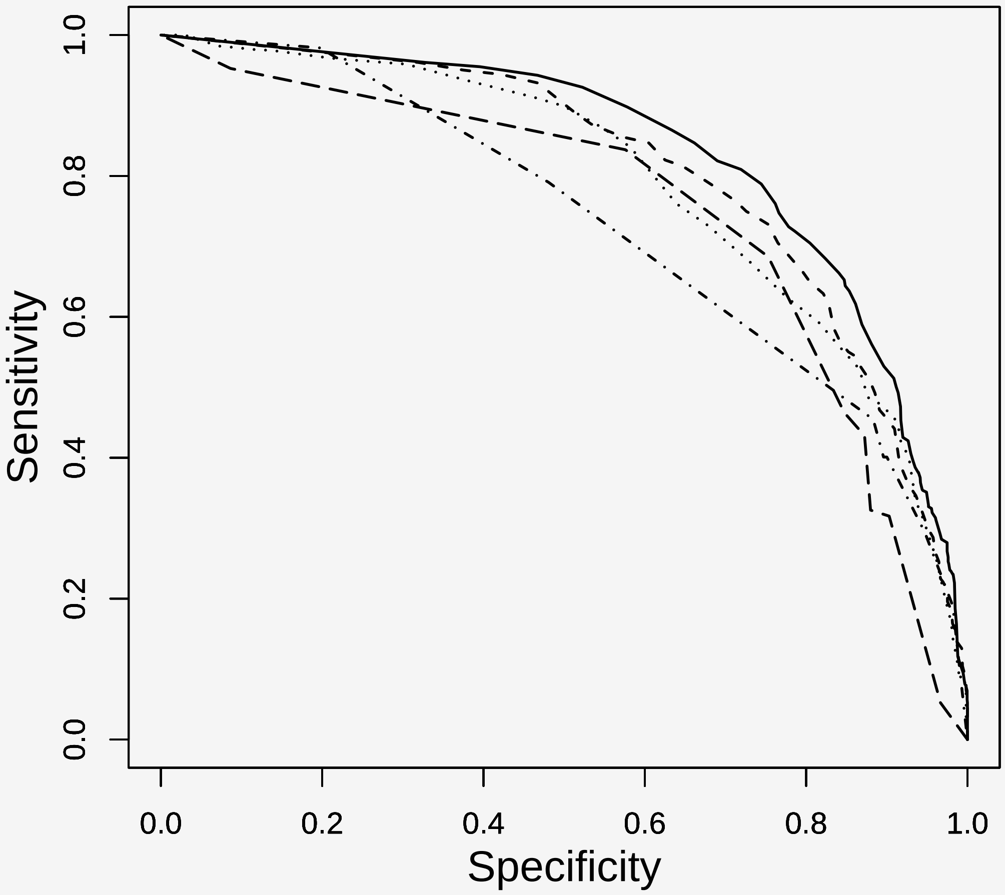

— H-BMARS (0.83)   - - BMARS (0.80)   · · · MARS (0.79)

- · - SVM (0.73)   – – Tree (0.75)

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- Current analysis uses the smoothest decision boundary leading to acceptable CV misclassification rate

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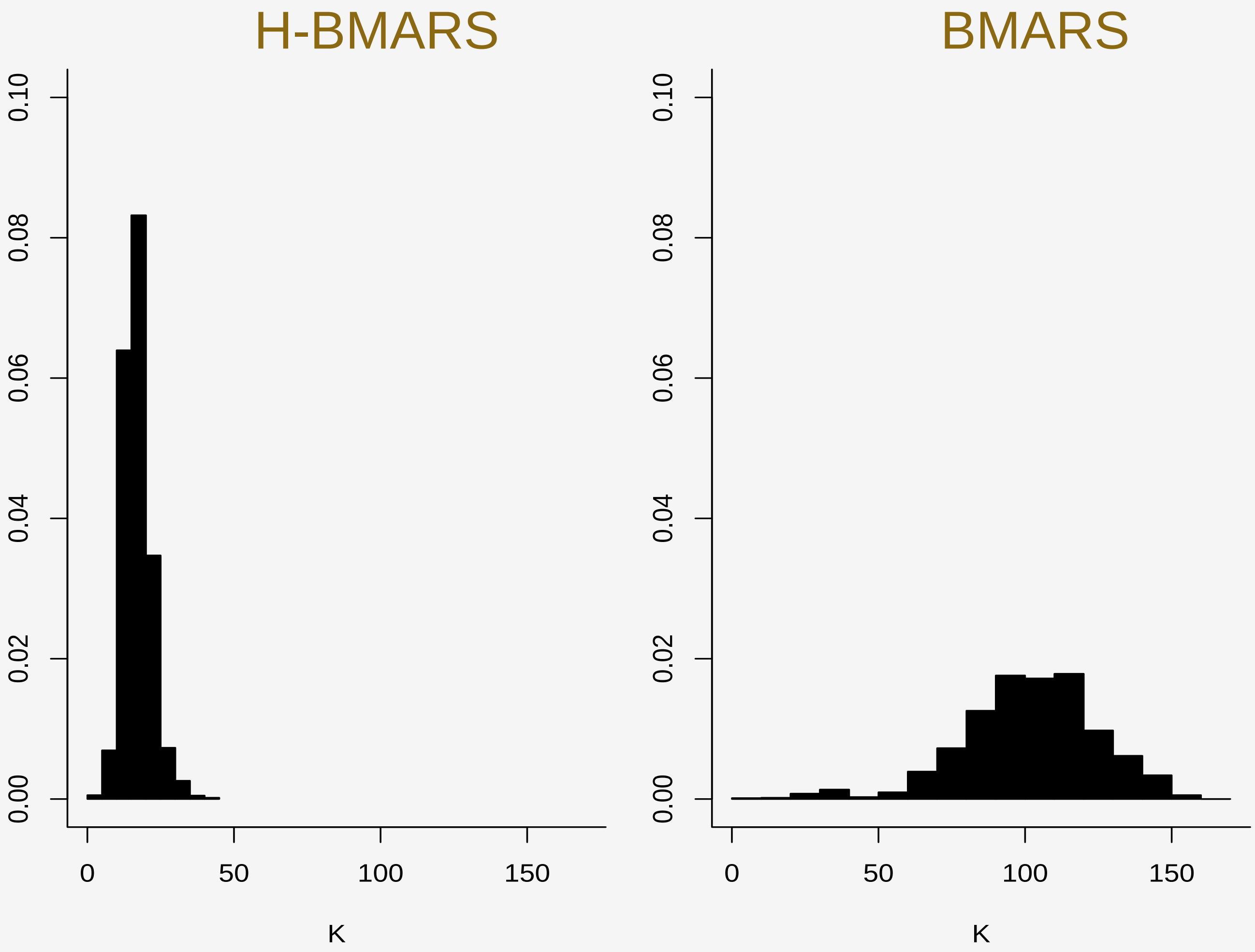

Posterior distribution of the number of basis functions

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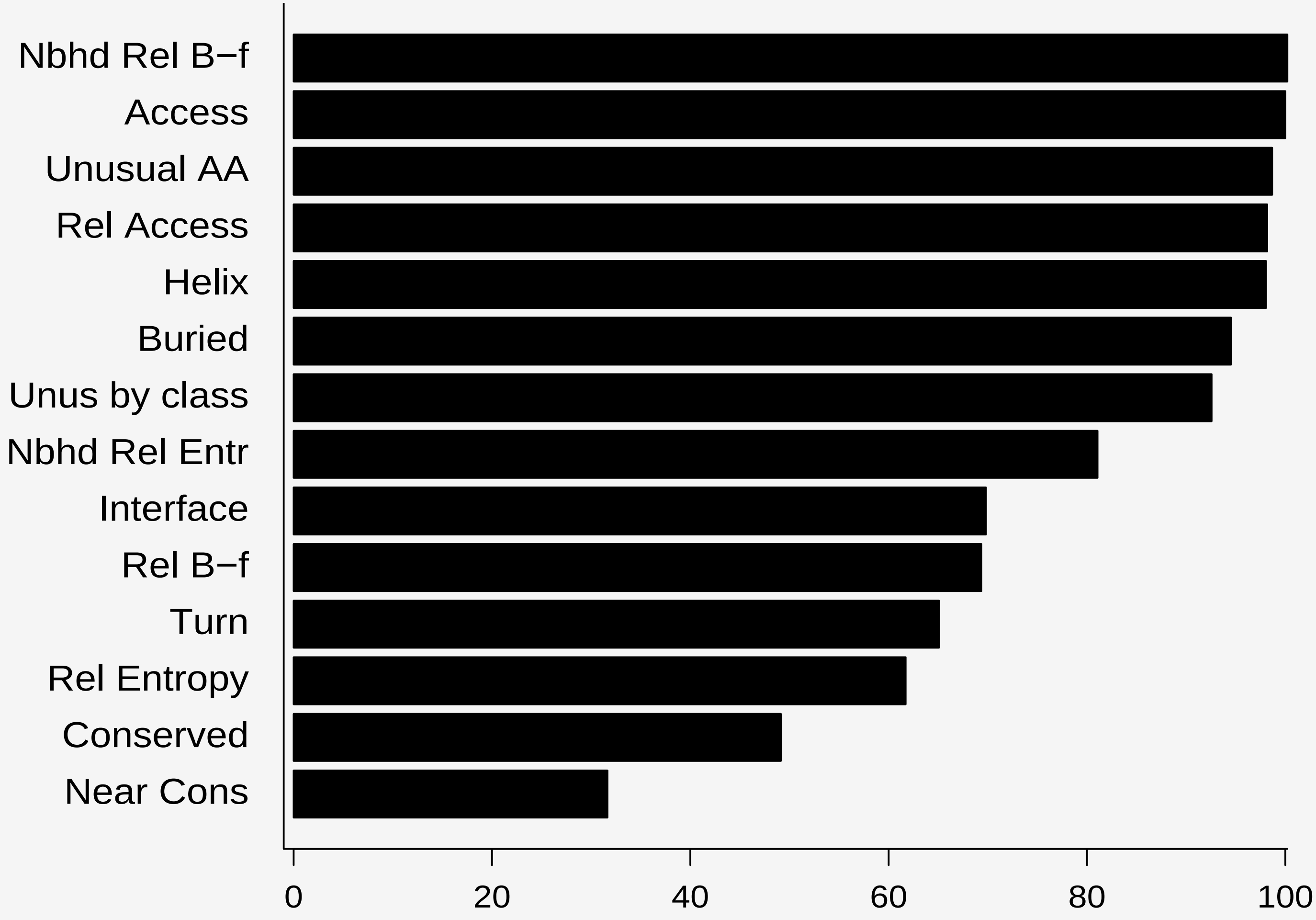

Relative importance of predictors in the generated sample

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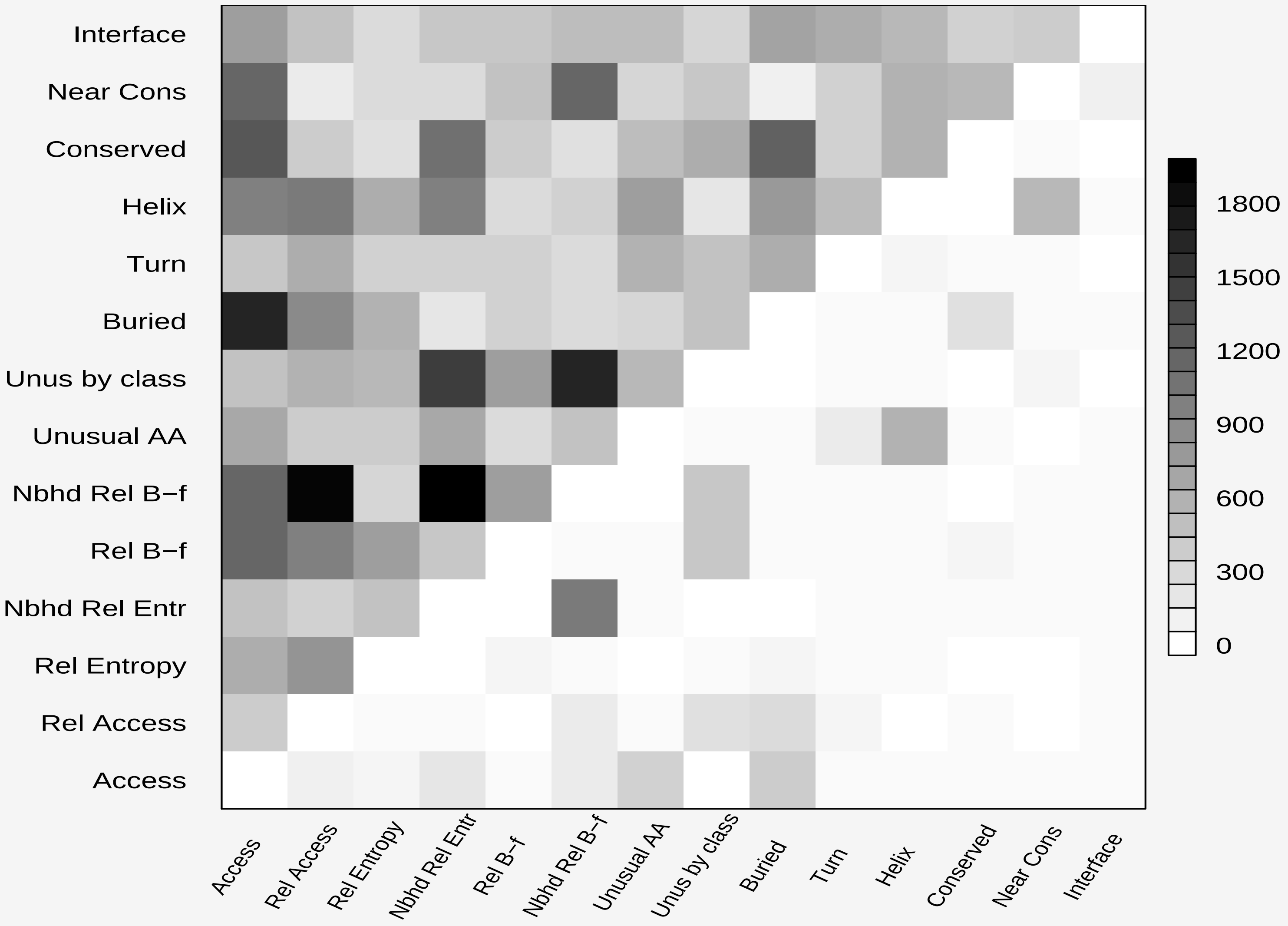

Interaction terms in the generated sample

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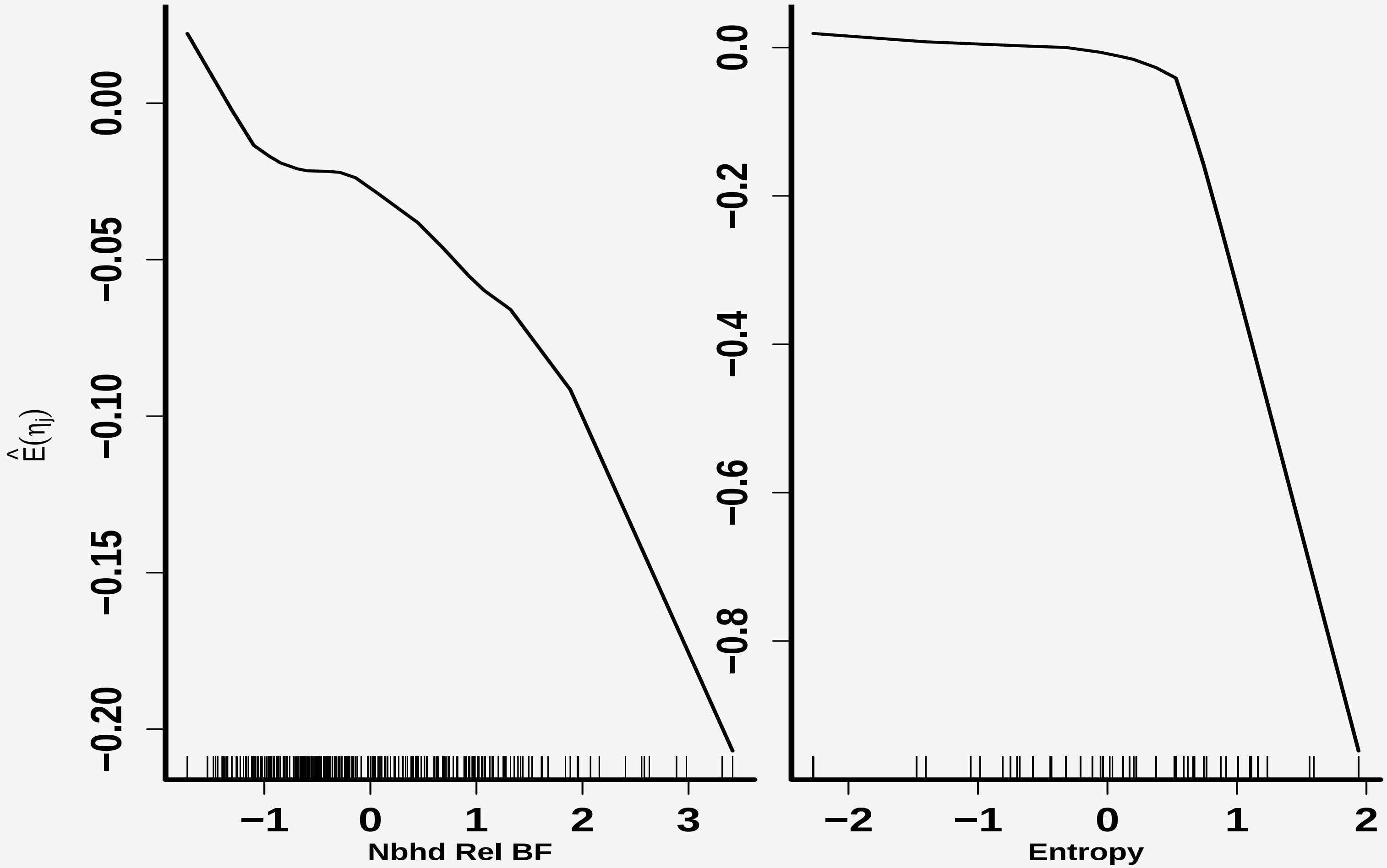
Application to mutagenesis data

The posterior main effect of generic predictor p may be quantified as

$$\hat{E}[\Phi_p(x)] = \frac{1}{L} \sum_{l=1}^{L} \sum_{\substack{k:J_k=1\\ w_{1k}=p}} \beta_k^{(l)} B_k^{(l)}(x)$$

from a posterior sample of size L.

Application to mutagenesis data



Posterior mean main effects (H-BMARS)

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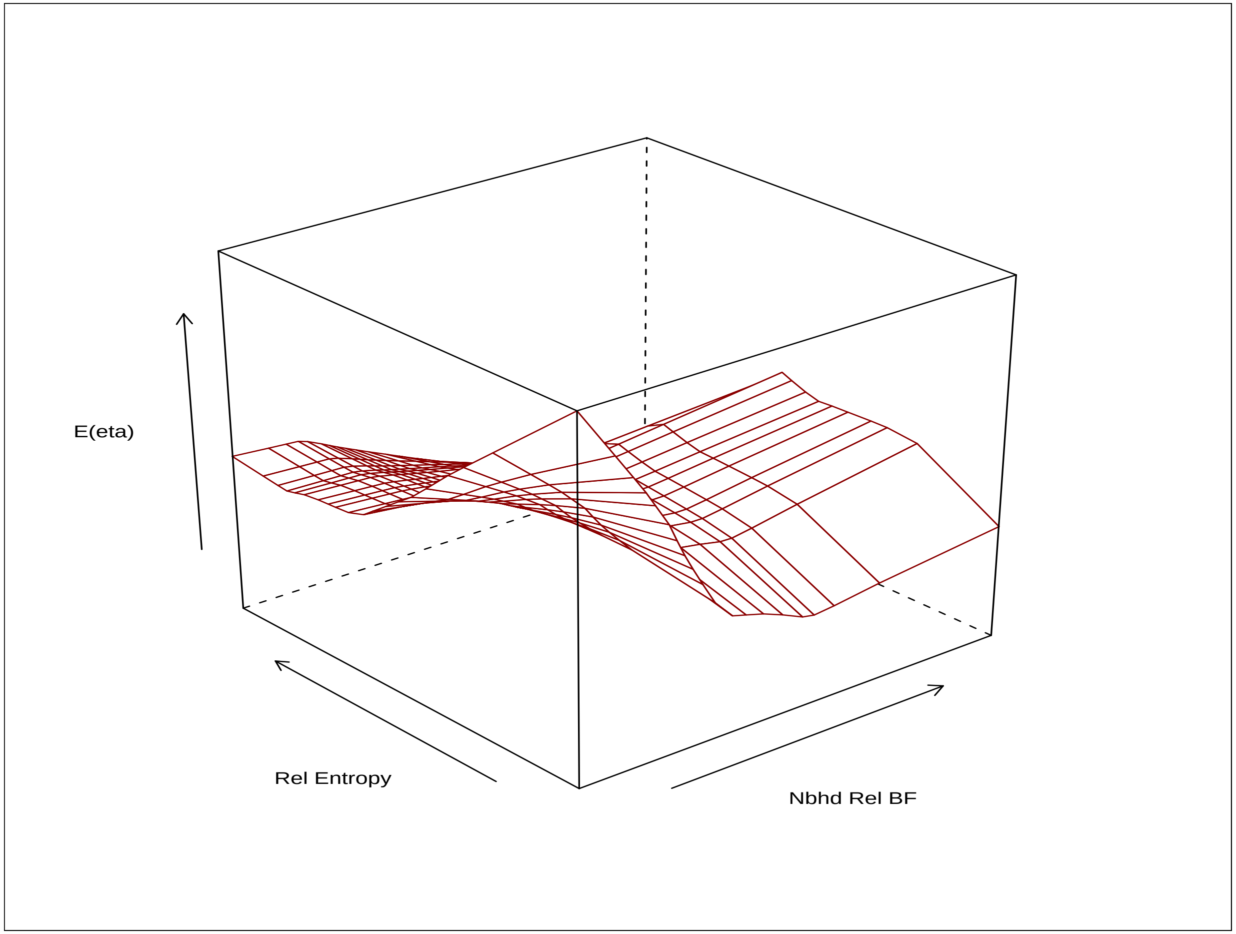

Posterior mean interaction between Entropy and Nbhd Rel BF

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- Solvent accessibility and molecular rigidity (B-factor) are good predictors of functionality.
- Code available as R package.

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- How useful is this?
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  - But functional biology is hard and expensive
  - Will nsSNPs disrupting function be interesting for genetic epidemiology/pharmacogenetics?