

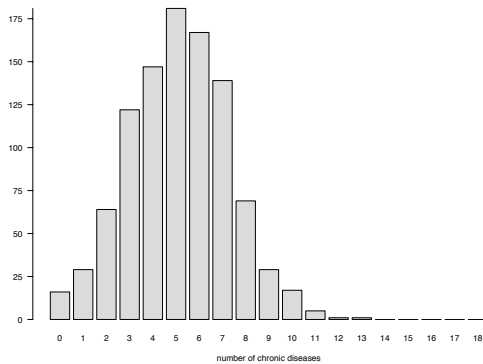
Logic Regression

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Example: The WHAS



Motivation

[Lucek and Ott]

“Current methods for analyzing complex traits include analyzing and localizing disease loci one at a time. However, complex traits can be caused by the interaction of many loci, each with varying effect.”

“... patterns of interactions between several loci, for example, disease phenotype caused by locus A and locus B, or A but not B, or A and (B or C), clearly make identification of the involved loci more difficult. While the simultaneous analysis of every single two-way pair of markers can be feasible, it becomes overwhelmingly computationally burdensome to analyze all 3-way, 4-way to N-way ‘and’ patterns, ‘or’ patterns, and combinations of loci.”

Example: The WHAS

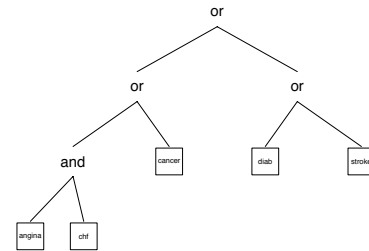
- The Women’s Health and Aging Study (WHAS) began in 1992 to study the causes and the course of disability in moderately to severely disabled older women living in the community.
- The WHAS is a population-based longitudinal study of women with at least mild disability, 65 years of age or older, living at home in eastern Baltimore city or county.
- 1002 women agreed to participate and provided written informed consent.
- The major chronic diseases at baseline were ascertained by using complex algorithms. Follow-up evaluations were conducted every 6 months for 3 years.
- There is evidence that disability results from chronic diseases, and that interactions between diseases (comorbidities) are of importance in causing disability.
- The chronic diseases recorder included cancer, congestion heart failure, diabetes, degenerative disc disease, hip fracture, myocardial infarction, arthritis, osteoporosis, Parkinson’s disease, pulmonary disease, stroke.

Reference: Fried LP et al (1999): Association of Comorbidity with Disability in Older Women: The Women’s Health and Aging Study, Journal of Clinical Epidemiology, 52 (1), pp 27-37.

Example: The WHAS

$$p = \Pr(\text{death in round } j \mid \text{survival to round } j-1, X, \text{age})$$

$$\text{logit}(p) = -9.01 + 0.06 \cdot \text{age} + 1.07 \cdot L(X)$$



Logic Regression

- X_1, \dots, X_k are 0/1 (False/True) predictors.

- Y is a response variable.

- Fit a model

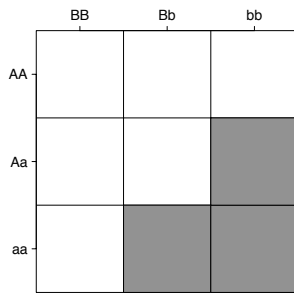
$$g(E(Y)) = b_0 + \sum_{j=1}^t b_j \cdot L_j$$

where L_j is a Boolean combination of the covariates, e.g. $L_j = (X_1 \vee X_2) \wedge X_3^c$.

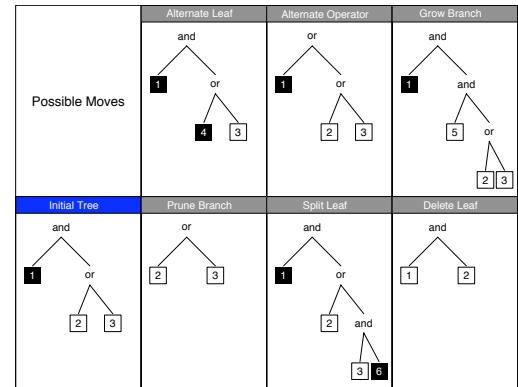
- Determine the logic terms L_j and estimate the b_j simultaneously.

	SNP X	X.R	X.D
• SNPs are usually coded as dominant and recessive:	AA	0	0
	AT	0	1
	TT	1	1

Double Penetrance Models



The Move Set for Logic Regression

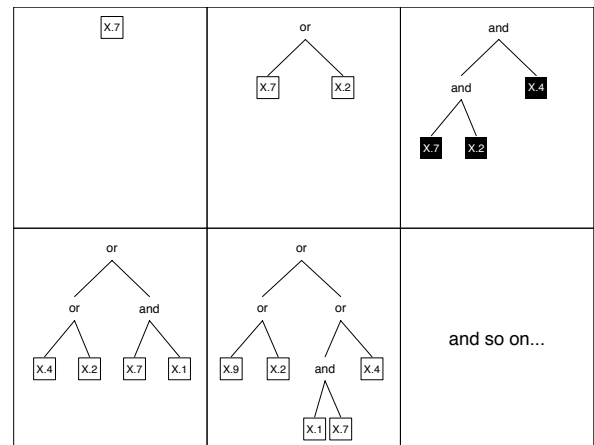


Simulated Annealing for Logic Regression

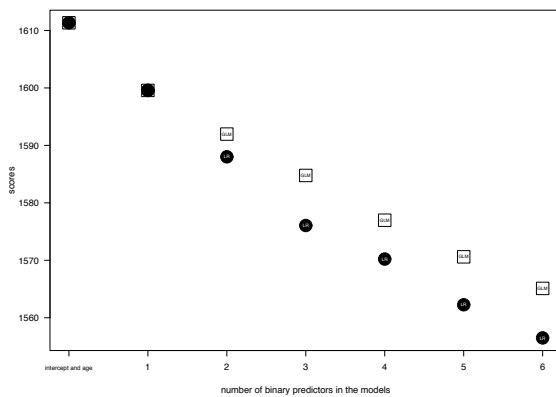
We try to fit the model $g(E(Y)) = b_0 + \sum_{j=1}^L b_j \cdot L_j$.

- Select a scoring function (RSS, log-likelihood, ...).
- Pick the maximum number of Logic Trees.
- Pick the maximum number of leaves in a tree.
- Initialize the model with $L_j = 0$ for all j .
- Carry out the Simulated Annealing Algorithm:
 - Propose a move.
 - Accept or reject the move, depending on the scores and the temperature.

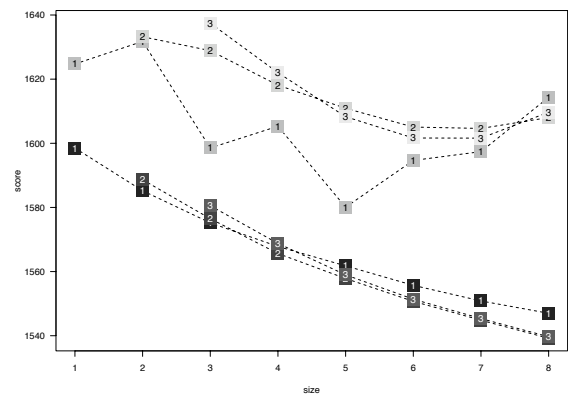
Growing Logic Models



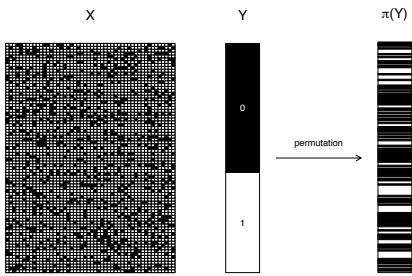
A Public Health Related Example



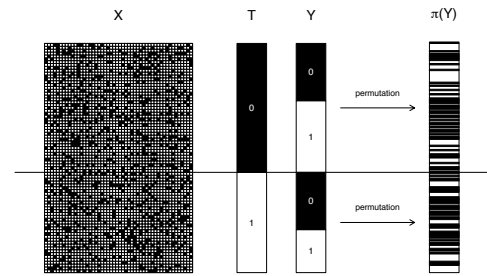
Model Selection 1 : Cross Validation



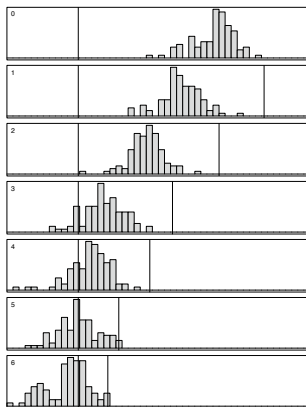
Model Selection 2 : Permutation Tests



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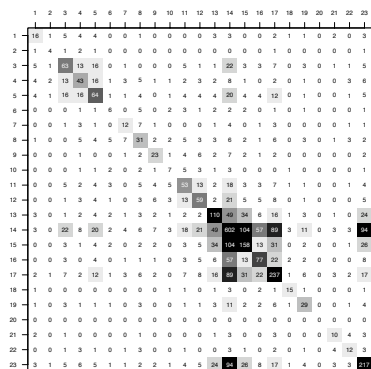
Example: The CHS

- The Cardiovascular Health Study is a study of coronary heart disease and stroke in elderly people.
- Between 1989 and 1993, 5888 subjects over the age of 65 were recruited in four communities in the United States.
- During 1992 and 1994, a subset of these patients underwent an MRI scan.
- For 3647 CHS participants, MRI detected strokes (infarcts bigger than 3mm that led to deficits in functioning) were recorded as entries into a 23 region atlas of the brain.
- The mini-mental state examination is a brief screening test for dementia. The response Y is a variable derived by transforming the mini-mental score.

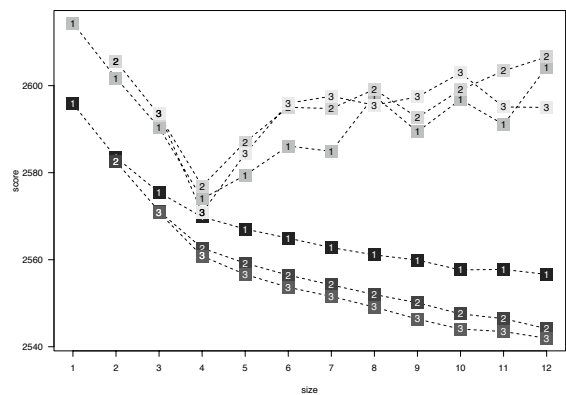
We investigated models of the form $Y = \beta_0 + \beta_1 \times L_1 + \dots + \beta_p \times L_p + \epsilon$.

Reference: Fried LP et al (1991): *The Cardiovascular Health Study: Design and Rationale*, Annals of Epidemiology 3, pp 263-276.

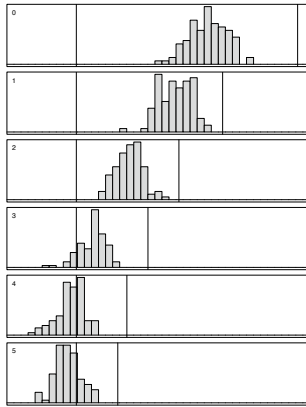
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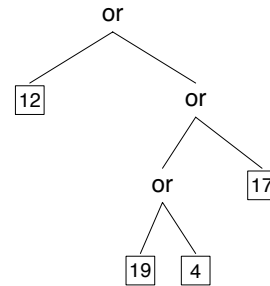


Example: The CHS



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The model we found was $Y = 1.96 + 0.36 \times L$ with the following Logic Tree:



Example: The CHS

Linear model:

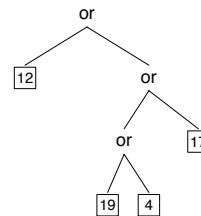
	$\hat{\beta}$	$se(\hat{\beta})$	t-value
Intercept	1.96	0.02	133.98
Region 4	0.52	0.13	4.06
Region 12	0.46	0.11	4.09
Region 17	0.24	0.06	4.17
Region 19	0.61	0.16	3.89

Example: The CHS

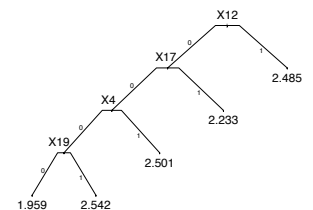
Logic model:

$$Y = 1.96 + 0.36 \times I_{\{X_4 \vee X_{12} \vee X_{17} \vee X_{19} \text{ is true}\}}$$

Logic Tree



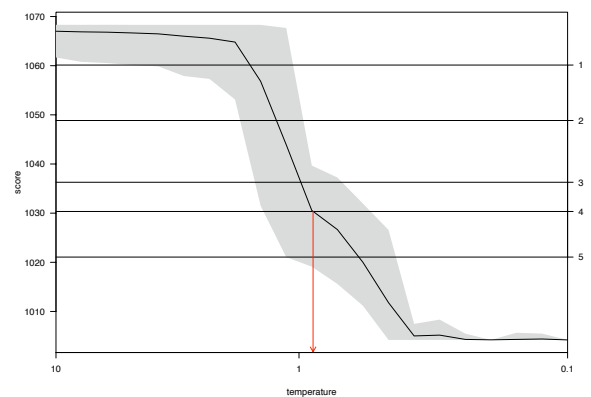
CART Tree



Multiple Models 1 : Monte Carlo LR

- Goal: identify all models and combinations of covariates that are potentially associated with the outcome.
- Use reversible jumps to implement an MCMC algorithm with priors on models and model size.
- The prior on model size does influence the total number of SNPs selected.
- The prior on model size has virtually no influence on the relative ordering of the SNPs or combinations thereof.

Multiple Models 2 : Metropolis-Hastings



Multiple Models 2 : Metropolis-Hastings

Let γ_S be the score of a certain state S .

- We use the acceptance function

$$\alpha(\gamma_{old}, \gamma_{new}, t) = \min\{1, \exp([\gamma_{old} - \gamma_{new}]/t)\}$$

- If we keep the temperature constant, this defines a homogeneous Markov chain.
- We constructed the move set to be irreducible and aperiodic, therefore each homogeneous Markov chain has a limiting distribution $\pi_t(S)$.
- If we know the model size where the signal ends and the noise starts, we can read off the corresponding temperature from the diagnostic plot!

Multiple Models 2 : Metropolis-Hastings

Example: Simulate 10 binary predictors X_1, \dots, X_{10} .

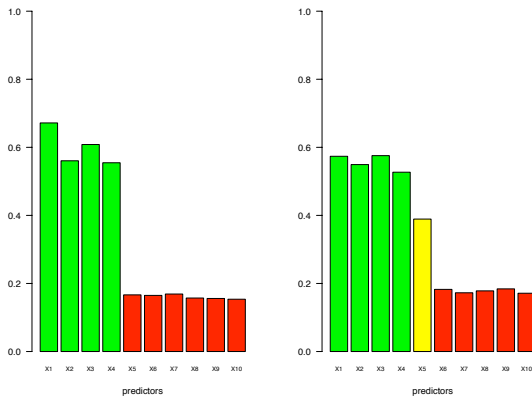
Let $Y = 5 + 1 \times L(X_1, X_2, X_3, X_4) + \epsilon$, $\epsilon \sim N(0,1)$.

Run a homogeneous Markov chain during “crunch time” for two separate cases:

Case 1 All X are independent.

Case 2 All X are independent, except X_4 (in the signal) and X_5 (not in the signal), which are heavily correlated.

Multiple Models 2 : Metropolis-Hastings



Multiple Models 2 : Metropolis-Hastings

