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

```
\begin{itemize}
  \item 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.
  \item 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.
  \item 1002 women agreed to participate and provided written informed consent.
  \item The major chronic diseases at baseline were ascertained by using complex algorithms. Follow-up evaluations were conducted every 6 months for 3 years.
  \item There is evidence that disability results from chronic diseases, and that interactions between diseases (comorbidities) are of importance in causing disability.
  \item 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.
\end{itemize}
```


Logic Regression

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```
\begin{itemize}
  \item $X_1, \ldots, X_n$ are 0/1 (False/True) predictors.
  \item $Y$ is a response variable.
  \item Fit a model
    \[ g(E(Y)) = b_0 + \sum_{j=1}^{l} b_j \cdot L_j, \]
    where $L_j$ is a Boolean combination of the covariates, e.g. $L_j = (X_1 \lor X_3) \land X_7^c$.
  \item Determine the logic terms $L_j$ and estimate the $b_j$ simultaneously.
\end{itemize}
```

<table>
<thead>
<tr>
<th>SNP</th>
<th>X</th>
<th>X.R</th>
<th>X.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>AT</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Example: The WHAS

```
p = Pr(death in round j | survival to round j-1, X, age)
logit(p) = -9.01 + 0.06 \cdot age + 1.07 \cdot L(X)
\begin{align*}
  \text{angina} & \quad \text{chf} \\
  \text{or} & \quad \text{or} \\
  \text{and} & \quad \text{or} \\
\end{align*}
```

Logic Regression

- $X_1, \ldots, X_n$ are 0/1 (False/True) predictors.
- $Y$ is a response variable.
- Fit a model
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Simulated Annealing for Logic Regression

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

- 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

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 $Y = \beta_0 + \beta_1 \times L_1 + \cdots + \beta_p \times L_p + \epsilon$.

Example: The CHS

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

```
  or
  12
  or
  17
  or
  19
  4
```

---

Example: The CHS

Linear model:

<table>
<thead>
<tr>
<th>$\hat{\beta}$</th>
<th>$\text{se}(\hat{\beta})$</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.96</td>
<td>0.02</td>
</tr>
<tr>
<td>Region 4</td>
<td>0.52</td>
<td>0.13</td>
</tr>
<tr>
<td>Region 12</td>
<td>0.46</td>
<td>0.11</td>
</tr>
<tr>
<td>Region 17</td>
<td>0.24</td>
<td>0.06</td>
</tr>
<tr>
<td>Region 19</td>
<td>0.61</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Logic model:

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

MARS:

$Y = 1.96 + 0.53 X_4 + 0.37 X_{12} + 0.24 X_{17} + 0.61 X_{19} + 1.05 (X_{12} \ast X_{15})$

---

Example: The WHAS

```
> install.packages("LogicReg")
> library(LogicReg)
> myanneal=logreg.anneal.control(start=-1,end=-4,
iter=100000,update=1000)
> fit1=logreg(resp=y,bin=x,type=2,select=1,ntr=2,
anneal.control=myanneal)
> plot(fit1)
> myanneal2=myanneal
> myanneal2$update=0
> fit4=logreg(select=4,anneal.control=myanneal2,oldfit=fit1,nrep=100)
> plot(fit4)
> fit2=logreg(oldfit=fit1,select=2,ntr=c(1,2),nleaves=c(1,7),
anneal.control=myanneal2)
> plot(fit2)
> fit3=logreg(select=3,oldfit=fit2)
> fit5=logreg(select=5,oldfit=fit2,nrep=100)
```
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

Let $\gamma_S$ be the score of a certain state $S$.

- We use the acceptance function
  $$
  \alpha(\gamma_{new}, \gamma_{old}, \epsilon) = \min(1, \exp[\gamma_{new} - \gamma_{old}] / \epsilon)
  $$
- 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 $\gamma(S)$.
- 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!

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

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.