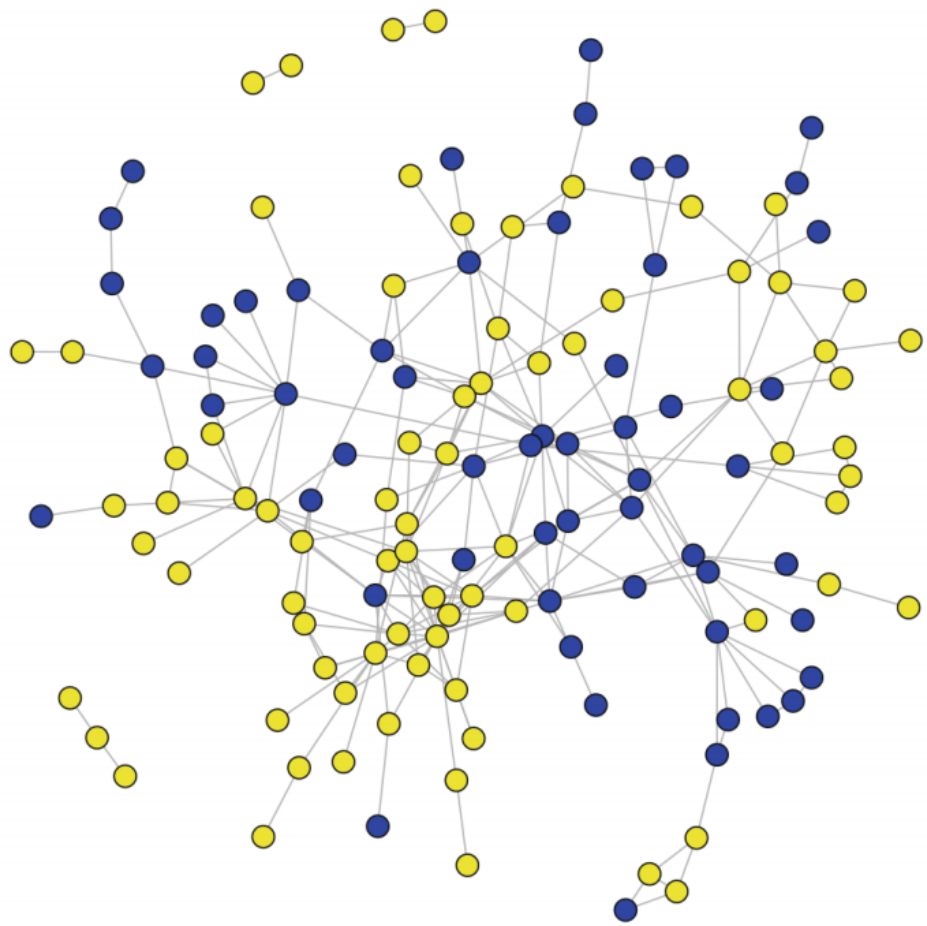
Vertex Property Prediction

Given graph structure and vertex attributes (x), predict target attribute of interest

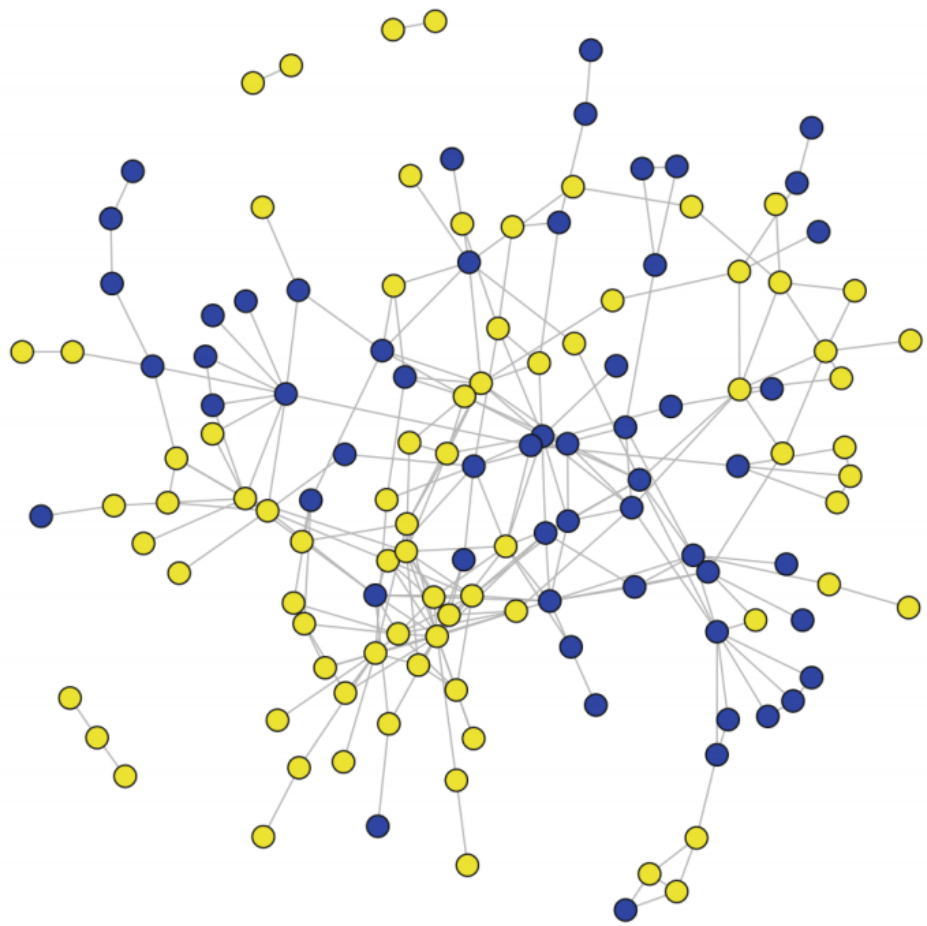
Example: protein function from a ppi network (guilt-by-association)



Vertex Property Prediction

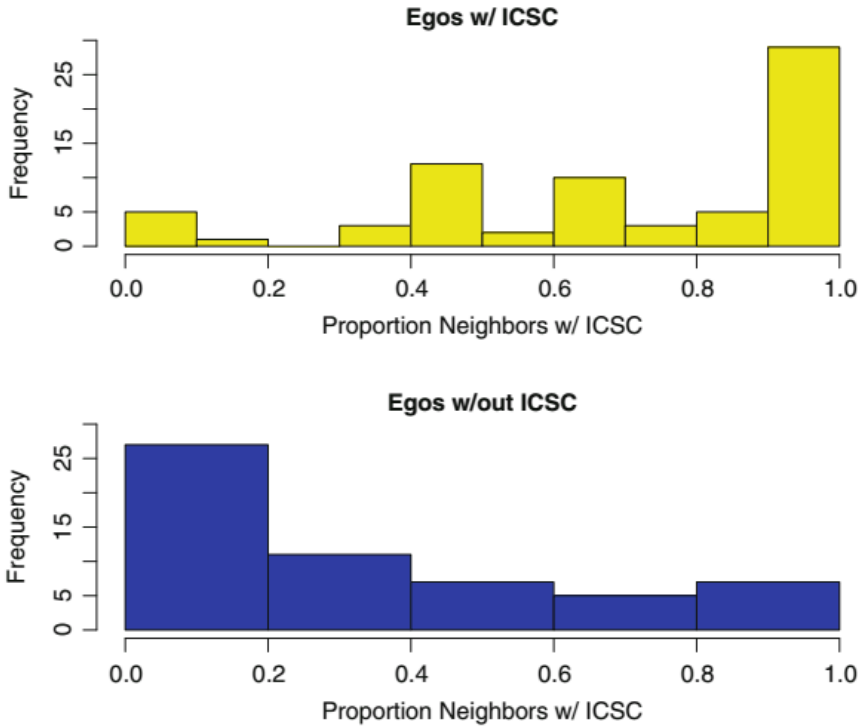
Simplest approach: use neighbors

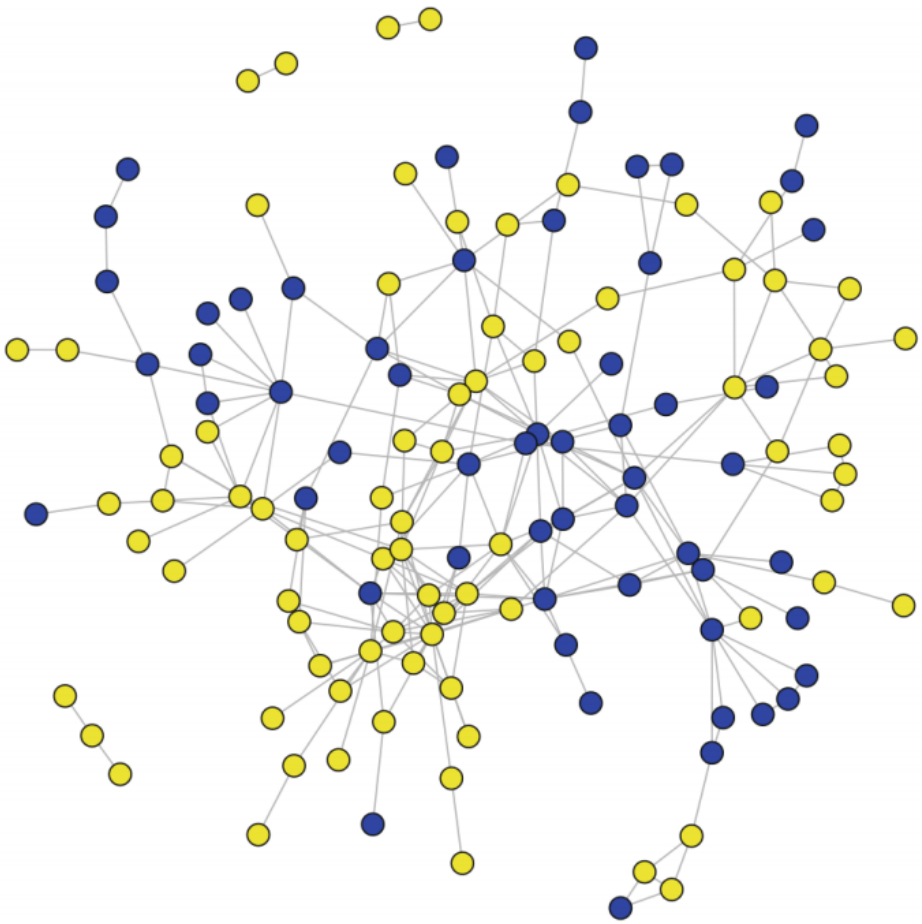
Use target values of graph neighbors:
- average for continuous
- majority class for categorical



Vertex Property Prediction

Simplest approach: use neighbors

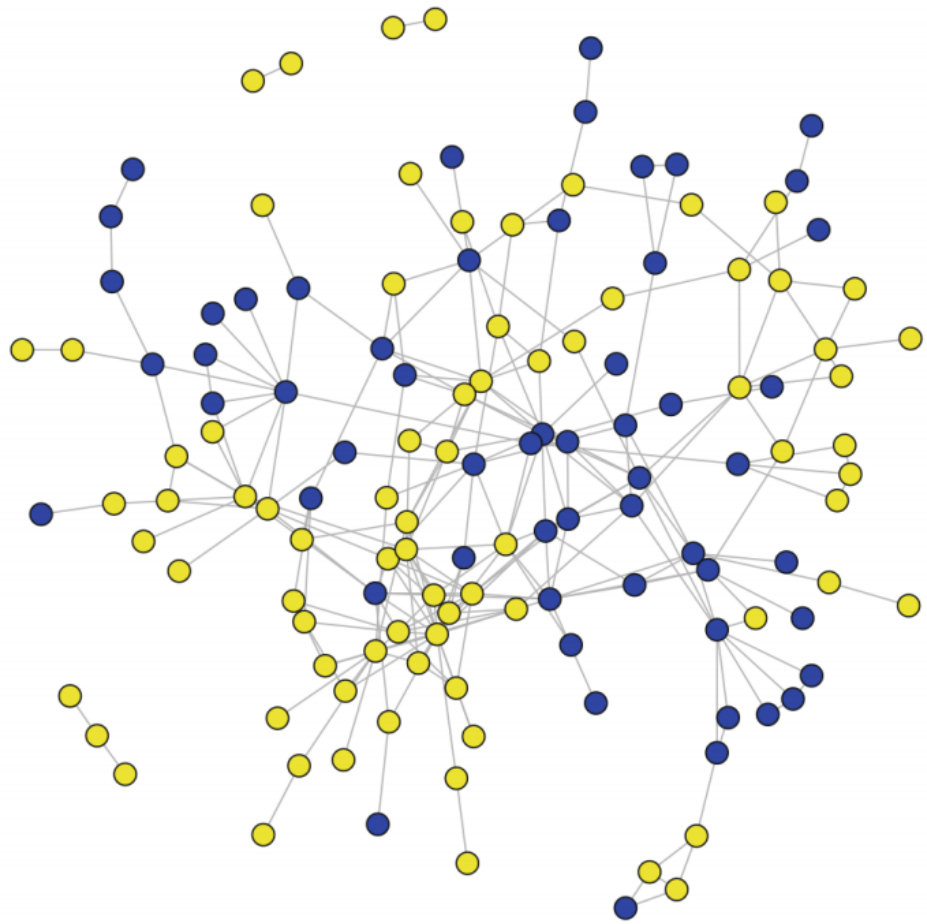




Vertex Property Prediction

Regression approach

Build a function $f(x)$ that is *smooth* over the graph



Smoothing Splines and the Beaver Dam Eye Study

- Great history of using smoothing spline (SS) models for analyzing Beaver Dam Eye Study (BDES) data [Wahba et al. 1998a, b,1999, 2000, 2002, 2006]
- In particular, smoothing spline ANOVA (SS-ANOVA) model of pigmentary abnormalities (PA)

  [Ann. Statistics 28 (2000)]

SS-ANOVA for Bernoulli

Binary outcome, disease/no disease

Predictors (bmi, sysbp...)

- Estimate o

$$p(x) = Pr\{y = 1|x\}$$

$$f(x) = \log \frac{p(x)}{1 - p(x)}$$

- *f* is nonparametric (or semiparametric)
- *f* has ANOVA-like decomposition

SS-ANOVA

- Model for pigmentary abnormalities (PA), female BDES subjects [Ann. Statistics 28 (2000)]

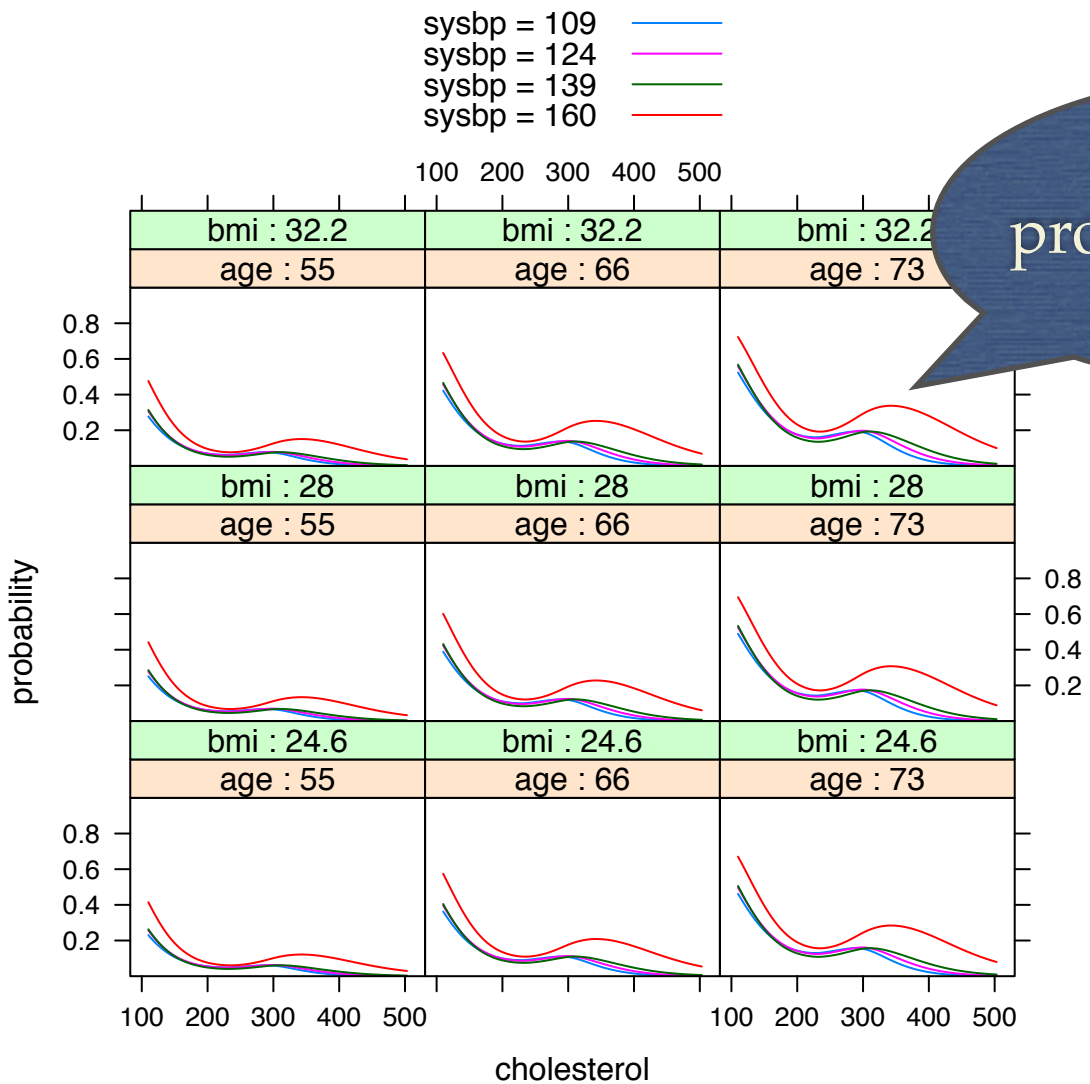
$$f(t) = \mu + f_1(\text{sysbp}) + f_2(\text{chol}) + f_{12}(\text{sysbp}, \text{chol}) + d_{\text{age}} \cdot \text{age} + d_{\text{bmi}} \cdot \text{bmi} + d_{\text{horm}} \cdot I_1(\text{horm}) + d_{\text{hist}} \cdot I_2(\text{hist}) + d_{\text{smoke}} \cdot I_3(\text{smoke}),$$

hormone replacement yes/no

history of heavy drinking

history of smoking

SS-ANOVA



nonlinear protective effect of cholesterol

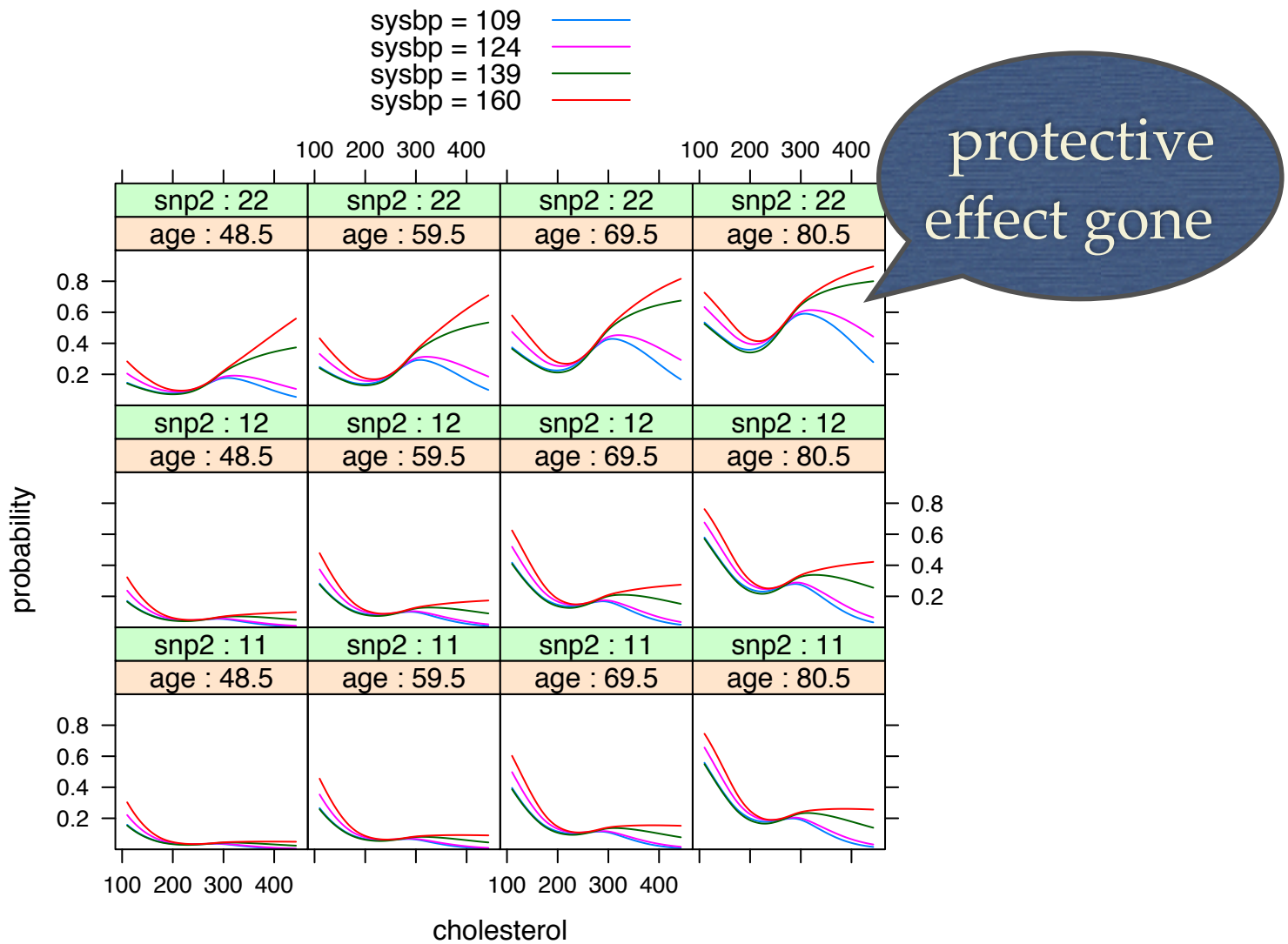
New Data Sources

1. Familial relationships were ascertained for BDES subjects
   - pedigrees later constructed for subset of subjects

New Data Sources

2. Results linking variation in specific genetic regions and AMD (age-related macular degeneration)
   - in particular, CFH and LOC387715 (ARMS2) genes
   - genetic marker data for specific SNPs, including these two gene regions, generated for subjects in pedigree data

SS-ANOVA (w/ ARMS2)



SS-ANOVA

- Goal: Extend SS-ANOVA model with genetic covariates and pedigree information
  - pedigrees are trickier
  - method: define a pedigree dissimilarity, incorporate to SS-ANOVA model

SS-ANOVA and Pedigrees

- Main idea: make use of ANOVA-like decomposition
- Term for each data type: environmental covariates (as in the original SS-ANOVA model), genetic markers, pedigree data
  - SS-ANOVA can give relative importance of each component

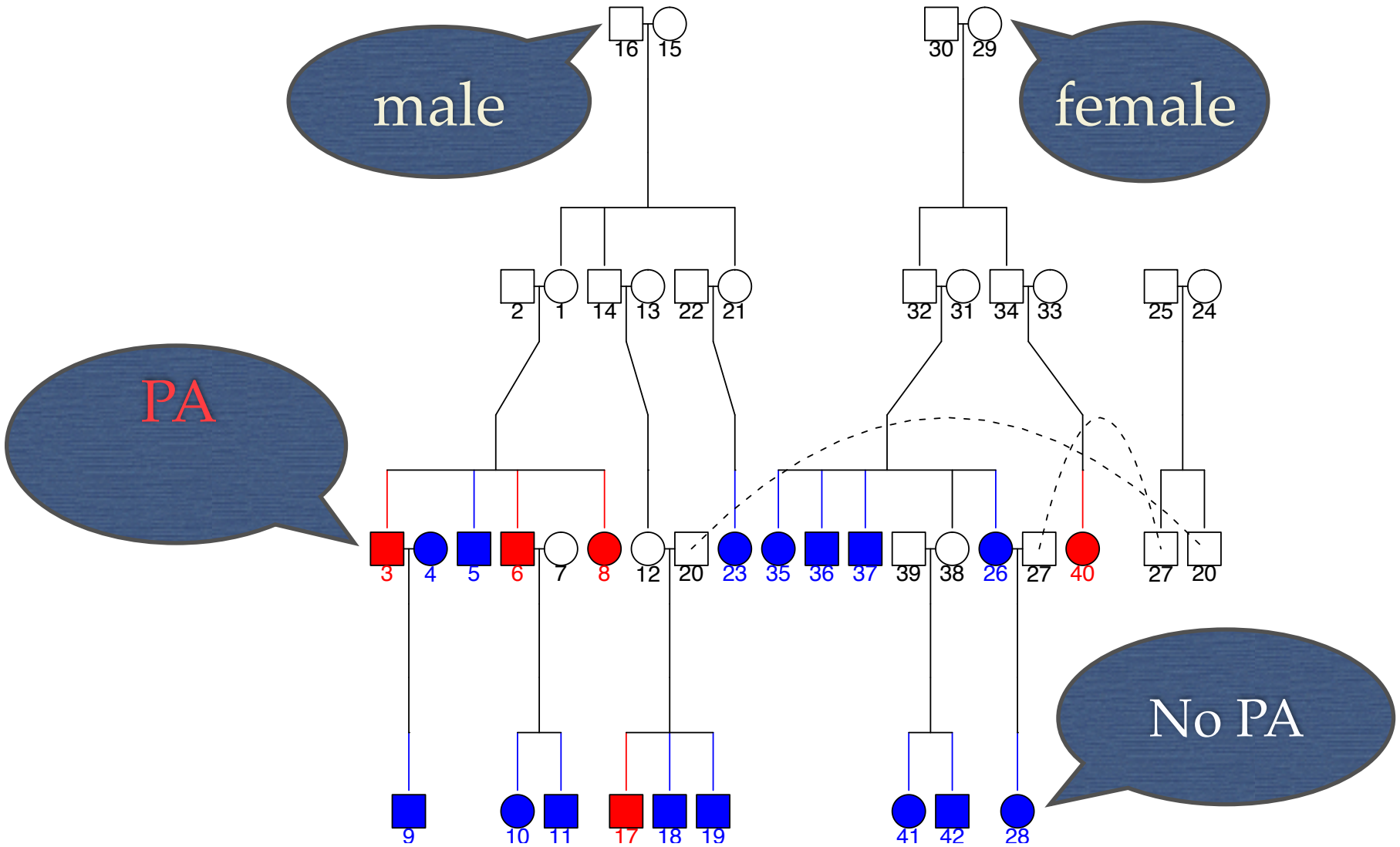
Graph-Based

- The method presented is quite general,
  - can incorporate data where relationships are represented by a graph
- Big Assumption:
  1. graph does not have determinant effect on outcome,
  2. instead, it is one of multiple, comparable, model components that affect outcome

Outline

1. Pedigrees and dissimilarities
2. SS-ANOVA models
3. Kernel representations of pedigree data
4. Case study: Beaver Dam Eye Study

Pedigrees


male
female
PA
No PA
16 15
30 29
2 1 14 13 22 21
32 31 34 33
25 24
3 4 5 6 7 8 12 20 23 35 36 37 39 38 26 27 40 27 20
9 10 11 17 18 19 41 42 28

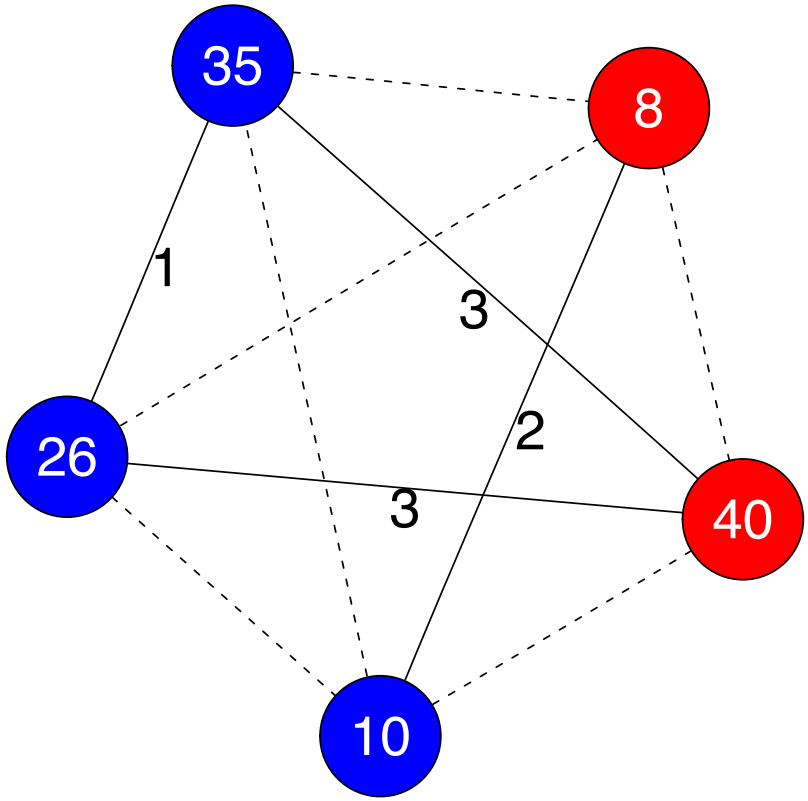
Pedigree Dissimilarity

- Use Malecot's kinship coefficient (φ):
  - for subjects *i* and *j*: the probability that randomly chosen alleles, one from each subject, are *identical by descent*
  - e.g. parent-offspring: 1/4
  - e.g. siblings: 1/4
- Pedigree dissimilarity: $$d_{ij} = -\log_2(2\varphi_{ij})$$

Relationship Graph

- In studies like BDES, not all members of pedigree are subjects
- Instead of full pedigree we have a *relationship graph*

Relationship Graph



Relationship	Distance
sibs	1
avuncular	2
first-cousins	3
unrelated	∞

We will extend the SS-ANOVA model with an encoding of this relationship graph

SS-ANOVA

- Recall: estimate log odds ratio

$$p(x) = Pr\{y = 1|x\}$$

$$f(x) = \log \frac{p(x)}{1 - p(x)}$$

- *f* is nonparametric (or semiparametric)
- *f* has ANOVA-like decomposition

SS-ANOVA

- Estimate is solution of penalized likelihood prob[illegible] reproduci[illegible]rt spa[illegible] of the [illegible]

parametric part

nonparametric part

$$\mathcal{H} = \mathcal{H}_0 \oplus \mathcal{H}_1, \mathcal{H}_0 \perp \mathcal{H}_1$$

- Parametric part specified by finite set of functions

$$\mathrm{span}(\phi_1, \ldots, \phi_M) = \mathcal{H}_0$$

SS-ANOVA

- $\mathcal{H}_1$ is RKHS with associated kernel *k*:

$$g \in \mathcal{H}_1 \Rightarrow \langle k(x,\cdot), g\rangle_{\mathcal{H}_1} = g(x)$$

$$k(x_i, x_j) = \langle k(x_i,\cdot), k(x_j,\cdot)\rangle_{\mathcal{H}_1}$$

- e.g. Gaussian kernel:

tunable hyper-parameter

$$k(x_i, x_j) = \exp\left\{-\gamma\|x_i - x_j\|^2\right\}$$

SS-ANOVA

- Estimate is the solution of a penalized likelihood problem

# of obs.

Log-odds ratio

penalty

$$\min_{f \in \mathcal{H}} I_\lambda(f) = \frac{1}{n} \sum_{i=1}^{n} \left[-y_i f(x_i) + \log(1 + e^{f(x_i)}) \right] + \lambda \| P_1 f \|^2_{\mathcal{H}_1},$$

negative log-likelihood

Tunable hyper-parameter

SS-ANOVA

- By Kimeldorf and Wahba representer theorem, minimizer of penalized likelihood problem has finite representation

$$f(\cdot) = \sum_{i=1}^{m} d_j \phi_j(\cdot) + \sum_{i=1}^{n} c_i k(x_i, \cdot).$$

parametric part

nonparametric part

SS-ANOVA

- Minimizer is solution to

kernel matrix

$$\min_{c\in\mathbb{R}^n, d\in\mathbb{R}^m} \sum_{i=1}^{n} \left[-y_i f_i + \log(1+e^{f_i})\right] + n\lambda c^T K c,$$

$$f = Td + Kc$$

$$T_{ij} = \phi_j(x_i)$$

$$K_{ij} = k(x_i, x_j)$$

SS-ANOVA

- For example,

cubic splines

nonparametric part

$$f(t) = \mu + f_1(\text{sysbp}) + f_2(\text{chol}) + f_{12}(\text{sysbp}, \text{chol}) +$$
$$\boxed{\begin{aligned} d_{\text{age}} \cdot \text{age} + d_{\text{bmi}} \cdot \text{bmi} + d_{\text{horm}} \cdot I_1(\text{horm}) + \\ d_{\text{hist}} \cdot I_2(\text{hist}) + d_{\text{smoke}} \cdot I_3(\text{smoke}), \end{aligned}}$$

Parametric part

SS-ANOVA

- In SS-ANOVA model, $\mathcal{H}_1$ is assumed to be direct sum of multiple RKHS so:

$$g(x) = \sum g_\alpha(x_\alpha) + \sum_{\alpha<\beta} g_{\alpha\beta}(x_\alpha, x_\beta) + \cdots$$

main effects

$$g_\alpha \in \mathcal{H}_\alpha$$

second-order interactions

SS-ANOVA

- For example,

main effects

second-order interaction

$$f(t) = \mu + f_1(\text{sysbp}) + f_2(\text{chol}) + f_{12}(\text{sysbp}, \text{chol}) + d_{\text{age}} \cdot \text{age} + d_{\text{bmi}} \cdot \text{bmi} + d_{\text{horm}} \cdot I_1(\text{horm}) + d_{\text{hist}} \cdot I_2(\text{hist}) + d_{\text{smoke}} \cdot I_3(\text{smoke}),$$

SS-ANOVA

- In SS-ANOVA model, $\mathcal{H}_1$ is assumed to be direct sum of multiple RKHS so:

$$g(x) = \sum_{\alpha} g_\alpha(x_\alpha) + \sum_{\alpha<\beta} g_{\alpha\beta}(x_\alpha, x_\beta) + \cdots$$

$$g_\alpha \in \mathcal{H}_\alpha$$

- So, we can write [illegible] term as:

tunable hyper-parameters

$$\lambda \|g\|^2_{\mathcal{H}_1} = \lambda \left[\sum_{\alpha} \theta_\alpha^{-1} \|g_\alpha\|^2_{\mathcal{H}_\alpha} + \sum_{\alpha<\beta} \theta_{\alpha\beta}^{-1} \|g_{\alpha\beta}\|^2_{\mathcal{H}_{\alpha\beta}} + \cdots \right]$$

SS-ANOVA

- A kernel $k_\alpha(\cdot,\cdot)$ function is associated with each component $\mathcal{H}_\alpha$

- For penalty with coefficients θ , the kernel for $\mathcal{H}_1$ is then

$$k(\cdot,\cdot) = \sum_\alpha \theta_\theta k_\alpha(\cdot,\cdot) + \sum_{\alpha\beta} \theta_{\alpha\beta} k_{\alpha\beta}(\cdot,\cdot) + \cdots$$

SS-ANOVA

- Coefficients θ may be interpreted as relative importance of each model component
- Hyper-parameters (λ, θ) tuned with GACV [Xiang and Wahba '96]
  - approximation of Kullback-Leibler divergence between estimate and unknown "true" function

Extending SS-ANOVA

- Add a main effect term to decomposition of $\mathcal{H}_1$ that encodes pedigree data:

$$f(t_i) = \mu + g_1(t_i) + g_2(t_i) + h(z(t_i)),$$

Extending SS-ANOVA

- Add a main effect term to decomposition of $\mathcal{H}_1$ that encodes pedigree data:

$$f(t_i) = \mu + g_1(t_i) + g_2(t_i) + h(z(t_i)),$$

- Requires properly defining a kernel matrix
- θ gives relative importance of model components

Regularized Kernel Estimation

- Given pedigree dissimilarity data
- Estimate a kernel matrix *K* that induces distances:

dissimilarity ~ distance

$$d_{ij}^2 = K_{ii} + K_{jj} - 2K_{ij}$$

- Add *K* to SS-ANOVA model
- Additionally, get an embedding in "pedigree" Euclidean space

Regularized Kernel Estimation

- Regularization: Minimize the rank of *K*?
  - Can help with estimation
  - Definitely helps with visualization
- Get a convex relaxation to rank minimization by minimizing trace of K.

Regularized Kernel Estimation

- Given, *N* objects and *some* dissimilarity information $d_{ij} \in \Omega$ where $|\Omega| < \binom{N}{2}$
- Solve:

regularization parameter

$$\begin{aligned} \min \quad & \textstyle\sum_{ij \in \Omega} |d_{ij}^2 - \hat{d}_{ij}^2(K)| + \lambda \mathrm{trace}(K) \\ \text{s.t.} \quad & K \succeq 0 \end{aligned}$$

- where $\hat{d}_{ij}^2(K) = K_{ii} + K_{jj} - 2K_{ij}$

Regularized Kernel Estimation

- It is a convex optimization problem
  - In particular, a linear semidefinite program
- There are interior-point methods (& code) of polynomial complexity to solve exactly
- DSDP5 [Benson & Yu '00], CSDP [Borchers '99], SDPT3 [Toh et al. '99]

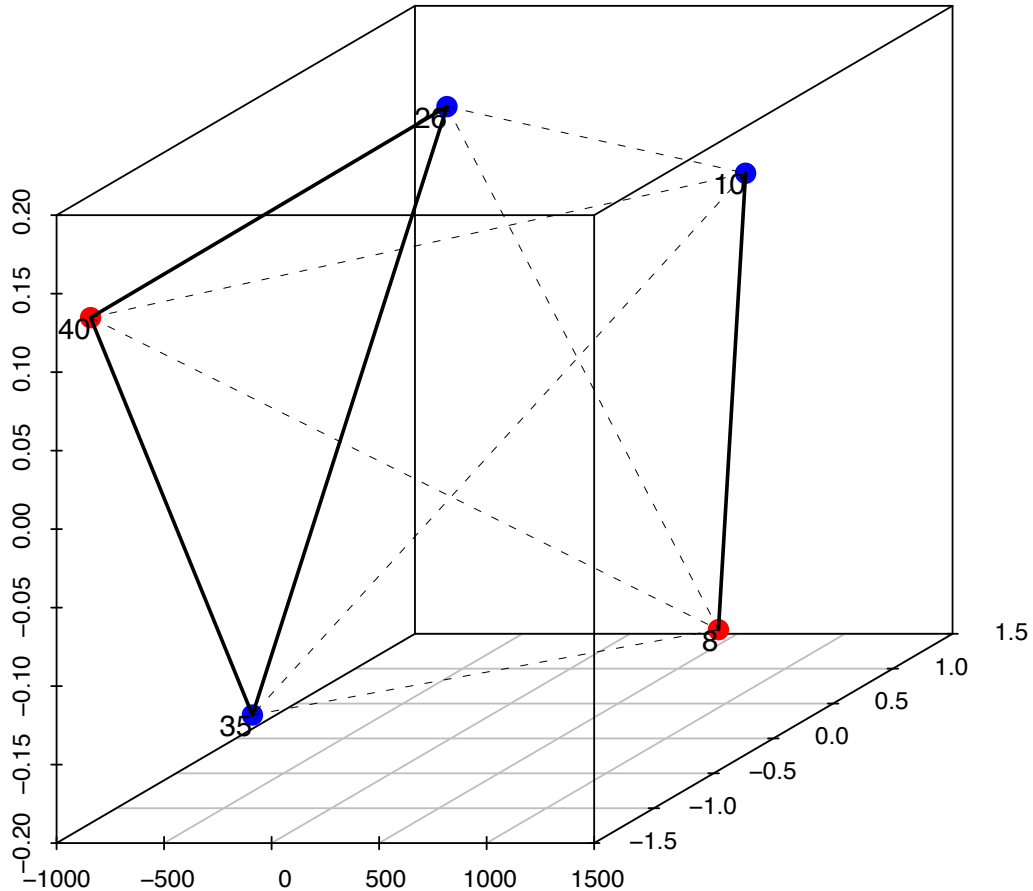
Regularized Kernel

- Also, can get embedding in "pedigree" space:
  - since solution to RKE *K* is positive semidefinite, we can write

$$K = XX^T$$

  - using *r* leading eigenvalues and eigenvectors of *K*
  - then, *X* is an *r*-dimensional embedding in "pedigree" space

Regularized Kernel Estimation



Interpretation: embedding gives pedigree *pseudo*-attributes over which a smooth function can be estimated, using, e.g. Gaussian kernel

Another Method

- Graph kernel: given pedigree dissimilarity, use

$$K_{ij} = \exp\{-\gamma d_{ij}^2\}$$

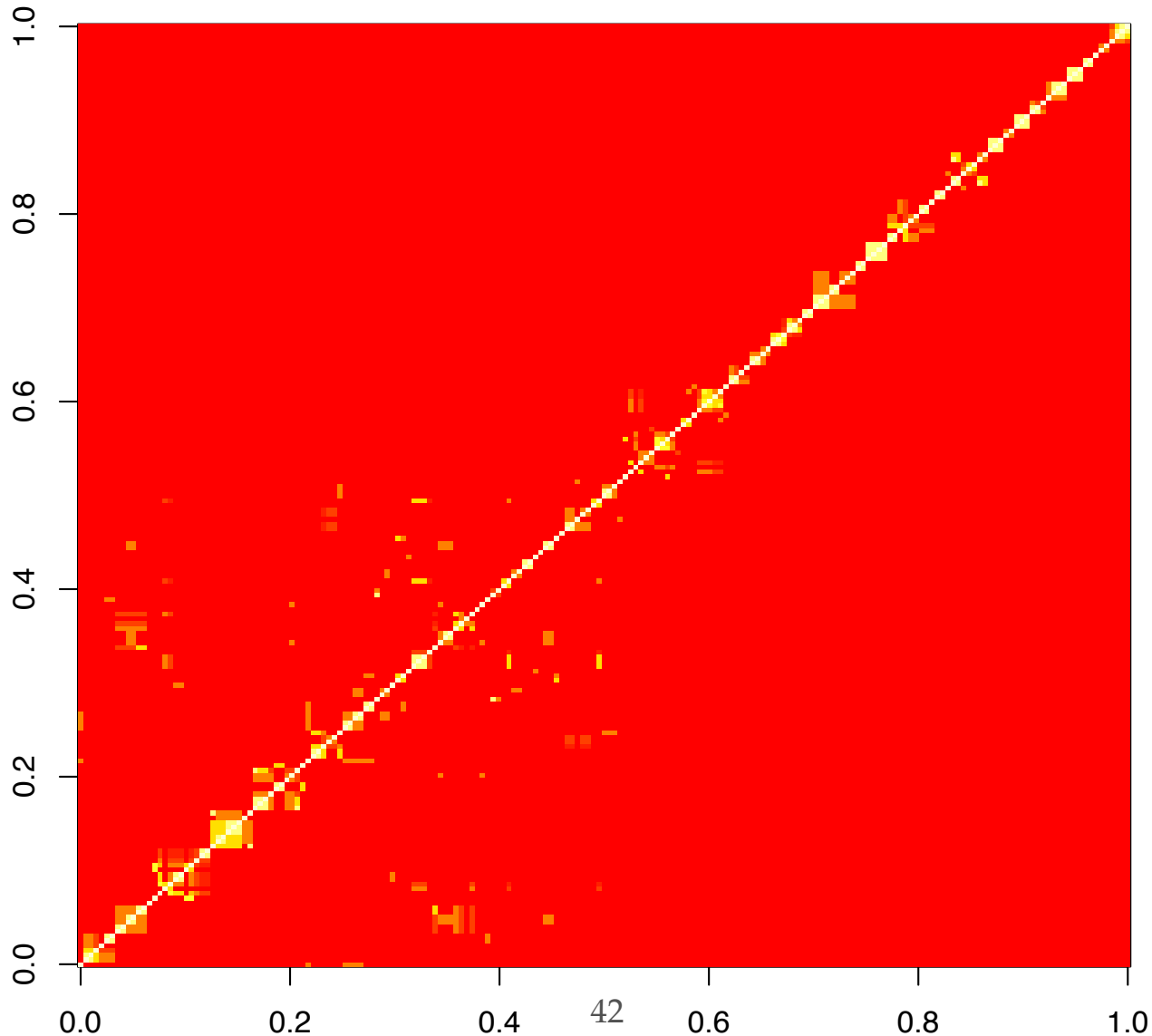
- Not necessarily positive semi-definite
- Project to space of psd matrices by truncating eigendecomposition

Diffusion Effect

- Gaussian kernels over pedigree graphs or RKE embedding result in kernels that are:
  1. very sparse: very few relationships in pedigree graphs
  2. very diffuse: using pedigree dissimilarity, there is rapid decay as relationship dissimilarity increases

Diffusion Effect

Gaussian kernel over graph, $\gamma = 0.1$



Diffusion Effect

- Would prefer kernels that:
  - depend only on distances, rotationally invariant
  - parameterized decay as relationship dissimilarity increases
- Solution: Matérn kernel family [Matérn ’86, Stein ‘99]

Matérn Kernels

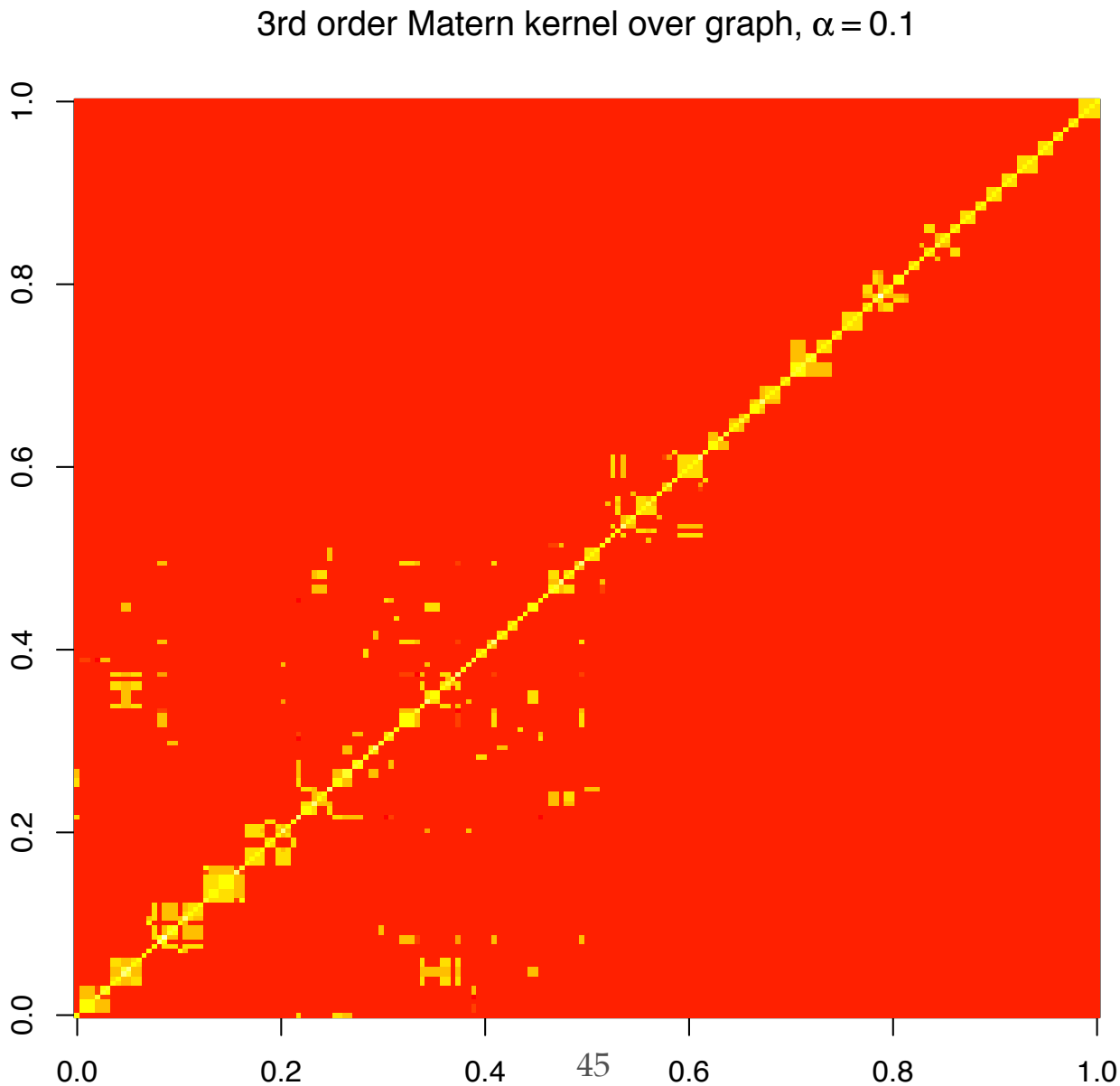
- General form Matérn kernel:

$$k_\nu(i,j) = \exp\{-\alpha d_{ij}\}\pi_\nu(\alpha, d_{ij}),$$

- π_ν is a polynomial, can control exponential decay, α is a scale parameter
- In experiments, we use 3rd order Matérn kernel:

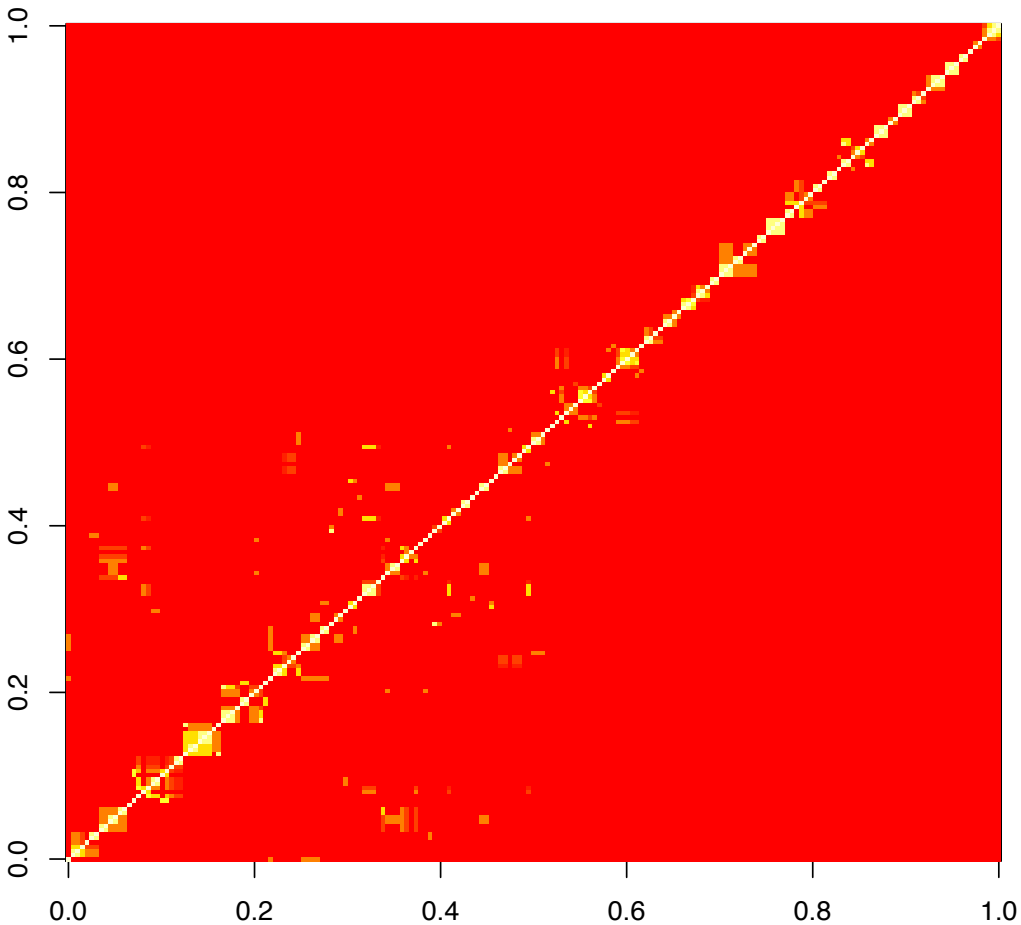
$$k_3(i,j) = \frac{1}{\alpha^7}\exp\{-\alpha\tau\}[15 + 15\alpha\tau + 6\alpha^2\tau^2 + \alpha^3\tau^3],$$

Matérn Kernel

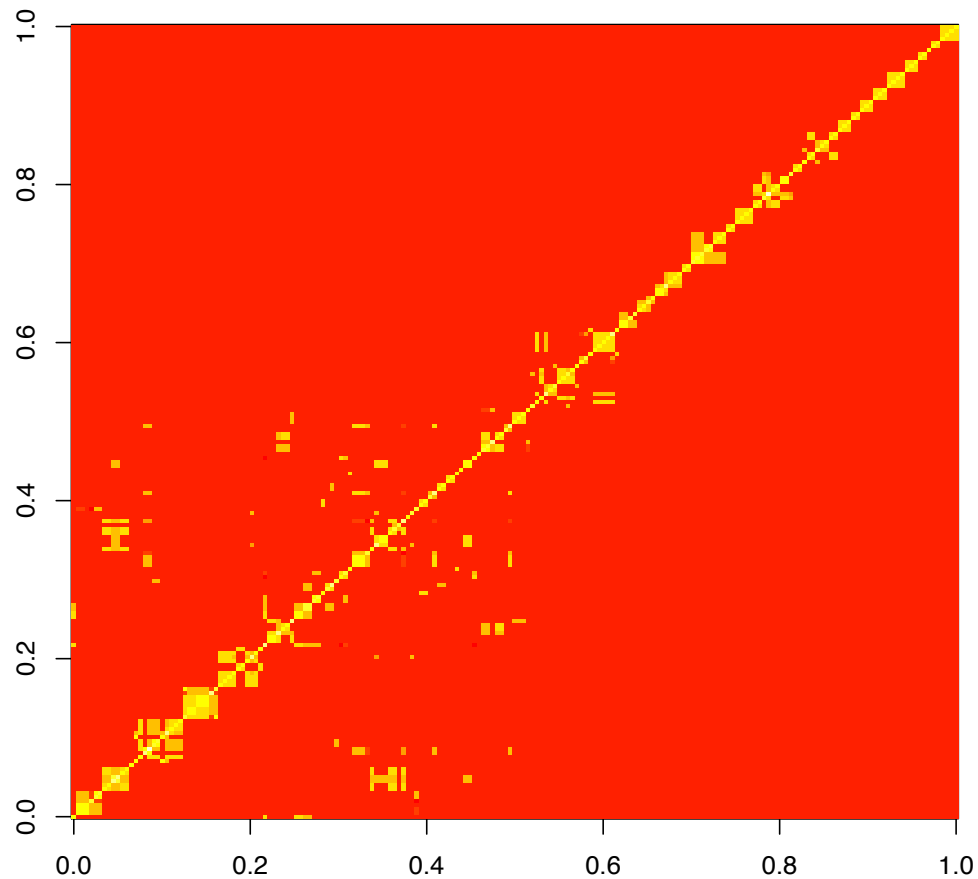


Diffusion Effect

Gaussian kernel over graph, $\gamma = 0.1$

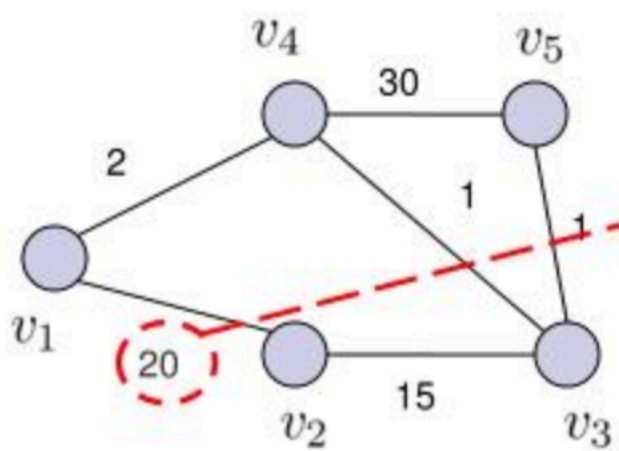


3rd order Matern kernel over graph, $\alpha = 0.1$



Another kernel alternative

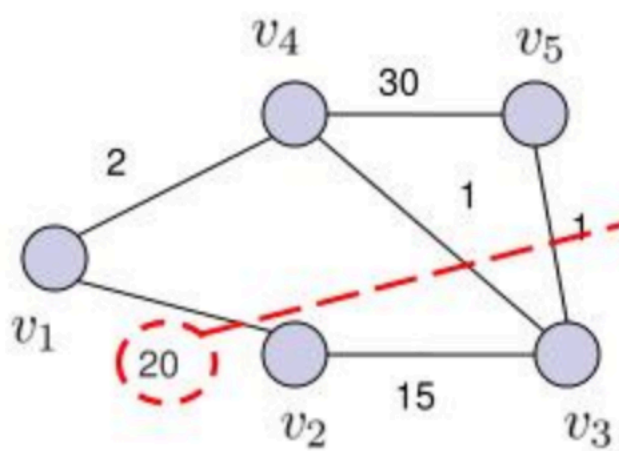
- Another commonly used kernel for graphs is based on the graph *Laplacian L=D-A* with *D* diagonal degree matrix and adj (or weight) matrix A



$$L = \begin{pmatrix} 22 & -20 & 0 & -2 & 0 \\ -20 & 35 & -15 & 0 & 0 \\ 0 & -15 & 17 & -1 & -1 \\ -2 & 0 & -1 & 33 & -30 \\ 0 & 0 & -1 & -30 & 31 \end{pmatrix}$$

Another kernel alternative

- We can use L as kernel matrix
  - Alternatively, the first few eigenvalues/ eigenvectors of L



$$L = \begin{pmatrix} 22 & -20 & 0 & -2 & 0 \\ -20 & 35 & -15 & 0 & 0 \\ 0 & -15 & 17 & -1 & -1 \\ -2 & 0 & -1 & 33 & -30 \\ 0 & 0 & -1 & -30 & 31 \end{pmatrix}$$

SS-ANOVA

- Recall SS-ANOVA setting:

$$\min_{c\in\mathbb{R}^n, d\in\mathbb{R}^m} \sum_{i=1}^{n} \left[-y_i f_i + \log(1+e^{f_i})\right] + n\lambda c^T K c,$$

- (Weighted) Laplacian as K makes penalty correspond to

$$\sum_{i\sim j} w_{ij}(f_i - f_j)^2$$

Case Study: BDES

- Cohort: female subjects in BDES I, with full ascertained data for: both genetic markers, pedigree, and covariates in model
- In pedigrees containing two or more of these subjects (n=684)

Case Study: BDES

- Use two SNPs:
  1. near complement factor H (CFH)
  2. near ARMS2
- Each SNP has three levels: 11, 12, 22
- Linear terms for levels 12 and 22 added to model (level 11 folded into intercept)

Case Study: BDES

- Full model:

$$
\begin{aligned}
f(t) = \mu + d_{\mathrm{SNP1,1}} \cdot I(X_1 = 12) + d_{\mathrm{SNP1,2}} \cdot I(X_1 = 22) + \\
d_{\mathrm{SNP2,1}} \cdot I(X_2 = 12) + d_{\mathrm{SNP2,2}} \cdot I(X_2 = 22) + \\
f_1(\mathrm{sysbp}) + f_2(\mathrm{chol}) + f_{12}(\mathrm{sysbp}, \mathrm{chol}) + \\
d_{\mathrm{age}} \cdot \mathrm{age} + d_{\mathrm{bmi}} \cdot \mathrm{bmi} + d_{\mathrm{horm}} \cdot I_1(\mathrm{horm}) + \\
d_{\mathrm{hist}} \cdot I_2(\mathrm{hist}) + d_{\mathrm{smoke}} \cdot I_3(\mathrm{smoke}) + \\
h(z(t))
\end{aligned}
$$

Marker data

environmental covariates

pedigree data

Case Study: BDES (Models)

- Indicate models by components:
  1. **S**: genetic markers
  2. **C**: environmental covariates
  3. **P**: pedigree data
- For example:
  - **S-only**: model containing only marker data
  - **S+P:** model contains marker and pedigree data
  - **S+C+P:** full model

Case Study: BDES

1. GAUSSIAN: Gaussian kernel over relationship graph
2. MATERN: 3rd-order Matérn kernel over relationship graph
3. RKE/GAUSSIAN: Gaussian kernel over RKE embedding
4. RKE/MATERN: 3rd-order Matérn kernel over RKE embedding

Case Study: BDES

- Parameters to tune:
  - regularization parameters in penalized likelihood and RKE
  - ANOVA decomposition coefficients
  - kernel hyper-parameters
- All tuning done by minimizing GACV criterion

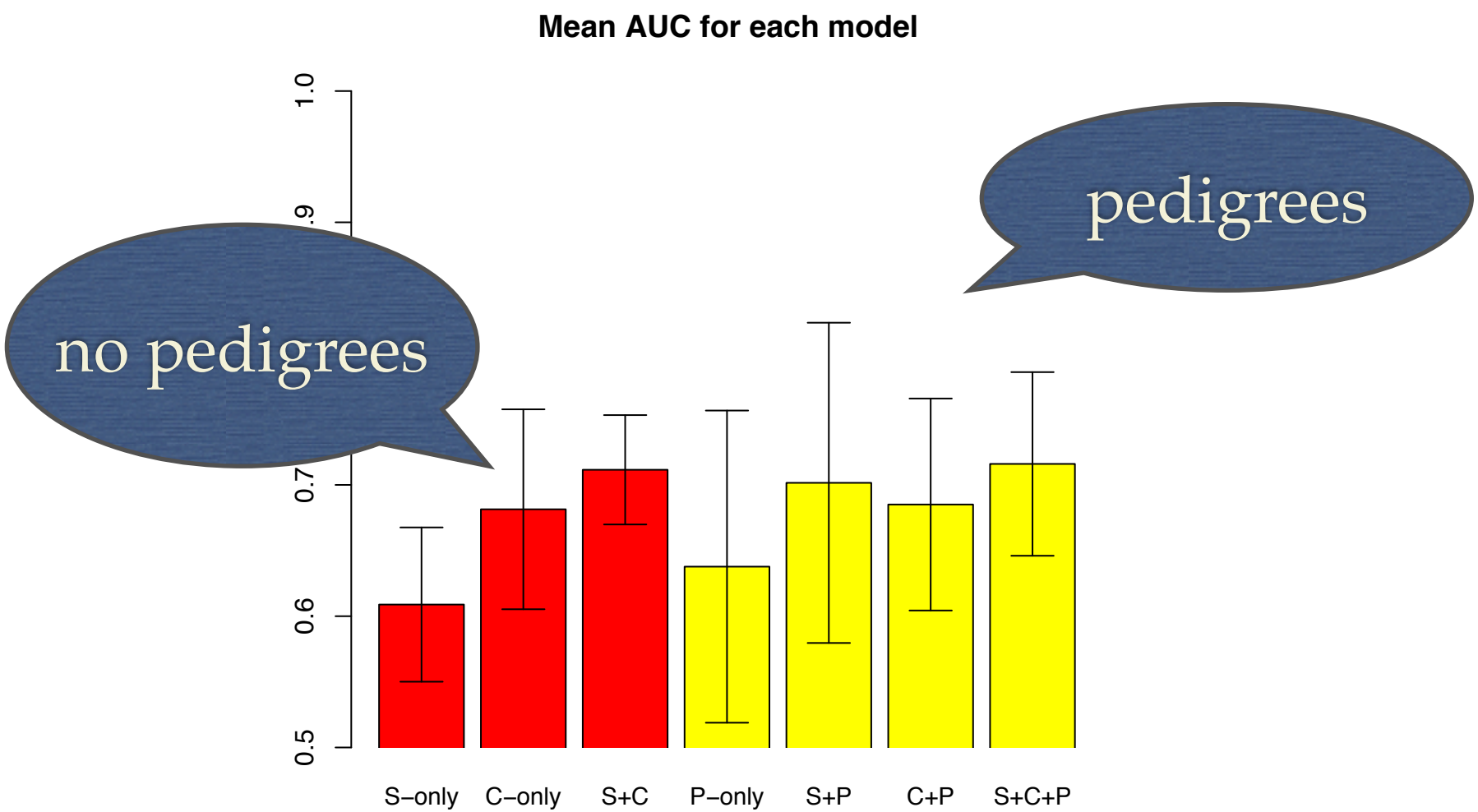
Case Study: BDES

- Penalized likelihood problem solved by quasi-Newton method (gss R package) [Gu '07]
- Tuning: gss finds ANOVA decomposition parameters using a quasi-Newton method
  - remaining parameters tuned by grid search
  - Rmpi library used for parallel grid search
- RKE problem solved by CSDP library [Borchers '99] (R interface)

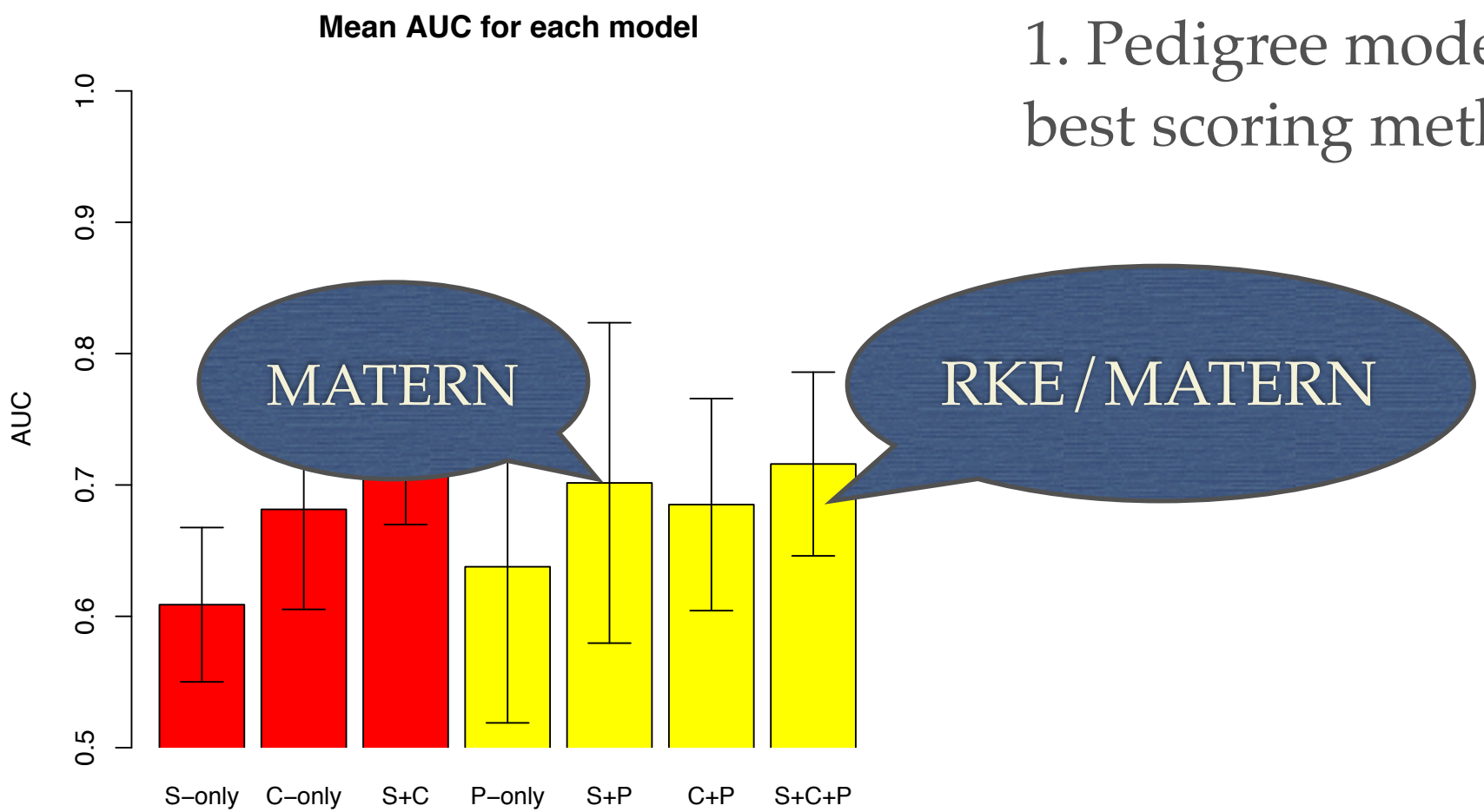
Case Study: BDES

- Prediction performance measured by area under ROC curve (AUC)
- Estimated by 10-fold cross validation

Case Study: BDES

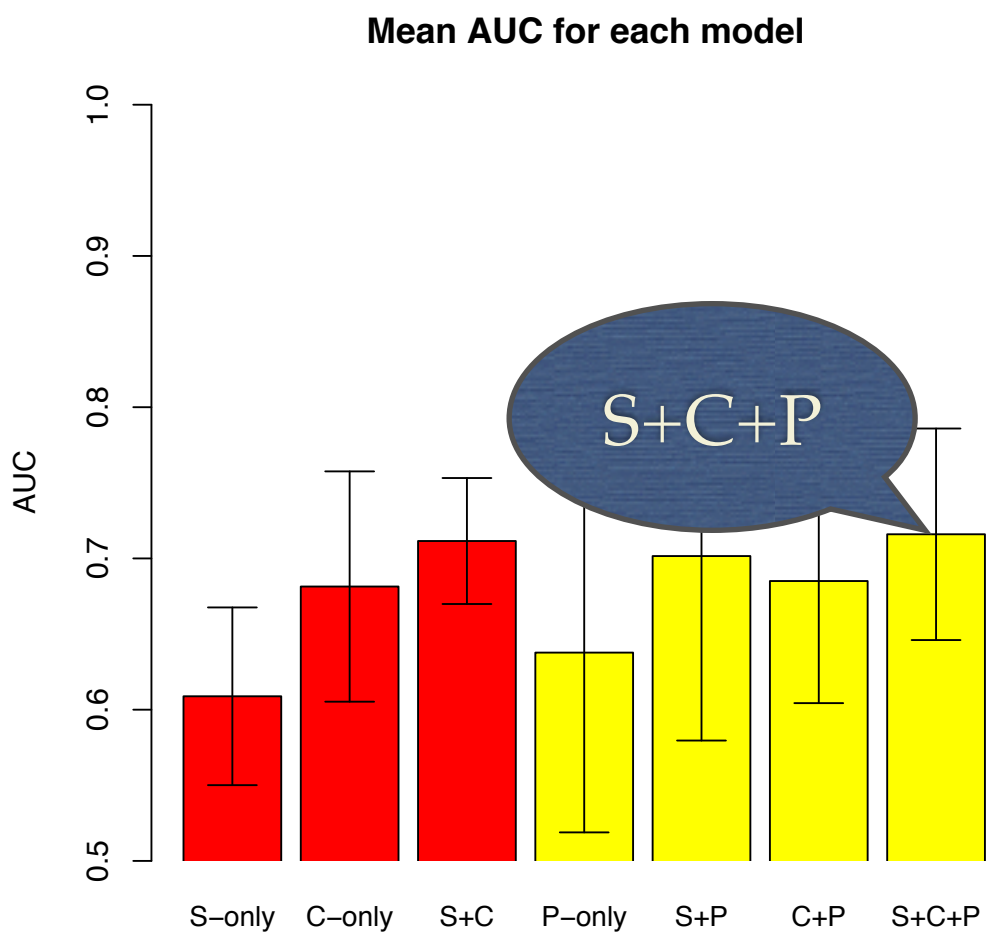


Case Study: BDES



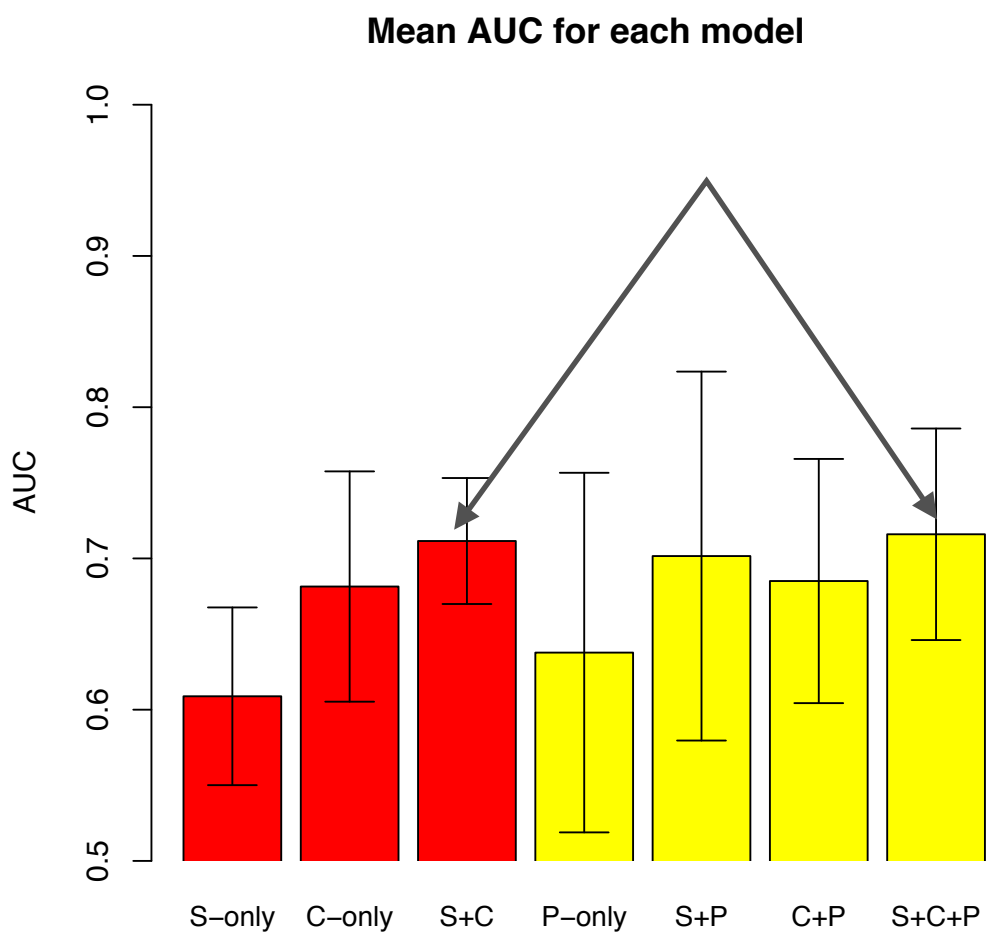
1. Pedigree models refer to best scoring method

Case Study: BDES



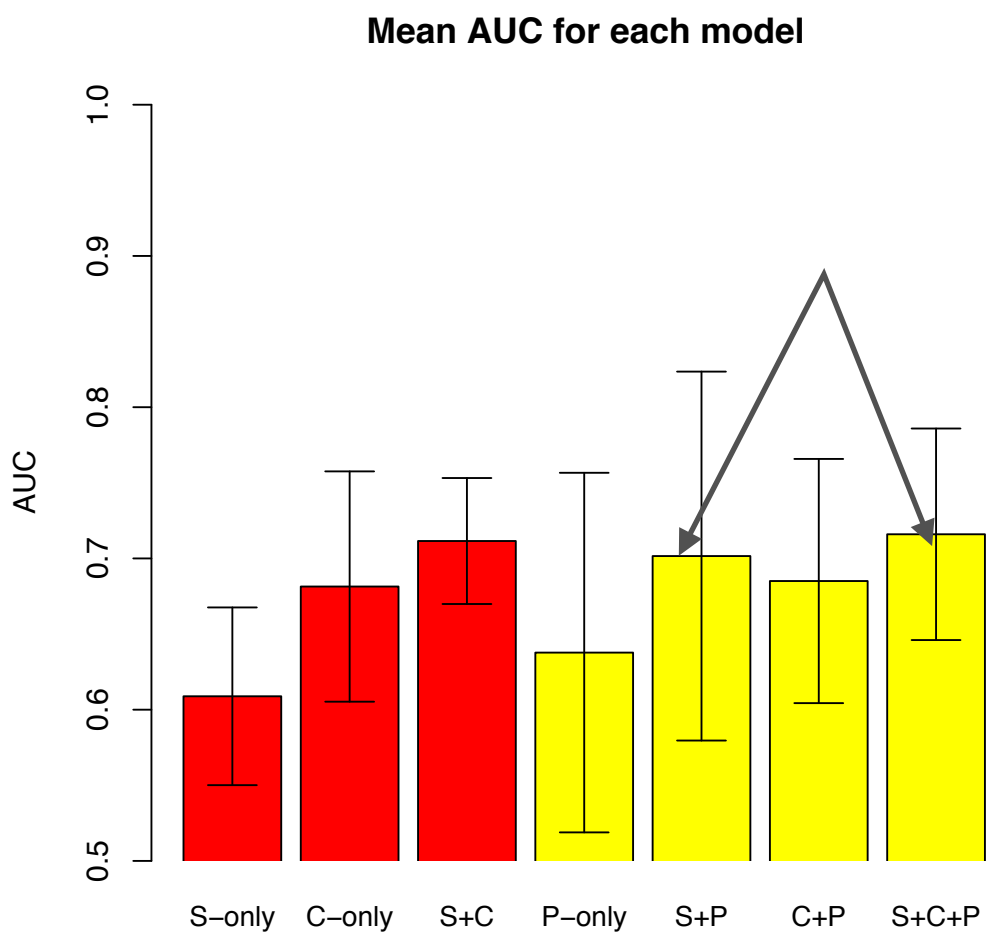
1. Pedigree models refer to best scoring method
2. Best scoring model is **S+C+P**

Case Study: BDES



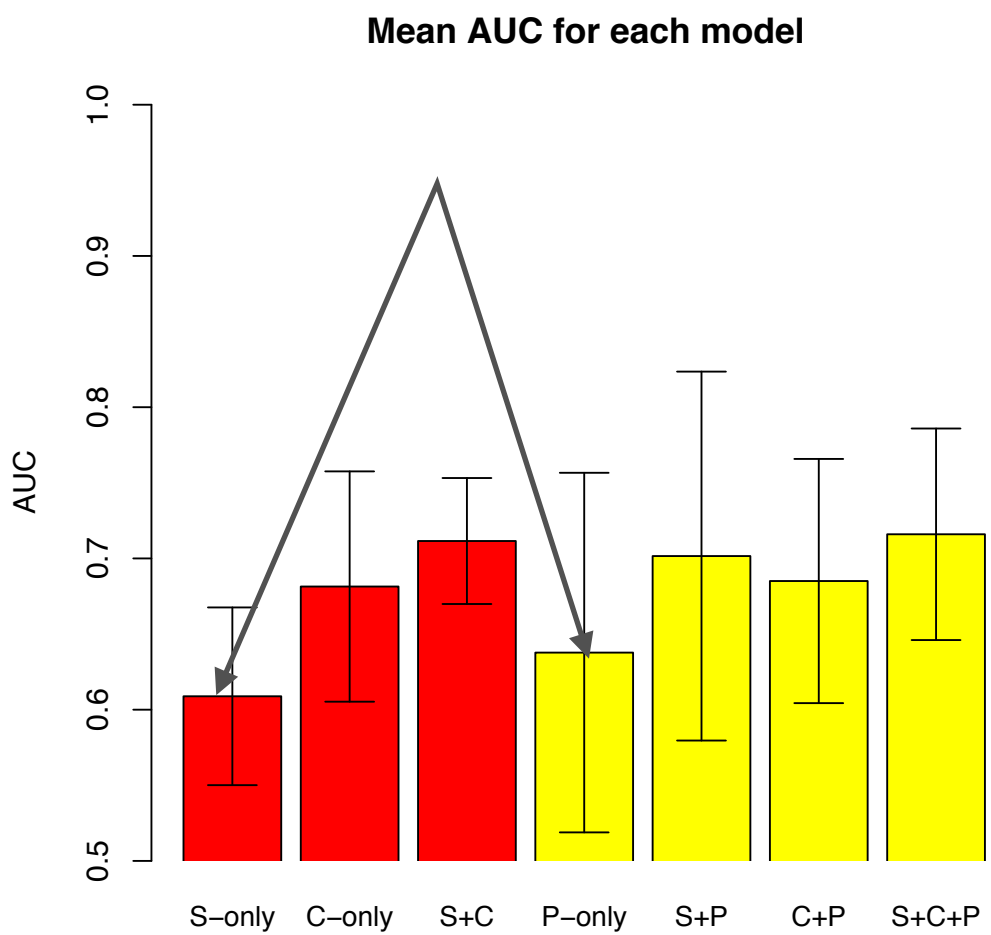
1. Pedigree models refer to best scoring method
2. Best scoring model is **S+C+P**
   a. **S+C**, similar

Case Study: BDES



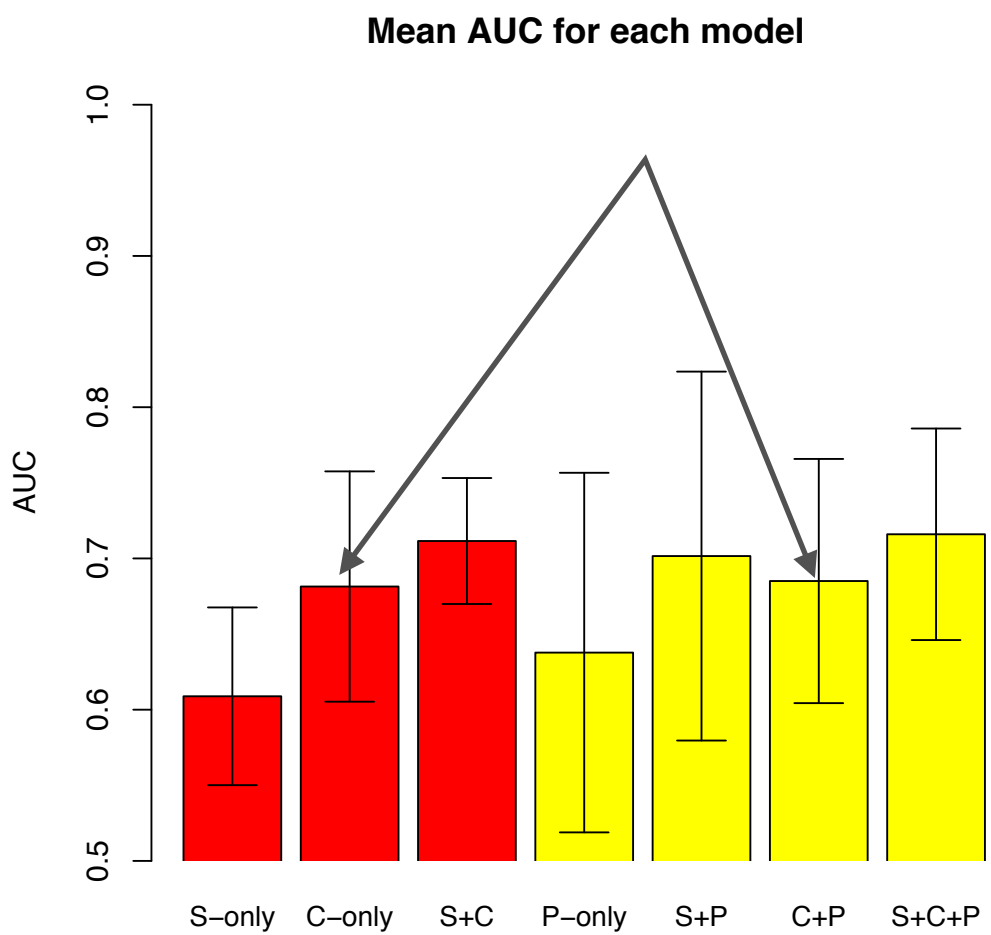
1. Pedigree models refer to best scoring method
2. Best scoring model is **S+C+P**
   a. **S+C**, similar
   b. **S+P**, similar

Case Study: BDES



1. Pedigree models refer to best scoring method
2. Best scoring model is **S+C+P**
   a. **S+C**, similar
   b. **S+P**, similar
3. **P-only ≈ S-only**

Case Study: BDES



1. Pedigree models refer to best scoring method
2. Best scoring model is **S+C+P**
   a. **S+C**, similar
   b. **S+P**, similar
3. **P-only ≈ S-only**
4. **S+P > S-only**
5. **C+P ≈ C-only**

Case Study: BDES

- Paper also has simulation results where **S+C+P > S+C**
- Simulates setting where markers (**S**) do not model entire genetic influence in disease risk
- then, pedigree data (**P**) models remaining genetic influence

Extensions

1. More complex models for marker data
   - multiple markers per gene, interactions

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2. Alternative pedigree dissimilarity measures
   - e.g., dissimilarity for spouses encoding *some* notion of environmental sharing
3. Multiple pedigree dissimilarity measures

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4. Interactions between components: **S*P + C**
5. Further understanding of diffusion effect:
   - depends on dissimilarity measure
   - when is Matérn better than Gaussian?

Summary

- Extended existing nonparametric disease risk model with relationship data
  - using general methodology encoding relationships in graphs
- Assumption: graph relationships is one of multiple, comparable, model components affecting outcome

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- Produce publicly-available software

Thanks!