Data exercise:

Predicting height using genetics

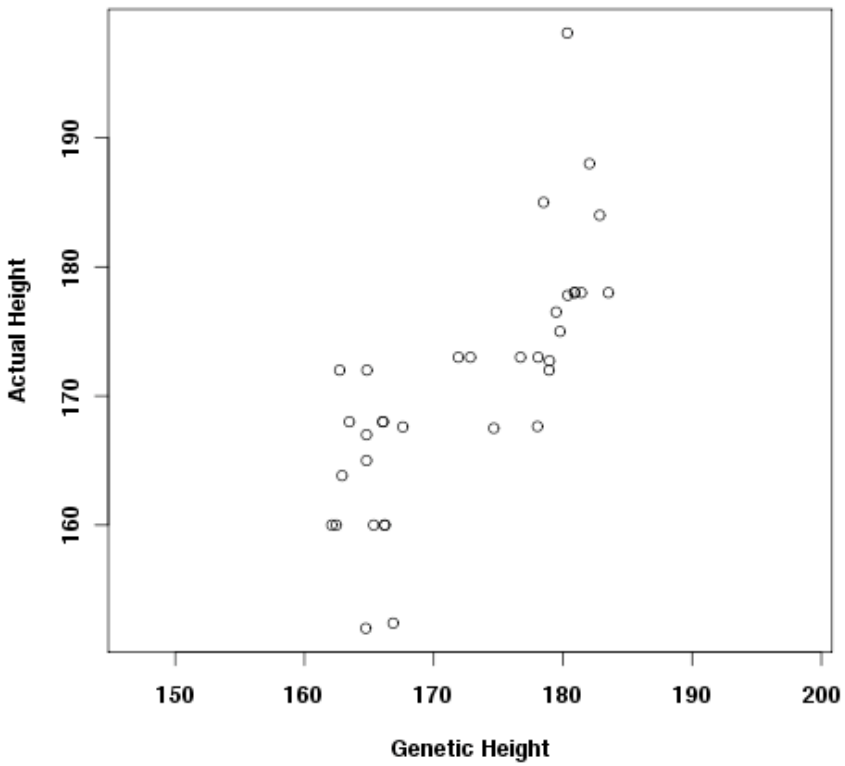
Height

- Classic quantitative trait, easily measurable
- Complex trait (polygenic and environmental factors)
- Highly heritable - $h^2 = 0.8$ (80% of variation in phenotype is due to genetic variation)
- If we knew all the variants contributing to height, and summed their effects within an individual, we could predict height using genetics with reasonable accuracy

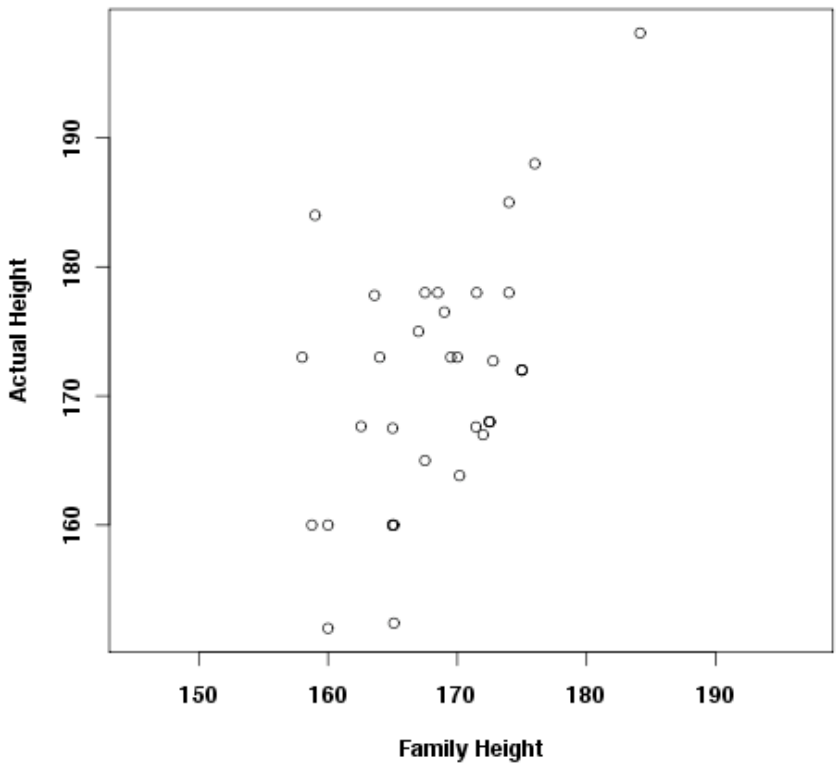
Height Prediction

- GWAS have identified ~150 SNPs associated with height
- Each SNP association has a "height-increasing allele" and a "height-decreasing allele"
- Start with avg. height (according to ethnicity, gender), and predict your height using the SNPs
- Compare with "family history" prediction (averaging your parents' height)

SNP prediction



Family History Prediction



% Variation Explained

- Total variation in a phenotype

$$SS_{\text{tot}} = \sum_i (y_i - \bar{y})^2, \qquad \bar{y} = \frac{1}{n}\sum_i^n y_i$$

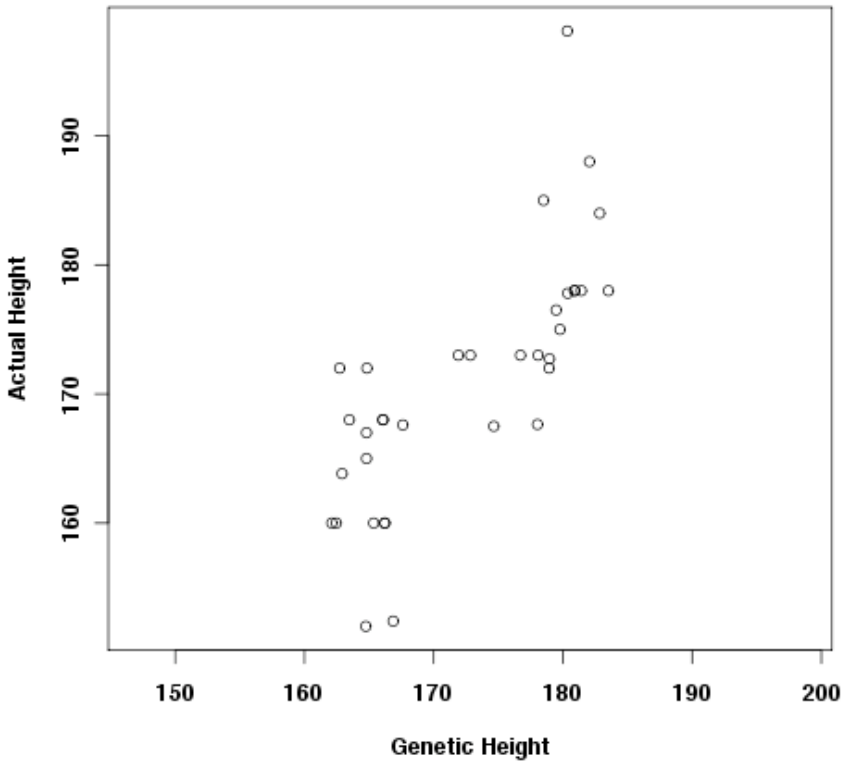
- Remaining variation after genetic prediction (f_i)

$$SS_{\text{err}} = \sum_i (y_i - f_i)^2$$

- % variation explained (R^2)

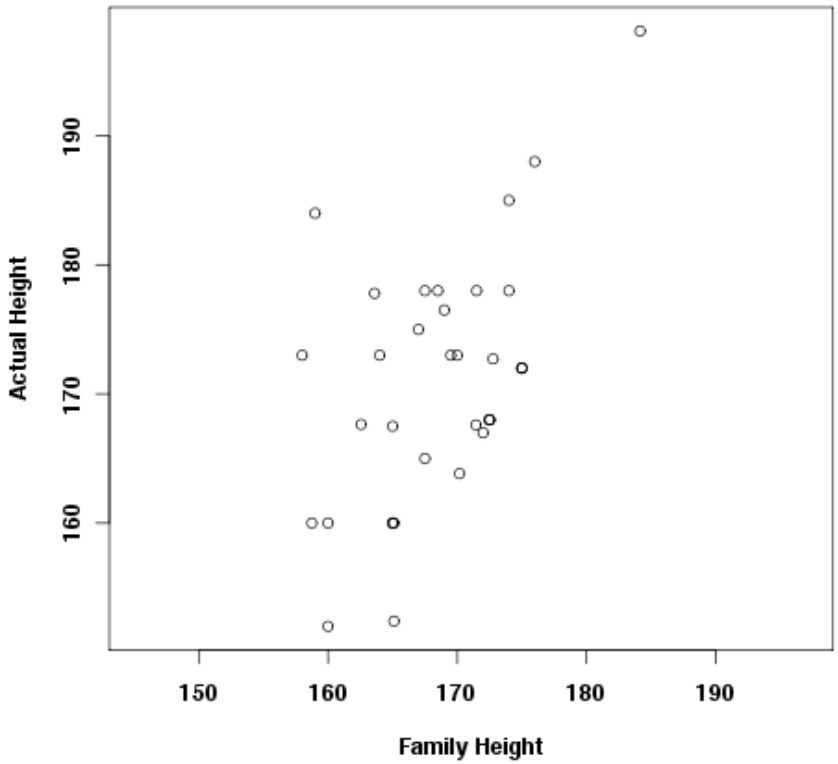
$$R^2 \equiv 1 - \frac{SS_{\text{err}}}{SS_{\text{tot}}}.$$

SNP prediction



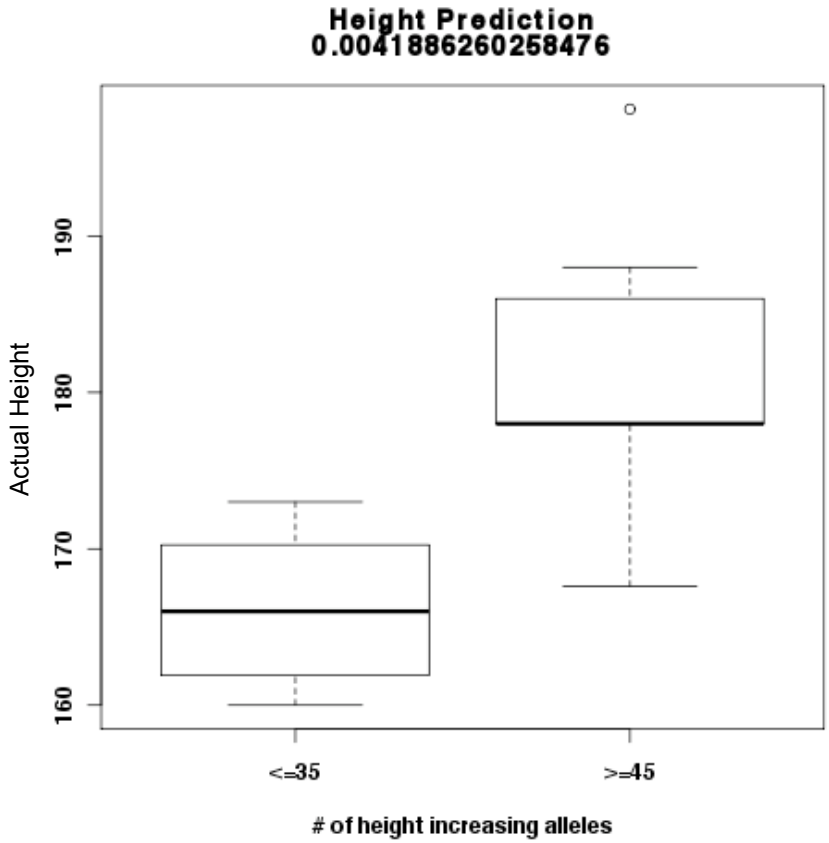
$R^2 = 0.55$

Family History Prediction



$R^2 = 0.21$

Students with <35 vs. >45 height-increasing alleles



Mean
166.2 cm

Mean
181.7 cm

p-value = 0.004

How much heritability can we explain right now?

Table 1 | Estimates of heritability and number of loci for several complex traits

Disease	Number of loci	Proportion of heritability explained
Age-related macular degeneration[72]	5	50%
Crohn's disease[21]	32	20%
Systemic lupus erythematosus[73]	6	15%
Type 2 diabetes[74]	18	6%
HDL cholesterol[75]	7	5.2%
Height[15]	40	5%
Early onset myocardial infarction[76]	9	2.8%
Fasting glucose[77]	4	1.5%

* Residual is after adjustment for age, gender, diabetes.

← More confidence in genetics-based prediction

← Less confidence in genetics-based prediction

- Different traits/diseases = different % heritability explained by common SNPs typed in GWAS
- This changes how much confidence you should have over predictions based on these SNPs!

Manolio *et al* 2009

Clinical Utility

- If % heritability is low, clinical utility likely to be low
- Clinical utility: important evaluate sensitivity, specificity, positive predictive value, and negative predictive value
- Family History vs. SNPs as predictors of disease
  - Wacholder et al. NEJM 2010 (Breast Cancer)
  - Meigs et al. NEJM 2008 and Lyssenko et al. NEJM 2008 (Type 2 Diabetes)
  - Talmud et al. BMJ 2010 (Type 2 Diabetes)

Student projects

- Exceptional Longevity (Sam Pearlman, Rob Tirrell, Noah Zimmerman)
  - Analyzes your probability of being a centenarian
- Which Habsburg Are You? (Joe Foley)
  - Analyzes your inbreeding coefficient and places you among the monarchs of history
- Neanderthal Index
  - Analyzes alleles in candidate Neanderthal regions of genome for Neanderthal inheritance

http://gene210.stanford.edu/projects/

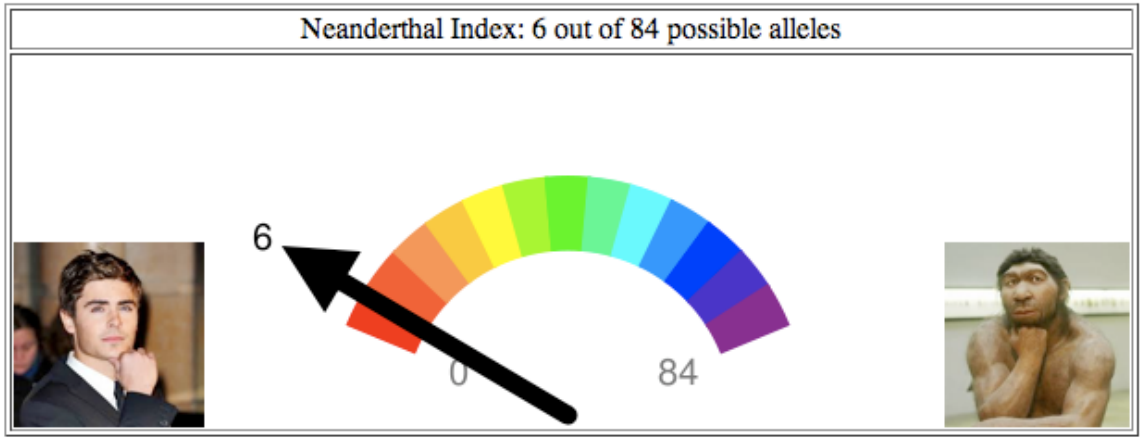
Which Habsburg are you?

You are Elisabeth of Valois (1545-1568)

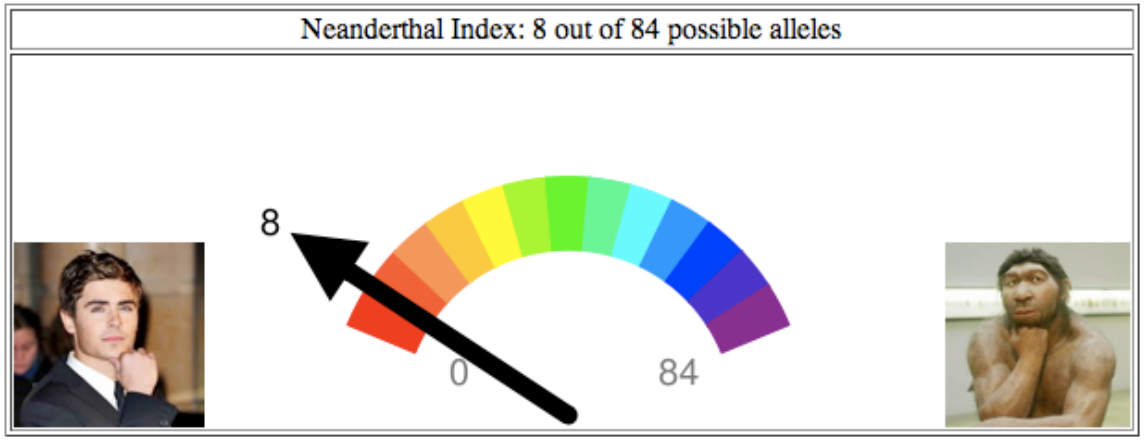
Born from a union of the French crown and the House of Medici, it is only natural that you should marry into one of history's largest empires at the age of 14. Your marriage is so happy that your husband abandons his mistress, but you produce only two daughters and die at 23 after miscarrying your first son.

F for Elisabeth of Valois (1545-1568): 0.001

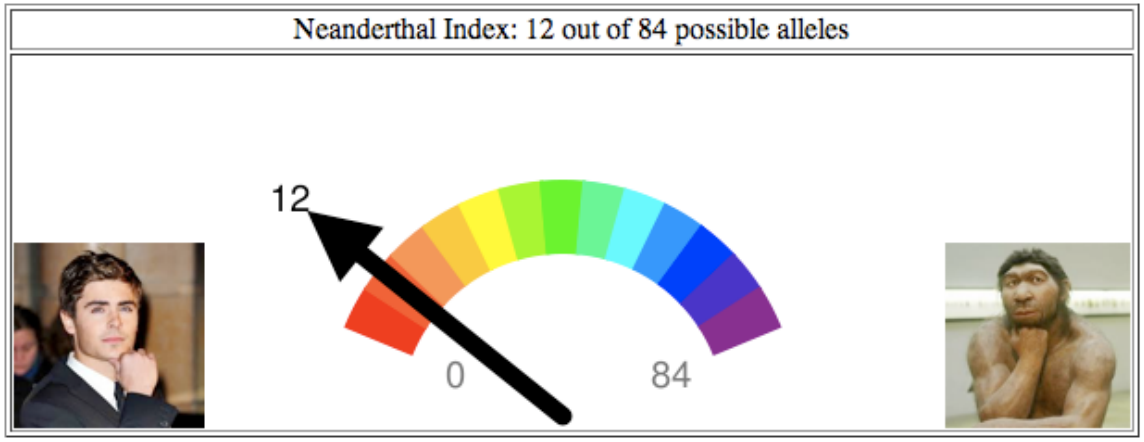
KS


Neanderthal Index: 6 out of 84 possible alleles
6
0
84

KK


Neanderthal Index: 8 out of 84 possible alleles
8
0
84

SK


Neanderthal Index: 12 out of 84 possible alleles
12
0
84

Feedback/survey/interviews

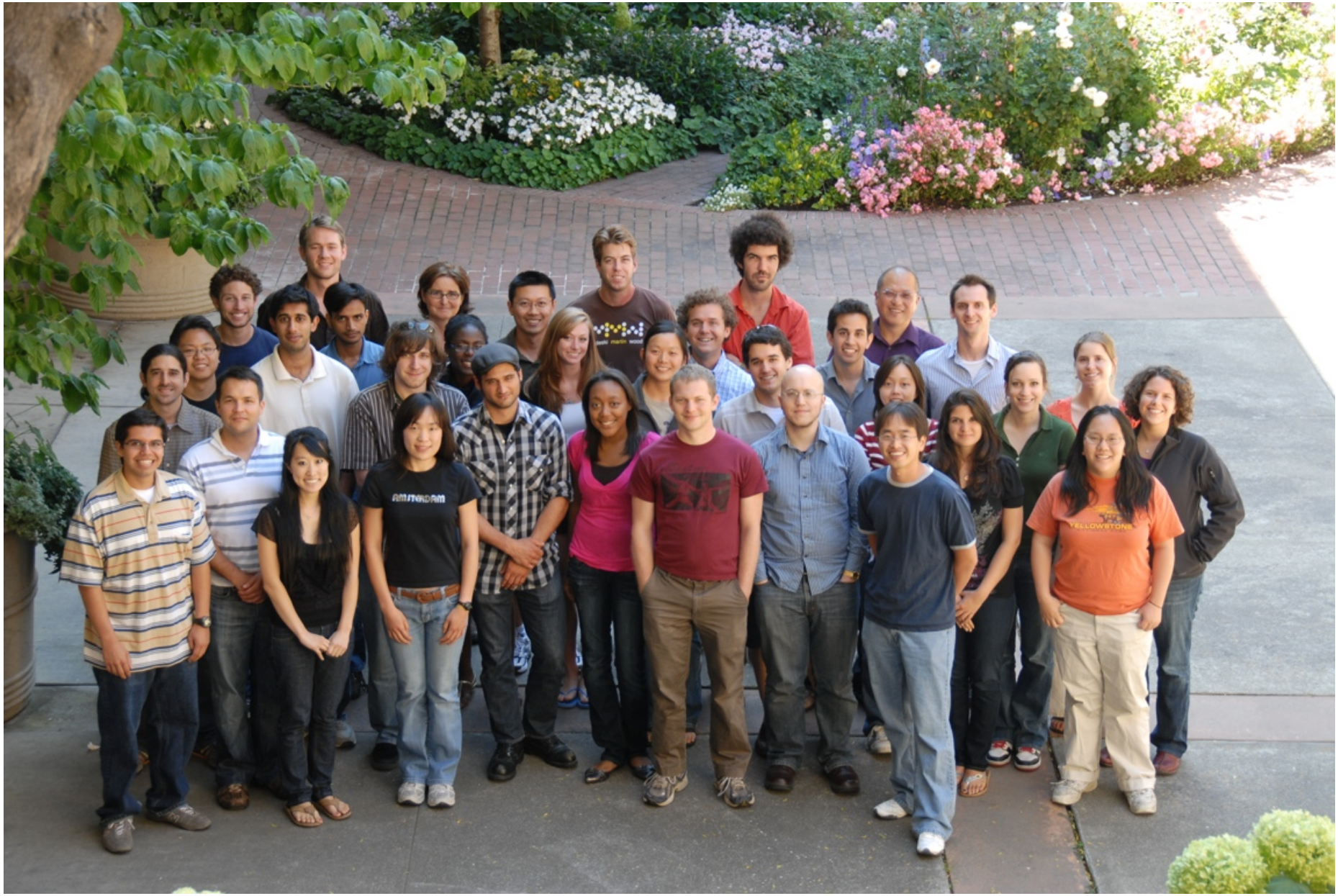
- Evaluations (paper, in-class)
- Post-course survey (electronic - second half of survey taken in week 1)
- Townhall meeting to discuss future of course
  - Wed 8/18 5pm in Beckman Library B302 (food provided)

Instructors





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