FaST Algorithms for Extremely Large Genome-Wide Association Studies

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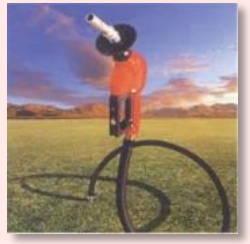
Tackling societal challenges with machine learning

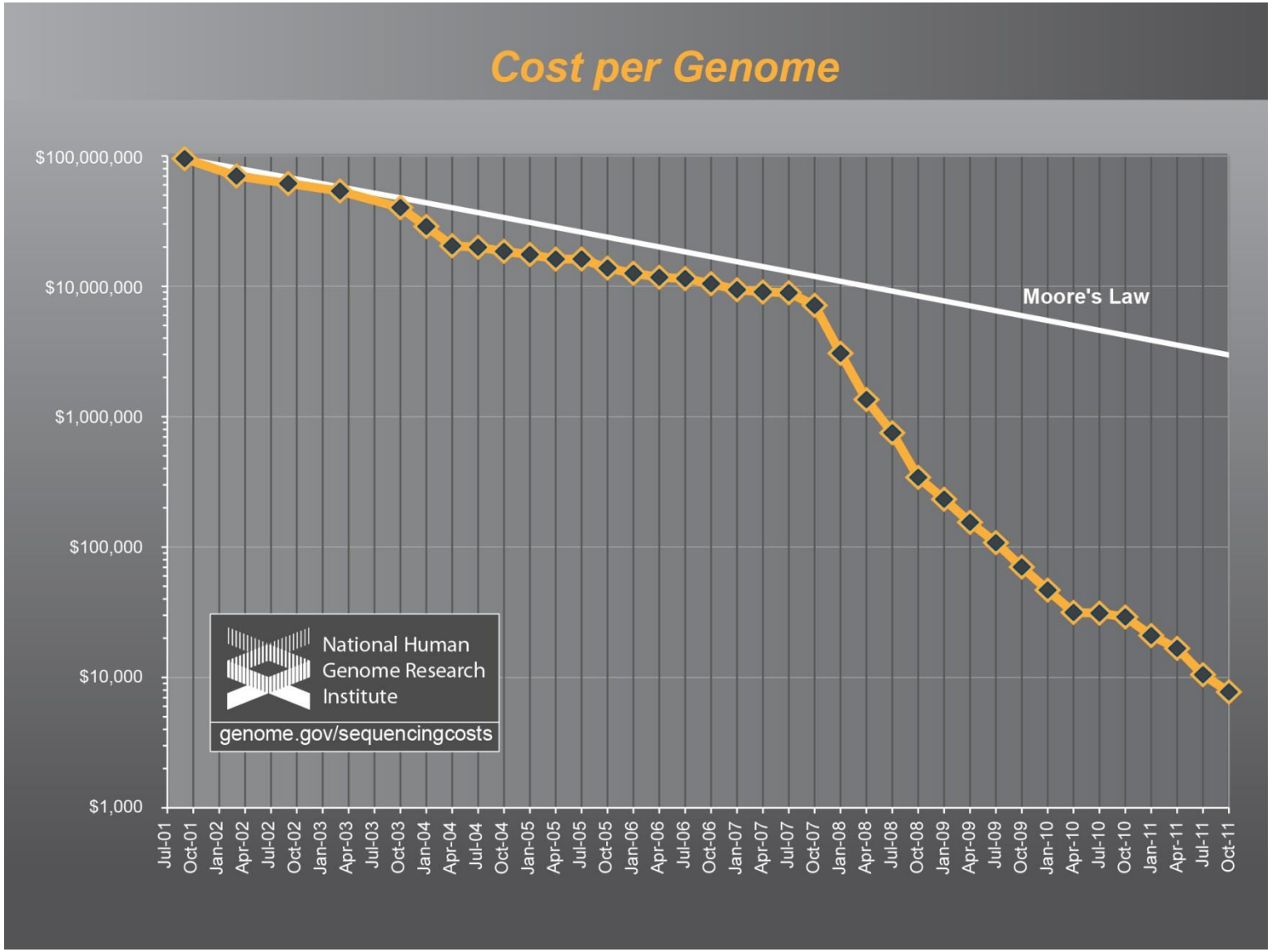
Human genomics and personalized medicine

Vaccine design
HIV, HCV, HRV

Genome assembly of sugar cane



The Genomics Revolution



Personalized Medicine

Use genetic markers to…

- Understand causes of disease
- Diagnose a disease
- Infer propensity to get a disease
- Predict favorable response to a drug
- Predict bad reaction to a drug

GWAS: Genome-wide association studies

...actgccgcgaC actgccgcgaggcctgactggcatccagtttagcggaactgccgcaa...
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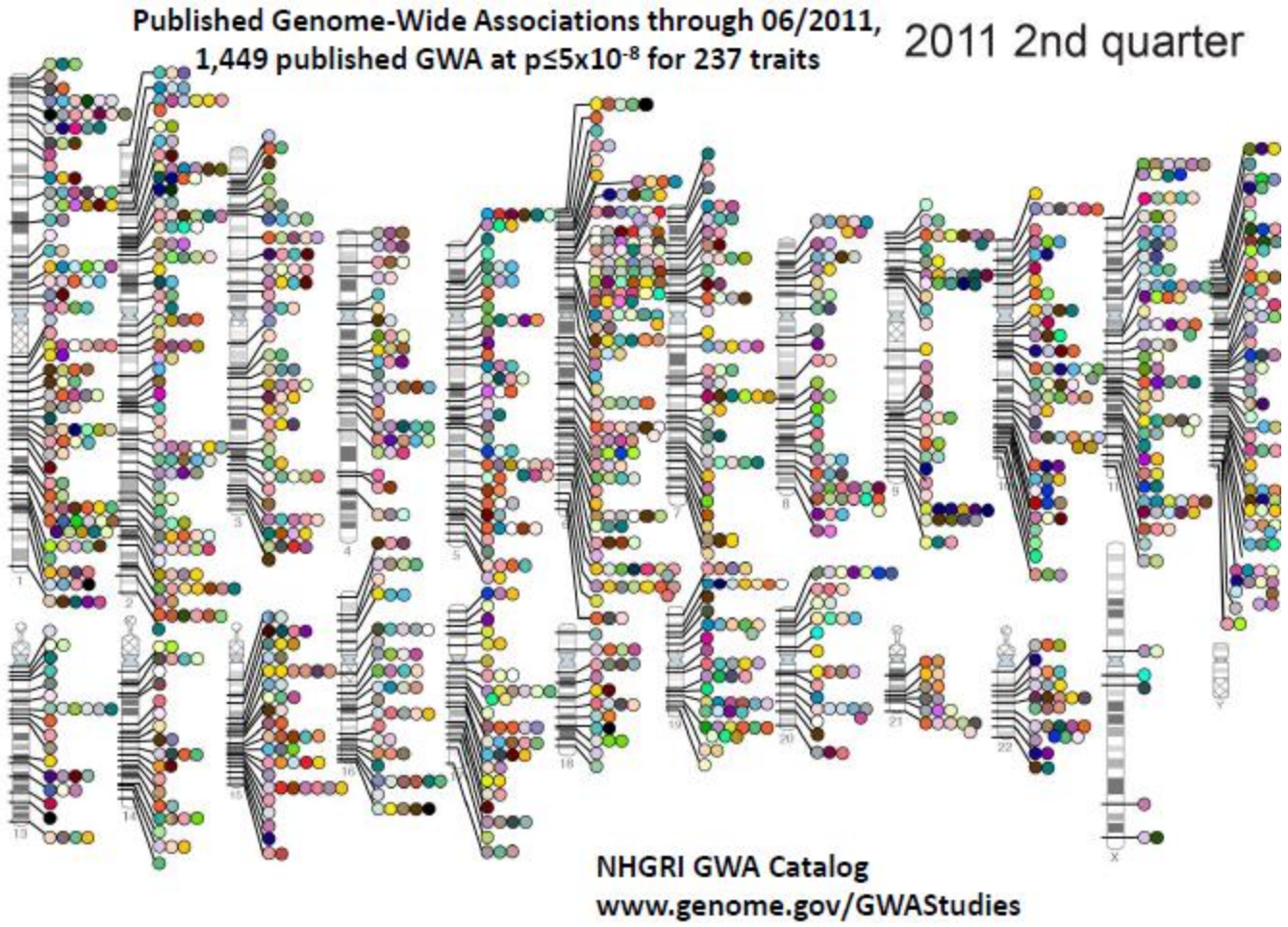
Genome-Wide Association Studies

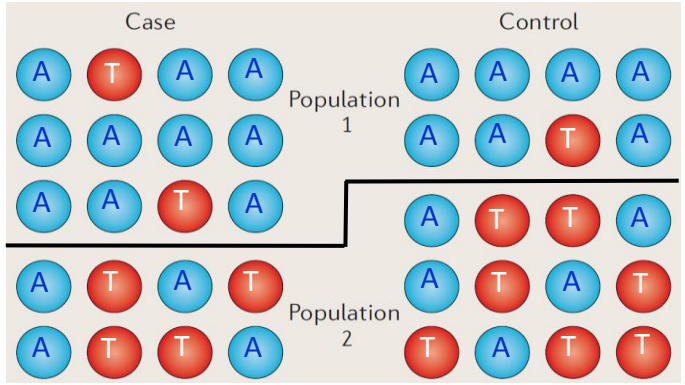


GWAS issues

- For common diseases, signals are spread out across the genome and weak
- To pick up these signals, we need lots of data
  - deCode
  - 23andMe
  - Kaiser
- Large data → confounding
  - Multiple ethnicities
  - Related individuals

Challenge: Confounding factors

- Suppose the set of cases has a different proportion of ethnicity X from control.
- Suppose we use linear regression to look for SNP-trait correlations.
- Then genetic markers that differ between X and other ethnicities in the study, Y, will appear artificially to be associated with disease.
- Problem gets worse with more data.



One solution: Throw out data

- Use one ethnicity
- Discard data for individuals who are too closely related

Bad idea: The most powerful comparisons are between closely-related individuals

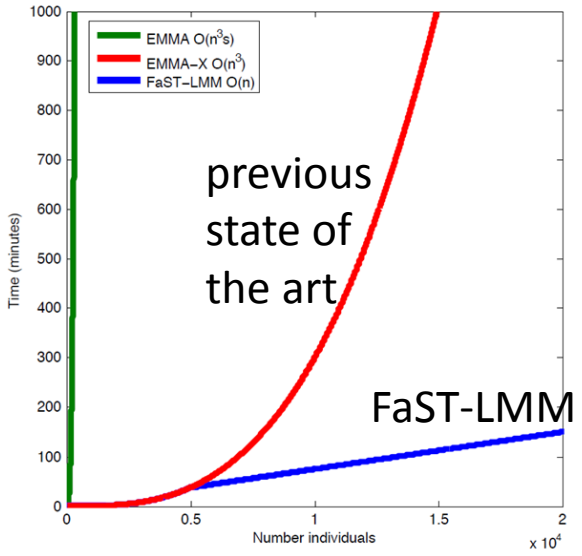
FaST-LMM: Factored Spectrally Transformed Linear Mixed Models

Linear mixed models:

- $O(N^3)$ runtime
  $O(N^2)$ memory use
  N<5,000
- FaST-LMM has O(N) runtime and memory use; N>100,000
- More power than traditional approach

nature | **methods** September 2011

nature | **methods** June 2012



Faster and more power: Really?

- LMM captures confounding structure by computing similarities between all pairs of individuals
- In this view, one would think all SNPs should be used
- BUT: LMM is equivalent to performing linear regression with these SNPS as covariates
- If someone gave you a million potential covariates, would you blindly use them all?
- Solution: Variable selection (“feature selection”)
- Result: ~100s of SNPs selected for similarity computation → less SNPs than individuals → O(N)

Application: Epistasis GWAS
(SNP-SNP interactions)

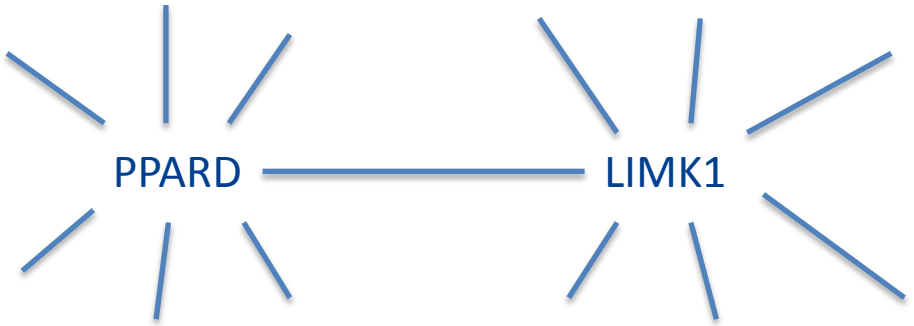
Seven common diseases:

- Type I diabetes
- Type II diabetes
- Coronary artery disease
- Hypertension
- Crohn's disease
- Rheumatoid arthritis
- Bipolar disorder

With FaST-LMM and Azure, can look at all SNP pairs (about 60 billion of them)

1,000 compute years; 20 TB output – we did it in 13 days on Azure

New results for CAD



SCIENTIFIC REPORTS

An Exhaustive Epistatic SNP Association Analysis on Expanded Wellcome Trust Data

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Software freely available for academic use (just bing “FaST-LMM”)