# Detecting Genetic Interactions in Genome-Wide Association Study

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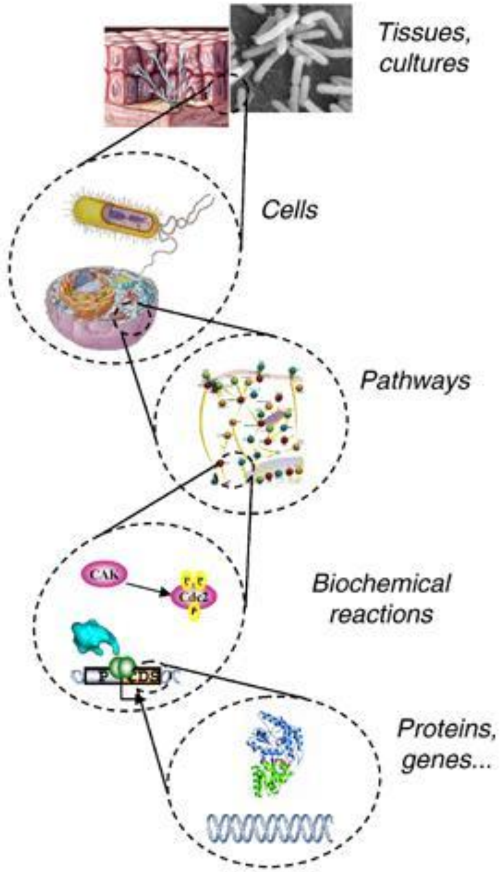
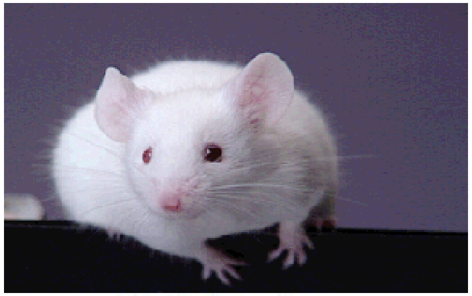
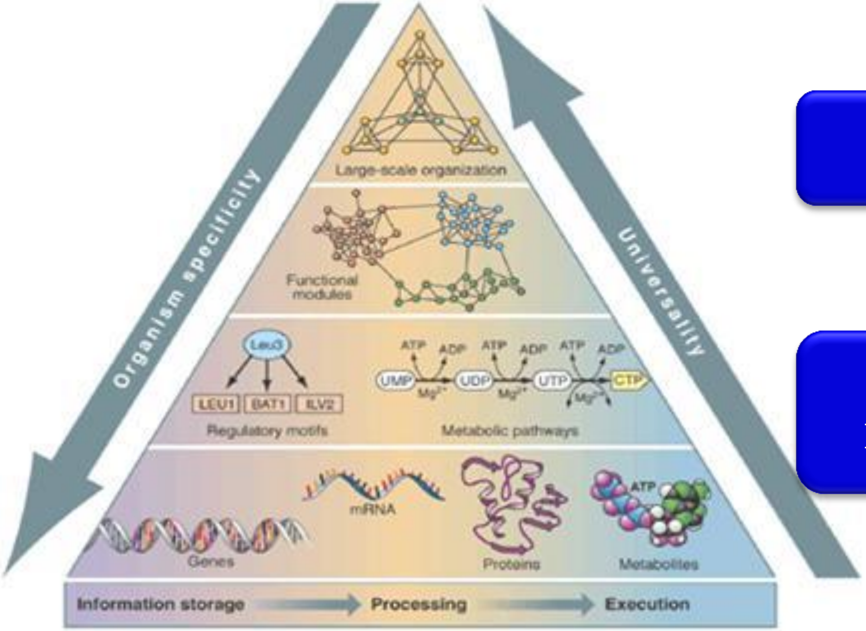
# Systems Genetics







**Complex Models**

↓

**Heterogeneous Data**

↓

**Powerful / Robust Methods and Systems**

# Why is GWA Important?

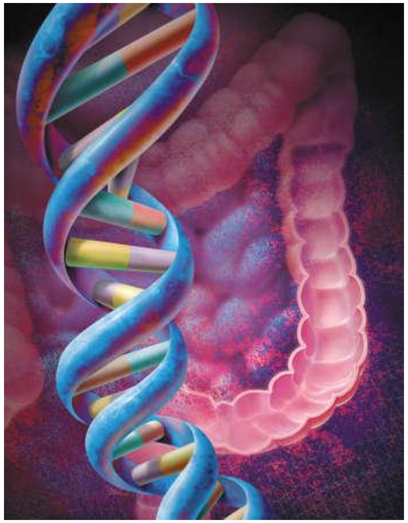
- **Once new genetic associations are identified**
    - ➢ **Researchers can develop better strategies to detect, treat and prevent the disease**
        - ❖ **Asthma, Cancer, Diabetes, Heart Disease**
    - ➢ **Health professionals can provide personalized medicine.**

# Why is GWA Important?

**A video clip from Gattaca (1997), (from youtube)**

# Detecting Genetic Interactions: Motivation

- Example: Mouse **Colon Cancer**



http://mycanceradvisor.com/

Two important genes

***Ptprj*** (chrom 2)
***Lrig1*** (chrom 6)

Detectible only when studying **interactions**

- True for many common diseases

# Detecting Genetic Interactions: Challenges

Statistical – Statistics to capture the interactions

Computational – **Hundreds of billions** of potential interactions

# Detecting Genetic Interactions: Previous Approaches

- Exhaustive [Moore et al. ’06, Purcell et al. ’07]
  - Not scalable
- Heuristic [Carlborg et al.’00, Nakamichi et al.’01]
  - Not optimal
- Two-step [Evans et al. ’06, Yang et al. ’09]
  - Filter, then search (Not optimal)
- Algorithm development is **in early stage**

# Detecting Genetic Interactions: Our Contributions

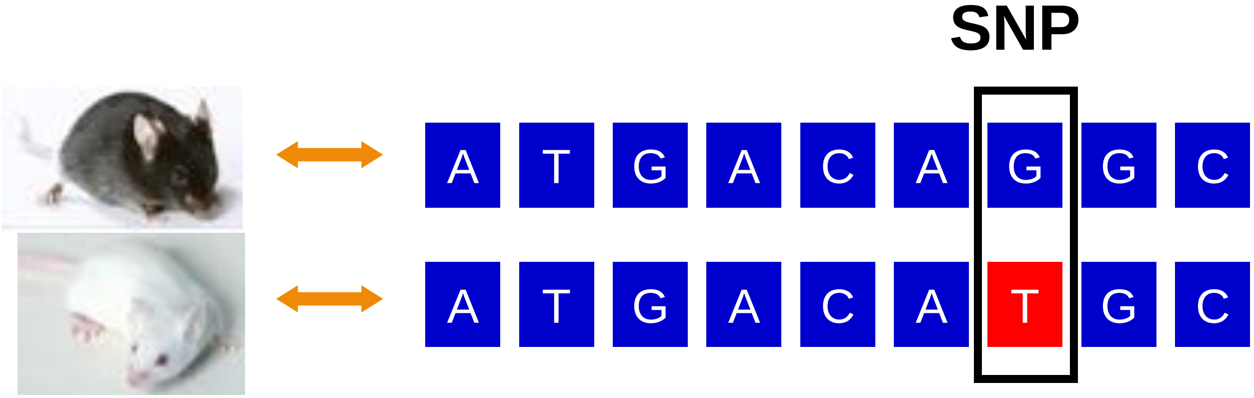
- **Efficiency** and **Optimality** [SIGKDD’08, PSB’09]
  - ➢ Dramatically reduced the computational burden
  - ➢ Guaranteed optimal solution
- **Applicability** [RECOMB’09, ISMB’10]
  - ➢ A wide range of study types and statistics
- The **first** to address these issues systematically

# Outline of the Talk

- Background
  - ➢ SNPs and their interactions
  - ➢ Computational problems
- Algorithms for Detecting Genetic Interactions

# Single Nucleotide Polymorphism: SNP

SNP – mutation of a single nucleotide in the DNA sequence



SNP

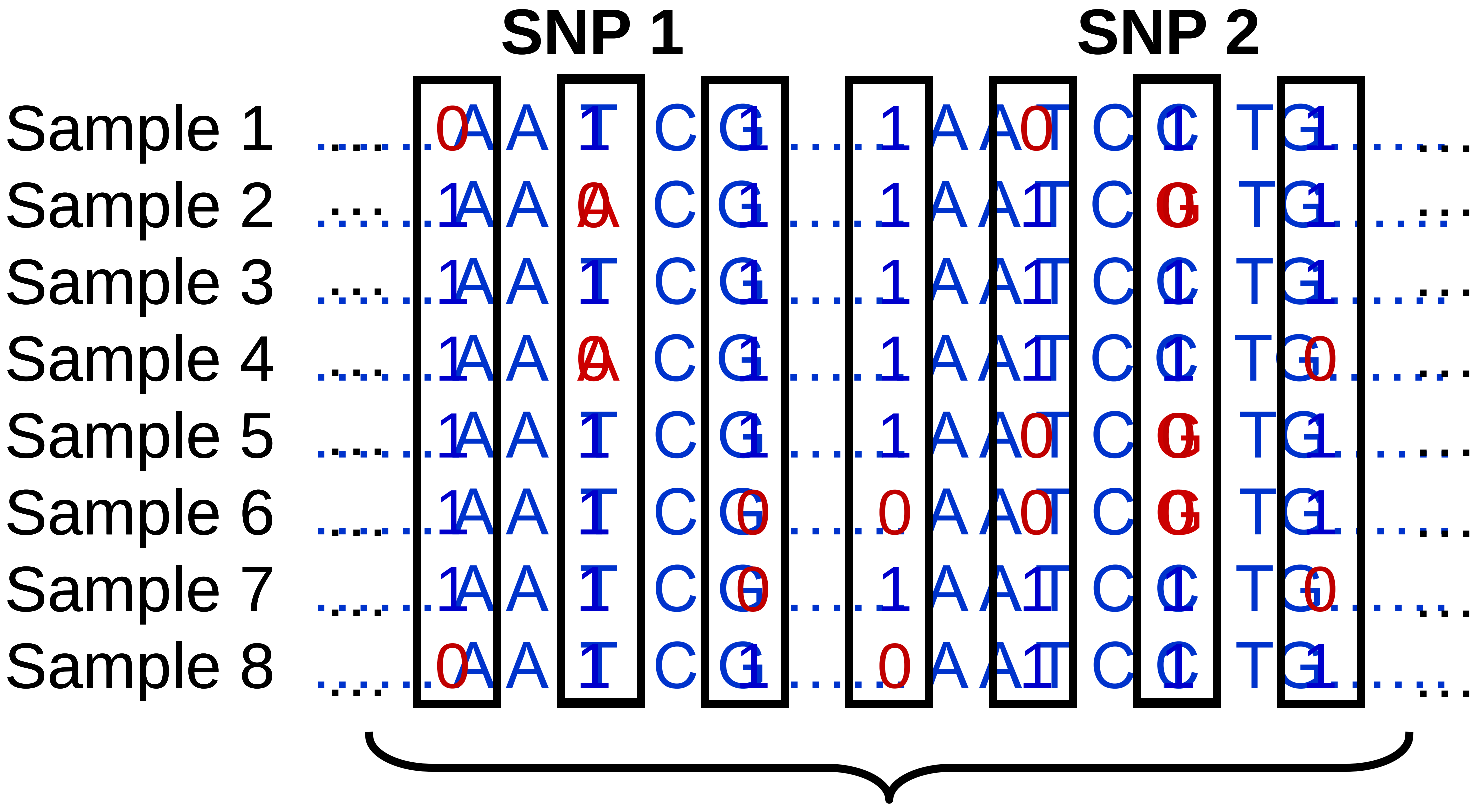
A T G A C A G G C

A T G A C A T G C

The most common form of genetic variation

Valuable for diagnostics and drug development

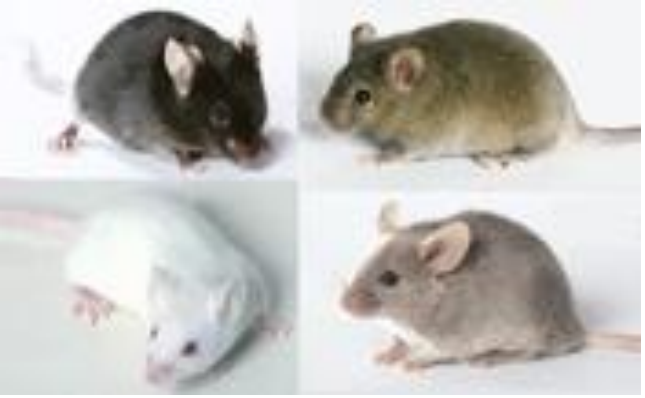
# SNPs as Binary Variables


SNP 1
SNP 2
Sample 1 ...... 0 A A 1 T C G 1 ...... 1 A A 0 T C 1 C T G 1 ......
Sample 2 ...... 1 A A 0 A C G 1 ...... 1 A A 1 T C 0 G T G 1 ......
Sample 3 ...... 1 A A 1 T C G 1 ...... 1 A A 1 T C 1 C T G 1 ......
Sample 4 ...... 1 A A 0 A C G 1 ...... 1 A A 1 T C 1 C T G 0 ......
Sample 5 ...... 1 A A 1 T C G 1 ...... 1 A A 0 T C 0 G T G 1 ......
Sample 6 ...... 1 A A 1 T C G 0 ...... 0 A A 0 T C 0 G T G 1 ......
Sample 7 ...... 1 A A 1 T C G 0 ...... 1 A A 1 T C 1 C T G 0 ......
Sample 8 ...... 0 A A 1 T C G 1 ...... 0 A A 1 T C 1 C T G 1 ......

Millions of SNPs in the whole genome

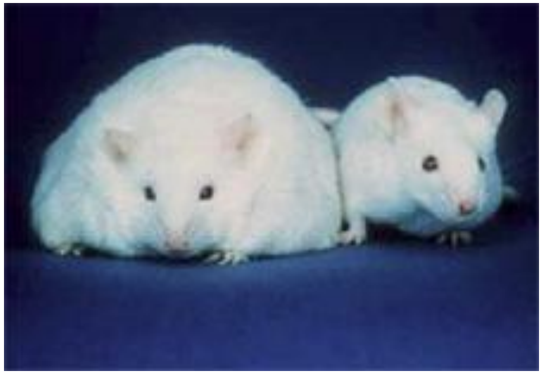
# Phenotype Variation

Phenotype – an observable characteristic or trait



http://www.jax.org/

Coat color



http://derc.ucsd.edu

Body weight

# SNP-Phenotype Association Study

- Which SNPs cause the phenotype variation?

| SNPs | Pheno. |
|---|---|
| ...... 0 1 0 1 0 1 ...... | 8 |
| ...... 0 0 0 0 0 1 ...... | 7 |
| ...... 0 1 1 0 0 1 ...... | 12 |
| ...... 0 0 0 0 1 0 ...... | 11 |
| ...... 1 1 1 1 1 1 ...... | 2 |
| ...... 1 0 0 1 0 1 ...... | 5 |
| ...... 1 1 0 1 0 1 ...... | 0 |
| ...... 1 0 1 1 0 0 ...... | 3 |

**Longstanding goal of genetic studies**

# Traditional Single-SNP Approach

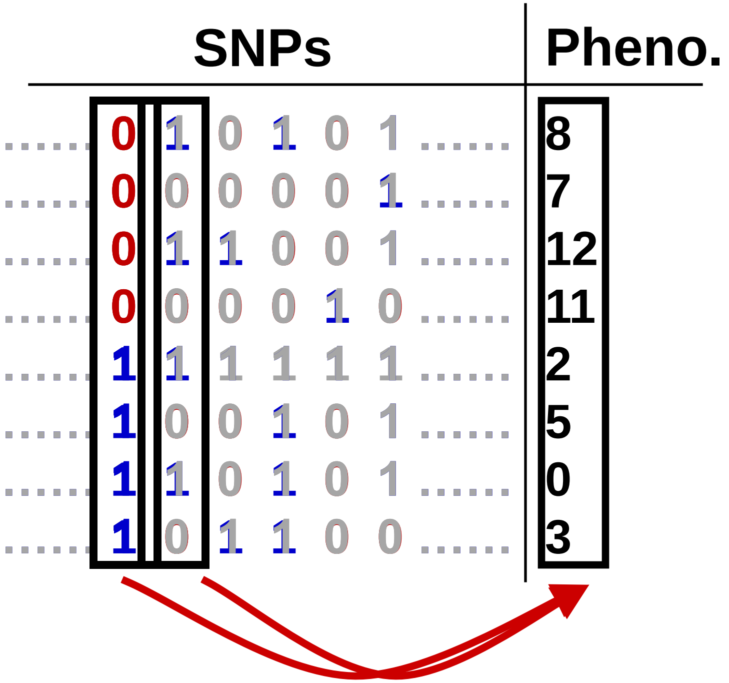
- For every SNP
- Do a statistical test

Large test value

⇒ Strong association

$$T(\text{SNP1},\text{pheno}) = 28.2$$

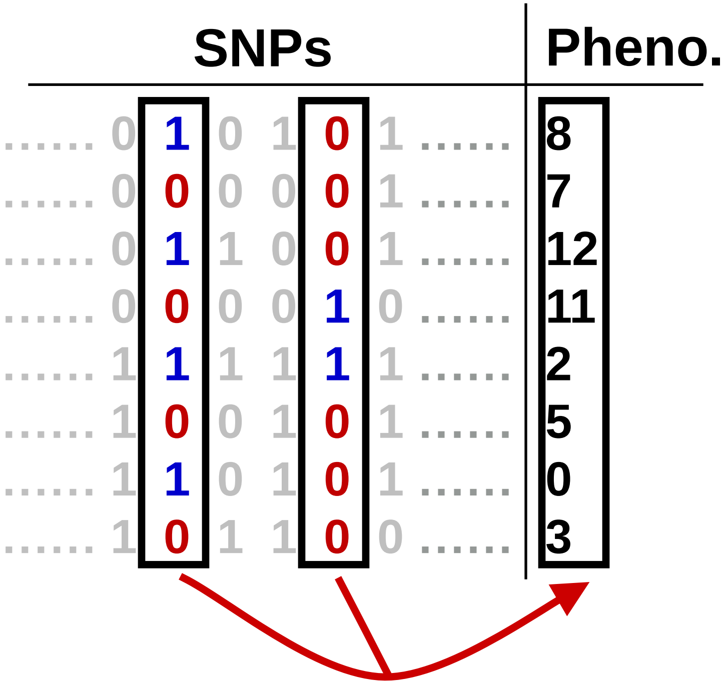
$$T(\text{SNP2},\text{pheno}) = 0.6$$



| | SNPs | | | | | | | Pheno. |
|---|---|---|---|---|---|---|---|---|
| ...... | 0 | 1 | 0 | 1 | 0 | 1 | ...... | 8 |
| ...... | 0 | 0 | 0 | 0 | 0 | 1 | ...... | 7 |
| ...... | 0 | 1 | 1 | 0 | 0 | 1 | ...... | 12 |
| ...... | 0 | 0 | 0 | 0 | 1 | 0 | ...... | 11 |
| ...... | 1 | 1 | 1 | 1 | 1 | 1 | ...... | 2 |
| ...... | 1 | 0 | 0 | 1 | 0 | 1 | ...... | 5 |
| ...... | 1 | 1 | 0 | 1 | 0 | 1 | ...... | 0 |
| ...... | 1 | 0 | 1 | 1 | 0 | 0 | ...... | 3 |

# Detecting SNP-SNP Interactions

- Complex phenotypes
  - ➢ Diabetes, heart disease, etc …
  - ➢ **Joint effect** of genetic factors
- SNP-SNP interactions
  - ➢ Test for every **SNP-pair**
- A hot research area in Bioinformatics community [Hoh et al.’03, Hirschhorn et al.’05, Musani et al. ’07]



| SNPs | | | | | | | | Pheno. |
|---|---|---|---|---|---|---|---|---|
| …… | 0 | 1 | 0 | 1 | 0 | 1 | …… | 8 |
| …… | 0 | 0 | 0 | 0 | 0 | 1 | …… | 7 |
| …… | 0 | 1 | 1 | 0 | 0 | 1 | …… | 12 |
| …… | 0 | 0 | 0 | 0 | 1 | 0 | …… | 11 |
| …… | 1 | 1 | 1 | 1 | 1 | 1 | …… | 2 |
| …… | 1 | 0 | 0 | 1 | 0 | 1 | …… | 5 |
| …… | 1 | 1 | 0 | 1 | 0 | 1 | …… | 0 |
| …… | 1 | 0 | 1 | 1 | 0 | 0 | …… | 3 |

# The Computational Problem

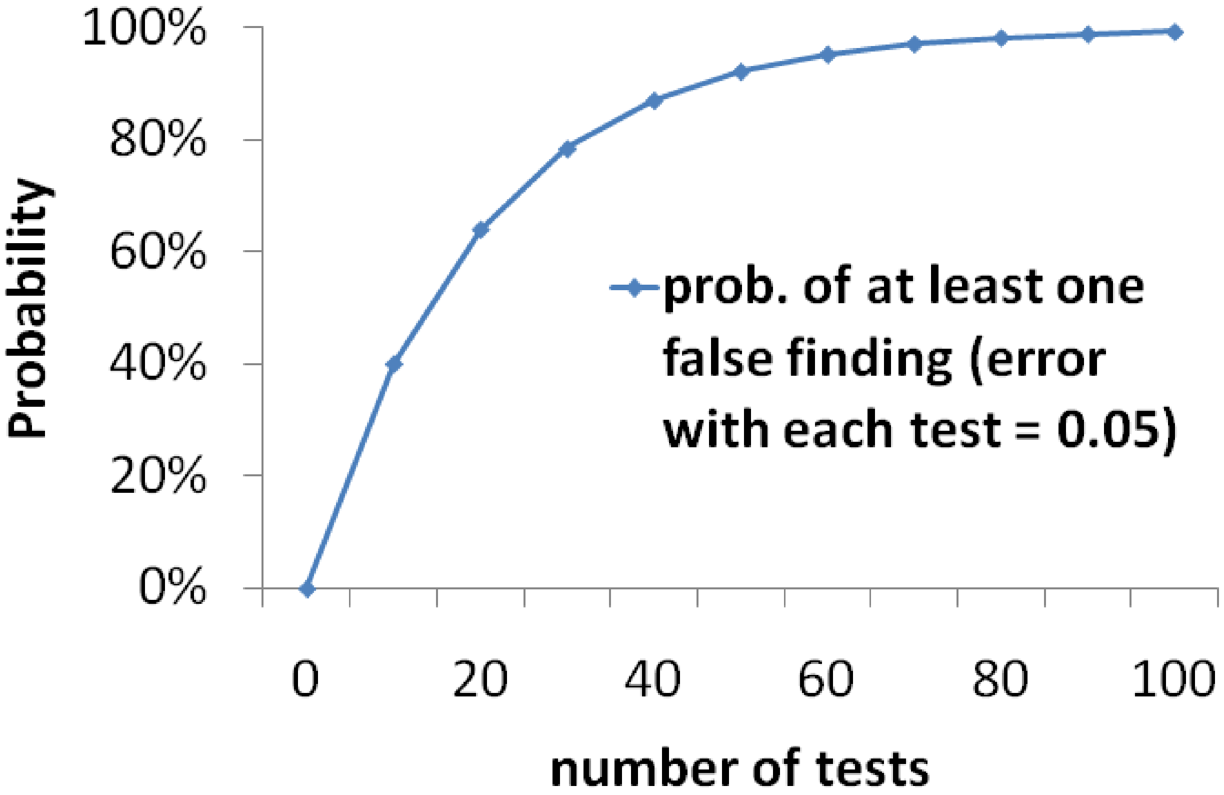
- Problem: Find all SNP-pairs that are **significantly associated** with phenotype

⬆

How to define it ?

# Multiple Testing Problem

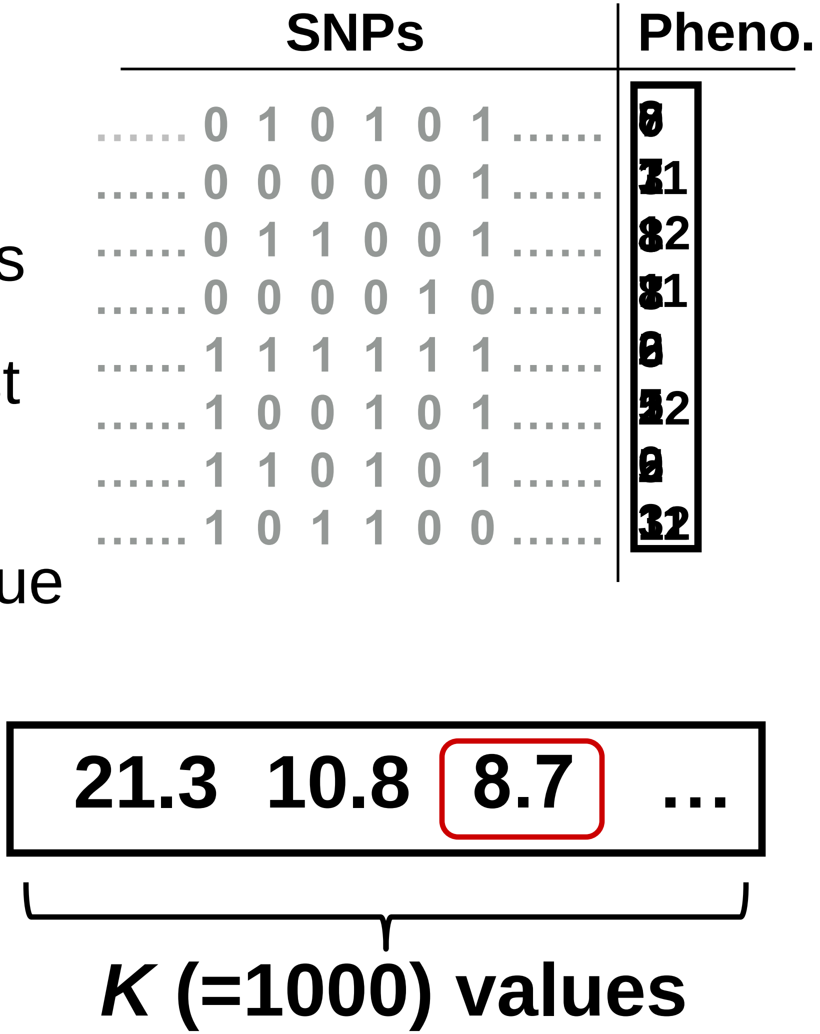
Multiple tests increase the probability of false findings



# Permutation Test for Error Controlling

**Goal**: Find a **threshold *θ***

- Permute phenotype $K$(=1000) times
- For each permutation, find max test value
- **Threshold *θ*** = $\boldsymbol{\alpha} \times K$ -th largest value ($0.01 \leq \boldsymbol{\alpha} \leq 0.05$)
- SNP-pairs ≥ ***θ*** are **significant**



| SNPs | Pheno. |
|---|---|
| …… 0 1 0 1 0 1 …… | [illegible] |
| …… 0 0 0 0 0 1 …… | [illegible] |
| …… 0 1 1 0 0 1 …… | [illegible] |
| …… 0 0 0 0 1 0 …… | [illegible] |
| …… 1 1 1 1 1 1 …… | [illegible] |
| …… 1 0 0 1 0 1 …… | [illegible] |
| …… 1 1 0 1 0 1 …… | [illegible] |
| …… 1 0 1 1 0 0 …… | [illegible] |

**21.3 10.8 8.7 …**

***K*** **(=1000) values**

# The Computational Problem (Revisited)

- Problem 1: Find threshold by **permutation test**
- Problem 2: Find all significant SNP-pairs ( ≥ $\boldsymbol{\theta}$ )
- Brute force: enumerate all SNP-Pairs
- Permutation test is **computationally intensive**

# Challenges

- Statistical – effective tests
  - ➢ ANOVA, chi-square, likelihood ratio, etc…
- Computational – huge search space
  - ➢ 100K SNPs and 1K permutations
    - – Number of tests: **500 Billion**
    - – Can be easily **MUCH LARGER**
- Must be handled together

# Our Solutions

- Efficiency and Optimality [SIGKDD'08, PSB'09]
  - ➢ **Bound** on test statistic
  - ➢ **Indexing** search space for bound estimation
- Applicability [RECOMB'09, ISMB'10]
  - ➢ Common statistics are **convex**
  - ➢ Computing contingency tables

# Outline of the Talk

- Background
  - SNP-SNP interactions
  - Computational problem & Challenges
- ➡ Detecting SNP-SNP Interactions
  - Algorithms for ANOVA and chi-square tests
  - A general approach COE
  - A more general approach TEAM

# FastANOVA - Key Ideas

## *SIGKDD 2008*

- **Bound** on test statistic
  - Filter out insignificant SNP-pairs
- **Indexing** structure
  - Compute the bound for **a group of** SNP-pairs
- Removal of redundant computation

# The Upper Bound

$$T(\text{SNP pair}, \text{pheno}) \le \underbrace{\text{constant} + R_1 + R_2}_{\text{Need to be } \boldsymbol{\geq \theta} \text{ to be significant}}$$

# The Upper Bound

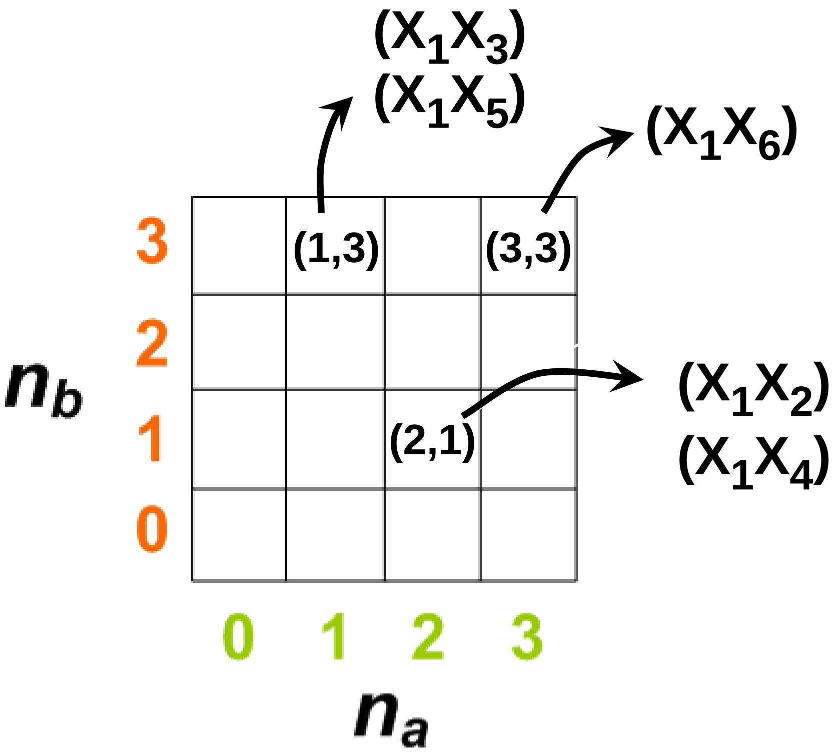
$$\begin{cases} R_1 = f(n_a) \\ R_2 = f(n_b) \end{cases}$$

$$\begin{cases} n_a \text{ : min \# \{0,1\} in } x_j \text{ (when } x_i = 0) \\ n_b \text{ : min \# \{0,1\} in } x_j \text{ (when } x_i = 1) \end{cases}$$

| $x_i$ | $x_j$ | |
|---|---|---|
| 0 | 0 | $n_a = 2$ |
| 0 | 0 | |
| 0 | 1 | |
| 0 | 1 | |
| 0 | 1 | |
| 0 | 1 | |
| 1 | 0 | $n_b = 1$ |
| 1 | 0 | |
| 1 | 1 | |
| 1 | 0 | |
| 1 | 0 | |
| 1 | 0 | |

# Indexing SNP-Pairs

| $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ | $X_6$ |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 1 | 0 | 1 |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 1 |
| 0 | 1 | 0 | 0 | 1 | 0 |
| 0 | 1 | 0 | 1 | 0 | 1 |
| 0 | 1 | 0 | 0 | 0 | 0 |
| 1 | 0 | 1 | 1 | 1 | 1 |
| 1 | 0 | 0 | 0 | 1 | 0 |
| 1 | 1 | 1 | 1 | 1 | 1 |
| 1 | 0 | 0 | 1 | 0 | 0 |
| 1 | 0 | 0 | 1 | 0 | 1 |
| 1 | 0 | 1 | 1 | 0 | 0 |



$(X_1X_3)$
$(X_1X_5)$

$(X_1X_6)$

$n_b$

3
2
1
0

(1,3)

(3,3)

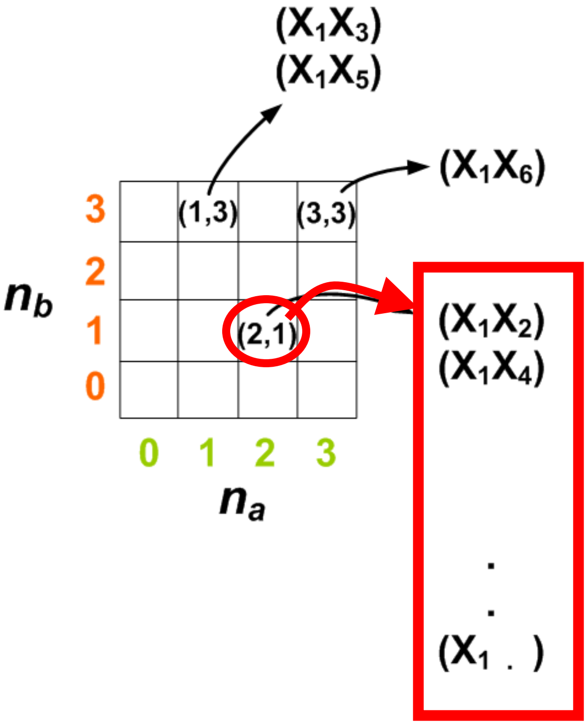
(2,1)

$(X_1X_2)$
$(X_1X_4)$

0 1 2 3

$n_a$

# Properties of the Indexing Structure



same upper bound

- Many pairs **share** an entry
- Pairs in an entry have the **same upper bound**
- **Built only once,** reused in all permutations

# FastANOVA - Overall Process

- For each SNP
  - Index its associated pairs
- For each permutation
  - Find the candidate pairs (*ub* $\geq \theta$ )
  - Evaluate test values of the candidates

# FastANOVA - Complexity

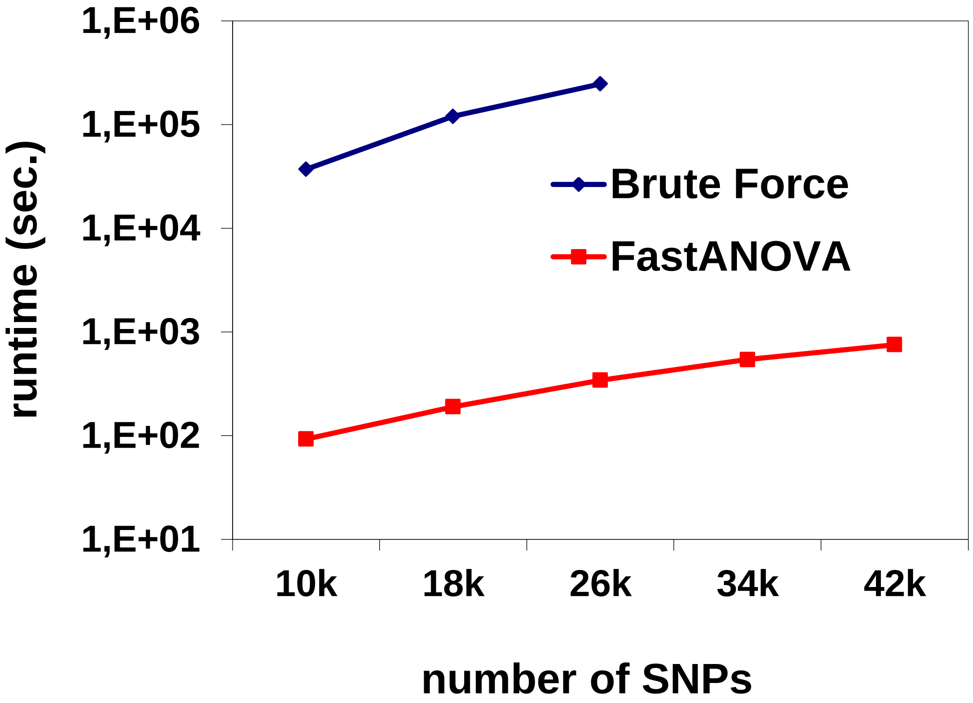
- Time
  - Brute force: $O(\underline{KN^2M})$
  - FastANOVA: $O(\underline{N^2M} + \underline{KNM^2} + CM)$
- Space
  - $O((N+K)M)$

$$\left.\begin{array}{l} \boldsymbol{N} = \#\ \textbf{SNPs} \\ \boldsymbol{M} = \#\ \textbf{individuals} \end{array}\right\}\ \boldsymbol{M \ll N}$$

***K* = # permutations**

***C* = # candidates**

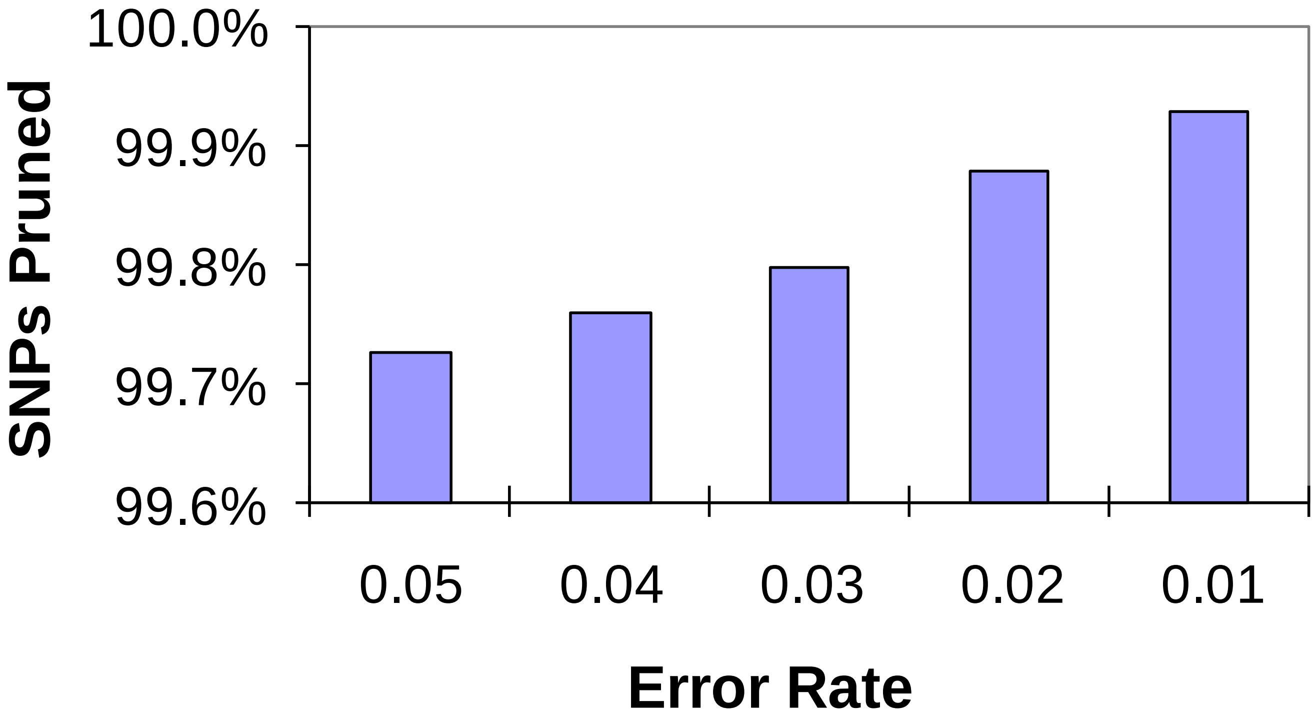
# Brute Force v.s. FastANOVA



**#SNPs = 44k, #individuals = 26, phenotype: metabolism (water intake)**

**Data available at http://www.jax.org**

# Pruning Power of the Bound



# The FastChi Algorithm

*PSB 2009*

**ANOVA (for quantitative pheno.)**

$$T(\text{SNP pair, pheno}) \le \text{constant} + \underbrace{R_1 + R_2}_{\textbf{(SNP-SNP relation)}}$$

**Chi-square (for binary pheno.)**

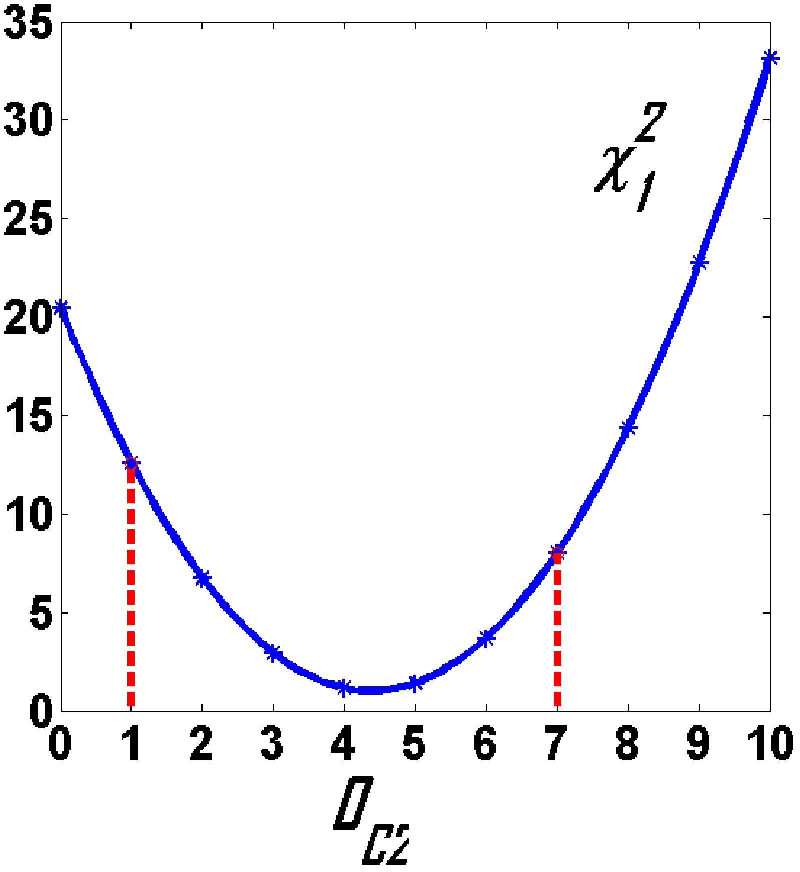
$$T'(\text{SNP pair, pheno}) \le \text{constant}' + \underbrace{R_1' + R_2'}_{\textbf{(SNP-SNP relation)}}$$

# COE – A General Approach

***RECOMB 2009***

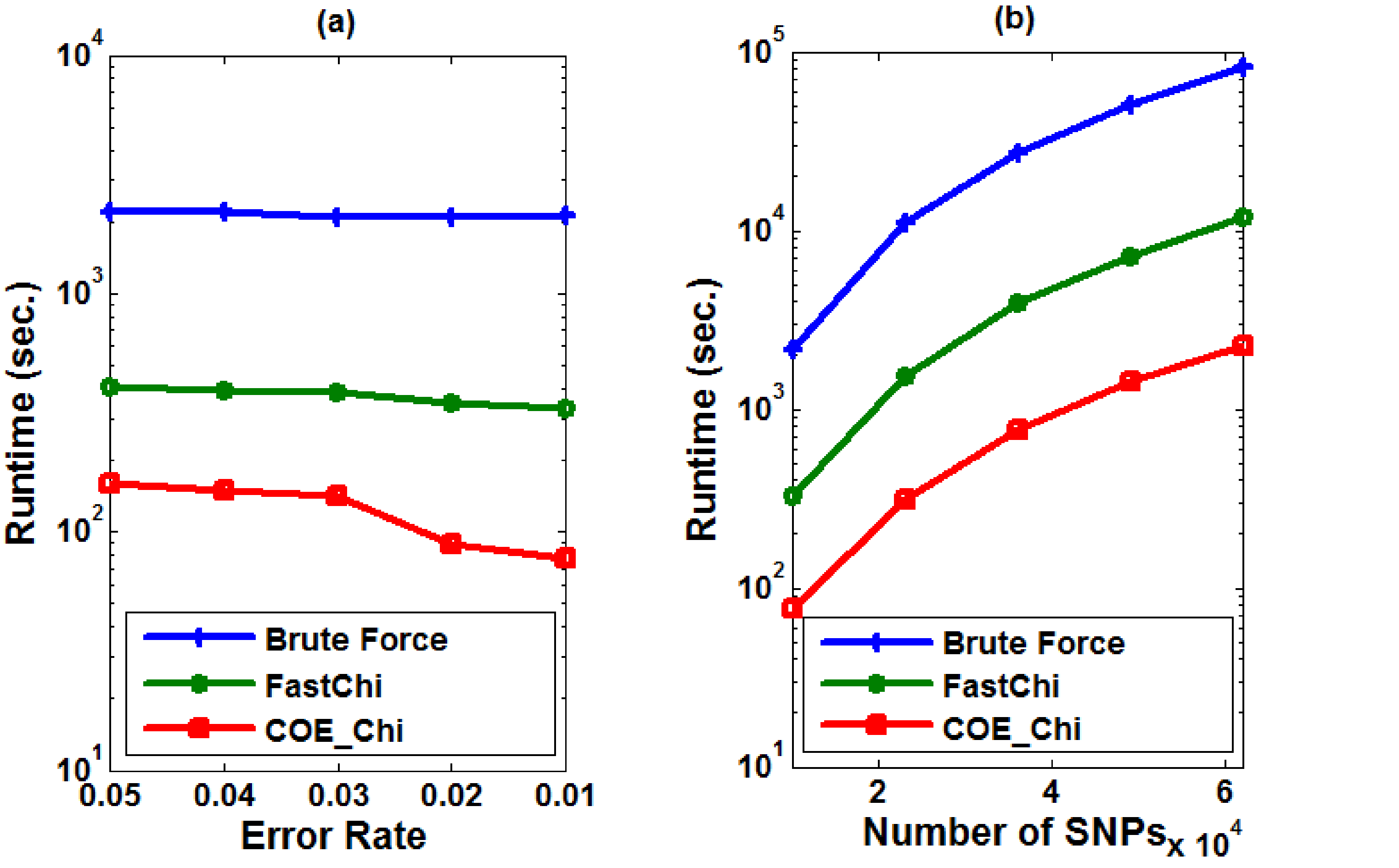
- Available tests
  - ➢ Chi-square, likelihood ratio, trend, entropy-based, etc …
  - ➢ Active research, more being proposed…
- A unified approach to all above tests?
- **Convexity** is the solution !

# Convexity Example: Chi-square Test

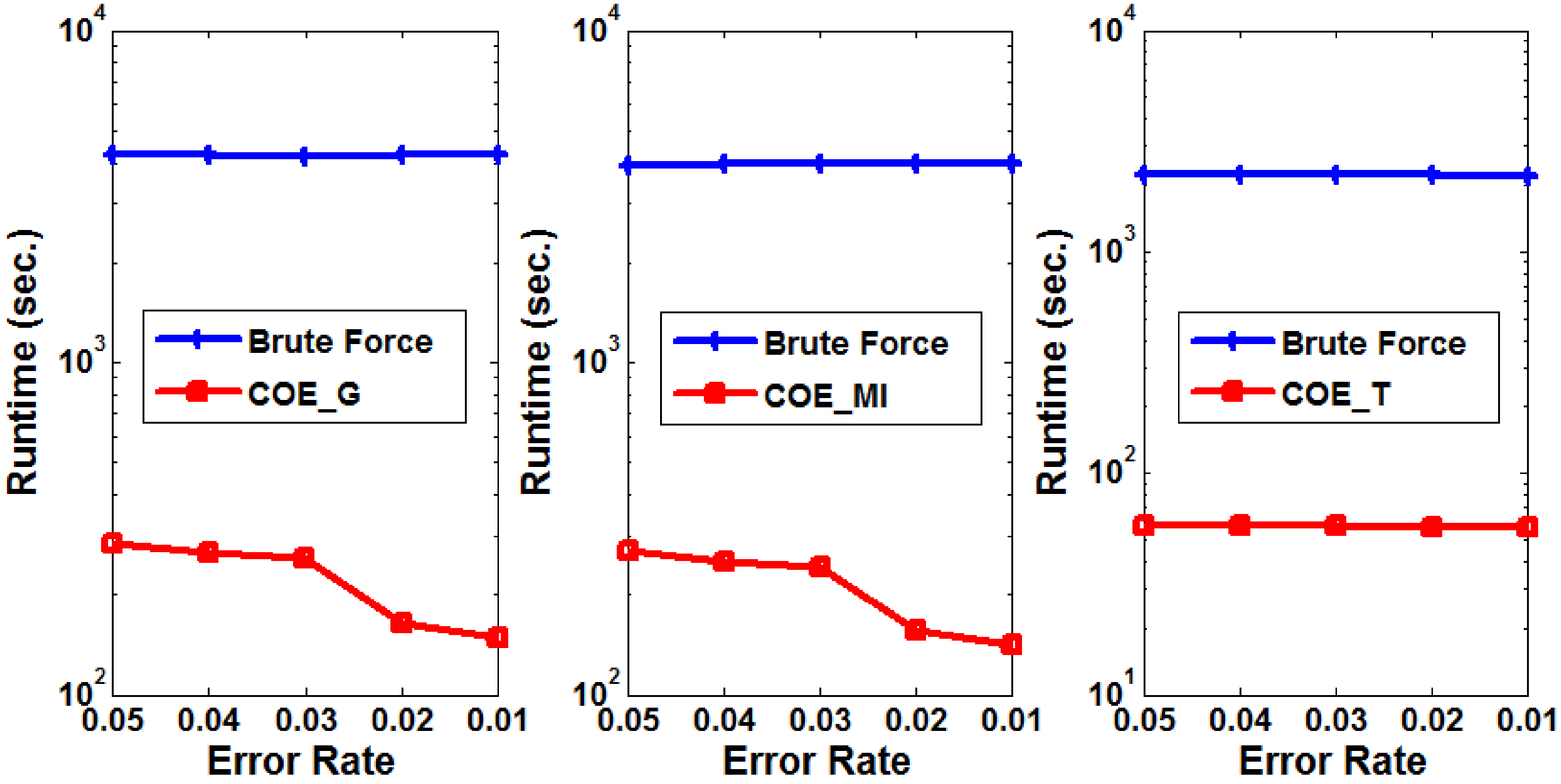


- **Theorem**: Convexity is a common property of many tests
- Determine the range of the *free variable* to get the upper bound

# Brute Force vs. FastChi vs. COE



# Brute Force vs. COE (on Various Tests)


G-Test Entropy-based Test Trend-Test

# Summary of the Algorithms

- Key ideas: bound, indexing, convexity

| Algorithm | Supported Test |
|---|---|
| FastANOVA | ANOVA test |
| FastChi | Chi-square test |
| COE | Convex tests |

- Designed for inbred mouse data: small sample size, binary SNPs

# TEAM - Overview

| | Previous | TEAM |
|---|---|---|
| **SNPs** | {0,1} | {0,1} & {0,1,2} |
| **Sample size** | Small | Large |
| **Error Control** | FWER | FWER & FDR |
| **Test Statistic** | With certain properties | Based on contingency table |

# The Computational Problem

- SNPs $\{\boldsymbol{X_1, X_2, \ldots, X_N}\}$
- Phenotype $\boldsymbol{Y}$, and permutations $\{\boldsymbol{Y_1, Y_2, \ldots, Y_k}\}$

Problem: Computing **Test Values** for SNP-pairs

↕

Computing **Contingency Tables**

# Contingency Table

| | $X_i = 0$ | | | $X_i = 1$ | | | $X_i = 2$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ |
| $Y = 0$ | $a_1$ | $a_2$ | $a_3$ | $b_1$ | $b_2$ | $b_3$ | $e_1$ | $e_2$ | $e_3$ |
| $Y = 1$ | $c_1$ | $c_2$ | $c_3$ | $d_1$ | $d_2$ | $d_3$ | $f_1$ | $f_2$ | $f_3$ |

# Contingency Table

| | $X_i = 0$ | | | $X_i = 1$ | | | $X_i = 2$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ |
| $Y = 0$ | $a_1$ | $a_2$ | $a_3$ | $b_1$ | $b_2$ | $b_3$ | $e_1$ | $e_2$ | $e_3$ |
| $Y = 1$ | $c_1$ | $c_2$ | $c_3$ | $d_1$ | $d_2$ | $d_3$ | $f_1$ | $f_2$ | $f_3$ |

↕

$\# ( X_i , X_j , Y ) = (1,1,1)$

# Contingency Table

| | $X_i = 0$ | | | $X_i = 1$ | | | $X_i = 2$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ |
| $Y = 0$ | $a_1$ | $a_2$ | $a_3$ | $b_1$ | $b_2$ | $b_3$ | $e_1$ | $e_2$ | $e_3$ |
| $Y = 1$ | $c_1$ | $c_2$ | $c_3$ | $d_1$ | $d_2$ | $d_3$ | $f_1$ | $f_2$ | $f_3$ |

**Only need to compute four variables**

# Contingency Table

| | $X_i = 0$ | | | $X_i = 1$ | | | $X_i = 2$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ | $X_j = 0$ | $X_j = 1$ | $X_j = 2$ |
| $Y = 0$ | $a_1$ | $a_2$ | $a_3$ | $b_1$ | $b_2$ | $b_3$ | $e_1$ | $e_2$ | $e_3$ |
| $Y = 1$ | $c_1$ | $c_2$ | $c_3$ | $d_1$ | $d_2$ | $d_3$ | $f_1$ | $f_2$ | $f_3$ |

↕

$\#\,(X_i, X_j, Y) = (1,1,1)$

# Incremental Update

| $Y$ | $X_1$ | $X_2$ | $X_3$ |
|---|---|---|---|
| 0 | 0 | 0 | 1 |
| 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 |
| 0 | 1 | 0 | 0 |
| 0 | 1 | 0 | 1 |
| 1 | 1 | 1 | 0 |
| 1 | 0 | 1 | 1 |
| 1 | 1 | 0 | 1 |
| 1 | 1 | 1 | 1 |
| 1 | 0 | 1 | 0 |

$\#(X_i, X_j, Y) = (1,1,1) \longleftrightarrow d_2$

# Incremental Update

| $Y$ | $X_1$ | $X_2$ | $X_3$ |
|---|---|---|---|
| 0 | 0 | 0 | 1 |
| 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 |
| 0 | 1 | 0 | 0 |
| 0 | 1 | 0 | 1 |
| 1 | 1 | 1 | 0 |
| 1 | 0 | 1 | 1 |
| 1 | 1 | 0 | 0 |
| 1 | 1 | 1 | 1 |
| 1 | 0 | 1 | 0 |

$\#(X_i, X_j, Y) = (1,1,1) \longleftrightarrow d_2$

$(X_1, X_2, Y) \longleftrightarrow d_2 = 2$

$(X_1, X_3, Y) \longleftrightarrow d_2 = ?$

# Incremental Update

| $Y$ | $X_1$ | $X_2$ | $X_3$ |
|---|---|---|---|
| 0 | 0 | 0 | 1 |
| 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 |
| 0 | 1 | 0 | 0 |
| 0 | 1 | 0 | 1 |
| 1 | 1 | 1 | 0 |
| 1 | 0 | 1 | 1 |
| 1 | 1 | 0 | 0 |
| 1 | 1 | 1 | 1 |
| 1 | 0 | 1 | 0 |

$\#(X_i, X_j, Y) = (1,1,1) \longleftrightarrow d_2$

$(X_1, X_2, Y) \longleftrightarrow d_2 = 2$

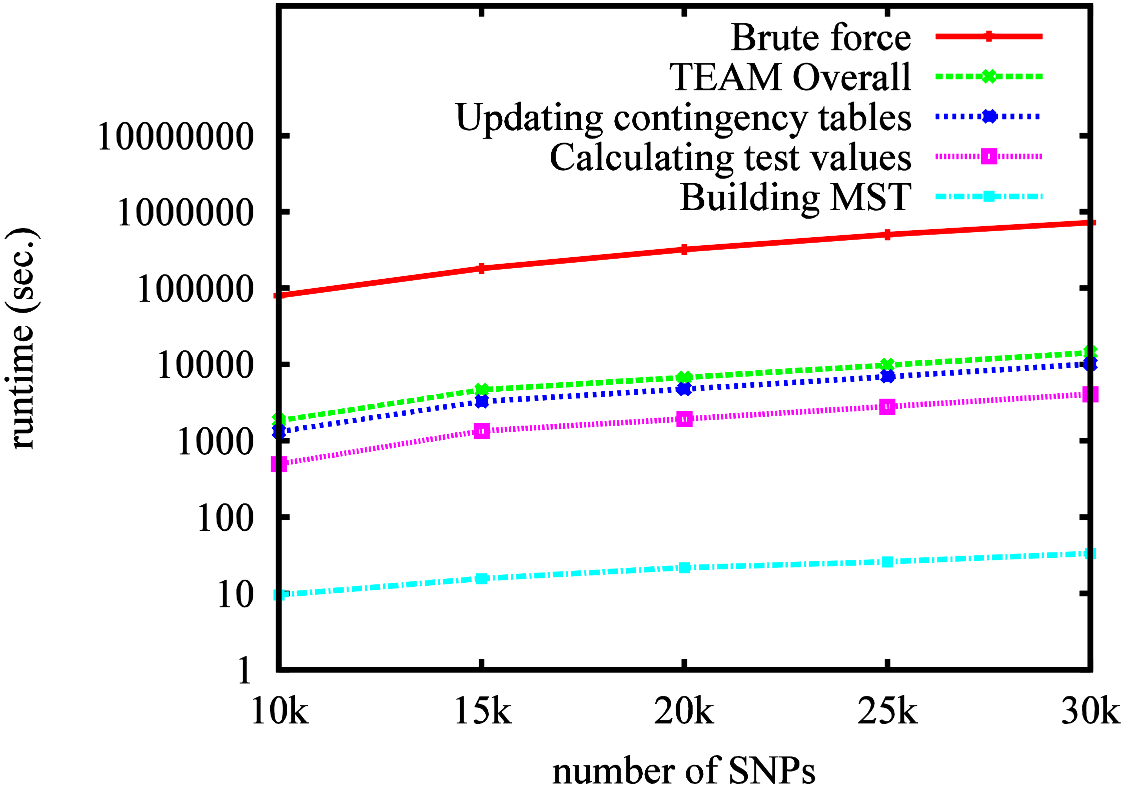
$(X_1, X_3, Y) \longleftrightarrow d_2 = 1$

**No need to scan all individuals**

**Cost proportional to the difference**

**Updating order? – Minimal Spanning Tree**

# TEAM v.s. Brute Force (Human Data)



**Data generated by Hapsample**

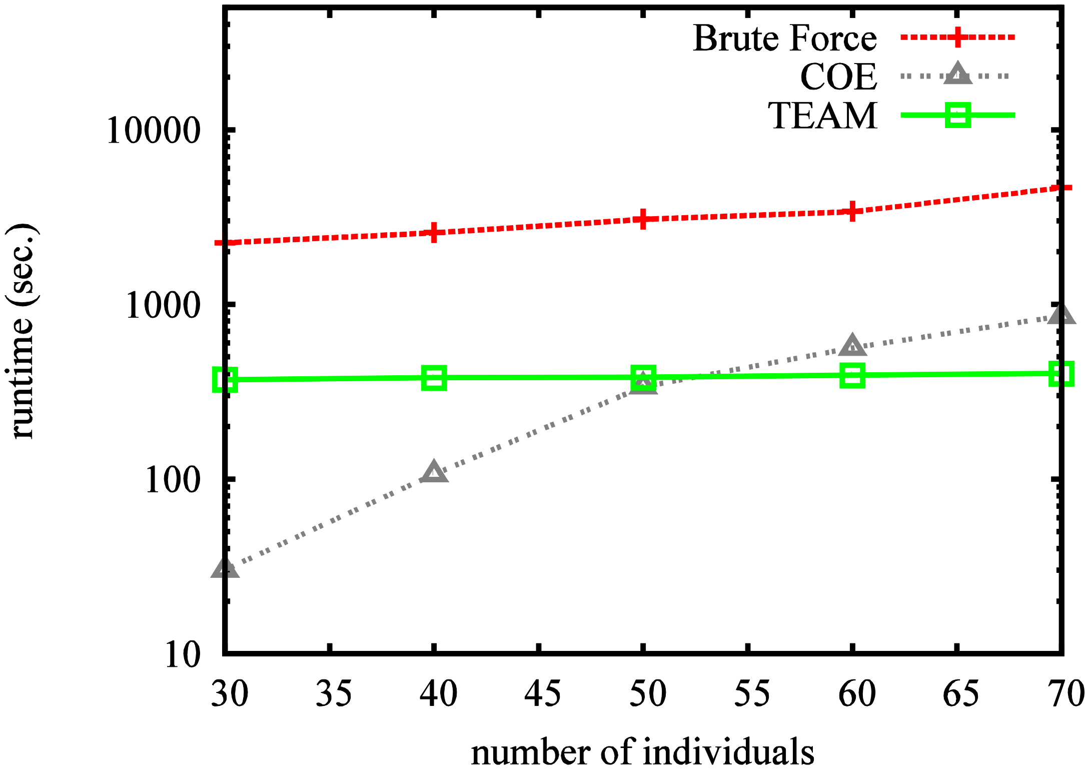
#SNPs = 100K

#Samples = 400

#Permutations = 100

Case/Control = 1

# TEAM v.s. COE (Inbred Mouse Data)



**Real Mouse Genotype Data (from Jackson Lab)**

#SNPs = 10K

#Samples = 71

#Permutations = 100

Case/Control = 1

# TEAM - Summary

- Designed for human study: large sample size, {0,1,2} SNPs
- Idea: incrementally update contingency tables

# Overall Summary on Detecting Genetic Interactions

- Studying SNP-SNP interactions is important
- Challenges
  - ➢ Statistical: effective statistics
  - ➢ Computational: enormous search space
- We provide first solutions to
  - ➢ Efficiency and Optimality
  - ➢ Applicability

# References

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