Data Integration and Iterative Testing

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Outline

Overview of Data Integration

Iterative Hypothesis Testing

- Community Detection
- Mining of Differential Correlation

Data Integration

Classical: Horizontal Integration

- Common measurement platform
- Multiple experiments or sample groups

Modern: Vertical Integration

- Common samples
- Multiple measurement platforms/technologies
- Data with and without response variables

Example: The Cancer Genome Atlas (TCGA)

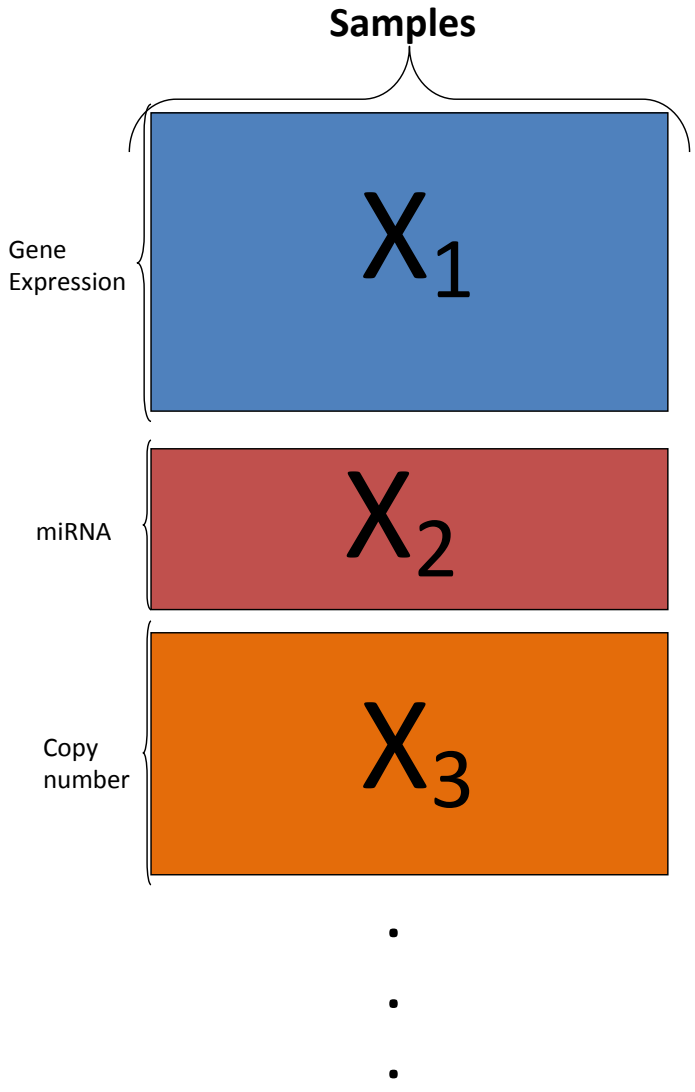
Representative Dataset: 350 breast cancer tumors

- Gene expression data (18K genes)
- miRNA data (650 miRNAs)
- Copy number data (200K probes)
- Methylation data (22K CG regions)
- Mutation data (12K genes)

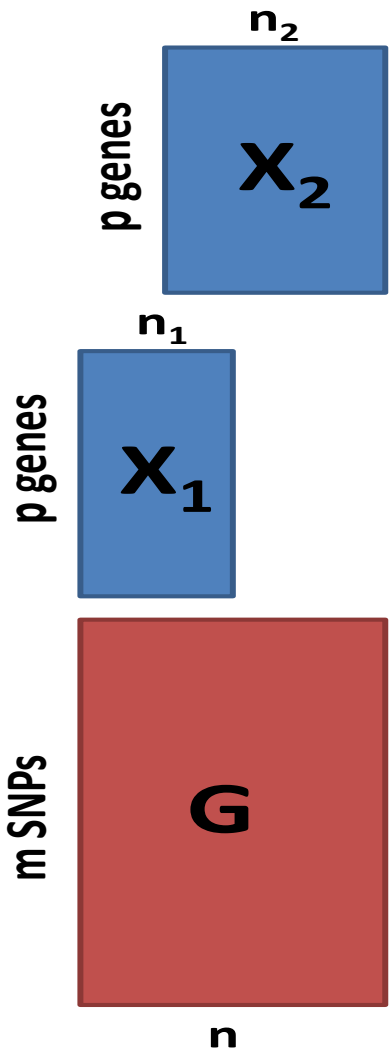
Responses

- Survival
- Response to therapy

TCGA: Data Matrix View



Multi-Tissue eQTL Analysis (GTEx)



Potential

- Borrowing strength across tissues
- Genetic basis of tissue variation

Complications

- Donors vary by tissue
- Configurations of association
  - Common across tissues
  - Tissue specific
- Large number of tissues

Potential of Vertical Integration

Statistics: Enhanced power, improved prediction

- Borrowing information across platforms
- Analysis of shared and individual variation across platforms

Genomics: New/enhanced insights into underlying biology

- Relationships between measured genomic features
- Role of genomic features in predicting outcome of interest

The Fine Print (in practice)

Genomics (upstream)

- Preprocessing: imputation, normalization, scaling
- Identification and removal of appropriate covariates

Statistics (midstream)

- Verifying distribution and sparsity assumptions
- Selecting free parameters
- Availability of robust/efficient software

Networks as Models or Summaries

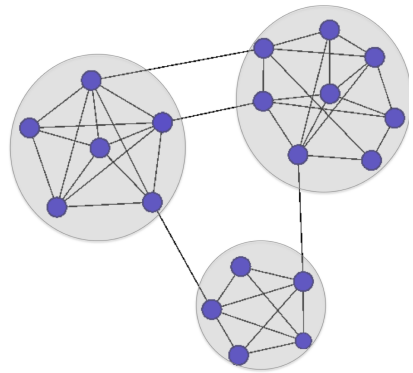
Positives

- Natural representation for pairwise (two-way) relationships
- Amenable to ready interpretation and visualization

Limitations

- Do not capture higher order interactions
- May not capture heterogeneity among samples

Motivating Example: Community Detection



Given network $G = (V, E)$ identify sets $C_1, \ldots, C_k \subseteq V$ such that

- Edge density within sets C_i is large
- Edge density between sets C_i is small

Iterative Testing for Community Detection

Given: $B_t \subseteq V$, level $\alpha \in (0, 1)$

For each $u \in [n]$ compute p-value

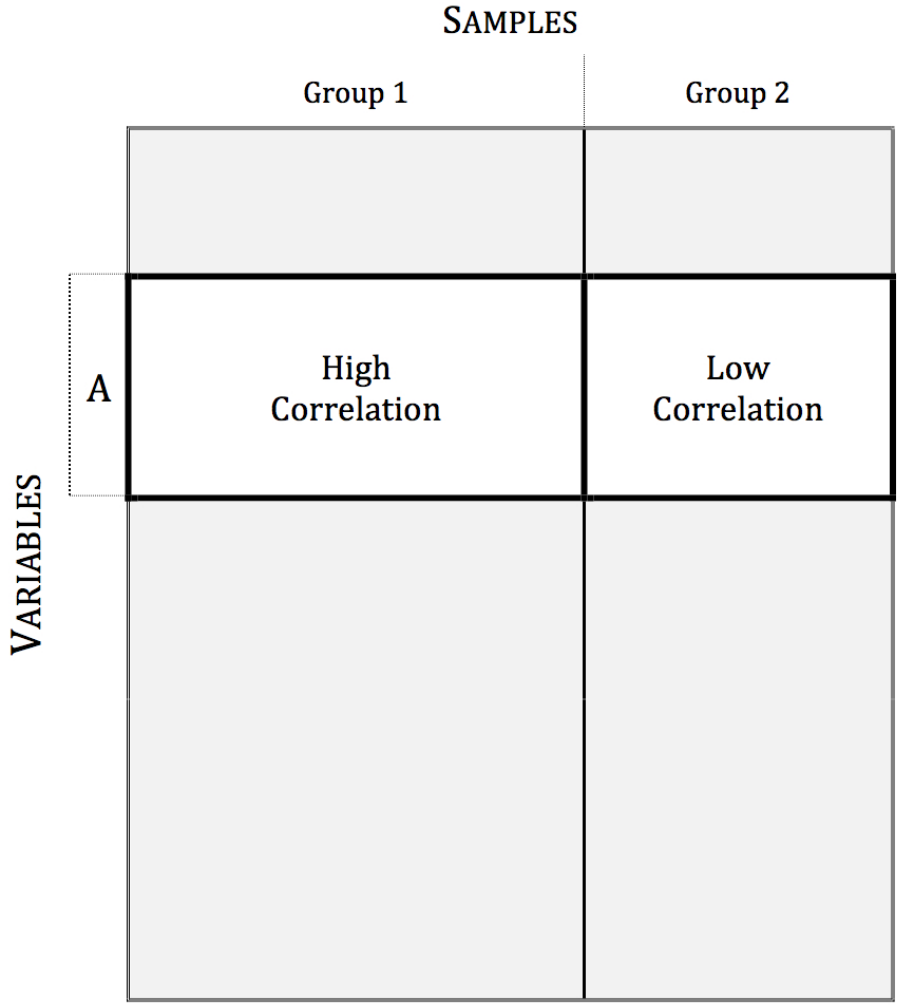
$$p(u : B_t) \approx \text{significance of connection between } u \text{ and } B_t$$

using configuration null model. Then

- Order nodes V s.t. $p(u_1 : B_t) \leq \cdots \leq p(u_n : B_t)$
- $k_0 :=$ largest k such that $p(u_k : B_t) \leq (k/n)\,\alpha$
- $B_{t+1} := \{u_1, \ldots, u_k\}$

Repeat until $B_{t+1} = B_t$

Differential Correlation Mining



- Two sample/treatment groups
- Common set of variables
- Identify sets of variables that are differentially correlated across groups
- Examples: genomic data, word usage frequencies, brain activity, etc.
- Distinct from differential expression and clustering

Example: Breast Cancer Subtypes in TCGA

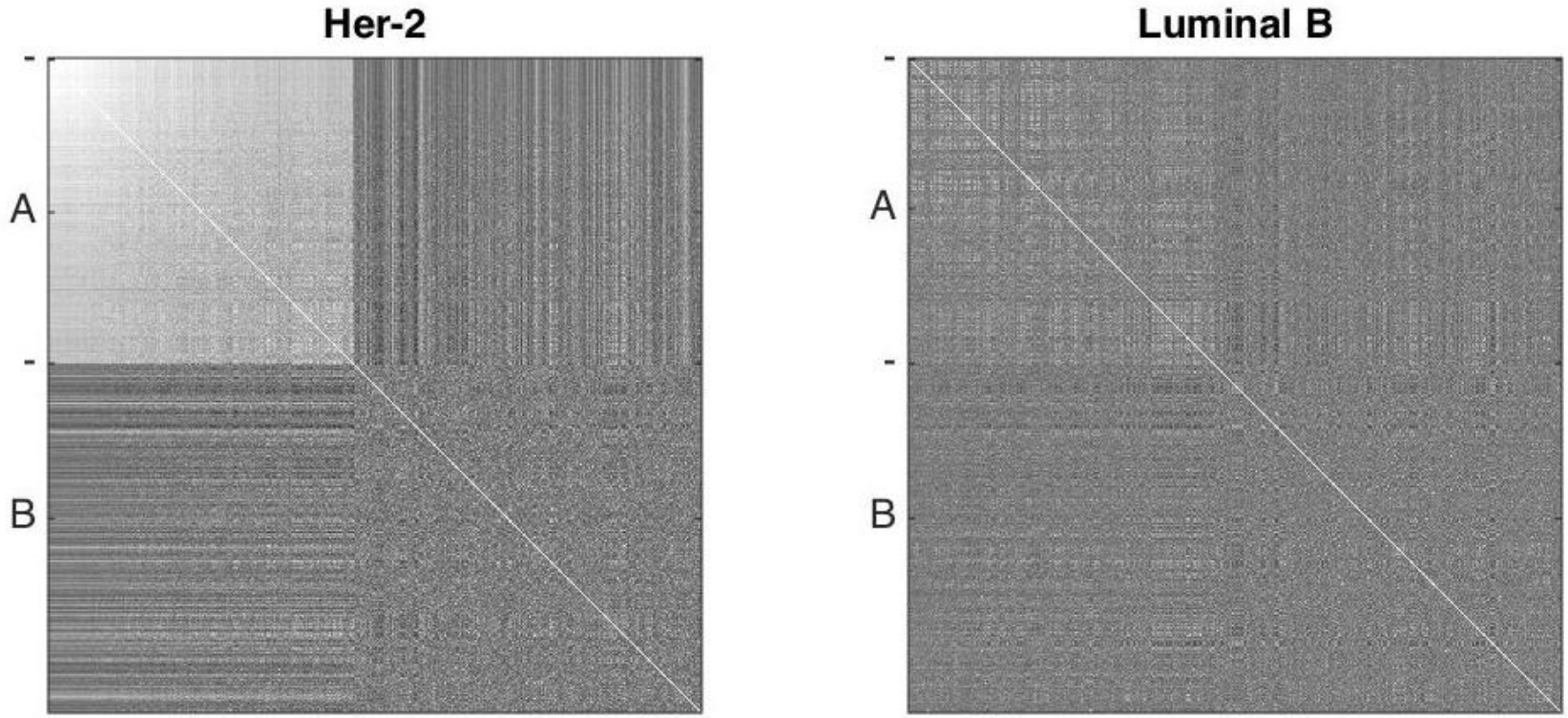


Figure: Sample correlation from Her-2 and Luminal B cancer subtype samples. Differentially correlated set of 165 variables (A) and 200 randomly chosen variables (B).

Example: Brain Connectome

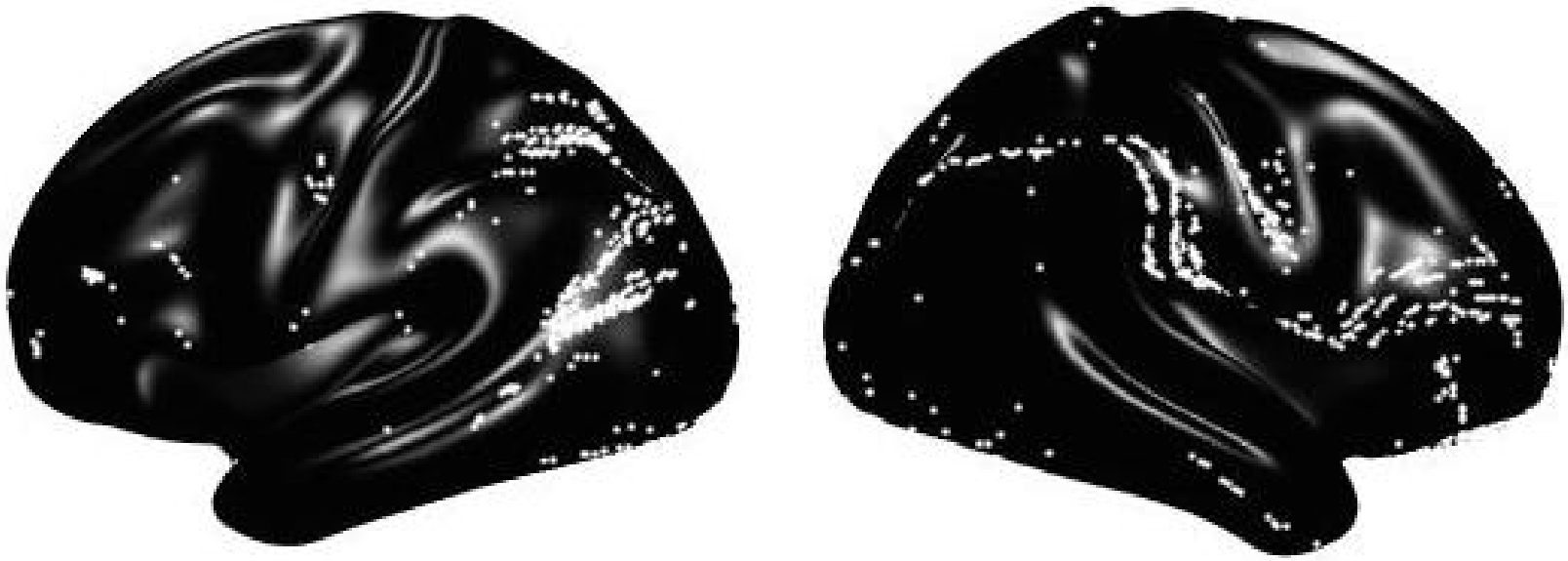


Figure: Brain locations of differentially correlated set for languages tasks versus motor tasks (Data: Human Connectome Project).

Overview

1. Data Integration
   - Horizontal
   - Vertical

2. Iterative Testing
   - Community Detection
   - Differential Correlation Mining

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