HEALTHY BIRTH,
GROWTH & DEVELOPMENT

New Information-Theory-Based Methods in the Analysis of Childhood Development Data

Nikita A. Sakhanenko,[1] David J. Galas,[1] Representing the Healthy Birth, Growth, and Development knowledge integration (HBGD*ki*) Community[2]

[1]Pacific Northwest Diabetes Research Institute, Seattle, WA, USA; [2]Bill & Melinda Gates Foundation, Seattle, WA, USA

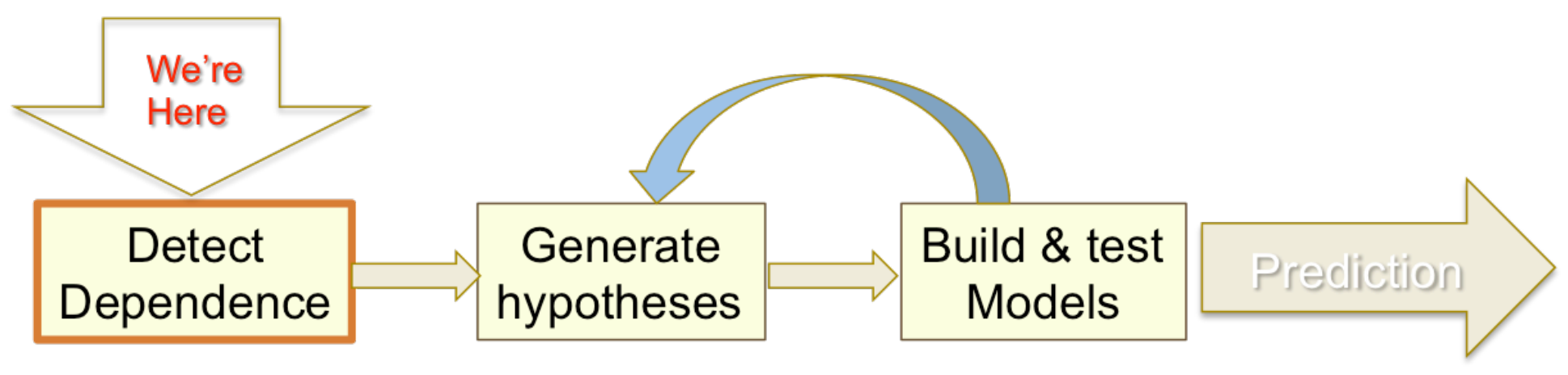
Introduction

The complexity of infant growth and development processes and resultant data reflect the deep complexity of biological systems.

The Problem: Can we detect complex dependencies of biological variables?

Given data sets with many instances of many variables:

- Can we find a measure for a subset of variables that is significantly nonzero if and only if the variables are interdependent?
- Can we separate detection of the existence of dependence from any models of the nature of dependence?


We're Here
Detect Dependence
Generate hypotheses
Build & test Models
Prediction

Dependency Measures

Information about one variable is contained in information about another.

Mutual information
$I(X_i, X_j) = H_i + H_j - H_{ij}$

"Interaction information"

$$I(X_i, X_j, X_k) = I(X_i, X_j) - I(X_i, X_j | X_k)$$

$$I(X_i,X_j,X_k) = H(X_i)+H(X_j)+H(X_k)-H(X_i,X_j)-H(X_i, X_k)-H(X_j,X_k)+H(X_i,X_j,X_k)$$

"Conditional mutual information, or differential interaction information"

$$-I(X_i, X_j | X_k) = I(X_i, X_j, X_k) - I(X_i, X_j)$$

$$\Delta_{ijk} = -I(X_i, X_j | X_k) = H_k - H_{ki} - H_{kj} + H_{ijk}$$

General dependency measures:

based on interaction information

Symmetric deltas

If $\{\tau_m\}$ are all subsets of $\nu_m \subseteq V_m$ that contain X_m

$$\Delta(V_{m-1}; X_m) = I(V_m) - I(V_{m-1}) = \sum_{\{\tau_m\}} (-1)^{|\tau_n|+1} H(\tau_m)$$

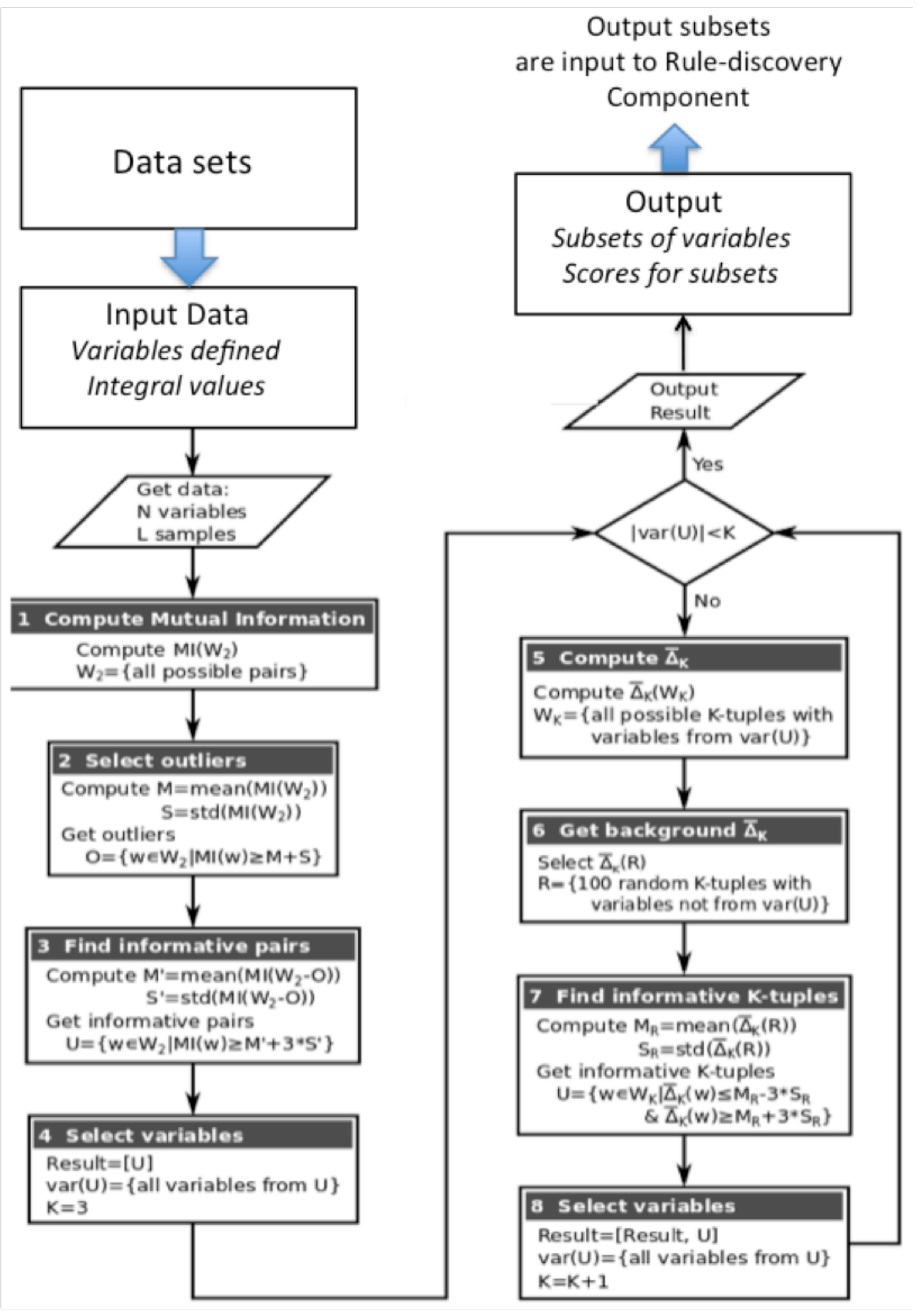
The general, symmetric measure is then

$$\bar{\Delta}(V_m) \equiv \prod_{permutations} \Delta(V_{m-1}; X_m)$$

Galas and Sakhanenko, J. Comp. Biol. (2014)

Avoiding the Combinatorial Explosion: the "Shadows Algorithm"

- For *N* variables, and subsets of size *m*,
- Number of combinations increases like $\sim N^m$
- For ~100,000 variables *m* = 3 & 4 gives 10^{15} & 10^{20}
- "Shadows algorithm" tracks *shadows* of the high degree dependencies in lower degree calculations.


Output subsets are input to Rule-discovery Component

Data sets

Input Data
Variables defined
Integral values

Get data:
N variables
L samples

1 Compute Mutual Information
Compute MI(W_2)
W_2={all possible pairs}

2 Select outliers
Compute M=mean(MI(W_2))
S=std(MI(W_2))
Get outliers
O={w∈W_2|MI(w)≥M+S}

3 Find informative pairs
Compute M'=mean(MI(W_2-O))
S'=std(MI(W_2-O))
Get informative pairs
U={w∈W_2|MI(w)≥M'+3*S'}

4 Select variables
Result=[U]
var(U)={all variables from U}
K=3

|var(U)|<K
Yes
No

5 Compute $\bar{\Delta}_K$
Compute $\bar{\Delta}_K(W_K)$
W_K={all possible K-tuples with variables from var(U)}

6 Get background $\bar{\Delta}_K$
Select $\bar{\Delta}_K$(R)
R={100 random K-tuples with variables not from var(U)}

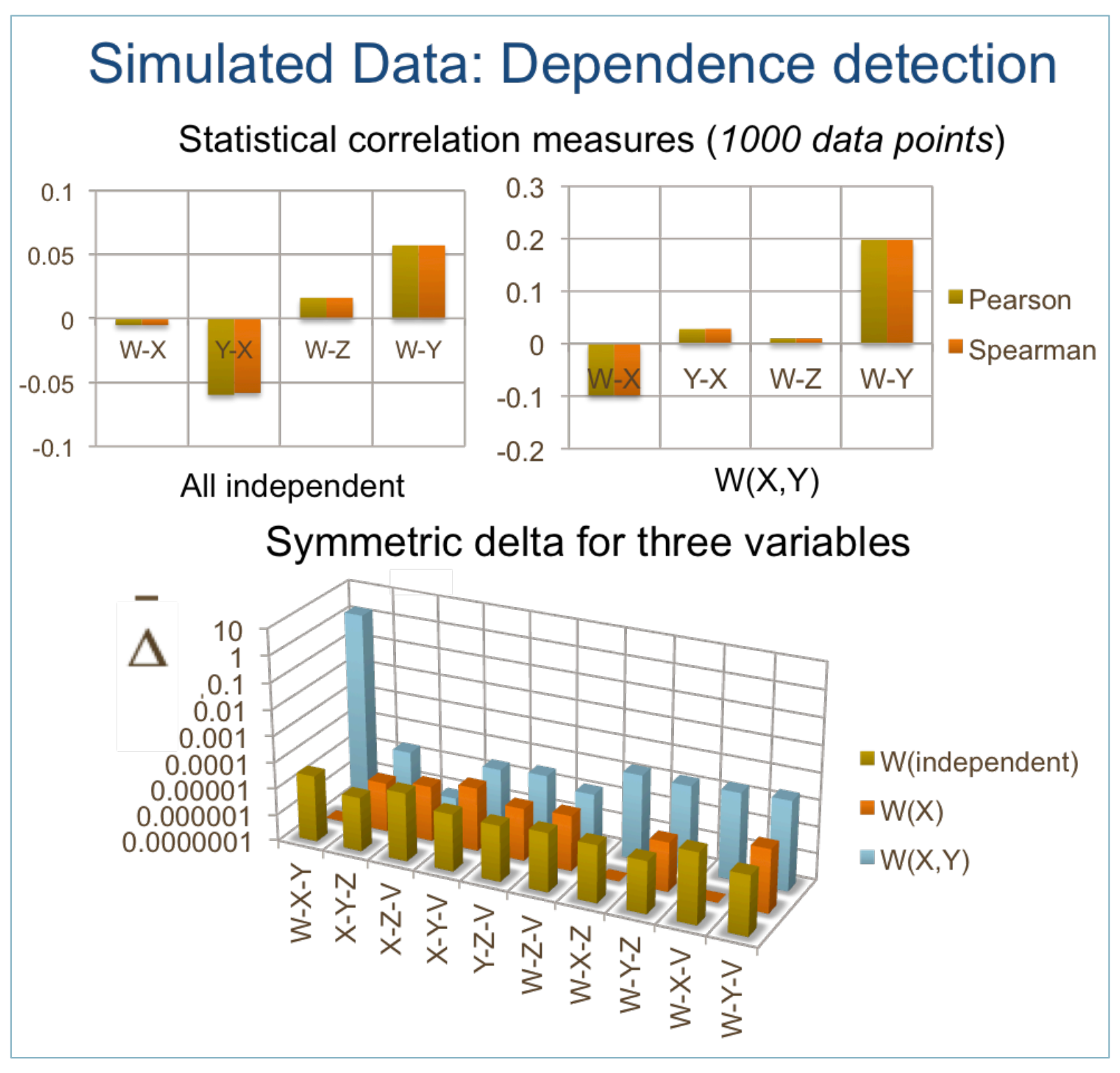
7 Find informative K-tuples
Compute M_R=mean($\bar{\Delta}_K$(R))
S_R=std($\bar{\Delta}_K$(R))
Get informative K-tuples
U={w∈W_K|$\bar{\Delta}_K$(w)≤M_R-3*S_R & $\bar{\Delta}_K$(w)≥M_R+3*S_R}

8 Select variables
Result=[Result, U]
var(U)={all variables from U}
K=K+1

Output Result

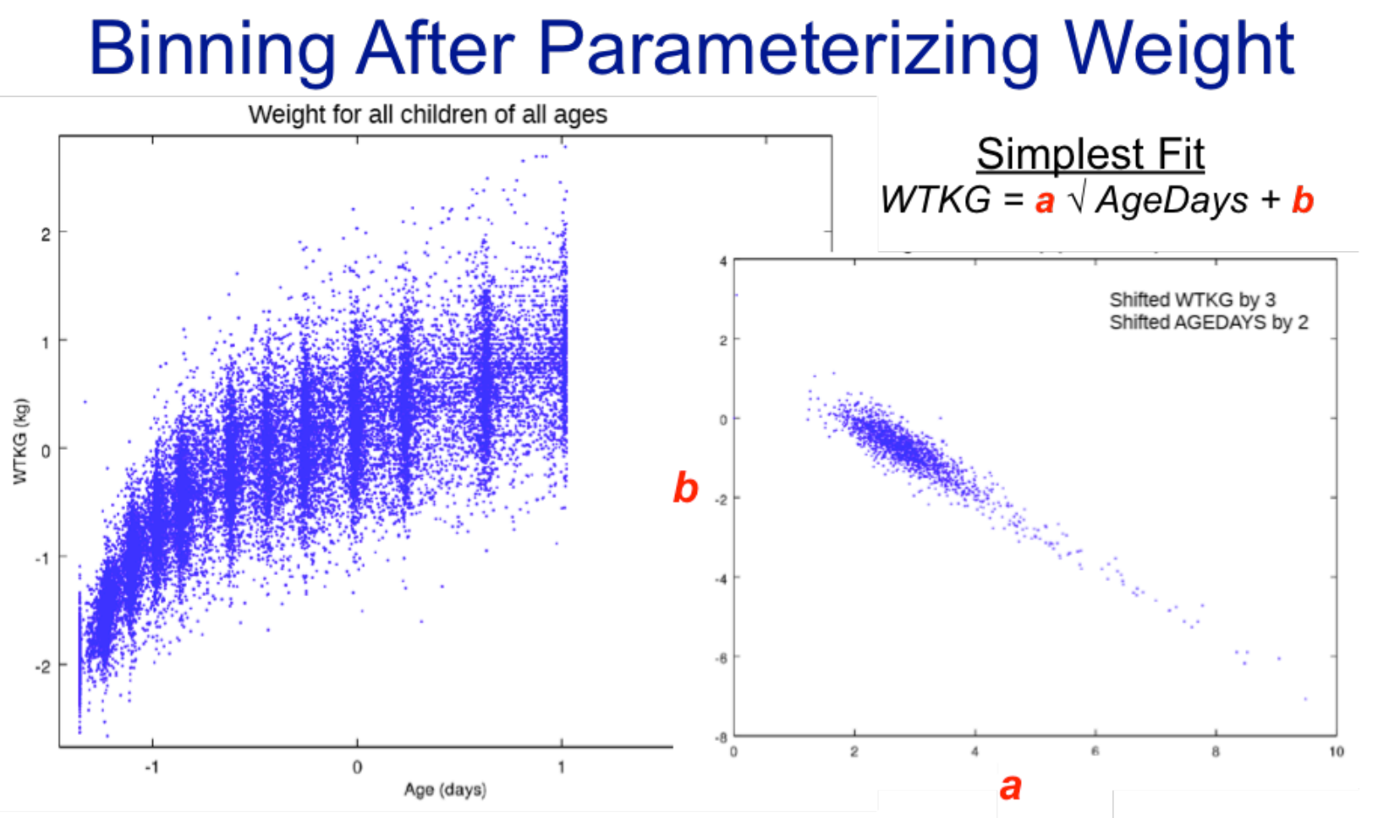
Output
Subsets of variables
Scores for subsets

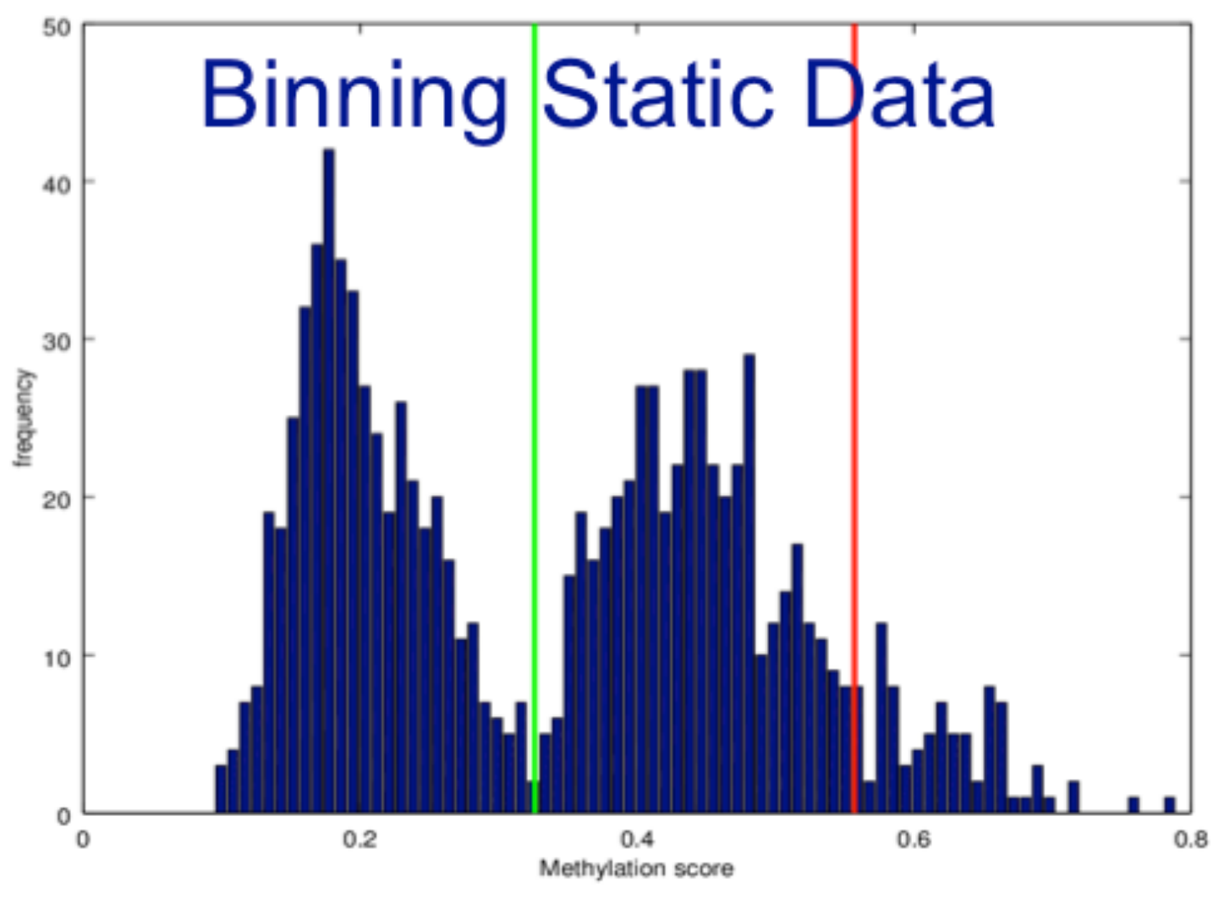
Sakhanenko and Galas , *J. Comp. Biol.* (2015)

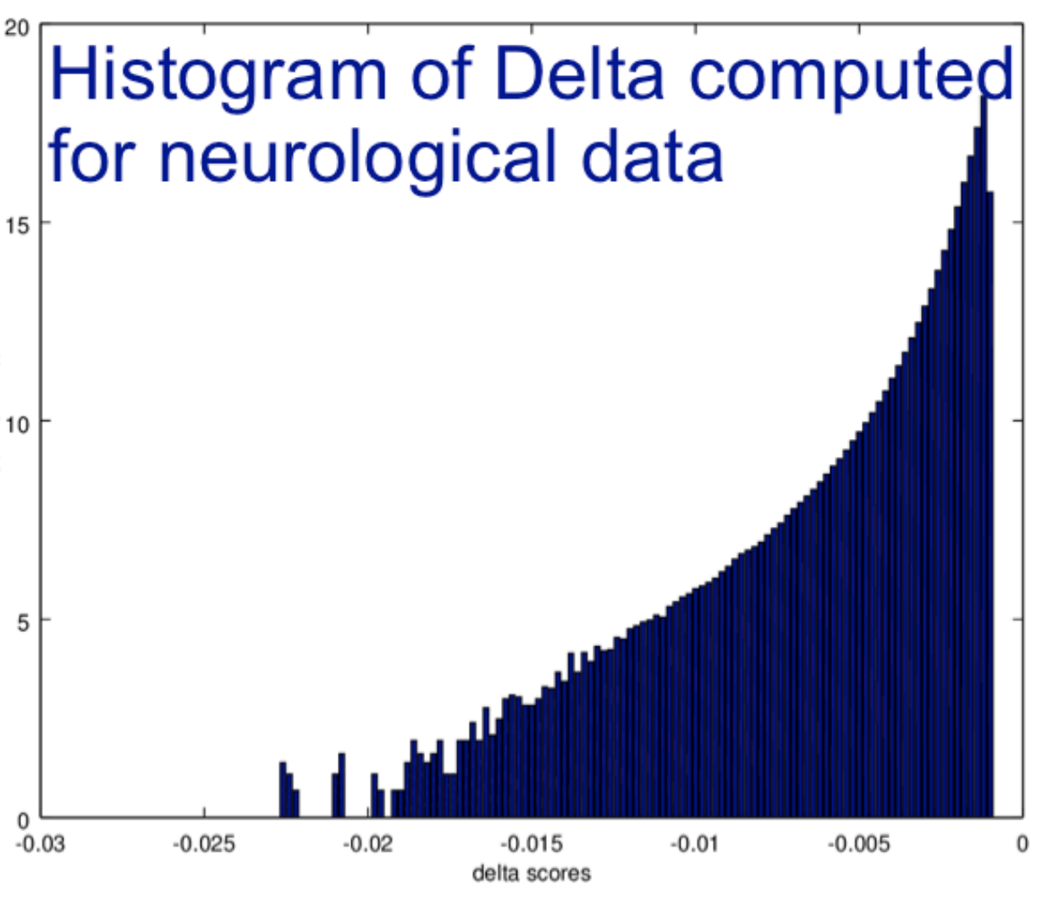

Simulated Data: Dependence detection

Statistical correlation measures (*1000 data points*)

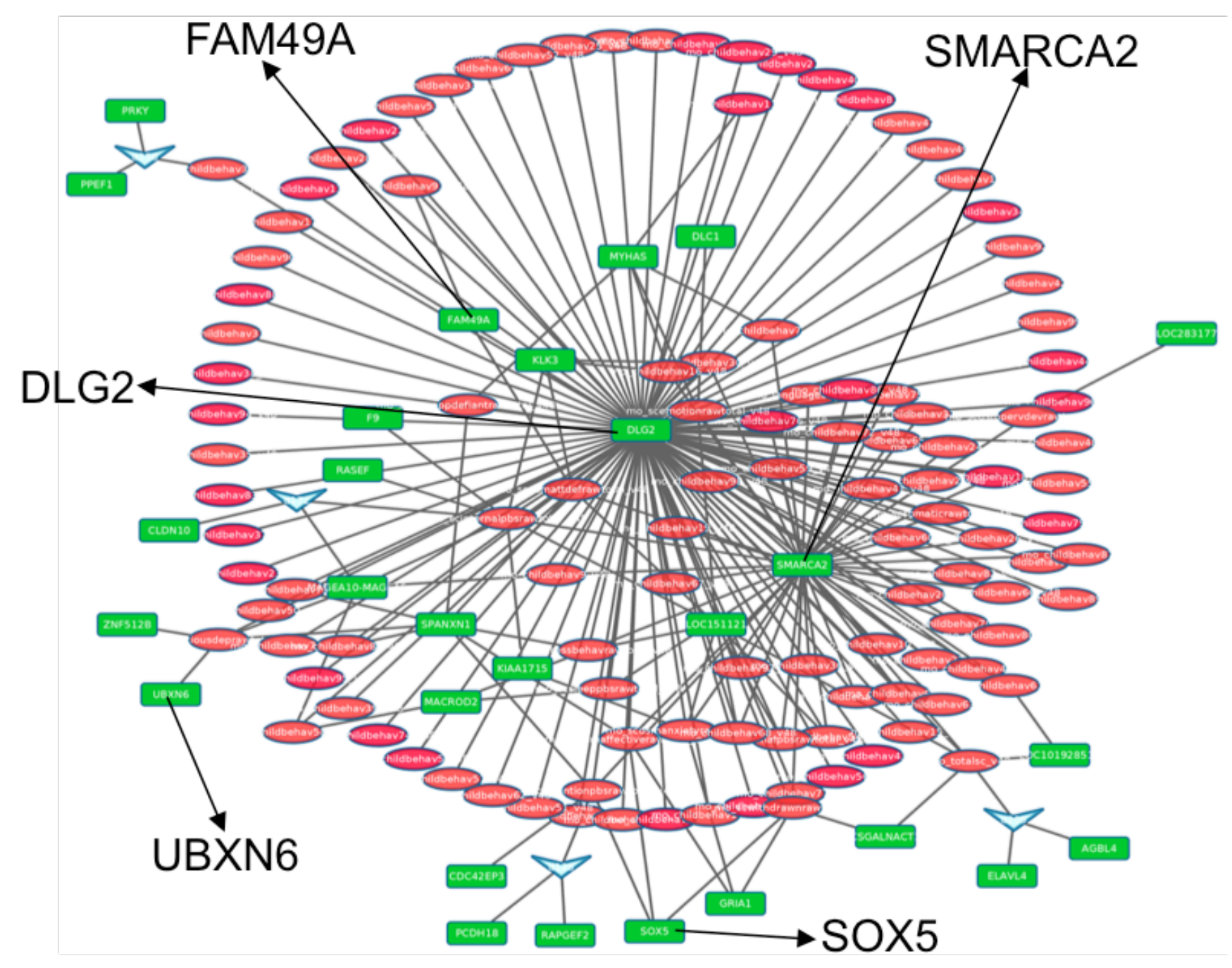
Symmetric delta for three variables


Binning After Parameterizing Weight


Binning Static Data


Histogram of Delta computed for neurological data

Example: 3-variable dependence (2 SNPs and 1 phenotype), illustrated by a hypergraph



Neuro data: top CBCL phenotypes & SNP connections
All point to genes with known neurological effects.

SNP1 (Gene1)	SNP2 (Gene2)	Phenotype	Description of the phenotype
Rs896996 **(DLG2)**	Rs1022308 **(DLG2)**	mo_totalsc_v48	Total score summary
Rs6475635 **(SMARCA2)**	Rs1555646 **(SMARCA2)**	mo_childbehav18_v48	Destroys things belonging to family
Rs751192 **(FAM49A)**	Rs888575 **(FAM49A)**	mo_scdsmattdefrawtotal_v48	Attention Deficit/ Hyperactivity total score
Rs741923 **(UBXN6)**	Rs4807584 (MPND)	mo_scanxiousdeprawtotal_v48	Anxious/Depressed: raw total score

Methods

- This method was model-free and insensitive to under sampling.
- The method was used to detect multivariable dependencies among variables.
- The measures were significantly nonzero only when the subset of variables had an essential, collective dependency [1].
- We used our approach to detect multivariable dependencies in childhood data in a large cohort of children with known genotype, environmental, and phenotype information (GUSTO data from Singapore).
- The approach was used to develop new hypotheses about causal relations.
- We calculated dependency values for variable sets of large degree; this enabled us to identify dependent subsets, but was limited by the combinatorial explosion:

Calculations ~ (Number of variables)^{degree}

- We used properties of the measure to avoid the combinatorial explosion by following the "shadows" that the multivariable dependency cast onto smaller subsets [2].
- The Shadows Algorithm enabled us to calculate measures of any degree of dependency.

Results

- We analyzed a large, high-dimensional data set about the development of Singapore children (GUSTO).
- The GUSTO study collected a diverse range of information about children to capture a full view of child development.
- We considered 3 categories of phenotypes – anthropometric, neurological, and asthma/eczema – and their dependence on genetic variation.
- We identified a small set of strong 2- and 3-variable collective dependencies among phenotypes and SNPs.
- These dependencies formed interconnected networks of variables and enabled us to seek biological relations in these dependencies and form new hypotheses.
- Our method returned a set of candidate multivariable dependencies, which were input to functional analysis.
- The SNP-phenotype dependencies and their networks suggested several involved biological pathways – essential for precise models.
- Genetics can help stratify populations to better detect environmental effect signals.

Conclusions

A. The method works.

- **The application of our method to the Singapore data (GUSTO) showed promising initial results.**
- **We identified complex dependencies in very large and heterogeneous data sets.**
- **We are adding other types of data to the analysis and integrating them into a more unified network.**

B. Preprocessing of data is extremely important.

- **Missing data and other noise can strongly affect our ability to detect dependencies.**
- **Binning variable quantities also is key.**
- **These issues are being actively investigated.**

References

1. Galas DJ, Sakhanenko NA, Skupin A, Ignac T. Describing the complexity of systems: multivariable "set complexity" and the information basis of systems biology. *J Comput Biol*. 2014;21(2):118-140.
2. Sakhanenko NA, Galas DJ. Biological data analysis as an information theory problem: multivariable dependence measures and the shadows algorithm. *J Comput Biol*. 2015;22(11):1005-1024.

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