Mining Imaging Genetics Data via Sparsity-Induced Machine Learning Models

Hua Wang, Ph.D.

Department of Computer Science

Colorado School of Mines

MInDS@MINES

Machine Learning ∘ Informatics ∘ Data Science

Machine Learning and Data Mining Are Everywhere of Our Lives

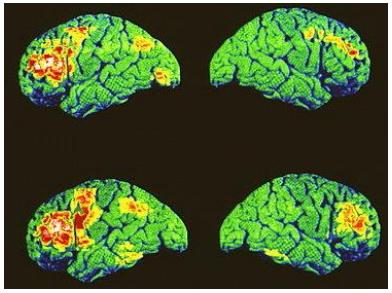
Game playing and problem solving

Machine Learning and Data Mining

Intelligent virtual environments for treatment and rehabilitation

Industrial and engineering applications

Homeland security applications



Medicine, bioinformatics and systems biology

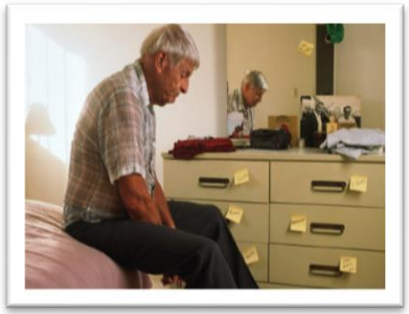
… …

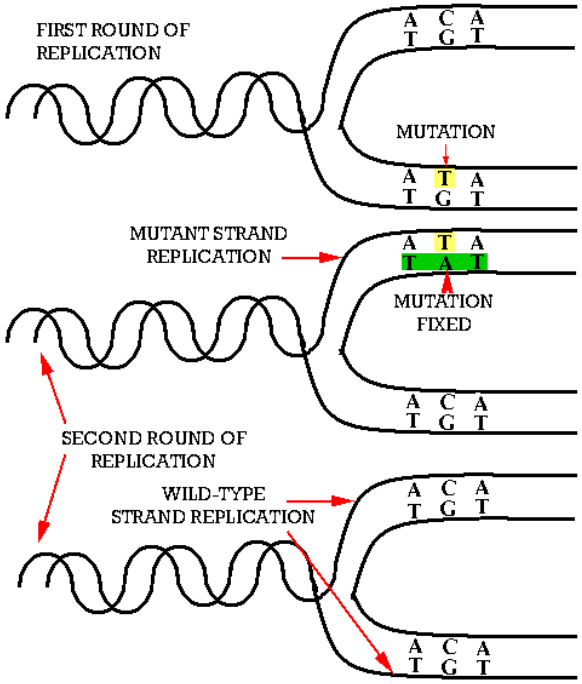
Economics, business and forecasting applications

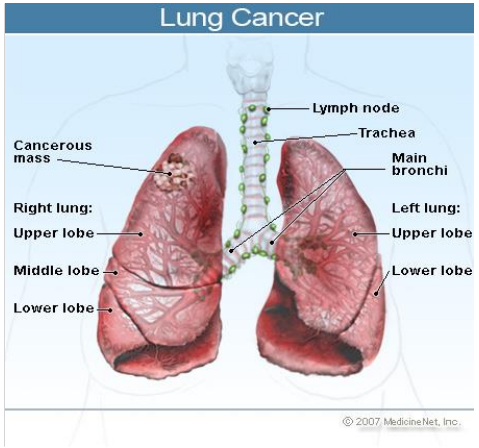
MInDS@MINES
Machine Learning ∘ Informatics ∘ Data Science

Many Major Human Diseases Have Been Connected to Gene Mutations

- Many major human diseases, such as cancer and neurodegenerative disorders, affects millions of people worldwide.
- Cause of these diseases: gene mutations (such as single-nucleotide polymorphism (SNP) or copy number variations).



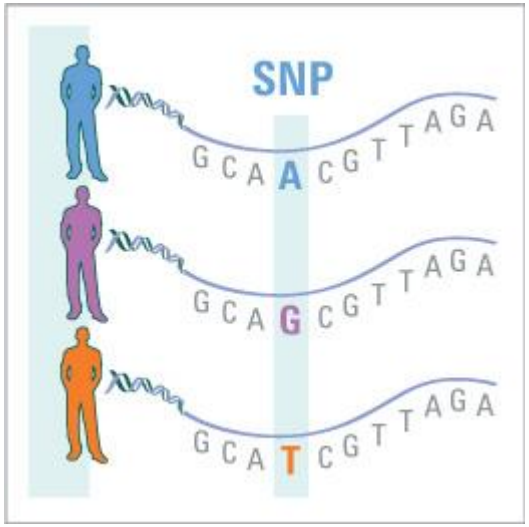




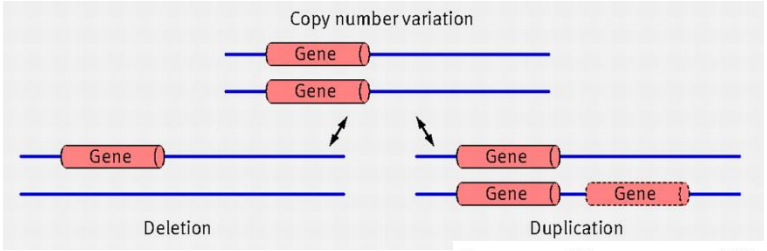
MInDS@MINES
Machine Learning • Informatics • Data Science

Identification of Genetic/Genomic Biomarkers for Diagnosis And Therapy

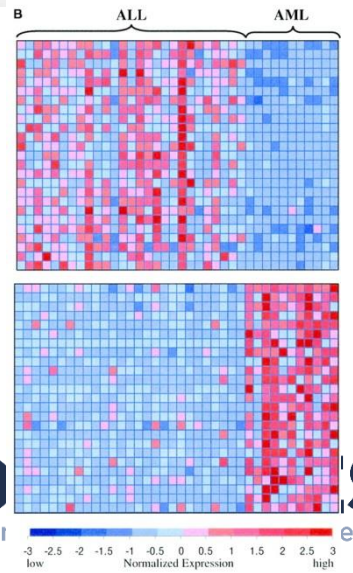
- Genetic variations characterized by SNP underlie differences in our susceptibility to, or protection from all kinds of diseases.
  - For example, a single base difference in the *Apolipoprotein E* is associated with a higher risk for Alzheimer's disease.



- CGH is a molecular-cytogenetic method for the analysis of copy number changes (gains/losses) in the DNA content of a given subject's DNA and often in tumor cells.



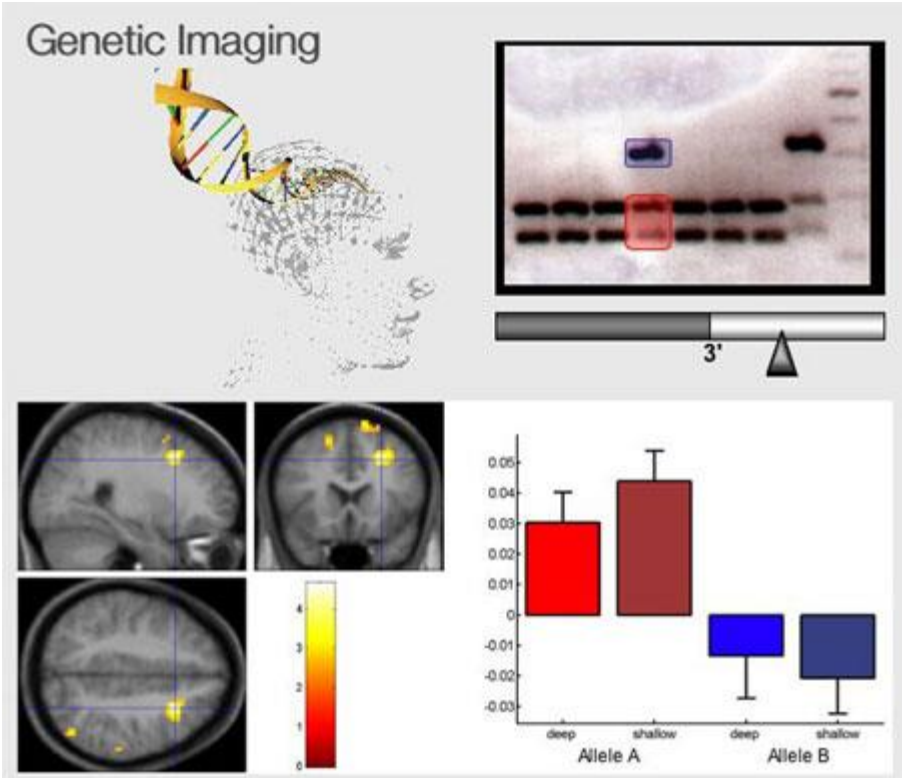
- Abnormal gene expression level could also indicate human diseases, such as cancers.



Imaging Genetics via Machine Learning

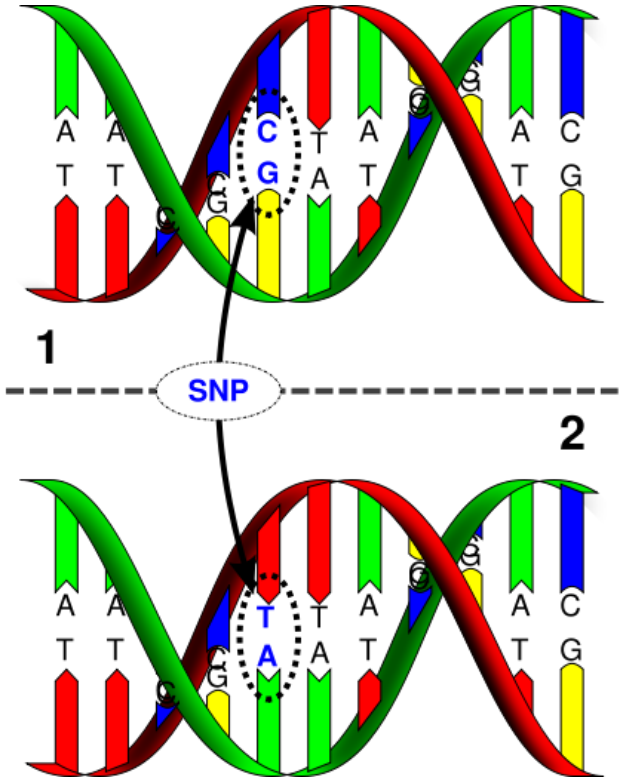
Imaging genetics refers to the use of anatomical or physiological imaging technologies as phenotypic assays to evaluate variations.

——wikipedia.org

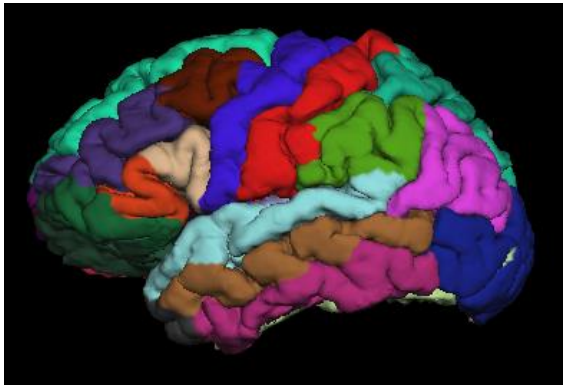
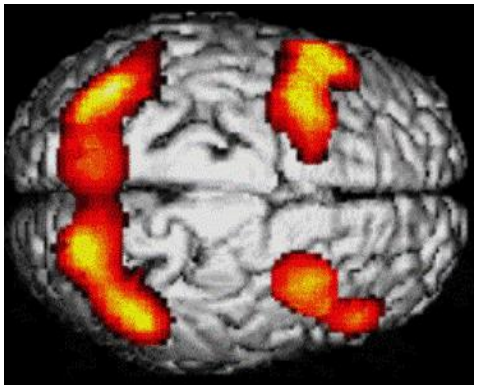
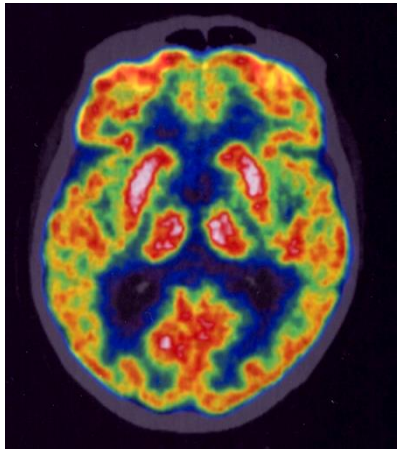
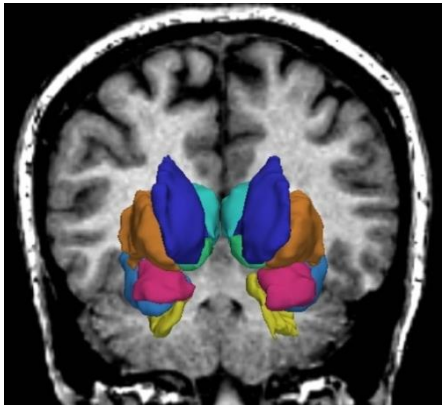
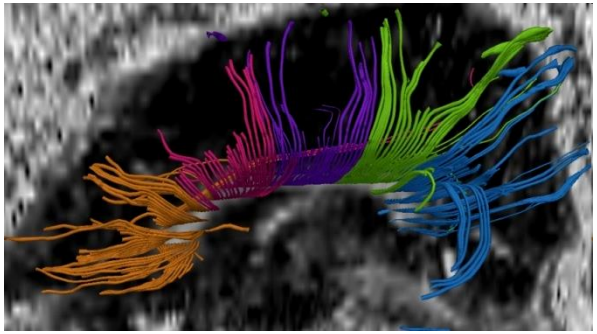
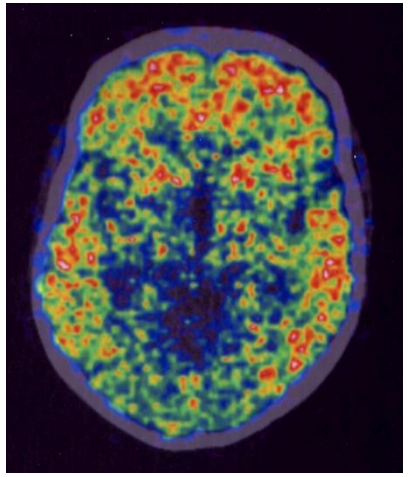


Genotypes: Human Genome and SNP

- SNP (Single Nucleotide Polymorphism) - single nucleotide site where two or more different nucleotides occur in a large percentage of population.
- Total number of SNP: In the current dbSNP build, 132, the number of uniquely mapped refSNP (rs) numbers has grown to about 59 million+. (October 2011)

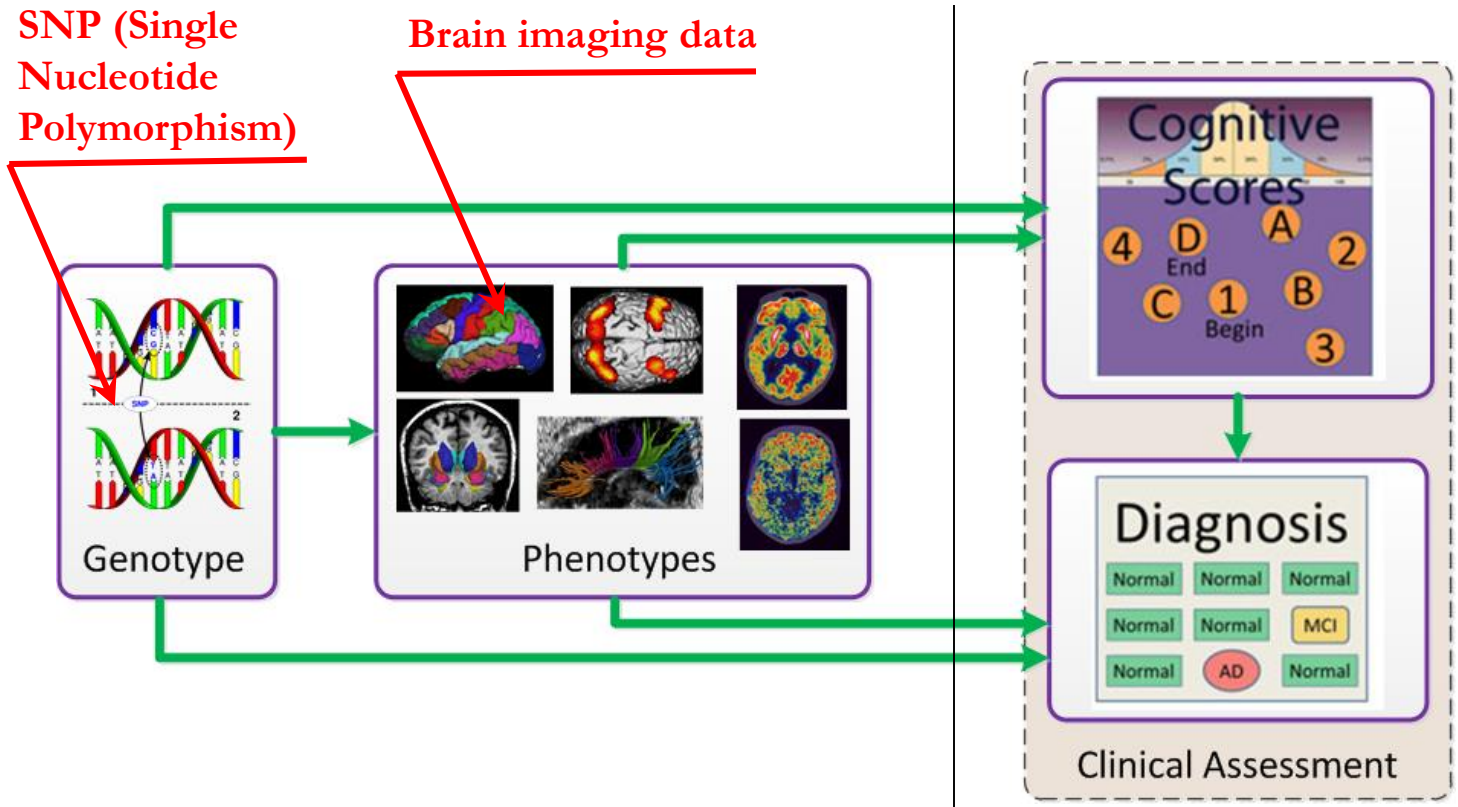


Quantitative Phenotypes

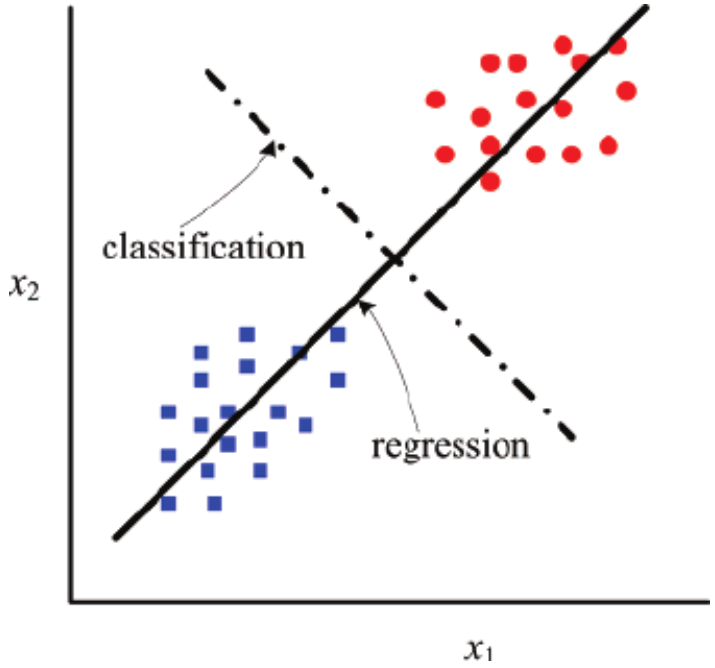
Structural, functional, diffusion MRI
FDG, PiB PET
Fluid, cognitive biomarkers

A Comprehensive Research Platform to Study Alzheimer's Disease - ADNI



- NIH recently funded the ADNI (Alzheimer's Disease Neuroimaging Initiative) project, which has provided a comprehensive platform for imaging genetics studies.

Association Studies in Statistical Learning



$$\min_{\mathbf{w}} f(\mathbf{w}; \mathbf{X}, \mathrm{y}) + r(\mathbf{w})$$

- **Classification**: associate a set of input samples into a set of predefined discrete targets.
- **Regression**: associate a set of input samples into a set of predefined continuous targets.

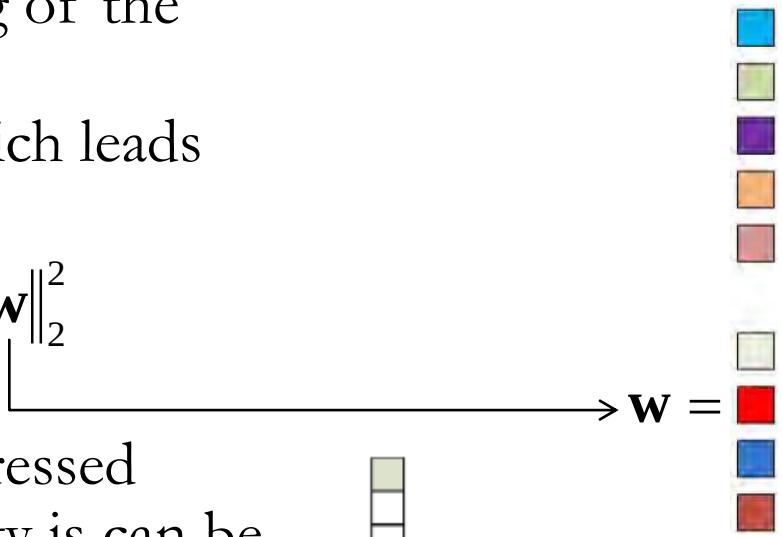
Structured Sparse Learning for Biomarker Identification

- Sparse learning has recently been successfully applied to solve a number of machine learning and data mining problems.
- Our structured sparse learning based biomarker selection approaches are able to
  - impose sparsity and
  - incorporate useful structural information contained in imaging and genetic data.

Sparsity Is Achieved by ℓ_1-Norm Regularization

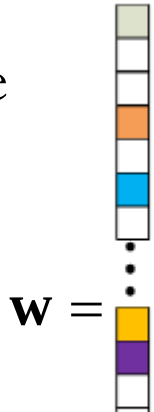
- In traditional statistical learning, in order to avoid over-fitting of the learning model, ℓ_2-norm regularization is used, which leads to non-sparse result.

$$\min_{\mathbf{w}} \; f(\mathbf{w};\mathbf{X},\mathbf{y}) + a\|\mathbf{w}\|_2^2$$

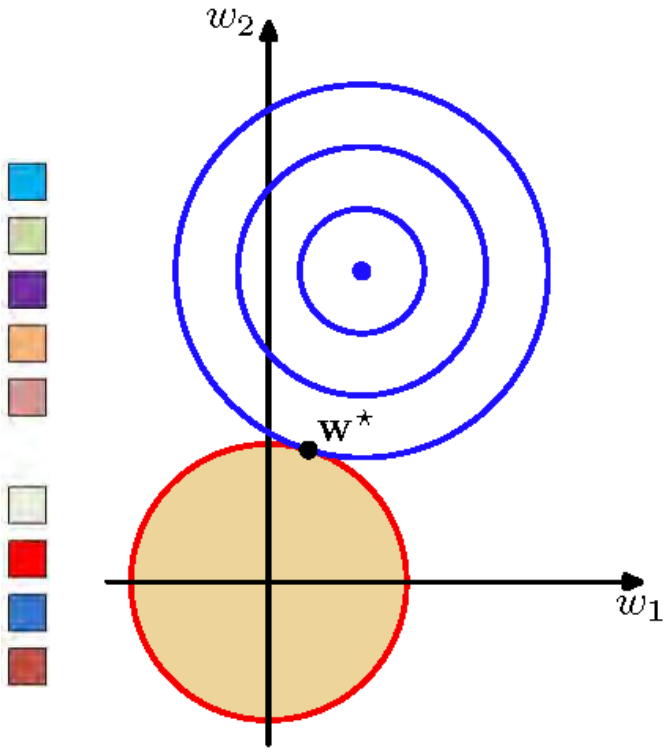


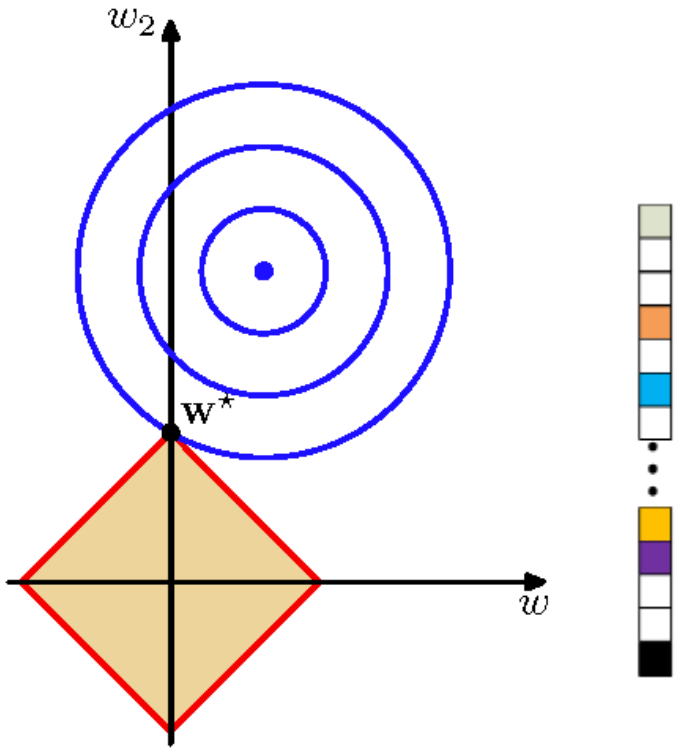
- Recent progress in compressed sensing shows that sparsity is can be achieved by ℓ_1-norm regularization:

$$\min_{\mathbf{w}} \; f(\mathbf{w};\mathbf{X},\mathbf{y}) + a\|\mathbf{w}\|_1$$



Sparsity Is Achieved by ℓ_1-Norm Regularization (cont.)

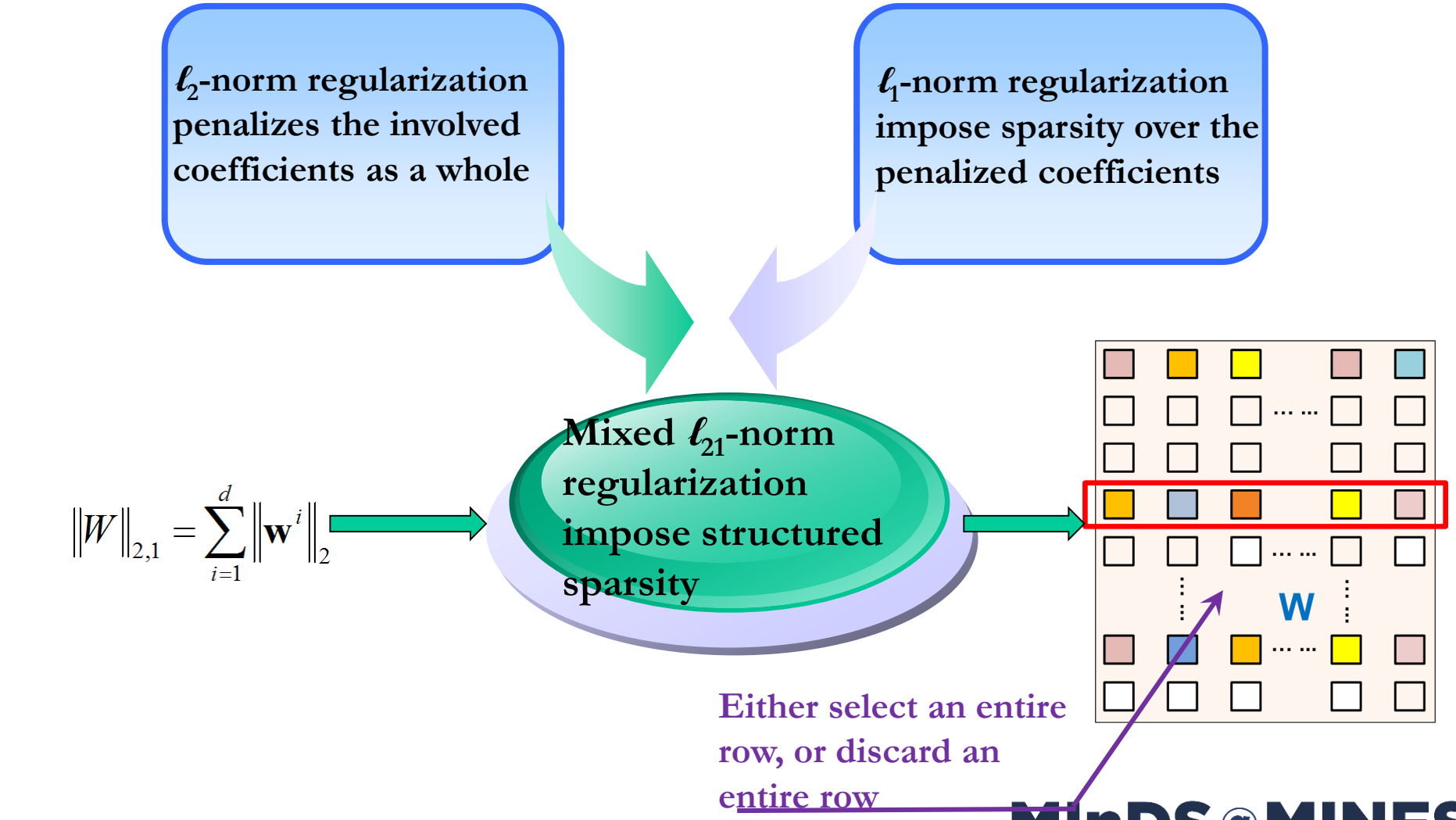




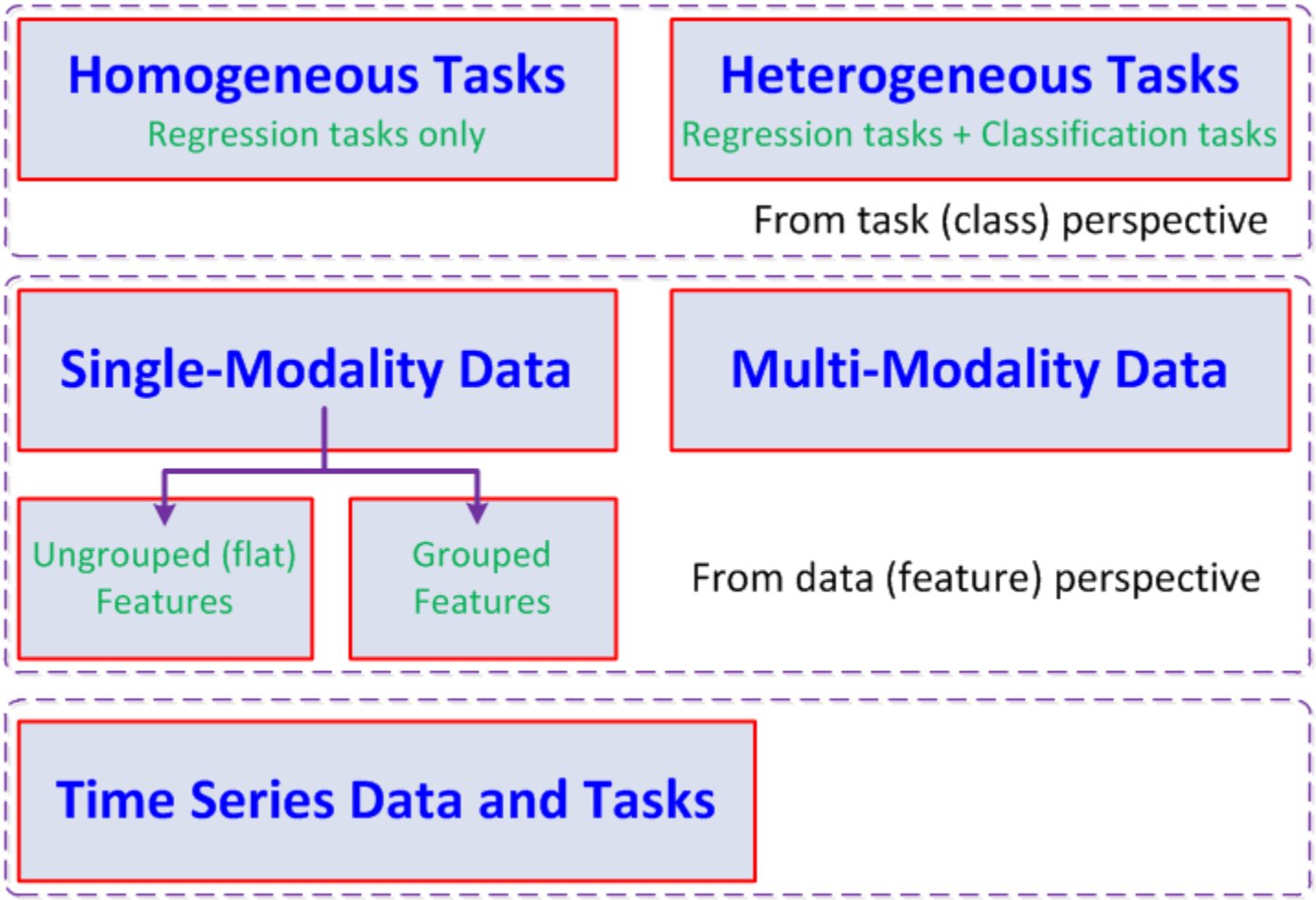
$$\min_{\mathbf{w}} f(\mathbf{w}; \mathbf{X}, \mathbf{y}) \quad s.t. \|\mathbf{w}\|_2^2 = c$$

$$\min_{\mathbf{w}} f(\mathbf{w}; \mathbf{X}, \mathbf{y}) \quad s.t. \|\mathbf{w}\|_1 = c$$

Structured Sparsity Is Achieved by Mixed Norm Regularization



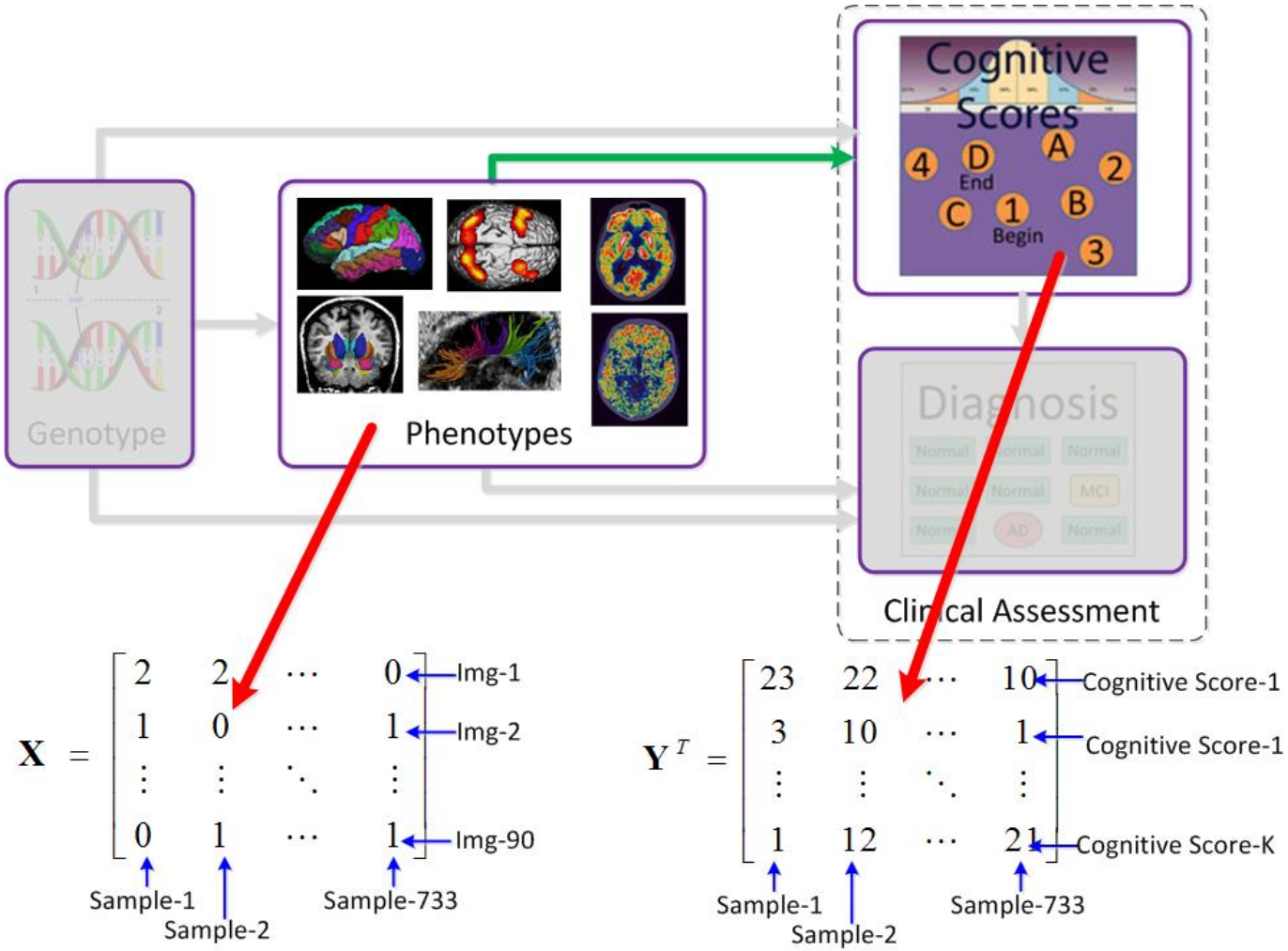
A unified structured sparse learning framework for imaging genetics studies



Outline

- Background and motivation
- **Learning with homogeneous tasks**
- Learning with heterogeneous tasks
- Learning with group-structured single-modality data
- Learning with multi-modality data
- Learning with longitudinal data

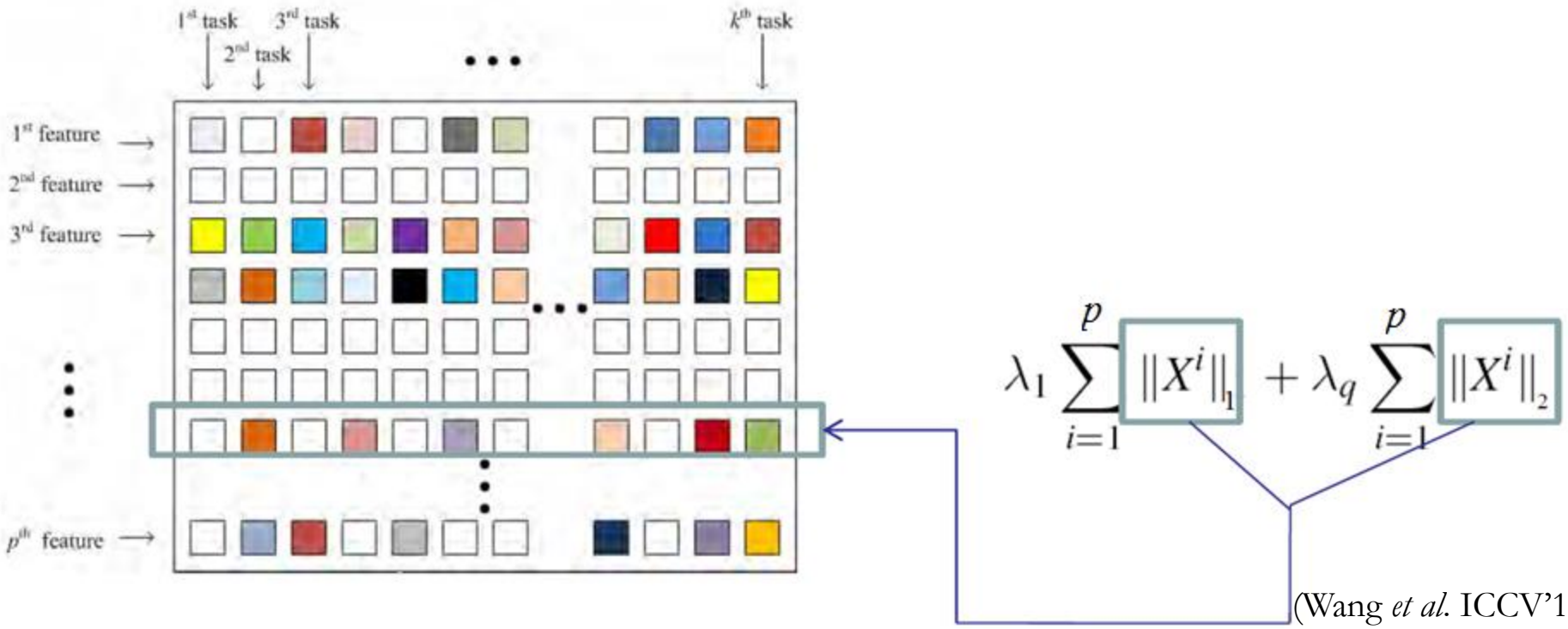
Learning with Homogeneous Tasks



$$\mathbf{X} = \begin{bmatrix} 2 & 2 & \cdots & 0 \\ 1 & 0 & \cdots & 1 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 1 & \cdots & 1 \end{bmatrix} \qquad \mathbf{Y}^T = \begin{bmatrix} 23 & 22 & \cdots & 10 \\ 3 & 10 & \cdots & 1 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 12 & \cdots & 21 \end{bmatrix}$$

A Convex Learning Objective

$$\min_W \left\| X^T W - Y \right\|_F^2 + \gamma_1 \left\| W \right\|_1 + \gamma_2 \left\| W \right\|_{2,1}$$



(Wang *et al.* ICCV'11)

An Efficient Iterative Algorithm with Global Convergence

Algorithm 1: Algorithm

Input: X, Y

Initialize $W^1 \in \mathbb{R}^{d\times c}, t = 1$;

while *not converge* **do**

1. Calculate the diagonal matrices $D_i^{(t)}(1 \le i \le c)$ and $\tilde{D}^{(t)}$, where the k-th diagonal element of $D_i^{(t)}$ is $\frac{1}{2|w_{ki}^{(t)}|}$, the k-th diagonal element of $\tilde{D}^{(t)}$ is $\frac{1}{2\|(w^{(t)})^k\|_2}$;
2. For each $i(1 \le i \le c)$, $w_i^{(t+1)} = (XX^T + \gamma_1 D_i^{(t)} + \gamma_2 \tilde{D}^{(t)})^{-1} X y_i$;
3. $t = t + 1$;

Output: $W^{(t)} \in \mathbb{R}^{d\times c}$.

(Wang *et al.* ICCV'11)

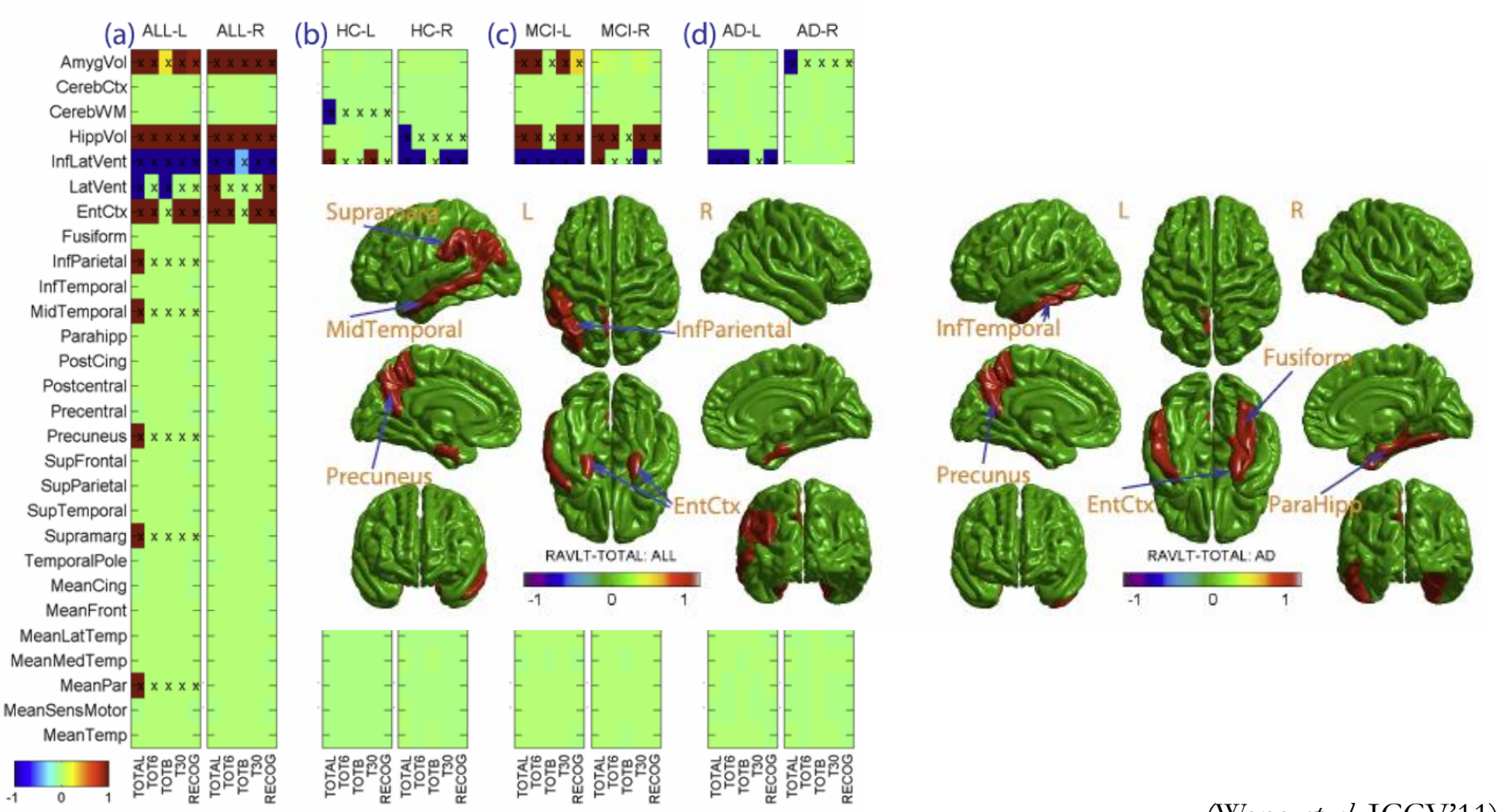
Experimental Results

Table 2. Prediction performance measured by RMSE.

Test cases		TOTAL	TOT6	TOTB	T30	RECOG
FreeSurfer_HC	MVR	8.762	4.362	3.281	4.305	4.021
	SMART	6.645	2.940	2.235	2.806	3.621
FreeSurfer_MCI	MVR	6.998	2.765	2.399	2.480	3.427
	SMART	5.600	1.990	1.953	1.709	3.181
FreeSurfer_AD	MVR	5.897	1.768	2.058	1.382	3.390
	SMART	5.042	1.452	1.716	1.050	2.830
FreeSurfer_all	MVR	5.926	2.238	2.036	2.090	3.342
	SMART	5.736	2.139	1.961	1.966	3.196
VBM_HC	MVR	8.651	3.772	2.885	3.496	4.776
	SMART	6.705	2.844	2.139	2.656	3.584
VBM_MCI	MVR	11.495	4.256	4.621	4.032	5.598
	SMART	5.584	1.832	1.931	1.669	3.017
VBM_AD	MVR	7.223	2.162	2.622	1.479	4.163
	SMART	5.120	1.518	1.826	0.904	2.781
VBM_all	MVR	6.090	2.290	2.140	2.141	3.396
	SMART	5.718	2.103	1.993	1.921	3.182
VBM+FreeSurfer_HC	MVR	12.265	5.416	4.349	5.089	6.703
	SMART	6.664	2.829	2.230	2.683	3.577
VBM+FreeSurfer_MCI	MVR	68.222	26.146	23.489	30.033	34.306
	SMART	5.533	1.901	1.869	1.606	3.114
VBM+FreeSurfer_AD	MVR	14.552	4.307	5.141	4.297	8.430
	SMART	4.805	1.218	1.731	0.858	2.865
VBM+FreeSurfer_all	MVR	6.505	2.596	2.258	2.540	3.582
	SMART	5.809	2.208	2.000	2.051	3.214

(Wang *et al.* ICCV'11)

Experimental Results (Cont.)

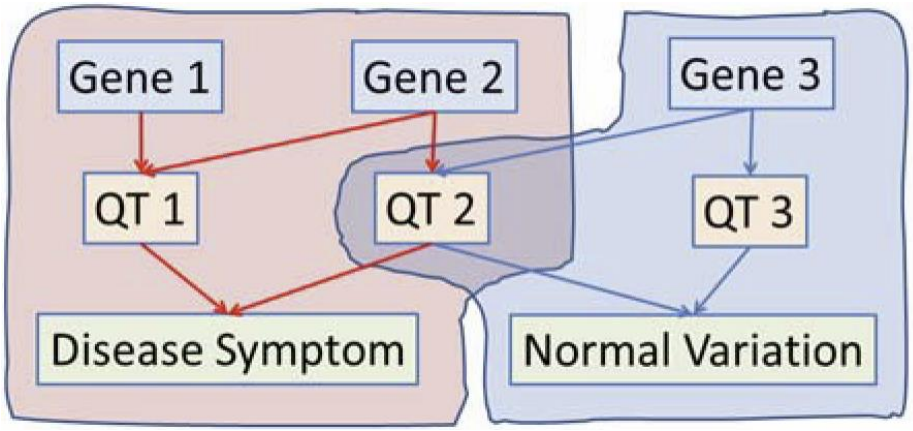


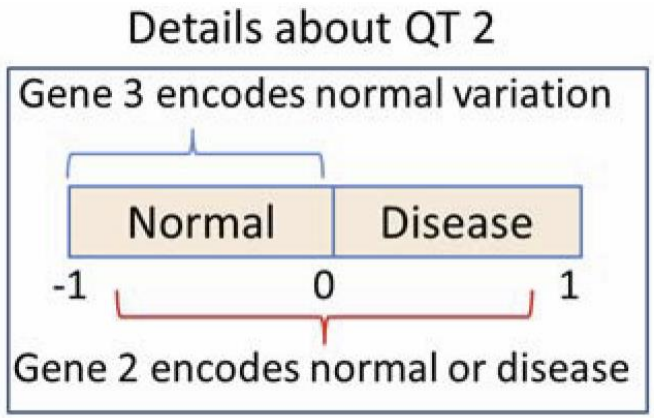
(Wang *et al.* ICCV'11)

Outline

- Background and motivation
- Learning with homogeneous tasks
- **Learning with heterogeneous tasks**
- Learning with group-structured single-modality data
- Learning with multi-modality data
- Learning with longitudinal data

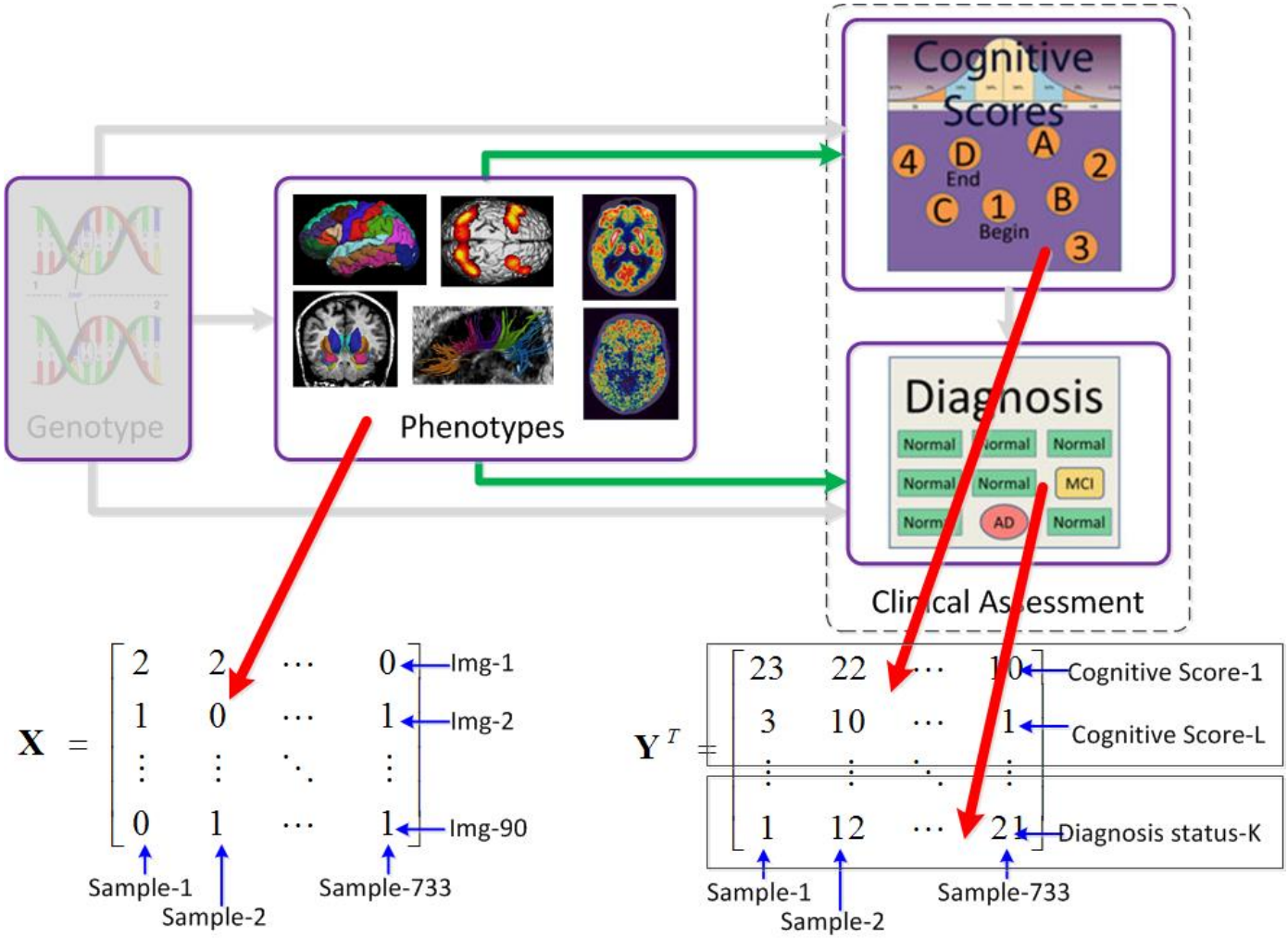
Learning with Heterogeneous Tasks





- A simplified schematic example of two pathways from gene to QTs to phenotypic endpoints:
  - the red one is disease relevant
  - while the blue one yields only normal variation.
- Traditional two-stage imaging genetic strategy identifies QT 1 and QT 2 first and then Genes 1, 2, 3.
- Our new method will identify only disease relevant genes (i.e., Gene 1 and Gene 2); and Gene 3 wont be identified because it cannot be used to classify disease status.

Learning with Heterogeneous Tasks (Cont.)



Our Objective for Joint Classification and Regression

- Out joint learning objective

$$\min \; J(\mathbf{V}) = l_1(\mathbf{W}) + l_2(\mathbf{P}) + \gamma \|\mathbf{V}\|_{2,1},$$

where $V = [W\ P] \in \boldsymbol{R}^{d \times (c1+c2)}$.

- Logistic loss for disease status classification:

$$l_1(\mathbf{W}) = -\log \prod_{i=1}^{n} p(\mathbf{y}^i \mid \mathbf{x}_i, \mathbf{W}) = \sum_{i=1}^{n} \sum_{k=1}^{c_1} \left(y_{ik} \log \sum_{l=1}^{c_1} e^{\mathbf{w}_l^T \mathbf{x}_i} - y_{ik} \mathbf{w}_k^T \mathbf{x}_i \right).$$

- Least square loss for memory degradation score regression:

$$l_2(\mathbf{P}) = \left\| \mathbf{X}^T \mathbf{P} - \mathbf{Z} \right\|_{\mathrm{F}}^2,$$

(Wang *et al.* MICCAI'11)

An Efficient Iterative Algorithm with Global Convergence

Algorithm 1. An efficient algorithm to solve Eq. (3)

Input: $\mathbf{X} = [\mathbf{x}_1, \ldots, \mathbf{x}_n] \in \mathbb{R}^{d \times n}$, $\mathbf{Y} = [\mathbf{y}_1, \ldots, \mathbf{y}_n]^T \in \mathbb{R}^{n \times c_1}$, and $\mathbf{Z} = [\mathbf{z}_1, \ldots, \mathbf{z}_n]^T \in \mathbb{R}^{n \times c_2}$.

1. Initialize $\mathbf{W} \in \mathbb{R}^{d \times c_1}$, $\mathbf{P} \in \mathbb{R}^{d \times c_2}$, and let $\mathbf{V} = [\mathbf{W}\ \mathbf{P}] \in \mathbb{R}^{d \times (c_1 + c_2)}$;

while *not converge* **do**

2. Calculate the diagonal matrix $\mathbf{D}$, of which the k-th element is $\frac{1}{2\|\mathbf{v}^k\|_2}$;

3. Update $\mathbf{w}$ by $\mathbf{w} - \mathbf{B}^{-1}\mathbf{a}$, where $(d \times (p-1) + u)$-th element of $\mathbf{a} \in \mathbb{R}^{dc_1 \times 1}$ is $\frac{\partial\left[l_1(\mathbf{W}) + \gamma\,\mathrm{tr}\left(\mathbf{W}^T\mathbf{D}\mathbf{W}\right)\right]}{\partial \mathbf{W}_{up}}$ for $1 \le u \le d, 1 \le p \le c_1$, the $(d \times (p-1) + u, d \times (q-1) + v)$-th element of $\mathbf{B} \in \mathbb{R}^{dc_1 \times dc_1}$ is $\frac{\partial\left[l_1(\mathbf{W}) + \gamma\,\mathrm{tr}\left(\mathbf{W}^T\mathbf{D}\mathbf{W}\right)\right]}{\partial \mathbf{W}_{up}\partial \mathbf{W}_{vq}}$ for $1 \le u, v \le d$ and $1 \le p, q \le c_1$.

Construct the updated $\mathbf{W} \in \mathbb{R}^{d \times c_1}$ by the updated vector $\mathbf{w} \in \mathbb{R}^{dc_1}$, where the (u, p)-th element of $\mathbf{W}$ is the $(d \times (p-1) + u)$-th element of $\mathbf{w}$;

4. Update $\mathbf{P}$ by $\mathbf{P} = \left(\mathbf{X}\mathbf{X}^T + \gamma\mathbf{D}\right)^{-1}\mathbf{X}\mathbf{Z}$;

5. Update $\mathbf{V}$ by $\mathbf{V} = [\mathbf{W}\ \mathbf{P}]$;

end

Output: $\mathbf{W} \in \mathbb{R}^{d \times c_1}$ and $\mathbf{P} \in \mathbb{R}^{d \times c_2}$.

(Wang *et al.* MICCAI'11)

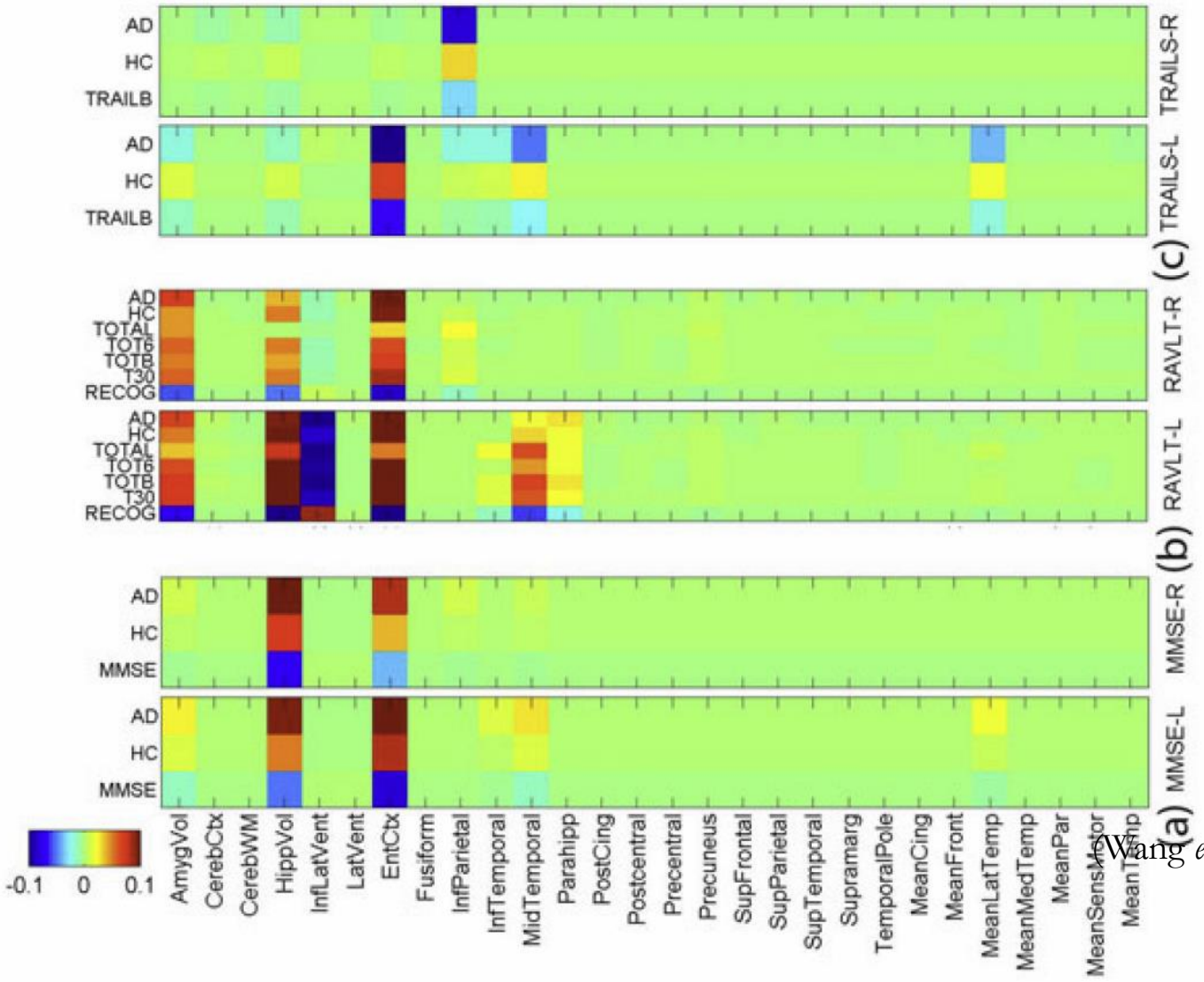
Experimental Results

Table 1. Comparison of classification and regression performance

				Our method		Classification accuracy		RMSE (mean ± std)	
Memory score	# subjects	# AD	# HC	Classification accuracy	Regression RMSE	Logistic regression	SVM	Multivariate regression	Ridge regression
MMSE	378	175	203	0.881	0.034 ± 0.002	0.832	0.783 (linear kernel)	0.041 ± 0.003	0.039 ± 0.004
RAVLT	371	172	199	0.884	0.019 ± 0.001		0.839 (Polynomial kernel)	0.028 ± 0.002	0.024 ± 0.003
TRAILS	369	166	203	0.864	0.043 ± 0.002		0.796 (Gausssian kernel)	0.049 ± 0.003	0.046 ± 0.003

(Wang *et al.* MICCAI'11)

Experimental Results (Cont.)

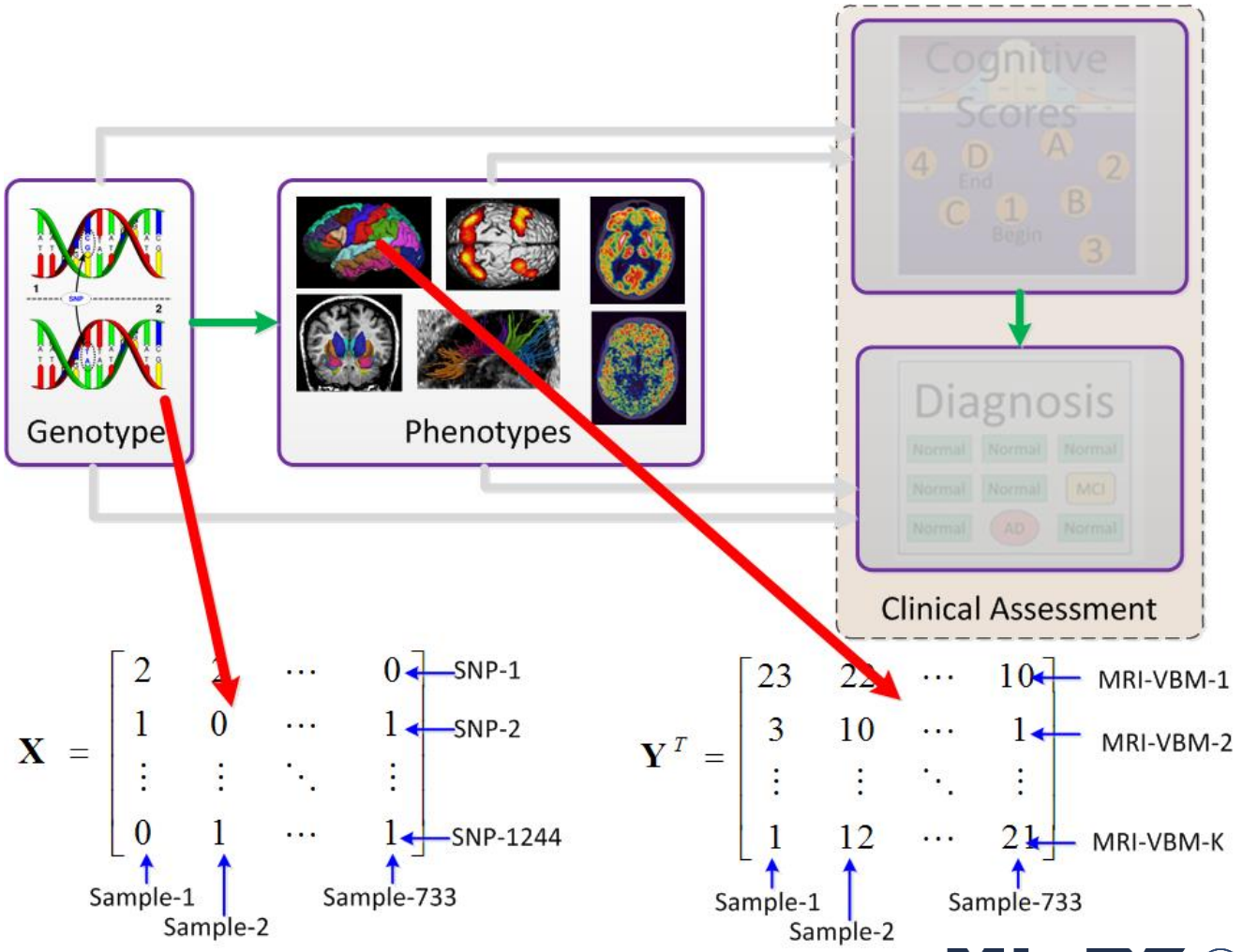


(Wang *et al.* MICCAI'11)

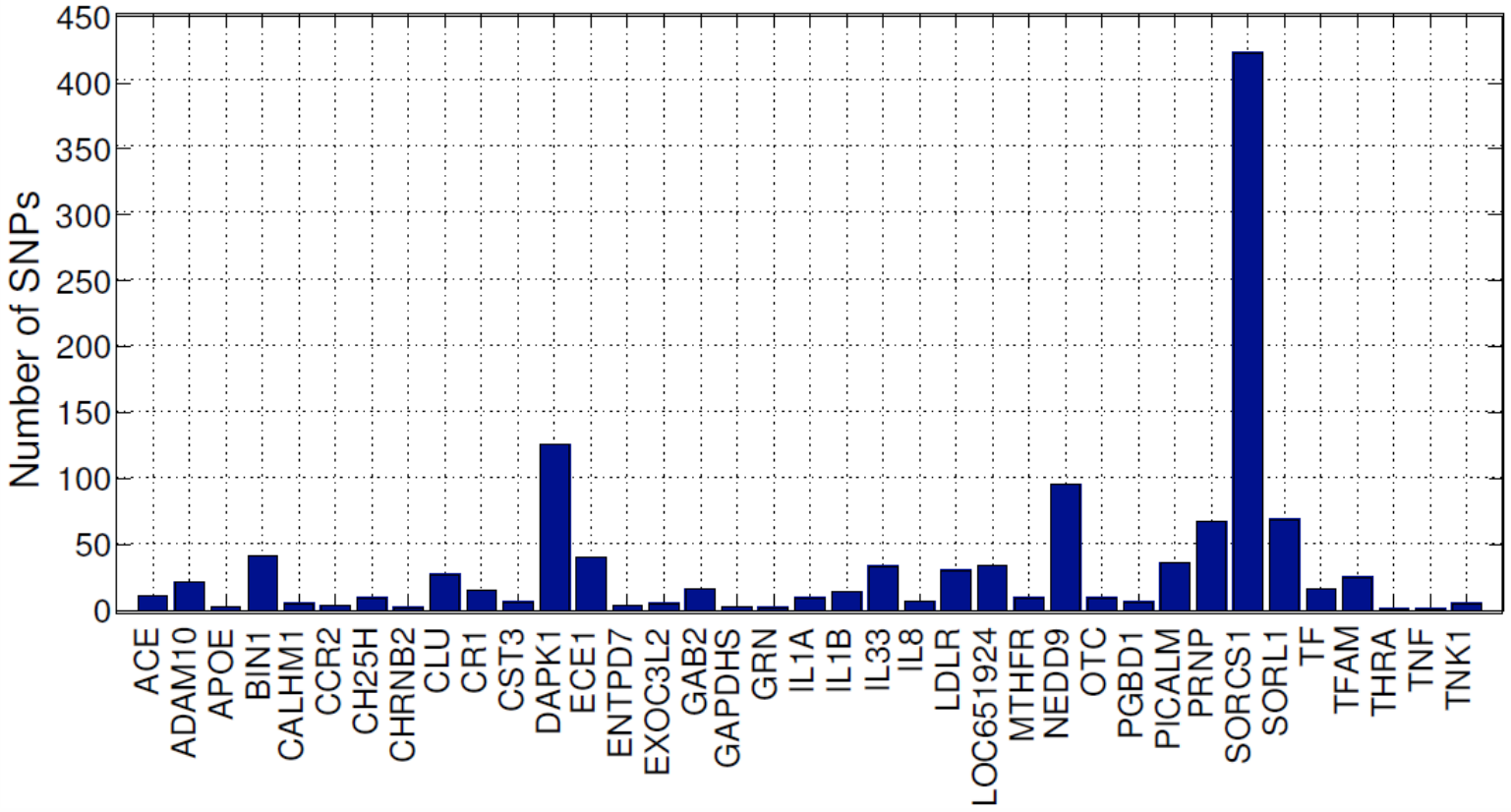
Outline

- Background and motivation
- Learning with homogeneous tasks
- Learning with heterogeneous tasks
- **Learning with group-structured single-modality data**
- Learning with multi-modality data
- Learning with longitudinal data

From Genotype to Phenotype

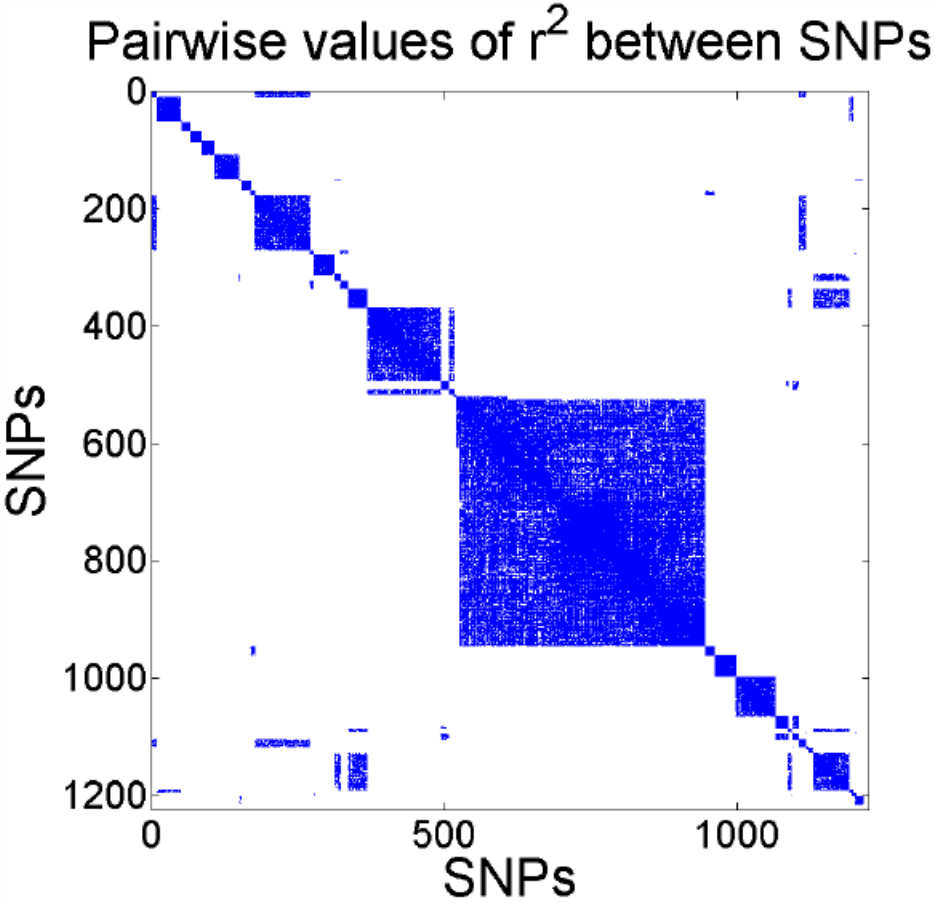


SNPs are Genetically Linked with Group Structures — Genes



(Wang *et al.* Bioinformatics'12)

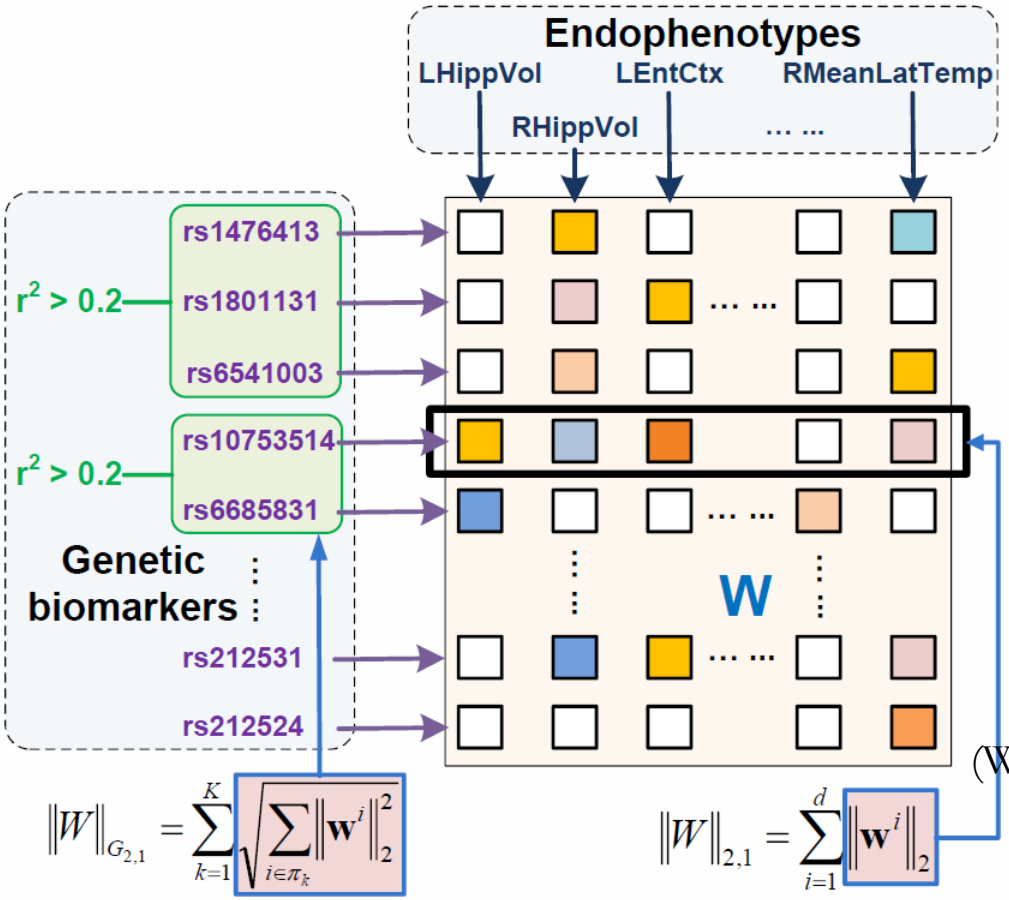
SNPs are Genetically Linked with Group Structures – Linkage Disequilibrium (LD)



(Wang *et al.* Bioinformatics'12)

A Novel Group-2,1 Norm to Capture Grouping Structures

$$\min_{\mathbf{W}} \sum_{i=1}^{n} ||\mathbf{W}^T\mathbf{X} - \mathbf{Y}||_F^2 + \gamma_1 ||\mathbf{W}||_{G_{2,1}} + \gamma_2 ||\mathbf{W}||_{2,1}$$



(Wang *et al.* Bioinformatics'12)

An Efficient Iterative Algorithm with Global Convergence

Input: $\mathbf{X} = [\mathbf{x}_1, \mathbf{x}_2, \cdots, \mathbf{x}_n] \in \mathbb{R}^{d \times n}$,
$\mathbf{Y} = [\mathbf{y}_1, \mathbf{y}_2, \cdots, \mathbf{y}_n] \in \mathbb{R}^{c \times n}$

Initialize $\mathbf{W}_1 \in \mathbb{R}^{d \times c}$, $t = 1$;

while *not converge* **do**

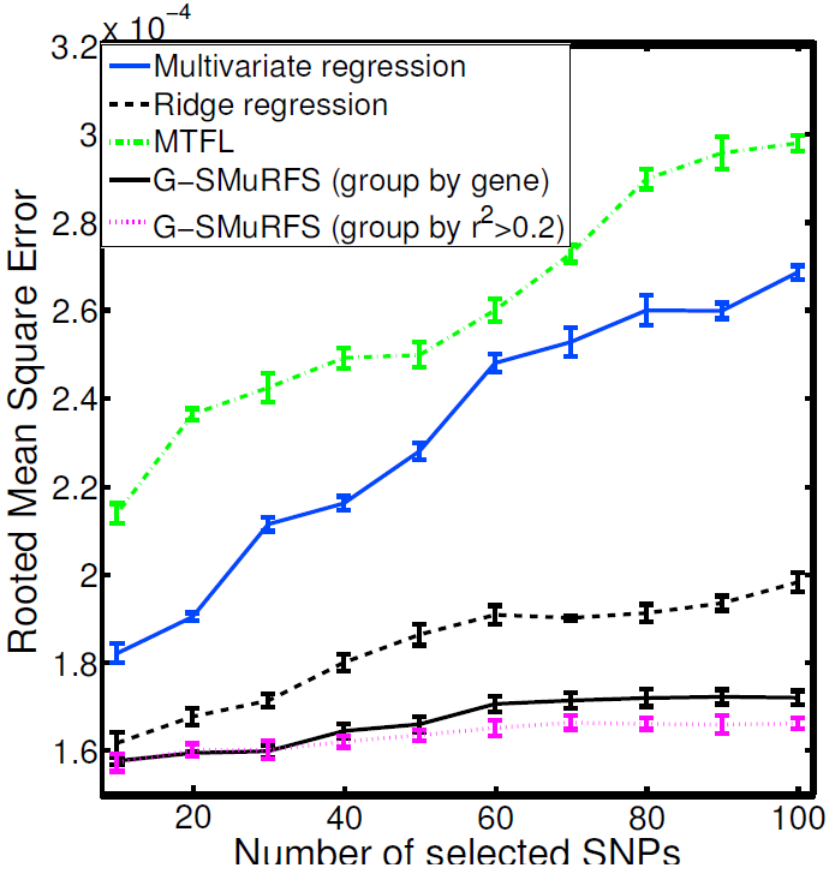
1. Calculate the block diagonal matrix $\mathbf{D}_t$, where the k-th diagonal is $\frac{1}{2\|\mathbf{w}_t^k\|_F}\mathbf{I}_k$; Calculate the diagonal matrix $\tilde{\mathbf{D}}_t$, where the i-th diagonal element is $\frac{1}{2\|\mathbf{w}_t^i\|_2}$;
2. $\mathbf{W}_{t+1} = (\mathbf{X}\mathbf{X}^T + \gamma_1\mathbf{D}_t + \gamma_2\tilde{\mathbf{D}}_t)^{-1}\mathbf{X}\mathbf{Y}^T$;
3. $t = t + 1$;

end

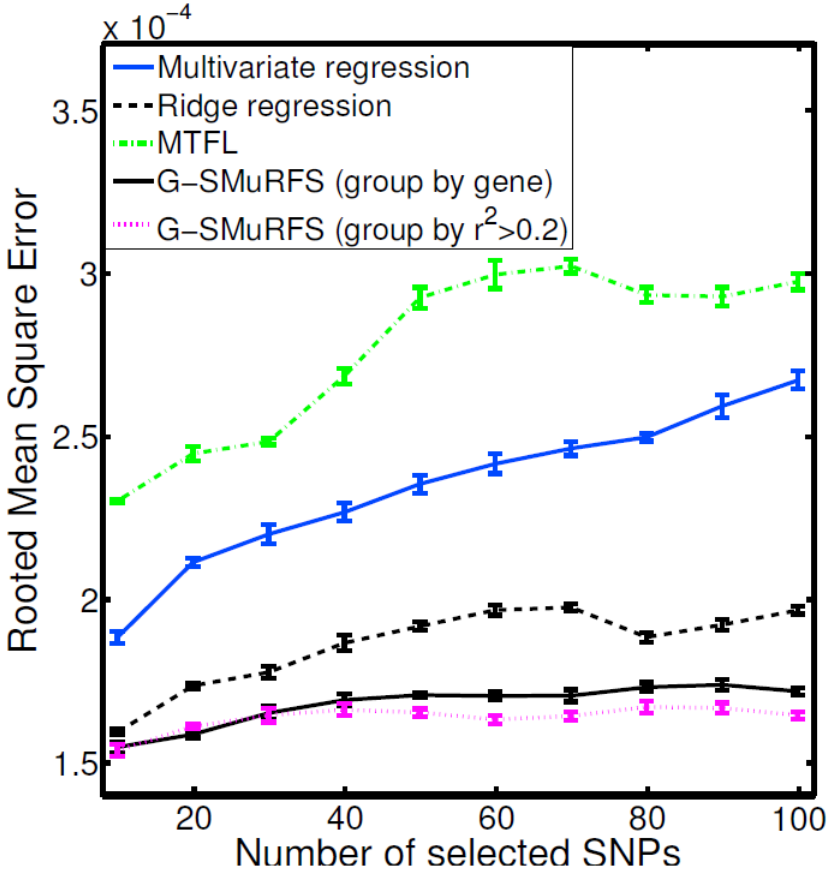
Output: $\mathbf{W}_t \in \mathbb{R}^{d \times c}$.

(Wang *et al.* Bioinformatics'12)

Experimental Results



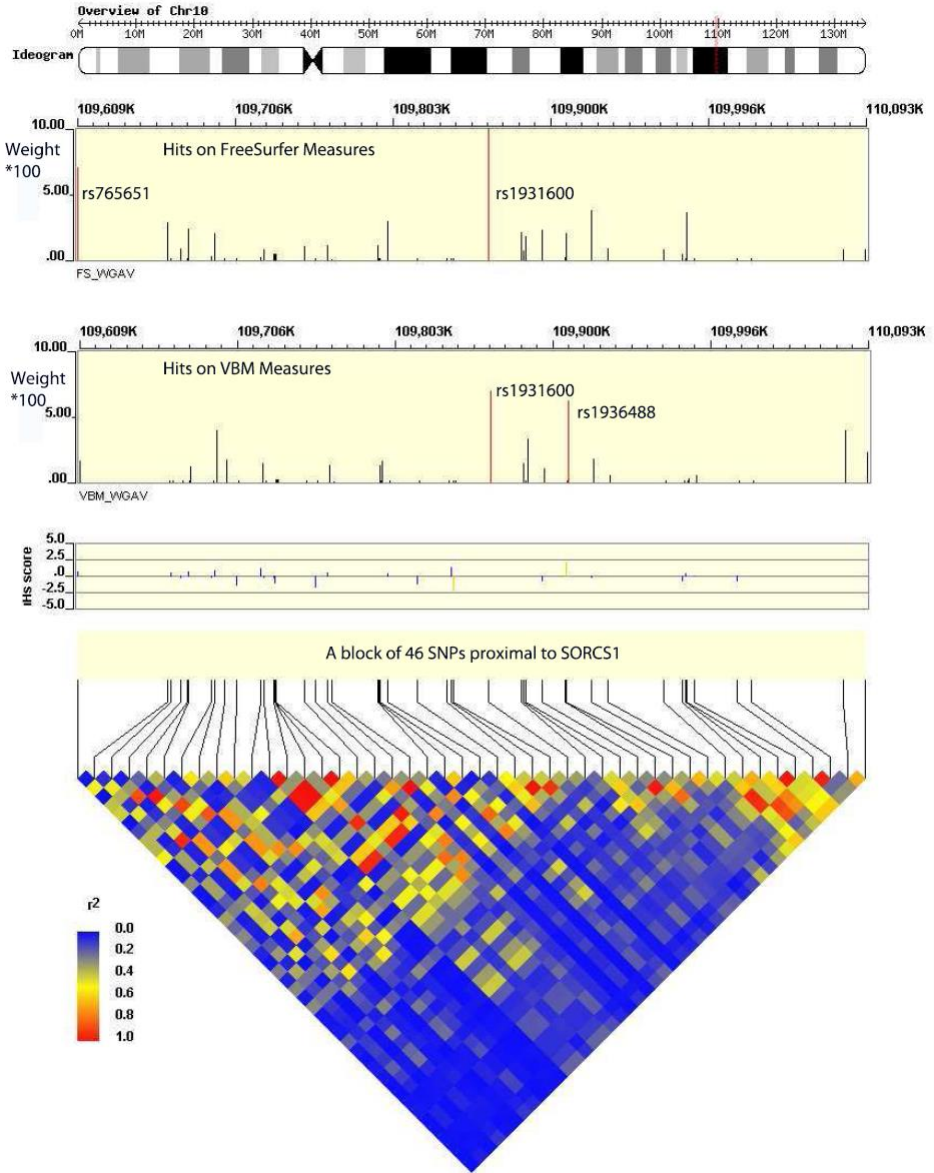
(a) FreeSurfer imaging genotypes.



(b) VBM imaging genotypes.

(Wang *et al.* Bioinformatics'12)

Experimental Results (Cont.)

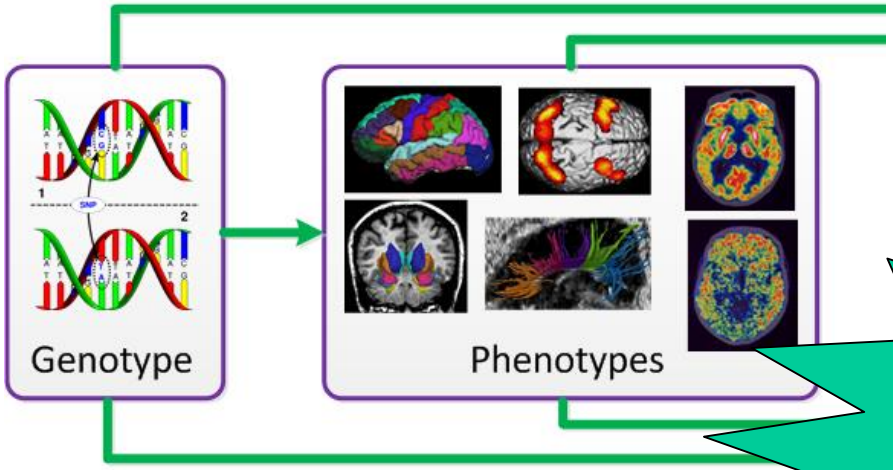


(Wang *et al.* Bioinformatics'12)

Outline

- Background and motivation
- Learning with homogeneous tasks
- Learning with heterogeneous tasks
- Learning with group-structured single-modality data
- **Learning with multi-modality data**
- Learning with longitudinal data

Integration of Genotypes and Phenotypes to Select Multi-Modal Biomarkers

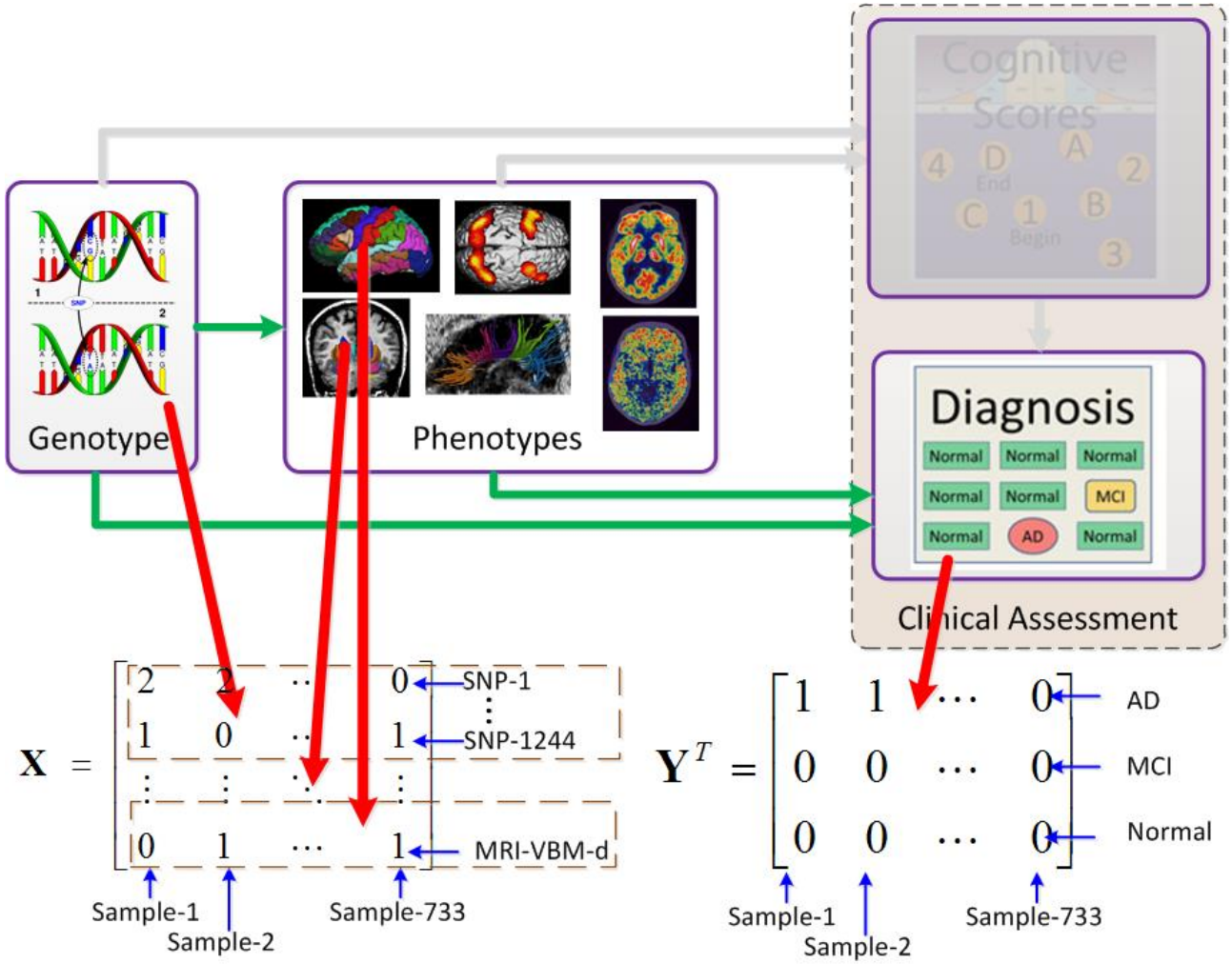


Multiple data modalities.

Feature Selection + **Data Fusion**

MInDS@MINES
Machine Learning ∘ Informatics ∘ Data Science

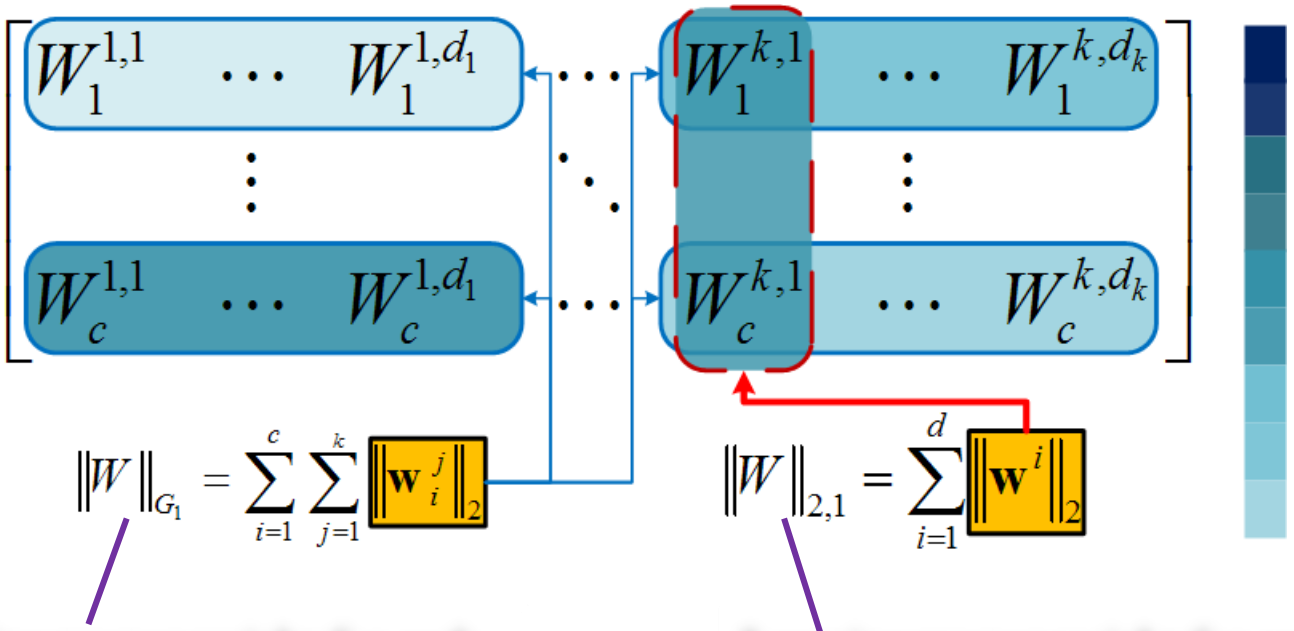
Integration of Genotypes and Phenotypes to Select Multi-Modal Biomarkers



MInDS@MINES
Machine Learning • Informatics • Data Science

New Objective Function for Multi-Modal Biomarker Integration

$$\min_{\mathbf{W}} \left\| \mathbf{X}^T \mathbf{W} - \mathbf{Y} \right\|_F^2 + \gamma_1 \left\| \mathbf{W} \right\|_{G_1} + \gamma_2 \left\| \mathbf{W} \right\|_{2,1}$$



Learning proper weight for each modality

Learning proper weight for each individual feature

(Wang *et al.* ISMB'12)

New Objective Function for Multi-Modal Biomarker Integration (cont.)

- The formulated objective is highly non-smooth due to the ℓ_{21}-norm regularization term and our new group ℓ_1-norm regularization term.

Input: $\mathbf{X} = [\mathbf{x}_1, \mathbf{x}_2, ..., \mathbf{x}_n] \in \mathbb{R}^{d \times n}$, $\mathbf{Y} = [\mathbf{y}_1, \mathbf{y}_2, ..., \mathbf{y}_c] \in \mathbb{R}^{n \times c}$.
Output: $\mathbf{W}_t \in \mathbb{R}^{d \times c}$.
1. Let $t = 1$. Initialize $\mathbf{W}_t \in \mathbb{R}^{d \times c}$.
repeat
2. Calculate the block diagonal matrices $\mathbf{D}_t^i (1 \leq i \leq c)$, where the j-th diagonal block of $\mathbf{D}_t^i$ is $\frac{1}{2\|(\mathbf{w}_t)_i^j\|_2}\mathbf{I}_j$. Calculate the diagonal matrix $\tilde{\mathbf{D}}_t$, where the i-th diagonal element is $\frac{1}{2\|\mathbf{w}_t^i\|_2}$.
3. For each $\mathbf{w}_i (1 \leq i \leq c)$, $(\mathbf{w}_{t+1})_i = (\mathbf{X}\mathbf{X}^T + \gamma_1 \mathbf{D}_t^i + \gamma_2 \tilde{\mathbf{D}}_t)^{-1}\mathbf{X}\mathbf{y}_i$.
4. $t = t + 1$.
until Converges

Simple, efficient, easy to implement

Theorem: **The objective value of**

$$\min_{\mathbf{W}} \left\|\mathbf{X}^T\mathbf{W} - \mathbf{Y}\right\|_F^2 + \gamma_1 \left\|\mathbf{W}\right\|_{G_1} + \gamma_2 \left\|\mathbf{W}\right\|_{2,1}$$

decreases in each iteration of the algorithm.

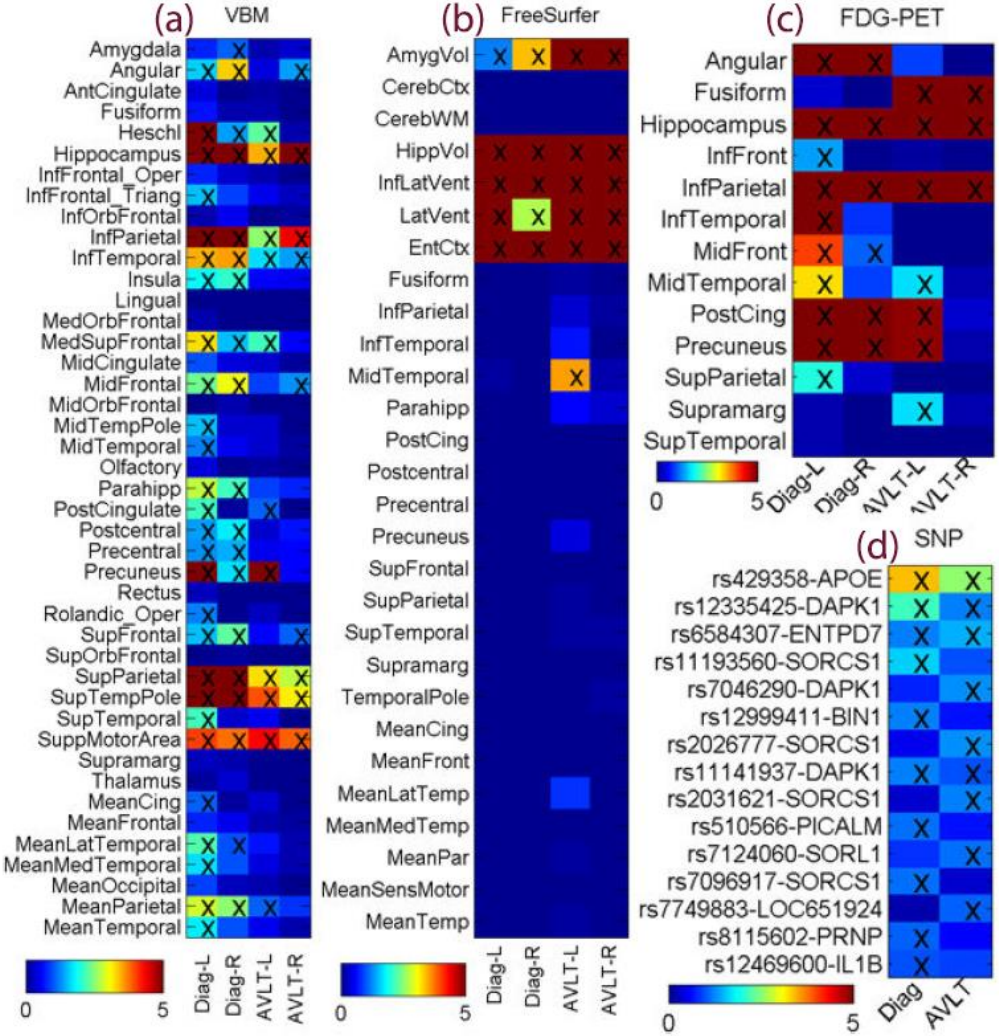
(Wang *et al.* ISMB'12)

Improved Early Alzheimer's Disease Detection

Methods	Accuracy (mean+std)
SVM (SNP)	0.561 ± 0.026
SVM (FreeSurfer)	0.573 ± 0.012
SVM (VBM)	0.541 ± 0.032
SVM (PET)	0.535 ± 0.026
SVM (all)	0.575 ± 0.019
SVM ℓ_∞ MKL method	0.624 ± 0.031
SVM ℓ_1 MKL method	0.593 ± 0.042
SVM ℓ_2 MKL method	0.561 ± 0.037
LSSVM ℓ_∞ MKL method	0.614 ± 0.031
LSSVM ℓ_1 MKL method	0.585 ± 0.018
LSSVM ℓ_2 MKL method	0.577 ± 0.033
Our method	$\mathbf{0.674 \pm 0.021}$

(Wang *et al.* ISMB'12)

Biomarker Selection

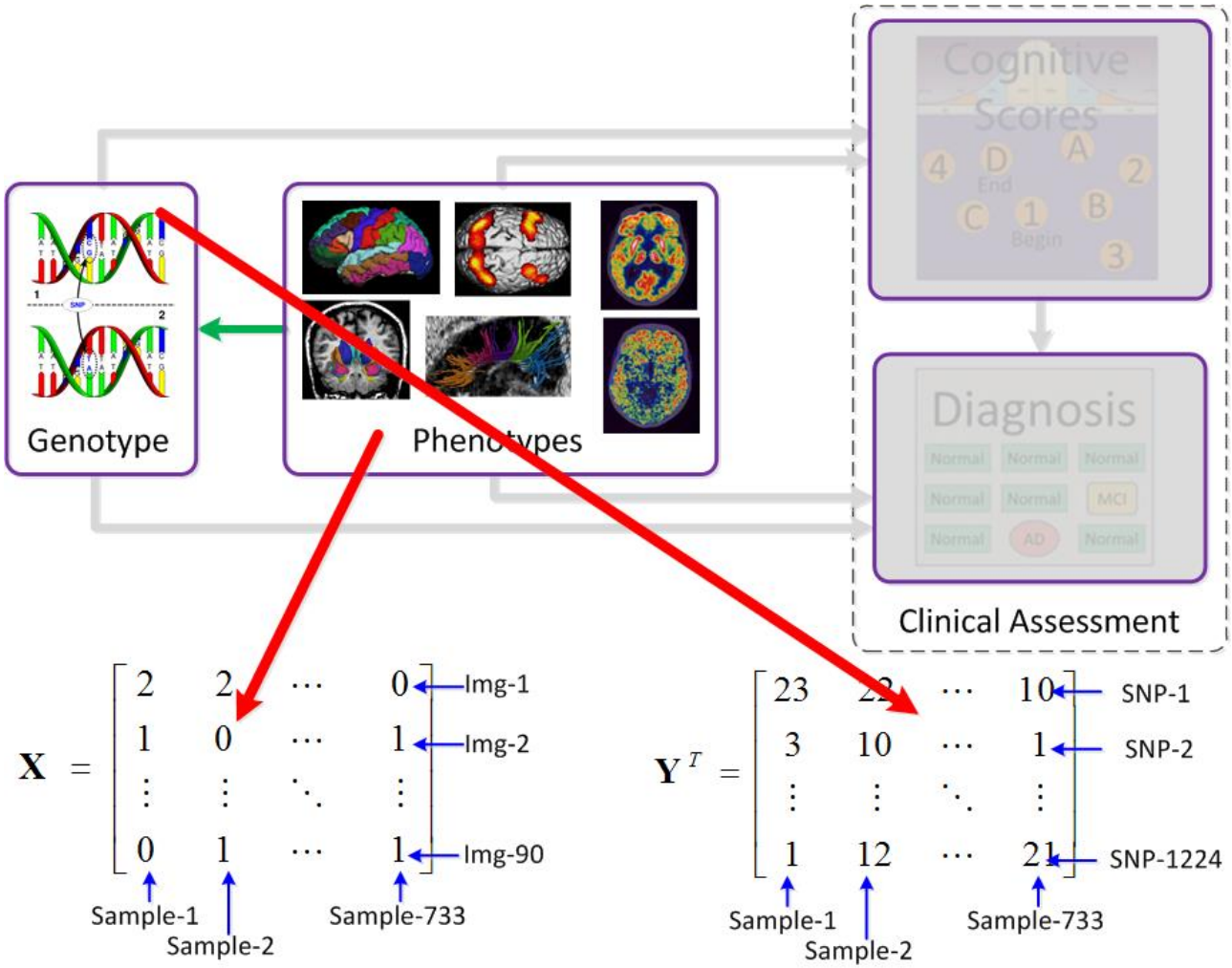


(Wang *et al.* ISMB'12)

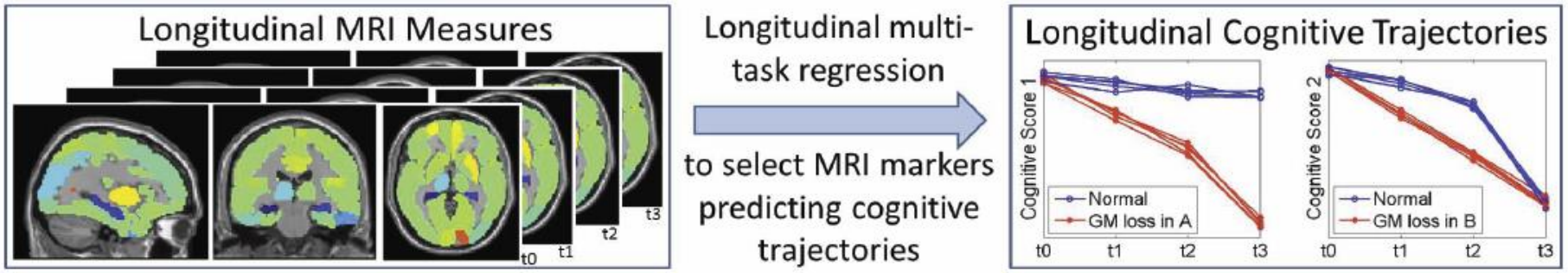
Outline

- Background and motivation
- Learning with homogeneous tasks
- Learning with heterogeneous tasks
- Learning with group-structured single-modality data
- Learning with multi-modality data
- **Learning with longitudinal data**

Association from Phenotypes to Genotypes



Longitudinal Multi-Task Regression Model



Learning A Tensor of Regression Model

- We need to learn T regression coefficient matrices, which forms up a tensor:

$$\min_{\mathcal{B}} J_2 = \mathcal{L}(\mathcal{B}) + \gamma_1 \sum_{k=1}^{d} \sqrt{\sum_{t=1}^{T} ||\mathbf{b}_t^k||_2^2} + \gamma_2 \|B\|_*$$

where longitudinal loss is defined as:

$$\mathcal{L}(\mathcal{B}) = ||\mathcal{B} \otimes_1 \mathcal{X}^T - Y||_F^2 = \sum_{t=1}^{T} ||X_t^T B_t - Y||_F^2.$$

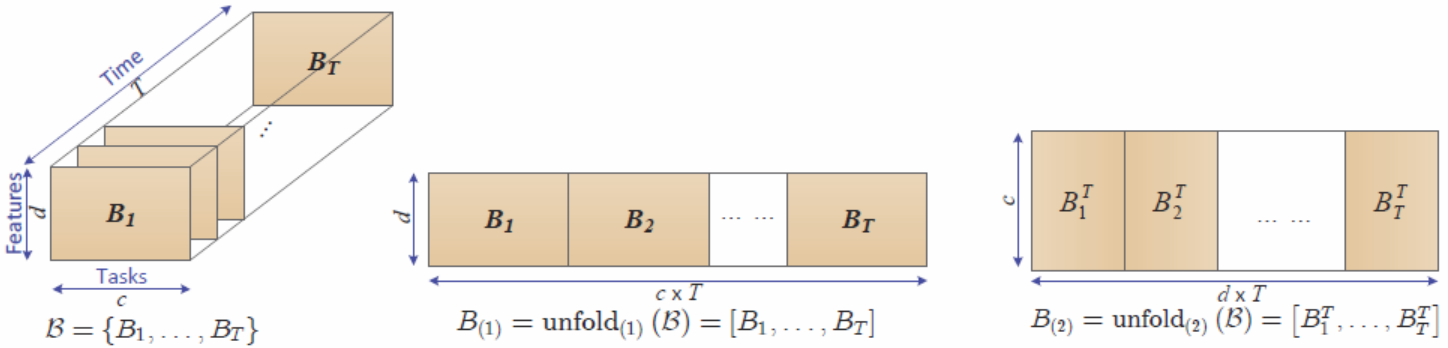


Figure 2: **Left**: visualization of the coefficient tensor $\mathcal{B}$ learned for the association study on longitudinal data. **Middle**: the matrix unfolded from $\mathcal{B}$ along the first mode (feature dimension). **Right**: the matrix unfolded from $\mathcal{B}$ along the second mode (task dimension).

An Efficient Iterative Algorithm with Global Convergence

Algorithm 1: A new algorithm to minimize J_2 in Eq. (4).

Data: $\mathcal{X} \in \mathbb{R}^{d \times n \times T}$, $Y \in \mathbb{R}^{n \times c}$.

1. Initialize $\mathcal{B}^{(0)} \in \mathbb{R}^{d \times c \times T}$ using the regression results at each individual time point.

repeat

2. Calculate the diagonal matrix D, where the k-th diagonal element is computed as $\frac{1}{2\sqrt{\sum_{t=1}^{T} ||\mathbf{b}_t^k||_2^2}}$.

3. Calculate $\bar{D} = \frac{1}{2}\left(BB^T\right)^{-\frac{1}{2}}$.

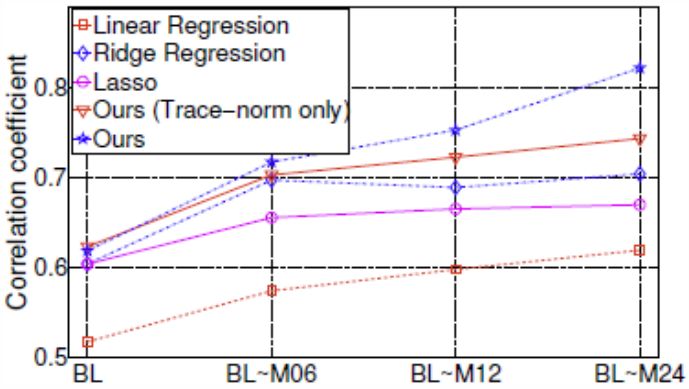
4. Update B_t by $B_t = (X_t X_t^T + \gamma_1 D + \gamma_2 \bar{D})^{-1} X_t Y$.

until *Converges*

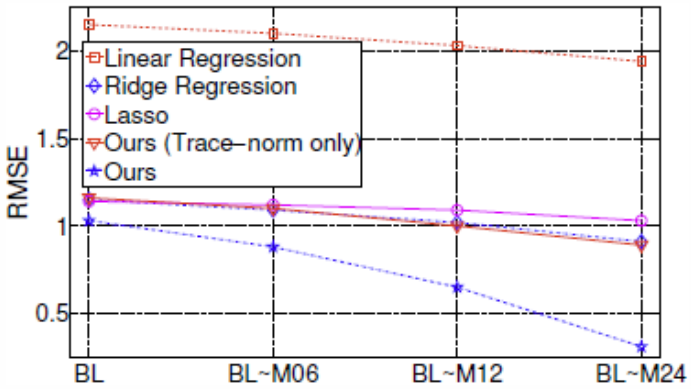
Result: $\mathcal{B} = \{B_1, B_2, \ldots, B_T\} \in \mathbb{R}^{d \times c \times T}$.

(Wang *et al.* ECCB'12, NIPS'12)

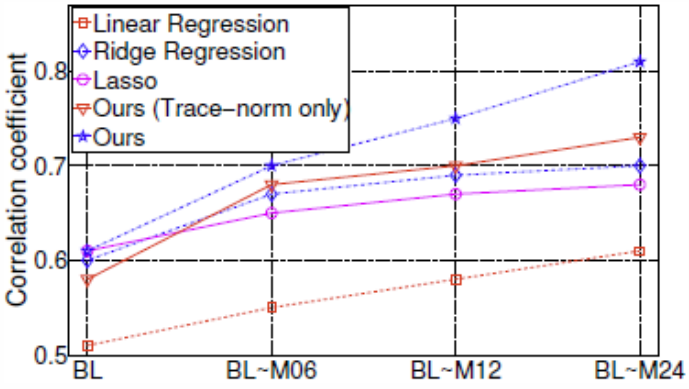
Experimental Results



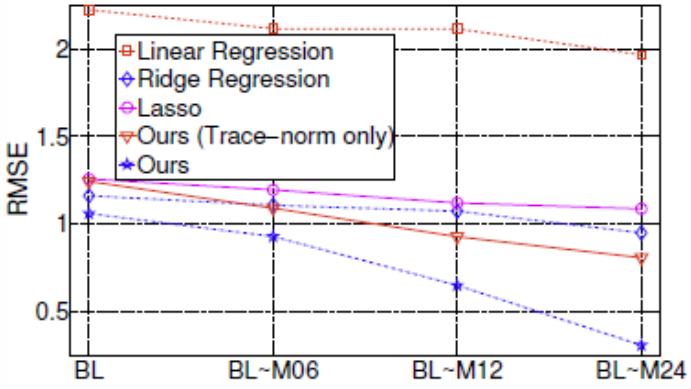
(a) VBM.



(b) VBM.



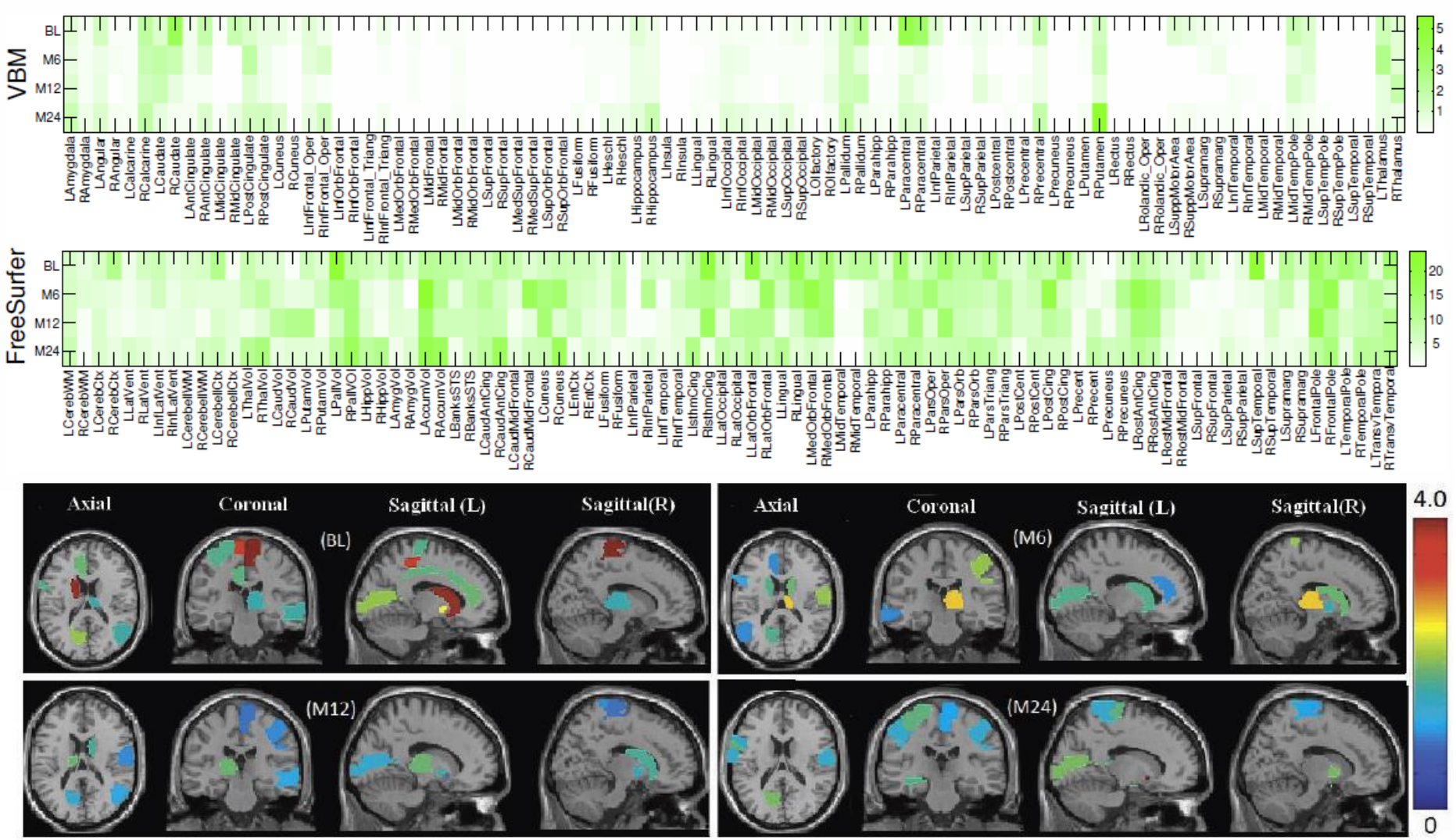
(c) FreeSurfer.



(d) FreeSurfer.

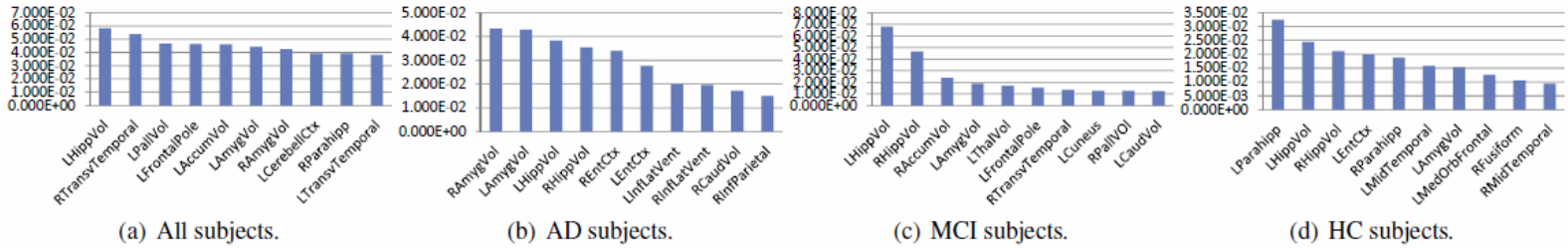
(Wang *et al.* ECCB'12, NIPS'12)

Experimental Results (Cont.)



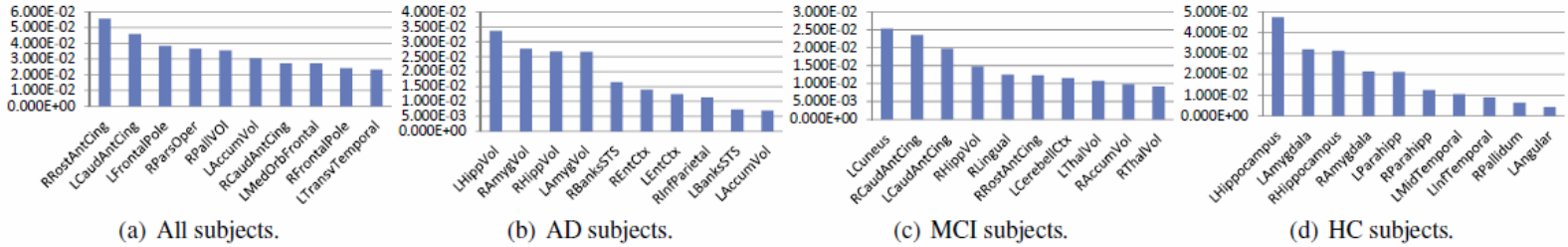
(Wang *et al.* ECCB'12, NIPS'12)

Experimental Results (Cont.)



(a) All subjects. (b) AD subjects. (c) MCI subjects. (d) HC subjects.

Fig. 4. Top 10 FreeSurfer markers identified for rs423958-APOE.



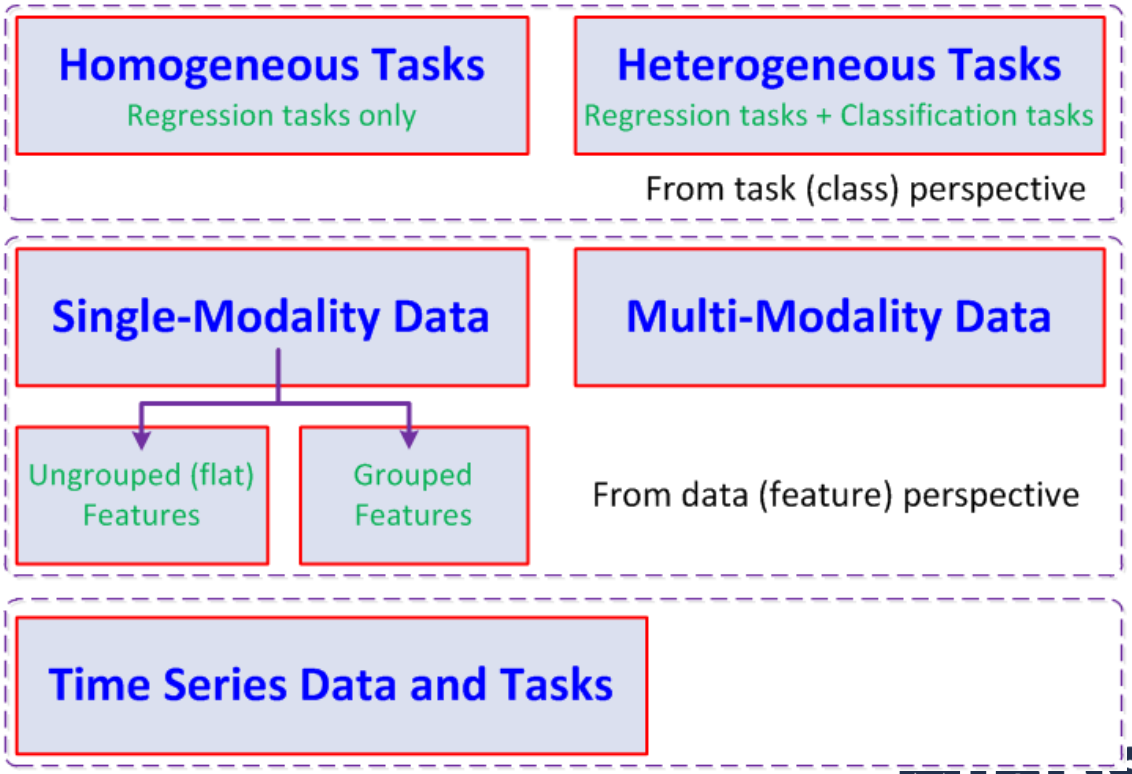
(a) All subjects. (b) AD subjects. (c) MCI subjects. (d) HC subjects.

Fig. 5. Top 10 FreeSurfer markers identified for rs11136000-CLU.

(Wang *et al.* ECCB'12, NETS'12)

Conclusions

- Our research results have shown the effectiveness of using multi-modal data in early AD detection.
- Our algorithms have proven to be theoretically elegant and computationally efficient.




Thank You!