Knowledge Enhancement through Intra-relation, Inter-relation, and Integration of Different Levels of Genomic Data

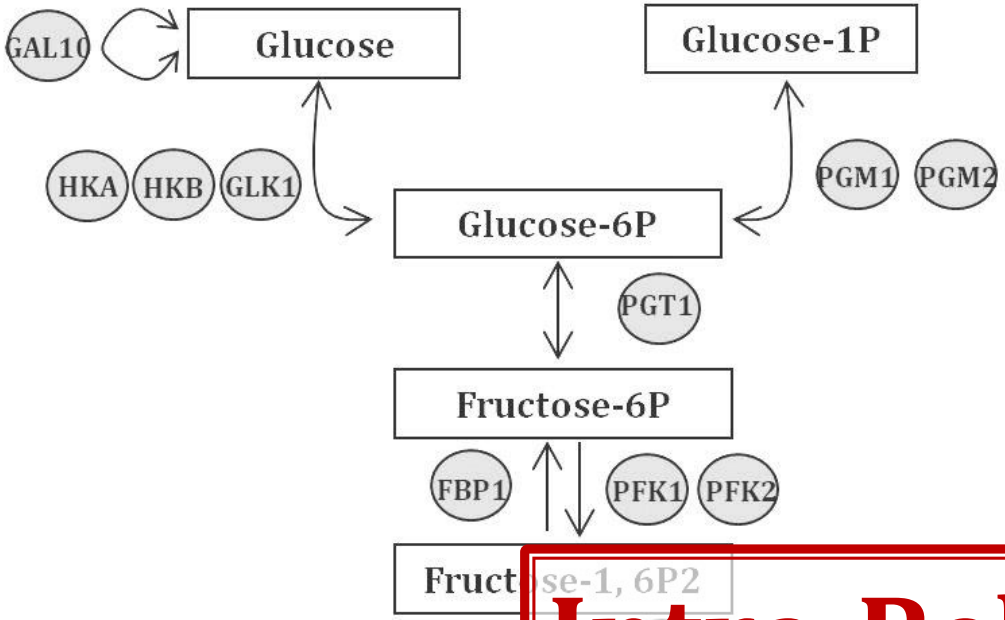
Hyunjung (Helen) Shin

Dept. of Industrial & Information Systems Engineering
Ajou University, Korea

shin@ajou.ac.kr
http://www.alphaminers.net
http://www.kyb.tuebingen.mpg.de/~shin

Outline

[Intra-Relation] **Breast Cancer Survivability Prediction**	**Graph Representation** **Graph-based Semi-Supervised Learning (SSL)**
[Integration] **Protein Functional Class Prediction**	**Data Integration Method based on SSL** **MIPS Yeast Proteins/PDBselect25-GO** **Prediction from Multiple Protein Networks**
Cancer Clinical Outcome Prediction	**Brain Cancer (GBM)/Ovarian Cancer (OV)** **Prediction from Multiple Genomic Data**
[Inter-Relation] **Cancer Clinical Outcome Prediction**	**Network Reconstruction using the Information From miRNA to Gene Expression**
Closing Remarks	**Future Work**



Objective Function

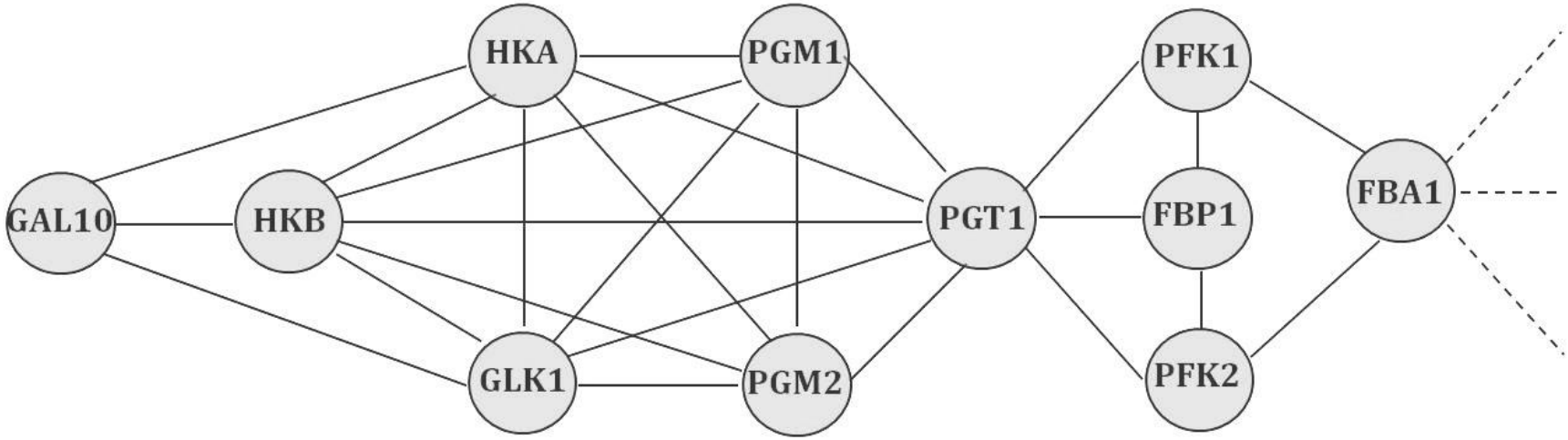
$$\min_{f} \quad \mu f^T L f + (f - y)^T (f - y)$$

Solution

$$f = \{ I + \mu L \}^{-1} y$$

where $L = D - W$, $D = diag(d_i)$, $d_i = \sum_j w_{ij}$

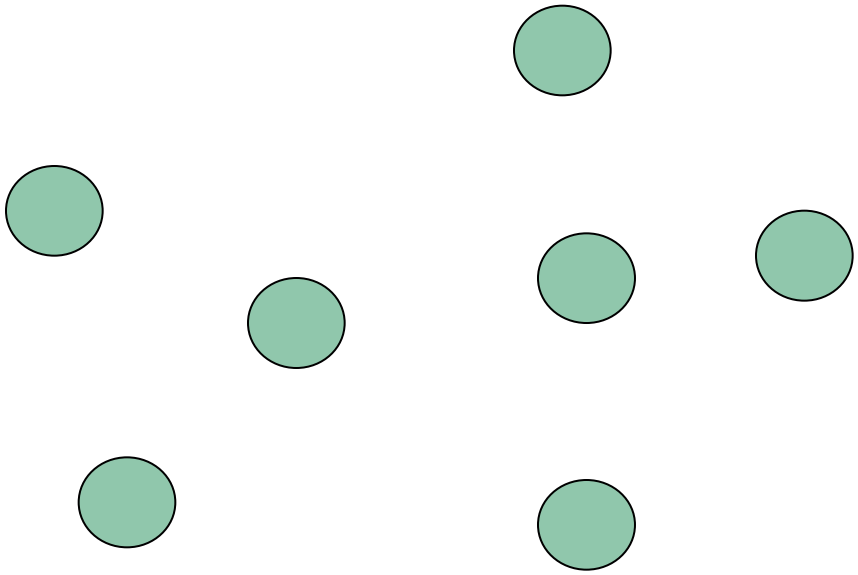
Intra-Relation



Intra-Relation: Graph Representation

Nodes : **Protein Network**
Proteins

: **Patient Network**
Patient Samples



Intra-Relation: Graph Representation

Labels

Patient Network

Clinical Outcome

(ex) Breast Cancer

: Survived (+1) or Not (-1)

(ex) Brain Cancer

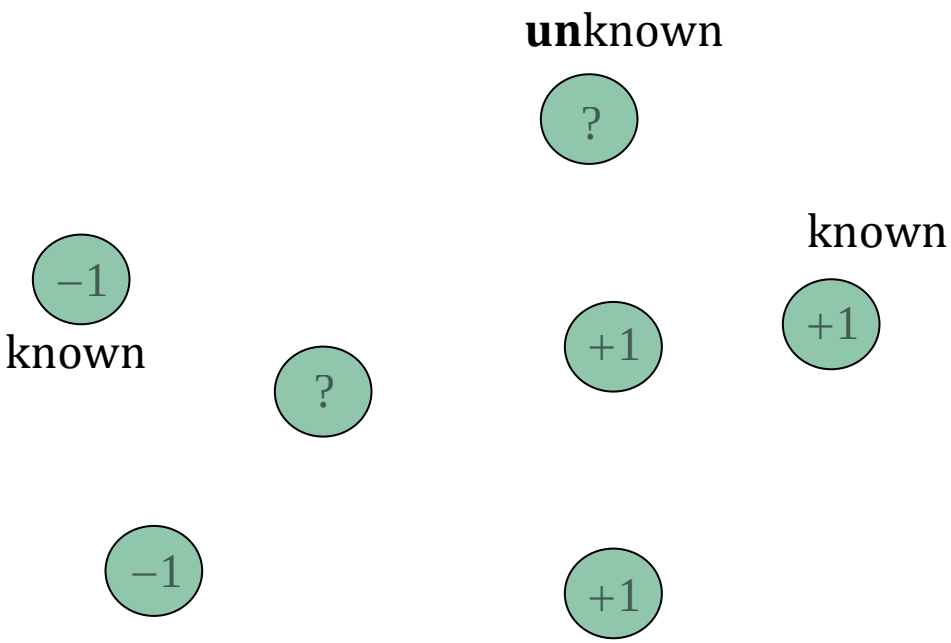
: Glioblastoma Multiforme

: Recurrent tumor (+1) or Initial (-1)

(ex) Ovarian Cancer

: Serous cystadenocarcinoma

: Early stage T1/T2 (+1) or
Late stage T3/T4 (-1)



+1/-1 : Labeled *patient samples* with/without a *specific clinical outcome*

? : Unlabeled patient samples

Intra-Relation: Graph Representation

Edges

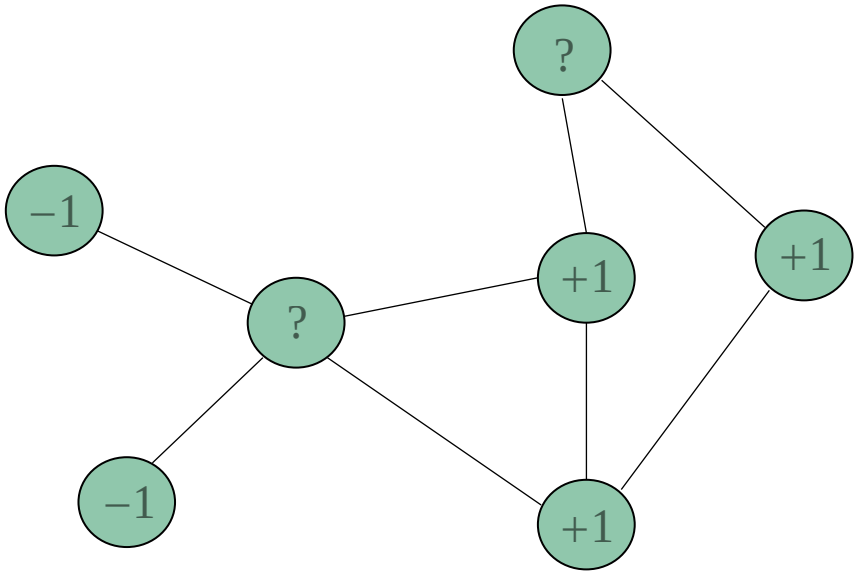
Protein Network

Similarities between Proteins

(ex) Physical Interaction
: Two proteins physically interact (e.g., docking)

(ex) Metabolic Pathway
: Two enzymes catalyzing successive reactions

(ex) Pfam domain structure
: Two proteins which show similar pattern in presence or absence of Pfam domains



Intra-Relation: Graph Representation – "Creating a Graph"

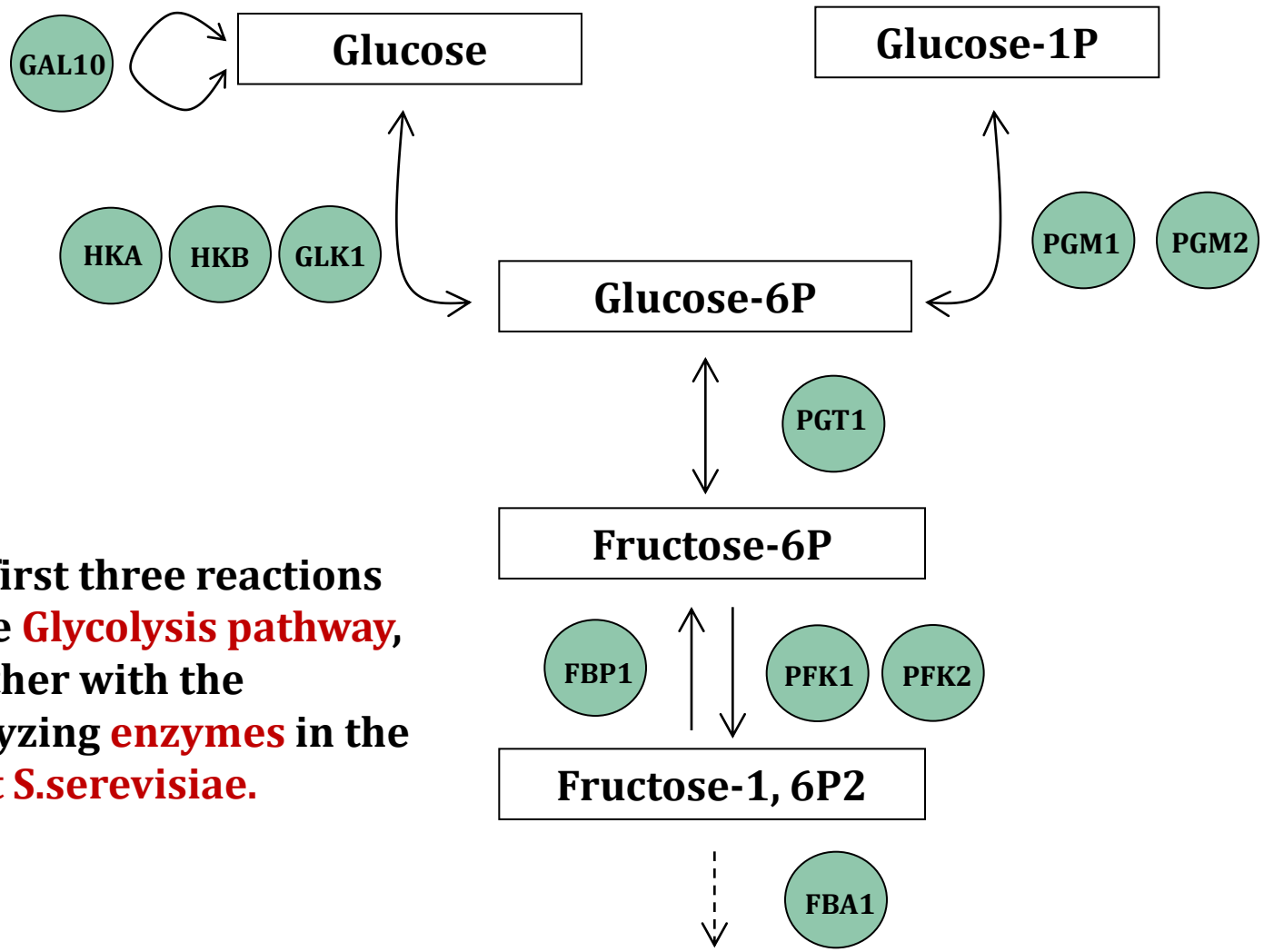
Naturally Given Graphs

Example: Metabolic Gene Network

- Graph Representation on Biological Networks

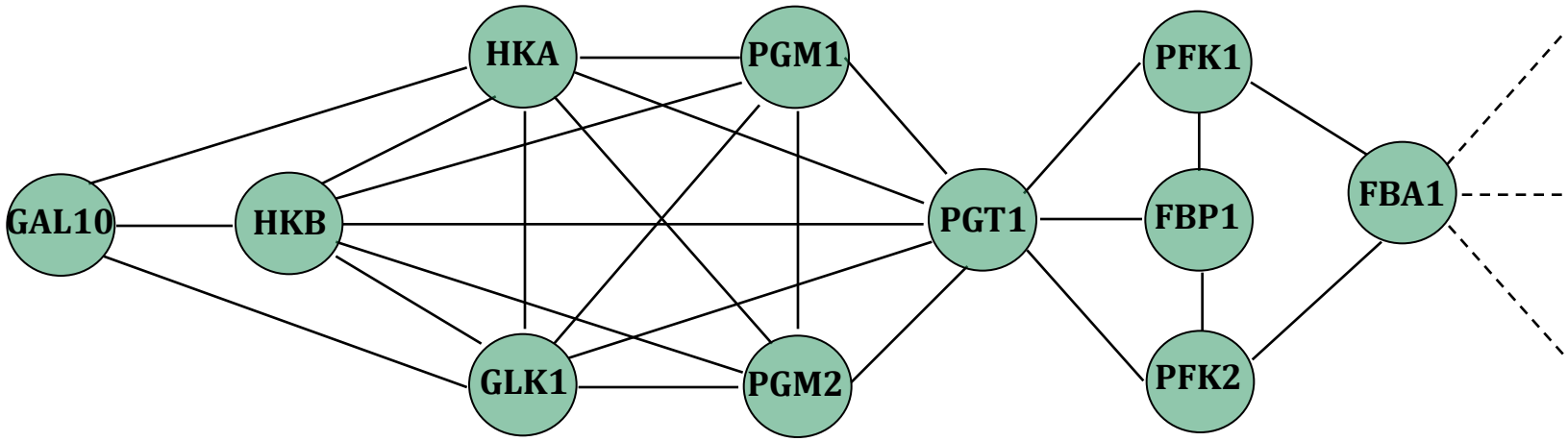
- The task is to predict (unidentified) functional classes of proteins using metabolic pathways

Intra-Relation: Graph Representation – "Creating a Graph"



The first three reactions of the Glycolysis pathway, together with the catalyzing enzymes in the Yeast S.serevisiae.

Intra-Relation: Graph Representation – "Creating a Graph"



$$\min_{\boldsymbol{\beta}} \; d(\boldsymbol{\beta}) \equiv \boldsymbol{y}^T (\boldsymbol{I} + \sum_{k=1}^{K} \beta_k L_k)^{-1} \boldsymbol{y} \qquad \boldsymbol{y} = \left\{ \boldsymbol{I} + \sum_{k=1}^{K} \beta_k L_k \right\} \boldsymbol{f}$$

Given Graphs

THEORY

SDP/SVM — *Kernel matrix*

Dense

$K(\mu)$

Prediction from Intra-Relation

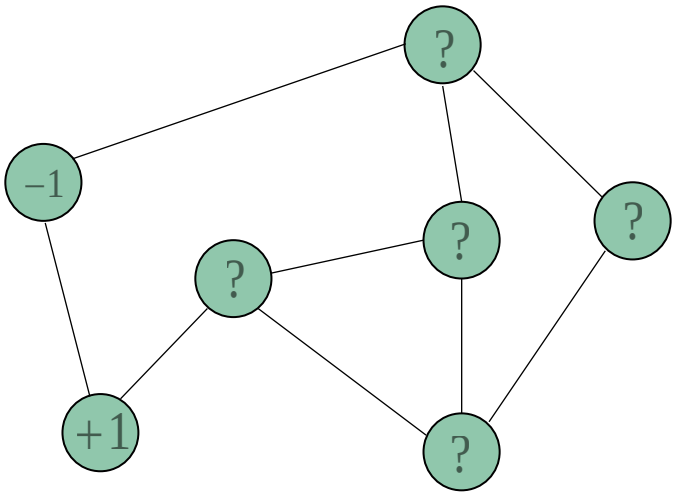
Mathematical Formulation

SSL — *Laplacian matrix L (or Similarity matrix W)*

Sparse

$$L(\beta) = \beta_1 \boldsymbol{L_1} + \beta_2 \boldsymbol{L_2} + \beta_3 \boldsymbol{L_3} + \cdots\cdots + \beta_k \boldsymbol{L_1}$$

Prediction from Intra-Relation: Graph-based SSL



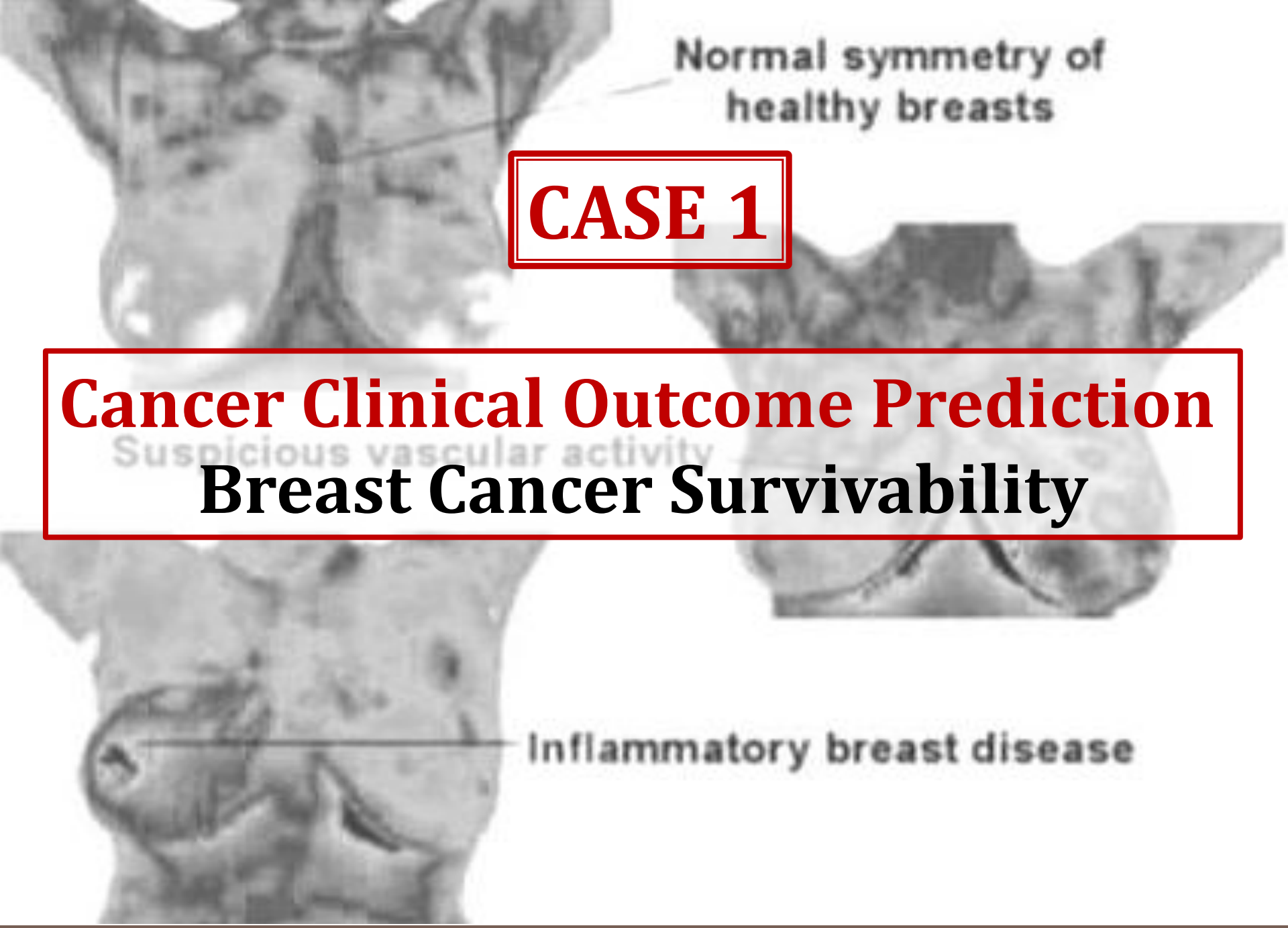
Objective Function

$$\min_{\boldsymbol{f}} \quad \mu\, \boldsymbol{f}^T L\, \boldsymbol{f} + (\boldsymbol{f} - \boldsymbol{y})^T (\boldsymbol{f} - \boldsymbol{y})$$

Solution

$$\boldsymbol{f} = \{\, \boldsymbol{I} + \mu L \,\}^{-1} \boldsymbol{y}$$

where $L = D - W,\ D = diag(d_i),\quad d_i = \sum_j w_{ij}$



CASE 1

Cancer Clinical Outcome Prediction

Breast Cancer Survivability

Background

According to ***American Cancer Society***…

- Estimated **new cases** of breast cancer in 2010 in US..
  - **Females: 207,090**
  - **Males: 1,970**

- Estimated **deaths**
  - **Females: 39,840**
  - **Males: 390**

Background

Prediction of Breast Cancer Survivability

- **"Survival"** is defined as patient remaining alive for a specified period of time after the diagnosis of cancer

- **Cancer Prognosis** helps in establishing a treatment plan **by predicting the outcome of a disease**

Data

Surveillance, Epidemiology, End Results (SEER) cancer incident data

162,500 Breast cancer patient records

16 attributes

1 class label (Survivability)

: +1 (not survive)

: - 1 (survived)

Data: Attributes

Stage	Defined by the size of cancer tumor and its spread
Grade	How does the tumor looks like and its resemblance to more or less aggressive tumors
Lymph Node Involvement	None, (1-3) Minimal, (4-9) Significant etc
Race	Ethnicity like White, Black, Chinese etc.
Age at Diagnosis	Actual age of patient in years
Marital Status	Married, Single, Divorced, Widowed, Separated
Primary Site	Presence of tumor at a particular location in body. Topographical classification of cancer
Tumor Size	2-5 cm, at 5cm prognosis worsens
Site Specific Surgery	Information on surgery during first course of therapy whether it was cancer directed or not.
Radiation	None, Beam Radiation, Radioisotopes, Refused, Recommended etc.
Histological Type	The form and structure of tumor
Behavior Code	Normal or aggressive behaviors of tumor have been defined in codes.
# of Positive Nodes Examined	When the lymph nodes are involved in the cancer, they are called "positive."
# of Nodes Examined	Total nodes (positive/negative) examined
# of Primaries	Number of primary tumors (1-6)
Clinical Extension of Tumor	Defines the spread of tumor relative to breast
Survivability	Target binary variable defines the class of survival of patient.

Model Comparison: Predictive models

- **Artificial Neural Network (ANN)**
- **Support Vector Machine (SVM)**
- **Semi-Supervised Learning (SSL)**
  with a patient network

Aspects of Comparison

Let the **oncologists** (medical specialists) run a predictive model **by himself** and **interpret** the results with his medical domain knowledge !

Then, a **predictive model** has the properties of

Reasonable Accuracy & **Robustness** over Parameter Variation

Aspects of Comparison

Model Parameters (to be tuned)

ANN

Random Seed = {1, 3, 5, 7, 10}

Hidden Node = {3, 6, 9, 12, 15}

SVM

C = {0.2, 0.4, 0.6, 0.8, 1}

Gamma = {0.0001, 0.001, 0.01, 0.1, 1}

SSL

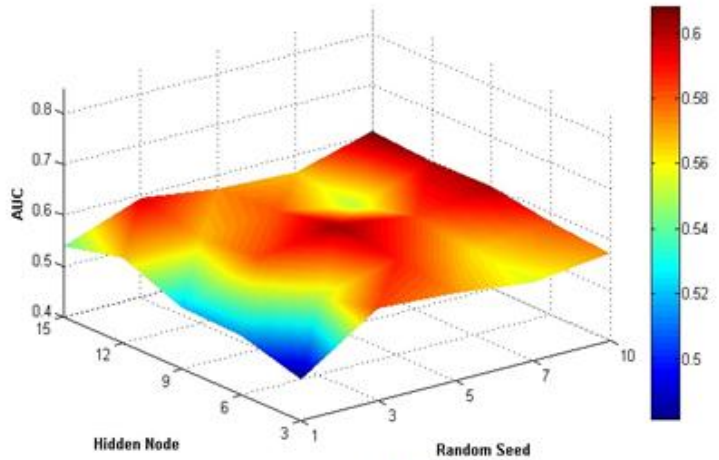
Mu = {0.0001, 0.01, 1, 100, 1000}

K = {3, 7, 15, 20, 30}

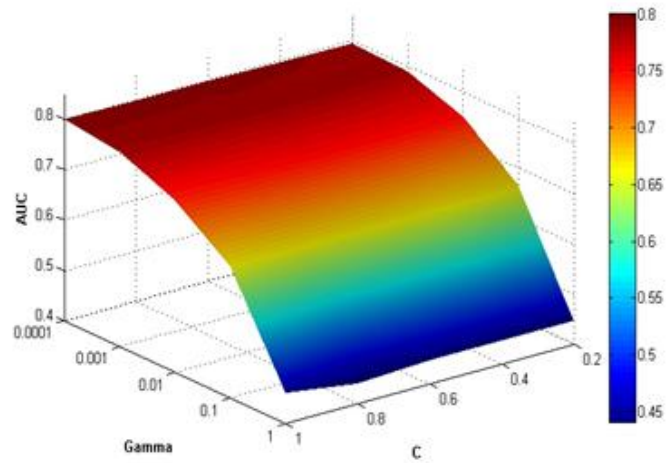
Experimental Results: Accuracy

Dataset	ANN	SVM	SSL
	Avg_AUC	Avg_AUC	Avg_AUC
1	0.59	0.68	0.76
2	0.56	0.69	0.77
3	0.55	0.68	0.75
4	0.56	0.68	0.75
5	0.56	0.70	0.77
6	0.54	0.71	0.75
7	0.57	0.67	0.75
8	0.58	0.69	0.78
9	0.56	0.70	0.76
10	0.59	0.71	0.76
Mean (St Dev)	**0.57 (±0.07)**	**0.69 (±0.13)**	**0.76 (±0.03)**

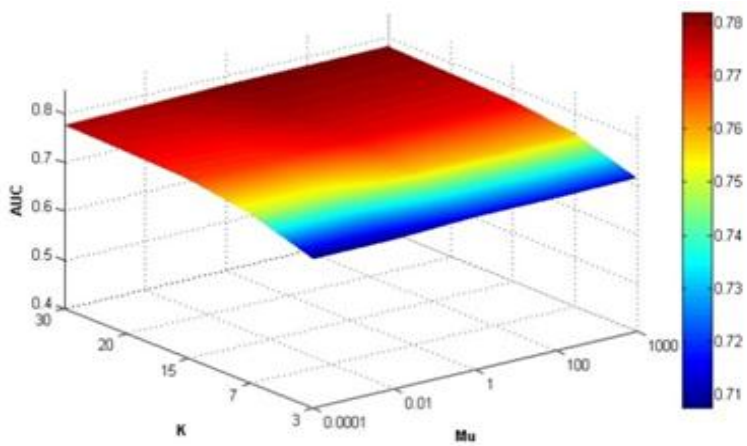
Experimental Results: Robustness over parameter variation



(a) ANN



(b) SVM



(c) SSL

Result Wrap-up

Building a patient network (Graph Representation) from patient samples is straightforward.

Prediction algorithms based on Intra-relation is well established.

The algorithm shows reasonably high accuracies, stability (or robustness) over model parameter variation, and is easy to use !

$$L(\beta) = \beta_1 \, G_1 + \beta_2 \, G_2 + \beta_3 \, G_3 + \cdots\cdots + \beta_k \, G_K$$

$$L(\beta) = \sum_{k=1}^{K} \beta_k L_k$$

Heterogeneous Data Sources

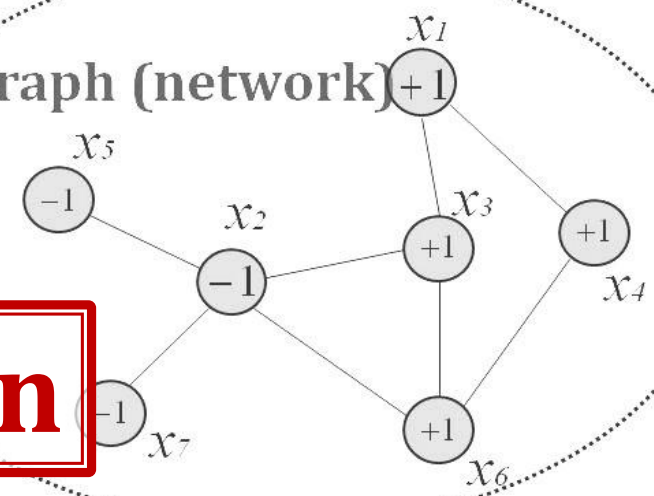
Vectorial Data

	A_1	A_2	…	A_{10}	
x_1	10	5	…	1000	1
x_2	6	6	…	3500	-1
x_3	7	7	…	400	1
…	…	…	…	…	…
x_7	3	88	…	700	-1

Integration

+

Graph (network)



+

Sequence (string)

x_1	agctgtttagctatatgcgtatagggct	1
x_2	cagtgtcgaatagccgctcgaaaaa a	-1
…	…	…
x_7	catgctgtatgcccgatagcgtgatcg	-1

Abstract: Data Integration

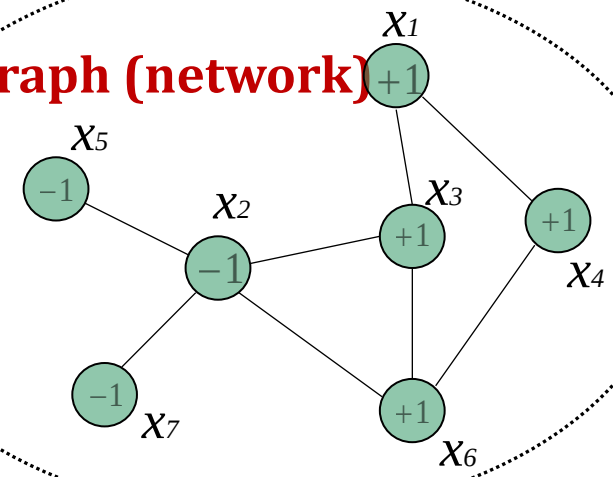
Heterogeneous Data Sources

Vectorial Data

	A_1	A_2	…	A_{10}	y
x_1	10	5	…	1000	1
x_2	6	6	…	3500	-1
x_3	7	7	…	400	1
…	…	…	…	…	…
x_7	3	88	…	700	-1

+

Graph (network)



+

Sequence (string)

x_1	agctgtttagctatatgcgtatagggct	1
x_2	cagtgtcgaatagccgctcgaaaaa a	-1
…	…	…
x_7	catgctgtatgcccgatagcgtgatcg	-1

Abstract: Data Integration

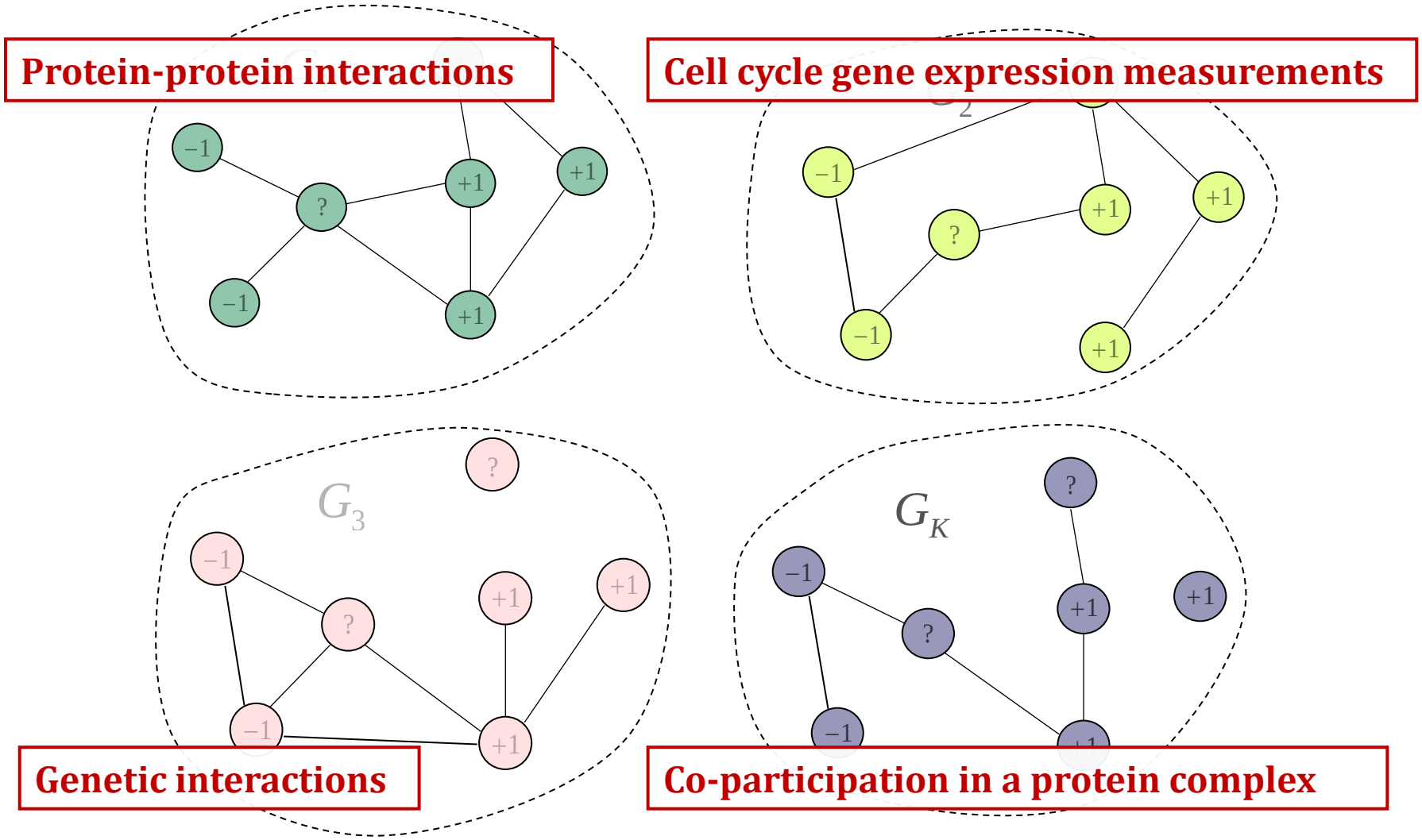
Data Integration is concerned with the **integration of different** **or** **heterogeneous data sources** in order to **enhance the total information** about the problem at hand**.**

Each of data sources contains **partly independent** and **partly complementary** pieces of information about the problem**...**

Outline

[CASE 2-1] Protein Function Prediction	**MIPS Yeast Proteins/PDBselect25-GO Prediction from Multiple Protein Networks**
[CASE 2- 2] Cancer Clinical Outcome Prediction	**Brain Cancer (GBM)/Ovarian Cancer (OV) Prediction from Multiple Genomic Data**

If Multiple Graphs are Given?



If Multiple Graphs are Given?

Example: Multiple Graph Sources on Proteins

Physical interactions of the proteins
[Schwikowski,et al., 2000, Uetz et al., 2000, von Mering et al., 2002]

Gene regulatory relationships
[Lee et al., 2002, Ihmels et al., 2002, Segal et al., 2003]

Edges in a metabolic pathway
[Kanehisa et al., 2004]

Similarities between protein sequences
[Yona et al., 1999]

etc.

$$\min_{\boldsymbol{\beta}} \; d(\boldsymbol{\beta}) \equiv \boldsymbol{y}^T (\boldsymbol{I} + \sum_{k=1}^{K} \beta_k L_k)^{-1} \boldsymbol{y} \qquad \boldsymbol{y} = \left\{ \boldsymbol{I} + \sum_{k=1}^{K} \beta_k L_k \right\} \boldsymbol{f}$$

Given Graphs

THEORY

Prediction from Integration

Mathematical Formulation

SDP/SVM — *Kernel matrix*

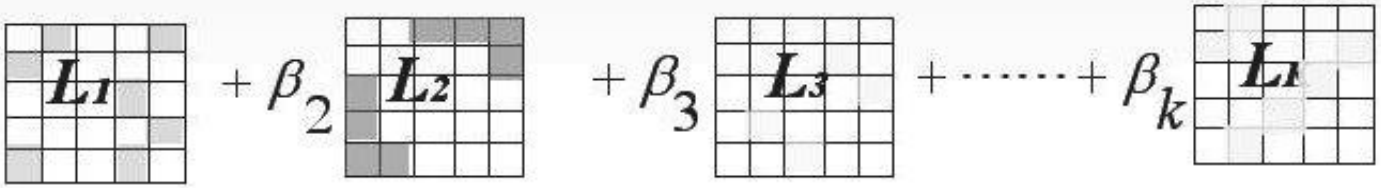
Dense

$$K(\mu) = \mu_1 \; + \; \mu_2 \; + \; \mu_3 \; + \cdots + \mu_k$$

SSL — *Laplacian matrix L (or Similarity matrix W)*

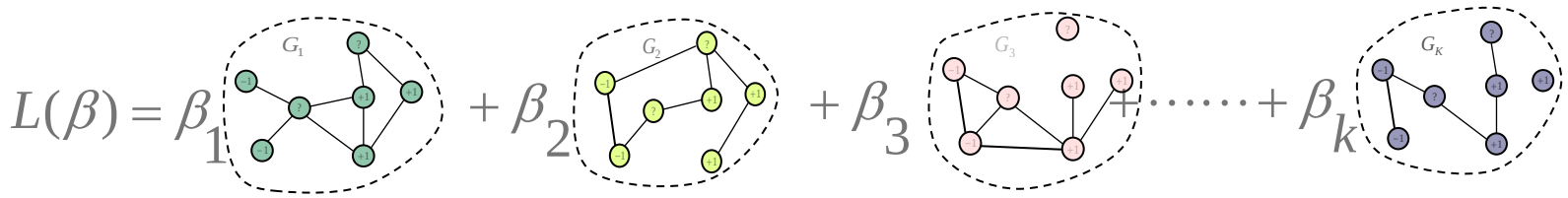
Sparse

$$L(\beta) = \beta_1$$



Graph Integration using SSL

Mutiple Graph (Data) Integration



Shin, H., Lisewski, A.M. and Lichtarge, O. (2007)
Graph sharpening plus graph integration: a synergy that improves protein functional classification, ***Bioinformatics***, 23, 3217-3224.

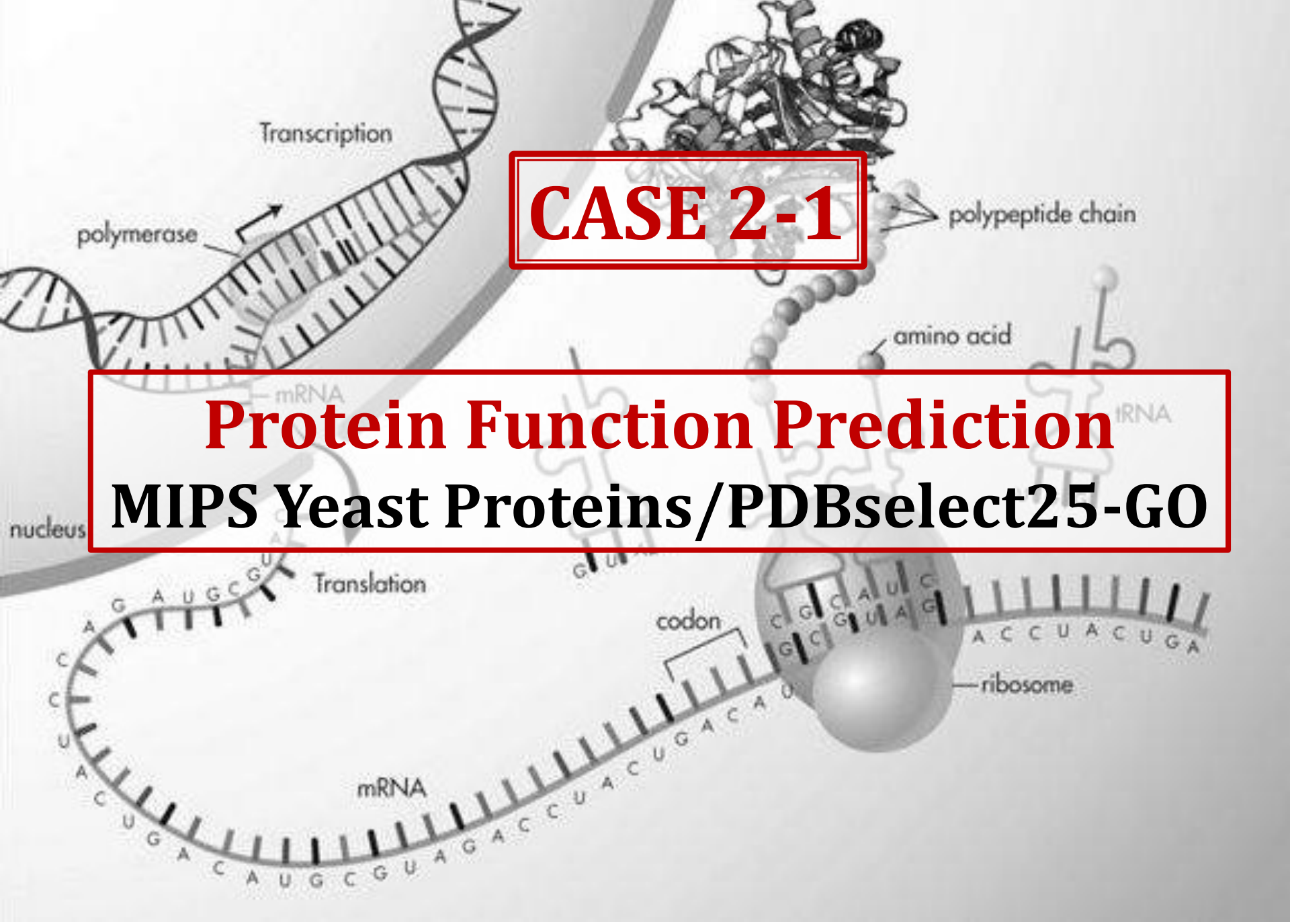
Shin, H. and Tsuda, K. (2006)
Prediction of Protein Function from Networks, *in Book:* ***Semi-Supervised Learning***, *MIT press*, Chapter 20, 339-352.

Tsuda, K., Shin, H. and Scholkopf, B. (2005)
Fast protein classification with multiple networks, ***Bioinformatics***, 21 Suppl 2, ii59-65.

CASE 2-1

Protein Function Prediction

MIPS Yeast Proteins/PDBselect25-GO



Experiement I

(H.Shin, K.Tsuda, and B.Schoelkopf, *Bioinformatics*, 2005)

Task : Protein Functional Class Classification

Model : Graph Integration based on SSL

Data : MIPS Comprehensive Yeast Genome Database

Protein Function Prediction: Experiment I

MIPS Comprehensive Yeast Genome Database (CYGD-mips.gsf.de/proj/yeast)

Data	**3588** yeast proteins
Output	**13** functional categories Binary classification for each category
Input	**5** networks
Setting	5 fold cross validation 5 times repetition

Protein Function Prediction: Experiment I

MIPS Comprehensive Yeast Genome Database (CYGD-mips.gsf.de/proj/yeast)

13 CYGD functional Classes

1. metabolism
2. energy
3. cell cycle and DNA processing
4. transcription
5. protein synthesis
6. protein fate
7. cellular transportation and transportation mechanism
8. cell rescue, defense and virulence
9. interaction with cell environment
10. cell fate
11. control of cell organization
12. transport facilitation
13. others

Protein Function Prediction: Experiment I

Input Data Sources (5 networks)

W_1 Network created from **Pfam domain structure**. A protein is represented by a **4950-dimensional binary vector**, in which each bit represents the **presence or absence of one Pfam domain**. An edge is created if the inner product between two vectors exceeds 0.06. The edge weight corresponds to the inner product.

W_2 **Co-participation in a protein complex** (determined by tandem affinity purification, TAP). An edge is created if there is a **bait-prey relationship** between two proteins.

W_3 **Protein-protein interactions** (MIPS physical interactions)

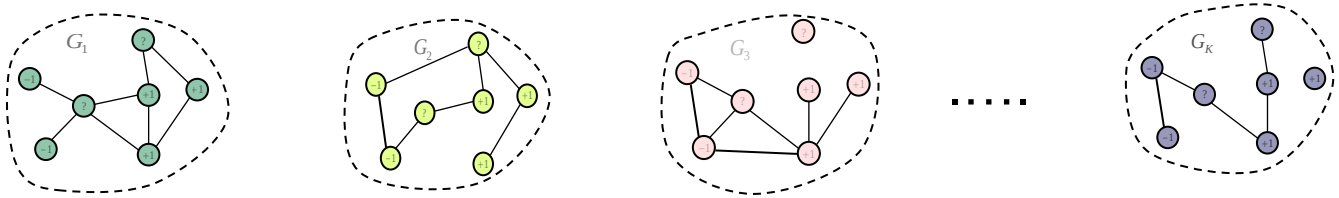
W_4 **Genetic interactions** (MIPS genetic interactions)

W_5 Network created from the **cell cycle gene expression measurements** [Spellman et al., 1998]. An edge is created if the **Pearson coefficient** of two profiles exceeds 0.8. The edge weight is set to 1. This is identical with the network used in [Deng et al., 2003]

Protein Function Prediction: Experiment I

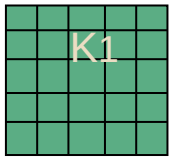
Density of Working Matrices

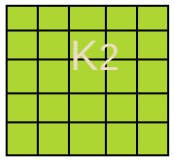
Given Graphs

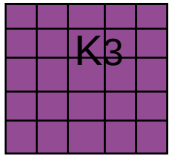


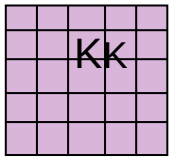
SDP/SVM **Kernel matrix**

Dense

$$K(\mu) = \mu_1$$ 

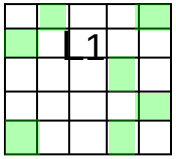
$$+ \mu_2$$ 

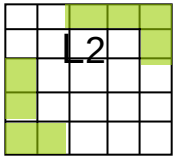
$$+ \mu_3$$ 

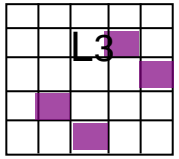
$$+ \cdots\cdots + \mu_k$$ 

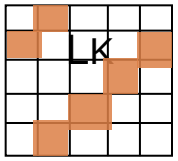
SSL **Laplacian matrix L (or Similarity matrix W)**

Sparse

$$L(\beta) = \beta_1$$ 

$$+ \beta_2$$ 

$$+ \beta_3$$ 

$$+ \cdots\cdots + \beta_k$$ 

Protein Function Prediction: Experiment I

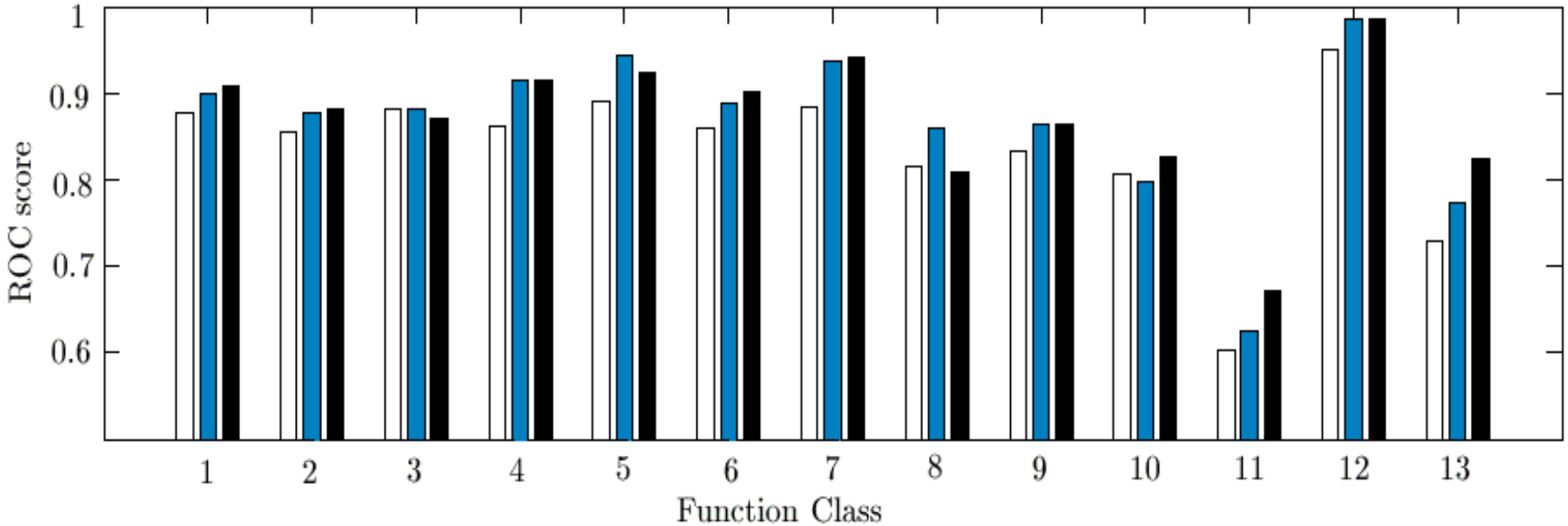
Methods in Comparison

L_k	Label propagation with an **Individual** Graphs (k=1…5)
L_{opt}	Laplacian of Combined Graph with **Optimized Weights**
L_{fix}	Label propagation with **Equal Weights**
MRF	**Markov Random Field**, proposed by Deng et al [2003]
SDP/SVM	**Semi-definite Programming** based **Support Vector Machines**, proposed by Lanckriet et al [2004]

Protein Function Prediction: Experiment I

Results : Integrated Network vs. the Best Performing Individual (ROC scores)

White: the best performing individual network
Blue: L_{fix}
Black: L_{opt}

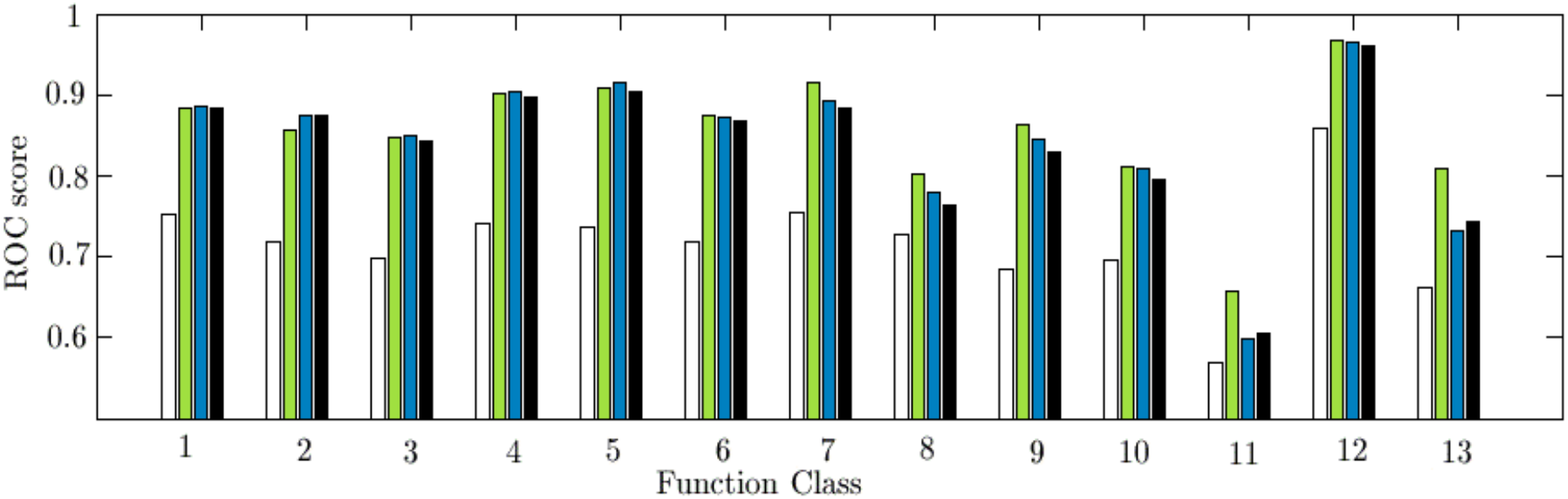


Across the 13 classes, the proposed integrated network outperforms the best performing individual.

Protein Function Prediction: Experiment I

Results : the proposed vs. others integration methods (ROC scores)

White: MRF
Green: SDP/SVM
Blue: L_{fix}
Black: L_{opt}

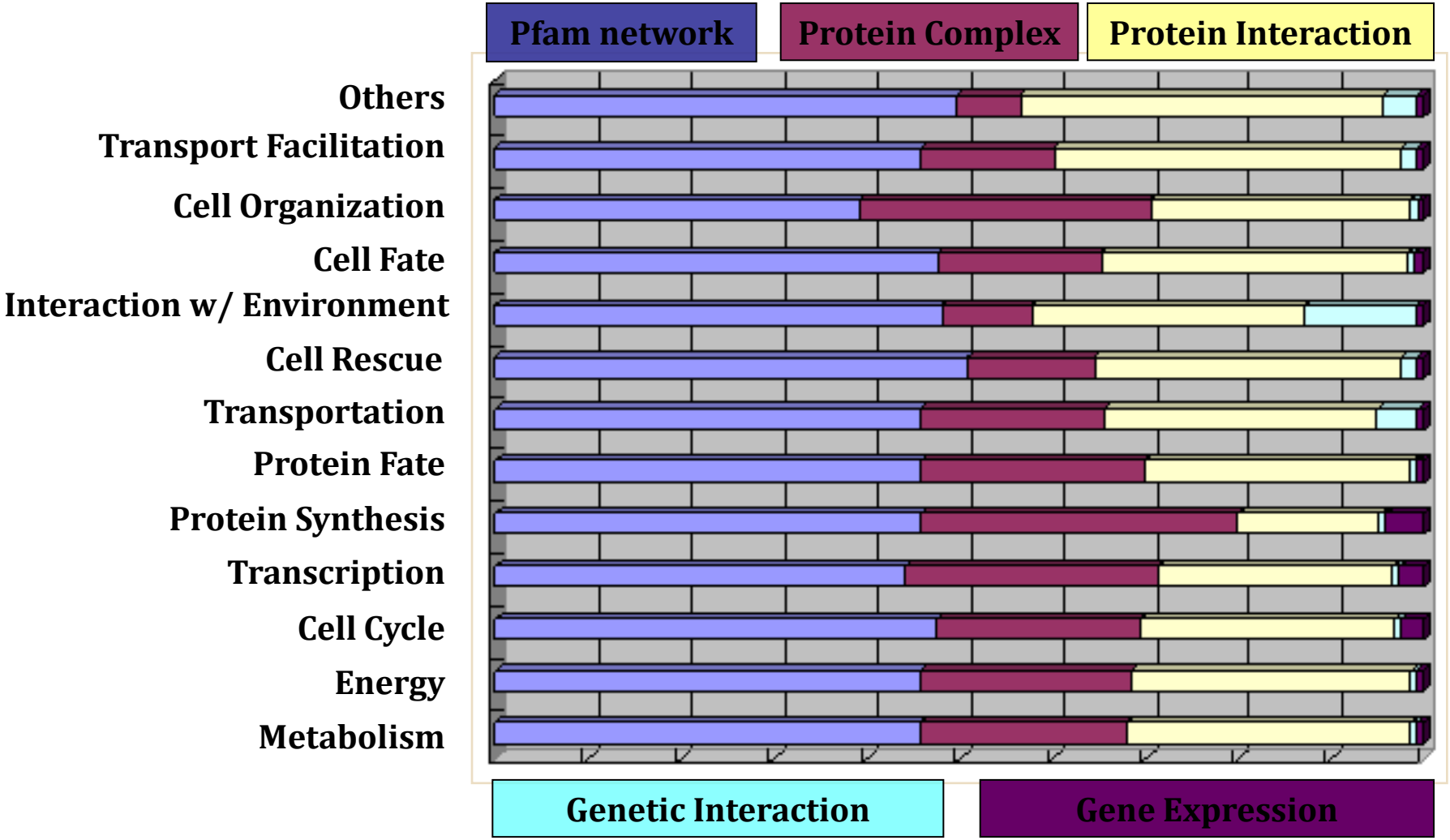


For most classes, the proposed method achieves high scores, which are similar to the SDP/SVM methods.

In classes 11 and 13, the proposed method performs poor (but still better than the MRF method), However, taking into account the Simplicity and Efficiency the method shows the promising results

Protein Function Prediction: Experiment I

Results : Which data source is more informative?



Protein Function Prediction: Experiment I

Results : Computational Time

The proposed:

49.3 seconds (std. 14.8)

SDP/SVM :

Approx. Several <u>CPU days</u>

(G. Lanckriet, personal communication)

* Measured in a standard 2.2Ghz PC with 1GByte memory

Protein Function Prediction: Experiment I

Results : Computational Time

The proposed:

Nearly <u>linearly proportional</u> to the number of non-zero entries of sparse matrices

SDP/SVM :

$$O((m+n)^2 n^{2.5})$$

Protein Function Prediction: Experiment I

Wrap-Up

The proposed integrated network of multiple data sources outperforms the best performing individuals.

The proposed integration method is simple, computationally efficient, scalable when compared with the existing integration method such as SDP/SVM.

$$\min_{\boldsymbol{\beta}} \; d(\boldsymbol{\beta}) \equiv \boldsymbol{y}^T (\boldsymbol{I} + \sum_{k=1}^{K} \beta_k L_k)^{-1} \boldsymbol{y} \qquad \boldsymbol{y} = \left\{ \boldsymbol{I} + \sum_{k=1}^{K} \beta_k L_k \right\} \boldsymbol{f}$$

Given Graphs

THEORY

SDP/SVM — *Kernel matrix*

Dense

$K(\beta) = \beta_1 K_1 + \beta_2 K_2 + \beta_3 K_3 + \cdots\cdots + \beta_k K_k$

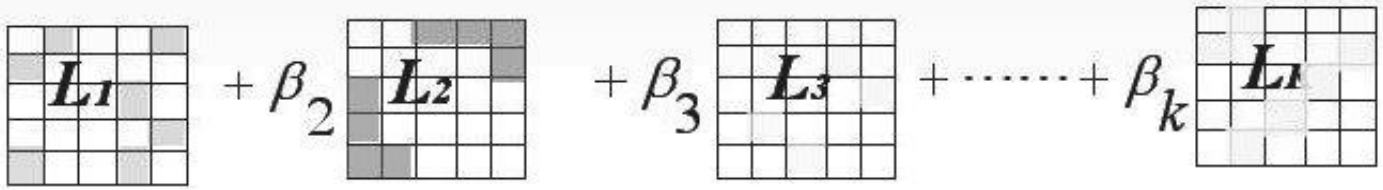
Prediction from "Inter"-Relation

Method & Mathematical Formulation

SSL — *Laplacian matrix L (or Similarity matrix W)*

Sparse

$L(\beta) = \beta_1 L_1 + \beta_2 L_2 + \beta_3 L_3 + \cdots\cdots + \beta_k L_k$



Inter-Relation: Method/Mathematical Formulation

G_O **Patient Graph from Gene Expression Data (Original)**

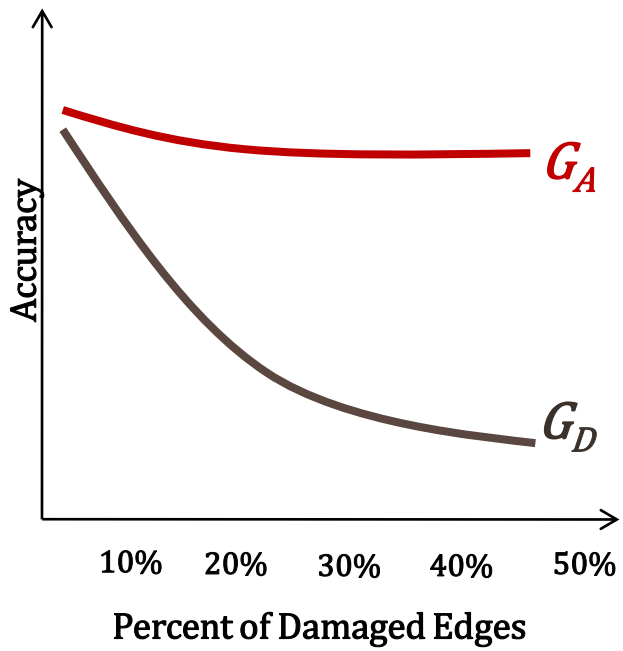
G_D **Damaged Graph**

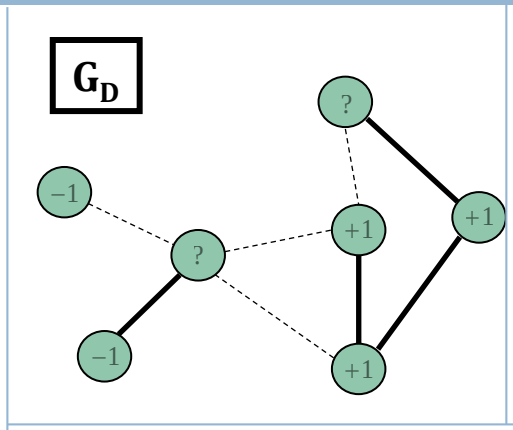
G_R **Reconstructed Graph (via inter-relationship)**

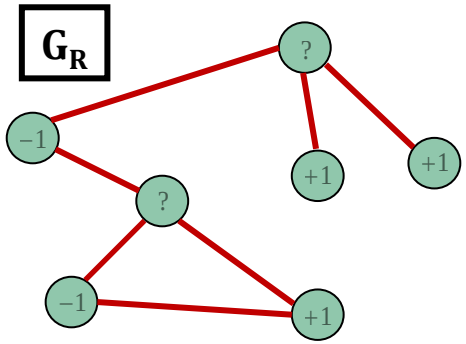
G_A **Augmented graph (G_D + G_R)**

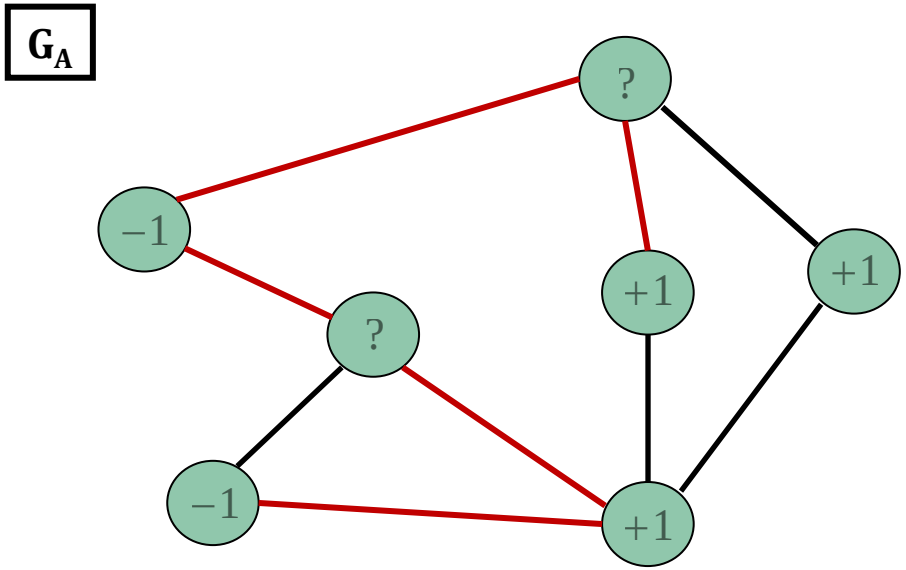
Inter-Relation: Method/Mathematical Formulation

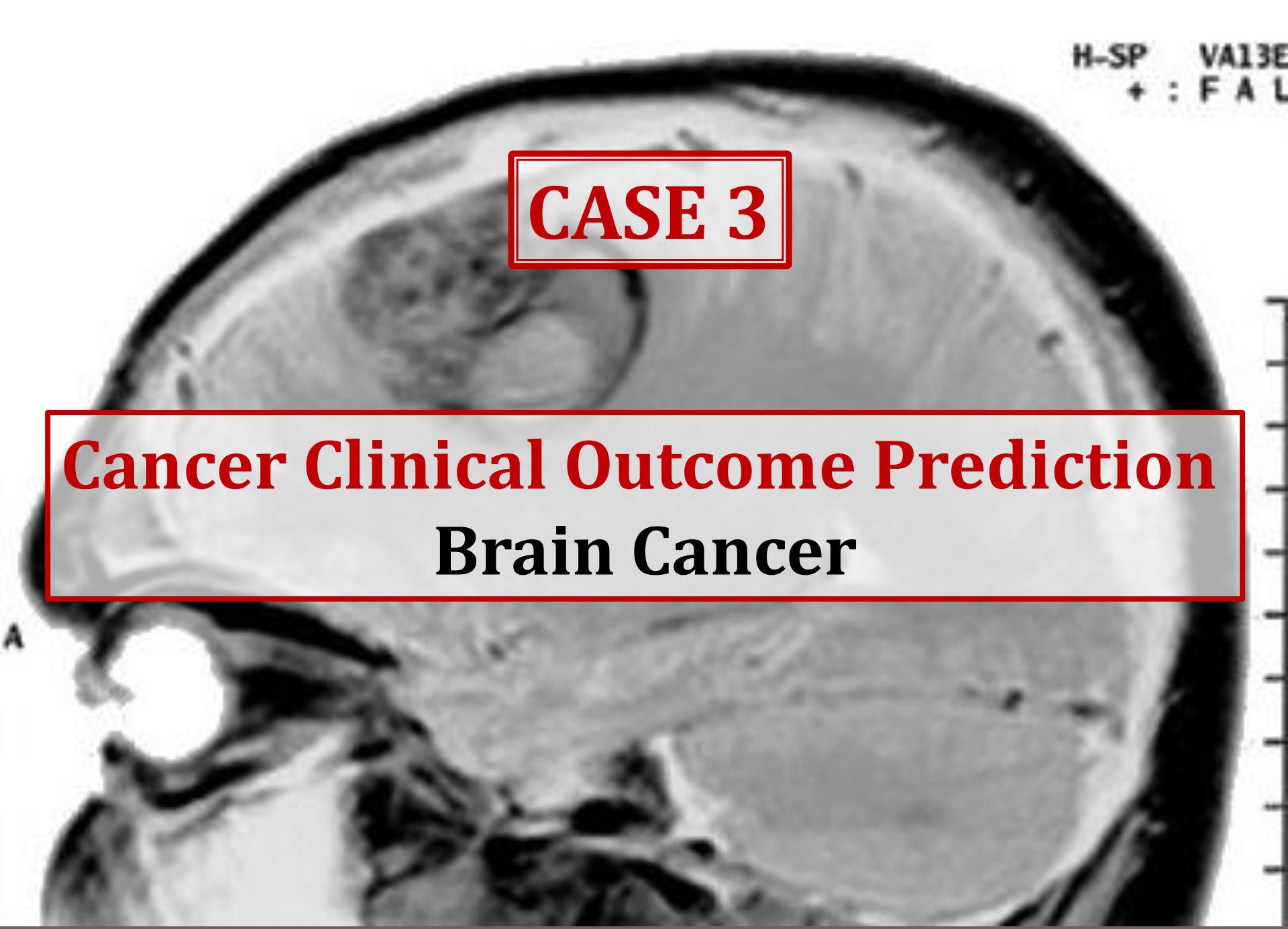
G_A **Augmented graph (G_D + G_R)**











CASE 3

Cancer Clinical Outcome Prediction

Brain Cancer

Experiment IV

(D.Kim, H. Shin, S. Lee and J. Kim, *TBC*, 2011)

Task : Brain Cancer Clinical Outcome Classification

Model : Inter-Relation + SSL

Data : The Cancer Genomic Atlas (TCGA database)

Inter-Relation: Experiment - Data

TCGA: Gene Expression & miRNA

82 patient samples of Brain Cancer (GBM)

1 class label (Survivability)

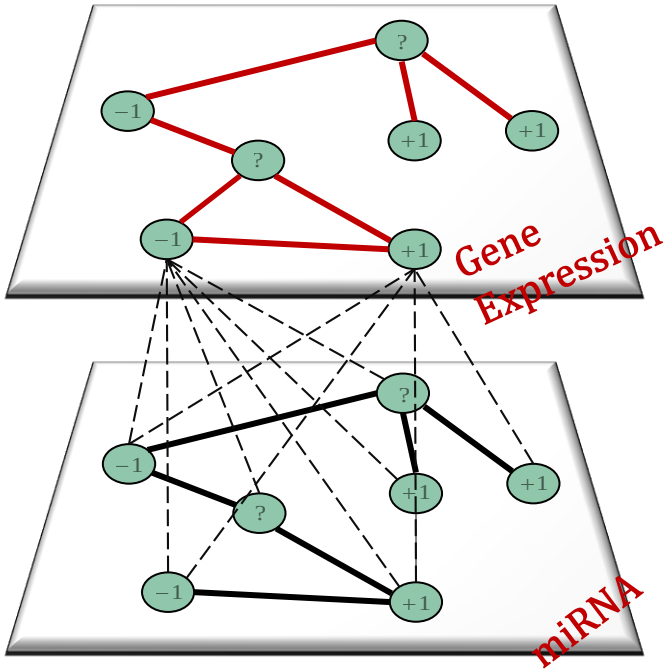
: - 1 (Short-term survival: #54)

: + 1 (Long-term survival: #28)

Data type	Platform	Num of Attributes
Gene Expression	Affymetrix HT Human Genome U133 Array Plate Set	12,043
miRNA	Agilent Human miRNA Microarray Rel12.0	799

Inter-Relation: Experiment - Data

miRNA & Target Gene (mRNA) Relation

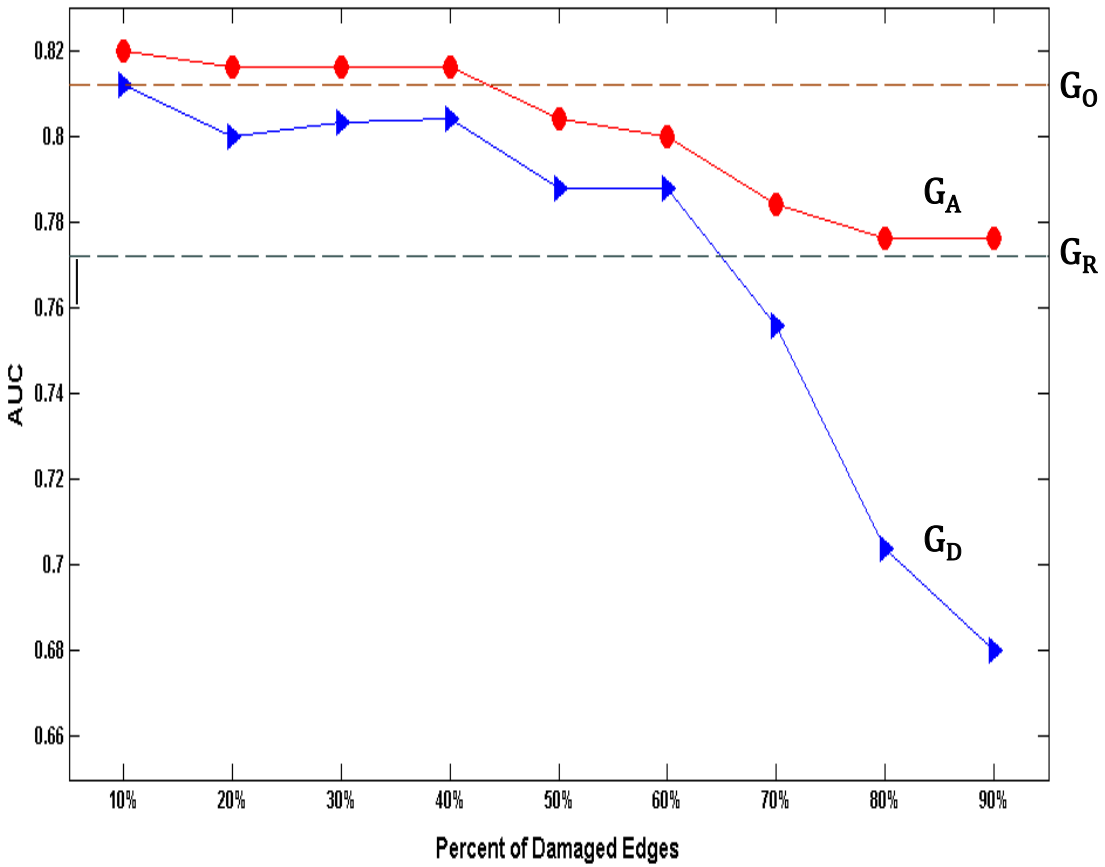


miRecords which is integrated resources of miRNA that store **target interactions** produced by **11 established miRNA target prediction program** (Xiao et al., 2009)

Among 11 algorithms, **a binary relation** between **miRNA** and **mRNA** was set when **more than 3 algorithms** provide the **target relation**

Inter-Relation: Experiment – Comparison Results

Improved Performance from Augmented Knowledge via INTER-RELATION between miRNA and Gene Expression



Inter-Relation: Experiment – Comparison Results

Significance for Differences in Performance

Percent of damaged edges	AUC of G_D	AUC of G_A	P-value
10%	0.812	0.820	1.87e-02
30%	0.803	0.816	2.09e-03
50%	0.788	0.804	3.43e-05
70%	0.756	0.784	9.59e-08
90%	0.680	0.776	1.24e-13

Improved Performance from Augmented Knowledge via INTER-RELATION between miRNA and Gene Expression

Inter-Relation: Wrap-up

FACT

Inter-Relation between Different Levels of Biological Data

There exist **Interactions** between **two or more layers** in the hierarchy of different biological levels

Ex) miRNAs regulate target genes

Inter-Relation: Wrap-up

CONTRIBUTION

Knowledge Reconstruction/Augmentation via Inter-Relation

This work shows **how to extract the Knowledge between two layers** of biological process and **how to use it to complete** the **incomplete knowledge** in other levels

A Method (or Mathematical frame work) incorporating **Inter-Relation** and **Intra-Relation** is **proposed** and **validated** through a case example of **Cancer Phenotype Prediction** based on **miRNAs** and **Genes**

Inter-Relation from **miRNAs** to **Genes augments** the **Intra-Relation** among Genes, which leads to **better accuracies** and **perception** in cancer phenotype prediction

Inter-Relation: Wrap-up

CONCLUSION

Knowledge from **Inter-Relation** helps to **Complete** the **Incomplete Knowing** about **Intra-Relation**

Future works

Future Works: Heterogeneity & Hierarchy

Biological Data

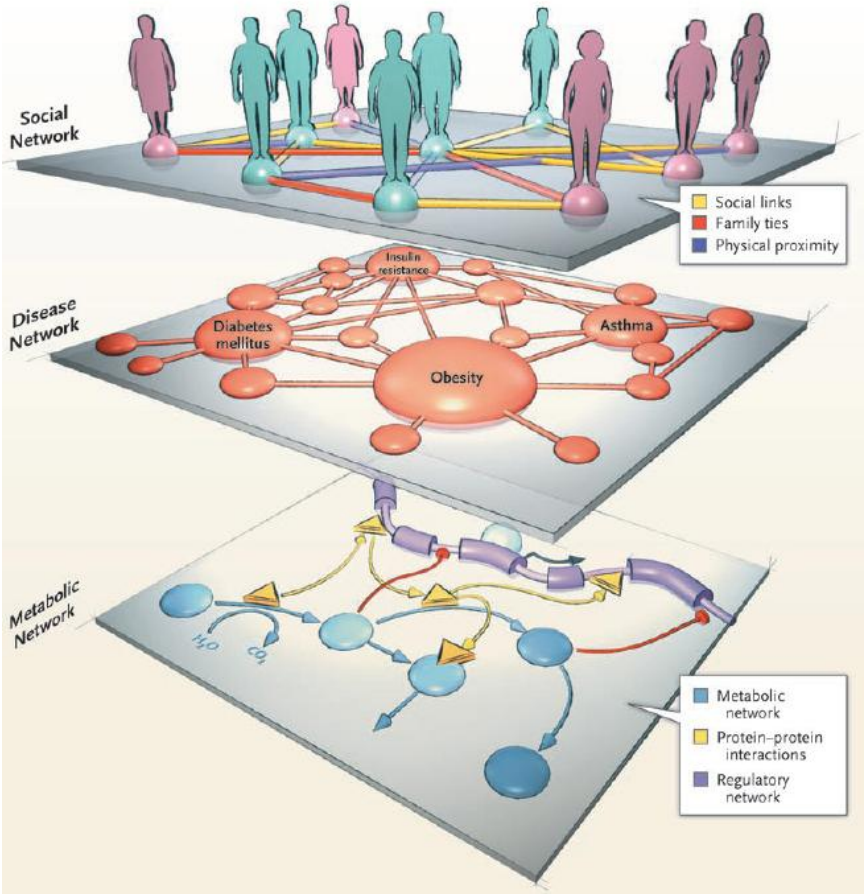
Heterogeneity & **Hierarchy**

Future Works: Heterogeneity & Hierarchy

Heterogeneous types and Hierarchical Structure of Biological Data

[Network Medicine]

Complex Networks of Direct Relevance



Barabasi, NEJM, 2007

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