

Machine Learning for Big Data "Complexity" in Biomedical Data Analytics

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OUR DATA-RICH WORLD



- Biomedicine
 - Patient records, brain imaging, MRI & CT scans, ...
 - Genomic sequences, protein-structure, drug effect info, ...
- Science
 - Historical documents, scanned books, databases from astronomy, environmental data, climate records, ...
- Social media
 - Social interactions data, twitter, facebook records, online reviews, ...
- Business
 - Stock market transactions, corporate sales, airline traffic, ...
- Entertainment
 - Internet images, Hollywood movies, music audio files, ...

BIG DATA CHALLENGES

- Data capturing (sensor, smart devices, medical instruments, et al.)
- Data transmission
- Data storage
- Data management
- High performance data processing
- Data visualization
- Data security & privacy (e.g. multiple individuals)
-

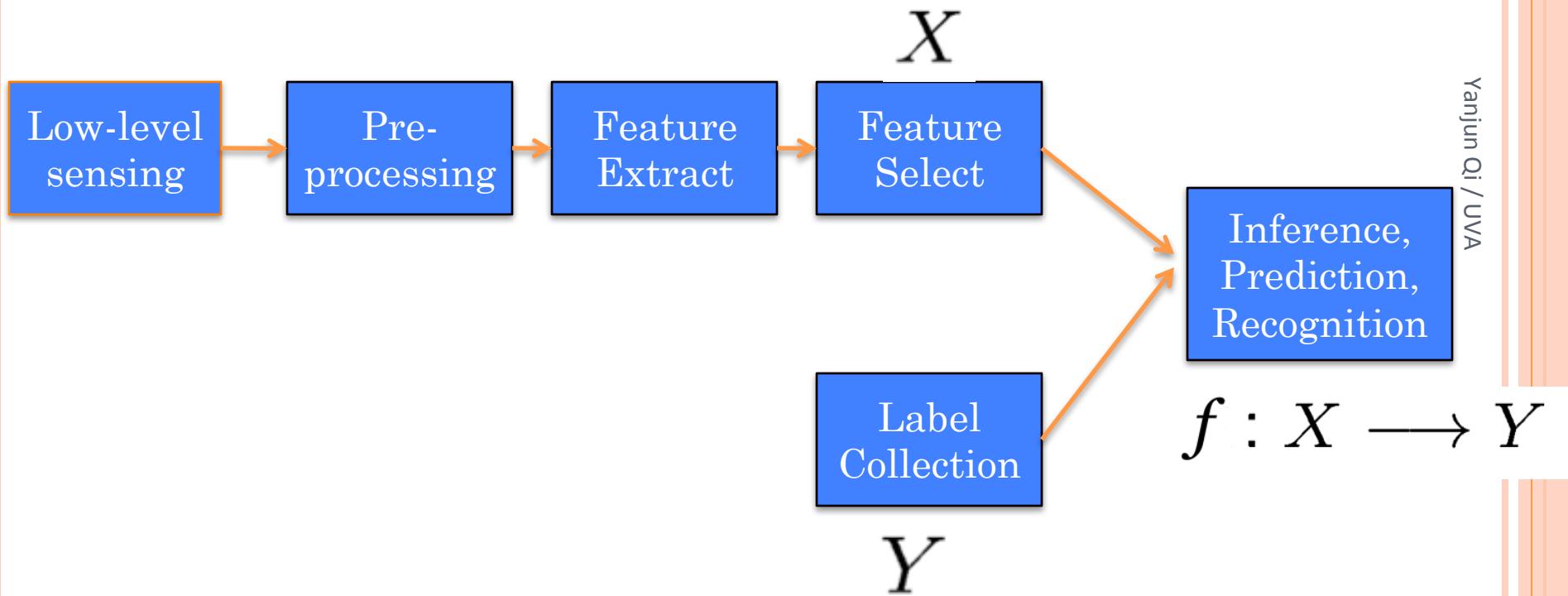
Today

- Data analytics
 - How can we convert this big data wealth to knowledge ?
 - E.g. Machine learning

BASICS OF MACHINE LEARNING

- “The goal of machine learning is to build computer systems that can **learn and adapt from their experience.**” – Tom Dietterich
- “**Experience**” in the form of available **data examples** (also called as instances, samples)
- Available examples are described with properties (**data points in feature space X**)

TYPICAL MACHINE LEARNING SYSTEM

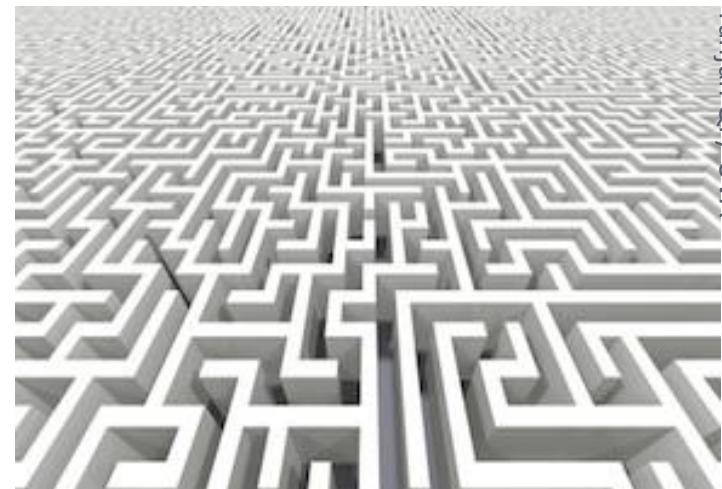


BIG DATA CHALLENGES FOR MACHINE LEARNING

LARGE-SCALE



Highly Complex



The situations / variations of both X (feature, representation) and Y (labels) are complex !

Today

When to use Machine Learning (ADAPT TO / LEARN FROM DATA) ?

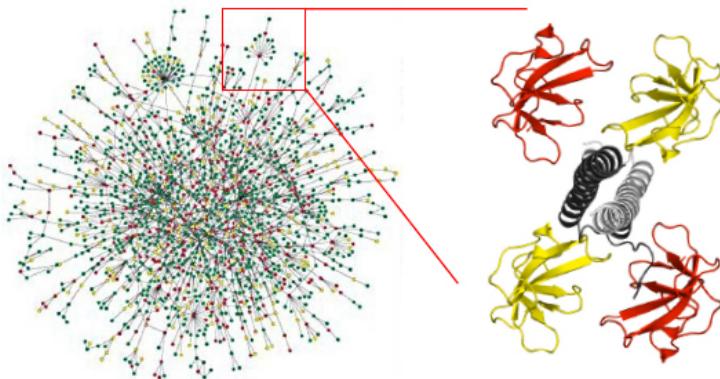
- 1. Extract knowledge from data
 - Relationships and correlations can be hidden within large amounts of data
 - The amount of knowledge available about certain tasks is simply too large for explicit encoding (e.g. rules) by humans
- 2. Learn tasks that are difficult to formalise
 - Hard to be defined well, except by examples
- 3. Create software that improves over time
 - New knowledge is constantly being discovered.
 - Rule or human encoding-based system is difficult to continuously re-design “by hand”.

Interesting Data Challenges in BioMed for Machine Learning

- Noisy measurements (e.g. weak/partial labels)
- Structured input (e.g. vector, strings, graphs)
- Structured output (e.g. trees, sequences, graphs)
- Combination of different data types is essential (e.g. information fusion)
- Large amount of data (e.g. lots of next generation sequencing data)

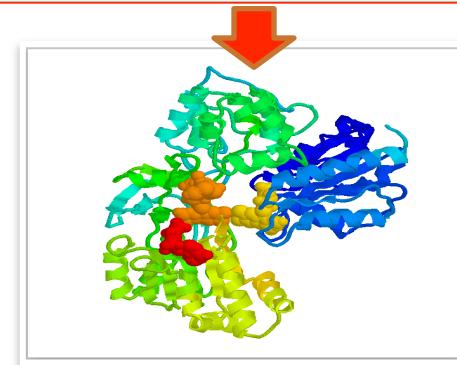
THIS TALK COVERS

I.



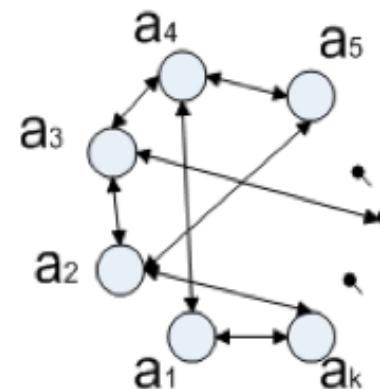
II.

MTYKLILNGKTKGETTEAVD...



III.

Cdk5 and its neuronal activator p35 play an important role in neuronal migration and proper development of the brain cortex. We show that p35 binds directly to **microtubules** and **microtubule polymers** but not the **microtubule heterodimers**. Cdk5 and its neuronal activator p35 play an important role in neuronal migration and proper development of the brain cortex. We show that p35 binds directly to **microtubules** and **microtubule polymers** but not the **microtubule heterodimers**. Cdk5 and its neuronal activator p35 play an important role in neuronal migration and proper development of the brain cortex. We show that p35 binds directly to **microtubules** and **microtubule polymers**. Microtubule polymers but not the **microtubule heterodimers** with p35 interacts with Cdk5 and therefore activate Cdk5/p35 activity. p35 is a neuron-specific isoform and truncated form of p39. It does not have the tubulin and microtubule binding activities, and Cdk5/p35 is insensitive to the inhibitory effect of microtubules. Furthermore, microtubules stabilized by p35 are resistant to cold-induced disassembly. In neurons, a significant proportion of p35 localizes to microtubules. When microtubules were isolated from rat brain extracts, p35 coimmunoprecipitated with microtubules, including cold-stable microtubules. Together, these findings suggest that p35 is a microtubule-associated protein that modulates p35-mediated Cdk5 activation. Thus, **microtubules** play an important role in the control of **Cdk5** activation.



THIS TALK COVERS

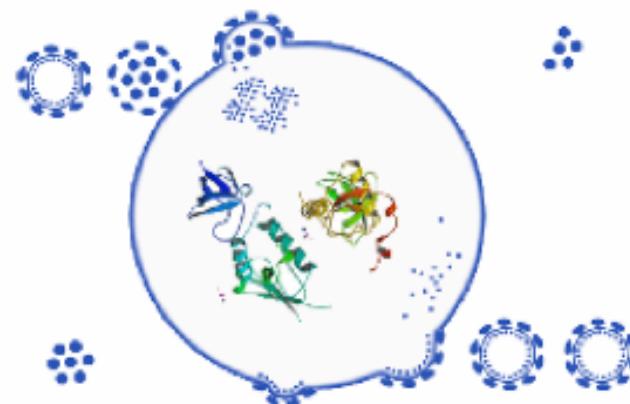
	<u>Project Topic</u>	<u>Complexity</u>	<u>HOW ?</u>
I	Protein interaction identification	Y	Training with auxiliary labels
II	Protein structure prediction	X & Y	Unified feature learning for multiple related tasks
III	Biomedical text mining	X	Add semi-supervision on features
IV	Conditional dependency graph among Genes / TFs	X	Model data example with feature interactions

Background

VIRUS VS. HUMAN PROTEIN INTERACTION

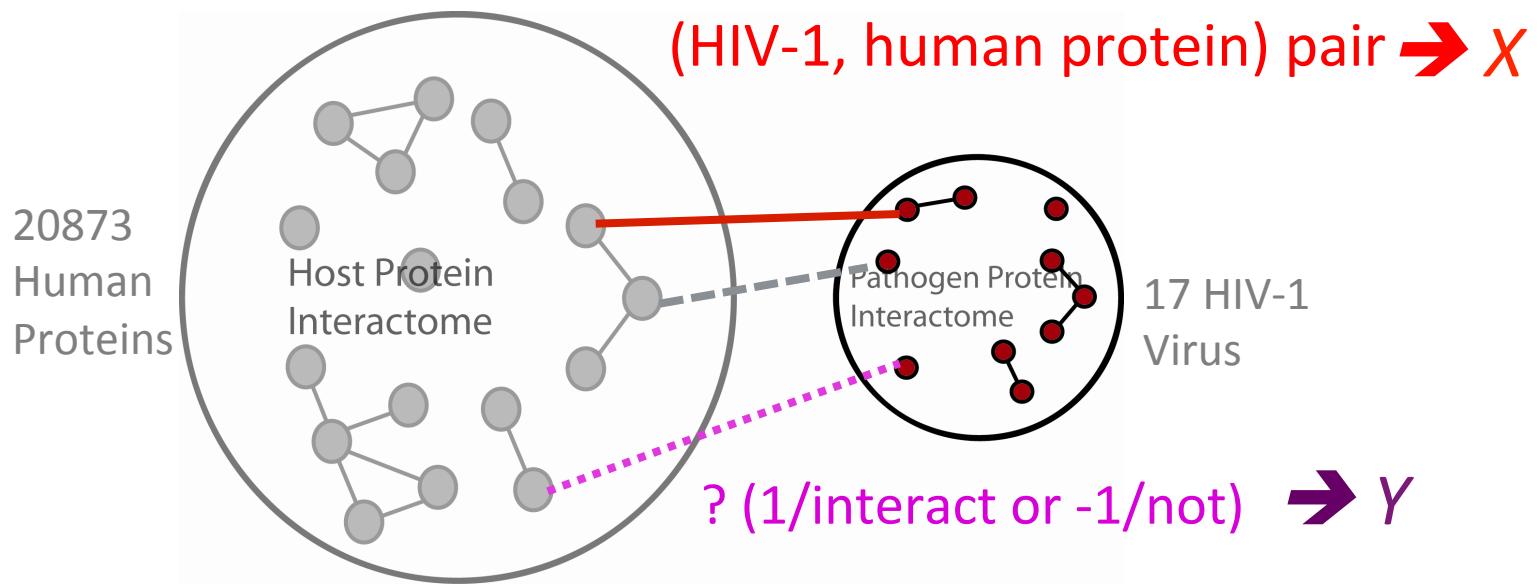
- Human Immuno-deficiency Viruses, (e.g. HIV-1 Virus), can cause life-threatening infectious diseases (like AIDS)
- Virus must communicate with the host to invade and infect
- Typical communication through interactions between virus and human host proteins (potential drug/vaccine targets)

[Y. Qi, et al, Bioinformatics 2010]
[Y. Qi, et al, Proteomics 2009]



Objective & Previous Work

- GOAL: to discover unknown direct physical interactions between HIV-1 and human proteins
→ (Help biologist prioritize potential interaction pairs)



- Model each (HIV-1, human protein) pair with (X, Y)
- State-of-the-art performance: Random forest (Tastan et al. (PSB 2009))

Simplified view: lost spatial / temporal information of interaction pairs

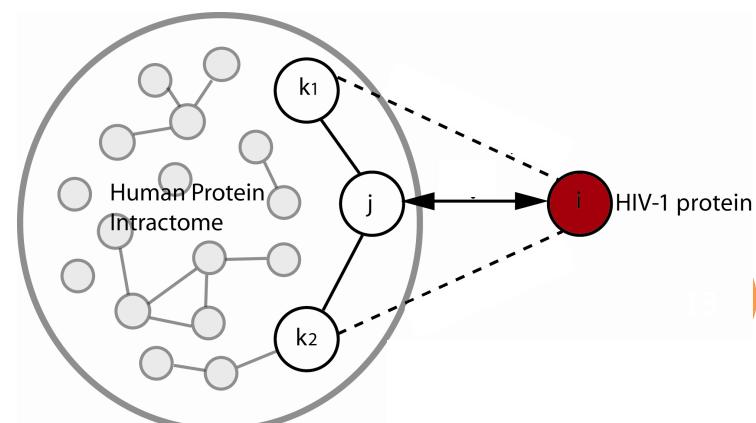
[Y. Qi, et al, Bioinformatics 2010] [Y. Qi, et al, Proteomics 2009]

Background: 18 Features describing each pair

- ❑ Differential gene expression in HIV infected vs uninfected cells (4)
- ❑ Human protein expression in HIV-1 susceptible tissues (1)
- ❑ Similarity of the two proteins in terms of (4)
 - Cellular location
 - Molecular process
 - Molecular function
 - Sequence



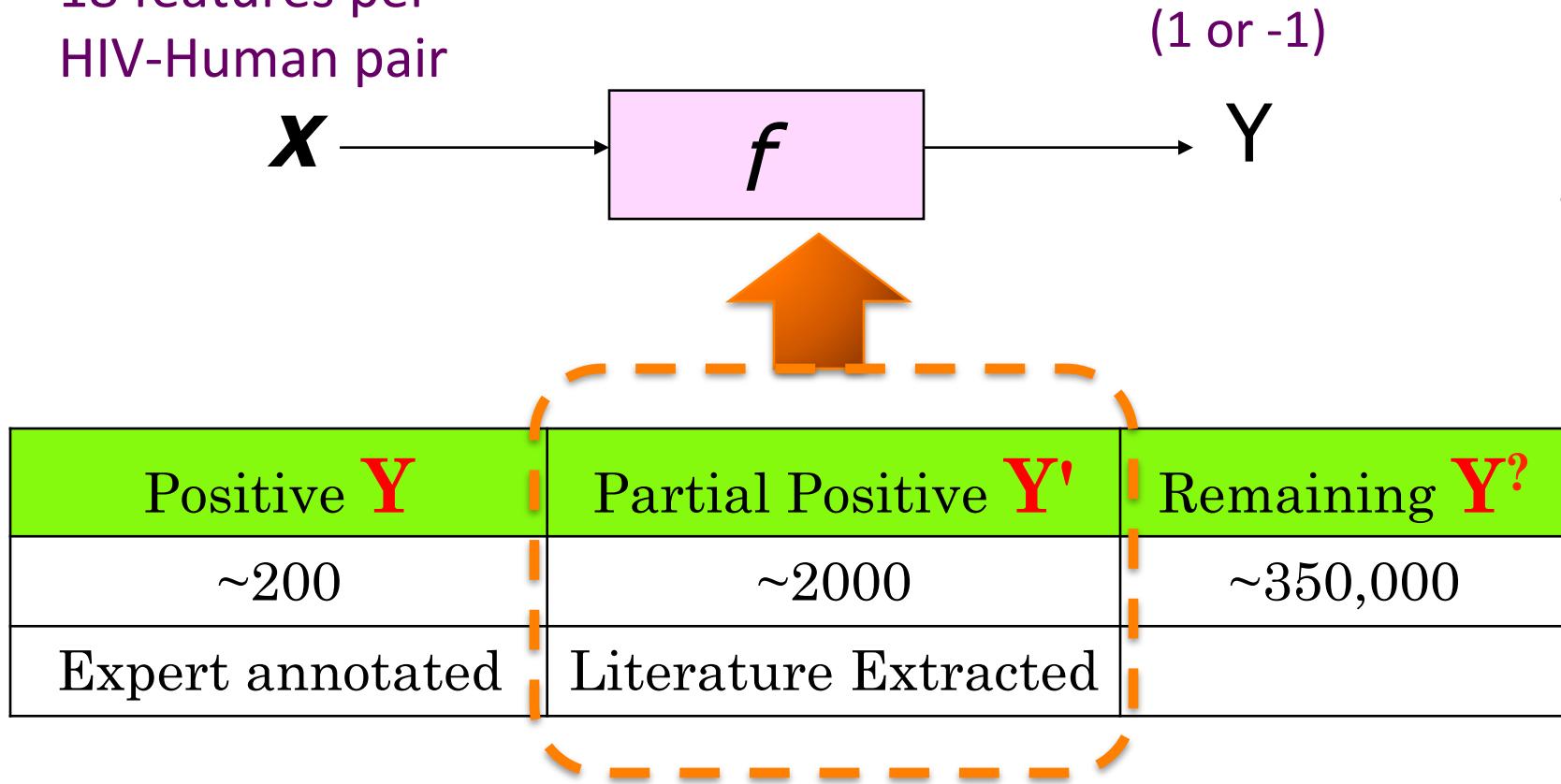
- ❑ ELM-ligand feature (1)
- ❑ Human PPI interactome features (8)
 - ❑ Similarity of HIV-1 protein to human protein's interaction partner (5)
 - ❑ Topological properties of human interaction graph (3)



Label Complexity: Auxiliary “Partial” Labels Y'

→ Improve with multiple tasking and semi-supervised learning

18 features per
HIV-Human pair



- Highly **skewed** class distribution (much more non-interacting pairs than interacting pairs)

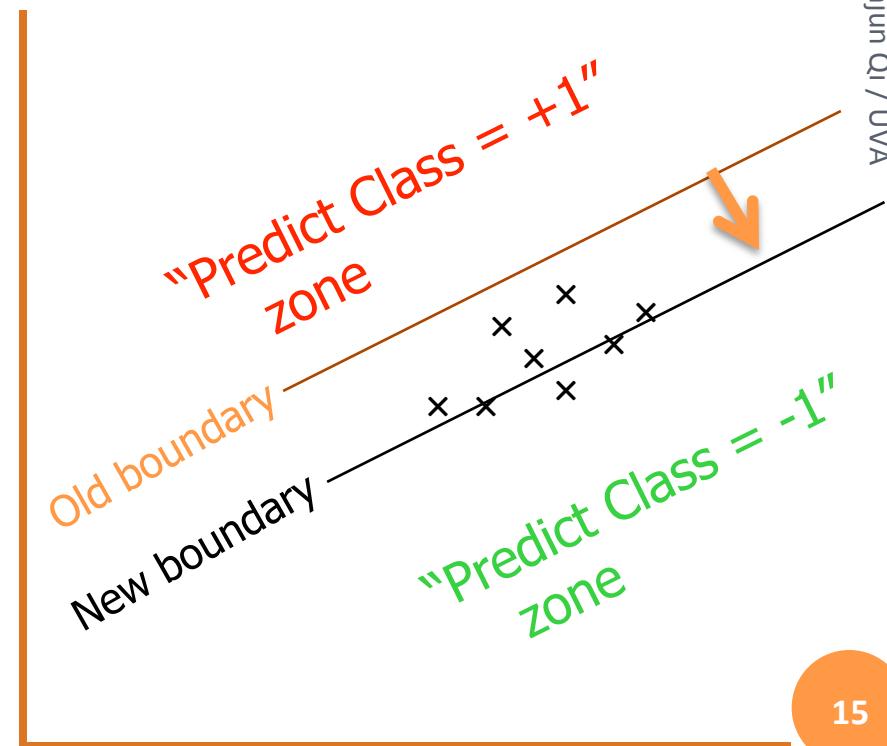
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Method: How to Utilize “Partial” Labels Y' ?

○ Multi-Tasking

- Supervised Classification (using Y)
- Auxiliary Task (using Y')

- ✓ Main Task: a candidate pair interacts OR not ?
- ✓ Auxiliary Task: e.g. a pair is more likely than random pairs to interact OR not ?



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x denotes Y'

Method: Main Classification + Three Possible Auxiliary Tasks

To Optimize : $\sum_{i=1}^L \ell(f(x_i), y_i) + \lambda \text{ Loss (Auxiliary Task)}$

Auxiliary task added as a regularizer on the supervised main task

Main: **MLP** classification

$$\sum_{i=1}^L \ell(f(x_i), y_i) = \sum_{i=1}^L \max(0, 1 - y_i f(x_i)).$$

Auxiliary (1): **SMLC** classification

$$\text{Loss (Auxiliary Task)} = \sum_{j=L+1}^{L+U} \max(0, 1 - y'_j g(x_j))$$

Auxiliary (2): **SMLR** pairwise ranking

$$\text{Loss (Aux.)} = \sum_{p \in P} \sum_{n \in N} \max(0, 1 - f(x_p) + f(x_n))$$

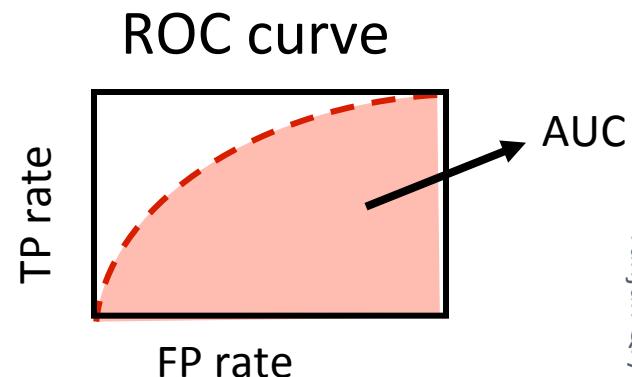
Auxiliary (3): **SMLE** embedding

$$\text{Loss (Aux.)} = \sum_{i,j=1}^{L+U} L(f(x_i), f(x_j), W_{ij})$$

Evaluation: Performance Comparison

- Improved performance to Random Forest classifier

METHOD	AUC 50	AUC
SMLR	0.310	0.919
RF-P	0.230	0.896
MLP-P	0.229	0.893



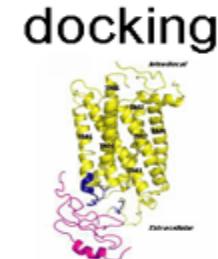
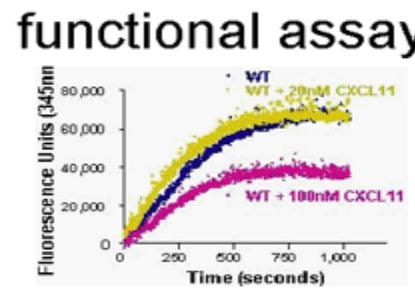
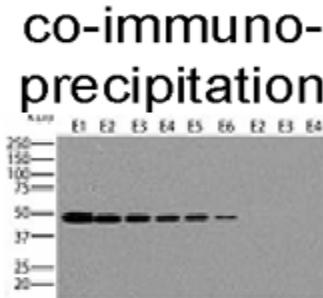
- Validation and confirmed by multiple recent available functional assay related to HIV (siRNA data & Virion data)
- Extra: similar framework applied to look for human protein partners for receptor proteins
 - Five of our predictions were chosen for experimentally tests and three were verified → 3 out of 5
 - If purely random chosen → 1 out of ~20,000

Evaluation: Experimental Validation of Predicted PPI wrt Human Membrane Receptors

→ (Help biologist prioritize potential interaction pairs)

- Five of our top predictions were chosen for experimentally tests and three were verified
 - EGFR with HCK (pull-down assay)
 - EGFR with Dynamin-2 (pull-down assay)
 - RHO with CXCL11 (functional assays, fluorescence spectroscopy, docking)
- Experiments @ U.Pitt School of Medicine

Details in the paper



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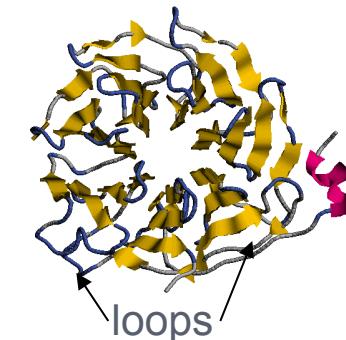
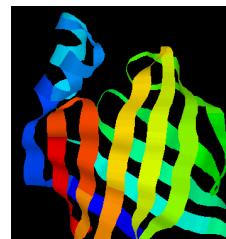
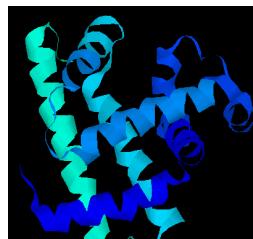
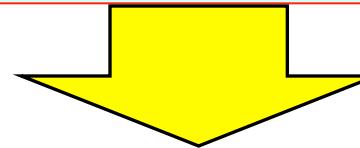
Target Problem

To Save Cost → very time-consuming and expensive to measure protein structures

PROTEIN SEQUENCE → STRUCTURAL SEGMENTS

- Input X: Primary sequence

MTYKLILNGKTKGETTTEAVDAATAEKVFQYANDNGVDGEWTYTE



- Output Y:

- Secondary structure (SS)
- Solvent accessibility (SAR)
- Coiled coil regions (CC)
- DNA binding residues (DNA)
- Transmembrane topology (TM)
- Signal peptide (SP)
- Protein binding residue detection (PPI)
-

Yanjun Qi / UVA

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*Y. Qi, et al, PLoS ONE (2012), ICDM10,
CIKM10, SDM 14, ECIR 14*

Target Problem

- ✓ INPUT: A STRING OF AMINO ACIDS (AA)
- ✓ OUTPUT: A STRING OF CLASS LABELS (OF AA)

X

Y¹

Y²

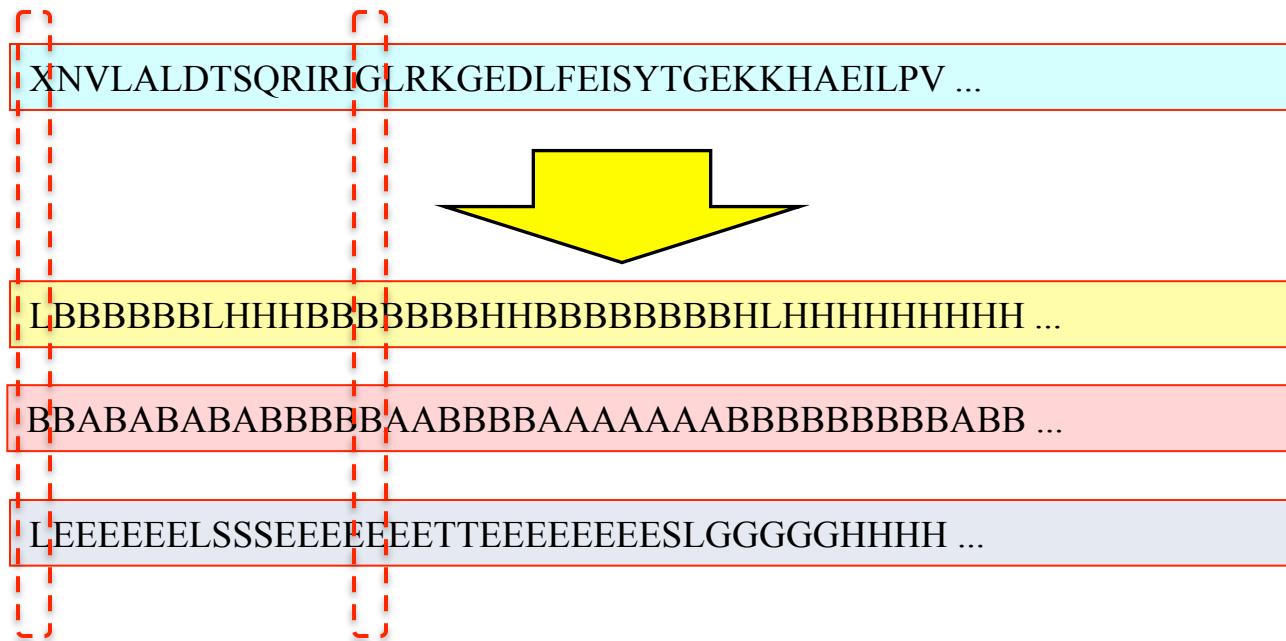
Y³

Multiple Targets:

Secondary structures

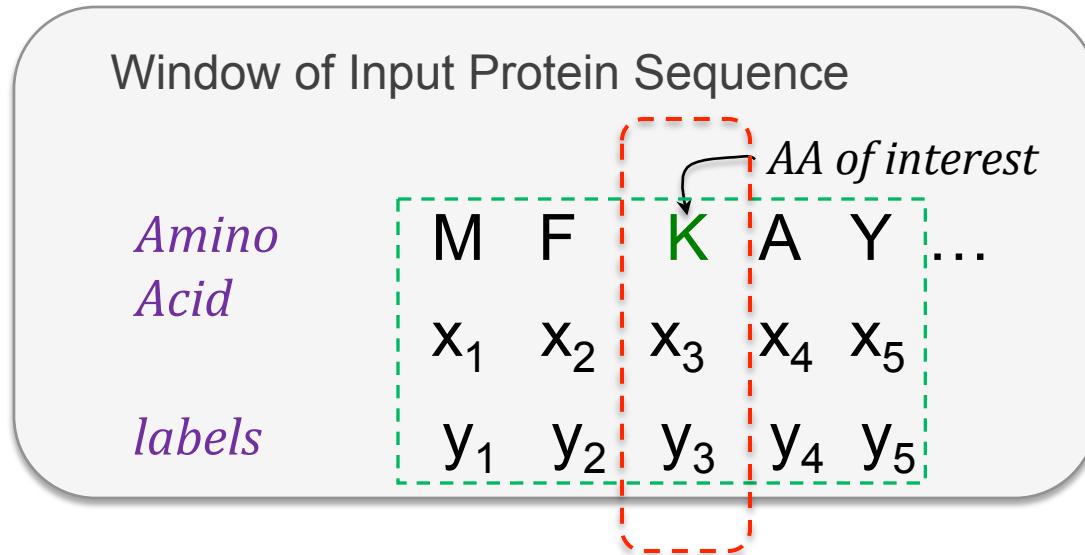
Solvent accessibility

.....



Essentially Sequence Labeling/Tagging Tasks

Y. Qi, et al, PLoS ONE (2012),
ICDM10, CIKM10, SDM14, ECIR14

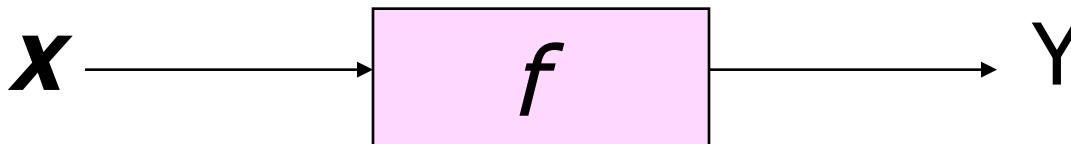


Yanjun Qi / UVA

+

- Labeling each residue amino acid (AA) using its context windows:

Using task “SS” as one example:



Each AA + its context window

$$x = (x_1, \dots, x_5)$$

Class label in terms of “SS” for current AA

$$y = y_3$$

Previous systems : Issue (1)

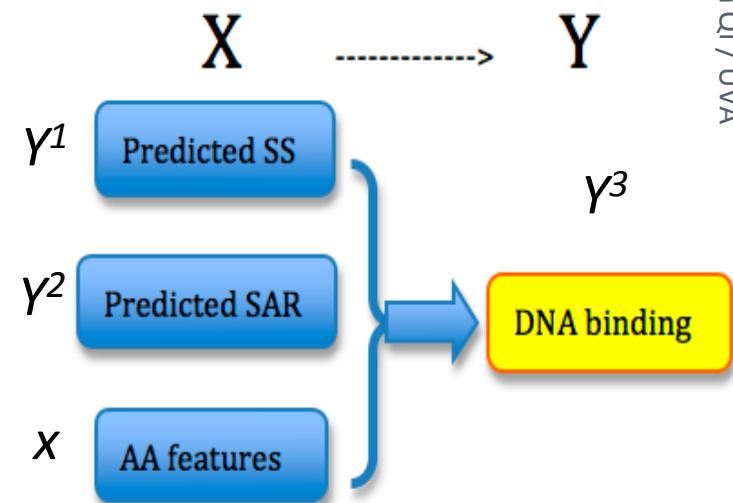
- Previous approaches focus on **one task at a time**
- Tasks **exhibit strong inter-task dependencies**, e.g.
 - ✓ Most transmembrane protein segments are alpha helice
 - ✓ Signal peptide prediction can be viewed as prediction of a particular type of transmembrane segment

→ Improve with multiple task learning

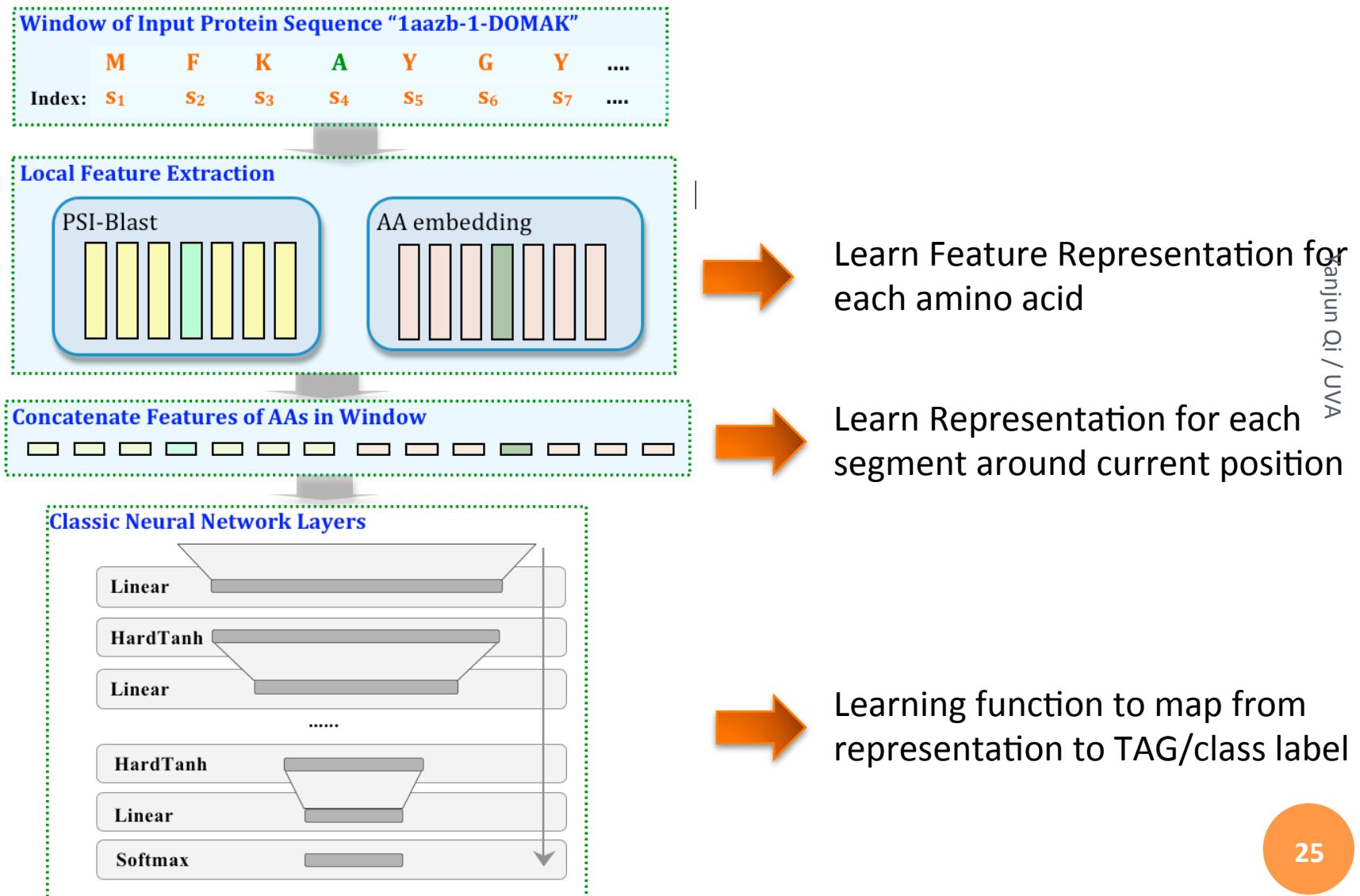
Previous systems : Issue (2)

- Previous work makes use of these dependencies in a **pipelined fashion**,
 - ✓ Hand-craft feature engineering for each task
 - ✓ Errors from one classifier get propagated to downstream classifiers

→ Improve with feature / representation learning

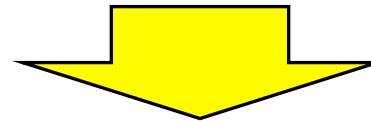


Method: Adapt deep CNN for Each Sequence Modeling Task



Method: Multi-Tasking to train a single, joint model for Ten tasks

XNVLALDTSQRIRIGLRKGEDLFEISYTGEKKHAEILPV ... X



Multiple Targets:

Secondary structures

LBBBBBLHHHHBBBBBBHBBBBBBBHLHHHHHHHHH ... Y¹

Solvent accessibility

BBABABABABBBBAABBBAAAAAAABBBBBBBBABB ... Y²

.....

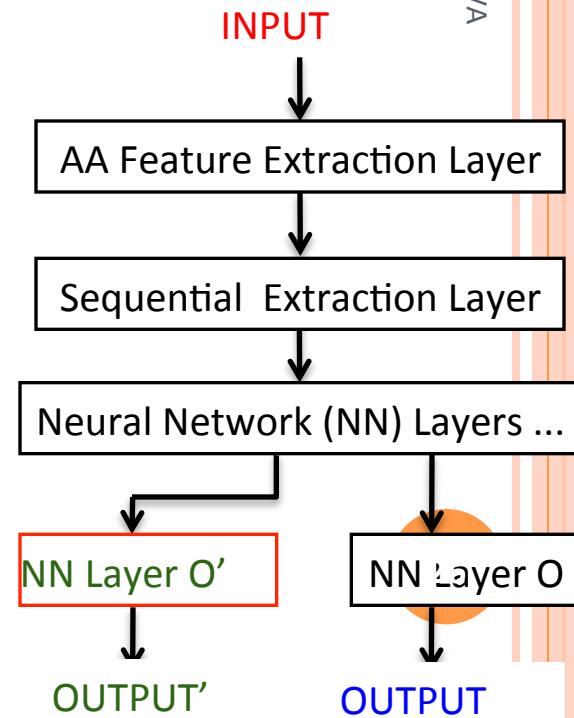
LEEEEEEELSSSEEEEEETTEEEEEEEESLGGGGGHHHH ... Y³

Parameters to learn
(assuming total T tasks)

$$\Theta_t = \{W, L^1, L^2, \dots, L^{L-1}, L_t^L\}$$

By optimize

$$\sum_{t=1}^T \sum_{n_t=1}^{N_t} E_t(\Theta_t, x_{n_t}, y_{n_t})$$



Method: Backpropagation & Stochastic Gradient Descent

- **Backpropagation**
 - Using backward recurrence it jointly optimizes all parameters
 - Requires all activation functions to be differentiable
 - Enables flexible design in deep model architecture
 - Gradient descent is used to (locally) minimize objective:

$$W^{k+1} = W^k - \eta \frac{\partial L}{\partial W^k}$$

- **Stochastic Gradient Descent (SGD)** (first-order iterative optimization)
 - SGD is an **online learning** method
 - Approximates “true” gradient with a gradient at one data point
 - Attractive because of low computation requirement
 - Rivals **batch learning** (e.g., SVM) methods on large datasets

Evaluation: Summary of Performance Comparison

tasks

Multitask + Embedding + Pretrain + Viterbi



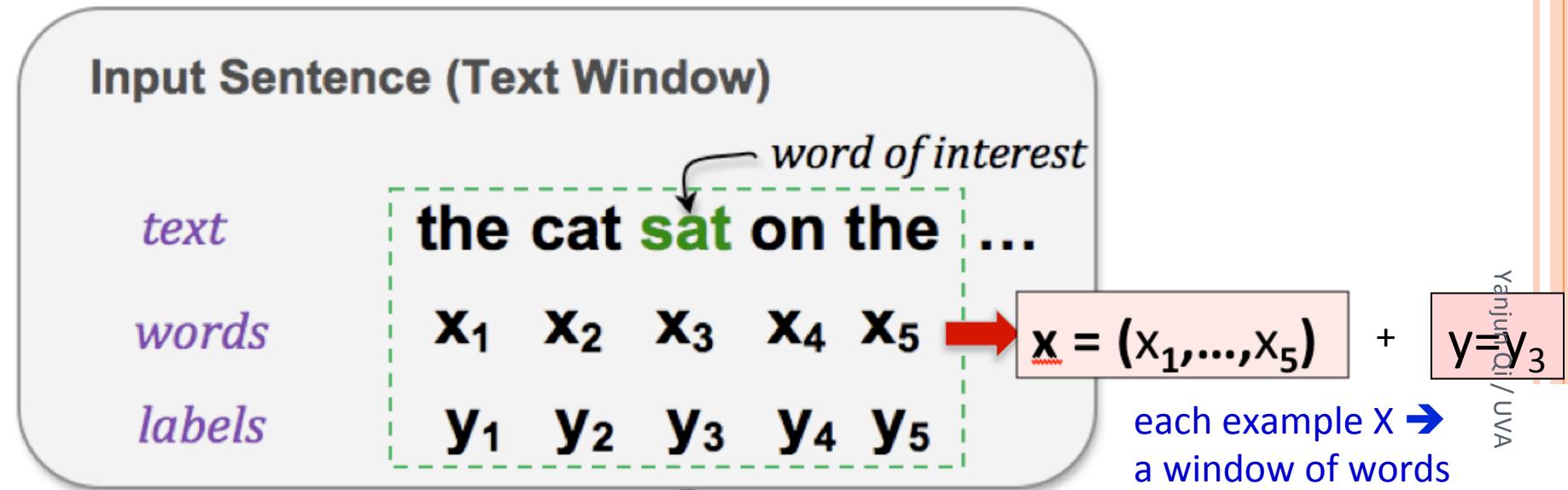
Embedding? Multitask? Natural protein?		✓		✓	*	*	*			p-value	Previous
Task	Single	Embed	Multi	Multi-Embed	NP	NP only	All3	All3+Vit			
ss	0.7907	0.7964	0.8050	0.8130	0.7968	0.6766	0.8174	0.8141	1e-4	—	
cb513ss	0.7610	0.7454	0.7976	0.8019	0.7479	0.6584	0.8020	0.8033	1e-3	0.800 [18]	
dssp	0.6548	0.6625	0.6708	0.6810	0.6627	0.5426	0.6821	0.6821	1e-4	—	
sar	0.7836	0.7979	0.7920	0.8100	0.7981	0.7306	0.8104	0.8106	1e-4	—	
saa	0.8069	0.8128	0.8170	0.8256	0.8130	0.7419	0.8263	0.8262	1e-4	—	
dna	0.8241	0.8222	0.8528	0.8702	0.8230	0.8113	0.8864	0.8917	1e-4	0.89 [7]	
sp	0.8092	0.8069	0.8363	0.8392	0.8071	0.6944	0.8408	0.9100	1e-4	Qi —	
sp (prot)	0.9947	0.9947	0.9982	0.9983	0.9980	0.9981	0.9965	0.9977	5e-2	0.97 [26]	
tm	0.8708	0.8754	0.8896	0.8931	0.8765	0.8582	0.8944	0.9212	1e-4	UV —	
tm (seg)	0.9095	0.9691	0.9738	0.9825	0.9674	0.9272	0.9837	0.9653	1e-4	0.94 [26]	
cc	0.8861	0.8988	0.9308	0.9421	0.9074	0.8725	0.9439	0.9660	1e-4	—	
cc (seg)	0.9067	0.9188	0.9454	0.9555	0.9198	0.8972	0.9573	0.9735	1e-4	0.94 [41]	
ppi	0.6983	0.7020	0.7436	0.7334	0.7111	0.7104	0.7375	0.7380	1e-4	0.68 [50]	

Ten different tasks

- ✓ All reach state-of-the-art performance
 - Unsupervised pretrain + Supervised pretraining (with large tasks)
- ✓ One unified framework for all task
 - Simple + powerful !
- ✓ No need for task-specific feature engineering

Y. Qi, et al, PLoS ONE (2012),
ICDM10, CIKM10, SDM 14, ECIR 14

Similar Models Applied Successfully on NLP Tagging Tasks



- Similar as natural language processing (**NLP tagging tasks** (e.g. part-of-speech, name entity recognition))
- Similar deep models have achieved **state-of-art results** on NLP tagging of English, German, Chinese

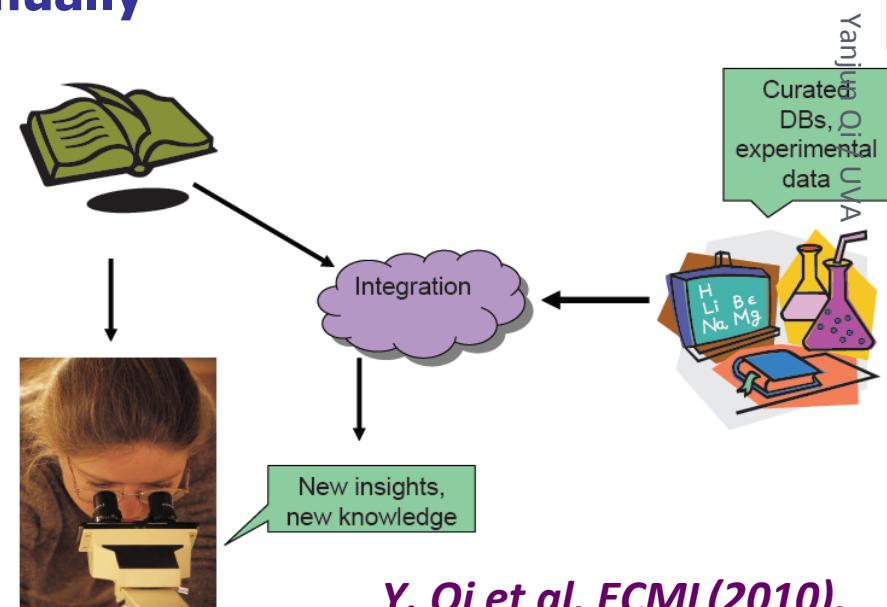
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Why Text Mining for Biomedicine ?

- ▶ Data Situation
 - ▶ MEDLINE: over 70 million queries every month and about 20 million publications
 - ▶ new terms (genes, proteins, chemical compounds, drugs) and discoveries constantly created/added in
 - ▶ **Impossible to annotate manually**

- ▶ Linking text to bio-databases and ontologies is crucial, for
 - ▶ Efficient access and discovery of facts and events in biosciences



*Y. Qi et al, ECML(2010),
SDM(2011), TREC MED(2012),*

→ Need text mining to (help) analyze /
organize biomedical literature

Two Benchmark Tasks

Mena <binds> directly to Profilin, an actin-binding protein that ...
a <complex> composed of SycN and YscB functions as a specific ...
...

Protein	Protein	Relation	Reference
Mena	Profilin	bind to	PubMed
SycN	YscB	complex	PubMed

► Related Tasks

- Protein Name Recognition
- Protein Interaction Event Recognition

*Y. Qi et al, ECML(2010),
SDM(2011), TREC MED(2012),*

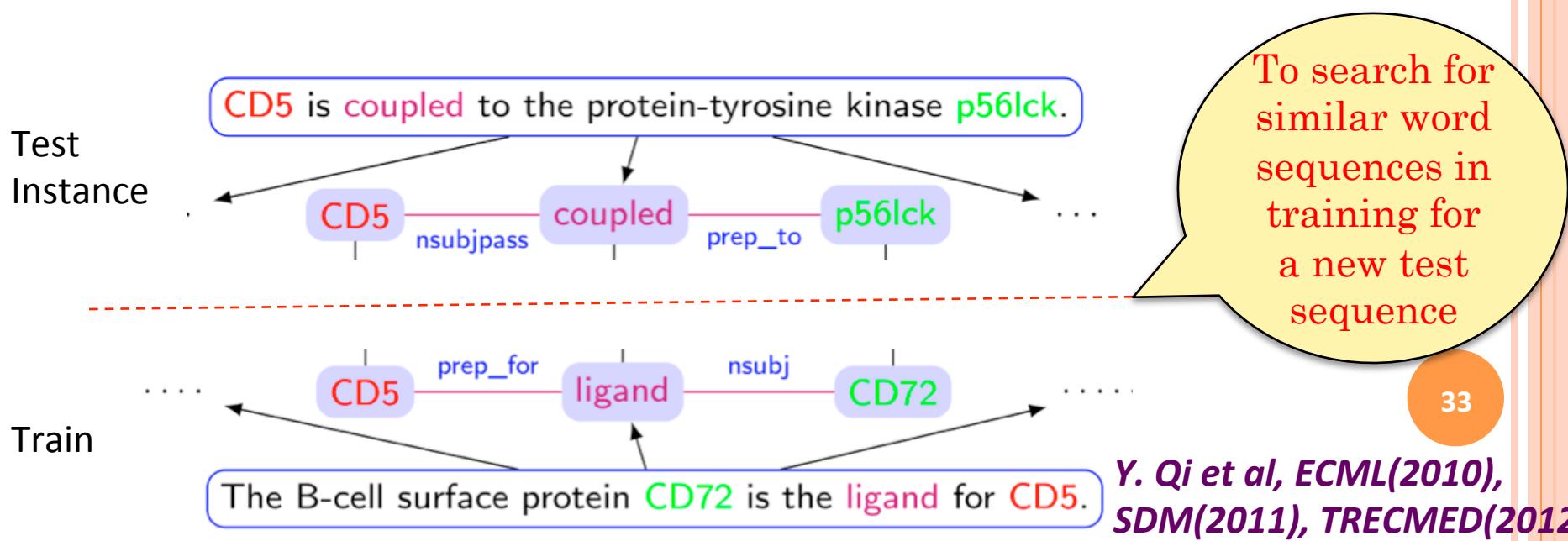
→ Many Similar Tasks

- Bio-Entity recognition (e.g. chemical terms, disease names,)
- Bio-Relational extraction (e.g. genetic interaction, disease to phenotype)

Challenges

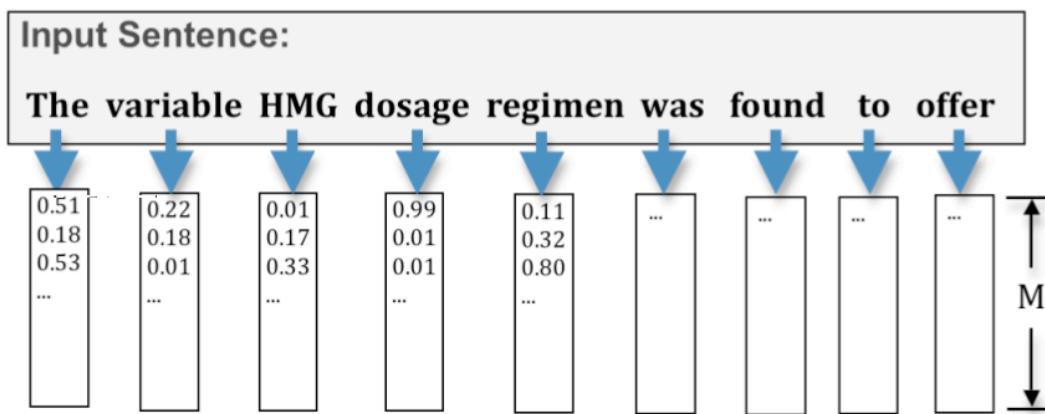
How to improve current approaches by learning from unlabeled examples X^* (e.g. Pubmed articles) ?

- Annotated training sets are small
 - Hardly cover words in vocabulary (~2 million in PubMed)
- Millions of Pubmed articles freely available
- To design learning methods able to measure semantic similarity between words or word sequences
 - Rigid symbolic matching could not capture such similarity



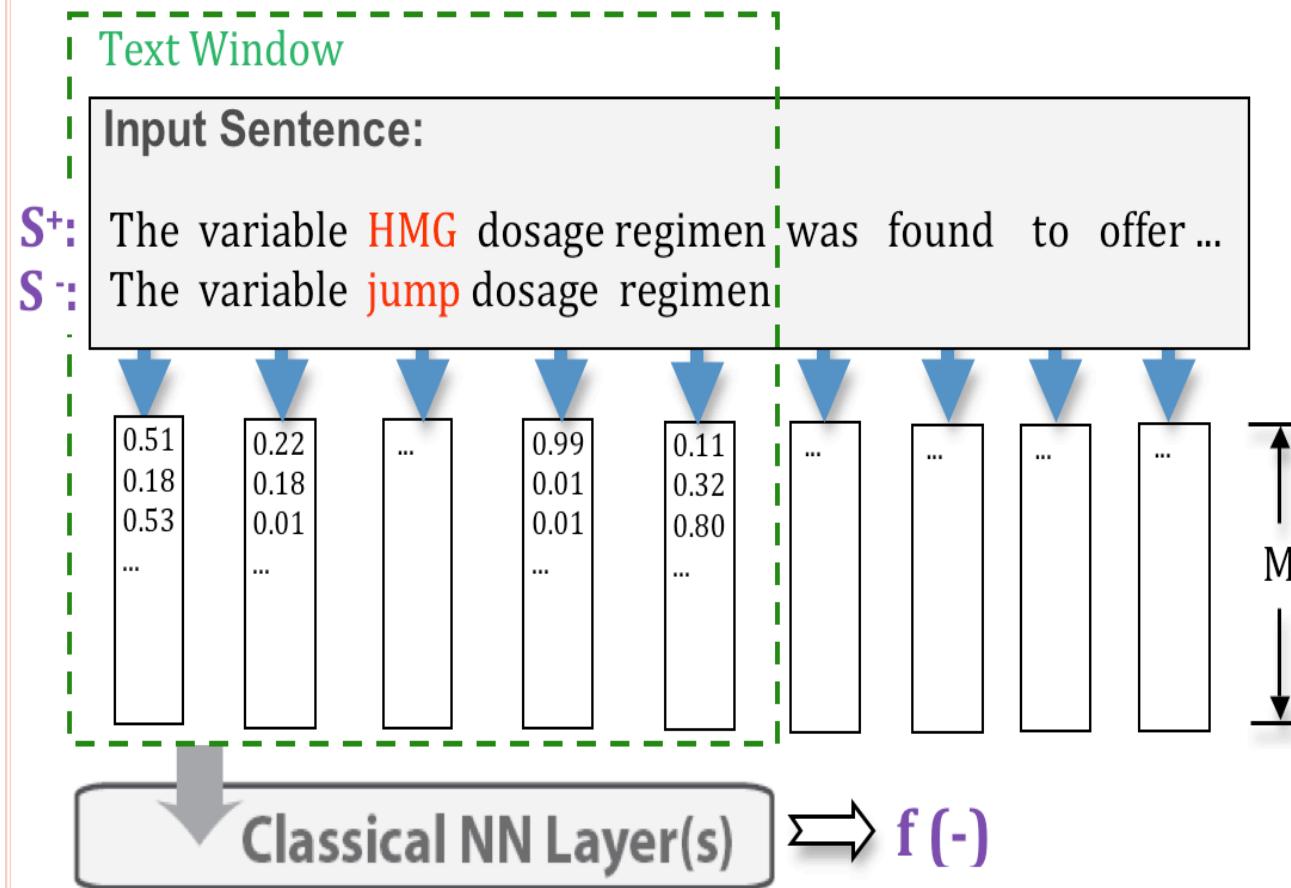
Learn Word Representation Reflecting Semantic Similarity

- Learn to embed each word into a vector of real values (with dimensionality M)
 - Based on unlabeled data (i.e. **PubMed abstracts 1995-2009, ~1.3G word tokens, ~4.5M abstracts**)
 - Semantically **similar** words have **closer** embedding representations



Y. Qi, et al, NIPS(2009), ICDM(2009), ECML(2010), CIKM(2011), SDM(2011), TREC MED(2012), NIPS(2012), ECML(2012), SDM (2014)

Local Embedding Based on Pattern of Short Text Window



Pseudo supervised signals

- Positive examples: Text window extracted from unlabeled corpus randomly
- Negative examples: Text window with middle word replaced by a random word

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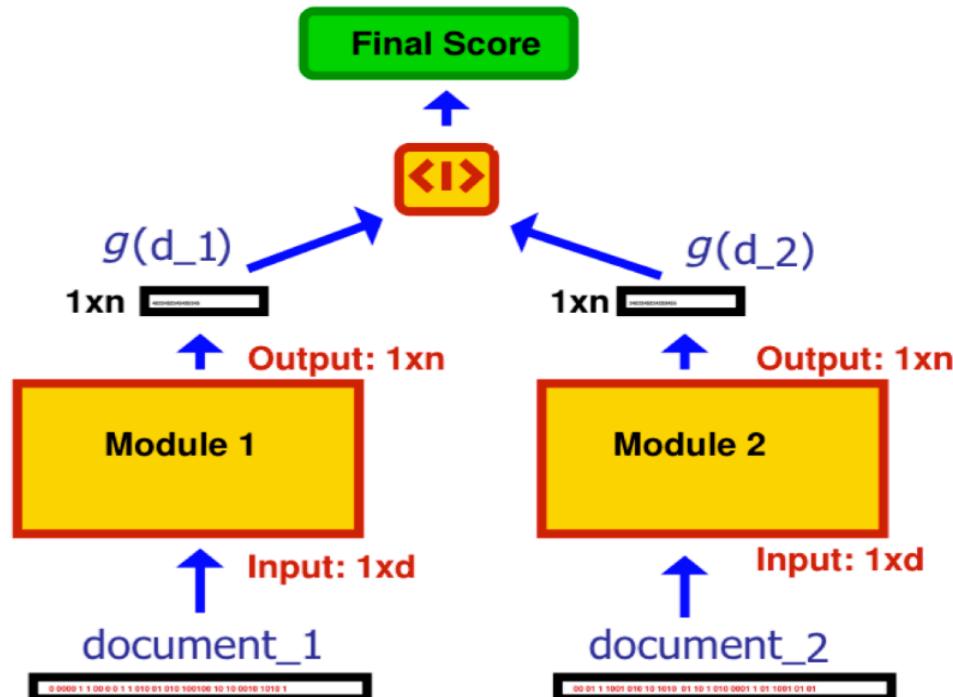
Y. Qi et al, ECML(2010),
SDM(2011), TREC MED(2012)

- Build a pairwise ranking task to train word embedding (first layer in deep neural network)

- $f(-)$ measures how likely a word segment exist in Pubmed ?
- Pairwise rank loss to optimize:

$$\sum \max(0, 1 - f(s^+) + f(s^-))$$

Global Embedding using Similarity between Text Documents



- $g(-) \rightarrow$ learned representation of each text document
 - first layer of $g(-)$ maps to “global” word embedding
 - Each document is represented as “bag-of-words”
- Learning $g(-)$ by forcing $g(-)$ of two documents
 - with similar meanings to have closer representations,
 - with different meanings to be dissimilar

- Pseudo supervised signals by splitting each **Pubmed abstract** into **two** documents (each with half)
 - **Similar** if from the same
 - **Dissimilar** otherwise

Results: Nearest Words of Sample Query Word

Query	Local Embed	Global Embed
protein	ligand, subunit, receptor, molecule	proteins, phosphoprotein, isoform,
medical	surgical, dental, preventive, reconstructive	hospital, investigated, research, urology
interact	cooperate, compete, interfere, react	interacting, member, associate, ligand
immunoprecipitation	co- immunoprecipitation, EMSA, autoradiography, RT-PCR	coexpression, two-hybrid, phosphorylated, tbp

Results: Performance

- Achieved **the state-of-the-art performance** (by using large amount of unlabeled data from Pubmed)
 - With word features only
 - Added on single base classifier (**string kernel + SVM**)
- **Previous best systems** used **complex** combination of many classifiers with many more linguistic features, dictionaries, and etc
- Semi-supervision **IMPROVES** both benchmark tasks

- Bio-Entity tagging
(genes, proteins, etc)



- Protein-Protein Interaction
(PPI) event extraction

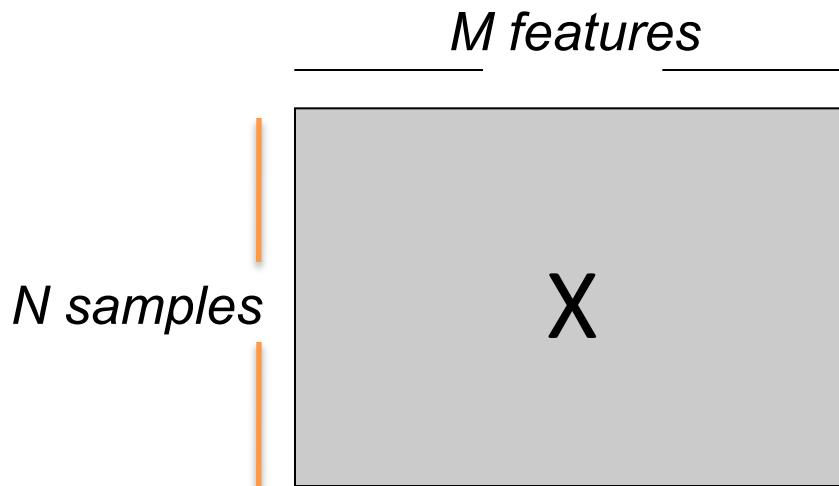


THIS TALK COVERS

	<u>Project Topic</u>	<u>Complexity</u>	<u>HOW ?</u>
I	Protein interaction identification	Y	Training with auxiliary labels Yanjun Qi / UVA
II	Protein structure prediction	X & Y	Unified feature learning for multiple related tasks
III	Biomedical text mining	X	Add semi-supervision on features
IV	Conditional dependency graph among Genes / TFs	X	Model data example with feature interactions

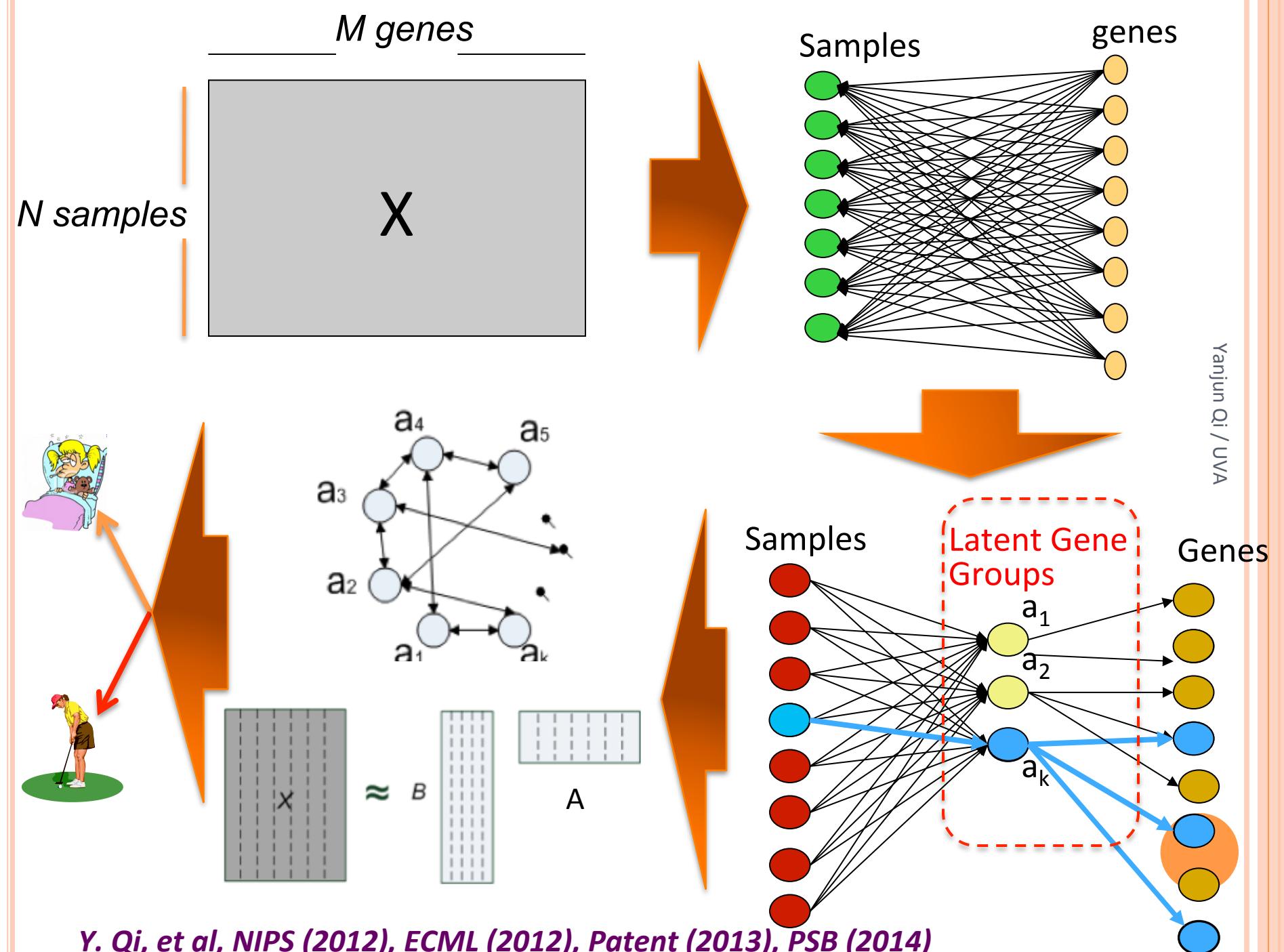
MODEL FEATURE DEPENDENCY TO GET BETTER FEATURES

- Feature variables have correlations or high-order conditional dependency relationship
 - E.g. genes work with other genes together to affect certain disease



Hypothesis:

→ May model samples better if considering feature dependencies / interactions



Task: Learning Dependency between Hidden Feature Groups

Method	SLFA	Lasso overlapped-group	Lasso	SVM	PCA
Cross-validation error rate	34.22 ± 2.58	35.31 ± 2.05	36.42 ± 2.50	36.93 ± 2.54	36.85 ± 3.02

Tumor classification based on gene expression values of 8141 genes for 295 breast cancer tumor samples. SLFA does not use prior knowledge like biological gene network graph.

NIPS(2012)

Yajun Qi / UVA

Same model successfully applied to learn dependency between text topics for modeling text documents

NIPS (2012)

A similar / simpler model successfully applied to learn conditional dependency between transcription factors using ENCODE data

Patent (2013)

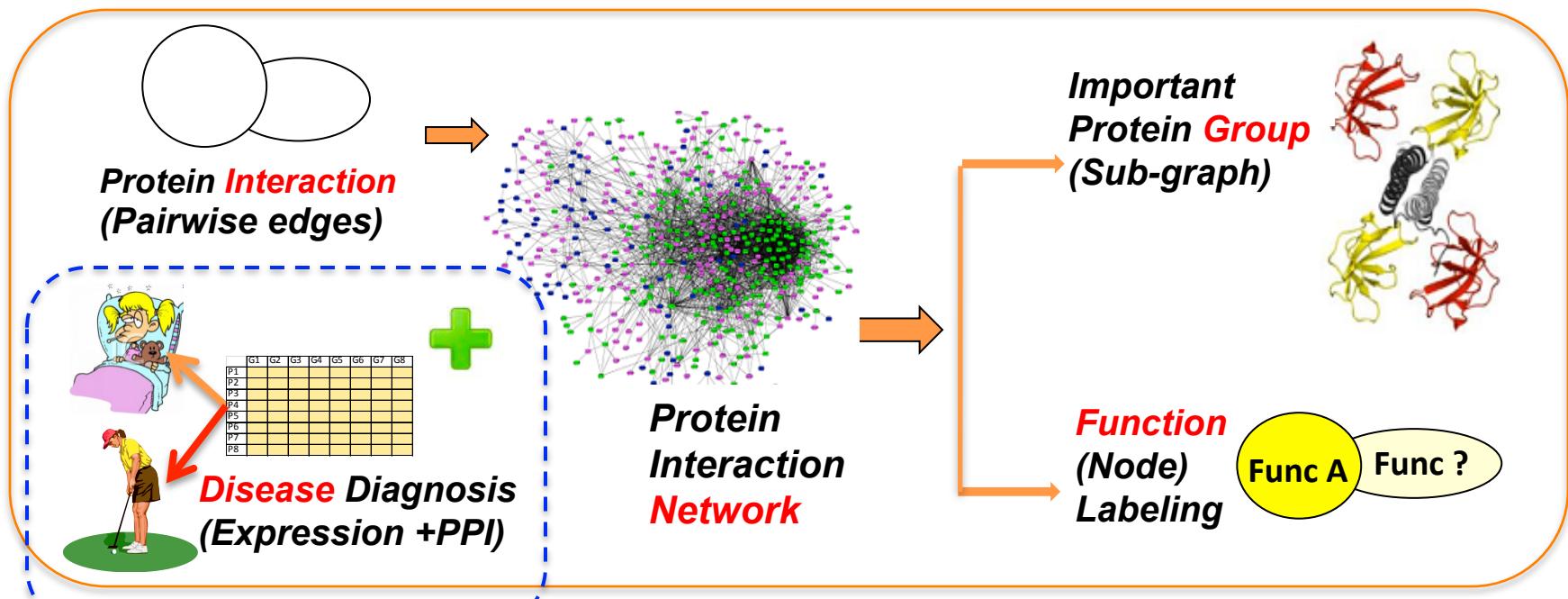


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MORE NOT COVERED OF MY PROJECTS

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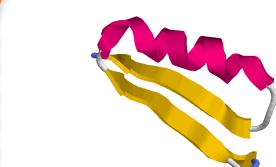


Relational (Graph) Data

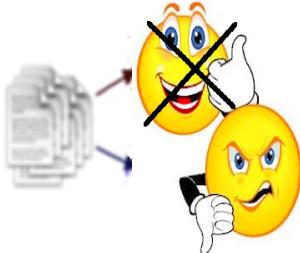
Applications are diverse but methods are generic

MORE NOT COVERED OF MY PROJECTS

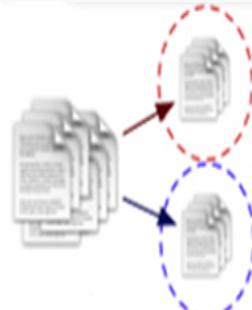
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Tagging Protein Sequence



Classifying Social Text Sentiment

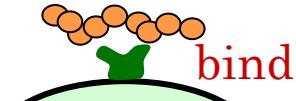


Retrieving Medical Records

Medical applications in clinical system collect patient MRNs to determine who is their doctor, what is their medical condition and what is their treatment plan. MRNs are often used to uniquely identify a patient. The unique MRN allows MRNs to be linked across different medical records. Specifically, MRNs can be used to predict patient's future health status by linking past medical records. MRNs can also be used to predict patient's future health status by linking past medical records.



Entity & Relation Recognition



Killer cell

MHC binding Peptide Prediction

Yang
Qian / Yanjun

Sequential Data

Video segmentation; Video retrieval,

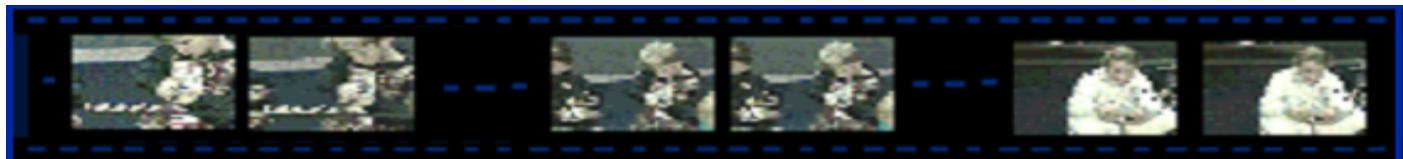
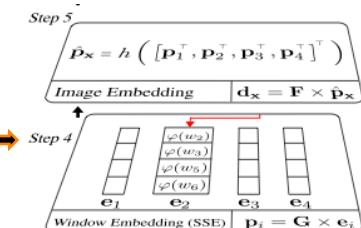
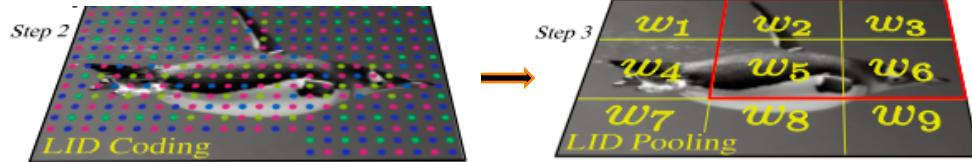


Image Classification

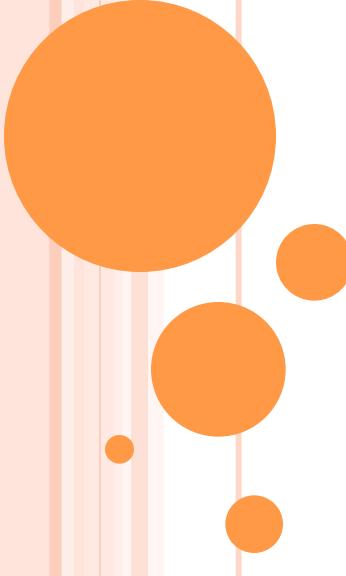


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Multimedia Data

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Applications are diverse but methods are generic



Actively Looking
for collaborations !



Contact: yanjun@virginia.edu

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