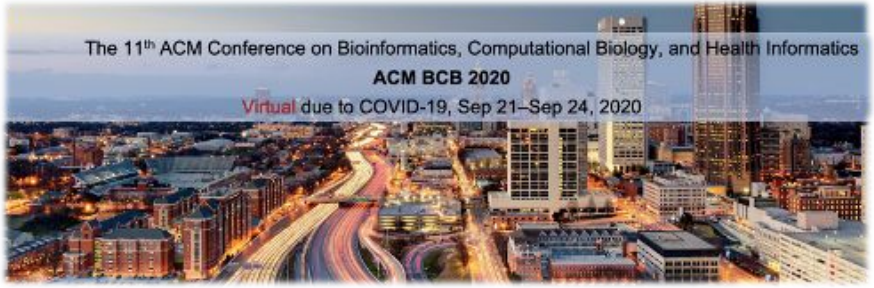

Bio-JOIE: Joint Representation Learning of Biological Knowledge Bases

Presenter: Junheng Hao

University of California, Los Angeles

Association for Computing Machinery

SIGBio Bioinformatics, Computational Biology and Biomedical Informatics

UCLA Samueli Computer Science

Outline

- Background: Cross-domain Biological Knowledge Graphs
- Bio-JOIE Modeling
- Experimental Results & Case Study
- Conclusion & Future Work

Outline

UCLA ScAi

- **Background: Cross-domain Biological Knowledge Graphs**
- Bio-JOIE Modeling
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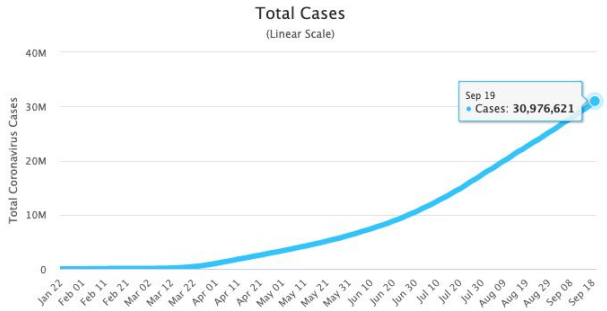
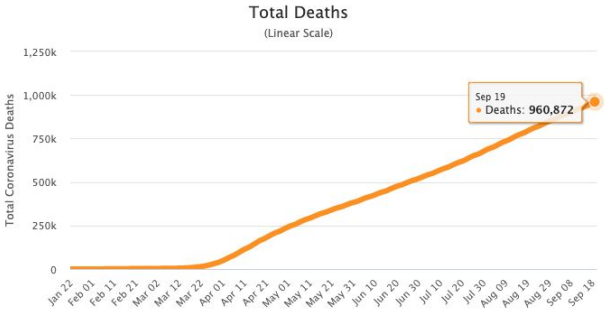
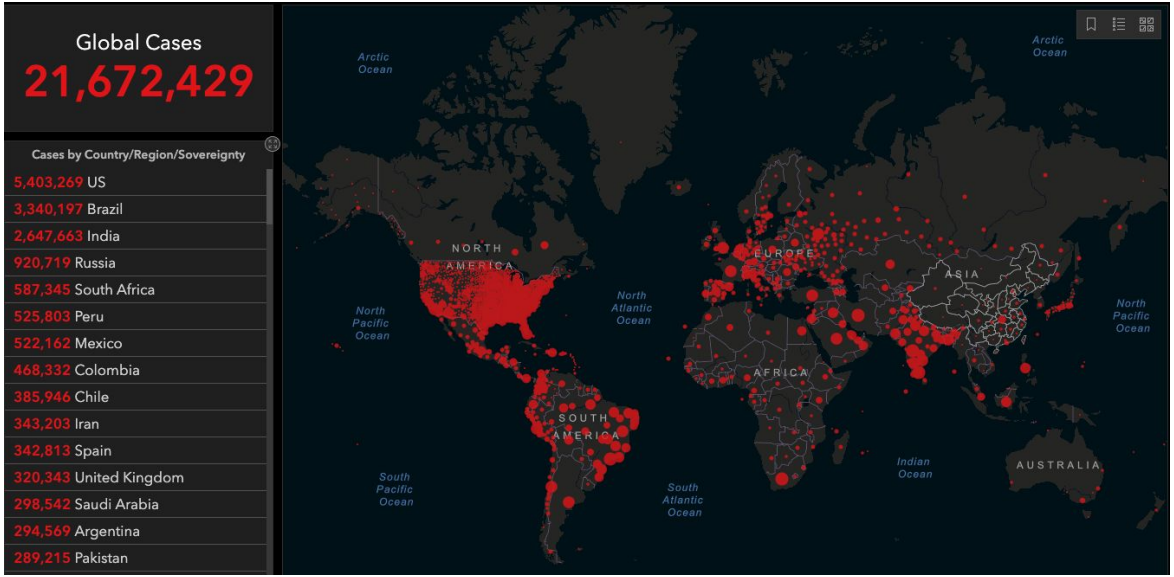
Fight of COVID-19

- The outbreak of COVID-19 has infected over 21 millions of people and caused high death tolls since the end of 2019, as worldwide social and economic disruption.



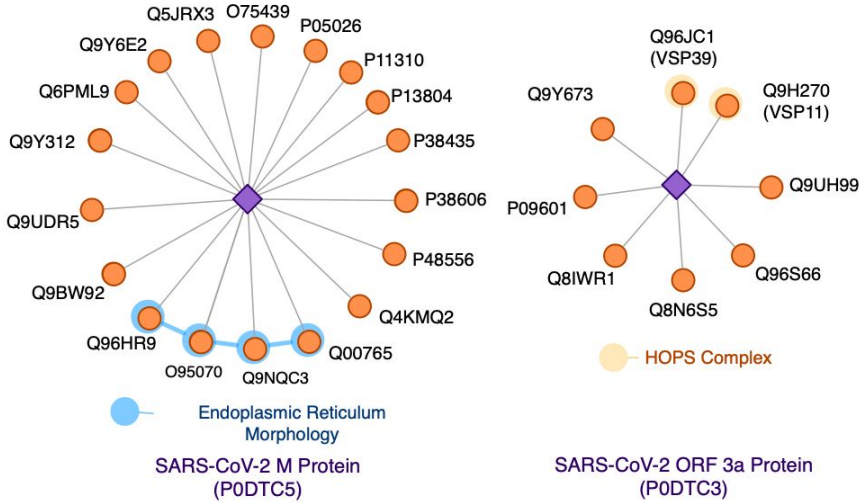




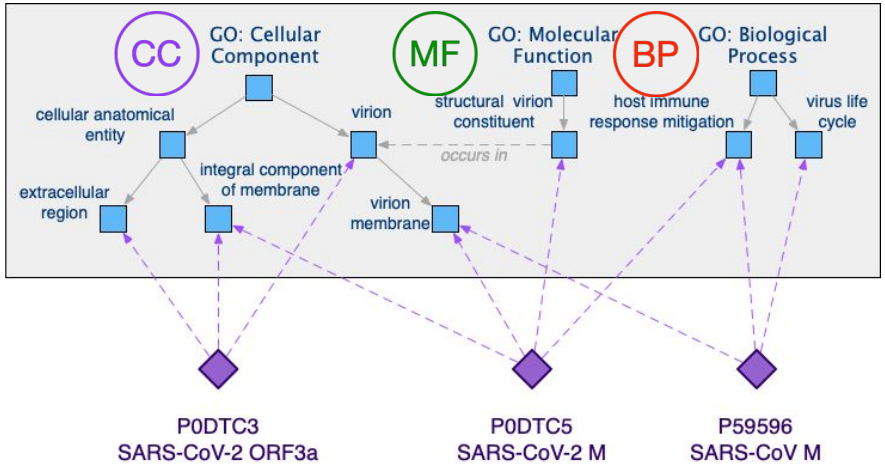
Data source: COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU), updated as 11pm (PST), 08/16/2020. Website: https://coronavirus.jhu.edu/map.htm

SARS-CoV-2 Knowledge Graph

- Tremendous efforts have been made to discover the infection mechanism of its causative agent, named SARS-CoV-2, from multiple perspectives.
- Knowledge about SARS-CoV-2: (1) Protein-protein interactions (PPI) between viral proteins and human co-host proteins; (2) Gene ontology (GO) annotations on viral proteins.



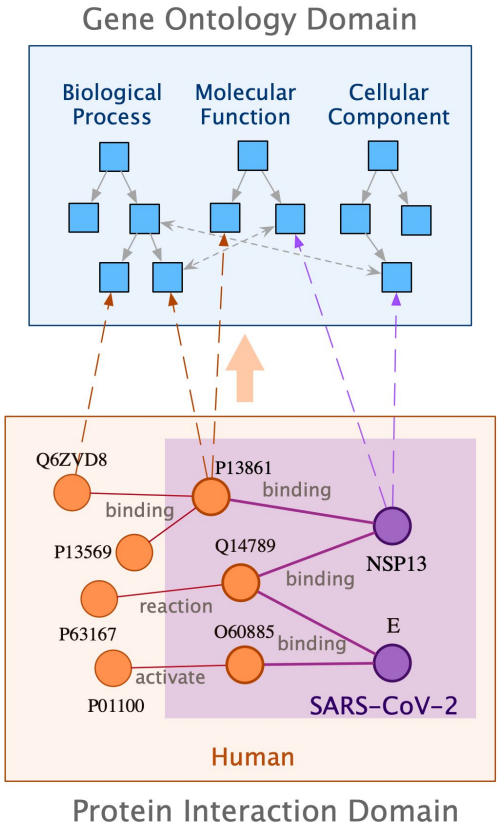
PPI of SARS-CoV-2 M and ORF3a Proteins [Gordon et al.]



GO annotations on SARS-CoV-2 M/ORF3a and SARS-CoV M

Cross-domain Bio-KG

- Not limited to SARS-CoV-2 KB above, many biological KBs, often stored as knowledge graphs (KGs), consist of biological entities of various kinds, together with their properties and relations.
- As essential sources of knowledge, these KBs can be categorized in different domains.
  - Gene Ontology Consortium → gene function annotation
  - STRING → Knowledge accumulated from functional proteomic analysis
  - DrugBank → cheminformatics resource for drug targets
- Domain-specific knowledge is often scarce and costly to collect.



Learning Embeddings for Bio-KG

UCLA ScAi

Input
Knowledge Graph(s)

MeSH

STRING

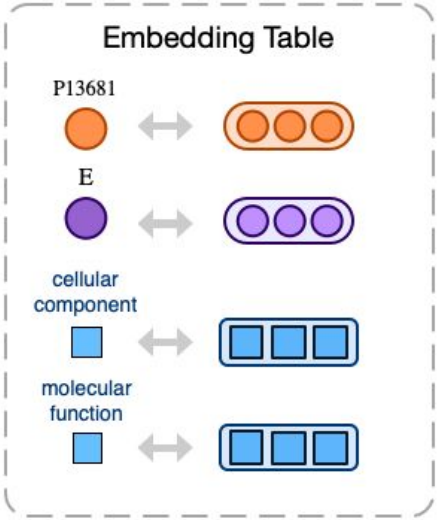
neXtprot

PubMed

GENEONTOLOGY
Unifying Biology

DRUGBANK

Output
Embeddings



Inference & Applications

PPI Type prediction

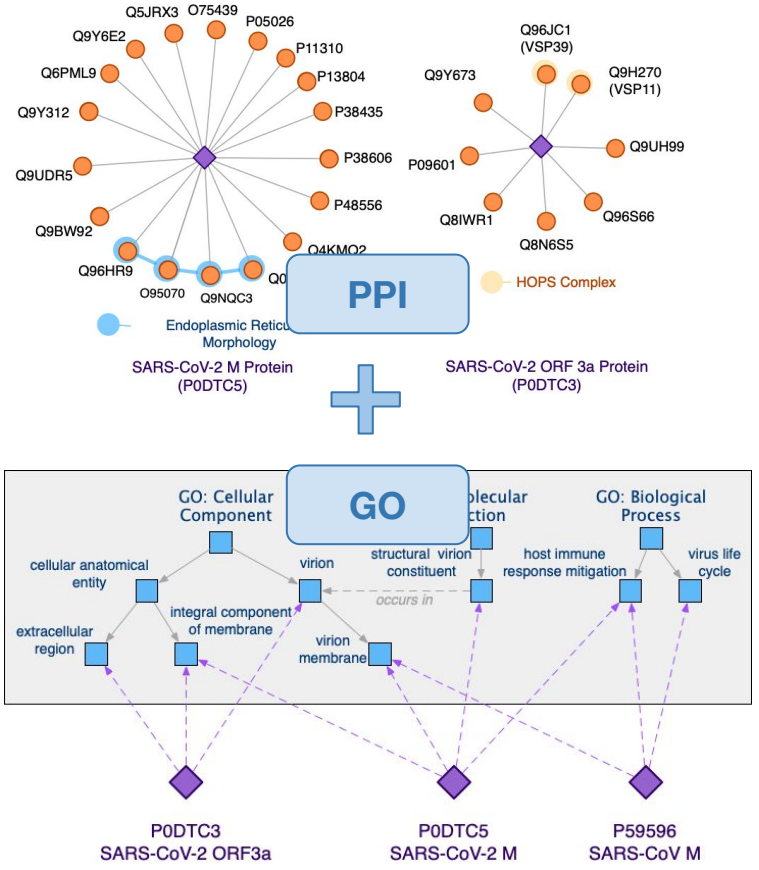
PPI Classification

GO Annotations

...

Motivation

- Relying on the KG from a single domain presents the risk of learning from limited and scarce information.
- The missing knowledge in one domain can be transferred from other domains with complementary knowledge, and thus provide more comprehensive representations of the biological entities.
- We aim at designing a plausible method to support the fusion and transfer of knowledge across multiple biological domains.



Outline

- Background: Cross-domain Biological Knowledge Graphs
- **Bio-JOIE Modeling**
- Experimental Results & Case Study
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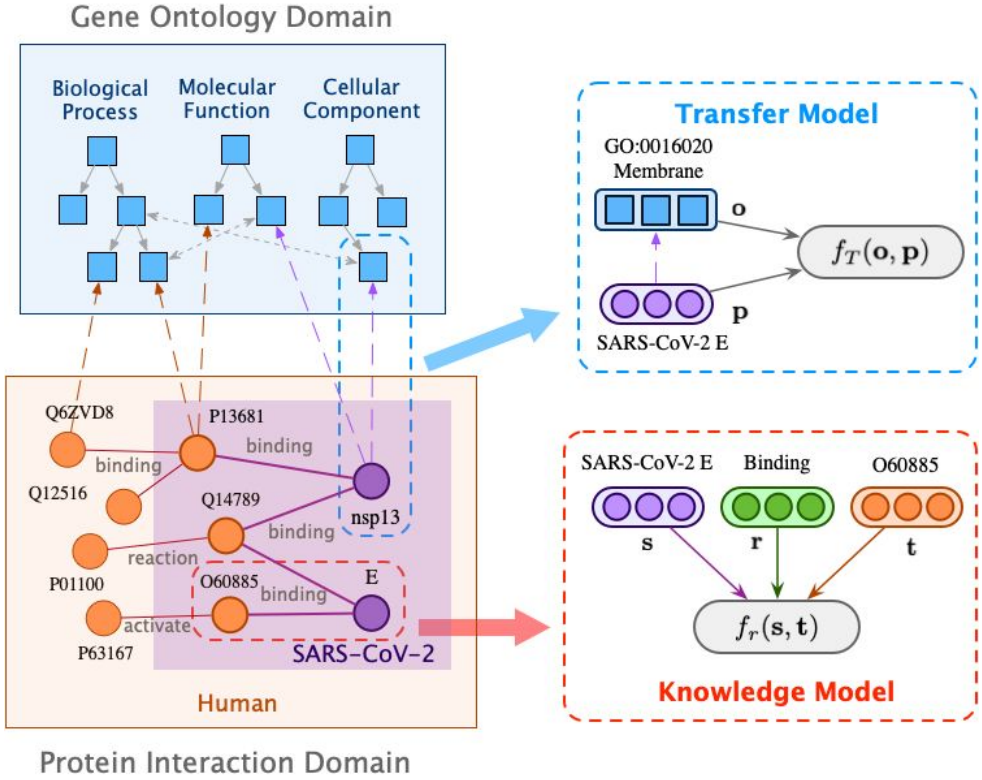
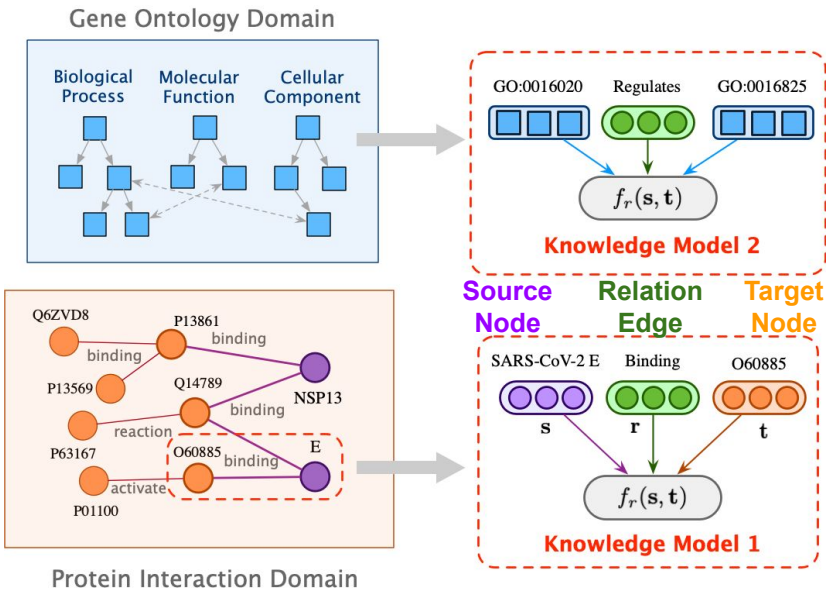
Model Overview: Bio-JOIE

Joint **E**mbedding Learning for multiple domains of **Bio**logical Knowledge Bases



Bio-JOIE: Knowledge Model



Knowledge Triple → {**S**ource, **R**elation, **T**arget}

- **Goal:** To embed the relational facts / structures in the each domain of the Bio-KG
- Three representative score functions: TransE, DistMult (selected), and HolE

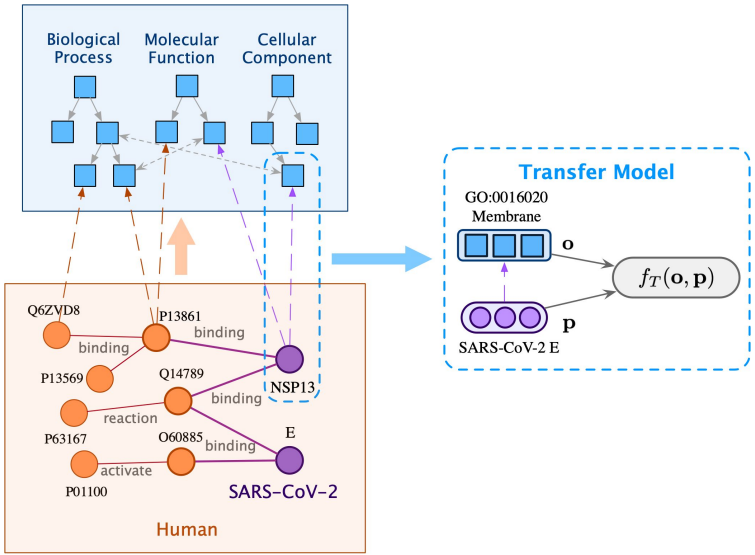
$$f_r^{\text{Trans}}(\mathbf{s},\mathbf{t}) = ||\mathbf{s}+\mathbf{r}-\mathbf{t}||_2$$
$$f_r^{\text{Mult}}(\mathbf{s},\mathbf{t}) = -(\mathbf{s}\circ\mathbf{t})\cdot\mathbf{r}$$
$$f_r^{\text{HolE}}(\mathbf{s},\mathbf{t}) = -(\mathbf{s}\star\mathbf{t})\cdot\mathbf{r}$$

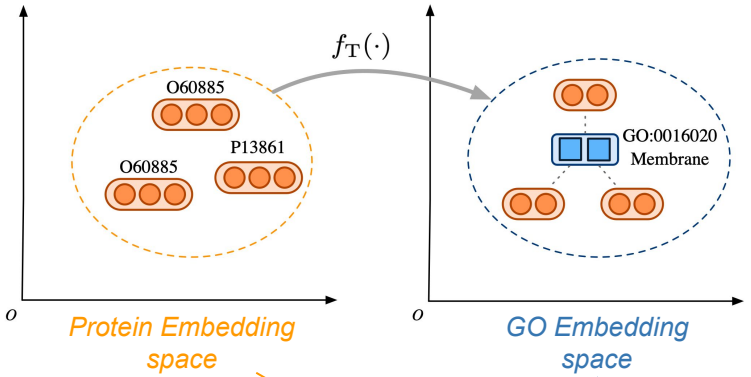
- **Loss:** Triple-wise margin ranking loss with negative sampling

$$\mathcal{L}_K^{\mathcal{G}} = \frac{1}{|\mathcal{G}|}\sum_{(s,r,t)\in\mathcal{G}} \max\left\{f_r(s,t) + \gamma^{\mathcal{G}} - f_r(s',t'),\ 0\right\}$$

Positive triples *Negative triples*

Bio-JOIE: Transfer Model





- Domain transfer function:

$$f_T(o,p) = \|\sigma\left(\mathbf{M}_T \cdot \mathbf{p} + \mathbf{b}_T\right) - \mathbf{o}\|_2$$

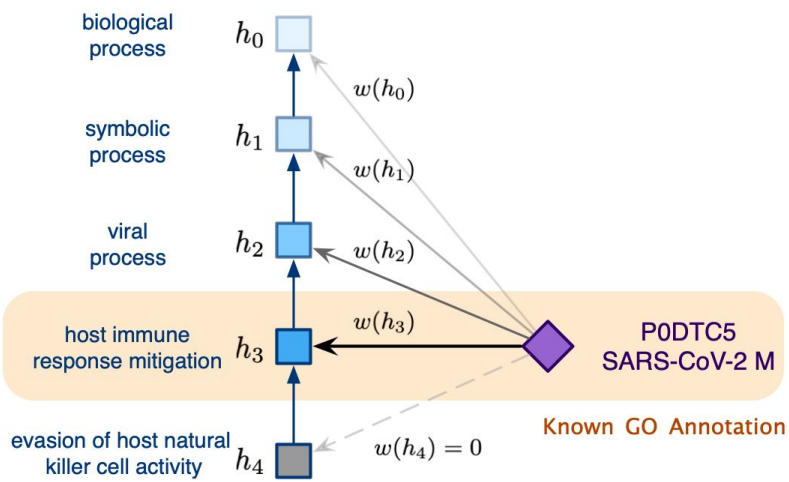
- Loss function given alignment pairs

$$\mathcal{L}_{T_1} = \frac{1}{|\mathcal{A}|} \sum_{(o,p)\in\mathcal{A}} \max\left\{f_{T_1}(o,p) + \gamma^{\mathcal{A}} - f_{T_1}(o',p'),\ 0\right\}$$

Positive alignments

Negative alignments

Bio-JOIE: Transfer Model (Weighted)



- Domain transfer function:

$$f_T(o,p) = \|\sigma\left(\mathbf{M}_T \cdot \mathbf{p} + \mathbf{b}_T\right) - \mathbf{o}\|_2$$

- Weighted alignments by GO term specificity
  - Options: Level weighted or degree weighted

$$\omega_1(o) = \frac{l}{l_{\max}}, \quad \omega_2(o) = \frac{1}{d(o)}$$

By level *By degree*

- Loss function given weighted alignment pairs

$$\mathcal{L}_{T_2} = \frac{1}{|\mathcal{A}|} \sum_{(o,p)\in\mathcal{A}} \max\left\{\frac{\omega(o)}{C}\left[f_{T_2}(o,p) + \gamma^{\mathcal{A}} - f_{T_2}(o',p')\right], 0\right\}$$

weighted alignments

Bio-JOIE: Joint Training & Inference

- Joint learning on two knowledge models in protein and GO and one transfer model (one species)

$$\mathcal{L} = \lambda^t \mathcal{L}_T + \lambda^p \mathcal{L}_K^{\mathcal{G}_p} + \mathcal{L}_K^{\mathcal{G}_o}$$

- In case of multiple species with one universal gene ontology, Bio-JOIE can apply one knowledge model and one transfer model, designated for each species → “Multi-way”

$$\mathcal{L} = \sum_{i=1}^{m} \lambda_i^t \mathcal{L}_T + \sum_{i=1}^{m} \lambda_i^p \mathcal{L}_K^{\mathcal{G}_p} + \mathcal{L}_K^{\mathcal{G}_o}$$

Outline

- Background: Cross-domain Biological Knowledge Graphs
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Datasets

- Protein-Protein Interaction Networks
  - 4 types of PPIs on three species (human, yeast and fly) from STRING database [1]
- Gene Ontology Datasets
  - Extracted from Gene Ontology Consortium [2]
  - Total 6 relations, such as is_a, part_of, regulates, etc.
  - Three aspects: biological process (BP), cellular components (CC), and molecular function (MF)

Table: Statistics of PPI Networks and GO annotations from 3 species

Species	# Proteins	# PPI Triples	# GO Annotations
Yeast	3,736	21,704	191,801
Fly	3,826	10,000	87,807
Human	8,204	36,400	102,759

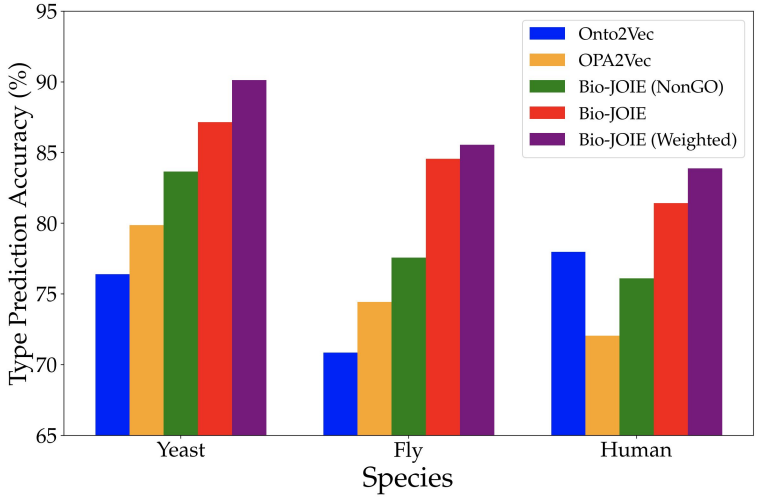
Table: Statistics of 3 aspects in GO

Aspects	BP	CC	MF
# GO entities	5744	1,147	1,764
# GO triples	19,021	2,116	2,190
# Protein-GO annotations (yeast)	72,956	58,729	60,116
# Protein-GO annotations (fly)	44,605	24,550	18,652
# Protein-GO annotations (human)	42,899	32,929	26,931

Experiment: PPI Type Prediction

Performance on PPI type prediction for three different species

- **Task:** Interaction type prediction given pairs of proteins
- **Evaluation metric:** Prediction accuracy
- **Baselines:** Onto2Vec (variants: Parent, Ancestor, Sum, Mean) , OPA2Vec, Bio-JOIE (NonGO)



Observation: Bio-JOIE outperforms all baselines in PPI type prediction on three different species.

Experiment: PPI Type Prediction

Effects of different aspects of GO terms on PPI type prediction

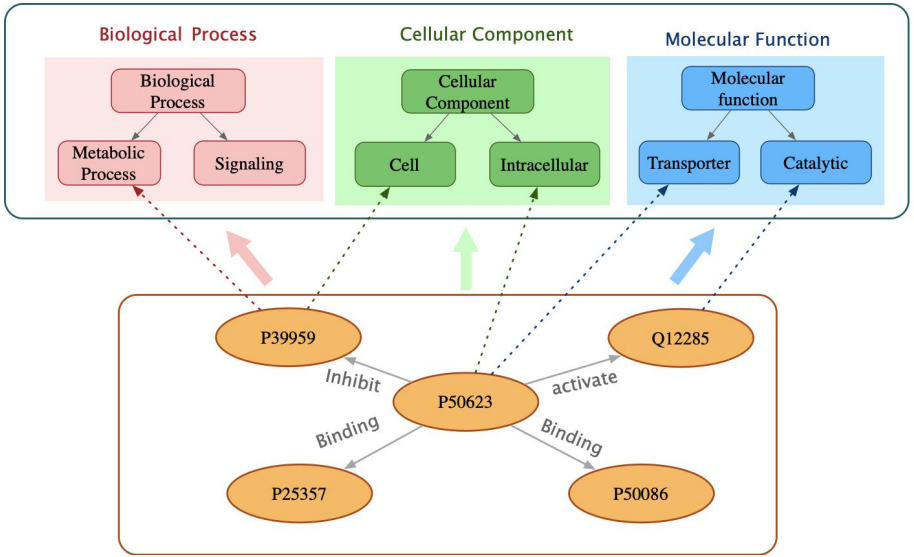


Table: Comparison of Bio-JOIE performance on combinations of three different aspects in GO.

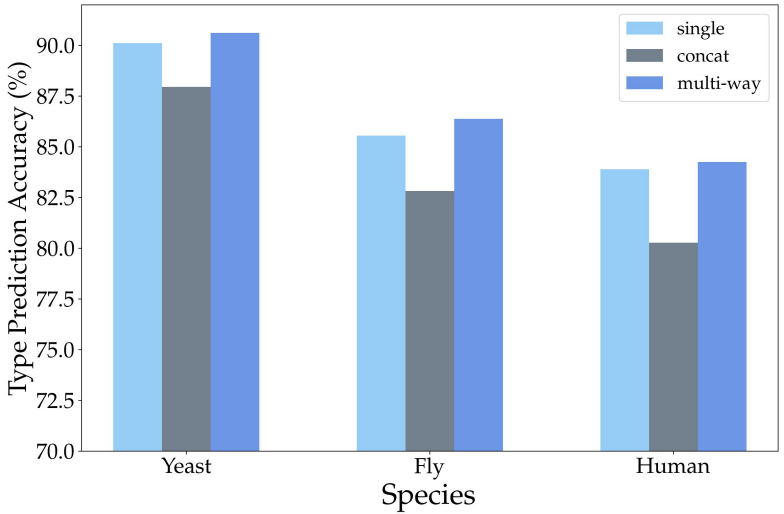
#	Aspects	Yeast	Fly	Human
1	BP	0.8794	0.8402	0.8153
	CC	0.8499	0.8272	0.8054
	MF	0.8539	0.8386	0.8165
2	BP+CC	0.8717	0.8473	0.8271
	BP+MF	0.8673	0.8471	0.8163
	CC+MF	0.8569	0.8466	0.8170
3	AllGO	**0.9012**	**0.8555**	**0.8389**

Observation: All aspects has help better predict PPI (among all three, BF contributes the most), which results that AllGO is the best performed variant.

Experiment: PPI Type Prediction

Joint-training from multiple species further benefits PPI type prediction

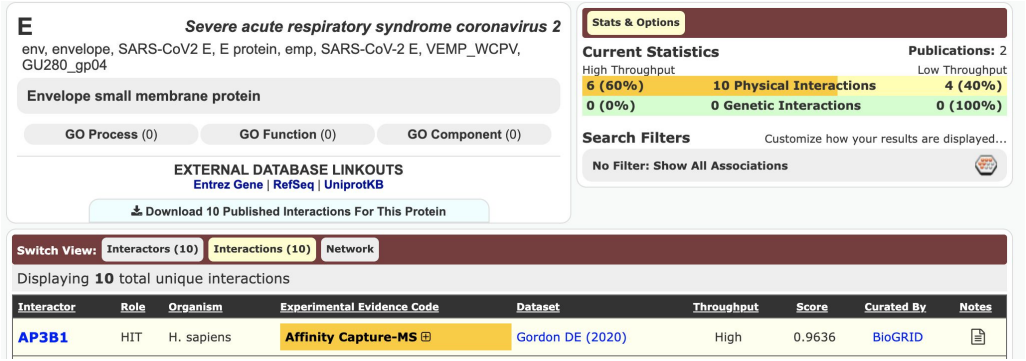
- **Model Setting:**
  - **Single** (Train and test on one species; no joint training)
  - **Concat** (Simply concatenate all PPI networks into one; one knowledge and transfer model for all three species)
  - **Multi-way** (Each species of the three has one knowledge model and transfer model to GO)



Observation: Joint training Bio-JOIE from multiple species can further benefit PPI type prediction in each of the involved species.

Case Study: SARS-CoV-2 Prediction

- Data sources for SARS-CoV-2
  - Data collected from BioGrid[1] on SARS-CoV-2, SARS-CoV and MERS-CoV
  - **26** SARS-CoV-2 proteins (associated with **282** GO terms) and **30** viral proteins of SARS-CoV and MERS-CoV (associated with **630** GO terms)
  - **332** highly possible interactions of SARS-CoV-2 identified by Gordon et al [2] and **1131** virus-human pairs with low MIST scores, as negative examples.
- All processed datasets are available at https://www.haojunheng.com/project/goterm.



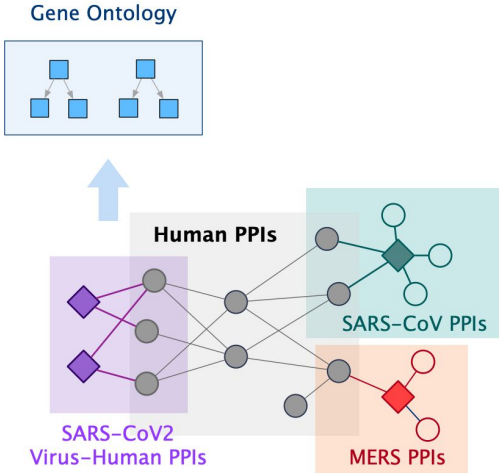
References:

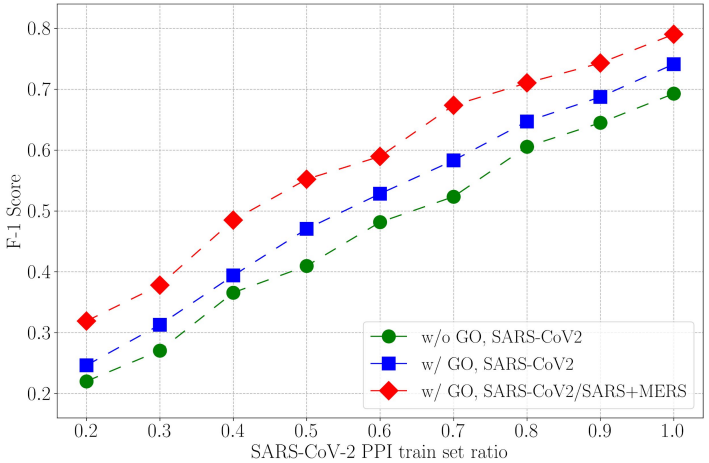
[1] BioGrid: https://wiki.thebiogrid.org/doku.php/covid, COVID-19 Related GO Terms: http://geneontology.org/covid-19.html

[2] David E Gordon, Gwendolyn M Jang, Mehdi Bouhaddou, Jiewei Xu, Kirsten Obernier, Kris M White, Matthew J O'Meara, Veronica V Rezelj, Jeffrey Z Guo, Danielle L Swaney, et al. 2020. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature (2020), 1–13.

SARS-CoV-2 Human PPI Classification

- **Binary classification:** Predict whether pairs of proteins (viral protein and human target protein) interact with each other or not.
- **Evaluation:** Compare F-1 Score on different Bio-JOIE variants



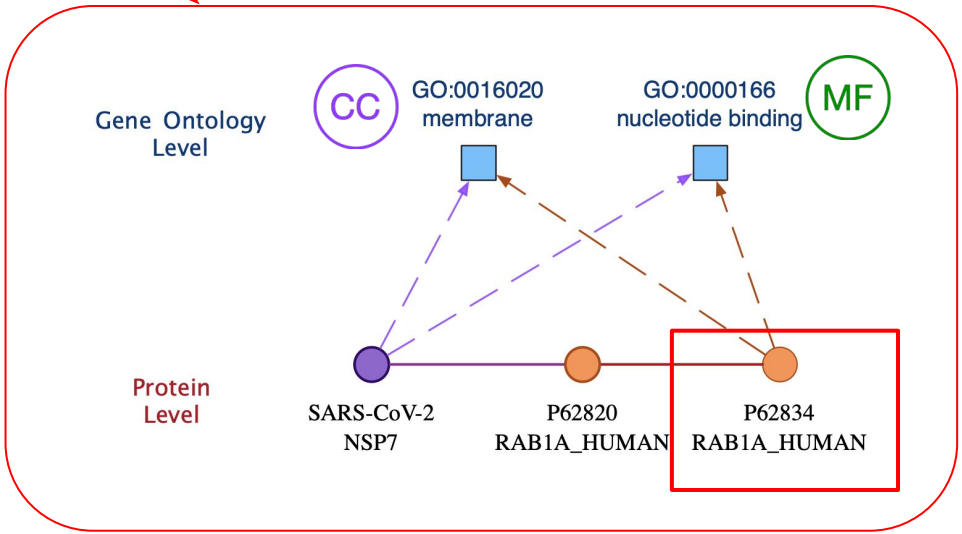


Observation: (1) Using GO provide additional knowledge about SARS-COV-2 proteins and better improve the classification performance; (2) Bio-JOIE can utilize the PPI information from similar coronavirus and further enhance the classification ability.

Example: Targeted Protein Prediction

SARS-CoV-2 Protein	Top Predicted Human Target Proteins
NSP7	P62834(0.685), P51148(0.879), P62070(0.418), P67870, O14578, Q8WTV0(0.854), P53618(0.350), Q9BS26, O94973, Q7Z7A1

Inside the Bio-KG



Outline

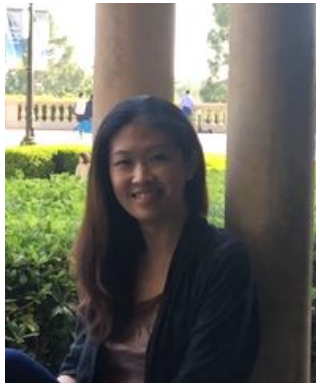
- Background: Cross-domain Biological Knowledge Graphs
- Bio-JOIE Modeling
- Experimental Results & Case Study
- **Conclusion & Future Work**

Conclusion & Future Work

- Bio-JOIE enables representation learning for cross-domain biological KBs capturing **in-domain interaction information** and **cross-domain knowledge transfer**.
- Bio-JOIE leverages **cross-domain complementary knowledge** to achieve SOTA performance on **PPI type prediction** and **clustering tasks**.
- As one important application, Bio-JOIE helps predict **human protein targets of SARS-CoV-2**, potentially benefits de novo drug discovery and disease mitigation.
- Some future directions:
    a. Incorporating multimodal features and gene annotations
    b. Extending Bio-JOIE to interconnected domains other than protein and gene ontology.

Acknowledgement

Muhao Chen
USC



Chelsea Ju
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Yizhou Sun
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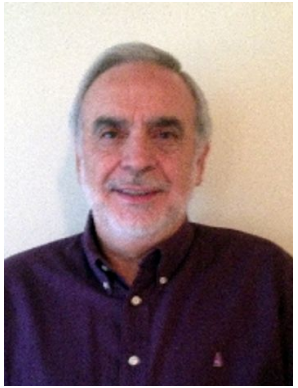


Carlo Zaniolo
UCLA

Wei Wang
UCLA

For more information, please check our BCB paper and webpage!

Paper Link: To be updated
Video Link: To be updated
Project webpage: https://www.haojunheng.com/project/goterm/

Association for Computing Machinery

Samueli Computer Science

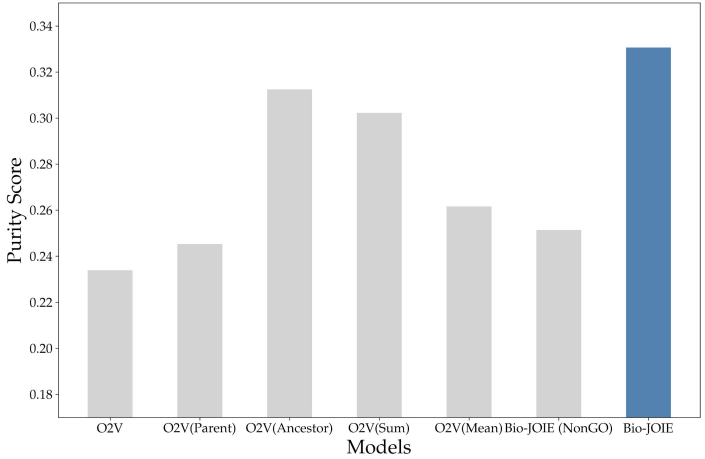
Thank you!

Q & A

Experiment: Enzyme-based Clustering

Using the learned embeddings for enzyme classification

- The Enzyme Commission number (EC number) defines a hierarchical classification scheme that provides the enzyme nomenclature based on enzyme-catalyzed reactions.
- 1340 yeast proteins collected from 7 classes of top-level EC numbers: oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases, and translocases.
- **K-means clustering** is applied to group them into seven non-overlapping clusters, based on the learned embeddings from Bio-JOIE, as well as baselines approaches.



Observation: The embeddings learned by Bio-JOIE can better preserve the enzyme-based features and perform better on clustering.

Supplementary: Data Sources

Datasets are collected from multiple sources such as STRING (human PPIs), BioGrid (virus-human PPIs) and AmiGO/QuickGO (gene ontology annotations).

Links:

- STRING: https://string-db.org/cgi/download.pl
- BioGrid (SARS-CoV/MERS/SARS-CoV-2): https://wiki.thebiogrid.org/doku.php/covid
- AmiGO 2: http://amigo.geneontology.org/amigo/dd_browse
- QuickGO: https://www.ebi.ac.uk/QuickGO/

- Project page: https://www.haojunheng.com/project/goterm/

Data Source

Virus-human Protein Interactions (PPI)

E — ***Severe acute respiratory syndrome coronavirus 2***

env, envelope, SARS-CoV2 E, E protein, emp, SARS-CoV-2 E, VEMP_WCPV, GU280_gp04

Envelope small membrane protein

GO Process (0) | GO Function (0) | GO Component (0)

EXTERNAL DATABASE LINKOUTS
Entrez Gene | RefSeq | UniprotKB

Download 10 Published Interactions For This Protein

Stats & Options

Current Statistics — **Publications:** 2

High Throughput		Low Throughput
6 (60%)	10 Physical Interactions	4 (40%)
0 (0%)	0 Genetic Interactions	0 (100%)

Search Filters — Customize how your results are displayed...

No Filter: Show All Associations

Switch View: Interactors (10) | Interactions (10) | Network

Displaying **10** total unique interactions

Interactor	Role	Organism	Experimental Evidence Code	Dataset	Throughput	Score	Curated By	Notes
AP3B1	HIT	H. sapiens	Affinity Capture-MS ⊞	Gordon DE (2020)	High	0.9636	BioGRID	
BRD2	HIT	H. sapiens	Affinity Capture-MS ⊞	Gordon DE (2020)	High	0.9066	BioGRID	
BRD4	HIT	H. sapiens	Affinity Capture-MS ⊞	Gordon DE (2020)	High	0.9785	BioGRID	
CWC27	HIT	H. sapiens	Affinity Capture-MS ⊞	Gordon DE (2020)	High	0.8931	BioGRID	
SLC44A2	HIT	H. sapiens	Affinity Capture-MS ⊞	Gordon DE (2020)	High	0.9503	BioGRID	
ZC3H18	HIT	H. sapiens	Affinity Capture-MS ⊞	Gordon DE (2020)	High	0.7964	BioGRID	

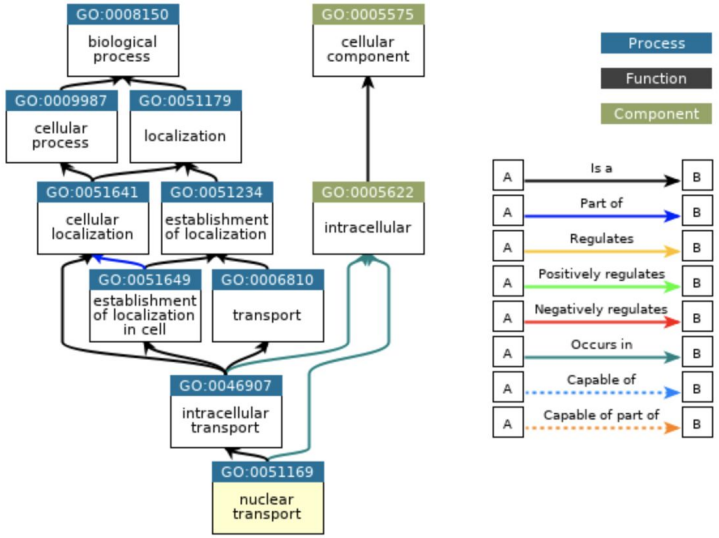
Data Source

Gene Ontology From AmiGO/QuickGO

AmiGO Drill-down Browser: [Demo] Biological Process Cellular Component Molecular Function

GoTerm Example: [Example: GO:0051169]

SARS-CoV-2 GoTerm annotations: [Example: P0DTC1 (R1A_HUMAN)]



P0DTC1

Gene Product	Symbol	Qualifier	GO Term	
UniProtKB:P0DTC1	P0DTC1	enables	GO:0036459 (F) thiol-dependent ubiquitinyl hydrolase activity	MF
UniProtKB:P0DTC1	P0DTC1	part_of	GO:0044220 (C) host cell perinuclear region of cytoplasm	CC
UniProtKB:P0DTC1	P0DTC1	part_of	GO:0030430 (C) host cell cytoplasm	CC
UniProtKB:P0DTC1	P0DTC1	part_of	GO:0033644 (C) host cell membrane	CC
UniProtKB:P0DTC1	P0DTC1	involved_in	GO:0090305 (P) nucleic acid phosphodiester bond hydrolysis	BP