GraphDTA

Prediction of drug-target binding affinity using graph convolutional networks

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KAICD

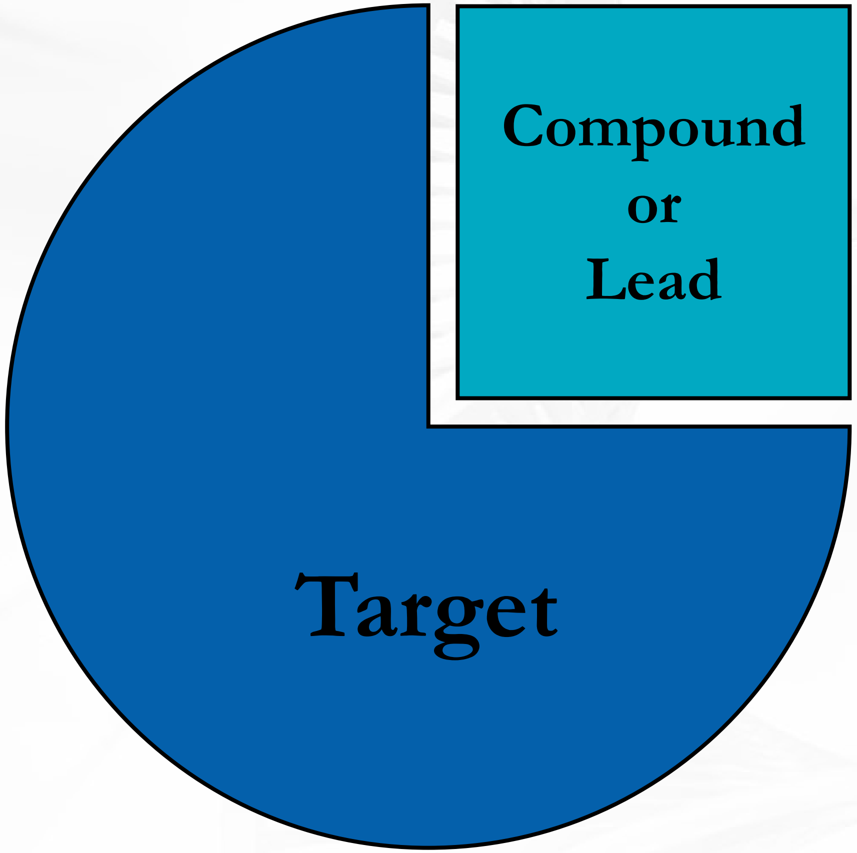
CENTER FOR AI-BASED NEW DRUG DEVELOPMENT FACILITATION

Time	Title	Contents
09:00 ~ 09:40	Introduction - GraphDTA	Introduction, Data Representation
10:00 ~ 10:40	Graph Structure	Graph, Graph Representation
11:00 ~ 12:00	Graph Convolutional Networks	Graph Convolution, Graph Convolutional Networks
12:00 ~ 13:00	Lunch Time	
13:00 ~ 13:40	GraphDTA Practice(Google Colab)	Data Structure Model Structure Predict with Pretrained Model
14:00 ~ 14:40		
15:00 ~ 15:40		
16:00 ~ 16:40	Introduction – Auto Encoder, Generative Models	AE, Stacked AE, VAE, feat.GAN
17:00 ~ 18:00	VAE Demo(Google Colab)	CHEM VAE Demo

Drug-Target Interaction

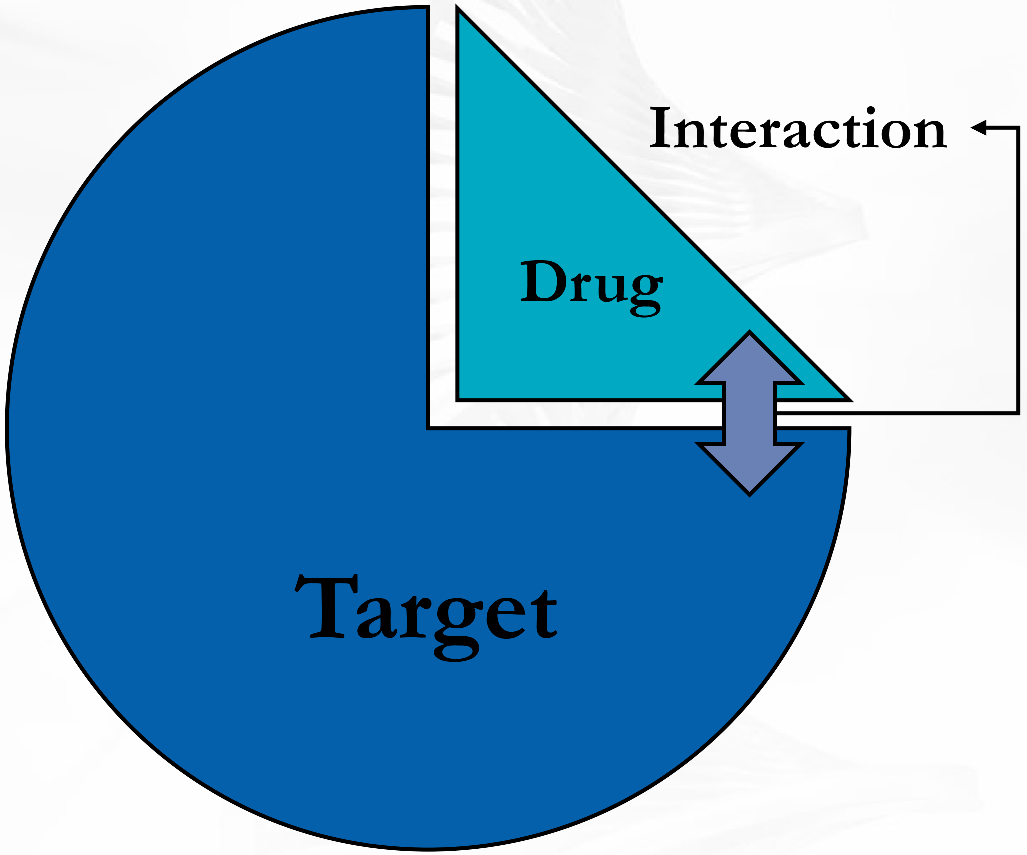
DTI

- 용어
  - Target : 질병과 관련된 특정 유기체 내의 분자 (단백질)
  - Compound or Lead : Target과 결합하여 Target을 제어할 수 있는 화학 물질



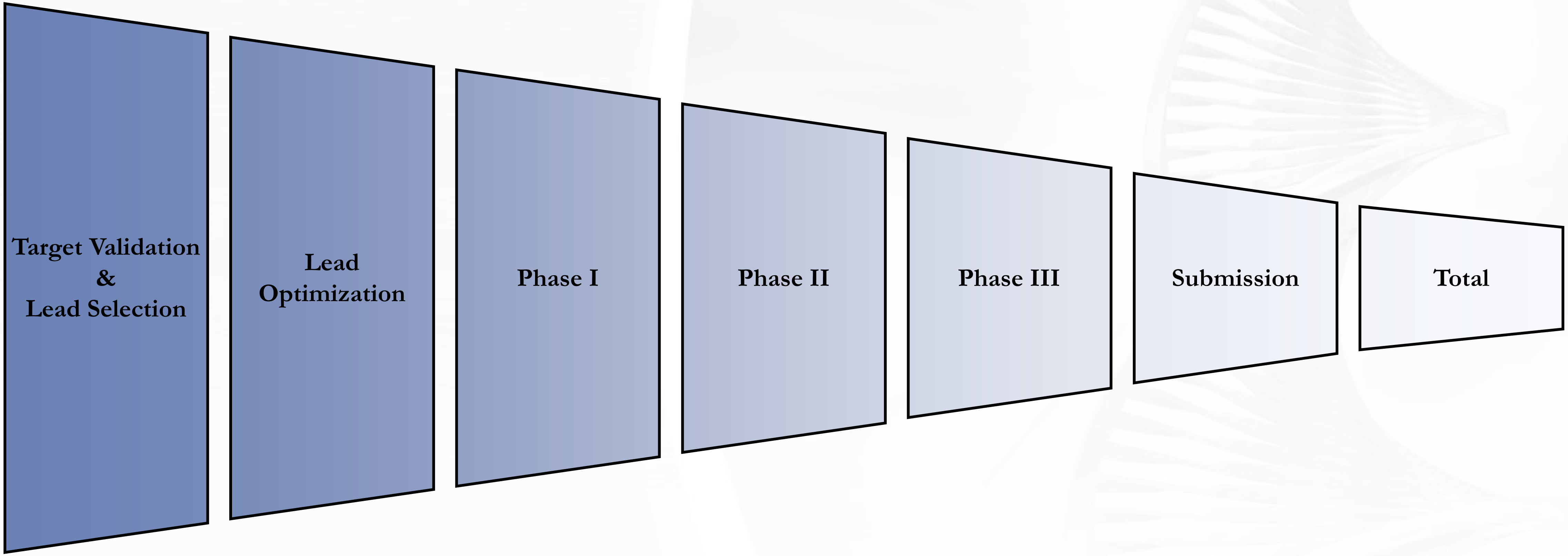
DTI

- 용어
  - ➢ Properties : 질병 치료를 위해 Compound or Lead 에서 원하는 모든 특성(뛰어난 효과, 낮은 부작용, 낮은 독성)
  - ➢ Drug : Properties가 완전히 최적화된 Compound
  - ➢ Interaction : Target과 Drug 사이의 상호 작용
  - ➢ DTI : Interaction 예측을 통한 **신약후보물질** 도출
  - ➢ DTA : Binding Affinity를 통해 interaction을 예측



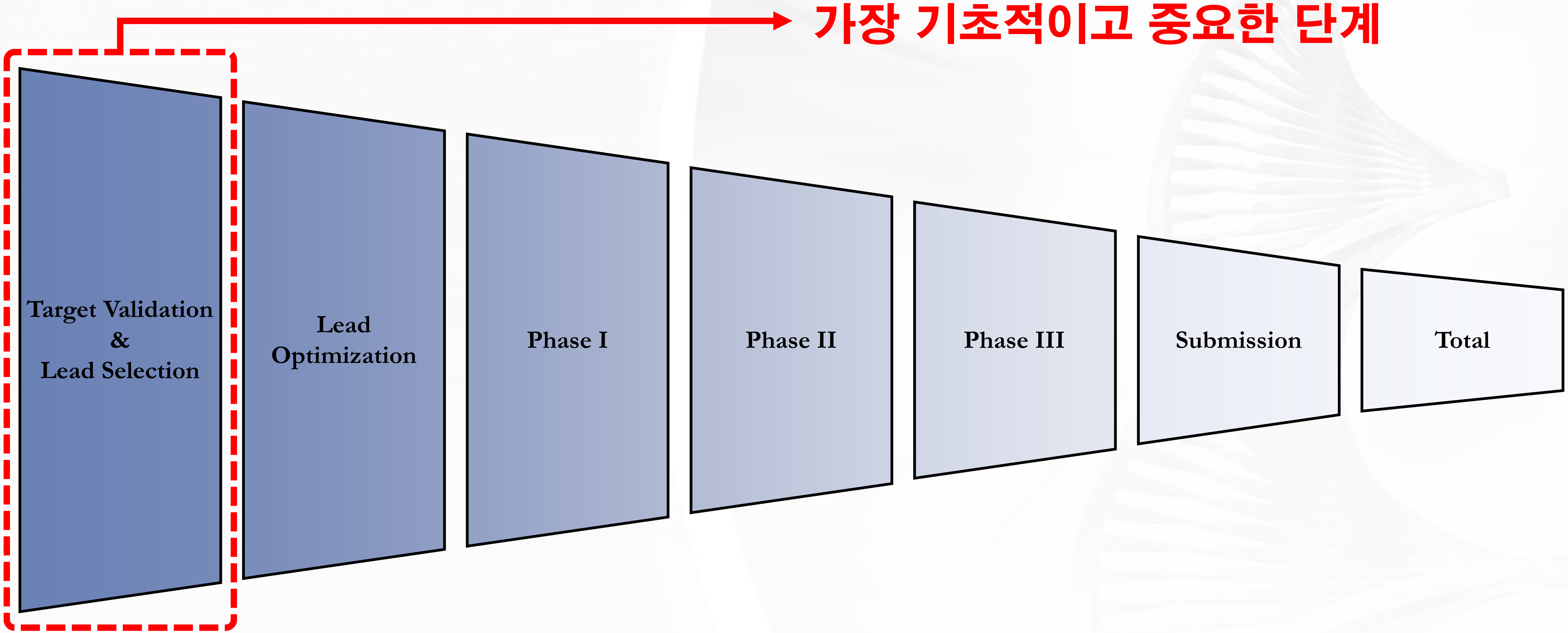
DTI

- 개요


Target Validation
&
Lead Selection
Lead
Optimization
Phase I
Phase II
Phase III
Submission
Total

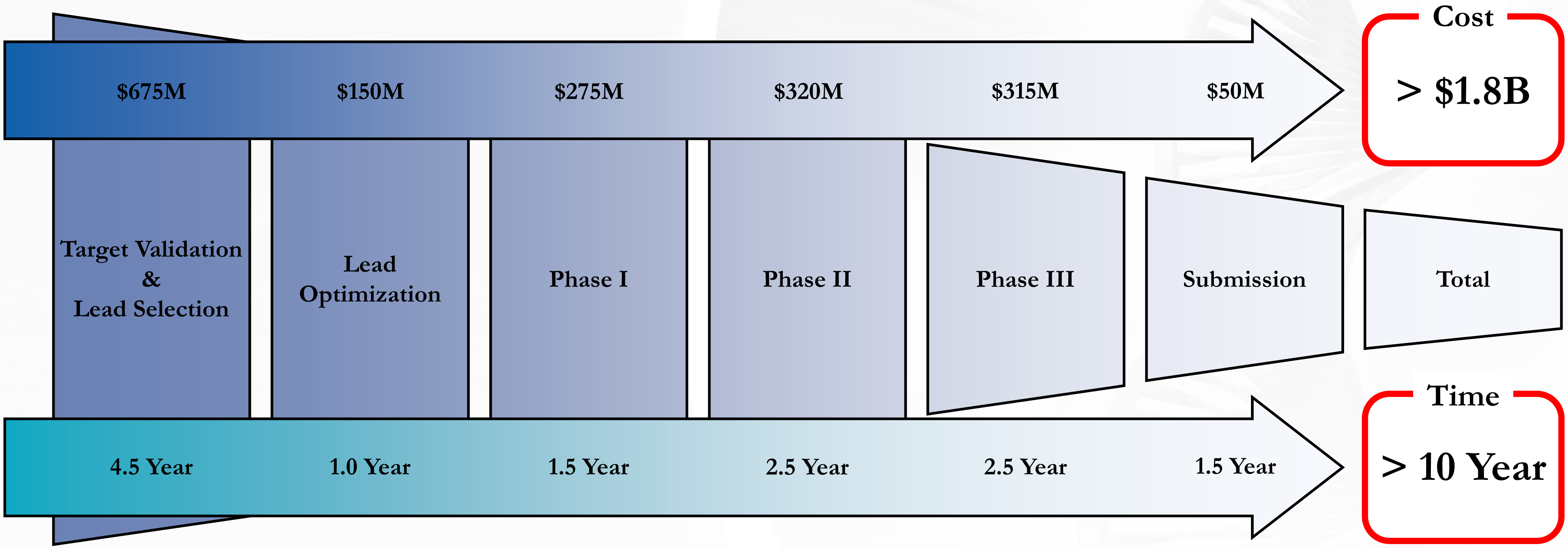
DTI

- 개요


가장 기초적이고 중요한 단계
Target Validation & Lead Selection
Lead Optimization
Phase I
Phase II
Phase III
Submission
Total

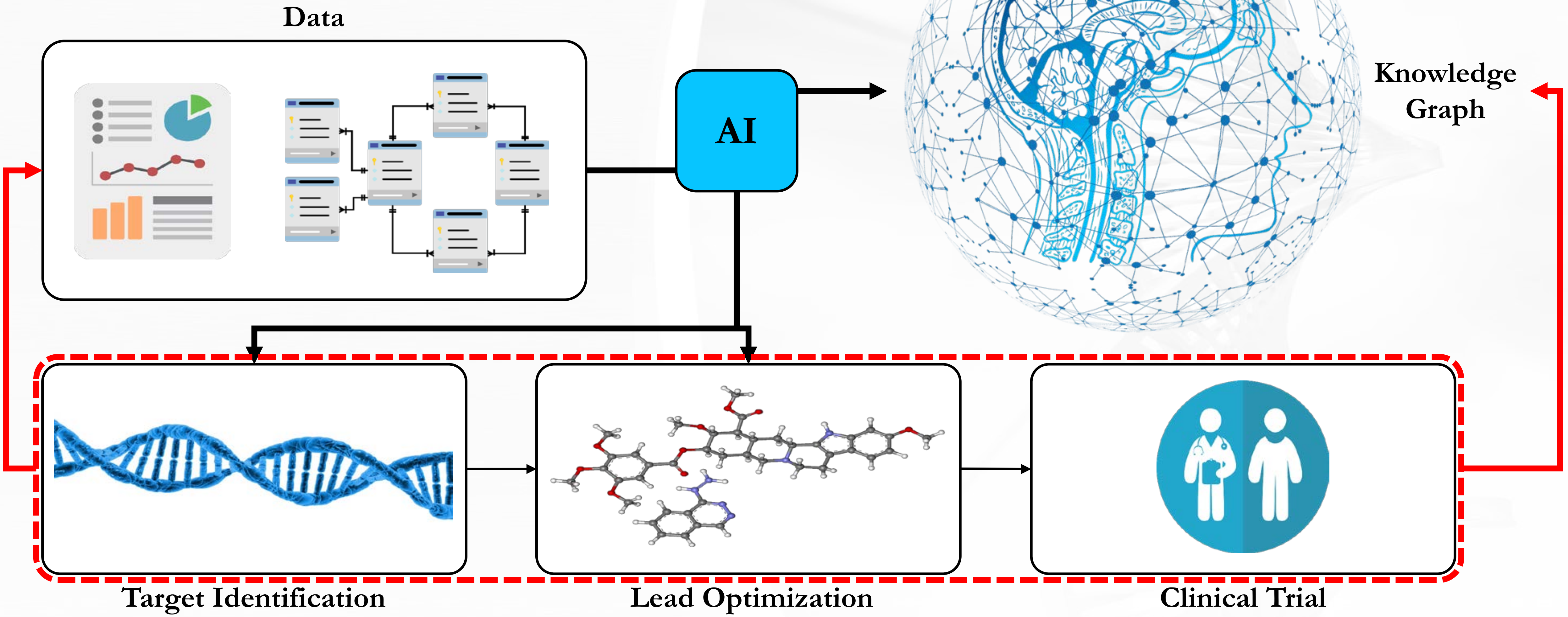
DTI

- 한계


$675M
$150M
$275M
$320M
$315M
$50M
Cost
> $1.8B
Target Validation & Lead Selection
Lead Optimization
Phase I
Phase II
Phase III
Submission
Total
4.5 Year
1.0 Year
1.5 Year
2.5 Year
2.5 Year
1.5 Year
Time
> 10 Year

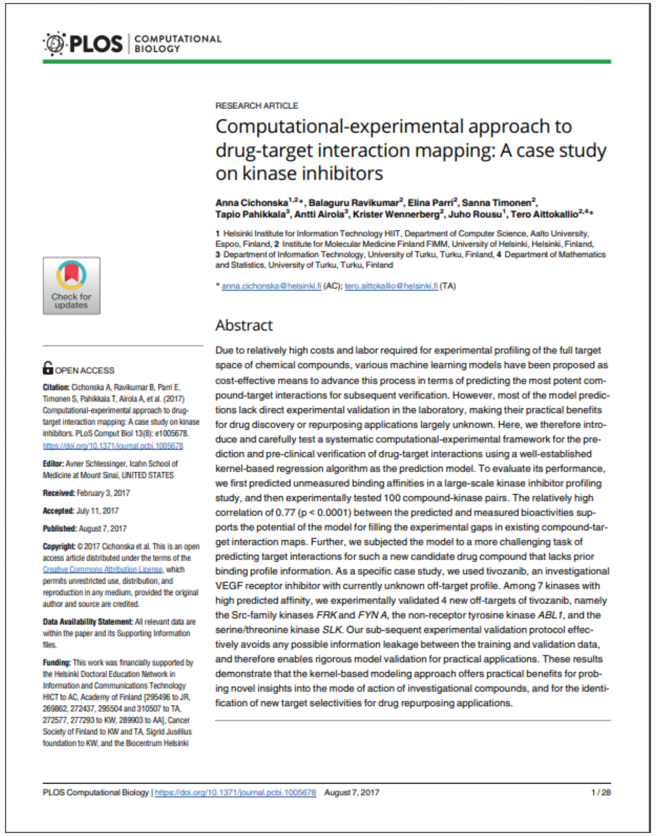
DTI

- DTI의 개선


Data
AI
Knowledge
Graph
Target Identification
Lead Optimization
Clinical Trial

DTI

- 기존 연구


PLOS | COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Computational-experimental approach to drug-target interaction mapping: A case study on kinase inhibitors

Anna Cichonska[1,2]*, Balaguru Ravikumar[2], Elina Parri[2], Sanna Timonen[2], Tapio Pahikkala[3], Antti Airola[3], Krister Wennerberg[2], Juho Rousu[1], Tero Aittokallio[2,4]*

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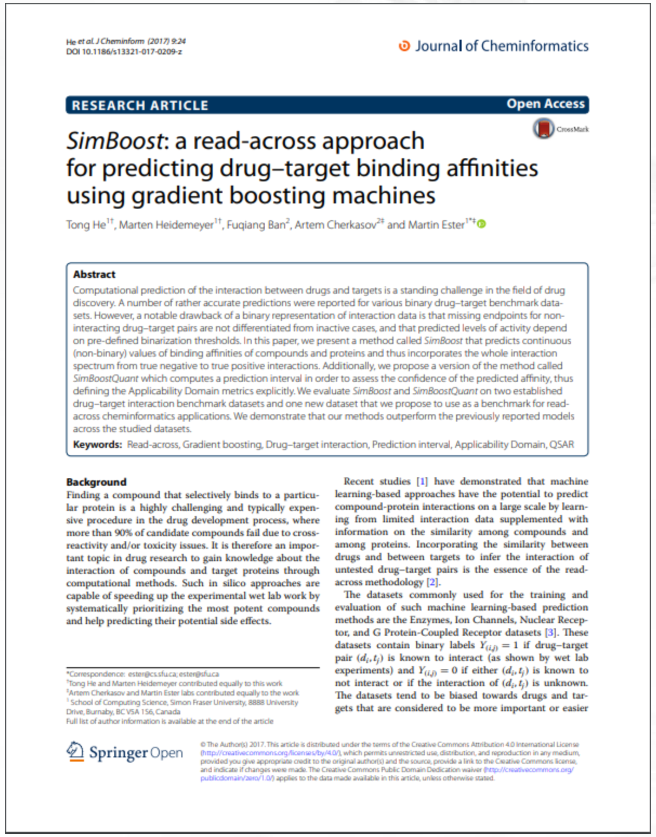
Abstract

Due to relatively high costs and labor required for experimental profiling of the full target space of chemical compounds, various machine learning models have been proposed as cost-effective means to advance this process in terms of predicting the most potent compound-target interactions for subsequent verification. However, most of the model predictions lack direct experimental validation in the laboratory, making their practical benefits for drug discovery or repurposing applications largely unknown. Here, we therefore introduce and carefully test a systematic computational-experimental framework for the prediction and pre-clinical verification of drug-target interactions using a well-established kernel-based regression algorithm as the prediction model. To evaluate its performance, we first predicted unmeasured binding affinities in a large-scale kinase inhibitor profiling study, and then experimentally tested 100 compound-kinase pairs. The relatively high correlation of 0.77 ($p < 0.0001$) between the predicted and measured bioactivities supports the potential of the model for filling the experimental gaps in existing compound-target interaction maps. Further, we subjected the model to a more challenging task of predicting target interactions for such a new candidate drug compound that lacks prior binding profile information. As a specific case study, we used tivozanib, an investigational VEGF receptor inhibitor with currently unknown off-target profile. Among 7 kinases with high predicted affinity, we experimentally validated 4 new off-targets of tivozanib, namely the Src-family kinases *FRK* and *FYN A*, the non-receptor tyrosine kinase *ABL1*, and the serine/threonine kinase *SLK*. Our sub-sequent experimental validation protocol effectively avoids any possible information leakage between the training and validation data, and therefore enables rigorous model validation for practical applications. These results demonstrate that the kernel-based modeling approach offers practical benefits for probing novel insights into the mode of action of investigational compounds, and for the identification of new target selectivities for drug repurposing applications.

KronRLS


He *et al. J Cheminform (2017) 9:24*
DOI 10.1186/s13321-017-0209-z

Journal of Cheminformatics

RESEARCH ARTICLE Open Access

CrossMark

SimBoost: a read-across approach for predicting drug–target binding affinities using gradient boosting machines

Tong He[1†], Marten Heidemeyer[1†], Fuqiang Ban[2], Artem Cherkasov[2‡] and Martin Ester[1*‡]

Abstract

Computational prediction of the interaction between drugs and targets is a standing challenge in the field of drug discovery. A number of rather accurate predictions were reported for various binary drug–target benchmark datasets. However, a notable drawback of a binary representation of interaction data is that missing endpoints for non-interacting drug–target pairs are not differentiated from inactive cases, and that predicted levels of activity depend on pre-defined binarization thresholds. In this paper, we present a method called *SimBoost* that predicts continuous (non-binary) values of binding affinities of compounds and proteins and thus incorporates the whole interaction spectrum from true negative to true positive interactions. Additionally, we propose a version of the method called *SimBoostQuant* which computes a prediction interval in order to assess the confidence of the predicted affinity, thus defining the Applicability Domain metrics explicitly. We evaluate *SimBoost* and *SimBoostQuant* on two established drug–target interaction benchmark datasets and one new dataset that we propose to use as a benchmark for read-across cheminformatics applications. We demonstrate that our methods outperform the previously reported models across the studied datasets.

Keywords: Read-across, Gradient boosting, Drug–target interaction, Prediction interval, Applicability Domain, QSAR

Background

Finding a compound that selectively binds to a particular protein is a highly challenging and typically expensive procedure in the drug development process, where more than 90% of candidate compounds fail due to cross-reactivity and/or toxicity issues. It is therefore an important topic in drug research to gain knowledge about the interaction of compounds and target proteins through computational methods. Such in silico approaches are capable of speeding up the experimental wet lab work by systematically prioritizing the most potent compounds and help predicting their potential side effects.

Recent studies [1] have demonstrated that machine learning-based approaches have the potential to predict compound-protein interactions on a large scale by learning from limited interaction data supplemented with information on the similarity among compounds and among proteins. Incorporating the similarity between drugs and between targets to infer the interaction of untested drug–target pairs is the essence of the read-across methodology [2].

The datasets commonly used for the training and evaluation of such machine learning-based prediction methods are the Enzymes, Ion Channels, Nuclear Receptor, and G Protein-Coupled Receptor datasets [3]. These datasets contain binary labels $Y_{(i,j)} = 1$ if drug–target pair (d_i, t_j) is known to interact (as shown by wet lab experiments) and $Y_{(i,j)} = 0$ if either (d_i, t_j) is known to not interact or if the interaction of (d_i, t_j) is unknown. The datasets tend to be biased towards drugs and targets that are considered to be more important or easier

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SimBoost

KAICD
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Korea AI Center for Drug Discovery and Development

DTI

- 최근 연구

DeepDTA

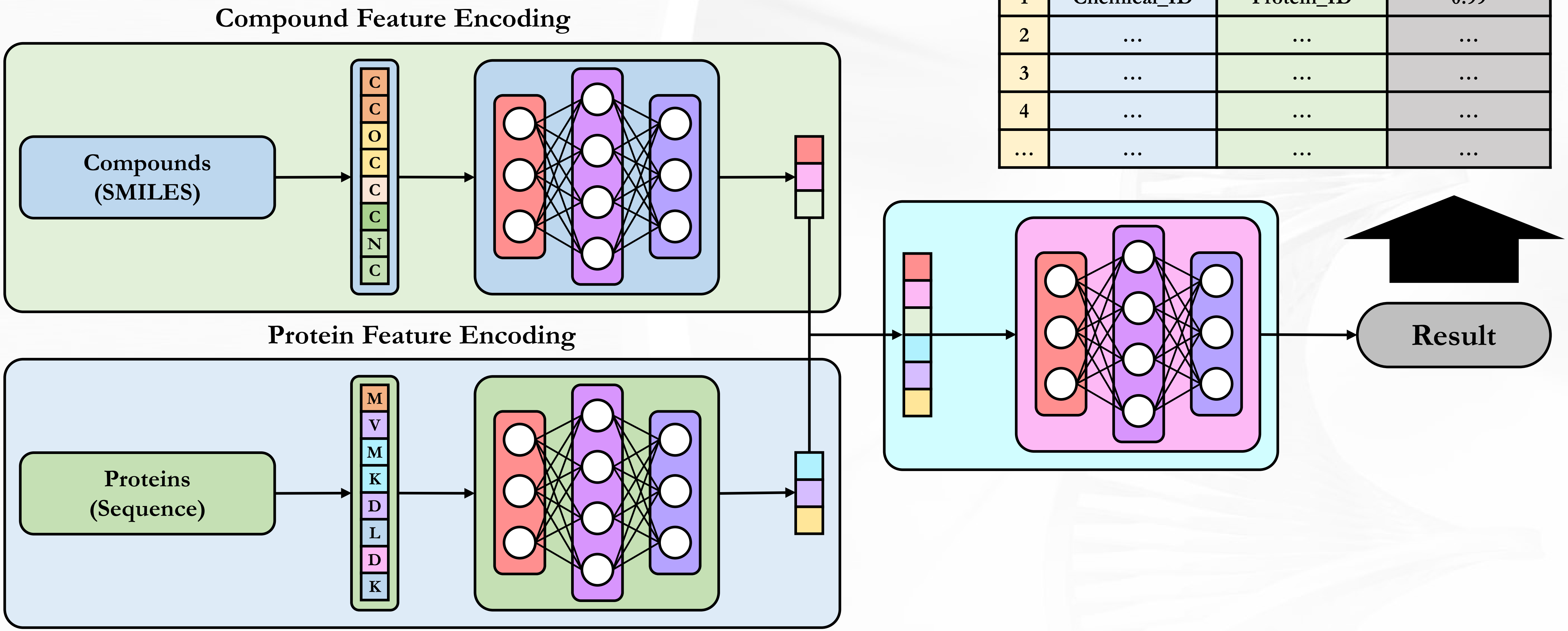
WideDTA

GANsDTA

DTI

- 프로세스(DeepDTA)

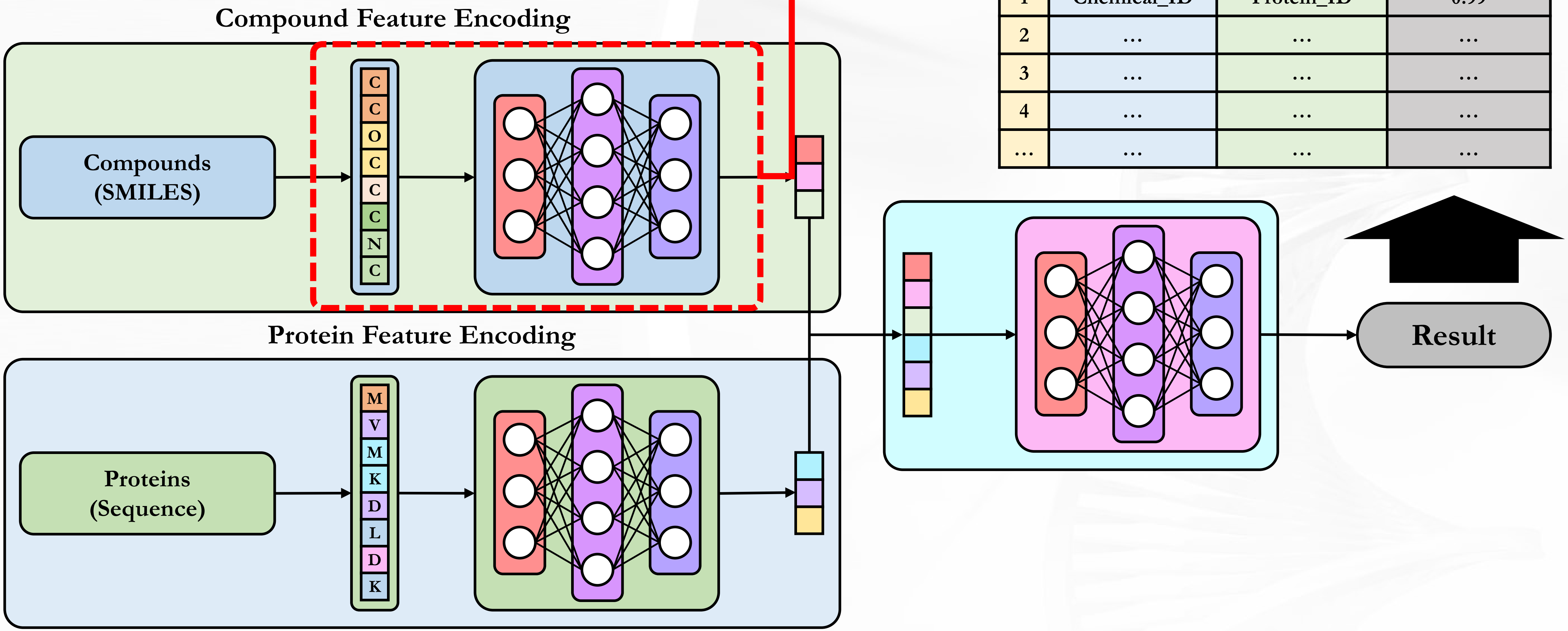
#	Compound	Protein	Prediction
1	Chemical_ID	Protein_ID	0.99
2	…	…	…
3	…	…	…
4	…	…	…
…	…	…	…



DTI

다양한 방법이 존재!

#	Compound	Protein	Prediction
1	Chemical_ID	Protein_ID	0.99
2	…	…	…
3	…	…	…
4	…	…	…
…	…	…	…



DTI

- **Proposed Model - GraphDTA**

GraphDTA: prediction of drug–target binding affinity using graph convolutional networks

Thin Nguyen[1*], Hang Le[2], Svetha Venkatesh[1]
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Abstract

While the development of new drugs is costly, time consuming, and often accompanied with safety issues, drug repurposing, where old drugs with established safety are used for medical conditions other than originally developed, is an attractive alternative. Then, how the old drugs work on new targets becomes a crucial part of drug repurposing and gains much of interest. Several statistical and machine learning models have been proposed to estimate drug–target binding affinity and deep learning approaches have been shown to be among state-of-the-art methods. However, drugs and targets in these models were commonly represented in 1D strings, regardless the fact that molecules are by nature formed by the chemical bonding of atoms. In this work, we propose **GraphDTA** to capture the structural information of drugs, possibly enhancing the predictive power of the affinity. In particular, unlike competing methods, drugs are represented as graphs and graph convolutional networks are used to learn drug–target binding affinity. We trial our method on two benchmark drug–target binding affinity datasets and compare the performance with state-of-the-art models in the field. The results show that our proposed method can not only predict the affinity better than non-deep learning models, but also outperform competing deep learning approaches. This demonstrates the practical advantages of graph-based representation for molecules in providing accurate prediction of drug–target binding affinity. The application may also include any recommendation systems where either or both of the user- and product-like sides can be represented in graphs.

Availability and implementation The proposed models are implemented in Python. Related data, pre-trained models, and source code are publicly available at https://github.com/thinng/GraphDTA.

1 Introduction

It costs 2.6 billion US dollars to develop a *de novo* drug [22] and takes about 10–17 years for the drug to be accepted/rejected by US FDA [1, 29]. Repurposing/repositioning a drug – identifying new use for an existing approved drug [33] – would reduce the time

1

➢ 입력 : 그래프 형식으로 나타낸 화학 화합물(Drug) 정보

➢ 입력 : 시퀀스 형태의 단백질(Target) 정보

➢ 출력 : 화학 화합물과 단백질 사이의 결합 친화도 예측 점수

➢ 기존 모델보다 더 뛰어난 성능을 보임

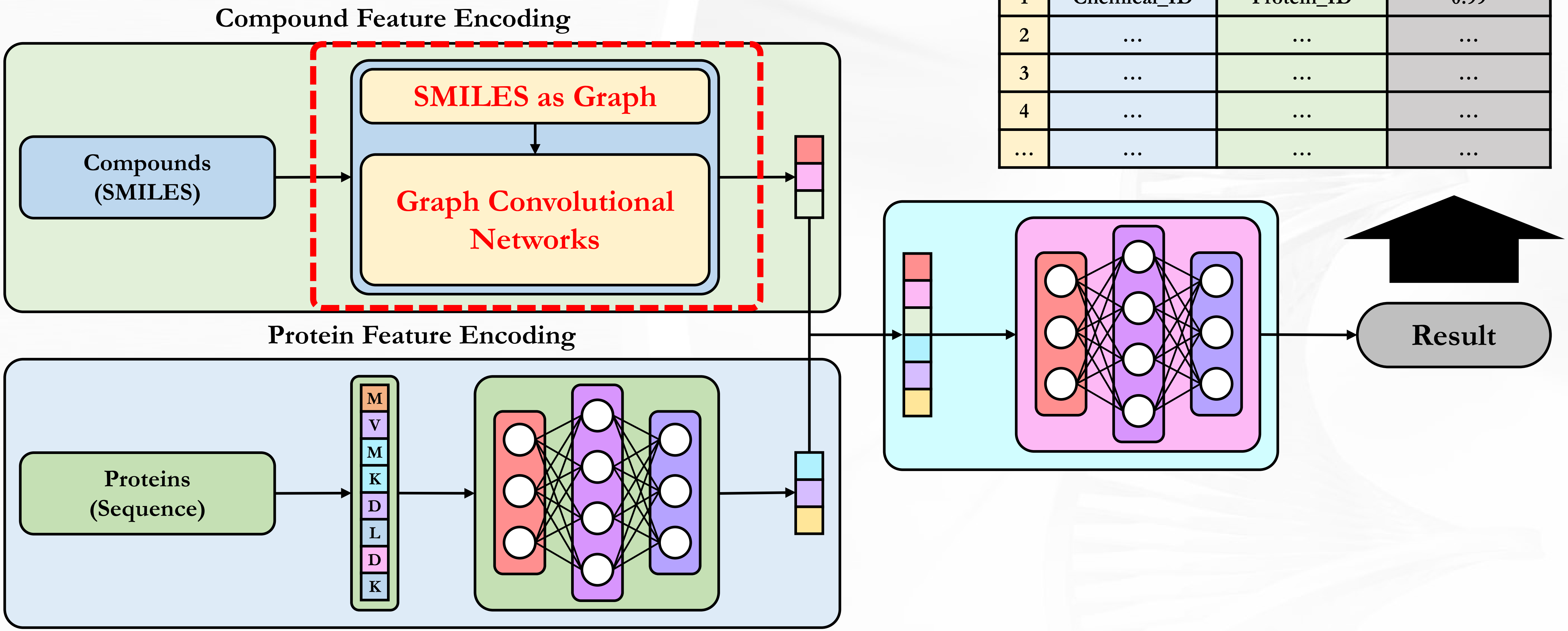
Method	Protein rep.	Compound rep.	CI	MSE
Baseline models				
DeepDTA	Smith-Waterman	Pubchem-Sim	0.790	0.608
DeepDTA	Smith-Waterman	1D	*0.886*	0.420
DeepDTA	1D	Pubchem-Sim	0.835	0.419
KronRLS	Smith-Waterman	Pubchem-Sim	0.871	0.379
SimBoost	Smith-Waterman	Pubchem-Sim	0.872	0.282
DeepDTA	1D	1D	0.878	*0.261*
WideDTA	1D + PDM	1D + LMCS	*0.886*	0.262
Proposed model - **GraphDTA**				
GCN [17]	1D	Graph	0.880	**0.254**
GAT_GCN	1D	Graph	0.881	**0.245**
GAT [37]	1D	Graph	**0.892**	**0.232**
GIN [40]	1D	Graph	**0.893**	**0.229**

HOW?

DTI

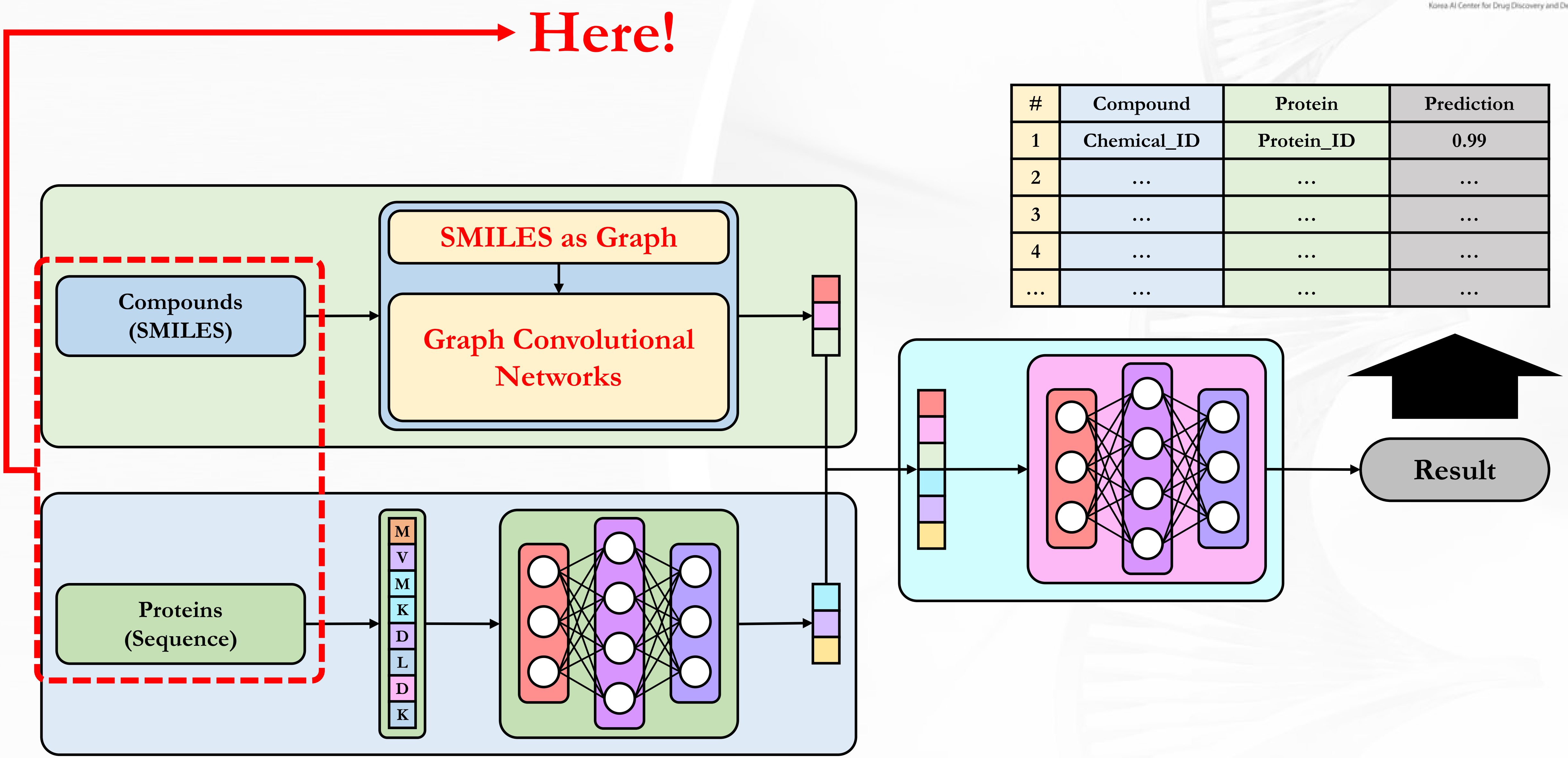
- **Proposed Model - GraphDTA**

#	Compound	Protein	Prediction
1	Chemical_ID	Protein_ID	0.99
2	…	…	…
3	…	…	…
4	…	…	…
…	…	…	…



Datasets

#	Compound	Protein	Prediction
1	Chemical_ID	Protein_ID	0.99
2	…	…	…
3	…	…	…
4	…	…	…
…	…	…	…



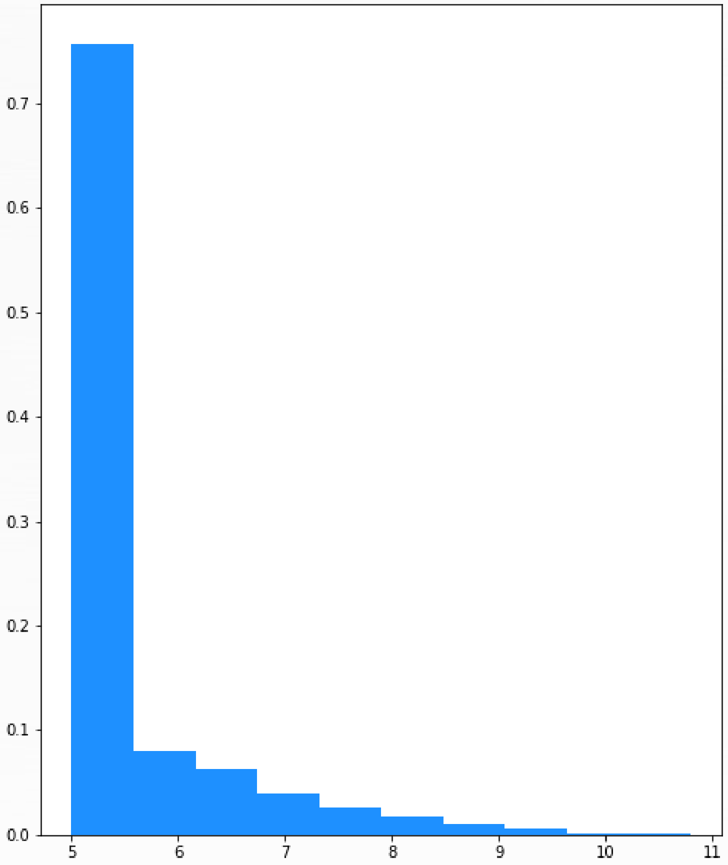
Datasets

- Davis
  - ➢ 결합 친화도 점수 : 평형 이온화 상수 K_D
- Kiba
  - ➢ 결합 친화도 점수 : KIBA score

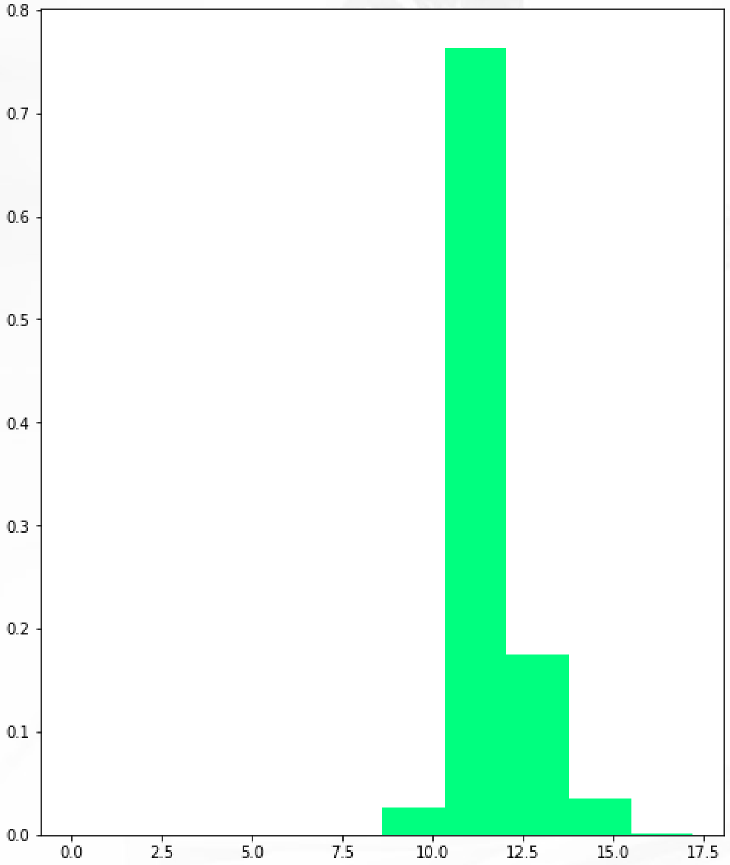
Dataset Name	Proteins	Compounds	Affinity value	Score
Davis	442	72	5.0 ~ 10.8	K_D
Kiba	229	2,116	0.0 ~ 17.2	KIBA

Datasets

- **Affinity Distribution**



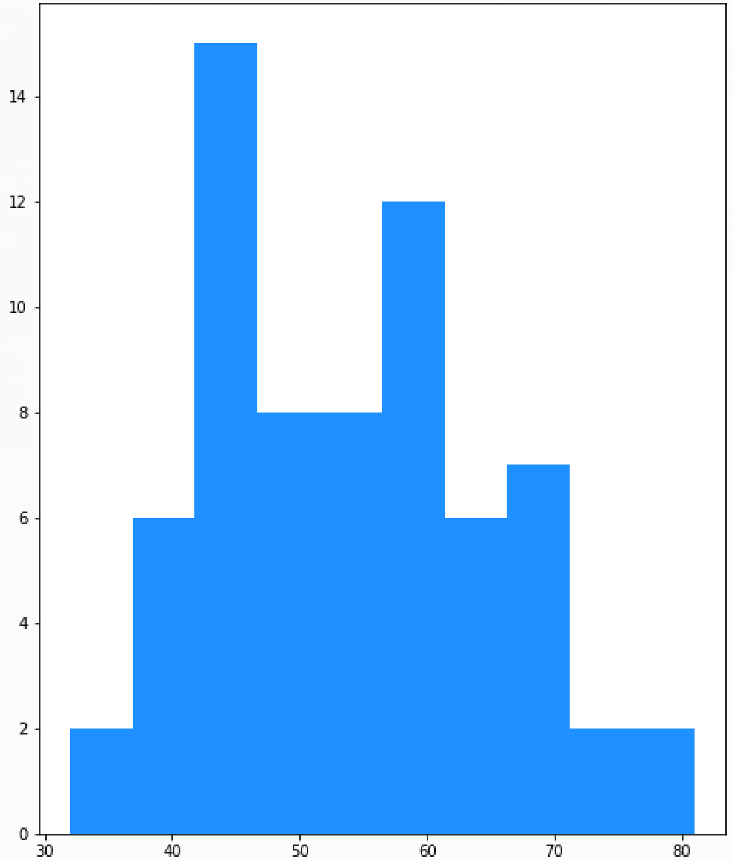
Davis Affinity Distribution



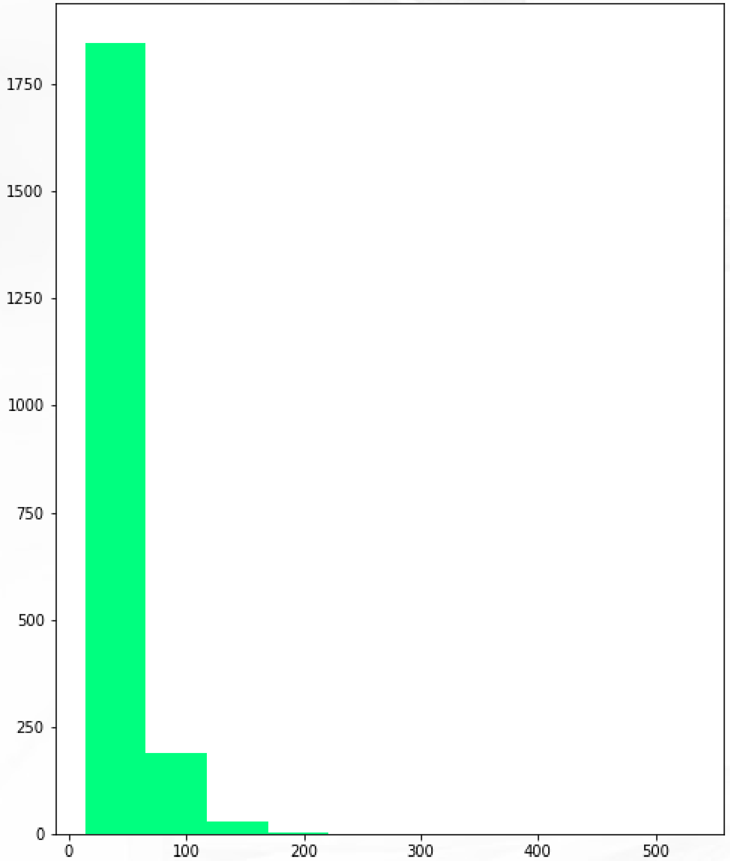
Kiba Affinity Distribution

Datasets

- **Length of SMILES Distribution**



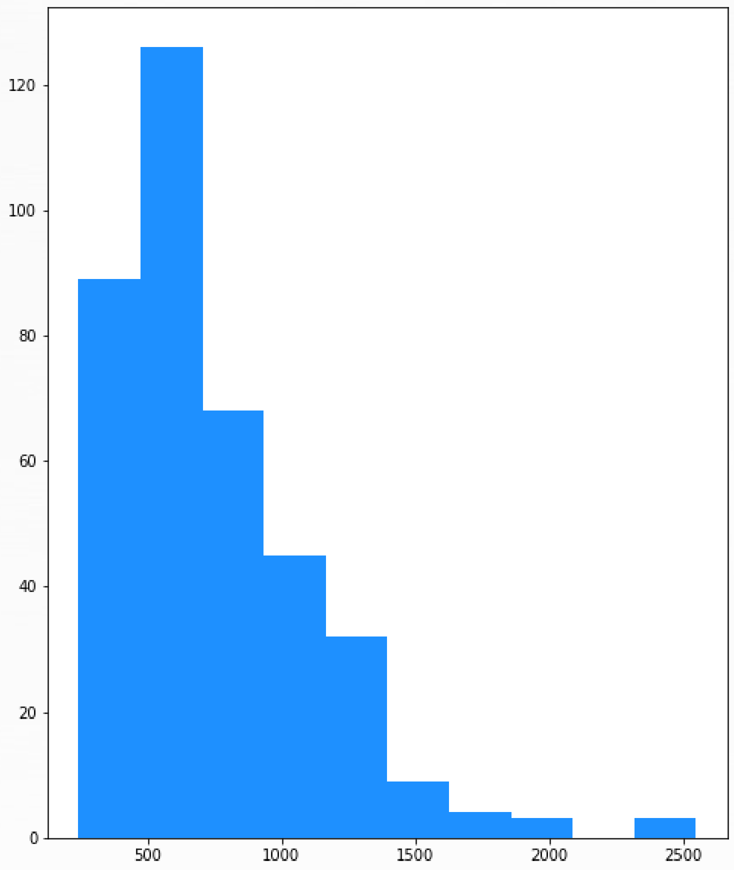
Davis Length of SMILES Distribution



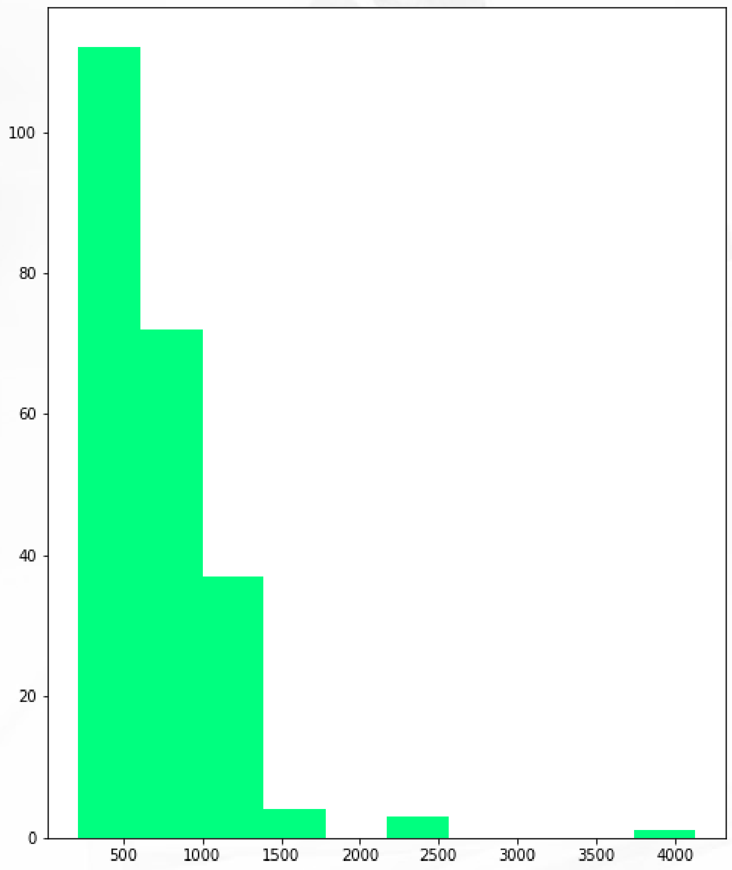
Kiba Length of SMILES Distribution

Datasets

- **Length of Protein Sequence Distribution**



Davis Length of Protein Sequence Distribution

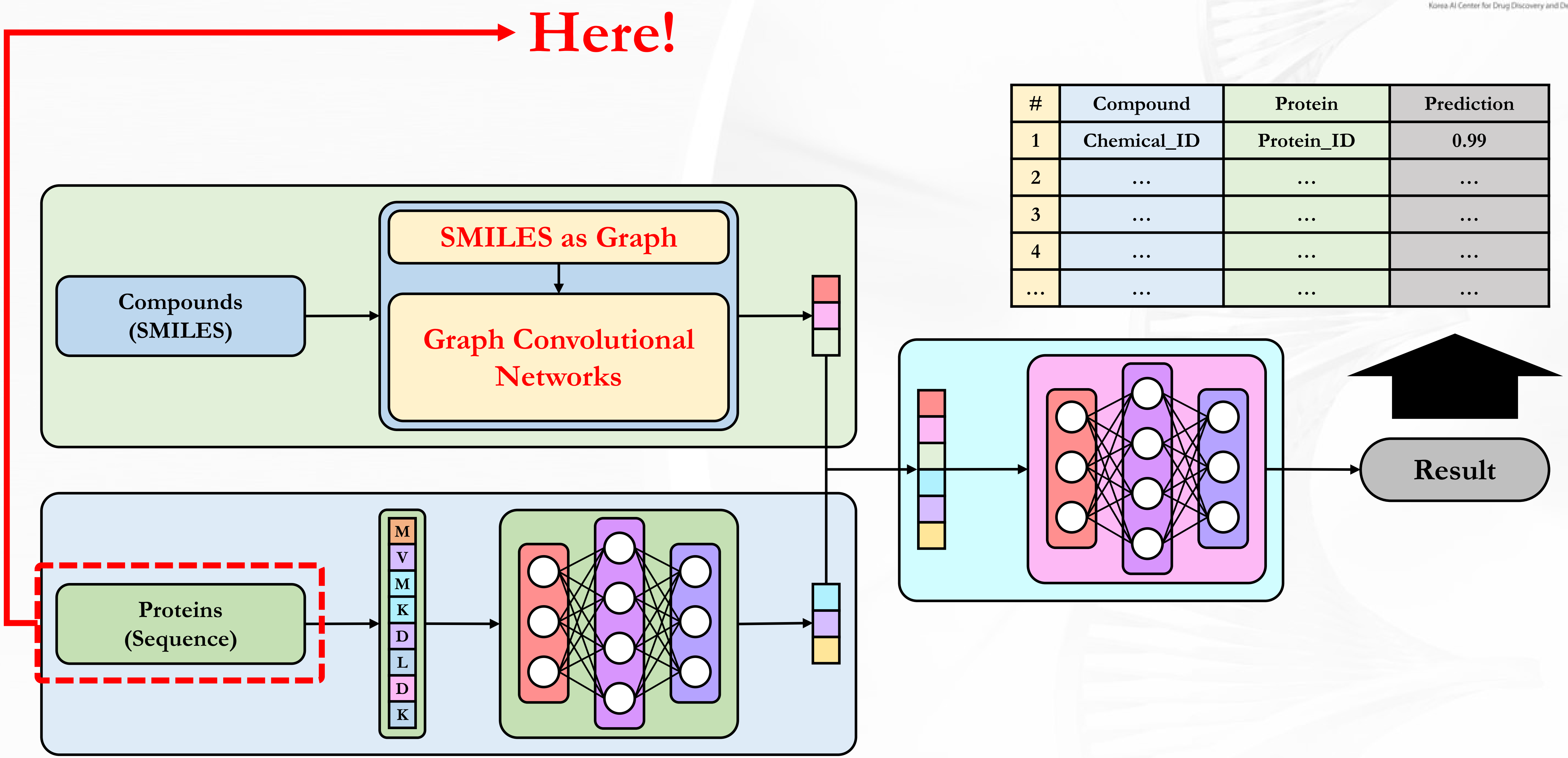


Kiba Length of Protein Sequence Distribution

Protein Representation

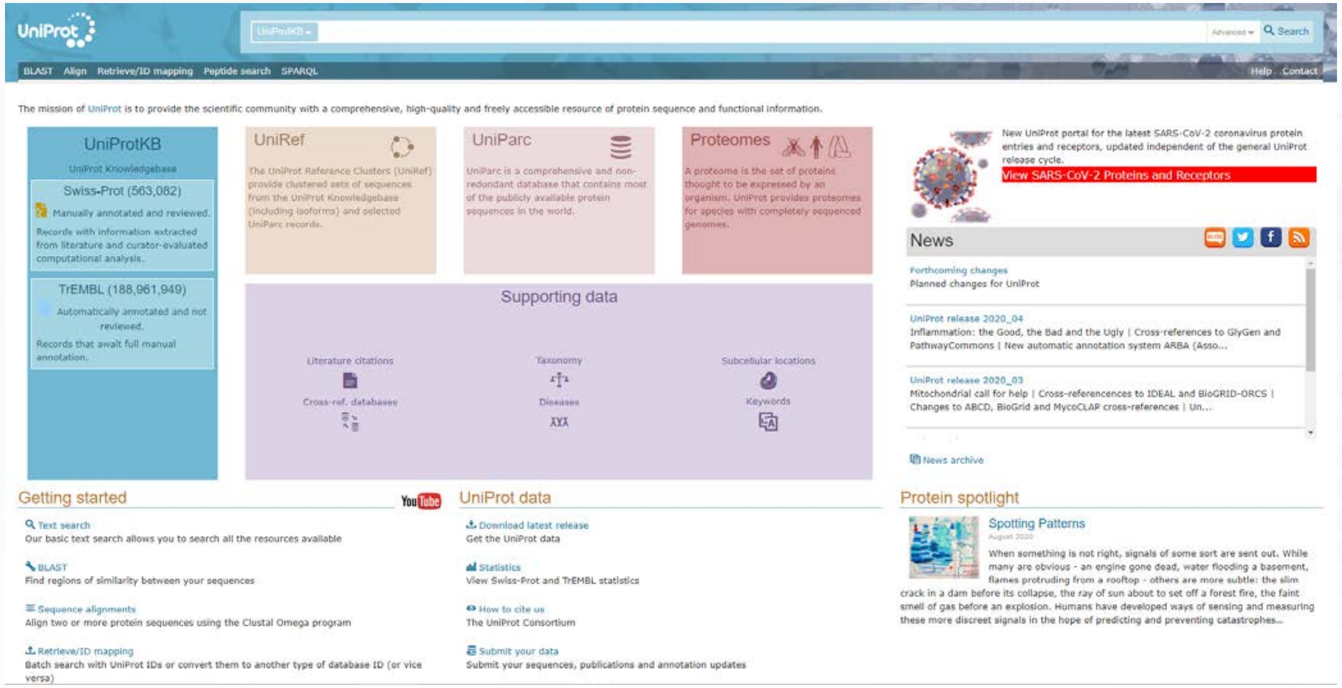
- UniProt -

#	Compound	Protein	Prediction
1	Chemical_ID	Protein_ID	0.99
2	…	…	…
3	…	…	…
4	…	…	…
…	…	…	…



Protein Representation

- UniProt
  - ➢ 단백질 서열 및 기능 정보에 대한 자유롭게 액세스 할 수 있는 데이터베이스
  - ➢ 'J'를 제외한 25개의 아미노산으로 단백질 염기 서열 표현



https://www.uniprot.org/

Protein Representation

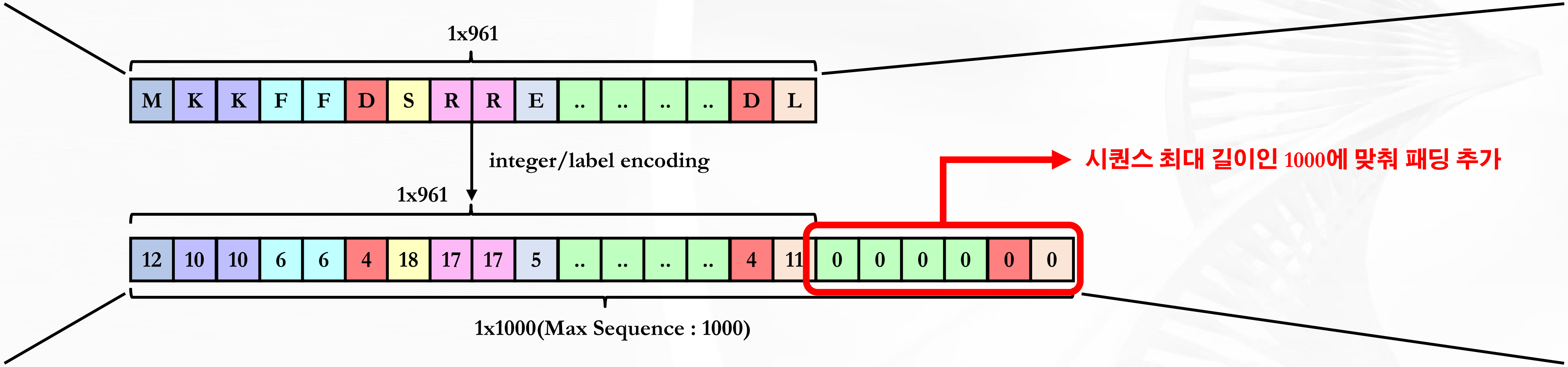
- 예시 - Real Data

Protein Representation

- **Proteins to Input Presentation(Integer/Label Encoding)**

AAK1 :

"MKKFFDSRREQGGSGLGSGSSGGGGSTSGLGSGYIGRVFGIGRQQVTVDEVLAEGGFAIVFLVRTSNGMKCALKRMFVNNEHDLQVCKREIQIMRDLSGHKNIVGYIDSSINNVSSGDVWEVLILMDFCRGGQVVNLMNQRLQTGFTENEVLQIFCDTCEAVARLHQCKTPIIHRDLKVENILLHDRGHYVLCDFGSATNK
FQNPQTEGVNAVEDEIKKYTTLSYRAPEMVNLYSGKIITTKADIWALGCLLYKLCYFTLPFGESQVAICDGNFTIPDNSRYSQDMHCLIRYMLEPDPDKRPDIYQVSYFSFKLLKKECPIPNVQNSPIPAKLPEPVKASEAAAKKTQPKARLTDPIPTTETSIAPRQRPKAGQTQPNPGILPIQPALTPRKRATVQPPPQAAGSSNQ
PGLLASVPQPKPQAPPSQPLPQTQAKQPQAPPTPQQTPSTQAQGLPAQAQATPQHQQQLFLKQQQQQQQPPPAQQQPAGTFYQQQQAQTQQFQAVHPATQKPAIAQFPVVSQGGSQQQLMQNFYQQQQQQQQQQQQQLATALHQQQLMTQQAALQQKPTMAAGQQPQPQPAAAPQPAPAQEPAIQAPVRQQPKV
QTTPPPAVQGQKVGSLTPPSSPKTQRAGHRRILSDVTHSAVFGVPASKSTQLLQAAAAEASLNKSKSATTTPSGSPRTSQQNVYNPSEGSTWNPFDDDNFSKLTAEELLNKDFAKLGEGKHPEKLGGSAESLIPGFQSTQGDAFATTSFSAGTAEKRKGGQTVDSGLPLLSVSDPFIPLQVPDAPEKLIEGLKSPDTSLLLPDLLPM
TDPFGSTSDAVIEKADVAVESLIPGLEPPVPQRLPSQTESVTSNRTDSLTGEDSLLDCSLLSNPTTDLLEEFAPTAISAPVHKAAEDSNLISGFDVPEGSDKVAEDEFDPIPVLITKNPQGGHSRNSSGSSESSLPNLARSLLLVDQLIDL"



[12. 10. 10. 6. 6. 4. 18. 17. 17. 5. 16. 7. 7. 18. 7. 11. 7. 18. 7. 18. 18. 7. 7. 7. 7. 18. 19. 18. 7. 11. 7. 18. 7. 24. 9. 7. 17. 21. 6. 7. 9. 7. 17. 16. 16. 21. 19. 21. 4. 5. 21. 11. 1. 5. 7. 7. 6. 1. 9. 21. 6. 11. 21. 17. 19. 18. 13. 7. 12. 10. 3. 1. 11. 10. 17. 12. 6. 21. 13. 13. 5. 8. 4. 11. 16. 21. 3. 10. 17. 5. 9. 16. 9. 12. 17. 4. 11. 18. 7. 8. 10. 13. 9. 21. 7. 24. 9. 4. 18. 18. 9. 13. 13. 21. 18.
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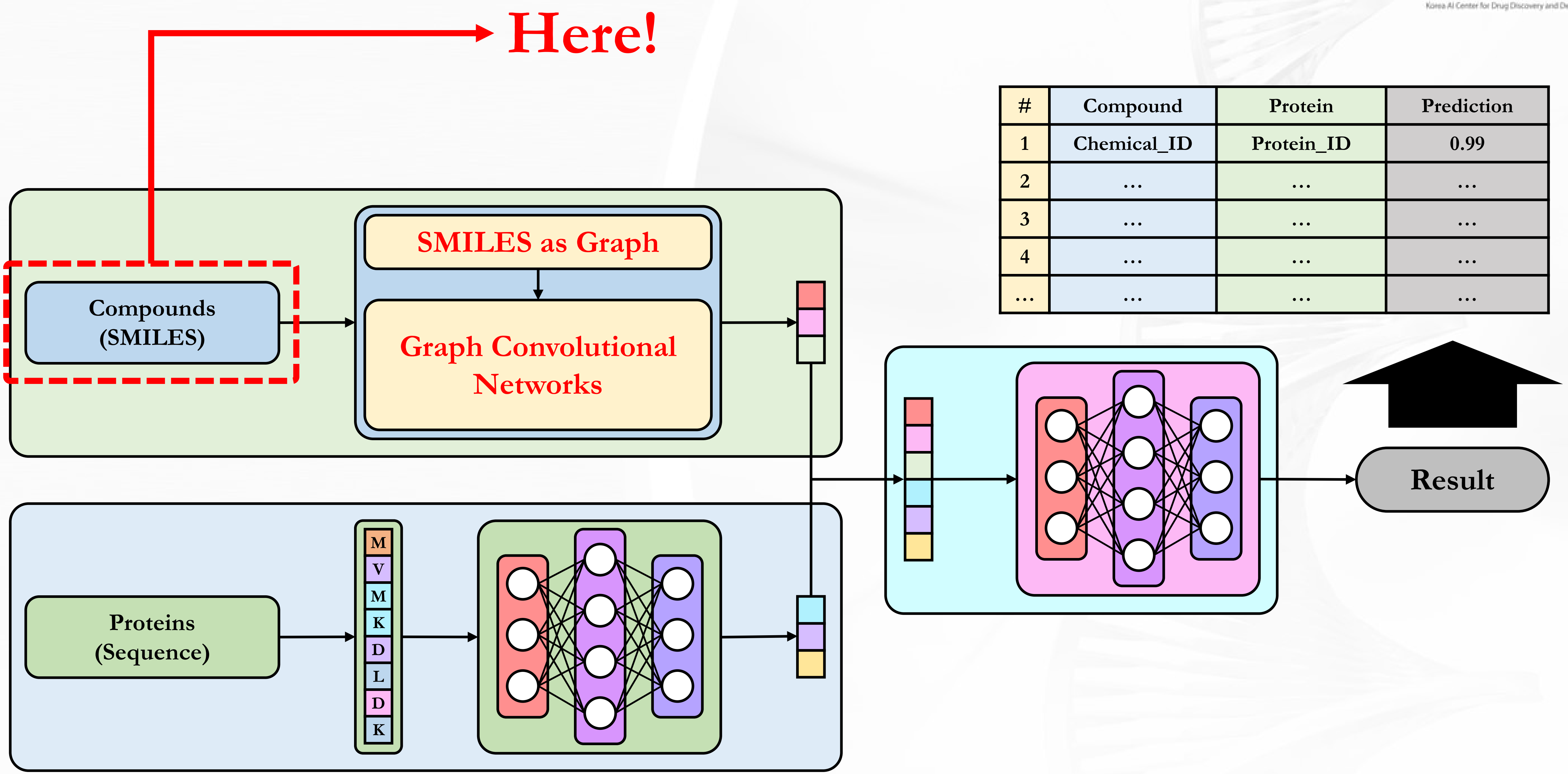
Molecule Representation

- SMILES -



#	Compound	Protein	Prediction
1	Chemical_ID	Protein_ID	0.99
2	…	…	…
3	…	…	…
4	…	…	…
…	…	…	…

KAICD 한국인공지능신약개발지원센터 Korea AI Center for Drug Discovery and Development

Molecule Representation

- 개요
  - 화학 물질의 구조를 표현하는 방법으로 문자열, 그래프 등 다양한 형태가 존재
  - 문자열로 표현하는 방법에서 대표적으로 WLN, ROSDAL, SMILES가 존재
  - Davis & Kiba Datasets에서는 SMILES를 통해 화학 물질을 표현

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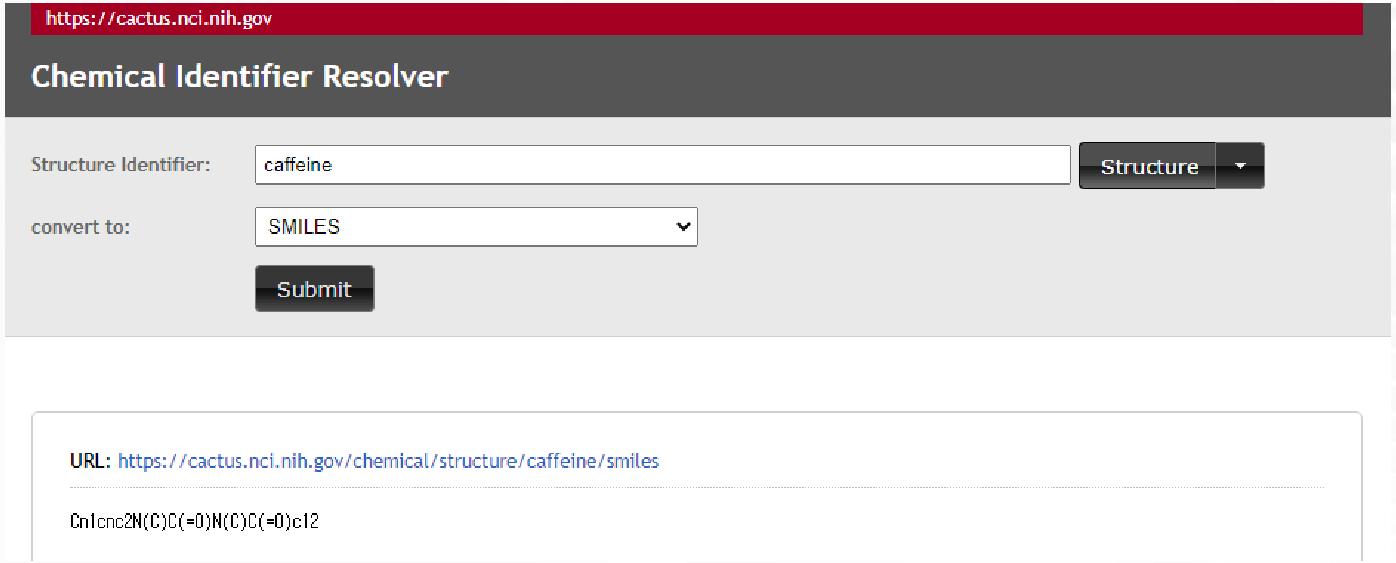
Korea AI Center for Drug Discovery and Development

Molecule Representation

- SMILES
  - Simplified Molecular Input Line Entry System의 약자
  - 화학물질의 구조를 문자열로 나타내는 방법
  - 구조를 문자열로 변환할 때, 6가지 규칙 적용

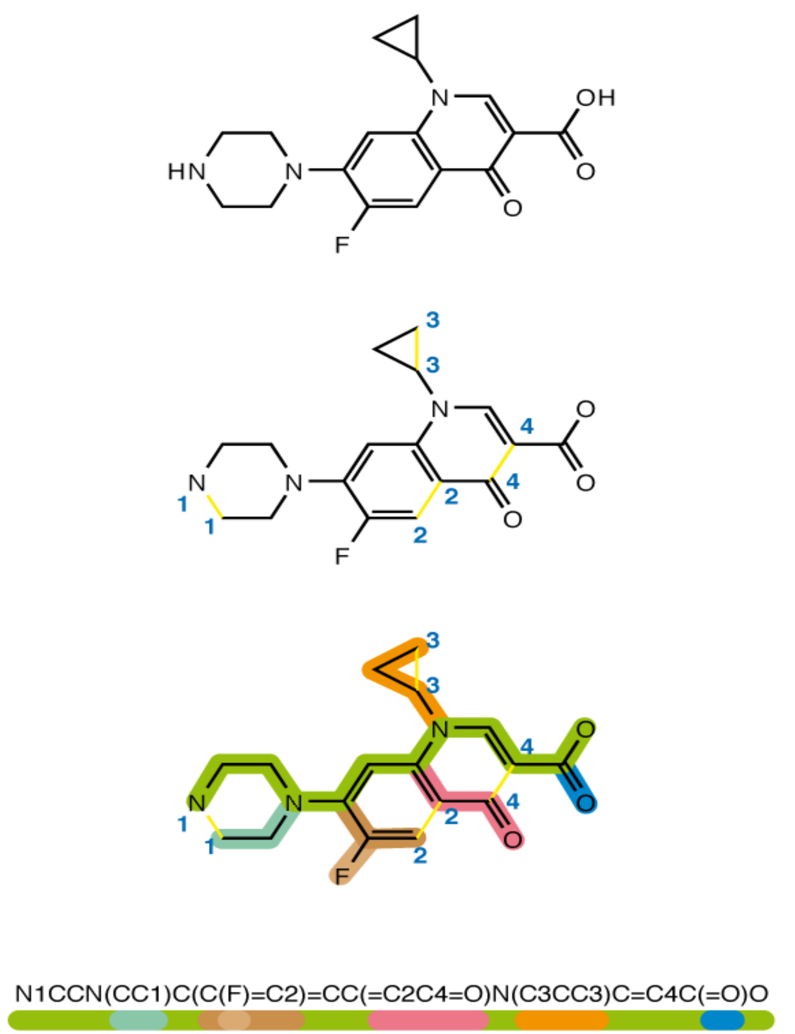


https://cactus.nci.nih.gov/chemical/structure

Molecule Representation

- **규칙**
  - ➢ 원자는 표준 원소 기호로 표기
  - ➢ 수소 원자는 가능한 모든 곳에 연결되어 있다고 가정, 표기 생략
  - ➢ 이웃한 원자는 인접해서 표기
  - ➢ 2중 결합은 '=', 3중 결합은 '#'으로 표기
  - ➢ 가지는 '()'로 표기
  - ➢ 고리는 고리를 생성하는 두 원자에 숫자를 표기

    (방향족 고리는 원자를 소문자로 표기)

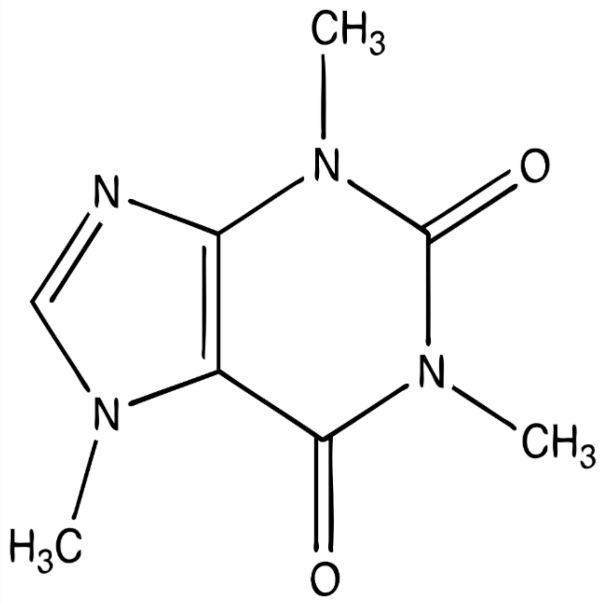


Molecule Representation

- **특성**
  - ➢ 원자(Atoms)
  - ➢ 결합(Bonds)
  - ➢ 고리(Rings)
  - ➢ 방향족성(Aromaticity)
  - ➢ 분기(Branching)
  - ➢ 입체배열(Stereochemistry)
  - ➢ 동위원소(Isotopes)

Molecule Representation

- 예시



Caffeine - $C_8H_{10}N_4O_2$

[Molecule Structure]

Cn1cnc2N(C)C(=O)N(C)C(=O)c12

[SMILES]

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Korea AI Center for Drug Discovery and Development

Molecule Representation

- 예시 - Real Data

Chemical_ID

SMILES_format

OC4CCOC4", "5287969": "CN1CCC(C(C1)O)C2=C(C=C(C3=C2OC(=CC3=O)C4=CC=CC=C4Cl)O)O", "6450551": "CNC(=O)C1=CC=CC=C1SC2=CC3=C(C=C2)C(=NN3)C=CC4=CC=CC=N4", "11364421": "CCC1C(=O)N(C2=CN=C(N=C2N1C3CCCC
NC4=C(C=C(C=C4)C(=O)NC5CCN(CC5)C)OC)C", "9926054": "CC1=CC2=C(C=C1)N=C(C3=NC=C(N23)C)NCCN.Cl", "16007391": "CCN(CCCOC1=CC2=C(C=C1)C(=NC=N2)NC3=NNC(=C3)CC(=O)NC4=CC(=CC=C4)F)CCO", "5328940":
"CN1CCN(CC1)CCCOC2=C(C=C3C(=C2)N=CC(=C3NC4=CC(=C(C=C4Cl)Cl)OC)C#N)OC", "11234052": "CC1=CC2=C(N1)C=CC(=C2F)OC3=NC=NN4C3=C(C(=C4)OCC(C)O)C", "11656518": "CN1C2=C(C=C(C=C2)OC3=CC(=NC=C3)C4=NC=C(N4
(F)(F)F)N=C1NC5=CC=C(C=C5)C(F)(F)F", "6918454": "C1CC1CONC(=O)C2=C(C(=C(C=C2)F)F)NC3=C(C=C(C=C3)I)Cl", "156414": "C=CC(=O)NC1=C(C=C2C(=C1)C(=NC=N2)NC3=CC(=C(C=C3)F)Cl)OCCCN4CCOCC4", "9933475":
"CC1=CC2=C(N1)C=CC(=C2F)OC3=NC=NC4=CC(=C(C=C43)OC)OCCCN5CCCC5", "11626560": "CC(C1=C(C=CC(=C1Cl)F)Cl)OC2=C(N=CC(=C2)C3=CN(N=C3)C4CCNCC4)N", "3062316": "CC1=C(C(=CC=C1)Cl)NC(=O)C2=CN=C(S2)NC3=NC(
(=C3)N4CCN(CC4)CCO)C", "156422": "CC1=CC=C(C=C1)N2C(=CC(=N2)C(C)(C)C)NC(=O)NC3=CC=C(C4=CC=CC=C43)OCCN5CCOCC5", "44150621": "CC(C(=O)O)O.CN1CCN(CC1)C2=CC3=C(C=C2)NC(=C4C(=C5C(=NC4=O)C=CC=C5F)N)N3
.O", "176167": "CN1C=C(C2=CC=CC=C21)C3=C(C(=O)NC3=O)C4=CN(C5=CC=CC=C54)C6CCN(CC6)CC7=CC=CC=N7", "176870": "COCCOC1=C(C=C2C(=C1)C(=NC=N2)NC3=CC=CC(=C3)C#C)OCCOC", "42642645": "COC1=CC2=C
(C=CN=C2C=C1OCCCN3CCOCC3)OC4=C(C=C(C=C4)NC(=O)C5(CC5)C(=O)NC6=CC=C(C=C6)F)F", "11717001": "C1CC(=NO)C2=C1C=C(C=C2)C3=CN(N=C3C4=CC=NC=C4)CCO", "16725726": "CCN1C2=C(C(=NC=C2OCC3CCCNC3)C#CC(C)(C)O
N=C1C4=NON=C4N", "11617559": "COC1=CC=C(C=C1)COC2=C(C=C(C=C2)CC3=CN=C(N=C3N)N)OC", "123631": "COC1=C(C=C2C(=C1)N=CN=C2NC3=CC(=C(C=C3)F)Cl)OCCCN4CCOCC4", "5291": "CC1=C(C=C(C=C1)NC(=O)C2=CC=C(C=C
CN3CCN(CC3)C)NC4=NC=CC(=N4)C5=CN=CC=C5", "4908365": "CN1CCN(CC1)C(=O)C2=CC3=C(N2)C=CC(=C3)Cl", "11427553": "C1CN(CCN1)C(=O)C2=CC=C(C=C2)C=CC3=NNC4=CC=CC=C43", "208908": "CS(=O)(=O)CCNCC1=CC=C(O1
C2=CC3=C(C=C2)N=CN=C3NC4=CC(=C(C=C4)OCC5=CC(=CC=C5)F)Cl", "126565": "CC12C(CC(O1)N3C4=CC=CC=C4C5=C6C(=C7C8=CC=CC=C8N2C7=C53)CNC6=O)(CO)O", "11485656": "CC1=CC(=C(C=C1)F)NC(=O)NC2=CC=C(C=C2)C3=C4
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"CC1=C(C=C(C=C1)NC(=O)C2=CC=C(C=C2)CN3CCN(CC3)C)NC4=NC(=CS4)C5=CN=CC=C5", "51004351": "CC12C(C(CC(O1)N3C4=CC=CC=C4C5=C6C(=C7C8=CC=CC=C8N2C7=C53)CNC6=O)N(C)C(=O)C9=CC=CC=C9)OC", "11667893":
"CC1(CNC2=C1C=CC(=C2)NC(=O)C3=C(N=CC=C3)NCC4=CC=NC=C4)C", "9915743": "CCOC1=C(C=C2C(=C1)N=CC(=C2NC3=CC(=C(C=C3)OCC4=CC=CC=N4)Cl)C#N)NC(=O)C=CCN(C)C", "644241": "CC1=C(C=C(C=C1)C(=O)NC2=CC(=CC(=C
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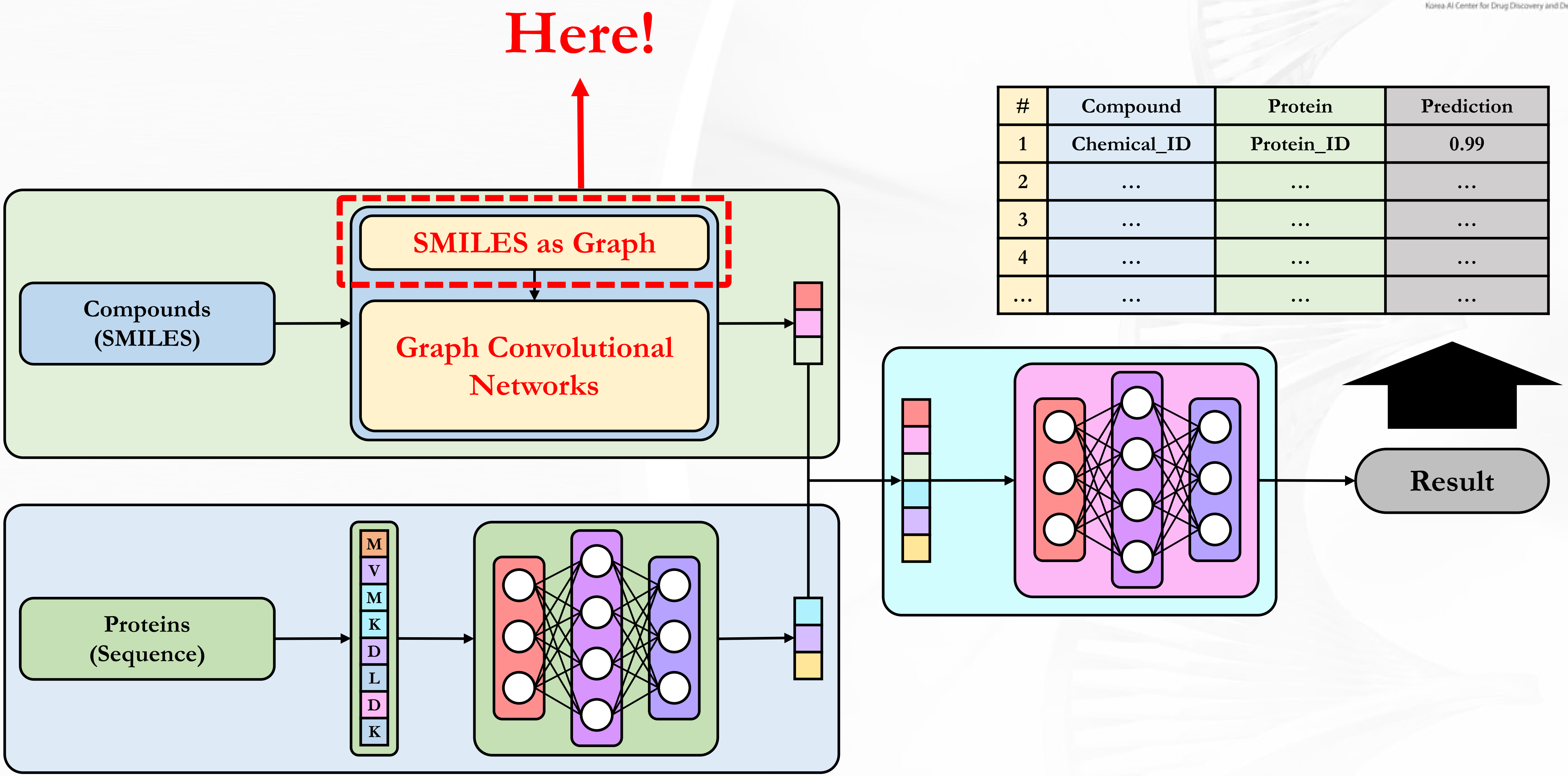
CC6=C(C=CC=C6Cl)Cl)NC4=O", "9884685": "C1COCCN1C2=NC(=NC3=C2OC4=C3C=CC=N4)C5=CC(=CC=C5)O", "24180719": "CCCS(=O)(=O)NC1=C(C(=C(C=C1)F)C(=O)C2=CNC3=NC=C(C=C23)Cl)F", "25243800": "CC(C)N1C2=C(C
(=C3C=C4C=C(C=CC4=N3)O)N1)C(=NC=N2)N", "10113978": "CC1=C(C=C(C=C1)NC2=NC=CC(=N2)N(C)C3=CC4=NN(C(=C4C=C3)C)C)S(=O)(=O)N", "17755052": "CS(=O)(=O)N1CCN(CC1)CC2=CC3=C(S2)C(=NC(=N3)C4=C5C=NNC5=CC=C
N6CCOCC6", "11984591": "CC1(C(=O)NC2=C(O1)C=CC(=N2)NC3=NC(=NC=C3F)NC4=CC(=C(C(=C4)OC)OC)OC)C.C1=CC=C(C=C1)S(=O)(=O)O", "153999": "CN(C)CC1CCN2C=C(C3=CC=CC=C32)C4=C(C5=CN(CCO1)C6=CC=CC=C65)C(=O)
NC4=O", "25127112": "C1CCC(C1)C(CC#N)N2C=C(C=N2)C3=C4C=CNC4=NC=N3.OP(=O)(O)O", "176155": "CS(=O)C1=CC=C(C=C1)C2=NC(=C(N2)C3=CC=NC=C3)C4=CC=C(C=C4)F", "24779724": "CN1C=C(C=N1)C2=NN3C
(=NN=C3SC4=CC5=C(C=C4)N=CC=C5)C=C2", "3025986": "CC(C)(C)C1=CN=C(O1)CSC2=CN=C(S2)NC(=O)C3CCNCC3", "10138260": "CC1=C(NC(=C1C(=O)NCC(CN2CCOCC2)O)C)C=C3C4=C(C=CC(=C4)F)NC3=O", "10127622":
"CN1C=NC2=C1C=C(C(=C2F)NC3=C(C=C(C=C3)Br)Cl)C(=O)NOCCO", "216239": "CNC(=O)C1=NC=CC(=C1)OC2=CC=C(C=C2)NC(=O)NC3=CC(=C(C=C3)Cl)C(F)(F)F", "44259": "CC12C(C(CC(O1)N3C4=CC=CC=C4C5=C6C
(=C7C8=CC=CC=C8N2C7=C53)CNC6=O)NC)OC", "5329102": "CCN(CC)CCNC(=O)C1=C(NC(=C1C)C=C2C3=C(C=CC(=C3)F)NC2=O)C", "16038120": "CC(C)S(=O)(=O)C1=CC=CC=C1NC2=NC(=NC=C2Cl)NC3=C(C=C(C=C3)N4CCC(CC4)N5CCN
(CC5)C)OC", "10427712": "C1=CC(=CC(=C1)O)C2=NC3=C(N=C2C4=CC(=CC=C4)O)N=C(N=C3N)N", "16722836": "CC1=CN=C(N=C1NC2=CC(=CC=C2)S(=O)(=O)NC(C)(C)C)NC3=CC=C(C=C3)OCCN4CCCC4", "3038522": "CC(C)OC1=CC=C
(C=C1)NC(=O)N2CCN(CC2)C3=NC=NC4=CC(=C(C=C43)OC)OCCCN5CCCCC5", "9926791": "CC1CCN(CC1N(C)C2=NC=NC3=C2C=CN3)C(=O)CC#N", "5494449": "CC1=CC(=NN1)NC2=NC(=NC(=C2)N3CCN(CC3)C)SC4=CC=C(C=C4)NC(=O)C5CC5

Molecule Representation

- 한계점
  - ➢ 문자열로 이루어진 SMILES 특성 상, 복잡한 화학 구조를 제대로 반영하지 못함
  - ➢ 화학 구조를 제대로 반영하지 못했다는 것은 정보 유실을 의미
  - ➢ 방대한 화합물 정보를 제대로 이용하지 못함
  - ➢ 신약후보물질 예측의 한계가 존재

Molecule Representation

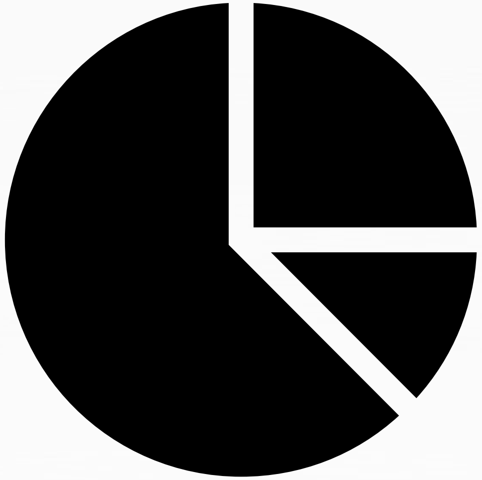
- Graph -

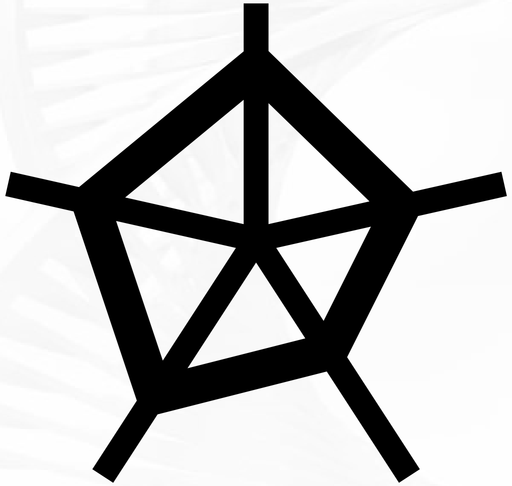


#	Compound	Protein	Prediction
1	Chemical_ID	Protein_ID	0.99
2	…	…	…
3	…	…	…
4	…	…	…
…	…	…	…

Graph

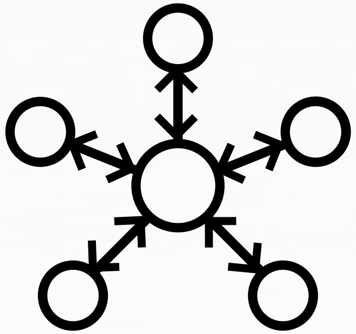
- Graph - Statistical Graph
  - ➢ 어떠한 데이터들을 그림상으로 시각화하여 나타낸 것을 의미



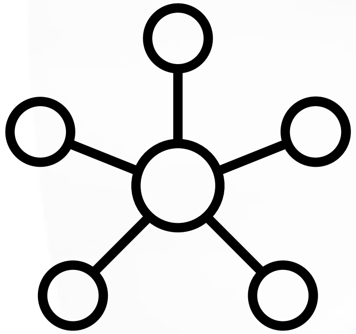


Graph

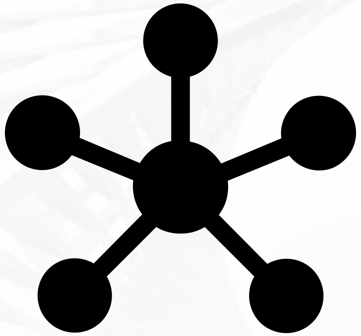
- Graph - Mathematical Graph
  - ➢ 일부 객체들의 쌍들이 서로 연관된 객체의 집합을 이루는 구조
  - ➢ 방향 / 無방향, 가중치 그래프로 구분



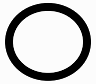
Directed graph



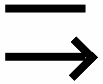
Undirected graph



Weighted graph



: Node

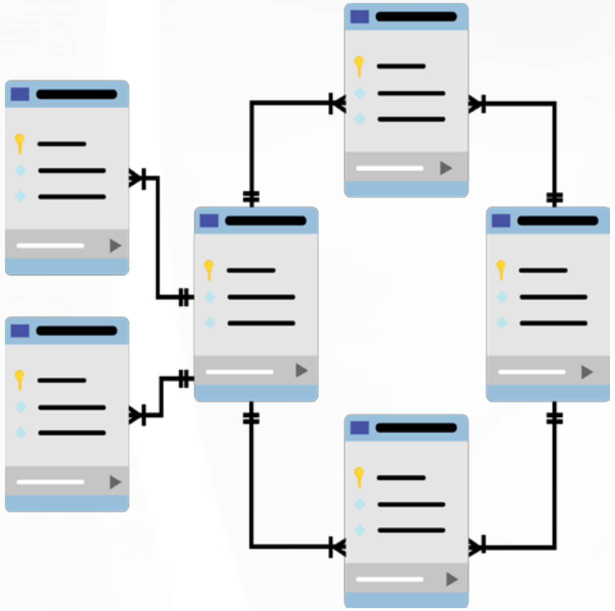


: Edge

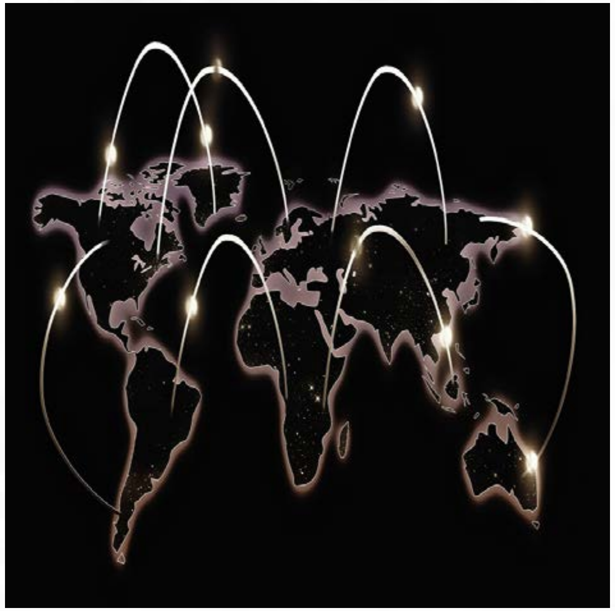
Graph

- Graph - Real Case
  - ➢ 객체를 정점, 객체 사이의 관계를 간선으로 표현

사회 관계망



관계형 데이터베이스

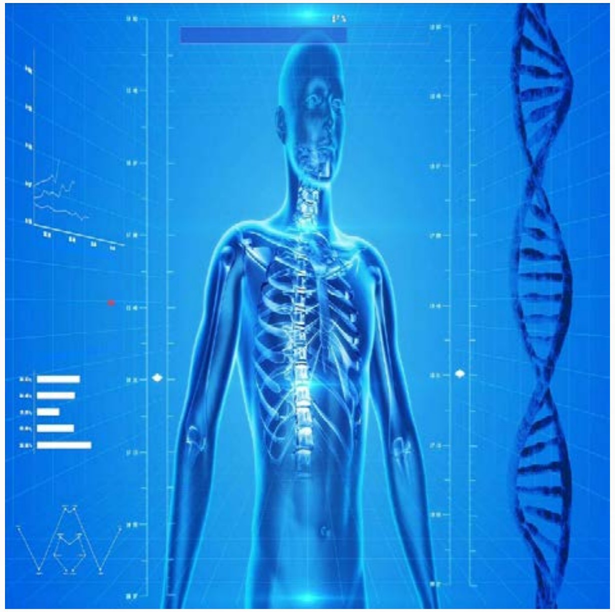


지도

Graph

- Graph - Real Case

  ➢ 객체를 정점, 객체 사이의 관계를 간선으로 표현



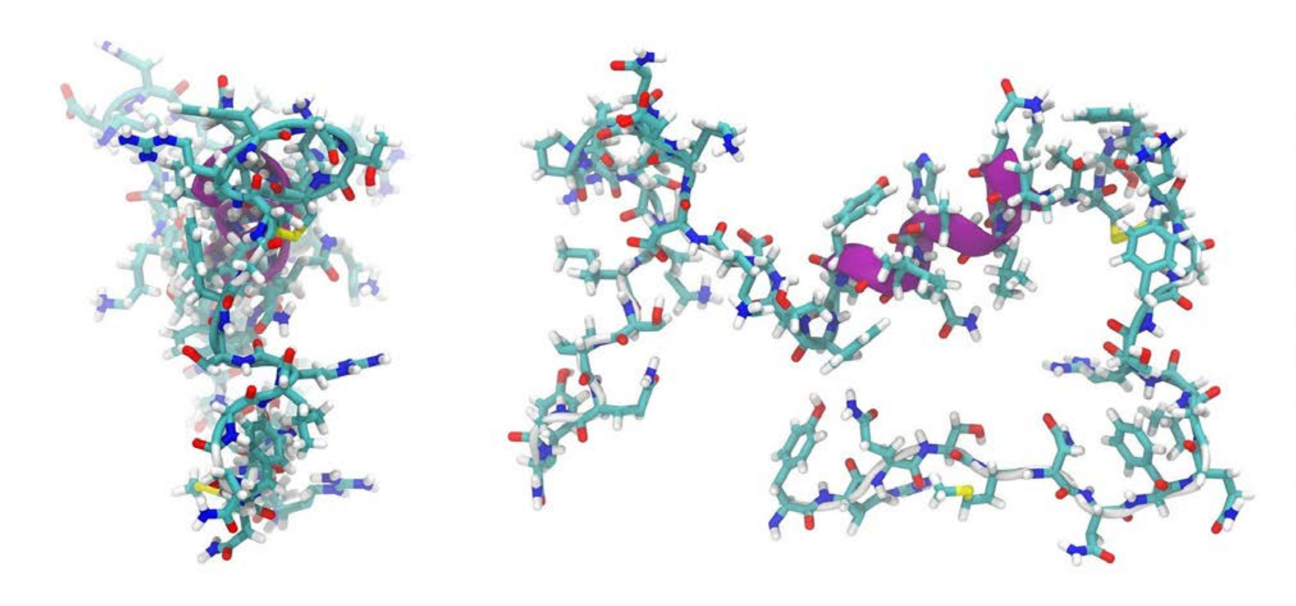
인체 구조

지식

우주

Graph

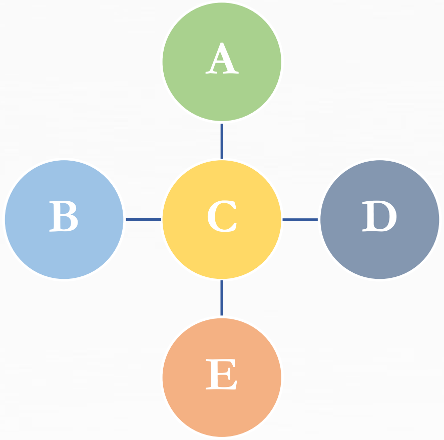
- **Graph - Real Case**
  - ➢ 객체를 정점, 객체 사이의 관계를 간선으로 표현



분자

Graph

- Graph - Graph Data Structure
  - ➢ 정점(Vertex or Node)과 그 정점을 연결하는 간선(Edge)을 하나로 모아 놓은 비선형 자료 구조
  - ➢ 정점 정보는 **특성 행렬**, 간선 정보는 **인접 행렬**로 표현



=

	A	B	C	D	E
A	0	0	1	0	0
B	0	0	1	0	0
C	1	1	0	1	1
D	0	0	1	0	0
E	0	0	1	0	0

인접 행렬

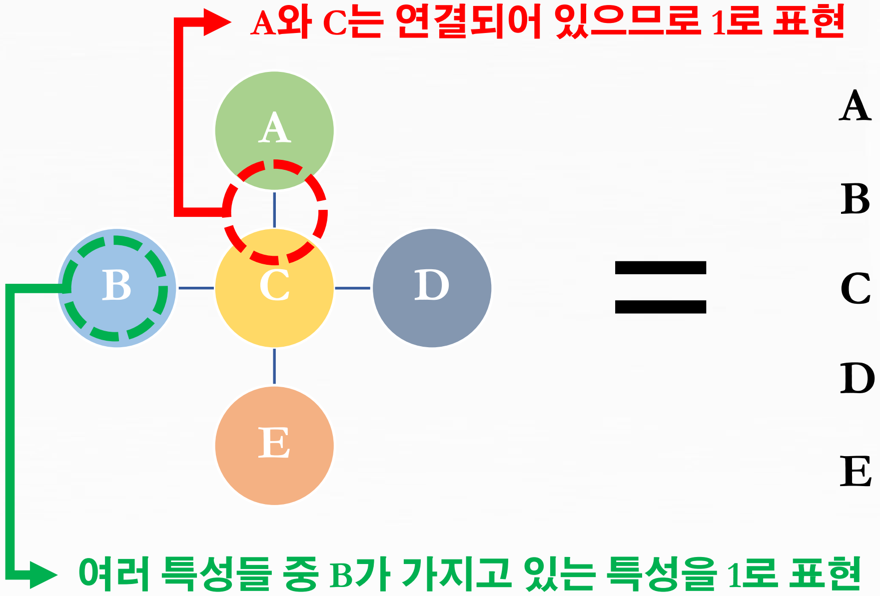
&

	1	2	3	4	5	6
A	0	1	0	1	0	1
B	1	1	1	0	0	1
C	1	0	0	0	1	0
D	1	1	1	0	0	1
E	0	0	1	1	0	0

특성 행렬

Graph

- Graph – Adjacency & Feature
  - ➢ 인접 행렬 : 그래프에서 어느 정점들이 간선으로 연결되었는지 나타내는 정사각 행렬
  - ➢ 특성 행렬 : 그래프에서 정점들이 가지고 있는 특성들을 나타내는 정사각 행렬



=

	A	B	C	D	E
A	0	0	1	0	0
B	0	0	1	0	0
C	1	1	0	1	1
D	0	0	1	0	0
E	0	0	1	0	0

인접 행렬

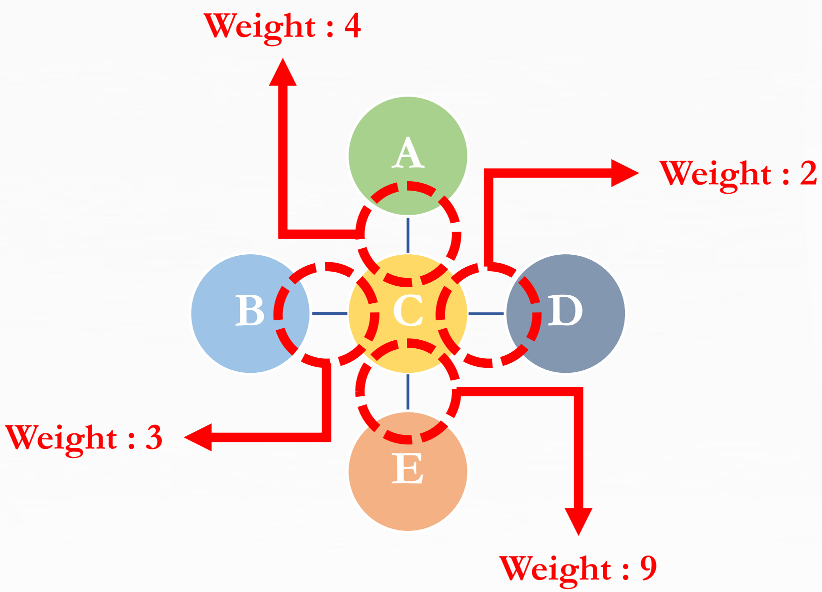
&

	1	2	3	4	5	6
A	0	1	0	1	0	1
B	1	1	1	0	0	1
C	1	0	0	0	1	0
D	1	1	1	0	0	1
E	0	0	1	1	0	0

특성 행렬

Graph

- Graph – Weight Matrix
  - 가중치 행렬 : 인접 행렬을 이용하여 표현
  - 간선이 존재하지 않는 경우, 가중치 범위 밖의 값 INF 등으로 표현



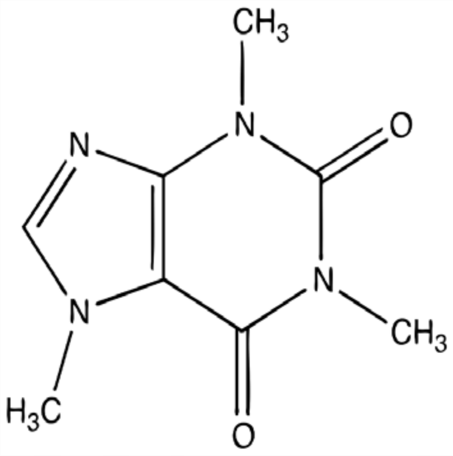
=

	A	B	C	D	E
A	INF	INF	4	INF	INF
B	INF	INF	3	INF	INF
C	4	3	INF	2	9
D	INF	INF	2	INF	INF
E	INF	INF	9	INF	INF

인접 행렬(가중치)

Graph – Molecule Representation

- SMILES as Graph
  - ➢ RDKit 라이브러리를 활용
  - ➢ 화학 물질의 정보를 담고 있는 데이터를 활용하여 구조 이미지(구조 식) 생성
  - ➢ 문자열로 구성된 SMILES를 신경망 학습을 위한 **그래프** 형식으로 변환



Caffeine($C_8H_{10}N_4O_2$)

[Molecule Structure]

Cn1cnc2N(C)C(=O)N(C)C(=O)c12

[SMILES]

0	0	1	0	0
0	0	1	0	0
1	1	0	1	1
0	0	1	0	0
0	0	1	0	0

0	1	0	1	0
1	1	1	0	0
1	0	0	0	1
1	1	1	0	0
0	0	1	1	0

[Matrix]

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Graph – Molecule Representation

- **SMILES to Input Presentation(Graph Representation)**

Toluene :"Cc1ccccc1"

c_size
원자 개수

→ 7

edge_index
결합 정보

→ [[0, 1, 1, 1, 2, 2, 3, 3, 4, 4, 5, 5, 6, 6],
[1, 0, 2, 6, 1, 3, 2, 4, 3, 5, 4, 6, 5, 1]]

features
원자 번호
원자 차원
수소 원자 총 개수
은닉 수소 원자 개수
방향족 여부

→
[[0.25, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.25, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. ,
0. , 0. , 0. , 0.25, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.25, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.],
[0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2,
0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2],
0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. ,
0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2],
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0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2],
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0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2],
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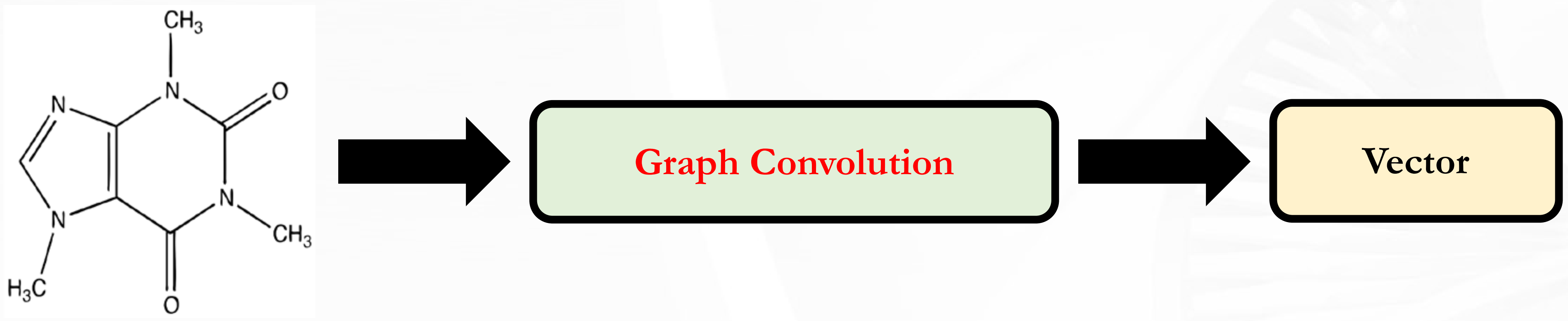
0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2],
[0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. ,
0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2, 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0. , 0.2]]

{"Cc1ccccc1" : c_size, edge_index, features}

Graph

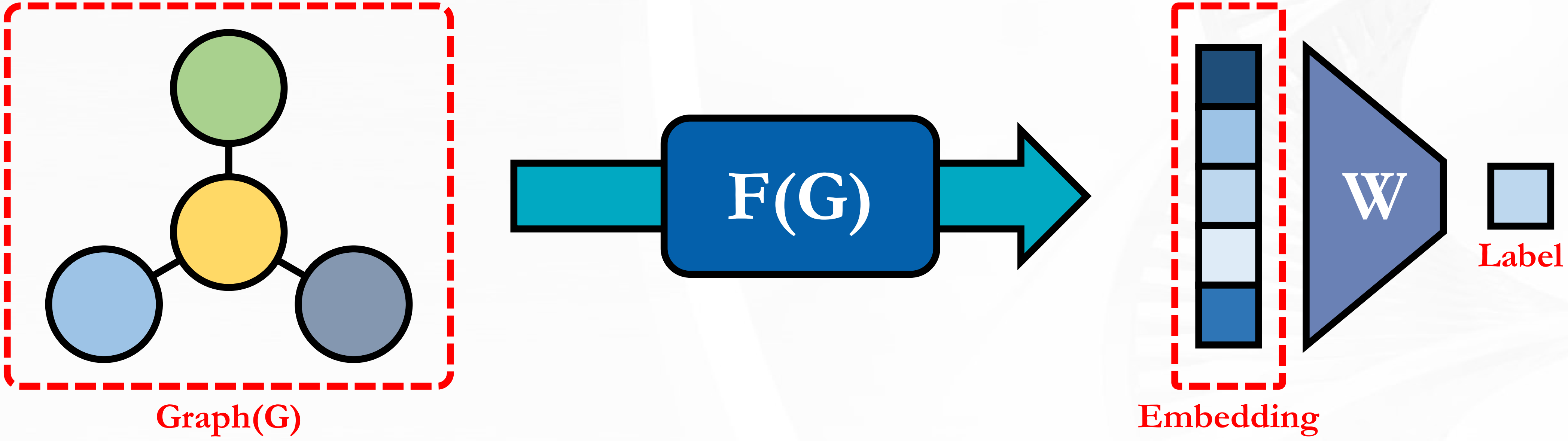
- **Graph - Problem & Solution**
  - 분자처럼 원자의 속성, 연결의 종류 등을 고려해야하는 경우, 속성 그래프로 데이터를 표현해야 함
  - 속성 그래프 데이터는 기존 방식으로 벡터의 형태로 변환하는 것이 불가능
  - 벡터의 형태로 데이터를 입력 받는 기존의 인공신경망으로는 분자 그래프 데이터를 처리할 수 없음
  - Graph convolution을 이용하여 **정점 또는 그래프 자체**를 **벡터 형태의 데이터로 변환**하여 해결



Graph Neural Networks

Graph Neural Network

- 개요
  - ➢ 그래프 구조에서 사용하는 인공 신경망
  - ➢ 입력이 그래프 구조라는 특징을 지님
  - ➢ 그래프에 존재하는 정점 사이의 관계를 모델링하고, 이에 대한 표현을 생성하는 것이 핵심



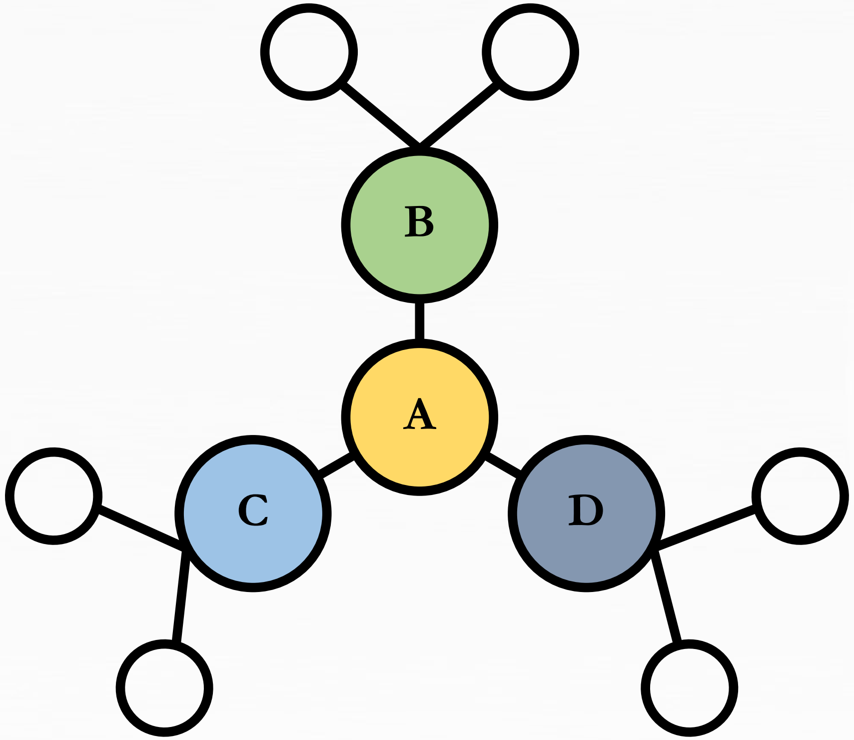
Graph Neural Network

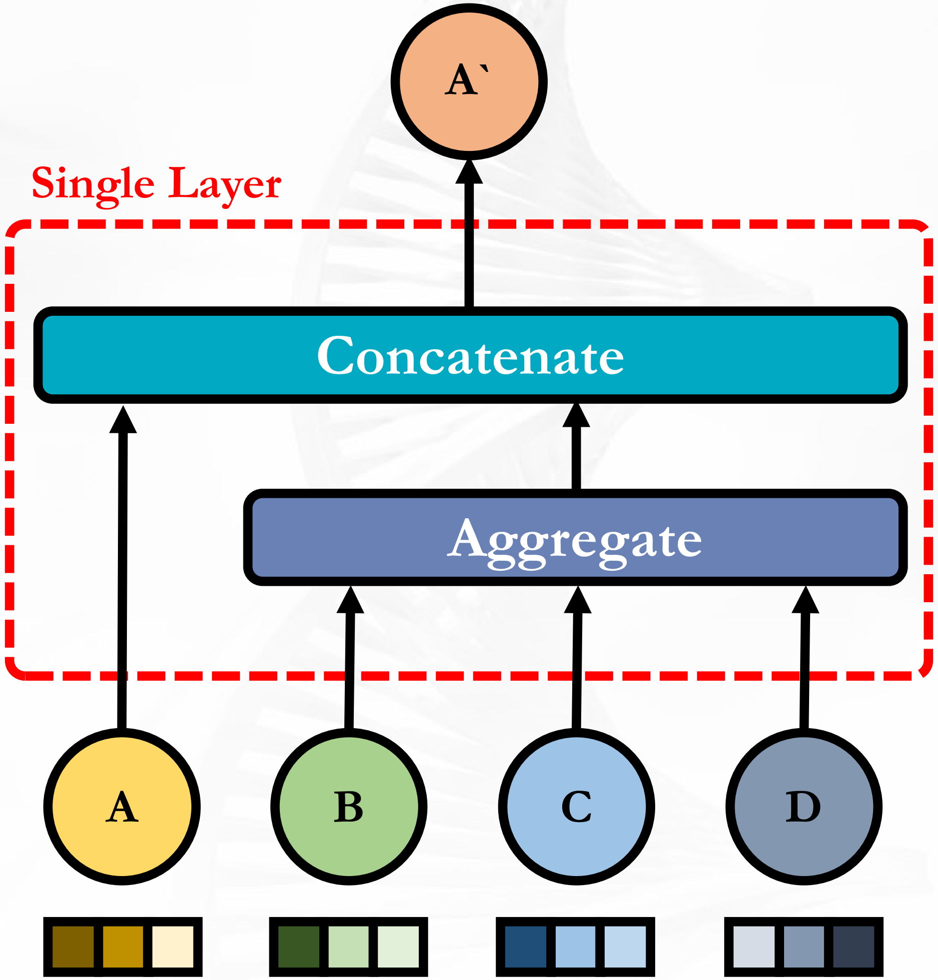
- **학습 과정**

General Artificial Neural Network	Graph Neural Network
신경망 구조 정의 및 input 준비	Aggregate, Concatenate 함수 정의 및 graph input 준비
↓	↓
Loss function 정의 및 optimizer 결정	Loss function 정의 및 optimizer 결정
↓	↓
Loss가 0에 가까워지도록 신경망의 parameter 학습	Loss가 0에 가까워지도록 신경망의 Aggregate, Concatenate parameter 학습

Graph Neural Network

- Neighborhoods Aggregation





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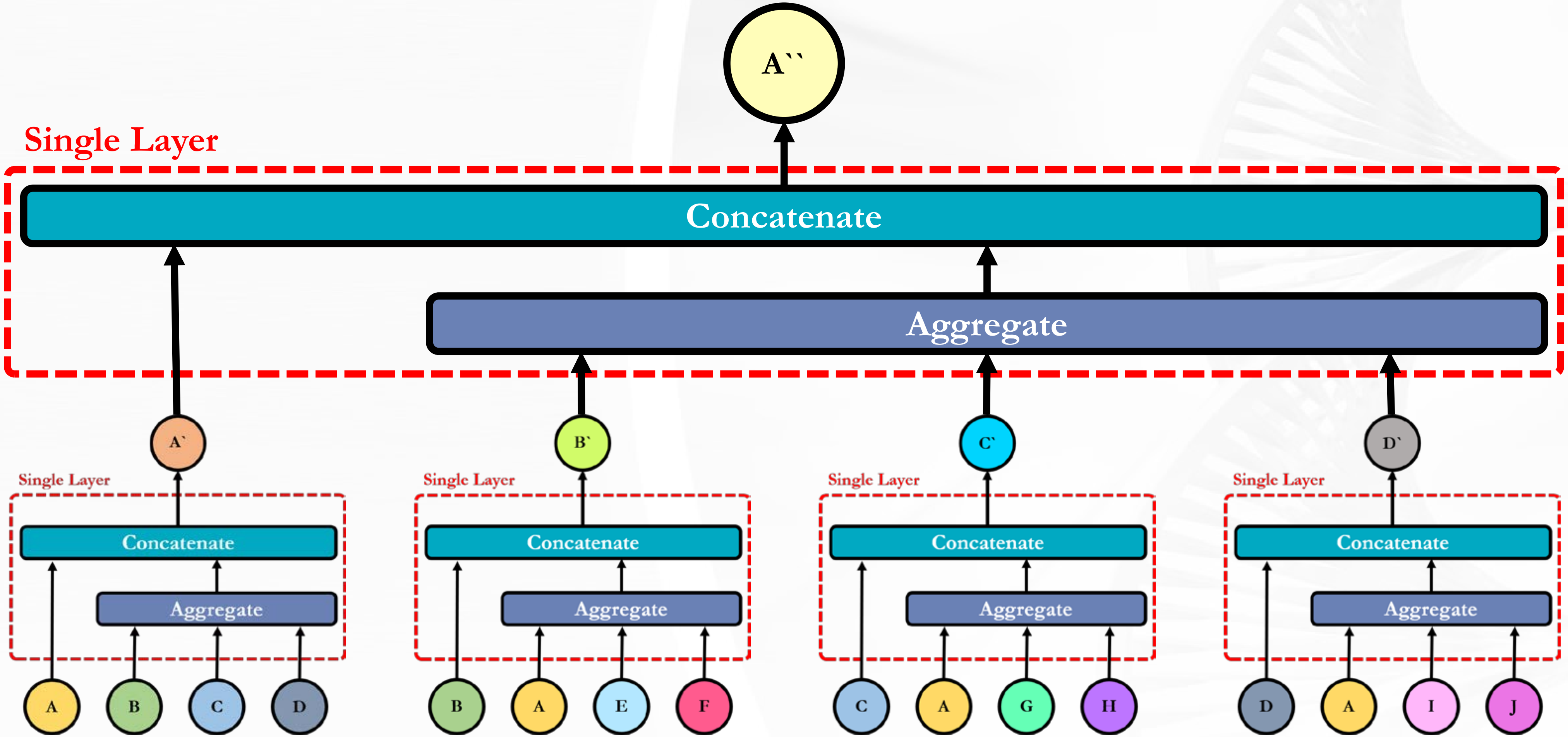
Graph Neural Network

- Neighborhoods Aggregation



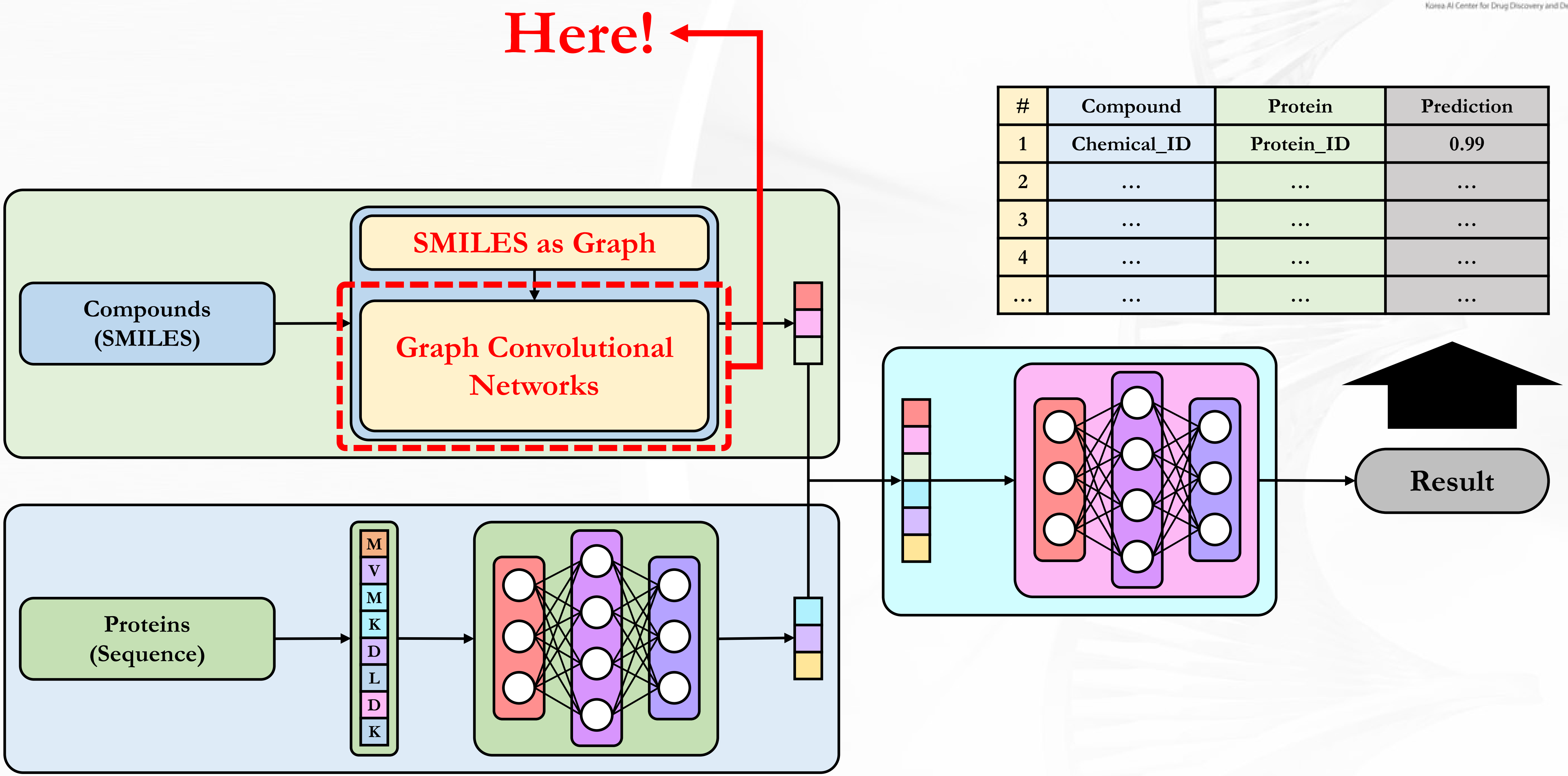
Graph Neural Network

- Algorithm

```
for v in V :
        h_{v}^{0} = v`s feature vector

for i in range(1, k+1) :
        for v in V :
                a = Aggregate({h_{u}^{i-1} | {u, v} in E})
                h_{v}^{i} = Concatenate(h_{v}^{i-1}, a)
```

Graph Convolutional Networks



#	Compound	Protein	Prediction
1	Chemical_ID	Protein_ID	0.99
2	…	…	…
3	…	…	…
4	…	…	…
…	…	…	…

Convolution

- **개요**
  - ➢ 행렬 내에서 특성을 뽑기 위한 연산
  - ➢ 입력 행렬과 특성 탐지를 통해 입력에 대한 특성 지도를 생성
  - ➢ 특성 지도를 통해 입력 행렬의 패턴 파악

$$\begin{bmatrix} 0 & 5 & 0 & 5 & 0 \\ 0 & 7 & 1 & 7 & 0 \\ 1 & 4 & 9 & 4 & 1 \\ 0 & 3 & 2 & 3 & 0 \\ 0 & 1 & 1 & 1 & 0 \end{bmatrix} * \begin{bmatrix} 1 & 3 & 0 \\ 0 & 2 & 1 \\ 0 & 2 & 3 \end{bmatrix} = \begin{bmatrix} 45 & 73 & 12 \\ 17 & 93 & 35 \\ 68 & 63 & 25 \end{bmatrix}$$

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Convolution

- 합성곱 연산 과정(Matrix)

$$\begin{bmatrix} 0 & 5 & 0 & 5 & 0 \\ 0 & 7 & 1 & 7 & 0 \\ 1 & 4 & 9 & 4 & 1 \\ 0 & 3 & 2 & 3 & 0 \\ 0 & 1 & 1 & 1 & 0 \end{bmatrix} * \begin{bmatrix} 1 & 3 & 0 \\ 0 & 2 & 1 \\ 0 & 2 & 3 \end{bmatrix} = \begin{bmatrix} 45 & & \\ & & \\ & & \end{bmatrix}$$

$$\begin{bmatrix} 0 & 5 & 0 & 5 & 0 \\ 0 & 7 & 1 & 7 & 0 \\ 1 & 4 & 9 & 4 & 1 \\ 0 & 3 & 2 & 3 & 0 \\ 0 & 1 & 1 & 1 & 0 \end{bmatrix} * \begin{bmatrix} 1 & 3 & 0 \\ 0 & 2 & 1 \\ 0 & 2 & 3 \end{bmatrix} = \begin{bmatrix} 45 & 73 & \\ & & \\ & & \end{bmatrix}$$

$$\begin{bmatrix} 0 & 5 & 0 & 5 & 0 \\ 0 & 7 & 1 & 7 & 0 \\ 1 & 4 & 9 & 4 & 1 \\ 0 & 3 & 2 & 3 & 0 \\ 0 & 1 & 1 & 1 & 0 \end{bmatrix} * \begin{bmatrix} 1 & 3 & 0 \\ 0 & 2 & 1 \\ 0 & 2 & 3 \end{bmatrix} = \begin{bmatrix} 45 & 73 & 12 \\ & & \\ & & \end{bmatrix}$$

$$\begin{bmatrix} 0 & 5 & 0 & 5 & 0 \\ 0 & 7 & 1 & 7 & 0 \\ 1 & 4 & 9 & 4 & 1 \\ 0 & 3 & 2 & 3 & 0 \\ 0 & 1 & 1 & 1 & 0 \end{bmatrix} * \begin{bmatrix} 1 & 3 & 0 \\ 0 & 2 & 1 \\ 0 & 2 & 3 \end{bmatrix} = \begin{bmatrix} 45 & 73 & 12 \\ 17 & & \\ & & \end{bmatrix}$$

Graph Convolution

- 특정 노드의 은닉 벡터를 해당 노드의 이웃 정보를 통해 표현
  - ➢ 그래프에 포함된 노드나 그래프 자체를 벡터 형태의 데이터로 변환
  - ➢ 노드의 특성과 연결 정보만을 고려하기 때문에 간선 특성은 사용되지 않음

은닉 노드 특성 행렬

인접 행렬 특성 행렬

$$\mathbf{H} = \Psi(\mathbf{A},\mathbf{X}) = \sigma(\mathbf{AXW})$$

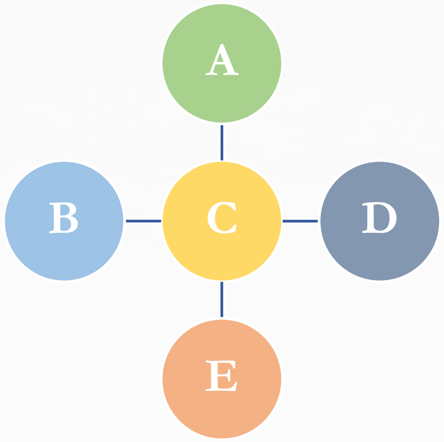
가중치 행렬

합성곱 연산 비선형 활성화 함수

Graph Convolution

- 행렬 계산 예시

$$G = (A, X)$$



=

	A	B	C	D	E
A	0	0	1	0	0
B	0	0	1	0	0
C	1	1	0	1	1
D	0	0	1	0	0
E	0	0	1	0	0

인접 행렬(A)

&

	1	2	3	4	5	6
A	0	1	0	1	0	1
B	1	1	1	0	0	1
C	1	0	0	0	1	0
D	1	1	1	0	0	1
E	0	0	1	1	0	0

특성 행렬(X)

Graph Convolution

- 행렬 계산 예시

$$A \times X = H$$

	A	B	C	D	E
A	0	0	1	0	0
B	0	0	1	0	0
C	1	1	0	1	1
D	0	0	1	0	0
E	0	0	1	0	0

인접 행렬(A)

×

	1	2	3	4	5	6
A	0	1	0	1	0	1
B	1	1	1	0	0	1
C	1	0	0	0	1	0
D	1	1	1	0	0	1
E	0	0	1	1	0	0

특성 행렬(X)

=

	1	2	3	4	5	6
A	1	0	0	0	1	0
B	1	0	0	0	1	0
C	2	3	3	2	0	3
D	1	0	0	0	1	0
E	1	0	0	0	1	0

은닉 정점 특성 행렬(H)

Graph Convolution

- 문제점
  - ➢ 인접 행렬에는 노드의 연결만 표현되어 있음
    - ▪ 합성곱 연산에서 각 노드 자체에 대한 정보 유실
  - ➢ 인접 행렬은 정규화 되어 있지 않음
    - ▪ 특성 벡터와 곱 연산을 수행할 경우 크기가 불안정하게 변할 수 있음

인접 행렬의 한계

Graph Convolution

- **해결 방안 적용**
  - 인접 행렬에 self-loop 추가
  - 인접 행렬을 $D^{-1/2}AD^{-1/2}$로 정규화

Self-loop를 추가한 인접 행렬

$$\Psi(\tilde{A},X) = \sigma(\tilde{D}^{-1/2}\tilde{A}\tilde{D}^{-1/2}XW)$$

$\tilde{A}$의 대각 차수 행렬

$\tilde{A}$의 정규화

Graph Convolution

- Self-loop 추가

Self-loop를 추가한 인접 행렬

$$\tilde{A} \times X = H$$

Self-loop 추가

	A	B	C	D	E
A	1	0	1	0	0
B	0	1	1	0	0
C	1	1	1	1	1
D	0	0	1	1	0
E	0	0	1	0	1

인접 행렬(A)

×

	1	2	3	4	5	6
A	0	1	0	1	0	1
B	1	1	1	0	0	1
C	1	0	0	0	1	0
D	1	1	1	0	0	1
E	0	0	1	1	0	0

특성 행렬(X)

=

	1	2	3	4	5	6
A	1	1	0	1	1	1
B	1	1	1	0	1	1
C	3	3	3	2	1	3
D	1	1	1	0	1	1
E	1	0	1	1	1	0

은닉 정점 특성 행렬(H)

Graph Convolution

- 인접 행렬 정규화

$$\tilde{D}^{-1/2} \times \tilde{A} \times \tilde{D}^{-1/2}$$

$$
\begin{array}{c|ccccc|}
 & A & B & C & D & E \\
\hline
A & \frac{1}{\sqrt{2}} & 0 & 0 & 0 & 0 \\
B & 0 & \frac{1}{\sqrt{2}} & 0 & 0 & 0 \\
C & 0 & 0 & \frac{1}{\sqrt{5}} & 0 & 0 \\
D & 0 & 0 & 0 & \frac{1}{\sqrt{2}} & 0 \\
E & 0 & 0 & 0 & 0 & \frac{1}{\sqrt{2}} \\
\hline
\end{array}
\times
\begin{array}{c|ccccc|}
 & A & B & C & D & E \\
\hline
A & 1 & 0 & 1 & 0 & 0 \\
B & 0 & 1 & 1 & 0 & 0 \\
C & 1 & 1 & 1 & 1 & 1 \\
D & 0 & 0 & 1 & 1 & 0 \\
E & 0 & 0 & 1 & 0 & 1 \\
\hline
\end{array}
\times
\begin{array}{c|ccccc|}
 & A & B & C & D & E \\
\hline
A & \frac{1}{\sqrt{2}} & 0 & 0 & 0 & 0 \\
B & 0 & \frac{1}{\sqrt{2}} & 0 & 0 & 0 \\
C & 0 & 0 & \frac{1}{\sqrt{5}} & 0 & 0 \\
D & 0 & 0 & 0 & \frac{1}{\sqrt{2}} & 0 \\
E & 0 & 0 & 0 & 0 & \frac{1}{\sqrt{2}} \\
\hline
\end{array}
$$

차수 행렬($\tilde{D}^{-1/2}$) 인접 행렬($\tilde{A}$) 차수 행렬($\tilde{D}^{-1/2}$)

Graph Convolution

- 인접 행렬 정규화

$$\tilde{D}^{-1/2} \times \tilde{A} \times \tilde{D}^{-1/2}$$

차수 행렬($\tilde{D}^{-1/2}$)

	A	B	C	D	E
A	$\frac{1}{\sqrt{2}}$	0	0	0	0
B	0	$\frac{1}{\sqrt{2}}$	0	0	0
C	0	0	$\frac{1}{\sqrt{5}}$	0	0
D	0	0	0	$\frac{1}{\sqrt{2}}$	0
E	0	0	0	0	$\frac{1}{\sqrt{2}}$

정규화 인접 행렬 ($\tilde{D}^{-1/2}\tilde{A}\tilde{D}^{-1/2}$)

	A	B	C	D	E
A	$\frac{1}{2}$	0	$\frac{1}{\sqrt{10}}$	0	0
B	0	$\frac{1}{2}$	$\frac{1}{\sqrt{10}}$	0	0
C	$\frac{1}{\sqrt{10}}$	$\frac{1}{\sqrt{10}}$	$\frac{1}{5}$	$\frac{1}{\sqrt{10}}$	$\frac{1}{\sqrt{10}}$
D	0	0	$\frac{1}{\sqrt{10}}$	$\frac{1}{2}$	0
E	0	0	$\frac{1}{\sqrt{10}}$	0	$\frac{1}{2}$

차수 행렬($\tilde{D}^{-1/2}$)

	A	B	C	D	E
A	$\frac{1}{\sqrt{2}}$	0	0	0	0
B	0	$\frac{1}{\sqrt{2}}$	0	0	0
C	0	0	$\frac{1}{\sqrt{5}}$	0	0
D	0	0	0	$\frac{1}{\sqrt{2}}$	0
E	0	0	0	0	$\frac{1}{\sqrt{2}}$

Graph Convolution

- **최종 계산**

$$\tilde{D}^{-1/2} \times \tilde{A} \times \tilde{D}^{-1/2} \times X = H$$

	A	B	C	D	E
A	$\frac{1}{2}$	0	$\frac{1}{\sqrt{10}}$	0	0
B	0	$\frac{1}{2}$	$\frac{1}{\sqrt{10}}$	0	0
C	$\frac{1}{\sqrt{10}}$	$\frac{1}{\sqrt{10}}$	$\frac{1}{5}$	$\frac{1}{\sqrt{10}}$	$\frac{1}{\sqrt{10}}$
D	0	0	$\frac{1}{\sqrt{10}}$	$\frac{1}{2}$	0
E	0	0	$\frac{1}{\sqrt{10}}$	0	$\frac{1}{2}$

정규화 인접 행렬

$\times$

	1	2	3	4	5	6
A	0	1	0	1	0	1
B	1	1	1	0	0	1
C	1	0	0	0	1	0
D	1	1	1	0	0	1
E	0	0	1	1	0	0

특성 행렬(X)

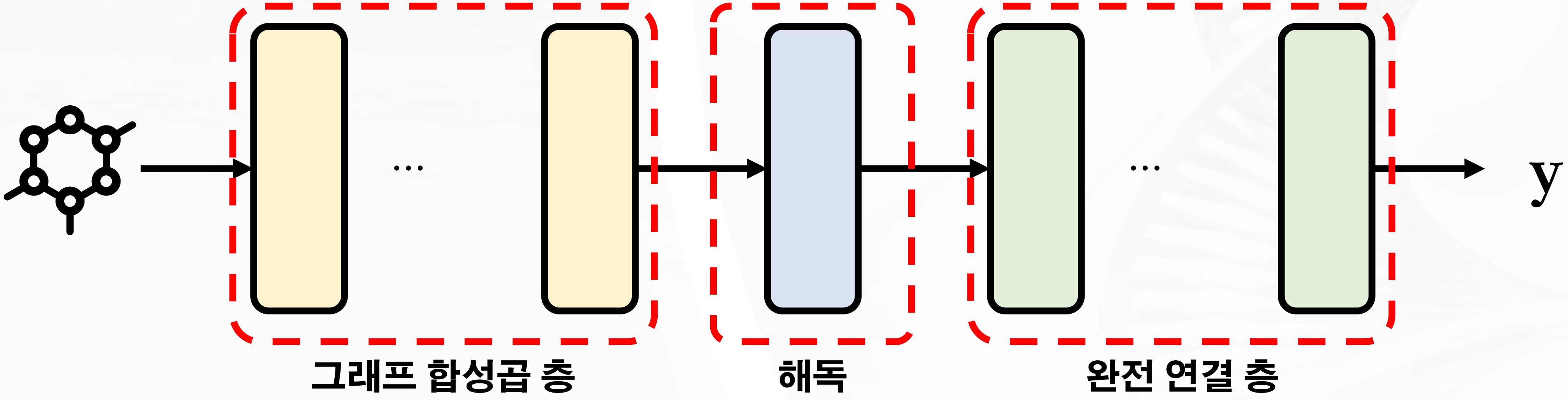
$=$

	1	2	3	4	5	6
A	$\frac{1}{\sqrt{10}}$	$\frac{1}{2}$	0	$\frac{1}{2}$	$\frac{1}{\sqrt{10}}$	$\frac{1}{2}$
B	$\frac{2+\sqrt{10}}{2\sqrt{10}}$	$\frac{1}{2}$	$\frac{1}{2}$	0	$\frac{1}{\sqrt{10}}$	$\frac{1}{2}$
C	$\frac{10+\sqrt{10}}{5\sqrt{10}}$	$\frac{3}{\sqrt{10}}$	$\frac{3}{\sqrt{10}}$	$\frac{2}{\sqrt{10}}$	$\frac{1}{5}$	$\frac{3}{\sqrt{10}}$
D	$\frac{2+\sqrt{10}}{2\sqrt{10}}$	$\frac{1}{2}$	$\frac{1}{2}$	0	$\frac{1}{\sqrt{10}}$	$\frac{1}{2}$
E	$\frac{1}{\sqrt{10}}$	0	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{\sqrt{10}}$	0

은닉 정점 특성 행렬(H)

Graph Convolutional Networks

- 개요
  - ➢ 일반적으로 그래프 합성곱 층과 완전 연결 층으로 구성
  - ➢ 그래프 분류 및 회귀 문제에서는 해독 과정이 필수
  - ➢ 노드 분류 또는 링크 예측의 경우 해독 과정이 필요 없음



Graph Convolutional Networks

- 연산

  - ➢ 각 그래프 합성곱 층은 그래프 합성곱 연산으로 정의
  - ➢ 그래프 합성곱 층을 반복적으로 적용
  - ➢ 그래프에 포함된 정점에서 추상화된 은닉 특성을 추출

k 번째 층의 가중치 행렬

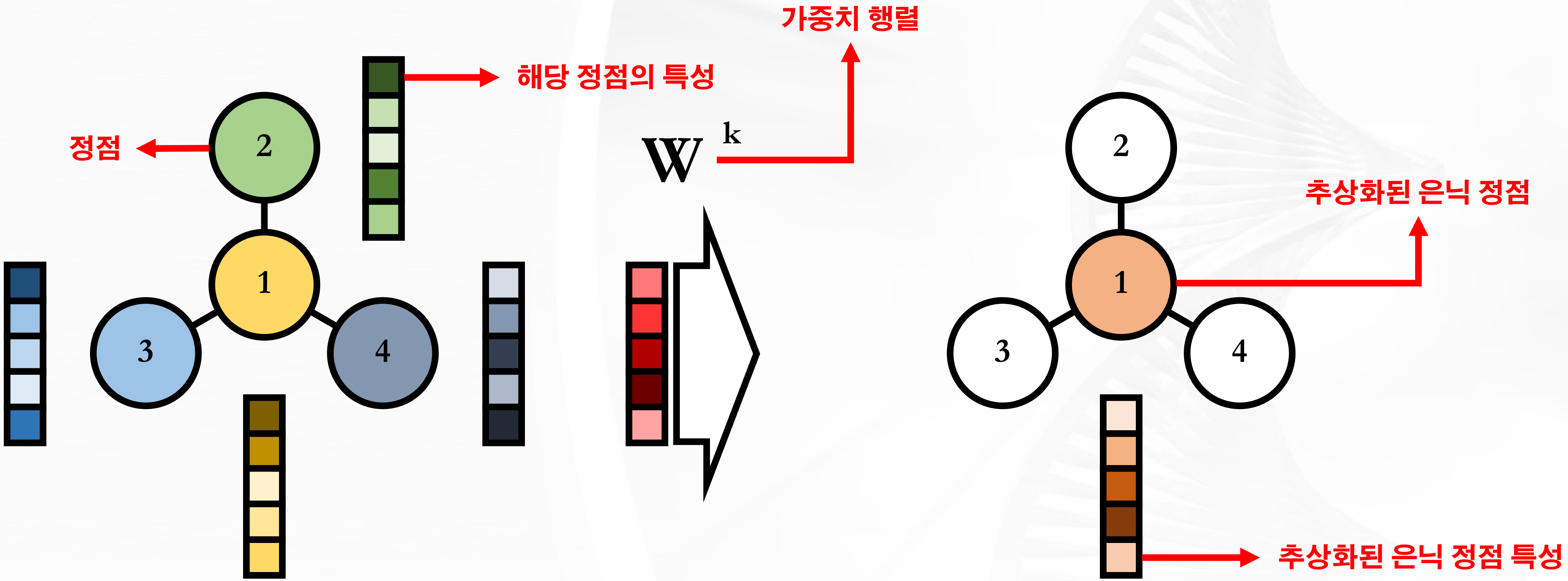
$$H^{(k)} = \sigma(\tilde{D}^{-1/2}\tilde{A}\tilde{D}^{-1/2} H^{(k-1)} W^{(k)})$$

k 번째 그래프 합성곱 층 출력

이전 그래프 합성곱 층 출력

Graph Convolutional Networks

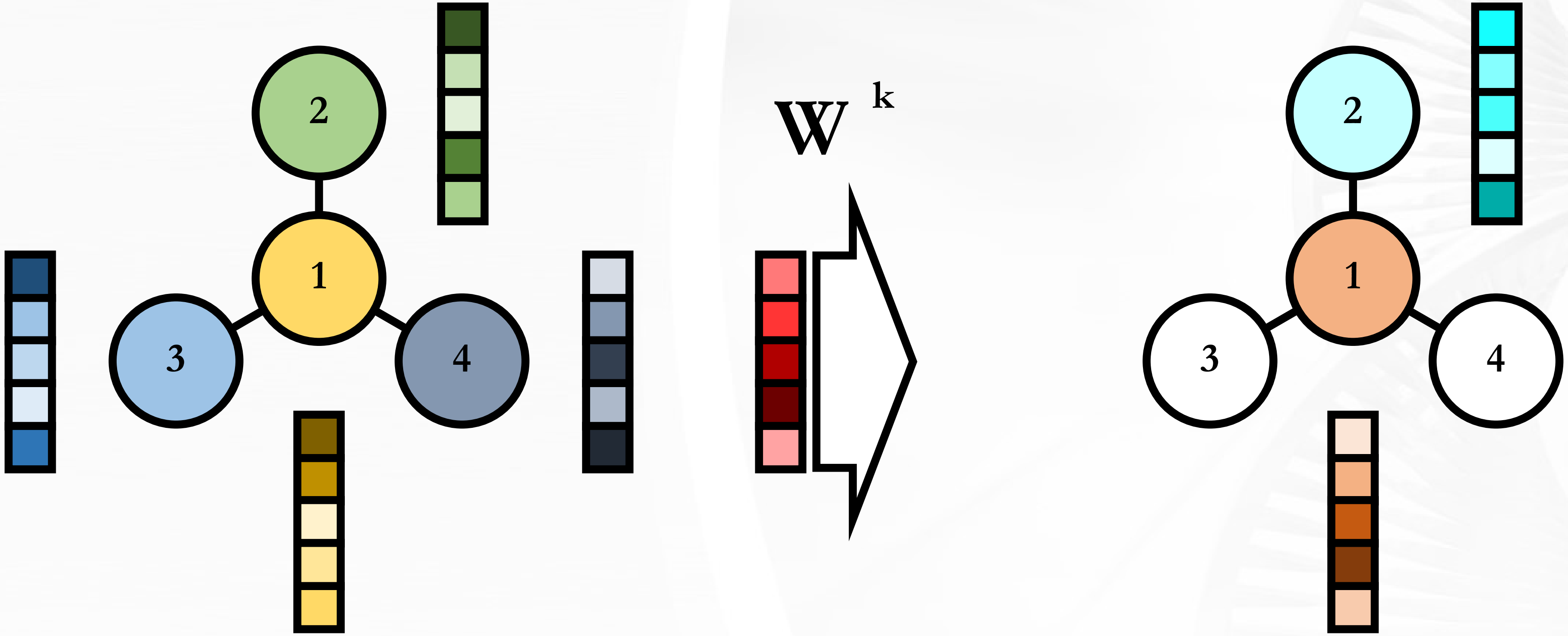
- 정점 특성 학습 과정



$$H_1^{k+1} = \sigma(H_1^k W^k + H_2^k W^k + H_3^k W^k + H_4^k W^k)$$

Graph Convolutional Networks

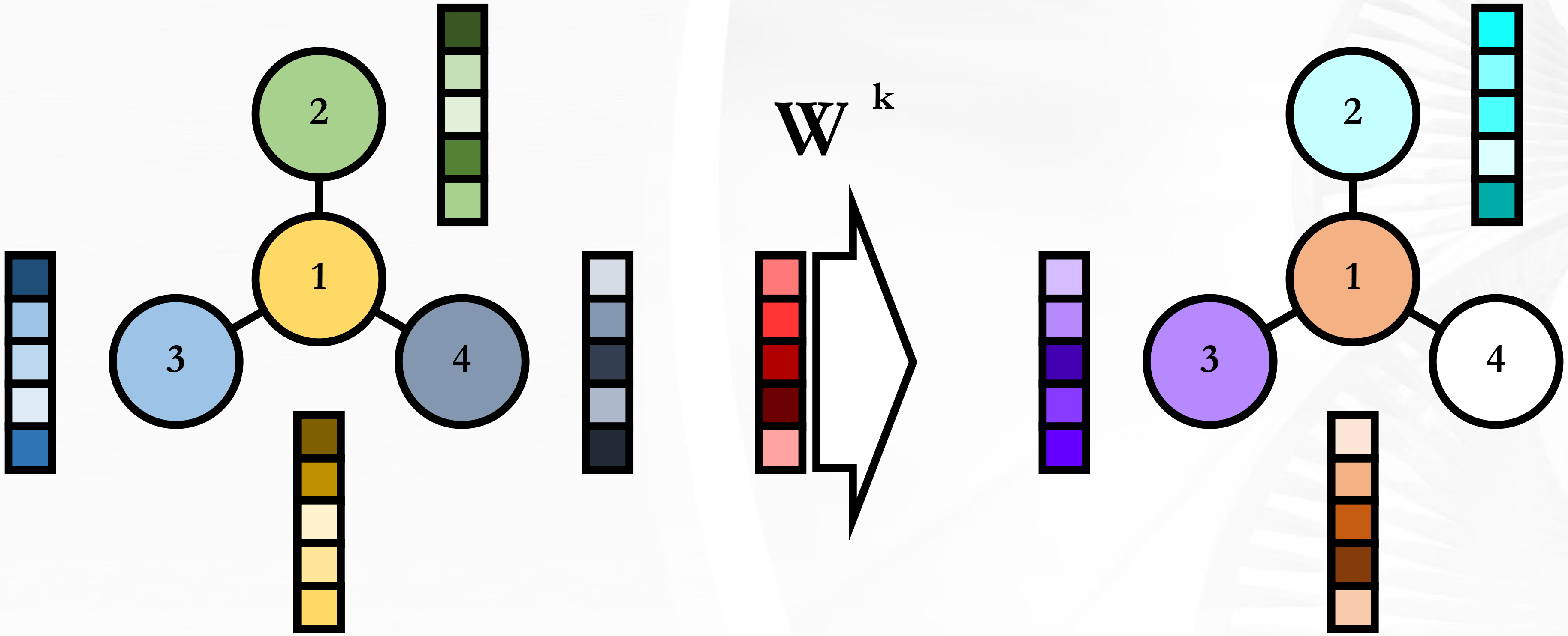
- 정점 특성 학습 과정



$$H_2^{k+1} = \sigma(H_1^k W^k + H_2^k W^k + \cancel{H_3^k W^k} + \cancel{H_4^k W^k})$$

Graph Convolutional Networks

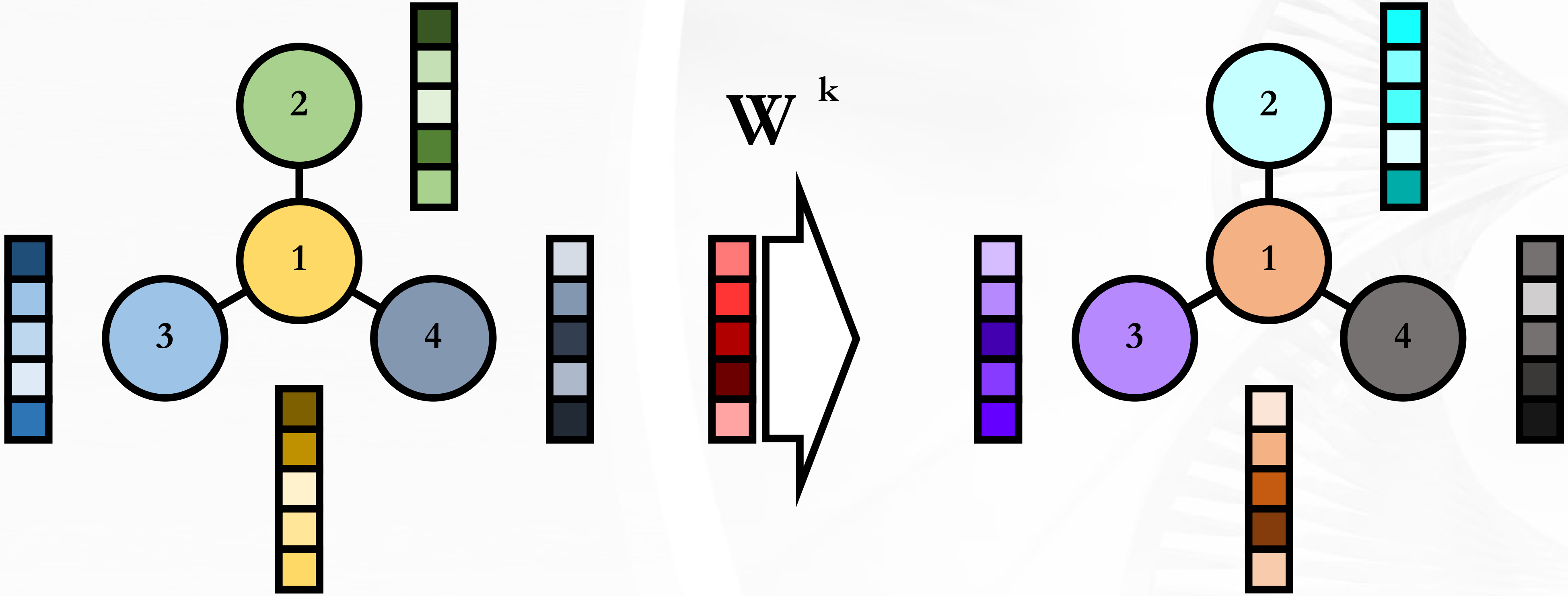
- 정점 특성 학습 과정



$$H_3^{k+1} = \sigma(H_1^k W^k + \cancel{H_2^k W^k} + H_3^k W^k + \cancel{H_4^k W^k})$$

Graph Convolutional Networks

- 정점 특성 학습 과정



$$H_4^{k+1} = \sigma(H_1^k W^k + \cancel{H_2^k W^k} + \cancel{H_3^k W^k} + H_4^k W^k)$$

Graph Convolutional Networks

- GCN 구현
  - 직접 구현 시, 인접 행렬 및 특성 행렬 추출부터 batch 생성까지 많은 어려움이 따름
  - PyTorch 기준, Deep Graph Library(DGL)와 PyTorch Geometric를 통해 간편하게 구현 가능
  - 본 강의(논문)에서는 PyTorch Geometric으로 GCN-based Model을 구현

```python
import torch
import torch.nn as nn
import torch.nn.functional as F
from torch_geometric.nn import GCNConv, global_max_pool as gmp

class GCNNet(torch.nn.Module):
    def __init__(self, n_output=1, n_filters=32, embed_dim=128,num_features_xd=78, num_features_xt=25, output_dim=128, dropout=0.2):

        super(GCNNet, self).__init__()

        self.n_output = n_output
        self.conv1 = GCNConv(num_features_xd, num_features_xd)
        self.conv2 = GCNConv(num_features_xd, num_features_xd*2)
        self.conv3 = GCNConv(num_features_xd*2, num_features_xd * 4)
        self.fc_g1 = torch.nn.Linear(num_features_xd*4, 1024)
        self.fc_g2 = torch.nn.Linear(1024, output_dim)
        self.relu = nn.ReLU()
        self.dropout = nn.Dropout(dropout)

        self.embedding_xt = nn.Embedding(num_features_xt + 1, embed_dim)
        self.conv_xt_1 = nn.Conv1d(in_channels=1000, out_channels=n_filters, kernel_size=8)
        self.fc1_xt = nn.Linear(32*121, output_dim)

        self.fc1 = nn.Linear(2*output_dim, 1024)
        self.fc2 = nn.Linear(1024, 512)
        self.out = nn.Linear(512, self.n_output)
```

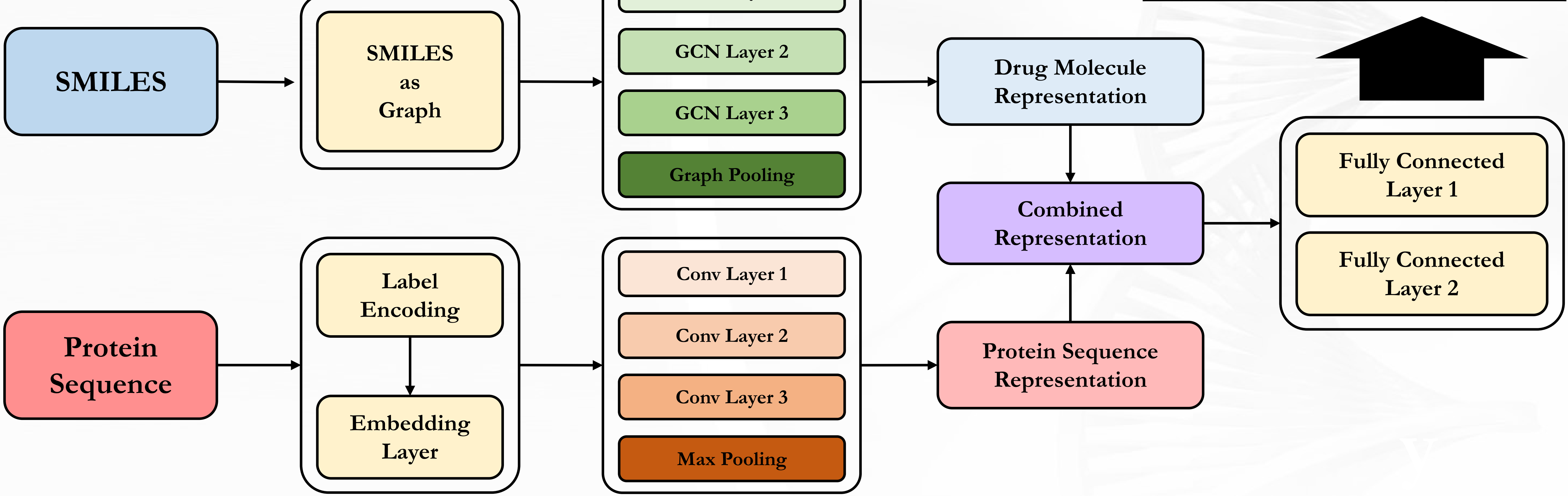
코드 구현 예시

GraphDTA Model

Model

- 프로세스

#	Compound	Protein	Prediction
1	Chemical_ID	Protein_ID	0.99
2	…	…	…
3	…	…	…
4	…	…	…
…	…	…	…



KAICD 한국인공지능신약개발지원센터 Korea AI Center for Drug Discovery and Development

Model

- 실험 설정
  - Davis, Kiba 두 데이터셋에서 DeepDTA, WideDTA와 동일한 train/test split을 사용함
  - 데이터 인스턴스의 80%를 훈련에 사용했으며, 나머지 20%를 테스트에 사용함
  - 기존 논문과 동일 선상에서 성능을 비교하기 위해 MSE와 CI로 성능을 평가함
  - MSE : Mean Square Error, 평균 제곱 오차(낮을수록 좋은 성능)
  - CI : Concordance Index, 일치 지수(높을수록 좋은 성능)
  - 실습 코드에선 다양한 성능평가지표의 시각화를 위해 RMSE, PCC, SRCC 추가
  - 하이퍼 파라미터 설정은 코드 리뷰에서 다룰 예정

Model

- **결과**

  ➢ Davis, KIBA 두 데이터 셋에서 Baseline(DeepDTA, KronRLS, SimBoost)보다 좋은 성능을 도출함

Method	Protein rep.	Compound rep.	CI	MSE
Baseline models				
DeepDTA	Smith-Waterman	Pubchem-Sim	0.790	0.608
DeepDTA	Smith-Waterman	1D	*0.886*	0.420
DeepDTA	1D	Pubchem-Sim	0.835	0.419
KronRLS	Smith-Waterman	Pubchem-Sim	0.871	0.379
SimBoost	Smith-Waterman	Pubchem-Sim	0.872	0.282
DeepDTA	1D	1D	0.878	*0.261*
WideDTA	1D + PDM	1D + LMCS	*0.886*	0.262
Proposed model - **GraphDTA**				
GCN [17]	1D	Graph	0.880	**0.254**
GAT_GCN	1D	Graph	0.881	**0.245**
GAT [37]	1D	Graph	**0.892**	**0.232**
GIN [40]	1D	Graph	**0.893**	**0.229**

Davis Dataset Prediction Performance

Method	Protein rep.	Compound rep.	CI	MSE
Baseline models				
DeepDTA	1D	Pubchem-Sim	0.718	0.571
DeepDTA	Smith-Waterman	Pubchem-Sim	0.710	0.502
KronRLS	Smith-Waterman	Pubchem-Sim	0.782	0.411
SimBoost	Smith-Waterman	Pubchem-Sim	0.836	0.222
DeepDTA	Smith-Waterman	1D	0.854	0.204
DeepDTA	1D	1D	0.863	0.194
WideDTA	1D + PDM	1D + LMCS	*0.875*	*0.179*
Proposed model - **GraphDTA**				
GAT [37]	1D	Graph	0.866	0.179
GIN [40]	1D	Graph	**0.882**	**0.147**
GCN [17]	1D	Graph	**0.889**	**0.139**
GAT_GCN	1D	Graph	**0.891**	**0.139**

Kiba Dataset Prediction Performance

Code Review

Code Review

- Google Colab
  - https://bit.ly/33aJfZp
  - 반드시 드라이브에 사본 저장 후 진행해주세요!