AI in Drug Discovery

Molecular Representation Learning

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Korean AI Center For Drug Discovery and Development

Sooheon Kim

KAICD
한국인공지능신약개발지원센터
Korea AI Center for Drug Discovery and Development

REPRESENTATION LEARNING

Tipping Points in Deep Learning

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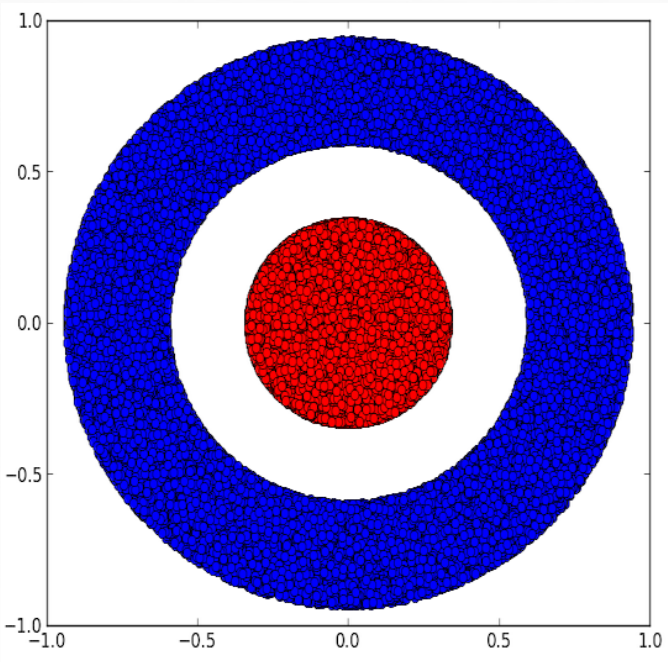
Mode	Dataset	Size	Model
Image	ImageNet	10^8 images	ResNet
Text	CommonCrawl	10^{11} tokens	GPT-3
Compound	PubChem, ChEMBL	10^7 compounds	???
Protein	UniRef100, BFD	10^9 proteins, 10^{11} amino acids	???

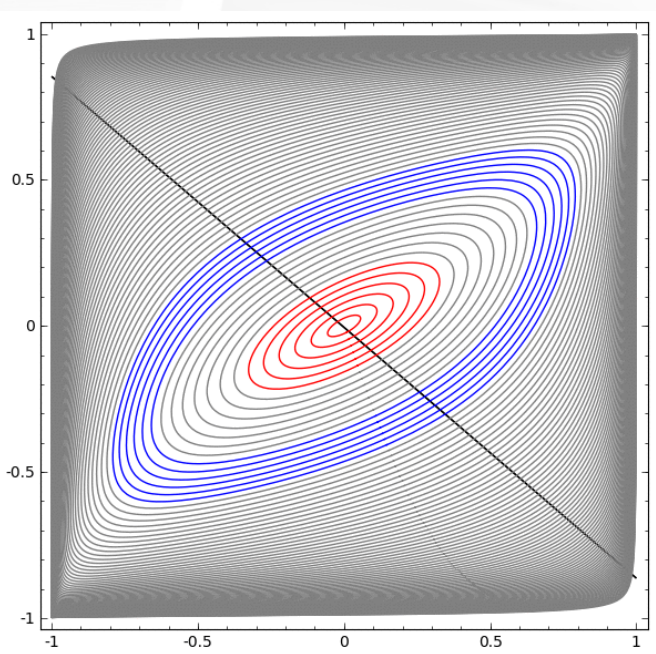
Tipping Points in Deep Learning

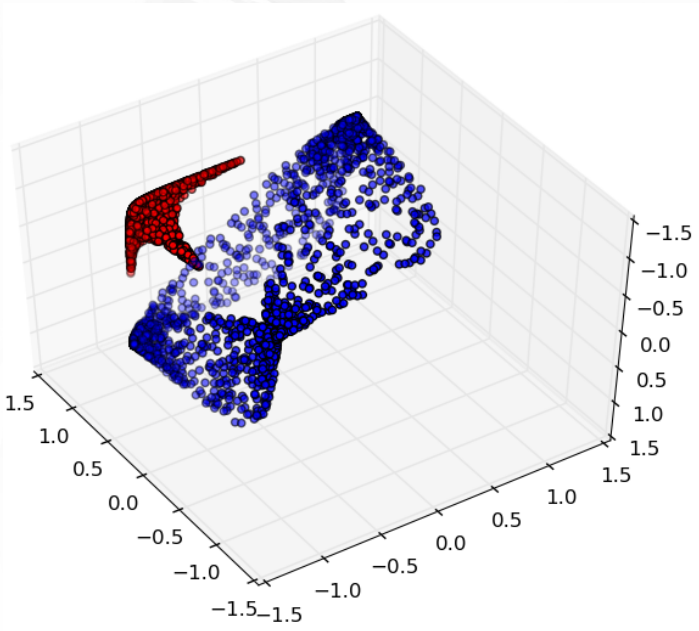
- How big is image space?
  - Pixels: 512x512
  - Color channels: 3
  - Color values: 256 (for 8 bit)
  - $256^{(3*512*512)} = 10^{1893916}$
- How big is language space?
  - 50k token vocabulary ^ 2048 context length = 10^{9623}
- How big is chemical space?
  - 10^{60}?
- Protein space?
  - 21 amino acids ^ 4096 protein length = $6 * 10^{5415}$

Representation Learning

- 데이터를 변형하여 추후 Task (분류, 회귀 등)에 용이하게 만드는 것
  - 표현이 적합할수록 모델의 복잡도는 내려갈 수 있다 (Ex. 딥러닝 모델의 Head로 얕은 Linear Model 활용)





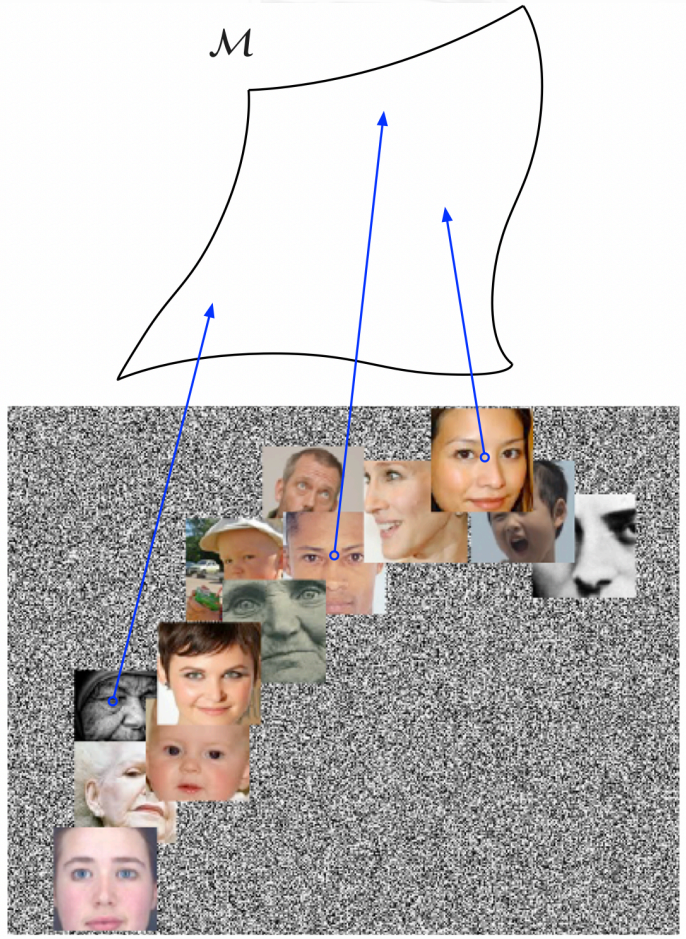


https://colah.github.io/posts/2014-03-NN-Manifolds-Topology/

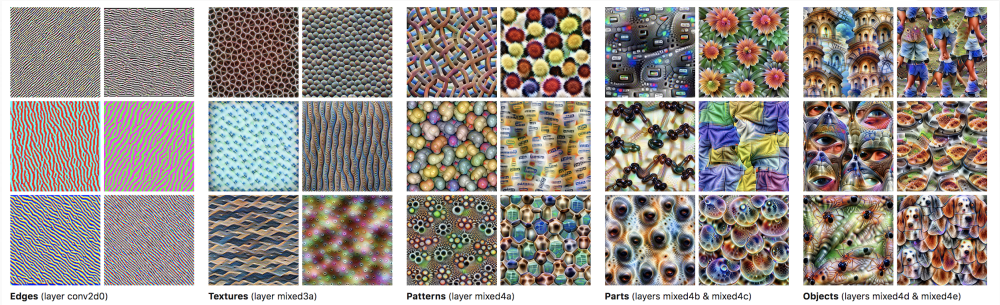
Representation Learning

Manifold Hypothesis

- 고차원으로 표현되는 현상데이터의 실제 **유용한** 정보는 저차원 manifold M에 몰려있다
  - Random image (256^(512^2)) vs. images of human face
  - Chemical space (10^60) vs. hits for given target
- 이 Manifold는 구조상 많이 "구겨지고 꼬여"있을 가능성이 높으니, 좋은 representation learning의 목적 중 하나는 이를
  - 찾아내고
  - "펴"주는 것



Representation Learning



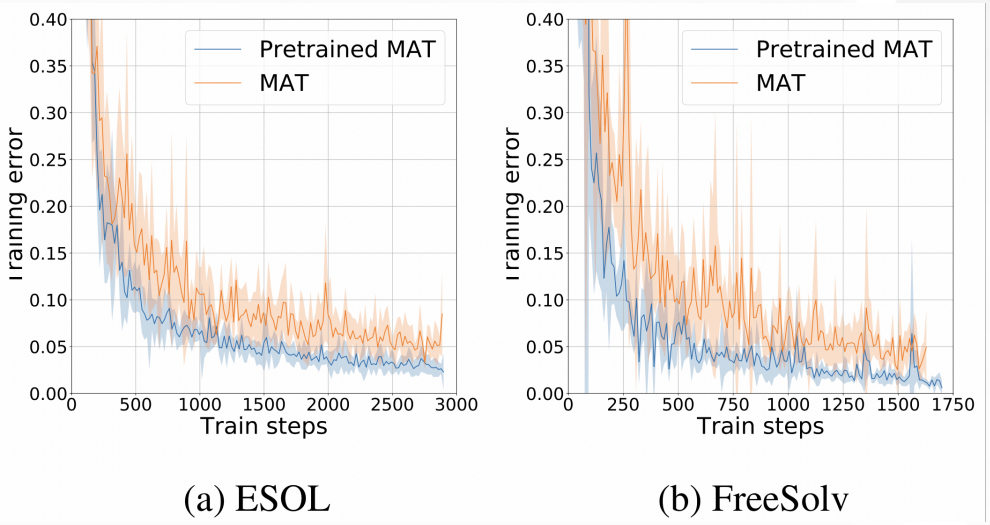
- a와 b가 유사하면 각각의 representation도 유사할 것
  - $a \approx b \Longrightarrow repr(a) \approx repr(b)$
- 다양한 Task, Dataset에 적용 가능할 것
  - Generalization이 잘 되야 유용
- 의미/특징의 Hierarchy가 내재되어 있으면 좋음

Szegedy et al., 2014

Representation Learning

”더이상 전이학습 없이 딥러닝 사용하는 것은 무모하다.”

-- Laurens van der Maaten



(a) ESOL (b) FreeSolv

Szegedy et al., 2014

Representation Learning

- Supervised
  - X -> explicit Y
  - Ex) “문제지 풀고 답 확인하기”
- Unsupervised
  - No **direct** supervision, but requires **indirect** supervision via task engineering
  - Ex) “읽다가 가려진 단어 뭘까 고민해본다”
  - 답안지 없이도 학습이 가능
    - 대이터에 내재된 패턴을 “답”으로 간주

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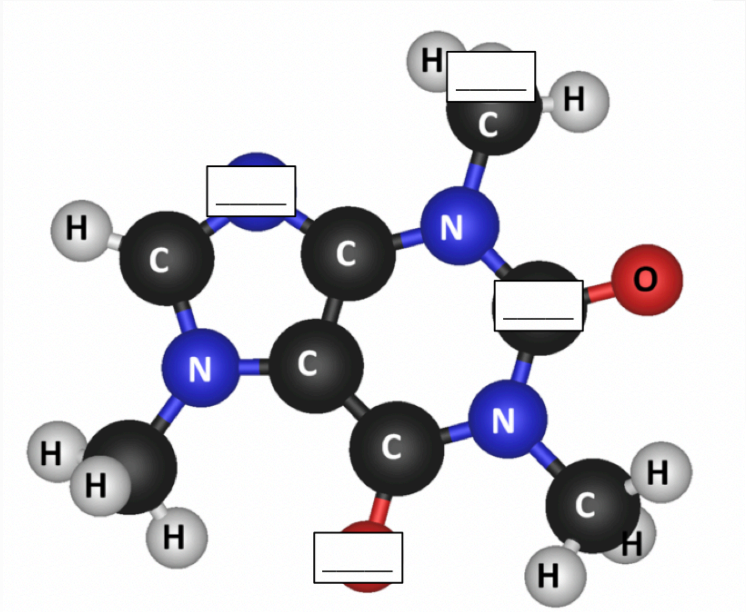
MOLECULE PRETRAINING

Pretraining

- Chemical 데이터에 Unsupervised task 구성은 어떻게?



It was a _____ , cold November day. I
(adjective)
woke up to the _____ smell of _____
(adjective) (type of bird)
roasting in the _____ downstairs. I
(room in a house)
_____ down the stairs to see if I could
(verb (past tense))
help _____ the dinner. My mom said,
(verb)
"See if _____ needs a fresh _____." So I
(relative's name) (noun)
carried a tray of glasses full of _____ into
(a liquid)
the _____ room. When I got there, I
(verb ending in -ing)
couldn't believe my _____! There were
(part of the body (plural))
_____ _____ on the _____!
(plural noun) (verb ending in -ing) (noun)

Pretraining

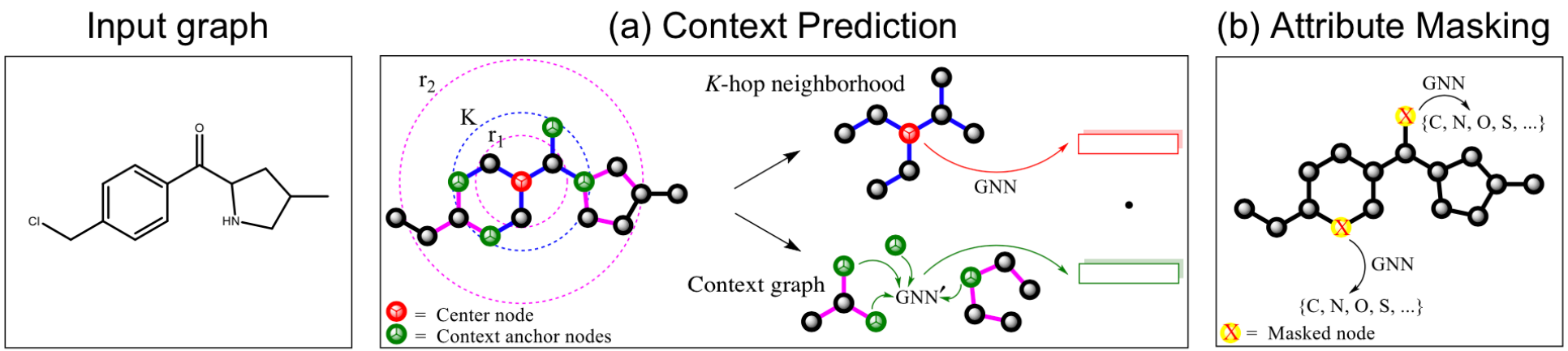


Figure 2: Illustration of our node-level methods, Context Prediction and Attribute Masking for pre-training GNNs. **(a)** In Context Prediction, the subgraph is a K-hop neighborhood around a selected center node, where K is the number of GNN layers and is set to 2 in the figure. The context is defined as the surrounding graph structure that is between r_1- and r_2-hop from the center node, where we use $r_1 = 1$ and $r_2 = 4$ in the figure. **(b)** In Attribute Masking, the input node/edge attributes (*e.g.*, atom type in the molecular graph) are randomly masked, and the GNN is asked to predict them.

Strategies for Pre-Training Graph Neural Networks. Hu et al., 2020

Pretraining

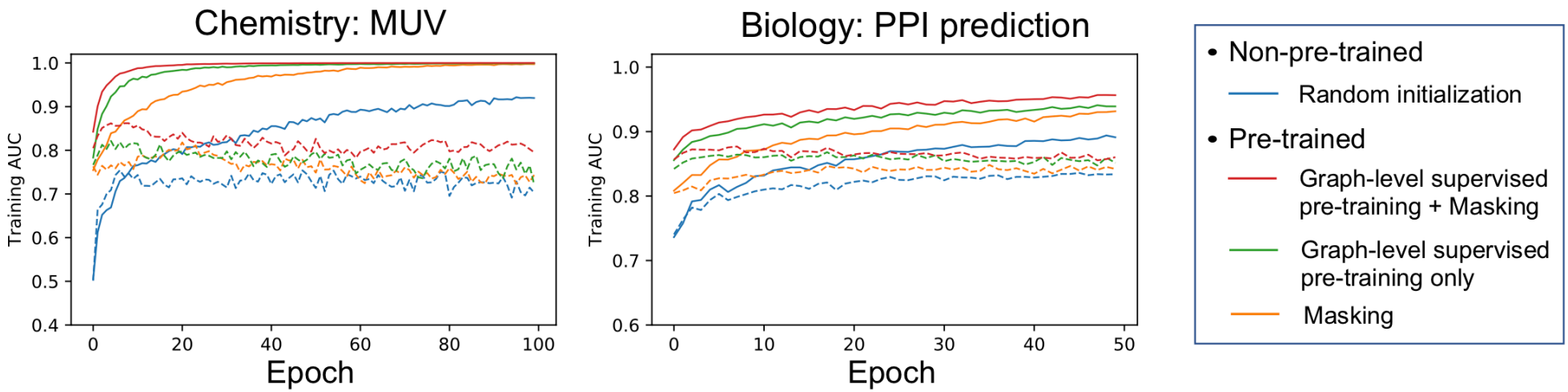


Figure 4: **Training and validation curves of different pre-training strategies on GINs.** Solid and dashed lines indicate training and validation curves, respectively.

- MUV: Maximum Unbiased Validation set (PCBA subset of 93k mols)
- PPI: 395k unlabeled protein ego-networks

Strategies for Pre-Training Graph Neural Networks. Hu et al., 2020

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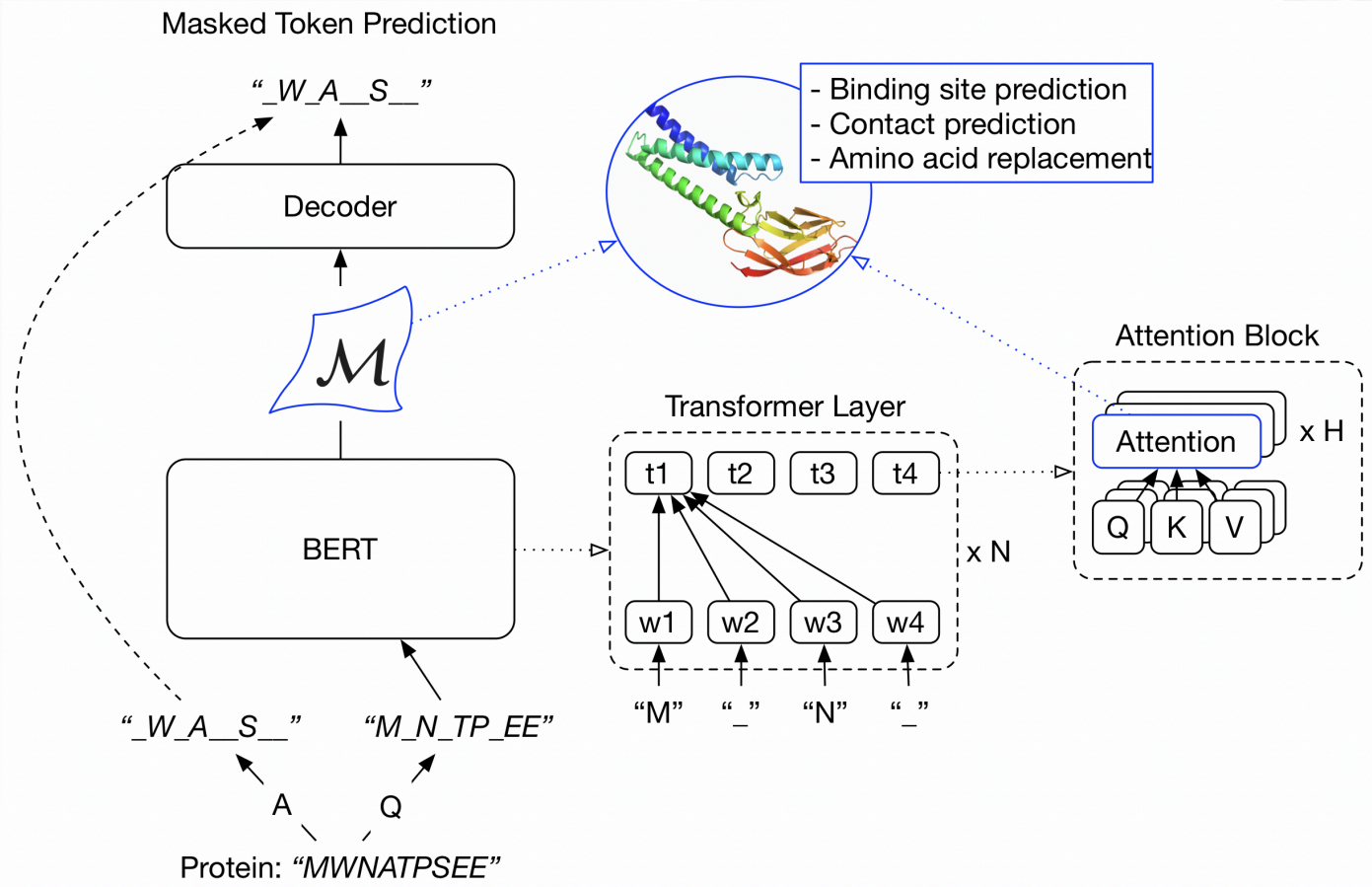
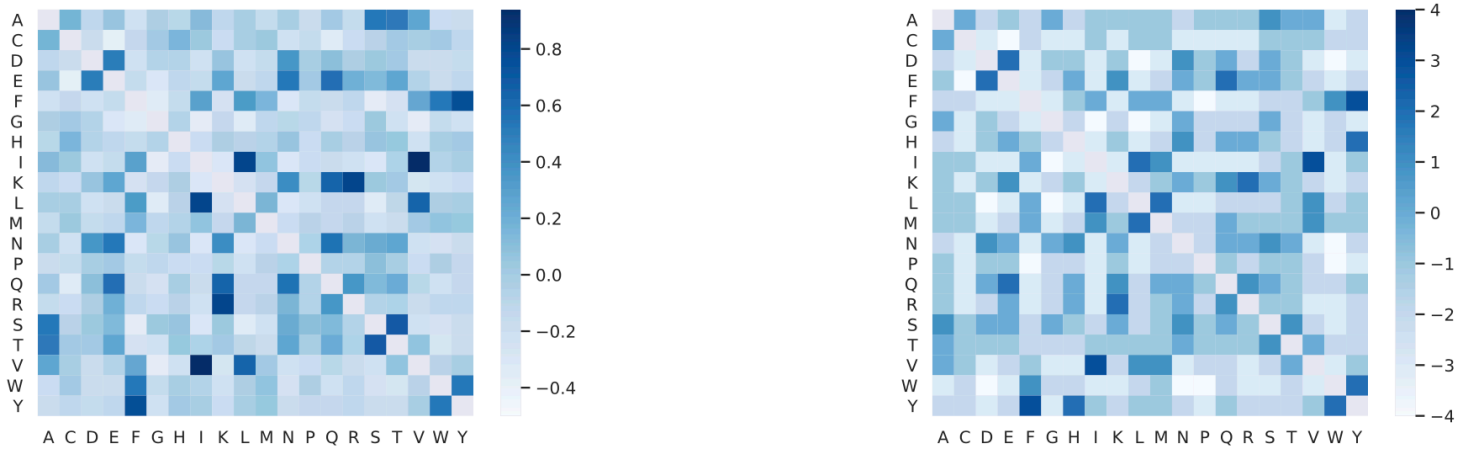
PROTEIN PRETRAINING

Protein BERT



Protein BERT

- Amino acid substitution relationship
  - Pearson r = 0.80 to BLOSUM62 matrix



(a) Attention similarity

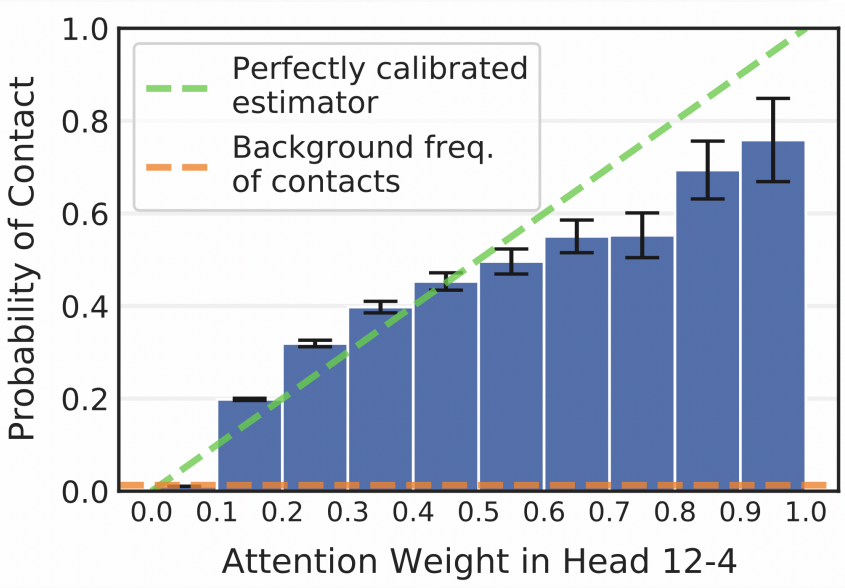
(b) BLOSUM62 substitution scores

Figure 3: Comparison of attention similarity matrix with the substitution matrix. Each matrix entry represents an amino-acid pair (codes in Appendix B.1). The two matrices have a Pearson correlation of 0.80 with one another, suggesting that attention is largely consistent with substitution relationships.

BERTology Meets Biology. Vig et al., 2020

Protein BERT

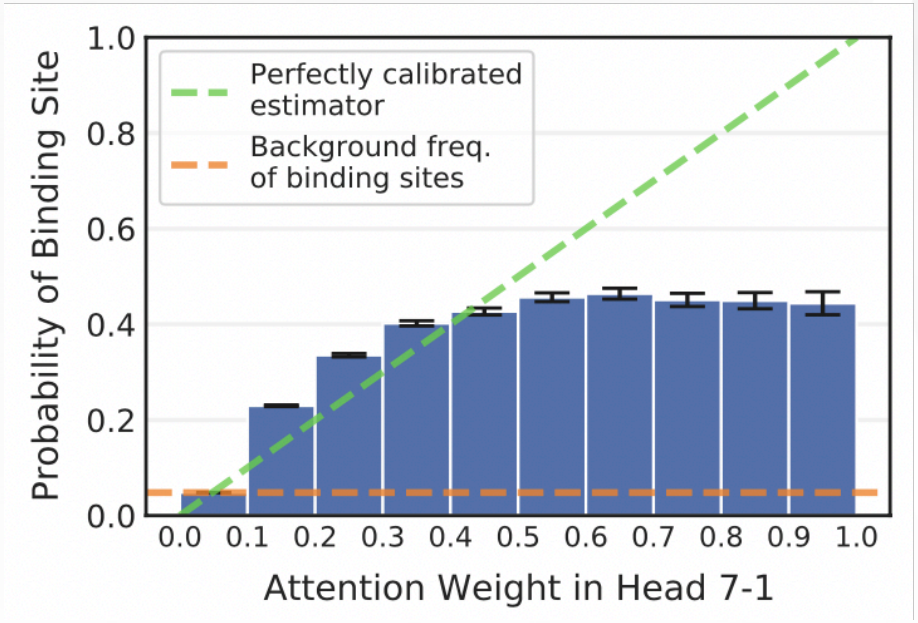
- Contact prediction
  - Ex) de novo TIM-barrel (5BVL) 내 서열상 거리가 머나 구조상 인접한 residue 인식

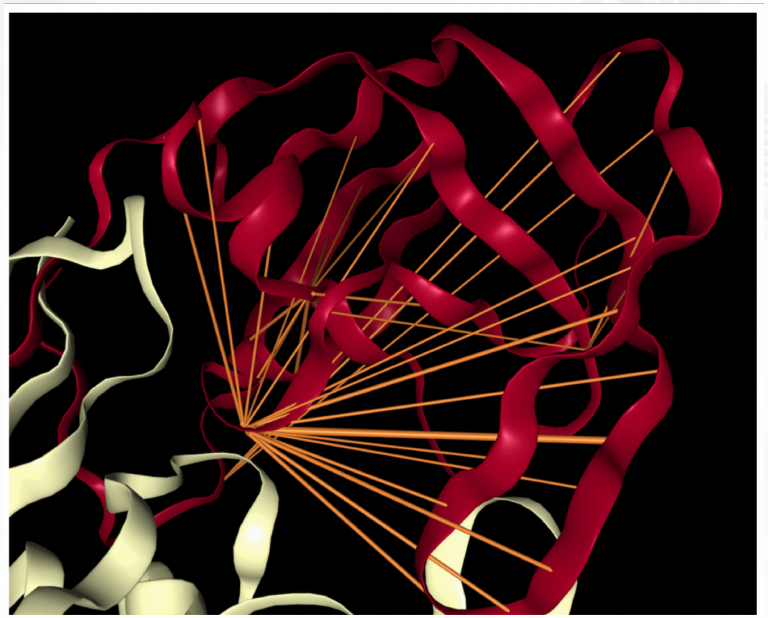


BERTology Meets Biology. Vig et al., 2020

Protein BERT

- Binding site prediction
  - Ex) HIV-1 protease (7HVP) binding site 인식





BERTology Meets Biology. Vig et al., 2020

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Thank You