DeepAffinity: Interpretable Deep Learning of Compound-Protein Affinity through Unified Recurrent and Convolutional Neural Networks

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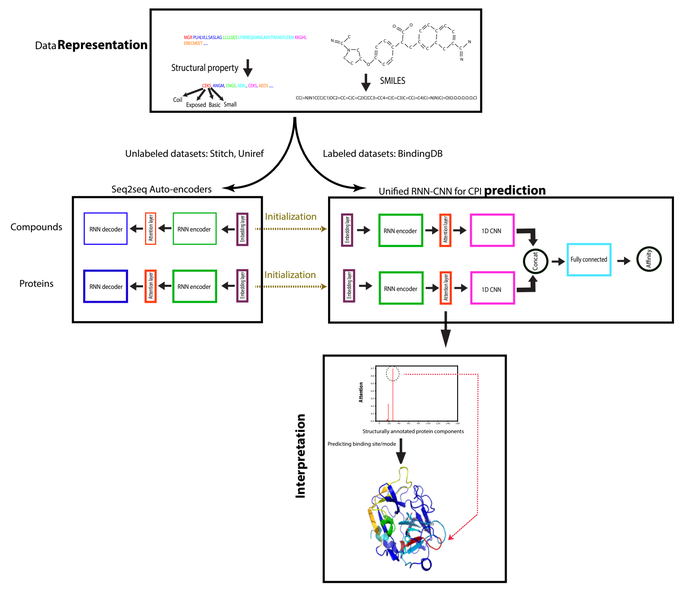
ABSTRACT

- **High-throughput drug discovery** through deep learning.
- **Novel representation** of structurally-annotated protein sequences.
- We present a **semi-supervised deep learning** model that unifies recurrent and convolutional neural networks to exploit both unlabeled and labeled data.
- **Transfer learning** for new protein classes with few labeled data.
- Embedded **attention mechanism** to gain **interpretability**.
- Our models **outperform** conventional options in achieving relative error in IC_{50} within 5 to 10-fold.

Availability: https://github.com/Shen-Lab/DeepAffinity

METHODS

Overall scheme



Data representation

- Compound: SMILES strings
- Protein: We developed Structural property sequence (SPS) based on predicted secondary structure elements (SSEs), solvent accessibility, physicochemical characteristics and lengths of SSEs.

Semi-supervised deep learning model

- Unsupervised learning: Seq2seq auto-encoder models with attention mechanism to exploit abundant unlabeled data.
- Supervised learning: Unified recurrent and convolutional neural networks with attention mechanism are jointly trained starting with pre-trained encoder part of seq2seq
- Interpretability through the embedded attention mechanism
- Deep transfer learning

RESULT

Novel Representations v.s. Baseline Pfam/Fingerprints

	Baseline representations			Novel representations		
	Ridge	Lasso	RF	Ridge	Lasso	RF
Training	1.08 (0.63)	1.11 (0.61)	0.70 (0.87)	1.13 (0.60)	1.13 (0.60)	**0.64** (0.90)
Testing	1.10 (0.60)	1.13 (0.58)	**0.87** (0.78)	1.13 (0.58)	1.13 (0.57)	**0.87** (0.78)
ER	1.54 (0.33)	1.54 (0.30)	1.53 (0.43)	**1.33** (0.43)	**1.33** (0.41)	1.36 (0.48)
Ion Channel	1.07 (0.33)	1.09 (0.20)	1.17 (0.10)	1.02 (0.42)	1.04 (0.40)	**0.97** (0.45)
GPCR	1.25 (0.62)	1.26 (0.57)	**1.17** (0.59)	1.36 (0.30)	1.37 (0.28)	1.20 (0.64)
Time (core hours)	4.0	6.97	1571.6	0.41	3.05	974.6
Memory (Gb)	7.6	7.6	8.2	7.7	7.7	6.4

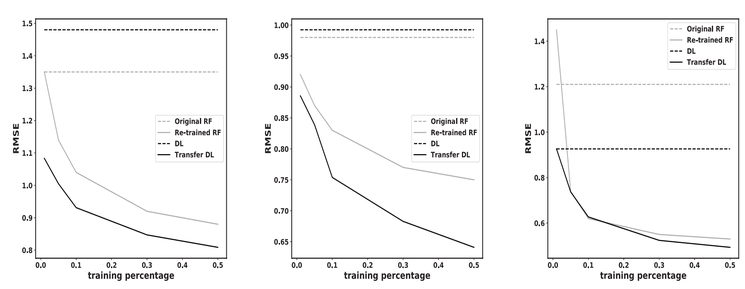
SPS representation saves 40% training time and 20% memory while achieving the similar or better performances over test set and lowered RMSE for generalization sets

Shallow Models v.s. Deep Models

	RF	Separate RNN-CNN Models			Unified RNN-CNN Models		
		single	parameter ensemble	parameter+NN ensemble	single	parameter ensemble	parameter+NN ensemble
Training	0.64 (0.90)	0.60 (0.92)	0.56 (0.93)	0.52 (0.93)	0.47 (0.94)	0.45 (0.94)	**0.42** (0.95)
Testing	0.87 (0.78)	0.89 (0.76)	0.87 (0.78)	0.84 (0.79)	0.74 (0.84)	0.73 (0.84)	**0.71** (0.86)
Generalization – ER	**1.36** (0.48)	1.40 (0.17)	1.48 (0.22)	1.42 (0.28)	1.43 (0.38)	1.44 (0.37)	1.47 (0.34)
Generalization – Ion Channel	**0.97** (0.45)	1.05 (0.33)	1.03 (0.34)	1.02 (0.42)	1.07 (0.36)	1.06 (0.37)	**0.97** (0.45)
Generalization – GPCR	1.20 (0.64)	1.18 (0.48)	1.15 (0.54)	1.19 (0.59)	1.01 (0.76)	1.01 (0.74)	**0.93** (0.78)

Unified RNN-CNN models outperform random forest and separate RNN-CNN models. Averaging ensembles of models lower RMSE by reducing the variance of model.

Deep transfer learning for new classes of protein targets



Deep transfer learning models increasingly improved the predictive performance compared to the original deep learning models, given increasing amount of labeled data. Even few labeled data is enough for significant improvement.

Predicting target selectivity of drugs

Protein-tyrosine phosphatase (PTP) family:

	Baseline rep. + RF			Novel rep. + RF			Novel rep. + DL		
Protein	comp1	comp2	comp3	comp1	comp2	comp3	comp1	comp2	comp3
PTP1B	7.80	7.83	7.80	**8.38**	8.15	**8.42**	**9.42**	**8.64**	**8.11**
PTPRA	7.80	7.83	7.80	8.18	**8.62**	8.19	8.38	8.39	7.62
PTPRC	7.81	7.84	7.81	8.22	8.49	8.19	8.41	8.44	8.03
PTPRE	7.80	7.83	7.80	8.23	8.53	8.26	7.96	8.21	7.31
SHP1	**7.82**	**7.84**	**7.84**	8.09	8.43	8.13	8.38	8.26	7.88

- Random forest using baseline representations cannot tell target specificity within the PTP family as the proteins' Pfam descriptions are almost indistinguishable.
- Using novel representations, random forest correctly predicted PTP1B selectivity for compounds 1 and 3 but not compound 2, whereas unified RNN-CNN models correctly did so for all three compounds.

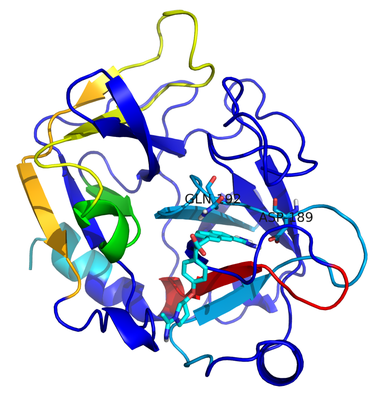
INTERPRETABILITY

How do the compound-protein pairs interact?

		Number of SSEs		Top 10% (4) SSEs predicted as binding site		
Target–Drug	PDB ID	total	binding site	# of TP	Enrichment	Highest rank for TP
Human COX2–rofecoxib	5KIR	40	6	1	1.67	2
Human PTP1B–OBA	1C85	34	5	1	1.70	4
Human factor Xa–DX9065	1FAX	31	4	1	1.94	2

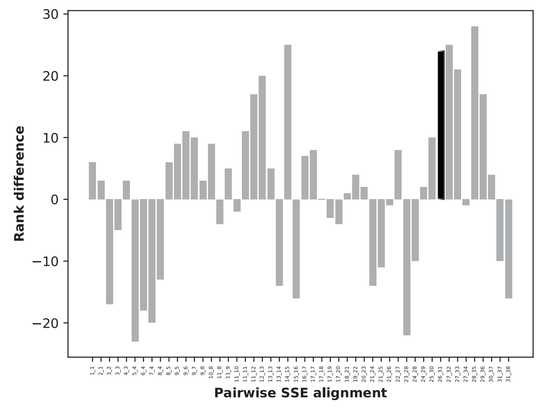
Compared to randomly ranking the SSEs, our approach can enrich binding site prediction by 1.6∼2.0 fold for the three CPIs.

Human factor Xa–DX-9065a interaction:



The binding site was correctly predicted with a high rank 2. And the SSE ranked first, a false positive, was its immediate neighbor in sequence.

How are targets selectively interacted?



- Position 192 has been identified as the source of specificity: it is a charge-neutral polar glutamine (Gln192) in Xa but a negatively-charged glutamate (Glu192) in thrombin.
- The ground-truth segment (black) was ranked the 4th among 50 segments.

REFERENCES

[1] Mostafa Karimi, Di Wu, Zhangyang Wang, Yang Shen. "DeepAffinity: Interpretable Deep Learning of Compound-Protein Affinity through Unified Recurrent and Convolutional Neural Networks", under revision for Bioinformatics.

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