Supporting Information

MSA-Regularized Protein Sequence Transformer Toward Predicting Genome-Wide Chemical-Protein Interactions: Application to GPCRome Deorphanization

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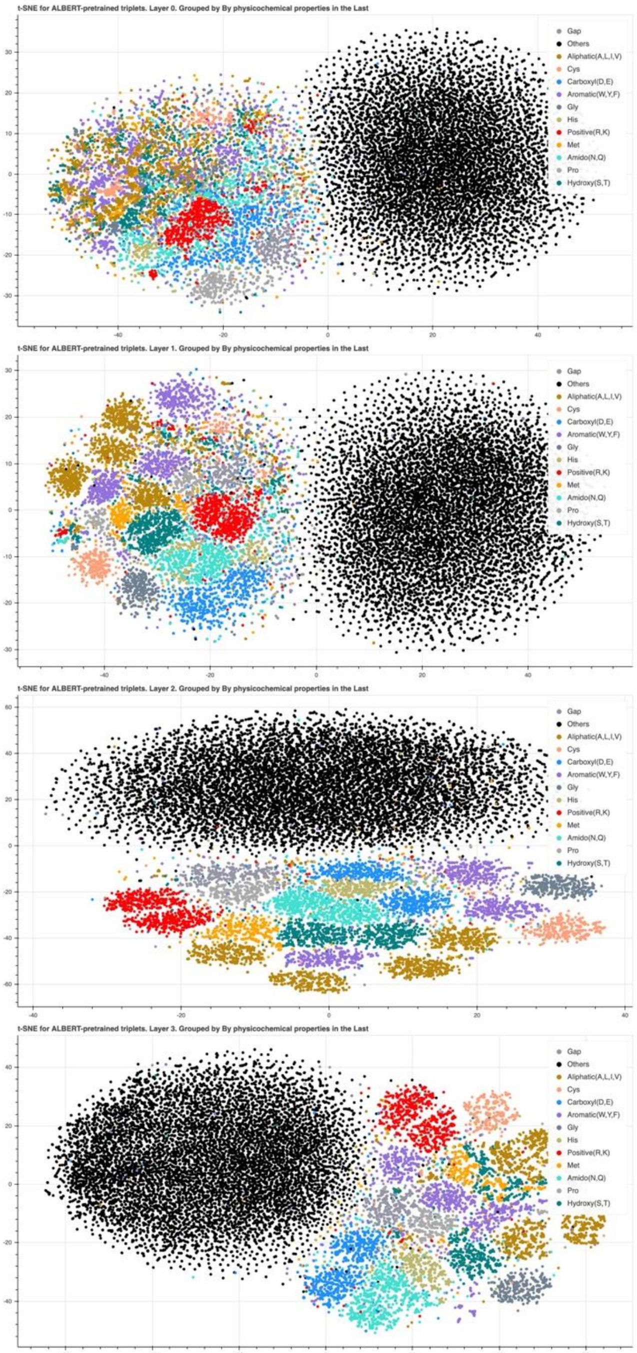
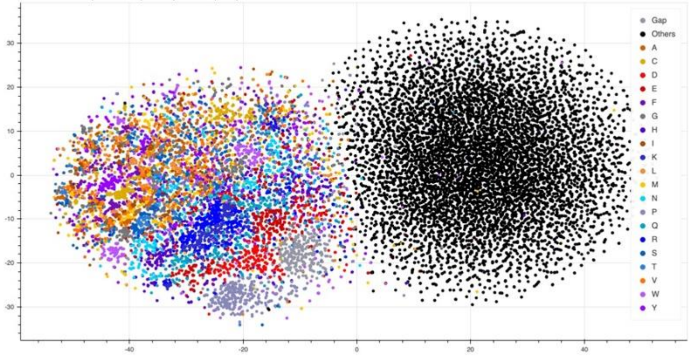
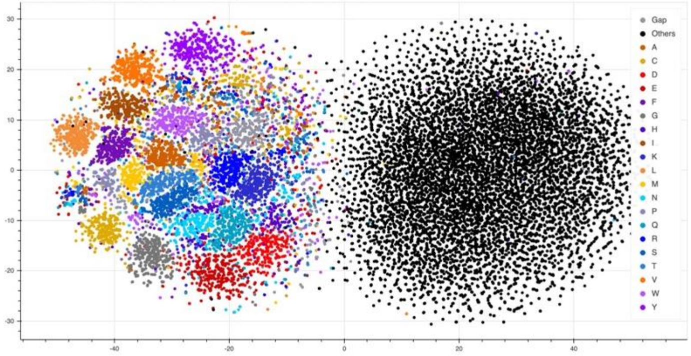


Figure S1: Clustering of pre-trained triplet DISAE vectors at (A) Level 1, (B) Level 2, (C) Level 3, and (D) Level 4 of ALBERT. The triplet is colored by the physiochemical properties of the third amino acid.

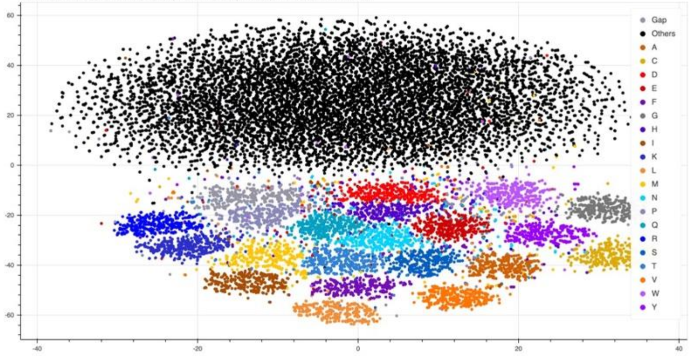
t-SNE for ALBERT-pretrained triplets. Layer 0. Grouped by Individual amino acids in the Last



t-SNE for ALBERT-pretrained triplets. Layer 1. Grouped by Individual amino acids in the Last



t-SNE for ALBERT-pretrained triplets. Layer 2. Grouped by Individual amino acids in the Last



t-SNE for ALBERT-pretrained triplets. Layer 3. Grouped by Individual amino acids in the Last

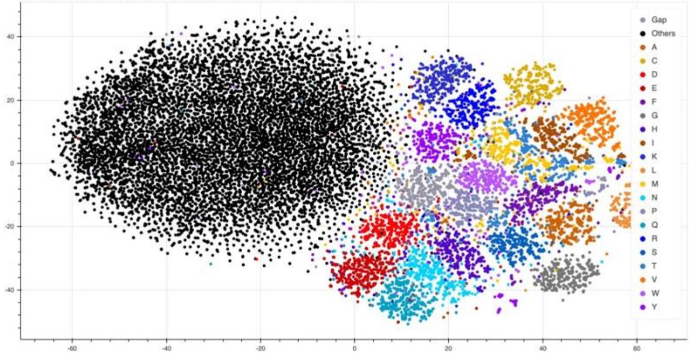


Figure S2: The same clustering trends as in Figure S1 were also observed when triplets are grouped by individual amino acid types, rather than their physicochemical properties of side chains.

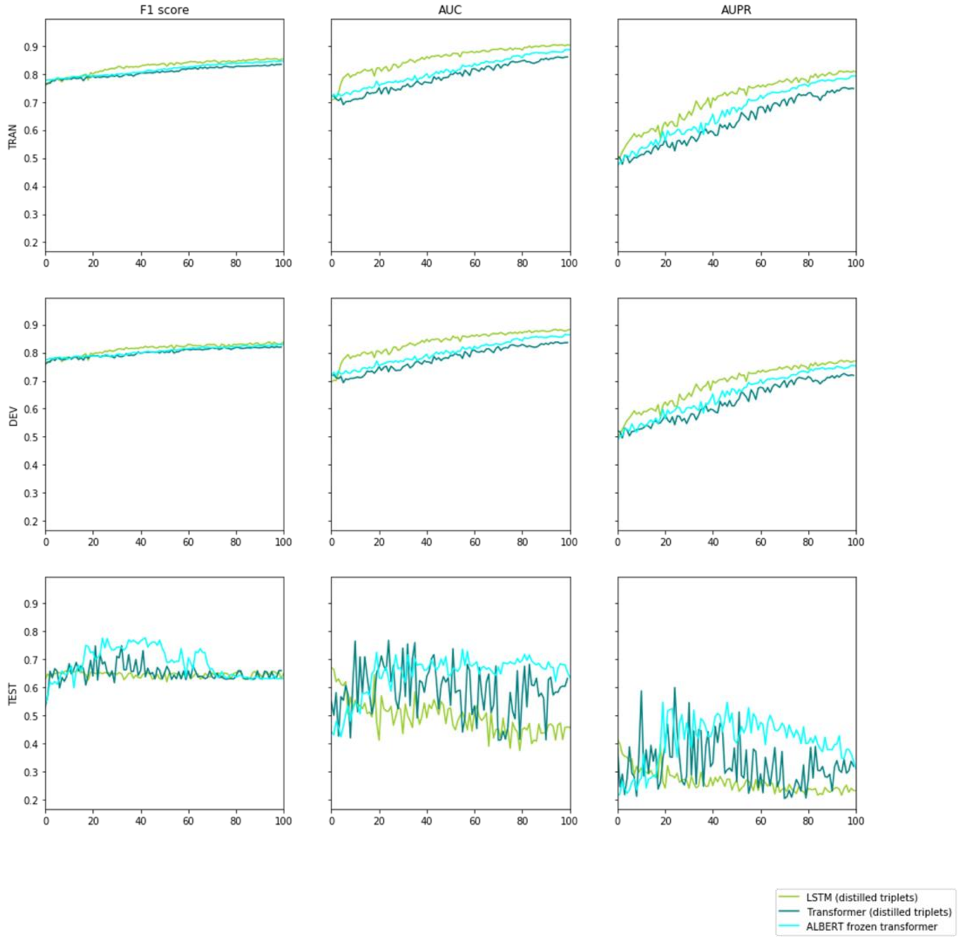


Figure S3: The three major models as in the AUC curves in the paper. All *x* axes are the number of epochs trained. ALBERT frozen transformer shows consistently better performance, which becomes the critical advantage of DISAE in deorphanization, where remote orphan proteins are significantly different from training data and overfitting is impossible to control given the unknown true labels for classification. Using DISAE, we could be confident that even if we train the model for too long or too short epochs, the prediction reliability on orphans will be robust.

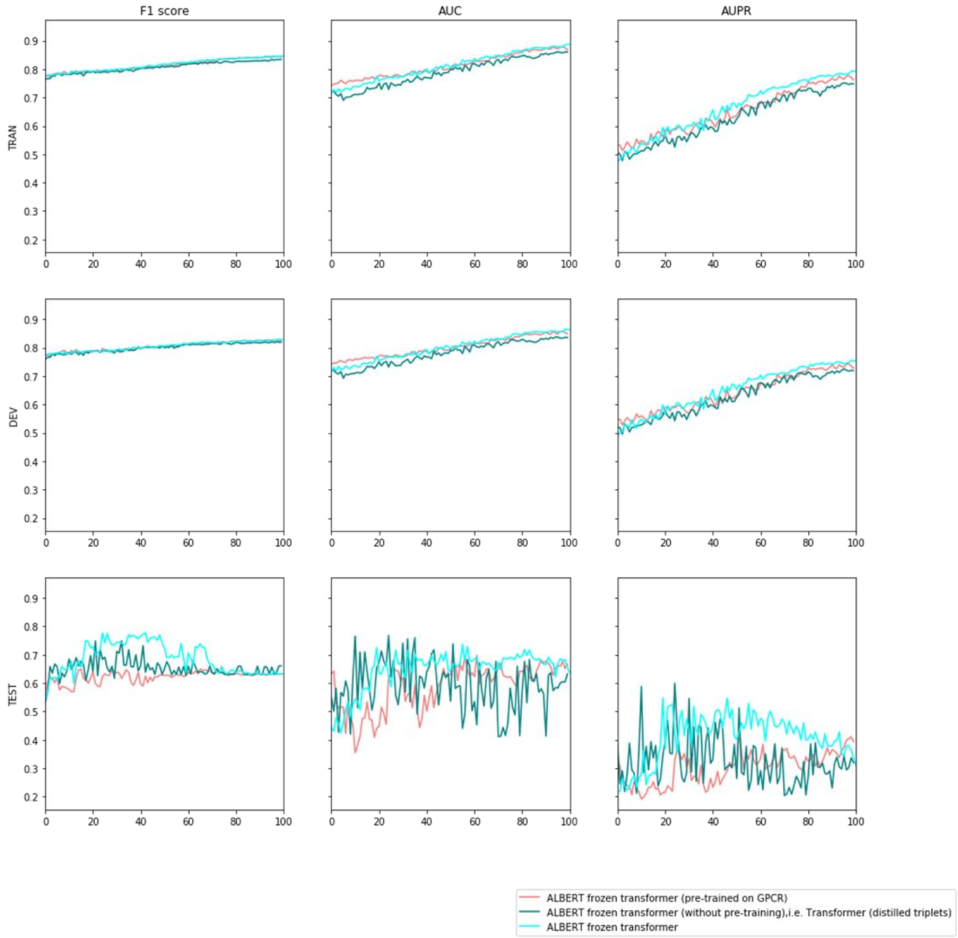


Figure S4: The effect of pre-training: ALBERT frozen transformer, i.e., the one pre-trained on whole pfams as proposed in DISAE, shows robust and consistent better performance. All *x* axes are the number of epochs trained.

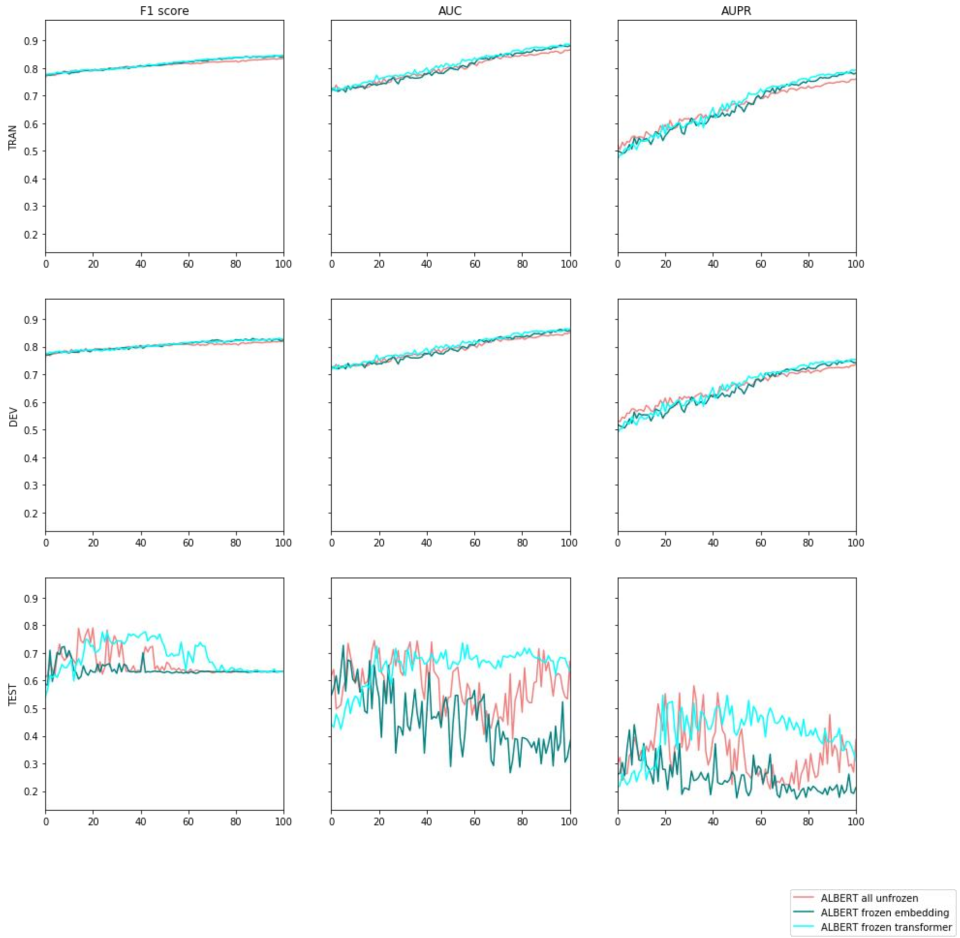


Figure S5: The effect of different fine-tuning strategy with freezing parts of ALBERT: Although the other setting could be as good as ALBERT frozen transformer in some epochs, but they all suffer from large performance variance by epoch. ALBERT frozen transformer proves consistent and robust high performance. All *x* axes are the number of epochs trained.

PF03402

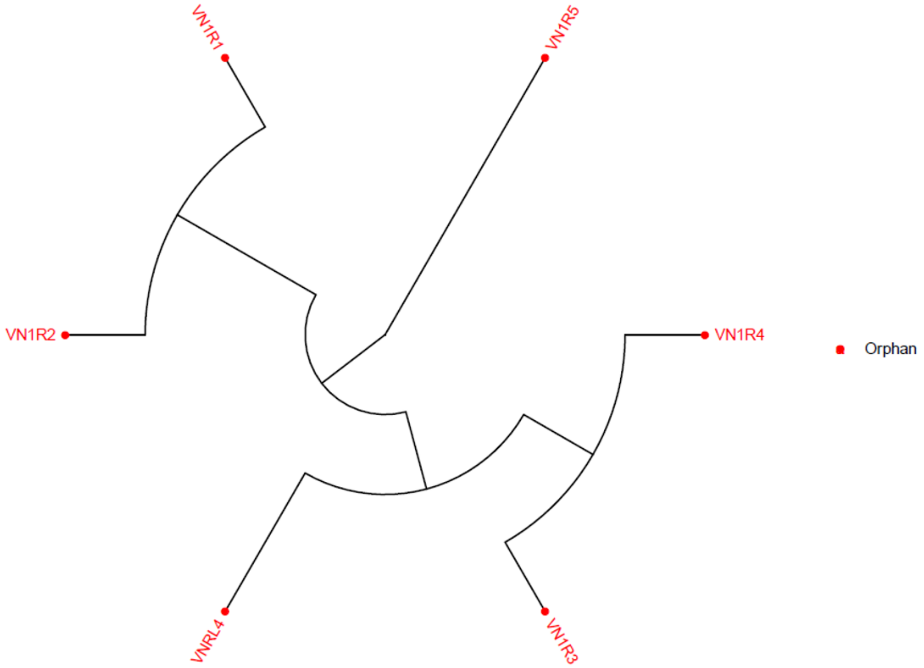


Figure S6: Phylogenetic tree for PF03402

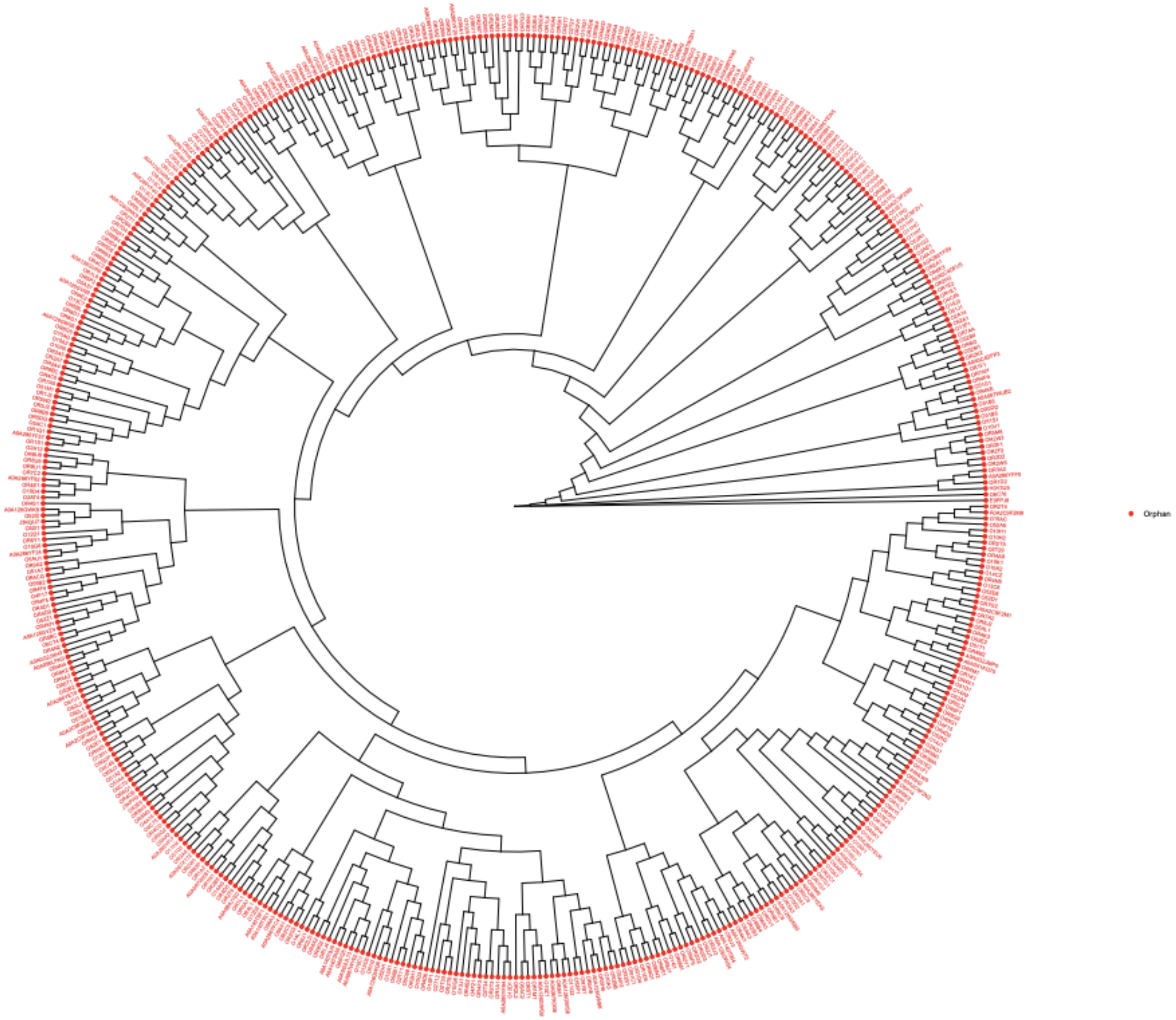


Figure S7: Phylogenetic tree for PF13853

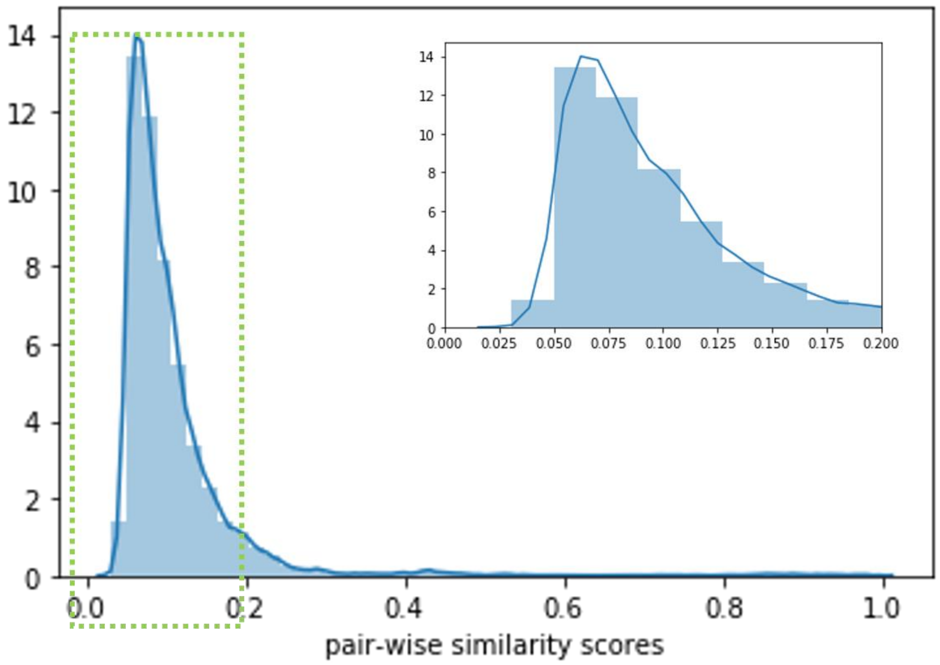


Figure S8: Protein pairwise similarity distribution of benchmark data: To simulate realistic deorphanization scenario, where remote orphan protein could be significantly different from data used to train models, we design a protein similarity-based data splitting strategy. First, pairwise bit-scores are calculated with standard BLAST+ package. A distribution could be found in Figure 8. Then, setting a threshold of 0.035, proteins with pairwise similarity lower than the threshold are keep separately in two groups. The protein-chemical activity pairs with protein in the relative smaller group will be used as testing data. The left samples are then split into training and validation.

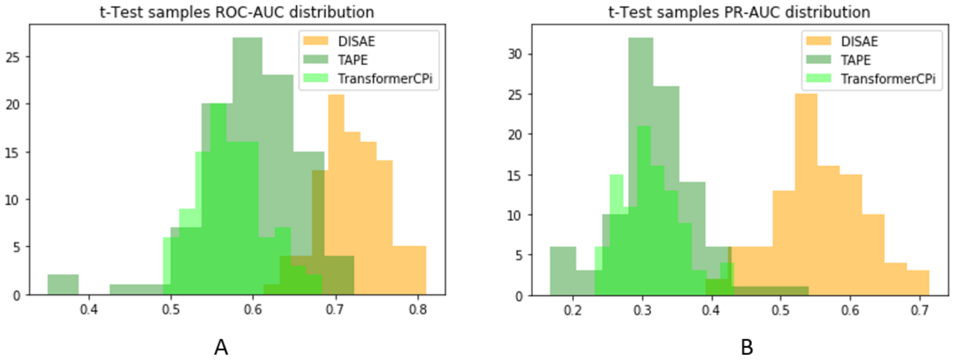


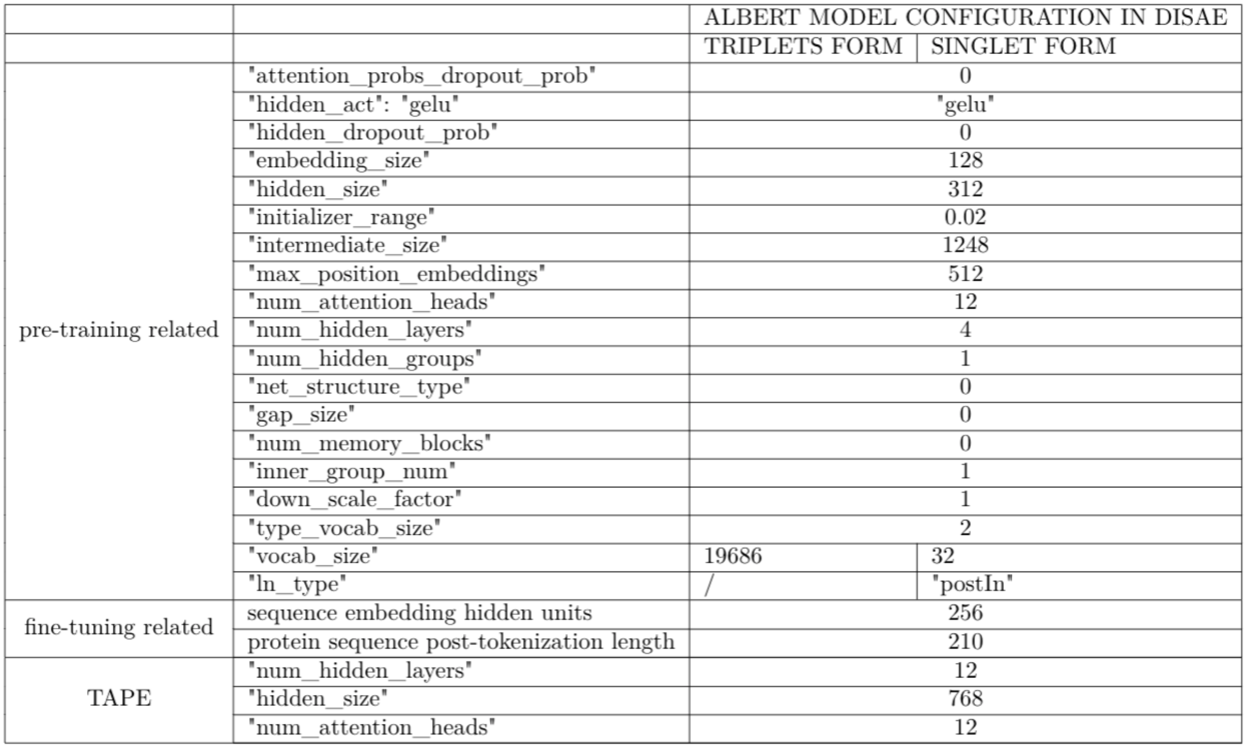
Figure 9: t-Test sample AUC distributions. The p-values of DISAE mean AUC scores against TAPE and TranformerCPI are close to 0.

Orphan Receptor	**Predicted Drug [Known binding protein]**
A0A087WY02	XXPANQJNYNUNES-UHFFFAOYSA-N [’P23975’, ’Q05940’, ’P31645’]
A0A0A0MQW8	BYJAVTDNIXVSPW-UHFFFAOYSA-N [’Q96RJ0’, ’P35348’, ’P43140’]
A0A0B4J1V8	RGCVKNLCSQQDEP-UHFFFAOYSA-N [’P33261’, ’P18901’, ’P08684’]
A0A0C4DFX5	MBUVEWMHONZEQD-UHFFFAOYSA-N [’P11509’, ’P33261’, ’Q16873’]
A0A126GVR8	BPZSYCZIITTYBL-YJYMSZOUSA-N [’P13945’, ’P11509’, ’P07550’]
A0A126GWK9	VQODGRNSFPNSQE-DVTGEIKXSA-N [’P46721’, ’P04083’, ’P20309’]
A0A126GWS4	VMWNQDUVQKEIOC-CYBMUJFWSA-N [’P18901’, ’P08684’, ’P50226’]
A0A1B0GTK7	ATALOFNDEOCMKK-OITMNORJSA-N [’P29371’, ’P11712’, ’P33261’]
A0A1B0GVZ0	OWQUZNMMYNAXSL-UHFFFAOYSA-N [’Q01959’, ’P31390’, ’P35367’]
A0A286YF86	BGDKAVGWHJFAGW-UHFFFAOYSA-N [’P08485’, ’P20309’, ’P17200’]
A0A286YF92	IRSCQMHQWWYFCW-UHFFFAOYSA-N [’Q13255’, ’Q96FL8’]
A0A286YFH6	BUGYDGFZZOZRHP-UHFFFAOYSA-N [’O00591’, ’P11509’, ’Q96FL8’]
A0A2C9F2M5	CYQFCXCEBYINGO-IAGOWNOFSA-N [’P47746’, ’P47936’, ’P11712’]
A3KFT3	KKZJGLLVHKMTCM-UHFFFAOYSA-N [’Q16678’, ’P33527’]
A6NFC9	BYJAVTDNIXVSPW-UHFFFAOYSA-N [’Q96RJ0’, ’P35348’, ’P43140’]
A6NH00	BGDKAVGWHJFAGW-UHFFFAOYSA-N [’P08485’, ’P20309’, ’P17200’]
A6NMS3	IYIKLHRQXLHMJQ-UHFFFAOYSA-N [’P11509’, ’P07550’, ’P51589’]
A6NMU1	BARDROPHSZEBKC-OITMNORJSA-N [’P08684’, ’P11712’, ’P25103’]
C9J1J7	YFGHCGITMMYXAQ-LJQANCHMSA-N [’P20815’, ’P11712’, ’P05177’]
C9JQD8	LWAFSWPYPHEXKX-UHFFFAOYSA-N [’P10635’, ’P07550’, ’P08588’]
C9JW47	BYBLEWFAAKGYCD-UHFFFAOYSA-N [’Q6PIU1’, ’P22001’, ’P33261’]
E7ENI1	OCJYIGYOJCODJL-UHFFFAOYSA-N [’P10635’, ’P02768’, ’P35367’]
E9PH76	ZSCDBOWYZJWBIY-UHFFFAOYSA-N [’P07550’, ’P33261’, ’P11229’]
E9PPJ8	OZYUPQUCAUTOBP-QXAKKESOSA-N [’P33535’, ’P35372’]
F8VUV1	CYQFCXCEBYINGO-IAGOWNOFSA-N [’P47746’, ’P47936’, ’P11712’]
G3V4Q5	XXPANQJNYNUNES-UHFFFAOYSA-N [’P23975’, ’Q05940’, ’P31645’]
H0Y622	UCHDWCPVSPXUMX-TZIWLTJVSA-N [’P11509’, ’P07550’, ’P21452’]
J3KQU7	IZTQOLKUZKXIRV-YRVFCXMDSA-N [’Q9NPD5’, ’P30553’, ’Q63931’]
O00590	JOATXPAWOHTVSZ-UHFFFAOYSA-N [’P13945’, ’P07550’, ’P18089’]
O15218	BYJAVTDNIXVSPW-UHFFFAOYSA-N [’Q96RJ0’, ’P35348’, ’P43140’]
O43869	UCHDWCPVSPXUMX-TZIWLTJVSA-N [’P11509’, ’P07550’, ’P21452’]
O60431	XXPANQJNYNUNES-UHFFFAOYSA-N [’P23975’, ’Q05940’, ’P31645’]
O76099	SHGAZHPCJJPHSC-YCNIQYBTSA-N [’P31025’, ’P11509’, ’Q02928’]
P04000	LUZRJRNZXALNLM-JGRZULCMSA-N [’P08684’, ’P34969’, ’P35462’]
P04001	XXPANQJNYNUNES-UHFFFAOYSA-N [’P23975’, ’Q05940’, ’P31645’]
P0C604	DGBIGWXXNGSACT-UHFFFAOYSA-N [’O00591’, ’O14764’, ’P48169’]
P0C628	HTIQEAQVCYTUBX-UHFFFAOYSA-N [’Q02641’, ’P08684’, ’P04798’]
P0C645	IRSCQMHQWWYFCW-UHFFFAOYSA-N [’Q13255’, ’Q96FL8’]
P0C7N5	VMWNQDUVQKEIOC-CYBMUJFWSA-N [’P18901’, ’P08684’, ’P50226’]
P0DMS8	DGBIGWXXNGSACT-UHFFFAOYSA-N [’O00591’, ’O14764’, ’P48169’]
P0DN77	XXPANQJNYNUNES-UHFFFAOYSA-N [’P23975’, ’Q05940’, ’P31645’]
P0DN78	XXPANQJNYNUNES-UHFFFAOYSA-N [’P23975’, ’Q05940’, ’P31645’]
P47804	QWAXKHKRTORLEM-UGJKXSETSA-N [’P21452’, ’P08684’, ’P35462’]
P58173	VHYCDWMUTMEGQY-UHFFFAOYSA-N [’P13945’, ’P07550’, ’P08588’]
Q15612	OIRDTQYFTABQOQ-KQYNXXCUSA-N [’P29275’, ’P55263’, ’P25099’]
Q15617	ZSCDBOWYZJWBIY-UHFFFAOYSA-N [’P07550’, ’P33261’, ’P11229’]

Q6IFH4	KWTSXDURSIMDCE-QMMMGPOBSA-N [’P25100’, ’Q8HZ64’, ’P10635’]
Q7Z5H5	IYIKLHRQXLHMJQ-UHFFFAOYSA-N [’P11509’, ’P07550’, ’P51589’]
Q8N0Y5	COUYJEVMBVSIHV-SFHVURJKSA-N [’P10632’, ’P07550’, ’P11712’]
Q8N6U8	BYJAVTDNIXVSPW-UHFFFAOYSA-N [’Q96RJ0’, ’P35348’, ’P43140’]
Q8NG76	IZTQOLKUZKXIRV-YRVFCXMDSA-N [’Q9NPD5’, ’P30553’, ’Q63931’]
Q8NG83	CJOFXWAVKWHTFT-XSFVSMFZSA-N [’Q9HB55’, ’P22086’, ’P10635’]
Q8NG85	IYIKLHRQXLHMJQ-UHFFFAOYSA-N [’P11509’, ’P07550’, ’P51589’]
Q8NGB2	BARDROPHSZEBKC-OITMNORJSA-N [’P08684’, ’P11712’, ’P25103’]
Q8NGC2	MEFKEPWMEQBLKI-AIRLBKTGSA-N [’P19623’, ’P31153’, ’P25099’]
Q8NGC8	COUYJEVMBVSIHV-SFHVURJKSA-N [’P10632’, ’P07550’, ’P11712’]
Q8NGD3	OCJYIGYOJCODJL-UHFFFAOYSA-N [’P10635’, ’P02768’, ’P35367’]
Q8NGD4	UCTWMZQNUQWSLP-VIFPVBQESA-N [’P07550’, ’O15244’, ’P08684’]
Q8NGE9	WNTYBHLDCKXEOT-UHFFFAOYSA-N [’P14416’, ’P31388’, ’P10275’]
Q8NGG2	BGDKAVGWHJFAGW-UHFFFAOYSA-N [’P08485’, ’P20309’, ’P17200’]
Q8NGI3	CYQFCXCEBYINGO-IAGOWNOFSA-N [’P47746’, ’P47936’, ’P11712’]
Q8NGI4	IRSCQMHQWWYFCW-UHFFFAOYSA-N [’Q13255’, ’Q96FL8’]
Q8NGI7	OCJYIGYOJCODJL-UHFFFAOYSA-N [’P10635’, ’P02768’, ’P35367’]
Q8NGJ5	JSWZEAMFRNKZNL-UHFFFAOYSA-N [’P11712’, ’P41595’, ’P05177’]
Q8NGJ9	GEFQWZLICWMTKF-CDUCUWFYSA-N [’P25100’, ’P18089’, ’P08913’]
Q8NGK2	LUZRJRNZXALNLM-JGRZULCMSA-N [’P08684’, ’P34969’, ’P35462’]
Q8NGK6	ZSCDBOWYZJWBIY-UHFFFAOYSA-N [’P07550’, ’P33261’, ’P11229’]
Q8NGL9	UCHDWCPVSPXUMX-TZIWLTJVSA-N [’P11509’, ’P07550’, ’P21452’]
Q8NGM9	BYJAVTDNIXVSPW-UHFFFAOYSA-N [’Q96RJ0’, ’P35348’, ’P43140’]
Q8NGN7	XXPANQJNYNUNES-UHFFFAOYSA-N [’P23975’, ’Q05940’, ’P31645’]
Q8NGR4	BGDKAVGWHJFAGW-UHFFFAOYSA-N [’P08485’, ’P20309’, ’P17200’]
Q8NGS1	XXPANQJNYNUNES-UHFFFAOYSA-N [’P23975’, ’Q05940’, ’P31645’]
Q8NGT5	ATALOFNDEOCMKK-OITMNORJSA-N [’P29371’, ’P11712’, ’P33261’]
Q8NGU2	UCHDWCPVSPXUMX-TZIWLTJVSA-N [’P11509’, ’P07550’, ’P21452’]
Q8NGW1	DRHKJLXJIQTDTD-OAHLLOKOSA-N [’P08684’, ’P34969’, ’P35462’]
Q8NGX9	URKOMYMAXPYINW-UHFFFAOYSA-N [’P31389’, ’P07550’, ’P33261’]
Q8NGY9	UCTWMZQNUQWSLP-VIFPVBQESA-N [’P07550’, ’O15244’, ’P08684’]
Q8NGZ2	IZTQOLKUZKXIRV-YRVFCXMDSA-N [’Q9NPD5’, ’P30553’, ’Q63931’]
Q8NGZ4	RUDATBOHQWOJDD-BSWAIDMHSA-N [’P52895’, ’Q96RI1’, ’P08684’]
Q8NH04	BYBLEWFAAKGYCD-UHFFFAOYSA-N [’Q6PIU1’, ’P22001’, ’P33261’]
Q8NH05	KKGQTZUTZRNORY-UHFFFAOYSA-N [’P21453’, ’O95977’, ’P43004’]
Q8NH41	OZVBMTJYIDMWIL-AYFBDAFISA-N [’P07550’, ’P08684’, ’P34969’]
Q8NH48	ZSCDBOWYZJWBIY-UHFFFAOYSA-N [’P07550’, ’P33261’, ’P11229’]
Q8NH51	BUGYDGFZZOZRHP-UHFFFAOYSA-N [’O00591’, ’P11509’, ’Q96FL8’]
Q8NH57	XXPANQJNYNUNES-UHFFFAOYSA-N [’P23975’, ’Q05940’, ’P31645’]
Q8NH61	RUDATBOHQWOJDD-BSWAIDMHSA-N [’P52895’, ’Q96RI1’, ’P08684’]
Q8NH74	BYJAVTDNIXVSPW-UHFFFAOYSA-N [’Q96RJ0’, ’P35348’, ’P43140’]
Q8NH87	GJPICJJJRGTNOD-UHFFFAOYSA-N [’P25101’, ’P11712’, ’O95342’]
Q8NH89	ZSCDBOWYZJWBIY-UHFFFAOYSA-N [’P07550’, ’P33261’, ’P11229’]
Q8NH95	DERZBLKQOCDDDZ-JLHYYAGUSA-N [’P11509’, ’O60840’, ’P11229’]
Q8TCB6	HTIQEAQVCYTUBX-UHFFFAOYSA-N [’Q02641’, ’P08684’, ’P04798’]
Q8TDV2	XXPANQJNYNUNES-UHFFFAOYSA-N [’P23975’, ’Q05940’, ’P31645’]
Q8WZA6	ZFXYFBGIUFBOJW-UHFFFAOYSA-N [’P29275’, ’P25099’, ’Q60614’]
Q96KK4	XXPANQJNYNUNES-UHFFFAOYSA-N [’P23975’, ’Q05940’, ’P31645’]
Q96R54	VMWNQDUVQKEIOC-CYBMUJFWSA-N [’P18901’, ’P08684’, ’P50226’]

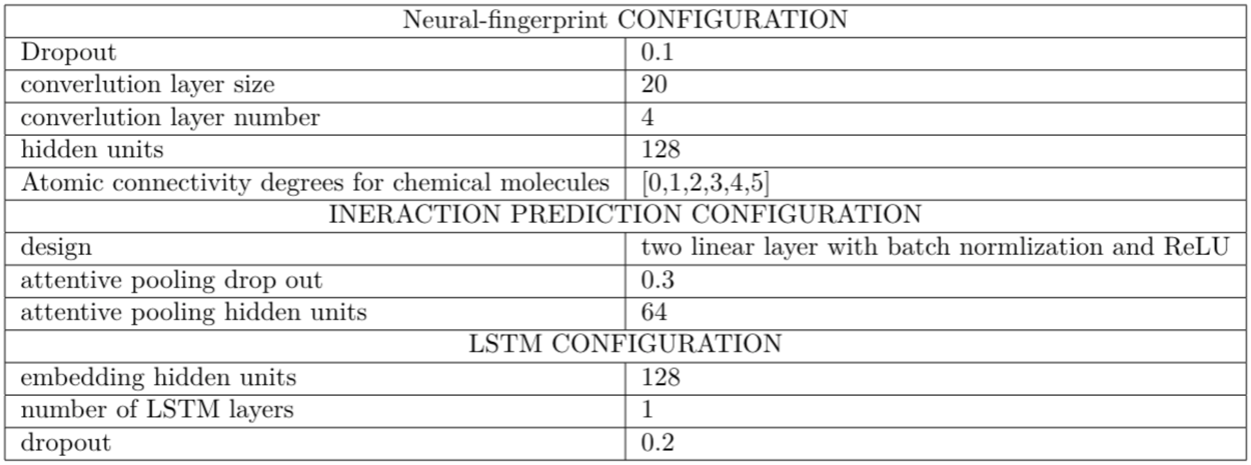
Q96R67	ZSCDBOWYZJWBIY-UHFFFAOYSA-N [’P07550’, ’P33261’, ’P11229’]
Q9BZJ7	UCHDWCPVSPXUMX-TZIWLTJVSA-N [’P11509’, ’P07550’, ’P21452’]
Q9BZJ8	KWTSXDURSIMDCE-QMMMGPOBSA-N [’P25100’, ’Q8HZ64’, ’P10635’]
Q9GZM6	PVNIIMVLHYAWGP-UHFFFAOYSA-N [’P49019’, ’Q15274’, ’Q80Z39’]
Q9H1Y3	FIVSJYGQAIEMOC-ZGNKEGEESA-N [’P10635’, ’Q9UNQ0’, ’P25103’]
Q9H210	IYIKLHRQXLHMJQ-UHFFFAOYSA-N [’P11509’, ’P07550’, ’P51589’]
Q9H339	IYIKLHRQXLHMJQ-UHFFFAOYSA-N [’P11509’, ’P07550’, ’P51589’]
Q9NZP2	IQVRBWUUXZMOPW-PKNBQFBNSA-N [’P29275’, ’Q96FL8’, ’P25099’]
Q9UGF5	GHOSNRCGJFBJIB-UHFFFAOYSA-N [’P30556’, ’P11712’, ’P23219’]
Q9UGF6	BTCSSZJGUNDROE-UHFFFAOYSA-N [’Q7Z2H8’, ’Q9Z0U4’, ’Q9UBS5’]
Q9UHM6	BGDKAVGWHJFAGW-UHFFFAOYSA-N [’P08485’, ’P20309’, ’P17200’]

Table S1: Predicted approved drug examples: 649 human orphan GPCRs, each paired to 555 approved GPCR-targeted drugs as novel samples chemical-protein pairs. Listed here are 106 of the orphan proteins paired with at least one approved GPCR-targeted drug with estimated false positive rate lower than 0.05. Proteins are presented with UniProt ID and chemicals are presented with InChIKey.



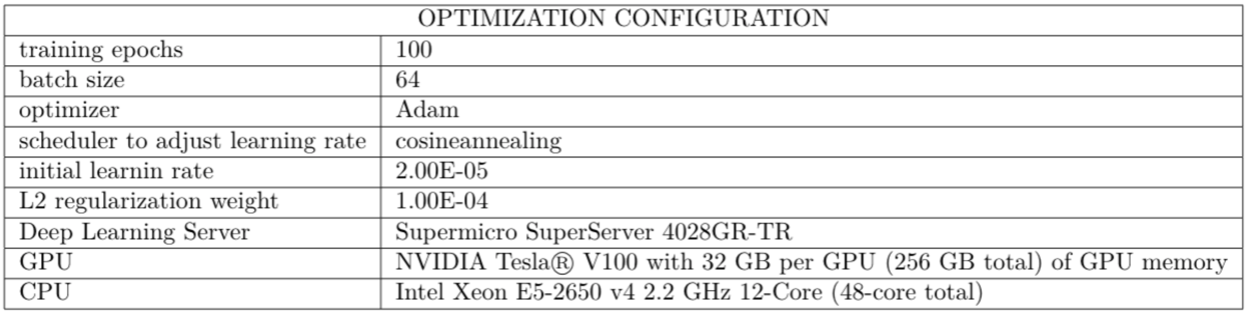
		ALBERT MODEL CONFIGURATION IN DISAE	
		TRIPLETS FORM	SINGLET FORM
pre-training related	"attention__probs__dropout__prob"	0	
	"hidden__act": "gelu"	"gelu"	
	"hidden__dropout__prob"	0	
	"embedding__size"	128	
	"hidden__size"	312	
	"initializer__range"	0.02	
	"intermediate__size"	1248	
	"max__position__embeddings"	512	
	"num__attention__heads"	12	
	"num__hidden__layers"	4	
	"num__hidden__groups"	1	
	"net__structure__type"	0	
	"gap__size"	0	
	"num__memory__blocks"	0	
	"inner__group__num"	1	
	"down__scale__factor"	1	
	"type__vocab__size"	2	
	"vocab__size"	19686	32
	"ln__type"	/	"postln"
fine-tuning related	sequence embedding hidden units	256	
	protein sequence post-tokenization length	210	
TAPE	"num__hidden__layers"	12	
	"hidden__size"	768	
	"num__attention__heads"	12	

Table S2: ALBERT configuration. ALBERT is using the package *Transformers* by Huggingface (https://github.com/huggingface/transformers). The author installed the package in Jan 2020.



Neural-fingerprint CONFIGURATION	
Dropout	0.1
converlution layer size	20
converlution layer number	4
hidden units	128
Atomic connectivity degrees for chemical molecules	[0,1,2,3,4,5]
INERACTION PREDICTION CONFIGURATION	
design	two linear layer with batch normlization and ReLU
attentive pooling drop out	0.3
attentive pooling hidden units	64
LSTM CONFIGURATION	
embedding hidden units	128
number of LSTM layers	1
dropout	0.2

Table S3: There are three major components of the fine-tuning model architecture: ALBERT to extract protein embedding, Neural-fingerprint to extract chemical embedding, and interaction prediction layers. LSTM serves as the baseline.



OPTIMIZATION CONFIGURATION	
training epochs	100
batch size	64
optimizer	Adam
scheduler to adjust learning rate	cosineannealing
initial learnin rate	2.00E-05
L2 regularization weight	1.00E-04
Deep Learning Server	Supermicro SuperServer 4028GR-TR
GPU	NVIDIA Tesla® V100 with 32 GB per GPU (256 GB total) of GPU memory
CPU	Intel Xeon E5-2650 v4 2.2 GHz 12-Core (48-core total)

Table S4: Optimization related configuration