SSnet: A Deep Learning Approach for Protein-Ligand Interaction Prediction

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SSnet model

The SSnet model was tested on SMU Maneframe II. The GPU node is equiped with 36 accelerator nodes with NVIDIA GPUs, dual Intel Xeon E5-2695v4 2.1 GHz 18-core "Broadwell" processors, 256 GB of DDR4-2400 memory, and one NVIDIA P100 GPU accelerator. Each NVIDIA P100 GPU has 3,584 CUDA cores and 16 GB CoWoS HBM2 memory. The P100 GPU is the based on the new Pascal architecture and an extremely high bandwidth (732 GB/s) stacked memory architecture. In the following we discuss the hyper-parameters inlovlved in the optimization of the model.

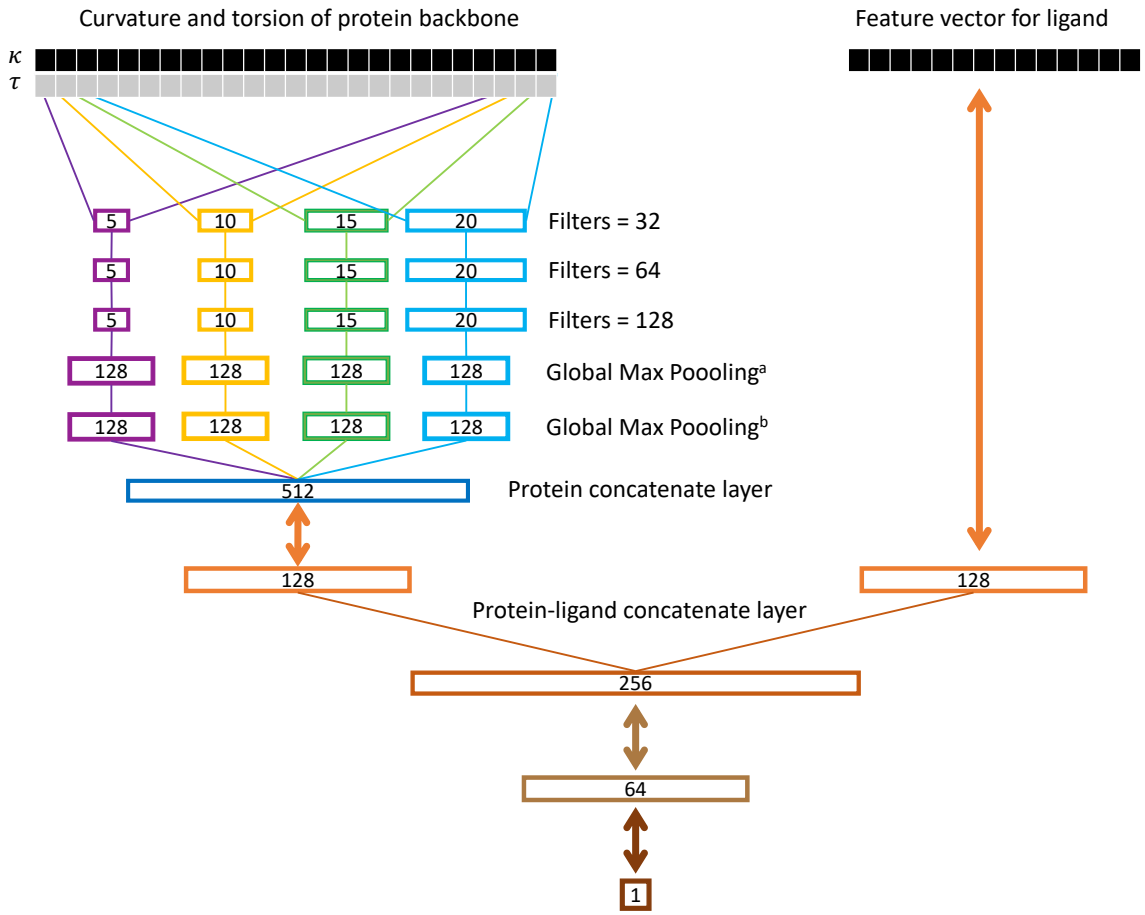


Figure 1: SSnet model. The curvature and torsion pattern of a protein backbone is fed through multiple convolution networks with varying window sizes as branch convolution. Each branch further goes through more convolution with same window size (red, orange, green and light blue boxes). A global max pooling layer is implemented to get the protein vector. The ligand vector is directly fed to the network. Each double array line implies a fully connected dense layer. The number inside a box represents the dimension of the corresponding vector.

Layer Width

The increase in layer width significantly reduces time, however, the loss remains almost constant. We came up with the optimized parameters as shown in Figure 1.

Model Depth

Model depth behaved similar to layer width. We observed a depth of three layers deep is optimal in performance compared to loss.

Pooling Type

We used two global max pooling layers. More details about the pooling layers are discussed in the main text. In sort using two global max pooling layers we tend to capture the variance of the data.

Fully Connected Layer

Modifications to the final fully connected layer had no discernible effects on predictive performance or training time, suggesting most of the learning is taking place in the convolutional layers.

Time comparisons

SSnet model takes on an average 332 seconds per epoch to train on DUD-E dataset (63,120 instances) and 1178 seconds per epoch on BindingDB dataset (233,573 instances).

Data augmentation

Drug augmentation is a technique to increase number of instances to train by adding some sensible noise from the train data. The SSnet model takes up 6 different chains arranged in

a stack of 1500 amino acids each (padded with zeros). The chains were randomly shuffled so that the model does not rely on the ordering of chains.

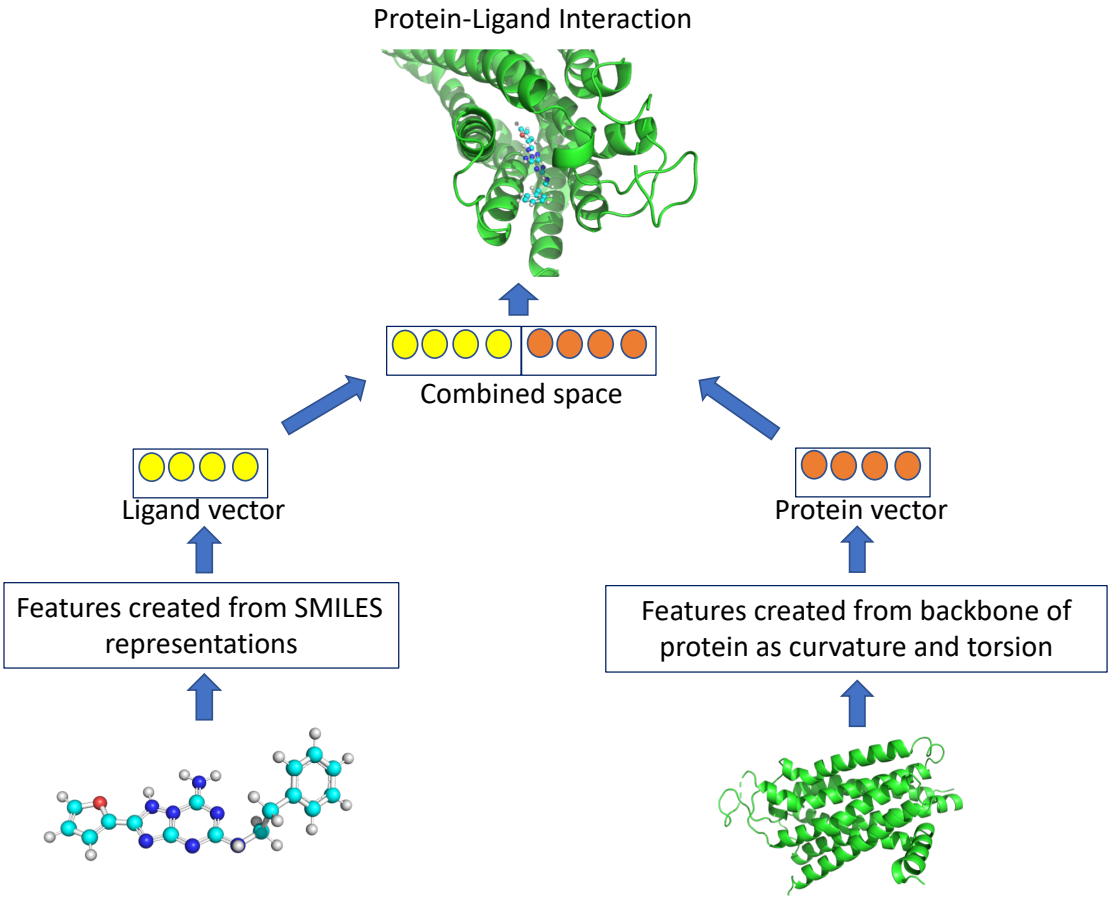
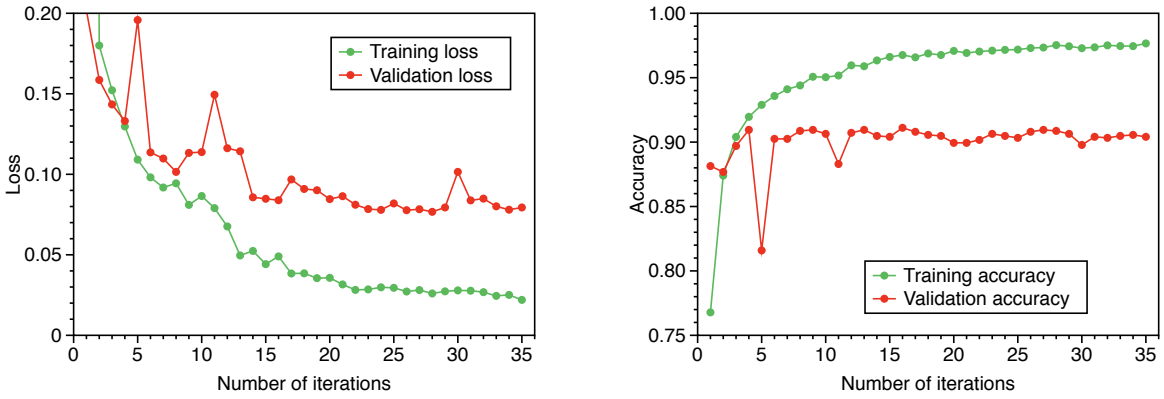


Figure 2: SSnet model overview. The SMILES string and the PDB file for ligand and protein respectively is fed to the model which is converted to ligand vector and protein vector respectively. The two vectors are then concatenated and fed to further networks for PLI predictions

Table 1: Model comparison on the DUD-E dataset for various ligand descriptors

Ligand descriptors	AUC
GNN	0.983
ECF	0.984
CLP	0.906
Avalon	0.964



(a) (b)

Figure 3: SSnet model overfits when convolution neural network is applied to smaller datasets such as human or C.*elegans*

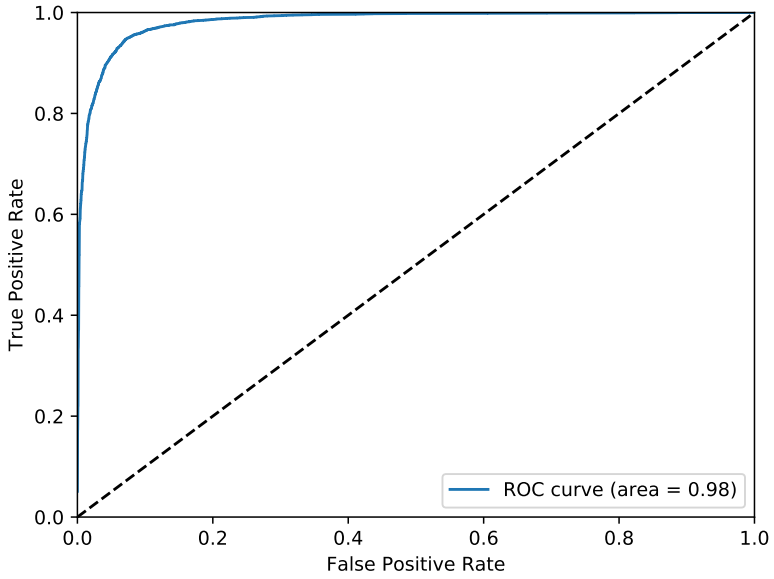


Figure 4: Receiver operating characteristics for the predictions on DUD-E dataset.

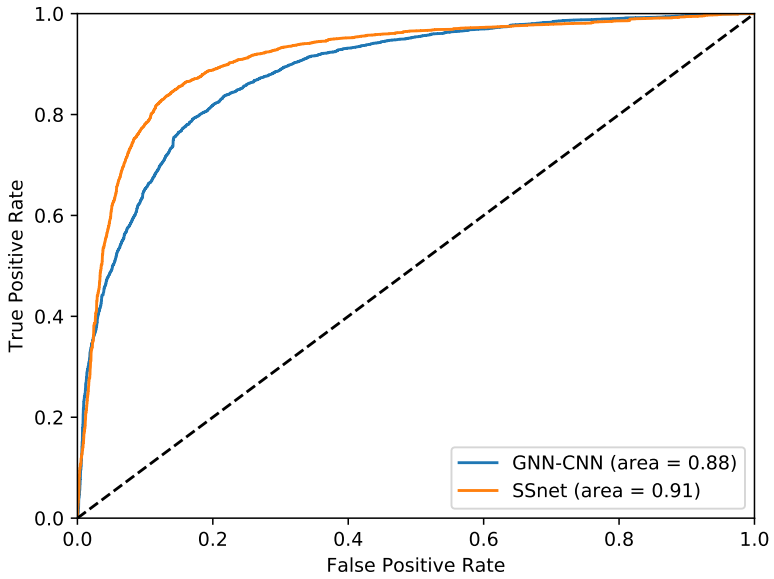


Figure 5: Receiver operating characteristics for the predictions on BindingDB dataset.

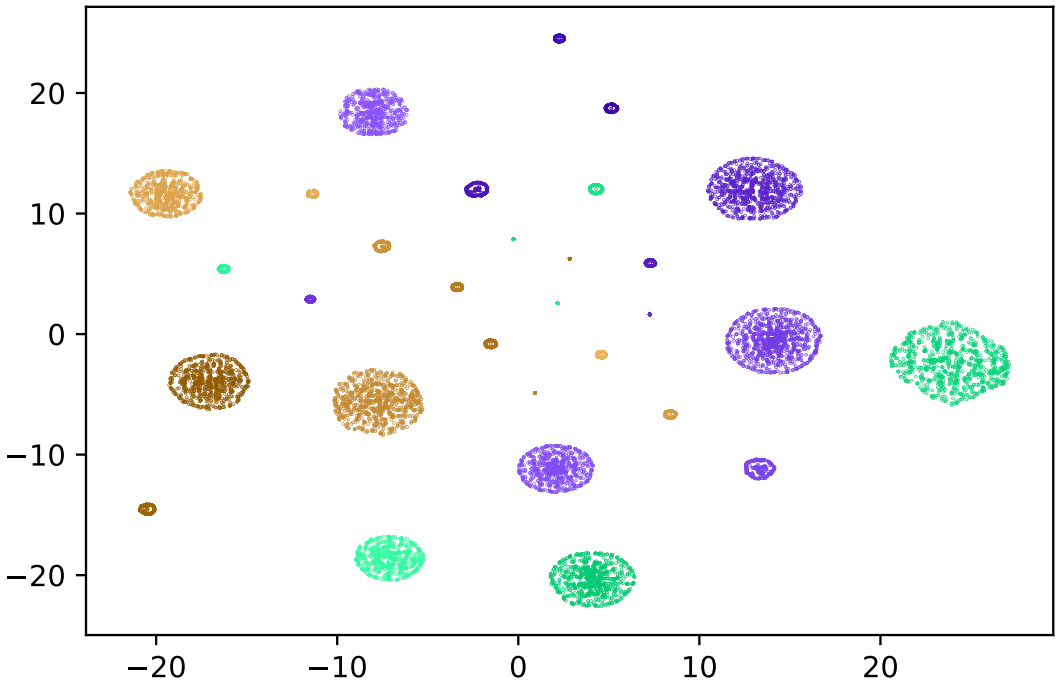
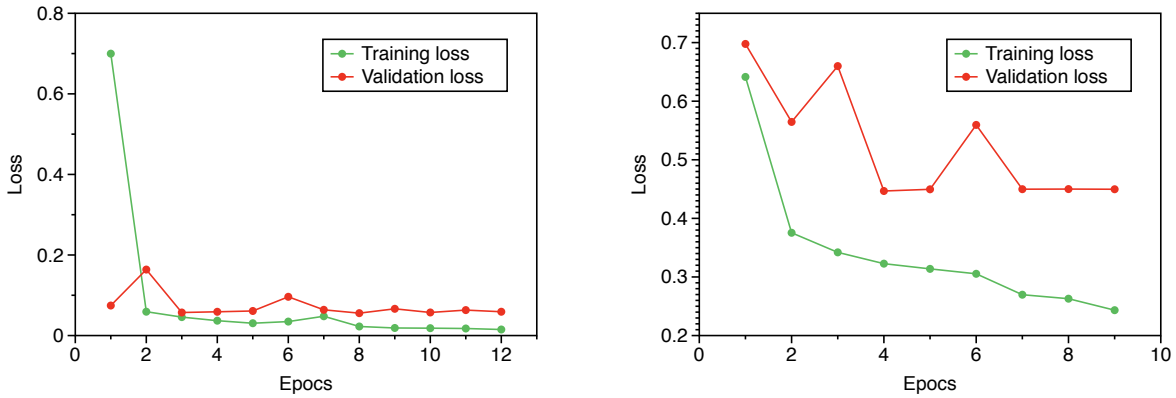


Figure 6: t-SNE plot for all the proteins (30) in the test set of DUD-E dataset. Each cluster is distinguishable with others and denotes a protein. Note that the SSnet model had no information about these proteins as they were in the test set and is yet able to distinguish them.



(a) (b)

Figure 7: SSnet model training loss over a) DUD-E dataset and b) BindingDB dataset

Hyper parameters in GNN-CNN

The parameters used for GNN-CNN are

- radius=2
- ngram=1
- dim=10
- layer_gnn=3
- side=5
- window=$((2*side+1))
- layer_cnn=3
- layer_output=3
- lr=1e-3
- lr_decay=0.5
- decay_interval=10
- weight_decay=1e-6
- iteration=100

Table 2: MUV data details

MUV ID	PDB ID	Ligand	Ki/IC50 (nM)	Assay type
600	1YOW	P0E	N/A	cell
692	1YOW	P0E	N/A	cell
859	5CXV	0HK	N/A	cell
852	4XE4	NAG	N/A	biochemical
548	3POO	S69	N/A	biochemical
832	1AU8	0H8	N/A	biochemical
689	2Y6O	1N1	25	biochemical
846	5EXM	5ST	N/A	biochemical
466	3V2Y	ML5	18-77	cell

Table 3: $EF_{0.5\%}$ comparison on MUV dataset

Target	3D-CNN	vina	SSnet:DUD-E	GNN-CNN	SSnet:BDB
692	0.000	0.000	0.000	0.000	**6.680**
859	0.000	0.000	0.000	0.000	**13.360**
548	0.000	0.000	0.000	0.000	0.000
600	0.000	0.000	0.000	0.000	**6.680**
852	0.000	0.000	0.000	0.000	0.000
846	**6.667**	0.000	0.000	0.000	0.000
832	0.000	0.000	0.000	0.000	0.000
689	**6.667**	0.000	0.000	0.000	0.000
466	0.000	0.000	0.000	0.000	0.000
mean	1.482	0.000	0.000	0.000	**2.969**
std. dev.	2.940	0.000	0.000	0.000	4.853

Table 4: $EF_{1.0\%}$ comparison on MUV dataset

Target	3D-CNN	vina	SSnet:DUD-E	GNN-CNN	SSnet:BDB
692	0.000	0.000	0.000	0.000	**3.340**
859	0.000	0.000	0.000	0.000	**6.680**
548	**6.667**	0.000	3.318	0.000	0.000
600	0.000	0.000	0.000	0.000	**3.340**
852	0.000	0.000	0.000	0.000	0.000
846	**3.330**	0.000	0.000	0.000	0.000
832	0.000	**3.330**	0.000	0.000	0.000
689	**3.330**	**3.330**	0.000	0.000	0.000
466	0.000	**3.330**	0.000	0.000	0.000
mean	**1.481**	1.110	0.369	0.000	**1.484**
std. dev.	2.421	1.665	1.106	0.000	2.426

Table 5: $EF_{5.0\%}$ comparison on MUV dataset

Target	3D-CNN	vina	SSnet:DUD-E	GNN-CNN	SSnet:BDB
692	0.000	0.000	0.000	0.000	**2.001**
859	**2.000**	1.330	1.332	1.665	1.334
548	**6.667**	0.000	2.665	0.690	0.667
600	1.330	**2.667**	1.999	0.667	**2.668**
852	0.000	0.667	0.666	**1.378**	0.000
846	**0.667**	**0.667**	0.000	0.000	**0.667**
832	0.000	**3.330**	0.000	1.332	0.667
689	**2.000**	**2.000**	1.332	1.379	0.000
466	1.330	1.330	0.666	0.000	**2.001**
mean	**1.555**	1.332	0.962	0.790	1.112
std. dev.	2.082	1.154	0.949	0.676	0.943

Table 6: AUCROC comparison on DUD-E test set

Targets	Vina	3D-CNN	GNN-CNN		SSnet	
			DUD-E	BDB	DUD-E	BDB
ABL1	0.75	0.93	0.98	0.86	0.98	0.79
ADRB1	0.74	0.88	0.98	0.78	0.99	0.71
AKT1	0.74	0.98	0.99	0.91	1.00	0.91
AKT2	0.78	0.99	0.98	0.94	0.99	0.93
ANDR	0.64	0.73	0.81	0.80	0.79	0.88
BRAF	0.84	0.99	0.98	0.91	0.99	0.86
CDK2	0.72	0.84	0.93	0.86	0.94	0.85
CP3A4	0.60	0.90	0.95	0.82	0.96	0.76
DYR	0.77	0.87	0.95	0.80	0.97	0.74
FAK1	0.80	0.99	0.96	0.66	0.99	0.93
FPPS	0.29	0.98	0.99	0.96	0.99	0.70
GRIA2	0.75	0.78	0.99	0.41	0.97	0.61
HIVPR	0.72	0.89	0.95	0.63	0.96	0.89
ITAL	0.60	0.94	0.96	0.93	0.87	0.91
JAK2	0.77	0.99	0.94	0.86	0.99	0.94
KPCB	0.76	0.86	0.98	0.93	0.97	0.81
LCK	0.80	0.92	0.96	0.82	0.98	0.87
LKHA4	0.82	0.94	0.96	0.88	0.99	0.74
MK01	0.85	0.93	1.00	0.77	0.98	0.93
NOS1	0.59	0.73	0.90	0.93	0.97	0.48
PGH2	0.74	0.84	0.95	0.50	0.93	0.62
PPARA	0.87	0.87	0.94	0.51	1.00	0.89
PPARG	0.80	0.92	0.99	0.80	0.99	0.82
PRGR	0.68	0.85	0.98	0.79	0.90	0.94
PYRD	0.77	0.92	0.88	0.85	0.98	0.80
SRC	0.65	0.95	0.94	0.64	0.99	0.88
THB	0.75	0.83	0.98	0.88	0.96	0.83
UROK	0.77	0.96	0.98	0.79	0.99	0.63
WEE1	0.83	0.99	0.98	0.66	1.00	0.95
mean	0.73	0.90	0.96	0.79	0.97	0.81
std. dev.	0.11	0.07	0.04	0.14	0.05	0.12

Table 7: $EF_{1\%}$ comparison on DUD-E test set

Targets	Vina	3D-CNN	GNN-CNN		SSnet	
			DUD-E	BDB	DUD-E	BDB
ABL1	10	69	42	23	46	24
ADRB1	5	19	36	14	50	7
AKT1	8	85	48	29	53	33
AKT2	15	67	33	31	42	36
ANDR	16	3	16	10	18	22
BRAF	18	78	42	25	56	18
CDK2	6	26	25	21	32	18
CP3A4	2	29	25	9	33	11
DYR	3	29	37	23	38	16
FAK1	5	87	38	2	40	16
FPPS	0	46	35	23	59	4
GRIA2	13	3	36	0	17	2
HIVPR	6	12	13	1	30	10
ITAL	0	41	26	27	19	26
JAK2	10	86	26	5	58	26
KPCB	10	5	42	23	35	13
LCK	7	54	26	7	51	22
LKHA4	7	36	44	17	45	7
MK01	4	46	51	6	40	41
NOS1	1	10	11	49	39	5
PGH2	13	18	31	0	18	1
PPARA	9	12	17	0	47	13
PPARG	6	22	41	6	49	14
PRGR	9	7	42	10	27	30
PYRD	8	42	19	19	49	12
SRC	3	61	47	0	54	30
THB	12	9	53	27	34	15
UROK	9	54	46	3	45	4
WEE1	8	77	39	4	56	19
mean	8	39	34	14	41	17
std. dev.	5	28	12	12	13	11

Table 8: AUCROC comparison on BDB test set

PDB	SSnet:DUD-E	SSnet:BDB	GNN-CNN:DUD-E	GNN-CNN:BDB	Actives	Inactives	PLIs
1CAH	0.689	0.94	0.678	0.839	3688	1094	4782
1CQP	0.334	0.90	0.251	0.818	258	145	403
1CVW	0.634	0.91	0.564	0.799	397	146	543
1D3D	0.712	0.91	0.617	0.855	2159	2702	4861
1D3G	0.607	0.94	0.753	0.787	270	413	683
1D6O	0.504	0.96	0.797	0.894	205	169	374
1DB4	0.773	0.88	0.800	0.889	114	145	259
1DHF	0.503	0.87	0.578	0.893	402	288	690
1DI9	0.744	0.93	0.615	0.812	2447	448	2895
1DKF	0.528	0.87	0.635	0.860	219	23	242
1E3G	0.393	0.92	0.469	0.838	1670	275	1945
1E3K	0.662	0.85	0.690	0.867	1365	39	1404
1ERE	0.915	0.93	0.873	0.930	2116	767	2883
1EUB	0.742	0.89	0.715	0.822	1715	230	1945
1EZQ	0.550	0.93	0.530	0.807	3174	772	3946
1F9X	0.848	0.83	0.723	0.911	393	512	905
1FAP	0.645	0.93	0.412	0.913	2705	216	2921
1FBY	0.635	0.87	0.479	0.904	667	42	709
1FKN	0.499	0.92	0.499	0.785	4758	1175	5933
1FMK	0.745	0.92	0.702	0.908	1401	1001	2402
1FT2	0.774	0.92	0.605	0.816	374	92	466
1GFW	0.900	0.88	0.859	0.890	529	872	1401
1GZK	0.518	0.89	0.367	0.846	495	49	544
1HRH	0.648	0.90	0.594	0.829	428	738	1166
1HRN	0.648	0.93	0.290	0.818	2728	239	2967
1HYV	0.761	0.92	0.466	0.846	373	1547	1920
1I44	0.789	0.96	0.678	0.802	333	227	560
1I7G	0.632	0.91	0.495	0.793	854	474	1328
1IAS	0.697	0.92	0.428	0.767	919	88	1007
1IKV	0.544	0.88	0.542	0.652	238	201	439
1JNK	0.725	0.98	0.736	0.895	284	456	740
1KWP	0.692	0.90	0.592	0.841	290	257	547
1NDE	0.896	0.92	0.862	0.871	1147	607	1754
1O86	0.638	0.90	0.353	0.896	267	282	549
1S9I	0.851	1.00	0.533	0.746	85	12	97
1S9J	0.721	0.85	0.611	0.815	474	74	548
1T64	0.773	0.92	0.751	0.839	133	347	480
1UK0	0.814	0.93	0.740	0.909	2083	288	2371
1UWJ	0.754	0.94	0.514	0.955	2176	150	2326
1V4S	0.669	0.87	0.547	0.811	243	61	304
1W0E	0.590	0.88	0.619	0.796	220	2557	2777
1Y6A	0.574	0.91	0.500	0.863	3987	646	4633
2B7A	0.323	0.91	0.453	0.959	5707	966	6673
2F2U	0.757	0.93	0.590	0.875	1777	254	2031
2FZJ	0.767	0.91	0.626	0.896	107	13	120
2KAV	0.370	0.90	0.555	0.843	2307	723	3030
2M2F	0.918	0.90	0.868	0.885	960	576	1536
3EML	0.640	0.89	0.724	0.866	2214	392	2606
3MAX	0.679	0.93	0.670	0.818	1707	666	2373
3O8Y	0.630	0.96	0.588	0.830	198	417	615
3VG9	0.850	0.93	0.595	0.884	955	576	1531
4PH9	0.571	0.92	0.578	0.854	1184	1224	2408
mean	0.669	0.911	0.602	0.849	1267	513	1780
std. dev.	0.143	0.032	0.144	0.055	1292	557	1545

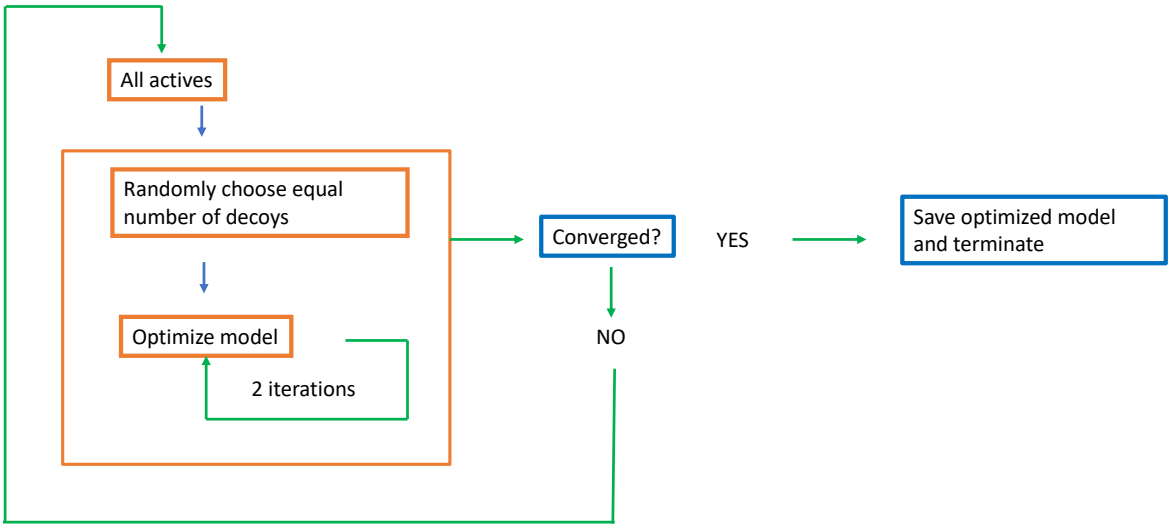


Figure 8: Dynamic model optimization for SSnet:DUD-E

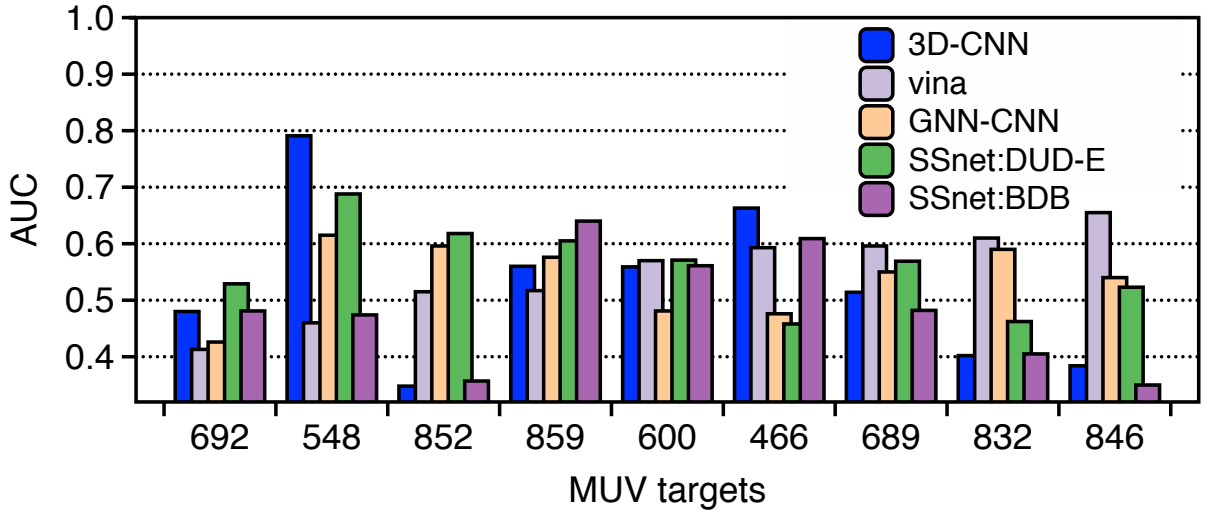


Figure 9: Various model performance on MUV targets for AUCROC

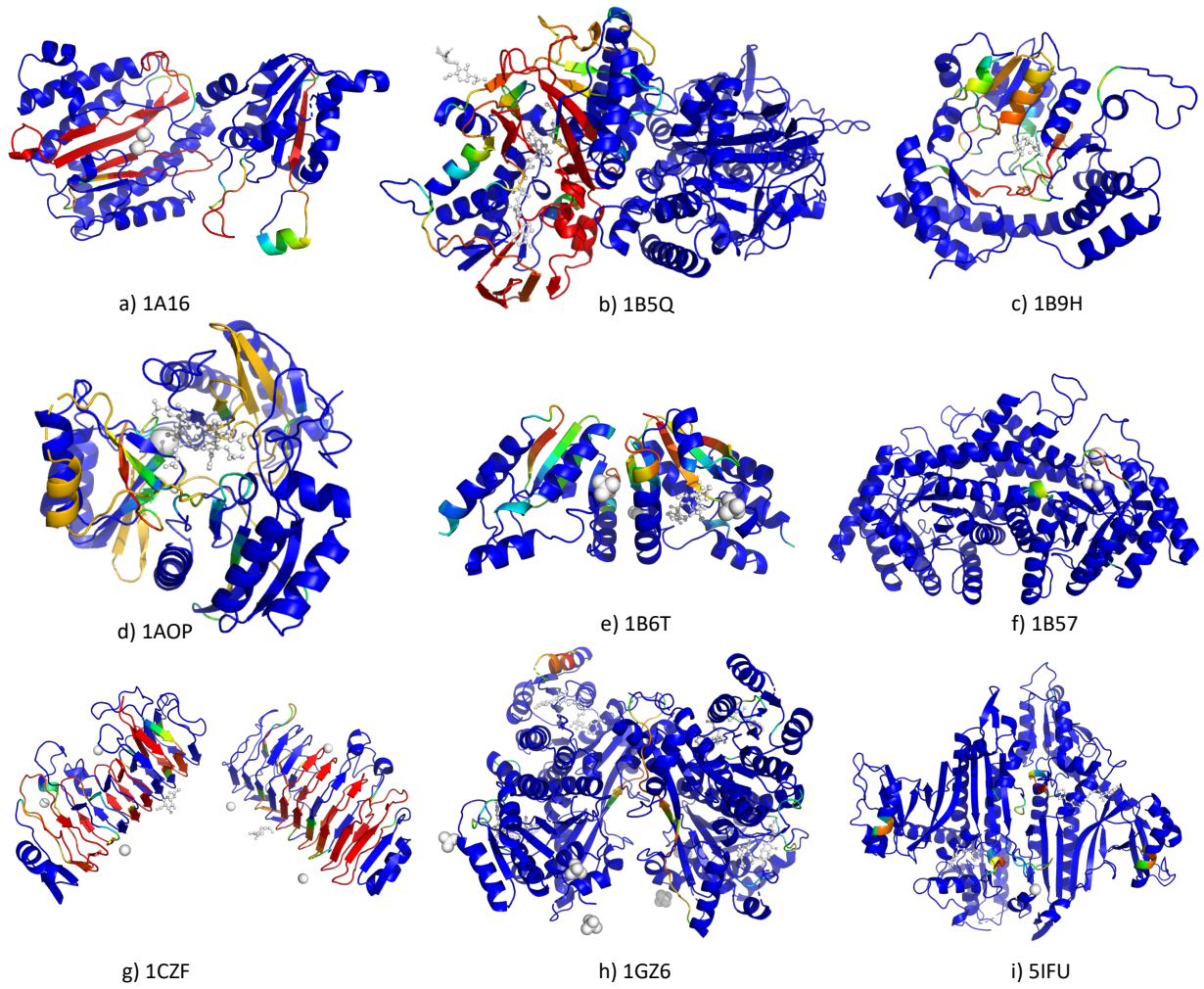


Figure 10: Grad-CAM visualization of the heatmap for nine different proteins with their PDB ID. The heatmap is a rainbow mapping with violet as the lowest and red as the highest value. The ligand and other small molecules are shown in grey.

Table 9: Ligand similarity for BDB train dataset to DUD-E dataset

DUDE Target	New[a]	Similar[b]	New[a] %
FNTA	52156	610	98.844
NRAM	6273	168	97.392
CAH2	31840	779	97.612
PYGM	3955	25	99.372
PYRD	6483	20	99.692
ACES	26658	390	98.558
CDK2	28191	382	98.663
FKB1A	5818	34	99.419

PA2GA	5184	42	99.196
AMPC	2850	1	99.965
SAHH	3455	16	99.539
DEF	5758	30	99.482
RXRA	7050	112	98.436
PUR2	2715	52	98.121
THB	7562	166	97.852
NOS1	8061	28	99.654
CP2C9	7462	44	99.414
AOFB	6995	70	99.009
ESR1	21130	418	98.060
UROK	9884	150	98.505
TYSY	6823	49	99.287
PDE5A	28027	441	98.451
HS90A	4860	38	99.224
GRIK1	6572	41	99.380
FA7	6271	130	97.969
HIVPR	36470	646	98.260
THRB	27815	955	96.681
FPPS	8868	24	99.730
MCR	5166	38	99.270
ANDR	14655	287	98.079
TRY1	26148	587	97.804
PTN1	7255	34	99.534
KITH	2869	27	99.068
CASP3	10810	148	98.649
ADA	5482	26	99.528
ROCK1	6342	49	99.233
ESR2	20680	448	97.880
PPARG	25530	224	99.130
INHA	2326	33	98.601
ALDR	9077	87	99.051
ABL1	10847	126	98.852
KPCB	8772	99	98.884
DPP4	41509	568	98.650
ITAL	8554	67	99.223
FABP4	2762	26	99.067
LCK	27727	372	98.676
ADA17	36497	606	98.367
IGF1R	9374	92	99.028
MK01	4577	53	98.855
PLK1	6864	79	98.862
PGH1	10855	79	99.277
VGFR2	25500	580	97.776
PPARA	19584	247	98.754
MK14	36478	695	98.130
EGFR	35544	499	98.616
GLCM	3804	21	99.451
ADRB1	15971	129	99.199
MK10	6625	51	99.236
TRYB1	7721	118	98.495

PPARD	12485	262	97.945
PNPH	7062	62	99.130
WEE1	6158	33	99.467
ACE	17180	212	98.781
GCR	15427	475	97.013
COMT	3862	18	99.536
FAK1	5359	32	99.406
FGFR1	8750	87	99.016
HMDH	8975	97	98.931
LKHA4	9514	66	99.311
KIF11	6925	98	98.605
AKT1	16689	223	98.681
AKT2	6971	105	98.516
BRAF	10072	115	98.871
SRC	34802	358	98.982
AA2AR	32378	715	97.839
MP2K1	8190	76	99.081
HDAC8	10469	38	99.638
HXK4	4701	21	99.555
DHI1	19724	127	99.360
KIT	10540	129	98.791
RENI	7129	184	97.484
XIAP	5155	38	99.268
TGFR1	8525	57	99.336
PRGR	16059	465	97.186
GRIA2	11869	80	99.330
FA10	29742	1544	95.065
CSF1R	12295	183	98.533
PARP1	30409	367	98.808
BACE1	18165	141	99.230
HIVRT	19058	214	98.890
PGH2	23477	349	98.535
JAK2	6583	88	98.681
MET	11328	106	99.073
MAPK2	6175	51	99.181
HDAC2	10359	90	99.139
HIVINT	6669	51	99.241
DYR	17588	489	97.295
CP3A4	11827	76	99.362
ADRB2	15233	241	98.443
CXCR4	3419	8	99.767
DRD3	34842	105	99.700
MMP13	37992	917	97.643

New[a] is the number of ligands for a given DUD-E target that has a TC score of at-max 0.85 compared to all ligands in the train set of BDB dataset

Similar[b] is the number of ligands for a given DUD-E target that has a TC score of more than 0.85 for at least one of the ligands in the train set of BDB dataset

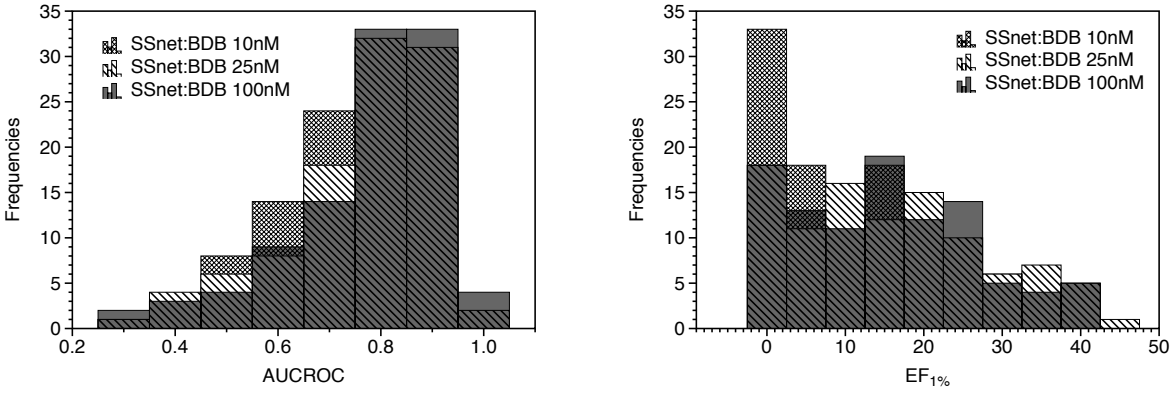
Table 10: Protein fold similarity from BDB train dataset to DUD-E dataset

DUDE Target	PDB ID[a]	TM score[b]	RMSD[c]
FNTA	3e37	0.9915	0.3098
NRAM	1b9v	0.7845	3.7806
CAH2	1bcd	0.9989	0.1957
PYGM	1c8k	0.9592	2.6551
PYRD	1d3g	0.2907	18.7665
ACES	1E66	0.6295	6.1308
CDK2	1h00	0.9736	0.4638
FKB1A	1j4h	0.3778	10.1247
PA2GA	1kvo	0.9162	0.8353
AMPC	1l2s	1.0161	0.6111
SAHH	1li4	0.3485	20.5637
DEF	1lru	0.4969	5.1474
RXRA	1mv9	0.7407	3.4699
PUR2	1njs	0.8192	1.6964
THB	1q4x	0.6715	4.7258
NOS1	1qw6	0.213	21.8076
CP2C9	1r9o	0.7681	4.5415
AOFB	1s3b	0.9995	0.1693
ESR1	1sj0	0.4802	7.9522
UROK	1sqt	0	None
TYSY	1syn	0.9935	0.3126
PDE5A	1udt	1	0
HS90A	1uyg	0.9949	0.3917
GRIK1	1vso	0.877	2.4381
FA7	1w7x	0	None
HIVPR	1xl2	1.1851	0.8561
THRB	1ype	0	None
FPPS	1zw5	0.2484	22.1821
MCR	2aa2	0.2185	22.4965
ANDR	2am9	0.2151	19.716
TRY1	2ayw	0	None
PTN1	2azr	0.9947	0.4789
KITH	2b8t	0.4344	9.8
CASP3	2cnk	0.6985	4.3383
ADA	2e1w	1.0114	0.7599
ROCK1	2etr	0.6554	5.7427
ESR2	2fsz	0.2613	21.7961
PPARG	2gtk	0.988	0.691
INHA	2h7l	0.6327	8.0146

ALDR	2hv5	1.0121	0.4038
ABL1	2hzi	0.9074	3.3718
KPCB	2i0e	0.2453	17.2618
DPP4	2i78	0.9969	0.5734
ITAL	2ica	0.3011	12.5923
FABP4	2nnq	0.9903	0.4331
LCK	2of2	0.5995	5.9375
ADA17	2oi0	0.2199	20.2387
IGF1R	2oj9	0.1986	19.5767
MK01	2ojg	0.9865	0.8589
PLK1	2owb	0.5951	9.799
PGH1	2oyu	0.9968	0.472
VGFR2	2p2i	0.2126	15.9029
PPARA	2p54	0.2704	11.3227
MK14	2qd9	0.9699	1.2875
EGFR	2rgp	1	0
GLCM	2v3f	0.9803	0.8264
ADRB1	2vt4	0.501	13.9601
MK10	2zdt	0.984	0.7317
TRYB1	2zec	0.3552	13.2652
PPARD	2znp	0.9722	1.5271
PNPH	3bgs	0.2638	14.7573
WEE1	3biz	0.2753	15.43
ACE	3bkl	0.2967	17.4192
GCR	3bqd	0.2232	17.8575
COMT	3bwm	0.3562	12.323
FAK1	3bz3	0.4928	7.3764
FGFR1	3c4f	0.218	20.4954
HMDH	3ccw	0.1975	25.8022
LKHA4	3chp	0.9982	0.3697
KIF11	3cjo	0.88	3.2
AKT1	3cqw	0.4937	16.3271
AKT2	3d0e	0.5112	5.9197
BRAF	3d4q	0.9685	0.7271
SRC	3el8	0.9651	1.1105
AA2AR	3eml	0.493	8.8696
MP2K1	3eqh	0.4598	12.9595
HDAC8	3f07	0.5263	10.1104
HXK4	3f9m	0.7628	5.353
DHI1	3frj	0.985	0.7379
KIT	3g0e	0.2521	16.2162
RENI	3g6z	0.4118	9.0758
XIAP	3hl5	0.6769	5.0688
TGFR1	3hmm	0.3684	11.9022
PRGR	3kba	0.2232	18.6436
GRIA2	3kgc	1.0415	0.7333
FA10	3kl6	0	None
CSF1R	3krj	0.3006	14.5581
PARP1	3l3m	0.2201	21.5598
BACE1	3l5d	0.2324	19.4109
HIVRT	3lan	0.9157	1.6354

PGH2	3ln1	0.2908	21.4865
JAK2	3lpb	0.9622	0.4771
MET	3lq8	0.955	0.7241
MAPK2	3m2w	0.3665	9.4891
HDAC2	3max	0.5089	9.7434
HIVINT	3nf7	0.2753	14.8852
DYR	3nxo	0.9517	0.9189
CP3A4	3nxu	0.6967	5.4898
ADRB2	3ny8	0.4392	1.4593
CXCR4	3odu	0.4207	14.0002
DRD3	3pbl	0.4123	23.6682
MMP13	830c	0.3137	9.3017

PDB ID[a] is the protein data bank id for DUD-E targets
TM score[b] is the maximum TM score obtained from the PDB ID[a] to all targets in the train set of BDB dataset
RMSD[c] is the root-mean-squared-distance between the PDB ID[a] and the maximum TM score obtained protein in the BDB train dataset



(a) (b)

Figure 11: SSnet:BDB performance when various cutoff for IC50 is applied and tested 102 targets of DUD-E dataset. The mean score for AUCROC are 0.77, 0.76 and 0.73 for 100, 25 and 10 nM cutoff respectively. The mean score for $EF_{1\%}$ are 15, 16 and 10 for 100, 25 and 10 nM cutoff respectively.

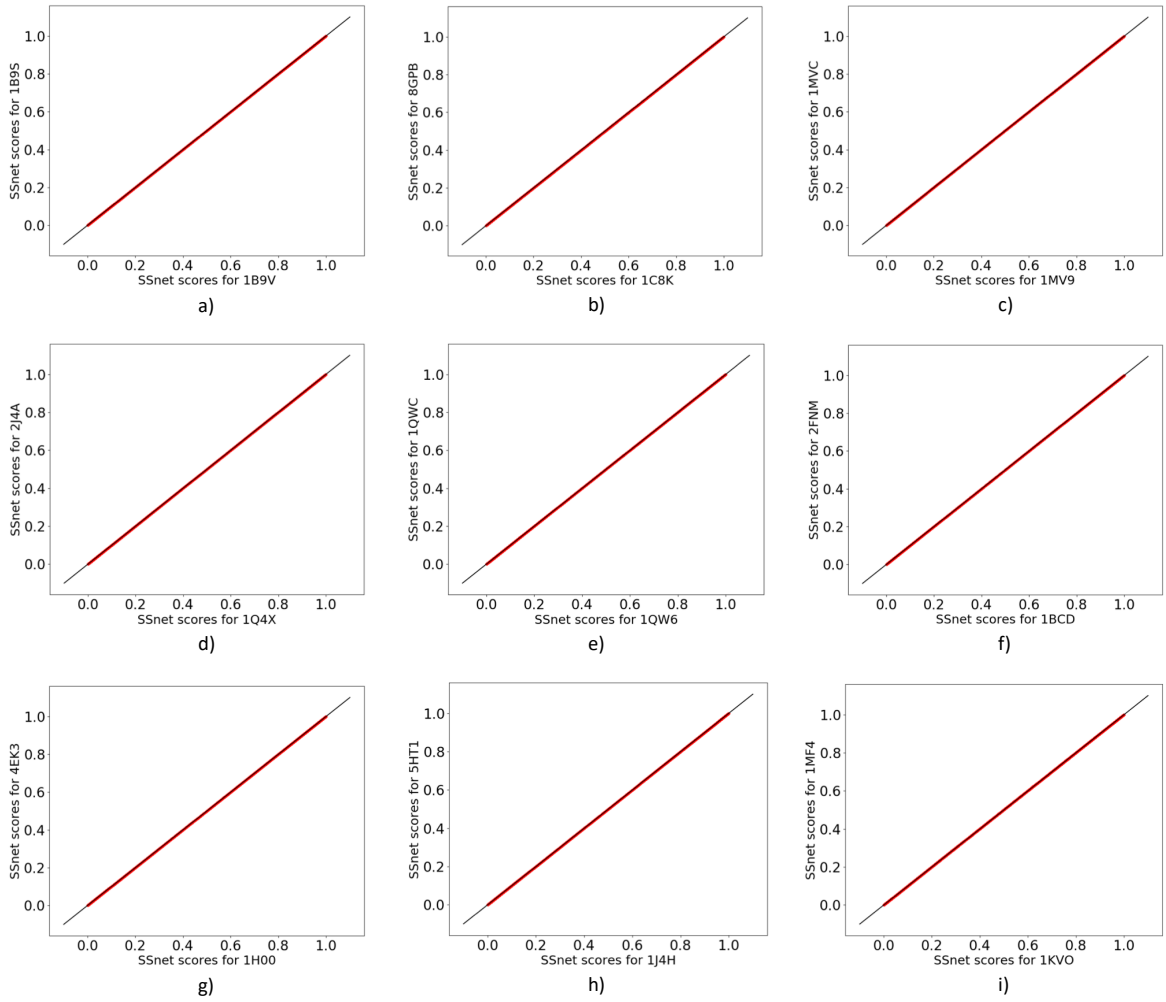


Figure 12: Relation of SSnet scores when different conformations of the same protein are used. The black line shows $y = x$ line.