Appendix

A. Pseudo-Code

Taking multimodal inference with protein sequences and structures as an example, the pseudo-code for pre-training, fine-tuning, and inference is summarized in Algorithm 1.

Algorithm 1: Algorithm for CPI Prediction (Multimodal)

Input: Compound Graphs $\{\mathcal{G}_C^{(j)}\}_{j=1}^M$, Protein Sequences $\{S^{(i)}\}_{i=1}^N$, and Protein Graphs $\{\mathcal{G}_{\mathcal{P}}^{(i)}\}_{i=1}^N$.

Output: Interaction pattern $\mathbf{P}^{\text{cont}}$ and strength y^{aff}.

 1: # *Pre-training*
 2: **while** *not convergence* **do**
 3:      Generate a set of subsequences and subgraphs by length-variable augmentation;
 4:      Pass the augmented subsequences and subgraphs through the sequence and structure encoders;
 5:      Pre-train the two encoders by intra-modality and cross-modality contrastive losses in Eq. (7)(8)(9).
 6: **end while**
 7: # *Fine-tuning*
 8: **while** *not convergence* **do**
 9:      Jointly train the two pre-trained encoders and compound encoder by loss in Eq. (10) or (11).
10: **end while**
11: # *Inference*
12: Predict interaction pattern $\mathbf{P}^{\text{cont}}$ and interaction strength y^{aff} for any given compound-protein pair.
13: **return** Interaction pattern $\mathbf{P}^{\text{cont}}$ and strength y^{aff}.

B. Evaluation on More Metrics and Architectures

We report the performance of CPI pattern prediction and strength prediction under four different test data splits on the Karimi dataset in Table. A1 and Table. A2, respectively. For unimodal inference with only protein sequences or structures, HRNN, LSTM (Hochreiter and Schmidhuber 1997), Bi-LSTM are considered as sequence encoders and GCN (Kipf and Welling 2016), GAT (Veličković et al. 2017), SAGE (Hamilton, Ying, and Leskovec 2017) are considered as structure encoders, respectively. For multimodal inference with both sequences and structures, we adopt HRNN as the sequence encoder and GAT as the structure encoder by default and consider two representation integrations, i.e., Concatenation and Cross Interaction (You and Shen 2022). We can observe from Table. A1 and A2 that PSC works well across various evaluation metrics and architectures.

Table A1: Performance comparison of *CPI pattern prediction* with AUPRC (higher is better) and AUROC (higher is better) as evaluation metrics under four different data splits on the Karimi dataset, where three inference settings with different sequence and structure encoders are evaluated, respectively. The best metrics for each inference setting are marked by different colors.

Inference Setting	Methods	Seen-Both		Unseen-Comp		Unseen-Prot		Unseen-Both	
		AUPRC↑	AUROC↑	AUPRC↑	AUROC↑	AUPRC↑	AUROC↑	AUPRC↑	AUROC↑
Sequence	HRNN	22.05	77.52	19.32	77.49	6.48	73.36	5.62	73.97
	pre-train w/ PSC	22.29	77.68	21.43	78.09	7.01	75.36	6.64	74.77
	LSTM	20.88	77.30	20.15	77.98	5.68	73.72	5.60	71.93
	pre-train w/ PSC	22.27	79.19	21.87	79.96	6.68	74.35	6.10	72.98
	Bi-LSTM	21.96	78.33	21.39	79.36	9.92	79.57	**9.13**	75.56
	pre-train w/ PSC	**23.29**	**80.14**	**22.07**	**81.02**	**10.77**	**80.40**	8.88	**78.20**
Structure	GAT	22.11	83.65	21.56	84.68	10.70	83.88	9.40	83.90
	pre-train w/ PSC	**24.26**	84.10	**23.78**	85.51	11.14	84.52	10.62	84.74
	GCN	22.37	83.69	22.09	85.02	10.12	85.47	9.58	85.35
	pre-train w/ PSC	24.12	84.53	23.52	**85.88**	11.78	**85.95**	10.62	**85.80**
	SAGE	22.73	**85.10**	21.95	84.33	11.95	84.94	10.84	85.63
	pre-train w/ PSC	23.64	84.83	23.49	85.86	**12.70**	85.63	**11.20**	85.51
Sequence & Structure	Concatenation	23.86	84.58	23.12	85.34	9.06	82.79	8.52	82.79
	pre-train w/ PSC	25.42	84.95	24.67	**86.12**	**11.03**	**86.41**	**11.65**	85.29
	Cross-Interaction	24.02	83.57	23.55	84.68	11.80	85.56	10.89	84.37
	pre-train w/ PSC	**26.56**	**85.33**	**25.12**	85.72	12.46	85.82	11.46	**86.19**

Table A2: Performance comparison of *CPI strength prediction* with Root Mean Square Error (RMSE, lower is better) and Pearson correlation coefficients (PPCs, higher is better) as evaluation metrics under four data splits on the Karimi dataset, where three inference settings are evaluated, and the best metrics for each inference setting are marked by different colors.

Inference Setting	Methods	Seen-Both		Unseen-Comp		Unseen-Prot		Unseen-Both	
		RMSE↓	PCCs↑	RMSE↓	PCCs↑	RMSE↓	PCCs↑	RMSE↓	PCCs↑
Sequence	HRNN	1.56	0.67	1.48	0.67	1.66	0.54	1.75	0.54
	pre-train w/ PSC	1.48	**0.70**	1.37	0.72	**1.54**	0.52	1.59	**0.58**
	LSTM	1.58	0.66	1.47	0.64	1.62	0.53	1.67	0.53
	pre-train w/ PSC	1.49	0.69	1.38	0.72	1.56	**0.54**	1.57	0.57
	Bi-LSTM	1.62	0.60	1.45	0.67	1.60	0.50	1.62	0.53
	pre-train w/ PSC	**1.46**	0.69	**1.35**	**0.73**	1.55	0.53	**1.55**	0.57
Structure	GAT	1.58	0.65	1.52	0.65	1.73	0.51	1.80	0.49
	pre-train w/ PSC	1.53	**0.66**	1.43	0.67	1.52	0.56	1.66	0.53
	GCN	1.64	0.59	1.47	0.64	1.71	0.52	1.64	0.54
	pre-train w/ PSC	**1.52**	**0.66**	**1.39**	**0.70**	1.53	0.55	**1.58**	0.55
	SAGE	1.61	0.61	1.48	0.65	1.62	0.52	1.69	0.51
	pre-train w/ PSC	1.55	0.64	1.42	0.68	**1.48**	**0.57**	**1.58**	**0.57**
Sequence & Structure	Concatenation	1.55	0.66	1.44	0.69	1.61	0.49	1.65	0.51
	pre-train w/ PSC	**1.42**	**0.71**	1.31	0.73	1.47	0.57	**1.52**	**0.60**
	Cross-Interaction	1.49	0.68	1.36	0.71	1.50	0.56	1.62	0.55
	pre-train w/ PSC	1.43	0.70	**1.30**	**0.74**	**1.42**	**0.59**	1.55	0.58