Supplementary Material for

Cyclome: Large-scale replica-exchange dynamics of 930 cyclic peptide reveal thermal stability and critical metal-binding behavior

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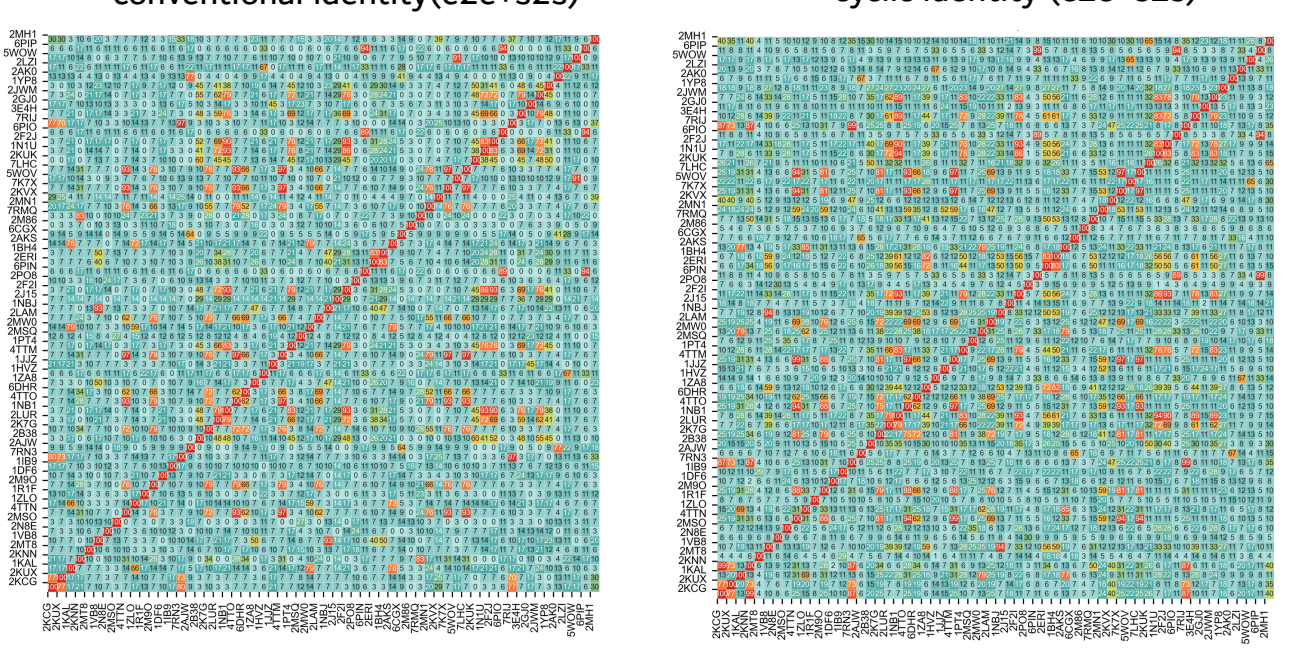
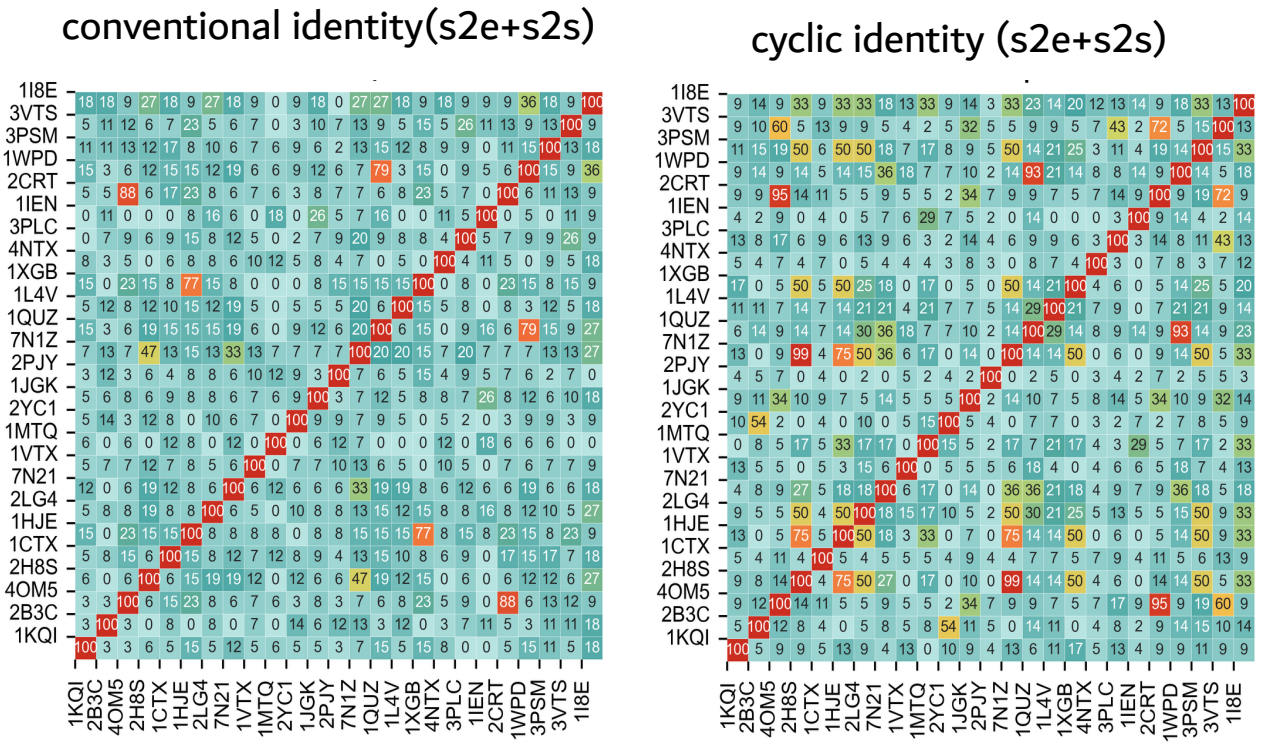
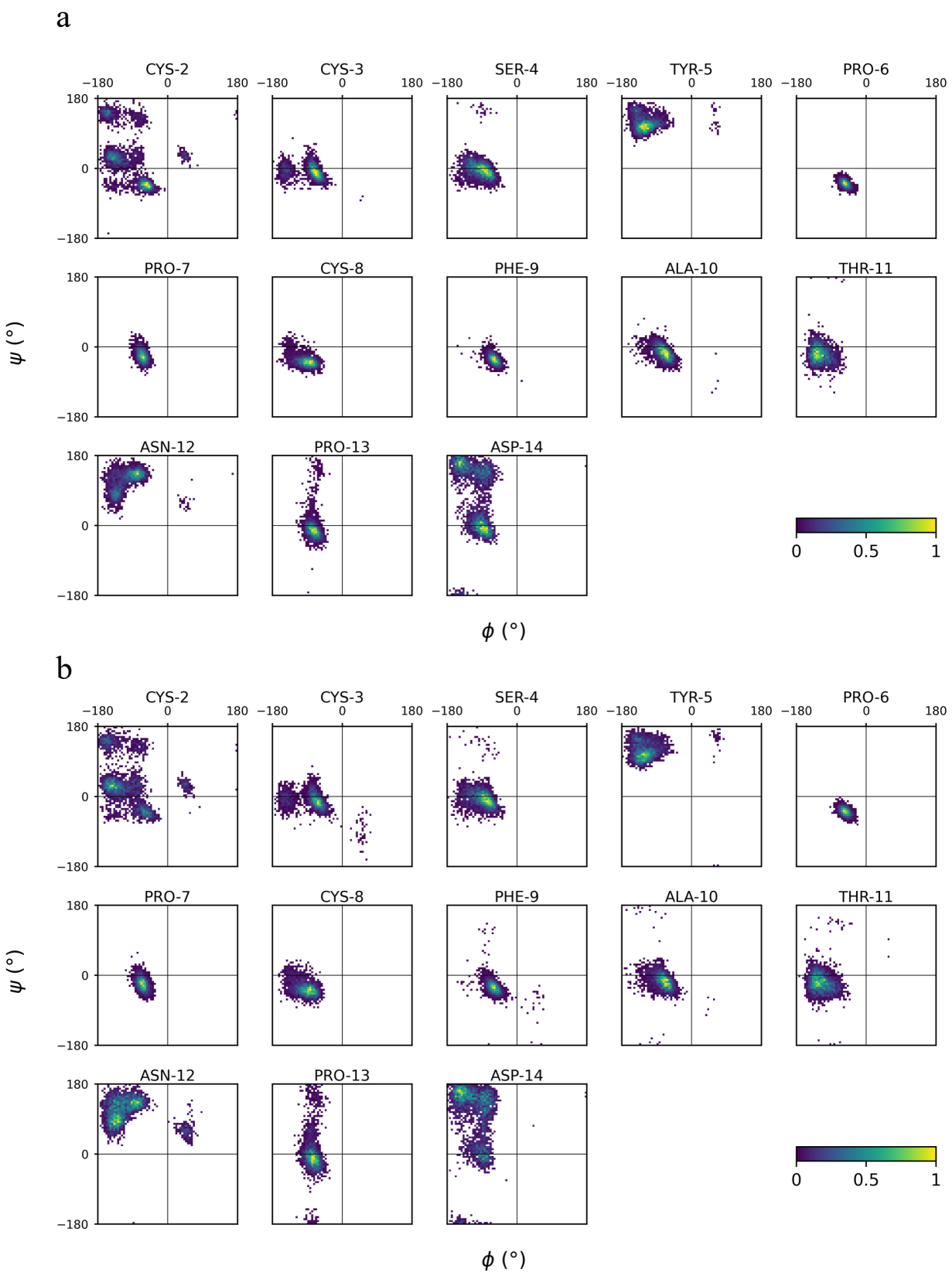
Supplementary Figures



S. Figure 1. Pairwise identity heatmaps illustrating sequence/structure relationships across the e2e+s2s cyclic peptide dataset using conventional scheme and cyclicity aware scheme. Each matrix encodes all-against-all similarities, with warmer colors indicating higher similarity and cooler colors indicating lower similarity. The strong diagonal corresponds to self-similarity, while the off-diagonal patterns reflect inter-peptide relationships. Compared to the baseline representation (left), the enhanced representation (right) exhibits improved contrast and organization in identity patterns, suggesting better discrimination of structurally and topologically related cyclic peptides.

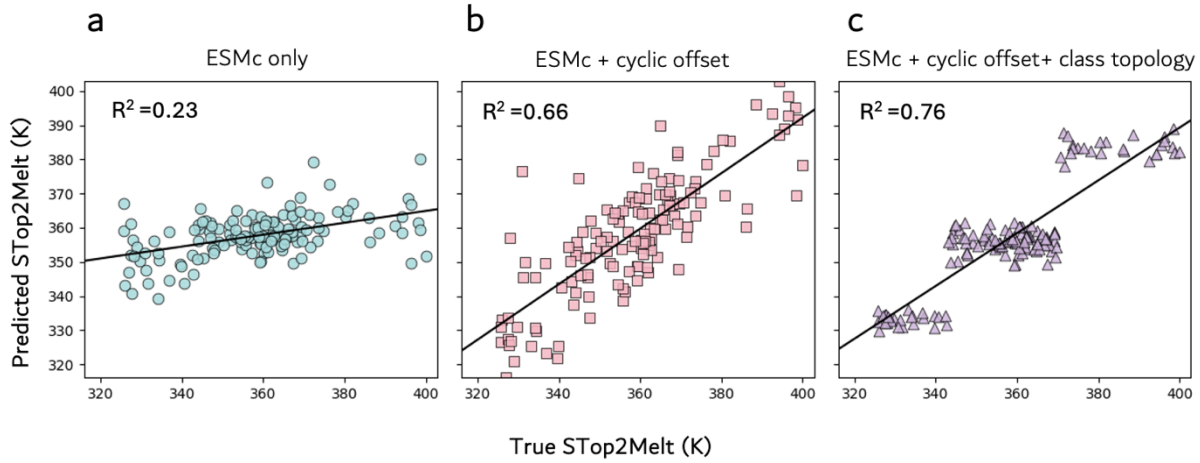


S. Figure 2. Pairwise identity matrices of s2e+s2s cyclic peptides highlighting sequence/structure relationships across the dataset under two alignment strategies. Each heatmap represents all-against-all similarity scores, with warmer colors indicating higher similarity and cooler colors indicating lower similarity. The diagonal reflects self-identity, while off-diagonal regions capture inter-peptide relationships. Compared to the conventional alignment (left), the cyclicity-aware alignment (right) exhibits sharper contrast and enhanced detection of related peptide clusters, demonstrating improved sensitivity to cyclic topology and sequence equivalence.



S. Figure 3. Residue-wise Ramachandran density distributions (ϕ, ψ) illustrating conformational sampling across the residues under two thermodynamic regimes. Each panel corresponds to an individual residue, with color intensity indicating normalized population density. (**a**) represents conformational ensembles below the STop2Melt transition, characterized by more localized and well-defined dihedral populations,

reflecting structurally constrained states. In contrast, (**b**) corresponds to ensembles at STop2Melt, where broader and more diffuse distributions are observed, indicating increased conformational flexibility and sampling of higher-energy states. Notably, residue-specific variations highlight differential flexibility across the peptide.



S. Figure 4. Comparison of true vs predicted values for STop2Pred cyclic peptides across progressively enriched feature representations. (**a**) Model trained using ESMc embeddings alone shows weak correlation with experimental values (R^2 = 0.23), indicating limited capture of thermodynamic determinants. (**b**) Incorporation of cyclic offset features substantially improves predictive performance (R^2 = 0.66), highlighting the importance of encoding cyclic topology. (**c**) Further inclusion of cyclization class topology descriptors yields the highest agreement with true values (R^2 = 0.76), demonstrating that explicit structural topology information enhances model accuracy. Solid black lines represent linear regression fits for each model.

S. Table 1. Performance metrics for STop2Melt model with ESMc only embedding

Model	Val MAE	Val RMSE	Val R^2	Test MAE	Test RMSE	Test R^2
SVR-RBF	11.27	14.68	0.22	11.39	15.28	0.23
GradientBoosting	11.90	15.43	0.14	11.63	15.45	0.21
RandomForest	11.30	14.33	0.25	11.69	15.33	0.22
ExtraTrees	10.96	14.05	0.28	11.77	15.46	0.21
KNN	11.48	14.94	0.19	12.30	16.17	0.13
Ridge	16.50	22.0	-0.76	18.27	24.80	-1.04
ElasticNet	17.33	22.62	-0.86	18.78	25.11	-1.09
Lasso	19.42	25.64	-1.39	20.24	27.02	-1.42
MLP	23.35	33.97	-3.19	22.70	31.50	-2.29

S. Table 2. Performance metrics for STop2Melt model with ESMc+ cyclic offset embedding

Model	Val_MAE	Val_RMSE	Val_R^2	Test_MAE	Test_RMSE	Test_R^2
ExtraTrees	7.417	82.46	0.70	8.43	102.72	0.66
RandomForest	7.51	84.24	0.69	8.64	112.44	0.63
GradientBoosting	7.69	89.42	0.68	8.86	129.27	0.57
SVR-RBF	10.93	198.51	0.28	10.94	212.48	0.30
KNN	11.40	219.49	0.20	12.01	249.90	0.17

Ridge	13.24	336.21	-0.22	13.58	325.92	-0.08
ElasticNet	14.03	389.51	-0.41	14.48	369.11	-0.22
Lasso	16.58	515.10	-0.87	17.43	520.98	-0.73
MLP	21.65	1057.24	-2.84	20.59	834.62	-1.77

S. Table 3. Performance metrics for STop2Melt model with ESMc+ cyclic offset +topology embedding

Model	Val_MAE	Val_RMSE	Val_R^2	Test_MAE	Test_RMSE	Test_R^2
RandomForest	6.67	63.99	0.77	7.20	71.14	0.76
GradientBoosting	6.91	71.18	0.74	7.29	75.20	0.75
ExtraTrees	6.94	71.91	0.74	7.63	82.16	0.73
SVR-RBF	10.75	190.37	0.31	10.68	200.57	0.34
KNN	11.36	214.12	0.22	11.98	247.80	0.18
Ridge	12.76	304.60	-0.11	13.38	299.95	0.01
ElasticNet	13.73	357.33	-0.30	14.52	350.02	-0.16
Lasso	14.76	416.56	-0.51	17.23	521.12	-0.73
MLP	22.59	1237.32	-3.49	20.10	854.29	-1.83