

Table 1: **More expressive multi-state pooling architecture and random decoding order.** Firstly, we consider Deep Set pooling (DS) of the final encoder representations for each state as well as Deep Symetric Set pooling (DSS , Maron et al., ICML 2020). DS pooling is described in Eq.3. In DSS pooling, after *each* encoder GNN layer, we (1) aggregate node embeddings from each single state representation into a pooled multi-state representation per node, (2) apply a Geometric Vector Perceptron update on the multi-state representation, and (3) add the updated multi-state representation back to each single state node representation. **Result:** DSS pooling does not significantly improve performance on out-of-distribution test sets for both the single- and multi-state splits. We do notice that DSS models fit the training data better, eg. final training loss goes from 0.40 to 0.36 when max #states = 3. Practically, while DSS pooling is theoretically more expressive than DS pooling, it also adds 200K more parameters to the model and doubles training iteration time (eg. 4 mins to 8 mins when max #states = 3). Additionally, we also present results for the impact of training gRNAd with random decoding order shaded in green, which leads to a negligible reduction in sequence recovery and 3D self-consistency, similar to ProteinMPNN.

Split	Max. #states	Model	GNN	Multi-state pooling	Perplexity (↓)	Native seq. recovery (↑)	Self-consistency metrics			
							2D – EternaFold scMCC (↑)	scRMSD (↓)	3D – RhoFold scTM-score (↑)	scGDT_TS (↑)
Single-state	1	AR	Equiv	-	1.29±0.02	0.530±0.01	0.585±0.03	11.70±0.56 (1.3%)	0.26±0.0 (24.8%)	0.25±0.0 (20.1%)
	1	AR, rand	Equiv	-	1.59±0.16	0.519±0.03	0.621±0.04	11.87±1.06 (1.9%)	0.25±0.0 (21.1%)	0.24±0.0 (18.1%)
	3	AR	Equiv	DS	1.23±0.05	0.539±0.01	0.620±0.01	11.47±1.05 (2.5%)	0.28±0.0 (31.4%)	0.28±0.0 (27.2%)
	3	AR	Equiv	DSS	1.25±0.01	0.534±0.00	0.628±0.04	12.13±1.28 (1.6%)	0.24±0.0 (22.0%)	0.24±0.0 (16.5%)
Multi-state	1	AR	Equiv	-	1.68±0.03	0.455±0.01	0.569±0.02	12.88±0.20 (4.1%)	0.11±0.0 (1.6%)	0.26±0.0 (22.6%)
	3	AR	Equiv	DS	1.60±0.03	0.467±0.03	0.561±0.03	13.31±0.38 (3.4%)	0.10±0.0 (2.6%)	0.24±0.0 (19.0%)
	3	AR	Equiv	DSS	1.63±0.04	0.464±0.02	0.586±0.03	12.92±0.03 (5.0%)	0.09±0.0 (2.3%)	0.26±0.0 (20.5%)
	5	AR	Equiv	DS	1.55±0.04	0.473±0.01	0.549±0.03	13.48±0.79 (3.3%)	0.10±0.0 (3.0%)	0.24±0.0 (20.2%)
	5	AR	Equiv	DSS	1.52±0.02	0.464±0.01	0.578±0.02	13.25±0.20 (4.2%)	0.08±0.0 (1.7%)	0.24±0.0 (18.0%)

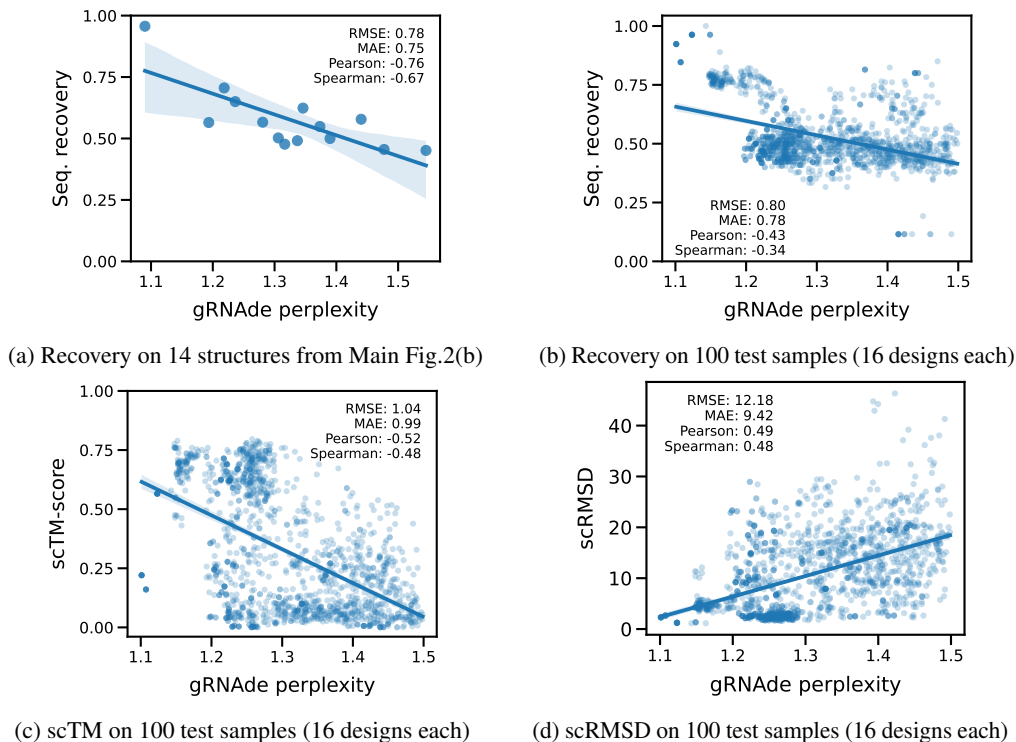


Figure 1: **gRNAd perplexity correlation with sequence and structure recovery.** Regression plots measuring correlation between gRNAd’s perplexity and computational metrics for designed sequences, such as native sequence recovery and 3D self-consistency scores for test set samples from the Single-state split (16 designs per sample). We find weak positive/negative correlation (depending on metric) as measured by Pearson/Spearman correlation coefficients.