

Supplementary File_ClusterSyn

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Supplementary Tables

Table S1: Comparison with regression-based drug synergy prediction methods under the LOEDO evaluation setting using alternative drug-combination response scoring functions. Lower RMSE indicates better prediction accuracy, whereas higher R^2 and PCC indicate stronger agreement with experimentally observed Bliss, ZIP, and HSA scores. The best value for each metric within each scoring function is shown in bold.

Method	RMSE, mean $\pm$ SD	R^2 , mean $\pm$ SD	PCC, mean $\pm$ SD
Bliss Independence			
ClusterSyn	6.09 $\pm$ 0.09	0.84 $\pm$ 0.035	0.83 $\pm$ 0.014
UniSyn	6.33 $\pm$ 0.16	0.81 $\pm$ 0.02	0.82 $\pm$ 0.034
CoSynLLM	6.91 $\pm$ 0.13	0.79 $\pm$ 0.32	0.78 $\pm$ 0.015
MGAE-DC	7.07 $\pm$ 0.16	0.78 $\pm$ 0.02	0.78 $\pm$ 0.067
PermutedDDS	7.12 $\pm$ 0.21	0.76 $\pm$ 0.03	0.75 $\pm$ 0.024
HypertranSynergy	7.58 $\pm$ 1.21	0.77 $\pm$ 0.12	0.76 $\pm$ 0.026
DTF	8.08 $\pm$ 0.19	0.73 $\pm$ 0.15	0.73 $\pm$ 0.044
HypergraphSynergy	8.45 $\pm$ 0.16	0.72 $\pm$ 0.08	0.73 $\pm$ 0.013
DeepSynergy	8.92 $\pm$ 0.04	0.67 $\pm$ 0.03	0.66 $\pm$ 0.015
Zero Interaction Potency (ZIP)			
ClusterSyn	3.35 $\pm$ 0.019	0.84 $\pm$ 0.025	0.84 $\pm$ 0.04
UniSyn	3.53 $\pm$ 0.021	0.83 $\pm$ 0.012	0.83 $\pm$ 0.04
CoSynLLM	3.93 $\pm$ 0.053	0.82 $\pm$ 0.02	0.83 $\pm$ 0.07
MGAE-DC	4.01 $\pm$ 0.06	0.80 $\pm$ 0.042	0.81 $\pm$ 0.07
PermutedDDS	4.15 $\pm$ 0.01	0.79 $\pm$ 0.03	0.80 $\pm$ 0.04
HypertranSynergy	4.50 $\pm$ 0.11	0.79 $\pm$ 0.02	0.80 $\pm$ 0.06
DTF	4.24 $\pm$ 0.09	0.78 $\pm$ 0.05	0.78 $\pm$ 0.04
HypergraphSynergy	4.45 $\pm$ 0.06	0.77 $\pm$ 0.018	0.78 $\pm$ 0.03
DeepSynergy	4.97 $\pm$ 0.64	0.76 $\pm$ 0.013	0.77 $\pm$ 0.05
Highest Single Agent (HSA)			
ClusterSyn	4.05 $\pm$ 0.09	0.84 $\pm$ 0.05	0.83 $\pm$ 0.14
UniSyn	4.01 $\pm$ 0.01	0.84 $\pm$ 0.012	0.84 $\pm$ 0.04
CoSynLLM	4.13 $\pm$ 0.03	0.83 $\pm$ 0.012	0.83 $\pm$ 0.09
MGAE-DC	4.21 $\pm$ 0.01	0.81 $\pm$ 0.02	0.82 $\pm$ 0.11
PermutedDDS	4.55 $\pm$ 0.11	0.80 $\pm$ 0.013	0.81 $\pm$ 0.02
HypertranSynergy	4.67 $\pm$ 0.01	0.79 $\pm$ 0.012	0.80 $\pm$ 0.26
DTF	4.74 $\pm$ 0.02	0.79 $\pm$ 0.06	0.79 $\pm$ 0.014
HypergraphSynergy	4.90 $\pm$ 0.08	0.78 $\pm$ 0.028	0.78 $\pm$ 0.013
DeepSynergy	5.07 $\pm$ 0.034	0.76 $\pm$ 0.023	0.77 $\pm$ 0.015

Table S2: Comparison with regression-based drug synergy prediction methods under the topology-preserving leave-one-drug-pair-out (LODPO) evaluation setting. Lower RMSE indicates better prediction accuracy, whereas higher R^2 and PCC indicate stronger agreement with experimentally observed Bliss, ZIP, and HSA scores. The best value for each metric within each scoring function is shown in bold.

Method	RMSE, mean $\pm$ SD	R^2 , mean $\pm$ SD	PCC, mean $\pm$ SD
Bliss Independence			
ClusterSyn	5.51 $\pm$ 0.019	0.84 $\pm$ 0.05	0.84 $\pm$ 0.04
UniSyn	6.03 $\pm$ 0.06	0.82 $\pm$ 0.12	0.82 $\pm$ 0.17
CoSynLLM	6.72 $\pm$ 0.33	0.80 $\pm$ 0.02	0.80 $\pm$ 0.05
MGAE-DC	6.89 $\pm$ 0.36	0.79 $\pm$ 0.062	0.78 $\pm$ 0.07
PermutedDDS	7.02 $\pm$ 0.01	0.78 $\pm$ 0.033	0.77 $\pm$ 0.030
HypertranSynergy	7.38 $\pm$ 0.038	0.77 $\pm$ 0.02	0.77 $\pm$ 0.021
DTF	7.88 $\pm$ 0.09	0.75 $\pm$ 0.05	0.75 $\pm$ 0.04
HypergraphSynergy	8.02 $\pm$ 0.06	0.74 $\pm$ 0.18	0.73 $\pm$ 0.083
DeepSynergy	8.32 $\pm$ 0.049	0.72 $\pm$ 0.087	0.71 $\pm$ 0.05
Zero Interaction Potency (ZIP)			
ClusterSyn	3.07 $\pm$ 0.029	0.83 $\pm$ 0.05	0.83 $\pm$ 0.024
UniSyn	3.13 $\pm$ 0.012	0.83 $\pm$ 0.02	0.83 $\pm$ 0.048
CoSynLLM	3.38 $\pm$ 0.033	0.82 $\pm$ 0.12	0.82 $\pm$ 0.077
MGAE-DC	3.59 $\pm$ 0.019	0.80 $\pm$ 0.02	0.80 $\pm$ 0.024
PermutedDDS	4.07 $\pm$ 0.011	0.79 $\pm$ 0.013	0.81 $\pm$ 0.02
HypertranSynergy	4.24 $\pm$ 0.017	0.78 $\pm$ 0.012	0.79 $\pm$ 0.11
DTF	4.38 $\pm$ 0.019	0.78 $\pm$ 0.011	0.79 $\pm$ 0.037
HypergraphSynergy	4.46 $\pm$ 0.016	0.77 $\pm$ 0.028	0.78 $\pm$ 0.019
DeepSynergy	4.91 $\pm$ 0.043	0.77 $\pm$ 0.023	0.77 $\pm$ 0.015
Highest Single Agent (HSA)			
ClusterSyn	4.11 $\pm$ 0.03	0.84 $\pm$ 0.02	0.84 $\pm$ 0.03
UniSyn	4.25 $\pm$ 0.09	0.83 $\pm$ 0.14	0.83 $\pm$ 0.02
CoSynLLM	4.70 $\pm$ 0.07	0.81 $\pm$ 0.03	0.82 $\pm$ 0.03
MGAE-DC	4.91 $\pm$ 0.01	0.78 $\pm$ 0.09	0.80 $\pm$ 0.06
PermutedDDS	5.02 $\pm$ 0.03	0.76 $\pm$ 0.04	0.79 $\pm$ 0.05
HypertranSynergy	5.78 $\pm$ 0.01	0.72 $\pm$ 0.03	0.75 $\pm$ 0.01
DTF	5.90 $\pm$ 0.05	0.70 $\pm$ 0.07	0.73 $\pm$ 0.05
HypergraphSynergy	6.01 $\pm$ 0.03	0.68 $\pm$ 0.04	0.7 $\pm$ 0.08
DeepSynergy	6.43 $\pm$ 0.25	0.66 $\pm$ 0.036	0.69 $\pm$ 0.023

Supplementary Figure

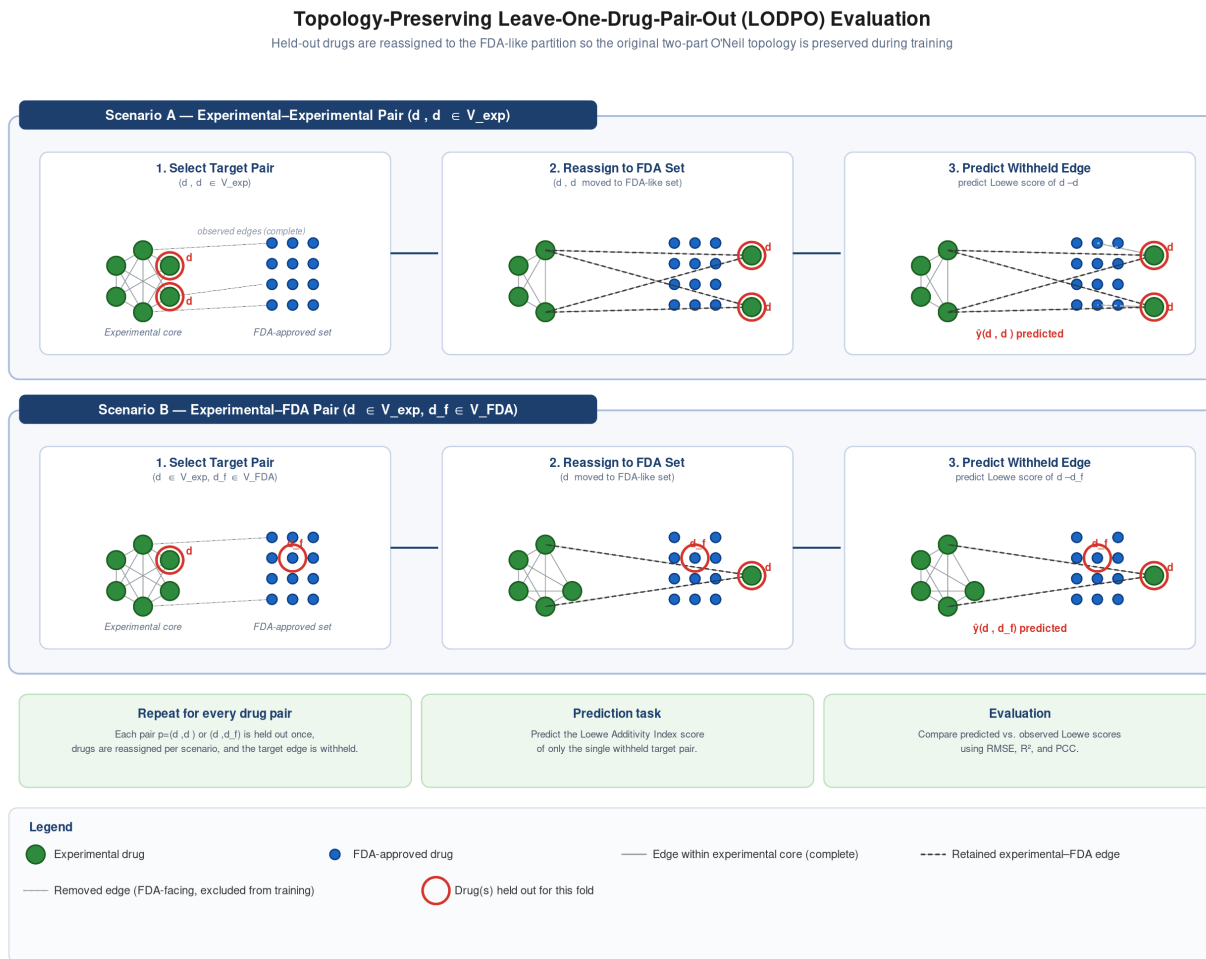


Figure S1: Topology-preserving leave-one-drug-pair-out (LODPO) validation workflow used for experimental-experimental and FDA-experimental drug pair out.