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Supplementary information

A generalized-template-based graph neural network for accurate organic reactivity prediction

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Supporting information

A Generalized Template-Based Graph Neural Network for Accurate Organic Reactivity Prediction

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S1. Examples of generalized reaction templates (GRTs)

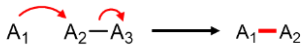
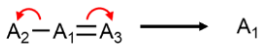
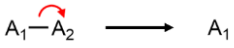
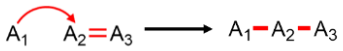
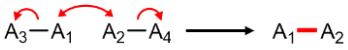
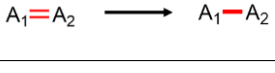
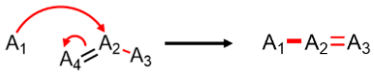
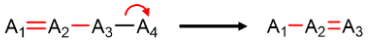
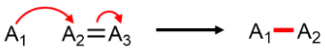
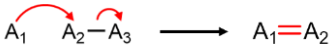
Rank (frequency)	Generalized reaction template	Rank (frequency)	Generalized reaction template
1 (38.1%)		6 (2.46%)	
2 (11.5%)		7 (2.43%)	
3 (6.85%)		8 (2.17%)	
4 (4.70%)		9 (2.12%)	
5 (2.50%)		10 (1.75%)	

Figure S1. Top ten most popular generalized reaction templates derived from the train set of USPTO-480k dataset.

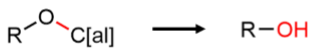
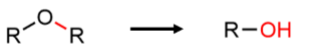
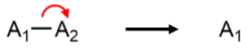
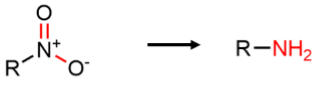
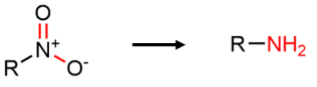
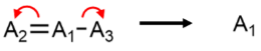
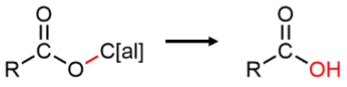
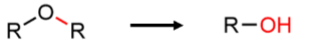
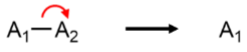
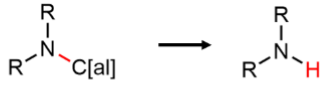
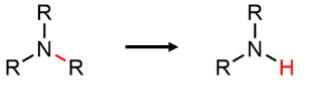
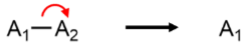
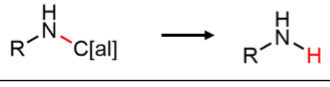
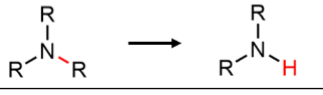
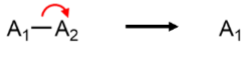
Reaction description	Previous reaction template	Local reaction template	Generalized reaction template
Hydrolysis of alkyl ether/ester			
Reduction of nitro to primary amine			
Hydrolysis of ester			
Dealkylation of tertiary amine			
Dealkylation of secondary amine			

Figure S2. Comparison between previous reaction template[1], local reaction template[2] and generalized reaction template (GRT) with five different reaction types.

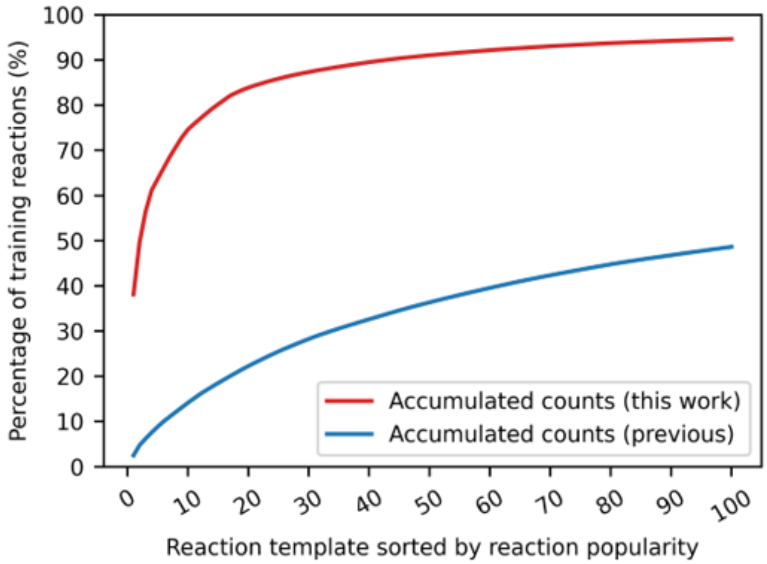


Figure S3. The percentage of the training reactions that are cumulatively covered by the top 100 most popular GRTs, compared with a previous template extraction method[1]

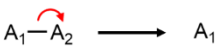
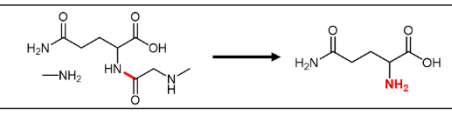
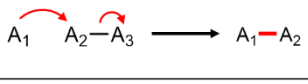
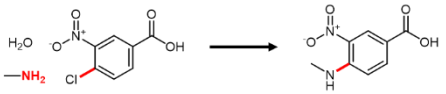
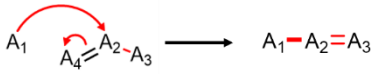
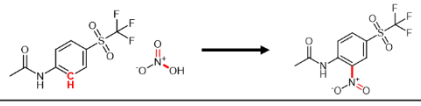
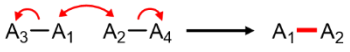
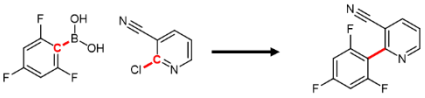
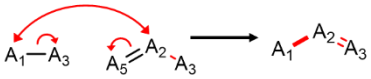
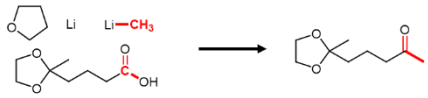
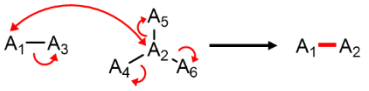
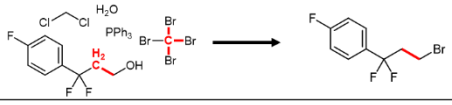
Number of actions	Generalized reaction template	Example reaction
1		
2		
3		
4		
5		
6		

Figure S4. The most popular GRTs requiring 1 to 6 actions and their example reactions. Note that the atom-mapping of the most popular GRT requiring 6 actions seems to be questionable.

S2 Results of separated prediction scenario

Table S1. Top-k exact match accuracy on USPTO-480k dataset in separated prediction scenario. The best top-k exact match accuracy is highlighted with bold font.

Model	Model type	Top-k Accuracy (%)			
		K = 1	2	3	5
Molecular Transformer[3]	Sequence-based	90.4	93.7	94.6	95.3
Augmented Transformer[4]	Sequence-based	91.9	95.4	/	97.0
Chemformer[5]	Sequence-based	92.8	/	/	94.9
WLDN[6]	Graph-based	85.6	90.5	92.8	93.4
MEGAN[7]	Graph-based	89.3	92.7	94.4	95.6
Symbolic[8]	Graph-based	90.4	93.2	94.1	95.0
NERF[9]	Graph-based	90.7	92.3	93.3	93.7
LocalTransform (this work)	Graph-based	92.3	95.6	96.5	97.2

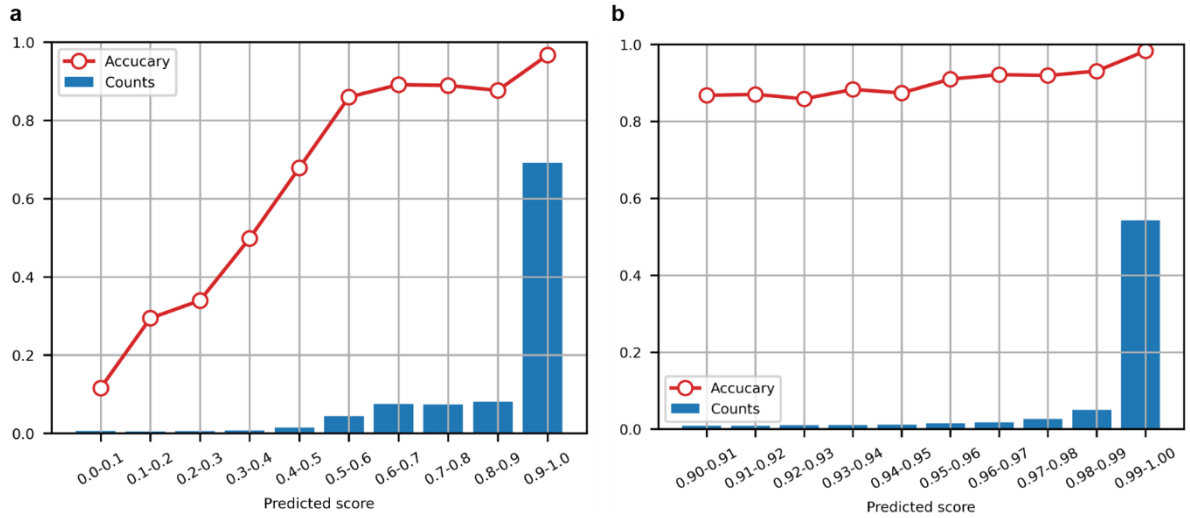


Figure S5. (a) The top-1 exact match accuracies and the accumulated counts compared with prediction score in the separated prediction scenario. (b) The top-1 exact match accuracies and the accumulated counts compared with prediction score between 0.9 and 1.0.

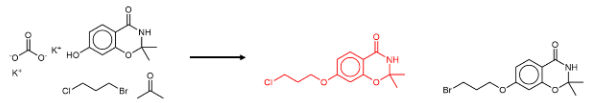
S3 Ablation studies

Table S2. Ablation studies of *LocalTransform*.

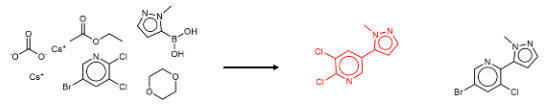
Prediction scenario	Model	Top-k Accuracy (%)			
		K = 1	2	3	5
Separated	*LocalTransform*	92.4	95.6	96.5	97.2
	wo/ bond-wise attention	91.8	95.3	96.2	96.7
	wo/ atom-wise attention	86.6	93.8	95.4	96.2
Mixed	*LocalTransform*	90.8	94.8	95.7	96.3
	wo/ bond-wise attention	89.8	94.2	95.4	96.0
	wo/ atom-wise attention	47.1	56.2	60.2	63.5

S4 highly-scored (>0.999) incorrect predictions

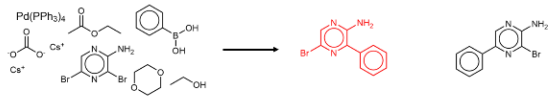
a



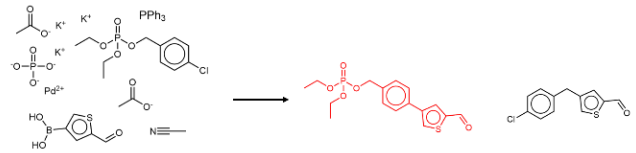
b



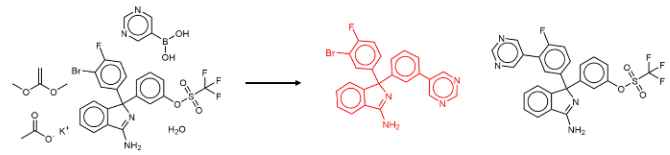
c



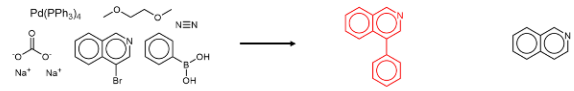
d



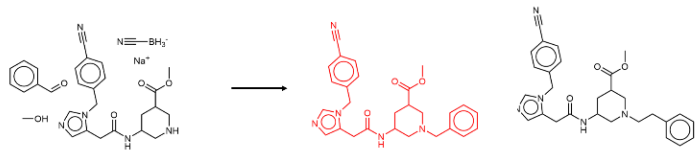
e



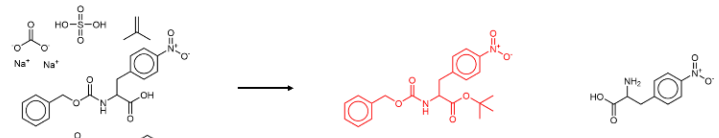
f



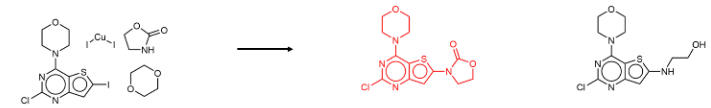
g



h



i



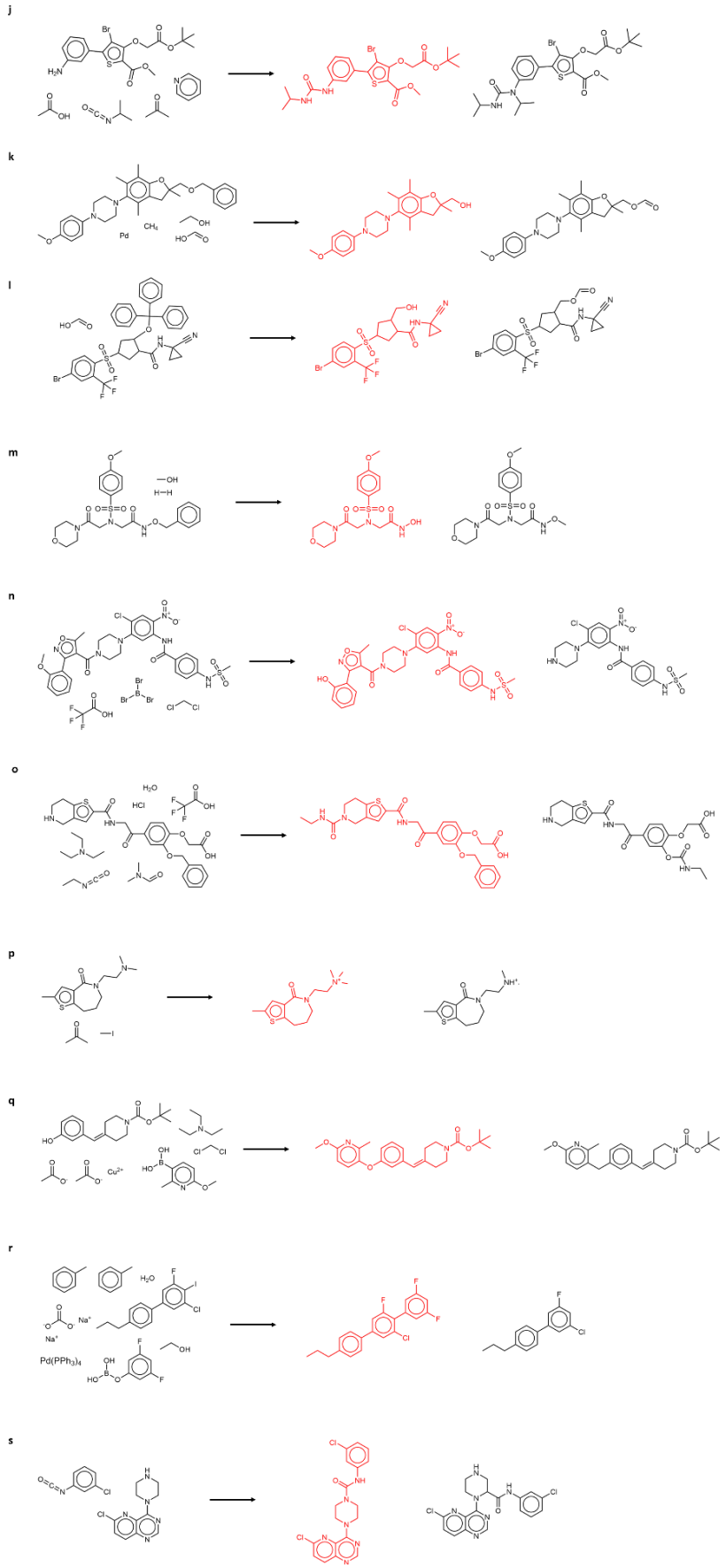


Figure S6. Predictions with very high score (>0.999) but inconsistent with ground truth product. The predictions of LocalTransform are color coded in red and the ground truths are color coded in black.

S5 Prediction accuracy as a function of template popularity

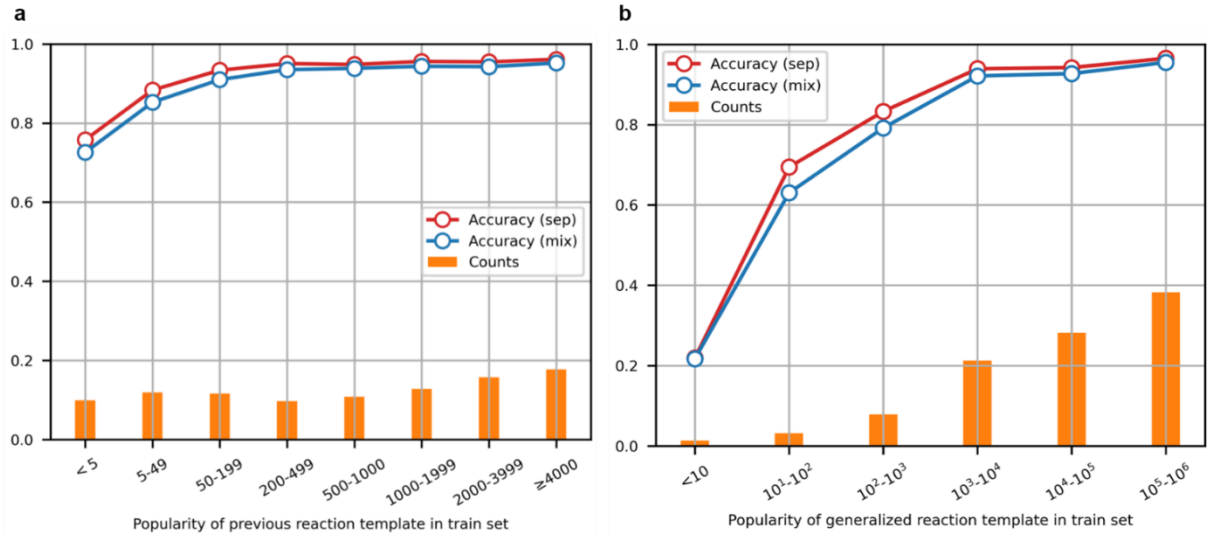
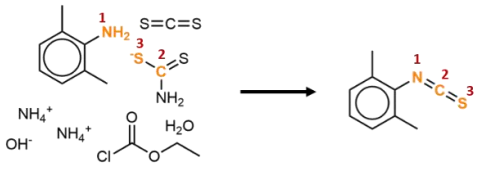


Figure S7. Prediction accuracy as a function of popularity of (a) previous reaction templates[1] and (b) GRTs.

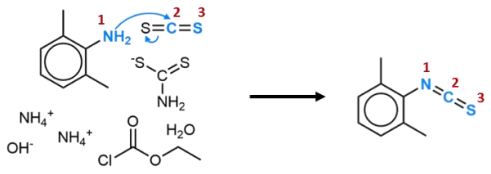
S6 Reactions with potential wrong atom-mapping

Reaction #1108

Original atom-mapping

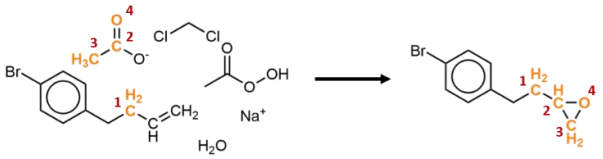


LocalTransform prediction (0.50)

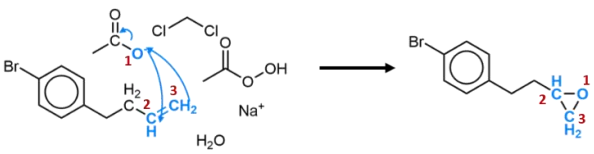


Reaction #16389

Original atom-mapping

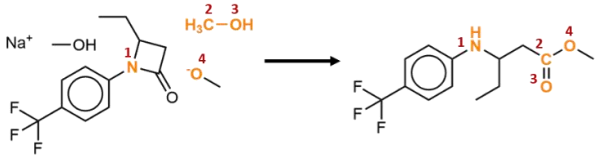


LocalTransform prediction (0.72)

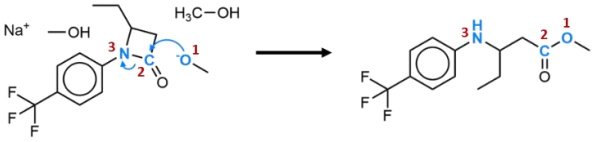


Reaction #27411

Original atom-mapping

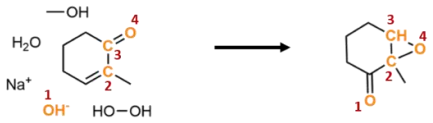


LocalTransform prediction (0.77)



Reaction #35298

Original atom-mapping



LocalTransform prediction (0.86)

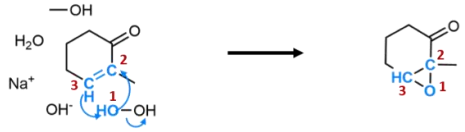


Figure S8. Reactions with potential wrong atom-mapping. The numbers written after "LocalTransform prediction" are prediction scores. The original atom-mappings of the shown reactions are questionable while *LocalTransform* predict the same products with reasonable GRT and yield more rational atom-mapping.

S7 Atom and Bond Featurization

Table S3. The chemical properties for initializing atom features and bond features.

Feature type	Chemical information
Atom features	atom types, chirality, formal charge, partial charge, aromaticity, hybridization, hydrogen bond donor/acceptor, the number of rings the atom belongs to
Bond features	Bond type, bond conjugation, bond in ring, stereo configuration

S8 Hyperparameter optimization

Table S4. A list of hyperparameters that are optimized in this work.

Hyperparameter	Values
Training batch size	8, 16, 32
Learning rate (starting)	10^{-3}, 10^{-4}, 10^{-5}
Hidden dimension of atom feature	128, 256, 512
Iteration of message passing	3, 4, 5
Number of attention blocks (both atom-wise and bond-wise)	2, 3, 4, 5

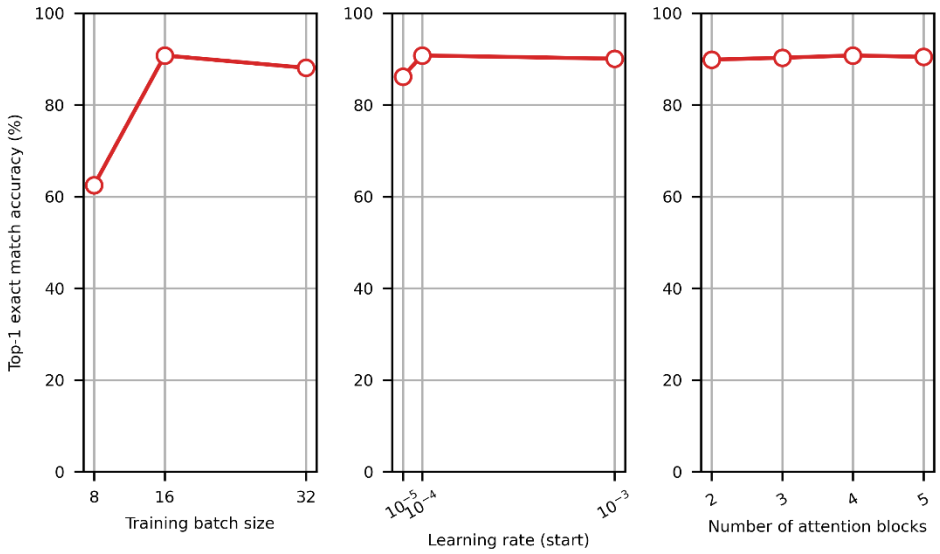


Figure S9. The effect of different hyperparameters on the top-1 exact match accuracy in mixed prediction scenario.

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