Differential top-k learning for template-based single-step retrosynthesis

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Abstract

Retrosynthesis is one of the core tasks in the organic molecule design cycle, yet it is still a computational challenge to produce suitable sets of precursors for a desired product. Commonly used template-based approaches reduce the problem to a multi-class classification task for single steps. However, reactions in available datasets are noisy and incomplete, making usual training methods problematic. In this work, considering that multiple disconnections are possible for a product, we propose training models using differential top-k losses. We show that using these loss functions yields improvements in every top-N metric, with little overhead relative to cross-entropy. The use of more powerful models, more diverse and complete datasets, and other methodologies, is expected to yield significant improvements on this task when combined with the training approach presented here.

1 Introduction

The development of novel materials and molecules is at the foundation of societal development towards a sustainable future. However, synthesis –i.e. the reaction steps for how to make a given molecule– remains one of the crucial bottlenecks during the design cycles of such substances [1], heavily slowing down the discovery and production of such novel materials and molecules. Human experts attempt to solve this problem by applying their chemical knowledge in retrosynthetic planning, where the goal is to find a synthetic path for a target molecule, such that it can be resolved to commercially available or easily synthetically accessible substances. The search is performed backwards by inspection of the target molecule, while suggesting sets of precursors that, upon reaction under adequate conditions, would lead to the desired product.

Current computational approaches for the multi-step problem [2–6] pair single-step retrosynthetic prediction models with search algorithms, that iteratively compose single-step predictions until a suitable synthetic plan is obtained from commercially available starting materials. In turn, multiple strategies have been published towards solving the single-step problem [7], such as template-based [8–12], graph edit-based [13,14] and sequence-based approaches [4,15–18]. Since the pioneering work of Corey [19,20], researchers have attempted to encode chemical transformations into expert-curated [21,22] and automatically extracted reaction rules [2,8], that describe types of reactions found in data –very much like "name reactions" in organic chemistry. When a template library is built, the single-step retrosynthetic problem can be reframed as a multi-class classification problem [2] where the task is, for the desired product, to find the most suitable reaction leading to it. Although such approaches are limited by the size of the template library, they are popular in synthesis planning tools thanks to their speed, as the problem is reduced to a much simpler classification task. In this work, we focus solely on template-based and single-step retrosynthesis approaches, and how mapping the training task closer to reality leads to overall prediction improvements.

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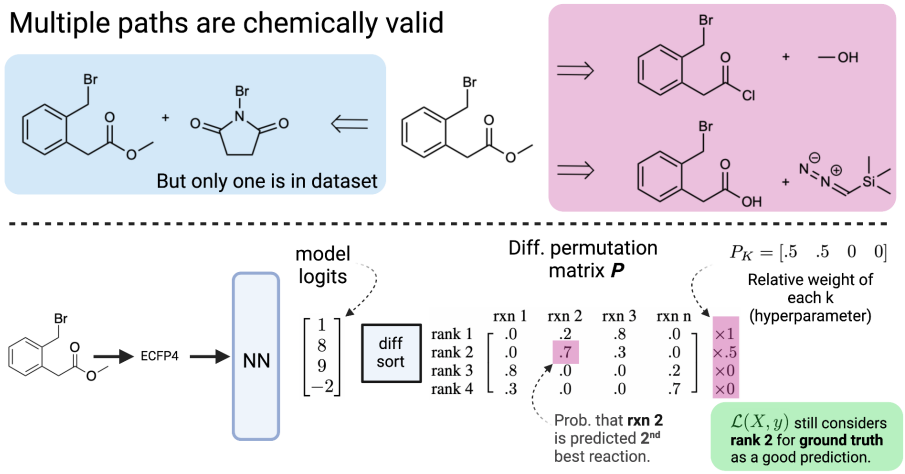

Figure 1: Multiple plausible synthetic paths exist for a given product (top), however only a small subset is found in datasets. Using cross entropy loss, models get punished for proposing synthetic paths alternative to the ground truth. Differentiable top-k based loss functions (below) help this by also considering higher ranks (k) as valid, their importance given by a distribution P_K.

The challenge with single-step retrosynthesis task is that multiple correct possibilities exist to synthesize the same target molecule[15] (Figure 1 top). However, typically only one of the correct possibilities is recorded in the current reaction benchmark datasets and hence the ground truth is generally incomplete. As reactions other than the ground truth ones could equally be correct, the cross entropy loss on which previous template-based approaches were trained is ill-posed[8–10,12].

Inspired by recent work in image classification by Petersen et al.[23], we introduce differential top-k learning for the single-step retrosynthetic task (Figure 1 bottom). We show that a straightforward change in the loss function, which relaxes the distribution over the target templates, leads better top-N accuracies compared to the same models trained on top-1 cross entropy. Most strikingly, even the top-1 prediction accuracy increases as a result. We conclude that the use of this type of cost functions is better suited for this task, both from the chemical and the computational perspectives. We expect top-k learning to become valuable for other applications in machine learning for chemical sciences, where the ground truth is incomplete and contains only a fraction of the correct classes.

2 Methods

2.1 Template-based single-step retrosynthesis models

Several template-based models and molecular representations have been proposed in the recent years to tackle the single-step retrosynthesis problem. In the seminal work of Segler et al.[2], the authors used a highway neural network architecture[24] that takes as input an ECFP4 fingerprint of the desired molecule[25], to predict the most suitable template from a set of automatically extracted transformations. More recent approaches are based on conditional graph logic networks[9], modern Hopfield networks[12], and re-ranking of predictions using energy-based models[26], which all improve over the simple highway neural network baseline. Though not ideal, all studies use top-k accuracy, whether the ground truth is found in the k most likely prediction or not, as a proxy for evaluating and comparing single-step retrosynthesis models.

We investigated the classifier proposed by Segler et al.[2]. The hyperparameters used are the same as those reported for this type of architecture in[26]. For each loss function, 15 models were trained and tested using the same set of randomly generated seeds (see Appendix **??**).

2.2 Differential top-k learning

Conventionally used loss functions for classification tasks are built to maximize top-k, for a given positive integer k[27,28], cross entropy loss being the special case for $k = 1$. Building on recent advances in differentiable sorting[29,30], Petersen et al.[23] further relaxed the need to choose a value of k, and instead use a distribution over this parameter, giving a relative importance to each top-k objective. They thus propose a family of loss functions, each being specified by such distribution. The authors thoroughly test the method in a range of benchmarks for image classification, and show that mixed top-k strategies not only improve top-5 accuracies but also top-1 accuracy, achieving a new state-of-the-art on ImageNet[31].

Differentiable sorting works by producing a differentiable permutation matrix $\mathbf{P}$[29] from a model's raw logits $f_\Theta(X)$. Each entry $\mathbf{P}_{k,j}$ of this matrix is interpreted as the predicted probability that class j is the k-th best prediction. Finally, the loss function is fully specified by the distribution over ks P_K, so that $P_K(k)$ is the relative importance assigned to the pure top-k objective.

The model is then trained by minimizing the following loss function

$$\mathcal{L}(X, y) = -\log\left(\sum_{k=1}^{n} P_K(k)\left(\sum_{m=1}^{k} \mathbf{P}_{m,y}(f_\Theta(X))\right)\right). \tag{1}$$

2.3 Data &representation

Schneider et al.[32] initially published the USPTO 50k dataset, and Liu et al.[15] later curated it and created the retrosynthesis benchmark dataset. It contains 50k reactions from 10 reaction superclasses. More recently, Dai et al.[9] introduced the USPTO full dataset, which they derived from the patent reaction collection by[33]. Here we only present the results on the most commonly used USPTO 50k dataset, with the same train/valid/test split and template library as used by Lin et al.[26]. The templates are extracted from atom-mapped reactions[34], and their quality might be limited by the quality of the mapping[35]. Following previous work[2,26], we represent the target molecules with extended-connectivity fingerprints (ECFPs)[25].

3 Results & Discussion

We investigate template-based single-step retrosynthesis prediction models on the USPTO 50k dataset, and compare a highway network-based model trained using standard cross entropy (baseline)[2,26] with the same model trained with differential top-k losses. For the baseline model, we find that the prediction accuracy increases by 21.67 % from top-1 to top5 accuracy. Figure 2 shows an example, where the correct template was predicted in the top-3. In such cases, we often observe that the highly ranked reactions other than the reported reaction correspond to equally valid disconnections and possible transformations. However the cross entropy loss still punishes the model for these "wrong" predictions. Differential top-k losses prevent this, thus giving more flexibility to the models which in turn allow them to predict more diverse disconnections and reaction types. See more examples in the Appendix **??**. As shown in appendix Table **??**, mixed top-k approaches to training provide as much as 3% improvement in some top-k accuracies in the precursors prediction task. Note that such gains in accuracy are achieved by simply changing the loss function while using the same hyperparameters as for cross entropy; this method thus provides better results with little extra overhead.

3.1 Mixed k approaches

The effect of different distributions of k in the model's performance was tested. Different strategies with mixed weights for values of k between 1 and 5 were used, and the results are shown in Table 1. The selected distributions were selected based on some of the results and suggestions from Petersen et al.[23].

The results show that using a mixed k approach for training, systematically improves over training with cross Entropy, and any other pure k approach, making this method suitable for classification tasks such as template based single-step retrosynthesis planning. The advantage of this new family of loss functions is clear when compared to the baseline cross entropy (Table 1). Pure top-k approaches,

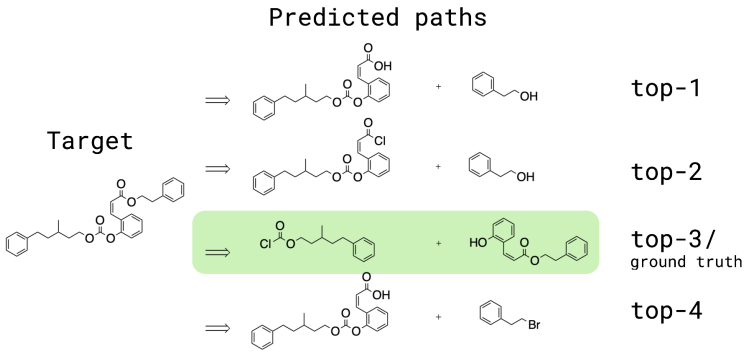

Figure 2: Example of model predictions where ground truth is not classified as the best template, but it is found within the top-4 predictions. The figure illustrates how in these cases, most of the other predicted top-4 sets of precursors corresponds to equally valid disconnections.

Loss Function	top-1	top-2	top-3	top-4	top-5	top-10	top-20
CrossEntropy	40.12	50.94	56.51	59.70	61.79	67.21	71.35
$P_K = \{0.1, 0, 0, 0, 0.9\}$	40.16	51.90	58.31	62.05	64.55	**69.98**	73.24
$P_K = \{0.3, 0, 0, 0, 0.7\}$	40.56	52.35	58.53	62.22	**64.68**	69.95	**73.29**
$P_K = \{0.5, 0, 0, 0, 0.5\}$	40.98	52.56	58.63	62.22	64.61	69.83	73.17
$P_K = \{0.7, 0, 0, 0, 0.3\}$	41.08	**52.62**	58.36	61.85	64.19	69.40	72.78
$P_K = \{0.9, 0, 0, 0, 0.1\}$	**41.10**	52.20	57.98	61.04	63.16	68.44	71.86
$P_K = \{1/5, 1/5, 1/5, 1/5, 1/5\}$	40.68	52.23	58.52	62.18	64.66	69.93	73.24
$P_K = \{1/4, 1/4, 1/4, 1/4, 0\}$	40.69	52.36	58.62	62.16	64.63	69.82	73.19
$P_K = \{1/3, 1/3, 1/3, 0, 0\}$	40.73	52.39	58.55	62.14	64.64	69.79	73.25
$P_K = \{1/2, 0, 0, 1/2, 0\}$	41.00	52.55	**58.65**	**62.23**	64.62	69.84	73.14
$P_K = \{1/2, 1/2, 0, 0, 0\}$	40.81	52.37	58.41	61.90	64.28	69.56	73.03
$P_K = \{1/10, 1/10, 1/10, 1/10, 6/10\}$	40.17	51.96	58.31	61.99	64.56	69.97	73.24
$P_K = \{6/10, 1/10, 1/10, 1/10, 1/10\}$	41.00	52.57	58.59	62.06	64.39	69.66	73.09

Table 1: Top-k accuracies on the template prediction task, from training with various mixed approaches. Results from systematic evaluations of ratios of $P_K(1)$ and $P_K(5)$ are shown in the second block, as proposed in[23]. Last block shows the results for other combinations.

in which a maximum weight is given to some k, were also tested. The idea of this type of training is to improve in particularly that specific metric, e.g. if a pure top-3 approach is carried out, the model is expected to improve on this metric, but not necessarily the others. The results in the Appendix **??** confirm this, and in particular show that pure top-k training, with k>1, tends to improve all metrics except from top-1, which decreases as k is increased.

4 Conclusion

Cross entropy is the most commonly used loss function for classification tasks in machine learning; here we argue that this function is inadequate for the task of single-step retrosynthesis planning, as datasets for this task are incomplete and different reactions are usually as valid. Differentiable top-k learning is proposed to alleviate this limitation, and it is shown that using this strategy for training, systematically leads to improvements on every top-k accuracy. The results of this work were obtained with a very simple fully connected architecture, on a standard benchmark dataset (see Data and Methods). However modest, the obtained improvements show that this training approach could lead to more substantial gains in accuracy when using more powerful models, in particular GLN[9], Modern Hopfield Networks[12] and others. We additionally expect this approach to be useful and become a standard for other multi-label classification tasks in chemistry[36,37], beyond template based retrosynthesis. In the future, our work will be extended to consider more diverse datasets, such as USPTO-full[9]. The code and data to reproduce the results will be made available upon publication.

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