ABSTRACT

Reaction prediction is a fundamental problem in computational chemistry. Existing approaches typically generate a chemical reaction by sampling tokens or graph edits sequentially, conditioning on previously generated outputs. These autoregressive generating methods impose an arbitrary ordering of outputs and prevent parallel decoding during inference. We devise a novel decoder that avoids such sequential generating and predicts the reaction in a Non-Autoregressive manner. Inspired by physical-chemistry insights, we represent edge edits in a molecule graph as electron flows, which can then be predicted in parallel. To capture the uncertainty of reactions, we introduce latent variables to generate multi-modal outputs. Following previous works, we evaluate our model on USPTO-MIT dataset. Our model achieves both an order of magnitude lower inference latency, with state-of-the-art top-1 accuracy and comparable performance on Top-K sampling.

1 Introduction

First formalized by [Corey & Wipke, 1969], reaction prediction, which aims to identify the probable chemical reactions given the reactants, reagents, and possibly other conditions, has become a fundamental problem in computational chemistry. The ability to predict outcomes of organic reactions allows chemists to analyze the feasibility of chemical reactions and design optimal synthesis routes for target molecules, which is of central importance for synthesis planning and drug discovery.

Machine learning based approaches [Struble et al.] have achieved great success in reaction prediction, thanks to the large amount of reaction data available. Existing end-to-end approaches either formulate reaction prediction as machine translation [Liu et al., 2017; Schwaller et al., 2019] or graph transformation [Coley et al., 2019; Do et al., 2019; Sacha et al., 2020]. The best-performing methods so far [Schwaller et al., 2019; Sacha et al., 2020] are autoregressive generative models. During inference, they generate each output item sequentially, conditioning on previously generated outputs. For machine translation based models, this inference process often takes hundreds of iterations and incurs high inference latency. Instead of generating from scratch, several graph-based models [Sacha et al., 2020] learn to predict a sequence of graph edits. Their output is usually much shorter than the machine translation models, largely reducing inference latency. However, these models cannot achieve state-of-the-art top-1 accuracy and still rely on a specific order and corresponding data augmentation.

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We propose a novel model for reaction prediction that predicts its outputs in parallel, namely the Non-autoregressive Electron Flow Generator (NEFG). Inspired by physical-chemistry insights, we recognize an edge in a molecule graph as a pair of shared electrons, and bond transformations as electron flows, which can be predicted in parallel. Our formulation of electron flow generalizes that of (Bradshaw et al., 2018), by allowing arbitrary, non-linear electron flows and parallel transformation. In this way, NEFG is capable of predicting chemical reactions in an end-to-end manner without additional data augmentation.

We evaluate our model on the USPTO benchmark dataset. Our model achieves an order of magnitude higher inference speed and excellent top-1 accuracy, compared to state-of-the-art methods. Enhanced with latent variables, our model can generate diverse multi-modal outputs, with top-k accuracy comparable to autoregressive baselines.

Our main contributions can be summarized as follows:

- We generalize the view of Bradshaw et al. (2018) to include non-linear electron flows and devise a novel decoder to generate arbitrary electron flow in parallel.
- We propose a non-autoregressive model for reaction prediction, which achieves state-of-the-art top-1 accuracy with an order of magnitude faster inference.
- We enhance our model with latent variables and apply a practical searching algorithm to generate diverse multimodal outcomes.

2 Related Work

Template-based Approach Previous works on reaction prediction mostly rely on reaction templates, which define sub-graph matching rules for a bunch of similar organic reactions. Products are generated by matching reactants with a set of reaction templates and applying to them pre-defined transformations, implicitly leveraging the domain knowledge encoded in reaction templates. For example, Coley et al. (2017); Segler & Waller (2017a,b) used heuristic algorithms to extract a large set of reaction templates from the database and introduced neural networks to select the major product by ranking the generated candidates. Wei et al. (2016) first learned a neural model to classify reactions into different types, based on which they selected templates for the given reactants. Despite their potential application in synthesis planning, these approaches suffer from poor generalization on unseen structures and can not scale well to larger data set as they require expensive graph isomorphism.

Template-free Approach Kayala & Baldi (2011) first proposed to bypass reaction templates by predicting a series of elementary mechanism steps for reactions, which still requires a rule-based expert system to generated mechanism-level supervision. Very recently, various data-driven template-free approaches Bradshaw et al. (2018); Do et al. (2019); Jin et al. (2017); Schwaller et al. (2018, 2019) have been proposed. Inspired by the recent advance in neural machine translation Bahdanau et al. (2014); Vaswani et al. (2017), Schwaller et al. (2018, 2019) novelly formulated reaction prediction as a sequence-to-sequence problem and employed a Transformer or long short-term memory (LSTM) architecture to translate canonical SMILES Weininger (1988) representation of reactant graphs to those of product graphs. However, such methods require learning complex syntactic and semantic rules of SMILES representation and also lack interpretability w.r.t. their predictions. Jin et al. (2017) built their method upon Weisfeiler-Lehman Networks (WLN) and proposed a two-stage framework for the problem. More specifically, they first trained a WLN to estimate the reactivity score of each atom pair in reactant graphs, based on which they enumerated all possible configurations of bond modification for reactants. Then they employed a separate network to rank all chemically-valid candidates. However, this learning scheme is not end-to-end and also requires extra label annotation. Herges (1994); Do et al. (2019); Sacha et al. (2020) formulated reaction prediction as a sequence of transformation on the molecule graph, where the supervised order of modification is decided by either random sample or heuristic search.

Non-autoregressive Generation (NAT Models) Gu et al. (2018) proposed non-autoregressive sequence generation for machine translation, in order to parallelize the inference process for better performance on modern hardware accelerators. Instead of conditioning each token on previous generated outputs, these approaches factorize the learning objective under the conditional independence assumption:

$$\log p(y|x) = \sum_{i=1}^{|y|} \log p(y_i|x)$$  \hspace{1cm} (1)

where $y_i$ denotes the target token. Various techniques are introduced to model the dependence between $y_i$ and generate multimodal outcomes. Łukasz Kaiser et al. (2018) enhanced the model with discrete latent variables. Shu et al. (2019) introduced continuous latent variable with delta posteriors via an EM-like approximate inference algorithm. Lee et al. (2020) proposed to optimize the translated sentence by iterative refinement in the latent space. However, to the
best of our knowledge, our approach is the first attempt to predict chemical reactions with non-autoregressive graph translation.

3 Preliminaries

In this section, we introduce our notations that build the connection between concepts in chemistry and graph theory, especially the equivalence of electron flow and edge transformation.

Notation In this paper, an organic molecule (or molecules, if the graph has multiple connected components) is represented as an undirected graph $G = (V, E, f)$, where $V$ and $E$ are the set of atoms and bonds respectively. Each node $v_i \in V$ is associated with a fix-length feature vector $f_i$, each dimension of which corresponds to a property of an atom, e.g., atom type and formal electric charge. Unlike previous works (Sacha et al., 2020) that typically represent bond type as an edge feature or edge type, we treat different bonds as various parallel edges, which is coherent with our view of bonds as shared electrons between atoms. By $e_{ij} \geq 0$ we denote the number of edges between node $v_i$ and $v_j$, i.e. the number of electrons provided by atom $i$ shared with atom $j$. We allow self-loops in $G$ and let $e_{ii} > 0$ denote valence electrons that are not shared with other atoms.

Chemical Reaction Formally, a chemical reaction is a pair of molecular graphs defined on the same set of vertices $(R, P)$, where $R = (V, E^r, f^r)$ is the reactant and $P = (V, E^p, f^p)$ is the product. Let

$$\Delta e_{ij} = e_{ij}^p - e_{ij}^r$$

The change in edges from $E^r$ to $E^p$ is precisely captured by the redistribution of electrons $\Delta e_{ij}$, around each atom $i$, $\Delta e_{ij}$ satisfies several chemistry constraints that we incorporate as implicit regularization in designing our decoder. For each node $i$, we have

$$\Sigma_j \Delta e_{ij} = 0, \quad \Sigma_j |\Delta e_{ij}| < 2D$$

The first equation indicates conservation of electrons, and the second indicates the fact that the number of valence electrons is bounded by a small number, and typically most bonds are unchanged by the reaction. As a generalization of the implementation of electron flow proposed by (Bradshaw et al., 2018), our formulation $\Delta e_{ij}$ includes arbitrary electron flow topology, instead of just linear electron flows (Figure 1). Moreover, it can be predicted in parallel, allowing non-autoregressive generation.

4 Non-autoregressive Electron Flow Generator

In this section, we describe the architecture of NEFG. The overall structure is illustrated in Figure 2. The encoder module first encodes the reactants $R$ into representation $h^r$, using a bi-level encoder framework consisting of a GCN module and a graph attention network. The variational encoder module then estimates the posterior distribution of latent variable $z$, which is concatenated with $h^r$ to obtain the product representation $h^p$. Finally, the decoder module takes $h^p$ as the input and predicts the products $P$. The transformation from $R$ to $P$ is predicted by estimating the
electron flows around each node. We use two groups of pointer networks to represent the incoming and outgoing electrons respectively, which we call the influx pointers and the outflux pointers.

The overall structure follows the conditional variational inference framework, where the variational encoder estimates $p(z|R,P)$ and the decoder models $p(P|z,R)$. The inference procedure is deterministic given latent variable $z$, without the need for autoregressive sampling.

### 4.1 Encoder

Our encoder consists of a GCN and stack of graph attention layers, following the bi-level information extraction framework (Rong et al., 2020). The low-level GCN message passing is guided by connectivity, and focus on local structures within its limited reception field, while the high-level graph attention network is guided by content, and may pass messages between distant parts of the graph to identify the global structure. Our encoder can be interpreted as a differentiable integration of the template-based approach, in which the GNN module explores the local neighborhoods of each atom to identify chemically reactive functional groups, and the inner product attention mechanism searches matched functional groups globally to find potential reaction centers.

The input to the encoder is the molecule graph $R = (V,E_r,f)$ of the reactants and the reagents. The structural information around each atom is first encoded via a GCN encoder.

$$
m^{r(l)}_v = \text{RELU}(W \cdot \text{SUM}\{h^{r(l-1)}_u | u \in N_v\})$$

$$h^{r(l)}_v = m^{r(l)}_v + h^{r(l-1)}_v \quad l \in \{1, 2, ..., L - 1\} \quad (4)$$

Inspired by (Xu et al., 2018), we employ sum pooling instead of mean pooling in each GCN layer. Afterward, following Veličković et al. (2018), the interaction between nodes is modeled with a stack of multi-head self-attention layers, which outputs the representation $h_v^r$ for each node $v$. Following Rong et al. (2020), we employ fully connected graph attention, in which each self-attention head can attend to all nodes in the graph, instead of just the neighborhood.

### 4.2 Non-Autoregressive Electron Flow Decoder

As illustrated in Fig [2] the decoder starts with a fully-connected graph attention network that transform the node embedding of reactants $h^{(l)}_{v^{(r)}}$ to that of products $h^{(l)}_{v^{(p)}}$. Given the representation for each node $h^{(l)}_{v^{(p)}}$, the decoder predicts node features $f^{(p)}$ (omitted in Fig 2) and the edge transformation (i.e. electron flow) from $E^{(r)}$ to $E^{(p)}$, as illustrated in Fig 1(c). The edge transformation is generated in parallel by predicting $\Delta e_{v}$ around each node $v$ with a multi-pointer network (Vinyals et al., 2015). Consistent with constraints on $\Delta e$ mentioned in equation 3 our decoder consists of $D$ influx pointers and $D$ outflux pointers, pointing to where electrons flow from/toward, respectively. By $w^{(d)}_{(v)}(\cdot)$ we denote the attention weight of the $d^{th}$ outflux pointers, and similarly $w^{(d)}_{(v)}(\cdot)$ denotes attention weight of the
influx pointers. The overall edge transformation around each node (Fig 1(b)) is computed combining the two group of weights.

\[
\Delta \tilde{w}_u(v) = \sum_{d=1}^{D} w_u^{(d)+}(v) - \sum_{d=1}^{D} w_u^{(d)-}(v)
\]  

(5)

where \(\Delta \tilde{w}_u(v)\) is the prediction for \(\Delta e_{uv}\).

An approximate inference step is used to sample discrete prediction for edge transformation \(\Delta e\) given continuous weights \(\tilde{w}\). First, the edges in the product is estimated by combing the edges in the reactant and the estimated edge modifications.

\[
\tilde{w}_{uv} = e_{uv}^r + \Delta \tilde{w}_{uv}
\]

(6)

\(\tilde{w}_{uv}\) is then rounded to integers with thresholds chosen heuristically.

\[
\bar{e}_{uv} = \text{round}(\min(\tilde{w}_{uv}, \bar{w}_{uv}))
\]

(7)

The decoder is trained via back-propagation with loss:

\[
L = \sum_{u,v} \| \tilde{w}_u(v) - e_u^p(v) \|_1
\]

\[
= \sum_{u,v} \| \Delta \tilde{w}_u(v) - \Delta e_u(v) \|_1
\]

(8)

here \(e_u^p(\cdot)\) and \(\Delta e_u(\cdot)\) are the ground truth product edges and edge changes respectively, and error \(\| \cdot \|_1\) denotes \(L_1\) norm.

### 4.3 Modeling Diverse Output Distribution

Chemical reaction is inherently a stochastic process. Given the reactant and reagents, multiple reactions may take place simultaneously yielding different products, and the dominant reaction varies with different reaction conditions (temperature, pressure, etc.). Therefore, to capture the diverse distribution of reactions, we introduce a latent vector \(z\) to encode the conditional distribution of the reaction given the reactants and reagents, and jointly learns the generative and inference with following the VAE framework [Kingma & Welling, 2013].

To infer the approximate posterior distribution \(p(z|R, P)\), we use a graph attention network that alternatively attends to nodes in \(P\) and \(R\). The final hidden representation is then pooled and passed through a dense layer to get the parameters of the approximate posterior of \(z\). We parameterize the posterior within the family of diagonal Gaussian distributions, \(q(z|R, P) \sim N(\mu, \sigma)\). The latent vector \(z\) is then concatenated with the reactant representation \(h^r\) to obtain the product representation \(h^p\). If the latent vector encodes enough information about \(p(P|R)\), it should completely determine the predicted product, such that the distribution \(p(P|R, z)\) degenerates into a single-point distribution. Therefore, the decoder can be deterministic conditioning on \(z\), allowing efficient parallel inference.

The log likelihood \(\log p(P|z, R)\) is approximated by the reconstruction loss (equation 8). \(KL[q(\cdot)||p(\cdot)]\) is the Kullback-Leibler divergence between \(q(\cdot)\) and \(p(\cdot)\). Following \(\beta\)-VAE [Higgins et al., 2017], we employ a hyperparameter \(\beta\) to scale the KL-divergence loss to control the diversity-quality trade-off.

\[
\mathcal{L}_\beta(P', z; R, P) = \text{recon}(P', P) + \beta KL[q(z|R, P), p(z|R)]
\]

(9)

Without loss of generality, we set the prior distribution \(p(z|R) = N(0, I)\), independent of \(R\).

### 5 Experiment

#### 5.1 Experiment Setup

**Dataset** We evaluate our model on the standard dataset USPTO-MIT, which has been used widely in previous works [Schwaller et al., 2018; Jin et al., 2017; Do et al., 2019; Bradshaw et al., 2018; Schwaller et al., 2019]. The dataset contains 480k reactions in 10 classes, where reactants, reagents, and products are represented as SMILES strings. We use the library RDkit [Landrum, 2016] to transform SMILES strings into molecule graphs.
Model Configuration  NEFG is implemented using Pytorch (Paszke et al., 2019). The encoder and decoder both contain 6 self-attention layers with 8 attention heads. The embedding dim is 256 and the dimension of latent representation is 64. The model is optimized with AdamW (Kingma & Ba, 2014) optimizer at learning rate $10^{-4}$ with linear warmup and linear learning rate decay and is trained for 100 epochs with a batch size of 128 on two Nvidia V100 GPUs for 3 days.

Metrics  Similar to Jin et al. (2017), we use top-k exact match accuracy as our evaluation metric, which is the percentage of reactions that have the ground-truth product in the top-k predicted molecules sets. Following previous works, we choose $k$ from $\{1, 2, 3, 5\}$ in our experiments.

Baselines  We evaluate the proposed approach using the following baselines:

- **WLDN** (Jin et al., 2017) is a two-stage approach built upon Weisfeiler-Lehman Network, which first identifies a set of reaction centers and then enumerates all possible bond configurations. WLDN5 (Coley et al., 2019) is an enhanced version of WLDN model.

- **GTPN** (Do et al., 2019) treats a chemical reaction as a set of graph transformations and employs reinforcement learning to learn a policy network for such transformations.

- **Transformer** (Schwaller et al., 2019) leverages the power of Transformer (Vaswani et al., 2017) to predict SMILES strings of product graphs.

- **MEGAN** (Sacha et al., 2020) models chemical reactions as a sequence of graph edits, and learns to predict the sequence autoregressively.

Among these methods, molecule transformer (Schwaller et al., 2019) achieves state-of-the-art top-k accuracy for $k=1, 2, 3$, while MEGAN (Sacha et al., 2020) is the state-of-the-art for $k=5, 10$.

5.2 Generating Multimodal Outputs

In order to draw (approximate) top-k samples from our VAE efficiently, we sample $m$ latent vectors ($m \geq k$) at increasing temperatures and take the first $k$ different predictions as an approximation to the top-k predictions. At temperature $t$, the latent vector is drawn from $tN(0, I)$. Using a temperature higher than 1 improves sampling efficiency by increasing diversity and therefore reducing duplicate samples.

We use the $k$ different samples drawn at the lowest temperature for the approximation of the top-k samples since samples drawn at high temperatures tend to be noisier and less credible. We find this sampling strategy works well in practice, and provides a lower bound of the real top-k accuracy.

5.3 Results

Table 1 shows our results on reaction prediction compared with several baselines on USPTO. Models are trained and tested with the reactants and reagents separated in the input. As shown in the table, the top-k accuracy of NEFG is comparable with the state-of-the-art methods across different $k$, and our method even reaches the highest for top-1 accuracy.

Autoregressive generation typically requires an output sequence for supervision, while molecules typically have a non-linear structure, without a natural sequential ordering. This arbitrary ordering may confuse the model from learning the structure of molecules, which can be alleviated by choosing ordering randomly each epoch during training. As table 1 shows, augmenting the train set by choosing 4 different orderings for each reaction is necessary for transformer to achieve state-of-the-art performance (Schwaller et al., 2019). On the contrary, since our model decodes in parallel, we do not rely on such data augmentation techniques to achieve excellent performance. Table 1 shows the performance of transformer with and without data augmentation.

5.4 Generalization and Speed

We compare the wall time and latency for inference with the state-of-the-art machine translation based model, molecule transformer. Molecule transformer employs a structure similar to transformer (Vaswani et al., 2017) for machine translation, which heavily depends on autoregressive sampling during inference. It iteratively samples the output tokens during inference, with the number of iterations equals to the sequence length. By contrast, our model predicts the reaction in a single parallel forward pass, leading to a significant improvement in computation efficiency.
Table 1: Top-k Accuracies for Reaction Prediction

| Model Name                  | Top-1 | Top-2 | Top-3 | Top-5 | parallel | end-to-end |
|-----------------------------|-------|-------|-------|-------|----------|------------|
| WLDN                        | 79.6  | -     | 87.7  | 89.2  | ✓        | ×          |
| GTPN                        | 83.2  | -     | 86.0  | 86.5  | ×        | ✓          |
| WLDN5                       | 85.6  | 90.5  | 92.8  | 93.4  | ✓        | ×          |
| Transformer, base           | 88.8  | 92.6  | 93.7  | 94.4  | ×        | ✓          |
| MEGAN                       | 89.3  | 92.7  | 94.4  | 95.6  | ×        | ✓          |
| Transformer, augmented      | 90.4  | 93.7  | 94.6  | 95.3  | ×        | ✓          |
| Ours                        | 90.7  | 93.0  | 94.0  | 94.7  | ✓        | ✓          |

Table 2: Accuracy for Different Reaction Topology and Inference Latency

| Model Name                  | non-linear | parallel | single-linear | wall time | latency | speedup |
|-----------------------------|------------|----------|---------------|-----------|---------|---------|
| Transformer (b=5)           | 82.1       | 86.8     | 89.8          | 9min      | 448ms   | 1×      |
| ours                        | 80.6       | 87.2     | 90.4          | 20s       | 17ms    | 26×     |

Figure 3: Illustration of different reaction topology.

we split the test set into single-linear, parallel linear, and non-linear according to the reaction electron flow topology (Herges, 1994), and compare the accuracy on each class separately. Figure 3 illustrates samples from the three subsets.

Results for both generalization and speed are revealed in table 2. Both models are evaluated on a single Nvidia V100 GPU. The wall-time is the total time used for evaluation on the test set of USPTO. The models are trained and tested with the reaction and reagents mixed, which is more challenging and close to the real application. As molecule transformer relies on beam search to find the most probable prediction, the beam size $b$ is a hyper-parameter that determines the trade off between the accuracy and computational efficiency. We show results of molecule transformer for $b = 5$, the default setting for top-5 inference, as further increasing $b$ leads to only marginal improvement in accuracy.

6 Conclusion

To the best of our knowledge, our proposed model Non-autoregressive Electron Flow Generator (NEFG) is the first non-autoregressive model for reaction prediction that achieves state-of-the-art top-1 accuracy. The key idea is to decompose edges into pairs of electrons, and edge changes into electron flows, which can then be predicted in parallel with the representation of atoms. Our model predicts chemical reactions with an order of magnitude lower inference latency, compared with the state-of-the-art autoregressive machine translation based model. The excellent performance of product prediction is consistent across multiple reaction topology, suggesting that the framework is a promising new tool for designing non-autoregressive algorithms for graph generation.
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