



공학박사 학위논문

Bayesian Reaction Optimization Guided by Machine Learning Models for Synthesis Conditions and Yield

합성 조건 및 수율 기계학습 모델을 이용한 베이지안 반응 최적화

2023 년 8 월

서울대학교 대학원 컴퓨터 공학부

권영천

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지도교수 김 선

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컴퓨터 공학부

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위원	빌 장	박근수
부위	원장	김선
위	원	 윤성로
위	원	최윤석
위	원	 김우연

Abstract

Bayesian Reaction Optimization Guided by Machine Learning Models for Synthesis Conditions and Yield

Youngchun Kwon Department of Computer Science & Engineering College of Engineering Seoul National University

Optimization of synthetic reactions represents a crucial step in expediting the exploration of innovative pharmaceuticals and materials, serving as an indispensable tool. To achieve a newly designed molecular structure that meets the desired properties, the optimization process involves skillfully navigating through diverse parameters associated with experimental conditions. Rapid identification of optimal reaction conditions stands as a pivotal element in mitigating the protracted cycle of discovering new drugs and materials. Given the substantial financial expenses, time investment, and specialized expertise required for synthetic experiments, it becomes imperative to minimize the developmental timeline effectively.

However, despite the need for expedited exploration of suitable reaction

conditions, there are several limitations to consider. Traditionally, the search for best conditional combinations has involved using design of experiment that require searching various literature sources. These approaches can be somewhat passive and inefficient, relying heavily on the knowledge and experience of synthesis researchers. Furthermore, machine learning models that predict reaction conditions solely based on three-dimensional molecular structure information have their own limitations, as the selection of appropriate representation and the consideration of condition compatibility are not clearly defined. Lastly, quantifying the difficulties associated with synthetic processes is crucial for optimizing strategies, yet it remains a challenging task.

In the present doctoral dissertation, I put forth a proposition to address the trade-off quandary in chemical reaction optimization. This proposal entails a fusion of machine learning methodologies and Bayesian optimization techniques, leveraging accumulated experimental data. The objective is to efficiently delineate the search space, gauge the complexity of experiments, devise an optimization strategy, and dynamically integrate the outcomes of iterative experiments into the strategy. The primary goal of this study is to significantly diminish the search domain for optimization while quantifying the synthesis level, thereby facilitating the guidance of efficient optimization strategies.

The first focal point of this research aims to efficiently narrow down the extensive array of conditions that need to be explored to align with the input reactions and structural information of the compound. Given the impracticality of conducting experiments on the vast number of potential combinations of synthesis conditions, I propose the use of a generative model that utilizes a graph-based representation of the input synthesis reaction and incorporates three-dimensional molecular structure details. This model generates diverse sets of condition combinations within a specified range, while considering the interdependencies among the conditions. In contrast to conventional

approaches that rank candidates solely based on input reaction information, the proposed model incorporates a variational auto-encoder to learn the compatibility between conditions. Consequently, it enables the prediction of diverse yet accurate condition combinations, effectively avoiding the inclusion of irrelevant or meaningless combinations.

The second aspect of this study aims to predict the yield of a chemical synthesis reaction while also accounting for the uncertainty associated with the prediction outcomes. Additionally, it involves generating a graph-based structural representation to capture the three-dimensional structural information of all reagents involved in the chemical reaction for machine learning purposes. Notably, the dataset employed comprises 1 million synthesis experiment records extracted and refined from research papers. To develop a highly accurate yield prediction model, I introduce a configuration that enhances model uncertainty in situations characterized by inconsistencies in experimental data. By quantifying the difficulty of the synthesis experiment through the deviation between the predicted yield value and the model based on learned patterns, this approach improves not only accuracy but also addresses issues related to bias and insufficient chemical reaction data, thereby surpassing previous studies in the field of synthesis experiment yield prediction.

The final study aims to optimize the combination of reaction conditions by leveraging the condition generation model and synthesis difficulty quantifying model introduced earlier. The optimization strategy entails defining the exploration region of conditions based on the synthetic representation (reactants and product structures) using the generative model. The priority is then determined by the yield prediction model, leading to the identification of 10 initial combinations of reaction conditions. Subsequently, actual synthesis experiments are conducted using the selected conditions to measure the yields obtained. A surrogate model (Gaussian process) of the Bayesian optimization algorithm is trained solely on the yields derived from these synthesis experiments. Once the initial 10 experiments are completed, the results from the condition acquisition function and the Bayesian optimization, chosen as the machine learning-based yield prediction models, are combined to select the subsequent combination of conditions to be tested. The weights assigned to these two acquisition functions are adjusted by evaluating the deviation between the machine learning-based yield prediction model value and the actual yield value. This comprehensive approach ensures an efficient optimization strategy that takes into account the difficulty of synthesis while demonstrating its performance across various optimization models.

In conclusion, this doctoral dissertation proposes an experiment optimization technique for exploring suitable conditions of organic synthesis experiments. It effectively reduces the exploration range and quantifies the difficulty of synthesis experiments, facilitating efficient exploration. The performance of the proposed approach is validated using real synthesis automation equipment.

Keywords: Bayesian Optimization, Organic synthesis, Experimental condition optimization, Generative modeling, Machine learning, Design of experiments, Quantifying synthetic feasibility

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Chapter 1

Introduction

Optimization of a chemical synthesis is a complex, multidimensional challenge that requires experts to validate various reaction parameters, such as catalyst, reagent, solvent, concentration, temperature and named reaction type. In a laboratory, chemists can evaluate only a small subset of these conditions during a standard optimization campaign owing to time, cost and equipment constraints. The chemist's art is to discriminate between millions of plausible configurations using a laboratory equipped to run only a tiny fraction of the possibilities. To do this, chemists typically conduct their experiments by searching the chemical literature for similar reactions and intuiting the most influential dimensions (*e.g.*, reaction parameters) for reaction success based on experience, mechanistic understanding, empirical data and simple heuristics.

In my doctoral study, I built a modular framework for efficiently exploring optimal chemical reaction conditions using Bayesian optimization and datadriven machine learning models. This approach is designed to integrate with existing synthetic-chemistry practices, is applicable to arbitrary search spaces that include continuous and categorically encoded reactions, and enables the inclusion of physics and domain expertise. Moreover, this method is arbitrarily parallelizable (that is, any number of experiments can be selected per batch of iterative experiments) and thus can facilitate both rapid screening and direct translation to large-scale process conditions. Most of the optimization performance results have been validated on high-throughput experimentation frameworks, and their generality has also been verified through experiments with different named reaction types (*e.g.*, Suzuki-Miyaura coupling reaction).

1.1 Optimization in organic synthesis experiments

1.1.1 Challenges in searching suitable chemical reaction conditions

Organic synthesis optimization plays a crucial role in the development of novel compounds with desired properties. Extensive work has been done on the optimization of conditions for specific reaction classes, using a combination of domain knowledge and empirical optimization techniques to automatically identify the best reaction condition. Nevertheless, the initial guess of reaction conditions for a new reaction is predominantly considered a human task. Chemists use heuristics and perceived similarity of new reactions to ones they are familiar with to propose candidate conditions. However, this approach has its limitations and challenges. The recommendation might be biased by chemists' preference and familiarity with certain types of reactions; the heuristic rules might not be all-encompassing or too abstract to narrow down to specific chemicals, and conditions of a precedent reaction may not be applicable to the new reactions even if the reactants are structurally similar. Many chemists, therefore, define very broad ranges of reaction parameters but it requires a lot of experimental resources and time. In Figure 1.1, it shows the prototypical chemical process optimization problem with reaction space. In



Figure 1.1: Prototypical chemical process optimization problem (Shields *et al.*, 2021)

this case, there are five types of reaction conditions : ligand, base, solvent, temperature, and reaction time. For each condition, if there are about 10 candidates, it can generate 10^5 configurations. Approximately, if it takes about a day for one experiment, it would take about 273 years to test the whole range of search space (Shields *et al.*, 2021).

1.1.2 Design of experiment in organic chemistry

Many chemists commonly utilize systematic, model-driven approaches to reaction optimization. Design of experiment (DOE) (Murray *et al.*, 2016; Lee, 2019; Weissman and Anderson, 2015; Olofsson *et al.*, 2019) finds to sample experimental conditions that facilitate modelling of reaction parameters and deconvolution of interactions. In conjunction with a response surface model, DOE enables the exploitation of knowledge gained from previous evaluations to guide the selection of future experiments. However, the exploration of reaction space is typically left in the hands of predefined optimal designs, sen-



Figure 1.2: Design of experiment.

sitivity analysis, literature precedence and the operator's intuition. In addition, although a typical reaction requires the fine-tuning of numerous discrete parameters, screening requirements grow exponentially with number of categorical components using optimal designs. Thus, in practice some variables may be held constant to enable optimization on a fixed experimental budget in Figure 1.2.

1.1.3 Bayesian optimization for exploring suitable reaction conditions

Bayesian optimization, an uncertainty guided reaction surface method used for the optimization of computationally expensive objective functions, has shown excellent performance, in many instances outperforming expert practitioners and other state-of-the-art global optimization algorithms (Wang *et al.*, 2020a; Mockus, 1975; Häse *et al.*, 2018; Griffiths and Hernández-Lobato, 2020; Ueno *et al.*, 2016). Bayesian Optimization is designed to balance the exploration



Figure 1.3: Bayesian optimization : one-dimensional visualization. (Shields *et al.*, 2021)

of areas of uncertainty and the exploitation of available information, leading to high-quality configurations in fewer evaluations. Importantly, Bayesian optimization algorithms can be applied to diverse search space that include arbitrary parameterized reaction domains and enables the selection of multiple experiments in parallel. Accordingly, this approach is well suited to the optimization of chemical processes to find optimal reaction conditions as represented in Figure 1.3 (Shields *et al.*, 2021).

However, Bayesian optimization has a cold-start problem owing to limitations in using accumulated other experimental data. Depending on the given reaction structure, the search space is changed and considered as a completely independent experimental environment. Combination of reaction conditions, which is discriminated variables.

1.1.4 Data-driven approaches to predict optimal reaction conditions

Artificial intelligence is driving one of the most important revolutions in organic chemistry (Kondo et al., 2020; Zhou et al., 2017; Reker et al., 2020; Clayton et al., 2019; Negoescu et al., 2011; Schweidtmann et al., 2018; Luo, 2016; Moriwaki et al., 2018; Reker and Schneider, 2015). Multiple platforms, including tools for reaction prediction and synthesis planning based on machine learning, successfully became part of the organic chemists' daily laboratory, assisting in domain-specific synthetic problems. In particular, AI is being used to solve a variety of problems throughout the synthetic experimentation process, which can be extremely costly, time-consuming, and labor-intensive. Models have been proposed to replace the skills of existing researchers in various organic synthesis tasks such as retrosynthesis, yield, and condition prediction. Also, in organic synthesis experiments, various papers have been proposed to suggest optimal reaction conditions using data, which minimizes the work of browsing numerous experimental papers, studying textbooks, and learning the know-how of experienced synthesis experts. Nevertheless, the completely new responses are independent of previous studies, and the experimental data to be trained is biased. In practice, experiments that are difficult to synthesize often deviate from the trends of previous experiments, and it is difficult to find experimental conditions that take into account analysis and purification.

1.1.5 Computational challenges in advanced approaches

Five types of critical challenges :

- 1. High dependence on individual chemists "experience" and "knowledge".
- 2. Non-convex problem, multi-global minimum points.
- 3. Considering the correlation among the conditions.

- 4. Measurement for difficulty level of synthesis.
- 5. Cold-start problem in novel reaction optimization.

In this doctoral dissertation, I attempt to overcome the limited ability of advanced approaches to determine the optimal reaction conditions led us to propose the hybrid-type dynamic reaction optimization method, which complements the previous two methodologies as data-driven approaches in that it is based on a graph neural network with BO. This approach enables us to efficiently explore the optimal combination of conditions compared with previous studies.

1.2 Formulating computational problems for the reaction optimization questions

1.2.1 Notations and descriptions

Throughout this dissertation, I use bold uppercase characters to denote matrices and bold lowercase characters denote vectors. Unless particularly specified, the notations used in this study are illustrated in table 1.1. I define the minimal set of definitions required to understand this study (Wu *et al.*, 2021).

Definition 1 (A graph representation): A graph is represented as G = (V, E) where V is the set of vertices or nodes (i will use nodes throughout the study), and E is the set of edges. Let v_i ∈ V to denote a node and e_{ij} = (v_i, v_j) ∈ E to denote an edge pointing from v_j to v_i. The neighborhood of a node v is defined as N(v) ={u∈ V |(v,u) ∈ E}. The adjacency matrix A is a n × n matrix with A_{ij} = 1 if e_{ij} ∈ E and A_{ij} = 0 if e_{ij} ∉ E. A graph may have node attributes X, where X ∈ R^{n × d} is a node feature matrix with x_v∈ R^d representing the feature vector of a node v.

- Definition 2 (A graph-type molecular structure representation): A molecule is represented as G that is a graph of molecular structure and = (V, E). can be defined as the connectivity relations between a set of nodes (V) and a set of edges (E). Naturally, a molecule can also be considered as a graph consisting of a set of atoms(nodes) and a set of bonds (edges).
- Definition 3 (A graph-type reaction representation): A reaction is a pair of two reactants and a product molecular structures. Generally, a reaction that a chemical reaction consists of a number of reactants and a single product. This chemical reaction is labeled with its reaction yield. Each instance is represented as (\$\mathcal{R}\$, \$\mathcal{P}\$, \$y\$), where \$\mathcal{R}\$ = {\$\mathcal{G}^{R,1}\$, \ldots, \$\mathcal{G}^{R,m}\$}\$ and \$\mathcal{P}\$ = {\$\mathcal{G}^{P}\$} are the set of \$m\$ reactants and the resulting product in the reaction, respectively, and \$y\$ is the reaction yield. The number of reactants \$m\$ can be different for each reaction.

Table 1.1: Notations.

Notations	Descriptions
.	The length of a set.
\odot	Element-wise product.
G	A graph type molecular structural representation.
ν	The set of nodes in a graph (Atoms).
v	A node $v \in \mathcal{V}$ (An atom).
Е	The set of edges in a graph (Connectivity of between atoms).
e_{ij}	An edge $e_{ij} \in \mathcal{E}$ (Connectivity).
N(v)	The neighbors of a node v .
A	The graph adjacency matrix.
A^T	The transpose of the matrix A .
\overline{n}	The number of nodes, $n = \mathcal{V} $.
m	The number of edges, $m = \mathcal{E} $.
\mathcal{D}	The dataset.
$X \in \mathbb{R}^{n \times d}$	The feature matrix of a graph.
\mathcal{R}	The set of reactants.
\mathcal{P}	The product molecule.
S	The set of search space(reaction parameters).
Ι	The priority of combination of conditions.
C	The set of conditions.
с	The reaction condition.
t	The trials of experiments.
<i>y</i>	The yield of an experiment.
Z	The latent variable.
\otimes	The concatenation.
\oplus	The summation.
$R \rightarrow P$	The Reaction representation (Reactants and a product).

1.2.2 Computational equations for the main methods in dissertation

Given a set of reaction $R \to P$ and a search space for conditions S, computational equations for optimizing reaction parameters (synthetic conditions) are followings:

< Input >

 $(\mathcal{R} \to \mathcal{P})_i$: a graph type reactions

 \mathcal{R}_i : a set of reactants, $\mathcal{R}_i = (\mathcal{G}_i^{r1}, \mathcal{G}_i^{r2})$

 \mathcal{P}_i : a product, $\mathcal{P}_i = (\mathcal{G}_i)$

 \mathcal{G}_i : a graph type molecular structure, $\mathcal{G}_i = (\mathcal{V}_i, \mathcal{E}_i)$

 $(\mathcal{V}_i, \mathcal{E}_i)$: a set of nodes and connectivity of molecules of \mathcal{G}_i

 \mathcal{S} : a search space of combination of conditions

< Output >

 $I : \mbox{Priority of all possible combinations of condition candidates in S} < Model >$

Using graph variational autoencoder (GVAE)

Uncertainty-aware yield prediction model (MPNN)

Bayesian optimization (BO)

1.3 Three computational problems for the optimization challenges in organic synthesis

The common issue of the three reaction optimization questions in my doctoral research that a search space for synthetic conditions such as catalyst, solvent, reagent, and temperature level is high dimensional data but of small number of samples to train surrogate model of Bayesian optimization. A lot of experiment dataset for training models is accumulated, but the dataset is biased to one side. Also, in chemical synthetiss optimization is a multi-global optimization problem that could have multiple optimal combinations of conditions. Therefore, since the individual reactions (with starting materials and a target product) are independent, so there are cold-start problem still remains. In order to address the reaction optimization questions by using the computer approach, it is necessary to effectively reduce the features such as reducing the number of combination of reaction conditions and measure the difficulty of presented reaction target through the hybrid-type optimization based on data-driven approaches and Bayesian optimization. In order to reduce a number of experiment trials to get expected yield results, my doctoral study defines three steps for efficiently searching one global combination of reaction conditions.

• Problem 1) Generative Modeling to Predict Multiple Suitable Conditions for Chemical Reactions (Kwon *et al.*, 2022b):

Challenges: There is not method that accurately predicts complete combinations of reaction conditions (catalysts, solvents, reagents, and temperature) suitable for use with a very large reaction corpus. The compatibility and interdependence of chemical context and temperature are not taken into account in this area. No previous studies have performed quantitative evaluation of reaction condition predictions on a large-scale reaction data set. There are two major challenges which have impeded progress: (i) There is not a machine readable large data set available with catalysts/solvents/reagents classified into different types. (ii) For the similarity-based approaches it is difficult to quantitatively assess the level of "correctness" of conditions when comparing entire sets of conditions associated with different literature reactions. (iii) There is multiple suitable combination of conditions from one reaction. Therefore, the model should consider the compatibility of conditions. Closer attention should be paid to balancing the generality/specificity of representing chemical context. If the representation is too general, such as manually encoded types/groups, it might not fully characterize functionality, and if it is too specific, e.g., copy-pasting the entire conditions from other reactions, it does not provide further information about chemical similarity.

Approach: I formulate the problem of predicting suitable reaction conditions as sampling from a generative distribution. I modeled the distribution by introducing a variational autoencoder augmented with a graph neural networks based on message passing neural networks. By using generative models, I was able to implement a model that could simultaneously consider the relationship of between conditions. Whereas traditional condition prediction models were tasked with predicting only one condition out of multiple correct answers, I was designed to explore as many combinations of correct conditions as possible, taking into account the real-world environment of an organic synthesis experiment.

• Problem 2) Uncertainty-aware prediction of chemical reaction yields with graph neural networks (Kwon *et al.*, 2022c):

Challenges: The ability to predict whether a reaction will be successful or not can save significant time and effort of organic chemists and expedite the process of generating chemical compounds. Existing methods still depend on handcrafted reaction rules or heuristically extracted reaction templates, and therefore, are not well generalizable to unseen reactions. Another major challenge is the availability of data on both failed and successful experiments. Existing research in the literature has mainly focused on successful experiments (i.e., reactions with a high yield), thus making it hard for a machine learning model to infer what makes a reaction successful. Recently, machine learning models have been proposed to predict the reaction performance based on molecular features. However, these methods only consider features such as molecular, atomic, and vibrational properties and do not use any information about the complex structure of molecular graphs. I argue that in order to solve this problem effectively, an intelligent AI system should have two key capabilities: (i) Understanding the molecular graph structure of the input reactants to identify complex interactions between reaction components, and (ii) Incorporating domain knowledge of organic chemists in the form of molecular, atomic, and vibrations characteristics of reactants to learn the rules that organic chemists use for predicting reaction success.

Approach: In order to effectively predict reaction yields with uncertainty, uncertainty-aware deep learning model is proposed by using graph neural networks. In order to increase the accuracy of the model, I designed a graph type representation that minimizes the loss of molecule structural three dimensional information. The information of the molecular heavy atoms was defined as the node of the graph representation in the formed as vectors. The bond information between atoms was used as graph connectivity. The trained graph neural networks was designed to output various predicted yield values through drop-out method, and the deviation of the yields was defined as the uncertainty of the model. In addition, when train the yield prediction model, if the deviation of the yield label value from the similar reaction descriptors is higher, increase the training loss of prediction model to reflect an uncertainty into model. Through this, I designed it to measure the difficulty of the proposed reaction.

• Problem 3) Exploring Optimal Reaction Conditions Guided by Graph Neural Networks and Bayesian Optimization (Kwon *et al.*, 2022a):

Challenges: Basically, Bayesian optimization based optimization approaches have a cold-start problem. In many case of experiments (*e.g.*, Suzuki-Miyaura reaction), suitable combination of conditions have mostly based on Pd-catalysts combination have resulted in high yield. Also, in Suzuki-Miyaura reaction, it is advantageous to take an exploitation strategy because there is a lot of training data. On the other hand, in the case of the Chan-lam reaction, it is good to take an exploring strategy because the exploration range is wide and the experimental data is small. As such, it is very important to take an optimization strategy that considers the situation.

Approach: I devised general and effective method for searching best chemical conditions. The proposed method complements the shortcomings of previous approaches and takes a strategy of dynamically modifying the objective function of optimization in consideration of the difficulty of the experiments. While solving the cold-start problem of the Bayesian optimization methodology as the yield prediction models, it was designed that sufficiently diverse conditions could be selected considering the difficulty of the reaction and the initial experimental results.

1.4 Outline of the dissertation

Chapters 2,3, and 4 introduce independent studies related to machine learning algorithms of prediction and optimization for exploring chemical reaction conditions. In Chapter 2, a generative modeling, which, given a chemical reaction, predicts a number of combination of suitable reaction conditions, including catalysts, solvents, ligands, bases, temperatures, and concentrations of reactants. Chapter 3 proposes a measurement method, which, given a chemical reaction, predicts the yield of reaction, and providing the uncertainty of the prediction. Chapter 4 proposes a strategy for efficiently exploring suitable chemical reaction conditions using Bayesian optimization with graph neural networks model. Chapter 5 summarizes the studies with my contributions in optimization for organic synthesis based analyses. The dissertation is concluded by an appendix of the bibliography of the cited references.

Chapter 2

Generative Modeling to Predict Multiple Suitable Conditions for Chemical Reactions

In synthesis planning, it is important to determine suitable reaction conditions such that a chemical reaction proceeds as intended. Recent research attempts based on machine learning have proven to be effective in recommending reaction elements for specific categories regarding critical chemical context and operating conditions. However, existing methods can only make a single prediction per reaction and do not directly provide a complete specification of the reaction elements as the prediction. Therefore, their achievable performance is limited. In this study, I propose a generative modeling approach to predict multiple different reaction conditions for a chemical reaction, each of which fully specifies critical reaction elements such that these elements can be directly used as a feasible reaction condition. I formulate the problem of predicting reaction conditions as sampling from a generative distribution. I model the distribution by introducing a variational autoencoder augmented with a graph neural network and learn it from a reaction dataset. For a query reaction, multiple predictions can be obtained by repeated sampling from the distribution. Through experimental investigation on the reaction datasets of four major types of cross-coupling reactions, I demonstrate that the proposed method significantly outperforms existing methods in retrieving ground-truth reaction conditions.

2.1 Motivation

Optimization of a chemical reaction is an important challenge in synthesis planning. (Coley *et al.*, 2019b; Shields *et al.*, 2021; Coley *et al.*, 2018) It requires the determination of various parameters for a reaction condition, including chemical context (*e.g.*, metal, ligand, base, and solvent) and operating conditions (*e.g.*, temperature and pressure). As a starting point, it is necessary to propose suitable reaction conditions that will allow the target chemical reaction to proceed as intended. (Gao *et al.*, 2018) To determine the best reaction condition, each candidate reaction condition under consideration can be evaluated in terms of the availability of chemicals, cost of experimental synthesis, expected reaction yield, etc.

[Problem Definition of this study]

For a chemical reaction $R \to P$, the proposed method generate condition set \mathcal{C} .

< Input >

 $(\mathcal{R} \to \mathcal{P})_i$: a graph type reactions

 \mathcal{R}_i : a set of reactants, $\mathcal{R}_i = (\mathcal{G}_i^{\mathrm{r1}}, \mathcal{G}_i^{\mathrm{r2}})$

 \mathcal{P}_i : a product, $\mathcal{P}_i = (\mathcal{G}_i)$

 \mathcal{G}_i : a graph type molecular structure, $\mathcal{G}_i = (\mathcal{V}_i, \mathcal{E}_i)$

 $(\mathcal{V}_i, \mathcal{E}_i)$: a set of nodes and connectivity of molecules of \mathcal{G}_i

 C_i : a set of labeled reaction conditions

< Output >

 \hat{c}_n : a set of generated conditions *n* is trials of sampling conditions

< Model >

Using graph variational autoencoder (GVAE)

2.1.1 Suggestion of reaction conditions

Traditionally, the proposal of reaction conditions for new chemical reactions has relied heavily on the knowledge and experience of chemists. When chemists recommend reaction conditions for a chemical reaction, they may refer to exactly matching or similar reactions found in a reaction database, such as Reaxys,(Goodman, 2009) United States Patent and Trademark Office (USPTO) (Lowe, 2017) and Open Reaction Database (ORD).(Kearnes *et al.*, 2021) These databases can be valuable sources of information for finding plausible reaction conditions that have been experimentally validated and published in the chemistry literature. Although many chemists use this approach implicitly, it has several drawbacks in practice.(Gao *et al.*, 2018) Recommendations are difficult to automate and can be influenced by the chemists' preferences. Searching a large database is computationally intensive. It is difficult to derive plausible reaction conditions for new reactions that are not in the database.

2.1.2 Existing method

Recently, a machine learning approach has been studied to predict suitable reaction conditions for arbitrary chemical reactions by learning from a reaction database on a large scale. Existing studies on this approach curated the reaction records in the Reaxys database to form a training dataset. Using the dataset, they attempted to build a prediction model that takes a chemical reaction as input and provides the probability scores of individual reaction elements as output, as shown in Figure 2.1(a). This led to fast and accurate recommendations of reaction elements for specific categories with respect to the critical chemical context and operating conditions, such as solvent and temperature, to derive suitable reaction conditions. The predictive performance was commonly evaluated according to whether the reaction elements of the ground-truth reaction condition appear in the top-k elements of the



Figure 2.1: Schematic comparison between existing methods and proposed method

prediction. Gao et al.(Gao et al., 2018) attempted for the first time to build a reaction condition prediction model using a large reaction dataset. They represented a chemical reaction using the Morgan circular fingerprint(Rogers and Hahn, 2010) and built neural networks to sequentially predict the catalyst, solvent, reagent, and temperature required for a given reaction. Walker et al.(Walker et al., 2019) used the MACCS key fingerprint and evaluated various prediction models for solvent prediction. Ryou et al.(Ryou et al., 2020) and Maser et al.(Maser et al., 2021a) adapted a graph neural network (GNN) as a multi-label classification model to predict multiple reaction elements for certain categories.

2.1.3 Two major drawback

Despite their effectiveness, the existing methods have two major limitations that should be considered in their practical application. First, the prediction model presented in the existing studies only provides a single prediction per chemical reaction. However, there can be many different reaction conditions under which a chemical reaction is feasible. For example, some chemical reac-
tions in my preprocessed datasets were annotated with hundreds of distinct ground-truth conditions. Second, the independent ranking of reaction elements for individual categories does not indicate the feasible combinations of reaction elements for all critical categories. Further analysis by chemists is required to determine the suitable reaction conditions for a chemical reaction. This is difficult because a small change in a reaction condition can drastically change the outcome of the reaction.(Gao *et al.*, 2018; Maser *et al.*, 2021a) To fully automate the recommendation, the model should directly provide a complete specification of the critical reaction elements such that they can be directly used as a feasible reaction condition to achieve the desired reaction outcome without manual effort.(Coley *et al.*, 2018)

2.1.4 An aim

The ambitious goal is to build a prediction model that allows the prediction of multiple plausible reaction conditions, each of which fully specifies the critical reaction elements, as shown in Figure 2.1(b). Herein, I propose a generative modeling approach to achieve so. For the prediction model, I adapt a variational autoencoder (VAE)(Kingma and Welling, 2014) augmented with a GNN.(Wu *et al.*, 2021; Gilmer *et al.*, 2017a) The model is trained using the dataset of a certain reaction type extracted from the Reaxys database. The trained model can be used to make multiple predictions of reaction conditions for a chemical reaction.

2.2 Methods

2.2.1 Problem Formulation

My goal is to predict as many feasible reaction conditions as possible for new chemical reactions. To formulate the problem, I refer to a chemical reaction as



Figure 2.2: Example of a chemical reaction and its ground-truth reaction conditions

 $R \to P$, where R and P are the sets of reactants and products, respectively. The reaction $R \to P$ is annotated with a set of its feasible reaction conditions experimentally validated in the past, which I denote as $C = \{\mathbf{c}_1, \ldots, \mathbf{c}_K\}$. The number of reaction conditions K can vary because there exist multiple feasible conditions for some reactions. Figure 2.2 shows an example of a set of reaction conditions annotated for a chemical reaction. In this study, the problem of predicting reaction conditions is formulated as sampling from a generative distribution $p_{\theta}(\mathbf{c}|R \to P, \mathbf{z})$ which involves the latent variable \mathbf{z} . The process consists of two steps. First, the value of \mathbf{z} is sampled from its prior distribution $p(\mathbf{z})$. Second, given the sampled value of \mathbf{z} and a chemical reaction $R \to P$, the reaction condition \mathbf{c} is sampled from the distribution $p_{\theta}(\mathbf{c}|R \to P, \mathbf{z})$.

To obtain the generative distribution $p_{\theta}(\mathbf{c}|R \to P, \mathbf{z})$, I introduce a VAE (Kingma and Welling, 2014) in which the graph representations of the molecules in R and P are processed by a GNN.(Wu *et al.*, 2021; Gilmer *et al.*, 2017a) Given a set of chemical reactions and their reaction conditions as a training dataset, I learn the parameters of the distribution $p_{\theta}(\mathbf{c}|R \to P, \mathbf{z})$ to maximize the log-likelihood of the dataset.

2.2.2 Prediction Model

As the prediction model, I use the generative distribution $p_{\theta}(\mathbf{c}|R \to P, \mathbf{z})$ parameterized by θ . For the latent variables \mathbf{z} , the prior distribution $p(\mathbf{z})$ is assumed to be $N(\mathbf{z}|\mathbf{0}, \mathbf{I})$. Owing to the intractability of the exact posterior distribution of \mathbf{z} , I use variational inference to approximate the distribution by $q_{\phi}(\mathbf{z}|R \to P, \mathbf{c}) = N(\mathbf{z}|\boldsymbol{\mu}_{\mathbf{z}}(R \to P, \mathbf{c}), \operatorname{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2(R \to P, \mathbf{c})))$, which is parameterized by ϕ .

For a chemical reaction $R \to P$, I represent each molecule in R and Pas a molecular graph, whose nodes and edges correspond to the heavy atoms and bonds in the molecule. For the annotated condition set C, each reaction condition $\mathbf{c}_k \in C$ is represented as a multi-hot vector in $\{0,1\}^L$ indicating the reaction elements it corresponds to, where the dimensionality L is the total number of elements considered in the representation.

I use neural networks to model the distributions q_{ϕ} and p_{θ} , which I respectively refer to as the probabilistic encoder and decoder of the VAE. The encoder q_{ϕ} takes the reaction $R \to P$ and its any reaction condition **c** to predict the mean $\mu_{\mathbf{z}}$ and log-variance $\log \sigma_{\mathbf{z}}^2$ of the distribution. It uses a GNN that embeds the reaction $R \to P$ into a vector. The decoder p_{θ} takes $R \to P$ and **z** as inputs to predict the probability estimates for individual reaction elements, which are decoded to obtain a predicted reaction condition $\hat{\mathbf{c}}$. It shares the parameters of the GNN part with the encoder q_{ϕ} .

2.2.3 Training

Using the variational lower bound of the log-likelihood for an instance $(R \rightarrow P, \mathbf{c})$, the loss function for the VAE is derived with respect to the parameters ϕ and θ as follows:

$$L_{\phi,\theta}(R \to P, \mathbf{c}) = \mathbb{E}_{\mathbf{z} \sim q_{\phi}(\mathbf{z}|R \to P, \mathbf{c})} \left[-\log p_{\theta}(\mathbf{c}|R \to P, \mathbf{z}) \right] + D_{\mathrm{KL}}(q_{\phi}(\mathbf{z}|R \to P, \mathbf{c})||p(\mathbf{z})),$$

$$(2.1)$$

where, in the first term, the latent vector \mathbf{z} is sampled from the encoder q_{ϕ} as $\boldsymbol{\mu}_{\mathbf{z}} + \boldsymbol{\sigma} \odot \boldsymbol{\epsilon}$, where $\boldsymbol{\epsilon} \sim N(\mathbf{0}, \mathbf{I})$. This reparameterization makes the loss function $L_{\phi,\theta}$ differentiable with respect to the encoder parameters ϕ . In the loss function $L_{\phi,\theta}$, the first term is associated with the reconstruction loss between the input condition \mathbf{c} and the output of the decoder p_{θ} . This loss is typically derived as the binary cross-entropy loss. The second term is the Kullback-Leibler divergence between the distributions $q_{\phi}(\mathbf{z}|R \rightarrow P, \mathbf{c})$ and $p(\mathbf{z})$. It works as regularization for the encoder output. To train the VAE including the encoder q_{ϕ} and the decoder p_{θ} , I suppose that a training dataset of N chemical reactions with their condition annotations is given in the form of $D = \{(R_i \rightarrow P_i, C_i)\}_{i=1}^N$. I extend the original dataset D by replicating instances with more than one reaction condition such that each instance is annotated with one condition, resulting in an extended training dataset $D' = \{(R_j \rightarrow P_j, \mathbf{c}_j)\}_{j=1}^{N'}$, where $N' = \sum_{i=1}^N |C_i|$. During training, the objective function J is described as:

$$J = \frac{1}{M} \sum_{(R \to P, \mathbf{c}) \in B} L_{\phi, \theta}(R \to P, \mathbf{c}), \qquad (2.2)$$

where the mini-batch $B \subset D'$ consists of M instances randomly drawn from D'. The parameters ϕ and θ are updated to minimize J over D'.

2.2.4 Inference

For inference, I only use the decoder of the VAE as the prediction model, which corresponds to the generative distribution $p_{\theta}(\mathbf{c}|R \to P, \mathbf{z})$. For a query chemical reaction $R_* \to P_*$, I generate its reaction conditions as follows. The latent vector \mathbf{z}_* is sampled from the prior distribution $p(\mathbf{z})$ instead of the encoder q_{ϕ} . Then, the reaction $R_* \to P_*$ and the vector \mathbf{z}_* are used as inputs to the decoder p_{θ} . I decode the probabilistic output of p_{θ} to derive the predicted reaction condition $\hat{\mathbf{c}}_*$. This stochastic generative process can be described as follows:

$$\hat{\mathbf{c}}_* = \underset{\mathbf{c}}{\operatorname{argmax}} \mathbb{E}_{\mathbf{z}_* \sim p(\mathbf{z})} \left[p_{\theta}(\mathbf{c} | R_* \to P_*, \mathbf{z}_*) \right].$$
(2.3)

Since the generative process provides a different output on each trial, I repeat the process T times to obtain a set of different reaction conditions for the query reaction $R_* \to P_*$, namely \hat{C}_* , as below:

$$\hat{C}_* = \{\hat{\mathbf{c}}_{*1}, \dots, \hat{\mathbf{c}}_{*T}\}.$$
 (2.4)

2.3 Experiments

2.3.1 Datasets

I performed experiments using four datasets extracted from the Reaxys database to investigate the effectiveness of the proposed method for predicting reaction conditions. Each dataset corresponds to one of the following major types of cross-coupling reactions: Suzuki coupling, C–N coupling, Negishi coupling, and Pauson-Khand reaction (PKR). The datasets were generated by following the procedure described in the work of Maser et al.(Maser *et al.*, 2021a) For each target reaction type, I queried the single-step reaction records to the Reaxys database. I selected records with one or two reactants and one product, during which records whose molecules could not be processed with RDKit were discarded. I then parsed the reaction conditions using the reaction element dictionary provided in the supporting information of the referenced paper. The reaction elements in the dictionary differed according to the characteristics of the target reaction type. Elements that were not included in the dictionary were discarded. Accordingly, each record was annotated with a reaction condition vector indicating whether each reaction element was used. It should be noted that, unlike in the referenced work, I did not use the NULL value for the categories, because it does not specify any reaction element. The other configurations unspecified here were set the same as those in the referenced work. After eliminating redundancies, I formed a data instance for each unique chemical reaction with its ground-truth reaction conditions.

Table 2.1 lists summary statistics of the four datasets after preprocessing. Many instances are annotated with more than one ground-truth reaction condition. For example, one instance in the Suzuki dataset had 336 different reaction conditions. In the experiments, each dataset was split in a ratio of 8:2 for training and test, respectively.

Dataset (reaction type)	Suzuki	C-N	Negishi	PKR
no. instances (unique count of reactions)	131,789	33,490	6891	2428
no. instances with >1 ground-truth conditions	42,546~(32.28%)	$5715\ (17.06\%)$	$1323\ (19.20\%)$	$408 \ (16.80\%)$
no. conditions per reaction (K, min/avg/max)	1/1.47/336	1/1.42/94	1/1.22/12	1/1.32/32
no. reaction elements considered (L)	113	200	100	75
				metal,
	motel	motel	motel	ligand,
	TTEPOT,	TTTA COT,	TTIGOGT,	temnerature
	ligand,	ligand,	ligand,	competante,
reaction element categories	base,	base,	temperature,	SULVELLU,
	$\operatorname{solvent}$,	$\operatorname{solvent}$,	$\operatorname{solvent}$,	acuvator,
	additive	additive	additive	gas,
				additive,
				pressure

 Table 2.1: Description of cross-coupling reaction datasets extracted from Reaxys database



Figure 2.3: Architecture of the VAE used in this study

2.3.2 Implementation

For the proposed method, which I refer to as **ReactionVAE**, the model architecture of the VAE is illustrated in Figure 2.3. In the encoder q_{ϕ} , I adapted the GNN part that embeds a chemical reaction $R \to P$ into the vector $\mathbf{h} \in \mathbb{R}^{2048}$ from Kwon et al.(Kwon *et al.*, 2022c)'s work. A concatenation of the reaction embedding vector \mathbf{h} and the reaction condition vector \mathbf{c} was further processed by a feed-forward neural network (FNN) that contains three hidden layers with 512 dimensions each. The output layer of the FNN produced $\boldsymbol{\mu}_{\mathbf{z}} \in \mathbb{R}^{128}$ and $\log \boldsymbol{\sigma}_{\mathbf{z}}^2 \in \mathbb{R}^{128}$. In the decoder p_{θ} , I processed a concatenation of the same reaction embedding vector \mathbf{h} of q_{ϕ} and the latent vector $\mathbf{z} \in \mathbb{R}^{128}$ using another FNN with three hidden layers of 512 dimensions each, and an output layer providing the probabilistic output vector with dimensionality of L, the number of reaction elements considered in the dataset.

The following configurations were used for training the VAE. In the training dataset, 90% of the reactions were used to perform parameter updating and the remaining 10% were used to monitor the validation performance. For parameter updating, the Adam optimizer was used with an initial learning rate of 10^{-3} and a mini-batch size of 128. The learning rate was reduced by a factor of 0.1 whenever the validation performance did not improve in 20 consecutive epochs. Training was terminated when the validation performance did not improve over 30 consecutive epochs or when the number of epochs reached 500.

In the inference phase, I varied the number of predictions per reaction, T, with 1, 10, 100, and 1000 to see how this affects the diversification of the reaction condition predictions for a chemical reaction. I implemented the proposed method based on the GPU-accelerated PyTorch.

2.3.3 Baseline Methods

The proposed method, **ReactionVAE**, was compared with two baseline methods: **ReactionFP** and **ReactionGNN**. Unlike the proposed method, the baseline methods provides only a single prediction per query chemical reaction. They used different model architectures and loss functions to build the prediction models. The other training configurations were set as the same as those of the proposed method.

ReactionFP was implemented with reference to Gao et al.(Gao *et al.*, 2018)'s work. This method used the Morgan circular fingerprint with a radius of 2 and chirality information included to represent molecules in a 16,384dimensional bit vector. The vector representation of a chemical reaction was obtained by subtracting the reactant fingerprint from the product fingerprint. To predict the reaction condition for the reaction, the vector was processed using a prediction model whose architecture was the same as the FNN part in the decoder p_{θ} of the proposed method. The model was trained to minimize the binary cross-entropy loss on the extended training dataset D'. **ReactionGNN** uses a GNN to process the graph representations of molecules in a chemical reaction, similar to the prediction models proposed by Ryou et al.(Ryou *et al.*, 2020) and Maser et al.(Maser *et al.*, 2021a)'s work. I built a prediction model with an architecture same as the decoder p_{θ} of the proposed method, except that the latent vector \mathbf{z} was eliminated from its input. The model was trained in the same way as **ReactionFP**.

2.3.4 Evaluation Protocol

The performance of reaction condition prediction was evaluated if groundtruth reaction conditions published in the Reaxys database are well-retrieved. In this respect, I used the following three measures: accuracy, macro-averaged recall, and micro-averaged recall. These measures were calculated on the test dataset $D_{\text{test}} = \{(R_i \rightarrow P_i, C_i)\}_{i=1}^{N_{\text{test}}}$. The accuracy is the proportion of reactions in which at least one ground-truth reaction condition is predicted by the model. It is calculated as:

Accuracy =
$$\frac{1}{N_{\text{test}}} \sum_{i=1}^{N_{\text{test}}} \mathbf{1}(|C_i \cap \hat{C}_i| > 0),$$
 (2.5)

where **1** is an indicator function that returns 1 if the condition is true and 0 otherwise. The macro-averaged recall is the average of the per-reaction proportion of the ground-truth reaction conditions that are predicted by the model. The per-reaction recall is averaged over individual reactions in the test set:

Macro-Recall =
$$\frac{1}{N_{\text{test}}} \sum_{i=1}^{N_{\text{test}}} \frac{|C_i \cap \hat{C}_i|}{|C_i|}.$$
 (2.6)

In the cases of the baseline methods and the proposed method with T = 1, the upper bound of this measure is $\frac{1}{N_{\text{test}}} \sum_{i=1}^{N_{\text{test}}} \frac{1}{|C_i|}$ because they can correctly predict at most one ground-truth condition per reaction. The micro-averaged recall is the overall proportion of the ground-truth reaction conditions in the test set predicted by the model. It is calculated globally by pooling all reactions in the test set:

$$\text{Micro-Recall} = \frac{\sum_{i=1}^{N_{\text{test}}} |C_i \cap \hat{C}_i|}{\sum_{i=1}^{N_{\text{test}}} |C_i|}.$$
(2.7)

For the baseline methods and the proposed method with T = 1, the upper bound is $\frac{N_{\text{test}}}{\sum_{i=1}^{N_{\text{test}}} |C_i|}$. All experiments were independently performed 10 times with different random seeds for data splitting and parameter initialization. I report the average and standard deviation of the results over the repetitions.

2.3.5 Results and Discussion

Table 2.2 compares the performance of the baseline and proposed methods in terms of accuracy, macro-recall, and micro-recall. The results show that **ReactionVAE** with a moderate T > 10 significantly outperformed **ReactionFP** and **ReactionGNN** in all three performance measures. The performance of **ReactionVAE** improved significantly as the number of predictions per reaction T increased. Among the baselines, **ReactionGNN** performed better than **ReactionFP** on the Suzuki, C–N, and Negishi datasets, whereas **ReactionFP** performed better on the PKR dataset which had the smallest size.

Table 2.3 shows the performance evaluation results only for the chemical reactions annotated with more than one ground-truth reaction condition, *i.e.*, K > 1. I found that the performance difference between the baseline and proposed methods became larger compared with Table 2.2. This indicates that **ReactionVAE** was more effective in predicting various reaction conditions for the same reaction. For the baseline methods, the accuracy increased slightly while both the macro-recall and micro-recall decreased drastically as they



Figure 2.4: Unique count of predicted reaction conditions per reaction according to T for ReactionVAE

could predict up to one reaction condition per reaction.

For **ReactionVAE**, I further investigated the diversity of the predicted reaction conditions. Figure 2.4 plots the unique count of predicted reaction conditions per-reaction against the number of predictions T for each dataset. **ReactionVAE** tended to generate more non-duplicated reaction conditions as T increased. The proportion of unique reactions was associated with the number of ground-truth conditions per reaction in the training dataset. More diverse predictions were generated and the maximum number of unique predictions was greater than 100 when T = 1000 for the Suzuki and C–N datasets. In contrast, the unique count was relatively fewer for the Negishi and PKR datasets.

Dataset	Measure	ReactionFP	ReactionGNN		${f ReactionV}$	AE (Proposed)	
				T = 1	T = 10	T = 100	T = 1000
Suzuki	Accuracy	$0.3263{\pm}0.0026$	$0.4036{\pm}0.0044$	$0.2829{\pm}0.0734$	0.4600 ± 0.0507	$0.5671{\pm}0.0462$	$0.6267{\pm}0.0479$
	Macro-Recall	0.2646 ± 0.0022	$0.3242{\pm}0.0035$	$0.2197{\pm}0.0599$	0.3912 ± 0.0478	0.5075 ± 0.0491	$0.5752{\pm}0.0519$
	Micro-Recall	$0.2231{\pm}0.0018$	$0.2760{\pm}0.0030$	$0.1934{\pm}0.0502$	$0.3633{\pm}0.0409$	0.4832 ± 0.0466	$0.5528{\pm}0.0508$
C-N	Accuracy	0.3732 ± 0.0036	$0.4230{\pm}0.0049$	0.3999 ± 0.0278	$0.5295{\pm}0.0155$	$0.6010{\pm}0.0160$	$0.6442{\pm}0.0179$
	Macro-Recall	$0.3469{\pm}0.0028$	$0.3935{\pm}0.0045$	$0.3692{\pm}0.0268$	$0.4839{\pm}0.0158$	$0.5532{\pm}0.0179$	$0.5980{\pm}0.0196$
	Micro-Recall	$0.2648 {\pm} 0.0026$	$0.3001{\pm}0.0035$	0.2837 ± 0.0197	$0.3976 {\pm} 0.0156$	0.4778 ± 0.0191	$0.5312{\pm}0.0209$
Negishi	Accuracy	0.4447 ± 0.0047	$0.4769{\pm}0.0095$	$0.4792{\pm}0.0119$	$0.5091{\pm}0.0137$	$0.5241{\pm}0.0133$	$0.5342{\pm}0.0122$
	Macro-Recall	$0.3931{\pm}0.0039$	$0.4244{\pm}0.0075$	$0.4256{\pm}0.0101$	$0.4579{\pm}0.0130$	$0.4753{\pm}0.0139$	$0.4878{\pm}0.0142$
	Micro-Recall	$0.3613{\pm}0.0038$	$0.3876{\pm}0.0077$	$0.3894{\pm}0.0097$	$0.4280{\pm}0.0144$	0.4495 ± 0.0170	$0.4657{\pm}0.0191$
PKR	Accuracy	0.4862 ± 0.0115	$0.4327{\pm}0.0249$	0.4393 ± 0.0203	$0.5068{\pm}0.0243$	0.5422 ± 0.0235	$0.5685{\pm}0.0250$
	Macro-Recall	$0.4548{\pm}0.0100$	$0.4021{\pm}0.0246$	$0.4089{\pm}0.0191$	$0.4692{\pm}0.0236$	$0.5015{\pm}0.0242$	$0.5266{\pm}0.0247$
	Micro-Recall	$0.3781{\pm}0.0090$	$0.3365{\pm}0.0194$	$0.3416{\pm}0.0158$	$0.4003{\pm}0.0212$	$0.4336{\pm}0.0205$	$0.4590{\pm}0.0228$

Table 2.2: Performance comparison results on chemical reactions in the test set

		T = 1000	$0.7688{\pm}0.0425$	$0.6094{\pm}0.0565$	$0.5476{\pm}0.0540$	$0.7722 {\pm} 0.0226$	$0.4866{\pm}0.0312$	$0.4017{\pm}0.0319$	$0.6120{\pm}0.0296$	$0.3798{\pm}0.0393$	$0.3744{\pm}0.0403$	$0.5688{\pm}0.0360$	$0.3142{\pm}0.0342$	$0.2562{\pm}0.0267$
	$\mathbf{AE} \ (Proposed)$	T = 100	$0.7142{\pm}0.0410$	$0.5297{\pm}0.0533$	$0.4713{\pm}0.0491$	$0.7088{\pm}0.0225$	$0.4134{\pm}0.0321$	$0.3277{\pm}0.0270$	$0.5920{\pm}0.0297$	$0.3472{\pm}0.0306$	$0.3420{\pm}0.0314$	$0.5275{\pm}0.0327$	$0.2802{\pm}0.0193$	$0.2269{\pm}0.0146$
	${f ReactionVA}$	T = 10	$0.5999 {\pm} 0.0436$	$0.3867{\pm}0.0378$	$0.3375{\pm}0.0327$	$0.5863{\pm}0.0243$	$0.3047{\pm}0.0253$	$0.2203{\pm}0.0178$	$0.5640{\pm}0.0306$	$0.3077 {\pm} 0.0214$	$0.3025{\pm}0.0218$	$0.4625 {\pm} 0.0453$	$0.2343{\pm}0.0254$	$0.1868{\pm}0.0206$
		T = 1	$0.3787{\pm}0.0831$	$0.1831{\pm}0.0406$	$0.1558{\pm}0.0342$	$0.3388 {\pm} 0.0160$	0.1492 ± 0.0073	0.0960 ± 0.0045	0.5105 ± 0.0288	$0.2420{\pm}0.0133$	$0.2368{\pm}0.0134$	$0.3525{\pm}0.0327$	0.1677 ± 0.0173	0.1288 ± 0.0119
	ReactionGNN		$0.4783{\pm}0.0068$	$0.2324{\pm}0.0031$	$0.1968{\pm}0.0028$	$0.3283{\pm}0.0102$	$0.1464{\pm}0.0046$	$0.0930{\pm}0.0029$	$0.5044 {\pm} 0.0270$	$0.2409{\pm}0.0133$	$0.2339{\pm}0.0125$	$0.3550{\pm}0.0446$	$0.1690{\pm}0.0215$	$0.1297{\pm}0.0163$
4	ReactionFP		$0.3711 {\pm} 0.0030$	$0.1803{\pm}0.0015$	$0.1527{\pm}0.0012$	$0.2966 {\pm} 0.0137$	$0.1339{\pm}0.0064$	$0.0840 {\pm} 0.0039$	$0.4938{\pm}0.0100$	$0.2354{\pm}0.0044$	$0.2290{\pm}0.0046$	$0.3675{\pm}0.0296$	$0.1764{\pm}0.0132$	$0.1342{\pm}0.0108$
	Measure		Accuracy	Macro-Recall	Micro-Recall	Accuracy	Macro-Recall	Micro-Recall	Accuracy	Macro-Recall	Micro-Recall	Accuracy	Macro-Recall	Micro-Recall
	Dataset		Suzuki			C-N			Negishi			PKR		

Table 2.3: Performance comparison results on chemical reactions with more than one ground-truth reaction condition

2.4 Conclusion

In this study, I present a generative modeling approach to predict multiple suitable reaction conditions for a chemical reaction. I modeled the generative distribution of reaction conditions by introducing a VAE augmented with a GNN. By repeated sampling from the distribution, multiple predictions for a query reaction can be obtained. Through experimental investigation using the datasets of four reaction types extracted from the Reaxys database, I found that the proposed method was able to retrieve significantly more ground-truth reaction conditions compared with existing methods.

A reaction database is a collection of chemical reactions and their groundtruth reaction conditions that have been experimentally validated and reported in the chemistry literature. Therefore, not every possible reaction condition is noted for each chemical reaction, but many feasible conditions have not yet been discovered. Compared with previous studies, this study is the first attempt to predict multiple reaction conditions, each in the form of a complete specification of the reaction elements for a chemical reaction. I believe that the proposed method can shed light on finding unknown feasible conditions for chemical reactions. An important consideration to further improve performance is to reduce the noise in the reaction databases.

Data quality is critical to the success of machine learning applications. However, because these databases are manually maintained, it is inevitable that the reaction records are noisy and contain incorrect information. While manual maintenance of the entire database by subject matter experts is very labor-intensive and time-consuming, recent research attempts to efficiently curate the database could help build more accurate prediction models for better predicting reaction conditions.

Chapter 3

Uncertainty-Aware Prediction of Chemical Reaction Yields with Graph Neural Networks

In this study, I present a data-driven method for the uncertainty-aware prediction of chemical reaction yields. The reactants and products in a chemical reaction are represented as a set of molecular graphs. The predictive distribution of the yield is modeled as a graph neural network that directly processes a set of graphs with permutation invariance.

Uncertainty-aware learning and inference are applied to the model to make accurate predictions and to evaluate their uncertainty. I demonstrate the effectiveness of the proposed method on benchmark datasets with various settings. Compared to the existing methods, the proposed method improves the prediction and uncertainty quantification performance in most settings.

3.1 Motivation

In organic chemistry, the prediction of chemical reaction yields is an important research topic in chemical synthesis planning (Meuwly, 2021; Davies, 2019). This enables the estimation of the overall yield of a complex synthetic pathway and the detection of low-yield reactions that negatively affect the overall yield. It also provides clues for designing new reactions that provide higher yields to save on the time and cost required for experimental syntheses.

Machine learning has achieved remarkable success in the data-driven prediction of chemical reaction yields (Meuwly, 2021; Ahneman *et al.*, 2018; Chuang and Keiser, 2018; Sandfort *et al.*, 2020; Schwaller *et al.*, 2021b; Saebi *et al.*, 2021). The main concept is to construct a prediction model that predicts the yield of a chemical reaction by learning from previously accumulated data comprising a number of chemical reactions annotated with their experimentally measured yields. The successful application of a prediction model enables fast and efficient estimation of chemical reaction yields without performing experimental syntheses, which are costly and time-consuming.

Early studies represented each chemical reaction as a fixed-size vector of handcrafted features, such as molecular fingerprints and chemical property descriptors, and constructed an off-the-shelf prediction model on top of the vector representation (Ahneman *et al.*, 2018; Chuang and Keiser, 2018; Sandfort *et al.*, 2020; Schneider *et al.*, 2015). The limitation of this approach is that the choice of adequate features relies on chemical knowledge and intuition, and some inherent information to the original reaction may be lost in the representation. With advances in deep learning (LeCun *et al.*, 2015), recent studies have applied deep neural networks constructed on a more informative representation of a chemical reaction. Schwaller *et al.* (Schwaller *et al.*, 2021b, 2020) used simplified molecular-input line-entry system (SMILES) to represent a chemical reaction. To predict the reaction yield, they fine-tuned a bidirectional encoder representations from transformers (BERT) model pretrained using a reaction SMILES database (Schwaller *et al.*, 2021a) to predict the yield. Saebi *et al.* (Saebi *et al.*, 2021) represented a chemical reaction as a set of graphs, on which a graph neural network was constructed to predict the yield.

In this study, I present an alternative method for predicting chemical reaction yields. As a prediction model, I adapt a graph neural network that directly operates on the graph representation of a chemical reaction in a permutationinvariant fashion. I use uncertainty-aware learning and inference in the model to make accurate predictions of yields and determine the confidence of predictions.

[Problem Definition of this study]

For a chemical reaction and conditions $(R \to P, C)$, the model predicts yield with uncertainty (μ, σ^2) .

< Input >

 $(\mathcal{R} \to \mathcal{P})_i$: a graph type reactions

 \mathcal{R}_i : a set of reactants, $\mathcal{R}_i = (\mathcal{G}_i^{r1}, \mathcal{G}_i^{r2})$

 \mathcal{P}_i : a product, $\mathcal{P}_i = (\mathcal{G}_i)$

 \mathcal{G}_i : a graph type molecular structure, $\mathcal{G}_i = (\mathcal{V}_i, \mathcal{E}_i)$

 $(\mathcal{V}_i, \mathcal{E}_i)$: a set of nodes and connectivity of molecules of \mathcal{G}_i

 C_i : a set of labeled reaction conditions

< Output >

 $\hat{y}: \mathbf{a} \text{ predicted yield } n$

 (μ, σ^2) : an average of predicted yields with a sigma

< Model >

Using message passing neural network (MPNN)

Using drop-out for measuring uncertainty for prediction model



Figure 3.1: Illustrative example of the graph representation for a molecule.

3.2 Methods

3.2.1 Data Representation

I suppose that a chemical reaction consists of a number of reactants and a single product. This chemical reaction is labeled with its reaction yield. Each instance is represented as $(\mathcal{R}, \mathcal{P}, y)$, where $\mathcal{R} = \{\mathcal{G}^{R,1}, \ldots, \mathcal{G}^{R,m}\}$ and $\mathcal{P} = \{\mathcal{G}^P\}$ are the set of m reactants and the resulting product in the reaction, respectively, and y is the reaction yield. The number of reactants m can be different for each reaction.

Each molecule in \mathcal{R} and \mathcal{P} is defined as an undirected graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$, where \mathcal{V} and \mathcal{E} represent the set of nodes and the set of edges, respectively. The node feature vectors $\mathbf{v}^j \in \mathcal{V}$ and edge feature vectors $\mathbf{e}^{j,k} \in \mathcal{E}$ are associated with heavy atoms (*e.g.*, C, N, O, and F) and their bonds (*e.g.*, single, double, triple, and aromatic), respectively. Hydrogen atoms are treated implicitly. The number of heavy atoms and bonds in each molecule is the same as the number of node feature vectors and edge feature vectors in the corresponding graph representation, respectively. Figure 3.1 illustrates an example of the



Figure 3.2: Architecture of the prediction model.

graph representation of a molecule. For the *j*-th atom, $\mathbf{v}^j = (v^{j,1}, \ldots, v^{j,p})$ is a vector indicating the atom type, formal charge, degree, hybridization, number of hydrogens, valence, chirality, whether it accepts or donates electrons, whether it is aromatic, whether it is in a ring, and associated ring sizes. For the bond between the *j*-th and *k*-th atoms, $\mathbf{e}^{j,k} = (e^{j,k,1}, \ldots, e^{j,k,q})$ is a vector indicating the bond type, stereochemistry, whether it is in a ring, and whether it is conjugated.

3.2.2 Prediction Model

To predict the reaction yield y, I introduce a predictive distribution for y conditioned on the set of reactants \mathcal{R} and product \mathcal{P} , denoted by $p_{\theta}(y|\mathcal{R}, \mathcal{P})$, which is modeled as a normal distribution as follows:

$$p_{\theta}(y|\mathcal{R}, \mathcal{P}) = \mathcal{N}(y|\mu, \sigma^2), \qquad (3.1)$$

where μ and σ^2 are the mean and variance of the distribution, respectively. I parameterize the predictive distribution p_{θ} using a neural network f that produces μ and σ^2 as a function of \mathcal{R} and \mathcal{P} with a set of parameters θ :

$$(\mu, \sigma^2) = f(\mathcal{R}, \mathcal{P}; \theta). \tag{3.2}$$

To construct the neural network f, I adapt the architecture presented by (Saebi et al., 2021) to process two sets of molecular graphs with advanced neural network modules. Figure 3.2 illustrates the architecture used in this study. The architectural details of each component are presented next. A message passing neural network (MPNN) (Gilmer *et al.*, 2017a) is used as the GNN component of f to process each molecular graph \mathcal{G} in \mathcal{R} and \mathcal{P} . The GNN is designed to take \mathcal{G} as the input and return the graph representation vector \mathbf{r} as the output:

$$\mathbf{r} = \text{GNN}(\mathcal{G}). \tag{3.3}$$

In the GNN, I apply multiple message passing steps using an edge network as a message function and a gated recurrent unit (GRU) network as an update function to generate node representation vectors. I then apply a set2set model (Vinyals *et al.*, 2015) as a readout function for global pooling over the node representation vectors to obtain a graph-level embedding that is invariant to the order of the nodes. The embedding is sparsified by a fully-connected layer to obtain the graph representation vector \mathbf{r} . The use of the GNN renders the representation invariant to graph isomorphism.

I summate the graph representation vectors for $\mathcal{R} = \{\mathcal{G}^{R,1}, \ldots, \mathcal{G}^{R,m}\}$. This makes the representation invariant with respect to the order of the reactants. The summated vector is concatenated with the graph representation vector $\mathcal{P} = \{\mathcal{G}^P\}$ to generate the reaction representation vector **h**:

$$\mathbf{h} = \left[\sum_{l=1}^{m} \mathbf{r}^{R,l}, \mathbf{r}^{P}\right].$$
(3.4)

The reaction representation vector **h** is further processed by a feed-forward neural network (FNN) with two output units. The first unit returns the predictive mean μ . The second unit returns the log predictive variance log σ^2 .

The main advantages of the prediction model f presented in this study can be summarized as follows. First, the input for the model is the graph representation of a chemical reaction, which can directly encompass various atom and bond features regarding their chemical properties that make the representation more informative. Second, the model can handle chemical reactions of varying sizes with different numbers of reactants as the input. Third, the output of the model is invariant to permutations of reactants in the input reaction and is also invariant to permutations of atoms in each of the reactants/products. Fourth, the output of the model specifies the corresponding predictive distribution, which allows for uncertainty-aware learning and inference.

3.2.3 Uncertainty-Aware Learning

The learning procedure aims to train the prediction model f such that it can estimate the predictive mean μ and variance σ^2 of the unknown yield yfor a chemical reaction $(\mathcal{R}, \mathcal{P})$. For the model f to learn from data, I construct a training dataset of N chemical reactions and their yields, denoted by $\mathcal{D} = \{(\mathcal{R}_i, \mathcal{P}_i, y_i)\}_{i=1}^N$. I train the model f based on the maximum likelihood estimation. Based on the normality assumption for the predictive distribution p_{θ} , the log-likelihood is given by:

$$\log p_{\theta}(y|\mathcal{R}, \mathcal{P}) = -\frac{1}{2}\log(2\pi\sigma^2) - \frac{1}{2}\frac{(y-\mu)^2}{\sigma^2} = -\frac{1}{2}\log(2\pi) - \frac{1}{2}\left[\frac{(y-\mu)^2}{\sigma^2} + \log\sigma^2\right].$$
(3.5)

Given a training dataset \mathcal{D} , the model is trained to minimize the objective function \mathcal{J} :

$$\mathcal{J}(\theta) = (1-\lambda) \cdot \frac{1}{N} \sum_{i=1}^{N} (y_i - \mu_i)^2 + \lambda \cdot \frac{1}{N} \sum_{i=1}^{N} \left[\frac{(y_i - \mu_i)^2}{\sigma_i^2} + \log \sigma_i^2 \right], \quad (3.6)$$

which involves two learning objectives with the hyperparameter λ that controls the relative strength of each objective. The first term is to minimize the conventional mean squared error over the training dataset \mathcal{D} , which corresponds to the maximization of the log-likelihood over \mathcal{D} under the homoscedasticity assumption. The second term is to maximize the log-likelihood over \mathcal{D} under the heteroscedasticity assumption. The first term contributes to stabilizing the training with respect to the predictive mean μ . The second term enables the predictive variance σ^2 to quantify the aleatoric uncertainty caused by the inherent noise in \mathcal{D} .

3.2.4 Uncertainty-Aware Inference

Once trained, the prediction model f is used to predict the yields of new chemical reactions. I employ the Monte-Carlo (MC) dropout (Gal and Ghahramani, 2016) for the Bayesian approximation of the model f. Following the Bayesian approach, the approximate predictive distribution q is given by

$$q(y_*|\mathcal{R}_*, \mathcal{P}_*) = \int p_\theta(y_*|\mathcal{R}_*, \mathcal{P}_*)q(\theta)d\theta.$$
(3.7)

Given a query reaction $(\mathcal{R}_*, \mathcal{P}_*)$, I wish to predict the unknown yield y_* of



Figure 3.3: Monte-Carlo(MC) dropout (Gal and Ghahramani, 2016).

the reaction as well as to quantify the uncertainty of the prediction. I empirically derive the MC estimates by sampling T predictions $\{(\hat{\mu}_*^{(t)}, \hat{\sigma}_*^{2(t)})\}_{t=1}^T$ based on stochastic forward passes through the model f with dropout applied. Because some hidden units are randomly dropped out at each forward pass, the T predictions vary for the same reaction. The variability in the predictions is primarily caused by the epistemic uncertainty of the model f owing to the insufficiency of the training dataset \mathcal{D} . For prediction, the predictive mean can be estimated by averaging over $\{\hat{\mu}_*^{(t)}\}_{t=1}^T$:

$$E_{q(y_*|\mathcal{R}_*,\mathcal{P}_*)}[y_*] \simeq \frac{1}{T} \sum_{t=1}^T \hat{\mu}_*^{(t)}.$$
(3.8)

This is used as the prediction of y_* . For uncertainty quantification, the predictive variance can be estimated as:

$$\operatorname{Var}_{q(y_*|\mathcal{R}_*,\mathcal{P}_*)}[y_*] \simeq \frac{1}{T} \sum_{t=1}^T \hat{\sigma}_*^{2(t)} + \frac{1}{T} \sum_{t=1}^T \left(\hat{\mu}_*^{(t)} - \bar{\mu}_* \right)^2, \quad (3.9)$$

where $\bar{\mu}_* = \frac{1}{T} \sum_{t=1}^T \hat{\mu}_*^{(t)}$. This is used as the uncertainty score for the predic-

Dataset	No. reactions	No. reactants	No. products
Buchwald-Hartwig	3,955	6	1
Suzuki-Miyaura	5,760	6-14	1

Table 3.1: Description of benchmark datasets

tion. The predictive variance can be decomposed into two types of uncertainty (Kendall and Gal, 2017). The first term corresponds to the aleatoric uncertainty, which accounts for the statistical uncertainty caused by inherent noise in the dataset \mathcal{D} . The second term corresponds to the epistemic uncertainty, which accounts for the systemic uncertainty in the model f caused by the insufficiency of \mathcal{D} .

The prediction of chemical reaction yields supports the identification of high-yield reactions from a pool of possible candidates in an efficient manner. The prerequisite is that the prediction model must be as accurate as possible. In practice, the prediction model may be imperfect and result in inaccurate predictions. To overcome this issue, I can selectively use the model based on uncertainty quantification. Because a high prediction uncertainty tends to cause erroneous predictions, the rejection of uncertain predictions would be beneficial for the actual use of the prediction model. If the prediction uncertainty is sufficiently low, I can use the model with confidence to identify whether a reaction has a high yield. Otherwise, the model abstains from predicting. Rejected cases can be carefully investigated by chemists in terms of their yields.

3.2.5 Experimental Investigation

Datasets

I investigate the effectiveness of the proposed method using the following two benchmark datasets: Buchwald-Hartwig (Ahneman *et al.*, 2018) and Suzuki-Miyaura (Perera *et al.*, 2018). In these datasets, each reaction was annotated with a measured yield ranging from 0% to 100%. The summary statistics of the datasets are presented in Table 3.1.

The Buchwald-Hartwig dataset was released by Ahneman *et al.* (Ahneman *et al.*, 2018). They conducted high-throughput experiments on the class of Pd-catalyzed Buchwald-Hartwig C-N cross-coupling reactions. They experimented on combinations of 15 aryl halides, 4 ligands, 3 bases, and 23 additives. A total of 3955 reactions were reported with their measured yields. The studies (Ahneman *et al.*, 2018; Chuang and Keiser, 2018; Sandfort *et al.*, 2020; Schwaller *et al.*, 2021b) evaluated the performance of the chemical reaction yield prediction on this dataset.

The Suzuki-Miyaura dataset was released by Perera *et al.* (Perera *et al.*, 2018). They conducted high-throughput experiments on the class of Suzuki-Miyaura cross-coupling reactions. 15 couplings of electrophiles and nucleophiles across combinations of 12 ligands, 8 bases, and 4 solvents were considered, resulting in measured yields for a total of 5760 reactions. The studies (Perera *et al.*, 2018; Granda *et al.*, 2018; Schwaller *et al.*, 2021b) have investigated this dataset. For experimental investigations, I use 10 random shuffles for each benchmark dataset and 4 out-of-sample splits of the Buchwald-Hartwig dataset (Ahneman *et al.*, 2018; Schwaller *et al.*, 2021b).

Implementation

In the experimental investigation, I use the following configurations for the proposed method. For the GNN component of the model, the node representation vectors and graph representation vectors have dimensions of 64 and 1024, respectively. The graph representation vectors were set to have higher dimensionality because they are summated over multiple reactants to obtain the reaction representation vector. The number of message passing steps and set2set processing steps are both set to 3. Increasing the size of the GNN component may provide better performance, but it also incurs higher computational costs and memory usage. Thus, I set it to moderately large so that it can be trained in a reasonable time. The FNN component of the model has two fully-connected layers with 512 dimensions, followed by an output layer. During training, I standardize the yield y to have a mean of 0 and a variance of 1 over the training dataset \mathcal{D} . A dropout rate of 0.1 is applied to the fully-connected layers in the FNN component. The hyperparameter λ in the objective function \mathcal{J} is set to 0.1. L2 regularization with a factor of 10^{-5} is applied to the parameters θ . To train the model f, I update the parameters θ for 500 epochs using the Adam optimizer with a batch size of 128. The learning rate is set to 10^{-3} for the initial epochs and decayed to 10^{-4} and 10^{-5} over the last 100 epochs. I did not consider hyperparameter optimization through holdout validation, because it is unsuitable when the training dataset is very small. At inference, I set the number of forward passes T to 30 for MC dropout. I use Equation 3.8 and Equation 3.9 for the prediction and uncertainty score, respectively. The proposed method is implemented using PyTorch in Python. The results of the experimental investigations are reported and discussed in the following section.

3.3 Results and Discussion

3.3.1 Prediction and Uncertainty Quantification

I investigated the effectiveness of the proposed method for predicting the chemical reaction yields on the Buchwald-Hartwig and Suzuki-Miyaura datasets. For the proposed method, I derived two ablations by adjusting the hyperparameter λ in the objective function \mathcal{J} . For the first ablation, the model was trained using only homoscedastic loss by setting $\lambda = 0$, which is equivalent to fixing the predictive variance σ to 1. For the second ablation, the model was trained using only heteroscedastic loss by setting $\lambda = 1$. For baselines, I considered YieldBERT (Schwaller et al., 2021b) and YieldBERT-DA (Schwaller et al., 2020), which demonstrated superior performance compared to the other methods presented in the literature (Ahneman et al., 2018; Chuang and Keiser, 2018; Sandfort et al., 2020). YieldBERT adapted a pre-trained BERT encoder (Schwaller *et al.*, 2021a) to predict the chemical reaction yield as a function of the reaction SMILES. YieldBERT-DA is an extension of YieldBERT based on data augmentation, which increases the quantity of the training dataset using SMILES randomization. For YieldBERT-DA, the prediction uncertainty score was computed using the prediction variance obtained from the test-time augmentation, as implemented in (Schwaller et al., 2020). Consequently, a total of five methods were compared: YieldBERT, YieldBERT-DA, and the proposed method with $\lambda = 0, 1, \text{ and } 0.1$.

For performance evaluation, I split each dataset into training and test sets. I then trained the prediction model using the training set and evaluated its performance on the test set. To examine the effects of training set size on performance, the training/test splits were varied as 70/30, 50/50, 30/70, 20/80, 10/90, 5/95, and 2.5/97.5. Regarding prediction performance, I used the following three measures calculated on the test set: mean absolute error

Dataset	Training/Test Split	Measure	YieldBERT	YieldBERT-DA		Proposed	
					$\lambda = 0$	$\lambda = 1$	$\lambda = 0.1$
Buchwald-Hartwig	70/30	MAE (%p)	$3.990 {\pm} 0.153$	$3.090 {\pm} 0.118$	$3.009 {\pm} 0.045$	$2.953 {\pm} 0.058$	$2.920{\pm}0.056$
		RMSE (%p)	$6.014{\pm}0.272$	$4.799 {\pm} 0.261$	$4.509 {\pm} 0.116$	$4.535 {\pm} 0.136$	$4.433{\pm}0.085$
		\mathbb{R}^2	$0.951 {\pm} 0.005$	$0.969 {\pm} 0.004$	$0.973 {\pm} 0.002$	$0.972 {\pm} 0.002$	$0.974{\pm}0.001$
		Spearman ρ	-	$0.439 {\pm} 0.037$	$0.254 {\pm} 0.027$	$0.445{\pm}0.020$	$0.421 {\pm} 0.031$
	50/50	MAE (%p)	$4.792 {\pm} 0.124$	$3.744{\pm}0.150$	$3.614{\pm}0.095$	$3.482{\pm}0.107$	$3.497{\pm}0.090$
		RMSE (%p)	$7.288 {\pm} 0.198$	$5.877 {\pm} 0.348$	$5.484{\pm}0.193$	$5.481 {\pm} 0.355$	$5.387{\pm}0.202$
		\mathbb{R}^2	$0.928 {\pm} 0.004$	$0.953 {\pm} 0.006$	$0.959 {\pm} 0.003$	$0.959 {\pm} 0.005$	$0.961{\pm}0.003$
		Spearman ρ	_	$0.460{\pm}0.021$	$0.227 {\pm} 0.021$	$0.419 {\pm} 0.020$	$0.401 {\pm} 0.014$
	30/70	MAE (%p)	$6.075 {\pm} 0.222$	$4.833 {\pm} 0.167$	$4.677 {\pm} 0.174$	$4.463{\pm}0.150$	$4.483 {\pm} 0.165$
		RMSE (%p)	$9.338 {\pm} 0.424$	$7.822{\pm}0.463$	$7.227{\pm}0.407$	$7.053 {\pm} 0.439$	$6.970 {\pm} 0.403$
		\mathbb{R}^2	$0.882{\pm}0.011$	$0.917 {\pm} 0.010$	$0.929 {\pm} 0.008$	$0.933 {\pm} 0.009$	$0.934{\pm}0.008$
		Spearman ρ	-	$0.464{\pm}0.020$	$0.229 {\pm} 0.035$	$0.407{\pm}0.022$	$0.385{\pm}0.029$
	20/80	MAE (%p)	$6.862 {\pm} 0.212$	$5.781 {\pm} 0.252$	$5.605 {\pm} 0.236$	$5.319 {\pm} 0.179$	$5.311{\pm}0.154$
		RMSE (%p)	$10.306 {\pm} 0.303$	$9.164{\pm}0.668$	$8.567 {\pm} 0.472$	$8.357 {\pm} 0.400$	$8.204{\pm}0.372$
		\mathbb{R}^2	$0.857 {\pm} 0.008$	$0.886 {\pm} 0.017$	$0.901 {\pm} 0.011$	$0.906 {\pm} 0.009$	$0.909{\pm}0.008$
		Spearman ρ	-	$0.457{\pm}0.017$	$0.208 {\pm} 0.044$	$0.373 {\pm} 0.040$	$0.343 {\pm} 0.029$
	10/90	MAE (%p)	$8.607 {\pm} 0.387$	$7.705 {\pm} 0.236$	$7.605 {\pm} 0.420$	$7.244{\pm}0.229$	$7.196{\pm}0.274$
		RMSE (%p)	$12.393 {\pm} 0.499$	$11.633 {\pm} 0.293$	$11.468 {\pm} 0.699$	$11.002{\pm}0.436$	$10.875 {\pm} 0.448$
		\mathbb{R}^2	$0.793 {\pm} 0.016$	$0.818 {\pm} 0.009$	$0.822 {\pm} 0.022$	$0.837 {\pm} 0.013$	$0.841{\pm}0.013$
		Spearman ρ	-	$0.432{\pm}0.024$	$0.148 {\pm} 0.036$	$0.384{\pm}0.040$	$0.345 {\pm} 0.031$
	5/95	MAE (%p)	$12.117{\pm}0.789$	$9.651{\pm}0.338$	$10.056 {\pm} 0.501$	$10.609{\pm}1.610$	$9.677 {\pm} 0.408$
		RMSE (%p)	$16.740 {\pm} 0.950$	$14.073 {\pm} 0.687$	$14.636 {\pm} 0.672$	$14.693{\pm}1.467$	$14.041 {\pm} 0.492$
		\mathbb{R}^2	$0.622 {\pm} 0.042$	$0.733 {\pm} 0.027$	$0.711 {\pm} 0.026$	$0.707 {\pm} 0.063$	$0.734{\pm}0.019$
		Spearman ρ	_	$0.411{\pm}0.024$	$0.002{\pm}0.058$	$0.398 {\pm} 0.141$	$0.399 {\pm} 0.058$
	2.5/97.5	MAE (%p)	$15.979 {\pm} 0.817$	$12.243 {\pm} 0.631$	$12.409 {\pm} 0.558$	$13.508 {\pm} 2.745$	$11.747{\pm}1.005$
		RMSE (%p)	$20.463 {\pm} 0.623$	$17.151 {\pm} 0.677$	$17.384{\pm}0.775$	$17.992{\pm}2.530$	$16.586{\pm}1.364$
		\mathbb{R}^2	$0.436 {\pm} 0.034$	$0.604{\pm}0.031$	$0.593 {\pm} 0.037$	$0.556 {\pm} 0.130$	$0.628{\pm}0.062$
		Spearman ρ	-	$0.381{\pm}0.038$	$0.016 {\pm} 0.067$	$0.309 {\pm} 0.176$	$0.300 {\pm} 0.075$

 Table 3.2: Comparison of prediction and uncertainty quantification performance on benchmark datasets (Buchwald-Hartwig)

(MAE), root mean squared error (RMSE), and coefficient of determination (\mathbb{R}^2). Uncertainty quantification performance was evaluated in terms of the Spearman rank correlation coefficient ρ between the absolute prediction error and uncertainty score on the test set (Schwaller *et al.*, 2020; Hirschfeld *et al.*, 2020).

Table 3.3 reports the average and standard deviation of the results over the 10 repetitions. In terms of prediction performance, the proposed method outperformed all the baseline methods. Although YieldBERT-DA was the best

Dataset	Training/Test Split	Measure	YieldBERT	YieldBERT-DA		Proposed	
					$\lambda = 0$	$\lambda = 1$	$\lambda = 0.1$
Suzuki-Miyaura	70/30	MAE (%p)	$8.128 {\pm} 0.344$	$6.598 {\pm} 0.270$	$6.233{\pm}0.207$	$6.118 {\pm} 0.212$	$6.116 {\pm} 0.223$
		RMSE (%p)	$12.073 {\pm} 0.463$	$10.524{\pm}0.482$	$9.522{\pm}0.454$	$9.495 {\pm} 0.430$	$9.467{\pm}0.459$
		\mathbb{R}^2	$0.815 {\pm} 0.013$	$0.859{\pm}0.012$	$0.885{\pm}0.010$	$0.885{\pm}0.009$	$0.886{\pm}0.010$
		Spearman ρ	-	$0.439{\pm}0.018$	$0.324{\pm}0.026$	$0.432{\pm}0.024$	$0.425{\pm}0.026$
	50/50	MAE $(\%p)$	$8.922 {\pm} 0.235$	$7.539 {\pm} 0.153$	$6.872{\pm}0.089$	$6.702{\pm}0.082$	$6.725 {\pm} 0.089$
		RMSE (%p)	$13.148 {\pm} 0.270$	$11.797{\pm}0.250$	$10.272{\pm}0.138$	$10.225{\pm}0.128$	$10.225{\pm}0.135$
		\mathbb{R}^2	$0.780 {\pm} 0.009$	$0.823{\pm}0.007$	$0.866{\pm}0.003$	$0.867{\pm}0.003$	$0.867{\pm}0.003$
		Spearman ρ	-	$0.439{\pm}0.019$	$0.322{\pm}0.021$	$0.432{\pm}0.017$	$0.430 {\pm} 0.012$
	30/70	MAE (%p)	$10.094{\pm}0.346$	$8.804{\pm}0.249$	$8.021 {\pm} 0.094$	$7.740{\pm}0.109$	$7.847{\pm}0.094$
		RMSE (%p)	$14.614{\pm}0.381$	$13.337 {\pm} 0.357$	$11.726{\pm}0.152$	$11.526{\pm}0.166$	$11.593{\pm}0.136$
		\mathbb{R}^2	$0.729 {\pm} 0.014$	$0.774{\pm}0.012$	$0.825{\pm}0.004$	$0.831{\pm}0.005$	$0.829{\pm}0.004$
		Spearman ρ	-	$0.432{\pm}0.018$	$0.292{\pm}0.012$	$0.428{\pm}0.013$	$0.417 {\pm} 0.008$
	20/80	MAE (%p)	$11.229 {\pm} 0.247$	$10.017 {\pm} 0.338$	$9.147{\pm}0.185$	$8.726{\pm}0.172$	$8.793 {\pm} 0.191$
		RMSE (%p)	$15.966 {\pm} 0.381$	$14.851{\pm}0.576$	$13.115{\pm}0.298$	$12.754{\pm}0.316$	$12.734{\pm}0.347$
		\mathbb{R}^2	$0.676 {\pm} 0.015$	$0.719 {\pm} 0.022$	$0.781 {\pm} 0.010$	$0.793{\pm}0.010$	$0.794{\pm}0.011$
		Spearman ρ	-	$0.432{\pm}0.014$	$0.274{\pm}0.020$	$0.429{\pm}0.017$	$0.408 {\pm} 0.018$
	10/90	MAE $(\%p)$	$13.528 {\pm} 0.395$	$11.954{\pm}0.443$	$11.439{\pm}0.185$	$10.625{\pm}0.249$	$10.739{\pm}0.211$
		RMSE (%p)	$18.734 {\pm} 0.530$	$17.129 {\pm} 0.683$	$15.967{\pm}0.326$	$15.097 {\pm} 0.421$	$15.164 {\pm} 0.344$
		\mathbb{R}^2	$0.554 {\pm} 0.025$	$0.627 {\pm} 0.030$	$0.676 {\pm} 0.013$	$0.711{\pm}0.016$	$0.708 {\pm} 0.013$
		Spearman ρ	-	$0.389{\pm}0.022$	$0.221{\pm}0.027$	$0.390{\pm}0.019$	$0.382{\pm}0.019$
	5/95	MAE (%p)	$15.695 {\pm} 0.618$	$14.294 {\pm} 0.507$	$14.214{\pm}0.504$	$13.364 {\pm} 0.223$	$13.451 {\pm} 0.353$
		RMSE (%p)	$21.181 {\pm} 0.724$	$20.016 {\pm} 0.661$	$19.421 {\pm} 0.588$	$18.463 {\pm} 0.308$	$18.511 {\pm} 0.392$
		\mathbb{R}^2	$0.430 {\pm} 0.040$	$0.491{\pm}0.034$	$0.521{\pm}0.029$	$0.567{\pm}0.014$	$0.565 {\pm} 0.018$
		Spearman ρ	_	$0.355{\pm}0.026$	$0.144{\pm}0.052$	$0.389{\pm}0.045$	$0.330 {\pm} 0.034$
	2.5/97.5	MAE (%p)	$17.666 {\pm} 0.496$	17.587 ± 0.690	$18.061 {\pm} 0.571$	$16.705{\pm}1.090$	$17.189{\pm}0.813$
		RMSE (%p)	$22.967 {\pm} 0.804$	$23.780 {\pm} 0.793$	$24.121 {\pm} 0.655$	$22.156{\pm}1.273$	$22.943 {\pm} 0.887$
		\mathbb{R}^2	$0.330 {\pm} 0.047$	$0.282{\pm}0.047$	$0.261{\pm}0.039$	$0.375 {\pm} 0.072$	$0.331 {\pm} 0.051$
		Spearman ρ	-	$0.291 {\pm} 0.025$	$0.028 {\pm} 0.054$	$0.280{\pm}0.074$	$0.223 {\pm} 0.081$

 Table 3.3: Comparison of prediction and uncertainty quantification performance on benchmark datasets (Suzuki-Miyaura)

baseline method, the MAE and RMSE values of the proposed method reduced by around 5~10% compared to those of YieldBERT-DA on both benchmark datasets. The higher prediction performance indicates that the proposed method can provide more accurate predictions of yields for new reactions. Regarding uncertainty quantification performance, the proposed method yielded a Spearman ρ comparable to that of YieldBERT-DA.

For the proposed method, the prediction performance with $\lambda = 1$ was slightly better than that with $\lambda = 0$. The uncertainty quantification performance with $\lambda = 1$ was far better than that with $\lambda = 0$, which implies that capturing the aleatoric uncertainty is beneficial. Compared to the ablations, setting $\lambda = 0.1$ yielded a better trade-off between prediction performance and uncertainty quantification performance. The results demonstrated that the use of both homoscedastic and heteroscedastic losses helped to improve performance.

3.3.2 Out-Of-Sample Prediction

I also evaluated the performance of the proposed method for out-of-sample prediction. As in (Schwaller *et al.*, 2021b, 2020), I used four out-of-sample training/test splits of the Buchwald-Hartwig dataset, which I denote by Test 1, Test 2, Test 3, and Test 4. In each split, certain additives are absent from the training set but only appear in the test set. The proposed method was compared with YieldBERT and YieldBERT-DA. The training configurations and evaluation scheme were the same as before. The experiments were repeated five times independently using different random seeds.

Table 3.4 summarizes the results averaged over the five repetitions. Overall, the proposed method was comparable to the best of the baseline methods for out-of-sample prediction. In terms of prediction performance, the proposed method performed best on Test 2 and Test 4, while was comparable or inferior to the best baseline on Test 1 and Test 3. Among the baselines, YieldBERT-DA yielded a lower performance than YieldBERT on average. For uncertainty quantification performance, the proposed method yielded the highest Spearman ρ for Test 1, Test 3, and Test 4.

3.3.3 Selective Prediction with Rejection

I investigated the effectiveness of the proposed method for selective prediction using 70/30 splits of benchmark datasets. For the proposed method, prediction

Out-Of-Sample Split	Measure	YieldBERT	YieldBERT-DA	Proposed $(\lambda = 0.1)$
Test 1	MAE (%p)	$7.351{\pm}0.099$	$7.015 {\pm} 0.758$	$8.082 {\pm} 0.827$
	RMSE (%p)	$11.441{\pm}0.342$	$11.761{\pm}1.398$	$13.746{\pm}1.175$
	\mathbb{R}^2	$0.824{\pm}0.010$	$0.811 {\pm} 0.047$	$0.744{\pm}0.042$
	Spearman ρ	—	$0.380{\pm}0.065$	$0.454{\pm}0.046$
Test 2	MAE (%p)	$7.266{\pm}0.724$	$6.588 {\pm} 0.328$	$6.300{\pm}0.647$
	RMSE (%p)	$11.144{\pm}1.267$	$9.886 {\pm} 0.741$	$9.476{\pm}1.027$
	\mathbb{R}^2	$0.829{\pm}0.037$	$0.866 {\pm} 0.020$	$0.876{\pm}0.026$
	Spearman ρ	—	$\textbf{0.494}{\pm}\textbf{0.044}$	$0.397 {\pm} 0.043$
Test 3	MAE (%p)	$9.129 {\pm} 0.745$	$11.052 {\pm} 0.950$	$8.986{\pm}0.314$
	RMSE (%p)	$14.276{\pm}0.820$	$18.041{\pm}1.395$	$14.939{\pm}0.622$
	\mathbf{R}^2	$0.741{\pm}0.030$	$0.585 {\pm} 0.067$	$0.717 {\pm} 0.024$
	Spearman ρ	—	$0.406 {\pm} 0.065$	$0.423{\pm}0.031$
Test 4	MAE (%p)	$13.671{\pm}1.067$	$18.422 {\pm} 0.620$	$13.190{\pm}0.754$
	RMSE (%p)	$19.679{\pm}1.397$	$24.279 {\pm} 0.494$	$18.774{\pm}0.566$
	\mathbb{R}^2	$0.444{\pm}0.077$	$0.157{\pm}0.034$	$0.496{\pm 0.031}$
	Spearman ρ	-	$0.366 {\pm} 0.100$	$0.461{\pm}0.040$

 Table 3.4:
 Comparison of prediction and uncertainty quantification performance on out-of-sample splits of Buchwald-Hartwig dataset

uncertainty was quantified using the total predictive variance in Equation 3.9. Because it can be decomposed into aleatoric and epistemic uncertainties, I conducted an ablation study to examine the effects of each component. The first ablation quantified the prediction uncertainty using the aleatoric uncertainty term. The second ablation used the epistemic uncertainty term. The proposed method was compared to the best baseline method, YieldBERT-DA, for which the uncertainty quantification was based on the test-time augmentation.

To evaluate the selective prediction performance, I rejected the prediction for a reaction if its uncertainty score was above a certain threshold. The threshold controls the trade-off between prediction accuracy and coverage. As performance measures, I computed the MAE and RMSE on the test set with various prediction coverage rates ranging from 100% to 30%. Tables 3.5 and 3.6 present the comparison results for the selective prediction performance in terms of the MAE and RMSE with various prediction coverage rates, which are summarized in Figure 3.4. The results clearly demonstrated that a high uncertainty score for a reaction causes its predicted yield to be less accurate for all compared methods. Reducing the prediction coverage with more rejections led to a significant improvement in the prediction performance. The proposed method outperformed YieldBERT-DA in most cases. The MAE and RMSE decreased by over 10% and were nearly halved at 90% and 40% coverages, respectively, for both datasets.

Regarding the two ablations of the proposed method, the selective prediction performance with the epistemic uncertainty was superior at higher prediction coverages, whereas that with the aleatoric uncertainty was better at lower coverages. Compared to the ablations, using the total predictive variance combining the aleatoric and epistemic uncertainty improved the performance by taking their individual strengths to detect erroneous predictions.



Figure 3.4: Summary for comparison of selective prediction performance on benchmark datasets: (a) MAE (%p) on Buchwald-Hartwig; (b) MAE (%p) on Suziki-Miyaura; (c) RMSE (%p) on Buchwald-Hartwig; (d) RMSE (%p) on Suziki-Miyaura

Dataset	Coverage	YieldBERT-DA		Proposed $(\lambda = 0$.1)
			Aleatoric	Epistemic	Total Pred. Var.
Buchwald-Hartwig	100%	$3.090 {\pm} 0.118$	$2.920{\pm}0.056$	$2.920{\pm}0.056$	$2.920{\pm}0.056$
	30%	$2.733 {\pm} 0.099$	$2.684{\pm}0.050$	$2.669{\pm}0.056$	$2.683{\pm}0.061$
	80%	$2.534{\pm}0.082$	$2.518{\pm}0.064$	$2.514{\pm}0.063$	$2.505{\pm}0.065$
	20%	$2.357{\pm}0.092$	2.302 ± 0.067	$2.292 {\pm} 0.067$	$2.293{\pm}0.064$
	80%	$2.191{\pm}0.103$	2.056 ± 0.099	2.070 ± 0.064	$2.041{\pm}0.069$
	50%	$2.020{\pm}0.105$	1.820 ± 0.093	1.847 ± 0.075	$1.803{\pm}0.061$
	40%	$1.824{\pm}0.106$	1.593 ± 0.086	1.672 ± 0.081	$1.582{\pm}0.077$
	30%	$1.560{\pm}0.098$	$1.368{\pm}0.112$	1.509 ± 0.115	1.372 ± 0.111
Suzuki-Miyaura	100%	$6.598{\pm}0.270$	$6.116{\pm}0.223$	$6.116{\pm}0.223$	$6.116{\pm}0.223$
	%06	5.902 ± 0.247	$5.589{\pm}0.178$	5.575 ± 0.191	$5.542{\pm}0.178$
	80%	5.415 ± 0.242	$5.298{\pm}0.174$	$5.269{\pm}0.210$	$5.219{\pm}0.192$
	20%	$5.052{\pm}0.211$	5.018 ± 0.196	4.966 ± 0.183	$4.939{\pm}0.208$
	80%	$4.690{\pm}0.181$	$4.641 {\pm} 0.218$	4.579 ± 0.140	$4.570{\pm}0.188$
	50%	4.213 ± 0.214	4.025 ± 0.252	4.064 ± 0.179	$3.989{\pm}0.203$
	40%	$3.921{\pm}0.188$	3.245 ± 0.140	3.372 ± 0.111	$3.195{\pm}0.145$
	30%	$3.549{\pm}0.120$	$2.510{\pm}0.093$	2.701 ± 0.118	2.514 ± 0.115

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Table 3.6: Comparison of selective prediction performance in terms of RMSE (%p) $\,$

3.4 Conclusion

I presented an uncertainty-aware method for predicting chemical reaction yields. I represented a chemical reaction as a set of graphs. I constructed a prediction model whose input was the graphs and output was the predictive mean and variance for the reaction yield. For a query reaction, the predictive mean of the model was used as the predicted yield and the predictive variance was used to quantify the uncertainty of the prediction, which allowed the model to avoid making predictions with high uncertainty. The effectiveness of the proposed method for chemical reaction yield prediction was successfully demonstrated through experimental validation on two benchmark datasets. I also demonstrated that a high predictive variance tends to cause a high prediction error, allowing for selective prediction with rejection.

The accurate prediction of chemical reaction yields with uncertainty quantification can assist in advanced synthesis planning considering imposed constraints in practice, including availability, variability, and budget limits. Future research directions for improving prediction performance will be to enrich the data representation of chemical reactions to make it more informative by incorporating various atom/bond features and molecular descriptors associated with reaction yields.

Chapter 4

Exploring Optimal Reaction Conditions Guided by Graph Neural Networks and Bayesian Optimization

The optimization of organic reaction conditions to obtain the target product in high yield is crucial to avoid expensive and time-consuming chemical experiments. Advancements in artificial intelligence have enabled various data-driven approaches to predict suitable chemical reaction conditions. However, for many novel syntheses, the process to determine good reaction conditions is inevitable. Bayesian optimization (BO), an iterative optimization algorithm, demonstrates exceptional performance to identify reagents compared to synthesis experts. However, BO requires several initial randomly selected experimental results (yields) to train a surrogate model (approximately 10 experimental trials). Parts of this process, such as the cold-start problem in recommendation systems, are inefficient.

Here, I present an efficient optimization algorithm to determine suitable

conditions based on BO that is guided by a graph neural network (GNN) trained on a million organic synthesis experiment data. The proposed method determined 8.0 and 8.7% faster high-yield reaction conditions than state-of-the-art algorithms and 50 human experts, respectively. In 22 additional optimization tests, the proposed method needed 4.7 trials on average to find conditions higher than the yield of the conditions recommended by five synthesis experts. The proposed method is considered in a situation of having a reaction dataset for training GNN.

4.1 Motivation

Substantial effort has been dedicated over the past few years to develop various technologies for optimizing chemical reaction conditions. Traditionally, depending on the particular scientific or engineering discipline, optimization was accomplished against a variety of criteria, for example, finding the lowestenergy state of a chemical structure, identifying the factors that most closely relate the molecular shape with the properties, or searching for the optimal set of conditions to increase the efficiency of experimental procedures. (Biegler and Grossmann, 2004; Yin and Gounaris, 2022; Wang and Dowling, 2022)

The Reaxys database(Goodman, 2009) has unbalanced data because it was extracted the experimental information described in the synthetic research papers. Below shows the number of biased data. Since the classification of reactions is ambiguous or overlapping, and the missing information is included, all reaction condition data are retrieved for Graph Neural Networks training for prediction suitable conditions given reactants with product structures. Plus, a newly redefined dataset based on notation and CAS-number is used as training in Figure 4.1.

The optimization algorithms capable of efficiently finding local optima are gradient-based algorithms, such as gradient descent (Ruder, 2016), con-



Figure 4.1: Biased dataset in chemical reaction (Reaxys)

jugate gradient (Hestenes and Stiefel, 1952), or the more sophisticated Broyden–Fletcher–Goldfarb–Shanno algorithm (BFGS) (Fletcher, 1987). Many optimization technologies have been specifically developed for chemistry. For example, chemical reaction conditions can be optimized using systematic methods such as the design of experiments (DOE) (I., 1936). Recent optimization procedures based on computational methods were designed to assist chemists to identify chemical derivatives of known drugs to best treat a given disease(Negoescu *et al.*, 2011), pinpoint candidates for organic photovoltaics, predict organic reaction paths, and conduct automated experimentation without human intervention (Nikolaev *et al.*, 2014; Fitzpatrick *et al.*, 2016; Nikolaev *et al.*, 2016; Duros *et al.*, 2017; Coley *et al.*, 2019b; Gao *et al.*, 2022; Pyzer-Knapp *et al.*, 2022; Huo *et al.*, 2019).

Often, these applications are subject to multiple local optima and involve costly evaluations of the proposed conditions in terms of the required experimentation or extensive computation. Bayesian optimization (BO) approaches have emerged as popular optimization solutions to search for the efficient global optimum (Kushner, 1964; Mockus, 1975; Mockus and Mockus, 1991; Snoek *et al.*, 2014, 2012; Srinivas *et al.*, 2012). BO schemes consist of two major steps: First, an approximation (surrogate model) to the objective function of the conditions is constructed. Second, based on this surrogate, a new set of conditions is proposed for the next evaluation to identify the global optimum. As such, BO predicts the experimental outcome using all previously conducted experiments and verifies its speculations by requesting the evaluation of a new set of conditions. Several different models have been suggested for approximating the objective function areas, ranging from random forests (RF) (Hutter *et al.*, 2011), over gaussian processes (GP) (Snoek *et al.*, 2014, 2012), to active learning models (Settles, 2012).

However, these models require numerous evaluations (depending on the

predefined search space) of data generated in the form of laboratory experiments or computations, and are thus not well suited for solving optimization problems in chemistry. This is because evaluations of the objective are often costly, and material synthesis is another major barrier in material development because it is still carried out laboriously by human researchers.

Lately, data-driven approaches have been employed to recommend conditions for specific types of reactions. The application of powerful machinelearning techniques to large data of organic reactions, such as the Reaxys database, has led to major advances both in searching for possible retrosynthetic pathways (Szymkuć *et al.*, 2016; Segler *et al.*, 2017; Law *et al.*, 2009; Liu *et al.*, 2017; Bøgevig *et al.*, 2015; Coley *et al.*, 2017a; Segler *et al.*, 2018; Kim *et al.*, 2021; Tetko *et al.*, 2020; Ucak *et al.*, 2022; Mo *et al.*, 2021; Wang *et al.*, 2020b) and in evaluating the feasibility of the proposed reactions (Kayala *et al.*, 2011; Kayala and Baldi, 2012; Jin *et al.*, 2017; Coley *et al.*, 2017b; Maser *et al.*, 2021b; Gao *et al.*, 2018; Kwon *et al.*, 2022b; Coley *et al.*, 2019a) and synthetic environments. Unfortunately, the disadvantage of data-driven methods is their limited predictive performance based on data that completely deviate from the training data distribution. In particular, the data extracted from most successful studies involving chemical experiments are likely to have been biased to one side (a lack of negative data).

In this study, I attempt to overcome the limited ability of advanced approaches to determine the optimal reaction conditions led us to propose the hybrid-type dynamic reaction optimization (HDO) method, which complements the previous two methodologies as data-driven approaches in that it is based on a graph neural network (GNN) with BO. This approach enables us to efficiently explore the optimal combination of conditions compared with previous studies. Modern advances in high-throughput experimentation (HTE) (Coley *et al.*, 2019a; Gao *et al.*, 2018) enabled the construction of

three named datasets ('Suzuki–Miyaura reaction', 'Buchwald–Hartwig reaction', and 'Arylation reaction') that contain different types of chemical reaction data. These data include all of the capabilities of a collection consisting of a few thousand data points under a limited set of conditions in datasets from (Shields *et al.*, 2021). In addition, I validated the proposed algorithm using additional reaction experiment ('Ullmann reaction' and 'Chan–Lam reaction') with five synthetic experts using my own HTE facilities, details of which are provided in Table 4.1.

[Problem Definition of this study]

Given a set of reactions, priority (I) from all possible combinations of condition cadidates S.

< Input >

 $(\mathcal{R} \to \mathcal{P})_i$: a graph type reactions

 \mathcal{R}_i : a set of reactants, $\mathcal{R}_i = (\mathcal{G}_i^{r1}, \mathcal{G}_i^{r2})$

 \mathcal{P}_i : a product, $\mathcal{P}_i = (\mathcal{G}_i)$

 \mathcal{G}_i : a graph type molecular structure, $\mathcal{G}_i = (\mathcal{V}_i, \mathcal{E}_i)$

 $(\mathcal{V}_i, \mathcal{E}_i)$: a set of nodes and connectivity of molecules of \mathcal{G}_i

 \mathcal{S} : a search space of combination of conditions

< Output >

 $I \colon \mbox{Priority of all possible combinations of condition candidates S} < Model >$

Using graph variational autoencoder (GVAE)

Uncertainty-aware yield prediction model (MPNN)

Bayesian optimization (BO)

4.2 Methods

4.2.1 Overview of hybrid-type dynamic optimization for exploring suitale chemical reaction

For efficient exploration, HDO consists of an MPNN, which was trained using approximately 1 million experimental-reaction data to predict suitable conditions, and a BO model, which explores conditions based on ongoing experimental results. I designed the optimization direction to be dynamically modified for experimental results by adjusting the weights of the above two models based on the obtained yield results. The overall condition optimization process is described in Figure 4.2.

Considering that all the reaction conditions are not efficient and could be unnecessarily costly, HDO narrows the search space using MPNN models that are able to predict the chemical context most suitable for any particular organic reactions. Combinations of conditions, selected from the narrowed area of candidates and expected to deliver the target yield, should be chosen for the experiment. When sampling the initial conditions, in the narrowed search space, my aim is to maintain a balance between exploitation and exploration. Therefore, I adapted the candidate conditions predicted by the MPNN as exploitation and selected the Maximin–Latin Hypercube sampling method (Stein, 1987) to ensure an effective distribution of exploration in Figure 4.2 (b). Moreover, I experimented with initial conditions and trained the surrogate model of BO by obtaining the yield result. Figure 4.2 (c), for the acquisition function of BO, I adopted upper confidence bounds (UCBs) (Carpentier *et al.*, 2015), which ranked the priority of the next combination of conditions, Figure 4.2 (d) as detailed in a separate subsection. Finally, HDO calculates the priority of the next candidates in the form of an ensemble by considering the historical results, MPNN, and BO. Figure 4.2 (e), depending on the outcome, the search space could be expanded to include additional reaction conditions. Figure 4.2 (f), for maximum efficiency, HDO was designed to perform comprehensive judgments using not only the results predicted by the MPNN but also the experimental results, frequency of past experiments, and uncertainties in the objective function of the predictive model.

The data-preprocessing and model-formulation steps are detailed in subsequent subsections. HDO proceeds iteratively until it determines the global optimal combination of conditions that produce the desired target yield, and it updates the objective functions whenever the complete results of each experiment are known. The proposed approach offers a platform on which fully automated organic-synthesis experiments can be conducted using robots and management software.



Figure 4.2: (a) Given a reaction representation, HDO specifies a search space using the best combination of conditions predicted by MPNN. (b) Initial experimental conditions are selected by adopting balanced methods that consider the trade-off between exploration and exploitation. (c) Reaction yields acquired via HTE to experiment with a selected combination of initial conditions. (d) The surrogate model of BO is trained using the initial experimental results (yield) and calculates the acquisition function of BO. (e) The priority is calculated, and the method determines whether to continue experimenting or to expand the search space. (f) If the number of experiments exceeds 20 and the maximum yield is less than 10, the initially narrowed range is expanded step by step (details in the text).

4.2.2 Dataset and graph-type representation for training MPNN

The dataset for all the reactions with their conditions for training the MPNN was extracted from the Reaxys reaction database consisting of 53 million reaction records. The data include structural expressions of the reactants, products, and conditions. I used the structural expressions of the reactants and each single product, the Reaxys chemical ID, and simplified molecular-input line-entry system (SMILES) notation (if available) or the name of the reaction. Each chemical reaction is labeled with the reagents that participate in the reaction. Each instance is represented as $(\mathcal{R}, \mathcal{P}, c)$, where $\mathcal{R} = \{\mathcal{G}_{r1}, \mathcal{G}_{r2}\}_i$ and $\mathcal{P} = \{\mathcal{G}_p\}_i$ represent the set *i* of the two reactants with the product structures in the reaction, respectively and *c* is the one-hot vector of the reaction conditions such as catalysts, bases, solvents, and ligands.

Owing to the different circumstances of each synthesis experiment, I did not include the reaction-condition datasets from the Reaxys database based on a pre-defined list of reagents in the experiments. In addition, number of reactions sets i and classes of conditions can be different for each type of condition and optimization task, respectively. Furthermore, I restricted my scope to include single-product and single-step reactions to ensure a closer alignment with the application to computer-aided synthesis planning. I also noted the ambiguous labeling of certain catalysts, solvents, and reagents in the Reaxys, in which many catalysts are recorded as reagents, causing the data to be sparser for catalysts and increasing the number of distinct reagents. This issue can hardly be completely eliminated because a strict separation between reagents and catalysts is difficult to achieve.

4.2.3 Message Passing Neural Networks for predicting suitable reagents

A chemical reaction consisting of two reactants was set as $\mathcal{R}_{1,2}$ and a single product as \mathcal{P} . This chemical reaction is labeled with its reaction conditions c, denoted by $f_{\phi}^{MPNN}(c|R_{1,2}, P)$. A graph is a data structure that presents a powerful non-Euclidean method for establishing the extent to which features (nodes) are connected to their relationships (edges). I defined each molecule in $\mathcal{R}_1, \mathcal{R}_2$ and \mathcal{P} as an undirected graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$, where \mathcal{V} and \mathcal{E} represent the sets of nodes and edges vectors, respectively. The node feature vector $v^j \in \mathcal{V}$ and edge feature vectors $\mathbf{e}^{j,k} \in \mathcal{E}$ were assumed to consist of heavy atoms (e.g., C, N, O and F) and their bonds (e.g., single, double, triple, and aromatic), respectively. Hydrogen atoms were not considered. The node feature \mathcal{V}^{j} is a vector indicating the atom type, formal charge, degree, hybridization, number of hydrogen atoms, valency, chirality, whether it accepts or donates electrons, whether it is aromatic, whether it is in a ring, addn associated ring sizes. For the bond between atoms j and k, $e^{j,k}$ is a vector indicating the bond type, stereochemistry, whether it is in a ring, and whether it is conjugated. The MPNN is designed to accept $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ as the input and to return the graph representation vector q as output as follows:

$$q = \mathbf{M}_{\theta}(\mathcal{G}). \tag{4.1}$$

The MPNN uses six message passing steps with an edge network as the message function and a gated recurrent unit (GRU) network as the update function to produce node-representation vectors, whose dimensionality was set to 64. Then, a set2set model, which uses six processing steps, is employed as the readout function for global pooling over the node-representation vectors to obtain graph-level embedding, which is invariant to the order of the

nodes, as described in Figure 4.3. The embedding is further processed by a fully connected layer of 512 ReLUs (Agarap, 2018), resulting in the graph representation vector q. The use of the MPNN ensures that the representation is invariant to graph isomorphism. I summate the respective graph representation vectors regarding $\mathcal{R} = \{\mathcal{G}_{r1}, \mathcal{G}_{r2}\}$ and $\mathcal{P} = \{\mathcal{G}_p\}$. In this manner, the representation becomes invariant to the order of reactants and products. The two summated vectors of reactants are concatenated to produce a reaction representation vector h, as follows:

$$h = \left[\sum_{l=1}^{m} q^{\mathcal{R}}, q^{\mathcal{P}}\right] \tag{4.2}$$

Here, m is the number of reactants. The reaction graph embedding vector h is further processed by a feed-forward neural network (FNN) having four fully connected layers, each of which contains 512 ReLUs is represented as $\mathbf{p}_{\pi}(\mathbf{h})$. The output functions of the FNN are equal to the length of the one-hot vectors by each condition type (c). The predictive model MPNN is trained as an independent model according to the type of reaction conditions and the predicted catalyst, ligand, base, and solvent as c_{category} , respectively. Once trained, the prediction model f_{ϕ}^{GP} is used for predicting the conditions of new chemical reactions. Given a query reaction (\mathbb{R}^* , \mathbb{P}^*), I predict condition types is depended on the reaction task). Then, the value of the priority is calculated by generating all possible combinations of conditions using the weight value of the one-hot vector c predicted by the model for each of the conditions. Therefore, the priority of condition combination I is defined as :

$$I = \sum_{k=0}^{t} N \cdot (f_{\phi}^{\text{GP}}(\mathcal{R}, \mathcal{P}))$$
(4.3)

The types of conditions vary for different experiments and have different ranges. In Equation (4.3), t represents the type of condition. Each condition prediction model f_{ϕ}^{GP} is normalized for reducing gab of weight values. Finally, the priority of combination of predicted conditions is represented by I. Moreover, the priority is represented as $I = N \cdot C_{\text{lig}} + N \cdot C_{\text{bas}} + N \cdot C_{\text{sol}}$, where N is the normalization to reflect the equivalent weights for each category of conditions. Figure 4.3 illustrates the training process for the condition prediction models.



Figure 4.3: Illustration of the process of MPNN models to predict suitable reaction conditions given garph-type reaction representations $\mathcal{G}(\bigoplus$ denotes the summation of q^R vectors, and \bigotimes represents the calculation of combinations among weights of one-hot vectors under different conditions c).

4.2.4 Bayesian optimization in HDO

The BO method is used to reduce the number of objective evaluations that need to be performed to solve an optimization problem. To achieve this, they iteratively suggest, in a careful and intelligent manner, an input location in which the objective that is being optimized should be evaluated for each experiment. At each iteration $N = 1, 2, 3 \dots$ of the optimization process, the BO method fits a probabilistic model, a Gaussian process surrogate model (GP) in my case, to the collected observations of the objective. The uncertainty in the potential values of the objective is provided by the predictive distribution of the GP. I modeled chemical-reaction outcomes, GP is defined in Shield's study48 and the Matérn52 kernel were used and represented as f_{ϕ}^{GP} . For each reaction, a numerical encoding was generated by concatenating descriptor vectors for each condition category and continuous variable. For example, the Suzuki–Miyaura reaction in Task 2 involved four categories: catalysts, bases, solvents, and ligands. The input description is described as $\mathbf{d}_i = \mathbf{d}_{\text{catalyst}} \bigoplus \mathbf{d}_{\text{base}} \bigoplus \mathbf{d}_{\text{solvent}} \bigoplus \mathbf{d}_{\text{ligand}}$ (where \bigoplus denotes concatenation).

Here, *i* is the number of all possible combinations of conditions, that is, the search space. The target was the yield. The target of BO objective function is the experimental yield results. In Gaussian process regression, the surrogate model determines the general shape of its function distribution. The trained parameters for the length scale set the relative variation per dimension, the amplitude calibrates the magnitude of the changes, and the noise captures the variation in measurements. In the acquisition function, upper-confidence-bound (UCB) algorithm was adopted to calculate the priority of the next best combination of conditions.

Uncertainty was used to generate an acquisition function AF_{UCB} , whose value at each input location indicates the expected utility of evaluating f_{ϕ}^{GP} at this location. The upper-confidence-boud (UCB) algorithm was adopted to calculate the priority of the next best combinations of conditions as

$$AF_{\rm UCB}(\chi_k;\lambda) = \mu(\chi_k) + \lambda \cdot \sigma(\chi_k). \tag{4.4}$$

With UCB, the exploitation vs. exploration tradeoff is straightforward and easy to tune via the parameter λ . Concretely, UCB is a weighted sum of the

expected performance captured by $\mu(\chi_k)$ of the Matérn52 kernels and of the uncertainty $\sigma(\chi_k)$, captured by standard deviation of the f_{ϕ}^{GP} . The next point x_k at which for evaluate f_{ϕ}^{GP} is the one that maximizes AF_{UCB} . After collecting this observation, the process is repeated. When sufficient data are collected, the GP predictive mean value f_{ϕ}^{GP} can be optimized to find the solution of the problem. Considering that the acquisition function AF_{UCB} is calculated using only the results currently being experimented with, it is possible to correct the process of navigating in the wrong direction due to the inaccurate prediction results of the MPNN model.

4.2.5 Acquisition function for HDO and rules for expanding the search space

In this section, I present my technique, named the learning to acquisition function, for efficient reaction optimization. To determine the next iterate χ_k based on the belief about f_{MPNN} and AF_{UCB} , given the history H_k , a sampling strategy is defined as follows:

$$AF_{HDO}\left(\chi_{k}\right) = \frac{N \cdot \left\{f_{\phi}^{MPNN}\right\}}{ln(t)} + N \cdot \left\{AF_{UCB}\left(\chi_{k}\right)\right\}.$$
(4.5)

In Equation 4.5, AF_{HDO} was designed for efficient optimization combining the current experiment driven priority model AF_{UCB} with the priority of f_{ϕ}^{MPNN} , obtained using a vast number of experimental documents for training. The normalization N is intended to prevent bias to one side by the values of the two acquisition functions and is calculated as equation 4.6 using min-max feature scaling.

$$N = \frac{x - x_{\min}}{x_{\max} - x_{\min}} \tag{4.6}$$

Under the influence of weight of AF_{UCB} , AF_{HDO} is induced to increase with the number of trials t to more closely reflect the results of the current experiment H. To dynamically expand the search space that was initially narrowed by MPNN models, if t exceeds 20 experimental trials and the accumulated maximum conversion yield is less than 10%, the search space is expanded by 10% after every five experiments. The MPNN model was implemented using PyTorch in Python. The BO module was facilitated by "scikit-optimize python library", and I used to "gp minimize function" for AF_{UCB} . The results of the experimental investigations are reported and discussed in the following section.

4.3 Performance benchmarking results

The ultimate goal of this study is to rapidly determine suitable conditions, given reactions with pre-defined search space. Optimizing reaction conditions is the process of exploring various types of reaction parameters, such as reagent, solvent, base, catalyst, concentration, and temperature. The number of their combinations could vary depending on the required parameter ranges. Owing to enormous cost and time, it is impossible to conduct all experiments for a combination of possible conditions. Therefore, an optimization process to define a reasonable scope of reaction conditions and to verify models that are rapidly navigable within that space is essential.

In Shields's study (Shields *et al.*, 2021), the authors provide experimentalyield results on all possible combinations of conditions in seven different reaction search spaces of three types of named reactions (Suzuki–Miyaura reaction, Buchwald–Hartwig reaction and Arylation reaction). Thanks to reasonable search scope with experimental yield results from through HTE, my proposed method was verified through that optimization dataset (Task 1). Moreover, 22 additional experiments were conducted using my HTE equipment to check how rapidly the proposed algorithm finds optimal conditions compared with organic synthetic experts (Task 2). The details of task and search spaces for Tasks 1 and 2 are described in Table 4.1. Table 4.1: Details of the two performance benchmarking tasks

			Summary	of seach spa	ce for each of task	(S		
		Task1 (vs	3. baselines, 50 huma	ns)		Task2(vs.	5 experties)	
	Target conditions	Suzuki-Miyaura	Buchwald-Hartwig	Arylation	Suzuki-Miyaura	Buchwald-Hartwig	Ullmann Reaction	Chan-lam Reaction
	/Reaction type	(1a)	(2a-2e)	(3a)	(4a-4j)	(5a-5h)	(6a, 6b)	(7a, 7b)
	Reactant1	3	I		I	ı	I	I
	Reactant2	4	3	I	I	ı	I	I
	Additive	I	22	I	I	ı	I	I
	Catalyst	I	4	I	6	6	2	2
No.	Base	7	3	4	×	6	13	3
	Solvent	4	I	4	4	5	IJ	4
	Ligand	11	ı	12	12	12	6	I
	Concentration	ı	I	3	I	ı	I	I
	Temperature	T	I	3	I	T	T	I
	Search space	3,696	792	1,728	3,456	4,860	4,095	84
	>95 (yields)	1.92%	4.48%	0.58%	T	T	T	I
	No. target products	1	5	1	10	×	2	2
No. 1	reactions to train GNN models	1,227,756	8,541	49,625	158,605	17,705	10,518	2,694

Task 1: Entire optimization dataset including search spaces with yield results of reactions are from Shields's study. In addition, methods as a baseline for verifying with previous works is also. Previous studies conducted highthroughput experiments on the class of Suzuki-Miyaura cross-coupling reactions. Twelve couplings of three electrophiles (Reactant 1) and four nucleophiles (Reactant 2) across the combinations of 11 ligands, seven bases, and four solvents were considered, thereby resulting in combinations for a total of 3,696 reactions with a product. Buchwald–Hartwig reaction (2a–2e): They conducted high-throughput experiments on the class of Pd-catalyzed Buchwald-Hartwig C-N cross-coupling reactions. They experimented with combinations of three aryl halides, four catalysts, three bases, and 22 additives for a total of 792 reactions per target product, of which there were five reactions. Arylation (3a): They studied the arylation of imidazoles, a key step in the commercial synthesis of the JAK2 inhibitor BMS-911543 (Fox et al., 2019; Ji et al., 2015). They selected a subspace consisting of 1,728 reactions including 12 ligands, four bases, four solvents, three temperatures, and three concentrations as a tractable set of experiments to be used as the ground truth. The data for the arylation reaction (3a) included results contributed by 50 expert chemists and engineers from academia and industry, who played the reaction-optimization game. The evaluation process employed by the experts did not rely on literature or dissertation data, as all optimization results were generated independently. The initial experiment involved carefully selecting a preferred combination of conditions based on the experts' extensive knowledge and experience. Subsequently, the experts meticulously examined the yield results, gradually identifying and selecting the most suitable combination of conditions, one step at a time. All the reaction data and expert information in reaction 3a used in Task 1 are accessible from https://github.com/b-shields/edbo/.

Task 2: Because HDO provides more general evaluations compared with

skilled synthetic experts, a total of 22 experiments were conducted on four named reactions. In this task, HDO was evaluated by comparing the yield results of the reaction conditions proposed by five experts in organic synthesis. A search space for each of the Suzuki–Miyaura (4a–4j), Buchwald–Hartwig (5a-5h), Ullmann (6a, 6b), and Chan–Lam reactions (7a, 7b) was defined by the experts and details are provided in Table 4.1.

4.3.1 Details of the list of candidates for optimization

Reaction condition candidate lists for optimal yield are determined in consideration of the subjective judgment and synthesis environment of experts. In particular, the definition of experimental conditions could be a reagent such as a catalyst and a solvent, or an experimental environment such as room temperature and pressure. In this study, I mainly focus on reagents. Experiments to find the optimal temperature and equivalent ratio are also included at (3a). In this section, the details of various experimental condition areas are defined. In task1, 1a), 2a-e) and 3a), the range set in Shields' study was benchmarked, and the details of candidates information are defined in Figure 4.4, 4.5 and 4.6 respectively. Fully experimental yield results for all combinations of conditions are provided in corresponding Shields' works. The list of candidates for task2 is described in Figure 4.7 and 4.8.

1a) Suzuki-Miyaura Reaction



Figure 4.4: Suzuki-Miyaura reaction with search space in task1

2a-e) Buchwald-Hartwig Reaction

NH2	×			Reaction	Y	Z	R
+	Î]	Additive (1 equiv.)		2a	CH	CH	CF3
Me	T_Z R	Base (1.5 equiv.) DMSO (0.1 M), 60 °C, 16 h	Me Z R	2b	CH	CH	OMe
	X = CI, Br, I	Dinoo (0.1 m), oo 0, 10 m	792 experiments each	2¢	CH	CH	Et
HTE results			Yield (%)	2d	Ν	CH	н
10 Ale 10	Strategy of the	CANANA COLOR	-100	2e	CH	Ν	Н
10 44 44	and the lot of	144 224	- 75				
1. 10 10	2.7.7	6.114 4.1.1	- 50				
		1999 - 111	- 25				
	and a start of the						

Target candidates of conditions.

	Count	Reactant2	Ligand	Base	Additive
	1	C1	XPhos	P2Et	4-Phenylisoxazole
	2	Br	t-BuXPhos	BTMG	5-phenylisoxazole
	3	I	t-BuBrettPhos	MTBD	3-Phenylisoxazole
	4		AdBrettPhos		Ethyl 3-Methylisoxazole-5-carboxylate
	5				3-Methylisoxazole
	6				Ethyl 5-methylisoxazole-3-carboxylate
	7				5-Phenyl-1,2,4-oxadiazole
	8				5-Methylisoxazole
	9				Ethyl isoxazole-3-carboxylate
Target	10				Anthranil
	11				Ethyl 5-Methylisoxazole-4-carboxylate
conditions	12				3,5-Dimethylisoxazole
	13				Ethyl isoxazole-4-carboxylate
	14				Ethyl isoxazole-5-carboxylate
	15				1,2-benzisoxazole
	16				5-(2,6-difluoro-phenyl)-isoxazole
	17				3-methyl-5-phenylisoxazole
	18				5-methyl-3-pyrrol-1-yl-1,2-oxazole
	19				5-furan-2-y1-isoxazole-3-carboxylic acid methyl ester
	20				Methyl 5-phenylisoxazole-3-carboxylate
	21				Ethyl 3-methoxy-1,2-oxazole-5-carboxylate
	22				N,N-dibenzyl-1,2-oxazol-5-amine

Figure 4.5: Buchwald-Hartwig reaction with search space in task1

3a) Arylation reaction



		030110	Ducit	08000110	0.100	120
	4	CsOPiv	DMAc	PPht-Bu ₂		
	5		-	PPhMe ₂		
Target	б		-	XPhos		
conditions	7		-	BrettPhos		
	8			t-BuPh-CPhos		
	9			JackiePhos		
	10			PPh ₂ Me		
	11			PPh ₃		
	12			P(fur)3		
-						

Figure 4.6: Arilation reaction with search space in task1

4a-j) Suzuki-Miyaura Reaction

Target candidates of conditions.	
----------------------------------	--

	Count	Catalyst	Base	Solvent	Ligand
	1	Pd(PPh ₃) ₄	NaHCO3	THF/H ₂ O (3:1)	PPh:
	2	$[PdCL(C_3H_5)]_2$	Na_2CO_3	Dioxane/H2O (3:1)	t-Bu₃P
	3	Pd(dppf)Cl ₂	K ₂ CO ₃	Toluene/Ethanol/H2O (3:1:1)	t-Bu3P-HBF4
	4	Pd(PPh ₃) ₂ Cl ₂	K ₃ PO ₄	DMF	PCy:
	5	Pd(OAc) ₂	Cs2CO3		BINAP
Target	6	Pd(dba)2	NaOh		XantPhos
conditions	7	Pd ₂ (dba) ₃	Ba(OH) ₂		DPEPhos
	8	PdCl ₂ (cod)	KOAc		Dppi
	9	PdC12			Dppp
	10				SPhos
	11				XPhos
	12				t-BuXPhos

5a-h) Buchwald-Hartwig Reaction

Target	candic	lates	of	cond	itions.
runger	ounone	nuces	~	cond	reromo.

	Count	Catalyst	Base	Solvent	Ligand
	1	Pd(PPh ₃) ₄	NaOtBu	THF	PPh
	2	[PdCL(C3H5)]2	NaOEt	Dioxane	t-Bu ₃ I
	3	Pd(dppf)Cl ₂	KOtBu	Toluene	t-Bu ₃ P-HBF
	4	Pd(PPh ₃) ₂ Cl ₂	KOEt	Xylene	PCy
Target	5	Pd(OAc) ₂	KOH	DMF	BINA
	6	Pd(dba)2	K ₂ CO ₃		XantPho
conditions	7	Pd ₂ (dba) ₃	K ₃ PO ₄		DPEPho
	8	PdCl2(cod)	Cs2CO3		Dpp
	9	PdC1 ₂	NaOH		Dpp
	10				SPho
	11				XPho
	12				t-BuXPho:

Figure 4.7: The candidates of conditions for Suzuki-Miyaura and Buchwald-Hartwig reaction in task2

6a-b) Ullmann Reaction

Target candidates of conditions.

	Count	Catalyst	Base	Solvent	Ligand
	1	Cu(I)	NaOtBu	MeCN	DL-Proline
	2	CuI	NaOEt	Dioxane	Picolinic acid
	3	CuBr	KOtBu	Toluene	DMEDA
	4	CuO	KOEt	DMF	DMCyDA
Target	5	Cu ₂ O	KOH	DMSO	Phenn
	6	Cu(OAc)2	K ₂ CO ₃		diMeO-Phenn
	7	CuSO ₄	K ₃ PO ₄		TetraMe-Phenn
conautons	8		Cs2CO3		Dipivloylmethane
	9		NaOH		Quinolinol
	10		NaHCO3		
	11		Na ₂ CO ₃		
	12		Ba(OH) ₂		
	13		KOAc		

7a, b) Chan-lam Reaction

Target candidates of conditions.

	Count	Catalyst	Base	Solvent
	1	Cu(I)	TEA	Methylene chloride
	2	CuI	Pyridine	Methanol
_	3	CuBr	DIEA	Ethanol
Target conditions	4	CuO		MeCN
contantons	5	Cu ₂ O		
	6	Cu(OAc) ₂		
	7	CuSO ₄		

Figure 4.8: The candidates of conditions for Ullmann and Chan-lam reaction in task2

4.3.2 Performance of MPNN condition prediction models

I evaluated the reaction condition prediction performance of the proposed HDO's message passing neural networks with other models. For each data set, an 80/10/10 train/ validation/test split was adapted for the validation. Training and test sets were randomly selected for consistent among the model types for comparability. As inputs for models were prepared as two reactants and one product structure pairs, with encodings tailored to each training model.

All models were trained using binary cross-entropy loss to output probability scores for all conditions labels in the reaction dataset. The top-k ranked labels in each category were selected as the final prediction, where k is userdetermined. Given the variable class imbalance in each category, accuracy is evaluated at the categorical level as follows:

$$A_c = \frac{1}{N} \sum_{i=1}^{N} \left[\hat{Y}_i \cap Y_i \right] \tag{4.7}$$

Where $_i$ and Y_i are the sets of top-k predicted and truth conditions for the i-th sample in condition category c, respectively. The correct values are summed and divided by the number of samples in the test set, N, to give the overall test accuracy in the category or A_c .

Proposed condition prediction model was tested on the four reaction type (Suzuki-Miyaura, Buchwald-Hartwig, Chan-lam and Ullmann reaction), graph convolution networks as reported by Schlichtkrull, et al. (GCN) my MPNNs developed here (MPNN), and deep neural networks model using extended connectivity finger print (ECPF) as a representation (Deep N.N) models as a baseline. Based on the top-k average measures for each category, the MPNN has good performance than the baselines. In particular, the prediction models using graph-type representation (GCN and MPNN) improve performance

		Reactio	on type	
	Suzuki-	Buchwald-	Illmann	Chan-lam
Catagory	miyaura	Hartwig	Omnann	Unan-iam
Category		Number	of Class	
Catalyst	9	9	7	7
Base	8	9	13	3
Solvent	4	5	5	4
Ligand	12	12	9	-
No. Train	128,605	$14,\!165$	8,416	$2,\!154$
/Validation	/15,000	/1,770	$/1,\!055$	/270
/ Test	/15,000	/1,770	$/1,\!051$	/270

 Table 4.2:
 Validation dataset for MPNN's performance.

by more than 10% and 11% on average compared to models using ECFP, respectively.

Dataset	Top-k	Category	Deep N.N	GCN	MPNN
		Average	74.88	80.89	83.48
		Catalyst	75.15	81.15	83.22
	Top-1	Base	77.15	80.41	84.71
		Sovent	78.35	84.80	88.90
Sugal: Miroupo		Ligand	68.87	77.20	77.10
Suzuki-imiyaura	Top-3	Average	87.29	90.41	92.97
		Catalyst	87.58	90.15	94.11
		Base	88.24	91.54	91.54
		Sovent	94.11	95.78	98.91
		Ligand	79.22	84.18	87.32
		Average	75.03	81.19	82.20
		Catalyst	77.34	80.19	83.22
	Top-1	Base	78.32	81.25	81.12
		Sovent	77.34	87.11	87.34
Buchwald-Hartwig		Ligand	67.12	76.21	77.11
	Top-3	Average	86.71	92.40	92.73
		Catalyst	84.35	93.58	94.11
		Base	84.49	91.75	92.38
		Sovent	88.11	97.41	97.11
		Ligand	89.88	86.85	87.32

 Table 4.3: Performance of accuracy in Suzuki-Miyaura reaction and Buchwald-Hartwig reaction

Dataset	Top-k	Category	Deep N.N	GCN	MPNN	
Chan-lam	Top-1	Average	85.39	93.04	93.08	
		Catalyst	85.42	90.28	91.22	
		Base	97.22	97.72	97.72	
		Sovent	78.44	92.52	91.31	
		Ligand	-	-	-	
	Top-3	Average	92.54	97.32	97.44	
		Catalyst	92.33	95.51	95.71	
		Base	100	98.25	98.41	
		Sovent	89.88	98.19	98.18	
		Ligand -		-	-	
Ullmann	Top-1	Average	75.28	81.13	80.06	
		Catalyst	88.22	90.18	90.22	
		Base	65.44	74.58	70.44	
		Sovent	85.12	88.65	88.85	
		Ligand	62.32	71.10	70.76	
	Top-3	Average	83.29	89.11	88.50	
		Catalyst	92.33	96.58	95.71	
		Base	74.22	81.18	81.65	
		Sovent	92.32	98.32	97.11	
		Ligand	74.26	80.15	79.54	

Table 4.4: Performance of accuracy in Ullmann reaction and Chan-ram reaction

4.3.3 Task1: Optimization of reaction conditions to benchmark the performance

I targeted a number of experimental trials (NT) to achieve the top 1, 5, and 10% yields in the entire search space of reaction conditions as a performance measurement.

$$AIR^{c} = \frac{1}{i} \sum_{i=1}^{k} \frac{ANT^{RS} - NT_{i}^{c}}{ANT^{RS}}$$

$$\tag{4.8}$$

I calculated the average improvement rate (AIR) over a "Random Search" of NT^{RS} as the performance indicator to allow for comparison with other baselines (Equation 4.8).

Here, i is the number of iterations required for the overall optimization process, and I used 1,000 iterations for all the models. In each optimization model, NT_i^c is the NT in the c category of baseline models (Random Forest(RF) (Pedregosa *et al.*, 2012), BO, humans (Shields *et al.*, 2021), and message passing neural network (MPNN) (Gilmer *et al.*, 2017b), and HDO). In table 4.2, ANT^{RS} represents the average of NT results from i iterations of random search, and I determined k to be 1,000 in this task.

Reaction	Target	Тор	Target	Random	RF BO		MPNN	Human	HDO
\mathbf{type}	Inget	-k	yield	Search	ItI	БО	1011 1010	(50 experts)	(Ours)
				ANT	Average Improvement R			ate over ANTRS (AIRc)	
Suzuki- Miyaura	1(a)	1	96.20	98.15	0.1884	0.5888	0.6589	-	0.6685
		5	92.52	19.55	0.0925	0.3750	0.4740	-	0.4740
		10	88.19	9.51	0.2460	0.4440	0.6900	-	0.6900
Buchwald- Hartwig	2(a)	1	52.67	99.15	0.2244	0.7585	-0.1985	-	0.6642
		5	47.94	18.54	0.1175	0.4245	-0.1725	-	0.3956
		10	44.65	8.99	0.1060	0.4850	0.3850	-	0.4420
	2(b)	1	83.09	97.54	0.2068	0.5846	0.5149	-	0.6885
		5	79.06	19.54	0.0750	0.4395	0.3220	-	0.5505
		10	73.58	9.15	0.1850	0.4555	0.3850	-	0.5850
		1	94.38	98.01	0.2844	0.5565	-0.0846	-	0.5585
	2(c)	5	86.76	19.44	0.0675	0.3725	-0.0670	-	0.3425
		10	81.27	8.95	0.1890	0.5420	-0.2510	-	0.3856
	2(d)	1	65.46	98.18	0.2549	0.6185	-0.1785	-	0.6745
		5	52.56	19.24	0.2175	0.1940	0.1440	-	0.2210
		10	49.15	8.97	0.2850	0.5100	0.3500	-	0.5850
	2(e)	1	97.56	99.54	0.3085	0.6785	-0.2485	-	0.6986
		5	91.05	19.54	0.2245	0.3984	0.1245	-	0.4125
		10	86.25	8.96	0.1850	0.3750	0.1200	-	0.4850
Arylation	3(a)	1	91.21	98.66	0.1846	0.7485	0.4785	0.6382	0.7243
		5	76.54	19.81	0.2520	0.4210	0.3345	0.4225	0.4560
		10	59.11	9.43	0.444	0.5812	0.4210	0.6750	0.6950

Table 4.5: Comparison of reaction optimization performance with the baselineson Task 1

 AIR^c represents the average improvement in the performance of baseline models (RF, BO, MPNN, and Human) and the proposed model (HDO) over the naive approach ANT^{RS} . AIR 0 indicates the same average number of trails as the random selection approaches. When AIR has a negative value, the number of trails to determine the combination of conditions with a target yield is more attempted than ANT^{RS} . Table 4.5 shows the top 1, 5 and 10% target yields in the entire search space and the AIR for the RF and BO models as reported by Shields et al. In message passing neural network (MPNN), the GNN-type-condition prediction models are trained separately for each condition type (*e.g.*, solvent, catalyst, etc.), and the highest-rank conditions inferred for each condition type were combined and chosen as first combination for an experiment. Furthermore, the yield results were not reflected, and the following conditions were selected considering only the inferred priority using MPNN models.

The results in Table 4.5 indicate that HDO significantly outperformed the base models across the categories for the top 1, 5, and 10% optimization tasks. HDO exhibited a stable optimization for the suitable combination of conditions in the case of Suzuki–Miyaura reaction, which had abundant training data, including the Buchwald–Hartwig reaction, which had a small reaction dataset for training models. The basic strategy of HDO is designed to be efficiently explored by conducting experiments of conditional combinations initially recommended by the MPNN but quickly modifying the weight of the conditional combination chosen by BO if the yield results are not better than those expected.

In the optimization task of Suzuki–Miyaura reaction 1(a), both HDO and MPNN trained approximately 1.2 million reaction data, finding optimal conditions very rapidly compared with others. However, in the case of Buchwald–Hatwig reaction 2(a–e), because of few training data, MPNN exhibited even less AIR than random search in a method recommended only by a combination of highly inferred conditions without optimization techniques. In case 2(a), BO achieved good performance, the distribution of yield values of all reactions within the search space were relatively lower than others.

Reaxys database, which I used for training MPNN models, tends to be biased because the data are extracted from relatively successful research papers (without negative data). Therefore, MPNN models trained using the corresponding data do not yield good results for the optimization task with low yield distributions. These scores indicate the limitations of an optimization approach based only on exploitation. Similarly, the HDO model also performed well in the Suzuki–Miyaura reaction over BO, which has a cold-start problem. Likewise, for the top 5 and 10% yield searching cases in Arylation reaction 3(a), the AIR of HDO was higher than those of the human experts and BO although BO is the best for the top 1%. Overall, the proposed model HDO determined the best combination of conditions for a high yield compared to other optimization algorithms and human experts. It is necessary to determine a strategy that stably and efficiently searches for the conditions via repeated optimization experiments.

Figure 4.9 shows the results of AIR^c , which were repeated 100 times, with a box-and-whisker plot to determine a condition combination with a yield value or more corresponding to the top 5% of the total search area. HDO stably determined suitable conditions in various optimization tests. In Suzuki–Miyaura reaction optimization test, where training data were abundant, the variance appears to be relatively small because the HDO rapidly determined the optimal conditions predicted by the MPNN initially embedded in the HDO.

To validate in the initial selection algorithm of the proposed HDO method, in the reaction experiment 1a), 12 experiments are split into reactants combinations to find the optimal solvent, base and ligand combinations. Through


Box plot for performance comparison between algorithms

Figure 4.9: Box-and-Whisker plot for comparison of performance (top-5%).

this, the proposed HDO confirmed that the initial experimental condition selection module finds the highest yield on average in nine of the twelve experiments. (Blue area)

This was additionally verified to efficiently determine the optimal conditions in the case of relatively large number of training data in Task 2. In the Buchwald–Hartwig case, which has little training reaction data, HDO stably exhibited best AIR^c results for the three reaction types (2b, c and e) of the five reactions. The BO including the initial 10 random selections could be luckly to find the best conditions rapidly, but it occurs less frequently and has a high



Figure 4.10: Task1 : Detailed results for Suzuki-Miyaura reaction experiments(1a-1)

variance value. The HDO is designed for stable and efficient optimization by immediately increasing the priority weight of BO in HDO when unsatisfactory yields appear in initial experiments chosen by the MPNN (the weight conversion process is discussed in detail in the methods sections).

Furthermore, HDO is designed to solve the cold-start problem of BO. Figure 4.13 shows the cumulative maximum observed (CMO) yield according to



Figure 4.11: Task1 : Detailed results for Suzuki-Miyaura reaction experiments(1a-2)

the number of experiment trials compared with BO and 50 experts in the Arylation reaction. The proposed HDO discovered high-yield conditions in the early stages compared to state-of-art algorithms and 50 synthetic experts (details of human information are described in Shields's study). However, the CMO of HDO appears to have stagnated search performance in approximately 42 experiment trails, where conditional combinations with yields of nearly 98%



Figure 4.12: Task1 : Detailed results for Buchwald-Hartwig experiments(2a-e)

or more were found.



Comparison of the performance in Arylation reaction

Figure 4.13: Performance comparison of the BO, 50 expert chemists, and HDO for the Arylation reaction. The results of 50 experiments with HDO and BO are represented by a dotted line, and the solid line represents their average values. Likewise, the different optimization results with 50 humans are represented by dotted lines, and their average values are represented by black solid lines.

4.3.4 Task2: Validation of the HDO compared to five human chemists

In task2, the performance of the proposed HDO was compared with five organic synthetic chemists in 22 additional optimization experiments. The purpose of this task was to determine the number of trials required for the HDO to determine the condition combination recommended by a group of five chemists. The five experts for Task 2 had doctorates with more than 10 years of experience in organic synthesis. The reaction experiments in Task 2 were 22 different named reactions of four types (the Suzuki-Miyaura, Buchwald-Hartwig, Chan-Lam, and Ullmann reactions).

As described in Table 4.1, I prepared 20 reactions to optimize around reagents, with a combination of 3,456 - 4,860 conditions, and two experiments of Chan-Lam reaction with only 84 search spaces were also tested. All of the experiments were conducted using my own HTE system including autonomous robots for synthesizing and calculating conversion yield values using liquid chromatography equipment (Burger *et al.*, 2020; Buitrago Santanilla *et al.*, 2015; Häse *et al.*, 2019; Perera *et al.*, 2018). First, five chemists were given a search space with reactants and product structures and the combination of conditions expected to have the highest yield was recommended.

I conducted experiments using the proposed combinations of conditions and averaged the yield values of each result. The average yield for the 22 reactions calculated by the five chemists was 64.48, as described in Figure 4.14. Likewise, given reactants and product structures, HDO recommended the six highest-priority conditional combinations in the search space for the initial experiment. When the experimental results are output, the yield value is reflected in the HDO objective function and the next optimal condition combination is recommended. I conducted up to 70 experiments per reaction and stopped the experiment early when conditions with a yield value of 95% or



Figure 4.14: Average cumulative maximum observed yields using the HDO (blue curve), and the average yield of the combination of conditions proposed by five experts (black dotted line). HDO required an average of 4.7 experiments to determine the conditions with the same average yield obtained with the combination of conditions proposed by the five experts for the 22 reactions.

more were found. The average cumulative maximum observed yields of HDO are shown in Figure 4.14 with the yield recommended by the five chemists. On average, HDO determined the suitable conditions with the yield value of condition combinations recommended by the five experts in 4.7 experiments. The performance varied for each of the four aforementioned named reactions. Because the Reaxys database contains 158,605 training data for the Suzuki-



Figure 4.15: Performance of HDO for the four named reactions. Comparison of the yield results of HDO with the conditions proposed by the experts for the Suzuki–Miyaura, Buchwald–Hartwig, Chan–Lam, and Ullmann reactions. On average, HDO identified suitable conditions after only 4.22, 1.90, 3.84, and 7.15 experimental trails for these four reactions, respectively.

Miyaura reaction, the HDO based on the MPNN quickly identified the reaction conditions that delivered the yield of the combination of reaction conditions recommended by experts in an average of 4.22 trials for 10 reactions.

However, as is evident from the cumulative number of experiments, synthesis with the Suzuki–Miyaura reaction is easier than with the other named reactions. Therefore, the experts also tended to swiftly determine an effective combination of conditions for this reaction. In the eight experiments based on the Buchwald–Hartwig reaction, both HDO and the experts experienced difficulties in identifying reaction conditions with a high yield. Except for the reaction shown in Figure 4.15, all of the reactions yielded poor results, yet, even in these difficult situations, HDO found expert-level yields after 1.9 trials on average. For the Ullmann and Chan-Lam reactions, HDO required an average of 7.15 and 3.84 attempts, respectively, to identify the combination of conditions proposed by the experts. The corresponding details are provided in Figure 4.15.

All reaction results for an individual experiment corresponding to the number of trials in Task2. In case of Suzuki-Miyaura reaction (4a-j), based on vast experimental data for Graph Neural Networks, the HDO found an optimal combination of conditions that conversion yield close to 100% in most 6 trails (initial experiments) in 8 of 10 experiments. In Ullmann and Chan-lam reaction, which has relatively small experimental data, it could be seen that the optimal conditions are not initially found, but the optimal yield is found while repeating. On average, HDO finds conditions within the 4.7 trials that satisfy the yield of the combination of conditions proposed by five organic synthesis experts as represented as Figure 4.16. Ten optimization process for HDO performance tests, in six experiments, HDO find the optimal combination of conditions that achieve 100% conversion yield within 10 trials.

Finally, Figure 4.18 shows the examples of each named reaction. In the Suzuki-Miyaura reaction 4(a) in Figure 4.18, HDO determined the same combination of conditions with the same yield value as the experts and required a single experimental trial. In examples 5(b) and 7(a) in Figure 4.18 for the Buchwald-Hartwig and Ullmann reactions, respectively, HDO obtained higher yield results than the experts with different combinations of reaction conditions and required two experimental trials in both cases. These are the ex-



Figure 4.16: Details of optimization for 4a-j, 5a-h, 6a-b, and 7a-b.

amples of the optimal condition combinations determined using the MPNN models for the initial five experiments.

In these cases, similar experiments were included in the training data, which are predicted examples. In marked contrast, the Chan-Lam coupling reaction in 6(b) required 20 experimental trials to identify the reaction conditions with a conversion yield similar to that of the reference. Nevertheless, the proposed HDO algorithm demonstrated optimization performance comparable to that of the experts and demonstrated reliable and efficient navigation



Figure 4.17: Task2 : The details of Suzuki-Miyaura reaction

capabilities for a variety of combinations of reaction conditions.



Figure 4.18: 4(a) is an example of Suzuki-Miyaura coupling reaction. The HDO found the same conditions as 5 experts in two trials. 5(b) showed that in just one experiment, finding better lists of conditions than 5 experts in Buchwald-Hartwig amination reaction. In 6(c), similar performance condition lists to those of experts were found 17 trials in Chan-Lam reaction that lacked reaction data for the training model. On the other hand, in the 7(d) experiment of the Ullmann reaction, HDO found a combination of high-yield conditions compared to experts in 3 trials.

4.4 Results and discussion

Searching for optimal high-yield reaction conditions requires a lot of resources and is time-consuming. In this study, I proposed a method for efficiently exploring suitable synthesis reaction conditions, given reaction structures (reactants and target a product) with a condition search space. As a baseline, BO is a progressive solution to determine suitable conditions, but initial experimental results are inevitably required for training surrogate models to infer conditions. This causes a cold-start problem. Moreover, data-driven approaches such as GNNs can determine optimal combinations of conditions in the early stages of the optimization if they have sufficient chemical-reaction data, such as that of the Suzuki–Miyaura reaction. However, for lack of training data and novel reactions, the predictive performance of the GNN model can be low.

Therefore, I designed the hybrid-type dynamic optimization (HDO) method to compensate for the above-mentioned shortcomings while utilizing the advantages of the two approaches. Given reaction structures, GNN models based on MPNN predict appropriate reaction conditions. I utilized priorities of combinations of predictive conditions using a GNN for initial experiments. The experimental results (yield) were used for BO surrogate model training to select the next combination of conditions, and the optimization direction was dynamically modified based on the number of trials and observed yields. This approach enables an intuitive sampling policy to efficiently accomplish global optimization.

As a result, in experimental simulations, HDO could determine the optimal conditions that satisfied the target yield faster than other baselines. To further investigate the performance of HDO, I additionally prepared condition optimization tasks for synthesizing 22 target products and confirmed the number of experiments for HDO to attain the level of five specialists in organic synthesis. The HDO approach also met the target yield by swiftly identifying a combination of reaction conditions that were either the same or similar to those proposed by the synthesis experts (requiring approximately 5, 10 times less time) for four named reactions. Ultimately, I expect this method to serve as an enabling tool for searching promising chemical species and optimizing the structures of materials for various applications in the field of materials discovery.

Chapter 5

Conclusions

In organic synthesis, chemical reaction optimization is an essential process to discover novel target materials. Chemical reactions typically have numerous controllable factors such as catalysts, solvents, bases, ligands, temperatures, and concentrations that need to be optimized to yield the desired products. But, an experiment with one combination of condition candidates is required approximately 12 hours, as well as the high costs needed for reagents with laboratory equipment, and specialized synthesis and analysis chemists. Therefore, minimizing the number of experiments to obtain high yields is an integral part of the discovery novel materials.

Previously, to handle this problem, in design of experiment, researchers adopted a this method of setting up plans and revising the direction of the next experiment by comparing hypotheses and results before conducting their own experiments. In this case, many unnecessary combinations of experimental conditions should have been tested, and inefficient biased experiments such as relying on expert background knowledge or searching for literature can be designed. In manual experiments, the periodic inspection of reaction state is a laborious work, so the reactions usually proceed for a sufficient time. This sometimes accompanies a problem of yield loss owing to side reactions or waste of time by providing excessive span than necessary. Also, considering various reaction conditions is caused the curse of dimensionality. Recently, in order to solve this inefficient design of experiments methodology, a machine learning algorithm has been proposed. But, they are all far from domain-knowledge of organic synthesis, which only predicts independent condition candidates, but does not consider combinations of condition factors. Finally, there was an approach to optimize reaction conditions using the Bayesian optimization. However, since they randomize the initial experiment without considering the difficulty of the reaction, the cold start problem still remains in the optimization strategy. In addition, most of the target conditions are composed of discriminated parameters, so they do not fit the traditional Bayesian optimization strategy.

Summary of the five challenges in traditional approaches:

- 1. High dependence on individual chemists "experience" and "knowledge"
- 2. Non-convex problem, multi-global minimum points
- 3. Considering the correlation among the conditions
- 4. Measurement for difficulty level of synthesis
- 5. Cold-start problem in novel reaction optimization

In my doctoral study, to efficiently explore the suitable chemical reaction conditions, I approach as follows to solve the five challenges of the traditional methods remarked.

• First study : a generative model that defines the search space and considers combinations of conditions to calculate priorities for initial experiments. (Challenges 1, 2, and 3)

- Second study : a predictive distribution of the yield is modeled as a graph neural network that directly processes a set of graphs with permutation invariance for inference of a difficult of synthesis. (Challenge 4)
- Third study : a strategy for efficiently searching best combination for high-yield product, given chemical reaction search scope. (Challege 5)

In the first study, I proposed a generative model to narrow the candidates of reaction conditions into a reasonable space. Because of the curse of dimensionality, the more diverse the candidates of a condition item, the more the search area can approach infinity. The method used in this study developed a variational auto-encoder model that can generate optimal conditions whiles considering the compatibility among conditions using proposed model. The method modeled the generative distribution of reaction conditions by introducing a VAE augmented with GNN. By repeated sampling from the distribution, multiple candidates of conditions can be obtained. Through this process, a narrowed initial search space was defined and it makes easier to explore the search space. Especially, in chemistry area, it does not have one correct conditions for one reaction, compared with previous studies, this study is the first attempt to predict multiple reaction conditions, each in the form of a complete specification of the reaction elements for a chemical reaction. I believe that the proposed method is the more general-purpose and realistic condition prediction model.

As the second experiment, a method for measuring a difficult of chemical reactions was built using the uncertainty-aware graph neural networks by training reaction and yield dataset. The model was designed to consider both the reliability of the biased reaction dataset and GNN models. Chemical synthesis experiments affect the results, but there are various factors that cannot be quantified. I measured the difficulty of the experiment by considering how sensitive the experiment is to the influence of these factors and the deviation that may occur due to the small number of data itself as uncertainty.

In the final study, I designed and implemented an algorithm that determines the priority of combinations of reaction conditions in predefined search space. Utilizing the two methodologies proposed above, I had proposed an algorithm that reduces the search space to a reasonable range and efficiently explores the optimal combination of conditions, taking into account the difficulty of the reaction. This algorithm effectively modifies the strategy as the reaction progresses, dynamically adjusting to select different candidates when the experiment is difficult and the yield of the initial reaction is low. The proposed algorithm had been directly verified with advanced approaches and synthesis experts in various experiments through a high-throughput experiments equipment.

Through the proposed tailor-made optimization algorithm fit in organic synthesis, the five challenges of previous works were clearly solved. However, the field of organic synthesis is still an unknown world, and there are many challenges such as synthetic mechanism, considering the by-product and etc. This dissertation critically examines the limitations inherent in the proposed optimization framework, encompassing three key perspectives.

First, a major limitation lies in the use of a synthetic reaction representation for machine learning. Specifically, the graph-type molecular structural representation employed in this study lack a crucial three-dimensional isomer structure representation. This limitation is of paramount importance since the isomer structure product ratio can have a profound impact on synthesis outcomes. Failure to incorporate this critical aspect can lead to detrimental results, undermining the reliability of the optimization framework. Furthermore, when machine learning models rely on a reaction representation, another limitation arises due to the absence of learning methods that account for physical properties. The exclusive focus on structural features while disregarding material-specific components results in the loss of valuable information.

Second, the reaction conditions and yield data in Study 1 and Study 2, which heavily rely on data extracted from published papers. Primarily, the majority of data available in these papers solely represent successful synthetic experiments, lacking relatively failed experimental data. Consequently, the synthesis difficulty prediction model exhibits limitations due to the absence of crucial information from unsuccessful attempts. To overcome this limitation, it is suggested that data accumulation includes the incorporation of by-products generated during synthesis and employs negative sampling techniques utilizing the by-product ratio. Moreover, for an accurate determination of the actual isolated yield value, it is imperative to include conditions for analysis and purification in the synthesis experiments. These particular limitations persist, demanding further attention and consideration for comprehensive and accurate yield calculations.

Third, This study focuses on the optimization of reaction condition categories, specifically examining the recommended rage of categories. Table 4.1 shows the current scope of condition categories proposed in the research. Each condition combination comprises approximately 10 candidates from each category, with up to five types of categories included. But it is acknowledged that beyond this scope, the categorization becomes increasingly complex, relying heavily on heuristic experience. Consequently, the search for high-yield condition combinations necessitates a significant number of experiments to explore the extensive parameter space effectively.

The framework presented in this study aims to facilitate the mounting and validation of equipment capable of synthesizing compounds in substantial quantities while assessing their yields through high-performance highthroughput experimentation (HTE) equipment. Although certain types of experiments may not yield quick identification of optimal conditions, the optimization strategy implemented in the framework allows for the selection of various condition combinations as the experiments progress. Through minor adjustments and the fixation of certain conditions, optimal conditions are eventually discovered. While the proposed framework remains incomplete, it holds immense potential for gradual improvement, especially with the anticipated advancement and mass production of HTE equipment in the future.

The dissertation outlines the following descriptions of its academic and industrial contributions. The academic contribution of this doctoral dissertation lies in the proposal and development of an innovative approach for optimizing chemical reaction conditions in organic synthesis. By combining machine learning methodologies and Bayesian optimization techniques, the study effectively reduces the exploration range, quantifies the difficulty of synthesis experiments, and guides efficient optimization strategies. The research encompasses three key areas: narrowing down the range of conditions to be explored based on input reactions and structural information, predicting yield and uncertainty in synthesis reactions with a focus on biased and inconsistent experimental datasets, and optimizing experiment conditions using a sequential approach that balances machine learning predictions and Bayesian optimization. This dissertation offers valuable insights and practical solutions to address the challenges and trade-offs involved in chemical reaction optimization, ultimately contributing to the advancement of the field and facilitating more efficient discovery of novel drugs and materials.

The industrial contribution of this study centers around the exploration of synthesis conditions, enabling the production of high-rate substances at double the previous speed. This advancement not only reduces total synthesis time and minimizes the consumption of expensive reagents but also offers quantitative and qualitative savings in human resources. Unlike relying solely on knowledge and experience, which can lead to varying optimization performance across experiments, the proposed approach provides stable and reliable searches for optimal conditions. Notably, skilled synthetic personnel can identify the optimal condition combinations within an average of 4.7 experiments, even successfully synthesizing high-yield objects in cases where researchers may have previously encountered challenges or considered abandonment, all facilitated through the implemented optimization framework.

In conclusion, this research has successfully developed an optimization algorithm specifically designed for the efficient exploration of suitable chemical synthetic conditions. By employing the approaches described above, it is anticipated that the proposed algorithm will make a meaningful contribution to the development of the cheminformatics society. This algorithm holds the potential to enhance the overall efficiency and effectiveness of chemical synthesis processes, furthering the advancements in the field of cheminformatics and its applications.

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국문초록

합성 반응 최적화는 신약, 신소재 발견 가속화를 위한 필연적 도구다. 목적에 따라 새롭게 설계된 분자 구조를 합성하려면, 다양한 실험 조건 변수들을 최적화해야 한다. 신속하게 최적 조합을 찾는 것은 신약, 신물질 개발의 긴 주기를 줄일 수 있 는 핵심 요소 중 하나다. 유기 합성물은 신약, 광학, 반도체, 베터리 소재 분야까지 다양한 산업에 직접적으로 기여하며 특히, 합성 실험은 매우 높은 금전적 비용, 합성 시간 그리고 전문가 인력이 요구되기 때문에 개발 시간을 단축시키는 것은 아주 중요한 일이다. 그러나 빠르게 합성 조건을 찾아 적절한 합성법을 제안하기 위해서는 몇 가지 문제가 있다. 먼저, 모든 실험들은 독립적 관계를 가지기 때문 에 기존의 최적화 방법론을 활용하기 위해서는 cold-start 문제를 가지고 있다. 또한 기계학습을 위해 3차원의 분자구조에 맞는 표현자를 고려해야 하며, 편향된 실험 데이터와 유기 합성의 미지영역에서 기인하는 난해한 합성 난이도 수치화는 최적화 과정을 더욱 어렵게 만든다.

본 박사학위논문은 축적된 실험데이터를 활용하는 기계학습적 접근법과 베 이지안 최적화 기법을 융합해, 효율적으로 탐색 범위를 정하고, 실험의 난이도를 수치화 하여 최적화전략을 구성하는 방법과 반복되는 실험 결과를 동적으로 최 적화전략에 반영해 합성 최적화의 trade-off 문제를 풀도록 제안한다. 본 연구는 최적화를 위한 탐색 영역을 효과적으로 줄이고 합성 난이도를 수치화 해 효율적인 최적화 전략을 취할 수 있도록 유도하는 것을 목적으로 한다.
첫 번째 연구는 입력되는 반응, 합성물들의 구조정보에 맞춰 수많은 조건 탐색 범위를 효과적으로 줄이는 것에 있다. 실험 합성 조건들의 조합은 적게는 수천개 에서 많게는 수십만개의 조합이 가능하며 현실적으로 모두 실험할 수 없다. 본 연구에서는 입력된 합성 반응, 합성물의 3차원 분자구조 정보를 그래프 형태의 표현자를 생성해 조건 간 의존성을 고려하여 범위 내에서 다양한 조건 조합을 생 성하는 모델을 제안했다. 기존에는 입력되는 반응 정보에 맞춰 조건 별 후보들의 순위를 매기는 형태로 접근했지만, 제안하는 모델은 variational auto-encoder를 활용해 조건 간의 궁합을 학습할 수 있도록 해 무의미한 조건 조합을 피하도록 설계해 다양하면서도 정확한 조건 조합을 예측하는 것이 가능했다.

두 번째 연구는 입력된 반응, 합성물, 조건 시약 구조 정보를 모두 학습에 용 이하며 3차원 분자구조 정보를 최대한 보존할 수 있는 그래프 형태의 표현자를 생성하고 실험의 수율을 예측하는 것에 있다. 특히 합성 실험 논문에서 추출하 고 정제한 100만건의 합성 실험 데이터는 다소 편향적이며 비일관적인 데이터가 존재해, 정확도가 높은 수율 예측 모델을 만들기 위해서 비일관적인 실험 상황 에서는 모델의 불확실성이 높아 지도록 구성했다. 학습된 모델을 토대로 예측된 수율값과 모델 간의 편차를 활용해 합성실험의 난이도를 수치화 했으며 합성 실험의 수율을 예측하는 기존 연구들에 비해 정확도 측면뿐만 아니라 편향되어 부족한 데이터에서도 성능을 개선했다.

세 번째 연구는 위 모델들을 활용해 합성 실험 조건 최적화에 대한 연구다. 효율적으로 좁혀진 탐색 범위에서 예측된 수율값과 불확실성을 토대로 실험의 우선순위를 정해 실험을 시작한다. 실험 결과가 순차적으로 입력되면 베이지안 최적화 방법의 예측 모델을 학습하고 기존 기계학습의 예측 결과 값과의 편차 에 따라 다음 실험 조건의 우선순위를 결정짓는 기계학습 모델 결과, 베이지안 최적화 모델, 두 모델의 가중치를 조절한다. 실험이 진행됨에 따라 기계학습 모 델의 예측값의 오차가 크고 실제 수율값이 지속적으로 좋지 못한 경우, 실험의 난이도가 높고 학습데이터 범위 밖의 실험으로 판단해 베이지안 최적화 모델의 가중치를 높이며 좁혔던 조건 범위를 점차적으로 늘려 나가도록 한다. 이러한 접근은 최적화 전략의 방향이 쉬운 실험은 exploitation 할 수 있게, 난이도가 높 은 실험은 exploration 할 수 있게 함으로써 trade-off 최적화 문제를 효율적으로 풀도록 설계 되었다.

결론적으로, 본 박사학위 논문은 유기합성 실험의 조건 최적화를 위해서 탐색 범위를 효과적으로 줄이고 합성 실험의 난이도를 수치화 해 효율적으로 탐색할 수 있도록 하는 실험 최적화 기법을 제안하며, 기존 최적화 연구와 비교하였으며 추가적으로 실제 합성 자동화 장비를 통해 반응 최적화 성능을 검증했다.

주요어: 베이지안 최적화, 유기 합성, 실험 조건 최적화, 생성 모델, 머신 러닝, 실험 설계, 합성 가능성 수치화 **학번**: 2019-31018