

QUBO-inspired Molecular Fingerprint for Chemical Property Prediction

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Abstract—Molecular fingerprints are widely used for predicting chemical properties, and selecting appropriate fingerprints is important. We generate new fingerprints based on the assumption that a performance of prediction using a more effective fingerprint is better. We generate effective interaction fingerprints that are the product of multiple base fingerprints. It is difficult to evaluate all combinations of interaction fingerprints because of computational limitations. Against this problem, we transform a problem of searching more effective interaction fingerprints into a quadratic unconstrained binary optimization problem. In this study, we found effective interaction fingerprints using QM9 dataset.

Index Terms—molecular fingerprint, QUBO, annealing machine, compounds design, molecular design.

I. INTRODUCTION

Predicting chemical properties using machine learning is one of the most popular topics in the material informatics. Molecular fingerprints are widely used because they can describe molecular structure as tabular data [1]. Many fingerprints have been proposed, and selecting appropriate fingerprints is important from them [2]. However, the factor of determining the chemical properties is complicated. Even if crucial factor is described by multiple fingerprints, treating them independently is not effective in terms of machine learning. In fact, interaction features that are the product of multiple features, are used as a feature engineering technique [3].

We generate new fingerprints on the assumption that a performance of prediction based on a more effective fingerprint is better. The performance of each fingerprint is evaluated by the prediction error of chemical properties based on splitting training samples using each fingerprint like decision trees with depth 1. Then we define interaction fingerprints. They are fingerprints that are described by the product of multiple base fingerprints, and we try to search effective fingerprints from them. We use existing fingerprints as base fingerprints. Examples of interaction fingerprints and molecules satisfying the interaction fingerprint are shown in Fig. 1. In this study,

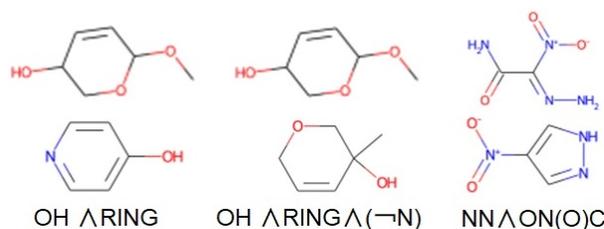


Fig. 1. Examples of interaction fingerprints using multiple MACCS keys fingerprint. OH[^]RING[^](-N) indicates interaction fingerprints means that molecules are with hydroxy group and ring structure and without nitrogen atom.

MACCS keys fingerprint [2] is used as base fingerprints, and the notation of each base fingerprint is based on RDKit [4].

However, it is difficult to evaluate all combinations of interaction fingerprints because of computational limitations. Against this problem, we transform a problem of searching more effective interaction fingerprints into a quadratic unconstrained binary optimization (QUBO) problem, which is called QUBO decision trees [5]. QUBO problem can be solve approximately faster by an annealing machine [6]. As a result, by using QUBO decision trees, it is expected to obtain effective interaction fingerprints.

II. RELATED WORK

Annealing machines. There has been a lot of research on annealing machines, both in hardware and software. They have strengths in solving combinatorial optimization problems and have been used in the real world [7]. Quantum annealing [6] and the adiabatic quantum evolution algorithm [8] drove the development of annealing machines. D-Wave provides a quantum annealing machine in the cloud [9]. Annealing machines that use GPUs with a technique called momentum annealing have also been introduced [10], [11].

Machine learning optimized as QUBO problem. There have been many attempts to solve problems with annealing technology by formulating it as a QUBO problem for machine

TABLE I
INTERACTION FINGERPRINT AND FINGERPRINT VECTOR.

Interaction Fingerprint	OH	-OH	RING	-RING	N	-N	U
OH^RING	1	0	1	0	0	0	2
OH^RING^(¬N)	1	0	1	0	0	1	3

learning algorithms. In [12], annealing machines have been used for clustering. In [13], three methods, linear regression, a support vector machine (SVM), and balanced k-means clustering were transformed into QUBO problems. Annealing machines have also been used in deep learning [14]–[16], image processing [17]–[19] and Bayesian network [20], [21].

III. PROBLEM SETUP

Let $\mathbf{X}_{i,j}$ be the value of base fingerprints j , $t^{(i)}$ be the target value for sample i , $y^{(i)}$ be the predicted value for sample i , and $g^{(i)}$ be the value of generated fingerprint for sample i . $g^{(i)}$ can be written as follow:

$$g^{(i)} = \prod_{f_j=1, j \in \mathbb{F}} \mathbf{X}_{i,j}, \quad (1)$$

where \mathbb{F} is the set of base fingerprints and f is the fingerprint vector. $f_j = 1$ means that generated interaction fingerprint uses fingerprint j , and such fingerprints are called produced fingerprints in this study. In the first column of Table I, The generated interaction fingerprint is OH^RING, the base fingerprints are OH, -OH, RING, -RING, N and -N, and the produced fingerprints are OH and RING. Let $N_{\mathbb{F}}$ be the number of prepared fingerprints. Then the number of fingerprints used for interaction fingerprints U can be written as follow:

$$U = \sum_{j \in \mathbb{F}} f_j.$$

Because there are $2^{N_{\mathbb{F}}}$ different combinations of fingerprints, it is difficult to search for the optimal solution in general. Therefore, in this study we use annealing machines, which have strengths in solving combinatorial optimization problems. Furthermore, let \mathbb{S} be the set of all samples, \mathbb{S}_1 be the set of samples that satisfied $g^{(i)} = 1$, and \mathbb{S}_0 be the set of samples that did not. The number of samples in \mathbb{S} is denoted by $N_{\mathbb{S}}$.

QUBO problem. In an annealing machine, the parameters to be optimized are represented by QUBO variables with binary values $\theta_l \in \{0,1\}$, and the objective variable is represented by the Hamiltonian of the QUBO form:

$$H = - \sum_{l < m} Q_{lm} \theta_l \theta_m - \sum_l b_l \theta_l, \quad (2)$$

where the Q_{lm} and b_l are coefficients that characterize the QUBO problem.

The QUBO problem is formulated by expressing the Hamiltonian as the sum of a loss function L and a constraint function C via the QUBO format, as follow:

$$H = L(\mathbf{X}, \mathbf{t}|\boldsymbol{\theta}) + C(\boldsymbol{\theta})$$

Here, $\boldsymbol{\theta}$ is a binary vector representing the model parameters. \mathbf{X} is the explanatory variable for sample i , and \mathbf{t} is a vector representing the target variable. In addition, L is the optimization target, and $C(\boldsymbol{\theta})$ is a set to obtain a valid solution, which is generally required to be $C(\boldsymbol{\theta}) = 0$. The annealing machine is used to find $\boldsymbol{\theta}$ such that the Hamiltonian is minimized.

IV. QUBO DECISION TREE

The mean squared error (MSE) is often used to learn decision trees. The MSE in a decision tree for regression can be written as follows:

$$\text{MSE} = \frac{1}{N_{\mathbb{S}}} \left(\sum_{i \in \mathbb{S}_1} \left(\text{pred}_1 - t^{(i)} \right)^2 + \sum_{i \in \mathbb{S}_0} \left(\text{pred}_0 - t^{(i)} \right)^2 \right),$$

where pred_1 is the estimated value when the interaction fingerprints is satisfied, and pred_0 is the estimated value when it is not satisfied. Learning in decision trees for regression involves finding the interaction fingerprints for splitting and the $\text{pred}_1, \text{pred}_0$ to reduce the MSE. It is obvious that pred_1 and pred_0 are the means of the samples divided by the interaction fingerprints. Therefore, the MSE is equal to the sum of the variance of the split sample groups weighted by the proportions of the sample groups. Accordingly, the MSE can be written as the following equation:

$$\begin{aligned} \text{MSE} &= \sum_{b=0,1} \text{Var} \left(\left\{ t^{(i)} \mid i \in \mathbb{S}_b \right\} \right) \frac{N_{\mathbb{S}_b}}{N_{\mathbb{S}}} \\ &= \sum_{b=0,1} \left(\frac{1}{N_{\mathbb{S}}} \sum_{i \in \mathbb{S}_b} t^{(i)2} - \frac{1}{N_{\mathbb{S}} N_{\mathbb{S}_b}} \left(\sum_{i \in \mathbb{S}_b} t^{(i)} \right)^2 \right). \end{aligned}$$

However, the MSE is difficult to formulate in a QUBO problem because it involves division using the variable $N_{\mathbb{S}_b}$ that is the sum of QUBO variables. Here, because $N_{\mathbb{S}}$ is the total number of samples and thus a constant, this is not a problem. Hence, we propose the square weighted MSE (SWMSE). In the SWMSE, instead of using the proportion of the sample group as the weight in calculating the sum of the variances, the square of that value is used:

$$\begin{aligned} \text{SWMSE} &= \sum_{b=0,1} \text{Var} \left(\left\{ t^{(i)} \mid i \in \mathbb{S}_b \right\} \right) \left(\frac{N_{\mathbb{S}_b}}{N_{\mathbb{S}}} \right)^2 \\ &= \sum_{b=0,1} \left(\frac{N_{\mathbb{S}_b}}{N_{\mathbb{S}}} \sum_{i \in \mathbb{S}_b} t^{(i)2} - \frac{1}{N_{\mathbb{S}}} \left(\sum_{i \in \mathbb{S}_b} t^{(i)} \right)^2 \right). \quad (3) \end{aligned}$$

Through this transformation, the MSE minimization problem becomes a QUBO problem.

A. Formulation as QUBO Problem

There are two types of QUBO variables to be optimized θ_F and θ_X , and their elements are denoted by $\theta_{F,j}$ and $\theta_{X,i,c}$, respectively. First, $\theta_{F,j}$ is a binary variable that represent the generated interaction fingerprints, and finally, based on the calculated result, we use $\theta_{F,j}$ as f_j and generate a new interaction fingerprint. $\theta_{X,i,c}$ is an auxiliary binary variable for calculating the SWMSE, where $\theta_{X,i,c} = 1$ indicates that there are c base fingerprints that sample i does not satisfy.

Note that $\theta_{X,i,0} = 1$ indicates that sample i satisfies all the produced fingerprints, i.e., $\theta_{X,i,0}$ indicates the splitting result. Here, c is an integer from 0 to M , where M is the maximum number of produced fingerprints to be used for generating interaction fingerprints, and is a learning parameter. The number of the produced fingerprints that samples i do not satisfy, denoted as $\text{unsatisfied_fingerprint}_i$, is expressed by the following equation:

$$\text{unsatisfied_fingerprint}_i = \sum_j (1 - \mathbf{X}_{i,j}) \theta_{F,j}.$$

If $\text{unsatisfied_fingerprint}_i = 0$, then the sample i satisfies all the produced fingerprints.

Loss function. The moment of $t^{(i)}$ appearing in Equation (3) can be expressed by using QUBO variables as in the following equations:

$$\begin{aligned} \sum_{i \in S_1} t^{(i)n} &= \sum_i \theta_{X,i,0} t^{(i)n} \quad (n = 1, 2, \dots), \\ \sum_{i \in S_0} t^{(i)n} &= \sum_i (1 - \theta_{X,i,0}) t^{(i)n} \quad (n = 1, 2, \dots). \end{aligned}$$

Similarly, the numbers of sample groups, N_{S_1} and N_{S_0} , that are split by a interaction fingerprint can be written as follows:

$$\begin{aligned} N_{S_1} &= \sum_i \theta_{X,i,0} \\ N_{S_0} &= \sum_i (1 - \theta_{X,i,0}). \end{aligned}$$

As a result, the SWMSE can be expressed as a problem in QUBO form via the following equation:

$$\begin{aligned} \text{SWMSE} &= \left(\sum_i \theta_{X,i,0} t^{(i)2} \right) \left(\sum_i \theta_{X,i,0} \right) \\ &\quad - \left(\sum_i \theta_{X,i,0} t^{(i)} \right)^2 \\ &\quad + \left(\sum_i (1 - \theta_{X,i,0}) t^{(i)2} \right) \left(\sum_i (1 - \theta_{X,i,0}) \right) \\ &\quad - \left(\sum_i (1 - \theta_{X,i,0}) t^{(i)} \right)^2. \end{aligned}$$

Constraint function. There are three types of constraints on QUBO variables, as represented by Equation (4)-(6) below. Here, Equation (4) is a constraint on the relationship between $\theta_{F,j}$ and $\theta_{X,i,c}$ for each sample. Satisfaction of this constraint indicates that $\theta_{X,i,c}$ can represent the number of satisfied base fingerprints used for interaction fingerprints. Equation (5) is a constraint on the validity of $\theta_{X,i,c}$ for each sample. Equation (6) is an optional constraint for narrowing down the search space. Though M can take values up to N_B , we can limit it for practical purposes.

$$\forall i \sum_j (1 - \mathbf{X}_{i,j}) \theta_{F,j} - \sum_c c \theta_{X,i,c} = 0 \quad (4)$$

$$\forall i \sum_c \theta_{X,i,c} = 1 \quad (5)$$

$$1 \leq \sum_j \theta_{F,j} \leq M \quad (6)$$

TABLE II
NUMBER OF THE TRIALS THAT GENERATED EFFECTIVE FINGERPRINTS.

	M=2	M=3	M=4	M=5
$N_S=50$	0	2	2	2
$N_S=100$	0	0	0	3
$N_S=200$	0	3	0	1

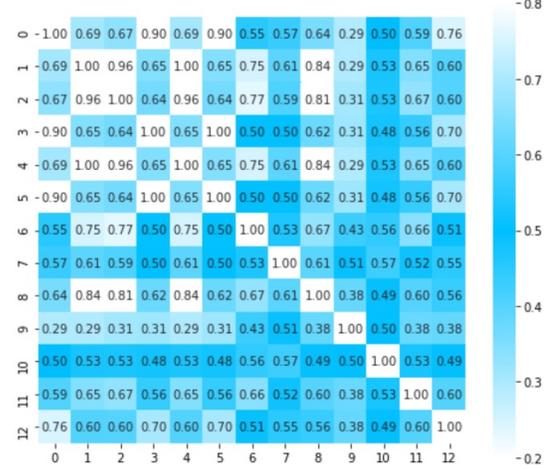


Fig. 2. The percentage of matched samples between the generated interaction fingerprints are shown. The value of 0 or 1 indicates that two fingerprints substantially the same fingerprints.

When all these constraints are satisfied, the actual SWMSE is equal to the SWMSE being calculated in the annealing machine.

Hamiltonian. The splitting method is explored by minimizing the Hamiltonian given below in Equation (7). In this equation, C_1, C_2 and C_3 are the Hamiltonians for the constraints expressed in Equations (4)-(6). Note that not all these constraints must be satisfied. In other words, even if there is a violated constraint, an estimator can be created using obtained $\theta_{F,j}$.

$$\begin{aligned} H &= \frac{1}{N_S} \text{SWMSE}(\mathbf{X}, \mathbf{t} | \theta_F, \theta_X) + \frac{1}{N_S} C_1(\theta_F, \theta_X) \\ &\quad + \frac{1}{N_S} C_2(\theta_X) + C_3(\theta_X). \end{aligned} \quad (7)$$

V. EXPERIMENT AND DISCUSSION

We evaluated whether QUBO decision trees found effective fingerprints using multiple fingerprints. Effective fingerprints mean that they reduce prediction error comparing minimum one using only one fingerprint. We used QM9 dataset [22] and predicted value was dipole moment. Input values were generated based on MACCS keys. The experiments were performed on a GPU using momentum annealing. with various N_S and M . Ten trials were conducted for each parameter. To see the impact of M , the samples used with the same N_S were unified.

Table II lists the number of the trials that generated effective fingerprints. In case that $M = 2$, no effective interaction

TABLE III
OBTAINED EFFECTIVE INTERACTION FINGERPRINTS.

ID	N_S	M	U	I	generated interaction fingerprint
1	50	3	3	1756	$\neg N-O \wedge \neg C\$=C(\$A)\$A \wedge \neg QCH3$
2	50	3	3	821	$\neg NC(O)O \wedge \neg ACH2N \wedge \neg FRAGMENTS$
3	50	4	3	1689	$\neg NC(O)O \wedge \neg QHAQH \wedge \neg ACH2N$
4	50	4	2	1027	RING $\wedge \neg QCH3$
5	50	5	2	151	$\neg NC(O)O \wedge \neg ACH2N$
6	50	5	2	116	RING $\wedge \neg QCH3$
7	100	5	5	2793	$\neg 7M \text{ RING} \wedge \neg NAAN \wedge \neg ACH2N \wedge \neg N=A \wedge \neg X \text{ (HALOGEN)}$
8	100	5	4	2660	$\neg N-O \wedge \neg QCH2Q \wedge \neg NC(O)N \wedge \neg ACH2AACH2A$
9	100	5	3	1900	$\neg C=CN \wedge \neg QNQA \wedge \neg ACH2QH$
10	200	3	3	1478	NCO $\wedge \neg NC(O)N \wedge \neg AROMATIC \text{ RING}$
11	200	3	3	3399	$\neg NC(O)N \wedge \neg CH3CH2A \wedge \neg 6M \text{ RING}$
12	200	3	3	2844	$\neg HETEROCYCLIC \text{ ATOM} > 1 (\& \dots) \wedge \neg CH2QCH2 \wedge \neg O=A > 1$
13	200	5	6	3452	$\neg N-O \wedge \neg NC(O)N \wedge \neg C=C(C)C \wedge \neg A\$A!A\$A \wedge \neg A!O!A \wedge \neg Anot\%A\%Anot\%A$

fingerprints were generated. Table III lists the obtained effective interaction fingerprints. I is the feature importance of each fingerprint when trained using all samples. Roughly speaking, the larger N_S and U , the higher I . If U is low, I tends to be low as well because of its high correlation with the base fingerprints. If N_S is low, I tends to be low as well because of instability associated with small sample size. Fig. 2 shows the percentage of matched samples between the generated interaction fingerprints. It can be seen that some similar fingerprints are generated, but overall, different fingerprints are generated for each of them.

We discuss computational cost comparing with a naïve full search method. The number of combinations to be searched is $N_F C_M$. When $M = 3$ and $N_S = 50$, calculation time is over three hours a naïve full search model in our environment, and it shows it is difficult to search fully when M is over 4. Our experiments using the proposed method were completed within two hours each, even at $M = 5$, suggesting a computational time advantage of our method.

VI. CONCLUSION

In this study, we attempted to find effective fingerprints for determining the chemical property using QUBO decision trees. As a result, we found interaction fingerprints using multiple fingerprints reducing prediction error. Considering the method to utilizing generated interaction fingerprints and to improve the performance are issues in the future.

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