Substructure search optimizations

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1 Introduction

Substructure search in chemical compound databases is a vital task in cheminformatics, underpinning broad applications in drug discovery, materials science, and toxicology. The objective is to identify all molecules in a database that contain a given query substructure, which typically corresponds to a specific chemical motif or functional group. This search has been a cornerstone in understanding the influence of specific substructures on a compound's biological activity, physicochemical properties, and reactivity, a recognized concept for decades [Barnard, 1993].

Historically, computer-based substructure search started with pioneers like Ledley and colleagues who developed the Chemical Substructure Search (CSS) algorithm in the 1960s and 1970s [Ledley et al., 1964]. This algorithm employed a graph-based approach to identify specific substructures in chemical compounds. Further advancements in the field came with the development of the Simplified Molecular Input Line Entry System (SMILES) notation by Weininger in the 1980s [Weininger, 1988], which provided a simple, linear representation of molecular structures as strings.

Substructure search fundamentally rests on the solution of the subgraph isomorphism problem, a problem known to be NP-complete [Ullmann, 1976]. Due to its high computational complexity, numerous heuristics and algorithms have been devised to accelerate the search process. Among these, the Filter-and-Verification paradigm has been a prevalent approach, involving an initial filtering step to quickly eliminate unsuitable candidate graphs, and a more computationally intensive verification step to confirm the presence of the query substructure in the remaining candidates [Cordella et al., 2004, Shasha et al., 2002]. Over time, graph-based subgraph isomorphism algorithms, such as the Ullmann algorithm [Ullmann, 1976] and the VF2 algorithm [Cordella et al., 2004], have emerged as more efficient and scalable solutions for substructure search in large chemical databases.

In addition to these, frequent subgraph mining algorithms like gSpan [Yan and Han, 2002], FFSM [Kuramochi and Karypis, 2001], and Gaston [Nijssen and Kok, 2004] have proven valuable in identifying frequently occurring substructures in large sets of chemical compounds. These approaches are particularly beneficial for ap-

plications such as structure-activity relationship (SAR) analysis and molecular classification.

Efficient filtering techniques often involve the use of binary and quantitative features, or fingerprints, to represent molecular structures. These fingerprints facilitate the rapid elimination of graphs that do not contain specific features required by the query subgraph, thereby speeding up the substructure search process [Bonchi et al., 2011, Klein et al., 2014].

However, as the number of known molecules and the size of chemical databases have grown significantly, the traditional approaches, which often require full or nearly full enumeration of candidates, have become increasingly challenging to implement efficiently. This development underlines the need for more scalable solutions.

Our work introduces a unique approach aimed at mitigating these challenges. While in certain cases the algorithm may resort to exhaustive enumeration, in most scenarios it employs a more sophisticated strategy, transcending the conventional full enumeration paradigm. Instead, we introduce a unique index structure: a tree that segments the molecular dataset into clusters based on the presence or absence of features. Inspired by the binary Ball-Tree concept [Omohundro, 1989, Clarkson, 1994], this structure demonstrates superior performance over exhaustive search on average, leading to a significant acceleration in the filtering process.

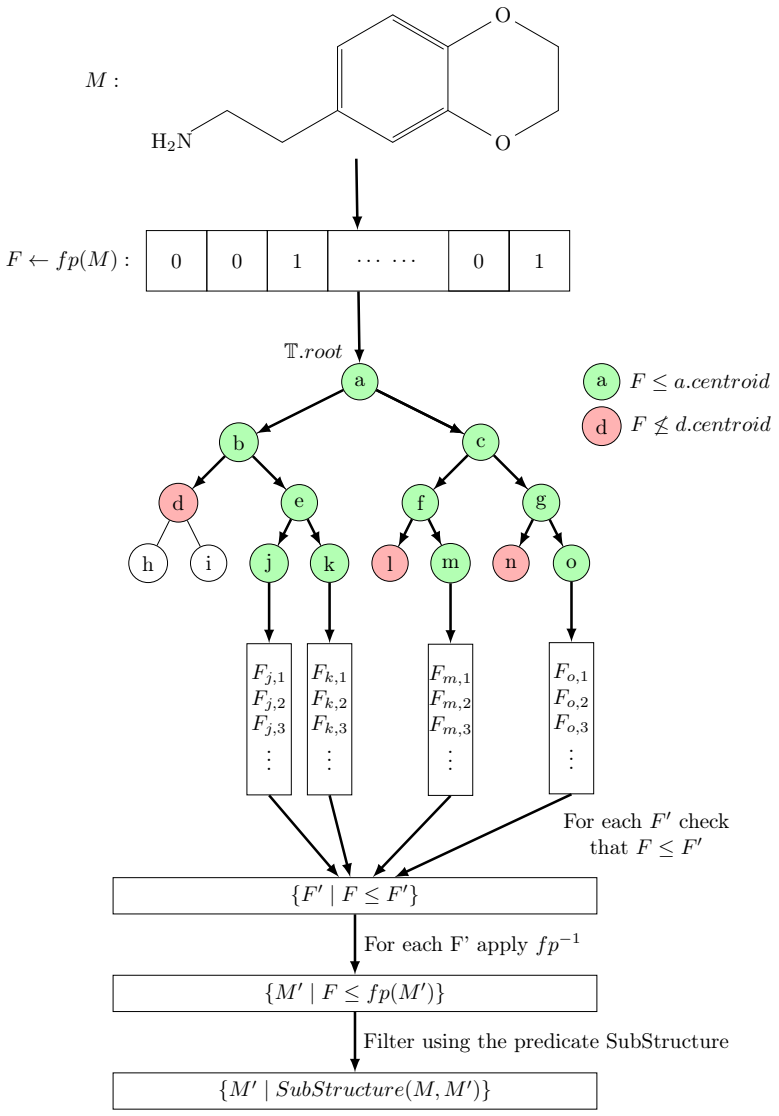
We provide a comparative analysis of our method based on Bingo [Pavlov et al., 2010] with the original Bingo algorithm, highlighting key differences.

While Bingo uses advanced filtering effectively, it relies on exhaustive search in a chemical space that continually expands. In contrast, our approach departs from exhaustive search and places an existing molecular fingerprint into a tree structure, rather than a conventional relational database. While our current version does not impact the verification stage, it speeds up the filtering stage. By introducing this innovative structure, we aim to cater to the growing scale of chemical databases and the escalating demand for efficient and scalable search solutions. Our approach offers potential for future research and application in the quest for more efficient and accurate substructure search techniques.

2 Algorithm description

2.1 Notation and main idea

The objective of our research is to facilitate the identification of specific substructures within the molecules from a database $\mathcal{M}$. For this, we utilize the concept of a "fingerprint", a binary string of constant length fl, corresponding to each molecule. To perform this mapping, we define a function $\mathsf{fp} : \mathcal{M} \to \mathcal{F}$ that takes a molecule from the set $\mathcal{M}$ and produces its corresponding fingerprint in the set $\mathcal{F}$. На мой взгляд написано слишком кратко про фингерпринты. Кажется, если человек не в теме, то он может не понять, что это за сопоставление молекулам бинарных строк, зачем оно нужно и почему оно эффективно


M :
O
H_2N
O
$F \leftarrow fp(M)$:
0
0
1
⋯ ⋯
0
1
$\mathbb{T}.root$
a
b
c
d
e
f
g
h
i
j
k
l
m
n
o
a $F \leq a.centroid$
d $F \not\leq d.centroid$
$F_{j,1}$ $F_{j,2}$ $F_{j,3}$ ⋮
$F_{k,1}$ $F_{k,2}$ $F_{k,3}$ ⋮
$F_{m,1}$ $F_{m,2}$ $F_{m,3}$ ⋮
$F_{o,1}$ $F_{o,2}$ $F_{o,3}$ ⋮
For each F' check that $F \leq F'$
$\{F' \mid F \leq F'\}$
For each F' apply fp^{-1}
$\{M' \mid F \leq fp(M')\}$
Filter using the predicate SubStructure
$\{M' \mid SubStructure(M, M')\}$

реализует этап filter

To make the substructure search process more efficient, we propose organizing these fingerprints in a binary search tree, denoted as $\mathbb{T}$. The tree is binary and complete, having a specific depth d.

In this tree, the root, left, and right subtrees of a node $\mathtt{v}$ are represented as $\mathbb{T}.\mathtt{root}$, $\mathtt{v}.\mathtt{left}$, and $\mathtt{v}.\mathtt{right}$, respectively. Each node also has a set of all leaves in its subtree, denoted as $\mathtt{v}.\mathtt{leaves}$. Each leaf ℓ in the tree $\mathbb{T}$ holds a set $\ell.\mathtt{set}$ of fingerprints. A unique concept to our approach is the centroid, $\mathtt{v}.\mathtt{centroid}$, recorded at each node v. The centroid is defined as a fingerprint F for which $F[i] = 1$ if and only if there exists another fingerprint F' in the subtree of $\mathtt{v}$ such that $F'[i] = 1$. This is represented as

$$\mathtt{v}.\mathtt{centroid} = \bigvee_{\ell \in \mathtt{v}.\mathtt{leaves}} \bigvee_{F \in \ell.\mathtt{set}} F.$$

This concept of the centroid is inspired by BallTree literature.

Our search process is designed to locate all fingerprints F' in the set $\mathcal{F}$ where F is a submask of F'. This search relies on the relation $F_1 \leq F_2$ for fingerprints F_1, F_2 that holds true if and only if for every $i \in 1, 2, \ldots, \mathsf{fl}$, $F_1[i] \leq F_2[i]$.

The search starts from the root and recursively descends into both subtrees. Note that here we can improve the performance by parallelizing this step to explore both subtrees simultaneously. We stop the recursive descent if we reach a node $\mathtt{v}$ where $F \not\leq \mathtt{v}.\mathtt{centroid}$. Conversely, if we reach a leaf ℓ and $F \leq \ell.\mathtt{centroid}$, we add to $\mathcal{F}_M$ the set $\{F' \in \ell.\mathtt{set} \mid \mathsf{fp}(M) \leq F'\}$.

Following the generation of $\mathcal{F}_M$, the next phase involves examining each M' in $\bigcup_{F' \in \mathcal{F}_M} \mathsf{fp}^{-1}(F')$. The objective is to determine whether each M' is a substructure of M. This determination is made by employing external algorithms to verify the predicate $\mathtt{SubStructure}(M', M)$, which is true if and only if M' is a substructure of M.

Further details on the BallTree and the utilization of the tree in the substructure search process will be provided in the subsequent sections.

The pseudocode for the fingerprint search function in the tree is described in Algorithm 1. The pseudocode for the function that searches for superstructures of a given molecule is described in Algorithm 2.

2.2 Building the tree

To start, let's create a trivial tree with a single node, denoted as $\mathbb{T}.\mathtt{root}$. Assign $\mathbb{T}.\mathtt{root}.\mathtt{set} = \mathcal{F}$. Next, we will inductively split the leaves of the tree into two parts, thereby adding new nodes to the tree.

More formally, for each leaf node ℓ of the tree, we will divide $\ell.\mathtt{set}$ using a specific function called SplitFingerprints: $\mathcal{F}_l, \mathcal{F}_r \leftarrow \text{SplitFingerprints}(\ell.\mathtt{set})$ ($\mathcal{F}_l \sqcup \mathcal{F}_r = \ell.\mathtt{set}$). Next, we will recursively build trees for $\ell.\mathtt{left}, \ell.\mathtt{right}$ using the sets $\mathcal{F}_l, \mathcal{F}_r$.

We will continue splitting the leaves in this manner until $\mathbb{T}$ becomes a full binary tree with depth d. The pseudocode for the algorithm described above

Algorithm 1 Searching for all matching fingerprints in a subtree

Require: v is a tree vertex, F is a fingerprint
Ensure: $\{F' \in \bigcup_{\ell \in \texttt{v.leaves}} \ell.\texttt{set} \mid F \leq F'\}$

1: **procedure** FindInSubtree(v, F)
2: **if** $F \not\leq$ v.centroid **then**
3: **return** $\varnothing$
4: **else if** v is leaf **then**
5: **return** $\{F' \in \texttt{v.set} \mid F \leq F'\}$
6: **else**
7: left $\leftarrow$ FindInSubtree(v.left, F)
8: right $\leftarrow$ FindInSubtree(v.right, F)
9: **return** Concatenate(left, right)
10: **end if**
11: **end procedure**

Algorithm 2 Searching for all superstructures of a given molecule

Require: M is a molecule
Ensure: $\{M' \in \mathcal{M} \mid \texttt{SubStructure}(M, M')\}$

1: **procedure** FindMetaStructures(M)
2: $F \leftarrow \mathsf{fp}(M)$
3: $F_M \leftarrow$ FindInSubtree($\mathbb{T}$.root, F)
4: **return** $\{M' \in \bigcup_{F' \in F_M} \mathsf{fp}^{-1}(F') \mid \textsc{SubStructure}(M, M')\}$
5: **end procedure**

can be found in 3.

We want to perform the splits in such a way that, on average, the search often prunes branches during the traversal. That is, the **if** statement in line 2 of algorithm 1 should be executed frequently. Let's discuss the function SplitFingerprints in more detail.

Initially, one might consider selecting a specific bit j and assigning all fingerprints F such that $F[j] = 0$ to the left subtree, and those with $F[j] = 1$ to the right subtree. In this case, when searching for superstructures of the fingerprint F', if $F'[j] = 1$, the entire left subtree would be cropped. However, in practice, this approach leads to significant differences between the left and right parts after a few splits, making it difficult to create a deep and balanced tree. Unfortunately, a shallow or unbalanced tree does not offer substantial improvements over a full search, as it barely eliminates any search branches.

Therefore, we suggest the following method: we will still select the bit as mentioned above, but we will divide the fingerprints in a way that ensures the sizes of the resulting partitions match. For instance, if the optimal division of n fingerprints yields parts with sizes $n_0, n_1 (n_0 < n_1 \ \wedge \ n_0 + n_1 = n)$, then all values with zero will be assigned to the left partition, while the values with

Algorithm 3 Building the tree

Require: $\mathcal{F}$ is the set of all fingerprints, d is the depth of the tree
Ensure: $\mathbb{T}$ is the BallTree for the superstructure fingerprint search

procedure BUILDTREE($\mathcal{F}, d$)
  $\mathtt{v} \leftarrow$ new node
  if $d = 1$ **then**
    $\mathtt{v.set} \leftarrow \mathcal{F}$
    $\mathtt{v.centroid} \leftarrow \bigvee_{F \in \mathcal{F}} F$
    return v
  else
    $\mathcal{F}_l, \mathcal{F}_r \leftarrow$ SPLITFINGERPRINTS($\mathcal{F}$)
    $\mathtt{v.left} \leftarrow$ BUILDTREE($\mathcal{F}_l, d-1$)
    $\mathtt{v.right} \leftarrow$ BUILDTREE($\mathcal{F}_r, d-1$)
    $\mathtt{v.centroid} \leftarrow \mathtt{v.left.centroid} \vee \mathtt{v.right.centroid}$
    return v
  end if
end procedure

Algorithm 4 Algorithm for splitting fingerprints in parts during tree construction

Require: set $\mathcal{F}$ of fingerprints to be split
Ensure: the split $\mathcal{F}_l, \mathcal{F}_r$ of the set $\mathcal{F}$

procedure SPLITFINGERPRINTS($\mathcal{F}$)
  $j \leftarrow \arg\min_i \{||\mathcal{F}| - 2k| \mid k = \#\{F \in \mathcal{F} \mid F_i = 1\}\}$
  $\mathcal{F}_l \leftarrow \{F \in \mathcal{F} \mid F[j] = 0\}$
  $\mathcal{F}_r \leftarrow \{F \in \mathcal{F} \mid F[j] = 1\}$
  if $|\mathcal{F}_l| > \lfloor \frac{n}{2} \rfloor$ **then**
    $\mathcal{F}_r \leftarrow \mathcal{F}_r \cup$ TAKELASTELEMENTS($\mathcal{F}_l, |\mathcal{F}_l| - \lfloor \frac{n}{2} \rfloor$)
    $\mathcal{F}_l \leftarrow$ DROPLASTELEMENTS($\mathcal{F}_l, |\mathcal{F}_l| - \lfloor \frac{n}{2} \rfloor$)
  else if $|\mathcal{F}_r| > \lceil \frac{n}{2} \rceil$ **then**
    $\mathcal{F}_l \leftarrow \mathcal{F}_l \cup$ TAKELASTELEMENTS($\mathcal{F}_r, |\mathcal{F}_r| - \lceil \frac{n}{2} \rceil$)
    $\mathcal{F}_r \leftarrow$ DROPLASTELEMENTS($\mathcal{F}_r, |\mathcal{F}_r| - \lceil \frac{n}{2} \rceil$)
  end if
  return $\mathcal{F}_l,\ \mathcal{F}_r$
end procedure

one will be distributed to achieve final left and right partition sizes of $\lfloor \frac{n}{2} \rfloor, \lceil \frac{n}{2} \rceil$ respectively. If $n_0 > n_1$, we will proceed symmetrically. The algorithm for the SplitFingerprints function can be found in the pseudocode 4.

3 Benchmarks

In this study, we have carried out comprehensive benchmarking to assess the performance of our algorithm, which is an extension of the Bingo fingerprinting system, in comparison with established index, namely Bingo [Pavlov et al., 2010]. Our benchmarking process was performed under the following conditions:

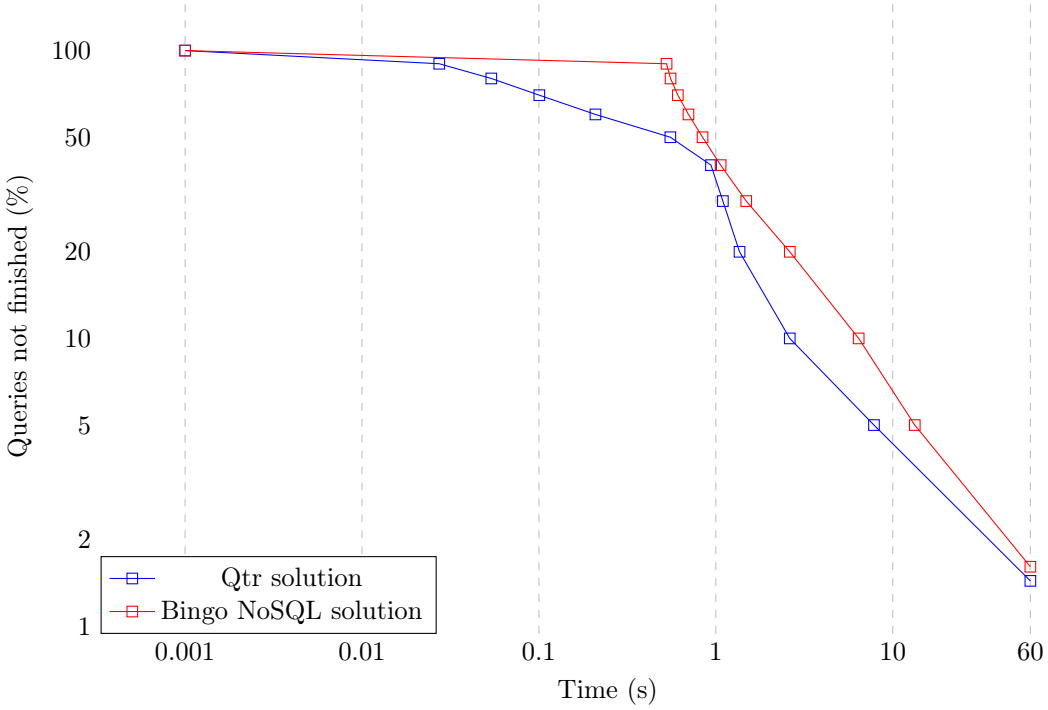
- OS: Ubuntu 22.04
- Processor: Intel Xeon E5-2686 v4 (Broadwell)
- Clock speed: 2.7 GHz
- RAM: 120 GB

The query dataset used for benchmarking was retrieved from `https://hg.sr.ht/~dalke/sqc/browse?rev=tip`, which contains 3488 relevant queries for substructure search. Ten queries were excluded due to various issues, resulting in a final set of 3478 compounds. Кажется, плохо так сильно обобщать проблемы. Мы выкинули те молекулы, на которых наш алгоритм работает заведомо плохо. Поэтому выкинув эти 10 молекул мы улучшили свои результаты.

For a single-threaded in-memory execution, our algorithm demonstrates competitive performance, and it also shows the potential for parallelization, exhibiting substantial improvements when executed on 16 threads in memory.

The table below summarizes these benchmark timings, providing a clear comparison between our Qtr algorithm and Bingo algorithm.

%	Qtr Algorithm, single-threaded, in-memory	Bingo NoSQL, single-threaded
10%	0.0273381	0.526846
20%	0.053802	0.554869
30%	0.100528	0.610074
40%	0.208735	0.700541
50%	0.553334	0.841574
60%	0.938981	1.06477
70%	1.09632	1.48609
80%	1.36175	2.61958
90%	2.61875	6.42211
95%	7.83572	13.3279
$\leq$ 60 seconds:	98.56%	98.39%



This thorough analysis offers valuable insights into the performance and potential scalability of our algorithm, especially when it comes to parallel computing. осталось получить тесты параллельной версии

4 Further Development

Fingerprints currently form the basis of our algorithm, but they do have certain limitations which don't make them the ideal fit for our tree-based approach.

Firstly, the fingerprint's condensed nature is aimed to ensure efficient computation, which often leads to grouping together several characteristics. For instance, a single attribute in a fingerprint often encapsulates multiple individual elements because these isolated items, while lacking substantial filtering power across the entire dataset, might be relevant for specific subsets. However, the fingerprint structure doesn't account for such instances. Contrarily, our approach could accommodate more complex functions, even if they operate slower than traditional filtering methods—for example, using a fingerprint variant that doesn't amalgamate different elements.

Secondly, fingerprints are designed to provide a universal filter across the entire dataset. This results in a significantly pared-down set of attributes applicable to the entire database. For example, Bingo utilizes 2584 attributes, which intuitively seems insufficient to capture all peculiarities of a 113M-sized

molecule dataset. Even a substantially enlarged fingerprint variant wouldn't be able to cover all exceptional cases. In contrast, our approach, by dealing with subsets, can extract a unique characteristic for a tree node relevant to the set in the given subtree, thus allowing for a much more effective coverage of the existing data nuances.

As a result, a potential enhancement of our algorithm might involve the use of a specific attribute in each tree node. Depending on its presence or absence, the search continues in both subtrees or only in the right subtree. This attribute would be chosen in advance to approximately bisect the set in the subtree. A leaf would contain several characteristics which would be examined when filtering elements from the leaf.

Employing the method described above, we could potentially improve the false positive rate, as the selected attributes would be relevant to the examined subsets. Moreover, these attributes could be utilized during verification, possibly resulting in substantial improvements in the verification stage speed, thanks to the relevance of these attributes to the molecule subsets.

5 Conclusion

The current version of our approach can serve as an extension to a fingerprint, enhancing the filtering speed by avoiding exhaustive enumeration. Moreover, the tree's ability to cluster molecules enables a more detailed examination of cluster-specific attributes, an aspect that existing algorithms struggle with, as they aim to find optimal ways to generalize across the entire dataset. Therefore, our approach could potentially be used in the future to improve both the false-positive rate and the verification speed.

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