Indexing chemical fingerprints for efficient querying of molecular databases

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Project Guide: Dr. Sayan Ranu

Overview

Motivation

- Fast database search is vital especially in drug discovery, where the aim is identifying chemical compounds with high similarity to known drugs.

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- When a candidate drug is discovered, millions of dollars are spent in laboratory for experiments and trials before it can see the light of day.

Definitions

- Indexing

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- Indexing
- Fingerprint

Definitions

- Indexing
- Fingerprint
- Querying

Problem Statement

Range Search Problem

Given a fingerprint, say *'f'*, a similarity measure *'sim'*, a threshold distance $'\theta'$ and a database of chemical compounds D, we find the subset $S \subset D$ of all fingerprints, such that:

$$S = \{g \mid g \in D, sim(f, g) < \theta\} \tag{1}$$

Some more concepts/definitions

- Tanimoto similarity

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- Distance measure? Metric?

Contribution

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- Proposed an inverted indexing technique.
- Explored range search techniques for the above.
- Extensions to non-binary fingerprints as well.
- Tested our method on 2 real world datasets by comparing with the "Bit bound technique".

M-tree

- Routing objects
- Covering radius

M-tree

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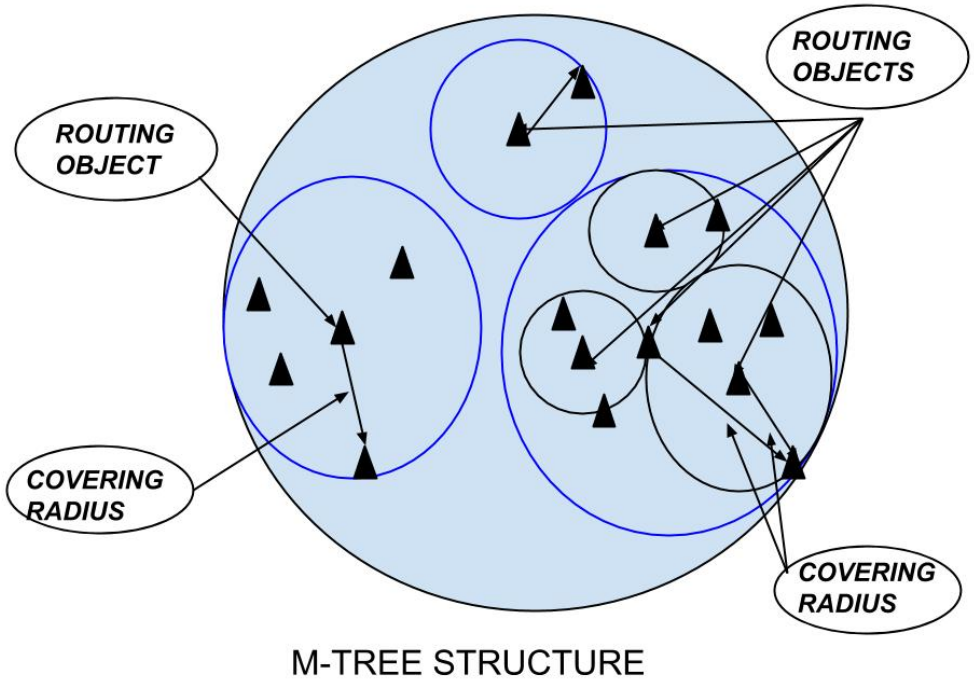

Figure : M-tree Structure Overview

Indexing approach ...

- Select pivots? Number?

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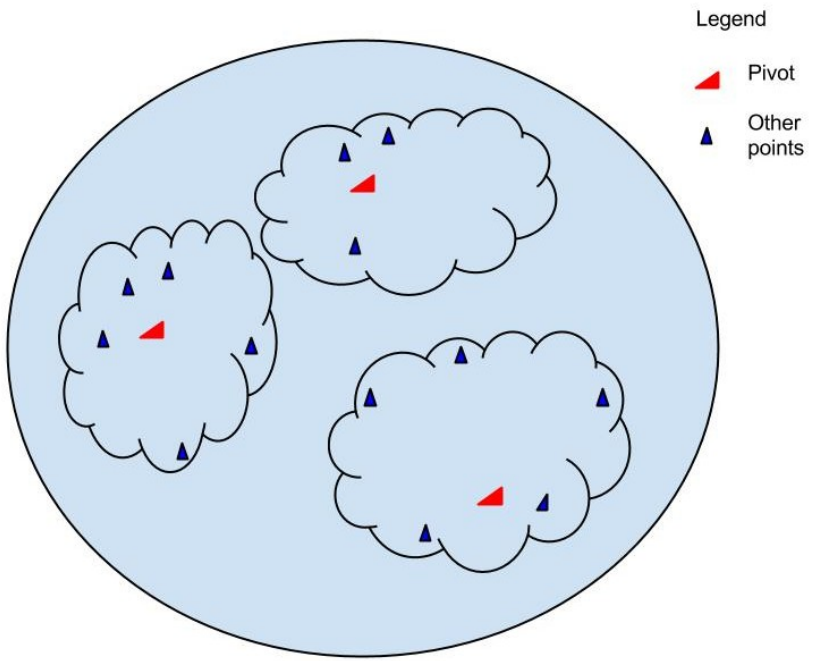

Indexing approach ...

- Choose outliers ?

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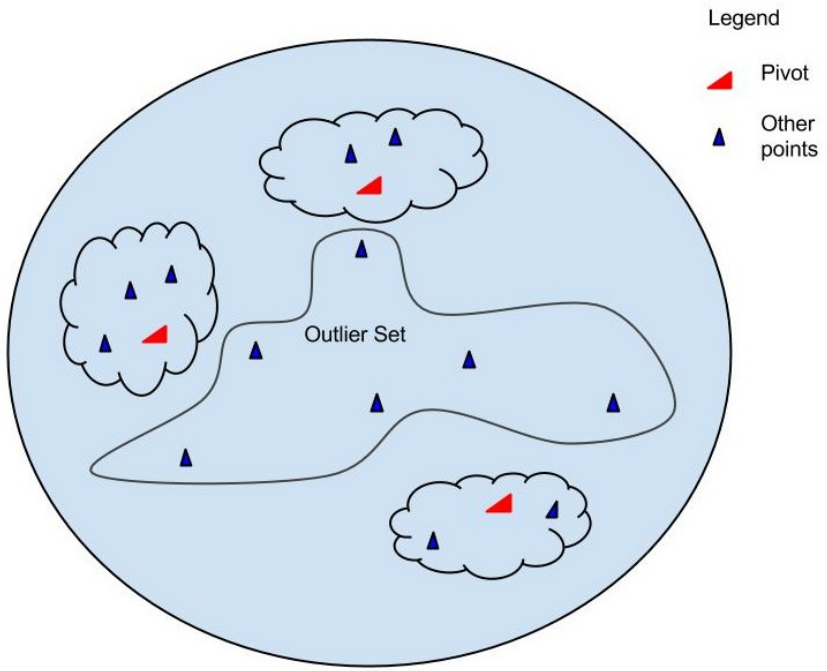

Indexing approach

- Repeat procedure on outlier set.

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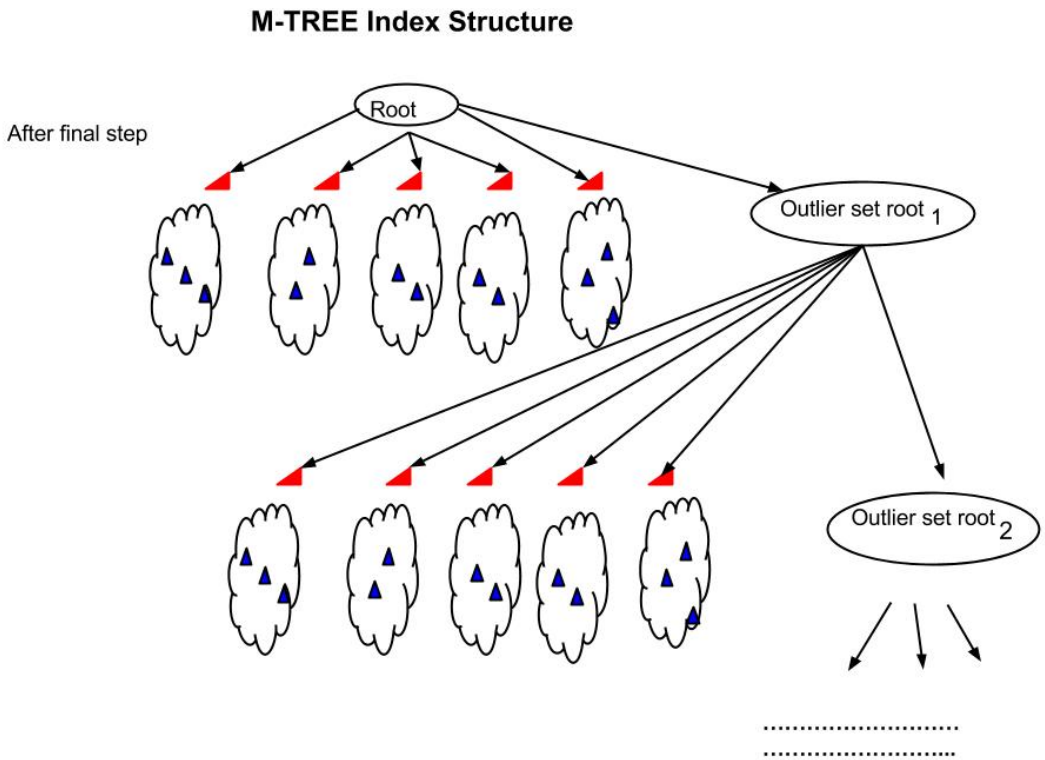

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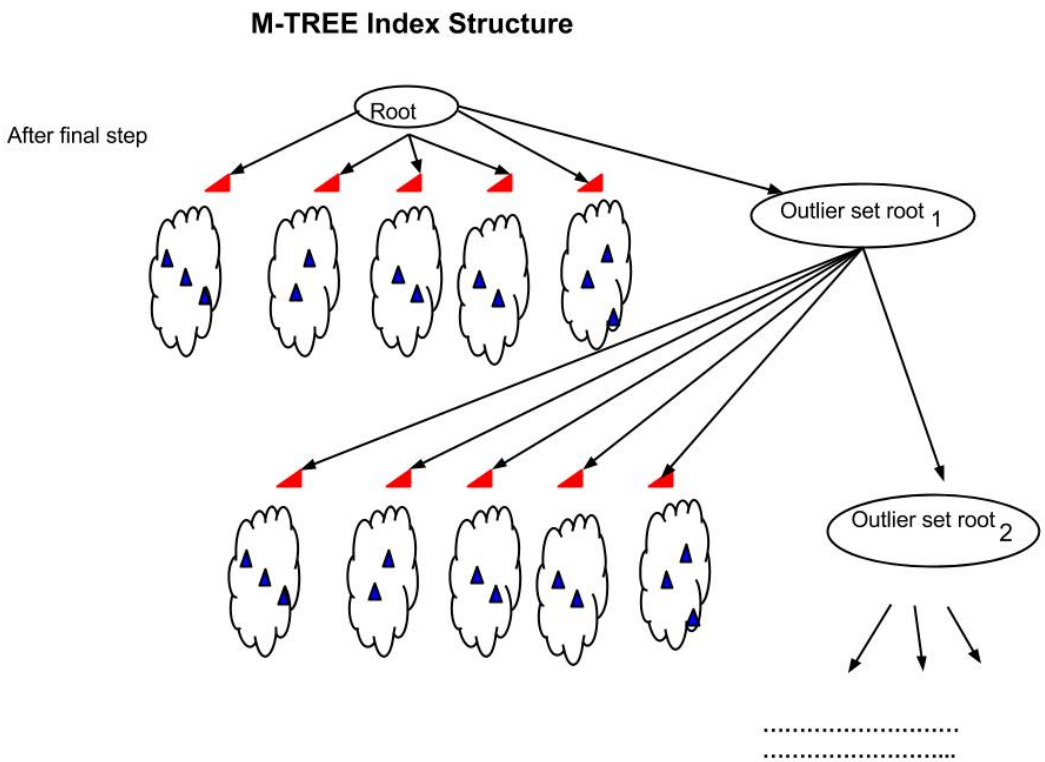


- Termination?

Range Search

- Start from the root
- Apply triangle inequality bounds.
- Covering radius of pivot p_i being r_i, the maximum distance of any node in S_i (subtree rooted at p_i) to the query q will be $dist(q, p_i) + r_i$.
- Use threshold t, to include the whole sub-tree.

Range Search ...

- Similarly the minimum distance of any node in S_i is $max(dist(q, p_i)$ - $r_i, 0)$.
- Prune?
- If not, then go to the children of p_i and repeat the process till we reach leaf.

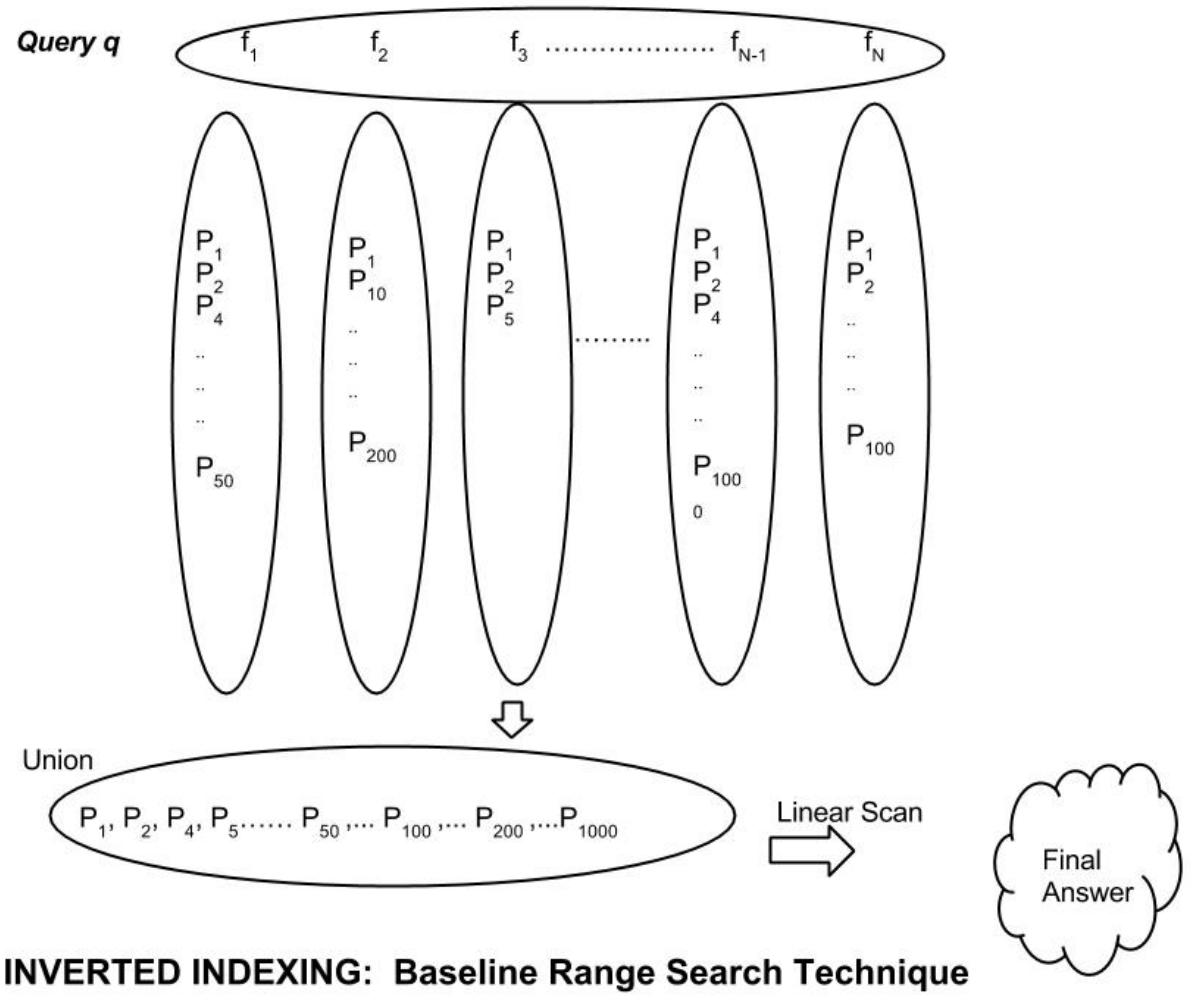
Inverted Index

- High dimensionality and sparsity of chemical data are an impediment to our indexing process.
- Use of inverted index motivated by its use in text mining.

Indexing process

- Index on features.
- Pre-processing?

Range Search



INVERTED INDEXING: Baseline Range Search Technique

Pruning features for binary fingerprints

- Consider f_i, if the following were to hold:

$$\frac{1}{N_q - 1 + V_i} < 1 - t \tag{4}$$

  we can prune the feature f_i
- Note: Here t is the threshold distance, V_i is the minimum number of features present among all points having the feature f_i

Proposed bounding theorem

Theorem

For a case of binary fingerprints, given a query q and a threshold t, consider the feature set $F = f_1, f_2, ...f_M$. If P is the set of points from the database, which has atleast one of the features f_k ($f_k \in F$) set to 1, then, we can prune all such points p_j of P from being present in the candidate range search set for query compound q if p_j does not have any other common feature other than in the set F, and it follows the following bound.

$$\frac{M}{N_q - 1 + \min\limits_{i \in (1,M)} (V_i)} < 1 - t \tag{5}$$

where M is the number of features in the set F,
N_q is the number of features in query q,
V_i is the minimum number of features present among all points having the feature f_i.

Greedy Technique

- Sort the features based on popularity

Greedy Technique

- Sort the features based on popularity
- Hence if till the i^{th} feature is considered, if j features (call it set R) have been pruned till now, we can prune the i^{th} feature as well if the following holds (as described in Equation 5)

$$\frac{j+1}{N_q - 1 + min(V_i, \rho)} < 1 - t \tag{6}$$

where ρ is the minimum number of features present in any point containing atleast one of the features pruned until now i.e $\rho = \min_{k \in R} V_k$

Extension to non-binary fingerprints

Theorem

Prune i^{th} feature if:

$$\frac{min(j_i, W_i)}{S_q - W_i - k_i + l_i + max(k_i, V_i)} < 1 - t \tag{7}$$

Here j_i is the maximum feature value taken for the feature f_i,
W_i is the i^{th} feature value of query q,
S_q is the sum magnitude of the feature values of the query q,
k_i is the is the minimum feature value taken for the feature f_i,
l_i is the minimum sum of feature values for any point containing the feature f_i ,
t is the threshold similarity.

Datasets

- PubChem Dataset (264016 compounds, 785985 features)
- DUD Dataset (128374 compounds, 32198 features)

Statistics on data

Table : Data Analysis: Statistics of the data-set PubChem-n

Number of data points	264016
Number of unique features is	785985
Maximum number of features in a data point is	1903
Minimum number of features in a data point is	7
Average number of features in a data point is	270.602966
Maximum number of data points with a feature is	259110
Minimum number of data points with a feature is	1
Average number of data points with a feature is	90
Maximum value of a feature	1870
Minimum value of a feature	1
Average value of a feature	1.142210
Maximum number of heavy-hitters	144
Minimum number of heavy-hitters	1
Average number of heavy-hitters	44.5

M-tree based index analysis

- Indexing time per compound on average increases linearly with data-set size as well as with size of pivot-set
- Outlier base limit size has no significant effect.

M-tree based index analysis...

- Range Search varies for different pivot-set sizes.

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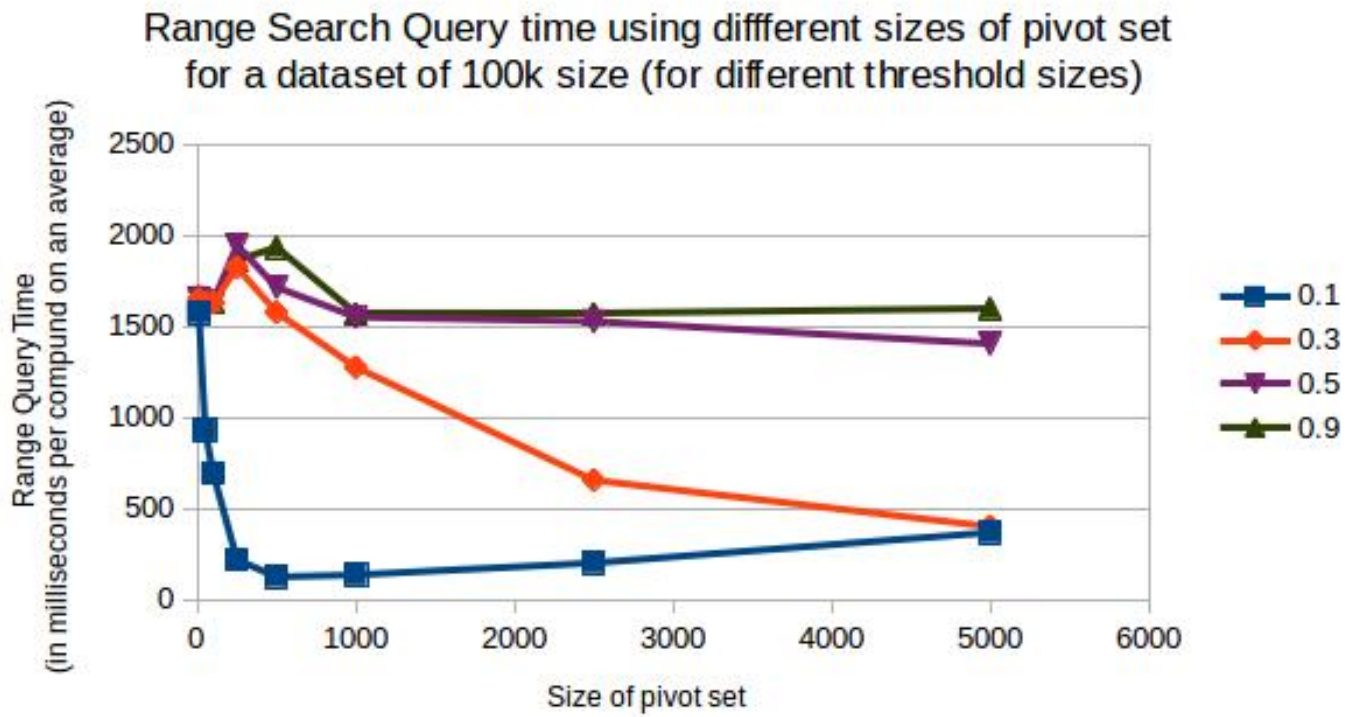


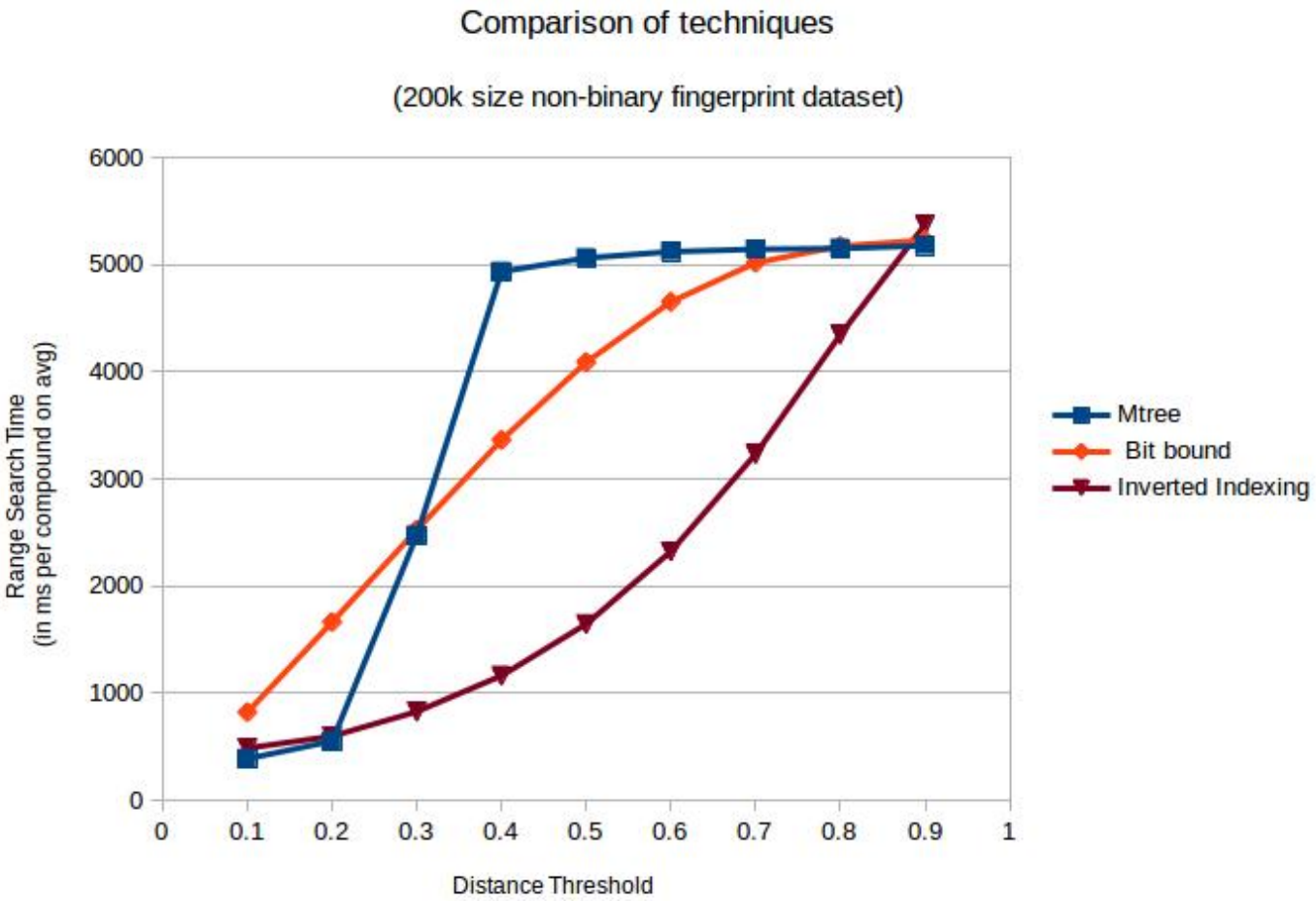
Inverted index analysis

- Indexing time per compound on average is constant. Does not change with data-set size.

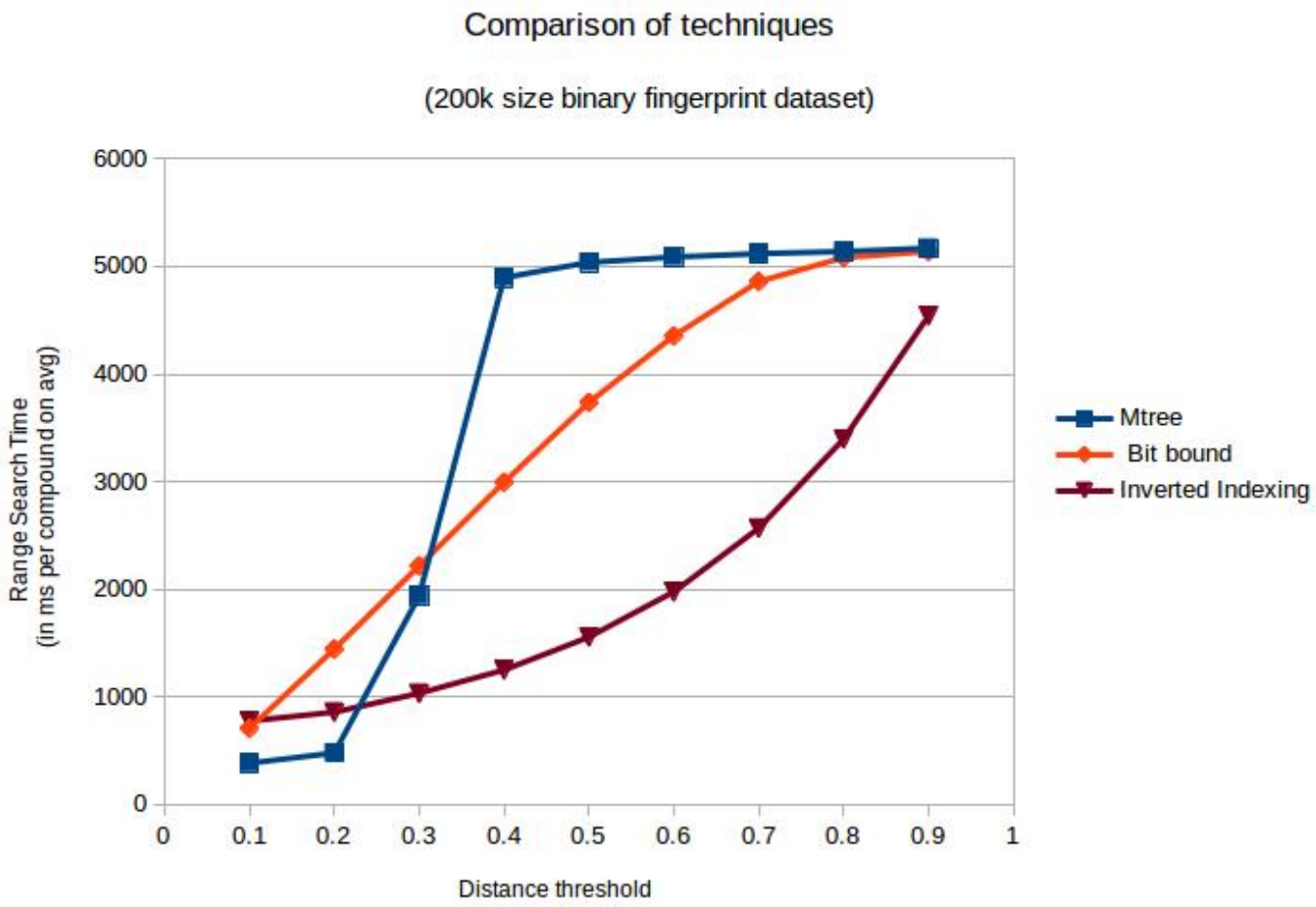
Inverted index analysis

- Indexing time per compound on average is constant. Does not change with data-set size.
- Pruning upto 50-100 features on average for low threshold distances.

Comparison


Comparison of techniques
(200k size non-binary fingerprint dataset)
Range Search Time
(in ms per compound on avg)
6000
5000
4000
3000
2000
1000
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Distance Threshold
Mtree
Bit bound
Inverted Indexing

Comparison ...


Comparison of techniques
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Range Search Time
(in ms per compound on avg)
6000
5000
4000
3000
2000
1000
0
0
0.1
0.2
0.3
0.4
0.5
0.6
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0.8
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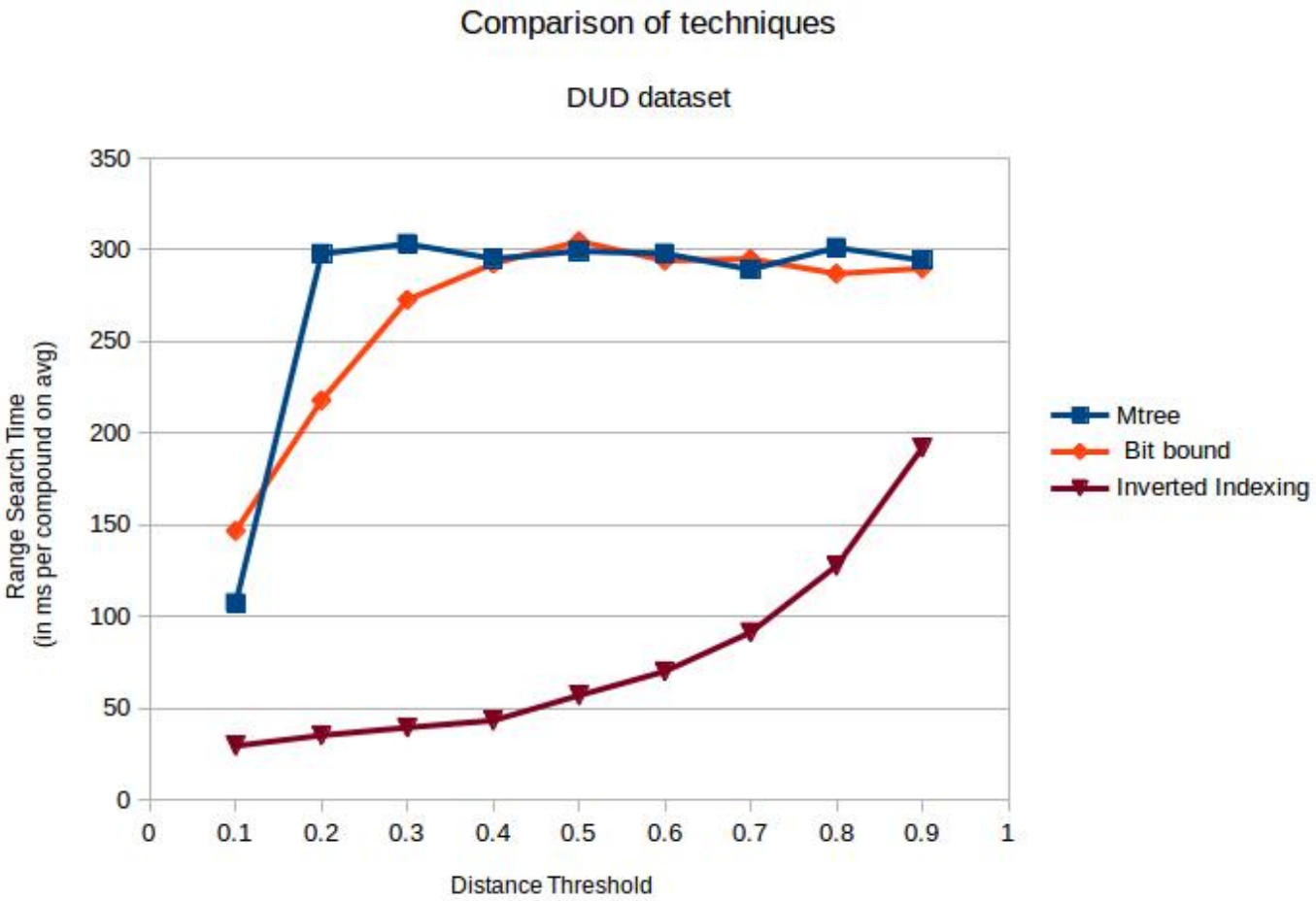
Comparison ...


Comparison of techniques
DUD dataset
Range Search Time
(in ms per compound on avg)
350
300
250
200
150
100
50
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
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1
Distance Threshold
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- Proposed an M-tree based index approach which exploited the metric property.

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- Proposed an M-tree based index approach which exploited the metric property.
- Proposed a novel inverted indexing technique which relied on pruning of features.
- Showed the effectiveness of our techniques through comprehensive analysis on 2 real world datasets.