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Improving the Similarity Search of Tandem Mass Spectra using Metric Access Methods

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Program of Presentation

- Introduction
- Tandem Mass Spectrometry (MS/MS)
  - basic principles
  - existing methods for interpretation of the mass spectra
  - common problems of interpretation
- Similarity Search Approaches
  - angle distance (cosine similarity)
  - parametrised Hausdorff distance
  - TriGen
- Experiments
- Conclusions and Future Work

Introduction

- biological motivation
  - all organisms – DNA – proteins

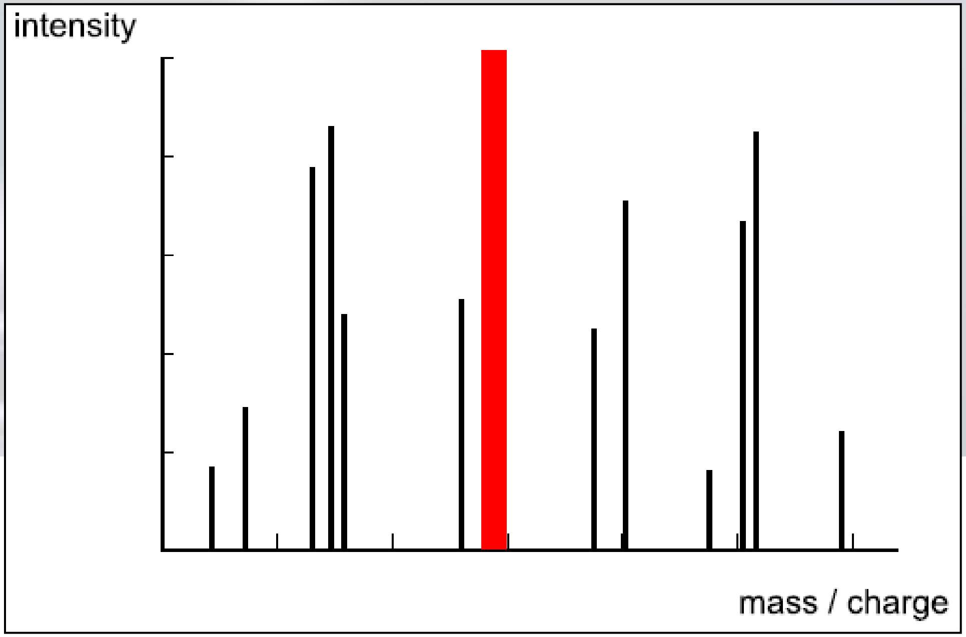
- proteins
  - cells function and structure
  - basic blocks – amino acids
  - linear sequence of amino acids
    (”linear sequence over 20-letter subset of the English alphabet”)

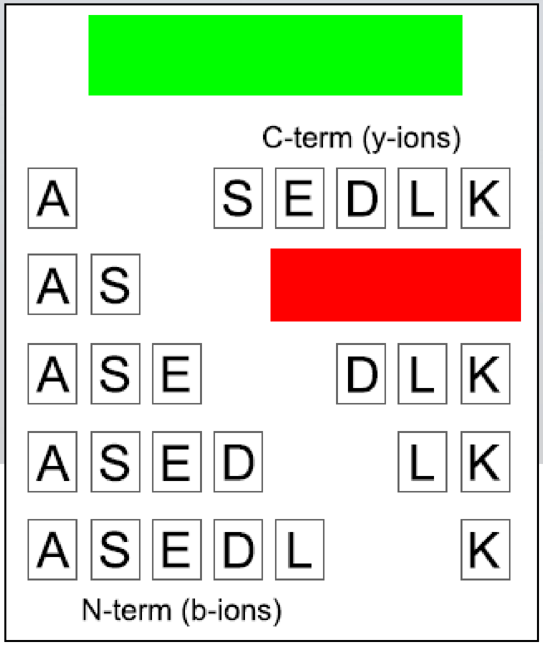
- peptides
  - short sequences

Tandem Mass Spectrometry (MS/MS)

- method for unknown protein sequences identification
  - proteins are splitted to peptides (one spectrum for each peptide is captured)
  - peptides are splitted to fragments
  - mass to charge ratio (x axis); intensity of occurrence (y axis)
  - y-ions (“from the right”); b-ions (“from the left”)

MGLSDGEWQLVLNVWGKVEADIPGHGQEVLIRLFKGHPETLE
KFDKFKHLKSEDEMKASEDLK...

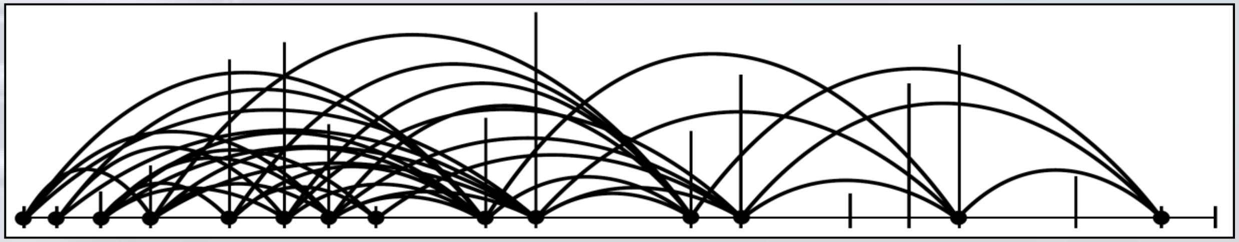




Interpretation of Spectra

- main idea: different amino acids ~ different masses

- graph approach "de novo"
  - direct spectra interpretation using graph algorithms
  - many paths in graph represent many peptide sequences corresponding to an experimental spectrum; quality of identification is about 30%



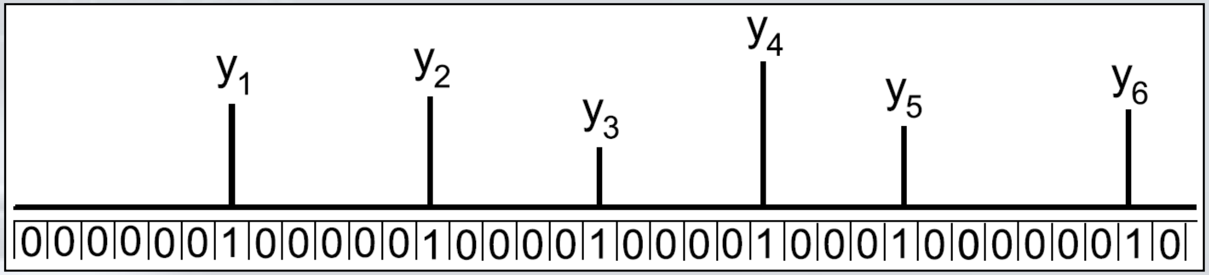
- database approach
  - search database of already known protein sequences
  - theoretical spectra are generated from stored sequences and compared with experimental spectra

Typical Problems of Interpretation

- noise
  - up to 80% of peaks
  - peaks of fragment ions with unpredictable chemical structure
- single amino acids (or groups) with similar masses can be mistaken
- some peaks important for identification (y or b-ions) are missing
  - fragment ions do not arise
- modifications of amino acids
  - amino acids masses are changed

Angle Distance (d_A)

- cosine similarity approaches are commonly mentioned in literature
- high-dimensional boolean vectors; compact representation <7, 13, 18, 23, 27, 34>
- bad indexability

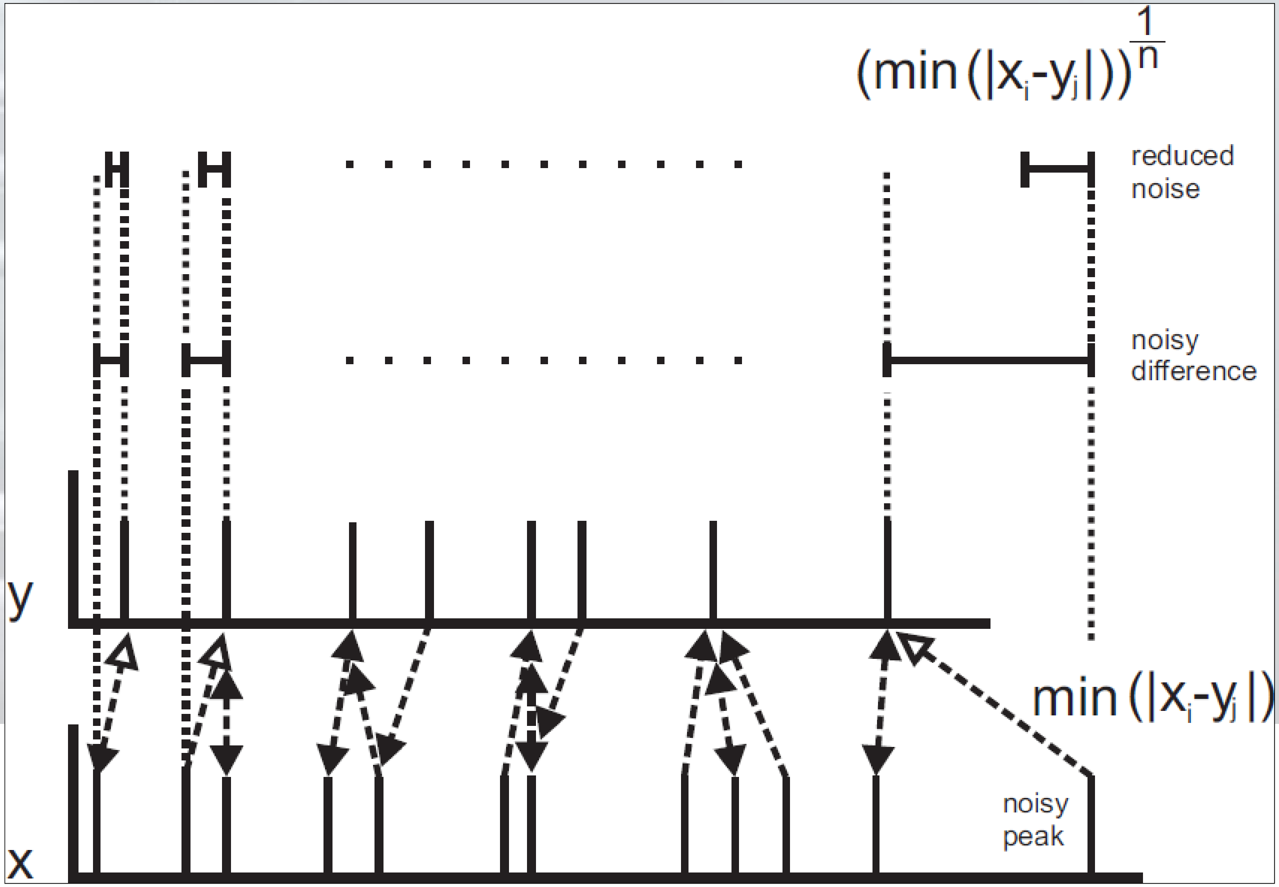


0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	1	0

- precursor mass
  - mass of a peptide before splitting (known as an additional information)
- precursor mass filter
  - spectra are indexed by their precursor mass
- $d'_A = d_A$ + precursor mass filter
  - indexable very well
  - it supports only spectra without chemical modifications

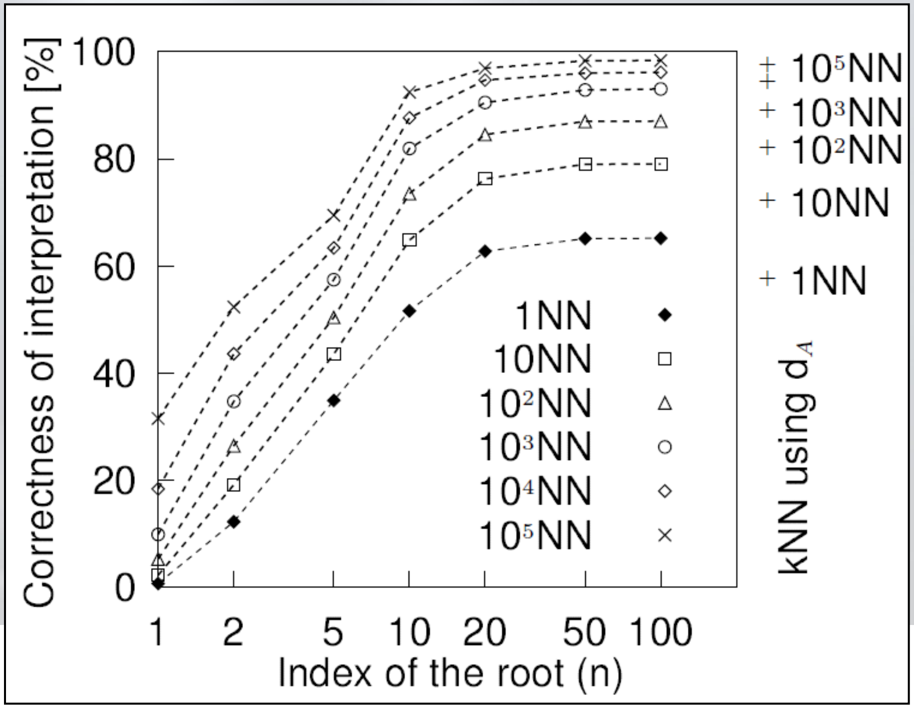
Parametrised Hausdorff Distance (d_{HP})

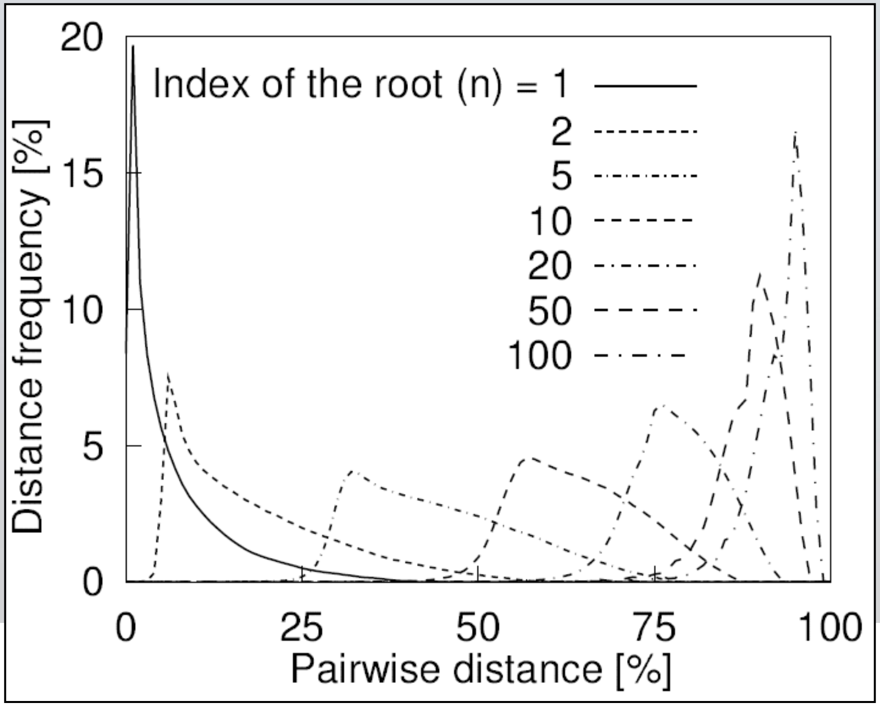
- for each number in the compact representation, the number with minimum difference in the other vector is found
- the average of n^th roots from the set of minima is computed
- d_{HP} can be also combined with precursor mass filter (for the spectra without chemical modifications)



Parametrised Hausdorff Distance (d_{HP})

- increasing n in nth root function
  - + the impact of noise peaks is lower (i.e., the similarity between the spectra is modeled better)
  - + the distance is semimetric (n ≥ 2)
  - – the indexability is worse



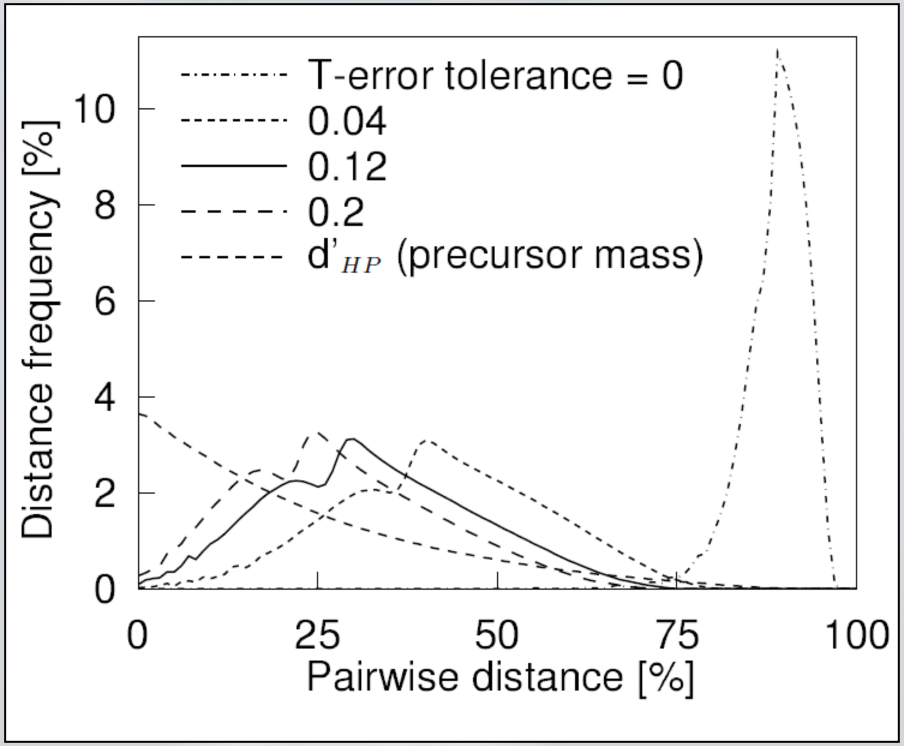


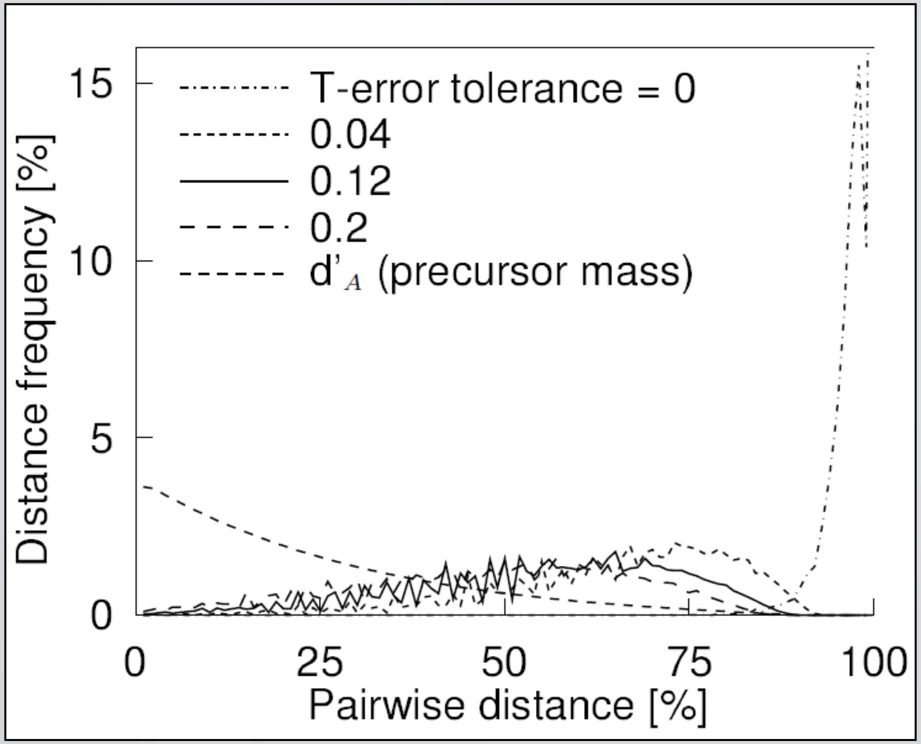
TriGen Algorithm

- controls the metricity (T-error) of the function *v*
  - the ratio of triplets, which do NOT satisfy the triangle inequality
- T-modifier
  - either concave or convex increasing function
  - e.g., Fractional-Power (FP) or Rational-Bézier-Quadratic (RBQ) modifier
  - concave function (w > 0)
    - increases the number of triplets
    - indexability is worse
    - exact search, but slower
  - convex function (w < 0)
    - decreases the number of triplets
    - indexability is better
    - approximate search, but faster
- M-tree, Pivot Table

$$\mathrm{FP}(v,w) = \begin{cases} v^{\frac{1}{1+w}} & \text{for } w > 0 \\ v^{1-w} & \text{for } w \leq 0 \end{cases}$$

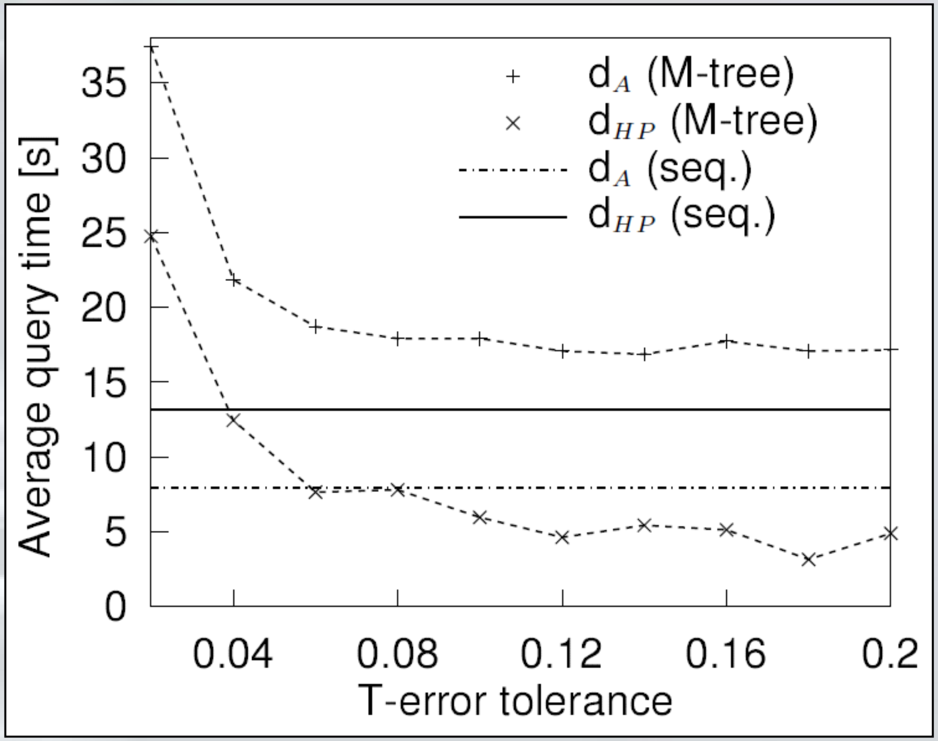
Indexability of d_{HP} and d_A





- d_{HP} – the indexability is better with increasing T-error tolerance
- d_A – about 35% of all pairwise distances in d_A=1 (uncorrectable)
- d'_{HP} and d'_A – indexable very well

Average Query Time



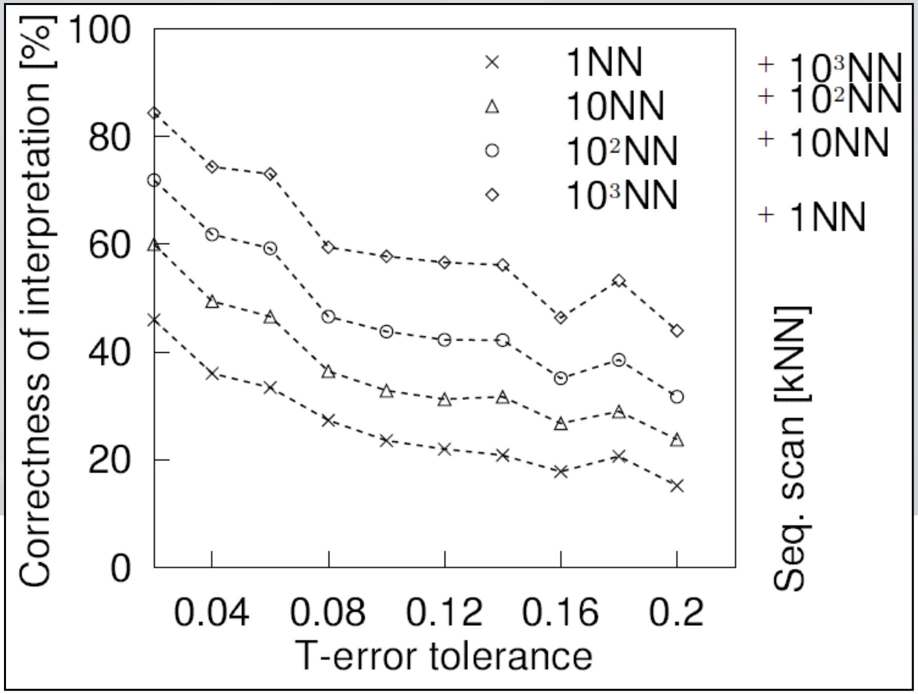
- d_{HP} – 1.6x faster than sequential scan
- d_A – 2.5x slower
- d'_{HP} and d'_A – 32.9x faster and 19.8x faster

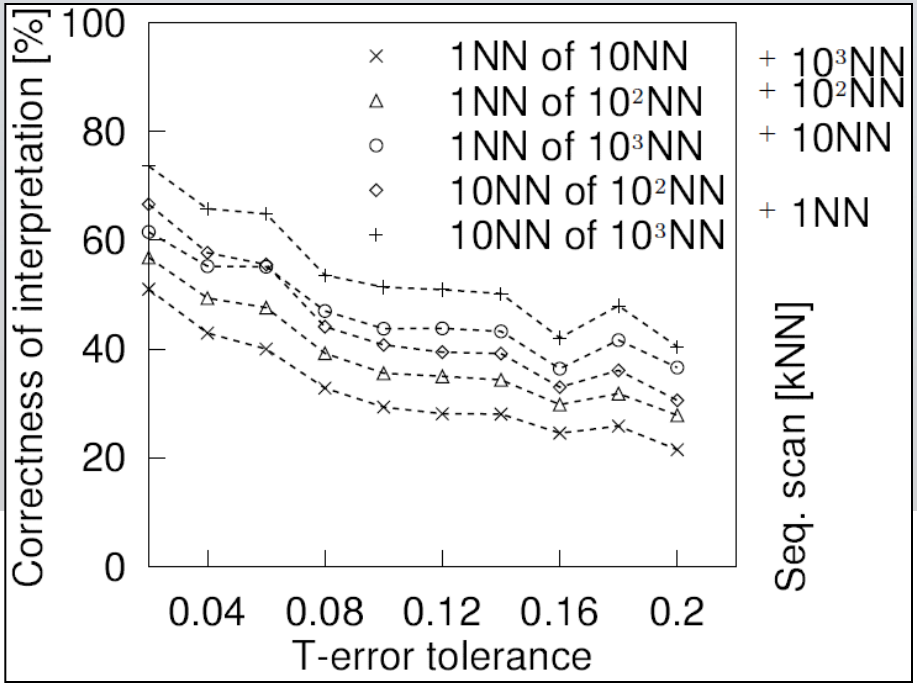
Correctness of Identification - kNN Queries

- correct peptide sequences are cumulated among a few nearest neighbors

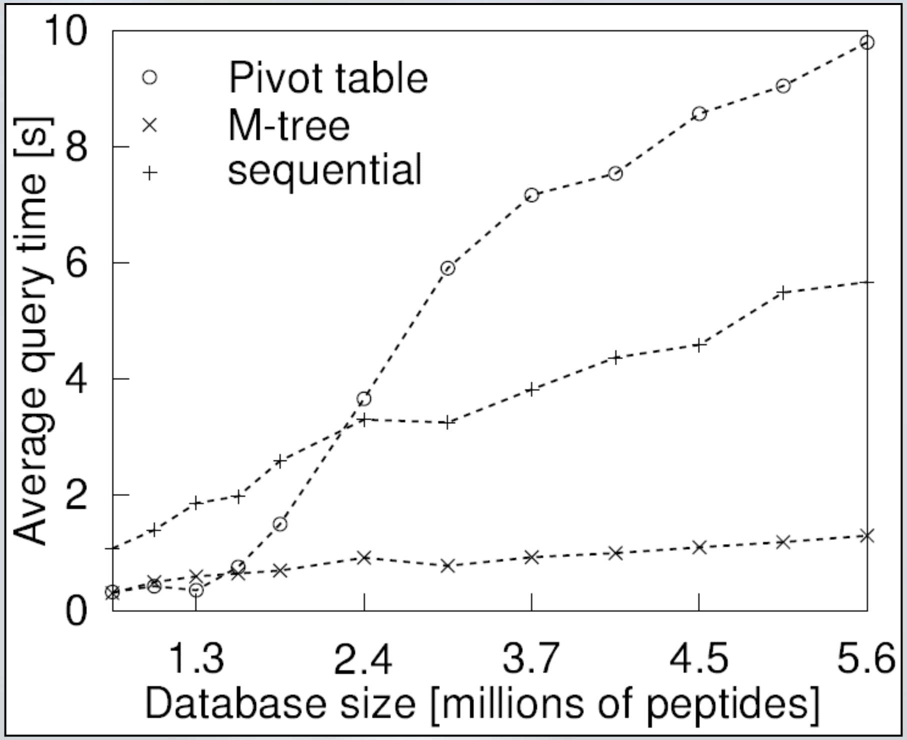
- 1-NN taken from the 100NN result is more likely to be correct than when taking 1-NN from 10NN result

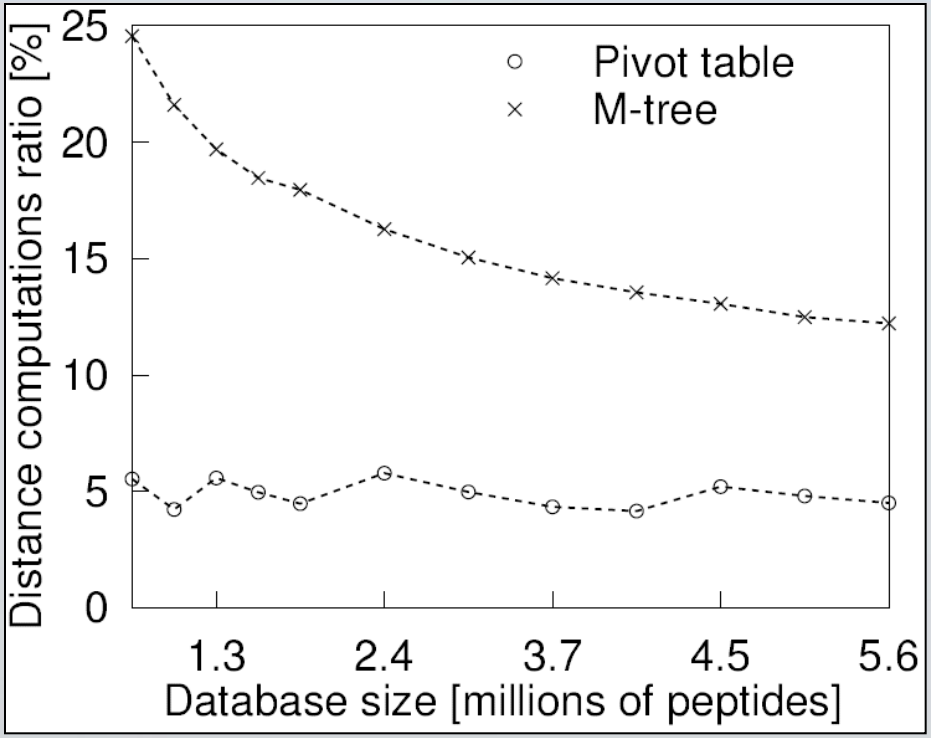
- e.g., at T-error tol. 0.06, correctness 75%, speed-up 1.7x, DC ratio 9.7%
- 1.4x higher for d_{HP} than d_A
- d'_{HP} 85.7% and d'_A 89.6%





M-tree and Pivot Table Comparison





- the Pivot table is faster than M-tree as long as all its blocks are stored in main memory, otherwise it becomes inefficient (moreover, it is outperformed by sequential scan)

- distance computations are misleading for Pivot tables

Conclusions

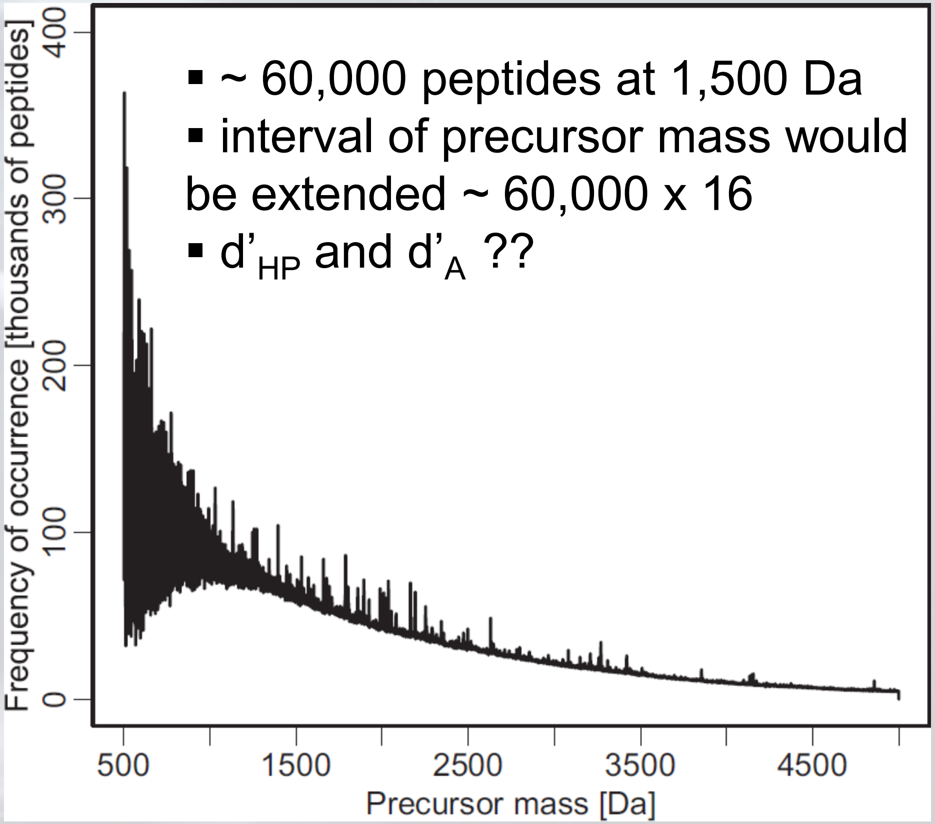
- parametrised Hausdorff distance (d_{HP})
  - models the similarity among spectra very well
  - can be utilized by MAMs when TriGen algorithm is employed
  - if the T-error is higher, then indexability is much better, the search is faster and correctness of interpretation is a little lower

- angle distance (d_A)
  - we verified that it has limitations for utilization by MAMs

- d'_{HP} or d'_A (in combination with the precursor mass filter)
  - indexable very well
  - an extension for mass spectra with chemical modifications may be very hard

Future Work

- dealing with modifications in the mass spectra - precursor mass of modified peptides can differ by more than a few tens to hundreds Daltons (e.g., M+16)



- ~ 60,000 peptides at 1,500 Da
- interval of precursor mass would be extended ~ 60,000 x 16
- d'_{HP} and d'_{A} ??

- d_{HP} seems to be suitable for particular kinds of modifications without an improvement

- NM+16INTFVPSGK
- IYFM+16AGSSK
- NSLESYAFNM+16K

- 30% correctness (1 NN)
- 50% (10NN)
- 84% (5000NN)

- PM-tree, …

Thank You…