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High-dimensional generative probabilistic models for peptide-spectrum matching in tandem mass spectrometry

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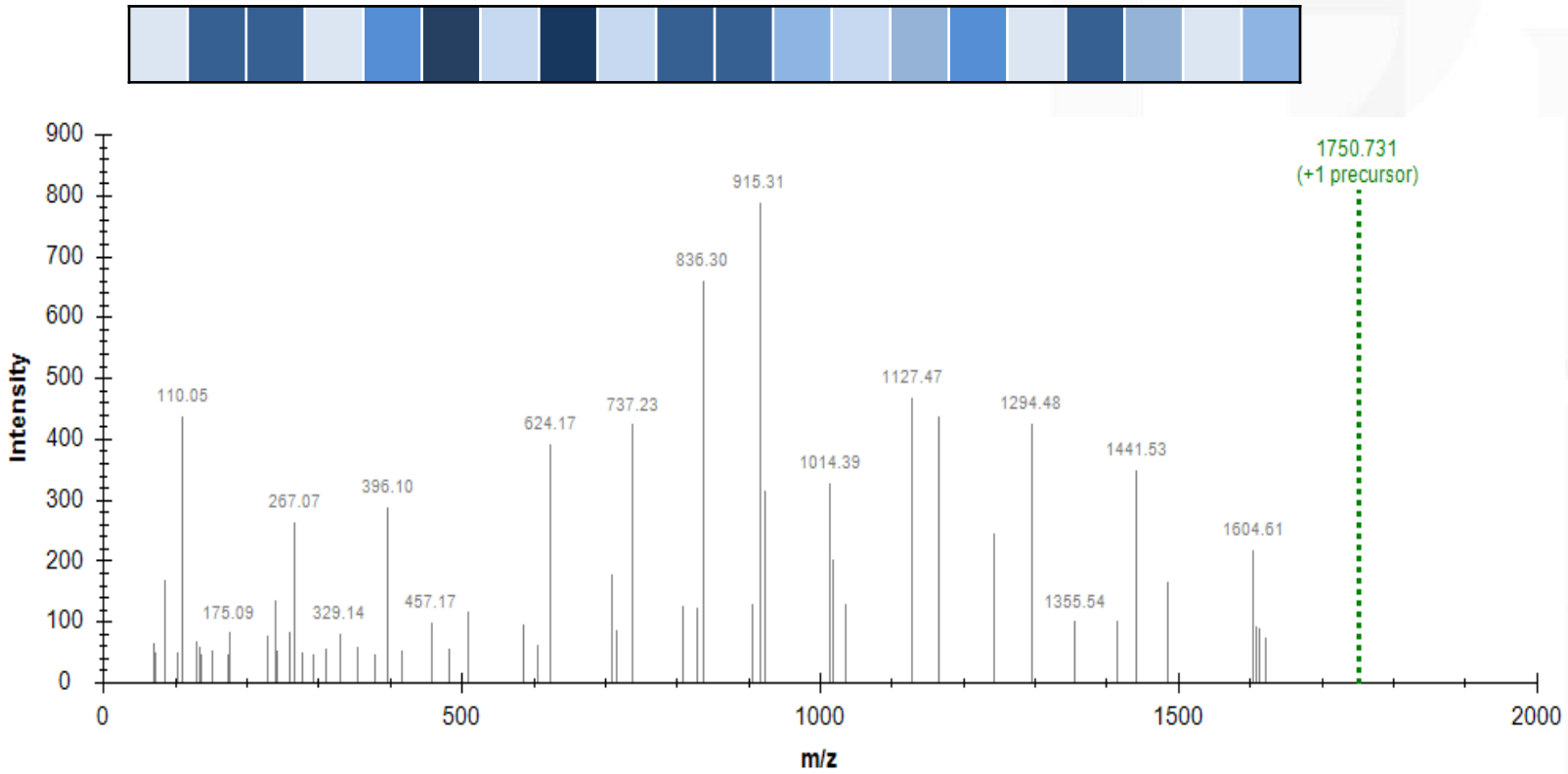
Problem statement

Input: data, obtained from spectrum (below)

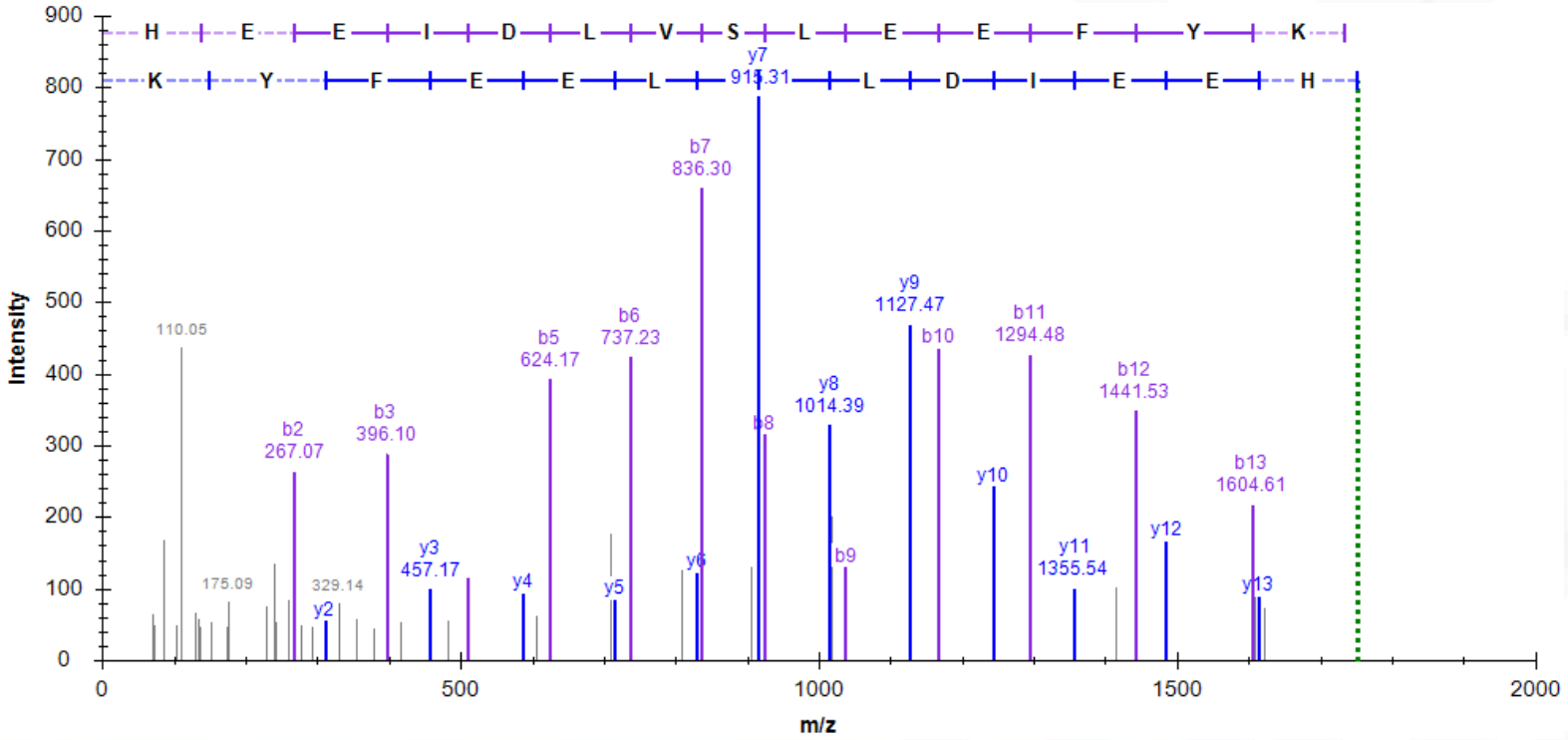
Target: identify the molecule which generated this observed spectrum



Problem statement

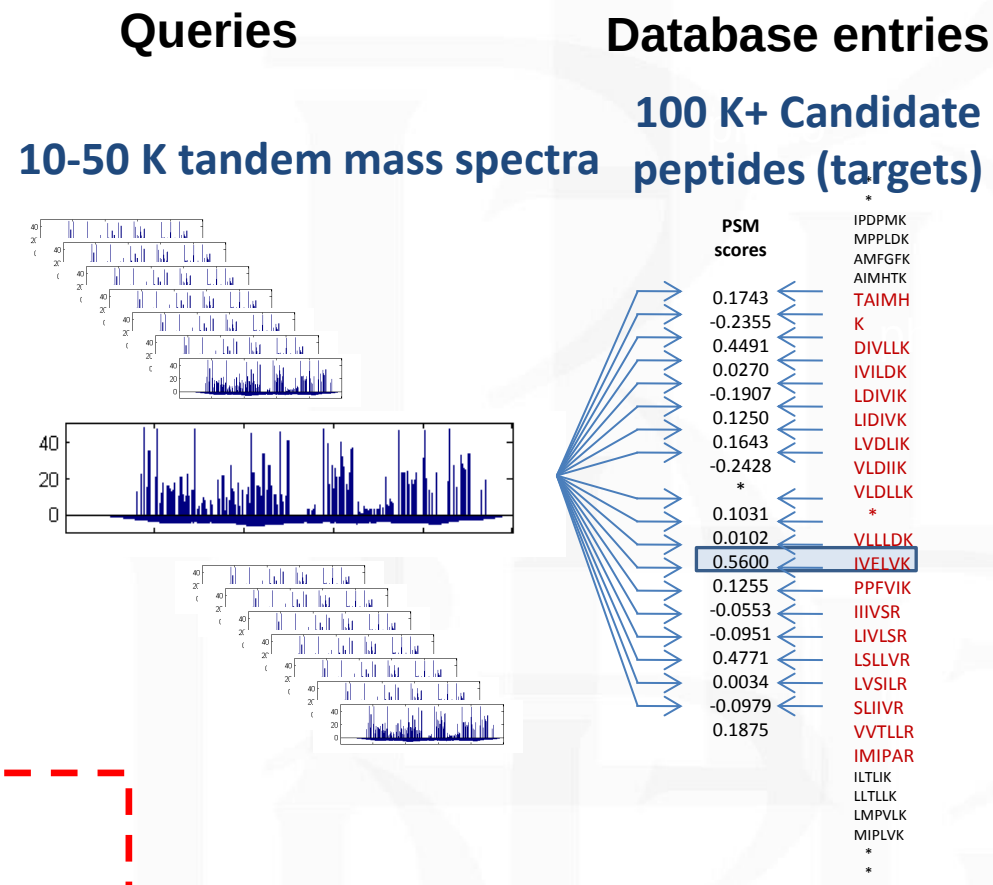
What is important for the identification?

- Location of the peak
- The distance between peaks



How annotation goes?

An experimental spectrum is iteratively matched against a large database, which contains a possible annotations.
The spectrum is annotated with the best scoring database entry.



Matching is based on simple scalar product scoring!

Dataset

Spectra type	Quantity	Volume (TB)
Experimental	9 092 380	7
Theoretical	19 874 734	1.9

The identification process is hampered by:

1. noise peaks
2. missing peaks
3. modifications in the data (correct annotations not included to the reference database)

50-80% of the data cannot be annotated with high confidence!

Expanding the reference dataset would decrease the statistical confidence scores (due to multiple testing correction) => we need a scoring function robust to multiple testing corrections!

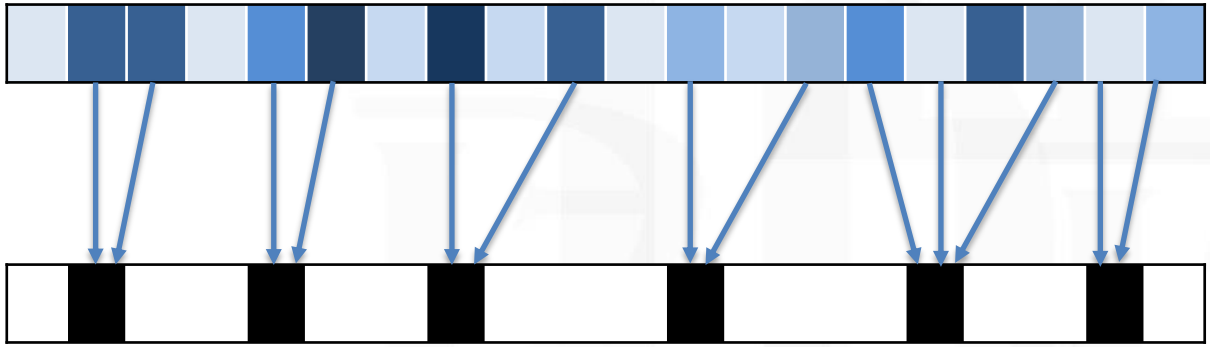
Our approach (under development)

Modeling method: Restricted Boltzmann Machines
Low resolution (old instruments): 2 000 bins
High resolution (new instruments): 1 000 000 bins

Experimental spectrum

W

Theoretical spectrum



$$P(v,h) = \frac{1}{Z}\exp(v^T W h)$$

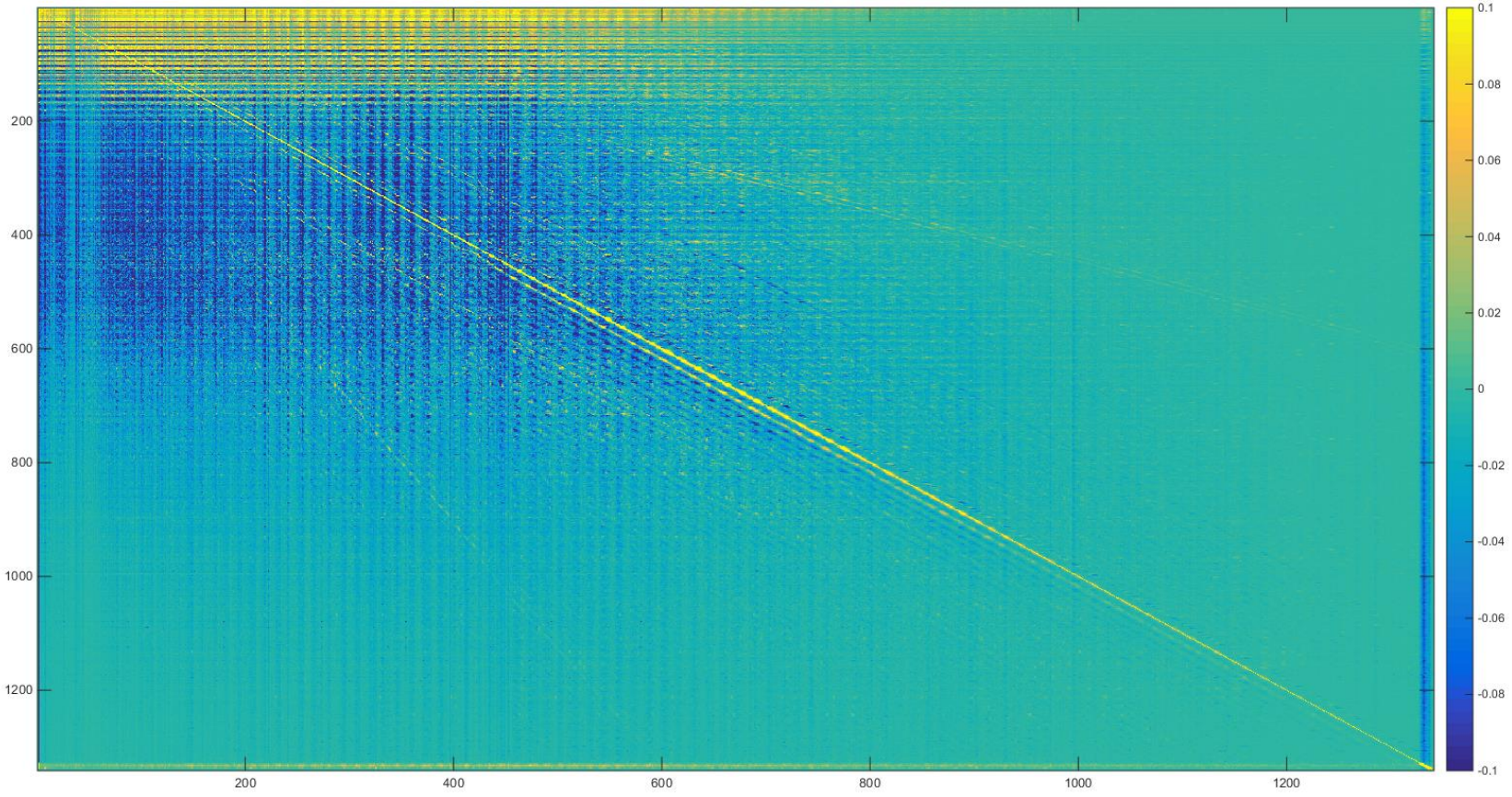
W (100K x 100K) will be very big to learn!

Challenges

- Large dimensions (for high resolution data)
- Traditional training methods do not work: they use sampling of h with MCMC, but then h will be garbage as usual weights update rule $\Delta w_{ij} = \eta(E[v_i h_j]^0 - E[v_i h_j]^\infty)$ => we approximate h from database
- For the training we approximate $P(v,h) \sim P(v,v)$
- Therefore we got a fully observed dataset so the training is straightforward
- Ubiquitous peaks they appear in every data and cause high correlation with all other data

Results

The weight matrix W learnt:



Future work

1. Suppress the effect from ubiquitous peaks using some regularization methods
2. Run experiment on high resolution data
3. Speeding up the training (there is a *log-sum-exp* in the training, so it would be nice to eliminate it with some accurate approximations)

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Thank you for your attention!

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