Spetrum Prediction with DNN

Review:

① Relative quantification

② Label free: peak area

- DDA: precursor intensity over RT.
- SRM/PRM: fragment ion

③ Labelling: isotope label & mix

④ MM:

- Find unique peptide
- PRM.

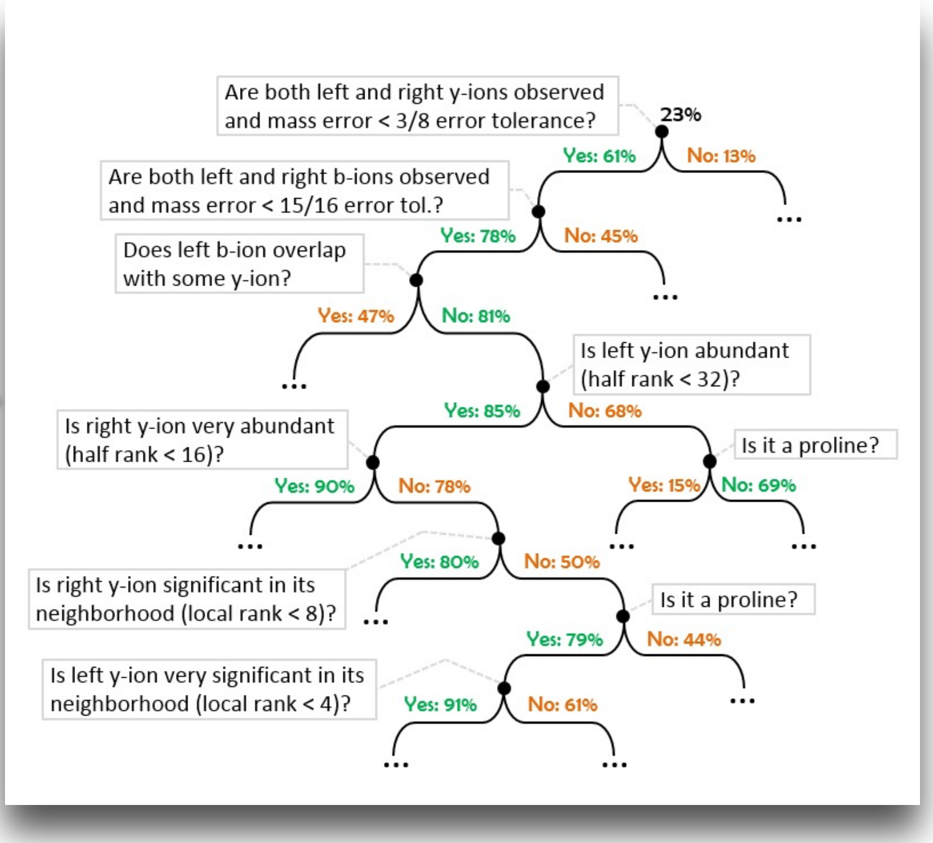
⑤ Machine Learning.

Machine learning

- We’ve briefly used machine learning twice now:
  - Use a decision tree to score an amino acid in a de novo sequence.
  - Combine multiple score features in database search.

Use a decision tree to determine the amion acid score in de novo sequencing.

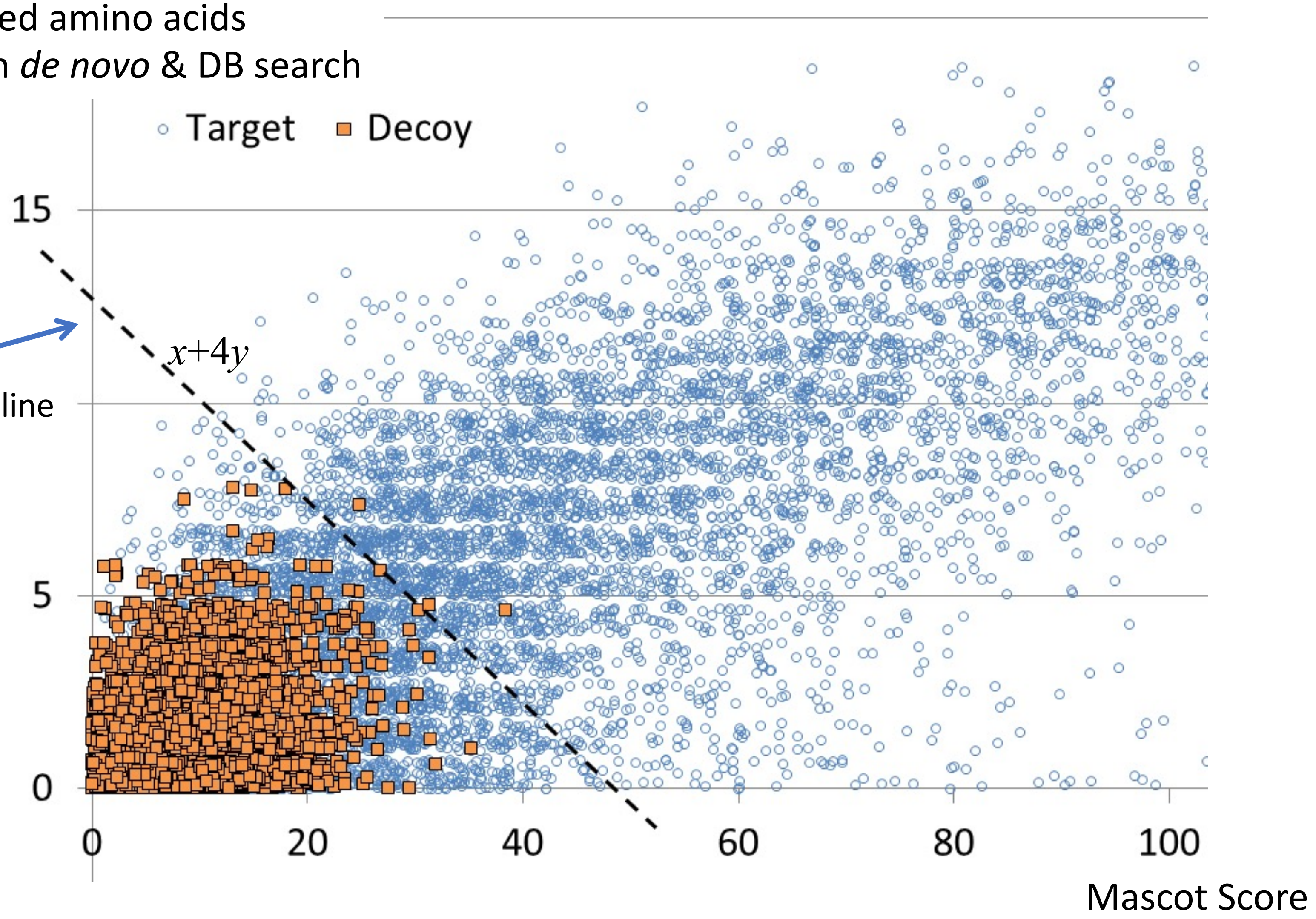
NIST Spectrum Library
340,000 spectra


Are both left and right y-ions observed and mass error < 3/8 error tolerance?
23%
Yes: 61%
No: 13%
Are both left and right b-ions observed and mass error < 15/16 error tol.?
Yes: 78%
No: 45%
Does left b-ion overlap with some y-ion?
Yes: 47%
No: 81%
Is left y-ion abundant (half rank < 32)?
Yes: 85%
No: 68%
Is right y-ion very abundant (half rank < 16)?
Is it a proline?
Yes: 90%
No: 78%
Yes: 15%
No: 69%
Yes: 80%
No: 50%
Is right y-ion significant in its neighborhood (local rank < 8)?
Is it a proline?
Yes: 79%
No: 44%
Is left y-ion very significant in its neighborhood (local rank < 4)?
Yes: 91%
No: 61%
...

169 features
14,000 internal nodes
average depth 18.4

Use multiple features in PSM score

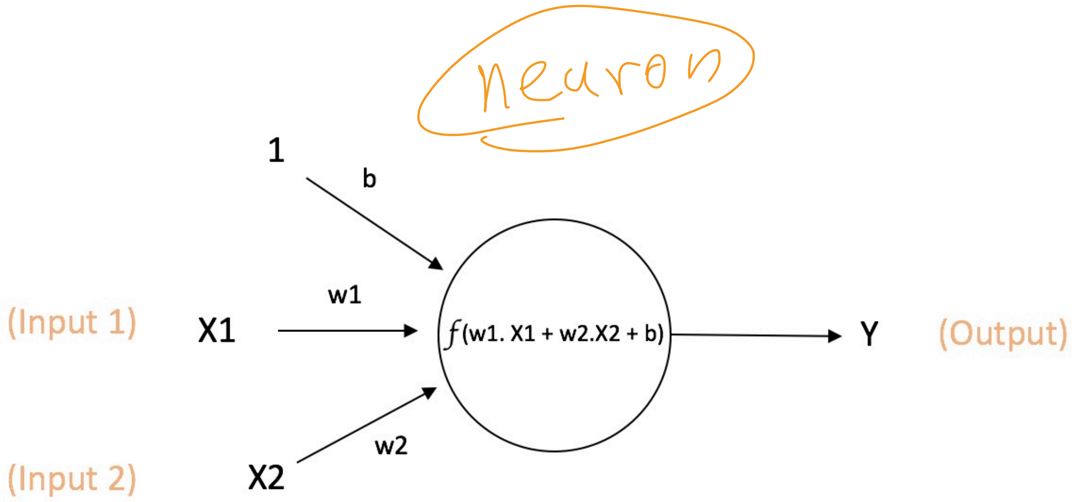
# matched amino acids
between *de novo* & DB search



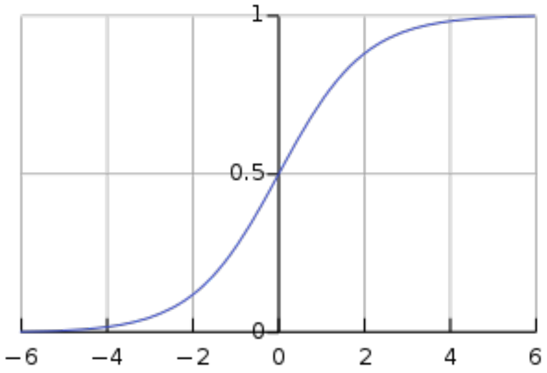
best
separation line

Mascot Score

Combine Multiple Features Together



Output of neuron = Y= f(w1. X1 + w2.X2 + b)



sigmoid

$$y = \frac{1}{1+e^{-z}}$$

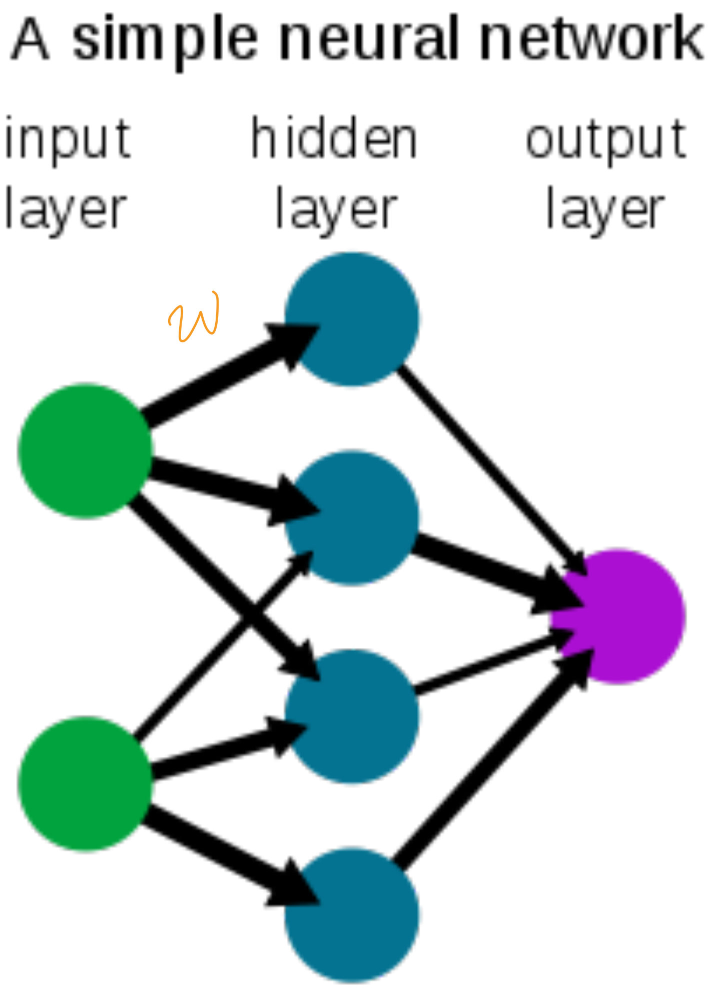
Activiation function

- Train the coefficients w and b to maximize the separation of true and false data points.
- For training, a cost function is defined and there are optimization algorithms to minimize the cost.
- Under certin cost function and sigmoid activiation, this is equivalent to the logistic regression.

Training

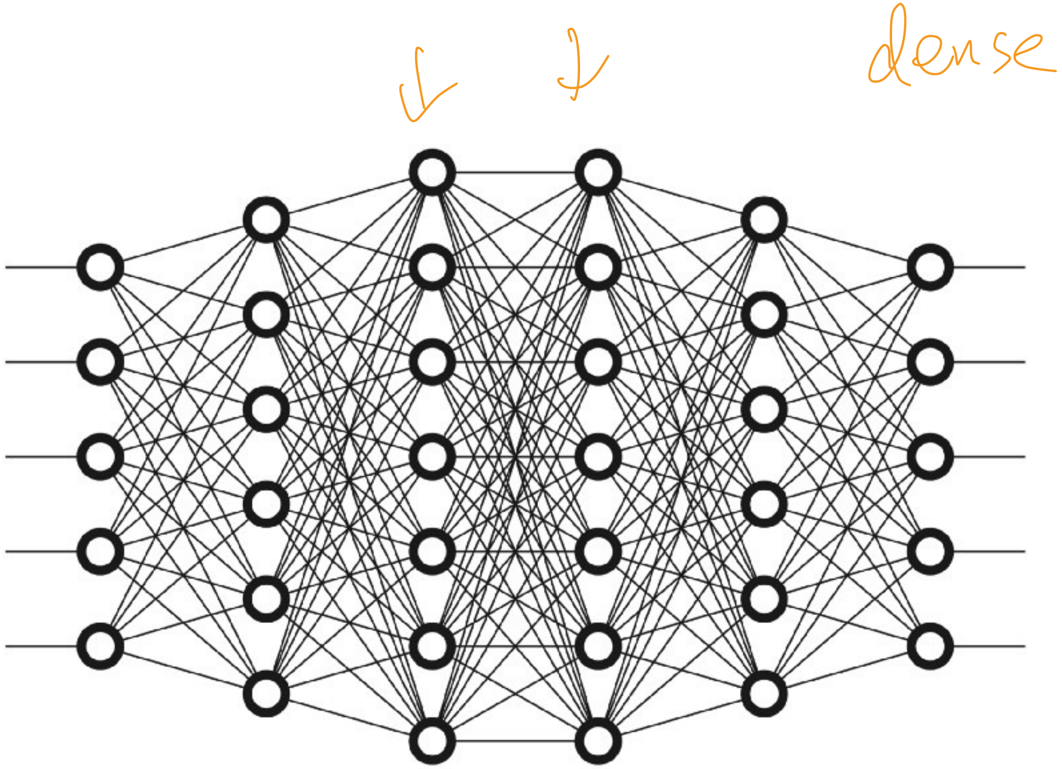
- Known correct (input, output) pairs.
- A cost function.
- Adjust the parameters gradually to reduce the total cost over all training data: gradient descent.
- Train$\overset{in}{\wedge}$g, validation and testing data are separate.
- Training: to learn parameters
- Validation: control the training process to avoid overfitting
- Testing: test the real performance after training

Neural Network



- A neural network just combines many neuons together to fit a more complex nonlinear function.
- Often these neurons are organized in layers.
- The algoritm for training is usually the so-called backpropagation algorithm.
- Main idea behind backpropagation is gradient descent implemented in a nice way.

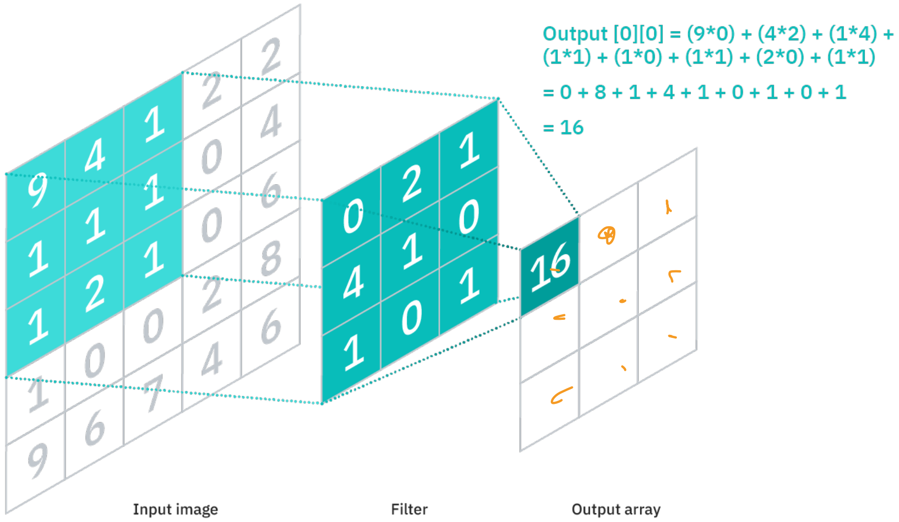
Deep Neural Network



dense layer

- DNN is just a neural network with MANY layers.
- MANY coefficients (parameters) to train.
- Require new training algorithms to both learn fast and avoid overfitting.
- GPU, big data, and new learning algorithm contribute to the development.

Convolutional Neural Network



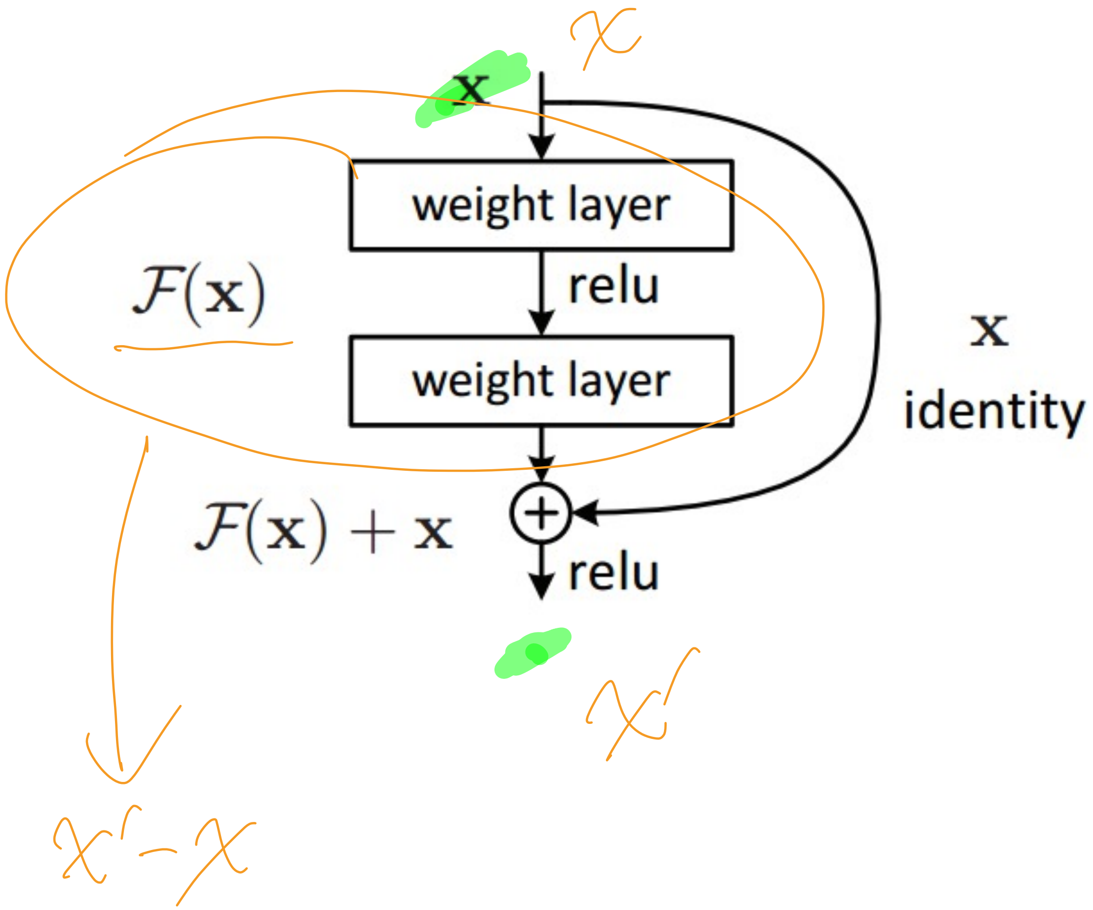
- When the input has spatial similarities, one can reuse the coefficients.
- A “filter” can be seen as a neutron on a local region of the input. kernel ,
- By sliding the filter over the input array, one can produce the output array. This is called convolution.
- Number of coefficients is reduced significantly.
  - Reduce overfitting.
  - Can afford more layers.
  - Capture the local spatial correlation by focusing on each local region.

Deep Learning

- Similar to CNN, deep learning researchers developed other structures to connect between layers that can boost up the learning performance.
- Some of these common structures can be reused as building blocks in other learning tasks.
  - Just like programming patterns.
- There are deep learning frameworks that allow the users to assemble the building blocks in a flexible way, and provide the learning and prediction support.
  - Tensorflow, Pytorch etc.

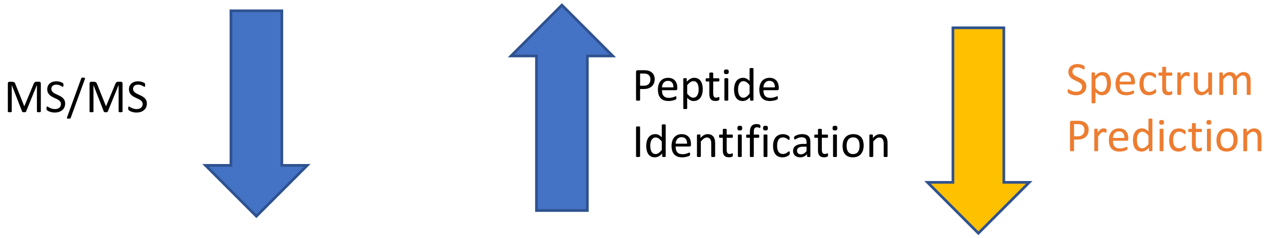
ResNet (Residual Neural Network)

- Another commonly used building block is the residual block.
- Intuitively, each additional residual block uses one or more layers to predict the difference between x and the desired output.
- This approach has proven to both improve the learning performance (both learning speed and accuracy).
- Residual blocks are supported by most of the popular deep learning frameworks.



Spectrum Prediction

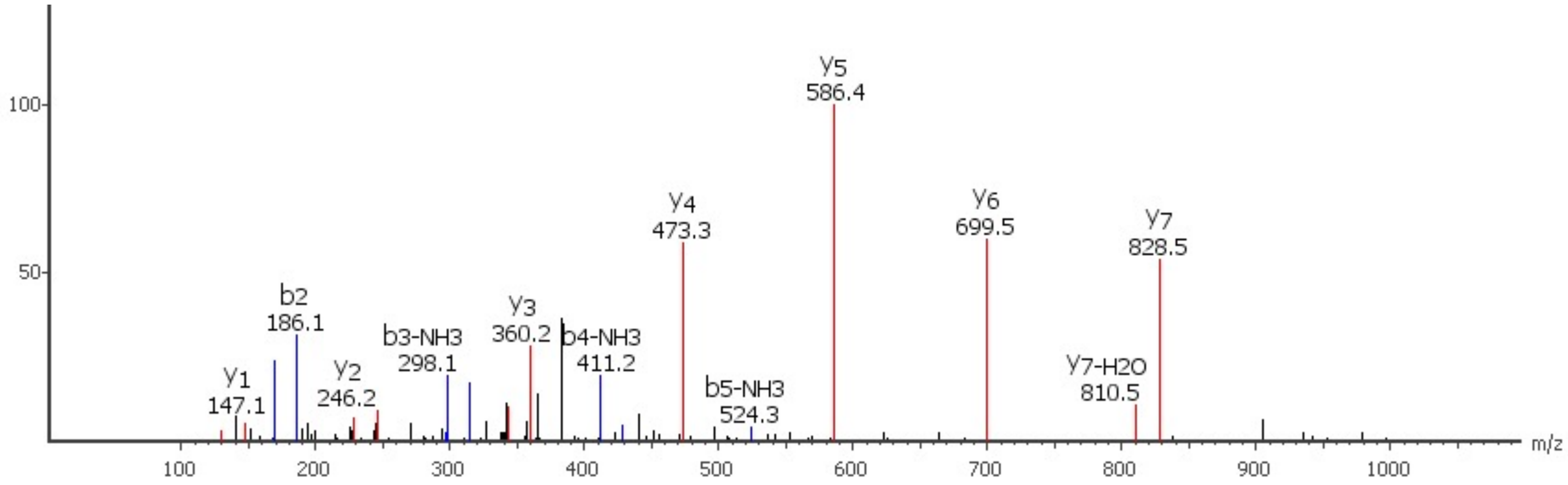
ANELLLNVK



MS/MS

Peptide Identification

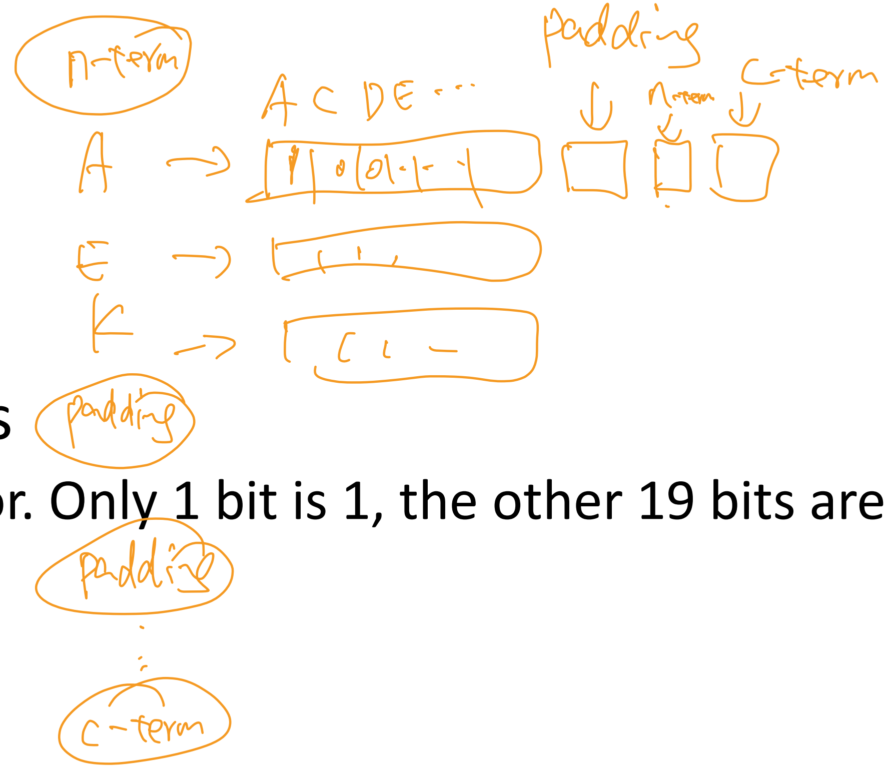
Spectrum Prediction



Predict Peptide Detectability

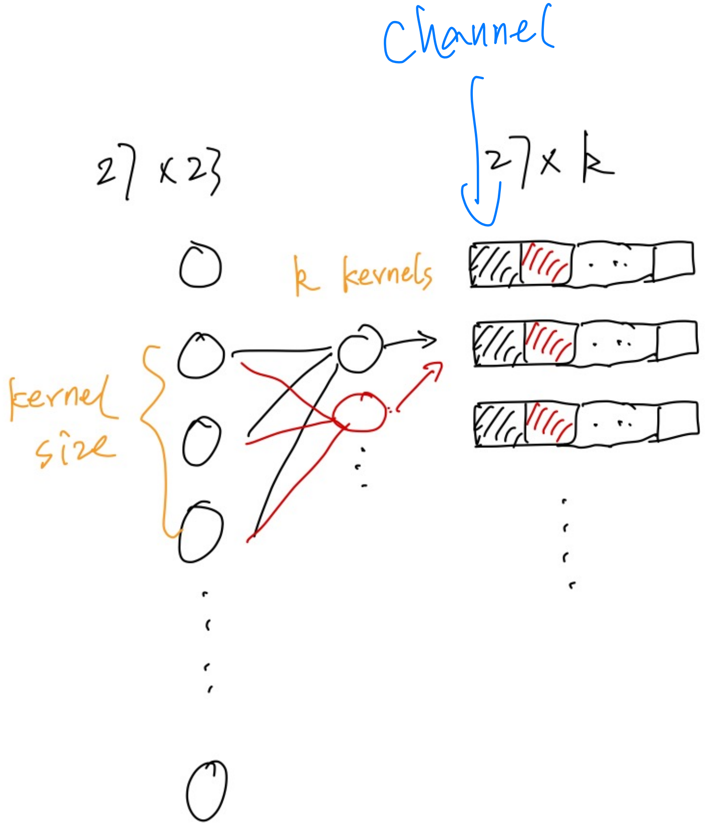
- Let’s start with a simpler task to learn the basics: To predict whether a peptide is detectable in a DDA experiment.
- Input: A peptide sequence.
- Output: 0 or 1. (or a probability that the peptide is detected).
- We also have a lot of training data: pairs of (input, true/false).
- Model adopted from the DNN model in following spectrum prediction paper.
  - *Liu et al.* **Full-Spectrum Prediction of Peptides Tandem Mass Spectra using Deep Neural Network**. *Anal. Chem.* 2020, 92, 6, 4275–4283
- The paper does not predict detectability but we adopted the model anyway for studying purpose. There can be many different DNN structures for the same task.

Encode a Peptide



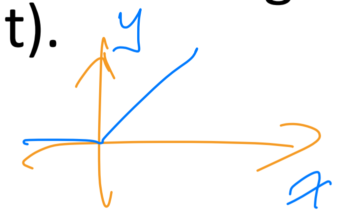
- Basic idea: one-hot encoding of amino acids
  - Each amino acid is mapped to a length-20 vector. Only 1 bit is 1, the other 19 bits are 0.
- Peptides have variable lengths.
  - Limit the length to be at most 25AA.
  - If <25AA, then padding with a special character.
- Also encode the two termini (n-term and c-term).
- In total 20+2+1 = 23 codes are needed. One-hot requires a length-23 vector.
- In total 25+2 = 27 positions to code. Therefore, each peptide is mapped to a 27*23 array.
- Note: PTM is not considered.

One convolution layer

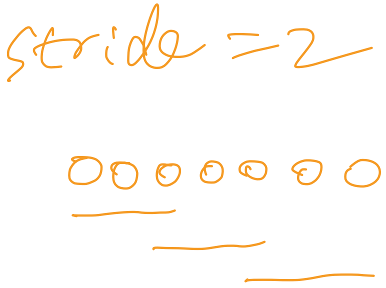


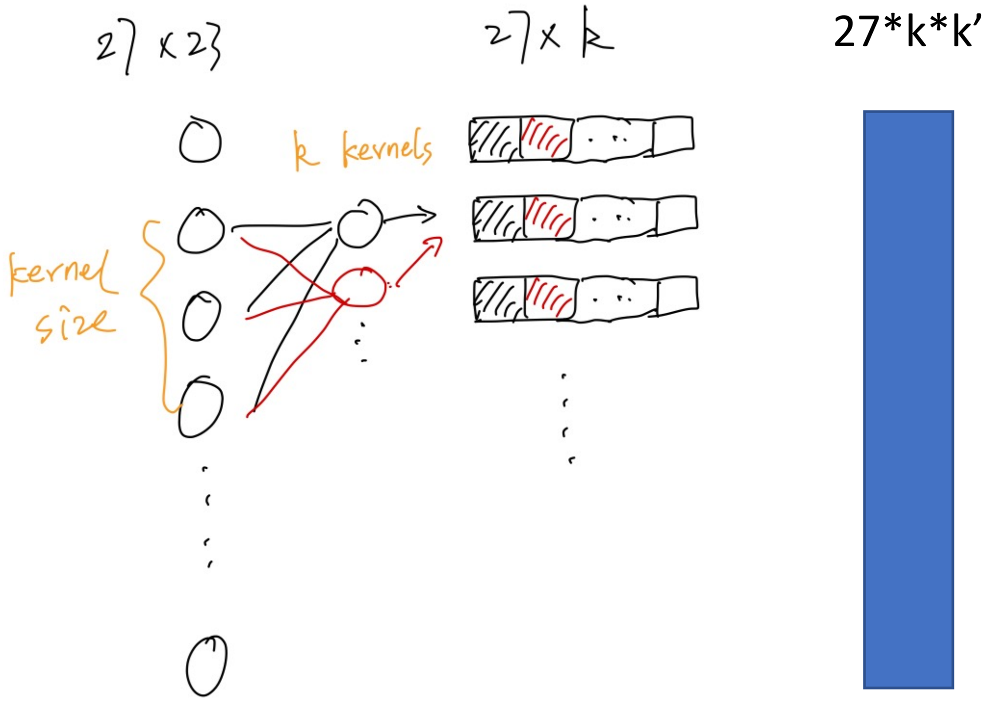
k: channels, filters, kernels.

- Recall each AA is a 23-dimention 1-hot encoding.
- A kernel is a function that computes a value from s adjacent amino acids. Sliding the same kernal will produce a 27 dimension vector. This is the convolution.
- Padding is needed to keep the dimension 27.
- There are k kernals. So the output of the convolutional layer is 27*k.
- # of parameters is k*s, which is relatively small.
- Activiation function for the filters: sigmoid or ReLU (Rectified Linear Unit).



More convolution layers

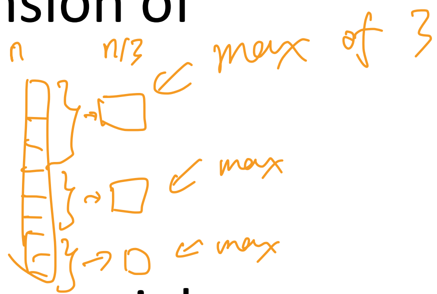




27*k*k'

k: channels, filters, kernels.

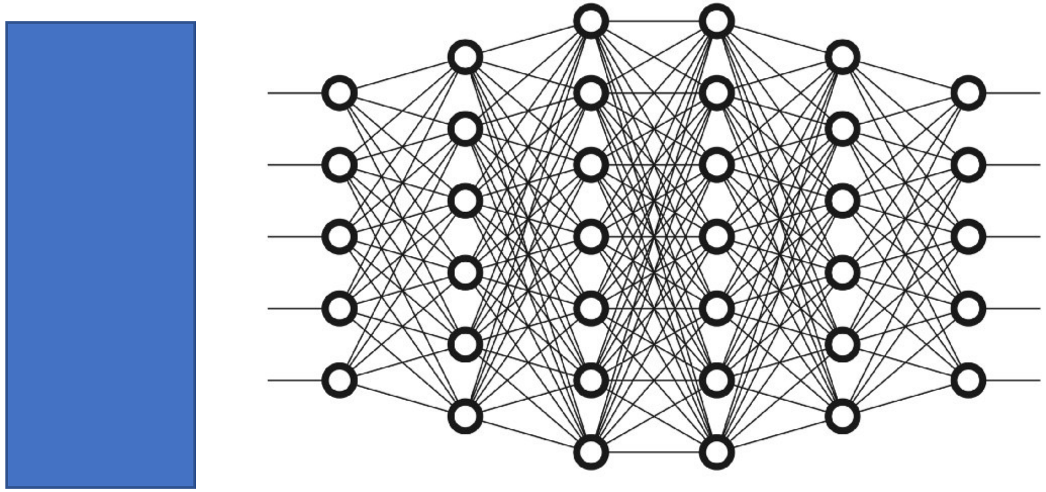
- For next layer, we can take each channel in the previous layer, and apply k' kernerls on it.
- k*k' kernels, producing k*k' channels.
- Three practices are often used to avoid exponential expansion of number of parameters
  - k'=1
  - Stride>1
  - Pooling
- With controlling of exponential growth, we can keep adding more and more layers.



Fully Connected Layers

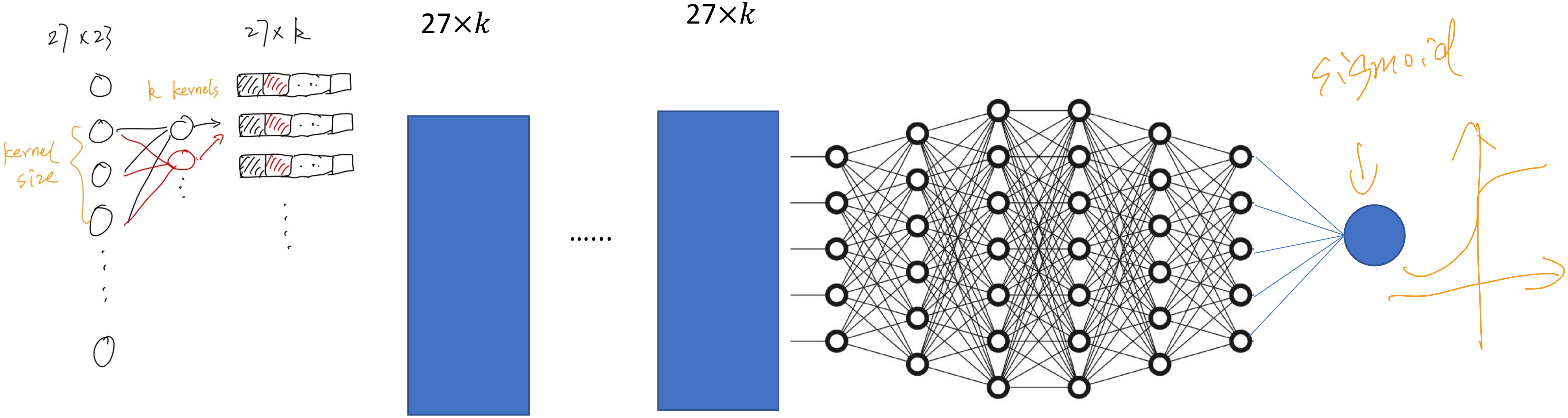
output of
convolutional layers

$n\times k$



- The output of the last convolutional layer is connected to a few fully connected (dense) layers.
- At last, the output layer computes the output.
- Output layer can contain one or more neurons – depending on the actual output format.
- The fully connected layers have the largest number of parameters to learn.

Overview of Whole Network



27×k

27×k

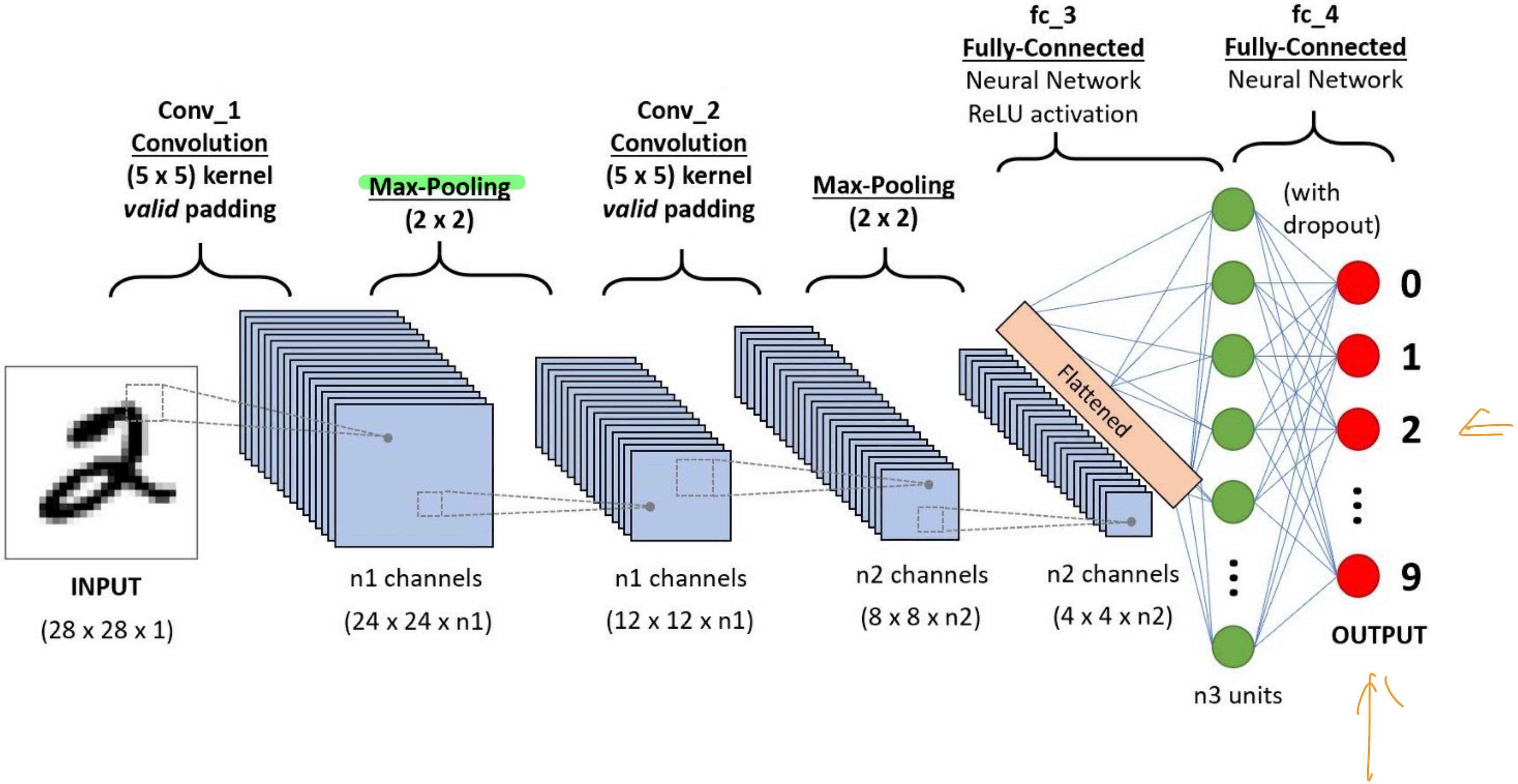
……

k: channels, filters, kernels.

Learning and Prediction

- Prepare training, validation, and testing data.
- Specify the network structure in a deep learning framework (e.g. Tensorflow)
- Learn parameters with the training data. Control the learning process with the validation data.
- Test the performance on the testing data ONLY after the training is done and parameters are fixed.
- Use the trained parameters to make prediction for future data.

Another Architecture for Handwriting Digit Recognition

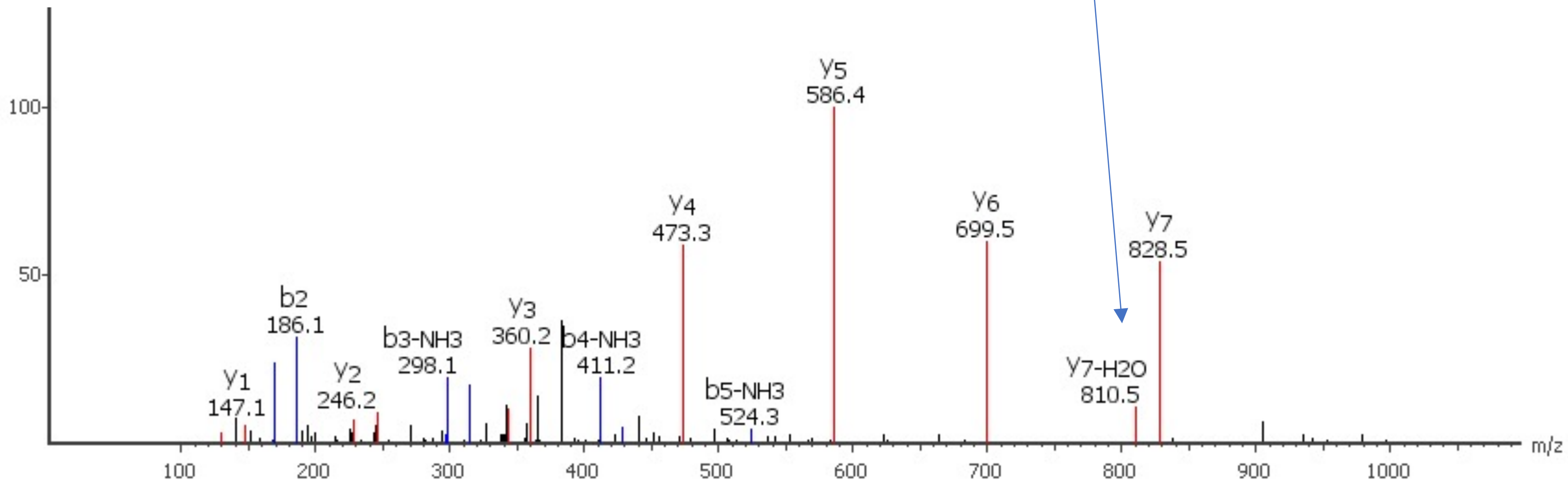


Spectrum Prediction

ANELLLNVK

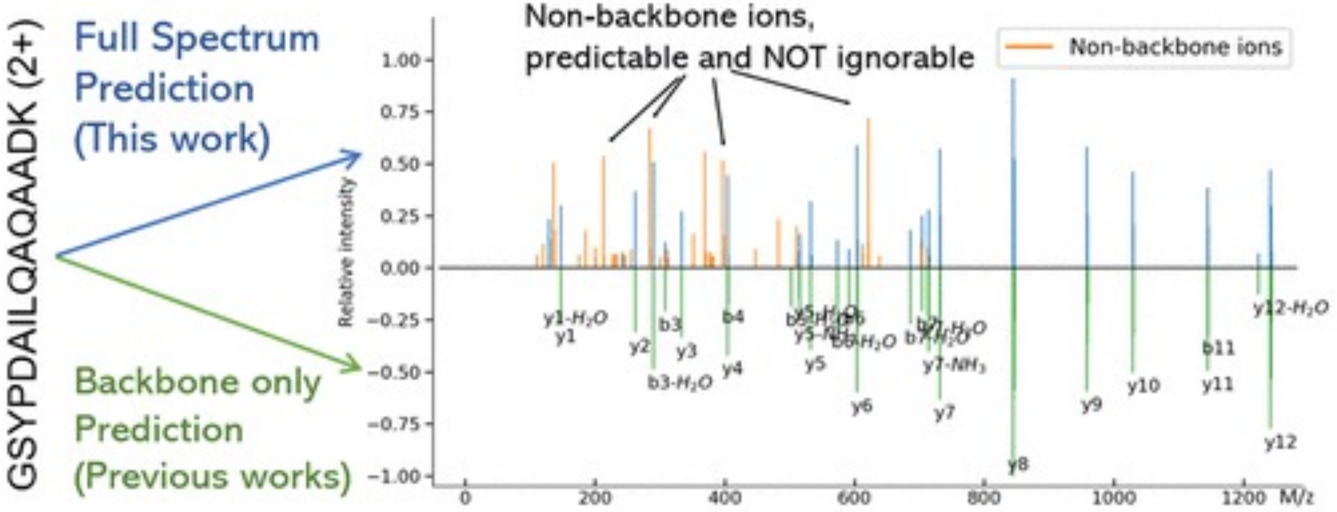
Spectrum Prediction

Should these minor ions (not y and b) be predicted?



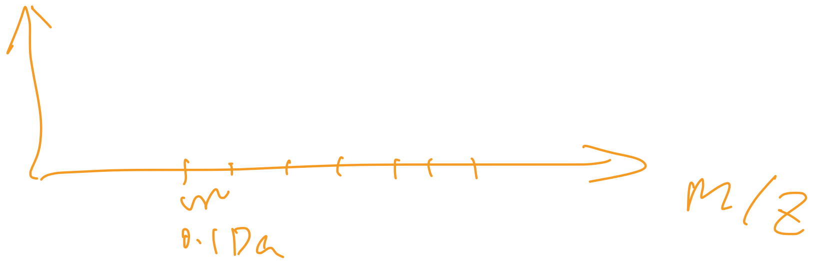
Spectrum Prediction

- Two lines of research:
  - To predict only the main fragment ions (e.g. b and y ions).
  - To predict the full spectrum.
- Both have been done in literature. We study the full spectrum prediction in the following paper.



Liu et al. **Full-Spectrum Prediction of Peptides Tandem Mass Spectra using Deep Neural Network**. *Anal. Chem.* 2020, 92, 6, 4275–4283

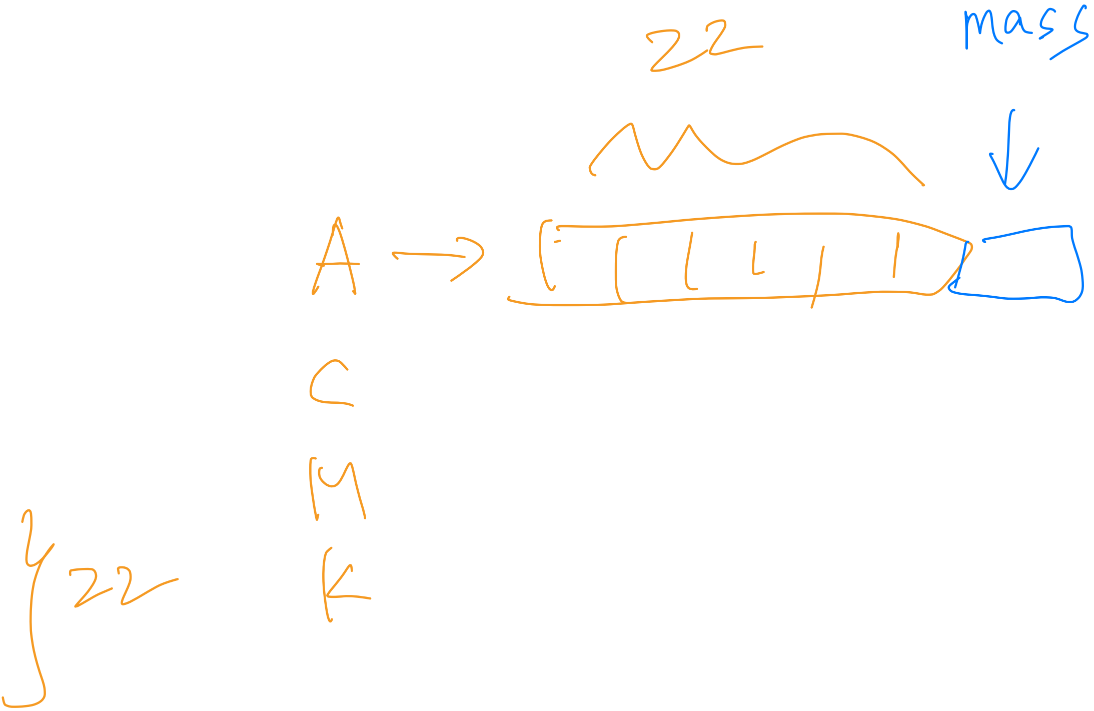
Output Format



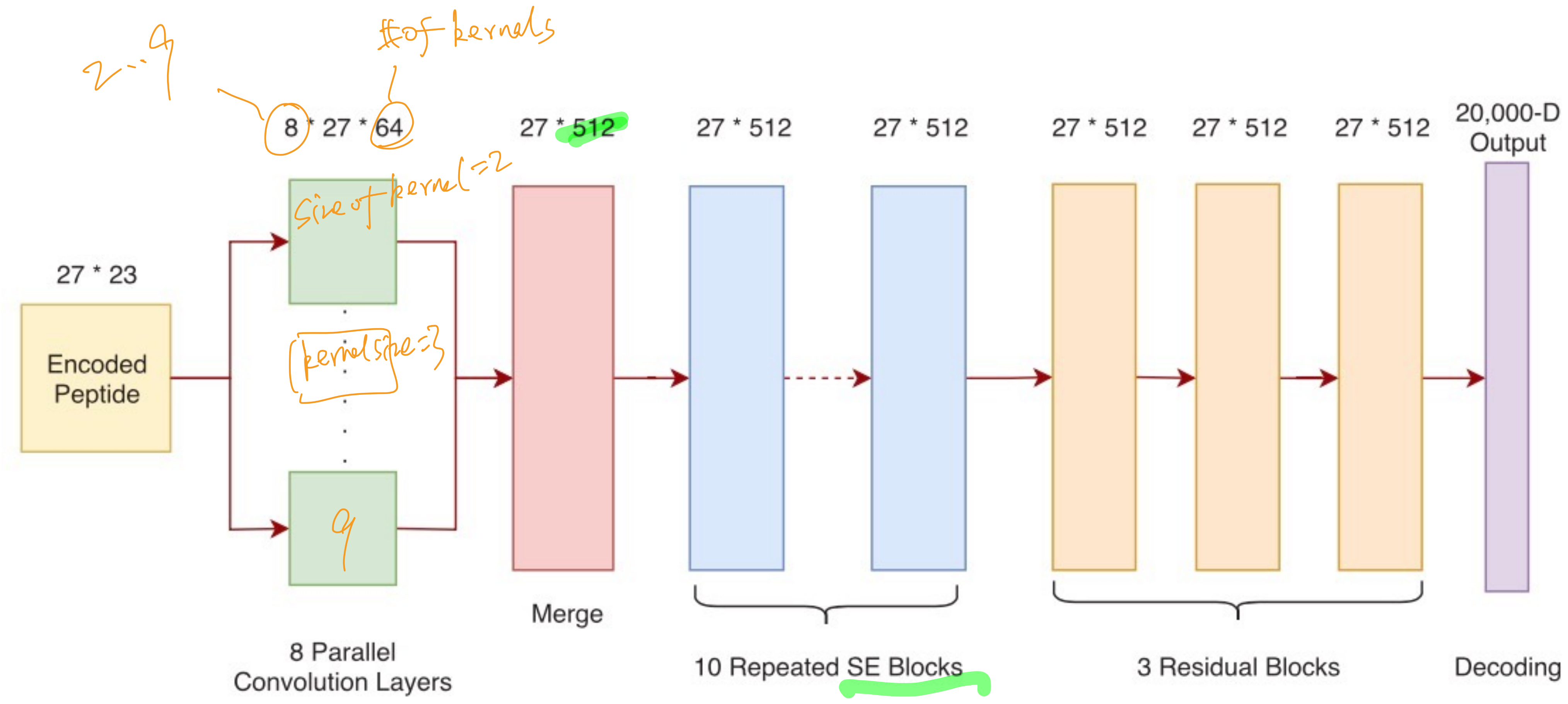
- A spectrum usually has a limited m/z range. The work only predicts peaks between 180-2000.
- The spectrum is represented by a sparse one-dimensional (1-D) vector by binning the m/z range between 0 and 2000 with a given bin width. The value stored is the peak intensity.
- With 0.1 Da bin width, a spectrum becomes a 20,000-dimension vector. (Note: most dimensions have value 0).
- The value in each bin is the relative intensity of the tallest peak in the bin.
- Prediction is to predict the values in all the bins.

Input

- Maximum length 25 peptide. Padding if shorter than 25.
- 1-hot encoding of each amino acid, the termini, and padding. Do not distinguish n and c term.
- Additionally provide the amino acid residue mass.
- Thus, 23 dimension vector for each amino acid and termini.



CNN Architecture for Spectrum Prediction

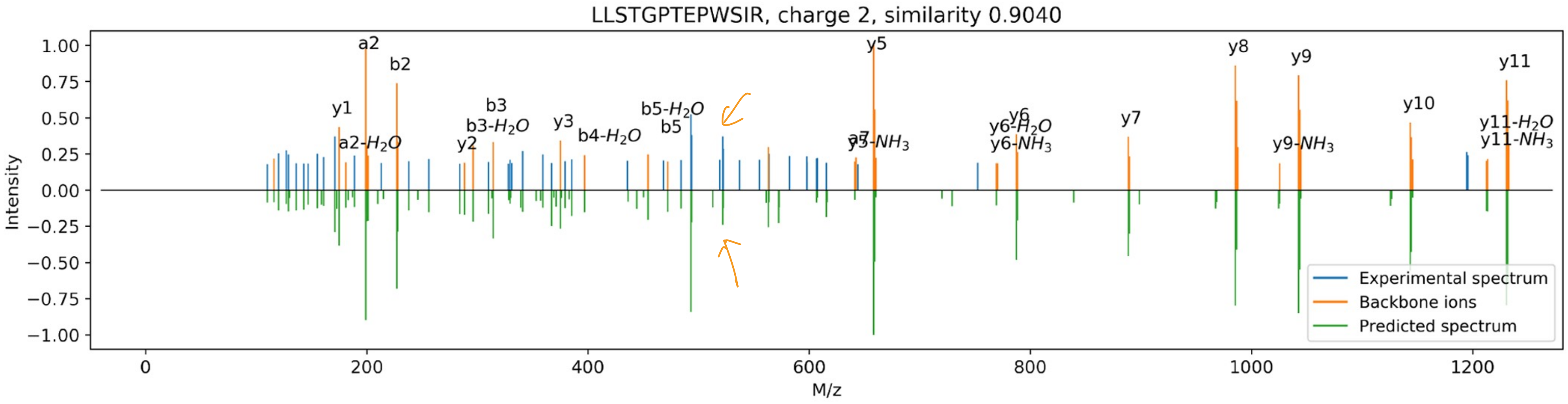


- The 8 parallel convolution layers use kernel size 2 to 9, respectively.
- SE (Squeeze-and-Excitation) blocks are another type of commonly used DNN building blocks.

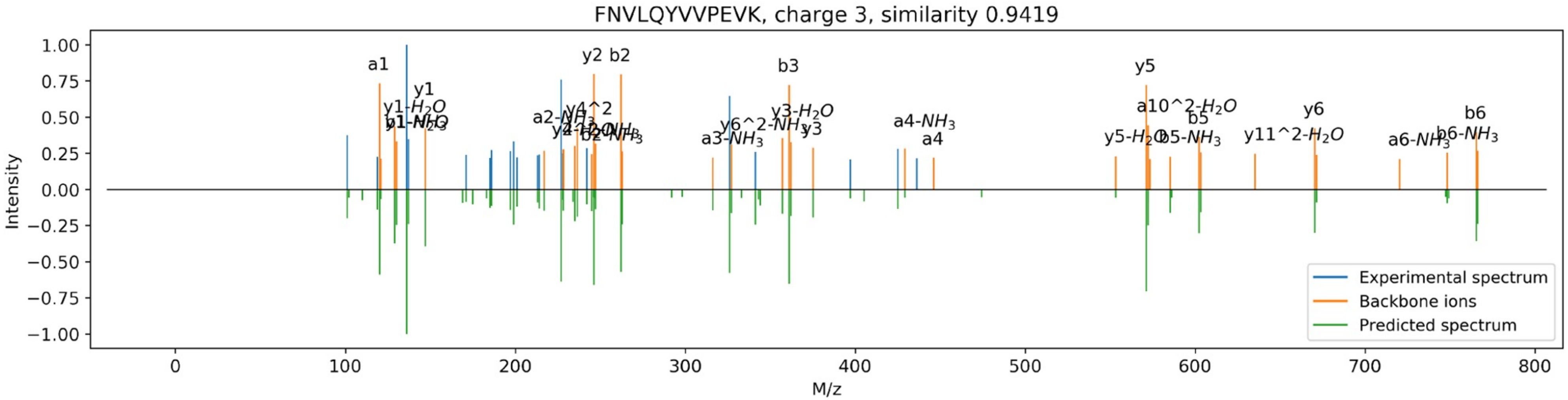
Training

- 2.2M spectra with known sequences were used for training.

Predicted Examples

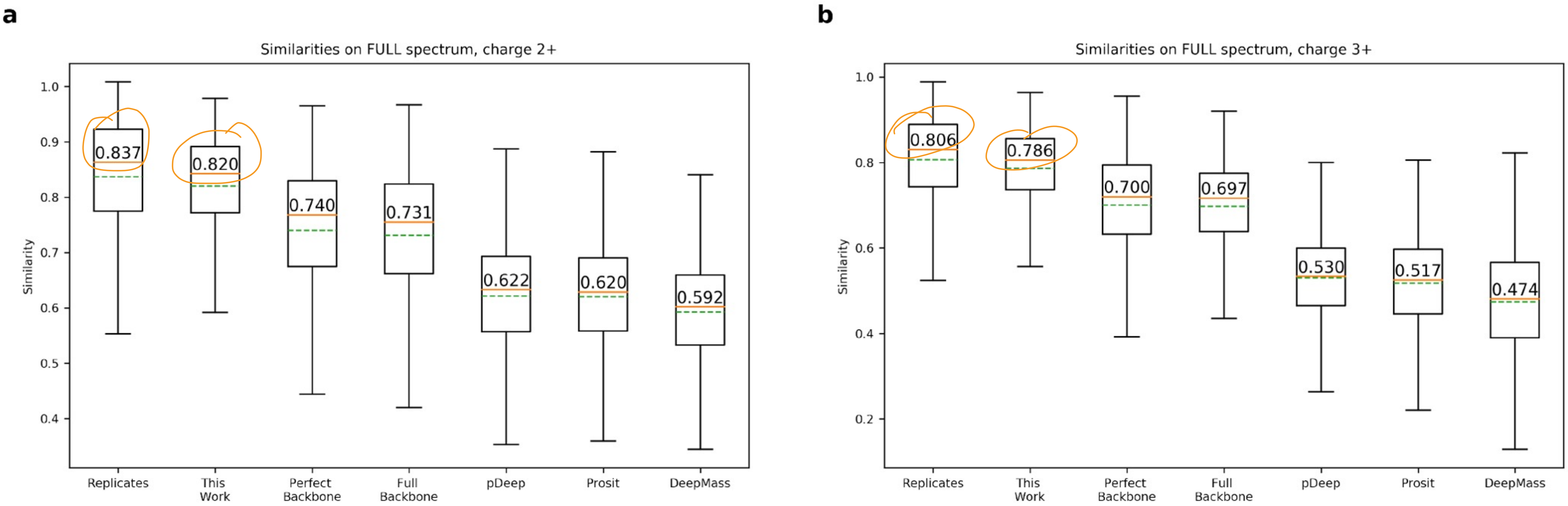


(a)

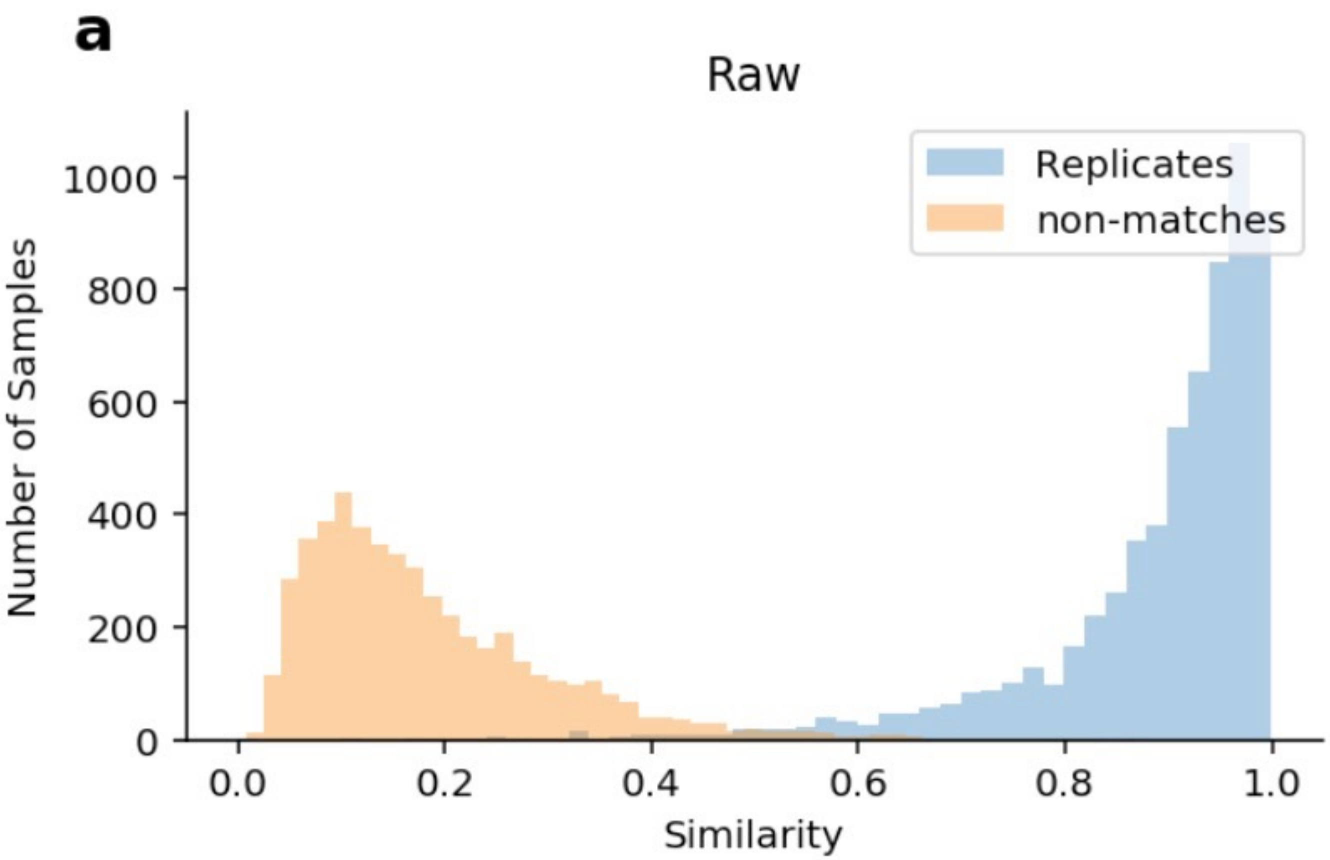


(b)

Comparison to Other Tools



Spectrum Prediction Helps Peptide Identification



$\vec{a}$ $\vec{b}$

$$\frac{\vec{a}\cdot\vec{b}}{\|\vec{a}\|\,\|\vec{b}\|}$$

If peptide is correct, then its predicted spectrum should match the experimental one with high similarity. Whereas the wrong peptides should have low similarity.