Uncertainty Quantification for Reliable Automatic Multiplet Classification in ^{1}H NMR Spectra

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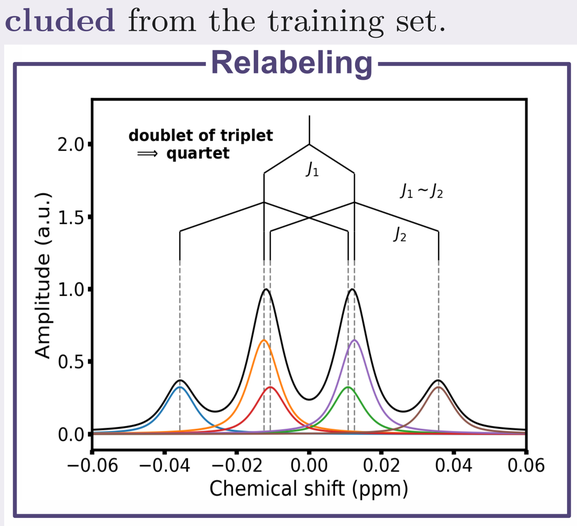
Introduction

Proton NMR is the fastest and most straightforward of all NMR experimental designs. Unfortunately, it suffers from lengthy annotation times and does not always have a clear and unbiased interpretation. Introducing an **automatic procedure** for the analysis of NMR data that can ease the chemical compounds characterization while ensuring consistency of the results across the scientific community is still an open challenge. Recently, we introduced a supervised deep learning model (*1*) that performs automated classification of signal regions for their coupling pattern. Here we show how including **uncertainty quantification** in deep learning frameworks applied to NMR serves a dual-purpose of **increasing the reliability** of the prediction and **detecting overlapping multiplets**.

Training set

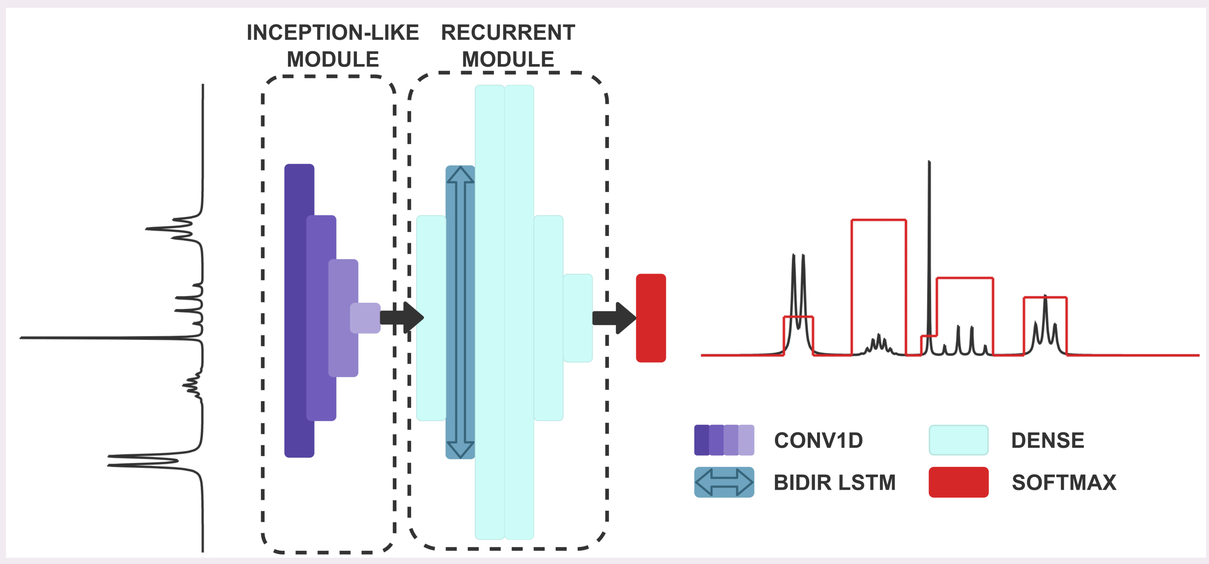
➔ 100′000 segments of synthetic ^{1}H NMR spectra.
➔ A **phenotype** with definite features was associated with each multiplet class.
➔ Certain combinations of couplings and linewidths turn one phenotype into another (e.g. a doublet of triplet into a quartet).
➔ **Feature consistency** within each class was achieved through a **Relabeling algorithm** which changed the label according to the resulting phenotype.
➔ If the resulting phenotype **doesn't match** any of the defined class phenotypes, the synthetic multiplet is **excluded** from the training set.



Feature similarity

Multiplet classification without any prior information on the molecule's structure is a **challenging task** because multiplets are all assembled from single peaks, which play the role of primary building units. This can result in a lower **inter-class variability** and an increased chance of sharing **similar features with overlapping multiplets**. In deep learning, this phenomenon is called **Feature Collapse**.

Point-estimate model



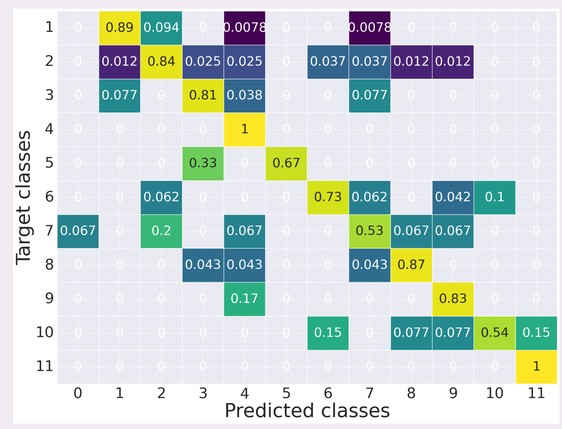
The algorithm (*1, 2*) can output a **point-by-point prediction** of a label value that corresponds to a given **coupling splitting** over the entire spectrum simultaneously, taking **only the amplitudes** of the spectrum **as input**.

Uncertainty in multiplet classification

➔ Trustworthy predictions (prior for following analysis)
➔ Detection of unseen features, **Out-Of-Distribution (OOD)** (e.g. **overlapping multiplets** are OOD)

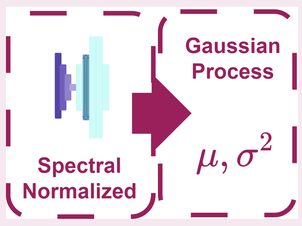
Statistics

We evaluated our model on 48 **experimental ^{1}H NMR spectra** annotated by expert spectroscopists. Here we show the confusion matrix of the classification performance.



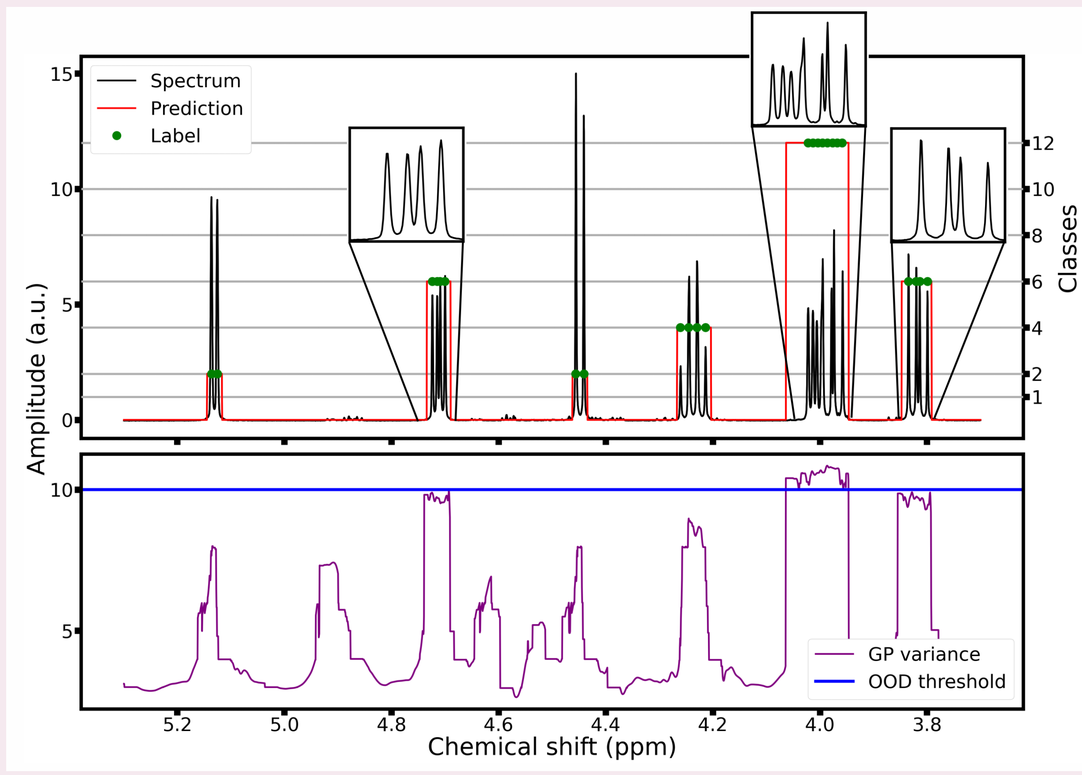
Legend: 0 - baseline (no signal), 1 - singlets, 2 - doublets, 3 - triplets, 4 - quartets, 5 - quintets, 6 - doublets of doublet, 7 - doublets of triplet, 8 - triplets of doublet, 9 - triplets of triplet, 10 - doublets of doublets of doublets, 11 - doublets of doublets of doublets

From a Point-estimate to a Probabilistic network



➔ **Spectral normalized** convolutional and fully connected layers to prevent **Feature collapse**
➔ **Gaussian Process (GP)** instead of Softmax output

We used a **Random Fourier Feature** expansion of a Gaussian process: the predictive distribution was retrieved from the **Mean-field approximation** while the posterior uncertainty was computed through the **Laplace approximation** (*3*).
Top panel: prediction (red line) of our probabilistic network on an experimental spectrum with ground truth labels (green dots). **Bottom panel**: Gaussian process variance (purple line) with the threshold (blue line) above which a multiplet is detected as OOD.



References

1. G. Fischetti, *et al.*, *Frontiers in Artificial Intelligence* **5** (2023).
2. N. Schmid, *et al.*, *Journal of Magnetic Resonance* (2023).
3. J. Z. Liu, *et al.*, *Journal of Machine Learning Research* **23**, 1 (2022).
4. M. Ganaie, M. Hu, A. Malik, M. Tanveer, P. Suganthan, *Engineering Applications of Artificial Intelligence* **115**, 105151 (2022).

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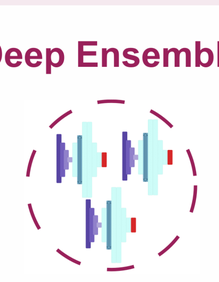
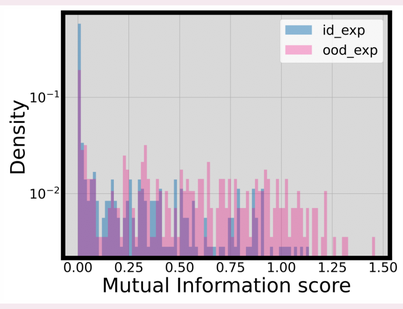
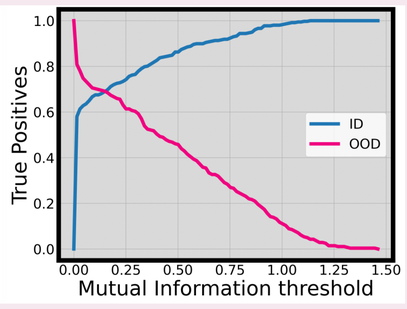
Bayesian approximation

Deep Ensemble







We combined the output of 10 **copies of our network** (*4*) and ran them on our experimental testing set. The distributions of **Mutual Information (MI)** values over OOD multiplets and multiplets represented in the training set (**In Distribution - ID**) were difficult to separate (right panel), due to **Feature collapse**.

Take-home messages

- Our model is able to produce an **accurate automatic classification** of signal regions in ^{1}H NMR spectra, reaching **at least** 80% **of true positives rate** on the majority of the multiplet classes.
- **Uncertainty quantification** is crucial in deep learning frameworks applied to NMR analysis, and can reliably **detect overlapping multiplets**.
- **The Gaussian Process** provided a **more accurate** estimation of the prediction uncertainty compared to the Deep Ensemble framework.