Metabolite Quantification with AI from MR Spectra

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Magnetic Resonance Spectroscopy (MRS)

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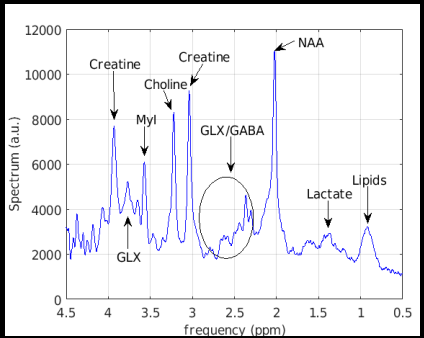
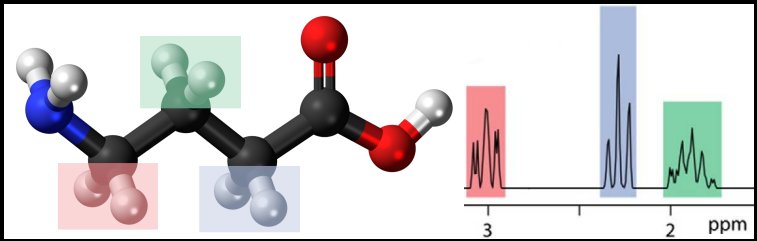
- Magnetic resonance signals from *molecules in tissue*
  - *Frequency response* to an RF signal in magnetic field (*amplitude* modulation)
  - Exploiting *spin* quantum property of nuclei (usually hydrogen / protons)
- Molecule has unique spectrum of split peaks due to
  - *Chemical shift*: frequency offset due to chemical bonds
  - *J-couplings*: splitting due to hyperfine interaction
- E.g. GABA, $H_3N^+ - CH_2 - CH_2 - CH_2 - COO^-$





MRS Quantification

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- *Quantification* of (relative) molecule concentrations
  - Identify *normal/abnormal processes* in the human body
  - E.g. *early, non-invasive diagnosis* of cancer, dementia
- Traditional Approaches
  - *Fit linear combination* of molecule spectra to signal

$$S = \sum_{\ell} c_\ell B_l + \epsilon$$

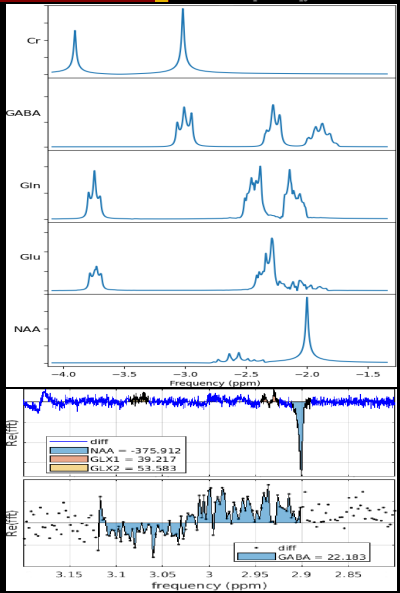
in frequency (LCModel, FSL-MRS) or
time (jMRUI, Tarquin) domain

  - *Peak integration* (LWFIT, GANNET)

$$c_\ell \sim \int_{\text{freq. ranges}} S(\nu)\, d\nu$$

S Shermer, et al. LWFIT. 2021. https://qyber.black/mrs/code-lwfit

- Main challenges
  - *Noise* from acquisition process and background signal
  - *Overlapping* molecule spectra
  - *Low signal strength* / low concentrations
  - *Uncertainty in basis spectra*



MEGAPRESS - GABA Quantification

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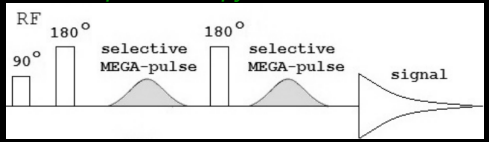
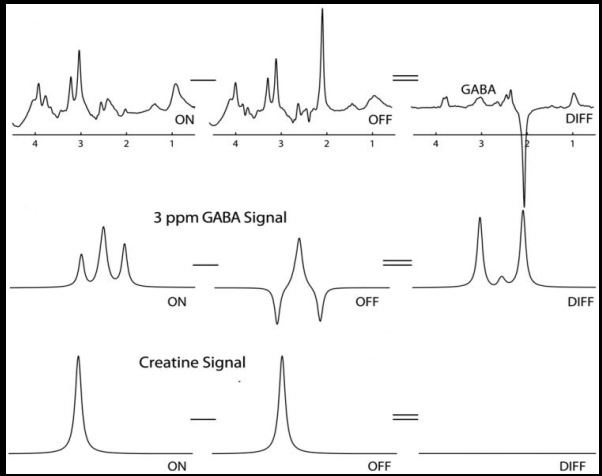
- GABA (γ-aminobutyric acid) neurotransmitter of particular interest
  - Glutamine, Gluatamate, GABA, Creatine, NAA
- *Edited spectroscopy*: MEGA-PRESS



  - Obtain two spectra:
    $$\text{ON} - \text{OFF} = \text{DIFF}$$
  - ON: refocus 1.9ppm to 3ppm J-coupling
  - OFF: free evolution of J-coupling
  - Most other peaks are unaffected



PG Mullins, et al. Current practice in the use of MEGA-PRESS spectroscopy for the detection of GABA. Neuroimage. 86:43-52, 2014.

MRSNet - Multiclass Regression CNN

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Paramtersied deep learning arch. for MRS quantification, specifically MEGA-PRESS.

input	Select([OFF, ON, DIFF], [Re, Im, Magn., Phase]) $\times$ 2048 freq. bins $1.5 - 4.5$ ppm
freq-conv1	$[f1 = 256]\times1\times[fc1 = 9]$ conv, $1\times[s1 = 2]$ stride, *BN* (no DO), ReLU, *Pool (instead of strides)*
freq-conv2	$[f1 = 256]\times1\times[fc2 = 7]$ conv, $1\times[s1 = 2]$ stride, *BN* (no DO), ReLU, *Pool (instead of strides)*
reduction1	$[f1 = 256]\times[2 - 3]\times[fc3 = 5]$ conv, *BN* (instead of DO), ReLU
reduction2	$[f1 = 256]\times[2 - 3]\times[fc3 = 5]$ conv, *BN* (instead of DO), ReLU
reductionX	... repeat until 1 row left (no padding)
conv1	$[f1 = 256]\times1\times[fc4 = 3]$ conv, *BN* (instead of DO), ReLU
conv1red	$[f1 = 256]\times1\times[fc4 = 3]$ conv, $1\times[s2 = 3]$ stride, *BN* (no DO), ReLU
conv2	$[f2 = 512]\times1\times[fc4 = 3]$ conv, *BN* (instead of DO), ReLU
conv2red	$[f2 = 512]\times1\times[fc4 = 3]$ conv, $1\times[s2 = 3]$ stride, *BN* (no DO),ReLU
dense1	$[d1 = 1024]$ FC Layer, DO2= 0.3
dense2	5 FC Layer, DO2= 0.3
output	softmax or *sigmoid*
	Normalised to $\sum_l c_l = 1$ or $\max_l c_l = 1$

M Chandler. *New methods in quantification and RF pulse optimisation for magnetic resonance spectroscopy*. PhD thesis, Cardiff University, 2019. [orca.cf.ac.uk/131875]

Model Selection

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- Trained on 10K (sufficient!) and 100K *simulated* spectra with 5-fold crossvalidation
  - FIDA-2D, capturing impact of gradients over 2D grid
    (also with FIDA-1D, lcmodel, pygamma and combinations, but no improvement)
  - Gaussian noise in time domain with $\sigma = 0.03$
- *Gaussian process optimisation* (GPyOpt) to select best parameters
  - input spectra and data types
  - size of kernels, strides, dropout/batch-normalisation
  - size of fully connected output layer
  - softmax vs. sigmoid output
- Optimisation over 12×472392
  - Exhaustive search over $1K$ models found same result than GPyOpt within 50 iterations
  - There is a range of similarly performing models
- *MRSNet* Python3 code with all data to be released soon - https://qyber.black/mrs/

M Chandler, C Jenkins, SM Shermer, FC Langbein. *MRSNet: Metabolite Quantification from Edited Magnetic Resonance Spectra With Convolutional Neural Network*. 2019. [arxiv:1909.03836]

Model Selection Results

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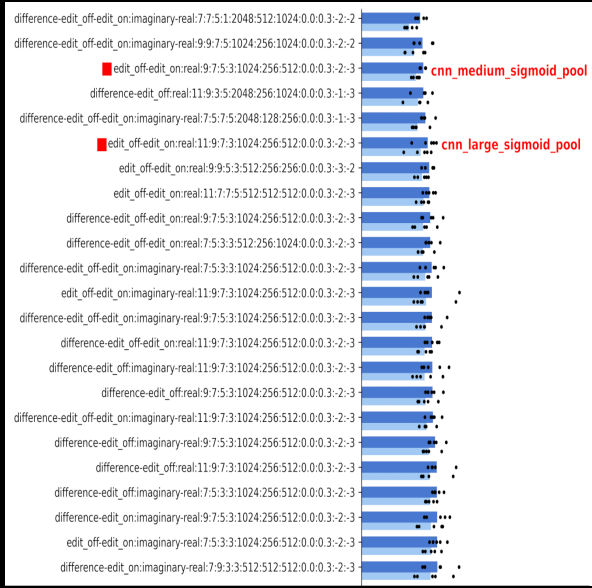

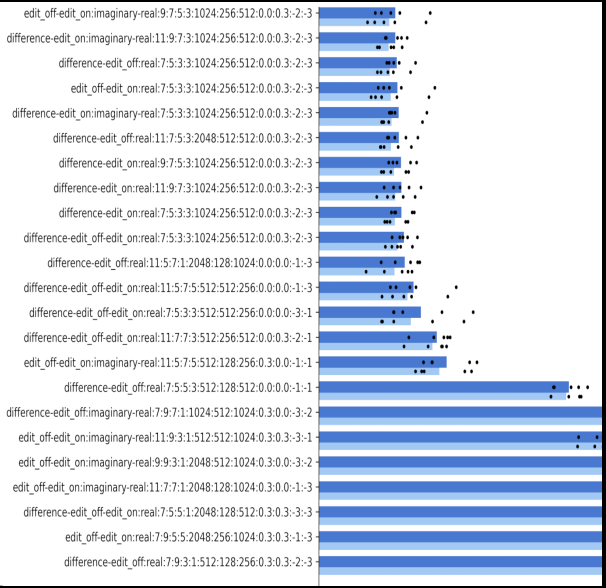

Best Model Performance on Simulated Test Data

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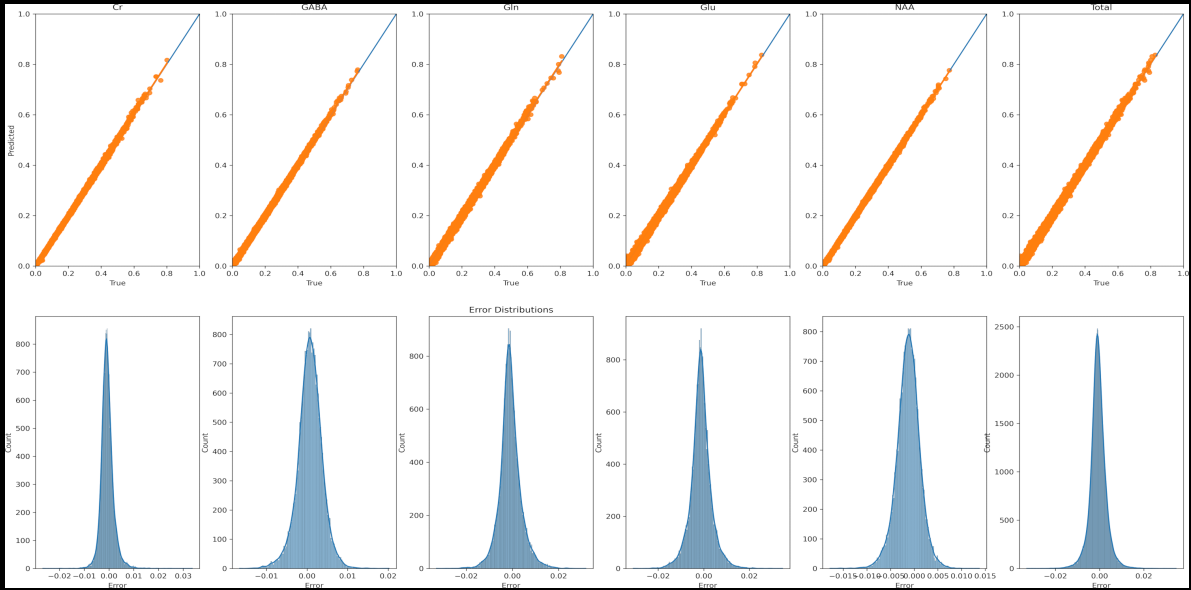

Best Model Performance on Real Unseen Data

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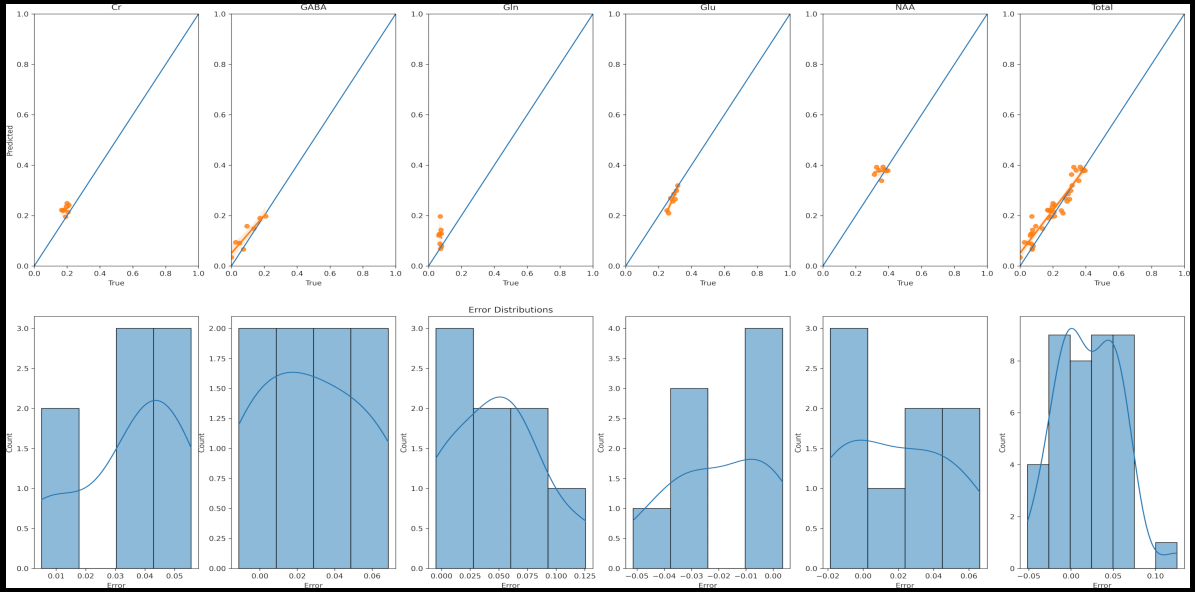

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GABA Benchmark

- *Performance similar to LCModel* gold standard, but hard to judge
  - Generally ML has not shown better results than traditional methods
- Validation via *simulated data is insufficient*
  - In-vivo behaviour in tissue may not match high-field NMR spectra in deuterium
  - Still some uncertainty in molecule models
  - Realistic noise and MR scanner characteristics
- *Ground-truth* from in-vivo data not feasible to obtain either
- *Tissue-mimicking phantoms*
  scan calibrated phantoms with known concentrations
  - NAA, Cr, Glu, Gln with varying GABA concentrations
  - Background signal / macro-molecules not considered (yet!)

SM Shermer, C Jenkins, M Chandler, FC. Langbein. *Magnetic resonance spectroscopy data for GABA quantification using MEGAPRESS pulse sequence*. Data set, IEEE Data Port, 2019. DOI:10.21227/ak1d-3s20

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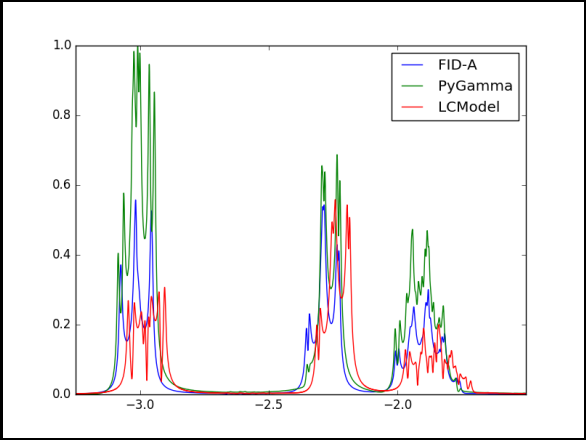
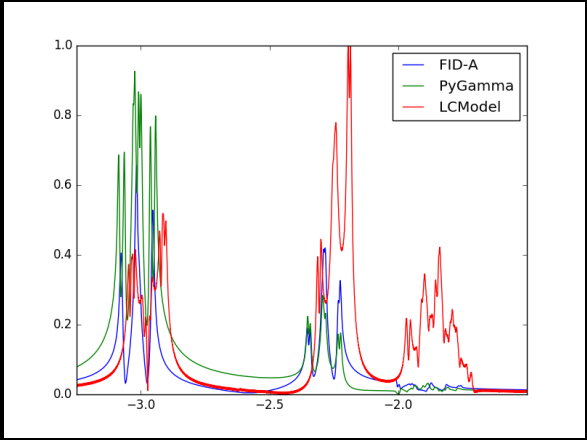
Uncertainty in Spectral Basis

- Comparison of spectral shapes between simulators
- E.g. GABA, edit-off and edit-on





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Conclusions

- *MRS* holds promise to improve non-invasive medical diagnosis and identify biochemical processes
- Presented *CNN for quantification*
- Deep learning quantification has comparable efficiency with traditional methods
- The real problem is ground truth, better data and simulators
- *Limits* – How well can we quantify molecule concentrations?