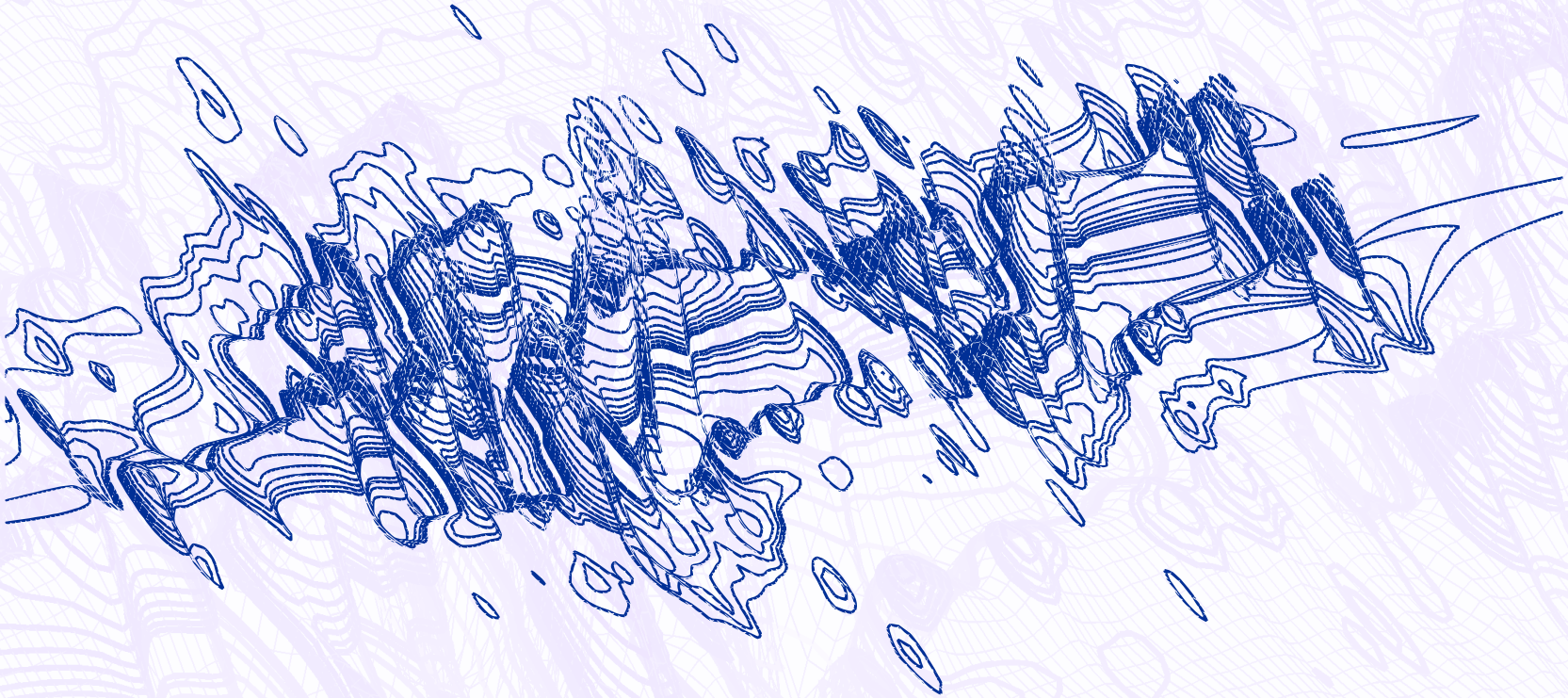


Cramé-Rao Lower Bounds

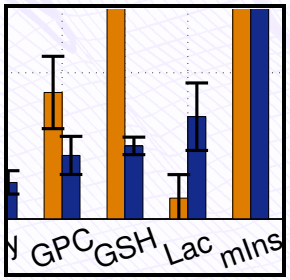
Definition

A Cramér-Rao Lower Bound (CRB) is the lower bound on the variance of estimators of a deterministic parameter. In other words, CRB represents the lowest estimation error of a parameter in the case of an unbiased estimator.

Bounds Calculation

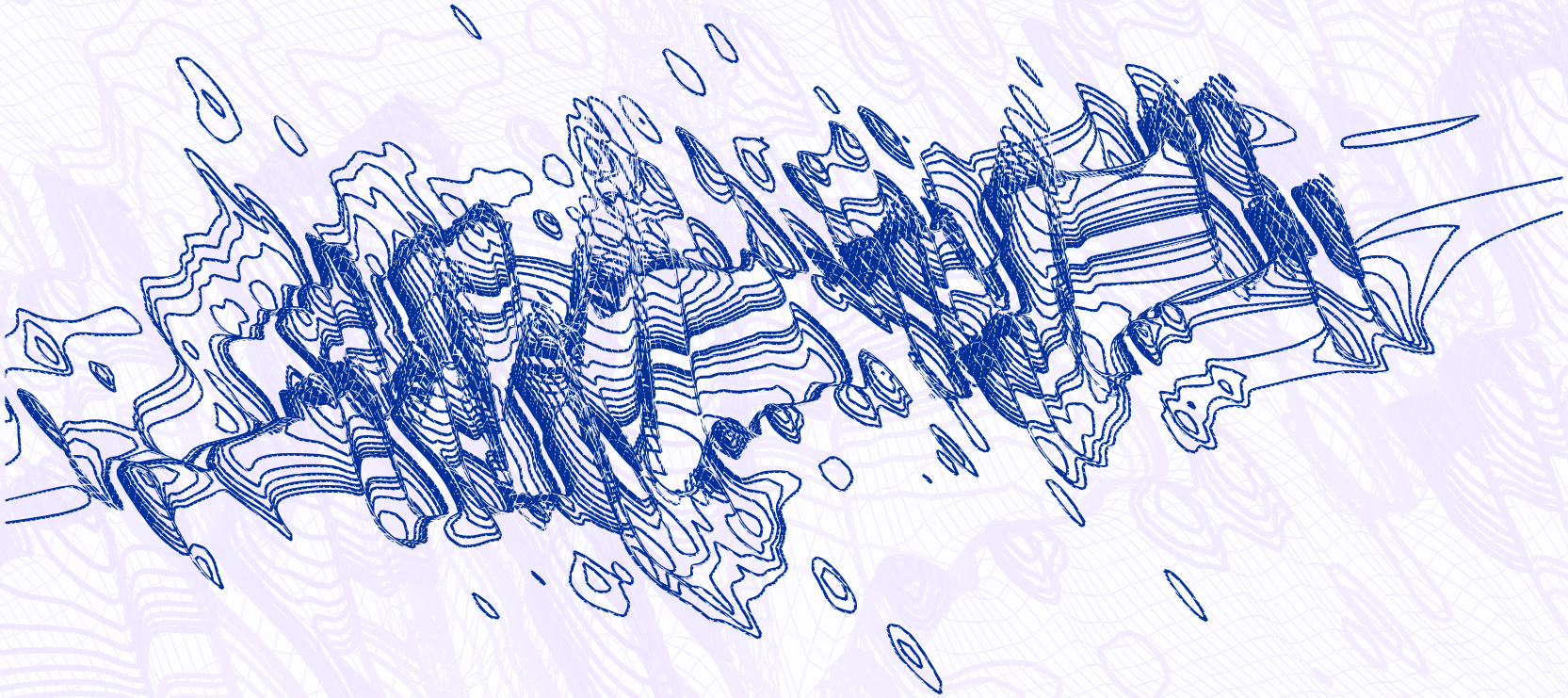
In theory, CRB are calculated from the "true" parameters values of the signal c_m, T_{2m}, $\triangle\alpha_m$, $\triangle\omega_m$ and ϕ_0. NEMESIS determine CRB from the estimated values of parameters by :

- Building the Fisher Information Matrix (FIM) knowing the second derivative matrix of the model function $\hat{x}(n_{t_2}, n_{t_1})$
- Inverting the (FIM)
- Extracting the diagonal values



Error bars

In order to calculate the estimation errors, CRB values should be normalised knowing the noise level of the signal.



Development of new acquisition strategies and quantification methods for *in vivo* 2D Magnetic Resonance Spectroscopy

PhD candidate : Tangi ROUSSEL

11th of July 2012

PhD Committee :

Examiners :	**Olivier LAFON**	*Professeur des Universités, Université de Lille I*
	Lotfi SENHADJI	*Professeur des Universités, Université de Rennes I*
	Serge AKOKA	*Professeur des Universités, Université de Nantes*
	Thomas LANGE	*PhD, University Medical Center Freiburg, Allemagne*
Supervisors :	**Sophie CAVASSILA**	*Professeur des Universités, Université de Lyon I*
	Hélène RATINEY	*Chargée de recherches, Université de Lyon I*

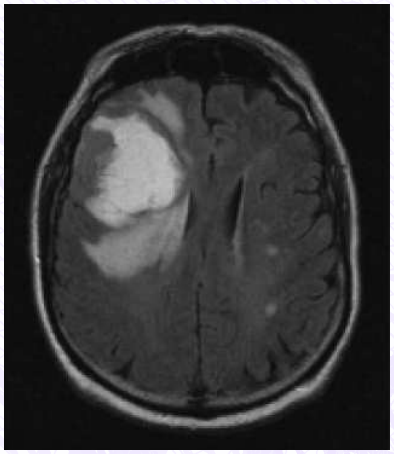
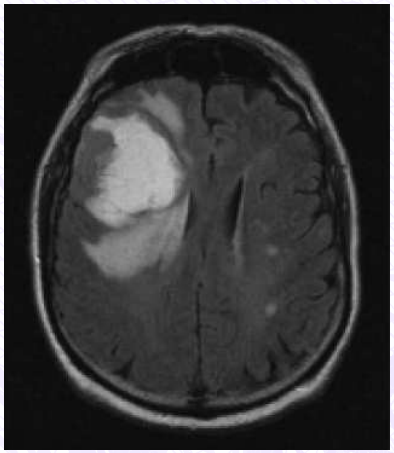


Fig. 1: 1.5 T Fast Spin Echo T_2-weighted image from the brain of a patient suffering with glioma

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a medical imaging technique used in radiology to visualize internal structures of the body. MRI makes use of the property of NMR to image hydrogen nuclei (protons) inside the body tissue.



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Magnetic Resonance Spectroscopy

Magnetic Resonance Spectroscopy (MRS) allows **non-invasive** and *in vivo* exploration of the molecular composition of tissue. It identifies certain **molecular constituents - metabolites - involved in physiological or pathological processes**.

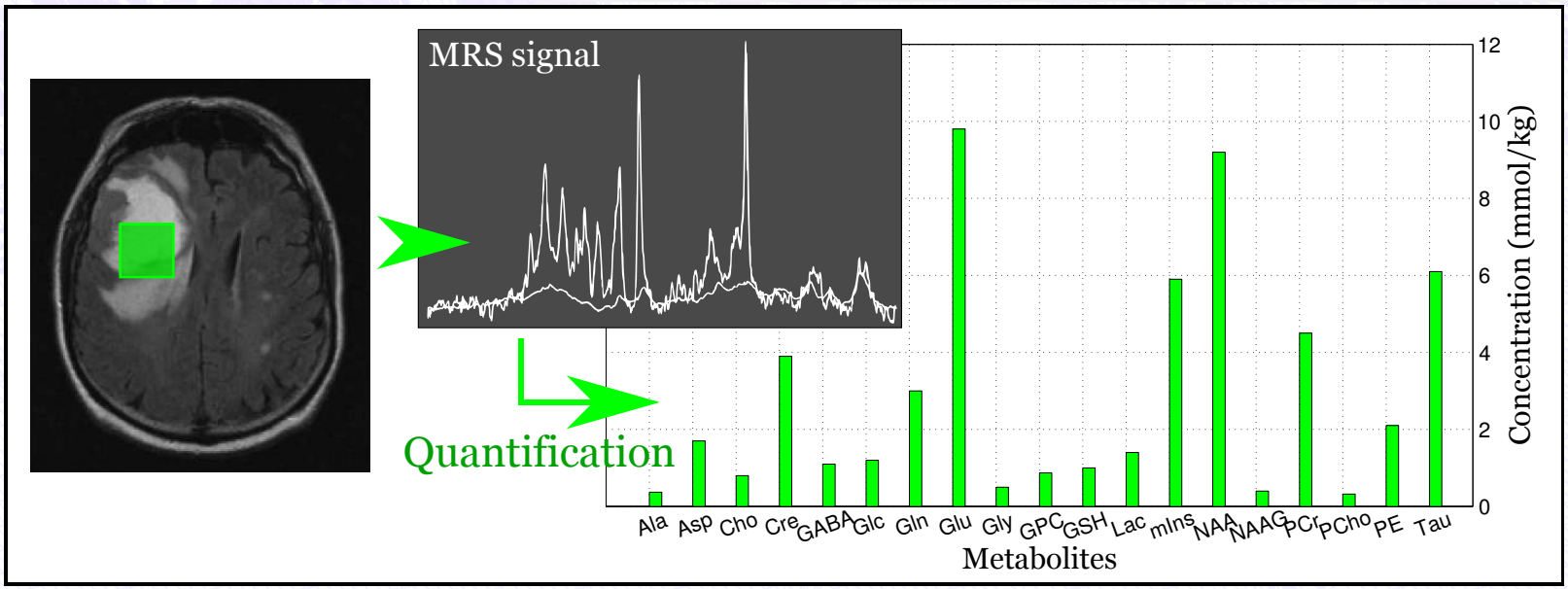


Fig. 2: Principle of quantitative MRS of human brain using a PRESS sequence

Interpreting an *in vivo* NMR spectrum

- 12 detectable metabolites at 4.7 T for short echo time
- **Linear combination of metabolic spectral signatures**
- **Baseline** (macromolecular contamination)
- **Noise**

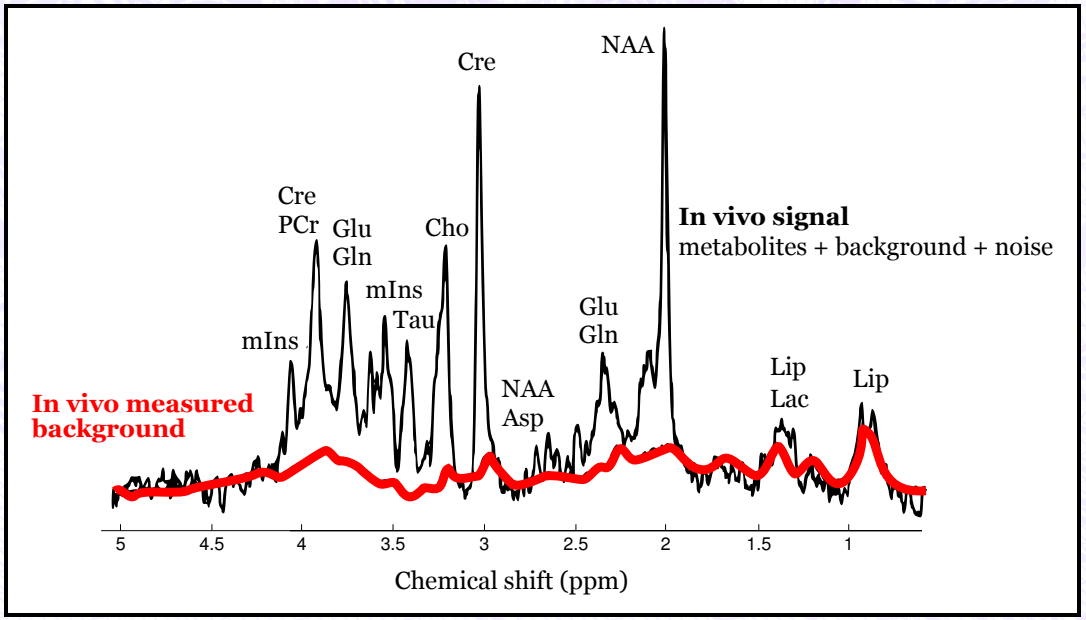


Fig. 3: *In vivo* MR spectrum acquired from a rat brain at 7 T (PRESS sequence, TE=20 ms, 10 min scan time)

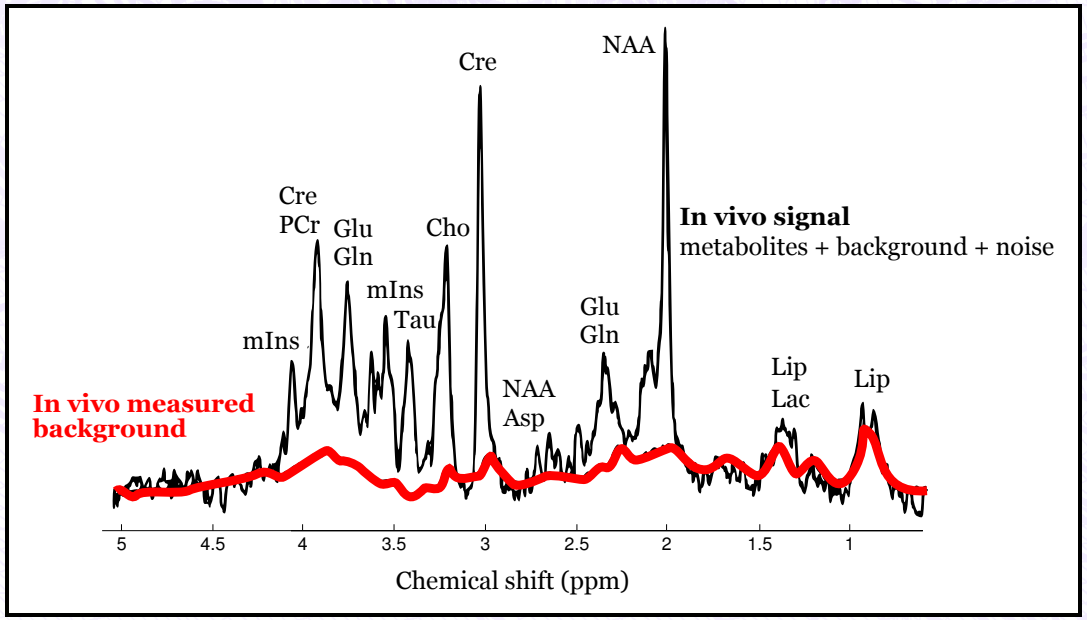
Interpreting an *in vivo* NMR spectrum

- 12 detectable metabolites at 4.7 T for short echo time
- **Linear combination of metabolic spectral signatures**
- **Baseline** (macromolecular contamination)
- **Noise**

Metabolic signature

Each metabolite has a spectral signature characterised by :

- **Chemical shifts** (ppm)
- **J-coupling constants** (Hz)
- **Concentration** (mmol/kg)



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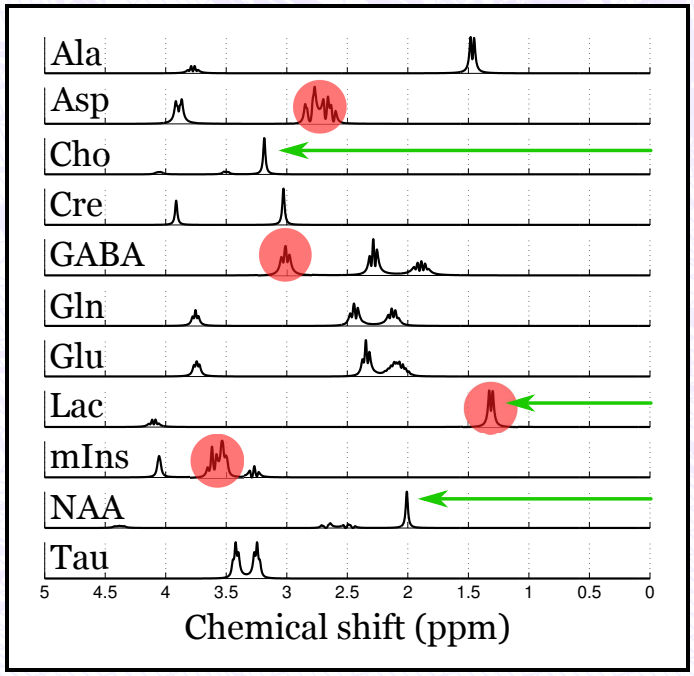
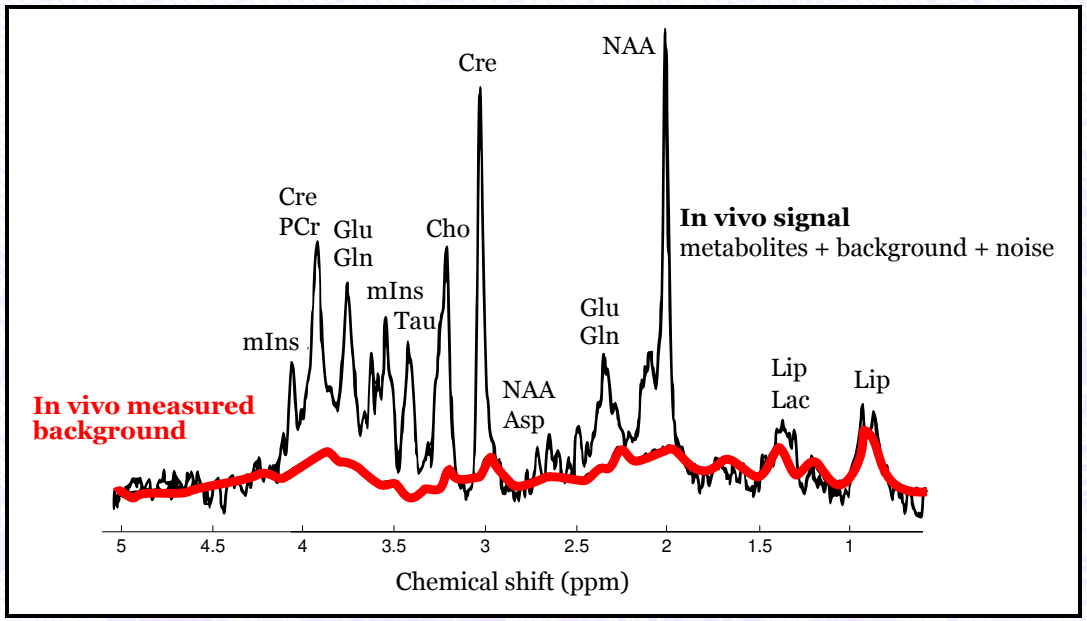


Fig. 4: Metabolic spectral signatures



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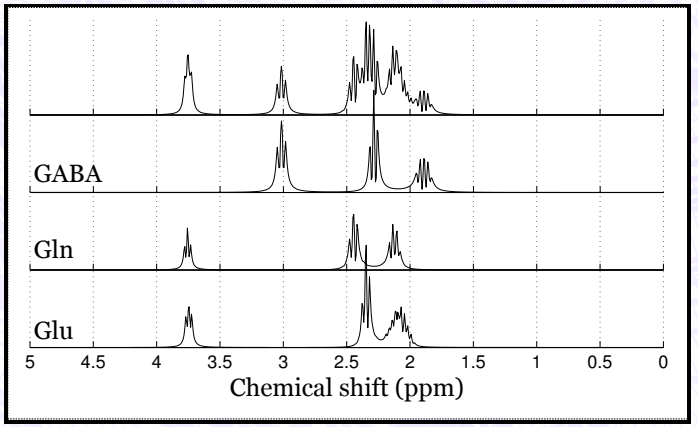

Fig. 6: Spectral overlapping between the metabolites

Limitations

1D MRS used with low B_0 fields suffers with :

- **Spectral overlapping** between metabolites (Glu/Gln)
- **Spectral overlapping** between metabolites and macromolecules (baseline)
- Low concentrated metabolites (GABA)

Conventional localised 2D J-resolved Magnetic Resonance Spectroscopy

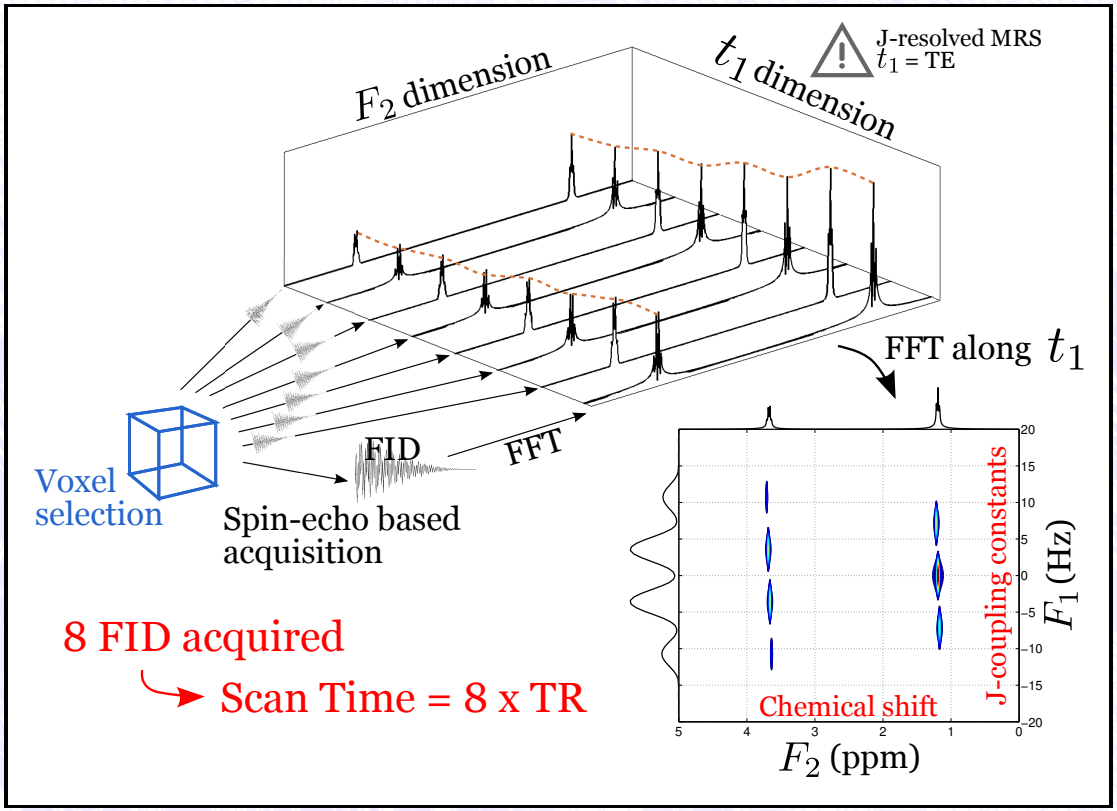

Fig. 7: Understanding conventional 2D J-resolved MRS

A conventional localised 2D J-resolved MRS experiment consists in :

- performing numerous acquisitions of FIDs for **various Echo Times**
- **Fourier transforming each FID** to obtain F_2 dimension
- **Fourier transforming the data set** following the t_1 dimension

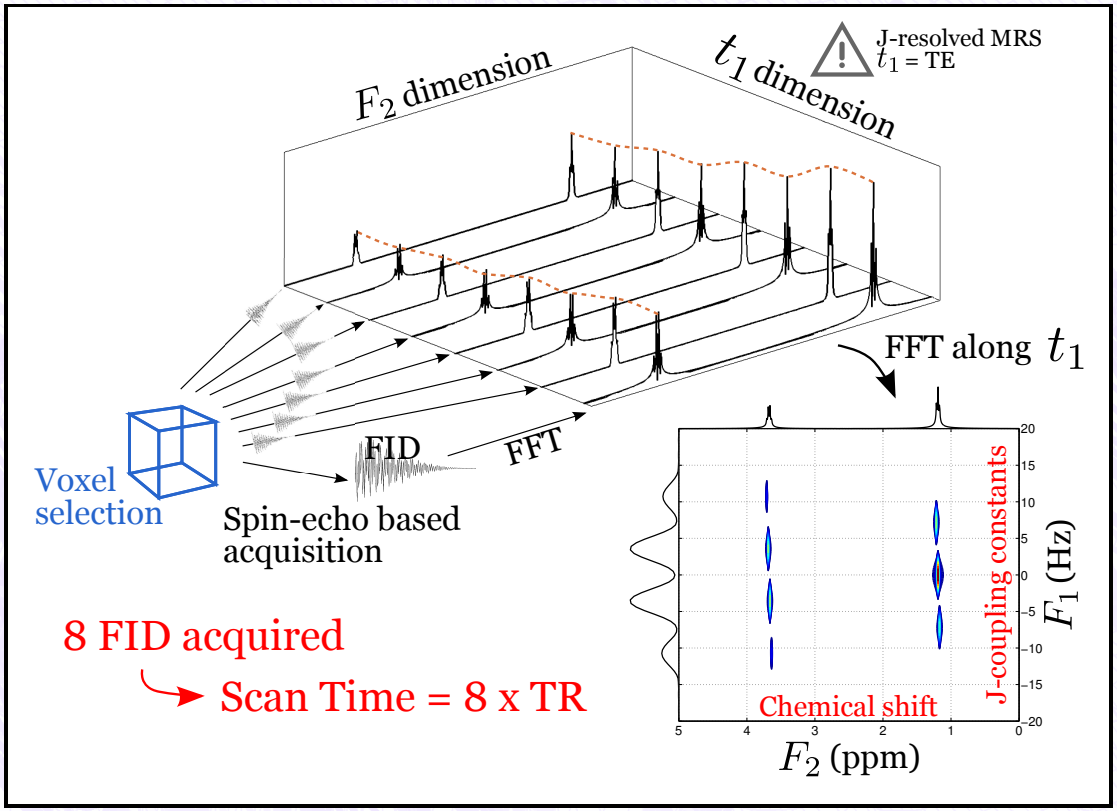

Fig. 8: Understanding conventional 2D J-resolved MRS

Pros/Cons

- ⊕ **Information following F_1 dimension : J-coupling constant**
- ⊖ Acquisition duration depends on the number of increments in Echo Time (n_{t1}) resulting in expensive scan time (up to 1h30)

In vivo 2D MRS since 1995

- More and more studies on human brain[1]
- **Few studies on small animal** consisting mainly in metabolite identification[2]

[1] Thomas M A et al, JMRI, 6 :453-459, 1996
[2] Meric P et al, MAGMA, 17 :317-338, 2004
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[4] Provencher S W et al, MRM, 30 :672-679,1993
[5] Golub G H et al, SIAM JNA, 10 :413-432, 1973
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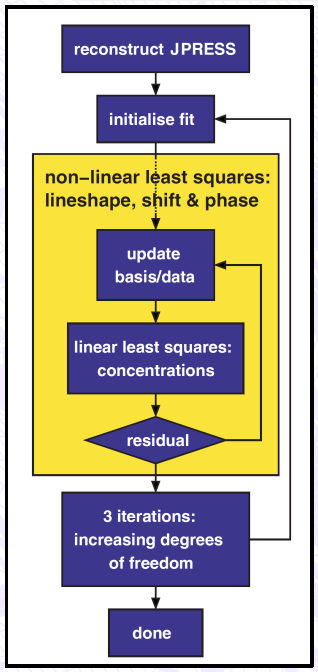

Fig. 9: ProFit algorithm

Few studies on quantitative 2D MRS

- One quantification algorithm dedicated to human brain 2D MRS at 3 T : ProFit[3] based on 1D quantification methods LCModel[4] & VARPRO[5]
- **No quantification algorithm for small animal brain 2D MRS**

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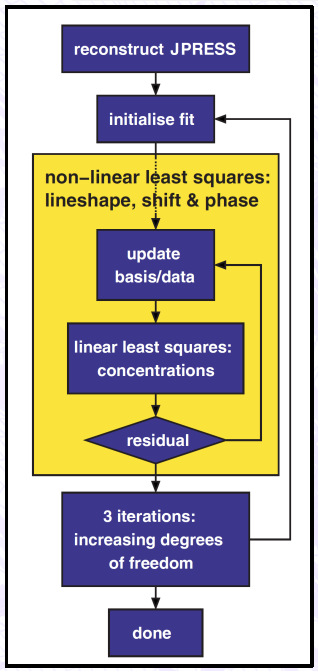

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Very few studies on acquisition time reduction of *in vivo* 2D MRS experiment

- **Few studies on reducing scan time** of 2D J-resolved MR spectroscopic imaging[6]
- In 2002, L. Frydman introduces "ultrafast spectroscopy"[7] for high resolution spectroscopy, a new technique allowing the acquisition of 2D MRS spectra in very short time.

[1] Thomas M A et al, JMRI, 6 :453-459, 1996
[2] Meric P et al, MAGMA, 17 :317-338, 2004
[3] Schulte R F et al, NMR Biomed, 19 :255-263, 2006
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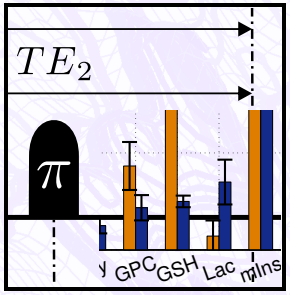

Quantitative 2D MRS for small animal brain

- Design a 2D MRS sequence on a 4.7 and a 7 T *Bruker Biospec* imaging systems
- Perform *in vivo* 2D MRS localised acquisitions on rat brain
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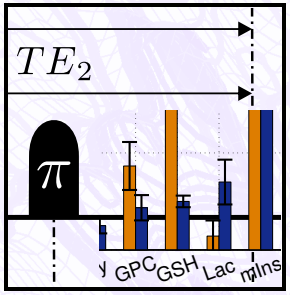

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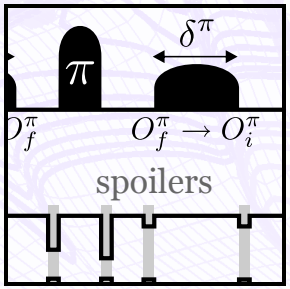
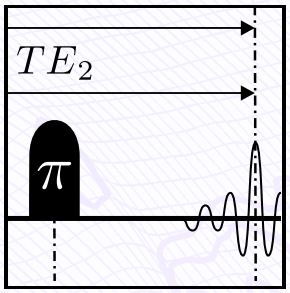


Acquisition time reduction of 2D MRS experiment

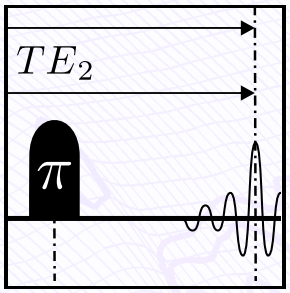
- Design an ultrafast localised 2D MRS sequence on a 4.7 and a 7 T *Bruker Biospec* imaging systems
- Optimise and validating the sequence on *in vitro* phantoms

Quantitative conventional 2D MRS



Design a 2D MRS sequence on small imaging systems

- 2D MRS J-resolved spectroscopy sequence
- Irregular data sampling following t_1 dimension
- Inversion-recovery excitation to acquire 2D baseline



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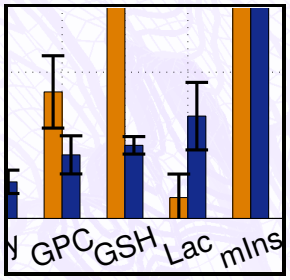

Develop a dedicated quantification algorithm

- Complex time domain quantification & strong prior-knowledge
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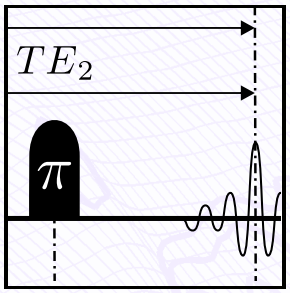

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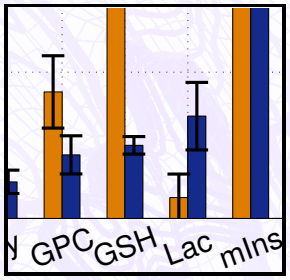

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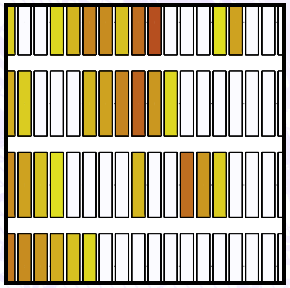
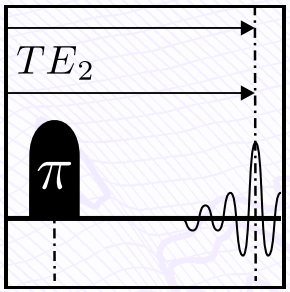


Develop an algorithm to optimise t_1 sampling

- Based on Cramér-Rao theory
- Calculation of optimised sampling following t_1 dimension in order to increase quantification accuracy



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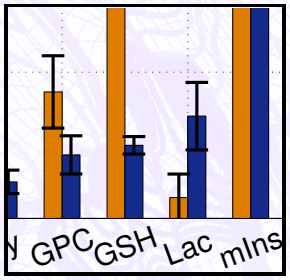

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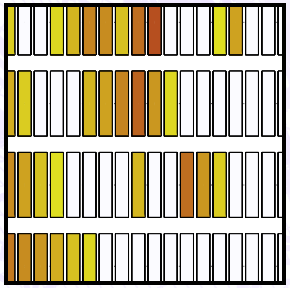

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Validate the methods on small animal

- *In vivo* acquisition performed on a 4.7 and a 7 T *Bruker Biospec* imaging systems
- Localised MRS experiments on mouse and rat brain

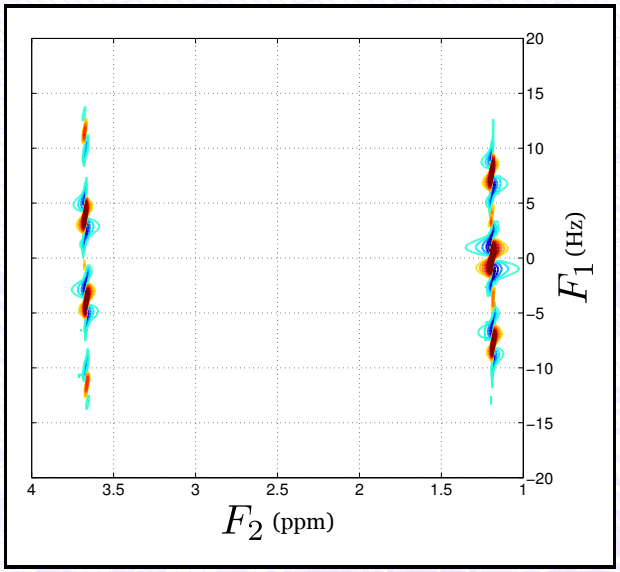
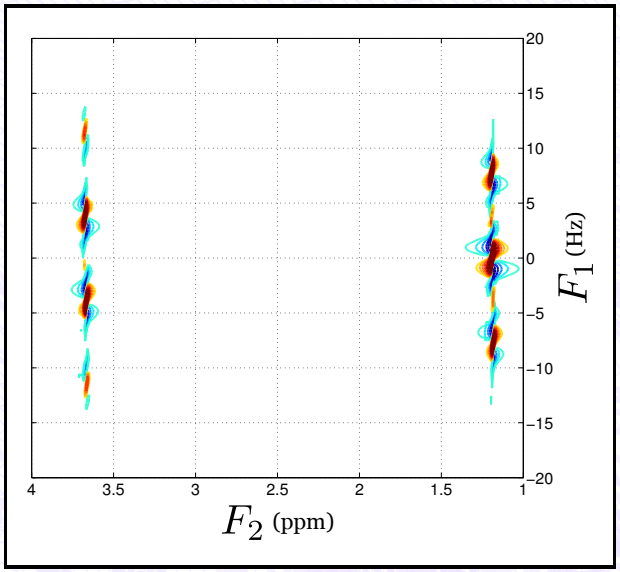


Fig. 10: Simulated 2D J-resolved MR spectrum of ethanol

2D J-resolved MRS

- $\oplus$ **Short acquisition time** (in comparison with COSY MRS) due to the small bandwidth required following F_1 dimension
- $\oplus$ Easy to implement on an MRI since the pulse sequence is close to PRESS scheme

[8] 2D J-Resolved Point Resolved SpectroScopy with Weighted Irregular Sampling Handling



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2D J-PRESS WISH[8] sequence : Preparation period

- **Water suppression scheme** (VAPOR module) to reduce water signal
- **Saturation bands** (OVS module) to reduce outer volume signal artefacts
- **Inversion pulse** (InvPulse module) to perform inversion-recovery excitation

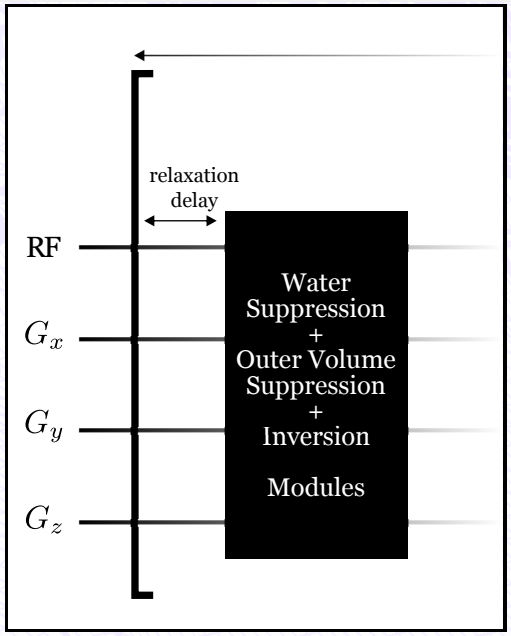

Fig. 11: 2D J-PRESS WISH preparation

[8] 2D J-Resolved Point Resolved SpectroScopy with Weighted Irregular Sampling Handling

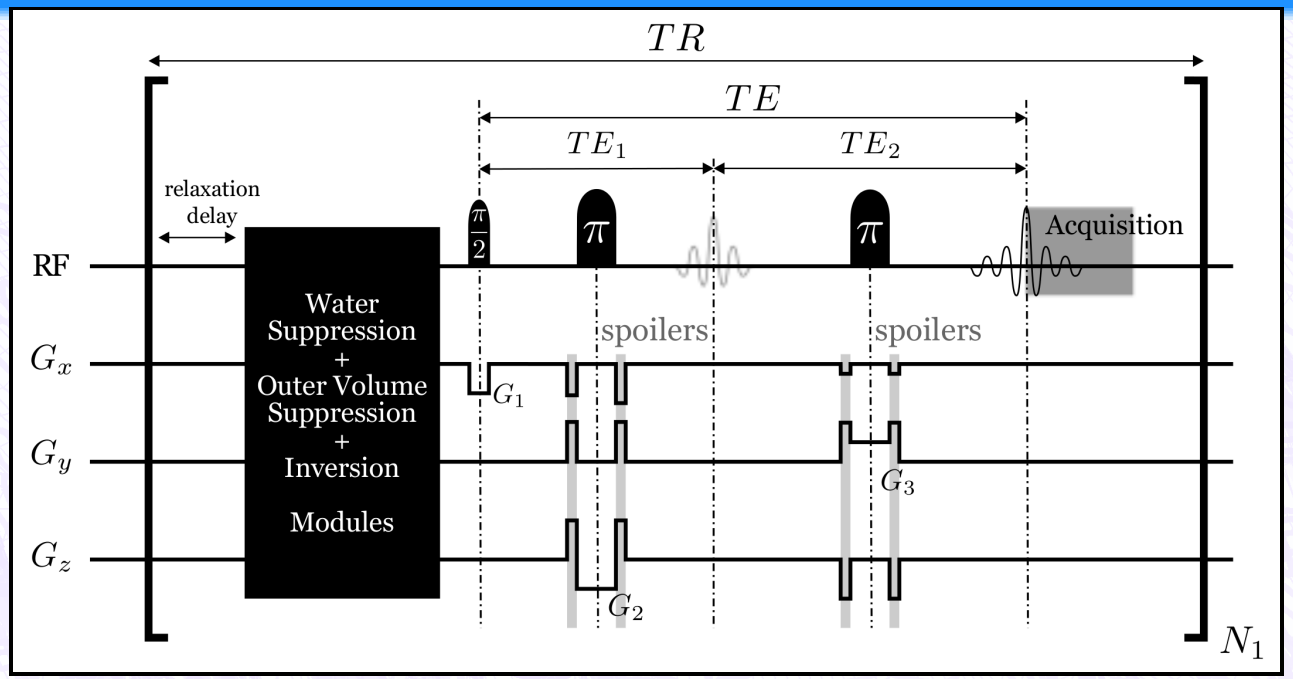

Fig. 12: 2D J-PRESS WISH[9] sequence

Excitation & Detection

- Strongly based on **PRESS excitation scheme**
- *TE* calculation mode can be chosen in order to profit from TE_1/TE_2

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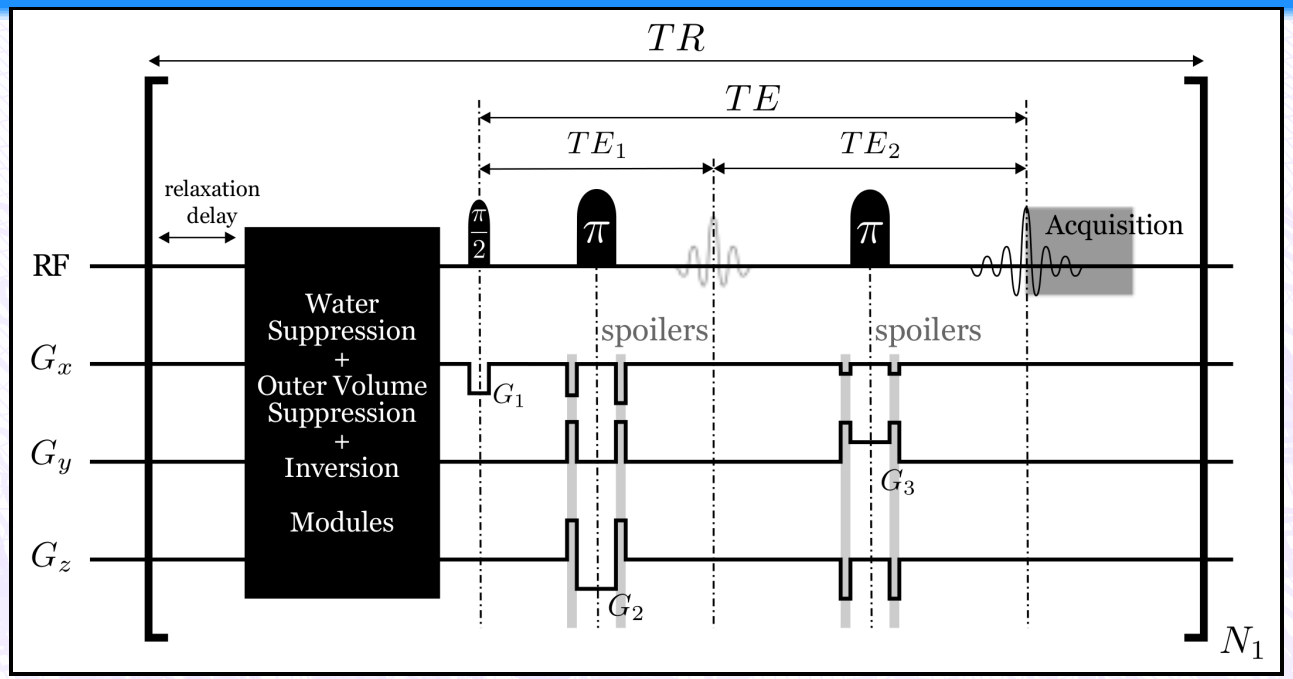

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Excitation & Detection

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Original functionalities

- Regular or **irregular sampling following t_1 dimension**
- *NA* **weighting** of the increments acquired following t_1 dimension

[9] 2D J-Resolved Point Resolved SpectroScopy with Weighted Irregular Sampling Handling

2D J-PRESS WISH experiment

- Performed on a horizontal 7T *Bruker Biospec* MRI
- A 5-month-old rat was anaesthetised by inhalation of isoflurane
- Volume coil for emission and surface receive coil
- The signal was collected from a 64 μL voxel
- 1^{st} and 2^{nd} order local shim adjustment
- TE=20 to 140 ms, N_1=24, TR=2.5 s, NA=96 (1h 36min acquisition time)

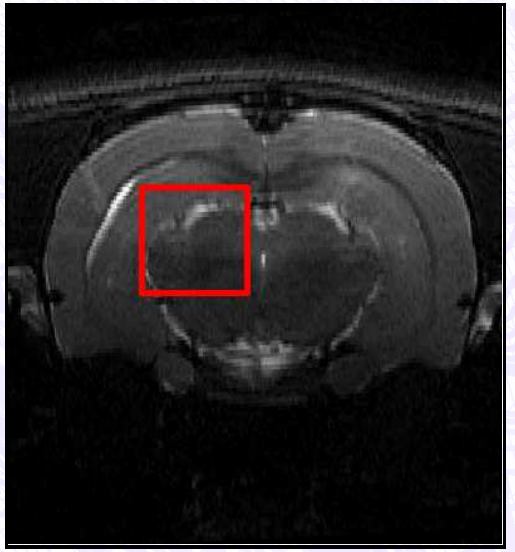

Fig. 13: Axial slice image of a rat brain (RARE, TE/TR=15/5166ms)

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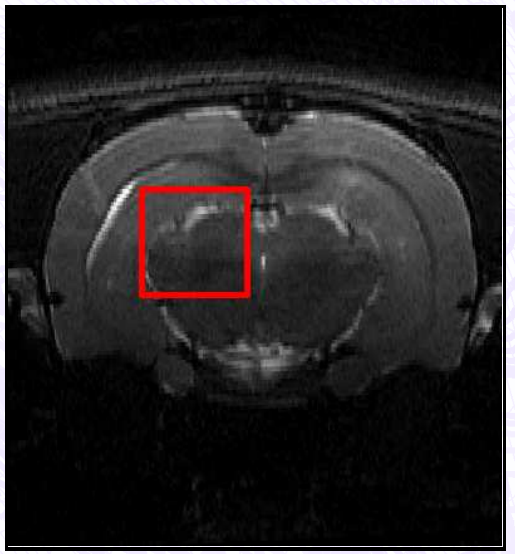

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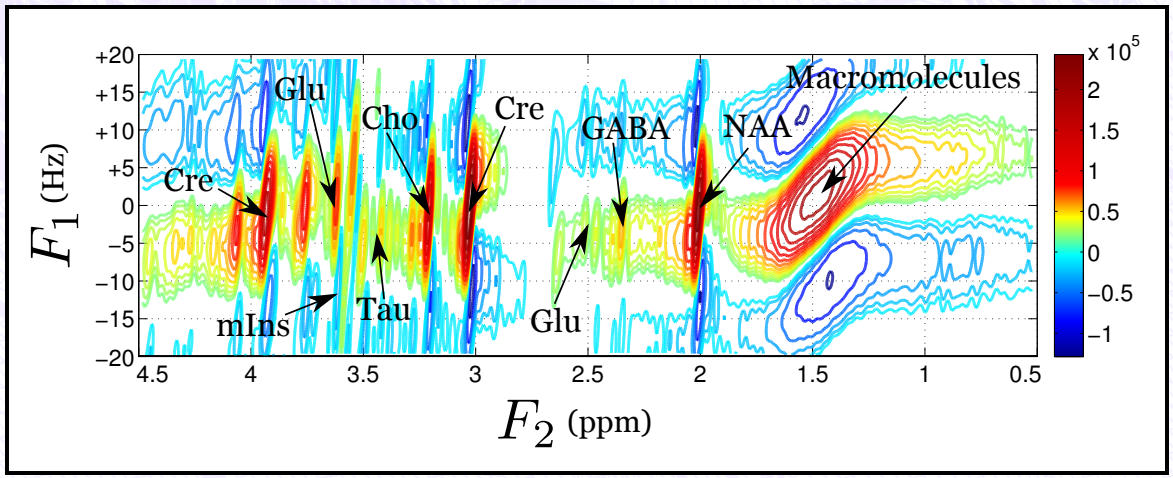

Fig. 14: *In vivo* MRS 2D J-resolved spectrum acquired in a rat brain with the 2D J-PRESS WISH sequence

NEMESIS[10] properties

- **2D complex time-domain model function** consisting in a linear combination of metabolite signals
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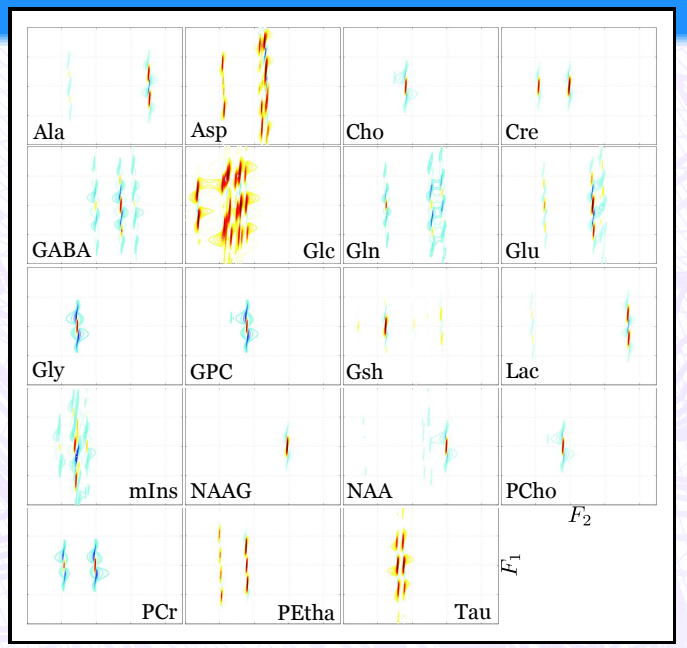

Fig. 15: Set of 19 2D metabolite signals

[10] Numeric Estimation Method for 2D Spectroscopy Irregulary Sampled data

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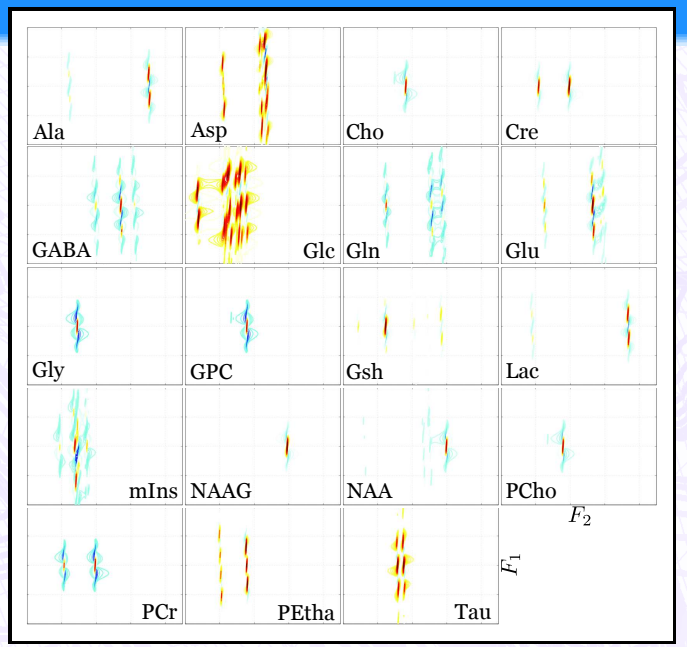

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$$\hat{x}(t_2,t_1) = exp(i\cdot\phi_0)\sum_{m=1}^{M} c_m\cdot\hat{x}(t_2,t_1)^m\cdot\exp\left[(-\frac{t_1}{T_{2m}})+(\triangle\alpha_m+i\cdot\triangle\omega_m)\cdot t_2\right]$$

- c_m : Amplitude/concentration of the metabolite signal $\hat{x}(t_2,t_1)^m$
- T_{2m} : Transverse relaxation time [s]
- $\triangle\alpha_m = \frac{1}{T_{2m}^*}$: Extra damping factor [Hz]
- $\triangle\omega_m$: Frequency shift [Hz]
- ϕ_0 : Global zero-order phase [rad]

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$$C = \sum_{n_{t_2}=0}^{n_{t_2}=N_2} \sum_{n_{t_1}=0}^{n_{t_1}=N_1} [x(n_{t_2}, n_{t_1}) - \hat{x}(n_{t_2}, n_{t_1})]^2$$

- $x(n_{t_2}, n_{t_1})$: data signal
- $\hat{x}(n_{t_2}, n_{t_1})$: model signal

[12] Asp, Ala, Cho, Cre, GABA, Glc, Gln, Glu, Gly, GPC, Gsh, Lac, m-Ins, NAA, NAAG, PCr, PCho, PE, Tau

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Optimisation

- 19 metabolites[12] + macromolecular contamination = up to 40 parameters !
- **Possible optimisation problems such as local minima**

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Multistart Optimisation

- For each quantification stage, multiple gaussian random starting values are initialised around the values evaluated at the last stage in order to **reduce optimisation problems related to initial parameters value**
- The estimated parameters are kept for a minimal fit residue

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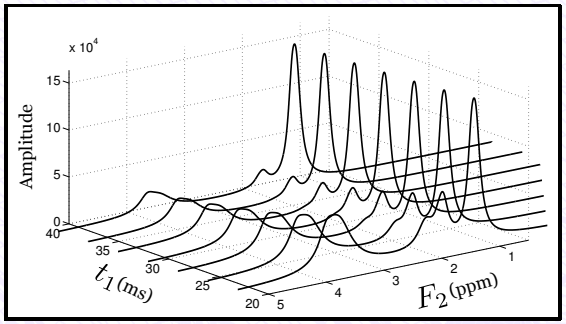
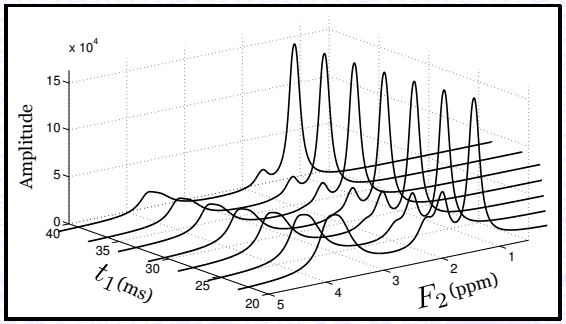


1. Base line estimation

- Quantification of inversion-recovery 2D MRS data
- Linear combination of 20 gaussian components
- Integration in NEMESIS prior-knowledge



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- Maximum peak detection of singlets : Cho, Cre, NAA
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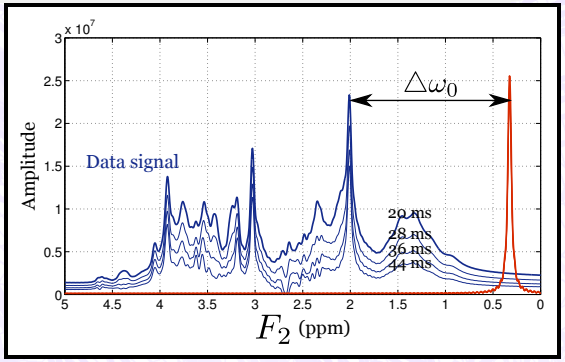

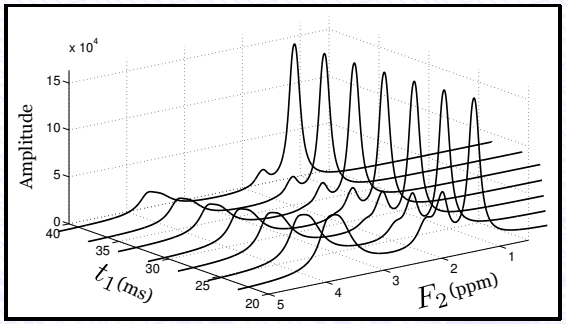

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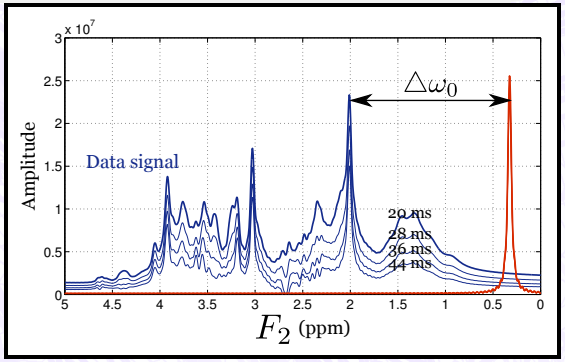
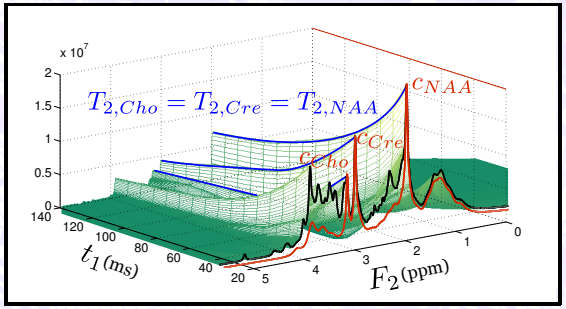
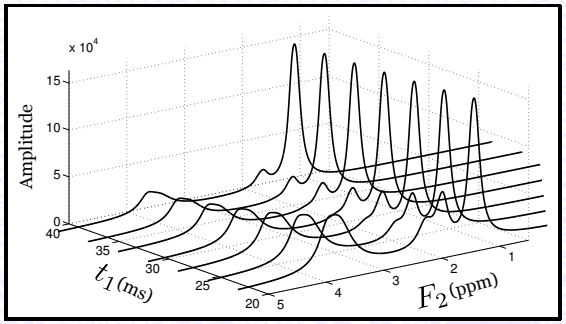




3. Singlets estimation

- c_m parameter is estimated for Cho, Cre et NAA
- Global estimation of the parameters T_{2m}, $\triangle\alpha_m$, $\triangle\omega_m$ and ϕ_0



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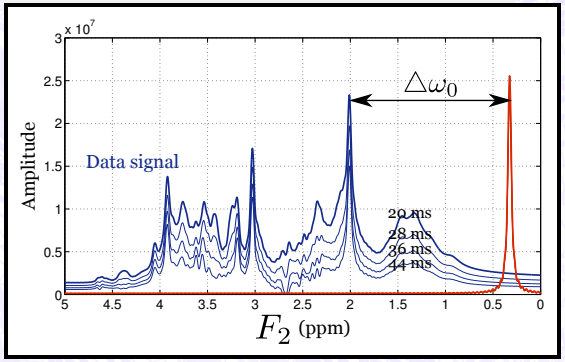

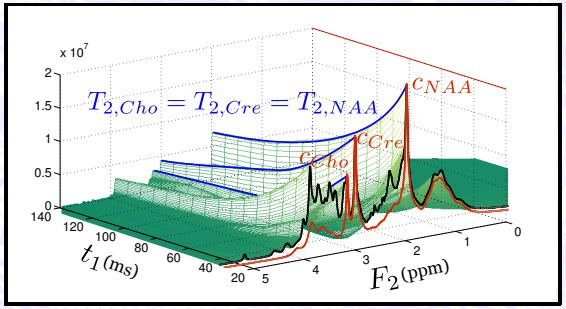

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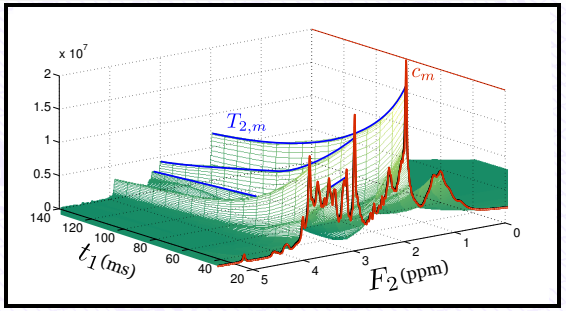
- Parameters c_m, T_{2m}, $\triangle\alpha_m$ and $\triangle\omega_m$ are estimated for each metabolite
- Global estimation of the phase parameter ϕ_0



Quantification strategy vs. Single quantification : study on simulated data

- A 2D simulated 7T MRS signal was generated with **typical in vivo parameter values and macromolecular contamination**
- 100 repetitions of the quantification procedure were performed for the above simulated data added to Gaussian noise
- Quantification was performed **with and without the quantification strategy**
- Biases and standard deviations were computed for the amplitude estimates

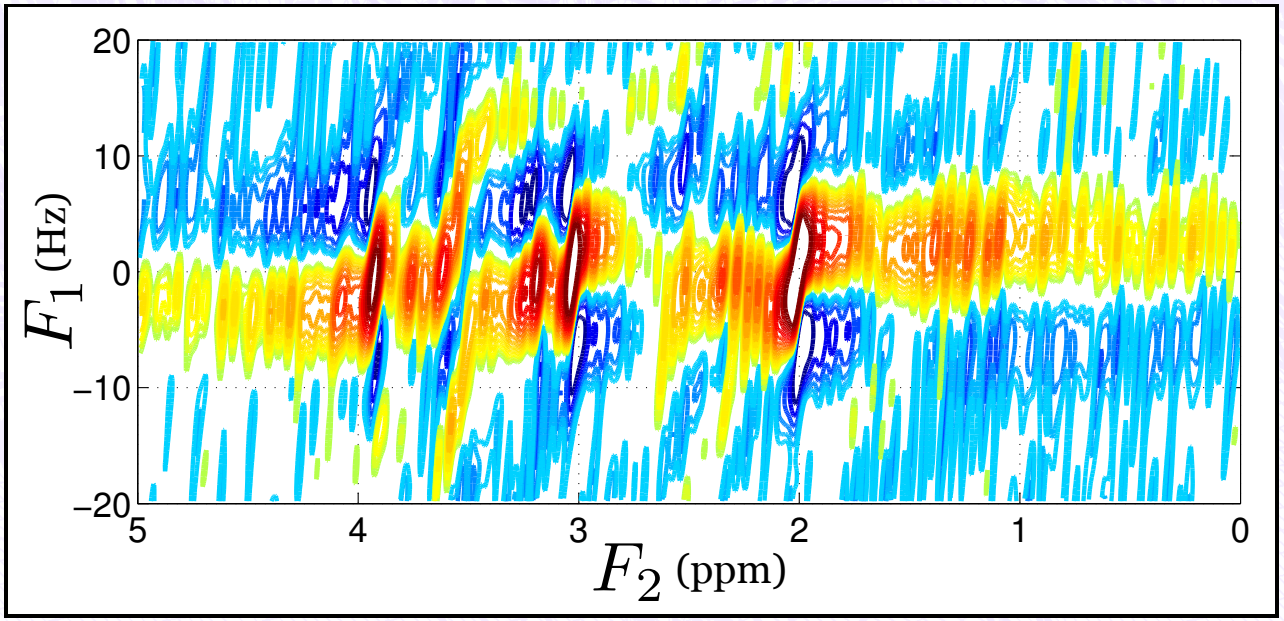


Fig. 16: Frequency representation of a simulated 2D J-resolved MR spectrum for B_0=7 T

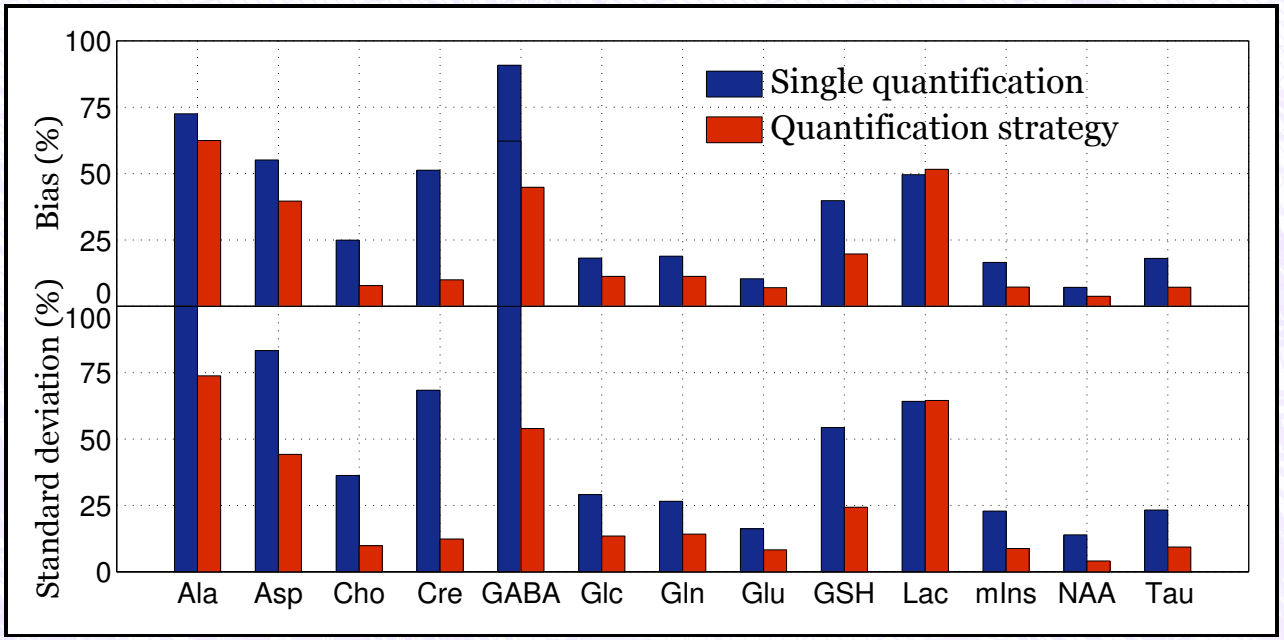


Fig. 17: Bias and standard deviations calculated of the amplitude estimates

Results

- **Global reduction of standard deviation** when using the quantification strategy
- Slight reduction for Ala and Lac whose spectral signatures are strongly overlapped with macromolecular contamination

CRISO[13] algorithm

- Strongly relies on **Cramér-Rao Lower Bounds** (CRB) : lowest estimation error of a parameter in the case of an unbiased estimator
- Calculates optimised sampling following t_1 dimension for each metabolite in order to minimize CRB
- Calculates a rank for each t_1 increments according to the CRB reduction induced

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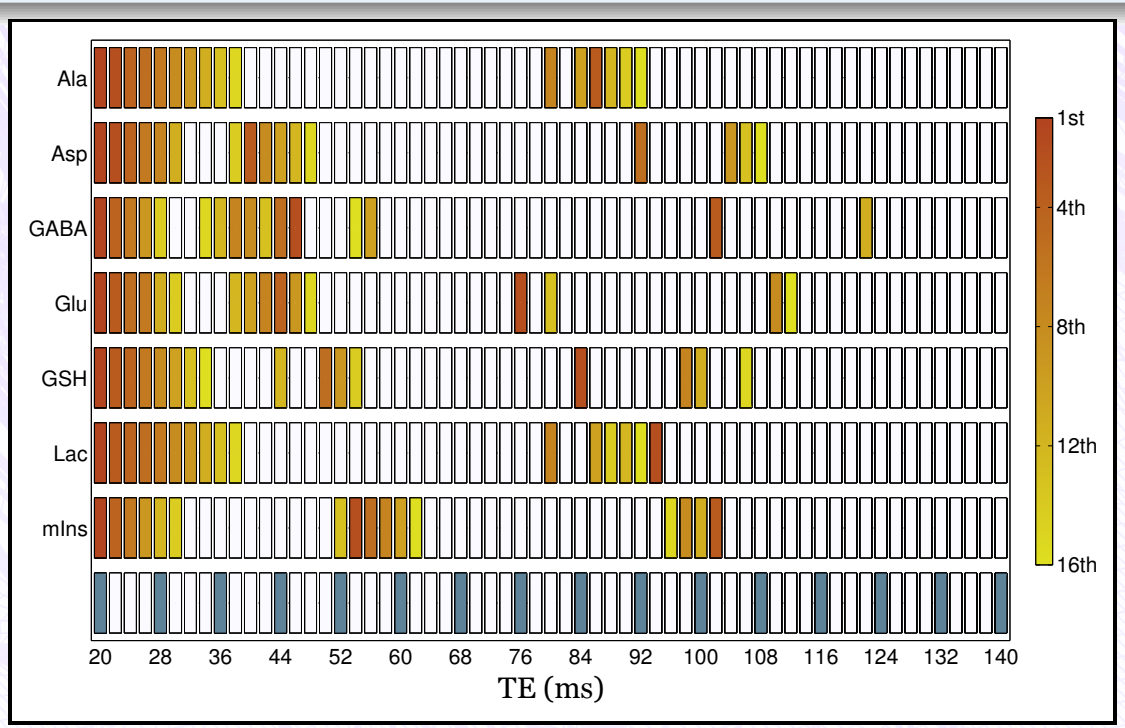

Fig. 18: Graphical representation of optimised sampling calculated with CRISO for 7 coupled metabolites

[13] Cramér-Rao guided Irregular Sampling Optimisation

Sampling optimisation on simulated data

- 200 repetitions of the quantification procedure
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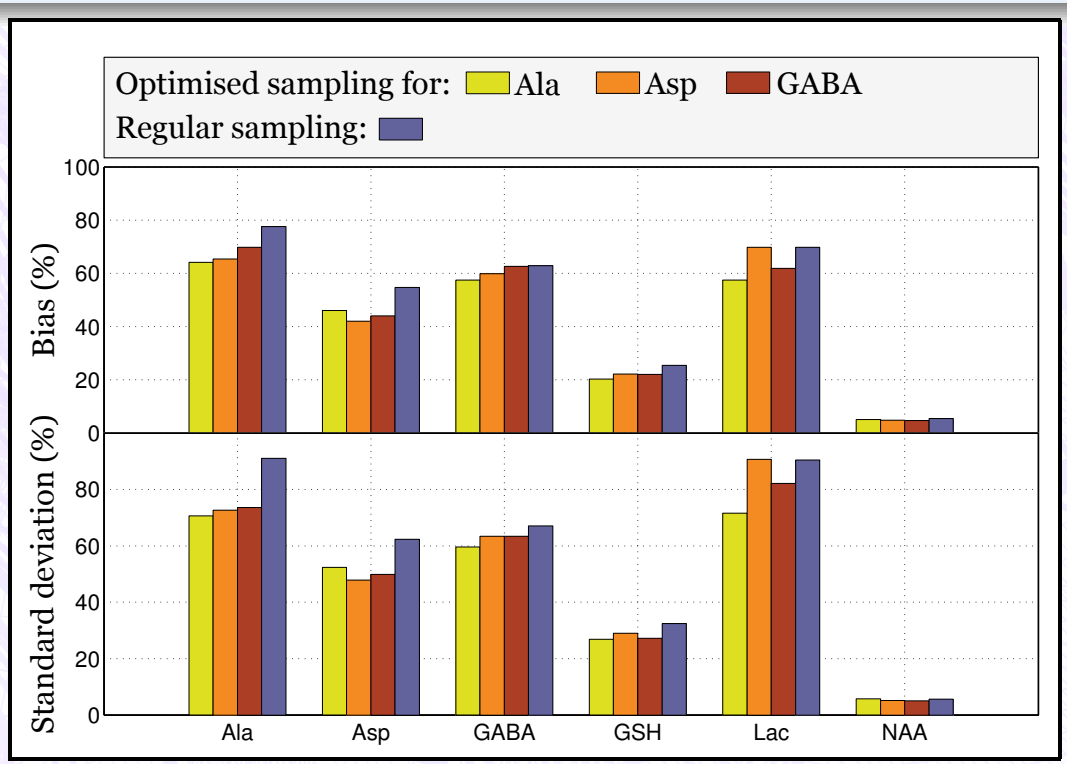

Fig. 19: Bias and standard deviations calculated of the amplitude estimates

Results

- **Global reduction of standard deviation** when using an optimised sampling
- Slight reduction of standard deviation for NAA which is not a strongly coupled

2D J-PRESS WISH experiment

- Performed on a horizontal 7T *Bruker Biospec* MRI
- A swiss mouse model anesthetised by inhalation of isoflurane
- Volume coil for emission and surface receive coil
- The signal was collected from a 90 μL voxel
- TR=3 s, NA=128, TE sampling was set up in order to cover the 4 previous tested strategies.

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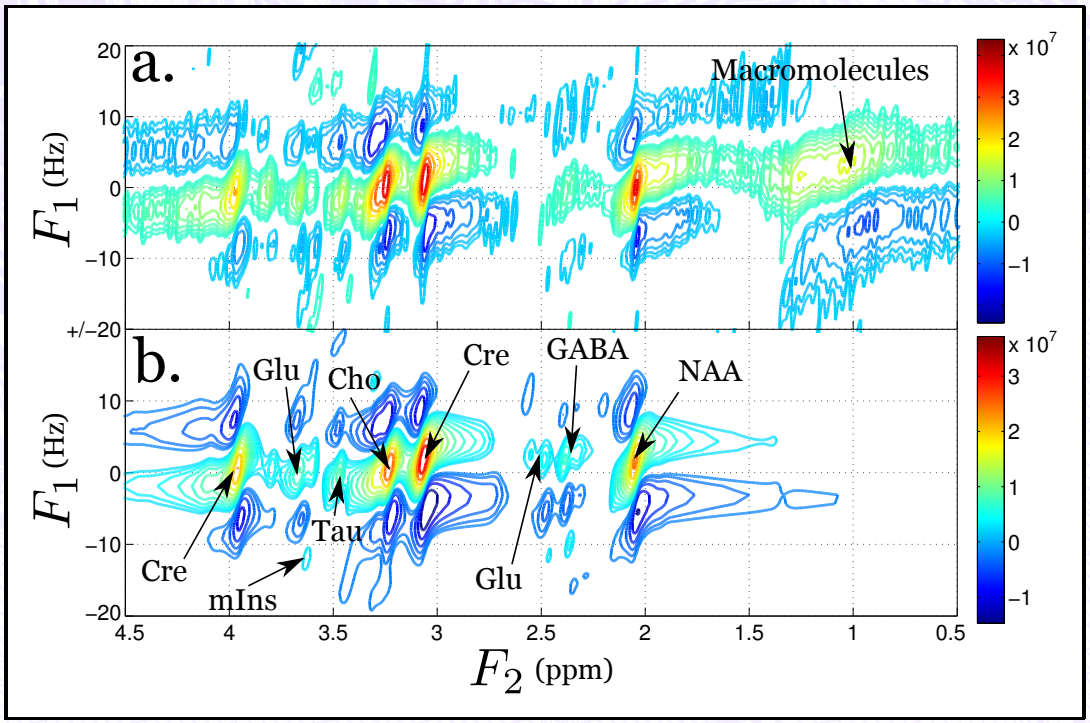


Fig. 20: A 7T *in vivo* 2D JPRESS spectrum (a) and its estimated spectrum (b)

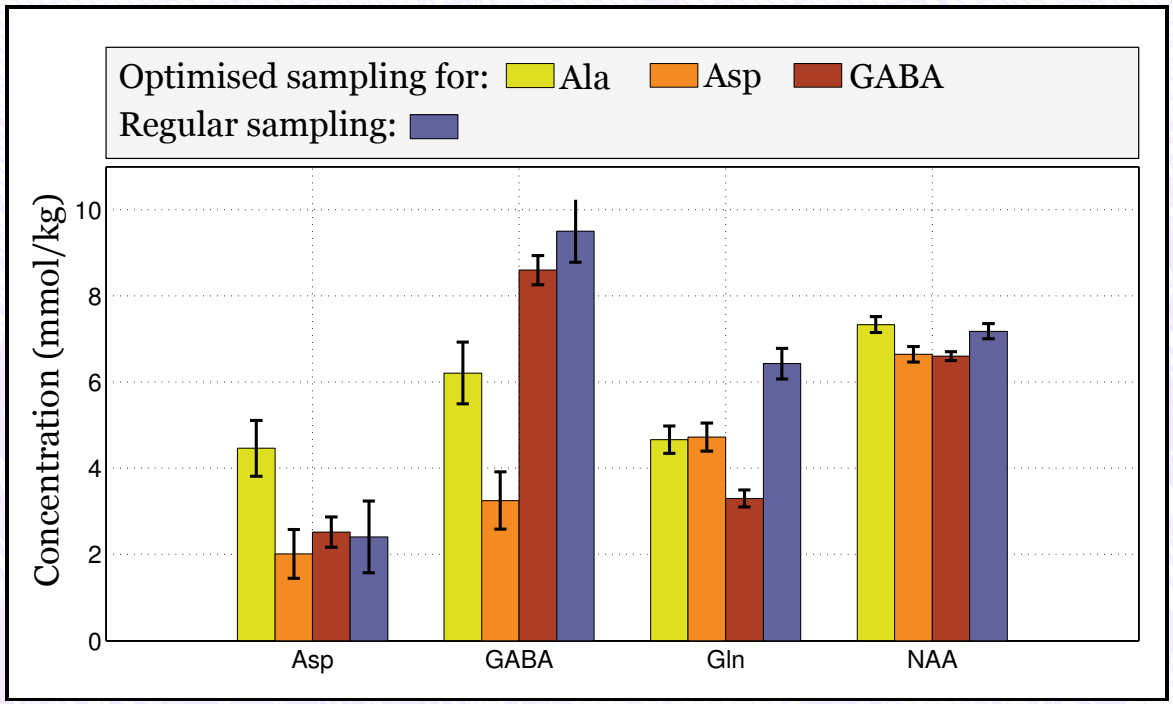
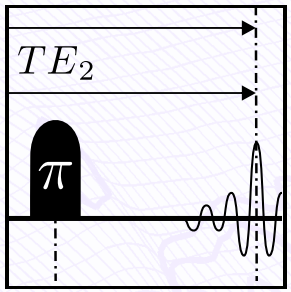


Fig. 21: *In vivo* quantification results : metabolite concentration estimates with CRB error bars

Results

- **Concentration estimates in agreement with literature** were found using the Asp dedicated optimised sampling
- In agreement with previous results, quantification results for NAA are independent of the sampling following t_1 dimension



2D J-PRESS WISH

A new localised 2D MRS sequence handling irregular sampling and inversion-recovery excitation was designed

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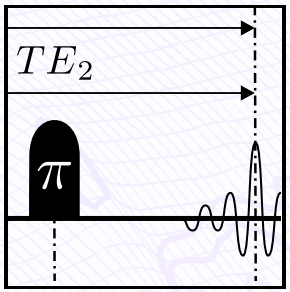

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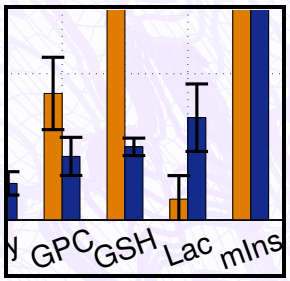

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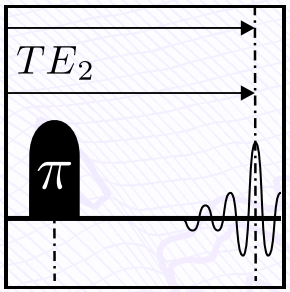

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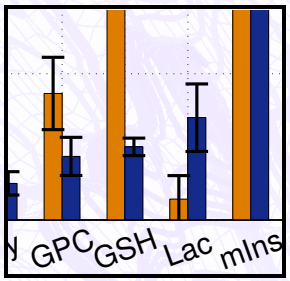

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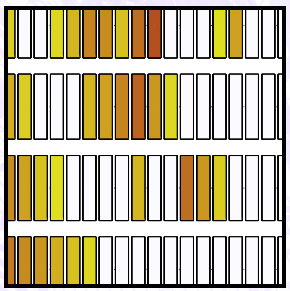

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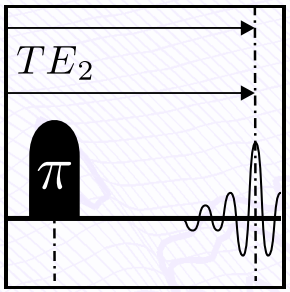

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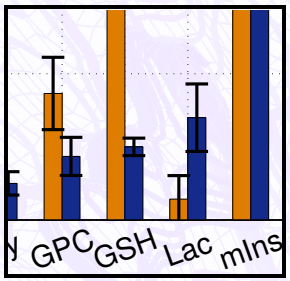

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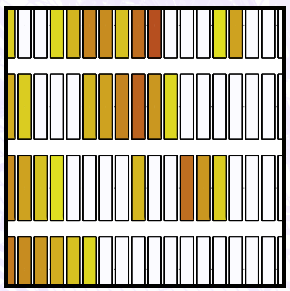

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Limitations

The CRISO method, despite promising results, has a limited interest for the reduction of 2D MRS experiment acquisition time for *in vivo* application.

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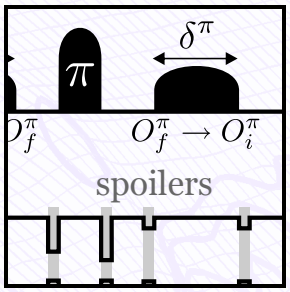
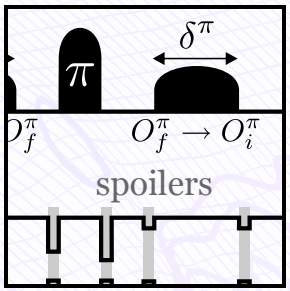
Ultrafast 2D MRS



Design an ultrafast 2D MRS sequence on small imaging systems

- 2D MRS J-resolved spectroscopy sequence
- Spatial localisation of the ultrafast signal



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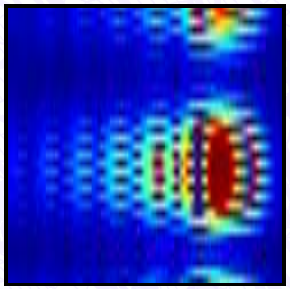

Develop a post-processing procedures

- 2D MRS spectrum reconstruction from raw data
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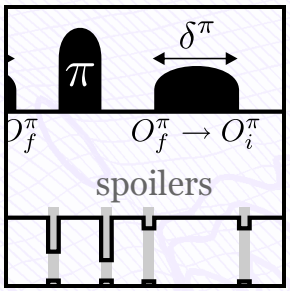

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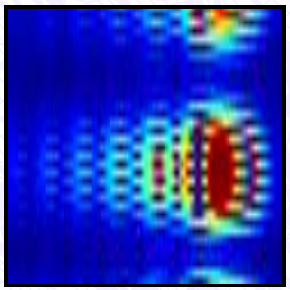

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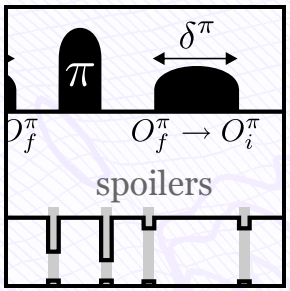

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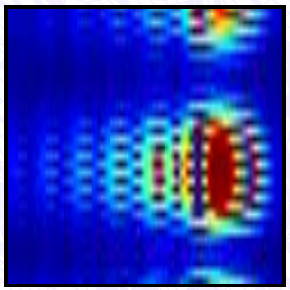

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This work was supported by CNRS ("SiqMu", PEPS-INSIS CNRS 2010 funding) and was carried out in close collaboration with P. Giraudeau and S. Akoka (CEISAM laboratory, Université de Nantes)

Ultrafast localised 2D J-resolved Magnetic Resonance Spectroscopy

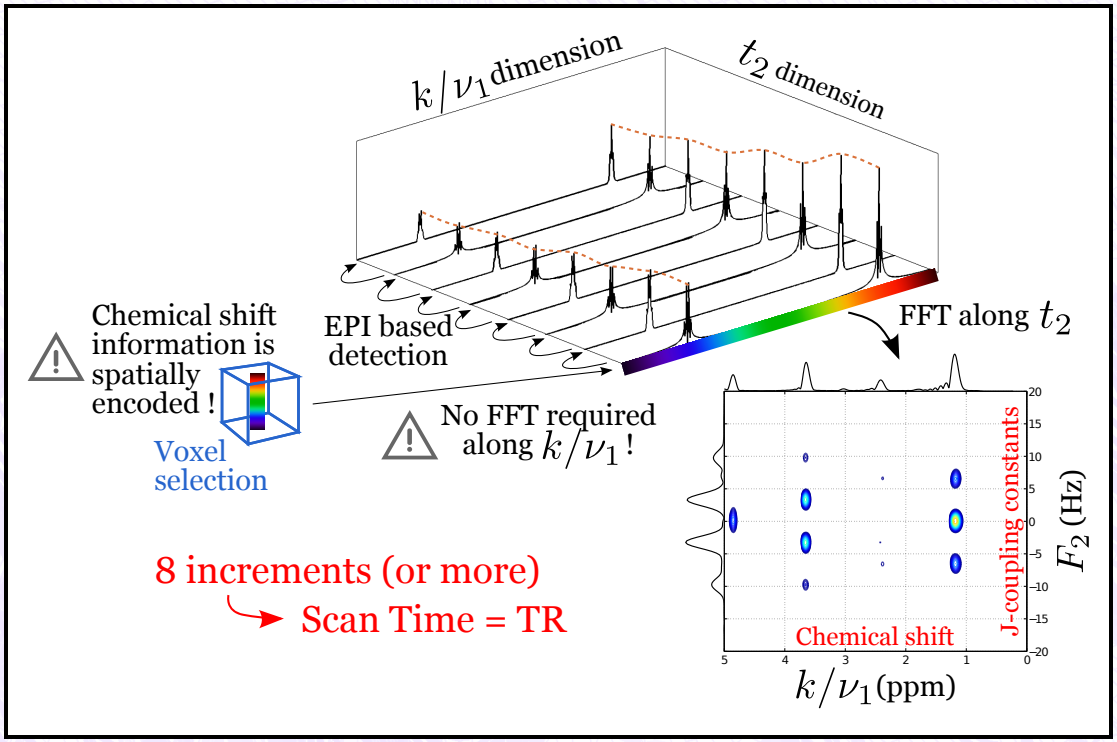

Fig. 22: Understanding ultrafast 2D J-resolved MRS

An ultrafast localised 2D J-resolved MRS experiment consists in :

- performing an ultrafast excitation that **spatially encodes the chemical shift information along one spatial dimension**
- performing an **EPI[16]-based detection to collect the ultrafast spectra for numerous t_1 increments**
- Fourier transforming the data set following the t_1 dimension

[16] Echo Planar Imaging

Designing the sequence

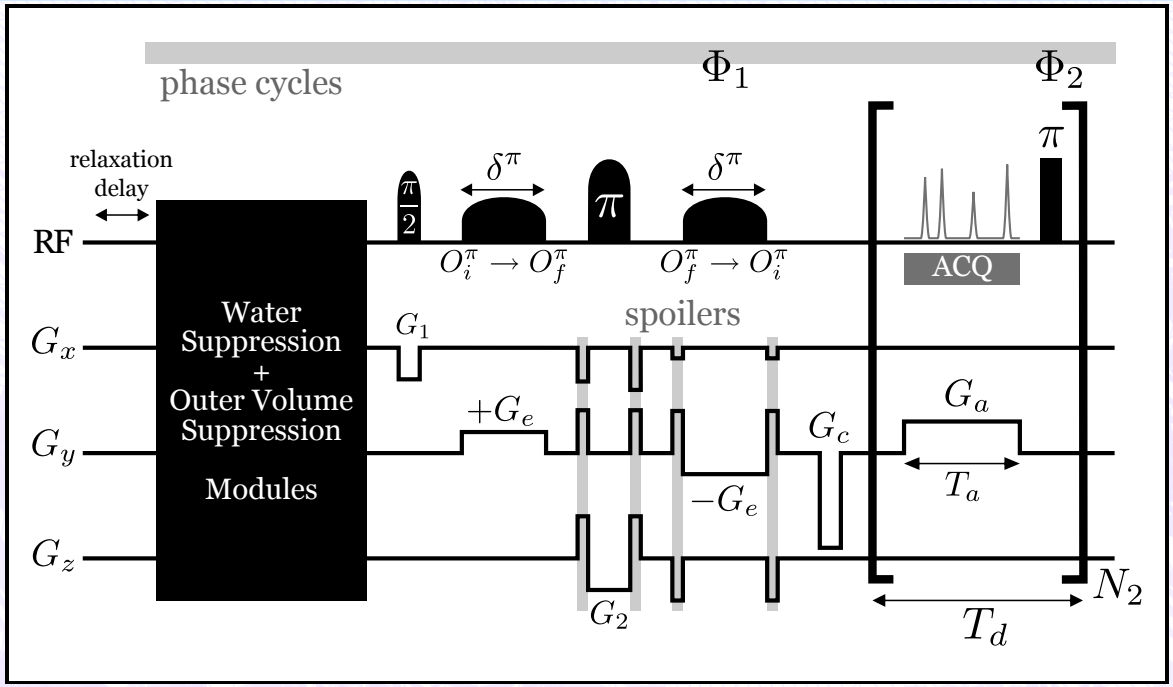

Fig. 23: ufJPRESS pulse sequence 3D localised 2D J-Resolved ultrafast MRS

[17] UltraFast J-resolved Point Resolved SpectroScopy

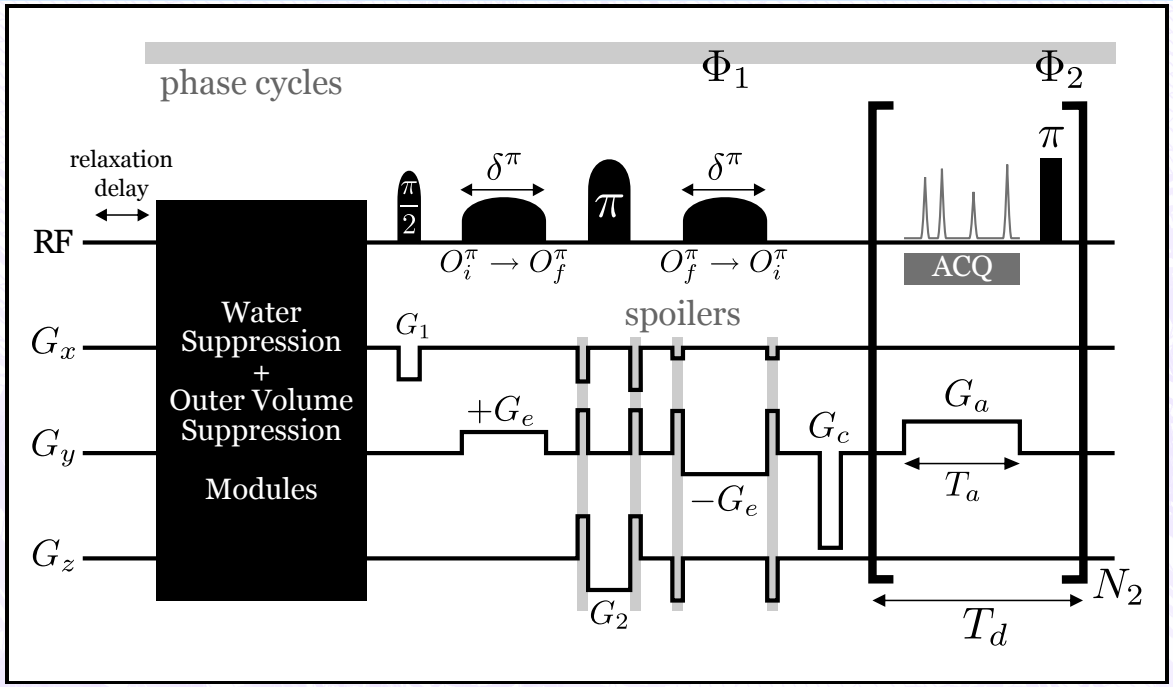

Fig. 23: ufJPRESS pulse sequence 3D localised 2D J-Resolved ultrafast MRS

ufJPRESS[17] : dedicated sequence to *in vivo* experiment

- **7T Bruker Biospec imaging system** (small animal) running with Paravision 5.1
- Signal collected with a **quadrature coil** (transmit/receive, 32 mm, Rapid Biomed)
- Preparation : **VAPOR module + OVS module**

[17] UltraFast J-resolved Point Resolved SpectroScopy

Ultrafast excitation scheme

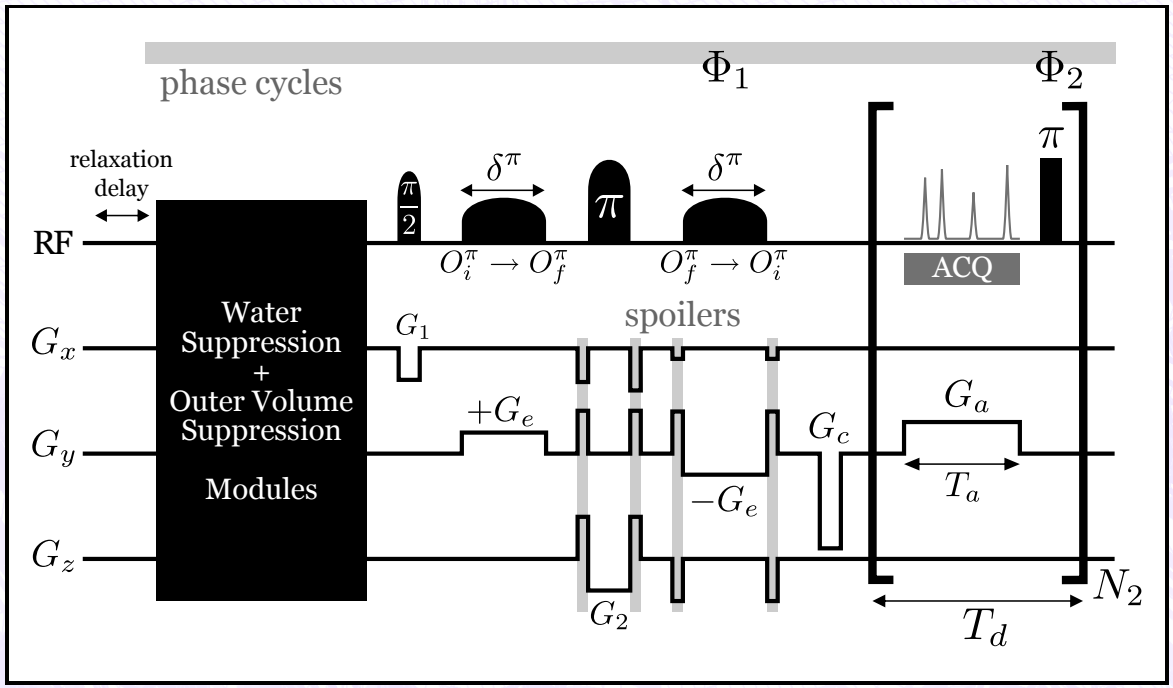

Fig. 24: ufJPRESS pulse sequence 3D localised 2D J-Resolved ultrafast MRS

Ultrafast excitation scheme

- **PRESS localisation scheme** nested in a modified version of the **ultrafast excitation scheme** proposed by Pelupessy et al.[18]
- Original 90° and 180° PRESS slice pulses applied during G_1 and G_2 gradients perform the **spatial selection in the first two dimensions**
- Adiabatic 180° chirp pulses applied during bipolar excitation gradients ($\pm G_e$) spatially **encode the chemical shift information along the third spatial dimension**

[18] Pelupessy P et al, JACS, 125 :12345-12350, 2003

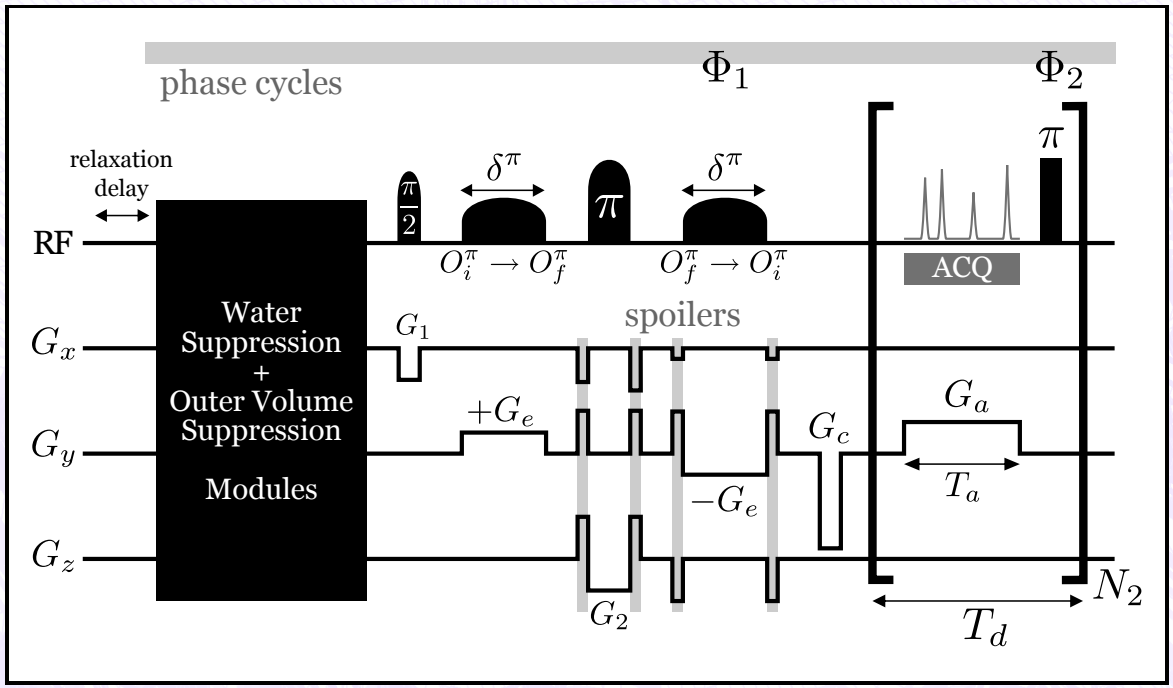

Fig. 25: ufJPRESS pulse sequence 3D localised 2D J-Resolved ultrafast MRS

Detection scheme

- **EPI-based detection scheme**
- **EPI bipolar gradients** are replaced by a positive acquisition gradient G_a followed by a 180° refocussing pulse[19]
- Preceded by a "shifting" gradient G_c to adjust the position of the spectral window
- Spectral resolution following the conventional dimension (F_1) depends in inverse proportion on the detection scheme duration T_d

[19] Giraudeau P et al, JPBA, 43 :1243-1248, 2007

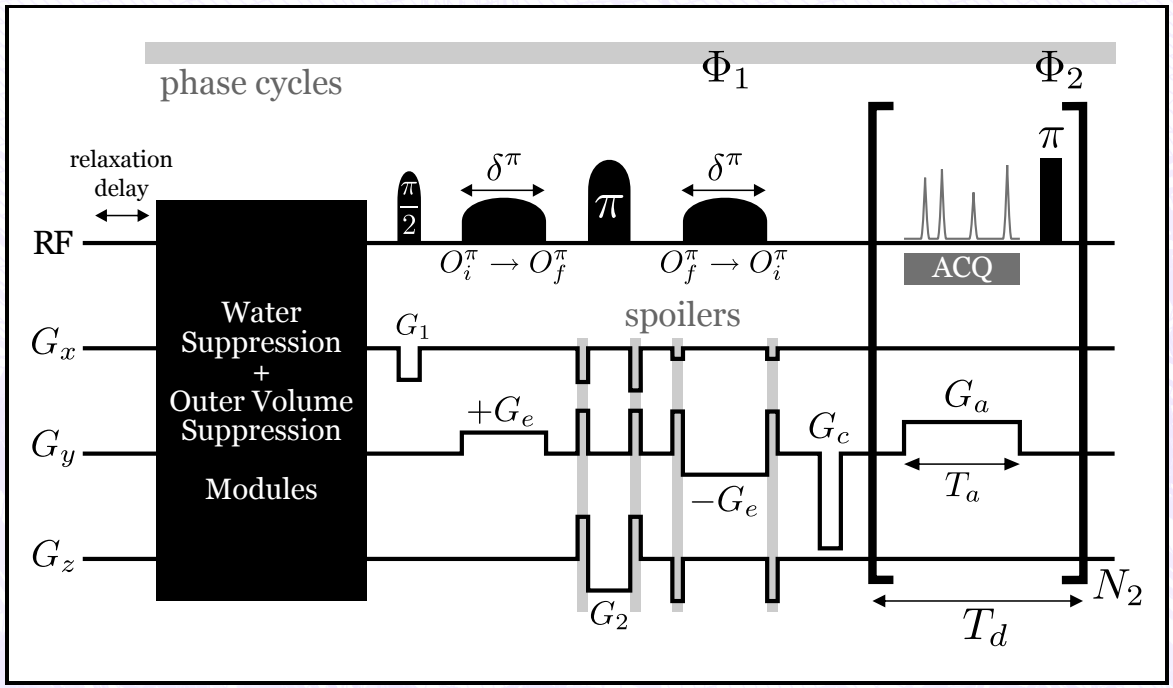

Fig. 26: ufJPRESS pulse sequence 3D localised 2D J-Resolved ultrafast MRS

Phase cycles

- ϕ_1 **[+x,+y]** phase cycle that reduces constant undesired signals (F_1=0 Hz)
- ϕ_2 **[+y,+y,-y,-y]** phase cycle that compensates imperfections of the 180° hard pulse (spurious stimulated echoes)
- ϕ_1 phase cycle requires a minimum number of 2 accumulations

Method

- Highly concentrated ethanol solution (70% w/w in water)
- Signal collected from a 8 mm x 8 mm x 8 mm voxel
- Ultrafast excitation duration $T_e = 2\tau^{\pi}$ optimisation
- Chirp pulse calibration using a spin-echo based sequence

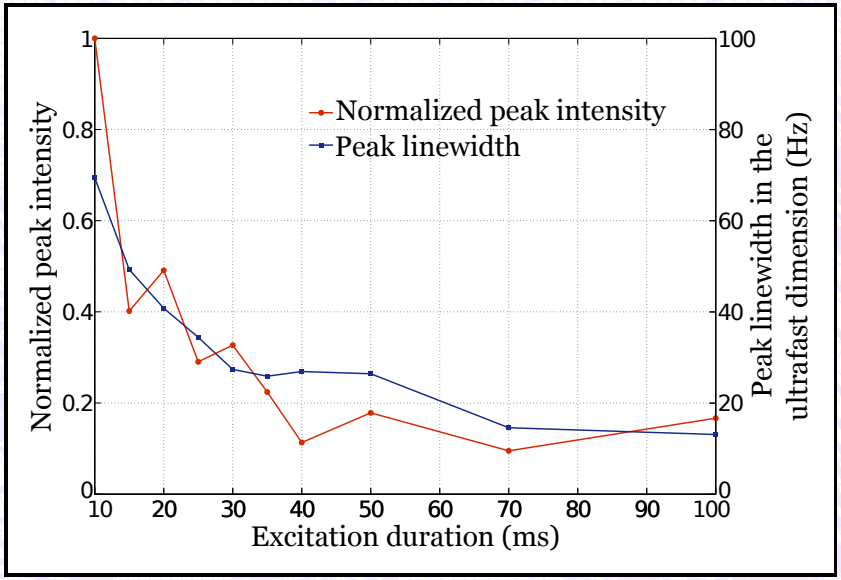

Fig. 27: CH_3 peak intensity and peak linewidths in the ultrafast dimension according to excitation duration (T_e)

[20] Giraudeau P, PhD Thesis, Université de Nantes, 2008

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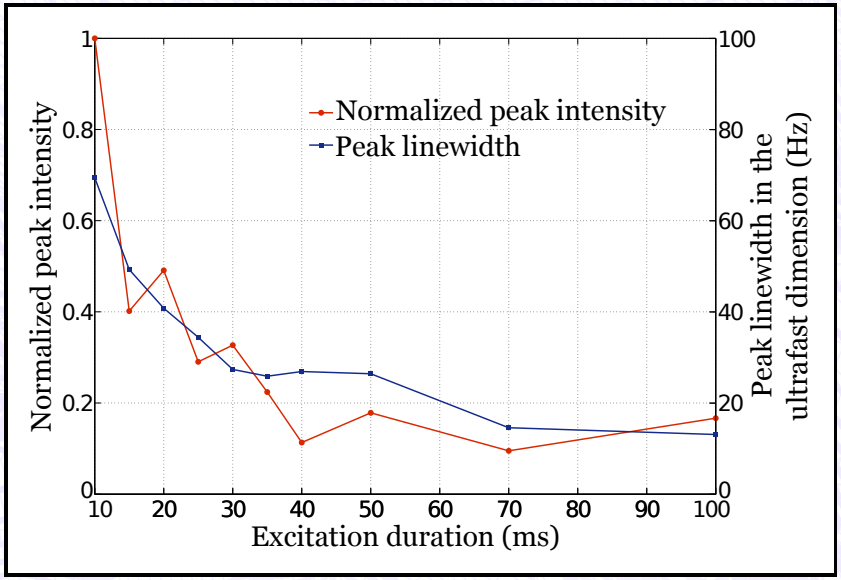

Fig. 27: CH_3 peak intensity and peak linewidths in the ultrafast dimension according to excitation duration (T_e)

Results

- Signal-to-Noise (S/N) ratio strongly decreases according to T_e[20]
- Ultrafast spectral resolution increases according to T_e
- **Good compromise is reached for T_e= 30 ms**

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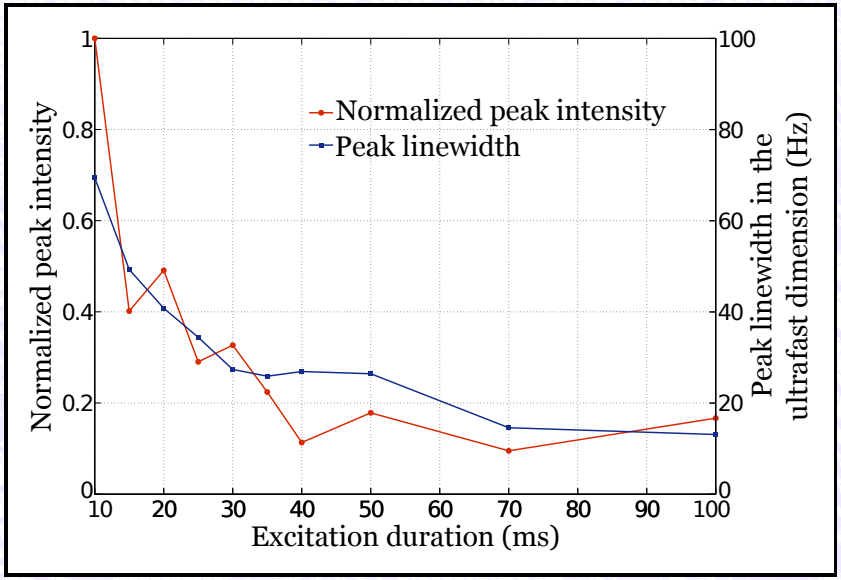

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- Ultrafast spectral resolution increases according to T_e
- **Good compromise is reached for T_e= 30 ms**

Limitations

- Short excitation duration T_e requires **high RF power** for chirp pulses
- Long excitation duration T_e requires **high gradient strength** for G_a

[20] Giraudeau P, PhD Thesis, Université de Nantes, 2008

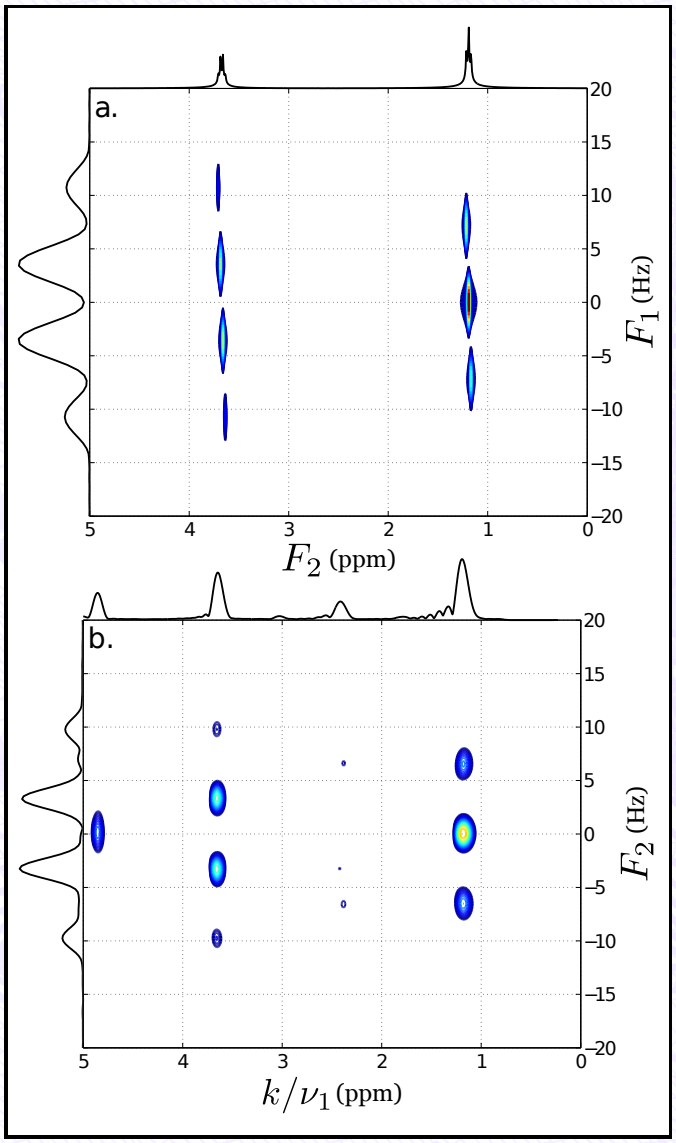
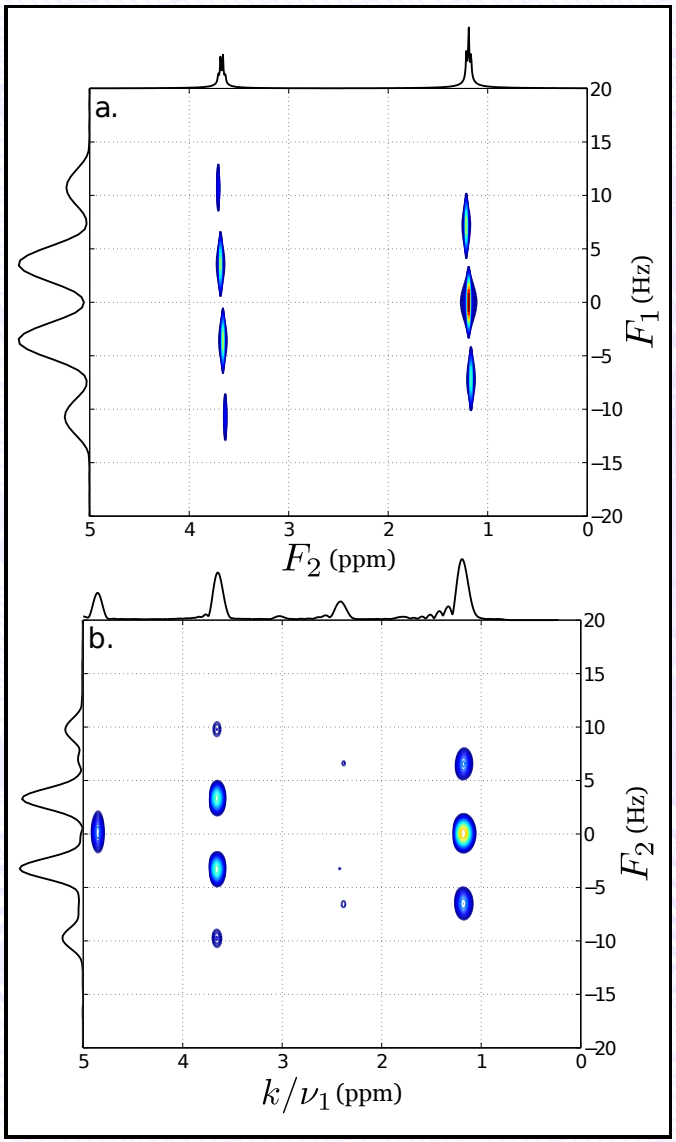


Fig. 28: Tilted conventional (a) and ultrafast (b) localised 2D J-resolved spectra

Method

- Concentrated ethanol solution (10% w/w in water)
- Signal collected from a 8 mm x 8 mm x 8 mm voxel
- Conventional and ultrafast 2D J-resolved experiments were performed with n_1=128 following t_1 dimension

Ultrafast vs. conventional 2D J-Resolved MRS



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	Ultrafast	Conventional
F_2 dimension	**17.0 Hz**	1.9 Hz
F_1 dimension	2.3 Hz	1.3 Hz
Scan time	**20 s**	21 mins

Tab. 1: CH_3 peak linewidths and scan time comparison between ultrafast and conventional 2D J-resolved MRS experiments

Observation

The chemical shifts and the J coupling values of both spectra are in good agreement with literature data

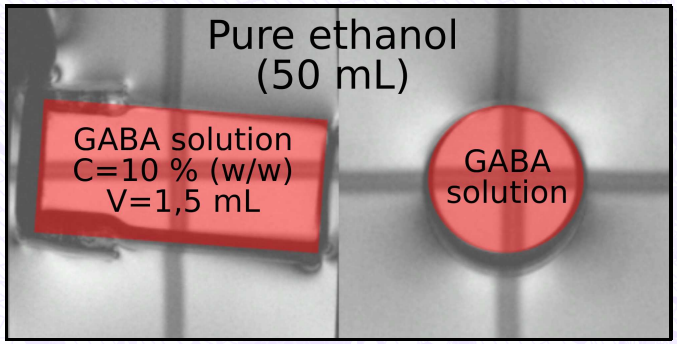


Fig. 29: Sagittal and axial images of the γ-Aminobutyric acid (GABA) *in vitro* phantom (FLASH, TE/TR = 5.4/100 ms)

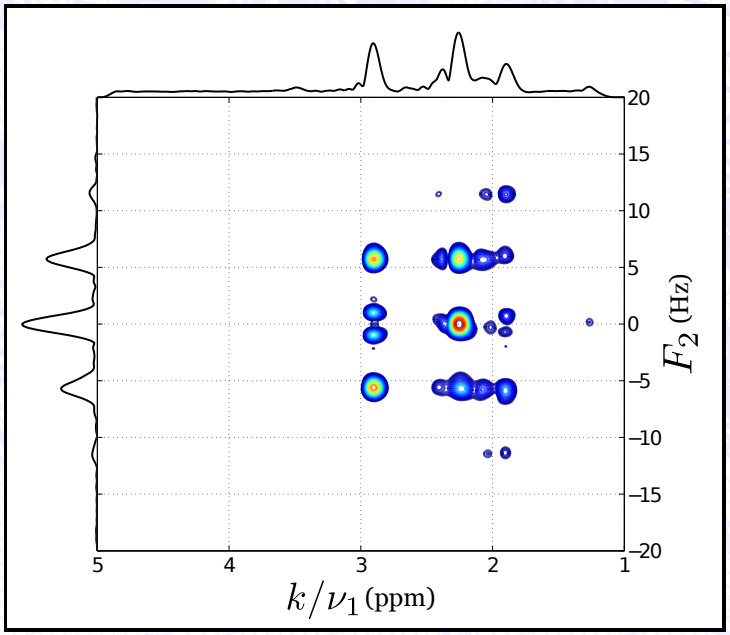
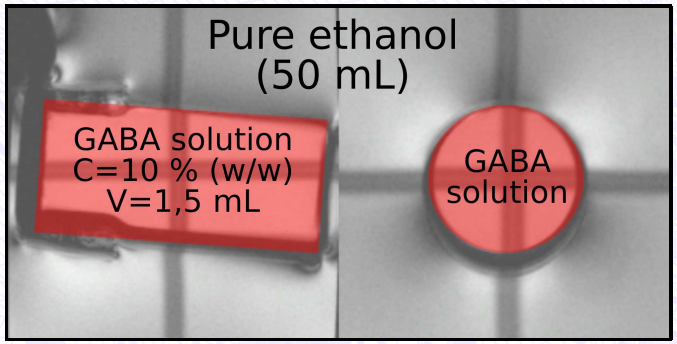


Fig. 30: 3D localised 2D ultrafast J-resolved spectrum of GABA

Method

- Purpose-built phantom for localisation tests : 1.5 mL tube containing a γ-**Aminobutyric acid (GABA)** solution (10% w/w in water) placed at the center of a 50 mL tube of **pure ethanol**
- Signal collected from a 5 mm x 5 mm x 5 mm voxel placed in the GABA solution
- 3 mm Outer Volume Saturation (OVS) bands with a 0.5 mm gap to voxel
- Number of Accumulations (NA) = 16 resulting in a 2 min 40 s scan time



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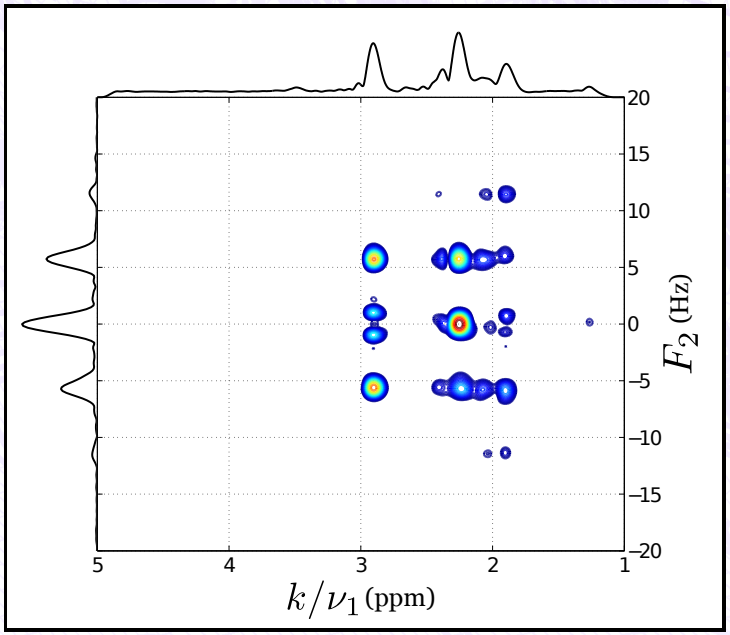

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Efficient 3D localisation

Very low intensity ethanol peaks (at 1.19 and 3.67 ppm) were reported

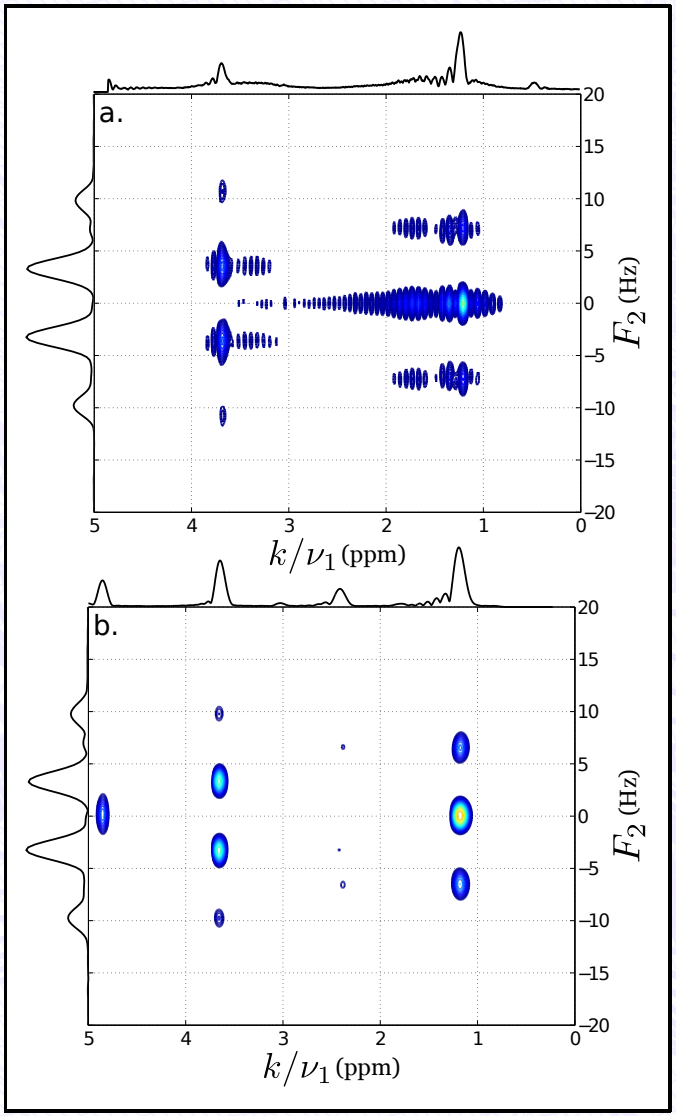
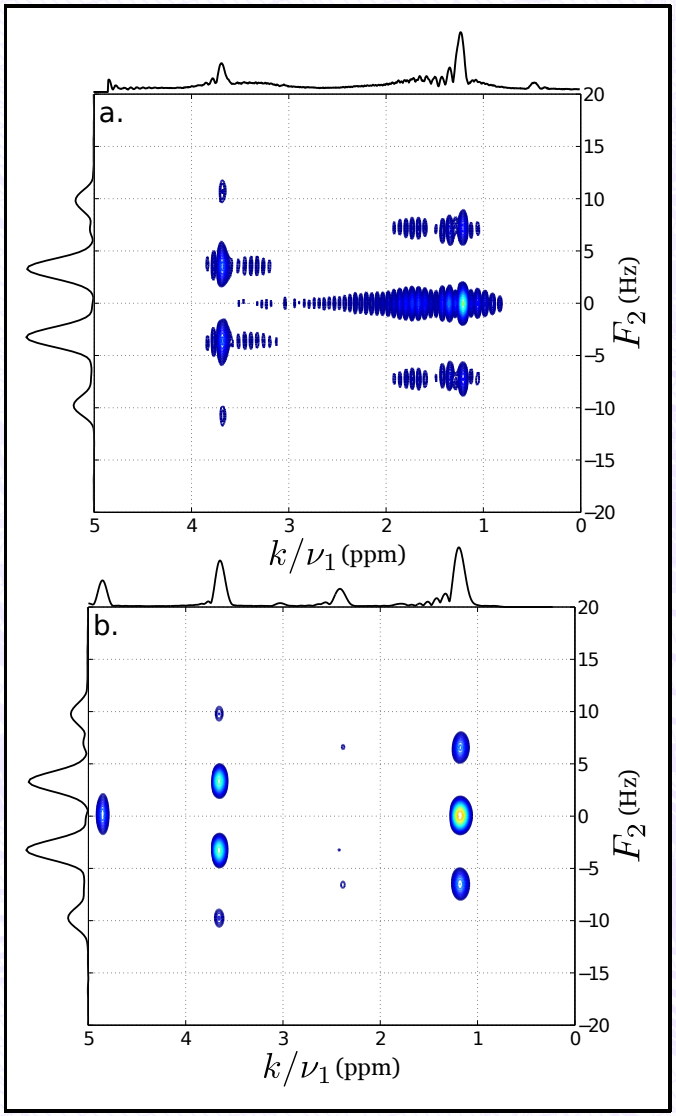


Fig. 31: Raw (a) and post-processed (b) ultrafast 2D J-resolved spectra of a highly concentrated ethanol solution (70% w/w in water)

Ultrafast artefacts

- Raw ultrafast spectra present **asymmetric sinc wiggles** around peaks of interest
- These wiggles are **inherent to ultrafast MR experiment**



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Automatic post-processing procedure

- Based on spatial apodization
- The optimal apodization window width is automatically estimated in order to improve S/N ratio without decreasing spectral resolution
- **The "apparent" S/N ratio is usually 2.5 times higher** while linewidth increases by only 2 Hz

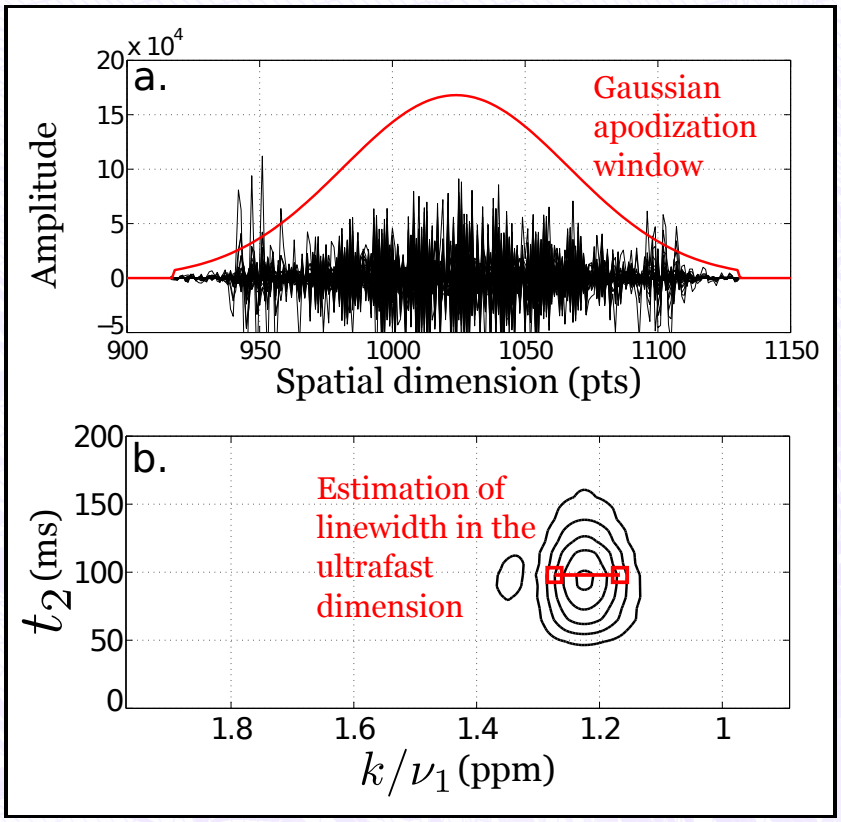

Fig. 32: Inverse Fourier transformed ultrafast signals apodised in the spatial dimension with an optimised gaussian window (a) and the corresponding CH_3 2D peak in the $F_2 t_1$ plan where linewidth estimation is performed (b)

Ultrafast artefacts

- Raw ultrafast spectra present asymmetric *sinc* wiggles around peaks of interest
- These wiggles are inherent to ultrafast MR experiment[21]

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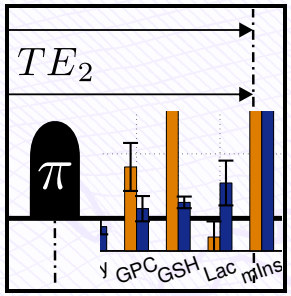
[21] Shapira B et al, JMR, 166 :152-163, 2004
[22] Giraudeau P et al, MRC, 49 :307-313, 2011



Quantitative conventional 2D MRS

- 2D J-PRESS WISH : a new localised 2D MRS sequence
- NEMESIS : a novel complex time domain quantification procedure
- CRISO : an algorithm for sampling optimisation

[23] Tkác I et al, MRM, 41 :649-656, 1999
[24] Roussel T et al, JMR, 215 :50-55, 2012
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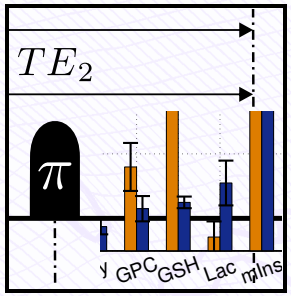

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Perspectives

- 2D J-PRESS WISH : ultra short TE acquisition[23]
- CRISO : integration of *NA* accumulation handling
- NEMESIS : regularisation terms

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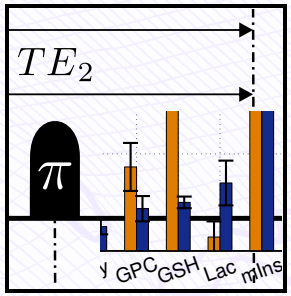

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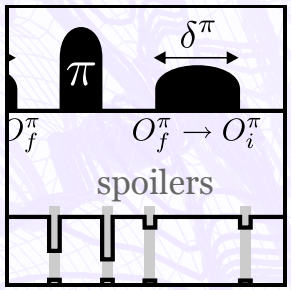

Ultrafast 2D MRS

- ufJPRESS : First 3D localised 2D J-resolved ultrafast MRS sequence
- Feasibility stage shows good quality for *in vitro* spectra[24] [25]

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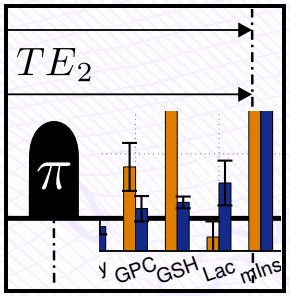

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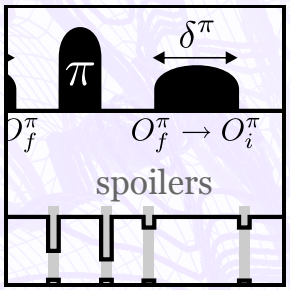

Ultrafast 2D MRS

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Perspectives

- Great potential as it could be combined to high SNR spectroscopy applications
- Optimised trajectory in the plan $(k/\nu_1, F_2)$ during detection
- Ultrafast spectroscopic imaging

[23] Tkác I et al, MRM, 41 :649-656, 1999
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Publications

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- **Scientific collaboration with Frydman group** in October 2012

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MRI facilities

- **4.7 T small animal Bruker Biospec MRI** : CREATIS, CPE, Villeurbanne
- **7 T small animal Bruker Biospec MRI** : ANIMAGE, CERMEP, Bron
- **Bruker pulse programming course**, Ettlingen, Germany

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Computer calculation facilities

CREATIS **computer cluster** for Monte Carlo studies

Thank you for your attention !