***Abstract*—This document describes some possible future researches in FAST in the context of short-echo time MRS quantitation. Proposals for simulating data are also given.**

I. Introduction

The goal of this paper is to discuss possible improvements in short-echo time MRS quantitation. The literature on the topic is huge but the results remain unsatisfactory, resulting in a very limited clinical use. Two principal obstacles show up when quantifying short-echo time MRS signals: the peaks of interest are widely overlapping and the macromolecular baseline is spread all over the frequency region of interest. In order to test quantitation methods, one needs to know the true composition of the signal and therefore simulated data are mandatory. Different possibilities to create simulated data are given below Section II. Quantitation methods are then discussed Section III and a special attention is paid on ideas that have not been yet investigated.

II. Simulated data

In order to be realistic, simulated short-echo time MRS signals need to be composed of several elements: signal due to the metabolite contributions, the saturated water signal and a macromolecular baseline. Furthermore, due to magnetic field inhomogeneities (imperfect shimming), body motion, etc, an ideal Lorentzian lineshape would be too optimistic. Therefore, we suggest to distort the lineshape (see below for more details). In spite of important hardware improvements, Eddy currents remain a major concern in MRS and should be taken care of when generating simulated data.

In this section, we discuss how to generate the different parts of what should mimic a real short-echo time *in vivo* MRS signal acquired from the brain. Offsets in the frequency domain are not considered in the generation of simulated data since they can be easily removed by removing the first point of the signal in the time domain.

A. Metabolite signals

Although *in vivo* MRS signals are composed of hundreds of metabolite contributions, only a few of them should be considered since the others are not detectable. The number of visible metabolites depends on the acquisition sequence and, in particular, on the external field intensity, but even at high field the database of metabolite profiles is often reduced to about twenty metabolites. We set up a list of metabolites that were used in several recent publications (see Table I on page 1): glutamate (Glu), myo-inositol (Ins), N-acetyl aspartate (NAA), taurine (Tau), phosphocreatine (PCr), creatine (Cr), choline (Cho), glycerophosphocholine (GPC), phosphocholine (PCh), glutamine (Gln), glutathione (GSH), lactate (Lac), phosphoethanolamine (PE), glucose (Glc), alanine (Ala), aspartate (Asp), γ-aminobutyric acid (GABA), scyllo-inositol (Scyllo), N-acetylaspartylglutamate (NAAG), ascorbic acid (Asc), glycine (Gly). In [21], LCModel [20] is used to quantify *in vivo* ^{1}H spectra from human and rat brains with fields from 1.5 to 9.4 T and a wide range of sequences.

Table I
List of metabolites used in recent publications for short-echo time in vivo MRS (brain).

	[21]	[6]	[25]	[2]	NMRSCOPE
Glu	x	x	x	x	x
Ins	x	x	x	x	x
NAA	x	x	x	x	x
Tau	x	x	x	x	x
PCr	x	x	x	x	x
Cr	x	x	x	x	x
Cho	x	x	x	x	x
GPC	x	x	x		
PCh	x	x	x		
GSH	x	x	x		
Lac	x		x		x
PE	x	x	x		
Gln	x	x	x	x	x
Glc	x	x	x	x	x
Ala	x		x		x
Asp	x		x	x	x
GABA	x		x		x
Scyllo	x		x	x	
NAAG	x		x	x	
Asc			x		
Gly			x		x

In [6], more than 10 metabolites were quantified from *in vivo* spectra acquired from rat brains with fields at 4.7 T. Schulte *et al.* [25] show that a wide range of metabolites in the human brain are detectable from *in vitro* and *in vivo* experiments with a whole-body 3 T MR scanner. At 1.5 T, Bartha *et al.* [2] quantified more than 10 metabolites from *in vivo* spectra using stimulated echo acquisition mode (STEAM, TE = 20 ms) localization. In NMRSCOPE [9] included in jMRUI (http://sermn02.uab.es/mrui), several metabolite profiles can be generated from quantum mechanics (see Table I on page 1). Most of the metabolites that are usually quantified in the literature are available in NMRSCOPE. We propose to use at least Glu, Ins, NAA, Tau, PCr, Cr and Cho to simulate short-echo time *in vivo* MR signals.

To generate the metabolite profiles from the spin information available in NMRSCOPE, the most common sequences, namely STEAM and PRESS, should be used.

In order to create realistic signals, one also needs to know the metabolite concentrations, which depends on several parameters (tissue location, age of patient, type of tissue, etc). Attempts for estimating these concentrations have been carried out in several papers. In [31], Zhu *et al.* quantified *in vivo* short-echo time MRSI data from healthy volunteers and reported the concentrations of several metabolites (Ins, NAA, Cr, Cho) with respect to the location of the sample in the brain. Mangia *et al.* [16] quantified single-voxel ^{1}H MRS brain data acquired from the visual cortex of healthy volunteers at 7 T and reported the concentrations of Asc, Asp, Cr, PCr, GABA, Glc, Gln, Glu, GSH, Ins, Lac, NAA, NAAG, PE, Scyllo, Tau and GPC+PCh. Note that standard deviations (SD) are also given in these papers. The latter paper seems to be a good starting point to generate realistic signals since it is recent and the data have been acquired at the highest magnetic field currently available for human studies. As illustration, we give the estimated concentrations obtained by LCModel in [16] in

Table II
CONCENTRATION ESTIMATES FROM [16]

	Concentration ($\mu mol/g$)	SD (%)
Asc	1.2	6
Asp	1.0	16
Cr	5.0	2
PCr	3.4	3
GABA	1.0	9
Glc	1.1	17
Gln	2.9	3
Glu	11.0	1
GSH	1.0	7
Ins	6.7	2
Lac	0.8	19
NAA	10.8	1
NAAG	1.4	5
PE	1.2	7
Scyllo	0.4	4
Tau	1.9	4
GPC+PCh	1.3	1

Table II on page 2.

Another possibility is to use measured *in vitro* signals for each metabolite we want to include into the database. However, in this case, we are limited in terms of acquisition sequences.

B. Water resonances

To simulate the saturated water resonances, one can use real MRS data and apply the following steps: select MRS signals for which a good Eddy current correction is possible using one of the classical methods, *i.e.* ECC [11], QUALITY [5] or QUECC [1] and apply this method on the MRS data, filter the water resonances using a SVD-based method (HLSVD-PRO [14] is advised for its performances in terms of accuracy and efficiency) and reconstruct the denoised water resonances using the resonances estimated by the SVD-based method. Note that the real MRS data should be acquired with a similar sequence as the one under investigation. It would be interesting to simulate also the water resonances since the tail of these resonances might corrupt the lineshape if it is not correctly removed.

C. Baseline

The baseline components are much more complicated to extract from real signals than the water resonances. The baseline may vary a lot from one signal to another and depends on several parameters: tissue type, location of the sample, acquisition sequence, etc. The baseline can be measured using specific sequences based on T_1 relaxation such as the inversion-recovery [3], [12] or the saturation-recovery sequences [10]. Baseline removal can also be based on T_2 relaxation by increasing the echo time [13]. However, the *in vivo* determination of the exact relaxation times for both macromolecules and metabolites is complicated and time consuming. Nevertheless, we propose the following three different ways to simulate the baseline:

- using an inversion-recovery sequence (collaboration with U. Himmelreich)
- measurement in a realistic phantom (collaboration with U. Himmelreich)
- based on Seeger *et al.*'s paper [26]

In [26], LCModel is used to quantify short-echo time MRS signals including, in the database, 5 components accounting for the baseline. The components are given in Table 1 in [26]. By using these components, they analyzed the content of lipids and macromolecules in different brain tumor tissue samples. As said for the water resonances, it would be interesting to model the baseline to be able to keep the same lineshape for the baseline and the metabolite signals. If the baseline is just added to the metabolite profiles as in (5), the signal will be composed of two different lineshapes.

D. Lineshape distortion and Eddy currents

The rapid switch of the gradient pulses can generate Eddy currents (EC) in the surrounding conducting surfaces around the gradient coils. In spite of the shielded gradients coils which strongly reduce the generation of Eddy currents, they remain present. Several effects can be observed in the acquired spectrum: phase changes, gradient-induced broadening of the linewidth, time-dependent but spatially invariant B_0 shift effects (which appears as ringing in the spectrum).

A simple representation of the Eddy currents effect is given by

$$y_{EC}(t) = y_0(t)e^{j\Phi_{EC}(t)} \tag{1}$$

where $y_{EC}(t)$ is the signal at time t distorted by EC effects, $y_0(t)$ the original signal and $\Phi_{EC}(t)$ the time-dependent phase shift. Dirk's proposal is to use a function of the form

$$\Phi_{EC}(t) = \sum_{l=1}^{L} a_l e^{-d_l t}, \tag{2}$$

where a_l, d_l are real-valued numbers, L is an integer.

Other phenomena can distort the lineshape and not only a phase distortion should be applied to the signal. Note that a method like ECC [11] only corrects the signal phase for the time-dependent field distortion ($\Delta B_0(t)$) , while QUALITY [5] and QUECC [1] also correct for the lineshape, taking into account space-dependent field distortions ($\Delta B_0(x, y, z)$ and $\Delta B_0(x, y, z, t)$). In (2), only a time-dependent field distortion ($\Delta B_0(t)$) is generated. Space-dependent field distortions should also be created to mimic genuine signals. In that regard, two possible distortion shapes have been proposed:

- the triangle shape
- the combined Lorentzian-Gaussian shape (one half Lorentzian, the other half Gaussian)

Both methods can be followed by some smoothing techniques to avoid discontinuities in the signal.

Let's first consider the triangle shape. The disorted signal becomes

$$y_L(t) = y_0(t)g_s(t) \tag{3}$$

where $g_s(t)$ is $g(t)$ transformed to be smoothed and

$$g(t) = \frac{1}{2\pi jt}\left[\frac{e^{x_1} - e^{x_2}}{x_2 - x_1} + \frac{e^{x_3} - e^{x_2}}{x_3 - x_2}\right] \tag{4}$$

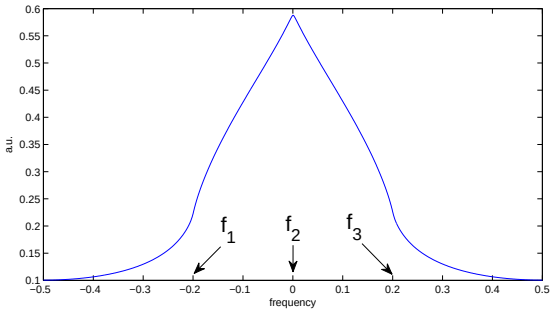

Figure 1. Illustration of the triangle lineshape (real values)

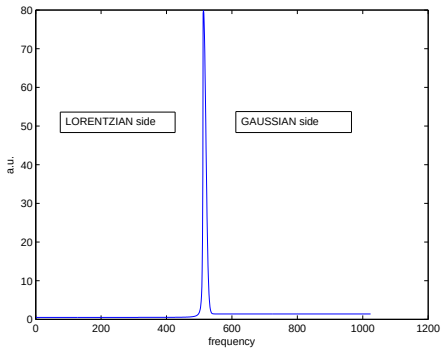

Figure 2. Illustration of the Lorentzian-Gaussian shape (real values)

where $x_i = 2\pi j f_i t$ for $i = 1, ..., 3$ and f_i are the 3 frequencies (real-valued numbers) which characterize the triangle (see Figure 1 on page 3). For $t = 0$, $g(0) = \lim_{t\to 0} g(t) = 0.5(f_3 - f_1)$. In order to avoid frequency shifts with respect to y_0, one should choose $f_2 = 0$. Similarly, to avoid changing the amplitudes of the peaks of interest, $g(t)$ should be divided by $g(0)$, i.e. $0.5(f_3 - f_1)$. Different smoothing techniques are possible. Three of them are proposed here:

- using a Lorentzian: $g_s(t) = g(t)e^{-dt}$
- using a Gaussian: $g_s(t) = g(t)e^{-dt^2}$
- using a Moving Average filter: In *discrete* notations, $g_s(n) = \sum_{m=0}^{M} g(n+m)F(m)$ where $F = [F(0) \dots F(M)]^T$ is the filter (M is the filter order) which can take different shapes (uniform, linearly decaying, exponentially decaying, etc). It is likely that an exponentially decaying shape is preferable to avoid a too severe smoothing. The influence of M is also smaller. One should also check whether adding M zeros at the end of the time domain signal g will not distort the signal.

Another possibility is to consider the Lorentzian-Gaussian shape. The following steps can be followed to construct the hybrid shape:

1) generate numerically a Lorentzian and a Gaussian curve in the time domain
2) take half of both Fourier transformed signals (left part for Lorentzian spectrum, right part for Gaussian spectrum)
3) normalize the Gaussian spectrum such that the height of its peak is equal to the height of the Lorentzian peak
4) joint the left-sided Lorentzian spectrum with the normalized right-sided Gaussian spectrum and apply the inverse Fourier transform to get back to the time domain.

An illustration is given in Figure 2 on page 3.

E. Summary

Simulated signals will be composed of the parts described above:

$$y_{TOT}(t) = y_M(t)g_s(t)e^{j\Phi_{EC}(t)} + B(t) + W(t) + N(t) \quad (5)$$

where $y_M(t) = \sum_{k=1}^{K} \alpha_k \nu_k$ (note that frequency shifts can be contained in the lineshape distortion $g_s(t)$), $B(t)$ is the baseline signal, $W(t)$ is the water signal and $N(t)$ is the circular white gaussian noise signal defined by

$$N(t) = R(t) + jI(t), \quad (6)$$

where $R(t), I(t) \sim \mathcal{N}\left(0, \sigma^2\right)$ and σ the standard deviation of the noise. Note that if one can model the water and the baseline signals, (5) can become

$$y_{TOT}(t) = \left(y_M(t) + B(t) + W(t)\right) g_s(t)e^{j\Phi_{EC}(t)} + N(t) \quad (7)$$

III. Quantitation methods

In short-echo time MRS, the baseline is probably the most problematic part to deal with. Numerous methods have been proposed to disentangle the baseline from the metabolites of interest but no one can be refered to as a gold standard. Only a few quantitation methods have been compared and, often, no strong conclusions have been drawn. A serious issue when comparing quantitation methods is the lack of benchmark MRS data. Indeed, the performances of a method may depend on the data under investigation and benchmark data approved by the MR community could give more credit to a method comparison. Furthermore, quantitation methods often require a lot of user interaction, which complicates a lot the comparisons since a wrong choice of hyperparameters may result in poor estimations, resulting in false conclusions. The section above should be the first step toward the construction of benchmark simulated MRS data. In parallel and based on these benchmark data, we need to develop new algorithms to improve quantitation results. The goal of this document is not to make a review of the state of the art but to identify leads which may improve existing algorithms. A first way to improve methods (specially optimization methods finding a local optimum) is to add correct prior knowledge. In that regard, not all prior knowledge has been used in MRS. Here are two points that could be exploited:

- The dominating lipid and macromolecule components always show up at known frequencies
- The lineshape is almost identical for the individual peaks in a spectrum

A second way is to develop new algorithms which do not present the drawbacks of existing algorithms. This requires an identification of these drawbacks, which is sometimes only possible by testing the algorithms. In this section, we formulate several quantitation issues which might be the source of future research. Our attention has been focussed on the baseline and the lineshape issues. First, existing methods are briefly reviewed and the most interesting methods to our opinion are identified. Then, some ideas to potentially improve existing methods are given. Finally, we conclude on the priorities in FAST.

A. Brief review of existing methods

The goal of this section is not to give an extensive overview of the existing quantitation methods but to summarize some interesting ideas that could be further investigated. The scope of this section will be limited to baseline removal methods and quantitation methods. As said before, disentangling the baseline from the metabolites of interest is probably the largest issue in MRS quantitation. The baseline can be removed in a so-called preprocessing step (*i.e.*, a step preceding the quantitation) or modeled during the quantitation step.

1) Baseline removal as preprocessing step: One possibility to extract the baseline is to use some specific acquisition sequence (like inversion-recovery). However, this requires an additional measurement and is far from being perfect since residual metabolite contributions remain present. Another possibility is to assume that the baseline is smooth and model an approximated baseline with something smooth which can be any type of function (splines, wavelets, polynomials, etc.). Some very simple methods based on the truncation of the original signal or on some apodization function can approximate the baseline. However, this will result in quite rough approximations. In order to improve this type of methods, iterative methods have been proposed [30], [23]. Young *et al.* [30] extract the baseline following the steps:

1) Initial spectral parameter estimation from the raw data giving a model spectrum composed of the metabolites of interest
2) subtraction of the model spectrum from the raw data giving an approximation of the noisy baseline
3) baseline modeling using wavelet shrinkage and denoising procedure
4) subtraction of the modeled baseline from the raw data to obtain a noisy metabolite spectrum, and possibly back to step 1.

In [23], Ratiney *et al.* extract the baseline following a different scheme:

1) truncation of the initial points and quantitation of the metabolites with QUEST [22]
2) subtraction of the metabolite signal (constructed from the parameter estimates) from the raw data to obtain the metabolite-free signal
3) estimation of the baseline from the metabolite-free signal by an SVD-based method or AMARES [29]
4) subtraction of the parametrized baseline from the raw data
5) parameter estimation from the baseline-free signal (or noisy metabolite signal), and possibly back to step 2.

Other non iterative methods deserve a special attention[4], [8]. These methods are based on a two-step approach (baseline recognition, baseline modeling). The idea is to recognize the points belonging to the baseline using some criterion (threshold values depending on the noise) and to "connect" these points using some smooth curve.

2) Baseline removal as quantitation step: The baseline can also be modeled in the quantitation model. Either the baseline components are considered as additional "metabolite" components and added to the metabolite database, or a semi-parametric model is used where non parametric terms in the model account for the baseline. In order to add components in the database, one can use measured or simulated baseline. An example of components constituing a simulated baseline is given by Seeger *et al.* (see II-C).

3) Quantitation methods: In this section, QUEST [23] and AQSES [18] are compared. The largest differences between the two methods are the following:

- water filtering: QUEST uses an SVD-based method (typically HLSVD [17]) in a preprocessing step, *i.e.* in a step preceding the 5 steps described above. AQSES uses a maximum-phase finite impulse response filter (MP-FIR [27]) inside the iterative optimization procedure.
- baseline removal: AQSES uses only one common optimization problem for the fitting of both the model and the baseline, while QUEST uses the iterative heuristic method described above.

In [28], QUEST and AQSES were applied to simulated MRS data and the effects of the nuisance components on the parameter estimates were studied. The results of AQSES combined with MP-FIR were better than QUEST with HLSVD on baseline-free signals (signals composed of metabolite contributions, water and noise). On the contrary, QUEST turned out to be better than AQSES when the signal under investigation contained a baseline. It appears clear that both methods have their advantages and their drawbacks and a new method should combine the advantages of each method while getting rid of the drawbacks (see III-B).

B. Future potential improvements

Potential improvements for quantitation methods of MRS data are given in this section. Starting with AQSES and QUEST, we will derive several ideas which might improve the existing methods.

First of all, it is good to remember that if the methods are often compared in terms of accuracy and efficiency, it is also important to study the influence of the hyperparameters on these two comparison criteria. A problem of QUEST is that its parameter estimates are relatively dependent on the truncation level (step 1, see III-A1). Similarly, the parameter estimates in AQSES are influenced by the smoothing level defined by the regularization parameter in the cost function (see [18] for more details). It has been noted in [19] that this influence was reduced when using MP-FIR which reduces

the baseline contribution. One of the problems in AQSES is that the only assumption used to model the baseline is that the baseline is smooth, but even the degree of smoothness should be defined by the user and will have an influence on the parameter estimates as said above. The prior knowledge in QUEST comes from the fact that the baseline dies out after a few points in the time domain. In reality, if the baseline contributions have indeed converged to almost zero after a few points, the metabolite contributions have also decayed (less however than the baseline components). Truncating the first time-domain points in QUEST might be a problem when the signal-to-noise ratio (SNR) is small. In that case, another method might be preferable. Young *et al.*'s method [30] (see III-A1) can also converge to wrong parameter estimates if the initial parameter estimates are not close enough from the true values. Therefore, it might be interesting to get a first approximation of the baseline by using a preprocessing method such as the one described by Cobas *et al.*'s [4]. After extraction of the baseline from the raw data, the iteration procedures described in III-A1 can be continued (at step 1 in Young *et al.*'s method and step 5 in Ratiney *et al.*'s method).

In AQSES, QUEST or other optimization methods finding a local optimum, starting values for the parameters to estimate are important avoid being stuck to a **local** optimum. Assuming that the lineshape is identical for all individual components in the signal reduces the number of parameters and allows a better approximation of the starting values. In that regard, a good estimation of $g(t)$ might be crucial. The metabolite profiles should be corrected by this lineshape before quantitation ($\nu_k(t) := \nu_k(t)g(t)$). The lineshape is implicitly contained in *in vitro* spectra and, in that case, an estimation of $g(t)$ should not be necessary. Let the metabolite signal

$$y_{ML}(t) = g(t)\sum_{k=1}^{K}\alpha_k e^{j2\pi f_k t}\nu_k(t) \tag{8}$$

where $g(t)$ is the lineshape common to each individual component in the signal (*e.g.*, for a Lorentzian lineshape $g(t) = e^{-dt}$, d being the real-valued damping factor), α_k is the complex amplitude of metabolite k, $\nu_k(t)$ is the metabolite profile k, f_k is the frequency shift. Suppose the damping factor(s) of $\nu_k(t)$ negligible compared to that of $g(t)$ (which is reasonable if the metabolite profiles have been constructed with NMRSCOPE [9]). In the case where the method used to estimate $g(t)$ does not use the metabolite profiles in its model, 8 becomes

$$y_{ML}(t) = g(t)\sum_{k=1}^{K}\alpha_k e^{j2\pi f_k t} \tag{9}$$

where K will not be similar to the one in 8.

Several methods can be used for estimating $g(t)$. Here are some of them:

- time-domain SVD-based method (like HLSVD [17] or HLSVD-PRO [14]):
  1) apply a time-domain SVD-based method to obtain the parameter estimates α_k, f_k and d_k(damping factor of the Lorentzian k)
  2) $g(t) = \frac{y_{ML}(t)}{\sum_{k=1}^{K}\alpha_k e^{j2\pi f_k t}}$ with the values α_k, f_k just calculated
- frequency-selective SVD-based method like FDM [15], [24] where the subband should contain as few peaks as possible (frequency region of Cr at 3.03 ppm can be used). The goal is to reduce the computation load since a unique peak should be enough to estimate $g(t)$.
  1) apply the frequency-selective method to obtain the parameter estimates α_k, f_k and d_k of the Lorentzians belonging to the frequency band of interest
  2) $g(t) = \frac{F(y_{ML}(t))}{\sum_{k=1}^{K}\alpha_k e^{j2\pi f_k t}}$ with the values α_k, f_k just calculated and $F\left(y_{ML}(t)\right)$ is the filtered version of $y_{ML}(t)$ which has only contributions in the frequency band of interest
- a frequency-selective quantitation method based on the use of a metabolite database like AQSES or QUEST:
  1) apply the quantitation method to obtain α_k, f_k and d_k in the frequency band where the metabolites of the database are found (from the model in 8)
  2) $g(t) = \frac{F(y_{ML}(t))}{\sum_{k=1}^{K}\alpha_k e^{j2\pi f_k t}\nu_k(t)}$ with the values α_k, f_k just calculated and $F\left(y_{ML}(t)\right)$ is the filtered version of $y_{ML}(t)$
- others...

We can easily simplify all quantitation methods if we consider that the lineshape is exactly the same for all individual components. However, this is probably a too strong assumption and small deviations from this unique lineshape should be allowed. As said before, $g(t)$ should only be used to define the starting values such that we get closer to the true ones.

The potential gain of considering a unique lineshape for all components of the signal has been discussed. Other interesting prior knowledge that could be introduced in the model is that the baseline components are located at known frequencies (see, *e.g.*, [26]). The way to include this prior knowledge in a quantitation or baseline removal method will depend on the method itself. Here are some examples:

- using a semi-parametric model as in AQSES where the baseline is modeled as a sum of splines: the density of splines can be chosen larger in the region where larger amount of baseline are expected, or additional weights in the cost function, taking into account that less/more contributions of baseline should be present at certain frequencies, can be added to the model
- using a baseline extraction method like in [4]: threshold values for the detection of the baseline can be adapted with respect to the frequency expectations of the baseline
- others...

This being said, here is a brief summary of processing methods and their possible combinations.

The **baseline** can be

- estimated after truncation of the begin points in the time-domain signal (see "subtract" algorithm in QUEST given in III-A1)
- extracted from the signal (see, *e.g.*, [4], [8])

- modeled in a semi-parametric model (see, *e.g.*, [18], [7])
- ...

Starting values for the **lineshape** can be

- estimated using one of the method cited above
- guessed (*e.g.*, often $g(t) = 1$ when using in vitro metabolite databases)
- ...

Quantitation methods can be

- **iterative** like in QUEST
- **iterative** like in Young *et al.*'s method [30]
- **not iterative** like in AQSES
- ...

Almost all combinations are then possible, for example, AQSES can be used where the metabolite profiles are modified by the estimated lineshape and prior knowledge about the baseline is included in the semi-parametric model (see Alg. 1).

Here is 3 new possible algorithms (water removal and Eddy current correction are not taken into account) but the list can be largely extended.

Algorithm 1 $\text{AQSES}_{\text{PKBL}}$: AQSES with prior knowledge about the baseline and the lineshape

1) extract the baseline from the signal using a preprocessing method (like Cobas *et al.*'s method [4]) to obtain the noisy metabolite signal
2) estimate the lineshape $g(t)$ using a method described above based on the model (8) (in vitro database) or (9)(quantum mechanically simulated database with a negligible damping factor)
3) modify the metabolite profiles: $\nu_k(t) := g(t)\nu_k(t)$
4) apply a modified version of AQSES (semi-parametric modeling) to the original signal to take into account the prior knowledge (PK) about the baseline (see above), PK extracted from the literature or from the extracted baseline in step 1 $\Rightarrow$ parameter estimates
5) if convergence is not reached (based on the values of f_k), recalculate $g(t)$ from the just calculated parameter estimates (using 8) and go back to step 3, otherwise stop

Algorithm 2 $\text{QUAQ}_{\text{PKBL}}$: QUEST-AQSES combination with prior knowledge about the baseline and the lineshape

1) use one or several iterations of QUEST-subtract to estimate the baseline
2) extract the baseline from the signal
3) estimate the lineshape $g(t)$ from the baseline-free signal (as in step 2 of Alg. 1)
4) modify the metabolite profiles: $\nu_k(t) := g(t)\nu_k(t)$
5) use the information of the estimated baseline in AQSES (as in step 4 of Alg. 1) $\Rightarrow$ parameter estimates
6) if convergence is not reached, recalculate $g(t)$ from the just calculated parameter estimates (using (8)) and the baseline by subtracting the metabolite signal from the original signal and go back to step 4, otherwise stop

Algorithm 3 QWAV_{PKL}:quantitation with complex wavelets and prior knowledge about the lineshape

1) extract the baseline from the signal using a preprocessing method (like Cobas *et al.*'s method [4]) to obtain the noisy metabolite signal = step 1 in Alg. 1
2) estimate the lineshape $g(t)$ using a method described above based on the model (8) (in vitro database) or (9)(quantum mechanically simulated database with a negligible damping factor)
3) modify the metabolite profiles: $\nu_k(t) := g(t)\nu_k(t)$
4) iteratively, for each metabolite, generate complex wavelet shapes (instead of the classical Morlet wavelet shape) which mimic the modified metabolite profiles $\nu_k(t)$ and extract such shapes from the baseline-free signal $\Rightarrow$ parameter estimates

C. Plan for the coming months

- **KUL**: testing how prior knowledge about baseline and lineshape can be included in quantitation methods (see, *e.g.*, Alg. 1 and 2)
- **UCL**: testing how wavelets can be applied to MRS quantitation (see, *e.g.*, Alg. 3) + ???
- **Emil**: implementation of the (P)EPSI sequence + effect of the lineshape on the parameter estimates + ???
- **Dirk**: eBook for FAST + ???
- Greek: ???

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