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# Volume localized spin echo correlation spectroscopy with suppression of 'diagonal' peaks

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ABSTRACT

Two dimensional homonuclear $^1$H correlation spectroscopy is of considerable interest for volume localized spectral studies, both *in vivo* and *in vitro*, of biological as well as material objects. The information principally sought from correlation spectra resides in the cross-peaks, which are often masked however by the presence of diagonal peaks in COSY, or 'pseudo-diagonal' peaks at $F_1 = 0$ in SECSY. It has therefore been a concern to suppress these diagonal or 'pseudo-diagonal' peaks, in order to ensure that cross-peak information is fully discernible. We present here a report of our work on volume localized DIagonal Suppressed Spin Echo Correlation specTroscopy (LDISSECT) and demonstrate its performance in comparison to the standard volume localized SECSY experiment, employing brain metabolite phantoms in a gel. The sequence works in the inhomogeneous, multi-component environment by exploiting the short acquisition time to suppress undesired information by employing an additional rf pulse. A brief description of the pulse sequence, its theory, and simulations are also included, besides experimental benchmarking on two brain metabolite phantoms in gel phase.



## 1. Introduction

The non-invasiveness of magnetic resonance imaging (MRI) [1] and its inherent ability to generate contrast make it a very popular technique in a wide range of research areas. However, techniques based solely on MRI do not always give sufficient information (e.g. chemical signature, concentration) about the object under investigation. MRI, in conjunction with volume localized magnetic resonance spectroscopy (MRS) [2,3] turns out to be a very fruitful technique and is widely used in biological, preclinical, clinical [4,5] and material sciences [6]. MRS is now used frequently as a research technique especially to provide complementary biochemical information in preclinical and clinical imaging studies, in order to understand various metabolic cycles in terms of biochemical changes of metabolite concentrations in the brain [7] and in various other body organs [8]. Volume localized 1D *in vivo* $^1$H MR spectroscopy provides very specific chemical information about several metabolites and their changes in concentration in some specific tissues and in organs. However, the limitation of 1D $^1$H MRS is that most of the important metabolites (some 30–35 in number) are found in a very small frequency range (0–4.5 ppm) and hence the resulting 1D spectral data suffer from severe overlap of metabolite peaks. Specifically, at low field strength some metabolites like glutamate (Glu), glutamine (Gln), γ-aminobutyric acid (GABA), myo-inositol (mIns) and glycine (Gly) are very difficult to quantify. Several methods, including optimization of echo time [9], indirect detection of $^{13}$C [10], localized $^{13}$C spectroscopy and spectral editing [11–13], etc. have been proposed to overcome this problem. However, most of these methods are suitable when only a relatively small number of metabolites (one or two) are of interest. Beside these methods, homonuclear 2D correlation spectroscopy provides a solution to resolve and assign many metabolites in terms of chemical shifts and couplings by spreading the information in a second frequency dimension. Among several volume localized 2D methods, COSY [14–16] is the most popular and is successfully used to study different physiological processes *in vivo* [17–19]. Cross peaks in COSY generally originate from scalar coupled spins systems, whereas both coupled and uncoupled spins contribute to diagonal peaks. In standard COSY data recorded from brain tissue, diagonal peaks including those of N-acetylaspartate (NAA) and Creatine (Cr) have in-phase dispersive lineshapes and could easily mask the cross peaks of several metabolites [17] with low concentration; the same problem could arise from the diagonal peaks of coupled spins as well. Several methods to suppress diagonal peaks in correlation spectra have been reported in the literature [20–22]. One of the earliest attempts to remove diagonal peaks in high resolution COSY was made by Cavanagh and Keeler [20], based on recording two spectra, one being conventional COSY and the other, COSY with diagonal peaks only: after *z*-filtration and subtraction, one can get COSY without diagonal peaks. The efficiency of suppression depends on the reproducibility of the two consecutive experiments and on

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the efficiency of the *z*-filter. Double-quantum filtered COSY (DQF-COSY) can also be used to get correlation spectra with suppression of diagonal peaks from isolated spins. In DQF-COSY half of the single quantum coherence (SQC) is converted to double quantum coherence (DQC) and hence cross peak intensity *as well as* diagonal peak intensity of coupled spins are *both* halved relative to the cross and diagonal peak intensities in COSY. It is also to be noted that in the *in vivo* context the time interval between the last two pulses in both methods needs to be several milliseconds (for the *z* filter in the Keeler method, and for gradients in DQF-COSY); this would lead to significant signal loss under both transverse relaxation and $B_0$ inhomogeneities.

One alternative to volume localized COSY is volume localized SECSY (spin echo correlation spectroscopy) [23,24]; it has some advantages [25] over COSY especially in inhomogeneous media and has been successfully demonstrated in *in vivo* applications. SECSY suffers however from mixed phase line shapes, besides what we may term 'pseudo-diagonal' peaks that are centered around $F_1 = 0$ (here after referred to simply as 'diagonal' peaks).

In this work we propose and demonstrate for the first time the volume localized version of a 2D sequence based on a modification of SECSY, which we term LDISSECT. In turn, LDISSECT draws on "Diagonal Suppressed Spin Echo Correlation Spectroscopy (DISSECT)", a sequence proposed some years back by one of us (NC), and whose slice selective implementation has been demonstrated [26], generating the 2D spectrum from a slice. This sequence offers a very effective way to get rid of the diagonal peaks from the correlation spectrum without any post-processing procedures such as digital filtering. Here we demonstrate and benchmark the application of the volume localized LDISSECT sequence with gel phantoms containing several important brain metabolites, measured on an Avance II 500 MHz mini-imaging system, together with theory and simulations.

## 2. Theory

The volume localized LDISSECT pulse sequence is shown in Fig. 1.

For a weakly coupled two spin – ½ system, the signal at the end of the $t_1$ evolution period (Fig. 1) and just before the third 90° pulse (DISSECT pulse) is given, in terms of observable parts of the density matrix, by:

$$I_{1z} \rightarrow \frac{1}{2}\begin{bmatrix} -\cos^2[\pi J t_1/2] I_{1x} - \cos[(\omega_1-\omega_2)t_1/2]\sin^2[\pi J t_1/2] I_{2x} \\ +\sin[(\omega_1-\omega_2)t_1/2]\sin^2[\pi J t_1/2] I_{2y} + \sin[(\omega_1-\omega_2)t_1/2]\sin[\pi J t_1] I_{1z}I_{2x} \\ +\cos[(\omega_1-\omega_2)t_1/2]\sin[\pi J t_1] I_{1z}I_{2y} - \sin[\pi J t_1] I_{1y}I_{2z} \end{bmatrix} \quad (1)$$

In a standard SECSY experiment this signal is acquired. Owing to evolution under couplings and chemical shifts during $t_2$, 2D Fourier transformation of the above signal produces two peaks: 'diagonal' peaks at frequencies $(F_1, F_2) = (0, \omega_1/2\pi)$ and $(\pm J/2, \omega_1/2\pi)$, and off-diagonal peaks at $(F_1, F_2) = ((\omega_1 - \omega_2)/4\pi, \omega_2/2\pi)$ and $((\omega_1 - \omega_2)/4\pi \pm J/2, \omega_2/2\pi)$. It is clear from Eq. (1) that in-phase cross-peak signal components are generated, modulated as a function of the evolution time $t_1$ at the frequency $((\omega_1 - \omega_2)/4\pi)$. These in-phase – albeit phase twisted – cross-peaks of SECSY are most attractive in the *in vivo* context because the broad lines of partially overlapping multiplet components could cancel each other if multiplets were anti-phase. It may be noted however that besides coupled spins, uncoupled spins also do contribute to the 'diagonal' peaks.

In DISSECT, as shown in Fig. 1, an additional $90^\circ_y$ pulse is used at the top of the coherence transfer echo; the signal observed after the final DISSECT pulse is shown below, after taking into account all the terms of the density matrix that are present just before this final pulse, and including the standard echo pathway selection, in addition to phase alternation of the final DISSECT pulse with co-addition of signals:

$$I_{1z} \rightarrow \frac{1}{2}\left[\sin[(\omega_1-\omega_2)t_1/2]\sin^2[\pi J t_1/2] I_{2y} - \sin[(\omega_1-\omega_2)t_1/2]\sin[\pi J t_1] I_{1x}I_{2z}\right] \quad (2)$$

It may be noted that multiple quantum terms may be rendered observable by the third DISSECT pulse; these terms are canceled by phase alternating this pulse, the receiver phase being held constant.

Crucially, the DISSECT pulse suppresses 'diagonal' peaks by converting in-phase and some of the anti-phase terms to longitudinal and multiple quantum terms respectively, which are not observable. The remaining terms produce detectable signal during the acquisition period ($t_2$), the contribution of the anti-phase term being negligible for the short acquisition times characteristic of *in vivo* studies ($1/\pi T_2^* \geqslant J$). The typical line-width of *in vivo* signals may vary from 10 Hz to 30 Hz, which is larger than the coupling constants of metabolites of interest. Transverse magnetization which is not modulated during the evolution period $t_1$ is produced by the third 90° DISSECT pulse (especially from regions of the object outside the chosen slices, and also from magnetization components of the selected slices that have undergone $T_1$ relaxation), and generates diagonal peaks. Such spurious signals can be effectively suppressed by phase alternating the final DISSECT pulse keeping the receiver phase constant, and also by the ISIS front-end; using suitable pairs of spoiler gradients around the second 90° pulse also

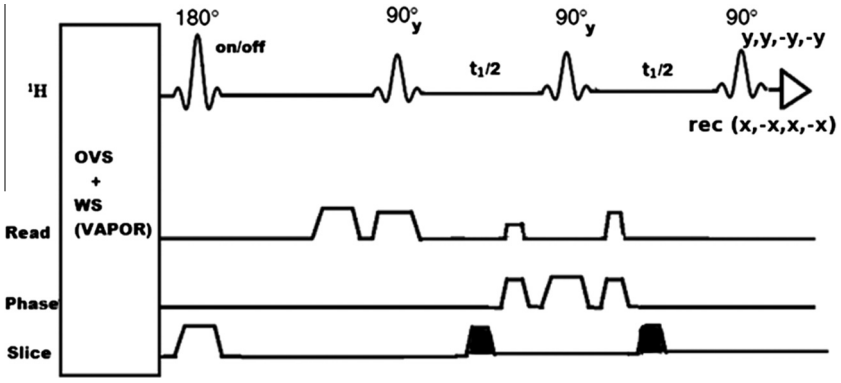


**Fig. 1.** Pulse sequence diagram of volume localized LDISSECT with front-end outer volume suppression (OVS) and water suppression (WS) VAPOR module. Volume localization is achieved with a 1D – ISIS module and two slice selective 90° SLR pulses (1.2 ms; bandwidth = 8.8 kHz). One pair of gradients of 2 ms each (hashed, in slice direction) is used for coherence pathway selection. In one implementation, the last 90° rf pulse is identical to the first two 90° rf pulses, although this last pulse is not slice selective.