SIRS sequence as frequency filter: A simulation and phantom study of spin-lock preparations among composite signals

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Abstract

Extracting quantitative information of neuronal signals by non-invasive imaging is an outstanding challenge for understanding brain function and pathology. However, state-of-the-art techniques offer low sensitivity to deep electrical sources. Stimulus induced rotary saturation (SIRS) is a recently proposed magnetic resonance imaging (MRI) sequence that detects oscillatory magnetic fields using a spin-lock preparation. Phantom experiments and simulations proved its efficiency and sensitivity, but the susceptibility of the method to field inhomogeneities is still not well understood. In this study, we present a simulation model for the double resonance effect that enables the simulation of any oscillating neuronal field. We analyzed the performance of three spin-lock preparations and their response to field inhomogeneities in the presence of a resonant oscillating field. We show that the composite spin-lock preparation is more robust against field variations within the double resonance effect at the expense of losing contrast amplitude. We studied the SIRS contrast as a filter of spectral frequencies and its capability to recover information about the spectral components of a composite signal. This study sets the bases to move one step further towards the clinical application of MR-based neuronal current imaging.

1 Introduction

Neuroscience seeks to understand brain activity and its pathologies but still struggles to extract electrical neuronal information in a non-invasive way. Non-invasive detection methods such as electroencephalogram[1] and magnetoencephalogram[2] measure electric potential and magnetic fields on the scalp and reconstruct the location of the electric sources. Unfortunately, the sensitivity of these methods is limited for in-depth activity sources[3;4]. On the other hand, conventional functional magnetic resonance (fMRI) detects $T_2$ and $T_2^*$ changes generated by blood oxygenation levels on the brain (BOLD contrast)[5]. This technique presents good spatial resolution, but it measures neuronal activity indirectly, and the hemodynamic response function limits its temporal resolution[6].

Stimulus Induced Rotational Saturation (SIRS) is an MRI-based sequence with the potential to directly detect neuronal activity with sufficient spatial resolution[7]. The SIRS contrast is based on the interaction between the magnetization locked by a spin-lock (SL) pulse and an oscillating magnetic field induced by neuronal activity. Several studies proved the capabilities of the method with simulations and phantom experiments[7–11]. Even more, the dependence of the contrast with the change of the excitation angle has been proposed as a new method for direct functional connectivity measurements[12].

The susceptibility of the SL preparations to $B_0$ and $B_1^+$ inhomogeneities hinders the further development and clinical application of this approach[12;13]. However, researchers in the field of $T_1\rho$ relaxometry thoroughly
studied the use of composite SL pulses to reduce the effect of field imperfections\textsuperscript{[14–16]}. Furthermore, some researchers within the SIRS community tested and used composite pulses\textsuperscript{[8;10;17]}. But, to the best of our knowledge, no comprehensive study of the influence of the double resonance effect in combination with field inhomogeneities has been presented. Magnetization dynamics during a spin-lock pulse changes radically in the presence of an oscillating resonant field. Here, we present an efficient simulation model based on rotation matrices that allow us to study the new dynamics and capture the effect of any oscillating field over time. We studied three well known SL preparations, the basic or standard SL pulse (BASL), the rotary echo SL pulse (RESL), and the composite rotary echo SL pulse (CRESL). Using the simulator and phantom experiments, we define the optimal strategy by examining the response of the preparations to field imperfections considering the new dynamics.

Physiological signals fluctuate in time and are composed of multiple frequencies\textsuperscript{[18–20]}. In addition, certain pathologies manifest with neuronal activity at specific frequencies. For example, high-frequency oscillations (HFOs) are considered markers of the seizure onset zone in epilepsy\textsuperscript{[21;22]}. This case is noteworthy because non-invasively outlining the seizure onset zone can have a direct impact on patient care quality. Therefore, we consider that the next step to take towards the clinical application of the SIRS sequence is a more realistic signal analysis. The use of a repetitive acquisition of successive measurements with and without SL preparation has previously been proposed\textsuperscript{[23]}. With this method, the BOLD effect and image artifacts are minimized by dividing the two signals. In the second part of this work, we tested the ability of this acquisition method to reconstruct the frequency distribution of multi-frequency signals.

The purpose of this study is to advance research towards the clinical application of the SIRS technique. First, we define the optimal SL preparation and metric to detect oscillating fields in the presence of field inhomogeneities and second, we analyzed the response of the SIRS sequence to composite signals.

2 Methods

2.1 Magnetization dynamics under spin-lock preparations schemes

The dynamics of the magnetization with the BASL preparation in the presence of simple sinusoidal oscillating fields has been analytically described\textsuperscript{[24]}. However, modulated oscillating fields are more representative of those found in physiological activity. In general, it is not possible to analytically describe these fields, and numerical simulations are the only option. Among the numerical simulation methods, solving differential equations\textsuperscript{[10]} and step-wise constant rotations as presented in this work, give similar results. Based on the performance and previous bibliography in the $T_1\rho$ field\textsuperscript{[15;16]}, we decided to adopt the rotation matrix method.

A traditional SL pulse, like the one shown in Figure 1(a.i), consists of three RF pulses. After a tip-down pulse of duration $T_{td}$, the magnetization in the simple rotating frame ($\hat{x}, \hat{y}, \hat{z}$) is

$$M(T_{td}) = R_{\hat{x}}(\alpha)M(0).$$  \hspace{1cm} (2.1)

Here $M(0) = [0, 0, M_{0z}]$ is the initial magnetization, and $R_{\hat{x}}(\alpha)$ represents a matrix rotation around $\hat{x}$, with $\alpha$ the rotation angle of ideally 90°. $B_0^\perp$ imperfections can vary significantly across the sample, deviating $\alpha$ from the ideal value depending on the location $r$ by $\alpha(r) = \gamma B_1(r)T_{td}$. The second RF applied along $\hat{y}$ is the SL pulse $B_{SL} = \omega_{SL}/\gamma$, of duration $T_{SL}$ with $\omega_{SL} = 2\pi F_{SL}$ the induced angular frequency. $B_{SL}$ locks the magnetization in the transverse plane, represented by

$$M(T_{td} + T_{SL}) = R_{\hat{y}}(\theta)M(T_{td}),$$  \hspace{1cm} (2.2)

where $\theta = \omega_{SL}T_{SL}$. In the presence of $B_0$ inhomogeneities, the magnetization will rotate around the effective field $B_{eff} = \frac{\omega_{SL}}{\gamma} \hat{y} + \frac{\Delta \omega}{\gamma} \hat{z}$ that forms an angle $\beta = atan\left(\frac{\omega_{SL}}{\Delta \omega}\right)$ to $\hat{z}$, where $\Delta \omega = \omega_0 - \omega_{RF}$. This results in
\[ \mathbf{M}(T_{td} + T_{SL}) = \mathbf{R}_z(\beta)\mathbf{R}_z(\theta)\mathbf{R}_{-z}(\beta)\mathbf{M}(T_{td}). \]  

(2.3)

Finally, the third tip-up pulse of duration \( T_{tu} \) tilts the magnetization back to the longitudinal axis, leading to the equation

\[ \mathbf{M}(T_{td} + T_{SL} + T_{tu}) = \mathbf{R}_{-z}(\alpha)\mathbf{M}(T_{td} + T_{SL}). \]  

(2.4)

After preparation, a gradient spoiler in \( \hat{z} \) eliminates the remanent transverse magnetization. The spoiler is followed by a slice selective 90° excitation pulse and an echo-planar imaging (EPI) readout. We can now consider the influence of the target oscillating field along \( \hat{z} \), that in its simplest form is represented by \( \mathbf{B}_{NC}(t) = B_{NC} \sin(\omega_{NC} t + \varphi) \hat{z} \), with \( B_{NC} \), \( \omega_{NC} \), and \( \varphi \) the amplitude, frequency, and initial phase of the field, respectively. If the field is in resonance with the induced SL frequency i.e., \( \omega_{NC} = \omega_{SL} \), \( \mathbf{B}_{NC} \) acts as an excitation pulse and the magnetization will be separated from the SL direction. After the preparation, the drop in the longitudinal magnetization depends on the torque generated by the oscillating target field. The dynamic response of the magnetization under the BASL preparation in the presence of a resonant oscillating field is shown in Figure 1(b.i). Given the variation of the magnetization direction and the change in the amplitude of the target field, each instant \( \tau \) during the SL period is represented by a step-wise rotation of the form

\[ \mathbf{M}(\tau) = \mathbf{R}_z(\gamma B_{NC}(\tau)dt)\mathbf{R}_z(\beta)\mathbf{R}_z(\omega_{SL}dt)\mathbf{R}_{-z}(\beta)\mathbf{M}(\tau - dt). \]  

(2.5)

Finally, the magnetization in the presence of relaxation is modified as \( \mathbf{M}(\tau) = \mathbf{A} \mathbf{M}(\tau - dt) + \mathbf{B} \), where the matrices \( \mathbf{A} \) and \( \mathbf{B} \) represent the effect of the standard \( T_1 \) and \( T_2 \) relaxation times (see Supplementary information 1). In our implementation, each rotation must be infinitesimal and within each step \( dt \), two relaxations of \( dt/2 \) are considered before and after the infinitesimal rotation. In this way, equation 2.1 becomes:

\[ \mathbf{M}(T_{td}) = \prod_{n=1}^{T_{td}/dt} \mathbf{A}[\mathbf{R}_z(\gamma B_1 dt)\{\mathbf{A}\mathbf{M}(dt(n-1)) + \mathbf{B}\}] + \mathbf{B}, \]  

(2.6)

and equation 2.5 changes to

\[ \mathbf{M}(T_{td} + T_{SL}) = \prod_{n=1}^{T_{SL}/dt} \mathbf{A}_p[\mathbf{R}_z(\gamma B_{NC}(n dt))\mathbf{R}_z(\beta)\mathbf{R}_z(\omega_{SL} dt)\mathbf{R}_{-z}(\beta)\{\mathbf{A}_p\mathbf{M}(T_{td} + dt(n-1)) + \mathbf{B}_p\}] + \mathbf{B}_p, \]  

(2.7)

where \( \mathbf{A}_p \) and \( \mathbf{B}_p \) represent the relaxations in the rotating frame of reference (see Supplementary information 1).

The RESL preparation divides the SL pulse into two parts with equal duration and opposite phase, as shown in Figure 1(a.ii). This pulse attempts to cancel out the error in the alpha angle generated by \( B_{1}^+ \) inhomogeneity\(^{[4]} \). Figure 1(b.ii) illustrates the magnetization dynamics for RESL under the influence of a resonant target field. To simulate this preparation, the inversion of the SL pulse sign is added in the equation 2.7, when \( n = T_{SL}/2dt \).

In addition, the CRESL preparation adds a 180° RF pulse along \( \hat{y} \) between the two halves of the SL pulse, i.e., when \( n = T_{SL}/2 \). This pulse compensates for the phase accumulated due to the influence of \( B_0 \) inhomogeneities. Figure 1(a.iii) shows the pulse sequence, and Figure 1(b.iii) shows the dynamics of the double resonance effect under this preparation.
2.2 Simulator implementation

The simulator was programmed in MATLAB (R2019b) using the method presented in section 2.1, together with the rotation and relaxation matrices shown in Supplementary information 1. Parameters that must be given to the simulator related to the sample are the relaxation times of the tissue and the target field as a function of time. Sequence control parameters are $F_{SL}$, $T_{SL}$, $T_{R}$, $T_{E}$, number of slices (always 1 for this work) and repetition number. In this way, the entire sequence time can be simulated, considering relaxation in preparation, readout and waiting times (time between slices, preparations without SL).

2.3 Experimental setup

We performed measurements in a 3T whole-body MR scanner (Siemens Medical Solutions, Erlangen, Germany), using a Single-Shot-EPI readout with fixed parameters: $T_E = 29.8$ ms, Res = 64x64 and FOV = 210 mm. The value of $T_R$ will depend on the selected value of $T_{SL}$. For the simulations, the relaxation times match the values measured on the phantom using commercial sequences. $T_1 = 1270$ ms and $T_2 = 200$ ms. We estimated $T_{1\rho}$ using a custom-made sequence that varies the duration of the spin-lock time $T_{SL}$ for a CRESL preparation and fitting the exponential formula $M = M_0 e^{(-T_{SL}/T_{1\rho})}$ obtaining $T_{1\rho} = 165$ ms.
Figure 2 shows the experimental setup used in this study. The phantom consists of a copper loop coil in the middle of a 17 cm diameter plastic sphere filled with saline solution to control the relaxation times. We positioned the phantom such that the loop is in the \( xy \) plane and the target oscillating field results in the \( B_0 \) field direction.

The coil connects to the function generator (Rigol DG1022Z) through a low pass filter. The generator allows controlling the amplitude, frequency, and initial phase of the output signal. The external trigger of the scanner gives the signal to the generator to start the output. For the experiments with composite signals, we designed them using MATLAB and imported the data files into the generator using a 1024Sa/s firing rate.

2.4 Preparation analysis

Depending on the initial phase of the target field, the SIRS contrast, i.e., the distance to the SL axis gained during the first part of the pulse, could be compensated during the second half. To study this effect, we simulated the sequence in the resonance condition (\( \omega_{NC} = \omega_{SL} = 2\pi 90 \) Hz) as a function of \( T_{SL} \) and the initial phase \( \varphi \), for the three preparations in Figure 1(a). For each value of \( T_{SL} \) moving between 70 and 100 ms in 1 ms steps, \( \varphi \) varies between \([-\pi, \pi]\) in 0.1 rad steps. The model simulations did not consider \( B_0 \) and \( B_1^+ \) inhomogeneities for this analysis.

To better visualize the phase dependency, we simulated and measured the signal contrast as a function of \( T_{SL} \) for random and non-random phases. The presented signal contrast was calculated as the ratio between the signal with and without the oscillating initial field (\( M/M_0 \)). For random phases, 100 repetitions were taken and averaged for each \( T_{SL} \). For non-random phases, we set the initial phase to 0 and 30 averages were acquired for each point.

To evaluate the robustness of the contrast against \( B_0 \) and \( B_1^+ \) imperfections, we calculated the standard deviation of the contrast for all the possible values of the initial phase \( \varphi \) varying between \([-\pi, \pi]\) in 0.1 rad steps. The map consists of the standard deviation for each combination of the field inhomogeneities. We considered \( B_1^+ \) imperfections to deviate the \( \alpha \) angle \( \pm 5^\circ \) from the desired 90° value, and \( B_0 \) inhomogeneity to vary the off-resonance frequency in a \([-30,30] \) Hz range.

2.5 Filter properties

The double resonant signal has a particular contrast amplitude and bandwidth depending on the value of \( T_{SL} \) and \( F_{SL} \). To evaluate the capability of the SIRS preparations to filter specific frequency components, we simulated and measured the contrast for a fixed \( F_{SL} = 90 \) Hz while varying the frequency of the target field. \( \omega_{NC}/2\pi \) changed between 60 and 120 Hz in 5 Hz steps with amplitude 75 nT and initial random phase. 100 acquisitions were acquired and averaged for each point. We repeated this procedure for each \( T_{SL} \) in the range of 70 to 100 ms in 5 ms steps. For each value of \( T_{SL} \), we estimated the full-width half maximum (FWHM) and used it as a measure of selectivity of the filter. The simulation was performed for the same parameters, raffling a random phase for each repetition.

2.6 Measurements of composite signals

In this section, we investigated the capability of the contrast to be used as a filter of spectral components when in the presence of composite signals. The first experiment consisted of measuring a signal represented by \( S(t) = a \sin(2\pi 53t) + (1-a) \sin(2\pi 97t) \) with \( a=(0, 1/4, 1/2, 3/4, 1) \). The amplitudes of the 97 and 53 Hz components ramp up and down in 30 s steps respectively but the maximum signal amplitude remains constant. The signal was acquired for \( F_{SL}=53 \) Hz and \( F_{SL}=97 \) Hz, with \( T_{SL}=100 \) ms, and \( T_R = 1017 \) ms. Measurements consist of successive alternating \( SL_{on} \) and \( SL_{off} \) acquisitions. \( SL_{on} \) acquisitions were described in section 2.1 and \( SL_{off} \) acquisitions are a non-prepared EPI readout where the \( T_{SL} \) is left empty. The double resonance effect cannot be separated from other factors influencing the contrast (BOLD, image artifacts, physiological noise, etc.). Here,
we propose to use the division of the successive $SL_{on}$ and $SL_{off}$ acquisitions to filter out the spurious effects encoded by the common EPI readout. Therefore, after the acquisition, the point-to-point division (ppd(t)) of the signals $SL_{on}$ and $SL_{off}$ was calculated. Each frequency component is computed as the standard deviation of the ppd for each time block.

Delineating the seizure onset zone in refractory epilepsy patients is, in our view, the most relevant clinical application for this sequence. This application requires locating that part of the brain having the highest component of frequencies associated with the epileptogenic activity. Therefore, the second experiment tested the sequence capability to reconstruct frequency components of individually acquired signals. Four signals intend to represent four different voxels of the brain. They all consist of a 60s 0.1 Hz sinusoidal with an amplitude of x=81 nT and a 30 Hz sine of amplitude x/2 is added the last 30s. For signals 2, 3, and 4, a 90 Hz sine is added with amplitude 0.1x and divided into blocks of 20, 10, and 2 seconds, respectively. To calculate the components of the original signal, we applied a band-pass filter of 20Hz around the target frequency and computed the standard deviation. We measured each signal in time alternating $SL_{on}$ and $SL_{off}$ acquisitions, setting $F_{SL}$ to 30, 60 and 90 Hz, with $T_{SL}=100$ ms and $T_R = 324$ ms. We chose these frequencies to comprehend the influence that slow variations of the signal can have on the detection of small amplitude fast oscillations. Finally, we reconstructed the frequency components for each $F_{SL}$ as the standard deviation of the ppd signal.

3 Results

3.1 Preparation analysis

Figure 3: SIRS contrast dependence with phase. a) Simulated contrast amplitude as a function of $T_{SL}$ and the initial phase of the target oscillating field $\varphi$ for a sinusoidal field in resonance with the SL pulse for i. BASL, ii. RESL and iii. CRESL. b) Measurement and simulation of the contrast in resonance condition as a function of $T_{SL}$ for the cases of triggered ($\varphi = 0$, circles and plain lines) and averaged non-triggered signal (random initial phase, triangles, and dashed lines). $B_{NC} = 75$ nT, $\omega_{NC} = \omega_{SL} = 2\pi 90$ Hz.

Figure 3 a) shows the contrast for the three preparations depending on the $T_{SL}$ and the initial phase $\varphi$. For RESL and CRESL, the opposite phase in the second SL pulse creates a dependency of the signal with $\varphi$. In this way, BASL sets the contrast upper limit, and the mean contrast of RESL and CRESL is half of the maximum value. However, in practice, field imperfections induce oscillations in BASL, decreasing its average
contrast. Figure 3 b) shows this effect by comparing simulations without inhomogeneity with measurements for both triggered ($\varphi=0$) and averaged non-triggered initial phase $\varphi$ in the range $[-\pi, \pi]$. $B_0$ inhomogeneities also influence the RESL contrast, but the theoretical curve qualitatively represents the experimental signal. For CRESL, instead, the signal corresponds best to its theoretical value for both the phase zero and the mean contrast cases.

This result shows that the acquisition of the signal in time will have an oscillating behavior, caused either by field imperfections or the phase of the oscillating field, as was previously suggested by [17]. The goal of this sequence is the location of oscillating fields, so the optimum contrast will be that whose variation depends solely on the double resonance effect. If the time-dependent variation of the signal is used as a measure to characterize the magnetic field associated with the neuronal current, the optimal contrast should have the same variation as a function of the $B_0$ and $B_1^+$ inhomogeneities. We decided to study the contrast standard deviation as a metric since it was already suggested for the SLOE approach [17,25].

This aspect was analyzed in Figure 4, where the variation of the signal was calculated for the three preparations as a function of both $B_0$ and $B_1^+$ inhomogeneities for two different values of $T_{SL}$ when fixing $F_{SL}$. While the mean value (average for all the initial phases) will vary for the three preparations, the maximum std of the contrast is minimum for the CRESL case. As expected, RESL presents an appreciable variation depending on $B_0$ while BASL is susceptible to both fields and therefore diagonal patterns are observed. This means that CRESL is the most robust against $B_0$ and $B_1^+$ inhomogeneities when using the standard deviation as the featured metric.

Neural oscillations lack phase coherence. Therefore, the defined metric must quantify the signal variability. Furthermore, the metric should be robust against both temporal and spatial imperfections. Otherwise, the double resonance effect could be weighted differently between volumes, leading to the incorrect localization of the maximum activity. On the other hand, RESL loses half of the maximum contrast and still depends on the inhomogeneities of $B_0$. In our opinion, this makes it the least practical preparation. Because of this, in the next section, we only studied the CRESL and BASL cases.

![Figure 4](image-url)

**Figure 4:** Simulated contrast variation map (signal standard deviation $\sigma$) as a function of the excitation angle $\alpha$ (°) and the frequency offset $\Delta \omega_0$ (Hz) in resonance condition, $\omega_{NC} = \omega_{SL} = 2\pi 90$ Hz. a) For $T_{SL}=90$ ms: i. BASL ($\sigma < 13\%$), ii. RESL ($\sigma < 18\%$), and iii. CRESL ($\sigma < 4\%$). b) For $T_{SL}=100$ ms: i. BASL ($\sigma < 13\%$), ii. RESL ($\sigma < 4\%$), and iii. CRESL ($\sigma < 4\%$).
3.2 Filter properties

Figure 5 shows the simulation and measurement of the FWHM as a function of $T_{SL}$ for CRESL and BASL. The FWHM diminishes when increasing $T_{SL}$ for both preparations, i.e., the longer the preparation time, the higher the frequency selectivity. Nevertheless, the Specific Absorption Rate (SAR) and the scanner’s hardware constraints will limit the highest $T_{SL}$ value. To avoid these limitations, $T_R$ must grow, but this means lowering the temporal resolution when signals are acquired in time. Therefore, the trade-off between increasing frequency selectivity and lowering the temporal resolution must be considered for future applications. In our setup, $T_{SL} = 100$ ms allowed us to sweep the frequency range 0-200 Hz, setting the bandwidth to 12 Hz for BASL and 17 Hz for CRESL, respectively. For BASL, the simulation without considering inhomogeneities sub-estimates the measured bandwidth. Still, it remains lower than the CRESL case for the entire $T_{SL}$ range by about 10 Hz.

![Figure 5: Simulation and measurement of the FWHM of the double resonance effect for BASL and CRESL preparations as a function of $T_{SL}$. For both cases $B_{NC} = 75$ nT, $\omega_{SL} = 2\pi 90$ Hz.](image)

Multiple factors play a role when selecting the optimal SL preparation. Becoming independent of $B_0$ and $B_1^+$ inhomogeneities means diminishing sensitivity and contrast amplitude. BASL presents the highest contrasts and frequency sensitivity from a theoretical point of view but is highly susceptible to field imperfections. Given the complexity of physiological signals, and the desire to compare the activity of independent spatial locations, we considered robustness as the most important feature. Therefore, we used CRESL for the next section that tackles the analysis of composite signals.

3.3 Measurements of composite signals

Figure 6(a) shows the measurement of the $SL_{on}$ and $SL_{off}$ signals in time for $F_{SL}$ set to 53 and 97 Hz. The signal behavior is well represented by the simulation shown in Figure 6(b). Figure 6(c) shows the point-to-point division (ppd) between the signals on and off, and Figure 6(d) the corresponding simulation. Both the $SL_{on}$ and the ppd show the expected changes in proportion between the two frequency components. In principle, there are no difficulties in the component’s reconstruction associated with interference or beat of the frequencies. However, the maximum amplitude detected for the two frequencies differs, although they are equal in the original signal. Likely explanations are the influence of the initial phase or a shift in the spin-lock induced frequency (see Supplementary information 2). Finally, Figures 6(e) and (f) present the measured and simulated normalized components of the two target frequencies. The sequence and metric presented in this work correctly...
reconstruct the frequency components. In addition, the proposed theoretical simulation successfully represents the empirical behavior.

Figure 6: Sequence response to a composite signal. a) Measured and b) Simulated $SL_{on}$ and $SL_{off}$ signals as a function of time for $F_{SL}$ set at 53 Hz and 97 Hz. c) Measured and d) Simulated ppd between $SL_{on}$ and $SL_{off}$ as a function of time for the two frequencies used in a). e) Measured and f) Simulated normalized frequency component every 30 s block.

Turning now to consider the response of the sequence to the acquisition of individual signals with different frequency components, we present Figure 7. Panel a) shows the input signals and panel b) the frequency components corresponding to each signal. Panel c) shows the components reconstructed from the measurement and panel d) from the simulation. The 0.1 Hz ripple appears in the measured signal even if the $F_{SL}$ is 30, 60 or 90 Hz, resulting in a higher ratio in each channel. Since the oscillation occurs in both the $SL_{on}$ and $SL_{off}$ signals, the reason is probably the $B_0$ variation due to the large amplitude of the low-frequency component (see Supplementary information 3). Although the point-to-point division of the signals on and off is designed to eliminate artifacts detected in the readout part of the sequence, those artifacts will only be filtered out when they are either static or vary much slower than $2T_R$. Nevertheless, if the signals represent different volumes in an image, the method can correctly locate the volume with the highest component of 90 Hz, despite its small amplitude.
Figure 7: Component reconstruction of individual signals. a) Input signals composed of a 0.1 Hz with a 30 Hz sine the last 30 s. A 90 Hz sine is added in 20, 10, and 2 s blocks for signals 2, 3, and 4 respectively, the shaded areas indicate the location of the 90 Hz wave. b) Frequency components of the signals showed in a) at 30, 60 and 90 Hz. c) Components reconstructed from measurement with $F_{SL}$ fixed at 30, 60 and 90 Hz. d) Frequency components reconstructed from the simulation with the same parameters as in the measurement.

4 Discussion

There were two main findings in this work. First, the reason behind the oscillations of the double resonance contrast depends on the type of SL preparation. $B_0$ and $B_1^+$ inhomogeneities induce oscillations for the BASL approach, RESL has a mixed behavior being dependent on $B_0$ and the initial phase of the oscillating field and finally, CRESL will oscillate exclusively due to the initial phase. Given the unavoidable oscillating nature of the contrast, we adopted the standard deviation as a metric to quantify the influence of the target field. Furthermore, we studied the susceptibility of the metric to field inhomogeneities by considering the dynamics of the double resonance effect for the three preparations. We found that CRESL is the most robust preparation even within the double resonance dynamic, which further supports the idea firstly proved in the field of $T_{1\rho}$ relaxation\[15;16\].

Second, the SIRS approach can separate and reconstruct the amplitude of the spectral components within individually acquired composite signals. These results are promising for the application in epilepsy patients. However, limitations such as the identification between pathological and non-pathological rapid oscillations would still affect this technique\[26–28\]. Even more, the presented ppd method works under the assumption of spurious effects varying slower than the time between two successive acquisitions. These experiments work as...
a proof-of-principle of the SIRS contrast as a robust tool for filtering specific frequencies for time-dependent composite signals. An in-vivo validation of this acquisition method and metric is necessary to evaluate clinical applicability.

This paper deepens the understanding of the double resonance effect and its response to factors that will potentially be present in a clinical setting. The presented simulation algorithm allows for more realistic simulations while maintaining time efficiency and simplicity. Although this study only focuses on the optimization of the SL preparation within the SIRS method, the presented simulator can be also applied to the SLOE approach.

The analysis of the metric is intended to show the capabilities and limitations of each preparation method. While we conclude that CRESL is the most robust, the consequence of compensating for field inhomogeneities is the direct decrease in the signal-to-noise ratio. Also, the susceptibility to $B_1^+$ error during the SL pulse is countered with calibration but not corrected.

Many studies have suggested applying this method to the ultra-low field to avoid the influence of field inhomogeneities and the BOLD effect\cite{11;29;30}. While we did not investigate that possibility, we believe that the BOLD effect could be counteracted with the use of ultra-short-echo time readouts. In addition, when encoded in the readout signal, division of successive acquisitions with and without SL would also diminish its effect as well as that of any static influence on the signal.

Some studies within the chemical exchange community suggest the use of adiabatic pulses for excitation to decrease the $B_1^+$ error in SL sequences\cite{31;32}. If $B_0$ were homogeneous, the adiabatic pulses would eliminate the need for the phase shift on the second half of the SL and the BASL approach could be used. This would increase SNR and avoid oscillations due to phase. As $B_0$ homogeneity cannot be assured, a more in-depth study that characterizes the weight of each inhomogeneity and its probability of occurrence could be useful to clarify if it is a viable path.

Regarding the post-processing of the signals, here we used the standard deviation as a metric to represent signal variation. However, the statistical processing through independent component analysis or granger causality could be applied to extract additional information. It is important to note that this work presents a tool and the necessary steps for a realistic simulation of the double resonance effect. The simulator can import all sorts of signals and quickly calculate the SIRS response in time. Then different signals can be analyzed to find the optimal statistical analysis depending on the data and application.

To summarize, based on the literature and the methodology presented in this paper, it is justified to conclude that the SIRS technique can help understand the intricate workings of neuronal activity and its pathological states. Nevertheless, to incorporate SIRS into the tools used in the clinic, more understanding between their interactions is necessary. The work presented here addresses important application issues, deepening understanding and showing the first steps towards realistic signal analysis. The next step in the development is to focus on tests on healthy volunteers or animals in which there is ground truth.

5 Conclusions

All three spin-lock preparations exhibit an oscillating contrast as a function of $T_{SL}$ or $F_{SL}$. Due to the oscillating behavior, we used the standard deviation of the signal acquired in time as a metric to quantify the influence of the target field. We showed the std metric within the CRESL preparation is the most robust against field inhomogeneities even in the presence of the double resonance effect. The known disadvantage of this preparation, however, is the loss of half the maximum theoretical contrast.

Additionally, the SIRS contrast can reconstruct the frequency components of individually measured signals. The detection limit of the sequence in realistic physiological and pathological conditions remains to be addressed in future works. These results indicate that the presented technique has the potential to be used for the detection and localization of oscillating fields with frequencies associated with specific pathologies.
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Acknowledgements

This study was supported by the Swiss National Science Foundation (SNSF) within the project: Predict and Monitor Epilepsy After a First Seizure: The Swiss-First Study (SNSF, CRSII5-180365, PI Roland Wiest), the Kommissionspräsident Kernen Fonds for neurological research and the Schweizerische Epilepsie-Liga (Swiss league against epilepsy).

We thank Hans Slotboom, Guodong Weng and Andreas Federspiel (Institute for Diagnostic and Interventional Neuroradiology, Support Center for Advanced Neuroimaging (SCAN), University of Bern, Bern, Switzerland) for their essential discussion of the work. We also thank Regina Reissmann (Biomedical analyst, NEUR, Inselspital, Bern) and Thierry Rumo (Medical technician, DT, Inselspital, Bern) for the technical help in the implementation of the phantom.

Author contributions

All authors conceived the idea of this work. M.C. designed the experiments, implemented the simulations, and wrote the manuscript. M.C. and F.T. performed the measurements and analyzed the data. C.K. and R.W. supervised this study. All authors provided discussion and reviewed the manuscript.

Data availability statement

Simulation source codes and data can be shared upon reasonable request to M.C.

Additional Information

The authors declare no competing interests.
Supplementary Information

1. Rotation matrices

The used rotation matrices $R_{\hat{x}}(\alpha)$, $R_{\hat{y}}(\alpha)$, $R_{\hat{z}}(\alpha)$ can be represented by

$$R_{\hat{x}}(\alpha) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos(\alpha) & \sin(\alpha) \\ 0 & -\sin(\alpha) & \cos(\alpha) \end{bmatrix}, \quad R_{\hat{y}}(\alpha) = \begin{bmatrix} \cos(\alpha) & 0 & -\sin(\alpha) \\ 0 & 1 & 0 \\ \sin(\alpha) & 0 & \cos(\alpha) \end{bmatrix}, \quad R_{\hat{z}}(\alpha) = \begin{bmatrix} \cos(\alpha) & \sin(\alpha) & 0 \\ -\sin(\alpha) & \cos(\alpha) & 0 \\ 0 & 0 & 1 \end{bmatrix}.$$ 

The relaxation matrices $A$, $B$, $A_\rho$ and $B_\rho$ can be represented by

$$A = \begin{bmatrix} e^{-t/T_2} & 0 & 0 \\ 0 & e^{-t/T_2} & 0 \\ 0 & 0 & e^{-t/T_1} \end{bmatrix}, \quad B = \begin{bmatrix} 0 \\ 0 \\ 1 - e^{-t/T_1} \end{bmatrix}, \quad A_\rho = \begin{bmatrix} e^{-t/T_2\rho} & 0 & 0 \\ 0 & e^{-t/T_1\rho} & 0 \\ 0 & 0 & e^{-t/T_2\rho} \end{bmatrix}, \quad B_\rho = \begin{bmatrix} \cos(\beta)(1 - e^{-t/T_1\rho}) \\ 0 \\ 0 \end{bmatrix}.$$ 

Here, $\beta = \arctan\left(\frac{\omega S L}{\Delta \omega_0}\right)$. Within the simulator, each rotation step of duration $dt$ will have two relaxation steps of $dt/2$, which means evaluating the four relaxation matrices in $t = dt/2$.

2. SL pulse calibration

An error in the excitation angle can be corrected by the change in the sign of the second half of the spin-lock pulse (RESL) and an error in the $B_0$ field can be corrected by the 180° pulse (CRESL). However, no compensation can be made for the $B_1^+$ inhomogeneity influence during the application of the SL pulse. This will induce a $F_{SL}$ different from the one of the target field and the resonant condition will not be fulfilled. To solve this problem, an SL calibration can be made to find the $B_1^+$ error for each target frequency.

![Figure 8: SL amplitude calibration. a) Percentual change of the signal as a function of $F_{SL}$ for different values of the target oscillating field frequency ($F_{out}$). b) Linear regression of the detected ($F_{SL}$) vs the expected frequency ($F_{out}$). The obtained slope was then used to define the amplitude of each SL pulse.](image)

3. Measurement of individual signals

Figure 9 shows the point-to-point division between the $SL_{on}$ and $SL_{off}$ acquisition of the 4 composite signals presented in Figure 7 a). The signal shows traces of the 0.1 Hz oscillation, despite the acquisition being performed for $F_{SL}$ equal to 30, 60 and 90 Hz. This influence is greater at 30 Hz and diminishes when increasing $F_{SL}$. This shows that slow drifts cannot be fully filtered out using the ppd between on and off acquisitions.
The reason behind this is that the two acquisitions have a time difference of TR. Therefore, any signal variation that occurs within a \( T_R \) will be registered differently in the \( SL_{on} \) and \( SL_{off} \) signal. An alternative to this is applying a high-pass filter to eliminate the influence of slow drifts if there is prior knowledge of the signals present. Nevertheless, the 90 Hz signal only has 10% of the amplitude of the slow-wave and is still the biggest detected component at \( F_{SL}=90 \) Hz.

![Figure 9: Point to point division (ppd) between \( SL_{on} \) and \( SL_{off} \) measured for the input signals shown in Figure 7 a). Each column corresponds to each of the input signals and each row to the ppd acquired at \( F_{SL} \) 30, 60 and 90 Hz.](image)