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VCO-based ESR-on-a-chip as a tool for low-cost, high-sensitivity point-of-care diagnostics

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Abstract—In this paper, we discuss the use of electron spin resonance (ESR) spectroscopy as a tool for future point-of-care diagnostic applications. Additionally, we present a new ESR sensor ASIC with an improved VCO tuning scheme as an extension to our previously presented portable, VCO-based ESR spectrometer. By using two VCO tuning voltages with widely different VCO gains, the proposed tuning scheme greatly relaxes the requirements on the digital-to-analog converter (DAC). This is because in the previous scheme a single DAC had to be used to generate both the tuning signals for the wide frequency sweep and the small frequency modulation signals at the same time. In contrast, in the new scheme two DACs with optimized dynamic ranges can be used, reducing the AM-to-FM-conversion noise in the varactor to optimize the overall system sensitivity.

I. INTRODUCTION: ESR AS A TOOL FOR POINT-OF-CARE ANALYSIS

Thanks to its unmatched specificity, electron spin resonance (ESR) spectroscopy is amongst the most powerful analytical techniques today with applications ranging from the life sciences over material science analysis to food quality control [1], [2]. By measuring the spin of an unpaired electron, ESR spectroscopy is specifically suited to analyze free radicals, which play a major role in many diseases and can also directly be related to premature cell aging. This is illustrated in Fig. 1, where in the left part of the figure, the balancing action between free radicals, e.g. reactive oxygen species (ROS), and antioxidants is illustrated for the case of oxidative stress where there is a surplus of ROS.

The ESR detection principle is illustrated in the center part of Fig. 1. According to the figure, the degeneration of the energy state for $B_0 = 0$ associated with the spin of the unpaired electron is removed, leading to distinct energy levels (Zeeman splitting), the transitions between which are assessed in ESR spectroscopy using a microwave field with photons at the appropriate energy of $E = h\omega = h\gamma B_0$, where $h$ is the reduced Planck constant and $\gamma$ is the gyromagnetic ratio of the electron, which for a free electron takes on a value of $\gamma = -2\pi \cdot 28$ GHz/T. Consequently, for typical magnetic field strengths of benchtop ESR spectrometers between 0.3 T and 2 T, the required ESR frequencies range from approximately 9 GHz to 56 GHz. Therefore, compared to the related and more widely known technique of nuclear magnetic resonance (NMR) spectroscopy, ESR electronics operate at significantly higher frequencies, rendering both the design of the required detectors and that of the required electronics more challenging. These elevated ESR operating frequencies in combination with the very short relaxation times of electron spins render pulsed experiments, as they are routinely used for NMR spectroscopy, very difficult and the required equipment very expensive. Therefore, the majority of all ESR experiments is still carried out in the continuous-wave (cw) mode which conventionally involves a sweepable magnetic field source in combination with a mechanically tunable resonator. As a result, the commercially available benchtop ESR spectrometers suffer from a bulky size and weight as well as a large instrument cost, which together prevent many in-field applications for ESR spectroscopy, including e.g. point-of-care ESR spectroscopy.

As a potential solution to this problem, in this paper, we will discuss a recently proposed approach [3] towards portable, point-of-care spectroscopy, which at its heart uses voltage-controlled oscillators (VCOs) as both microwave source to excite the spin ensemble and detect the resulting ESR-induced changes in sample magnetization as a modulation of its oscillation frequency. Moreover, as an extension to the state-of-the-art in VCO-based ESR sensing, we propose an improved VCO tuning scheme compared to [3], which greatly relaxes the hardware requirements for the overall experimental setup.

II. CONVENTIONAL ESR DETECTION VS. VCO-BASED ESR-ON-A-CHIP

A conventional setup for continuous-wave ESR experiments is shown in Fig. 2a. According to the figure, in this setup the sample is contained inside a resonator which in turn is placed inside a large magnetic field to produce the required Zeeman splitting. Then, the ESR experiment is performed by irradiating the sample with a second magnetic field, the so-called $B_1$-field, at a fixed frequency, which corresponds to the Larmor frequency $\omega_L$ of the spins at the resonant field strength, $B_{0,\text{res}}$, $\omega_L = -\gamma B_{0,\text{res}}^L$, and sweeping the static magnetic field strength of benchtop ESR spectrometers between 0.3 T and 2 T, the required ESR frequencies range from approximately 9 GHz to 56 GHz. Therefore, compared to the related and more widely known technique of nuclear magnetic resonance (NMR) spectroscopy, ESR electronics operate at significantly higher frequencies, rendering both the design of the required detectors and that of the required electronics more challenging. These elevated ESR operating frequencies in combination with

![Fig. 1: Illustration of oxidative stress and free radical detection using ESR including a list of diseases which are directly related to oxidative stress.](image-url)
**Fig. 2:** (a) Conventional ESR detection setup, (b) the VCO-based ESR detection scheme proposed in [3] and (c) newly proposed modification of the scheme of (b) to relax the constraints on the DAC producing the sweep and modulation waveforms.

Field $B_0$ through the resonance condition $B_0 = B_{0,\text{res}}$. In this setup, the detection sensitivity can be improved by introducing a small modulation field (tenths of G (1 G = 0.1 mT) to a few G) $B_m$, parallel to $B_0$, which effectively translates the ESR signal to the modulation frequency and thereby allows for a low-noise detection using a lock-in amplifier (LIA). To illustrate the bottlenecks of this conventional ESR setup, we have highlighted those components in Fig. 2a which prevent a straightforward miniaturization and cost reduction of the setup.

In contrast, in the VCO-based ESR setup of Fig. 2b, which was recently proposed by our group in [3], the sample is directly placed on top of the tank inductance of an integrated CMOS LC-tank VCO such that the magnetic field generated by the tank inductance produces the resonant magnetic field $B_1$, which triggers the ESR transitions. Thereby, the need for a sweepable magnet is removed because the sweep-frequency excitation, which is required to operate at a fixed static magnetic field $B_0$, can be conveniently produced by a sawtooth waveform applied to the VCO tuning voltage $V_{\text{TUNE}}$. While such a frequency sweep experiment is in principle also possible using the conventional setup of Fig. 2a, applying a swept frequency excitation at a fixed $B_0$-field in the traditional setup introduces an intrinsic tradeoff between detection sensitivity (requiring high-Q resonators) and sweep range (requiring low-Q, high bandwidth resonators). In contrast, when performing a frequency sweep using a VCO, its resonant tank is intrinsically tuned to the correct excitation frequency. This is because the change in tuning voltage changes the effective tank capacitance, which in turn modifies the tank resonant frequency of the LC tank, $\omega_{\text{LC}} = 1/\sqrt{L_1C}$, finally producing a new oscillation frequency, $\omega_{\text{osc}}$, which intrinsically follows the resonant frequency of the LC tank according to:

$$\omega_{\text{osc}} \approx \omega_{\text{LC}} \left(1 - \frac{(\alpha_{\text{od}} - 1)^2}{16 \cdot Q_{\text{coil}}^2}\right),$$

where $\alpha_{\text{od}}$ is the so-called overdrive parameter indicating how much the tank loss is overcompensated by the negative small signal resistance of the active devices in the VCO of Fig. 3\(^1\), cf. [4], and $Q_{\text{coil}}$ is the coil quality factor. Therefore, in the VCO-based detection scheme, wide frequency sweeps can be performed which cover all resonances inside the sample with a constant detection sensitivity and the sweep range is essentially only limited by the achievable tuning range of the utilized VCO. Moreover, in the VCO-based detection scheme, the frequency-modulation required to perform a lock-in amplification for enhanced sensitivity can be conveniently performed by applying a small sinusoidal signal on top of the voltage ramp for the frequency sweep.

**III. DESIGN TRADEOFFS FOR THE VCO-BASED ESR DETECTOR**

Despite the many advantages of the VCO-based detection setup presented in [3], one fundamental tradeoff in this scheme is associated with the selection of the VCO gain. Here, a large VCO gain maximizes the achievable frequency sweep range to ideally cover a sweep range $>1$ GHz. However, a large VCO gain makes it harder to generate the required amplitudes of the frequency modulation (required modulation amplitude between 300 kHz and 10 MHz). As an example the VCO utilized in [3], had a VCO gain of approximately 1 GHz/V.

\(^1\)More precisely, $\alpha_{\text{od}}$ is given $\alpha_{\text{od}} = G_{\text{m}}/2/G_{\text{t}}$, where $G_{\text{m}}$ is the transconductance of a single transistor in the crosscoupled transistor pair and $G_{\text{t}}$ is the equivalent parallel tank conductance [4].
resulting in a sweep range which is sufficient to cover all transitions associated with common spin traps used for ROS detection. However, to generate the small frequency modulation amplitudes for the lock-in detection, this large VCO gain required a DAC capable of producing sinewaves with amplitudes around 300 μV, placing a stringent requirement on the DAC dynamic range which has to be around 16 bit or better to both produce the required sweep range and modulation signals. Moreover, voltage noise in the DAC becomes more important as the VCO gain is increased due to the larger AM-to-PM conversion associated with higher gains.

IV. Prototype realization and measurements

A. VCO characteristics

The setup used to perform the ESR experiments is similar to that presented in [3], except for the detector ASIC, whose VCO was modified to remove the VCO gain tradeoff described in the previous section. To remove this tradeoff, we use a VCO with two tuning ports. The first one has a large VCO gain of \( K_{V1} \approx 0.734 \text{GHz/}V \), which is used to perform the required frequency sweeps with a sufficiently large sweep range. The second tuning port displays a significantly smaller VCO gain of \( K_{V2} \approx 44.4 \text{MHz/}V \) and is therefore ideally suited to produce the small frequency modulation signal required for lock-in detection. Splitting the VCO tuning in this way allows for the use of two DACs with greatly relaxed dynamic range requirements. Moreover, their respective outputs can be conveniently filtered with a low-pass filter before the sweeping port and a bandpass filter before the modulation port to minimize AM-to-FM conversion noise.

B. ESR measurements

To perform an ESR experiment with our PoC spectrometer, first, a sample has to be placed on top of the on-chip detection coil, which is then inserted into the permanent magnet using a PCB-based probe head. Next, to obtain an ESR spectrum, the tuning voltage at the sweep port is used to produce a frequency ramp while simultaneously the modulation port is used to produce the frequency modulation required for the subsequent lock-in detection as explained in section III. The frequency ramp produced by the voltage ramp at the sweeping port, \( V_{\text{tune,1}} \), is chosen to include the resonance frequency \( \omega_{\text{osc, res}} = \gamma B_{0,\text{res}} \). The frequency-divided VCO output signal is then digitized and FM-demodulated using a digital PLL before a digital lock-in amplifier is used to extract the ESR information from the modulation frequency. To subtract the baseline signal due to the VCO gain, the \( B_{0}-\text{field} \) is slightly offset to an off-resonance value and a second sweep with identical range is performed.

To measure the limit of detection (LOD), i.e. the minimum number of spins detectable with an SNR of three in one second of measuring time, of our ESR spectrometer, we used the conventional ESR standard DPPH as sample. Then, using the definition of the LOD and a small grain of DPPH as sample, we have estimated a spin sensitivity around

Fig. 4: Measured spectra of (a) DPPH and (b) TEMPOL. Modulation frequency \( f_m = 10\text{kHz} \) and LIA time constant \( T_L = 10\text{ms} \), modulation amplitudes of 0.66 Gpp, 1 Gpp, and 2 Gpp for DPPH and fixed amplitude of 2 Gpp for TEMPOL.

4 \times 10^9 \text{spins/(G} \cdot \sqrt{\text{Hz}}). The corresponding measured spectrum is shown in Fig.4a.

Furthermore, as a proof-of-principle that the proposed portable ESR spectrometer can also be used in combination with standard spin traps for ROS detection experiments, we have also measured a spectrum of the common spin trap TEMPOL in water with a concentration of 10 mM. The corresponding spectrum, which displays the three characteristic peaks due to the hyperfine splitting between the electron spin and the spin of the nitrogen nucleus, is shown in Fig.4b.

For both experiments, the lock-in time constant was set to a value of 10 ms to ensure a fast acquisition of the spectra despite the large number of measurement points.

V. Conclusion

In this paper, we have presented an improved setup of a portable VCO-based ESR spectrometer. The system uses a modified tuning scheme to relax the stringent requirements for the VCO tuning DAC. As a proof-of-principle we have shown measured ESR spectra with different samples and report a competitive spin sensitivity of around 4 \times 10^9 \text{spins/(G} \cdot \sqrt{\text{Hz}}).

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