A Galvanically Coupled Electron Paramagnetic Resonance Spectrometer for Deep Tissue Hypoxia Diagnosis

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Abstract

An electron paramagnetic resonance (EPR) spectrometer for deep-tissue oximetry and hypoxia diagnosis is presented. The existing *in vivo* EPR spectrometers suffer from a direct tradeoff between operation frequency (thereby sensitivity) and sensing depth due to tissue absorption, and only achieve 1.2GHz/15mm or 9GHz/2mm. To break the tradeoff, this work galvanically couples an external 30MHz source into the body and multiplies it up with an integrated SSPLL to reduce tissue EM absorption. It achieves 14GHz EPR frequency and 50mm sensing depth. *In vitro* hypoxia detection is demonstrated for validation.

Introduction

Hypoxia is a deficiency of tissue oxygen, i.e., below normal partial pressure of oxygen (pO_2). It is a cancer hallmark and limits the efficacy of the chemo and radiation therapy. Hence, deep-tissue pO_2 sensing is important for cancer diagnosis and treatments. To date, EPR is the only non-invasive tool capable of direct, quantitative, and repeatable pO_2 measurements.

Fig.1 illustrates the EPR operation principle. It detects the interaction between the EM field and free radicals. Under a dc magnetic field B_0, the free radical's energy level splits, producing an absorption peak at f_0, where $f_0/B_0 \approx 28$GHz/T. The O_2 molecules interact with certain free radicals and increase their spectral linewidths linearly. Such a response is independent of temperature and pH, making EPR ideal for pO_2 sensing.

However, deep-tissue EPR pO_2 sensing has not advanced to clinical practices. The biggest challenge is the body absorption of the EPR signal. The optimal EPR frequency f_0 is >10GHz, and its sensitivity increases with f_0. Existing EPR practice places the radical inside the body, and measures from the outside. The signal path is prohibitively lossy as the penetration depth at 10GHz is only 1mm. This leads to a direct tradeoff between the sensing depth and the frequency (i.e., sensitivity).

Galvanically Coupled EPR Spectrometer

This work proposes a galvanically coupled EPR spectrometer which is placed inside the body along with the free radical, as shown in Fig.2. The EPR spectrometer consists of a 14GHz LC resonator as the sensing front-end, and a subsampling PLL (SSPLL) as the excitation source. An external MHz reference is galvanically coupled to the in-body SSPLL and converted to 14GHz. The frequency-depth tradeoff is thereby mitigated.

EPR Sensing Frontend: The EPR spectrum can be measured through the radical's magnetic susceptibility, χ' [1]. An inductor covered by free radicals can serve as an EPR sensor, since its inductance $L=L_0(1+\eta\chi')$ varies with χ', and the filling factor η is <1 as the radicals occupy part of the magnetic field. Fig.2 shows the diagram of the sensing frontend, which is a capacitively coupled LC tank. With B_0=0.5T, C_T and C_{INJ} in parallel resonate with the inductor L at f_0=14GHz, so that V_{INJ} and V_T are in quadrature. When $f \neq f_0$, a quadrature error θ between V_{INJ} and V_T is produced, given by $\theta=Q(\delta L/2L+\delta f/f_0)$, and $\delta L/L=\eta\chi'$ is the EPR signal. θ is converted to a voltage by a passive mixer through self-mixing, and is then amplified by a VGA. Since the mixer downconverts the phase signal θ to dc, the injection signal V_{INJ} is on-off modulated at 50 kHz to avoid signal contamination by the offset and flicker noise of the mixer and VGA.

Galvanic Coupling: Galvanic coupling around 10-50MHz [2] has been utilized for body channel communication to support >10cm tissue depth. It is thereby selected to couple a MHz subharmonic of the 14 GHz EPR frequency through the tissue. Following the methods in [2], the galvanic channel is characterized with slabs of animal tissues and dielectric human phantoms of different thickness. To mimic the implant, batteries are used for power supply and baluns are inserted for earth ground isolation. Fig.3 shows the TRX electrode design, measurement setup and results. The best coupling frequency range is shown to be 30-35MHz. Moreover, the channel loss is insensitive to the tissue thickness thanks to the TRX electrode design, which provides a stable channel for various implant depths.

Frequency Multiplier: Converting 30MHz to 14GHz requires a large multiplication factor (M=480). SSPLLs are superior in low PN signal generation with minimal power when M is high. As a SSPLL by itself is vulnerable to disturbances, a frequency lock loop (FLL) is needed to ensure robust lock over PVT. In classical high-M SSPLLs, the FLL charge pump (CP) needs inordinate power for loop stability. At M=480, the current ratio of FLL-CP and SSPLL-CP is ~600 to achieve similar phase margin (PM) in both loops. To save power, a proportionally divided SS-CP with a new loop filter design is utilized, as shown in Fig.4 [3]. The FLL-CP current is reduced without PM degradation. In this work, the SS-CP and FLL-CP consumes 650μA and 350μA, respectively, and both have PM>53°.

Measurement Results

The spectrometer IC is fabricated in the 28nm CMOS process. Fig.7 shows the chip photo. It has two EPR sensors driven by one SSPLL. Total power is 9.6mW with one sensor and 11.4mW with both operating. The chip can be powered by ultrasound, as an ultrasonic power transfer depth of 10cm has been realized to support an implant with 12.4mA current [4].

The SSPLL covers 13.2-17.3GHz and consumes 6.6mW with the FLL. Fig. 5 shows its PN spectrum with a 30MHz reference from a signal generator (R&S SMA100A). The integrated jitter is 153.4fs. When the SSPLL is galvanically coupled through a 5cm thick pork loin to the signal generator, its jitter increases to 2.79ps due to a higher clock buffer noise and ground bounce. The latter can be mitigated by differential coupling.

In vitro pO_2 sensing and hypoxia detection were performed with a free radical lithium phthalocyanine (LiPc). As shown in Fig.6, samples are deposited onto the IC placed inside a 0.5T magnet. A 30MHz 13dBm source (FCC compliant) couples to the chip through the 5cm pork loin. To obtain the LiPc EPR linewidth at different pO_2 levels, the 30MHz source is swept at 1kHz step

(0.48MHz at 14GHz). The EPR linewidth broadens linearly as pO_2 increases (23.5kHz/mmHg). Since the Allan derivation of the galvanically coupled SSPLL is <1ppm (23.5kHz/14GHz), sub-mmHg accuracy is easily achievable with a finer sweeping frequency step. Fig.7 compares our work with prior arts [5-9].

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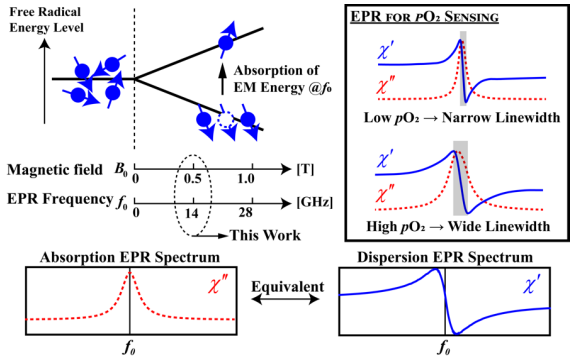


Fig.1 EPR operation principle and its usage for pO_2 sensing.

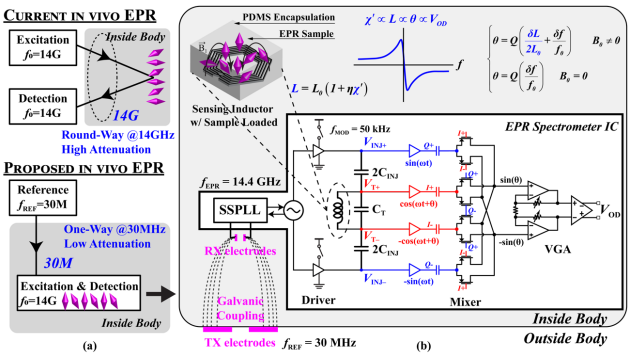


Fig.2 Block diagram of the proposed deep-tissue EPR spectrometer.

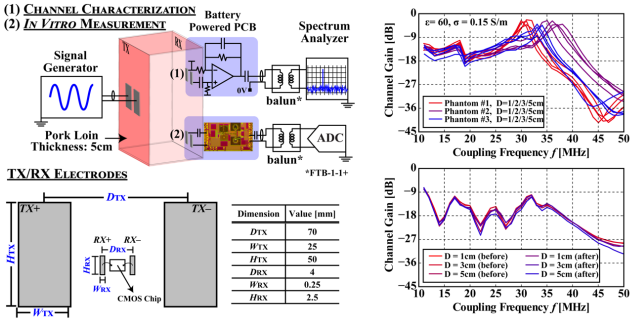


Fig.3 Galvanic channel characterization and TRX electrode design. Dielectric tissue phantoms (recipe by *AMRI, NIH*) and pork loin (before and after EPR measurements) were characterized.

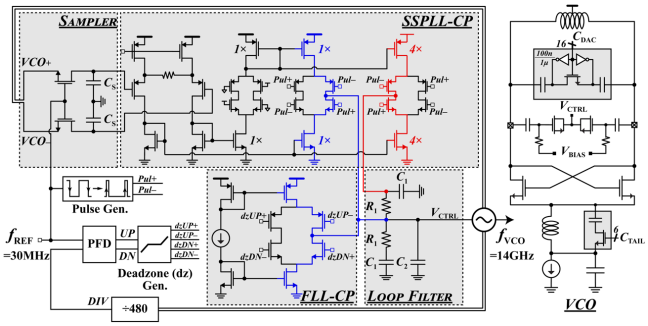


Fig.4 Block diagram of SSPLL. The SSPLL-CP is divided with a current ratio of 1:4 and connects to a new loop filter topology to achieve good PM for both SS-loop and FLL with minimal power.

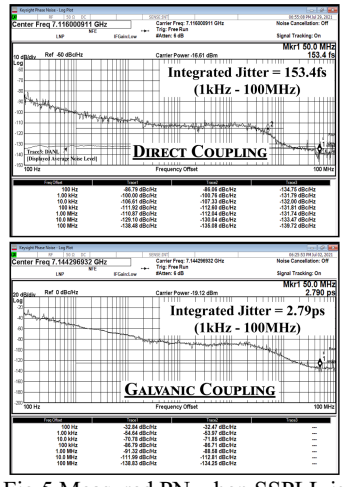


Fig.5 Measured PN when SSPLL is directly and galvanically coupled to the reference (after a divide-by-2).

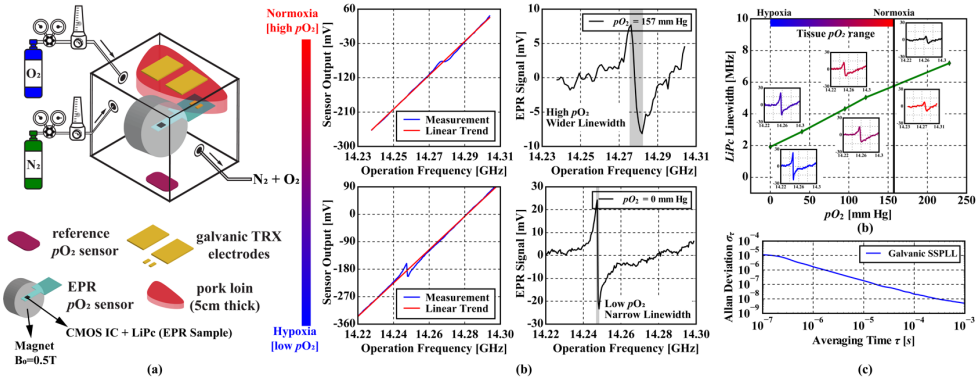
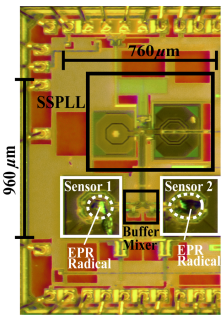


Fig.6 *In vitro* pO_2 and hypoxia sensing, (a) measurement setup, (b) sensor output and measured LiPc EPR linewidth at different pO_2 levels, and (c) Allan derivation of the galvanically coupled SSPLL.



	JSSC'16 [5]	ISSCC'18 [6]	Anal.Chem.'18 [7]	Front.Oncol.'20 [8]	Sci.Rep.'21 [9]	This Work
Technology	130 nm BiCMOS	130 nm CMOS	Laboratory Instrument	Laboratory Instrument	Laboratory Instrument	28 nm CMOS
EPR Freq. [GHz]	3.8-4.8	11.8-14.2	0.75	1.2	9.53	13.2-17.3
Spectrum Type	Absorption	Dispersion	Absorption	Absorption	Absorption	Dispersion
ASIC Power [mW]	10000	15/sensor	N/A	N/A	N/A	9.6 (1 sensor) 11.4 (2 sensors)
Implantable	No	No	Yes	Yes	Yes	Yes
Parts Implanted/ Dimension [mm^3]	N/A	N/A	EPR radical/ liquid	EPR radical/ 5 × 0.6 × 0.6	EPR radical/ N/A	EPR radical + spectrometer/ 2.5 × 4 × 1
Coupling Method/ Frequency	N/A	N/A	RF 750 MHz	RF 1.2 GHz	RF 9.53 GHz	Galvanic 30 MHz
Coupling Distance/ Medium	N/A	N/A	25 mm/ Mouse Leg	15 mm/ Human Body	2 mm/ Fingernail	50 mm/ Pork Loin
Application	Hand-held scanner	Hand-held scanner	Tumor pH	Tissue pO_2	Fingernail dosimetry	Tissue pO_2

Fig.7 Chip micrograph and comparison table.

References [1] L. Zhang, LMWC, 2021, p.819. [2] B. Xiong, JSSC, 2020, p.1698. [3] L. Zhang, ISSCC, 2022. [4] J. Charthad, JSSC, 2015, p.1741. [5] X. Yang, JSSC, 2016, p.2408. [6] A. Chu, ISSCC, 2018, p.354. [7] D. Komarov, Anal. Chem. 2018, p.13938. [8] P. Schaner, Front. Oncol. 2020, p.2223. [9] J. Guo, Sci. Rep. 2021, p.2883.