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ABSTRACT
This paper describes an experimental investigation of the noise characteristics of a 750-MHz electronically tunable resonator for electron paramagnetic resonance (EPR) spectroscopy. The RF noise of the tunable resonator and its influence on the baseline noise of an EPR spectrum were systematically measured, considering both the noise of varactor diodes used in the impedance matching network of the resonator and noise from the ambient environment. The influence of magnetic field modulation and its amplitude on the baseline noise of the EPR spectrum was also measured. The tunable resonator itself increased the noise level of the spectral baseline of a home-built 750-MHz continuous-wave (CW) EPR spectrometer. A significant decrease in the noise level of the EPR spectral baseline was demonstrated by replacing the varactor diodes in the matching network by a trimmer capacitor, which led to a 6.1-fold improvement in EPR spectrum signal-to-noise ratio.

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I. INTRODUCTION
The partial pressure of oxygen and extracellular pH are essential parameters for understanding the pathophysiological status of solid tumors. Among several potential imaging methods, electron paramagnetic resonance (EPR) spectroscopy shows promise for the visualization of both oxygenation and pH for tumor animal models in a noninvasive manner. To achieve high-sensitivity EPR spectroscopy and spectroscopic imaging of tumor oxygenation or extracellular pH, maximization of the signal-to-noise ratio (SNR) of EPR spectra is required, i.e., by reduction of the noise in the spectral baseline and/or increase of the signal intensity of the spectra. In particular, noise proximal to or at the same frequency as the EPR absorption peak can cause errors in interpretation of the EPR spectra and constrains the sensitivity of EPR spectroscopy and imaging. Therefore, understanding and assessment of the possible noise sources in an EPR spectrometer are essential for sensitivity improvement. While the conversion efficiency of the RF magnetic field of the resonator gives the relative signal intensity of the EPR spectrum, the noise sources in the EPR spectrometer and the magnitude of the noise associated with the RF resonator require investigation.

For X-band EPR spectroscopy, Pfenninger et al. reported a noise analysis of EPR spectrometers. However, they did not present a general formula for calculating the noise voltage on a specific resonator for small animal experiments. For nuclear magnetic resonance measurements, Suits et al. proposed a noise-immune coil design that can reduce the noise voltage from the ambient environment without the need for radio-frequency (RF) shielding. In addition, Kumar et al. reported the noise figure as a function of the frequency for a circular loop resonator. From these studies, it is clear that the configuration, geometrical and electrical parameters of the RF resonator govern its noise figure in magnetic resonance spectroscopy and thus EPR for small animal experiments. There are three types of noise sources typically present in in vivo EPR spectroscopy experiments: (i) the noise from a subject animal (sample noise), (ii) the noise from the EPR spectrometer, including the resonator (system noise), and (iii) the noise from the ambient environment (environmental noise). In this study, we focused on assessment of the baseline noise of the EPR spectrum obtained for a 750-MHz
electronically tunable resonator developed for the measurement of murine tumors.\textsuperscript{13,14} The noise from the tunable resonator is composed of thermal noise and noise from the varactor diodes. However, the characteristics of the RF noise of the tunable resonator and its effect on the spectral baseline noise have been unclear to date. Since our tunable resonator employs a semi-open RF shielding structure for accommodating a mouse tumor-bearing hind leg, the shielding and coil geometry differs from that of a standard X-band cavity resonator, and as such, results of existing studies cannot be directly translated to model the noise figure of our 750-MHz EPR spectrometer.

The goal of this study was to experimentally investigate the influence of several noise sources and determine the dominant noise source of the resonator on the EPR spectrum. In this article, we quantitatively investigated the noise intensity level of the baseline of the EPR spectrum and the influence of the RF noise from the ambient environment. These insights should help to realize high-sensitivity \textit{in vivo} EPR spectroscopy and imaging.

II. METHODS

A. Electronically tunable EPR resonator operating at 750 MHz

The 750-MHz electronically tunable resonator used for \textit{in vivo} EPR spectroscopy and imaging has been described previously.\textsuperscript{13,14} The application of reverse bias potentials to varactor diodes can control the resonant frequency and impedance matching of the resonator. The central part of the tunable resonator is a multi-coil parallel-gap resonator (MCPGR) with a diameter of 18 mm and a height of 20 mm, suitable for measuring a mouse tumor-bearing hind leg. In addition to the MCPGR, the resonator consists of a parallel transmission line, a varactor-based matching network, varactor-based tuning circuitry using microstrip line couplers, a half-wave line balun, and a partial (semi-open) RF shield. Figure 1 shows photographs and a circuit diagram of the tunable resonator. Two types of varactor diodes were used for the tunable resonator: 1SV217 (Toshiba, Tokyo, Japan) for the matching network and BB181 (NXP Semiconductors, Eindhoven, Netherlands) for the tuning circuitry. The measurement of the spectral baseline noise was conducted both with and without the varactor diodes (1SV217) for the matching network to investigate the noise associated with the varactor diodes themselves. When the varactor diodes were removed, a non-magnetic trimmer capacitor (NMAM15HV, Voltronics Corp., Salisbury, MD) was used instead for resonator matching adjustment.

B. CW-EPR spectrometer

Figure 2 shows a simplified diagram of the home-built 750-MHz continuous-wave (CW) EPR spectrometer used in this study. The main change from our previously reported spectrometer setup\textsuperscript{15,16} is the use of a double-balanced mixer (DBM) for RF detection. The frequency of magnetic field modulation was 90 kHz, and the Helmholtz coil pair (mean diameter 100 mm) used for magnetic field modulation was mechanically fixed to the structure of the resonator. The conversion efficiency of the RF magnetic field was 80 $\mu$T/W\textsuperscript{1/2} at the center of the unloaded resonator.\textsuperscript{14} The resonant
frequency of the tunable resonator was stabilized using automatic tuning control (ATC) that locked the resonant frequency to the frequency of the RF source. Note, the ATC circuit has been omitted from Fig. 2 for clarity; details have been reported previously.17,18 (Also, isolators in the spectrometer have been omitted to simplify the spectrometer diagram.) The RF source phase noise is an important factor contributing to the spectral baseline noise.10 In the datasheet of the RF source (Agilent Technologies E8257D with ultra low phase noise performance option UNX), the typical single sideband (SSB) phase noise at 100 kHz offset from the carrier (500 MHz to 1 GHz) was –135 dBc/Hz.

C. Noise measurement of EPR spectral baseline

To measure the noise of the spectral baseline, EPR spectroscopy of a nitroxyl radical, 4-oxo-2,2,6,6-tetramethylpiperidine-d16,15N-1-oxyl (15N-PDT) (CDN Isotopes, Quebec, Canada), was performed. 15N-PDT was dissolved in 2 mL of phosphate buffered saline (PBS) and filled in a plastic microtube (9 mm inner diameter and 37 mm long). Figures 3(a) and 3(b) show the chemical structure of 15N-PDT and its characteristic EPR spectrum, indicating the definition of the signal and noise intensities, respectively. The magnitude of the baseline noise of the EPR spectrum was defined as twice the standard deviation (SD) of the intensity of the EPR spectrum over 100 data points in a region spectrally distinct from the absorption peaks of 15N-DPT. Measurements of EPR spectroscopy of 15N-PDT were repeated five times to obtain the mean values of the baseline noise level and the signal intensity. The spectral baseline noise and the EPR signal intensity were measured for three cases:

(i) The varactor-based tunable resonator (circuit shown in Fig. 1(c)) was connected to a 180-degree hybrid. The baseline noise level was measured as a function of the incident RF power $P_{\text{in}}$. The conversion efficiency of the RF magnetic field was 102 μT/W$^{1/2}$ at the center of the sample space of the unloaded resonator using the varactor-based matching network.

(ii) The trimmer capacitor-based tunable resonator was connected to the 180-degree hybrid. The varactor diodes (15V217) in the matching network of case (i) were replaced by a non-magnetic trimmer capacitor (NMAM15HV). The varactor diodes (BB181) for frequency tuning were unchanged. This case allows us to investigate the influence of the varactor diodes in the matching network on the spectral baseline noise level. As for case (i), the baseline noise level was measured as a function of the incident RF power $P_{\text{in}}$. The conversion efficiency of the RF magnetic field was 132 μT/W$^{1/2}$ at the center of the sample space of the unloaded resonator using the trimmer capacitor-based matching network.

(iii) The trimmer capacitor-based tunable resonator with full RF shielding shown in Fig. 1(d) was connected to the 180-degree hybrid. In addition to the semi-open shielding of the resonator described earlier (see also Fig. 1(a)), double-layered aluminum foil (each layer 11 μm thick) was used to fully...
enclose the resonator and the modulation coils in attempt to completely remove the influence of RF noise from the ambient environment on the EPR spectrum. Double-layered aluminum foil was calculated to have a transfer coefficient of $0.8 \times 10^{-3}$ for the RF current (skin depth was estimated to be $3.1 \, \mu m$ at 750 MHz; electrical conductivity of aluminum was set to $36 \, MS/m$). The influence of the RF noise from the ambient environment on the spectral baseline noise level was measured by comparing the noise levels of cases (ii) and (iii) under typical operating conditions; RF power $P_{in} = 5.5 \, mW$.

In addition to the above three cases, the noise figure of the spectrometer excluding the resonator was measured by connecting a 50-ohm dummy load (Mini-Circuits Laboratory Inc., Brooklyn, NY, ANNE-50) to a 180-degree hybrid instead of the resonator. While this setting does not represent a realistic experimental condition in EPR spectroscopy, it permits evaluation of the receiver system noise level of the EPR spectrometer. Measurement parameters for EPR spectroscopy were as follows: duration of field scanning 100 ms, magnetic field scanning 5.0 mT, magnetic field modulation 70 $\mu T$, modulation frequency 90 kHz, time-constant of lock-in amplifier 30 $\mu s$, number of data points per scan 2048, number of scans 100, and incident RF power 5.5 mW (below the saturation level of typical EPR signals). The impact of magnetic field modulation on the spectral baseline noise was evaluated by comparing the noise levels of the case (i) with various amplitudes (0 to 80 $\mu T$) of magnetic field modulation. A two-tailed Student’s t-test was used to compare the mean values of the baseline noise levels. The sample size of each group was 5.

III. RESULTS AND DISCUSSION

A. Impact of the matching varactor diodes on the spectral baseline noise

Figure 4(a) shows representative EPR spectra measured from $^{15}$N-PDT in PBS with and without the varactor diodes in the matching network ($P_{in} = 5.5 \, mW$), (b) the RF power dependency of the baseline noise level for case (i) and (ii), (c) baseline noise level as a function of the amplitude of magnetic field modulation (case (i), $P_{in} = 5.5 \, mW$), (d) RF power dependency of the EPR signal intensity, and (e) the signal-to-noise ratio (SNR), obtained from (b) and (d). In (b), (d), and (e), red closed circles correspond to data for case (i) (varactor-based matching network), and black closed circles correspond to data for case (ii) (trimmer capacitor-based matching network). The data points and error bars represent the mean and standard deviation (SD). The sample size $n$ was 5 in panels (b)–(e).
matching network (case (i) and (ii)) when the incident RF power was 7.4 dBm (5.5 mW). The baseline noise intensity of the spectrum recorded with the resonator using the trimmer capacitor matching network is considerably smaller than that of the spectrum recorded with the resonator using the varactor diodes matching network. Figure 4(b) shows the dependence of the spectral baseline noise on the incident RF power ($P_{\text{in}}$) for case (i) and (ii). Red closed circles represent the baseline noise level in case (i), and black closed circles represent the baseline noise level in case (ii).

The baseline noise level with the varactor-based matching network was observed to increase rapidly beyond an incident RF power of ~10 dBm (0.1 mW), while for the trimmer capacitor-based matching network, the baseline noise level remained low for all incident powers measured. By comparing the baseline noise levels shown in Fig. 4(b), it can be concluded that the increase in the noise level for case (i), beyond the incident RF power of ~10 dBm is dominated by the noise generated by the varactor diodes in the matching network. Hence, we can infer that the noise from the varactor diodes is the primary source of baseline noise in the spectral data acquisition at the incident RF power of 5.9 mW (see Fig. 4(a)). Fig. 4(b) also provides evidence that the baseline noise level is less sensitive to the incident RF power when the trimmer capacitor is used for the matching network. At the incident RF power of 7.4 dBm (5.5 mW), the baseline noise level with the varactor-based matching network was 3.55 in arbitrary units, and that with the trimmer capacitor-based matching network was 0.76; a 4.7-fold improvement.

B. Impact of magnetic field modulation on the spectral baseline noise

Figure 4(c) shows the baseline noise levels of the spectra at different amplitudes of magnetic field modulation ranging from 0 to 80 μT, exhibiting an increase with increasing magnetic field modulation amplitude (52% higher mean noise level at 80 μT compared with the no modulation condition). This increase of the noise level may be explained by considering that at increased magnetic field modulation amplitudes, the tunable resonator is forced to vibrate with an increasing intensity due to the Lorentz force associated with the applied static magnetic field (27 mT) and the current flowing in the Helmholtz coil pair for magnetic field modulation. Since the Helmholtz coil pair was mechanically connected to the supporting structure of the tunable resonator (see Fig. 1), the Lorentz force associated with the Helmholtz coil pair can contribute to mechanical vibrations and instability of the resonator, and hence to the baseline noise of the spectrum.

C. Power-dependence of the signal intensity

Figure 4(d) shows the mean value of the EPR signal intensity ($n = 5$) obtained when using the resonators with and without varactor diodes. The EPR signal of $^{15}$N-PDT was not saturated in the RF power region studied, and the signal intensities in both cases were found to be proportional to the square root of the incident RF power until an input power of 6.9 mW (8.4 dBm). The SD of the signal intensity was very small, and thus error bars were not shown. At an incident RF power of 5.5 mW, the signal intensity measured with the varactor-based matching network, case (i), was 446 in arbitrary units. In contrast, the signal intensity measured with the trimmer capacitor-based matching network, case (ii), was 579 in arbitrary units. This 1.3-fold higher signal intensity can be attributed to the difference in the quality factor of the resonator. The loaded quality factor of the resonator using the varactor-based matching network was 150, and that of the resonator using the trimmer capacitor-based matching network was 214.

D. Overall improvement of the signal-to-noise ratio

Figure 4(e) shows the incident RF power dependence of SNR, derived from the data in Figs. 4(b) and 4(d). Since the baseline noise level was increased for the varactor-based matching network, case (i), the SNR did not increase according to the behavior of the signal intensity. In contrast to case (i), the SNR under the condition of case (ii) increased significantly as the incident RF power was increased. At an incident RF power of 7.4 dBm (5.5 mW), the SNR with the varactor-based matching network was 127, and the SNR with the trimmer capacitor-based matching network was 771; a remarkable overall improvement of 6.1-fold, realized by a 4.7-fold decrease in the baseline noise level and a 1.3-fold increase in the signal intensity.

In our baseline noise measurements, while we did not observe the effects of single-sideband (SSB) phase noise of the RF source, it is prudent to be aware that SSB phase noise can become apparent at high-powers. Indeed, after removal of the noise contribution from the varactor-diodes for the matching network, the effect of the phase noise of the RF source may become the dominant noise source for EPR spectroscopy in high-power regimes. Since the RF source and its frequency are typically fixed in the CW-EPR spectrometer, the resonator is the primary factor that can be further optimized for improvement of the spectrometer to achieve high-sensitivity in vivo EPR spectroscopy and imaging experiments, e.g., of murine tumors. The insights into the noise characteristics of the tunable resonator reported in this study should aid future improvement of the resonator of the EPR spectrometer for in vivo tumor experiments.

E. Influence of the RF noise from the ambient environment

The influence of the RF noise from the ambient environment on the baseline noise level was also investigated. The resonator using the trimmer capacitor-based matching network and full RF shielding of the MCPGR, case (iii) was compared to that with semi-open shielding, case (ii). Figure 5 shows the baseline noise levels obtained under typical EPR spectroscopy measurement conditions ($P_{\text{in}} = 5.5$ mW). The other measurement parameters were the same as given in the Methods (Sec. III C). The data for the baseline noise level measured with the resonator using the varactor-based matching network (case (i), indicated as V) and the trimmer capacitor-based matching network (case (ii), indicated as T) are identical to the data shown in Fig. 4(b). The baseline noise level when the 50-ohm dummy load was connected to the 180-degree hybrid instead of the resonator is also shown as DL in Fig. 5. The baseline noise level of the trimmer capacitor-based resonator combined with full RF shielding, case (iii), is given as T+S. The mean value of the baseline noise level (0.74) for case (iii) was slightly lower than the noise level (0.76) for case (ii), however, this difference was not statistically
diodes for frequency tuning are still a remaining noise source for the matching network (cf. V and T in Fig. 5). However, the varactor by the varactors diodes for frequency tuning on the spectral baseline of the resonator.

13 Thus, the impact of the noise generated by the varactors diodes for frequency tuning on the spectral baseline is considerably smaller than the varactor diodes for the matching network (cf. V and T in Fig. 5). However, the varactor diodes for frequency tuning are still a remaining noise source for the resonator.

The baseline noise level without magnetic field modulation is also shown as V (Mod-) in Fig. 5. The mean value of the no modulation condition was 2.77 in arbitrary units, which is 22% lower than the mean value of the baseline noise level of the varactor-based matching network (V) under the magnetic field modulation amplitude of 70 µT, clearly indicating that magnetic field modulation amplitude makes a significant contribution to baseline noise level. Further investigation of possible remaining noise sources regarding the resonator and magnetic field modulation may lead to additional opportunities for further reduction of the baseline noise level in future studies.

IV. CONCLUSION

In this study, we found that (i) the noise generated within the resonator itself has a significant impact on the baseline noise of the EPR spectrum, (ii) varactor diodes in the matching network were the primary source of the measured spectral baseline noise, and (iii) the noise from the ambient environment had negligible contribution to the spectral baseline noise. By replacing the varactor diodes of the matching network by a trimmer capacitor, the SNR was improved 6.1-fold. These results can be used to guide the design of EPR resonators for optimal SNR in vivo spectroscopy and imaging in the future. Moreover, optimization of the mechanical structure of the Helmholtz coil pair used for magnetic field modulation should lead to further SNR improvements.

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REFERENCES

1 F. Collier, B. Gallego, and B. F. Jordan, Front. Oncol. 7, 10 (2017).
2 O. Thews and A. Riemann, Cancer Metastasis Rev. 1 (2019).
3 B. Epel, M. Kotecha, and H. J. Halpern, J. Magn. Reson. 280, 149 (2017).
4 H. Yasui, S. Matsumoto, N. Devasaheyam, J. P. Munasinghe, R. Choudhuri, K. Saito, S. Subramanian, J. B. Mitchell, and M. C. Krishna, Cancer Res. 70, 6427 (2010).
5 A. A. Gorodetsky, I. A. Kirilyuk, V. V. Khramtsov, and D. A. Komarov, Magn. Reson. Med. 76, 350 (2016).
6 D. A. Komarov, Y. Ichikawa, K. Yamamoto, N. J. Stewart, S. Matsumoto, H. Yasui, I. A. Kirilyuk, V. V. Khramtsov, O. Inanami, and H. Hirata, Anal. Chem. 90, 13938 (2018).
7 G. Feher, “Sensitivity considerations in microwave paramagnetic resonance absorption techniques,” Bell Syst. Tech. J. 36, 449 (1957).
8 W. Froncisz and J. S. Hyde, J. Magn. Reson. 47, 515 (1982).
9 W. L. Hubbell, W. Froncisz, and J. S. Hyde, Rev. Sci. Instrum. 58, 1879 (1987).
10 S. Pfenninger, W. Froncisz, and J. S. Hyde, “Noise analysis of EPR spectrometers with cryogenic microwave preamplifiers,” J. Magn. Reson. Ser. A 113, 32 (1995).
11 H. Suits, A. N. Garraway, and J. B. Miller, “Noise-immune coil for unshielded magnetic resonance measurements,” J. Magn. Reson. 131, 154 (1998).
12 A. Kumar, W. A. Edelstein, and P. A. Bottomley, “Noise figure limits for circular loop MR coils,” Magn. Reson. Med. 61, 1201 (2009).
13 T. Amida, R. Nakaoka, D. A. Komarov, K. Yamamoto, O. Inanami, S. Matsumoto, and H. Hirata, IEEE Trans. Biomed. Eng. 65, 1124 (2018).
14 R. Nakaoka, D. A. Komarov, S. Matsumoto, and H. Hirata, Appl. Magn. Reson. 49, 853 (2018).
15 H. Sato-Akaba, H. Fujii, and H. Hirata, Rev. Sci. Instrum. 79, 123701 (2008).
16 H. Sato-Akaba, Y. Kuwahara, H. Fujii, and H. Hirata, Anal. Chem. 81, 7501 (2009).
17 H. Hirata and Z.-W. Luo, Magn. Reson. Med. 46, 1209 (2001); Erratum, 49, 977 (2003).
18 H. Hirata, T. Kuyama, M. Ono, and Y. Shimoyama, J. Magn. Reson. 164, 233 (2003).
19 W. Froncisz, T. Oles, and J. S. Hyde, Rev. Sci. Instrum. 57, 1095 (1986).
20 P. Lesniewski and J. S. Hyde, Rev. Sci. Instrum. 61, 2248 (1990).
21 J. S. Hyde, M. E. Newton, R. A. Strangeway, T. G. Camenisch, and W. Froncisz, Rev. Sci. Instrum. 62, 2969 (1991).