Journal of Magnetic Resonance 306 (2019) 36–41

Contents lists available at ScienceDirect

Journal of Magnetic Resonance

journal homepage: www.elsevier.com/locate/jmr

Quo vadis EPR?

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ARTICLE INFO

Article history:
Received 18 March 2019
Revised 21 March 2019
Accepted 8 July 2019
Available online 13 July 2019

Keywords:
Miniaturization
Integrative structural biology
Catalysis
Machine learning
Shaped pulses
Rapid scan
Spin dynamics
Dynamical decoupling

ABSTRACT

Complexity of paramagnetic catalysts and materials increases, and the same applies to systems targeted by integrative structural biology. Hence, EPR spectroscopists must find ways to enhance information content of their data. I argue that a third major wave of method development in EPR spectroscopy, which is triggered by recent advances in digital electronics and computing, can achieve this. Transfer of NMR methods to EPR will go on, but part of the new EPR methodology will depend on completely new concepts.

1. Introduction

Electron paramagnetic resonance (EPR) spectroscopy is the most informative technique on the electronic structure of paramagnetic species [1]. For systems with strongly localized electron spin density EPR spectroscopy is also a unique source of information on spatial structure close to the center of spin density. Therefore, EPR spectroscopy is often the method of choice for studying reactions or biological processes that involve free radicals [2] or photoexcited triplet states [3]. It is also a major source of information on paramagnetic transition metal and rare earth ion compounds and complexes, which feature prominently in many catalytic processes [4,5] and in bioenergetics [6,7]. Semiconductor and organic electronics materials [8] may depend on paramagnetic species for their function. Orbital delocalization, which can be probed by electron spins,[9] is related to conductivity of the space or bonding network between them, thus making EPR spectroscopy a tool for obtaining information on molecular mechanisms of conduction.

In conjunction with spin probes and labels, in particular with site-directed spin labeling of proteins [10] and nucleic acids [11], EPR spectroscopy can address problems in molecular biology on length scales beyond the ones accessible by NMR spectroscopy. The technique does not require high structural order, as X-ray diffraction and high-resolution cryo-EM do, and provides higher resolution and information content than small-angle scattering techniques. As compared to fluorescence resonance energy transfer (FRET) pulsed dipolar spectroscopy (PDS) techniques in EPR [12,13] allow for less involved and more reliable access to distance and, in particular, distance distribution information in the nanometer range [14]. On the other hand, PDS techniques usually must be applied at cryogenic temperatures. Information from EPR measurements is thus complementary to the one accessible by other techniques. It is valuable for integrative structural biology approaches to systems that cannot be well described on the basis of data obtained by a single technique [15–17].

The application of EPR spectroscopy is hold back mostly by the complexity of data analysis and by the level of expertise required for identifying the optimal experiment for a given problem. Lack of local expertise leads to underuse of EPR spectroscopy, which in turn leads to the perception that it is not necessary to have local expertise. This vicious cycle can only be broken by developing better tools for data analysis and, finally, data interpretation. Possible ways of doing this will be discussed below.

Many systems of current interest are, in principle, accessible to EPR spectroscopy, but require method development in order to obtain the required information on structure or dynamics. Partially, this is due to lack of sensitivity or resolution. However, after decades of work to improve these, future efforts should also focus on enhancing information content. In many cases, this will require correlation of interactions rather than the mere separation of interactions that was the main focus in previous work.

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https://doi.org/10.1016/j.jmr.2019.07.008
1090-7807/

Past method development in EPR spectroscopy came in two waves. The first of the waves was based on continuous-wave (cw) EPR and electron nuclear resonance (ENDOR) experiments and on the understanding of the spin Hamiltonian of paramagnetic systems and of electron spin relaxation in crystalline solids. Although some notable work in these fields is still done, the wave petered out in the 1970s, leaving in its wake many groups working with established methodology on problems in chemistry, molecular biology, and materials research. The work on pulse EPR started by Mims in the 1960s remained a rather exotic niche throughout the 1970s, with the Novosibirsk group being the only other major player. In the 1980s pulse EPR [18] started the second wave of widespread method development and by about 2000 it had become the main driver for new applications. It can be argued that, in terms of concept development, this wave has petered out around 2010.

So what is next? Are we just incrementally improving our techniques and focusing on extending the application fields? I think not. Several developments in other fields of science and engineering enable a third wave that is just coming up. Around 2010 sampling rate of digital electronics matched and later exceeded the width of common microwave bands. This is highly significant, since excitation bandwidth of monochromatic pulses is much smaller than spectral width for all but a few exotic paramagnetic systems. The newly available bandwidth is by at least one order of magnitude larger [19,20], thus promising new correlation experiments and higher sensitivity. The first experiments with shaped pulses grabbed low-hanging fruit, by either relying on concepts developed for NMR spectroscopy [21] or adapting frequency-swept pulses to the special requirements of EPR spectrometers [22]. However, arbitrary waveform excitation allows for fundamentally different manipulation of multi-level quantum systems, especially in intermediate-coupling regimes that are common in EPR. Furthermore, shaped pulses allow for more than just exciting more spin packets, they provide a means of more precise quantum control [23]. Much knowledge on quantum control has been accumulated in the quest for quantum information processing [24] and is ready to be used in more mundane EPR spectroscopy.

Work in the direction of quantum information processing has focused on reducing decoherence [25], known in magnetic resonance as transverse relaxation. Use of these concepts in EPR spectroscopy promises improved resolution and a range extension in distance measurements based on dipole–dipole interaction [26–28]. Furthermore, better understanding of decoherence due to the surrounding spin bath and of dynamical decoupling may help to characterize the environment of spin labels. Thereby, additional low-resolution information on the structure of proteins and protein complexes could become available.

Another opportunity for method development arises from fast progress in data processing, including but not limited to, machine learning approaches [29]. Processing of time-domain EPR data by Fourier transformation is often not optimal and interpretation of spectra often not as straightforward as in NMR spectroscopy. Modern data processing should, in principle, allow for directly converting time-domain data to the information of interest for an application problem. That way the expertise bottleneck in application work could be removed, at least for the most typical scenarios.

In this paper I discuss open problems in EPR spectroscopy (Section 2), how spectrometers are expected to change in the next decade or so (Section 3), what the open questions are in understanding spin dynamics (Section 4), what new opportunities arise in pulse sequence design (Section 5), and how improved data processing could help to make EPR spectroscopy a more accessible source of information (Section 6). I will focus on developments in measurement and data processing methodology that are likely to impact application work of a large number of laboratories within a decade. Undoubtedly exciting and important fundamental work on completely new concepts will be cited only on occasion and sample preparation issues, such as the quest for spin labels with higher chemical stability and longer decoherence times, will be left out.

2. Open problems in EPR spectroscopy

Despite much progress in the past 75 years, sensitivity of cw EPR spectroscopy is still lacking for a few important applications. Typical scenarios are direct detection of free radicals during chemical reactions and in radical enzymes, spin trapping of radicals at low, but potentially toxic concentrations, and line shape analysis of nitroxide spin labels attached to proteins at physiological protein concentration. Sensitivity is also limiting the application of pulse EPR spectroscopy to spin-labeled proteins in cell or at concentrations that avoid aggregation for aggregation-prone proteins. While concentration sensitivity is most pressing, occasionally only small amounts of material are available and then absolute sensitivity may be lacking. Absolute sensitivity is also an issue for potential coupling of EPR spectroscopy and microfluidics in high-throughput analysis.

Resolution problems in hyperfine spectroscopy are largely solved by high-field ENDOR [30] and by hyperfine sublevel correlation spectroscopy (HYSCORE)[31], especially if the latter technique can be applied in multiple bands, such as X band and Q band. An important open problem in hyperfine spectroscopy is that HYSCORE fails for low transition moments of formally forbidden electron-nuclear transitions, whereas the corresponding time-domain ENDOR experiment HYEND [32] has low sensitivity. Hyperfine spectroscopy is currently most lacking for *moderately-sized* couplings that are not resolved in EPR spectra and lead to very broad and thus low-amplitude cross peaks in HYSCORE. Such hyperfine couplings often occur in catalysts and metalloproteins that feature bonds between metals and main-group elements.

PDS is mostly used for the measurement of distance distributions [12,13]. In this application, resolution in frequency domain corresponds to the upper limit of the accessible distance range. With ever larger systems being targeted in structural biology, resolution needs to be enhanced [33] in order to not lose the advantage of a distance range that matches the dimensions of the studied systems. At the same time, the problem of *moderately-sized* couplings also exists in PDS. Current techniques are limited to point-dipole distances longer than 1.5 to 1.8 nm [34], whereas some systems of interest, such as organic conductors, polarizing agents for dynamic nuclear polarization (DNP), and multi-nuclear metal complexes, may have distances between paramagnetic centers that are shorter. For part of these systems it is insufficient to measure the coupling between electron spins separately from other interactions - rather the relative orientation of the coupling tensor with respect to other anisotropic interactions is of interest [35]. At longer distances, information on correlation between distance distributions is required to fully characterize ensembles of conformations in partially ordered proteins [36].

After more than a decade of research, the problem of automated, reliable conversion of primary PDS data to distance distributions is still not fully solved [37]. Different approaches have been proposed and claims made on their relative reliability that are not yet backed up by a systematic study. While it is generally known what data quality can be trusted, large temptations exist to draw conclusions from data with borderline quality, if only such data can be obtained on a system of great interest. Clearly, limits to such interpretation must be established.

Time-resolved EPR of transient paramagnetic species [38] is hold back by a time resolution of only tens of nanoseconds, which compares unfavorably to optical techniques. Resonator-less

spectrometers [39] and new resonator technology, combined with the high time resolution of excitation waveforms and digitizers available nowadays, could lead to a revival of this field, which has stalled since the turn of the millenium.

Spin dynamics is conceptually well understood for systems consisting of a small number of spins that undergo free evolution or are subjected to a sequence of monochromatic rectangular pulses [18,40,41]. With frequency-modulated pulses, spin dynamics can become more intricate [42,43]. The many-body problem of one spin of interest interacting with a spin bath is still understood only in broad terms, even for sequences of ideal π pulses [44]. This problem is of interest for understanding decoherence of electron spins in the low-temperature limit and polarization flow between electron and nuclear spins in DNP.

For many, if not most recurring data analysis problems in EPR spectroscopy generally accepted protocols are missing. Automated data processing is a rare exception. This concerns such seemingly simple problems as optimal processing of HYSCORE data to a two-dimensional spectrum, as well as more intricate problems, such as interpreting a high-quality HYSCORE spectrum in terms of spin Hamiltonian parameters, where first progress with a neural network approach has been made [45].

3. The future of the EPR spectrometer

Modern cw EPR spectrometers are already based on digital electronics for signal generation and acquisition, wherever this is economical and useful. For narrow spectra up to about 20 mT, rapid-scan technology [46] has become commercially available that can alleviate some of the sensitivity problems mentioned in Section 2. Development of rapid-scan technology for EPR imaging [47] is expected to go on. Miniature EPR spectrometers ("EPR-on-a-chip") can be based on CMOS LC Tank Oscillators [48,49] rather than on common microwave resonators. This opens up new possibilities not only with respect to absolute sensitivity, but also with respect to EPR experiments that can be performed without investing in a high-power amplifier. As the technology is applicable at high frequencies [50], where sample volume is small anyway, losses in concentration sensitivity [51] may not be too dramatic.

Typical widths of EPR spectra in the solid state, where pulse EPR is mostly applied, range from 500 MHz to a few GHz. Microwave components, except for the resonator, typically cover bandwidths from 1 GHz to 4 GHz. For frequency-swept excitation, the resonator characteristics can be largely compensated [22] and dedicated overcoupled resonators with increased bandwidth can be developed [52]. By using high microwave power at high frequencies, pulse EPR experiments can be performed without a resonator [39] and problems due to microwave field inhomogeneity in such setups can be alleviated by composite pulses [53]. Taken together, these findings imply that a high-end pulse EPR spectrometer should have a detection bandwidth of 1 to 2 GHz and an excitation bandwidth of up to 4 GHz [20]. Arbitrary waveform generators (AWGs) with a sampling rate of 12 GSa/s, as they are commercially available since 2011, suffice for signal generation. Sufficiently fast analog–digital-converters have recently come to the market. An AWG including a sequencer replaces almost the complete pulse microwave bridge [20], thus reducing system complexity and inter-device communication as well as improving spectral purity of the excitation. It is thus reasonable to build the spectrometer around the AWG and invest the design effort mainly into a flexible control software that allows for running experiments with any required pulse shape and any variation scheme for delays, amplitudes, phases, and magnetic field. Such a concept supports, for instance, fast non-uniform sampling or correlated variation of field and frequency. Any excitation scheme within the supported bandwidth becomes feasible, which enables spin control schemes previously accessible in NMR, but not EPR spectroscopy. Future spectrometers should allow for defining an EPR experiment in very broad terms and should then be able to derive the waveform sequence, range and increment of variable parameters, and necessary steps of signal processing and data-to-information conversion automatically. The user should supervise and correct the spectrometer, rather than having to program it. This will probably take more than a decade to develop.

Cost of an EPR spectrometer is a matter of concern for wider application and a magnet with high homogeneity contributes a substantial part of this cost. A spectrometer dedicated to pulsed dipolar spectroscopy does not require high field homogeneity and could be built around a smaller and cheaper magnet.

While several other detection modalities for EPR have been tested and can provide high absolute sensitivity, inductively detected EPR is most versatile for spectroscopic applications [54]. It has been argued that, by reducing thermal noise from the resonator and from the first amplifier, a few tens of spins can be inductively detected at 10 K [55]. Since many samples cannot be measured at such low temperatures, cryoprobes that could measure a higher-temperature sample appear attractive for sensitivity enhancement. Inductively detected EPR in the quantum limit has been demonstrated at very low temperatures with a superconducting resonator [56]. Although the current realization is applicable to only a narrow range of systems, this approach may have the potential to provide a step change in sensitivity that would make EPR applicable to systems that currently cannot be accessed.

4. Understanding spin dynamics

4.1. Control of coupled spin systems

In many paramagnetic spin systems, at least one coupling term in the high-field basis spin Hamiltonian has off-diagonal elements that connect levels with a splitting not much larger than these elements. Thus, formally forbidden transitions become allowed and give rise to complicated spin dynamics during frequency-modulated pulses [43]. To date, this has been considered mainly as a nuisance that causes magnetization loss and phase errors. If the effects were better understood, they could be used to effect magnetization transfer. This may give rise to a new family of pulse EPR correlation experiments or could be useful for polarization transfer from electron spins to nuclear spins. Application of such schemes may transcend EPR spectroscopy, as some of them would be DNP methods. For their development pulsed EPR experiments may be very useful, as they access a time scale different from the one of NMR and have high sensitivity even if the polarization transfer to nuclear spins is not yet optimized.

4.2. Spin bath behavior

In the low-temperature limit, usually below 40–50 K, electron spin decoherence is dominated at sufficiently low concentration by hyperfine field fluctuations that stem from nuclear spin diffusion. The effect can be partially suppressed by a Carr-Purcell sequence or other dynamical decoupling sequences [25], thus prolonging the observation time and improving resolution [26,27]. The underlying spin dynamics is a many-body problem and is understood only in broad terms, with hierarchical cluster models allowing for an approximate numerical treatment [44], especially for crystalline materials, where the spatial arrangement of the nuclear spins around an electron spin is known. The same type of spin dynamics underlies the spread of nuclear polarization in DNP experiments. In most applications, including DNP, samples are

not crystalline but rather glassy. Dynamical decoupling is effective in glassy solids at low temperatures, but only partially understood [57]. Both resolution enhancement in pulse EPR and optimization of solid-state DNP would profit from better understanding of this problem.

5. New vistas in EPR pulse sequence development

As compared to NMR spectroscopy, EPR spectroscopy operates with a rather small set of pulse sequences. The main reason is that each additional pulse leads to magnetization loss due to lack of bandwidth and unintended excitation of formally forbidden transitions. For a long time, lower versatility and precision of microwave excitation further hampered pulse sequence development. Modern AWG technology has solved the versatility and precision problems, although some obstacles remain. Either a resonator is used, which then limits waveform bandwidth or, at high frequencies where sensitivity without a resonator can be high [39], the microwave field is very inhomogeneous across the sample [53]. Working at high frequencies has the advantage that for many systems, albeit not for nitroxide spin labels, forbidden transitions are then indeed forbidden. In hyperfine spectroscopy and DNP, one may want to enhance such forbidden transitions by new excitation schemes.

With the notable exceptions of electron spin echo envelope modulation (ESEEM) [58] and relaxation-induced dipolar modulation enhancement (RIDME) [59], most pulse EPR methods were either copied from NMR or reinvented. I expect this to change in the future for the following reason. Interactions in EPR often exceed the bandwidth of the shortest available monochromatic rectangular pulses, but not anymore the bandwidth of an AWG spectrometer. While it may be possible to proceed by analogy to heteronuclear NMR sequences, this will not necessarily lead to optimal experiments. This is because in EPR anisotropies of several interactions are often of the same order of magnitude. Therefore, the different spin types do not have disjoint spectral ranges, as is the case in heteronuclear NMR. That said, multi-pulse schemes developed in solid-state NMR before the advent of magic-angle sample spinning [60], whose concepts have recently met new interest, [61] may have some potential in EPR, now that spectrometer hardware can support them.

6. Advanced data processing

New spectrometer hardware in principle enables non-uniform sampling in EPR, which has been previously shown by simulations to be advantageous for the widely used HYSCORE experiment [62,63]. Further work will be required to assess reliability and the sensitivity advantage. Denoising techniques have been tested [64,65]. Before they can be considered as reliable, open accessible software and a protocol for its use need to be developed. For the long-standing problem of processing PDS data, global fitting of multi-Gaussian models [66], global Tikhonov regularization [67], better estimators for the Tikhonov regularization parameter [68], alternative regularization techniques [69], and neural network processing (machine learning) [29] have been suggested and are all available in open-source packages. This bewildering zoo may require some signposts, lest visitors get lost. Especially for scientists using PDS in application work without being involved in method development, robust and reliable processing protocols need to be established. Only that way they can benefit from recent improvements in data processing without being fooled or fooling themselves.

In fact, broader use of EPR spectroscopy may depend on development of data processing protocols for other recurring application scenarios. It is probably unrealistic, except for simple analytical tasks, to achieve push-button access for laymen, but it would already help a lot if existing EPR groups could offer a broader portfolio for collaboration in their universities. Nowadays, experiment setup on a new-generation spectrometer, data processing, and, in some cases, even analysis of the spectra could be largely automated. The difficulty lies in identifying which scenarios occur sufficiently often to justify the effort. Furthermore, scenarios must be defined broadly enough for the protocol to be widely applicable, without defining them so broadly that development effort becomes prohibitive.

Machine learning can solve inverse problems in signal processing and spectrum interpretation if simulation of data for the forward problem is possible [29,45]. This is very often the case and good software packages for training and processing exist. The main problem is the lack of an uncertainty estimate, which can be partially relieved by running the computation on a set of similarly trained networks [29]. However, this approach does not necessarily guard against wrong answers for cases not covered by the training sets. The problems of defining a sufficiently broad training set and of obtaining a reliable error estimate will probably need to be solved individually for each particular application scenario. Such an endeavor profits from having an alternative, more robust data processing approach for the same scenario, wherever this is possible.

Data-to-information processing will profit from fast spin dynamics simulations [70–72] and will require open-accessible EPR databases.

7. Conclusions

There is plenty of room for further method development in EPR. Advances are limited by the number of research groups and by funding opportunities for method development rather than by maturity of the field. Complexity of application problems in catalysis, materials science, and integrative structural biology is increasing. Therefore, the focus of method development may shift from sensitivity and resolution enhancement towards obtaining more information from a given sample. That said, hardware development and better understanding of spin bath behavior create some opportunities for increasing sensitivity and resolution that should not be foregone. The third wave of major developments in EPR spectroscopy is mainly driven by two trends: First, the speed of digital electronics has recently passed the width of EPR spectra and, second, advances in computing allow us to tackle problems whose data processing component could previously not be implemented. We can expect that the ways how EPR data are measured and processed will change profoundly during the next decade.

Acknowledgements

This manuscript has profited strongly from talks with many EPR and NMR scientists at conferences during the past few years. Specific ideas resulted from work with Frédéric Allain, Frauke Breitgoff, Christophe Copéret, Andrin Doll, Christoph Gmeiner, Luis Fábregas Ibáñez, Daniel Klose, Ilya Kuprov, Claire Motion, Yevhen Polyhach, Stephan Pribitzer, Janne Soetbeer, Stefan Stoll, Nino Wili, and Maxim Yulikov. I am grateful to an anonymous reviewer for suggesting a few important points.

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