Magnetic Resonance – from spectroscopic tools to practical technological devices

Aharon Blank
Schulich Faculty of Chemistry, Technion- Israel Institute of Technology, 3200003, Haifa, Israel

Email: ab359@technion.ac.il

Abstract:

Magnetic resonance, a well-established field, has historically been utilized primarily in spectroscopy and medical imaging. From its inception, it has also underpinned practical technological devices, including microwave sources and amplifiers. This trend persists today, with ongoing technological advancements in magnetic resonance enhancing its applications in both spectroscopy and medicine. Furthermore, these advancements facilitate the development of innovative devices and instruments, such as sensitive sensors, advanced amplifiers, and tools for quantum computing. In this brief review, I will focus on the recent developments emerging from the magnetic resonance laboratory at the Technion. These advancements are not only enhancing the spectroscopic applications of magnetic resonance but are also leading to the creation of novel microwave devices.

1. Introduction

Magnetic resonance is a pivotal technique in both spectroscopy and medical imaging, offering profound insights into molecular structures and human anatomy. In spectroscopy, magnetic resonance manifests primarily as nuclear magnetic resonance (NMR) spectroscopy and electron spin resonance (ESR) spectroscopy. NMR spectroscopy exploits the magnetic properties of certain atomic nuclei, which absorb and re-emit electromagnetic radiation at characteristic frequencies when subjected to a strong magnetic field. This process provides detailed information about molecular structure, dynamics, reaction states, and chemical environments. NMR is invaluable in various fields such as organic chemistry, biochemistry, and material science. In addition to NMR, ESR spectroscopy (also known as electron paramagnetic resonance, EPR) is another vital application of magnetic resonance. ESR is used to study materials and molecules that contain unpaired electrons, which occur in various systems, including transition metal complexes, free radicals, and defects in solid materials. By analyzing the interaction of these unpaired electrons with a magnetic field, ESR provides insights into the electronic structure, local environment, and dynamics of these species. This makes ESR an essential tool for investigating reaction mechanisms in chemistry, studying the properties of conductive and magnetic materials in physics, and deciphering molecular structure and understanding the behavior of free radicals in biological systems.

Magnetic resonance is also valuable tool in the context medical diagnostics, primarily known for magnetic resonance imaging (MRI). MRI focuses on the hydrogen nuclei in water and fat molecules within the body to produce detailed images without ionizing radiation. This non-invasive technique

Aharon Blank is a full professor at the Schulich Faculty of Chemistry, Technion – Israel Institute of Technology. He was born in 1972, and graduated from the Hebrew University of Jerusalem in 1992 with degrees in mathematics, physics and chemistry (cum laude). He completed his master's degree at Tel Aviv University in 1997 in electrical engineering – physical electronics under the supervision of Prof. Raphael Kastner and finished his PhD in 2002 at the Hebrew University of Jerusalem in physical chemistry – electron spin resonance (ESR), under the supervision of the late Prof. Haim Levanon. During the years 1992–1998, he served at the Israeli Air Force (IAF) as a scientific officer. Following that he was the CTO in a medical device company (TopSpin Medical), developing miniature intravascular MRI. After his PhD, he spent 3 years at Cornell University (2002–2005) as a postdoc in the group of Prof. Jack Freed (on a Rothschild post-doctoral fellowship), developing the subject of electron spin resonance microscopy, and since 2005 he is a faculty member at the Technion. He is the recipient of the 2022 ICS–Adama Prize for Technological Innovation.

is particularly effective for soft tissue imaging, aiding in diagnosing various conditions, planning treatments, and tracking disease progression.

NMR spectroscopy, ESR spectroscopy, and MRI are all applications of magnetic resonance, each serving distinct purposes: NMR and ESR in molecular-level analysis in various scientific fields, and MRI in detailed, non-invasive medical imaging and diagnostics.

Magnetic resonance has also found practical applications in a variety of technological devices, extending its influence beyond the realms of spectroscopy and medical imaging. Two notable examples of such applications are masers and yttrium iron garnet (YIG) microwave sources. Masers, which stand for "Microwave Amplification by Stimulated Emission of Radiation," are devices that amplify microwave radiation through the principle of stimulated emission. Many of the first masers, built in 1950's, used the electron spins in paramagnetic species. When these spins are aligned in a magnetic field, their energy levels are typically separated by microwave frequency (~1-10 GHz), and can be made to have population inversion (more spins in the upper energy than in the lower one). Under these conditions, small incoming microwave radiation will be amplified by the stimulated emission of the spins. This principle has since been applied in various contexts, such as ultra-precise atomic clocks and deep-space communication systems. Masers serve as the predecessors to lasers and operate on similar principles but at microwave frequencies. Yttrium iron garnet (YIG) microwave sources are another application of magnetic resonance. YIG is a ferrimagnetic material and exhibits a strong magnetic resonance effect. When a YIG sphere is placed in a magnetic field, it can resonate with microwave radiation at a frequency dependent on the strength of the magnetic field. This property makes YIG an excellent frequency-tuning element for microwave oscillators and filters. YIG-tuned oscillators are used in radar systems, electronic warfare, and signal processing, where precise control of microwave frequencies is essential. The ability to adjust the magnetic field allows for a wide range of frequency tuning, making YIG devices incredibly versatile.

Both masers and YIG microwave sources demonstrate the adaptability of magnetic resonance principles in creating practical, high-performance technological devices. Masers leverage magnetic resonance for signal amplification, while YIG devices utilize it for frequency tuning in microwave technology. These applications showcase the broad potential of magnetic resonance beyond its traditional scientific uses, contributing significantly to advancements in communication, navigation, and electronic systems.

2. Scope of activity

The magnetic resonance (MR) laboratory at the Technion operates over the broad range of scientific and technical fields described above. These activities include:

- Improving the spectroscopic capabilities of MR by primarily providing more sensitive detection, which enables the measurements of smaller samples.
- Providing better spectral resolution for unique type of MR techniques, thus providing better molecular structure information.
- Enabling new capabilities for MRI by enhancing the NMR signal of some specific metabolites of interest.
- Developing and testing new microwave devices for sensitive detection of microwave signals.

In this short review we will describe some of our activities in relation to the abovementioned items, thereby providing an overview of how advanced MR spectroscopic capabilities can evolve to realize practical unique microwave devices.

3. Results

3.1 Improving the sensitivity and spectroscopic capabilities of MR

One line of action we recently took with respect to improving the spectroscopic capabilities of MR is to enable the detection of liquid samples in microfluidics systems with ESR. Microfluidics is a well-established technique to synthesize, process, and analyze small amounts of materials for chemical, biological, medical, and environmental applications. Typically, it involves the use of reagents with a volume smaller than ~1 microliter—ideally even nano- or picoliters. When the sample of interest contains paramagnetic species, it can in principle be quantified and analyzed by ESR spectroscopy. However, conventional ESR is typically carried out with a sample volume of ~1 ml, thereby making it incompatible with most microfluidics applications. In a recent work, we showed that by using a new class of miniature surface resonators combined with photolithography to prepare microfluidic patterns, ESR can be applied to measure small liquid samples, down to picoliter volumes, without considerable sacrifice of concentration sensitivity [1]. Our experiments, carried out with resonators whose mode volumes range from ~1 to 3.6 nL, showed that with a sample volume of ~0.25 nL good signals could be obtained from solutions with spin concentrations of less than 0.1 μM. All our experiments are performed at room temperature, making our technique compatible with future microfluidics applications that might employ a complete system of compact resonators, microfluidic chips, miniature magnets, and a compact ESR-on-a-chip spectrometer. This could result in a completely new approach to processing and measuring paramagnetic liquid samples for use in a

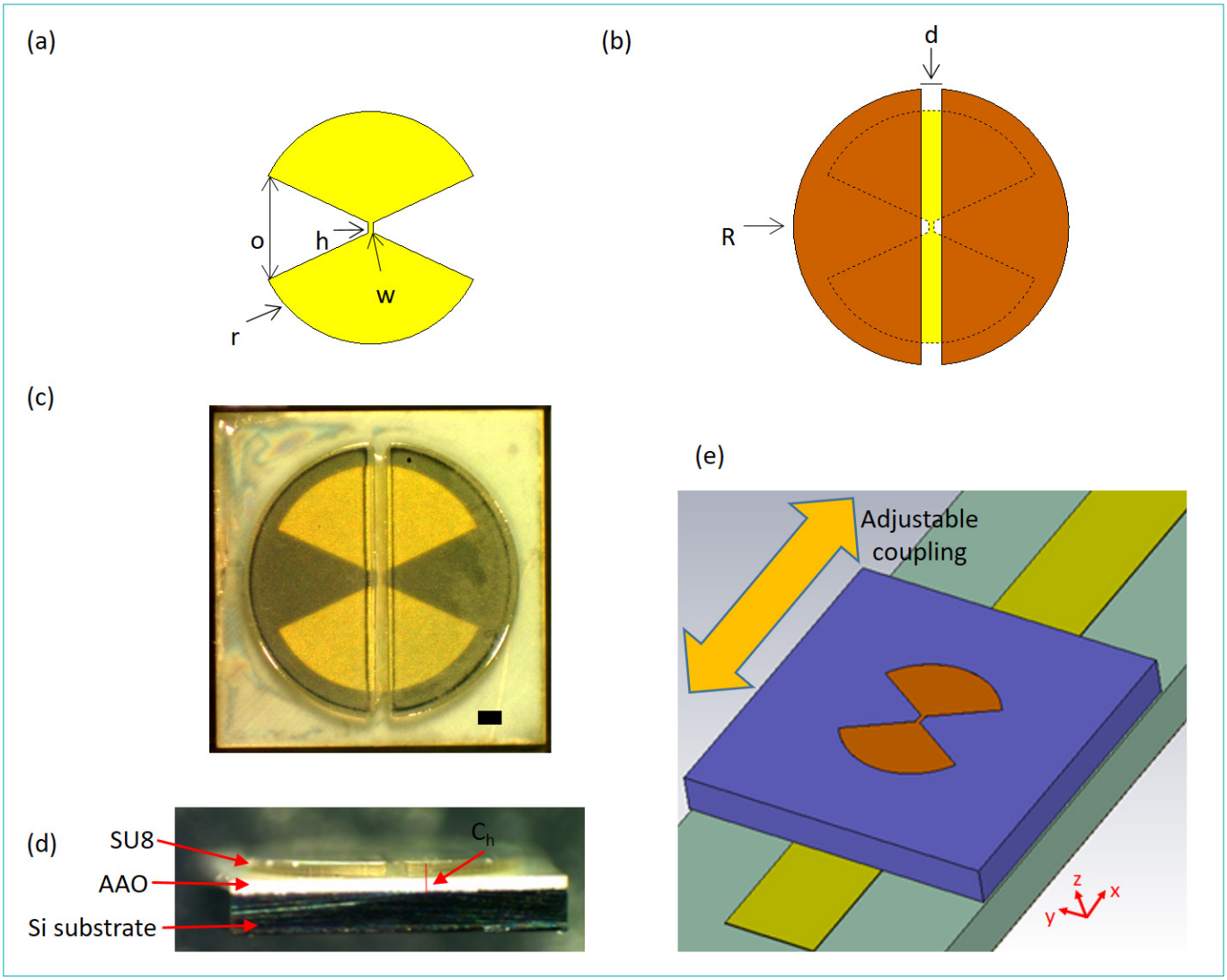

Figure 1. Microfluidics system with ESR detection. (a) Schemes of a miniature ESR resonator (yellow) and **(b)** the microfluidic channel placed on it (brown). The resonator is realized with a Ti(10 nm)/Cu(500 nm)/Au(10 nm) metallic layer on a single crystal of intrinsic silicon measuring 1.6×1.6×0.2 mm. **(c)** and **(d)** show images of the fabricated resonator with an anodic aluminum oxide (AAO) wafer and a microfluidic channel implemented on its surface. The AAO wafer minimizes sample dehydration. **(c)** Top view (scale bar is 100 mm). **(d)** Side view. **(e)** Coupling of the resonator to microwave is achieved via a thin microstrip line mechanically placed exactly below the resonator's central bridge (the narrow part of the resonator). Coupling is adjusted by moving the resonator along the x-axis of the microstrip (orange arrow in the figure). In this position, magnetic inductive coupling is maximal between the microstrip and the bridge.

variety of chemical, biological, medical, and environmental applications.

Figure 1 shows the microfluids ESR system we developed. It includes a miniature resonator for concentrating the microwave magnetic field used to excite the electron spins and detect the ESR signal of the small liquid sample placed on it. The liquid sample is confined to flow in a narrow (~ 50 μm) channel at the center of the resonator. This system was tested with a test sample of liquid free radical solution (trityl radical, 0.83 mM concentration) and demonstrated absolute spin sensitivity of up to ~5.2×10^6 spins/√Hz and concentration sensitivity as good as 0.03 μM/√Hz.

3.2 Improving the spectral resolution of MR

As noted above, nuclear magnetic resonance (NMR) spectroscopy provides atomic-level molecular structural information. However, in molecules containing unpaired electron spins, some NMR signals, for nuclei close to the electron spins, are difficult to measure directly. In such

cases, data is obtained using the electron-nuclear double resonance (ENDOR) method, where nuclei are detected through their interaction with the nearby unpaired electron spins. Unfortunately, electron spins spread the ENDOR signals, which challenges current acquisition techniques, often resulting in low spectral resolution that provides limited structural details. In a recent work, we showed that by using miniature microwave resonators to detect a small number of electron spins, integrated with miniature NMR coils, one can excite and detect a wide bandwidth of ENDOR data using a single radiofrequency pulse (called "time-domain ENDOR") [2]. This facilitates the measurement of ENDOR spectra with narrow lines spread over a large frequency range at much better spectral resolution than conventional approaches, which helps reveal details of the paramagnetic molecules' chemical structure that were not accessible before.

Figure 2 shows the unique setup we developed with the micro-ESR resonator and the corresponding micro-NMR coil. Figure 3 compares the NMR spectral data for a test sample of γ-irradiated single crystal of malonic acid, showing the enhanced resolution obtained with our new setup and methodology.

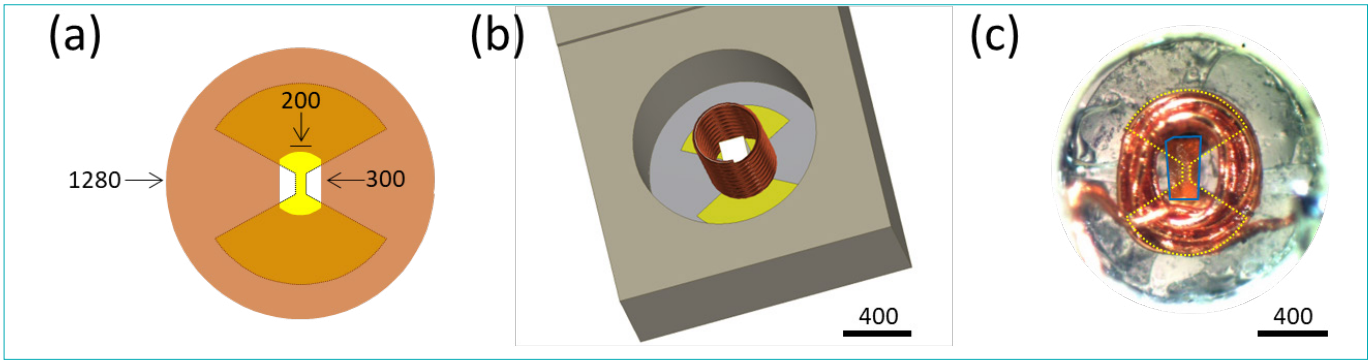

Figure 2. A miniature ESR resonator with an ENDOR coil placed on it. (a) Drawing of the resonator with a 25-μm-thick sample-positioning well placed on top. **(b)** Illustration of the resonator (with a sample and RF coil) attached to a sample holding stick (gray). **(c)** A micrograph of the resonator with a photolithographic well, an RF coil, and a test sample mounted inside the well (emphasized by the blue line). The yellow dotted line shows the metallic resonator layout positioned under the RF coil. All dimensions are in microns.

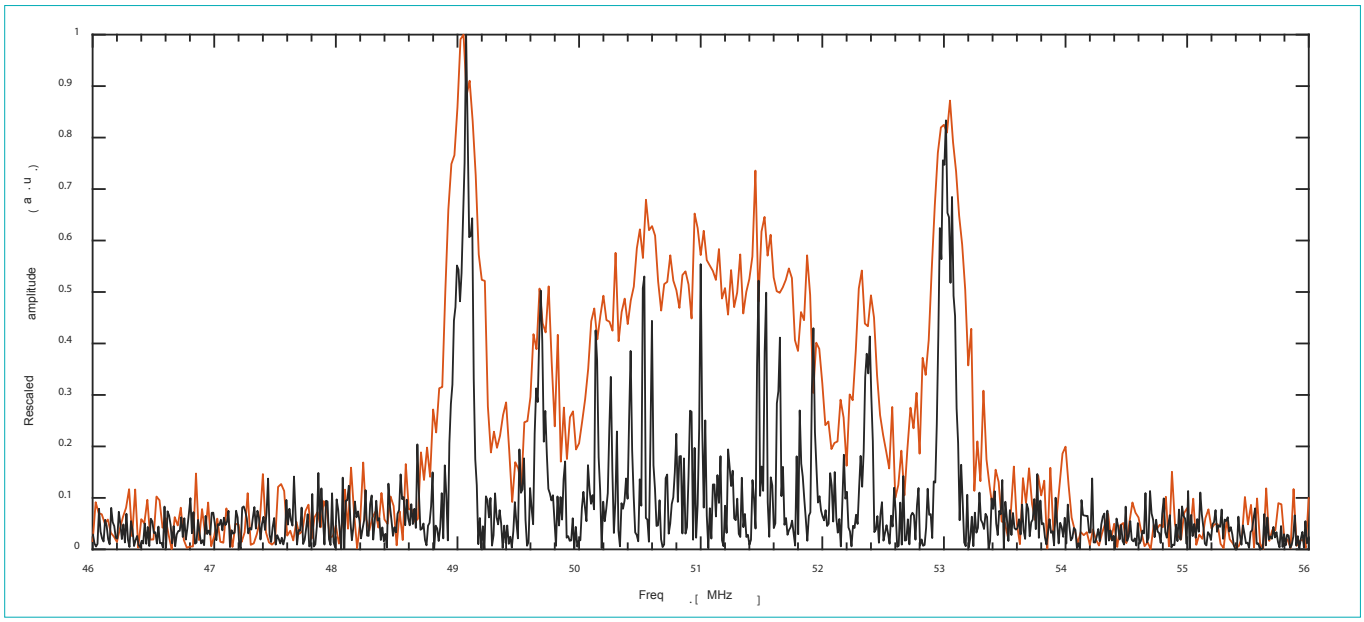

Figure 3. Comparison of Davies and time-domain ENDOR measurements for an irradiated malonic acid single crystal. Fourier transform of the time-domain ENDOR signal collected around 51 MHz (solid black line), and Davies ENDOR frequency sweep, acquired with a 40-μs RF pulse and 25-kHz frequency steps (solid orange line).

3.3 Enhancing the NMR signal of metabolites of interest and maintaining it for a long period of time

Non-invasive tracking of biochemical processes in the body is paramount for diagnostic medicine. Among the leading techniques is spectroscopic magnetic resonance imaging (MRI) that tracks metabolites with amplified (hyperpolarized) magnetization signal. Clinical imaging with such hyperpolarized metabolites can detect chemically specific tissue signatures through nuclear magnetic resonance (NMR) spectroscopy. It merges MRI's superior soft tissue contrast and spatial resolution with improvement in specificity by amplifying the magnetization of targeted metabolites introduced to the subject just before scanning.

Until now, the short-lived magnetization window of these magnetization-enhanced agents has generally been too brief for clinical imaging. In our recent work, we offer a possible solution to this problem [paper in preparation]. By amalgamating two materials – one possessing diagnostic/metabolic activity and the other characterized by robust magnetization retention, we can significantly slow the magnetization decay of the diagnostic metabolic probe. The probe continuously receives fresh magnetization from its companion material, effectively creating a magnetization vehicle for clinical practice. The resulting magnetization lifetime is found to be in some cases more than 10 minutes long, with magnetization enhancement factors of more than four orders of magnitude. These diagnostic probes could retain their magnetized state from the time of injection until they reach the organ of interest. Once validated, this innovative metabolic MRI approach could have numerous impactful applications for human clinical imaging. Its potential spans the fields of diagnostic imaging, therapeutic monitoring, and surveillance after treatment.

Figure 4 shows an example from our recent results. In this experiment we prepared a sample of glycine co-crystalized with $CaCO_3$. This sample was then subjected to γ-irradiation which generated stable paramagnetic defects in the crystal. These defects have unpaired electrons, which can be used to transfer their high magnetization to nearby nuclei under specific conditions of low temperature (~1.5 K), static magnetic field of ~6 T and microwave irradiation. Once this magnetization transfer was complete, we took out the sample from the device and measured its signal relaxation time, which proved to be more than 4 minutes (Figure 4 – left). This is much longer than the few tens of seconds at most found for solid glycine at normal conditions. The reason for this extra-long magnetization lifetime is the fact that the accompanying crystal, $CaCO_3$, has a long intrinsic magnetization lifetime and it can keep replenishing the lost magnetization of the glycine. After the measurement of the lifetime of the magnetization in the solid state, we dissolved the glycine-$CaCO_3$ crystallites in acidic water and measured their NMR signal, which showed enhancement of a few tens of thousands compared to the regular thermal signal of dissolved glycine (Figure 4 – right).

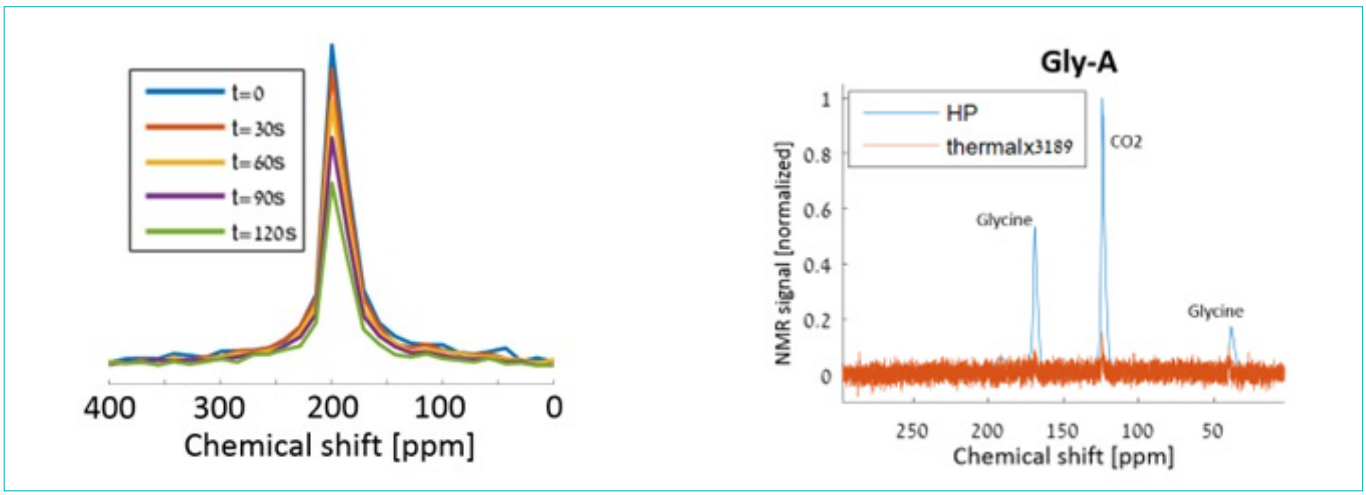

Figure 4. Hyperpolarization experiments for glycine in $CaCO_3$. (left) ^{13}C NMR signals acquired for the solid-state sample in the spectrometer immediately after shuttling of the sample from the polarizer to the spectrometer. The acquisitions take place 30 s apart and employ a ~10 degree tip angle. (right) Hyperpolarized spectra shortly after dissolution vs. thermal spectra. The data demonstrates the preservation of hyperpolarization in ambient conditions and the enhancement factors that remain available in the liquid state after a considerable time interval. Thermal signal was averaged over 3189 scans representing an enhancement of up to ~10,000 (depending on the spectral peak chosen).

3.4 New microwave devices for sensitive detection of microwave signals

Up to this point in our story, magnetic resonance was used only as an observation tool – mainly seeking spectroscopic information that is vital for chemical and biological analysis, as well as improving medical diagnostics. In this part, however, we see that magnetic resonance can be used to construct actual practical technological devices – namely, ultra-low noise microwave amplifiers.

The technology for amplification and detection of microwave (MW) signals with minimal addition of noise is critical to a variety of applications, such as deep-space communications, radio astronomy, radar, microwave spectroscopy, and quantum technology (e.g., quantum computing, quantum sensing, and quantum communication). In these applications, the signal of relevance is very weak, sometimes at the level of tens to hundreds of MW photons per second. Therefore, any noise added to the signal during the amplification process might overwhelm it and eliminate the possibility of detecting it within a reasonable averaging time. Currently, three main types of amplifiers are used to amplify and subsequently possibly detect MW signals with very low addition of noise. (a) Conventional electronic amplifiers, predominantly based on high-electron-mobility transistor (HEMT) semiconductor technology. They optimally operate at ~5 K or below and add ~10 noise photons to the signal in 1 second for 1 Hz bandwidth [3]. (The number of noise photons per second is linear with the acquisition bandwidth.) (b) Amplifiers based on superconducting circuits. These include the families of SQUIDs (superconducting quantum interference devices) based amplifiers, radio frequency (RF) single electron transistors, and quantum Josephson parametric amplifiers [4], as well as the more recent Josephson traveling-wave parametric amplifier [5] and kinetic inductance parametric amplifiers [6]. Such amplifiers typically operate at ~10–25 mK and make use of a variety of nonlinear phenomena occurring in superconductors to amplify microwave signals with quantum-limited noise performance (e.g., adding 0.5 photons of noise per second for 1 Hz of bandwidth). (c) Solid-state maser (microwave amplification by stimulated emission of radiation) devices. These amplifiers rely on paramagnetic species, mainly ions embedded in a crystal such as ruby (Cr^{3+} in a crystal of Al_2O_3). Under an external static magnetic field, the paramagnetic species in the solid-state maser have at least three energy levels for their unpaired electrons (Figures 5a, b). One can use microwave pumping to reach a state of population inversion in which there are more electrons in a higher energy level than in a lower one. Under such conditions, incoming microwave radiation causes the stimulated emission of additional microwave radiation – namely, the amplification of the incoming signals. Solid-state masers operate efficiently only at low temperatures (~1 K) and typically add a few photons of noise to the signal per second for 1 Hz bandwidth [7].

Until now, maser technology, developed in the 1950s and 1960s, was used mainly in niche yet important applications in space communication and radio astronomy. (For example, detection of the black body radiation of the universe, remnant of the "Big bang".) At present, it has been mostly abandoned in favor of the conventional electronic amplifiers mentioned above due to its complicated implementation, requirement for low operation temperature, and limited bandwidth/gain performance.

With the rising age of quantum technology, new scientific and technological endeavors are coming into play, requiring amplification of very weak MW signals with quantum-noise limited performance for applications ranging from the read-out of quantum bits [8] to dark matter detection [9]. These needs can currently be met only by the superconducting-based amplifier technology mentioned above, which necessitates the use of ultra-low cryogenic temperatures that make its operation very complicated and limited in scope. Clearly, it would be very beneficial to have a complementary technology for quantum-noise-limited microwave amplifiers that could be operated at much higher temperatures, even at room temperature.

In a recent work, we demonstrated the operation of such an amplifier, based on maser technology that, when optimized, could be used to amplify weak microwave signals at moderate cryogenic temperatures (~ 10 K) with quantum limited noise performance [10]. Our device is based on a new type of active maser material – namely, single crystal diamond with high concentration of color defects in it. These defects, called NV (nitrogen-vacancy) centers, are made of nitrogen that substitutes one of the carbons in the diamond lattice with a missing carbon (vacancy) near it (Figure 5c). The negatively-charged defect is paramagnetic, with 2 unpaired electron spins. Under the influence of a static magnetic field, its ground state splits into three energy levels and at this point light illumination can be added to pump the spin states to the central level (Figure 5d). The resulting population inversion state can be used for low noise microwave amplification.

Figure 6a shows a photo of the maser device, when one of its bounding walls is removed. A green LED light illuminates the diamonds that are situated inside a specially-designed microwave cavity. As noted above, the light pumps the energy levels of the NVs in the diamond to their inverted spin state (Figure 5d) so that incoming irradiation can be amplified. Figure 6b presents the gain of the maser device vs. input frequency, for various input power levels, at a temperature

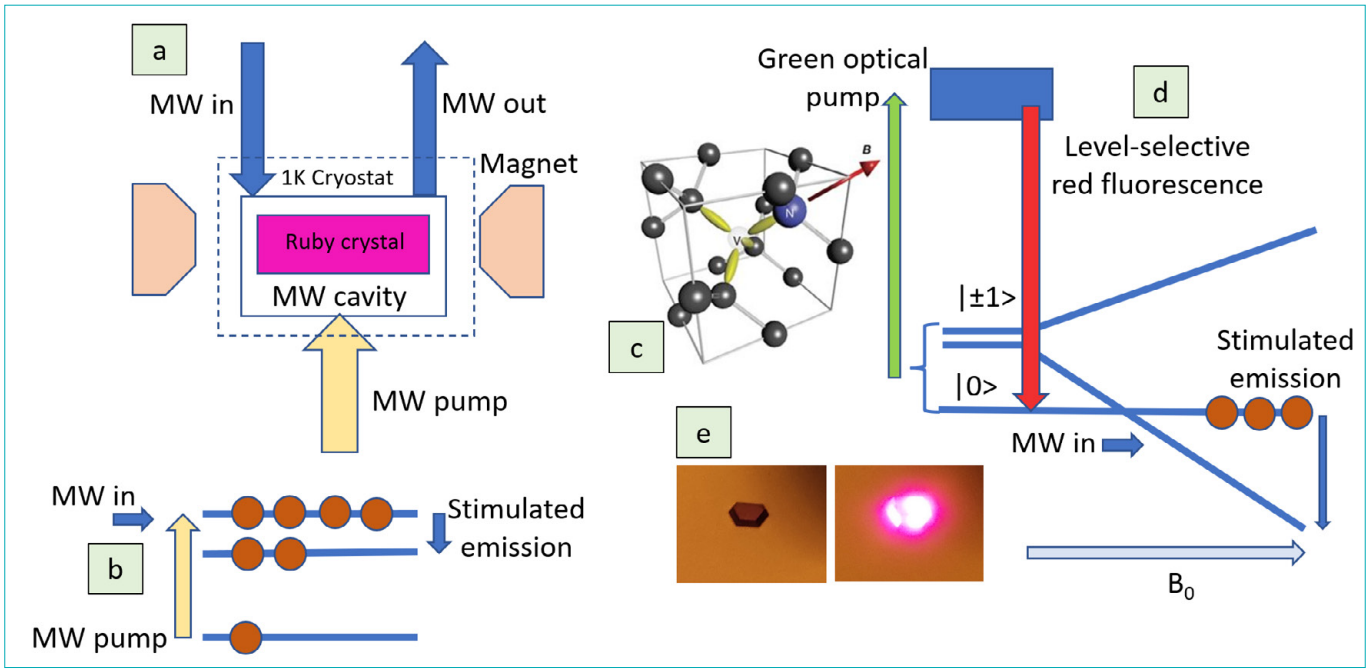

Figure 5. Conventional solid-state maser as compared to diamond-based maser. (a) Schematic overview of a conventional solid-state maser employing a ruby single crystal embedded in a microwave (μw) cavity and subjected to a static magnetic field. **(b)** The relevant three energy levels of a typical solid-state maser. The separation between levels is dictated by the strength of the static magnetic field. Microwave radiation is used to create population inversion, enabling stimulated emission also in the μw regime (albeit for lower energy than the pumped one). This type of maser can operate only at a temperature of ~1 K or below; at higher temperatures, all the levels are almost equally populated, and the spin-lattice relaxation time, T_1, becomes too short. **(c)** The structure of a nitrogen-vacancy (NV) color defect in a diamond crystal, with spin S = 1. **(d)** The three Zeeman levels of NV- ground state. At zero magnetic field, the $m_s = 0$ level (|0>) is situated below the two degenerate $m_s = \pm 1$ levels. When subjected to green light, it undergoes red fluorescence with other non-radiative transitions leading to enhanced population of the |0> state. By applying a static magnetic field, one obtains population inversion between the |0> and |-1> states. In contrast to conventional solid-state masers, the selective population mechanism performs well also at room temperature. The spin temperature is given by: $T_s \approx (\hbar\omega_0/2k_B)(N/\Delta n)$, where ω_0 is the transition frequency, N is the number of spins and Δn is the level population difference. For Δn→ N the spin temperature approaches ~ 0 K. **(e)** Photo of a synthetic diamond crystal processed in by our lab with many NVs.

of 30 K. The maser's small signal (< -90-dBm input) gain reaches more than 20 dB at 30 K. The bandwidth is ~0.5 MHz for the high gain at 30 K and increases up to ~5 MHz for the small gain at high input power. Overall, the voltage gain × bandwidth is found to be ~5.8 ± 0.5 MHz for all power levels at 30 K.

4. Summary and conclusions

Magnetic resonance stands as one of the most adaptable fields in science, with its applications spanning from the determination of chemical structures to medical imaging and quantum information processing. This technique's multidisciplinary nature draws researchers from diverse domains, including natural and life sciences, as well as engineering. From a scientific perspective, magnetic resonance has been a focal point for at least seven Nobel Prizes across physics, chemistry, and medicine to date. Industrially, it represents a multibillion-dollar sector targeting a broad spectrum of medical and chemical applications.

In this concise review, we have observed that despite magnetic resonance being discovered nearly 70 years ago, and magnetic resonance imaging (MRI) being over 40 years old, the field still harbors significant potential for innovation in methodologies, approaches, and applications. These innovations include novel methods to enhance the sensitivity and spectral resolution of magnetic resonance, advancements in MRI's ability to provide chemical insights from within the body, and the development of new technical devices based on magnetic resonance principles. These ongoing developments ensure that the field remains dynamic. We believe it will continue to evolve, rejuvenating itself and offering surprising resolutions and solutions to contemporary challenges in science, technology, and medicine.

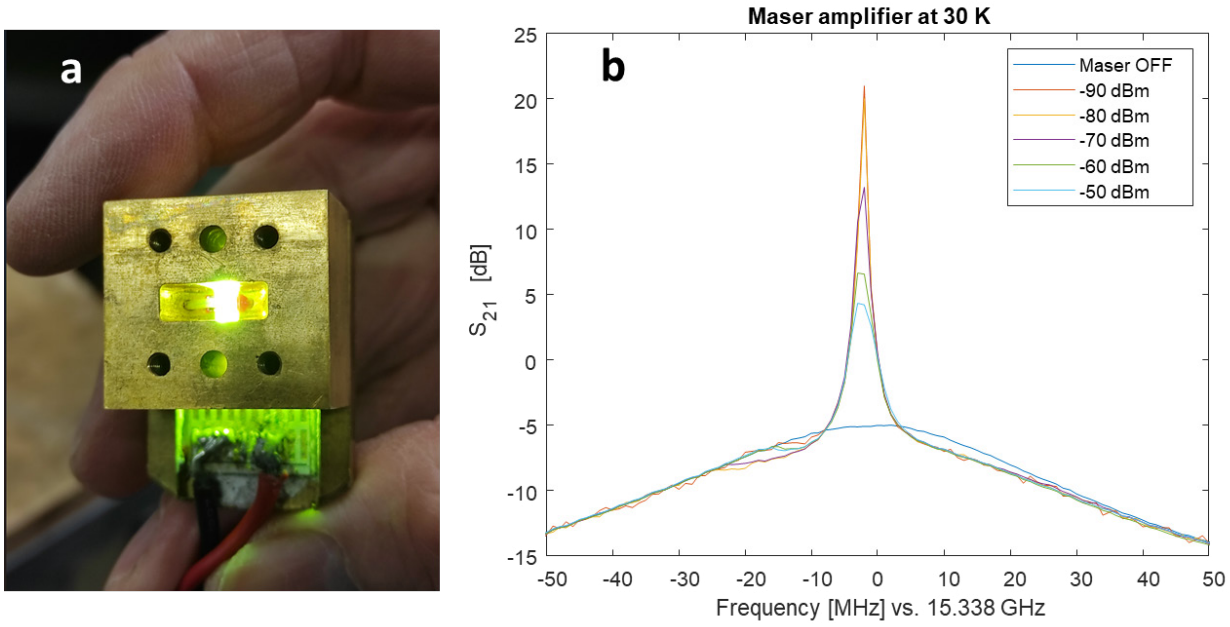

Figure 6. Diamond-based maser device in action. **(a)** Photograph of the maser device with optical pumping turned on. **(b)** Gain of the maser amplifier when operated at 30 K, with varying levels of input power.

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