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Quantum photonics sensing in biosystems

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ABSTRACT

Quantum sensors emerged among quantum technologies as the ones with promising potential applications in the near future. This perspective reviews two leading quantum sensing platforms and their advancements toward biological applications: quantum light sources and color centers in diamonds. Quantum light, including squeezed states and N00N states, allows enhanced phase measurements by surpassing the classical shot noise limits. This advantage can be exploited in several contexts, enabling improved resolution and sensitivity, which are particularly valuable in biological contexts where traditional high-intensity illumination could damage or alter delicate samples. In parallel, color centers in diamonds, specifically nitrogen-vacancy and silicon-vacancy centers, also emerged as promising for sensing applications due to their high sensitivity and biocompatibility. These sensors enable detailed intracellular measurements, such as temperature detection, and show potential for measuring magnetic fields of biological origin. Despite these advancements, significant challenges remain in translating these technologies from a controlled laboratory environment to practical, widely applicable devices for diverse biological applications. Overcoming these challenges is crucial for unlocking the full potential of quantum sensors in the biological field.

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I. INTRODUCTION

Biological systems are outstanding models of complexity. They host numerous emergent phenomena, occurring at different scales, ranging from those of a cell down to single macromolecules and below, and these are often actively triggered and catalyzed by specialized compounds, such as enzymes. For this to occur, specific conditions must be met for what concerns concentrations, temperature, pH, and so forth.

Investigating biological processes as they take place thus imposes a relevant challenge in carrying out a sufficiently precise measurement while keeping its invasivity to a minimum. This not only has to consider the sheer size taken up by instruments but, more crucially, any disruption to the operating conditions imposed by the measurement procedure. For instance, illuminating a sample too strongly may cause the sample to heat due to absorption,

although the increased flux would provide *per se* a better signal-to-noise ratio (SNR). Thus, we are in the presence of contrasting needs of high precision and low invasivity.

For the most advanced measurement techniques, the main source of experimental uncertainty does not arise from instrumental noise but rather from intrinsic physical aspects. A notable example is that of shot noise in optical measurements: this is ultimately due to the discrete nature of light manifesting in the interaction with electrons, and, while its impact is proportionally reduced as the intensity is increased, in the actual case there are technical reasons why this simple route may not be taken—one of them is increased invasivity, but also considerations on detector saturation, to name one issue, do play a part.

Since these limitations are fundamental in nature, it is then reasonable to look for a solution in the most basic description of matter, quantum mechanics. The adoption of quantum effects,

notably those involving coherence, does provide the means for obtaining superior measurement performance;^{1–5} at the very least, it is capable of suggesting practical tools that, although they may not exhibit genuinely coherent behaviors, represent interesting technical solutions.

This perspective is dedicated to reviewing two main platforms under investigation for quantum sensing that are based on photonics:⁶ the first is, unsurprisingly, quantum light itself, and the second is color centers. Optics plays a crucial role in sensing applications across various scientific and technological fields, offering not only high precision measurements but also remarkable versatility. Optical sensors operate by detecting changes in light properties tailored to the specific application, including intensity, phase, polarization, and wavelength, upon interaction with the target. In biology and medical diagnostics, optics is essential to several applications, with imaging and microscopy techniques at the forefront. These techniques enable the detailed study of cellular structures and molecular processes with unprecedented resolution and depth of field. Furthermore, spectroscopy allows the characterization of molecular composition, structure, and dynamics of biological systems, providing fundamental insights into the chemical bonds of the investigated sample. Techniques such as interferometry are also often considered in sensing applications,⁷ thanks to the high sensitivity to changes in distance and refractive index. Exploiting quantum light offers a stimulating path to curtail the impact of shot noise, allowing for improved sensitivity and SNR compared to classical light at the same photon budget.^{8–12}

Color centers in diamonds, particularly nitrogen-vacancy (NV) and silicon-vacancy (SiV) color centers, represent a promising system for various quantum sensing applications. Numerous studies have explored the use of color centers for sensing magnetic fields,^{13–16} electric fields,^{17,18} pressure,¹⁹ and temperature.^{20–23} Furthermore, probes based on color centers in diamonds have found applications in medicine, cellular biology,^{20,24} and neuroscience^{21,25} due to their nanoscale spatial resolution, compatibility with biological systems, stability, high sensitivity, and compatibility with imaging techniques commonly used in cell biology, such as fluorescence microscopy. In this short article, we limit our analysis focus to NV- and SiV-based diamond sensors, their application for medicine and cell biology for the temperature and electromagnetic field sensing, and comparison with alternative sensors such as fluorescent dyes, proteins, nanoparticles, etc.

II. QUANTUM OPTICS

The study of living systems entered a phase of unprecedented progress when microscopes were first used to look at the microscopic world in the 17th century. Ever since shining light on samples has brought about formidable progress in biology. It has long evolved from a simple tool for observation, and it now allows us to collect quantitative information through the changes imparted. At the present time, advanced techniques can resolve details evading Rayleigh's limit by means of structured illumination.²⁶ Light is also used to hold and displace specimens by optical tweezers,²⁷ ensuring more delicate manipulation than with mechanical means. However, illumination is not exempt from causing modifications of behavior or even damage, as highlighted in different studies.^{28–32} Thus, there

exist then physical limits to how much optical power and energy can be delivered to samples.³³

This precaution comes at a cost: all optical measurements are affected by noise, some of it technical and, at least in principle, avoidable, some of it intrinsic to the detection process. The latter cannot be eliminated, but one can aim at finding conditions for which its impact is reduced. Shot noise is a case in point: when light with an intensity equivalent to N photons on average is detected by a linear detector, there are fluctuations in the registered number of the order of \sqrt{N} . Therefore, the SNR scales such as \sqrt{N} , and an improvement is expected when increasing the intensity. However, this strategy may not be suitable for the reasons exposed above, and alternative ways are then sought after. These are based on the idea that shot noise has its origin in poor control of the quantum state describing light: the \sqrt{N} -sized fluctuations are indeed associated with photons behaving independently, as it happens in classical light in the absence of technical noise.⁵ Quantum mechanics is then invoked to reduce fluctuations in the observable of interest, although at the expense of increasing those of a conjugate one that, crucially, should not partake in the actual measurement.

Notably, the vacuum state exhibits a characteristic level of fluctuations in its quadratures, captured by the variance of its quadratures $\Delta^2 X_1 = N_0$. This same level is also found in coherent states that are used to describe classical fields. These fluctuations then constitute a form of quantum noise whenever quadratures are measured, corresponding to the shot noise level. The process by which such noise is reduced is named quadrature squeezing^{34,35} and is typically achieved by means of nonlinear optical processes. This allows us to reduce quantum noise in one field quadrature with respect to the vacuum, yielding $\Delta^2 X_1 = e^{-2r} N_0$ and, thus, enabling sub-shot-noise precision. This reduction, however, must be accompanied by a proportional increase in the fluctuations in the conjugate quadrature: $\Delta^2 X_2 \geq e^{2r} N_0$. In the typical situation, parasitic processes lead to excess noise on the quadrature X_2 , and its variance largely exceeds the minimal value, which would correspond to a pure quantum state. The actual scheme must then ensure that the measurement is only sensitive to the squeezed quadrature. This is achieved by introducing a phase reference by means of a local oscillator [see Fig. 1(a)].

Quadrature squeezed states are ordinarily prepared starting from the vacuum state; thus, they have vanishing average values for the quadrature, only fluctuations, but a displacement operation can be applied to provide an average intensity and an average phase. Current advancements have demonstrated measurements with up to 15 dB shot-noise reduction,³⁶ making squeezed light already a valuable resource in high-precision applications such as gravitational wave detectors.^{37,38} Squeezing devices can be used to reduce fluctuations in the intensity of light, possibly with respect to a second beam that then acts as a reference; this is called relative intensity squeezing.³⁹ The optical apparatus needed to produce squeezing is at the present time quite compact and can exploit second-order nonlinearities in monolithic cavities⁴⁰ or microstructures⁴¹ or third order nonlinearities in atomic media⁴² or optical fibers.⁴³ Squeezed light now enjoys a solid reputation as a valuable tool in astronomical observations, as it has played a key role in reducing noise in the new experimental runs of the Laser Interferometer Gravitational Wave Observatory (LIGO) and GEO600.⁴⁴ This brings good hope that

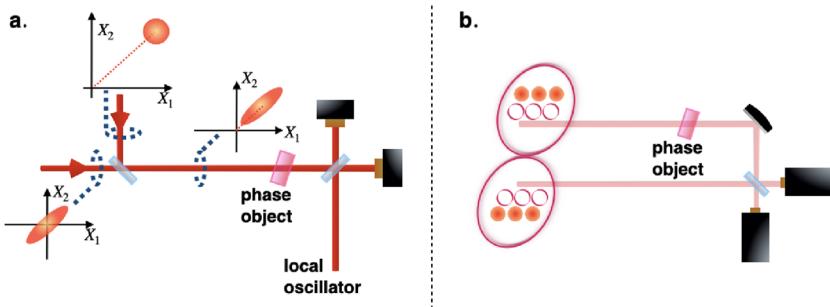


FIG. 1. Measurement schemes adopting quantum light based on (a) squeezed states and (b) $N00N$ states.

squeezing could hold its promise in the field of quantum microscopy as well. Recent proof-of-principle demonstrations have highlighted the potential of squeezed light to enhance imaging resolution and sensitivity in biological applications, marking an important step forward in quantum-enhanced microscopy. A quantum microscope utilizing squeezed light has been developed for quantum-enhanced 2D cell imaging.⁴⁵ In this setup, squeezing was employed to reduce the noise floor in a coherent Raman microscope, enabling improved SNR while imaging lipid concentrations within yeast cells, beyond what it would have been possible considering the photodamage limit.

An alternative approach considers quantum states that have a fixed photon number. Among these, $N00N$ states, which involve superpositions of N photons in one path and zero photons in another [see Fig. 1(b)], give rise to unique quantum interference effects that allow us to reach the highest possible sensitivity in phase measurements, i.e., the so-called Heisenberg limit, which stands out as a prime example where quantum sensing with light can make significant contributions.^{46,47} This key advantage is, therefore, exploited in interferometric phase measurements and in imaging, where the use of these entangled quantum states of light enables superresolution,⁴⁸ allowing the spatial resolution of imaging systems to surpass the classical diffraction limit.⁴⁹ This precision scales with the number of photons N in the entangled state.

Considering a phase estimation experiment, the achievable precision is limited by the average number of photons $\langle N \rangle$ in the probe. For coherent states, this precision is bounded by the standard quantum limit (SQL),

$$\Delta\phi_{coh} = \frac{1}{\sqrt{\langle N \rangle}}. \quad (1)$$

Such limits can be surpassed by employing either squeezed or $N00N$ states that enable reaching improved precision. For squeezed states, the estimate of the phase in an interferometer can lead to the following precision:⁵⁰

$$\Delta\phi_{sqz} \geq \frac{1}{2\sqrt{2}} \frac{1}{\sqrt{\langle N \rangle^2 + \langle N \rangle}}, \quad (2)$$

where, as mentioned above, the average number of photons in the state is related to the squeezing parameter r as follows: $\langle N \rangle = 2 \sinh^2|r|$. $N00N$ states, on the other hand, can lead to reaching the Heisenberg scaling,

$$\Delta\phi_{N00N} \geq \frac{1}{N}. \quad (3)$$

Optical sensors based on these quantum states thus enable non-invasive probing of delicate specimens, minimizing the risk of damage while obtaining high-resolution data.^{33,51,52} This capability is vital when studying photosensitive or fragile biological samples, where traditional methods could disrupt the sample or alter its behavior. For this reason, one of the most sought applications of the quantum metrology field is the implementation of quantum biosensors, which demand high sensitivity without the risk of damaging the investigated specimen by using high-energy probes. This could also be promising for drug development by offering unprecedented capabilities for precise and sensitive measurements at low exposure levels. Harnessing quantum probes to achieve ultra-sensitive detection of molecular signatures could enable the identification of subtle changes in biomolecular structures and interactions, offering rapid and precise analysis of drug-receptor interactions and drug metabolism.⁵³ Photonic sensors are among the most promising ones thanks to the relative simplicity in the generation, manipulation, and detection of the required quantum features. Reaching quantum-enhanced sensitivity when studying such systems is, therefore, fundamental when the estimation precision cannot be improved simply by increasing optical power due to power constraints introduced by optical damage. Several studies have now proven the concrete possibility of using quantum photonic probes to enhance measurement sensitivity in a wide range of biological applications.^{33,54–56}

Entangled photons and, in particular, the Hong-Ou-Mandel effect have been used to enhance imaging performances in microscopy⁵⁷ and in Quantum Optical Coherence Tomography (Q-OCT).⁵⁸ It has been demonstrated that Q-OCT can achieve superior imaging resolution and contrast compared to classical Optical Coherence Tomography (OCT). This improvement is especially beneficial for imaging biological tissues, enabling non-invasive, high-precision 3D visualization as demonstrated in the imaging of onion skin cells.⁵⁹ This level of detail and contrast in Q-OCT is beneficial for non-invasive biological imaging, including photosensitive samples and wavelengths outside the detectable range of conventional systems. One promising approach in this direction, known as imaging with undetected photons or coherence-induced imaging,⁶⁰ decouples the wavelengths of sensing and detection, therefore allowing new possibilities for quantum imaging.⁶¹ This technique employs a nonlinear interferometer with two nonlinear crystals illuminated with the same pump in a low-gain regime, where spontaneous emission dominates. The idler mode passes through

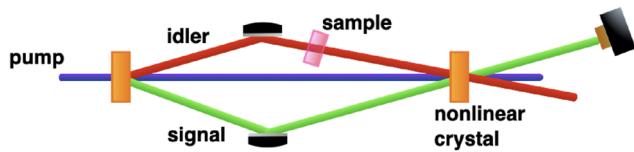


FIG. 2. Schemes for applying induced coherence for measurements. The nonlinear interferometer is realized by means of two nonlinear crystals, and detection only occurs on the higher-frequency beam.

the sample, and it is then overlapped with the idler generated in the second crystal, enabling first-order coherence and interference in the signal fields, with idler photons remaining undetected, as depicted in Fig. 2. A crucial advantage results in the flexibility of the wavelength of the probe photons that do not have to fulfill any detector constraints. The signal photons, typically in the visible or near-infrared range, are then detected, making this method ideal for imaging in mid-infrared regions—wavelengths that fall outside the sensitivity of conventional detectors. This wavelength range can be indeed particularly interesting for biological applications since many samples exhibit unique absorption characteristics in this region; therefore, imaging in this range can yield valuable insights into their composition and structure. Furthermore, this approach enables the use of advanced quantum interference effects, which can amplify the signal and improve the contrast of the images obtained. As a result, this method holds promise for a variety of applications, including 3D imaging through OCT with undetected photons,⁶² holography,⁶³ and broadening its applications in high-resolution,⁶⁴ non-invasive microscopy of delicate biological samples.⁶⁵

Quantum correlated light and, in particular, amplitude squeezed states have been employed to enhance the information extracted per photon to track living yeast cells,³³ demonstrating the possibility of using squeezed light in the frequency range of interest for such biological applications and solving challenges related to classical noise and spatial mode distortion. Entangled photons were also exploited to study biological samples. In Ref. 66, measurements of the refractive index of a solution within a microfluidic device were used to determine the solution's protein concentration. A two-photon $N00N$ state was passed through an integrated Mach-Zehnder interferometer with a microfluidic channel passing through one arm. A standard interferometric phase measurement was then used to infer the refractive index of the fluid within the channel. While the generation rate of quantum light sources, especially for complex quantum states such as $N00N$ states, and detection losses remain significant limiting factors to show an unconditional quantum advantage,⁶⁷ recent advancements have shown promising developments in utilizing quantum states of light for practical applications. Current technology enables the tracking of dynamics with sub-second resolution, showcasing the potential application of entangled single-photon states in monitoring chemical and biological processes occurring within such timescales. For instance, in Ref. 68, two-photon $N00N$ states are employed for real-time monitoring of a test-bed reaction consisting of the acid hydrolysis of sucrose. The same reaction has also been studied in Ref. 69, exploiting a single-photon source.

Such reactions, involving chiral molecules as both reagents and products, are ideal candidates to be investigated with photonic probes due to their distinct optical activities throughout the reaction process. As the reaction proceeds, differences in the refractive indices for right- and left-circularly polarized light cause one polarization to accumulate a slight delay relative to the other, resulting in a measurable phase difference. Monitoring this phase difference, therefore, provides a direct insight into the dynamic of the reaction.

To illustrate the capability of tracking diverse dynamics over timescales ranging from tens of minutes to several hours, the behavior of a sucrose solution mixed with varying concentrations of acid has been explored. The study has been carried out in the multiparameter framework,^{70–72} simultaneously estimating the parameter of interest to track the reaction, i.e., the optical phase, together with the level of noise affecting the probe state.^{73–76} This approach is essential to guarantee the accuracy of the obtained results since a wrong assessment of the actual probe states could introduce a bias into the parameter estimation process, thus enhancing the robustness of the experimental findings. The reason why using quantum probes becomes evident when monitoring the same reaction when catalyzed instead by an enzyme.⁷⁷ In this case, stringent constraints on light exposure are necessary to prevent photoinduced damage and an alteration of the reaction. Notably, the study demonstrates a difference in the enzymatic activity when monitoring the reaction using a standard laser source vs employing single-photon entangled states. When subjected to illumination from a standard laser source, even at low power levels (such as a continuous-wave laser with a power of the order of milliwatts), a discernible alteration in enzyme activity is observed. In particular, the rate of molecule hydrolysis over time is reduced, leading to a decelerated reaction kinetics. This phenomenon can be attributed to the inhibitory effect of laser illumination on the activation of the enzyme site, underscoring the adverse impact of conventional light sources on biological processes. Hence, even in this test-bed scenario, a low-light exposure level is required to avoid any alteration of the sample. When entering such a regime, therefore, single-photon entangled states allow us to achieve, for the same photon number, enhanced measurement precision, resulting in a valid solution, offering a non-invasive means of probing biological systems with enhanced sensitivity.

Significant progress has been made in generating $N00N$ states with photon numbers reaching tens of particles,^{78–80} advancing the feasibility of practical quantum-enhanced metrology. However, scaling these systems to even higher photon numbers presents substantial technological challenges due to the increased sensitivity of entangled states to losses and decoherence, which can rapidly diminish the quantum advantage as the number of resources N increases. To circumvent these scalability challenges, alternative techniques have been developed that maintain improved measurement precision without relying on large-scale entanglement. One approach involves multi-pass strategies, where a single photon is repeatedly passed through the sample to effectively emulate an entangled state with fewer physical resources.^{81,82} Another valid alternative exploits the orbital angular momentum (OAM) of single photons, allowing also in this case to achieve sub-shot-noise precision without requiring entanglement.⁸³ When addressing specific tasks, these strategies mimic the super-resolution behavior

of N00N states, allowing for improved measurement sensitivity while avoiding the scalability issues inherent in entangled states. In particular, the OAM degree of freedom of light allows us to generate high-dimensional states useful to measure rotations with enhanced sensitivity.⁸⁴ These works demonstrate a possible alternative for achieving sub-shot-noise-limited precision in practical settings.

The development of quantum optical sensors has thus advanced significantly, playing a fundamental role in the new quantum technology era by offering clear advantages over classical light-based sensing for the same photon budget. The ability to perform high-precision measurements at low light levels makes quantum optical sensors ideal for applications ranging from advanced imaging techniques to the detection of biomolecular interactions. For instance, in microscopy and imaging, quantum metrology enhances the SNR of measurements without increasing illumination power.^{85,86} This is particularly beneficial in scenarios where boosting illumination power to improve measurement sensitivity could negatively impact delicate, photosensitive samples.

Unfortunately, the quantum advantage is severely reduced by the presence of loss, and it can be so severe that the Heisenberg scaling is lost.⁸⁷ Nevertheless, there can remain an increase in the precision of suitably designed probe states.^{88,89} Quantum state engineering is generally designed starting from parametric downconversion sources providing photon number-correlated beams,^{90–92} making the generation intrinsically probabilistic. Novel schemes may be spurred by the availability of high-quality near-deterministic photon sources based on solid state devices.^{93–95}

III. COLOR CENTERS IN DIAMOND

Recently, numerous probes have been developed to meet the urgent demand for measuring different parameters such as temperature, magnetic field, pH, etc. in a biological sample. Among these emerging sensors (such as quantum dots,^{96,97} polymeric nanoparticles,^{98–100} and fluorescent molecular thermometers^{101,102}), color centers in diamonds offer exceptional potential for sensing applications, capitalizing on their unique optical properties and sensitivity to environmental changes.

The primary methods for producing nanodiamonds (NDs) include the high-pressure high-temperature (HPHT) process, chemical vapor deposition (CVD), and detonation. Detonation nanodiamonds (DNDs) are typically small (<10 nm) and contain a high concentration of imperfections, limiting their use in sensing applications. HPHT NDs come in a wide range of sizes (10–300 nm) and are commercially available. They lead the field of quantum sensing due to their easily controllable color center introduction and a variety of surface functionalization options (e.g., polymer coatings, acids, amines, etc.).¹⁰³ An alternative CVD method can produce high-quality NDs with enhanced NV spin properties; however, these are low-yield techniques, and such NDs are not yet commercially available. In recent years, new fabrication techniques have been proposed to optimize the quality and consistency of commercial ND sensors. One approach involves engineering diamond surfaces through surface functionalization, which stabilizes internal defect centers^{103,104} and improves colloidal stability in biological media. Another approach modifies the surface, for instance, using

non-thermal plasma to extend the transverse spin-coherence time T2 of NV centers, thereby enhancing quantum sensing sensitivity.¹⁰⁵ Advances have also been made in the fabrication technique of color centers. Ion implantation, a common method for generating color centers in diamonds, damages the diamond lattice, limiting the production of high-quality quantum sensors. A new technique, deterministic ion implantation with controlled concentration and distribution of color centers, aims to overcome these limitations.^{106,107}

NV and SiV based diamond probes are two of the most commonly utilized sensing platforms in bio-applications. Despite the similar nature of NV and SiV, their optical properties and sensing techniques have different characteristics and operating principles, which will be described in the following.

A. Silicon-vacancy centers

SiV color centers in nanodiamonds have shown great potential for thermometry, as they can be excited and detected optically within the biological transparency window. Its zero phonon line (ZPL) at ~738 nm with the full width at half-maximum (FWHM) of ~4 nm shifts as a function of temperature changes, rendering it suitable as a high resolution and high sensitive thermal probe. In bulk diamond with SiV centers, a ZPL shift of about 0.0124 nm/K was demonstrated,¹⁰⁸ which corresponds to a sensitivity of 0.36 K/Hz^{1/2}. In the same work, nanodiamonds (NDs) of 200 nm diameter with SiV centers were also characterized, and a sensitivity of 0.52 K/Hz^{1/2} was achieved at the best experimental conditions.

All-optical temperature measurement methods, based on the temperature-dependent shift of the photoluminescence spectra of color centers in diamond, including SiVs (see Fig. 3), have already been used in proof of principle experiments in cell biology. For example, recently, it was reported about a temperature measurement of isolated mitochondria, measured by a diamond thermometer (DT), which is insensitive to external non-thermal parameters.²² The DT was based on a single fluorescent microdiamond with a SiV fixed on the tip of the glass capillary and temperature pre-calibrated. Intracellular thermometry and correlated challenges associated with sensors based on SiV in NDs were investigated and discussed for the first time in Ref. 109. The authors demonstrated that, in a real experiment with living cells, the expected linear red shift of the ZPL peaks is not always observed, or the sensitivity is not suitable for precise thermometry in the cells. Such a behavior relates to ND crystal strain, which varies from ND to ND due to different defects, SiV location, and ND shapes, which lead to a shift of a ZPL peak position from 738.20 nm and its broadening. Therefore, accurate detection of small temperature changes can be difficult, and the initial properties of SiV ND sensors and calibration should be evaluated prior to thermometry measurements. Unfortunately, this pre-calibration step is the Achilles' heel of all temperature probes for the intercellular measurements.

B. Nitrogen-vacancy centers

The key feature of the NV center is the possibility to discriminate the spin components of the electronic state optically, due to the dependence of the NV center fluorescence on the electronic spin

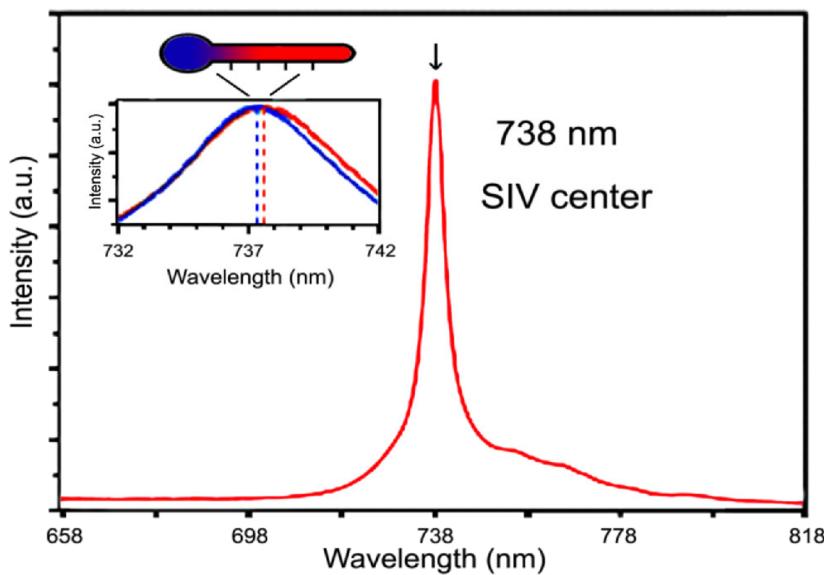


FIG. 3. Typical spectra of SiV centers photoluminescence at room temperature. Inset: PL spectra of SiV at different temperatures (blue and red curves).

state. This method, referred to as Optically Detected Magnetic Resonance (ODMR), forms the basis of most NV-center-related quantum sensing measurements.

The technique consists of the application of a microwave field (MW) on the sample, simultaneously with its exposure to a laser with a frequency sufficient to excite the color center from the ground state 3A_2 to the excited state 3E , generally performed by a green laser at 532 nm (see Fig. 4). The main allowed optical transition between ground state 3A_2 and excited state 3E has a resonant wavelength of 637 nm (zero-phonon line). However, only a few percent of the photons are emitted into the ZPL. At room temperature, off-resonant excitation leads to the population of the excited state via fast vibrational transitions, resulting in emission across a broad spectrum from 630 to 800 nm, in which most of the photoluminescence occurs (96%).

Next, microwave radiation is applied to the sample at varying frequencies. When the frequency matches the energy separation D_g between the $|m_s = 0\rangle$ and $|m_s = \pm 1\rangle$ states of the NV center, a resonant interaction occurs, altering the NV center's fluorescence emission. This is allowed by the different coupling of the $s = 0$ state, with a metastable level, compared to the $s = 1$ state and manifests as a dip in the ODMR spectrum. The positions and shapes of the dip in the spectrum provide information about the NV center's electronic structure and its interaction with the surrounding environment, including temperature variations and electromagnetic fields (Fig. 4). For example, when a constant magnetic field is applied, the $|m_s = \pm 1\rangle$ states of the NV center split due to the Zeeman effect, causing a separation between the dips in the ODMR spectrum. This distance between the dips is proportional to the projection of the magnetic field [Fig. 5(a)]. The energy structure of the NV center also undergoes a temperature-dependent Zeeman splitting in the absence of a magnetic field (the so-called zero-field splitting frequency, D_g , in Fig. 4). An increase in temperature leads to a decrease in the resonant frequency D_g , and conversely. This temperature dependence enables the determination of the temperature at the location

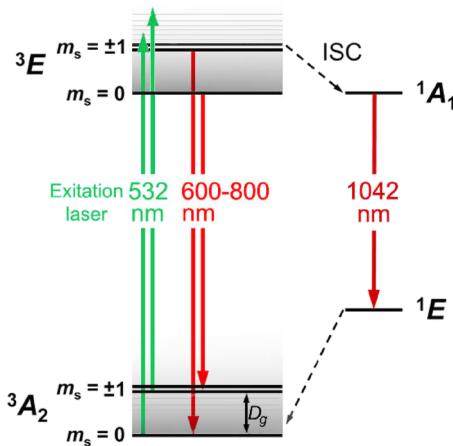


FIG. 4. The energy level structure of the negatively charged NV center ($S = -1$) involves electronic transitions that are excited into vibrational continuum states with green light, subsequently emitting red light. The $|m_s = \pm 1\rangle$ spin level shows reduced red fluorescence due to the presence of an alternative, non-radiative decay path. ISC stands for Intersystem Crossing.

of the diamond probe by measuring the frequency shift [Fig. 5(b)]. It is important to underline that when NDs are used as sensors instead of bulk diamonds, the degeneration of the $|m_s = +1\rangle$ and $|m_s = -1\rangle$ levels is removed by mechanical stress. In this case, two dips are observed in the ODMR spectrum. Both show a shift in the resonance frequency in the same direction as the temperature changes.

The unique sensing capabilities of sensors based on NV color centers in diamonds, their biocompatibility, and their insensitivity to third-party parameters such as pH, viscosity, and concentration make them ideal for biological sensing applications. Furthermore,

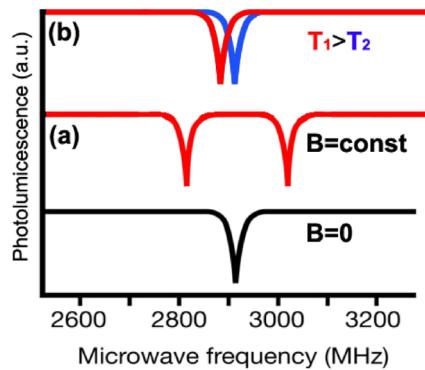


FIG. 5. Example of magnetic and thermal shifts of the spin resonance in ODMR spectra. Dips with equal colors correspond to paired resonances.

their versatility allows for a wide range of applications, from intracellular temperature sensing to magnetometry of biological samples and tissues. For example, NV-magnetometry with a bulk diamond substrate was successfully demonstrated for the detection of action potentials in the giant axon of a marine worm.¹³ In the other study, a new method was described to link subcellular magnetic field gradients to magnetic resonance imaging (MRI) contrast using NV diamond magnetometry, enabling the study of dynamic processes in living cells.¹¹⁰ The notable achievement in the field of NV-based magnetometers promises a wide application of an incoming generation of NV based sensors as a facile tool for use in neuroscience labs worldwide and in the clinical setting. However, after the proof-of-principle experiments with a macroscopic biological object, more complex tasks, for example, single neuron cell activity, remain challenging due to the extremely faint magnetic fields involved. To predict the electromagnetic field intensity created by action potentials (APs) and understand the necessary sensitivity of NV sensors, it is essential to theoretically study how the neuron current develops and propagates. A thorough treatment of the complexities involved in this calculation is out of the scope of this paper, in following some considerations based on previous studies^{111,112} estimating the spatiotemporal characteristics of neural magnetic fields in brain slices. Based on this analysis, the magnetic field pulses from a single action potential caused by neural activity are expected to have the following parameters: an amplitude of ~ 3 pT, a duration of ~ 1 ms, and a sensing volume of $\sim 10 \mu\text{m}^3$. These parameters impose strict requirements for the NV magnetic field sensors: a sensitivity of ~ 30 fT/Hz $^{1/2}$, a temporal resolution better than 0.1 ms, and a spatial resolution of $\sim 10 \mu\text{m}^3$. The fundamental sensitivity limit for spin-based magnetometers is determined by the noise intrinsic to quantum projection. For example, the estimation for the diamond sensor used in the work¹³ (15 pT/Hz $^{1/2}$) gives a spin projection noise of 7 pT/Hz $^{1/2}$ for the sensing volume of $\sim 10 \mu\text{m}^3$, which exceeds more than 200 times the estimated sensitivity for a single action potential detection. This challenges the use of NV-based magnetometers for detecting single action potentials in neurons; nevertheless, magnetometry of brain slices or tissues appears feasible.

Another important biosensing application of NV color centers in diamonds is focused on thermometry. For intracellular

measurements, NDs with a diameter of ~ 100 nm are typically used. Although bulk crystal sensors commonly reach higher sensitivity with respect to NDs (principally due to a much more controlled crystal quality), they are not suitable for thermometry at the cell scale due to their high thermal conductivity. In fact, the velocity at which thermal equilibrium is reached allows only a measure of the average temperature variation on the whole diamond sample, impeding the evaluation of local temperature gradients and even variations between different cells in the cell culture.¹¹³

The first proof-of-concept experiment that revealed the ability of ODMR to measure temperature in human embryonic fibroblast cells was conducted by Kucska *et al.*²⁰ Recently, numerous studies have been published on the use of ND thermometers for biological applications.^{20,21,114–116} In one such study, Fujiwara *et al.*²³ utilized ND probes to monitor thermogenic responses in adult *C. elegans* under pharmacological treatment. Subsequently, NDs were employed as thermometers for intraneuronal temperature mapping in primary cortical neurons by Simpson *et al.*¹¹⁴ and in the primary culture of neurons under a stimulated spiking activity.²¹ The state-of-the-art sensitivity of temperature sensors based on NV centers in NDs is limited to $1\text{--}2$ K/Hz $^{1/2}$ (Refs. 13 and 21). This limitation is not only due to their smaller size, which results in a reduced photoluminescence signal (because of a reduced number of color centers at equal concentration) and broader ODMR linewidth compared to bulk diamond sensors, but also due to the currently achievable quality of NDs. In practice, each ND exhibits a different split in the ODMR spectrum due to varying lattice strains, leading to high measurement errors. Consequently, calibration curves need to be recorded for each ND, or an average calibration constant must be used, which can result in under- or overestimation of the measured temperature. These considerations underline the necessity of producing homogeneous NDs, where a single calibration curve fits all NDs. We anticipate that novel fabrication techniques and advancements in surface modification/coating of diamond may address this issue.^{103,117}

In conclusion, NV-based sensors are extremely promising candidates for biosensing with potential applications in biology and medicine. From the point of view of magnetometry, the detection of action potential remains challenging, while the detection of small magnetic fields/currents in tissues is feasible. From the point of view of thermometry, NV-based nanodiamonds are more promising in applications where an evaluation of local temperature in cells and neurons is targeted.

IV. FUTURE DIRECTIONS

The progress accomplished up until now in quantum metrology does not yet cover all the needs to proceed with the implementation of fully validated devices. In our opinion, this is not only hampered by the availability of technical solutions or lack thereof; to date, there are no established blue prints for actual devices, and even their conceptualization trails behind. The community has not reflected in an organic way on what real applications may entail. The main drive of research has been the observation of novel fundamental effects, and we are probably still far from demonstrating sufficient robustness; it would nevertheless be crucial to establish what the expected requirements for real-life operation are and compare their possibly contrasting needs. In order

to accomplish that, a concept for a machine performing a well delineated task, or a set of tasks, should be put forward: if we are aiming for a phase imaging device, we should have an idea of its intended field of view, wavelength operation range, bandwidth, speed, compatibility with classical measurements, and so forth, to make any advancement in its implementation. In this respect, the production of quantum light is routinely achieved in the near-infrared domain, especially around 800 and 1550 nm, with the aim of ensuring compatibility with telecom components. These may also be relevant for the investigation of biological material but do not cover all relevant cases. For instance, intensity squeezing can help detect small features in the circular dichroism trace, but the spectral region of interest is typically in the UV. Some effort has been put into extending the spectral region over which quadrature squeezing can be available,^{118,119} as well as introducing some spectral tuneability.¹²⁰ On the other end of the spectrum, reaching operation in the THz region may provide an interface to existing biosensors.¹²¹

The operation of sensors in open environments, such as biological matter, is also affected by nuisance parameters that describe dissipative and, in general, noise processes taking place as the measurement is carried out. Keeping track of such parameters can improve the performance of the device,¹²² however, this entails an increase in the experimental complexity⁷⁵ as well as conceptual challenges in the adoption of such a multiparameter scenario.² This perspective could be embraced also in actual devices, implying they should be complemented with the possibility of running characterization, also simultaneously with the actual measurement. Quantum metrology, however, is unable to provide general guidelines for multiparameter estimation,^{123,124} and case-specific considerations must be brought up.

Prototypes of quantum sensors are generally run on meticulously crafted setups controlled by specialized operators. This paradigm would be untenable in view of the broad employment of quantum devices. In particular, calibration is a time and resource consuming step, but, in light of its relevance, it should be run as a routine operation. This is by no means a secondary aspect, in that it could largely affect the operation cost, hence determining what kind of measurement device should be targeted. There has been some exploration of the use of machine learning for the calibration of quantum sensors.^{125–128} The approach has yielded interesting results, in that the performance of phase estimation close to the quantum limit has been observed with a reasonable dataset and simple algorithms; however, it is not clear to what extent this applies

beyond individual examples. At low light levels, it is also known that image reconstruction techniques¹²⁹ are beneficial, if not necessary, yet their consequences on the uncertainties have received little attention.

The adoption of integrated optics can open the way to more compact, efficient, and stable solutions, especially for the analysis of *in vitro* or *ex vivo* specimens. Demonstrations that have been accomplished in the past are solid and convincing,^{5,46,125,130,131} although it is remarkable that investigations in microfluidic chips have received limited attention;⁶⁶ this is most peculiar, considering the positive impact of this solution on biology and biochemistry.¹³² In the same vein, the employment of plasmonics and nanophotonics structures has found widespread use for biomaterials, due to the possibility of confining fields in small modal volumes, contained in high quality factor cavities. This enhances the interaction with the samples, leading to improvements in sensitivity and precision.^{133,134} Significant effort has been put into exploring these structures in the quantum regime;^{135–139} the combination of the two techniques, however, is still to be thoroughly explored beyond pioneering work.¹⁴⁰ The appeal of these platforms is reduced by the presence of loss: squeezing could then represent a more suitable solution than fixed-photon number states, but stringent tests on relevant cases should be carried out to assess whether the gain in sensitivity actually justifies the increased complication of the light source.

The potential of quantum sensors as a promising avenue for further investigation has long been debated; the challenges of employing these sensors for biomedical applications have recently been addressed in Refs. 142–146. With notable exceptions, for instance, in magnetometry¹⁴⁷ and magnetic resonance,¹⁴⁸ the field has not yet engaged in a complete pathway to extend its reach to medicine, with applications to diagnostics. The employ of quantum sensors opens up the possibility of detecting weak signals *in situ*, hence allowing for earlier or more reliable detection of pathologies. Figure 6, which is taken from a recently published overview,¹⁴¹ gives a glimpse of the current state-of-the-art in terms of the several quantum sensors' sensitivity and how it is limited by its trade-off with the sensor's size. Nanodiamonds, included in the aforementioned overview, have shown excellent biocompatibility; thus the prospect of exploiting them in biomedicine should not be considered far fetched. It is rarely the case that pathological conditions can be identified by anomalies in a single figure, whereas an extended clinical picture must be assessed by comparing distinct outcomes. These are also time-dependent traces, such as for echo

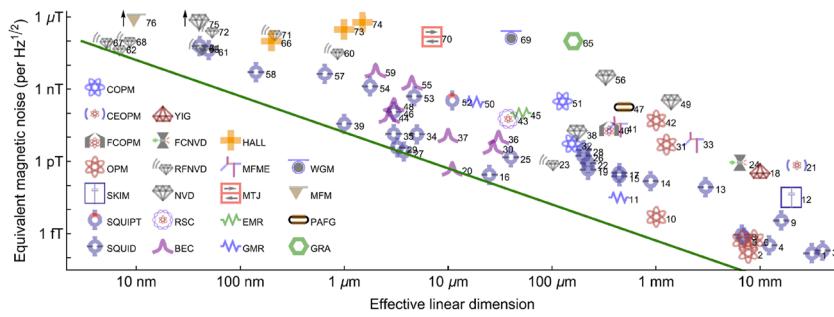


FIG. 6. Reproduced with permission from M. W. Mitchell and S. P. Alvarez, Rev. Mod. Phys. **92**, 021001 (2020). Copyright 2020 American Physical Society. Overview of the state-of-the-art in magnetic sensitivity vs size of the sensitive region for different classes of quantum sensors.

signals or evoked potentials; hence, we may be faced with the problem of seeking quantum enhancement in waveform estimation.¹⁴⁹ The paradigm should also be shifted from that of a single sensor to that of a network of devices whose outcomes are to be compared and cross-correlated, a significant extension with respect to the current understanding.

Remarkably, the use of quantum sensors has never ventured into looking at quantum effects in biological systems. There have been several investigations on the possibility that biomatter could sustain coherent effects despite, foremost, its high temperature. Experiments have addressed proton tunneling in enzymes,¹⁵⁰ the avian magnetic compass,^{151,152} and energy transfer in photosynthetic complexes,^{153–155} although the exact nature of these processes has been questioned,¹⁵⁶ as well as the cooperative effects in fluorescent amino acids.¹⁵⁷ There is also scope to investigate single-photon illumination in vision, including coherent effects.^{158,159} Attempting to measure such effects by means of quantum sensors may benefit from the increased sensitivity of these devices; the preservation, or even the emergence, of quantum features in the probes can provide some indication that quantum effects are taking place in the sample, as highlighted in Ref. 155.

V. CONCLUDING REMARKS

Quantum sensing may have much to say on biology, biochemistry, and biomedicine. Whether this vision can be realized is mostly a matter of moving on to imagine what real devices may look like. As the progress associated with this stage will produce stimulating challenges to fundamental and applied science, as well as to photonics engineering, it is likely that it will keep its appeal for researchers for many years to come. It is vital that such devices respond to actual needs; hence, we will likely witness an increasing number of multidisciplinary teams to investigate new solutions for sensing under all points of view. There could be days full of possibilities: let's go exploring.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

E.M. and V.C. contributed equally to this work.

Ekaterina Moreva: Conceptualization (equal); Writing – original draft (equal). **Valeria Cimini:** Conceptualization (equal); Writing – original draft (equal); Writing – review & editing (supporting). **Ilaria Gianani:** Conceptualization (supporting); Supervision (lead); Writing – original draft (supporting). **Ettore Bernardi:** Conceptualization (supporting); Writing – original draft (supporting). **Paolo Traina:** Conceptualization (supporting); Writing – original draft (supporting). **Ivo P. Degiovanni:** Conceptualization (supporting); Funding acquisition (lead); Writing – original draft (supporting); Writing – review & editing (equal). **Marco Barbieri:** Conceptualization (supporting); Funding acquisition (lead); Writing – original draft (supporting); Writing – review & editing (supporting).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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