SARS-CoV-2 Quantum Sensor Based on Nitrogen-Vacancy Centers in Diamond

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ABSTRACT: The development of highly sensitive and rapid biosensing tools targeted to the highly contagious virus SARS-CoV-2 is critical to tackling the COVID-19 pandemic. Quantum sensors can play an important role because of their superior sensitivity and fast improvements in recent years. Here we propose a molecular transducer designed for nitrogen-vacancy (NV) centers in nanodiamonds, translating the presence of SARS-CoV-2 RNA into an unambiguous magnetic noise signal that can be optically read out. We evaluate the performance of the hybrid sensor, including its sensitivity and false negative rate, and compare it to widespread diagnostic methods. The proposed method is fast and promises to reach a sensitivity down to a few hundreds of RNA copies with false negative rate less than 1%. The proposed hybrid sensor can be further implemented with different solid-state defects and substrates, generalized to diagnose other RNA viruses, and integrated with CRISPR technology.

KEYWORDS: COVID19 pandemic, Virus diagnosis, Nitrogen-vacancy center, Nanodiamond

INTRODUCTION

The rapid spread of the coronavirus disease 2019 (COVID-19) has shown the importance for rapid and cost-effective testing of emerging new viruses. In the absence of specific drugs, early diagnosis and population surveillance of the virus load are crucial to slow down and contain an outbreak. Unfortunately, as of November 9, 2021, there has been more than 250 million reported COVID-19 cases with over 5 million deaths.1 This huge cost in human life highlights the need for developing accurate testing for novel viruses with low false negative rate (FNR) and false positive rate (FPR), which enable taking appropriate preventive measures. Indeed, just the past 15 years have seen 4 pandemics (severe acute respiratory syndrome (SARS), Swine flu, Ebola, Middle East respiratory syndrome (MERS)) in addition to the severe acute respiratory syndrome coronavirus 2, SARS-CoV-2.

The diagnostic testing field for COVID-19 is rapidly evolving and improving in quality,2 but it has not yet been able to match the demand.2−4 Diagnostics that is able to detect active infections are typically molecular-based, gauging the presence of the pathogen. The SARS-CoV-2 has a single-positive strand RNA genome, which remains in the body only while the virus is still replicating, and can be detected by various virology methods, most preeminently by the reverse transcriptase quantitative polymerase chain reaction (RT-PCR). Faster and more portable tests are provided by rapid antigen tests that detect specific viral proteins found on the virus surface, such as spike proteins. Unfortunately, these faster tests are less reliable and cannot quantify the amount of virus. Serology tests, such as antibody tests, require a lag after infection and cannot catch the transmitting window.

While RT-PCR has been the primary method of viral genome detection for SARS-CoV-2, it has several drawbacks, as it requires trained personnel, special equipment, and careful design of the primer and probe. The samples need to undergo RNA extraction as well as an amplification process which can take several hours and might degrade the diagnosis accuracy. The RT-PCR method also suffers from high FNR,5,6 which can be above 25% depending on the viral load of samples. False negative results are especially consequential since they might lead to infected persons not isolating and infecting others. These challenges emphasize the imperative of finding a highly sensitive, accurate, and rapid diagnosis method for optimal diagnosis of COVID-19 and other viral outbreaks.

In recent years, quantum sensors5 have emerged as powerful tools to detect chemical and biological signals. In particular, nitrogen-vacancy (NV) centers in diamond act as stable fluorescence markers and magnetic field sensors and have been investigated as quantum sensors for applications ranging from material science to chemistry and biology. A promising avenue to detect biological signals is to transduce them into magnetic noise, e.g., using magnetic molecules, such as gadolinium (Gd)
complexes. Then, similar to FRET-based biosensors, the presence of a stimulus (in this case the virus) is detected as it induces a change in the NV fluorescence, following its separation from the magnetic nanoparticle. NV centers in nanodiamonds (NDs) have thus already demonstrated their ability to detect biological processes with high spatial resolution and are the object of intense study due to their many favorable properties, ranging from very high photostability and thermal stability to biocompatibility, in contrast to many florescent biomarkers in FRET-based approach.

Here, we introduce a quantum sensor based on NV centers in NDs that is capable of detecting virus RNA, focusing on the SARS-CoV-2 virus. We show with numerical simulations that the proposed sensor can detect as low as a few hundred of viral RNA copies in a 1 s measurement time window when interacting with virus RNA sufficiently. Considering the distribution of relevant parameters in realistic experiments, we show that the sensor can reach a FNR of less than 1% (considerably smaller than RT-PCR) even without the RNA amplification process. The signal can be optically read out with a short acquisition time. The proposed diagnosis method has a low material cost and is scalable to simultaneous measurement of many samples. We further discuss the potential integration of the proposed RNA quantum sensor with CRISPR technology to achieve even higher sensitivity, as shown in the Supporting Information.

While these ideas can be generalized to other RNA viruses (or more broadly any nucleic acid) and other solid-state defects, in the following we build a theoretical model of how the NV fluorescence is affected when the virus RNA cleaves the bond of Gd molecules with the ND surface. We show how the quantum properties of the NV spin, which make it extremely sensitive to external perturbation, together with its nanoscale size combine to provide the exceptional performance of the proposed sensor.

**VIRUS RNA SENSOR BASED ON SINGLE NV CENTERS**

Our proposed diagnosis technique is based on the detection of viral RNA as shown in Figure 1a. As in the standard RT-PCR method, viral RNA taken from an upper respiratory sample of patients is isolated and purified using fast spin columns. Contrary to RT-PCR, reverse transcription is not be needed, as the sensing technique is based on direct detection of the virus RNA. Moreover, our sensor does not require nucleic acid amplification due to its high sensitivity to viral RNA, reducing the complexity, cost, and time of the test. The sample solution is directly ejected into microfluidic devices where the NV-based hybrid sensor is loaded beforehand.

The negatively charged nitrogen-vacancy (NV) center is a point defect in the diamond lattice, consisting of a substitutional nitrogen atom with an adjacent vacancy. The NV electronic spin has a triplet ground state, with the spin levels \( |m_s = 0 \rangle \) and \( |m_s = \pm 1 \rangle \) separated by a zero-field splitting \( \omega_0 = 2.87 \text{ GHz} \). A short laser illumination can polarize the spin into the \( |m_s = 0 \rangle \) level (Figure 1), a state of effective low temperature, that can be recognized by its high fluorescence intensity. The system then relaxes to its thermal equilibrium state that displays a lower fluorescence intensity. The thermalization process occurs in a characteristic time (the longitudinal relaxation time \( T_1 \)) dictated by the quantum spin magnetic environment, which can be indirectly affected by biological processes. In particular, paramagnetic molecules such as gadolinium (Gd) complexes can induce strong transverse magnetic noise and significantly reduce the NV spin relaxation time.\(^{9,11,12}\)
As shown in Figure 1c, we noncovalently coat NDs by cationic polymers, such as polyethyleneimine (PEI), which can form reversible complexes with viral complementary DNA (c-DNA) sequences. Magnetic molecules such as Gd\(^{3+}\) complexes can be incorporated into the sequence, forming hybrid c-DNA-DOTA-Gd\(^{3+}\) complexes. For example, the amine modified end of the c-DNA is able to bind to a Gd\(^{3+}\) chelator such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaetic acid (DOTA) through an amide covalent bond. Due to the molecular electrostatic interactions between PEI and c-DNA-DOTA-Gd\(^{3+}\), the Gd\(^{3+}\) complexes will tend to lie on the ND surface, in close proximity to NV centers, thus efficiently increasing the magnetic noise strength felt by NV spins and quenching their relaxation time.

In the presence of viral RNA, the c-DNA-DOTA-Gd\(^{3+}\) pair will detach from the ND surface due to c-DNA and virus RNA hybridization. An analysis of the binding reactions (see Supporting Information) reveals that the formation rate of c-DNA-RNA hybrids is considerably higher than the binding hybrid c-DNA-DOTA-Gd\(^{3+}\) pairs. For example, the amine acid (DOTA) through an amide covalent bond. Due to the magnetic noise induced hybrid quantum sensor not only to detect the presence of the virus RNA but even to quantitatively estimate the viral load with high sensitivity. This capability would allow more accurately capturing the infectivity window and catching more contagion cases (even when the viral load is too small for other methods), thus playing an important role in accurate...
estimation of epidemic trajectories. To quantify the sensor’s performance, we thus consider the minimum number of detectable RNA copies in a total integration time $T$. This is related to the quantum sensitivity, $\delta n_{\text{min}} \sqrt{T}$, to variations in the surface c-DNA-DOTA-Gd$^{3+}$ density (see Supporting Information for details). Figure 2b shows the calculated sensitivity for varying parameters and an integration time $T=1$ s. As expected, a smaller distance between NV and Gd$^{3+}$ complex (smaller ND diameter and Gd bound) would result in a better sensitivity.

To evaluate the practical sensor performance, we need to take into account variations in the NV sensor parameters that affect the sensitivity, such as the randomness in ND diameter $d$, Gd$^{3+}$ surface density $n$, as well as position of the NV centers with respect to the origin (see the Supporting Information). These variations give rise to broad distributions of the sensitivity shown in Figure 2c, which predicts the probability that a single hybrid sensor containing one NV center can detect a certain amount of RNA copies, without any precharacterization. We remark that when the sensor sufficiently interacts with the virus in sample, the minimal detectable number of RNA copies in 1 s integration time can be as low as 100. This is well below the viral load for positive clinical samples, which typically has $10^5$–$10^6$ RNA copies per throat or nasal swab without nucleic acid amplification. Therefore, in this single-NV scenario, our sensor would reach an ultralow FNR (<1%) compared to the common RT-PCR diagnosis method which can have a FNR above 25%.$^3$

**SENSOR PERFORMANCE WITH ENSEMBLE MEASUREMENTS**

While measuring a single ND before and after introducing virus RNA can yield a considerably large $T_1$ difference, as we have demonstrated above, this protocol suffers from low photon counts and the challenge of addressing the same single ND. Moreover, for single NDs, the detectable number of RNA copies is upper-bound by the number of c-DNA-DOTA-Gd$^{3+}$ molecules on the ND surface, which is in turn limited by the surface area and surface density of c-DNA-DOTA-Gd$^{3+}$. We thus analyze a more practical scenario where the fluorescence signal from an ensemble of NDs is measured after a fixed dark time $\tau$ following the initialization laser pulse, which allows
inferring the relaxation rate. Each NV center in the ensemble is characterized by different parameters, including its random position inside the ND, and (normal) distributions of the ND diameters and surface density of c-DNA-DOTA-Gd\(^{3+}\) around their nominal values.

We then calculate the distribution of normalized photoluminescence (PL) counts at a fixed waiting time \(t\) for a large number of NDs (see Figure 3). When the observed photon count is below a chosen threshold, indicating a large relaxation rate, we classify the result as negative for the presence of the virus, while PL above the threshold indicates the virus presence. The FNR and FPRs arise when a misclassification occurs (e.g., the photon count is low even if virus RNA was present). The threshold is found by maximizing the balanced accuracy \(= 1 - (\text{FNR} + \text{FPR})/2\) from the calculated PL distributions, which describes the average of sensitivity (1 − FNR) and specificity (1 − FPR).

In Figure 3a we show how the PL arising from single NVs with/without the virus RNA is distributed. Due to the variation in ND diameters and other parameters, the two PL distributions arising from single NDs have a considerable overlap, leading to FNR(FPR) = 0.14(0.239). To resolve this problem, a small number of NDs can be measured simultaneously, leading to well-resolved distributions. As few as 10 NDs can reach an accuracy of >99.6% with FNR(FPR) < 0.1(0.9)% (Figure 3b). The potential FNR of our quantum sensor is thus much lower than for the common RT-PCR method.

To further show the performance of the quantum sensor in ensemble measurements, in Figure 3c we present the FNR (FPR) as a function of the number of SARS-CoV-2 RNA copies that can be detected by a group of NDs. When a larger number of NDs are measured simultaneously, the PL distributions are more well-resolved, leading to lower FNR (FPR) as expected. To take into account the effects of photon-shot noise on the PL distribution overlap, we plot the two extreme cases: the photon shot noise can indeed either add or subtract from the (average) PL signal. Correspondingly, the noise moves the signal PL distributions close to each other (worst case, shown in solid lines) or separate them further away (best case, shown in dashed lines). Even when considering photon shot noise, the FNR(FPR) achievable is still outstanding (only the largest diameter ND is considerably affected by the noise, since their average PL distributions are narrower).

Further optimization of the ND parameters can lead to significant advantages, as already demonstrated in our simulations. For example, a large contributor to the dispersion in the PL curve of Figure 3a is due to the random position of the NV in the ND, as in Figure 3d where the FNR (FPR) for different distributions of NV position is shown. NV centers near the ND surface would also significantly suffer from random surface charge noise, potentially leading to deleterious charge dynamics of the NV centers. This can be mitigated by better engineering the NV-containing NDs (for example, with surface coating\(^{28,58}\)) to produce NV centers that are well-below the ND surface and close to the NDs’ origin. In addition, precharacterization of the charge environment the NV centers would also help interpret the PL curves.\(^{30,31}\)

### DISCUSSION

Until now we focused on variations in the quantum sensor properties that might limit the viral RNA detection. Indeed, we expect that variations in other steps of the protocol, e.g., in the detachment of Gd molecules due to the interaction between viral RNA and c-DNA on ND surface, will have a negligible influence. While other external factors could have been expected to induce the detachment even in the absence of viral RNA (increasing the FPR), previous studies\(^{13,32,33}\) have demonstrated that the ND-PEI-DNA hybrid nanomaterial is a stable and efficient gene or drug delivery systems and survives both sonication and storage for several months. The binding between c-DNA-DOTA-Gd\(^{3+}\) and ND surface should thus be stable against moderate temperature and mechanical fluctuations. Furthermore, the hybridization of c-DNA and viral RNA is a highly efficient process\(^{20,21}\) and FNR induced by insufficient detachment of surface c-DNA-DOTA-Gd\(^{3+}\) should be considerably small.

Finally, to ensure sustained efficacy and specificity, it is imperative that the diagnosis methods target parts of the viral genome that are not considerably affected by naturally occurring viral mutations and are unique to SARS-CoV-2.\(^{2,35}\) Several methods that are based on sequence alignment currently exist to find the conserved parts of a viral genome (see for example ref 35). A generic text-mining method has been recently developed for rapid identification of segments of a whole genome that are likely to remain conserved during future genomic mutation events.\(^{36}\)

Due to the rapid spreading of the pandemic, a high throughput diagnosis capacity is needed, which can be achieved by our technique. Single or ensemble NDs can be incorporated in microfluidic devices with separated channels. Samples that possibly contain viral RNA are injected into the channels, and the resulting fluorescence signal is collected by a charge-coupled device camera. Although it is beyond the scope of this theory proposal, we note that practical issues such as bubbles or leakages in microfluidic chips might slightly degrade the performance of the sensor. Alternative ways of mixing ND with the virus sample might be proposed to bypass the potential problems with microfluidic setup. In addition to such simultaneous diagnosis of multiple samples, two other factors ensure the scalability of our protocol: Contrary to the general impression on the price of diamonds, synthesizing NDs that contain NV centers has become a mature technology and the material cost of single NDs is negligible. On the same note, NDs can make the technique more scalable than bulk diamonds with reduced cost. The system involves only short sequences of c-DNA and RNA, thus further limiting the cost in the chemical synthesis process.

The presented technology can be generalized to diagnosing other RNA virus such as HIV and MERS by using surface c-DNA that is specific to target virus. The technique can also be applied to detect DNA genome by replacing the c-DNA with an appropriate RNA sequence. While we consider NV centers in nanodiamonds, alternative quantum sensors or host materials might be adopted. For example, sensors based on silicon-vacancy centers in silicon carbide\(^{57}\) might be developed.

### CONCLUSION

We propose a hybrid quantum sensor for detecting the RNA of SARS-CoV-2 virus based on ND in nanodiamonds. We built a theoretical model to describe the quenching of NV’s relaxation time due to dipolar interactions between NV center and Gd\(^{3+}\) molecules and to evaluate the sensor’s performance. As the viral RNA detaches the Gd\(^{3+}\), large changes in the NV photoluminescence yield a detection limit as low as several hundred viral RNA copies. The FNR can reach less than 1%,
which is considerably lower than the state-of-art RT-PCR diagnosis method. The present diagnosis method is scalable, fast, and low-cost, which can meet the requirements of accurate estimation of epidemic trajectories and slowing down the current COVID pandemic.

■ ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.nanolett.1c02868.

CRISPR-based diagnosis, sensitivity analysis, magnetic noise from free Gd molecules in solution, and binding reactions in the sensing protocol (PDF)

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Notes
The authors declare the following competing financial interest(s): P.C., M.K., C.L., and R.S. are inventors on the U.S. Patent Application No. 63/248,106 filed by Massachusetts Institute of Technology.

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