

# Detection of SARS-CoV-2 Viral Particles using Direct, Reagent-Free Electrochemical Sensing

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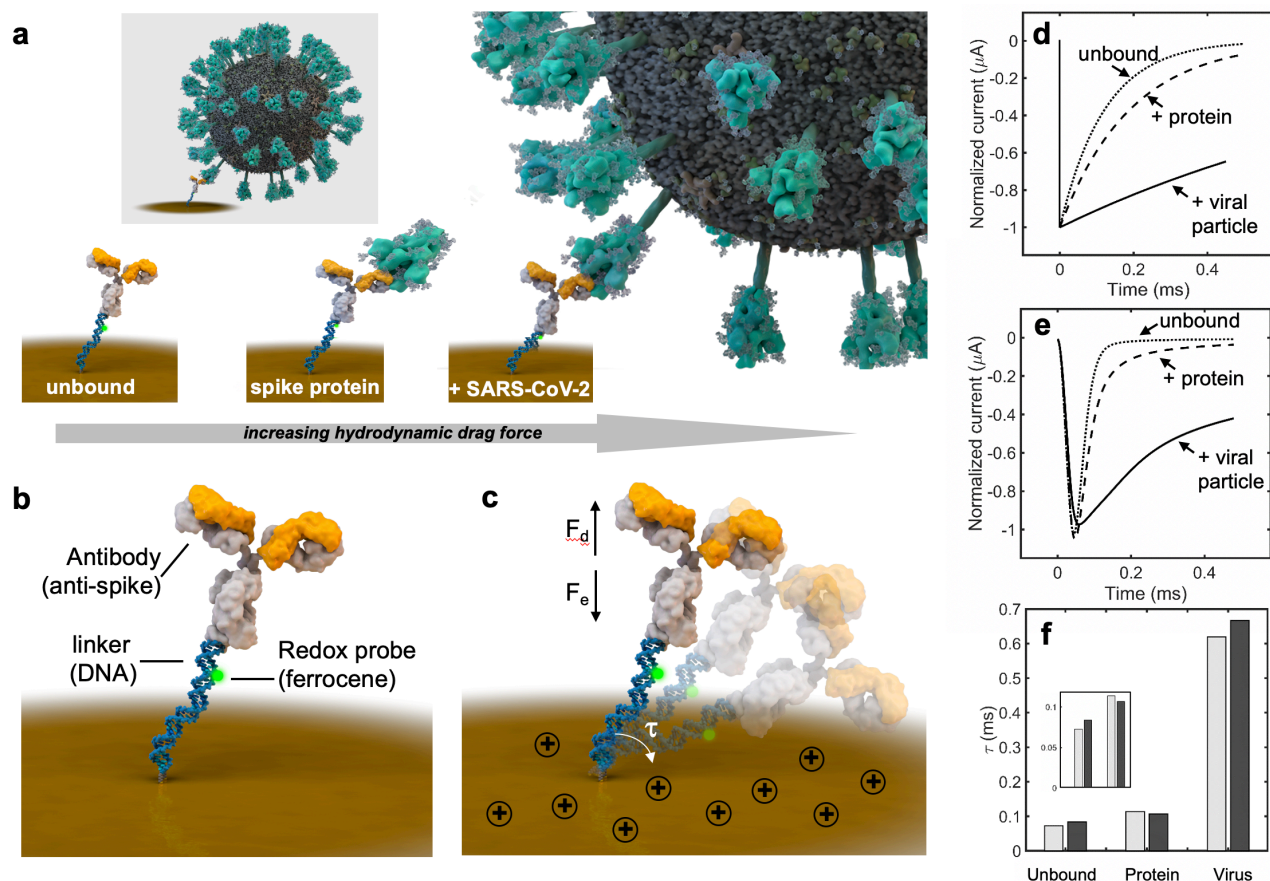
**ABSTRACT:** The development of new methods for direct viral detection using streamlined and ideally reagent-free assays is a timely and important, but challenging, problem. The challenge of combatting the COVID-19 pandemic has been exacerbated by the lack of rapid and effective methods to identify viral pathogens like SARS-CoV-2 on-demand. Existing gold standard nucleic-acid based approaches required enzymatic amplification to achieve clinically-relevant levels of sensitivity and are not typically used outside of a laboratory setting. Here, we report reagent-free viral sensing that directly reads out the presence of viral particles in five minutes using only a sensor-modified electrode chip. The approach relies on a class of electrode-tethered sensors bearing an analyte-binding antibody displayed on a negatively charged DNA linker that also features a tethered redox probe. When a positive potential is applied, the sensor is transported to the electrode surface. Using chronoamperometry, the presence of viral particles and proteins can be detected as these species increase the hydrodynamic drag on the sensor. This report is the first virus-detecting assay that uses the kinetic response of a probe:virus complex to analyze the complexation state of the antibody. We demonstrate the performance of this sensing approach as a means to detecting, within five minutes, the presence of the SARS-CoV-2 virus and its associated spike protein in test samples and in unprocessed patient saliva.

The detection of viral pathogens can be accomplished by devising assays that target viral proteins or nucleic acids.<sup>1,2</sup> Nucleic acid-based analysis typically conducted using the polymerase chain reaction or other types of enzymatic amplification reactions is the gold standard method for clinical detection of viral pathogens.<sup>3</sup> However, this approach is most often used in centralized laboratories with the necessary levels of sterility and trained personnel to minimize the risk posed by contamination and false positives. The detection of viruses using specific proteins or other features of the viral particle is also used clinically, but typically in the form of lateral flow assays with moderate sensitivity or ELISA assays that require external reagents and a laboratory environment.<sup>4</sup> Particularly with the increasing frequency of viral pandemics like COVID-19, there is a need for approaches to viral detection that are rapid, sensitive and straightforward for point-of-care or even at-home testing.

The development of reagent-free approaches for the detection of pathogenic species like viruses would permit the development of a new class of devices that could be used anywhere to facilitate pandemic management and safeguard the health of individuals. By removing the requirement for external reagents, the complexity of fully-integrated testing devices can be minimized for optimal user friendliness. While fluorescence and surface-enhanced raman spectroscopy<sup>5</sup> are candidates for reagent-free detection approaches, they are not readily amenable to the development of miniaturized devices with the needed levels of sensitivity.<sup>6, 7</sup>

Electrochemical readout, which can be implemented in devices with minimal footprint and complexity, has been used in a reagent-free format to detect a variety of protein and nucleic acids analytes,<sup>8,9</sup> but existing assay formats are not compatible with the direct detection of viral particles.

Reagentless electrochemical sensors based on the structural switching of DNA aptamers and other DNA-based structures containing recognition elements have been applied broadly to biomolecular detection.<sup>10,11</sup> Aptamer-based E-AB sensors are based on target-induced conformational changes that bring a redox reporter close to an electrode surface, triggering an increase in electrochemical signal.<sup>12</sup> Sensors based on double-stranded DNA with a small recognition element displayed distal to the electrode surface - E-DNA sensors - have also enabled readout of a variety of antibodies and other proteins.<sup>13</sup> These types of sensors have addressed many challenging problems including *in vivo* sensing of small molecules and the detection of antibodies related to infectious disease.<sup>14-16</sup> However, they are limited to recognition agents based on small molecules, peptide epitopes, and small proteins because diffusion of the sensor complex to the surface is relatively slow at the potentials used for readout.<sup>17,18</sup> These recognition agents are not suitable for viral particle detection and therefore new solutions are required.



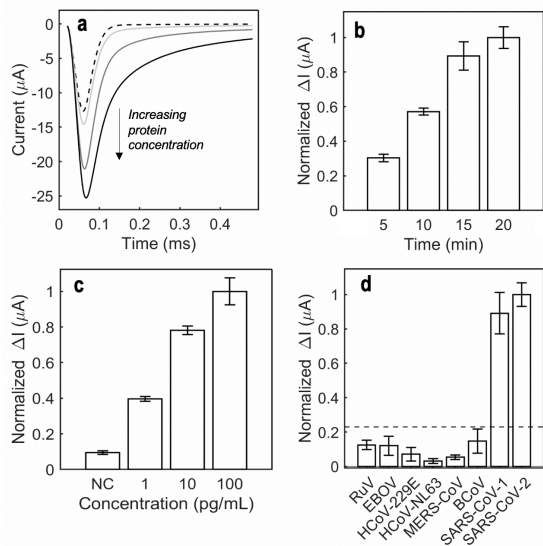
**Figure 1. Reagent-free sensing of viral particles using an electrochemical approach monitoring the kinetics of transport for a DNA-antibody complex.** **a) Sensor complexation with the SARS-CoV-2 viral particles.** The sensor will undergo a large change in hydrodynamic diameter in the presence of the spike protein and a viral particle, which would then influence the time required for the sensor to contact the electrode surface. **b) Sensor architecture.** The sensor features an analyte-specific antibody tethered to a linker composed of double-stranded DNA that also includes the redox probe ferrocene. With the application of a positive potential, the negatively charged complex is electrostatically attracted to the surface. **c) Development of a model describing sensor transport to the electrode surface.** The sensor experiences two opposing forces – a hydrodynamic drag force ( $F_d$ ) and a force induced by the applied electric field ( $F_e$ ). The transit time of the sensor to the surface is measured as  $\tau$ . **d) Simulated time-dependent current transients.** Chronoamperometry traces predicted by the model for an unbound sensor, a sensor bound to the viral S protein, and a sensor bound to a viral particle when an applied potential of +0.5 V is used. **e) Experimental time-dependent current transients.** Chronoamperometry data collected in the presence of the SARS-CoV-2 viral S1 protein (1 ng/ml) and viral particles ( $10^7$ /ml). **f) Comparison of theoretical and observed data for different complexation states of the sensor.** The simulated  $\tau$  values for the unbound, S protein bound, and SARS-CoV-2 bound cases match the behaviour seen experimentally. The  $\tau$  values from experimental data are extracted by collecting the current value at  $1/e$  the peak chronoamperometric current.

Here, we describe an electrochemical and reagent-free sensing approach that permits the rapid, sensitive and straightforward detection of SARS-CoV-2 viral particles (Figure 1). It is based on the field-induced transport of a sensor complex on the surface of an electrode and the modulation of the kinetics of transport by the binding of viral components. Despite the significant size of the viral particle and corresponding hydrodynamic force, we are able to visualize changes in the transport kinetics both in simulations and experiments and establish the presence of the virus in minutes. This work provides the foundation for the development of simple devices facilitating on-demand viral detection.

The sensor (Figure 1) consists of an analyte-recognizing antibody attached to a rigid, negatively-charged linker composed of DNA.<sup>19, 20</sup> A ferrocene redox probe is attached to the DNA linker to provide a way to track the interaction of the sensor with the electrode surface.<sup>21</sup> When a positive potential is applied to the surface, the sensor complex is attracted to the surface because of the negative charges in the DNA linker.<sup>22, 23</sup> When the ferrocene label comes into contact with the electrode, electron transfer occurs and ferrocene is oxidized with a characteristic time constant,  $\tau$ . This

approach was recently applied to proteins,<sup>9</sup> but we wondered whether targeting a virus like SARS-CoV-2 would be feasible given the size of the virus relative to the sensor and the large hydrodynamic drag force that would be exerted on the sensor if a binding event occurred (Figure 1a).

To explore the feasibility of this approach, we modeled the behavior of an uncomplexed sensor compared to sensor bound to viral protein or particle as an inverted molecular pendulum that experiences opposing forces generated by the applied electric field ( $F_e$ ) and a hydrodynamic drag force ( $F_d$ ) (see supporting information for all methods and materials). The drag force is affected by the size of the bound analyte and increases with the hydrodynamic diameter. This behavior was modeled to predict the current transients that would be generated in chronoamperometry experiments where a positive potential was applied to trigger sensor transport and oxidize ferrocene. As seen in Figure 1d, the current decay is slowed by the presence of the spike protein, but even more significantly in the presence of a virus with the approximate dimensions of SARS-CoV-2. A similar trend is observed when the sensor is incubated with high concentration of spike protein or viral particles (Figure 1e). It is noteworthy that the faradaic response from the

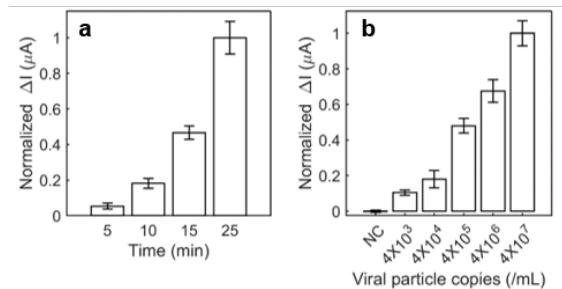


**Figure 2. Performance of reagent-free sensor in the presence of SARS-CoV-2 spike protein and analogues.** **a)** Sensor response to increasing protein concentration. Raw data for sensors exposed to varying levels (1 pg/ml, 10 pg/ml and 100 pg/ml – solid lines) of SARS-CoV-2 spike protein versus the unbound sensor (dotted line). See Figure S1 for comparison with capacitive currents generated by a sensor lacking ferrocene. **b)** Quantitation of concentration dependence. Sensors were able to distinguish binding of S protein down to 1 pg/mL. The negative control condition was 1 ng/mL of a non-target protein, troponin T. **c)** Time-dependency of the signal increase. Detection of S protein is distinguishable within 5 minutes. **d)** Specificity of viral detection. The sensor featuring an anti-SARS-CoV-2 Spike S1 antibody used as the recognition element can distinguish SARS-CoV-2 protein relative to most spike proteins of a panel of viruses. The sensor shows binding to SARS-CoV-1 given the homology of this protein for CoV-1 and CoV-2. The control line represents mean plus 3 times of the standard deviation of current changes after incubation of the sensor for 50 minutes with the non-target analytes (RuV, EBOV, HCoV-229E, HCoV-NL63, MERS-CoV, and BCoV) in buffer solution (N=5).

ferrocene label is easily distinguishable from the capacitive current observed with unlabeled sensors (see Figure S1,b). The results of the modeling match the experiments closely, with  $\tau$  values being extracted from each study that agreed within  $\sim 20\%$  (Figure 1f).

To test the analytical performance of this sensor, we challenged the system with recombinant S1 spike protein from SARS-CoV-2 as well as related proteins. In the presence of the cognate spike protein, statistically significant changes in the measured current are observed with the addition of as little as 1 pg/mL of target S1 protein in a buffer solution (Figure 2 a,b). We explored the kinetics of the sensor response by collecting current transients as a function of incubation time and determined that changes in the current could be observed within 5 minutes (Figure 2c). We then challenged the specificity of our sensor by introducing non-target proteins of several viruses, including seasonal human coronaviruses, Ebola, MERS, Rubella, and SARS-CoV-1 in addition to SARS-CoV-2 (Figure 2d). We utilized a CR3022 antibody for sensor construction which is an IgG against SARS-CoV and recognizes the RBD region of the spike protein on SARS-CoV-2. We observed that all of the viral proteins except for SARS-CoV-1 showed little cross-reactivity with the sensor. The SARS-CoV-1 and SARS-CoV-2 spike proteins display extensive homology and therefore it is not surprising that cross-reactivity was observed. The SARS-CoV-1 virus is currently extinct in humans; thus, this cross-reactivity can be tolerated in a clinical test.

To characterize the response of the reagentless sensor to viral particles, we used a pseudotyped virus, a lentiviral particle displaying SARS-CoV-2 spike proteins, as a detection target. Significant changes in the current could be observed

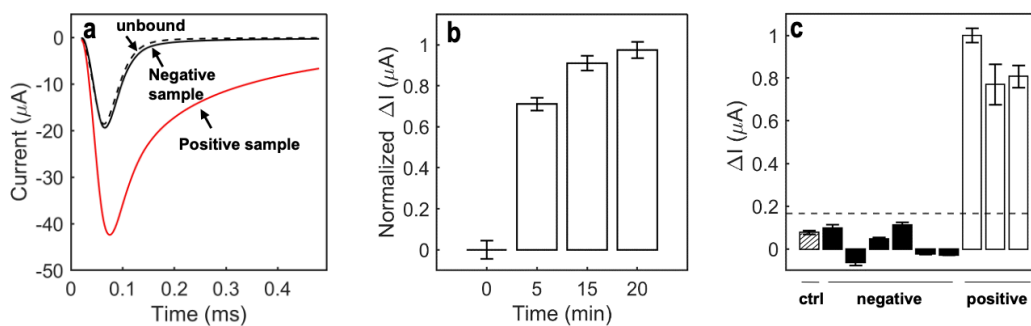


**Figure 3. Performance of reagent-free sensor in the presence of pseudotyped viral particles bearing the SARS-CoV-2 spike protein.** **a)** Time-dependent current response in the presence of pseudotyped virus. Significant changes in measurable current were observed within  $\sim 10$  minutes. **b)** Concentration dependence and limit of detection for pseudotyped viral particles. The reagent-free sensors were able to distinguish binding of  $4 \times 10^3$  viral particles per mL. The negative control (NC) contains  $4 \times 10^4$  viral particles per mL of lentivirus not expressing spike protein. For both a and b,  $50 \mu\text{L}$  of sample was used. Currents represent background-subtracted values where the signal from the unbound sensor was used. Error bars represent standard deviations, and currents were normalized to the highest concentration for b or maximum time for a. At least 3 independent measurements were performed for each of the conditions.

within 10 minutes of incubation (Figure 3a) when as low as 4000 copies per mL of viral particles were used (Figure 3b). This level of sensitivity is commensurate with many tests based on enzymatic amplification<sup>24</sup> of nucleic acids and is significantly better than existing reagent-free lateral flow tests that have limits of detection in the ng/mL range.<sup>4</sup> The use of electrochemical detection for antigen recognition appears to provide a sensitivity boost relative to optical detection methods of detection while preserving a user-friendly testing format.

We envisioned that the ideal application of this sensing system would be the detection of SARS-CoV-2 directly in the saliva of infected patients. This testing approach could be used for rapid screening without the need for invasive sampling reliant on nasopharyngeal swabbing and given the literature evidence supporting the presence of high viral loads in the oral cavity, viral detection using this biological fluid should be possible.<sup>25, 26</sup> To assess the feasibility of this type of testing, we analyzed a panel of representative saliva samples from SARS-CoV-2 RT-PCR positive and negative human subjects in a blinded study. The saliva samples provided from a clinical site were heat treated to deactivate the virus; as shown in Figure S3, heat treatment does not appear to disable our detection approach. The current changes observed for the clinical saliva specimens are summarized in Figure 4 and indicate that our approach can return results comparable with gold-standard RT-PCR approaches, but in minutes instead of days. Furthermore, prior studies support the collection of electrochemical signals using reagent-free sensors directly in the mouth,<sup>9</sup> indicating that this type of screening could be performed *in situ* using an oral probe without any sampling required.

Here we have described a viral detection technology based on a kinetic sensing mechanism that monitors the potential-triggered transport of a DNA-antibody conjugate. The viral detection sensors are unique as no additional reagents are required for readout, which permits the use of a very simple device – a standalone sensor chip – for detection. While several new technologies for SARS-CoV-2 have been reported recently that represent significant advances,<sup>27, 28</sup> this is the first with the ability to directly detect whole SARS-CoV-2 viral particles in undiluted saliva samples from COVID-19 infected patients within minutes. This highly effective viral detection method can be utilized for screening individuals



**Figure 4. Analysis of patient saliva samples.** a) Analysis of SARS-CoV-2 positive saliva sample (red solid line), a SARS-CoV-2 negative saliva sample (black solid line) and unspiked human saliva (dashed lines). Chronoamperometry traces were collected with a potential step of +500 mV. b) Time-dependent current modulation observed in the presence of SARS-CoV-2 positive patient saliva sample. An undiluted and unprocessed (except for heat inactivation) whole saliva sample collected from a SARS-CoV-2 positive patient was used in this study. The time-dependent current demonstrates the significant change in measurable current within ~ 5 minutes. c) Blinded patient saliva sample analysis. Sensors were challenged with saliva samples collected from SARS-CoV-2 positive and SARS-CoV-2 negative patient. The threshold line indicates mean current + 3 times of standard deviations of signals collected from sensors acting as negative controls. If the current change for any sample was higher than the threshold, the samples was considered as SARS-CoV-2 positive. Error bars represent standard deviations. At least 3 individual measurements were performed for each of the conditions.

for viral infections, an important capability for pandemic management. In addition, the testing approach can be easily extended to the detection of other viral targets simply by changing the antibody used to construct the sensor, and thus we envision that this sensing platform will find broad applications.

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. The Supporting Information includes materials, methods, modeling details and additional experimental data.

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##### Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally

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#### ABBREVIATIONS

CA, Chronoamperometry; RuV, Rubella Virus; EBOV, Ebola Virus; HCoV-229E, Human Corona Virus (strain 229E); HCoV-NL63, Human Corona Virus (strain NL63); MERS-CoV, Middle East Respiratory Syndrome Corona Virus; BCoV, Bovine Corona Virus; RBD, Receptor Binding Domain.

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TOC Graphic

