A low-cost, versatile and portable impedimetric biosensor for SARS-CoV-2 detection

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Abstract

On March 11th 2020, Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) was declared as a worldwide pandemic by the World Health Organization (WHO) [1]. This virus is considered highly infectious and can lead to an acute respiratory disease, from mild to fatal, with an increase in severity linked to underlying medical conditions [2].

The gold standard for SARS-CoV-2 diagnosis is still Reverse Transcript Polymerase Chain Reaction (RT-PCR), which is a laboratory-based molecular diagnostic method. Although PCR provides a sensitive and specific detection of the viral load, it is quite costly and needs trained personnel and equipment. Typically PCR analysis takes also very long time for the sample transport, preparation and analysis (6-72 hours) [3]. Because of these reasons, it has already been reported that these techniques are unable to combat a highly infectious pathogens specifically in a state of low-resources, where the costs are high for mass screening and the high spread rate dictates the need for a fast early diagnosis [4]–[7].

Although there have been enormous efforts for developing Point of Care (POC) test devices that guarantee the so-called 'ASSURED' criteria (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users) demanded by the WHO, there is still an urge to improve the existing platforms [8].

For instance, lateral flow immunoassays (LFIAs) tests as POC platform still suffer from low analytical performance [9]–[11] and there is still a controversy over their sensitivity and accuracy [12]–[15].

On the other hand, an early modelling study by Larremore et. al. highlighted the importance of performing continuous diagnosis of the disease for controlling the transmission of the virus, where even with an every-3day instantaneous testing scheme, the estimated infection transmission would be zero even if the tests are not so precise [16].

However, these LFIAs tests are only recommended to be used for individuals who are showing symptoms [17], [18], because it is challenging to detect the virus in carriers who host a reduced concentration and whose symptoms are not so predominant as before. For this reason, it is crucial to develop sensitive, cheap and portable sensors which reliably detect low viral loads.

Electrochemical biosensors are promising technologies for the POC devices, since they are cheap, compact, scalable, and user friendly. They are more sensitive compared to other POC devices like LFIA [8], [19]–[22], and they have the potential to be completely quantitative or semi-quantitative [23], [24]. In general, electrical measurement is performed employing an electrode that traces changes caused by the kinetic of a binding reaction, which indeed causes a change in electrochemical state of system (the electron transfer from the sample to the transducer) [25].

Although Differential Pulse Voltammetry (DPV) and Square Wave Voltammetry (SWV) have been adopted for detection of SARS-CoV-2 and tend to be faster in their response time, Electrochemical Impedance Spectroscopy (EIS) based biosensors are becoming more popular due to their versatility and label-free nature [26].

There are four major features in an electrochemical POC platform: 1. scalable, cheap, reliable and reproducible electrodes, 2. optimized and reliable preparation protocol, e.g. biofunctionalization steps, 3. automated or semi-automated sample handling and data acquisition, 4. reliable, sensitive, accurate and cheap readout. [25], [27]. Despite the astonishing improvements short time after the virus breakout, there are few works that combine more than two of these features at once for a POC.

The aim of this work is to develop an electrochemical biosensor platform based on EIS, which has the potential of satisfying all of these requirements. The proposed biosensor fabrication is very simple and straightforward, and involves no complicated technique or functionalization step. A microfluidic channel has been designed to make the sample handling and data acquisition in a semi-automated manner, and it is also integrated on a Card-Edge Printed Board Circuit (PCB) to make it more user-friendly and deliverable. The sensor chip was also used with both a desktop-portable electrochemical workstation and a mobile phone version, to demonstrate the capability of becoming a POC device.

First, we detected the Spike Glycoprotein of SARS-CoV-2 in physically relevant solution to characterize the developed biosensor and after optimizing the performance of the biosensor using Design of Experiment (DOE), a Limit of Detection (LOD) in fM range was achieved. Afterwards, the sensor performance was tested with nasopharyngeal

samples of patients, where it was able to detect the positive samples of patients with a CT (Cycle Threshold) as high as 27, which refers to low concentration of virus. Additionally, we demonstrated the versatility of this platform for being employed as a highly portable test device with smartphone-based readout, and also by integration of multiple electrodes for multiplexing and parallel analyte detection by simple connection to commercially available adapters. Figure 1 shows the concept and photos of the biosensor as well as its detection performance.

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Figures

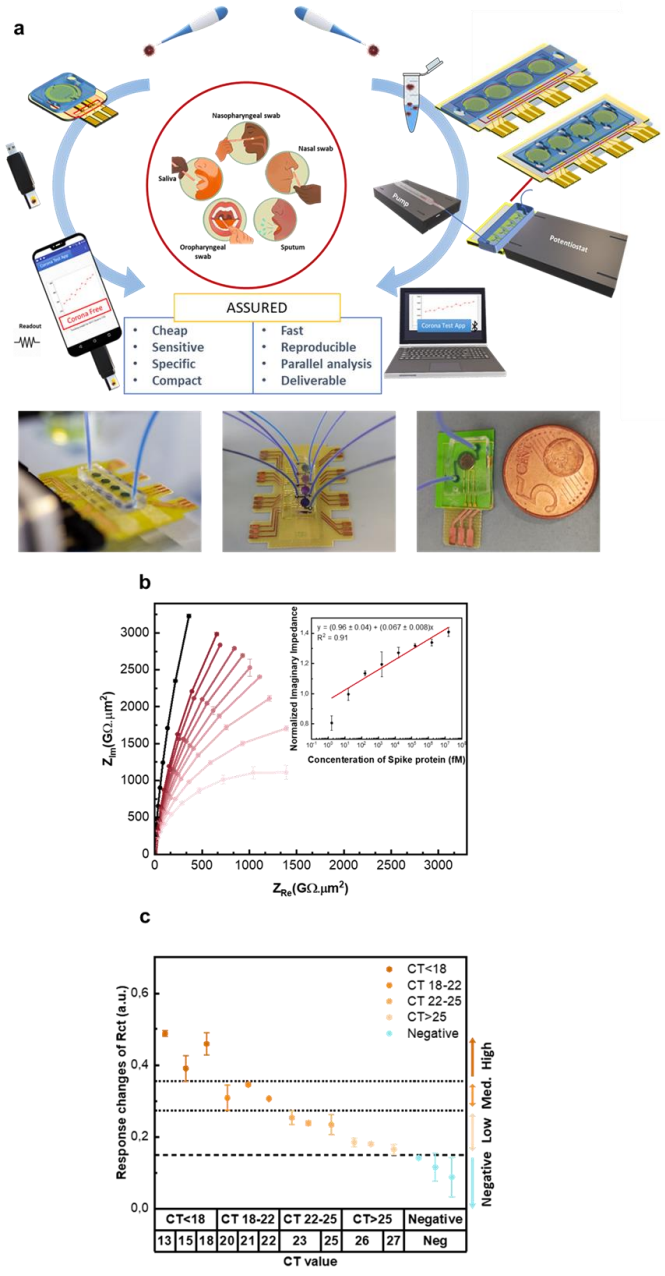

Figure 1. a) A schematic representing the concept of the proposed biosensor with a real image of fabricated sensors, b) Nyquist graph showing the response of biosensor with different concentration of SARS-CoV-2 Spike protein ranging from 1.6 fM to 1.6 nM, c) Changes of the charge transfer resistance with changes of Ct-value.