

## Development and characterization of electronic noses for the rapid detection of COVID-19 in exhaled breath

Christelle Ghazaly<sup>1\*</sup>, Krystyna Biletska<sup>2</sup>, Etienne A.Thevenot<sup>3</sup>, Philippe Devillier<sup>4</sup>, Emmanuel Naline<sup>4</sup>, Stanislas Grassin-Delyle<sup>4</sup>, Emmanuel. Scorsone<sup>1</sup>

<sup>1</sup>CEA, LIST, Diamond Sensors Laboratory, F-91191 Gif-sur-Yvette, France

<sup>2</sup>CEA, LIST, Laboratoire Sciences des Données et de la Décision, F-91191 Gif-sur-Yvette, France

<sup>3</sup>Département Médicaments et Technologies pour la Santé (DMTS), Université Paris-Saclay, CEA, INRAE, MetaboHUB, Gif-sur-Yvette, France

<sup>4</sup>Hôpital Foch, Exhalomics, Département des maladies des voies respiratoires, Suresnes, France

(\*) [christelle.ghazaly@cea.fr](mailto:christelle.ghazaly@cea.fr)

**Keywords:** Breath-analysis; electronic nose (e-Nose); COVID-19; volatile organic compounds (VOCs); diagnostics.

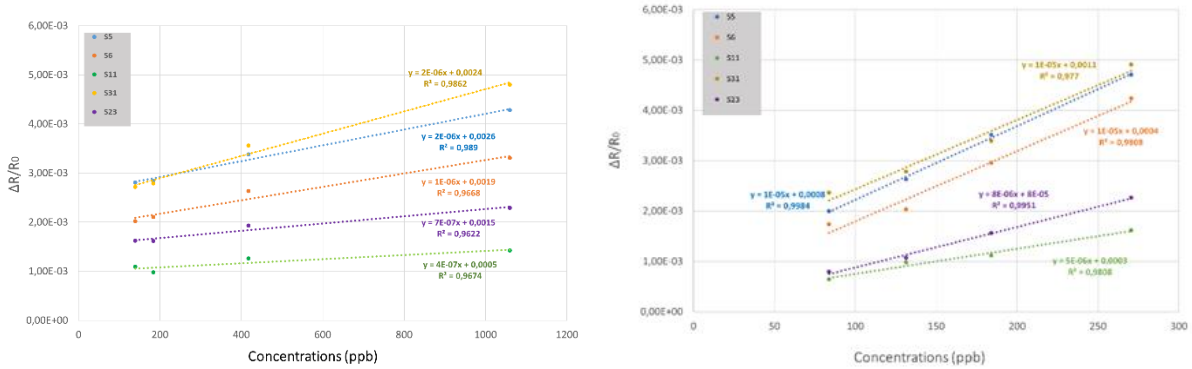
**ABSTRACT:** Non-invasive and rapid approach is potentially needed for diagnosis of COVID-19. In this work, exhaled breath analysis using e-Nose, is presented as an innovative technique to identify the COVID-19 specific VOCs. The analytical performances of Cyranose<sup>®</sup>, a commercial e-Nose device, were investigated under controlled conditions. Sensitivity, limit of detection and reproducibility of standardized VOCs existing in the breath was assessed. In addition, the effect of various experimental conditions on sensor response was evaluated, including temperature, relative humidity, flow and sampling time, aiming to select the optimal parameters and to validate it in clinical trials to detect the COVID-19 biomarkers. Cyranose<sup>®</sup> exhibits high sensitivity and reproducible response towards acetone and nonanal, with a limit of detection of 63 ppb and 20 ppb respectively. Furthermore, results show that the variability of relative humidity, temperature and flow sampling, induced a significant sensors response variation, whereas, varying the sampling time does not affect significantly the sensor response.

### Motivation and results

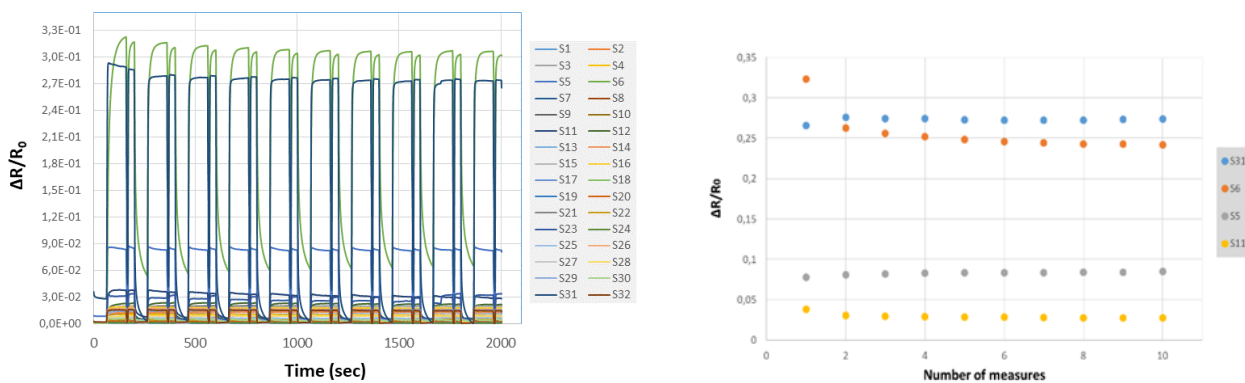
Covid-19 is a coronavirus disease caused by the SARS-CoV-2 virus. In December 2019, a first alert was launched from China, in Wuhan, before spreading to the rest of the world and caused more than 248 million infections and an excess of 5 million deaths (as of November 5th, 2021). Rapid and accurate detection of COVID-19 is a necessity to the prevention and effective control of the pandemic. The current standard diagnostic method and the dominant technique is a real-time reverse transcriptase-polymerase chain reaction (RT-PCR), based on a nasopharyngeal or oropharyngeal swab, exhibiting a very high specificity. However, the high occurrence of false-positive or false-negative due respectively to swab contamination or the non-presence of SARS-Cov-2 in the oropharyngeal environment renders this method less sensitive [1]. In addition, RT-PCR relies on an invasive and expensive procedure. Other identification tests for COVID-19 infection exist, including serological and immunological tests and chest CT scans [2]. All these tests consume time, are expensive and require trained personnel. Breath analysis could be an alternative method to identify biomarkers in exhaled breath and thus a promising technique for a rapid and easy diagnostic of the COVID-19 disease. Various breath analysis techniques have been used for the detection of specific VOCs for a particular disease: GC-MS, laser spectroscopy and other miniature, low cost e-Noses devices [3].

The objective of this collaborative work with Hospital Foch, Paris, is to evaluate the application of Cyranose<sup>®</sup>320, a commercial e-Nose, for rapid COVID-19 diagnostic. In particular, the goal here is to assess the sampling conditions of exhaled breath on the e-Nose performances to discriminate between COVID-positive and COVID-negative patients. This technology is equipped with 32 nanocomposite chemiresistive gas sensors, measuring in real-time the sensor's resistance variations of the VOCs present in the sample. We have evaluated sensors response towards acetone, presents in the exhaled breath of the normal population, and towards nonanal, presents in the breath of COVID-19 patients as identified by PTR-MS at Hospital Foch team [4]. Different concentrations were generated in dry nitrogen by using corresponding permeation tubes and a controlled gas rig. The e-Nose was operated at a constant flow rate of 120 mL/min for 60 seconds of baseline recording with ultra-pure nitrogen, and then for a sample recording of 90 seconds. *Figure 1* illustrates the calibration curves of five sensors, exhibiting a significant response to acetone and

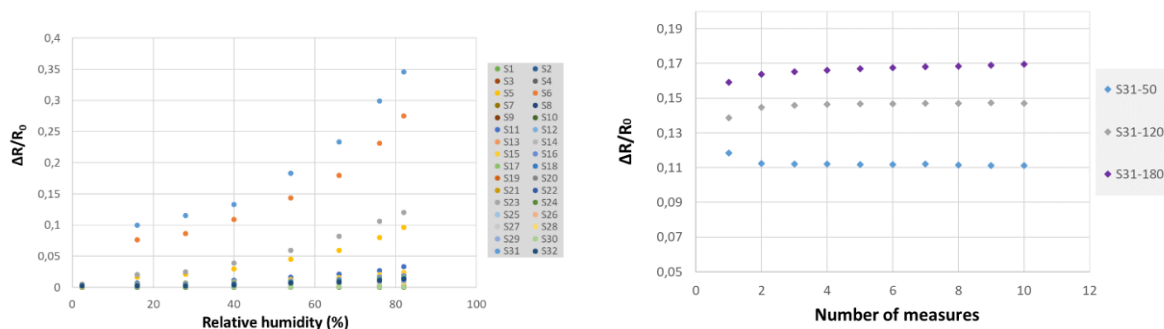
nonanal. In addition, Tedlar bag containing exhaled breath of a control patient was tested, an example of sensors signals resulting, is illustrated in *Figure 2 (a)*. Sensor variations calculated for ten successive measurements show sensors response repeatability, as presented in *Figure 2 (b)*. The effect of varying relative humidity rate and of the sampling flow rate on sensor response is presented in *Figure 3 (a)* and *(b)* respectively. Thus, the sensor's response is highly affected by humidity and show greater variability by increasing the flow rate sampling. The influences of temperature and sampling time variations was also evaluated.



a) b)  
 Figure 1: Resistance variations of sensors S5, S6, S11, S23 and S31 under different concentrations of (a) acetone and (b) nonanal.



a) b)  
 Figure 2: (a) Real-time resistance measurement of 32 sensors for an exhaled breath of a control patient during ten successive measurements and (b) the corresponding resistance variations of sensors S5, S6, S11 and S31.



a) b)  
 Figure 3: Sensors response variation as a function of (a) relative humidity changes under nitrogen from 2% to 84% and (b) Sampling flow rate changes from 50 mL/min to 200 mL/min for ten measurements under 92% RH.

## References

[1] A. Tahamtan, A. Ardebili (2020), Real-time RT-PCR in COVID-19 detection: issues affecting the results; *Expert review of molecular diagnostics*, **20**(5), 453-454.  
 [2] D. Shyu, J. Dorroh, C. Holtmeyer, D. Ritter, A. Upendran, et. Al (2020), Laboratory tests for COVID-19: A review of peer-reviewed publications and implications for clinical Use; *Missouri medicine*, **117**(3), 184.

[3] G. Giovannini, H. Haick, D. Garoli (2021), Detecting COVID-19 from Breath: A Game Changer for a Big Challenge; *ACS sensors*, **6**(4), 1408-1417.

[4] S. Grassin-Delyle, C. Roquencourt, P. Moine, G. Saffroy, S. Carn, et. Al (2021), Metabolomics of exhaled breath in critically ill COVID-19 patients: A pilot study; *EBioMedicine*, **63**, 103154.