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MEMS Biosensors and COVID-19: Missed Opportunity

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ABSTRACT: The acceleration of climatic, digital, and health challenges is testing scientific communities. Scientists must provide concrete answers in terms of technological solutions to a society which expects immediate returns on the public investment. We are living such a scenario on a global scale with the pandemic crisis of COVID-19 where expectations for virological and serological diagnosis tests have been and are still gigantic. In this Perspective, we focus on a class of biosensors (mechanical biosensors) which are ubiquitous in the literature in the form of high performance, sensitive, selective, low-cost biological analysis systems. The spectacular development announced in their performance in the last 20 years suggested the possibility of finding these mechanical sensors on the front line of COVID-19, but the reality was quite different. We analyze the cause of this *rendez-vous manqué*, the operational criteria that kept these biosensors away from the field, and we indicate the pitfalls to avoid in the future in the development of all types of biosensors of which the ultimate goal is to be immediately operational for the intended application.

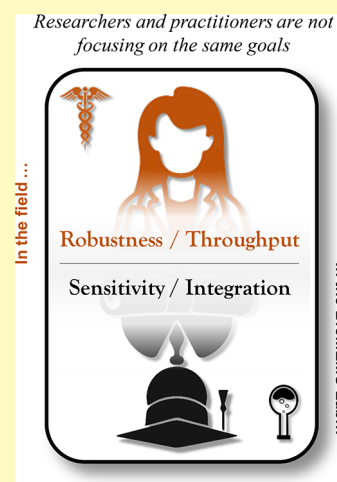
KEYWORDS: MEMS, BioMEMS, biosensors, COVID-19, SARS-CoV-2

In 2008, two of the authors of this article published a review article presumptuously titled “Biosensors and Tools for Surface Functionalization from the Macro- to the Nanoscale: The Way Forward”.¹ The aim of the article was to present a global view of the functionalization and transduction techniques used in the field of biodetection as well as to provide a perspective in this same field for a new category of biosensors (new at that time), namely, that of nanobiosensors. Being researchers from the micro- and nanoelectromechanical systems (M(N)EMS) community, the emphasis was on mechanical transducers. The last two sentences of the article’s conclusion were, “Finally, is it the fact that having such a tremendous choice of systems would sometimes complicate the choice itself [of the right biosensor for a given application]? This is another question that remains to be solved”.

Twelve years later, in the midst of the COVID-19 pandemic, these two sentences resonate as a premonition. Indeed, among the plethora of biosensors and functionalization methods described in the review, none has been the subject of a viable alternative to the gold-standard techniques such as PCR (Polymerase Chain Reaction) and ELISA (Enzyme Linked ImmunoSorbent Assay) to carry out virological or immunological tests for the detection of viral antigens and antiviral antibodies (informing about a current or past infection).² However, while the successively affected countries were confining their populations one after the other from the end of January 2020 (first, China, followed by Italy, France, Spain,

and the UK), and as we were witnessing the shortage of conventional tests and reagents necessary to make them work, the scientific community mobilized to seek to implement new testing methods able to identify sick people and monitor the spread of the virus—identified as one of eight research action priorities by the World Health Organization (WHO).³ As scientists in the biological microelectromechanical systems (bioMEMS) community, we had two immediate reflexes: (1) look through our own arsenal of microdevices for the available technological bricks to create an operational system; (2) send a call to friends and colleagues in our community to elicit the same reaction and try to get an immediate operational response. These two actions produced the same result, namely, the inability to deliver any viable technical solution.

Once the excitement of the moment was overcome, we faced the reality that principally molecular diagnosis tools such as real-time reverse transcriptase PCR (qRT-PCR), and to a lesser extent—since not recommended by the WHO for clinical decision-making⁴—ELISA and LFA (Lateral Flow



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Assays) were going to definitively lead the battle⁵ (each technique with its limits, well-known and assumed). We quickly witnessed the approval and the commercialization of kits for COVID-19 diagnostic,^{6,7} but none relying on MEMS or other micro- and nanotechnology-based sensors. Hence, we resorted to the idea that we had to carry out a retrospective analysis of the *rendez-vous manqué* between the mechanical biosensors and the actual historical pandemic.

If we analyze the bibliography during the last 20 years, we observe that despite the “pandemic” growth of papers related to “mechanical biosensors” (almost 1700% growth, with more than 160 journal papers published last year (from Web of Science analysis)), none of the systems described as ultimate tools have been able to provide a viable solution to the needs of virological and immunological tests for clinical diagnosis and surveillance or to the fundamental questions related to the mechanisms of the SARS-CoV-2 infection.

The main question is, why this failure? Why, despite more than 20 years of research in this field involving universities from 65 different countries and relying on funding from more than 220 different funding agencies (from Web of Science analysis), no mechanical biosensor (whatever its level of maturity) has opened any prospect in terms of response to the needs arising from the current health crisis?

The purpose of this article is to open the horizon beyond the field specific to bioM(N)EMS and to invite similar communities to avoid the pitfall of too much confidence and self-sufficiency by offering turnkey solutions that have no reality suited to the real world. This will save time and money and will allow digging into other, much more promising leads that we will attempt to outline at the end of the article.

■ THE PROCESS OF MOLECULAR ANALYSIS: GENERAL CONSIDERATIONS, SPECIFIC CONTEXT OF SARS-COV-2, AND HOW BIOMEMS HAPPENED TO BE UNFIT FOR THE REAL WORLD

In medical biology, molecular analysis is carried out following specific steps, from sample collection to the interpretation of the results. The analytical procedure can be broken down in three elements.⁸ First of all, the analytical principle that concerns the measurement or detection technique and that physicists and engineers call the *biosensor*. A biosensor consists of a bioreceptor coupled to a transducer that translates a biorecognition event into a measurable signal, where MEMS is a class of mechanical transducers.⁹ Second, the analytical method which includes the sample preparation steps used to optimize the conditions suitable for detection (i.e., adapted to the detection technique), as well as the technological means implemented for the correct operation of the sensor (e.g., fluidics, temperature control, measurement electronics, user interface, etc.) corresponds to the *instrument*. Finally, the complete *analytical procedure* covers the entire measurement chain, from sampling to the final information.

The steps of collecting and interpreting the results are the responsibility of medical professionals: qualified personnel collect samples following specific protocols to ensure validity and conformity, and only a medical doctor is ultimately authorized to issue a diagnosis based on the results of the analysis. This is the procedure followed in medical analysis laboratories equipped with high-performance measuring instruments (that have benefited from major technological advances since the 1960s and today offer the possibility of carrying out

precise and exhaustive analyses on a large number of samples with a quality approach that leads to minimized errors¹⁰). This is not the case for point-of-care (POC) tools or bedside devices that are divided into two subcategories:¹¹ benchtop analyzers, which are ultimately miniaturized versions of conventional systems, and portable devices, such as immuno-chromatographic tests on strips/LFA or *in vivo* sensors. For example, diabetics now have access to analytical tools for monitoring their blood sugar levels and, in this context, take their own sample—a drop of blood obtained by pricking one's finger.¹² They are then able to interpret the results of the measurement and make decisions regarding their diet. Of course, this example cannot be transposed to more complex pathologies at the moment, but it is the most emblematic case of the bedside analytical tool, as opposed to centralized analysis platforms. Still, the main reason for the use of POC tools is the speed of turnaround and response, which is crucial, for example, to determine in emergency departments through cardiac biomarker assays whether a patient with acute chest pain is having a myocardial infarction or, in the present COVID-19 crisis, if a patient with flu-like symptoms should self-quarantine because of infectious risks.

Before getting further into the discussion of key elements in biosensing, especially in the context of the current COVID-19 outbreak, let us argue about what went wrong with the application of bioMEMS as virological and serological tools on the battlefield against the SARS-CoV-2 virus. BioMEMS can be defined as electromechanical devices or systems fabricated using micro/nanoscale technologies and dedicated to the analysis/sensing/identification of specific biological entities or the interaction in between them. If we consider that areas of research and applications of bioMEMS range from micro-fluidics and surface functionalization to tissue engineering, implantable microsystems, etc.; then, bioMEMS have been designed, developed, and promoted for more than 20 years as the ultimate tools for rapid, low-cost, ultrasensitive diagnosis of all kinds of pathologies that are affecting human beings. In all this, not to mention their nanoscale counterparts, the bioN(ano)EMS, which ultimately have been advertised as the future nanosystems for complex biosensing,¹³ meaning that for such a basic challenge of quantifying the viral load of a known virus (SARS-CoV-2) or the amount of antibodies anti-SARS-CoV-2 in a patient serum, bioNEMS would have done the job more easily and brightly than standard tools such as PCR or ELISA.

In the past two decades, the conviction that BioM(N)EMS, and especially resonators, of all shapes and sizes, were to revolutionize the market of biological detection was strong. Seminal papers were published to demonstrate the potential of nanomechanical resonators to ultrahigh sensitivity to mass loading.^{14–16} Simultaneously, complementary metal oxide semiconductor (CMOS) integration of MEMS/NEMS resonators and parallel addressing of thousands of NEMS became feasible.¹⁷ Finally, many works demonstrated the ability of attaching aptamers,¹⁸ antibodies,¹⁹ enzymes,²⁰ and DNA probes²¹ to the surface of cantilevers to specifically capture biological targets of interest—including viruses²²—within a sampled liquid volume.

Every single specification from high sensitivity (generally more often very low limit-of-detection), specificity to target, and massive multiplexing (multiplexed electrical/optical addressing) has been demonstrated, and a road to a hand-held, on-field biological testing unit relying on the prowess of

The smoke and mirrors of mechanical biosensors

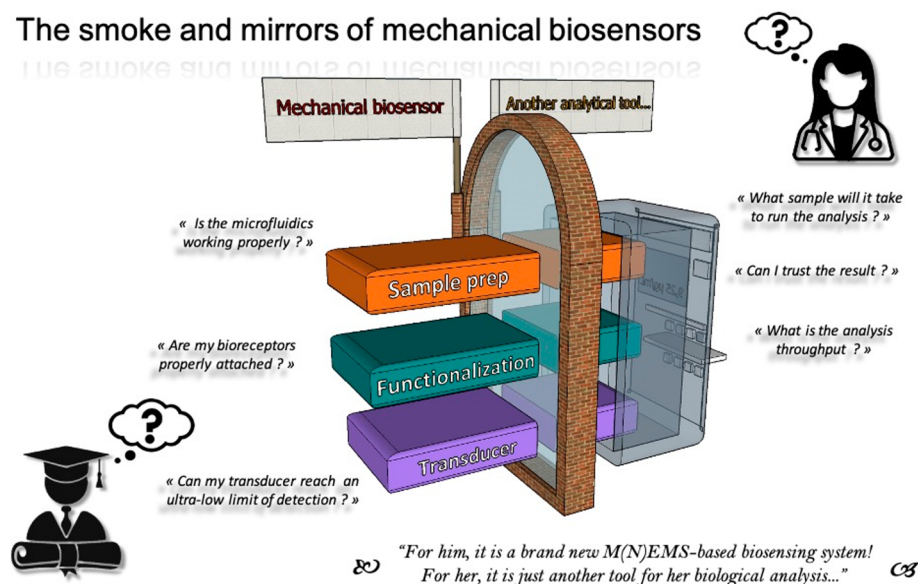


Figure 1. “The smoke and mirrors of mechanical biosensors” illustrates the gap between the questions researchers and end-users are aiming to answer.

M(N)EMS seemed imminent. Moreover, with numerous companies already developing and selling physical sensors that include MEMS solutions, we were expecting to see MEMS-based devices invading the market of point-of-care biological sensing. Even if we have witnessed the successful use of MEMS sensors for health monitoring such as CardioMEMS, the very first implanted biomedical MEMS sensor for monitoring the pulmonary arterial pressure developed by Mark Allen in the early 2000s at Georgia Tech, and which is now a device recommended for patients with heart failure in Europe,²³ these physical sensors are not, by definition, biosensors. Hence, the only evidence we can observe is that the invasion of MEMS biosensors has not happened yet, and the next paragraphs will provide part of the explanation for such broken promises.

The overwhelming majority of point-of-care tests actually performed in the field on a daily basis are of two types: 1, fast response time tests that can provide results in a matter of minutes with moderate sensitivity and mostly consisting of rapid diagnostic strip tests;²⁴ and 2, ultrasensitive molecular tests in which sampling is done in the field, but analysis (that requires chemicals and primers) is done in a lab setting and provide results within a few hours. One could argue that molecular tests, such as PCR, are not performed “in the field”, yet, in developed countries, the network of laboratories that can perform these analyses can be sufficiently meshed so that the travel to these facilities can be integrated in the total analysis time. Moreover, with the advent of isothermal amplification techniques (e.g., loop-mediated isothermal amplification, clustered regularly interspaced short palindromic repeats-triggered amplification), several scientific teams are now able to bring the entirety of the chain of analysis to the field with microfluidic lab-on-chip devices and lateral flow readouts that prove efficient in reducing the analysis response time.^{25–31}

Both rapid tests and molecular diagnosis tools have a monopoly in answering the need for in-the-field biological tests with respectively very different features and technical means. They have been able to do so because they have the figure of

merit that mostly matters for the users: confidence in the result. For authorities and healthcare operators relying on these tests to cope with important decisions, the advent of false positive or false negative tests could lead to critical decisions such as population lockdown, whereas there is no need, or vice versa. Applying aggressive counter-measures to a situation falsely identified as sanitary-threatening can have dire consequences.

MEMS biosensors (here shortly called bioMEMS) consist of two parts: a means of transduction of the biological event happening on the active surface and a layer of biologically specific recognition molecules; thus, their development is intrinsically pluridisciplinary. BioMEMS is currently pushed by scientific experts from the field of micro- and nano-technologies. Immunologists, molecular biologists, and functionalization experts still have little involvement in the development of the bioMEMS solution. As a result, the first key mistake is that functionalization of bioMEMS is often put last, using standard (and too often inadequate) techniques and paying too little attention to its implementation. Obviously, the transducer is the means to ultralow mass or charge sensitivity and can detect a small handful of biological species, but the biological receptors layer held to the transducer is the actual interaction space between the biological target in its medium and the sensor itself. It is natural to consider that one needs to better understand the mechanics of bioreceptor–target interaction at the sensor’s active surface level to increase the confidence level in BioMEMS.

The second key mistake when developing biological total analysis systems based on BioMEMS with the intent of transferring this technology to end users lies in poorly identifying the figures of merit the final system needs to ensure acceptance by the users. BioMEMS scientific teams usually center most of the developments on performance such as ultralow limits of sensing, massive multiplexing, and miniaturization. Despite ultralow mass sensitivity for resonant bioMEMS, as a matter of fact already demonstrated for virus detection,³² or massive multiplexing of the bioNEMS functionalization,³³ these techniques will fail to convince end

users if they do not take into account the issue of the robustness of the provided detection answer. Ultimately, micro- and nanotechnological bricks for biological analysis will not be considered as alternative technologies to the conventional gold standards on the field, because users will prefer the latter ones as best providers regarding the confidence in the final result and the ability to answer the real needs of specific biosensing applications (Figure 1), as will be discussed in the following sections.

■ BIOSENSORS

Microelectronics-Derived Technologies for Molecular Analysis. The expected contribution of technologies derived from microelectronics (i.e., microsystems, microfluidics, nanotechnologies) to the field of molecular analysis is twofold: first, the miniaturization of systems and the possible reduction of device costs and, second, the development of new detection principles to improve sensitivities and lower detection thresholds.

The vast majority of biosensors, which transform biological recognition into a measurable physical signal, are based on electrochemical and optical transductions,³⁴ but many other approaches have also been proposed, including ones calling for electrical and mechanical, e.g., MEMS, transducers. Thus, the literature on this subject is comprehensive and even if very few products have made it to the market with regard to the volume of research (we can nevertheless cite the surface plasmon resonance (SPR), quartz crystal microbalance (QCM), and other digital PCR technologies), the expected impact of these technologies on the world of molecular analysis is tremendous. However, in order to have a real medical utility, and this is especially true to fight the COVID-19 pandemic the world is now facing, the specifications to be met are extremely demanding and there are still many challenges to overcome.

What is the Role for the Biosensor: Screening/Diagnosis/Prognosis/Disease Management? Molecular assays that look for specific biomarkers can have several clinical uses. Thus, the first question that should be asked when developing or wishing to use a biosensor in the biomedical field is for what purposes and in which cases should it be used? Indeed, even if in the introductions of publications presenting detection platforms, the application is often fairly well tailored in terms of biomarkers to be detected and pathologies to be treated, the role of the biosensor is often less well-defined.

Pendley and Linder have recently discussed the role of the biosensor from the end-user's (i.e., the physician) perspective.³⁵ What emerges from their study is that the appropriateness of using a biosensor depends less on its performance than on the prevalence of the target disease. Indeed, because the sensitivity and specificity of a sensor (i.e., the ability to appropriately deliver true positive and true negative results) cannot be 100%, the use of a sensor to diagnose a low-prevalence disease in a large population seems unrealistic and useless (the authors take the example of influenza diagnosis during and outside of epidemic periods). Worse still concerning screening: it is, for example, vain to imagine being able to conduct a routine screening test for pancreatic cancer without having multiple false positives to treat (and in this case, what should be communicated to the patient?). If, on the other hand, the test is restricted to a population at risk or during a pandemic, then the analysis obtained by the sensor will be more useful: it is obviously the case of sensors developed to monitor the spread of COVID-19. More

specifically, while high sensitivity tests (with low false negatives) are mandatory for properly diagnosing COVID-19 cases, surveillance of the population requires kits with high specificity (i.e., low false positives).⁶ If former tests can be carried out in central laboratories, it is highly desirable to have access to low-cost POC devices for surveillance means.

Whatever the purpose of the biosensor, it is crucial to consider the context of the analysis as much as the performance of the instrument. In the case of biomarkers that are highly diluted in the samples to be analyzed, such as circulating DNA in oncology, the analysis is likely to be more limited by the method of sample collection than by the performance of the detection method. The sampling location and sampling time are also of utmost importance, as illustrated by the variability of viral loads of the SARS-CoV-2 in respiratory samples (throat and nasal swabs, sputum samples), urine, and stool.^{36,37} Additionally, the sampling time, which in the case of the COVID-19 translates to the number of days after infection, provides a snapshot of the stage of the disease and is thus also a crucial parameter to take into account when choosing the test type: while virological tests seek a current infection, immunological tests will prove more useful days after the infection to look for antibodies produced against the virus.³⁸ Similarly, while it is obvious that the detection limit of a sensor is one of its main characteristics that is often the first consideration, as long as this detection limit is sufficient to detect the lowest level of analyte necessary for a clinical decision with minimum uncertainty, it does not need to be optimized. Furthermore, for this characteristic to be relevant, it must have been measured under real conditions, i.e., on the final sample (e.g., detection in serum and not in buffer). Unfortunately, articles presenting detection methods often report detection limit values without justification of the method and calculation used for their determination.

Double Requirement: Sensitivity and Specificity.

Considering the level of concentration of some biomarkers in liquid biopsies, which is below $\sim 3 \times 10^3$ copies/mL for a positive diagnosis of SARS-CoV-2 by qRT-PCR assay,³⁹ it is obvious that there is a need for highly sensitive biosensors for many clinical applications. Sensors based on new technologies display very high sensitivities, although the decrease in active surface area and lower concentrations are also accompanied by a longer analysis time.⁴⁰ It should also be noted that the measurement of very low concentrations involves analyzing volumes large enough to minimize statistical errors due to sampling and to work within a comfortable confidence interval.⁴¹

The specificity of a biosensor determines its ability to avoid false positives. It is therefore a crucial characteristic. It is the bioreceptor layer, due to the affinity of the probe molecules used for the targets, that provides the specificity of the biosensor. In complex samples such as liquid biopsies, the presence of many molecules can interfere with the measurement by nonspecific interactions with the sensor. The concentration of many plasma proteins is several orders of magnitude higher than that of protein biomarkers.⁴² Hence, even if the affinity of the interfering molecules is very low, they are the source of a strong biological background, which can exceed the nanomolarity.⁴³ The consequence of this background noise is that it drastically reduces the effective sensitivity of the sensor, as it has been shown during the detection of miRNAs by hybridization using microcantilevers in the presence of total RNAs.⁴³ It is therefore important to

minimize the influence of this biological background noise, either by differential measurement or by suitable sample preparation.

■ ANALYTICAL METHOD

Point-of-Care Liquid Biopsy Analyses: Desired Characteristics. The term liquid biopsy is used to refer to a test performed on a body fluid as opposed to a conventional biopsy, which consists of removing a small piece of organ or tissue. Liquid biopsy, and particularly blood or saliva sampling, can ultimately be considered the most widely used sample format in molecular analysis. The determination of biomarkers in liquid biopsies using sensors at the patient's bedside is particularly demanding: the ideal sensor would thus have the characteristics of being simultaneously portable, cheap, robust, fast, sensitive, specific, and multiplexed (i.e., allowing multi-analyte determination) and requiring a very small volume for analysis;⁴⁴ the order of importance of these criteria varies, of course, depending on the application.⁴⁵

Role and Importance of the Preanalytical Sample Preparation. Sample preparation is an essential step in the analytical process that makes the sample compatible and optimized to a given measurement technique. The functions commonly used to perform sample preparation include sample purification and suspension (removing interfering species and dissolving the sample in a suitable solvent by filtration and extraction separation techniques), sample concentration (increasing the local concentration of analytes lowers the detection limit of the analytical technique), and sample modification (using, e.g., derivatization, amplification, cell lysis, or enzymatic digestion).⁴⁶

These steps commonly involve centrifugation, phase separation, and extraction kits. They generally lead to dilution of the sample, which is obviously not favorable when low concentration biomarkers are to be detected. Most of the sample preparation steps are not automated, and the results are highly dependent on the lab technician and the protocol followed. In addition, it has been shown that despite the use of commercial products, the wide variability in their performance—such as, for example, the yield rate of miRNA extraction kits that is not always consistent⁴⁷—has a tremendous influence on the analytical results. Hence, preanalytical steps, including sample preparation, are recognized as the predominant source of errors in laboratory medicine.¹⁰ As a result, the need to improve preanalytical procedures has been highlighted in a number of studies on diagnostic methods.⁴⁸

From a biosensor point of view, it is essential to detail and take into account the sample preparation procedures in order to correctly assess the performance of an analytical technique, especially with regard to analysis time and sensitivity. Besides, in order for a miniaturized analysis technique to be as efficient as possible—in the sense that it must bring significant improvements over existing techniques (and obviously in terms of portability or overall assay time), it is important to minimize the on-bench steps of sample preparation. While one strategy is to develop analytical techniques that require minimal sample preparation, another strategy is to integrate on the chip as many of these steps as possible within the biosensor's instrument. Numerous technological solutions for integrating specific preanalytical functions on a chip can now be found in the literature, even if sample preparation can still be considered a real obstacle to the deployment of POC biosensors.⁴⁹

Finally, it is obvious that the preparation must be adapted to the analytical technique. The latter imposes tight specifications, more or less restrictive, in terms of sample format and composition. For example, the amplification of nucleic acids by PCR requires the presence of numerous biomolecules in solution (primers, DNA polymerases, mixture of the four deoxyribonucleotides), direct electrical detection on silicon nanowires can only be carried out in low ionic strength buffers that display a fairly large Debye length⁵⁰ and dosing with mechanical microresonators is largely influenced by the viscosity of the solution.⁵¹ In this respect, since physiological liquids have viscosities close to that of water, the latter MEMS technology is particularly suitable for the analysis of liquid biopsies with minimal sample preparation, as demonstrated by Raj Mutharasan's team for the direct determination of miRNA biomarkers in serum.⁵² Thus, among the solutions offered by new technologies, some biosensors offer undeniable advantages with regard to preanalytical requirements and are therefore more or less likely to provide truly nomadic analytical instruments.

■ ANALYTICAL PROCESS

Portability and Cost. Works dealing with biosensors based on micro- and nanotechnologies always emphasize the benefits of integration and cost reduction. As a matter of fact, MEMS physical sensors such as accelerometers and pressure sensors commercialized by Bosch, ST Microelectronics, or Analog Devices are as small and lightweight as packaged integrated circuits and are very cheap, typically a few USD, because they are mass produced: it turns out that the current need for COVID-19 tests, especially for surveillance means, corresponds to the large volume of sensor units required to achieve a low cost per unit. While integration capability can indeed lead to portable solutions, it should be noted that unlike the sensor itself, the instrument is much more complicated to miniaturize.⁵³ Fortunately, microfluidics now provides answers to miniaturization through lab-on-a-chip approaches,⁵⁴ but there are many other factors that still limit the deployment of in-the-field operational sensors for biomarker dosing, such as biocompatibility and robustness of the device or the reliability and stability of the measurement.

Furthermore, it is important to note that the significance of these criteria is relative and depends solely on the application. For example, the cost of a disposable sensor for the diagnosis of infectious diseases in high-risk areas is a decisive criterion and must obviously be as low as possible, which is not necessarily the case for a sensor used in a hospital environment to accompany cancer treatment:⁵⁵ the same applies to the fight against COVID-19 where, while it is highly desirable to have disposable low-cost devices to massively test the population in public spaces, such as airports, the cost of tools to back up computed tomography (CT) scans for SARS-CoV-2 diagnosis on a selected population in a hospital might not be that critical.⁵⁶ From this example, other characteristics and technological choices can be discussed according to the application context.⁵⁷

The Importance of Multiplexed Analysis. The determination of PSA levels in the blood has been used since the 1980s for the early detection of prostate cancer before the appearance of clinical signs. However, an elevated PSA level is not specific for cancer but simply marks the presence of an abnormality in the prostate. Thus, the diagnosis must be confirmed or disproved by further tests or clinical examina-

tions. While this test is of great value given the prevalence of prostate cancer and the slow progression of the disease, it is now clear that the use of multiple biomarkers provides more accurate information about the presence and the stage of a cancer. The CancerSEEK test introduced in 2018⁵⁸ perfectly illustrates this point: an assay of 8 circulating proteins and the search for mutations on circulating tumor DNA from 61 amplicons was proven able to diagnose the presence of cancer (among 8 types of cancer) with a sensitivity above 70% and a specificity above 99% (on a sample of 1005 patients). In the framework of the COVID-19 pandemic, genetic tests require the analysis of a number of viral genome sequences (e.g., the RdRP, E, and N genes) to identify the 2019-n CoV and discriminate it from other coronaviruses, such as MERS-CoV or SARS-CoV.⁵⁹

Being able to detect several molecules on the same platform is an absolute necessity in practice in order to provide at least one reference and to take the biological background noise into consideration. Ideally, it would also be appropriate to have a means of calibrating the sensor by dosing molecules present in the sample at steady and known concentrations (so-called “housekeeping molecules”,⁶⁰ such as the gene coding for the human Ribonuclease P used as a reference in RT-PCR for SARS-CoV-2 detection⁶¹). Multiplexing poses real technological challenges: in addition to making multiple sensors on the same chip, it is necessary to be able to interrogate them individually and deal with the disparity in response sensitivities. In addition, it requires providing biofunctionalization solutions allowing the grafting of several probes on the same surface.

On the Lack of Standardization. The literature on micro- and nanotechnology-based biosensors for molecular analysis is now extremely rich. However, it is sometimes difficult to find one’s way around because the experimental configurations vary so much from one transduction means to another. In an excellent paper published in 2014 that reviewed the various techniques for the detection of miRNA without amplification,⁴⁵ the authors presented and discussed experimental results and pros/cons of each platform. However, there was no means to carry out a quantitative comparison of their performances (sensitivity, detection limit, analysis time, volumes required, etc.). This is largely due to the lack of uniformity and standardization of the samples tested, which concerns both the source and preparation of the samples and the choice of the biomarker. Although there have been attempts to organize comparative tests of biosensors, such as the EILATox-Oregon Biomonitoring Workshop held in 2004,¹ it seems complicated to systematize this approach and to involve the numerous research groups active in this field. An alternative solution would be to carry out comparative analyses using standard techniques, but even this route faces the limits of the equipment currently in use (particularly in terms of limit of detection). A last path: could we imagine having access to standard samples made available to the various research laboratories?

■ CONCLUSION

While the scientific community predicted that micro- and nanotechnology would change our approach to biology,⁶² MEMS included, it is clear that we are still a long way from the announced revolution: few new medical devices today result from these technologies. Even worse, we realize that it is impossible to propose a standard and generic technological response, as opposed to what has been achieved by the

microelectronics industry. That makes the parallel between the two worlds complicated, even if there is a technological filiation. This feels like we have oversold the impact of these technologies in the field of diagnostic aid and that we have not kept our promises—this can be disturbing for citizens and political leaders who control the sources of funding, which is all the more detrimental at a time when the spotlight is turning on actual and future outbreaks in order to answer pragmatic questions such as virological and serological tests, new treatments, new vaccines, etc., with the barely veiled dream of one day being able to break free from the animal models.

However, it is important to temper this analysis. Indeed, the resounding success of the in vivo glucose sensor has changed the lives of many diabetics around the world and sets an example to follow: what an incredible advance that was just an abstract idea a few decades ago! Still, in his excellent editorial published in August 2013 in *Angewandte Chemie International Edition*, Otto Wolfbeis wonders why the development of new molecular probes is not accompanied by the widespread deployment of biosensors if it is only a matter of engineering, as some believe. He notes that researchers proposing new sensors must ask themselves the right questions: “(1) Will it be possible to monitor the evolution of the biochemical parameter over time, for example in the bloodstream (…)? (2) Will the sensor operate continuously for up to 12 h for use in surgery, up to 2 weeks for monitoring in a bioreactor (…)? (3) Will it respond reversibly as a temperature, oxygen or pH sensor?”⁶³ We should add: “Will the sensors be available within days for billions of people all around the world at an affordable cost and *modus operandi*?”

So, why is there such a gap between promises and reality? For many years, the literature trend on new technologies biosensors was racing after the lower limit of detection, without always being linked to concrete application needs and issues raised by sample composition and environment. Fortunately, there are glimpse of hope: a good example is a HEMT (high-electron-mobility transistor) sensor that uses a specific gate configuration to overcome the limits of electrical detection, which usually requires working at low ionic strength, and which enable the measurement of troponin I, a cardiac marker, directly in physiological solutions in a truly integrated format with validation of the results on clinical samples using a commercial instrument⁶⁴—and we are now seeing a growing number of these examples in the literature.

Thus, in order to provide tools that can assist medical decision-making as close as possible to the patient, criteria other than sensitivity must be fulfilled: most importantly, robustness and reproducibility, but also portability, low cost, minimal and generic sample preparation, and a multiplex approach allowing access to precise molecular signatures with integrated reference and calibration. In order to meet these criteria, it is important to design the tools as a whole rather than taking care of the sole sensor and its sensitivity: how to integrate, functionalize, passivate, and store the sensor, how to multiplex the measurement, which sample preparation to use or adapt, and how to standardize the measurement protocols must be the generic set of specifications for future biosensors and, specifically, for MEMS/mechanical biosensors, which so far have not demonstrated any in-the-field capability.

During the writing of this paper, among the few publications presenting biosensors based on microtechnology for the detection of SARS-CoV-2, a graphene-based field effect transistor demonstrated very promising results in terms of

sensitivity.⁶⁵ Let us hope these promises will soon turn into a widely commercially available device for the current COVID-19 crisis or at least to fight future pandemics. However, will it withstand the test of robustness, reliability, or even large-scale manufacturing in this specific case?

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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.

Notes

The authors declare no competing financial interest.

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Due to a production error, this paper was published on the Web October 19, 2020, with text errors in the second column

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