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Perspective

Biosensors for Public Health and Environmental Monitoring: The Case for Sustainable Biosensing

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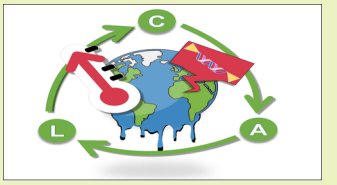
ABSTRACT: Climate change is a profound crisis that affects every aspect of life, including public health. Changes in environmental conditions can promote the spread of pathogens and the development of new mutants and strains. Early detection is essential in managing and controlling this spread and improving overall health outcomes. This perspective article introduces basic biosensing concepts and various biosensors, including electrochemical, optical, mass-based, nano biosensors, and single-molecule biosensors, as important sustainability and public health preventive tools. The discussion also includes how the sustainability of a biosensor is crucial to minimizing environmental impacts and ensuring the long-term availability of vital technologies and resources for healthcare, environmental monitoring, and beyond. One promising avenue for pathogen screening could be the electrical detection of biomolecules at the single-molecule level, and some recent developments based on single-molecule bioelectronics using the Scanning Tunneling Microscopy-assisted break junctions (STM-BJ) technique are shown here. Using this technique, biomolecules can be detected with high sensitivity, eliminating the need for amplification and cell culture steps, thereby enhancing speed and efficiency. Furthermore, the STM-BJ technique demonstrates exceptional specificity, accurately detects single-base mismatches, and exhibits a detection limit essentially at the level of individual biomolecules. Finally, a case is made here for sustainable biosensors, how they can help, the paradigm shift needed to achieve them, and some potential applications.



KEYWORDS: *Single-Molecule Bioelectronics, Biomolecular Electronics, STM Molecular Junctions, Environmental Monitoring, Sustainable Materials, Biosensing, Sustainability*

Climate change is the main challenge that humanity faces and it directly and indirectly poses significant implications for human health.[1,2] Climate science is a vastly studied subject, but an overwhelming consensus has been established in the last decades.[3,4] The latest models and observations indicate that warming is accelerating at unprecedented rates.[5] Beyond the obvious health implications of extreme temperatures and weather conditions resulting from the climate crisis, other indirect consequences could threaten human well-being (and possibly civilization itself in the long run).[2] Besides immediately stopping (or at least greatly reducing) carbon emissions, it is clear that some adaptation considerations will be necessary. Changes in temperature and weather patterns can create new settings for diseases to thrive,[6] resulting in new infectious diseases or the resurgence of old ones.[7] Therefore, it is important to identify key drivers of health threats and develop targeted interventions to mitigate their impact.[8] *E.g.,* climate and weather affect the distribution and risk of many vector-borne diseases, such as malaria;[9,10] or warm spring temperatures and heavy winter rainfall cause more mosquitoes to breed, making it easier for the West Nile virus to spread in the European Union.[7] Furthermore, climate change affects the prevalence of infectious diseases by altering the behavior and range of disease vectors and hosts.[11] There is strong evidence pointing to the fact that the COVID-19 pandemic is the result of an animal coronavirus transmitted to humans, a process favored by the ecological and biodiversity crisis.[12,13] Also, the mutation rates of infectious agents make them highly adaptable to changing environmental conditions, which may increase disease outbreaks.[14] Our *"arms race"* against COVID-19 has shown a dangerous fact: pathogens with high mutation rates can evolve quickly, becoming resistant to existing treatments and vaccines.[15] As of July 2023, COVID-19 has affected more than 690 million people worldwide, leading to more than 6.9 million deaths. Currently, the global death rate for the pandemic is 1.02%.[16] This pandemic has reiterated the importance of early detection to reduce mortality and hospitalization rates.[17] Early diagnosis of infectious diseases allows the effective isolation of confirmed cases, thus reducing transmission.[18] Early detection is crucial in many noninfectious conditions as well, such as cancers and cardiovascular diseases.[19] Cancer mortality rates increase significantly when detected in

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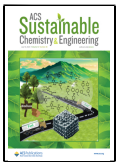

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late stages. *E.g.,* diagnosed pancreatic cancer has an overall 5-year survival rate of only 5%.[20] However, the prognosis is much better when diagnosed during imaging of an unrelated condition than in symptomatic cases; this underpins the importance of early detection and diagnosis.[21,22] Therefore, there is a clear need for fast and sensitive biosensing methods and devices. The development of new biosensors could facilitate the easy detection of diseases,[19,23] improving survival rates.[24] Moreover, new designs and materials could enable the manufacture of automatic and sustainable biosensors, becoming innovative and essential tools to address environmental and public health challenges.[25,26] The COVID-19 pandemic showed us dangerous dynamics and feedback loops with serious implications. I.e., the appearance of a new pathogen can require fast detection and testing methods that, in many cases, are designed for single use.[27] Also, in the case of COVID-19, many policies encouraged the use of single-use PPE and packaging.[28] This, in turn, promotes higher levels of consumption and waste, worsening the long-term challenges of a climate crisis driving these public health crises.[29,30] With the climate crisis becoming an increasingly alarming threat to our planet, there is a shared responsibility to make processes and products more sustainable, including biosensors. In this perspective, different types of biosensing techniques are overviewed, and the latest developments are discussed, showcasing single-molecule electrical biodetection. The future of sustainable biodetection as a crucial need is discussed. Human activities have resulted in accelerated global warming and more likely extreme weather events[5] that make that new diseases could emerge or old ones spread in new places,[2] increasing the risk of pandemics. This requires new monitoring and prevention methods to maintain a healthy society, including fast and reliable detection mechanisms. The resulting widespread use of single-use sensing or testing methods could result in unprecedented levels of waste and high use of resources contributing to greenhouse gas emissions that reinforce and contribute to the accelerating global warming situation. There is a need for a general paradigm shift to change these dynamics.

A Brief Introduction to Biosensors. Biosensors are analytical devices that detect and quantify biological substances.[33,34] They can detect biomolecules by converting the physical or chemical signal into an optical or electrical signal, which can be further processed to yield analyte detection and its concentration. The purpose of a biosensor is to provide rapid, accurate real-time, and reliable information about the analyte of interrogation.[35−37] Biosensors can also be highly specific to a particular analyte, enabling accurate detection, typically without interference from other compounds in the sample.[38,39] Leland C. Clark, Jr. and Champ Lyons introduced the first biosensor in 1962.[40−42] The field has witnessed considerable progress, including the development of novel biosensors and enhancements.[43] Although there is a wide variety of biosensors with biomedical applications to detect different analytes such as cholesterol, lactate, or creatine,[44] among others, one of the most used biosensors is the glucose meter.[45] It is based on enzymes such as glucose oxidase (GOx) and glucose dehydrogenase (GDH), and these enzymes currently dominate 75% of the global market for biosensors and are projected to contribute to a market worth $38 billion by 2027.[45]

Today, the use of nanomaterials such as functionalized graphene oxide paper allows improved glucose detection.[46] However, the basic glucose biosensor (shown in Figure 1) is based on simple electrochemical principles and consists of a

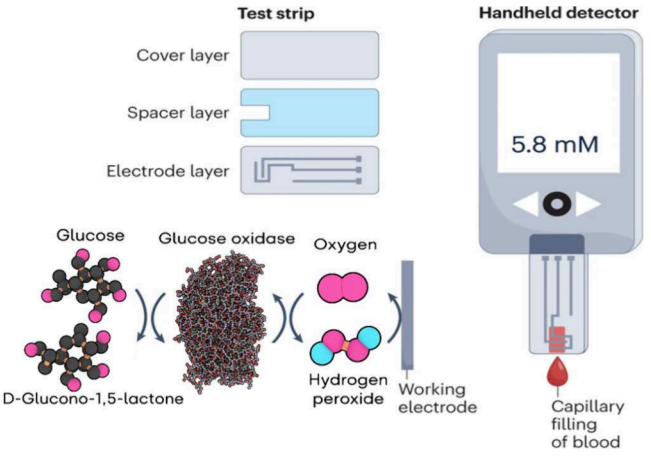

Figure 1. *Glucose biosensor*. **Glucose molecules are oxidized at the working electrode surface by the glucose oxidase (GOx) enzyme and converted to gluconic acid and hydrogen peroxide. The diagram also shows a** hand-held electrochemical detector and disposable test strips used in continuous blood glucose monitoring. Adapted with permission from.[31,32] Copyright IUCR 1999 and NPG 2023.

meter and disposable test strips. Test strips are holders with a printed circuit that contains the working, reference, and counter electrodes of the miniaturized electrochemical cell. One end of the strip is typically coated with GOx. When the enzyme is in contact with blood glucose, it produces hydrogen peroxide. Subsequently, the oxidation of peroxide generates an electric current proportional to blood glucose concentration.[47−49]

As demonstrated by the paradigmatic example of the glucose meter, biosensors can be miniaturized and are highly versatile,[50] making them suitable for integration into small portable devices. Biosensors can be produced using different manufacturing techniques, such as microfabrication and nanotechnology, fine-tuning their properties and performance.[51,52] The ability to identify specific biomarkers such as proteins, peptides, or nucleic acids is essential for understanding and diagnosing diseases.[53] To this end, novel bioreceptor and electrical transduction mechanisms should allow greater sensitivity and specificity.[54] Advances in different disciplines, such as molecular biology, nanotechnology, and electrical engineering, have converged to allow next-generation biosensors in the quest for rapid, sensitive, specific, and reliable biodetection.[55]

Biosensors can be classified based on the biological element and the transducing agent they use, as shown in Figure 2. These

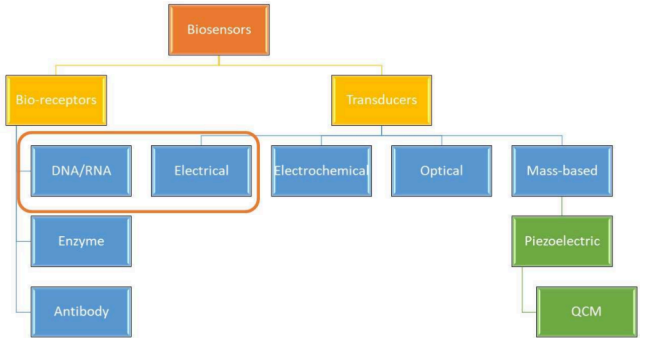

Figure 2. One possible classification of biosensors based on analytical methodologies, sensing principles, bioreceptors, and transducing systems. The square shows the main focus of the examples shown in the section below about single-molecule electrical biodetection.

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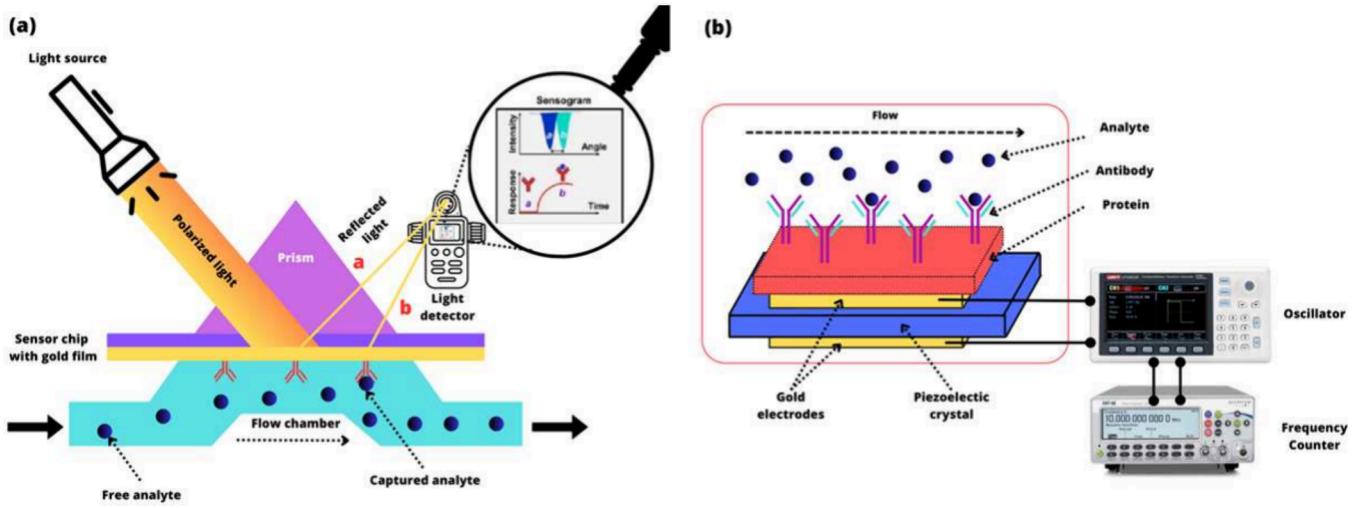

Figure 3. Schematic diagram of (a) Surface Plasmon Resonance (SPR), and (b) piezoelectric-based biosensors. Adapted with permission under a Creative Commons CC BY 4.0 License from ref[55] (7b and 8a), Copyright 2021, MDPI.

transducers convert the biorecognition event into measurable signals. In this perspective, some common biosensors will be reviewed, but a complete survey is beyond the scope of the work, and there are several excellent reviews in the literature that discuss different types of biosensing.[56−58]

Electrochemical Biosensors. Electrochemical biosensors are one of the most widely used types of biosensors, and the glucometer introduced above is an example. As shown in Figure 1, they are based on electrodes, which are often used to immobilize biomolecules.[59] These electrodes can be used to measure biochemical events, such as enzyme−substrate reactions or antigen−antibody interactions, by converting them into electrical signals.[60] More importantly, a crucial feature is that they use electrical signals, which makes them fully compatible with the electronics industry, an obvious advantage for manufacturing.[61,62] These features have made them a popular choice in different biosensing applications, including but not limited to the food industry, the medical industry, and environmental monitoring.[63] Additionally, their small size and affordability make them good potential candidates for clinical diagnosis, as they could meet some of the demands for the detection of diseases at an early stage.[64] Although electrochemical sensors may have limitations such as a restricted temperature range, short shelf life, and cross sensitivity, their low cost makes them an accessible option.[65,66]

Optical Biosensors. Optical biosensors are based on the change in the optical characteristics of the analyte as it interacts with the biorecognition element. This change is transformed into an electrical signal by the transducer coupled to the system.[67,68] They are specially amenable for samples that are colored or turbid, including biomolecules or microorganisms such as viruses, bacteria or other pathogens.[69] This sensing method has the potential to be specific, compact and cost-effective.[68] Detection through optical devices can be performed using either a label-based or a label-free methodology. Label-based sensing requires that the bioanalyte be properly labeled to obtain an appropriate optical response. Environmental monitoring of pathogens, for example *Escherichia coli* or *Salmonella typhimurium* in water and food, can be performed using different label-based techniques such as fluorescence[70] or colorimetry;[71] however, this methodology shows certain limitations: the labeling process, in addition to slowing the process, can modify the activity of the bioanalyte. Moreover, a heterogeneous labeling process can lead to an error in the quantification of the biomolecule. This has prompted scientists to turn their attention to label-free methods for ecology analysis. Label-free techniques, in contrast, require only the simple interaction of the bioanalyte with the transducer.

One of the most common[72] of this type of techniques is Surface Plasmon Resonance (SPR).[73] The setup, as shown in Figure 3(a), consists of a polarized light source, a detector, a metal layer (usually gold) between a prism with a refractive index n_1 and a flow chamber with a refractive index n_2, where $n_1 > n_2$. When polarized light is incident through the prism at an angle equal to or greater than the critical angle onto the metal layer, total internal reflection (TIR) occurs and an evanescent wave is formed. The evanescent electric field excites the free electrons in the gold, and the resulting quasiparticle is known as a plasmon.[74,75] When SPR occurs, the intensity of the reflected light decreases abruptly. The angle required for the resonance, θ_{SPR}, is related to n_2. Therefore, monitoring the θ_{SPR} change can be used to analyze the interactions that occur on the gold surface between the analyte-biorecognition element.[76,77] The SPR technology finds applications in drug discovery, medical research, food quality control, and monitoring molecular interactions.[78] However, there are obvious limitations in the miniaturizaiton, portability, and the pathway toward sustainability for this kind of biodetection.

Mass-Based Biosensors. A mass-based biosensor operates on the principle that binding events between the analyte and the biorecognition element cause a change in the overall mass of the biosensor system.[79−81] This mass change can be detected through a transducer, such as piezoelectric devices.[82] By responding to mechanical stress, piezoelectric biosensors generate an electrical signal that can be correlated with the concentration of the analyte.[83] An example of a mass-based biosensor is the quartz crystal microbalance (QCM) biosensor (Figure 3(b)).[84,85] This technology has found numerous applications in research and environmental monitoring.[86] In biological applications, QCM sensors[87,88] offer certain advantages over other biosensor technologies, such as outstanding sensitivity, simplicity, and affordability which makes it a promising tool in analytical chemistry and beyond. This versatility stems from its ability to detect molecules, chemicals,

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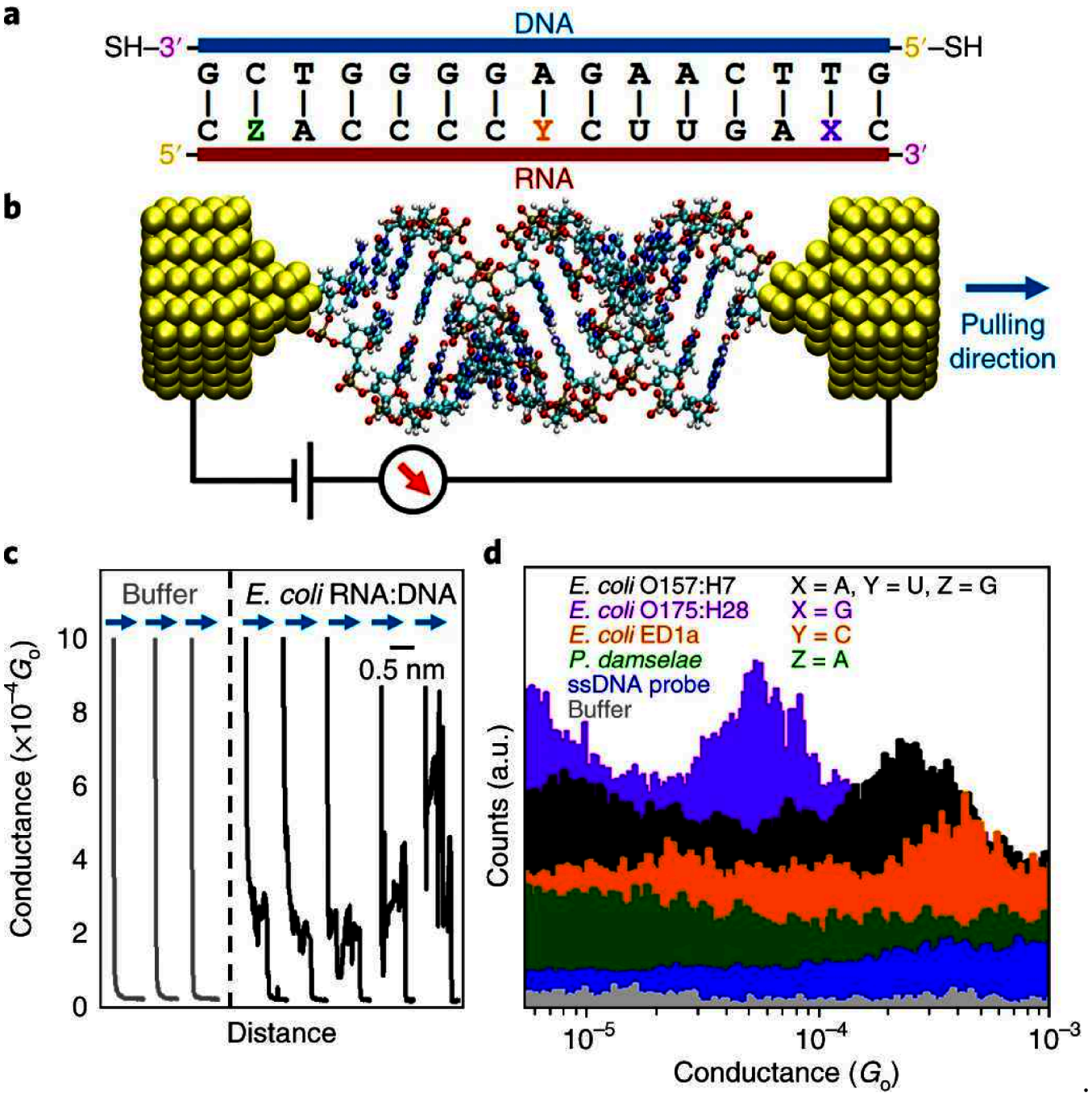

Figure 4. ***The first single-molecule electrical study on a biologically relevant oligonucleotide.***[96] (a) Schematic of the 15 bp RNA:DNA sequences studied. The blue side represents the DNA probe with thiol linkers and the red side represents the RNA sequences targeted. For *E. coli* O157:H7 X = A, Y = U, and Z = G (perfectly matched). In the other three cases, there is a mismatch. For *E. coli* O175:H28 X = G, for *E. coli* ED1a Y = C and for Photobacterium damselae Z = A. (b) Idealized schematic of the experimental setup showing the RNA:DNA molecule bound between two gold electrodes. (c) Representative conductance versus distance traces obtained from O157:H7 hybrids during break junction measurements. The black curves (with steps) are measured when a molecule binds between the electrodes, and the gray curves occur when no molecules bind. All curves are offset horizontally for clarity. (d) Conductance histograms for the four RNA:DNA hybrids and two control experiments performed for the single-stranded DNA probe and blank buffer. Histograms are vertically offset for clarity. A total of 5000 traces were collected for each sample. Reproduced with permission from ref,[96] Copyright NPG 2018.

polymers, and even biological samples.[89,90] But one of the predominant unresolved challenges in this field relates to modulating the methodology of crystal coating to ascertain the formation of uniform and cohesive deposition layers. By focusing on sustainability, the full potential of QCM sensors can be fully unlocked to make them a more viable option for wider applications.[91]

Nanobiosensors and Single-Molecule Biosensors. The influence of nanoscience and nanotechnology becomes evident when considering the advancements in biosensor technology over the past several decades.[92] The use of nanomaterials such as functionalized nanoparticles, nanowires or nanotubes has enabled increased sensitivity, improved selectivity and improved performance in nanobiosensor applications.[93] This is due to the

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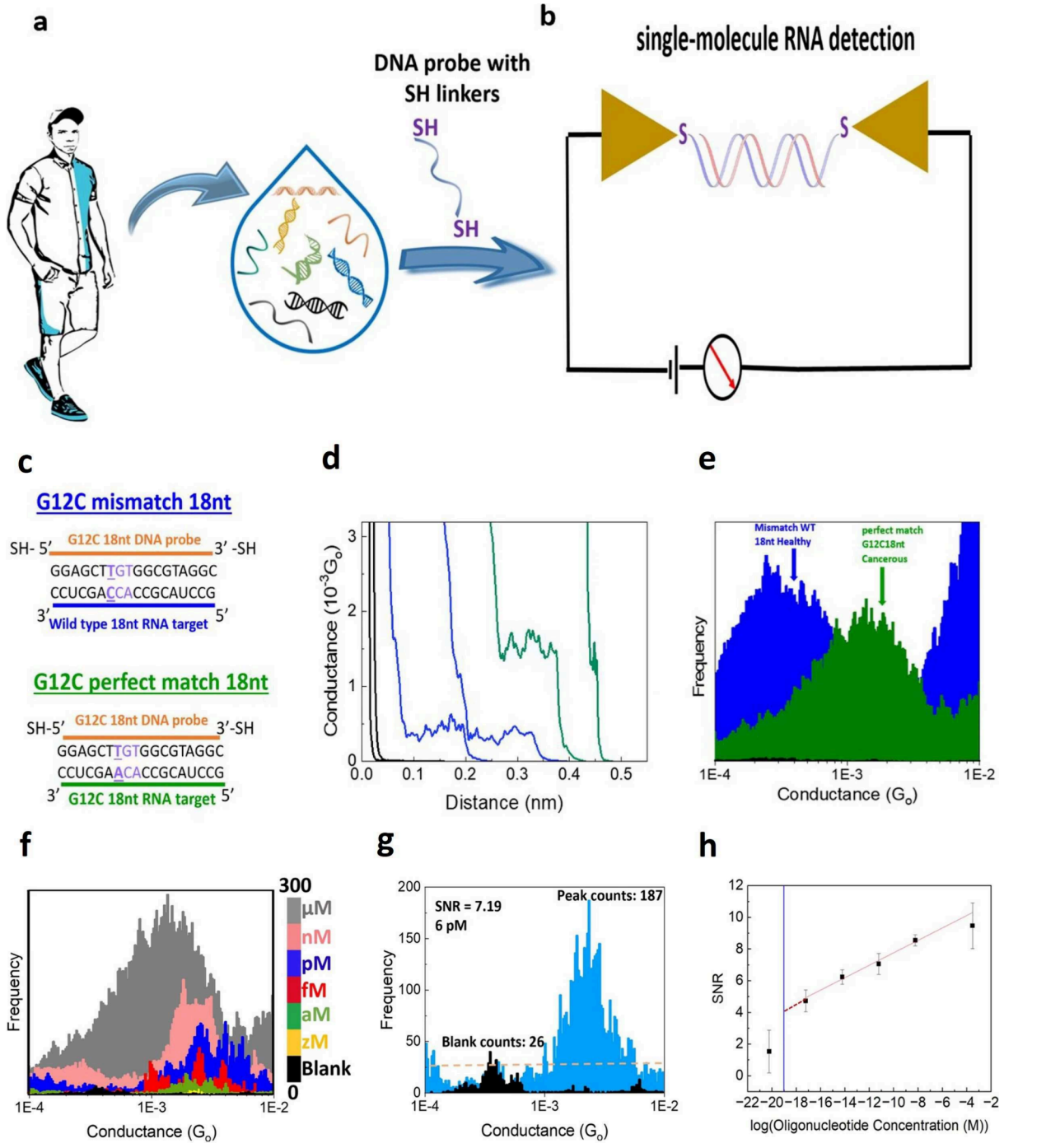

Figure 5. *Single-molecule RNA detection approach for cancer biomarkers.*[22] (a)Liquid biopsy samples contain circulating nucleic acids that can be detected with a complementary DNA probe capable of binding to STM electrodes.(b)STM-BJ detection of the hybridized biomarker, resulting in a step in the conductance-distance signal.(c)Sequences for G12C 18nt mismatch (healthy) and perfect match (cancerous).(d)Example conductance vs distance curves (Black:blank, Blue:mismatch, Green:Perfect match).(e)Histograms for G12C mismatch and perfect match overlapped with phosphate buffer blank (Blue: G12C 18nt mismatch, Green: G12C 18nt Perfect match, Black: Phosphate buffer blank).(f)Conductance histograms for G12C titration experiments (concentration varies from 300 μM to 0. The control experiment in phosphate buffer solution (black) shows no peaks in the histogram.(g)Limit of detection (LoD), Example of SNR calculation for a 6 pM concentration sample. (h) Average SNR for each concentration (with a linear fit) to obtain the concentration for a SNR = 3, Blue vertical line: theoretical concentration where a single molecule is present in the sample volume: around 0.1 aM). Adapted with permission under a Creative Commons CC BY 4.0 License from ref[22] Copyright 2023, Nature Publishing Group.

exotic characteristics of nanomaterials compared to bulk and micromaterials: shape and size-dependent properties, large surface area, and low cost. However, several challenges still limit the practical application of next-generation biosensors to detect biomolecules and prevent diseases. These include low concentrations of analytes that require sensitivity, mutations, and evolution of target sequences in oligonucleotides and proteins, and the need to balance cost and performance in the development of sensors for various applications.[61,94]

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One possibility is to explore the properties of individual molecules, something that cannot be exploited through traditional detection methods. This could address the need for the detection of biological molecules with single-molecule resolution.[95] Researchers can push boundaries with these biosensing technologies, opening up new possibilities for highly sensitive and specific detection methods. Some proof-of-concept examples based on the electrical detection of individual RNA biomarkers follow.

Recent developments in single-molecule electrical biosensors have demonstrated proof-of-concept devices that can detect microorganisms[96,97] and cancer biomarkers[22] with high specificity. They are based on RNA BioMolecular Electronics[98] and, in particular, usually use the scanning tunneling microscopy-assisted molecular break junctions (STM-BJ) technique. The approach has been used to target specific regions of mRNA, such as those that encode Shiga toxins in E. coli.[96] This method eliminates the need for PCR-based amplification and cell culture steps, making it faster and more efficient than traditional pathogen detection methods. The current-distance STM-BJ approach[96] uses an STM to repeatedly bring electrodes into contact and retract them in a buffer solution while applying a moderate bias voltage to measure the current in the molecular junction (Figure 4b). Conductance vs distance traces (Figure 4c) can be recorded and combined into conductance histograms (Figure 4d), which show distinct characteristics for the target nucleic acid sequence and are highly responsive to changes in length,[99−102] conformation,[103] and basepairing alterations.[96,104] With this STM-BJ approach, a tailored DNA or RNA probe complementary to the target nucleic acid biomarker is functionalized to have chemical anchoring groups at both ends. This allows the closing of a biomolecular electronics circuit established through the individual double-stranded biomolecule that bridges both STM electrodes. It is important to note that this approach is distinct from electrical sequencing technologies based on ionic currents. In contrast to these methods, the charge transports through the bases parallel to the strand, whereas sequencing approaches block the ionic current in a nanopore with the nucleic acid[105] or, in some exotic cases, measures the charge transport perpendicular to each base.[106]

As a single biomolecule sensor, this approach offers remarkable specificity and can accurately discern single-base mismatches[96] since the conductance histograms demonstrate that changes in an individual base can significantly affect electrical conductance. Furthermore, this method offers the advantage of extremely high sensitivity, with a detection limit in the low attomolar range.[22,96,107] Furthermore, some recent studies have shown that this technique produces different electrical signals efficiently based on the conformation[103,108] and the helicity[109] of individual nucleic acids. However, the method has some disadvantages, as this single molecular biosensor can detect known sequences quickly and sensitively, but it is not designed to identify novel sequences. The success of the STM-BJ technique also relies on its stability and reproducibility. Likewise, sample preparation, regular calibration of the STM, strict standardized data analysis, and meticulous documentation of experimental conditions enhance the chance of producing repeatable scientific data. These aspects are some of the clear challenges that have to be solved for automatizing and miniaturizing this single-molecule electrical biodetection method. Recent efforts are also paving the way in this direction, demonstrating molecular electronic studies with microfabricated devices.[110]

Recently, the same approach has been adapted for the detection of cancer biomarkers.[22] The scheme, as shown in Figure 5 (ab), again involves the use of specific dithiol-modified DNA probes to target a liquid biopsy sample containing multiple circulating tumor nucleic acids (ctNA) for single-molecule electrical detection of RNA cancer biomarkers (a KRAS mutation, in this case). Alternative chemical linkers could be used in DNA probes (e.g., amines), as this does not significantly affect the conductance signal in the oligonucleotide junction, as previously demonstrated.[103] When the DNA probe hybridizes with the target RNA, the biomolecular electronics circuit is "closed", and electrical fingerprint measurements are recorded. When this experiment is repeated several times, single-molecule electrical fingerprints can be accumulated to perform statistical analysis, resulting in a conductance histogram that shows the most likely conductance value for this particular DNA:RNA hybrid. Figure 5 shows the STM-BJ applied to measure the conductance of G12C KRAS mutations associated with a high incidence of colorectal or pancreatic adenocarcinomas.[111] Titration experiments have shown a low limit of detection (low aM range, effectively an individual biomolec ule) for this proof-of-concept electrical biosensor, with a signal-to-noise ratio (SNR) of around four. In this case, it is not trivial to define an SNR for a single-molecule technique, and a method based on comparing histogram counts with background noise counts that occur in control blank buffer experiments was established.[22] These results are a significant step in the direction of rapid and early detection of cancers with high sensitivity and specificity. The results of the measurements on a KRAS G12C biomarker are shown in Figure 5 (cd). The graph showing the conductance distance curve of the G12C sequence is shown in green as an example raw data trace. The same graph for the wild-type KRAS sequence is represented in blue. This experiment had a KRAS G12C DNA probe that could hybridize, causing a single-base mismatch when encountering wild-type KRAS (present in all human samples). Perfect match G12C DNA:RNA conductance measurements are higher than those for mismatched sequences, allowing the clear distinction between the cancer biomarker and a regular wild-type KRAS RNA sequence. The histograms in Figure 5(e) indicate the most probable conductance value obtained by fitting a Gaussian distribution to the peak of the G12C histogram (the mutant is four times higher than that of the mismatched wild-type RNA sequence), allowing the discrimination of individual cancer biomarker molecules from the regular wt KRAS sequence, which will probably be present in any sample of human origin.

Titration experiments were performed on KRAS G12C to determine the system's limit of detection(LOD). By varying the concentrations of the 18-base pairs KRAS G12C perfect match DNA:RNA hybrids from 6 zM to 300 μM, the conductance measurements as shown in Figure 5(f) were obtained. The black histogram represents the control experiment corresponding to a buffer blank. To determine the limit of detection (LOD), the minimum target concentration that yields a signal-to-noise ratio (SNR) of at least three was established. In Figure 5(g), the SNR values obtained from various concentrations of target RNA are shown, with a vertical blue line marking the expected concentration of a single molecule (0.1 aM). The experiments demonstrated that the LOD effectively detects an individual molecule in 100 μL with an SNR of around 4. This is the lowest LOD obtained with this kind of biosensor, as the lowest to date

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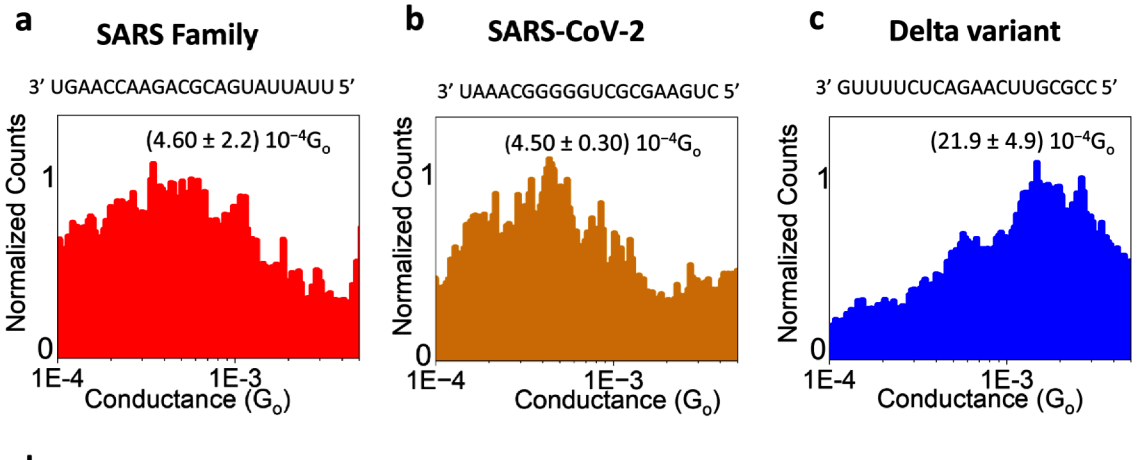

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Sample	Channel				
	SARS Family	SARS-CoV-2	Delta	Omicron BA2	Omicron BA5
MERS-CoV	+	-	-	-	-
Alpha	+	+	-	-	-
Delta	+	+	+	-	-
Omicron BA2	+	+	-	+	+
Omicron BA5	+	+	-	-	+
Omicron XBB.1.5	+	+	-	+	-
New Omicron Subvariant	+	+	-	+*	+*
New Unknown SARS-CoV-2 Variant	+	+	+/-	+/-	+/-

Figure 6. Electrical detection of biomarkers from SARS-CoV-2 variants and subvariants (A) conductance histogram for SARS-family (B) conductance histogram for SARS-CoV-2 (C) conductance histogram for Delta (D) Strategy to detect emerging variants of the human coronavirus families with STM-BJ method. This figure was adapted with permission under a Creative Commons CC BY 4.0 License from ref[97] Copyright 2023, ELSEVIER.

was approximately 20 aM (see the E. coli[96] study discussed above). At concentrations lower than LOD, the results were similar to those of the control buffer experiments, and the SNR value became stochastic and generally low.

This biodetection method is also a suitable approach for detecting COVID-19 biomarkers down to the single base resolution.[97] Figure 6(d) shows a diagram for the single-molecule electrical detection of RNA sequences related to human coronavirus families, including highly pathogenic strains such as SARS-CoV, MERS-CoV, and SARS-CoV-2,[112,113] the Delta variant, and two Omicron subvariants (BA2 and BA5).[114] This single-molecule electrical biosensing strategy enables us to differentiate between various coronavirus variants on the basis of their unique sequences and the resulting electrical fingerprints. As shown in Figure 6, conductance histograms for these variants of coronaviruses were obtained; histogram a in Figure 6 shows the single-molecule conductance of a sequence that is conserved in the entire SARS-CoV family, while histograms b and c show the conductance histograms for conserved sequences specific for SARS-CoV-2 and the Delta variant, respectively. The results of the study highlight the effectiveness of the screening method in distinguishing various types of SARS-CoV-2. This capability is essential for early diagnosis and screening. These findings align with recent theoretical approaches that suggest using variations in conductance resulting from single nucleotide differences to detect COVID-19 and its variants of concern (Alpha, Beta, Gamma, Delta, and Omicron).[115,116] These results also pave the way for future possibilities such as highly automatized and miniaturized electrical biosensors to monitor these RNA sequences, if obvious roadblocks in miniaturization and microfabrication of nanoelectrodes can be solved. In a scenario where these sensors can be miniaturized and parallelized into several single-molecule electrical detection channels, future strategies can be proposed for the electrical fingerprinting of COVID-19 samples (Figure 6(d)). The table showcases the possible signals for each channel (columns) that can be expected for various samples (rows), assuming that all the individual electrical measurements of single molecules depicted here can be executed on a single platform with five channels as an example. Even with only five channels, it is reasonably possible to predict and identify new COVID-19 samples and identify the strain with high probability (including new ones related to known variants of concern). With the advancements in miniaturization and automation, this idea could be expanded to several parallel detection channels and combined with machine learning or other artificial intelligence approaches. This can lead to unprecedented resolution and predictive capabilities, making this a blueprint for developing an approach to detect (and identify) novel pathogens during outbreaks, epidemics, and potential pandemics. Or, simply, this could be used to prevent these outbreaks by monitoring the environment for RNAs from "usual suspects" and pathogens that are likely to become a concern with new climates. This concept can be extended to most infectious diseases or any other public health application.

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Table 1. Sensor Performance: Limit of detection (LOD) in Concentration Units and Advantages and Disadvantages for Different Sensing Technologies[a]

Technology	LOD	Advantages	Disadvantages
Chemical sensor	nM[118]	• Utilization of low-cost materials for manufacturing without sacrificing sensor performance, Compact and portable design for practicality[119] • Real-time monitoring capability enhances versatility[120,121]	• Low selectivity in complex media • Low sensor stability in harsh environmental conditions • Require frequent recalibration and maintenance[119]
Electrochemical sensor	fM[122]	• Use of electrical signals enhances compatibility with the electronics industry and facilitates cost-effective manufacturing[61,62] • Potential candidate for clinical diagnosis due to their small size and affordability[64]	• Limited temperature tolerance • Brief shelf life • Susceptibility to cross-sensitivity[65,66]
Optical sensor	pM-nM[76,123]	• Specific[72] • Cost-effective[72] • Ability to miniaturize, allowing chip-level integration and inclusion of additional functionalities like microfluidics in a single platform, thereby contributing to the development of compact lab-on-a-chip devices[124]	• Low signal-to-noise ratio • Environmental interference • Limited detection limit • Requires large and complex equipment • False positive and false negative results arise from intensity changes of a single emitter[125]
STM-based single-biomolecule electrical detection	aM(0.1−20)[22,96]	• Eliminates the need for PCR-based amplification and cell culture steps, enhancing speed and efficiency[96] • Demonstrates remarkable specificity, accurately discerning single-base mismatches[22,96] • Exhibits extremely high sensitivity, with a low attomolar range limit of detection[22,96] • Enables miniaturization and automation[22,97]	• Challenges arise when performing in complex media, where numerous biomolecules can block nanoelectrodes[117]

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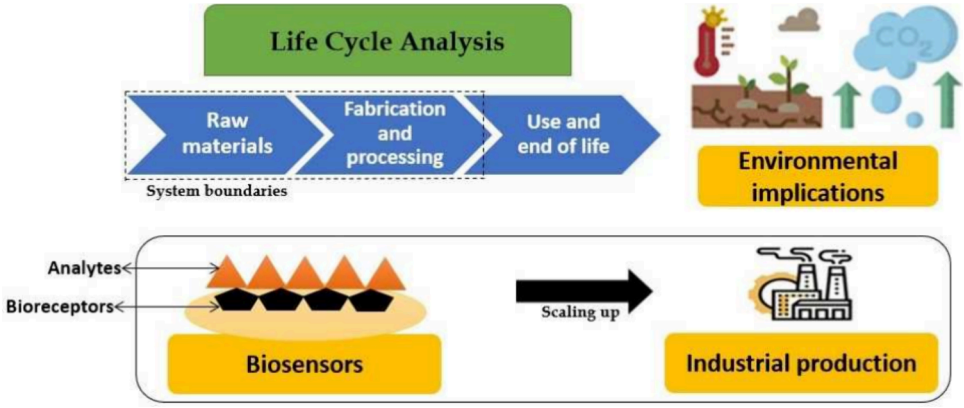

Figure 7. Environmental analysis using life cycle analysis methodology on the industrial production of biosensors. Reproduced with permission under a Creative Commons CC-BY 4.0 from ref[130] Copyright 2023, American Chemical Society.

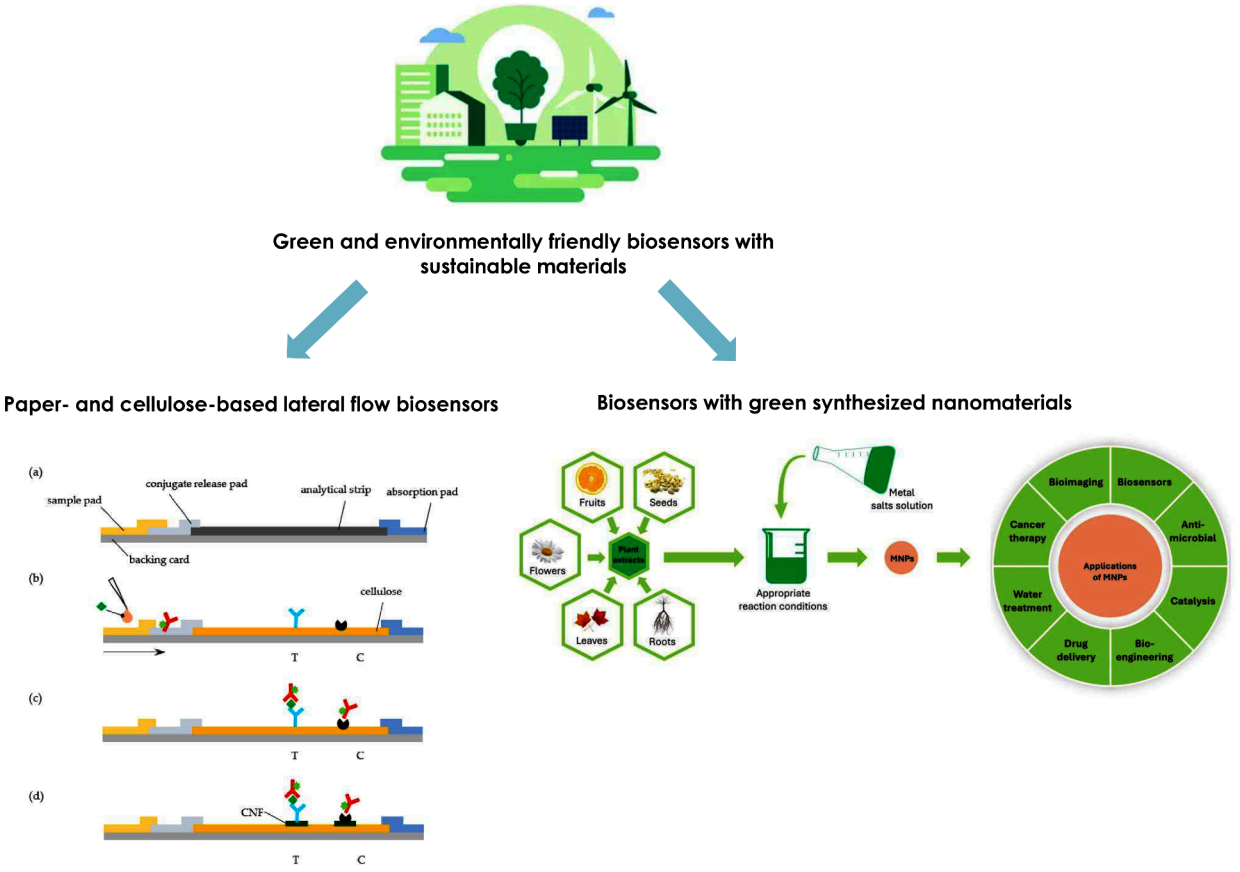

Figure 8. Schematics of examples of biosensors using sustainable materials. Paper-based, cellulose-based, and green nanomaterial-based optical sensors offer recyclability and mass production using sustainable methods; adapted with permission from Creative Commons CC BY-NC-ND 4.0 License from refs[143−145] Copyright 2022, Elsevier.

Table 1 puts all these ideas in context, showing the typical LOD of different biosensing approaches as a figure of merit for comparison, as well as the advantages and disadvantages of various biosensing approaches. When comparing these merit figures, single-molecule electrical biodetection reveals itself as a promising biodetection method. This, combined with the fact that it is compatible with the conventional electronics industry and is all electrical, makes it a good candidate for the next generation of biosensors in several crucial applications. However, single-molecule electrical biosensing presents a series of obvious challenges that have to be solved before this becomes a reality. First, there is evidence showing that this approach will not perform well in complex media where several other biomolecules can block nanoelectrodes, resulting in fouling.[117] This can be solved by integrating sample preprocessing steps prior to biodetection and/or integrating this technique with electrochemical detection and purification.[117]

WHAT THE FUTURE SHOULD BRING: TOWARD SUSTAINABLE BIOSENSING

In light of rapid technological progress and an increasing environmental crisis, biosensing technology also has exciting

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and crucial potential to create a sustainable future.[126] Sustainable biosensors should play a vital role in adapting and addressing these global challenges. As the emergence of new pathogens is faced,[2] the need for fast and affordable detection methods is crucial. Unfortunately, many of these methods are designed for single use, adding only to pollution and the growing waste levels, and will eventually worsen these crises or result in new ones. This fact stresses the importance of taking action to make our processes and products more sustainable, including the case of biosensors discussed here. Whatever sensing technology ends up being the most practical for each application, challenges in design, engineering, and even in the early lab research and development phases are also clear opportunities to consider sustainability as a key factor.

All aspects of the biosensing market need to be considered and a Life Cycle Analysis (LCA) should be performed when proposing new biosensors so that they can become important tools in environmental monitoring. The assessment of the potential environmental impacts is vital and LCA serves as a crucial tool for this. It helps identify opportunities for environmental improvement, informs decision makers, guides indicator selection and measurement techniques, and also supports environmental performance marketing efforts. LCA methodology is widely used to evaluate the environmental sustainability of emerging technologies and new products in their initial phases.[127−129]

Figure 7 shows a potential avenue for determining the environmental impact and efficiency of a biosensor, and this should be considered from its raw materials to its disposal strategy.[131] Taking into account the varying environmental factors that touch on local land use and global climate change, it is possible to improve sustainability in the field of biosensing through a more precise assessment of environmental conditions and impacts of the sensors themselves.[132] By integrating LCA and studying fabrication strategies, one could pave the way for the development of sustainable sensors and biosensors. New approaches should allow the creation of compact and exceptionally effective sensors, while reducing (or ideally avoiding) the associated environmental footprint.[133] The LCA for biosensors will likely have implications for sensor design and development at different levels, which can also influence each other and result in synergies. At bare minimum, we should consider the following.

- The raw materials necessary for the biosensor
- The production process and its energy efficiency
- The lifetime of the biosensor
- The potential for reusing, repurposing, or recycling the sensors or parts of them
- The final "disposal" of nonrecyclable parts, if any.

Although the first two factors seem the most obvious and those more related to the biosensor initial R&D process, all of them should be taken into account when proposing new biosensors or developing close to an initial prototype. Considering which materials are used in biosensing devices can be a good start, but, eventually, a whole paradigm shift is needed toward a new mentality that integrates all the factors from the earliest stages of biosensor development. In the following paragraphs, some of the applications and possibilities of future sustainable biosensors are discussed. In Figure 8, examples of a first approach to sustainable biosensing are shown. Here, the most crucial aspect is the materials chosen for the device, but a new holistic view is needed to go beyond that, and start considering all the possibilities for the next generations of biosensors.

Creating biosensors that meet specific requirements and scaling them up for commercial use can be challenging due to various factors. These may include making sure they are sensitive and selective in the detection of substances they are meant to detect, ensuring that they are stable and reliable, making them cost-effective, meeting regulatory standards, simplifying the manufacturing process, ensuring that they are easy to use, and meeting market demands, between others.[134] In materials science, biorecognition elements such as enzymes, antibodies, and DNA are important for sensing, and luckily biomolecules are biodegradable. However, the stability and shelf life of the biocomponents can be limited, and this should be taken into account either by stabilizing them or by devising strategies to reuse and regenerate the sensors. One of the most crucial parts on the raw materials side will be the choice of the Supporting Information for the biosensor itself (like in Figure 8). Finding eco-compatible materials with the desired properties is not trivial. Materials that could be used to create disposable electrodes include paper[135] or (truly) biodegradable plastic-based materials[136] that can be used to immobilize biomolecules of interest. Lately, paper-based biosensing electrodes have gained popularity due to their convenient disposable features,[137] but it is likely that bioplastics through 3D printing or similar technologies could also play a key role in the near future. Biopolymer-based hydrogel materials represent a sustainable alternative to synthetic polymers in various biomedical and environmental applications.[138] Also, from the nanoscience field, the unique conductivity of graphene has been shown to enhance the performance of biosensors by improving signal sensitivity.[139] However, challenges such as limited mechanical strength and compatibility with existing production lines need to be addressed before these new materials can fully replace conventional alternatives. The achievement of miniaturization and portability of biosensors in real-world applications requires an integrative strategy that incorporates LCA and a commitment to sustainable material selection. SPR or STM-BJ are incipient biodetection technologies that may only be a necessary option for certain applications, and a proper LCA should be implemented before scaling them up. This could begin with the selection of substrate materials, where eco-friendly options are prioritized for their unique properties like sensitivity and reusability. Future biosensing technologies should focus in minimizing energy and resource use, aligning with green chemistry and circularity.[140,141] Sustainable biosensors have a wide range of potential applications in various fields, including clinical diagnostics, the food industry, and environmental monitoring.

Biosensors can potentially increase productivity, reduce waste, and advance sustainability in industrial sectors. For example, in the food industry biosensors can be used to detect contaminants and pathogens[142] in food products, ensuring food safety and reducing the risk of contracting foodborne diseases. Furthermore, industrial processes such as fermentation can be monitored and improved with the help of biosensors.[51]

Environmental monitoring is another area where sustainable biosensors can have a significant impact. Biosensors can detect and monitor pollutants and toxins in air, water, and soil. For example, biosensors can be used to detect toxic compounds in water sources, allowing early detection and intervention to prevent contamination.[146] Biosensors can also monitor soil conditions such as temperature, pH, pollutants, nutrients or

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fertilizers to optimize agricultural practices and reduce waste.[147,148] The application of sustainable biosensors in environmental monitoring can improve community health and well-being while protecting natural resources. As an additional example, there is the paper biosensor,[149] which uses the principles of paper microfluidics to provide information about the analyte.[150] Paper biosensors are typically composed of porous cellulose paper with reagents such as antibodies, nucleic acids, or nanomaterials immobilized in the pores to react when exposed to liquid samples.[151] They are similar to electrochemical and optical biosensors because they are cost-effective. However, an additional benefit of paper-based biosensors is their simple and user-friendly designs. Paper-based biosensors do not require additional lab equipment to provide their results, allowing them to be used remotely.[152] These qualities have made paper-based biosensors a commonly used tool in many different settings, ranging from the detection of biomarkers in the body to the detection of contaminants in water sources.[151] For example, eco-friendly paper-based sensors now offer affordable and convenient on-site monitoring of exhaled H_2O_2.[153] However, paper-based approaches may suffer from low sensitivity or specificity necessary for some applications. Nevertheless, they are an attractive option toward sustainable recyclable biosensing.

On the other hand, new materials based on well-known and novel biodegradable plastics could also offer many advantages in terms of sustainability and tunability (if regulations ensure that their expansion does not interfere with basic food sources).[154] These materials could be promising for microfabrication or nanofabrication using 3D printing or traditional methods to employ them as electrode substrates in electrochemical or electrical biosensors. The objective is to advocate for this kind of strategies that allow for the scaling up of the most needed biosensors with their promising applications without feeding back into the root causes of most of the crises (climate and ecological emergency) by generating even higher waste levels and environmental problems.

CONCLUSION

In summary, in this perspective, basic concepts related to biosensing and biodetection were introduced, briefly reviewing its history and some of the most common types of biosensors. The focus was on recent demonstrations of single-molecule electrical biosensors for different applications such as pathogen or cancer screening using biomolecular electronics RNA molecular junctions. The case was made here for sustainable biosensing as a paradigm shift in the field to make biosensors a useful tool for adapting to the climate emergency without contributing to making it worse, opening avenues for environmental monitoring and pollution prevention. The application of basic sustainability concepts, such as life cycle analysis, has been proposed. Only with such a strategy or similar sustainable efforts could biosensors fulfill their promising applications.

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Notes

The views expressed are purely those of the authors and may not in any circumstances be regarded as stating an official position of the ERCEA and the European Commission.

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