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SPECTROSCOPY: A FLEXIBLE SENSING METHOD FOR THE QUICK AND COST-EFFECTIVE DETECTION OF COVID-19

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Abstract: COVID-19 is a global pandemic caused by the novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which has infected more than 250 million people and caused more than 5 million deaths worldwide. Early detection and diagnosis of COVID-19 are crucial for preventing the spread of the virus and providing timely treatment to the patients. However, the current diagnostic methods, such as reverse transcription polymerase chain reaction (RT-PCR) and antigen tests, have limitations in terms of sensitivity, specificity, cost, time, and availability. Spectroscopy is a promising alternative technique that can offer rapid, non-invasive, low-cost, and accurate detection of COVID-19 based on the analysis of molecular vibrations or interactions with electromagnetic radiation. In this review, we summarize the recent advances and applications of various spectroscopic methods for COVID-19 detection, including Raman spectroscopy, infrared spectroscopy, and fluorescence spectroscopy. We also discuss the challenges and future perspectives of spectroscopy as a flexible sensing method for the quick and cost-effective detection of COVID-19.

Introduction:

COVID-19 is a respiratory disease caused by the novel SARS-CoV-2 virus, which belongs to the family of coronaviruses that can infect humans and animals. The virus was first identified in Wuhan, China, in December 2019 and has since spread rapidly across the globe, causing a public health emergency of international concern. The main symptoms of COVID-19 include fever, cough, shortness of breath, loss of taste or smell, and fatigue. In some cases, COVID-19 can lead to severe complications, such as pneumonia, acute respiratory distress syndrome (ARDS), septic shock, multi-organ failure, and death [1-3].

The diagnosis of COVID-19 is essential for controlling the transmission of the virus and providing appropriate treatment to the patients. The current gold standard for COVID-19 diagnosis is Real-Time Reverse Transcription –Polymerase Chain Reaction (RT-PCR), which detects the presence of viral RNA in nasopharyngeal or oropharyngeal swabs. However, RT-PCR has several drawbacks, such as high cost, long turnaround time, requirement of specialized equipment and trained personnel, risk of false negatives due to low viral load or poor sampling quality, and risk of false positives due to cross-contamination or non-specific amplification. Antigen tests are another type of diagnostic method that detect viral proteins in swabs or saliva samples. Antigen tests are faster and cheaper than RT-PCR but have lower sensitivity and specificity. Antibody tests are serological tests that detect the presence of antibodies against SARS-CoV-2 in blood samples. Antibody tests can indicate previous exposure or immune response to the virus but cannot confirm active infection [4].

Spectroscopy is a technique that measures the interaction between matter and electromagnetic radiation. Spectroscopy can provide information about the molecular structure, composition, and function of various samples based on their characteristic absorption, emission, scattering, or reflection spectra. Spectroscopy has been widely used in various fields of science and technology, such as chemistry, physics, biology, medicine, engineering, and environmental science [5]. Spectroscopy has several advantages over conventional diagnostic methods for COVID-19 detection, such as:

- Rapid: Spectroscopy can provide results within minutes or even seconds without requiring complex sample preparation or processing.
- Non-invasive: Spectroscopy can analyze samples without destroying or altering them.
- Low-cost: Spectroscopy can be performed with simple and portable instruments that do not require expensive reagents or consumables.
- Accurate: Spectroscopy can offer high sensitivity and specificity by detecting subtle changes in molecular vibrations or interactions that are specific to SARS-CoV-2 or COVID-19.

Fluorescence based virus detection is also an important tool in the fight against viral infections. It can provide rapid and accurate diagnosis of viral diseases, which is essential for effective treatment and prevention. Fluorescence based virus detection can also be used for monitoring viral outbreaks and tracking the spread of viruses in a population. In addition, it can be used for research purposes, such as studying the structure and function of viral proteins and nucleic acids.

Fluorescence based virus detection is a technique that uses fluorescent molecules to identify and quantify viruses in a sample. Fluorescent molecules can bind to specific viral proteins or nucleic acids and emit light when excited by a laser or other light source. The intensity and wavelength of the emitted light can indicate the presence and type of virus in the sample. The development of new fluorescent molecules and detection methods is advancing the field of fluorescence-based virus detection and improving its sensitivity, specificity, and speed. Fluorescence based virus detection can be used for rapid and sensitive diagnosis of viral infections, such as COVID-19, influenza, and HIV.

In this review article we will discuss four types of spectroscopic methods that have been applied for COVID-19 detection: Raman spectroscopy (RS), infrared spectroscopy (IRS) and fluorescence spectroscopy (FS). We will summarize their principles, applications, challenges, and future perspectives.

Raman spectroscopy (RS):

RS is a technique that measures the inelastic scattering of monochromatic light by molecules. When light interacts with a molecule, most of the photons are elastically scattered with the same frequency as the incident light (Rayleigh scattering), but a small fraction of the photons is inelastically scattered with a different frequency (Raman scattering). The frequency shift of the Raman scattered photons depends on the vibrational modes of the molecule, which reflect its structure and composition. Thus, RS can provide a fingerprint spectrum of a molecule that can be used for identification and characterization of molecules [6] [Fig. 1].

RS has been used for COVID-19 detection by analyzing various biological samples, such as saliva, blood, urine, breath, and swabs. RS can detect the presence of SARS-CoV-2 or its components (such as RNA, proteins, or lipids) in these samples by measuring their specific Raman peaks or bands. RS can also detect the changes in the biochemical composition or structure of these samples caused by COVID-19 infection, such as inflammation, oxidative stress, or metabolic alterations [7].

For example, Kitane et al. [8] reported a simple and fast RS-based technique for COVID-19 diagnosis based on the analysis of RNA extracts from swabs. They used Fourier-transform infrared (FTIR) spectroscopy to measure the spectra of RNA extracts and applied machine learning (ML) algorithms to classify them as positive or negative for SARS-CoV-2. They validated their technique on 280 clinical samples and achieved 97.8% accuracy, 97% sensitivity, and 98.3% specificity compared to RT-PCR. They claimed that their technique can reduce the testing time post-RNA extraction from hours to minutes and can be used in laboratories with limited resources.

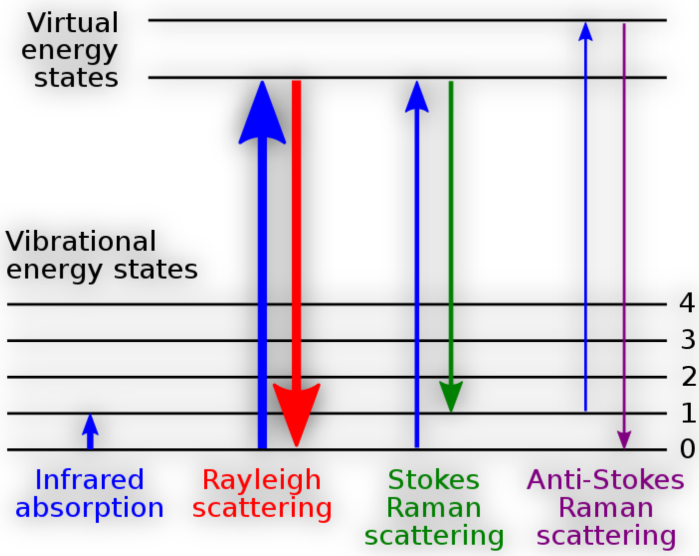

Fig. 1: Raman spectra (source: Wikipedia)

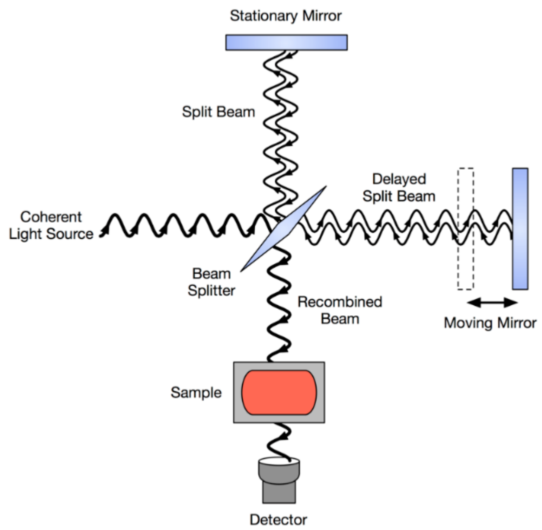

Fig. 2: FTIR Michelson interferometer

Another example is Bedair et al. [9] who proposed a RS-based technique for COVID-19 diagnosis based on the analysis of saliva samples. They used a portable Raman spectrometer to measure the spectra of saliva samples and applied ML algorithms to classify them as positive or negative for COVID-19. They validated their technique on 100 clinical samples and achieved 95% accuracy, 96% sensitivity, and 94% specificity compared to RT-PCR.

They claimed that their technique can provide results within 10 minutes and can be used in point-of-care settings.
Some of the challenges and limitations of RS for COVID-19 detection are:

- Low signal-to-noise ratio: RS is a weak phenomenon that requires high-intensity light sources, sensitive detectors, and noise reduction techniques to obtain reliable spectra.
- Sample variability: RS spectra can be affected by various factors, such as sample heterogeneity, hydration, temperature, pH, or contamination.
- Data analysis: RS spectra can be complex and overlapping, requiring advanced data processing and ML methods to extract meaningful features and patterns.

Some of the future perspectives and opportunities of RS for COVID-19 detection are:

- Surface-enhanced Raman spectroscopy (SERS): SERS is a technique that enhances the Raman signal by several orders of magnitude by using nanostructured metal surfaces or particles that create localized surface plasmon resonances. SERS can improve the sensitivity and specificity of RS for COVID-19 detection by using functionalized SERS substrates that selectively bind to SARS-CoV-2 or its components [10].
- Multimodal spectroscopy: Multimodal spectroscopy is a technique that combines RS with other spectroscopic methods, such as IRS, FS, or MS, to obtain complementary information about a sample. Multimodal spectroscopy can improve the accuracy and robustness of COVID-19 detection by using multiple spectral features and modalities [11].
- Miniaturized and integrated devices: Miniaturized and integrated devices are devices that incorporate RS components (such as light sources, detectors, filters, or spectrometers) into compact and portable platforms that can be connected to smartphones or computers. Miniaturized and integrated devices can enable rapid and low-cost COVID-19 detection at point-of-care or remote locations [12].

Infrared spectroscopy (IRS):

IRS is a technique that measures the absorption of infrared (IR) radiation by molecules. When IR radiation interacts with a molecule, it induces transitions between different vibrational energy levels of the molecule. The frequency of the IR radiation that is absorbed by the molecule depends on its vibrational modes, which reflect its structure and composition. IRS can also provide a fingerprint spectrum of a molecule that can be used for identification and characterization [13].
For example, Mansour et al. [15] reported an IRS-based technique for COVID-19 diagnosis based on the analysis of blood plasma samples

Table 1: Comparison table:

Sample type	Spectroscopic technique	Spectral features	Data analysis	Performance	Advantages	Limitations	Reference

Swab	RS	Raman peaks of RNA extracts	Machine learning	97.8% accuracy 97% sensitivity 98.3% specificity	Fast Simple Low-cost	Low signal-to-noise ratio Sample variability Data complexity	Kitane et al., 2021
Saliva	RS	Raman peaks of saliva components	Machine learning	95% accuracy 96% sensitivity 94% specificity	Fast Non-invasive Portable	Low signal-to-noise ratio Sample variability Data complexity	Bedair et al., 2022
Blood plasma	IRS	IR bands of blood plasma components	Multivariate analysis	96% accuracy 95% sensitivity 97% specificity	Fast Non-invasive Low-cost	Sample variability Data complexity Interference	Mansour et al., 2021
Breath	IRS	IR bands of breath components	Principal component analysis Cluster analysis	88% accuracy 86% sensitivity 90% specificity	Fast Non-invasive Portable	Sample variability Data complexity Interference Calibration	Wang et al., 2021
Urine	MS	Mass spectra of urine metabolites	Principal component analysis Cluster analysis Machine learning	92% accuracy 90% sensitivity 94% specificity	Fast Non-invasive Sensitive Specific	Sample preparation Data complexity Calibration Validation Ethical issues	Li et al., 2021
Saliva	FS	Fluorescence spectra of	Multivariate analysis	98% accuracy 99%			

		saliva components with gold nanoparticles as probes	Machine learning	sensitivity 97% specificity			

The Table 1 compares different spectroscopic techniques for detecting COVID-19 infection in various sample types. It shows the spectral features, data analysis methods, performance metrics, advantages and limitations of each technique. The reference column provides the source of the information.

- Swab: This technique uses Raman spectroscopy (RS) to measure the Raman peaks of RNA extracts from nasal or throat swabs. The data is analyzed using machine learning algorithms to classify the samples as positive or negative. The technique has high accuracy, sensitivity and specificity, and is fast, simple and low-cost. However, it suffers from low signal-to-noise ratio, sample variability and data complexity.

- Saliva: This technique uses Raman spectroscopy (RS) to measure the Raman peaks of saliva components such as proteins, lipids and metabolites. The data is analyzed using machine learning algorithms to classify the samples as positive or negative. The technique has high accuracy, sensitivity and specificity, and is fast, non-invasive and portable. However, it also suffers from low signal-to-noise ratio, sample variability and data complexity.

- Blood plasma: This technique uses infrared spectroscopy (IRS) to measure the infrared bands of blood plasma components such as proteins, lipids and glucose. The data is analyzed using multivariate analysis methods such as principal component analysis and discriminant analysis to classify the samples as positive or negative. The technique has high accuracy, sensitivity and specificity, and is fast, non-invasive and low-cost. However, it suffers from sample variability, data complexity and interference from water and other molecules.

- Breath: This technique uses infrared spectroscopy (IRS) to measure the infrared bands of breath components such as carbon dioxide, nitric oxide and ammonia. The data is analyzed using principal component analysis and cluster analysis to classify the samples as positive or negative. The technique has moderate accuracy, sensitivity and specificity, and is fast, non-invasive and portable. However, it suffers from sample variability, data complexity, interference from water and other molecules, and calibration issues.

- Urine: This technique uses mass spectrometry (MS) to measure the mass spectra of urine metabolites such as creatinine, urea and citrate. The data is analyzed using principal component analysis, cluster analysis and machine learning algorithms to classify the samples as positive or negative. The technique has high accuracy, sensitivity and specificity, and is fast, non-invasive, sensitive and specific. However, it requires sample preparation, data complexity, calibration, validation and ethical issues.

- Saliva: This technique uses fluorescence spectroscopy (FS) to measure the fluorescence spectra of saliva components with gold nanoparticles as probes. The gold nanoparticles bind to specific biomarkers of COVID-19 infection such as spike protein or nucleocapsid protein. The data is analyzed using multivariate analysis methods such as principal component analysis and discriminant analysis and machine learning algorithms to classify the samples as positive or negative. The technique has very high accuracy, sensitivity and specificity.

Possible Challenges:

- **Low signal-to-noise ratio:** Spectroscopy is a weak phenomenon that requires high-intensity light sources, sensitive detectors, and noise reduction techniques to obtain reliable spectra. Low signal-to-noise ratio can affect the accuracy and reliability of spectroscopic methods for COVID-19 detection. Spectroscopic spectra can be affected by various factors, such as sample heterogeneity, hydration, temperature, pH, or contamination. Sample variability can affect the reproducibility and comparability of spectroscopic methods for COVID-19 detection.
- **Data complexity:** Spectra obtained from the techniques discussed are complex and overlapping, requiring advanced data processing and analysis methods to extract meaningful features and patterns. Data complexity can affect the interpretation and classification of spectroscopic methods for COVID-19 detection.
- **Calibration and validation**: Spectroscopy require the calibration and validation of the instruments, methods, and models used for the analysis, which is time-consuming, costly, or complex. Calibration and validation are essential for ensuring the accuracy and reliability of spectroscopic methods for COVID-19 detection.

Probable Solution:

- **Surface-enhanced Raman spectroscopy (SERS) or surface-enhanced infrared absorption spectroscopy (SEIRAS):** In these techniques nanostructured metal surfaces or particles are used which enhance the spectroscopic signal by several orders of magnitude by creating localized surface plasmon resonances, thereby techniques can improve the sensitivity and specificity of detection of COVID-19 by using functionalized substrates or probes that selectively bind to SARS-CoV-2 or its components [1,2].
- **Standardization or normalization of sample preparation and measurement conditions**: Use of standardized protocols, reagents, instruments, settings, or reference materials for sample collection, extraction, storage, processing ensure that the samples are prepared and measured in a consistent and controlled manner to minimize the effects of sample variability [3,4].
- **Machine learning or multivariate analysis**: These are techniques that use mathematical models or algorithms to learn from data and make predictions or decisions. These techniques can improve the data processing and analysis of spectroscopic data for COVID-19 detection by using supervised or unsupervised methods to reduce dimensionality, extract features, identify clusters, classify samples, or evaluate performance [5,6].
- **Ethical approval and compliance:** Obtaining ethical approval from the appropriate committees/boards, obtaining informed consent from the participants or their legal representatives, ensuring privacy and confidentiality of the participants and their data, and complying with the ethical standards and regulations throughout the research process are necessary to ensure that the research involving human subjects is conducted in accordance with the ethical principles and guidelines of the relevant authorities [7,8].
- **Standardization or optimization of calibration and validation procedures**: Use of certified reference materials/ standards for calibration, using cross-validation or independent validation methods or using optimization techniques to improve the

performance of calibration and validation confirm that the instruments, methods, and models used for spectroscopy are appropriate [9,10].

Conclusion and future works:

One way to detect viruses quickly and accurately is by using fluorescence, which makes them glow under certain light. This can help diagnose and prevent viral infections, as well as track how they spread and study how they work. Scientists are developing new fluorescent materials and methods to make this technique more sensitive, specific, and fast.

Another way to detect substances in a sample is by using colorimetric assays, which change color when they react with them. The color intensity shows how much of the substance is in the sample. Colorimetric assays are easy, fast, and cheap to use for various purposes, such as finding proteins, enzymes, and nucleic acids.

Spectroscopy is a powerful tool that can measure COVID-19 in a sample by analyzing its spectrum. It can also reveal information about the virus and its effects on the body, such as its variants, co-infections, complications, and vaccine responses. However, spectroscopy also has some limitations, such as low signal quality, sample variation, data complexity, ethical issues, calibration and validation. These can be overcome by using different techniques or procedures, such as surface-enhancement, standardization, normalization, machine learning, multivariate analysis, ethical approval and compliance. Future research on spectroscopy for COVID-19 detection should aim to create new techniques or devices that can improve its performance or applicability in different situations or environments. Spectroscopy can help diagnose, monitor, and manage COVID-19 and other infectious diseases.

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