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Grand Challenges and Perspectives in Biomedical Analysis and Diagnostics

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INTRODUCTION

The importance of analytical sciences and biosensing to medical diagnosis has been well recognized by those involved in the field; the recent global pandemic due to severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2) has further elevated the topic to paramount worldwide prominence and urgency (Lippi et al., 2020). While the pandemic may be contained in the near future due to the heroic efforts of medical staff and biotechnologists around the world, the research interest in analytical sciences toward more efficient medical diagnosis will undoubtedly remain for the foreseeable future. Aside from innovative schemes that offer new angles for detection and quantification, evaluations and reevaluations of the state and efficacy of analytical sensing are also required when applied to medical samples. For a broader conversation of the directions of research, it is important to assess the state-of-the-art and significant trends across the field. There have been exciting technical developments in recent years that push forward the accuracy and sensitivity of techniques, expand the scope of analyses beyond simple biomarkers, and improve the accessibility and applicability of analytical methods. In addition, clinical data of increasing depth and complexity are gathered at an extraordinary pace in recent years due to "Big Data" movement in healthcare. Therefore, one of the most prominent trends in analytical science appears to be the application of artificial intelligence and machine learning models to correlate sensed or imaged markers from patients to diagnosis (Rajkomar et al., 2019). Recent examples include an artificial intelligence system that outperformed doctors by 11% in diagnosing breast cancers (McKinney et al., 2020), and a study of machine learning models that used imaging biomarkers and predictive models for rapid diagnosis of COVID-19 (Wynants et al., 2020). This dense, complex approach toward information accumulation also requires a scale-up in the sophistication of models by which the information is treated so that relevant outcomes and knowledge can be obtained. Clearly, the need for technical advances in medical diagnosis is ever-present, and this is manifested in the current pandemic. Mature technologies such as PCR and immunoassays continue to provide reliable tests for the rapidly spreading disease, while in the meantime we have seen a wave of new approaches rolling out of unconventional sectors that are shaping the course of diagnostic development (mass spectrometry, 3D printing, and CRISPR-Cas12, to name a few). The challenges in this field also suggest a range of opportunities, which we aim to describe in this Article. In the interest of brevity, we will organize the discussion into *analysis targets*, *technological developments*, and *data processing*.

ANALYSIS TARGETS

Biomedical disease diagnosis is often associated with detection of specific biological molecules of either a pathogen or the patient that is in a disease-indicative state. Quick diagnosis and implementation of tailored therapies have drastically improved the quality of life observed in patients and may potentially lead to cures for many of the diseases that plague the society. The major categories of analytical measurements currently employed in diagnostic activities include spectroscopy/optics, electrochemistry, and mass spectrometry. They have found broad applications in all of the major targets discussed in this section.

Nucleic Acids

For the purpose of medical diagnostics, detection and quantification of DNA and RNA are most closely associated with identification of microbial pathogens, as the fundamental gene sequences that encode the characteristics of a species are essentially the fingerprint for the microbe. Subsequently, DNA and RNA are highly enticing targets for the detection of infectious diseases. The most prominent techniques of this category are polymerase chain reaction (PCR) for DNA and reverse transcription PCR (RT-PCR) for RNA, which catalyze the cyclical synthesis and re-synthesis of the nucleic acid strands, amplifying the amount of target material for quantification through a reporter (Sin et al., 2014). Many alternate designs based on nucleic acid amplification are currently under intense development, which has led to techniques such as loop amplified isothermal amplification (LAMP), rolling circle amplification (RCR), and recombinase polymerase amplification (RPA) (Özay and McCalla 2021). These types of detections have been reported for a broad swath of pathogens, including SARS-CoV, SARS-CoV-2, norovirus, hepatitis, salmonella, *listeria monocytogenes*, *staphylococcus aureus*, and *Escherichia coli* (Law et al., 2015). These methods have the benefit of very high sensitivity, though that sensitivity has the known drawback of contaminant amplification along with the target.

DNA amplification-based methods typically use fluorescent dyes as the signal readout, thus making the overall technique an optical approach. However, nucleic acids, with their single-molecule fingerprinting association, are also targets for other analytical detection methods, especially electrochemically based (Sadighbayan et al., 2019). Frequently, guide strands of DNA and RNA are immobilized to a solid support, and the hybridization with the target analyte strand leads to a shift in signal readout. This strategy is foundational in a wide range of work with DNA and RNA microarrays (Mortazavi et al., 2008; Ritchie et al., 2015), along with electrochemical and optical detections that show very high sensitivity and selectivity (Borum and Jokerst 2021). This approach is less practical for endogenous diseases, such as cancer or Alzheimer’s disease, where the associated DNA is simply that of the patient. Since PCR techniques are viewed the “gold standard” of COVID-19 detection, we expect that there will be an increased interest in DNA- and RNA-based amplification-based research in various diagnostics.

Proteins

Proteins are one of the major targets for biosensing and diagnosis applications. There are extensive varieties of proteins within the living organisms exhibiting broad functions and as antigenic sites. Proteomic studies have been instrumental in identifying and linking proteins to diseases (Sobsey et al., 2020). Enabling analytical scientists to formulate detection schemes for proteins provides new marks intimately linked to the spread, progression, and effects of the diseases. Recent advancements have pushed the limits of detection and taken advantage of characteristics such as binding affinity to enable accurate detection of proteins that facilitates diagnoses. In addition, development of new methods for simultaneous screening of various proteins improves on rapid characterization of disease progression (Tobos et al., 2020). Antibodies are possibly the most prominent of protein biomarkers based on their high affinity to pathogenic targets and their important connection to immune response. The detection and monitoring of antibodies concentration levels in relation to specific diseases has become a major focus for analytical studies (Iwanaga 2020; Elledge et al., 2021). In the process of vaccine development antibody sensing plays a critical role in determining vaccine effectiveness (Yadav et al., 2021).

Protein quantification for diagnosis has been prominently achieved by immunoassay, which has been developed with many different signal transduction schemes. Optical labeling approaches such as enzyme-linked immunosorbent assay (ELISA) (Cheng et al., 2020), fluorescent labeling (Jeon et al., 2020), chemiluminescence (Zhang H. et al., 2020) and colorimetric assays (Liu et al., 2020) are well established. Label-free optical techniques including surface plasmon resonance (SPR) (Rezabakhsh et al., 2020; Sankiewicz et al., 2021), surface enhanced Raman scattering (SERS) (Gahlaut et al., 2020), interferometry (Goodwin et al., 2020), and ellipsometry (Caglayan and Ustundag 2020) have become broadly adopted. Electrochemical techniques have also found extensive use (Zhang H. et al., 2020; Raziq et al., 2021). Furthermore, mass spectrometry-based techniques have enabled quantification of proteins either as a whole macromolecule (Sisley et al., 2020) or as peptide fragments through enzymatic cleavage (Ihling et al., 2020). Other avenues to protein sensing and diagnosis include quartz crystal microbalance (QCM) (Lim et al., 2020), Western blot (Zhao et al., 2020), and lateral flow assays (LFA) (Baker et al., 2020).

The detection of trace amount of protein biomarkers in complex samples such as blood, saliva and cerebrospinal fluid is technically challenging. Determining their significance in patient samples must eliminate factors that potentially result in false positives or negatives. Statistically complex, post-acquisition data analysis is broadly used, and methodologies to account for nonspecific and cross reactivity have been reported (Jiang et al., 2020; Zhang W. et al., 2020).

Metabolites/Lipids

Many recent studies have focused on monitoring metabolic changes and associating them with various diseases and disease states (Bereman et al., 2020; Metwaly et al., 2020). Metabolic pathways represent integral points in complex cell signaling networks that can give insight into the overall health of an organism as well as that of individual cells. For a pathophysiological process, metabolites are the final products associated with the disease state or exposure to environmental factors. Because of their rich presence in bodily fluids, they can be sampled from a plethora of sources to give a holistic view of the process occurring. The process by which these metabolites are profiled is known as metabolomics, and has provided novel insights into a vast array of pathophysiological processes (Zhang X. w. et al., 2020). Lipid metabolism disorders have been observed in various diseases such as cancers, autoimmune disorders, and cardiovascular diseases, and a number of studies have looked toward lipids to gain a deep understanding of the cellular processes (Boutte and Jaillais 2020; Butler et al., 2020; Flores-Romero et al., 2020; Chausse et al., 2021), where changes in the lipid profile are linked to signs of disease. Antibody biomarkers against target lipids such as sulfatides and gangliosides are used for monitoring disease progression (Malinick et al., 2020; Mata et al., 2020; Rodriguez-Carrio et al., 2020; Roggenbuck et al., 2020; Kusunoki et al., 2021). Lipids are particularly relevant for monitoring bacterial populations and infections as a number of profiling studies have shown to differentiate bacteria and other microorganisms (Watson 2006; Ting et al., 2011; Li et al., 2016; Li Q. et al., 2019; Shanta et al., 2020). The analysis of lipidome, however, proves to be challenging due to the heterogeneity of lipid classes and their intrinsic properties that cause the variations of these classes. Nevertheless, the study of chemical diversity of lipids can lead to better understanding of biological processes and their relevance to diseases, making lipids ideal biomarkers for probing both infectious and noninfectious diseases.

TECHNOLOGICAL DEVELOPMENTS

The progress of technological innovations impacts every facet of society, and analytical science is no exception. While the ingenuity and curiosity of researchers are vital to analytical science developments, it is the improvements in fundamental technology that serve to elevate what is possible to translate basic science into real-world applications. A number of significant trends are emerging based on newly developed or enhanced versions of existing bio- and nanotechnologies, and they form the sources of very high upside exploration in current literature.

A prominent example is the technique associated with the nucleic acid-targeting approach known as clustered regularly interspaced short palindromic repeats (CRISPR), which has significant analytical potential beyond the standard gene knockout/knockin that CRISPR is originally designed for (Li Y. et al., 2019). Fusion of CRISPR-associated proteins with specific reporting for non-DNA molecular targets has opened up possibilities for sensing of a diverse array of analytes such as proteins (Chen et al., 2020), small molecules (Liang et al., 2019), and metal ions (Xiong et al., 2020). The more recent discovery and development of effector domains that can cleave not only double-stranded DNA, but also ssDNA and ssRNA (Aman et al., 2020), further expands the scope of biosensing along the line of previously developed SHERLOCK and DETECTR systems (Mustafa and Makhawi 2021). Fundamental innovations in these areas will serve to push the boundaries of what is possible in the analytical sciences.

Three-Dimensional (3D) Printing

3D printing technology, aside from being popular in the wider culture, has had a concurrent rise in academic interest, especially in analytical applications. The relative low cost and ease of use has enabled labs to take advantage of the manufacturing flexibility and rapid prototyping in a wide array of both in-lab and product development environments (Fan et al., 2020). There are a variety of methods collectively put under the banner of 3D printing, such as inkjet, binder jetting, selective laser sintering, and direct printing (Gross et al., 2017), each with advantages and limitations. The two most common techniques are stereolithography (SLA), which uses a photopolymer bath onto which a UV laser traces and polymerizes each layer, and fused deposition modeling (FDM), which uses printing material filaments extruded through a nozzle to trace out successive layers from the bottom up. For medical diagnostic purposes, 3D printing has a particular benefit toward point-of-care testing (POCT), a key component for daily health testing and community health management in an outbreak. Implementation of standardized methods and parts that utilize 3D printing would provide better access to point of care *manufacturing* (Chan et al., 2017), and a wealth of research has been reported for components 3D printed as parts of electrochemical, lateral-flow, and fluorescence-based assays (Munoz and Pumera 2020). A number of examples involved assemblies onto the camera of a smartphone (Carrasco-Correa et al., 2021), pointing toward a future diagnostic trend where the general public can benefit from technologies in their homes.

A very exciting area of 3D printing is its application to microfluidics (Wang and Pumera 2021), which has emerged as a vital component of modern analytical science due to high detection sensitivity and low sample volumes. The complex geometries frequently involved in microfluidic designs present no fabrication barrier to the typical building strategy of 3D printing. A large number of complex microfluidic components have appeared in the literature (Au et al., 2016; Waheed et al., 2016; Song et al., 2018; Li F. et al., 2019; Parker et al., 2019). Recent development of transparent polymer resins has allowed fabrication of parts that are spectroscopically functional and may serve similarly as high end optics for diagnostic sensing (Lambert et al., 2018). New smoothing strategies have led to the implementation of flexibly designed optical components such as lenses, prisms, waveguides, and diffraction gratings, as well as custom-built niche designs (Comina et al., 2015; Squires et al., 2015; Comina et al., 2016; Hinman et al., 2017; Busch et al., 2018; Vaidya and Solgaard 2018; Shao et al., 2020).

Diagnostic Imaging

From a diagnostic perspective, imaging-based approaches have enormous value. Spatially resolved images of disease states or processes such as drug delivery and biomarker distribution allow for better development of medical intervention strategies and more complete profiles of patient health conditions (Tempany et al., 2015). Traditional techniques such as MRI, CT, and PET are being combined with luminescent or plasmonically enhanced materials to form hybrid imaging modalities such as X-ray excited luminescence imaging, Raman imaging and Cerenkov luminescence imaging (Pogue and Wilson 2018). New imaging strategies, such as terahertz (Sun et al., 2017) and photoacoustic imaging (Fu et al., 2019), show promise for groundbreaking applications. These technologies have been developed tremendously over the past 20 years and will continue to evolve and improve for a considerable time.

Materials for aiding in diagnostic imaging are also under continuous development. For example, the range of nanomaterials-based luminescent approaches has expanded rapidly, providing fluorescent, chemiluminescent, and bioluminescent probes for both *in vivo* applications and more traditional *in vitro* studies (Smith and Gambhir 2017; Zhou et al., 2020). Plasmonic nanoparticles, typically synthesized of fortuitously nontoxic gold and silver, take advantage of photothermal conversion of incident localized radiation to induce fluorescence at their localization point (Sharifi et al., 2019). 2D materials such as graphene, molybdenum disulfide and carbon nitrides are under heavy investigation due to their high compatibility with current imaging modalities (Bhimanapati et al., 2015). Other benefits of nanomaterials include tunable optical properties, functionalizable surfaces, and high surface area-to-volume ratio. Though a comprehensive listing of all new materials designed for imaging diagnosis is beyond the scope of this Article, this area is likely to remain a hotbed of research due to these fundamental benefits.

Another significant trend is the combination of imaging data with the power of machine learning, which itself will be discussed in more detail in the next section. This high-order, meta-level analysis is an important component of improving health outcomes around the world (Athamanolap et al., 2019; Singh et al., 2019; Shin et al., 2020).

DATA PROCESSING

Application of rigorous statistical analysis to biosensing and diagnosis of human disease has become a key step in reducing data complexity due to biological heterogeneity and to ensure signal association with targeted biomolecules. It is increasingly utilized for complex, multiplexed sensing and detection of trace biomarkers (Malinick et al., 2020; Arima et al., 2021; Kim et al., 2021). Analytical merits including limits of detection, standard deviation, and working range are important components for a diagnosis work, and the analyses must be properly performed to ensure results are reproducible among labs (Urban 2020). Methodology development can be strengthened by statistical analysis terms of total variance, PCA (Corradi et al., 2020) and PLS (Henao-Escobar et al., 2015) when applied to demonstrate specific detection of target biomolecular analytes.

Statistical tools are instrumental in enabling new techniques and enhancing current methodologies for diagnosis (Taylor et al., 2019; Cui et al., 2020; Meng et al., 2021). This is evidenced by Fourier transform infrared spectroscopy (Ghassemi et al., 2021), impedance spectroscopy (Mahdavi et al., 2020), and mass spectrometry imaging (Wang et al., 2021), which are made possible by implementing robust statistical methods. While these traditional statistical models have allowed evaluation and depiction of data based upon unique trends, the need for more advanced statistical algorithms has grown strong as more sophisticated detection schemes are being developed. Recently, machine learning has shown their practicality in aiding analytical measurements through advanced pattern recognition (Alafeef et al., 2020; Arima et al., 2021; Liu et al., 2021). As sensing applications grow to answer emerging clinical problems, machine learning is expected to aid strongly in data deconvolution from complex systems and provide highly sensible outcome. Machine learning can also enable personal targeted medicine and diagnosis, as well as automated analysis, which is vital in translating some of the labor-intense lab work to commercial and clinical operation.

FUTURE PERSPECTIVES

Aside from the current pandemic, there are several fronts of pressing need for new tools that enable swift diagnosis, notably for early stages progression of diseases like cancers and Alzheimer's disease, both of which are on a global upward trajectory (Sung et al., 2021; El-Hayek et al., 2019). Additionally, many new avenues of technical improvement are currently under heavy investigation that will advance what is possible in achieving these overall goals, especially at the multidisciplinary interface between chemistry, biology and materials science, such as novel methods for mass spectrometry, microfluidics, microextraction and sample enrichment. As such, we anticipate increasingly high demands for new, improved and highly innovative analytical techniques in the field of medical diagnosis, and this Journal aims to encourage technical development toward these ends. Two areas are of principal importance: 1) high sensitivity and specificity in detection and 2) translations that bridge laboratory development and field use. The increased attention on analytical science and the launch of this new Journal can serve as an extremely powerful opportunity to explore, harness, and capitalize on the most promising recent developments in biotechnology.

AUTHOR CONTRIBUTIONS

QC contributed to manuscript writing and revision, and approved the submitted version.

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