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Challenges in lab-on-a-chip technology

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Introduction

Lab-on-a-chip technologies, also known as μ-TAS (or micro-total analytical systems), involving the integration of analysis methods into devices and systems, have made significant impacts for over 3 decades, providing methods to analyze real samples, on microengineered chips. The field is, by its nature highly multi-disciplinary, bringing together aspects of chemistry, engineering, computing science, biophysics, biochemistry, molecular biology, as well as the environmental, clinical and veterinary sciences.

Such integration of different subject areas and technologies has already provided striking examples of how analysis can be performed outside of the laboratory. The small size of devices used in lab-on-a-chip technologies result in reduced sample volumes, short times for mass transfer across reduced distances, and/or unique materials' properties arising from the nanoscale dimensions of materials used in the sensors. Commercially-available examples of such sensors comprise sample-to-answer solutions, including, finger-stick and continuous glucose monitoring, as well as paper microfluidic lateral flow technologies, associated with, e.g., pregnancy testing. These latter immunoassay technologies have also found broad application in medical diagnostics, with examples of these including testing for endemic infectious diseases, such as malaria, as well as, more recently during the current pandemic, to enable SARS-CoV-2 detection in community settings.

Challenges in diagnostics

Generally, lab-on-a-chip technologies involve the use of microengineered devices to enable sample preparation, analyte separation, and detection, performed in miniaturized formats providing testing away from the laboratory with examples including medical, veterinary (pen-side) and environmental analysis. Despite the analytical advantages associated with microfluidic technologies and lab-on-a-chip technologies, many challenges still exist.

For example, there is a continued need to move analytical tests, such as personal health diagnostic assays, away from specialist centralized laboratories and into community settings (as evidenced in the current COVID-19 pandemic). Although lateral flow testing using paper microfluidics can provide diagnostics at home or in work, there is a current need to translate more sensitive molecular testing of nucleic acids (as markers of disease), onto low-cost, autonomous lab-on-a-chip systems (Guo et al., 2021; Witkowska McConnell et al., 2021).

The future key challenges in the development of such technologies are manyfold and include sample processing on a low cost and preferably disposable platform for "sample-to-answer" analysis. Such new technologies will have important roles for a range of infectious diseases globally, not just to mitigate the effects of pandemics, but also to meet the challenges set by the World Health Organization around elimination of endemic disease (WHO, 2020), particularly in the global south. This includes a number of "neglected" diseases such as schistosomiasis, as well as more familiar diseases, including malaria and hepatitis.

New, more sensitive diagnostics, based upon molecular testing, are just one key future challenge needed for elimination, for the identification of disease reservoirs within remote and under-served communities, capable of detecting both asymptomatic and or pre-symptomatic individuals (Alvar et al., 2020).

The key requirements involve the need for tests with the sensitivity provided by the amplification of the biomarker, afforded either by Polymerase Chain Reaction or isothermal assays. In the case of RNA viruses, such as SARS-CoV-2, Ebola or hepatitis, for example, the "sample preparation" steps must also overcome the challenges of performing a reverse transcription step to form DNA, prior to amplification, adding significantly to the challenge of sample preparation (Witkowska McConnell et al., 2021).

Challenges in digitalisation

Most recently, and as one noticeable trend over the last 5 years, the field has evolved to include the use of expert systems with deep learning, involving artificial intelligence and machine learning being developed and implemented in order to provide users with informed decision support. Such work includes helping to guide or inform clinical or environmental analysis in the field, when experts may not be present to guide the decision.

One example, where such systems have found application, has been in clinical applications where clinical diagnostics need to be performed in remote, low-resource settings, where laboratory facilities are not available (Guo et al., 2021). The ability to collect data, using for example mobile phones, and running deep learning algorithms, either on the phone's GPU or by connecting to the cloud, can provide diagnostic decision support to guide or inform a treatment or care pathway. The challenge of how such lab-on-a-chip systems will link to central medical databases and digital health infrastructure in a secure and trusted environment will help to shape the field and the acceptability of the techniques. Such questions need to be addressed through a multi-disciplinary approach involving technologists as well as social scientists.

Beyond applications-led lab-on-a-chip, the field of intelligent microfluidics is also emerging, using machine learning for the monitoring and control of microfluidic systems providing new challenges and opportunities to accelerate chemical exploration and synthesis at reduced costs. These concepts will underpin a new generation of high throughput discovery tools associated with digital chemistry (Caramelli et al., 2021), developing new methods in important areas such as new medicines synthesis and screening, as well as in, e.g., advanced materials discovery.

This burgeoning field has recently expanded to include the challenge resulting from the convergence of microfluidic chip fabrication and tissue engineering to give rise to organs-on-a-chip and organoid research (as *in vitro* organ models based on self-organized, stem cell-derived multicellular constructs). In such cases, the potential benefits of integrating machine intelligence into artificial biological organs is an emerging challenge for *in vitro* prediction of drug efficacy and toxicity *in vivo* (Galan et al., 2020).

Challenges in wearable lab-on-a-chip technologies

Wearable technologies, including those involved in continuous glucose monitoring, have more recently become associated with patches for measuring physiological and biochemical parameters more broadly. The sensing devices can be interfaced with mobile phones and-or smart watches to display and interpret data, providing information which can be downloaded to guide personal or clinical decision. Whilst technologies for accurate measurements of physiological parameters (including heart rate, heart function, blood pressure and temperature) have progressed rapidly, challenges still exist in using lab-on-a-chip biochemical measurements.

Challenges in environmental sustainability and reaching net-zero

The field of lab-on-a-chip needs to meet important challenges around our global targets in sustainability and net-zero. This includes not only the development of smart analytical systems that are able to sense the changes that are occurring within the environment but also, more generally, the mitigation of single-use plastics in analysis and the use of low-power, recyclable microsystems technologies.

In the context of probing or monitoring the environment, lab-on-a-chip technology offers the opportunity to probe pollutants and toxins providing simple sample-to-answer technologies that can inform scientists of environmental change (Nightingale et al., 2019). These systems will also enable experts to collect data on the effect of the changing environment, with future examples including systems that are able to probe the effects of our warming seas, not just in terms of nutrient or dissolved gas availabilities, but also capable of measuring the dynamic changes in the microflora or microfauna. It is anticipated that such expert systems will include deep learning to predict trends as well as data logging either as discrete (one off) measurements or as remote continuous sensors.

In the context of sustainability, most lab-on-a-chip devices are currently single use, made from plastic materials derived from non-renewable sources and contributing to the burgeoning amounts of medical waste. Whilst some of these devices are disposed of in an environmentally "friendly" manner, increasingly these materials find their way into land fill or rubbish tips (Street et al., 2022). New biodegradable materials, including those derived from natural sources, such as cellulose/paper, may in future replace halogenated plastics such as polyvinyl chloride (with the caveat that natural biopolymers such as cotton present their own environmental risks).

The need to examine the whole product life cycle, moving towards a circular economy, will include consideration of the overall carbon footprint (measured as its quantitative equivalence, eCO2). A recent review provides a comprehensive overview of the "plastic problem," including the presence and future of bioplastics and how their use can open a path to a more sustainable future, including, some challenges to bioplastics implementation framed by eCO2 considerations (Rosenboom et al., 2022).

The role of expert systems, particularly in digital health, in providing key information at the point of need, where treatment is carried out, will also serve to reduce the overall environment footprint of measurement systems, reducing transport costs and the burden placed on transport and infrastructure systems. Similarly, local manufacturing has the potential to contribute to net-zero by staying close to where devices are being used, such as by the Diatropix initiative in Senegal (where it is proposed diagnostic devices will be manufactured in Africa, close to where they are needed).

Challenges in manufacturing

Thought leaders in lab-on-a-chip will be encouraged to present opinion on how advances in technologies may impact society in the coming years. Connected to this will be the impact of new sustainable manufacturing technologies, that continue to reduce production costs, whilst improving product reliability, but not at the expense of the environment. Inevitably, new manufacturing technologies will involve optimization and rationalization of existing conventional both micro- and nano-lithographic methods, as well as the integration of less conventional methods for hybrid lab-on-a-chip manufacturing methods (Ha et al., 2016) using additive manufacturing methods (such as 3D-printing) as well as self-assembly at the nanoscale. New methods in molding, embossing and reel-to-reel processing have also been adapted to produce hybrid devices at micro- and macro scales.

Challenges in education and training

Finally, it is worthwhile to note that the broad cross-disciplinary nature of the field provides a significant challenge to those involved in research and development, arising from the need to bring teams of individuals with disparate skills, together. For the early career researcher starting out in the field of lab-on-a-chip, there is the need to be able to understand a wide range of technologies and techniques that extend beyond what they may have encountered during their undergraduate degree. Even within a broad discipline such as engineering, which may encompass electronics, fluid mechanics, manufacturing, bioengineering and aspects of materials science, the breadth of knowledge that a graduate student may need to acquire during their graduate studies represents a challenge as they apply their knowledge to the understanding of the working of a system.

In is notable that the best aspects of applied research often bring together larger teams with skills drawn from across many different disciplines to address important global challenges, including, for example, antimicrobial resistance, infectious disease or environmental monitoring and sustainability.

Summary

The Frontiers in Lab-on-a-Chip Technology journal covers all of these topics—a timely offering that will make a major contribution to the entire range of research—from fundamental knowledge, modelling, simulation, device and systems optimization, as well as production/manufacturing—through to emerging applications and implementations. As stated, a key challenge is the bringing together of groupings of individuals to deliver impact through the development of new techniques and technologies, building ambitious implementations that go significantly beyond current knowledge.

We aim to invite the finest creative minds in the field to speculate on where the future lies. The new journal has a commitment to diversity and inclusion evidenced through the broad range of backgrounds of the editorial boards, drawn from across the world and representing researchers at all stages of their careers.

Author contributions

JC developed the conceptual content and wrote the manuscript.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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