



Lab at home: a promising prospect for on-site chemical and biological analysis

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Abstract

The continuing pursuit for a healthy life has led to the urgent need for on-site analysis. In response to the urgent needs of on-site analysis, we propose a novel concept, called lab at home (LAH), for building automated and integrated total analysis systems to perform chemical and biological testing at home. It represents an emerging research area with broad prospects that has not yet attracted sufficient attention. In this paper, we discuss the urgent need, challenges, and future prospects of this area, and the possible roadmap for achieving the goal of LAH has also been proposed.

Keywords Microfluidic analysis · On-site analysis · Lab at Home · Biochemical analysis

Introduction

Currently, on-site analysis technology is playing an increasingly important role in human life and social development. In recent years, the development of the Internet of Things (IoT) and wearable devices has also placed high demands on on-site chemical and biological analysis. In the past decade, various on-site analysis techniques, such as point-of-care testing (POCT) [1], microfluidic analysis [2], and portable chemo/biosensors [3], have undergone rapid development. POCT is defined as medical testing at or near the site of patient care [4]. It uses portable reagents and apparatus to perform rapid and convenient medical testing outside the central clinical laboratory and can notably accelerate the diagnostic procedure and subsequently earn precious treatment time for the patients. Furthermore, due to the features

of low cost, portable devices, and less need for professional operation skills, the POCT systems have the potentials to be used as ideal diagnostic facilities in large numbers of remote rural clinics and community health service centers. Currently, the POCT technology has become one of the most active areas in the *in vitro* diagnosis and has been applied in clinical testing of blood glucose [5], blood gas [6], electrolytes [7], coagulation [8], cardiac injury markers [9], and tumor markers [10].

Microfluidics is the technology and science of manipulating microfluids in micrometer-scale channel networks. Microfluidic chip systems have the characteristics of micro-amount consumption, high efficiency, high throughput, and a high level of system miniaturization, integration, and automation. Various microfluidic systems have been widely used in biochemical analysis [11], biological research [12], clinical diagnosis [13] (including POCT), high-throughput drug screening [14], forensic identification [15], and environmental monitoring [16]. The unique features of microfluidic systems in system miniaturization and integration make them particularly suitable for realizing the aim of POCT, and currently, it has become the main technology to promote the development of POCT instruments (Fig. 1). A variety of microfluidic chip systems for POCT have been reported in the field of biomedicine [17] and life sciences [18].

Generally, a complete on-site analysis procedure should include multiple steps of sample introduction, pretreatment, reagent storage and addition, multistep reactions, separation, and detection. Among these operations, the most essential

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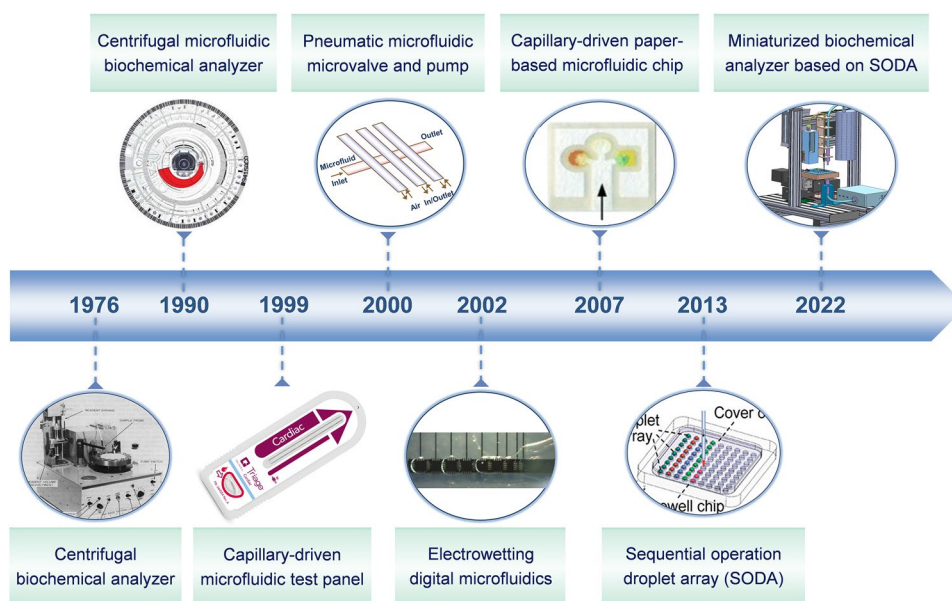
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Fig. 1 Milestone diagram of some nodal technique in the development of POCT and microfluidic chips



core operation lies in the driving and control of microfluids in the system. At present, a number of microfluidic POCT systems based on different driving and control methods are reported, including micropump [19, 20], centrifugal force [21, 22], capillary action [23, 24], and electrowetting methods [25, 26]. To varying degrees, these systems can achieve the automation of liquid-handling operation and the integration and miniaturization of the analytical systems. Among them, the systems based on centrifugal force and capillary action control show relatively high levels in achieving system integration and miniaturization.

Applications and challenges for LAH

Although the above analytical techniques have undergone rapid development, they still face some major challenges. The sensors widely used in cell phones, wearable devices, and IoT mainly belong to physical solid-state sensors, such as temperature sensor, gravity sensor, acceleration, position, and gas sensor. However, chemical and biological sensors are usually absent in these devices, most likely because they all need to use liquid reagents and to perform complex and multistep liquid manipulations for sample introduction, pretreatment, reagent addition, sample-reagent reaction, separation, and detection, resulting in severe difficulties in achieving system miniaturization and integration.

Performing all of the above operations in a portable analysis system sets high demands on the system's miniaturization, integration, and automation. The dry chemical technique using test strips based on capillary action driving is the frequently used POCT technique with typical applications in blood glucose analysis and on-site immunoassay. In

the measurement, the sample is dropped on a test strip, and the sample components are driven by capillary action to flow along the test strip and react with the reagents preloaded on the strip. The reaction product is detected using visual colorimetric, absorption spectrophotometric, fluorescent, or electrochemical methods.

Although the test strip technique has the advantages of low cost, tiny system size, and easy operation, only qualitative or semi-quantitative analysis results can be obtained in most test strip systems due to the lack of precise liquid control to sample and reagents. Currently, most of the analysis work in clinical diagnosis including biochemical analysis, nucleic acid analysis, immunoassay, and cell counting still relies on various desktop instruments in central laboratories of hospitals, such as biochemical, immunoassay, and PCR analyzers, as well as flow cytometers.

Complex fluid operations, including liquid metering, transferring, addition, mixing, reaction, separation, and detection, are required to be accomplished in these instruments. These operations are usually carried out by precise mechanical pumps, control valves, complex flow conduits, and sensitive detectors equipped in the instruments, resulting in the complex instrument structure and expensive cost. To integrate all of these operations in a miniaturized analysis system is a very challenging work, even with the microfluidic chip technology that is unique in achieving miniaturization and integration of analytical systems. Currently, a variety of microfluidic chip systems for on-site analysis have been reported in literatures. However, many microchip-based systems can only perform part of the above operations. There are few microfluidic systems that are capable of integrating all of these operations. Even if there are, the system structure will be quite

complicated, and the microfabrication cost for the microchip will also be high, which may limit their application in on-site analysis. In addition, most of the currently used microchip-based systems usually adopt specialized chips for detection of one or several specific biochemical targets. The measurements to more different targets are usually conducted using different microchip systems or even different instruments. Therefore, under the current technical conditions, it is still a great challenge to integrate multiple measurement modules for different types of targets into a portable analytical instrument.

For the POCT techniques, the World Health Organization (WHO) has announced the ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, Deliverable to the end user) criteria which is now widely accepted by researchers. In addition, we noticed an obvious tendency in current on-site analysis field that most of the researches mainly focus on the development of portable devices that can be carried by individuals, which, of course, is the ultimate goal of on-site analysis. However, it is worth pondering how many biochemical tests really need to be carried out on-site quickly.

In the field of POCT, two typical examples of urgent on-site testing are the assays of blood glucose and myocardial zymogram with the feature of rapid variation and significant impact on life activities. The rapid on-site monitoring of these targets can provide important information for timely treatment of diabetes and myocardial infarction. However, a large number of blood biochemical tests, such as blood lipid, blood uric acid, liver function, renal function, and tumor markers, usually only need to be performed possibly once a week or once a month (or 3 or 6 months) without the requirement of urgent on-site testing, due to the relatively slow variation of these components. Therefore, the personal portability requirements of these detection devices are less urgent. In fact, such situations that do not require immediate detection around the individuals account for most of the current biochemical tests. It is obvious that the current demand for individualized biochemical testing is still extensive and urgent. However, as mentioned above, most of these tests may not necessarily need to be performed on the site of each individual, but can be implemented in higher-level units, the families, to meet the vast majority of requirements of individualized testing.

In this article, we propose that on-site analysis in the home, i.e., LAH, should be the major development area of on-site analysis in the future. From the current published literature, it seems that such an area has not yet attracted sufficient attention of most researchers. In fact, as the most basic units of human life, the families have a wide range of requirements for analysis and testing, which penetrate into all aspects of life, far exceeding the scope of individual POCT. These broad demands are manifested in the aspects

of personal health monitoring, household food and environmental testing, and so on (Fig. 2).

Personal health monitoring includes family members' regular health biochemical tests (such as blood glucose, glycosylated hemoglobin, blood lipids, and uric acid), screening of severe diseases (such as tumor marker screening), and initial diagnosis of emergency diseases (such as influenza, infectious disease, myocardial infarction, and diarrhea). If

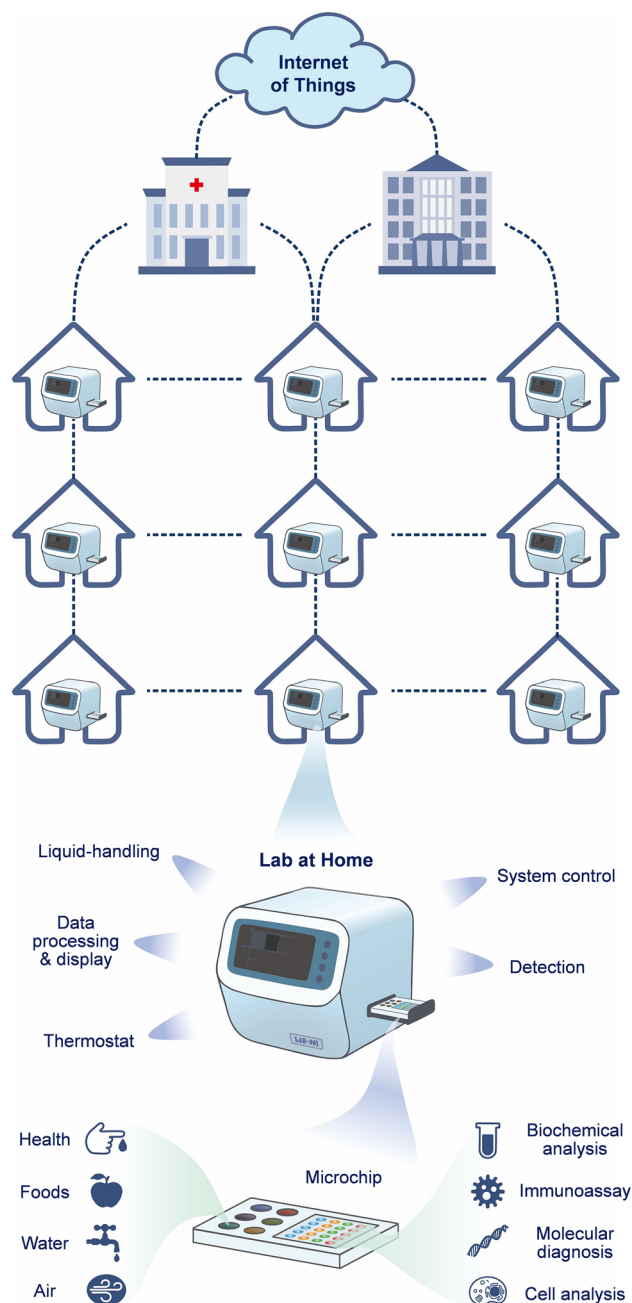


Fig. 2 Conceptual diagram of the composition and application of Lab-at-Home systems

the initial test at home has a serious result, it can prompt the patient to go to the hospital immediately.

Household environmental testing includes the monitoring of indoor air, such as the measurements of formaldehyde from decorative materials and furniture, sulfur dioxide, nitrogen oxides, sensitized pollens or microparticles, and polycyclic aromatic hydrocarbons (PAHs) in kitchen soot. Household food safety testing includes the analysis for harmful food additives, spoiled foods (such as sodium nitrite or aflatoxin), food freshness, pesticide residue in vegetables and fruits, and drinking water quality. There are also some home animals, aquariums, and gardening that need a home device for testing, such as pet health, water quality, plant-soil testing, and so on.

Wireless sensors have the advantages of extremely small size and low cost and possess the capabilities of sensing, signal processing, and wireless communication, which can be applied in health and environmental monitoring [27]. With the rapid development of the LAH technique, LAH systems may also be used as a special type of wireless sensors to achieve the wireless transmission of chemical and biological data. As mentioned above, there are many urgent needs for home testing, while it is also facing great challenges.

1. There are many types of biochemical analysis targets in homes, and diverse working principles, reagents, and operation processes are required in the analysis of these targets. This presents a high requirement for the versatility and diversity of the household analytical instruments. Differing from conventional in-laboratory analysis using different instruments for different targets, home testing needs to use as few instruments as possible to achieve as many target analysis as possible, for reducing the users' financial burden.
2. The users of household instruments are ordinary people without professional training. Therefore, these instruments need to complete the highly automated operation of sample-to-answer, i.e., to automatically realize the operations of sample introduction, sample pretreatment, reagent preparation and addition, multistep reaction, detection, data recording and processing, and result display. If quantitative detection is needed, the preparation of serial standard solutions and determination of standard curve, as well as the quantitative liquid metering and addition, should also be automatically completed.
3. Household analytical instruments should have relatively low cost and market price, which can be easily afforded by the majority of families. Because household instruments do not need to be carried by individuals like portable POCT instruments, they have lower requirements in instrument miniaturization, and an instrument size like a bread maker or a microwave oven is acceptable. This will be favorable for reducing the difficulty of instru-

ment development and the instrument cost. In addition, compared with POCT instruments, household analytical instruments have relatively low requirements in analysis speed and sample/reagent consumption.

To address the above challenges, four key issues should be solved including sample introduction, automatic and reliable liquid handling, multi-mode detection, and reagent prepackaging for different targets. Regarding these issues, firstly, various chips can be designed for different types and physical forms of samples, and multiple functions for sample pretreatment should be integrated into the specific chips. Due to the diversity and complexity of samples involved at home, manual pretreatment of the samples may be required before on-chip sample processing, and it may be necessary to use off-chip samplers to interface the samples with the chips. For example, fingertip blood is usually sampled with a blood needle and then delivered to the chip, on which all the subsequent steps are performed. Some gas samples, such as indoor formaldehyde, can be directly processed on the chip by dissolving the formaldehyde in air into the absorption solution. Some solid samples, such as peanuts, are sampled using a dedicated container and then dissolved, introduced into the chip to complete the reaction and detection. In general, the sample processing should meet the following rules: small sampling device, complete by hand, and easy to be coupled with instruments.

Due to a large variety of detection targets and variable instrument operation procedures, automatic liquid handling is the most critical and difficult issue among them, especially when quantitative detection is required instead of qualitative and semi-quantitative detection, as in most POCT systems. LAH systems can complete complex operations due to its flexible liquid manipulation capability, and can automatically analyze and correct data. With the series of standard solutions of test targets stored on the chip, accurate quantitative analysis of samples can be realized using the standard calibration curve method. It is a distinct advantage of LAH over other systems, which is a challenge to implement in other POCT instruments. The detection for different targets usually requires multiple detection methods, such as UV-vis absorption, fluorescence, chemiluminescence, or electrochemical methods. Prepackaging of reagents is a necessary issue existed in all on-site biochemical analysis.

At present, it is difficult to achieve the above goals using the current POCT systems due to their limitations in performing quantitative analysis and complex operations. At the same time, it is also difficult to solve this problem by integrating different microfluidic chips developed previously. It is also not realistic to solve these issues by integrating different functional microfluidic chips reported previously into one household system due to the difficulty and cost in system microfabrication and integration.

A highly feasible strategy to achieve home-based chemical and biological analysis is to combine a versatile liquid handling-detection instrument with specialized microchips, i.e., the liquid handling-detection instrument can be reused and the specialized microchips are disposable. For the detection module of the instrument, if three spectroscopic detectors including absorption, fluorescence, and chemiluminescence are available in one instrument, it can cover almost all current fields of biochemical analysis, immunoassay, and nucleic acid analysis. It is possible to realize such a goal because with the 30-year development of microfluidic chip technology, significant progress has been made in the miniaturization and integration of various detectors. The disposable microchips are designed and fabricated specially for different targets, in which reagents required for detection are prepackaged for long-term storage.

Currently, among the liquid-handling techniques used in microfluidic systems reported in the literature, centrifugal control, micropump/microvalve, digital microfluidics, and sequential operation droplet array (SODA) techniques have the potential to meet the requirements of a household analyzer in high versatility and complex manipulation ability.

The centrifugal control technique was applied in conventional biochemical analyzers in the 1970s [28], and then microfluidic chips from the 1990s [29] (Fig. 1). It is now the most used microfluidic technique in commercial microfluidic chip-based biochemical analyzers. The advantage of the centrifugal control systems lies in their simple driving device and convenient operation [30] (Fig. 3a). By changing the rotation speed of a rotary motor and coupling it with the breakthrough valves on the chip, the multi-channel liquids on the chip can be driven and controlled to perform multi-step operation. The centrifugal control systems have been successfully used in on-site biochemical analysis [31, 32], immunoassay [33, 34], and isothermal amplification-based nucleic acid analysis [35, 36]. However, these systems still have challenges in performing multistep quantitative liquid manipulation due to the limitation of the liquid-handling strategy based on centrifugal driving and breakthrough valve control. Microfluidic chips with microvalves and micropumps [37] (Fig. 3b), such as pneumatic PDMS microvalves and micropumps, have a strong ability in performing various types of manipulations of nanoliter to picoliter liquids. However, different liquid manipulation programs usually need to

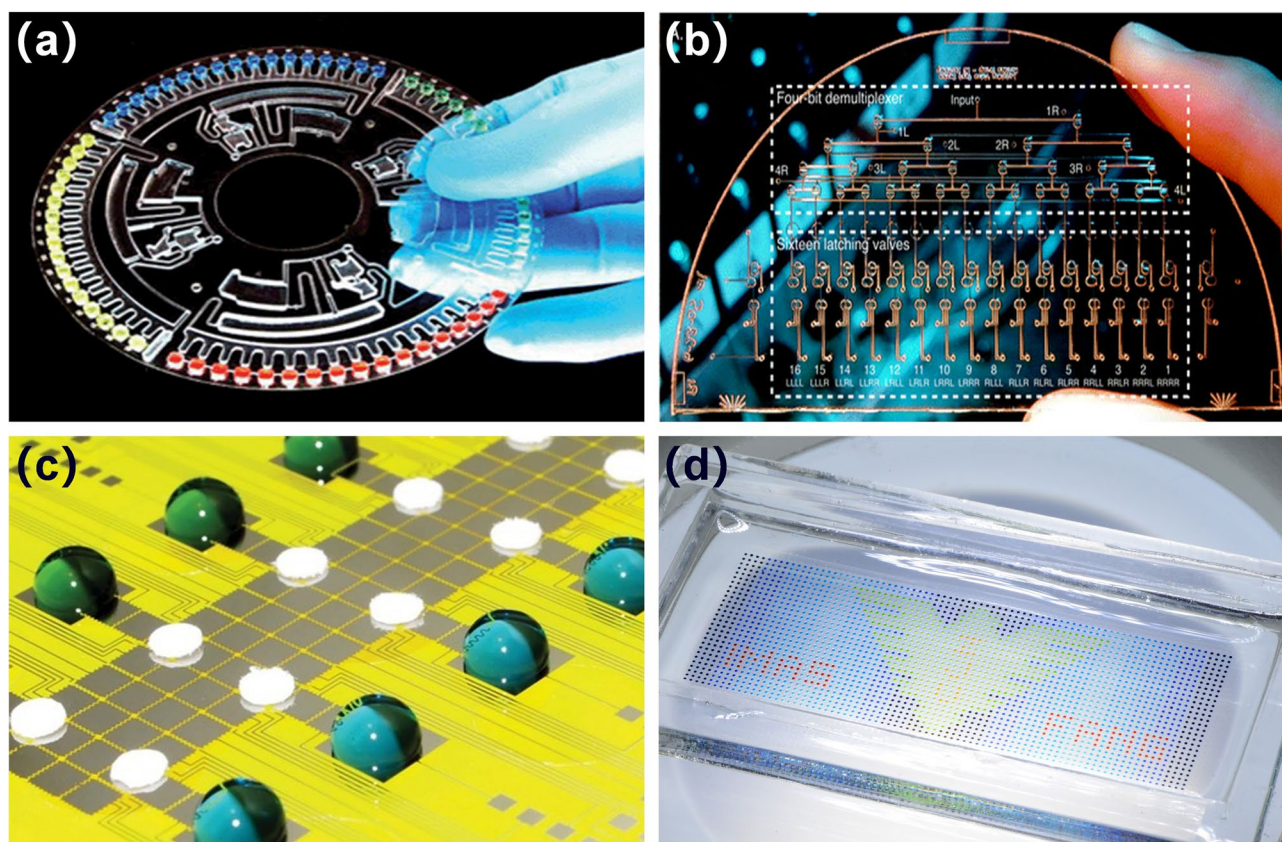


Fig. 3 Microfluidic liquid-handling techniques with potentials to meet the requirements of a household analyzer in high versatility and complex manipulation ability. **a** Centrifugation control; **b** Micro-

pump/microvalve; **c** Digital microfluidics; and **d** Sequential operation droplet array (SODA)

specially design different combinations of microvalves and micropumps on the chips. This chip specialization characteristic makes the structure and cost of these type of chip systems increase with the complexity of the chip operation program, leading to a major obstacle to their application in-home analysis. So far, there is no report of the application of such systems in field analysis.

The digital microfluidic technique uses the dielectric (electrowetting) effect to change the surface tension of droplets to achieve droplet manipulation. It has flexible liquid manipulation ability and has been applied to a variety of analysis of biochemistry [38] (Fig. 3c), life science [39], and clinical diagnostics [40]. However, at present, there are few application reports that can use this technique to complete the total liquid-handling operations of an on-site analysis process. The main challenges lie in how to achieve accurate quantification manipulation of liquids with different compositions, and how to solve the problem of prepackaging and on-site use of reagents.

In 2013, the authors' group developed a SODA system for performing automated and flexible droplet manipulation in the picoliter to nanoliter range [41]. A typical SODA system consists of a tapered capillary probe connected with a syringe pump for liquid metering, a two-dimensional droplet array chip for loading droplets, and a multiwell plate for loading different samples and reagents. Both the droplet array chip and multiwell plate are fixed on an x - y - z translational stage for switching them to the capillary probe. On the basis of the SODA system, we developed a flexible liquid-handling strategy using the programmable combination of three elemental operations as capillary-based liquid aspirating-depositing and the moving of the droplet array and sample/reagent plate, i.e., "aspirating-depositing-moving" (ADM) mode. Multiple liquid manipulations in the picoliter to nanoliter range, including droplet assembling, generation, indexing, transferring, splitting, fusion, sorting, and capturing, could be automatically achieved [42] (Fig. 3d). The SODA technique has been applied in drug screening [43], protein crystallization screening [44], single molecule analysis [45], microscale cell experiments [46], and microsample analysis [47], as well as single cell microRNA quantification [48] and single cell proteomic analysis [49], demonstrating its high versatility and broad applicability in performing complex microfluid manipulation and diverse types of analysis.

Based on the characteristics of the SODA technique, we envision that it is possible to construct a novel type of SODA-based LAH system, i.e., the SODA system will be used as a versatile liquid-handling "robot" module, equipped with different spectrophotometric (such as absorption, fluorescence, or chemiluminescence) detection modules, coupled with different disposable chips with reagents prepackaged to meet the diverse needs of different target analyses. The on-site analysis at home has relatively low requirements

for the miniaturization of liquid volume and the device positioning accuracy, but has high demands on the flexibility and versatility of the liquid manipulation. This is conducive to fully use the unique advantages in liquid handling of the SODA technique to simplify the system structure and reduce costs. The miniaturization of the spectrophotometric detection modules can use the previously reported miniaturization approaches [50] or the commercialized micro-detection instrument. For the disposable chips, the droplet array chip and multiwell plate used in the original SODA systems can be integrated into one disposable chip. Specialized reagents for different target detection are prepackaged in different types of disposable chips in the form of lyophilized powders or frozen liquids.

Most recently, we developed an integrated microfluidic system for multi-target biochemical analysis of a single drop of blood [51], which could provide an example for achieving the SODA-based LAH concept. The system could perform multiple operations including micro-volume blood collecting, quantitative plasma extraction, plasma dilution, plasma distribution, transferring, biochemical reaction and absorption spectroscopy detection, and standard curve-based data calibration, achieving the quantitative analysis of glucose, cholesterol, and total protein in 30 μ L of blood samples. By using the calibration curve method and the preloading standard solutions of glucose, cholesterol, and triglyceride on the disposable chip, quantitative measurement of the three targets in blood samples could be realized with results consistent to the conventional analysis methods.

Wash-free or maintenance-free is an important feature that a LAH system should have. To achieve this goal, in a LAH system based on the SODA technique, the combination of reusable syringe pump and detector with a disposable liquid-handling probe and microfluidic chip could be used. For assays with complex multistep reactions, the required reagents are pre-stored in the reagent wells on the chip, the quantitative dilution, transfer, mixing, and reaction of samples and reagents are conducted in the reaction wells on the chip by a replaceable, disposable liquid-handling probe connected with the syringe pump, and the spectral detection of the reaction solutions filled in the chip detection wells is performed by the absorption spectroscopy detector integrated in the system. After the assay, all parts in contact with the sample and reagents, including the liquid-handling probe and the chip with various functional wells, are disposed, thus avoiding cleaning and maintenance operations on the system.

The strategy we proposed for a SODA-based LAH system is to use universal liquid-handling and detection modules coupled with specialized disposable microchips prepackaged with diverse reagents for analysis of different targets in household healthcare, environment safety, food health, etc. With this strategy, multiple functions for meeting various

application requirements can be integrated into a versatile LAH platform by using individualized control programs to these functions. The SODA-based LAH systems can automatically complete many operations conducted in various routine analytical systems, including sampling, sample pretreatment, reagent preparation, accurate metering of samples, mixing and reaction of sample and reagents, detection of reaction products, and instrument calibration. Therefore, if equipped with an UV–vis spectroscopy detection module, in principle, the LAH system will be able to be applied to most fields of conventional spectrophotometric applications, such as colorimetric analysis, biochemical analysis, enzymatic analysis, and immunoassay. As an example of analysis of pollutants (such as formaldehyde or PAHs) in household air, usually a disposable air sample collector needs to be used to pre-collect and enrich the target analytes from the air with an analyte absorption solution or filter membrane. After that, formaldehyde collected in the absorption solution can be quantitatively measured using the formaldehyde chromogenic-reaction based colorimetric method. For analysis of household PAHs, such as benzopyrene, a carcinogenic PAH commonly occurred in cooking grilled and fried foods, it can be measured using the competitive ELISA by first pre-loading the benzopyrene antibody and other immunoassay reagents on a disposable chip, and then completing multistep competitive immunoassay operation in the microwells on the chip, with a similar procedure to those used in conventional immunoassay based on multiwell plates, microplate reader, and liquid-handling platform.

Outlook

In summary, the above discussion reveals the importance and great development potential of the Lab-at-Home field. It is an up-and-coming area that has not received sufficient attention and, of course, has not been vigorously developed. We can imagine a prospect from the perspective of analytical chemistry, i.e., if the Lab-at-Home instruments can be successfully developed, the majority of non-professional people will be able to perform various chemical and biological tests at home. This would be an exciting scene and undoubtedly a meaningful and worthy development direction. If great efforts are devoted to and focused on the development of LAH systems, we believe that such a goal will come true in the not-too-distant future.

With the development of the Lab-at-Home instruments, ordinary people will be able to purchase a Lab-at-Home instrument at home, and then purchase suitable disposable chips as needed from supermarkets, vending machines, or e-commerce platforms for immediate use or storage at home for future use. For the measurement, without complicated professional training, the user only needs to add the sample

to the detection region of the chip, then start the operation program and wait for the final measurement result of the sample, achieving the concept of “sample-to-answer.” With this strategy, various analyses for food, environment, and biochemical targets of the family members can be conducted at home. If the Lab-at-Home instruments can be popularized in many homes, then the data obtained from these household tests can enter a network database via the Internet. Furthermore, the Lab-at-Home instrument of each family can be used as a chemical sensor/biosensor of a node of the IoT, which will generate a large amount of chemical and biological big data (Fig. 2). Therefore, popularizing chemical and biological testing to a wide range of non-professionals can not only meet the needs of ordinary families for analysis and testing but also provide scientific researchers, hospital doctors, and public administrators with support for decision-making and rule mining. The development of Lab-at-Home instruments has the potential to become a widely used tool in daily life and may even change people’s lifestyles to a certain extent. Generally, there are two forms of POCT realized by rapid kits and fully automated devices, respectively. To obtain a CLIA (Clinical Laboratory Improvement Amendments) Waiver, the POCT devices need to be simple, safe, portable, and easy to use. For ease of use, the CLIA-waived devices such as Alere® i, BioFire FilmArray® Respiratory Panel EZ, and Xpert® Xpress Flu/RSV usually use disposable consumables including cartridge type and chip type.

In addition, the successful development of Lab-at-Home instruments will also provide powerful tools for other on-site analysis fields, such as clinical tests at grassroots or community hospitals, screening of public health emergencies, on-site food analysis, environmental monitoring, and on-site analysis of customs inspection.

As of this writing, the world is still experiencing the severe effects of the new coronavirus (COVID-19) epidemic. In this incident, viral nucleic acid detection based on real-time qPCR has become the main testing method for disease screening and diagnosis. However, this kind of testing operation is complicated and tedious and can only be performed by professionals in centers for disease control, large hospitals, and testing companies; thus the number and throughput of tests are greatly limited, forming a bottleneck in a large number of sample analysis in epidemic prevention and control. If the goal of LAH can be realized, the nucleic acid testing for infectious diseases will be carried out in grassroots hospitals, communities, airports, train stations, and even homes; the bottlenecks in epidemic prevention testing will be largely solved, which will greatly facilitate the prevention and treatment of infectious diseases. In addition to being a virtual node of the Internet of Things, how to integrate LAH with the IoT needs to be high on the agenda. The data of LAH can be used for clinical testing, analysis, and treatment and can provide users with a reference for

health diagnosis and subsequent treatment. However, it cannot be used as a basis for clinical diagnosis. The LAH data can be transmitted to the family doctors of the users through the network to help analyze symptoms, and is not for the purpose of replacing hospital diagnostic. Such a system is more suitable for promoting and early warning. For the use of large-scale health or environmental data in a region, it is a premise question to figure out who has the right and needs to manage and use these data. Furthermore, the data can only be used with the knowledge and consent of the user. The users of LAH systems can choose the data's access authority and confidentiality. The LAH manufacturers should be strictly responsible for the transmission process's security and cannot use it for other purposes. In conclusion, before LAH joins the IoT, a series of corresponding supporting measures and regulations must be established to ensure that data will not be leaked and misused. For example, information confidentiality measures should be strengthened in cooperation with the IoT, and sufficient security guarantees for personal privacy should be provided to prevent the leakage of the users' information and results.

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Declarations

Competing interests The authors declare no competing interests.

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