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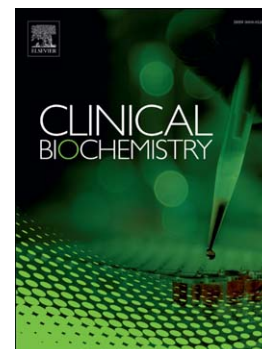
Miniaturization: The future of laboratory medicine

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Miniaturization: The future of laboratory medicine.

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The first reported clinical laboratory analysis occurred over 3,000 years ago when Indian physicians detected glucosuria by observing the attraction of ants or flies to urine (1). Medical testing has come a long way since then, and a great many advances have been made (for a review see references (2;3)). We now have the ability to test for thousands of biomarkers in any type of bodily fluid and have developed fully automated systems that can perform tests at a rate of well over a thousand analyses per hour using only a few microlitres of sample per analysis. These feats were not even imaginable a few decades ago. Technology continues to evolve, and of the many emerging technological advances, miniaturization is a key driver in shaping the future of Laboratory Medicine.

A key to miniaturizing clinical testing is the successful application of microfluidics. In the past few decades, microfluidics has allowed for the development of inkjet printers and DNA microarrays. In clinical laboratory practice, microfluidics will lead to the ability to robustly

handle sample and reagent volumes that are orders of magnitude lower than that of our current instruments. Microfluidic techniques have now advanced to the point where femtolitre amounts of solutions can be manipulated with sufficient accuracy and precision to allow for the creation of functional micro total analysis systems (μ TAS), commonly referred to as a 'lab on a chip'. With this technology, researchers have been able to perform polymerase chain reactions in 20 fL droplets (4), immunoassays using virus-coated magnetic beads to detect the presence of Rubella antibodies in reaction volumes under 2 μ L (5) and various other micro-scale reactions relevant to laboratory medicine (for a review and more examples see (6)). Additionally, researchers have recently demonstrated the ability to manipulate micro droplets in 3 dimensions, making the technology even more amenable for use in high-throughput devices (see Figure 1A) (7). Microfluidics in laboratory medicine is already making headlines (8) and there is no denying that it will shape the medical laboratories of the future.

The mass spectrometer (MS), an instrument being used in many clinical laboratories to measure various small molecules, proteins and microorganisms, has enormous potential for miniaturization. In fact, simple compact gas chromatography-mass spectrometers have already been in use for years as airport screening devices and in many remote research missions, including that of the Mars Curiosity rover. The mass spectrometers that are suitable for the clinical laboratory have excellent specificity, sensitivity and multiplexing capabilities and are considered the reference method for many current laboratory analyses. However, their high upfront cost and complexity have limited their implementation into clinical laboratories. This may be circumvented by the development of reliable miniature mass spectrometers (mini-MS) that are suitable for use by personnel both in the laboratory and at the point of care. Their

introduction into clinical testing appears to be imminent as demonstrated by the development of the proof-of-concept prototype mini-MS, the 'Mini 12', that has the capability to be used by untrained personnel to perform analyses on whole blood without any sample processing steps (9). Although current miniature mass spectrometers are limited to ion traps as their mass analyzer (the Mini 12 uses a Reticular Ion Trap), progress is also being made in minitizing triple-quadrupole analyzers to be used for quantitative applications. Recently, the first functional miniature triple-quadrupole made with microelectromechanical system components and measuring a mere 24cm, was reported (see Figure 1B) (10). Although these instruments are not as sensitive as full-sized models, it is only a matter of time before mini-MS improve to the point where they become suitable for clinical use.

One final miniature technology that is destined to make its way into the clinical laboratory is that of nanopore technology, which senses molecules by detecting the change in the electrical current associated with their movement through a molecular pore. Nanopore technology has garnered much attention with the recent commercial debut of the MinION DNA Sequencer by Oxford Nanopore Technologies (see Figure 1C). Approximately the size of a cell phone and utilizing consumable flow cells, the MinION can attach to any PC via USB connection in order to sequence individual DNA molecules with kilobase-long read lengths. What makes this technology even more exciting is its potential for adaption beyond nucleotide sequencing. By customizing nanopores to be selective for a particular molecule (e.g. coupling them to antibodies or enzymes), one can theoretically use this technology to detect any molecule of interest. As proof, Wang *et al.* used nanopore technology to detect botulinum toxin in a complex mixture at nanomolar levels within minutes (11). With their small size, simple

detectors and ability to analyze complex mixtures, this technology has the potential to be adapted for use both in the laboratory and at the point-of-care.

Although we are years away from having these technologies fully integrated into our routine analyzers, it will inevitably happen. With clinical laboratories facing budget restraints and increasing workloads, we need to find ways to make testing more affordable.

Miniaturization has the potential to transform the clinical laboratory as we know it by greatly reducing the size of our analyzers, the volume of sample, reagents and consumables required and the speed at which analyses are performed. Together, clinical testing will become cheaper, faster and most importantly, better.

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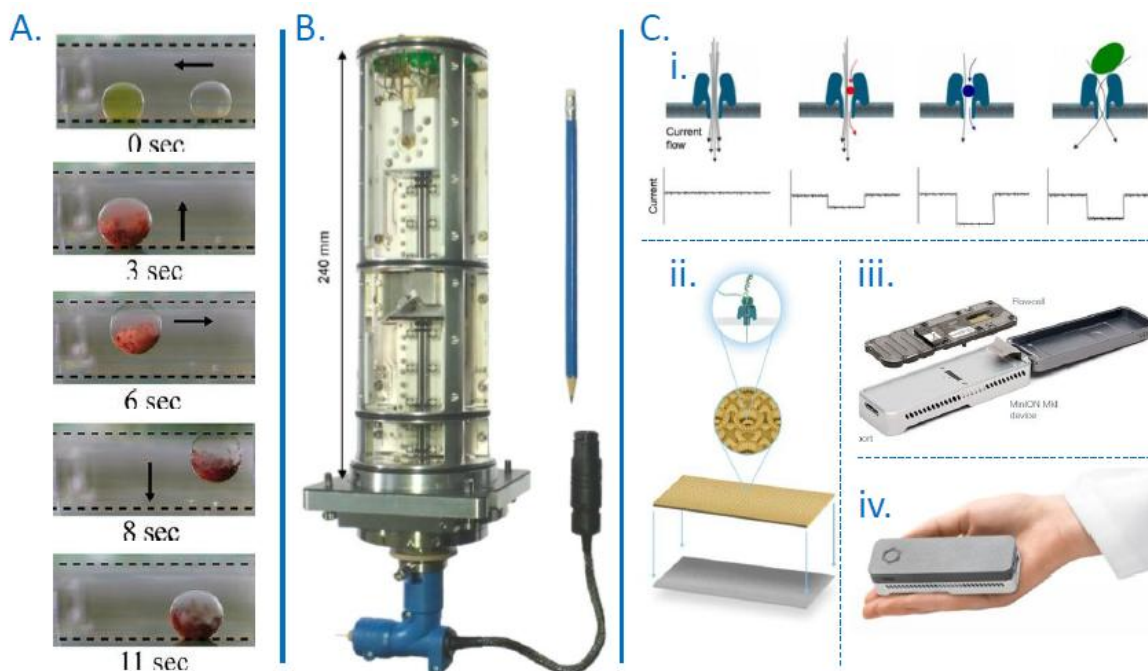


Figure 1. Miniaturized Technologies

A. Three dimensional Digital Microfluidics. In this time capture, 3 μL droplets of aqueous potassium chromate (K_2CrO_4 ; left) and silver nitrate (AgNO_3 ; right) are mixed together to form a red precipitate of silver chromate (Ag_2CrO_4) and precisely maneuvered around in three dimensions. The dashed lines represents the electrode plates and the arrows depict the direction of movement of the droplet. **B. A miniature triple-quadrupole mass spectrometer.** An image of the assembled complete ion optics bench of a functional miniature triple-quadrupole mass spectrometer. It consists of the microspray, vacuum interface, Q0, Q1, Q2, Q3 and detector (bottom to top). From Q0 to detector it measures 24 cm in length, slightly longer than an average pencil. **C. Nanopore technology.** The current flowing through a nanopore is altered as different molecules pass through it (i. top row). The current can be accurately measured (i. bottom row) and used to identify molecules passing through the pore. The MinION Mk1 by Oxford Nanopore Technologies, has several hundred nanopores embedded into a single membrane (ii.) which is then incorporated into a flow cell that is clicked onto the MinION device (iii.). The MinION is about the size of a cellular phone (iv.) and attaches to any PC via USB cable. Figures taken from: Hong *et al. Scientific Reports* **5**, Article number: 10685 (2015) (A.); Wright *et al. Anal. Chem.* 2015, 87, 3115–3122 (B.); and <https://nanoporetech.com/> (C.);