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Novel signal transduction methods based on the pyroelectric effect are poised to revolutionize point-of-care diagnostics.

What alternative signal transduction methods are emerging for the measurement of clinically relevant parameters in biological samples, and which of these are important for use at the point-of-care (POC)? This article focuses on technologies based on the piezo- and pyroelectric effects (i.e., detection methods that rely on measurement of thermal or mechanical effects). The more relevant methods are highlighted, with a focus on a novel method for homogeneous assays using a pyro-optical method that can deliver lab-quality results in minutes.

Established Technologies in Clinical Diagnostics

Clinical diagnostics is a discipline that covers a range of techniques to measure a wide number of parameters in clinical samples.. Most measurements are carried out using dedicated equipment, which can range from a large automated workstation offering a large panel of measurements to a simple handheld glucose meter. This article focuses on the signal transduction method: How do we accurately measure the parameter of interest, what are the pros and cons of different methods, and what new technologies are out there to improve upon current methods?

The two most common signal transduction methods are optical and electrochemical and their various subgroups. Optical methods still dominate diagnostic measurements, but they have one major drawback – the measurement must be carried out in a “clean” sample, which invariably requires the removal of cellular material. The use of radioactive tracers was common in the past but less so now. There has been a flurry of interest in recent years in magnetic signal generation, but this has yet to be fully established in commercial products.

POC Diagnostics

In POC testing, there is always a trade-off between performance and cost, and trying to balance these requires a robust and inexpensive signal detection method that can also deliver the performance required to give the end user (physician, nurse, home user) confidence in the results. Integration of electronics and chemical-biological reagents is a far from trivial task, and the lab-on-a-chip concept has not yet seen major breakthroughs in the diagnostics world.[1]

Piezoelectric and Pyroelectric Technologies

Piezoelectric and pyroelectric signal transduction methods are used in numerous applications outwith diagnostics, including motion sensors, accelerometers, pressure sensors, and compact disc players. Pyroelectric methods are mainly used for sensing, whereas piezoelectric methods can be used in both sensors and actuators.

The great benefit of the piezo- and pyroelectric effects are that they are direct methods for converting energy from one form to another. This means the mechanical or thermal event is converted directly into an electrical signal, without the need for an intermediate step.

Mechanical Detection Technologies in Diagnostics

There are three main signal transduction methods in which the measurement method involves mechanical parameters: Quartz crystal microbalance (QCM) and associated technologies, surface acoustic wave (SAW) technologies, and methods using microcantilevers.

QCM. The QCM has received much attention in the field of biosensors.[2] The piezoelectric properties of quartz lead to mechanical deformation under an applied voltage. A given quartz crystal will have a fundamental bulk resonance frequency that can be probed by applying a varying ac voltage. The fundamental frequency is highly dependent upon the environment of the crystals, and deposition of mass on the surface of the crystal leads to a change in the resonance frequency, which can be used as a measure of materials binding to the surface.

Importantly, the analyte need not be labelled for specific binding events to be monitored.

The key benefit of the QCM is also one of its key drawbacks: The resonance frequency is highly dependent upon other environmental factors, so it is common to have a reference channel to ensure that the measurement is due solely to the presence of the binding event.

Mass detection limits of QCM sensors are in the ng/cm^2 range, which is not sensitive enough for the demanding requirements of many immunoassays. However, better sensitivities have been achieved, either through mass amplification, (through labels or amplification methods) or by changing the surface morphology such that the effective surface area is increased.[3,4] An example is the use of nanorods on the surface of a QCM, which reportedly increased the sensitivity 30-fold compared with the naked sensor.[5] Figure 1 shows a typical quartz resonator.

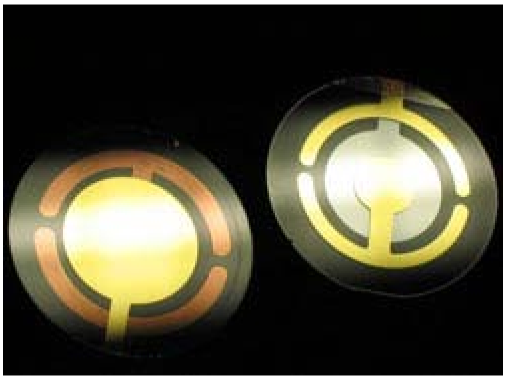

Figure 1. A typical quarts resonator is shown.

SAW. The SAW sensor is similar to the QCM, except that, as the name implies, the vibration is largely limited to the surface of the sensor, decaying exponentially with distance into the bulk material. SAWs are microelectromechanical systems (MEMS) that function through interdigitated electrodes on piezoelectric substrates. They are multifunctional sensors in that they can be used to monitor many physical properties, such as pressure, strain, torque, temperature, and mass. The global market in SAW devices is a multibillion dollar industry, primarily because SAW filters are essential components in mobile phones. This has significantly reduced the cost of the core components.

Microcantilevers. The microcantilever is another example of a MEMS device and in its simplest form it is simply a miniaturized projection (cantilever) of micron dimensions that oscillates (or deflects) in a manner that is dependent upon the local environment.[6] Deflection of the cantilever can be monitored in a number of ways, including electrical (e.g., capacitive), optical, and, in particular, piezoresistive monitoring. Microcantilevers are found in a number of applications, particularly in atomic force microscopy, for monitoring surface morphology. They have also been used as sensors for both chemical and biological analytes, including nerve agents, viruses, cells, nucleic acids, and proteins.[7] Other applications include the measurement of conformational changes in proteins and measurement of membrane protein-ligand interactions.[8,9]

While a powerful research tool, there is still some development required to turn these into simple disposable devices for diagnostics. One benefit of the microcantilever could be high sensitivity in very small sample volumes.

Thermal Detection Technologies in Diagnostics: Calorimetry

Calorimetry is the process of quantifying the heat generated (or lost) as part of a chemical or physical process and has been known, in various forms, since the end of the 18th century. Modern methods can be used to measure a range of binding events, giving information on binding constants in combination with the enthalpies and entropies involved in those binding events.[10] The two main techniques used are isothermal titration calorimetry (ITC) and differential scanning calorimetry (DSC). In ITC, the binding of a potential binding agent (e.g., drug) with a receptor can be monitored as the two reagents are mixed. DSC measures changes to a system as the temperature is ramped up and provides more information on the stability of systems at different temperatures. The key benefit of these methods is that the target molecule does not need to be labelled, making them suitable for high-throughput screening.

Several calorimetric methods based upon thin-film sensors and thermopile sensors have been reported, mainly for the enzymatic detection of glucose.[11] These sensors commonly use differential measurements against a reference detector to avoid problems with ambient temperature drift. As previously discussed, the benefit of these systems is that no label is required on the analyte. However, these systems only work with analytes that can be configured to generate sufficient heat upon binding or enzymatic turnover, and they are limited in terms of sensitivity.

While these methods are powerful tools in drug discovery, for identifying and optimising lead compounds, the sample volumes and concentration ranges are probably not appropriate in diagnostic settings, particularly for nanomolar or picomolar concentrations, which is regularly required for immunoassay detection of proteins.

One interesting recent development is a calorimetric biosensor that uses a noncontact quartz resonator for the thermal detection method.[12] The noncontact method allows temperature perturbations to be measured without any effects of mass loading or matrix variability. A detection limit of <10 µM for glucose is reported.

Pyro-optical Detection

Vivacta Ltd. (Sittingbourne, Kent, UK) has developed a signal transduction methodology for homogeneous immunoassays that measures the microheating effects at the surface of the pyroelectric polymer film PVDF (polyvinylidene fluoride).[13,14] Unlike calorimetric methods, this technology uses an optical input for the generation of heat in the sample.15 Use of a high-powered LED source to induce the heating effect allows deficiencies in the signal-to-noise ratio to be overcome, enabling the use of small sample volumes.

The technology relies upon time-resolution of the electrical output from the PVDF sensor to distinguish the distribution of light-absorbing carbon particles throughout the depth of a sample chamber (see Figure 2). Particle binding to the sensor surface can be monitored in real time, giving a quantitative measurement of a range of analytes, including proteins, small molecules and nucleic acids. Critically, time-resolution of the signal distinguishes particles bound to the sensor from other interfering materials, so the measurement can be carried out in whole blood samples, without separation of the red cells. The measurement process, from sample collection (30 µL, from a fingerstick) to test result, takes 5–10 minutes, depending upon the analyte being measured.

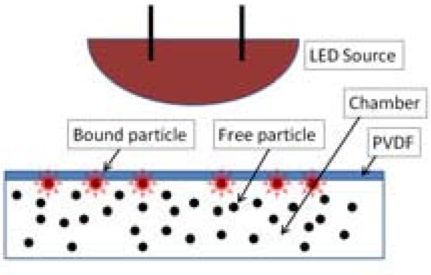

Figure 2. This diagram depicts pyro-optical detection.

The cartridge (Figure 3) contains an entry channel (which fills by capillary action), a mixing channel (with dried-down reagents) and three measurement chambers, which are pre-coated with reagents. Two of the chambers are for control measurements, to ensure the cartridge is fully functioning and to also function as internal calibrators. Batch calibration data is stored on a 2-D barcode.

A six-chamber cartridge is also in development, which has the capability to measure up to 4 different analytes simultaneously.

Instrumentation Considerations

The instrumentation for this technology has evolved from an original prototype-breadboard system into a fully ready commercial system (see Figure 4). Although certain aspects of the instrumentation remain proprietary, the following design points are worthy of mention

Figure 3. Shown is a Vivacta cartridge.

Instrument complexity. The basic system components are ITO-coated PVDF polymer film, a light source, and a means of amplifying and measuring the charge generated in the cartridge. The area illuminated per chamber is large (around 30mm2), hence precision optics is not necessary and LEDs are ideal as the light source. Advances in LED technology, driven by lighting and automotive applications, means very high-powered LEDs (around 80 mW per 1mm die) are available in a range of wavelengths and at very low cost. The LEDs are pulsed sequentially, allowing a single-channel amplifier.

There are only two moving parts in the instrument. The first is a small displacement pump, which moves the sample from the entry channel, mixes it with the onboard reagents, and then moves the mixture into the reaction chambers. The second is a multifunctional sled, which operates the door mechanism and locks the floating readhead into position for sensor insertion or for transport.

Figure 4. Shown is a Vivacta instrument.

User interface is via a touchscreen, which prompts the user on how the sample should be collected and when to insert the cartridge into the instrument. The user is also prompted to dispose of the cartridge properly before the result is displayed on the screen.

Signal-to-noise. PVDF film is a mechanical transducer as well as a thermal one. Thus, the system has been designed to minimise interference from shocks and vibrations in the environment. Vivacta has collaborated closely with the Institute of Sound and Vibration Research at Southampton University to understand the parameters that are critical to minimizing vibrational interference. Noise is rejected at a number of different levels in the system. For example, the cartridge and instrument have been specifically designed so that specific resonance frequencies are not present. There is also a sprung readhead in the instrument to isolate the measurement from the environment . Electronic filters in the amplifier circuits prevent high and low frequencies from affecting the measurement. Finally, data averaging and noise rejection algorithms remove the last traces of noise from the sensor. The only interference left is the natural low-level noise in the electronic circuitry.

Applications

The first application of the technology is for the quantitative determination of thyroid stimulating hormone (TSH) in whole blood. Other applications in the pipeline include tests for cardiac markers (troponin I and NTproBNP), which are useful both in the emergency room and in decentralized settings. More recently, the system has been shown to work equally well for small molecules, including vancomycin and vitamin D. This opens the door to use for regular patient monitoring of both drugs and response to therapy or disease progression. Analytical sensitivity is around 10–20 pg/mL, and mid-range precision of 5–8% is achievable for most assays. Figure 5 shows the correlation between the Vivacta TSH measurement (in whole blood) against the Siemens Centaur lab analyser (in plasma).

Proof-of-principle for the measurement of multiple analytes has already been carried out. In particular, a concept assay for both vancomycin and TSH has demonstrated the simultaneous performance of an immunometric and a competitive assay in the same cartridge at 2 different dynamic ranges.

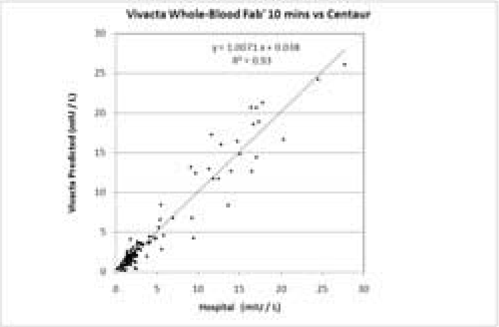

Figure 5. Shows the correlation between the Vivacta TSH measurement (in whole blood) and the Siemens Centaur lab analyser (in plasma).

By enabling simultaneous and rapid quantitation of small molecules (including drugs) and large molecules, which may be biological drugs or biomarkers, this and other new POC technologies are poised to revolutionise healthcare delivery as we move towards an era of personalised medicine and theranostics, in which patients will need to be monitored more frequently to ensure optimal outcomes, both clinical and economic. In fact, POC testing is often viewed as an advantage primarily where rapid generation of data provides treatment benefits. However, as the medical industry moves toward personalised patient management, where frequent testing will be necessary to satisfy regulators and payers that promised outcomes are being delivered, an equally important driver will be access to patients (or from the patient's point of view, access to the monitoring system). The emerging point-of-care systems described in this article will be critical in converting this vision to reality.

Conclusion

Methods for quantifying biological materials using piezoelectric or pyroelectric methods are still largely the preserve of the academic community. Table 1 summarises the benefits and drawbacks of the methods described herein.

The main commercial application of these techniques is in label-free screening in drug discovery, yet there is also significant potential in applying them to clinical diagnostics and monitoring systems at the point-of-care. That said, making the transition to a commercial product for PoC clinical diagnostics with a new technology is always a challenge, with many of these technologies facing technical and manufacturing issues, which coupled with the complexity of regulatory hurdles, will ensure that not all are successful.[1] Because of its broad applicability, high performance, and relevance to the personalisation of healthcare delivery, the PVDF approach described in this article looks particularly promising. However, only time will tell which of these technologies can truly compete at the point of care.

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