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APPLICATIONS OF ELECTRIC DEVICES INMODERN ANALYTICAL CHEMISTRY: A REVIEW

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INTRODUCTION

The ready availability and affordability of information technology (IT) and communications equipment offer possibilities in analytical chemistry that once were scarcely imaginable. The ubiquity and versatility of modern IT equipment, and the availability of tools for chemical manipulation and imaging and data interpretation, have the potential to make low-cost chemical analysis more accessible to society at large. The last decade of research in analytical chemistry has seen the emergence of a variety of microfluidic chips, paper and other devices, and the nexus of these with IT equipment provides the means for the development of simple, fast and/or low-cost chemical analysis and screening tools. These developments are already assisting in improved point-of-care (POC) clinical diagnosis [1-3], and in future will facilitate low-cost, more frequent monitoring of occupational health, the environment, and agricultural and food production. Given the uptake of IT devices worldwide, these developments should not be restricted to developed nations, but will also be beneficial to develop countries. This paper reviews some recent developments in the combination of colorimetric chemistries with devices that can be visualized using everyday communications and IT equipment (mobile phones, digital cameras, computers, etc.) and provides a comparison of the performance of some of these devices.

DETECTION REACTION FORMATS

Lab on Chip devices

There is a huge volume of literature on the development and application of microfluidic devices (Lab on Chip, µTAS[1], etc.) for clinical analysis, immunoassay, cell manipulation, drug and environmental analysis. These typically consist of silica, glass or polymer (e.g. PDMS[2], PC[3], COC[4] or PFPE[5]) [4] chips or plates incorporating enclosed flow channels that are prepared byetching, micromachining, injection moulding or hot embossing. Sample and liquid reagents are transported through these channels by syringe, electroosmotic or piezoelectric pumpingor by capillary flow, and analytes are detected on-chip, using e.g. photometry, fluorometry, chemiluminescence, conductometry, electrochemistry or cytometry. While many of these devices are physically compact, and their reagent and sample use is minuscule, their application may be restricted to the laboratory because of the size and complexity of ancillary equipment required for their operation and detection, e.g. power supplies, fiber optic detection systems, microscopes for viewing narrow channels, and epifluorescence microscopes for cell detection.

There are a number of reports of the use of lab on chip (LOC) or microfluidic devices that utilize photometric detection, but their characteristically micro sized channels offer only a small path length for optical interrogation, and hence sensitivity may be curtailed. Commercial micro spectroscopic detection cells typically range in volume from 0.5 to >20 µ L, with optical path lengths of 0.05 – 2 mm. Ideally the detection zone should be incorporated into the chip, and for this reason intrinsically more sensitive detection methods such as electrochemistry or fluorescence are often favored.

However, where the absorptivity of chromogenic products is large or analytes are present at higher concentrations (say ≥ mg L^{-1}), photometric detection offers a viable means of detection. For example, Bowden et al have described a laminated glass microfluidic chipfor the determination of phosphate in water, based on the formation of yellow vanado molybdic

phosphoric acid. A UV LED[6] ($_{max}$ = 370nm) was embedded in the glass chip, and light was directed across the flow channel, giving an optical path of ca. 400 µm, into a portable optical fiber spectrometer. This system exhibited a linear response from 0.1 to 50 mg L^{-1} P, and excellent long-term accuracy and precision [15], and is illustrative of the advantages of microfluidics combined with integrated photometric detection. Given that microfluidic chips are often prepared using glass or transparent polymers, the approach lends itself to the application of optical imaging techniques such as digital photography as a means of detection. However, because of the small channel size, a microscope must often be used in order to obtain an image of the reaction zone.

Paper-based devices

The manufacture of glass or polymer microfluidic chip devices with any complexity is often expensive and technically demanding, and has often been restricted to specialist laboratories or companies. To overcome this limitation, microfluidic paper-based analytical devices (µ-PADs) were proposed by Whiteside's et al. as a means of performing reagent-efficient analyses with cheap, disposable materials. Paper has historically been used as a platform for analysis since Boyle developed the litmus paper in the 17th century, and more recent examples include test strips for glucose and pregnancy detection. However, microfluidic paper-based devices differ from test strips in that they are prepared with patterns of hydrophobic barriers that constrain aqueous capillary flow to within defined hydrophilic zones of the paper. This then enables either sequential or multiple reactionsto be performed as samples reagents intermix from different regions in route to one or more detection zone. The patterning of hydrophilic channels or zones onto paper-based devices has been achieved by various techniques including the use of photolithography, hot wax or PDMS printing. More recently, simple ink jet printing of hydrophobic paper sizing agents has been described, and the same technique can be used to apply reagents, enzymes or indicators to the paper devices. Unlike microfluidic chips, the channels in paper-based devices need not be miniaturized in order to achieve reagent and sample savings, because only a few microliters of both is required to wet the hydrophilic reaction zones. Consequently, the detection zone may have a surface area of the order of a few square millimeters, which is quite compatible with the use of visual imaging methods for detection, such as digital cameras and scanners, as described in the section that follows.

Discrete reaction zones: well plates and test strips

Microliter or well plates are polymer plates containing from 6 to 1536 wells arranged ina 2:3 configurations. The best known is the 96 well version that has well volumes of 100-200 µL. Reactions performed in these plates are ubiquitous for clinical and pharmaceutical testing and screening. Detection of reaction products is usually performed on an automated well-plate reader that makes rapid, discrete measurements of absorbance, fluorescence, chemiluminescence, or light scattering. The format of the well plates, and the range of available accessories, such as multi-tip autopipettors make them an attractive format for conducting simple colorimetric that can be imaged, as described below.

Test strips are commercially available for a large range of clinical, food, beverage and environmental tests. They can be used for both semi-quantitative analyses using visual comparison with a colour card (e.g. Merckoquant® strips), or for quantitative determinations by using reflectometry measurements (e.g. the Merck Reflectoquant® system). Waters et al. have reported a comparison of both visual and reflectometry test strip measurements of nitrate and chromate in wastewaters with standard methods. They obtained consistently more accurate measurements using reflectance measurements than visual comparison, and good agreement between the former and thereference methods. Their findings imply that test strips could be used more effectively if simple imaging techniques were applied in preference to visual comparison.

Separation systems.

Optical scanning densitometry using specialized scanners (e.g. Shimadzu® CS 920) has been used extensively in planar chromatography and gel electrophoresis as the basis for quantification using specialist software such as Image J or Un-Scan-It Gel®. More recently, flatbed scanners have been successfully used for imaging of planar chromatographic separations. With respect to column-based separations, Wu et al. and Huang and Pawliszyn have described the use of whole column imaging for CE and HPLC using purpose built systems comprising photodiode arrays and CCD's for detection of transmitted or fluorescent emission from separated analytes. The application of whole column imaging techniques to low-pressure liquid chromatographic separations of coloured analytes would be instructive and warrants further investigation.

VISUALISATION OF ANALYTICAL RESPONSE

Rapid advances in microelectronics in the last decade has resulted in the ready availability of digital and video cameras, mobile phones and scanners with continually enhanced specifications at very modest cost. For example, an Apple® Quick take 200 digital camera bought in 1998 for A$900 had only a 0.3 megapixel CMOS and very limited exposure and processing options, whereas in 2011 the same sum would purchase a top-shelf single lens reflex camera with 18-megapixel capacity and a formidable list of imaging options. The availability of these high specification cameras at reasonable price makes low cost imaging of colorimetric analytical test devices readily accessible. The section that follows discusses some examples of how these everyday photographic and imaging devices have been usedin a range of chemical and biochemical assays; summary details of these examples and more are listed in.

Digital cameras

One of the earlier examples of the analytical use of a digital camera was reported by Lau et al. for the determination of ammonia in water based on the Berthelot reaction. They prepared immobilized reagent spots on polymer strips and detected the formation of indophenol blue after exposure to ammonia with a black and white digital camera. The discrete reaction zones were illuminated by red, green and blue LEDs, using the system shown.

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The larger the amount of indophenol blue formed in response to exposure to ammonia, the more Bwas reflected, and hence the greater the absorption of R and G. Improved sensitivity was therefore achieved by the use of the grayscale spot images collected during pulsed R illumination. Another recent example of the use of a digital camera in analytical imaging has been described by Songjaroen et al. who determined glucose and protein on a paper based device prepared by hot wax dipping. Sample introduced into the hydrophilic channel migrates to separate reaction zones in one glucose undergoes reaction in one zone with glucose oxidase, peroxidase and iodide to produce iodine, while in the other, protein is stained with bromocresol green. The reaction zone was photographed using a digital camera and the colour intensities quantified as grayscale values using Adobe Photoshop®. This example illustrates a major advantage of the use of paper baseddevices with photographic imaging for quantification, viz; that the aspect ratio (surface area: volume) available for detection greater, by one or two orders of magnitude, than that of a lab on chip containing a comparable volume of liquid (e.g. in a 200 µm 200 µm cross section channel). Hence, in paper based devices, there is no need for the use of a microscope or other optics to view the detection zone.

A recent paper by Lapresta-Fernández and Capitán-Vallvey [42] highlights some of the advantages of using a low-cost digital camera in conjunction with optical sensor chemistry. They describe the development of disposable polymeric membranes containing for chromo-ionospheres, such as normally used in opcodes, for detection of Mg^{2+}, K^{+}, and hardness in water. After exposure to samples containing analyte/s the membranes were photographed using an inexpensive, 6-megapixel digital camera, held on a simple supportat a fixed focal distance, using illumination from the camera flash against a matt white background. Image analysis was performed using Adobe Photoshop®, and the concentration computed using a series of linearized calibration functions.

Video Cameras and Webcams

The distinction between digital video and still cameras has become quite blurred, given that so-called still cameras now have the ability to operate in both modes. Nevertheless, there have been some older reports on the use of video cameras, and increasingly on the application of webcams for analytical quantification. Either CMOS or CCD sensors may be used for image capture, with the former being most common in lower cost, still cameras, webcams and surveillance cameras. Frame rates used can range from 15-30 s^{-1} for webcams to ≥30 s^{-1} for video cameras, while specialized sensors may use frame rates of up to 300 s^{-1}. Budantsev [58] described the use of a video camera for study of transmittance, rather than reflectance, of paper disks treated with Congo Red dye. He argued this approach was advantageous compared with conventional bulk medium transmittance measurement, because it enabled measurement and quantification at a pixel scale, and provided a means of evaluating the homogeneity of the paper. The approach of measuring transmittance through paper was also adopted by Ellerbee et al. who investigated the useof paper-based devices for bovine serum albumin (BSA) measurement in urine, albeit using a simple handheld photometer for POC measurement.

Safavi et al determined pH using an array of triacetylcellulose opcode membranes treated with five different indicator dyes. All membranes were exposed to standards of different pH and were photographed with a video camera. The red, green, blue (RGB) colour space values for each sensor were measured, giving 15 data points per pH determination. Calibration functions were derived using artificial neural networks, partial least squares and Microsoft Excel® Solver. All three approaches yielded calibration models with high correlation between true and measured pH values, and the opcodes were good for at least40 measurements of pH.

In a slightly different approach, Diaz et al. used a video camera to film the chemiluminescent emission from an indirect competitive enzyme linked immunosorbent assay for the determination of the herbicide trichlopyr. The immunoassay was based onconjugation of an anti-rabbit secondary antibody to horseradish peroxidase (HRP) which when reacted with luminal and hydrogen peroxide produced chemiluminescence. The assay was performed in a 96 well plate and was monitored with a monochrome videocamera for up to 30 minutes after chemilumiescence emission commenced. Diagraph IC-PCI frame grabber and some purpose written C++ software was used to quantify the light emission from each well. Very low detection limits (0.8 ng L^{-1}) and excellent precision(3.07 % RSD for n= 10) were achieved for trichlopyr determination using this approach. The ready availability of either cheap stand-alone webcams or those that are incorporated inlaptop computers makes these devices an attractive option for analytical image capture. Wongwilai et al. have described the use of a webcam with a lab on chip for thedetermination of acid concentration based on visualization of the migration of the reaction interface between an acid sample and an intersecting base stream. The lab onchip channels had an internal diameter of 1.2 mm, and a viewing length of somemillimeters, and unlike many LOC systems which use very small channel sizes, this wasquite advantageous because it allowed the zone to be visualized without the need for anyadditional magnification.

An intriguing application of a webcam is the so-called Computer Screen Photo-assisted Technique (CSPT) described by Filippini et al. In this arrangement a computer screen is used to illuminate a test strip with a range of different wavelengths for reflectance (or fluorescence) measurement by a webcam. This approach was applied to urine test stripsthat detect changes in seven different parameters (hemoglobin, blood, proteins, nitrites, ketones, glucose and pH) by visual interpolation from a standard colour card. The reflectance data for the strips obtained using 15 different illumination wavelengths were analyzed using multivariate statistics, and gave excellent results with an error rate of only 2.24% for 580 separate classifications.

Mobile phones

Most, if not all, modern mobile phones include a camera, which typically uses a CMOS sensor of 2 to 5-megapixel image size, similar to that of a web camera. The portability andintegration of the camera with the ability to transfer photographic data either by image sharing or Bluetooth® makes the mobile phone a potentially powerful tool for remote monitoring and POC diagnosis. Garcia et al have described how the built-in camera of a mobile phone can be used for the imaging of opcode membranes for the determination of potassium aqueous media. The basis for the determination is the equilibrium between the K^+ ionosphere and an H^+ chromoionophore (Nile blue) in the PVC membrane matrix. As more K^+ exchanges with the ionosphere, the chromoionophore deprotonates, causing a colour change in the membrane.

Membranes were photographed inside a small photo-studio optical tent to ensure a constant level of illumination, and test strips were fixed on a mount so that the most reproducible exposure could be achieved. The authors performed an image processing procedure to remove optical edge effects from the membranes before determining the H (hue) value, which was computed from normalized RGB data. H values have been used asthe basis for calculation of concentration because it is claimed that they are less dependent on factors such as membrane thickness or concentration of dye [63]. The developed method was shown to respond over a wide dynamic range and (3.1×10^{-5} –0.1 M) and within inter-membrane repeatability of 1.6 % RSD.

Martinez et al. have demonstrated the use of paper-based devices for the determination of glucose and protein, bovine serum albumin (BSA), and have compared the imaging of these using digital cameras, mobile phones and both desktop and portable scanners. While mobile phone cameras showed less sensitivity than scanners and digital still cameras, there was little difference in the quality of results obtained for glucose and BSA in artificial urine using all imaging devices tested. Even the addition of a PDMS focusing lens to a mobile phone without autofocus only marginally improved the response for glucose, and had no effect on the accuracy for BSA measurements. In this example, glucose intensity was measured using grayscale values, while those for BSA were calculated from the cyan (C) signal after RGB data were converted to CMYK; this was done because the cyan signal gave the widest dynamic range for BSA measurements. The authors strongly advocated the use of mobile phones both as a means of acquiring data, and for transmission of the data collected, e.g. for medical treatment in remote areas where POC analytical data could be relayed to a physician for specialist diagnosis.

Scanners

Scanners, both flatbed and portable, are being increasingly used for imaging, and their popularity is in part due to their low cost, but also due to the ability to scan under much more controlled illumination conditions than is possible under ambient or even flash light conditions. Jaywardene et al. have developed paper-based devices for the determination of phosphate based on the determination of phosphoantimonyl molybdenum blue. After preparation and addition of sample, at least 10 minutes is allowed for formation, after which the credit card- sized laminated device isscanned using a flatbed scanner, and intensity data plotted as RGB. Figure 5 shows that while there are quite discernible grayscale peaks, the blank to signal ratio is high, and thisrestricts the limit of detection to ca. 0.2 mg L^{-1} P.

Another, quite different application of a flatbed scanner, has been described by Teasedaleet al. for the determination of sulfide in anoxic estuarine sediments. Diffusive gradients in thin films (DGT) probes containing a sulfide- binding gel that incorporated AgI were deployed at the water- sediment interface for less than 24 hours. The gel sheets were removed from the DGT probes, dried and the black Ag_2S that had formed was imaged with a flatbed scanner, and quantified against the images of gels containing known sulfide concentrations, prepared in the same manner. This “chemical snapshot” offered a relatively easy means of obtaining sub millimeter profiling of the sediment sulfide profile, and gave results that agreed closely with those obtained by other chemical methods and model predictions.

Image Processing

A coloured sensing/detection zone e.g. in a flow system or paper-based device, can be imaged using programs such as Adobe Photoshop® which readily permit conversion of digital images obtained from cameras or scanners to grey, RGB, CMYK (cyan, magenta, yellow, key) or other colour scales for the purposes of sample quantification and data transfer.

Colour digital images consist of pixels which are comprised of the colours red, green and blue. There are several different colour space modes that can be used to describe a particular colour, and some of these are summarized.

The values of colour in each mode that correspond to the change in colour intensity, e.g. of an indicator, or to the formation of a chromogenic product can be used to plot a calibration graph. Grey scale can be plotted directly if there is only a single colour change, and there is no interference from stray light, otherwise more selectivity can be achieved by the use of RGB or CMYK color space data. Colour values may also be transformed before use. Birch and Stickle used a Beer-Lambert plot i.e. $\log(I_0/I)$ vs concentration to give a straight line plot, where I_0 and I are the reflected or transmitted intensities of the blank and standard respectively.

Collection, dissemination and traceability of results

There has been enormous growth in digital communications worldwide, especially in mobile phone usage, and to a lesser extent in internet connectivity. In less developed countries, mobile phone subscriptions have increased from 2 to 280 million (i.e. 34 per 100 population) from 2000 to 2010, while in the same period, internet subscriptions increased from only 0.1 to 4.6 per hundred populations. In the developed nations during this time, mobile subscriptions exceeded saturation (114.3 per 100 people) and internet connection reached 68.8 per 100 [68, 69]. The increasing coverage of both mobile phone and internet, with enhanced bandwidth, thus provides the *modus operandi* for sharing data on a scale hitherto unimaginable.

Many authors have alluded to the future role of mobile phones and other IT devices in POC for clinical diagnosis. There is an equally large need for monitoring of the aquatic environment, especially as it impacts on human health. More than 884 million people do not have access to safe drinking water supplies, and millions die of water-related disease every year. The use of mobile phone or digital cameras i low-cost sensing devices for water quality measurement in less developed countries has the potential to assist in assessment and improved management of water resources and sanitation both by government organizations and volunteer environment groups.

The ability of smartphones to perform the image analysis and associated computation required to determine a concentration value is now a reality, with recent examples of their application for the determination of soil colour and for chlorine measurement in water.

It is likely that sharing and dissemination of this data can be readily achieved using aspects of social media and the web. Current work at Chiang Mai University involves posting of water quality monitoring data as it is collected to an online database that is accessible through Google® Map. The information covers parameters such as T, Dissolved Oxygen, $\%O_2$ Saturation, electrical conductivity and TDS, phosphate and nitrate concentrations, and calculated loads for these parameters at some sites. This data will be of value in planning water quality management strategies and pollution abatement measures in the Ping River and its catchment (NW Thailand).

However, in all of this there is the need to ensure that traceability of results is maintained. It will be necessary to establish protocols for the collection and archiving of analytical data e.g. scanned images, computations, as well as its validation, if the data collected by this IT-led analytical revolution is to be believable and useful.

There is therefore huge potential for the use of simple analytical sensing devices that are interfaced with data acquisition, processing and dissemination using everyday communications and image capturing equipment to revolutionize the way in which health and environmental monitoring is performed worldwide.

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