Light-Emitting Diodes for Analytical Chemistry

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Abstract

Light-emitting diodes (LEDs) are playing increasingly important roles in analytical chemistry, from the final analysis stage to photoreactors for analyte conversion to actual fabrication of and incorporation in microdevices for analytical use. The extremely fast turn-on/off rates of LEDs have made possible simple approaches to fluorescence lifetime measurement. Although they are increasingly being used as detectors, their wavelength selectivity as detectors has rarely been exploited. From their first proposed use for absorbance measurement in 1970, LEDs have been used in analytical chemistry in too many ways to make a comprehensive review possible. Hence, we critically review here the more recent literature on their use in optical detection and measurement systems. Cloudy as our crystal ball may be, we express our views on the future applications of LEDs in analytical chemistry: The horizon will certainly become wider as LEDs in the deep UV with sufficient intensity become available.

1. INTRODUCTION

1.1. Device Types, History, and Evolution

Light-emitting diodes (LEDs) are solid state semiconductor diodes wherein hole-electron recombination leads to light emission. The emitted photon energy or color depends on the bandgap of the semiconductor. Presently, LEDs are available with center emission wavelengths from 4.6 μm (InAs semiconductors) to 240 nm (AlGaN semiconductors). At either extreme, however, photon conversion efficiency is poor and the device costs high. The largest range of applications involves near-infrared (NIR) to near-ultraviolet (NUV) LEDs; these have by far the highest radiation output, and at a low cost. White LEDs are currently displacing fluorescent lamps for lighting applications and are also used in some limited wavelength range spectrophotometry applications. Presently, there is a large push to drive the lower range of LED wavelengths down to 200 nm, for sterilization and sensing applications (1). The web (**http://en.wikipedia.org/wiki/Light-emitting_diode**) provides the semiconductor types used for different emission wavelengths, as well as a description of the early history of LEDs. The bandgap energy distribution is relatively narrow in LEDs, hence so is the wavelength distribution of light emission. The energy bandwidth is relatively the same for the different semiconductors; as a result, the UV emitters have a much narrower emission half width [full width at half maximum (FWHM) 12–15 nm] compared to the NIR and IR emitters (>100 nm). For LEDs of single junction construction, the threshold voltage at which the LED first conducts (and emits light) is a very good indication of the peak emission wavelength. For example, red AlGaAs LEDs typically turn on between 1.8 and 1.9 V; they have a peak emission wavelength of ~660 nm (1.8 and 1.9 eV correspond to, respectively, 689 and 652 nm). White LEDs have been created primarily for lighting, displays, entertainment electronics, and automotive industries (2). Although their significance as light sources in the context of this review has so far been limited, some information can be found in, e.g., Reference 3. A brief discussion of their properties can be found in the supplementary information (follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**).

Supplemental Material

1.2. Impact of Light-Emitting Diodes, Previous Reviews, and Scope of this Review

LEDs as light sources are used increasingly in research, technology, and consumer applications (4, 5). The annual number of scientific publications on LEDs is growing exponentially (**Supplemental Figure 1**). From 1964 to 1990, the average annual number of scientific publications on LEDs was <100. The invention of the blue LED in 1991 represented a breakthrough and completed the tricolor set; the annual number of publications has doubled every five years since. Importantly, during the past decade, patents have outnumbered publications. The number of publications in analytical chemistry that utilize LEDs now ranges in the tens of thousands.

Schubert's (6) book on LEDs summarizes the history and physical principles governing the behavior of LEDs. Other notable articles center on LEDs as the future of lighting (7) and on the challenge of achieving high electron-to-photon conversion efficiency (4, 5). Reviews specifically focusing on analytical applications of LEDs are few; only two reviews (8, 9), both now dated, specifically address the use of LEDs, especially in flow-through detectors. Three reviews by Landgraf (10–12), all now dated, focus on the use of LEDs in time-resolved fluorometry. Other reviews focus on specific platforms, e.g., microchips (13), capillary electrophoresis (CE) (14, 15), LED-induced fluorescence (LEDIF) in CE (16), and portable CE (17), but do include significant

discussion of the use of LEDs for detection. The present review focuses on current commercially available LEDs as they are used in optical detection and sensing. The period covered is 2008 to mid-2013, with some exceptions. LEDs are particularly well suited for flow-through detector applications. They are easily coupled to optical fibers and the actual size of the emitter chip is small (for 5 mm, also called T-$1^3/_4$ LEDs, ~250 μm square). These characteristics enhance their compatibility with capillary scale detectors. LEDs have also been widely used in portable sensors because of their small size and low power consumption. Most articles on "sensors," however, describe small analysis systems rather than a true sensor, e.g., one that measures temperature, pressure, or pH.

2. PHYSICAL PRINCIPLES

2.1. Laser Diodes versus Light-Emitting Diodes

Laser diodes (LDs) are based on the same principle as LEDs (p-n junction and carrier recombination). Stimulated emission and optical gain are achieved by shaping the active region of the chip into a form of optical waveguide enclosed by parabolic mirrors forming an optical resonator (18). LD emission is much narrower than LEDs, but not as narrow as gas lasers; FWHM is in the single digit nanometer range. The emission has much greater spatial coherence than LEDs and far greater fluence (photons cm^{-2} s^{-1}). LDs may also have much greater total output power. The conversion of electrical to light energy is substantially more efficient in LDs. A type of edge-emitting LED combines the high-power capability of an LD with the lack of coherence of an LED; they are often called superluminescent LEDs (SLEDs). However, temporal noise from an LD or an SLED is much higher than that from an LED; LEDs are therefore preferred for absorbance measurements (19).

2.2. Energy Conversion Efficiency and Thermal Effects on Light-Emitting Diode Stability

For lighting applications, efficient conversion of electrical energy to light is of great importance. White LEDs are mostly used in such applications; they consist of a broadband phosphor capped blue LED. Fortunately, blue LEDs can be made with very high efficiency; up to ~70% electrical-to-light energy conversion efficiency has been demonstrated (7). Commercially available blue LEDs are generally <50% efficient, but white LEDs, despite their consisting of these blue LEDs, have recently crossed the 100-lumens/Watt (lm/W) line, the approximate benchmark for the best fluorescent lamps. However, most fully packaged LED-based bulbs have much lower overall efficiency. High light intensity and stability are the desired criteria for analytical use. The less efficient the LED, the more heat is generated. This has two effects: As the temperature increases, luminous efficiency decreases and the peak emission wavelength shifts to higher values. In rapidly pulsed operations, the luminescence lifetime also changes (20). [Indeed, these apparent detriments can be used to measure either temperature (20) or electrical current (21).] Although constant-current operation is most commonly used, the light output does not remain constant if the ambient temperature changes. This is particularly true if the LED is driven at high currents and significant heat is produced. Thermal management using good heat sinks, in some cases cooling with Peltier devices, is essential to maintain a constant temperature. When the temperature varies within a limited range, the light output can be kept constant by serially connecting an appropriately chosen thermistor with a negative temperature coefficient, and operating at constant voltage can also provide constant output (9).

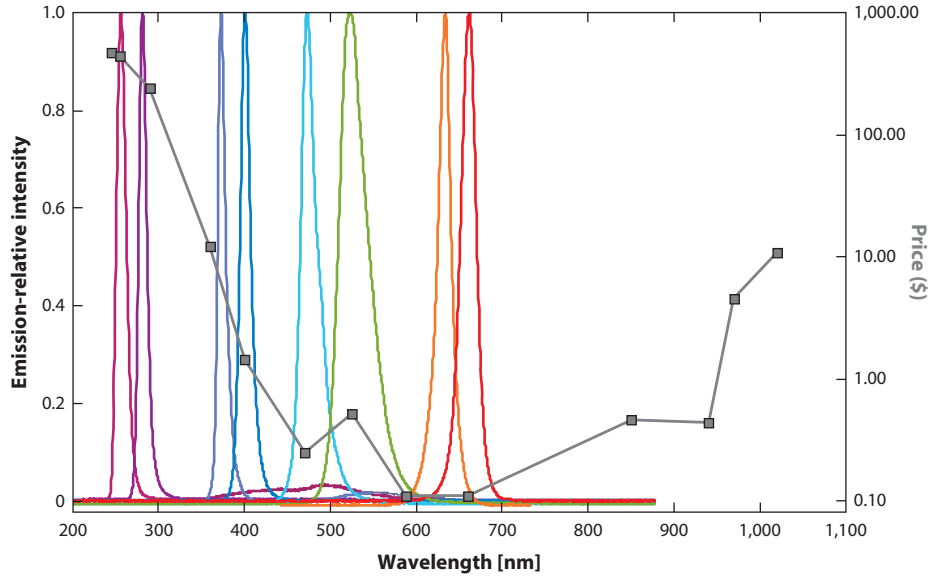

Figure 1

Emission spectra and typical prices for a range of commercially available light-emitting diodes. Conditions: Relative intensities measured using an Ocean Optics (Dunedin, FL) USB2000 fiber optic spectrometer. The prices shown are from manufacturers (**http://www.dotlight.de**, **http://www.roithner-laser.com**).

2.3. Advantages and Shortcomings

Supplemental Material

Figure 1 shows the typical emission bands (the ordinates are all normalized to unity) for different available LEDs in the UV-visible range and their prices; emission spectra of three different phosphor-coated white LEDs can be found in **Supplemental Figure 2**.

LEDs in the 350-nm–NIR range provide high-power output at a low cost. Most LEDs produce very little heat relative to the amount of light produced and exhibit very long life with low optical noise. They can be turned on and off at very high frequencies. Their small size permits miniaturization and complete integration into microchip devices. However, the output of LEDs does not have as high fluence as LDs. The output of the low-wavelength UV LEDs is still much lower than traditional sources. The lack of true monochromaticity also occasionally causes problems. However, because absorption bands are generally quite broad in the near-UV–visible range, this rarely poses a problem in absorbance detection. The lack of monochromaticity can be treated as a stray light effect; at low overall absorbance values such as that encountered in CE, this has little effect on the measured absorbance or its linear relationship with concentration (22); however, sensitivity and linearity are both seriously affected at the high end. In fluorometry, the longer-wavelength part of the emission spectrum can interfere with selective detection of the fluorescence; high quality bandpass or shortpass filters are needed to filter the excitation light (23). UV-LEDs generally have a parasitic broadband emission in the visible range, as shown in **Figure 2**. In our experience, this type of parasitic emission at long wavelengths is common to most, if not all, LEDs emitting at $\leq$400 nm; this is also common to LDs nominally emitting at 405 nm. However, the parasitic band intensity is relatively much greater in LEDs than LDs. Aside from high fluence, this factor also makes LDs attractive in UV/NUV-excited fluorescence.

In absorbance measurements, the inherently low optical noise of an LED is advantageous over conventional light sources (24). It results from a combination of several factors: spatial stability,

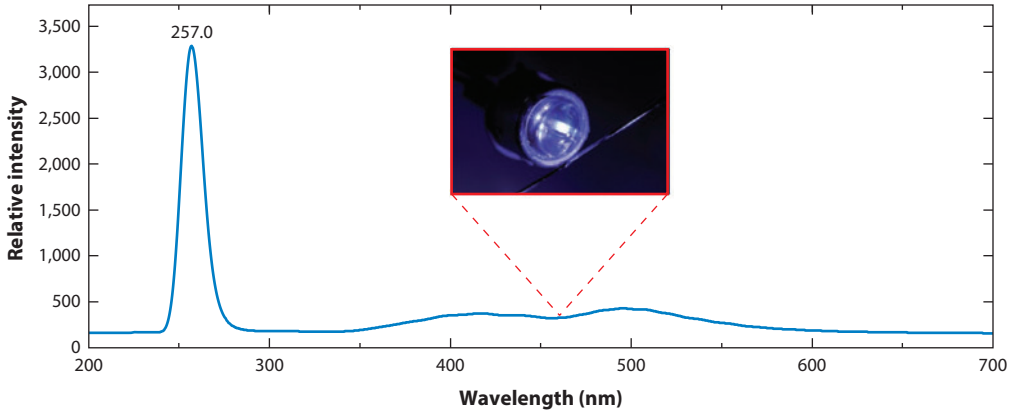

Figure 2

Spectrum of a deep-UV light-emitting diode and corresponding image (*inset*) showing significant parasitic emission in the visible range. Adapted from Reference 112 with permission.

intensity stability, and output at a specified wavelength. This can ultimately result in better limits of detection (LODs) than with conventional sources (24–27). Ultimate performance is compromised by power supply noise, temperature fluctuations, mechanical stability of optics, etc.

2.4. Practical Issues

Numerous suppliers with web-based catalogues and various LED-oriented websites make the search for commercially available LEDs and their choices relatively easy.[1] A somewhat eccentric and eclectic "museum" site also sells a variety of LEDs (**http://ledmuseum.candlepower.us/ledleft.htm**). Although this may not guarantee constant output as discussed before, most commonly LEDs are powered at a constant current. At 25°C, the maximum permissible continuous currents for 5-mm clear epoxy devices range from 15 to 150 mA, for NUV to NIR LEDs, respectively, typically being 30–50 mA in the visible range. High-power, heat-sinked multi-chip LEDs may allow continuous currents of several amperes. Such larger devices generally come mounted on a heat sink, but additional heat sinking may be required. Polarity of connection is typically marked on such devices, and reverse voltage can result in irreversible damage. For discrete through-hole LEDs, the longer lead is the + connection. UV LEDs are particularly susceptible to catastrophic failure from electrostatic damage (ESD), and precautions must be taken in handling them. Some of the more expensive UV/NUV LEDs have a Zener diode connected in parallel to provide ESD/accidental reverse polarity protection. For homebuilt LED arrays, several parallel branches, each with the same number of serially connected LEDs, are preferred. Each branch should also have a current limiting resistor—as voltage drops across individual LEDs may not be identical—and much greater current through one branch than another may otherwise result. As different LEDs have their optical output given in different units [typically UV and NIR/IR LEDs in W, visible spectrum LEDs in candela (cd), and white LEDs in lm], a direct comparison is not straightforward. Specifically, a comparison of LED outputs in candela units without consideration of the viewing/output angle is not meaningful. The radiometry of LEDs is

[1] See, for example, the following websites: **http://www.en.wikipedia.org/wiki/Light-emitting_diode**, **http://www.dolight.de**, **http://www.roithner-laser.com**.

Supplemental Material

a complicated task (see the **Supplementary Materials** for more information and References 28 and 29 for a more extensive discussion).

Thermal management is especially important with deep-UV and high-power LEDs. The operational temperature may already be high (~150°C), but poor heat dissipation or overdriving can greatly shorten the life and cause a gradual output loss. This may not always be obvious (especially for UV-LEDs); the optical output should therefore be monitored. Ideally, UV LEDs should be monitored with UV-sensitive detectors, which, however, are significantly more expensive than standard silicon photodiodes (SiPDs). As stated previously, all of these devices have sufficient parasitic or tailing visible emission (the visible output decays in tandem with the main emission); however, standard visible-light-sensitive photodiode-op-amp detectors can be used for this purpose.

Although, unlike LDs, LEDs are not directional coherent sources, the use of a reflecting cup–shaped anode on which the chip rests and a lens-shaped top can result in a reasonably narrow beam of light (15° viewing angle is usually minimum) with a modest degree of collimation. In some cases, the very high refractive index (RI) of the semiconductor (at $\lambda < 700$ nm, the RI of GaInP is >3.5) can also lead to substantially directional emission (7, 30).

3. FIELDS OF APPLICATION IN OPTICAL DETECTION

Because of their numerous advantages, LEDs are not only being used for analytical chemistry and microreactor applications; other related application areas include illumination for microscopy (31), synthetic organic chemistry, etc. LEDs are increasingly making inroads to health care applications. Examples include the blue LED illumination for neonatal jaundice (32) and red LED illumination for faster healing of wounds (33); their use in optical coherence tomography is also being explored (34), while fingertip blood oximeters are already commonplace (35).

LEDs are extensively used in analytical chemistry, especially for absorbance and fluorescence measurements on various analysis and separation platforms, and in sensors (9). Unique properties of LEDs make them attractive for sensor applications, e.g., the measurement of pH (36, 37); oxygen (38); and other reactive gases (39, 40), water (41), soil nutrients (42), and smoke (43). Most commercial flow-through RI detectors today use LEDs as light sources. An LED is used as the light source in an interesting surface plasmon resonance–based sensor that uses various thicknesses of gold films deposited all around the core of an optical fiber. Depending on this film thickness and the wavelength of the probe LED, the RI response range can be tailored; the sensitivity is comparable to that of an Abbe refractometer (44).

3.1. Photodiode or Light-Emitting Diode Detector?

Almost from its inception, SiPDs have been the preferred light sensors for LED-based absorption detectors (45). LEDs themselves were investigated as detectors early on (46); Dasgupta et al. (8) provided the response matrix for 555-, 570-, 605-, and 660-nm LEDs as emitter-detector combinations. Contrary to what may be expected, the same wavelength LED as emitter and detector did not provide the best response; the longest wavelength LED was the best detector for all the emitters. However, Dasgupta et al. (8, p. 59) concluded that this is merely a curiosity: "LEDs are photodiodes, but pretty poor ones!" Nevertheless, the use of LEDs of the same wavelength as both the emitter and the detector was reintroduced by Dietz et al. (47) in 2003. Shortly thereafter, the same approach was adapted by Lau and coworkers (40) and O'Toole et al. (48) for flow-through detectors. They coined the term paired emitter-detector diode detection (PEDD). A PIC microcontroller was used for manipulation of both the LEDs. The photocurrent was not

directly measured. With the emitter LED off, the detector LED was charged to +5 V (logic HI) for a very brief period (~0.1 ms), its junction acting as a capacitor. Next, the detector LED was connected to the high impedance digital input of the PIC, and the emitter LED was turned on. As the resulting photocurrent drained the detector LED capacitance, the time for the input to register a low logic level (from the instant the emitter LED was turned on) was measured. This time was taken as a measure of the photocurrent. The principal benefits were stated to be the direct digital output of the system, thus resulting in lower cost (49). The scheme has since been applied to a variety of sensors (50–52). Whether the stated cost benefit justifies this configuration may depend on the specific situation.

More recently, Koncki and colleagues (53) have taken a different and in some ways a more defensible approach to the use of LEDs as detectors. In most absorbance detection situations, the emitter LED is driven at or close to the maximum permissible continuous current level to provide as much light to the detector as possible; this minimizes shot noise. At high illumination, the output voltage of a diode detector is proportional to the logarithm of the light intensity; the detector output signal can therefore be linearly proportional to the analyte concentration at least within the domain that Beer's law is obeyed (53). The one apparent advantage over a photodiode in this photovoltaic-operational mode is that the saturation output voltage of an LED is considerably higher than that of an SiPD (<0.4 V), making better use of the minimum span of a typical data acquisition card. In an immediately subsequent paper (54), however, the authors measured the voltage output of the LED detector over a large range of illumination (by varying emitter drive current) with both a high impedance voltmeter (using a pH meter) and a common multimeter (which presumably was of low impedance; a specific value was not stated). They reported that true voltage measurements, as obtained with a pH meter, result in the detector voltage output being proportional to the logarithm of the light intensity, whereas in the case of the low impedance meter, this is observed only at high illumination levels. This is not exactly correct. Although the true voltage reading will indeed not be attained if photoelectrons drain through the measurement system, even with high impedance measurement, the detector output voltage does not linearly change with the logarithm of the light intensity at low light levels. The Shockley equation for the ideal diode states that

$$I = I_s \left(e^{V_D/V_T} - 1\right), \qquad 1.$$

where in the present situation, I is the generated photocurrent that results in a potential V_D across the diode; I_s is the reverse saturation current, a constant at constant temperature; and V_T is the Boltzmann noise kT expressed in electron volts, ~25 mV at room temperature. At high illumination levels (large I), V_D will be much higher than 25 mV; as such, the exponential term will be much greater than unity, and Equation 1 would reduce to

$$V_D = a \ln I + b, \qquad 2.$$

where a is V_T, b is $V_T \ln I_s$, and the detector voltage will indeed be proportional to ln I. However, at very low illumination levels, V_D/V_T can be very small, and as such Equation 1 reduces to

$$V_D = a I + b, \qquad 3.$$

where a is V_T, b is $V_T I_s$, and the detector voltage becomes linearly proportional to the light intensity. **Figure 3** demonstrates that this behavior is common to both photodiodes and LEDs as detectors, and both exhibit reasonable fits to the Shockley equation.

The LED emitter–LED detector (55) and its manifold applications have been described in numerous papers; topics include the use of UV LED emitters in bioanalytical assays, e.g., determining alkaline phosphatase activity (56), demonstration of a single standard calibration system

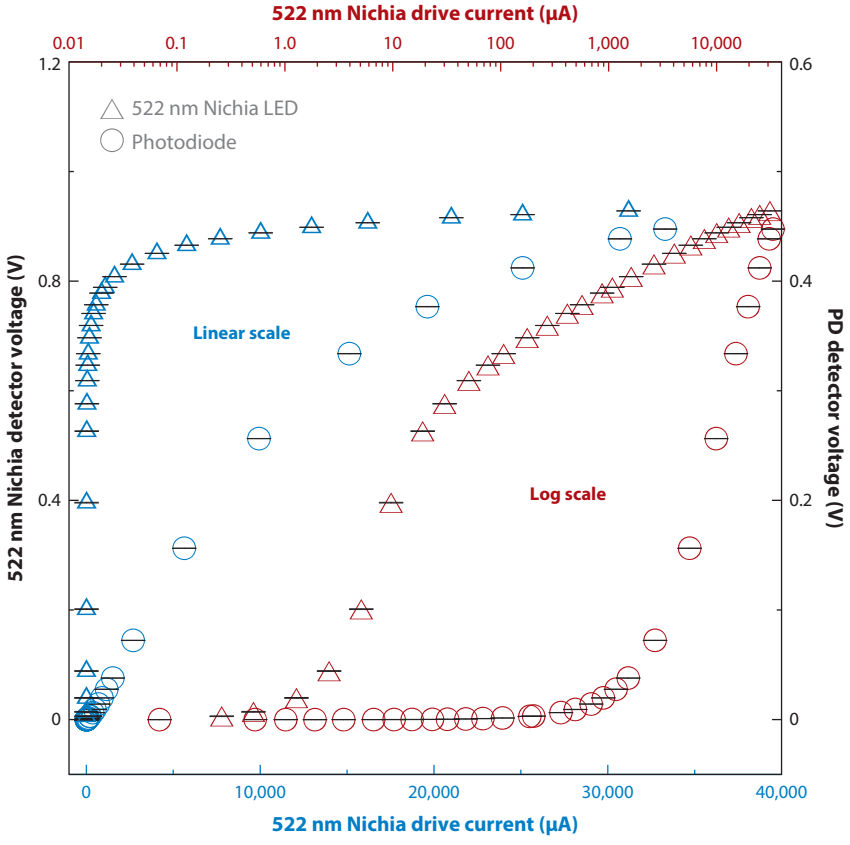

Figure 3

Photovoltaic response of a photodiode (Siemens BPW34) and a green 5-mm light-emitting diode (LED) (Nichia NSPG500DS) to an NSPG500DS LED in a head-to-head configuration isolated from ambient light. Emitter LED drive currents in the range of 70 nA to 31 mA. Data acquired with 0.2-μV resolution. Error bars indicate ±1 standard deviation ($n = 3$). Figure courtesy of Bo Yu, the University of Texas at Arlington.

(57), characterization and use of open tubular reactors with covalently wall-bonded enzymes (58), measurement of hemoglobin (59), demonstration of a Prussian blue film (PBF)–based redox sensor (60), serum alkaline phosphatase assay (61), protein determinations in biosamples (also by fluorometry) (62), glucose in serum via glucose oxidase and the aforementioned PBF (63), creatinine in physiological fluids via the Jaffe reaction (64), simultaneous determination of both acid and alkaline serum phosphatase (65), etc. Others have also adopted the PEDD concept demonstrating, e.g., in the determination of Cr(VI) with diphenylcarbazide (66) and/or Fe^{3+} with SCN^- (67), simultaneous detection of sugar and phosphate by a single PEDD in cola drinks (68), etc. It is true that in virtually all of these determinations, the analyte concentration is high and photovoltaic determinations and the logarithmic response behavior at high light levels permit a more direct linear relationship with concentrations.

Recently, Bui & Hauser (69) compared LEDs and SiPDs as photodetectors in both voltage and current source modes. In comparing a flat window 1-mm^2 active area SiPD with typical 5-mm clear epoxy dome-shaped T-$1^3/_4$ visible LEDs, they reported that they behave largely similarly but the SiPD produces an order of magnitude greater current. The typical 5-mm LED has a

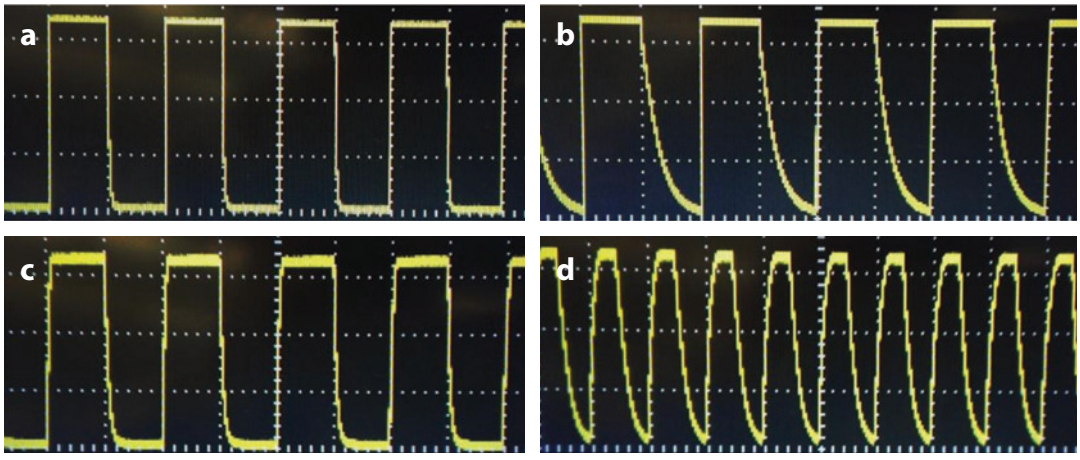

Figure 4

High impedance photovoltaic measurements of pulsed illumination at (*a*) 200 Hz and (*b*) 2 kHz. Similar photocurrent (20-k Ω drain resistor) measurements at (*c*) 20 kHz and (*d*) 100 kHz. The departure from the illuminating waveform is primarily on the falling edge, demonstrating negligible capacitance in the presence of the photocurrent. Nichia NSPR510CS 635-nm light-emitting diodes as both emitter and detector. Figure courtesy of Brian N. Stamos, the University of Texas at Arlington.

chip area of 0.25 × 0.25 mm, but the dome acts as a lens and focuses the collected light on the chip, a feature only rarely available in inexpensive photodiodes. Our experience indicates that, when exposed to broad uniform illumination, removing most of the plastic on a dome-shaped LED and grinding it flat reduces the photocurrent by a factor of 3–4. So on an equivalent active area basis, LEDs are not an order of magnitude worse photodetectors than SiPDs; however, for practical purposes the devices must be compared as they are. In applications where larger active detector area has merit (not small bore detector applications), large chip area LEDs may be worthy of exploration. LEDs with monolithic chips up to 7 × 7 mm are commercially available (**http://www.luminus.com/products/Luminus_SBT-70C_DataSheet.pdf**). They are in fact less expensive than SiPDs with comparable active areas. Bui & Hauser (69) reported that the SiPDs exhibited greater reproducibility than LEDs, largely due to the greater photocurrent generated. They also found that the LED detectors displayed a greater settling time, which we find perplexing. In our experience, in the photovoltaic mode most common LEDs can easily respond faithfully to 200-Hz pulsed waveforms and to much higher frequencies in the photocurrent mode, as shown in **Figure 4**. In any case, the authors found that the peak response of any LED as a detector was 40–60 nm blue-shifted relative to the peak emission wavelength of the same LED (this could in fact be higher because it is not clear if these data incorporate corrections for spectral energy distribution of the W lamp source used), suggesting once again that the same type of LED is not the best detector for a given emitter, if LEDs must be used as detectors.

3.2. Absorbance Measurements

The first reported use of an LED in a measurement instrument appears to be in a skin reflectance–based oximeter (70). The first use of LEDs in chemical analysis followed shortly for absorbance measurement (71), and the first review article on analytical application of LEDs was also on this topic (8). A 2004 review (72) specifically discusses the use of liquid core waveguides (LCWs) for analysis; the majority of the applications utilized LEDs as light

sources. More recent reviews by Xiao et al. (14, 15) focus on on-capillary detection in CE but provide informative overviews of the early and current uses of LEDs as light sources in analytical chemistry. The present analytical uses of LEDs primarily involve absorbance or fluorescence measurements.

Picking the right LED (matching the peak emission wavelength to the analyte absorption maximum) is the key to low LOD absorbance measurements and a large linear dynamic range (LDR). The LDR also depends on the FWHM of the LED emission, and a wide LDR is attained only with relatively narrow bandwidth LEDs. A low LOD is often of greater importance, and at very low absorbance levels, this is relatively less affected by the mismatch between the LED emission and the analyte absorption (the mismatch results basically in a stray light effect) (22).

3.2.1. General applications of light emitting diode–based absorbance measurement. In some cases, indicator-based titrations being a notable example, only binary information is sought from an optical detector. In these circumstances, very simple fast responding detector designs suffice (73). Early on, multiple LEDs were used for multiwavelength measurement (74); up to an array of eight LEDs have been used in a fiber optic coupled multiwavelength photometer for multivariate calibrations (75). More recently, a handheld nanoliter-scale LED-source LCW-based photometer has been demonstrated (76). Red, green, and blue (RGB) LED–based photometers have also been reported (77). The advent of inexpensive charge-coupled device (CCD) array-based spectrometers and high-intensity white LEDs presently make this combination potentially more attractive (78); such spectrometers with long path LCW cells have been described (79). Most such detectors have been developed for use with continuous or intermittent flow-based methods. Two wavelengths can be used to decrease noise (50). A four-channel automated creatinine analyzer using four thermostated on-tube detectors (80) has been developed. A flow-through fluoride measurement system relies on the liberation of the dye SPADNS from the Zr-SPADNS chelate (81); the feasibility of a fiber optic evanescent wave device for the same measurement, remarkably of only 2 cm active length, has also been proven. A 420-nm LED has been used to measure glutathione based on its reaction with dithionitrobenzoate on a mesofluidic platform (82). Aqueous NH_3-N was measured by liberating the ammonia and following the color change of a bromothymol blue infused glass fiber filter permitted an LOD of 50 μg/L (83). Ethanol in beverages has been measured by diffusive vapor transfer to an acidic Cr(VI) receptor, and the decrease in Cr(VI) concentration was photometrically measured (84). Similar membraneless transport of amines was studied using the color change of an indicator (85).

Similar to the measurement of lipid hydroperoxides by reaction with Fe(II) and SCN^- (86), Fe(II) in oils has been measured by reaction with SCN^- (87). Another remarkable paper reported an LED-LCW cell made of mirrored tubes and achieved an LOD of 70 pM phosphate as bismuth phosphomolybdate (88). Although Teflon AF or Teflon AF clad silica tubes have been most commonly used as LCW conduits, the measurement medium can sometimes be so concentrated (or sufficient salt can be added to it without affecting the reaction outcome) for inexpensive fluorinated ethylene propylene copolymer (FEP Teflon) tubes to behave as an LCW. Acetone reacts with salicylaldehyde in a concentrated NaOH medium to form a colored product—this has been used to measure breath acetone in FEP tube–based LCW cells (89). Similar measurements of gaseous H_2O_2 have been made (90).

Arsenite and arsenate have been differentially determined by a pH-differentiated reduction step leading eventually to molybdenum blue, measured by a LED-photodiode detector (91). A similar application is the measurement of silicate in natural waters via silicomolybdate and molybdenum blue in an LCW cell (92).

Blood cyanide measurement is an important rapid emergency need in smoke inhalation victims. Cobinamide forms an intensely purple product with cyanide (λ_{max} 583 nm); this has been used for nanomolar-level cyanide measurement with a white LED-LCW cell using two additional wavelengths beside 583 nm for blank and baseline correction (93, 94). The principle has also been used in an impregnated filter–based (95) and a porous membrane petri dish–based platform (96), both disposable.

Broadband cavity enhanced spectroscopy uses absorbance amplification between two highly reflective mirrors; a white LED has been used in this context as a light source to obtain up to a 45x gain in path length in HPLC detection (97). Similarly, a large chip blue LED (460-nm peak) has been used to measure aerosol extinction coefficient between 450–480 nm (98).

NIR LEDs have not been as commonly used. Two notable examples include the measurement of aromatic hydrocarbons in water (following extraction) at 1,689 nm with a 1,300-nm LED acting as a reference (99). In another, LEDs complemented a tungsten lamp source for making temperature corrected assays for alcohol content in the wine industry (100).

Salinity mismatch creates RI-induced artifact absorbance signals that can be a major problem in some applications; reflection across a radial path is known to reduce this considerably. With light entering and exiting an externally mirrored tube (101, 102) or capillary (103) at an angle, a remarkable immunity to RI effects is also observed. An interesting strategy in compensating for both RI and turbidity effects is to make simultaneous multiple wavelength measurements with the same detector, with each LED being pulsed at different frequencies and balanced demodulator circuitry being used to extract individual signals (104).

3.2.2. Capillary scale absorbance detection. In small aperture applications, light throughput is a prime consideration to limit shot noise. In this case, LEDs excel as the actual chip emitting area is small and often can be coupled with little or no focusing optics. As early as 1997, noise levels as low as $\sim 10^{-5}$ absorbance units have been reported (105). Over the past decade, LEDs were used in miniaturized photometric detectors for CE, resulting in low baseline noise and detection limits comparable to commercial CE instruments using D_2 lamps (14, 15, 25, 106–110); facile estimation of the effective path length and stray light that govern the performance of the detector has been suggested (111).

Supplemental Material

More recent examples with the relevant papers from 2009 are summarized in **Supplemental Table 1**. They include the use of a large chip high output white LED as the source in a commercial CE instrument without modification [relative to RGB LEDs, the phosphor-based LED performed better (3)], a UV LED for CE detector applications (112), and a 3-in-1 detector that combines contactless conductivity and LED-based absorbance and fluorescence detection in a single device (shown in **Figure 5**) intended for any capillary scale application (113). Standard subminiature version A (SMA) fiber optic holders permitted precise alignment for photometric detection while another optical fiber at a 45° angle collected the emitted fluorescence. LEDs of 255 nm for absorbance and of 470 nm for fluorescence detection were used. The advantages of concurrent single point triple detection were demonstrated with model mixtures.

Microfluidic chips represent capillary conduits that are often smaller than CE or capillary chromatographic analysis systems. As LEDs are more easily scaled down than other light sources, external and on-chip microfabricated LEDs are potentially attractive for optical detection in lab-on-a-chip microfluidic devices (114–118). Micro-LEDs with ~10-μm diameter have been fabricated (119) and open a new horizon for small analytical systems. The use of traditional LEDs for microfluidic chips must, however, compete with LDs and organic LEDs that can be more easily fabricated on-chip.

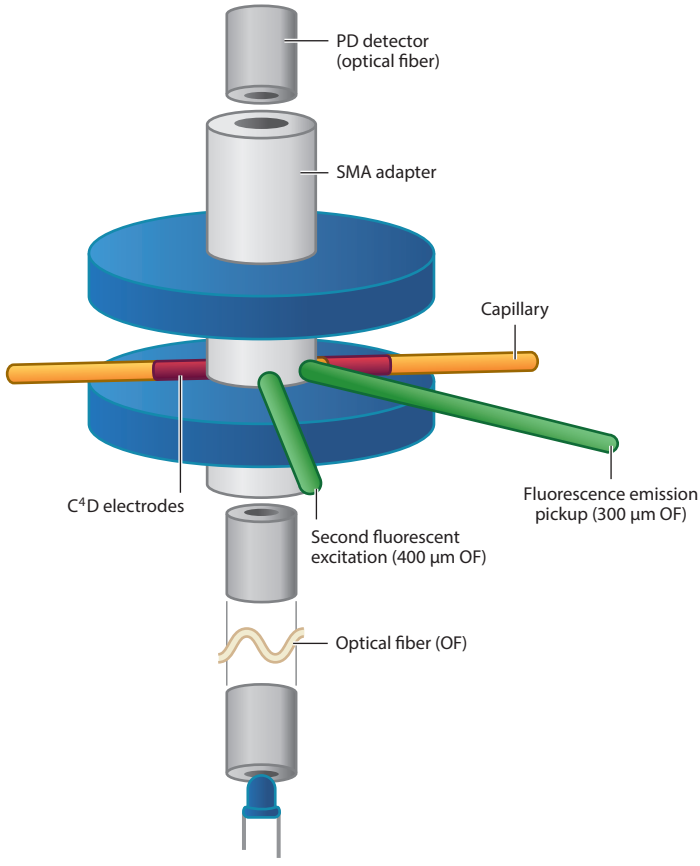

Figure 5

Detector for simultaneous absorbance, fluorescence, and contactless conductance detection. The LED used for absorbance measurement can also be used for fluorescence excitation (113). Abbreviations: LED, light-emitting diode; OF, optical fiber; PD, photodiode; SMA, subminiature version A.

3.3. Fluorescence Measurements

The most important light source for high sensitivity fluorometry in dedicated applications is still a laser source; the ability to create a focused spot with very high fluence provides high signal-to-noise ratios and in most cases its monochromaticity obviates the need for an excitation cutoff filter (120). On the emission side, the rejection of the stray laser radiation is very important, and very high rejection ratio (10^6:1) notch filters are available for most laser wavelengths. With recent increases in optical power at low wavelengths, LEDs are gaining popularity as low-cost, high-stability, low-noise, direct modulation robust fluorescence excitation sources for continuous as well as time-/frequency-domain fluorometry. Fast (300 MHz) pulsed LED frequency-domain fluorometry dates back to 2000 (121), followed shortly in 2001 by frequency-domain fluorescence microscopy (122). LEDs suitable for time-resolved fluorometry (this requires a single short duration pulse) have been available for some time, and variations of this technique have been described (10–12); LEDs permitting frequency-domain (phase-resolved) fluorometry (123) are also now routine adjuncts to commercial fluorometers.

UV-LEDs present an alternative to xenon flash lamps or nitrogen lasers. At the time of this writing, LEDs with peak wavelengths down to 240 nm are commercially available and 275-nm devices are being made in high volume. Even 210-nm devices have been experimentally realized (124). LEDs have the advantage that shorter lifetimes can be measured in the time-resolved mode, and they permit very fast repetition rates (125). Although longer wavelength devices have limited utility, available individual LEDs span a very large wavelength range. The limitation of (especially UV) LEDs is the presence of a longer wavelength component that may overlap the fluorescence emission (126, 127). Low-pass excitation filters or narrow band interference filters must be added atop the LEDs (116, 128–130): Small-diameter optical filters of sizes suitable for mounting on 5-mm LEDs are available as are interference filter–equipped photodiodes (**http://www.intor.com**). An elegant fluorescence detector using a blue LED, a dichroic mirror, a photodiode detector, and a lock in amplifier, all integrated on a chip, was demonstrated (131).

Because of the ability to utilize high-speed pulsed operations, gated fluorescence detection can be attractive. In this technique, the LED source is turned off before the fluorescence from long lifetime fluorescent analytes is measured. Many lanthanide complexes have very long fluorescence lifetimes because of intersystem crossing; they also display a very large Stokes shift. Gated fluorescence detection using early 290-nm LEDs has been used for the detection of the Tb(III) complex of dipicolinic acid, a major constituent of anthrax spores (132, 133).

3.3.1. Macroscale flow-through fluorescence detectors and sensors. A multiwavelength LED array for fluorescence excitation in an LCW was described early for a portable analyzer (74). The advent of deep-UV LEDs (266 and 280 nm) has allowed a field-portable fluorimeter that can measure phenanthrene and tryptophan-like compounds in natural waters with an LOD of $\sim$1 μg/L (134).

Fluorescence, being one of the most sensitive analytical techniques, permits measurement of small molecule atmospheric gases. On-line scrubbing into an aqueous collector and an appropriate on-line aqueous phase fluorogenic reaction are used, e.g., for H_2S (135, 136), HCHO (137, 138), NH_3 (139), and NO_2 (140). Similar measurements have been made for NH_4^+ in seawater (141–143) or HCHO in foods (144), etc. In many cases, multiple LEDs, with or without interference filters and/or ball lenses for focusing, can be arranged around the flow tube, and an integral photodiode-operational amplifier detector, with or without additional amplification, provides sufficient sensitivity for the end application.

With high sensitivity not being an important need, PEDD-based fluorescence sensing has been used to determine calcium with calcein (62, 145). Turbidimetry and nephelometry resemble fluorescence detection configurationally; the nephelometric determination of sulfate was demonstrated early on (146, 147). More recently, PEDD-based turbidimetry and, more sensitively, nephelometry have been used for urinary albumin measurement on a flow injection analysis (FIA) platform (148) with a fast throughput rate (60 samples/h).

Human vision distinguishes different colors better than different shades of the same color. In a popular urinary paper strip glucose assay, for example, the actual assay produces various shades of yellow. The distinction is much better perceived in the presence of a blue screening dye whence the observed scale ranges from light blue through green to brown. Ye et al. (149) designed a rhodamine derivative that is not fluorescent but that reacts with Hg(II) liberating the fluorescent dye and producing green fluorescence when excited by a 520-nm LED. Again, shades of red through brown through green are easier to differentiate than different shades of green; background illumination was provided by a red LED to accomplish this. Such approaches may merely constitute a novelty presently, given electronics are inexpensive enough to quantitatively display the green fluorescence as a readout.

Supplemental Material

A recently described reusable LED-induced CL detection system (**Supplemental Figure 3**) for riboflavin attained LODs of 8 pg/ml and could be used 100+ times. Immobilized aptamers captured the analyte that was subsequently eluted by alkaline luminol. Activated by a pair of high-power blue LEDs, strong CL was observed post photoreactor (150).

3.3.2. Liquid core waveguide–based fluorescence detection. A transversely excited LCW provides spatial discrimination against the excitation light and considerably reduces optical filtration requirements (45), often achieving excellent detection limits with only rudimentary optical filtration of the fluorescence signal. The principles were first established in 1999 (146, 147). In sensitive fluorimetric applications, a photomultiplier tube (PMT) is the detector of choice and is generally the single most expensive component in the entire system. In an interesting application, multiple LCW fluorescence cells were excited by alternately pulsed LEDs and the resulting fluorescence was coupled to a PMT by optical fibers. As only one excitation LED is on at a time, individual fluorescence signals are easily sorted by software (151).

Numerous studies have exploited LCWs on the capillary or chip scale for fluorescence detection; indeed, one of the initial papers (146, 147) demonstrated the detection of 200-amol fluorescein in a CE arrangement with excitation by two blue LEDs. The first paper on LED-excited fluorescence detection on an LCW-based chip is now more than a decade old (152). Fang and colleagues (153) use LCW-CE platforms for their work on LEDIF.

Song et al. (154) used a Teflon AF coated fused silica capillary as the transversely excited LCW. A conventional or high-power (210 mW) 365 nm LED or a 405-nm LD (5 mW) was used as the source. The authors used a LD from a Blu-ray player; conveniently, this was already equipped with focusing optics. A novel cell with the capillary tip directly on the PMT window was used. Al-sulfoxine and Coumarin 30, respectively, were detected with the LEDs and the LD. The conventional LED with a photodiode detector allowed an LOD of ~1 μM Al. The HP LED and the LD allowed respective LODs of 0.8 nM Al and 3 nM Coumarin 30.

3.3.3. Other capillary scale fluorescence/chemiluminescence detectors. Principal CE fluorescence detector designs have been reviewed (14, 15). Most frequently, optical fibers and/or microscope objectives are used for coupling light in/out. The relevant papers from 2009 are provided in **Supplemental Table 2**.

Tyrosine enantiomers were derivatized with a chiral fluorescent tag, separated by CE and then detected with a fluorescence detector configuration that the authors previously developed (155): The excitation light from an LED was brought in by a 40 μm fiber that was inserted into the capillary to reach the detection location [fiber-in-capillary (FIC) configuration]. The emitted light was collected by a microscope objective and filtered spatially and then optically by a high pass filter. Zhang et al. (156) used blue LEDs for LED-induced chemiluminescence for CE: The analyte photooxidized luminol under LED irradiation and generated CL. A low cost blue LED-SiPD detection system for CE permitted an LOD of ~1 μM for fluorescein isothiocyanate (FITC)-labeled amino acids (157).

The previously discussed 3-in-1 detection system (**Figure 5**) of Ryvolová et al. (113) permitted a 10 nM LOD for fluorescein. An array of LEDs (430, 450 and 480 nm) focused with a series of lenses and coupled to a single-mode optical fiber in the FIC configuration (**Figure 6**) achieved 1–100 nM LODs for asparagine, epinephrine, and L-leucine with various fluorescence tags (158).

The CE analysis of naphthalenedialdehyde derivatized amino acids/amines in breast cancer cells by a previously developed 405-nm LEDIF system permitted 2–20 nM LODs (159). Gan et al. (161) demonstrated CE separation/detection of FITC-tagged IgG (160) and epinephrine/dopamine with a 475-nm LEDIF detector with LODs of 20–30 nM in plasma. Diao et al. (162) achieved

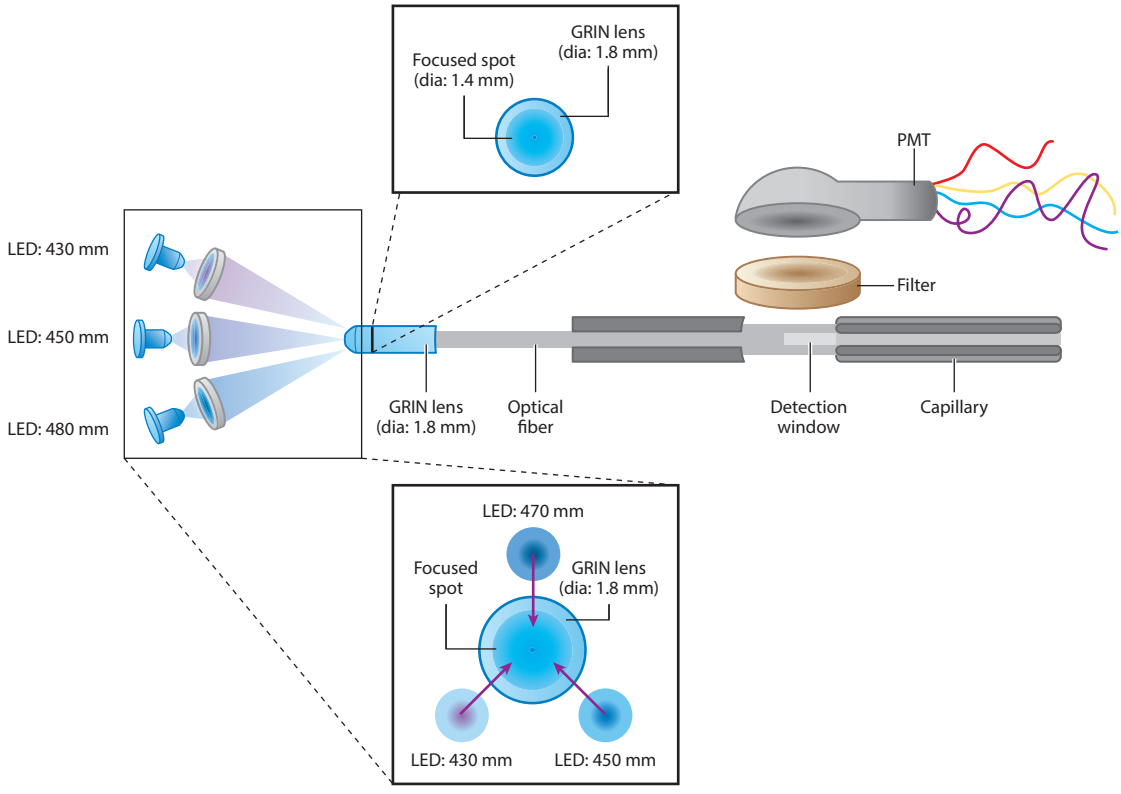

Figure 6

Detection scheme for the multiwavelength LED array—CE-LEDIF detection. The three LEDs (430, 450, and 480 nm) are focused through the end-face of a GRIN lens (1.8 mm in diameter) with an antireflection coating. The focused spot diameter was 1.4 mm. Multiwavelength LED excitation light is introduced directly to the detection window to detect the fluorescence sample. Adapted from Reference 158 with permission. Abbreviations: CE-LEDIF, capillary electrophoresis light emitting diode–induced fluorescence; GRIN, gradient index; LED, light-emitting diode; PMT, photomultiplier tube.

0.3–1 nM LODs for the simultaneous CE determination of FITC-derivatized catecholamines in a FIC configuration (**Supplemental Figure 4**). A blue-red bicolor dual wavelength alternately pulsed LED permitted the detection of six different fluorescent dyes (including fluorescein and FITC) separated by CE with LODs of 40–300 nM (163). Rodat-Boutonnet et al. (16) compared laser-induced fluorescence (LIF) (488-nm Ar^+ laser) with LEDIF for the commercial capillary fluorescence detector (Picometrics). For various tags, the LODs were either identical or for 5-carboxytetramethylrhodamine succinimidyl ester (5-TAMRA.SE), LEDIF provided an ~6-fold lower LOD, primarily due to a better match with the excitation spectrum.

Supplemental Material

A blue-LEDIF system permitted the determination of FITC-tagged ephedrine and pseudoephedrine with LODs of 1.8–2.3 nM in a CE system (164). A 490-nm LED permitted detection of SYTO 9 tagged ribosomal RNAs in a CE system with an LOD of 50 pg/μL (165). A compact light–LEDIF system with spatial and optical filtering improved the LOD for fluorescein to 0.75 nM (166), a 3.5-fold improvement over a previous system.

A pen-shaped capillary cartridge system (**Figure 7**) using LEDIF detection has been recently described for rapid haplotyping of putative microRNA-binding sites in a gene associated

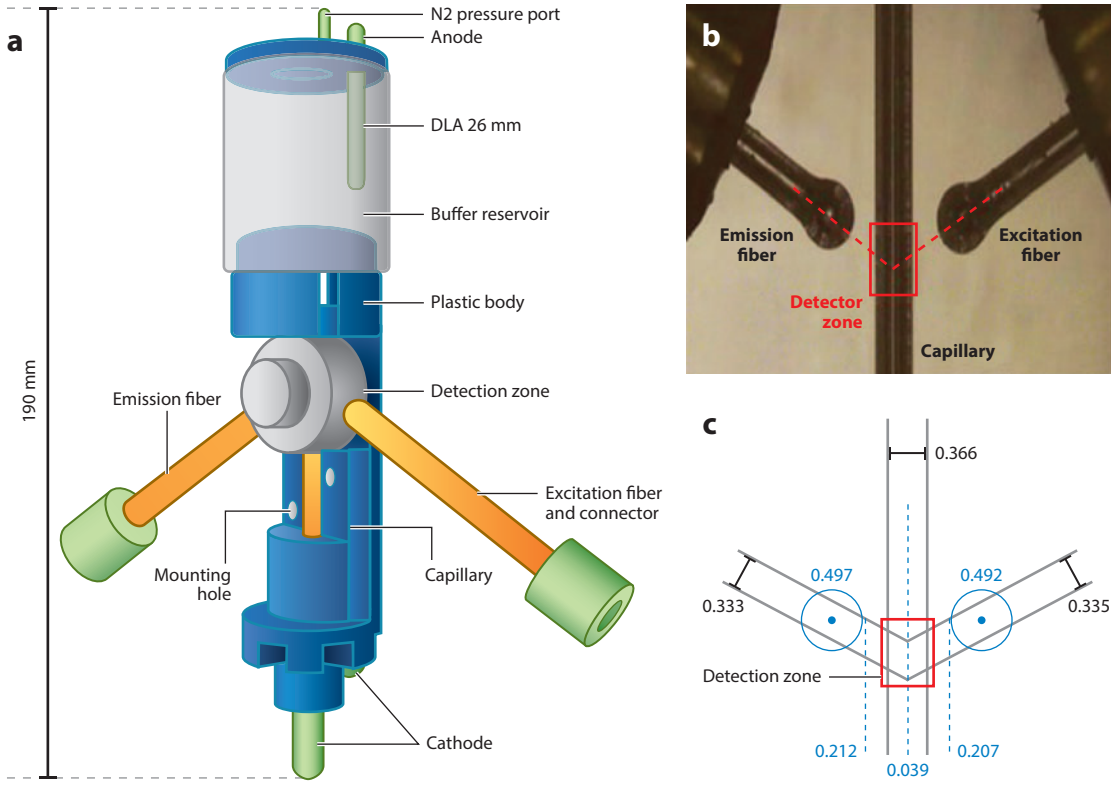

Figure 7

Detection optics design. (*a*) Schematic illustration of the detection section of the pen-shaped capillary cartridge incorporating the detection optic configuration. (*b*) The actual center plane sectional view at the detection region in the capillary cartridge in panel *a*. (*c*) Dimensions of the micro-ball ended incident and output optical fibers, as well as the separation capillary. Adapted from Reference 178 with permission.

with type 2 diabetes mellitus (167). With electrokinetic injection, an LOD of 2 ng/ml was possible.

3.3.4. μChip scale fluorescence detectors. Blue LEDIF provided 0.25–0.5 μM LODs of fluorescein and FITC in a simple SiPD detector setup for a μchip-CE platform (168). FITC-derivatized creatinine could be determined with an LOD of ~3 μM in urine by LEDIF (169), more than adequate for the application. FITC-labeled sulfonamides, pharmaceuticals, and rabbit plasma were determined by LEDIF with LODs of 0.4–0.5 μM (170). The light from a high-power blue LED was spatially filtered; the emission light was filtered by a 510-nm longpass filter and detected by a photodiode placed at 45° to the excitation beam (**Supplemental Figure 5**).

Supplemental Material

Numerous papers describe the use of a commercial μchip-CE platform (Agilent Bioanalyzer) equipped with a blue LEDIF detector and variously report separation and detection of derivatized carbohydrate oligomers and glycans, as well as microorganisms (171, 172). The use of isotachophoresis with indirect LEDIF detection to determine benzoate in sodas and lactate in plasma was also demonstrated (173–175). Morioka et al. (176) used 525-nm LEDIF detection in a chip-on-a-compact disc rotating setup following the enzyme-linked immunosorbent assay (ELISA); the authors argue that unlike commercial ELISA instruments, this can be made portable.

4. CONCLUSIONS

LED technology is still far from mature, and, in particular, significant further gains are needed in price and performance in the sub-275-nm region; progress is being made (177). Analytical chemistry is not a sufficient market driver to make this possible for analytical purposes but sterilization and field sensing needs of various types (including those involving national security) are fortunately pushing this issue. Meanwhile, from the NIR-to-NUV range, LEDs provide an unmatched power-to-cost ratio, and the ability to modulate them in a very simple fashion facilitates numerous otherwise sophisticated techniques such as lock-in detection, phase-resolved fluorometry, etc. For integrated and dedicated analysis platforms, LEDs, especially organic LEDs, now offer the possibility of holistically integrating the light source into the analytical platform. Their very long lifetime relative to other sources is a further boon to the user.

SUMMARY POINTS

1. LEDs as solid state light sources are revolutionizing illumination: Analytical chemistry is one of the many beneficiaries.
2. The broad availability of LEDs is market driven, and in NUV-NIR, the cost is orders of magnitude lower than other sources, making them suitable for devices intended for pedagogic use.
3. LEDs display exceptional intensity stability if at constant temperature and a constant current is maintained.
4. LEDs exhibit long lifetimes, in the range of 10^5 hours, and they provide efficient energy conversion: A "cold light source" requires less thermal management, resulting in less power consumption.
5. LEDs are especially robust light sources, and their size and power consumption makes them ideally suited for incorporation into portable devices.
6. LEDs are quasi-monochromatic sources with a typical half-height bandwidth of 20–30 nm, suited for most analytical applications often without additional optical filtration; white LEDs can be used as broadband visible light sources.
7. LEDs can be operated in the pulsed mode up to the GHz range, permitting fluorescence lifetime measurements.
8. LEDs excel in dedicated applications where changes in wavelength are not needed. At a given wavelength, in the NIR-NUV range, an LED can output more power in a limited wavelength range than most other sources.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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P.K.D. would like to dedicate this article to the memory of his friend and colleague Henryk Temkin, who, as the director of the UV Photonics program of the Defense Advanced Research Projects Agency, contributed more to the commercial advancement of deep UV LED technology in the United States than any other individual.

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