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An ultrasensitive method of real time pH monitoring with complementary metal oxide semiconductor image sensor

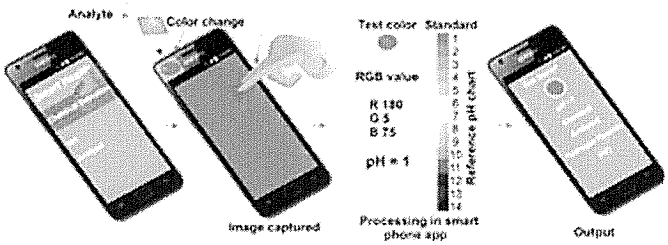
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HIGHLIGHTS

- A new approach on quantifying various pH solutions with a CMOS image sensor.
- pH indicator blended hydrogel film was fabricated for pH analysis.
- A distinct RGB color change analyzed by CMOS image sensor.
- Chromaticity diagram and Euclidean distance represent the RGB color space.
- The CMOS image sensor based pH measurement produces sensitive pH detection.

GRAPHICAL ABSTRACT



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ABSTRACT

CMOS sensors are becoming a powerful tool in the biological and chemical field. In this work, we introduce a new approach on quantifying various pH solutions with a CMOS image sensor. The CMOS image sensor based pH measurement produces high-accuracy analysis, making it a truly portable and user friendly system. pH indicator blended hydrogel matrix was fabricated as a thin film to the accurate color development. A distinct color change of red, green and blue (RGB) develops in the hydrogel film by applying various pH solutions (pH 1–14). The semi-quantitative pH evolution was acquired by visual read out. Further, CMOS image sensor absorbs the RGB color intensity of the film and hue value converted into digital numbers with the aid of an analog-to-digital converter (ADC) to determine the pH ranges of solutions. Chromaticity diagram and Euclidean distance represent the RGB color space and differentiation of pH ranges, respectively. This technique is applicable to sense the various toxic chemicals and chemical vapors by situ sensing. Ultimately, the entire approach can be integrated into smartphone and operable with the user friendly manner.

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1. Introduction

pH sensor is one of the most important biosensor applied in chemical industries, environmental and biomedical field [1]. Conventional methods of pH strips and pH meters are reliable analytical systems for pH measurement. And the meters are employed in bio and chemical laboratory to find the hydrogen ions of the substances. However, limited applicability and non-

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portability are the reasons to replace the conventional pH meters, and attract the people to associate with modern sensors. Recently, various chemical sensors have been combined with pH based chemical detection hence the reaction rate, stability, solubility of chemicals and bio-molecules dependent on pH [2,3]. In addition, the optoelectronic method of calorimetric sensors is developed to find the pH ranges, toxic chemical compounds, toxic gas and volatile organic compounds using various pH indicators, vapochromic/solvatochromic dyes and redox indicators [4]. Calorimetric arrays are developing the color based on the pH range of the chemicals; array reader analyzed the RGB intensities, and statistical information confirmed the pH ranges or chemical compounds [5]. However, the total response time is little longer for real time application. Further, MEMS based pH sensing systems such as ion sensitive field-effect transistor (ISFET) [6], complementary metal oxide semiconductor (CMOS) based pH imager [7], optical fiber [8], magnetoelastic [9], conductometric [10], cantilever [11], fluorescent pH sensor [12] and potentiometric pH sensors [13] have constructed based on the requirement and applications. These kinds of sensors are capable of applying in various fields of chemical, biological, clinical, ecology, etc., as a real time pH sensor. Above the sensors, CMOS based ISFET pH sensor is a well-known sensor for real time pH application with visible images. Previously, the CMOS sensor was proven in bioscientific applications as a DNA, RNA, protein and peptide sensor, array platform [14], impedance sensor [15], antigen–antibody sensor [16,17], blood glucose sensor [18,19] and chemical sensor, etc. [20]. In addition, CMOS integrated pH sensor has been utilized in DNA analysis [21] that proves the sensor is capable to apply in the biochemical analysis. CMOS image sensor integrated electric sensing functionality has performed as an optical pH sensor [22], multifunctional pH image sensor [23] and dual pH sensor [24]. This system contains temperature sensor, heat resistant, signal processing and control circuitry integrated on-chip platform [21], and few sensors are time-consuming process in pH monitoring. As an advanced approach, smartphone carried out the calorimetric based pH paper analysis by RGB color intensities [25]. According to the aforementioned concepts, we have developed an improved method of digital type calorimetric pH monitoring system using CMOS image sensor with the aim of real time toxic chemical detection. In addition, the CMOS based pH detection system has not required any sensor modification approaches, constant light requirement, and provided the semi-quantitative and quantitative results with on-site monitoring approach.

Currently, we have developed a CMOS image sensor based pH monitoring for real time applications. pH indicator blended polyvinyl alcohol (PVA) was used to fabricate the thin hydrogel film. Various pH solutions (pH 1–14) were applied over the hydrogel film, and different color produces from red, green and blue (RGB) based on the pH range. The chip could analyze semi-quantitatively by naked eyes, and CMOS image sensor monitored the accurate quantitative detection. Moreover, physical and chemical properties of the chip can be easily modified by applying the cross linking agent and titanium dioxide (TiO_2) nanoparticles. The cross linkers and nanoparticles control the chip structure and color enhancement, respectively. The study proves the CMOS image sensor based pH measurement system is reliable methods and proved that this is the suitable tool for pH and could be applied for chemical vapor measurement.

2. Materials and methods

2.1. CMOS image sensor

In this study, analysis was performed by NOON0PC30L, 110,000 active pixel single chip, RGB color CMOS image sensor (sponsored by Silicon File Technologies). The sensor chip contains 376 × 314 multi-pixel photon arrays, and is connected with 10 bit range of analog to digital conversion (ADC) circuits to convert the photons into a digital number. The experiment was performed under ordinary living room lights (visible region 400–700 nm) that fixed on the ceiling. The background light intensity could be standardized in sensor by changing the exposure time, and analog gain value.

2.2. Fabrication of hydrogel film

For film fabrication, 1:100 ratio of polyvinyl alcohol (PVA) dissolved in water and kept under stirring with 90 °C till dissolved. Then, 500 μL glutaraldyhyde added as cross linking agent and kept stirring for 30 min. Followed by, 0.2 g of TiO_2 nanoparticles was added into the hydrogel mixture and kept for probe sonication with 50 A for 10–15 min to disperse the particle uniformly into the hydrogel mixture. Then, 8 mL of the readily available universal pH indicator was added and mixed thoroughly. Approximately 1 mm thickness of thin film prepared by hydrogel casting on the cover glass slips (22 mm × 22 mm) and the cast films were dried in hot air oven under 60 °C.

2.3. pH buffers preparation

In buffer preparation, acidic and basic range of various pH solutions (pH 1–14) were prepared using di-sodium phosphate, citric acid, hydrochloric acid, sodium hydroxide, sodium carbonate and sodium bicarbonate with the linear pH level. Conventional pH meter and pH paper confirmed pH ranges of prepared solutions. Fig. 1 shows the accuracy of the pH solution measured by pH paper, which corresponded to the pH standard. CMOS image sensor based pH analysis is the very simple and rapid method. Small drops of different pH level (pH 1–14) solutions were applied to the 14 individual hydrogel films. After few seconds, hydrogel absorbed the solutions and developed the color based on the pH range. Red, green, blue and RGB-related colors developed in the film and were exposed on the CMOS image sensor to analyze the pH range quantitatively.

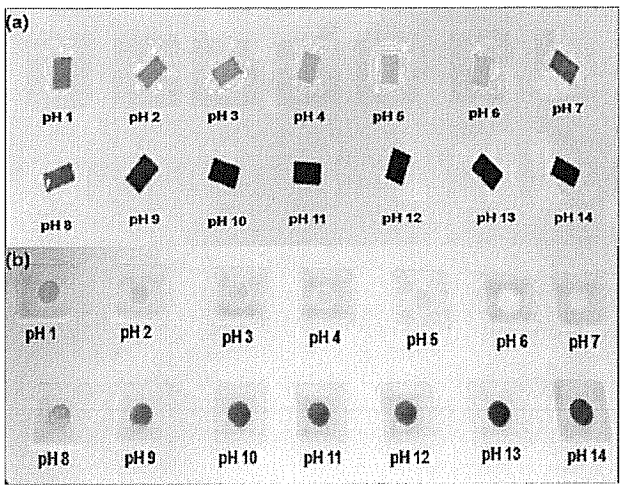


Fig. 1. Various pH level analyses on pH paper and hydrogel film shows different color based on the pH range. (a) pH paper not showing color variation after pH 11 and (b) hydrogel film shows the color differentiation till pH 14.

3. Results and discussions

3.1. Suitable hydrogel film for pH analysis

Thin hydrogel films were fabricated using PVA. Generally, PVA hydrogel has been swelling and shrinking nature when treated with acidic and alkaline solution that may influence the reproducibility of the experiment. Thus, glutaraldehyde has used as a cross linking agent to eliminate the swelling and shrinking of the thin hydrogel layer. According to the previous report, glutaraldehyde can protect the structure of hydrogel and control the swelling and shrinking ratio up to 90%. Here, the small amount of applied pH solution absorbed fully by the hydrogel film and no swelling, and shrunken has developed in the film. Previously, hydrogel films were highly transparent, glassy surface and easily transport the atmospheric light through the film that may influence in consistence of pH analysis, photon transfer or color developing (see ESI, Fig. S1). To control the external influences in pH analysis, TiO_2 nanoparticle applied in chip fabrication, which helps to develop the opaque chip and enhance the accurate color development. Moreover, hydrogel matrix and TiO_2 nanoparticles has not influenced to the reaction. And the film could develop the consistent color based pH range that is not associated with chemicals. Hence, it will produce the same color and digital out data when applied the real sample. In addition, powder form of TiO_2 is great opacifier, chemical vapor depositors [26] and whitener in the products of paints, coating, inks, etc. Thus, TiO_2 nanoparticles help to develop the technically suitable opaque chip that allowed to pass the consistent photons which proves the hydrogel film is suitable to analyze the various pH solutions by CMOS image sensor.

3.2. CMOS image sensor based pH analysis

For pH analysis, hydrogel films reacted with pH solutions and produced a different color on each pH range. Color development was confirmed the pH level as semi-quantitatively by naked eyes. pH 1 shows red color, and the color faded in subsequent pH ranges; and no color changes observed in neutral pH 7. Further, the color turned to greenish blue in pH 8 and changed to deep purplish blue at pH 14. Fig. 1((a) and (b)) shows the various color developments on pH paper and hydrogel film, respectively. Herein, no color differences were observed after pH 11 in pH paper. However, hydrogel films exhibited the accurate color differences until pH 14. Subsequently, CMOS image sensor absorbed the film's color and RGB photon intensities converted into digital numbers with the aid of an ADC. The digital output RGB intensities given in Fig. 2(a) show the individual value of each pH range. Moreover, RGB color value has been determined by CMOS image sensor how CMOS eyes captured the film color. Since, CMOS image sensor can capture and store the film color when exposed on the sensor. Fig. 2(b) shows the various RGB color images captured by CMOS sensor, and the RGB intensities corresponded with the screen shot images stored by the sensor.

3.3. RGB lab color space analysis

Moreover, CIE 1931 lab color space indicated RGB color code of the hydrogel film and regulates to simple RGB analysis. The most recognized methods of CIE system determine the chromaticity of the color by X and Y parameters. Fig. 3(a) represents the hydrogel pH film's RGB intensities on 2D chromaticity diagram obtained from CMOS image sensor. Moreover, Fig. 3(c) Euclidian distance shows the color differences of ΔRGB value between the untreated hydrogel film and each pH solution treated hydrogel film. And is a simple and convenient method to differentiate the pH range. The formula of Euclidian distance has been given in the Supplementary information (see ESI S2). The CMOS sensor based chemical or biological analysis is an efficient method in recent times. Indeed, the CMOS based pH monitoring system is very simple and highly desirable one due to the capability of rapid on-site monitoring, equipment-free user friendly system and needless to spend more time to calibrate the instrument or analysis. Further, the pH sensing system moves toward the next level of study, which is CMOS image sensor based toxic chemical detection and their concentration detection. Based on the concepts Fig. 4 schematic representation has displayed as proposed model of smartphone based toxic chemical detection. Generally, CMOS image sensors are available in mobile phone camera and easy to incorporate into other portable devices. The film has to modify to sense the chemical compounds, concentration of chemicals along with the pH level. The sensor observed the calorimetric film, and the RGB values are converted into the digital units with the help of ADC. Further, the chemical detection application will confirm the pH level, chemical compounds and the concentrations; subsequently, the respective information will be displayed on the smartphone screen with the on-site monitoring approach.

Recently, a number of chemical sensor arrays have been developed in an expensive manner. Certainly, conventional analytical tools such as high-performance liquid chromatography (HPLC) [27], gas chromatography (GC) [28], capillary electrophoresis and mass spectroscopy are considered as the most reliable system for the chemical analysis [29]. However, expensive device, requirements of well trained operator, time-consuming process and non-portability are reasons for the peoples associate with modern sensors. In addition, chemical sensing with fluorescence [30], carbon-nanotubes [31], microcantilever [32] and liquid crystals [33] have been developed with limited ability. Here, the

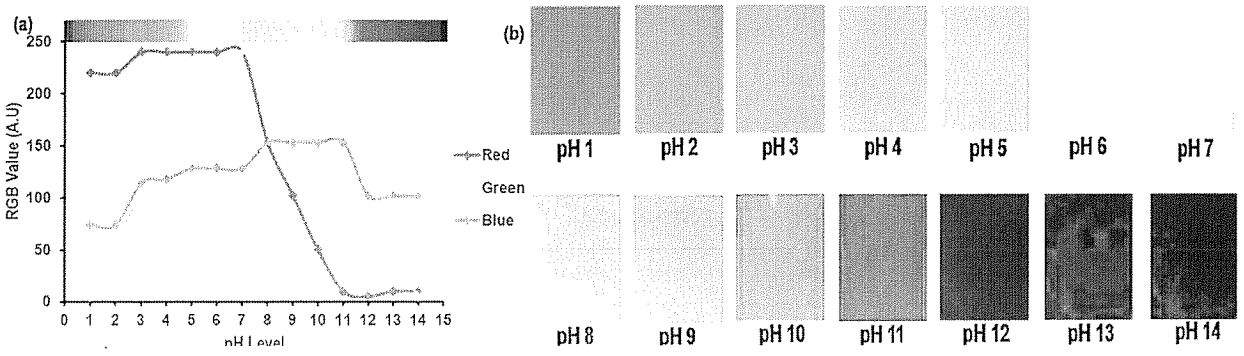


Fig. 2. CMOS image sensor based RGB detection (a) RGB photon intensities of various pH level solutions and (b) CMOS image sensor captured the hydrogel film images of various pH level solutions.

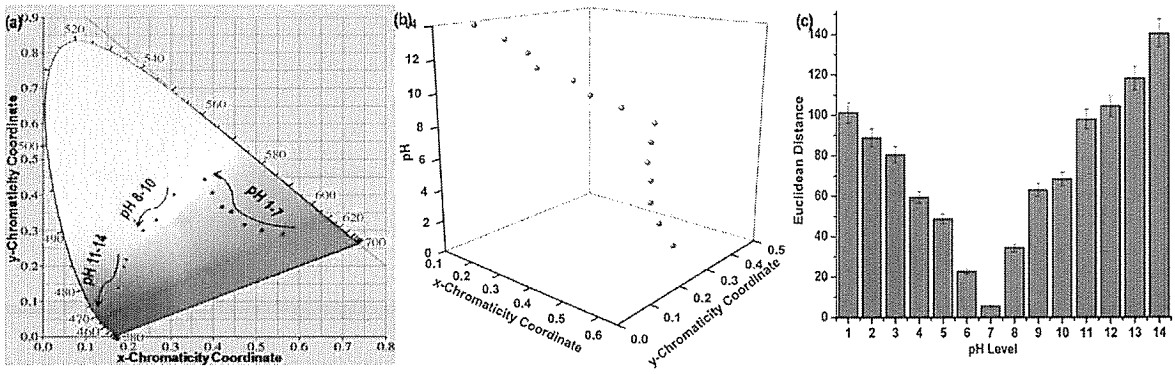


Fig. 3. pH hydrogel colors in CIE 1931 color space and Euclidean distance value (a) RGB color represented in CIE 1931 color space, (b) the relation between xy coordinates with the pH values and (c) total Euclidean distance of the ΔRGB represents the distances of each pH value.

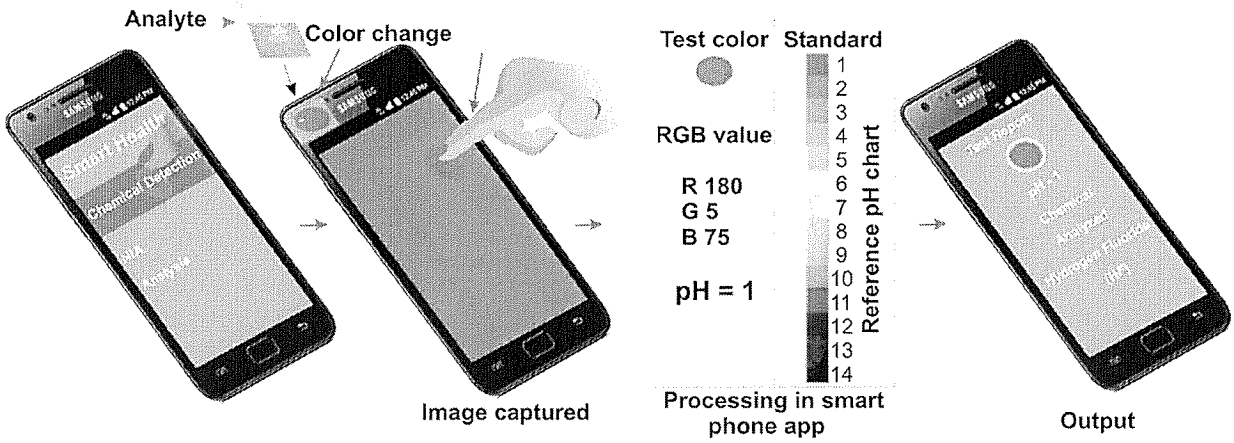


Fig. 4. Schematic representation of smartphone based pH and toxic chemical analysis with on-site monitoring system.

hydrogel film has been potential to absorb the HCL, ammonia, formaldehyde, and hydrogen fluoride vapor, hence, the TiO_2 nanoparticle act as chemical vapor deposition on the substrate [26]. However, necessary modification is needed for the toxic chemical detection.

4. Conclusions

A new challengeable sensing method has developed to quantify the chemical ions by CMOS image sensor based RGB color variation. The technically suitable hydrogel film produces the accurate color development, according to the pH range of solutions. The accurate color difference shows the efficiency of pH detection system and RGB intensities linearly correlated to color developed in the hydrogen film. A detailed study under progress on CMOS image sensor based toxic chemical detection with necessary modification in the detection system will be communicated in the near future. This highly sensitive and user friendly CMOS image sensor based pH detection is a promising approach for real time pH analysis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.aca.2014.12.015.

References

[1] D. Wencel, T. Abel, C. McDonagh, Optical chemical pH sensors, Anal. Chem. 86 (2013) 15–29.
[2] Y. Wang, M.S.S. Chow, Z. Zuo, Mechanistic analysis of pH-dependent solubility and trans-membrane permeability of amphoteric compounds: application to sildenafil, Int. J. Pharm. 352 (2008) 217–224.
[3] M. Yuqing, C. Jianrong, F. Keming, New technology for the detection of pH, J. Biochem. Biophys. Meth. 63 (2005) 1–9.
[4] L. Feng, C.J. Musto, J.W. Kemling, S.H. Lim, K.S. Suslick, A colorimetric sensor array for identification of toxic gases below permissible exposure limits, Chem. Commun. 46 (2010) 2037–2039.
[5] M.C. Janzen, J.B. Ponder, D.P. Bailey, C.K. Ingison, K.S. Suslick, Colorimetric sensor arrays for volatile organic compounds, Anal. Chem. 78 (2006) 3591–3600.
[6] S. Yajima, T. Nakajima, M. Higashi, K. Kimura, Drastic selectivity reversal on crown-ether based ion-sensing membranes made of ordered mesoporous silica and conventional sol–gel derived one, Chem. Commun. 46 (2010) 1914–1916.
[7] S.R. Chang, H. Chen, A CMOS-compatible, low-noise ISFET based on high efficiency ion-modulated lateral-bipolar conduction, Sensors (Basel) 9 (2009) 8336–8348.
[8] S.K. Mishra, B.D. Gupta, Surface plasmon resonance based fiber optic pH sensor utilizing Ag/ITO/Al/hydrogel layers, Analyst 138 (2013) 2640–2646.
[9] Q. Cai, K. Zeng, C. Ruan, T.A. Desai, C.A. Grimes, A wireless, remote query glucose biosensor based on a pH-sensitive polymer, Anal. Chem. 76 (2004) 4038–4043.
[10] Y. Chen, S.C. Mun, J. Kim, A wide range conductometric pH sensor made with titanium dioxide/multiwall carbon nanotube/cellulose hybrid nanocomposite, IEEE Sens. J. 13 (2013) 4157–4162.

[11] H.-F. Ji, K.M. Hansen, Z. Hu, T. Thundat, Detection of pH variation using modified microcantilever sensors, Sens. Actuators B: Chem. 72 (2001) 233–238.
[12] S. Uchiyama, Y. Makino, Digital fluorescent pH sensors, Chem. Commun. 19 (2009) 2646–2648.
[13] K.-K. Shiu, F. Song, H.-P. Dai, Potentiometric pH sensor with anthraxquinone sulfonate adsorbed on glassy carbon electrodes, Electroanalysis 8 (1996) 1160–1164.
[14] V. Stadler, M. Beyer, K. Konig, A. Nesterov, G. Torralba, V. Lindenstruth, M. Hausmann, F.R. Bischoff, F. Breitling, Multifunctional CMOS microchip coatings for protein and peptide arrays, J. Proteome Res. 6 (2007) 3197–3202.
[15] K.T.C. Chai, J.H. Davies, D.R.S. Cumming, Electrical impedance tomography for sensing with integrated microelectrodes on a CMOS microchip, Sens. Actuators B: Chem. 127 (2007) 97–101.
[16] J.P. Devadhasan, M. Marimuthu, S. Kim, M.G. Kim, A CMOS image sensor to recognize the cardiovascular disease markers troponin I and C-reactive protein, Anal. Bioanal. Chem. 402 (2012) 813–821.
[17] J. Devadhasan, S. Kim, CMOS image sensor based HIV diagnosis: a smart system for point-of-care approach. BioChip J. 7 (2013) 258–266.
[18] J.P. Devadhasan, S. Kim, Toward CMOS image sensor based glucose monitoring, Analyst 137 (2012) 3917–3920.
[19] J.P. Devadhasan, S. Kim, C.S. Choi, CMOS image sensors as an efficient platform for glucose monitoring, Analyst 138 (2013) 5679–5684.
[20] A. Hierlemann, D. Lange, C. Hagleitner, N. Kerness, A. Koll, O. Brand, H. Baltes, Application-specific sensor systems based on CMOS chemical microsensors, Sens. Actuators B Chem. 70 (2000) 2–11.
[21] C. Toumazou, L.M. Shepherd, S.C. Reed, G.I. Chen, A. Patel, D.M. Garner, C.-J.A. Wang, C.-P. Ou, K. Amin-Desai, P. Athanasiou, H. Bai, I.M.Q. Brizido, B. Caldwell, D. Coomber-Alford, P. Georgiou, K.S. Jordan, J.C. Joyce, M. La Mura, D. Morley, S. Sathyavruthan, S. Temelso, R.E. Thomas, L. Zhang, Simultaneous DNA amplification and detection using a pH-sensing semiconductor system, Nat. Meth. 10 (2013) 641–646.
[22] H. Nakazawa, M. Ishida, K. Sawada, Progressive-type fused pH and optical image sensor, Jpn. J. Appl. Phys. 49 (2010) 04DL04.
[23] H. Nakazawa, H. Ishii, M. Ishida, K. Sawada, Reduction of interference between pH and optical output signals in a multimodal bio-image sensor, IEEE Sens. J. 11 (2011) 2718–2722.
[24] Tokuda, A. Yamamoto, K. Kagawa, M. Nunoshita, J. Ohta, A CMOS image sensor with optical and potential dual imaging function for on-chip bioscientific applications, Sens. Actuators A: Phys. 125 (2006) 273–280.
[25] L. Shen, J.A. Hagen, I. Papautsky, Point-of-care colorimetric detection with a smartphone, Lab Chip 12 (2012) 4240–4243.
[26] P. Carmichael, D. Hazafy, D.S. Bhachu, A. Mills, J.A. Darr, I.P. Parkin, Atmospheric pressure chemical vapour deposition of boron doped titanium dioxide for photocatalytic water reduction and oxidation, Phys. Chem. Chem. Phys. 15 (2013) 16788–16794.
[27] R. Subramaniam, C. Astot, L. Juhlin, C. Nilsson, A. Östin, Direct derivatization and rapid GC–MS screening of nerve agent markers in aqueous samples, Anal. Chem. 82 (2010) 7452.
[28] W.A. Harris, P.T.A. Reilly, W.B. Whitten, Detection of chemical warfare-related species on complex aerosol particles deposited on surfaces using an ion trap-based aerosol mass spectrometer, Anal. Chem. 79 (2007) 2354–2358.
[29] J. Lee, S. Seo, J. Kim, Colorimetric detection of warfare gases by polydiacetylenes toward equipment-free detection, Adv. Funct. Mater. 22 (2012) 1632–1638.
[30] (a) T.J. Dale, J. Rebek, Fluorescent sensors for organophosphorus nerve agent mimics, J. Am. Chem. Soc. 128 (2006) 4500–4501;
(b) T. Dale, J. Rebek, Hydroxy oximes as organophosphorus nerve agent sensors. Angew. Chem. Int. Ed. 48 (2009) 7850–7852;
(c) S.-W. Zhang, T.M. Swager, Fluorescent detection of chemical warfare agents: functional group specific ratiometric chemosensors, J. Am. Chem. Soc. 125 (2003) 3420–3421.
[31] K.A. Joshi, M. Prouza, M. Kum, J. Wang, J. Tang, R. Haddon, W. Chen, A. Mulchandani, V-type nerve agent detection using a carbon nanotube-based amperometric enzyme electrode, Anal. Chem. 78 (2005) 331–336.
[32] Y. Yang, H.-F. Ji, T. Thundat, Nerve agents detection using a Cu2+/l-cysteine bilayer-coated microcantilever, J. Am. Chem. Soc. 125 (2003) 1124–1125.
[33] K.D. Cadwell, N.A. Lockwood, B.A. Nellis, M.E. Alf, C.R. Willis, N.L. Abbott, Detection of organophosphorous nerve agents using liquid crystals supported on chemically functionalized surfaces, Sens. Actuators B: Chem. 128 (2007) 91–98.

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