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Research review paper

Photonic hydrogel sensors☆

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ABSTRACT

Analyte-sensitive hydrogels that incorporate optical structures have emerged as sensing platforms for point-of-care diagnostics. The optical properties of the hydrogel sensors can be rationally designed and fabricated through self-assembly, microfabrication or laser writing. The advantages of photonic hydrogel sensors over conventional assay formats include label-free, quantitative, reusable, and continuous measurement capability that can be integrated with equipment-free text or image display. This Review explains the operation principles of photonic hydrogel sensors, presents syntheses of stimuli-responsive polymers, and provides an overview of qualitative and quantitative readout technologies. Applications in clinical samples are discussed, and potential future directions are identified.

Contents

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1. Introduction

1.1. The need for photonic sensors

The *in vitro* diagnostics (IVD) market was valued at $53.3 B in 2013 and projected to reach $69.1 B by 2017 (Markets&Markets, 2013; Shields and Sale, 2014). While the global IVD market is expected to grow at a compound annual growth rate (CAGR) of 5.4% until 2020, the emerging markets (Brazil, China, and India) are projected to experience 10–15% growth (Grand View Research, 2014; Park, 2014; Rosen, 2014). This growth is mainly driven by (i) the shift to personalized medicine, (ii) the need for minimally invasive rapid diagnostics, (iii) aging populations in the developed world, and (iv) geographical market expansion and the increase in the demand from emerging economies due to infectious and chronic diseases (Akram et al., 2015; Yetisen et al., 2015b). Although the market is restrained by stringent regulations (Mansfield et al., 2005), there is a growing number of commercial products such as diagnostic tests for HIV, hepatitis, HPV, diabetes, blood coagulation, fertility, immunoassays, hematology, urinalysis, molecular diagnostics, and blood gas analyses (Roche, 2014; Siemens, 2014).

The fastest growing segments of the IVD market are molecular diagnostics and point-of-care (POC) testing, which have attracted $650 million in investments over the past five years (Kalorama Information, 2014; Parmar, 2013; St John and Price, 2014). The expansion of POC diagnostics may be attributed to the government policies to reduce high-cost healthcare provisions by decreasing the number of patients in secondary and tertiary hospitals (Price and Kricka, 2007). POC diagnostics consist of small benchtop or handheld devices that provide qualitative and semi-quantitative information of target analytes in the field or at home (Chin et al., 2012). Benchtop products include critical care analyzers, as well as hematology and immunology assays. Handheld devices consist of blood glucose tests, dipsticks for urinalysis and lateral-flow tests (Yetisen et al., 2013). These handheld devices are simple, rapid, robust in storage and usage, and low cost. Thus, they are universally applicable for disposable and sensitive POC diagnostics. The sensing mechanisms of handheld POC diagnostics are based on molecular probes, enzymes, antibody–antigen interactions, and electrochemistry. Dipstick tests such as urine test strips utilize molecular dyes and enzymatic reactions. Such assays are multiplexed and allow the analyses of up to 12 biomarkers. Recently, new capabilities have been proposed for these formats to execute multistep processes (Cate et al., 2015). A significant limitation of assays based on molecular dyes is that they have different absorption peaks in the visible spectrum (Martinez et al., 2008). The interpretation of such assays may be erroneous due to the subjective readouts and uneven development of colors throughout the surface. Their semi-quantitative readouts require handheld analyzers. Additionally, the number of analytes and molecular reactions that can be combined with chromogens is limited. Hence, standardization of color shift in the visible spectrum and expansion to a broad range of analytes are significant challenges in molecular dye based assays (Yetisen, 2015f). Furthermore, while the colorimetric information is universal, some applications require written readouts for reporting the concentration of a target analyte. The lateral-flow format is typically based on immunochromatography involving immobilized antibodies and functionalized gold nanoparticles, which were originally designed for qualitative readouts. Recently, newer capabilities were introduced to this platform to obtain semi-quantitative readouts. For example, ClearblueDigital Pregnancy Test (Swiss Precision Diagnostics) offers on-chip quantification of chorionic gonadotropin (hCG) to estimate the conception date (Pike et al., 2013). Among the over the counter products, blood glucose monitoring is the largest market segment due to the prevalence of 382 million diagnosed diabetics worldwide (Danaei et al., 2011; Diabetes Atlas, 2013). Glucose assays are based on enzymes such as glucose oxidase (GOx), glucose dehydrogenase (GDH) or hexokinase, which are read out by handheld devices. However, such electrochemical and enzymatic assays are prone to error due to interference from high partial pressure of oxygen, maltose, and hematocrit (Tonyushkina and Nichols, 2009). Additionally, these assays do not allow real-time or on-demand reusable measurements due to the irreversibility of reactions and assay configurations. The development of all-in-one platforms that can report on the concentrations of target analytes by either utilizing the entire visible spectrum, or producing written information or display images without electrical components is needed to create low-cost, robust and quantitative POC diagnostics.

The limitations of the existing sensors have motivated the investigation of label-free structural color platforms that quantitatively report on the concentration of target analytes (Zhao et al., 2010a). Structural coloration was first observed by Robert Hooke and Isaac Newton in peacock feathers and mother of pearl (nacre) (Hooke, 1665; Newton, 1704). To understand structural coloration, Thomas Young demonstrated that light could behave like a wave, producing diffraction from sharp edges or slits (Young, 1804). A wide array of mechanisms has evolved to create diverse optical structures, including multilayer reflectors, photonic crystals, and light scattering structures (Fudouzi, 2011; Zhao et al., 2012). These structural colors also coincidentally form in composite and fibrous structures (Martinez-Hurtado et al., 2013; Vignolini et al., 2012; Vukusic and Sambles, 2003). Structural coloration in nature occurs mainly through diffraction, but also refraction, plasmonics, or a combination of both, sometimes complementing pigments. The fundamentals of dynamic coloration in photonic structures in nature represent a potential for constructing transducers that can be modulated by physical changes.

Structural color-based transducers have advantages over traditional signal processing approaches in terms of response-range tuning and label-free reporting. Advances in photography, polymer chemistry, laser physics, and organic synthesis have enabled bottom-up and top-down fabrication of photonic structural colors. Hence, the developments in photonic structures have set the stage for the incorporation of structural colors in analyte-sensitive hydrophilic polymers (hydrogels) for sensing applications. In contrast to the absorption of light by chromophores and electrochemistry, photonic hydrogel sensors incorporate nanostructures that modulate the optical properties of incident light. Such photonic structures can be created in/on hydrogels through self-assembly or laser writing techniques. Upon interacting with a target analyte, hydrogels undergo volumetric changes, which affect the physical and/or optical properties of the photonic structures. These photonic structures serve as transducers to quantify the concentration of analytes through changes in spatial periodicity in their dielectric constants, plasmonic resonance shifts, or effective refractive index. They typically modulate the optical characteristics of electromagnetic