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3D hydrogel scaffold doped with 2D graphene materials for biosensors and bioelectronics

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ABSTRACT

Hydrogels consisting of three-dimensional (3D) polymeric networks have found a wide range of applications in biotechnology due to their large water capacity, high biocompatibility, and facile functional versatility. The hydrogels with stimulus-responsive swelling properties have been particularly instrumental to realizing signal transduction in biosensors and bioelectronics. Graphenes are two-dimensional (2D) nanomaterials with unprecedented physical, optical, and electronic properties and have also found many applications in biosensors and bioelectronics. These two classes of materials present complementary strengths and limitations which, when effectively coupled, can result in significant synergism in their electrical, mechanical, and biocompatible properties. This report reviews recent advances made with hydrogel and graphene materials for the development of high-performance bioelectronics devices. The report focuses on the interesting intersection of these materials wherein 2D graphenes are hybridized with 3D hydrogels to develop the next generation biosensors and bioelectronics.

1. Hydrogel as 3D material

1.1. Hydrogels as an adhesive scaffold for biotech applications

Hydrogels are three-dimensional networks of hydrophilic polymers that can store a large amount of water or biological fluid compared to their own mass. They closely resemble natural tissues due to their significant structural water content and relatively soft consistency (Peppas et al., 2000). Their ability to swell by enclosing water within their structure is determined by polymer types (e.g., hydrophilicity) as well as the degree of polymer crosslinking. For example, the degree of crosslinking defines the pore size of swollen network, and hence the rate of passive diffusion, which is one of the key design parameters in a controlled drug delivery system (Hamidi et al., 2008; Zubris et al., 2012). The swelling capacity can be further engineered to be responsive to certain stimuli, such as temperature (Jeong et al., 1997; Park, 1999), pH (Chen et al., 2004; Siegel and Firestone, 1988; Torres-Lugo and Peppas, 1999), light (Charati et al., 2010), magnetic field (Satarkar and Hilt, 2008; Zrinyi, 2000), electric charge (Hou et al., 2012; Liu et al., 2003), and antigen-responsive (Lu et al., 2003; Miyata et al., 1999). Relatively porous network formed through this swelling process allows the rapid movement of target drugs.

Another advantage of most hydrogels is their capability to gel at the desired location through in situ polymerization, allowing for materials that precisely match the contours of the tissue, improving tissue-material integration. This feature allows hydrogels to be injected into or implanted at the target site (Jeong et al., 2000, 1997, 1999), while in situ crosslinking can be triggered chemically or photochemically. In the latter, the energy source such as UV photons activates photosensitive groups in the polymer backbone or pendant groups, initiating polymerization. Conversely, certain functional moieties such as o-nitrobenzyl can initiate the cleavage of the polymeric chains. This photosensitizing capability was found instrumental for precise control of material crosslinking, whereas other types of polymerization cannot be controlled on demand.

Common hydrogel materials include dextran-dendrimer (Artzi et al., 2011; Conde et al., 2015; Oliva et al., 2015a, 2012; Segovia et al., 2015), star-shaped PEO-PLA block co-polymers (Jeong et al., 1999), PEG-PLGA-PEG (Jeong et al., 2000), chitosan (Bhattarai

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et al., 2010; Ruel-Gariepy et al., 2004), PEG-grafted chitosan (Bhattarai et al., 2005), gelatin (Di Silvio and Bonfield, 1999; Yaffe et al., 2003) or heparan sulfate proteoglycan analog (Cai et al., 2005). These hydrogels are highly biocompatible providing with facile encapsulation of cells or drugs. Delicate bioactive functionalities such as growth factors, peptides, and even genes can be readily incorporated into the hydrogel structure without affecting their activity.

A large number of hydrogels conjugated to cell adhesive molecules have been developed in the field of tissue engineering over the last decade (Luo and Shoichet, 2004; Lutolf et al., 2003; Mann et al., 2001; Schukur et al., 2013). They have been mostly used as biomimetic substrates to support three-dimensional cell growth. The use of hydrogels as tissue adhesives has not been as widely reported and can serve as a depot for local release of drugs (Artzi et al., 2009b; Mehdizadeh et al., 2012; Wang et al., 2012b; Xu et al., 2012). It was recently reported that aldehyde-based adhesive chemistry affords tissue- and disease-specific adhesion and that its adhesion strength and degradation rate can be tailored by controlling the physicochemical properties of the hydrogel-forming macromolecules (Artzi et al., 2011; Conde et al., 2015; Oliva et al., 2015a, 2012; Segovia et al., 2015). Dendrimer:dextran adhesive hydrogels developed by *Artzi* and co-workers present a new generation of tissue-specific drug-delivery materials that combine the biocompatibility of hydrogels, capability to be directly injected through in situ polymerization, controlled adhesion and degradation for local and controlled cargo delivery.

Adhesive hydrogels are versatile and promising candidates that can overcome the limitations of traditional tissue adhesives that have been used in various medical procedures and applications, including topical wound closure, supplementing or replacing surgical sutures or staples, and more recently for drug delivery (Oliva et al., 2015b). Some of these adhesive materials have poor mechanical strength and release toxic degradation byproducts (Suzuki and Ikada, 2010). In contrast, hydrogels can mimic the physical-chemical and biological properties of most types of tissues and cellular microenvironments (Hoffman, 2013, Kamata et al., 2015). In addition, hydrogels can effectively carry different nanomaterials (organic and inorganic nanoparticles) or biomolecules (drugs, proteins, DNA/RNA, antibodies, dyes). Extensive review of surface chemistries and biomolecules used in nanomaterials assembly can be found elsewhere (Conde et al., 2014). From stimuli-responsive sensors and actuators to pharmaceutical and biomedical applications, nanocomposite hydrogels have the potential to influence the lives of patients and improve their quality of life.

1.2. Hydrogel as 3D scaffold

Incorporating nanoparticles within the 3D hydrogel network either physically or covalently has been emerging as a viable approach to reinforce hydrogels and to embrace various functionalities, since hydrogels alone often suffer from poor mechanical stability and limited responsiveness to stimuli. The incorporation of 2D nanomaterials such as graphene, for example, can provide hydrogels with unique magnetic, electrical, catalytic, and optical properties as well as remote control actuation capability (see Fig. 1). Nanomaterial-hydrogel conjugates consisting of inorganic nanomaterials (Conde et al., 2014) such as gold (Atala et al., 2006; Conde et al., 2012; Doria et al., 2012), magnetic iron oxide (Lu et al., 2007), silica (Malvindi et al., 2012), quantum dots (Conde et al., 2014), and organic nanomaterials such as carbon nanotubes (Bianco et al., 2005), graphene (Goenka et al., 2014), polymers (Gaharwar et al., 2014), liposomes (MacLachlan 2007), micelles (Park et al., 2006), and dendrimers (Restani et al., 2012) have already been developed as drug and gene delivery systems (Gaharwar et al., 2014). Over the last decade, nanocomposite hydrogels or nanogel-nanoparticles conjugates have found applications in sensing and targeting (Mastronardi et al., 2014), gene therapy (Smith and Lyon, 2012), and drug delivery (Zubris et al., 2012). Recently, variety of nanoparticles were embedded as building blocks into a unifying hydrogel matrix serving as advanced delivery platform (Gaharwar et al., 2014). Hydrogels such as PEG (Dunn et al., 2012; Kim et al., 2012; Sekine et al., 2012), polyacrylamide (Wang et al., 2012a), poly(amine-ester) (Zhang et al., 2010), chitosan (Demarchi et al., 2014), dendrimer (Kojima et al., 2013; Navath et al., 2011), dextran (Artzi et al., 2011, 2009a; Segovia et al., 2015), and gelatin (Ding et al., 2011), have been widely employed as the host matrix.

Nanocomposite hydrogels with tailored functionalities have opened up new possibilities of developing innovative biomaterials for various biomedical applications. The combination of nanomaterials with robust hydrogels can allow for the design of multifunctional, tunable materials that can target, sense, and deliver therapeutics specific to the diseased tissue microenvironment (Ahmad, 2013; Gaharwar et al., 2014). Personalizing nanomaterials can further aid the development of technologies for the early detection, imaging, and identification of molecular signatures of diseases, via individual patient's cellular and molecular profiles. The ultimate goal is sparing patients from the pain and multiple side effects of manifold surgical treatments through a simple and single local administration. Here, we overview and propose the

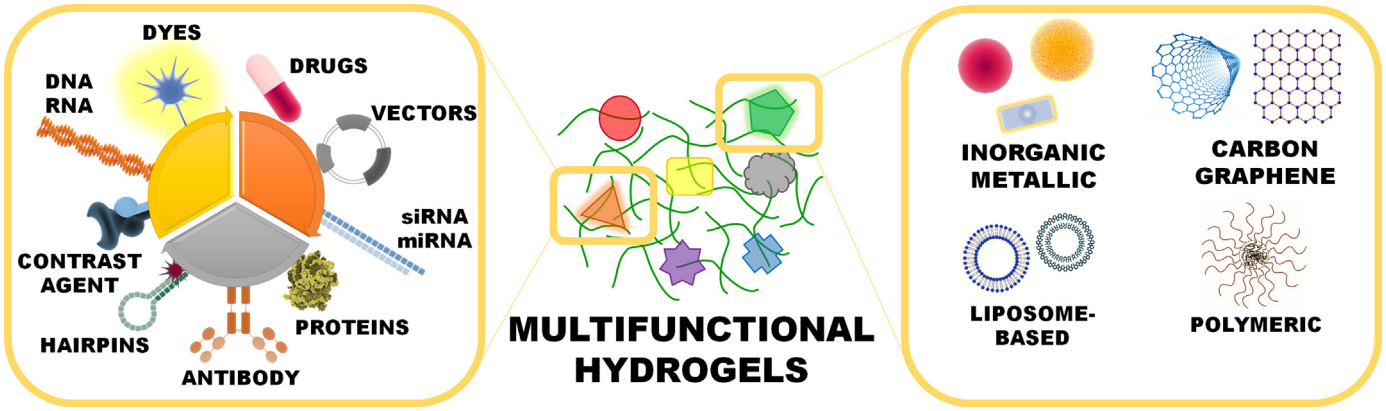

Fig. 1. Multifunctional hydrogels doped with inorganic (gold, iron oxide magnetic, silica, quantum dots, carbon nanomaterials) and organic nanomaterials (polymeric and liposome-based) can be tuned to include multiple functionalities like nucleic acids such as RNA (siRNA, miRNAs) and DNA (molecular beacons, plasmid vectors) used for gene silencing approaches or anti-cancer drug molecules for delivery to the target cell/tissue/organ. Responsive nanomaterials can also trigger a response following external stimuli through the introduction of smart polymers or peptides. Multifunctional systems can carry fluorescent dyes that are used as reporter molecules for tracking and as contrast agents.

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use of 3D hydrogel networks doped with 2D nanomaterials such as graphene to improve the sensing and therapeutic capacity of these hydrogels.

1.3. Intelligent hydrogel 3D materials for biosensing and bioelectronics

The stimuli-responsive hydrogels are an effective signal transducer for sensors and electrical devices (Gawel et al., 2010; Mac Kenna et al., 2015). These materials serve as an intelligent surface for relaying physical, chemical and electrical stimuli to secondary signal transducers (Kumar et al., 2007). In addition to the high fluid-holding capacity, hydrogels can host a large amount of functional moieties that can function as recognition elements for enhanced biosensor selectivity and sensitivity (Wang et al., 2009). In addition, the ability of hydrogels to closely mimic the natural microenvironment contributes to the increased stability of these moieties (Burrs et al., 2015). In the following section, the use of hydrogels as an intelligent substrate for optical, mechanical and electrical transducers in biosensors and bioelectronics applications is discussed (Fig. 2). The responsive behavior of stimuli-responsive hydrogels in terms of wettability switching can be used to develop smart systems for stimuli-responsive release (using pH-, temperature-, and light-responsive hydrogels) of therapeutic cargos or diagnostic molecules and to create smart devices based on electrical, optical or mechanical transduction. For example, hydrogels including specific polymers such as acidic poly(acrylic acid), acidic poly(vinyl pyridine), and basic poly(dimethyl aminoethyl methacrylate) have been developed and used for switching of hydrophilicity or volumetric change. Alternatively, the use of certain polymers that show responsive behavior through changes of inter and intra molecular interactions of chemical groups within the polymer depending on temperature [i.e. poly(N-isopropylacrylamide) or light (i.e. nitrobenzene or azobenzene-based hydrogels] (Kang do et al., 2013). All together, these characteristics incorporated on the hydrogels can be used to produce specific optical, chemical or mechanical output signals.

1.3.1. Optical transduction

Hydrogels have been considered ideal host surfaces particularly for optical sensors owing to their high transparency and optical quality (Haraguchi and Takehisa 2002; Holtz and Asher 1997). Optical sensors based on surface plasmon resonance (SPR) (Endo et al. 2008; Tokarev et al. 2010) and optical waveguide mode spectroscopy (OWS) (Bagal et al. 2007; Wang et al. 2010b) have been reported using hydrogels as a primary optical transducer. In this section, we review the most common applications of hydrogels as optical transducers for SPR-based biosensors.

SPR-based optical sensors offer label-free detection of biomolecular interaction (Srivastava et al. 2015; Yoo and Lee 2015), wherein the plasmonic particles are stimulated by incident light to exert surface plasmon enhanced signal emission. When placed at the interface between materials with different permittivities, they are sensitive to certain changes on thin film such as refractive index change caused by binding of the analytes (Yin et al., 2004). SPR biosensors can detect macromolecules with large molecular weight but only at concentrations above ng/mL, limiting their use in biomedical applications where much lower sensitivity for low molecular weight analytes is typically desired (Kavanagh et al., 2015; Matsui et al., 2005). Coating hydrogel layer on the surface of SPR particles can significantly enhance the sensor sensitivity and selectivity (Andersson et al., 2008; Bahram et al., 2014). These

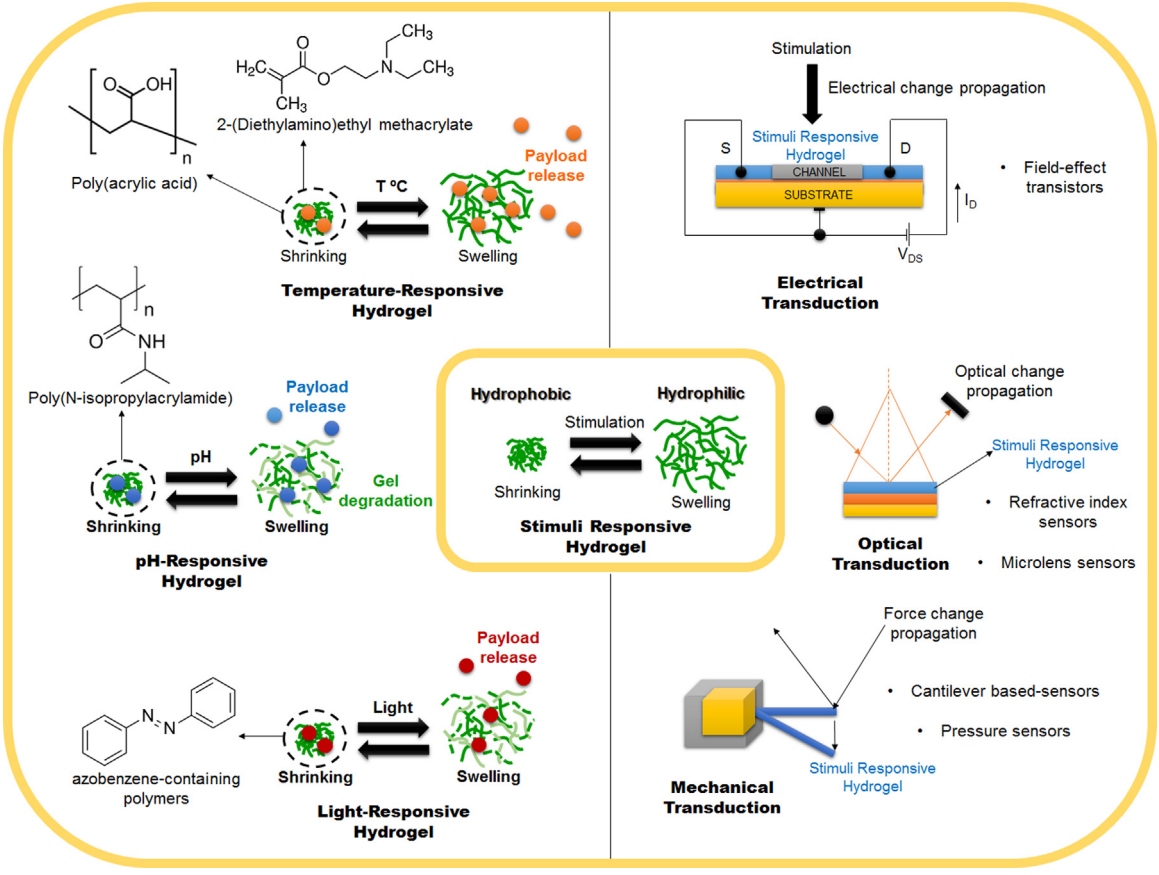

Fig. 2. A schematic diagram showing the application of stimuli-responsive hydrogels used for temperature, pH or light responsive release as intelligent surface for electrical, optical and mechanical transductions.

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hydrogels are impregnated with recognition bioprobes such that they bind and swell/de-swell in the presence of specific analytes. The increase of gel length caused by gel-swelling results in the increase of refractive index (Tierney et al., 2008). The change in swelling state affects the refractive index on the surface of the SPR and amplifies the sensing signal (Mesch et al., 2015). Bioprobes such as enzymes (Endo et al., 2008; Tokarev et al., 2010; Zourob and Goddard, 2005), nucleic acid (Yang et al., 2008; Zhu et al., 2010), and antibodies (Andersson et al., 2008; Huang et al., 2011) have been conjugated with hydrogels to develop highly selective SPR-based sensors. They have been applied to enable the recognition of small molecules such as glucose (Bagal et al., 2007; Tokarev et al., 2010; Zourob and Goddard, 2005), neurotransmitter (Matsui et al., 2005), cholesterol (Tokareva et al., 2006), and NADPH (Raitman et al., 2004).

Hydrogels whose swelling degree changes as a function of pH have been employed as optical transducers for pH measurement (Mishra and Gupta. 2013). For example, an SPR-based optical-fiber pH sensor functions as hydrogels swell or de-swell in response to pH change and subsequently affects the refractive index (Singh and Gupta. 2012). The pH-sensitive hydrogel combined with plasmonic silver nanoparticles were also used to develop an optical sensor that detects an analyte such as glucose (Tokarev et al.. 2010). In this sensor, the glucose levels are measured by detecting the pH changes resulting from the catalytic oxidation of glucose in the presence of glucose oxidase (GOx). This hydrogel was also shown to effectively prevent biomolecules (especially enzymes) from nonspecific binding to nanoparticles, ensuring high specificity to target analytes.

1.3.2. *Mechanical transduction*

Mechanical transduction can be achieved based on hydrogel's 3D polymeric network capability to expand in response to changes in osmotic pressure of the system (Han et al., 2002; Lin et al., 2009). The swelling or shrinking of hydrogel by the stimuli generates large interfacial stresses and, consequently, reversible bending of the cantilever (Bashir et al., 2002; Mao et al., 2006; Peng et al., 2012b). This mechanical stress-induced bending can be amplified and recoded by optical or piezoelectric detectors. Based on this approach, a micro-cantilever coated with pH-responsive hydrogel was developed for pH sensing (VanBlarcom and Peppas, 2011). Many examples of utilizing hydrogels for mechanical transduction can be also found in quartz crystal microbalances (QCM). In QCM, a piezoelectric element made of quartz crystals vibrates at a defined frequency and amplitude (VanBlarcom and Peppas, 2011). This resonance frequency changes as an analyte binds to the hydrogel that is coated onto the surface of piezoelectric element and increases the mass. Such QCMs have been applied for the detection of DNA (Åsberg et al., 2005), glucose (Malitesta et al., 1999), biomarkers (Carrigan et al., 2005), proteases (Stair et al., 2009), and viruses (Wang and Li, 2013) using hydrogels functionalized with selective bioprobes.

1.3.3. *Electrical Transduction*

Electrical sensors are emerging as an attractive alternative strategy for biosensor development due to their exceptionally high sensitivity, sometimes down to femtomolar concentration of analytes (Song and Park, 2011). However, low selectivity is a critical limitation for some applications, especially selective detection of biological analytes (Kim et al., 2009; Song et al., 2012). Therefore, electrical sensors have been often functionalized by bioprobes that have high specificity to biological analytes. The hydrogel surface is an ideal host to carrying bioprobes on the electrodes and transduce target ligand-selective biological reactions to electrical sensors (Heller, 2006). For example, an electrochemical sensor using platinum (Pt) nanoparticles-doped hydrogel as an electrical transducer has been reported (Zhai et al., 2013). The hydrogels offer a capacity to immobilize a large amount of glucose-specific enzymes (i.e., glucose oxidase) as well as an electronically conductive channel for efficient charge transfer. This sensor was found to exhibit high sensitivity and fast response time for the glucose detection.

Another example can be found in an alternative biosensor architecture based on field-effect transistor (FET) which provides high sensitivity, low noise level, and low power consumption. In a typical FET design (Kwon et al., 2015), a semiconductor path (channel) is placed between the source and drain electrodes and the electric current across this channel is determined by a voltage applied through a gate electrode. A change in gate voltage induced by analyte interaction causes a large variation of the current flow through the channel and exerts sensing signal. A number of studies have demonstrated that hydrogels can be efficient electrical transducers for FET-based sensors (Liu and Cui, 2007; Maeda et al., 2012; Sallacan et al., 2002; Zayats et al., 2002). In particular, a FET with hydrogel-coated graphene electrodes and channel has been recently reported (Kim et al., 2014). Hydrogels also provide a physically stable solid-state structure containing large amount of electrolytes to enhance ion sensitivity for FET A large amount of biocompatible polyelectrolyte made of metal-substituted DNAs (M-DNA) was incorporated into the hydrogel network. The hydrogel was then immobilized on source, drain, and gate electrodes as well as the channel. This hydrogel gating allowed enhanced ion selectivity, improved mechanical properties, and exhibited a dynamic response consistent with the superior capacitive (Fig. 3). This was accomplished by dissolving metal-substituted DNA polyelectrolytes into water, which enhanced the ionic conductivity of the system.

2. Graphene

2.1. *General properties of graphene*

Recently, numerous 2D nanomaterials, including metal oxides, hydroxides and chalcogenides, and metal-organic frameworks have been published owing to their changes in properties. Single-layer 2D nanomaterials including MoS_2, WS_2, TiS, TaS_2, and ZrS_2 can be prepared by micromechanical cleavage, lithium intercalation, liquid exfoliation, and hydrothermal reaction (Feng et al., 2015; Huang et al., 2013b; Mas-Balleste et al., 2011). Those ideal methodologies have been extended by graphene preparations. New possibilities for 2D nanomaterials have been realized with emerging graphene applications such as energy, biological and environmental applications. With this in mind, this review will focus on graphene as model 2D nanomaterials and discuss the opportunities imparted by doping 3D hydrogel materials with graphene.

Graphene, has become one of the most attractive materials of choice for solar cell, display device, and sensor components during the past decade. Graphene's sp^2-hybridized carbons in 2D structure shows distinctive properties such as extremely high carrier mobility and capacity, ambipolar field-effect, and a highly tunable conductance unlike other carbon-based nanomaterials including carbon nanotubes and fullerenes. The preparation methods can be divided to two categories: top-down and bottom-up approaches. The top-down methods involve various ways to peel off single graphene sheets from graphite. For example, micromechanical process involves the application of mechanical forces to separate graphene from graphite (e.g. a scotch tape method: Fig. 4**A**) or graphene oxide exfoliation process which produces graphene by chemical or thermal methods in a large scale (Fig. 4**B**). In a bottom-up approach, the graphene is epitaxially grown from carbon

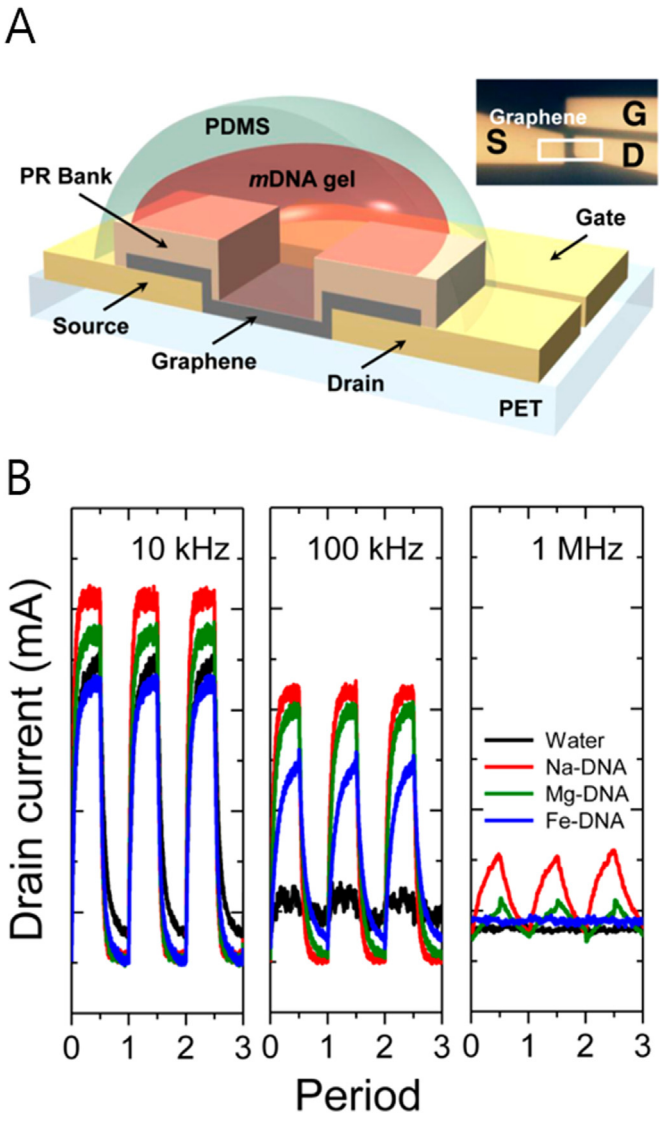

Fig. 3. (A) A schematic cross-section and a photographic plan view (inset) of a metal-substituted DNA (M-DNA) water-gel-gated graphene transistor. (B) Transient current response to square waved V_G pulsed with different frequencies of M-DNA water-gel- and water-gated graphene transistors. Measurements were carried out at V_D=0.1 V and V_G was pulsed between 1.5 and 0.0 V at 10 k, 100 k, and 1 M Hz. (Reprinted with permission from Kim et al. (2014). Copyright 2014 American Chemical Society.)

precursors through chemical vapor deposition (CVD; Fig. 4**C**). Among many existing and potential applications in diverse fields, the use of graphene as a signal transducer is of particular interest in this review. We herein summarize the recent technologies that take advantage of graphene's unique electrical and optical properties to develop high performance biological sensors.

2.2. Graphene-based biosensors

There are various application cases for sensors with graphene such as chemiresistive toxic gas sensors, plasmonic sensors, piezoelectric graphene sensors, and graphene acoustic sensors. Although there are numerous graphene sensors, the two major applications include electrical and optical biosensors based on graphene as those sensors can provide excellent sensing performance compared to other graphene sensors. Consequently, we introduced two cases of graphene biosensors in this review article: Electrical and Optical biosensors.

2.2.1. Electrical biosensors

Graphene-based electrical signal detectors can be readily integrated into existing systems to develop highly sensitive biosensors. For example, graphene-chitosan nanocomposite was used for direct electrochemical detection of glucose through GOx immobilization (Kang et al., 2009). Similar GOx-graphene biocomposite augmented with Au nanoparticles was developed for glucose biosensing (Zhou et al., 2010). These glucose biosensors measure changes in electrochemical properties due to a catalytic oxidation response between glucose and GOx. Alternatively, changes in impedance due to bio-recognition events such as protein binding, DNA binding, and antibody-antigen reactions at the surface of electrodes can be utilized for biosensing. Electrochemical impedance sensing based on functionalized graphene sheets has been developed for the detection of HIV-1 pol gene sequence (Hu et al., 2011). In this example, single-stranded DNA was covalently immobilized on the functionalized graphene and a surface charge change due to target binding was monitored using an electrochemical impedance spectroscopy.

One of the most promising approaches using graphene is an aforementioned FET system. Such integration allows label-free, sensitive, and rapid detection of biomolecules such as DNA, aptamer, protein, and receptors. For example, a large-sized graphene transistor fabricated by transferring as-grown CVD graphene films from Ni to glass substrates was used to host probe-DNA and detect target DNAs (Dong et al., 2010). This graphene-FET biosensor exhibited exceptional sensitivity with detection limit down to 0.01 nM and excellent specificity to distinguish single-base mismatch. Aptamer-modified graphene-FET biosensor also showed label-free, real-time responses against IgE protein at very low concentration (Ohno et al., 2010). This aptasensor enables electrical detection between aptamer and protein at low concentrations by optimizing Debye length, i.e., the distance required for screening the surplus charge. A bioelectronic nose based on graphene transistors with

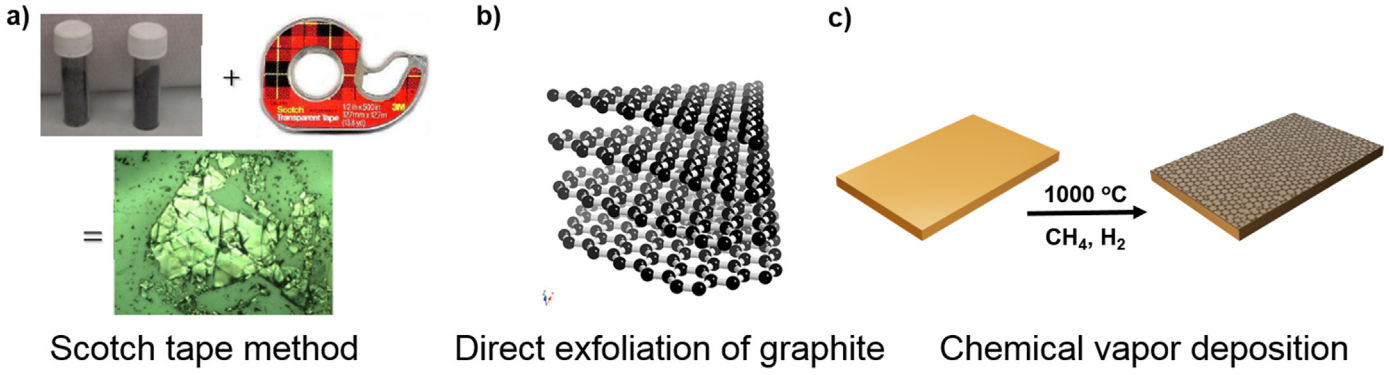

Fig. 4. Various graphene production methods: (A) micromechanical process, (B) graphene oxide exfoliation, and (C) chemical vapor deposition.

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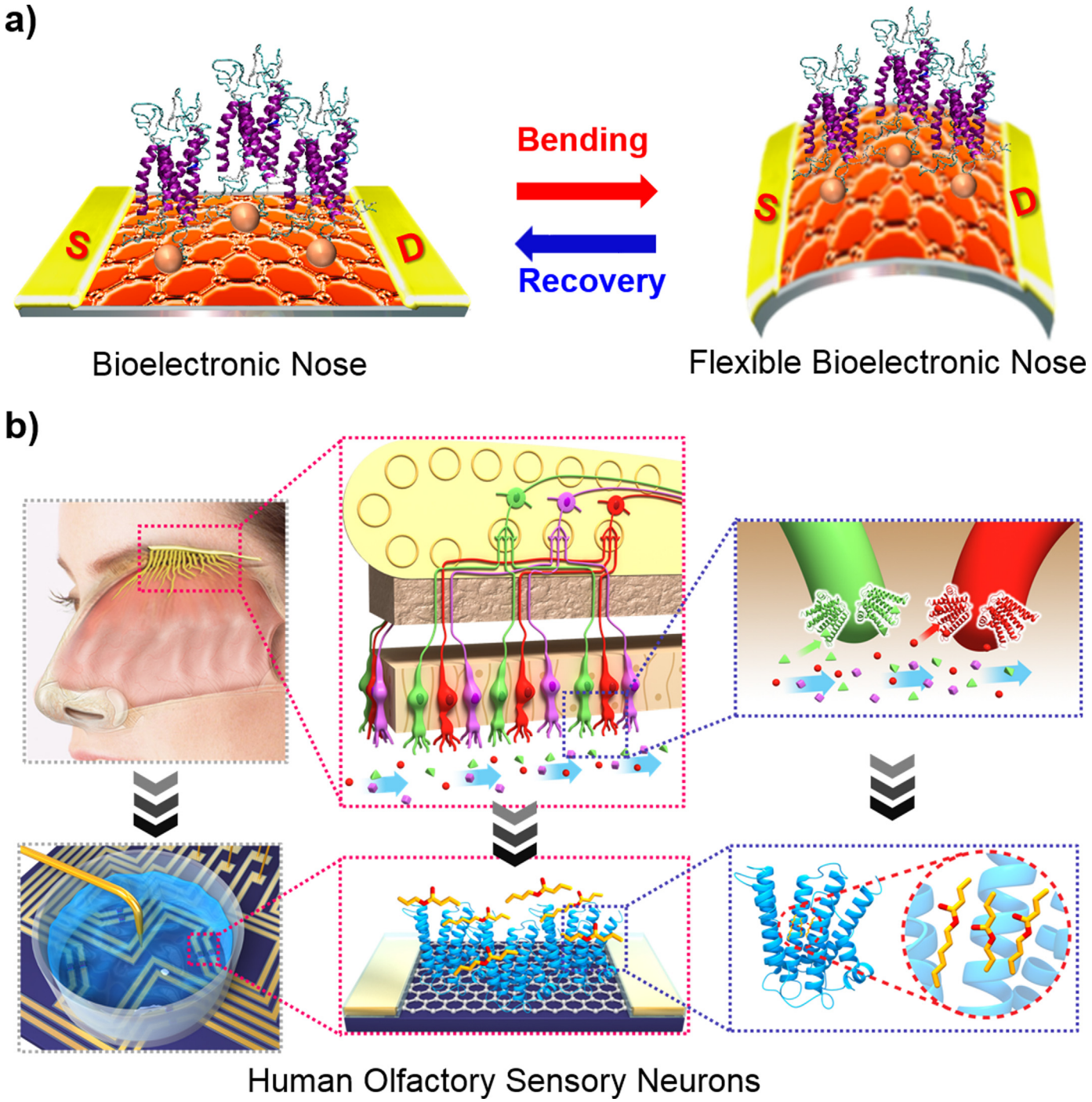

Fig. 5. Bioelectronic noses based on graphene: (A) single and (B) multi-bioelectronic noses. Reprinted with permission from Park et al. (2014) and Kwon et al. (2015). Copyright 2014 and 2015 American Chemical Society.

p-and n-type behaviors, prepared by ammonia and oxygen plasma treatment, respectively, was recently reported to achieve atomic-resolution at extremely low concentrations of odorants (Fig. 5**A**) (Park et al., 2012). A multiplexed graphene-FET system prepared by micropatterning of graphene by photolithography was also developed for human sensory-mimicking system (Fig. 5**B**) (Kwon et al., 2015) that can discern a specific odorant in a mixture.

2.2.2. *Optical biosensors*

Graphene-based optical biosensing systems exploit graphene's unique properties such as photoluminescence and quenching capabilities. The oxidized form of graphene, or graphene oxide (GO), possesses photoluminescence capability resulting from electron-hole pairs localized within a small sp^2 carbon domain embedded in an sp^3 matrix (Loh et al., 2010; Morales-Narváez and Merkoçi, 2012). The GO photoluminescence can be tuned by preparation methods. For examples, GO synthesized by microwave-assisted method has an emission peak at 750 nm under 500 nm excitation (Luo et al., 2009) while GO obtained by Hummers method shows an emission peak at 475 nm under 350 nm excitation (Mei et al., 2010). Further passivation of surface reactive sites by surface alkylamine functionalization under mild conditions renders GO to achieve remarkable fluorescence that is instrumental for biosensing system fabrication (Mei et al., 2010).

Moreover, the GO has various functional groups at its edges (carboxyl) and its basal planes (ester, hydroxyl, and epoxide) which not only enable facile probe anchoring but also high affinity toward water. Alternatively, graphene quantum dots (GQDs) with 1–4 nm diameter and 1–3 nm thickness, prepared by chemical exfoliation of carbon fibers, also exhibit unique optical properties that are useful in biosensing systems (Peng et al., 2012a).

Another popular optical sensing system is based on fluorescence resonance energy transfer (FRET). Graphene can function as either donor or acceptor in FRET scheme in optical biosensing systems. As a donor of FRET, GO-based photoinduced charge transfer (PCT) near-IR fluorescent biosensor was demonstrated to be able to detect dopamine (DA) (Chen et al., 2011). In such a sensor, DA adsorbs onto the surface of GO via multiple noncovalent interactions, such as electrostatic interactions, π-π stacking, and hydrogen bonding thus quenching GO fluorescence. GO-based immune-biosensor was also developed for rapid pathogen detection that can be used for medical diagnostics, food safety screening, and environmental pollution monitoring (Jung et al., 2010). In this biosensor, capturing a target cell is signaled through GO fluorescence quenching due to FRET between the GO and antibody-loaded Au nanoparticles. As a FRET acceptor, GO has been hybridized with an aptamer for DNA detection (Liu et al., 2012) (Fig. 6). In this DNA detection system, fluorophore-labeled DNA probe is attached to the surface of GO. When bound with target DNA, the fluorophore luminescence is quenched by GO. Similar approach of employing dye-labeled peptides has been taken to detect proteins such as thrombin and matrix metalloproteinase (Feng et al., 2011; Liu et al., 2011a).

2.3. Flexible graphene electronics

Graphene's unique electronic properties such as ultra-high charge carrier mobility, high Fermi velocity, a high carrier saturation velocity along with its excellent thermal conductivity, high mechanical strength, and flexibility (Wu et al., 2013) make it an excellent candidate material in electronics such as energy-storage systems, nanotransistors, radio-frequency devices, non-volatile memories, solar energy, energy harvesting system, and flexible display. Examples are abundant and we will herein focus on the use of graphene for flexible electronic device design and fabrication.

Graphenes have been applied to flexible electronics including supercapacitors, nonvolatile memory, touch screens, organic solar cells, electronic paper, light-emitting diodes, heaters and so on. One of the most notable examples is a large-scale flexible plastic electronic based on inkjet-printed graphene (Torrisi et al., 2012). A nonvolatile flexible memory array based on a GO thin film is another interesting example (Jeong et al., 2010). While nonvolatile memory technology based on metal oxides requires a high-temperature fabrication process, flexible graphene memory can produce large-area flexible substrates via spin-casting synthesis at room temperature. This device was demonstrated to exhibit reliable and reproducible bipolar resistive switching with an on/off ratio of ~100 and a retention time of longer than 10^5 s. A package-free flexible organic solar cells with graphene top electrodes was also reported for solar energy application (Liu et al., 2013). In this research, CVD-produced graphene was found to be a viable substitute for common indium tin oxide (ITO) and could offer even higher transparency and better conductance than ITO. When graphene was doped with PEDOT:PSS (Au NPs), the electrode exhibited excellent flexibility and bending stability. A high-performance, flexible, transparent heater based on large-scale graphene with sheet resistance as low as ~43 Ω/sq and ~89% optical transmittance was also reported (Kang et al., 2011).

3. 3D materials doped with 2D materials: hydrogel-graphene hybrids

3.1. Do hydrogel-graphene hybrids impart improved electrical and mechanical properties?

Hydrogels are widely used as biological scaffolds because of their high biocompatibility and water content. However, bulk hydrogels are mechanically week and not sufficiently conductive,

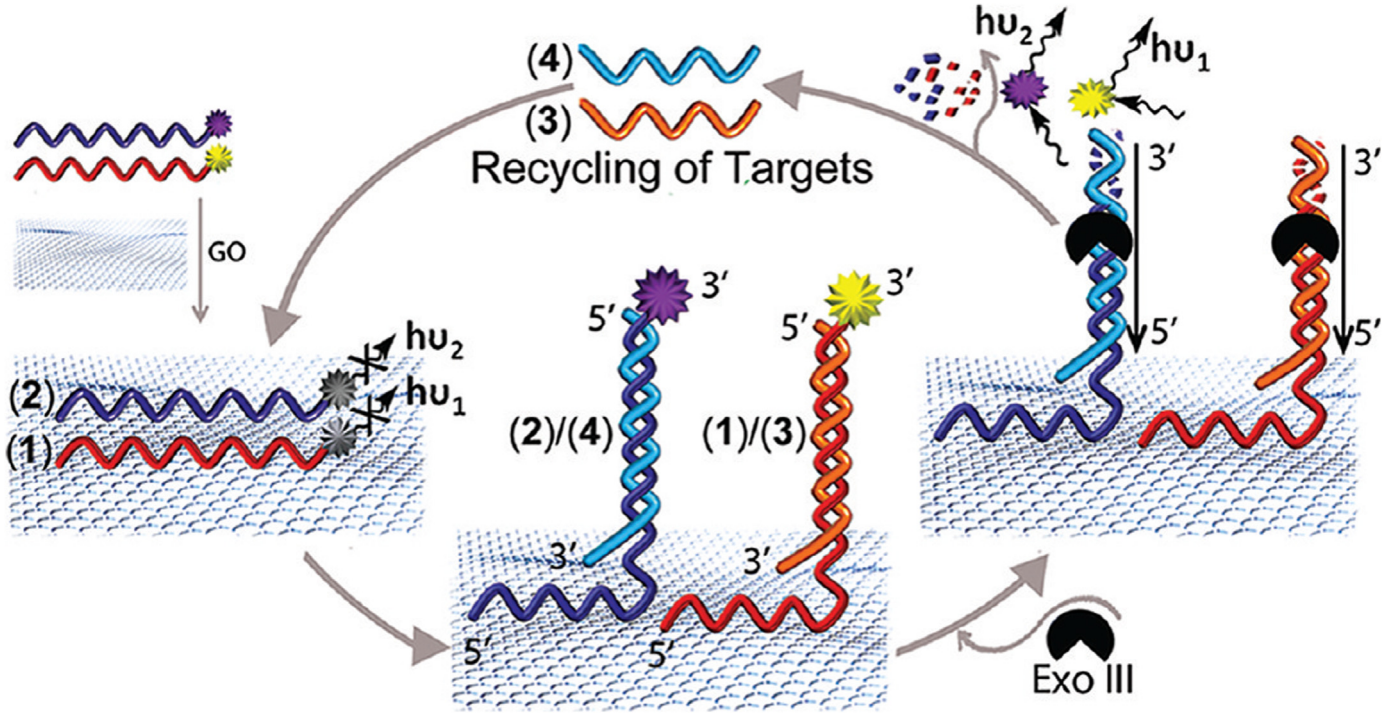

Fig. 6. Amplified multiplexed analysis of DNA using GO as support and the Exo III-triggered recycling of the analytes. Reprinted with permission from Liu et al. (2012). Copyright 2012 American Chemical Society.

limiting their applications to thin film configuration (Ahadian et al., 2014; Wu et al., 2015). Significant efforts have been made to improve electrical and mechanical properties of hydrogels to construct desirable 3D scaffolds, and using 1D and 2D nanomaterials as doping partners within the hydrogel network has been considered a promising approach (Dvir et al., 2011; Shin et al., 2013; You et al., 2011). In particular, graphene has been proposed as an excellent filler for hydrogels due to their outstanding physical, mechanical, and electrochemical properties. The hydrogel-graphene hybrids can tune up electrical, mechanical, and stimuli-responsive properties of hydrogels (Worsley et al., 2012; Zhang et al., 2013). In fact, it has been reported that pristine carbon nanomaterials including graphene show cytotoxicity under specific conditions. Although, the reactivity and the general behavior of carbon nanomaterials in biological media are not fully understood, the toxicity of carbon nanomaterials is often governed by the state of aggregation, length and stiffness. (Jia et al., 2005; Kolosnjaj-Tabi et al., 2012; Zhang et al., 2012). Hydrogels provide an excellent 3D scaffold and porous structure to effectively host a large amount of graphenes and maximize their reactive surface area (Sun and Hur, 2015; Tungkavet et al., 2015). The porous hydrogel network also allows for efficient infiltration of ions or electrolytes, which is critical for developing electrical devices such as capacitors and biosensors (Wang et al., 2010a; Xu et al., 2013a; Zhang et al., 2015). Therefore, the hydrogel-graphene composite structure enables leveraging the excellent sensing properties of graphene while eliminating its potential cytotoxicity.

3.2. Hydrogel-graphene chemistry

Hydrogels possess attractive properties including high biocompatibility and controlled degradation kinetics, as determined by the inherent chemical structures of the 3D scaffold network. Hydrogels produced with synthetic polymers are susceptible to hydrolytic degradation while natural polymers are degraded mainly by enzymatic reactions. Therefore, stability, pore-size, and degradation rate can be controlled by type and degree of cross linking.

The crosslinking of polymers by imine bond formation following the reaction between aldehydes and amines offers rapid and high yield reaction under mild conditions (Artzi et al., 2009a). Imine bond-containing hydrogels have been applied as tissue adhesive materials by virtue of their reaction with reactive amine group on tissue surfaces (Artzi et al., 2009a; Bianco et al., 2005; Goenka et al., 2014; Oliva et al., 2015a, 2012). Carbodiimide agents, such as 1-Ethyl-3-[3-dimethylaminopropyl] carbodiimide (EDC) have also been widely used for crosslinking by activation of carboxylic acid and the reaction with amine groups, generating amide bond (Liang et al., 2004; Rafat et al., 2008). The intermediate state of carbodiimide chemistry is unstable and N-Hydroxysuccinimide (NHS) was used to enhance the reactivity.

Several studies have been reported to investigate the production method and characteristics of 3D hydrogel doped with graphene for numerous bio-applications. Two strategies have been mostly applied to fabricate 3D hydrogel-graphene composite; (1) graphene self-assembly inducing gelation in contrast to the conventional graphene reduction process using hydrothermal (Chen et al., 2013; Lim et al., 2011; Xu et al., 2010) or chemical methods (Chen and Yan, 2011; Sheng et al., 2011); and (2) the use of 2D graphene as a filler to dope previously crosslinked polymeric hydrogel matrix (Fan et al., 2013; Huang et al., 2013a).

Leveraging the hydrogels' characteristics of biocompatibility and tunability, doping of graphene in polymeric hydrogel matrices to create hydrogel-graphene hybrids would potentially eliminate embedded fillers' toxicity. Among the 2D nanomaterials, graphene was chosen as the best candidate for doping hydrogel matrices because of its excellent electrical and mechanical properties and facile conjugation reactions. GOs display plenty of hydroxyl, epoxy and carboxyl groups on the surface and provide for multiple conjugation avenues to polymeric matrices (Bai et al., 2010; Liu et al., 2011b). In addition, the treatment of grapheme surfaces with aromatic compounds that have proper functional groups provide additional conjugation strategies.

3.3. Hydrogel-graphene supercapacitor

A supercapacitor is an electronic device that can store energy in the form of ion adsorption or reversible Faradic reactions. The supercapacitor technology has continuously progressed in accordance with the development of nanostructured electrode materials. Several approaches exist to develop high-performance supercapacitors, which include enhancing the surface area of electrodes, stabilizing electrolyte solution for power delivery and so on. Various nanomaterials have been introduced as electrode materials such as nanoscale activated carbon because of their large surface area, low cost, and facile synthesis process. However, the energy storage capacity of conventional activated carbon materials is relatively low and typically under 200 F/g. Recently, graphene-based nanomaterials, including three-dimensional graphite, have emerged as an attractive electrode material due not only to their exceptional electrical and mechanical properties but also to their flexibility to form different shapes such as wrapping, rolling, and stacking sheets.

A graphene-based ultracapacitor based on chemically modified 1-atom thick graphenes (Stoller et al., 2008) was reported to achieve specific capacitances of 135 and 99 F/g in aqueous and organic electrolytes, respectively. Carbon nanosheets prepared through CVD method were also deposited on conventional carbon fibers and carbon papers to prepare electrodes (Zhao et al., 2009). These carbon nanosheets are comprised of 1–7 graphene layers, which are vertically oriented with respect to a substrate. A novel 3D graphene network produced using Ni as a sacrificial template during CVD process was found to have a large specific surface area and allows the rapid access of electrolyte ions to the NiO surface (Cao et al., 2011). This NiO/graphene composite achieved the capacitance of 816 F/g at a scan rate of 5 mV/s and a stable performance over 2000 cycles without any loss of its specific capacitance.

Graphene coupled with hydrogel is a potentially superior material of choice for supercapacitors fabrication than graphene alone owing to high specific surface area, nano-micropore network, and multidimensional electron transport pathways provided by 3D gel network (Wu et al., 2011; Xu et al., 2013b, 2010). Recently, the first example of graphene/hydrogel-based ultrafast supercapacitor was reported (Chen et al., 2013). The graphene hydrogel was doped with nitrogen using organic amine and GO as precursors in one-pot hydrothermal process, which leads to the high-performance supercapacitors (113.8 F/g, 205.0 kW/kg power density). A flexible solid-state supercapacitor based on 3D graphene hydrogel film was also recently reported (Fig. 7) (Xu et al., 2013a). Flexible solid-state supercapacitors can provide mobile power supply for future flexible electronics, but conventional flexible supercapacitors have limitations of weak capacitance due to the ultra-small electrode thickness (a few micrometers) and very small mass loading. In the above study, a high-performance flexible supercapacitor was realized by 3D graphene hydrogel with 120 μm thick film that consisted of H_2SO-PVA gel electrolyte and GO. This 3D graphene hydrogel provided a high gravimetric specific capacitance (186 F/g at 1 A/g), an unprecedented area-specific capacitance (372 mF/cm^2), and excellent rate capability (70% retention at 20 A/g).

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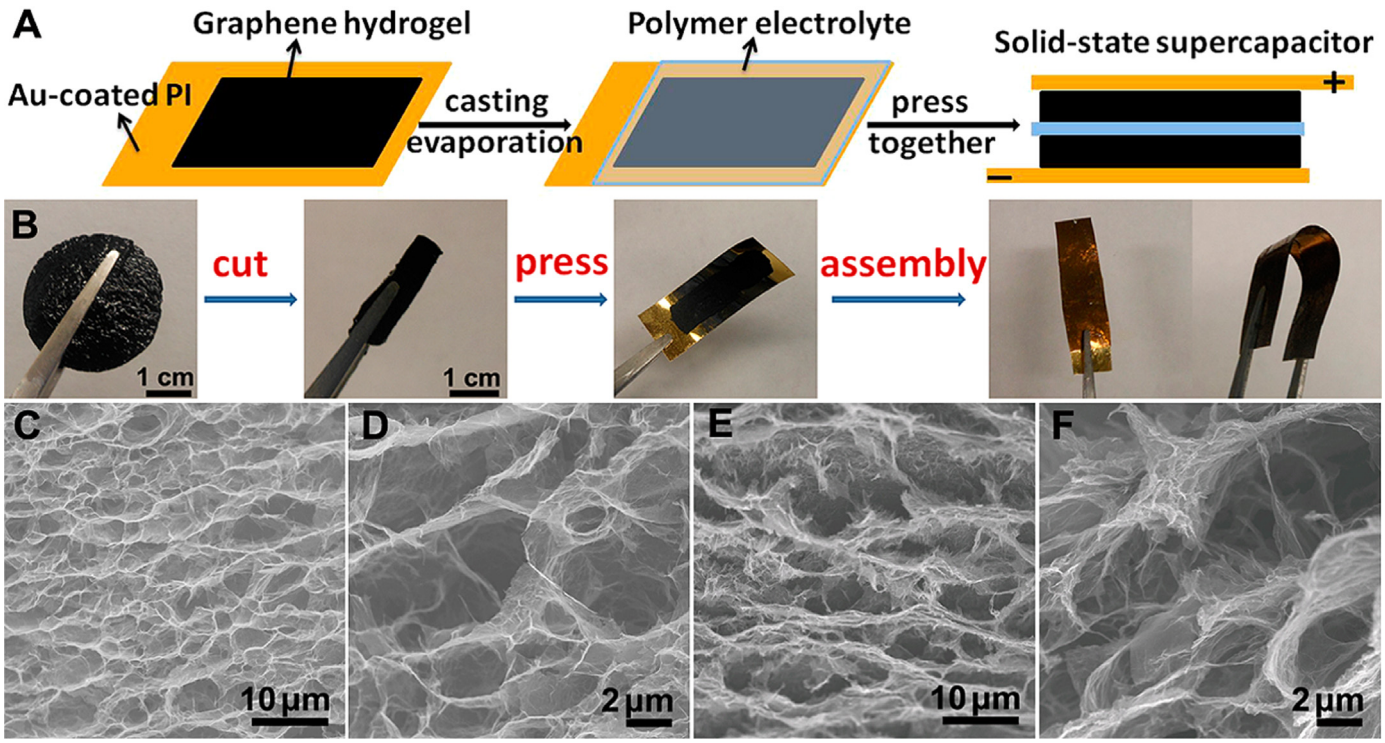

Fig. 7. (A) Schematic diagram and (B) photographs of the fabrication process of flexible solid-state supercapacitors based on graphene hydrogel films. (C) Low- and (D) high-magnification SEM images of the interior microstructure of the graphene hydrogel before pressing. (E) Low- and (F) high-magnification SEM images of the interior microstructure of the graphene hydrogel film after pressing. Reprinted with permission from Xu et al. (2013a, 2013b). Copyright 2013 American Chemical Society.

3.4. *Stimuli-responsive graphene-hydrogel as actuators*

Excellent stimuli-responsive capacity of graphene-hydrogel composite was found to be useful for the synthesis of an active component in actuator systems (Zhang et al., 2011). Graphene can work as a filler material to enhance the actuation performance in terms of conductivity and mechanical strength, whereas hydrogels can reversibly change their shapes and dimensions upon stimuli. Hydrogels have several advantageous features in such applications, especially in biological applications due to their flexibility and biocompatibility as previously mentioned. Accordingly, several studies have demonstrated that hydrogel-graphene composite can act as pH- (Ha et al., 2013) electrical- (Tai et al., 2013; Zhang et al., 2011) and photonic- (Lo et al., 2011) responsive-actuators.

Graphene can generate heat upon NIR absorption; this unique photothermal capacity has been also found useful for light-responsive actuators constructed with hydrogel scaffolds. The flexible hydrogel-graphene hybrid structure can change its shape by the stimulation of heat generated by applying NIR, as recently demonstrated in an NIR-controllable graphene-hydrogel actuator (Wang et al., 2013). The construction of graphene-hydrogel was achieved by crosslinking of elastin-like peptides immobilized on reduced graphene oxide (rGO) surfaces. The bending motion of graphene-hydrogel was induced by the irradiation of NIR light that could locally shrink hydrogel matrix. The rapid and tunable actuation was controlled by the position, intensity and path of NIR irradiation, and allowed actuators to have specific motions such as finger-like flexing and crawling (Fig. 8). These NIR-responsive graphene-hydrogel hybrid structures have been utilized to fabricate actuators in many follow up studies.

4. Perspective

Graphene has attracted tremendous attention in a wide range of applications due to their high surface to volume ratio, excellent electrical and thermal conductivity, and mechanical robustness. Constructing 3D structures from 2D graphenes enables significantly larger active surface area and thus offers the opportunity to develop high performance electrical, mechanical and optical devices including sensors and actuators that are difficult to achieve in 2D design. However, stacking 2D graphene sheets to build up functional 3D architectures is often prohibited due to formation of irreversible agglomerate structure through strong π-π stacking and *van der Waals* interaction. Consequently, employing hydrogels as a porous 3D scaffold to host 2D graphene is an effective strategy to construct 3D graphene architectures. In such composite structures, hydrogels can acquire an excellent conductivity and mechanical strength through the integration with graphene. Hydrogels also offer excellent flexibility, biocompatibility and stimuli-responsive properties to maximize the useful properties of graphene. We provide below examples for applications of hydrogel-graphene hybrid structures for sensing, electronic and mechanical devices.

4.1. *Injectable biosensor system*

Injectable hydrogels that polymerize through in situ crosslinking or by sol-gel transition process that forms gel structure on site have been attracting enormous attention for the development of drug delivery devices and technologies to regenerate bone defects. One of the most promising methods to develop in vivo biosensors is the utilization of optical systems using long wavelengths of light as an external stimulus. The longer wavelength light has been widely utilized for in vivo detection and photothermal therapy as it permits deeper tissue penetration and less cell damage compared to shorter wavelength light. Some carbon and graphene nanomaterials adsorb low frequency photons and exhibit excellent photostability. Carbon nanomaterials and graphene have been reported as an NIR-II light-to-heat converter for photothermal therapy of cancer cells (Kam et al., 2005; Wang

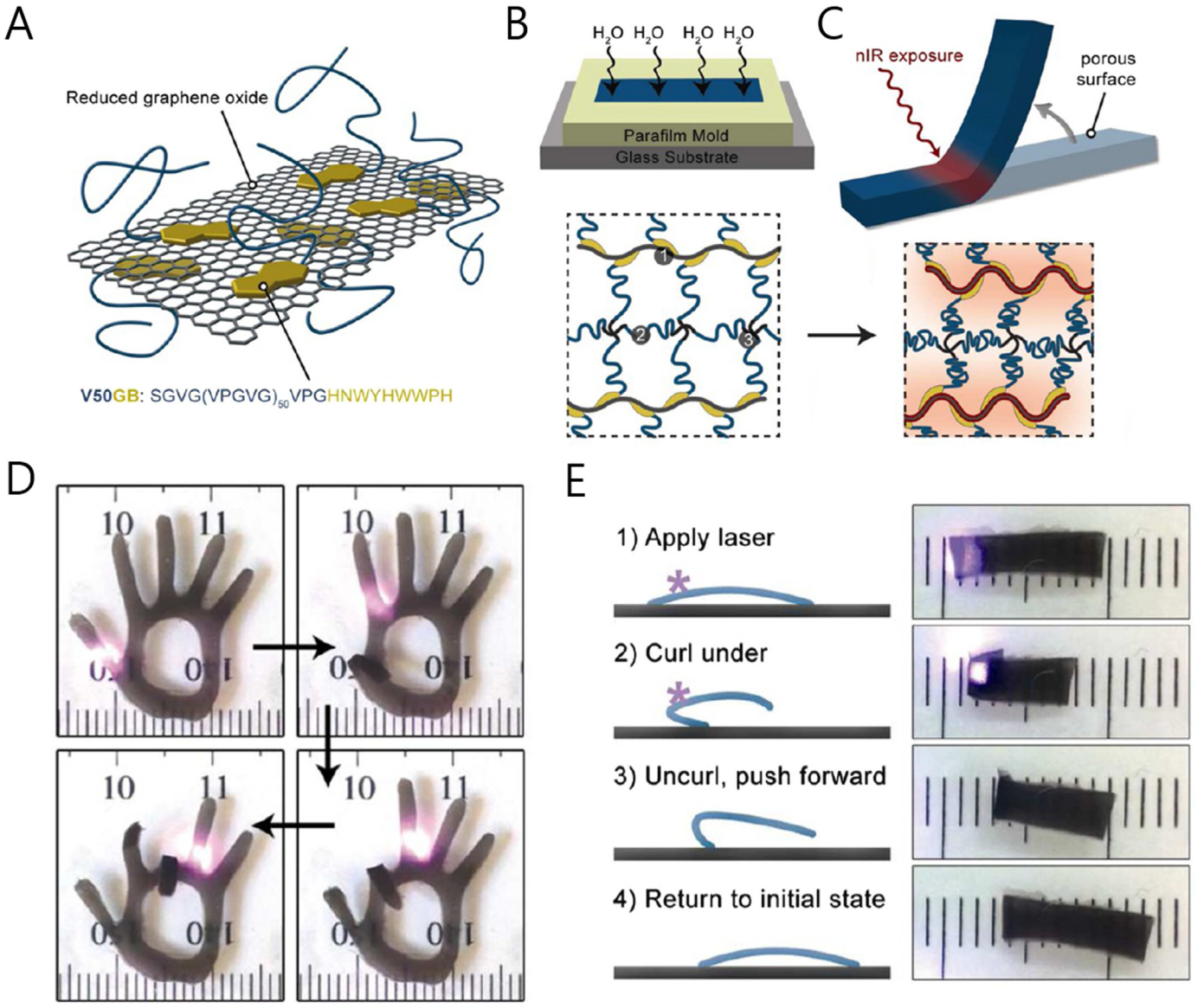

Fig. 8. (A) Schematic of elastin-like peptides binding to an idealized rGO sheet. (B) Schematics showing method to introduce anisotropic porosity using water vapor exposure during the cross-linking process and of the resulting hydrogel network composed of (1) 50 pentapeptide long graphene-binding peptide (V50GB) bound to rGO, (2) V50CK1, and (3) 4-arm cross-linkers. (C) Schematics of site-specific NIR-initiated bending of an anisotropic hydrogel and the corresponding local deswelling of the gel network. (D) Images of the fingers of a hand-shaped hydrogel bending and unbending in response to the location of a NIR laser spot. (E) Schematic and images of a light-driven crawler. A hydrogel molded with a slight curvature is placed with porous side facing down. The laser is applied so as to induce gel curling. Subsequent uncurling during recovery after the laser is removed pushes the gel forward (1 mm tick marks). (Reprinted with permission from Wang et al. (2013). Copyright 2013 American Chemical Society.).

et al., 2011). Based on these, we suggest that injectable hydrogels integrated with graphene can offer a unique opportunity to develop a new platform of injectable biosensors. The hydrogel-graphene composite shall provide facile control of positioning of sensing through in situ gel formation, biocompatibility, and 3D scaffolds to maximize the unique properties of graphene.

4.2. Flexible and biodegradable biosensors

Significant efforts have been made to develop implantable bioelectronics. The most sensitive sensor systems, especially semiconductor-based systems, require a solid substrate, normally silicon wafers, for the fabrication. Developing soft and flexible sensor systems fitting to curvilinear tissues or organs for measuring various biological signals has been challenging (Kim et al., 2010; Viventi et al., 2011). The hydrogel-graphene hybrids can be one of the most promising candidates for the fabrication flexible and implantable bioelectronics platform including sensors and electrodes. Graphene on hydrogel substrates can function as electrodes to monitor biological signals while exploiting biodegradable hydrogels as the substrate of implantable sensors, to eliminate the need for device removal when its action is no longer necessary.

4.3. Drug release systems

Graphene materials can serve for triggered drug delivery systems. Graphene has emerged as an efficient drug carrier due to its high drug loading capacity owing to high mechanical strength, adequate chemical stability, high surface area and unique π-π stacking interaction. Graphene with semiconducting properties, generates heat by adsorption of NIR. Drugs with aromatic rings on their chemical structures immobilized on carbon surface by π-π stacking interaction are released by exposure to heat so that the

release can be controlled by NIR stimulation. Hydrogel 3D scaffolds can provide facile control of positioning and biocompatibility for both sensing and controlled drug release.

5. Concluding remarks

Hydrogels have been widely used for biological scaffolds owing to their high biocompatibility and water content. However, weak mechanical properties and insufficient conductivity of the bulk hydrogels limit their utility. To overcome these limitations, 3D hydrogels can be doped with 2D nanomaterials, as was extensively discussed using graphene as a model filler material. Such composite materials afford biocompatibility and tunable properties serving as biosensors, supercapacitors, and actuators. Moreover, this review offered forward looking examples of new generation injectable biosensor material systems including flexible/biodegradable biosensors and smart triggered drug release systems that utilize 3D hydrogels:2D graphene hybrids.

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