CHEMICAL REVIEWS

REVIEW

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Organization of Glucose-Responsive Systems and Their Properties

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1. INTRODUCTION

Diabetes is a disorder of glucose regulation, which is performed by an accumulating of glucose concentration in the blood. Although it is a chronic disease, it threatens human health seriously. The worldwide prevalence of diabetes is predicted to double to 366 million by 2030 from 171 million in 2000.[1] Thus, it will become one of the most important health concerns in this century. However, so far, the major treatment of this disease has been insulin injection. The injection suffering, the diet restriction, the endless hospital traveling, and sometimes the adverse reaction from the treatment confuse the patients' lives. All of these provoke a desire for an alternative treatment, which can direct responses to blood glucose levels and provides a continuous and noninvasive system of insulin administration, to form a feedback-controlled and closed-loop insulin-release system. Therefore, stimuli-responsive polymers have received more and more concern in the recent decades.[2]

Stimuli-responsive polymers have attracted a great deal of research interest over the past several decades. They can convert environmental stimulus, such as temperature,[3] pH,[4] ironic strength,[5] and glucose concentration,[6] into the signal to trigger the change in physical properties of the polymers. Consequently, it enabled us to develop various types of stimuli-responsive and "self-regulated" systems, which are called "intelligent" and "smart" materials. When it comes to the glucose-responsive one, the system responds to the change of the glucose concentration of the surroundings, which has a promising future within the application of diabetes treatment.

The study of glucose-responsive systems can be classified by two dimensionalities: glucose-responsive mechanism and application. By mechanism, they fall into three categories: the glucose oxidase (GOx), lectin, and phenylboronic acid (PBA) modified systems. By application, they fall into two categories: insulin release and glucose concentration diagnosis. Although there are some reviews published over the past few years with depth analysis and summary relating to glucose-responsive systems,[7] this article is the first one that covers both of the classification dimensionalities, trying to provide a comprehensive prospect for the recent research of glucose-sensitive systems. Thus, it reviews three different kinds of glucose-responsive systems, with secondary classification of application area.

2. GLUCOSE OXIDASE MODIFIED SYSTEM

As diabetes has become one of the social health problems, the research on glucose-responsive polymers has attracted expanding interest up to now. The polymer responds to the vibration of the glucose concentration in the form of physical properties change. The glucose oxidase modified system is one of the traditional glucose-responsive systems that have been researched in the past few decades. Historically, the first glucose-responsive material was made by combining glucose oxidase (GOx), as the sensing section, with pH-sensitive hydrogel serving as the backbone. The immobilization of GOx can endow the pH-sensitive materials with glucose-responsive properties, basically because GOx converts glucose to gluconic acid in the presence of oxygen as shown in the following reaction:[8]

$$\text{glucose} + O_2 + H_2O \xrightarrow{\text{GOx}} \text{gluconic acid} + H_2O_2$$

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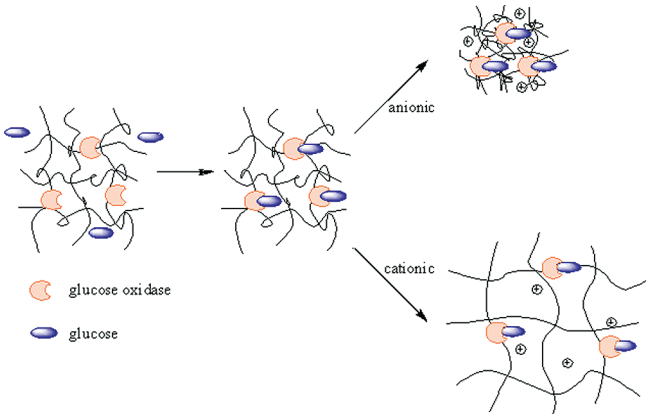

Figure 1. Glucose-responsive mechanism of GOx-based hydrogel.

The formation of acid results in a lowering of pH, which triggers swelling or deswelling of the pH-sensitive polymer chains, and consequently causes the change of their morphology. Owing to the glucose-triggered properties, glucose oxidase has been widely researched within the insulin-release and glucose-concentration detection areas.

2.1. Insulin Delivery and Release

Since GOx modified material was first used in the glucose-responsive systems, it gained plenty of interest from researchers all over the world, especially in the drug-delivery field. Among all the research, swelling of hydrogels and films[9] represents a large proportion of that in the insulin delivery and release area. In addition, gating of membranes,[10] destabilization of liposome,[11] degradability of hydrogel,[12] and permeability of microcapsules[13] were also reported as glucose-responsive systems for drug release.

2.1.1. Swelling of Hydrogels and Films. Hydrogels are hydrophilic polymer networks that can absorb large amounts of water but remain insoluble because of the presence of cross-links. The glucose-responsive hydrogel is usually composed of pH-sensitive polymer as the network and GOx as the glucose-responsive sensor. With entrapped and covalently linked GOx in and upon the polymer, the hydrogel swells or collapses according to change of pH, which results from the generation of gluconic acid by glucose. The pH-sensitive polymer can be divided into cationic and anionic ones. The response behavior of swelling and deswelling depends on the charge nature of the backbone monomer. More specifically, when the surrounding pH value is higher than the pK_a of the cationic groups, the copolymer is hydrophobic and excludes water from the system; on the other hand, when the pH value is lower than the pK_a, the cationic groups would change into protonated form. In consequence, the system becomes hydrophilic and absorbes water. Thus, the network swells, as shown in Figure 1. Conversely, the anionic polymer follows a similar mechanism to deswell according to the shift of the environmental pH value.

Poly(methacrylic acid-*g*-ethylene glycol) (P(MAA-*g*-EG)) hydrogels, to serve as a "squeezing gel" with high glucose concentration, were reseached by Peppas and co-workers.[9c] To overcome the problem that the activity of GOx would be limited by the amount of oxygen available, catalase was introduced to facilitate the GOx-based reaction, with enzymatic reaction of catalase:

$$H_2O_2 \xrightarrow{\text{catalase}} \frac{1}{2}O_2 + H_2O$$

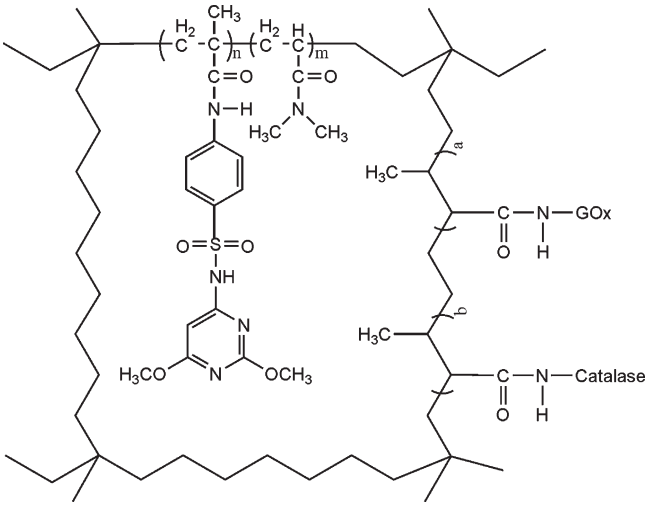

Figure 2. Structure of conjugated glucose oxidase and catalase by sulfonamide chemistry.

Oxygen was generated from the catalase reaction, which solved the problem of oxygen requirement. Moreover, hydrogen peroxide generated from the GOx enzymatic reaction was consumed, which reduced the peroxide-induced degradation of the GOx enzyme. Thus, a series of hydrogel matrixes that entrapped and immobilized both GOx and catalase were synthesized and researched.[9d,g,h,14] It was demonstrated that the introduction of catalase increased the swelling rate of the hydrogel and improved the stability of the enzyme.

Besides the stability in the environment, the enzymatic stability within the polymer was also considered. Compared to physically entrapping, the covalent linking[14d,15] was preferred to keep efficient settlement of enzyme onto the polymer chain. In the research of Khalid and co-workers,[16] GOx was first immobilized on cellulose acetate polymethylmethacrylate (CA-PMMA) membrane, to obtain the thermal and operational stability of GOx.

Making pH-sensitive behavior occur under physiological conditions was another aspect that needed to be highlighted. Bae and coworkers[14d,17] established a hydrogel with covalently conjugated GOx and catalase by sulfonamide chemistry, as shown in Figure 2, which exhibited swelling transition in the pH range 6.5−7.5, close to the physiological conditions.

2.1.2. Gating of Membranes. Ishihara and co-workers[18] first reported insulin permeation across a glucose-sensitive membrane. Afterward, other reseachers established porous films, such as cellulose[10b] and polyvinylidene fluoride (PVDF),[10d] with poly(acrylic acid) (PAAC) grafted on the pores. GOx were covalently linked on the PAAC chain. The release mechanism[10c] depended on the protonation of carboxylate groups on the graft chain with the presence of glucose. Because glucose was converted to gluconic acid by GOx, the electrostatic repulsion was reduced, resulting in the shrinkage of the chain and, hence, opening of pores in the membrane. At last, the insulin released, as shown in Figure 3. The report also showed that the PAAC grafting yield heavily affected the glucose-responsive permeability of the porous membrane.[10d]

Polymeric composite membrane was another system that was used in drug release. The composite membranes were cast by dispersing GOx, catalase, and pH-responsive nanoparticles in a solution of hydrophobic polymer.[10e,f] As shown in Figure 4, as glucose concentration increased in the system, pH decreased,

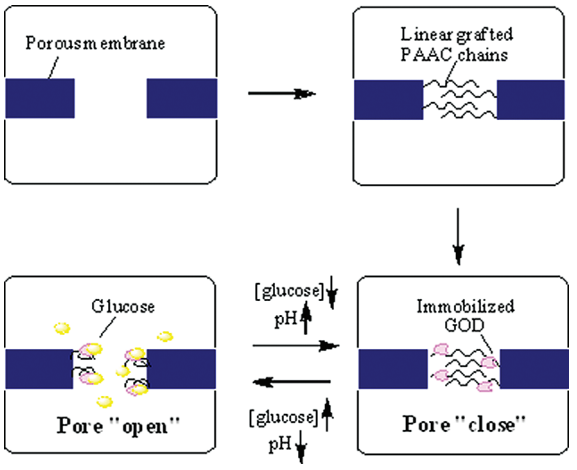

Figure 3. Schematic illustration of process of glucose-responsive insulin releasing through the gating membrane.
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which led to the collapse of the pH-sensitive nanoparticles. As a result, the insulin released from the hollow parts. A bioinorganic nanohybrid membrane was constructed based on the same mechanism.[19] The progress was the use of MnO_2 nanoparticles conjugated within the porous bovine serum albumin (BSA)-based membrane. It not only reinforced the mechanical strength but also enhanced the long-term stability of the enzymes, making it close to practical application.

2.1.3. Other Mechanisms. The pH-sensitive liposomes containing encapsulated insulin and GOx were prepared and studied.[11a,b] It was reported that due to the enzymatic reaction of GOx and glucose, gluconic acid was generated, leading to the destabilization of pH-sensitive liposomes and the delivery of insulin. To accelerate the insulin release, poly(*N*-isopropylacrylamide-*co*-methacrylic acid-*co*-octadecylacrylate) (P(NIPAM-*co*-MAA-*co*-ODA)) and GOx were conjugated on the surface of the liposome.[11c] High activity and sensitivity were obtained.

H_2O_2-degradable hydrogel, which can regulate insulin release according to the change in the glucose concentration, was prepared by Kiritoshi and co-workers.[12] The addition of glucose caused the enzymatic reaction of GOx. The produced H_2O_2 caused the degradation of the hydrogel and, consequently, the release of insulin, as shown in Figure 5.

In the last several years, natural polymers were also introduced into a glucose-sensitive system. Hemoglobin is one of them. Qi and co-workers[13] fabricated glucose-sensitive protein hollow microcapsules, as shown in Figure 6, by the alternate assembly of hemoglobin and GOx via layer-by-layer technique with glutaraldehyde (GA) as cross-linking agent. Besides the advantage of the biocompatible and biodegradable nature, the stability entrapment of GOx and the permeability of the fabricated capsule were both enhanced, owing to the special structure. Therefore, with the glucose-triggered permeable wall, the fabricated Hb/GOx capsules may be a promising candidate for the advanced drug-delivery devices.

2.2. Glucose-Concentration Detection

In general, a glucose-concentration detection device consists of a recognition part and a signal transition part. The recognition part is the biosensor, GOx. It responds to a certain stimuli, glucose, and gives a corresponding respond. The signal transition

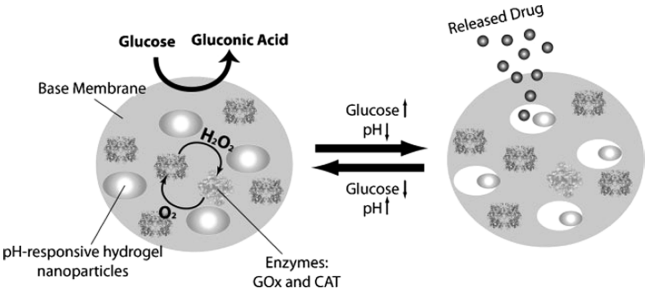

Figure 4. Schematic illustration of the glucose-responsive process of the composite membrane.
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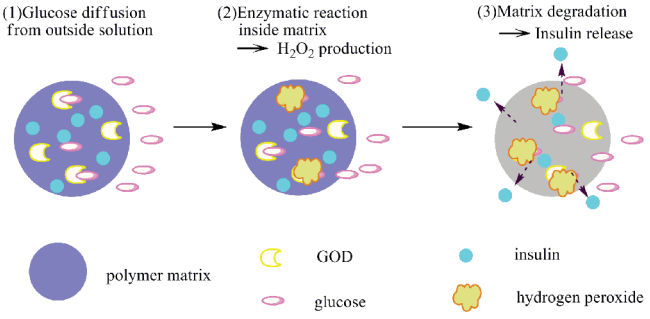

Figure 5. Schematic representation of insulin release synchronized with glucose concentration.
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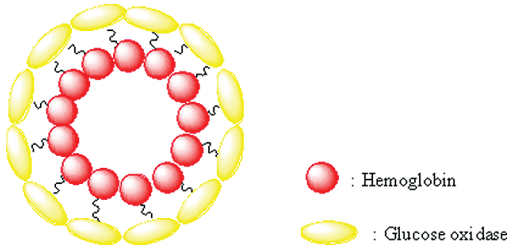

Figure 6. Microcapsule fabricated by hemoglobin and glucose oxidase.

part is an energy converter, a device that can convert the vibration of glucose concentration into another signal that can be detected, such as electrochemical, optical, thermometric, and fluorescent ones. By analysis of these signals, the glucose-concentration data is obtained.

2.2.1. Electrochemical Sensors. Among various glucose biosensor platforms, electrochemical methods have received considerable attention, since Clark and Lyons[20] proposed the initial concept of glucose enzyme electrodes in 1962. According to the review written by Wang,[7d] the electrochemical glucose biosensor could be divided into three generations, which are based on different mechanisms of electron transfer. They were the systems using natural secondary substrates, artificial redox mediators, and direct electron transfer, known as the first, second, and third generation of glucose biosensors, respectively, as shown in Figure 7. On one hand, compared to the first generation of biosensor, the second one possessed more efficient electrons transfer, because of the utilization of mediator; on the

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other hand, by using oxygen in air as the mediator, the first generation may exhibit good stability in long-term use. Thus, both of these systems were unceasingly researched with amelioration in the past few years. As for the third generation, spatial separation of the donor−acceptor pair was the problem that needed to be overcome, and few successful efforts were obtained.

2.2.1.1. First-Generation Sensors. The first generation, natural secondary ones, based on the detection of hydrogen peroxide that is generated by oxidation of Gox, is shown in Figure 8. To eliminate the effect of electroactive interferences was the main stream of the research to improve performance of the biosensor. The permselective material[21] based on charge and porous size and metal-based transducer[22] were studied in this area.

To enhance selectivity of the biosensor from the interference, a variety of polymers were reseached, including poly(*p*-phenylenediamine),[21a] poly(ethacridine),[21b] and polyacrylonitrile.[21c,d] It was reported that these systems exhibited high sensitivity to glucose and fast response time. The charge-controlling method to eliminate electroactive interference was also reported. The first positively charged polyelectrolyte was constructed by Shen and co-workers,[23] who achieved a system with biocompatibility, stability, reproducibility, and, of course, selectivity. An anionic clay matrix[24] and Nafion[25] were also employed for the same purpose, obtaining favorable properties for glucose detection.

A ruthenium-based carbon fiber microelectrode was creatively prepared by Kuwabata and co-workers.[22b] The resulting metalized carbon electrodes performed high catalytic activities for hydrogen peroxide; in addition, the positive electrode potential of hydrogen peroxide oxidation made the system free of interference even without any aforementioned permselective membrane.

2.2.1.2. Second-Generation Sensors. In the second generation, the electron transfer, from the reduced form to the oxidized form of the mediator, was detected as current signal, as shown in Figure 9. The key issue of the system was the choice of an appropriate mediator. Ferrocene derivatives,[26] quinone compounds,[27] transition-metal complexes,[25b,28] and nanomaterials[29] were all used as mediators recently.

Actually, the dividing line between the two generations of biosensors was not quite clear; in other words, lots of systems integrated both of them to obtain advanced ones with both high selectivity and efficient electron transfer. For instance, mixed ferrocene−cobaltocenium dendrimers (Figure 10) were introduced into the electrochemical system,[26c] where ferrocene units played the role of mediators, while the cobaltocenium moieties acted as electrocatalysts.

2.2.2. Optical Sensors. Optical methods provided another mechanism to determine the glucose concentration, usually with high sensitivity, selectivity, and reproducibility. There were two branches of research in this area. They were based on fluorescent signals and surface plasmon resonance signals, respectively. Fluorescent ones attracted more attention. The establishing of the quenching process was significant to this kind of system. Oxygen,[30] GOx,[31] and H_2O_2[32] were all researched as the quenchers that contributed to the detection of glucose.

Fluorescent oxygen-sensitive systems[30] were highlighted among the optical methods for glucose monitoring. The device comprised GOx, catalase, and oxygen transducer, immobilized into the matrix. The glucose concentration was monitored by measuring the consumption of oxygen in the glucose-oxidated reaction. Furthermore, the detection of the amount of consumed oxygen was based on the fluorescent change of the oxygen transducer. A series of similar systems exhibited high sensitivity,

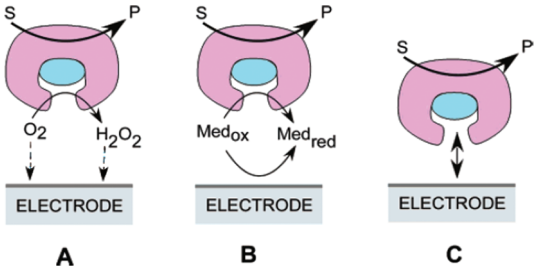

Figure 7. Three generations of amperometric enzyme electrodes for glucose based on the use of natural oxygen cofactor (A), artificial redox mediators (B), and direct electron transfer between GOx and electrode (C).

$$\text{GOD(OX)} + \text{glucose} \longrightarrow \text{GOD(Red)} + \text{gluconolactone}$$

$$\text{GOD(Red)} + \text{O}_2 \longrightarrow \text{GOD(OX)} + \text{H}_2\text{O}_2$$

Figure 8. Reaction that occurred in the first-generation glucose biosensor.

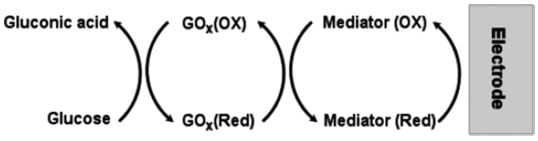

Figure 9. Sequence of events that occurred in the second-generation glucose biosensor.
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good selectivity, and excellent reproducibility, as reported. The favorable stability was gained by the modification on the enzyme-immobilization platform.

Wolfbeis and co-workers[30a] employed sol−gel structure, specifically xerogel, as the substrate of the biosensor to entrap ruthenium ligand (Ru) complex and enzyme, where Ru complex served as the fluorescent oxygen probe. The emission of the fluorescent oxygen probe was quenched by oxygen. With similar oxygen transducer and enzymes, Wu and Choi[30b] prepared a novel hybrid organic−inorganic silica gel, to elongate the storage time and increase the stability of the system. A novel biomaterial, bamboo inner shell membrane, was first introduced as an enzyme immobilization platform by Xiao and co-workers,[30c] to obtain biocompatibility, stability, and high sensitivity. It also made the immobilization process simple and cost-effective.

Taking modified GOx as the one of fluorescent counterparts to detect the glucose concentration was also studied. Chaudhary and Srivastava[31] established a sensor that consisted of tetramethyl rhodamine isothiocyanate (TRITC)-conjugated apo-GOx as the fluorescent acceptor and fluorescein isothiocyanate (FITC)-conjugated dextran as the donor. Fluorescence resonance energy transfer from the donor to the acceptor was tested to monitor the glucose concentration. To improve the sensitivity and stability of the system, uniform-sized alginate microspheres were used as the platform of the fluorescence-based sensor.

Semiconductor quantum dots (QDs) were an alternative to be researched because they possess a large specific surface area as well as excellent optical properties. Using the layer-by-layer assembly

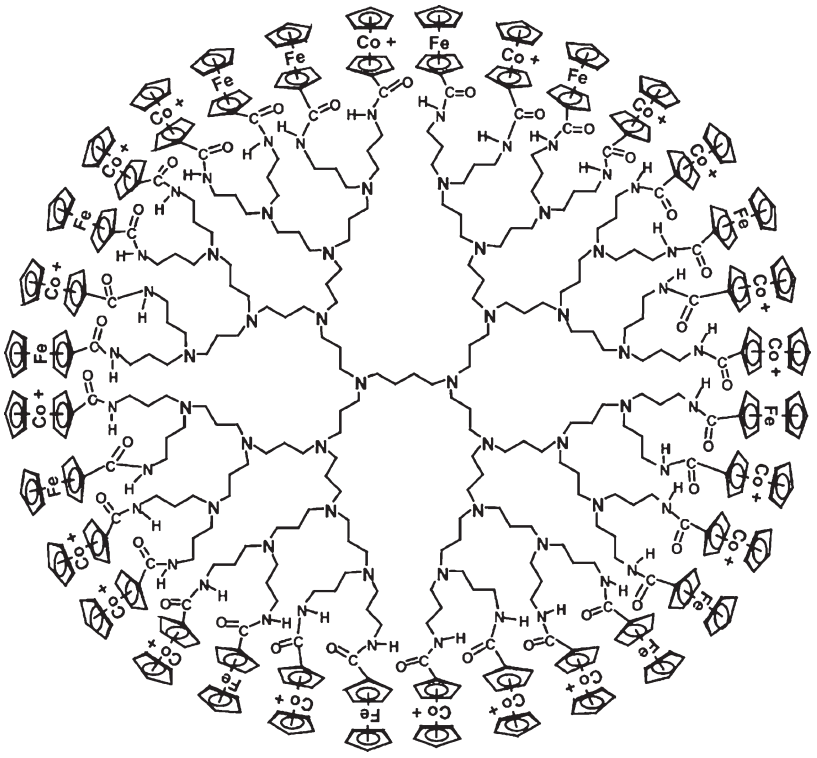

Figure 10. Structure of ferrocene−cobaltocenium dendrimers.

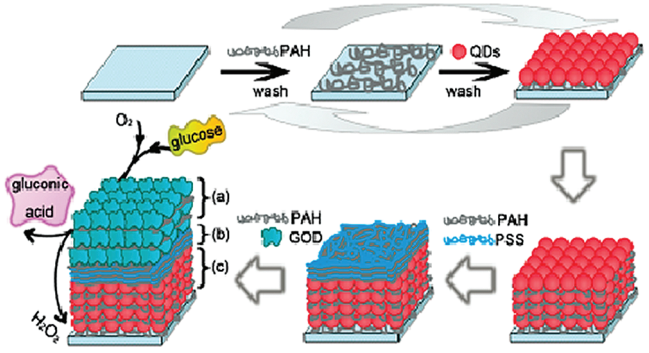

Figure 11. Sensing assembly: (a) top 3 bilayers of poly(allylamine hydrochloride) (PAH)/glucose oxidase (GOD), (b) 3 bilayers of PAH/sodium polystyrenesulfonate (PSS), and (c) 12 bilayers of PAH/CdTe QDs.

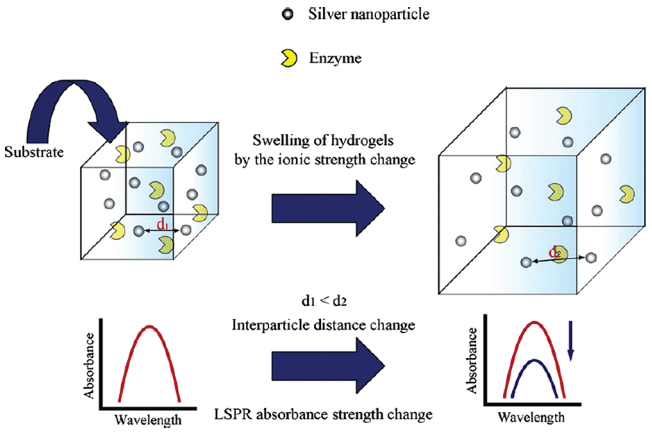

Figure 12. Schematic illustration of detection principle of LSPR-based optical enzyme biosensor using stimuli-responsive hydrogel−silver nanoparticles composite.
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technique, Li and co-workers[32] prepared a system with multilayer films of GOx and CdTe QDs, as shown in Figure 11. The glucose concentration was determined by the testing of the quenching rate of photoluminescence of QDs in the films, which resulted from the production of H_2O_2. The performance of this system was certified to obtain the successful determination of the glucose concentration in real serum samples, with satisfactory reproducibility and accuracy.

Surface plasmon resonance signal was also employed to determine the glucose concentration. A localized surface plasmon resonance (LSPR)-based optical enzyme biosensor was composed of stimuli-responsive hydrogel with GOx and silver nanoparticles immobilized inside.[33] The glucose monitoring of this system was based on the change of LSPR strength, as shown in Figure 12. With the presence of glucose, the hydrogel swelled, leading the interparticle distances of the silver nanoparticles to increase. Consequently, the absorbance strength of LSPR decreased. Moreover, it was reported that the system possessed cost-effective, highly simplified, and highly sensitive properties.

2.2.3. Other Sensors. Some other methods to detect the glucose concentration via the GOx systems have been creatively introduced, such as thermometric[34] and magnetoelastic[35] ones. These methods provided us different trains of thought for the determination of glucose concentration, to evade some shortcomings of other systems.

Thermometric measurement for glucose detection was constructed[34] by entrapped GOx and catalase upon the surface of reticulated vitreous carbon cylinder, with sol−gel as binder. The glucose concentration was monitored by the recording of the

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thermometric peak height according to the heat content change of the circulating buffer. This established system had good stability; in addition, the testing process of it exhibited no interference.

To overcome the drawback of electrochemical methods that are submitted to the interference of the electroactive species in the tested liquid, a wireless magnetoelastic glucose biosensor was produced, by coating magnetoelastic sensor with chitsan onto a conventional GOx and catalase-modified pH-sensitive polymer system[35] (Figure 13). The gluconic acid that was converted by glucose led to shrinking and corresponding mass decrease in the pH-responsive polymer, consequently increasing the resonance frequency of the magnetoelastic sensor. This kind of glucose biosensor had already been successfully applied to measurement of glucose concentrations within urine samples, attributing the linear response to glucose concentration within a certain range, without the effect of interference.

3. LECTIN-MODIFIED SYSTEM

Lectins are one kind of carbohydrate binders. Like GOx, they can also be used as biosensors to develop glucose-sensitive systems. They possess the properties to adhere cellular and regulate hormone on the surface of cells, because they interact with glycoproteins and glycolipids. Concanavalin A (Con A), which was first reported by Brownlee and Cerami,[36] has been one of the glucose-responsive lectins that was studied most. With these four binding sites, Con A complexes with saccharide residues are combined to the polymer chain usually. This property makes the Con A modified system a candidate for a glucose-responsive drug-release system as well as the glucose-monitoring system.

3.1. Insulin Delivery and Release

Compared to the application of glucose testing, the insulin-delivery system based on Con A received more attention.[37] Basically, the system consisted of Con A, insulin, and glycosylated polymer. The basic mechanism for glucose-responsive drug release is that Con A is entrapped and immobilized in the polymer chain by bonding with glycosylated moieties upon the chain, forming a three-dimensional structure, in which insulin is contained. With the presence of glucose, the complex between Con A and the saccharide residue broke, because free glucose has priority over saccharide residue to bind with Con A. Therefore, the complex glucose is competitively displaced by the free one, causing low viscosity within the gel network and allowing a flux of insulin. (Figure 14).

On the way toward the real application of a Con A-based system, plenty of factors should be considered: the leakage of Con A, the stability and solubility of the Con A system in water, the length of the response time, and the bioactivity. Thus, reseachers tried their best to optimize the glucose-responsive systems for drug release, to ensure the insulin appropriately released from the systems under the physiological environment, and in the mean time, to prevent the leakage of Con A. Therefore, how to establish the interaction among the three components within the system was attached great importance in the research. The modification of insulin,[38] the modification of Con A,[39] the optimized link of Con A,[40] and the utilization of new structures or techniques[41] were the methods that were used to overcome the mentioned matters.

To optimize the "insulin component" of the delivery system, succinyl amidophenyl glucopyranoside insulin (SAPG-insulin)[38b,c] and succinyl amidophenyl mannopyranoside insulin (SAPM-insulin) were researched.[38c] With monosubstituted monoglucosyl

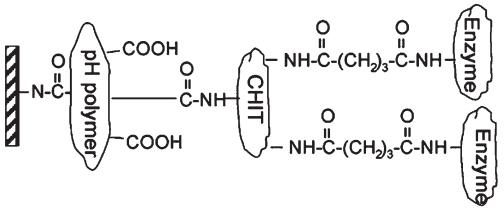

Figure 13. Structure of wireless magnetoelastic glucose biosensor.

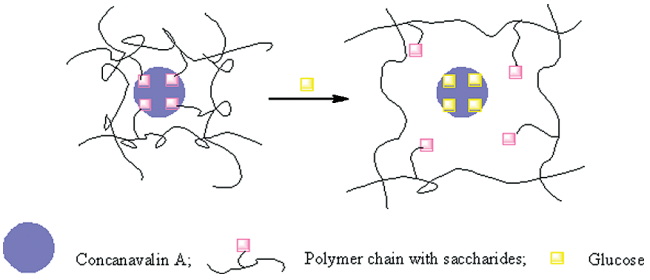

Figure 14. Hydrogel swelling process upon glucose addition for polymer bearing saccharide moieties complexed with Con A.

poly(ethylene glycol) (G-PEG) on the amino group, PheB1 insulin conjugates were prepared by Kim and co-workers;[38a] with short-chain methoxypoly(ethylene glycol) (mPEG) on the amino groups of each residue, PheB1 and LysB29 insulin were also reseached by the same group.[37b] It was demonstrated that, with the modified insulin, the system exhibited bioactivity, improved solubility, and solution stability at neutral pH. Moreover, the unwanted lag time was shortened.

In the sol−gel phase-reversible hydrogel system, Con A still suffered from poor aqueous solubility and stability. The modification of Con A was one of the methods that considered ameliorating solubility and stability of the system. Con A grafted with poly(ethylene glycol) (PEG) molecules was studied.[39] When the number of grafted PEG chains per Con A was increased up to 5, the binding affinity of glucose was gradually increased to the maximum. The system was constructed by mixing PEGylated Con A and glycosylated polymer chain. The result showed that PEGylated Con A had improved aqueous solubility, enhanced long-term stability, and higher glucose sensitivity, compared to native Con A.

Compared to mixing Con A, the covalent linking proved to bear a better performance to keep the stability of the system.[42] Tanna and co-workers prepared the gel by connecting Con A with specific polysaccharides through the covalent bonding between the amine groups on Con A and carboxylic moieties on different carbomer resins, such as Carbopol 974P NF,[40e] Carbopol 934P NF, and 941P NF,[43] using carbodiimide chemistry. The covalent couplings were used to increase the stability of the gel and reduce the leaching of the gel components.

Tanna, Taylor and co-workers established systems using dextran.[40a−c,44] They prepared acrylic derivatives of dextran and Con A, to endow these components with the properties of being covalently cross-linked by photopolymerization, as shown in Figure 15. The viscoelasticity, rheological behavior, and leaching property of the system were studied. It was reported that the system underwent sol−gel reversible transition with the presence of glucose as well, and the cross-link reduced the

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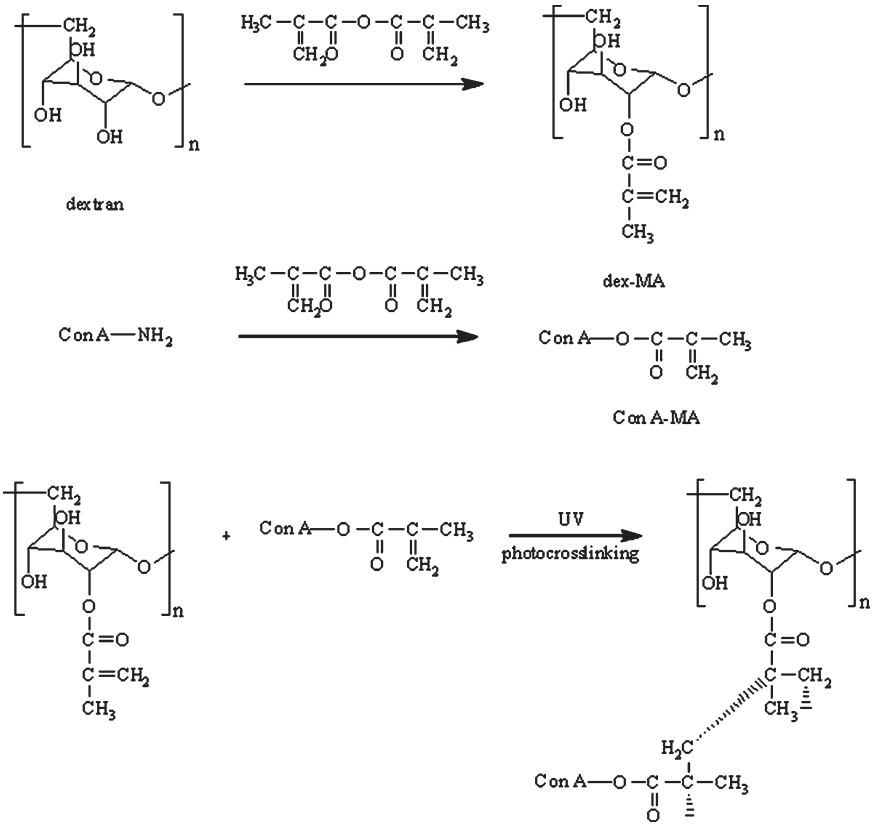

Figure 15. Photopolymerization of dex-MA and Con A-MA.

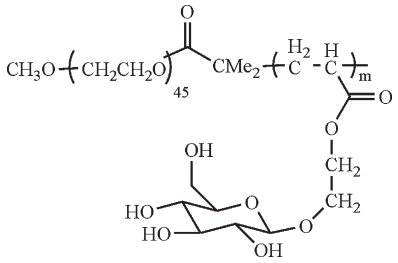

Figure 16. Structure of hydrophilic−hydrophilic diblock copolymer.

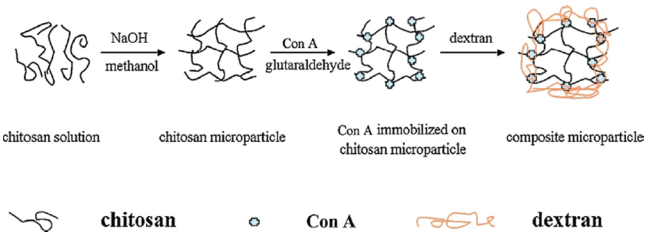

Figure 17. Fabrication process of the blank composite microparticles. Reprinted with permission from ref 41c. Copyright 2010 Elsevier Ltd.

leakage of Con A effectively. A facile procedure was reported by Zhang et al.,[40d] through which glucose-sensitive hydrogel membranes based on cross-linking carboxymethyl dextran (CM-dextran) and the glucose-binding ConA were synthesized. The advantages of the system were that it was biocompatible and charge properties were controllable.

Besides the modification upon the components and the optimizing of the link within the system, some novel techniques and new structures were also creatively researched. For example, hydrophilic−hydrophilic diblock copolymer, poly(ethylene-oxide)-*block*-poly(2-glucosyloxyethylacrylate), was novelly synthesized (Figure 16) by atom transfer radical polymerization.[41a] It self-assembled in glucose-responsive nanoaggregate reversibly, which showed potential biomedical applications such as the drug-delivery system.

A breakthrough conception, achieving postinhalation self-regulated insulin release, was established by Karathanasis and co-workers.[45] They constructed a microparticle agglomerate of nanosized liposomal particles, which exhibited a diameter within the human respirable range, and long residence times in the lungs to adjust insulin release according to systemic glucose levels.

Chitosan-modified poly(acrylonitrile-*co*-acrylic acid) (PAN-CAA) nanofibrous membranes were first prepared by Xu and co-workers.[41b] The system could keep relatively stable at pH 5.3, which demonstrated its potential as a glucose-responsive device.

Recently, Nie and co-workers first prepared glucose-responsive microparticles that integrated by chitosan, Con A, and dextran, as shown in Figure 17.[41c] Insulin was effectively loaded into the microparticles because of electrostatic and intermolecular interactions. With reversible response and favorable insulin release profiles as tested, this system was also a promising one for a glucose-responsive drug-delivery system. On the basis of glycidyl methacrylate-modified dextran (Dex-G), ethylene glycol acrylate methacrylate modified concanavalin A (Con A−E) (Figure 18) and poly(ethylene glycol) dimethacrylate (PEGDMA), another group of glucose-responsive hydrogels, were synthesized by

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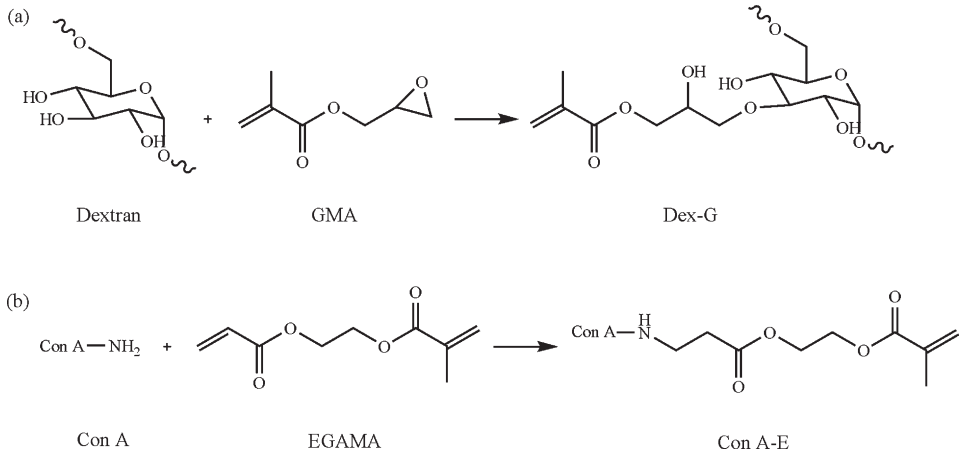

Figure 18. Reaction process of Dex-G (a) and Con A−E (b). Reprinted with permission from ref 41d. Copyright 2010 Elsevier Ltd.

photopolymerization by the same group;[41d] these hydrogels exhibited high glucose sensitivity and biocompatibility.

3.2. Glucose-Concentration Detection

Glucose-concentration testing of the Con A-containing system is also researched. On the basis of the system, various analytical techniques were developed for glucose monitoring, including fluorescent,[46] viscometry,[47] and electrochemical[48] based assays and sensors.

3.2.1. Fluorescent Sensors. The fluorescent sensor for the glucose monitoring depends on fluorescence resonance energy transfer (FRET). The basic system consists of fluorescent donor and acceptor. Con A and glycosylated polymer modified by diverse dye and fluorescent structures were able to serve as donor and acceptor, respectively.

The basic mechanism of the system is based on the quenching−dequenching process. Before the glucose addition, Con A and glycosylated polymer were counterparts to each other, and the fluorescence of the system was quenched. In the present of glucose, the free glucose in the aqueous phase replaced the glycosylated polymer and was competitively bound to Con A; thus, the fluorescence dequenched. The change of fluorescent intensity was tested to monitor the glucose concentration.

According to this mechanism, a system, with dextran labeled with Alexa Fluor 568 as fluorescent donor molecule and ConA labeled with Alexa Fluor 647 as acceptor molecule, was synthesized by Liang and co-workers.[46a] Near-infrared-compatible donor and quencher dyes were linked to dextran and ConA, respectively.[46b] Permeability-controlled hydrogel pads were employed to serve as the platform of the bioassay, with Con A−dextran system entrapped inside, as shown in Figure 19.[46e] Selective permeability and signal reproducibility were the significant advantages of the novel system.

A glucose assay that was composed of Con A labeling with Alexa Fluor 647 and glycodendrimer was prepared by Beier and co-workers.[46c] It was described that the spheroidal shape of the dendrimer molecule eliminated perplexity, the multibinding of the same dextran chain to Con A; thus, the system exhibited a large dynamic response to physiological concentrations of glucose.

QDs and nanostructures were also introduced, for the sake of gaining hyperefficient FRET. A novel system, with CdTe QDs as donor and gold nanoparticles (AuNPs) as acceptor, was first reported by Tang and co-workers.[46d] It was demonstrated that the nanobiosensor had high sensitivity, low detection limit, and excellent selectivity for glucose over other sugars, which made a stride in the research of Con A-based glucose-determination devices.

3.2.2. Other Sensors. Viscometric glucose sensors have been reseached. Owing to the complexes of Con A and dextran, the solution had high viscosity. With glucose addition, the free glucose competitively replaced dextran and bound to Con A, resulting in the reduction of cross-links and, hence, the decrease of viscosity. The solution containing ConA and dextran, which served as sensitive liquid, was used as a viscometric affinity sensor for glucose.[47] Different contents and ratios of the components were researched, and it was reported that low viscous sensitive fluids were able to be applied at physiological temperature and glycemia for glucose testing.

Electrochemical sensors have also attracted a large amount of attention lately. With the excellent electrical properties and high ratio of surface area to volume, a single-walled carbon nanotube was considered. It was first utilized to establish chemiresistive affinity biosensors in glucose detecting (Figure 20) by Mulchandani and co-workers.[48a] As Con A was displaced by combining with glucose, the resistance and conductance of the device changed. The change was determined to measure the glucose concentration with high selectivity and sensitivity.

A competitive capacitive glucose biosensor was creatively used in the glucose testing by Labib and co-workers.[48c,d] A multilayer structure was constructed within the novel system. As shown in Figure 21, a layer of polytyramine was electrochemically polymerized on the surface of a gold electrode; gold nanoparticles, which formed a lay to cover the polytyramine layer, were employed to serve as the platform of Con A. After screening, the combination of dextran and Con A was chosen. The system proved to have a linear response to glucose, with high sensitivity and reusability.

4. PHENYLBORONIC ACID MOIETIES MODIFIED SYSTEM

In the previous sections, we mentioned two common processes to construct glucose-sensitive systems. One of them is the utilization of an enzymatic reaction between GOx and glucose. The other is based on the competitive binding to Con A, between

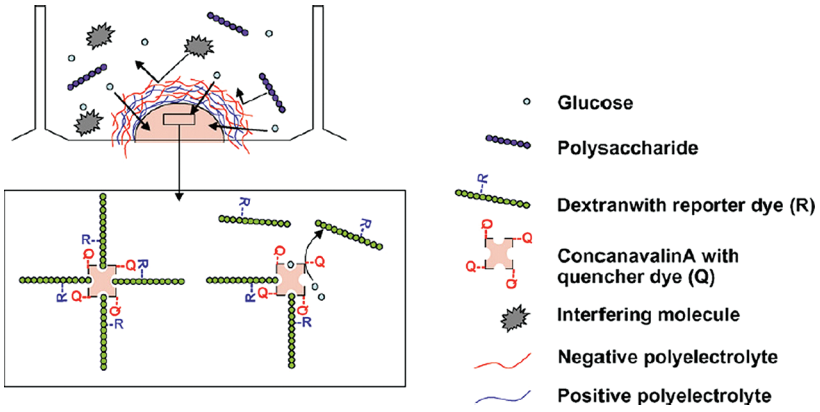

Figure 19. Schematic diagram of a LbL hydrogel pad and the entrapped Q-Con A/R−dextran glucose-sensing system. Reprinted with permission from ref 46e. Copyright 2010 Elsevier Ltd.

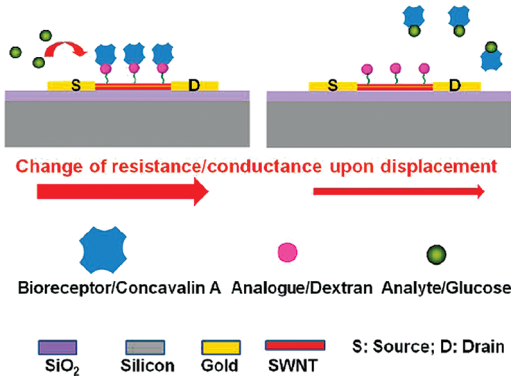

Figure 20. Schematic of the displacement-based chemiresistive biosensor. Reprinted with permission from ref 48a. Copyright 2010 American Chemical Society.

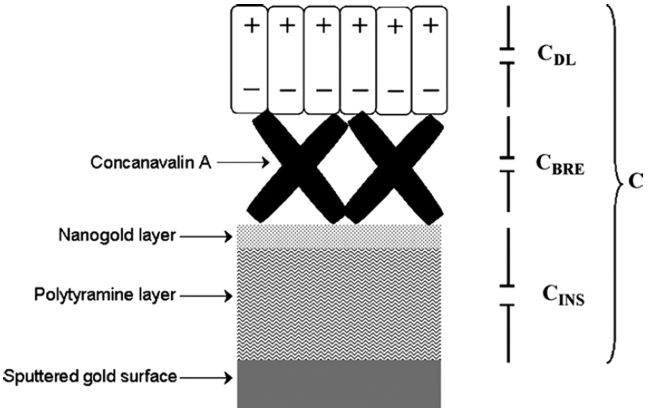

Figure 21. Schematic drawing of the different layers covering the electrode surface contributing to the registered total capacitance. Reprinted with permission from ref 48d. Copyright 2010 Elsevier Ltd.

synthetically glycosylated polymer chain and glucose. However, these protein-based components are quite subjective to environmental changes and could potentially be denatured. Therefore, there is a limitation when the system is required to be used and stored for a relatively long period of time. The third kind of

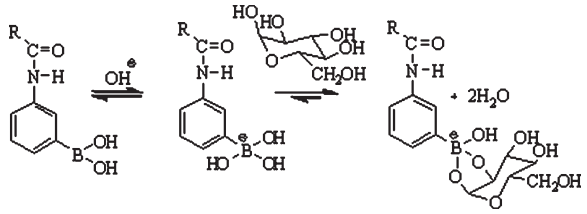

Figure 22. Reversible binding of glucose to APBA.

system, a phenylboronic acid (PBA)-functionalized one, using nonnatural and synthetic components as the glucose sensor, provides us a novel alternative with durability and stability. The combination of PBA and saccharide was first reported by Kuivila and co-workers[49] in 1954. With the following research involved,[50] the mechanism became clear. As PBA and its derivatives are known to form reversible covalent complexes with diol units, they serve as promising components for glucose-responsive sensors. As shown in Figure 22, the PBA compounds have two forms, which exist in equilibrium in water. One is uncharged and thus a relatively hydrophobic form; the other is charged and thus a hydrophilic form. When the glucose is added into the aqueous system, the charged form of phenylborate can form a stable complex with glucose through reversible covalent bonding. Therefore, the equilibrium shifts toward the direction of the increasing charged (hydrophilic) forms of phenylborate. Employing the glucose sensor with this glucose-responsive equilibrium, different devices and systems can provide different functions, which we will introduce in the following part.

4.1. Insulin Delivery and Release

Owing to the desire of diabetes treatment, the insulin-delivery and -release systems became a study focus over the past few years, and significant progress has been made thanks to the contribution of all the researchers in the area. From the mechanism of the binding of polyol complexes and benzeneboronate ion,[50a,b,51] to the swelling[52] and thermo[3,53] behavior, and also the insulin-release kinetics,[54] step by step their efforts have given us a clear prospect of this research area. The response time, biocompatibility, and physiological application are the obstacles that remain in the way of human body utilization, and they are all the factors that have been taken into the researchers' consideration. Thus, various morphologies,[55] technologies,[55d,56] and drug-release

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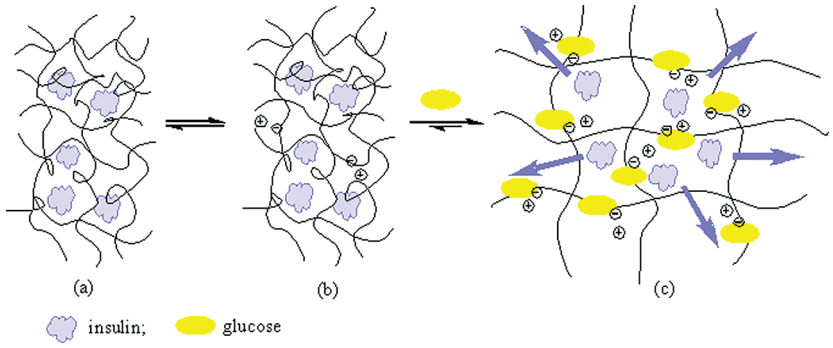

Figure 23. Network swelling and insulin-release model of the hydrogel-containing APBA.

mechanisms[55d,57] were introduced to solve these problems. According to different release mechanisms, the progress that has been made in the recent years is reported as follows.

4.1.1. Hydrogel Swelling. The majority of researchers in the field have chosen hydrogel swelling to realize the drug-release process, because of the controllability and reversibility of the system. To endow the glucose-responsive property with hydrogel, PBA moieties were incorporated into the three-dimensional polymer network. According to the glucose-responsive mechanism of PBA, the shift of the equilibrium results in the increase of charge density of the biofeedback network, leading to stretch and untwist of the polymer chain and driving a swelling response (Figure 23) via both direct charge−charge repulsion effects and Donnan equilibrium.[7a] Consequently, the insulin is contained in the network release.

Following the initial research of glucose-induced lower critical solution temperature change of the poly[*N*,*N*-dimethylacrylamide-*co*-3-(acrylamido)phenylboronic acid] (DMA-*co*-APBA),[53a] and the research of terpolymers of APBA, *N*,*N*-dimethylaminopropylacrylamide (DMAPAA),[58] Kataoka and co-workers first reported a glucose-sensitive and insulin-release system with APBA gel.[55a]

Afterward, the polymer that was modified by APBA became the main stream of the drug-release system via swelling, with varying melioration. Kataoka and co-workers researched on phenylboronic-derivative-based hydrogels, obtaining a discontinuous change in the swelling volume at each critical glucose concentration for various temperatures in a pH 9 solution.[52a] The hydrogels took at least 500 min to reach the equilibrium swelling with high glucose concentration, which cannot catch the change rate in human blood.

Microgels opened up a novel area in the morphology of glucose-sensitive material. Its nanosize endowed it with faster response to glucose; what is more, its network provides it self-regulation and reversible volume change. Zhang et al.[59] fabricated monodisperse glucose-sensitive microgels containing APBA with a diameter of several hundred nanometers. Comparing to bulk gels, microgels underwent a more rapid phase transition in response to glucose; in addition, microgel particles can be readily assembled to meet diversity application requirements. Hoare and Pelton[60] synthesized the poly(*N*-isopropylacrylamide)-based microgels incorporated with APBA. They explored the effects of the distribution of functional groups and the total content of functional groups within microgels on the glucose sensitivity of PBA-graft microgels; they concluded that the more PBA functional groups localized in the outer shell of the microgel and more randomly distributed within the gel network subchains could conduce stronger swelling response of the microgels.

Comb-type grafted hydrogel was another structure that was able to lead to rapid response. Poly(NIPAM-*co*-AAPBA) networks grafted with poly(NIPAM-*co*-AAPBA) as side chains were synthesized[61] for the first time. The novel structure was proven to successfully respond to the glucose addition at physiological temperature.

As the pK_a of APBA is 8.6, which is quite higher than pH value in human body, the system cannot be used in vivo. Therefore, Hoare and Pelton synthesized charge-switching polymer by acrylic acid (AA) as the anionic monomer and *N*,*N*-dimethylamino ethylacrylate (DMAEA) as the cationic monomer. The polymer was also functionlized by APBA.[62] Owing to the amphoteric structure, the system responded to glucose in the physiological environment; because of the nanostructure, it bore a short response time. Furthermore, it was demonstrated to afford large amounts of insulin for the release within the physiological pH and ionic strength.

Changing the structure of the PBA functional group was also a feasible and effective way to make the system available for the physiological environment. Kataoka and co-workers introduced {4-(1,6-dioxo-2,5-diaza-7-oxamyl)phenylboronic acid},[63] DDOPBA (Figure 24), to replace APBA in the similar system, because the pK_a of DDOPBA was 7.8, close to the physiological pH. The employment of the alternative glucose-responsive group may serve as a landmark step for a self-regulated glucose-sensitive device that makes progress for in vivo use.

Core−shell nanostructure was also introduced into the glucose-responsive drug-delivery field. Lapeyre and co-workers synthesized a multiresponsive microgel, with a temperature-responsive/hydrophilic core inside a glucose-responsive shell.[64] This structure would lead to more accurate and precise response to an environmental change. Moreover, the employing of a functional group, DDOPBA, enabled the microstructure to respond to glucose under the physiological environment.

4.1.2. Insulin Replacement. Different from the swelling system, the release of insulin is not leading by charge−charge repulsion effects or Donnan equilibrium but by the competition between modified insulin and added free glucose. In other words, the insulin was modified and then combined with the glucose-responsive chain. When the glucose was added into the system, it replaced the modified insulin to connect with the polymer chain. As a result, the insulin releases.

Gluconated insulin (G-Ins) (Figure 25) within the PBA-contained polymer was one of such systems that was prepared by Okano and co-workers.[57a] Further progress made by the research that deserves mention is amino group incorporation. The introduction of amino groups into the polymer, near the

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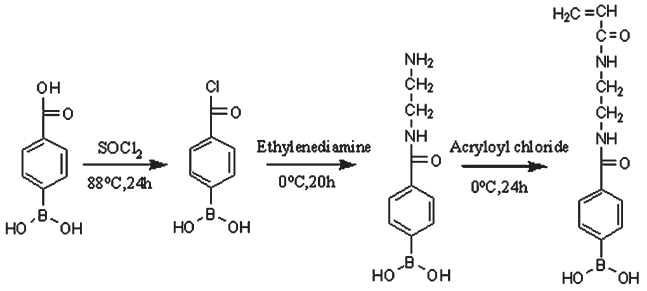

Figure 24. Preparing routine of 4-(1,6-dioxo-2,5-diaza-7-oxamyl) phenylboronic acid.
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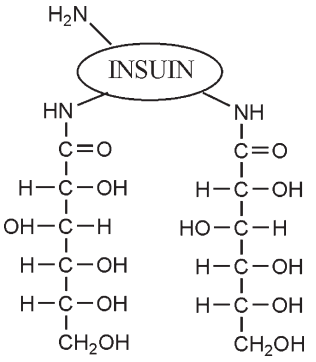

Figure 25. Structure of G-Ins.
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PBA groups, not only improved the stability of gel beads with G-Ins but also endowed the system with the physiological applicability.

Jensen and co-workers reported a D-glucamine polyamide polymer-based insulin-release system.[57b] Sulfonamide phenylboronic acids were chosen both to serve as the glucose sensor and to modify the insulin. Because the pK_a values of 4-sulfonamide phenylboronic acids were ~7.4, the system was also supposed to respond at the physiological environment. Moreover, the modification of insulin led to steeper glucose sensitivity and improved release profile.

The nanostructure is employed in the research field. Zhao and co-workers were the first group to use PBA-functionalized mesoporous silica nanoparticle (MSN) to construct the drug-release system with gluconic acid-modified insulin,[57c] as shown in Figure 26. It was demonstrated that the device served as an efficient insulin-release system for glucose response, because of its good biocompatibility and cellular uptake properties.

4.1.3. Disassembling and Degradation. The insulin release due to disassembling and degradation relies on structures that destroy the insulin container, when glucose is added in the aqueous solution. Usually, there are two kinds of structure fitting for the system: multilayer[55b,d] and core−shell.[6,55c,56a]

Multilayer structure is always made up of polyelectrolyte and by the layer-by-layer technique.[65] Using this technique, De Geest and co-workers first fabricated a glucose-responsive polyelectrolyte capsule, containing PBA.[55b] When exposed to a certain glucose concentration that was higher than the concentration in the bloodstream of a healthy human, the capsules disassembled in <5 min.

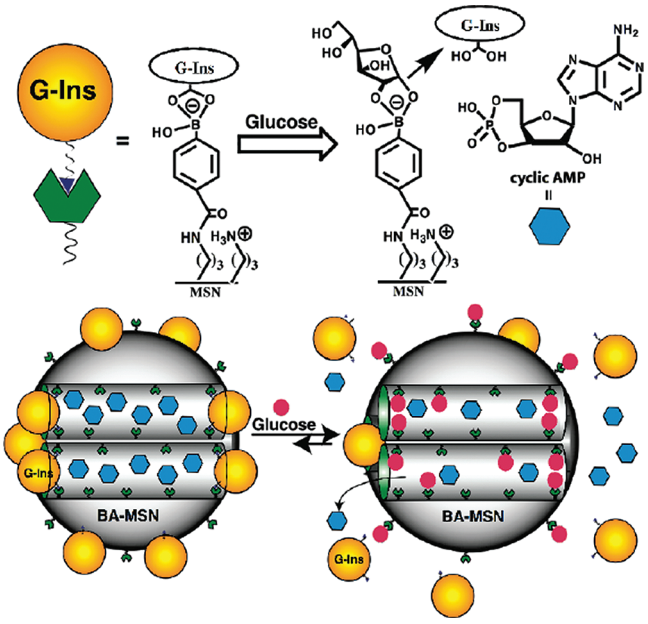

Figure 26. Schematic representation of the glucose-responsive MSN-based delivery system for controlled release of bioactive G-Ins and cyclic adenosine monophosphate (cAMP).

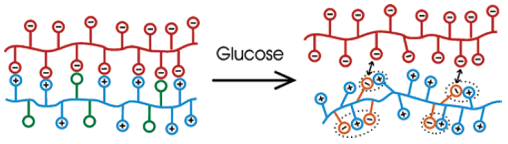

Figure 27. Proposed mechanism of the glucose-induced decomplexation of a polyelectrolyte bilayer. The red circles represent the sulfonates, and the blue circles represent the amino groups. The green circles represent the uncharged phenylboronic acid groups that become anionic (orange circles) after addition of glucose.

This was because the electrostatic interactions change between the polyanion and PBA-containing polycation (Figure 27), after the glucose addition. However, there was one factor, the response pH, that limited the utilization of this system in vivo. As we mentioned above, the pK_a value of the introduced glucose sensor was higher than the physiological one. A few years later, Ding and co-workers introduced another system to solve this problem. As shown in Figure 28, they prepared multilayer films from poly(vinylalcohol) (PVA) and poly[acrylamide-*co*-3-(acrylamido)phenylboronic acid] by the use of covalent phenylboronate ester bonding as the driving force.[55d] As the covalent bonding was broken with the addition of glucose under the physiological pH value, and the process was reversible, the multilayer film served as a promising insulin-release system.

Core−shell structure was designed and synthesized by Zhang et al.,[55c] with degradable core and nondegradable shell, to optimize the process of insulin release. The complexation of PBA groups with glucose could loosen the net of the shell, and thus increase the permeability of the degraded core. Jin and co-workers employed a self-assemble technique to prepare amphiphilic nanoparticles,[56a] as shown in Figure 29. The swelling behavior, insulin loading, and release process were studied, which suggested that the glycopolymers had the potential to be used in a self-regulated insulin-delivery system. Core−shell micelles

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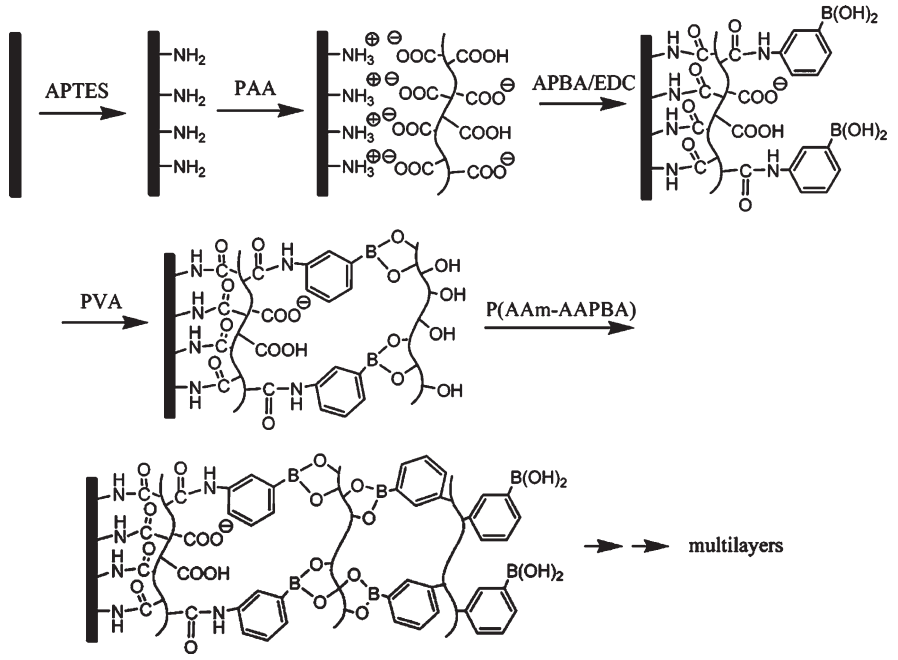

Figure 28. Fabrication of PVA/P(AAm-AAPBA) multilayers using phenylboronate ester bonding as the driving force. Reprinted with permission from ref 55d. Copyright 2009 The Royal Society of Chemistry.

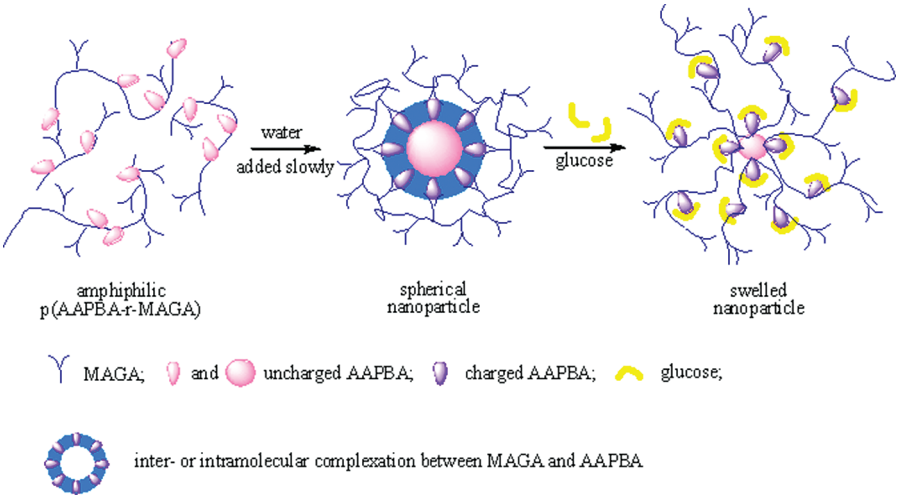

Figure 29. Self-assembly of the glycopolymers without/with insulin and glucose-sensitive release.

were prepared by the self-assembly of synthesized poly(ethylene glycol)-*block*-poly(acrylic acid-*co*-acrylamidophenyl boronic acid).[6] The core was hydrophobic and composed of poly(acrylamidophenylboronic acid) (PAAPBA), whereas the shell was hydrophilic and composed of PEG. In aqueous solution at pH 7.4, the core−shell structure disaggregated as it was exposed to glucose (Figure 30).

In addition, controlled radical polymerizations, such as atom transfer radical polymerization (ATRP)[66] and fragmentation chain transfer (RAFT) polymerization,[56b,67] were also innovatively used in the block glucose-responsive polymers. So far, the systems with this attractive technique were well developed, and the authors that did the related research provided us a hint and broke new ground for the preparation of self-assembly of the polymer, which was used for insulin release.

4.2. Glucose-Concentration Detection

PBA functional groups also have been utilized to determine the glucose concentration. Compared to GOx and Con A sensors, as we mentioned above, PBA bears the advantage of stability. Nevertheless, all three kinds of sensors have the same problems in the glucose-concentration testing. The researchers have to make steps on the shoulders of the predecessors, to boost the performance of sensitivity, selectivity, and biocompatibility, through fluorescent-based methods,[52b,68] holographic ones,[69] colorimetric ones,[70] optical fiber-based ones,[71] and some others.[72]

4.2.1. Fluorescent Sensors. Owing to the unique properties of the boronic acid and derivatives among the three kinds of glucose sensors, the PBA functional groups were used as the fluorescent receptors for the glucose-concentration detection.

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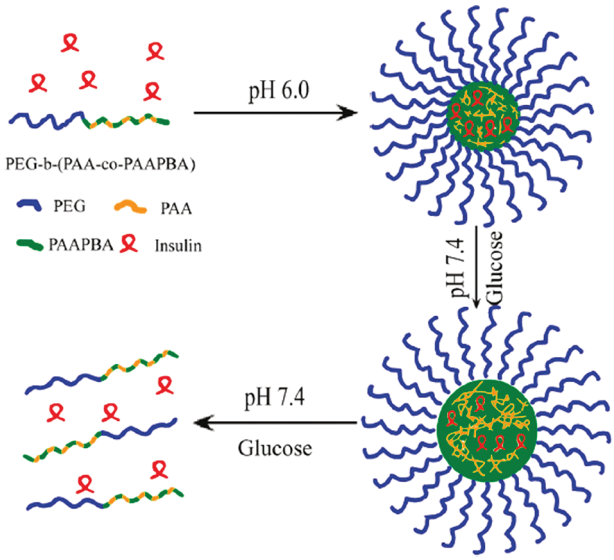

Figure 30. Schematic illustration of the formation, swelling, and disaggregation of insulin-loaded micelle and release of insulin from the micelle according to glucose responses.

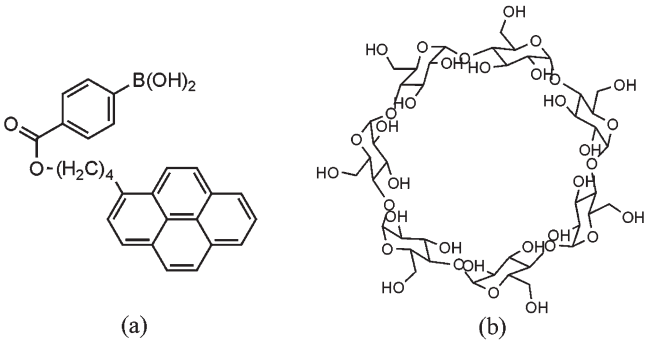

Figure 31. Structure of (a) fluorescent probe and (b) β-CyD.

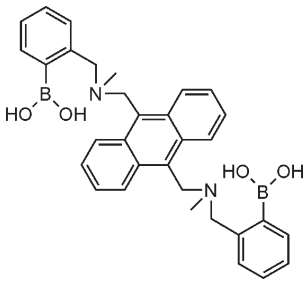

Figure 32. Structure of a diboronic acid.

The advantage of the boronic acid-based probes are the fast and reversible interaction with sugars; thus, they have been widely researched.[73] Fluoren-2-yl-boronic acid was the first molecule that was used for saccharide detection.[50a] However, this initial system bore merely feeble fluorescent change before and after the glucose combination. Thus, various structures were introduced to try to enlarge the fluorescent change based on glucose response. The use of an appropriate functional group, the structure modification of fluorescent-related unit, and the exploration of nanostructure and topological structure were the main strategies that were researched to make progress on the way of achieving favorable application performance.

Among the boronic acid-based fluorescent systems, the photoinduced electron transfer (PET) model has been prevalently studied. With the link between fluorophor and PBA-based receptor, when the receptor combined with glucose, the fluorescence quenched, because of the electron transfer. Thus, the essential question of this system is the molecular design of the chemsensor with facile electron transfer.

Anthrylboronic acid was reported to enhance the quenching, and consequently the change of fluorescence by chelation.[74] Taking anthracene as fluorophore, and diethanolamine as a bridge between anthracene and PBA,[75] the system showed a large increase in fluorescent intensity in the presence of millimolar concentrations of PBA.

A novel fluorescent probe (Figure 31a) was prepared by Teramae and co-workers,[76] where 1/β-cyclodextrin (β-CyD) (Figure 31b) was imported to increase the fluorescence emission of the sugar response. Before the glucose addition, the PET was from the pyrene donor to the phenylboronic acid acceptor in the probe; thus, the fluorescence quenched. When the probe had bound to the glucose, the PET was inhibited. Consequently, the fluorescence intensity of the pyrene moiety increased.

To be used in vivo, a response in physiological pH was required. Therefore, James and co-workers[77] introduced amino into the ortho-position of both mono- and diboronic acid systems, to ensure the fluorescent response occurring at a pH of 7.77. They also concluded that a diboronic acid system (Figure 32) with a cleftlike structure was particularly selective and sensitive for glucose.

Ionic counterparts were also employed to enhance the fluorescent change and to fulfill the requirements of the physiological utilization with another mechanism. The two-component sensing system was composed of anionic dye and cationic quencher. Usually, pyranine, its derivatives,[78] and aminopyrene trisulfonic acid and its derivatives[79] were used as anionic dye, while the boronic acid-substituted benzyl viologens[78,79] served as cationic quencher. Without glucose, the two parts combined to each other with weak fluorescence emission. In the presence of glucose, glucoboronic ester formed and the quenching efficiency decreased, so the fluorescence became strong, as shown in Figure 33.

With both photostability and fluorescence, naphthalic anhydrides and their derivatives (Figure 34a) have been researched by Cao and co-workers.[80] The result demonstrated that, with appropriately substitution at both the naphthalic and phenyl rings of *N*-aryl-1,8-naphthalimide, three sensors, as shown in Figure 34, that exhibited a dual emission and remarkable sensitivity for glucose were obtained.[80b,c]

CdS QD, a kind of nanostructure with fluorescent performance, was also used for the optical detection of glucose as well.[81] The glucose response of the novel structure was first reported by Cordes and co-workers.[82] Recently, Wu and co-workers prepared the copolymer microgels of poly(*N*-isopropylacrylamide acrylamidephenylboronic acid) [p(NIPAM-AAm-PBA)], with CdS QD fixed inside.[83] The fluorescence of the system could be reversibly quenched and antiquenched, as the microgels swell and deswell according to the glucose concentration change, as shown in Figure 35. This system integrated the structure of QD and microgel; therefore, it possessed not only the advantages of size-controlled fluorescence properties, high quantum yield, and stability against photobleaching from QD but

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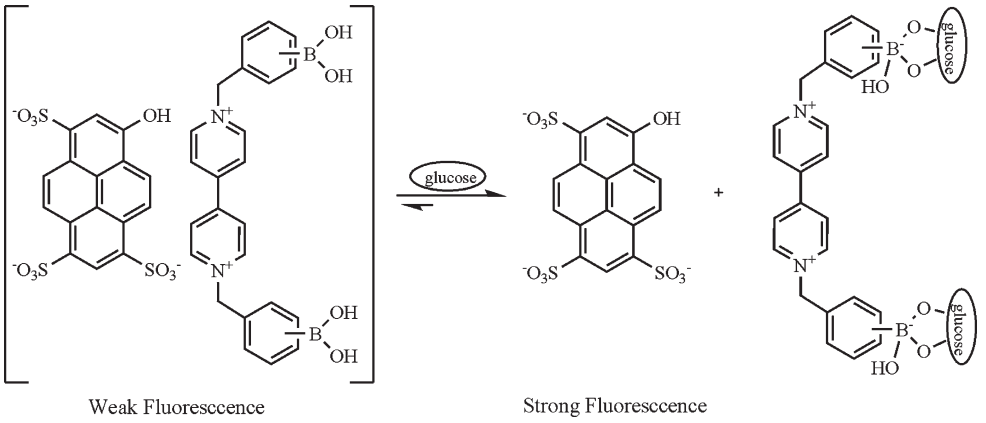

Figure 33. Proposed mechanism of glucose detection: glucose-induced dissociation of ground-state complex results in fluorescence increase.

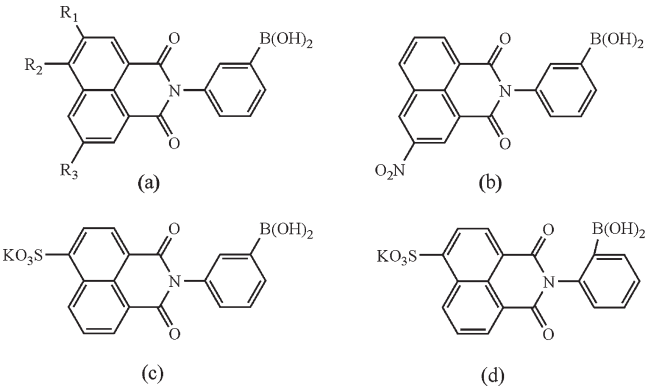

Figure 34. Structure of naphthalic anhydride derivatives mentioned.

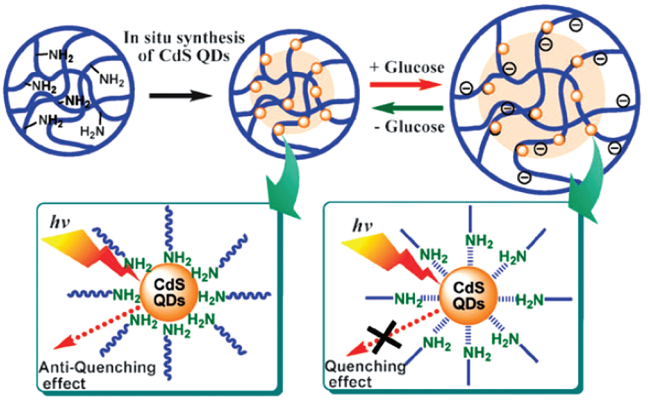

Figure 35. Reversible fluorescence quenching and antiquenching of CdS QDs embedded in the interior of p(NIPAM-AAm-PBA) microgels in response to the change in glucose concentration.
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also the superiorities of simple synthesis, easy functionalization, uniform size distribution, tunable dimension, potential biocompatibility, and short response time from microgel.

Some other devices were also explored with a macroscopic view. For example, PBA-based nanoparticles, which contained two kinds of fluorophores with overlapping emission, were prepared by Zenkl and Klimant.[84] Glucose led to the swelling of the nanoparticles; as a result, the distance between the fluorescent donor and acceptor inside was enlarged. The quenching by the acceptor was weakened, and thus a dramatic change in the fluorescence emission spectra was tested. Topological structure was a novel strategy that has been recently researched in the glucose-responsive area. A water-soluble hyperbranched poly(*p*-phenylene) bearing boronic acid groups was synthesized (Figure 36) by Kim and co-workers.[85] Compared to linear polymer, hyperbranched polymer exhibited high sensivity toward glucose, owing to distribution of functional groups.

4.2.2. Colorimetric Sensors. Colloidal crystalline arrays (CCAs) were a novel structure that attracted a large amount of research. CCAs were periodic arrays of colloidal particles (~100 nm) that embedded within a certain polymer matrix, hydrogel. On the basis of the Bragg diffraction of visible light, the lattice structure within the hydrogel exhibited structural colors. The wavelength of diffracting light was determined by the spacing of the colloidal particles. As PBA groups were copolymerized onto the matrix, the hydrogel responded to glucose in the form of volume change. The change resulted in the alteration of the lattice spacing and, thus, the change of the wavelength of the diffracted light. As a result, we could monitor the glucose concentration by observing the visible color change.[70]

As shown in Figure 37, Asher and co-workers[70b] first fabricated a colorimetric sensor that employed a crystalline colloidal array incorporated into a polyacrylamide hydrogel, with 3-APBA serving as the glucose-recognition agent. However, this colorimetric system responded only in low ionic strength solutions, which cannot match physiological condition. With a similar system, polyacrylamide−poly(ethylene glycol) (PEG) hydrogel and a polyacrylamide-15-crown-5 hydrogel suspending phenylboronic acid groups[70a] were used to serve as the backbone, to solve the ionic strength problem and provide a new recognition motif. With the presence of glucose, the functional groups, boronic acid and PEG (or crown ether), self-assembled into a supramolecular, to increase the cross-linking of hydrogel, so the blue shifts of the photonic crystal diffraction occurred. This system was available to use at high ionic strength to meet the physiological requirement. To improve the application to noninvasive monitoring of glucose, some new boronic acid derivatives were studied.[86] It was reported that the prepared photonic crystal glucose-sensing material could serve as ocular inserts and diagnostic contact lenses for patients with diabetes mellitus. To speed up the glucose response, Asher and co-workers[87] tried to

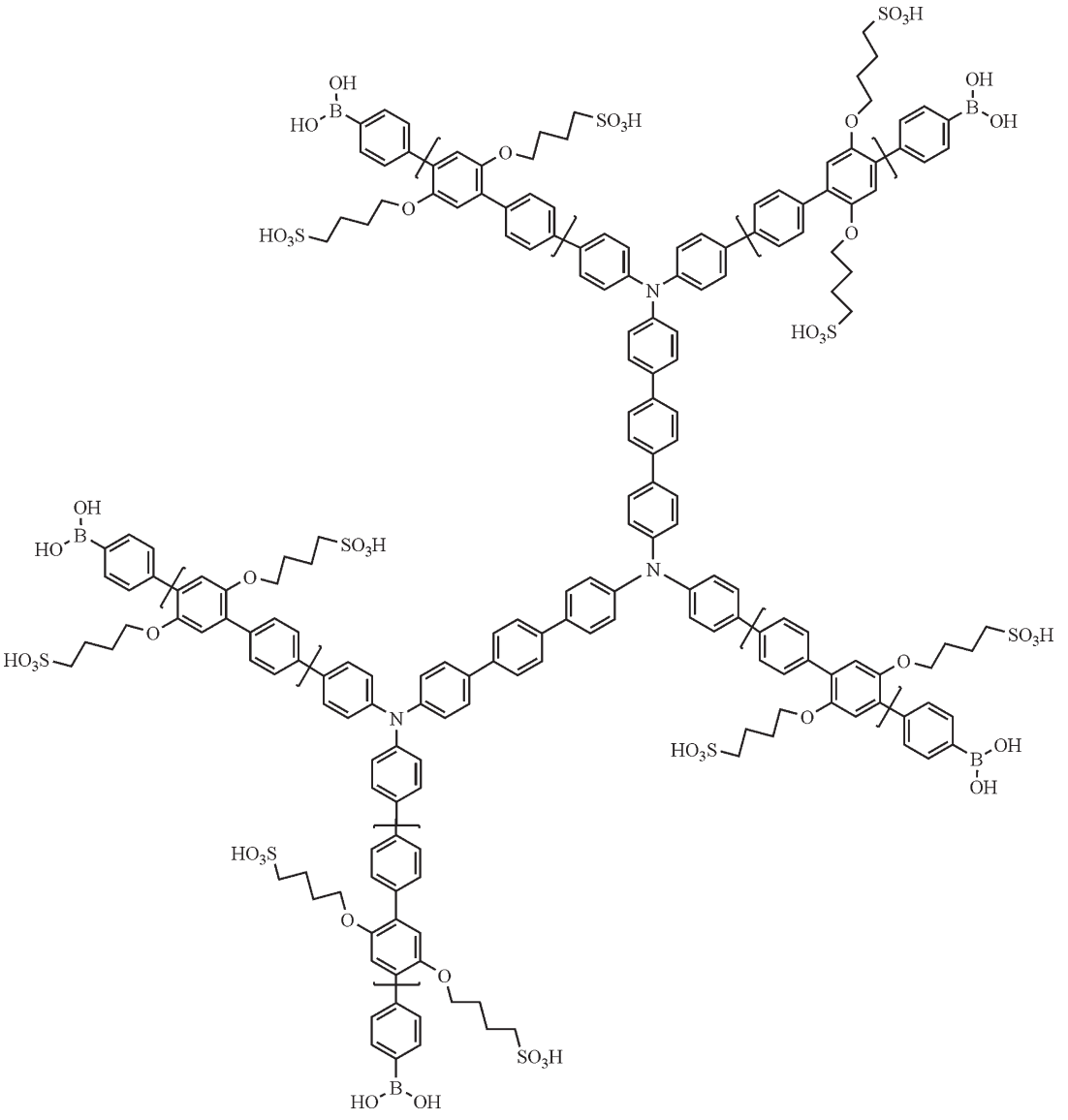

Figure 36. Synthesized hyperbranched polymer (HP). structure.

control the elasticity and the hydrophilic−hydrophobic balance of the hydrogel system by copolymerizing *n*-hexylacrylate into an acrylamide−bisacrylamide hydrogel. As reported, it took no more than 90 s to respond to the average glucose concentrations in blood and 300 s to respond to the average glucose concentrations in tear fluid. Recently, the same group[88] ameliorated the system of the colorimetric sensor and made it available to high concentrations of glucose, especially in blood. It was also demonstrated that the sensor was reversible over a single week.

An inverse opal structure was also used as the colorimetric glucose sensor. The first inverse opal system for glucose monitoring was reported by Takeoka and co-workers,[70c] as shown in Figure 38. Through the system, it was facile to determine the glucose level by color change. Furthermore, easy fabrication and controlling, as well as rapid achievement of swelling equilibrium, made the system more attractive and promising to be used for glucose-concentration monitoring.

4.2.3. Holographic Sensors. A holographic sensor system is one of the novel optical methods to be explored in the application of detection of glucose concentration. The robust, inexpensive, and remotely interrogatable properties and mass manufacture possibility of the system attracted large amounts of attention in recent years.[69c,89]

The basic mechanism of the holographic sensor was interference pattern between the incident beam through the gratings and the reflected one. According to the Bragg's law, $m\lambda = 2nd \sin\theta$, the changes in the distance of the fringes (d) would bring about significant changes in the wavelength (color) of the reflection hologram. Thus glucose-responsive polymer matrix, which served as fringes, was constructed.[90] With the presence of glucose, the matrix swelled, and hence the space between the fringes increased, generating the red-shift of hologram. Conversely, shorter wavelength would be observed if the matrix deswelled. Therefore, tracking the change of diffraction wavelength allowed one to monitor the glucose concentration of the surroundings.[69a]

Kabilan and co-workers[69a] established hydrogel film with holographic sensor for monitoring glucose, based on 4-vinylphenylboronic acid (4-VPBA), which responds to glucose reversibly. This system provided the primary holographic device for glucose

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testing. However, the established system merely responsed to glucose at pH 9, so physiological pH application became the main topic of the subsequent research. In addition, there are some other saccharides with *cis*-diol groups that are able to react with boronic acid groups in human blood, so selectivity also has been a problem worth considering. In a study almost published at the same time with the above article, Lee and co-workers[91] synthesized inverse opal hydrogel by photopolymerizing 2-hydroxyethylmethacrylate and 3-APBA within the interstitial space of a colloidal crystal template. This system reversibly responded to glucose at physiological concentrations and ionic strength.

Exploring diverse PBA derivatives structure can also solve the problem, to some extent. For example, 3-acrylamidophenylboronic acid (3-APBA),[92] 2-acrylamido-5-fluorophenylboronic acid (5-F-2-MAPBA),[92] and 2-APB[93] were all researched (Figure 39). It was found that high concentrations of 3-APBA and introduction of 5-F-2-MAPBA exhibited an increased selectivity to glucose at physiological pH and ionic strength. Thanks to the neighboring effect of amido group, 2-APBA preferred a zwitterionic tetrahedral form at physiological pH values and gave priority to bind with glucose.

On the basis of 4-VPBA, incorporation of a tertiary amine (Figure 40) along with PBA was a befitting choice.[69b,94] The tertiary amine endowed the boronic acid with the reactive tetrahedral state at physiological pH through intermolecular electron donation from the amine. What is more, it improved the selectivity of the system toward glucose over other *cis*-diol groups in human blood. Recently, Worsley and co-workers[95] described a thin-film polymer hydrogel with similar holographic sensor. A breakthrough was made in that they first used the system to test real human blood plasma samples with different glucose concentrations successfully.

4.2.4. Optical Fiber Sensors. The glucose sensor based on optical fiber was an innovation in optical glucose-determining system. The glucose-responsive hydrogel with size ~50 μm was bound to the tip of an optical fiber and made a Fabry−Perot cavity. The monitoring of glucose relied on the determination of the changes in properties of the interference wave of the light reflected at two interfaces: the fiber−gel and the gel−solution. With a precision of ~2 nm to detect the relative gel length changes of the ~50-μm hydrogel, the system exhibited high resolution and good degree of reproducibility.

Using acrylamide-based hydrogels, tertiary amine, PBA, and optical fibers, Tierney and coworkers[71,96] constructed a series of systems (Figure 41). It was reported that, by varying the

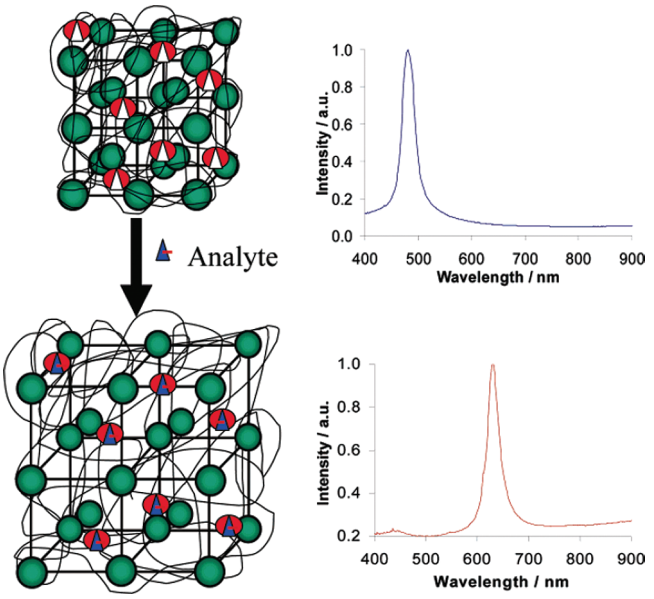

Figure 37. PCCA photonic crystal sensing materials consist of an embedded CCA surrounded by a polymer hydrogel network that contains a molecular-recognition element.
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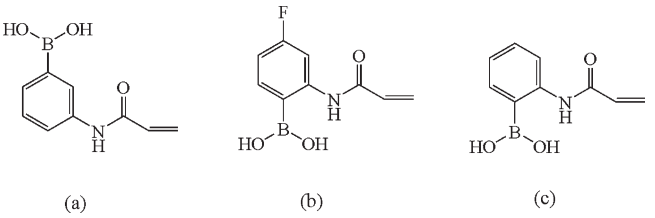

Figure 39. Mentioned structure based on PBA.

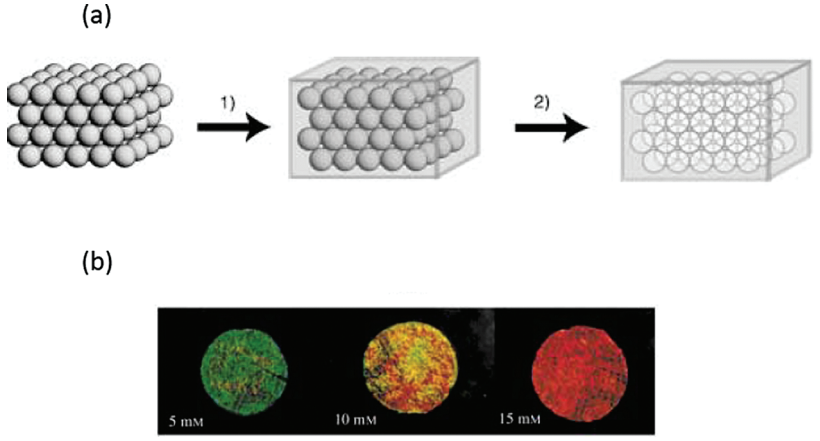

Figure 38. (a) Preparation of a periodically ordered interconnecting porous gel by using a closest-packing silica colloidal crystal as a template. (b) Photographs of periodically ordered interconnecting porous poly(NIPA-co-AAPBA) gel in a 2-(cyclohexylamino)-ethanesulphonic acid (CHES) buffer aqueous solution including different concentrations of glucose at 28 °C. Reprinted with permission from ref 70c. Copyright 2003 Wiley-VCH Verlag GmbH & Co. KGaA.

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3-PBA/tertiary amine ratio, sensitivity and selectivity toward glucose could be tuned.[71a] In addition, it was also demonstrated that the gel composition with 10 mol % dimethylaminopropyl acrylamide was the most promising for detection of glucose at both physiological pH and ionic strength.[71b]

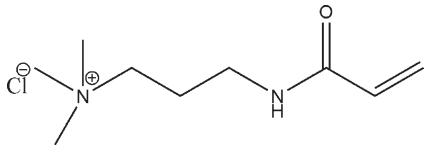

Figure 40. Molecular structure of the quaternary monomer (3-acrylamidopropyl)trimethylammonium chloride.

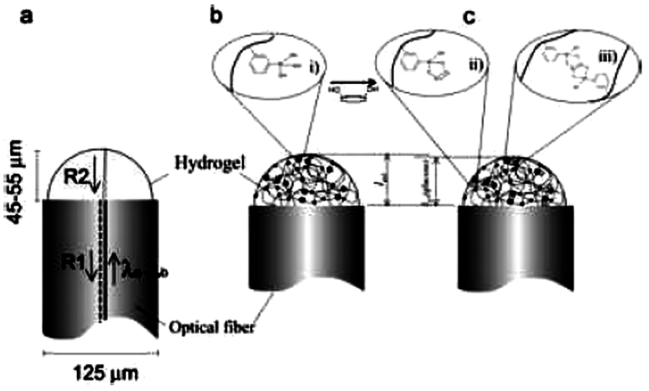

Figure 41. Schematic illustration of the principle for determination of changes in the optical length of the half-spherical biosensitive hydrogel covalently bound at the end of an optical fiber.
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4.2.5. Other Sensors. With the development of technology, other novel techniques and creative ideas have been introduced unceasingly into the glucose-monitoring systems.

The complex of PVA, copolymer of PBA, and tertiary amine were synthesized by Kikuchi and co-workers.[72a] The complexes were coated on platinum electrode, to form a membrane. The glucose-induced swelling of the membrane resulted in the increased diffusion of ion species, and hence, measurable current change was observed.

Chen and co-workers[97] used phenylboronic acid derivative to self-assemble on Au surface to form a monolayer. Surface plasmon resonance (SPR) spectroscopy was used to test the saccharide sensing. The system had good sensitivity of monosaccharide sensing, but it was not aimed for glucose only.

Through synthesizing the glucose-responsive polymer brushes upon gold substrates and microcantilever arrays, Chen and co-workers[72b] prepared glucose-responsive micromechanical cantilevers that were promisingly serving as glucose detectors, as shown in Figure 42.

5. CONCLUSION

Above all, we discussed the application of the glucose-sensitive systems according to three categories: glucose oxidase, Con A, and phenylboronic acid. They have been utilized in self-regulated insulin-release process and glucose-concentration detection. Although the GOx and Con A, the natural glucose-responsive biosensors, provide the advantages of biocompatibility and biodegradability, they suffer from instabilities due to denaturizing from the environment changes. Thus, to format a continuous sensor, phenylboronic acid is the better choice to serve as the glucose-sensitive part. As a result, this synthesized sensor has attracted expanding interest up to now. Research on glucose-sensitive systems will keep on removing the obstacles in the way

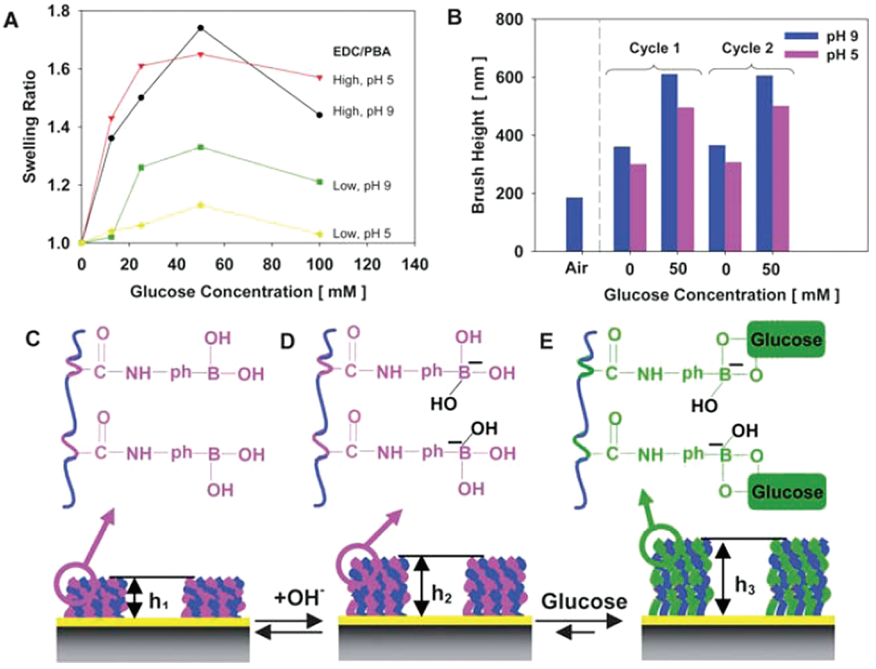

Figure 42. (A) Equilibrium brush swelling ratio plotted as a function of glucose concentration. (B) Brush height in air, in buffer, and in glucose solution. Key: brushes exposed to 50 mM glucose at pH 9.0 (blue bar) and brushes exposed to 50 mM glucose at pH 5.0 (purple bar). (C−E) PBA in neutral trigonal form, charged boronate anion, and complex with glucose, and ensuing brush heights (h), where $h_3 > h_2 > h_1$.
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of practical applications. The promising application of the research really makes sense: alleviating the suffering of diabetes patients and increasing the convenience of testing for them.

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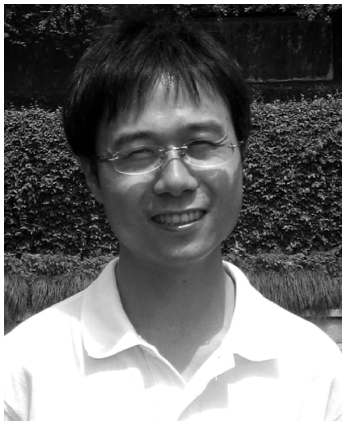

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