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Autonomous and Continuous Stimuli-Responsive Polymer Surface for Antibacterial Application via Enzymatic Self-Propagating Reactions

Chao Ding,[a,b] Zhengqing Yan,[a,b] Jinsong Ren,[a] and Xiaogang Qu*[a]

Abstract: Stimuli-responsive polymer materials inspired by biological materials have invoked increasing research interest; however still suffer from limitations such as finite amplified responses and poor sensitivity of the unstimulated parts. Here, we describe a new strategy for creating H^+ responsive polymer surfaces that are capable of transforming specific local, fleeting stimuli into global, macroscopic changes. The introduction of self-propagating reactions into the polymer surface systems endows them with excellent stimuli amplification properties and calls up response of the unstimulated parts. Based on this design, a polymer and enzymatic reaction are empolyed, which enable specific stimuli response and then lead to macroscopic changes of the surface. We further show that the prepared H^+ responsive polymer surfaces can be empolyed for antibacterial application. This work provides a good example for achieving the autonomously reconfigureable materials that respond to local, fleeting stimuli.

Introduction

The surface of materials determines their interactions with the surrounding environment,[1] and surface chemistry has been received great interest, particularly in the design and study of nature-inspired responsive and adaptive surfaces.[2] The surfaces of natural leaves react autonomously and macroscopically to specific stimuli which are controlled by the biological materials inside the leaves.[3] These biological materials are able to transform local, usually fleeting stimuli (like touch, heat, etc) from one part of the leaf to a response of the whole leaf via self-propagating reactions. The stimuli-responsive polymer materials that respond to the local changes via self-propagating reactions (light, chemicals, etc.), which impart an autonomous, macroscopic response to the system, have attracted much attention in recent bio-inspired surface design [4]. The responsiveness and switchability like the biological materials enabled a variety of bio-mimetic applications for such polymer materials, with the most studied systems being chemical responsive materials [2a, 2b, 2d, 5].

For achieving the desired functionalized surface, modification procedures have long been of significant interest. Particularly, numerous methods have been developed to impart antibacterial properties to inert surfaces. Two strategies for design of antibacterial surfaces are often empolyed. One is to coat the surfaces with non-fouling materials that can effectively prevent the attachment of bacteria [6]. The other is to link bacterial killing compounds that can efficiently kill various bacteria [7]. However, the functionalized surfaces for antibacterial are always on their activated state which is a great concern about the biocompatibility. Accordingly, it is highly desirable to develop a surface that switches the macroscopic properties in response to bacteria attacking and turns the entire surface into the defending forms.

By the inspiration of leaves, we presented a new strategy for design of stimuli-responsive polymer surface systems that exhibit the ability to transform local, fleeting stimuli to global macroscopic properties change of the surface (Scheme 1). In the design demonstration, we illustrated the construction of the self-propagating polymer surfaces and the capability of the responsive surface that switches from biocompatible to bacterium killing (Scheme 1), thus providing a new way for amplifying a stimuli-responsive event into a macroscopic change on the surface. The global and autonomous properties changes of the polymer surfaces are attributed to the self-propagating reactions arose from the polymers that are functionalized with specific repeating units. These self-propagating reactions endow the surfaces spontaneous communications with the distant portions while also change the properties of the surfaces without requiring additional stimuli. Here we are particularly interested in the polymer materials that respond to pH change of the local surrounding medium, like boronate ester complexes that hydrolysis at acidic condition. [6b, 8] In the designed polymer surfaces, hydrolysis of prepared glucose boronate ester polymer (Scheme 1c) with H^+ stimuli releases glucose that can further react with the immobilized glucose oxidases and continue the self-propagating reactions. The spreading of the self-propagating reactions within the surface leads the global macroscopic properties change. In brief, this work shows: (i) a bio-inspired surface system which contains self-propagating reactions thus enabling stimuli spreading, (ii) the surface can be autonomously in response to local and even fleeting stimuli to kill bacteria. Our work may offer a new way for achieving

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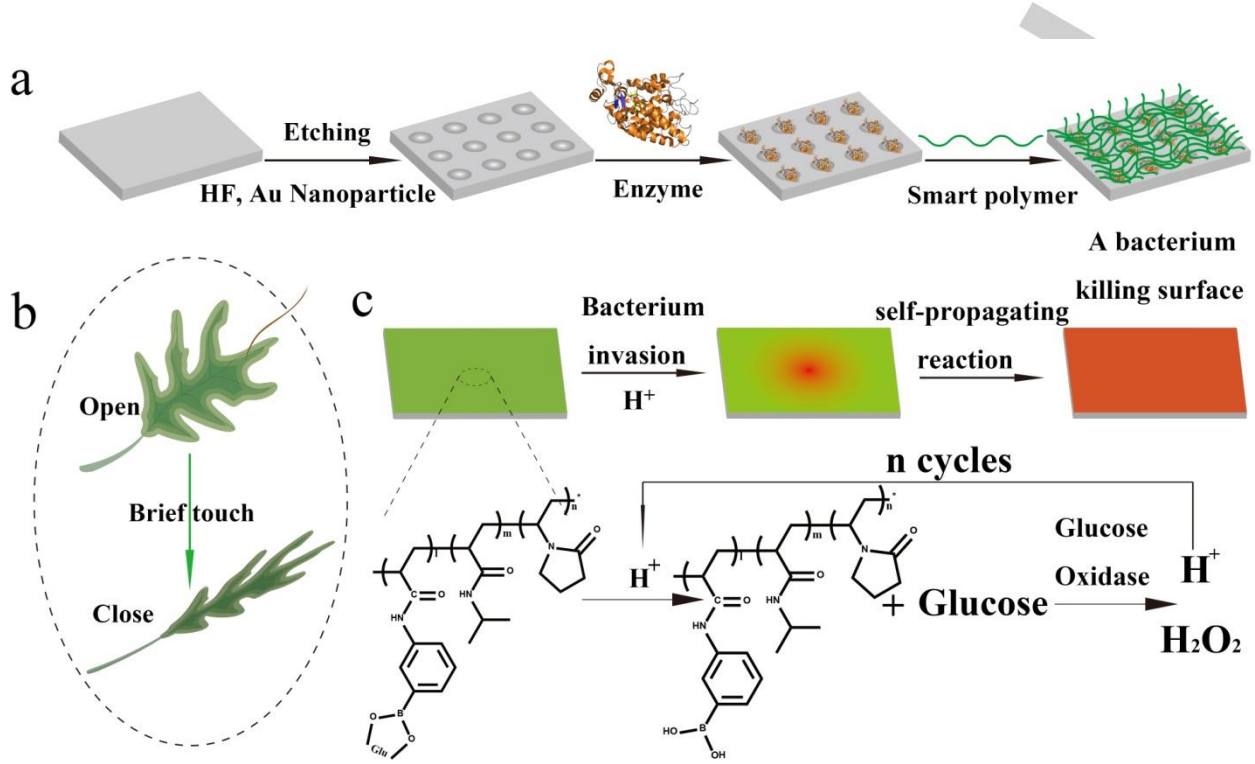
the autonomously reconfigure materials that respond to local, fleeting stimuli.



Scheme 1. Schematic illustration of a) the preparation precedures of the polymer surface, b) the nature Venus flytrap that respond to brief touches and c) the leaf-inspired surface that transform local, fleeting stimuli into global, macroscopic properties changes of the surface. The bacterium invasion releases H^+ that initiates the self-propagating reactions within the surface that amplifies the H_2O_2 and H^+ output, the spreading of H_2O_2 and H^+ leads to the whole properties change of the surface. The bottom half of c) depicts the specific boronate ester polymer and self-propagating reaction A+B→C+A that provides the global change across the whole surface.

Results and Discussion

Design and construction of the surface that responds to local and fleeting stimuli via self-propagating reactions

The design for the bio-inspired surface requires a specific functionalized polymer and an enzymatic reaction, where the repeating functionalities of the polymer are glucose boronate esters and the immobilized enzyme is glucose oxidase (GOx) that leads to a reaction with glucose (Scheme 1). The acid responsive boronate esters (the structure in Scheme 1c) on the surface respond to a local fleeting H^+ stimulus by undergoing a hydrolysis reaction that releases glucose, the released glucose diffuses across the surface freely and initiates the self-propagating reaction (the reaction in Scheme 1c) by reacting with GOx to produce H_2O_2 and H^+. The H^+ reacts further with the other boronate esters of the polymer, which ultimately leads to release of glucose and then propagates the release of H_2O_2 and H^+ which change global surface properties. Upon completion of the self-propagating reactions, the former surface has been transformed to H^+ and H_2O_2 concentrated surface and could be used to kill bacteria. As the above illustration, the surface designed can be tuned by the self-propagating reactions that change the properties of the surface as a whole.

Scheme 1a depicts the preparation progress of the surface we designed to simulate nature leaves. With the help of Au nanoparticles (Figure S1, the average size was 55.8 nm), we first constructed nanohloes on the glass surface for enzyme immobilization.[9] The glass surfaces were cleaned with piranha solution and subsequent immersion in the etching solution. The nanoholes formed on the surfaces were characterized by AFM and SEM. As shown in Figure 1a and S2, 10 nm deep nanoholes formed after etching. We then immobilized GOx onto the surface by immersing the surface in the GOx solution at 4 °C for 2 h. Subsequently, the surface was rinsed with water to remove weakly absorbed GOx. The AFM image in Figure 1b indicated the nanoholes were filled with GOx. Further results of XPS and ATR spectra (Figure S3 and S4) exhibited the successful immobilization of GOx due to the appearance of N 1s peak at 399.2 eV in Figure S3 and characteristic amide A (3278 cm^{-1}), amide I (1640 cm^{-1}), amide II (1539 cm^{-1}) and amide III (1248 cm^{-1}) bands of GOx in Figure S4. The activity assay of the free GOx and immobilized GOx showed that GOx after immobilization kept most of its activity (Figure S5 and table S1). The last step was the deposition of the polymer on the surface

through the hydrogen bond formation between silanol groups on the surface with the nitrogen atom on the pyrrolidone group of the polymer. [10] Prior to the deposition, we prepared and characterized the monomer N-acryloyl-3-aminophenylboronic acid (Figure S6) and its boronate ester (Figure S7). Free radical polymerization of the monomers provided the polymers (Figure S8 and S9). The H^+ responsive property of the boronate ester polymer was characterized by optical transmittance measurement (Figure 2). As shown in Figure 2, the precipitation temperature for boronate ester polymer was larger than N-acryloyl-3-aminophenylboronic acid polymer at basic conditions, while exhibited no differences at acid conditions. The larger precipitation temperature at basic conditions could be attributed to the maintain of boronate ester polymer that contains hydrophilic glucose, however at acid condition the hydrolysis of hydrophilic boronate esters to uncharged hydrophobic boronic acid lead to similar precipitation temperature. Overall, the results indicated that the prepared boronate ester polymer was stable at basic condition and hydrolyzed at acid condition. After the successful preparation and characterization of the acid responsive polymer, the deposition of the polymer to the designed surface was conducted. As results, the surface height raised and the peak at 189 eV corresponded to B 1s presented due to the polymer deposition, as evident from the AFM and XPS imaging analysis (Figure 1 and S3).

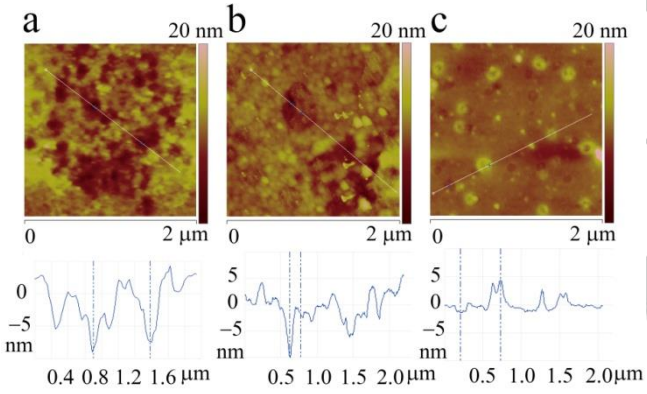


Figure 1. AFM images of the surface after a) Au nanoparticles assisted surface etching, b) enzyme immobilization and c) polymer deposition.

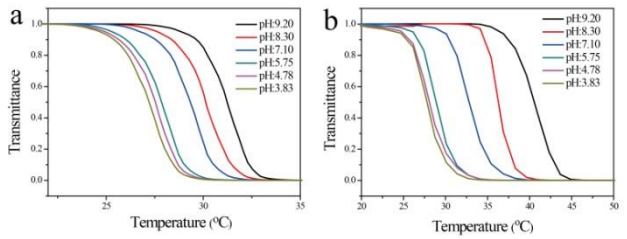


Figure 2. Temperature dependent optical transmittance of a) the N-acryloyl-3-aminophenylboronic acid polymer and b) the prepared H^+ responsive boronate ester polymer at various pH values.

Characterization of the surface in response to a local fleeting stimulus and the change of its macroscopic properties

After successful construction of the responsive surface, we then estimated the feasibility of the proposed self-propagating reaction in the surfaces. The fluorescence micrograph was used to verify the self-propagating response of the surface to the external H^+ stimuli. The pH responsive carboxyfluorescein was used as a reporter of the pH change on the polymer surface (Figure S10). As shown in Figure 3, after adding a drop of 0.1 M HCl solution at the corner of the surface the fluorescence changed across the surface quickly, as a comparison experiment the surface deposited with only polymer showed a slower propagation (Figure S11) which indicated the self-propagating reaction took place along the responsive surface.

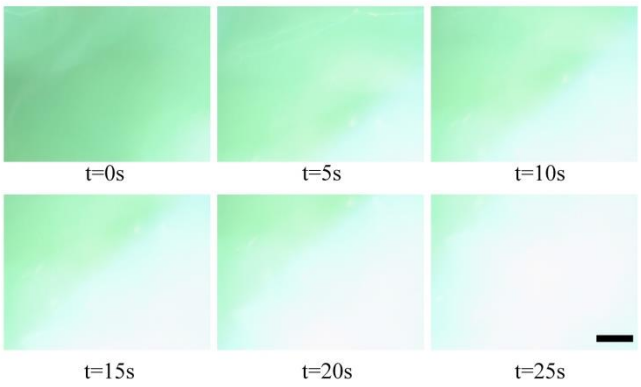


Figure 3. The fluorescence micrographs of the prepared surface at different time after adding a drop of 0.1 M HCl at a corner of the surface were demonstrated. Scale bar is 25 μm.

Global change in antibacterial effect of the surface in response to a local bacterium stimulus

Since the surface performed successfully the self-propagating property as designed, we applied the surface to an antibacterial system. The bacterium E. coli was used as a model for the investigation of the antibacterial properties of the designed surface systems. Immersion of each surface in 5.0 mM pH 7.4 PBS solutions to provide a suitable environment for self-propagating reaction was first carried out. Then a part of the surface was stained with bacteria E. coli, while the other part was kept unstained. After 6 h incubation, the bacteria presented on the unstained part of the surface were characterized by using a fluorescence assay as well as standard plate count method [11]. The SEM was used to observe bacteria E. coli with different surface treatment, as shown in Figure 4a and 4b bacteria E. coli treated with glass and glass modified with polymer only were both with smooth and intact cell walls, which demonstrated that these two surfaces showed little toxicity against bacteria E. coli. However, for the designed surface the bacterial cell walls became rough and broken (Figure 4c) since H_2O_2 can oxidize and destroy the bacterial cell membranes. [12] Propidium (PI) staining was used to further verify the cell membrane conditions

and the results demonstrated that neither the glass nor the polymer surface alone was able to have a significantly affect on the viability of bacteria E. coli as shown in Figure 4d, 4e, 4g and 4h. However, for the designed surface a significant loss in viability was exhibited by the substantial increase in the PI permeable red fluorescent bacteria (Figure 4f and 4i). It is unlikely that the polymers themselves contributed to the observed fluorescence, as the results of the glass modified with polymer only showed low red fluorescence (Figure 4e and 4h). Further results of the plate count method were consent to the fluorescence-based assessment, as shown in Figure 5 a significant decrease in the number of E. coli colonies was observed for the designed surface (Figure 5c and 5d) compared to the glass surface (Figure 5a and 5d) and the glass surface modified with polymer only (Figure 5b and 5d). The occurrence of dead bacteria on the unstained parts of the surfaces indicated that the unstained parts exhibited antibacterial properties. The appearance of antibacterial properties in the unstained parts could be attributed to the communication via self-propagating reactions between the stained parts and unstained parts of the surfaces. Thus, the prepared polymer surface systems, behaved similarly like nature leaves in their abilities to impart macroscopic responses to local fleeting stimuli, could be used for antibaterial application.

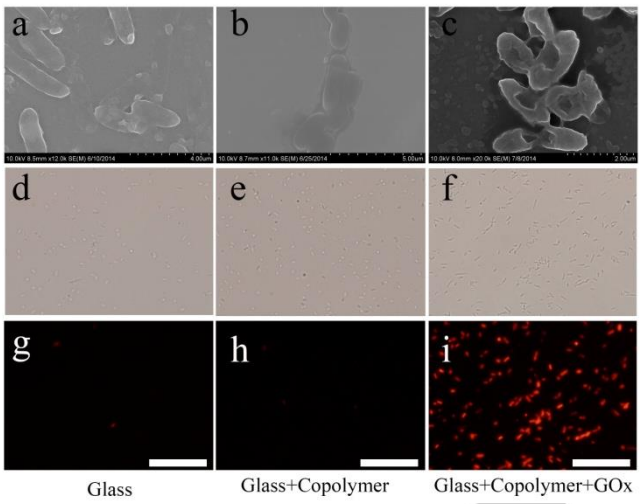


Figure 4. SEM and fluorescence microscope images of E. coli treated with glass (a, d, g), glass modified with polymer only (b, e, h) and glass modified with GOx and polymer (c, f, i). Scale bars for fluorescence microscope images are 20 μm.

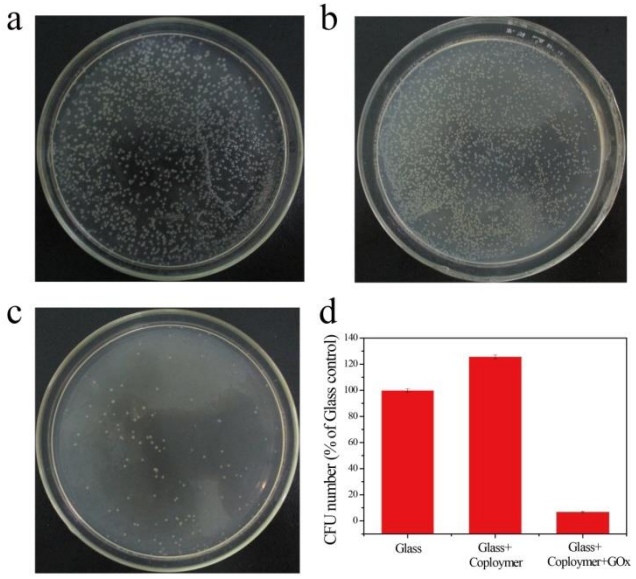


Figure 5. The number of E. coli colonies after the treatment with a) glass, b) glass modified with polymer only, c) glass modified with GOx and polymer and d) the quantified results of the palte count method (the data were from three independent experiments).

Conclusions

In summary, a surface with the ability to respond to local and fleeting stimuli and translate the stimuli globally via self-propagating reactions was designed and constructed. The self-propagating reaction initiated by H^+ released by bacteria could lead to the entire properties change of the surface and amplify the release of H_2O_2 to endow the surface with the antibacterial property. The designed surface exhibited significant antibacterial properties against H^+ release E. coli bacteria. This bio-inspired design may provide new insights into developing the autonomously reconfigure materials that respond to local, fleeting stimuli.

Experimental Section

Materials and methods

All reagents were commercially available and used without further purification. Acryloyl chloride (96%, contains 200ppm MEHQ as stabilizer) and N-vinyl-2-pyrrolidone (99%) were purchased from Aladdin Chemistry. 3-aminophenylboronic acid hydrochloride (98%), 2, 2-azobis (2-methylpropionitrile) (AIBN, 98%), glucose oxidase, and N-isopropylacrylamide (97%) were obtained from Sigma-Aldrich. 5(6)-carboxyfluorescein (99%, exhibit pH-dependent absorption spectra with a pKa~6.5 (pH5~9)) was obtained from Acros organics. Escherichia coli (E. coli, ATCC 25922) bacterial strains were obtained from Chuanxiang Biotechnology, Ltd. (Shanghai, China). Unless specified otherwise, all other reagents

were of analytical grade. Ultra-pure water (>18.2 MΩ cm^{-1}, Milli-Q, Millipore) was used for the preparation of all the buffers and for all experiments.

X-ray photoelectron spectra (XPS) were acquired on an ESCALab220i-XL electron spectrometer from VG scientific with 300 W Al Kα radiations as the X-ray source for excitation. Scanning electron microscope (SEM) images were recorded with a HITACHI S-4800 FE-Scanning electron microscope. Attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR) spectra were recorded on a Bruker Vertex 70 FTIR spectrometer. Ultraviolet-vis spectroscopy (UV-vis) absorbance measurements were carried out on a JASCO V-550 UV-vis spectrophotometer, equipped with a Peltier temperature control accessory. All spectra were recorded in a 1.0 cm path length cell. Atomic force microscopy (AFM) images were performed using a Nanoscope V multimode atomic force microscope (Veeco Instruments, Santa Barbara, CA, USA) in tapping mode. Fluorescence images were captured using an Olympus BX-51 optical equipped with a CCD camera. All the photographs were taken by a Canon camera.

Preparation of N-acryloyl-3-aminophenylboronic acid and N-acryloyl-3-aminophenylboronic acid glucose ester

The reaction of acryloyl chloride with 3-aminophenylboronic acid was used to prepare N-acryloyl-3-aminophenylboronic acid according to the previous report [13]. 3-aminophenylboronic acid hydrochloride (10 mmol, 1.73g) was dissolved in 25.0 mL 2.0 M NaOH solution and cooled with ice bath. Acryloyl chloride (10 mmol, 0.8 mL) was added to the solution dropwise with vigorous stirring at 4 ºC. After stirring for one hour with an ice bath, the reaction was completed at room temperature overnight. 2.0 M HCl was added to the reaction solution dropwise to adjust pH to 1.0. The precipitate was separated by filtration and then washed by cold water for three times. Subsequently, the precipitate was dissolved in 40 mL water on heating to 60 ºC and the insoluble precipitate was filtered off. The product was finally obtained by crystallization of the solution in a refrigerator overnight. The product was filtered off, washed with cold water, and dried under vacuum. The structure of the product was confirmed by the 600 MHz ^{1}H NMR spectrum.

N-acryloyl-3-aminophenylboronic acid glucose ester was prepared according to the previous reports [14] after the successful synthesis of N-acryloyl-3-aminophenylboronic acid. The solution of N-acryloyl-3-aminophenylboronic acid (5 mmol, 955 mg), glucose (5.25 mmol, 945 mg) and 20 mL of dichloromethane were added to a dried flask. The solution was stirred for 30 minutes under N_2 atmosphere at room temperature and then magnesium sulfate (5 mmol, 600 mg) was added. The solution was further stirred for 4 h under N_2 atmosphere to complete the reaction. Subsequently, the solution was filtered and washed with dichloromethane. The filtrate was concentrated with rotary evaporator under reduced pressure and dried in vacuum to obtain the desired product. The structure of the product was confirmed by the 600 MHz ^{1}H NMR spectrum.

Copolymerization of prepared N-acryloyl-3-aminophenylboronic acid or N-acryloyl-3-aminophenylboronic acid glucose ester with N-vinyl-2-pyrrolidone and N-isopropylacrylamide

The polymers were synthesized via the free radical polymerization [13]. N-acryloyl-3-aminophenylboronic acid (0.5 mmol, 95.5 mg) or N-acryloyl-3-aminophenylboronic acid glucose ester (0.5 mmol, 167 mg), N-isopropylacrylamide (7.0 mmol, 791 mg), N-vinyl-2-pyrrolidone (2.5 mmol, 277 mg) and AIBN (0.1 mmol, 16 mg) were dissolved in 10 mL of 1, 4-dioxane. The reaction was taken place in a two-necked flask with a cooling condenser and started by heating to 70 ºC under nitrogen protection. After 6 h reaction, a highly viscous solution was obtained and added dropwise to 80 mL diethyl ether for precipitation. The precipitate was filtrated and washed with diethyl ether for three times. The obtained product was dried under vacuum and characterized by 600 MHz ^{1}H NMR spectrum.

The pH reponsive properties of prepared polymers

Polymers were dissolved in 5.0 mM PBS solutions with various pH values (1.0 mg mL^{-1}). The optical transmittance of the polymer solutions at different temperatures was measured at 500 nm using UV-vis spectrophotometer.

The Au-assisted chemical etching processes

The etching of glass surface (2.0×2.0 cm) assisted by Au nanoparticles was performed following the previous reports [9]. Prior to the etching, glass substrates were cleaned by ultrasonication in ethanol and water for 30 min each and followed by freshly prepared 3:1 concentrated H_2SO_4/30% H_2O_2 solution for 1h. After washing with water, an aqueous solution containing HF, H_2O_2 and Au nanoparticles was dropped on the surface and etched at 50 ºC for 30 min. After etching, the samples were washed with water and ethanol.

Immobilization of glucose oxidase (GOx) and enzyme activity evaluation

The etched glass surfaces were rinsed with 5.0 mM pH 5.0 PBS and then immersed in the GOx solution (160 μg·mL^{-1} in 5.0 mM pH 5.0 PBS) for 2 h at 4 ºC to achieve GOx immobilization [15]. The glass surfaces were then thoroughly rinsed with water and stored in a refrigerator 4 ºC [16]. After GOx immobilization, the activity of the free GOx and immobilized GOx were assessed by monitoring the oxidation rate of glucose. Briefly, 10 μL 40.0 mM ABTS in 5.0 mM pH 5.0 PBS, 10 μL 50 μg·mL^{-1} HRP in 5.0 mM pH 5.0 PBS, 10 μL glucose with different concentration (20, 40, 80, 160, 200, 320, 400 and 800 mM in 5.0 mM pH 5.0 PBS), the immobilized GOx and 370 μL 5.0 mM pH 5.0 PBS were reacted at 37 ºC and the absorbance at 417 nm was recorded with the UV-vis spectrophotometer. The activity assays were repeated with a series of appropriate concentrations of glucose to get a series of catalytic rates, followed by fitting the Michaelis−Menten equation to obtain the constants V_{max} and K_m. All the samples are run in triplicate.

Deposition of the polymer onto the surface

The deposition of the polymer was carried out via a typical procedure of absorption.[10] The surfaces after enzyme immobilization were immersed into the polymer solution (10.0 mg mL^{-1}, 5.0 mM pH 5.0 PBS) for 4 h, then the surfaces were thoroughly rinsed with 5.0 mM pH 5.0 PBS to remove the unbound polymer.

Bacterial culture and antibacterial experiments

Mono-colony of E. coli on solid Luria-Bertani (LB) agar plate was transferred to 20 mL of liquid LB culture medium and grown at 37 ºC for 12 h under 180 rpm rotation. Then the bacteria were diluted with broth to 10^5 cfu·mL^{-1}.[12] The bacteria concentrations were

determined by measuring the optical density at 600 nm ($OD_{600\ nm}$). The prepard surfaces were stained with the prepared bacteria solution (10.0 μL) at one corner for 3 h. Then, the unstained part of surface was rinsed with 5.0 mM pH 7.4 PBS and the obtained solution was placed on solid medium by spread plate method and cultured at 37 °C for 24 h before observing the number of the bacteria colonies. The number of colony forming units was counted through visual inspection. Control experiments were performed in parallel with glass surface and surface modified with only polymer.

Fluorescence assay for the integrity of bacteria cell membranes

After rinsed with 5.0 mM pH 7.4 PBS for the unstained part of the surface, the cell death and the extent of bacterial cell invasion were analyzed by propidium iodide (PI) staining. The solution was stained with PI (10 $\mu g \cdot mL^{-1}$) for 10 min in the dark and washed twice with PBS, then the dead bacteria were visualized with a fluorescence microscope [11]. The observed areas were randomly photographed for each sample.

Acknowledgements

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Keywords: autonomous and continuous response • stimuli-responsive polymer • surface • self-propagating reactions • local fleeting stimuli

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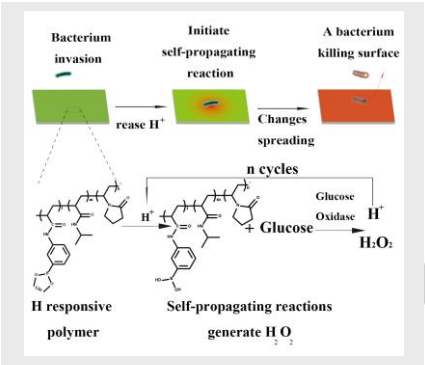
Entry for the Table of Contents

FULL PAPER

pH responsive polymer surfaces that are capable of transforming specific local, fleeting stimuli into global, macroscopic properties changes were designed by the introduction of self-propagating reactions into the polymer surface systems. The prepared H^+ responsive polymer surfaces can be empolyed for antibacterial application and this design strategy offers methods for achieving autonomously reconfigureable materials.



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