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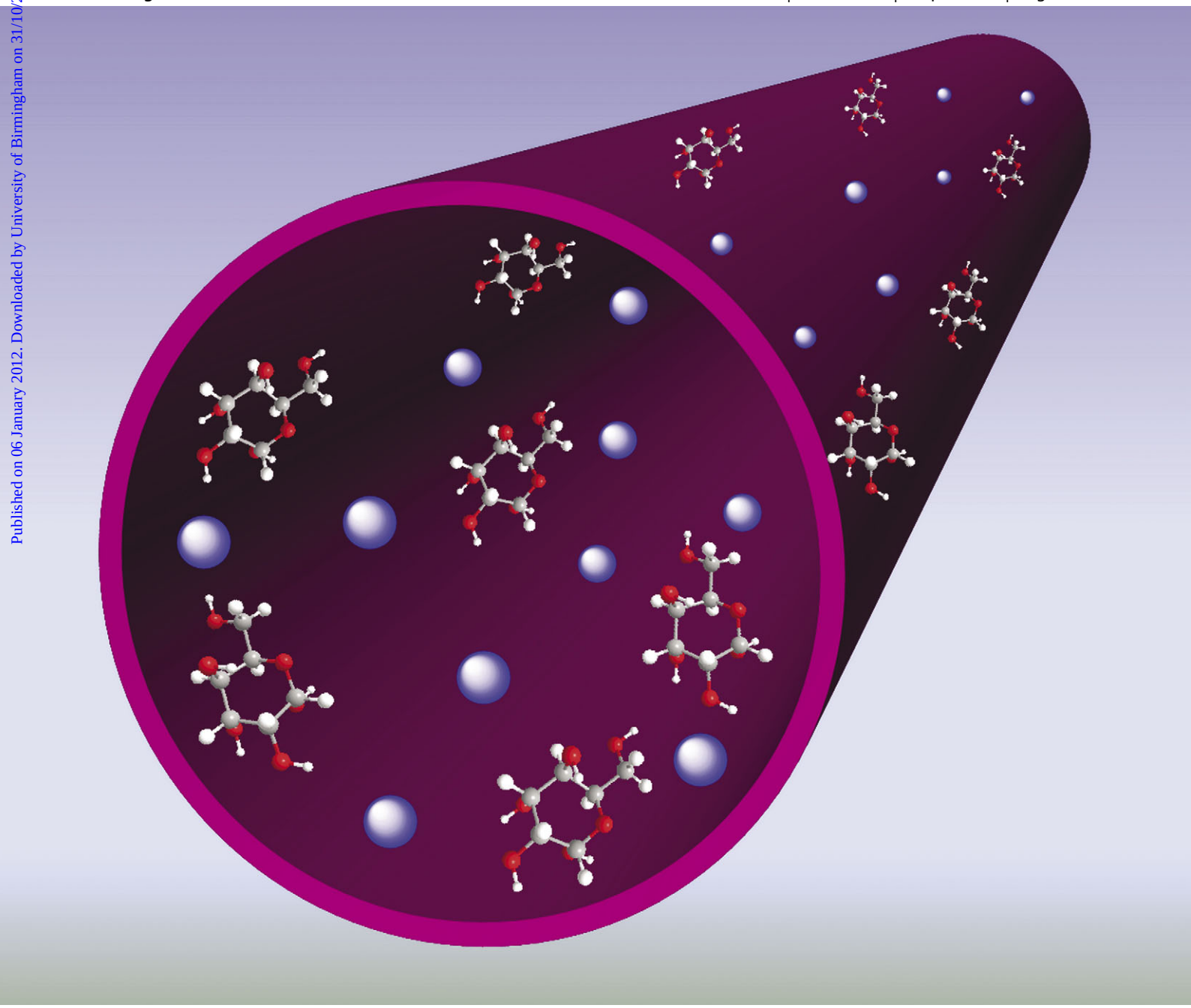

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pH gated glucose responsive biomimetic single nanochannels†

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The development of pH gated glucose (Glu) biosensor is of great significance to human health. Herein, we have designed a pH gated Glu responsive biomimetic nanochannel, modified with 3-aminobenzeneboronic acid. The Glu responsive property can be regulated by pH which can switch nanochannels from the "on" to "off" state.

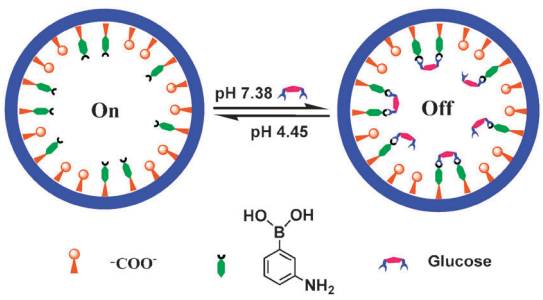
The metabolism of glucose (Glu) in the body is very important and an unusual Glu level is a signal of disease such as diabetes.[1,2] In nature, organisms use pH as a chemical gate to regulate the ionic transport through cell membranes.[3] Inspired by nature, novel intelligent materials, for example, smart pH-switching surfaces,[4] have been developed, and are attracting more and more interest for their unique properties.[4] It is well known that pH change will cause disorders of Glu metabolism.[5] Therefore developing pH gated Glu biomimetic devices, addressing the transmission mechanism in living organisms and exploring the relationship between Glu metabolism and pH is of great significance. To our knowledge, little work has been reported to discuss pH gated Glu responsive biomimetic switches.

Recently, synthetic single nanochannels which were inspired by biological ion channels have drawn enormous research attention, because they are considered to be novel vectors in simulating biological processes and have mechanically and chemically robust properties.[6,7] Many specific responsive biomimetic nanochannels which have the potential in mimicking transport processes in organisms have developed rapidly in recent years.[8–12] For example, Azzaroni *et al.* fabricated a proton responsive biomimetic nanochannel modified with poly (2-(methacryloyloxy)ethyl phosphate) brushes.[9a] Additionally, a potassium ion biomimetic nanochannel based on a G-quadruplex DNA functionalized nanochannel system has been reported.[11b] Recently a chiral amino acid biomimetic nanochannel modified with β-cyclodextrin has been fabricated.[13] All in all, synthetic single nanochannels functionalized with certain molecules can be designed as specific biomimetic nanodevices.

Phenylboronic acids can bind with saccharides containing *cis*-1,2- or 1,3-diols in aqueous media and form cyclic esters. This means that phenylboronic acid and its derivatives can be designed as saccharide probes.[14] It is worth mentioning that the boronate ester bonds that form between saccharides and boronic acids are sensitive to pH conditions.[15] With this knowledge, we designed a pH gated Glu responsive biomimetic nanochannel by chemical modification with 3-aminobenzeneboronic acid into the nanochannels.

Single conically nanochannels were prepared by chemical etching of a 12 μm thick polyethylene terephthalate (PET, Hostaphan RN12 Hoechst) membrane containing a single ion track in the center. Diameter measurements of single nanochannels were conducted with a commonly used electrochemical method.[16] The large-diameter opening (base) was about 600 nm, and the small-diameter opening (tip) was 14–23 nm. The fabrication procedure of the pH gated Glu responsive biomimetic nanochannels is shown in Scheme 1. During the chemical etching process, the carboxyl groups ($-COO^-$) were generated on the nanochannel surface, and then 3-aminobenzeneboronic acid was linked with $-COO^-$ by a classical EDC/NHSS cross-linking reaction (details in ESI†). The functionalized nanochannel exhibited excellent Glu responsive capability, which can be regulated by pH. After exposing the functionalized nanochannel into Glu solution the transmembrane ionic current decreased ("off" state). Then immersing this membrane in pH 4.45 PBS solution, Glu is released from the channel surface, and the ionic current measured at pH 7.38 increased again ("on" state).

The Glu responsive property was evaluated by transmembrane ion current measured in 0.1 M KCl solution prepared in 0.1 M phosphate saline buffer (PBS, pH 7.38 and 4.49). All the experiments were carried out at room temperature (25 °C). Ion currents were measured after adding different saccharide



Scheme 1 Fabrication of pH gated Glu responsive biomimetic nanochannel.

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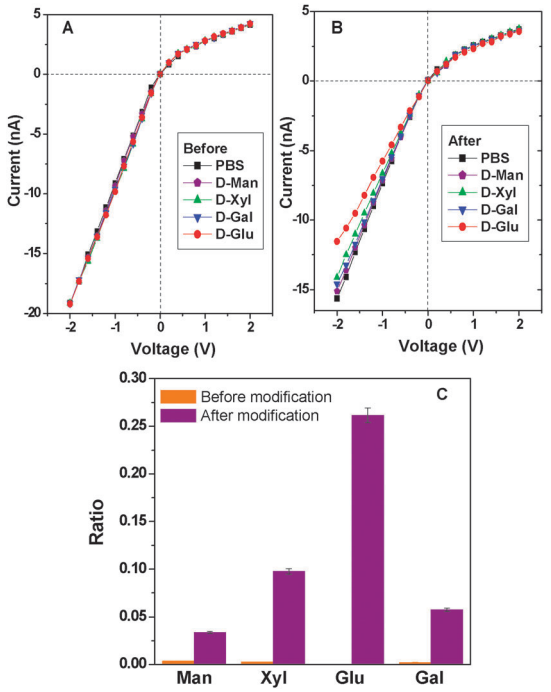

Fig. 1 *I–V* curves of the single nanochannel before (A) and after (B) 3-aminobenzeneboronic acid modification in 0.1 M KCl (pH 7.38) without or with the addition of 1 mM Man, Xyl, Gal and Glu, respectively. (C) Current change ratios measured at −2 V of modified nanochannel with the addition of 1 mM Man, Xyl, Gal and Glu, respectively. 3-Aminobenzeneboronic acid modified nanochannel can achieve a selective Glu response *via* the change in the ionic current. Before modification, the diameter of the tip is about 21 nm.

solutions and co-existing species for 5 min. The unmodified conical shaped single PET nanochannel at pH 7.38 was negatively charged due to ionized carboxyl groups, so it presented a slightly rectified ionic current. After immobilization of 3-aminobenzeneboronic acid, the current decreased because 3-aminobenzeneboronic acid existed in equilibrium between the uncharged and charged forms at pH 7.38. Thus the negative charge on the channel surface decreased (Fig. S3, ESI†). The success of the 3-aminobenzeneboronic acid immobilization on the surface of the PET nanochannel was confirmed by contact angle measurements (Fig. S1, ESI†) and X-ray photoelectron spectroscopy (XPS) analysis (Fig. S2, ESI†).

The recognition of saccharide solutions based on 3-aminobenzeneboronic acid modified PET nanochannel was investigated through measuring the ionic current across the nanochannel. Fig. 1A depicts *I–V* curves of a single nanochannel before and after 3-aminobenzeneboronic acid modification in the presence of electrolyte containing 1 mM mannose (Man), xylose (Xyl), galactose (Gal) and Glu. The ionic currents of the unmodified PET nanochannel showed no significant changes upon placing into the saccharide solutions. When 3-aminobenzeneboronic acid modified PET nanochannel was exposed into 1 mM Glu, a significant decrease in the transmembrane ionic current was observed, while in the presence of 1 mM Man, Xyl, Gal and Glu, there was only slight change in the ionic current. Fig. 1B shows the ionic current change ratios (defined here as absolute value of the current change ratio at −2 V *i.e.*, $(I - I_0)/I_0$) of modified nanochannel in the presence of 1 mM Man, Xyl, Gal and Glu. It is obvious that the 3-aminobenzeneboronic acid modified nanochannel shows a selective positive response to Glu. The possible responsive mechanism is as follows: 3-aminobenzeneboronic acid modified on the surface of the nanochannel can form a reversible cyclic ester with *cis*-diol moieties of saccharides in aqueous solution[15] and Glu contains a pair of *cis*-diol units in the 1,2- and 5,6-positions. In a previous study, it was found that when two boronic acids possess the appropriate geometry they can selectively form a 2 : 1 complex with Glu, so leading to glucose selectivity.[17] In our system, Glu reacted with two adjacent boronic acids to form 1 : 2 complexes on the inner walls of channel. The steric hindrance of this structure screens the charge of the boronic acid unit, which in turn results in a significant decrease in the transmembrane ionic current. The other saccharides tested, Man, Xyl and Gal only have one *cis*-diol moiety, and can not form such 2 : 1 complexes, so the changes in the ionic current are not significant.

I–V characteristics of 3-aminobenzeneboronic acid modified nanochannel upon the addition of Glu with different concentrations under the same conditions was investigated (Fig. S4A, ESI†). We define the rectification ($R_{\pm}$) ratio as ratio of the currents recorded at +2 V to the absolute values of currents recorded at −2 V. The degree of $R_{\pm}$ generally increased with increasing Glu concentrations from 10^{-4} to 10 mM (Fig. S5, ESI†). This is because the reaction of boronic acid with glucose leads to an decrease in the negative charge on the channel surface with increasing Glu concentration. The experimental data was found to provide a perfect fit to the Langmuir model. A linear correlation exists between C and $R_{\pm}$ for concentrations of Glu solution in the range of 10^{-4} to 10 mM, where C is the concentration of Glu (Fig. S4B, ESI†). The linear equation is found to be $C/R_{\pm} = 63.41037 + 3.03343C$with a regression value (r^2) > 0.99462.

The formation and dissociation of the phenylboronic acid cyclic ester was realized depending on the pH of the aqueous solution.[14] On the basis of this principle a pH gated nanochannel was achieved. In this paper we define high current state as "on" state and low current state as "off" state at same voltage. Fig. 2 presents the reversible variation of the transmembrane ionic current measured at −2 V, with (A) formation (red circles) and (B) hydrolysis (black squares) of the cyclic ester (experimental details in ESI and Fig. S6†). Glu reacted with boronic acid units to form the 1 : 2 cyclic ester under 0.1 M KCl at pH 7.38. This structure shields the charged boronic acid units and the current at −2 V decreased ("off" state). Hydrolysis of the cyclic ester was achieved at pH 4.49. Glu breaks away from the channel surface and the boronic acid unit is exposed on the channel surface. Then *I–V* curves were recorded at 0.1 M KCl (pH 7.38) and the ionic current at −2 V increased ("on" state). The measurements confirmed the pH regulated nanochannel can be switched between the "on" state and "off" state in response to Glu. This system can be used for multiple sensing experiments without any loss of the sensing signal and with excellent reversibility.

In living organisms, some co-existing species might disturb the Glu recognition and transport, for example, ascorbic acid (Vc), glycine (Gly) and urea (Ur), *etc*. In this work, the effect of these potential interferents on the recognition of the Glu was evaluated by measuring the ionic current of a

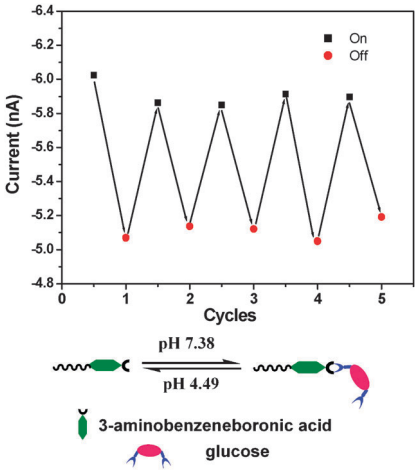

Fig. 2 Responsive switching ability of the pH gated modified nanochannel. Reversible variation of the ionic current transport of a single nanochannel at −2 V (dissociation of cyclic ester, "on" state; black squares and formation of cyclic ester, "off" state; red circles). The data shows the gating function of the modified nanochannel can be regulated by pH. Before modification, the diameter of the tip is about 14 nm.

nanochannel in the presence of electrolyte containing 1 mM of each interferant (Fig. S7, ESI†). As shown in Fig. 3, the nanochannel before and after addition showed no response to Vc, Gly and Ur. Thus the 3-aminobenzeneboronic acid modified single nanochannel maintains a selective response to Glu even in the presence of interferents.

In summary, we have designed pH gated Glu responsive biomimetic single nanochannels based on 3-aminobenzeneboronic acid modification. These nanochannels can achieve Glu response with pH switching from "on" to "off" states. This system provides a novel sensing platform to recognize Glu through controlling environment stimulus and has potential applications for simulating the transport properties and gating functions of specific biological channels.

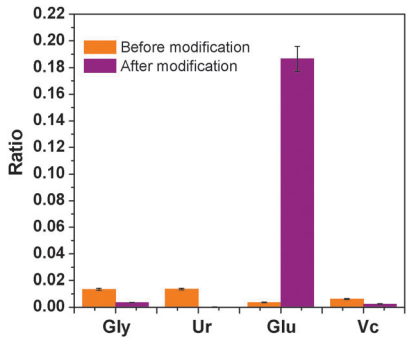

Fig. 3 Current change ratios ($R = (I - I_0)/I_0$) of a 3-aminobenzeneboronic acid modified nanochannel measured in 0.1 M KCl (pH 7.38) at −2 V before (red) and after (green) addition of 1 mM Gly, Ur, Glu, Vc, respectively. This modified nanochannel maintains a good response to Glu in the presence of other interferents. Before modification, the diameter of the tip is about 23 nm.

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