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Multisegment nanowire/nanoparticle hybrid arrays as electrochemical biosensors for simultaneous detection of antibiotics

Zhiyang Li, Chuqing Liu, Victor Sarpong, Zhiyong Gu*

Department of Chemical Engineering, University of Massachusetts Lowell, One University Ave, Lowell, MA 01854, USA

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ABSTRACT

Antibiotics such as penicillin and tetracycline drugs are widely used in food animals to treat, control, and prevent diseases, and penicillin is approved for use to improve growth rates in pigs and poultry. However, due to the overuse of antibiotics in food and medical industry, the antimicrobial resistance is starting to show up in some developing countries. The antibiotic abuse may cause allergic reactions, resistance in microorganisms and general lowering of immunity in consumers of meat and dairy products. It is important and necessary to develop an easy, inexpensive, and quantitative sensing method to monitor and analyze the antibiotics concentration in real samples such as milk or meat. In this research, an electrochemical biosensor based on hybrid nanowire/nanoparticle array with various bio-molecular receptors was fabricated for the simultaneous detection of penicillin and tetracycline. The vertically aligned Pt-Au nanowire array has been prepared by an electrodeposition method within anodic aluminum oxide (AAO) membranes; L-cysteine was used to form a monolayer on the Au segment as the bio-receptor for tetracycline detection; electroless plating of Au nanoparticles was applied on the Pt nanowire segments, and then the penicillinase was immobilized on the Au nanoparticles using EDC/NHS cross-linker. The prepared Au(L-cysteine)-Pt(penicillinase) nanowire array electrode showed simultaneous detection ability and remarkably high sensitivity of penicillin and tetracycline, which are 41.2 $\mu A\,\mu M^{-1}\,cm^{-2}$ for penicillin detection and 26.4 $\mu A\,\mu M^{-1}\,cm^{-2}$ for tetracycline detection. The sensitivities of each analytes with different segment length were also investigated. Real sample tests with chicken and beef extract were conducted, which showed good recovery performance. Due to the advantages of the hybrid nanowire/nanoparticle array structure, this new sensor can serve as an enhanced platform for simultaneous detection of various bioanalytes.

1. Introduction

Penicillin and tetracycline drugs are approved in most countries for use in food industry to treat, control, and prevent diseases, and penicillin is approved for use to improve growth rates in pigs and poultry (Babington et al., 2012; Bhattacharya, 2010; Cox et al., 2009; Economou and Gousia, 2015; Marshall and Levy, 2011; Martinez, 2009; Miller, 2002). It considered that high dose of uses might increase the possibility of antibiotic resistance of animal origin in human infections, which will result in hospitalization and mortality increasing due to the decreased response to penicillin, tetracycline, or other antibiotics (Babington et al., 2012; Phillips et al., 2004; Spellberg et al., 2008; Ventola, 2015). In some researches, the risks are evaluated from continued use of penicillin-based drugs in livestock animals in the United States and other countries (Cox et al., 2009; Landers et al., 2012). For example, by investigating the intensive care unit (ICU) patients with some estimated factors, it is suggested that less than 0.04–0.14 excess mortalities per year might be prevented if current use of penicillin drugs in livestock animals was discontinued (Bhattacharya, 2010; Mungroo and Neethirajan, 2014; Ventola, 2015). These investigations indicated that current penicillin usage in livestock animals in the United States still presents very low (possibly zero) human health risks (Cox et al., 2009). However, the antimicrobial resistance is starting to show up in some developing countries due to the overuse of antibiotics in food and medical industry (Landers et al., 2012; Lin et al., 2013). The antibiotic abuse may cause allergic reactions, resistance in microorganisms and general lowering of immunity in consumers of meat and dairy products (Kivirand et al., 2015; Marshall and Levy, 2011; Muhammad et al., 2016).

For the current antibiotic detection methods, HPLC, GC-MS and ELISA are widely used (Abou El-Magd et al., 2015; Chen et al., 2013; Guascito et al., 2011; Muhammad et al., 2016; Mungroo and Neethirajan, 2014). However, these methods have their limitations such as slow, expensive, and not portable (Landers et al., 2012;

* Corresponding author.
E-mail address: Zhiyong_Gu@uml.edu (Z. Gu).

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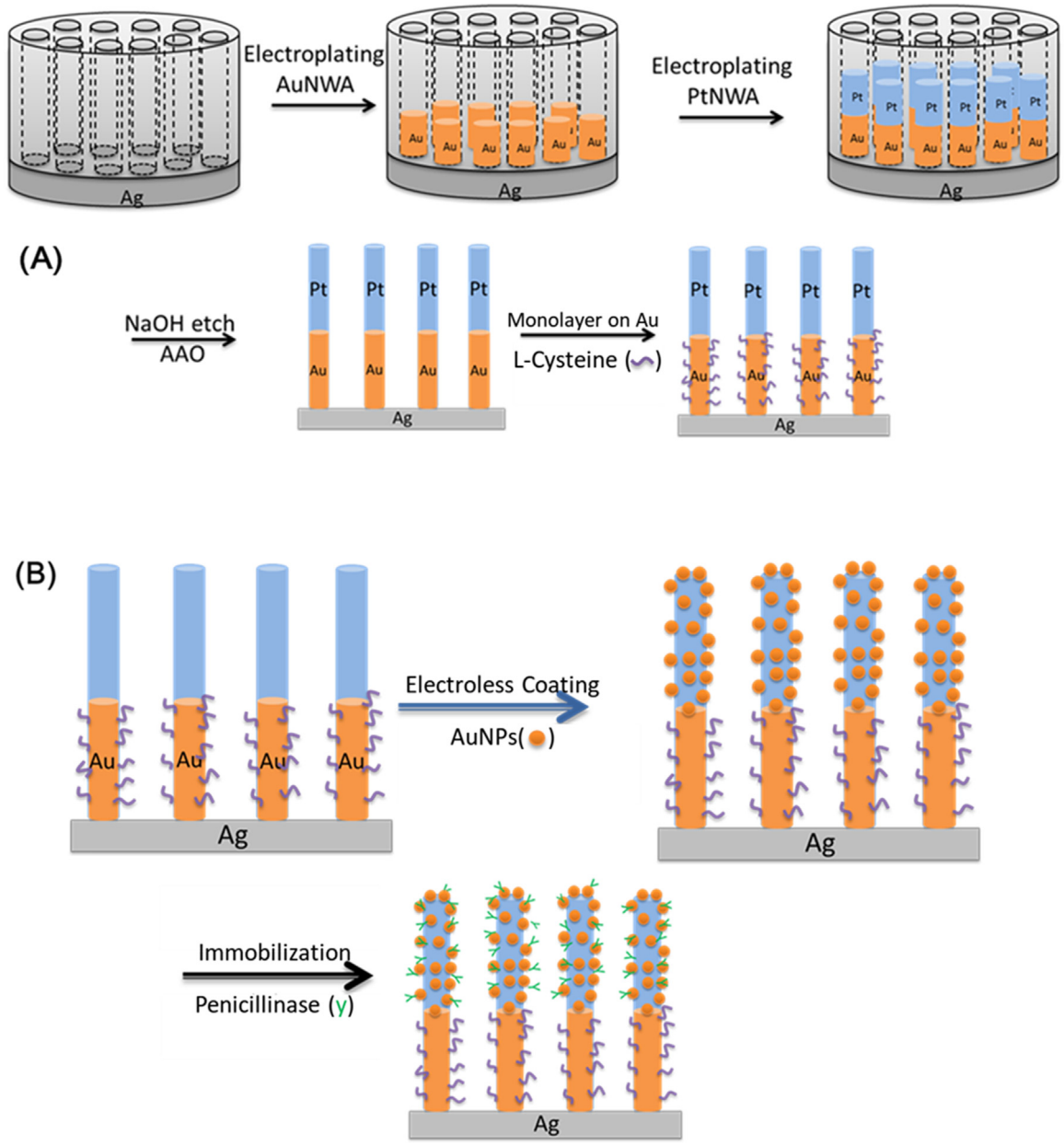

Fig. 1. Schematic illustration of the fabrication process of (A) the Au-Pt multisegment nanowire array, and with L-cysteine immobilization on Au segment; (B) electroless plating of Au nanoparticles on Pt segment followed by penicillinase enzyme immobilization.

Mungroo and Neethirajan, 2014). It is necessary to develop a fast, inexpensive and portable sensing method to quantitatively analyze different antibiotics simultaneously in real samples such as milk or meat. Electrochemical measurements have been studied in the past decade for antibiotic detection, because it's more efficient, especially with nanomaterials, which exhibit significantly larger surface area and unique properties (Chen et al., 2010; Gonçalves et al., 2014; Ju and Kim, 2016; Mu et al., 2014; Muhammad et al., 2016; Siqueira et al., 2009; Thavarungkul et al., 2007; Wu et al., 2014; Zhu et al., 2015). Simultaneous and multitasking sensing applications towards simple molecules have attracted more attentions in recent years (Chen et al., 2013; Guo et al., 2016; Kong et al., 2013; Sun et al., 2011; Wang et al., 2013a, 2013b); however, simultaneous detection of various antibiotics is still challenging.

Recently, vertically aligned 3D nanowire arrays have been studied and reported (Jamal et al., 2013; Li et al., 2017; Liu et al., 2018, 2011; Livi et al., 2015; Zhong et al., 2009). In the array structure, all nanowires are uniformly distributed and vertically aligned on a metallic substrate, and no Nafion has to be used to cover the functionalized nanowires on the surface of glassy carbon electrode, which results in lower signal noise and better sensor durability (Gao et al., 2014; Li et al., 2015). The vertically aligned structure also improves the contact area between the nanowires and the analytes, leading to higher sensitivity and lower detection limit (Cao et al., 2015; Huang et al., 2015; Sun et al., 2015; Yang et al., 2015). Furthermore, nanowires can be easily synthesized to achieve multisegment structure, which will enable the nanowire for multifunctional applications, especially as high sensitivity and multitasking electrochemical biosensors (Bangar et al., 2009; Burdick et al., 2009; Callegari and Demoustier-Champagne, 2011; Callegari et al., 2009; Gerola et al., 2014; Lee et al., 2012; Matei et al., 2010; Ozkale et al., 2015; Pearce et al., 2007).

In this research, a new multisegment nanowires/nanoparticles hybrid array structure was successfully developed as an electrochemical biosensor for simultaneous detection of penicillin and tetracycline.

Penicillinase was immobilized on the Pt segment with the help of electroless plated Au nanoparticles and EDC/NHS crosslinker; L-cysteine as the tetracycline bio-receptor (Sun et al., 2017) was immobilized on the Au segments as a monolayer. The electrochemical sensing characteristics of the prepared biosensors towards pure penicillin, pure tetracycline and the mixture of penicillin/tetracycline were investigated through cyclic voltammetry measurements. The sensitivity, limit of detection and linear range of this new hybrid biosensor were measured, and the recovery test in real samples in chicken and beef extract was also studied for practical applications.

2. Materials and methods

2.1. Apparatus and reagents

Anodic aluminum oxide (AAO) membrane was purchased from Whatman Company (Anodisc, 25 mm diameter, 200 nm pore diameter, 60 μm thickness). Pt and Au electroplating solutions (Platinum TP RTU and Elevate Gold 7990 RTU) were directly used as purchased from Technic Inc. Chloroauric acid (99%), thioctic acid (99%), 100 KU penicillinase and L-cysteine (99%) were purchased from Acros Organics. 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxysuccinimide (NHS) were purchased from Thermo Scientific. The analyte chemicals for sensing measurements, including penicillin (reagent ACS, anhydrous, 99 + %) and tetracycline (99 + %), were purchased from Acros Organics and used without further purification. The phosphate buffer solution (PBS) was prepared with sodium chloride (99 + %), potassium chloride (99 + %), potassium dihydrogen phosphate (99 + %), sodium phosphate (99 + %) (all from Acros Organics) and DI water, with pH adjusted to 7.4. Chicken and beef were bought from a local grocery store and extracted to get the serum, which were then stored at − 4 °C.

A VersaSTAT 4 electrochemical station (Princeton Applied Research) was used for electrodeposition of Au and Pt nanowires and the following cyclic voltammetry (CV) measurements. Three electrode system was used with Ag/AgCl/Sat. KCl as the reference electrode, Pt wire as the counter electrode, and the new hybrid array as the working electrode. The morphology and elemental characterizations were measured by a JEOL JSM-7401F field emission scanning electron microscope (FE-SEM). The pH value of all analytes was measured by pH/Ion 510 bench pH/Ion/mV meter from Fisher Science Education. The chicken and beef extracts were diluted 10 times with PBS buffer solution before the measurements

2.2. Preparation of multisegment Au-PtNWA

The gold and platinum multisegment nanowire array was fabricated by an electrodeposition method using AAO membrane, as shown in Fig. 1. One side of the AAO membrane was coated with 200 nm of Ag layer in a CHA 6 Pocket Electron Beam Evaporator (CHA's solution™ Process Development System) with the deposition rate of 0.2 nm s^{-1}. According to our previous studies (Li et al., 2017, 2015), the current density and deposition time of Au nanowire deposition were controlled at 1 mA/cm^2 and 2 h to obtain the Au segment with a length around 2 μm. Then the Au plating solution was removed and the AAO membrane was washed with DI water for five times. Next, 2 μm of Pt nanowire segments were electroplated within the AAO pores at 1.5 mA/cm^2 for 2 h on top of the gold nanowire segment (Gao et al., 2014; Ruan et al., 2014a, 2014b). Then, the AAO membrane was etched away in 1 M NaOH solution for 30 min to release the Au-Pt multisegment nanowire array, followed by 5 times of washing with DI water. At last, 5 mL of 20 mM L-cysteine solution was applied overnight on the surface of prepared Au-Pt nanowire array to form a monolayer of L-cysteine on the Au segment as the bioreceptor for the detection of tetracycline (Sun et al., 2017), as shown in Fig. 1(A).

2.3. Electroless plating of AuNPs and penicillinase immobilization

After the L-cysteine monolayer formation, the Au-Pt multisegment nanowire array was washed by DI water for 5 times. Then, the prepared nanowire array was immersed into 3 mM $HAuCl_4$ aqueous solution for 3 s, and then immediately washed by DI water to remove the residual $HAuCl_4$ solution. This electroless deposition procedure was repeated for three times to obtain uniform Au nanoparticles on the surface of the Pt segment (Li et al., 2017). Then, the hybrid nanowire array was treated by the mixture of 250 mM thioctic acid and EDC/NHS crosslinking solution (EDC 1% (v/v), NHS 2.5% (v/v) in 0.05 M phosphate buffer solution with 0.05 M KCl) for 5 h with continuous stirring. At last, 100 μL penicillinase enzyme solutions (25 KU/mL) was applied on the activated surface and left overnight at 4 °C, and then washed repeatedly with DI water to remove the extra enzyme, as shown in Fig. 1(B). After drying in air, the prepared electrode was attached to a larger Cu electrode using double-sided Cu tape; a non-conductive inert glue was used to seal all the Cu area except the nanowire area which was exposed as working electrode for the electrochemical measurement, as shown in Fig. S1.

3. Results and discussion

3.1. Characterizations of hybrid nanowire/nanoparticle array and surface modification

The structure and morphology of the Au-Pt multisegment nanowire array with AuNPs coated on the Pt segment were examined by SEM and TEM. Fig. 2(A) shows the SEM images of 2 μm single segment Au nanowire (left inset), 4 μm multisegment Au-Pt nanowire (right inset) and

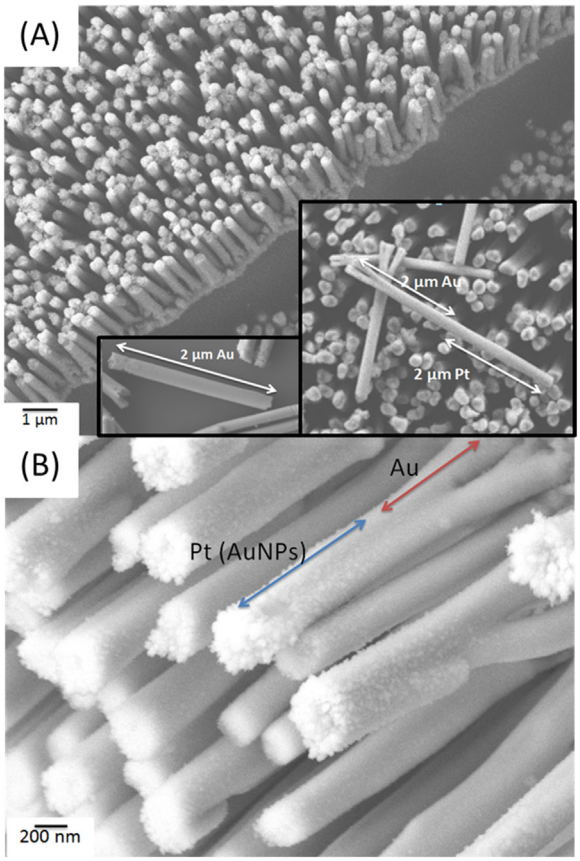

Fig. 2. FESEM images of (A) Au-Pt multisegment nanowire array, insets are single Au nanowire and single Au-Pt nanowire; (B) AuNPs coated on Pt segment after being treated by 3 mM $HAuCl_4$ solution.

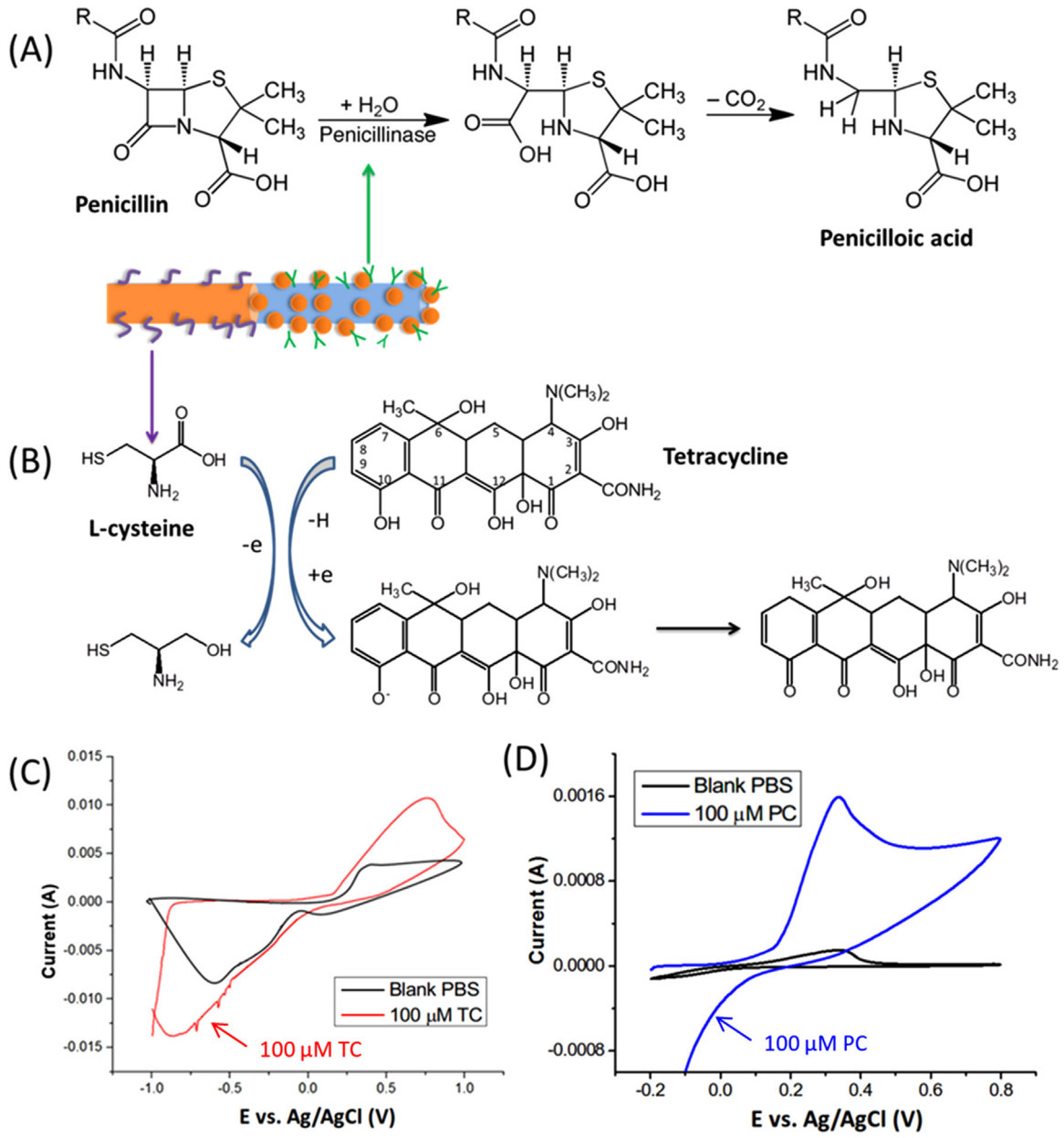

Fig. 3. The sensing mechanism of (A) penicillinase with penicillin; (B) L-cysteine with tetracycline. And cyclic voltammetry (CV) scan of (C) Au(L-cysteine) nanowire array sensing 100 μM tetracycline in 1 mM PBS buffer solution and (D) Pt(Penicillinase) nanowire array sensing 100 μM penicillin in 1 mM PBS buffer solution.

the multisegment nanowire array structure. It can be observed that the nanowires were all vertically aligned on the surface of Ag subtract with an average diameter of 240 nm and length of 3.8 μm, and no overlapping or aggregation was observed. Fig. 2(B) showed a zoom-in SEM image of each multisegment nanowire with AuNPs. It is showed that after the electroless deposition in 3 mM $HAuCl_4$ solution for three times, high density and uniform Au nanoparticles formed on the surface of each Pt segment in the nanowire array. The average diameter of the Au NPs is around 10 nm; beneath the Pt segment, which is the Au segment, no AuNPs were found, and a smooth surface condition could be observed. This hybrid array structure was used as the working electrode for the following penicillin and tetracycline electrochemical measurement.

The TEM image of the interfacial connection part of Au and Pt segments and the EDS elemental analysis results were shown in Fig. S1. Due to the physical properties are similar and the locations on periodic tables are close to each other, Au and Pt segments showed similar features under the TEM image, but the interconnection part could still be distinguished in Fig. S2(A). Also due to the characteristic EDS peak location of Pt and Au are close (2.05 keV vs. 2.12 keV), and the Au nanoparticles are uniformly covered on the Pt segment, a dominate elemental signal of Au (2.12 keV) could be observed in Fig. S2(B).

3.2. Tetracycline and penicillin sensing

The sensing mechanisms of penicillin and tetracycline and respective cyclic voltammetry measurements are shown in Fig. 3. In Fig. 3(A), on the Pt segment, the immobilized penicillinase could selectively catalyze penicillin to produce penicilloic acid (Babington et al., 2012; Ju and Kim, 2016; Rahman and Asiri, 2015). On the Au segment, the immobilized L-cysteine could have a redox reaction with the hydroxyl group from the tenth carbon atom on tetracycline, which would lose a proton and a free oxygen radical was produced. Then due to the instability, the tetracycline molecule with oxygen radical lost

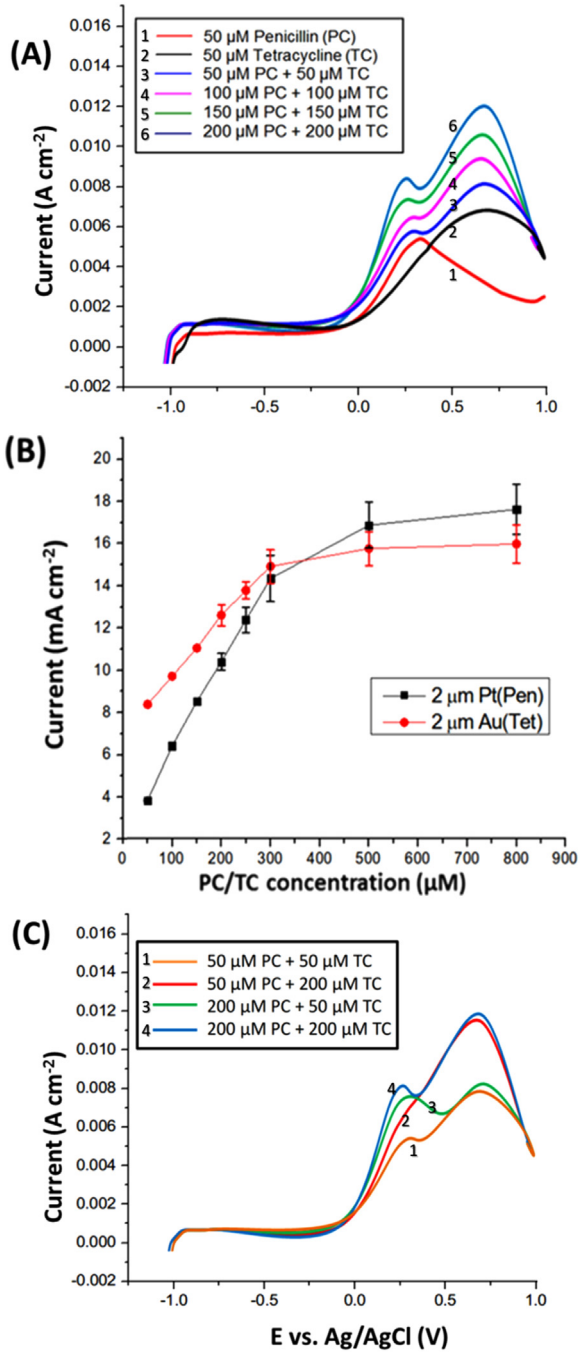

Fig. 4. (A) Cyclic voltammetry scan of Au(L-cysteine)-Pt(Penicillinase) multisegment nanowire array measuring equal concentration of penicillin/tetracycline mixture solution; (B) Corresponding peak current vs. mixture analyte concentration; (C) Cyclic voltammetry scan of penicillin dominant/ tetracycline dominant mixture solution in 1 mM PBS buffer solution.

another electron rapidly, and a double oxygen bond would be formed, leading to a new compound (Sun et al., 2017), as shown in Fig. 3(B).

The cyclic voltammetry (CV) was first performed from −1.0–1.0 V to test the sensing ability of Au(L-cysteine) nanowire array for the detection of 100 μM tetracycline with a scan rate of 50 mV/s, as shown in Fig. 3(C). Comparing with the CV scan in blank PBS, an obvious cathodic peak could be observed around 0.8 V due to the reaction of L-cysteine and the hydroxyl group of tetracycline, which is consistent with the reference (Sun et al., 2017). The above results indicated that Au nanowire array modified with L-cysteine had a good performance for detecting tetracycline.

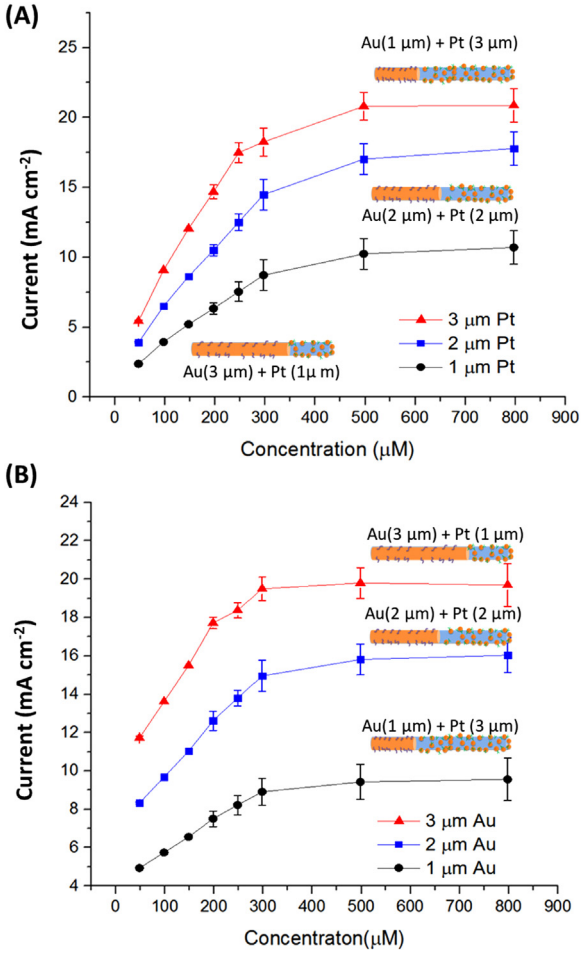

Fig. 5. Cyclic voltammetry scan of Au(L-cysteine)-Pt(Penicillinase) multisegment nanowire array measuring penicillin and tetracycline mixture solution; specific cathodic peak current in CV scanning of (A) varying Pt segment length and (B) varying Au segment length.

Cyclic voltammetry was then performed at 50 mV/s on Pt (Penicillinase) nanowire array to examine the penicillin sensing ability, as shown in Fig. 3(D). By reacting with the penicillinase on the Pt(Penicillinase) nanowire array, penicillin was hydrolyzed to form penicilloic acid and hydrogen ions by releasing electron. The electrochemical signal was detected by the Au nanoparticles and transferred to the electrochemical station along the Pt nanowires. Comparing with the same scan in blank PBS buffer solution, a cathodic peak could be observed at 0.35 V on the CV scanning with 100 μM penicillin. The result from this measurement indicated that penicillinase was successfully immobilized on the Au nanoparticles, which were densely coated on Pt segment, resulting in good sensing capacity for the detection of penicillin (Chen et al., 2010; Gonçalves et al., 2014; Siqueira et al., 2009; Wu et al., 2014).

3.3. Simultaneous sensing of antibiotic mixtures

With the final Au(L-cysteine)-Pt(Penicillinase) multisegment nanowire array, cyclic voltammetry scans of the mixture of penicillin and tetracycline were performed, as shown in Fig. 4. Frist, CV measurements of 50 μM pure tetracycline (TC) and 50 μM pure penicillin (PC) were performed, respectively, and similar cathodic peaks could be observed at 0.75 V for TC (black curve) and at 0.31 V for PC (red curve), as shown in Fig. 4(A), which are consistent with the results shown in Fig. 3(C)(D). Then, mixtures of TC and PC solutions with successive concentrations (50 μM to 200 μM) were tested in the same condition.

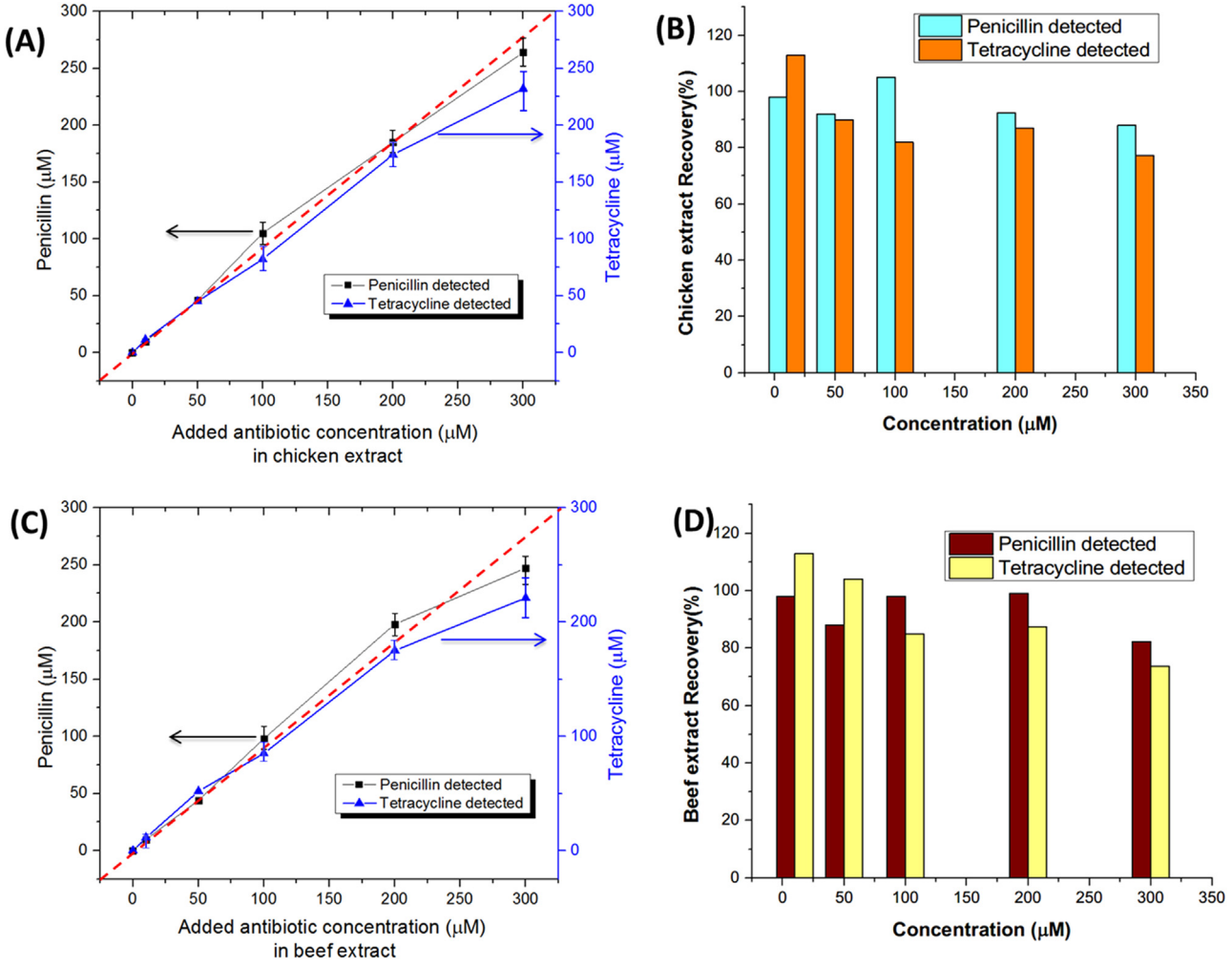

Fig. 6. Real sample test of penicillin and tetracycline in (A) chicken extract, (C) beef extract, and the corresponding recovery charts in (B) chicken extract and (D) beef extract.

For the mixture analytes, two cathodic peaks could be observed at 0.3 V and 0.8 V in a single CV scan, which were identical with the peak location observed above. As the concentration increased, the intensity of both peaks went higher, and a slight left shift of PC peak could be observed, while the TC peak kept the same location. A corresponding plot of cyclic voltammetry peak current vs. concentration of the TC/PC mixture solution was shown in Fig. 4(B). The sensitivity of this hybrid biosensor is 41.2 μA μM^{-1} cm^{-2} for penicillin detection (R^2 = 0.994), and 26.4 μA μM^{-1} cm^{-2} for tetracycline detection (R^2 = 0.987). A linear detection range of both PC and TC could be observed from 20 μM to 310 μM, and the corresponding limits of detection (LOD, signal to noise ratio of 3) were 10.5 μM for PC and 15.2 μM for TC, respectively. Error bars represent standard deviations based on the electrochemical responses of Pt segment towards PC, and Au segment towards TC. The sensitivity of penicillin is higher than that of tetracycline. One of the possible reasons is due to that the surface area of Pt segment coated with Au nanoparticles is larger than the Au segment, which results in more bio receptor immobilization and thus leads to higher sensitivity. These results indicate that simultaneous measurement of tetracycline and penicillin with this hybrid multisegment nanowire array sensor is feasible.

Fig. 4(C) showed the CV measurement results of penicillin dominant (200 μM PC vs. 50 μM TC) and tetracycline dominant (200 μM TC vs. 50 μM PC) mixture solutions. It can be observed that if the concentration of penicillin is too low compared to the concentration of tetracycline (50 μM vs. 200 μM), the cathodic peak of penicillin at 0.3 V become less visible compared to the cathodic peak of tetracycline at 0.8 V. However, if the penicillin concentration is much higher than the tetracycline concentration (e.g., 200 μM vs. 50 μM), the specific peak of tetracycline could still be observed at 0.8 V.

In order to further investigate the performance of this multisegment hybrid nanowire array biosensor, the length of each segment was varied from 1 μm to 3 μm, with the total length kept at 4 μm, as shown in Fig. 5. It can be observed that by making the Pt (or Au) segment longer, the slopes of the curves became larger, which indicated a higher sensitivity, due to the larger amount of bioreceptor (L-cysteine or penicillinase) immobilized on each segment. When the nanowire segment is less than or equal to 2 μm, the linear detection ranges were found up to 300 μM; however, longer segments (~3 μm) would lead to narrower linear detection range, up to 240 μM for PC and 210 μM for TC, but with higher sensitivity as shown in Table S1. Based on five times measurements results, Au segment and Pt segments (2 μm + 2 μm) showed relative standard deviation (RSD) of 3.4% and 4.5%, respectively, within their linear detection range (up to 300 μM), indicating a good stability and repeatability.

3.4. Real sample test from chicken/beef extract

In order to test the sensing performance of this hybrid biosensor in real application, chicken breast and beef were chosen and squeezed to get the extract. Both chicken and beef extract were diluted by PBS buffer solution for 10 times followed by cyclic voltammetry scans, as

shown in Fig. 6. Due to the restricted regulation in US and Canada (0.05 ppm of penicillin and 0.2 ppm for tetracycline), neither penicillin or tetracycline was detected with this biosensor. Then, certain amounts of antibiotics were added into the extract samples for the recovery test. It is found that the recovery rate of penicillin and tetracycline in the chicken extract was higher than in the beef extract, as shown in Fig. 6(A)(C), especially when the antibiotic concentration was high ($> 250\,\mu M$). The recovery rate of penicillin was found to be more accurate than that of tetracycline in both chicken and beef extract, as shown in Fig. 6(B)(D). The detection performance of tetracycline was not as good as it performed in pure PBS, which may be due to the various bio chemicals and proteins in the extract which would interfere with the L-cysteine in a certain extent. The long term stability was also tested as shown in Table S2. The tetracycline detection capability dropped to 97% in 10 days and 95% in 20 days, indicating that the L-cysteine on Au segments has good long term stability. However, the penicillin sensing performance decreased to 87% in 10 days and 79% in 20 days, which may be due to the deactivation of penicillinase enzyme during long term storage.

4. Conclusions

In the present work, multi-segment Au-Pt nanowire/nanoparticle hybrid array was fabricated for simultaneous electrochemical sensing of penicillin and tetracycline. L-cysteine and penicillinase were immobilized on the surface of Au segment and Pt segment as bio-receptor, respectively. Due to the unique structure of multisegment and vertically aligned 3D nanowire array, the prepared hybrid electrode showed simultaneous detection ability and remarkably high sensitivity of penicillin and tetracycline, which are $41.2\,\mu A\,\mu M^{-1}\,cm^{-2}$ for penicillin detection and $26.4\,\mu A\,\mu M^{-1}\,cm^{-2}$ for tetracycline detection. The nanowire array biosensor also showed good recovery performance in real sample tests of chicken and beef extract, though L-cysteine showed some limitations for highly selective tetracycline detection due to the interference of other biomolecules. In the future work, other different bio-receptors can be investigated to functionalize different segments of the nanowire array; it is believed that due to the advantages of this hybrid array structure, this new sensor can serve as an enhanced platform for simultaneous detection of various bioanalytes.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bios.2018.10.025.

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