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An Interference-Free Glucose Biosensor Based on an Anionic Redox Polymer-Mediated Enzymatic Oxidation of Glucose

Huimin Deng, Wei Shen, and Zhiqiang Gao*[a]

Dedicated to the 80th birthday of Prof. Adam Heller

Herein a novel strategy for the construction of an amperometric biosensor for highly sensitive and selective determination of glucose is described. The biosensor is made of a biocomposite membrane of glucose oxidase (GOx) and an $Os(bpy)_2$ (bpy = 2,2′-bipyridine)-based anionic redox polymer (Os-RP) mediator. The biosensor is fabricated through the co-immobilization of GOx and the Os-RP on the surface of a glassy carbon electrode by a simple one-step chemical crosslinking process. The crosslinked Os-RP/GOx composite membrane shows excellent catalytic activity toward the oxidation of glucose. Under optimal experimental conditions, a linear correlation between the oxidation current of glucose in amperometry at 0.25 V (vs. Ag/AgCl) and glucose concentration up to 10 mM with a sensitivity of 16.5 $\mu A\,mM^{-1}\,cm^{-2}$ and a response time <5 s. Due to the presence of anionic sulfonic acid groups in the backbone of the redox polymer, the biosensor exhibits excellent selectivity to glucose in the presence of ascorbic acid and uric acid. The low hydrophobicity of the composite membrane also effectively retards the transport of molecular oxygen within the membrane.

1. Introduction

Diabetes mellitus,[1] resulting from the failure of glucose breakdown in the human metabolic process, has long been a worldwide public problem. According to the World Health Organization, the number of people with diabetes mellitus worldwide will reach approximately 300 million by the year 2025. Diabetes is directly reflected by the blood glucose concentration which is lower or higher than the normal range of 80–120 $mg\,dL^{-1}$ (4.4–6.6 mM). Hypoglycemia, blood glucose level lower than the normal range, may cause blackouts and it is even life-threatening in severe cases, whereas hyperglycemia, blood glucose level higher than the normal range, lead to kidney failure, circulatory disease, blindness, stroke, amputations, and nerve degeneration. Thus, highly sensitive and selective glucose determination is of paramount importance for diabetes mellitus diagnosis and control.

Since the first glucose enzyme electrode proposed by Clark and Lyons,[2] numerous glucose detection methodologies, such as amperometric,[3,4] potentiometric,[5,6] and impedimetric[7,8] electrochemical glucose biosensors have been developed and reviewed by several experts in the field.[9–11] Currently, glucose biosensors employ two types of glucose detection strategies, namely, direct glucose detection and indirect measurement of glucose through measuring the concentration of either hydrogen peroxide or molecular oxygen. Selectivity of the biosensors is commonly achieved by the use of glucose oxidase (GOx).[9–11] However, the indirect detection strategy is less sensitive and severely compromised by oxidizable interferants such as ascorbic acid and uric acid in blood. Moreover, high concentrations of hydrogen peroxide adversely affect the activity of GOx, and hence the stability of the biosensors. Being the limiting factor in the enzymatic oxidation of glucose, molecular oxygen in blood is at a much lower level than glucose, which is undesirable in the development of highly sensitive glucose biosensors. On the other hand, high sensitivity is usually realizable for the direct glucose detection strategy. Instead of relying on molecular oxygen as the co-reactant in the enzymatic oxidation of glucose, an artificial co-reactant, an electron mediator, is employed in the construction of the glucose biosensors. The electron mediator electrically "wires" the redox centers of GOx to a substrate electrode and shuttles electrons from GOx to the substrate electrode.[12] As a result, the analytical signals produced in those biosensors, primarily determined by the concentration of glucose, are usually much higher than those found in the indirect detection systems. In these biosensors, however, the natural enzymatic oxidation of glucose by molecular oxygen is considered as a side reaction. Depending on the kinetics of the mediated glucose oxidation reaction, this side reaction may affect the accuracy and sensitivity of the biosensors. Thus, glucose biosensors based on the direct detection strategy still face several challenges, for example anti-interference ability and durability. The commonly encountered interferants in blood, such as ascorbic acid and uric acid, are prone to be oxidized at relatively low working potentials and thus contribute to the analytical signal. Therefore, immunity to

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molecular oxygen and redox-active interferants is one of the major criteria for the fabrication of a reliable glucose biosensor.

To alleviate the interference problem, many approaches have been proposed to regulate the transport of solution species to the glucose biosensors. For example, Nafion membranes have been utilized in the fabrication of glucose biosensors,[13,14] which can prevent the diffusion of anionic interferants such as ascorbic acid and uric acid toward the electrode. However, the detection sensitivity is seriously affected in the presence of the glucose-diffusion-impeding Nafion membrane. In another attempt to eliminate the interferences from ascorbic and uric acid, it has been observed that the engagement of a micromembrane relieves the disproportionately large interference from both ascorbic and uric acid.[15] It has also been observed that the less permeable the membrane is, the better the stability of the glucose biosensor.[15] More recently, some new materials have also been exploited. Wu and coworkers developed a novel chemically reduced MoS_2 single-layer nanosheet for selective enzymatic glucose sensing in the presence of ascorbic acid and uric acid.[16] In addition, mediated enzyme electrodes are known to be less susceptible to interferences when they are operated at sufficiently low potentials.[17] Thus, the development of different types of low redox potential mediators has been intensively investigated. Several mediated glucose biosensors working at very low applied potentials have been reported. For instance, Jiang et al. proposed an osmium-complex-based mediator that works at 0 V (vs. Ag/AgCl).[4] Tian et al. developed a ruthenium-purple-mediated glucose microelectrode that works at −0.05 V (vs. Ag/AgCl).[18] These low working potentials effectively eliminate possible interferences commonly found in blood.

Herein, an amperometric biosensor based on immobilized GOx and an $Os(bpy)_2$ (bpy = 2,2′-bipyridine)-based anionic redox polymer (Os-RP) mediator was developed for the determination of glucose. GOx and the water-soluble crosslinkable Os-RP were co-immobilized on a glassy carbon electrode (GCE) in one step by employing glutaraldehyde as a crosslinker. In addition to its excellent electrocatalytic power, the crosslinked membrane acted as a thin permselective polymeric membrane with excellent selectivity for glucose over interferants such as ascorbic and uric acid. The interferant-eliminating property was obtained through the presence of a large number of sulfonic acid groups in the redox polymer. In addition, the high hydrophilic nature of the membrane effectively retarded the diffusion of molecular oxygen. This biosensor showed high sensitivity and excellent selectivity for glucose over interferants such as molecular oxygen, ascorbic acid, and uric acid.

2. Results and Discussion

2.1. Electrochemical Characteristics of the Biosensor

In the absence of glucose, cyclic voltammetric tests of the biosensor in phosphate-buffered saline solution (PBS) (pH 7.4, 0.15 M NaCl, 20 mM phosphate) showed a pair of well-defined current peaks that were assigned to the reversible electrochemical transformation between Os^{2+} and Os^{3+} embedded in the Os-RP/GOx membrane.[19] The charge under either the oxidation or the reduction current peak indicated the amount of the redox polymer deposited on the GCE surface (Figure 1, trace 1). Moreover, the magnitudes of the anodic and cathodic peak current were practically the same and the peak-to-peak potential separation was ~60 mV, close to the theoretical value of 59 mV at 25 °C. This implies that the electron exchange process between the redox polymer and the substrate GCE is rapid and the electrode process is diffusion-controlled[20] due to the relatively thick membrane on the electrode surface.[12] It can also be inferred from the cyclic voltammogram of the Os-RP/GOx membrane that GOx in the membrane does not noticeably affect the electrochemistry of the Os^{2+}/Os^{3+} redox couple.

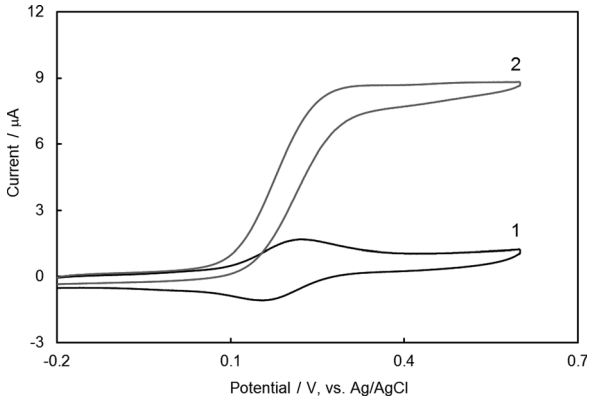


Figure 1. Cyclic voltammograms of an Os-RP/GOx/GCE biosensor 1) in the absence and 2) in the presence of 10 mM glucose under air. Coating composition: 0.25:50:0.025 μg (Os-RP/GOx/GA). Supporting electrolyte: PBS, Potential scan rate: 50 mV s^{-1}.

On the other hand, as depicted by trace 2 of Figure 1, in the presence of glucose the cyclic voltammogram became sinusoidal with a greatly increased oxidation current and a severely diminished reduction current—a typical electrocatalytic voltammogram,[21] resulting from the Os-RP-mediated glucose oxidation by GOx. Supportive evidence was found from the low hysteresis of the voltammogram between the oxidation and reduction branches. The absence of the reduction current peak in the cyclic voltammogram implies that the Os-RP/GOx membrane is homogenously maintained in the reduced state by the excellent electron relaying power of the redox polymer in the membrane through the transfer of electrons from the reduced GOx to the oxidized Os-RP (Os^{3+}) sites and to the substrate GCE. This means that the Os^{2+}/Os^{3+} moieties in the Os-RP/GOx membrane act as artificial electron donors in the place of molecular oxygen for GOx and electron shuttles between GOx and the substrate GCE. As illustrated in Figure 2, glucose

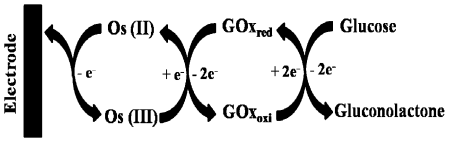


Figure 2. Working principle of the Os-RP-mediated glucose-sensing process.

in solution is first enzymatically oxidized to gluconolactone, leaving behind two electrons. Meanwhile, the redox center (FAD) of GOx receives the two electrons returning to its reduced state. The electrooxidized Os-RP (Os^{3+}) then reacts with the reduced GOx, accepting the aforementioned electrons from the reduced GOx to become reduced (Os^{2+}) and regenerating the oxidized GOx. The reduced Os-RP then gives up its electrons to the substrate GCE, generating a current while Os^{2+} returns back to its oxidized state Os^{3+}. Since the redox potential of GOx is −0.36 V,[21] which is much more cathodic than that of the Os^{2+}/Os^{3+} couple in the redox polymer and as there are plenty of Os^{3+} ions in the vicinity of the redox centers of GOx, the electron transfer between Os^{3+} and the reduced GOx is kinetically rapid, consuming all Os^{3+} moieties in the membrane as soon as they are formed. The oxidation current is now controlled by either the diffusion of glucose or by the kinetics of the enzymatic oxidation of glucose, depending on the concentration of glucose. For the amperometric determination of glucose, in order to maximize the sensitivity of the biosensor, to minimize background current, and to eliminate possible interferences from oxidizable species, the potential should be poised on the anodic side of the current peak and in the vicinity of the peak potential. So in this case, 0.25 V was chosen as the voltammogram peaked off at ~0.22 V. The time needed to reach 90% of the maximum response (response time) in amperometry at 0. 25 V was within 5 s.

2.2. Optimization

The above results confirmed that Os-RP-mediated enzymatic oxidation of glucose is successfully achieved at the proposed biosensor with sufficient sensitivity. In the case of electrocatalytic oxidation of glucose, the oxidation current must be determined by one or a combination of the following processes: 1) mass-transport of glucose, 2) GOx-catalyzed oxidation of glucose at the biosensor–solution interface and within the membrane, and 3) the electron-mediating power of the redox polymer. However, for a successful adaptation of the biosensor in the quantification of glucose, the oxidation current must be exclusively associated with the concentration of glucose in a straightforward manner, preferably a linear correlation between the oxidation current and the glucose concentration. This solely glucose-controlled process can only be achieved by speeding up the electron-mediating power and the enzymatic oxidation process. High electron-mediating power is easily attainable when working with a high concentration of the redox polymer in the membrane and high enzymatic reaction rate is achievable by increasing the loading of GOx in the membrane.

The effect of Os-RP loading on the performance of the biosensor was first evaluated and the results were summarized in Figure 3a. The loading mass of GOx and GA both were fixed, the loading amount of Os-RP was evaluated from 0.1 to 0.6 μg. As seen in Figure 3a, as the redox polymer loading in the membrane was increased, the oxidation current of glucose rose rapidly at first, but then leveled off at ~0.50 μg. It was observed that the oxidation current of glucose is practically independent of the redox polymer loading beyond 0.50 μg, suggesting that the mediating power of Os-RP reaches its maximum at this quantity. In addition to the detrimental effect on the background current, too high an Os-RP loading may also adversely affect its mediating power. Therefore, 0.50 μg Os-RP was chosen for all subsequent experiments. The oxidation current of glucose is now determined by either the enzymatic oxidation or the diffusion of glucose. Figure 3b describes the dependence of the oxidation current of glucose on the loading of GOx in the Os-RP/GOx membrane. As anticipated, the GOx loading had a profound effect on the oxidation current of glucose. The loading mass of Os-RP and GA were both fixed, the loading amount of GOx was evaluated from 10 to 100 μg. As illustrated in Figure 3b, when the GOx loading was increased from 10 to 50 μg, the oxidation current increased sharply, due to the increase in the enzymatic oxidation rate, because the reaction rate of a catalytic process generally scales up with the catalyst, GOx in this case. The highest current was attained when 50 μg of GOx was loaded on the biosensor. A further increase in GOx loading did not result in any appreciable increase in the oxidation current. On the contrary, being a natural insulator, it was found that the oxidation current decreases when an excessive amount of GOx was loaded. For example, a ~50% drop in the oxidation current was observed when 100 μg of GOx was loaded onto the biosensor, probably due to a drastically reduced electron exchange rate between the Os-RP/GOx membrane and the substrate GCE, since GOx itself does not exchange electrons with the substrate electrode. On the contrary, the presence of the large excess of GOx in the membrane severely impedes (blocks) the electron exchange pathways between the redox polymer and the substrate GCE. Therefore, the amount of GOx loaded onto the biosensor was fixed at 50 μg to ensure sufficiently high sensitivity and good signal-to-noise ratios.

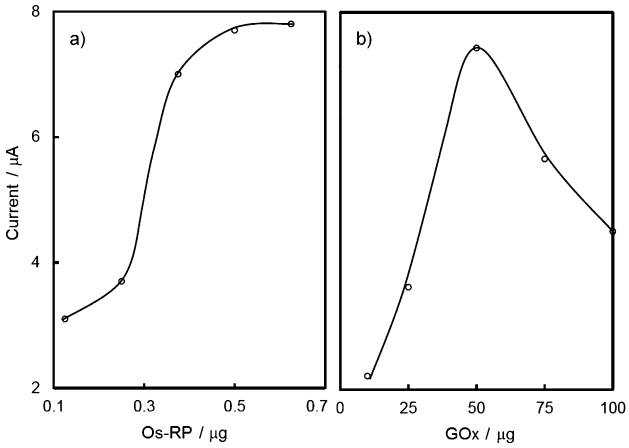


Figure 3. The effect of a) Os-RP loading and b) GOx loading on the amperometric response of 10 mM glucose. Supporting electrolyte: PBS, poised potential: 0.25 V.

2.3. Analytical Performance of the Biosensor

The performance of the proposed biosensor was investigated through a calibration and interference study. The correlation

between the amperometric response and glucose concentration was studied in a series of glucose solutions in PBS under optimized experimental conditions. The interference study was carried out in PBS that contained 5 mM glucose, 0.1 mM ascorbic acid, or/and 0.2 mM uric acid, which are all in the normal ranges that exist in human blood.[17,22]

Under the optimized experimental conditions, a linear correlation between the oxidation current in amperometry and the glucose concentration was found between 0 and 10 mM at the Os-RP/GOx/GCE glucose biosensor with a correlation coefficient of 0.992 and a detection sensitivity of 16.5 $\mu A\,mM^{-1}\,cm^{-2}$ (Figure 4). In this concentration range, glucose is the limiting

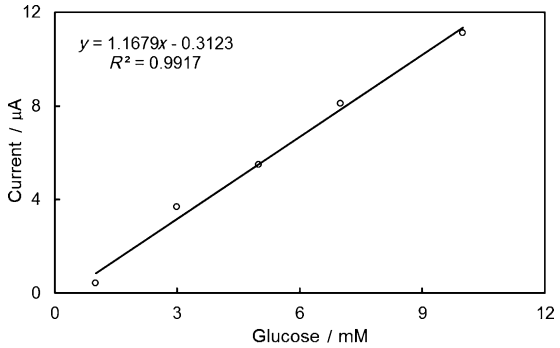


Figure 4. Calibration curve of the Os-RP/GOx/GCE glucose biosensor. Supporting electrolyte: PBS, poised potential: 0.25 V.

factor in the reaction and GOx is in excess. Above 10 mM the current increased at a much lower rate and it eventually started to level off beyond 15 mM. As all the active sites on the enzyme were fully saturated and operating at a maximum speed at 40 mM, any further increase in glucose concentration beyond 40 mM did not appreciably increase the catalytic oxidation current.

Because of their low redox potentials,[23,24] ascorbic acid and uric acid are the common redox active interferants in blood when detecting blood glucose using the amperometric method. In the absence of an analyte-regulating mechanism, the electrochemical oxidations of anionic ascorbic acid and uric acid were disproportionately high since the redox polymer used was usually polycationic.[15,25] This is due to the accumulation of anionic interferants within the redox polymer scaling with the density of cationic sites.[15,25] The introduction of a high density of sulfonic acid groups into the redox polymer is expected to result in a marked improvement of the performance of the biosensor in terms of selectivity. To confirm this hypothesis, the anti-interference ability of the proposed glucose biosensor was studied in a 5 mM glucose solution in the presence of 0.1 mM ascorbic acid and 0.2 mM uric acid. As shown in Figure 5, the presence of ascorbic acid and uric acid contributed less than 5% to the overall oxidation current. This is mainly due to the presence of a high density of anionic sulfonic acid groups in the redox polymer. Strong electrostatic repulsion between sulfonic acid groups and the ascorbic acid and uric acid greatly suppress the access of these anionic species to the biosensor.

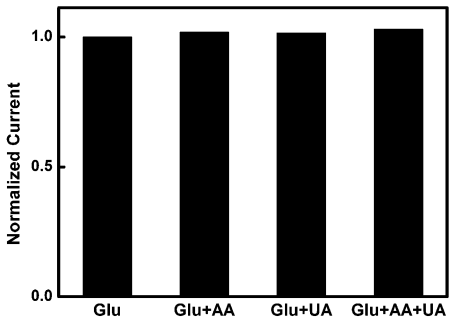


Figure 5. Normalized amperometric responses of 5 mM glucose, 5 mM glucose + 0.1 mM ascorbic acid, 5 mM glucose + 0.2 mM uric acid, and 5 mM glucose + 0.1 mM ascorbic acid + 0.2 mM uric acid, respectively. Supporting electrolyte: PBS, poised potential: 0.25 V.

As mentioned earlier, depending on the kinetics of the mediated glucose oxidation, dissolved molecular oxygen may affect the sensitivity of the biosensor. In the proposed biosensor, the introduction of the high density of anionic sulfonic acid moieties in the redox polymer made the Os-RP/GOx membrane highly hydrophilic, which efficiently facilitates electron transfer and effectively suppresses the transport of molecular oxygen as molecular oxygen is largely hydrophobic, granting the biosensor good insensitivity to dissolved molecular oxygen. Indeed, a difference smaller than 2% was observed between the amperometric responses of 5.0 mM glucose solution before and after thorough purging with nitrogen. The engagement of the anionic redox polymer in the construction of the glucose biosensor allows glucose to be selectively determined by the biosensor at its maximal sensitivity. In practice, this level of selectivity satisfactorily meets the requirement for the quantification of glucose in human blood samples. The only drawback of this biosensor was the relatively low mechanic strength.

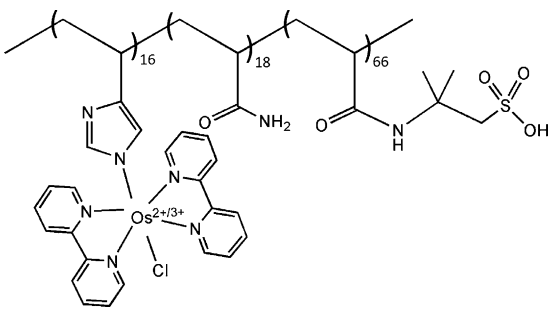
3. Conclusions

In this work, an enzymatic amperometric glucose biosensor was fabricated by using an anionic $Os(bpy)_2$-based redox polymer as a mediator. The analytical signal of the biosensor was directly generated from the catalytic oxidation of glucose in the sample. This contributes to the high sensitivity of this biosensor and sets it apart from other glucose sensors that relying on indirect measurements of glucose through dissolved molecular oxygen or hydrogen peroxide. A linear dynamic range between 0 and 10 mM glucose with excellent sensitivity was obtained. More notably, the biosensor showed high anti-interference ability. Practically no interference from the common coexisting species such as dissolved molecular oxygen, ascorbic acid, and uric acid were observed. As compared to other approaches, the much enhanced selectivity and sensitivity are attractive features for further study, particularly in the development of miniature implantable glucose biosensors.

Experimental Section

Materials and Apparatus

GOx, (EC 1.1.3.4, from *Aspergillus niger,* 191 units mg^{-1}) was purchased from Fluka (CH-9407 Buchs, Switzerland). Glucose, glutaraldehyde (25%), ascorbic acid, and uric acid were obtained from Sigma–Aldrich (St. Luis, MO, USA). All other reagents were of analytical grade and used without further purification. Ultrapure deionized water with an electric resistance of 18.3 MΩ was used for all solution preparations. Glucose stock solutions were allowed to mutarotate for 24 h before use. Freshly prepared ascorbic acid and uric acid solutions were used in the interference study. PBS was used as the supporting electrolyte and was prepared weekly using deionized water. $[Os(bpy)_2Cl_2]$ was synthesized from $(NH_4)_2OsCl_6$ by the procedure developed by Lay and coworkers.[26] The water-soluble and crosslinkable Os-RP (Scheme 1), poly(4-vinylimidazole-co-acrylamide-co-2-acrylanmido-2-methylpropanesulfonic acid) partially complexed with $[Os(bpy)_2Cl]^+$, was synthesized following a previously reported procedure.[27] Spectroscopic and elemental analysis showed that the synthesized redox polymer, on average, consisted of 16 $[Os(bpy)_2Cl]^+$, 18 amide, and 66 sulfonic acid moieties.



Scheme 1. Structure of the Os-RP.

Electrochemical experiments were carried out on a CHI760D electrochemical workstation (CH instruments, Austin, Texas). A conventional three-electrode system, consisting of the GCE working electrode, an Ag/AgCl (saturated KCl) reference electrode, and a platinum wire counter electrode, was employed. All potentials reported in this work were referred to the Ag/AgCl reference electrode. Cyclic voltammetric tests of the biosensor were performed at a potential scan rate of 50 mV s^{-1} in a potential window between −0.20 and 0.60 V. In amperometry, the background current was allowed to stabilize first before readings were taken. Small aliquots of glucose stock solution were added sequentially to reach the desired glucose concentrations in the test solutions.

Glucose Biosensor Fabrication

As for the biosensor fabrication, the GCE was first polished on a microcloth with 0.05 μm alumina slurry, followed by sonication in ultrapure water and ethanol for 5 min, successively. After drying the cleaned electrode, 4 μL of a mixed solution consisted of GOx, Os-RP, and glutaraldehyde was applied onto the GCE surface. The GCE was then incubated for at least 12 h under ambient conditions. During incubation Os-RP/and GOx were irreversibly crosslinked, forming the desired glucose sensing membrane on the GCE. The biosensor was kept at 4 °C when not in use. Little activity loss was observed within six months of storage.

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Keywords: 2,2′-bipyridine · biosensor · glucose · glucose oxidase · osmium · redox polymer

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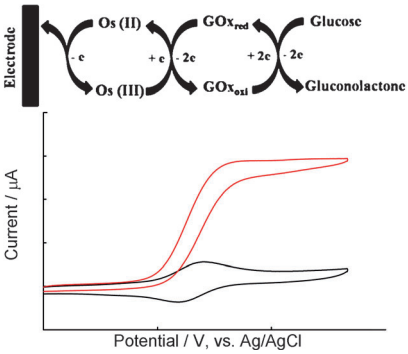

Sweet! A highly selective and sensitive glucose biosensor is constructed through the co-immobilization of glucose oxidase and an anionic redox polymer on the surface of a glassy carbon electrode.