# *Microneedle Electrodes Toward an Amperometric Glucose-Sensing Smart Patch*



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# Microneedle Electrodes Towards an Amperometric Glucose Sensing Smart Patch

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**Keywords**: conducting polymers ; glucose oxidase ; glucose sensors ; microneedles ;

subcutaneous

**Abstract**: Conventional glucose sensing and insulin delivery requires the placement of separate, potentially painful subcutaneous sensing wire and drug delivery elements. Here we describe efforts towards the development of a microneedle glucose sensor, or "Smart Patch" for

intradermal glucose sensing. We developed functional microneedle electrodes for use as direct amperometric glucose sensors. A conducting polymer, poly(3,4-ethylenedioxythiophene) (PEDOT) was used to immobilize glucose oxidase (GOx) in a thin film on a platinum-coated stainless steel microneedle array. These sensors exhibit linearity within the physiologically relevant range of 0–432mg/dL glucose (0–24mM). They exhibited no cytotoxicity when stored for up to one week and platinum microneedle sensor performance remained linear even after 7 days of wet and dry storage. This work represents the first steps towards the development of painless, transdermal sensing devices for continuous glucose monitoring.

**Main Text**

Currently, diabetes affects over 285 million people worldwide, and is predicted to impact 1 in 10 individuals by the year 2030, according to the World Health Organization.[1] The American Diabetes Association states that type 1 and type 2 diabetes affects over 25 million people alone in the US.[2] Long-term, accurate sensing of blood-glucose concentration is a major concern for diabetic patients,[3] and satisfactory compliance with testing is difficult to achieve, given the painful, repetitive nature of the commonly-used finger-prick method.[4] Efforts for longer-term, implantable sensors require the development of highly sensitive, fast-responding, accurate, and biocompatible sensing elements. A recent review by Bratlie *et al.* describes the various current approaches, therapies, and state of the art technologies in this field.[5] Much effort has been focused towards implantable, continuous sensors, with some commercial success.[6] Currently, the state of the art continuous glucose sensing devices suffer from poor and variable lifetimes, precluding FDA approval for independent glucose sensing without supplemental blood pricks.[7] Further, these are single sensor systems with no redundancy for signal averaging or

failure detection or replacement. Continuous sensors, such as the DexCom SEVEN+ system, must be frequently changed and have a bulky external component.[6]

Microneedle based arrays can be utilized for a variety of therapeutic and diagnostic systems.[8] They have generated significant interest, owing to their potential for painless sampling and delivery to the intradermal space.[9] To date, microneedles have been used for the injection of insulin,[10,11,12,13] and as sensors for a variety of analytes.[14,15,16,17,18,19] There have been attempts to use microneedles as a means of drawing blood or other fluids for amperometric glucose sensing using a separate sensor array.[20,21,22,23] Here we develop microneedles to address the current limitations in glucose sensing devices. We develop a prototype microneedle-based electrode system for the amperometirc detection of glucose that uses the needle itself as the functional electrode array. The ultimate goal of this device is to provide simple, painless, redundant, and continuous glucose monitoring system (CGMS) for diabetic patients.

Towards that end, we sought to develop a microneedle based "Smart Patch" sensor platforms for painless, continuous intradermal sensing. **Figure 1** shows images of the microneedle arrays used in this study, the schematic design of our sensor approach, and an envisioned "Smart Patch" based on this technology. We utilized conducting polymers, such as poly(3,4-ethylenedioxythiophene) (PEDOT), as electrical mediators for the sensing of glucose, as well as an immobilization agent for the glucose specific enzyme, Glucose Oxidase (GOx). Glucose oxidase, currently used in blood glucose strips, converts glucose (consuming oxygen) into gluconic acid (produces hydrogen peroxide). Flavin adenosine dinucleotide (FAD) cofactor, associated with GOx, undergoes reversible oxidation and reduction during this process. As glucose is converted, the associated current produced can be sensed by applying a voltage. Using GOx immobilized in PEDOT, this signal can be transduced at safe low voltages, affording

accurate and fast responses to physiological changes in glucose concentration. Similar sensing mechanisms have been employed in the past,[24] and other systems may also work on this microneedle platform; for this study we chose the conducting polymer architecture due to its unique advantages towards immobilization and signal transduction without loss of signal over time, unlike small molecule mediators, like quinones.[24]

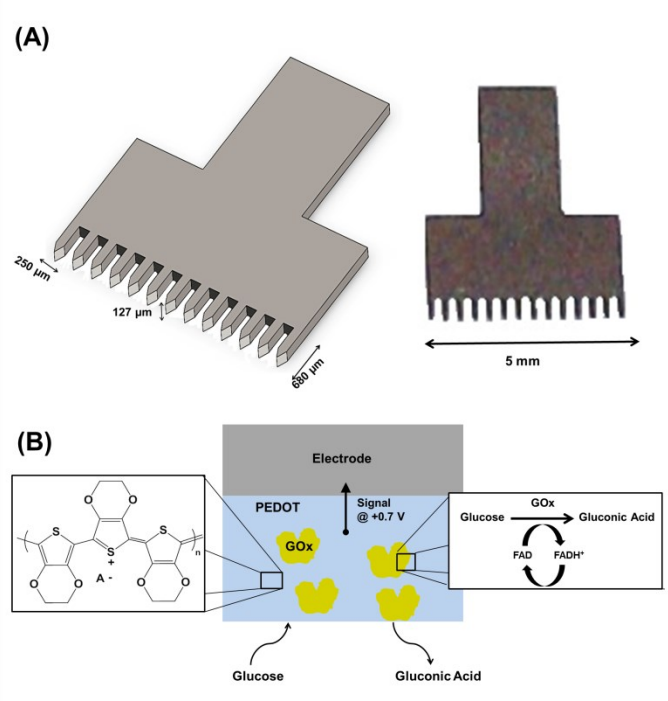


**Figure 1.** (A) Image of the microneedle arrays. (B) Sensor design schematic.

Cytotoxicity and biocompatibility are among the largest issues facing such sensors, as poorly compliant materials result in unwanted inflammation, fouling, and other adverse physiological effects. Herein, we investigate the potential of conducting polymers for glucose sensors, as well as various film parameters as they pertain to stability and accuracy. The final sensor design is comprised of a platinum-coated stainless steel in-line 2D microneedle array

coated with a film of PEDOT in which GOx has been immobilized. These sensors have proven to be efficacious within the physiological range of 0–432mg/dL (0–24mM) glucose (**Figure 2**). The average healthy blood glucose level for a patient is 100mg/dL (5.6mM) and current finger-prick test strip sensors are rated from 20–500mg/dL (1.1mM–27.8mM).[25] These results suggest that a conducting polymer based continuous glucose monitoring patch is a realistic platform for diabetes theranostics.

PEDOT was electrochemically polymerized on 316L grade stainless steel and platinum microneedles in the presence of glucose oxidase, resulting in thin films composed of GOx immobilized within an electrically conducting polymer matrix. The conducting film acts as a mediator for transducing the signal generated by the enzymatic oxidation of glucose. By applying a +0.7V potential bias with respect to a Ag/AgCl reference electrode, changes in amperometric response can be observed upon successive additions of glucose (**Figure 2**). These signals were then correlated to a concentration of glucose and a linear curve across the physiologically relevant range was generated (**Figure 2**).

We tested the sensors in PBS using sequential additions of glucose, and measured current response at +0.7V. A linear response was observed with increasing glucose concentrations (**Figure 2**, $R^2$>0.97 for all coatings). The platinum button control sensor was able to sense in the physiological glucose range of 36–468 mg/dL (2–26mM, S/N=9.0). Steel microneedles were found to have significantly lowered efficacy, however they still functioned linearly between 72–216 mg/dL glucose (4–12mM, S/N=33.8). Once coated with platinum, sensor performance returned, as expected, to nearly the same performance as the control. Platinum coated needles exhibited linearity between 36–432 mg/dL glucose (2–24mM, S/N=10.7). Other background data on sensor storage and stability has been generated, including an investigation of the effect of

various interferents in human blood (see Supporting Information). Glucose exhibits a far higher signal than any other analyte present in blood and ~~What did we learn from this? w~~We expect the sensors to perform similarly to our observations as subcutaneous sensing suffers less from these interferents.[26] We also evaluated the potential biocompatibility of the sensors through a cytotoxicity assay (MTT). Sensors were soaked in PBS for 1, 3, and 7 days and mammalian cells were exposed to the incubated solution. Figure 2 also shows the cytotoxicity profiles of these sensors over the course of 1, 3, and 7 days soaked in 5mL of PBS. No statistically significant changes in cell viability were observed for any of the sensors tested, indicating that toxic components were not excreted from the sensor.

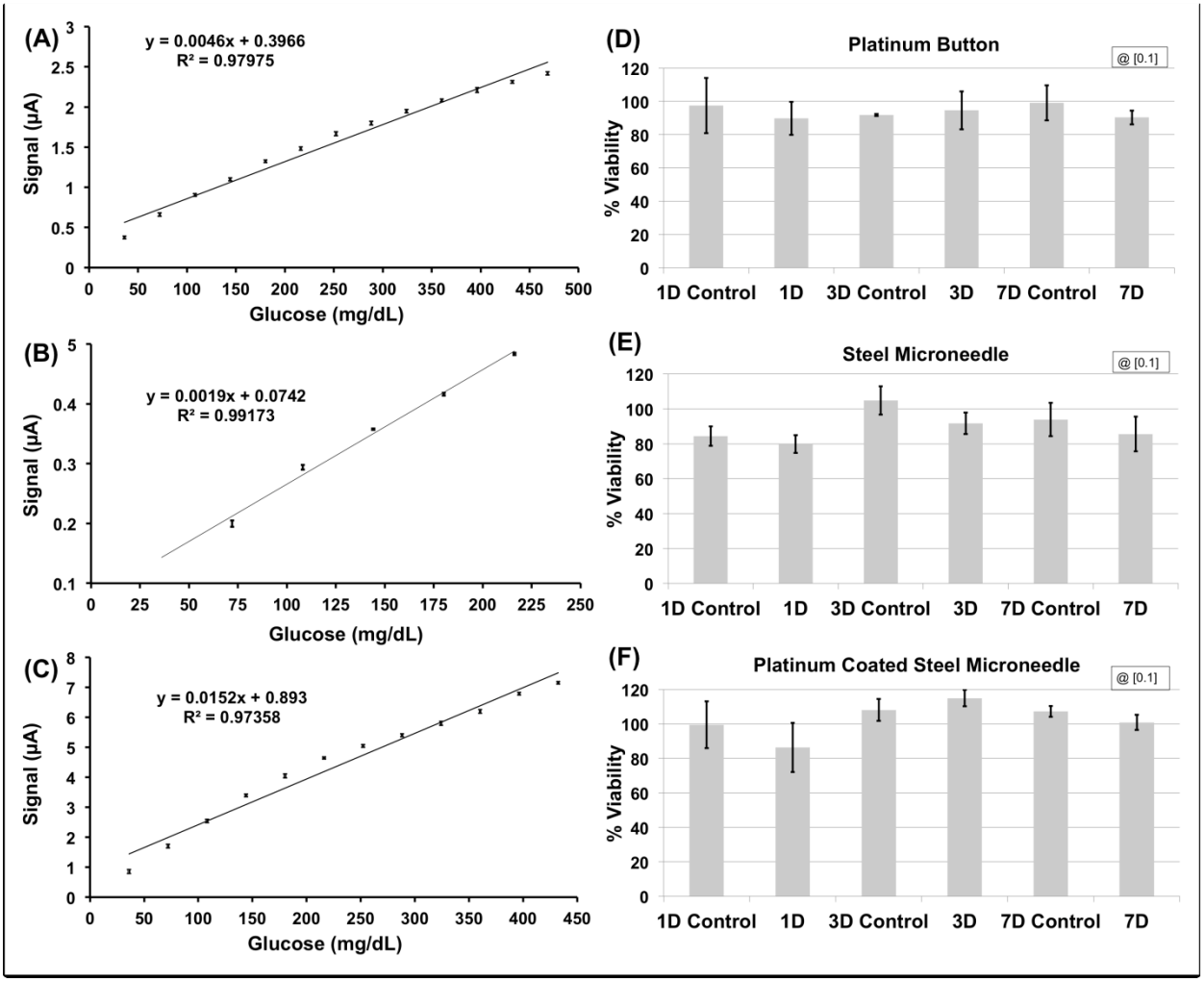


**Figure 2.** Representative concentration curves for amperometric sensors on (A) platinum button, (B) steel microneedle, and (C) platinum-coated steel microneedle electrodes. Corresponding cytotoxicity data for 1, 3, and 7 days of storage in PBS for (D) platinum button, (E) steel microneedle, and (F) platinum-coated steel microneedle sensors.

We next investigated their long-term stability of the glucose sensors for their use as part of a patch-based theranostic system. Films were prepared on platinum button controls, steel microneedles, and platinum-coated steel microneedles and subjected to 1, 3, and 7 days of storage at room temperature either wet (PBS) or dry (in an empty parafilmed vial). The

performance of the platinum button sensors was not significantly altered by any of these storage conditions. Wet storage resulted in a more reproducible slope of the calibration curve with a deviation of 18% as compared to 67% variability for dry storage~~(CITE DATA)~~. Following 1-day, 3-day, and 7-day dry storage, sensors were linear up to 486mg/dL ($y=0.0079x+0.2947$ ; $R^2=0.99$, S/N=11), 288mg/dL ($y=0.0047x+0.1295$; $R^2=0.99$, S/N=10), and 360mg/dL ($y=0.0177x+0.6762$ ; $R^2=0.99$, S/N=35), respectively. Wet-stored platinum buttons showed more similar calibration equations. Following 1-day, 3-day, and 7-day wet storage, sensors were linear up to 216mg/dL ($y=0.0279x+0.8447$ ; $R^2=0.98$, S/N=30), 288mg/dL ($y=0.0217x+0.7373$ ; $R^2=0.97$, S/N=56), and 324mg/dL ($y=0.02x+1.4734$ ; $R^2=0.94$, S/N=26), respectively.

Steel-based sensors demonstrated relatively poor performance, exhibiting low sensor ranges and, in the case of 7-day wet, essentially ceased to function entirely ~~(CITE DATA/FIGURE~~Figure 3E). Sensor responses for 1-day, 3-day, and 7-day dry storage were up to 144mg/dL each ($y=0.0033x+0.1077$ ; $R^2=0.99$, S/N=30), ($y=0.0014x+0.0425$ ; $R^2=0.99$, S/N=9), and ($y=0.0029x-0.0068$ ; $R^2=0.99$, S/N=23), respectively. 1-day, 3-day, and 7-day wet sensors showed linearity to 216mg/dL ($y=0.0332x-0.0302$ ; $R^2=0.99$, S/N=39), 180mg/dL ($y=0.0515x+1.1087$ ; $R^2=0.98$, S/N=24), and 216mg/dL ($y=0.001x+0.0213$ ; $R^2=0.99$, S/N=13), respectively. The signal for the 7-day wet sensor, however, was an order of magnitude lower than that for the other sensors.

Finally, both wet and dry storage yielded very similar calibration trends for the platinum-coated steel microneedles, with high linearity and S/N ratios. In the case of dry sensors, it was more typical for the 7-day systems to have an extended sensing ratio. 1-day and 3-day dry sensors had ranges up to 324mg/dL ($y=0.0186x+0.832$ ; $R^2=0.98$, S/N=13) and ($y=0.0157x+0.9182$ ; $R^2=0.97$, S/N=12), respectively, while the 7-day sensor made it to

396mg/dL (y=0.0162x+1.1239 ; $R^2$=0.97, S/N=18). Platinum coated steel microneedles stored wet had shortened ranges with the same linearity, however, 252mg/dL (y=0.007x+0.1707 ; $R^2$=0.98, S/N=5), 216mg/dL (y=0.0073x-0.0659 ; $R^2$=0.99, S/N=8), and 252mg/dL (y=0.007x+0.1305 ; $R^2$=0.99, S/N=23), respectively. These results are encouraging for the use of the microneedle sensor *in vivo* over the course of the "Smart Patch" lifetime.

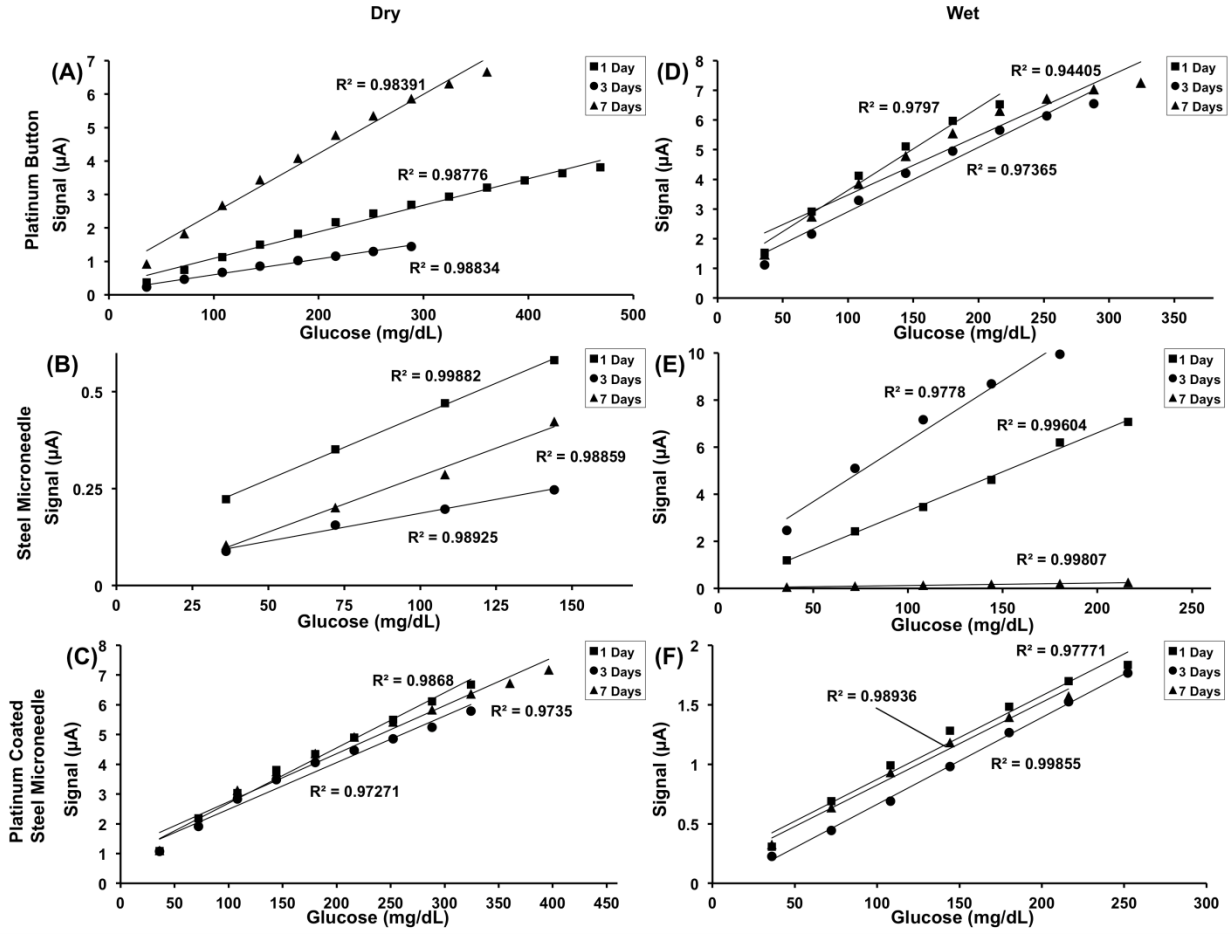


**Figure 3.** Long term storage of prepared sensors showing dry (left) and wet (right) storage conditions. A and D are platinum button electrodes, B and E are steel electrodes, and C and F are platinum coated steel electrodes.

The microneedle patch holds the potential for a non-invasive, non-encumbering platform for both sensing and delivery. Multiple sensor arrays may be used to address the issue of redundancy (for signal averaging as well as combating single-sensor failure). The patch could be easily applied and removed, aiding patient compliance with blood glucose monitoring, a major concern for many diabetics. Our data indicate that these sensors are linear and reliable throughout the physiological range and are non-toxic. The concept of a transcutaneous electrode array that can accomplish numerous functions for diabetes theranostics is an attractive solution to the treatment of this disease. The sensors investigated in this study represent one potential component of such a "Smart Patch."

## Experimental

### Sensor Preparation

The polymerization bath was prepared by adding 13.3mg of p-toluenesulfonic acid (PTSA, Sigma-Aldrich) to 100mL of deionized water. The pH of the bath was 3.4. For initial platinum button controls, fresh polymerization solution was prepared by adding 50mg of glucose oxidase from Aspergillus Niger (Sigma-Aldrich) to 5mL of polymerization. The vial was then shaken to mix. Next, 15µL of 3,4-ethylenedioxythiophene (EDOT, ALDRICH) was added to the solution. The solution was then stirred with a magnetic stir bar at 600 rpm for 1hr. Fresh polymerization solution was prepared on each day of experiments. Polymerization was carried out at 1.5V for 15s. The platinum electrodes (CH Instruments) were polished using micropolish powder (0.05µm, CH Instruments) between uses.

Stainless steel (316L) 2D arrays (4.901mm across by 5.693mm tall by 127µm thick) of microneedles were purchased from eMachineShop. The microneedles are 680µm in length and

250µm wide. Needles were used as-is and coated with platinum. Platinum was deposited using sputter coating (using an AJA Orion 5 Sputterer) using a 50nm titanium base and an overcoat of 450nm of platinum metal.

For both types of microneedle arrays, fresh polymerization solution was prepared by adding 50mg of glucose oxidase from Aspergillus Niger (SIGMA) to 4 mL of polymerization bath. The vial was then shaken to mix. 15µL of EDOT was then added to 1mL of acetonitrile (Sigma-Aldrich). These two solutions were then mixed. The solution was then shaken and stirred with a magnetic stir bar at 600rpm for 1hr. Fresh polymerization solution was prepared on each day of experiments. Polymerization of the sensor onto steel microneedles was carried out in the same manner as the platinum buttons excepting the polymerization duration was 30s.

Steel microneedles were initially cleaned by sonication in acetone for 1min. Teflon tape (PTFE Thread Sealant Tape) was used to cover the microneedle platform and solely expose the microneedle portion. The polymerization and sensing protocols used were identical to the ones used for platinum buttons. Platinum coated microneedles were tested with the same protocol (15s polymerization duration).

**Sensor Testing**

The platinum buttons were dried in air for 1hr prior to sensing. A 2.0M solution of glucose (Acros Organics) was prepared in phosphate buffered saline (-calcium chloride, -magnesium chloride, pH 7.4, 1X, GIBCO life technologies). This was used to make sequential additions to the sensing bath. 10mL of PBS were added to the electrochemical cell. The electrode (sensor), a counter electrode flag (platinum), and a reference electrode (silver) were submerged together to form the cell. A magnetic stir bar was added and allowed to stir at 300rpm.

Chronoamperometry was used to measure the change in current with time over the course of glucose additions to the stirred bath (300rpm). The potentiostat was initially allowed to stabilize to a steady horizontal current value prior to sensor calibration. 10μL of the 2.0M glucose solution (corresponding to a 2mM final concentration of glucose, or 36mg/dL) was added to the vial and the signal was allowed to stabilize. The stable current was then recorded. Addition of 10μL aliquots of glucose were added, stabilized, and recorded up to a maximum of 40mM. For long-term stability tests, the sensors were stored either dry in air or in PBS for 1, 3, and 7 days prior to sensing.

**Cytotoxicity Assay**

Platinum button and both microneedle type sensors were used to prepare sensors which were then submerged in 5mL of PBS for 1, 3, and 7 days. The PBS was used to carry out a biocompatibility screen (cytotoxicity) using an MTT assay. CHO (ATCC) cells were seeded into 96 well plates at 2,500cells/well and allowed to grow overnight before treatment. After 48hrs exposure, cells were given MTT (20μL, 5mg/mL) and incubated for 4hrs. Cells were subsequently lysed with 100μL DMSO and viability was measured with a plate reader (Tecan M200Pro) at 565nm. Serial dilutions of the stock solution in which the sensors were stored was carried out to give a wide range of possible concentrations for comparison (0.1, 0.01, 0.001, 0.0001, 0.00001, 0.000001, and 0.0000001).

**Acknowledgments**

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Published online: ((will be filled in by the editorial staff))

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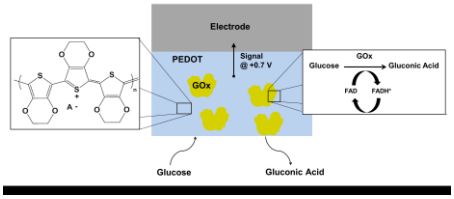
**Table of Contents**

**Herein we describe efforts towards the development of a microneedle-based glucose sensor, or "Smart Patch" for intradermal glucose sensing**. Metallic microneedle array electrodes, conducting polymers, and glucose oxidase form the sensor platform. This work represents the first steps towards the development of painless, transdermal sensing devices for continuous glucose monitoring.

**Keyword:** microneedles

M. A. Invernale, B. C. Tang, R. L. York, L. Le, D. Y. Hou, D. G. Anderson

**Microneedle Electrodes Towards an Amperometric Glucose Sensing Smart Patch**



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# Supporting Information

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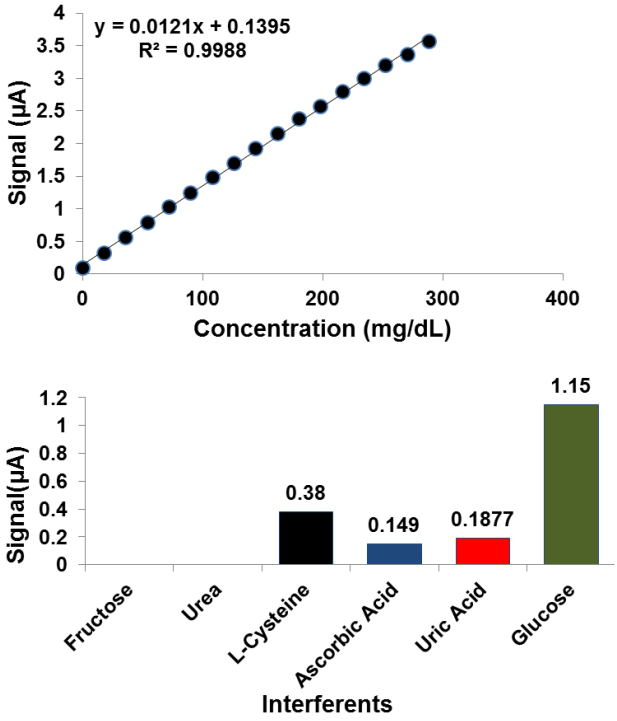
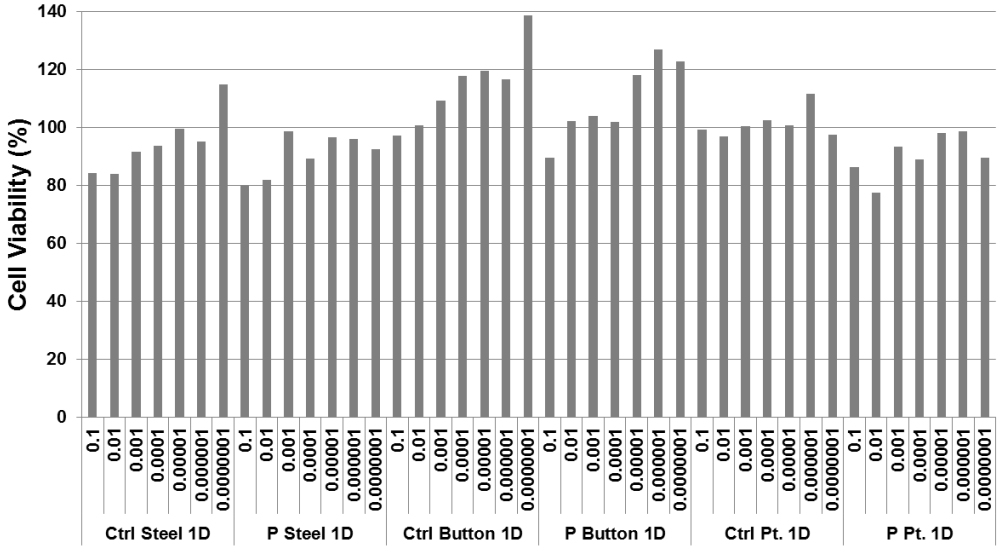
**Microneedle Electrodes Towards an Amperometric Glucose Sensing Smart Patch**

*Michael A. Invernale, Benjamin C. Tang, Royce L. York, Long Le, David Yupeng Hou, and Daniel G. Anderson*

Glucose sensors were prepared, as described, and were subjected to sequential additions of fructose, urea, L-cysteine, ascorbic acid, uric acid, and glucose (keeping to physiological ranges of each of these chemicals). Amperometric sensor responses were recorded for each of these interfering analytes and the maximum current response was compared to that of glucose. It is clear that glucose, by far, exceeds the signal for any of the other interferents. Furthermore, sensors that were tested in the presence of physiological concentrations of *all* of the interfering analytes studied above were able to perform as linearly as before, indicating that these sensors are robust and would not suffer upon use in blood. Supporting Figure 1 shows the data for these experiments. (W.M. Reichert *et al*., *Biomaterials*, **2007**, *28*, 3687-3703).




**Supporting Figure 1.** Intereferents in Blood Comparison of Sensor Performance. Sensor performance on a platinum surface (top), with corresponding bar graph of relative response of each interfering species present in serum (bottom).


Cell Viability (%)
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20
40
60
80
100
120
140
0.1
0.01
0.001
0.0001
0.00001
0.000001
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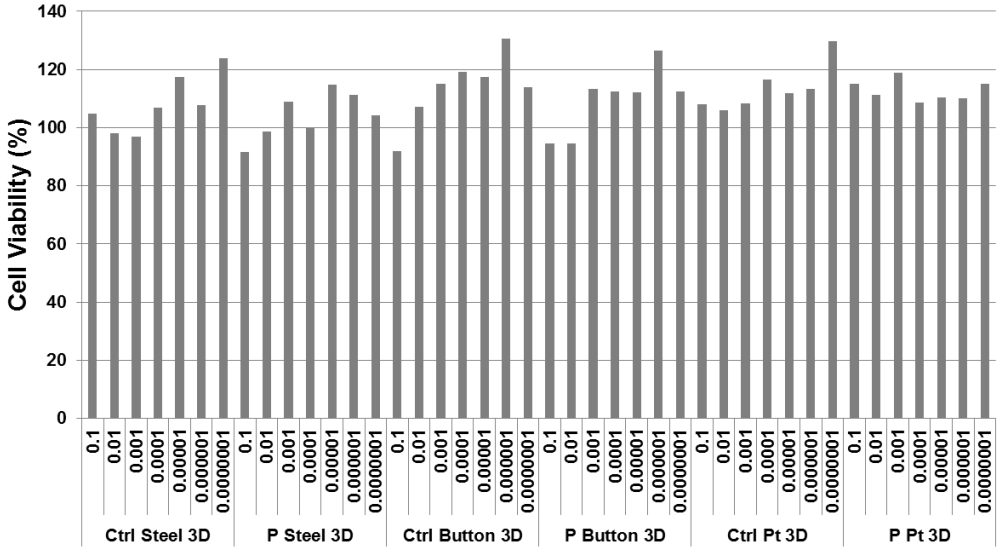
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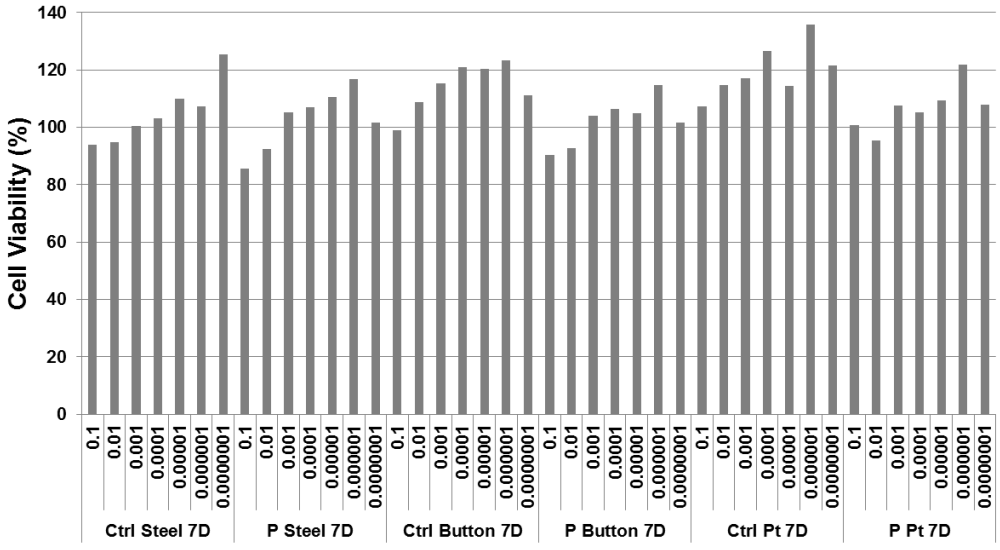
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0.001
0.0001
0.00001
0.000001
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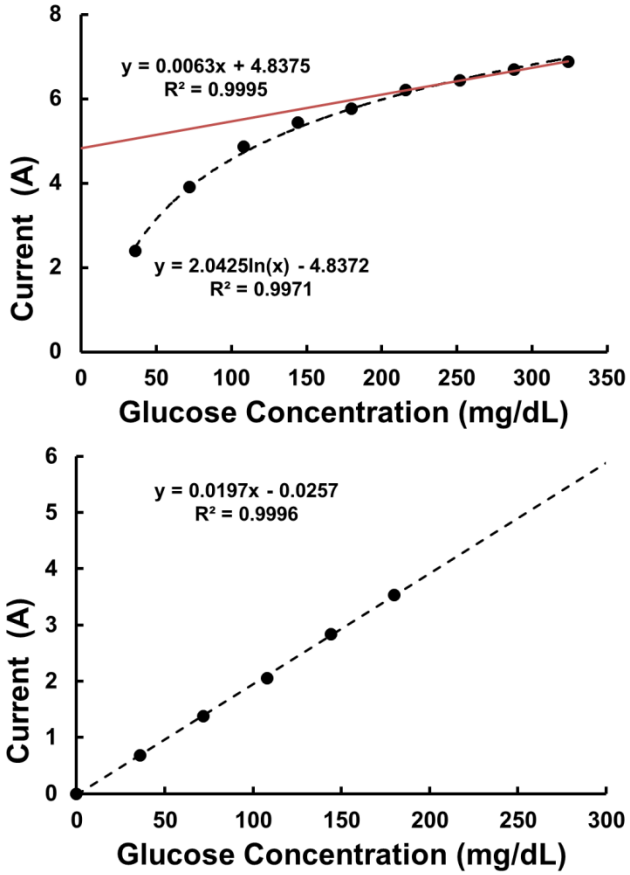
Ctrl Steel 7D
P Steel 7D
Ctrl Button 7D
P Button 7D
Ctrl Pt 7D
P Pt 7D

**Supporting Figure 2.** Cytotoxicity plots for the full dilution series for each material tested. Experiments were performed as described in the main manuscript.

Sensors were also tested for their performance at lower driving voltages. Side reactions due to interferents in blood or serum can be significantly reduced by using a voltage of +0.4V instead of the +0.7V standard experiment. Using this sensor architecture, we examined the linearity of the current response as before. It was found that a thinner sensor (5s polymerization time versus the standard 15 or 30) yielded a linear response but one that did not reach 200mg/dL in sensitivity.




**Supporting Figure 3.** Sensors at Lower Voltages. Performance of a normal sensor, showing a logarithmic performance (top, S/N = 5.1) and one polymerized for 5 seconds (bottom, S/N = 5.7) exhibiting good linearity but low range.