Biosensors and Bioelectronics 42 (2013) 256–260

Contents lists available at SciVerse ScienceDirect

Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios

Electrochemically deposited iridium oxide reference electrode integrated with an electroenzymatic glutamate sensor on a multi-electrode array microprobe

Vanessa M. Tolosa [a], Kate M. Wassum [b], Nigel T. Maidment [b], Harold G. Monbouquette [a,*]

[a] Chemical and Biomolecular Engineering Department, UCLA, Los Angeles, CA, USA
[b] Department of Psychiatry & Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, UCLA, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 13 August 2012
Received in revised form
17 October 2012
Accepted 17 October 2012
Available online 6 November 2012

Keywords:
Iridium oxide
Reference electrode
Glutamate sensor
Micro-electrode array
Amperometric sensor
Enzymatic sensor

ABSTRACT

An implantable micromachined multi-electrode array (MEA) microprobe modified for utilization as a complete electrochemical biosensor for rapid glutamate detection is described. A post-fabrication method for electrochemical deposition of an iridium oxide (IrOx) film onto a designated microelectrode enabled incorporation of an IrOx reference electrode (RE) on the microprobe. The on-probe IrOx RE provides an alternative to the commonly utilized Ag/AgCl wire RE, which has been shown to be unstable and to cause an inflammatory response in living tissue. The IrOx film electrodeposited onto a platinum site was tested as part of a complete chemical sensing system that included a platinum counter electrode and enzymatic glutamate sensing electrodes all on a single silicon-based MEA platform. The thin film IrOx was mechanically robust enough to endure conditions of repeated heating and wetting during the MEA fabrication process. The pH dependence of the IrOx open circuit potential (OCP) was measured at -77 ± 0.4 mV/pH and remained stable over a two-week period. The on-probe IrOx RE was tested in a two- and three-electrode system with glutamate biosensors. The biosensors were shown to detect a physiologically relevant range of glutamate concentrations and to reject the interferents, dopamine and ascorbic acid. By incorporating all of the electrodes onto a single device, baseline noise was reduced by an average of ~61% *in vitro* and ~71% *in vivo* with reduced tissue damage, since only a single probe needed to be implanted.

1. Introduction

Miniaturization, which can be accomplished by employing micromachining techniques developed for the integrated circuits industry, has been the focus of recent progress on the development of neural biosensors (Varney et al., 2011; Frey et al., 2011; Johnson et al., 2008; Kim et al., 2004; Lowinsohn et al., 2006; Motta and Judy, 2005; Rospert et al., 1997; Yoon et al., 2000). Smaller electrodes provide improved spatial and temporal resolution as well as reduced tissue damage. The reference electrode (RE) is an important component of an electrochemical system; however, it usually is not integrated into the same micromachined probe with the biosensing electrode. Currently, most biosensors used for *in vivo* studies rely on a separate RE, usually a Ag/AgCl wire (Hu et al., 1994; Lee et al., 2007; Thomas et al., 2009; Walker et al., 2007; Wassum et al., 2012). Yet, there are key advantages to combining both the working and REs of an electrochemical biosensing system onto a single microprobe in a multi-electrode array (MEA) format. Such an integrated MEA biosensor for *in vivo* application simplifies surgery and reduces tissue damage, as only a single foreign body has to be implanted in the brain (Karp et al., 2008). Use of an on-probe RE also is expected to result in reduced noise arising from external sources (*e.g.*, 60 Hz noise) and from within the brain, which can lead to improved detection limits (Clark et al., 2009; Peteu et al., 1996). Clearly, these are compelling reasons to combine the reference and working electrodes on a MEA microprobe for *in vivo* sensing applications.

Although separate wire Ag/AgCl REs are used commonly in electroanalytical applications as mentioned above, incorporation of a miniature Ag/AgCl RE onto microprobes has been achieved through techniques such as electrochemical wet processing or plasma deposition (Park et al., 2003; Suzuki et al., 1998). However, these techniques are less than optimal due either to the cumbersome nature of the method and/or instability of the deposited film. AgCl film instability through delamination or dissolution of the chloride salt (Franklin et al., 2005; Yang et al., 2003) makes these REs non-ideal for long-term *in vivo* studies,

* Corresponding author. Tel.: +1 310 825 8946; fax: +1 310 206 4107.
E-mail address: hmonbouq@ucla.edu (H.G. Monbouquette).

0956-5663/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bios.2012.10.061

as AgCl film loss causes a drift in electrode potential resulting in inaccurate signal readings (Yang et al., 2003). In addition to the compromised signal, the dissolved film is toxic and causes significant inflammatory responses (Dymond et al., 1970; Tivol et al., 1987; Yuen et al., 1987). Successful implementation of an implantable RE in a MEA format requires several criteria to be met: (1) the RE fabrication method must be compatible with the MEA platform; (2) the RE must exhibit sufficient chemical and mechanical stability; (3) the RE must provide a stable reference potential over the applicable range of conditions associated with its intended use; and (4) the chosen RE should be biocompatible.

Many of the negative issues encountered with Ag/AgCl REs can be avoided by using iridium oxide (IrOx) as the reference electrode material, and in fact, IrOx has unique properties that make it attractive for *in vivo* neuroscience applications. Recent studies have addressed use of IrOx as a pH sensor, an electrode for electrophysiological recording and stimulation, and as a quasi-RE (Ges et al., 2008; Johnson et al., 2008; Karp et al., 2008; Li et al., 2007; Meyer et al., 2001; VanHoudt and Lewandowski, 1992; Wipf et al., 2000; Yang et al., 2004). Although the IrOx potential shows strong pH dependence, the small dynamic range of normal brain pH (7.15–7.4) makes this issue unimportant in most cases (Franklin et al., 2005). More importantly, IrOx is stable over a range of potentials and in the presence of the ions and other components of brain extracellular fluid (Marzouk et al., 1998). Finally, IrOx films exhibit excellent mechanical stability and biocompatibility, both of which allow for long-term implantation with minimal damage to living tissue (Slavcheva et al., 2004; Weiland and Anderson, 2000).

IrOx films can be fabricated by several different methods. Some of the most popular protocols entail electrochemical activation of either a bulk Ir metal electrode or an Ir film sputtered onto an appropriate substrate (Glab et al., 1989; Katsube et al., 1982; Kreider et al., 1995; Slavcheva et al., 2004). However, incorporation of an IrOx reference site on a MEA microprobe by these methods would require major changes to our current MEA probe microfabrication process requiring costly materials and additional processing steps. A simple and cost-effective method for IrOx film deposition would be desirable for the development of a practical on-probe RE.

In this paper, we describe IrOx deposition on specified platinum (Pt) microelectrodes of an MEA by a simple one-step electrochemical method (Yamanaka, 1989) to give fully functional REs. We investigated IrOx film robustness during the microprobe manufacturing process, temporal stability in solution, reproducibility, as well as working electrode noise when an on-probe IrOx RE is used as opposed to a separate Ag/AgCl reference. Finally, in an effort to demonstrate practical utility, we conducted preliminary testing of an integrated working and RE microprobe for glutamate biosensing both *in vitro* and *in vivo*. Glutamate is the primary excitatory neurotransmitter in the brain and has been linked to many neurological disorders and diseases, including autism, schizophrenia, Huntington's and Parkinson's disease (Carlsson and Carlsson, 1990; Cha et al., 1998; Purcell et al., 2001) and therefore constitutes a relevant test case for this study.

2. Materials and methods

2.1. Reagents and equipment

Nafion (5 wt% solution in lower aliphatic alcohols/H_2O mix), bovine serum albumin (BSA, min 96%), glutaraldehyde (25% in water), pyrrole (98%), L-glutamic acid, L-ascorbic acid, 3-hydroxytyramine (dopamine, DA), iridium tetrachloride hydrate, oxalic acid dehydrate (99%), hydrogen peroxide (30 wt% solution in water) and anhydrous potassium carbonate were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). L-Glutamate oxidase (GlutOx) from *Streptomyces* sp. X119-6, with a rated activity of 24.9 units per mg protein (U mg^{-1}, Lowry's method), produced by Yamasa Corporation (Chiba, Japan), was purchased from Associates of Cape Cod, Inc. (Seikagaku America, MA, USA). Phosphate buffered saline (PBS) was composed of 50 mM Na_2HPO_4 with 100 mM NaCl (pH 7.2). Ultrapure water generated using a Millipore Milli-Q Water System was used for preparation of all solutions used in this work.

Electrochemical preparations, open circuit potential (OCP) and calibration measurements were performed using a Versatile Multichannel Potentiostat equipped with the 'p' low current option and low current N′ stat box (VMP3, Bio-Logic USA LLC, Knoxville, TN, USA) or a multichannel FAST-16 potentiostat (Quanteon, LLC, Lexington, KY, USA). Flow cell experiments were conducted with the FAST-16 system. A standard three-electrode system was used with the VMP3 system, consisting of either an on-probe Pt site or a separate Pt-wire as a counter electrode, modified sites on our MEA as the working electrodes, and as RE, either an on-probe IrOx site, a separate Ag/AgCl electrode (Bioanalytical Systems, Inc., West Lafayette, IN, USA), or a AgCl-coated Ag wire, as specified. All measurements *in vivo* were conducted with the FAST-16 system in two electrode mode (no separate counter electrode).

2.2. Device fabrication and polymer modification

The microelectrodes used in this work were silicon-based multielectrode arrays manufactured at UCLA using micro-electro-mechanical-system (MEMS) technologies. The fabrication and array details are described in previous work (Wassum et al., 2008). The MEA consists of four ~4000 μm^2 Pt sites, situated in pairs at the tip of a 9 mm shank. The pair nearest the shank tip is 100 μm from the pair farthest from the shank tip, and the paired sites are 40 μm apart. Each site was modified accordingly, to act either as a working, reference, or counter electrode.

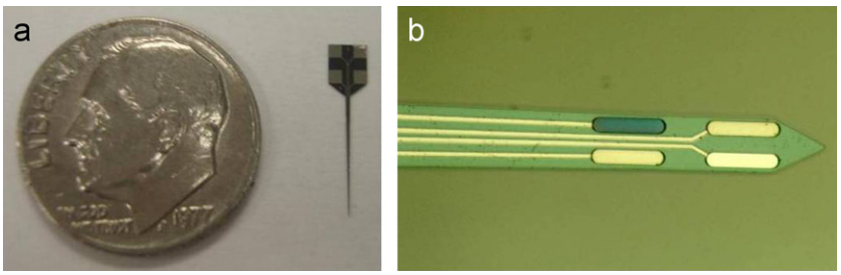

Fig. 1. (a) A released MEA with 9 mm shank. (b) Four platinum electrode sites at the tip of a MEA, each ~4000 μm^2 in area. The dark site on the upper left-hand side has been modified with electrodeposited IrOx. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

IrOx was electrodeposited following the method described by Yamanaka (Yamanaka, 1989). Briefly, an aqueous solution of 4.5 mM iridium tetrachloride was stirred for 30 min followed by the addition of 500 mL of hydrogen peroxide and stirring for 10 min. Oxalic acid dihydrate was then added to reach a concentration of 55.5 mM and stirred for another 10 min. Potassium carbonate was added in small aliquots until the solution reached a pH of 10.5. The resulting solution was allowed to sit without stirring for at least 48 h before electrodeposition. IrOx was deposited anodically on an electrode site by cycling between 0.0 V and 0.6 V *versus* Ag/AgCl at a scan rate of 50 mV s^{-1} for 100 cycles resulting in a total charge transfer of $\sim$1 C/cm^2. Fig. 1a shows a photograph of a single four-electrode MEA with a 9 mm shank. Fig. 1b is a photomicrograph of the tip of an MEA where the four platinum sites are located. The darkened blue site on the upper left-hand side is a platinum site that has been coated with an electrodeposited IrOx film.

The glutamate sensing microelectrodes were created according to our previously developed procedure (Wassum et al., 2008). Polypyrrole (PPy) was electrodeposited from a 200 mM Ar-purged solution of pyrrole in PBS (pH 7.2) by holding the voltage constant at 0.85 V for 5 min. The anionic polymer, Nafion, was deposited on all sites by rapid dip-coating of the probe tips in the Nafion solution and oven-casting at 180 °C for 4 min, followed by a 4-min cooling period in ambient air. This process was repeated twice. Nafion forms a permselective film useful for blocking negatively charged species such as ascorbate from the electrode surface. After the polymer treatments, enzyme immobilization by chemical crosslinking was accomplished using a solution consisting of GlutOx (2 wt%), BSA (2 wt%) and glutaraldehyde (0.125%). A $\sim$0.1 μL drop of the solution was formed on a syringe tip and the drop was gently swiped across the bottom two microelectrode sites at the probe tip. This procedure was repeated four times with each application consisting of three swipes. The resultant working electrodes (WEs) were used to sense glutamate by electroenzymatic amperometry where the immobilized GlutOx catalyzes the oxidation of glutamate to α-ketoglutarate with generation of the electroactive byproduct, hydrogen peroxide. Hydrogen peroxide then diffuses through the polymer barriers to the Pt electrode surface where it is oxidized, thereby giving rise to the output current signal. Microelectrode sites coated with PPy, Nafion and GlutOx are referred to here as glutamate biosensors. The biosensors were sealed in a container with desiccant and stored dry at 4 °C for 48 h prior to testing. Fig. 2 illustrates three platinum electrodes on a single silicon microprobe, each modified with the appropriate polymer and/or enzyme coating to give the WE, RE and counter electrode (CE).

2.3. Iridium oxide RE testing and characterization

To test the potential stability of the IrOx film under varying pH conditions, the open circuit potentials (OCPs) of IrOx films were recorded while the PBS pH was incrementally increased from pH 6 to 12 with addition of dilute NaOH solution. OCP measurements were made of the same IrOx films and recorded in this manner over several days, up to two weeks.

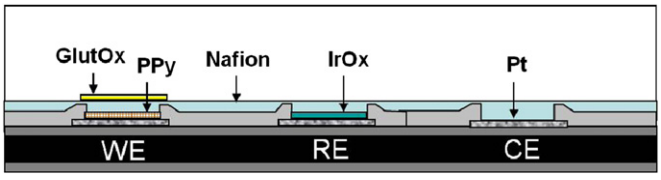

Fig. 2. Representative cross-section of a multielectrode device (not to scale) for glutamate biosensing showing the Pt microelectrode modifications undertaken to give the WE, RE, and CE sites.

The robustness of the IrOx film was challenged during the glutamate biosensor fabrication process. For each probe, IrOx was first deposited on the designated RE site. Pyrrole was then polymerized on the working electrodes and Nafion was deposited over all four sites and oven-casted. By fabricating in this order, the IrOx film was subjected to immersion in a wet environment during pyrrole deposition, as well as relatively high temperature dry conditions during Nafion oven-casting (180 °C). GlutOx was then manually deposited on the sites (bottom pair) designated as glutamate sensors to complete biosensor fabrication.

The on-probe IrOx RE was tested *in vitro* and *in vivo* as a reference for adjacent glutamate sensing sites using constant potential amperometry with the FAST-16 electrochemistry system. For tests *in vitro*, a constant potential of 0.6 V was applied to the working electrodes against the IrOx RE in 40 mL of stirred, PBS at pH 7.4 in a beaker housed within a Faraday cage. After the current detected at the electrodes equilibrated to a constant current value (approx. 30 min during which time the PPy film was overoxidized), three successive 40 μL aliquots of glutamate stock solution (20 mM) were added to the beaker to reach final glutamate concentrations of 20, 40, and 60 μM glutamate. Additionally, aliquots of the potential interferents, AA (250 μM final concentration) and DA (5–10 μM final concentration), were added to assess selectivity for glutamate. For calibration tests, successive aliquots of glutamate stock solution were added over time to give step concentrations of glutamate ranging from 5 μM to 300 μM.

For tests *in vivo*, female Sprague Dawley rats (250–300 mg) were anesthetized with isoflorene and placed in a standard stereotaxic frame for surgery. The MEA was unilaterally implanted in the striatum (anterior–posterior +0.7 mm, medial–lateral +2.4 mm, dorsal–ventral 7.0 mm, according to the atlas of Paxinos and Watson, 4th edition). A 200 μM-diameter Ag/AgCl wire reference electrode implanted contralaterally or an on-probe IrOx reference elcectrode was used. Animals remained under anesthesia during experiments and were subjected to an overdose of isoflorene for euthanization at the conclusion of the study. All experimental procedures were approved by the Institutional Animal Care and Use Committee at UCLA and conducted in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

3. Results and discussion

3.1. Iridium oxide film stability

An important characteristic of a RE for applications *in vivo*, is its ability to maintain a stable potential over time under physiological conditions. In this study, the IrOx RE was subjected to a broad pH range, beyond the physiological, over a period of two weeks. The IrOx film OCP was measured against a separate Ag/AgCl reference while immersed in PBS. The PBS was titrated with NaOH to vary the pH from 6 through 12 while the OCP was recorded. The OCP response to pH was estimated at −77.5 mV/pH (std. error ± 0.4, R^2 = 0.9995) over the examined pH range. This pH dependence of OCP is consistent with previously published data for an electrochemically deposited IrOx film (Yang et al., 2004). Depending on the method by which IrOx is deposited, the pH dependence of the IrOx OCP can range from $\sim$ −59 mV–90 mV/pH (VanHoudt and Lewandowski, 1992; Wipf et al., 2000). Given the narrow normal range of brain pH, 7.15–7.4 (Franklin et al., 2005), the OCP of an electrochemically deposited IrOx RE would be expected to vary less than 20 mV. This is a relatively small potential range compared to the applied potential of 600 mV for

rapid H_2O_2 electrooxidation (Hall et al., 1998). Thus, the pH sensitivity of the IrOx RE should have little or no measurable impact on the response of the adjacent glutamate sensing microelectrodes. The OCP responses of the IrOx films to varying pH were tested for two weeks. After this time period, visual inspection under a microscope showed no obvious signs of film delamination or other form of degradation, indicating strong adhesion of the IrOx film. Moreover, the OCP response of the IrOx film to varying pH remained at an average of -75 mV/pH with random variation of ± 5 mV/pH over the two-week period, suggesting very little potential drift.

3.2. Glutamate sensing in vitro and in vivo using an on-probe IrOx RE

The IrOx-coated microelectrode was tested as an on-probe RE to glutamate biosensing microelectrodes in both two-electrode and three-electrode configurations. A potential of 0.6 V was applied to the biosensors *versus* the on-probe IrOx RE (corresponding to ~0.7 V *versus* Ag/AgCl), with a separate Pt wire as the counter electrode. With this setup, the glutamate biosensors were able to detect varying concentrations of glutamate from 5 μM to 300 μM. Fig. 3 shows the current response of a representative glutamate biosensor to increasing analyte concentrations *in vitro*. This biosensor had a detection limit of 0.32 μM and sensitivity of 7.3 ± 0.4 pA/μM ($R^2 = 0.98$) over a glutamate concentration range of 5–300 μM, which is equivalent to or better than we have achieved with a separate Ag/AgCl RE wire (Wassum et al., 2008) or a commercial Ag/AgCl RE (sensitivity $= 7.7 \pm 0.4$ pA/uM).

The amperometric current generated by glutamate microbiosensors *in vivo* are often in the pico- to nano-amp range. Such low currents can allow for the use of a two-electrode electrochemical system, where the RE acts as the counter electrode as well, instead of the more conventional three-electrode system. A two-electrode system test was performed using the IrOx site as the RE/CE and a glutamate biosensor as the working electrode on the same microprobe. The glutamate biosensor amperometric response to increasing concentrations of glutamate from 5 μm to 250 μM was recorded. Results showed that at concentrations in the physiological range, <10–100 μM (Castillo et al., 1997; Davalos et al., 2000; Ince et al., 1997; Lada and Kennedy, 1996; Miele et al., 1996), the current response is stable, however at higher glutamate concentrations above 200 μM, the additional current through the RE adversely affects sensitivity and the current signal stability was lost (Fig. 4). This signal loss at higher glutamate concentrations was reflected in a calibration curve showing a nonlinear, unstable response at higher concentrations. Nevertheless, the on-probe IrOx RE sensitivity to glutamate concentrations over a range of 5–100 μM is 7.4 ± 0.3 pA/uM,

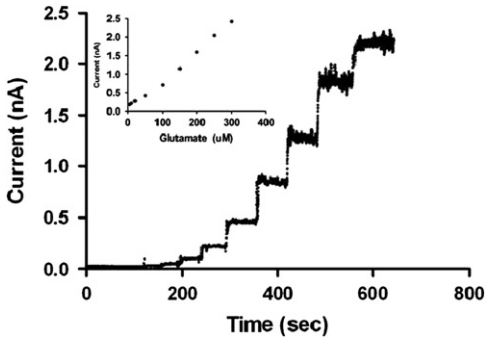

Fig. 3. Glutamate sensing using on-probe reference electrode and a separate Pt wire as the counter electrode. The biosensor can detect glutamate over a range of 5–300 μM with a sensitivity of ~7.3 pA/μM.

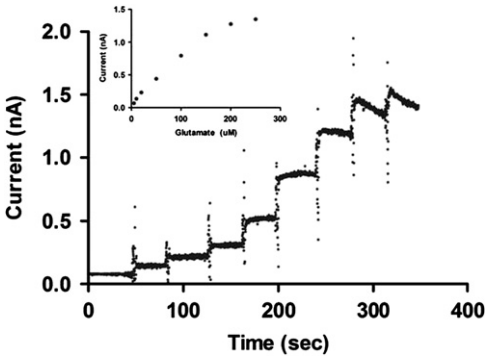

Fig. 4. Glutamate sensing using on-probe IrOx film as the reference electrode and as the counter electrode. The IrOx film does not act as a stable reference electrode at higher concentration ranges.

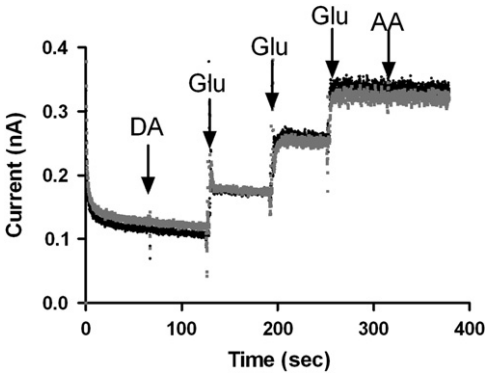

Fig. 5. Testing *in vitro* of a complete three-electrode electrochemical system fabricated on a single MEA showed the glutamate biosensors responding amperometrically to 20 μM glutamate injections (black and gray traces), while rejecting the interferents, 5 μM DA and 250 μM AA.

comparable to glutamate sensitivity when used in a three-electrode system over a 5–300 μM concentration range.

In an effort to provide a complete electrochemical cell on a single probe, we tested the IrOx electrode's performance when a complete three-electrode system was fabricated on a single MEA. Tests *in vitro* were performed using an MEA with one site as the IrOx RE, two sites as glutamate biosensors, and the remaining site as the Pt counter electrode (a bare Pt site coated with Nafion only). Using a three-electrode system on a single probe, the current response was stable even at higher concentrations and the sensitivities of the electrodes match those of the glutamate biosensors shown earlier when the on-probe IrOx was used as the RE and a separate Pt wire was used as the counter electrode.

In addition to detecting changes in physiological concentrations of glutamate, these biosensors must also be selective against common electroactive species in brain extracellular fluid, of which AA and DA are most important. Fig. 5 shows data illustrating the successful rejection of interferents and rapid detection of glutamate *in vitro* with a response time of ~1 s while using on-probe reference and counter electrodes. These results demonstrate that a single implantable MEA platform can house the counter, reference, and working electrodes and work as a practical, selective glutamate sensor capable of rejecting interferents and detecting glutamate.

3.3. Working electrode noise comparison for Ag/AgCl and IrOx REs

By placing the RE on the same platform as the working electrode, noise is expected to be reduced as discussed earlier. Signal noise can vary from one working electrode to another, therefore it is important to compare REs using the same working

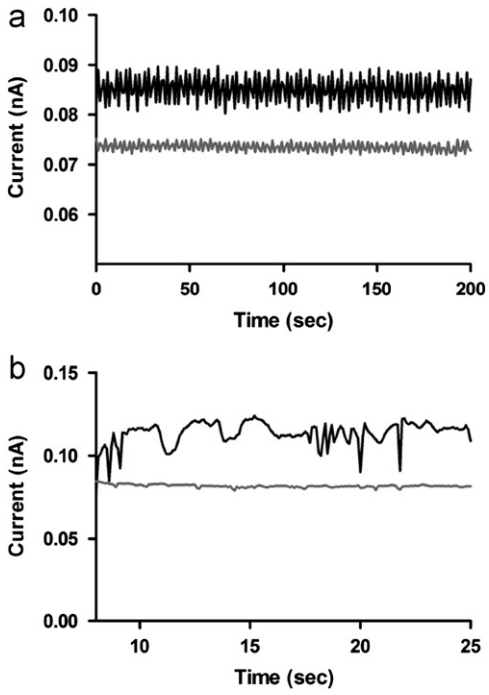

Fig. 6. Baseline signal (recorded prior to glutamate injection *in vitro* or glutamate release *in vivo*) at a glutamate-sensing microelectrode using an on-probe IrOx RE (—) *versus* baseline signal at the same working electrode using a separate Ag/AgCl wire RE (—): (a) conducted *in vitro* showing a 67% reduction in noise when using the on-probe IrOx RE and (b) conducted *in vivo* showing an 85% reduction in noise.

electrode when evaluating noise in relation to REs. Baseline RMS noise at the working electrode was found to be diminished by $61 \pm 8\%$ (95% confidence interval, $n=23$) when using the on-probe IrOx RE (0.6 V working electrode potential) compared to the same working electrode against a separate Ag/AgCl RE (0.7 V working electrode potential). Fig. 6a shows representative data illustrative of a 67 rms% noise reduction at the baseline.

A noise comparison at the working electrode using a separate Ag/AgCl reference *versus* using an on-probe IrOx RE was conducted *in vivo*. A MEA with IrOx deposited on one site and glutamate biosensors on the other sites was implanted in the striatum of an anesthetized rat. A 200 μm-diameter Ag wire coated with AgCl was used as the RE while the signal was allowed to baseline prior to inducing glutamate release. Using the same biosensor while still implanted in the striatum of the same rat, the on-probe IrOx was used as the RE and allowed to baseline. Fig. 6b shows a noise reduction of 85% from one of the biosensors. In this case, the limit of detection is reduced from 0.85 μM using the Ag/AgCl wire to 0.19 μM using the on-probe IrOx. The average RMS noise reduced on the three biosensors on the MEA was 71%. This noise reduction could have significant impact on sensing electrode detection limit through the improved signal-to-noise ratio, especially in freely-moving rodent studies where noise is increased due to animal movement.

4. Conclusions

A stable and reproducible IrOx film on a Pt microelectrode can be used as an on-probe RE for amperometric sensing systems. The electrochemical method employed for IrOx film deposition permits straightforward deposition onto selected micron-size electrodes in a MEA format. The IrOx film is stable during the heating, wetting and drying steps used to deposit polymer films and enzyme on the biosensing (*i.e.*, working electrode) sites of the MEA probe. Inclusion of the RE on the same microprobe as the working electrodes reduces background noise levels significantly thereby improving detection limits and overall signal resolution, which is important for sensing *in vivo*. Our MEA platform can accommodate on a single probe either conventional three electrode (reference, counter, and working electrodes) or two electrode (reference and working electrodes) systems.

Acknowledgments

This work was supported by JPL/NASA Contract no. 1250587 and by a Hatos Research Center Scholarship to V. Tolosa.

References

Carlsson, M., Carlsson, A., 1990. Schizophrenia Bulletin 18 (3), 425–432.
Castillo, J., Davalos, A., et al., 1997. Cerebrovascular Disease 7, 245–250.
Cha, J.J., Kosinski, C.M., et al., 1998. Proceedings of the National Academy of Sciences 95 (11), 6480–6485.
Clark, G.A., Warren, D.J., Ledbetter, N.M., Lloyd, M., Normann, R.A., 2009. US Patent 2009/0283425 A1.
Davalos, A., Shuaib, A., et al., 2000. Journal of Stroke Cerebrovascular Disease 9 (6 Pt. 2), 2–8.
Dymond, A.M., Kaechele, L.E., et al., 1970. Journal of Neurosurgery 33, 574–580.
Franklin, R., Johnson, M.D., et al., 2005. IEEE Sensors Journal, 1400–1403.
Frey, O., Rothe, J., et al., 2011. In: Proceedings of the 16th International Solid-State Sensors, Actuators and Microsystems Conference (Transducers), June 5–9. pp. 1829–1832.
Ges, I.A., Dzhura, I.A., et al., 2008. Biomedical Microdevices 10, 347–354.
Glab, S., Hulanicki, A., et al., 1989. Critical Reviews in Analytical Chemistry 21 (1), 1989.
Hall, S.B., Khudaish, E.A., et al., 1998. Electrochimica Acta 43 (14–15), 2015–2024.
Hu, Y., Mitchell, K.M., et al., 1994. Brain Research 659, 117–125.
Ince, E., Karagol, U., et al., 1997. Acta Paediatrica 86 (12), 1333–1336.
Johnson, M.D., Franklin, R.K., et al., 2008. Journal of Neuroscience Methods 174, 62–70.
Karp, F.B., Bernotski, N.A., et al., 2008. IEEE Sensors Journal 8 (1), 104–112.
Katsube, T., Lauks, I., et al., 1982. Sensors and Actuators 2 (4), 399.
Kim, S.K., Hesketh, P.J., et al., 2004. Biosensors and Bioelectronics 20 (4), 887–894.
Kreider, K.G., Tarlov, M.J., et al., 1995. Sensors and Actuators B 28, 167–172.
Lada, M.W., Kennedy, R.T., 1996. Analytical Chemistry 68 (17), 2790–2797.
Lee, K.H., Katarina, K., et al., 2007. Brain Research 1162, 121–129.
Li, J., Du, Y., et al., 2007. Electroanalysis 19 (5), 608–611.
Lowinsohn, D., Peres, H.E.M., et al., 2006. Sensors and Actuators B 113, 80–87.
Marzouk, S.A.M., Ufer, S., et al., 1998. Analytical Chemistry 70, 5054–5061.
Meyer, R., et al., 2001. IEEE Transactions and Neural Systems and Rehabilitation Engineering 9, 1.
Miele, M., Boutelle, M.G., et al., 1996. Journal of Physiology 497 (Pt. 3), 745–751.
Motta, P.S., Judy, J.W., 2005. IEEE Transactions on Biomedical Engineering 52 (5), 923–933.
Park, S., Jun, S.B., et al., 2003. IEEE Sensors Journal 3 (3), 267–273.
Peteu, S.F., Emerson, D., Worden, R.M., 1996. Biosensors and Bioelectronics 11 (10), 1059–1071.
Purcell, A.E., Jeon, O.H., et al., 2001. Neurology 57 (9), 1618–1628.
Rospert, M., Mokwa, W., et al., 1997. Sensors and Actuators B 43 (1), 87–93.
Slavcheva, E., Vitusshinsky, R., et al., 2004. Journal of The Electrochemical Society 151 (7), E226.
Suzuki, H., Hirakawa, T., et al., 1998. Sensors and Actuators B 46 (2), 146–154.
Thomas, T.C., Grandy, D.K., et al., 2009. Neuropsychopharmacology 34, 436–445.
Tivol, W.F., Agnew, W.F., et al., 1987. Journal of Neuroscience Methods 19 (4), 323–337.
Varney, M.W., Aslam, D.M., et al., 2011. Biosensors 1, 118–133.
VanHoudt, P., Lewandowski, Z., 1992. Biotechnology and Bioengineering 40, 601–608.
Walker, E., Wang, J., et al., 2007. The Analyst 132, 1107–1111.
Wassum, K.M., Tolosa, V.M., et al., 2012. Journal of Neuroscience 32 (8), 2747–2761.
Wassum, K.M., Tolosa, V.M., et al., 2008. Sensors 8, 5023–5036.
Weiland, J.D., Anderson, D.J., 2000. IEEE Transactions on Biomedical Engineering 47 (7), 911–918.
Wipf, D.O., Ge, F., et al., 2000. Analytical Chemistry 72, 4921–4927.
Yamanaka, K., et al., 1989. Japanese Journal of Applied Physics 28 (4), 632–637.
Yang, H., Kang, S.K., Shin, D.-H., Kim, H., Kim, Y.T., 2003. In: the Proceedings of the 12th International Conference on Solid State Sensors, Actuators and Microsystems, Boston, June 8–12. pp. 103–106.
Yang, H., Kang, S.K., et al., 2004. Lab Chip 4, 42–46.
Yoon, T.H., Hwang, E.J., et al., 2000. IEEE Transactions on Biomedical Engineering 47 (8), 1082–1087.
Yuen, T.G.H., Agnew, W.F., et al., 1987. Biomaterials 8, 138–141.