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Design and characterization of a microfabricated hydrogen clearance blood flow sensor

Lindsay R. Walton[a], Martin A. Edwards[a,1], Gregory S. McCarty[b], R. Mark Wightman[a,c,*]

[a] Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[b] Department of Chemistry, North Carolina State University, Raleigh, NC, USA
[c] Neuroscience Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

HIGHLIGHTS

- An electrolytic hydrogen clearance sensor is microfabricated and characterized.
- Micron-scale dimensions enhance the technique's temporal and spatial resolution.
- Computational modeling anticipates deviations from ideal sensor performance.
- Sensors are sensitive to physiologically expected cerebral blood flow rates.
- Low-noise systems improve accuracy and electrode cycling ensures reproducibility.

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ABSTRACT

Background: Modern cerebral blood flow (CBF) detection favors the use of either optical technologies that are limited to cortical brain regions, or expensive magnetic resonance. Decades ago, inhalation gas clearance was the choice method of quantifying CBF, but this suffered from poor temporal resolution. Electrolytic H_2 clearance (EHC) generates and collects gas in situ at an electrode pair, which improves temporal resolution, but the probe size has prohibited meaningful subcortical use.
New method: We microfabricated EHC electrodes to an order of magnitude smaller than those existing, on the scale of 100 μm, to permit use deep within the brain.
Results: Novel EHC probes were fabricated. The devices offered exceptional signal-to-noise, achieved high collection efficiencies (40–50%) in vitro, and agreed with theoretical modeling. An in vitro chemical reaction model was used to confirm that our devices detected flow rates higher than those expected physiologically. Computational modeling that incorporated realistic noise levels demonstrated devices would be sensitive to physiological CBF rates.
Comparison with existing method: The reduced size of our arrays makes them suitable for subcortical EHC measurements, as opposed to the larger, existing EHC electrodes that would cause substantial tissue damage. Our array can collect multiple CBF measurements per minute, and can thus resolve physiological changes occurring on a shorter timescale than existing gas clearance measurements.
Conclusion: We present and characterize microfabricated EHC electrodes and an accompanying theoretical model to interpret acquired data. Microfabrication allows for the high-throughput production of reproducible devices that are capable of monitoring deep brain CBF with sub-minute resolution.
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1. Introduction

Cerebral blood flow (CBF) increases in activated brain regions to deliver energy in the forms of glucose and O_2—a phenomenon known as functional hyperemia (Attwell et al., 2010; Haydon and Carmignoto, 2006; Iadecola, 2004). This increase also serves to maintain non-cytotoxic levels of metabolic products and conserve physiological pH following neuronal activity. Disease states such as ischemia can dysregulate hyperemia and generate or perpetuate brain damage, as neurons become both deprived of energy

* Corresponding author at: Department of Chemistry and Neuroscience Center, Campus Box 3290, Caudill and Kenan Laboratories, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.
E-mail addresses: waltonlr@email.unc.edu (L.R. Walton), martin.edwards@utah.edu (M.A. Edwards), gsmccart@ncsu.edu (G.S. McCarty), rmw@unc.edu (R.M. Wightman).
[1] Present address: Department of Chemistry, University of Utah, Salt Lake City, UT, USA.

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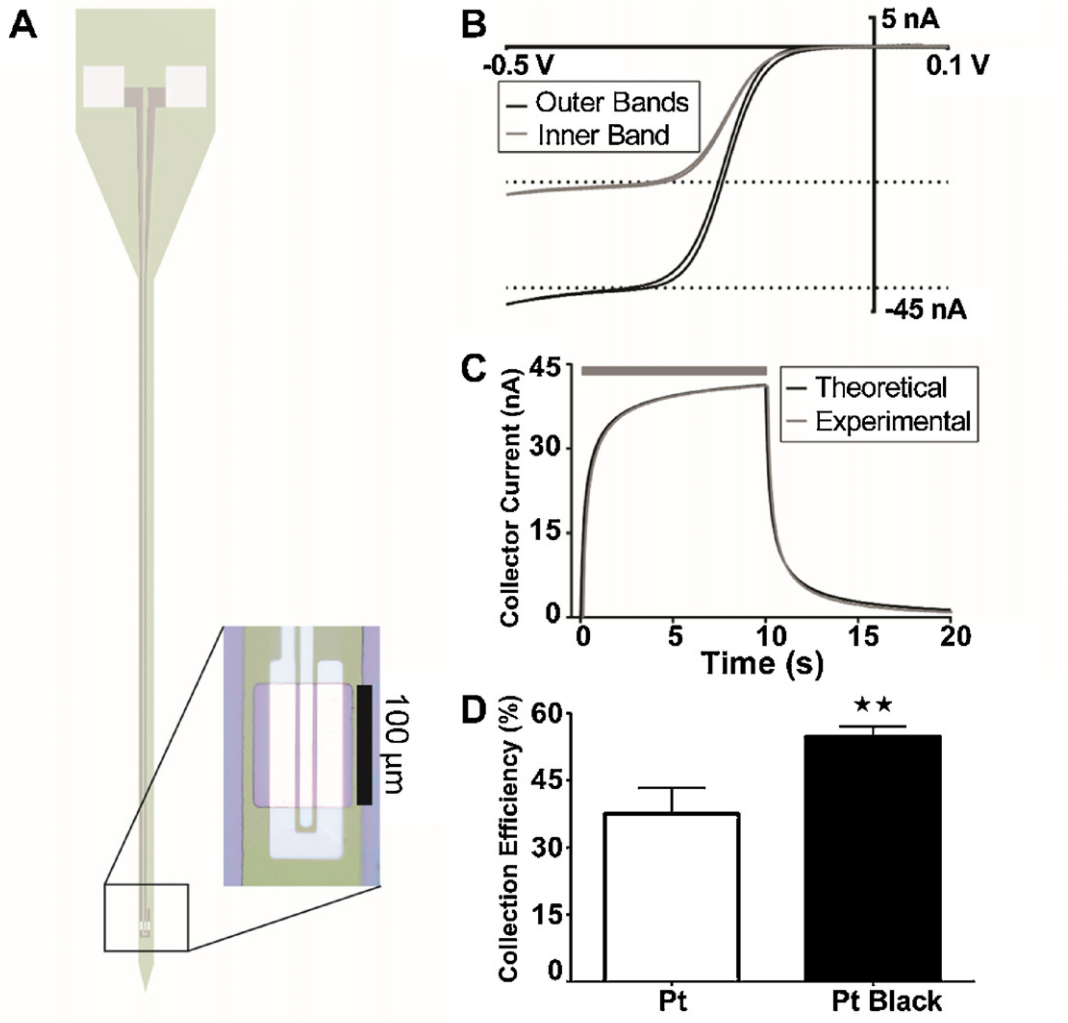

Fig. 1. Microfabricated platinum arrays are characterized by voltammetry and amperometry. (A) Model (to scale) of the full device shows two separately addressed, 100 μm long electrodes (inset: micrograph) selectively exposed at the tip. Inset color key: Purple is exposed silicon, green is silicon nitride, grey is insulated platinum beneath the nitride and white is bare platinum. (B) Cyclic voltammogram (5 mV s^{-1}) in degassed solution containing 2.5 mM RuHex and 0.1 M KCl. Theoretical steady state currents, indicated as dashed lines, were used to confirm active electrode surface areas. (C) Clearance curves obtained from generating RuHex(II) (35 mM) in the period indicated by the grey bar, and collecting RuHex(III). Outer electrodes used −100 nA pulses to reduce RuHex(III). The inner electrode, held at +0.25 V, detects RuHex(II) oxidation as faradaic current. Experimental RuHex clearance shows excellent agreement with simulations of the same system. (D) The collection efficiencies, taken at the plateau current, significantly increases when all electrodes are electroplated in platinum black (Student's *t*-test: $t_{(2,6)} = 4.804$, $P = 0.003$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

substrates and exposed to toxic levels of neurotransmitters and metabolic products (Haydon and Carmignoto, 2006; Iadecola, 2004; Hossmann, 1994). Beneath the cerebral cortex, densely packed capillaries fine-tune CBF activity to maintain homeostasis (Attwell et al., 2010; Iadecola, 2004). A broad literature exists studying cortical CBF (Harper and Glass, 1965; Dirnagl et al., 1989; Takano et al., 2006), but studying microvasculature control in the deep brain can provide new insight into pathologies hallmarked by CBF dysregulation, as well as flow activity in the behaving brain.

Numerous techniques have been used to measure CBF, including optical methods and tracer clearance approaches (Shih et al., 2012; Boas and Dunn, 2010; Ter-Pogossian et al., 1970; Prinzen, 2000; Kety, 1951). Laser Doppler flowmetry and laser speckle imaging are the most popular optical techniques, but the size of commercially available probes (500 μm or greater in diameter) risks extensive tissue damage to areas below the cortical surface (Dirnagl et al., 1989; Shih et al., 2012; Dunn et al., 2001). Clearance techniques, which rely on detecting the transport of an inert tracer to quantify flow, can measure CBF throughout the brain. However, these methods are costly (e.g., magnetic resonance imaging) and/or have a finite number of measurements per animal dictated by the number of unique labels available (e.g., fluorescent tags for microspheres) (Prinzen, 2000; Edvinsson and Krause, 2002). Sensitivity to motion artifacts further excludes the most commonly used techniques, optical and magnetic resonance imaging, from CBF measurements in behaving subjects. As an increasing number of common anesthetics (e.g., isofluorane) are known to have vasoactive effects (Ueki et al., 1992; Lindauer et al., 1993; Matta et al., 1999), development of a technique capable of exploring deep within the brain during conscious activity is highly desired.

Inert gases are attractive clearance tracers in biological subjects, as gas clearance can make an unlimited number of measurements per subject, detect CBF below the cortex, and perform in both anesthetized and freely-moving animals, all while quantifying CBF in ways that correlate highly with values obtained from competing techniques (Kety, 1951; Pell et al., 2003; Machens et al., 1995; DiResta et al., 1987; Aukland et al., 1964; Fellows and Boutelle, 1993; Lowry et al., 1997). The most affordable clearance gas is H_2, introduced through inhalation, injection of H_2-saturated saline, or electrolytic generation (Aukland et al., 1964; Stosseck et al.,

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