

Electrochemical Sensors and Biosensors for Biomedical and Clinical Applications

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Summary:

Electrochemical sensors offer many advantages for point-of-care and wearable sensors. Clinical and biomedical applications present unique challenges for sensors ranging from sensor fouling to signal interpretation. I shall provide an overview of the field drawing on my own research. Topics covered will include biofouling, sample selection, exhaled condensed breath, microneedles, signal processing and validation,

Keywords: Electroanalysis, wearables, point-of-care, biosensors, clinical applications.

Background

Point-of-care (PoC) and wearable devices[1] have demonstrable real world benefits for patients in the diagnosis of disease and in the management of chronic conditions. This is seen clearly in greatly improved outcomes in diabetes with PoC and in the vibrant and growing research into distributed healthcare [2], driven in part by healthcare needs of ageing populations [3].

There are significant scientific and engineering challenges associated with clinical measurement throughout the signal chain: selection of sampling site and medium, sensor fouling, selective molecular recognition, transduction, analogue front-end design, signal processing and unambiguous presentation of results to patients and their clinicians.

Sensor fouling arising from foreign body response causes, *inter alia* diffusional blocking, partitioning of analytes into adsorbed layers, deactivation of electrocatalytic sites, and compromised recognition chemistry performance. From the patient perspective adverse problems include inflammation and consequent analyte entrapment, blood vessel occlusion, pain, bleeding and risk of infection.

Minimally-invasive sampling

We have been investigating two minimally-invasive approaches to clinical measurement: Microneedle biosensors implanted into viable epidermis have been applied to β -lactam antibiotics

[4], [5] for closed-loop control of drug levels and to lactate concentrations [6],[7]. Lactate has applications in sepsis and septic shock, respiratory diseases and fitness monitoring.

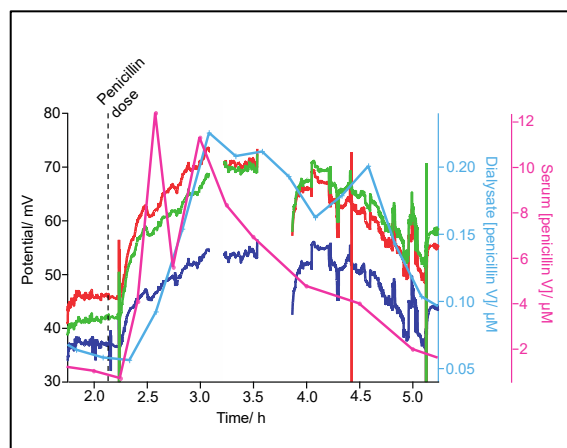
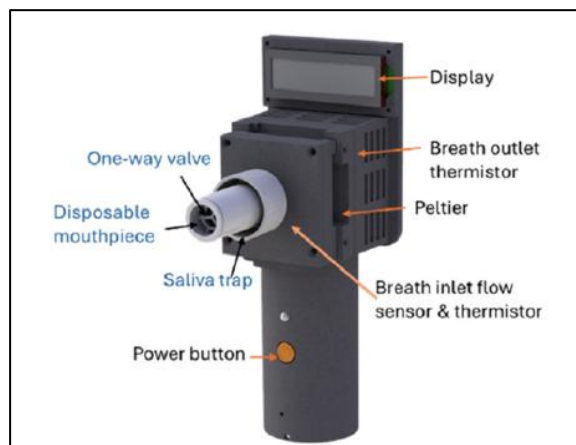


Fig.1. Microneedle determination of benzyl penicillin in a healthy volunteer. Red, green, dark blue traces are sensor data, Pink and pale blue traces are free drug concentrations from venous draws and microdialysis determined by LC-MS

Exhaled condensed breath (ECB) is a non-invasive analytical matrix and source of biomarkers. We have developed a novel portable device for the collection of ECB that enables correction for natural breathing patterns and optimization with respect to target analyte concentration [8]. We have applied this to lactate measurements in humans [9] and undertaken a preliminary clinical

evaluation in healthy volunteers and COPD patients [10]

a)



b)

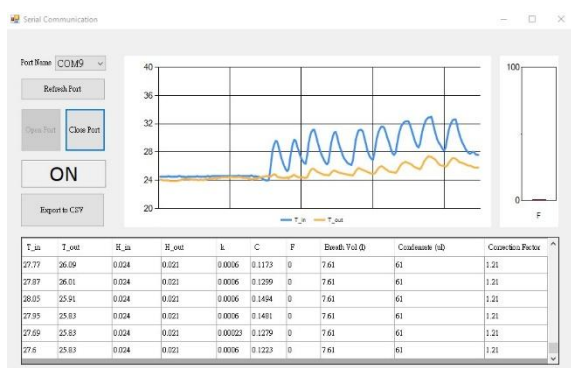


Fig 2 (a) The EBC collector and (b) typical data enabling on-the-fly correction for flow velocities and temperature

Electrodes and scaleability

Biosensor fouling and foreign body responses are inevitable. There is no 'magic bullet' fix: consequences depend on timescale, target analyte and application, and fixes are typically bespoke. We have shown that electrode materials such as boron-doped diamond are generally less affected [11], [12] but this comes at considerable costs of manufacturing that are incompatible with single use PoC devices.

Signal processing strategies can usefully be employed to improve selectivity. We have shown

that the Hilbert transforms of electrode responses to frequency-modulated voltages improve selectivity and monitor changes in double-layer capacitance, an important marker of sensor fouling [13]

Scaleable manufacture is frequently considered too late in biosensor design, yet is essential for any clinical study as well as potential commercial exploitation. Collaboration with Respire Diagnostics Ltd has led to low cost (< €1 ea.) disposable glassy carbon electrodes which are sufficiently reproducible to be single use, need no pre-calibration and have applied them to biomarker measurement (xanthine oxidase) and therapeutic drug monitoring. Preliminary data of of nitrofurantoin, a first-line antibiotic used in urinary tract infections are shown in Figure 3.

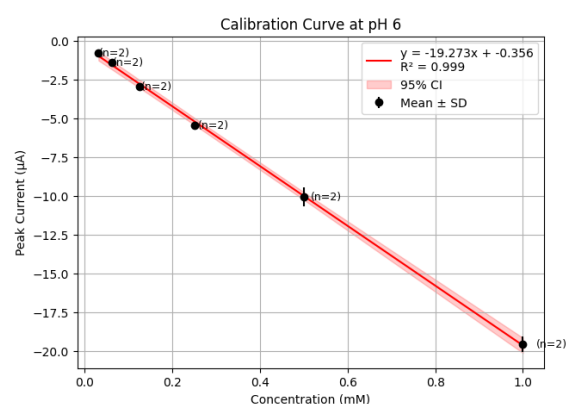


Fig. 3 Disposable GC sensor DPV calibration for nitrofurantoin in spiked artificial urine. Each concentration used two separate sensors. The pink shading is the 95% confidence limit of the fit.

Endotracheal activities

Minimally invasive sensing for cortisol and other adrenal hormones. The first task will be development of the electrochemical aptasensor. We have a new approach using three-dimensional conducting polymer-hydrogel electrodes to stabilise local environment and minimise the impact of aptamer losses. We hope to apply this strategy to minimally-invasive EBS and microneedle samples following validation in plasma and venous draws.

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