Characterisation of the electrochemical behavior of gastrointestinal fluids using a multi-electrode sensor probe.

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Abstract— A characterization of gastrointestinal fluids has been performed by means of an electrochemical sensor which has potential for clinical *in vivo* and *in vitro* monitoring applications. The sensor comprised a three-electrode cell with a counter, reference and four working electrodes, Au, Pt, Ir and Rh. Cyclic voltammetry was used to obtain chemical information from faecal water (*in vitro*) and gut model (*in vivo*) fluids. Stable voltammetric responses were obtained for both fluids at these noble metal working electrodes. The responses differed in shape which demonstrated the discrimination capability and the potential for practical use as a tool for gastrointestinal fluid investigation. Analysis of the stability profiles in faecal water over a 14-hour duration has indicated a possible adsorption mechanism with the formation of a biolayer on the sensor surface. The stability in gut model fluids over a 42 hour duration has demonstrated a more stable profile but the mechanisms involved are more complicated to determine.

***Index Terms*— electrochemical, electrode, gastrointestinal fluids, voltammetry**

I. Introduction

Gastrointestinal diseases are growing in incidence in particular across the Western World. The gold standard in diagnosis is endoscopy, an invasive technique that is not suitable for all candidates, where high-resolution colour images are taken of the gut wall. Therefore, there have been significant efforts to develop reliable alternative approaches that could provide a noninvasive diagnosis e.g. by application of different analytical methods for gastrointestinal fluid analysis. For example, mass spectrometric investigation of gut fluids has determined differences in the spectra from healthy humans versus patients with inflammatory bowel disease (IBD) [1]. An analysis of gut lavage fluid using chromatographic techniques has also shown that mucin levels differ between samples from healthy and IBD subjects [2]. Faecal calprotectin levels in faeces have been proposed as a marker for intestinal inflammation [3,4]. In spite of these studies, the gut environment is still poorly investigated, and this fundamental limitation, in turn, leads to difficulty in understanding the causes and behaviour of diseases of the gut.

This paper describes an electrochemical study of two biomimetic fluids related to the gut environment, faecal water and gut model fluids, which have potential for i*n vitro* and *in vivo* applications. For *in vitro* applications, faecal water was prepared from stool samples of healthy volunteers. A gut model system was used for access to gut model fluids. The electrochemical system under investigation adapts an electronic tongue (e-tongue) approach, which is a multi-sensor system incorporating high sensitivity sensors and signal processing routines [5,6]. It has been proven that this methodology can be effectively used for analysis of complex solutions including recognition of different flavours. This approach has been well established in the analysis of complex liquids in food and environmental applications where a qualitative assessment on conditions of liquid foods [7-9] and waste water [10,11] (e.g. as part of water treatment processes) is needed.

The first of these e-tongue systems can be attributed to Toko, who in 1990 introduced a sensor that could distinguish between the five basic tastes salt, sweet, sour, bitter and umami. [12]. Other sensors followed, with potentiometric [13], voltammetric [14-16] and surface acoustic wave array sensors [17] being developed for applications ranging from tasting the freshness of milk, different fruit juices and the quality of drinking water. Among these systems, the voltammetric e-tongue tends to be favoured for robust applications. It consists of an array of noble metal electrodes that do not require selective coatings and can be cleaned *in situ*. These electrodes can be deposited on a sensing substrate using microfabrication techniques [18] which facilities miniaturisation, batch production, high reproducibility, low cost, and a disposable option (so surface fouling and cross contamination is not an issue).

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The aim of this paper is to evaluate the suitability of an e-tongue approach for the analysis of gastrointestinal fluids. To the best of our knowledge, such an investigation has not been reported before. This paper concentrates on understanding the behavior of e-tongue electrodes in fluids which mimic gastrointestinal fluids. The approach taken is the use of cyclic voltammetry (CV) to characterize the two biomimetic fluids at four noble metal electrodes (Au, Pt, Ir and Rh). This also offers advantages in comparison with other analytical techniques which require expensive bulky equipment (spectrometry, chromatography) or special labs and reagents (immunoassays). The approach reported here can form the basis of a sensor method or device for biofluid investigation, including the prospect for label-free sensitive detection. This would facilitate a move from the current laboratory-based methods to a simple, single-step procedure which provides a rapid and sensitive measurement deployable at the point-of-care and easily miniaturized using microfabrication technology. The results presented here provide the basis for a sensor and methodology for a portable benchtop analysis device (*in vitro* application) or the sensing element of a swallowable capsule device for *in vivo* investigation. The stability of the sensor in both solutions, which is an important sensor parameter for practical deployment, was extensively examined. Due to the complexity of the fluids, which include many organic and biological molecules that may undergo interactions (including adsorption and electron transfer) at the surface of the sensor electrodes, appropriate reference solutions were also explored in order to further understand the sensor operation.

II. Materials and Methods

A. Sensor Fabrication and Preparation

The probe employed in these studies consisted of four working electrodes and a counter electrode, see Fig 1. This probe was used in conjunction with a Ag/AgCl reference electrode, (from IJ Cambria, UK). The counter electrode was a 2 mm diameter stainless steel rod. The working electrodes were 1 mm diameter noble metal wires (Au, Pt, Ir and Rh), which were symmetrically located at a distance of 1 mm around the counter electrode. Electrical connection was made to the working electrode wires at one end. The fabrication of the sensor probe necessitated preparation of a mold, in poly(tetrafluoroethylene) (PTFE), which was used to hold the electrode wires in place while it was filled with a suitable epoxy using a Cam/alot 1414 (Camelot Systems, Inc. Haverhill Ma, 01835 USA) automatic dispensing machine. This assembly was placed in a vacuum chamber oven where a vacuum was applied for a few minutes to ensure no air-bubbles remained trapped in the epoxy, and it was then cured at 150^{o}C for 90 minutes. Once cured, the outer PTFE mold was cut away, leaving the epoxy-encased wires as the probe for experimental studies. A Metaserv 2000 grinder/polisher (Buehler UK Ltd. Coventry, England) was used to polish the exposed ends of the wires in the epoxy casing. Before each electrochemical experiment, the electrodes was polished with an aqueous alumina suspension, and the gold, platinum and rhodium electrodes underwent electrochemical cleaning by potentiodynamic cycling in 0.1 M H_2SO_4 solution.

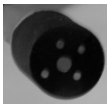


Fig. 1. Photograph of the surface of electrochemical sensor assembly showing the central counter electrode surrounded by the four metal working electrodes.

B. Materials

The noble metal wires were purchased from Goodfellow Ltd., Cambridge, UK, and had the following purities: Au 99.95%, Pt 99.99%, Ir 99.9%, Rh 99.9%. The stainless steel was A.I.S.I. (American Iron and Steel Institute) 316 grade (Fe/Cr18/Ni10,Mo3). The epoxy material was Amicon 50300HT from Hitek Electronic Materials Ltd. All of the chemicals were from Sigma Aldrich.

C. Electrochemical technique

Electrochemical behavior of the gut fluids using the sensor probe was studied by CV in a three electrode cell configuration at a scan rate 200 mVs^{-1}. All electrochemical experiments were conducted at room temperature using commercial electrochemical instruments, either a PalmSens (Palm Instruments, The Netherlands) or a CHI620A potentiostat (CH Instruments, USA). Current densities were obtained by dividing the experimental current values by the geometric area of the electrode employed.

D. Faecal Water Preparation

Stool material (400 mg) was weighed using an Ohaus Explorer Pro balance and 2 volumes of pure deionised water (800 µL) were added. This water was homogenized by mixing and centrifuged in a benchtop centrifuge for 30 minutes at 16,000 g. The resulting supernatant was clarified by passing it through a filter spin column (Whatman cat. number 6832-0401 Centrifuge Tube Filter 400 µL, polypropylene, 0.45 µm, 100/pk). The samples were stored at -20^{o}C. Prior to experiments, the samples were allowed to thaw for ca. 20 minutes, and 500 µL were transferred to a suitable vessel for electrochemical investigation. The pH of the samples was determined with an Orion pH meter, model 520A and averaged pH 6.6.

E. The Gut Model System

The three stage continuous culture model of the human colon (gut model) [19] comprised three glass fermenters of increasing working volume, simulating the proximal (280 ml), transverse (300 ml) and distal colon (320 ml). The 280 ml vessel was fed, by means of a peristaltic pump, a complex medium containing (g/l): soluble potato starch, 5; peptone water, 5; tryptone, 5; yeast extract, 4.5; NaCl, 4.5; KCl, 4.5; pig porcine mucin, 4; milk casein, 3; pectin, 2; larch wood xylan, 2; arabinogalactan, 2; $NaHCO_3$, 1.5; $MgSO_4$, 1.25; guar gum, 1; cysteine-HCl, 0.8; KH_2PO_4, 0.5; K_2HPO_4, 0.5; bile salts, 0.4; $CaCl_2.6H_2O$, 0.15; $FeSO_4.7H_2O$, 0.005; haemin, 0.05; Tween 80, 1 ml; vitamin K_1, 10 µl; resazurin, 4 ml.). The three fermenters were connected in series, with the 1st vessel feeding the 2nd and so on to the 3rd vessel, which finally

overflowed into the waste. All vessels were kept at 37°C by means of a circulating waterbath. Each gut model vessel was connected to a pH controller (Fermac 260; Electrolab, Tewkesbury, UK) which continuously monitored the pH and regulated it at 5.5 (proximal), 6.2 (transverse) and 6.8 (distal) by addition of 0.5N NaOH or 0.5N HCl, as required. The system was kept anaerobic by continuously sparging with oxygen free nitrogen. Each vessel was inoculated with 100ml faecal water (20% w/w in phosphate buffered saline, pH 7.2) homogenized in a stomacher 400 (Seward, Norfolk, UK) for 2 minutes at normal speed. The total system transit time was 48 hours.

The electrode probe was placed in the sampling port of the vessel simulating the distal colon. The humidity inside each vessel was close to 100% RH, which required waterproofing of the electrical connections between the probe and the electrical measurement equipment. CV was carried out periodically at each working electrode over a 48 hour duration.

III. Results and Discussion.

A. Electrode behavior in faecal water and deionised water

The CVs obtained with the multielectrode sensor, comprising Au, Pt, Ir and Rh working electrodes, immersed in the faecal water and deionised water (reference solution) over 14 hours (maximum daily testing time) are shown in 3D form, to better show the variation over time, in Figures 2(a-d) (faecal water) and 3(a-d) (deionised water). In these and subsequent figures, the current density values are shown on the z-axis, applied potential is plotted on the x-axis and the time difference between experiments is shown on the y-axis.

In order to maintain the native properties of the faecal material, faecal water fluid samples were prepared in deionised water. By preparing the faecal samples in water, an insight into the sensor behavior in gut fluids (which has similar properties to faecal samples) could be obtained. The preparation of the faecal water samples in a redox inactive background electrolyte or buffer solution often used in electrochemical characterization would have compromised the samples' behavior because the ions added from the electrolyte or buffer may have dominated the electrochemical response.

The CVs at four metal electrodes were different in both fluids and will be discussed separately. Overall, there were larger oxidation/reduction currents at electrodes in the faecal water than at electrodes in the reference solution, which indicated higher electrochemical activity. This is a consequence of the higher resistivity of deionised water relative to faecal water: the latter contains dissolved ions which enable a higher current to pass through the liquid. The other general observation is that waves were observed for the electrodes in faecal water, whereas peaks were dominant for the electrochemistry in water. This may be a consequence of the organic matter in faecal water adsorbing on the surface of the electrodes and partially inhibiting the electrochemical reactions occurring there.

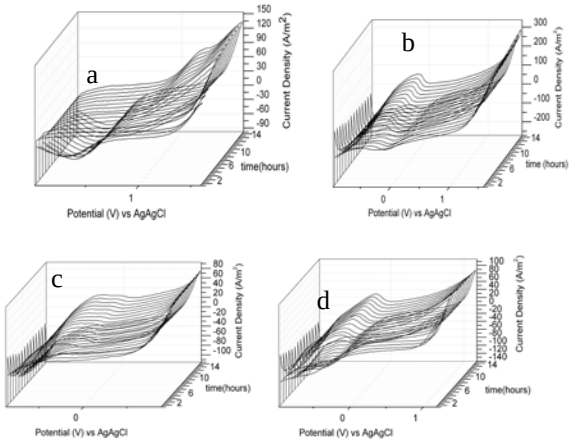


Fig. 2 Cyclic voltammograms in faecal water in faecal water over a 14 hour duration: (a)Au, (b) Pt, (c) Ir, (d) Rh at scan rate 200 $mVs^{-1.}$

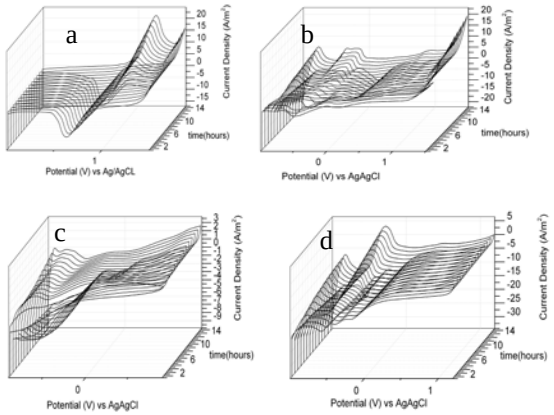


Fig. 3 Cyclic voltammograms in deionised water over a 14 hour duration (a) Au, (b) Pt, (c) Ir, (d) Rh at scan rate 200 $mVs^{-1.}$

The Au electrode was investigated over the potential range -0.10 to 1.40 V, see Figs. 2a and 3a for the behavior in faecal and deionised water. In faecal water it exhibited a broad oxidation wave at 1.22 V over the positive sweep, and a reduction wave at 0.33 V over the negative sweep. The corresponding oxidation and reduction peaks in deionised water were at 1.20 V and 0.64 V. With repeated cycling in faecal water, the oxidation amplitude increased, with the wave-shape becoming more pronounced. A similar behavior was noted in deionised water.

The Pt electrode was investigated over the potential range -0.70 to 1.50 V, see Figs. 2b and 3b. In faecal water it exhibited a clear oxidation peak at -0.19 V over the positive sweep, and a clear reduction peak formed at -0.09 V during the negative direction sweep. These two peaks coincided with the peaks present in the CVs of the Pt electrode in water at -0.24 V and 0.16 V. With repeated cycling, the changes of the voltammogram shape and the peak magnitude in faecal fluids was less than at the Au electrode. The variations of the Pt voltammograms over time in water were significant and the peak amplitude increased with continued cycling. The shape of the Pt electrode voltammograms in deionised water was

more complex than in faecal fluid and also more complex than the shape of Au electrode response in deionised water. At Pt, there was an additional pair of reduction/oxidation peaks at -0.74 V/-0.36 V.

The Ir electrode was investigated over the potential range -0.7 to 1.3 V (Figs. 2c and 3c). In faecal water it exhibited a broad oxidation peak at -0.25V over the positive sweep. A broad oxidation peak formed at 0V and a broad reduction peak at -0.06 V. There was no corresponding reduction peak at Ir in faecal water. Besides these two peaks, the Ir voltammograms in deionised water demonstrated an additional oxidation peak at -0.65 V, which with repeating cycling formed a double-peak shape with the second peak at -0.80 V, and a wide reduction peak at -0.59 V. With repeated cycling the changes of the voltammogram shape and the peak magnitudes in faecal fluids were less evident in comparison with the Au electrode but more pronounced in comparison with Pt electrode response. The changes in Ir response in deionised water with repeated cycling were significant.

The Rh electrode was investigated over the potential range -0.7 V to 1.5 V (Figs.2d and 3d). In faecal water, it exhibited a clear oxidation peak at -0.21 V over the positive sweep, and as a weakly formed reduction peak at -0.47 V during the negative potential sweep. By comparison, these peaks corresponded to the well defined peaks formed at -0.2 V and -0.5 during repeated cyclic voltammetry at Rh electrode in deionised water . Similar to the Ir electrode the voltammogramms of Rh in water had also an additional oxidation peak at -0.80 V. With repeated cycling the changes of the voltammogram shape and the behavior of the peak in faecal fluids were close to Pt responses.

The parameters which were used for evaluation of the electrode stability were $I_{re,}$ I_{ox}, I_{max}, I_{min} I_{mm} and S, where I_{re} is the reduction current, I_{ox} is the oxidation current, I_{max} is the maximum current, I_{min} is the minimum current, I_{av} is the average current value, I_{mm} is the difference between I_{max} and I_{min} and S is the area of the voltammogram. The trends of the selected parameters with time and their fitting with exponential (for faecal water) and linear (for deionised water) functions are shown in Figures 4 and 5 with symbols (experimental data) and solid lines (fitted profiles).

The analysis of these profiles demonstrated a good correlation, with R^2 values in the range of 0.878 – 0.999 for both of the investigated fluids. The profiles in faecal water had a clear exponential shape with the correlation coefficient between the fitted and the raw profiles were in the range of 0.88 – 0.98. For deionised water the profiles were linear with correlation coefficients in the range of 0.84 – 0.99. The presence of a single exponential process in the time profiles can point to a first order reaction e.g. adsorption of the biomolecular species to the electrode surface resulting in the formation of a bio-layer. The time to form this layer was estimated by the exponential fitting of the profiles, to be within the range of 2-6 hours. An inflection point is seen to occur at ~4 hours for Rh, in comparison with ~3 hours for the Au, Ir and Pt. Also, there is a larger variation from the trend line seen in particular for Rh and the I_{mm} parameter. Further investigation is needed to determine the reason for this. Overall, the deviation is within a statistically acceptable range and does not compromise the chosen fit and resulting conclusion about the transient behavior of the response.

The adsorption is not a significant issue for benchtop testing where the complete measurement may be of the order of minutes. The stability tests have demonstrated that the adsorption process is slow in comparison with this measurement rate, forming over the aforementioned 2-6 hour time frame. For integration within a capsule, where the sensor can be expected to operate for up to 24 hours, the adsorption needs to be considered. It should be addressed by corresponding signal processing or modification of the electrode surface.

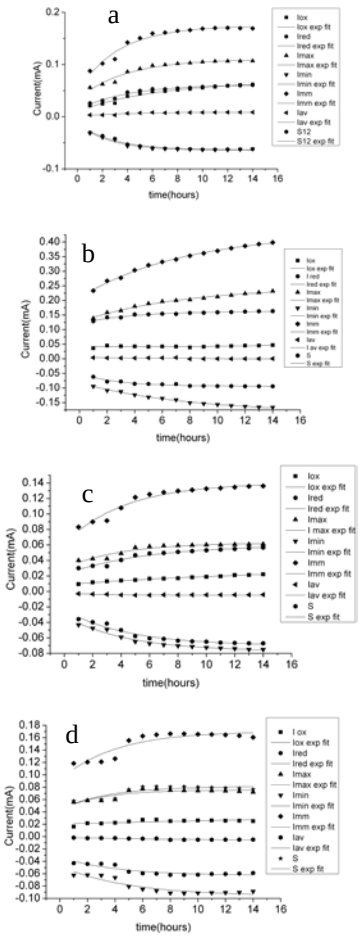
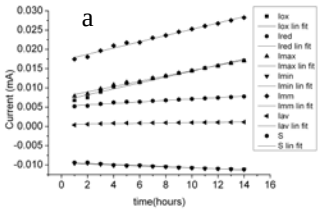


Fig. 4 Stability profiles in faecal water over a 14 hour duration at (a)Au, (b) Pt, (c) Ir, (d) Rh for different CV parameters.



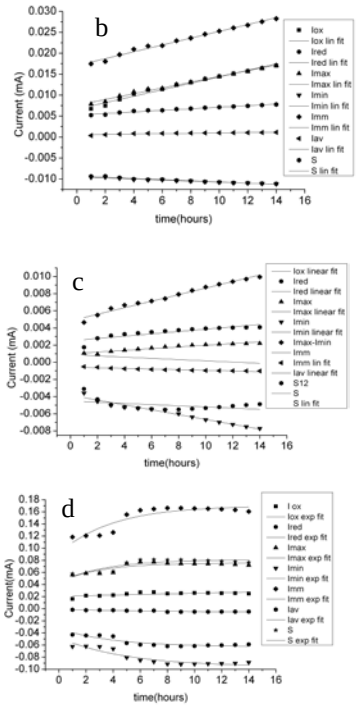


Fig. 5 Stability profiles at different electrodes in deionised water over a 14 hour duration at (a)Au, (b) Pt, (c) Ir, (d) Rh for different CV parameters.

B. Electrode behavior in Gut Model fluids and HCl solution

The voltammetric responses of the electrodes in gut model fluids over 48 hours (12 hour measurement intervals) and in 0.1 M HCl (a constituent of stomach fluids) over 14 hours (with a 1 hour time resolution) are shown in figs.6 and 7. The electrodes exhibited different electrochemical behavior in the gut model fluids than in the faecal water. There were notable differences observed, in particular for Au and Pt (figs 6a and 6b). These electrodes demonstrated well-defined oxidation peaks at 1.2V, with a corresponding reduction wave seen for Au at 0.6V. For Rh the oxidation was distinct at 1V and in the case of Ir no obvious oxidation reactions were observed. Over the initial 12 hour measurement period, a reduction in oxidation amplitude was noted and the reaction occurred at more negative applied potentials (fig. 6 and 7). This oxidation peak could be attributed to the HCl constituent of the gut model fluid. It can be seen that during initial cycling in HCl solution, an increasing oxide and corresponding reduction peak formed for Au and Pt. Continued cycling demonstrated a stabilizing of the peaks with an eventual decrease observed in current amplitude. This was due to chloride adsorption, which inhibited the surface electrochemical behavior [20-21]. Although Rh did not exhibit noticeable oxidative behavior, two reduction peaks were seen (also seen in other acid media [22]), which decreased in amplitude with continued cycling. This behavior has been attributed to chloride adsorption [21]. No noted effect of chloride adsorption was observed at Ir (fig.5c). The shift in oxidation activity in the gut model fluids in comparison with HCl may indicate adsorption of organic matter from the gut model liquid/solid/gas multi-phase system onto the metal electrode surfaces, although some shift in the potential of the Ag/AgCl reference electrode is also possible.

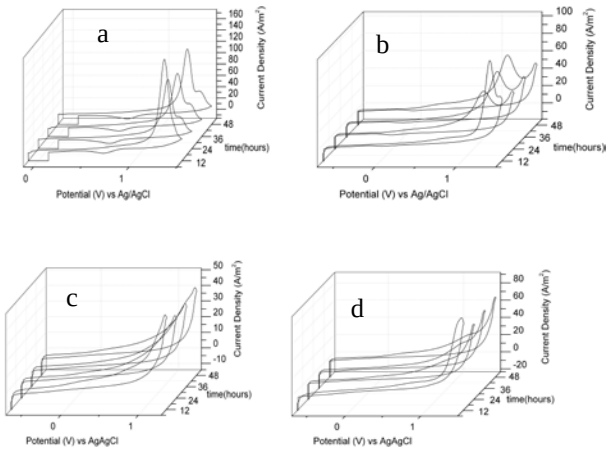


Fig.6 Voltammetric response of working electrodes in gut model fluids over 48 hour duration (a)Au, (b) Pt, (c) Ir, (d) Rh at scan rate 200 $mVs^{-1.}$

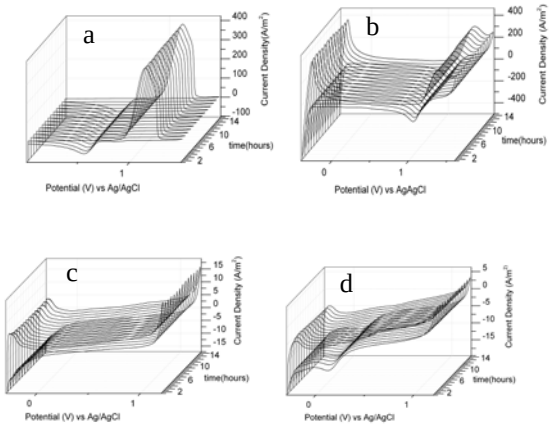


Fig.7 Voltammetric response of working electrodes in HCl over 14 hours (a)Au, (b) Pt, (c) Ir, (d) Rh at scan rate 200 mVs^{-1}.

The parameters I_{ox} and V_{ox} (Au and Pt) and I_{mm} , *S, and* I_{max} (Ir, Rh) normalized to their absolute maximum values were used for evaluation of the electrode stability in these two fluids. The normalized profiles are shown in figs 8 and 9. The observed profiles had a more complex shape than the stability profiles in faecal water and deionised water. They also are more stable (especially in HCl where the parameter change is less than 10 %, with the exception of Rh where maximum changes were less than 25%). The mutual correlation of the selected voltammogram parameters is lower and dependant on the electrode material. Unlike the previous situation with the faecal water stability analysis, where a definite time dependence for the different parameters was noted, for the gut model fluids there is no time dependence for any of the parameters.

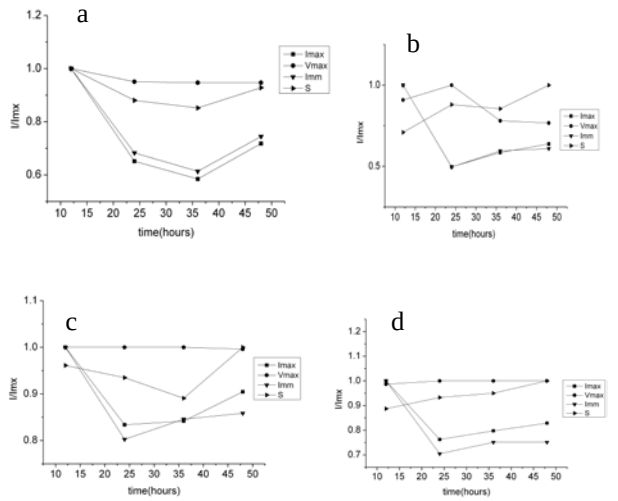


Fig. 8. Normalized profiles in gut model fuids at (a)Au, (b) Pt, (c) Ir, (d) Rh for different CV parameters.

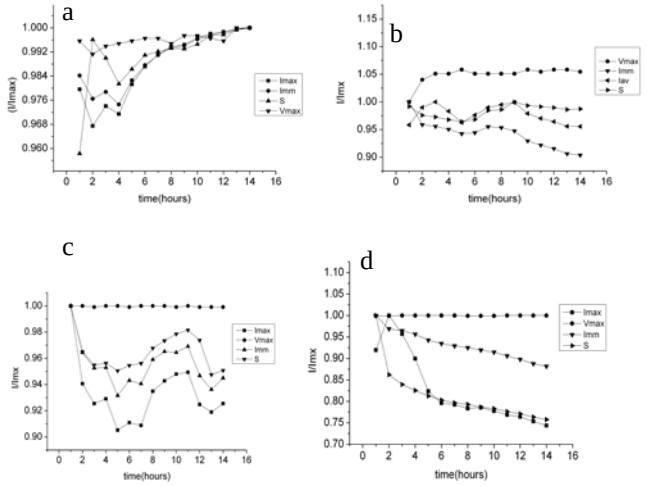


Fig. 9. Normalized profiles in HCl at (a)Au, (b) Pt, (c) Ir, (d) Rh for different CV parameters.

IV. Conclusion

This paper presents the behavior of gastrointestinal fluids using a four electrode voltammetric probe approach. It is clearly demonstrated that the metal electrodes retain their electroactivity in these complex media and stable characteristic shapes are obtained for the different biological fluids tested. Biomimetic fluids for *in vivo* and *in vitro* applications have been investigated and the sensor probe has demonstrated the ability to distinguish between the two media. The CV behavior in faecal fluid and gut fluid is dominated by the surface electrochemical behavior of the metal electrodes. In faecal fluid, there is a time-dependence indicative of a slow adsorption of organic matter to the metal electrode surfaces; this may inhibit electrochemical reactions. In contrast, there is no distinct time-dependence for the gut fluid data. There does not appear to be any electrochemical processes that are not attributable to the metal electrodes i.e. the organic matter itself does not seem to undergo redox reactions. This could be because the organic matter has been fully oxidized by the processes or digestion and excretion.Therefore, by combining the results obtained from each electrode, the discrimination capability of the system can be increased and an overall qualitative assessment of the solution properties can be made to facilitate noninvasive patient investigation. The electrochemical analysis of biological fluids could provide additional information, which could be useful for disease diagnosis.

The suitability of the e-tongue approach for a biological application has been established; the next step will target a particular gut disease and data using this method will be gathered. A suitable procedure will be determined and statistical signal processing and data interpretation methods will be developed to extract the important information from the raw data. Future work on device design will concentrate on two directions, the development of integrated microelectrode array devices using microfabrication techniques [18], for *in vitro* measurements, and the development of a strategy for integration of these electrodes into a swallowable capsule [23-28]. In the development of the microelectrode array, different dimensions will be investigated including micro- and nano-electrode range, and an optimum design chosen. A reduction in dimension size will facilitate operation in smaller sample volumes and faster measurements due to a higher mass transport rate at the electrodes.

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