*J. Biochem.* **144,** 87–93 (2008)
doi:10.1093/jb/mvn045

# Carbon Fibre Composites: Integrated Electrochemical Sensors for Wound Management

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Received January 21, 2008; accepted March 18, 2008; published online April 4, 2008

**The applicability of employing a carbon fibre mesh as an electrochemical sensing substructure for assessing urate transformations within wound exudates is evaluated. Prototype sensor assemblies have been designed and their response characteristics towards uric acid and other common physiological components are detailed. Modification of the carbon fibre sensor through surface anodization and the application of cellulose acetate permselective barriers have been shown to lead to optimized responses and much greater sensitivity (1440% increase) and specificity. These could enable the accurate periodic monitoring of uric acid in wound fluid. The performance characteristics of the composite sensors in whole blood, serum and blister fluid have been investigated.**

**Key words: carbon fibre, smart bandage, urate, uric acid, wound infection.**

Abbreviations: HAI, hospital acquired infection; ROS, reactive oxygen species.

The threat of wound infection is an ever present hazard in modern healthcare whether the patient is being treated locally or within a hospital environment. A recent survey has put the incidence of hospital acquired infections (HAI's) relating to surgical wound management at around 10% (*1*, *2*) and it has been estimated that complications arising from these can increase the length of hospitalization to between 6 and 13 days (*3*, *4*). There are obvious implications for the patient and health service with the cost to the UK NHS alone within the billion pound region (*3*). In many cases, the origin is simply the colonization of the wound by adventitious opportunistic bacteria such as *Pseudomonas aeruginosa* or *Staphylococcus aureus* (*5–7*) as a consequence of poor hygiene. Irrespective of the cause, there is a need for a more intelligent approach to wound management. While this clearly dictates that improvements are made to basic hygiene, technology also has a part to play and recent advances in nano-particle science have seen the development of antibacterial dressings, frequently Silver-based (*8*). Nevertheless, the inherent adaptability of micro-organisms means that there remains a need for a failsafe system that can alert either the patient or the health care professional to the advent of a potential infection. The present communication has sought to explore the use of an electrochemical sensing system capable of measuring urate directly within the wound fluid as an indirect marker for assessing both the physiological response to the injury and, importantly, as a generic indicator for the presence of bacterial colonization. Whilst surgical wounds as a whole may be considered; of particular importance regarding infection and other complications is the management of thermal burn injuries. These are ascribed to the large, open surface of such wounds, especially following debridement, and the generation of reactive oxygen species (ROS's) and inflammatory mediators which may induce systemic injury (*9*).

The underlying rationale behind the choice of urate lies in the fact that the molecule has a significant physiological role for the patient (*10*) and is degraded by certain pathogenic and opportunist pathogenic bacteria including the aforementioned infectants (*11*).

It could be anticipated that its inherent anti-oxidant properties may mean that the local concentration and fluctuations therein reflect the nature of ongoing oxidative stress processes within the body, which may lead to serious and potentially fatal systemic complications *e.g.* Cardiac mitochondrial damage (*12*). Thus, uric acid determination could provide a semi quantitative diagnostic assessment of the severity of the local and systemic injury; or the effectiveness of the anti-oxidant treatment as part of the requisite fluid resuscitation.

Another possibility is that the local consumption of urate could, in principle, occur where certain bacterial colonies effectively metabolize the urate. The critical point in the latter rests upon the fact that urate is the final end product of purine catabolism within humans and hence the relatively large concentration within serum [150–420 μM (*13*)]. Many organisms, both pathogens and opportunist pathogens, have the ability to metabolize uric acid; importantly, the two major causes of burn wound infection: *S. aureus* and *P. aeruginosa* are included (*11*, *14–16*). Both of which have been reported to rapidly metabolize uric acid, via microbial uricase synthesis. Microbial uricase catabolizes uric acid to allantoin (*17*) as is commonplace in the human gastrointestinal tract.

Therefore, it could be envisaged that reductions in urate concentration may provide a generic indicator for monitoring the change from bacterial contamination

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to colonization. A substantial depletion of urate may consequently provide a vital, early warning flag that can alert the patient or healthcare professional such that remedial action can be taken prior to the onset of 'critical colonization' and the subsequent wound infection (*18*). As well as a decrease in mortality, it is reasonable to assume that this may help reduce the generation of antibiotic resistant bacterial strains, by the theory, the fewer bacteria treated with an antibiotic, the fewer mutant organisms expressed.

The foundations of the sensor design rest upon the exploitation of a carbon fibre mesh both as the detection element and the transduction conduit. The electro-oxidation of urate at various forms of carbon is well documented and there are numerous analytical methodologies incorporating such (*19–24*). The uses of carbon fibre electrodes for biomedical applications are also well documented for the detection of: nitric oxide (*25*), lactate dehydrogenase (*26*), perphenazine (*27*), haemoglobin (*28*), ascorbate, catechol and indole (*29*), chloramphenicol (*30*) and uric acid (*31*, *32*) However, the aforementioned detection of uric acid was performed *in vitro*, using diluted sample and a large surface area sensor. Single fibre electrodes are commonly used for *in vivo* monitoring for many other analytes, commonly used to measure analytes within the brain; acetylcholine and choline (*33*), dopamine (*34–36*), acetaminophen (*37*), nitric oxide (*38*) and glucose (*39*). The challenge, and the emphasis of the current investigation, is to develop a processing strategy that allows the material to be harnessed in a way that can allow the rapid production of sensors that could be easily incorporated within a smart bandage and which can facilitate 'reagentless' and 'periodic' monitoring of urate directly within a range of biofluids.

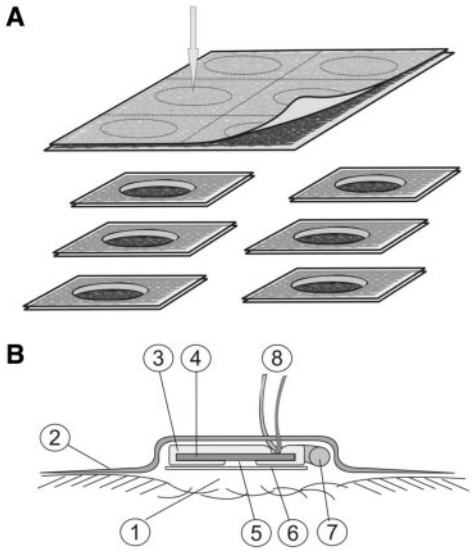


Fig. 1. (**A**) **Schematic of the lamination process and (B) the prototype sensing assembly.** (1) wound aperture, (2) adhesive plaster backing, (3) insulating laminate, (4) carbon fibre sensor, (5) sensing window, (6) cellulose acetate barrier, (7) combined Ag/AgCl reference/counter electrode, (8) contacts to measuring device.

The core rationale is outlined in Fig. 1A where the carbon fibre sheets are thermally sandwiched between polyester laminate. The underlying carbon is selectively exposed to function as the sensing element by laser etching through the encapsulating sheet—which can then be divided up into individual sensing structures and thereby offers an opportunity for mass manufacture. The proposed application of the laminate as a smart sensor is shown in Fig. 1B. The system is integrated within a conventional adhesive plaster—replacing the absorbent pad component traditionally associated with the latter.

The principal aim of this investigation was to determine the potential applicability of the process outlined in Fig. 1 through assessing the response of the carbon fibre composite sensor to urate in various biofluids of direct relevance to wound management.

## EXPERIMENTAL DETAILS

*Materials*—All reagents were of the highest grade available and used without further purification. Stock solutions of uric acid (typically 10 mM) were prepared in 0.1 M NaOH. All other solutions were prepared using Britton–Robinson buffer (acetic, boric and phosphoric acids—each at a concentration of 0.04 M) adjusted to pH 7 through the addition of sodium hydroxide. Standard solutions were generally prepared in deionized water from an Elgastat (Elga, UK) water system and refrigerated when not in use. Toray carbon fibre cloth was purchased from E-Tek Inc (USA) and used as received. Lamination pouches (Rexel UK) were a commercial stationary variety with a film thickness of 75 μm each side. Copper Shielding tape (100 μm thick, adhesive backed) was obtained from RS electronics.

*Instrumentation*—Electrochemical measurements were conducted using a μAutolab type III computer controlled potentiostat (Eco-Chemie, Utrecht, The Netherlands) using a two electrode configuration consisting of the carbon fibre assembly working electrode, a chloridized silver wire as the combined counter/reference electrode.

*Sensor Construction*—Laminated carbon fibre prototypes were prepared by thermally sandwiching carbon fibre sheet between sleeves of a pre-etched (1 or 2 mm diameter window) resin-polyester lamination pouch using a commercially available laminator. Electrical connection to the carbon film was made through the presence of a strip of copper shielding tape. The electrodes were baked at 100°C for 1 h in order to ensure the complete permeation of the resin between the fibres within the laminate. This is necessary to ensure the mechanical integrity and coherence of the seal between the sensing fibre layer and the insulating polyester sheath such that no solvent creep or de-lamination would occur during extended monitoring periods times (up to 18 replicate scans over 30 min or 7 replicate scans over 120 min).

## RESULTS AND DISCUSSION

The morphology of the laser patterned laminate—carbon composite was examined using scanning electron microscopy with the interface between the exposed fibre

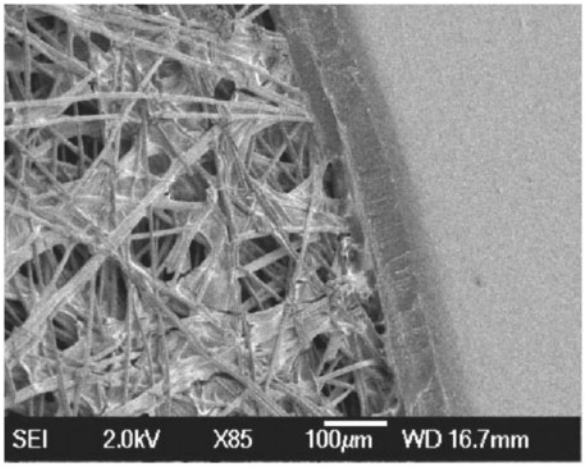


Fig. 2. **Scanning electron micrograph of the carbon fibre mesh/laminate composite.**

substructure and the insulating laminate detailed in Fig. 2. The sensing element is effectively a random assembly of discrete and amalgamated fibres presenting a large 3-dimensional network and is in marked contrast to the planar designs found in conventional macro or micro sized urate sensor formats (*40*, *41*). The initial analytical characterization of the applicability of the network towards the sensing of urate was conducted in buffered solution—containing up to 500 μM ascorbate. The addition of latter is significant in that it is ubiquitous within biofluids and easily electro-oxidized at potentials not dissimilar to those required for urate detection. Square wave voltammograms detailing the response of the carbon network to equimolar urate and ascorbate are detailed in Fig. 3 (dashed line). A single, broad peak is observed with no resolution between the two compounds.

Pre-treatment of the carbon fibre sensor through oxidation in 0.1 M sodium hydroxide (+2 V, 10 min.) yielded a very different response. A single sharp peak is observed at +0.23 V, which is attributed solely to the oxidation of urate. It has been previously shown that the anodic fracturing of carbon substrate as a consequence of such pre-treatment gives superior resolution between ascorbate and urate and markedly reduces the electron transfer kinetics of the former such that, under normal physiological concentrations, it provides a negligible contribution to the voltammetric profile. The anodizing of the carbon fibre created a substantial gain (1440% increase) in the magnitude of the urate peak as detailed in Fig. 3. Confirmation that the sharp peak at +0.23 V is indeed urate with no contribution from ascorbate was provided by repeating the experiment but with a markedly increased concentration of ascorbate. Square wave voltammograms detailing the response to 100 μM urate in the presence of ascorbate (2.2 mM) are shown in Fig. 3 solid line. The ascorbate emerges as a broad peak (+0.03 V) to the left of the sharp urate process. This highlights the fact that even in the presence of massive ascorbate concentration—it is still possible to obtain an unambiguous assessment of urate concentration and is in marked contrast to the result obtained with

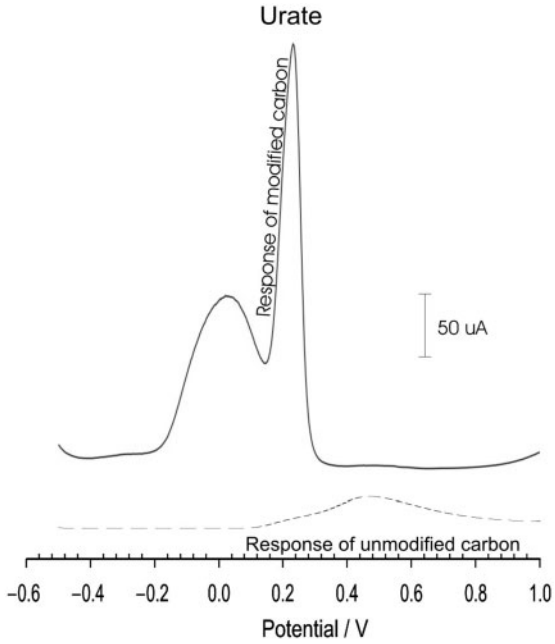


Fig. 3. **Square wave voltammogram comparing the response of an untreated carbon fibre in equimolar 100 μM UA and AA, with an anodized electrode in 100 μM UA and 2.2 mM AA.**

the un-modified carbon fibre (Fig. 3—dashed line). The anodization effect leads to the exfoliation of the fibre structure of the mesh—increasing the surface area at the nanoscale and increasing the population of hydrophilic (typically hydroxyl and carboxylic acid) functionalities on the resulting exposed surface and confirmed by XPS studies. The delamination effect also has the influence of creating more edge plane sites which also serves to increase the electron transfer rate and hence improve the response to urate (*42*, *43*).

The influence of real biofluids on the sensor response was again assessed using square wave voltammetry; the real biofluids were used early in this prototype development, as these are fluids in which a smart-bandage sensor is required to function. The responses of the untreated and modified fibre sensors assemblies to whole blood are detailed in Fig. 4A. In this instance, the untreated blood was applied directly to the sensing surface and the measurement conducted almost immediately. The response of the un-modified fibre sensor shows effectively no discrimination between the different physiological components with a single broad peak found at +0.69 V. The pre-anodized sensor, however, displays a peak profile similar to that observed in the control buffer solution (Fig. 3—solid line). The magnitude of the peaks could be enhanced through increasing the degree of surface pre-treatment prior to applying the blood. Thus, extending the pre-anodization time to 30 min results in a markedly enhanced signal (Fig. 4A has been baseline offset for clarity) with three, clearly resolved peak processes. The first (–0.12 V) is attributed to the redox groups within the fibre substructure, the second (+0.23 V) is the urate and the third (+0.66 V) is

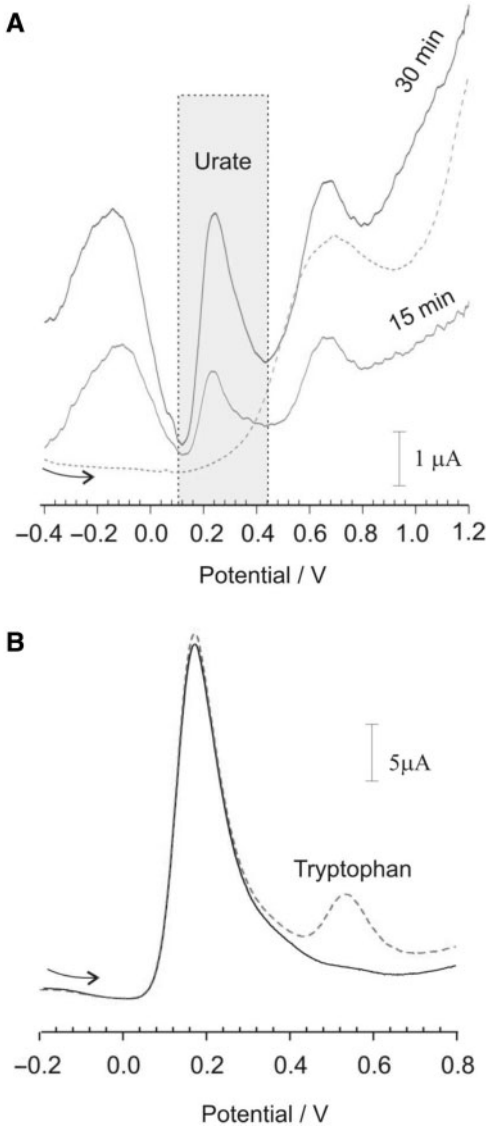


Fig. 4. **(A) Square wave voltammograms detailing the response of the untreated carbon fibre (dashed line) and the anodized fibre (after 15 and 30 min pre-treatment) towards whole blood.** (B) Response of 400 μM urate in the presence and absence of 100 μM Tryptophan.

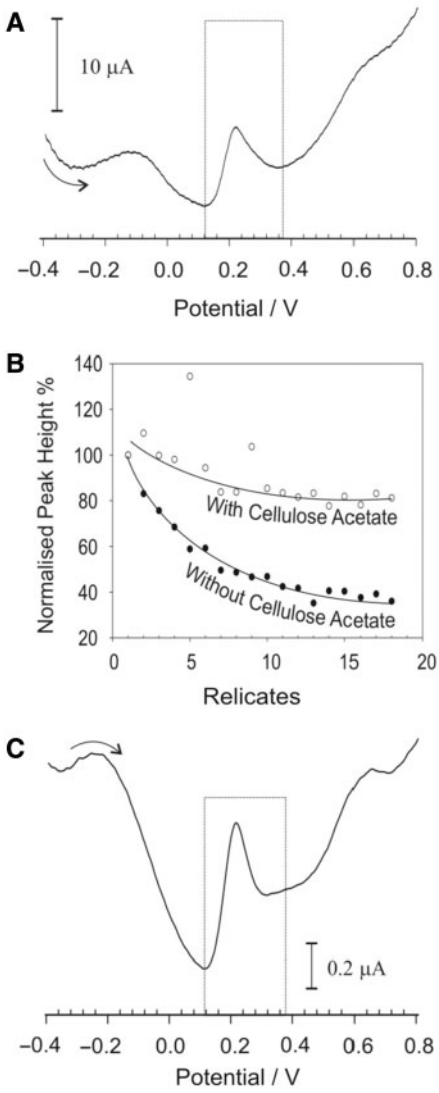


Fig. 5. **(A) Square wave voltammograms detailing the response of an anodized carbon fibre sensing assembly towards human serum.** (B) Influence of cellulose acetate on the periodic response monitoring of urate in serum. (C) Response of the pre-treated, cellulose acetate coated, sensor towards blister fluid.

liable to be a combination of other, less easily oxidized biological components such as tyrosine, tryptophan as well as other purines. This was corroborated by comparing the response to urate in the presence of tryptophan (Fig. 4B). The emergence of a second peak at +0.53 V is located in a similar position to that observed with the whole blood sample. Similar responses were observed with tyrosine with near identical peak positions between tyrosine and tryptophan highlighting both the limitation of the sensor for speciation in such complex fluids but, in the present instance, the supreme advantage of facilitating the almost unique discrimination of urate from the other blood constituents.

Given that the sensor can clearly detect urate in a complex biofluid, the next issue to be addressed relates to whether or not it is indeed capable of monitoring urate beyond the initial scan. The intended application requires periodic scanning of the biofluid for differences in urate concentration and hence alerts the patient/clinical staff to the possibility of wound colonization. Serum samples were used in this instance to avoid the complications of clotting and the need for exogenous agents to prevent such (*e.g*. Lithium heparin). This would allow multiple replicate measurements on the same sensor assembly over a prolonged period and hence would mimic the conditions under which a prototype could be expected to operate. A square wave voltammogram detailing the initial response to the application of the serum sample is shown in Fig. 5A. The urate peak is again clearly resolved and is consistent with both the

control urate solution and the responses observed in whole blood. The variation in peak height as a function of replicate scans (up to 18 replicates: same sensor, same sample) is highlighted in Fig. 5B (solid circles). It can be seen that the peak height response decreases markedly with increasing measurements. It was envisaged that the sustained decay in the response could be attributed to the fouling of the electrode surface by the extracellular components—principally protein and fats—effectively reducing the active sensing area and hence the response.

To counter this problem, the electrode surface was coated with cellulose acetate to act as a protective permselective barrier acting by size exclusion (prepared by drop casting from an ethanol solution). The response characteristics of this second modification have been included within Fig. 5B (white circles) for comparison. There is an initial decay in response, similar to that observed with the uncoated anodized fibre mesh, but, in contrast to the latter, the response soon stabilizes. It is possible that the initial responses are simply a consequence of the equilibration of the anodized fibre in the new medium. The difference in response characteristics (normalized to the peak height measured on the first scan) between the cellulose acetate modified sensor and the uncoated, anodized, system is marked with only a minor loss in performance (~20%) observed with the former whereas the latter suffers significantly (>60% decrease) over 18 replicate scans. The application of this semi-permeable coating reduced the signal current by between 3x and 5x due to decreasing surface area, as to be expected. The subsequent results however show this does not have a substantial impact on the overall sensitivity of the sensor detection as sufficient currents have been detected, even for uric acid concentrations far below the physiological range for biofluids. Whilst carbon fibre and cellulose acetate have previously been used in conjunction; this is the first reported use of them together for detection of uric acid or for use in wound management, again highlighting this novel approach to smart bandage development.

The last hurdle in the preliminary assessment of the applicability of the sensing system was to determine whether or not it could detect urate in a blister wound—typical of the open wound liable to be subject to common bacterial infection. A square wave voltammogram detailing the response of the anodized sensor system towards the blister exudate is shown in Fig. 5C. The profile is again similar to that found with the other biofluids and highlights the potential for applying the sensor system within a number of biomedical contexts where it may be necessary to monitor wound status.

To ensure that accurate quantification of uric acid is possible a series of standard curves were run throughout the investigation, whilst the lower and more physiologically relevant range (0–500 μM) fit a linear equation ($y = 0.025x + 0.561$), with an $R^2$ value of 0.97, it was found possible to extend the analytical range up to 1 mM but fitting a more complex, one-site saturation standard curve (Fig. 6A) [$y = (B_{max}.x)/(K_d + x)$ where $B_{max} = 1.5654$ and $K_d = 178.4328$) with an $R^2$ value of 0.99]. The linear increase in uric acid concentration (Fig. 6B), as measured by the proposed electrochemical system, correlates with

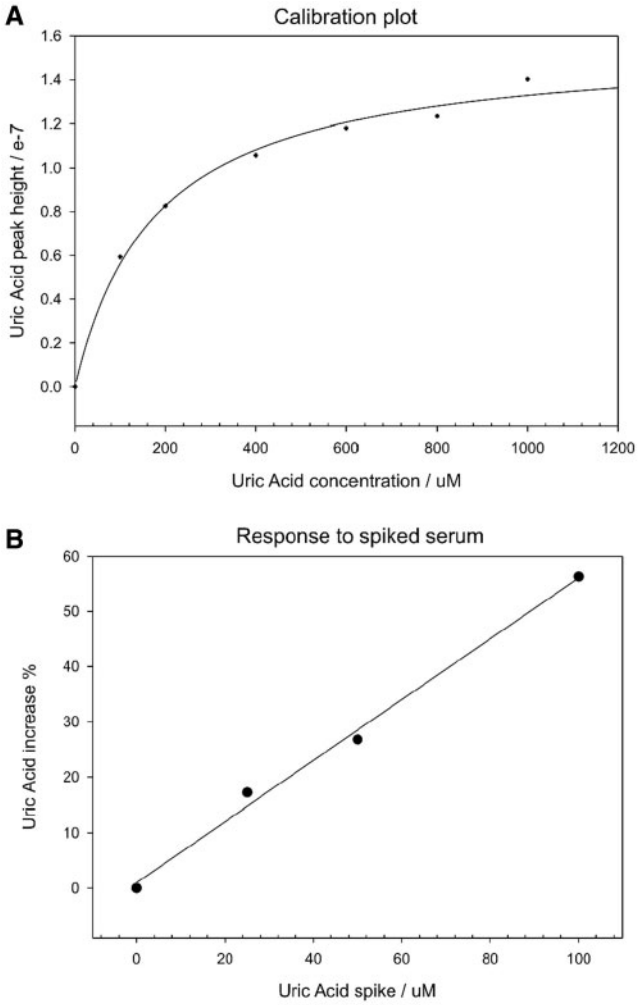


Fig. 6. **(A) Calibration plot, with data, for the quantification of uric acid (in pH 7 buffer) using an anodized carbon fibre sensor.** (B) Uric acid measurements in a serially spiked (25, 50 and 100 μM urate) serum sample.

the spiking of the biofluid (serum) highlighting the ability of the sensor to monitor minor fluctuations of the uric acid concentration. The three serum spikes (25, 50 and 100 μM urate) were chosen to show both the sensitivity to urate concentration changes and by doubling the spike each time allow a simple spiked-serum standard plot to be established. The relative change of the uric acid is highlighted as this is of most importance for the proposed application.

## CONCLUSIONS

The carbon fibre system has shown to be capable of easy integration into a robust and versatile sensing system. Modification of the carbon network either pre- or post-lamination provides superior resolution and sensitivity of urate detection across a number of biomedical contexts. Periodic monitoring has been shown to be feasible and hence the system could facilitate short to moderate term wound management in a smart bandage application for

the monitoring of bacterial metabolism of uric acid. Hence, in addition to the *in vitro* quantification of uric acid in common biofluids this direct electrochemical sensor has proven successful for the detection of uric acid in blister/wound fluid, a previously unexplored application, and the closest to a truly *in vivo* uric acid carbon fibre sensor. The only thorough investigation using carbon fibre electrodes to measure uric acid in biofluids (serum) (*32*) was performed using much larger electrode diameters (Typically 5 mm–25x greater surface area!) and using diluted serum samples for the analysis, however, the proposed design offers similar specificity, and due to having a much smaller surface area, substantially less uric acid would be metabolized by the electrochemical oxidation (via detection) thereby causing minimal affects on wound physiology.

Given the reagent-less and stable nature of the sensors proposed within, there are no issues with stability or storage conditions unlike enzyme-based sensors and throughout this investigation the batch produced sensors had shown no indications of instability or degradation. Longer term studies of shelf life would however be required but are beyond the scope of the present preliminary-proof of concept investigations presented herein. The ease with which the sensor can be fabricated, the unambiguous and sensitive nature of the signal is clearly an advantage over conventional urate measurements systems. Therefore the proposed electrochemical system clearly proffers a strong foundation for quantitative smart bandage technologies.

The authors thank the EPSRC for supporting this work.

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