# Noninvasive *In-Situ* Measurement of Blood Lactate Using Microwave Sensors

A. Mason*, O. Korostynska, J. Louis, L. E. Cordova-Lopez, B. Abdullah, J. Greene, R. Connell, and J. Hopkins

***Abstract*—*Goal:*** **This paper reports a novel electromagnetic sensor technique for real-time noninvasive monitoring of blood lactate in human subjects.** ***Methods:*** **The technique was demonstrated on 34 participants who undertook a cycling regime, with rest period before and after, to produce a rising and falling lactate response curve. Sensors attached to the arm and legs of participants gathered spectral data, blood samples were measured using a Lactate Pro V2; temperature and heart rate data was also collected.** ***Results:*** **Pointwise mutual information and neural networks are used to produce a predictive model. The model shows a good correlation** $(\mathrm{R} = 0.78)$ **between the standard invasive and novel noninvasive electromagnetic wave based blood lactate measurements, with an error of 13.4% in the range of 0–12 mmol/L.** ***Conclusion:*** **The work demonstrates that electromagnetic wave sensors are capable of determining blood lactate level without the need for invasive blood sampling.** ***Significance:*** **Measurement of blood metabolites, such as blood lactate, in real-time and noninvasively in hospital environments will reduce the risk of infection, increase the frequency of measurement and ensure timely intervention only when necessary. In sports, such tools will enhance training of athletes, and enable more effecting training regimes to be prescribed.**

***Index Terms*—Electromagnetic wave, microwave, noninvasive, point of care, sensor, wearable.**

## I. Introduction

LACTATE is key in two fundamental metabolic processes, glycolysis and oxidative phosphorylation, which serve as the basis for energy production in the human body [1]. Glycolysis is the process of converting glucose into the intermediate molecule pyruvate. Oxidative phosphorylation completes the process, in conjunction with oxygen, to form carbon dioxide; both processes also result in the production of adenosine triphosphate (ATP) which provides energy for cells to function.

When the body is in a resting and/or healthy non-active state, lactate levels in the blood stream are maintained at a relatively low steady state. According to Andropoulos [2], whole blood lactate should be in the range 0.2–1.7 mmol/L in a healthy patient, with some variation noted based on age. However, when stress is introduced to the body (e.g., via exercise or acute illness) the energy requirements of the body can alter significantly. Typically, glycolysis can accelerate rapidly to meet the new energy demand; however, oxidative phosphorylation does not. This means that the body produces significant amounts of pyruvate, which it must then convert to lactate (via the enzyme lactate dehydrogenase, or LDH) so that glycolysis can continue accelerating and producing both pyruvate and ATP. Once the lactate level in the cells becomes saturated, it will be transported into the blood stream; during acute exercise lactate may exceed 20 mmol/L, as shown by Goodwin *et al* [3] for example. In a healthy person post-exercise, the lactate level will steadily drop back to normal levels, with oxidative phosphorylation being able to clear the excess lactate.

When the stress placed on the body is due to illness, the tendency for the body to accumulate lactate is prolonged, perhaps resulting in lactic acidosis. It is therefore commonplace in contemporary medicine for lactate to be used as a means to evaluate the severity of acute illness, diagnose disease states, predict mortality, and assess response to resuscitation [4]. Furthermore, in sport, lactate is one of the most often measured parameters when performance testing athletes and prescribing exercise intensities [3].

Current off-the-shelf *Point of Care* (PoC) technologies (further detailed in Section II) necessitate a blood sample. While steps have been taken to speed up the process of measurement and analysis, the requirement of extracting blood is still considered a major inconvenience. In a hospital environment, this carries significant infection control risks, and the frequency of sampling is rarely sufficient for clinicians to understand whether intervention is necessary. Leading clinicians at Alder Hey Childrens Hospital (Liverpool, UK) suggest that even if patient blood is sampled and measured 4–6 times per day, as may be the case in intensive care environments, this does not readily enable one to understand if the lactate level is rising (i.e., worsening condition) or falling (i.e., recovery). Furthermore, in cases where the patient is an infant, the amount of blood available is small and so extraction of even 1–3 ml of blood represents a significant

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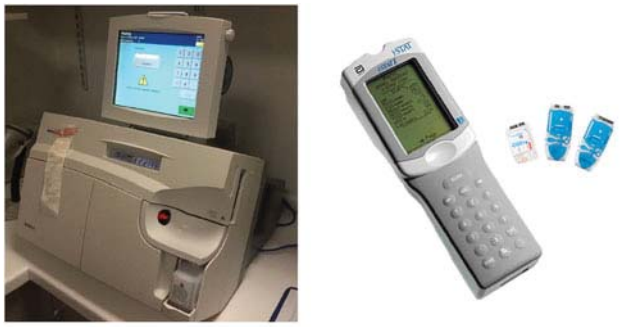


(a) (b)

Fig. 1. (a) An example of a Siemens BGA used by the authors, with capacity to measure and predict 24 different parameters based on an input of approx. 0.1 ml of blood, and (b) a handheld Abott BGA offering a greater level of portability and requiring 65 $\mu$L blood volume.

Fig. 2. Lactate Pro V2 LT–1730 in use by the authors.

percentage of overall blood volume if sampling frequently and leads to considerable stress to the patient.

For athletes, the issue of blood volume is less challenging since they are typically adult and in a good state of health. However, blood sampling is still cumbersome in sport since athletes typically have to reduce exercise intensity (or stop altogether) to provide a measurement which prohibits continuous high resolution monitoring during exercise.

This paper describes the use of a microwave-based sensor for the measurement of lactate non-invasively by simple application to the skin of a subject. The authors have worked in this area for some years [5]–[9] mainly considering in-vitro measurement of lactate and the varying types of microwave-based sensor design depending on specific applications. This work takes a considerable step forward, and shows the potential of in-vivo application of the sensor technology with human participants in a controlled environment.

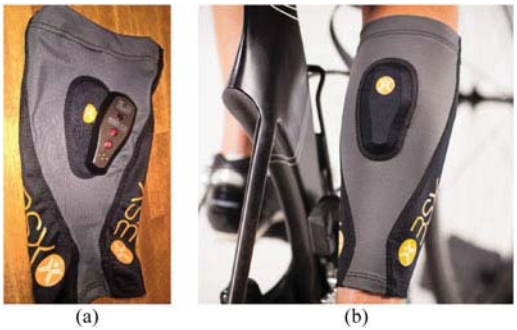
## II. State of the Art in Lactate Monitoring

In a clinical environment blood gas analysis has become an integral part of patient monitoring, particularly in the case of acute illness (i.e., in emergency wards or intensive care units), with clinical staff relying upon inclusion of blood gas analysers (BGAs) to assist in diagnostic workups and development of treatment plans [10]. A BGA, such as that shown in Fig. 1(a), can directly measure pH, partial pressure of oxygen ($PO_2$) and carbon dioxide ($PCO_2$), a variety of electrolytes, and various metabolites including glucose, lactate, blood urea nitrogen, and creatinine [11]. Compared with laboratory analysis, a BGA offers rapid measurement time (approx. 1 minute, excluding sampling and transit times) and a wealth of information upon which assessment of patient condition can be made. It is no surprise therefore that the BGA has become the gold standard against which clinicians compare emerging point of care technologies.

Measurement with a BGA is not without its drawbacks however, since the process of extracting blood from a patient is an invasive procedure, with potential complications which include artery occlusion, digital embolisation leading to digital ischemia, sepsis, local infection, pseudoaneurysm, hematoma, bleeding, and skin necrosis [12]. As a result of infection risk, resource availability, and patient capacity to provide blood, BGA does not give a high resolution assessment of patient condition over time, which many clinicians argue would provide information relevant to understanding the necessity and form of intervention. Furthermore, the drive toward more point of care monitoring equipment located at the patient bedside has clinicians looking toward smaller and more portable devices. Some attempts to produce portable BGAs, such as the Abott i-STAT device illustrated in Fig. 1(b), have been commercialised and studies show they give levels of accuracy for lactate comparable with larger desktop systems [13]. However, the required blood volume (65 $\mu$L), long sampling times (approx. 65 seconds) and skilled handling procedure preclude use at the bedside.

BGAs offer a broad range of measurements, but a number of devices have been released to the market that offer single metabolite measurement. These are typically based on an electrochemical principle, using an electrochemically sensitised strip which, when exposed to blood, changes its electrical properties. When inserted into a device designed to interface with these strips, users are able to obtain a lactate reading within 15–60 seconds. While these devices still require blood to be extracted from a subject, the volume requirement is significantly lower than a BGA–for example the Lactate Pro V2 LT–1730 system (see Fig. 2) used regularly by the authors requires only 5 $\mu$L of blood.

An in-depth study [14] considered the reliability of such handheld electrochemical devices, concluding that although all devices tested exhibited varying characteristic (error, accuracy), all could be used for longitudinal studies and have particular relevance in prescribing exercise regimes. A smaller study [15] also demonstrated that such electrochemical sensors give acceptable results in clinical settings, and some are approved for medical use, however there is little evidence to show significant uptake in this context. This is perhaps due to uncertainty regarding the unknown sources of error with point of care devices (e.g., temperature, operator training, equipment condition, etc.) when compared with clinical laboratory facilities [16], and the remaining infection control risk due to extraction of blood, albeit in smaller volumes. In addition, some caution against the use of a fingertip test for lactate due to inferior accuracy. Gaieski *et al.* [17] note that this may not be an issue in all patients,



(a) (b)

Fig. 3. BSX Insight athlete lactate prediction system, (a) with sensor removed from its wearable sleeve and (b) as worn by a cyclist.

but compares the case of those undergoing intensive care with those presenting at emergency departments. In the former case, patients will be given significant volumes of intravenous fluid which, coupled with continued capillary leak and decreased intravascular osmotic pressure, can lead to diffuse tissue oedema [18]. In the latter case however, patients are often hypovolemic, potentially decreasing the amount of extravascular fluid that enters a fingertip blood sample.

Devices such as the Lactate Pro and i-STAT represent the current state-of-the-art in terms portable point of care systems for determining absolute blood lactate, and work continues in this field to improve cost, reliability and accuracy. A comprehensive review of electrochemical sensor techniques to realise lactate measurement has been produced by Singh *et al* [19], and work by other researchers continues to improve this field through new fabrication techniques and methods to move toward wearables, with researchers utilising sweat rather than blood for lactate measurements [20], [21]. The desire for devices to be wearable is well known across a range of blood metabolites, to remove completely the need for blood extraction and revolutionise healthcare practices.

The options for non-invasive lactate monitoring remain limited for practitioners in either healthcare or sports, and perhaps the best example to reach the market is the BSX Insight lactate prediction system (see Fig. 3). This is a validated [22] wearable system to predict *lactate threshold*, the point at which the concentration of blood lactate begins to exponentially increase during exercise. This system uses near infrared (NIR) sensors to monitor oxygenation in the gastrocnemius muscle and, via a patented algorithm, detects inflection points in the muscle oxygenation curve at increased workloads.

Other optical based techniques for monitoring lactate are evident in the literature [23]–[27], however little of that work appears to have made a significant presence on the PoC market. Largely speaking, these types of devices combine a chemical approach (e.g., a colour change) which then infers a lactate concentration. However, these suffer from the same drawback as current electrochemical methods, namely the limited reusability of the sensitive elements of the device themselves. Boldt [16] demonstrates that costs from such point of care devices depend on many factors which can be categorised in terms of *pre-analytical*, *analytical* and *post-analytical* costs which may vary from one organisation to the next thus making the cost benefit difficult to establish.

## III. Electromagnetic Wave Sensors

A review of the current state of the art reveals that techniques available to practitioners in both clinical and sports contexts present challenges for measuring lactate in real-time. Most systems rely upon the extraction of blood, which presents infection risks and is a barrier to providing high-resolution lactate information. Furthermore, the single use model of portable electrochemical PoC devices, such as the Lactate Pro and others described in [14] pose challenges for clinical environments in terms of budgeting and training. While there have been steps to move toward wearable devices, those reported recently in the research domain, particularly for monitoring sweat, have a limited lifespan and therefore present similar issues.

Therefore, the authors have proposed the use of an electromagnetic (EM) wave sensor system, operating at microwave frequencies, to provide a chemical-free sensor for real-time monitoring of athletes. Although the main aim of the authors has been to develop the system for medical use, it is clear also that the technology has relevance to sport science, namely the monitoring of athletes to ensure applicability of training regimes, as well as to assist in their prescription.

EM wave sensors operating at microwave frequencies are seeing an increasing interest across a variety of applications, including for measurements in the food industry [28]–[31], for water analysis [33], as well as for in-vitro, minimally-invasive [36], [37] and non-invasive [38]–[40] medical purposes. The sensors can typically be characterised as requiring low power ($< 1$ mW) while retaining a good level of penetration into a target material so that they may assess properties beneath a surface–in this case, determination of blood lactate through the skin of a subject. The sensors are also highly adaptable, with cavities, fluidic channels, flexible and even fabric based devices being demonstrated by researchers. It is these characteristics, combined with their low-cost, that make them an interesting proposition across so many potential application areas.

In this work, measurements from the EM wave sensor (described in Section IV) are captured in the form of S-parameters for reflected ($S_{11}$) and transmitted ($S_{21}$) energy. As energy is coupled into the sensor, both the $S_{11}$ and $S_{21}$ signals vary depending upon properties of the analyte presented to the sensor, such as conductivity and permittivity [40]. Conductivity is a measure of a material's ability to conduct an electric current, whereas permittivity is a measure of how an electric field is affected by a dielectric medium. This is determined by the ability of a material to polarise in response to the field, and reduce the total electric field inside the material. Therefore, permittivity ($\varepsilon_r$) as defined in (1) relates to a material's ability to transmit an electric field and is a complex value which varies with frequency, and accounts for both the energy stored by a material ($\varepsilon'$) as well as any losses of energy ($\varepsilon''$) which might occur.

$$\varepsilon_r = \varepsilon' + j\varepsilon'' \tag{1}$$

The permittivity of a material is derived from a number of characteristics (e.g., temperature, chemical structure, molecular composition, etc.) and is a measure of various polarisation phenomena that occur over different frequency ranges when exposed to an alternating EM field [41]. This causes dipolar polarisation in polar molecules (such as lactate), which causes them to rotate over a time period proportional to their dipole moment and local conditions (e.g., viscosity). Since there is a delay between the dipolar polarisation and the applied alternating EM field, dispersions exist whereby the molecule does not have sufficient time to fully align to the field, giving rise to dielectric relaxation in the microwave region of the EM spectrum. A number of mathematical models have been developed by Cole and Cole [42], Cole and Davidson [43], [44] and Havriliak and Negami [49] to explain relaxation phenomena. It is based upon these principles that EM wave sensors, operating at microwave frequencies, can selectively detect molecules such as lactate.

## IV. Methodology

This section of the paper describes the sensor used during the work, the testing regime employed using cyclists to test the sensor response to lactate levels, and detail regarding placement of the sensor itself on participants.

### A. Test Regime

A testing regime was designed to enable the development of a lactate profile in participants. The regime was based on the use of a Lode Excalibur Sport ergometer, which enables increase in pedal resistance up to 1500 W. The protocol adhered to was phased as follows:

1) Begin with a rest period after fitment of sensors and other preparation for 5 minutes to enable stabilisation of a baseline lactate level;
2) Warmup for a period of 5 minutes at 80 W, encouraging participants to maintain a constant cadence (approx. 70-80 rpm) throughout;
3) Increment resistance every 2 minutes by 20 W, maintaining similar cadence, and maintain resistance increment regime until cyclist cadence falls below 60 rpm, indicating exhaustion.
4) Conclude with a 10-minute rest period to observe falling lactate post-exercise.

Throughout this test regime, measurements were taken with various devices as follows:

1) EM wave sensor measurements, comprising an $S_{11}$ and $S_{21}$ spectra, every 30 seconds (see Sections IV-B and IV-C for detail of the sensor and placement).
2) Blood lactate measurements using a Lactate Pro V2 electrochemical analyser, drawing blood samples from the tip of a finger on the left hand. In respect of the test regime, measurements were taken at the beginning and end of phase 1, the end of phase 2, every minute during phase 3, and then every 2 minutes during phase 4. This device was chosen not only due to its use in research work noted by other authors, but also due to it being one of the only such devices with medical approval.

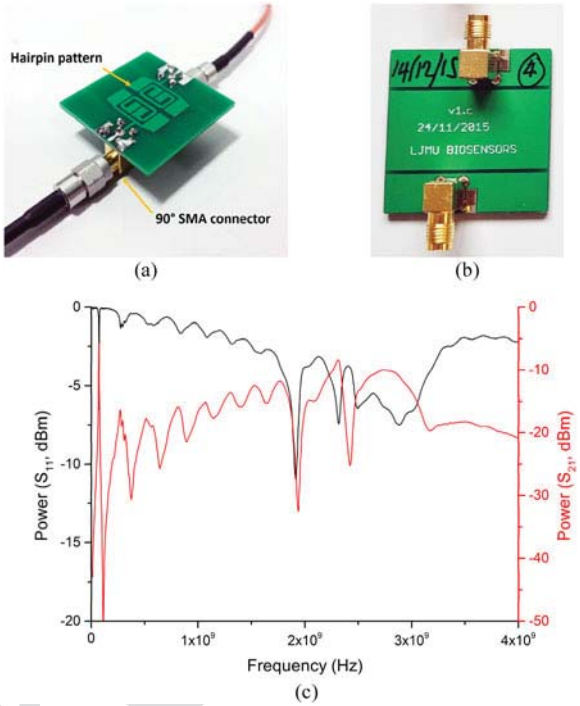



Fig. 4. The (a) top view and (b) bottom view of the physical sensor used in this work, and (c) S-parameter measurements (10 MHz–4 GHz).

3) Temperature measurements using a thermocouple taped to the arm and leg of participants.
4) Heart rate via a Polar V800 chest strap and watch combination.

All data was date and time stamped so that it could be retrospectively synchronised for comparison and analysis. Testing took place between December 2015 and May 2016, with 34 participants being recruited for the trial. The majority of the participants were male and aged between 25 and 40; 20% of the test subjects were female. There is no significant difference noted in expected blood lactate levels in these groups [2]. In total, from all participants, 367 lactate measurements were taken using the Lactate Pro V2 device, which acted as the reference method in this study.

### B. Electromagnetic Wave Sensor

For this work, a so-called *hairpin resonator* configuration of sensor has been designed and constructed as illustrated in Fig. 4(a). The sensor dimensions are 40 mm × 40 mm × 1.6 mm ($l \times w \times h$), with coaxial (SMA) feeds to the decoupled hairpin conductors.

The sensor is manufactured via a standard etching process, and the substrate is FR4 epoxy glass coated with a biocompatible mask that helps to prevent leeching of the copper conductor when worn by test subjects. The SMA connector contacts, shown as exposed in Fig. 4(a) were also masked with insulating tape when in use to prevent direct conductor contact with the skin. The rear of the sensor has a discontinuous ground plane that isolates ports 1 from port 2, as pictured in Fig. 4(b). This is to enable resonance of the device, while also ensuring that

the generated EM energy is directed toward the test material and providing the hairpin pattern with shielding from outside sources of interference.

S-parameter measurements for the sensor in air are illustrated in Fig. 4(c), showing that the senor tends to resonate at approx. 2 GHz. The sensor is designed such that the EM field closely coupled to the surface of the sensor, so that the field may penetrate through the skin of a target and interact with the fluids beneath. Maintaining a field close to the sensor surface has some advantages, namely that of reducing interference from objects other than the surface to which it is directly attached. The hairpin configuration of the device supports this notion well, and has the primary reason for its use.

Each sensor was connected to a separate Rohde and Schwarz ZVL13 Vector Network Analyser (VNA), and $S_{11}$ and $S_{21}$ measurements were recorded every 30 seconds via a bespoke LabView interface. The equipment was configured to capture data between 10 MHz and 4 GHz, with 4000 discrete data points recorded. The equipment was set to output 0 dBm (1 mW) power. The system configuration was selected based upon discussion with the project partners, as well as knowledge obtained in prior published (e.g., [5], [6], [8], [39]) and unpublished work. Previous work suggested that lactate and similar metabolites were quantifiable within this selected frequency range, although some uncertainty of the precise response frequency was present due previous work being ex-situ. From a commercial perspective, it was desirable to have an upper limit of 4 GHz to limit unit cost and size of a future "all-in-one" wearable solution.

### C. Sensor Placement

The sensor was placed on the left arm and leg of each participant; the leg due to this being the source of lactic acid production during exercise, and the arm due to blood being drawn from the finger tip for lactate measurement. Specific placement on the leg was over the *Rectus femoris* muscle and on the wrist approx. one-third distance between the wrist and elbow joints, where there would be significant blood flow owing to the *Arteriovenous fistula*. The left side of each participant was chosen simply due to accessibility within the testing space itself; the setup is shown in Fig. 5(a), with a closer view of the sensors adhered to a participant in Fig. 5(b).

The sensors were fixed to the participant using 75 mm × 100 mm surgical dressings, modified by cutting to allow the right-angled SMA connectors to protrude. Cables were secured to the limbs of the participant using a surgical tape, primarily for mechanical strength. Prior to placement, the sensor and area under test was cleansed with an alcohol wipe. No shaving or other preparation of the skin was undertaken.

## V. Results and Discussion

With 34 participants and a total of 367 blood lactate measurements, on average there were 11 blood samples taken per participant. Naturally, this varied depending on the fitness level of participants, and thus their ability to maintain a steady cadence despite the increasing work rate. Fig. 6 gives an indicative

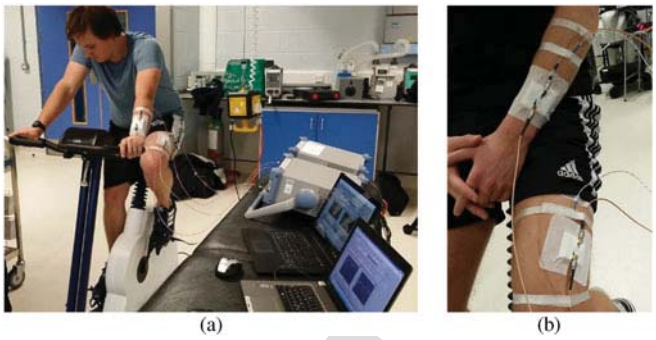



Fig. 5. (a) Experimental setup, with participant on ergometer and sensors attached to data acquisition hardware; (b) illustrates placement of sensors on both arm and leg with another participant.

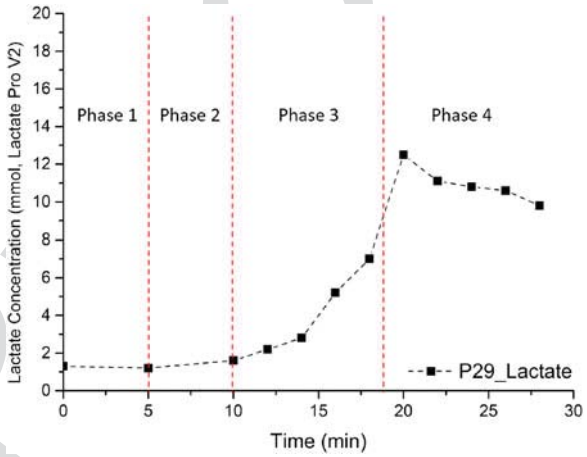



Fig. 6. Illustrating the test regime implemented, as described in Section IV.

lactate profile, with markers denoting the four phases discussed in the methodology section.

Separating the collected data into the groups 0–5 (48.2%), 6–10 (22.1%), 11–15 (26.3%) and >16 (5.8%) by lactate concentration (in mmol/L) gave an indication of data distribution. The majority of data collected is in the range of 0–5 mmol/L, with an approximately even split then between the 6–10 and 11–15 mmol/L groups. This is reasonable given participants would spend 5 minutes resting at the beginning and end of the resting regime, and a further 5 minutes warming up with little exertion (for most) experienced in this period. Few participants were able to raise their lactate level above 15 mmol/L, and so the data availability > 15 mmol/L for the purposes of creating relevant models linking EM sensor output with actual lactate level is limited.

A number of techniques were considered for providing robust analysis and models to test the correlation between EM wave sensor outputs and lactate level measured via Lactate Pro V2. Typical linear models, which have proven successful for in-vitro laboratory based tests (for example, see previous work of the authors in this field [5]–[9]) yielded relatively low correlation across the complete data set.

Therefore, for this work, the authors applied the approach of Pointwise Mutual Information (PMI), combined with Neural

Networks (NNs). PMI is a useful method for establishing the relationship between datasets and their supposed target data, and producing rankings that indicate the prominence of relationships. In this work, PMI was used to consider the relationship between the lactate value measured with the Lactate Pro V2, and the corresponding spectral data captured using the EM wave sensor. By doing this, it was possible to rank the spectral data by frequency in order of its relevance, and therefore reduce the spectral dataset being provided to the NN. This has significance for two reasons since: 1) it reduces the amount of irrelevant information being provided to the NN, thereby improving the likelihood of a suitable model being generated and; 2) it assists in the commercial objectives of the work since limiting the frequency of operation reduces cost, size and power requirements, all of which are barriers to implementing a wearable system.

A number of reduced datasets were produced using the PMI method, based on the top 10, 20, 50, 100, 250 and 500 frequencies of interest per measurement with the EM sensor, where originally data was acquired at 4000 discrete frequencies between 10 MHz and 4 GHz. This was replicated for data collected from both the arm and leg of each participant, as well as for each measurement mode, i.e., $S_{11}$ and $S_{21}$.

The NN approach was applied in Mathworks MatLab software for each dataset. The data was split into a training set (225 values, 65%), validation set (75 values, 22%) and test set (45 values, 13%). Splitting of the data was performed at random and 10-fold cross validation was performed. It is noted that the volume of data available for lactate levels exceeding 15 mmol/L is limited and so this part of the dataset was excluded from this machine learning exercise. Thus, the total number of lactate measurements available was reduced from 367 to 345. Results corresponding to each mode of measurement (i.e., $S_{11}$ or $S_{21}$), each location (i.e., arm or leg) and each frequency ranking (i.e., 10, 20, 50, 100, 250 and 500) were recorded, and are shown in Table I. On average, the best performing measurement was achieved with the sensor located on the arm, and with the $S_{11}$ mode of measurement; this consistently achieves an $R_{test} > 0.75$ once the number of discrete frequencies used for training approaches or exceeds 100. Typically speaking, the results produced from the NN modelling indicate that once 100 frequencies of interest are exceeded, there is a little relative improvement in model performance with further increase in the number of frequencies–this is evident in the plateau effect for both R and RMSE shown in Fig. 7.

The measurements conducted on the leg, also in the $S_{11}$ mode, tend to give next best performance, achieving an R-value of approx. 0.7 with 100 frequencies of interest fed into the training model. It is noted that the error in this case is reported to be higher, which is thought to be a result of the sensor (and particularly the cables) moving during the exercise, which increase noise apparent in the acquired data. A better mechanical fit of the sensor to the skin might resolve such issues, as might the future integration of the electronics into an all-in-one wearable device, which would completely remove the need for cables.

Fig. 8(a) illustrates the training model created for the top 100 ranked frequencies of interest using the $S_{11}$ arm combination, which tended to be most significantly concentrated in the

TABLE I
NEURAL NETWORK TRAINING AND TEST R AND RMSE VALUES FOR EACH MODEL CREATED ACROSS THE MEASUREMENT MODES, LOCATIONS AND NUMBER OF TOP RANKED FREQUENCIES FROM THE INPUT DATASET

| No. Freq | Data Type | $S_{11}$ Arm | $S_{21}$ Arm | $S_{11}$ Leg | $S_{21}$ Leg | Ave. |
|---|---|---|---|---|---|---|
| **10** | $R_{training}$ | 0.8719 | 0.7191 | 0.7669 | 0.7252 | 0.7708 |
| | $R_{test}$ | 0.5543 | 0.4268 | 0.5936 | 0.3682 | 0.4857 |
| | $RMSE_{training}$ | 2.0721 | 2.9301 | 2.7149 | 2.9213 | 2.6596 |
| | $RMSE_{test}$ | 4.4068 | 4.1791 | 3.7223 | 4.7677 | 4.2690 |
| **20** | $R_{training}$ | 0.8311 | 0.8897 | 0.8140 | 0.7998 | 0.8337 |
| | $R_{test}$ | 0.5267 | 0.2213 | 0.6107 | 0.2734 | 0.4080 |
| | $RMSE_{training}$ | 2.3543 | 1.9321 | 2.4589 | 2.5413 | 2.3217 |
| | $RMSE_{test}$ | 4.775 | 5.6949 | 3.7047 | 5.4118 | 4.8966 |
| **50** | $R_{training}$ | 0.9529 | 0.8424 | 0.9245 | 0.8016 | 0.8804 |
| | $R_{test}$ | 0.6456 | 0.50900 | 0.7060 | 0.5160 | 0.5942 |
| | $RMSE_{training}$ | 1.2949 | 2.2721 | 1.6149 | 2.5297 | 1.9279 |
| | $RMSE_{test}$ | 4.0165 | 4.0477 | 3.8603 | 4.278 | 4.0506 |
| **100** | $R_{training}$ | 0.9653 | 0.9225 | 0.8571 | 0.9469 | 0.9230 |
| | $R_{test}$ | 0.7827 | 0.3274 | 0.7270 | 0.2575 | 0.5237 |
| | $RMSE_{training}$ | 1.1087 | 1.6316 | 2.1857 | 1.3698 | 1.5740 |
| | $RMSE_{test}$ | 2.8786 | 5.1848 | 3.081 | 8.7872 | 4.9829 |
| **250** | $R_{training}$ | 0.9486 | 0.9607 | 0.9247 | 0.9765 | 0.9526 |
| | $R_{test}$ | 0.8047 | 0.4747 | 0.5700 | 0.3718 | 0.5553 |
| | $RMSE_{training}$ | 1.3589 | 1.1724 | 1.625 | 0.9148 | 1.2678 |
| | $RMSE_{test}$ | 2.7426 | 4.8635 | 4.6707 | 5.4387 | 4.4289 |
| **500** | $R_{training}$ | 0.9163 | 0.9589 | 0.7968 | 0.9606 | 0.9082 |
| | $R_{test}$ | 0.7632 | 0.5449 | 0.6871 | 0.3945 | 0.5974 |
| | $RMSE_{training}$ | 1.7621 | 1.228 | 2.5578 | 1.2061 | 1.6885 |
| | $RMSE_{test}$ | 3.242 | 5.0805 | 3.2657 | 5.743 | 4.3328 |
| **Ave.** | $R_{training}$ | 0.9144 | 0.8822 | 0.8473 | 0.8684 | - |
| | $R_{test}$ | 0.6795 | 0.4174 | 0.6491 | 0.3636 | - |
| | $RMSE_{training}$ | 1.6585 | 1.8611 | 2.1929 | 1.9138 | - |
| | $RMSE_{test}$ | 3.6769 | 4.8418 | 3.7175 | 5.7377 | - |

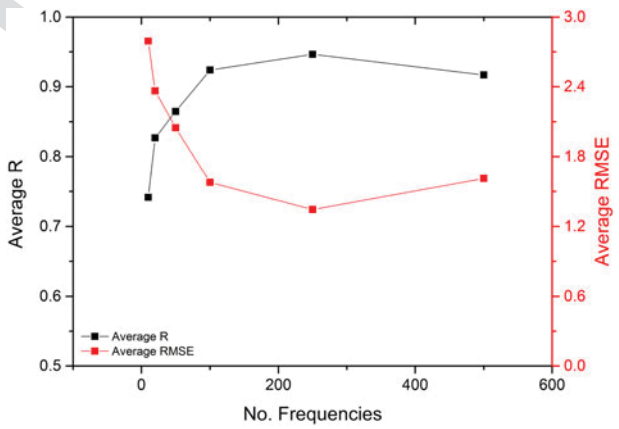



Fig. 7. Average R and RMSE values for all modes of measurement vs. number of frequencies used to create a prediction model.

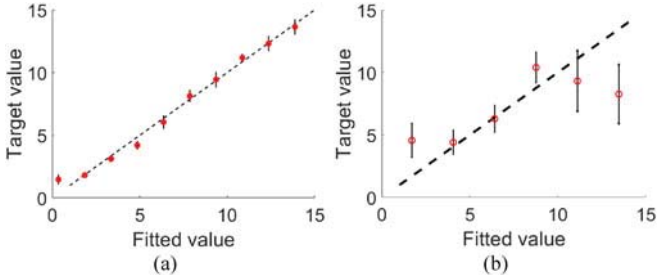



Fig. 8. Correlation for the top 100 frequencies selected via the PMI method for $S_{11}$ arm; (a) training model and (b) test data fit in the range 0-15 mmol/L

3.4–3.6 GHz region of the measured spectra. It is noted that the RMSE reported for the test data (see Table I) is typically higher than that for the training mode, which is to be expected with NN methods.

The data contained in Table I is relevant for the range 0–15 mmol/L, based upon the categories used to represent the distribution of lactate values collected. The best performing combination of sensor position and measurement mode in this study was the $S_{11}$ arm combination, which in part is thought to be a result of the arm location having little movement during the experimentation. Using the top 100 ranked frequencies, the training model error is 7.4%, and the test error 19.2% in the range 0–15 mmol/L. However, Fig. 8(b) demonstrates that the NN model does not perform well at lactate levels >12 mmol/L; in the range 0–12 mmol/L the test error is reduced to 13.4%.

It is planned to conduct further trials to augment the current collected data, which it is hoped will reduce the sensor error at higher lactate levels. Trial of the sensor on athletes for example will assist in this, since they will be able to maintain high lactate levels for longer and therefore provide more data in the range >12 mmol/L. Ideally this additional data collection should be coupled with the earlier suggestions regarding improved mechanical fit of the sensor to the skin.

A parallel study, conducted by the authors at Alder Hey Children's Hospital to assess the expected levels of blood lactate in patients undergoing intensive care, found that only 0.87% of blood samples reported a lactate concentration >12 mmol/L. This was based on 1,000 blood samples taken over a 3 month period and measured using the standard BGA method. This therefore suggests that the sensor, even in its current form, can report clinically relevant information.

A major benefit of real-time on-patient monitoring noted earlier was the potential to be able to monitor live patient information. Current blood sampling does not give enough resolution to understand whether a patient's lactate level is rising or falling, and therefore deciding on an intervention strategy can be challenging. Thus, being able to track the direction of lactate change is perhaps as important as knowing its absolute value. The capability of the sensor to do this is illustrated in Fig. 9, where all of the collected data from the 34 participants is overlaid with the predicted data from the NN model, trained using 100 discrete frequencies.

Temperature and heart rate were measured in this study to understand if they influenced the sensor output. It is known that temperature is crucial in the use of EM wave devices, particularly due to the resultant change in $\varepsilon_r$ [46]. During this study, it was noted that the average absolute skin temperature variation between the end of phase 1 and beginning of phase 4 was 2.28 °C (min 0.92 °C, max 4.30 °C). It was also noted that the temperature recorded by the thermocouple sensors tended to fall during exercise, most likely due to participant perspiration [47].

Heart rate on the other hand, tended to rise as work output increased from a resting average of 85 bpm to a maximum of 172 bpm. Notably however, whereas heart rate tended to fall almost immediately post-exercise, lactate level would continue to rise due to the latency inherent in lactate metabolism. As a result,

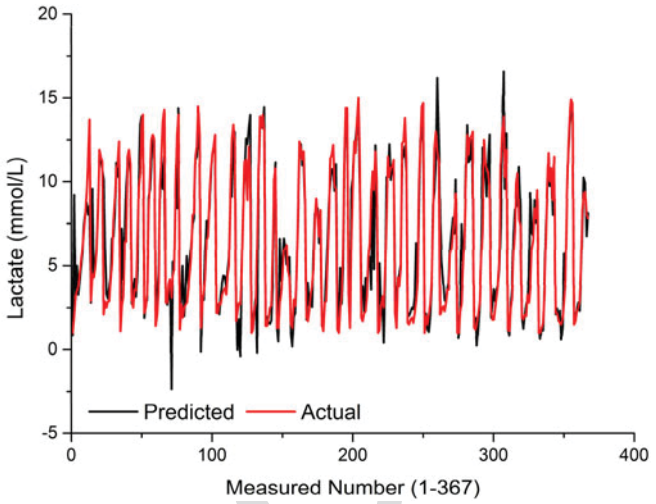



Fig. 9. Actual data measured vs. neural network model, highlighting the capability of the model to predict the lactate profile, not only absolute value.

both temperature and heart rate failed to yield a significant correlation with the EM wave sensor measurements, with $R < 0.4$ in both cases. This adds further weight to the previously discussed correlation between the EM wave sensor and blood lactate, as it shows that other parameters such as temperature and heart rate do not significantly influence the sensor.

## VI. Conclusion

This work has demonstrated the novel application of an EM wave sensor for the non-invasive real-time monitoring of blood lactate, as correlated with the well-known Lactate Pro V2 electrochemical analyser. In total 34 participants, generating a dataset of 367 blood lactate measurements, took part in the study through a static cycling test regime designed to promote a traceable blood lactate profile. Using a PMI method to reduce the necessary dataset acquired from the sensor, and a NN machine learning algorithm to create a predictive model, it was demonstrated that a reliable correlation $(R = 0.78)$ could be obtained when the sensor was configured in the $S_{11}$ measurement mode, and located on the arm of the test subjects. In the range 0–12 mmol/L lactate, the sensor was shown to have an error of 13.4%. In addition, it was demonstrated that this model has relevance in not only predicting absolute lactate values, but also tracking their direction for the purposes of, for example, prescribing patient interventions. Furthermore, it was shown that participant temperature and heart rate did not have a significant influence on the results. This work therefore shows the potential for EM wave sensors as PoC systems. Future work in this area will focus on two areas: (1) the collection of further data to improve the predictive model and; (2) the improvement of the sensor design toward an "all-in-one" wearable solution. The present study has provided useful information in this regard, since the best performance was noted in the $S_{11}$ measurement mode, and in the range of 3.4–3.6 GHz. This information will enable reduction of the number of cables (and the associated electronics) required for a commercial solution, in addition to focusing ef-

forts to enhance the sensor design in the noted frequency range for improved sensitivity and robustness of measurement, as well as a reduction in sensor size.

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## References

[1] J. Bakker *et al.*, "Clinical use of lactate monitoring in critically ill patients," *Ann. Intensive Care*, vol. 3, 2013, Art. no. 12.
[2] D. B. Andropoulos, "Appendix B: Pediatric normal laboratory values," in *Gregory's Pediatric Anesthesia*, ed. Hoboken, NJ, USA: Wiley, 2012, pp. 1300–1314.
[3] M. L. Goodwin *et al.*, "Blood lactate measurements and analysis during exercise: A guide for clinicians," *J. Diabetes Sci. Technol.*, vol. 1, pp. 558–569, 2007.
[4] N. C. Watson and S. O. Heard, "The use of lactate as a biomarker," *J. Intensive Care Med.*, vol. 25, pp. 301–302, 2010.
[5] J. H. Goh *et al.*, "Non invasive microwave sensor for the detection of lactic acid in cerebrospinal fluid (CSF)," *J. Phys., Conf. Series*, vol. 307, 2011, Art. no. 012017.
[6] A. Mason *et al.*, "Real-Time monitoring of bodily fluids using novel electromagnetic wave sensor," *J. Public Health Frontier*, vol. 2, pp. 201–206, 2013.
[7] R. T. Blakey *et al.*, "A fluidic cell embedded electromagnetic wave sensor for online indication of neurological impairment during surgical procedures," *J. Phys., Conf. Series*, vol. 450, 2013, Art. no. 012024.
[8] J. H. Goh *et al.*, "Using a microwave sensor as an online indicator of neurological impairment during surgical procedures," *Key Eng. Mater.*, vol. 453, pp. 368–372, 2013.
[9] M. Fok *et al.*, "A novel microwave sensor to detect specific biomarkers in human cerebrospinal fluid and their relationship to cellular ischemia during thoracoabdominal aortic aneurysm repair," *J. Med. Syst.*, vol. 39, 2015, Art. no. 37.
[10] A. Arias-Oliveras, "Neonatal blood gas interpretation," *Newborn Infant Nursing Rev.*, vol. 16, pp. 119–121, 2016.
[11] A. L. Gonzalez and L. S. Waddell, "Blood gas analyzers," *Topics Companion Animal Med.*, vol. 31, pp. 27–34, 2016.
[12] M. Brzezinski *et al.*, "Radial artery cannulation: A comprehensive review of recent anatomic and physiologic investigations," *Anesthesia Analgesia*, vol. 109, pp. 1763–1781, 2009.
[13] F. Ismail *et al.*, "The accuracy and timeliness of a point of care lactate measurement in patients with Sepsis," *Scandinavian J. Trauma, Resuscitation Emergency Med.*, vol. 23, 2015, Art. no. 68.
[14] J. M. Bonaventura *et al.*, "Reliability and accuracy of six hand-held blood lactate analysers," *J. Sports Sci. Med.*, vol. 14, pp. 203–214, 2015.
[15] S. Singh *et al.*, "The handheld blood lactate analyser versus the blood gas based analyser for measurement of serum lactate and its prognostic significance in severe sepsis," *Med. J. Armed Forces India*, vol. 72, pp. 325–331, 2016.
[16] J. Boldt *et al.*, "Point-of-care (POC) testing of lactate in the intensive care patient," *Acta Anaesthesiologica Scandinavica*, vol. 45, pp. 194–199, 2001.
[17] D. F. Gaieski *et al.*, "Accuracy of handheld point-of-care fingertip lactate measurement in the emergency department," *Western J. Emergency Med.*, vol. 14, pp. 58–62, 2013.
[18] H. A. Koomans and W. H. Boer, "Causes of edema in the intensive care unit," *Kidney Int. Suppl.*, vol. 59, pp. S105–10, 1997.
[19] K. Rathee *et al.*, "Biosensors based on electrochemical lactate detection: A comprehensive review," *Biochem. Biophys. Rep.*, vol. 5, pp. 35–54, 2015.
[20] W. Gao *et al.*, "Fully integrated wearable sensor arrays for multiplexed in situ perspiration analysis," *Nature*, vol. 529, pp. 509–514, 2016.
[21] E. L. Tur-García *et al.*, "Novel flexible enzyme laminate-based sensor for analysis of lactate in sweat," *Sensors Actuators B, Chem.*, vol. 242, pp. 502–510, 2017.
[22] N. R. Borges and M. W. Driller, "Wearable lactate threshold predicting device is valid and reliable in runners," *J. Strength Conditioning Res.*, vol. 30, pp. 2212–2218, 2016.
[23] T. McCormack *et al.*, "Optical immunosensing of lactate dehydrogenase (LDH)," *Sensors Actuators B, Chem.*, vol. 41, pp. 89–96, 1997.
[24] X. Wang *et al.*, "Glucose oxidase-incorporated hydrogel thin film for fast optical glucose detecting under physiological conditions," *Mater. Today Chem.*, vol. 1–2, pp. 7–14, 2016.
[25] C.-I. Li *et al.*, "Sol–gel encapsulation of lactate dehydrogenase for optical sensing of l-lactate," *Biosensors Bioelectron.*, vol. 17, pp. 323–330, 2002.
[26] S. A. Arnold *et al.*, "In-situ near infrared spectroscopy to monitor key analytes in mammalian cell cultivation," *Biotechnol. Bioeng.*, vol. 84, pp. 13–19, 2003.
[27] D. Lafrance *et al.*, "In vivo lactate measurement in human tissue by near-infrared diffuse reflectance spectroscopy," *Vibrational Spectroscopy*, vol. 36, pp. 195–202, 2004.
[28] A. Mason *et al.*, "Theoretical Basis and application for measuring pork loin drip loss using microwave spectroscopy," *Sensors*, vol. 16, 2016, Art. no. 182.
[29] S. G. Bjarnadottir *et al.*, "Assessing quality parameters in dry-cured ham using microwave spectroscopy," *Meat Sci.*, vol. 108, pp. 109–114, 2015.
[30] J. Yang *et al.*, "Rapid determination of the moisture content of milk powder by microwave sensor," *Measurement*, vol. 87, pp. 83–86, 2016.
[31] D. Agranovich *et al.*, "A microwave sensor for the characterization of bovine milk," *Food Control*, vol. 63, pp. 195–200, 2016.
[32] M. Jilani *et al.*, "A microwave ring-resonator sensor for non-invasive assessment of meat aging," *Sensors*, vol. 16, 2016, Art. no. 52.
[33] O. Korostynska *et al.*, "Electromagnetic wave sensing of $NO_3$ and COD concentrations for real-time environmental and industrial monitoring," *Sensors Actuators B, Chem.*, vol. 198, pp. 49–54, 2014.
[34] B. Camli *et al.*, "A microwave ring resonator based glucose sensor," *Procedia Eng.*, vol. 168, pp. 465–468, 2016.
[35] T. Chretiennot *et al.*, "Microwave-Based microfluidic sensor for non-destructive and quantitative glucose monitoring in aqueous solution," *Sensors*, vol. 16, 2016, Art. no. 1733.
[36] R. Blakey *et al.*, "Real-Time monitoring of pseudomonas aeruginosa concentration using a novel electromagnetic sensors microfluidic cell structure," *IEEE Trans. Biomed. Eng.*, vol. 60, no. 12, pp. 3291–3297, Dec. 2013.
[37] O. Korostynska *et al.*, "Microwave sensors for the non-invasive monitoring of industrial and medical applications," *Sensor Rev.*, vol. 34, pp. 182–191, 2014.
[38] M. Salazar-Alvarez *et al.*, "Label free detection of specific protein binding using a microwave sensor," *Analyst*, vol. 139, pp. 5335–5338, 2014.
[39] A. Mason *et al.*, "A resonant co-planar sensor at microwave frequencies for biomedical applications," *Sensors Actuators A, Phys.*, vol. 202, pp. 170–175, 2013.
[40] H. Choi *et al.*, "Design and in vitro interference test of microwave non-invasive blood glucose monitoring sensor," *IEEE Trans. Microw. Theory Tech.*, vol. 63, no. 10, pp. 3016–3025, Oct. 2015.
[41] R. T. Blakey and A. M. Morales-Partera, "Microwave dielectric spectroscopy–A versatile methodology for online, non-destructive food analysis, monitoring and process control," *Eng. Agriculture, Environ. Food*, vol. 9, pp. 264–273, 2016.
[42] K. S. Cole and R. H. Cole, "Dispersion and absorption in dielectrics I. Alternating current characteristics," *J. Chem. Phys.*, vol. 9, pp. 341–351, 1941.
[43] D. W. Davidson and R. H. Cole, "Dielectric relaxation in glycerine," *J. Chem. Phys.*, vol. 18, pp. 1417–1417, 1950.
[44] D. W. Davidson and R. H. Cole, "Dielectric relaxation in glycerol, propylene glycol, and n-propanol," *J. Chem. Phys.*, vol. 19, pp. 1484–1490, 1951.
[45] S. Havriliak and S. Negami, "A complex plane representation of dielectric and mechanical relaxation processes in some polymers," *Polymer*, vol. 8, pp. 161–210, 1967.
[46] G. P. Srivastava and Y. P. Varshni, "Variation of dielectric constant with temperature," *Physica*, vol. 22, pp. 584–586, 1956.
[47] M. Torii *et al.*, "Fall in skin temperature of exercising man," *Brit. J. Sports Med.*, vol. 26, pp. 29–32, 1992.

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