A Model for Safe Transport of Critical Patients in Unmanned Drones with a ‘Watch’ Style Continuous Anesthesia Sensor

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We envision unmanned aerial vehicles (UAV) for rapid evacuation of critically-ill patients from hazardous locations to health care facilities in safe zones. For safety, medical teams accompany patients to monitor vital signs and titrate anesthesia dose during transport. UAV transports would require continuous automated remote monitoring of both vital signs and of sedative dose to be feasible and safe. Volatile anesthetics (isoflurane) are the only anesthetic agents that can be monitored continuously with infrared spectroscopy (IR) devices; but unsuitable for transport. Our objective is to devise a safe UAV transport protocol incorporating novel technology for gas monitoring. Our group has developed and tested a minaturized wearable fuel cell sensor that can detect isoflurane gas vapors as low as 40 ppm (within therapeutic range) with a sensitivity of 0.0112 nA ppm$^{-1}$ cm$^{-2}$. Ambient signal interference was resolved by principal component analysis (PCA). Data variance of 1st and 2nd principal components was 88.68% and 11.31%, respectively. The PCA regression model reported here can determine accurate Isoflurane concentrations. Electronic IoT platform has been built constituting micro-fuel cell, miniaturized electronic components with Bluetooth. This wearable sensor can be incorporated into a comprehensive life support system for casualty evacuation in conjunction with autonomous UAV emergency medical operations.

Increasing numbers of critically-ill patients require rapid transfer to critical care units for life saving specialist intervention. Transporting critically wounded war fighters safely from the battlefield to trauma centers while monitoring vital signs is crucial to life saving. Unmanned aerial vehicles (UAVs) or drones have been extensively studied for quick transport of medical supplies. It won’t be long before these autonomous drones are fitted with bio-sensors for monitoring of vitals during aeromedical transport. During these transports, it is essential to administer, titrate and continuously monitor anesthetic action for sedation and pain control. Intravenously administered propofol is the most commonly used anesthetic for sedation but has no analgesic properties and its plasma concentration cannot be monitored continuously. Only volatile gas anesthetics such as isoflurane are both sedatives and analgesics and their dose monitored on a continuous basis via detection of exhaled concentration using infrared spectroscopy.

One such widely used gas anesthetic compound is isoflurane (Forane or 1-chloro-2, 2,2-tri-fluoro-ethyl di-fluoro-methyl ether). In hospitals, 2% to 3% isoflurane gas mixed with oxygen, air or nitrous oxide is delivered via inhalation with anesthesia machines equipped with vaporizers. The inhaled and exhaled concentrations are monitored with infrared spectroscopy sensors built-into modern anesthesia machines. However, these anesthesia machines are not designed to operate in the field or during patient transport. Therefore, in order to facilitate safe autonomous UAV transport there is a need for an easy to use anesthetic monitoring and feedback systems. In this work, a miniature fuel cell sensor employing a pattern recognition method to monitor isoflurane vapor concentrations and multivariate calibration is reported. The role of this wearable anesthesia sensor in a comprehensive autonomous transport system has been given in Figure 1. The anesthesia sensor reading can be monitored remotely, and an automated feedback loop system consisting of inhaled or exhaled isoflurane delivered via infusion pump can be used to administer isoflurane to maintain the anesthesia within therapeutic range during transport.

Other than autonomous transport applications for UAV, the proposed IoT device can be valuable in (i) conventional battlefield combat casualty care and for anesthesia delivery onboard naval vessels; (ii) critical care in austere environments such as oil rigs, cargo ships, polar regions or in disasters; (iii) hospitals in underdeveloped regions with substandard anesthesia and surgical resources; (iv) professional organizations tasked with regulating limits of volatile anesthetic gas exposure on anesthesia care providers and other health care workers. According to National Institute for Occupational Safety and Health (NIOSH), the recommended exposure limit (REL) is 2 ppm for isoflurane. It was reported that there were approximately 100,000 medical scientists, surgeons, anesthesiologists, nurse anesthetists in the United States frequently exposed to waste anesthetic agents in their workplace. The proposed device in this work will help to detect the occupational exposure of waste anesthetic vapors in ambient air on healthcare workers.

Among various analytical sensors, metal oxide-based and infrared sensors are the most commonly used to monitor isoflurane gas concentrations. The major disadvantages of infrared sensors are their fragility, high operational and maintenance cost and requirement for regularly scheduled manual calibration. By default, they are built into the anesthesia machine with anesthesia gas vaporizers, which makes the system bulky. Although metal oxide-based sensors are smaller in size and sensitive, they are not selective, and need high operating temperature and power management. Therefore, a fuel cell sensor was used in this work for isoflurane detection which was miniaturized, capable to operate at low temperature, and eliminates the necessity of additional equipment for its operation.

Fuel cells are electrochemical devices that convert chemical energy to electricity. These devices exist in different forms specifically designed for its intended role. For example, miniaturized proton exchange membrane (PEM) fuel cells have been widely used in breathalyzers. The PEM fuel cells operate at low temperatures and therefore can be used as a sensor in wearable devices. Compared to
infrared based sensors, PEM fuel cell sensors are portable and its long working life is an advantage. However, all the above-mentioned sensors suffer from high interference due to humidity and other volatile compounds. Due to high signal interference in the multivariate environment, these sensors cannot be used for continuous monitoring. These signal interferences also lead to signal fluctuation and overlapping over time. Therefore, the standalone sensor provides false positive and negative results, which makes the linear calibration model obsolete for quantification of isoflurane or any volatile compound. Moreover, these environments exist in biological fluids and vapors. The fuel cell sensors alone are incapable of specifically separating a single volatile compound signal in biological environment. The non-specific detection of existing sensors is mainly due to the PEM dependency on different ambient parameters such as, humidity, pressure, and temperature for its function.

Data mining and pattern recognition techniques have become popular for selective and accurate detection of volatile compounds in the multi-dimensional environment. These tools interpret datasets from single or multiple sensors to selectively quantify a specific compound. This can be achieved by training the computational algorithms with large and diverse data sets before implementing the sensor for real-time measurements. Among these techniques, multivariate statistics is a robust tool which provides precision measurement and classification. The most common multivariate statistical techniques are principal component analysis (PCA), discrete factorial analysis (DFA), and partial least squares analysis (PLS). PCA is a pattern recognition method that reduces the redundancy and dimensionality of the data sets through simplification and interpretation of the data by the first few major components. These data plots contain most of the variance in the data without having preceding information on the data sets. This work presents a study of PCA with predictive regression model driven isoflurane biosensor.

Experimental

Materials and methods.—Nafion424 reinforced with poly-tetrafluoro-ethylene (PTFE) from Sigma Aldrich was used as proton exchange membrane (PEM). A micro-perforated stainless-steel sheet (thickness 200 μm, 180 μm pore size) coated with Nickel from the Advanced Materials Engineering Research Institute, Florida International University was employed as the electrode material. Nickel was deposited on stainless-steel electrochemically following Watt’s deposition technique as mentioned previously. Nickel chloride anhydrous, nickel sulphamate, boric acid, 95% sulfuric acid (H₂SO₄) and 37% hydrochloric acid (HCl) were obtained from Sigma-Aldrich for electrodeposition. Lead and nickel sheet were purchased from McMaster-Carr for the electroplating process. Acetone (95.27%) and isoflurane were obtained from Fisher scientific Inc. and Baxter healthcare corporation. All other used chemicals were of analytical grade.

The preparation of aqueous solutions was done with de-ionized (DI) water. A vacuum oven (Model 280A) was purchased from Fisher Scientific. A hydraulic hot press (model 2100 from PHI), was used to prepare the membrane electrolyte assembly (MEA) of the fuel cell sensor. Two different potentiostats: CHI 1230B having MC470 Replicator 2) for the experiments. A 3D printed chamber was built using Makerbot (model: Replicator 2) for the experiments.

Sensor fabrication.—The area of the fuel cell working (anode), counter (cathode), and reference electrodes were (1 cm x 0.8 cm), (1 cm x 1 cm) and (1 cm x 0.2 cm), respectively. The electrolyte membrane, Nafion (2 cm x 1 cm) was sandwiched in between the nickel-clad stainless-steel electrodes to form the membrane electrode assembly (MEA). Since the counter electrode is the primary current accumulator, the overall area of the counter electrode was designed to be larger than the working and reference electrodes. In contrast, the area of the reference electrode was designed to contain the smallest surface area. This distance (L = 0.2 cm) was maintained greater than three times (L/h > 3) of the membrane thickness (h = 0.018 cm) to avoid asymmetrical current distribution and potential variation on working electrode due to edging effect. The sandwich structure of MEA was obtained by hot pressing at 80 °C and 2500 psi for 10 min. Before experiments, a constant relative humidity was maintained for each sensor, by treating the sensors in humid chamber for 30 min at room temperature (25 °C).

Sensor set-up and measurement.—A chamber was used for the sensor setup, where the cathode had a window of (1.5 cm x 1 cm) so that the atmospheric oxygen can interact with the counter electrode. On the other side, the sealed chamber had an opening of 1 cm diameter cylinder (1.57 cm²) to expose the working electrode to the isoflurane environment. During the experiment, the headspace remained constant at a height of 2 cm. During the measurement, the concentration of isoflurane at headspace was calculated using Henry’s formula at constant temperature, as follows:

\[
\text{Concentration of isoflurane in the liquid phase} = K_{w/a} \times \text{Concentration of isoflurane in the vapor phase}
\]

Here, \(K_{w/a}\) is the ‘Ostwald partition coefficient’. If a diluted isoflurane solution is brought to equilibrium in air, the partial pressure of isoflurane in vapor phase is a function of the system temperature (25 °C) and the isoflurane concentration in liquid phase. The partition coefficient of isoflurane is 1.18 at 25 °C. Different concentrations (40 ppm, 80 ppm, 160 ppm, 320 ppm, and 775 ppm) of isoflurane were exposed...
Anodic reaction can be expressed by the Equations 2–4, where oxidation at the anode and reduction at the cathode. The reaction involves oxidation at the anode and reduction at the cathode. The reaction, rate of diffusion, and rate of evaporation are the limiting parameters. If the concentration of the interfering compound (example: humidity) is much higher than that of isoflurane, the sensors’ accuracy will be low. These limitations of the fuel cell sensor were studied in the presence of isoflurane with five different concentrations in ambient temperature and humidity as given in the experimental section. Each concentration was measured eight times and plotted in a linear plot as given in Figure 2a. Even though the current signal increases with respect to the concentration of isoflurane, the linear calibration plot shows: (i) significant overlapping in between concentrations, (ii) excellent linearity with $R^2 = 0.9307$, and (iii) very low sensitivity (0.0112 nA ppm$^{-1}$ cm$^{-2}$). The magnification of each data point (in Figure 2b) reveals that there was a significant overlapping of the signals in between the different concentrations, which impedes reliability in ppm level of detection. For the overlapping, between 80 ppm to 160 ppm and 160 ppm to 320 ppm were determined as 2.03 nA and 0.9 nA, respectively. Although the sensor shows excellent linearity, its poor sensitivity and overlapping of the signals in the calibration curve significantly affects the determination. To overcome these calibration issues, PCA was explored.

**Reaction mechanism.**—The reaction mechanism of the fuel cell involves oxidation at the anode and reduction at the cathode. The anodic reaction can be expressed by the Equations 2–4, where oxidative addition of isoflurane occurs instead of direct oxidation reaction.

**Anode reaction:**

$$\text{Ni} + R - \text{Cl} \rightarrow \text{RNi(II)}^- + \text{Cl}^-$$  \[2\]

$$\text{Cl}_2 + \text{H}_2\text{O} \rightarrow \text{HCl} + \text{HClO}$$  \[3\]

$$4\text{HCl} + 2\text{Ni} + 12\text{H}_2\text{O} \rightarrow 2\text{NiCl}_2.6\text{H}_2\text{O} + 4\text{H}^+ + 4\text{e}^-$$  \[4\]

where, R-Cl is the isoflurane. As given in Equation 3, the by-product HCl gets oxidized on the anode and the electrons are produced in this process. On the cathode, the oxygen gets reduced as given in Equation 5.

**Cathode reaction:**

$$\text{O}_2 + 4\text{H}^+ + 4\text{e}^- \rightarrow 2\text{H}_2\text{O}$$  \[5\]

During this reaction, the electrons and H$^+$ ions flow from anode to cathode generating faradic current proportional to the concentration of isoflurane. This faradaic current was detected by amperometric method and for this study, the biasing voltage across working and counter electrodes, avoiding polarization of the reference electrode.23 All experiments were executed at a temperature of 25°C, pressure of 101.325 kPa and humidity of 42%.

**Results and Discussion**

**Fuel cell sensor response for isoflurane.**—The amperometric signals from different concentrations of isoflurane exposure varies causing signal overlapping at narrow concentration ranges. In the case of low concentration and low measurement volumes, the rate of the reaction, rate of diffusion, and rate of evaporation are the limiting values (d) were 14.3088 and 1.8255, respectively. Here, the number of dimensions of the principal components, $k = 2$ in the subspace and

$$\text{PC}_k = \sum_{j=1}^{n} a_{ik} x_{ij}$$  \[6\]

where $n$ is the number of variables and $a_{ik}$ is the eigenvector for the $i_{th}$ variable. Then the original data was multiplied by the eigenvectors to re-orient the data onto the new axes, and these newly oriented data were plotted subsequently.

For the mathematical calculations, two response variables: steady state current ($I_{ss}$) and difference ($\Delta I$) in between of $I_{ss}$ and control signal considered, as shown in Figure 3a. 40 × 2 matrix was created for each variable and 5 datasets (5 different concentrations) contains 8 × 2 matrix. The mean of each data set was governed and standardized. A covariance matrix was developed for those two variables and the eigenvectors (V) were determined from this matrix. The eigenvalues (d) were 14.3088 and 1.8255, respectively.
where \( R \) and \( C \) are the scores and loading matrix respectively. The eigenvalues (or, eigenvectors) are equal to the principal components (\( k = d \)); therefore, both were considered as principal components. The data variances of first principal and second principal components are 88.68% and 11.31%, respectively. The final datasets were plotted from the standardized eigenvector data. It is observed from the plot that there is a marginal overlap between the domains of 160 ppm, 320 ppm, and 750 ppm.

Results show that (in Figure 3b), data can be separated into five different clusters according to specific concentration, which removed the redundancy and reduce the dimensionality of the linear calibration data of isoflurane. The same figures show 8 data points having maximum of 2 outliers from each cluster or concentration group. The clusters are obvious and distinguishable, though there are few overlapping in between of the data points due to indefinite variables (Figure 3). The indefinite variables can be listed as: (i) fuel cell membrane degradation over time, (ii) electrode surface fouling, (iii) membrane water content variation and (iii) temperature variation. It is observed from the plot that the cluster of 750 ppm dispersed more comparing with the other data sets due to the above-mentioned reasons. Though the clusters of the PCA are isolated from each other for the five different concentrations, this cluster model is incapable to determine any regression model for the isoflurane concentrations within the physiological range.

**Regression analysis for calibration.—** The objective of this study was to develop a PCA regression model from the data matrix. It was achieved by considering all the data points from the data matrix of the above-mentioned variables. In these calculations, the matrix was expressed in another form given in Equation 7.

\[
D = RC
\]

where \( D \) and \( C \) are the scores and loading matrix respectively. The eigenvalues (d), eigenvectors (V) and covariance matrix (Z) are directly related with the data matrix, D. To minimize the residual error the eigenvectors were derived by subtracting \( D \) and \( V \) from \( Z \). This iteration process was continued for eigenvectors till the eigenvalue reached below 0.001 of the maximum one. Equation 7 was modified by employing a transformation matrix as \( R \) and \( C \) matrices, which do not exhibit any chemical and physical connotation. This transformation can be executed as follows:

\[
D = (RT)(T^{-1}C)
\]

Here, \( T \) is a square matrix having with a dimension ‘n’. Here, n is the number of significant factor which determined by PCA. This transformation matrix can be expressed as below:

\[
T = \begin{bmatrix}
xcos(\delta) & -ysin(\delta) \\
ysin(\delta) & wcsin(\delta)
\end{bmatrix}
\]

The values of the coefficient \( x, y, z, \) and \( w \), are unity when this matrix is orthogonal or else it can be determined considering the information of the real factors. In our case, \( x = 1, y = -2.5, z = 2, w = 5, \) and \( \delta = 354^\circ \). For regression fitting, loading fractions \( C_1 \) and \( 1-C_1 \) were determined empirically from PCA and fitted with respect to concentration of isoflurane, as shown in Figure 4. As all the experimental parameters are constant, the sum of the loading fractions was approximately unity. Therefore, the regression plot was obtained from loading fraction (\( 1-C_1 \)) vs. concentration (c). A polynomial function was fitted with the regression curve using MATLAB following the Equation 10 below:

\[
c = \alpha(1-C_1)^2 + \beta(1-C_1) + \gamma
\]

The values of coefficient \( \alpha, \beta, \) and \( \gamma \) are \( 1.87 \times 10^4, -2.437 \times 10^4, \) and \( 7.974 \times 10^4, \) respectively. Any isoflurane concentration within the physiological range can be determined by fitting the loading fraction (x) in this regression model, as shown in Figure 4.

**Operation of the miniaturized potentiostat.—** A wearable platform (Figure 5a) with a miniaturized potentiostat has been developed for a sustainable solution for isoflurane detection. The fabricated
The functionality of the potentiostat has been reported previously.\textsuperscript{21,39} The detection method used in this system was amperometric and the output voltage, \( V \), is the current, generated from the micro fuel cell, \( I_w \) represents output voltage, \( V_{\text{REF D}V} \) represents divided reference voltage, and \( R_{\text{f}a} \) is the feedback resistance of the trans-impedance amplifier (shown in Figure 5d). This detected current \( (I_w) \) corresponds to the concentration of isoflurane which can be determined through calibration. The current from LMP91000 is converted to a potential and fed to the internal analog-to-digital converter (ADC) of the wireless microcontroller. This information is then sent wirelessly via Bluetooth to the end device (e.g. Bluetooth hub) which can send the data to the cloud.

### Power management of wearable device

The algorithm for precise calibration requires computational power which is demanding on both devices used. Hence, the calibration algorithm for precise results can be done on the cloud once the data is uploaded. This saves battery power and comparatively limited computational power over the device and Bluetooth hub. Power consumption of the device depends on different parameters: i. run time current drawn from the central processing unit (CPU), ii. BLE transmission and communication; and iii. LMP91000’s amperometric operation. Since most of these operations only occur for only the emergency period, the modules that run them can be pushed to a lower power state, thereby reducing its consumption. The CPU runs for a short time during BLE transmission and ADC of analog output from LMP91000. The remaining time can be utilized by the CPU to run other peripheral operations consuming \( \sim 2.6 \mu A \) at a lower power. LMP91000, while in amperometric mode, consumes \( \sim 10 \mu A \). It consumes an average current of \( \sim 7.95 \mu A \) over the time with a total uptime of 39%. Including \( \sim 5 \mu A \) for cell conditioning, the current for this sensor is calculated as 9.75 \( \mu A \) with the LMP in ‘stand mode’ for 60% of the time. While the nRF51822 runs for \( \sim 5 \) seconds at a lower power from the CPU, it can be shown that the total power consumption is \( \sim 56 \mu W \). Using a 3.7 V and 365 mAh battery, the operational lifetime of the system is \( \sim 5 \) days.

### Database management and user interactivity

The database system was designed around the required flow of information which is a general design for such systems (shown in in Figure 6a). The device captures the raw data and sends it via Bluetooth low energy or Bluetooth smart to a compatible hub. The hub serves as a gateway for the data to the cloud. The cloud hosts the database, storing data of relevant subjects/ users securely. The data can be accessed in a hierarchical scheme with server admin having the highest level of access. This is to ensure proper handling of sensitive medical information. Analytical tools can be built on the cloud to provide data analysis for corresponding isoflurane level in blood. An APP or a web portal was developed at the end interface for the anesthesiologist to monitor this data.

The database system consists of three layers (shown in Figure 6b): i. user interface (UI), ii. logic interface, and iii. data subsystems. Each of the three layers of this system be a subsystem of the whole. User Interface allows the anesthesiologist to control the system with touchscreen presses. It provides him an option to scan for and connect to a device, initiating the connection services in the next layer via an APP or a web portal. The UI displays to him the state of the patient and measurements of the isoflurane concentration in blood and allows him to select what kind of graphs they would like to view, as shown in Figure 6b. The UI was programmed in Java and XML. Logic is the bridge in between of the UI and data subsystems and it transmits data between the UI and the data subsystems (shown in Figure 6b). This subsystem is made up of the BLE Connection service and the Database Connection service. They allow the APP to connect to the micro-fuel cell sensor device and the database, respectively. The BLE Connection service also manages this sensor on the device and formats the data from them to make it readable. Contrarily, data subsystems consist of the BLE biosensing device, where the data originates from, and the database, where the data is stored. In between this, the data moves through the Logic layer for processing. The database runs on a MS SQL Server.

### Conclusions

We have proposed novel anesthesia monitoring modalities, including a novel miniaturized wearable biosensor that can detect therapeutic concentrations of volatile anesthetic on a continuous basis to facilitate safe transport of critically-ill patients in austere environments using UAV (ambulance drones). During testing of the isoflurane sensor PCA and its predictive regression analysis were successfully implemented for the isolation of signals in the sub-nano ampere range of the isoflurane data. The conventional linear calibration method has limitation to

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Figure 5. (a) Wearable device for isoflurane detection, (b) Design of micro-fuel cell sensor (c) Printed circuit board of four layers miniaturized potentiostat (left) it’s size, and (right) it’s design, (d) LMP91000 potentiostat integrated with three electrodes micro-fuel cell sensor.
isolate signals for minute fluctuations due to lower sensitivity (0.0112 nA ppm⁻¹ cm⁻²), which has substantial standard deviations. PCA accurately classified and discriminated different concentrations in the data subspace. The eigenvalues for two variables were 14.3088 and 1.8255, respectively which inferred the command of 1st principal component (88.68%). The cluster plot of PCA is unable to demonstrate the relationship in between of inter-calibration points. Therefore, a predictive model is derived from PCA which can be employed for the regression fitting. A miniaturized fuel cell sensor was constructed in a wearable platform for isoflurane detection that can operate in a low power mode having with 5 days battery life.

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