Sensors and Actuators A 314 (2020) 112216

Contents lists available at ScienceDirect

Sensors and Actuators A: Physical

journal homepage: www.elsevier.com/locate/sna

An arduino-based sensor to measure transendothelial electrical resistance

Curtis G. Jones, Chengpeng Chen*

Department of Chemistry and Biochemistry, University of Maryland Baltimore County, MD, United States

ARTICLE INFO

Article history:
Received 8 June 2020
Received in revised form 14 July 2020
Accepted 18 July 2020
Available online 26 July 2020

Keyword:
TEER
Arduino
biophysical
Endothelial cells

ABSTRACT

As the most popular microcontroller, Arduino is gaining interest for prototyping and optimizing instruments. Here, we report for the first time the use of Arduino as a standalone instrument to measure cell barrier integrity. Specifically, a transendothelial/epithelial resistance (TEER) meter was fabricated with an Arduino unit. TEER is an essential biophysical measurement to evaluate the integrity of biological barriers. Characterization of the device showed that the meter could accurately measure TEERs between 132 and 82,500 $\Omega{\cdot}cm^2$ with <3% errors, which covers the typical TEER ranges. The temporal resolution, measurement duration, and electrode configurations can be customized to meet a broad range of experimental designs. We have successfully applied the meter to measure the TEERs of endothelial cell monolayers, finding that cells treated with histamine had lower TEER values compared to untreated cells ($793.4 \pm 190.5\ \Omega{\cdot}cm^2$ vs. $3027.5 \pm 664.4\ \Omega{\cdot}cm^2$; $p < 0.001$), which were validated and consistent with literature standards. In conclusion, we invented a low-cost Arduino-based TEER sensor capable of accurately measuring TEERs in relevant biological ranges. We also included detailed tutorials in the supplementary information to promote translation of the technology.

1. Introduction

Endothelial andepithelial cells form biological barriers in every organ throughout the body; endothelial cells comprise the inner linings of blood vessels, and epithelial cells form protective wrappings along the exterior of vital organs such as the lungs and liver [1–3]. The tight junctions between the cells are critical for the maintenance of whole-body homeostasis by controlling the permeability of substances across the cellular barriers that separate the luminal and abluminal sides of the body [4]. Therefore, the permeability of endothelial/epithelial cell monolayers has been widely studied in physiological and pharmaceutical research [5,6]. This aspect of biological behavior is commonly characterized by electrical resistance. Transendothelial/epithelial electrical resistance (TEER) is a quantitation technique to measure the permeability of cellular barriers [7,8], which measures the electrical resistance across a monolayer of cells [9]. With tightly packed cells, a high resistance value is obtained because the barrier prevents the charge exchange, while loosely packed cells reduce the charge blockage and thus causing resistance to drop [10].

Although commercial TEER meters are available, these bulky systems are costly (thousands of USD) and inflexible for customization in specific applications, which can yield significant hindrances to researchers looking to implement this into their existing experimental systems. Given the fact that TEER detection is indispensable in numerous research activities, new technologies that are cost-effective, simple, and customizable are needed. TEER is essentially an electricity-based biophysical measurement. The cellular barrier being measured is treated as a resistor and can be detected using simple circuitry. In the past few years, microcontrollers have risen in popularity for electrical signaling and general programming, of which Arduino is the most popular platform because of its scalability, simplicity (open source programming), and low price point [11–13]. Indeed, Arduino has found applications in fabricating/controlling instruments in the scientific community for both research and educational purposes. For example, Kennedy et al. applied Arduino for automated data acquisition from gas chromatography and electrophoresis [12]. Chen et al. developed an Arduino-based controller to process and measure samples on mass spectrometry robotically [14]. Recently, an Arduino-carbon dioxide fountain was reported as a noteworthy experiment to enhance students' understanding of basic chemical concepts [15].

In this paper, we present our invention of a customizable TEER meter based on Arduino, which enables continuous measurements and automated data recording. Both standard and cell-based experiments were conducted to validate the accuracy and usefulness

* Corresponding author at: Department of Chemistry and Biochemistry, University of Maryland, Baltimore County, Baltimore, MD, 21250, United States.
E-mail address: cpchen@umbc.edu (C. Chen).

https://doi.org/10.1016/j.sna.2020.112216
0924-4247/

of the instrument. This is the first TEER meter constructed from Arduino with reliable performance. The simplicity of the design and the low-cost to purchase the needed components (~50 USD) make the technology translational to other laboratories to facilitate TEER research. The design and coding details of the instrument are also included in the supplementary information.

2. Experimental

2.1. Construction of the TEER meter

2.1.1. The electrode

A TEER meter utilizes a "chopstick" style electrode, which has two metal leads placed across both sides of a cellular barrier. Two methods were developed to fabricate such an electrode. The first method employed a spacer fabricated by 3D-printing, which was a 15 mm (diameter) disc. Around the center of the disc, two holes were placed 5 mm apart for the leads to reside. Stainless-steel wire (0.032 in., McMaster-Carr, NJ, USA) was cut into 6 cm sections and inserted through the holes in the spacer, protruding 13 mm and 16 mm from the disc surface. To avoid metal cation contamination during measurements, the steel leads were dipped in carbon conductive ink (M.G. Chemicals, Ontario, CA) followed by air drying for 24 h to coat a layer of carbon on the steel surfaces. In the second design, three polystyrene sheets (250 μm thick; Shrinky Dinks, MI, USA) were stacked, and the edges fused using a soldering iron. Two holes were punched through the sheets with a heated wire. The same carbon coating protocol for the leads was followed.

2.1.2. The circuit

The Arduino board served as both the 5 V power source for the measurements and the sampling input (Fig. S1 in the SI). A jump wire coming from the 5 V port on the board was connected to one lead of the electrode utilizing the male and female connectors at the ends of the jump wire. A standard resistor (117 kΩ) was connected to the other lead by wrapping the resistor tightly around the exposed metal of the male jump wire connector. At this point, two wires branched off from this junction, with one wire going to the ground port (GND) to form a closed circuit, and the other wire connected to the A_0 analog input port for voltage reading (Fig. S3).

2.2. Programming of the arduino

The program was written in the free Arduino IDE (integrated development environment) software. The entire code is shown with a detailed explanation in the results and discussion section. An instructional tutorial is included in the SI (Fig. S4 and Table S1) to explain the coding line by line and demonstrate how the program can be customized in terms of detection duration, measurement frequency, and variable labeling.

2.3. Validation of the TEER meter

Resistors of known values were connected to the electrode leads. A variation of the coding was used to take measurements every 5 s for 1 min (12 measurements). Signals from one resistor were averaged and compared to the known value (measured by a calibrated multimeter). Then, the recovery was calculated, which is equal to the (measured value/known value) X 100 %.

2.4. Application of the meter to measure TEERs across endothelial cell monolayers

Cell culture in transwell membrane inserts. Bovine pulmonary aortic endothelial cells (BPAECS; ATCC, VA, USA) between passages 4 and 6 were used for the study. DMEM media (Thermo Fisher Scientific, MA, USA) containing 10 % fetal bovine serum (MilliporeSigma, MO, USA) and 1 % Penicillin Streptomycin (Thermo Fisher Scientific, MA, USA) was used for culturing the cells. The 24-well plate membrane inserts (0.4 μm pore size; Corning, NY, USA) were precoated with 0.3 mg/mL of collagen for 24 h, followed by the addition of 300 μL of BPAECs suspension (in DMEM media, 150,000 cells/mL) into each insert. The cells were cultured in a 37 °C incubator (5 % CO_2, humid). With these protocols, the cells were confluent after 4 days of culture, which was confirmed by optical microscopy.

2.4.1. Sterilization of the TEER electrode

The electrode was immersed in 70 % ethanol for 15 min, followed by air drying in a UV biohood. After sterilization, the electrode was fitted onto the transwell membrane insert inside the sterilized hood.

2.4.2. TEER measurements of untreated endothelial cells

An aliquot of 300 μL of DMEM media was placed in a membrane insert and 1 mL of the same media in the well outside of the membrane. The short lead of the electrode was placed inside the insert (where the cells were cultured), and the longer one was placed in the well. This setup permitted the flow of current through the endothelial monolayer for resistance measurements when needed. The 24-well plate with the membrane insert was placed in a 37 °C incubator, and the wires that connected the electrode to the Arduino board were threaded through the gasket seal of the incubator door. The Arduino board was then placed on the outside of the incubator and set to acquire TEER measurements at 1-min intervals for 1 h.

2.4.3. TEER measurement of endothelial cells with histamine treatment

A 20 μM histamine (MilliporeSigma, MO, USA) solution was made in DMEM media. Before the study, the spent media in the insert was decanted and replaced by the histamine spiked media, followed immediately by placing the electrode into the transwell insert and recording resistance measurements using the protocol described above.

2.4.4. Verification of the endothelial TEER measurements with microscopy

After each trial, the cells were immediately fixed in methanol (VWR, CT, USA) for 10 min at −20 °C. Then, the fixed cells were washed with 1X HEPES buffer (MilliporeSigma, MO, USA) and stained with a 0.5 % crystal violet (VWR, CT, USA; w/v) solution for 10 min at room temperature [16,17]. The cellular monolayers were then imaged on an optical microscope. Using ImageJ, the intercellular gaps were measured (n = 70 for each trial).

2.4.5. Data, calculations, and statistics

All TEER measurements were repeated in triplicates. The Arduino IDE enables real-time visualization of the recorded data in a window called serial display. The data were recorded in two columns displayed by the program: time (min) and resistance (Ω). The data columns were copied out of the serial monitor and exported to Microsoft Excel for graphing. TEER values are commonly reported as the flux of resistance across a known area in the unit of $\Omega \cdot cm^2$. Thus, the resistance values recorded were multiplied by 0.33 cm^2, which is the area of a 24-well membrane insert, as the final reading output. The TEER values were then plotted as a function of time. The Student's *t*-test was applied to compare data groups, and a significant difference was determined only when p-values were smaller than 0.05.

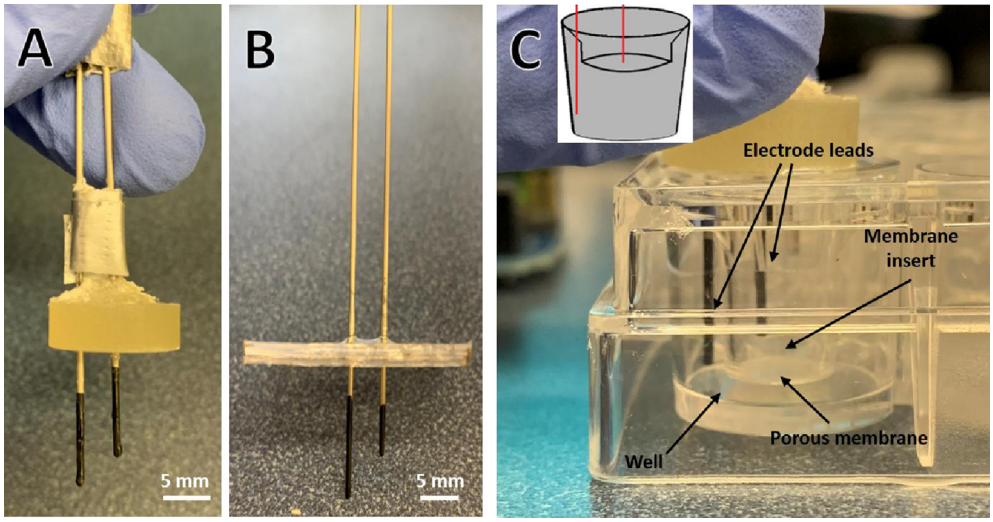

Fig. 1. Fabrication of the electrode. An electrode with two leads that could be placed on both sides of a cell monolayer was used in TEER measurements. **(A)** shows a 3D-printed spacer to house the two leads coated with carbon. **(B)** was a different fabrication method where stacked polystyrene sheets housed the electrode. **(C)** shows the electrode placement across a transwell membrane insert. A layer of endothelial cells was cultured on the top side of the membrane. The shorter lead was placed within the insert, while the longer one was outside so that the resistance across the cells could be detected.

3. Results and discussion

Arduino is emerging as a low-cost, versatile module in research laboratories to prototype/optimize instruments [11,18]. In this work, we present the feasibility of using Arduino as a standalone unit for the input and detection of electrical signals to measure TEER, a quantitative biophysical assessment of biological barrier integrity. The fabrication, validation, and application of the meter are discussed below.

3.1. Fabrication of the TEER meter

3.1.1. Electrode fabrication

A typical configuration of TEER electrodes utilizes two leads, shaped like a pair of forceps, which are deployed on both sides of a barrier to measure the electrical resistance. Although commercial electrodes are available, they come preassembled and therefore offer limited customizability of shapes and dimensions. Here, two fabrication techniques to obtain customizable TEER electrodes are presented. In the first method, a disc of 15 mm diameter was 3D printed with two holes (0.8 mm diameter; 5 mm apart) that could fit 0.032 inch (0.8 mm) stainless steel wires (Fig. 1A). The two wires served as the electrode leads. The 5 mm space between the leads allowed the electrode to fit a 24-well insert on both sides of the membrane (Fig. 1C). To avoid iron cation contamination during electrical detection, the two leads were coated with a layer of conductive carbon.

The second method did not require a 3D-printer. As demonstrated in Fig. 1B, three squares were cut out of a polystyrene sheet, and the edges melted together with a soldering iron to create a rigid support. The two holes for the leads were created by passing a heated steel wire through the polystyrene layers. The stainless-steel leads that made up the electrode were affixed in the holes using epoxy. This electrode construction protocol not only emphasized simplicity but also displayed the customizability of the electrode. The electrode system can be manufactured to any desired dimensions and fastened to an experimental setup with ease. Stainless steel was used as the electrode material due to the low cost. Still, other metals such as gold and platinum can be used as well—the connected leads simply need to be conductive. The application of either electrode design tested in this experiment resulted in successful TEER measurements. However, other conceivable dimensions (e.g., microelectrodes) and shape can also be employed. Commercial TEER electrodes usually contain Ag/AgCl wires as the reference electrodes to control the voltages between the working electrodes. For our TEER meter, the two electrode leads were connected to the 5 V and GND ports on the Arduino board, between which, the potential drop is know to be 5 V constantly. Therefore, Ag/AgCl electrodes were not required.

3.2. Device circuitry and programming

The circuit had two resistors connected in serial with a sampling point (A_0) in between (Fig. 2A). TEER was measured based on the voltage splitting principle derived from Ohm's Law. As shown in Eq. 1 and illustrated in Fig. 2A, there were two resistors (R_1 and R_2) in serial across 5 V. The voltage drop across the resistors was defined as V_1 and V_2, respectively. Based on Ohm's law, V_1 and V_2 split the input voltage (5 V) contingent on the magnitude of the resistances.

$$\frac{V1}{V2}=\frac{R1}{R2} \text{ or } \quad R2=V2\frac{R1}{V1} \tag{1}$$

In our application, R_2 was the resistance across a sample (cell monolayer), and R_1 was a known resistor. Therefore, if V_1 and V_2 were measured, the value of R_2 could be calculated. R_1 was implemented as a 117 kΩ resistor because previous research suggested that with such a resistor in a 5 V circuit, the resulting current does not affect endothelial cells [19].

Fig. 2B and C illustrate the schematic and actual wiring of the TEER meter. A jump wire connected the 5 V port on the Arduino board to a lead of the electrode (with two leads; R_2). The known resistor, R_1, was attached to the other lead and then terminated at a ground port (GND) on the board. At the junction of the electrode and R_1, a second wire was connected to the analog sampling port A_0 in order to sample the voltage V_1. The voltage difference across the sample (V_2) was then calculated as $V_2 = 5\,V - V_1$.

The program was written in the Arduino software (Fig. 3). There were three main modules of the codes: defining parameters and variables, the Arduino microcontroller setup, and the analog measurements.

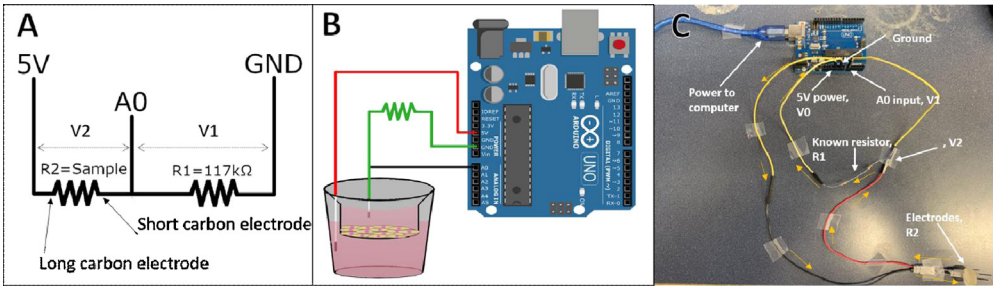

Fig. 2. The principle and design of the TEER meter. **(A)** The voltage splitting principle: with two resistors in a serial circuit, the voltage drop across each resistor is proportional to the resistance, or R1/R2 = V1/V2. If the total voltage applied to the circuit and R1 are known, and V1 can be detected, R2 can be calculated. **(B)** The schematic of the TEER meter. A sample (resistance across a monolayer of cells in the well) and a 117 kΩ resistor were connected in serial starting from the 5 V power port (red line) and ending on a ground (GND) port (green line). The voltage across the 117 kΩ resistor was measured between the A0 analog input (black line) and the GND (green line). **(C)** A picture of the instrument. The arrows indicate the current flow direction (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

```
int analogPin=0;
int PinReading=0;
int V0=5;
int t=0;
int i=1;
float V1=0;
float V2=0;
float R1=117000;
float R2=0;

void setup() {
  Serial.begin(9600);
  Serial.println ("Time/min;Resistance/Ohm");
}

void loop() {
 PinReading=analogRead(analogPin);
 if(i<=61){
  V1=V0*(PinReading/1024.0);
  V2=V0-V1;
  R2=(V2*R1)/V1;

  Serial.print (t);
  Serial.print (";");
  Serial.println(R2);
  delay(60000);
  t=t+1;
  i=i+1;
 }
}
```

Define Parameters

Arduino Setup

Measurements

Fig. 3. The Arduino code to measure TEER every 1 min for 1 h.

3.2.1. *Defining parameters and variables*

All the variables needed to be defined first to globally carry their definitions over the rest of the program. There are two types of numerical variables in the Arduino coding: integers and float numbers. Integers are whole numbers typically used for counting and comparison purposes. The following variables were defined as an integer: the analogPin() = 0 which stated that the analog pin A_0 was used (there are 6 analog ports numbered 0–5); the pinReading variable that held the voltage value read from the analog port A_0; the variable t that was the timestamp of each reading with the initial value being t = 0; and the i variable that served as a loop controller for how many measurements to be taken.

On the other hand, variables stored as float numbers can contain decimal places and are commonly used for mathematical calculations. The following variables were defined as floating numbers: the voltage V_1, which was the voltage drop across the known resistor (R_1), and the voltage V_2, which was the voltage across R_2 (the resistance of a cell monolayer).

3.2.2. *Arduino setup*

The Serial.begin() function set the data rate (in bits per second) that the Arduino transmitted to the serial monitor, which was the window that displayed the results the program detected. The default Arduino data exchange rate is 9600 bit/sec, so the serial monitor was set to 9600. The Serial.printline() function printed/displayed two columns in the serial display defined by the contents in the parenthesis: time as the first column in the unit of min and resistance as the second one in the unit of Ohms (Ω), and a ";" was printed as the separator between the columns.

3.2.3. *The measurements*

The resistance measurements were calculated and printed to the serial monitor in a void loop. A void loop in Arduino runs continuously until the condition is voided. First, the PinReading() function read the signal from the analog pin A_0 on the Arduino board, which was the analog voltage drop across the known resistor (V_1). The coding "if (i<=61)" defined that 61 measurements were

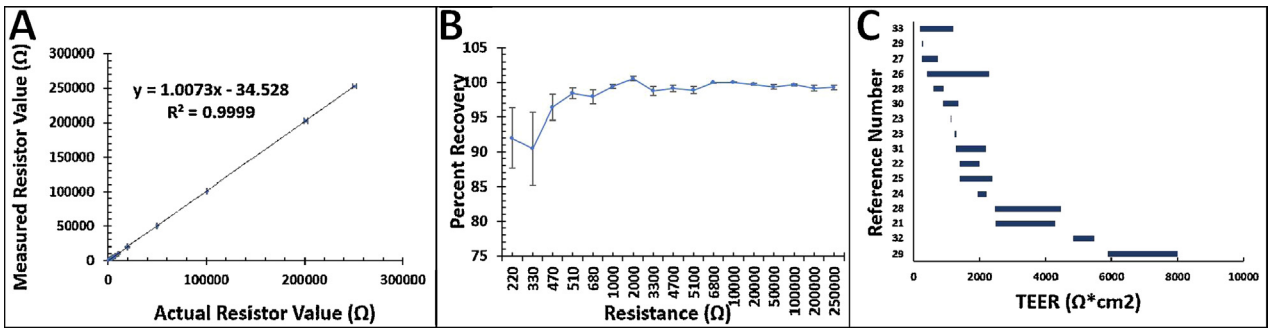

Fig. 4. Quantitative characterization of the TEER meter. **(A)** Results of measuring resistors of known resistance values. The slope and small intercept suggest quantitative recovery of the resistors. N = 15; error bar = stdev. **(B)** Percent recovery of known resistors. Within the range of 400-250,000 Ω, the measurement variance was < 3 %. The TEER meter can accurately measure TEER values in the range of (400-250,000 Ω), and when multiplied by the area of a standard transwell insert (0.33 cm), 132-82,500 Ω · cm^2, which is the preferred unit of TEER. N = 15; error bar = stdev. **(C)** A literature study revealed that most of the reported TEER values fell between 200 and 8000 Ω · cm^2, which our TEER meter completely covered. The bars were the TEER ranges that the literature reported.

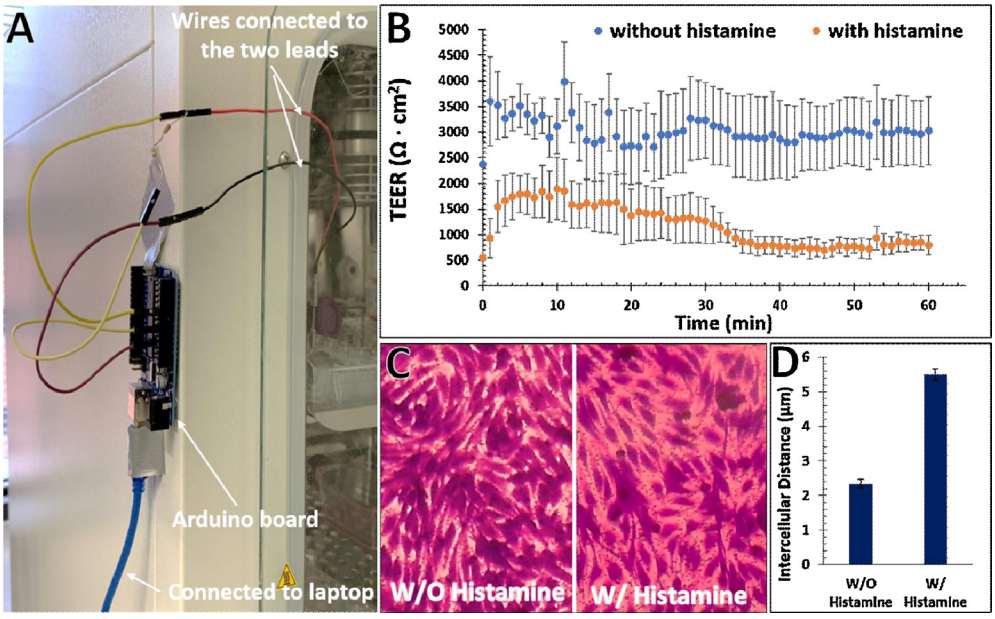

Fig. 5. **(A)** The TEER meter could simply be taped on an incubator to measure cells cultured inside. (**B)** Average TEER measurements across endothelial cell monolayers, without histamine application (3027.5 Ω·cm^2) and with histamine in the media (793.4 ± 190.5 Ω·cm^2) during 1 h. N = 3; error bar = S.E.M; $p < 0.01$ for all points. Lower signal upon histamine treatment is consistent with the known effects of histamine on barrier integrity. **(C)** Crystal Violet staining of the monolayers after the TEER was measured. The cells with histamine appeared to show larger intercellular gaps. **(D)** Analyzing the images using ImageJ demonstrated that histamine effectively doubled the intercellular gap, which corresponded to the TEER measurements. N = 3; error bar = S.E.M; $p < 0.001$.

taken (1 min per measurement for 1 h, including the 0-time point). Once the value of i = 62, the conditions for the void loop were not satisfied, and the loop was terminated.

R_1 and V_0 in the circuit were known, which were 117,000 Ω and 5 V, respectively. As discussed in Eq. 1, to measure R_2 (sample), both V_1 and V_2 needed to be known. The PinReading()=(analogPin) read V_1 in the format of how many parts out of 1024. A total of 1024 parts equal 5 V, and thus PinReading()/1024 X V_0 (which was 5 V) resulted in V_1. Because R_1 and R_2 were serial resistors, V_2=V_0-V_1, and then R_2 could be calculated. The next section of this part was to print the data. The measurement timestamp "t" was printed, followed by ";" and then the measured R_2. A delay of 60,000 milliseconds (the coding "delay(60,000)") or 1 min was executed before the next measurement (this detection frequency is customizable). Subsequently, another timestamp that was 1 min later was assigned to the t variable (the coding "t = t+1″), and the next measurement looped through. A more detailed explanation of the coding and a tutorial about how to change the temporal resolution and detection duration was included in the SI (Fig. S4 and Table S1).

3.3. Validation of the TEER meter

A TEER meter is essentially a resistance meter. Therefore, standard resistors were measured by the TEER meter, and the measured and the true values were compared to validate the accuracy of the instrument. Fig. 4**A** shows the measured values plotted as a function of the true values, with a linear regression curve of y = 1.0073× −34.528. The small intercept and a slope close to 1 indicated the quantitative recovery of the standard resistors. Indeed, further analyses revealed that when above 400 Ω, the variance between the measured and the true resistances was within ±3 % (Fig. 4B). In other words, the TEER meter could accurately measure resistance in the range of 400 and 250,000 Ω with an error of <3 %. Since TEER is commonly measured across a 24 well plate membrane inserts (area = 0.33 cm^2) or smaller microfluidic interfaces [20], the equivalent quantitative TEER range of our meter could be converted to 132–82,500 Ω·cm^2, which covered the majority of reported TEER values based on a literature study (Fig. 4**C**) [21–33].

Table 1
Estimated costs to make the TEER meter.

Item/Labor	Cost
Arduino UNO board	$12
Arduino software	Free
Jump wires and connectors	$10
Stainless steel wire	$8
Carbon ink	$15
Resistors	$10
Build time	~2 h

3.4. Measuring endothelial TEER using the meter

Endothelial cells are responsible for the exchange of molecules such as drugs and nutrients between blood and other tissues [34], the dysfunction of which can cause serious health consequences. TEER measurement is an indispensable assessment of endothelial barrier integrity in physiological and pharmaceutical studies [20,34]. Therefore, endothelial cell monolayers were chosen as a model to test our TEER meter. The cells were cultured in 24-well plate transwell membrane (0.4 μm pore size) inserts. Histamine was applied to treat the endothelial, which is known to be able to break barrier junctions of endothelial cells and thus induce greater barrier leakage [35].

In addition to the simple construction, our TEER meter was easy to set up adjacent to a cell culture incubator. The Arduino board was taped to the side of an incubator (Fig. 5A). Due to the thin diameter of the jump wires (1 mm) and the flexibility of the sealing gasket on the incubator door, we did not see a temperature or CO_2 drop during the experiments. Once the electrode was placed in the membrane insert, the serial reading was started in the Arduino software installed on a laptop next to the incubator.

As shown in Fig. 5B, the TEER of the endothelial monolayer that was not treated with histamine was consistent for 1 h with a magnitude around $3027.5 \pm 664.4\ \Omega{\cdot}cm^2$ (average of triplicate experiments ± stdev). However, when treated with histamine, the TEER rapidly dropped to $1744 \pm 505\ \Omega{\cdot}cm^2$ within 10 min and kept decreasing during the 1 -h study to a final value of $793.4 \pm 190.5\ \Omega{\cdot}cm^2$. Statistical calculations showed a p-value < 0.01 for all data points attained, suggesting that histamine significantly reduced the TEER or endothelial barrier integrity, which was consistent with literature [36].

To verify that the TEER drop was caused by histamine, the cells were immediately fixed and stained with crystal violet after the measurements. Images of the cell monolayers were then taken on an optical microscope. It appeared that the intercellular gaps between endothelial cells treated with histamine were more prominent than those of the untreated cells (Fig. 5C). We then quantitated the gaps using ImageJ, finding that the average intercellular gap between the cells without histamine was 2.34 ± 0.12 μm, while the cells treated with histamine had significantly larger gaps (5.49 ± 0.17 μm; $p < 0.001$; Fig. 5D). This data suggested that the histamine caused larger intercellular gaps, which must lead to lower TEER values. Overall, the results validated the usefulness of our TEER meter.

4. Conclusion

In this paper, we report the design, fabrication, and application of a low cost and accurate TEER meter using Arduino and a few other easily accessible materials. In total, it cost ~$50 (Table 1) to purchase the parts and about 2 h to construct the meter. Also, our design allowed for customization in terms of electrode material, dimensions, geometry, and measurement settings (e.g., detection frequency), etc. The accuracy of the meter was validated by using it to measure known resistor values. We also demonstrated the usefulness of the meter in measuring TEERs of endothelial cell monolayers with or without histamine. Design and programming details are included as the SI. The simplicity and customizability of this instrument will broadly benefit biological barrier research in the scientific community.

CRediT authorship contribution statement

Curtis G. Jones: Writing - review & editing. **Chengpeng Chen:** Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.sna.2020.112216.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Biographies

Curtis G. Jones is a second-year Ph.D. student pursuing his degree in the field of bioanalytical chemistry. He graduated from UMBC in 2016 with a B.S. in chemistry and has returned to UMBC for the completion of his Ph.D. His areas of interest include microfluidics and electrochemical sensing, with a specialty in the incorporation of these techniques into bioanalytical systems. Outside of the research laboratory, he is an avid lacrosse player, playing year-round in different men's leagues.

After Dr. **Chengpeng Chen** received a B.S. degree in chemistry from the Ocean University of China in 2011, he joined Dr. Dana M. Spence's lab at Michigan State University as a graduate student in analytical chemistry and obtained his Ph.D. degree in 2015. After a 3-year postdoc training with Dr. R. Scott Martin at Saint Louis University (MO, USA), he became an assistant professor in the Department of Chemistry and Biochemistry at the University of Maryland Baltimore County in 2018. His research lab is interested in integrating scaffolding materials in microfluidic devices for 3D cell culture for quantitative pathophysiological studies.