Presented at the 6th DLSU Innovation and Technology Fair 2018
De La Salle University, Manila, Philippines
November 22 & 23, 2018

Liver Transplant Preservation Machine

Dr. Nilo T. Bugtai[1], Madon L. Arcega[2], Tristan Joseph C. Limchesing[3], Joshua Paul L. Manalili[4], Samantha June M. Rice[5], and Marie Bernadette A. Tuason[6]

Manufacturing Engineering and Management Department, De La Salle University
2401 Taft Avenue, Malate, Manila, Philippines
nilo_bugtai@dlsu.edu.ph, madon_arcega@dlsu.edu.ph, tristchesing@gmail.com, joshuapaulmanalili@gmail.com, samantha_rice@dlsu.edu.ph, marie_tuason@dlsu.edu.ph

Abstract: With the current method of liver preservation through chilled preservation solution, surgeons are restricted with a time constraint to complete a liver transplant, which greatly decreases the donor pool of liver grafts. Moreover, this type of preservation poses risk of cell damage due to fluid crystallization. The main objective of this study is develop, assemble, and test a cost effective medical machine that is designed to prolong the preservation time span of a donated liver that would be used for transplantation by normothermic preservation. Thus, the medical machine should be able to maintain physiological parameters similar to the body. The machine must be able to maintain a pH level of 6.8 - 7.4, a temperature level of 36.5- 37.5 degrees Celsius, and a continuous fluid flow within the machine, with a flow rate of 200 - 300 mL/min for the hepatic artery and 600 - 900 mL/min for the portal vein. All these parameters will be displayed on a monitoring system. The researchers have concluded that the constructed temperature regulator using the Peltier pads and dual fan pipe heat sink demonstrated successful results in regulating the temperature with efficiency rates of 120.66% for when heating is required and 52.74% when cooling of the fluid, in terms of time duration. These results can be attributed to external factors such as external temperature in which the reservoir is fairly close to the laptop, which gives off excess heat, thus attributing to an efficiency rate greater than 100%. The pH module system was able to produce accurate pH readings and serve as a reliable, autonomous pH adjuster. Concerning the flow rate, the machine will be able to maintain the desired flow rate for at least 8 hours. Furthermore, the monitoring system has accurately displayed the parameters that was needed and was able to save patient records through a database system but is also only limited to operating systems with Microsoft Excel 2007 or later.

Key Words: Liver Transplant; Normothermic Preservation; Perfusion Machine

1. INTRODUCTION

The liver is the body's largest gland and has a dark reddish-brown color. It is a vital organ that supports almost every other organ in the body. Without a healthy liver, a person cannot survive. Common liver diseases include hepatitis infection, fatty liver disease, and cancer, as well as damage from alcohol, the pain reliever acetaminophen, and some cancer drugs ("Liver: Anatomy, Definition, Symptoms, and More", n.d.). In the event of the liver not being able to sustain its primary functions, liver dialysis is recommended. Liver failure is a serious and many times fatal diagnosis. Although medications can decrease the symptoms caused by the liver failure, liver transplantation represents the only permanent cure (Roayaie & Feng, 2018). Treatment for these diseases are typically liver transplantation if you are considered a candidate for that procedure.

According to the American Liver Foundation, around 17,000 adults and kids have been medically approved for liver transplants and are sitting tight for donated livers to wind up accessible. The waiting develops each year. Furthermore, it is only when an individual is announced "brain dead" can organs be recovered to spare the lives of others ("Organ Donation - American Liver Foundation. Your Liver. Your Life.", 2015). Moreover, according to an interview by Trisha Macas of GMA News to NKTI Chairman Dr. Jade Jamias, for some transplants, donors only need to give part of the organ—a segmental transplantation—since the liver has a high regenerative rate. But for patients who need an entire liver, the search for donors becomes much more difficult. Jamias said that liver centers in the Philippines just rely on their network of hospitals to provide referrals, usually cadavers or brain-dead patients. Although the DOH has no concrete data on the number of Filipinos who need liver transplant, Jamias explained that one in every eight Filipinos have hepatitis B, a main cause of liver disease. Moreover, 15 to 25 percent of these will develop chronic hepatitis B, which can eventually lead to liver cirrhosis and the need for liver transplantation (Macas, 2014).

Transplantation methods according to University of Maryland Medical Center, the technique of transplantation have different steps. First and foremost, before transplantation, liver-support therapy might be indicated (bridging-to-transplantation). Artificial liver support like liver dialysis or bioartificial liver support concepts are currently under preclinical and clinical evaluation. Virtually all liver transplants are done in an orthotopic fashion, that is, the native liver is removed and the new liver is placed in the same anatomic location. The donor's blood in the liver will be replaced by an ice-cold organ storage solution, such as UW (Viaspan) or HTK until the allografts liver is implanted. Implantation involves anastomosis (connections) of the inferior vena cava, portal vein, and hepatic artery. After blood flow is restored to the new liver, the biliary (bile duct) anastomosis is constructed, either to the recipient's own bile duct or to the small intestine. The American Society of Transplantation estimates a total surgery time of eight to ten hours (Lee & Mangino, 2009).

As of the moment, transplantation is the only remedy for liver failure, as devices or machines that could effectively execute all the functions of the liver are yet to be discovered. The process of liver transplantation involves replacing a diseased or failing liver with another that is normal and healthy through a medical operation. A study of the current method of preservation which involves placing the liver in the cold-storage preservation pointed out that the use of lower temperatures in order to alter the metabolism of the organ and the use of perfusion pumps and circuits, solutions of electrolytes, solutes and vitamins as replacement for blood have been studied by scientists in as early as the 1960s (Guibert, et al, 2011). Moreover, because of its high success rates of the chilled preservation solution, the process of liver transplantation has been widely used by medical practitioners to treat patients with end-stage liver disease and acute liver failure. However, since cold storage may lead to ice crystals, which could damage the tissues, it is not the best solution to providing a lasting organ for the patient.

Almost all methods of organ preservation are trying to discuss the issues and complications that taking an organ of the body undergoes such as, preventing cellular edema, delaying cell destruction, and maximizing organ function. Over the past few years, organ transplantation has progressed greatly with the help of the technology that is present today and one of the advancements in organ transplantation is normothermic machine perfusion. In comparison to cold-storage preservation of donor organs, normothermic machine perfusion may possibly reduce preservation damage, improve graft viability and potentially allow ex vivo assessment of graft viability before the organ transplantation (Watson & Dark,2012).

With the current method of preserving a donated liver in a chilled preservation solution, surgeons are restricted with a time constraint to complete a liver transplant, which greatly decreases the number of available and viable liver grafts. Moreover, this type of preservation poses risk of cell damage due to fluid crystallization; hence there is a need to design and develop a medical machine that can prolong the viability of a donated liver once harvested. The study involves experiments that show the reliability of the Arduino based regulators and the monitoring system. However, the study does not include a comparison of effectiveness between the developed liver transplant preservation machine and current liver transplant methods.

2. DESIGN CONSIDERATIONS

2.1 Mechanical and Electrical System Design

The frame has a total length of 85 cm, a total width of 35 cm, and a total height of 60 cm. It was made of 1.5 x1.5 inch stainless steel bars and the fiberglass windows and doors are 1 cm thick. The whole design is divided into two main compartments: Liver Chamber and Electrical Housing.

Fig. 1. Liver Transplant Preservation Machine

Inside the chamber are the major components of each system, namely the one motor, flow rate sensors, temperature regulator, acid and basic solutions, and the peristaltic pumps. The proponents have placed, inside the chamber, a container to help hold the sensors and serve as a drainage basin in case of a leak.

Fig. 2. Inside of Liver Chamber

All of the electrical components is housed in the smaller compartment next to the liver chamber. The wires that connect the sensors to the microcontrollers pass through tubes used to protect and distinguish the wires for each module. The Arduinos are connected to a USB2.0 4-port hub then connected to the laptop on top of the smaller compartment. The electrical system is powered by 220V AC, 60Hz single-phase power outlet. The 220V is controlled by breakers to prevent current surge. From there, the 220V is shared to four (4) DC power supplies, with a Panther PSP 1102 Extension cord, that serve as a power supply for the modules.

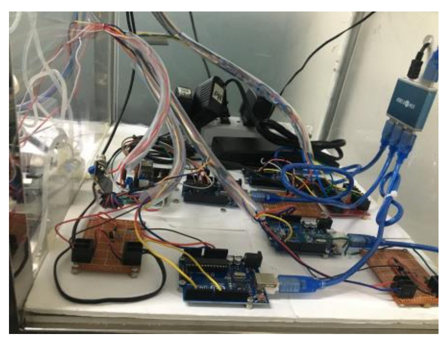

Fig. 3. Inside of Electrical Housing

2.2 Temperature Regulator Module

The thermal regulator is positioned inside the liver chamber, and is controlled based on the reading of the thermal sensor, specifically, a DS18B20 sensor is utilized, which is ideal for measuring temperatures far from the microcontroller, and

Presented at the 6th DLSU Innovation and Technology Fair 2018
De La Salle University, Manila, Philippines
November 22 & 23, 2018

measuring in wet conditions. attached to the reservoir. The sensor works great with any microcontroller using a single digital pin, and is usable with 3.0-5.0V systems. A 4.7k resistor is added, which is required as a pullup from the DATA to VCC line when using the sensor. It measures the temperature of the perfusion fluid, which should be between 36.5 - 37.5 °C. It operates using the concept of conduction. A cooling block, where the perfusion fluid flows, is positioned between two Peltier pads using thermal paste. The upper Peltier block has its heating side facing the cooling block, while the lower Peltier block has its cooling side facing the block. A small heat sink was attached to the upper Peltier pad, to further increase the temperature difference of the two sides making the heating element increase potential. A larger heat sink is attached to the lower Peltier pad, as the heating side often overpowers the cooling side. In addition, two PC fans are connected to the heat sink to further disseminate the heat dissipated.

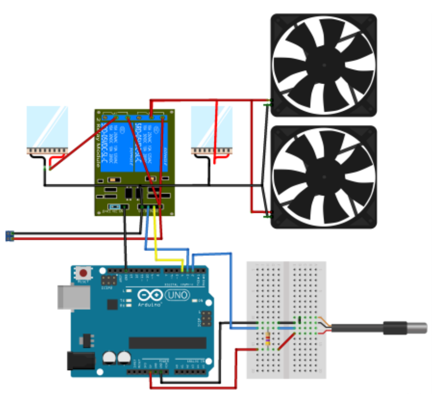

Fig. 4. Thermal Regulator Circuit Diagram

2.3 Flow Rate Regulator Module

The flow system is what makes the bulk of the machine. The system consists three major parts. The pump system, the sensors, and the pathways. The pathways are plastic silicone tubing. Each have different diameters depending on where it is attached to. The pump system consists of two centrifugal pumps and 2 microcontrollers. The proponents opted to use a 12V brushless DC centrifugal pump rather than the traditional roller pump because modern medical pulmonary bypass machines have already been adapting medical grade centrifugal pumps for their flow systems. Moreover, it was decided to have separate controllers for each of the pump system because simultaneous readings and adjustments should be taking place. The sensors will act as a feedback system in order to control the flow speed. The perfusion fluid is placed on a reservoir. The main pump would be directly connected to the reservoir. This pump would serve as an inlet to the flow system since it pumps the perfusion fluid onto the system.

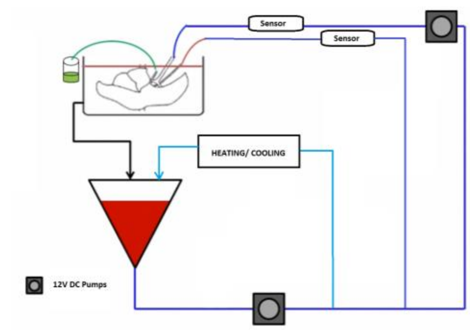

Fig. 5. Circulatory System Flow Diagram

2.4 pH Regulator Module

The buffer dispenser design aids the monitoring and regulation of the pH levels of the fluid that flows throughout the artificial liver system. There are two main components of the buffer dispenser design, the peristaltic pumps which are connected to a microcontroller and to two buffer solutions (acidic and basic), and the pH probe that is also connected to the microcontroller to aid the latter component in pH regulation.

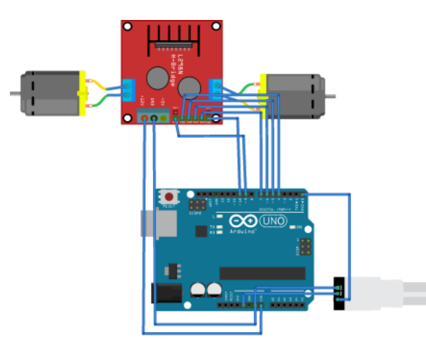

Fig. 6. PH Regulator Circuit Diagram

The pH probe is the core of the pH monitoring system. It is the device used to measure the pH value of the fluid flowing throughout the artificial liver system. The SEN0169 pH Meter Pro Analog Sensor was used by the proponents due to its industrial grade classification and specifications, which provides a more reliable and durable device as compared to other commercially available pH probes.

Figure 7. SEN0169 pH Meter Pro Analog Sensor

2.5 Monitoring System

The monitoring system has a fundamental principle of allowing data capture, process, and dissemination in a systematic way. In this case, the monitoring system enables the user to view all the sensor's data in a single interface. By having a monitoring system, it is ensured that progress toward the objectives is measured, and problems may easily be identified. The monitoring system was made with four tabs or pages, namely: Donor Information page, Liver Status page, Database page, Setup page, and User Manual Page.

It is made using Visual Studios 2017 Community Windows Forms (WinForms) .NET Framework and has a combination of both C++ and C#, moreover, the data received through the SerialPort object, a graph is continuously plotted at every second tick of the Timer control. These graphs were made and customized using an open source library called Live-Charts. The graphs monitoring system was made using a constantly changing line chart.

Fig. 8. Liver Status Page

In order to program and control the required physiological parameters (temperature, pH, and flow), Arduino UNOs are used. Moreover, the ATmega328 provides a Universal Asynchronous Receiver and Transmitter (UART) serial communication. This connection is channeled through a USB and appears as a virtual communication (COM) port on the Arduino IDE. Through Arduino's Serial Monitor, the data that was sent one bit at a time, can be displayed through the *Serial.print()* command. Additionally, a common connection between the microcontrollers of the project and the monitoring system was made to insure fast and reliable data transfer. Through a serial connection between the microcontrollers and the monitoring system, the user is presented with real-time data of the sensors.

3. EXPERIMENTATION, RESULTS, AND DISCUSSION

3.1 Experiments conducted on Temperature Module

3.1.1 Experiment on Temperature Regulation

The objective of this experiment was to test whether the thermal sensor was accurate in determining the temperature of the system. To do this, the readings from the Arduino microcontroller were compared to that of a laboratory grade thermometer (LGT). The results in Table 1 show that the Arduino thermal sensor (ATS) reading is accurate in reading temperatures, with a percent difference of less than 3%. The results can be attributed to that of the configuration of the waterproof sensor prior to experimentation process. On the other hand, the difference in readings can be due to external factors and fluctuations affecting the reading process. In this case, a resistor with a slightly less value than 4.7 kΩ can be used to further decrease the percent difference.

Table 1. ACCURACY OF TEMPERATURE SENSOR

Test #	LGT Reading	ATS Reading	% Difference
1	24.253	24.18	0.30%
2	26.454	26.12	1.27%
3	29.302	28.89	1.42%
4	32.459	32.23	0.71%
5	36.340	36.03	0.86%
6	37.956	37.45	1.34%
7	40.508	39.43	2.70%
8	40.752	40.05	1.74%
9	42.254	41.94	0.75%
10	43.604	43.04	1.30%

3.1.2 Experiment on Temperature Accuracy

The objective of this experiment was to test the efficiency of the temperature regulator in maintaining the temperature of the system. To do this, 125ml of a disturbance with various temperatures were added to the reservoir, and the time it took for the system to respond and adjust was recorded. The recorded data was compared to a theoretical data calculated using the equation

$$t = \frac{Cpm\Delta T}{P}$$

wherein t is the theoretical time, Cp = 4190 J/kgK, m is the total mass of the water in the system = 1.325 kg, ΔT is the temperature difference, and P is the power output of the peltier pads (P_{cooler} = 16.4W, P_{heater} = 24W).

Efficiency is calculated by actual time vs, theoretical time. Based on the results seen in Table 2, it can be observed that the thermal regulator is able to regulate the temperature back to the allowable range despite the disturbances placed in the system. The heating element of the temperature regulator is efficient in maintaining the temperature at a desired time. The cooling element, however, was only half as effective in regulating the temperature back to the ideal value. These results can be attributed to external factors such as external temperature in which the reservoir is fairly close to the laptop, which gives off excess heat, thus attributing to an efficiency rate greater than 100%. In addition, ambient temperature might also be a cause as to why there is a difference in the time duration.

Table 2. COMPARISON OF ACTUAL AND THEORETICAL TIME OF REGULATION

Test #	Temperature Disturbance (°C)	T actual	Theoretical	% Efficiency
1	0	0:20:23	0:17:43	88.59%
2	10	0:14:22	0:12:31	89.44%
3	20	0:08:37	0:07:20	91.58%
4	30	0:01:15	0:02:08	213.03%
			Average	120.66%
5	50	0:03:00	0:01:56	13.77%
6	60	0:04:46	0:05:34	39.75%
7	70	0:05:45	0:09:12	65.73%
8	80	0:06:55	0:12:50	91.71%
			Average	52.74%

3.2 Experiments on PH Module

3.2.1 Experiment on PH Regulation

The pH regulation experiment involves the correlation between the pH disturbance and volume of buffer needed for the perfusion fluid to go back within the range. The objective of this experiment is to determine the relation between different pH values and buffer solutions and to get the time data. The duration between the addition of the pH disturbance and the neutralization of the perfusion fluid through the automatic adjustments of the monitoring system are directly proportional as seen in the results in Table 3. The lowest neutralization duration is 4 minutes and 1 second for the pH disturbance of 6.0 and the highest is 15 minutes and 43 seconds for the pH disturbance of 3.0. The duration also increases if the difference of the pH disturbance from the initial pH of the fluid system increases.

Table 3. PH DISTURBANCE AND BUFFER VOLUME CORRELATION

Initial pH	pH of Disturbance	Volume of Buffer Added	Time
6.86	3.02 ≈ 3.00	164.85 mL	15:43
6.81	4.10 ≈ 4.00	158.91 mL	15:09
6.88	5.02 ≈ 5.00	131.99 mL	12:35
6.82	5.95 ≈ 6.00	42.13 mL	4:01
6.93	8.02 ≈ 8.00	66.61 mL	6:21
6.82	8.98 ≈ 9.00	86.01 mL	8:12
6.91	9.98 ≈ 10.00	97.72 mL	9:19

3.2.2 Experiment on PH Accuracy

This pH experiment conducted was concerned in testing the accuracy of the Arduino powered pH probe. As a reference point, a laboratory grade pH meter was tested in conjunction with the machine's pH probe. 3 tests were conducted using 4.0, 7.0, and 10.0 laboratory buffers. The acid buffer (4.0 pH) test resulted to a 0.25% difference between the laboratory pH meter reading and the Arduino pH probe reading, as shown in Table 4. Meanwhile, the neutral buffer (7.0 pH) test resulted to both the pH readings to have the same value. Lastly, the basic buffer (10.00) test had the highest percent difference of 0.71%. Another factor to consider is the difference of both the pH readings and the actual pH value of the buffers based from the manufacturer. Based from the tests, the readings of the Arduino pH probe were closer to the real pH values of the buffers as compared to the readings of the laboratory pH meter.

Table 4. LABORATORY PH METER AND ARDUINO PH PROBE READING COMPARISON

Buffer Solution	Laboratory pH Meter Reading	Arduino pH Probe Reading	% Difference
Acid 4.0	3.99	4.00	0.25%
Neutral 7.0	6.98	6.98	0.00%
Basic 10.0	9.85	9.92	0.71%

3.3 Experiments on Flow Module

3.3.1 Experiment on Flow Regulation

The first flow rate experiment was to test whether the system can maintain the desired flow rate range for 8 hours. The system was left to run for at least 8 hours. Readings was then collected from the GUI for every hour during the duration of the 8 hours. The system should be able to maintain a flow rate of 200-300 mL/min for the Hepatic Artery and 700-900 mL/min for the Portal Vein. During the experiment, the upper bound reading of the flow rate for the hepatic artery was 276 mL/min and the lower bound was 240 mL/ min. As shown in Table 5, both the upper bound and lower bound readings were still within the required range of stability thus making the hepatic artery system a success. For the Portal vein, the upper bound reading was found to be 817 mL/min and the lower bound reading was 746 mL/min. Both the upper bound and the lower bound readings were still within the required range of stability thus making the Portal vein system a success.

Table 5. FLOW RATE STABILIZATION GIVEN A PERIOD OF TIME

Period (hr)	HA Flow Rate (ml/min)	PV Flow Rate (ml/min)
1	250	800
2	250	817
3	276	764
4	276	746
5	240	800
6	250	817
7	263	782
8	250	817

3.3.2 Experiments on Flow Accuracy

The second flow rate system experiment was focused on the accuracy of the readings from the GUI coming from the sensors. In order to determine the accuracy, an external measurement for the flow rate must be performed. Total flow rates from the GUI and the manual measuring will be compared. A volume of perfusion fluid was collected for 10 seconds from the outlet or the system and was measure its volume. The volume is then multiplied by 6 to make an mL/min unit. It was found that there is an average of 0.62% difference of the GUI readings from the manual testing, as seen in Table 6. The group has calculated the deviation to be insignificant given the required flow rate range that is needed to be maintained by the system.

Table 6. GUI FLOW RATE AND MANUAL FLOW RATE COMPARISON

Period (hr)	GUI Total flow rate (ml/min)	Manual Total flow rate (ml/min)	% Difference
1	1050	1043	0.67%
2	1067	1070	0.28%
3	1040	1045	0.48%
4	1022	1017	0.49%
5	1040	1046	0.58%
6	1067	1063	0.38%
7	1045	1059	1.33%
8	1067	1075	0.75%

3.4 Experiments on Monitoring System

The objective of the internal acceptance testing was to check for possible issues, limitations, and defects from user input (text input, button click, etc), and check for the accurate connection between the microcontrollers and user interface. The results from the simulated operational testing proved useful in creating a systematic workflow of the monitoring system.

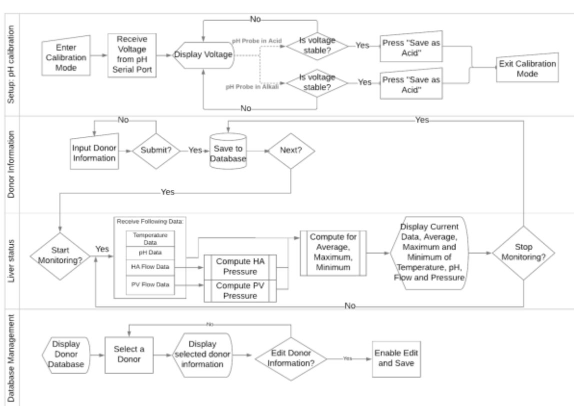

Figure 9. Monitoring System Flow Chart

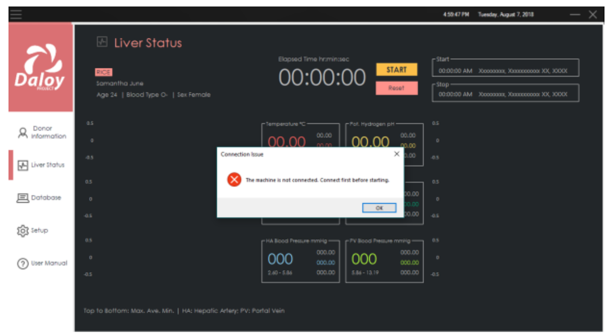

Figure 10. Liver Status Error Message

It was observed that by incorporating certain fail-safe features (i.e. Error Notifications) in the monitoring system possible sources of failures were anticipated. During the development of this user interface, such features were placed in user input events such as when texts are inputted or when buttons are clicked. However, upon observation of other possible failures, the monitoring system still lacks in other safety measures such as the possibility of starting the monitoring at the Liver Status page without completion of the donor information and pH probe calibration. This will create an incomplete database entry and inaccurate pH reading. In addition, the database management system is compatible with Microsoft Excel 2007-2010 version; thus, the monitoring system is not recommended for computers with older Microsoft Excel versions.

4. CONCLUSIONS

Based on the study, the use of the DS18B20 thermal sensor proves to be an effective means of determining the temperature of a system using a microcontroller, with a percent difference of less than 3%. In addition, the constructed temperature regulator using the Peltier pads and dual fan pipe heat sink demonstrated successful results in regulating the temperature with efficiency rates of 120.66% and 52.74% in terms of time duration.

The use of a commercially available acetic acid and sodium hypochlorite as the acidic and basic buffer solution of the perfusion system proved to be effective as they were able to adjust the pH value of the perfusion fluid when disturbances were added. In addition, the Arduino pH probe assembled and used by the researches had minimal percent differences between its readings and the readings of the laboratory grade pH meter. The pH monitoring system was able to produce accurate pH readings and serve as a reliable, autonomous pH adjuster.

Concerning the flow rate, the machine would take 2-3 minutes to reach stabilization for the flow rate. The machine will be able to maintain the desired flow rate for at least 8 hours. The upper bound and lower bound readings were still very well within the required range that is needed. The Hal sensors that were utilized by the researchers has a minimal percent differences between the reading from the GUI and the manual calculations. The percent difference would not in any way affect the required range as based on the upper and lower bound data that were collected from the flow stability experiment.

The internal acceptance testing proved useful in creating a systematic algorithm of the monitoring system. The monitoring system consists of four main pages: Donor Information, Setup, Liver Status, and Database. Each page was made for a specific purpose of receiving information, user interface-to-Arduino communication, Arduino-to-user interface communication, and data management system, respectively. Additionally, certain fail-safe features (confirmation message, warning message, error message) were incorporated to guide the user into a systematic approach operating the monitoring system. The monitoring system is also only limited to operating systems with Microsoft Excel 2007 or later.

5. ACKNOWLEDGMENTS

The completion of this study would not have been possible without the help of medical professionals, Dr. Ryan Vicerra, Mr. Renann Baldovino and Mr. Homer Co in the conceptualization and evaluation of the research.

Also this would not have been possible without the support of friends especially Raphael Luta and Biomedical Devices Innovations and e-Health Research Group.

6. REFERENCES

Liver: Anatomy, Definition, Symptoms, and More. Retrieved from https://www.healthline.com/health/human-body-maps/liver

Roayaie, K., & Feng, S. (2018). Transplant Surgery - Liver Transplant. Retrieved from https://transplant.surgery.ucsf.edu/conditions--procedures/liver-transplant.aspx

Organ Donation - American Liver Foundation. Your Liver. Your Life. (2015). Retrieved from https://liverfoundation.org/for-patients/resources/organ-donation/

Macas, T. (2014). Shortage of donors a challenge for liver transplants in PHL. Retrieved from http://www.gmanetwork.com/news/lifestyle/healthandwellness/379773/shortage-of-donors-a-challenge-for-liver-transplants-in-phl/story/

Lee, C., & Mangino, M. (2009). Preservation methods for kidney and liver. Organogenesis, 5(3), 105-112. doi: 10.4161/org.5.3.9582

E. E. Guibert, A. Y. Petrenko, C. L. Balaban, A. Y. Somov, J. V. Rodriguez, and B. J. Fuller, “Organ Preservation: Current Concepts and New Strategies for the Next Decade,” Transfus. Med. Hemother., vol. 38, no. 2, pp. 125–142, Mar. 2011.

C. J. E. Watson and J. H. Dark, “Organ transplantation: historical perspective and current practice,” Br. J. Anaesth., vol. 108, no. suppl 1, pp. i29–i42, Jan. 2012.