Sepsis is a medical condition that results from an overwhelming immune response to infection and is the cause of 1 in 5 deaths worldwide. In the US it results in hospitals spending about $56.6 million on sepsis care every day and still 1 in 3 hospital deaths in the US are septic patients. As terrible as these statistics are for wealthy countries like the US, the problem is even more severe in low-and middle-income countries where 85% of the global sepsis cases actually occur. Currently, the most common method to detect sepsis is by culturing, which is invasive and takes 24 hours for a conclusive diagnosis. The delayed diagnosis, together with the need to first recognize the symptoms to initiate the blood draw, increase the risk of a patient to progress into severe sepsis. It is crucial to detect sepsis and administer the correct treatment as early as possible, as each hour delay reduces the chances of survival by 7.6%. Sepsis is a global health issue, and the only ability to quickly detect and treat it will save millions of lives.

As part of the international Genetically Engineered Machines (iGEM) 2021 team, I have developed a wearable biosensor that can continuously measure sepsis. This non-invasive approach allows for a diagnosis in the early stages of sepsis by reporting real-time concentrations of a customizable set of biomarkers. By addressing this project through five competencies (Research, Interdisciplinary, Global, Entrepreneurship, and Service), I have contributed to the National Academy of Engineering's Grand Challenge of Engineering Better Medicines.

Research Competency

In order for our biosensor to work it was necessary to collect and transport sweat from one part of the body to the sensing electrodes. I found microfluidic principles to be the best approach for our project and after consulting with the team, the Bio-sensing research labs within the field of biosensing, such as Dr. McGrath and Jeffrey Bean, I first created an initial design of the microfluidic device in COMSOL.

The microfluidic device is composed of three main sections: one for the collection of sweat, one for the actual electrochemical reaction and output, and a final reservoir for used and excess sweat. I decided to use an inverted pine tree-like structure composed of very narrow capillaries for the collection of sweat (see left most part on Figure 1). This part will be in contact with the skin and allow the sweat to wick into the capillaries and, due to pressure differences, move slowly towards bigger capillaries and our electrodes. A single, closed, long and relatively wide (in comparison) channel will be used for the electrochemical reading. The sweat electrodes are placed in series in this channel. The final component is a reservoir into which the ‘used’ sweat pools after flowing over the electrodes. It will contain micropillars (5mm pillars evenly spread out in a microfluidic device to increase surface area) to act as a passive pump and help wick the sweat all the way to the end. The last wall (furthest to the right on Figure 1) will be left open to the atmosphere to allow for the evaporation of sweat. This will prevent the build-up of sweat and eliminate the need to empty the reservoir every so often, allowing for continuous collecting and flowing of sweat from beginning to end.

I 3D printed a mold of the micropillar prototype with ABS plastic and consequently used POM to create the microfluidic prototype, which I could then use to test real fluid flow rates and compare to those modeled by the COMSOL simulation through imaging, I injected a mixture of food coloring and water into the device and documented the flow rates at the three different sections outlined above. Afterwards, average flow rates were calculated for each section and at varying inlet flows (Figure 2). Low standard deviations confirmed the precision of the results between trials.

Next, by adjusting the inlet fluid flow velocity in COMSOL, I was able to generate flow velocity profiles through the entire device. I was especially interested in the fluid flow in the main channel, as this is the most crucial part where the actual electrochemical reaction occurs. Flow that is too fast could hinder the binding and dissociation of biomarkers to the aptamers, while flow that is too slow could result in delayed reactions. Figure 3 below shows an example of the COMSOL simulation on when the inlet flow rate was 0.067 m/s. The center velocity is about 0.01m/s or 10mm/s. The experimental results gave a velocity of 8.11m/s. The slightly slower flow can be explained from human error when cutting out the device using a scalpel. Small irregularities when cutting can alter the dimensions of the device minimally, but enough to affect the flow rate. However, given that a slightly slower flow from the outlet towards the center is crucial for enough time for the biomarkers to bind and dissociate from the aptamers, these results were thus great. All velocities were consistent with the data collected during the experiments thus confirming the accuracy of the simulation.

The confirmation of the accuracy of the COMSOL simulations was important to be able to implement the input from the fluid-flow model our modeling team was working on. Their goal was to determine a suitable flow rate of sweat in the main channel that would allow for binding and dissociation of the biomarkers to happen without having to pass the sweat at the electrodes. This would allow us to have a continuous flow and thus real-time monitoring of sweat and biomarker concentrations. The optimum volumetric flow rate found by the model was 0.13 m/s, and the average human sweat rate at rest when induced pharmacologically is about 0.007 m/s. Based on this information I could then run COMSOL simulations and adjust the parameters of the device as needed to match the flow rate in the main channel and produce a correct and accurate microfluidic device for our purposes.

Global Competency

As a global competition with over 300 teams from all over the world, iGEM is the perfect platform for international collaboration. I was able to exchange ideas, give and receive feedback, and share expertise with different teams and experts from all over the world. I especially helped a team from Brazil design an electrode mask in Onshape while they could help us find the best to measure the signal produced when biomarkers are present in sweat. I was also in contact with countless professionals from all over the world to get feedback on our project and receive help whenever needed. In particular, professionals from TU Delft in the Netherlands and from the Universidade Presbiteriana Mackenzie in Brazil were of great support and shared their knowledge with us via many zoom calls. Being able to collaborate internationally showed me the importance of open science and especially showed me to see science as a common path to intercultural understanding.

Entrepreneurship/Innovation

Innovation was a big part I considered when creating the final design of what would become the Bio-sensing device. It was important to me to design a device that can be easily adapted to other medical conditions to continuously monitor a patient. The Bio-sensing device is modular, as the sensing electrodes can be adapted to be able to recognize sets of biomarkers special to any other application. When designing and building the biosensor I just extra emphasis on creating a device that uses cheap materials, is easy to manufacture without special equipment and is at least partially disposable, so that it can specifically have an impact in the low-resource environments worldwide.

The cost of production is about $375 per device, with only the electrodes needing frequent replacement. Even if selling it for $5,000 to leave room for profit, the sensor is much cheaper than typical biosensor diagnostic devices, which cost between $2,000 and $5,000. As a team, we have used the Bio-sensing device to develop a business executive plan and have participated in the New York Business Plan Competition, the Forbes Entrepreneurial Competition, and the Mark Ain Business Model Competition.

Service Competency

To make science accessible for everyone, the team and I incorporated inclusivity efforts into as many parts of the project as possible. We particularly tried to increase exposure and access to STEM fields and specifically synthetic biology for autistic students here at the University of Rochester. As a part of these efforts, we wrote a ‘Best Teaching Practice’ document that focuses on universal design learning to provide professors with suggestions on how to help and support autistic and neurological students alike. The document is now available to professors through the iGEM library resources. Additionally, these practices were used to create a new laboratory course in collaboration with Dr. Alexis Stein to help neurodiverse students but also interested neurotypical students to acquire the necessary skills to feel confident in finding research opportunities on and off campus. This course will be officially offered at the University of Rochester starting Fall 2022.

References


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