SENSUS COMPETITION

# UppSense Team Results Document


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# Contents

# 1 Website Summary

With increasing population and interconnectedness, the availability of a reliable, rapid and affordable virus testing kit becomes essential in the fight against viral infections; as further emphasized by the ongoing Covid-19 pandemic.

It is estimated that yearly, 650,000 people die of respiratory diseases related to seasonal influenza world-wide [1]. In order to combat rising concerns, UppSense has come forward to develop a robust biosensor against Influenza A, the most common strain of Influenza. Through this platform, we aim to supplement the current healthcare facilities with faster and simpler testing methods, thereby mitigating the spread of viral agents.

We are a team of fifteen students with diverse academic and cultural backgrounds, held together by our shared passion for creating a safer future. Our device - InfluSense 1.0 utilizes a single-use-chip that employs the principle of an antigen-antibody complex formation. It is tested to confer rapid detection and quantification of hemagglutinin (viral surface protein) of the H1N1 variant, directly from saliva. With InfluSense 1.0, our ultimate aim is to offer affordable and easily accessible testing in the form of a point-of-care device.

We are excited to share our work with the world as a part of the SensUs competition!

# 2 Biosensor System & Assay

## 2.1 Molecular Recognition and Assay Reagents

The molecular mechanism is based on antibody-protein recognition. In order to increase the specificity (*i.e.* decrease detection of familial viral strains), monoclonal antibodies (MAbs) were chosen. For the recognition of H1N1, mouse monoclonal IgG1 recombinant antibody (SinoBiological, cat No. 11055-MM04T) against the recombinant H1 particle of California/04/2009 H1N1 influenza A strain was used. An epitope of the HA particle in artificial saliva samples is specifically detected by hydrogen, weak, ionic, and hydrophobic interactions. Paratope of the antibody N-termi conists of from three hypervariable loops from heavy and light chains, forming an antigen binding site on each of the Fab regions. However, MAb binding to H1 does not ensure specificity to the H1N1 influenza strain, as it cross-reacts with H1N2 and H1N3 complexes that share same H1 protein. To that end, and noting that murine antibodies have an isoelectric point of between pH 5.9-8.3 [2], the MAbs were immobilized in phosphate buffered saline (PBS, pH 7.4). This should increase the yield of the surface binding to the electrode by decreasing solubility of the antibody molecules in the range of their isoelectric point. The biorecognition element(s) are the aforementioned MAbs, covalently immobilized onto our carbon electrode with gold nanoparticles (AuNPs), making them relatively independent of mechanical changes that may occur during washing steps, or similar. The bifunctional molecule, 4-ATP, was used to functionalize the AuNPs through thiol bonding to the metal. The amine group remains free in the p-position from the S-Au linkage so maximal degrees of freedom could be provided for antibody binding (see Figure 1).

## 2.2 Physical Transduction

Differential Pulse Voltammetry (DPV) is an electrochemical technique in which a series of potential pulses on a linear ramp are applied; the current of the system is measured before and after each pulse. The difference in current between those two points is recorded for the series of pulses and later used to characterize the surface of the electrode. DPV is a suitable technique for quantitative determination as the application of differential pulses minimizes the background current and improves the sensitivity of biosensor systems [3].

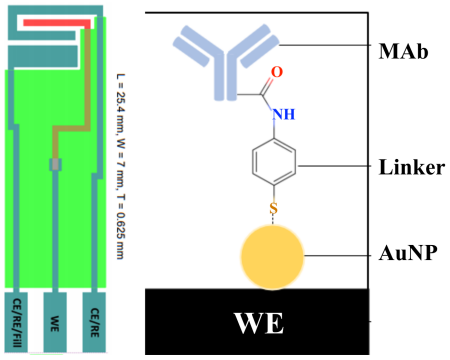


**Figure 1:** The schematic representation of the electrochemical chip (left), and chemistry of the functionalisation (right). On the schematic, from left to right: CE, WE (outlined in red) and RE. The green area represents a layer of the insulator. On the right hand side: the WE functionalised with MAb through AuNP and a linker molecule.

InfluSense 1.0, utilizes screen-printed electrochemical chips with carbon-based working (WE) and counter electrode (CE) surfaces, and a silver/silver chloride surface on the reference electrode (RE) (see Figure 1). The WE is modified with AuNPs, bearing sizes from 150 to 200 nm (characterized by scanning electron microscopy (SEM), Figure 10), capped with 4-ATP through a gold-sulphur bond. These nanostructures amplify the electrochemical signal by increasing surface area and, at the same time, are used to anchor the biorecognition element through the formation of a stable, amide covalent bond to the surface of the electrode. This is aided by using site directed immobilization of monoclonal antibodies with EDC/NHS chemistry [4]. The assay employs 5 mM $[Fe(CN)_6]^{3-/4-}$, as an electrochemical probe to detect changes in the surface of the electrode. A base signal is established when there is no presence of the H1 protein in the sample. When the electrode has contact with a sample containing H1 protein, the protein is captured by the MAb inducing a blocking effect that decreases the current measured by DPV. The decrease in the current is proportional to the concentration of H1 in the sample.

## 2.3 Microfluidic System & Cartridge Technology

The microfludic system depicted in Figure 2 creates the optimal conditions for a DPV measurement, by working in three steps: sample introduction onto the WE, washing of sample with buffer (PBS), and introduction of $[Fe(CN)_6]^{3-/4-}$. The system has cartridges with sufficient volume of PBS and the $[Fe(CN)_6]^{3-/4-}$ for 10 tests. This design mixes assay and sample components while extracting H1 protein at the same time.

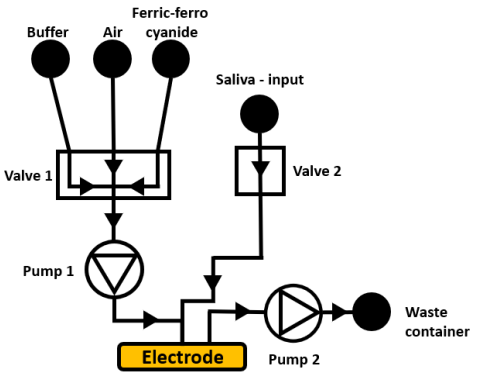


**Figure 2:** Schematic of the microfluidic system from fluid reservoirs to the electrode and to the waste container. Peristaltic pumps control the flow rate to and from the electrode while valves control which fluid is manipulated by the system. Valve 1 controls the buffer, air and $[Fe(CN)_6]^{3-/4-}$, while valve 2 controls the saliva sample. Pump 1 controls the flow rate for washing and testing the electrode while pump 2 controls the removal of the fluids from the electrode. Both the pumps and the valves are controlled by the Raspberry Pi.

The electrode is glued onto a 3D printed chip and sealed by plexiglass with appropriate connections to create a water-tight environment. After a small setup stage of introducing the electrode and slotting the saliva's tubing into the valving system, the biosensor becomes completely controllable via the motors and valves and thus can be automated. The number of tubes is reduced to a minimum, as sample contaminated tubes are discarded after each use, making tube replacement easier for the handler after each iteration. The chip is connected to a potentiostat which then runs DPV, measuring electron exchange between the WE and the redox mediator.

## 2.4 Reader Instrument and User Interaction

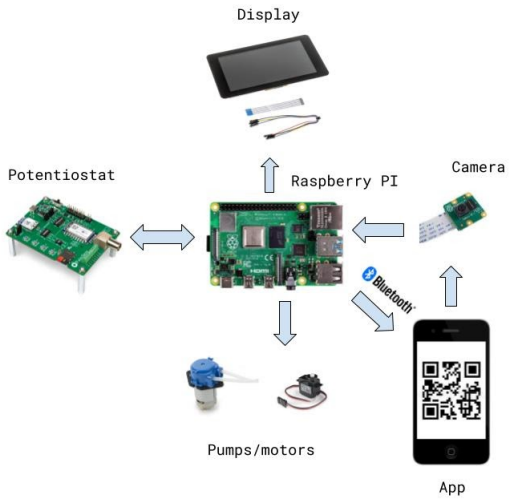


**Figure 3:** Overview of the system hardware. Raspberry Pi 4 chip is connected to the potentiostat, the display, the camera, pumps, and motors, serves as main computational component. A bluetooth connection with a smartphone enables instant result visualization.

The size of the entire biosensor is 288 mm $\times$ 200 mm $\times$ 150 mm (containing all components besides the app, shown in Figure 3) and is battery powered to make the biosensor portable. As the system itself is fully automated, the patient applies the saliva sample, while trained staff inserts the chip, presses start and later removes it.

To obtain the result, the biosensor's camera scans a QR code from UppSense's smartphone app (see Figure 9), designed with end-user preferences in mind. The QR code carries a randomly generated Universally Unique Identifier (UUID), which is read by the Raspberry Pi and used to communicate over the Bluetooth Low Energy (BLE) protocol, exclusively to the user's smartphone. The staff may view the test result on the display.

The EmStat Pico Development kit potentionstat from PalmSense, handles the electrochemical measurements. This, together with all other hardware is controlled via the Raspberry Pi, with a finite state machine program that tracks the entire system and uses different signal events to invoke different processes. This is essentially a scalable and modularized, high granularity algorithm, containing a flexible routine structure which runs the control routine that it's class set. Please refer to Appendix 8.1 for more detailed discussion about the operational and app softwares, as well as how we aim to handle the data.

# 3 Technological Feasibility

## 3.1 Microfluidic System

Following the schematics given in Figure 2, the pump-valve and microfluidic system has been set up accordingly and run with 50 $\mu$l of distilled water, simulating the input saliva. The buffer and ferro-ferricyanide were simulated using coloured water. This gave us qualitative proof that the microfluidic system can control the direction and the fluid utilised. Two tests of the flow rate were then performed repeatedly, namely at 32 $\mu l\, s^{-1}$ and 22 $\mu l\, s^{-1}$, corresponding to 5% and 1% of the maximum working power of both of the pumps. These tests give us an overview of the flow rate for the pump. Adjusting the power of the motor gives us full control over the rate of fluid entering and exiting the electrode.

## 3.2 Electrode Modification

The carbon electrodes are modified in several steps, each preparing it to be functionalisable with the MAb in the last step. Figure 4 shows the Cyclic Voltammetry (CV) characterisation of each step, where the bare carbon electrode corresponds to purple curve and each subsequent step corresponds to a different colour. The first step is to coat the surface of the carbon electrode with AuNPs, using electro-deposition. The green curve in Figure 4 corresponds to the electrode after AuNPs have been deposited to it. The AuNPs amplify the signal, which is reflected in the increased amplitude of the voltammetric peaks.

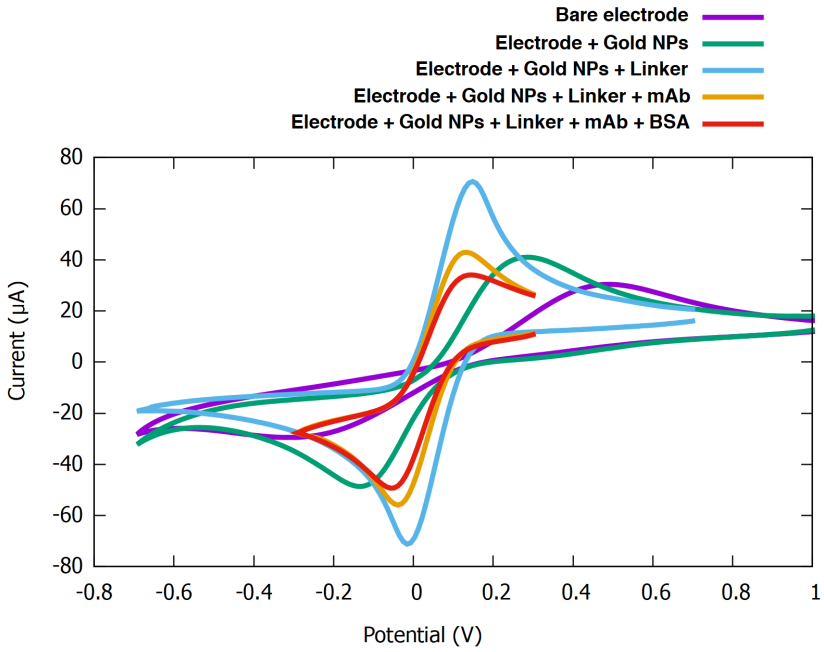


**Figure 4:** Cyclic Voltammetry characterisation of all the distinct layers the carbon electrodes were modified with.

The deposition of AuNPs is followed by the second step - applying the linker molecule characterised by the (light) blue curve in Figure 4. The linker amplifies the signal due to tunneling charge transfer. This phenomenon occurs as the linker has many different resonance states for electrons which helps the electrons to travel towards the electrode. The antibodies are subsequently conjugated to the linker which creates a barrier thus reducing the signal - orange curve. Finally, the electrode is covered with BSA which surrounds the linker molecules, filling in the bare electrode spaces and thus decreasing unspecific binding to the antibody (red curve). This decreases the signal as it adds further resistance.

### 3.3 Measurement Calibration

The biosensor has been calibrated using a series of standard solutions in artificial saliva, these solutions contained H1 protein in a concentration range that is clinically relevant (1 to 10,000 $pg$ $ml^{-1}$) as shown in Figure 5, below. This experiment was performed at room temperature (22° C) for 25 minutes. As demonstrated in Figure 6, there is a clear trend between the concentration of H1 and the current that can pass through the electrode, indicating that the biosensor can be utilised for detecting and quantifying H1 protein. For lower concentrations, the detection becomes less reliable, but down to 100 $pg$ $ml^{-1}$ it is accurate.

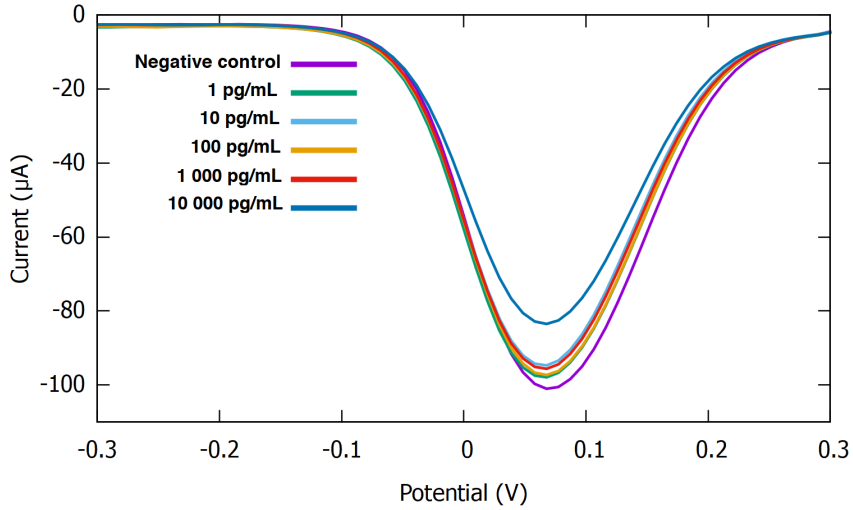


**Figure 5:** Differential pulse voltammogram obtained with the biosensor after incubation with H1 protein at room temperature for 25 minutes, at various concentrations. (Electrochemical parameters: pulse amplitude of 86 mV, potential increment of 4 mV and scan rate of 100 $mVs^{-1}$).

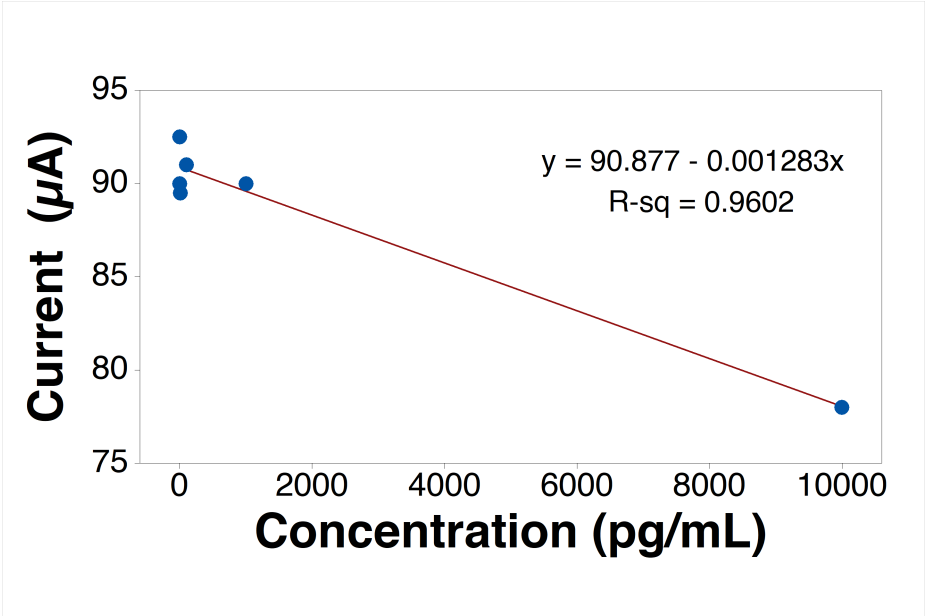


**Figure 6:** Calibration curve obtained from the DPV measurements shown in Figure 5 with different concentrations of H1 protein in artificial saliva.

# 4 Originality

## 4.1 Team

Our biosensor has four novel characteristics: the amplification of the electrochemical signal, the microfluidic chip, the portability/automation of the whole system, and the corresponding app. To our knowledge there is no assay or system where the system is completely automated to detect H1N1, especially not with how the sensor interacts with the user through the app and camera on the biosensor. To the best of our knowledge, the code and what is included in our app is novel. The business plan and marketing strategy was contrived by motivated members of the team. Outside guidance was used only in validation of the plan and ideas.

Electrochemical biosensors for the detection of H1N1 as well as the use of gold nanostructures to amplify the electrochemical signal in biosensors have been reported previously [5, 6, 7]. However, our biosensor is novel in view of the fact that we coated the gold nanoparticles with a molecule that undergoes tunneling charge transfer. Due to that we managed to enhance and amplify the electrochemical signal to an extent which exceeds the one achieved by using bare gold nanoparticles.

Our app is also novel and was based on ideas from the team that were realized by our engineers. Apps like this exist and hence inspiration may have come from others. To the best of our knowledge, the code and what is included in our app is novel.

We also got support from our sponsors who graciously provided us with the following parts: electrodes (Zimmer and Peacock), and technical advice (PalmSense).

Jayendra Ellamathy
Team Captain

Viktoria Langwallner
Team Captain

## 4.2 Team Supervisors

The team has been working independently and professionally with two approaches during the project, an optical and an electro-chemical-based sensor. Before summer they decided to focus all their attention on the electro-chemical sensor since they managed to obtain good signal to noise with low levels of target protein spiked in PBS solution. After doing literature studies and brainstorming discussions, the team came up with the biomaterials and technology, which they used to build their biosensor by themselves. The students have been proactive discussing with experts in different fields to design and fabricate the different parts of the biosensor. However, the students can take all the credit for conceiving, selecting, adjusting and testing their biosensor. They have also been very successful getting in touch with partners, who contributed with small pieces of equipment that could be integrated together. As mentioned in the originality section of the report, although the general concept of creating an antibody-based biosensor with electro-chemical technology to detect H1N1 is not entirely new, the students designed new chemical reactions to more efficiently bind the antibody on the electrode. The supervisors confirm hereby that the statements made by the team and by ourselves are true.

Assoc. Prof. Gemma Mestres
Coach team UppSense 2021

Masood Kamali-Moghaddam
Digitally signed by Masood Kamali-Moghaddam
Date: 2021.08.16 12:13:31 +02'00'

Prof. Masood Kamali-Moghaddam
Supervisor team UppSense 2021

# 5 Translational Potential

## 5.1 Business Model Canvas

We kindly invite you to Appendix 8.3, where Figure 11 displays our business model canvas.

## 5.2 Market Description

Within Sweden alone, the annual, average number of Influenza A tests is approximately 55,000, with laboratory confirmed positive tests amounting to only about 13% of that [8] (see Table 6). This hints at a possible business opportunity for UppSense in the Swedish market.

In Sweden, viral tests may be provided by hospitals, healthcare centers, general practitioners or pharmacies. Among these, pharmacies are the most accessible to patients; not requiring bookings or long waiting times and having longer opening hours than healthcare centers. About 60% of the Swedish population already goes to one of the 1,426 community pharmacies to purchase over the counter drugs and other retail goods [9]. Swedish pharmacies already offer a variety of testing such as taking blood, performing certain blood tests, and most recently, antigen tests [10]. Pharmacists are thus trained personnel, able to handle infectious waste, as well as provide consultation for patients once diagnosed with InfluSense 1.0.

UppSense aims to target its domestic, Swedish healthcare market first, and later expand to other Nordic countries such as Finland, Norway, Denmark and Iceland, which have similar healthcare infrastructures and demographics. In the market expansion phase, hospitals, healthcare centers and general practitioners are considered as potential customers as well.

## 5.3 Stakeholder Desirability

As in the ongoing SARS-CoV-2 pandemic, Influenza tests in Sweden mainly comprise of invasive nasopharyngeal sampling, with hours of detection. In some cases blood tests are also taken in order to rule out other diseases. The sample is then analyzed in either the hospital or an external lab. Currently, PCR and rapid tests are being used to analyze Influenza samples [11]. The public health agency uses one-step real-time PCR to detect, distinguish and assure good quality detection which takes up to an hour, plus they require a lot of steps, manpower and equipment [12]. See Table 4 for more information about the current tests. During the interviews (Tables 1, 2 & 3), we found that the time required for these tests ended up overworking health care workers and generating anxiety in patients due to the long wait. In the case of a respiratory virus outbreak, health care workers might need to be PPE suited, further emphasizing the importance of a fast and simple detection system.

With these issues in mind, UppSense has developed a biosensor - InfluSense 1.0, that accurately measures the presence of H1 in saliva, detecting Influenza strains H1N1, H1N2, and H1N3, in under 15 minutes. InfluSense 1.0 is aimed to be widely accessible with chips priced at €5, and minimizing long waiting queues at testing centers. With pharmacies being our primary customer, health care centers and hospitals will have decreased workload. Due to increased popularity of online pharmacies, on-site pharmacies are faced with declining revenues and are in dire need of additional revenue streams. We aim on selling our entire biosensor testing system to them as a one-time purchase, while chips containing the biorecognition elements are sold recurrently to them, as needed. In the future UppSense will be able to adapt their chips to changing virus strains or even very different viruses.

In practice, patients purchase their test, walk to the prescription pick-up/help desk where InfluSense 1.0 is stationed, and give their sample to the pharmacist. The pharmacist inserts the chip and presses start, and InfluSense 1.0 analyses the sample in 15 minutes. The patient scans the QR code on InfluSense 1.0 and momentarily receives their results in the UppSense app. The pharmacist can then safely remove the chip, and dispose of the waste chamber when needed. From

the interviews we discovered the need for mental support, hence the pharmacist also has access to the results and can provide guidance to the patient in regards to treating their symptoms if the test is positive. The patient then may purchase relevant medicine at the same pharmacy, further aiding the pharmacy financially. The app also allows the patient to contact a doctor for a virtual consultation if antiviral drugs need to be prescribed.

### 5.4 Business Feasibility

UppSense is financed by Uppsala University and supported by its sponsors. The two main sponsors are Zimmer & Peacock (ZP) who provide the electrochemical chips, and PalmSens providing the hardware and software for the electrochemical analysis. UppSense, aims to form a supplier contract with SinoBiological for supplying the antibodies and other chemicals, with ZP for their chips, and with PalmSense for their EmStat Pico potentionstats. UppSense is potentially interested in working with Oriola and Tamro for expansion in the market since the latter provides pharmacies from all Nordic Countries with their utilities [13]. Thus, getting the benefit of their experience to reach pharmacies with InfluSense 1.0.

UppSense's commercialization strategy is based on selling InfluSense 1.0, the chips (as one-time tests), and the cartridges (as resupplies) to pharmacies and later to other healthcare institutions. The commercialization strategy therefore begins at a regional level, advertising the virus recognition chips at pharmacies, hospitals, and elderly care homes. We think that the recommendation of workers from the healthcare system is key for the expansion in Sweden. As the customers' ideals align with the EU goal of "enhancing preparedness and management of future pandemics" [14], UppSense hopes to fit well into the current healthcare system. Additionally, UppSense will attend biomedical conferences and scientific fairs to further their know-how and meet potential partners. Finally, Uppsala has Drivhuset, a known StartUp incubator in Uppsala, which could collaborate with UppSense.The commercial implementation of the technology presents other alternatives, as already mentioned the chips can be prepared for detection of other viruses. Lately, collaborations with already existing services such as Kry that offer telemedicine [15]. Since they can see your medical history via your social security number, they could be a partner and be integrated into our app. Where they could offer a consultation, provide a diagnosis and prescribe prescription drugs (antivirals).

### 5.5 Financial Viability

Following the business model laid out in the sections above, UppSense's financial plan contains three revenue streams: the biosensor - InfluSense 1.0, single use electrodes or "chips", and resuppliable cartridges.

As the cartridges and chips are replaceable parts, the biosensor itself is a one-time purchase, able to handle a large number of tests. It comes as a complete package including a Data Analysis software, aid in setting it up, as well as repairs due to unforeseeable issues. Each pharmacy in Sweden and the Scandinavian countries is sold InfluSense 1.0 for €1,000, which includes a full cartridge as well as 10 chips.

In order to estimate the production/sales forecast, a simple bottom-up approach has been used. The number of pharmacies in Sweden (or other scandinavian countries) gives the market cap of maximum of 1,500 InfluSense 1.0 biosensors, which UppSense is estimated to reach within 3 years after market entry in 2025. This is 4 years after establishing UppSense as a Swedish startup in 2022, which should give sufficient time for enlisting InfluSense 1.0 as a medical device, obtaining a CE marking, undergoing the necessary clinical trials and further optimisation. During this "developmental" phase, UppSense does not expect any revenue.

The number of pharmacies, however, does not provide any information about how many patients would get tested. From information gathered over the past 8 years (summarised in Table 6), there is an estimated total of 50,000 Influenza A tests issued per year, in Sweden. Since this covers the

whole country, UppSense confidently estimates distributing 10,000 chips (*i.e.* single tests) at the market entry. Each test is sold for €5, yielding a competitive price for a rapid test even after the pharmacies' markups. With economies of scale, the cost of a single electrode is reduced by about 90%, to roughly €0.7. The estimation of the number of cartridges follows from that of the chips, as each cartridge holds enough solution for 10 chips. The cartridges are sold at €30 per unit and require minimal human input to be manufactured.

Figure 7 shows UppSense's Profit & Loss account overview across 8 years. The other two revenue streams are not displayed as they do not contribute to the revenue as significantly in the amounts modelled in Table **??**. The estimation starts with the assumption that an initial investment of €200k is made to UppSense, and implies that UppSense becomes profitable at the end of 2026, but only gets out of debt sometime in 2028.

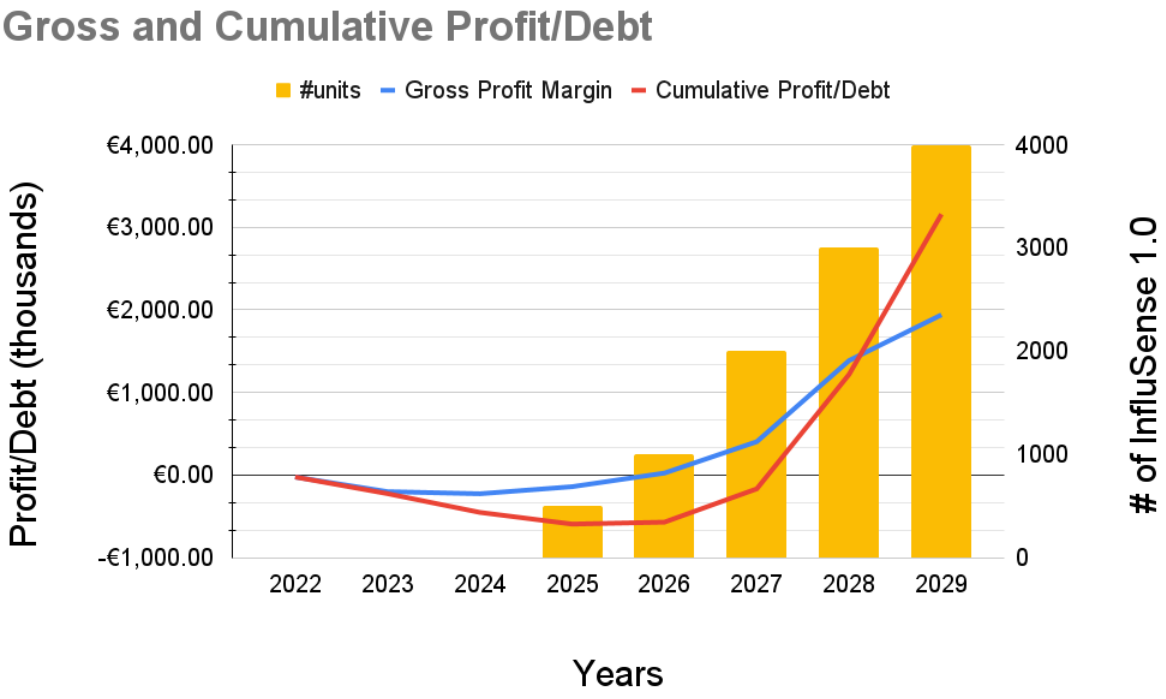


**Figure 7:** Financial overview of UppSense; blue and red line showing Gross Profit margin and Cumulative Profit/Debt, respectively. The yellow bars refer to units of UppSense's most profitable revenue stream - InfluSense 1.0.

The time period spent in debt and/or without profit can be reduced mostly by lowering costs. The largest cost is the EmStat Pico potentiostat at roughly €290 when purchased in batches of 1,000 units. This could lowered by either 'stripping' the component down to a simpler version or entering into a favourable supplier contract with even higher economies of scale. This would also allow for more competitive price point and possibly a wider reach in the market.

Apart from that, many diversification strategies could be beneficial for UppSense. Not only do governments demand for gathering disease-related data (which could be sold), but there may be other institutions apart from pharmacies that could benefit from InfluSense 1.0, as mentioned in earlier sections. UppSense's chips may also be modified for other viral strains, provided that an antibody for those strains is commercially available. Hence, given a demand for other strains, UppSense could diversify in that direction, as well. While those strategies have not been taken into account in this analysis, please refer to Appendix 8.3 for further information about the financial aspects.

# 6 Team & Support

## 6.1 Contributions of the Team Members

| Name | Contributions |
|---|---|
| Carlos Torres | Electrochemical development, patient survey, biosensor development and lab work. |
| David Bern | Software development, microfluidic design, financial plan. |
| Ines Berrojo | Biology team, social media (Instagram), patient survey. |
| Ivana Jovanovic | Biology team, biosensor development and lab work. |
| Javier Sebastián | Microfluidic design, business plan, patient survey, biosensor development and lab work. |
| Jayendra Ellamathy | Team captain, software development, microfludics design and testing, App development, biosensor case development. |
| Jovanna Gkountana | Biology team, business plan, social media, biosensor development and lab work. |
| Klara Martinovic | Biology team, biosensor development and lab work, 1-min pitch. |
| Maike Lüftner | Biology team, business plan, biosensor development and lab work, animations. |
| Maria Lysandrou | Biology team, initial electrochemical development, business plan, biosensor development and lab work. |
| Patrizia Kühne | Biology team, business plan, biosensor development and lab work. |
| Sam Taylor | Microfluidic design and testing, Software development, biosensor case development, 1-min pitch. |
| Sharmilee Nandi | Biology team, electrochemical development, social media (LinkedIn takeover), biosensor development and lab work, SensUs connect posts. |
| Viktoria Langwallner | Team captain, initial electrochemical development, business plan, LinkedIn takeover, 1-min pitch, animations. |
| Yifan Liu | Software development, microfluidic design and testing, biosensor case development. |

## 6.2 External Support

Firstly, we want to thank everyone who was involved in our process. Then, we would like to thank Christoph Langwallner, for guiding us through a workshop on how to come up with ideas, and collaborate to find novel solutions and for providing us with tools and advice in regards to our business model. We would also like to extend our deepest gratitude to Abdul Raouf Atif and Ehsan Manouchehri for being such supportive lab supervisors. We would also like to thank Quentin Palomar-Marchand and Zhen Zhang for the constant troubleshooting and guidance through figuring out the electrochemical system. We would also like to thank Máté Erdélyi and Scott Wilcox for allowing us to work in your lab, and guiding us through making our own linker. Finally, we would like to thank Gemma and Masood for the advice and guidance through this project.

## 6.3 Sponsors

We want to thank Ibsen Photonics, Dyenamo, BrightComSol, Ligand Tracer and Magnetic Bioprocessing for all your help with the optical biosensor. Zimmer and Peacock have so graciously provided us with our first shipment of electrodes and endless advice and troubleshooting help. PalmSense had provided a potentiostat in the previous years and they have so graciously guided us on how to use their software and provided troubleshooting as well. Lastly we really want to thank our partners, Bronkhorst, Micronit, TTP, and Medtronic who through numerous meetings and calls provided us with feedback and guidance. We really appreciate their insight and all the expertise that they shared with us. We also want to thank Uppsala University for allowing us to take part and giving us financial support.

# 7 Final Remarks

Firstly, we want to thank everyone who has given us support. It has been quite a challenging time, due to the Sars-Cov-2 pandemic. However, we were able to organize meetings virtually with many different experts, and organize phone calls with nurses and doctors who took time out of their busy schedules to help us. We are very grateful for all the knowledge that was shared and gained.

We would also like to thank the SensUs organization for allowing us to participate in this year's competition and doing their best despite the circumstances. We have learned so much through this process and are extremely grateful for this. We were able to explore learning from a self-directed, hands-on process that is not readily accessible in ordinary classes, which is a great way to learn and explore.

We are also honoured to be able to contribute to the scientific community by developing a biosensor that has shown to detect Influenza, and has four novel characteristics, as mentioned in section 4. However, our biosensor needs to be further refined before being able to be utilized by the medical industry to detect and trace influenza. We believe that our chip design, with small adjustments regarding antibody specificity and sampling procedure, could be used to detect other (pandemic) viruses. It could even eventually be used in multiplex assessment of different viruses.

With the constraints that we had due to the pandemic, with very limited lab access, constant regulation changes, and limited in-person meetings, we did our best to produce a biosensor that we are proud of. We have preliminary data that shows proof of concept. We believe that with more time in the lab we could optimize our biosensor and greatly reduce detection time.

# 8 Appendices

## 8.1 Appendix A - Biosensor System & Assay

The portable potentiostat, EmStat Pico Development kid from PalmSense, handles the electrochemical measurements. The affordability, compactness, wide community support, and Raspberry Pi ease of use made it a good fit for our application. A small touch-screen display module aids the user-interface. As the entire biosensor comprises of many individual components that need to work in conjunction with each other, the operational software on the Raspberry Pi needs to be robust. The implementation of such a complex system requires a high granularity control algorithm that is scalable and modularized. To that end, we created a program with a finite state machine that tracks the status of the whole process and uses different signal events to invoke different processes. A routine structure that takes all its inherited classes is built, running the control routine that this class sets, so that the reading process can be changed with addition of new classes. After all the sample handling process is done automatically, the state machine will invoke the reader instrument to apply voltage and read the current, after that, the data will be passed to the next step.

Our user-interface has been designed keeping the end user and various deployment scenarios in mind. To obtain the test result on smartphones, the QR code in the UppSense app is scanned by the camera on the biosensor. The QR code (Figure 9) encodes the device information which is used by the biosensor. Here, a randomly generated universally unique identifier (UUID) is encoded in the QR code. This UUID is read with the aid of a camera by the RaspberryPI, which is then used to communicate over the Bluetooth Low Energy (BLE) protocol with the user's smartphone exclusively. The entire procedure of transferring the result is almost instant without any configuration steps from the user. The information sent is encrypted for security. Additional information, such as: passport numbers, emails, or Swedish national identity numbers can also be encoded on the QR code for the purpose of generating a travel certificate. This method also ensures a contact free method thereby minimising the risk of spread of the virus.

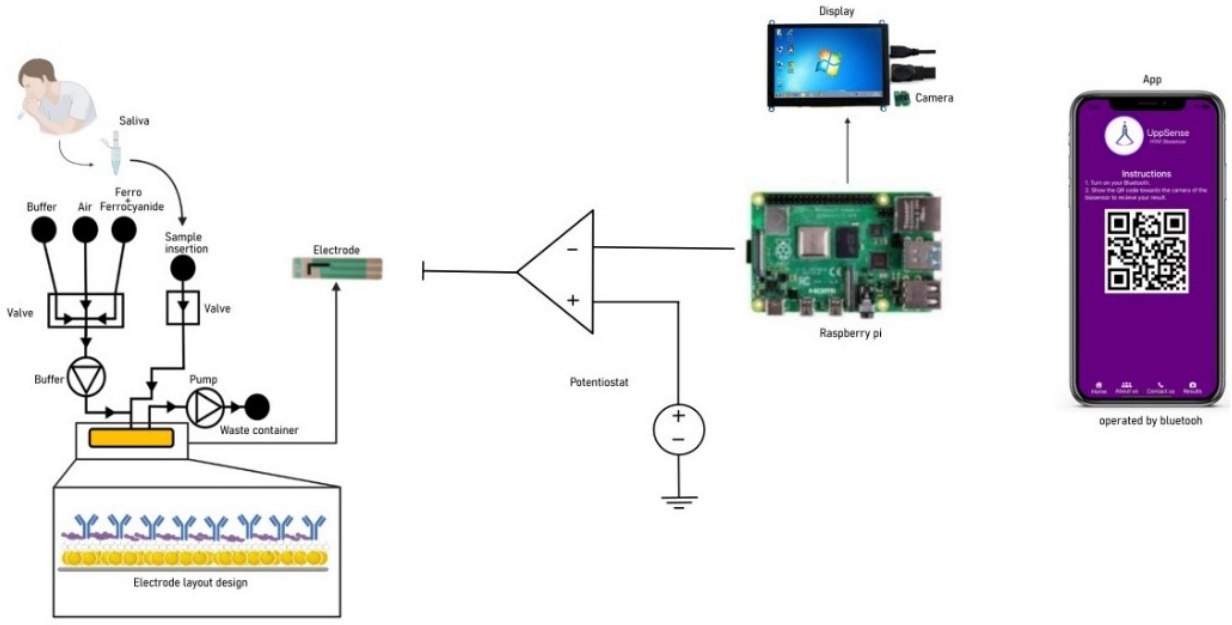


**Figure 8:** Schematic overview of Biosensor System including sampling principle, cartilage technology, biosensor assay, signal transduction and conversion into test results displayed in the app.

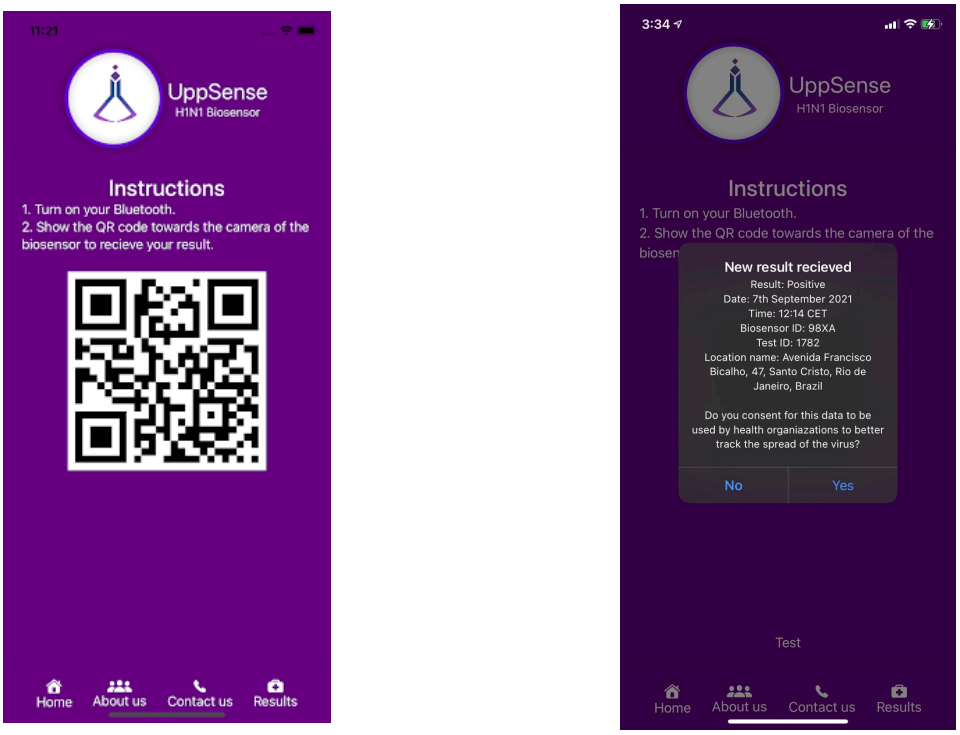


**Figure 9:** The free app that enables patients to obtain and save/share their results. Left: Homepage of the UppSense app with the QR code. Right: An example of a typical result obtained on the UppSense app.

Data can be an useful analytical tool for health organizations/government. An example of the results can be found on the right screenshot in Figure 9, which typically includes useful information such as the test result, date-time, biosensor/test ID and location. Hence, with the consent of the user, this information can be saved on a cloud server. With the location information collected from the user, it is possible to identify nearby biosensors available to conduct tests. Also, it would be possible to find out how many positive cases have been tested in a particular region. This might be of great use to track the spread of the virus.

## 8.2 Appendix B - Technological Feasibility

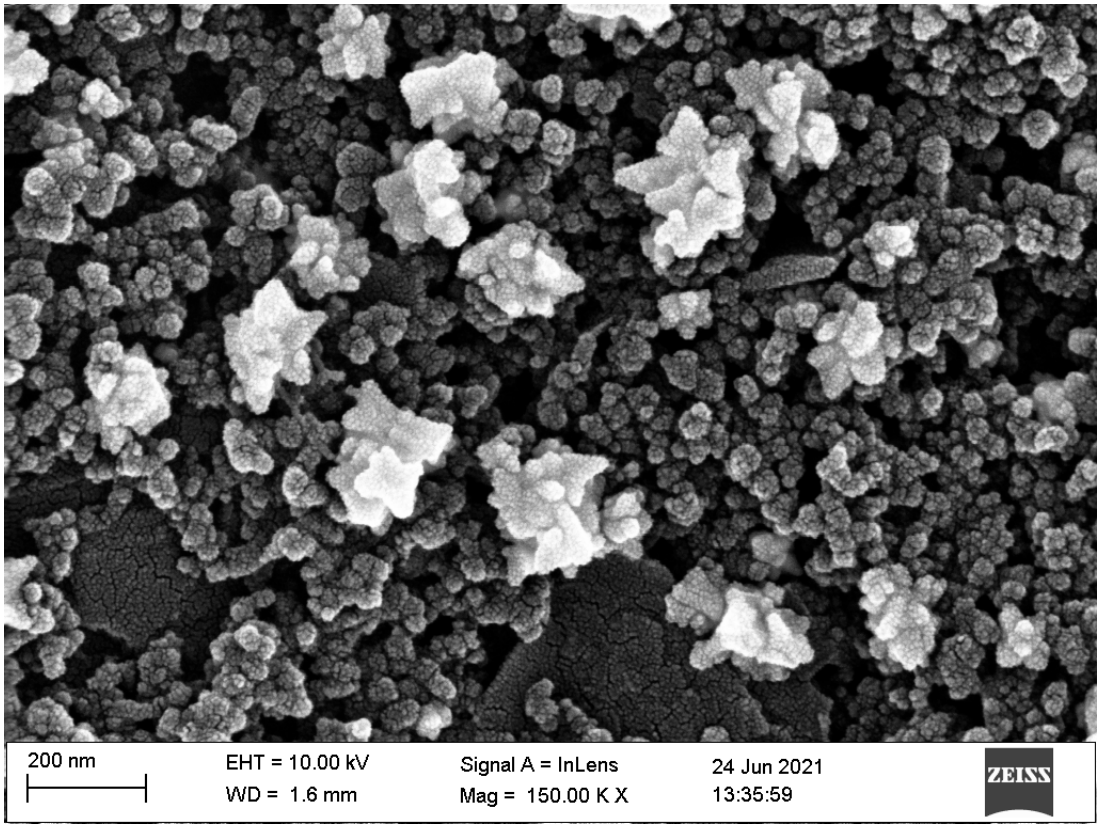


**Figure 10:** Scanning electron micrography of AuNPs electrodeposited on top of the SPCE.

## 8.3 Appendix C - Translational Potential


**Figure 11:** UppSense's business canvas - a summary of all business-relatated matters.

### 8.3.1 Interviews

**Table 1:** Interview with Paula Del Corral, a nurse in Mallorca.

| **Professional Name** | Paula Del Corral |
|---|---|
| **Short description about professional** | Paula Del Corral is a Nurse currently working at Palma de Mallorca. She has an incredible international background which is in the following order. Firstly, she went to Cameroon in the Project of Madrid Rumbo al Sur going for one summer to Africa as a Volunteer under the security of the Spanish ARMY. Secondly, she went to Cambodia with me as a nurse at the cost city of Sihanoukville in the south of Cambodia where I could see with my eyes how she always took care of children and seniors independently of heir own health state. A person that never steps back when a difficulty pops up on the way, a vocational nurse. Thirdly, she enrolled under the masters at Universidad Autónoma de Barcelona in a project at Equator with the aim of developing the telemedicine in the most recondite parts of the country. All of the above experiences make here not only an incredible professional but also a really adequate person to give us tips about our project. Her humane as well as long experience inside and outside Europe give her the possibility to visualize and predict the viability of this device at different parts of the globe. |
| **Conducted by** | Javier E. Sebastian Alonso |
| **Date** | 20th June 2021 |
| **Preparation time** | 30 min |
| **Duration** | 45 min |
| **Summary** | Via phone call was possible to reach the Nurse Del Corral. Firstly, we began with a short of validation of the business model. With a simple look on the diagram miss Del Corral already optimized our approach towards the point of care (POC) application. She highlighted that the chip must present a trustworthy sensitivity in order to track the spread of a virus in a pandemic scenario. Moreover, she explained that a biosensor should work at room temperature if possible because at some locations there won´t be a possibility for refrigeration. Furthermore, the chip must be easy to handle so at POC the people could just receive the device, use it independently so the nurses/ doctors can focus on the real urgencies. Astoundingly, Del Corral gave us a perspective never received before in other interviews. She considered the mental health of the patient since an early stage. She said that it is very useful that a device can be easy to handle so no specialist is needed, but the results of the test should always be given with the support of a Nurse or a Doctor because in case of an unpleasant result there is a high risk that the patient enters in a mental breakdown. She defended that technology development should not dehumanize the health care system of any society because above any development we are humans that need company a support. Finally, Miss Del Corral encouraged us to use the Covid – 19 outbreak as an example to develop a technology that can avoid a healthcare system collapse as it has happened all over the globe. |
| **Evaluation** | Personally, Miss Del Corral gave us the most humane side of the healthcare system which is very difficult to consider. Moreover, her international background made it possible to realized how much a biosensor need to improve. All of these together makes out of this interview a great perspective for the device implementation. |

**Table 2:** Interview with Dr. Álvaro Palazón.

| **Professional Name** | Álvaro Palazón |
|---|---|
| **Short description about professional** | Recently graduated in medical school at Universidad Autónoma of Madrid. Dr. Palazón was a great student since an early stage of life, at his high school the tutors realized about his potential. This doctor entered the University with a scholarship due to having great academic grades. At University he has obtained in many courses the best grade of the class. Additionally, over his graduation thesis project he developed a smart system with the finality to automatize the healthcare system of the Comunidad De Madrid by informing automatically to every doctor about the surgeries that were taking placing all the time. Thereafter, a limited number of doctors could join the surgeon to learn in person about it. In this way it could be potentially possible to track the interventions that are taking at a hospital. Furthermore, with the right agreements between hospitals this system could be applicable to the entire country. Additionally, Dr. Palazón created a Start-up (Próximo) to help at a regional level the development of voluntourism. Through this project it could be possible that all NGOs post their activities at a regional level and volunteers could fast track the activities that are taking place around them making possible to have a better-quality volunteer and volunteerism. Dr. Palazón has also joined international volunteering projects out of Europe as the known and hard to enter project of Madrid Rumbo al Sur. Over this project he went to Cameroon to help people in the country under the security of the Spanish ARMY. |
| **Conducted by** | Javier E. Sebastian Alonso |
| **Date** | 17th June 2021 |
| **Preparation time** | 30 min |
| **Duration** | 45 min |
| **Summary** | Via phone call was possible to reach the Dr. Palazón. Dr. Palazón highlighted the importance of the distance practice of medicine. Firstly, we asked him about the importance of developing a device able to transfer remotely the information of the detection of the virus, he described that technology is there to be used and that in a pandemic case it is a suitable tool since the spread of a virus over an outbreak is hardly followed. Secondly, we asked him about the importance of how expensive a chip should be and he described that we should see how much families pay nowadays during the Covid-19 outbreak to be able to visit each other. He gave us the importance of a daughter to be able to visit it´s mother at the elderly house over a pandemic as fast as possible. Therefore, it is needed to have a chip that gives fast a trustable diagnose since over Covid-19 the ratio of depression in society has increased tremendously. Finally, he suggested us that the device must be easy to use and would be best to function at room temperature since at certain countries the weather is not as convenient for the antibody's stability. |
| **Evaluation** | Personally, as a European doctor this young and ambitious doctor gave us the overview of a device that could function efficiently all over the globe. That is a key point for the development of our product because it is difficult to get an insight in the particular demands that the regions could have, and he gave us a tool to follow up the demands at a regional level. |

**Table 3:** Interview with Gonzalo Suela.

| **Professional Name** | Gonzalo Suela |
|---|---|
| **Short description about professional** | Recently graduated in medical school at Carlos III University of Madrid. Gonzalo was a brilliant student since a really early stage of life. The kind of student that at the age of 12 could read books of any indole, topic or discipline. Since at the high school professors realized about his talent, they decided that at the age of 16 he should join the excellency school where this person could study the international high school in order to open him the doors of the entire globe. However, this doctor decided to remain in Spain to learn the medical system of the country over its bachellor´s education. Now comes his opportunity to grow internationally at the best hospitals of the world. Surprisingly, he is interested in coming to Uppsala´s Universitet Sjukhus to specialise for a couple of years. |
| **Conducted by** | Javier E. Sebastian Alonso |
| **Date** | 24th June 2021 |
| **Preparation time** | 30 min |
| **Duration** | 45 min |
| **Summary** | Via phone call was possible to reach the doctor Suela. The student is specialising in pandemic diseases and holds a scholarship due to being one of the highest graded students of the region of Comunidad de Madrid. Firstly, we began asking the point of view about what a biosensor should have to be the most suitable for a case of a pandemic due to an outbreak. To this question he told us that the most important thing to expect from a biosensor is specificity rather than viral load because what matters during an outbreak is the prevention of the spreading of the virus that could collapse the healthcare system. Indeed, a chip/ device capable to guarantee at a 100% the presence or absence of the virus is the most suitable thing so the patient could just isolate even though it is not possible to quantify the viral load. Additionally, doctor Suela highlighted the fact that an automatic device would make it easier for the rest of the society to work it out since it could be possible to avoid the need to train people of to pay nurses or specialist analysing the data. Plus, the capability to track the spread of the virus. When it comes to the possible costumers that would for instance potentially purchase the device, his opinion was to focus on the point of care institutions. Herein, he describes that in European countries the healthcare system is either totally free or pseudo free for society (i.e., countries such as Sweden or Spain) meaning that the healthcare system has already a stabilized chain that works out. Finally, to improve the efficiency of the chip itself, doctor Suela describes that it is necessary to develop a technology able to include the detection of new strains based on Epidemiologic Statistics of the Region. |
| **Evaluation** | Personally, as a European doctor this young and ambitious doctor gave us the overview of a device that could function efficiently all over the globe. That is a key point for the development of our product because it is difficult to get an insight in the particular demands that the regions could have, and he gave us a tool to follow up the demands at a regional level. |

### 8.3.2 Financial Viability

The financial analysis makes a number of assumptions that apply for the time period the financial model concerns. Namely that the economy is not changing and thus inlation stays constant, no large technological advances that could render InfluSense 1.0 and its functioning principles useless or less profitable and lastly, that UppSense may have access to a sufficient financial aid for the initial costs. We also assume that the interest rates remain at the current values, and so will the tax rates.

**Table 4:** An overview of the duration and price of current Influenza A tests.

| Test | PCR [16] | Viral Cultures [3] | Rapid Molecular Assay [3] | Rapid Influenza Test [4] |
|---|---|---|---|---|
| Steps | 21 | | 18 | 6 |
| Time | 1-8 h | 5-10 days | 45 minutes | 15 minutes |
| Price (€) | ≈200 | ≈5 | ≈5 | ≈12 |

**Table 5:** The number of potential customer - pharmacies, hospitals and health care centers, across Sweden and the rest of the Nordic countries. UppSense's primary focus is on pharmacies, while retaining a keen mind on diversification to support the entire healthcare system.

| | **Sweden** | **Denmark** | **Norway** | **Finland** | **Iceland** |
|---|---|---|---|---|---|
| **Pharmacies** | 1426 | 227 | 994 | 810 | 43 |
| **Hospitals** | 100 | 32 | 75 | 241 | 6 |
| **Healthcare Centers** | 1000 | 54 | | 160 | 16 |

**Table 6:** A summary of the number of positive cases as well as tests for Influenza A, in Sweden, across the most recently accessible 8 year period.

| **Influenza A in Sweden** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** | **Average** | **Expected annual # patients** |
| **Total # Samples Analysed** | 31750 | 22330 | 42668 | 48135 | 68241 | 88837 | 83325 | 75819 | 57638.125 | **56018** |
| **Total positive for Influenza A** | 5340 | 2372 | 6671 | 6727 | 12361 | 7406 | 13664 | 5441 | 7497.75 | |
| **Proportion of Sample** | 16.82% | 10.62% | 15.63% | 13.98% | 18.11% | 8.34% | 16.40% | 7.18% | 13.38% | |

Tables 5 & 6 show that the production of chips will be in the order of tens or hundreds of thousands, annually. To this end, the following table presents costs, with econopmies of scale in mind. First, Table 7 & 8 shows cost berakdown of InfluSense 1.0 and approximate fixed annual costs, below.

**Table 7:** Cost breakdown of InlfuSense 1.0 in Euros

| **Component** | 1000+ units | 500+units |
|---|---|---|
| Raspberry Pi | 39.2 | 39.2 |
| EmStat Pico | 290 | 350 |
| Peristaltic pump | 45.08 | 45.08 |
| Dual motor driver | 25.48 | 25.48 |
| Display | 97.51 | 97.51 |
| Camera | 34.202 | 34.202 |
| Case | 9.8 | 9.8 |
| Tubing | 2.7636 | 2.7636 |
| Cuvette | 15.9 | 5.3 |
| Pi Juice | 58.8 | 58.8 |
| **Total** | **618.74** | **668.14** |

**Table 8:** Approximation of annual Fixed costs.

| Fixed Costs | |
|---|---|
| Laboratory | 60000 |
| Swedish Medicines Agency | 210.7 |
| Annaul Added fee | 98 |
| Approval fee | 50000 |
| Cloud Solutions | 22200 |
| Small Office | 7056 |
| Electricity | 1080 |
| Patenting Sweden | 5000 |
| Patenting No/DK/Fi | 10000 |
| AB (limited company) | 4900 |
| **Total** | 155544.7 |

**Table 9:** Secondary costs for materials required to manufacture UppSense' chips, with economies of scale.

| Supplier | Material | Amount per electrode (resp. units) | Secondary Materials Costs with Economies of Scale | | | | |
|---|---|---|---|---|---|---|---|
| Z&P | Z&P Hypervalue Carbon | 1 | Amount (units) | 200 | 10000 | 100000 | 10000000 |
| | | | Cost | 200 | 5000 | 25000 | 500000 |
| | | | Cost per electrode | 1 | 0.5 | 0.25 | 0.05 |
| Sigma Aldrich | Gold(III) chloride trihydrate | 0.000039 | Amount (g) | 1 | 5 | 10 | 25 |
| | | | Cost | 192.08 | 557.62 | 1120.14 | 1912.96 |
| | | | Cost per electrode | 0.0075 | 0.0043 | 0.0044 | 0.0030 |
| Sigma Aldrich | Sulfuric Acid | 0.3 | Amount (mL) | 100 | 500 | 1000 | 2500 |
| | | | Cost | 38.61 | 51.45 | 78.20 | 107.8 |
| | | | Cost per electrode | 0.116 | 0.031 | 0.023 | 0.013 |
| Sigma Aldrich | N-Hydroxysuccinimide (NHS) | 0.0115 | Amount (g) | 5 | 25 | 100 | 250 |
| | | | Cost | 21.364 | 31.164 | 98.98 | 230.3 |
| | | | Cost per electrode | 0.049 | 0.014 | 0.011 | 0.011 |
| Sigma Aldrich | EDC | 0.02 | Amount (g) | 0.5 | 1 | 5 | 25 |
| | | | Cost | 25.186 | 22.246 | 77.126 | 259.7 |
| | | | Cost per electrode | 1.007 | 0.445 | 0.309 | 0.208 |
| Sigma Aldrich | linker | 10 | Amount (uL) | 3846000 | 19230000 | | |
| | | | Cost | 50.3 | 151.9 | | |
| | | | Cost per electrode | 0.000131 | 0.000079 | | |
| Sigma Aldrich | Ferrocyanide | 50 | Amount (uL) | 10000000 | 50000000 | 250000000 | |
| | | | Cost | 65.072 | 72.716 | 259.7 | |
| | | | Cost per electrode | 0.000325 | 0.000073 | 0.000052 | |
| Sinobiological | Swine Flu 2009 Mouse MAb | 0.146 | Amount (uL) | 200 | 500 | 2000 | 3000 |
| | | | Cost | 227.36 | 227.36 | 2044.77 | 2691.86 |
| | | | Cost per electrode | 0.166 | 0.066 | 0.149 | 448.644 |

**Table 10:** Salaries based on projected production

| Salaries (EUR) | | Optimization & Certification | | | | Market entry | | Market Exp. | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **2021** | **2022** | **2023** | **2024** | **2025** | **2026** | **2027** | **2028** | **2029** |
| **Engineer/IT** | Yearly Salary | 30576 | 30576 | 30576 | 30576 | 30576 | 30576 | 30576 | 30576 | 30576 |
| | # employees | 0 | 1 | 1 | 1 | 2 | 3 | 4 | 5 | 6 |
| **Lab Assistant** | Yearly Salary | 25872 | 25872 | 25872 | 25872 | 25872 | 25872 | 25872 | 25872 | 25872 |
| | # employees | 0 | 1 | 1 | 1 | 2 | 3 | 6 | 8 | 10 |
| **Lawyer** | Yearly Salary | 49392 | 49392 | 49392 | 49392 | 49392 | 49392 | 49392 | 49392 | 49392 |
| | # employees | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Marketting** | Yearly Salary | 30576 | 30576 | 30576 | 30576 | 30576 | 30576 | 30576 | 30576 | 30576 |
| | # employees | 0 | 0 | 0 | 1 | 1 | 1 | 4 | 4 | 4 |
| **Sales/Accounting** | Yearly Salary | 34104 | 34104 | 34104 | 34104 | 34104 | 34104 | 34104 | 34104 | 34104 |
| | # employees | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| **CEO** | Yearly Salary | 38808 | 38808 | 38808 | 38808 | 38808 | 38808 | 38808 | 38808 | 38808 |
| | # employees | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| **Total Costs** | | **0** | **105840** | **105840** | **136416** | **265776** | **322224** | **522144** | **604464** | **686784** |

**Table 11:** Profit & Loss Accounts

| Costs (EUR) | | Optimization & Certification | | | Market Entry | | | Market Exp. | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **2021** | **2022** | **2023** | **2024** | **2025** | **2026** | **2027** | **2028** | **2029** |
| **InfluSense 1.0** | Cost/unit | 618.74 | 618.74 | 618.74 | 618.74 | 618.74 | 668.14 | 668.14 | 668.14 | 668.14 |
| | # units | 0.00 | 0 | 0 | 0 | 500 | 1000 | 2000 | 3000 | 4000 |
| **Chip** | Cost/unit | 0.64 | 0.64 | 0.64 | 0.64 | 0.64 | 0.64 | 0.64 | 0.64 | 0.64 |
| | # units | 0.00 | 0.00 | 0.00 | 0.00 | 10000.00 | 20000.00 | 70000.00 | 200000.00 | 250000.00 |
| **Cartridge** | Cost/unit | 16.39 | 16.39 | 16.39 | 16.39 | 16.39 | 16.39 | 16.39 | 16.39 | 16.39 |
| | # units | 0.00 | 0.00 | 0.00 | 0.00 | 1000.00 | 2000.00 | 7000.00 | 20000.00 | 25000.00 |
| **Total Devices** | | 0.00 | 0.00 | 0.00 | 0.00 | 500.00 | 1500.00 | 3500.00 | 6500.00 | 10500.00 |
| **Production Costs** | | 0.00 | 0.00 | 0.00 | 0.00 | 332181.52 | 713763.04 | 1495967.23 | 2460681.17 | 3242885.36 |
| **Salaries** | | 0.00 | 105840.00 | 105840.00 | 136416.00 | 265776.00 | 322224.00 | 522144.00 | 604464.00 | 686784.00 |
| **Fixed costs** | | 0.00 | 118444.70 | 95644.70 | 90644.70 | 118444.70 | 90644.70 | 118444.70 | 118444.70 | 90644.70 |
| **Total Costs** | | 0.00 | 224284.70 | 201484.70 | 227060.70 | 716402.22 | 1126631.74 | 2136555.93 | 3183589.87 | 4020314.06 |

| Revenue Streams | | **2021** | **2022** | **2023** | **2024** | **2025** | **2026** | **2027** | **2028** | **2029** |
|---|---|---|---|---|---|---|---|---|---|---|
| **InfluSense 1.0** | Price/unit | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 |
| | # units | 0 | 0 | 0 | 0 | 495 | 990 | 1980 | 2970 | 3960 |
| **Chip** | Price/unit | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| | # units | 0.00 | 0.00 | 0.00 | 0.00 | 10000.00 | 20000.00 | 70000.00 | 200000.00 | 250000.00 |
| **Cartridge** | Price/unit | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| | # units | 0.00 | 0.00 | 0.00 | 0.00 | 1000.00 | 2000.00 | 7000.00 | 20000.00 | 25000.00 |
| **Total Devices** | | 0 | 0 | 0 | 0 | 495 | 1485 | 3465 | 5940 | 8910 |
| **Revenue** | | 0 | 0 | 0 | 0 | 575000 | 1150000 | 2540000 | 4570000 | 5960000 |
| **Investments** | | | 200000 | | | | | | | |
| **Gross Profit Margin** | | 0 | -24284.70 | -201484.70 | -227060.70 | -141402.22 | 23368.26 | 403444.07 | 1386410.13 | 1939685.94 |
| **Cumulative Profit/Debt** | | 0 | -24284.70 | -225769.40 | -452830.10 | -594232.32 | -570864.06 | -167419.98 | 1218990.15 | 3158676.08 |

It should be noted that we estimate a 1% mistake rate, hence for every 100 InfluSense 1.0 devices we make, 1 will not make any revenue. The fixed costs vary from year to year, as in some years, such as during the market expansion, UppSense will need to pay more.

## 8.4 Appendix D - Other

### 8.4.1 Contributions

All 15 team members contributed through literature reviews, brainstorming for prototypes, brainstorming solutions for problems, being chair and secretaries for meetings, preparing presentations, reports, and pitches. The distinct contributions of each member can be found in the table below.

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