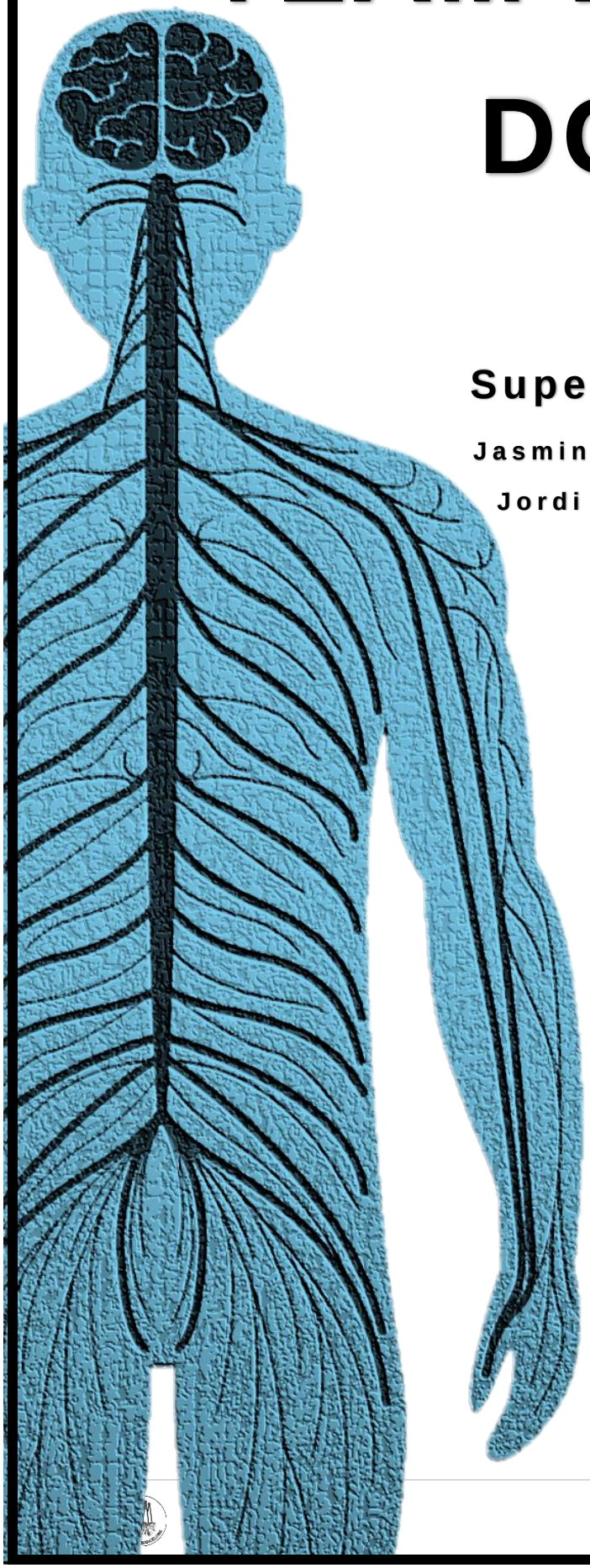
TEAM RESULT'S DOCUMENT



13th Agust

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CONTENTS

1. Summary for the SensUs website (max. 200 words)

The forces between liquid molecules are responsible for the phenomenon known as surface tension; tendency of liquid surfaces to shrink into the minimum surface area possible.

Valproate (VPA) is an anticonvulsant drug widely used to treat epilepsy. Patients may experience a long period in which the drug seems to control seizures. However, the dose or the drug may stop working. Therapeutic drug monitoring could help to obtain better results allowing the dose to be adjusted according to the individual. Its amphiphilic molecular structure, has a behaviour in solution similar to a surfactant, affecting the surface tension of the blood.

The idea is to have a T-shaped channel. Through it we have a constant flow of the solution and, on the other cannel, a constant flow of air. Therefore, bubbles are created and when the size of the bubble is critical it is carried away by the solution's flow. This effect is dependent on the surface tension of the solution. The higher the VPA concentration, the lower the surface tension of the solution is and the sooner the bubble breaks. The frequency of the bubbles is measured using a LED and a photodetector.

2. Biosensor system and assay (max. 2 A4)

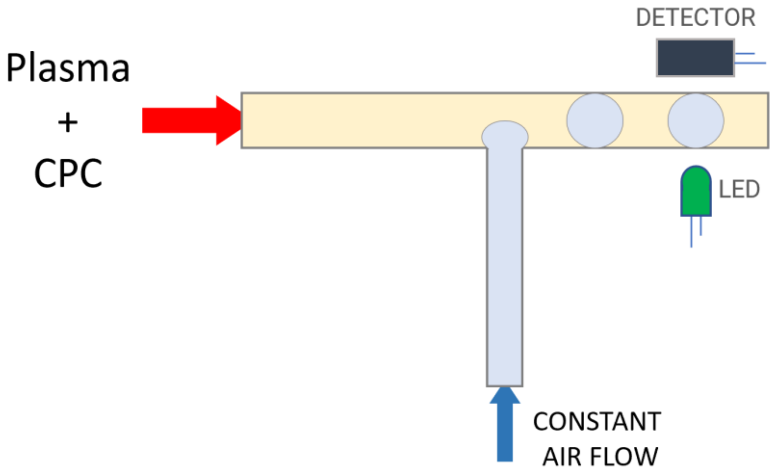

Figure 1. Basic structure of the device

2.1. Molecular recognition and assay reagents

The amphiphilic structure of the VPA molecule acts as a surfactant or detergent, which changes the surface tension of the solution where it is found, including the blood [1]. However, at therapeutic concentrations, this change in surface tension is not measurable. Therefore, a surfactant is used to increase the resolution and detect this change. The surfactant that has shown the highest resolution is cetyl pyridinium chloride (CPC) [1] (figure 1).

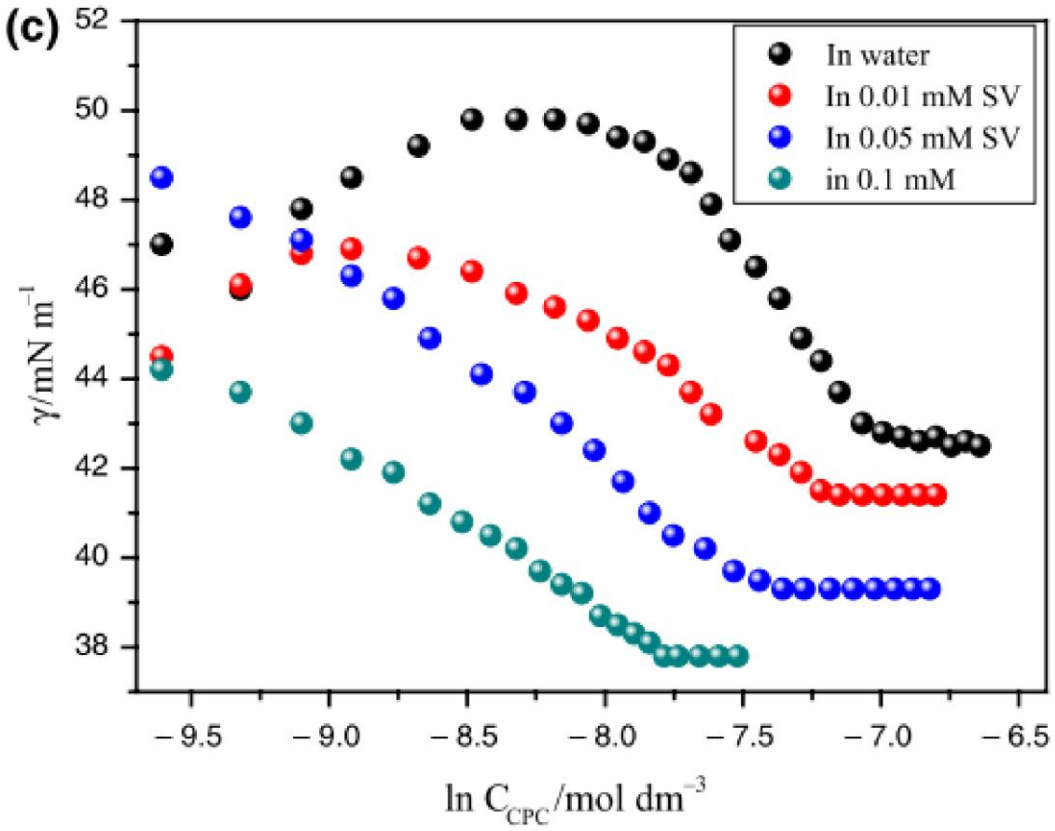

Figure 2. Sodium valproate with cationic surfactants and effect on surface tension [1].

We are certain that if we make a plasma solution with VPA and CPC at an ideal theoretical concentration, we can correlate the surface tension of the plasma with the concentration of VPA in the plasma.

2.2. Physical transduction

The idea is to generate two continuous flows, one from the solution and one from the air, which converge at a point prior to a photo detector. At the point where the two flows converge, a bubble is generated, which will move with the solution when it reaches a critical size. This critical size depends on the surface tension of the solution. As surface tension decreases, the bubble will reach its critical size sooner, and will move with the solution. The air flow is continuous, so the bubble frequency increases with decreasing surface tension [2]. These bubbles are detected by a photo detector (Figure 3), which records the data.

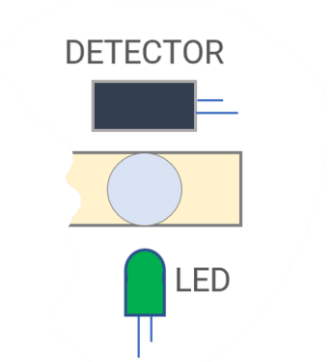

Figure 3. Detection spot

Having a previous pattern of data on bubble frequency and VPA concentration, we will be able to know what concentration we have of VPA.

2.3. Cartridge technology

The cartridges in the prototype device are made of PDMS on glass. The manufacture is simple. On a glass, a pattern is created with SU8, creating a pattern. Pouring PDMS and making a UV treatment, we will obtain the channel with the desired shape. It is a fast and cheap process. However, we think it has great potential for scalability with other technologies.

The cartridge is very simple, as it is a T-shaped form, with two inputs and one output. In one of the inlets, between the pumped serum sample in constant flow. In the other inlet, there is continuous air flow pumping.

Sample pre-treatment (removal of blood cells and mixing with CPC solution) is not covered by the cartridge. However, there are solutions in the literature that use the same PDMS technology to separate the blood cells [3], [4] and mix them with the solution [5] to improve resolution, appropriately, by simply adding those patterns to ours consecutively.

2.4. Reader instrument and user interaction

The device consists of three main parts: the hardware, the software and the mechanical package. The hardware is based on a PCB with an optical sensor, specifically a linear array, that measures the amount of incident light depending on the bubbles created over a certain time. This PCB is connected to a microcontroller myRIO, from NI, which is an embedded portable reconfigurable hardware device [6]. The NI myRIO consists of a technology that offers an FPGA and at the same time includes a processor that runs a real-time operating system. The dimensions of the PCB are 64x46,5 mm and the myRIO device measures 136,6x86 mm.

The myRIO together with the PCB are connected to the computer which will receive and process the information and, once run the program designed, the data will be lastly displayed in the main program window.

As it is used the NI microcontroller, the software will be developed with the NI language, LabView. The software created combines the myRIO's field-programmable gate array (FPGA) and modules with new programmed VIs. The FPGA continuously monitors the sensor response while the main function of the other part of the software is executing the received data and displaying it on the computer, which means that is a real-time code since the objective is to evaluate live data of different samples.

For covering the hardware from light, it has been designed a mechanical package that has also the function as a sample holder. Its dimensions are 33x29x10 mm.

3. Technological feasibility (max. 2 A4)

Due to the measures taken by our government and our universities, the prototype sensor cannot be completed. However, we have been able to obtain data that support our detection concept.

Preliminary results obtained to measure the correlation between valproate concentration (independent variable) and surface tension, has been done by OCA 15EC sessile drop technique (Optical contact angle measuring), using different concentrations of valproate saline solution (0.9% NaCl) with 1 µM CPC (figure 4):

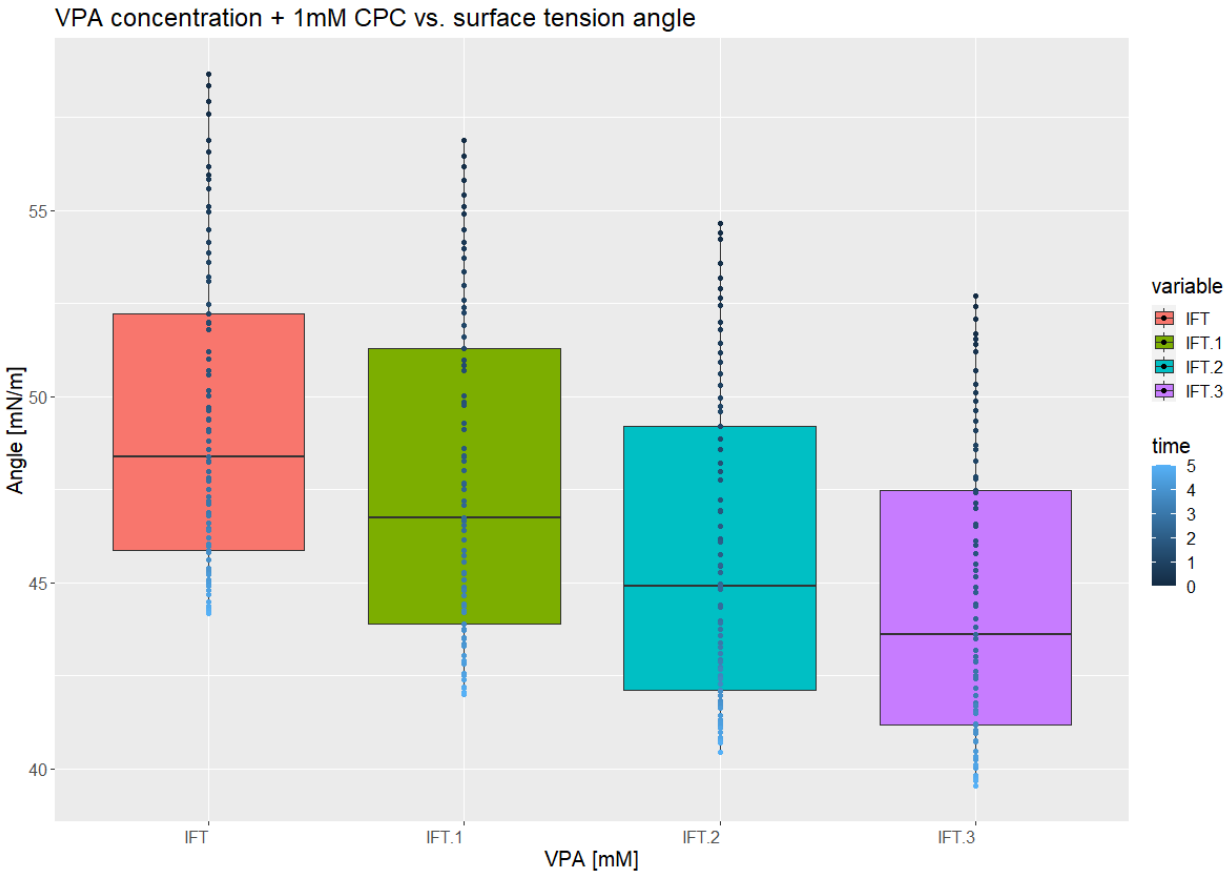

Figure 4. Results of contact angle measurements at different VPA concentrations with 1mM CPC.

The graph shows the angles formed by the sessil drops. The angle of the sessil drop decreases with time, as its surface tension is low compared to water (72 mN/m). For this reason, 5 seconds have been measured for each concentration, in order to eliminate the variable time (difficulty to choose the exact time of measurement of each drop) of the results. Thus, the standard deviations seen in the graph belong to the difference of the measurements over time, not to the deviations of the repetitions, since the averages have been worked out. The complete data of the different measurements are not shown.

With the data, a linear correlation model was carried out and the results obtained through the statistical software R are as follows:

```
Call:
lm(formula = IFN ~ values, data = df)

Residuals:
    Min      1Q  Median      3Q     Max
-2.1619 -0.7627 -0.1634  0.8131  2.4580

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 48.80660    0.06848  712.75   <2e-16 ***
values      -4.37320    0.12201  -35.84   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.9607 on 398 degrees of freedom
Multiple R-squared:  0.7635,    Adjusted R-squared:  0.7629
F-statistic:  1285 on 1 and 398 DF,  p-value: < 2.2e-16
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Figure 5. Results lineal correlation model in R.

As it can be seen, the model has a beta parameter of -4.37, so to predict the angle of the sessil drop, we should multiply the concentration of VPA in mM by -4.37, and add the interceptor, 48.81. The R-square shows that the data explain 76.3% of the proposed model, with statistical significance.

However, in our device, the frequency of bubbles in the solution flow is used, so the model does not serve to directly predict the behavior of different VPA concentrations in the device's optical reading. But it should be noted that sessil angle measurements and the frequency of bubbles generated by continuous air and solution flows are governed by the same physics.

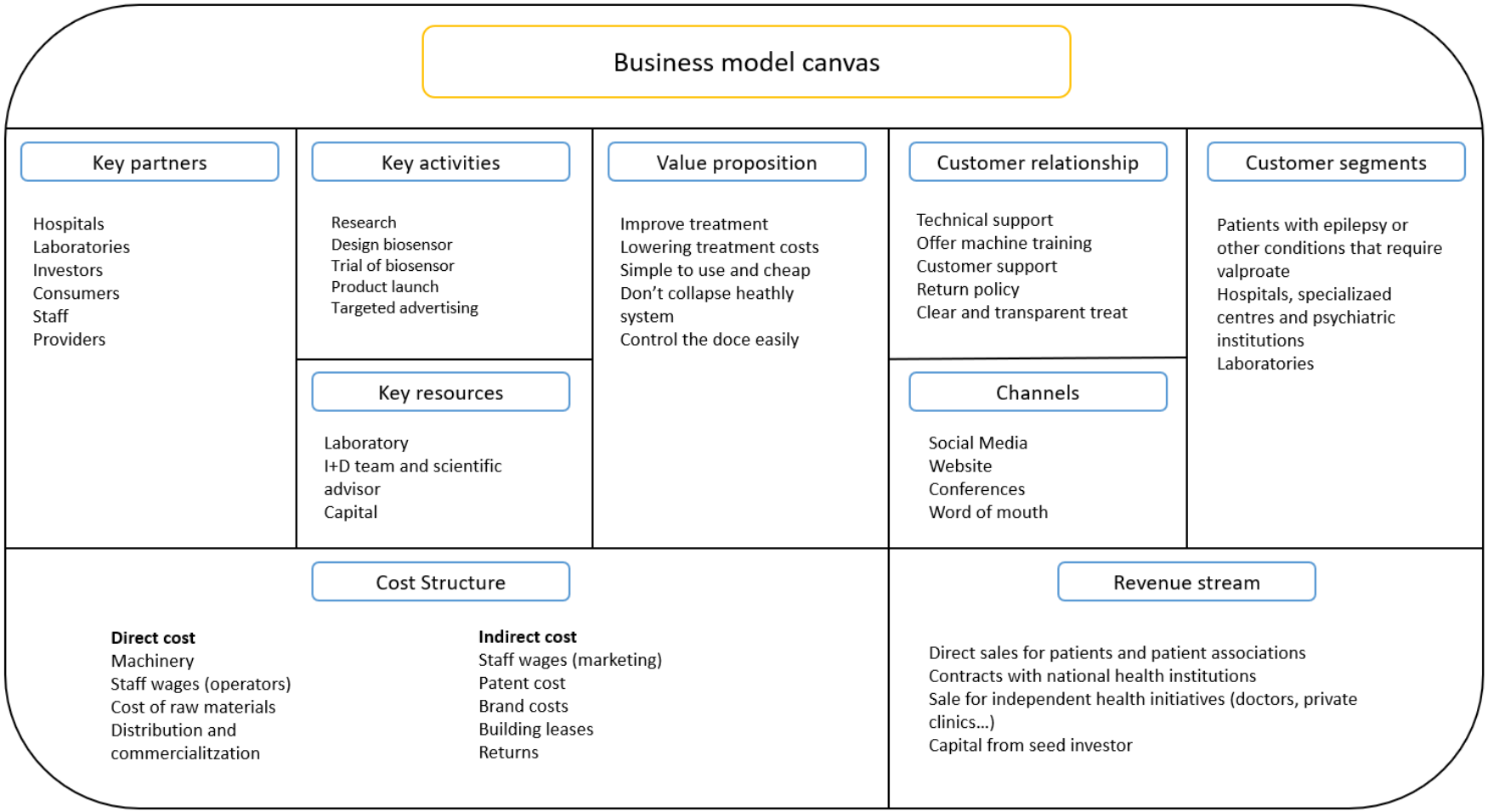
4. Originality (max. 1 A4)

The main novelty of this device is the capacity to measure the concentration of a drug in the plasma through the change of free energy or surface tension. Currently, surface tension is used in the clinic to evaluate lung condition [7], [8], and its use in the prognosis of heart disease is being investigated [9]. However, no studies have been found that evaluate its use to determine drug concentrations. Both the detection concept, which is in a state of the art in different detection devices, and the prototype have been carried out by the SensingBarcelona team as a whole, without the help of any partners. In the design of the prototype, the role of Claudia Noya stands out, a design that was part of her final Bachelor thesis. However, due to the global health

crisis, our device has not been able to move beyond the prototype design phase. We believe that the idea has relevance, because its individual parts are documented in different studies, however, we believe that a proof of concept would have been totally necessary.

5. Translation potential (max. 3 A4)

6.1. Business model canvas



6.2. Stakeholder desirability

Valproate (VAP) is an anticonvulsant medication, indicated for the treatment of epilepsy and certain cases of bipolarity. The drug has a highly variable absorption and distribution in the body, so at therapeutic concentrations, VAP can effectively stop seizures. In contrast, with a low concentration of VPA, there are no therapeutic effects on patients, and in the case of a higher concentration, we can observe toxic effects on the liver. For this reason, it is critically important to have the patient's VPA levels monitored on a periodic basis. Depending on the results, the clinical staff should assess each anomalous situation and correct the drug dose. However, determining valproate currently requires the patient to travel to the clinic, going through a protocol that is costly in time and resources.

A device of the nature that we present, could save many resources, both to the patient and to the hospital, since the patient himself can monitor the concentration of the drug from his home (saving of the trip to the hospital), with a device easy to use and cheap (now of specialized personnel in the hospital and of the cost of the test). Movement to a health centre would be reduced exclusively for the adjustment of the dose administered to the patient.

6.3. Business feasibility

The importance of market and industry planning and study is key to product development, along with the availability of scientific and technical resources for product development. In addition, in the medical device industry it is even more important and this was reflected in the tools developed by Gruber and Tal (2013) used to assess market potential. However, an unexpected event such as the current health crisis is likely to occur, hence the misconception of considering entrepreneurship as a matter of chance rather than a matter of choice. Despite this, epilepsy is still present and the proposed solution reaches the problems inherent in the current methods used by hospitals (time, cost, drug resistance) and also reaches the patient segment by reducing the possibility of suffering from seizures and hospital appointments. On the other hand, the pharmaceutical segment is also considered because of its interest in opening lines of research in order to better understand the behavior of drugs.

6.4. Financial viability

Financial viability is key to starting any project. There are multiple options, which have advantages and disadvantages. A private bank loan can provide us with somewhat limited start-up capital, with the problem that we would have to pay for the interest and other costs associated with this type of financing. On the other hand, we would maintain 100% control over the company. Another better option would be an official credit from the State, eliminating some of the previous expenses but with great difficulty to obtain. On the other hand, we can look for a capital investor, it would not cost much to get one and there would be no need to pay, besides, a great amount of initial capital is obtained. The main disadvantage is that to some extent you lose control over the business. Another option could be collective financing on platforms like kickstarter.

Table 1. Total cost of the device development.

Task or component	Price (€)
PCB components and manufactures	66.48
Mechanical package manufacture	190
Ni myRIO	582
Licensing	275
TOTAL COST	1113.48

However, if a production line is set up, the cost of production could fall. The labour costs would depend on the volume of work, so we think that it can have a total cost of approximately 1000€ the device. The cartridges are consumables made of glass and PDMS, which in a mass production could be very cheap.

The price could be considered expensive, however, this can be solved with financing systems for individual customers, likely subsidies from public health programs and patient associations, even the availability of rental of the devices in exchange for a fee that would cover maintenance costs and recover the investment and make a profit on sales of the consumables, as it is economical to manufacture.

6. Team and support (max. 1 A4)

6.1. Contributions of the Team Members

Oriol Caro: As a captain, I have done an intensive literature search to get the best idea of detection for the device. I've also been involved in organizing the team.

Ignacio Moragues: I have been in charge of the business aspects of the device as well as guiding the new members of the team throughout the year.

Carlota Mestre: As a member who has participated in previous editions, I have served as a guide and helped with the research work.

Clàudia Noya: I have been developing my final degree thesis based on this project, and so, I have been in charge of the electronic development of the sensor.

Arnau Marin: As a first-time participating member I have helped the most experienced team members on the business and entrepreneur aspects of the competition.

Hamid Khosravi: Team captain. He has provided expertise in microfluidics, with active literature search and PDMS channeling for the prototype.

Teo Mayayo: He has worked actively on the potential translational.

6.2. People who have given support

The team has not received any help outside of the team itself.

6.3. Sponsors

The team has used only the facilities at each of their universities. We have not received any sponsorship.

7. Final Remarks (max. ½ A4)

This year, the team presented a novel drug detection concept, which is currently not used. To this end, each of the studies that support the idea was presented, as well as empirical data that support the proposal.

Unfortunately, due to the causes known to everyone, we have not been able to carry out the project in its entirety, even though we think our idea has great potential.

However, we will continue to work on it, as a serious proposal for the determination of this and other drugs with a similar molecular structure.

8. References

[1] R. Kaur, P. K. Banipal, and T. S. Banipal, “Binding ability of sodium valproate with cationic surfactants and effect on micellization: calorimetric, surface tension, light scattering and spectroscopic approach,” *J. Therm. Anal. Calorim.*, 2019, doi: 10.1007/s10973-019-09036-4.

[2] N. T. Nguyen, S. Lassemono, F. A. Chollet, and C. Yang, “Interfacial tension measurement with an optofluidic sensor,” *IEEE Sens. J.*, 2007, doi: 10.1109/JSEN.2007.894927.

[3] J. Karimi, S., Mehrdel, P., Farré-Lladós, J., & Casals-Terré, “A passive portable microfluidic blood-plasma separator for simultaneous determination of direct and indirect ABO / Rh blood typing,” 2019, doi: 10.1039/c9lc00690g.

[4] H. Madadi, J. Casals-Terré, and M. Mohammadi, “Self-driven filter-based blood plasma separator microfluidic chip for point-of-care testing,” *Biofabrication*, 2015, doi: 10.1088/1758-5090/7/2/025007.

[5] P. Mehrdel, S. Karimi, J. Farré-Lladós, and J. Casals-Terré, “Novel variable radius spiral-shaped micromixer: From numerical analysis to experimental validation,” *Micromachines*, 2018, doi: 10.3390/mi9110552.

[6] C. Noya, “Integral Management of the SensUs – EIT Health 2020 Project Development and Electronic Detection System Analysis and Design,” Universitat de Barcelona, 2020.

[7] S. Schürch, H. Bachofen, and F. Possmayer, “Surface activity in situ, in vivo, and in the captive bubble surfactometer,” in *Comparative Biochemistry and Physiology - A Molecular and Integrative Physiology*, 2001, doi: 10.1016/S1095-6433(01)00316-6.

[8] A. Fathi-Azarbayjani and A. Jouyban, “Surface tension in human pathophysiology and its application as a medical diagnostic tool,” *BioImpacts*, 2015, doi: 10.15171/bi.2015.06.

[9] J. S. O. Chunhwa Ihm, Dae-Sik Lee, Kyung Hyun Ahn, “Viscosity Measurement of Whole Blood with Parallel Plate Rheometers,” *BioChip J.*, 2020.