EPFSens
Team Results Document

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1 Summary

EPFSens device is a biosensor for measuring the concentration of adalimumab, the active component of the Humira drug, in blood plasma. This drug is a monoclonal antibody used to treat rheumatoid arthritis, an autoimmune disease destroying the joints of patients.

Our optical technique uses a chip functionalized with capture antibodies and gold nanoparticles covered with detection antibodies. Both antibodies target Humira. When the drug is captured by a gold nanoparticle close to the array, this induces a local change in refractive index. In practice, the intensity of the transmitted light is reduced at these locations. This variation of light intensity can be easily measured using a camera and used to quantify the drug concentration.

Currently, patients suffer from long waiting periods and poor treatment monitoring. Our device will help reducing the time of diagnosis. They could have a better treatment monitoring by quickly adjusting the drug they need without being having to send their blood samples to analysis labs. This new approach will optimize the schedule of health professionals and reduce healthcare costs. In the future, our device will be multiplexable to allow the detection of other disease-related molecules in the direction of personalized health.

2 Biosensor system and assay

2.1 Molecular recognition and assay reagents

The EPFSens bioassay, is designed as a 1-step ELISA-like sandwich assay. It uses two monoclonal antibodies, each recognizing a different part of the target analyte. We decided to use monoclonal antibodies to ensure high specificity and little background because of their inability to bind more than one antigen through their epitope. We selected two anti-adalamimuab (anti-ADA) antibodies from GenScript, the capture antibody (clone 15C7) is the one at the surface of the chip. The detection antibody (clone 3C2) is the one bound to the signal generating particle [1] [2].

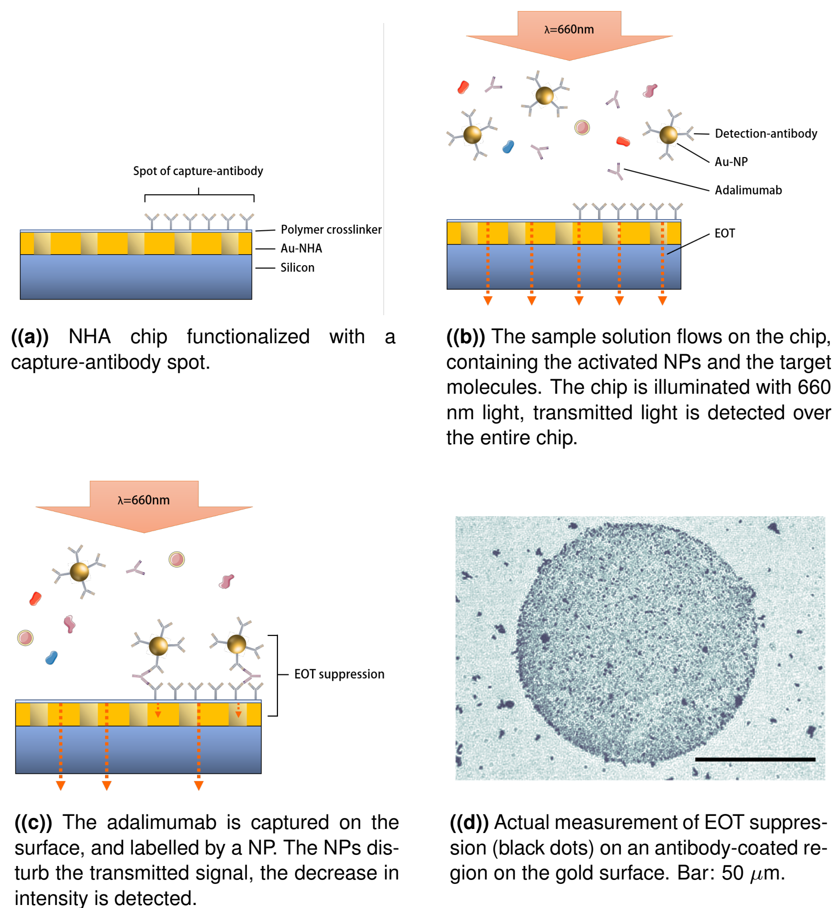
The detection antibody is attached onto gold nanoparticles (Au-NPs) coated with N-hydroxysuccinimide (NHS) [3]. Those Au-NPs are commercially available (by Cytodiagnostics) and the attachment is performed following manufacturer instructions.

In order to conduct the assay, additional reagents are required and mixed in two specific buffers. First, a blocking buffer composed of bovine serum albumin (BSA) diluted a hundred times in phosphate buffer saline (PBS). This buffer is used to activate the capture antibodies located at the surface of the chip. Secondly, we prepare a reaction buffer composed of NaOH (50 mM), BSA (1%) and Tween 20 (2.5%) in PBS. The role of this reaction buffer is to ensure an appropriate basic pH of approximately 9, to limit non-specific interactions, to maximize the binding and to generate a signal.

Note that for the plasma samples, we are still optimizing the blocking buffer. We tried with PBS and 5% of nonfat dry milk (Sigma).

2.2 Physical transduction

The detection principle used in this project is based on the variation of extraordinary optical transmission (EOT) intensity that a gold nanohole array (Au-NHA) presents when a gold nanoparticle (Au-NP) of 100nm diameter is located in close vicinity of a nanohole. Our Au-NHA chip is functionalized with anti-ADA antibodies (clone 15C7) on specific spots as in Figure 1.a and illuminated with 660nm light to generate the EOT via a plasmonic effect at the gold surface. This effect is enhanced by the nanohole array found on our chip. Without any sample on it, the chip has a uniform transmission. A sample solution containing the target analyte (adalimumab), activated Au-NPs functionalized with detection antibodies (clone 3C2) and reaction buffer is put on the chip 1.b. The adalimumab protein will eventually bind to the capture antibodies fixed on the Au-NHA surface. The bounded adalimumab alone induce only very little change in intensity of the extraordinary plasmonic transmission. A small frequency peak shift is known to happen, but cannot be detected with a standard camera (it would be the scheme of a label-free detection). What triggers the detection is the binding of a Au-NP on top of the adalimumab, as in Figure 1.c. The vicinity of this NP to the NHA induces a local change in refractive index, which strongly affects the plasmonic resonance peak present on the surface of the Au-NHA. The intensity of transmitted light at the NP locations will be reduced, thus making it possible to digitally measure variation of intensity on a far-field image (black dots will appear, representing a NP).



((a)) NHA chip functionalized with a capture-antibody spot.

((b)) The sample solution flows on the chip, containing the activated NPs and the target molecules. The chip is illuminated with 660 nm light, transmitted light is detected over the entire chip.

((c)) The adalimumab is captured on the surface, and labelled by a NP. The NPs disturb the transmitted signal, the decrease in intensity is detected.

((d)) Actual measurement of EOT suppression (black dots) on an antibody-coated region on the gold surface. Bar: 50 μm.

Figure 1: Plasmonic biosensor detection principle.

2.3 Cartridge technology

In our assay, the capture antibodies are deposited with a spotting machine (Scienion sci-FLEXARRAYER S3) on the gold nanohole array (Au-NHA). The spots have a diameter of 100 μm and are spaced every 300 μm. The machine is programmed to spot both the capture antibody used for the assay and a mouse antibody that is used as a negative control for reference. On the chip, a silicon rubber is placed to form a well. The sample is added inside and then a round cover slip is used preventing the evaporation of the sample. The volume of the sample is around 20 μm. At the moment, the mixes are prepared by the user through pipetting steps but we fully intend to automatize the process in future iterations of our prototype. Furthermore, to facilitate the insertion of the chip in our device, a single use holder as been cut in PMMA.

2.4 Reader instrument and user interaction

The reader's dimensions (Figure 2) are estimated at 42x30x24 cm. It is composed mainly of two parts. The hexagonal tower contains the optical setup presented in Figure 2 as well as a slot for inserting the chip and a z-axis translation mount accessible to the user for focus adjustment. As for the base support, it contains the switching power supply for the LED and the raspberry pi used for user-machine interaction.

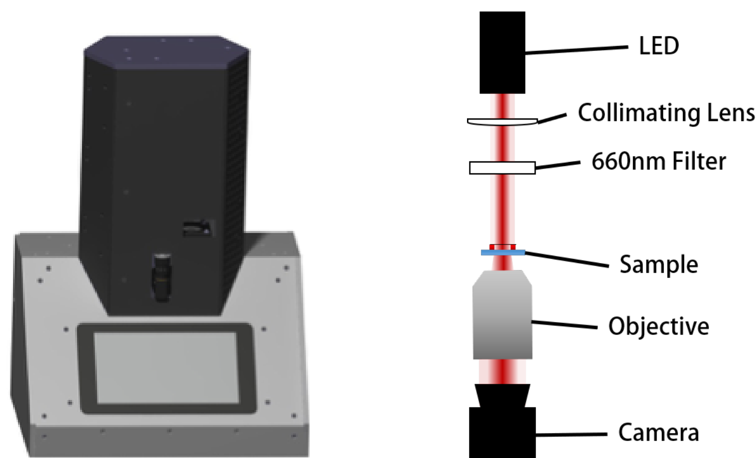


Figure 2: Our biosensor (*left*) and its optical system (*right*).

In order to provide an accessible device, we implemented an intuitive user interface for our touchscreen. The user chooses to refer back to previously recorded results or make a measurement. The measurement process is simplified by a provided tutorial displayed with instructions on the handling of the cartridge and the result acquisition. The user is also guided during the focus adjustment before starting the measurement in order to ensure the best image quality for the analysis. The implemented software is continuously printing the image on the screen, as the user is changing the z-axis translation mount for focus adjustment. As part of the development of our prototype, we intend to implement an autofocus algorithm so as to further simplify the user interaction.

The main job of the software consists in acquiring the images of the assay over a certain time period and then it uses image analysis algorithms to detect capture antibody spots locations, where the detection takes place. For the moment, as our device is still at a prototype stage, we added the possibility for the user to visually check the position of the spots and, if needed, to adjust the detected circle position, but this step would ultimately only take place in the background without any user input.

After spot detection, the camera takes regular captures of the spots, showing the increased binding of adalimumab on the nanohole gold array over time, which is translated by the increasing number of black dots on the captured image. The software measures the variation of the image intensity in time and outputs the detected adalimumab concentration, based on a well established calibration curve. The result is saved and printed on the screen.

3 Novelty and creativity

3.1 Already available

The photonic detection principle used in this project is adapted from the plasmonic biosensor developed by Alexander Belushkin and the BIOS laboratory at EPFL [4]. The chip is a thin layer (120 nm thick) of gold deposited on a substrate of SiO_2. An array of holes (200 nm in diameter, pitch of 600 nm) are etched by Deep Reaction Ion Etching (DRIE). With this hole-array configuration, surface plasmon polaritons are excited if the surface is illuminated with a coherent light source of 660 nm. This surface plasmon resonance re-emits light through the gold layer, giving rise to an extraordinary optical transmission (EOT), which is strongly dependent on the local index of refraction. The actual transduction principle takes advantage of this refractive index dependence, enhanced by dielectric media variation to disturb the plasmon resonance (see section 2.2).

The assay used to measure protein concentration is optimized to work in serum. It uses PBS with 1% BSA as a reaction buffer, NaOH to set the assay PH to 9, Tween 20 as a surfactant and detection antibody activated gold nanoparticles. A protocol provided by Cytodiagnostics [3] is used to coat those nanoparticles.

3.2 New developments

Technology adaptation and robustness development The method presented in [4] allows detection of biotinylated bovine serum albumin (bBSA) and human C-reactive protein (CRP). Our first achievement was to successfully adapt the biological assay to detect our target molecule adalimumab. By doing this, we demonstrated the versatility of our technique, which could, if we followed the same protocol, be easily adapted to the detection of any molecule for which a capture and detection antibody pair are available, opening the possibility for multiplexing in further improvements.

We first optimized the assay in serum by adapting the different reagents volumes and concentrations. Moreover, though we are still in the process of optimizing and calibrating it, we managed to adapt the protocol which only worked in serum to make it functional in plasma by switching the blocking buffer to a 5% non-fat dry-milk solution.

Although SPR technology has already been used in the context of biosensors, the technique from Belushkin was only used so far in a research context. Thus we are the first ones who adapted and and showed the viability of this novel technique in a small, fast and affordable biosensor. The most notable advantages of our technique are that, thanks to its intensity based measuring principle in comparison to a frequency or resonant peak shift, it can be easily implemented for parallel detection of molecules in patients blood and it allows to use a regular CCD/CMOS camera instead of bulky and expensive optical read-out. Our machine thus presents a competitive advantage over existing SPR based biosensors.

Intensity measurements In the context of our biosensor, we needed fast and robust computations. We noticed that analyzing the concentration by counting the observed binding events of Au-NP was a reliable method but was however sometimes subject to significant local variability and could become computationally expensive thus increasing analysis time. For these reasons, we adapted the analysis technique by measuring the local intensity variations instead of counting the individual Au-NP. We discovered that this not only allowed for faster computations, but also for more robust results as well as easier calibration since the intensity curves to fit were linear instead of following the Langmuir model previously used by Belushkin[4].

Image processing development For the reader instrument we have also managed to adapt a Raspberry pi to our specific camera and created a simplified application programming interface (API) to control it. Moreover, to replace the user based spot detection, we used the recent advances in artificial intelligence to implement a deep learning model in the form of a U-Net which was much more efficient than the image analysis algorithms that were tested.

4 Analytical performance

Prior to use plasma, we first carried out several experiments with human serum in order to validate the performance of our assay. Each measurement was made according to a protocol that we optimized during the semester. For serum, the assay is run on a final volume of 25 µL and only 5 µL is taken from the sample volume (serum mixed with adalimumab), the rest consists of reaction buffer and Au-NP solution.

We first add the blocking buffer (20 µL of PBS with 1% BSA) during around 3 minutes directly on the Au-NHA chip, then we remove it and add the sample mixture. The latter is prepared in a lab tube by first mixing the dilution buffer (composed of 7µL of PBS with 1% BSA, 2.5 µL of NaOH 50 mM and 0.5 of Tween 20 at 2.5%) with the serum and a certain concentration of adalimumab protein (5 µL). At this point we add the nanoparticles (10 µL) and quickly apply the solution on the chip surface (25 µL with a final dilution of 10). At the end a glass slide is added to close the liquid chamber and the measurement can begin. The setup allows measurements of one chip at a time. The chip is placed under a collimated 660 nm light-source, and a focused image is recorded by the camera at 2 frames per minute. The measurements on serum were made between the boundaries of the dynamic range concentration of the competition (0.3 to 10 µg/mL).

Measurements are shown in Figure 3. We can observe positive results, showing that our detection scheme is working with serum for adalimumab protein. The sample with the highest concentration of adalimumab protein has the steepest curve and the lowest one is flat. We can see on the Image 4 of our assay, black little dots on the antibody spot after 1 hour. Those dots correspond to nanoparticles bindings on the Au-NHA surface. Since the antibodies will absorb gradually on the surface, those dots will increase over time until reaching saturation, according to the specific binding kinetics.

In order to assess the concentration of our sample, a Langmuir model was used. This model describes the surface coverage kinetics and is dependent on the concentration. We used this dependence to build a predictive model based on the binding event measurements.

In the Figure 3, we fitted in red the measurements. We can observe that the match between our Langmuir model and the measurements is confirmed. Thus, when analyzing a sample wit unknown concentration, only the linear part of the slope (at the beginning, first 10-15 min) will have to be determined.

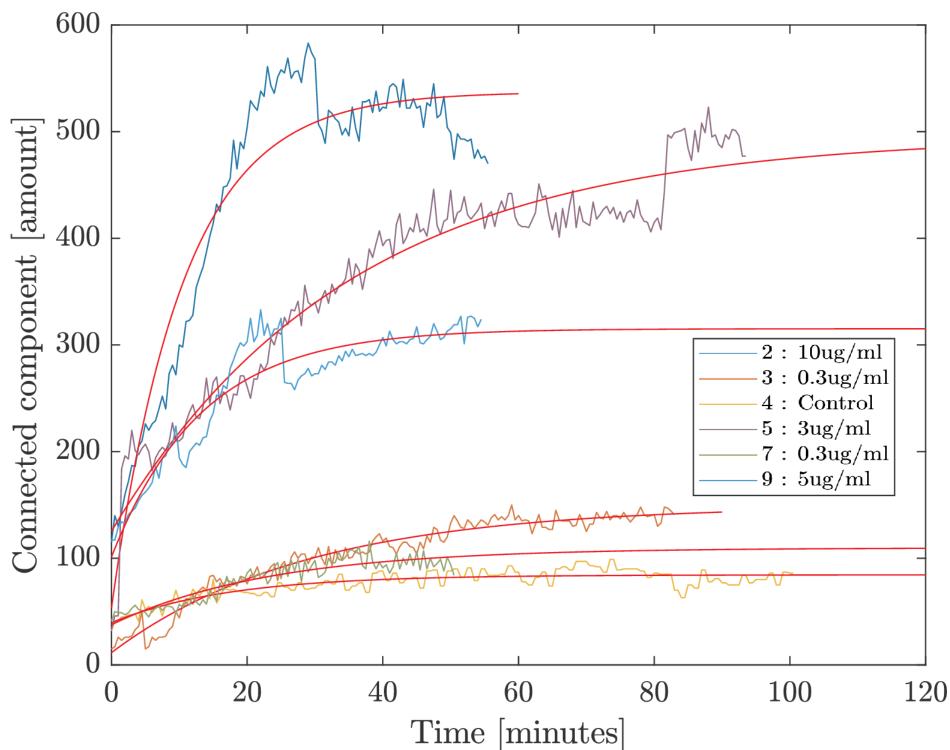


Figure 3: Measured adalimumab binding events on Au-NHA chip. The Langmuir model was fitted in red on each curve, to precisely retrive the slope at origin.

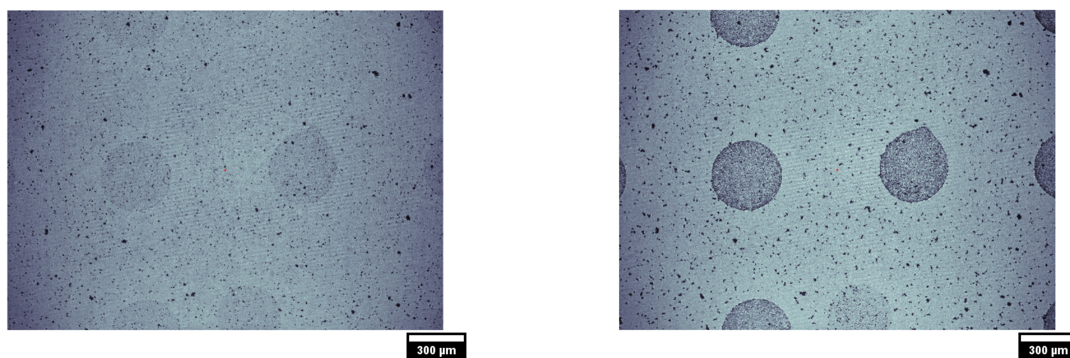


Figure 4: Image at the beginning of the measurement, (*left*) and after 1 hour of measurement (*right*).

Measurements for plasma sample are still in process of optimization, and we are currently trying to do the calibration with our biosensor. As mentioned in 3.2, we have now switched to local intensity variation measurements instead of individual particle counting, and have adapted the calibration to this technique.

5 Translational potential

5.1 Business model canvas

Key partners
- ✓ Investors
  - ➢ Seed capital
  - ➢ Venture capital
- ✓ Strategic partners
  - ➢ DBS system
  - ➢ Monoclonal antibodies manufacturers
- ✓ Suppliers
  - ➢ Nanohole wafer manufacturer
- ✓ Medical/health-related entities

Key activities
- ✓ Develop a robust, fast and reliable bioassay
- ✓ Develop the optical system and user-friendly user interface
- ✓ Manufacturing, delivery, customer service

Key resources
- ✓ Detection technologies
- ✓ Lab infrastructures
- ✓ Key scientific advisors
- ✓ Freedom to operate and IP

Value proposition
- ✓ Improved treatment monitoring and medical feedback
- ✓ Lowering of treatment costs
- ✓ Personalized medicine
- ✓ Low-cost, easy-to-use
- ✓ Adaptable to numerous drugs and biomarkers
- ✓ Possibility of multiplexing
- ✓ Remote patient monitoring app

Customer relationship
- ✓ Acquire and lock-in approach
- ✓ Customer support
- ✓ Technical support and maintenance
- ✓ Patient-driven approach
- ✓ Offer machine training

Channels
- ✓ On-site solicitation
- ✓ Website and mail order
- ✓ Conventions

Customer segments
- ✓ Diversified approach within the medical devices market: target hubs to maximize machine use and chip consumption

Point-of-care approach:
- ✓ Medical group practices
- ✓ Hospitals/Clinics
  - ➢ 290 in CH
- ✓ Medical-social establishments
  - ➢ 1558 in CH

Cost structure
- ✓ Cost-driven approach
- ✓ Fixed costs: working space, workforce
- ✓ Variable costs: R&D, manufacturing, supplies, marketing and advertising

Revenue stream
- ✓ Capital from seed investors and venture funds
- ✓ Asset sales in CH/Europe

Figure 5: Business model canvas.

5.2 Stakeholders desirability

The current situation is sub-optimal for the patients due to **long waiting periods and poor treatment monitoring**. Our product aims to change that. There is a need for an **affordable** monitoring device that would act directly at the point-of-care thus maximizing the patient-doctor interaction and bypassing the need to send a blood sample to analysis labs. The doctor could directly adapt the treatment following the result without the standard 1-2 months waiting period before the next appointment. We expect this approach to **reduce healthcare costs and optimize the time schedule of health professionals**. This would benefit patients, health insurance companies and doctors. Moreover, we expect treatments such as Humira to grow towards what can be seen with insulin pens, where the patient can adapt adapt the injection doses depending on his current needs. Our device would become even more efficient in such a setup, as close and optimized monitoring of the treatment would furthermore decrease the costs associated with the treatment.

Our device is also **adaptable and multiplexable** which goes in the direction of **personalized medicine**. With one assay, we can monitor the concentration of adalimumab and other important disease-related biomarkers. Furthermore, our solution is completely customizable and allows us to expand beyond the scope of adalimumab and chronic inflammatory diseases.

We also intend to develop, in collaboration with institutions such as the Swiss Anti-Rheumatism League, a **remote patient monitoring app**, that would help patients and doctors use our products and improve the medical feedback and interaction between the involved parties.

5.3 Financial viability

Our target market is currently focused on Humira (adalimumab) and rheumatoid arthritis in Switzerland. In 2017, Humira (Adalumimab) and Remicade (Infliximab) costed a combined $**212.7 Mio.** to health insurances in Switzerland [5]. We expect to grow towards more anti-inflammatory drugs in the chronic inflammatory diseases market in the near future and expand our scope to the European market. Moreover, due to the high adaptability of our assay we are confident that other diseases and drugs can be reached following the build-up of our operations.

The manufacturing costs of the biosensor and the consumable, hourly wages and equipment use included, are currently of $**2410 and** $**14.7** respectively (Fig.6), based on the Ashby model of manufacturing cost estimation [7]. This can be reduced by assay optimization, lean manufacturing processes and production volume increase. First estimates, indicate that we will be able to **reduce the manufacturing costs** of our consumable to at least $**10** and the manufacturing costs of our biosensor to $**2100**.

For the pricing of the biosensor we also have to factor the costs generated by R&D and the customer/technical support we intend to offer. Once these costs have been determined we will set the price of our biosensor in order to obtain a

gross margin of 20-30% as per the medical devices industry standards [6]. At present, it is difficult to estimate these costs. However, on average, these costs seem to be approximately twice the product costs of the device [6]. Thus, we expect the maximum price of our biosensor to attain $**7500** and we intend to price the consumable at $**50**. Discussion with doctors led us to understand that **sending a sample to an analysis lab costs** $**515**. We expect the lifespan of our device to be of 5 years with an average activity of 300 tests per year. With these price settings, a health professional buying our machine and using it for its full lifespan will be paying approximately $**5** per test **instead of the current** $**515**. We are confident that these prices will allow full reimbursement of the test by the health insurances thus relieving the patient from heavy health-related fees.

As a first funding round, we will rely on seed and angel investors in order to raise capital and maintain our rate of development. We expect this first round of funding to reach $500'000. This will cover our expenses and ensure that we can reach our primary objectives development-wise as well as start the regulatory approval processes. Our next step will be to secure additional funding in the form of a staged-series A investment amounting to $5 Mio. and split into two increments of $2.5 Mio. each. This additional investment will ensure a successful market entry and keep us on target regarding growth and early production. Finally, we intend to secure a series B investment for a total of $10 Mio. to build-up our market presence and grow beyond the Swiss market, into Europe.

We expect to sell 150 biosensors during the first year post-market entry. A financial forecast and corresponding costs, revenues and profits for the first 3 years of activity can be found in the appendix.

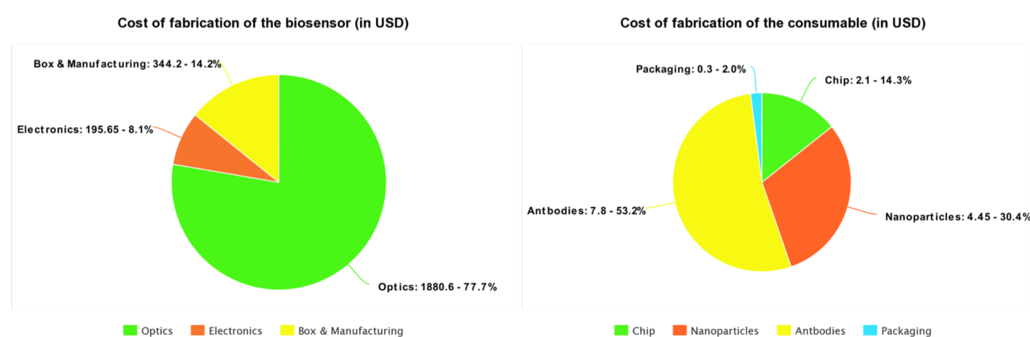


Figure 6: Pie charts of the cost repartition for our device and consumable [7].

5.4 Business feasibility

The feasibility of our business relies on the acquirement and correct deployment of key assets and resources. To increase the value of our product and reach our target we also count on 4 types of relationships:

- **Investors**
- **Strategic partners** that we define as companies whom could be beneficial to our sales strategy and vice versa.
- **Suppliers**
- **Medical/health-related entities**

The most critical targets are the strategic partners as they are paramount to our value proposition. We identified **3 potential strategic partners** that we think would help us immensely. First, **DBS system**, a Swiss medical equipment manufacturer, currently developing a passive plasma/serum separation device from micro blood samples [9, 10]. This technology would allow us to bypass the current disadvantages regarding blood sample collection and separation. Hyphenating this technology to ours will allow everything to take place directly at the point-of-care. Our team supervisor, Pr. Renaud, is a scientific advisor to DBS system and, as such, we benefit from a **privileged position for partnership talks**. Secondly, we aim to develop a strategic partnership with a **monoclonal antibody manufacturer**. Antibodies are a critical component of our detection method and are essential to both customization and multiplexion, two of our most important value propositions. Finally, we intend to establish a partnership with a **nanohole wafer manufacturer** as their products would be an integral part in the manufacturing of our consumables. Such partnership could even lead to lower manufacturing costs.

The key resources that we rely on are mainly technology-related. Indeed a knowledge of the detection technique, its freedom to operate and mainly an access to its IP is compulsory [11]. These conditions are met in our case. We also need an access to specialized infrastructures namely labs, offices and manufacturing spaces to further develop our technology and manufacture our products efficiently. Such spaces can be offered by EPFL in the Innovation Park [12] at competitive prices.

Our business would rely on different teams each in charge of a key activity. As we are mainly developing consumables and one model of biosensor, the manufacturing and calibration of our machines are our priority. And since we are

aiming at expanding our activity beyond the scope of adalimumab and rheumatoid arthritis, our R&D team would be working on our chips adaptability to other drugs as well as the multiplexing possibilities to allow doctors to obtain most of the critical information they need in one test.

But we are not only providing a tool, we are also offering **additional customer-related services**. Indeed, the delivery and after sales service will later play a huge part in our business routine and a whole team would be responsible for it. Finally, in order to enhance the patient care and patient-doctor relationship, we intend to develop a **remote patient monitoring** mobile application that would remind the patient of his appointments, how to use the blood/serum separation device, provide an update on the new products and improvements available and also keep track of the past drug doses and results.

6 Team and support

6.1 Contribution of the team members

The team consists of 11 Master students from Ecole Polytechnique Fédérale de Lausanne (EPFL), in Switzerland. We study Microengineering or Bioengineering and we all share a common minor in biomedical technology. In the context of the SensUs competition, each team member has contributed equally to the conception of the biosensor and to the elaboration of the required submissions. In order to allocate work equally and to be effective, the members were assigned each to multiple parts of the project. The contribution of each team member is listed as follows:

- Alexandre is our team captain. He managed the team and all the administrative processes in link with SensUs. He was also responsible for the development and optimization of the bioassay.
- Aude and Marion were responsible of the development and optimization of the bioassay.
- Brahim and Katia were responsible of the design and elaboration of the biosensor prototype.
- Clara and Emile were assigned to the implementation of the user interface and the detection program.
- Lenaic was responsible to design the chip holder and to make some microfluidics test. He has also contributed to the design and elaboration of the prototype.
- Ludovic worked on the technique used for the competition (see section 7). He was also responsible for the design and elaboration of the biosensor prototype.
- Mark was responsible of the translational potential part of the projetct. He has also contributed to the development and optimization of the bioassay.
- Raluca was responsible to design the chip holder and to make some microfluidics test. She has also contributed to the detection program.

Brahim, Clara, Katia, Lenaic, Marion and Raluca have also contributed to the translational potential part.

6.2 People who have given support

Many different people kindly gave us their support to improve quality of our project and make our choices possible. We would like to list and thank all those people who, until the end, helped and supported us:

Alexander Belushkin, who supervised Ludovic during his semester project, which was finally selected as our technique for the competition. He also helped us during the summer period by answering our questions and helping us with the various lab manipulations. Pr. Hatice Altug and the BIOnanophotonic Systems laboratory, who welcomed Ludovic for his semester project and have always supported the EPFSens team. Pr. Scharf Toralf, who lent us optical material and helped us in the choice of material to order. Pr. Philippe Renaud, Thamani Dahoun and Margaux Duchamp, who supervised us and came to our meetings every week. Cédric Meinen, who advised us for the design of electrical circuits. Student Kreativity and Innovation Laboratory (SKIL) staff, who provided us with some of the necessary equipment to create our biosensor, helped us to carry out some manipulations when needed and advised us. Workshop of the institute of mechanical engineering (ATME), who have proposed and make us a good structure to support our optical system. The Covance contract research organization, for its very good advice and the guided tour of its laboratory. Finally, all the people who have taken the time to give us interviews: including doctors, associations, medical laboratories and patients having rheumatoid arthritis.

6.3 Sponsors

Two main companies supported our team. The first is Spinomix, who provided us with some advice during the semester about magnetic beads. The second is Advanced MicroFluidics, who gave us some technical support and lent us a pump for microfluidic tests.

7 Final remarks

During the spring semester, in the context of the competition, we divided our team in 4 groups to explore different techniques in parallel and determine the best. The first group composed of Brahim and Alexandre worked on a detection method using superparamagnetic beads. The second one composed of Aude, Emile and Mark worked on a method using TIRF technology. The third one composed of Ludovic worked on the selected method. The last group composed of Clara, Katia, Lenaic, Manon and Raluca started to elaborate and think about the business plan.

After the competition we plan to improve our biosensor and present it to the START competition in Lausanne, which could be of great help to set up a start up afterwards.

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Appendix

FINANCIAL FORECAST (in years post-market entry)	Year 1	Year 2	Year 3
SALES (in units)			
Biosensors	150	350	700
Consumables	60000	140000	280000
SALES REVENUE (in $)			
Biosensors	1125000	2625000	5250000
Consumables	3000000	7000000	14000000
Total	**4125000**	**9625000**	**19250000**
MANUFACTURING EXPENSES (in $)			
Biosensor	315000	735000	1470000
Consumable	600000	1400000	2800000
Sub-Total	915000	2135000	4270000
NON-MANUFACTURING EXPENSES (in $)			
Taxes (14% of revenue)	577500	1347500	2695000
R&D (30% of revenue)	1237500	2887500	5775000
G&A (10% of revenue)	412500	962500	1925000
Customer aftercare (10% of revenue)	412500	962500	1925000
Sub-Total	2640000	6160000	12320000
TOTAL EXPENSES (in $)	**3555000**	**8295000**	**16590000**
NET INCOME(in $)	**570000**	**1330000**	**2660000**
NET INCOME (in CHF)	**587629**	**1371134**	**2742268**

Figure 7: Financial forecast post-market entry [8].