Tech Challenge: Technical Project Documentation

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1 Introduction

1.1 Mission and target Group

We, BioQube, want to revolutionize blood testing with Quantum Diamonds. Therefore we have developed a compact measuring device that can fully automatically measure many biomarkers in given samples. With this device, the testing process for many diseases could be revolutionized, offering faster diagnostics without the need for highly skilled labor. The main target area of application is point of care diagnostics, enabling cheap, reliable and accurate testing method without the need for a laboratory. With its ease of use and sensitivity to detect small quantities of biomarkers, it can allow for earlier disease detection, leading to better treatment and ultimately lives saved.

2 Theoretical Background

2.1 Biology

2.1.1 Proteins

Proteins are large, complex molecules that play many critical bodily roles. They do most of the work in cells and are required to structure, function, and regulate the body's tissues and organs. Proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached in long chains. Precise measurement of proteins is important because they are widely used to diagnose

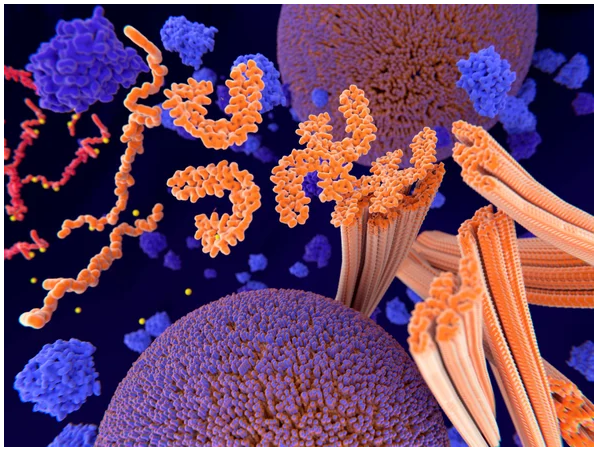


Figure 1: Tau Protein, indicator for Alzheimers [1]

diseases. They can be estimated from tissue and blood samples of a diseased patient. For example, diseases like HIV or hepatitis can be detected through precise measurements. Proteins also play a vital role in regulating the concentrations of acids and bases in the blood and other bodily fluids. Precise measurement of proteins can help maintain this balance, ensure the proper functioning of the body, and prevent many different diseases.

2.1.2 Antibodies

Antibodies, also known as immunoglobulins, are protective proteins produced by the immune system in response to a foreign substance called an antigen. Antibodies recognize and latch onto antigens to remove them from the body.

Monoclonal antibodies are immune system proteins that are created in the lab. Like the body's own antibodies, monoclonal antibodies recognize specific targets, e.g. specific proteins. Once monoclonal antibodies for a given substance have been produced, they can be used to detect the presence of this substance. Proteins can be detected by connecting matching antibodies to detectable molecules, e. g. fluorescent dyes or, in our case, magnetic nanoparticles. Precise antibody measurement can help diagnose diseases and monitor the immune response to treatment.

2.1.3 Blood-based Biomarkers for AD

There are several blood-based biomarkers that can be used to detect Alzheimer's. The most appropriate of these are the ratio of Aß42 to Aß40, the tau proteins p-tau 181 and p-tau217 and misfolding of the amyloid beta protein.[2] Antigens for research purposes are already available for all three biomarkers.

2.2 NV-Diamonds

2.2.1 NV-Centers

The nitrogen-vacancy center (NV center) is a point defect in the diamond lattice. It consists of a nearest-neighbor pair of a nitrogen atom, which substitutes for a carbon atom, and a lattice vacancy. They can either form naturally during diamond growth or artificially. They are typically produced by irradiating the diamond, creating single substitutional nitrogen centers, followed by annealing at temperatures above 700 °C. A wide range of high-energy particles is suitable for such irradiation, including electrons, protons, neutrons, ions, and gamma photons.

2.2.2 Measuring Magnetic Fields

A negatively charged NV^- center has two free electrons that make up a spin triplet. The different energy levels are displayed in the image 2. While measuring, they are continually pumped up to the exited triplet state (3E). When decaying back into the ground state the lower $m_s = 0$ level almost exclusively decays straight back to the ground $m_s = 0$ state emitting red light. But the excited

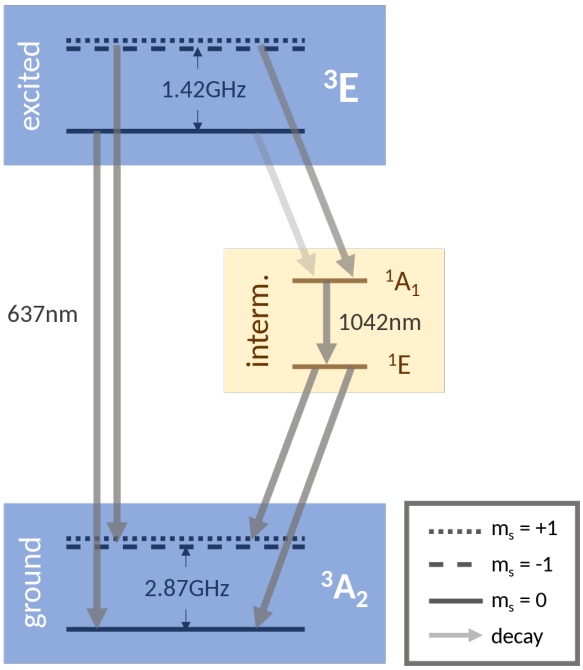


Figure 2: Energy Levels of NV-Center [3]

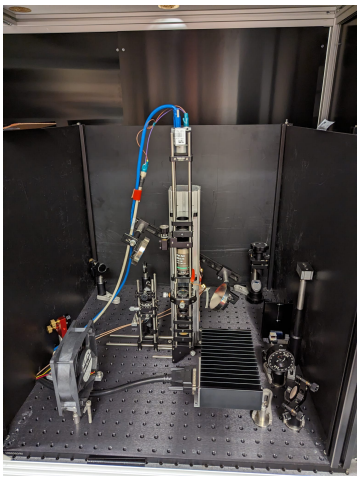
$m_s = \pm 1$ state will also take a path through a intermediate state and decay into the $m_s = 0$ ground state emitting no visible light that way. After a few iterations all spin states will be $m_s = 0$ and there will be a constant stream of emitted red light when the states are pumped to the exited levels. If via a microwave antenna the $m_s = 0$ ground state is brought to the $m_s = \pm 1$ ground state, there will be less light emitted if the spin is brought to the exited state, because a significant portion of the spins will decay through the intermediate state.
Suppose now an external magnetic field is applied along the defect axis (the axis which aligns with the nitrogen atom and the vacancy) of the NV center. In that case, it does not affect the ms = 0 states but splits the ms = ± 1 levels (Zeeman effect). This changes the microwave frequency needed to stop the emission of red photons. If the frequencies where this happens are known, the magnetic field at the nv centers can be measured. Because this effect depends on the angle between the defect symmetry and the magnetic field, the direction of the magnetic field can also be calculated.

2.3 Microfluidic Chips

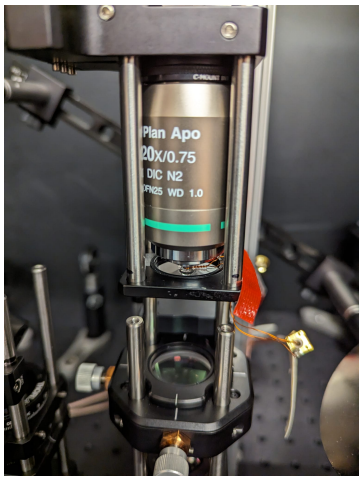
Microfluidic chips are compact testing tools made up of tiny channels carved on a chip, which allow biomedical researchers to test the properties of liquids, particles and cells at a microscale. They are made out of many different Materials, from oft polymers to glass. Microfluidic chips are crucial to drug development, diagnostic testing and medical research in areas such as cancer, diabetes and now COVID-19 as they have many advantages. They decrease sample and reagent consumption, increase automation capabilities, provide excellent data quality and substantial parameter control, minimize analysis time, and offer portability and flexibility of device design. They can also be directly coupled to downstream analysis systems like the NV measurement setup in our device.

2.4 Existing NV-Setups

In our research we got to see a few different NV-Setups. The first was a experimental setup on an optical table at Bucherlab. This setup is built to experiment on and not optimized for usability and transportability. But all the interesting components can be seen and changed. The whole setup and specifically the nv-diamond optical setup is shown in image 3. Research on this setup shows, that magnetic particles can be localized in 2D space with high precision. We were able to access preliminary data from Bucherlab, shown in image 4. This data shows older measurements, newer measurements will be able to have much higher precision.



(a) Complete Setup



(b) Diamond closeup

Figure 3: NV Setup at Bucherlab

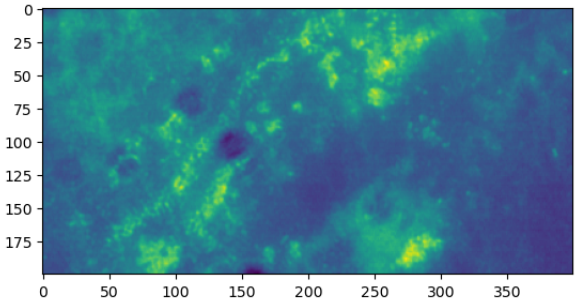


Figure 4: Example measurement data

Figure 5: NV-measurement setup displayed by Element6

Another example is the magnetic field measurement setup of Element Six. It shows that extremely compact measurements are possible. Their NV-setup is contained in a cube with a length of ca 15 cm was shown at the World of Quantum 2023 by Element6. This device is depicted in picture 5 Element6 claims it can be made even smaller.

3 Prototype

To show our idea and concept we designed, developed and constructed a prototype design and process. Our prototype is still in the stage of a CAD design, as the construction of one would be to costly for the scope of Tech Challenge. Both the prototype and measurement process are described in the following sections. Also many pictures were made by rendering the CAD design.

The BioQube aims to measure very small quantities of interesting proteins and other biomarkers. Antibodies bind these biomarkers. This process is already widely understood and used in processes like ELISA. Our product doesn't use fluorescent markers. Instead, we use magnetic nanoparticles bound to the antibodies. The BioQube will be able to detect these magnetic nanoparticles with high precision and spatial resolution using the nv-centers in the diamond chip.

Measurement Our measurement process relies on two or more magnetic markers binding to one protein. Even if this is not always the case, the chance of this happening can be calculated, and the total concentration extrapolated. When this happens, two antibodies with attached magnetic nanoparticles will appear very close together on the spacial measurement of the magnetic field. Because such low distances will not likely be measured by chance, this specific orientation of two particles will signal that a wanted protein has been found. This process is also shown in image 6.

To dose and mix reagents and samples our setup uses microfluidic chips. With these small amounts of samples can be processed relatively easily. Because the microfluidic channels are only about 0.1 mm thick, only a tiny sample, e. g. a drop of blood, is needed. Another advantage is that the chips can already be prefilled with all the necessary reagents, making it easier for the untrained user to use the machine. With one chip ca. 10 test suites should be possible. There is no need for pipetting samples from one place to another as everything happens inside the chip.

The BioQube uses two different microfluidic chips, one big and one small. The big microfluidic chip houses the reagent reservoirs, the fields to input the sample, and the mixing and dosing setup. The only part of the measurement setup not included in the big chip is the nv-diamond measuring setup itself. This would be too costly to replace every few tests. While the big chip will be made with a soft

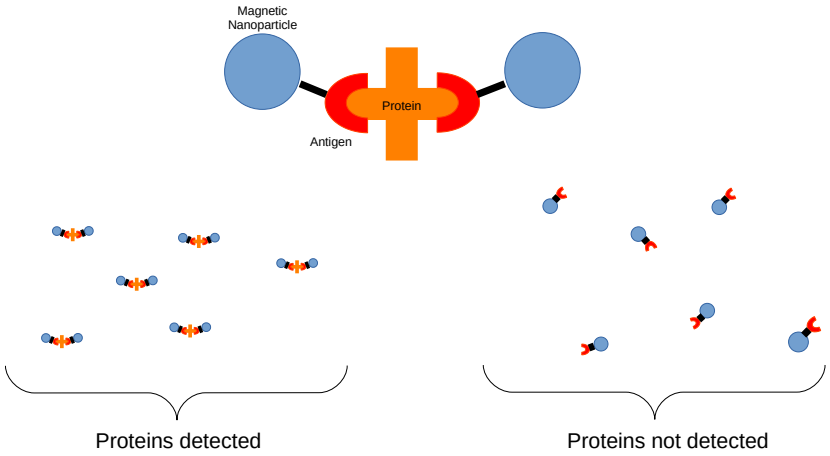


Figure 6: detection mechanism

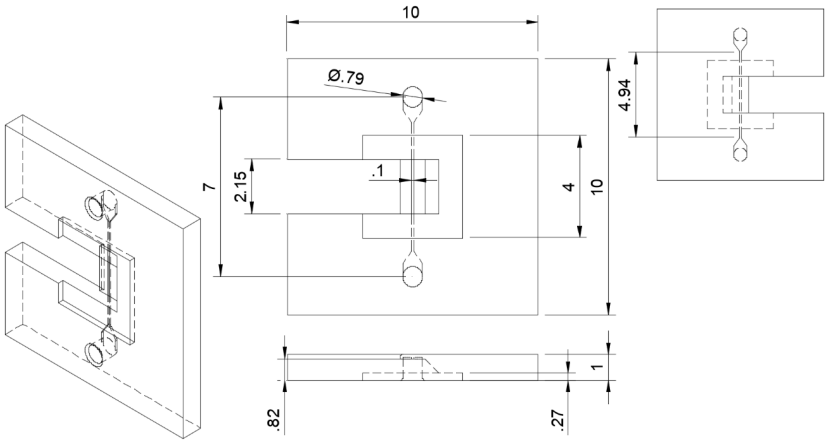


Figure 7: glass microfluidic chip design by Bucherlab [4]

polymer called PDMS, the small chip is made entirely out of glass, as described in [4] and shown in 7. This will enable the diamond to be reused almost indefinitely.

The BioQube is designed to integrate all necessary components into a compact but easily accessible and usable device. Great lengths were taken to design a functional prototype of the microfluidic chips in CAD. A cross section of the setup is shown in **??**. Shown are the two different microfluidic Chips. The traces are routed so that a precise dosage of sample and reagents can be delivered to the NV-diamond solely by applying pressure and vacuum at the different ports of the microfluidic chips. A top down view of the PDMS-Chip can be seen in figure 8. Then the sample and the nanoparticles needed for the testing are pushed through the channels and mixed in the Tesla mixer. The mixed and prepared sample is then passed on to the NV-Chip for the diagnostics. The Chip has 7 compartments for different nanoparticles so each sample can be tested for up to 7 different diseases per diagnostic run. Figure 9 displays the sample microfluidic chip design from a different angle. Next, the prepared fluid enters the NV-Measurement chip (to be seen in Fig. 10 from the port on the top left and is then routed over the top of the NV-Diamond. The sample is analysed by the NV-Setup and then discarded. After the analysis has been done the PDMS-Chip flushes itself with a cleaning solution, making it ready for the next run. The glass chip also gets cleaned automatically leaving no need for human labour.

The ease of use was also taken into account with our prototype. The big display enables intuitive controls of all parameters of the BioQube. The microfluidic chip, which is user changeable, can be

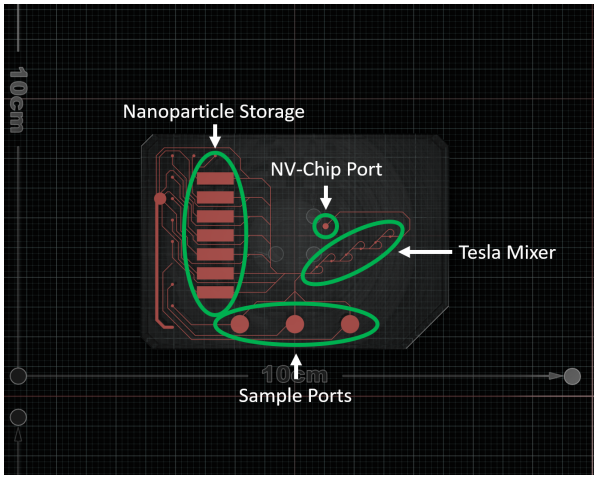


Figure 8: Top down view of the Sample Handling Chip

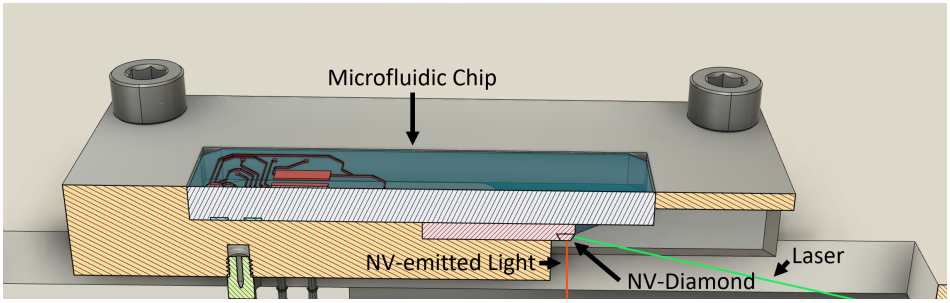


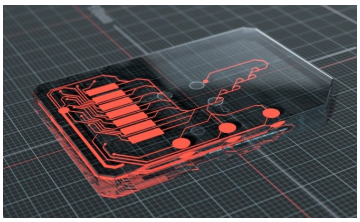
Figure 9: Chipstack of the BioQube

press-fit into the device from above. All connections to ports happen automatically from the bottom. Also, all consumables can be refilled quickly, the big lid protects both user and device while in use and enables easy access to all needed parts.

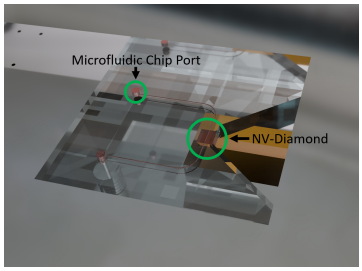
4 Usage

4.1 Change cartridge

BioQube will be able to conduct a variety of tests depending on the used cartridge. The medical professional chooses which test scenario he would like to run on our website by buying one of our predesigned cartridges or tailoring the cartridge precisely to his needs. Depending on the shelf life



(a) PDMS microfluidic chip



(b) glass microfluidic chip with nv-diamond

Figure 10: proposed designs of the used microfluidic chips

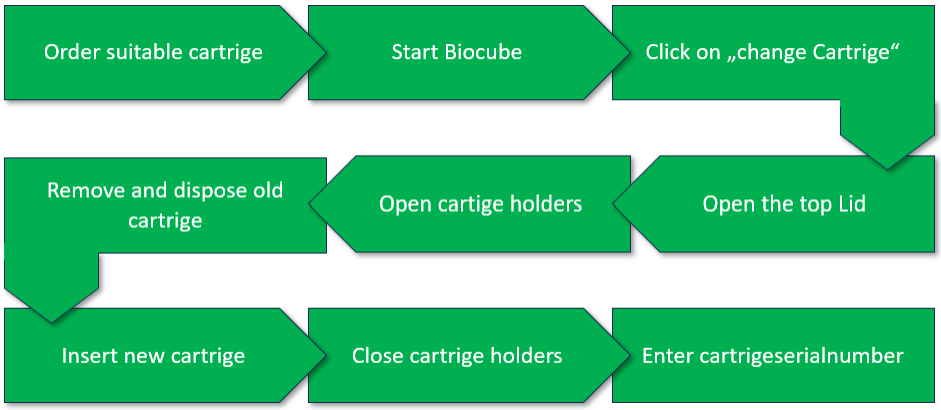


Figure 11: change cartridge

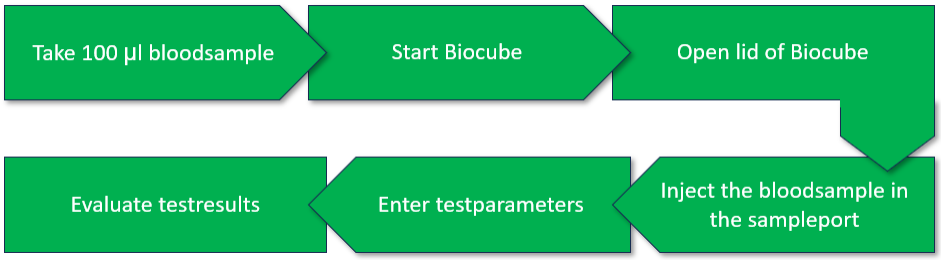


Figure 12: insert sample

of the components in the cartridges, they will arrive in a cooled package at the designated testing location a few days after ordering. The cartridges are changed according to 11. By entering the serial number, BioQube knows the preprogrammed testing scenarios for the dedicated cartridges, reducing the needed knowledge to conduct tests.

4.2 Usage flow chart

BioQube will be able to detect trace amounts of protein in the patient's blood without difficult sample preprocessing. Therefore, only $100\mu l$ blood samples are needed to achieve a significant result (depending on the specific test scenario). The sample is injected in one of the three sample ports on the chip using a syringe or a similar device 12. The medical professional may optimize the test parameters, such as trading speed for higher precision. After the user starts the test, BioQube automatically initiates the following steps. 1. precleaning the system, 2. pumping the test sample and the magnetic nanoparticles into the mixing chamber, 3. pumping the fluid to the NV-sensor, 4. spacially measuring the spions in the fluid and moving the fluid forward in succession until a suitable significance is achieved, 5. clean the setup 6. Preprocess the measurement results.

5 Outlook and further opportunities

With so much potential in the novel technology of Quantum Diamond Diagnostics there is more research to be done. Future research may consider but is not limited to the following open research questions:

- Is the spatial resolution of the NV setup enough to differentiate bound from unbound nanoparticles? How small can the Proteins be?

  Possible Solution: longer linkages between magnetic nanoparticles and antibodies or changing measurement concept to binding the antibodies to the surface - only small changes needed. Stop Brownian motion by cooling sample

- How high is the binding probability of antibodies to targeted proteins versus other proteins?
- Will using "dirty" fluids (e. g. blood) interfere with our measurements?
- What is the minimal measurable concentration of our device?

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