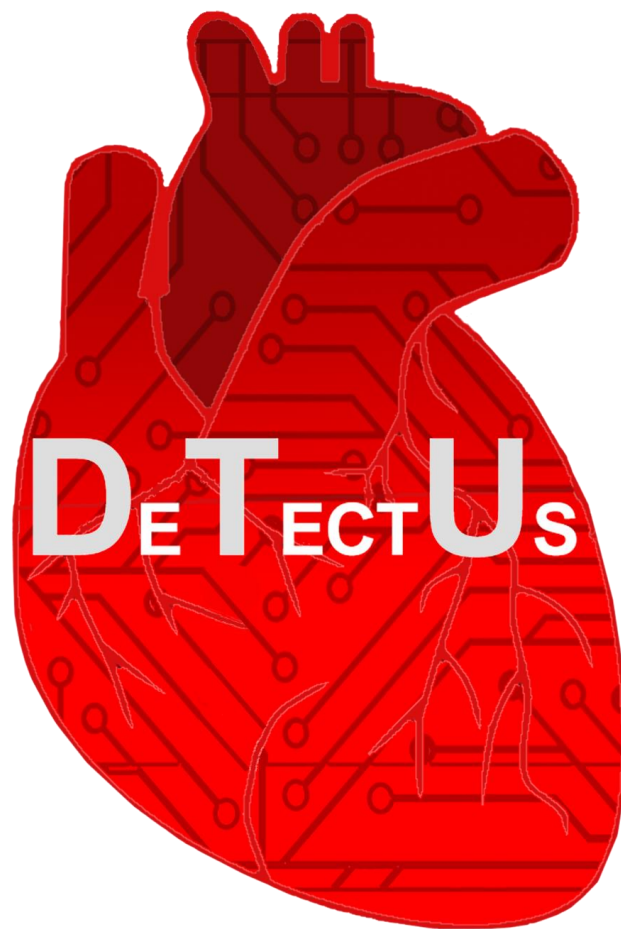




Sensus



Technical University of Denmark

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Summary for the SensUs website

DeTectUs biosensor is based on the immobilization of antibodies specific for the target molecule on the surface of a nanowire transistor. The binding of the NT-proBNP molecules in these antibodies has an effect in the current flowing through the nanowire. By measuring the current as an electrical readout, the detection of low concentrations of NT-proBNP is possible. Our sensor consists of the nanowire biosensor, the electronic board and an LCD screen to display the result. The biosensor will enable for the establishing of a baseline level of NT-proBNP that is known to be prone to variability. Through a process of self-monitoring the patient will be able to report significant deviation from the baseline using an intuitive smartphone application or suggest the patient to go to the emergency room if need be. The biosensor will be found with the Hospitals, Emergency rooms, Elderly care staff, home-visiting nurses and health enthusiasts.

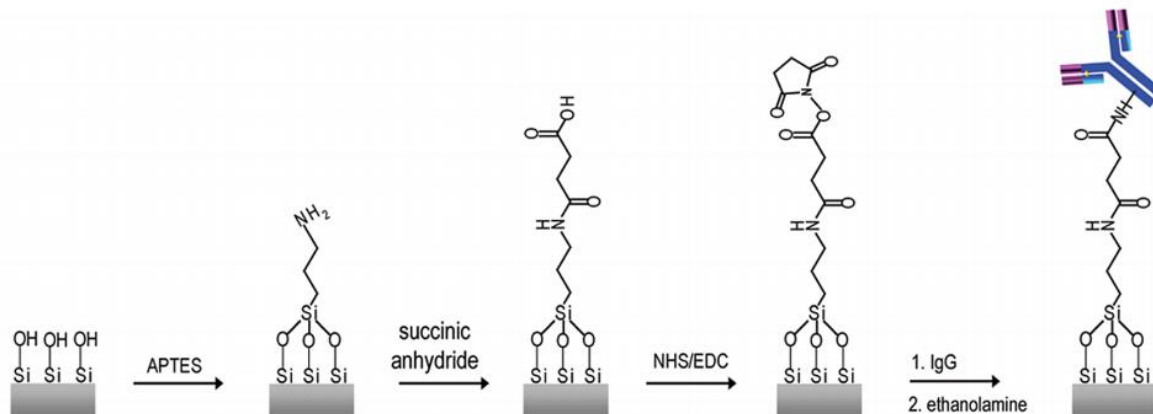
1. Biosensor System and Assay

A silicon nanowire field effect transistor (SiNW-FET) device is composed of a semiconductor channel, a source, a drain and gate electrodes, all of which are located on a Si wafer with an insulating surface layer. The silicon oxide coating on silicon nanowires can be linked to target receptor groups. Thus the SiNW-FET can be functionalized by immobilizing receptor molecules on its surface and selectively bind target analytes. A steady current is passed through the nanowire by applying a voltage drop over it. Target-receptor binding will be observed through a semiconductor device analyzer. When the sensor is exposed to macromolecules in a charged solution, specific binding will lead to an increase or decrease in conductance and thus current. The SiNW-FETs have been proven to be highly sensitive and selective sensors in numerous applications, including the detection of proteins, DNA, RNA and other biomolecules.

The SiNW sensors were functionalized with 3-Aminopropyl-triethoxysilane (APTES) with oxygen plasma treatment. APTES binds to the surface of the nanowire through a bond between the Si atom in APTES and oxygen atoms on the sensor.

APTES has an amine group in its free terminus, which can be treated to create a bond with antibodies. Through an activation of the amine group by a reaction with 1-Ethyl-3-(3-dimethylaminopropyl) Carbodiimide (EDC) and N-Hydroxysuccinimide (NHS), the antibodies are then bound to APTES, finalizing the functionalization of the sensor.

The measurements are output through an electrical readout device, measuring the current (nA) flowing through the wires of the biosensor. A change in the current is observed if NT-proBNP molecules are bound to the antibodies.

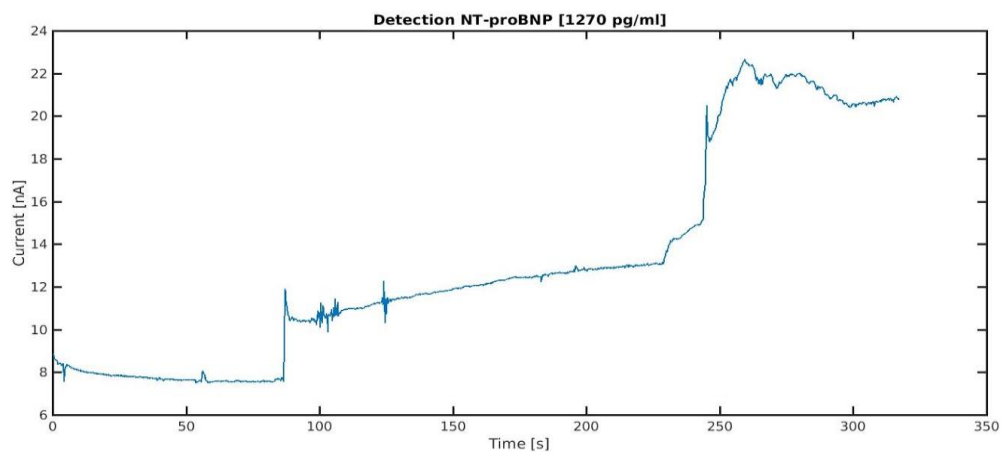
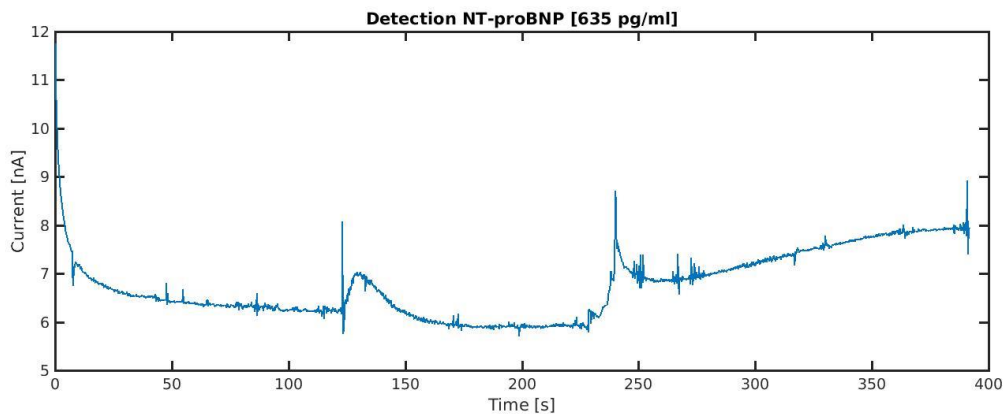


Functionalization scheme

2. Analytical Performance

The detection of NT-proBNP is based on current measurements of the SiNW. In the plots below is possible to see the responses of the chip in three different stages:

- I. when the SiNW is inserted in the ZIF socket, a DC voltage of 0.3 V is applied to the sensor, and the current stabilizes in around 30-60 seconds.
- II. PBS is added on the surface of the chip, and the current changes, until it reaches again a steady state.
- III. Sample of NT-proBNP are added on the SiNW, and the current increases significantly, meaning that the peptide bonds with the antibodies.
- IV. The current is measured by using a low-sensing resistor that allows to convert the current value to a voltage value, which can be read by the ADC of the microcontroller. The difference between the three stages described above is then used to derive the concentration of NT-proBNP in the sample.
- V. Our data shows we were able to detect low concentrations of NT-proBNP, which are relatable to the reference ranges for the molecule's concentration in the blood of patients who are in risk of heart failure.



3. Novelty and Creativity

The concept of using silicon nanowires which has been surface functionalized with APTES and antibodies in order to measure the concentration of a biomarker has been demonstrated before in research papers. Even for BNP and NT-proBNP. However, integrating the nanowire into a fully functioning electronic device working with whole blood and developing a graphical user interface for it in order to make it user friendly for the patient, that's novel.

As the main end user is the patient and neither doctors nor hospitals, we have developed an app which is super simple and easily gives an overview of the patient's current health status. Furthermore, most patients are in their 70's which requires simplicity together with easy and close contact with the doctor. To achieve this we have implemented a feature enabling the patient to easily contact the doctor and send the results for further evaluation. Doctors are pressed on time, so we also implemented a feature which gives a quick overview over the patient's NT-proBNP levels over the past weeks and months. This is a cost and time saving process as most work is done by the patient at home.

4. Translation Potential

4.1. Healthcare application potential

NT-proBNP is prone to variability, day to day levels has been demonstrated to vary as much as 50% in healthy subject and 33% in patients diagnosed with HF.(3) It is measured once the patient is checked in the hospital, and monitored flowingly by multiple visits to hospitals. This is time-consuming, laborious and costly for all parties involved. The one time measurements will not take this variability over time into account due to obvious reasons.

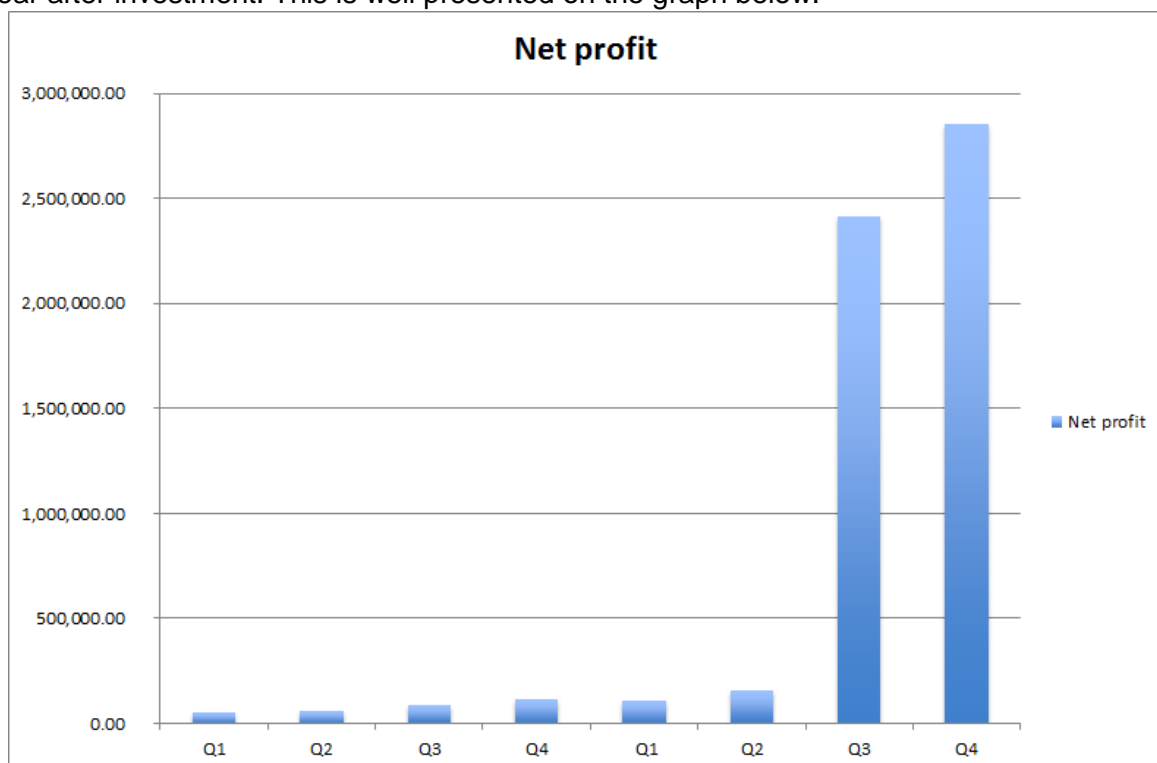
Our device enables for establishing a baseline value for the patient by the patient self-monitoring over a duration of a week. If that baseline is transgressed by the upper limit of the CV for NT-proBNP, in our case 30%) the patient will both report the data to the doctor and go for immediate treatment.

This device will be available in emergency rooms, and nursing staff at nursery homes and homecare. Also serving as an acute measurement device that will yield results under a minute.

4.2. Industrialization and commercialization potential

The solution proposed by the DeTectUs team is based on the whole system containing sensors, docking station and the communication system which is collecting the measurement data and visualize it both in the Patient app as well as doctors' interface. It is the solution changing the current way of diagnosis of heart failure.

With the investment of 2bln DKK coming from the private funds or Markedsmodningsfonden (Public found donated by Danish government for startups) <https://markedsmodningsfonden.dk/> it will be possible to run the pilot project in Denmark which reach breakeven point in 1,5 year after investment. This is well presented on the graph below:



The calculation table and projections for the next two years are done in Attachment.

The projections are based on the assumption of manufacturing 10 000 sensors which will be distributed continuously to the hospitals in Denmark. After a year it would be 5000 sensors already in use which will fulfill day to day costs and sustain the business development.

The price per sensor is presented in the attachment as well. With the quantity of production on the level of 5000pcs there will be 100DKK profit on each of the sensor sold for 250 DKK, If we assume the production level on 10 000pcs then the reduction in costs and price per sensor are implemented. The net profit is then 75DKK per sensor and the price is 175DKK.

The market projection has been focused on Danish market but it has a potential to be scaled for different countries within EU. The final goal would be to reach US market but it requires a lot of effort and experience with dealing with FDA. That is why this step is considered as the one when the technology is matured and well documented to be ready to apply for FDA.

5. Team and Support

5.1. Contributions of the team members

Apostolos Dragoumanos: Printing Circuit Board (PCB) design, Programming the Microcontroller Unit (MCU) for A/D and Bluetooth communication.

Dionysia Valkani: Administrative and coordinating tasks, Responsible for the promotion of the team in the social media and in promoting events, Research on NT-proBNP in current market solutions, Performing AB functionalization experiments.

Emil Ludvigsen: Research into different sensor types resulting in SiNW being one of the two chosen options, Fabrication of larger SiNW test sensors for functionalization experiments.

Exarchos Kanelis: Performing AB functionalization, Optimization of the functionalization protocol of antibodies.

Marc Baiget Francesch: Coordinating tasks, Team meetings arrangement, Designing and performing AB functionalization experiments to SiNW surface.

Mihai Gurei: Development of the Android application for showing results and history, Simulations of electric circuit designs and their implementation with the prototype, Microcontroller programming.

Mohamad El Lakany: Administrative tasks, Arranging meetings with industry, academia and working professionals, Research on NT-proBNP in relation to cardiac physiology, current treatment and monitoring solutions on the market.

Nicolai Jensen: Fabrication of the sensor.

Konstantinos Kalogeropoulos: Functionalization of SiNW, Design and optimization of the functionalization protocol, Measurements, analysis and interpretation of the results.

Selgin Deniz Cakal: Performing AB functionalization experiments for further measurements.

Stine Løvholt Grue: Research on different sensor types, Fabrication of larger pads with the structure of SiNW used as test sensors for functionalization.

Przemysław Mikulski: Assisting in developing the app - UX side of the development. Financial projection and business plan. Market analysis and research the possibilities of founding solution.

Qihui Yu: Assistance to AB functionalization experiments for SiNW.

5.2. People who have given support

Charalampos Papakontastinopoulos (DTU Nanotech) Member of Creative9/last year's DTU team for the SensUs competition: Characterization of SiNW, Functionalization of SiNW, Measurements and Data Analysis.

Yan Romano (DTU Nanotech) Chemist: Optimization of the functionalization protocol of antibodies, verifying the success of the functionalization.

Elise Delannoy (DTU Nanotech) Internship student: Electrical characterization of the SiNW.

Companies

Sanna Wallenborg, AQT, Software Manager at Radiometer: For arranging a meeting with the AQT group with staff calling in from Finland to give feedback on our device, challenges and opportunities

Jens Frimann, Vice President, Front-end System Innovation hos Ambu A/S: For sitting in and organizing a meeting with him and the Technology Research Manager at Ambu A/S - Finn Albert Sonnenborg and our group. We received considerations in disposables vs. re-use and health care economics.

Health care sector

Olav Wendelboe Nielsen, Chief Cardiologist, Bisbebjerg Hospital: Gave very valuable feedback on the needs of the patient and the health care sector. Whether Hospitals would use a device such as this. We expanded our knowledge of the standard treatment the patients receive and how our device would fit into that. This made us reconsider the application and made us see the grander scheme of things, for example the option of integrating with the already established openTele system in place that enables patients to post data on blood-pressure and weight.

5.3. Sponsors

5000dkk sponsorship from POCsolutions

POCsolutions is a medical device, software and big data company working in the field of clinical nanotechnology.

We thank POCsolutions for their support!

6. Final remarks

The DeTectUs biosensor, will enable for the self-monitoring of cardiac stress, by the measuring the of the cardiac stress biomarker, NT-proBNP from blood taken from a prick of the fingertips.

Measurements can be taken even when the patient is not at the Hospital. This is important to us as we would like nothing more for the patient to return to a life of normalcy without the constant reminder of having cardiac stress by visiting the hospitals. Only going there when necessary.

The DeTectUs biosensor will enable for the establishment of a NT-proBNP baseline level taking the variability in this biomarker into account. For meeting better monitoring needs of the patient and the doctor.

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