Team Results Document
AixSense



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SensUs

1. Abstract: Summary for the SensUs website

Parkinson's disease is commonly treated with levodopa (L-DOPA), but finding and maintaining the right dose for each patient can become challenging as the disease progresses. Our goal is to develop a biosensor that could continuously monitor L-DOPA levels and provide valuable information on how treatment response changes over time.

Our sensor uses a conductive and optically active metal-organic framework called $Cu_3(HHTP)_2$ combined with the crown ether AB18C6, a stable molecule that can selectively interact with L-DOPA. Unlike biological recognition elements such as enzymes or antibodies, the crown ether and MOF used in our sensing system are synthetic materials with the potential for improved chemical stability over extended periods of use. This could reduce the need for frequent replacement of the sensing layer and support the development of a more durable and cost-effective sensor. However, long-term stability and resistance to biofouling under physiological conditions still need to be experimentally evaluated

When L-DOPA interacts with the sensing surface, it produces an electrical change that can be measured using electrochemical impedance spectroscopy (EIS). Machine learning is being developed to analyze these signals and improve the reliability of concentration measurements over time.

Ultimately, our approach aims to enable long-term L-DOPA monitoring, helping researchers and healthcare professionals better understand treatment response and supporting more personalized Parkinson's disease care.

2. AP award: Biosensor developed for the Eindhoven Testing Event

Molecular Recognition

The molecular recognition is carried out by a copper hexahydroxy triphenylene ($Cu_3(HHTP)_2$) Metal Organic Framework (MOF) functionalized with the L-DOPA-specific 4'-Amino-benzo-18-crown-6 (AB18C6).

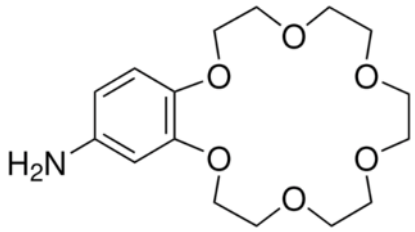


Figure 1 4'-Amino-benzo-18-crown-6 (Source : Merck, 2026)

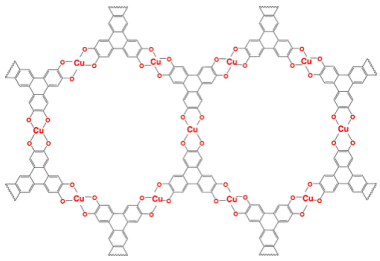


Figure 2 Cu3(HHTP)2 Metal Organic Framework (Source : Lister et al., 2025, S. 15114)

In our novel concept, the $Cu_3(HHTP)_2$ MOF creates the system's basis for favorable interactions with the analyte via oxygen-copper coordinative bonds between L-DOPA's catechol structure and unsaturated copper ions in the MOF. Furthermore, the affinity is increased via $\pi - \pi$ Stacking of the benzene rings from the MOF between the catechol structure of L-DOPA and additional hydrogen bonds formed via the hydroxyl, amino, and carboxyl groups of L-DOPA to oxygen atoms from the MOF. The specificity of the system is achieved through the functionalization of the MOF with the L-DOPA-specific crown ether AB18C6.

Using fluorometric titration screening reinforced by in silico docking simulations, the interaction of various crown ethers with L-DOPA was studied. Upon increasing the crown ether concentration in the cuvette filled with a fixed amount of L-DOPA, fluorescence quenching was observed. The influence of the crown ether, the analyte, and the presence of MOF were systematically studied in solution and in a solid glass substrate. Fluorometric titrations using phenylalanine and tyrosine show that each hydroxylic group increases the specificity, making the system suitable for L-DOPA detection. Additionally, the obtained fluorescence spectroscopy data reveal high potential in optical sensing methods. The described fluorometric titrations were conducted based on the literature (Zhou et al., 2011; Avilés-Moreno et al., 2013).

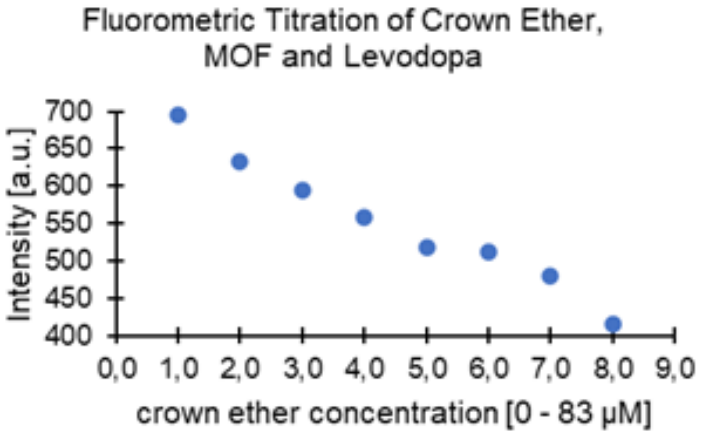


Figure 3 Fluorometric Titration of Crown Ether, MOF and L-DOPA

All in all, 18-crown-6, (−)-(18-crown-6)-2,3,11,12-tetracarboxylicacid, 4'-Aminodibenzo-18-crown-6 and 4'-Amino-benzo-18-crown-6 were analyzed. Among all the selected crown ethers, AB18C6 showed the most reliable quenching effect. Furthermore, in silico docking simulations revealed that the interaction with the crown ether is based on hydrogen bonds of L-DOPA's amino group to the oxygen atoms of the crown ether. The amino group fits in the pore formed by the crown ether, and the selectivity is enhanced by $\pi - \pi$ Stacking with the crown ether's benzene ring.

2.2. Physical transduction

We use electrical transduction in our sensor with impedance as the quantity of interest. The highly conductive $Cu_3(HHTP)_2$ MOF-film is contacted by gold electrodes, and its impedance change due to the specific binding with the analyte is measured.

The sensor chip consists of 24 interdigitated-electrode devices, each coated with a MOF-film (Figure 5) (Jiang, Huijie 2025). Two-electrode setup is the standard here, but a third pseudo-reference electrode is also available on each device (figure2).

Initial electrochemical impedance spectroscopy (EIS) testing will be performed over a frequency range of 1 Hz to 100 kHz to identify the most informative frequencies for L-DOPA detection. First, hierarchical clustering will be used to group frequencies showing similar response patterns. If clustering alone does not clearly identify the most informative frequencies, partial least squares (PLS) regression will be used to evaluate their relevance to L-DOPA concentration. Based on these results, further EIS measurements will be performed with higher frequency resolution in the most informative ranges. The resulting data will then be used to train a Random Forest regression model to predict L-DOPA concentration from EIS measurements.

For continuous monitoring, the potential of machine learning to improve robustness against confounding factors such as sample carryover, electrode degradation and fouling, temperature variations, interfering analytes, and sensor faults will also be investigated.

2.3. Cartridge technology

Cartridge design and fluidic system

The proposed cartridge consists of a glass sensing chip bonded to a PDMS microfluidic layer, which forms the flow cell. Fluidic connections are provided by two LabSmith CapTite™ Bonded Port Connectors (T132-400) integrated into the PDMS layer, as shown in Figure X. These connectors interface with LabSmith CapTite™ One-Piece Fittings (T132-100) and PEEK capillary tubing (1/32" OD, 0.010" ID, P/N: TUBE132-010P), providing a reliable and leak-tight connection between the external fluidic system and the microfluidic cartridge.

The complete cartridge assembly, including the glass chip in Figure 5 (gray, with purple sensing zone), PDMS microfluidic layer (gray transparent), and T132-400 connectors (yellow), is illustrated in Figure 4.

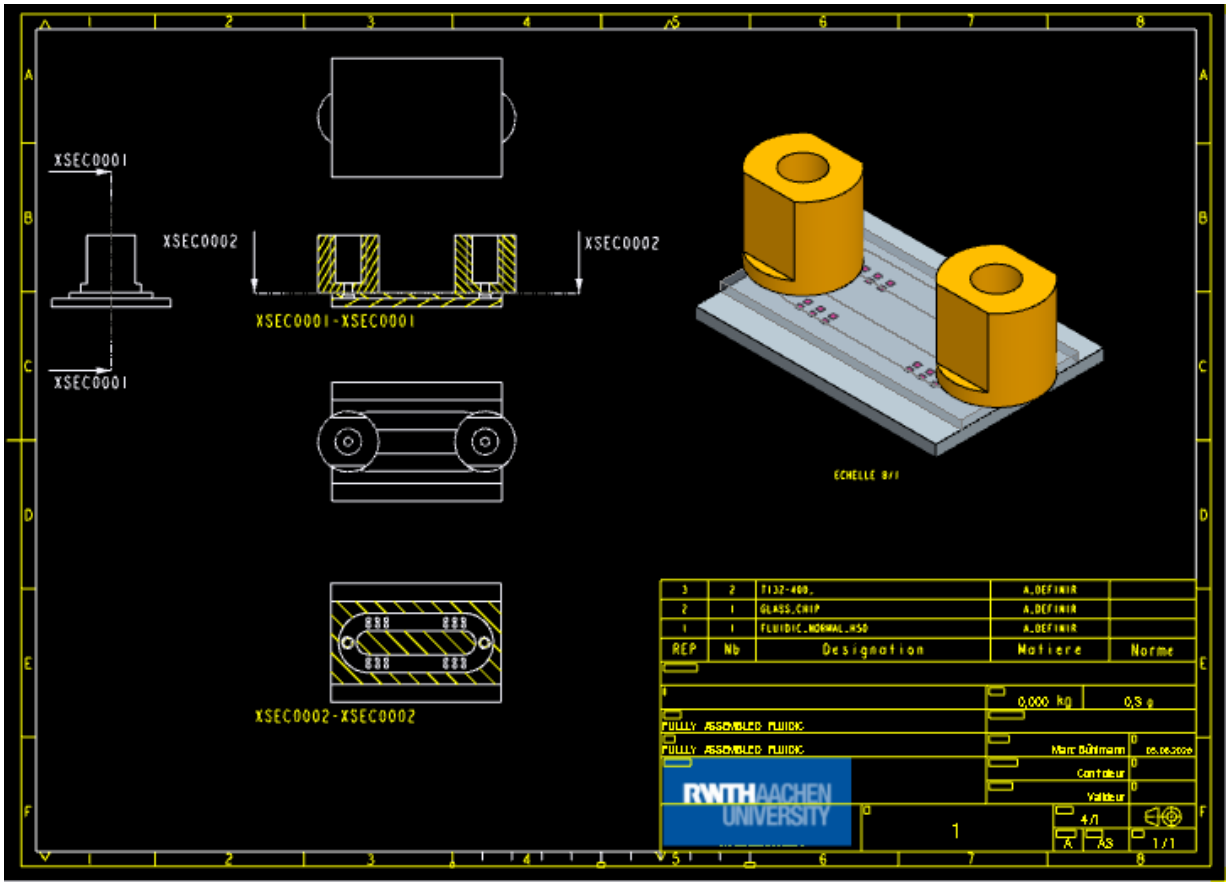


Figure 4 Technical drawing of the cartridge system

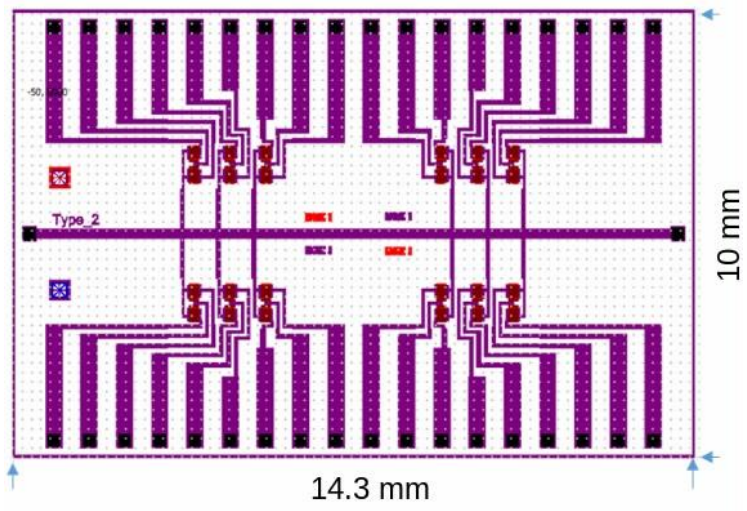


Figure 5 Glass chip layer

The external fluidic setup is mounted on a LabSmith uPB-05 breadboard and consists of a LabSmith SPS01 syringe pump (100 µL, 1/32" tubing), a LabSmith AV201 three-port automated microfluidic valve, a 4VM02 uProcess Manifold for Valve Control, and an EIB200 Electronic Interface Board.

Sample introduction and continuous biosensing

An ISF (Interstitial fluid) reservoir is connected to the cartridge inlet through the PEEK capillary tubing. The syringe pump is connected at the outlet and aspirates the liquid through the microfluidic channel, ensuring a stable and controlled flow over the sensing electrodes where the EIS measurement is performed.

For measurement, the ISF sample is introduced into the flow cell and transported across the four sensing zones, where EIS measurements are performed. After each measurement, the sample is removed and the sensing surface is washed to promote sensor regeneration before the next sample is introduced. Repeating this automated sample–measurement–wash cycle enables consecutive measurements using the same sensing cartridge and represents the basis for future continuous monitoring of L-DOPA levels over time.

2.4. Reader instrument and user interaction

Hardware and Software

The hardware consists of our functionalized three-electrode system, which is built on a glass chip. This chip is wire-bonded to a custom PCB carrier designed to break out the pins to a ScioSpec MEA Rack, enabling interface with the ScioSpec CSX-64 impedance spectroscopy machine. A 3D-printed PDMS microfluidic setup is mounted directly onto this PCB carrier to manage sample delivery.

The external fluidic platform is constructed on a LabSmith µPB-05 breadboard that connect to the chip's microchannel using microfluidic tubing. Both the ScioSpec CSX-64 impedance analyzer and the LabSmith fluidic platform are interfaced with a dedicated host station, which is responsible for real-time data acquisition, device control, and running machine learning algorithms.

Size and design

The ScioSpec CSX-64 mounted on top of a ScioSpec MEA Rack forms a unit measuring 13 cm × 17 cm × 7.3 cm (L × W × H). The LabSmith uPB-05 breadboard measures 13.3 cm × 18.4 cm, with a maximum height of 10 cm. It accommodates the syringe pump, the automated valve, the electronic control boards and the fluidic tubing. The complete laboratory prototype is designed to fit within an enclosure measuring less than 32 cm × 23 cm × 15 cm.

User interface & user-friendliness

In a commercial point-of-care or wearable biosensing device, the user interface would be intentionally kept as simple as possible. The sensing system would operate autonomously, continuously repeating the measurement cycle without user intervention, while only the processed L-DOPA concentration and relevant alerts would be displayed to the patient. This operating principle is similar to that of commercial continuous glucose monitoring systems, where users only receive clinically relevant information rather than the raw sensor data.

For the SensUs competition, however, the operating conditions are fundamentally different. Individual ISF samples are manually provided after each measurement cycle, and the performance of the biosensor must be continuously monitored throughout the experiment. Consequently, the software was designed as an engineering interface rather than a patient interface, providing access to measurement parameters, hardware status, process control and raw measurement data. This approach allows rapid troubleshooting, parameter adjustment and system validation during the competition.

The graphical user interface is organized into three parts: Parameters, Control, and Results.

Parameters

The Parameters page (Figure 6) is used to configure the experimental protocol before starting a measurement campaign. The user specifies the number of samples and the total available measurement time, configures the washing procedure (total wash volume and number of washing steps), defines the EIS acquisition parameters (measurement volume and frequency range), and verifies the connection status of the ScioSpec impedance analyzer and the LabSmith fluidic system. The interface also displays timing information, including the target time per sample, campaign progress, and the duration of the previous washing and measurement cycles.

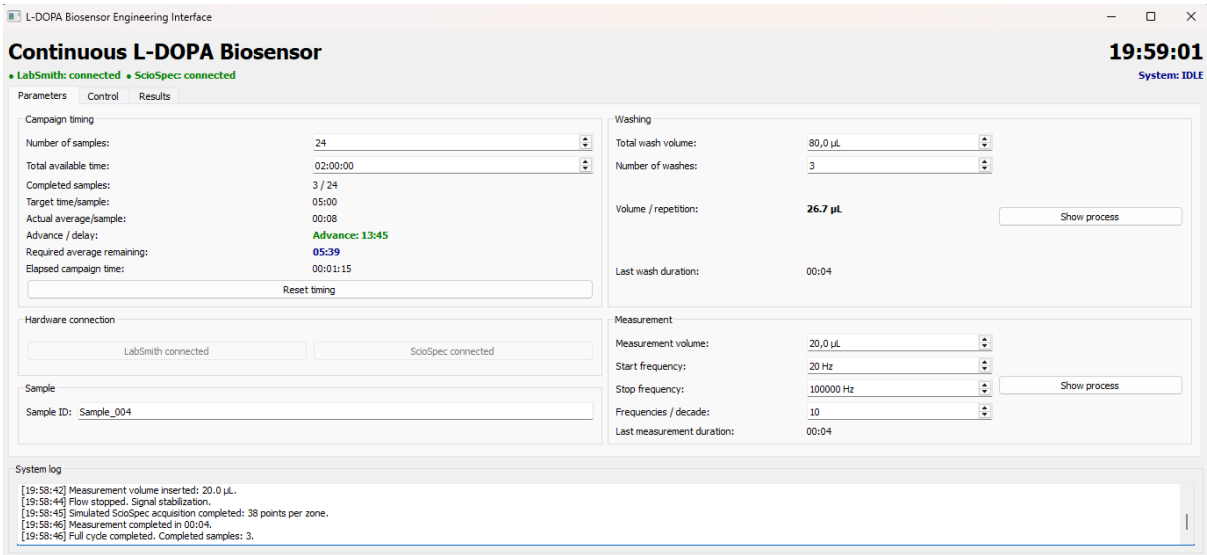


Figure 6 Engineering software interface: Parameters

Control

The Control page (Figure 7) allows the user to operate the system. A complete measurement cycle, a washing cycle, or a measurement cycle can be executed independently. During operation, the interface displays the current process, a real-time progress bar, elapsed times, and continuously records all operations in the system log, allowing rapid troubleshooting if required.

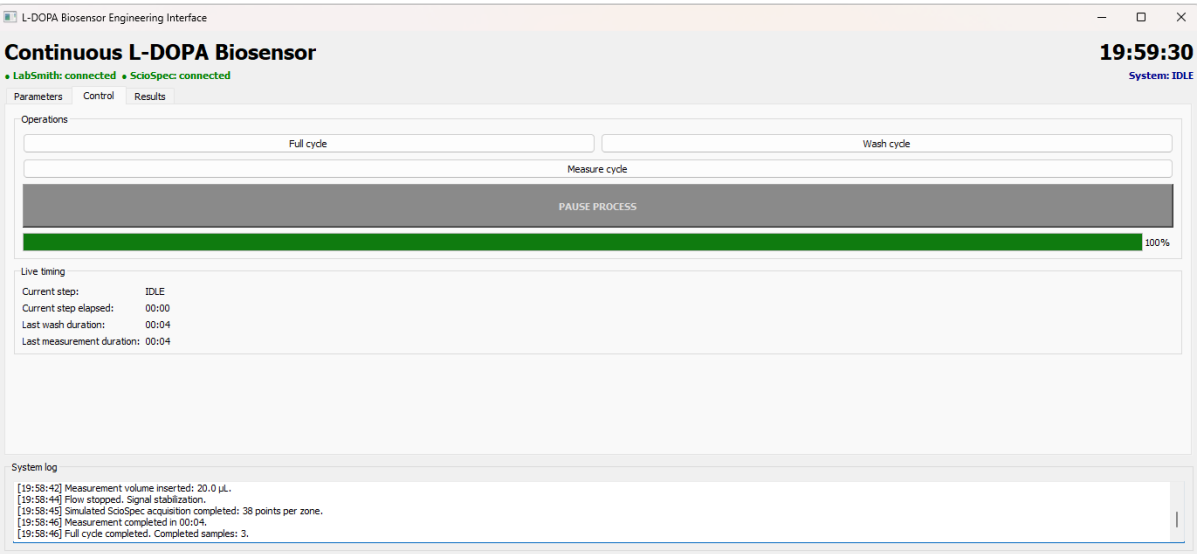


Figure 7 Engineering software interface: Control

Results

The Results page (Figure 8) displays the estimated L-DOPA concentration together with measurement quality indicators. For engineering validation, the acquired EIS data can be visualized in multiple formats, including raw data tables, Nyquist plots, Bode plots, and separate real (Re) and imaginary (Im) impedance representations. Individual sensing zones (Z1–Z4) can be selected independently, allowing direct comparison of the measurements obtained from each sensing area.

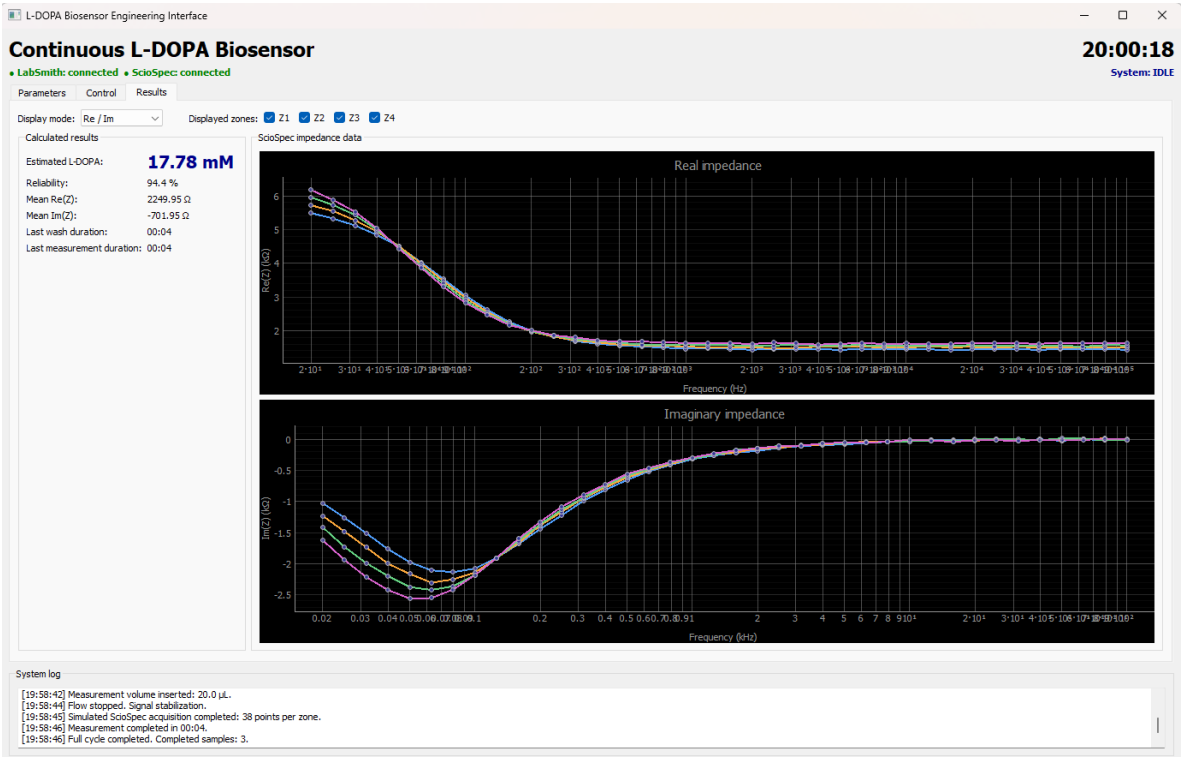


Figure 8 Engineering software interface: Results

3. IN award: Biosensor innovation

The project has established and validated the core selectivity rationale (recognition through 4´-aminobenzo-18-Crown-6 (AB18C6) on $Cu_3(HHTP)_2$computationally through docking studies and fluorometric titration. It is now generated experimental binding data across the full panel of relevant analytes: L-DOPA, Dopamine, Phenylalanine, L-Tyrosine. Our data shows significant selectivity for our analyte L-DOPA as shown Figure 9.

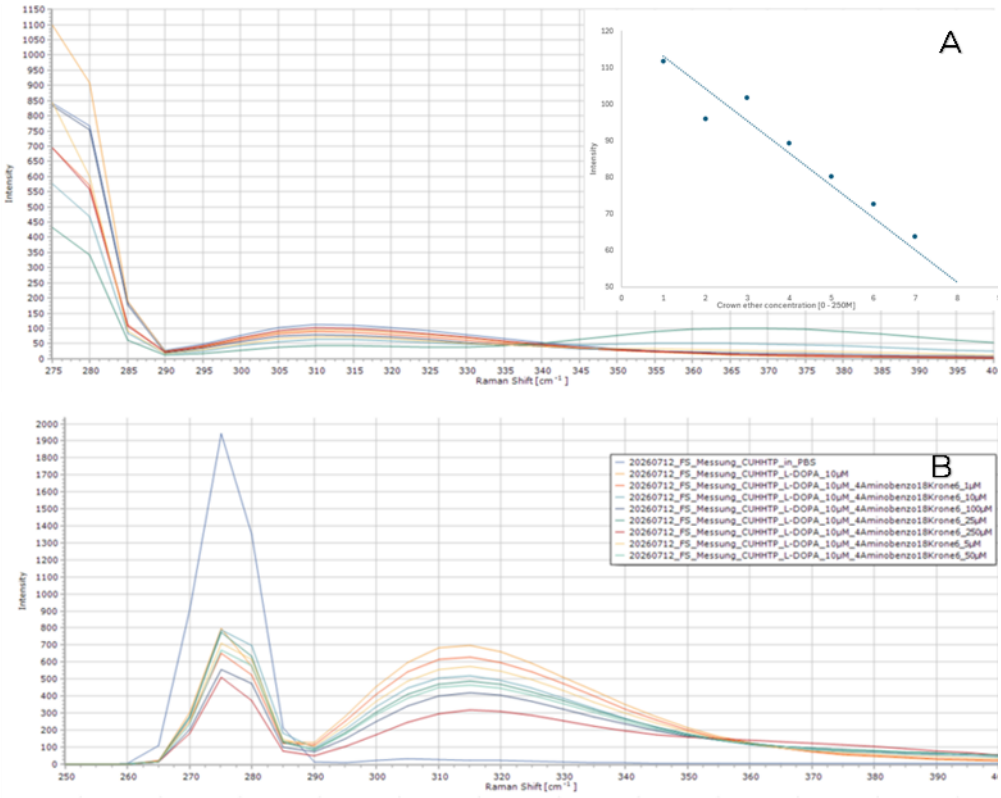


Figure 9 Fluorometric titration – Graph shows substantial quenching effect due to the conjugated π - π interaction of L-DOPA and AB18C6 – by looking at the intensity a linear regression is shown. Graph B Flourometric titration with Cu3(HHTP)2

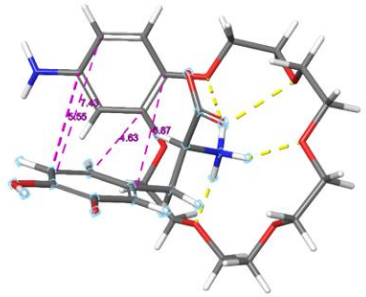


Figure 10 A MD Simulation performed with Schrödinger Maestro – Shows the interaction between L Dopa and AB18C6

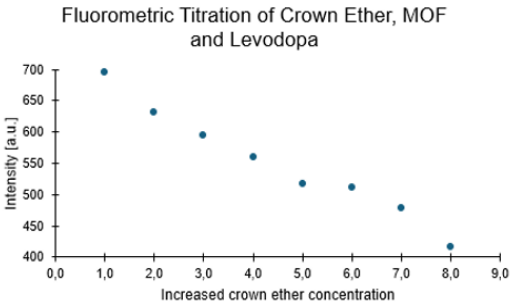


Figure 11 Fluorometric Titration of Crown Ether, MOF and L-DOPA

The graph illustrates significant quenching occurring between L-DOPA and AB18C6, along with enhanced quenching facilitated by $Cu_3(HHTP)_2$. The emphasis in our work is depicted by the optimized workflow with Schrödinger Maestro, which is a software that allows users to perform molecular dynamics simulations with an accuracy and efficiency that is unparalleled in the field. The dockings that have been performed seem to corroborate our findings and therefore strengthen our hypothesis.

The sensor innovation is supported by literature. Using crown ethers and metalloorganic frameworks is not widely researched in a biomedical context, but it does provide a significant advantage over other methods such as enzymes, aptamers and antibodies. While most enzymes and aptamers demonstrate promising selectivity for a broad spectrum of molecules, their intricate nature complicates the process of achieving and refining selectivity, a challenge even for natural systems. Our methodology uses simple, reliable, long-lasting compounds, making our sensor more affordable and reliable than other methods in the case of biofouling. Nevertheless, long-term sensing would improve our understanding of different diseases and treatments by enabling the collection of a large amount of quality data.

Initial electrochemical impedance spectroscopy (EIS) testing will be conducted across a frequency range of 1 Hz to 100 kHz, with hierarchical clustering applied to identify the most informative frequencies. This helps filter out noise and exclude frequencies that carry little useful information. The resulting dataset will be used to train a Random Forest model, producing an initial predictive model for predicting L-DOPA concentration from EIS measurements. Model accuracy will be assessed by calculating the mean squared error and applying cross-validation. If the error proves too high, a partial least squares model will again be used in place of Random Forest to reduce the risk of overfitting.

3.1. Wearable sensor

3.1.1. Technological novelty of wearable sensor

Our sensor utilizes the material combination of a conductive MOF ($Cu_3(HHTP)_2$) and a crown ether. This detection principle has not been documented yet for the detection of L-DOPA, which presents a possible innovative biosensing solution.
Another important factor is that the device is small (the chip is 14.3x10mm and the height of chip and fluidic cartridge is 1.2mm), which makes it easily integrable into a wearable device.

3.1.2. Technical feasibility of wearable sensor

The transition from the current prototype to a wearable device requires addressing several challenges that are specific to continuous sensing. One of the most critical is access to interstitial fluid (ISF). In the current prototype, ISF samples are introduced manually into the microfluidic system. A future wearable device would therefore require an integrated method for continuously extracting small volumes of ISF from the skin, for example through a minimally invasive sampling interface, and transporting them to the sensing area.

A second critical aspect is the reversibility of the molecular recognition. Continuous monitoring requires the sensor to detect both increasing and decreasing L-DOPA concentrations. Therefore, L-DOPA bound to the sensing layer must be released sufficiently rapidly when its concentration decreases. The current fluidic system allows the sensing surface to be washed between measurements and can therefore be used to experimentally investigate regeneration, carryover and recovery of the baseline signal. The required regeneration conditions and their effect on the long-term stability of the sensing layer still need to be determined.

Long-term operation also requires the sensor to remain reliable despite biofouling, temperature variations, changes in ISF composition and gradual changes in the sensing surface. The multiple sensing areas and control electrodes incorporated into the chip provide a basis for detecting abnormal or non-specific responses, while the data-processing strategy described in Section 3.2 is intended to further improve measurement robustness.

The current prototype therefore demonstrates several components required for a future wearable system, but not yet the complete wearable concept. Continuous ISF extraction, reversible sensing, long-term stability and regeneration must still be experimentally validated. Demonstrating these aspects represents the main next step toward translating the current laboratory prototype into a continuous wearable L-DOPA sensor.

3.2. Reliability of sensor output

One of the major challenges in continuous biosensing is maintaining reliable sensor output over time. Electrode fouling, carryover from previous samples, interference from other analytes, sensor-to-sensor variability, and changing environmental conditions can introduce noise or drift into the measurements. Machine learning is therefore being investigated as a strategy to improve the robustness of the sensor output. PLS regression and Random Forest regression were identified as promising methods for extracting relevant information from EIS data and predicting L-DOPA concentration. In future long-term experiments, additional features such as measurement time could also be evaluated to determine whether they help the model account for systematic sensor drift. However, the ability of the proposed machine-learning approach to compensate for these effects still needs to be experimentally validated.

3.2.1. Technological novelty of reliability concept

The system achieves measurement reliability by combining multi-channel hardware redundancy, differential signal subtraction, and outlier rejection.

At the hardware level, the chip integrates 24 devices distributed across four independently measured sensing zones, with six devices per zone. All four zones are exposed to the same fluidic flow, while their electrical responses can be measured and compared independently. The zones can also be functionalized differently, for example with MOF and crown ether, MOF only, or left unfunctionalized to serve as control areas. This configuration provides measurement redundancy and enables differential comparison between sensing and control zones, helping to distinguish L-DOPA-specific responses from non-specific effects.

At the chemistry and sensing layer, differential measurements cancel out environmental noise and non-specific binding. Having one of the chambers filled with samples containing no L-DOPA establishes a baseline to subtract background drift and temperature changes. Additionally, comparing signals between crown-ether-functionalized electrodes and control electrodes without crown ethers isolates true guest-host binding from non-specific adsorption.

At the software layer, reading from multiple devices concurrently provides redundancy for the machine learning model to identify and filter out compromised sensors caused by surface fouling or micro-fabrication flaws, combining the remaining valid signals into a stable concentration readout.
While machine learning has expanded research and applications across numerous fields, fewer studies have explored its combined potential with biosensing. If utilized more widely, this synergy could significantly increase the efficiency of biosensing, as it helps address many of the field's persistent challenges, including drift and noise from changing environments, carryover from previous samples, and fouling of the electrode.

3.2.2. Technical feasibility of reliability concept

Reliable quantification of L-DOPA is challenging due to signal drift, environmental variations, non-specific interactions, and measurement noise. Therefore, the proposed biosensor incorporates multiple strategies to improve reliability and reproducibility of the sensor output.

Electrochemical impedance spectroscopy

Electrochemical impedance spectroscopy (EIS) provides multiple independent parameters, such as the real and imaginary impedance, phase, and impedance magnitude. The complete impedance spectrum can be used for concentration estimation, making the sensing approach more reliable against noise and measurement fluctuations.

The electrode–electrolyte interface can be modelled using a Randles equivalent circuit, as illustrated in Figure 12 Randles equivalent circuit model. Reproduced from Laschuk et al. (2021), under CC BY-NC 3.0.. The model consists of the solution resistance (Rs), double-layer capacitance (Cdl), charge-transfer resistance (Rct), and Warburg impedance (Zw), which accounts for diffusion-related processes. Changes occurring at the sensing interface upon interaction with L-DOPA can affect these impedance parameters. By monitoring the impedance response over a range of frequencies, these changes can be used to estimate L-DOPA concentration.

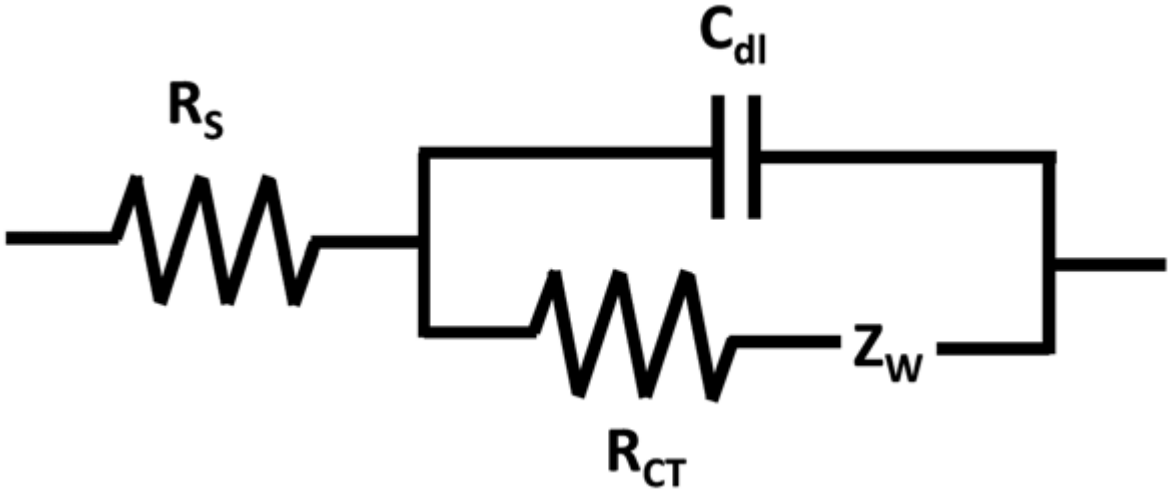


Figure 12 Randles equivalent circuit model. Reproduced from Laschuk et al. (2021), under CC BY-NC 3.0.

Microfluidics

The microfluidic device contributes to reliability by ensuring controlled sample handling and reproducible transport conditions. Since the test event limits the sample volume to 100 µL, the microfluidic design enables reproducible measurements under low-volume (Cartridge volume of ~3 µL) conditions while minimizing operator-dependent errors. In addition, the ability to perform measurements with only small sample volumes is highly desirable for future clinical applications, where minimizing sample consumption can improve patient comfort and facilitate more frequent monitoring.

Machine Learning

Initial EIS measurements will be performed over a frequency range of 1 Hz to 100 kHz. Hierarchical clustering will first be used to group frequencies with similar response patterns and identify potentially informative frequency ranges. If required, PLS regression will then be used to evaluate which frequencies are most relevant to L-DOPA concentration. Based on these results, additional EIS measurements will be performed with higher frequency resolution within the most informative ranges. The resulting dataset will be used to train a Random Forest regression model to predict L-DOPA concentration from the EIS measurements. Model performance will be evaluated using cross-validation and quantitative error metrics such as RMSE and MAE. Final performance should subsequently be assessed using independent test data that was not used during model training.

3.3. Original contributions

3.3.1. Team contribution

The novel idea of using crown ethers for biosensing of L-DOPA was independently developed by one of our team members and refined solely by students of the surface chemistry team. With the support of the idea by our supervisor, Dr. Vivek Pachauri, everything else from crown ether selection to experimental design and lab work was conducted by the students themselves. The work was supported by Dr. Pachauri through discussion about our lab results and about next experimental steps. Dr. Pachauri advised the team to create a model of specificity through varying the analyte and in conducting 3D-Spectra-Analysis of our target molecules, enabling FRET pair identification. In addition, suspending the MOF and conducting solid-state fluorescence spectroscopy were discussed with Dr. Pachauri. However, it is crucial to mention that the lab work and final experimental design were developed and conducted by the students themselves. The Institute for Materials in Electrical Engineering 1 supplied independent lab access, which laid the foundation for the high amount of independent scientific work shown by the students of the surface chemistry team.

The idea of implementing machine learning to improve the reliability of the sensor output was independently conceived by M. Bühlmann. Based on his initial research, he identified PLS regression as a suitable method for evaluating the relevance of EIS frequencies to L-DOPA concentration, Random Forest regression as a potential method for concentration prediction using the selected EIS features, and XGBoost as an alternative approach for capturing potentially non-linear relationships between EIS data and analyte concentration.

The ML team, composed of M. Bühlmann and H. Rannu, then worked together on the development of the machine-learning approach. H. Rannu independently proposed the use of hierarchical clustering to identify initial informative frequency ranges and also investigated additional modelling approaches, including LASSO, gradient boosting regression, and support vector regression. The selection and refinement of the proposed ML workflow were therefore developed collaboratively within the ML team.

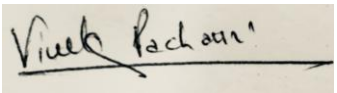
As the available dataset is currently too limited for reliable scientific validation, the proposed models have not yet been experimentally evaluated. A suitable validation strategy would be to collect a sufficiently large dataset with repeated measurements at known concentrations, divide the data into independent training and test sets, use cross-validation during model development, and evaluate performance using metrics such as R^2, RMSE, and MAE. Robustness should additionally be assessed using measurements from different sensors, experimental days, and concentration ranges to verify that the model generalizes beyond the data used for training.

3.3.1. Supervisor's comments

Biologically sensitive electrical devices based on AC- and DC-readout principles have been reported for the detection of levodopa. High technological readiness and clinical translation of platforms for continuous levodopa monitoring, however, remain elusive due to limitations related to molecular selectivity, reversibility, biofouling, signal drift and long-term stability. For the SensUs 2026 Parkinson's disease challenge, the AixSense team considered these limitations from the beginning and formulated an original, non-enzymatic sensing concept based on a conductive $Cu_3(HHTP)_2$ metal-organic framework functionalized with 4'-amino-benzo-18-crown-6. The creativity of the team lies in combining the molecular-recognition properties of the crown ether with the porosity, chemical tunability and electrical conductivity of the MOF. This specific material combination enables cooperative interactions with L-DOPA and provides a direct route for electrical transduction using electrochemical impedance spectroscopy. Compared with biologically derived recognition elements, the synthetic interface offers potential advantages in chemical robustness, process compatibility and systematic molecular optimization, while its long-term stability and resistance to biofouling remain subjects for further experimental validation. The recognition concept was independently conceived and refined by the students. The team screened several crown ethers, selected AB18C6, investigated interactions with L-DOPA and structurally related molecules, and supported the proposed binding mechanism using fluorometric titration and molecular-docking simulations. My contribution as supervisor was limited to scientific guidance, including recommendations for systematic specificity studies, three-dimensional spectral analysis, investigation of suspended and solid-state MOF systems, and discussion of subsequent validation experiments. The experimental protocols, laboratory work, computational workflows and interpretation of the results were developed and carried out by the students.

Following these recognition studies, the team translated the chemical concept into a coherent laboratory sensor platform comprising a cleanroom-fabricated multidevice chip, control electrodes, a low-volume microfluidic cartridge, automated fluid handling, impedance-spectroscopy instrumentation and a dedicated engineering interface. The 24-device architecture, four independently measured sensing zones and differential control strategy provide redundancy and create a strong basis for identifying non-specific responses, defective sensing areas and time-dependent drift. The integration of multivariate EIS data with machine-learning approaches offers an additional opportunity for robust concentration estimation once a sufficiently large, independent and longitudinal dataset has been generated. The translational potential is strengthened by stakeholder consultations with a neurologist, a patient and a caregiver, which established patient comfort, operational simplicity, long-term reliability and clinical interpretability as central design criteria. The proposed progression from analytical validation to continuous-flow robustness studies and, subsequently, preclinical and clinical evaluation represents a technically credible development pathway. At its present stage, the system should be regarded as an advanced laboratory prototype rather than a completed wearable sensor; continuous ISF extraction, reversible detection, regeneration, long-term operation and machine-learning generalization still require validation. In view of the team's interdisciplinary contributions to surface chemistry, simulations, cleanroom fabrication, microfluidics, electrical readout, software and translation planning, I consider the biosensor development plan well thought out, technically promising and highly original in its specific implementation, and give it my full recommendation.

Dr. Vivek Pachauri



Marc Bühlmann



Kerem Üçok



4. TP award: Translation potential

4.1. Customer interviews

To better understand the clinical relevance and practical implementation of our biosensor, we identified several stakeholder groups involved in Parkinson's disease management, including neurologists, Parkinson's disease patients, caregivers, and clinical researchers.

We conducted an in-depth interview with Prof. Dr. Marc Ziegenbein, Medical Director at Klinikum Wahrendorff, who provided valuable insights into current clinical workflows, challenges in Parkinson's disease management, and the potential integration of continuous L-DOPA monitoring into routine care.

Additionally, we conducted an informal interview with a Parkinson's disease patient and their primary caregiver. This discussion provided first-hand perspectives on the daily challenges associated with symptom fluctuations, medication management, and quality of life. Since informed consent for recording or publication of interview details was not obtained, individual responses are not reported in this document. Instead, only general insights that informed our design process are included.

The combination of clinician and end-user perspectives allowed us to better understand both the clinical and practical requirements of a continuous L-DOPA monitoring biosensor.

4.1.1. Identification of potential stakeholders

A semi-structured interview guide was developed using open-ended questions focusing on current treatment challenges, unmet clinical needs, and expectations for continuous L-DOPA monitoring.

Topics included:

- Current limitations of Parkinson's disease management.
- Challenges related to L-DOPA dosing and symptom fluctuations.
- Desired characteristics of a wearable biosensor.
- Potential barriers to clinical implementation and patient acceptance.

The interview with Prof. Dr. Marc Ziegenbein was recorded and the important parts were noted and discussed with the team in the weekly meetings. The discussion with the Parkinson's disease patient and caregiver was conducted informally to better understand user experiences. Because consent for recording or publishing identifiable interview data was not obtained because the doctor did not let us, detailed quotations and personal information are intentionally omitted in accordance with ethical research practices.

4.1.2. Interview approach and execution

We adopted a semi-structured interview methodology, which allowed us to maintain a consistent interview framework while adapting the discussion to the expertise and role of each stakeholder. Before conducting the interviews, we developed a general interview guide covering three main themes: (1) the clinical problem and unmet needs, (2) the proposed technical solution, and (3) implementation and commercialization aspects.

Core questions explored topics such as:

- Current challenges in Parkinson's disease management.
- Perceived need for continuous L-DOPA monitoring.
- Potential risks and limitations of our proposed biosensor.
- Priorities for technical development.
- Expected benefits for patients and healthcare professionals.
- Barriers to clinical implementation and adoption.
- Recommendations for future collaborations, sponsors, and clinical validation.

Although the overall interview structure remained the same, the specific questions were tailored to each stakeholder group. During the interview with Prof. Dr. Marc Ziegenbein, the discussion focused on implementation challenges, reimbursement, commercialization strategies, and long-term clinical impact.

In contrast, the interview with the Parkinson's disease patient and caregiver emphasized everyday experiences with Parkinson's disease, medication routines, symptom fluctuations, treatment burden, usability expectations, and willingness to use a wearable continuous monitoring device. Technical questions were intentionally minimized, and the discussion was conducted in a conversational and empathetic manner to encourage participants to openly describe their experiences and unmet needs.

Prior to each interview, participants were informed about the purpose of the project and the voluntary nature of their participation. No sensitive personal information was collected. The clinician interview was partly documented through written notes. For the patient and caregiver interview, informed consent for recording or publication of personal statements was not obtained; therefore, no recordings or identifiable quotations are included in this report. Instead, only general design insights derived from the discussion are presented.

Using this semi-structured approach ensured that each interview remained relevant to the participant's expertise while still allowing us to systematically compare findings across stakeholder groups and translate these insights into design requirements for our biosensor.

4.1.3. Interview results and conclusions

The interviews provided valuable insights into the clinical relevance, technical priorities, and translational potential of our proposed continuous L-DOPA biosensor.

During the interview with Prof. Dr. Marc Ziegenbein, several aspects critical for successful implementation were discussed. He emphasized that reimbursement by health insurance providers will be one of the key factors determining future adoption. While he considered the concept clinically valuable, he noted that widespread implementation would depend on demonstrating sufficient patient benefit and healthcare cost reduction to justify reimbursement.

Regarding usability, high patient compliance is expected, provided that the device remains simple and comfortable to wear. He suggested a wearable adhesive patch comparable to existing continuous glucose monitoring (CGM) systems, with an operational lifetime of approximately two weeks, as this format is already well accepted by patients. He also pointed out that objective L-DOPA measurements are currently performed only occasionally (or not at all) in routine clinical practice, reinforcing the need for continuous biochemical monitoring.

From a development perspective, Prof. Dr. Ziegenbein recommended prioritizing the establishment of a technically robust sensing platform before initiating patient studies. He advised focusing on sensor optimization and reliability before progressing toward larger validation studies. Furthermore, he emphasized that the project should demonstrate tangible clinical benefits, such as improved quality of life, increased therapy safety, and the potential to reduce unnecessary hospital admissions through more individualized treatment.

He also highlighted the importance of generating long-term clinical evidence and presenting the technology at neurological and clinical conferences to increase visibility among clinicians, researchers, and potential collaborators. For future funding and collaboration opportunities, he recommended approaching organizations such as the Deutsche Parkinson Stiftung, medical technology companies working on continuous monitoring devices, and additional neurological experts.

The discussion with the Parkinson's disease patient and caregiver complemented the clinical perspective by providing insight into the daily challenges of living with Parkinson's disease. They described the uncertainty associated with fluctuating symptoms, the difficulty of determining whether changes are caused by medication timing or disease progression, and the burden of relying solely on subjective symptom assessment. Both expressed that an easy-to-use wearable device providing continuous and objective information about L-DOPA levels could increase confidence in therapy management and reduce uncertainty in everyday life.

Taken together, both interviews consistently identified continuous L-DOPA monitoring as an important unmet clinical need. The stakeholders agreed that successful implementation depends not only on analytical performance but also on patient comfort, simplicity, and long-term reliability.

The stakeholder interviews primarily confirmed the clinical relevance of continuous L-DOPA monitoring and highlighted the importance of patient comfort, ease of use, and long-term reliability. Based on these findings, subsequent discussions during our weekly project meetings with our supervisor focused on translating these user requirements into concrete design decisions. In particular, biofouling was identified as one of the major challenges for continuous biosensing in biological fluids during these meetings. To address this issue, we decided to prioritize a crown ether-functionalized conductive MOF sensing platform over biological recognition elements such as aptamers, as crown ethers are expected to offer greater chemical stability and improved long-term robustness. These discussions directly shaped our development strategy, with robustness, reproducibility, and continuous operation becoming the primary design objectives of the biosensor.

Overall, the stakeholder interviews confirmed the clinical relevance of our proposed solution and directly influenced the development strategy of the project. The collected feedback reinforced our decision to prioritize a reliable, user-friendly, and chemically stable sensing platform capable of providing continuous L-DOPA monitoring, thereby supporting safer and more personalized Parkinson's disease therapy.

4.2. Design of validation study

4.2.1. Selection of the problem

The stakeholder interviews consistently identified a common limitation in current Parkinson's disease management: the lack of objective, continuous monitoring of L-DOPA levels. Clinicians reported that treatment adjustments are primarily based on patient-reported symptoms and clinical observations, while patients and caregivers described the uncertainty associated with fluctuating symptoms and the difficulty of determining whether these fluctuations result from medication timing, disease progression, or individual pharmacokinetic differences.

Although L-DOPA is the gold standard treatment for Parkinson's disease, its concentration changes rapidly throughout the day due to absorption, metabolism, and patient-specific variability. Currently, objective L-DOPA measurements are rarely performed in routine clinical practice because available analytical methods require laboratory equipment and provide only single point measurements.

Our stakeholders emphasized that an ideal solution should provide continuous, minimally invasive and reliable monitoring while remaining easy to use in everyday life. They also highlighted that long-term reliability and patient comfort are essential for successful clinical adoption.

These findings directly motivated our project. Our proposed biosensor aims to continuously monitor L-DOPA concentrations in interstitial fluid (ISF), providing objective biochemical information that may support more personalized treatment decisions while minimizing patient burden.

4.2.2. Conceptual design and use case

Our proposed biosensor consists of a wearable electrochemical sensing platform combining a microfluidic sampling system with a conductive $Cu_3(HHTP)_2$ metal-organic framework (MOF) functionalized with immobilized crown ethers as the molecular recognition element.

Interstitial fluid is continuously transported through a microfluidic channel onto the sensing surface. Binding of L-DOPA to the crown ether-functionalized MOF alters the interfacial charge-transfer resistance, which is quantified using Electrochemical Impedance Spectroscopy (EIS). These impedance changes are correlated with L-DOPA concentration through calibration measurements.

The intended use case is a wearable patch that continuously monitors L-DOPA levels throughout daily activities. Measurement data could be transferred to a mobile application and made available to clinicians during follow-up appointments, enabling more informed medication adjustments.

Compared with conventional laboratory-based measurements, the proposed system offers several potential advantages:

- continuous rather than single-point monitoring,
- minimally invasive sampling through interstitial fluid,
- objective biochemical data to complement symptom-based assessment,
- improved therapy optimization and patient safety.

The stakeholder interviews also highlighted the importance of robustness for long-term monitoring. Because biofouling and long-term degradation remain major challenges in continuous biosensing, our design intentionally employs crown ethers as synthetic recognition elements. Compared with biological receptors such as aptamers, crown ethers are expected to provide greater chemical stability, improved resistance to degradation, and more reproducible long-term performance under continuous measurement conditions. Consequently, robustness and long-term stability have become central design priorities throughout the development process.

4.2.3. Validation study design

Due to the limited duration of the SensUs competition, comprehensive validation of the proposed biosensor was beyond the scope of the current project. Therefore, a structured validation framework is proposed for future work. The validation strategy is based on the current technical maturity of the sensor and the key priorities identified during the stakeholder interviews, particularly the need to demonstrate technical robustness before clinical implementation.

Phase I – Analytical Validation

The first phase would focus on evaluating the analytical performance of the biosensor under controlled laboratory conditions. Artificial interstitial fluid (aISF) containing known concentrations of L-DOPA would be used to establish calibration curves. Electrochemical Impedance Spectroscopy (EIS) measurements would determine the relationship between L-DOPA concentration and the charge-transfer resistance (Rct) of the sensing surface.

The analytical performance would be assessed using quantitative parameters, including:

- Sensitivity
- Limit of detection (LOD)
- Linear dynamic range
- Response time
- Repeatability (coefficient of variation)
- Calibration linearity (R^2)

These experiments would demonstrate whether the sensing platform can detect L-DOPA accurately and reproducibly over the clinically relevant concentration range.

Phase II – Robustness and Long-Term Stability

Since the proposed biosensor is intended for continuous monitoring, robustness would represent a critical part of the validation process.

Continuous-flow experiments using the developed microfluidic platform would be performed to investigate long-term sensor stability, signal drift, and resistance to biofouling. In addition, sensor performance would be evaluated at different temperatures to determine whether environmental or physiological temperature variations influence sensitivity, reproducibility, or overall sensor performance during prolonged operation.

Selectivity experiments would also be conducted by exposing the sensor to physiologically relevant interfering compounds, including dopamine, ascorbic acid, uric acid, glucose, and common electrolytes present in interstitial fluid. These measurements would evaluate whether the sensing platform selectively responds to L-DOPA while minimizing interference from other biomolecules.

Phase III – Preclinical and Clinical Validation

Following successful laboratory characterization, the biosensor could be evaluated under physiologically relevant conditions before progressing to pilot studies involving Parkinson's disease patients.

These studies would investigate not only analytical performance but also practical feasibility, including ease of use, patient acceptance, comfort, and continuous operation under realistic conditions. The objective would be to determine whether continuous biochemical monitoring could provide clinically meaningful information to support medication optimization beyond current symptom-based assessment.

The stakeholder interviews also highlighted the importance of generating long-term clinical evidence. Therefore, a longitudinal comparative study could subsequently be conducted in which patients using the biosensor are compared with a control group receiving standard clinical care. Outcome measures could include therapy optimization, frequency of medication adjustments, patient-reported quality of life, treatment adherence, and hospitalization rates. Such studies could provide both clinical and health-economic evidence supporting future translation of the biosensor into routine clinical practice.

4.3. Bonus criteria Translation Potential

The innovation of our sensor is finalized by the molecular recognition concept. With computational chemistry methods and fluorescence titration, we were able to understand and reinforce the amount of potential the chemical method has. Our concept of using Crown ethers in a MOF thin film has high amounts of potential due to the high variety of optimization that is possible with our chemical platform. Endlessly modifying Crown ethers or Crown ether like molecules opens us a huge library for sensing any disease marker there is. In combination with the data gathered and the rise of computational performance in Chemistry and Biotechnology, it is possible to make Metalorganic Frameworks specific to any disease marker out there with an optimized workflow. In the outlook of the competition, it is being considered to further investigate possible optimization for reversibility for our sensor. Given the rise of Photochemistry, it is thought of using reversible “photobases” to change the pH to cleave the attraction of our molecules and make our method reversible. If a start-up is being realized, user interface optimization is possible. Based on the experimental design using fluorometric titrations, we actively contributed to the widely acknowledged research topic of optical sensing.

5. Team and support

5.1. Contributions of the team members

Marc Bühlmann

Team Captain and Technical Team Leader. Responsible for team organization and communication with SensUs. Designed and fabricated the complete 3D cartridge system, developed the graphical user interface, contributed to the machine-learning model (with Holger Rannu) and created the team logo.

Kerem Üçok

Team captain and Buisness Team leader. He coordinated the overall project and the activities of the business team. He contributed to market analysis, budgeting, sponsor outreach, commercialization planning, the preparation of business-related deliverables as well as the cleanroom fabrication.

Alexander Schleiser

The group leader of the Surface Chemistry team. Using computational chemistry and fluorometric titration, designed a specific metal-organic framework interface for measuring L-DOPA. In addition to chemistry, also organized computational tools for the development of surface chemistry and was responsible for experimental design and characterization of $Cu_3(HHTP)_2$.

Heino Soetbeer

Conducted independent research and identification of L-DOPA specific crown ether via fluorescence spectroscopy and computational Chemistry as the group leader of Surface Chemistry team. Responsible for experimental design and evaluated crown ether interaction with various amino acids to develop a tuned system for L-DOPA biosensing. Conducted fluorescence characterization of $Cu_3(HHTP)_2$ MOF in solution, on glass surface and in combination with our L-DOPA specific sensing system.

Holger Rannu

Member of the electrical readout team, where he conducted EIS measurements, assisted in assembly of the electrical hardware, conducted independent research on machine learning and completed the whole part of data analysis (with Marc Bühlmann), including the machine learning model.

Nikoletta Palatiana

Member of the cleanroom fabrication team. She was involved across the full pipeline of the sensor chip fabrication. She also contributed to the PCB design of the carrier board used to interface the sensor chip.

Rohith Ninan

Member of the cleanroom fabrication team. They were involved in the chip carrier PCB design.

Sara Nishma

Member of the electrochemical readout team. She also helped in the process of fabricating the microfluidic system used for the biosensor platform.

Yllka

Member of the cleanroom fabrication team, helped in processes like optical lithography, etching and many other fabrication steps. Helped coordinate the clean room work with members of the IWE1 institute.

Ulça Sade Demirbüken

Contributed to the business development of the project, including market analysis, sponsor outreach, commercialization planning, and the preparation of business-related deliverables. She was also responsible for managing the team's social media presence and external communication throughout the competition.

Zeynep Aslan

Contributed to the business development of the project, with a focus on market analysis, budgeting, commercialization planning, and the preparation of business-related deliverables.

5.2. People who have given support

We sincerely thank our supervisor, Dr. Vivek Pachauri, for his continuous guidance, scientific expertise, and support throughout the project. His valuable feedback and discussions helped us refine our ideas, overcome technical challenges, and further develop our biosensor concept.

We sincerely thank Prof. Dr. Marc Ziegenbein for sharing his clinical expertise and valuable feedback, which helped us better align our biosensor concept with clinical practice and future validation.

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We also thank the Parkinson's disease patient and their caregiver for sharing their experiences and perspectives, which provided valuable insights into user needs and reinforced the importance of a reliable and user-friendly monitoring solution. To protect their privacy, they remain anonymous.

5.3. Sponsors and partners

Schrödinger gave us access to their software. With Schrödinger we were able to do molecular dynamic simulations

6. References

Avilés-Moreno, J. R., Quesada-Moreno, M. M., López-González, J. J., & Martínez-Haya, B. (2013). Chiral recognition of amino acid enantiomers by a crown ether: Chiroptical IR-VCD response and computational study. The Journal of Physical Chemistry B, 117(32), 9362–9370. https://doi.org/10.1021/jp405027s

Bocan, A., Siavash Moakhar, R., Del Real Mata, C., Petkun, M., De Iure-Grimmel, T., Guptha Yedire, S., Shieh, H., Khorrami Jahromi, A., Mahshid, S. S., & Mahshid, S. (2025). Machine-learning-aided advanced electrochemical biosensors. Advanced Materials, 37(33), Article 2417520. https://doi.org/10.1002/adma.202417520

Kubik, S. (2022). Synthetic receptors based on abiotic cyclo(pseudo)peptides. Molecules, 27(9), 2821. https://doi.org/10.3390/molecules27092821

Laschuk, N. O., Easton, E. B., & Zenkina, O. V. (2021). Reducing the resistance for the use of electrochemical impedance spectroscopy analysis in materials chemistry. RSC Advances, 11(45), 27925–27936. https://doi.org/10.1039/D1RA03785D

Lister, A. M., Armitage, B. I., Wang, Y., Chen, R., Li, W., & Castell, M. R. (2025). Electrochemical synthesis of $Cu_3(HHTP)_2$ metal–organic frameworks from Cu nanoparticles for chemiresistive gas sensing. ACS Applied Nano Materials, 8(30), 15114–15121. https://doi.org/10.1021/acsanm.5c02304

Merck. (n.d.). 4'-Amino-benzo-18-crown-6 (Product No. 444022). Sigma-Aldrich. Retrieved August 7, 2026, from https://www.sigmaaldrich.com/DE/de/product/aldrich/444022

Weißenstein, A., Saha-Möller, C. R., & Würthner, F. (2018). Optical sensing of aromatic amino acids and dipeptides by a crown-ether-functionalized perylene bisimide fluorophore. Chemistry – A European Journal, 24(31), 8009–8016. https://doi.org/10.1002/chem.201800870

Zhou, X., Jin, X., Li, D., & Wu, X. (2011). Selective detection of zwitterionic arginine with a new Zn(II)-terpyridine complex: Potential application in protein labeling and determination. Chemical Communications, 47(13), 3921–3923. https://doi.org/10.1039/c0cc05771a