Team Results Document

SensETH



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SensUs

1. Abstract: Summary for the SensUs website

Managing Parkinson's Disease (PD) requires precise dosing of the medication levodopa (L-DOPA), as drug levels fluctuate constantly in the body. Therefore, SensETH developed a biosensor for continuous, real-time L-DOPA monitoring based on an electrochemical detection strategy. At the core of the device is tyrosinase immobilized on MWCNT-modified screen-printed carbon electrodes (MWCNT-SPCEs). Compared to traditional electrochemical sensors, screen-printed carbon electrodes offer key advantages, including high portability, low cost, and ease of production, in addition to favorable electrochemical properties. The multilayered sensor design combined with leveraging the underlying enzymatic reaction kinetics, enhances selectivity, specificity, and long-term stability.

To prevent inaccurate readings caused by other natural substances in body fluids (like vitamin C or uric acid), our sensor uses an advanced electrical filter and a four-channel sensor array. Two active channels measure the medication, while two control channels automatically correct for background noise and signal drift. Their integration enables an accurate concentration-dependent readout. Designed with patient and physician feedback, a wireless sensor connection to a user-friendly software app was designed. The app enables real-time evaluation of L-DOPA levels, supporting clinicians in personalizing treatment. Ultimately, this sensor lays the groundwork for a fully automated, "closed loop" system that can monitor L-DOPA levels and deliver precise doses automatically through a wearable pump.

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

2.1. Molecular recognition

The SensETH biosensor employs an electrochemical L-DOPA sensing strategy based on tyrosinase-mediated enzymatic recognition and subsequent electrochemical signal transduction (Moon et al., 2021). The sensor architecture corresponds to a three-electrode system composed of a silver auxiliary electrode, a carbon counter electrode, and a multi-walled carbon nanotubes (MWCNTs) modified working electrode featuring a multilayer structural organization designed to enhance sensitivity, selectivity and sensor stability.

Tyrosinase was immobilized by drop-casting, following a previously described methodology adapted to the selected electrode type (Cembalo et al., 2023). Glutaraldehyde (GA) is subsequently added to cross-link the proteins, thereby securely anchoring the enzyme matrix to the MWCNT surface (Cembalo et al., 2023). Aquivion, a selectively permeable membrane, repels negatively charged species in interstitial fluid (ISF), such as ascorbic acid, a major interferent in enzymatic L-DOPA sensing. (Cánovas et al., 2020; Kelarakis, 2025). Finally, a very thin layer of Polyurethane helps with long-term stability and reduces fouling (Fang et al., 2022).

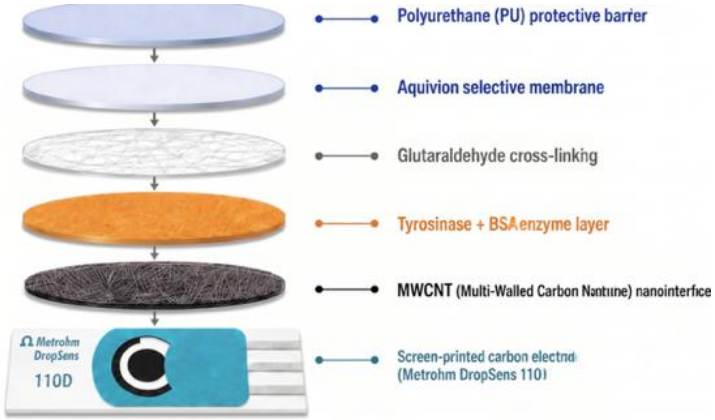


Figure 1 Graphic of the different layers on the MWCNT electrode

2.2. Physical transduction

The biosensor relies on an electrochemical signal transduction mechanism. Tyrosinase oxidizes L-Dopa to dopaquinone. By applying an anodic potential, dopaquinone is electrochemically reduced back to L-Dopa at the electrode surface. The MWCNT-functionalized electrode provides a high electroactive surface area, producing a clear and sharp signal, that can be measured by Chronoamperometry (CA) (Cembalo et al., 2023).

Equation 1 Oxidation of L-DOPA to dopaquinone

$$\text{L-DOPA} + \frac{1}{2}\text{O}_2 \xrightarrow{\text{Tyrosinase}} \text{Dopaquinone} + \text{H}_2\text{O}$$

Equation 2 Reduction of Dopaquinone to L-DOPA

$$\text{Dopaquinone} + 2\text{H}^+ + 2\text{e}^- \xrightarrow{\text{Electrode } (-V)} \text{L-DOPA}$$

2.3. Cartridge technology

The biosensor utilizes a transparent PEEK/polypropylene wall-jet flow cell (Metrohm) with a magnetic, leak-proof assembly optimized for DropSens SPEs. A Jobst CPP1 peristaltic pump drives fluid from the provided 100 µL sample to the electrode. The total fluidic system volume is 64.5 µL, consisting of 56.5 µL in the connecting tubing and an 8 µL internal O-ring measurement chamber.
The system is initially primed with PBS to wet the system. Continuous biosensing, the inlet tube is moved between sample vials without intermediate flushing. The outlet leads to a tube that collects the waste.

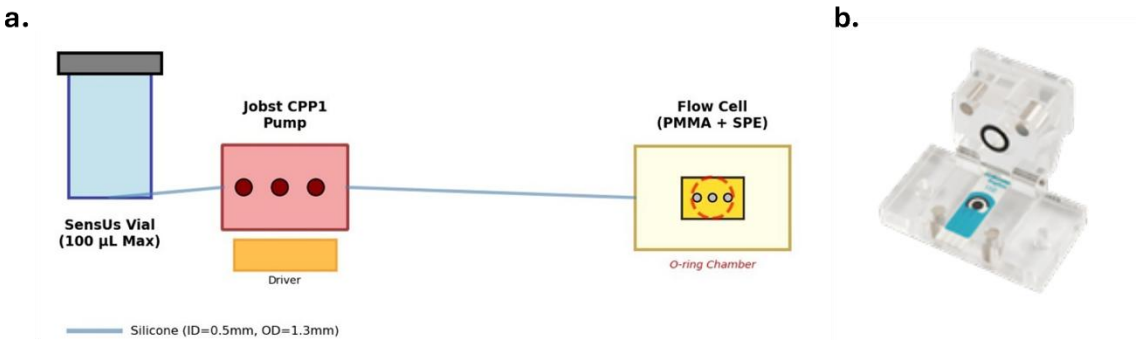


Figure 2 Illustration of the Hardware Setup and Continuous Flow System. (a) Schematic Illustration of the hardware setup. (b) Methrom Flow Cell used for the measurements.

2.4. Reader instrument and user interaction

To measure the redox reaction current, the system uses the Army Corps of Engineering Potentiostat (ACEstat). Built on the Analog Devices ADuCM355 integrated circuit, this compact, low-power device consolidates a potentiostat amplifier, data converters (DAC/ADC), microprocessor, Trans-Impedance Amplifier (TIA), and signal processing hardware into a single package (Brown et al., 2022). System operation is controlled through an open-source Graphical User Interface (GUI) that enables the configuration of measurement parameters. User interaction is straightforward: the operator loads the biofluid onto the sensor and initiates the assay through the interface. The software then executes CA by stepping the working electrode potential to a fixed value while recording oxidation and reduction currents.



Figure 3 ACEstat Potentiostat

The acquired signal is post-processed using baseline subtraction against pre-acquired reference measurements, alongside noise reduction via a Savitzky-Golay filter. Finally, the GUI extracts the steady-state current and total charge, calculates the levodopa concentration using a pre-calibrated fitting function, and displays the numerical result directly to the user.

3. IN Award: Biosensor innovation

3.1. Wearable sensor

Plasma Liquid Chromatography-Mass Spectrometry (Plasma LC–MS) is the gold standard for L-DOPA, but its cost and reliance on central laboratories keep it out of routine care, so dosing is guided by symptoms rather than a measured concentration. ISF, by contrast, is continuously available and suitable for real-time tracking (Teymourian et al., 2022). In ISF, L-DOPA is directly oxidisable at a bare electrode, but only at anodic potentials at which ascorbate and urate also oxidise (Mollamohammadi et al., 2023). We therefore use an enzymatic recognition element that relocates the readout to a reducing window where these interferents are strongly attenuated.

3.1.1. Technological novelty of wearable sensor

The device is a skin-adhered patch incorporating a microneedle electrode array, an electrochemical analog front end (AFE), a Bluetooth Low Energy (BLE) microcontroller, power management circuitry, and an inertial motion unit (IMU), enclosed in a biocompatible medical grade ABS housing. L-DOPA is sampled from dermal ISF via microneedles that penetrate the stratum corneum and is measured amperometrically via an enzyme-mediated electrochemical reaction. Data are digitized on device, buffered, and transmitted wirelessly to a paired smartphone application for display and logging (*Figure 4*).

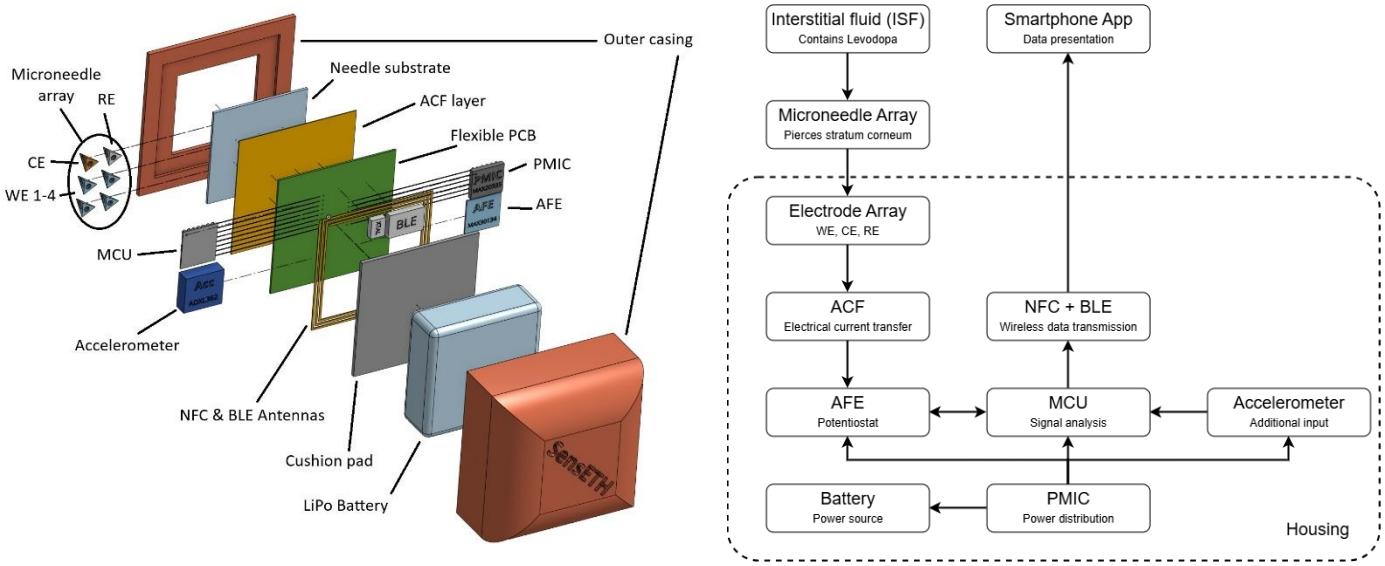


Figure 4: Exploded view of the wearable biosensor (left) and diagram of the components function and their interconnection (right)

Its 1.5 mm needles reach the dermis regardless of gender, age, ethnicity and BMI, with, suprascapular and waist as preferred sites (Laurent et al., 2007). The dermis holds the largest ISF volume and exchanges molecules below 3 kDa freely with plasma, so these appear near their unbound plasma concentration (Wu et al., 2024). Each needle is a hollow pyramid with a 1250 µm triangular base edge and a 425 µm cylindrical bore in one face packed with carbon paste (Windmiller et al., 2011), on a 2 mm pitch, far above the spacings at which insertion force rises (Olatunji et al., 2013)and the bed-of-nails effect impairs insertion (Makvandi et al., 2021). The needles are made in e-Shell 200 acrylate

photopolymer, because of their Class-IIa biocompatibility per ISO 10993 (Windmiller et al., 2011). They stand on a 10 × 10 mm, 500 µm base plate (Windmiller et al., 2011) set in a silicone-rubber patch body beneath a 3D-printed lid, a format already run in vivo in rats from a wireless potentiostat (Wei et al., 2026).

Four working electrodes share one Ag/AgCl reference and one counter electrode, the miniaturisation step proposed by Fang et al. (2022). Two of them carry tyrosinase co-crosslinked with bovine serum albumin by glutaraldehyde (Cembalo et al., 2023). The ratio follows from a 1D transport-kinetics model (Section 3.2.2). Selectivity is ensured through multiple steps: Aquivion (Section 2.1) blocks anions (Cánovas et al., 2020), the reducing window excludes anodic interferents, and the inactive channel subtracts the rest. Aquivion further protects from ascorbate, which reduces dopaquinone back to L-DOPA and inhibits tyrosinase (Cembalo et al., 2023), at a cost in sensitivity.

The remaining two carry heat-inactivated tyrosinase, otherwise identical. Subtracting the inactive channel removes the residual contribution together with baseline drift, allowing levodopa to be tracked across a dosing interval.

The novelty lies in three elements: moving microneedle L-DOPA detection out of the anodic window (+0.3 V vs Ag/AgCl; Goud et al., 2019) into a reducing one at −0.3 V (Moon et al., 2021); referencing it against a channel carrying the same enzyme, heat-inactivated, rather than a BSA-matched blank (Fang et al., 2022); and optimising the combination by finite-element simulation in COMSOL Multiphysics.

3.1.2. Technical feasibility of wearable sensor

Dual-channel background subtraction and orthogonal biomarker monitoring have established precedent in wearable electrochemical platforms, such as L-DOPA sensing systems (Goud et al., 2019). To ensure structural reliability, the microneedle array design incorporates optimized geometric dimensions engineered to resist shear and bending stresses during epidermal penetration, paired with biocompatible substrate materials. The electronic architecture relies on commercially available, integrated circuits (ICs) on a compact Printed circuit board (PCB) layout, facilitating reliable scalable manufacturing. In particular, the selected ultra-low-power microcontroller unit (MCU) has demonstrated performance in similar wearable sensing devices (Section 8.3), confirming its suitability for continuous data acquisition and power

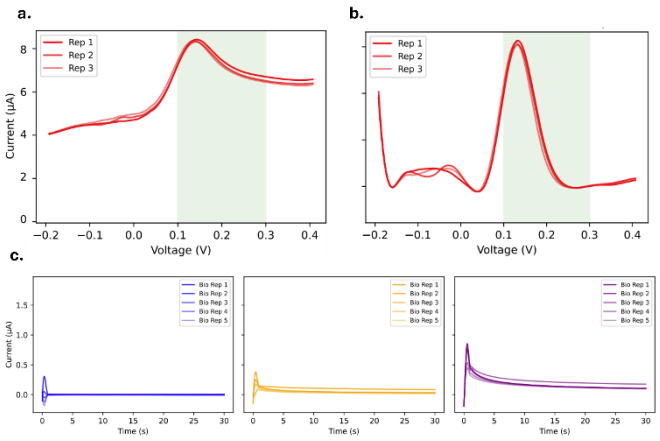


Figure 5 Electrochemical measurements and data processing

All measurements were performed in a PBS solution. (a) CV measurement of a 50 µM sample following Savitzky-Golay filtering. (b) The same CV measurement after ALS baseline correction. (c) CA measurements after baseline subtraction for sample concentrations of 0.0, 3.0, and 10 µM.

management. To meet regulatory safety requirements for dermal contact, the outer casing is fabricated from medical-grade polymers complying with ISO 10993 standards (e.g., cytotoxicity, skin irritation, and sensitization tests), aligned with materials proven in commercial continuous glucose monitoring (CGM) systems.

3.2. Reliability of sensor output

Three criteria were defined for our continuous wearable sensor: **stable kinetics** are maintained by a diffusion-limited electrochemical response, accurate analyte quantification in dynamic environments is guaranteed by high **sensitivity and linearity** (Tesoro et al., 2023) and high tyrosinase **specificity** for L-DOPA (Probst et al., 2024).

Enzyme degradation, oxygen fluctuation, biofouling, and hysteresis are drift sources expected in our wearable, which are addressed in a three-stage calibration. First, the specific reduction peak is identified by CV. Faradaic currents are then extracted by the asymmetric least squares (ALS) algorithm (Safavi et al., 2013). The signal is thereby cleaned (Figure a and Figure b) and the exact reductio
n and oxidation voltages are identified for continuous CA analysis.

Additionally, a patient-specific baseline is established by precise techniques, such as LC-MS. A simple differential sensing approach is then used for the CA analysis. The steady-state current is isolated and analysed by subtracting the background signal (measured from inactive control electrodes) from the active tyrosinase-coated electrode signal (Figure 5). Because minimal computing power is required, this differential method is easily integrated into low-power wearable devices.

3.2.1. Technological novelty of reliability concept

Three fundamental novelties are introduced by this wearable design. First, a **self-characterizing signal architecture** is employed. Rather than using a fixed potential, the system is dynamically characterized before each monitoring phase to ensure the applied potential is optimally calibrated for the specific device and time. Second, inter-patient biological matrix effects are compensated for by **personalized calibration**. Third, **battery life** is extended and prolonged wear is supported by the CA data processing architecture that minimizes computational demand. Unlike empirical enzyme-layer designs (Fang et al., 2022), ours is computationally optimized (Section 3.2.2). The sensor's enzymatic layer was systematically optimized by a computational model (Section 3.2.2). A reduction - not oxidation-protocol further isolates the L-DOPA signal (Moon et al., 2021).

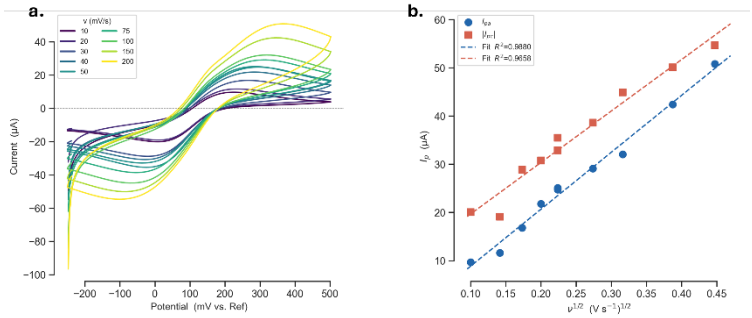


Figure 6. Chronoamperometric evaluation and calibration of Tyr Aqv functionalized MWCNT electrodes. All measurements were performed in PBS across a concentration range of 0.0 to 50 µM. (a) Calibration curves when increasing and decreasing concentrations. (b) Multi-day analysis and their corresponding calibration curves. (c) CA responses under static conditions. (d) Calibration curve under static conditions.

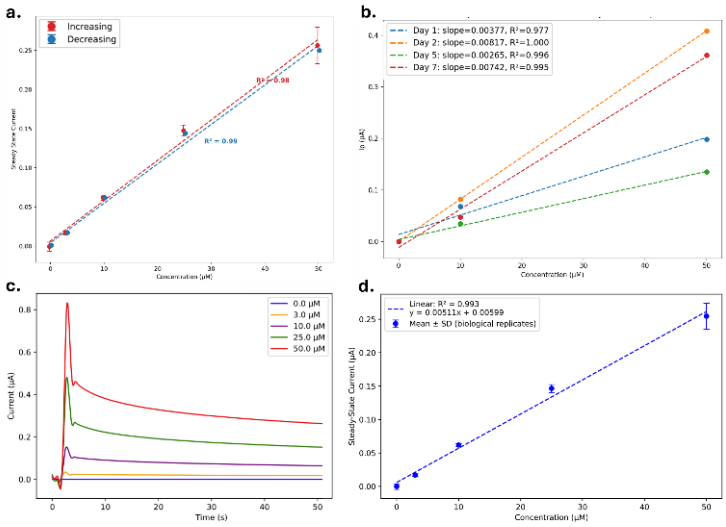


Figure 7. Electrochemical measurements and data processing. All measurements were performed in a PBS solution. (a) CV measurement of a 50 µM sample following Savitzky-Golay filtering. (b) The same CV measurement after ALS baseline correction. (c) CA measurements after baseline subtraction for sample concentrations of 0.0, 3.0, and 10 µM.

3.2.2. Technical feasibility of reliability concept

Stable Kinetics. GA and BSA stabilize tyrosinase biosensors (Barbosa et al., 2013; Bounegru & Apetrei, 2021; Raja et al., 2022), but dense cross-linking impedes diffusion (Raja et al., 2022) and activity (Barbosa et al., 2013; Bounegru & Apetrei, 2021). To optimize this balance (Cui & Jia, 2015), we simulated mass transport and enzyme kinetics using a 1D COMSOL model (see Section 8.1. Optimization of BSA:Glu:Tyr Ratio using Comsol Multiphysics) identifying an ideal tyrosinase:GA:BSA ratio of 1:0.5:2. As shown in Figure 7 a Randles-Ševčík analysis confirmed that this optimized coating maintains a freely diffusing, diffusion-controlled reaction, evidenced by the preserved linear relationship for both the anodic (I_{pa}) and absolute cathodic ($|I_{pc}|$) peak currents.

Parameter	Bare	Aqv Tyr	Aqv Tyr (FC)
Linear Range (µM)	0 – 50	0 – 50	0 – 25
Sensitivity (µA/µM)	0.00816	0.00511	0.00473
LOD (µM)	1.80	2.75	6.30

Table 1 Calibration parameters and limits of detection across electrode configurations.

Sensitivity and Linearity. Steady-state CA and calibration curves (Figure 7c-d) confirmed this: compared to bare electrodes, the fully coated MWCNT electrode improved linearity and reduced inter-replicate variance (Figure 7b) shows the expected trade-off: the Tyrosinase-Aquivion coating lowers sensitivity and raises LOD ($= 3.3(\sigma/S)$, S=Sensitivity, σ =the blank's standard deviation), but improves stability and linearity. In a continuous flow cell (FC), the reliable linear range narrow to 0–25 µM and LOD rises to 6.30 µM (baseline variance). Yet the response stays proportional and linear, supporting reliability under continuous fluid delivery.

Specificity. Sensor specificity is enhanced by the multilayer architecture, particularly through the selectively permeable Aquivion membrane and the catalytic activity of tyrosinase toward L-DOPA. "Tyrosinase provides stereoselectivity toward the L-enantiomer, exhibiting a lower Michaelis constant (Km) for L-DOPA than for D-DOPA. Optimized chronoamperometric parameters minimize signals from interfering electroactive matrix components, such as ascorbic acid.

Drift Analysis. Hysteresis analysis showed no significant difference between increasing and decreasing concentration gradients (a). A 7-day stability analysis showed no consistent degradation trend (Figure 7 b), so periodic recalibration should suffice. Because the device samples pseudo-continuously (discrete intervals with stabilization time between reads), oxygen dependency is theoretically eliminated.

3.3. Original contributions

Contributions from Team SensETH

We evaluated different matrices and detection routes for levodopa and focused on dermal ISF with enzymatic electrochemical detection. Because direct oxidation at a bare electrode requires anodic potentials at which ascorbate and urate co-oxidise, we selected a tyrosinase-based method read in a reducing window at −0.3 V.

For the sensor interface we combined literature methods: carbon-paste-packed hollow microneedles, BSA/glutaraldehyde co-crosslinking, ionomer coating (Aquivion), and polyurethane protection. In place of the conventional enzyme-free control, we used a heat-inactivated, protein-matched control electrode, removing drift, temperature, and residual background by real-time subtraction.

In parallel, a Subteam functionalised commercial screen-printed electrodes with custom L-DOPA-targeted NanoMIPs. These tracked concentration accurately from 3 to 50 µM in PBS and simulated ISF but saturated unpredictably under rapid reuse, so we consolidated on enzymatic sensing and retain NanoMIPs as a drop-in replacement or parallel channel for future iterations (Section 3.4).

We designed the microneedle patch, readout electronics, firmware, and mobile application in house. The modular design separates a single-use needle patch from a reusable readout module, with four working electrodes sharing one reference and counter electrode, reducing size and cost. The enzyme layer composition was set by our own COMSOL reaction–diffusion model. Concept selection, design, and testing were completed independently by the SensETH team. External contributions were limited to reference literature and advisor suggestions.

By the Team Supervisor

After interviewing over 25 students, I assembled the SensETH team from across multiple ETH departments. While I provided lab access, the students worked entirely on their own initiatives. Leveraging their multidisciplinary backgrounds, they took a step-by-step approach to master the core technical concepts required to develop a biosensor for continuous levodopa monitoring in ISF.

Their core novelty lies in bypassing the cross-reactivity of standard electrochemical measurements through a multi-layered interface: first, a tyrosinase-BSA matrix enzymatically oxidizes L-DOPA to dopaquinone, which is subsequently quantified via cathodic reduction at a negative potential;

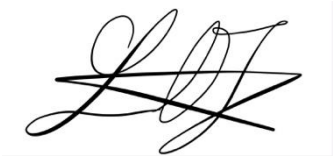
second, an integrated Aquivion ionomer membrane electrostatically repels anionic interferents like ascorbate; and finally, an ultrathin polyurethane barrier mitigates general biofouling.

The team also demonstrated competence by engineering the readout electronics and measurement workflow. They customized both the firmware and software architectures, proposed a smart approach to compensate for motion-induced artifacts using an integrated buffer system, and developed a corresponding software pipeline for signal processing and the user interface. The analytical competence was demonstrated by developing a multiparametric data analysis approach to systematically compare and evaluate biosensors across various conditions, as well as to obtain reproducible calibration curves.

I am impressed by their scientific and technical rigor, independence and efficient team work. I am confident they will be an exceptionally competitive team.







Prof. Morteza Aramesh	Syrin El Korany	Lucia Oestergaard Frank
SensETH supervisor	Team Captain	Team Captain

3.4. Bonus criteria Innovation

We investigated Nano Molecularly Imprinted Polymers (NanoMIPs) as a synthetic alternative to enzymatic detection. The NanoMIP Subteam functionalised the same commercial SPEs (Metrohm DropSens) with custom L-DOPA-targeted NanoMIPs, adapting the coating and synthesis methodology outlined by Zhou, Y., Li, J., Xu, Z. *et al., 2025. (Zhou et al., 2025)*. We evaluated these functionalised SPEs across the same range of target concentrations as with the enzymatic approach in both PBS and simulated ISF. As visualised in our test results (Figure 8), when operating nominally, the NanoMIP sensor demonstrated remarkable precision. In non-saturated states, the sensor readings converged tightly with true concentration values in physiological media. However, the primary technical bottleneck was an unpredictable tendency toward saturation, where readings plateaued at a value of 50 µM, regardless of actual sample concentration drops (e.g. Runs 1, 3, and 7). Because this saturation behaviour occurred sporadically during rapid sequential reuse, it introduced an element of unreliability that required further fundamental investigation. While the NanoMIP mechanism proved capable of high-accuracy target tracking, its unpredictable saturation profile made it less reliable for immediate deployment compared to our enzymatic baseline. Crucially, this research was designed to integrate seamlessly into our current main sensor, unlocking two clear deployment strategies for future iterations:

Once saturation kinetics and washing protocols are fully optimised, NanoMIPs can completely replace the enzymatic layer. This transition would eliminate reliance on delicate biological consumables, drastically increasing device shelf-life and thermal stability for long-term wear. Alternatively, NanoMIPs can be deployed alongside our enzymatic electrodes replacing one redundant pair of tyrosinase/deactivated tyrosinase for a NanoMIP/NIP pair. Operating both mechanisms in parallel leverages the immediate signal reliability of enzymes alongside the physical robustness of synthetic polymers, providing cross-validation of sensor outputs and enhanced fault tolerance.

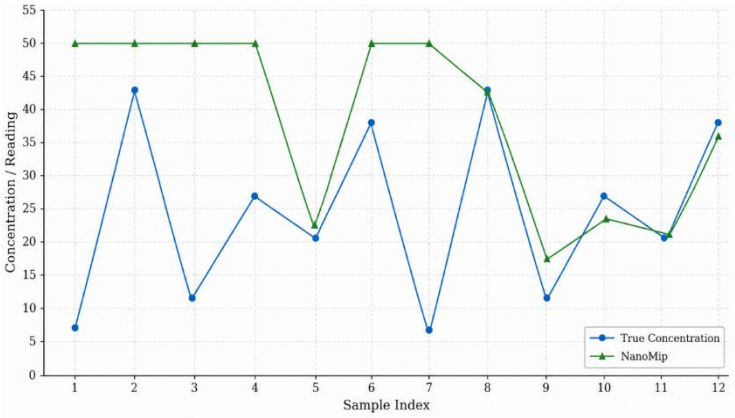


Figure 8 Comparison of NanoMIP readings and True Labels.

4. TP award: Translation potential

4.1. Customer interviews

To understand the scope of our task, SensETH put an early focus on receiving insight into treatment, diagnosis and daily life with Parkinson Disease (PD) through interviews with patients and neurologists. With their input, we identified potential applications and target groups of a wearable biosensor continuously measuring L-DOPA. Further interviews with movement disorder specialists and industry experts guided the development of a translatable, clinically meaningful product.

To ensure efficient and conclusive interviews, questions were prepared according to the expertise of each stakeholder, scheduling enough time for discussion. All interviews began with an introduction of our team and the task, and, with permission, were voice recorded for processing. Summaries and transcripts can be found in Section 8.4.

4.1.1. Identifying stakeholders, needs and developing product candidates

Our first interview was with a 75-year-old retired physician diagnosed with PD in 2022. Upon telling us about his treatment schedule and the associated daily rhythm of fluctuating symptoms and impairment, he reported feeling like his dosing regimen was not optimally adjusted and emphasized the burden of medication management and monitoring. His attempts to maintain diaries about symptoms and medication, required by physicians to guide therapy adjustments, failed. The dilemma of symptoms peaking when medication is due, making self-dosing a difficult challenge, inspired the idea of a closed-loop system integrating drug monitoring and direct delivery. A control algorithm based on measured L-DOPA concentration data and the personal therapeutic target defined by physicians would allow the autonomous administration of L-DOPA via a small pump. Pump therapies can be used to ensure that a drug therapy has a continuous effect in the brain (Burton et al., 2026). This is a major advantage over pills, which are taken every few hours and produce correspondingly unstable active levels in the brain.

While the shortcomings of PD therapy mentioned by patients were recapitulated by neurologists, the ideas on how to improve them differed. According to a clinician at Istituto di Neuroscienze Cliniche della Svizzera Italiana, motor fluctuations and dyskinesia commonly emerge as the therapeutic window narrows and dosing regimens become more complicated. In his opinion, a sensor assisting medication decisions of physicians would require the combination of L-DOPA concentration data with reliable motor symptom monitoring. An accelerometer unit, worn on the wrist of the affected limb, can capture motion data on tremor frequency and amplitude, bradykinesia and dyskinesia (Sander et al., 2025). The addition of an IMU to the wearable sensor design follows this insight too. Combining this with electrochemical L-DOPA sensing would allow the continuous sampling of symptom severity and timing relative to dosing, supporting medication adjustment decisions by physicians.

4.1.2. Validation of clinical relevance and translatability

To assess the clinical interest in the two explored technologies, we presented the two approaches to a board of three neurologists working in the Parkinson's outpatient clinic of the Neurology Department at the University Hospital of Zurich. They saw the benefit of having a sensor monitoring motor symptoms, they pointed an overlapping presentation of dyskinesia and tremors, and a frequent inability to precisely distinguish between the two. Precise data on motor symptoms could assist in developing the dosing strategy and would circumvent the frequent misunderstanding of the patient regarding their symptoms: *"Patients often have an impaired perception of the on and off state. […] Their personal judgement is not always correct."* Another doctor added: *"I see the medical need in having a sensor to identify the misconception of dyskinesia, this could be very helpful for patients that confuse dyskinesia and tremor."* However, when it comes to the endpoint product, the clinicians agreed that they would see a greater benefit for the patient through facilitating and automatizing drug intake by newly emerging continuous delivery systems based on objective data. Such a design could prevent the onset of strong symptoms; by keeping drug concentrations within the desired range, the patient can be helped directly, both by automating L-DOPA intake and by preventing strong fluctuations.

To validate the clinical viewpoint and investigate its feasibility, we spoke with a neuroscientist working in research and development at Neurimmune AG, who agreed that a closed-loop system could overcome the challenge of pharmacokinetic variability in PD treatment. However, we were warned of the regulatory pathway such a device would face. Because the system combines a diagnostic sensing component with an active drug-delivery function, it would likely be classified as a combination product, subject to review by both device- and drug-focused regulatory bodies, requiring evidence not only of sensor accuracy but of the safety and efficacy of automated dosing decisions.

Taken together, the various insights highlight that designing a meaningful end stage product to assist the therapeutic management of PD requires a pipeline of validation steps. The foundation of an innovative product is the L-DOPA biosensor, designed to assist the patient in treatment scheduling and delivering parameters required by their physicians. Once sufficiently validated, development can move towards integrating a drug pump, tailored to each patient's pharmacokinetics, progression status and needs, allowing automatization of L-DOPA intake within the desired range. An assistive unit, measuring motor symptoms and fluctuations, can be employed to test safety and efficacy of the product during development and validation stages.

4.2. Design of validation study

As identified through our interviews, current PD treatment decisions are strongly based on subjective patient recall and infrequent clinic visits. Disease progression increasingly complicates maintaining symptom-tracking diaries, medication and the reliable differentiation between motor symptoms. Building on this gap, we aim to design a wearable sensor measuring levodopa concentrations, as the

first step towards a closed-loop system, ensuring continuous, in-range drug levels in the brain, preventing strong symptom fluctuations. The sensor validation study is structured around accuracy and clinical utility, and should, as a first step, provide insights on the pharmacokinetics and bioavailability of levodopa via real-time transmission to both the patient and doctors, for which an interface was designed. The dose-response results generated throughout this phase should lay the foundation on which a drug delivery control algorithm will be built, assisted by the use of accelerometers providing an independent, quantitative readout of motor symptoms, testing whether algorithm-driven dosing decisions translate into measurable clinical improvement and flagging safety concerns. Together, this staged, quantitative approach validates not only the sensor itself, but its integration into a future automated therapy system.

4.2.1. Conceptual design and use case

To lay the basis for the transition toward the closed-loop delivery system envisioned as the pipeline's end goal, we designed the first validation study to gather pharmacokinetic and dosing-response data to serve as the training foundation for a control algorithm. Sensor readings, transmitted via Bluetooth to a paired smartphone, can be relayed to a secure cloud backend. Querying from this, we developed a system that pairs the wearable L-DOPA biosensor with a dual-facing interface (Figures 9-10), based on the parameters deducted from patient and clinician interviews. The patient app shows real-time L-DOPA levels against a physician-set target range, dosing schedule and adherence, and a symptom check-in automatically timestamped to sensor readings, replacing the failed written diaries reported in our interviews. The physician dashboard gives an overview of the patients in the cohort, highlighting those needing attention, plus a detailed live view of individual pharmacokinetic traces and suggested regimen adjustments. Together, these interfaces convert the raw sensor signal into clinically relevant parameters, addressing the lack of objective, shared data identified across our interviews. The selection and presentation of these parameters, relevant to both clinicians and patients, were refined through iterative user testing, guided by two core questions: what information would be useful for you, and how would you like to see it?

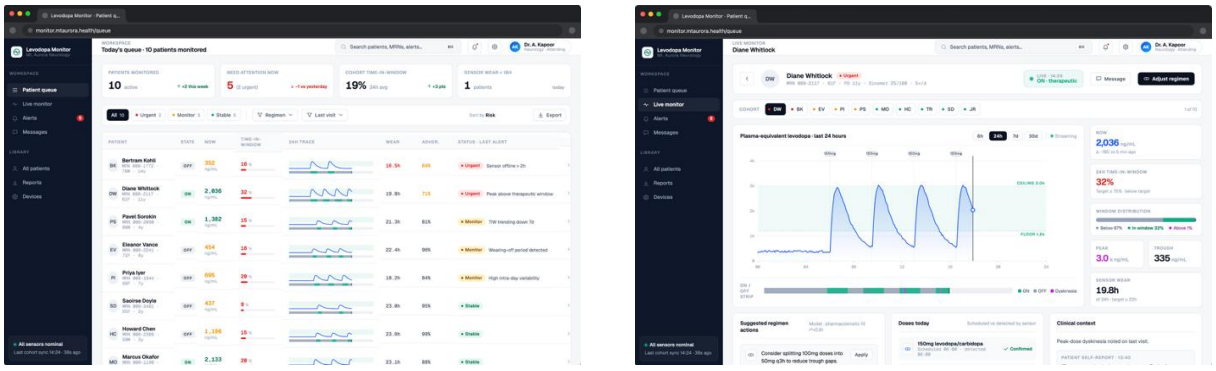


Figure 9 Screenshots of the doctor interface. Full interactive interface: https://levodopa-sensor.vercel.app

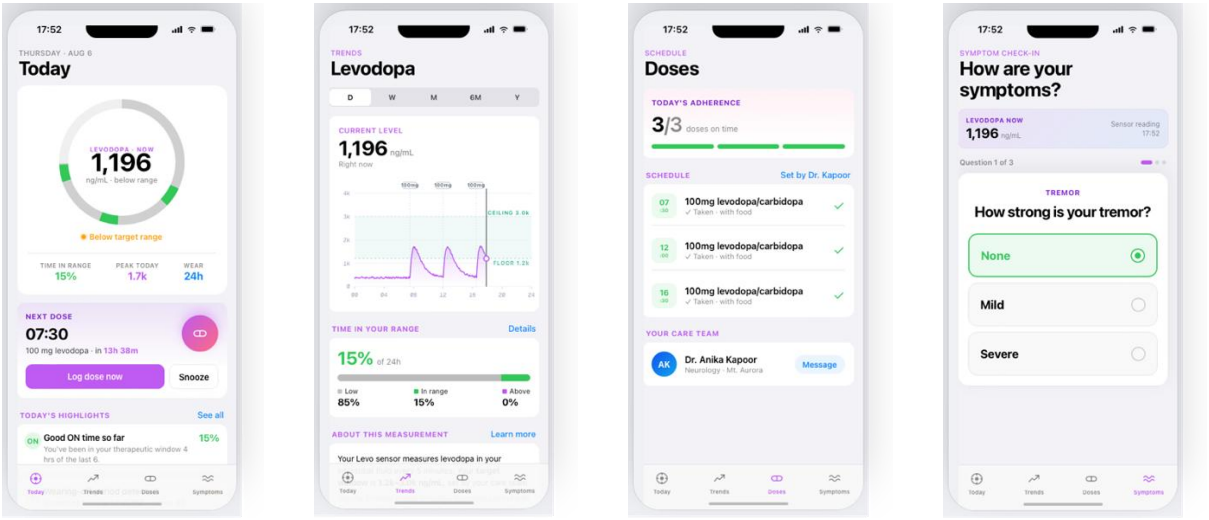


Figure 10 Screenshots of the patient interface. Displaying key features of the app. Full interactive interface: https://levodopa-sensor.vercel.app

4.2.2. Validation study design and outlook

On one hand, the validation study of this system should evaluate sensor accuracy, clinical utility and usability. To advance to the next stage, sensor measurements need to match the gold-standard plasma High-Performance Liquid Chromatography measurements in PD patients on stable L-DOPA regimens. To assess this, blood samples are drawn at fixed intervals following a standard dose and compared to concurrent ISF sensor readings, quantified using Pearson correlation coefficient and mean absolute percentage error (MAPE), with pre-defined thresholds (e.g., $r > 0.85$, MAPE < 15%). Clinical utility and usability can be assessed by comparing dosing adjustment decisions and confidence, as well as treatment adherence, patient-reported symptoms and clinician motor scores with versus without sensor use. This should be accompanied by regular questionnaires, allowing updates to match needs.

On the other hand, the study should establish the foundation for closed-loop development. Pharmacokinetic and dosing-response data will initially be collected from patients with established motor fluctuations (typically 5+ years on L-DOPA), the population identified in our interviews as facing the greatest dosing complexity and the most to gain from automation. On this cohort data, a model predictive control algorithm can be used to map sensor readings to required dose adjustments. This algorithm should first be validated in silico against historical patient data, then tested in a bench setup pairing the sensor with a subcutaneous infusion pump of confirmed accuracy and reliability, such as AbbVie's VYALEV subcutaneous delivery system for foscarbidopa and foslevodopa, approved in 2024. (Olanow et al., 2021, Monje et al., 2026). Once concordance and safety thresholds are met, real-time delivery can be tested, initially under clinical supervision with manual override capability.
Throughout the validation stages, devices such as smart watches and accelerometers (Moreau et al., 2023) can be employed to track both motor and non-motor symptoms, providing independent efficacy and safety readouts by testing whether automated dosing decisions correspond to measurable symptom improvement.

5. Team and support

5.1. Contributions of the team members

- **Wetlab SubTeam:**

Awad Erik: Built and validated NanoMIP Sensor, sponsor acquisition and pitching.
El Korany Syrin: Team Co-Captain, Wrote WetLab protocols, Built and validated enzymatic sensor and Organized Meetings and the professional event
Grimm Johanna: Sponsorship acquisition, built and validated enzymatic sensor, Partner session, stakeholder and expert interviews
Jankauskas Arnas: Built and validated NanoMIP sensor
Oestergaard Frank Lucia: Team Co-Captain, contributing to team coordination, planning and performing wet-lab for sensor design optimization, external expert consultation, sponsor acquisition"
Roberts Lillie: Wet lab to build and validate the NanoMip sensor, sponsor acquisition, social media, outreach activities, Team T-shirts, and One-minute pitch.
Palm Sabine: Built and validated NanoMIP sensor, Partner Session
Ulmer Anouk: Built and validated enzymatic sensor. Optimization and validation of the lab protocol. Website design.
Wisniowska Magdalena: Built and validated enzymatic sensor, Optimized the protocol, Designed the logo
Zuliani Sabina: Built and validated NanoMIP sensor, Organized the professional Event

- **Hardware and Software SubTeam:**

Lopez Nerea: Co-developed data processing pipeline, Comsol Model, Contribution to Hardware Developement, Innovation Award (Reliability), Organized Meetings, Partner Meeting
Pukall Quentin: Contributed to sensor hardware development and the core concept, and secured project sponsorship, Innovation Award.
Torrico Espiga Álvaro: Contributed to hardware development and CAD models, coordinated Entrepreneurship Sessions, assisted with Partner Sessions and meetings with clinicians, Innovation Award (Wearable Sensor)
Tschuemperlin Pascal: Continued Development on Potentiostat Firmware and User Software, Co-developed data processing pipeline
Pang Shuqi: Designed the App for L-DOPA monitoring and Supported the NanoMIP Team

5.2. People who have given support

Laboratory of Single-Molecule and Single-Cell Biophysics (BMC) and Laboratory of Biosensors and Bioelectronics (LBB): Lab access.

Prof. Dr. Morteza Aramesh: Program responsible (lab access, university admin)

Petrella Lorenzo: Responsible of the Lab
Cronk Justin: DTE SPO
Hengsteler Julian: Technical Advice
Stuber Annina: WetLab Support
Ustinov Oleksii: Technical Advice
Viol Amelie: DTE DO
Methrohm: Electrode supplier, technical advice
Xuesong Ye & Bo Liang: Collaboration and technical support for the Nano-MIP-based sensing approach (Biosensor National Special Laboratory, Key Laboratory of Biomedical Engineering of Ministry of Education, College of Biomedical Engineering and Instrument Science, Zhejiang University, and Binjiang Institute of Zhejiang University, Hangzhou, PR China))

Technical advice from experts across multiple disciplines.
Dr. David Probst: Technical support in enzymatic L-Dopa biosensing
(Joint Department of Biomedical Engineering, The University of North Carolina at Chapel Hill and North Carolina State University, Chapel Hill, NC, USA)

5.3. Sponsors and partners

Innovative Sensor Technology AG : Financial Support

Sensirion: Financial support and Technical advice

COMSOL: Financial support and Training

ETH Foundation Sponsorship: This project is supported by Mr and Mrs Steffen and Marina Meister via the ETH Zurich Foundation.

Private Sponsors: Financial Support

6. Final remarks

Changes in the biosensor architecture and performance are expected with regard to the ongoing process of sensor development. Deviations from the described design will be properly communicated to the jury. In order to exploit the maximal potential of the SensETH sensor, further research and development needs to be conducted addressing conformity with the EU-MDR and FDA requirements. To advance the biosensor toward in vivo applications, our next objectives are sensor miniaturization the evaluation of its biocompatibility followed by subsequent preclinical studies evaluating performance, safety and reliability. Finally, we would like to acknowledge the invaluable support we received throughout this project, including financial contributions, expert advice, and methodological guidance (Sections 5.2 and 5.3).

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8. Appendix

8.1. Optimization of BSA:Glu:Tyr Ratio using Comsol Multiphysics

To optimize the operational performance of the L-DOPA tyrosinase biosensor, a one-dimensional continuum model was developed in COMSOL Multiphysics. While GA improves matrix stability, it can denature tyrosinase and create diffusion barriers; adding BSA minimizes this denaturation. The model resolves these multi-variable trade-offs by coupling steady-state and transient mass transport, Michaelis-Menten enzymatic kinetics, and Butler-Volmer electrode kinetics across both the enzyme-loaded gel film and the bulk electrolyte (Figure 9).

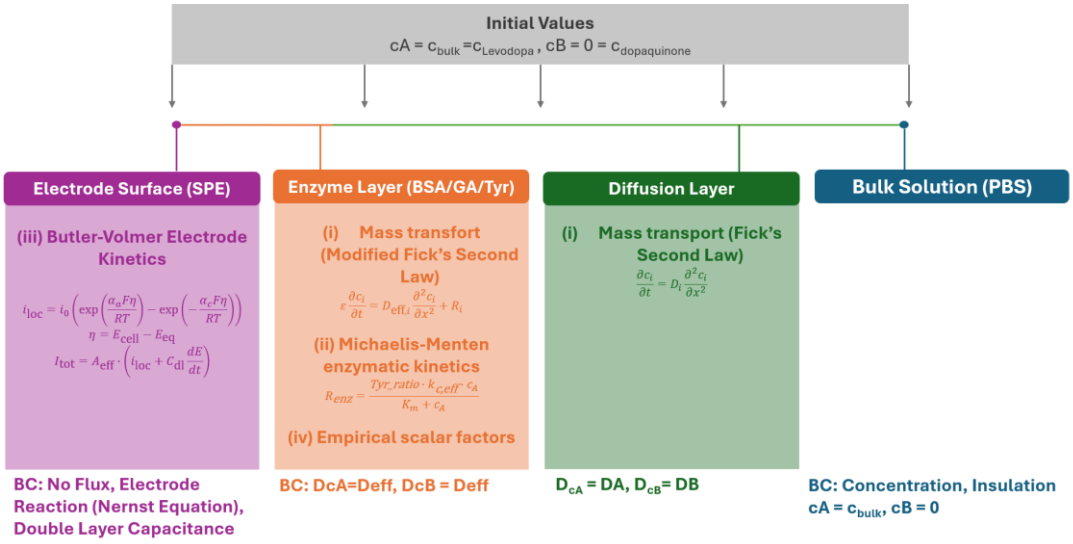


Figure 9. 1D CV Biosensor Geometry and Physics.

A 5x5 parametric sweep was executed to map the resulting cyclic voltammetry peak currents across 25 distinct BSA and GA ratio combinations. As shown in Figure 10. **Comparison of experimental and simulated cyclic voltammograms for L-Dopa oxidation.** Solid lines represent the experimental baseline measurements recorded at a bare electrode in the presence of 0, 3, 25, and 50 µM L-Dopa at a scan rate of 50 V/s. Dashed lines indicate the corresponding simulation results generated in COMSOL Multiphysics.

, prior to introducing the enzymatic functionality, the baseline simulation results correlated strongly with experimental measurements of the bare electrode, verifying the transport and electrode kinetics.

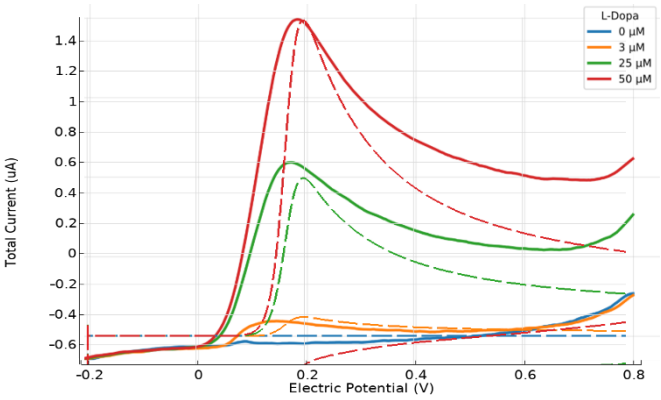


Figure *10*. Comparison of experimental and simulated cyclic voltammograms for L-Dopa oxidation. Solid lines represent the experimental baseline measurements recorded at a bare electrode in the presence of 0, 3, 25, and 50 µM L-Dopa at a scan rate of 50 V/s. Dashed lines indicate the corresponding simulation results generated in COMSOL Multiphysics.

Results and Discussion

The parametric optimization sweep provided a systematic evaluation of how varying structural compositions impact the overall electrochemical signal. The resulting heat map (Table 2) identified the maximum anodic peak current by balancing the stabilizing structural effects of the GA/BSA scaffold against the mass transport penalties introduced by dense cross-linking. Based on this simulation, we chose an ideal tyrosinase:GA:BSA ratio of 1:0.5:2.

	BSA_Ratio						
Glu_Ratio	0.05	0.1	0.35	0.5	1	1.5	2
0.05							-2.86E-05
0.1	-1.19E-04	-1.15E-04	-1.37E-04	-1.47E-04	-1.55E-04	-1.49E-04	-1.46E-04
0.35	-1.17E-04	-1.24E-04	-1.53E-04	-1.52E-04	-1.76E-04	-1.94E-04	-2.19E-04
0.5	-1.15E-04	-1.37E-04	-1.47E-04	-1.62E-04	-1.91E-04	-2.07E-04	-2.31E-04
1	-1.35E-04	-1.43E-04	-1.62E-04	-1.70E-04	-2.04E-04	-2.10E-04	-2.23E-04
1.5	-1.39E-04	-1.47E-04	-1.65E-04	-1.74E-04	-1.95E-04	-1.99E-04	-2.09E-04
2	-1.42E-04	-1.48E-04	-1.64E-04	-1.73E-04	-1.82E-04	-1.87E-04	-1.93E-04

Table 2. Final Glu:BSA combinations. Resulting an optimal combination of BSA of 2 and Glu of 0.5.

8.2. Further Experimental Data

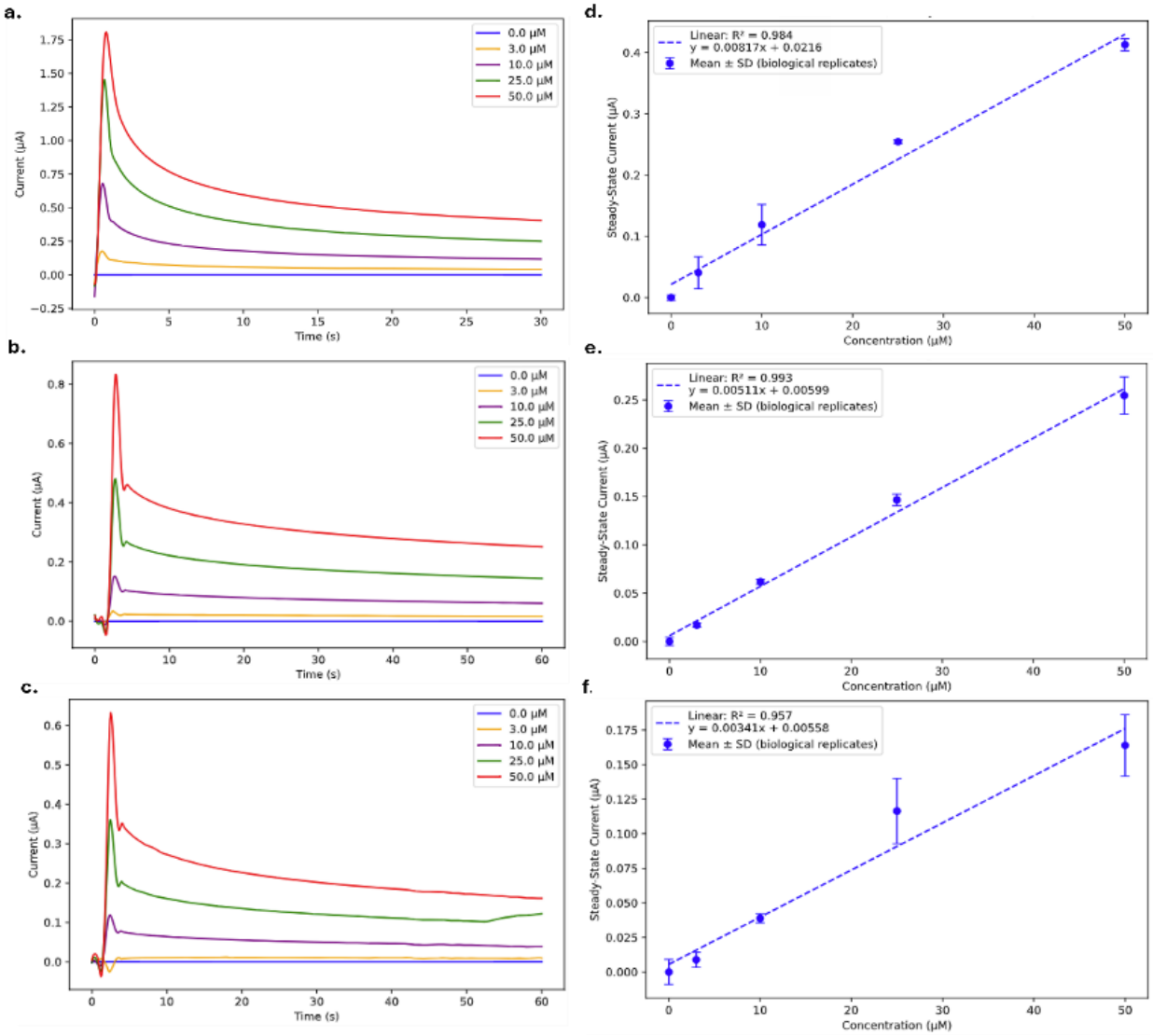


Figure 11. Chronoamperometric evaluation and calibration of bare and Tyr Aqv functionalized MWCNT electrodes. All measurements were performed in PBS across a concentration range of 0.0 to 50 µM. (a) Chronoamperometric responses of the bare MWCNT electrode recorded at varying analyte concentrations. (b) Chronoamperometric responses of the fully modified MWCNT electrode (Tyr Aqv coating) at corresponding concentrations under static conditions. (c) Chronoamperometric responses of the fully modified MWCNT electrode (Tyr Aqv coating) measured in a flow cell setup. (d) Calibration curve for the bare MWCNT electrode, demonstrating a strong linear correlation between the steady-state current and analyte concentration. Error bars represent the mean ± SD of biological replicates. (e) Calibration curve for the fully coated MWCNT electrode under static conditions. (f) Calibration curve for the fully coated MWCNT electrode under flow cell conditions.

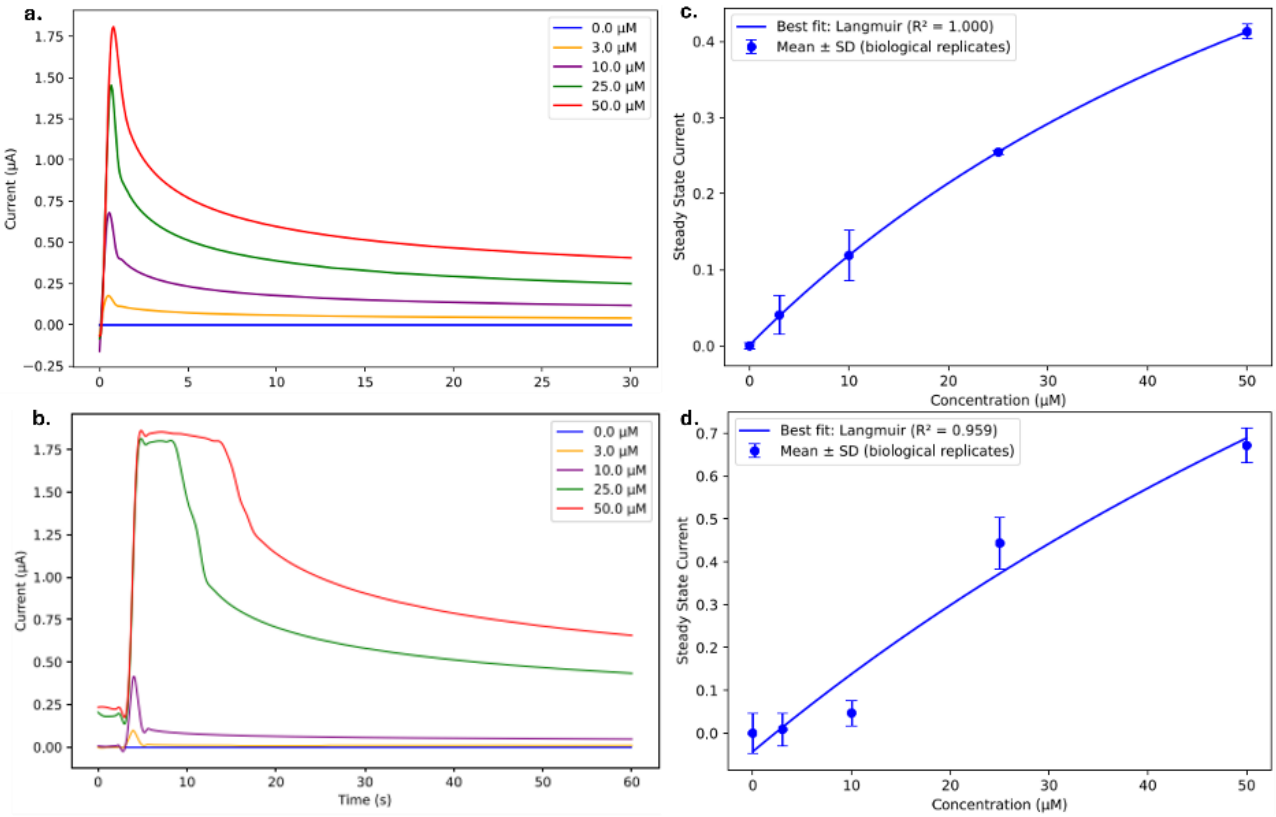


Figure 14. Electrochemical response and calibration of MWCNT electrodes to varying analyte concentrations (0 to 50 µM). (a) Mean blank-subtracted current transients for a bare MWCNT electrode measured in PBS. (b) Mean blank-subtracted current transients for a fully coated MWCNT electrode (Tyr Aqv) measured ISF using a flow cell setup. (c) Calibration curve for the bare MWCNT in PBS, derived from steady-state currents and fitted to a Langmuir isotherm (R^2 = 1.000). (d) Calibration curve for the fully coated MWCNT in ISF, derived from steady-state currents and fitted to a Langmuir isotherm (R^2 = 0.959). Error bars represent the mean ± standard deviation across biological replicates.

8.3. Component description

The flexible printed circuit carrying the six electrode traces (WE1–4, RE, CE) and the SPI communication bus to the AFE is bonded to the microneedle backing substrate using anisotropic conductive film (ACF), a resin adhesive loaded with conductive microparticles that establishes electrical continuity in the vertical (through-thickness) direction only, while remaining electrically insulating in the lateral direction This property is required to prevent shorting between fine-pitch adjacent contact pads. Bonding is achieved by thermo-compression at approximately 180°C and 4 kgf/cm² for approximately 20 seconds and has been validated for biomedical use (Baek et al., 2011).

Electrode current is transduced and digitized by the MAX30134 (Analog Devices), a four-channel electrochemical AFE with an additional switchable electrochemical impedance spectroscopy (EIS) channel. The four working-electrode channels are sampled simultaneously rather than multiplexed: the device provides four independent 12-bit DACs and four independent 16-bit current ADCs, one dedicated signal path per working electrode, rather than a single potentiostat time-shared across electrodes as in multiplexed designs. The EIS channel supports assessment of electrode-skin contact quality and detection of electrode fouling (Goh et al., 2021, Lee et al., 2026), functioning as a built-in diagnostic check on electrode condition rather than a second measurement of the target analyte. The device also includes an onboard 16-bit temperature sensor, relevant given that enzymatic reaction rates are temperature-dependent and its rated operating temperature range is 0–70°C, adequate for on-body operation. Power draw is under 5 µA in typical operating configurations, and the device is supplied in a 25-bump wafer-level package (WLP) measuring 2.93 × 2.93 mm, smaller than the comparable alternatives [AD5940 (56-lead WLCSP, 3.6 × 4.2 mm) and ADuCM355 (72-lead LGA, 6 × 5 mm)]. An onboard 256-word FIFO buffer enables autonomous, low-power sampling without continuous microcontroller intervention, which further decreases power consumption. Sensor-facing pins carry a ±15 kV air-discharge and ±8 kV contact-discharge ESD rating, a relevant specification given that these pins interface directly with skin-contacting electrodes. The device is marketed explicitly for continuous glucose monitoring, sweat sensing, and wearable biosensor applications and communicates with the host microcontroller over a four-wire SPI interface.

Firmware execution and wireless data transmission are handled by the nRF52832 (Nordic Semiconductor), built around an Arm Cortex-M4F core (64 MHz) with 512 kB flash and 64 kB RAM, available in a 3.0×3.2 mm WLCSP package for production. It supports both Bluetooth Low Energy (BLE) and an on-chip NFC-A tag interface. NFC operates over a range of approximately 1.5 inches at data rates of 106–424 kbps, and on this device is used exclusively for out-of-band pairing: bringing a smartphone into proximity to authenticate and establish a Bluetooth connection without manual device selection. Continuous data streaming is handled by BLE, which supports data rates up to 2 Mbps at substantially longer range and is purpose-designed for intermittent, low-duty-cycle transmission from battery-powered devices. This component has direct precedent in a comparable regulated wearable: it provides wireless connectivity for ActiGraph's CentrePoint Insight Watch, a medical-grade wearable

used in clinical and academic research settings. A 32.768 kHz crystal oscillator provides the timing reference required for BLE connection-interval scheduling and for the microcontroller's low-power sleep-mode timer.

The device is powered by a 3.7 V nominal single-cell lithium-polymer pouch battery. This was chosen over a non-rechargeable coin-cell because their rigid, non-conformal geometry is a poorer fit for a flexible skin-adhered patch than a thin, custom-shaped pouch cell. A single-cell lithium-polymer battery's terminal voltage varies from approximately 4.2 V at full charge to approximately 3.0 V near depletion. Because the AFE, MCU, and accelerometer each require a stable input voltage within specified tolerances, a dedicated power management integrated circuit (PMIC) is required to regulate the variable battery voltage to fixed output rails. The BQ25120A (Texas Instruments) was selected for this function; it is a comparably integrated wearable-focused PMIC, combining a linear charger, configurable LDO, load switch, and buck converter in a smaller 2.5×2.5mm WCSP package, and is advertised with an ultra-low quiescent current of 700nA.

Mechanical movement of the wearer alters the contact pressure between microneedles and skin, which can produce a change in the measured electrochemical signal indistinguishable, without additional information, from a genuine change in levodopa concentration. An ADXL362 (Analog Devices) accelerometer is incorporated to enable software compensation for motion-induced measurement artifact. It draws less than 2 µA at a 100 Hz output data rate (as low as 270 nA in motion-triggered wake mode), operates from a 1.6–3.5 V supply, communicates via SPI. The accelerometer also provides a FIFO buffer capable of retaining over 13 seconds of acceleration data recorded prior to a detected motion event, which is valuable for retrospectively flagging electrochemical readings taken immediately before an artifact-triggering movement. This approach of correlating accelerometer output with a physiological or electrochemical signal to identify and correct motion-corrupted readings is precedented in a wearable ECG monitoring system employing the same accelerometer for the same purpose (Ai et al., 2019). Furthermore, this same technology could be potentially used in the future for automatic motor symptom detection.

8.4. Stakeholder interviews: Transcripts and summaries

8.4.1 Patient Interview

J. P. is a 75-year-old man and retired medical doctor who was diagnosed with Parkinson's disease in 2022. Before the progression of the disease, he was very active and regularly played tennis, but he is now no longer able to work as a doctor or continue playing tennis as he used to. His main symptoms include frequent falls, balance impairment, and difficulties with sitting down and standing up. He also experiences marked motor fluctuations during the day, with mornings being significantly better than afternoons.

When were you diagnosed with Parkinson's disease? What were the main difficulties you experienced after the diagnosis?

The patient was diagnosed with Parkinson's disease in 2022, although initial symptoms had appeared earlier. Early signs included nausea and a loss of sense of smell, followed by a gradual slowing of movement and increasing rigidity. However, the condition was only seriously considered when more severe symptoms developed, particularly sudden falls and balance disturbances. These issues, together with difficulties in standing up and sitting down, became some of the most significant challenges following diagnosis.

How did the disease develop over time? What were your first symptoms? Are you currently taking levodopa? If so, for how long have you been taking it?

Over time, the disease has progressed, and the patient now experiences clear motor fluctuations throughout the day. He is currently treated with levodopa, which he has been taking for approximately two and a half years. According to his experience, the effect of the medication is highly time dependent. After taking a dose, he typically begins to feel an improvement after about one hour, while the effect tends to wear off after approximately four to five hours. He reported that mornings are generally the best period of the day, with good motor function shortly after taking the medication. In contrast, the afternoon represents the most difficult period, particularly between 2 p.m. and 6 p.m., during which he feels significantly worse, slower, and more impaired. In this context, he also explained that his neurologist is currently trying to reduce the levodopa dosage in order to preserve its effectiveness over time.

Based on your experience, how important is it to receive the right dose at the right time?

He emphasized that the correct timing of medication is highly individual. In his case, the timing is particularly important in relation to daily activities such as working or playing tennis. He reported that he is now only able to work effectively in the early morning, roughly between 7 a.m. and 10 a.m., and that both his professional activity and his ability to play tennis are strongly limited by symptom

fluctuations. Activities that were previously central to his life are now difficult or no longer possible due to the disease.

Do you keep track of your symptoms or the timing of your medication intake?

Regarding the management of his condition, the patient reported that he had initially tried to keep a symptom and medication diary for a few days but did not continue, although he expressed the intention to restart. He stated that it is not particularly difficult for him to describe his condition to his neurologist, but he sometimes feels that the physician already has a predefined understanding of his situation, which may reduce his motivation to ask further questions. He also mentioned that standardized assessments are performed during consultations and that his condition is generally considered stable, with only minor worsening over time.

Do you think a wearable biosensor that continuously monitors drug levels could be useful to better understand how the medication works during the day? Would you be willing to wear such a device? What characteristics should it have, and do you have any concerns about it?

When discussing the potential use of a wearable biosensor, the patient expressed a positive attitude. He believes that there is a clear link between his well-being and the level or timing of levodopa in his body, and therefore sees potential value in a system that could monitor this continuously. He stated that he would be willing to wear such a device, especially if it were simple and easy to use, similar to modern glucose monitoring systems. Ideally, he would prefer not only monitoring but also a system capable of delivering the correct dose automatically in anticipation of symptom worsening. He did not express significant concerns regarding such a device.

Finally, the patient also noted that, from his perspective, there have been no major revolutionary developments in Parkinson's treatment beyond levodopa since its introduction decades ago. He suggested that more research and investment should be directed toward developing new therapeutic approaches, although he acknowledged that this may be limited by funding constraints.

8.4.2 Interview with neurologist

Dr. Claudio Städler is a neurologist based in Ticino, Switzerland, currently working at the Istituto di Neuroscienze Cliniche della Svizzera Italiana (EOC), with clinical activity at Ospedale Regionale di Lugano, Civico, and Ospedale Regionale di Mendrisio, Beata Vergine. He is specialised in vascular neurology and movement disorders, with a particular focus on Parkinson's disease and advanced therapeutic approaches such as deep brain stimulation (DBS). From 2012 to 2023, he served as Head of the Neurology Service at EOC Lugano and was also responsible for the EOC Stroke Center in Lugano. He currently follows a large number of Parkinson's patients, ranging from newly diagnosed individuals

to advanced and complex cases, and is highly experienced in the long-term management of motor fluctuations and treatment-related complications.

Questions:
1. What is your clinical specialization, and how long have you been working with patients affected by Parkinson's disease?
2. Approximately how many Parkinson's disease patients do you currently follow, and at which stages of the disease are most of them?
3. How is Parkinson's disease currently diagnosed in clinical practice?
4. In your experience, what are the main challenges in managing Parkinson's disease patients treated with levodopa?
5. How is levodopa therapy currently adjusted in your patients, and how do you decide which dose to prescribe to each individual?
6. What kind of information do you mainly rely on when deciding to modify the therapy?
7. How frequently are patients re-evaluated for treatment adjustments, and in your opinion, is this frequency sufficient?
8. Do you see a potential clinical benefit in having a wearable device able to continuously monitor levodopa levels in Parkinson's disease patients?
9. In which patients or clinical situations would such a device be most useful, and which characteristics should it have to be clinically relevant?
Interview with attending physicians of Parkinson's outpatient clinic of the University Hospital Zurich, Department of Neurology.

The interview focused on the current diagnosis and clinical management of Parkinson's disease, with particular attention to levodopa therapy and the potential value of continuous monitoring. Parkinson's disease is still diagnosed primarily on a clinical basis, through neurological examination and the patient's response to levodopa. A clear response to levodopa is considered an important diagnostic criterion for idiopathic Parkinson's disease, whereas a lack of response may suggest another degenerative parkinsonian syndrome. In addition to the clinical examination, complementary tests can be used in selected cases. These include dopaminergic imaging, such as DaT-SPECT, which assesses the dopaminergic system and is abnormal in degenerative parkinsonian disorders, as well as myocardial MIBG scintigraphy, which evaluates cardiac sympathetic innervation and can help differentiate Parkinson's disease from other syndromes. In the past, PET imaging was also used in some cases. Despite these tools, it was pointed out that even in specialized centers, clinical diagnosis alone may still have an error rate of around 20–30%.
A major difficulty in treatment appears in more advanced stages of the disease. After about 5–6 years of levodopa treatment, many patients develop motor complications, including unpredictable "on/off" fluctuations and dyskinesias. These complications become more relevant as the dopaminergic system

progressively degenerates and the therapeutic window narrows. The effects of levodopa can become erratic and difficult to predict: patients may suddenly become blocked while outside or develop troublesome dyskinesias, and these effects can vary substantially both between patients and within the same patient from day to day. The younger the patient is at disease onset, the more aggressive and fast the progression may be, making long- term management even more challenging. Treatment adjustments are currently based almost entirely on clinical information. There is no absolute objective criterion used in daily practice to determine the correct levodopa dose. Instead, physicians rely on patient-reported symptoms, clinical observation, caregiver input, and especially detailed motor diaries. Patients may be asked to record when they take their medication and whether they are in an "on" state, an "off" state, or experiencing dyskinesias. Standardized tools such as the MDS-UPDRS can also be used, but they only provide a relatively rough quantification of symptoms. As a result, treatment remains highly individualized and often requires long consultations and close collaboration between physician and patient. In some cases, patients who are cognitively intact learn to recognize their own fluctuations and partially adapt the timing of therapy themselves.
Follow-up frequency depends on the stage of the disease and on whether therapy is being changed. In earlier and more stable stages, patients may be seen every six months, while others are reviewed every three months. When major therapeutic changes are introduced, reassessment may happen after four to six weeks, and in some cases patients are hospitalized so that the response to levodopa can be observed daily in a more controlled manner. Regularity in dosing is essential, and treatment often needs to be fractionated very carefully, sometimes as often as every hour and a half, depending on the patient's condition. In many cases, treatment is highly dynamic: patients may need different doses, different drug combinations, and even different types of medication within the same day, depending on their symptoms and fluctuations. The regimen often also differs between daytime and nighttime, making therapy highly individualized and complex to manage.
The discussion also addressed advanced therapies used when oral treatment is no longer sufficient. These include intestinal levodopa infusion pumps, subcutaneous apomorphine pumps, and deep brain stimulation and newer continuous subcutaneous levodopa delivery systems. The overall therapeutic goal is to keep levodopa levels as stable as possible in the blood, because more stable systemic levels lead to more stable delivery to the brain and therefore more stable symptom control. Regarding the proposed wearable sensor, it was considered potentially useful if it can provide a reliable correlation with clinical effects and, ideally, help anticipate changes before symptoms become obvious. Its clinical value would likely be greatest in advanced patients, since early in the disease levodopa usually works so well that patients may almost forget they have Parkinson's disease. On average, more problematic fluctuations and dyskinesias begin to appear after about five years. A monitoring tool could therefore become particularly relevant in this later phase, especially if it could eventually be linked to a drug delivery system as part of a future closed-loop therapeutic approach.

8.4.3 Interview with board of neurologists

Dr. med. Sujitha Mahendran

PD Dr. med. Fabian Büchele
Dr. med. Evdokia Efthymiou

[Introduction on:
What is the SensUs competition?
Who is SensETH?
The task: a wearable levodopa sensor for continuous monitoring
Our ways of solving the problem: Translational potential]

What is the standard treatment for Parkinson's Patients?
PD Dr. med. Fabian Büchele:
levodopa is a symptomatic treatment and usually the first line of treatment. As the disease progresses and fluctuations occur, the dose is increased and combined with MAOB and COMPT inhibitors. We also add dopamine agonists. We are proactive with regard to escalation therapies like deep brain stimulation or pumps going into the intestine. They are the biggest center in Switzerland doing both.
In Switzerland, there is subcutaneous apomorphine, but there are no sub cutaneous treatment injections. FOS levodopa is available in all of Europe, except Switzerland.

What is the biggest challenge with the treatment with levodopa. How do you assess whether the dose being administered is correct. Can the patient themselves evaluate whether they are receiving a dose suitable for their progression state.
Dr. med. Evdokia Efthymiou:
In the first years, re-evaluations happen rarely. Once the fluctuations start, this may become necessary.
PD Dr. med. Fabian Büchele:
Asking the patients: some keep timetables, the basis lies in talking. Research-wise, a lot of deep brain stimulation is done. There is a sensing capability that can detect the on-off states, allowing the use of an electrophysiological marker of the motor state. There is also the adaptive stimulation with closed-loop deep brain stimulation based on beta-power specific brain sensing. (It senses and stimulates).
For oral therapy, to have a sensor might not be that important, rather to have a continuous treatment.

Do you see a clinical advantage of a closed loop system that allows drug delivery as a feedback mechanism to real-time sensor data?
PD Dr. med. Fabian Büchele
If you have a sensor and have a closed loop supplying FOS-levodopa, that would be able to get rid of the fluctuations.
"Right now, if the patients had a pump, they can adapt [the dose] depending on how they feel. Patients often have an impaired perception of the on and off state. Even though they may be highly hyperkinetic, they can think they are in an off-state. And then they will press and press and press, and

nothing will happen. Their personal judgement is not always correct. That would be a selling point for a sensor to have a closed-loop system with a levodopa pump, be it subcutaneous or intestinal."

Would it facilitate dosing decisions?

Dr. med. Sujitha Mahendran

In the earlier stage, you can take levodopa three times per day, and you have a stable concentration. With ongoing disease progression, you have the fluctuations and an increase of the symptoms so you have to adapt the dosage and the frequency of the intake, and there's no routine that works for all.

To develop a routine for difficult to asses patients, they are "invited as in-patients, we can monitor them, observe them, and depening on their impression and adapt".

How often is this done?

Dr. med. Sujitha Mahendran

"if the patients have any problem (new onset of fluctuations), they are invated as in-patients". Patients are seen every three months.

Would you see a personal gain from having a sensor that tells you the concentration of levodopa in ISF?

Dr. med. Evdokia Efthymiou:

"I see the medical need in having a sensor to identify the misconception of dyskinesia, this could be very helpful for patients that confuse dyskinesia and tremor. The other application would ne in a preventative way. After a while of treatment, the patients develop fluctuations. This could be improved by starting earlier with levodopa treatment, to understand it a bit better.

Dosing strategy:

PD Dr. med. Fabian Büchele:

"as much as needed, but as little as possible" The more you take the earlier you get dyskinesia.

"There is no biomarker in Parkinsons, so it's all about this talk [between doctor and patient]".