EE-517 Bio-Nano-Chip Design– Groups 2024

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Jennifer Joey	Ayer	Amperometric multiplex sensor to monitor glucose and hydration via arginine vasopressin (AVP) detection.
Maïlys Mina Rose	Bayer	
Fábio André	Vilar Lourenço	
Benoît Thomas Marie	Vignon	
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Charles Louis Pierre Bogdan	Boissier	ACTN4 point-of-care nanobiosensor for cervical cancer detection
Farouk	Himmiche	
Linkai	Dai	
Martina	Curcuruto	
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Tala	El Kaissi	Non-Invasive Sweat Chloride Sensor for Cystic Fibrosis Detection
Iouri Loup Hugues Vincent	Prost	
Charlotte Heidi Marie	Alers	
Maeva Céline	Anfossi	
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Ivonne Joanne	Koedam	A sensor for salivary estradiol monitoring: supporting research in menstrual, menopausal and other hormone studies.
Irene	Vardabasso	
Daniel Abraham	Elmaleh	
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Laetitia Mercedes	Schwitter	Electrochemical Detection of Gluten Immunogenic Peptides in Urine for Monitoring Gluten-Free Diet Compliance in Celiac Patients
Léo Maxime	Matokwong	
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Group 6		
Alizée Anna	André	Continuous monitoring of blood ammonia levels to reduce life-threatening conditions in hospitals.
Thomas	van Spaendonk	
Fanny Sophie	Ghez	
Raphaëlle Claude Michèle	Dahan	
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Antea	Ceko	Wearable, high-precision microneedle biosensor for continuous levodopa monitoring in Parkinson’s Disease (PD) patients.
Yuwei	Liu	
Dufour	Timothé	
Dimitrios	Papadopoulos	
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Pietro	Boiardi	Bioresorbable and implantable chip for troponin monitoring in high-risk postoperative patients prone to myocardial infarction
Antoine Henri Maurice	Violet	
Hoang Son	Thai	
Marianne	Civit Ardevol	
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Alves Lopes	Daniel	Development of a biosensor for early detection of Amyloid-Beta 42 in saliva for Alzheimer’s disease.
Dominik	Helbing	
Maximilian	Grobbelaar	
Francesco	Andolfi	

EE-517 Bio-Nano-Chip Design

Student Projects - Project Proposal

Name and Surname: Jennifer Joey Ayer

Section: Life Science

Previous Experience Checklist (put a check mark if applicable):

- Transistor-level Bi/CMOS circuit design *Theoretical course only (Analog design for Biochip)*

o PCB-level circuit design

o SPICE simulation software use (e.g., LTspice)

o Multiphysics finite element analysis software use (e.g., COMSOL)

o Microfluidics (design or simulation or fabrication) *Design only*

o Development/simulation of MEMS/NEMS

o Development/simulation of a gas sensors

o Development/simulation of a magnetic or an optical sensor

o Development/simulation of an acoustic or an ultrasonic sensors

Title of the project (provisional): Amperometric multiplex sensor to monitor glucose and hydration via arginine vasopressin (AVP) detection.

Short description/summary (250 words max):

Microneedle patch to monitor an individual's glucose and hydration status. Placed on the arm, the wearable would communicate wirelessly with a smartphone app. The patch consists of a dual working electrode coupled to their respective microfluidics to avoid contamination and crosstalk. A single potentiostat ensures that different voltages are applied for the two different metabolites. The same reference and counter are used to miniaturise the device and reduce electronics and power management.

Sections you want to implement (1 sentence description for each):

● **Bio:** The detection of the hormone arginine vasopressin (AVP) [3] is achieved via aptamers 5] to monitor hydration status, while glucose is detected using glucose oxidase (GOx), with the resultant hydrogen peroxide (H2O2) being reduced by horseradish peroxidase [6].

● **Nano:** Aptamers are immobilized on carbon nanotubes, as described in [5], and for glucose detection, carbon nanofibers are used, as detailed in [6].

● **CMOS:** A potentiostat with a common source and counter is developped, but with dual working electrodes, allowing for the application of different voltages within the same cell.

● Other (if applicable): Microfluidics: Microneedles are used to extract the interstitial fluid (ISF), with a special design to address the difficulty of extracting ISF compared to blood, and incorporate microfluidics to guide the fluid to the working electrode as in [1], [2], preventing contamination and crosstalk.

More Details:

● **Application (250 words max)**: There is increasing evidence that hydration can affect glycaemic control [4]. This can lead to false readings from continuous glucose monitors (CGMs), which typically operate in interstitial fluid (ISF), and dehydration directly affects the amount of ISF, which can lead to errors. For diabetics, a biosensor coupling glucose and hydration status could help to better control their glycaemic levels. More generally, the proposed sensor would be in the emerging field of continuous health monitoring and complementary health indication.

● **Motivation (250 words max):** Hydration has been shown to have glucoregulatory effects. Research suggests that low water intake can lead to increased plasma osmolality and increased AVP levels, which are associated with impaired glucose metabolism [7].

● **Problems to be solved (250 words max):** The aim is to develop a reliable wearable continuous glucose and hydration sensor. Monitoring two analytes simultaneously is a difficult task because of the high risk of crosstalk. Microfluidics can help with this, while keeping the size as small as possible for the purpose of the wearable. Particular attention must be paid to the biosafety of the materials used. The transducing mechanism in the form of a three-electrode configuration coupled to a potentiostat has to be modified to accept two different working electrodes to allow monitoring of the two analytes. The potentiostat must not only ensure that the correct voltages are applied, but also that there is no saturation. It also has to have the lowest possible power consumption to allow miniaturisation. The same applies to the wireless communication system. Finally, you need to be able to integrate all the elements in a single device, reducing the number of layers and ensuring that the mechanical properties of the entire device (e.g. stress, strain) are maintained.

● **Proposed solutions (250 words max):** Microneedle patch is coupled with appropriate microfluidic to lead to two individual chambers where respective functionalised electrodes are placed. The AVP-sensitive electrode is functionalised with specific aptamers bound to the surface by carbon nanotubes. The glucose-sensitive electrode is modified with carbon nanofibres that immobilise the enzyme glucose oxidase. These two electrodes are placed in the same cell with a common reference and counter electrode to enable amperometric measurements. The current generated is later converted into a voltage and amplified before being converted into a digital signal and then sent wirelessly (e.g. via an antenna) to a smartphone app.

● **How will you implement your solution? (250 words max):**

First, finalise the choice of bioreceptors and nanomaterials to enhance the signal, avoid interference and facilitate implementation. Then design the potentiostat so that the desired voltages are applied without saturation. Take inspiration from what has been done for microfluidics and, if possible, simulate to avoid turbulent flow and/or contamination from one chamber to another, and choose biocompatible materials (e.g. glass) to avoid crosstalk with the electrochimical reaction. Finally, it is necessary to find components on the market that correspond to the specificities (ampli-op, resistor, etc.) and to deal with power management.

● **Novelties of your proposal** (Bullet points, each point 1 sentence):

-Multiplex
The detection of more than one analyte at a time is not easy due to cross-talk and interference, but is a booming field as personalised medicine demands it.

-Combination of analytes monitored
There is no sensor that I know of that has been designed to measure both glucose and hydration.

-Potentiostat, dual working electrodes
Although the concept of multiple working electrodes is well established, the specific combination proposed isn't, leading to different choices of electronic components (e.g. resistors) to achieve the desired voltages and avoid saturation.

-System
The aim is to develop a stand-alone biosensor, similar to the glucose patches on the market, but with the advantage of also monitoring hydration levels; this approach could then be reused to add or change the combination of biomarkers under consideration.

● **References (at least one, no limits):**

1.Sempionatto JR, Lin M, Yin L, et al. An epidermal patch for the simultaneous monitoring of haemodynamic and metabolic biomarkers. Nat Biomed Eng. 2021;5(7):737-748. doi:10.1038/s41551-021-00685-1

2.Zhu L, Liu X, Yang J, He Y, Li Y. Application of Multiplex Microfluidic Electrochemical Sensors in Monitoring Hematological Tumor Biomarkers. Anal Chem. 2020;92(17):11981-11986. doi:10.1021/acs.analchem.0c02430

3.Perrier E, Vergne S, Klein A, et al. Hydration biomarkers in free-living adults with different levels of habitual fluid consumption. Br J Nutr. 2013;109(9):1678-1687. doi:10.1017/S0007114512003601

4.Vanhaecke T, Perrier ET, Melander O. A Journey through the Early Evidence Linking Hydration to Metabolic Health. Ann Nutr Metab. 2020;76 Suppl 1:4-9. doi:10.1159/000515021

5.He P, Oncescu V, Lee S, Choi I, Erickson D. Label-free electrochemical monitoring of vasopressin in aptamer-based microfluidic biosensors. Analytica Chimica Acta. 2013;759:74-80. doi:10.1016/j.aca.2012.10.038

6.Al Mamun KA, Islam SK, Hensley DK, McFarlane N. A Glucose Biosensor Using CMOS Potentiostat and Vertically Aligned Carbon Nanofibers. IEEE Transactions on Biomedical Circuits and Systems. 2016;10(4):807-816. doi:10.1109/TBCAS.2016.2557787

7.Seal A, Colburn AT, Suh H, Kavouras SA. The Acute Effect of Adequate Water Intake on Glucose Regulation in Low Drinkers. Annals of Nutrition and Metabolism. 2022;77(Suppl. 4):33-36. doi:10.1159/000520479

Boissier Charles

Neuro-X

Previous Experience :

- PCB-level circuit design (Altium designer)

Note: I was previously in Communication Systems; therefore, I am new at biology and electronics.

Title of the project: ACTN4 point-of-care nanobiosensor for cervical cancer detection

Short description/summary:

ACTN4 is a protein overexpressed in the case of cervical cancer. It has also been observed to be overexpressed in other kinds of cancers (e.g., kidney, prostate)[2][3]. This project aims to develop a cheap, easy-to-use point-of-care sensor that detects ACTN4 concentration in cervical vaginal fluid. The sensor could then be connected to a medical database. It could help collect more samples for research purposes in the first part. If the research is validated, this same device could be incorporated in tampons or in sanitary towels to detect cancerous development daily.

The section you want to implement

- Bio: researching antibodies that have high affinity to ACTN4
- Nano: the concentration of ACTN4 in CVF is in the order of fM; therefore, the sensitivity of the sensor needs to be enhanced
- CMOS: a voltammetric sensor for higher sensitivity with a low-power RF module for data collection.
- Other: it could be interesting to build the software stack of the database

More Details:

Application:

The sensor would be a point-of-care sensor. The idea would be to collect women's CVF in tampons or regular sanitary towels and put it in a buffer so that the solution diffuses into the solution and the ACTN4 protein is free to move in the liquid. Lastly, a drop would be collected in the sensor for detection. The sensor could then send the data to a database.

Motivation:

Cervical cancer is the fourth most common female cancer worldwide. As for now, the diagnosis is done with a Pap test, which implies front in the vaginal region and observing signs of cancerous features on collected

cells. This methodology needs the expertise of a doctor; therefore, it can't be extended to self-testing.

Problems to be solved:

The main problem to be solved is to find an easy-to-use self-diagnosis for cervical cancer.

Proposed solution:

An easy-to-use point-of-care biosensor that detects the concentration of ACTN4 in a CVF sample and sends it to a database. The next step would be to reevaluate the cutoff value to obtain the best possible ROC curve. As for now, some researches have already demonstrated a sensitivity and specificity of 86% and 84%, respectively with a cutoff value of 10 pg ACTN4/mg total protein in CVF[1]. This was with a small sample of patients but is, however promising.

How will you implement your solution ?:

The concentration of ACTN4 in CVF is less than 100 fM. The molecule binding to ACTN4 could either be an aptamer or an antigen. The aptamers on the market don't have a high enough affinity and can detect ACTN4 up to nanomolar concentration. Therefore, the sensor would be used with an antigen. Having limited knowledge of CMOS design and nano technologies, I don't have the resources to plan exactly the implementation in those fields.

Novelties of your proposal:

- Point of care sensor for cervical cancer detection
- ACTN4 nanobiosensor

References:

1. Van Ostade X, Dom M, Tjalma W, Van Raemdonck G. Candidate biomarkers in the cervical vaginal fluid for the (self-)diagnosis of cervical precancer. Arch Gynecol Obstet. 2018 Feb;297(2):295-311. doi: 10.1007/s00404-017-4587-2. Epub 2017 Nov 15. PMID: 29143101; PMCID: PMC5778162.
2. Feng, D., DuMontier, C. & Pollak, M.R. The role of alpha-actinin-4 in human kidney disease. *Cell Biosci* **5**, 44 (2015). https://doi.org/10.1186/s13578-015-0036-8
3. Park S, Kang M, Kim S, An H-T, Gettemans J and Ko J (2020) α-Actinin-4 Promotes the Progression of Prostate Cancer Through the Akt/GSK-3β/β-Catenin Signaling Pathway. *Front. Cell Dev. Biol.* 8:588544. doi: 10.3389/fcell.2020.588544

EE-517 Bio-Nano-Chip Design
Student Projects - Project Proposal

Name and Surname: Tala El Kaissi
Section: Neuro-X

Previous Experience Checklist:

- SPICE simulation software use (e.g., LTspice)
- Development/simulation of a magnetic sensor
- Transistor-level Bi/CMOS circuit design (theory)
- PCB-level circuit design (Done once in a course)

Project Title (Provisional):

Non-Invasive Sweat Chloride Sensor for Cystic Fibrosis Detection

Project Summary (250 words max):

Cystic Fibrosis (CF) is a genetic disorder that causes serious damage to the lungs, digestive system, and other organs. The current diagnostic gold standard involves a laboratory-based sweat test using iontophoresis (IP) with pilocarpine[1]. This method, however, can cause skin irritation, discomfort, and requires a clinical setting, making it time-consuming[1][2]. This project proposes developing a non-invasive, real-time sweat chloride sensor using a wearable patch for continuous monitoring. The sensor will be designed to detect chloride ions in passive sweat, addressing the challenge of lower sweat volumes. To enhance selectivity and sensitivity, graphene oxide nanosheets will be used[3]. The device will also integrate microfluidic channels for sweat management, enabling effective biomarker detection over time[1]. Key aspects of the design include optimizing materials and the electronics system for signal amplification and measurement. The goal is to provide a portable, user-friendly diagnostic tool that can be worn continuously, improving patient comfort and diagnostic efficiency.

Sections to be Implemented:

- **Bio:** Detection of chloride in passive sweat for CF diagnosis.
- **Nano:** Use of graphene oxide nanosheets to enhance selectivity.
- **CMOS:** Develop integrated circuits and PCB for signal amplification and conductance measurement.

Application (250 words max):

This project aims to create a non-invasive, wearable diagnostic tool for Cystic Fibrosis (CF) patients. The current sweat chloride test is accurate but involves laboratory procedures that

are uncomfortable and inconvenient for patients[1]. The proposed sensor, integrated into a wearable patch, will provide real-time monitoring of chloride levels in passive sweat, reducing the time needed for testing and enhancing patient comfort. The passive nature of sweat detection minimizes patient effort. Furthermore, this wearable device could enable long-term monitoring, allowing healthcare providers to track chloride levels over extended periods without the need for frequent hospital visits, thus improving disease management and diagnostic speed.

Motivation (250 words max):

Cystic Fibrosis arises due to mutations in the CFTR gene, which lead to dysfunctional chloride channels, disrupting ion transport across epithelial membranes. This results in an imbalance of salt and water, causing thick, sticky mucus in organs like the lungs and digestive system. If untreated, the condition can lead to life-threatening complications[4]. Sweat chloride levels in CF patients are significantly higher, typically ranging from 80–100 mM compared to 20–30 mM in healthy individuals[1]. Although the sweat chloride test using iontophoresis (IP) is effective, it is uncomfortable and requires clinical intervention. There is a pressing need for a more comfortable and continuous monitoring solution that patients can wear, improving early detection and easing disease management.

Problems to be Solved (250 words max):

Current sweat chloride sensors in development are designed for athletes and focus on measuring chloride levels in sweat produced during physical activity. For example, one sensor [5] detected chloride concentrations of 21.4 ± 14.1 mM, but it relied on active sweat, which is unsuitable for CF patients who produce passive sweat. The small volumes of passive sweat present challenges in terms of sensitivity and the risk of contamination. To address this, the sensor must be highly sensitive to low sweat volumes and capable of isolating chloride ions for precise measurement. Moreover, graphene oxide has been shown to enhance sensor sensitivity and selectivity[6]. [3], demonstrated effective detection ranges of 30 to 400mM of [Cl-], but the sensors were disposable strips, not suitable for continuous monitoring. The proposed device must overcome these limitations by supporting prolonged, stable sensing for long-term patient use.

Proposed Solutions (250 words max):

The proposed solution involves developing a potentiometric chloride sensor coated with graphene oxide nanosheets, integrated into a wearable patch. Graphene oxide enhances both the sensitivity and selectivity of chloride detection. Microfluidic channels will be used to manage low volumes of passive sweat, offering control over biomarkers and requiring minimal sample volumes[1][5]. These channels help prevent contamination, ensuring accurate results. The design will also include an optimized electronic circuit capable of

detecting changes in chloride concentration through voltage measurements. Signal amplification will be a key focus to ensure accuracy and minimize noise. This combined approach of sweat management, sensitive chloride detection, and real-time monitoring aims to provide a reliable diagnostic tool.

Implementation Plan (250 words max):

- **Design the electrode:** The electrode will be coated with graphene oxide nanosheets to improve chloride ion selectivity.
- **Develop a circuit:** This circuit will detect voltage changes that correlate with variations in chloride concentration.
- **Microfluidic channels:** These will be integrated into the patch design to ensure efficient sweat collection and handling of small volumes.
- **Optimize biomaterials:** Sensitivity and selectivity will be enhanced, ensuring a linear detection range.
- **Amplifying circuit:** The circuit will be designed and tested for optimal signal amplification and processing.
- **System integration:** The graphene-coated sensor, microfluidic channels, and electronics will be combined into a fully integrated, real-time monitoring patch.

Project Novelty:

- Incorporates graphene oxide nanosheets to enhance chloride detection sensitivity and selectivity.
- Offers real-time, non-invasive monitoring of chloride levels in passive sweat, targeting continuous CF diagnostics.
- Utilizes microfluidic channels for effective sweat collection, crucial for low sweat volume conditions.
- Combines bio-sensing, nanomaterials, and CMOS technology into a single wearable diagnostic device.

References:

[1] Saha, T., Del Cano, R., De la Paz, E., Sandhu, S. S., & Wang, J. (2023). Access and management of sweat for non‐invasive biomarker monitoring: a comprehensive review. *Small*, *19*(51), 2206064.

[2] Hauke, A., Oertel, S., Knoke, L., Fein, V., Maier, C., Brinkmann, F., & Jank, M. P. (2020). Screen-printed sensor for low-cost chloride analysis in sweat for rapid diagnosis and monitoring of cystic fibrosis. *Biosensors*, *10*(9), 123.

[3] Kumar, P. A., Pradeep, A., Nair, B. K. G., Babu, T. S., & Suneesh, P. V. (2024). Highly sensitive disposable test strips for sweat chloride detection using silver nanoparticles decorated reduced graphene oxide. *Journal of Electroanalytical Chemistry*, *971*, 118569.

[4] Brasier, N., & Eckstein, J. (2020). Sweat as a source of next-generation digital biomarkers. *Digital biomarkers*, *3*(3), 155-165.

[5] Baker, L. B., Model, J. B., Barnes, K. A., Anderson, M. L., Lee, S. P., Lee, K. A., ... & Ghaffari, R. (2020). Skin-interfaced microfluidic system with personalized sweating rate and sweat chloride analytics for sports science applications. *Science advances*, *6*(50), eabe3929.

[6]Zhang, J., Zhou, Q., Cao, J., Wu, W., Zhang, H., Shi, Y., ... & Ma, H. (2021). Flexible textile ion sensors based on reduced graphene oxide/fullerene and their potential applications of sweat characterization. *Cellulose*, *28*, 3123-3133.

EE-517 Bio-Nano-Chip Design

Student Projects - Project Proposal

Name and Surname: Ivonne Koedam

Section: Neuro-X

Previous Experience Checklist (put a check mark if applicable):

☑ **(beginner)** Transistor-level Bi/CMOS circuit design

☑ **(beginner)** PCB-level circuit design

☑ **(beginner)** SPICE simulation software use (e.g., LTspice)

o Multiphysics finite element analysis software use (e.g., COMSOL)

o Microfluidics (design or simulation or fabrication)

o Development/simulation of MEMS/NEMS

o Development/simulation of a gas sensors

o Development/simulation of a magnetic or an optical sensor

o Development/simulation of an acoustic or an ultrasonic sensors

Title of the project (provisional): A sensor for salivary estradiol monitoring: supporting research in menstrual, menopausal and other hormone studies.

Short description/summary (250 words max):

Development of a device for the long term monitoring of estradiol in the saliva through a device that can be adhered to the back of a tooth.

Sections you want to implement (1 sentence description for each):

● Bio: Sensing the molecule estradiol (17-beta-estradiol), the most potent and abundant form of estrogen during a woman's reproductive years, present in the saliva.

● Nano: Based on current literature, aptasensors[6] or immunosensors could be used to measure the concentration of the salivary estradiol by measuring the current resulting from the reduction of the sensing molecule (to be further investigated/ specified following acquired knowledge from the lectures) on electrodes.

● CMOS: A CMOS circuit could include a read-out and signal amplification circuit (to be further investigated/specified following acquired knowledge from the lectures).

● Other (if applicable): The general building blocs for a whole device from market components (battery, Bluetooth module, ...).

More Details:

● **Application (250 words max):**

The application of the sensor would be aimed as a hormonal monitoring tool for studies concerning female reproductive health. It could however also be implemented for personal use.

● **Motivation (250 words max):**

Estradiol and progesterone and their fluctuations, crucial to the female reproductive system, are only since recently being studied for numerous effects they have on the body, such as brain function, cognition, emotional status, physiological pain, body temperature, and many more [1]. Despite half of the population suffering from these symptoms, there remains a lot of unknowns as to how to improve their quality of life. Research is frequently based on measuring hormonal fluctuations, that can be evaluated in saliva, blood, urine,[3] and sweat [6]. Studies show high correlation between salivary and serum estradiol, and have used saliva samples as a long term monitoring since it could be done at home by participants, easing long term monitoring [4].

● **Problems to be solved (250 words max):**

Such studies are based on subject compliance, who are required to take saliva samples at home daily, store them in their freezer, and bring them to the laboratory once a month [4] [5].

● **Proposed solutions (250 words max):**

The motivation is to further facilitate such studies, creating a device for long term monitoring of hormone fluctuations, requiring minimal subject intervention. The sensor could be aimed at monitoring any of the major reproductive hormones; estradiol progesterone or the luteinizing hormone. There is a lot of literature concerning estradiol, which is why, for the sake of the project, it was selected. The sensor could however further be developed in sensing multiple hormones, or different sensors for each hormone could be made, where the subjects could wear a sensor for each hormone.

● **How will you implement your solution? (250 words max):**

There already exists a wearable device for the monitoring of estradiol in sweat [6]. Similarly, the proposed solution is the creation of an oral wearable sensor [7] adhered to a tooth, monitoring estradiol in saliva, extensively more studied than the one found in sweat. The aim would be for it to be implanted on the long term, to allow for the convenient, at-home monitoring of hormonal fluctuation over the duration of a couple of months. The data would be transmitted from the device via Bluetooth, and the contain a battery powering it for the duration of the implant [7].

● Novelties of your proposal (Bullet points, each point 1 sentence):

- As stated previously, a sensor for the monitoring of estradiol in sweat already exists [6], however, such a device to monitor salivary estradiol does not exist.

- Different methods exist to monitor saliva from home [5] [8], but these require a substantial ammount of subject involvement by preparing different salivary samples at home. The proposed device would aid studies by creating a way to obtain the data by reducing subject compliance issues.

- Current state of the art usually focuses on obtaining the data once a day, which, for example, is more than sufficient for the monitoring of estrogen for menstrual status. Nevertheless, the device could allow for a monitoring on an hourly basis, if necessary.

● References (at least one, no limits):

[1] Farage, Miranda A., Thomas W. Osborn, and Allan B. MacLean. "Cognitive, sensory, and emotional changes associated with the menstrual cycle: a review." *Archives of gynecology and obstetrics* 278 (2008): 299-307.

[2] Critchley, Hilary OD, et al. "Menstruation: science and society." *American journal of obstetrics and gynecology* 223.5 (2020): 624-664.

[3] Schmalenberger, Katja M., et al. "How to study the menstrual cycle: Practical tools and recommendations." *Psychoneuroendocrinology* 123 (2021): 104895.

[4] Schmalenberger KM, Tauseef HA, Barone JC, Owens SA, Lieberman L, Jarczok MN, Girdler SS, Kiesner J, Ditzen B, Eisenlohr-Moul TA. How to study the menstrual cycle: Practical tools and recommendations. Psychoneuroendocrinology. 2021 Jan;123:104895. doi: 10.1016/j.psyneuen.2020.104895. Epub 2020 Oct 13. PMID: 33113391; PMCID: PMC8363181.

[5] Gandara, Beatrice K., Linda Leresche, and Lloyd Mancl. "Patterns of salivary estradiol and progesterone across the menstrual cycle." *Annals of the New York Academy of Sciences* 1098.1 (2007): 446-450.

[6] Ye, C., Wang, M., Min, J. *et al.* A wearable aptamer nanobiosensor for non-invasive female hormone monitoring. *Nat. Nanotechnol.* **19**, 330–337 (2024). https://doi.org/10.1038/s41565-023-01513-0

[7] Li, Yuanfang, et al. "Oral wearable sensors: health management based on the oral cavity." *Biosensors and Bioelectronics: X* 10 (2022): 100135.

[8] Ylinen, Jerry. "Emerging technologies and materials in female hormone monitoring." (2024).

EE-517 Bio-Nano-Chip Design
Student Projects - Project Proposal

Name and Surname: Laetitia Schwitter
Section:SV

Previous Experience Checklist (put a check mark if applicable):

- o Transistor-level Bi/CMOS circuit design
- o PCB-level circuit design
- o SPICE simulation software use (e.g., LTspice)
- o Multiphysics finite element analysis software use (e.g., COMSOL)
- x Microfluidics (design or simulation or fabrication)
- o Development/simulation of MEMS/NEMS
- o Development/simulation of a gas sensors
- o Development/simulation of a magnetic or an optical sensor
- o Development/simulation of an acoustic or an ultrasonic sensors
- x Development of a sensor for creatinine using pH sensing ISFETs

Title of the project (provisional):

Electrochemical Detection of Gluten Immunogenic Peptides in Urine for Monitoring Gluten-Free Diet Compliance in Celiac Patients

Short description/ summary (250 words max):

1% of the world population has Celiac disease (CeD), an immune-mediated disease caused by gluten intake. A life-long gluten free diet (GFD) is the only treatment to prevent long-term damage to the intestinal mucosa. However, monitoring GFD compliance is either unregular and invasive through biopsies and blood tests, insensitive to low-level dietary transgressions, or difficult to access.
This project proposes the development of a low-cost, portable and non-invasive electrochemical biosensor to detect gluten immunogenic peptides (GIP) in urine samples, providing a real-time, accurate, and user-friendly tool to monitor gluten ingestion. The system incorporates a highly sensitive GIP-specific antibody (G12 monoclonal antibody) integrated with a nanomaterial-enhanced sensor to capture and detect trace levels of GIP electrochemically. This device could offer celiac patients an easy and effective way to track accidental or intentional gluten consumption, helping them adhere to a GFD and preventing long-term damage to the intestinal mucosa.

Sections you want to implement (1 sentence description for each):

- ● Bio: Development of a GIP-specific aptamer and antibody functionalization on the sensor surface to obtain high selectivity.
- ● Nano: The nanoscale design to optimize signal transduction and amplification, while choosing materials that help enhance the selectivity and stability of the biosensor.

● CMOS: Create a CMOS interface for efficient signal processing, data processing and data display
● Other (if applicable): Develop a filter to remove interference to improve the electrochemical sensing.

More Details:

● **Application (250 words max):**

The proposed biosensor is designed to help patients with celiac disease monitor their adherence to a gluten-free diet by detecting Gluten Immunogenic Peptides (GIP) in urine, which appear after gluten ingestion. This non-invasive, point-of-care tool provides rapid feedback, enabling patients to track inadvertent gluten exposure. Its primary application is for individuals who are newly diagnosed, asymptomatic, or unsure about their dietary adherence, particularly in situations like eating out, traveling, or transitioning to a gluten-free lifestyle.

The sensor's ability to deliver immediate results would allow patients to adjust their diet quickly, avoiding the long-term damage caused by gluten intake. By offering a portable, easy-to-use device, the biosensor empowers celiac patients to take proactive control over their condition, reducing the risks of gut damage and promoting faster recovery.

● **Motivation (250 words max):**

Celiac disease is a lifelong condition that requires strict adherence to a gluten-free diet for therapy. However, 1 in 4 Celiac patients consume gluten voluntarily or inadvertently, leading to potential long-term damage **[2]**. *Although the disease is common, many people are unaware that they are affected by it. This allows the disease to progress and damage the villi.*

Furthermore, despite following an exact gluten-free diet, 30% of celiac patients continue to experience abdominal pain, as the damage caused to the intestine can temporarily cause other food intolerances unrelated to gluten such as histamine intolerance **[5]**.

Allowing celiac patients to obtain more immediate feedback on their gluten intake instead of being limited to periodic blood tests, could greatly improve their quality of life, by offering them greater control over their condition and reducing the anxiety associated with sticking to the strict diet.

● **Problems to be solved (250 words max):**

Delayed Feedback: Current accessible methods of monitoring, such as periodic blood tests to detect the antibody level or biopsies to monitor the health of the intestinal mucosa, require visits to a clinic. To detect any changes, these tests are done 6 months after starting the GFD [6]. As this does not provide any real-time information, the necessary dietary adjustments are delayed, causing more damage.

Inadvertent Gluten Exposure: Celiac patients often unknowingly consume gluten, leading to intestinal damage. Asymptomatic patients will however have no noticeable and immediate symptoms to signal the damage.
Newly diagnosed patients may struggle with adhering to a gluten-free diet. It is easy to be unaware of the gluten content of certain foods when getting familiar with GFD. Others might accidentally eat gluten-contaminated foods when eating out, sharing cooking spaces or while traveling [1].
Patient Anxiety: The lack of immediate feedback on gluten ingestion can cause anxiety and uncertainty, particularly for patients with more severe celiac disease or those new to the diagnosis [1].
Easy to handle: The purification and extraction step for the point of care solution should be simple for the user.

● **Proposed solutions (250 words max):**

The solution is to develop a portable electrochemical biosensor that measures the level of Gluten immunogenic peptide (GIP) in urine. GIP are detectable as early as 4-6 hours after gluten intake and they remain detectable for 1-2 days [1]. This point of care sensor then allows patients to quickly test their GIP levels with a non-invasive, simple and user friendly application.

A1 and G12 monoclonal Abs have been designed to specifically target the most active and dominant GIP (alpha-gliadin 33-mer) with high sensitivity [4]. Aptamers have also been developed to target the same GIP [8].
The solution is based on a low cost gluten detection method for food. The technique uses a sandwich-type electrochemical biosensor that exploits a pair of both an aptamer and antibody pair to enhance the sensitivity and selection to detect the gluten.The aptamers used for recognition are then fixed on a paper disc **[3]**. The prepared disc is placed onto a screen-printed carbon electrode and the signal read out using chronoamperometry.
Another similar method, would alter the adherence of the aptamer onto the screen printed carbon electrode by optimizing the carbon nanostructure using graphite and gold. This reduced the detection limit to 3.4ng/L which is comparable to a good non-electrochemical sensing method [7].
The CMOS design incorporates an amplifier for the signal, cyclic voltammetry or EIS. It also integrates signal processing and data visualization.
By offering real-time data, the sensor would reduce anxiety and provide patients with greater confidence in managing their condition.

● **How will you implement your solution? (250 words max):**

Electrochemical sensing for gluten has been explored for food. The detection mechanism can therefore be adapted to urine. Other inspiration can be drawn from urine detection kits that already exist.

For the aptamers and / or the antibodies the sensitivity would have to be explored. Possible urine sample preparation techniques would have to be investigated to avoid electrochemical interference.
Consequently, the sensor would be developed using electrochemical impedance spectroscopy (EIS) or amperometric detection methods, chosen for their precision in detecting low concentrations of biomolecules. The sensor would then be integrated with an electronic processing unit and a digital interface, such as a smartphone app for tracking, which would display the results to the user.
Prototype testing would involve calibrating the sensor with known concentrations of gluten and conducting trials with celiac patients to validate its performance in real-world conditions. Finally, feedback from patients and healthcare providers would be essential to provide a final easy to use and reliable product.

● **Novelties of your proposal (Bullet points, each point 1 sentence):**

- Development of a new electrochemical assay that uses both aptamers and antibodies for maximum sensitivity and selectivity to rapidly detect GIP in urine for more immediate feedback on gluten exposure.
- Small design for easy transport and use in everyday settings, including travel.
- Integration with digital platforms for trend tracking and personalized dietary recommendations.
- Addresses the unmet need for frequent, non-invasive monitoring of gluten exposure.
- Low-cost gluten detection

● **References (at least one, no limits):**

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Food Chem
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A new label-free impedimetric aptasensor for gluten detection
Food Chem

Project proposal

Name and Surname: Alizée Anna André

Section: Microtechnique (MT)

Previous experience:

o Transistor-level Bi/CMOS circuit design

o PCB-level circuit design

o SPICE simulation software use (e.g., LTspice)

o Multiphysics finite element analysis software use (e.g., COMSOL)

o Microfluidics (design or simulation or fabrication)

o Development/simulation of a gas sensors

o Development/simulation of a magnetic or an optical sensor

o Development/simulation of an acoustic or an ultrasonic sensors

Title of the project (provisional): Continuous monitoring of blood ammonia levels to reduce life-threatening conditions in hospitals.

Short description/summary:

High levels of ammonia in the blood are linked to conditions involving the liver, the urea cycle, and kidneys. Hyperammonemia is a primary factor responsible for the development of hepatic encephalopathy (HE) [1], a life-threatening condition. Early detection and treatment are crucial to prevent complications. Currently, cirrhosis patients, who are at high risk, are monitored by nurses through time-consuming clinical assessments and frequent checkups [2, 3]. Given the acute and chronic nature of hyperammonemia, continuous automatic monitoring would alleviate the workload on healthcare providers, enabling more precise follow-up. Indeed, the patient's condition can become life-threatening within a few hours. Despite global interest in monitoring ammonia levels, current innovations are limited to point-of-care devices and sensors using the breath and the skin's vapor, lacking sensitivity [4, 5].

This project proposes transforming a point-of-care device into a **wearable** device, combining an existing **microneedles** array system for **capillary blood** sampling with an **ammonia electrochemical sensor** connected through a **microfluidics system**. **Wireless communication** will be used for power and data transmission, and the sensor will be optimized for patient **comfort** using flexible materials and comfortable encapsulation.

Sections you want to implement (1 sentence description for each):

• **Bio**:

The electrochemical sensor will be adapted to interface effectively with biological tissues, ensuring accurate ammonia detection combined with the biocompatible and safe design of the microneedles.

• **Nano**:

A microfluidics system directly linked to the microneedles for continuous sampling of capillary blood will be designed while miniaturizing and adapting the materials of the sensor for wearable use and nano-bio sensing.

• **CMOS**:

Low-power circuitry will be designed to process the signals (amplification, etc.), control the microfluidics system and communicate wirelessly (data and power transmission).

More Details:

• **Application:**

The proposed wearable system will provide continuous monitoring of patients at risk of suffering from hyperammonemia. In hospital settings, this solution could help the diagnosis that are for now mostly established through unspecific symptoms such as acute confusional state [2]. Even though monitoring the ammonia levels needs to be combined with clinical assessments, it would relieve the workload of the nurses and doctors while providing more continuous information about the state of the patient. Real-time data provided to a computer enables early detection and intervention, will be integrated into the hospital information systems, ensuring timely access to patient data for healthcare providers. This system could also be considered for free-living systems.

• **Motivation:**

Ammonia monitoring takes a considerable amount of time for nurses caring for patients with liver damage, sometimes leading to disastrous situations due to HE. Indeed, ammonia is normally used by the liver to create urea. Whenever it is not processed, it can accumulate, resulting in high levels in the blood and traveling towards the brain. Once ammonia has reached the brain, it can cross the blood-brain barrier and cause different unspecific symptoms such as shaky hands and unconsciousness, ultimately causing death [6]. Overt hepatic encephalopathy (OHE) occurs in 30%-40% of patients with liver cirrhosis, leading to progressive disorientation, inappropriate behavior, acute confusion, stupor, and coma [2]. Early detection and continuous monitoring are crucial to prevent these severe outcomes while monitoring the liver or kidneys condition. Multiple conditions are linked to ammonia levels in the blood, thus giving a broader spectrum of applications to the sensor [7].

This proposal is based on a brief talk with a nurse working at the CHUV in Lausanne. This interview led to show the clinical application of such a sensor would relieve considerable the workload in the hospital.

• **Problems to be solved:**

Current methods do not provide real-time continuous monitoring. Oftentimes, they use intermittent tests or assessments. Several ammonia sensors have been developed, exploring multiple applications [4]. As state-of-the-art, ammonia levels are measured from blood samples sent to laboratories. However, the ammonia levels evolve due to both storage and contamination, making normalization, protocols and accurate measurements hard to implement [8]. These issues paved the way towards a point-of-care gas-phase sensor, using capillary blood [9]. Lately, non-invasive solutions exploring measurements of the patient's breath or skin ammonia were explored. However, the relationship with the blood's concentration hasn't been proven yet [4]. Moreover, a wearable, continuous-monitoring device has yet to be implemented. In order to do so, capillary blood must be sampled to get an accurate result through a wearable system, continuously, and the existing point-of-care electrochemical sensor must be adapted to this constant flux through a microfluidics system. The system should be comfortable and compliant, as miniaturized as possible and should communicate wirelessly the measurements to ensure that an intervention can be triggered in case of abnormal activity. The first issue to consider is thus to find which fluid to sample and how it can be done.

• **Proposed solutions:**

Sweat, breath and interstitial fluid are not yet proven to yield a strong enough relationship with the ammonia blood levels, thus reducing the non-invasive possibilities for now. However, capillary blood is already used for measurements with the commercialized point-of-care device [9]. Thus, long microneedles are needed to reach the cutaneous capillary network (≥1500 µm), which represents a technical challenge but has been implemented already [10]. Additionally, the blood vessel density in the skin significant variation between locations needs to be taken into account [11].

In order to pump blood from capillary blood vessels, stainless steel hollow microneedles with a self-powered microfluidic patch can be used. This patch can be positioned on the upper arm, as it has been shown to lead to higher flowrates and minimal pain [11]. Once the blood has been collected, it must be connected through a microfluidics system to the sensor. The system is minimally invasive by positioning the sensor outside of the upper arm. Additionally, integration of signal processing and data transmission should be implemented to ensure continuous monitoring. Finally, the overall encapsulation of the system should be adapted to improve comfort and ease of use, by using a compliant design.

Further improvements could be the implementation of a lactate sensor for complementary diagnosis, as it has been shown to help detecting hyperammonemia, or the integration of a machine learning algorithm to predict the outcome of the patient's condition based on the data transferred.

• **How will you implement your solution?**

First, the **microneedles array** system should be adapted to the need of the application. Other possibilities should be explored to find the best solution to interface with capillary vessels.

Second, the **ammonia electrochemical sensor** should be made compliant to the overall system. Starting from the point-of-care sensor, improvements should be made to match the needed input and output corresponding to the others building blocks.

Then, the junction between the microneedles array and the sensor should be designed. A **microfluidics system** should be designed, using simulations to understand its behavior for continuous sampling.

Afterwards, the **analog circuit** shall be designed to accommodate wireless communication with data encryption, charging as well as signal processing.

Finally, the **encapsulation** should be adapted to reach high comfort and ease of use standards. The patient should not be troubled by the sensor.

Once that is implemented, the integration of an **algorithm** could be considered, which could predict the at-risk levels of ammonia as they depend on parameters such as the age of the patient and can also vary depending on each person.

• **Novelties of your proposal (Bullet points, each point 1 sentence):**

- Implementation of a wearable ammonia sensor with accurate sensing.
- Implementation of continuous ammonia monitoring and real-time communication.
- Integration of a microneedles array and microfluidic patch to sample capillary blood vessels with an ammonia sensor.

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EE-517 Bio-Nano-Chip Design
Student Projects - Project Proposal

Name and Surname: Antea Ceko
Section: Neuro-X

Previous Experience Checklist (put a check mark if applicable):

o Multiphysics finite element analysis software use (e.g., COMSOL)--> I will learn it during the semester in my semester project.

Title of the project (provisional):

Wearable, high-precision microneedle biosensor for continuous levodopa monitoring in Parkinson's Disease (PD) patients.

Short description/summary (250 words max):

This project aims at developing a wearable microneedle array biosensor for real-time monitoring of levodopa (L-Dopa) levels in the subcutaneous interstitial fluid for PD patients. L-Dopa represents an important therapy for managing motor symptoms, such as tremor, in these patients, but defining the right dosage is crucial for the treatment efficacy and the minimization of side effects. Therefore, continuous monitoring of L-Dopa levels offers valuable insight into its fluctuations, unlike current clinical methods that rely on sporadic blood sampling.

The proposed biosensor will use a differential approach to monitor L-Dopa fluctuations over time and address the challenges posed by interfering agents and biofouling, which limit the device application to clinics by compromising sensor stability over time. Finally, the integration of CMOS electronics will facilitate real-time signal processing and wireless communication.

Sections you want to implement (1 sentence description for each):

- **Bio:** subcutaneous interstitial fluid L-Dopa detection.
- **Nano:** first aim is to incorporate tyrosinase for L-Dopa oxidation to dopaquinone. In addition, the incorporation of nanostructured materials (Gold, nafion, PANI [9]) will improve the performance by increasing the surface area and the sensor sensitivity. To improve the device precision, incorporation of an antibiofouling protecting agent (still to be defined and tested with a deeper research).
- **CMOS:** measuring the difference in the current response between two working electrodes (differential detection principle). The differential current response is then related to the concentration of L-Dopa.
- **Other (if applicable):** incorporate a biocompatible and flexible material for the substrate technology in order to obtain a long-term biosensor that is easy to wear.

More Details:

- **Application (250 words max):**

Parkinson's disease patients require precise dosage control during L-Dopa therapy in order to manage motor symptoms and mantain the efficacy of the treatment [1]. A wearable, minimally invasive biosensor

is able to continuously monitor the concentration of L-Dopa in the subcutaneous interstitial fluid in real time (limited by the time resolution of the biosensor) , reducing the associated risk of side effects like dyskinesia and psychosis. In Parkinson's patients, peak plasma concentrations of administered L-Dopa typically range from 1.26 to 12.27 µM, compared to 30-40 nM in healthy individuals [5], which is a sufficient range for the sensor to monitor these levels. In fact, only 1-5% of orally administered L-Dopa reaches the brain. By using a microneedle array biosensor, it is possible to provide continuous monitoring of L-Dopa values in subcutaneous interstitial fluid with high sensitivity, allowing doctors to adjust L-Dopa dosages based on real-time feedback.

- **Motivation (250 words max):**

PD is a neurodegenerative brain disorder affecting more than 10 million people worldwide. PD is associated with the loss of dopaminergic neurons in the substantia nigra pars compacta and the striatum. L-Dopa, has been considered one of the most effective therapies for the reduction of motor symptoms in Parkinson's disease patients; however, its effectiveness decreases with time, as shown in Figure 1. In particular, precise dosing is crucial since an improper administration can decrease the quality of the treatment and the patient's quality of life. In addition, the differences in metabolism and drug sensitivity among patients, lead to the need to adjust the dosage specifically for each patient.
Current clinical practices consist of episodic blood sampling, which however fails to capture real-time fluctuations in L-Dopa levels. A minimally invasive and wearable biosensor, able to provide continuous monitoring is needed in order to enable real-time, personalized care, improving the outcome of the therapy.

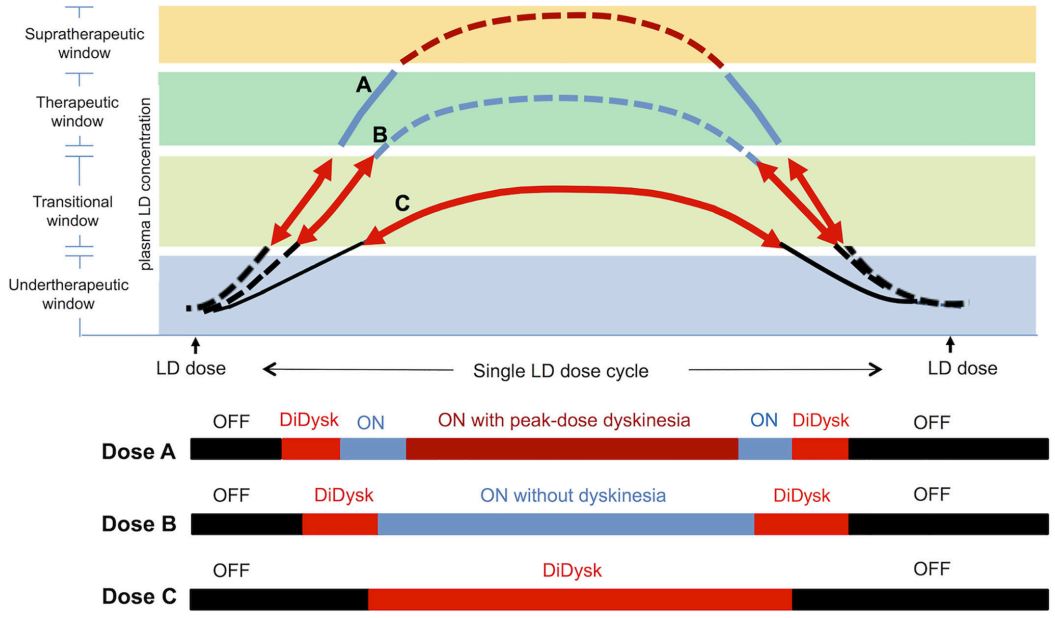

Figure 1: effect of single dose L-DOPA therapy over time [2].

- **Problems to be solved (250 words max):**

Electrochemical monitoring of L-Dopa in vivo is subject to numerous interfering electroactive agents, such as ascorbic acid, and is made more difficult because of the low concentration of L-Dopa. The work of Goud et.al. [3] has shown a relatively stable recording of L-Dopa variation levels in the interstitial fluid.
However, microneedles for interstitial fluid monitoring are subject to surface biofouling effects, which decrease the sensor's response by 14% after 2 hours of experimental period, meaning that it can be

unstable over a long period of time. Currently, biofouling is a big challenge to solve before proceeding to the clinics, where the long-term stability of the device is a priority.
Furthermore, to bridge the gap between measured data and therapeutic intervention, patients should receive continuous updates on their treatment based on real-time biosensor measurements [4].

- **Proposed solutions (250 words max):**

The proposed solution involves a flexible differential microneedle array having two working electrodes: one modified with tyrosinase for selective L-Dopa detection and the other unmodified to capture background interference. The difference in signals between these electrodes enables precise measurement of L-Dopa concentration [5].
Microneedles represent an innovative penetration technology that utilizes numerous micron-sized fine tips for enhanced delivery [6]. However, microneedles are subject to biofouling. To overcome this problem, applying a hydrogel coating like agarose can help prevent the adsorption of large biological molecules such as proteins and cells. Additionally, antifouling zwitterionic membranes or conductive polymers, such as hyaluronic acid-modified electrodes, offer promising alternatives to further improve sensor stability and minimize nonspecific protein adsorption [8]. The project will focus on identifying the most suitable solution for precise L-Dopa detection from among different possible options.
Finally, an important part will consist in incorporating CMOS electronics for signal processing and wireless communication in order to enable real-time, continuous monitoring of L-Dopa levels and direct integration with therapeutic management.

- **How will you implement your solution? (250 words max):**

The differential current between the two electrodes will be used to calculate the L-Dopa concentration. Signal processing will be handled by a CMOS chip, which will also wirelessly transmit the data to an external device for continuous monitoring and patient follow-up. The entire system will be integrated into a flexible, biocompatible design for patient long-term usage.
An important part will consist in finding an effective antibiofouling protecting agent for microneedles coating. This part will require extended research and material optimization to reach the maximal sensing precision.

- **Novelties of your proposal (Bullet points, each point 1sentence):**

- Applying a multi-layered biocompatible coating to the microneedles that enhance long-term stability and extend the device's lifespan in vivo.
- Integration of feedback mechanisms that notify patients or medical caregivers in real time when L-Dopa levels fall outside therapeutic ranges, allowing for immediate intervention.
- Eventually, implement a self-dosage adjustment system responding to the measured L-Dopa levels and the patient's current needs.
- Eventually, explore the detection of additional biomarkers related to Parkinson’s disease to monitor its progression more effectively.

- **References (at least one, no limits):**

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EE-517 Bio-Nano-Chip Design
Student Projects - Project Proposal

Name and Surname: Pietro Boiardi
Section: Life Sciences Engineering

Previous Experience Checklist (put a check mark if applicable):

- [x] Transistor-level Bi/CMOS circuit design
- [ ] PCB-level circuit design
- [x] SPICE simulation software use (e.g., LTspice)
- [x] Multiphysics finite element analysis software use (e.g., COMSOL)
- [ ] Microfluidics (design or simulation or fabrication)
- [ ] Development/simulation of MEMS/NEMS
- [ ] Development/simulation of a gas sensors
- [ ] Development/simulation of a magnetic or an optical sensor
- [ ] Development/simulation of an acoustic or an ultrasonic sensors

Title of the project (provisional):

Short description/summary (250 words max):

Sections you want to implement (1 sentence description for each):

- Bio:
- Nano:
- CMOS:
- Other (if applicable):

More Details:

- Application (250 words max):
- Motivation (250 words max):
- Problems to be solved (250 words max):
- Proposed solutions (250 words max):
- How will you implement your solution? (250 words max):
- Novelties of your proposal (Bullet points, each point 1 sentence):
- References (at least one, no limits):

Bioresorbable and implantable chip for troponin monitoring in high-risk postoperative patients prone to myocardial infarction

Short Summary

Recently, research in the field of implantable and bioresorbable microelectronic devices has seen significant growth due to the thorough understanding and thoughtful utilization of biocompatible materials. These degradable materials could potentially enable, in the near future, the complete abandonment—at least in certain applications—of non-recyclable and surgically explantable electronic components, thus reducing waste and avoiding invasive procedures when these are not advisable.

For example, the properties of composite nanofibers made from silk fibroin and PVA have been investigated. These nanofibers have demonstrated modifiable bio resorption kinetics and have proven to be highly flexible, potentially suitable for the structure of transient electronic microdevices. [1]

This project aims to combine degradable CMOS electronic technology, the foundation of the biochip's integrated circuit and essential for its miniaturization, with bioresorbable materials for the scaffold. In addition, it will be necessary to develop a dedicated interface for electrochemical biosensing. This is made possible by the functionalization of conductive nanomaterials used to enhance the selectivity and conductivity of the electrode interface, with agents for the molecular recognition of the target biomarker (monoclonal antibodies used for cardiac-specific troponins I and II [2]).

The chip should detect changes in current/impedance through amperometric/potentiometric sensors when the biomarker binds to the interface.

Given the intended use of the subcutaneously implantable device, it is not only necessary to select materials based on their bio resorption kinetics, but also to implement a low-consumption, self-sustaining power system that operates passively during monitoring. This could be achieved through environmental energy harvesting methods, such as piezoelectric or thermoelectric technologies.

Sections to implement

- **Bio:** selection of appropriate troponin-binding monoclonal antibodies and careful choice of bio-degradable and compatible materials.
- **Nano:** selection of the most suitable nanomaterials at the bio-CMOS surface for the enhancement of selectivity and their functionalization.
- **CMOS:** sizing of an integrated electronic circuit aimed at the transduction of biosensing stimuli and the possible wireless transmission of data.

Application

The development of the device proposed in this text could ideally be aimed at monitoring high-risk cardiovascular patients for myocardial infarction during the postoperative period. The detection of troponin, a protein abundantly present in the blood plasma during myocardial stress, fatigue, and possible damage, would thus be continuously ensured in real time for a predetermined period. The degradation timeline of the materials would be set based on this monitoring duration.

In the literature, examples of biochips dedicated to the evaluation of troponin levels can be found. These include a sensor with gold electrodes enriched with GQD and PAMAM for the immobilization of cTnI monoclonal antibodies and detection through CV and DPV in blood plasma serum [3].

In addition to being bioresorbable, the sensor should feature an innovative power management system, such as a passive power supply provided by a thermoelectric generator, which could be derived from both inorganic or organic materials, whose properties have been extensively documented in the literature [4] (though piezoelectric systems could also be further explored).

Other studies have also developed a versatile platform for real-time, label-free biomolecule detection using selectively functionalized SnO_2 nanobelt field effect transistor devices. Specific bioreceptors were precisely positioned on the active component of the nano-FET, specifically the nanobelt channel surface, ensuring that the FET's electrical response (conductance changes) to molecular binding directly indicates the presence of biomolecules complementary to the receptors. [5]

Motivation

Postoperative complications in high-risk myocardial infarction patients can be monitored through real-time evaluation of blood troponin levels. Patients undergoing invasive procedures such as cardiac, abdominal, vascular, and major orthopaedic surgeries (e.g., coronary bypass, stenting for aneurysms, SAVR, total hip arthroplasty) may be predisposed to ischemic stress, particularly if they are elderly and show associated comorbidities such as a history of infarction, atherosclerosis, hypertension, or diabetes.

To manage the postoperative course without subjecting the patient to another surgical explant for the sensor, once the observation window has ended, a subcutaneous and degradable biochip for continuous troponin monitoring could be employed. The device would communicate data and send alert signals to healthcare personnel via a wireless transmission system if troponin levels rise to indicate likely myocardial fatigue and damage.

While the subcutaneous implantation of such a device can be performed during the surgical procedure itself, it is crucial to avoid subjecting high-risk patients to additional invasive retrieve procedures that would require anaesthesia and may pose further dangers, like infections. This

has led to the concept of designing an electrochemical sensing biochip with a modulated bio resorption rate, tailored to the desired monitoring period.

Challenges

Although functional organic materials, which can be used for both passive and active components of on-chip bio-resorbable electronics, are well documented in the literature, their behaviour in terms of dissolution upon contact with biofluids/water solutions and their degradation kinetics still require thorough investigation. [6]

Regarding the passive power supply system, the efficiency of bioresorbable thermoelectric materials remains uncertain, particularly in terms of the voltage generated for a given temperature gradient, the output power required for the biosensing task , and the long-term safety of the implanted material (e.g., absence of rejection or adverse reactions).

Given the slight physiological temperature gradients due to thermoregulation, it is crucial to optimize both the efficiency and energy consumption of the device to ensure that the energy harvesting system is sufficient. Additionally, there is a scarcity of evidence supporting fully biodegradable or at least biosafe thermoelectric materials for *in vivo* use.

It is also essential to maximize the sensitivity of the biomarker detection system and ensure the stability of the electrode functionalization at the nanoscale interface level throughout the entire monitoring period. The feasibility of a wireless transmission system (e.g., RFID technology) compatible with the low power supply required to operate the device remains to be determined.

Furthermore, potential issues regarding biocompatibility of the transient electronics substrate, the toxicity of the byproducts from the degradation of the chip's functional elements, the control of biodegradation kinetics, as well as regulatory and clinical approval challenges, may arise

Possible solutions

In the literature, reviews can be found discussing conjugated polymers that can be used as thermoelectric generators. PEDOT (Poly(3,4-ethylenedioxythiophene)) stands out for its biocompatibility, notable conductivity, transparency, flexibility, and processability. [4]

Additionally, extensively studied and available are synthetic polymer substrates that are flexible and mechanically compatible with soft tissues, often produced as thin films. These materials are suitable for implantation due to their harmless degradation or for encapsulating the biochip itself. Examples include silk fibroin, PVA (polyvinyl alcohol), and PLGA (poly (lactic-co-glycolic acid)), among others.

Regarding functional materials for electronics (interface, electrodes, and CMOS technology integrated circuits), inorganic materials have been particularly successful due to their stable performance. Elements such as magnesium and zinc (used in electrodes), and semiconductors like silicon, have found extensive applications in bioresorbable electronics due to their ability to hydrolyse and dissolve totally and controllably in aqueous environments.

Monocrystalline silicon nanomaterials are a notable example. To slow down the bio resorption kinetics, when necessary, dielectric layers and inorganic encapsulation materials (e.g., MgO, SiO_2) can also be employed. [6]

Implementation

In light of the objectives, implementing an implantable device for continuous blood troponin biosensing requires meticulous selection of materials, including those for the support structure, functional electronics, electrodes, and molecular recognition elements complementary to the biomarkers. It also demands careful consideration of degradation times, resorption mechanisms, and biocompatibility. Additionally, optimizing the device to operate the electrochemical transducer under low-energy conditions is a significant challenge.

An alternative to commercially available materials for CMOS biochips, as documented in the literature, is emerging zinc oxide (ZnO). Such semiconductor oxides are gradually replacing conventional electronic materials, where advantageous. ZnO could be pivotal in transient, flexible, and transparent electronics due to its excellent piezoelectric properties (a potential energy harvesting method), good electron mobility, transparency, and biocompatibility. This material, which is completely water-soluble, has been combined with magnesium electrodes and magnesium interconnections, silk fibroin packaging and substrates, and magnesium oxide dielectrics. [7]

Research on thin-film transistors made from zinc oxide illustrates the potential for developing implantable biochips that are compatible with human biological tissues and exhibit controllable degradation characteristics.

To conclude, it is crucial to determine the elements for the functionalization of the electrodes, to ensure selectivity in the biomarker-interface binding, and to successfully immobilize the antibodies dedicated to molecular recognition.

Alternatively, if the development of a power supply system for the degradable transient electronics circuit proves to be too challenging, it could be feasible to leave only the implantable and bioresorbable sensor subcutaneously, equipped with an interface for electrochemical sensing, electrodes, an encapsulation layer as the substrate, and functionalized FETs for the recognition and transduction of the binding event. This approach would eliminate the challenge of passive powering the system: externally, an antenna could be used for the wireless reception and transmission of the signals electrically transduced at the CMOS level, and a system leveraging radio frequencies, or electromagnetic radiation in general, could be employed to supply energy to the underlying electronics.

Novelties of proposal

- Continuous monitoring by the biochip during a variable and tuneable time window.
- There is no need for the patient to rely on point-of-care screening since clinical real time evaluation is conducted directly by healthcare personnel through data transmission to the medical facilities, while the patient stays home.
- No need for invasive surgical removal at the end of the usage period.
- Sustainability and absence of e-waste due to material degradation.
- Electrodes, scaffold, and integrated electronics are fully degradable in biofluids.
- Independent power management of the device, based on piezoelectric or thermoelectric energy harvesting systems, sufficient for the low power consumption of CMOS technology (to be assessed).

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[2] C. O. Ma, «The role of antibody-based troponin detection in cardiovascular disease: A critical assessment,» *Journal of Immunological Methods,* 2021.

[3] K. K. Bhatnagar, «Ultrasensitive cardiac troponin I antibody based nanohybrid sensor for rapid detection of human heart attack,» *International Journal of Biological Macromolecules,* 2017.

[4] N. N. M. A. Hasan, «Thermoelectric Generator: Materials and Applications in Wearable Health Monitoring Sensors and Internet of Things Devices,» *Advanced Materials Technologies,* 2022.

[5] C. H. C. Cheng, «Functionalized SnO2 nanobelt field-effect transistor sensors for label-free detection of cardiac troponin,» *Biosensors and Bioelectronics,* 2011.

[6] S. M. H. P. Yu, «Materials, Processes, and Facile Manufacturing for Bioresorbable Electronics: A Review,» *Advanced Materials,* 2018.

[7] H. S. K. C. G. H. O. H. R. dagdeviren, «Transient, biocompatible electronics and energy harvesters based on ZnO,» *Small,* 2013.

EE-517 Bio-Nano-Chip Design
Student Projects - Project Proposal

Name and Surname: Alves Lopes Daniel
Section: SV

Previous Experience Checklist:
- o Transistor-level Bi/CMOS circuit design
- o PCB-level circuit design
- o SPICE simulation software use (e.g., LTspice)
- o Multiphysics finite element analysis software use (e.g., COMSOL)
- ● Microfluidics (design or simulation or fabrication)
- o Development/simulation of MEMS/NEMS
- o Development/simulation of a gas sensors
- o Development/simulation of a magnetic or an optical sensor
- o Development/simulation of an acoustic or an ultrasonic sensor

But I am eager to learn!

Provisional title of the project: Development of a biosensor for early detection of Amyloid-Beta 42 in saliva for Alzheimer's disease.

Short description/summary (250 words max):

The goal of this project is to develop a portable biosensor for the early detection of Amyloid-Beta 42 (Aβ42) in saliva which is a biomarker for **Alzheimer's Disease (AD).**
Aβ42 is an important protein in Alzheimer and is commonly studied in **cerebrospinal fluid (CSF)** and blood. However, studying the protein in those fluids can be invasive and saliva gives a more accessible way for routine tests. From (Boschi *et al*, 2022), we can see that concentrations of Aβ42 in saliva are generally low and were found to be **127.11 ± 33.44 pg/mL for AD patients** which is close from its levels in **non-AD patients** which were found to be **88.03 ± 39.04 pg/mL**.
We would need to design a sensitive biosensor capable of detecting these low concentrations of Aβ42 in saliva for early diagnosis particularly in asymptomatic people. By developing a strong detection system using nanomaterials and electrochemical techniques, this sensor could make Alzheimer diagnosis more accessible and less invasive than current methods that use cerebrospinal fluid (CSF) or other expensive imaging techniques. The innovation is in the ability to use the saliva's easy access and combine it with advancements in biosensor technology to create a user-friendly, accurate and affordable diagnostic tool. This could open new avenues for early Alzheimer's screening and monitoring, improving patient outcomes through early interventions.

Sections you want to implement (1 sentence description for each):
● Bio:
From (Kim *et al*, 2021), we see that we could use an ELISA (Enzyme Linked Immunosorbent Assay) using biological specificity of antibodies/aptamers which target Aβ42.

● Nano:
From (Khalil *et al*, 2016), we see that we could use a hybrid sensor that would combine gold nanoparticles (enhanced surface binding of Aβ42) and graphene (Live electrical signal transduction) which would yield a sensitive and efficient sensor for low concentrations of Aβ42.

● CMOS:
A CMOS-based electrochemical sensor would allow for miniaturisation of the biosensor and could detect electrical changes when Aβ42 binds to specific receptors and convert this binding into a measurable signal.

● Other (if applicable):
We could use microfluidics in the sensor to automate the saliva sample processing and potentially concentrate Aβ42 for a better detection. We can also use machine learning to analyse the data to help distinguish noise from actual Aβ42 signals.

More Details:
● Application (250 words max):
The goal would be to develop a cheap, non-invasive portable and easy to use device which would allow a person to spit their saliva into the device and the biosensor would detect very low concentrations of Aβ42 which is a key biomarker of Alzheimer's disease. Early detection of Aβ42 will help identify Alzheimer's pathology long before symptoms appear which would potentially allow for earlier intervention and improved patient outcomes. This sensor could also be used for monitoring the progression of the disease or assessing the effectiveness of treatments and enhance care strategies for patients at different stages of Alzheimer's disease.

● Motivation (250 words max):
Alzheimer is the principal cause of dementia in the world and early detection is still an important challenge we face today. Current diagnostic methods like CSF analysis and PET scans are expensive, invasive and not practical for routine screening.
Also, Alzheimer often starts years before symptoms appear which shows the need for a practical sensor for early detection of low concentration of biomarkers of the disease. For this, we can propose saliva which is an easily accessible fluid but existing diagnostic tools for detecting Aβ42 in saliva are limited by sensitivity and cost. This means that developing a biosensor capable of detecting Aβ42 at low concentrations in saliva could greatly help in Alzheimer diagnosis, particularly in populations with low income and far from specialised centres.

● Problems to be solved (250 words max):
There is 5 possible problems to be solved:

- Low concentration of Aβ42 in saliva which means we need a very sensitive detection method.
- Current methods for Aβ42 detection are invasive and/or expensive which means the device must be non-invasive and as cheap as possible.
- In the current state of things, we need to go to a specialised place to get detection of Aβ42 which means routine testing is difficult. This means that there is a need for a portable and easy to use device.
- We need high specificity and as minimum interferences as possible from other proteins and compounds present in saliva.
- Since the concentrations of Aβ42 in saliva are very close for AD patients and for non-AD patients, this could yield **false positives (FP)** or even **true negatives (TN)**.

● Proposed solutions (250 words max):
We can propose a portable biosensor that uses nanomaterials (gold nanoparticles and graphene) and CMOS technology for signal processing and amplification. Then, by using highly specific antibodies/aptamers that bind to Aβ42 the sensor could detect low concentrations of the biomarker in saliva. Finally, microfluidics could be used to allow some kind of sample filtering and

machine learning could help with data analysis to enhance the accuracy of results and distinguish Aβ42 signals from noise. Lastly, to adress the FP and TN problems, we could ask the patient to do multiple "spittings" during the month/week/day and use proper data analysis to reduce to the minimum the number of FP and TN.

● How will you implement your solution? (250 words max):
We would start by developing nano-based detection surfaces that are used with antibodies specific to Aβ42. These surfaces will be integrated into a CMOS to detect changes in electrical signals when there is binding of Aβ42. Then, we would design and then test microfluidic channels/chambers for saliva collection and then processing to ensure minimal loss of sample and maximal concentration of Aβ42 for easier detection. The sensor would be optimised to detect Aβ42 levels as low as possible. Then, we would do validation studies using saliva samples from both non AD and AD patients. Then, machine learning would be used to analyse the data and improve the accuracy and sensitivity of the device to reduce FP and TN. Finally, we would focus on making sure that the sensor is affordable, portable and as user-friendly (easy to use) as possible for mass distribution.

● Novelties of your proposal (Bullet points, each point 1 sentence):
For Aβ42 detection:

- It's non-invasive, affordable and can be easily used at home.
- The use of nanomaterials and CMOS technology for live signal amplification and processing.
- The use of microfluidics for better sample collection and for better accuracy.
- The use of machine learning to improve the accuracy of the sensor and to reduce false results (FP/TN).

● References (at least one, no limits):

Boschi S, Roveta F, Grassini A, Marcinnò A, Cermelli A, Ferrandes F, Rainero I & Rubino E (2022) Aβ42 as a Biomarker of Alzheimer's Disease: Is Saliva a Viable Alternative to Cerebrospinal Fluid? *Brain Sci* 12: 1729

Khalil I, Julkapli N, Yehye W, Basirun W & Bhargava S (2016) Graphene–Gold Nanoparticles Hybrid—Synthesis, Functionalization, and Application in a Electrochemical and Surface-Enhanced Raman Scattering Biosensor. *Materials* 9: 406

Kim S-H, Lee E-H, Kim H-J, Kim A-R, Kim Y-E, Lee J-H, Yoon M-Y & Koh S-H (2021) Development of a Low-Molecular-Weight Aβ42 Detection System Using a Enzyme-Linked Peptide Assay. *Biomolecules* 11: 1818