Proposed PhD title:

SiC-based devices for the electrical detection of neurotransmitters/hormones.

Research area: Bionanoelectronics

Key words: Biosensor; Sensing through field-effect; ISFET; JFET; Surface functionalization; Microfluidics, neural interfaces

Scientific background & motivation:

Neural interfaces and biosensors are key areas of research and technology at the intersection of neuroscience, biomedical engineering, and computing. Biosensors are essential components of neural implants because they enable the detection and monitoring of neural signals. These signals can be used to diagnose neurological disorders, monitor treatment efficacy, and adjust therapies in real time. Biosensors can detect a range of neural signals, including electrical activity, neurotransmitter release, and changes in neural metabolism.

Neural interfaces that incorporate biosensors to detect neurotransmitter levels or metabolic markers represent the frontier of neurochemical sensing and brain–machine interface (BMI) development. Unlike traditional neural interfaces that primarily record electrical signals (e.g., ElectroEncephaloGram -EEG or neuronal spikes), these systems measure the chemical environment of the nervous system, providing molecular-level insights into neural activity and metabolic state. The development of rapid, sensitive devices for simultaneous neurotransmitter and hormone detection has significant clinical implications, particularly for disease management.

For example, levels of "feel-good" hormones HBE(dopamine, serotonin, endorphins, and oxytocin) and stress-related hormones (e.g., cortisol) in the human body are crucial for understanding and addressing severe disorders such as major depressive disorder, as well as milder conditions like chronic stress. However, these neurotransmitters and hormones are difficult to measure in real time because they:

(i) exist at extremely low concentrations (often nanomolar to picomolar levels),

(ii) degrade quickly in biological fluids, and

(iii) are typically measured using methods such as high-performance liquid chromatography coupled with mass spectrometry (HPLC–MS) or enzyme-linked immunosorbent assays (ELISA), which, although accurate, are slow, expensive, and laboratory-based.

Currently, there is no equivalent of a glucose meter for measuring hormones such as cortisol or "feel-good" neurotransmitters in a simple, rapid, and low-cost manner.

Field-effect transistors (FETs) have attracted considerable attention for biomolecule detection due to their label-free operation, high sensitivity, fast response time, real-time capability, and miniaturized form factor, making them ideal for on-site medical diagnostics, biosensing, and environmental monitoring. Promising results have already been demonstrated for the simple, rapid, and low-cost detection of dopamine [1], serotonin [2], oxytocin [3] and cortisol [4] using FETs. Notably, oxytocin and cortisol are non-electroactive molecules (i.e., they have no direct redox activity). Detecting these molecules typically requires surface modification of the transistor material with specific

biorecognition elements (e.g., antibodies, aptamers, or molecularly imprinted polymers). Nevertheless, the same biorecognition-based approach is often employed even for dopamine and serotonin detection, as it improves selectivity and sensitivity.

Among the various strategies available for surface biomodification, techniques based on successive covalent grafting steps are widely used [5]. These approaches are preferred because they enable stable, robust immobilization of functional biomolecules, ensuring enhanced durability under demanding operational conditions. However, many studies have shown that covalent grafting reactions are not always quantitative. As a result, incomplete or heterogeneous surface coverage often occurs, producing surfaces with variable chemical composition and topography. Such heterogeneity significantly affects the reproducibility and reliability of functionalized devices, ultimately limiting their performance and scalability [6]. Ionic liquids are being investigated as an alternative, enabling non-covalent attachment of receptors to surfaces and addressing these limitations. These molecules offer numerous advantages and have been successfully used to permanently immobilize catalysts on inorganic surfaces and modify electrodes for selective detection in aqueous media [7].

Most FET-based detection work for "feel-good" hormones and cortisol has focused on materials such as graphene, carbon nanotubes (CNTs), and silicon nanowires, resulting in nanoscale devices (e.g., nanowire-FETs, CNT-FETs). Silicon is generally considered the material of choice for commercialization because it benefits from a mature microfabrication ecosystem (developed by the semiconductor industry) and exhibits excellent electrical properties. However, silicon is brittle, not inherently biocompatible, and lacks long-term chemical stability in physiological environments [8]. Consequently, silicon surfaces must be modified (e.g., with amorphous silicon carbide or parylene-C) for safe use in neural tissue.

Silicon carbide (SiC), which also benefits from a mature microfabrication ecosystem, overcomes many limitations associated with silicon. SiC is chemically inert in physiological environments (e.g., saline), resists oxidative corrosion, is impermeable (especially to water), and exhibits no measurable toxicity [9, 10]. Additionally, SiC electrode probes have shown excellent neural compatibility. Amorphous SiC (a-SiC) has emerged as a promising material for encapsulating implanted neural devices, as demonstrated by its successful use as a coating for intravascular stent [11].

Despite impressive results in both animal and human studies, neural electrode probes often exhibit poor temporal stability, limiting their long-term effectiveness [12]. As a result, there is intense research aimed at improving the temporal stability of implanted electrodes by mitigating both biotic and abiotic responses following implantation.

SiC addresses the issue of neural implant longevity, particularly regarding abiotic degradation. Indeed, abiotic failure in bioelectronic devices typically arises from degradation of insulating films and delamination at conductor–insulator interfaces. Neural interfaces, which are typically composed of structural materials, metallic conductors, and polymer insulators, are susceptible to in-vivo device degradation due to surface chemistry incompatibilities. SiC can meet all these requirements by adjusting its phase and doping to create all-SiC electrodes.

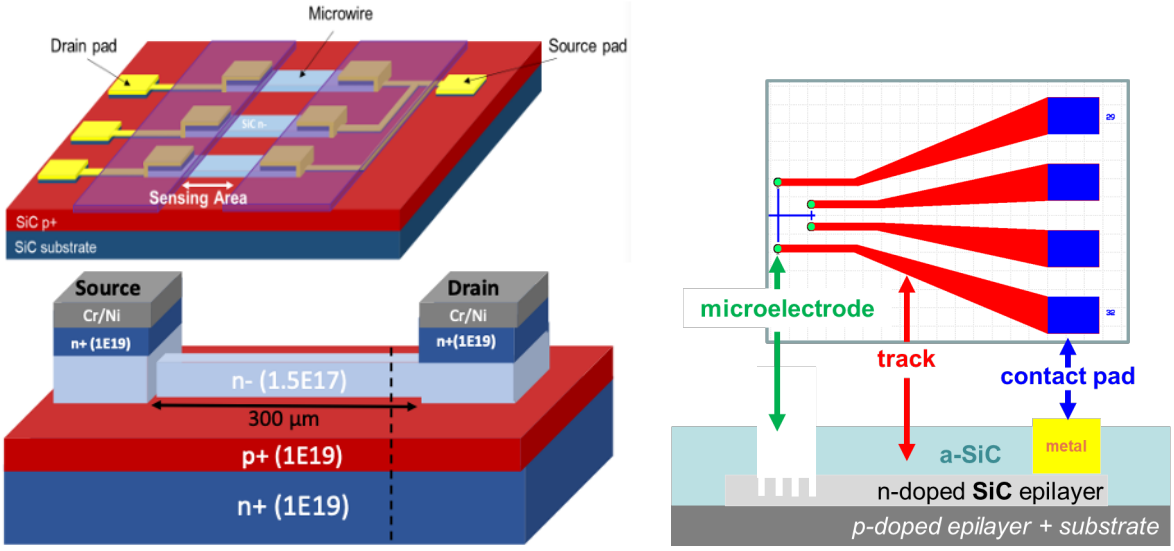
Biotic issues can be addressed using non-cytotoxic electrode materials that minimize inflammation and foreign body response (FBR). Strategies for reducing FBR include polymer electrodes that minimize stiffness mismatch with surrounding tissue [13], wireless interfaces, thin electrodes (<10 μm in diameter) [14], and optimized electrode packaging [15]. Despite the biocompatibility of popular packaging materials (Polydimethylsiloxane-PDMS, polyimide-PI), they often induce FBR because their surfaces lack ligands for cell adhesion receptors. In contrast, porous collagen-based scaffolds (PCS) interact well with neural cells, downregulate inflammation [16] and their stiffness (<1 kPa) matches brain tissue. PCS are biomaterials with major clinical applications in regenerative medicine

[16]. Moreover, PCS properties match key requirements (high stretchability & flexibility) for packaging electrodes.

Objective of the PhD work:

The **main objective** of the proposed PhD work is to develop SiC-based platforms and optimized grafting processes for the detection of "feel-good" hormones and cortisol, as well as for reducing the foreign body response.

Two different platforms will be initially used for studying the grafting processes. The 4H-SiC Ion Sensitive Junction FETs (ISJFETs) [17] (see schematic in Fig 1a) and the SiC electric detection cell [18] (see schematic in Fig. 1b).



(a) (b)

Fig.1. (a) Schematic of a single cel (bottom) and 3-cells 4H-SiC ISJFET. (b) Schematic of the cross-section of single electric detection cell (bottom) and top view of 4 cells (top).

The 4H-SiC ISJFET platform will be used to investigate novel approaches for immobilizing receptors targeting specific neurotransmitters (dopamine, serotonin, oxytocin, and cortisol), eliminating the need for covalent grafting onto device surfaces. Figure 2 schematically illustrates the proposed configuration. The specific objectives of this investigation (Platform 1) are as follows:

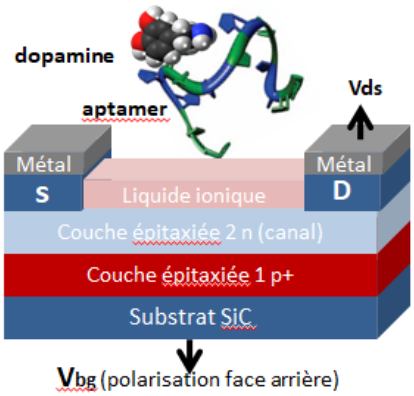


Fig.2. (a) Schematic of the 4H-SiC ISJFET with the ion liquid on the front gate and the aptamer serving as dopamine receptor.

1. Ensure the adhesion of an ionic liquid film (1–5 µm thick) on the device surface and verify its stability in physiological serum over periods ranging from 2 to 12 months.
2. Achieve dissolution and long-term retention of receptors within the ionic liquid film in the presence of physiological fluids for durations of 2 to 12 months, without undesired release.
3. Demonstrate reversible interactions

between receptors and metabolites (HBE and cortisol) within or in close proximity to the film surface.

4. Establish a quantitative field-effect response of the biosensor as a function of hormone concentration in model physiological fluids, specifically within the range of 10–100 nM for cortisol and HBE.

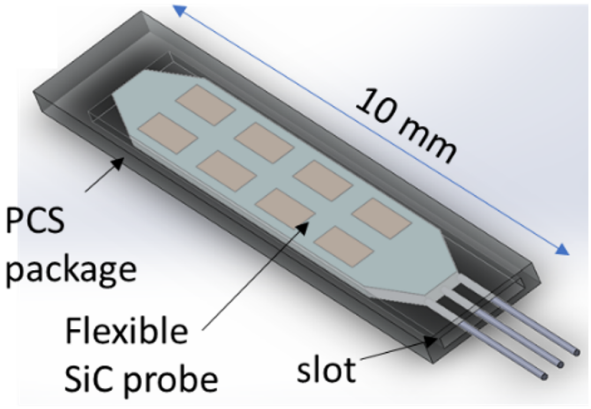


Fig.3. (a) Schematic of the 4H-SiC ISJFET with the ion liquid on the front gate and the aptamer serving as dopamine receptor.

The platform of electrically detecting cells (Platform 2) will be used to enhance the longevity of neural probes by simultaneously addressing the two main mechanisms that limit electrode stability following implantation in the central nervous system (CNS).

Abiotic stability: Avoiding delamination issues commonly observed in conventional electrode technologies by developing novel all-SiC thin, flexible electrodes.

Biotic stability: Minimizing the foreign body response (FBR) triggered after implantation by packaging SiC electrodes inside microfabricated porous collagen scaffolds (PCS), leveraging the ability of PCS to downregulate inflammation at injury sites.

The planned configuration is shown in Figure 3. The specific objectives are as follows:

1. Develop fabrication processes for SiC-based planar rigid and flexible electrode arrays.
2. Establish a packaging method for flexible SiC-based electrode arrays within microfabricated porous collagen scaffolds.
3. Quantify the long-term stability and cytotoxicity of PCS-packaged flexible SiC-based electrode arrays.

Achieving these objectives will enable the future development of long-life neural interfaces that integrate biosensors for detecting specific neurotransmitter levels (dopamine, serotonin, oxytocin, and cortisol).

Funding

The PhD student will receive a grand from LABEX GIMED (https://gimed.univ-grenoble-alpes.fr/).

International joint supervision:

A joint supervision agreement is envisaged between Grenoble INP – UGA and the University of Crete, Heraklion, Greece in the frame of a corresponding framework agreement already been put in place.

Involved researchers.

Prof. Edwige BANO, edwige.bano@grenoble-inp.fr

Dr. Olivier Lavastre, olivier.lavastre@univ-smb.fr

Dr. Valérie STAMBOULI, valerie.stambouli-sene@grenoble-inp.fr

Dr. Konstantinos ZEKENTES, konstantinos.zekentes@grenoble-inp.fr

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