

Fundamental and Transduction Limits of Nanobiosensors: An Sensors-to-System Perspective

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Background:

Biotechnology and bio-sensing are often mentioned as the next frontier of electronics that could rival semiconductor industry's broad and revolutionary impact on society. Since any disease is a signature of either a genetic defect or broken signaling pathways that occur far in advance of any overt signature detected by classical sensors, one of the grand challenges of modern bio-sensing is to find cost-effective, reliable, fast methods for gene sequencing (as an ultimate "Finger-print" of one's biological make-up and possibly early intervention for genetic anomaly) and the detection/identification of the irreducible and emergent protein networks for application in proteomics and system biology. Bio-sensors based on nanoscale electrical devices promise highly sensitive detection of bio-molecules unmatched by existing classical techniques.

Goals:

There have been numerous publications on various aspects of nanobiosensors since the 1970s. The two goals of our work were: 1) to create a coherent theoretical foundation for understanding the fundamental limits of nanobiosensors and 2) to develop the first end-to-end modeling framework for integrated nanobiosensors that translates the charge of biomolecules onto the response of variety of sensors.

What was accomplished?

Before the NEEDS program, our group had already established the three key parameters to quantitatively evaluate the performance of modern bio-sensors, namely, response time, sensitivity, and selectivity (see Figure 1, left column). Our key contribution was a deep and fundamental appreciation of the role of device geometry in defining the performance limits of nanobiosensors [1-4]. In other words, we provided a geometric-physical description of nanobiosensors. Based on the geometrical considerations of the relevant physical processes, we developed predictive models for sensor response and proposed design guidelines to optimize the performance. While the development of the models was supported from a variety of sources, NEEDS provided the critical resources to develop the compact models and make the software platform accessible to the community.

Contribution 1: Devices Physics of Potentiometric, Amperometric, Electromechanical Nanobiosensors.

One of our main contributions to the field is a systematic study of the device physics and performance limits of various types of electronic nanobiosensors that are in active development in various academic and industrial laboratories. Several examples are listed in Table below.

1) *Potentiometric Biosensors*. We proposed the application of simple planar structure with double-gated field-effect transistors (DGFETs) as potentiometric biosensors [5,6]. We considered the electrostatics of the system which involves nanoscale silicon body surrounded by top and bottom oxides, electrolyte biomolecules, fluid gate and back gate, etc. as shown Figure 1, column 2. We established the physics and scaling prospects of pH-based genome sequencers [7].

We explained various factors related to the scaling behavior of the pH-based genome sequencers, as well as the sequencing accuracy of homopolymers and the sequencing efficiency problem.

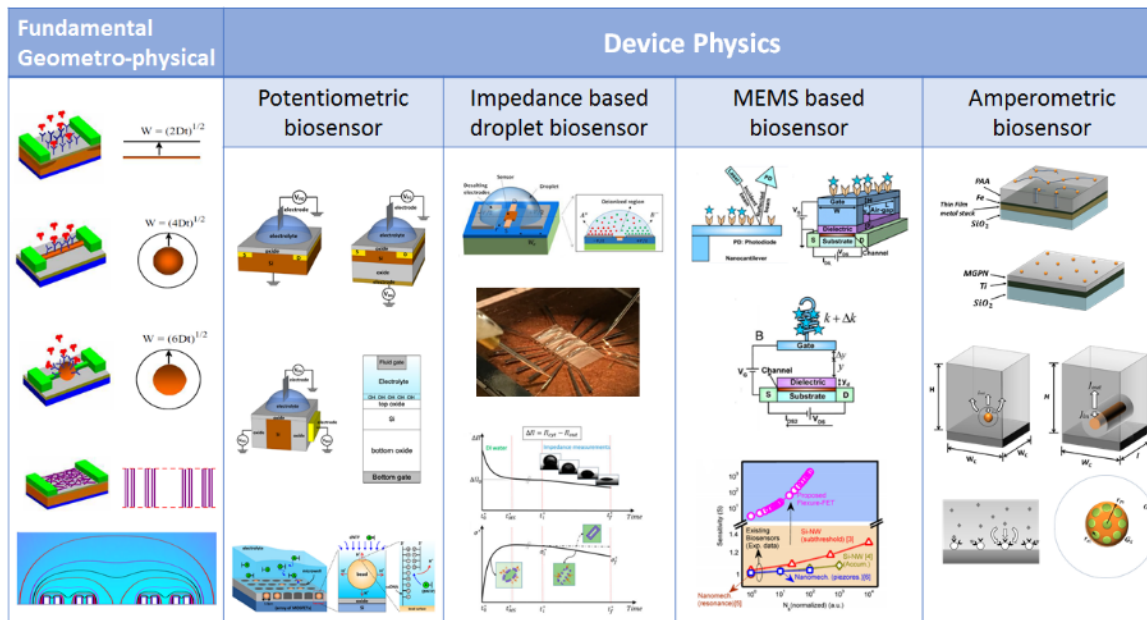


Fig. 1: (Left column) Fundamental limits of diffusion defines the detection limits of nanobiosensors. (Columns 2-5) Within the diffusion limit, the geometry and transduction physics define additional practical limits regarding the design/optimization of biosensors.

2) **Non-Faradic Droplet Biosensors.** We developed label-free, droplet-based biosensors, compatible with “open” digital microfluidic systems, see Fig. 1 column 3 [8-12]. The low-cost droplet-based biosensors overcome some of the fundamental limitations of the classical sensors, such as diffusion limit, response time, and screening, enabling timely diagnosis. By applying this droplet-based biosensor framework, we proposed a fundamentally different approach for label-free determination of bacterial viability based on stimulating their osmoregulatory response in an artificially created microenvironment.

3) **Electro-mechanical Biosensors.** We propose a Flexure-FET (flexure-sensitive field effect transistor) ultrasensitive biosensor that utilizes the nonlinear electromechanical coupling to overcome the fundamental sensitivity limits of classical electrical or mechanical nanoscale biosensors [13]. The extremely high sensitivity of Flexure-FET breaks the fundamental limits of linear or logarithmic sensitivity of classical nanoscale electrical or mechanical biosensors.

4) **Amperometric Nanobiosensors.** We studied the physics of amperometric glucose sensors with nanoparticle(NP) electrodes [14]. This type of biosensor promises fast and highly sensitive detection of glucose concentration in both in-vivo and in-vitro applications. We developed physics-based analytical model that captures the functional dependence of the parameters of an NP glucose sensor. The model facilitates predictive design and optimization of NP-based amperometric biosensors that can eventually be integrated into wearable platforms. The compact models and simulation tools related to these biosensors are posted at BiosensorLab and as compact models at the NEEDS website.

Contribution 2: System Integrated Nanobiosensors. Once the sensors have been developed, their ultimate performance must be evaluated within a system’s context, see Fig. 2 [15]. Specifically, we explore two issues of implantable biosensor applications: biocompatibility and

fluid-stability. As shown in Fig. 2 (top right) Hydrogel-based sensors address the challenge of biocompatibility by using hydrogels as the sensor materials. We have developed numerical and analytical frameworks for Hydrogel-based sensors. The model shows that there is a fundamental tradeoff between the performance parameters, i.e., sensitivity/dynamic range versus response-time/response-asymmetry in hydrogel sensors under constrained swelling conditions. For implantable biosensor fluid-stability problems (Fig. 2, bottom right), we have developed an analytical framework and scaling theory for the design of encapsulation layer of wearable and implantable electronic devices [16]. The model suggests optimum design such as a bi-layer or tri-layer encapsulation design for multi-objective protection, see Fig. 2.

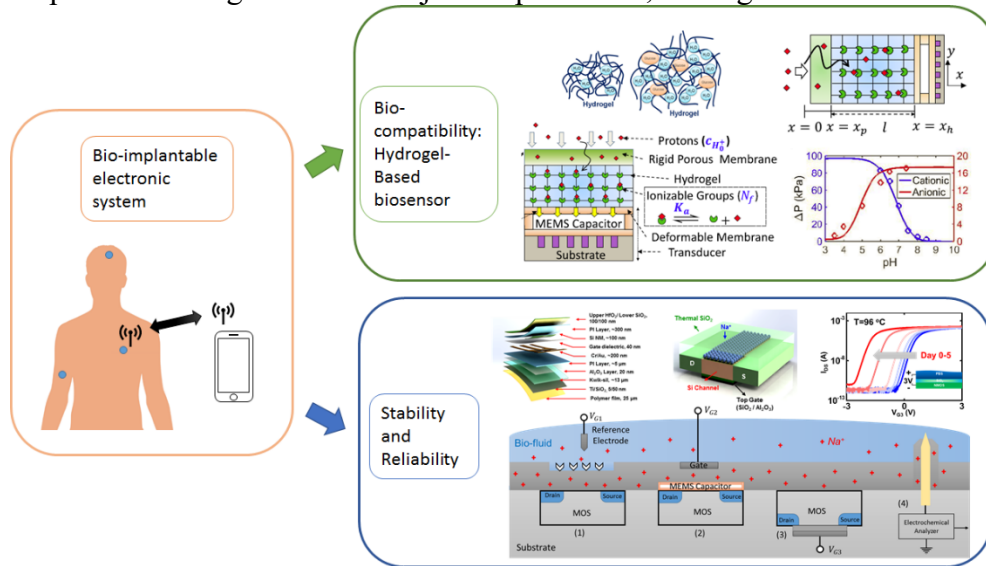


Fig. 2: Implantable/wearable electronics (left) must simultaneously be biocompatible (top right) and immune to the harsh microfluidic environment (bottom right). The model developed by Alam group have answered fundamental questions related to the physics of both problems.

Why was it important?

The contributions discussed above have had significant impact. Before our work in 2006, there were many reports in the literature that appeared to violate the fundamental diffusion limit. Since the creation of the theoretical foundation, today readers and reviewers are aware of the limits and the papers today seldom contain results that are inconsistent with diffusion limit. A course on “Principles of Nanobiosensors” have been created and have been taken by thousands of students. A related simulation tool called BiosensorLab [17] has been posted. The tool can be used to calculate the fundamental limits, as well as the practical response limits associated with the sensors. Finally, a set of Verilog-A tools have been posted at the nanoHUB site so as to facilitate system design [18, 19]. The tool has been downloaded by many groups across the world. The system integration provides the next fundamental challenge for modern nanobiosensor, especially in the context of electroceuticals. We look forward to the continued opportunity to contribute to the field.

References. (* denotes work supported or partially supported by NEEDS)

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