Progress in Biosensor and Bioelectronics Simulations: New Applications for TCAD

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Abstract— **Scaling of devices in the semiconductor industry has reached an extremely impressive level; electronic device dimensions are approaching atomic scales and can also have dimensions comparable to many biological microstructures. In this paper, we present an overview of the new challenges in modeling electronics that interface with and bridge into the domains of biotechnology. In particular, we will discuss the applications of conventional integrated circuits technology computer-aided design (TCAD) in these new and emerging areas. Furthermore, we will examine the unique modeling requirements of biosensors in molecular identification and quantification applications. As we will discuss in this paper, there are exciting research challenges for the electronics community—new opportunities to leverage lessons learned from scaling.**

Keywords-Bio-TCAD, biosensors, affinity-based detection, nano-pore, charge-based sensing, noise

I. INTRODUCTION

Scaling of IC technology has reached impressive levels of functional density (>10^8 devices/cm^3) where individual solid-state device dimensions are approaching atomic scales (transistor sizes comparable to the size of virus molecules). In concert with the ongoing (Moore's Law) scaling of conventional IC technology, there has been the emergence of biological-centric applications which try to leverage the capabilities of IC micro-fabrication technologies, to address the needs of the existing biotechnology devices and systems. For example, there has been a significant push in the area of high throughput molecular screening, using microarrays of sensors [1]. At the same time, the atomic-scale patterning and device fabrication capabilities have generated nano-pore structures [2] as well as nano-tube and nano-wire [3] devices, with potential applications for single or few molecules sensing. This diversity of sensor structures provides two extremes: (1) devices which detect a large ensemble of biological events, and (2) devices which can observe single biological events.

It is beyond the scope of this paper to present a comprehensive review of the biosensing landscape and the associated modeling approaches. However, it is useful to consider initially the implications of the goal of the biosensors on the sensing approaches before delving deep into the specific examples of modeling that implement conventional TCAD techniques. We will first highlight biosensing applications from a high level perspective and subsequently narrow down our focus onto specific sensing techniques such as direct electrical sensing of bio-molecules. Finally, specific case studies will be used to illustrate various modeling approaches. Additionally, some comparisons will be made between the emerging biological sensing applications and conventional TCAD solutions for IC scaling.

II. BIOSENSING APPLICATIONS – THE BIG PICTURE

The scope of the biosensing applications considered in this paper can be visualized as shown in Figure 1. From the organism level downwards the organs and tissue levels are on scales ranging from μm to mm which can be analyzed using direct observation techniques (e.g., microscopy and other conventional imaging techniques). The sensing applications considered in this paper focus on bio-molecular detection at dimensions where direct observation is not feasible and are comparable to IC solid-state device dimensions.

If we consider the individual bio-molecule concentrations per sample volumes (ml), many of the targets of interest for medical diagnostics and screening applications have extremely low abundance. For example, bacteria in the blood can be less that 10 per ml and food poisoning agents can be less than one per ml. Other bio-threat agents after extraction, purification, and enrichment have sometimes concentration levels of less than 100 per ml [4].

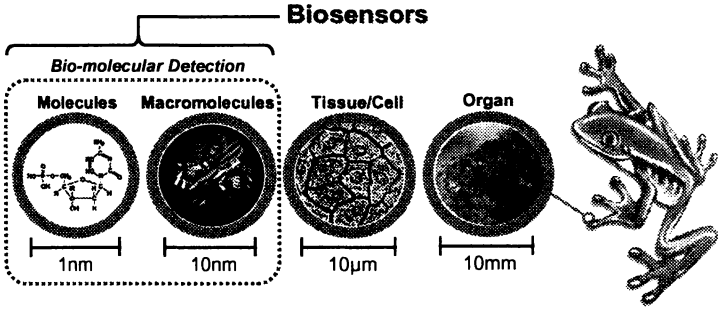

Figure 1: Associated length scales of biological structures. The focus area of biosensors is indicated which emphasizes on bio-molecular detection.

From a systems perspective, sensitivity levels for three classes of sensor-based platforms are of broad interest: spectroscopy (e.g., nuclear magnetic resonance (NMR) spectroscopy) >10^{-8} M; high-throughput screening (e.g., DNA microarrays) with sensitivities in the range of 10^{-12}-10^{-8} M; point-of-care (PoC) molecular diagnostics <10^{-12} M. The first two areas are well established commercially. For example, microarray technology now plays a major role in high throughput screening applications in Genomics and Proteomics

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[1]. The third area faces many research challenges and at the same time, PoC integrated biosensors offer the most potential.

Biosensors implement various transducer structures using optical, electrical and other more specialized and hybrid structures [5]. The physical scale for these sensors ranges from micoarrays, where a large ensemble of analytes are detected in parallel to nano-scale, single-analyte detection schemes such as nano-pore sensors. Additionally, there is a diversity of sample preparations techniques including: separation, to control the range of analysis; labeling, attaching extrinsic reporter structures (labels); and target amplification. This range of sensing techniques and sample preparation in view of the physical scales and diversity of sample types, provide an exciting yet challenging venues for modeling.

Figure 2 illustrates the flow of information in biosensor systems. For a specific application, the information flow goes from biophysics, sensing and transduction to the electrical domain where analog-to-digital conversion (ADC) and digital signal processing (DSP) brings the results into the level of bioinformatics. The domains of biophysics which includes the biosensor assay is a rich area of research and the recent discoveries in biotechnology has inspired the development of new methods and deeper understanding of the associated physical and sensing limits [6]. On the side of sample-handling (including preparation) processes has evolved dramatically over the past decade, owing to BioMEMS and other fluidic handling technologies [7]. Our focus in this paper is specifically on the transduction and sensing and the interface between the biology and the electronic domain.

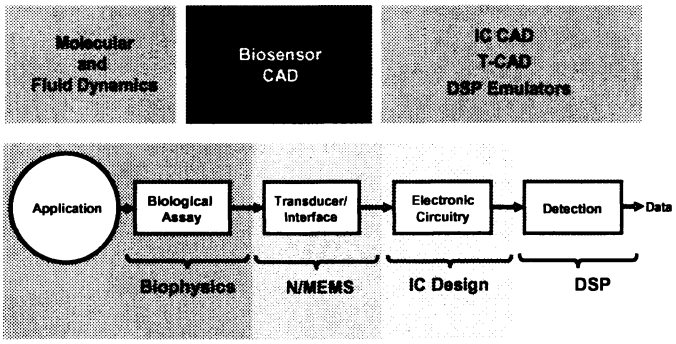

Figure 2: The flow of information and the associated functional blocks in biosensors.

III. Sensing and Transducing – The Nano-Scale View

In going from biophysics to sensing and transduction, a key concern is signal-to-noise ratio (SNR) which determines resolution and accuracy of the biosensing applications. Different sensing methods (e.g., microarrays or pore) have different noise contributors and hence different SNR characteristics. In Figure 3, we show a schematic of an affinity-based biosensor in the incubation step where the sensing area and number of captured analytes determines the signal strength. The attachment process takes time and is essentially a stochastic random process, which in itself contributes noise and uncertainty to the measured signal.

Another example of important biosensor systems is the nano-pore device which detect analytes passage through the structure by detecting the change in the channel electrical characteristics. These devices, depending on the application, can range in type and size (for both natural to artificial types) with scales from nano-meter (nm) to multi-nm. At the nm scales, both for natural and artificial pores, the transport of analyte is geometrically constrained and the analysis methods must consider statistical, stochastic behavior. At the larger, but still nm-scale, pore sizes the physics can in fact be treated with continuum-scale models and the issues of noise and other parasitic effects become a major concern. Three examples are shown below that illustrate these trends and differences.

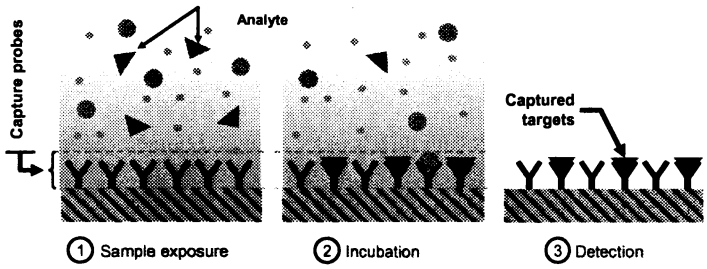

Figure 3: An affinity-based biosensor element in a sensor array where sample if exposed to the capturing probes and after incubation, the captured analytes are detected.

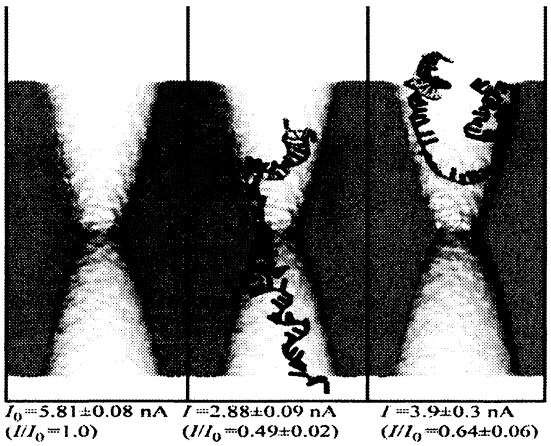

Figure 4: Molecular Dynamic (MD) simulations that give current flow (I_O), as a function of the bio-molecule and relative geometric configuration within the nano-pore [8].

Figure 4 shows modeling results for state-of-the-art nano-fabricated pores (1.5nm<d<2.3nm) where nucleic acid hairpins are passed through the pores that result in measured changes in the observed current ratios (I/I_O) [8]. The experimental results and atomistic-level simulations, using molecular dynamics (MD), are used to understand the electro-mechanical properties of the hairpins, including differentiation of the secondary structure.

All-atom MD simulations are usually computationally expensive, which prohibits simulations of large structures and they require long computation times. Enhanced Monte Carlo (MC) techniques such as Bio-MOCA [9] can remedy this by making reasonable physical approximations. The particle and stochastic nature of ion transport is still maintained. An

example in Fig. 5 shows a large natural ion channel, found in Escherichia coli (E. coli) bacteria; the channel gates in response to changes in membrane tension, protecting the E. coli cell from hypo-osmotic shock. Based on conformation information simulated with MD, Monte Carlo simulations provide 3D maps at slices along the channel transport direction, showing voltage and ion distributions; results indicate a strong separation of anion and cations through the channel. [9].

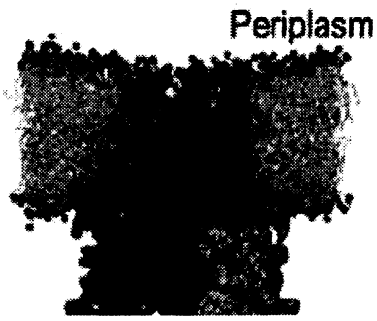

Figure 5: View of a large ion channel found in E. coli bacteria. Ion transport through the channel is analyzed using Bio-MOCA; results are given in detail elsewhere [9].

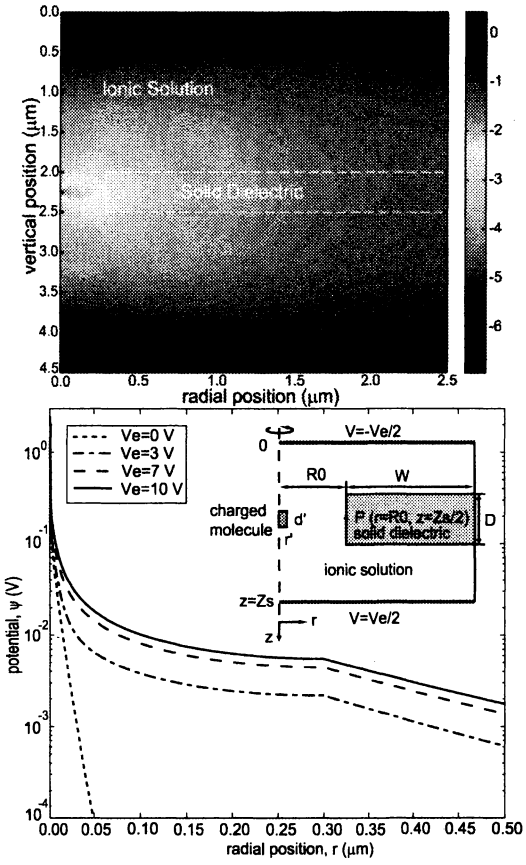

Figure 6: Contour plot of electrostatic potential change (a) for a 0.3μm nano-pore due to charge located at the center (axis of symmetry). Simulations use the PNP model; 1D slice of potential (b) compares results with and without current flow; details of the results are reported in [10].

The third example illustrates the use of larger nano-pores (R~300 nm) for charge-sensing at single molecular level. The relative large pores enable integration with sensing electronics. In this case, the continuum-based Poisson-Nernst-Planck (PNP) equations are applicable to model the ionic current flow. The introduction of current flow is found to dramatically suppress the counter-ion screening effect, and make long-range charge sensing possible [10]. Figure 6a shows a plot of potential change about the axis of symmetry due to a charge located at the center of the pore. In the presence of current flow, an appreciable amount of induced potential reaches the solid dielectric where the charge sensors can be placed. Figure 6b shows the potential in the radial direction at a slice through the charged molecule; several bias voltages are shown, including zero bias where screening makes the potential fall off extremely rapidly. Depending on the pore size and ionic solution concentration, the expected range of detectable signals is on the order of 1-10mV.

The above three examples illustrate interesting and important modeling challenges for biosensing at the nano-scale; the first is based on alteration of current flow in very small pores (~1-2nm); the third demonstrates that charge sensing appears to be possible in much large artificial pores. The use of charge sensing is fundamental to mainstream electronics—analog, digital, logic and memory. It would be interesting to see more simulation studies of bio-sensor systems that self-consistently treat both the sensing front end and the integrated electronics. Sensitivity limits in electronics and bio-sensing are set by the respective noise floors. While both domains face limits due to parasitic capacitance as well as leakage currents, the issues related to noise in bio-sensing applications are unique due to the aqueous and conducting solution environment.

IV. Noise in Biosensor Applications

Modeling of noise for biosensor applications ranges from that of attachment-related considerations for affinity-based sensors to device-level noise contributions (i.e. thermal, shot- and 1/f noise) for nano-pore sensors. As noted above, compared to conventional electronics, the biosensors are in conductive, aqueous solutions where most targets have finite charge and mobility. Fundamentals of noise modeling in such systems have been summarized in an earlier publication [11]. It is useful to highlight some of the effects since they impact scaling considerations for bio-sensors and can motivate further study—much is still to be learned and modeling for biotechnology applications.

For a wide range of interfaces in aqueous solution the drift-diffusion (DD) formulation for multi-species ions controls the behavior. Two different cases are of interest: faradaic (reactive, with current flow) and nonfaradaic (no dc current at the electrode). Figure 7 shows the nonfaradaic case with multiple ions species present in the double layer which result in net charge distributions that lead to observed capacitance. Based on detailed consideration of these models it is possible to extract compact models for capacitance as well as noise behavior [11].

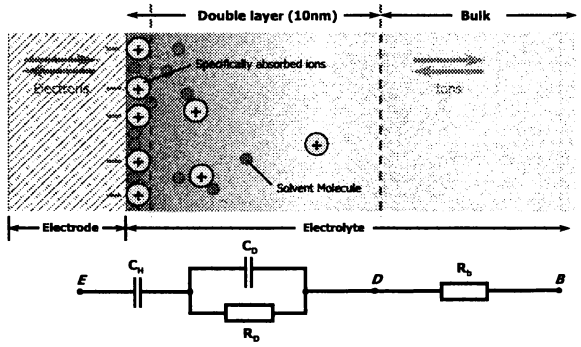

Figure 7: Model of nonfaradaic electrode ion and charge distribution in the double layer [11].

The extraction of capacitance and its scaling behavior with size and sensor geometry is one key application area. The issues of noise contributions and their spectral behavior are another important area for modeling. Generally speaking the down-scaling of electrode sizes results in increased noise levels. In addition, in the faradaic cases, where there are non-equilibrium current flows present, the frequency-dependent behavior is more complicated than for the nonfaradaic cases, since the diffusive-reactive properties involve ions with different mobility.

Noise in affinity-based sensors has many interesting properties, beyond the aforementioned issues. The statistical fluctuations occur related to the transport and binding processes are generally modeled using homogeneous and inhomogeneous Markov chains [12-13]. This approach provides key insight that helps to address SNR, response time, and linearity of the biosensor (i.e., saturation level). Typical modeling results are shown in Figure 8 where the number of captured analytes is plotted versus time. In this example, MC analysis is used as the benchmark for determining the bounds on uncertainty. Implications of this modeling work are the ability to project noise figure (NF) as well as dynamic range (DR) between minimum and highest detectable signal levels [12].

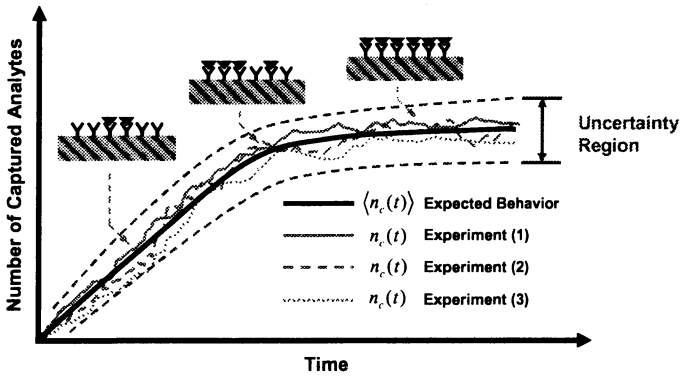

Figure 8: Number of captured analytes versus time for an affinity-based biosensors. The uncertainty reflects stochastic behavior, using simulated experiments (1-3) with Monte Carlo (MC) analysis [12].

The above examples of noise modeling are only representative of a diversity of approaches and application drivers. In the final analysis it will be higher-level figures of merit (i.e. SNR, NF, DR etc.) that will determine the performance in new biosensor systems. Moreover, in contrast to purely electrical systems where the noise sources are comparatively well-known, in this new application space, there are still many new things to discover, understand and model. In addition, the means to resolve, partition, and represent the components of noise is an ongoing challenge. In short, the areas of noise modeling and signal detection and calibration provide a broad vista for research in the biosensor area.

V. DISCUSSION AND SUMMARY

Biosensor applications involve a range of interesting device (bio-) physics; the cross-over between TCAD and Bio-TCAD can leverage decades of development of existing tools and techniques. Additionally, there are many new physical effects (and unknowns) that provide excellent research challenges. This paper highlights only a few examples from a very rapidly growing field; in contrast to digital IC end-of-the-Roadmap scaling, biosensors and bio-electronics will opportunistically exploit devices at all scales—from nano- to mesoscopic to macroscopic.

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