Integration, Models, and Circuits for Silicon-based Chemical/Biological Sensors

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Acknowledgments

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Background

Biological sensor field-effect transistors (BioFETs) are of interest for point-of-care medical diagnostics. Rapid detection of DNA, proteins, viruses, etc.

Charged species can be detected by replacing the gate of a traditional MOSFET with an electrolyte solution.

In affinity-based sensors, the insulator surface is functionalized with receptor molecules. Ideally, no chemical modification of detection species is required (label-free).

Numerous applications have been demonstrated, but current versus time measurements say little about whether this technology is feasible.
Background

- Proteins contain amine (-NH$_2$) and carboxyl (-COOH) groups that become charged based on the pH of the electrolyte.
- Combined charges on these amino acids result in a net charge of the biomolecule.
- Attachment of biomolecules to receptors forms a semi-permeable charged membrane. This may take some time (up to ~1000 seconds) depending on device geometry and reaction rate constants.
Reliability – Effect of pH

Reliability test in buffer solution show long chains more reliable

Stability – Effect of Mobile Ions

Procedure:
1. Expose sample to Na- and K-based pH solutions
2. Clean with solvents and DI water
3. Dry and measure

- Na ions enter oxide and cause hysteresis
- K ions do not cause hysteresis
- SAMs protect oxides from ion contamination

Circuit Design

Differential pair amplifier with output $\Delta V_{out} = V_{out2} - V_{out1}$

- Sensor_ref does not respond to target analyte, while sensor does
- Back gate and electrolyte are tied in each device
- Noise due to electrolyte, binding events, etc. shows up in $\Delta V_{out}$
SPICE Macromodel for BioFET

- FET model is BSIM-IMG
- Surface potential is calculated using analytical equations

Biotin-Avidin

<table>
<thead>
<tr>
<th>Protein Concentration (Nm/cm³)</th>
<th>Salt Concentration (M)</th>
<th>Δψ₀ (Hideshima) (mV)</th>
<th>Δψ₀ (UTD) (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6x10⁻¹⁸</td>
<td>0.1M (1xPBS)</td>
<td>0.930233</td>
<td>0.4</td>
</tr>
<tr>
<td>1.3x10⁻¹⁹</td>
<td>0.01M (0.1xPBS)</td>
<td>31.6279</td>
<td>24.4</td>
</tr>
<tr>
<td>2.8x10⁻¹⁹</td>
<td>0.001M (0.01xPBS)</td>
<td>111.86</td>
<td>99.7</td>
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</tbody>
</table>


DNA

<table>
<thead>
<tr>
<th></th>
<th>Immobilization Δψ₀</th>
<th>Hybridization Δψ₀</th>
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</thead>
<tbody>
<tr>
<td>Uslu</td>
<td>4 mV</td>
<td>5 mV</td>
</tr>
<tr>
<td>Model</td>
<td>10.4 mV</td>
<td>9.1 mV</td>
</tr>
</tbody>
</table>


$N_m$ Versus Concentration

In steady-state, membrane charge density as a function of analyte concentration depends on reaction rate constants.

If $N_m=3e18 \text{ cm}^{-3}$, detection limit is $\sim 1\text{pM}$ for biotin-streptavidin, and $\sim 10 \text{nM}$ for DNA.
SPICE Model Characteristics

SPICE macromodel for biosensor FET responds to membrane charge $N_m$ (detection species attached to sensor surface)

Threshold voltage shift depends on (a) site-binding charge and (b) salt concentration

With realistic electrolyte concentrations and pH/site-binding charge, response to membrane charge $N_m$ is small

‘Ideal’ gate voltage bias for sensing is slightly above threshold; $V_G=0$ V used for all simulations
Noise Simulation Setup

Add 1/f noise to the gate voltage of each sensor FET.
Run transient simulation for each value of $N_m$ and calculate average $\Delta V_{out}$.
Each data point is a single transient simulation (with unique noise signals)

The minimum measurable concentration depends on the noise level.
Detection Using Neuromorphic Hardware

- Neural networks perform efficiently at tasks involving pattern recognition and classification in large datasets.
- A biosensor microarray with a large number of surface functionalizations would provide a large set of imprecise and noisy data.
- Neurons may naturally perform auto-zeroing or sampling-like noise reduction.

Alternative architectures for sensor signal detection on alternative substrates

A two-neuron network connected with a memristive synapse exhibits average firing rate Hebbian learning rule. But there is also some dependence on spike timing (phase) if the input signals are noisy sinusoids. Exploit this property for biosensor signal detection.

Detecting Phase Shift

If one or two sinusoids are phase-shifted or their frequency is altered, the network recognizes the signal is different from the general population, and increases the synaptic weight.

Apply phase shift modulation to noisy sinusoidal input that is a function of biosensor signal.
Detecting Biosensor Signals

3.5 μA to 4.5 μA sensor drain current corresponds linearly to 0-360° phase shift

\[ N_m \approx 1 \times 10^{20} \text{ cm}^{-3} \]

\[ N_m \approx 3 \times 10^{18} \text{ cm}^{-3} \text{ level is detectable in about 100 s} \]

\[ N_m \approx 5 \times 10^{18} \text{ cm}^{-3} \]

\[ N_m \approx 4 \times 10^{17} \text{ cm}^{-3} \]
Conclusions

• Numerous applications of biosensors have been demonstrated, but current versus time measurements say little about technology feasibility.

• Reliability and stability are the key integration challenges.

• Circuit level models provide key insights into system limitations. Simulation is much faster than experiment and can help narrow experimental matrices/conditions.

• Adaptive analysis schemes (e.g. neuromorphic) on alternative substrates (e.g. flexible) may hold long term promise for detecting noisy, drifting signals from 1000s of sensors.