Multi - Scale Modeling and Simulation of Field-Effect Biosensors

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Abstract

BioFETs (biologically sensitive field-effect transistors) are field- effect biosensors with semiconducting transducers. Their device structure is similar to a MOSFET, except that the gate structure is replaced by an aqueous solution containing the analyte. The detection mechanism is the conductance modulation of the transducer due to binding of the analyte to surface receptors. The main advantage of BioFETs, compared to currently available technology, is label-free operation. We present a quantitative analysis of BioFETs which is centered around multi-scale models. The technique for solving the multi-scale problem used here is the derivation of interface conditions for the Poisson equation that include the effects of the quasi-periodic biofunctionalized boundary layer. The multi- scale model enables self-consistent simulation and can be used with any charge transport model. Hence it provides the foundation for understanding the physics of the sensors by continuum models.

1 INTRODUCTION

BioFets (biologically sensitive field-effect transistors) are field-effect biosensors with semiconductor transducers. Their structure is similar to that of mosfets (metal-oxide-semiconductor field-effect transistors), but the gate structure is replaced by a biofunctionalized surface layer in an aqueous solution and an electrode (see Fig. 1 for the structure of a nanowire BioFet). BioFets are an emerging nanotechnology that have the potential to revolutionize biosensing. Recently experiments with BioFets based on silicon nanowires have been published, where their selectivity and high sensitivity was demonstrated [2] ,[8], [14]. In a further experiment, silicon-nanowire sensors were fabricated in a CMOS - compatible (complementary metal oxide semiconductor) wet-etch process [13] which supersedes the labor-intensive assembly of nanowires previously fabricated in the vapor-liquidsolid growth mode. The main advantage of BioFets is label-free operation, whereas currently available technology works by first labeling the analyte with, e.g., fluorescent or radioactive probes and then applying appropriate detection techniques. Label-free devices simplify analyte preparation thus giving technical and economic advantages. Due to label-free operation, further advantages are (near) real-time operation and high sensitivity.

The BioFet concept is also a very general one: sensors for various classes of biomolecules have been demonstrated by functionalizing the surface of the transducer suitably. To detect ssDNA (single-stranded deoxyribonucleic acid), the transducer surface is functionalized with immobilized complementary ssDNA strands; this enables, e.g., the detection of single-nucleotide polymorphisms. To detect various proteins as, e.g., tumor markers, the transducer surface is functionalized with monoclonal antibodies.

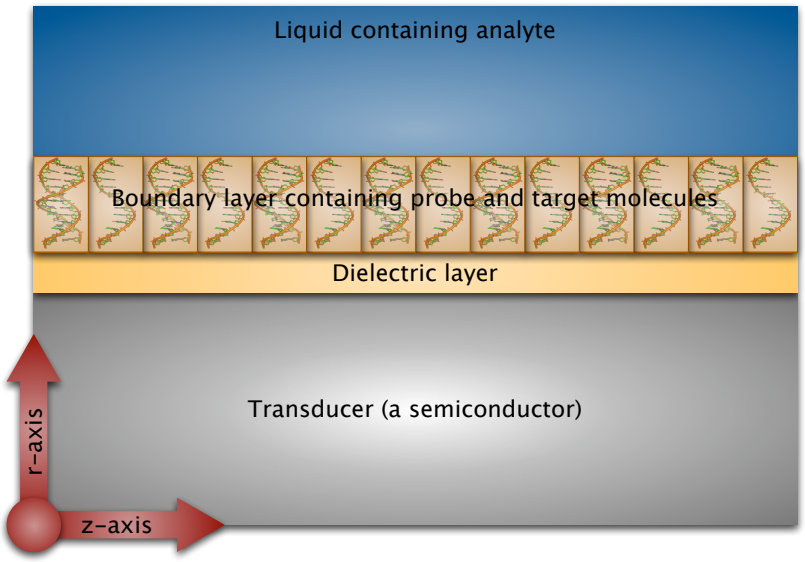

Figure 1: Schematic diagram of a nanowire BioFet. In a DNA-sensor, shown here, the immobilized probe molecules are ssDNA (single-stranded deoxyribonucleic acid) and the target molecules are the complementary strands. After hybridization of the two strands at the sensor surface to form dsDNA (double-stranded DNA), the charge distribution in the biofunctionalized boundary (or surface) layer is changed and modulates the conductance of the semiconductor transducer. The conductance is measured between the two contacts on the left and on the right.

BioFets have been reproduced by different groups and there are now good experimental indications that the sensing mechanism is indeed a field effect [4], i.e., as analyte molecules bind to the immobilized probe molecules in the surface layer, the charge distribution changes and modulates the conductance of the semiconductor transducer similarly to the effect that a change in gate voltage has on a MOSFET. Although consensus has been reached among experimentalists that a field effect is measured, the functioning of BioFets has not been understood quantitatively [7],[10], [11] , [12]. The modeling and simulation of BioFets is complicated by several facts. First, two systems must be coupled, namely a biological system, i.e., the biofunctionalized surface layer with the analyte in the aqueous solution containing ions, and an electronic system, i.e., the semiconductor transducer. The electrostatics of the biosensors must be calculated self-consistently, and especially the electrostatics of the biofunctionalized surface must be taken into account. Second, the modeling of BioFets poses a multi-scale problem. The diameters of the biomolecules are in the nanometer range; for example, the diameter of the double helix of b-DNA oligomers (which is the DNA conformation generally found in aqueous solutions) is 2.0nm and each nucleotide unit is about 0.34nm high. The spacing between DNA strands on a functionalized silicon-oxide surface has been measured to be between ca. 3nm and ca. 10nm [9]. Therefore the charge distribution and the electric potential in the vicinity of the biomolecules varies on the Angstrom or nanometer length scale. On the other hand, the length of the transducers, i.e., the distance between the two contacts of the sensors, cannot be smaller than a few dozen nanometers because of technical reasons and in experiments it is much larger, measuring hundreds of nanometers or a few micrometer. Hence at least four or five orders of magnitude of difference in length scale must be covered in simulations, and therefore existing device simulators with very large grids that resolve the fine structure of the biomolecules cannot

be used due to their computational cost.

In Section 2 we present an outline of a homogenization procedure, leading to an aggregate model on the length scale of the sensor which is numerically tractable. In Section 3 we verify the validity of the aggregate model on a test case and investigate the influence of the surface charges, produced by the DNA molecules, on the conductance of a nanowire.

2 A MULTISCALE APPROACH

One of the main problems in the simulation of BioFets is that we are presented with an inherent multiscale problem. That is, the part of the functionalized surface occupied by a single strand of DNA is of the order of $O(10nm^2)$ while the whole sensor surface is of the order of $O(10^4nm^2 - 10^5nm^2)$. We are therefore not able to resolve each DNA molecule on a computational grid covering the sensor surface. On the other hand, experimentally determining the precise location, state and orientation of each DNA molecule would be an impossible task anyway. The goal is therefore to develop an appropriate aggregate model which takes only some more global information about the state of the DNA strands as input and computes the electrical response of the sensor based on this global information. The key to this approach is a proper parameterization of the interface between the sensor and the liquid and a corresponding representation of the surface charges due to the biological molecules. In the following we give a sketch of the derivation of an aggregate multiscale model. We refer the reader to [6] for a more detailed analysis.

2.1 THE BASIC MODEL

The basic underlying model consists of the Poisson equation of the form

$$(a)\ \nabla_x \cdot (\varepsilon E) = n = n_V + n_{dna}, \quad (b)\ E = -\nabla_x V, \tag{1}$$

with $E(x)$ the electric field and $V(x)$ the electrostatic potential. The Poisson equation is posed on a domain $\Omega \subseteq \mathbb{R}^3$ which includes the sensor as well as the surrounding aqueous solution. The charges on the right hand side of equation (1) are split into a self consistent part $n_V(x)$, which is computed self consistently from a transport model (including a background densities due to the doping concentration inside the sensor), and a part n_{dna} which are the additional charges created by the DNA molecules and the probe molecules. The domain Ω is decomposed into $\Omega = \Omega_- \bigcup \Omega_+$ where Ω_- corresponds to the the sensor and Ω_+ corresponds to the aqueous solution. We denote the interface between Ω_- and Ω_+, i.e. the bio - functionalized surface, by $\partial\Omega_S$. The dielectric constant ε will be discontinuous across the interface $\partial\Omega_S$, and we have

$$\varepsilon(x) = \begin{pmatrix} \varepsilon_- & for & x \in \Omega_- \\ \varepsilon_+ & for & x \in \Omega_+ \end{pmatrix} .$$

The transport models used to compute the self consistent part n_V of the charges can, and usually will, be different in the sensor and in the solution. Depending on the size and geometry of the sensor, $n_V(x)$ will usually be computed from a drift - diffusion model or from a Boltzmann equation for $x \in \Omega_-$. In the solution, it usually suffices to compute n_E from a Poisson - Boltzmann model, i.e.

n_V is assumed to be a function of the exponential of the potential V. The transport models will require boundary conditions at the boundary $\partial\Omega$ as well as the interface $\partial\Omega_S$. Depending on the sensor geometry, these will consist of far field conditions for the solution and contact conditions for the parts of $\partial\Omega$ corresponding to the ground contact of the sensor. At the interface $\partial\Omega_S$ the boundary conditions are given by the fact that the interface can be assumed to be an insulator. The precise form of the transport model used to compute n_V is not relevant to the discussion in this paper. We refer the reader to [3], [4],[5], [6] for the details.

2.2 THE AGGREGATE MODEL

The key to developing a useful aggregate model is to parameterize the DNA charge n_{dna} in such a way that the model is amenable to a geometric coarse graining, while still retaining information about the microscopic charges and their geometry. We parameterize the two dimensional interface $\partial\Omega_S$ by a function $\Gamma(s)$, so

$$x \in \partial\Omega_s \iff x = \Gamma(s), \quad s \in \mathbb{R}^2$$

holds. At each point of the surface, there will be a tangent plane spanned by two orthonormal tangent vectors, forming the 3×2 matrix $T(s)$. In addition, there will exist a unit normal vector $N(s)$, pointing form the sensor domain Ω_- into the solution domain Ω_+. So, a local coordinate transformation will involve the orthogonal 3×3 matrix $(T(s), N(s))$, satisfying

$$(T(s), N(s))^{-1} = (T(s), N(s))^T, \quad det(T, N) = 1 \ .$$

The charges n_{dna} due to the DNA attached molecules are are concentrated close to the surface. We express this by using the local coordinate transformation $x \to (s, r)$ close to the surface, given by

$$x = \Gamma(s) + \lambda r N(s) \ . \tag{2}$$

Here, $\lambda << 1$ is a dimensionless geometry parameter, namely the ratio between the length scales of the DNA strands and the whole sensor. We make the following ansatz for the DNA charge density n_{dna}:

$$n_{dna}(\Gamma(s) + \lambda r N(s)) = \begin{pmatrix} \rho(r, \frac{s}{\lambda}, s) & for & r > 0 \\ 0 & for & r < 0 \end{pmatrix} \tag{3}$$

with ρ decaying to 0 for $r \to \infty$. The ansatz (3) has the following interpretation:

- The DNA charges are concentrated close to the interface, i.e. they decay with distance from the interface divided by λ.
- Along the interface n_{dna} varies rapidly (on a scale $\frac{s}{\lambda}$).
- Overlaying these rapid variations is a smooth $O(s)$ variation, arising from the dependence of ρ on the third variable.

In addition we make the assumption that neighboring DNA strands are similar. We express this by the assumption that the function $\rho(r, \eta, s)$ is periodic with period L in the second variable $\eta = \frac{s}{\lambda}$. So,

$$\rho(r, \eta + \begin{pmatrix} L \\ 0 \end{pmatrix}, s) = \rho(r, \eta, s), \quad \rho(r, \eta + \begin{pmatrix} 0 \\ L \end{pmatrix}, s) = \rho(r, \eta, s)$$

holds. This implies that, if we move a distance λL along the surface in the paremeter space, we obtain almost the same value for n_{dna}, except for the $O(\lambda)$ variation of ρ in its third variable. In practice, we will set

$$\rho(r, \frac{s}{\lambda}, s) = P_{bound}(s)\rho_{bound}(r, \frac{s}{\lambda}) + P_{unbound}(s)\rho_{unbound}(r, \frac{s}{\lambda}) \tag{4}$$

where $\rho_{(un)bound}(r, \frac{s}{\lambda})$ is the charge due to a DNA strand unbound or bound to a probe molecule, and $P_{(un)bound}(s)$ is the slowly varying probability that the DNA strand is bound at the site s.

The key to deriving an aggregate model is to replace the charge n_{dna} on a macroscopic scale by a point charge and a dipole. Computing the integral of n_{dna}, given by (3) against any test function gives

$$\int \psi(x) n_{dna}(x)\ dx = \int \psi(\Gamma(s) + \lambda r N(s))\rho(r, \frac{s}{\lambda}, s)|\frac{\partial x}{\partial r s}|\ dr ds$$

Because of the periodicity of the density ρ in the second variable, this integral can be replaced asymptotically by

$$\int \psi(x) n_{dna}(x)\ dx = \lambda \int |\frac{\partial x}{\partial r s}|[\psi(\Gamma(s)) + \lambda r N(s) \cdot \nabla_x \psi(\Gamma(s))][\int_{[0,L]^2} \rho(r, \eta, s)\ d\eta]\ dr ds + O(\lambda^3)$$

which can be written as

$$\int \psi(x) n_{dna}(x)\ dx = \int \psi(\Gamma(s)) C(s) + [\nabla_x \psi(\Gamma(s)) \cdot N(s)] D(s)\ ds$$

with $C(s)$ and $D(s)$ defined by

$$C(s) = \int_{[0,L]^2} d\eta \int_0^\infty dr\ \rho(r, \eta, s)|\frac{\partial x}{\partial r s}|, \quad D(s) = \lambda \int_{[0,L]^2} d\eta \int_0^\infty dr\ r\rho(r, \eta, s)|\frac{\partial x}{\partial r s}| \tag{5}$$

$C(s)$ is the charge density produced by a single (bound or unbound) DNA strand, averaged over one cell $[0, L]^2$ in the parameter space. $D(s)$ is the corresponding dipole moment in the direction orthogonal to the interface. Note, that the moment $D(s)$ in (5) provides geometric information about the orientation of the molecule, i,e, one and the same DNA strand will have a different moment density D, depending on its orientation relative to the surface.

So, in the averaging procedure the DNA charge density n_{dna} can be replaced asymptotically by the term

$$n_{dna}(x) \approx \delta(r) C(s) + \delta'(r) D(s), \quad x = \Gamma(s) + \lambda r N(s)\ ,$$

i.e. a point charge of strength $C(s)$ and a dipole of strength $D(s)$, and the homogenized Poisson equation (1) becomes

$$(a)\ \nabla_x \cdot (\varepsilon E) = n = n_V + \delta(r) C(s) + \delta'(r) D(s), \quad (b)\ E = -\nabla_x V, \tag{6}$$

In order to arrive at a tractable numerical problem on the macroscopic scale (the length scale of the sensor) the following steps have to be performed:

1. Find a parameterization Γ of the interface surface $\partial\Omega_S$.

2. Compute the charge and the dipole charge $C_{(un)bound},\ D_{(un)bound}$ produced by a single molecule in the bound and unbound state.

3. Compute the charge and dipole densities $C(s),\ D(s)$ from $C_{(un)bound},\ D_{(un)bound}$ and the binding probabilities $P_{(un)bound}$ according to (4) and (5).

4. Solve the Poisson equation (6) with n_{dna} replaced by the point and dipole charges of strength $C(s)$ and $D(s)$. (This means solve the self consistent problem with n_V computed from the transport model of choice in the sensor and in the liquid.)

Remark: Point number 4 of the above list can either be implemented by a direct numerical approach using a finite element discretization and a corresponding weak formulation of Poisson's equation. This allows for the direct evaluation of the $\delta-$ function and the dipole, since they are integrated against the test functions. Alternatively, we can reformulate the problem analytically by translating the $\delta-$ function and the dipole on the right hand side of (6) into modified jump conditions on the electric displacement εE and the potential V (see [6] for details). Using this formulation, the homogenized problem would be of the form

$$(a)\ \nabla_x \cdot (\varepsilon E) = n = n_V, \quad (b)\ E = -\nabla_x V, \tag{7}$$

together with the interface jump conditions

$$lim_{r\to 0+}(\varepsilon E)(x + rN(s)) - (\varepsilon E)(x - rN(s)) = -C(s),$$

$$lim_{r\to 0+}V(x + rN(s)) - V(x - rN(s)) = \frac{1}{\varepsilon_+}D(s),$$

Remark: Formally the strengths $C(s)$ and $D(s)$ of the point charge and of the dipole in (5) are of order $O(\lambda)$ and $O(\lambda^2)$ respectively. In order to produce a relevant contribution to the solution the DNA charge density ρ has to be of order $O(\frac{1}{\lambda}$ and $O(\frac{1}{\lambda^2})$ respectively, i.e. although the DNA charges are concentrated close to the surface they have to be much larger locally then then the self consistent charges n_V from the transport model. If this were not the case, then the sensor simply would not work, i.e. there would be no significant influence of the DNA strands on the response of the transistor. Note, that n_{dna} and ρ model the total charge of the DNA strand, i.e. the sum of the positive and negative charges sitting on the molecule. Therefore ρ will change signs. Therefore it is possible that, although formally there is a difference of $O(\lambda)$ in the magnitude of the two terms, they are actually of roughly the same size. This is the (practically relevant) case of a molecule which is almost externally charge neutral, but this neutrality is achieved by many large charges of different signs, distributed throughout the molecule.

3 SOME NUMERICAL RESULTS FOR NANOWIRE SENSORS

We apply the multi-scale model and the drift-diffusion equations to the numerical simulation of silicon-nanowire BioFets. For the simulations below the transport models used were the standard

drift - diffusion equations in the sensor domain Ω_- and a Poisson model in the liquid Ω_+. The nanowire is modeled as a cylinder with radius a sitting on a base plate. The parametrization of the interface, its normal vector and the volume element are given by

$$\Gamma(s) = \begin{pmatrix} a\cos s_1 \\ a\sin s_1 \\ s_2 \end{pmatrix}, \quad T = \begin{pmatrix} -\sin s_1 & 0 \\ \cos s_1 & 0 \\ 0 & 1 \end{pmatrix}, \quad N = \begin{pmatrix} \cos s_1 \\ \sin s_1 \\ 0 \end{pmatrix}, \quad |\frac{\partial x}{\partial rs}| = \lambda(1+\lambda r) + O(\lambda^3)$$

in this case. For simplicity we only consider the two dimensional case, so we compute cylindrically symmetric solutions of the drift diffusion equations and the Boltzmann - Poisson model. The electric potential of the electrode in the liquid and of the bulk liquid is assumed to be zero. This assumption is valid for small voltages applied to the electrode, since then the ions of the electrolyte screen the potential of the electrode and the bulk liquid is neutral.

We first verify the multiscale approach by placing a limited number of DNA strands on the surface and resolve them on a fine grid. Figure 2 shows the potential computed by resolving all DNA strands and and by employing the the homogenization procedure in Section 2. Since in experiments the

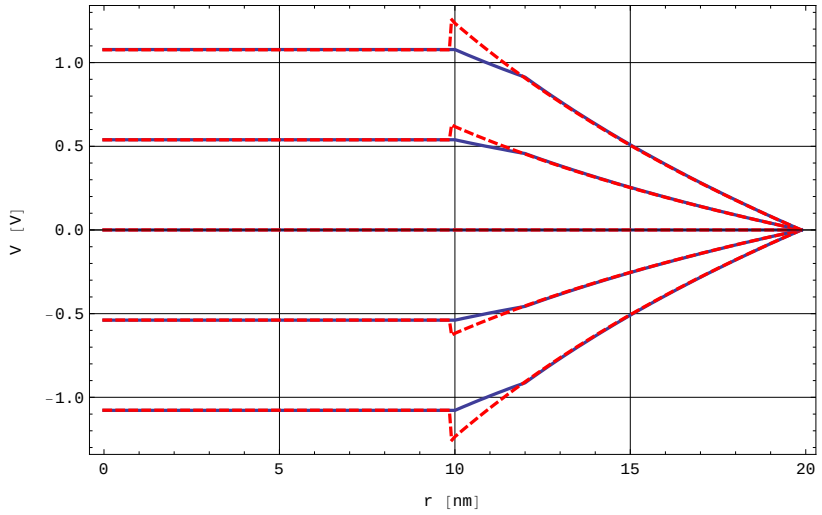

Figure 2: The electrostatic potential as function of radius. The grid spacing is $1/8nm$, $a = 30nm$. The blue, solid lines are solutions of the full problem. The red, dashed lines are the solutions of the homogenized problem

conductance (or resistance) is recorded and published, we calculate the specific conductance of the nanowires. The homogenization of the boundary layer has shown that the electric potential near transducer-liquid boundary and therefore in the transducer depends on a higher order parameter, namely the dipole moment density D of the biofunctionalized layer in addition to its surface charge density C. Hence the main question is how different values of C and D affect the conductance values and thus if the conductance measurements can be attributed to the field effect of target molecules. It can be argued that the charge density C of the cells in the biofunctionalized layer must (nearly) vanish because of the presence of counter-ions around the biomolecules and a reconfiguration of the electric double layer. Therefore the dipole moment of the boundary layer can provide the actual detection mechanism. In the following we therefore quantify the influence of the values of

C and D on the conductance. In one set of experiments [4], silicon nanowires with diameters from 5nm to 50nm and lengths from $1\mu m$ to $1000\mu m$ were fabricated and the relative resistance change after binding of target ssDNA strands was recorded. A maximum resistance increase of 250% was measured. Unfortunately many important sensor parameters, especially those pertaining to the biofunctionalized layer, have not been characterized in the recently published BioFet experiments. This is certainly due to the fact that proper characterizations of, e.g., the nanowires, the probe spacing, the electric double layer, the counter-ions, and the orientations of the probe and target molecules involve separate research projects each.

Figure 3 shows the specific conductance of a nanowire sensor as a function of the surface charge density C and the dipole moment density Dr of the biofunctionalized surface layer. The figure shows that both C and Dr have an exponential influence on the conductance. Therefore not only the total charge of the boundary layer modulates the conductance of the transducer, but its dipole moment as well. This numerical evidence shows that the conductance variations in nanowire BioFets upon binding of analyte molecules observed in experiments can be explained by a field effect. It also implies that higher-order effects, i.e., the influence of the dipole moment of the biofunctionalized boundary layer, must be included in models and simulations of field-effect biosensors.

4 CONCLUSIONS

The multiscale approach presented allows for the simulation of whole sensors at a reasonable numerical cost, while still incorporating the relevant features of the microscopic structure of the bio - molecules. The simulation results show that different orientations of the biomolecules with respect to the surface, i.e., different dipole moments, affect the conductance of the transducer significantly. This implies that the investigation of the orientations of biomolecules at charged surfaces requires attention. Depending on the electric free energy of the configuration, Brownian motion of the biomolecules may have great impact on the noise level of the biosensors and thus their sensitivity. This question is especially important for nanoscale sensors working at the detection limit.

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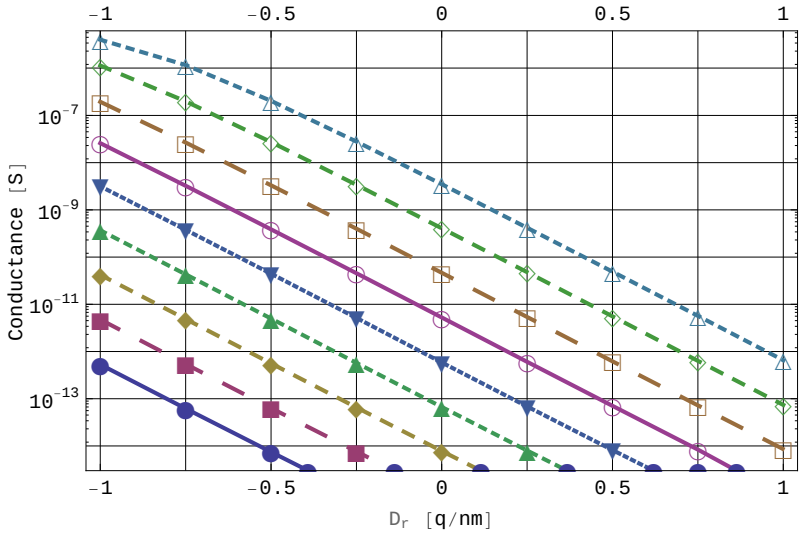

Figure 3: The specific conductance of a nanowire as a function of the dipole moment D_r for different values of the surface charge density C on a logarithmic scale. The bottom line (blue, solid line with solid circles) is for C $= -0.5q \cdot nm^{-2}$; the top line (light blue, dashed line with hollow triangles) is for C $= +0.5q \cdot nm^{-2}$; the lines in between correspond to steps of $0.125q \cdot nm^{-2}$. The nanowire is p-doped with $10^{16} q \cdot cm^{-3}$, it is 100nm long, the silicon core has a radius of 5nm, and the siliconoxide layer has a thickness of 2nm.

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