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Nano-Bio Interfacing with Living Cell Biochips

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3.1 Introduction

Biochips are micro-fabricated platforms that use either biological elements for detection, sensing, and monitoring, or use components interacting with biological material, for example, DNA or protein biochips that use biochemical components as part of the detection mechanism along with the support of electronics and electro-optical systems. Such chips may include also other micro-system technologies such as micro-fluidics or micro-electro-mechanical-actuators. Another example is a biochip that detects biological components, such as glucose or urea, using physical, electrical, or chemical effects.

A subset of the biochip-technology family is the whole-cell biochips (WCBC) technology. These chips are platforms that integrate cells as part of their operation. Until recently, the leading application for such technology was for environmental monitoring such as monitoring drinking water safety and checking for pollution hazards (Belkin 2003, Belkin et al. 1997, Mitchell and Gu 2004, Nivens et al. 2004, Hyung-Lee et al. 2005, Popovtzer et al. 2005, Elad et al. 2008, Li et al. 2008). These applications include the development of the biological part, the micro-system technology, and the integration, including cell storage and sampling methods (Bjerketorpet et al. 2006, Dejene et al. 2006). Based on the success of these applications, more applications emerged, such as cells monitoring for cancer (Popovtzer et al. 2006, 2007, 2008). We expect that more applications will emerge for whole-cell biochips in the near future, as their unique capability will be recognized and their technology will mature.

One key feature of the whole-cell biochip technology is that they interface the biology in a way that explores the cell response as a system (Daniel et al. 2008). Therefore, they are characterized by nonspecific functional sensing unlike most other sensors today that are target specific. The target for most common specific sensors can be a known molecule or a physical condition (i.e., pH, temperature of specific gas, etc.). The whole-cell biochip senses the functional response of the cell; thus, the information they provide is based on the cell system behavior. For example, whole-cell biochips that integrate microbes for water toxicity (English et al. 2006) answer the question "Is the water safe?" and not "Is there a specific toxin in the water?"

In this chapter, we present a simple model of the basic mechanisms of the whole-cell biosensor (WCBS) technology that uses living cells, integrated on a micro-fabricated platform, as the sensor elements. These chips can be classified according to (a) their mode of use and (b) mode of sensing. The mode of use defines two classes of whole-cell biosensors: (1) long-term use whole-cell biosensors and (2) short-term use whole-cell biosensors. The "mode of use" classification is based on the way the cells are handled prior to integration and their integration mode (Bjerketorpet et al. 2006, Dejene et al. 2006). Here are some details of the two classes of use:

1. Whole-cell biosensors for long-term usage—where cells are stored for long term, activated for their application,
and are used for various time lengths, either for one time usage or continuous sensing that may take days, weeks, or even months. These sensors are truly biosensors in the classical sense where biology is used for functional detection; that is, the cell’s functional response to external excitation is an intrinsic part in the detection process and the biology is part of the detection mechanism that also uses electronics and photonic circuits. Integrating living cells on a chip for long-term usage is not an easy task since both technologies use different materials and processes that may seriously interrupt one another. For example, processing chips requires aggressive cleaning and etching procedures and elevated temperature far beyond the limits of biology while the biological materials may include alkali metal contamination that is hazardous to semiconductor devices. Therefore, most whole-cell biochip technologies today first process the micro-system, then deposit the biology, and finally apply the sample. Also they are currently limited to prokaryotes with specific storage and handling procedures (Bjerketorpe et al. 2006, Dejene et al. 2006). It may be extended to eukaryotes, most likely yeast; however, it is a great challenge to integrate more complex prokaryote cells on simple biochips that are poorly equipped platforms for cell maintenance with limited supply of all the needed cell support. For this purpose, we need to develop an “incubator on a chip” that integrates all the “life support” for the cells.

2. Whole-cell biosensors for short-term use—in this type, the cells are placed shortly before the analysis is done. In this case, the issue of storage, handling, and care of the cells are separated from those of the biochips. The cells can be harvested shortly before application or stored for a long time under optimal conditions in larger and better-equipped facilities.

The mode of sensing is based on the way the information generated by the cells is converted and translated to electronic information. The mode of sensing classification is more complicated than the “mode of use” classification. In this chapter, we will try to define a unified method for that purpose.

A variety of biological assays has been devised for sensing, including colorimetric, fluorescent, bioluminescent, and electrochemical detection (English et al. 2006, Popovtzer et al. 2006, Daniel et al. 2008). The key issue is how to detect the cell response providing the desired information without affecting the cells’ viability and metabolism. Note, that we define whole-cell biosensor as a system that includes whole, alive, and functional cells, integrated with photonics and electronics subsystems. We do not consider here methods that break the cell membrane for “postmortem” interrogation of the cell response; we focus on systems that integrate live and functioning cells and explore their response.

Since typical enzymes and other large molecules do not penetrate the cell membrane, we need to use methods that “interrogate” living cells without compromising their viability. Here is a short list of such methods:

2. Find ways to penetrate the membrane using small-enough probes, for example, carbon nano-tubes, that will not cause damage (English et al. 2006)
3. Interface the membrane in a way that will allow the desired signals to be transferred from the cell to the external world (e.g., deposit metal dots on the membrane (Dagan-Moscovitch et al. 2007, Ben-Yoav and Freeman 2008, Vernick et al. 2008))
4. Interrogate molecules that are expressed at the membrane
5. Use remote methods such as
   a. Optical sensing detecting photo- and bioluminescence effects (Belkin et al. 1998, Belkin 2003)
   b. Electrical methods (such as impedance spectroscopy) that are sensitive to the changes of the dielectric constant inside the cells due to the cell response (Ron et al. 2008)

Another family of whole-cell biochips that is not discussed in detail in this chapter is using multielectrode arrays for neural electrical sensing. This unique application deserves special treatment. The coupling can be either with conducting electrodes, either in close proximity or penetrating, or using field effect devices (Fromherz 2008). So far, a coupling of living cells with electrochemical insulator semiconductor (EIS)-based field-effect devices has been utilized for recording the spontaneous or triggered action potential of some electrogenic cells as well as for cell-acidification detection only (Poghosian and Schöning 2007).

There are many cell-on-chip papers dealing with functional response. A sample of these papers appears in the references (Simpson et al. 2001, Choa 2004, Dalzel et al. 2002, Belkin 2003, Sagi et al. 2003, Mitchell and Gu 2004, Nivens et al. 2004, Sørensen et al. 2006, Poghosian and Schöning 2007, Polyak and Marks 2007). In this chapter, we focus on whole-cell integration where the sensing is due to the expression of proteins by the cells due to some external interaction. We will model the specific sensing equations, in the various cases, in a way that is similar to the modeling of electronic systems. We model the cell operations using a set of state equations with input and output. This approach will utilize the cell as another building block in the system allowing complete modeling using conventional engineering concepts (Daniel et al. 2008). This approach may be useful in the future for other applications such as using cells for biocomputing (Vera et al. 2007).

3.2 System Description

The schematic block diagram of a whole-cell biochip is shown in Figure 3.1. The input can be any signal that causes protein expression that can be detected later. Whole-cell biosensors can operate either as sensors to some external excitation (e.g., toxicity, heat)
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FIGURE 3.1 Schematic block diagram of a whole-cell biochip (r is position, t is time).

FIGURE 3.2 Schematic diagram of the cell sensors (q, are the state variables, t is time).

or as differential sensors monitoring changes in the pattern of behavior of cells.

The biological response can be modeled using a set of state equations linking a set of internal variables \( \{q_i(t)\} \) that are related to the protein expression. We assume that a small number of rate-limiting equations determine the biological response function, thus simplifying the system. Typically, the signal generation mechanism is nonlinear and is the result of the simultaneous response of \( 10^3-10^7 \) cells integrated on the microchip. We assume that each cell generates the signal independently. We do not treat here collective phenomena, such as “quorum sensing” and we assume that all the cells respond similarly. This is probably a very simple assumption and it helps to understand the basic phenomena. A more complex behavior of the cell-on-chips should require a more complex model (Figure 3.2).

The generating function \( f \) depends on the following fundamental issues:

1. The output type—there are few fundamental options:
   a. Electrochemical output—in this case, we are looking for a single protein that is generated in response to the excitation. That protein reacts with the substrate, generating products diffusing toward the anode where they are oxidized. Typically, these sensors operate in an amperometric mode where a fixed bias is applied and the current is measured against time.
   b. Optical output—here we have two possible generating functions:
      i. Photoluminescence—where the signal is proportional to the concentration of a photoluminescent protein that is generated in response to the excitation.
      ii. Bioluminescence—in this case, the signal is the result of the reaction between few enzymes that are generated in response to the excitation. The situation here can be rather complicated since the generation of the proteins involves some genetic processes that are either direct, that is, the generation is proportional to the induction, or indirect, that is, the response of a built-in inhibition mechanism is affected by the cell response (Belkin 2003, Polyak and Marks 2007).
   c. Electrical response—probing the electrical properties of the cells, for example, the generation of proteins that can be detected by impedance spectroscopy (Ron et al. 2008). In this case, we assume that the signal is proportional to the concentration of the proteins; therefore, it is, in principle, similar to case a.

Next, we present simple models for optical and electrochemical whole-cell biosensors on chips.

3.3 Model

We assume two parts to the model:

1. The protein generation
2. The signal generation in response to the generated proteins

The first part, the protein response, is modeled assuming that the expression rate depends on the excitation. The generated signal depends on the concentration of the expressed protein. That dependence may follow three basic functions as follows.

3.3.1 Case A: The Signal Is Generated by a Single Product

In this case, we assume that the signal output, \( Y \), is proportional to the concentration of the generated product in response to the excitation:

\[
Y = f(C_{pr}) = a \cdot C_{pr} + b \tag{3.1}
\]

where

- \( C_{pr} \) is the product concentration
- \( a \) and \( b \) are parameters

In this case, we may assume that the output is generated via a first-order reaction. For example, light generation from green fluorescent proteins where the emitted light is proportional to the concentration of the proteins plus an additional background light that is generated from molecules that already exist in the sample under test.

3.3.2 Case B: There Is More Than One Relevant Product

In this case, the cells generate protein and substrate that co-interact to generate the signal. Assume a two-component system:

\[
Y = f(C_{pr,1}, C_{pr,2}) \tag{3.2}
\]

where \( C_{pr,1} \) and \( C_{pr,2} \) are the product concentrations. In this case, we assume that there are few precursors generated as a response to the external excitation. These precursors can be enzymes and substrates that interact and the result is the signal, for example, emitted light in the case of bioluminescence. The function depends on the input as well as the output. The possibility of
having an internal feedback mechanism may complicate the solution and additionally (the basic mechanism may be non-linear) require special care in the noise calculation.

### 3.3.3 Case C: The Signal Is Generated by Interaction between an Enzyme and an Added Substrate

In this case, the signal is generated due to the interaction by the products of the cell’s response and an external substrate added to the solution:

$$Y = f(P) = a_1 \cdot P + b_1$$  \hspace{1cm} (3.3)

where $P$ is the by-product concentration $a_1$ and $b_1$ are constants

In this case, the reaction continuously generates by-products and the signal is the result of the detection of those by-products. The enzyme ($E$) reacts with the substrate ($S$) generating an intermediate ES complex that reacts to form the by-product $P$ and the enzyme at a rate of

$$\frac{dP}{dt} \propto ES$$  \hspace{1cm} (3.4)

A full analysis of this expression will be presented in Section 3.4.3.

Therefore, there are two coupled systems: (a) the reactions that determine the rate of generation of the by-products and (b) the reaction that generates the signal from the by-products.

Note that in all of these equations the assumed concentrations are the effective values as the system is not necessarily at equilibrium. For example, there is transport of species from excitation-sensing sites. We assume that since the system is very small, the transport is fast enough and its characteristic time constants are much lower than the cell response rates. However, for larger systems, if needed, the transport effect can be added to the solutions that are presented here.

In the following parts of this chapter, we bring three examples demonstrating whole-cell biochips with different signal-generating equations. The first is a genetically modified $E. coli$ on-chip system where green fluorescent proteins are generated in response to the excitation by toxic material. The second is also an $E. coli$ on-chip system with a bioluminescent response to toxicant excitation. The last example is an $E. coli$ on-chip system with an electrochemical response.

### 3.4 Examples

In the following section, we bring three examples demonstrating the application of the method that is described in this chapter. The examples are based on three previously published works:


#### 3.4.1 Example Case A: Photoluminescent Whole-Cell Biochip

In this case, the $E. coli$ expresses green fluorescent proteins (GFP) in response to the acute toxicity in its environment. We assume that the signal output, for example, light, is directly proportional to the concentration of the fluorescent protein ($C_{GFP}$). However, the GFP concentration depends on its generation rate by the microbes. This process depends on the type of the reporters, promoters, toxicant, and ambient conditions. As an example to this system, we present here the response of genetically engineered $E. coli$ to the induction by nalidixic acid in water (Figure 3.3). The overall response is given in Figure 3.4.

The protein is generated in response to the toxic effect and its generation rate is proportional to the responding promoter concentration that triggers the reporters expressing GFP (Daniel et al. 2008):

$$\frac{dC_{GFP}}{dt} = \alpha \cdot P_i$$  \hspace{1cm} (3.5)

where $P_i$ is the responding activated promoter’s concentration. This variable depends on the bacteria concentration and the concentration of the chemical that is responsible to the

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**FIGURE 3.3** Fluorescence emission from genetically engineered $E. coli$ that were induced by nalidixic acid (NA) (Rabner et al. 2006). The chip integrated $1.5 \times 10^5$ microbes per micro-well. The microbes were engineered at the lab of Prof. S. Belkin at the Hebrew University in Jerusalem.
induction. In some cases, we may assume a simple first-order approximation:

\[
\frac{dP_r}{dt} = \mu \cdot G_0 \cdot C_{Tox}
\]  

(3.6)

where

\(\mu\) is the rate constant
\(G_0\) is the concentration of the bacteria (M)
\(C_{Tox}\) is the concentration of the toxin that induces the overall response

This model is correct only at the initial stages for a short time. At longer time, the toxicity can turn on all the available promoters and the rate of their generation drops to zero. However, the low concentration regime is the one that is of interest for toxicity sensors, thus this model (Equation 3.6) is relevant to those sensors. This model seems to fit various inducers, such as nalidixic acid, under certain concentrations. When the concentration becomes too high, above the range of 2–5 mg/L for nalidixic acid, we start to see a decline in the overall response, and for higher concentration, above 10 mg/L the microbes’ response starts to decline with the increasing concentration of the inducer. This is probably due to the toxic effect on other systems of the cell.

The output, the light intensity is proportional to the GFP concentration, \(C_{GFP}\) and the excitation, \(I_{ex}\):

\[Y \triangleq I_{out} = \eta \cdot C_{GFP} \cdot I_{ex}\]

(3.7)

Thus the complete set of equations can be rewritten using an internal variable set \(\{q_i\}\), input \(x(t)\), and output \(y(t)\) where \(x = C_{Tox}\), \(q_1 = P_r\), \(q_2 = C_{GFP}\), and \(y = I_{out}\).

### 3.4.2 Example Case B: Bioluminescent Whole-Cell Biochip

The exact modeling of such a system is under investigation and the first model appears in Popovtzer et al. (2005). The typical response of such a system appears in the bioluminescent microbe’s response to external inductions (Daniel et al. 2008). An example of such a response of the genetically engineered \(E. coli\) bacteria is shown in Figure 3.5.

The biophysical system in the whole-cell biosensor is reduced to Figure 3.6.

To build the system’s state equations, the following variables are defined:

\(P\) is the concentration of the fatty acid
\(S\) is the concentration of the long-chain aliphatic aldehyde that acts as the substrate
\(E_L\) and \(E_P\) are the concentrations of the luciferase and reductase enzyme complex, respectively

![FIGURE 3.4 Schematic drawing of the fluorescent response of the microbes [13] to toxic material in water.](image)

![FIGURE 3.5 Bioluminescence vs. time from the genetically engineered bacteria as a function of time for nalidixic acid induction at various concentrations (\(E. coli\), recA promoter).](image)
The output, that is, light, is proportional to $P$, the fatty acid concentration. $P$ depends on the substrate concentration at $t = 0$, $S(0)$ and the enzymes concentration as

$$\frac{dP}{dt} = -\frac{dS}{dt} = \alpha_s \cdot E_L \cdot S - \alpha_p \cdot E_p \cdot P$$ (3.8)

where

- $\alpha_s$ is the rate constant in which the luciferase combines to the substrate, in M/min
- $\alpha_p$ is the rate constant in which the reductase enzyme complex combines with the substrate

In this case, when the initial substrate concentration is $S(0)$ and any substrate molecule is converted to the product, we may assume that in any time after the reaction starts, $S(t) + P(t) \sim S(0)$. Therefore, we can rewrite the previous expression:

$$\frac{dP}{dt} = \alpha_s \cdot S(0) \cdot E_L - (\alpha_s \cdot E_L + \alpha_p \cdot E_p) \cdot P$$ (3.9)

The enzymes (luciferase and reductase) concentration can be determined by the following rate equations:

$$\frac{dE_L}{dt} = \alpha_L \cdot P_t$$ (3.10)

$$\frac{dE_p}{dt} = \alpha_L \cdot P_t - \frac{E_p}{\tau_p}$$ (3.11)

where $P_t$ is the promoter products’ concentration (Daniel et al. 2008). This variable depends on the bacteria concentration and the concentration of the chemical that is responsible to the induction. A zero-order approximation is based on the assumption that the generation of the promoters’ products is proportional to the inducer concentration:

$$\frac{dP_t}{dt} = \mu \cdot G_0 \cdot C_{\text{Tox}}$$ (3.12)

where

- $\mu$ is the rate constant
- $G_0$ is the concentration of the bacteria (M)
- $C_{\text{Tox}}$ is the concentration of the toxic material

In this case, $C_{\text{Tox}}$ is the input and $P$ is the output. This assumption may be acceptable for a low concentration of the inducer. At a higher concentration it will affect the cell in a way that generally slows down the promoters’ generation rate. At high enough concentration, the promoter products’ generation rate will decrease as the inducer concentration rate will increase. For the sake of simplicity, we limit ourselves to the condition of low inducer concentration that is usually the useful regime of toxicity sensing. However, in future modeling, medium and high inducer concentration effects should be included.

All the other variables, $S$, $E_p$, $E_L$, and $P_t$ are internal state variables that are a function of $C_{\text{NA}}$ and the initial conditions. Thus the complete set of equations can be rewritten using an internal variable set $\{q_i\}$, input $x(t)$ and output $y(t)$ where $x = C_{\text{Tox}}$, $q_1 = P_t$, $q_2 = E_p$, $q_3 = E_L$, and $x = C_{\text{Tox}}$. The initial conditions are determined by the specific problem. Usually the internal state and the output are zero before the excitation. However, there might be a situation where they are not equal to 0.

### 3.4.3 Example Case C: Bioelectrochemical Whole-Cell Biochip

A simple example of a mathematical model for the whole-cell biosensor with electrochemical detection is presented in Popovtzer et al. (2006). In that system, the electrochemical signal was generated by the oxidation of the by-products of the reaction between an external substrate (i.e., $p$-aminophenyl-$\beta$-d-galactopyranoside...
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[PAPG]) and a protein (i.e., β-galactosidase) that is expressed in the cell either in response to an external excitation or due to another internal mechanism. Such an electrochemical signal appears in Figure 3.7.

There are few models for the cell response to the toxic material. One option is given as

\[
\frac{dE}{dt} = \mu \cdot C_{\text{tox}} \tag{3.13}
\]

The generation of the enzyme is assumed to be proportional to the promoter concentration:

\[
\frac{dE_{T}}{dt} = \alpha \cdot P_{\text{r}} \tag{3.14}
\]

\(E_{T}\) is the total enzyme concentration in the system. Assuming a linear relation between the promoter’s concentration and the toxic material concentration the total enzyme concentration is given as

\[
\frac{dE_{T}}{dt} = k_{0} \cdot C_{\text{tox}} \tag{3.15}
\]

The enzyme can appear in its free state, \(E\), or in its captured state, \(ES\), there for the total concentration is given by the following equation:

\[
E_{T} = E + ES \tag{3.16}
\]

The enzyme–substrate indication was modeled by the Michaelis–Menten equation (Michaelis and Menten 1913). The substrate–enzyme interaction is given as

\[
E + S \xrightarrow{k_{1}} ES \xrightarrow{k_{2}} P + E \tag{3.17}
\]

where
- \(E\) is the free enzyme concentration
- \(S\) is the substrate concentration
- \(ES\) is the enzyme–substrate complex concentration
- \(P\) is the product concentration

Whole-cell biosensors are not in equilibrium since they respond to an external excitation and there is a functional response increasing the total concentration of the enzyme. However, we will assume that the total enzyme generation rate, \(dE_{T}/dt\), as given by expression (3.15) to be much slower than the rate at which the Michaelis–Menten equation (3.17) reaches its equilibrium.

In this case, the rate of generation of the \(ES\) complex which is given by

\[
\frac{d(ES)}{dt} = k_{1} \cdot E \cdot S - k_{2} \cdot ES - k_{3} \cdot ES \tag{3.18}
\]

can be presented as

\[
\frac{d(ES)}{dt} = k_{1} \cdot (E_{T} - ES) \cdot S - k_{2} \cdot ES - k_{3} \cdot ES
= k_{1} \cdot E_{T} \cdot S - (k_{1} \cdot S + k_{2} + k_{3}) \cdot ES
= k_{1} \cdot E_{T} \cdot S - \frac{ES}{\tau} \tag{3.19}
\]

where \(\tau\) is the effective time constant that describes the characteristic time in which \(ES\) reaches its quasi-equilibrium:

\[
\tau = \frac{1}{(k_{1} \cdot S + k_{2} + k_{3})} \tag{3.20}
\]

The assumption that \(ES\) reaches quasi equilibrium is similar to the assumption for equilibrium in the classical treatment of the Michaelis–Menten equation

\[
k_{1} \cdot E_{T} \cdot S = \frac{ES}{\tau} \rightarrow ES = E_{T} \cdot \frac{k_{1} \cdot S}{k_{1} \cdot S + k_{2} + k_{3}} \tag{3.21}
\]

For relatively large concentration of substrate \([ES] = E_{T}\) (Michaelis and Menten 1913). This can be controlled since the substrate is externally added to the chip.

The rate of production of the product \(P\) is

\[
\frac{dP}{dt} = k_{3} \cdot ES = k_{3} \cdot E_{T} \cdot \frac{k_{1} \cdot S}{k_{1} \cdot S + k_{2} + k_{3}} \tag{3.22}
\]

The overall reaction is shown in Figure 3.8. In this diagram, \(E_{T}\) is the total enzyme generated by the cell response, \(ES\) is the enzyme concentration due to the \(ES\) complex decomposition, \(\tau\) is the effective time constant which is a function of the Michaelis–Menten
parameters and \( P \) is the by-product concentration. The state equations for this system can be rearranged so that \( x \) is the input \( C_{\text{in}} \), \( q_1 = E_p \), \( q_2 = ES \), and \( y \), the system's electrical output signal is proportional to \( P \).

The intrinsic output variable here is the by-product concentration \( P \). However, the real readout is at the electrode that operates at positive bias to oxidize the by-products. The by-products diffuse through the medium toward the electrode and there is a collection efficiency in which it is described by a parameter \( k_e \).

### 3.5 Summary and Conclusions

In this chapter, we present a simple model for the intrinsic signal of a whole-cell biochip using a relatively simple set of equations. Using an electrical equivalent for the Michaelis–Menten equation was already presented (Kopelman 1986, 1988, Grima and Schnell 2006). We adapt a rigorous mathematical model linking the biology to the electronics circuits. There are few variations depending on the specific application. They all define the output, \( y \), as a function of internal variables, \( \{q_i\} \) that depends on the input \( x \). This approach will simplify the calculation of the system response, that is, signal and noise. This will allow the modeling of system variables such as

- a. Minimum detectable signal (MDS)
- b. Signal-to-noise ratio (SNR)

Note that the intrinsic signal is fed onto an electrical signal that amplifies the system, but also contributes some noise. There is also the issue of the bandwidth of the system operation. For linear systems, it can be easily determined from the state equations. It would be more complicated for nonlinear detection in nonlinear systems, it can be easily determined from the state equations.

Another issue that should be included in a full model is the products' transport in the cell container. This is not important in sensors where the total emission luminescence is almost independent of the by-products' distribution, assuming uniform microbes' distribution. It should be taken into consideration when the microbes are fixed in a solid matrix and their by-products diffuse into the liquid medium. In sensors where the by-products diffuse toward the sensing device—electrodes in the case of electrochemical sensing—the transport may play an important role (Popovtzer et al. 2007) and should be included in the model.

### Acknowledgments

The authors thank Prof. Shimshon Belkin from the Hebrew University at Jerusalem with whom we have collaborated on various whole-cell biochip projects in the last 7 years. His research achievements on the genetically engineered *E. coli* for the detection of water toxicity are the base of this work.

### References


