

# Computer Aided Simulation and Verification of Forward Error-Correcting Biosensors

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**Abstract**—Factors that affect the accuracy of the biosensor systems range from errors in device fabrication to stochastic interaction between biomolecules. In this paper we present a framework for designing and evaluating biosensor encoding and decoding algorithms based on forward error-correcting (FEC) principles, which can improve the accuracy of pathogen detection. The model biosensor used in this paper is an immunosensor that uses computational primitives inherent in antigen-antibody interaction to achieve a transistor like operation. Fundamental logic gates have been embedded into an equivalent low-density parity check (LDPC) biosensor encoder and a corresponding sum-product decoding algorithm is presented for error correction. The performance of the encoding-decoding algorithm has been verified using behavioral simulations demonstrating its utility for designing reliable biosensors. The simulation study also reveals a novel co-detection principle that can be a promising method for significantly enhancing the pathogen detection limit.

**Index Terms**—Forward error-correcting biosensors, sum-product algorithm, co-detection

## I. INTRODUCTION

Biosensors have emerged as important analytical tools for the rapid detection of food-borne pathogens, which according to The United States Department of Agriculture (USDA) cause approximately 5,000 deaths every year [1]. A typical architecture of a biosensor consists of a biological recognition layer as a reactive surface in proximity to a transducer. The transducer converts the binding between the analyte and the recognition layer into a measurable electrical or optical signal [2]. However, the stochastic interaction between the biomolecules, transducer device artifacts and environmental variability (eg. pH of the analyte) directly affect the reliability and the accuracy of the biosensor. Irrespective of its principle of operation the overall efficiency of any biosensors can be expressed by the following relationship:

$$E \propto E_p \times E_t \times E_s \times E_b \times G \quad (1)$$

where  $E_p$  represents the efficiency of pre-concentration and filtration step (eg. polymerase chain reaction for DNA biosensors);  $E_t$  represents the transducer efficiency;  $E_s$  represents the efficiency of the measuring the transducer signal;  $E_b$  represents the cross-reaction between non-target analyte with the recognition layer (efficiency of biomolecular level interaction) and  $G$  represents efficiency of any encoding schemes used to introduce redundancy.

In this paper we present a systematic approach where coding gain  $G$  can be improved by use of forward error-correction (FEC) techniques. The principle is similar to those used in communication and storage systems, where FEC techniques have been successfully employed to improve system reliability. Recently, several studies have applied FEC principles for designing nano-scale fault tolerant systems [3] and for analyzing biological systems [4], [5], [6]. In the study of [3], a defect-tolerant error-correcting code where redundant demultiplexers were used for compensating defects in nano-wire connections. In another study [5], the method of detection and reconstruction of error-control codes for engineered biological systems was proposed. Redundant gene spotting techniques have been proposed in [6] to reduce drop-out errors in microarrays.

A one dimensional biosensor is examined as a model to construct such FEC biosensor systems. The biosensor use polyaniline nanowires as labels to antibody and also transducers. The encoder is directly constructed in biosensor and basic logic gates (OR and AND) are achieved by biomolecular transistors using polyaniline nanowires. Corresponding decoding scheme based on sum-product algorithm is proposed. To our best knowledge this paper is the first reported work that proposes sensing and encoding on an integrated biosensor and presents a decoding algorithm for compensating random artifacts. The behavioral simulations are conducted by using virtual FEC biosensor model, which is derived by experimental results. The simulations show that the original biological information can be recovered by using encoding/decoding scheme in biosensor systems, thus enhancing the reliability and the accuracy of the biosensor systems. The simulation environment presented in this paper also obviates the requirement for painstaking and controlled biosensor experiments to validate the efficacy of the encoding-decoding algorithms.

The paper is organized as follows: Section II briefly describes the principle of operation, behavioral model of fundamental logic gates, and the biosensor LDPC encoder based on a structure of the immunosensor. Section III describes a sum-product decoding algorithm based on the structure of the biosensor LDPC encoder. Section IV presents simulation results demonstrating the potential of encoding and decoding algorithms in improving biosensor detection accuracy. Section

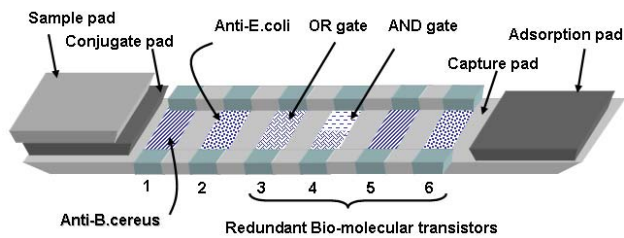


Fig. 1. The biosensor encoder

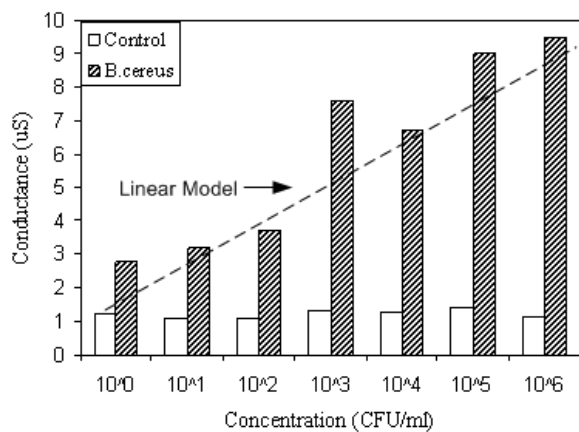


Fig. 2. Conductance measurement of a single biomolecular transistor [7]

V concludes the paper with some final remarks.

## II. BIOSENSOR ENCODER

In this section, we describe how to construct encoder directly in biosensor system by using a one dimensional model biosensor as an example. The architecture of the biosensor encoder is shown in figure 1, and it is based on our previously reported biosensor architecture [7]. The biosensor encoder is formed by several biomolecular transistors, which were triggered by antibody-antigen binding events. Due to the biological channel noise or the device artifacts, the biomolecular transistors may be corrupted and the information about the presence of pathogens will be inaccurate or even be lost. To prevent this drop-out, redundant biomolecular transistors are added and the encoder is formed by those redundant biomolecular transistors together with the original biomolecular transistors.

Basic logic functions are needed to be constructed to form encoder in the biosensor structure. Due to the limitation of one dimensional structure, XOR logic is too difficult (maybe not possible) to build while AND and OR logic functions are relatively easy to construct by patterning the antibodies along different spatial locations on the capture pad. As an example, region 3 in figure 1 is formed by mixing two antibodies together, thus forming an OR logic gate. Similarly, region 4 in figure 1 constitutes a cascade of two antibody regions, which act like an AND logic gate. Region 5 and 6 are just

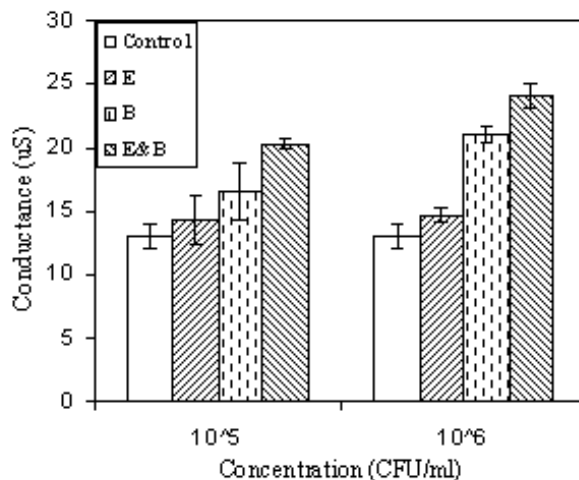


Fig. 3. Conductance measurement of the AND logic gate [7]

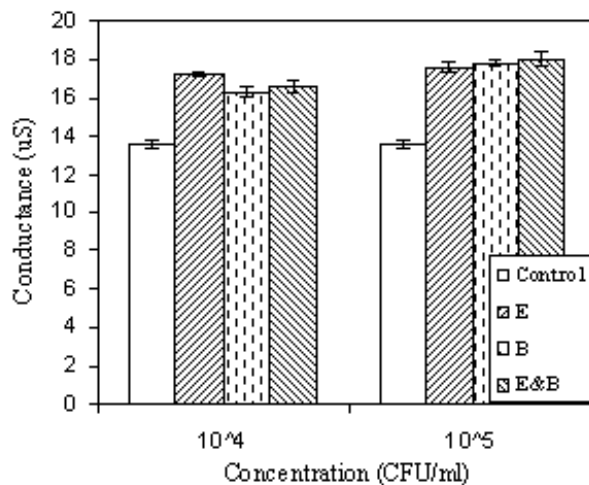


Fig. 4. Conductance measurement of the OR logic gate [7]

the repetition antibodies of the region 1 and 2 respectively. One can easily show that at least 4 redundant bits are needed to correct one bit error because of the absence of XOR logic function.

We have fabricated and characterized the response of a single biomolecular transistor (region 1,2 in figure 1), a single OR gate (region 3 in figure 1) and a single AND gate (region 4 in figure 1) using antibodies against pathogens *B. cereus* and *E. coli*. Figure 2, 3 and 4 show the response of a single pathogen biosensor, AND and OR logic gates formed by *B. cereus* and *E. coli* antibodies. The behavioral model that captures the response of these fundamental gates and typical values and meanings of device parameters can be found in [7]. The fundamental building blocks (AND, OR, and Equality gates) can now be organized to form a biosensor encoder. However, the absence of XOR gates in the library of building blocks

obviates direct application of linear codes (eg. Hamming codes). In this paper, we can show that the encoder can still be constructed based on only AND and OR logic gates and efficient decoding algorithms can be designed based on the encoder structure. As shown in figure 1, we constructed an equivalent parity check code that consists of two primary gates (corresponding to *B. cereus* and *E. coli*) and four redundant bits formed by AND, OR and equality gates.

The structure of the code can be represented by a Forney-style Factor Graph (FFG) as shown in figure 5. FFG is a generic graphical tool to model complex real-world systems and it also depict logical relationships between different measurement variables [8]. In figure 5,  $y_i (i = 1, 2, \dots, 6)$  represent conductance measured across the electrodes of each logic gate in figure 1 and these measurements are indicative of pathogens presence in the analyte. The “T” block represents a transducer function converting pathogen concentration into equivalent conductance measurements and the biological channel. The normalized scores  $P_j (j = 1, 2, \dots, 6)$  similarly represent normalized concentration levels for each logic operation (AND, OR, Equality). By use of FFG representation of the biosensor code, one can easily design corresponding decoding algorithm operating on the FFG.

### III. SUM-PRODUCT DECODING ALGORITHM

Sum-product algorithm is one of the popular message propagation algorithms and was invented by Gallager [9] as a decoding algorithm for LDPC codes. In this paper, we proposed a decoding algorithm based on the FFG and the corresponding sum-product message updated rules, which operates on the factor graph. Details about the principle of sum-product algorithm can be found in [8], [9].

The objective of a decoder for the proposed FEC biosensor is to determine the probability of pathogens (*B. cereus* and *E. coli* in this study) being present given the set of noisy measurements  $y_i (i=1,2,\dots,6)$ , which is expressed as posteriori probabilities  $P(x_B|y_1, y_2, \dots, y_6)$  and  $P(x_E|y_1, y_2, \dots, y_6)$ . In communication systems, the function nodes in FFG are usually constructed by XOR logic while only AND, OR, and Equality function nodes are available in this specific application. Due to the asymmetric nature of AND and OR function nodes, there are two different sets of message updated rules, which we could call them as forward reasoning (where in the direction of inputs are x and y, output are z) and backward reasoning (where in the direction of outputs are x or y). The asymmetric message schedule is unique to the proposed FEC biosensor as it uses only AND, OR and Equality logic functions for computation. The messages are iteratively propagated between the nodes of the FFG till either convergence is achieved or total number of iterations is exceeded. Unlike message passing formulations used in linear codes (eg. Hamming codes), the flow of messages is also not symmetric. Figure 6 summarizes the sum-product message updated rules for OR, AND, and Equality nodes where  $\mu_x(0)$ ,  $\mu_x(1)$  represents probability of the random variable when  $x=0$ ,  $x=1$ .

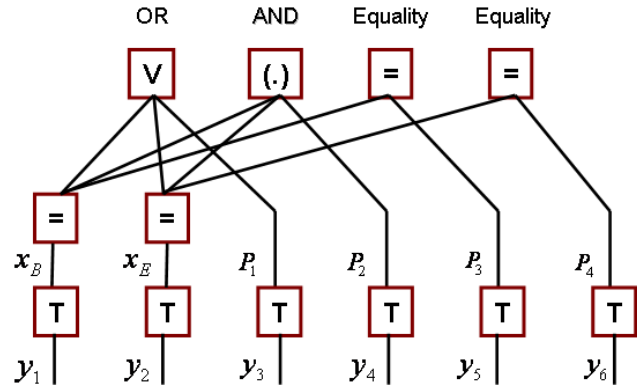


Fig. 5. A FFG of the biosensor code

	$\begin{pmatrix} \mu_z(0) \\ \mu_z(1) \end{pmatrix} = \begin{pmatrix} \mu_x(0)\mu_y(0) \\ \mu_x(1)\mu_y(1) \end{pmatrix}$
	$\begin{pmatrix} \mu_z(0) \\ \mu_z(1) \end{pmatrix} = \begin{pmatrix} \mu_x(0)\mu_y(0) \\ \mu_x(0)\mu_y(1) + \mu_x(1)\mu_y(0) + \mu_x(1)\mu_y(1) \end{pmatrix}$ $\begin{pmatrix} \mu_y(0) \\ \mu_y(1) \end{pmatrix} = \begin{pmatrix} \mu_x(0)\mu_z(0) + \mu_x(1)\mu_z(1) \\ \mu_x(0)\mu_z(1) + \mu_x(1)\mu_z(1) \end{pmatrix}$
	$\begin{pmatrix} \mu_z(0) \\ \mu_z(1) \end{pmatrix} = \begin{pmatrix} \mu_x(0)\mu_y(0) + \mu_x(0)\mu_y(1) + \mu_x(1)\mu_y(0) \\ \mu_x(1)\mu_y(1) \end{pmatrix}$ $\begin{pmatrix} \mu_y(0) \\ \mu_y(1) \end{pmatrix} = \begin{pmatrix} \mu_x(0)\mu_z(0) + \mu_x(1)\mu_z(0) \\ \mu_x(0)\mu_z(0) + \mu_x(1)\mu_z(1) \end{pmatrix}$

Fig. 6. Sum-product message updated rules

### IV. BEHAVIORAL SIMULATION RESULTS

System level simulations have been conducted to validate the effectiveness of encoding and decoding algorithms proposed in this paper. For the simulation, different concentrations of both pathogens (*E. coli* and *B. cereus*) are tested with a virtual FEC biosensor using the mathematical model of the biosensor and the fundamental logic gates. The probabilities of the presence of pathogens were obtained after applying sum-product algorithm to the conductance measurement obtained for different levels of pathogen concentrations. Figure 7 compares the probability (confidence score) quantifying the presence of *B. cereus* (represented by B in figure 7 and 8) and *E. coli* (represented by E), obtained with and without the FEC decoding algorithm. In the figures, the x-axis and y-axis refer to a 10-fold dilution of pathogen concentration starting from 10 CFU/ml on a log scale. Figure 8 shows a corresponding two dimensional projection of figure 7 to clearly illustrate the benefits of FEC principles and non-linear dependency between detection of *B. cereus* (B) and *E. coli* (E). It can be clearly seen from figure 7 and 8, in which the confidence of detection increases in the case when FEC principles are used. Also as expected the detection confidence increases with increase in

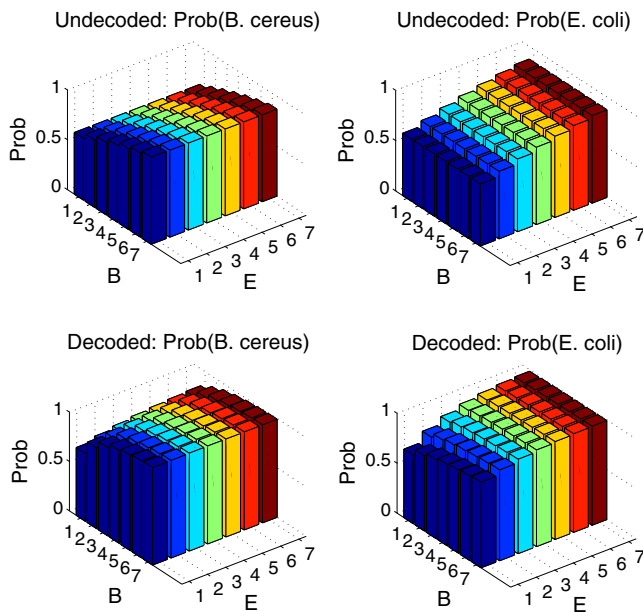


Fig. 7. Probability of the presence of pathogens

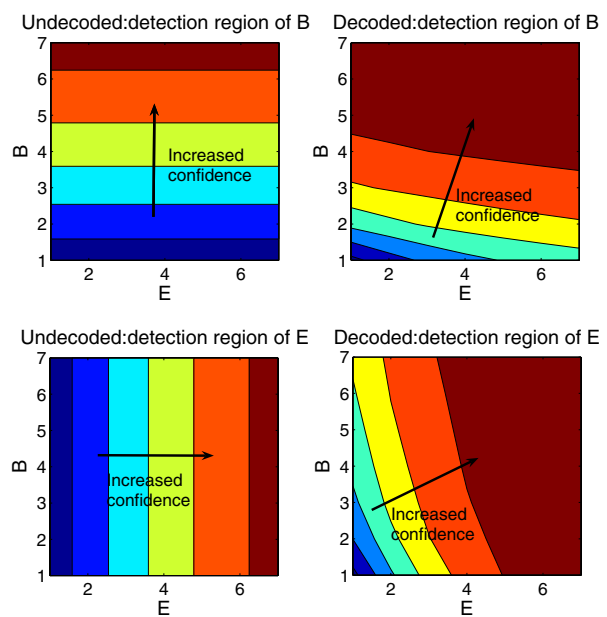


Fig. 8. Detection regions of the pathogens

pathogen concentration. It can be seen in figure 7, 8 that the use of FEC also introduces a dependency between detecting two pathogens while this relationship does not exist in the case of direct measurement (without use of FEC). This non-linear dependence is the core principle behind the forward error-correcting codes and can be studied extensively using the proposed simulation environment. An interesting outcome of this simulation study is that low concentration of one of the pathogen can be detected if the large concentration of another is present in the sample. This principle which we call “co-detection” can be attributed to the nonlinear interaction of the AND and OR gate in conjunction with the message passing algorithm. Even though the underlying mechanism of this non-linear interaction is difficult to quantify, it gives us a promising method to detect trace quantities of pathogens.

## V. CONCLUSIONS

Even different kinds of biosensors have been designed to detect pathogens, those systems still suffer low reliability and low reproducibility due to the complexity nature of biological systems. By applying encoding/decoding principles, which is widely used in communication systems, to engineered biological systems, some fundamental limitations of those systems and stochastic nature of complex biomolecular interaction could be better understood and these limitations are expected to be alleviated. In this paper, we have explored a novel encoding/decoding application on the biosensor systems to solve those basic problems. Using our experimentally validated electrical models for fundamental building blocks (AND, OR, EQ), we proposed the architecture of an FEC biosensor. A corresponding decoding technique based on sum-product algorithm has been used to demonstrate benefits of FEC in

improving pathogen detection rate. Also using the simulation environment we proposed a novel technique called “co-detection” that can be used for detecting trace quantities of pathogens. Even some further fundamental issues need to be addressed, the application of error-correcting techniques on the biosensor systems is a promising method for improving the accuracy and providing robustness to the biosensor systems.

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