

# Forward Error Correcting Biosensors: Modeling, Algorithms and Fabrication

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**Abstract**—Advances in micro-nano-biosensor fabrication are enabling the integration of a large number of biological recognition elements within a single package. As a result, hundreds to millions of tests can be performed simultaneously and can facilitate rapid detection of multiple pathogens in a given sample. However, it is an open question as to how to exploit the high-dimensional nature of the multi-pathogen testing for improving the detection reliability of typical biosensor systems. Our research over the past few years has addressed this question and in this paper we briefly summarize our approach. Our underlying principle is based on a forward error correcting (FEC) biosensor where redundant patterns are synthetically encoded on the biosensor. A decoding algorithm then exploits this redundancy to compensate for systematic errors due to experimental variations and for random errors due to stochastic biomolecular interactions. The key milestones in this research are : (a) fabrication and modeling of biomolecular circuit elements used for constructing the FEC biosensor; (b) development of a simulation environment for rapid evaluation of encoding/decoding algorithms and (c) development of a “co-detection” protocol that exploits non-linear interaction between different biomolecular circuit elements. As a proof-of-concept our study and experimental results have been based on a conductimetric lateral flow immunosensor that uses antigen-antibody interaction in conjunction with a polyaniline transducer to detect the presence or absence of pathogens in a given sample.

**Index Terms**—Forward error correcting biosensors, factor graph, 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 which converts the binding between the analyte and the recognition layer into a measurable electrical or optical signal [2]. With advances in micro-nano fabrication, biosensor technology is now available that can integrate a large number of recognition and transducer sites on a portable device. As a result a large number of simultaneous detection experiments can be conducted in parallel, an example being nanoscale arrays reported in [3]. At the same time detection technology has also seen significant improvements where analyte concentration levels ranging from pico-molar ( $pM$ ) to femto-molar ( $fM$ ) can now be detected [4]. Both these trends are summarized in Fig.1,

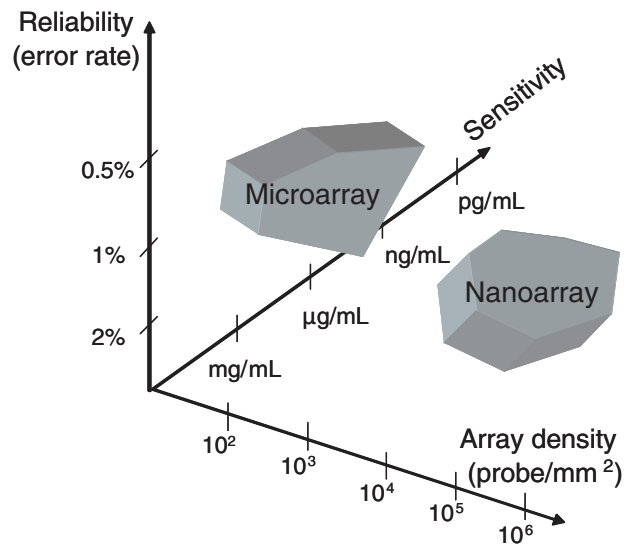


Fig. 1. Summary of biosensor technology trends.

which also depicts another important performance parameter that is typically overlooked in biosensor design. Unfortunately, with miniaturization the reliability of biosensors typically deteriorates as have been observed in large scale gene-chip arrays. Irrespective of the choice of the detection technology (DNA, aptamers or antibodies) the biosensors artifacts can be categorized as [5]: (a) systematic errors that were induced by sample handling errors, variations in experimental conditions (pH or temperature), and errors introduced by device artifacts; and (b) random errors introduced due to stochastic nature of biomolecular interactions. From a modeling point of view, these artifacts are similar to those that are observed in nanoscale storage and computing systems for which forward error correction (FEC) techniques have been successfully employed [6].

The objective of this research is to replicate the success of FEC principles in designing reliable computing and storage systems towards designing reliable biosensors. In this regard, the study addresses some of the key challenges in this long-term goal. The first step involves mathematical abstraction where simulation models are developed that capture the ex-

perimentally measured response of the biosensor circuit. These simulation models are then used to: (a) understand the nature of the biosensor channel and in the process derive fundamental limits of biosensor FEC; (b) rapid design and evaluation of different FEC encoding and decoding algorithms without resorting to painstaking experimental procedures. Our final objective is to close the design loop, where the reliability of the biosensor encoding and decoding algorithms are validated using in-lab experiments. In this paper, we summarize some of the highlights of this research and present some of the key results.

## II. FUNDAMENTAL BUILDING BLOCKS: FABRICATION AND MODELING

Even though the encoding and decoding methods being developed can be applied to any multi-pathogen detection principle based on either antibody, DNA or aptamers, we have chosen a conductimetric lateral flow immunosensor as a model biosensor. The immunosensor utilizes a polyaniline nanowire based transducer to convert the binding between a target antigen and its antibody into an electrical signal. Fig. 2 shows the visualization of a multi-pathogen immunosensor and the principle of a single immunosensor is illustrated in Fig. 3, which shows a cross-sectional view of the immunosensor. Before the sample is applied, the gap between the electrodes in the capture pad is open. Immediately after sample is applied to the sample pad, the solution containing the antigen flows to the conjugate pad, dissolves with the polyaniline-labeled antibody and forms an antigen-antibody-polyaniline complex. The complex is transported using capillary action into the capture pad containing the immobilized antibodies. A second antibody-antigen reaction occurs and forms a sandwich (Fig. 3). Polyanilines in the sandwich extend out to bridge the two electrodes, which leads to a change in conductance measured across the electrodes. The conductance change is determined by the number of antigen-antibody bindings, which is related to the antigen concentration in the sample. In Fig.3. we also show scanning electron microscope (SEM) images of the capture pad before and after the sample with pathogen has been applied. The change in material texture can be attributed to the formation of the antibody-antigen-antibody-polyaniline complex connecting the electrodes. In this modality, the immunosensor acts like a biomolecular transistor whose inter-electrode conductance is controlled by the pathogen concentration in the sample. In [7], we have used the biomolecular transistor described in Fig. 2,3 to construct biomolecular OR and AND logic circuits. An AND operation is achieved by cascading two different antibodies in between the biosensor electrodes. Thus, in an ideal condition, conduction between the electrodes occurs only when both the pathogens are present in the sample (for completing the polyaniline bridge as shown in Fig. 4 (1)). An OR operation is achieved by immobilizing a mixture of antibodies between the electrodes. Thus, in an ideal condition a polyaniline nanowire bridge is formed when either one of the antigen is present. The responses of logic gates are shown in Fig.5,6 which have been obtained for different

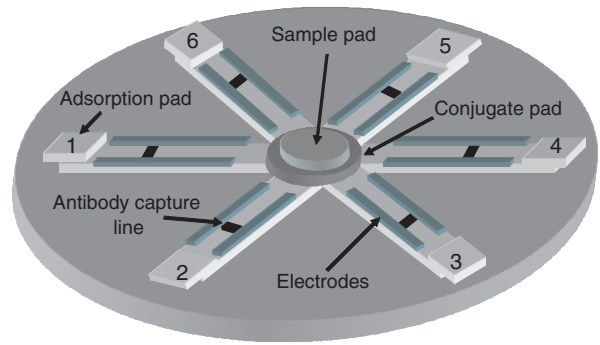


Fig. 2. A visualization of multi-pathogen biosensor that can implement the encoding methods.

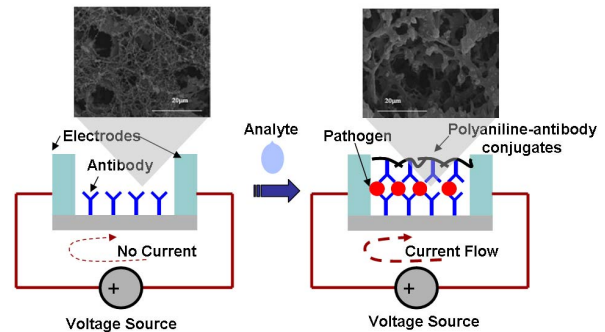


Fig. 3. The principle of operation of a single immunosensor.

concentration of pathogens *E. coli* and *B. cereus*. In [7] we have reported an equivalent circuit models corresponding to these logic gates. Unfortunately, XOR circuits which are used extensively in conventional FEC techniques are un-realizable for our model biosensor. Hence our encoding (also referred to as an asymmetric code) functions will only be based on OR and AND biomolecular circuits.

## III. BIOSENSOR ENCODER

The simplest encoding method is the “repetition” code where biomolecular transistors that detect single pathogen are replicated multiple times. This form of code has been used in microarrays for compensating occurrence of “drop-out” errors. Another form of encoding function that we have investigated uses the biomolecular OR and AND logic circuits that we have

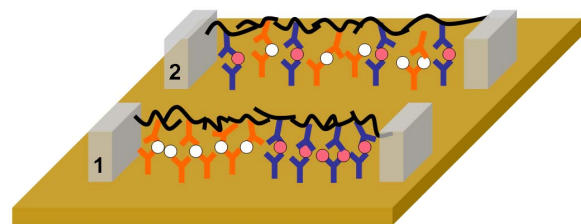


Fig. 4. Principle of operation of biomolecular logic gates (AND gate (marked by 1), OR gate (marked by 2)).

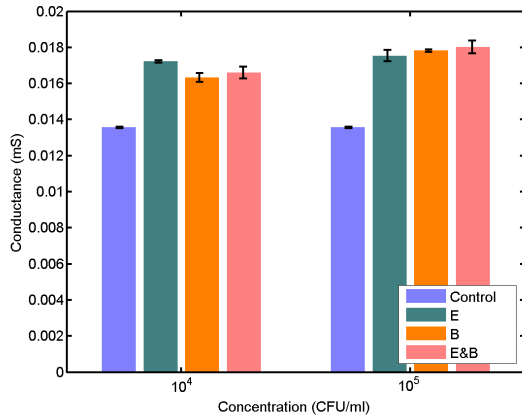


Fig. 5. Steady-state conductances measured across an OR gate for different pathogen concentration levels.

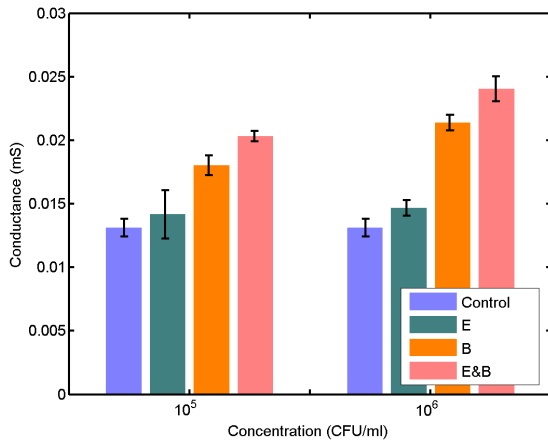


Fig. 6. Steady-state conductances measured across an AND gate for different pathogen concentration levels.

developed. One specific instance of a (6,2) encoder function is summarized in Table I, where  $X_1, X_2$  are boolean variables corresponding to the absence or presence of *B. cereus* and *E. coli*. The variable  $X_3$  represents a logical OR operation between  $X_1$  and  $X_2$  and variable  $X_4$  corresponds to a logical AND operation. The variables  $X_5$  and  $X_6$  are repetition of variables  $X_1$  and  $X_2$ . One possible realization is illustrated in Fig. 2, which includes 6 lateral flow immunosensors where six corresponding biomolecular circuits can be patterned.

TABLE I  
(6,2) ASYMMETRIC CODE

$X_1$	$X_2$	$X_3$	$X_4$	$X_5$	$X_6$
0	0	0	0	0	0
0	1	1	0	0	1
1	0	1	0	1	0
1	1	1	1	1	1

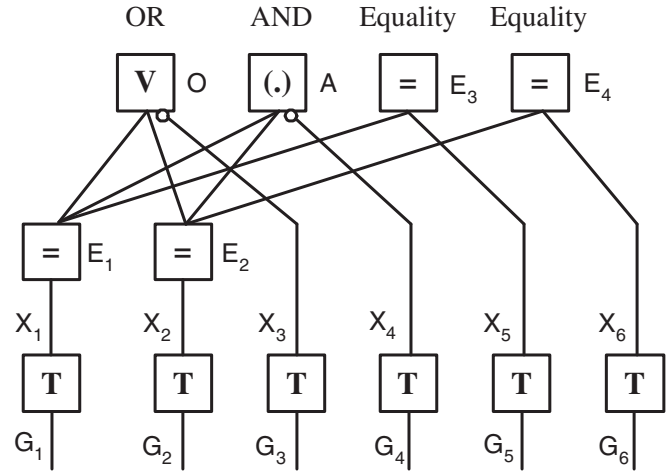


Fig. 7. Factor graph model of a (6,2) biosensor asymmetric code

#### IV. BIOSENSOR DECODER

The conductance values measured across each of the biomolecular circuit elements are presented as inputs to a decoder which produces the final decision indicating the presence or absence of target pathogens. One of ways to decode the measured conductances is to capture the dependencies between the biomolecular circuit elements using a “factor-graph”. For example, a Forney-style factor graph [8] corresponding to a (6,2) biosensor asymmetric code is shown in Fig. 7. The transducer node (T) captures the relationship between the measured conductances  $G_1, \dots, G_N$  and the indicator variables  $X_1, \dots, X_N$ . The edges in the factor graph that represent the functional dependencies between the nodes connect the pathogen indicator variables ( $X_1, \dots, X_6$ ) using the AND, OR and equality nodes. Decoding on the factor graph then proceeds by propagating messages along the edges to each of its immediate neighbors. The transducer nodes in Fig. 7 are first initialized using the conductance measurements obtained from the biomolecular circuits. These normalized measurements are used as messages which are sent to the neighboring Equality, AND and OR nodes. The Equality, AND and OR nodes also compute messages locally and transmit it to their neighbors. Messages are propagated back and forth between the nodes for a pre-determined number of iterations before a decision on the boolean variables  $X_1, \dots, X_6$  is made [9].

We have evaluated the reliability of different encoding-decoding strategies using Monte-Carlo simulation. The simulation models developed in the previous milestones were used to generate conductance parameters which were then corrupted by measurement noise. The noise was modeled as a zero-mean additive white Gaussian noise (AWGN) whose variance was experimentally determined. The noisy conductance parameters were then presented as an input to the factor graph model and the probability of the presence of *B. cereus* and *E. coli* was estimated using the factor-graph algorithm. An example of the detection error rate (DER) obtained using the Monte-Carlo simulation of a (6,2) code is shown in Fig. 8, which shows that

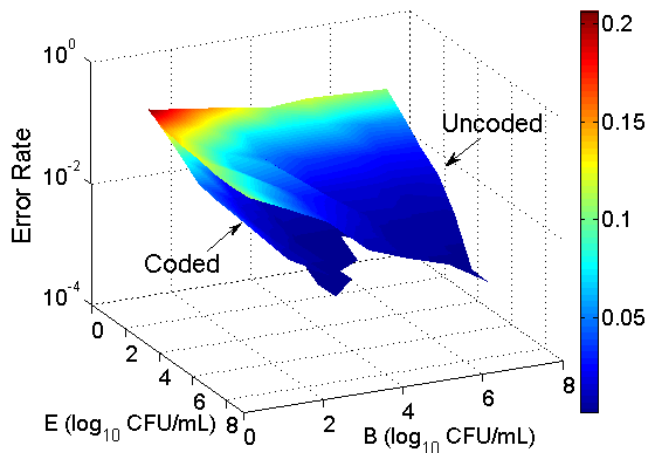


Fig. 8. DER curve of (6,2) asymmetric code when the concentration of *B. cereus* and *E. coli* is varied.

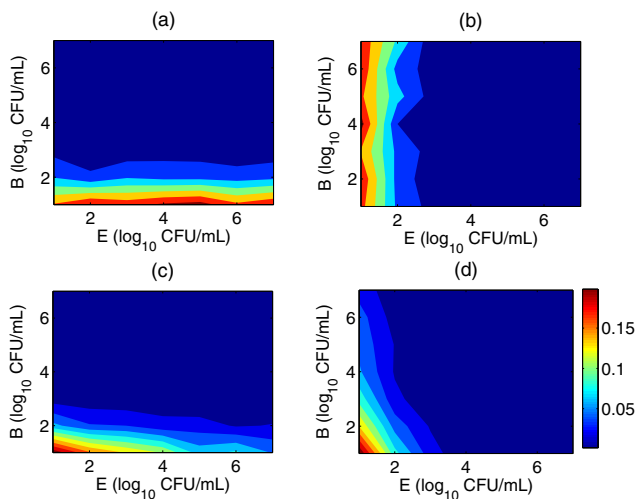


Fig. 9. 2D projection of DER curve (a,b) repetition code; (c,d) asymmetric code.

the reliability of the biosensor significantly improves compared to an un-coded biosensor.

## V. INSIGHTS AND DISCUSSIONS

The Monte-carlo study reveals several key insights that form the basis of future directions of this research. We have been able to show that compared to an un-coded case or even a simple repetition code, a complex code like the (6,2) asymmetric code can potentially improve the reliability of the biosensor. This concept leads to the question if there exists an equivalent concept of “Shannon-Limit” that is applicable to biosensors. In this regard, there might exist a fundamental limit namely “biosensor channel capacity” which could be a function of the detection technology being employed and determine the minimum amount of redundancy required to obtain perfect reliability.

Another important insight that was obtained from the Monte-carlo study is a novel detection principle which we label as “co-detection”. The principle can be clearly seen if the DER for each of the pathogens are separately projected on a 2-D plot. This is shown in Fig. 9 (a) and (b) for a repetition code and in Fig. 9 (c) and (d) for the asymmetric code. Fig. 9 (a) shows the colormap of the DER corresponding to *B. cereus* illustrating that the DER is independent of the *E. coli* concentration that is expected since there is no coupling between the two detection mechanisms. Similar DER plot for the *E. coli* is shown in Fig. 9 (b). However, equivalent plots for the asymmetric code shown in Fig. 9 (c) and (d) demonstrate a strong coupling between the concentration of *E. coli/B. cereus* in the input sample and the DER corresponding to *B. cereus/E. coli*. This suggests that for the asymmetric code, one pathogen with larger concentration could in fact improve the detection performance of trace quantities of another pathogen because of the mutual coupling of detections.

## VI. CONCLUSIONS AND FUTURE DIRECTIONS

In this paper we have summarized some of the key milestones that have been achieved in our effort to integrate FEC principles with biosensor technology. Using a lateral flow immunosensor as a model biosensor we have developed biomolecular circuit models, noise models and a simulation framework for evaluating the reliability of different encoding and decoding strategies. Our current research is focussed on experimentally verifying the performance of the asymmetric code and also verifying the use of the “co-detection” protocol in detecting trace quantities of pathogens.

## ACKNOWLEDGMENT

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