# Multianalyte Digital Enzyme Biosensors with Built-in Boolean Logic

**ARTICLE** *in* ANALYTICAL CHEMISTRY · MAY 2012

Impact Factor: 5.64 · DOI: 10.1021/ac3007076 · Source: PubMed



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# Multianalyte Digital Enzyme Biosensors with Built-in Boolean Logic

**Novel biosensors based on the biocomputing concept digitally process multiple biochemical signals through Boolean logic networks of coupled biomolecular reactions and produce output in the form of a YES/NO response. Compared to traditional single-analyte sensing devices, biocomputing approach enables a high-fidelity multianalyte biosensing, particularly beneficial for biomedical applications.**

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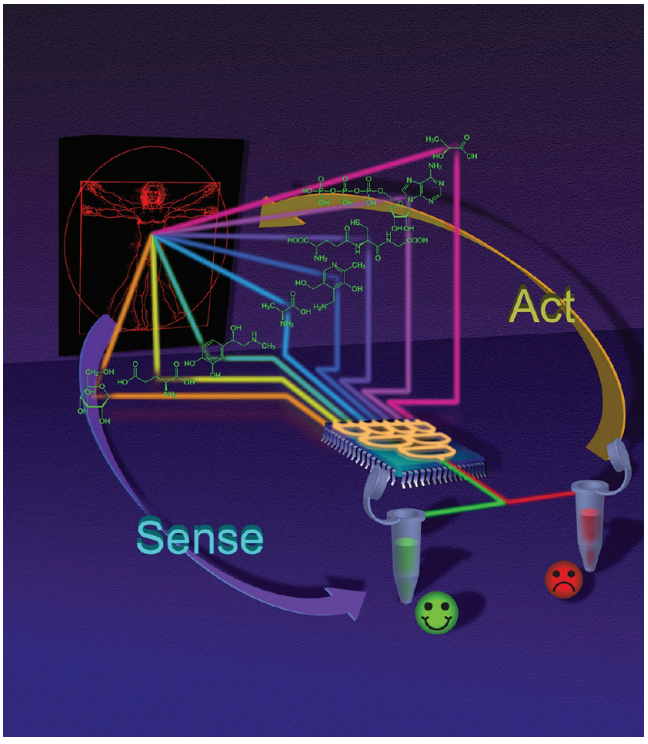
Supporting Information




Robert Gates

Biosensors, from the very first prototype pioneered by Clark[1] in 1962 to sophisticated modern devices,[2] are all based on the same general concept: a biomolecular reaction with analyte species followed by transduction of a chemical signal to an electronic one. Suitable biomolecular reactions can be based on enzyme-catalyzed processes[3] or biorecognition/bioaffinity events[4] using immune-specific,[5] DNA-specific,[6] or bioreceptor-specific[7] interactions. The major advantage of all these processes is the high specificity in the biorecognition of a single selected analyte. The results of the biochemical reactions are usually transduced to electronic signals by electrochemical,[8] optical,[9] or other[10] physical means. The entire biosensor assembly includes a biosensing interface integrated with an electronic transduction instrument, a power supply, and an electronic (frequently computerized) signal-processing unit, Figure 1A. Usually, the output signal is linearly proportional to the analyte concentration and can be characterized by its dynamic concentration range, where the linear dependence on the analyte concentration is preserved, and selectivity (being independent of various interfering species). Typically, a biosensor provides quantitative information on the concentration of a single analyte, e.g., glucose.[11] Many different bioanalytical assays, e.g., enzyme-linked immunosorbent assay (ELISA),[12] while relying on different recognition events, function in a similar manner. Sometimes the differences between biosensors and bioanalytical assays are merely technical, e.g., when the biomolecular reaction is not fully integrated with the transduction interface of the instrument converting the chemical signal to electronic one.

Simultaneous analysis of several different species is carried out by biosensor or bioassay arrays. Such arrays generate signals from multiple analytical channels working in parallel, each channel providing quantitative information on one specific analyte.[13] The resulting signals can then be processed by a computer, Figure 1B. In "field" situations when extensive use of computers or human involvement is not practical, drawing quantitative conclusions from the results obtained by multichannel analysis can be challenging, because the concentrations of different analytes typically span wide ranges of values, and their direct inspection is not definitive. Presently, very few applications generate a bioanalytical result with a qualitative YES/NO conclusion. This format can be useful when there is no need for precise, quantitative measurements, e.g., in a pregnancy test[14] or for detection of chemical weapons on a battlefield,[15] when a rapid answer is important. Novel approaches to qualitative analysis providing the final result in the YES/NO form would be beneficial for various end-users and point-of-care applications[16] in medicine, homeland security, or military applications, requiring rapid simultaneous analysis of multiple analyte species.

**Published:** May 29, 2012

   dx.doi.org/10.1021/ac3007076 | *Anal. Chem.* 2012, 84, 5463−5469

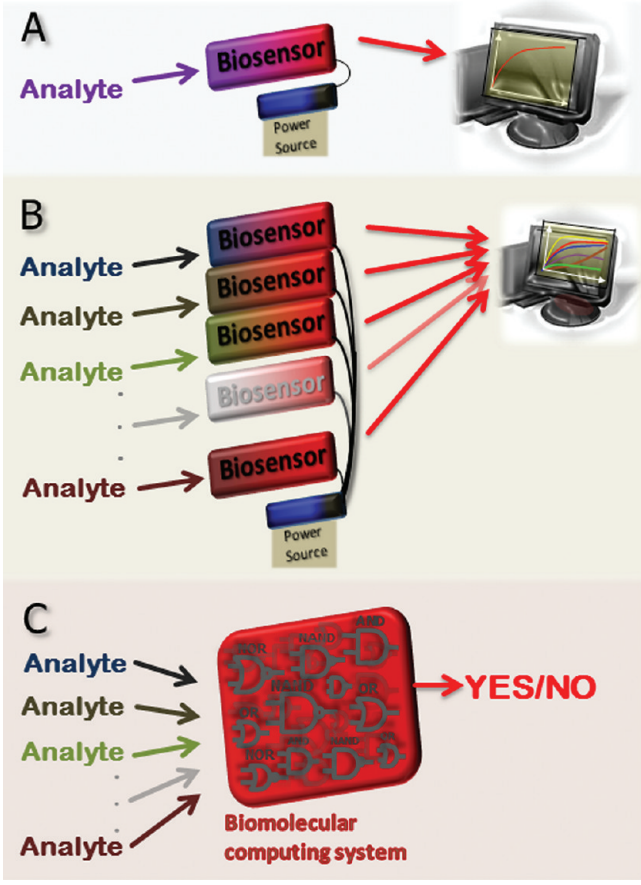


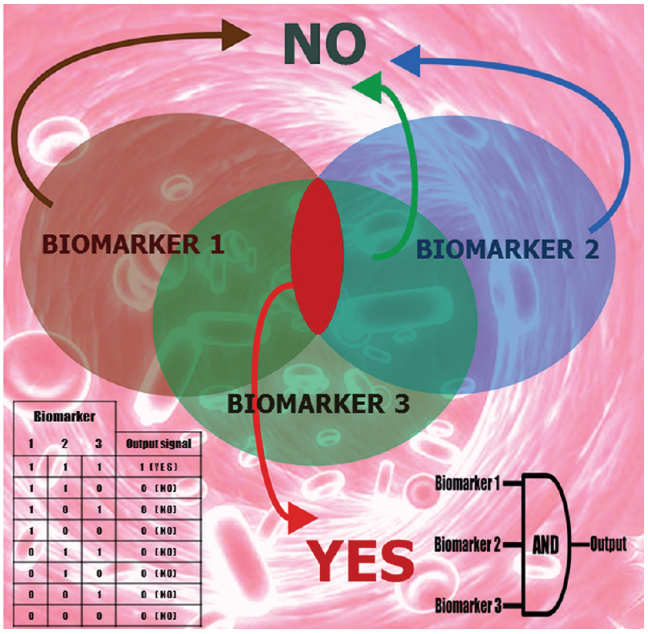

**Figure 1.** Different approaches to biosensing: (A) a single-analyte biosensor; (B) an array of parallel biosensors for multianalyte analysis with the computer-processed multichannel signals; (C) multianalyte analysis carried out by a biomolecular logic system with the input signals chemically processed and the final output generated in the binary YES/NO form.

A successful approach has recently been advanced based on unconventional chemical computing,[17] specifically, recently pioneered biomolecular computing systems.[18] Such biocomputing systems based on proteins/enzymes,[19] DNA,[20] RNA,[21] DNAzymes,[22] and whole cells[23] can perform logic operations processing multiple biochemical input signals. On the basis of biomolecular systems, various Boolean logic operations, such as **AND**, **OR**, **XOR**, **NOR**, **NAND**, **INHIB**, **XNOR**, etc., were realized.[18] Sophisticated networks composed of several concatenated biomolecular logic gates performing complex logic operations were designed for unconventional computing applications.[18] Particularly, rapid progress was recently achieved in the area of enzyme-based biocomputing systems allowing their assembling in the form of concatenated logic networks composed of many gates performing various Boolean logic operations and including non-Boolean elements, such as enzyme-based multiplexer and demultiplexer, amplifier, filter, etc, mimicking their electronic counterparts.[19] Although chemical information processing systems were originally considered exclusively for computational applications,[24] it has recently been realized that they have features suitable for analytical/bioanalytical use.[25] These systems can analyze several biochemical signals according to a predesigned "program" and generate a binary "YES/NO" answer without using a computer. Such chemical testing, analogous to a pregnancy test, might be convenient for certain end-user and point-of-care applications, Figure 1C. Networks with computational steps that involve only biochemical processes[18,19] are being investigated for new technological capabilities that include multi-input biosensors with new functionalities.[25] New approaches are being explored, allowing one to reduce the use of batteries, inorganic leads, and electrical power supply for those stages of information processing that occur during biomedical testing, in implantable devices, and toward fast-decision making steps (e.g., therapeutic intervention). The first section of this Feature article describes how the biomedical analysis can benefit from the use of biomolecular information processing (biocomputing) systems. The next section illustrates logic systems processing biomarkers signaling liver injury.

When a biomedical analysis aimed at recognizing a pathophysiological dysfunction is performed with a biosensor, each specific biomarker should be analyzed separately according to a traditional approach. The search for biomarkers signaling various medical problems has become a very important area of medical research.[26] However, diagnostic conclusions can rarely be based on the analysis of just a single highly specific biomarker. Moreover, biomarkers may appear at low concentrations in a complex mixture with many other biomolecular species of similar structure and properties. For example, neuron-specific enolase is considered as a specific biomarker for traumatic brain injury (TBI).[27] However, its concentration in physiological fluids is much lower than that of generic enolases with similar biocatalytic properties. Furthermore, elevated levels of neuron-specific enolase might result from some other brain dysfunctions which are not directly related to TBI.[28] Therefore, even the species which is considered as a biomarker might not be specific enough to draw a reliable biomedical conclusion based on a single-species analysis. A standard solution of the specificity problem has been to analyze a set of less specific biomarkers present simultaneously with overlapping specificity, Figure 2, and in the biocomputing approach, such analysis is realized via a cascade of biocatalytic reactions.

A biocomputing approach can reduce technical problems in the analysis of highly specific biomarkers by analyzing species appearing at much higher concentrations. For example, glutamate and lactate dehydrogenase, analyzed together for their pathophysiologically elevated concentrations, could provide an attractive alternative for the challenging analysis of neuron-specific enolase to diagnose TBI.[29] Analysis of several biomarkers, each with limited selectivity, requires a proper design of a logic network for processing of the analyte signals. For example, analysis of two biomarkers for their simultaneous presence requires a biochemical reaction mimicking the Boolean **AND** logic operation.[30] In case of multiple biomarkers, more sophisticated logic networks composed of several logic gates performing various logic operations might be needed.[31] For example, a multienzyme/multi-input logic network composed of many concatenated **AND**/**OR** gates equipped with different biomolecular switches controlling the pathways involved in the input processing was designed for the analysis of different injury biomarkers.[31] These logic operations can be performed as a sequence of biochemical reactions without the use of electronic computers.[18,19] Both optical and electrochemical transduction modes can be used for detecting the products of such logic operations. Biomedical use of logic gates and sophisticated logic networks is a rather new and undeveloped research area, being advanced in parallel with


dx.doi.org/10.1021/ac3007076 | *Anal. Chem.* 2012, 84, 5463−5469




| Biomarker | | | |
|---|---|---|---|
| 1 | 2 | 3 | Output signal |
| 1 | 1 | 1 | 1 (YES) |
| 1 | 1 | 0 | 0 (NO) |
| 1 | 0 | 1 | 0 (NO) |
| 1 | 0 | 0 | 0 (NO) |
| 0 | 1 | 1 | 0 (NO) |
| 0 | 1 | 0 | 0 (NO) |
| 0 | 0 | 1 | 0 (NO) |
| 0 | 0 | 0 | 0 (NO) |

**Figure 2.** Simultaneous presence of biomarkers with limited specificity indicates a definitive YES conclusion, schematically represented by the overlapping region in the diagram. In the biochemical computing approach, this conclusion is realized as the output YES (or **1**) of a multi-input **AND** logic gate, obtained only when all the three inputs are in the ranges corresponding to **1**. The output NO (or **0**) is obtained for all the other combinations of inputs. The "truth table" for such a three-input gate and its logic diagram are also shown.

similar developments, such as logic operations realized with synthetic organic molecules aimed at computational applications.[17,32]

Biomolecular information processing systems have already been successfully applied to analyze protein libraries associated with multiple sclerosis.[33] Biosensor systems for detection of genetic modifications in avian influenza were developed based on the DNA computing principles, involving various oligonucleotide signals being processed by a DNA logic network.[34] Coupling enzyme logic systems with controlled self-assembly of nanoparticles allowed **AND**/**OR** logic responses to matrix-metalloproteinases MMP2 and MMP7.[35] In this study, the enzymes used as the input signals were important cancer biomarkers. MMP2 is overexpressed in many cancers, including breast cancers, and is an indicator of cancer invasiveness, metastasis, and angiogenesis, while MMP7, a protease with broader substrate specificity, is thought to facilitate early stages of mammary carcinoma progression.

The use of input signals with obvious biomedical relevance has represented a significant first step in the development of enzyme logic systems. However, the following important issues have required additional attention: (i) In model studies, the logic **0** values of the input signals were frequently taken as the complete absence of the biomaterial, whereas for practical applications they should be defined as normal physiological concentrations. (ii) The logic **1** values of the input signals did not always correspond to the concentrations expected in vivo. Instead, they were selected as convenient concentrations which sometimes significantly exceeded pathophysiological levels. (iii) The processing of the input signals according to different logic schemes did not always correspond to their diagnostic uses. For example, the proteases MMP2 and MMP7 were applied to activate the **AND** as well as **OR** logic gates without justification of the logic operation needed for the appropriate biomedical conclusion.[35] Some of these issues, which are particularly important for practical biomedical applications, were addressed

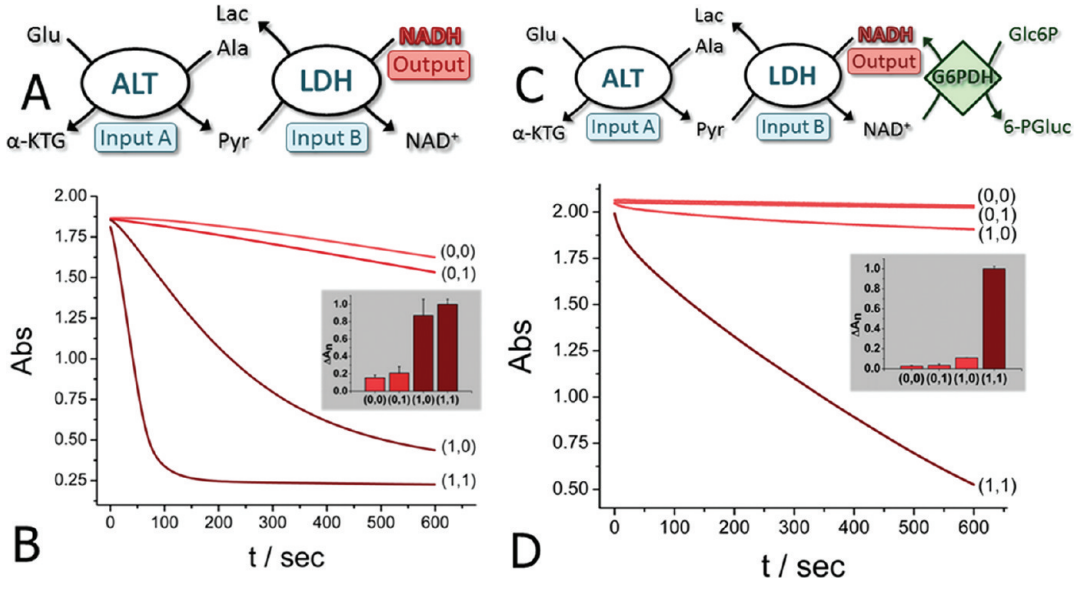



**Figure 3.** (A) Biocatalytic cascade for analysis of LI, activated by enzymes ALT and LDH as inputs for the **AND** logic gate. (B) Optical absorbance changes corresponding to the decreasing concentration of NADH upon application of different combinations of input signals. The inset shows the normalized output signals measured at 600 s from the reaction initiation. (C, D) The biocatalytic cascade and absorbance changes for a similar system operating with the added biochemical "filter" partially resetting the output signal, back to nearly its zero level, as long as the filter-activating substrate is not consumed. The inset in (D) shows the normalized output signals measured at 600 s with the improved separation between the logic outputs **0** and **1**. The following abbreviations for products and intermediates are used: Pyr for pyruvate, Lac for lactate, Glu for glutamate, Ala for L-alanine, and $\alpha$-KTG for $\alpha$-ketoglutaric acid. The filter enzyme is glucose-6-phosphate dehydrogenase (E.C. 1.1.1.49); the substrate and product in the filter step are D-glucose-6 phosphate and 6-phospho-gluconic acid, respectively.


dx.doi.org/10.1021/ac3007076 | *Anal. Chem.* 2012, 84, 5463−5469

in our recent research. Logic systems for the analysis of biomarkers characteristic of various battlefield injuries, which are important for immediate field-based decision making and therapeutic action (in the absence of hospital facilities), have been developed[31,36,37] and then theoretically modeled and optimized.[38]

Let us illustrate how logic gates can be optimized for practical biomedical analytical applications and interfaced to electronic transducing interfaces amplifying the chemical signal. For this discussion, in order to keep it simple, we will consider only one example-system performing a single **AND** logic operation. The selected example will allow one to follow the development of the system from its biosensoric use to bioactuation and from analysis of model solutions artificially spiked with biomarkers to the assay of real biological samples containing naturally produced biomarkers. It should be noted, however, that much more sophisticated logic networks composed of many concatenated logic gates and processing more than two input signals were designed for computational and biosensoric applications (the readers can find their examples in the Supporting Information and recent reviews[18,19]).

We consider the system[37] activated by two biomarkers mimicking an **AND** logic gate and signaling liver injury when the concentrations of both are elevated from the normal to pathophysiological levels. The two inputs are enzymes alanine transaminase (ALT, E.C. 2.6.1.2) and lactate dehydrogenase (LDH, E.C. 1.1.1.27), which are biomarkers characteristic of liver injury (LI).[39] It should be noted that each of them alone is not specific enough to indicate LI; however, their simultaneous increase in concentration, from normal to pathophysiological levels, provides an unambiguous evidence of LI.[40] Logic **0** and **1** levels of ALT (0.02 and 2 $U{\cdot}mL^{-1}$) and LDH (0.15 and 1 $U{\cdot}mL^{-1}$) input signals were selected in order to mimic meaningful circulating levels of these biomarkers under normal and pathophysiological conditions, respectively.[39−42] On the basis of the sequence of the biochemical reactions, Figure 3A, the final result, oxidation of NADH which causes the decrease in the optical absorbance, Figure 3B, should be obtained only upon concerted work of the two enzyme biomarker inputs. However, it should be remembered that logic-**0** values in their present definition are not the absence of the enzymes but rather their presence at normal physiological levels. Therefore, the decrease in absorbance is observed not only for the **1**,**1** input combination but also to some extent for inputs **0**,**0**, **0**,**1**, and **1**,**0**, Figure 3B. When the readout time interval is limited to 50−200 s, the absorbance decrease is measurably larger for the **1**,**1** input combination, defining output **1**. The other three input combinations yield smaller absorbance changes, defining output **0**, Figure 3B. However, for reaction times exceeding 200 s, which are relevant for recently investigated actuation applications,[43] the absorbance decrease for the **1**,**0** input combination becomes comparable with one for **1**,**1** inputs, Figure 3B. At sufficiently long reaction times, the results for the **1**,**0** and **1**,**1** input combinations will become indistinguishable, and the **AND** gate will no longer be realized, Figure 3B, inset.

In order to increase the gap separating output signals **0** and **1**, a "filter" process[44] was added consuming the chemical product $NAD^+$, converting it back to NADH for small input concentrations, Figure 3C. This has allowed us to achieve high-quality signal separation for times as large as 600 s and beyond, Figure 3D. It is likely that such "filter" processes can potentially be implemented with any so-called $NAD^+$-dependent dehydrogenase,[45] e.g., glucose dehydrogenase activated by physiological amounts of glucose. However, aiming at the eventual application of our system in a physiological environment, we selected glucose-6-phosphate dehydrogenase (G6PDH, E.C. 1.1.1.49) as the filter-enzyme. It is activated by D-glucose-6 phosphate (Glc6P) which does not interfere with glucose naturally existing in blood, thus allowing one to tune the Glc6P concentration independently on the physiological glucose concentration. The filter system works in the following way: In the presence of G6PDH and Glc6P, the biocatalytically produced $NAD^+$ is converted back to NADH. Thus, absorbance changes are prevented until Glc6P is totally consumed. Only then the depletion of NADH can fully set in, resulting in the absorbance decrease. The delay in the biocatalytic oxidation of NADH is controlled by the amount of the added Glc6P and can be optimized. A comprehensive approach to the filter performance optimization could include detailed analysis of the reactions kinetics.[44] However, a simple experimental optimization might suffice. Addition of the G6PDH-Glc6P filter to the biocatalytic cascade activated by ALT-LDH biomarker inputs, Figure 3C, has allowed a much better separation of the output signals generated by the system for the **1**,**1** vs all the other combinations of the inputs, Figure 3D. However, while improving the binary-signal separation, such filtering can decrease the overall signal strength which could be an added source of relative noise.[46] Thus, filtering is useful at sufficiently large times, such that the decrease in the absorbance reaches its saturation, of relevance in actuation applications.[43] When the output signals were measured at 600 s, the desired system operation corresponding to the high-tolerance **AND**-logic realization was obtained in the presence of the filter, Figure 3D, inset. Good-quality separation of the **0** and **1** output signals was found to persist at much larger times as well, up to 3 h. The robustness of this analytical system has allowed its use in human serum solutions.[37]

A system similar to that described in Figure 3C, but with glucose dehydrogenase (GDH, E.C. 1.1.1.47) as the filter-enzyme, was used for electrochemical transduction/amplification of the signals generated by the **AND** logic gate activated by ALT and LDH biomarkers, Figure 4.[43] The reaction biocatalyzed by the filter-enzyme provided improved resolution between the output **0** and **1** signals as described above. In addition, glucose was oxidized in the "filter" biocatalytic step resulting in the formation of gluconic acid and lowering the pH value. A pH-switchable electrode modified with poly(4-vinyl pyridine) (P4VP) was activated for electrochemical reactions only when the solution pH value reached the $pK_a$ of the P4VP polymer brush. In the pH range below $pK_a$, protonation of the polymer brush produced a swollen state permeable for anionic redox species, Figure 4A. The pH changes resulting in the electrode activation were achieved only when both biomarker inputs, ALT and LDH, were applied at their **1**,**1** logic values corresponding to the conditions of LI injury. Any other combinations of the input signals (**0**,**0**, **0**,**1**, and **1**,**0**) did not produce pH changes reaching the polymer $pK_a$ value and thus did not result in the electrode activation, Figure 4A. The inactive state of the pH-switchable electrode was characterized by cyclic voltammetry and Faradaic impedance spectroscopy, which demonstrated no peaks and a large electron transfer resistance, respectively, Figure 4B−C. This is consistent with the properties of the P4VP polymer brush in the neutral (nonprotonated) state which is hydrophobic and nonpermeable to ionic redox species. The active state of the electrode was obtained only upon application of the **1**,**1** combination of the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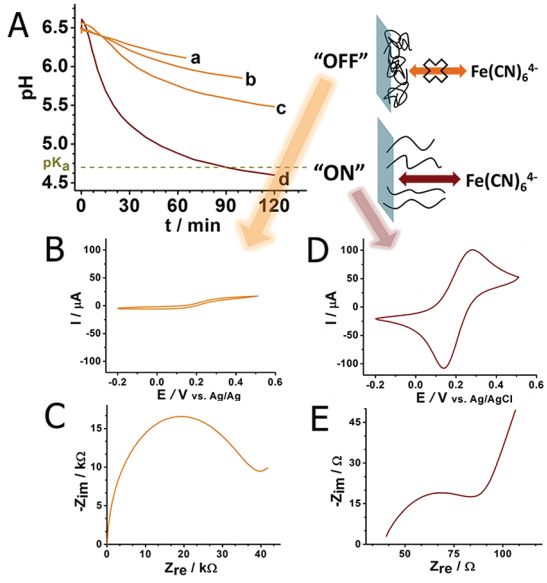


**Figure 4.** Electrochemical transduction of the signals generated by the **AND** logic gate for analysis of LI activated by ALT and LDH input signals: (A) pH changes generated in situ by the biocatalytic cascade activated with various combinations of the ALT/LDH signals: a-(**0**,**0**), b-(**0**,**1**), c-(**1**,**0**), and d-(**1**,**1**). The dotted line corresponds to the p$K_a$ value of the P4VP-brush immobilized on the electrode surface. (B, D) Cyclic voltammograms, 10 mM $K_4[Fe(CN)_6]$, 100 mV·$s^{-1}$, obtained at the electrode in the OFF and ON states, respectively. (C, E) Impedance spectra, 10 mM $K_4[Fe(CN)_6]$, bias potential of 0.17 V, obtained at the electrode in the OFF and ON states, respectively. The biocatalytic cascade is the same as in Figure 3C, but here the filter enzyme is glucose dehydrogenase (GDH, E.C. 1.1.1.47), the substrate and product operating with it are glucose and gluconic acid, respectively.

input signals and showed peaks in the cyclic voltammogram typical for the reversible electrochemical reaction of $[Fe(CN)_6]^{3-}$ redox probe, Figure 4D, while the impedance spectrum showed the corresponding decrease in the electron transfer resistance, Figure 4E (note the difference in the impedance scales of the C and E panels). Utilization of a pH sensitive-electrode allowed not only electrochemical transduction of the biochemical output signal generated by the biocatalytic cascade but also its significant amplification. Small concentration change of $NAD^+$, which is required for glucose oxidation, sufficed for the electrode activation for the redox probe used at a large concentration.

It should be noted that the filter-reaction increasing the separation between the output signal **0** and **1** logic values is critically important for achieving the results described above. In the described systems, ALT and LDH were systematically added to the analyte solutions in four different combinations: **0**,**0**; **0**,**1**; **1**,**0**; and **1**,**1**, where **0** and **1** input values corresponded to the normal and pathophysiological concentrations of the biomarkers. The input combinations **0**,**0** and **1**,**1** correspond to the normal physiological and liver-injury conditions, respectively, while the combinations **0**,**1** and **1**,**0** have medical meanings unrelated to the liver injury. In order to analyze performance of the system under real physiological conditions, the samples containing biomarkers should be obtained from biological sources rather than prepared in a laboratory. A well-established previously described[47] model for porcine injury was utilized to obtain samples mimicking physiological conditions of human liver injury. Assuming that porcine samples contain the biomarker concentrations similar to the human physiology,[48] they were analyzed for the simultaneous presence of ALT and LDH. Since the biomarkers were not artificially added to the samples but rather naturally appeared under varying the animal physiological conditions,[48] only two major categories of the samples were expected, with **0**,**0** and **1**,**1** logic levels of ALT and LDH for the control and liver injured groups of animals, respectively. Within these two groups, the porcine samples still had fluctuations in the concentrations of the enzyme biomarkers.[48] This is illustrated in Figure 5, which shows the

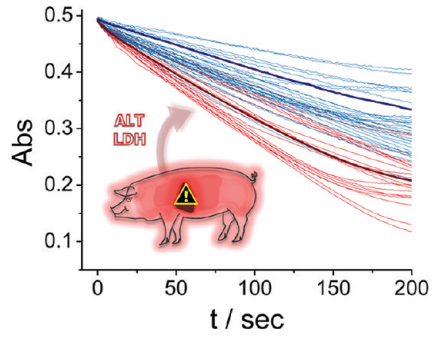


**Figure 5.** Absorbance changes corresponding to the consumption of NADH upon operation of the analytical system activated by porcine samples naturally containing ALT and LDH biomarkers. The bottom (red) traces correspond to the application of porcine samples from the liver-injured animals, while the top (blue) traces correspond to the control group of animals without liver injury. Bold solid curves show the average responses for both groups.

time-dependent decrease of NADH absorbance during the reaction of the analytical system with the porcine serum samples. The bottom section of the absorbance decay corresponds to the porcine samples originating from the liver injured animals (elevated concentrations of the biomarker–enzymes), while the top part was obtained for control animals without the liver injury (with the biomarker–enzymes present at the normal physiological concentrations). These responses are statistically different from each other (see the details of their statistical analysis in the Supporting Information). The established difference between normal physiological and pathophysiological levels of the biomarkers thus allows one to distinguish liver-injured animals from the control group.

## ■ CONCLUSIONS AND PERSPECTIVES

Applying novel concepts from the area of unconventional computing[24] (specifically from biomolecular computing)[18] to biosensing and bioanalytical assays has resulted in the design of biomolecular systems logically processing several chemical signals and converting them to a single binary output in the format of YES/NO. Information processing in biomolecular systems does not require electronic computers and proceeds at the level of chemical reactions. The "program" for processing chemical inputs can be implemented in the composition of the biomolecular system and can include various logic operations applied in different combinations. The systems exemplified above demonstrated the simplest **AND** logic applied to two biochemical input signals. However, many other logic operations integrated in various logic circuitries are possible with the use of different enzymes[19] and other biomolecules,[20−22] to allow high-fidelity detection of diverse pathophysiological conditions and medical emergencies. The resulting digital biosensors would thus benefit different


dx.doi.org/10.1021/ac3007076 | Anal. Chem. 2012, 84, 5463−5469

important fields, ranging from biomedical analysis[25] as well as environmental monitoring and security screening,[49] by enabling on-demand immediate intervention or corrective action on the basis of reliable analytical data.

An important challenge in developing this kind of the digital multisignal biosensor system is obtaining a significant difference between the logic **1** and **0** output values (in other words, a well-defined YES/NO answer). One should remember that in case of biomedical applications the input signals appear at their physiological levels, where the logic value **0** may not correspond to the physically zero concentration. Moreover, there might be a relatively small difference in the physical concentrations of the input signals corresponding to the logic **0** and **1**. In order to obtain significant difference in the output signals, the response function should be sigmoid rather than linear.[46] In other words, the system should demonstrate a nonlinearity with a sharp transition between the **0** and **1** states. The first steps in this direction have been already done experimentally and analyzed theoretically.[44] However, extensive research effort aimed at designing chemical "filter" systems similar to the electronic counterparts is needed.[50] The thresholds separating the logic **0** and **1** values could be personally tailored for a given patient by following circulating biomarkers in the physiological liquids. This will be an important step toward future personalized medicine.

Biochemical computing and logic-gate systems based on biomolecules have the potential to revolutionize the field of biosensors. Interfacing biocomputing elements with sensing processes would allow multisignal analysis followed by biochemical processing of the data, giving a final digital ("YES" or "NO") analytical answer. Such "YES/NO" information allows also direct coupling of the signal processing with signal-responsive materials[43] and chemical actuators[51,52] to offer a closed-loop "Sense/Act" operation. Biochemical networks can offer robust error-free operation upon appropriate optimization of their components and interconnections. Chemical stability of the biomolecular components will be improved upon their immobilization in signal-responsive materials or at functional interfaces. Further development of this research area requires collaborative efforts of engineers, biochemists, and computer specialists. The ultimate goal of this work will be the design of a microfluidic lab-on-a-chip performing multienzyme-catalyzed cascades and operating similarly to an electronic chip by being able to integrate large networks for processing biochemical signals.

## ■ ASSOCIATED CONTENT

### Supporting Information

Additional information as noted in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


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### Notes

The authors declare no competing financial interest.

### Biography

Evgeny Katz received Ph.D. in Chemistry from Frumkin Institute of Electrochemistry (Moscow) in 1983. He was a senior researcher in the Institute of Photosynthesis (Pushchino), Russian Academy of Sciences (1983−1991), a Humboldt fellow at München Technische Universität (Germany) (1992−1993), and a research associate professor at the Hebrew University of Jerusalem (1993−2006). From 2006, he has been the Milton Kerker Chaired Professor at the Department of Chemistry and Biomolecular Science, Clarkson University, NY (USA). He has (co)authored over 340 papers in the areas of biocomputing, bioelectronics, biosensors, and biofuel cells (Hirsch-index 67). He is a Chair of the "Bioelectrochemistry" Division of the International Society of Electrochemistry. He also serves as Editor-in-Chief for *IEEE Sensors Journal* and a member of editorial boards of many other journals. Joseph Wang received a Ph.D. from Israel Institute of Technology in 1978. He held Regents Professorship and a Manasse Chair position at NMSU, served as the director of Center for Bioelectronics and Biosensors of Arizona State University (ASU), and is currently a Professor in the Department of Nanoengineering at University of California, San Diego (UCSD). Prof. Wang has published more than 840 papers and 10 books, and he holds 12 patents (Hirsch-index 94). He received 2 ACS National Awards in 1999 and 2006 and 4 Honorary Professors from Spain, Argentina, and Slovenia. He became the most cited electrochemist in the world and received the 4th place in the ISI's list of "Most Cited Researchers in Chemistry" in 1996−2006. Prof. Wang is the Editor-in-Chief of *Electroanalysis* (Wiley). His scientific interests are concentrated in the areas of nanomachines, bioelectronics, biosensors, bionanotechnology, and electroanalytical chemistry. Marina Privman received her B.Sc. in Chemistry from the Hebrew University of Jerusalem (1980), M.Sc. from Technion—Israel Institute of Technology (1982), and Ph.D. from Clarkson University (1991). Her postdoctoral training was at the University of Oxford, UK, and at Clarkson University. She joined the faculty of Empire State College (ESC) of the State University of New York (SUNY) in 1998. Presently she holds the rank of Associate Professor and is the ESC site coordinator at the US Army Educational Center in Fort Drum (NY). Her research covers topics in bioelectrochemistry, with recent interest in complex information and signal processing, and in innovative approaches to college education of diverse adult student populations. Jan Halámek received his Ph.D. degree in the Department of Biochemistry at Masaryk University in Czech Republic, in 2003. In 2003−2006, he worked as a postdoctoral fellow (Individual Marie Curie Fellowship) at the Department of Analytical Biochemistry, Potsdam University, Germany. In 2007−2008, he worked as a research fellow at the Department of Biophysical Engineering, Twente University, Netherlands. Currently, he is Research Assistant Professor at Clarkson University, NY (USA). He has co(authored) more than 45 papers and 3 patents in the areas of bioelectronics, affinity-based logic system, and biocomputing (Hirsch-index 14).

## ■ ACKNOWLEDGMENTS


This work was supported by the Office of Naval Research (Award #N00014-08-1-1202) and NSF (Awards #CBET-1066397 and #CBET-1066531). The authors thank all students, postdoctoral researchers, and collaborators who made this interesting research possible.


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