Enzyme-Based Multiplexer and Demultiplexer

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A digital 2-to-1 multiplexer and a 1-to-2 demultiplexer were mimicked by biocatalytic reactions involving concerted operation of several enzymes. Using glucose oxidase (GOx) and laccase (Lac) as the data input signals and variable pH as the addressing signal, ferrocyanide oxidation in the output channel was selectively activated by one from two inputs, thus mimicking the multiplexer operation. A demultiplexer based on the enzyme system composed of GOx, glucose dehydrogenase (GDH) and horseradish peroxidase (HRP) allowed selective activation of different output channels (oxidation of ferrocyanide or reduction of NAD^+) by the glucose input. The selection of the output channel was controlled by the addressing input of NAD^+. The designed systems represent important novel components of future branched enzyme networks processing biochemical signals for biosensing and bioactuating.

Introduction

Chemical computing,[1] representing a branch of unconventional computing, has received high attention in the past decade, resulting in the development of various Boolean logic gates, such as **AND**,[2] **OR**,[3] **XOR**,[4] **NOR**,[5] **NAND**,[6] **INHIB**,[7]and **XNOR**.[8] Sophisticated molecular design allowed reversible,[9] reconfigurable,[10] and resettable[11] logic gates for processing chemical information. The combination of chemical logic gates in groups or networks resulted in simple computing devices performing basic arithmetic operations[12] such as half-adder/half-subtractor[13] or full-adder/full-subtractor.[14] Other chemical systems mimicking various non-Boolean components of digital electronic devices were designed, including molecular comparator,[15] digital multiplexer and demultiplexer,[16] encoder−decoder,[17] flip-flop and write−read−erase memory units.[18] Artificial abiotic systems mimicking elementary properties of neuron networks were developed demonstrating that scaling-up the complexity of chemical computing systems can be inspired by biological principles.[19] However, many of the recently developed chemical computing systems[1] operate as single logic gates without the possibility to be concatenated in networks.

Most of the problems in the networking logic gates and scaling-up the complexity of the chemical computing systems hardly addressable by synthetic chemical systems can be solved easily and naturally by application of biomolecular systems. The recently emerged research field of biocomputing, based on application of biomolecular systems for processing chemical information, has achieved higher complexity of information processing while using much simpler chemical tools, due to the natural specificity and compatibility of biomolecular components.[20] Recently, pioneered enzyme-based logic systems[21,22] were concatenated in networks,[23] optimized for error reduction,[24] and coupled with electronic transducers[25,26] and signal responsive materials[27] to use the biochemically processed signals for controlling multisignal biosensors and actuators. Rapid progress in the assembling of the enzyme-based logic gates in complex multicomponent networks requires developments of additional components mimicking electronic counterparts, such as **FANOUT** gate,[25] amplifier,[28] signal convertor,[28] flip-flop memory unit,[29] etc., which are necessary for the effective operation of the biochemical computing networks and devices. The important network components needed for branching the biocomputing pathways are multiplexer and demultiplexer. While a few examples of the multiplexer/demultiplexer chemical design were recently published,[16] the enzyme-based systems performing their functions are not available yet. It should be noted that nonbiochemical multiplexer/demultiplexer systems were based on fluorescent output signals, which are not compatible with biochemical pathways and cannot be used to switch signals between different branches of biochemical networks.

The present paper reports on the first examples of an enzyme-based multiplexer and demultiplexer, aiming at their future use in complex biocatalytic logic networks. These networks, when applied for biomedical sensing, will process multiple biochemical signals through branched biocatalytic cascades, finally resulting in the logic analysis of various patterns of biochemical signals originating from different physiological conditions of a patient.[30]

Experimental Section

Chemicals and Materials. The chemical reagents and enzymes for the biochemical systems were obtained from Sigma-Aldrich and used without further purification: glucose oxidase (GOx) from *Aspergillus niger* type X-S (EC 1.1.3.4); horseradish peroxidase (HRP) type VI (EC 1.11.1.7), laccase (Lac) *Trametes versicolor* (EC 1.10.3.2), glucose dehydrogenase (GDH) from *Pseudomonas sp*. (EC 1.1.1.47), potassium hexacyanoferrate (II) trihydrate, 2,2′-azino-*bis*(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), β-nicotinamide adenine dinucleotide sodium salt (NAD^+) from yeast, and D-(+)-glucose. Ultrapure water (18.2 MΩ cm) from NANOpure Diamond (Barnstead) source was used in all of the experiments.

Instruments and Methods. All optical measurements were performed using a UV-2401PC/2501PC UV−vis spectrophotometer (Shimadzu, Tokyo, Japan) in 1 mL disposable poly-

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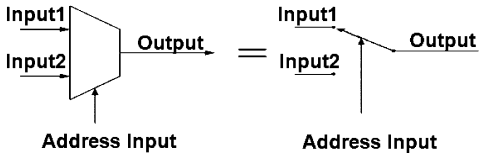
SCHEME 1: Schematics of the 2-to-1 Multiplexer (*left*) and the Equivalent Switching Device (*right*)



(methyl methacrylate) (PMMA) or 2 mL quartz cuvettes thermostatted at 37 ± 0.2 °C.

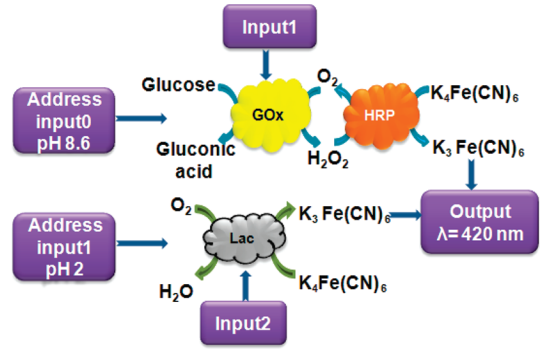
Results and Discussion

In electronics, a multiplexer is a device that performs multiplexing − selection of one of many analog or digital input-signals and forwarding the selected input into a single output channel. When it is combined with digitally processed inputs, the signals are represented by logic **0** and **1** values. In the simplest example of a 2-to-1 multiplexer, the device should select one of two digital data input signals (**Input1**; **Input2**) and direct it to the single output channel (**Output**). An additional input signal (addressing input, **Address**) should switch between the two input channels, selecting one of them to direct the signal to the output channel, Scheme 1. When the addressing signal **Address** appears as **0**, the input data signal from **Input1** channel is directed to the **Output** channel regardless of its logic value (**0** or **1**). If the addressing channel **Address** has value **1**, the data input signal is directed from **Input2** to **Output** also, regardless of its value (**0** or **1**).

In order to mimic the 2-to-1 digital multiplexer function, we designed a system where two enzymes, GOx and Lac, were used as the data input signals (**Input1** and **Input2**, respectively), activating two biocatalytic input channels. The presence of these enzymes in optimized concentrations (0.1 units·mL^{-1} GOx and 0.5 milliunits·mL^{-1} Lac) was considered as logic **1** input for the data input channels, while their absence was used as logic **0** input. It should be noted that the optimized concentrations of the enzymes were selected based on the experimental convenience for generating similar output signals in convenient time. In the present work, the "optimized" concentrations imply neither noise reduction[24] nor physiological levels for biomedical applications.[30] The "machinery" of the biochemical system included 10 units·mL^{-1} HRP, 10 mM glucose, 10 mM $K_4[Fe(CN)_6]$, and oxygen (in equilibrium with air) dissolved in 50 mM phosphate buffer solution at the initial pH 7.5. The biocatalytic activities of the both input enzymes have optimums at very different pH values. GOx reveals the highest activity at pH ca. 7, while Lac has the best activity at pH ca. 4.[31] Thus, we applied different pH values to separate the enzyme activities and to perform the biocatalytic reactions selectively. However, as Lac shows significant activity at the GOx optimum pH and vice versa, we applied pH 8.6 (above the optimum value) to activate GOx and pH 2.0 (below the optimum value) to activate Lac to be sure that only the appropriate enzyme is working. In the preliminary experiments (see details in the Supporting Information), we demonstrated that GOx activates the biocatalytic cascade (Scheme 2), finally resulting in the oxidation of ferrocyanide at pH 8.6, while Lac was unable to oxidize ferrocyanide at this pH value. On the other hand, at pH 2.0 only Lac was catalytically active to oxidize ferrocyanide, while GOx was almost inactive for the reaction (Scheme 2).

Keeping this result in mind, we performed a set of experiments to mimic the 2-to-1 multiplexer using the biocatalytic reactions shown in Scheme 2. Various pH values were applied

SCHEME 2: The Biocatalytic System Mimicking the 2-to-1 Multiplexer, Where GOx and Lac Are the Data Input Signals (Input1 and Input2, Respectively) and the pH Change Is the Addressing Signal (Address)[a]



[a] The same **Output**, $K_3[Fe(CN)_6]$, is produced in both reacting pathways.

as addressing inputs to select between the biocatalytic channels: pH = 8.6 was defined as the logic **0** input for **Address**, while pH = 2.0 was considered as the logic input **1**. The reacting solution was adjusted to the selected pH values by the titration with H_2SO_4 or NaOH. The final output signal of the biochemical multiplexer was defined as the biocatalytic formation of ferricyanide analyzed by the optical absorbance measurements at $\lambda = 420$ nm. Figure 1A shows the absorbance spectra obtained at pH 8.6 (**Address** = **0**). The absorbance peak, $\lambda_{max} = 420$ nm, characteristic of $[Fe(CN)_6]^{3-}$ was obtained when GOx was added regardless of the presence or absence of Lac (input combinations: **1**,**1** and **1**,**0**, respectively, where the first digit corresponds to **Input1** (GOx) and the second - to **Input2** (Lac)). On the other hand, the absorbance was not changed when GOx was absent regardless of the presence or absence of Lac (input combinations: **0**,**1** and **0**,**0**, respectively). This experiment demonstrated that **Address** = **0** selects the channel **Input1** to generate the output signal, while the channel **Input2** is mute, Figure 1A, inset. Figure 1B shows the absorbance spectra obtained at pH 2.0 (**Address** = **1**). In this case, the high absorbance reflecting the $[Fe(CN)_6]^{3-}$ formation was obtained only when Lac was present (input signals **0**,**1** and **1**,**1**), while in the absence of Lac (input signals **1**,**0** and **0**,**0**) the absorbance was not changed. This experiment demonstrated that **Address** = **1** selects the channel **Input2** to generate the output signal, while the channel **Input1** is inactive (Figure 1B) inset.

The demonstrated pH-controlled switching between two biocatalytic channels mimics the 2-to-1 digital multiplexer (Table 1), and it can be represented by the electronic equivalent circuitry shown in Scheme 3. In this scheme, two **AND** logic gates operate in parallel, while the **Address** input has the opposite effect on them being inverted for one of the **AND** gates. The concerted operation of the gates results in the production of the same output signal being, however, activated by two different data inputs. This equivalent circuit allows the multiplexer operation, similarly to the electronic counterpart.[32] It should be noted that application of pH changes as the addressing input would be very convenient in many biocomputing networks, and many examples of enzyme logic gates[26,27] and their networks[25] producing pH changes were already designed. Also, application of enzymes as input signals in the logic systems has been studied.[22,27]

The opposite process of forwarding one data input signal (**Input**) into two different output channels (**Output1** and **Output2**) can be performed by a 1-to-2 demultiplexer. In this

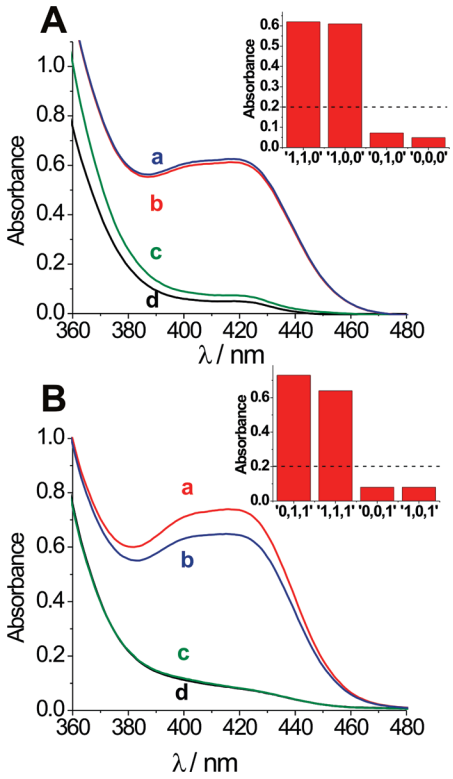
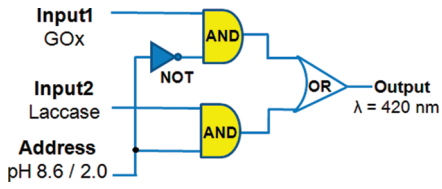


Figure 1. Spectra generated by the biocatalytic 2-to-1 multiplexer upon different combinations of the data and address signals. (A) **Address** = **0**: (a) **Input1** = **1**, **Input2** = **1**; (b) **Input1** = **1**, **Input2** = **0**; (c) **Input1** = **0**, **Input2** = **1**; (d) **Input1** = **0**, **Input2** = **0**. Inset: Bar diagram of the output signals (**Output**) generated by different combinations of the **Input1**, **Input2**, **Address** signals. (B) **Address** = **1**: (a) **Input1** = **0**, **Input2** = **1**; (b) **Input1** = **1**, **Input2** = **1**; (c) **Input1** = **0**, **Input2** = **0**; (d) **Input1** = **1**, **Input2** = **0**. Inset: Bar diagram of the output signals (**Output**) generated by different combinations of the **Input1**, **Input2**, **Address** signals. The dashed line is the threshold separating the logic **0** and **1** output values. The system composition and operation are described in the text.

TABLE 1: Truth Table for the Operation of the Biomolecular Digital 2-to-1 Multiplexer

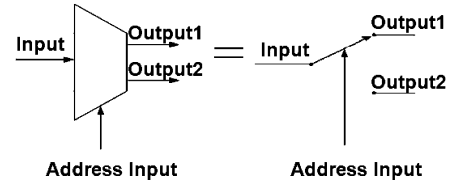
data input		address input	data output
Input1 GOx	**Input2** **Lac**	pH 8.6 (0)/2.0 (1)	λ = 420 nm
0	0	0	0
1	0	0	1
0	1	0	0
1	1	0	1
0	0	1	0
1	0	1	0
0	1	1	1
1	1	1	1

SCHEME 3: The Electronic Equivalent Circuitry of the 2-to-1 Multiplexer Based on the Enzyme Catalyzed Reactions

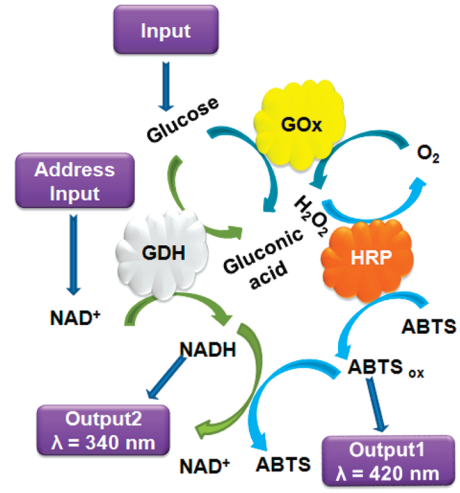


case, the additional addressing input (**Address**) selects either output channel to be used to take the data input signal (Scheme 4). In order to mimic this electronic device, we designed a

SCHEME 4: Schematics of the 1-to-2 Demultiplexer (*left*) and the Equivalent Switching Device (*right*)



SCHEME 5: The Biocatalytic System Mimicking the 1-to-2 Demultiplexer, Where Glucose Is the Data Input Signal (Input) and NAD$^+$ Is the Addressing Signal (Address)[a]



[a] Two different output channels (**Output1** and **Output2**) are represented by $ABTS_{ox}$ and NADH, whose production is triggered by the same data input and selected by the addressing input.

biochemical system with the "machinery" part composed of three enzymes: 0.01 units·mL^{-1} GOx, 1 units·mL^{-1} GDH, and 0.1 units·mL^{-1} HRP. In addition to the enzymes, the system included 0.05 mM ABTS and oxygen (in equilibrium with air) dissolved in 50 mM phosphate buffer solution, pH 7.5. Glucose applied at the concentration of 5 mM was defined as logic data signal **1** in the only **Input** channel, while the absence of glucose was defined as logic input **0**. The addressing signal was the addition of NAD$^+$ at a concentration of 0.1 mM for the logic value **1**, and the absence of NAD$^+$ was defined as logic input **0**. The output signals were detected optically at two different wavelengths: λ = 420 nm (**Output1**) corresponding to the oxidized ABTS ($ABTS_{ox}$) and λ = 340 nm (**Output2**) corresponding to the reduced NAD$^+$ (NADH) (Scheme 5). When the data **Input** channel had logic value **0** (the absence of glucose), none of the reactions was activated, and both output channels had the logic value **0** regardless of the **Address** logic value. However, in the presence of glucose (**Input** = **1**), the biocatalytic reactions were activated, and depending on the presence (**Address** = **1**) or absence (**Address** = **0**) of NAD$^+$, different catalytic processes resulted in different optical changes, thus activating **Output1** or **Output2** channels. Specifically, in the absence of NAD$^+$, glucose was oxidized by GOx, yielding H_2O_2 and finally resulting in the oxidation of ABTS biocatalyzed by HRP (Scheme 5). This resulted in the increased absorbance at λ = 420 nm (**Output1**). However, in the presence of NAD$^+$, the glucose oxidation was mostly performed by GDH (note 100-fold higher activity of GDH compared to that of GOx), resulting in the formation of NADH and an increase in the absorbance at λ = 340 nm (**Output2**). The biocatalytically generated NADH

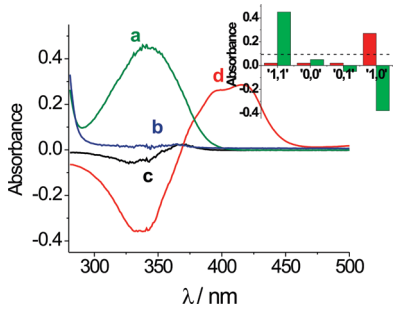


Figure 2. Spectra generated by the biocatalytic 1-to-2 demultiplexer upon different combinations of the data and address signals: (a) **Input1 = 1**, **Address = 1**; (b) **Input1 = 0**, **Address = 0**; (c) **Input1 = 0**, **Address = 1**; (d) **Input1 = 1**, **Address = 0**. Inset: Bar diagram of the output signals (**Output1** and **Output2**) generated by different combinations of the **Input**, **Address** signals. (Note that the **Output1** for the **1,0** combination was measured at $\lambda = 420$ nm, while the **Output2** for the **1,1** combination was measured at $\lambda = 340$ nm. The dashed line is the threshold separating the logic **0** and **1** output values. The system composition and operation are described in the text.

TABLE 2: Truth Table for the Operation of the Biomolecular Digital 1-to-2 Demultiplexer

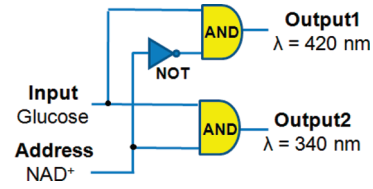
data input	address input	data output	
glucose	NAD^+	**Output1** $\lambda = 420$ nm	**Output2** $\lambda = 340$ nm
0	0	0	0
1	0	1	0
0	1	0	0
1	1	0	1

reduced $ABTS_{ox}$, which was produced through the reaction catalyzed by GOx, thus eliminating the optical changes at $\lambda = 420$ nm and inhibiting the **Output1**.

The experimental spectra obtained for different combinations of the **Input** and **Address** logic values are shown in Figure 2 (note that the initial absorbance of ABTS was subtracted from the obtained spectra, thus resulting in the differential spectra). In the absence of glucose (**Input = 0**) the absorbance was practically unchanged at both of the analyzed wavelengths (Figure 2), curves b and c for **Address = 0** and **1**, respectively. In the presence of glucose (**Input = 1**) and in the absence of NAD^+ (**Address = 0**) the absorbance was increased at $\lambda = 420$ nm (**Output1 = 1**) due to the formation of $ABTS_{ox}$ (Figure 2, curve d). Note that the absorbance was also decreased at 340 nm in the differential spectrum, reflecting conversion of ABTS to $ABTS_{ox}$. This change was opposite to the increasing absorbance in the case when **Output2** channel was activated. In the presence of glucose (**Input = 1**) and in the presence of NAD^+ (**Address = 1**) the absorbance was increased at $\lambda = 340$ nm (**Output2 = 1**) due to the formation of NADH (Figure 2, curve a). In this case, the absorbance at $\lambda = 420$ nm was not changed at all.

The demonstrated NAD^+-controlled switching between two output channels mimics the 1-to-2 digital multiplexer (Table 2), and it can be represented by the electronic equivalent circuitry shown in Scheme 6. In this scheme, two **AND** logic gates operate in parallel producing, however, different output signals read optically at different wavelengths. The selection of the output channel depends on the logic value of the addressing input being inverted at one of the gates. This equivalent circuit allows the demultiplexer operation similarly to the electronic counterpart.[32] The use of glucose as the data input and NAD^+ as the addressing input is very convenient since both biochemicals are typical components of many developed enzyme logic systems.[25−27]

SCHEME 6: Electronic Equivalent Circuitry of the 1-to-2 Demultiplexer Based on the Enzyme Catalyzed Reactions



It should be noted that the designed biochemical multiplexer and demultiplexer were activated by the chemical/biochemical signals (data inputs and addressing inputs), and they also produced the chemical outputs. This allows their direct integration into biochemical logic networks, giving an obvious advantage over chemical multiplexers/demultiplexers producing only light emission (fluorescence) signals,[16] which cannot be used for the next step of the biochemical information processing.

Conclusions

In summary, the present paper represents a new step in the development of enzyme information processing systems. Rapid developments of recently pioneered enzyme logic gates resulted in the formulation of many different types.[21,22] The new challenging aim important for their practical applications in multisignal digital biosensors and actuators is scaling-up the complexity of the enzyme logic systems by networking individual logic gates.[23] New demands for the biochemical gates networking require novel biochemical systems performing non-Boolean operations in the signal processing. Some of these biochemical systems were recently designed and integrated in simple biocomputing networks, including signal converters and amplifiers,[28] **FANOUT** and feedback circuitries,[25] flip-flop memories[29] and filters.[33] The present paper demonstrates a new kind of biochemical system mimicking operations of a digital 2-to-1 multiplexer and a 1-to-2 demultiplexer. These biochemical units will be critically important for further scaling-up complexity of branched biocomputing networks processing biomoleculer signals in digital biosensors and actuators with built-in logic. We also note that the present research is the very beginning step, and the achieved results are incomparable with state-of-the-art in the electronics. However, the electronic counterparts were developed over 100 years,[34] while the biochemical systems mimicking their operations are only a few years old - still keeping great promise for the future.

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Supporting Information Available: Experimental details and comparison of the enzyme activity at different pH values. This material is available free of charge via the Internet at http://pubs.acs.org.

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