Bioelectronic Systems Logically Controlled by Biochemical Signals: Towards Biologically Regulated Electronics

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Recent research activity in unconventional chemical computing resulted in the development of various chemical systems processing information and performing Boolean logic operations in response to several chemical input signals. Novel horizons were opened in the chemical computing research area upon introducing biochemical systems and formulating biomolecular computing (biocomputing) concepts. Biocomputing elements of moderate complexity could allow effective interfacing between complex physiological processes and nano-structured materials or/and electronic systems. In a short perspective such interface could be applicable in implantable devices, providing autonomous, individual, "upon-demand" medical care, which is the objective of the new nanomedicine concept. In the future this will result in novel human-computer interfaces providing direct coupling of brain (or at least physiological processes) with computers. On the conceptual level, development of biocomputing concepts might help us to understand how living organisms manage to control extremely complex and coupled biochemical reactions, i.e., interpret metabolic pathways in the language of information theory. The complexity of metabolic pathways is comparable with the complexity of computing electronic circuits, operating on internal physiological thresholds and enzymatic decision making much like the electrical thresholds and logic gates of a computer processor.

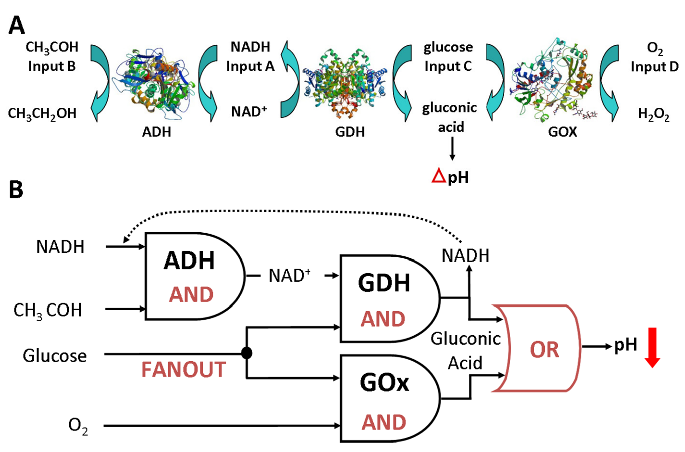

Fig. 1. (A) The multi-gate / multi-signal processing enzyme logic system producing *in situ* pH changes as the output signal. (B) The equivalent logic circuitry for the biocatalytic cascade.

Achieve the interface between biochemical systems performing computing operations and electronic transducers is a challenging goal for future studies in the biocomputing area. Some experimental steps have already been done in this direction. Multi-enzyme systems allowed logic processing of many biochemical signals mimicking Boolean logic networks, Fig. 1, [1]. Coupling of the enzyme logic networks with signal-responsive electrodes resulted in electrochemical transduction of the enzyme-processed information, Fig. 2. Upon designing standard universal logic gates, modular design of biomolecular logic networks became possible, Figure 3.

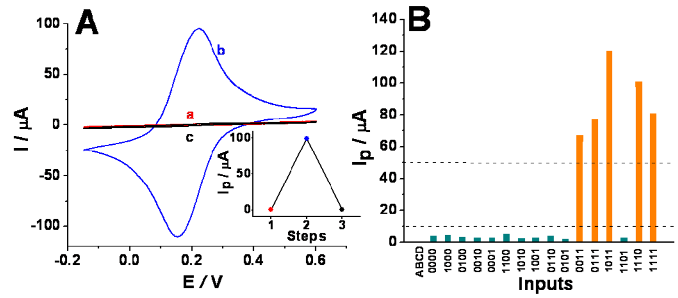

Fig. 2. (A) Cyclic voltammograms obtained for a signal-responsive switchable electrode controlled by the enzyme logic network: a) initial OFF state, b) ON state enabled by the input combinations, c) *in situ* reset to the OFF state. Inset: reversible current changes upon switching the electrode ON-OFF. (B) Anodic peak currents, I_p, for the 16 possible input combinations.

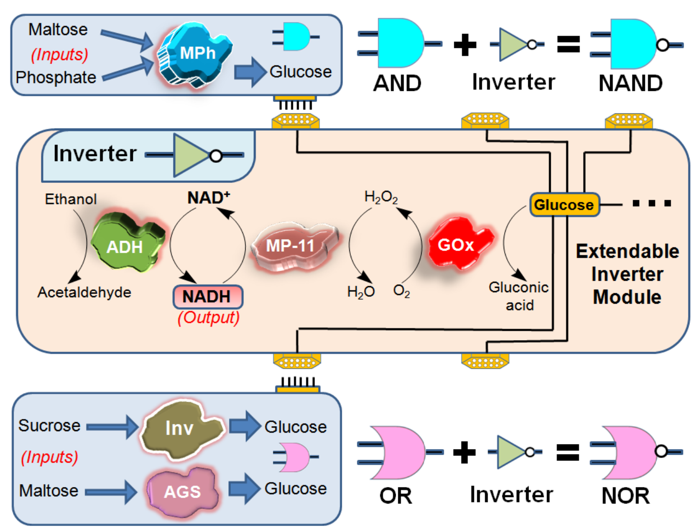

Fig. 3. Modular design of the enzyme-based **NAND** and **NOR** gates.

Biocomputing systems can be based on the existing chip technologies currently used for biosensing (particularly DNA chips, micro-fluidic lab-on-chip) [2]. Coupling of biocomputing systems, specifically enzyme-based logic gates or their networks, with signal-responsive biocatalytic interfaces would allow "smart" bioelectrochemical systems controlled by many biochemical signals coming simultaneously and processed logically according to the built-in Boolean program, Fig. 4, [3]. Further scaling down of biocomputing devices to nano-size is possible. Computing problems can be solved at the level of a single molecule, resulting in dramatic miniaturization and allowing parallel computation performed by numerous molecules. This approach will finally result in miniaturized multi-signal-responsive biosensors.

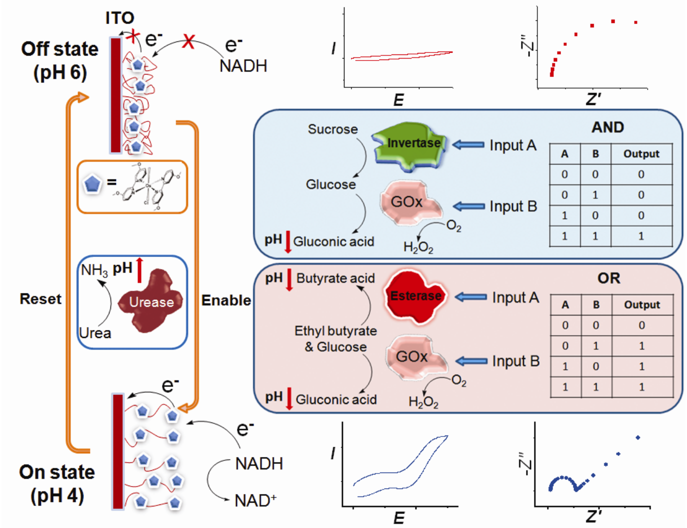

Fig. 4. Logic operations **AND**/**OR** performed by the enzyme-based systems resulting in the **ON** and **OFF** states of the bioelectrocatalytic interface followed by the **Reset** function to complete the reversible cycle.

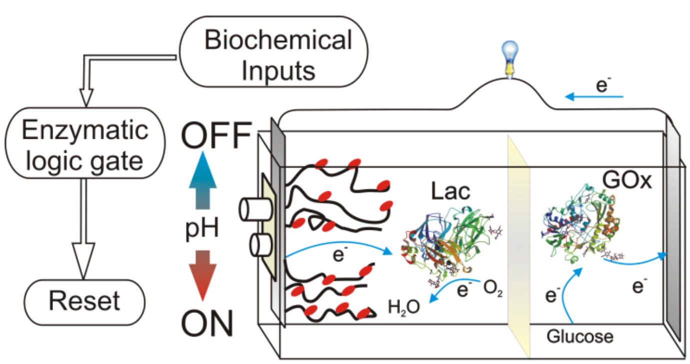

Fig. 5. The switchable biofuel cell controlled by pH changes produced *in situ* by the enzyme logic systems processing biochemical inputs.

We demonstrated the first realization of enzyme-based set-reset systems operating as a flip-flop memory with the possibility to write and erase information via the introduction of biochemical or chemical signals while the read-out of the stored information is relayed by optical and electrochemical means. To demonstrate the concept, we developed a multi-enzyme system processing set-reset biochemical signals. Future biomedical applications of this system are envisaged.

Biofuel cells with switchable power release controlled by biochemical signals logically processed by biomolecular computing systems have been designed, Fig. 5, [4-7]. The switchable properties of the biofuel cells were based on the polymer-brush-modified electrodes with the activity dependent on the solution pH value. The pH changes generated *in situ* by biocatalytic reactions allowed the reversible activation – inactivation of the bioelectrocatalytic interfaces, thus affecting the activity of the entire biofuel cells. Boolean logic operations performed by either enzymes- or immune-based systems were functionally integrated with the switchable biocatalytic process allowing logic control over them. Scaling up the complexity of the biocomputing systems to complex multi-component logic networks with built-in "program" resulted in the control of the bioelectronic systems by multi-signal patterns of biochemical inputs. Future implantable biofuel cells producing electrical power on-demand depending on physiological conditions are feasible as the result of the present research.

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