Multisignal digital biosensors for medical applications

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Abstract. Biocomputing has recently gained a place beneath other computing paradigms. Utilizing the natural rules of interaction between biochemical substances, new ways and techniques of solving computing problems have been developed. This review covers the concept of combining so called biosensors, devices that analyse single-input bioprocesses, with the technical possibilities of more complex biochemical logic systems. This combination, utilizing enzymes as the "machinery" of biochemical logic systems, aims to create complex analytical biosensors for medical application.

Keywords: Multisignal Biosensors · Biosensors · enzyme-based logic gates · logic networks · biomedical applications

1 Introduction

1.1 Context

s In the medical field biosensors (analytic devices to convert a biochemical response into an electric signal) are an essential tool for the monitoring and detection of a wide range of medical conditions. The currently available sensors work as single-input devices, that can analyse only one specific substance. New concepts aim to create devices, that can analyse multiple inputs and transform those into a single output signal. This change allows for more possible applications.

Once realized, those biosensors could revolutionize a great number medical treatments and therapies. Through the analysis of multiple inputs, the sensors could scan specific injuries or diseases. More complex models could even create sense-act-treat devices, that immediately apply the correct treatment after a specific result of the analysis. Especially in medical emergencies, where rapid reactions are of paramount importance, these developments would mark a ground-breaking change. Even personalized medical treatment, which could autonomously adjust the treatment tailored to a patients needs, is imaginable.

In the medical field Biosensors, analytic devices to convert a biological response into a electric signal, are a essential tool for monitoring and detection of a wide range of medical conditions from Diabetes to ..... While common biosensing devices are limited to a single input, the novelty of Biosensors based on enzyme-based logic systems can process muliple biochemical signals. This article concentrates on the concept of the mulisignal processing Biosensors and the resulting challenges.

The basic principle of biosensors are two layers: the receptor, that processes the inputs and the transducer, that translates the received signals to a yes/no-output. The main innovation of the new concept is to replace the current one-input receptor with a biochemical system, that allows a re-creatable analysis of multiple inputs, which are then transformed into one output. The receptor usually consists of enzymes (research also produced working systems using DNA and RNA), which react with specific substances.

As the result of that reaction is reliable by definition, it produces an exploitable substance, that gets transduced into a yes/no signal.

This document is structures as follows. In Section 2 the concept of Biosensors with enzyme-based logic is introduced. Subsection 2.1 describes the principle of enzyme-based gates and Subsection 2.2 networks of logic gates and the combination with transducers. While section 2 only dealy with the concept of Biosensors section 3 concentrates on the designing of multisignal Biosensors for medical applications. In section 4 considerations. Section 5 summarize and outlook.

2 concept

The multisignal processing biosensors in this article are based on enzyme-based logic systems, consisting of chemical logic gates mimicking Boolean operations. Like in common biosensors with single inputs the biosensor is composed by several layers. The receptor, that in common biosensors recognices the selected analyte of interest, is replaced by a enzyme logic systems The transducer converting biological recognition interaction into a type of signal that is oberservable, for example a electrical current.worthnlichkeit senses physical changes and converts it into an electrical signal. missing biochemical substances

2.1 Enzyme-based logic gates and networks

Logic gate In Biocomputing enzyme as logic in combination with chemical inputs resulting in a end product is used to mimick Boolean logic gates such as AND and OR. To digitalize chemical processes two levels of concentrations of chemical reaction materials are considers as input signals. 0 is usually considered as the absence of a enzyme, but it can be altered. 1 equals a significantly difference to the absence or the as 0 defined concentration. Output signal ein vorher bestimmter stoff, falls dieser vorhanden regel 1 falls nicth regel 0. (Katz)

Beispiel AND In Fig 1 the enzymes glucose oxidase (short Gox. It catalyses the oxidation of glucose to hydrogen peroxide and D-glucono--lactone and is often used for analysing free sugar in blood) and catalase(catalyzes the decomposition of hydrogen peroxide to water and oxygen) operate as the logic gate machinery. The two input signals H2O2 (Hydrogen peroxide) and glucose (blood sugar) . When both substrates present the inputs react and produc gluconic acid, which results in an optical absorbance change, that was defined as the ouput signal of the enzyme logic gate. The optical absorbance change just appeared in the presence of both inputs, mimicking the Boolean operation AND.

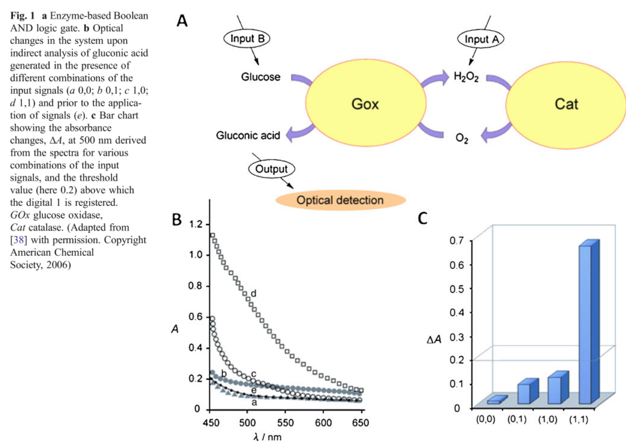

Fig. 1. Network diagramm

networks with electrochemical transduction By assembling these single logic gates, mimicking Boolean operations,it is possible to create small logic networks(e.g. half-adder/ half subtractor)/enzyme logic systems. By adding a transducer, it is possible to convert the physical change into a electrical signal.

As example a combination of different enzym-based logic gates, functioning as AND or OR. The cascade of reactions, when all four input chemicals present, result in ph changes. ph measures the degree to which a solution is acidic or alkaline. The scale is defined from 0 (acid solution) to 14 (lye solution). The logic network is composed of four concatenated logic gates. As logic gates the enzymes alcohol dehydrogenase(ADH, Abbau von toxischen Alkoholen), glucose dehydrogenase(catalyst for the oxidation of glucose) and glucose oxidase VERBMISSING and four specific different input signals NADH (resulting through reduction from Nicotinamid-Adenin-Dinukleotid NAD, which is a coenzyme found in all living cells) actealdehyde (also named ethanal and is a organic chemical compound, for example natually occuring in coffee, bread, and ripe fruit), glucose and oxygen (O) When all inputs present the reaction yiels to a acid medium, lowering the origin pH value of the solution from initial ph-value 6-7 to approximately 4.

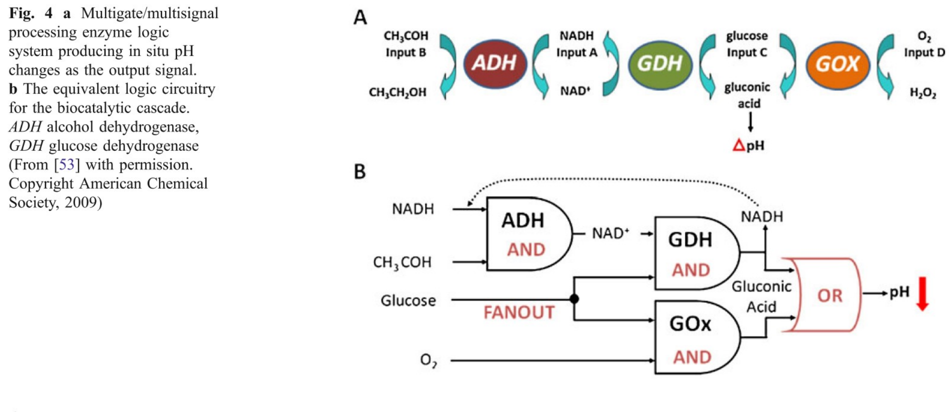

Fig. 2. Network diagramm

The lower pH value resulted in switching to ON of a electrochemical interface that functioned as transducer and the electrical signal can be read out.(low voltage as 0 and MISSING as 1). While 16 different combinations of input signals where possible (present and absent) only four of these resultet in an ON state.

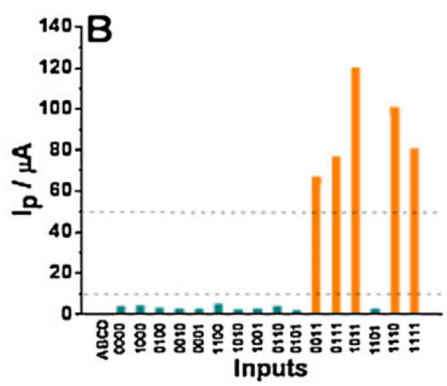

Fig. 3. Network diagramm

This combination is a example for a multisignal processing enzyme logic system coupled with an electrochemical transduction readout of the output signal (pH change)

3 designing for biomedical analytic applications

To recognize various medical relevant conditions, it is necessary to use characteristic biomarkers as inputs for the biochemical logic system. For example for recognition of various injury related physiological conditions. The concentration of some biochemical substances changes in a body, typical for distinct pathological conditions.

brain injury To process information related to brain injuries and hemorrhagic shock designed to process information related to conditions originating from traumatic brain injury and hemorrhagic shock(). Use of AND and IDENTITY logic gates, three enzymes lactate oxidasse, horseradish peroxidase and glucose dehydrogenese. designed to process information related to conditions originating from traumatic brain injury and hemorrhagic shock. As markers: glucose, lactate and norepinephrine. increase glucose = hemorrhagic shock, higher lactate = hem or brain truama and high nore = any traumatic injury
physiologically normal concentration as 0, abnormally high as 1 as input. ouput signals: norepquinone and NADH (eight different combinations possible 23 for input signals)
truth table. insert here

4 considerations

Being only a concept yet, there are plenty of challenges, that must be solved until a successful realization of complex applicable biosensors. The most current are as follows:

Surface confinement In recent research, the success of enzymatic reactions was growingly dependant on the immobilization of the reagent layer. Early experiments with enzyme logic dissolved the gate constituents and chosen inputs in a solution. With the aim of complex networks that require multiple different gate constituents and inputs, each section needs to be differentiated and isolated, to prevent cross-reactions. To achieve multiple and stackable logic systems, the biocomputing layer needs to be immobilized. Agglomerations of multiple logic systems also induce further challenges. All reacting components need to be carefully evaluated to prevent cross-reactions, while the outside coating of the device must simultaneously protect the reagents within the device but be permeable to the desired inputs. The impact of an immobilization on the performance of biosensing devices has yet to be examined.

Optimal transduction More complex setups require better and more versatile transducers. With the universal goal of processing an arbitrary number of inputs into only one output signal, the development of versatile transducers becomes crucial. The transducer must be able to process multiple logic-gate results and yet translate those into one (optical or electrical) output signal. Current research had to apply variant transducing strategies for complex devices, but aims to develop a multipurpose transducer, which can be generally utilized.

0- and 1-values In every transduction, there has to be a defined 0 and a respectively defined 1 value. 0 should mark the biological standard value, 1 the critical value. The definition of the 1-value is also problematic. In research, the 1 value has mostly been defined as a random convenient value, instead of using applicable medically critical values. Within the same field, the difference between a relevant 0 and a relevant 1 can be minimal. This leads to difficulties with the transduction. An offered solution would be a sigmoidal signal translation rather than the usual linear, to emphasise the difference an allow more reliable reading. Scalability One central aim of research is to achieve a maximal flexibility of sensors. In the end, it is highly expected to be able to scale every parameter of the sensor, from the complexity of the logic system to the specificity of the transducer. The aim is, to potentially stack any given number of logic systems into greater networks, that create more and more complex logic systems and respectively allow new applications.

Relevant inputs A majority of laboratory projects worked with biomedical irrelevant substances for their proof of concept. A crucial step is to make the concept work with relevant inputs. Not only the inputs themselves need to be practicable. In recent studies, scientists realized networks with biomedically relevant substances. The used logic networks yet did not depict a senseful logic context to the substances. Thus not only the work with relevant substances needs to be developed further, but also the logic networks need to be adjusted to depict relevant ???

Challenges of drug delivery One slightly more distant concern is the functionality of drug delivery devices. One of the key goals of research is to develop autonomous devices, that analyse certain physiological parameters and offer an immediate reaction. Experiments have shown a need for different methods and technology to distribute the correct treatment within the cycle of those devices.

4.1 surface immobilization of the biocomputing machinery

5 Conclusion

- design of biosensoric systems with logically processes signals represented by varous biomarkers characteristic for different abnormal physiological conditions

- analysis of the chemical output signals generated by biomolecular logic systems is often limited.
- Enzyme logic system: multiassemblies to perform simple arithmetic functions
- idea: applicatoin of biomolecular logic system for analytical purpose new class of biosensors that accept many input signals and produce binary outputs in form yes/no
- example analyse protein libraties associated with muliple sclerosis(58)

- not just chronic but also ....
- state of the art
- feedback loop currently devoted to management of diabetes through integration of an electrochemical glucose sensing element with an insulin-delivery feedback loop for the optimal dose of insulin (69-71)
- example analyse protein libraties associated with muliple sclerosis(58) ENzyme logic system recognizing various injury-related physiological conditions
  - types of injuries result in concentrations of chemical substances in the body
  - example: lactate axidase, horeserasish peroxidase and glucose dehydrogenase = designed to process biochemical information related to pathophysiological conditions from brain injury
  - markers: glucose(hemorrhagic shock),lactate(rhagic shock or traumic brain injury) and norepinephrine(traumatic injury)
  - logic 0 = normal concentrations
  - change results into different numbers 1,2,3 - convenient
  - = biocomputing logic system
  - challenge: difference between normal and unnormal minimal =¿ not linear, should be sigmoidal

- optimal surface confinement of the biocomputing layer
- engineering enzyme microenvironment (transducer layer)
- contact between biocomputing layer and transducing surface
- combine individual logic-gates and maintain high enzymatic stability and reataining individual reagents
- leakage of cosubstrate
- no cross-reactions
- surface confinement? layer-by layer? more efficient and rational
- level of the surface confined reagents tailored for account of different input concentrations /enzyme activities
- coating: optimized for transport and excluding potential interfernece and protecting the surface

5.1 optimal transduction of biocomputing signal processes

- simultaneous measurements of multiple outputs require different transduction strategies (common: fixed potential)

- Requires:interface of biocomputing systems + electronic transducer
  Therefore
- scalability (increasing nuber of logic gates, assembling into complex networks)
- complexity(coupling of gates abd non boolean elements)
- composition, preparation and immobilization of the biocomputing surface layer
- layer by layer
- optimal surface confinement
- careful engineering of the enzyme microenvironment(on transducer surface) for performance
- biocomputing layer + transducing layer + combine individual logic-gate elements

good but needs lot of work
sums up bla
Profound impact

Through processing automatically several biochemical inputs(physiological information), it can provide a rapid and reliable assessment of overall physiological conditions. This can help a optimal timley therapeutic intervention. They will realize sense/delivery feedback loops by coupling signal processing with chemical actuators to revolutionize patient monitoring and drug delivery.

In the Biosensors processing multiple biochemical signal, the core idea is to add a biocomputing layer that produces a final output in form of a yes/no response. Kapitel 1.2

Chances:

In contrast to recent biosensors, those with a 11111111111 logic promise a higher fidelity, a greater range of processable inputs, more complex applications such as sense-act-treat loops and rapid assessment of the respective substances.(mehr ausformulieren)

5.2 Biosensors logic systems

Biosensors logically processing multiple biochemical signals
-such procassed information produces a final output yes/no
- boolean logic networks composed of biomolecular systems

- multiple target analytes(inputs) for enzyme gates
- high-fidelity compared
- closed loop/feedback loops possible (sense/act/treat)
- rapid and reliable assessment of overall physiological condition
- could initiate optimal timely therapeutic intervention
- biosensors + enzyme logic gates

- allows direct coupling of signal processing with chemical actuators
- application og biomolecular logic systems for analystic purposes could yield a novel class of biosensors: many input signals and binary outputs
- logically processed feedback between drug appl. and physiological conditions can signifacntly imprive drug targeting and efficiency
- difficulties: complexity by assembling individual logic gates into complex logic networks (intelligent by molecular logic) (43-34-67)
- new approach for the sensor design and operation, interfach biocomputing system and electronic transducers

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