Multisignal digital biosensors for medical applications

Maren Krafft

Lehrstuhl fr technische Informatik, Universitt Passau, Germany

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: Biomolecular computing · Biosensors · enzyme logic gates · biosensing · biocomputing systems · enzyme logic circuits · 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 simple 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 summed up 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

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 glucose oxidase and catalase, which are enzymes, operate as the logic gate machinery. The two input signals H2O2 and glucose.

When both substrates present the inputs reacted and produces gluconic acid, which results in anoptical 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 **a** Enzyme-based Boolean AND logic gate. **b** Optical changes in the system upon indirect analysis of gluconic acid generated in the presence of different combinations of the input signals (*a* 0,0; *b* 0,1; *c* 1,0; *d* 1,1) and prior to the application of signals (*e*). **c** Bar chart showing the absorbance changes, ΔA, at 500 nm derived from the spectra for various combinations of the input signals, and the threshold value (here 0.2) above which the digital 1 is registered. *GOx* glucose oxidase, *Cat* catalase. (Adapted from [38] with permission. Copyright American Chemical Society, 2006)

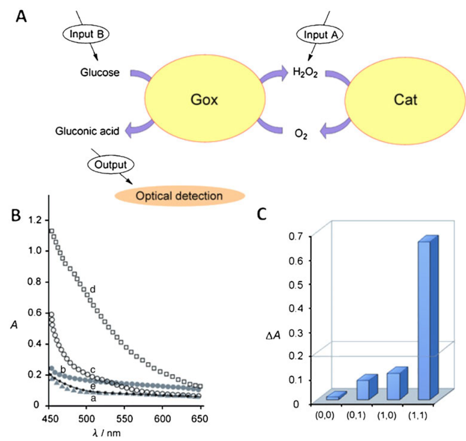

Fig. 1. Network diagramm

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. Transducers missing

For example, a logic network with three enzymes alchol dehydrogenase, glucose dehydrogenase and glucose oxidase operating as four concatenated logic gates and four different input signals (NADH, actealdehyde,glucose and oxygen) The cascade of reactions resulted in ph changes. successful case: yielding acid medium,lowering pH from initila ph 6-7 to approcimately 4. The pH scale is defined from 0 (acid solution) to 14 (lye solution).

Fig. 4 a Multigate/multisignal processing enzyme logic system producing in situ pH changes as the output signal. **b** The equivalent logic circuitry for the biocatalytic cascade. *ADH* alcohol dehydrogenase, *GDH* glucose dehydrogenase (From [53] with permission. Copyright American Chemical Society, 2009)

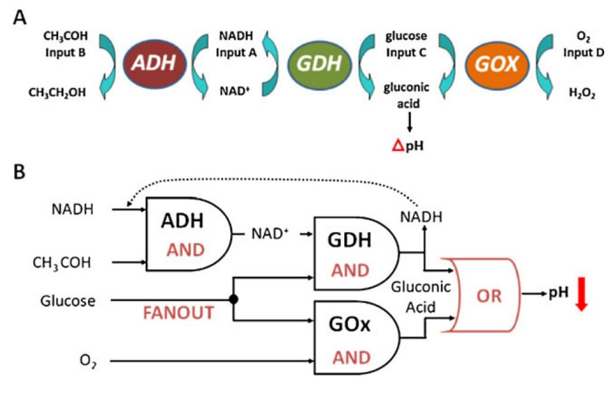

Fig. 2. Network diagramm

The lower pH value resulted in switching to ON of a electrochemical interface that functioned as transducerand and read out by whatever, volt usw While 16 different variants where possible only four combinations resultet in a ON state.

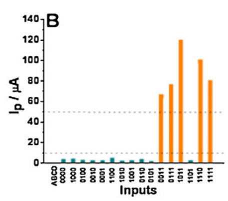

Fig. 3. Network diagramm

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 biochemical analytic applications

- 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

4 considerations

stabilization and confinement// optical transduction

4.1 surface immobilization of the biocomputing machinery

- 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

4.2 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

5 Conclusion

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)

5.1 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

References

1. Parikha Mehrotra, Biosensors and their applications - A Review (2016)
2. Daniel R. Thevenot, Klara Toth, Richard A. Durst, George S. Wilson, Electrochemical biosensors: recommended definitions and classifications In: Biosensors and Bioelectronics 16 (2001) 121- 131
3. Joseph Wang, Evgeny Katz, Digital biosensors with build-in logic for biomedical applications- biosensors based on a biocomputing concept, in: Anal Bioanal Chem(2010) 1591-1603
4. Shengbo Sang, Wendong Zhang and Yuan Zhao, State of the Art in Biosensors, in: State of the Art of Biosensors(2013) 89-110
5. Evgeny Katz, Enzyme-Based Logic Gates and Networks with Outout Signals Analyzed by Various Methods, In: ChemPhysChem 2017, 18 1688-1713