

# Multisignal digital biosensors- digital Biosensors integrated with enzyme logic systems

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**Abstract.** – biochemical logic systems

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**Keywords:** Biomolecular computing · Biosensors · enzyme logic gates  
· biosensing · biocomputing systems · enzyme logic circuits · biomedical  
applications

## 1 Introduction

### 1.1 Context

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 multiple biochemical signals. This article concentrates on the concept of the multisignal processing Biosensors and the resulting challenges.

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 timely 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 1111111111 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)

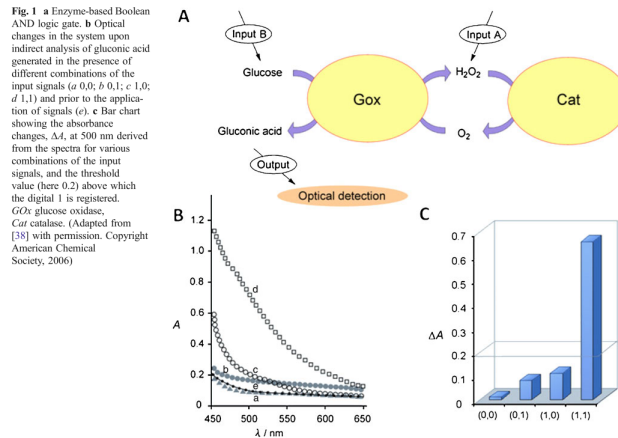
## 2 concept

To understand the concept of biocomputing biosensors it is fundamental to know the basics about biosensors and enzyme-based logic systems. A Biosensor is a device that transforms biochemical information, into an analytically useful signal. It contains usually the two basic components, the receptor and a transducer.

convert a biocolical response into an electrical signals. the receptor can recognise biological moluculas include enzymes and the transducer senses physical changes and converts it into an electrical signal

### 2.1 Biocomputing: concept

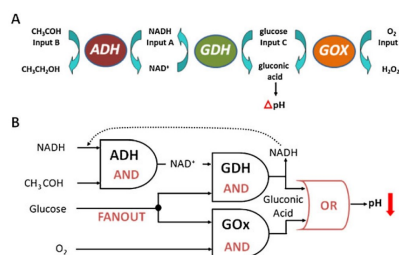
**allgemein** In Biocomputing the reaction of different biomolecular tools, including enzyme, resulting in a desired end product is used to mimic Boolean logic gates such as AND and OR. To digitalize chemical processes two levels of concentrations of chemical reaction materials (enzymes) are considered as input signals. 0 is usually considered as the absence of an 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 nicht regel 0. (Katz) In glucose oxidase and catalase operate as the logic gate machinery. The two input signals H<sub>2</sub>O<sub>2</sub> and glucose. When both substrates present the inputs reacted and produces gluconic acid and this optical absorbance change was defined as the output signal of the enzyme logic gate, mimicking the Boolean Operation AND.



**Fig. 1.** Network diagramm

By assembling these single logic gates, mimicking Boolean operations, it is possible to create small logic networks (e.g. half-adder/ half subtractor)

**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 diagram

analysis of the chemical output signals generated by biomolecular logic systems is often limited. to digitalize chemical process two levels of concentrations of chemical reaction species are considered as input signals. 0 = usually absence of enzyme. 1 significantly different to absence. the chemical inputs are applied in different binary combinations (Katz)

- biomolecular logic systems: definition
- subarea of chemical computing
- single logic gates to small logic networks (for example half-adder/ half subtractor)
- biomolecular systems for processing chemical information
- different biomolecular tools (including proteins/enzymes) assemble biocomputing systems processing biochemical information

### what would bring it to biosensors

- Enzyme logic system: multiassemblies to perform simple arithmetic functions
- idea: application 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 libraries associated with multiple sclerosis(58)

### how enzyme-based logic gates work Enzyme logic gates

- enzymatic reactions
- coupling of logic gates with electronic transducers and signal responsive materials
- transducers:
- signal responsive material

example theoretical with graphics

- glucose oxidase and catalase operating as logic gates:

- input : H<sub>2</sub>O<sub>2</sub> and glucose
- gluconic acid = biocatalytic oxidation of glucose
- only when both present optical output signal. = AND
- define logic values: small changes = 0 and large absorbance changes as 1 = AND
- similar possible with XOR, AND, OR, NOR, INHIBIT
- with logic gates with modular structure that enables their assembly in networks NAND/ NOR possible
- logic gates and their networks = biomolecular information processing systems
- = biosensoric systems with logically processed signals represented by various biomarkers (characteristic of different abnormal physiological conditions)

example pH

- pH changes in solution as logic responses to input signals
- AND invertase + glucose oxidase (from 5.8 to 3.5)
- OR esterase and glucose oxidase in glucose and ethyl butyrate - when one of both present - acidification
- neutral pH = 3.5

Conclusion:

- don't solve real computing problem nor operate as useful biosensors
- represent first step toward the development of digital biosensors
- funfact optimization of enzymatic reaction, up to 10 logic gates concatenated with low noise in the system

### for biochemical analytic applications

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

## 2.2 Biosensors logic systems

Biosensors logically processing multiple biochemical signals  
 - such processed 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 of biomolecular logic systems for analytical purposes could yield a novel class of biosensors: many input signals and binary outputs
- logically processed feedback between drug appl. and physiological conditions can significantly improve 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, interface biocomputing system and electronic transducers

### 3 possible application

- 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 libraries associated with multiple 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 oxidase, horseradish peroxidase and glucose dehydrogenase = designed to process biochemical information related to pathological physiological conditions from brain injury
  - markers: glucose(hemorrhagic shock), lactate(rhagic shock or traumatic brain injury) and norepinephrine(tramatic 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 retaining 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 interference 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 number of logic gates, assembling into complex networks)
- complexity (coupling of gates and 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

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