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Construction and application of novel electrochemical biosensor devices of variable structure

Summary of Ph.D. Thesis

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Preliminary studies

In relation to biosensors, the research work resulting in the findings presented in this dissertation has evolved from three leading ideas / strategic requirements:

1. Realization of experimental biosensor setups that awakened my interest, with the least amount of reagents possible (that is, at as low costs as possible or with more expected results from the same overall budget) with as high flexibility as possible,
2. Acquisition and dissemination, as thoroughly and as widely as possible, of the measurement methods of the models and concepts from among electrochemical biosensors that do not require prior aspecific labelling of the sample (e.g. Electrochemical Impedance Spectroscopy is such a labelfree method).
3. Finding and nurturing the synergy between the potential offered by electronics technology and microelectronics as well as biosensors in a variety of fields, in order to construct biosensor based devices of a performance beyond the state of the art.

The general structure and principle of operation of biosensor based devices can be seen in Figure 1. The fact in the background of the selective concentration measurement capacity of biosensors is that in nature there exist countless specific recognition mechanisms at the molecular level that can always be observed between a biomolecule and a complementary molecule fitting its morphology (3-dimensional structure, electric charge distribution, etc.). This sensitive and selective 'key-and-lock' fit can be exploited **in case we can generate a measurable signal at the time when the phenomenon takes place**.

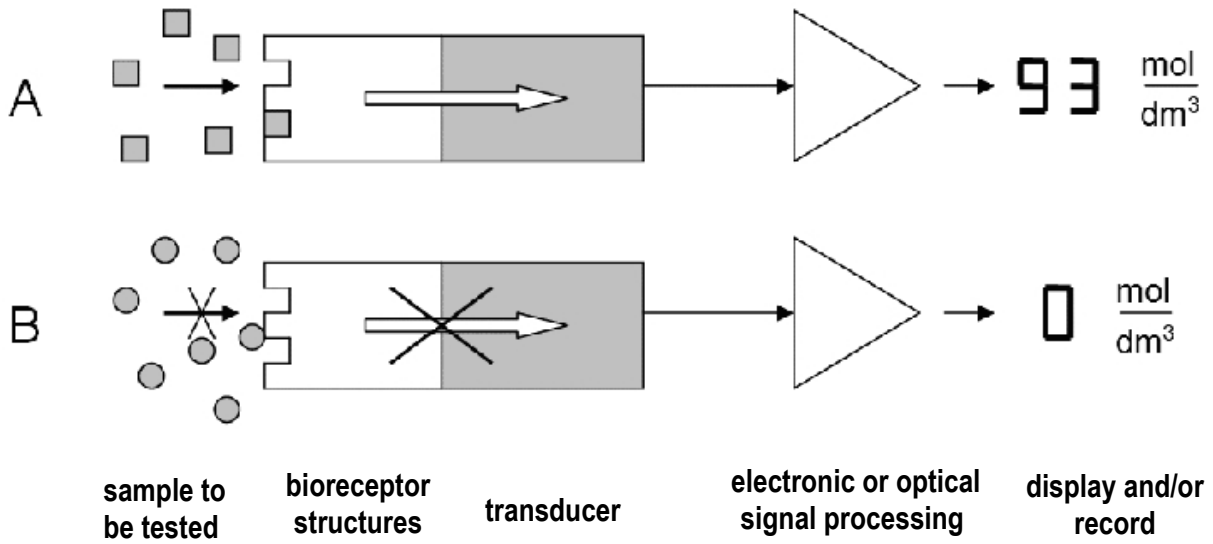

Figure 1: The general structure and principle of operation of biosensor based devices

Research and development fields of biosensor based devices

In any research and development activity related to sensors, the fundamental objectives are accuracy, durability, reproducibility and the improvement of the cost-requirement. In order to achieve these objectives, Research and Technological Development ('RTD') work related to the structure of biosensors may, in accordance with the scheme portrayed in Figure 1 above, focus on three areas.

1. To find or realize new / further developed 'analyte' recognition systems (hereinafter: bioreceptors). Such activities are connected with above all with disciplines like biology and chemistry. Molecular biology, genomics, protein engineering, proteomics and microbiology are examples for specialized sciences dealing with this field.

2. To find or realize new / improved physico-chemical transducer methods / structures. Materials science, electronics and optics are the main sciences here to build on.

3. To find or realize new / improved methods for the integration of an appropriate analyte recognition system with a certain physico-chemical transducer. This activity is in fact the research and development of immobilisation methods. Such issues necessitate knowledge mainly in organic chemistry, biochemistry, materials science and technology.

Regarding the functionality of biosensors, i.e., biosensor based devices **a further RTD field exists**, namely, the one focussed on the improvement of **the operation processes and operation circumstances of biosensors and the validation methods of these**. In this topic both theoretical and experimental researches have room to improve the state of the art, since biosensor based devices are, despite the nearly half century that has passed since the invention of the biosensor, still considered as non-robust, short-lifetime devices with moderate reproducibility and long time-to-result as against classic electronic sensors. Obviously there is an immense contrast in comparison with, e.g. 'bio-less' electronic sensors like a capacitive pressure sensor or a thermistor based temperature sensor. On the other hand, the selective differentiation of the parameter to be measured is an ample compensation for the basic weaknesses of the biosensors listed above, because, regardless of technology it applies in general that a well-constructed biosensor based device provides unique selectivity and sensitivity in comparison to any traditional, 'non-biosensor-based' device in case one looks for a quasi 'one-shot' or a point-of-care solutions.

A good biosensor based device may eliminate the need for lengthy laboratory based analytical procedures. However the present situation in biosensor research is that on the one hand, hundreds of biofunctional recognition systems and several dozens of different transducers exist already, while on the other hand, there are only a very limited number of genuine biosensor based devices that meet the definition in the introduction commercially available.

Objectives

In general, the reduction of the time-to-result of biosensors and the increase of the accuracy of the result received constitute the most challenging issue, therefore it is these two areas that most occupied me, too. In my interpretation, high accuracy requires first of all precision, and the correctness has to be examined only in the second approach, because a precise device can, in general, be calibrated to the required accuracy.

On account of the miniaturization possibilities and trends resulting from the rapid growth in microtechnology / microfuidics, I was, from the very beginning of my research, first of all interested in questions of sizing of biosensor based devices and of the biosensors constituting the basis of their operation. Based on the dissertation's detailed overview of technical literature and the results published, I would like to point out, among others, that **regarding the performance capacity of a biosensor based device, not only the active surface of the biosensor transducer is decisive, but so are the structure of the entire reaction space and the dynamics of the operation processes of the biosensor**, as well as, the time course of the treatment of the examination sample. For this reason, it is expedient to perform the research and development of the comparison methods and the experimental methods according to an approach taking into consideration all the above aspects.

One of the main set of ideas formulated in the course of my research concerns the examination of such possibilities of the reaction space of biosensor based devices that are independent of the active surface of the biosensor and do not require any prior processing, aspecific modification or labeling of the sample in the reaction space. The examination of the biosensor reaction space in this way may have two advantages. 1. Experiments aiming at achieving an increase of the accuracy of biosensor based devices or a reduction of their time-to-result through accelerating the transport processes going on in the sample can, by applying such a solution, be evaluated in an independent way, even in case the biosensor surface itself does not exactly function as it is expected to, for some reason. 2. Native-state (i.e., unlabelled) molecules are guaranteed to behave like in a real sample.

In relation to this, my Thesis 1 and its sub-theses resulted in a widely applicable novel concept in the experimental methods of electrochemical biosensors which I successfully demonstrated through the electrophoretic manipulation of unlabelled DNA molecules and the spectrophotometric monitoring of the process. I expect that my solution, based on cheap technology yet, uniquely customizable, may facilitate the work of creative biosensor researchers who are not confined exclusively to the usage of devices readily available in commerce.

The regeneration of the active surface of affinity biosensors (i.e., rendering it re-usable) is another major problem of the automated biosensor based devices of the future, because the solution based on the presently most widely researched method (pH-shift based regeneration) set up from regeneration solution reservoirs (with volume limits in many applications) and the necessary complex liquid-handling microfluidic system can, in some applications, be utilized only with drawbacks. Accordingly, I have extended my work carried out in connection with bio-macromolecule manipulation also on this subject.

In connection with this, in my Thesis 2 and its sub-theses I have laid down the fundamental thoughts about the *in situ* spectrophotometric monitoring possibilities of the reaction space of biosensors, and I am also simplifying the calculation method by introducing a material characteristic specifically suited for this task. By using the simplified method I have designed and prepared a biosensor reaction-cell suited for a new type of experiment and its measurement environment.

The second set of ideas that has been formulated during my research was organized around various transducer structures – e.g., interdigitated transducer (IDT) electrode – and the application and comparative examinations of certain electrochemical measurement techniques not requiring preliminary labeling of the sample with the general goal again: reducing time-to-result and increasing accuracy.

In connection with this, my Thesis 3 and its sub-theses demonstrate the application of a new parameter ($\mathbf{R}_{ct\ 100/0}$) regarded by me as suited for comparison in the first instance and therefore suggested for use in

case of biosensors of electrochemical impedance spectroscopic measurement technique, and formulate the conclusions of a comparative series of experiments of an electrochemical measuring technology performed along two parameters (parameter 'A' : 4 types of electrode geometry, parameter 'B': 3 types of electrode connection regimes).

In addition, in connection with this, my Thesis 4 and its sub-theses were born as a result of the intuitive exploitation of the so-called 'edge effect' and/or 'corner effect' having caused me many problems at the beginning of my research work, as well as owing to the identification of the proper application field.

New scientific results

Thesis 1 [related publications: P1, P2]

I have constructed and demonstrated at the prototype level a **novel modular biosensor reaction-cell** concept based on Poly-DiMethyl-Syloxane (PDMS) casting technology and thin film technologies.

a) The reaction cell according to the concept, with its reaction space that can be realized in the order tens or hundreds of microliters and of a shape definable uniquely as well as its space-saving fluidic connection points **is well adjusted** to **experiments** requiring expensive reagents and to be realized with little sample volumes. In addition, with its help, the **biosensor-substrates** to be examined **are built together with the reaction space in an exchangeable way** for the time of an experiment.

b) The concept allows for ***in situ*** **electr**och**emical and optical spectrophotometric examinations** providing information independently from each other **to be performed simultaneously** during the examination of the interactions of solutions containing biomolecules and electrode surfaces suited for biosensor sensing or other goals in case of varying solutions-compositions and at **variable electric excitations and temperatures.**

c) I demonstrated in course of biomolecule-manipulation experiments based on the low field strength electrophoresis of unlabelled DNA molecules, that the prototypes prepared according to the concept **can be well utilized considering both the simultaneous electric and spectrophotometric function**.

d) I demonstrated experimentally that the measurement setup is capable of measuring, with **a standard deviation below 5 %,** the changes of optical density of the solution in the realized system equipped with the micro dip probes of the Avantes optical**-**spectrophotometer attachable to it, if they reach or exceed the **0.028 Absorbance Unit / cm 'minimum detection limit'** (hereinafter: " $\Delta O.D._{min}$ "), however, **it cannot be used above maximum optical density changes above 1.103 Absorbance Unit /cm**, in case we set the maximum reference intensity to the pure solvent and deploy the probes with **optical pathlengths of 10 mm.**

e) I demonstrated experimentally that the measurement setup is capable of measuring, with **a standard deviation below 5 %,** the changes of optical density of the solution in the realized system equipped with the micro dip probes of the Avantes optical**-**spectrophotometer attachable to it, if they reach or exceed the **0.084 Absorbance Unit / cm 'minimum detection limit'** (hereinafter: " $\Delta O.D._{min}$ "), however, **it cannot be used above maximum optical density**

changes above 2.269 Absorbance Unit /cm, in case we set the maximum reference intensity to the pure solvent and deploy the probes with **optical pathlengths of 5 mm.**

Thesis 2 [related publications: P2]

Considering the target molecule and its bioreceptor molecule as one entity, for *in situ* optical-spectrophotometric examinations of the concentration changes of the target molecules in the bulk of the sample solution interacting with the bioreceptor layer of the affinity biosensors, I introduced the ***'native optical-monitorability factor' ('NOMF')*** calculable from the data of the molecule used as a bioreceptor and its target molecule, and I also described the way of its usage.

a) 'NOMF' is of an Absorbance Unit (A.U.) measuring unit and it can be calculated from the following equation

$$NOMF = Const. \times OD_{target\ molecule} \times A.B.S.D._{bioreceptor/target\ molecule}$$

from two factors: On the one hand, from the '**Optical Density' value** ($OD_{target\ molecule}$, its dimension: [A.U. · cm^{-1} / pc · cm^{-3}]) characteristic of the target molecule intended to be optically observed. On the other hand, from the **'active bioreceptor surface density' value** ($A.B.S.D._{bireceptor\text{-}target\ molecule}$, its dimension: [piece / cm^{-2}]) **determined by the higher value** from among **the size of the larger one** of the bioreceptor molecule immobilized onto the active **biosensor** surface or of the target molecule **and the steric hindrance arising during either the immobilization or the capturing**., in which equation, inserting the value $OD_{target\ molecule}$ measured at 1 cm optical pathlength in a solution of a concentration of 100 spread in the practice and the value of the A.B.S.D. expressed in [piece / cm^2], the value of the constant (*Const.*) is:

$$Const. = \frac{1}{6{,}022 \times 10^{16}}$$

b) **'NOMF',** according to the equation below,

$$\frac{V}{A}\,max = \frac{NOMF}{"\Delta\, O.D._{min}"}$$

determines the maximum volume/active surface (V/A_{max}) **ratio** of a reaction chamber in case of which it is **still possible** , in the bulk of the liquid sample interacting with the given affinity biosensors active surface, to detect the **optical density change accompanying the final state of the target-molecule capturing or releasing** on the active surface, by means of a **spectrophotometric setup having a particular** '**minimum limit of detection**' (" $\Delta O.D._{min}$ ") specified in O.D.

c) **Taking into consideration *'NOMF'* and the above equation** I have constructed a biosensing **reaction cell of a ratio with reduced volume / active surface (V/A)** and shaped like a truncated pyramid which **can be suited**, in case of 51 base length 5'-CAC TAC GTC TCG AAT CTC ACT ACG TCT CGA ATC TTT CCA ACT TTC GGA ACC-3' DNA oligonucleotide target

molecules, for the **examination of regeneration methods** of DNA biosensing transducers **not based on the addition of reagents**.

Thesis 3. [related publications: P6]

I *introduc*ed the parameter**'$R_{ct\ 100/0} = R_{ct\ 100\%} / R_{ct\ 0\%}$'** facilitating the comparability of the performance and therefore the research and development of affinity biosensors applying Electrochemical Impedance Spectroscopy (hereinafter: EIS), where '**$R_{ct\ 0\%}$**' is the charge transfer resistance measurable on the transducer entirely free from target molecules (i.e., containing only the empty bioreceptor layer) and '**$R_{ct\ 100\%}$**' is the charge transfer resistance measurable on the transducer covered with target molecules to a maximum extent (i.e., all active bioreceptors are bound together with target molecules), furthermore, I performed series of measurements for the **comparison** of 3 possible electrode connection regimes and 4 types of working electrode geometries **based on the utilization of $R_{ct\ 100/0}$**

a) Using a standardized thiol-gold chemisorption immobilization technique, I have fabricated DNA bioreceptor layers on gold thin films deposited on glass substrates. (1. on 5mm diameter electrodes of disc geometry, 2. on "tradIDT" electrodes, 3 on „symIDT" electrodes and 4. „asymIDT" electrodes) and I designed a measurement setup which is capable, at a solution volume of 250 µl, of receiving the tip of a traditional Ag/ AgCl or SCE (saturated calomel electrode) glass-macroelectrode as a reference electrode, if necessary, of receiving a Pt-wire bent to a ring of a diameter of 8 mm as a counter-electrode and, in an experiment, permits the characterization of 1 piece 5 mm diameter disc electrode or the comparative measurements of 4 pieces of 4,0 mm x 2,3 mm IDT electrodes.

b) I demonstrated experimentally that in a measurement setup constituted by a disc shaped working electrode (W) most widespread in the technical literature on EIS, an Ag/AgCl reference-macroelectrode (R) and a counter-electrode made of a counter-Pt-wire (C), in case of immobilization technique uniformly applied in my measurements (24-hour room-temperature thiol-gold chemisorption), measuring solution (10 mM $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ content), measurement setting (DC = 180mV, AC = 10mV_{pp}), bioreceptor molecule (SHC3-$^{5'}$GGT TCC GAA AGT TGG$^{3'}$) and target molecule ($^{5'}$TTC CAA CTT TCG GAA CC$^{3'}$), the comparative parameter suggested by me is **' $R_{ct\ 100/0}$' =** 178% with a standard deviation of 7 %, which experimental result may be used as a reference value when the changes in measurement technique are monitored.

c) Regarding electrode geometries I have pointed out that, in comparison with the disc electrodes, the application of electrodes of IDT geometry biofunctionalized with the identical technique is – irrespective of the presence of possible side branches – not more favorable either in case of the application of the 'traditional' electrode connection regime, (W – one IDT electrode-half covered with bioreceptor layer, R - Ag/AgCl macroelectrode, C -Pt wire), or in that of the 'common' R&bio-C' electrode connection regime (W – one IDT electrode-half covered with bioreceptor layer, R and C (connected together) – the other IDT electrode-half covered with bioreceptor layer), or, in that of the 'biofunctionalized C' electrode connection regime (W –one IDT electrode-half covered with bioreceptor layer, R - Ag/AgCl macroelectrode, C - the other IDT electrode-half covered with bioreceptor layer), in case the parameter **'$R_{ct\ 100\%} / R_{ct\ 0\%}$'** introduced

in my work and its standard deviation are also taken into consideration in the EIS measurement results.

d) Regarding the three types of possible electrode connection regimes using IDT electrodes and using a the same EIS measurement technique and biochemical protocol, I pointed out that **in comparison to 'traditional' electrode connection** (W : one IDT electrode-half covered with bioreceptor layer, R: Ag/AgCl macroelectrode, C: Pt wire), **the presence of the biofunctional layer** on **the counter electrode (C**) ('biofunctionalized C' electrode connection regime: W – one IDT electrode-half covered with bioreceptor layer, R - Ag/AgCl macroelectrode, C - the other IDT electrode-half covered with bioreceptor layer) **caused an increase of 3 to 6 %, and the connection of the biofunctionalized counter electrode (C) as a combined counter- and reference electrode (R&C)** ('common R&bio-C' electrode connection regime (W – one IDT electrode-half covered with bioreceptor layer, R and C connected together – the other IDT electrode-half covered with bioreceptor layer) **caused an increase of 30 to 40 % in the value of the** parameter **'$R_{ct\ 100/0}$'** introduced by me, **however, in parallel to this the standard deviation has increased strongly.** (Specific increase of standard deviation for the standard deviations of the 'traditional' electrode connection regime – symIDT: 5,27% , tradIDT: 17,63% , asymIDT: 0,89%. Further, normalized to the results of the traditional electrode connection regime: 'biofunctionalized C' connection regime: symIDT: 4.87 x , tradIDT: 8.80 x , asymIDT: 7.45 x ; 'common R&bio-C' connection regime: symIDT: 2.32 x , tradIDT: 6.69 x , asymIDT: 20.95 x)

Thesis 4. [related publications: P3, P4, P5]

I have elaborated novel interdigitated transducer (IDT) electrode geometries – also known as comb electrodes – which have side branches penetrating in between each other on the comb-teeth and which may – by the better reproducibility of the biosensor production process or by increasing the sensitivity – render biosensors of certain types significantly more accurate in comparison to traditional IDT electrodes that can be manufactured on the same surface area and with the same devices and technologies.

a) On prototypes prepared by laser ablation, I demonstrated experimentally that, in a conductometric measurement setup the sensitivity of the version with asymmetric side branches ('asymIDT') from among my new IDT electrode geometries, normalized to the effective size of active surface, exceeds the sensitivity of the traditional interdigitated electrode geometry ('tradIDT') that can be manufactured on the same surface area and with the same devices and technologies by an average of 27 %, while, calculated with the same method of normalization, the sensitivity of the version with symmetric side branches ('symIDT') did not differ more than 1% from the performance of 'tradIDT' (considering the response signal caused by the addition of a NaCl quantity inducing 10 mg/l concentration in relation to its baseline measured in the pH=7.5 phosphate buffer.)

b) I demonstrated experimentally that, in a Proteinase K-based conductometric biocatalytic BSA (Bovine Serum Albumin) sensor, the sensitivity of the version with asymmetric side branches ('asymIDT') from among my new IDT electrode geometries, normalized to the effective size of active surface, exceeds the sensitivity of the traditional interdigitated electrode geometry

('tradIDT') that can be manufactured on the same surface area and with the same devices and technologies by an average of 79 %, while, calculated with the same method of normalization, the sensitivity of the version with symmetric side branches ('symIDT') did not differ more than 1% from the performance of 'tradIDT' (considering the response signal caused by the addition of a BSA quantity inducing 4 mg/l concentration in relation to its baseline measured in the pH=7.5 phosphate buffer.)

c) With the help of the standard deviation data of my conductometric results received with the IDT prototypes, I pointed out that in case of preparation by laser ablation each of my new IDT electrode geometries have better reproducibility than the IDT electrodes with traditional geometry that can be manufactured on the same surface area and prepared with the same devices and technologies. (Standard deviations, in NaCL-solution: asymIDT- 1.5 %, symIDT – 2.7 %, tradDT – 3.6 %. Standard deviations, in BSA-solution: asyimIDT – 1.3 %, symIDT – 2.8 %, tradDT – 3.6 %.)

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