Micro– and Nanosensors for Biological Applications

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Recent progress in microsystems technologies for creating small, integrated and reliable microelectronic devices in combination with biological sensing elements has raised the expectation to get a comprehensive insight into dynamic cellular metabolic events and subsequently a complete understanding of the metabolism of human biology. Such micro– and nanobiosensor in combination with appropriate micro fluidics enable the simultaneous description and moreover monitoring of gene, protein expression and metabolic states in a biosystem. This knowledge will undoubtedly lead to new future pharmaceutical therapies. There are a lot of challenging problems to be overcome to reach this goal: Microsystems monitoring of physical parameters in biological systems are well established whereas chemo and biosensors are available for only a few parameters and mainly as in vitro devices. Gene-arrays entered the research market but are up to now not clinical practice and protein arrays are in a developmental state with promising results however far from a mature reproducible state. For getting insights into metabolic events intra- and extracellularly some new and promising technologies are under research and will undoubtedly revolutionize system biology.

Microsensors

At present, all intermediate acute testing of metabolic parameters are made using small POC analysers which admittedly work with miniaturized sensor arrays (1).

Here the electrochemical and optical determination of blood gases, electrolytes, but also of concentrations of metabolic parameters as glucose and lactate are of importance.
To detect a variety of metabolic parameters precisely and selectively in a complex analyte matrix as e.g. blood, special sensors – the so-called biosensors – have to be used.
Trying a definition of biosensors reveals a long history but recently IUPAC published a standardized definition (2):
“A biosensor is a self-contained reversible integrated device using a biological recognition element which is retained in direct spatial contact with a transduction element”.
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Chiefly miniaturized glucose sensors faced an immense boom due to monitoring of diabetic patients at home with an inexpensive diagnostics instrument allowing a more precise adjustment of insulin.
The classical biosensor is an enzyme biosensor with an optical or amperometric transduction principle. The enzyme catalyses the conversion of an analyte e.g. blood glucose to a molecule which can be measured.

The different products vary not only in enzyme and electrochemical protocols but also in arrangement of electrodes. One of the most successful biosensor is the electrochemical glucose biosensor as disposable device for intermittent blood glucose measurements (Fig.1).

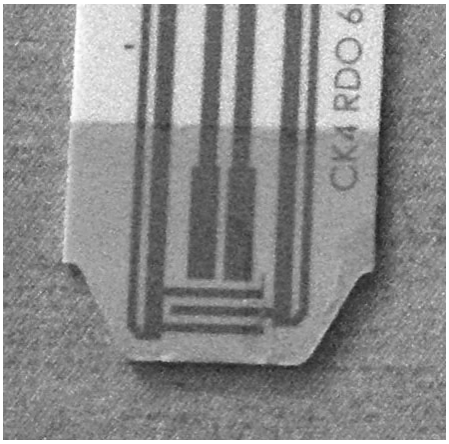

Fig.1 Micrograph of a disposable glucose sensor (company ROCHE) with integrated electrochemical and impedance measurement electrodes for hematocrite detection

Such microbiosensors can be also integrated to analyze different blood parameters at once (3) and implemented in a microfluidics long term monitoring of body fluids was accomplished (4).
The next step in the field of biosensors will see a change in technologies approaching the nanoscale as well as new transduction principles using nanotransducer approaches.

Nanosensors

An example for the use of nanotransducers are cantilever based sensors which utilize a micromechanically produced cantilever in a similar manner as for production of AFM probes. A several 100nm thick cantilever is bended due to biosensing interaction on the surface (fig. 2) which can optically sensed by a laser. The sensitivity can be tuned down to single molecule interaction analysis. Multifunctional cantilevers have a great potential in diagnostics for label-free, non-amplified analysis of biological samples for gene expression or proteomics. (5-7).

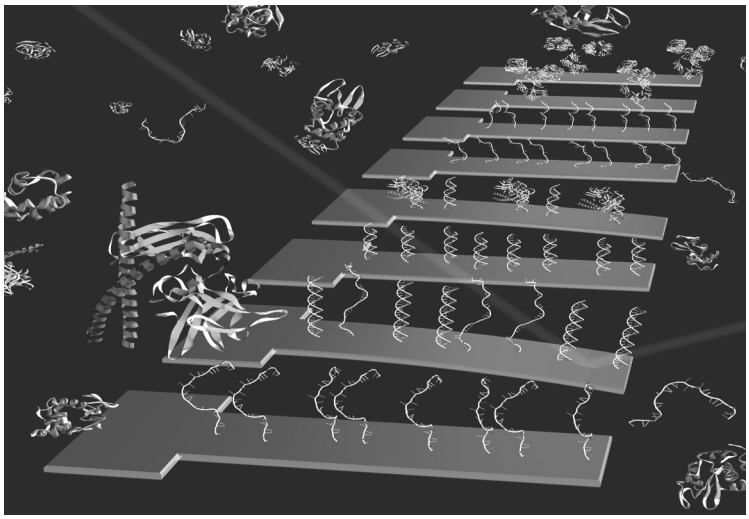

Fig. 2 Principle of a cantilever based biosensor for oligonucleotide detection (courtesy: Hegner)

The cantilever consists of micromachined silicon which can be produced by standard silicon technology. Cantilevers can be arranged in a row allowing multiple measurements at once by individual immobilization of biomolecules on their surface (Fig.3).

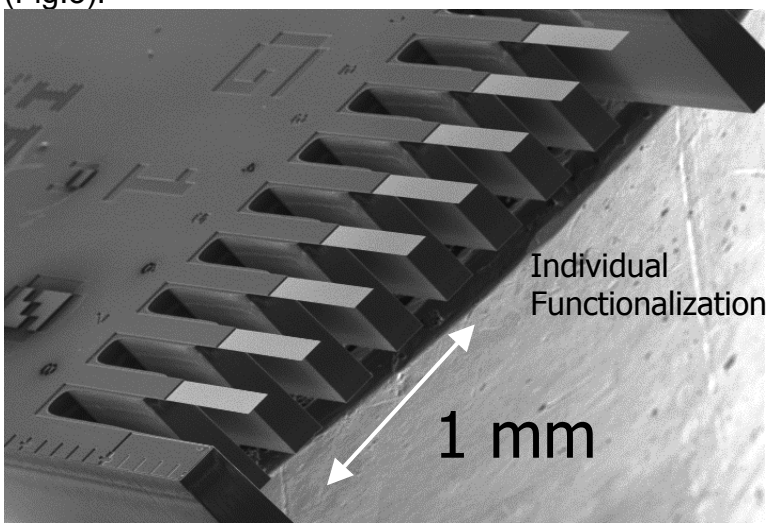

Fig. 3 Array of silicon based cantilevers with individual functionalised surfaces (courtesy: Hegner)

Due to this mass fabrication feasibility of cantilevers commercialisation of such products was accomplished (8).

Recently the field of nanobiosensors emerged rapidly with different technologies to get insight into cellular metabolic events (9).

Also electrochemical sensing methods can be scaled down (10). Special attention was laid on carbon nanotubes modification of electrochemical working electrodes (11). A very exciting field is the use of nanowires as new tool for biosensing (12).

However, such tools are still in its infancy with excellent potentials to be established in the future.
A more mature field is the use of microarrays for DNA and protein detection which may be also revolutionized by use of nanoparticles.

Labeling of DNA and protein arrays

Hybridised chip arrays are usually labelled with the fluorescent organic dyes 5-N.,N'-diethyltetramethyl-indocarbocyanine (Cy3) and 5-N.,N'-diethyltetramethylindodicarbocyanine (Cy5). Readout occurs by means of a laser-scanning device. The detection sensitivity of such techniques is limited by the brightness, quantum yield and the photobleaching rate of the fluorescent dye. The replacement of Cy3 and Cy5 by nanocrystal dyes promises an increased sensitivity, because they do not show photo bleaching effects and the potential possibility of realizing quantitative measurements. Efforts are made using metal nanocrystals as well as luminescent nanocrystals as labels.
The use of nanocrystals as labels for DNA and immuno assays promises an increased sensitivity and ability for quantitative assays (13-16).

Conclusion

Microbiosensors entered the market already and nanobiosensors are still an exciting field of research. In any case it seems obvious that such nanotools will enter the diagnostic world in biology as well as medicine in the mid future.

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