Disposable biosensor arrays with integrated microfluidics for biomedical- and biotechnology process -monitoring

Moser, Isabella und Jobst, Gerhard
Jobst Technologies GmbH
Engesserstr. 4b
79108 Freiburg, www.jobst-technologies.com

Abstract

A generic technology platform based on polymer laminate technologies with integrated electro-chemical biosensors utilizing nano- composite membranes allows the fabrication of fully flexible devices comprising biosensor arrays. The flexible manufacturing technologies used for these devices also allow a cost effective customisation of them.

Devices for the simultaneous monitoring of lactate, glucose, glutamine, and of flow rate were realized with the biosensor array integrated in a flow-through cell with a total internal volume of 0.15 µl and less. Performance and applications of devices fabricated by this generic platform technology are presented.

Keywords: biosensor arrays, disposable, biotechnology, microfluidic, biomedical.

Introduction

Currently higher life expectancy is changing our society structure to one with a higher amount of elderly persons. Together with the changes in family structures new life models for a save, but nevertheless independent life, have to be developed for this group of persons. One of the most important aspects is to provide for healthcare and medical assessment at home. One of the models contemplated is pervasive healthcare, a maximum and all pervasive support based on ubiquitous computing, which uses the monitoring information provided by sensors. But till now only appreciable progress in patient- home-monitoring was achieved by automatic blood glucose monitoring for diabetic patients. In near future continuous glucose monitoring systems should provide actual blood glucose concentrations at any time thus helping to avoid severe and therefore harmful blood glucose concentration fluctuations.

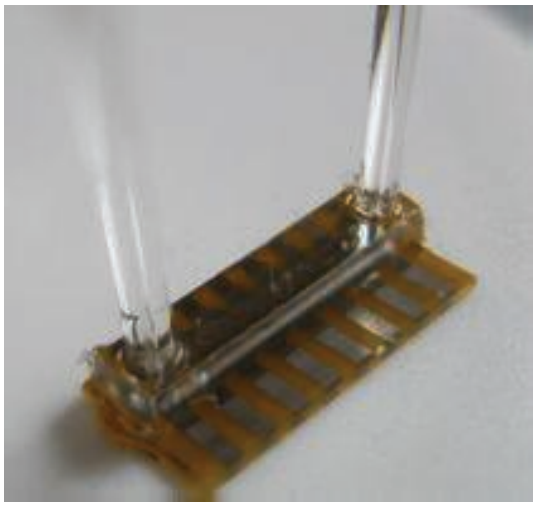
Whereas at the moment a complete human health monitoring is in the early stages, “vitality monitoring” is common and very important in biotechnology. However the number of measurable parameters in this field is small too and it is highly desired to increase the monitoring parameters. Therefore beside the above mentioned important biomedical application, metabolic research both in vivo and in vitro, emerging therapeutic praxis of metabolic typing of cells and tissues, bioprocess development and fermentation control would benefit from a timely knowledge of metabolic parameters, e.g. glucose, glutamine, lactate, etc. - enabling adequate intervention, maximisation of product yield, and providing tools for the reliable and traceable processing of cells used as therapeutics, which is an important issue in e.g. process analytical technology (PAT).

For feeding- and specific metabolite concentration-control biosensors are the analytical tools of choice. In reality the availability of appropriate biosensors is very limited. This is even true for the analyte glucose. In principle estimated 50 different single-use glucose sensors developed for diabetes care are on the market. But most of them are single-shot sensors. Real glucose monitoring systems, so-called “cgms” for “continuous glucose monitoring system” are very rare and limited to glucose as the analyte and dedicated to biomedical use only.

In contrast, Jobst Technologies GmbH presents a low flow rate multi-parameter monitoring system for glucose, lactate, glutamine, and flow rate in nanoliter volumes. Cost-effective foil-based mass production of the disposable devices is a prerequisite for biotechnology and biomedical application.

Disposable biosensor arrays

A generic technology platform based on polymer laminate technologies with integrated electro-chemical biosensors utilizing nano-composite membranes allows the fabrication of fully flexible devices comprising biosensor arrays. The flexible manufacturing technologies used for these devices also allow a cost effective customisation of them.
Devices for the simultaneous monitoring of lactate, glucose, glutamine, and the flow rate were realized with the biosensor array integrated in a flow-through cell with a total internal volume of 0.15 µl and less. The devices also provide ultra-low volume fluidic connection extensions enabling a highly variable use of it.
Performance of these devices shows physiological dynamic ranges, good to acceptable precision and operational stabilities of minimally two weeks for continuous operation for all the biosensors in the array. Flow rates used range from 0.1 to 100 µl/min. These systems were successfully applied for monitoring of cell cultures and *ex vivo* applications.



A fully assembled multi-parameter device with the flow cell on top, the tubing connected, and the electrical contacts can be seen in Figure 1. The flow cell has a volume of 150 nl and covers 6 platinum working electrodes together with one reference and one counter electrode (device ”LV5”).
The devices- the flow cell included- are produced totally on wafer-level.

Figure 1. “LV5” Disposable biosensor array

A “wafer”-sheet for so-called “LV6” devices is shown in Figure 2. Up to 12 platinum working electrodes allow redundant biosensors, which maximizes operational reliability. In figure 2 also the backside of a device with the unique bar code is visible allowing traceability of the devices by means of these labels.

As a detail view an integrated flow rate sensor is shown on the left.

Figure 2. “LV6” Expanded biosensor array with additional flow rate sensor, 12 platinum working – one reference – one counter electrode

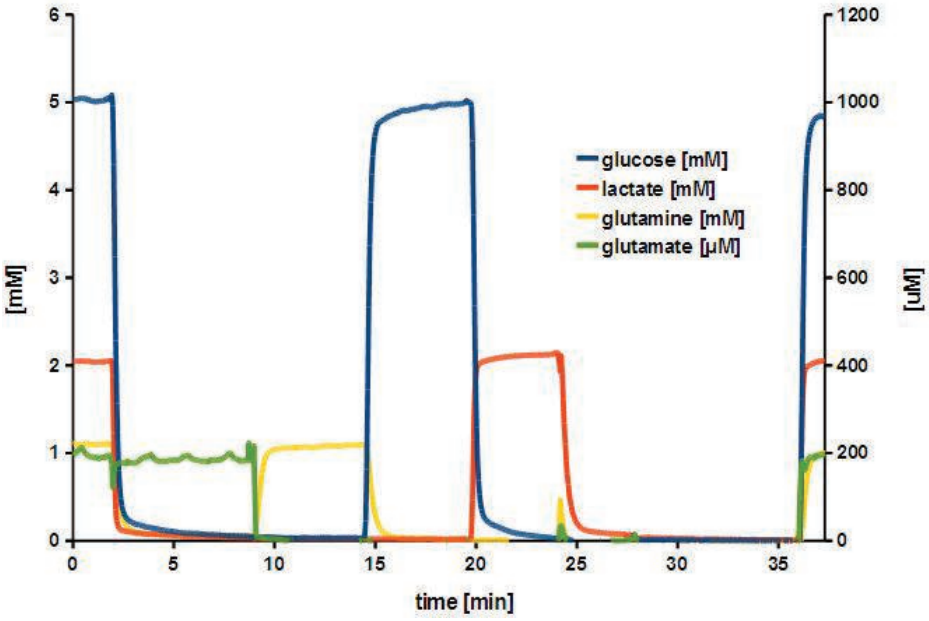


Figure 3. Simultaneous multianalyte monitoring of a mixture (5 mM glucose, 2mM lactate, 1 mM glutamine, and 0.2 mM glutamate) and 4 one-analyte solutions followed by buffer, and the 4-analyte mixture again (glutamate: µM scala on the right)

For simultaneous measurement of glucose, lactate, glutamine, and glutamate a biosensor array is implemented in a micro flow-system with nanoliter volume (Figure 1). The biosensors with no crosstalking and high long term stability were produced by modifying the electrochemical transducers and utilizing photopatternable nano- composite membranes enzyme membranes. The activity optimum of all biosensors in the array is in the neutral pH range allowing therefore direct and simultaneous monitoring of glutamine together with glucose, lactate, and glutamate (Figure 3). The measurement shown in Figure 3 started with a mixture of 5 mM glucose, 2mM lactate, 1 mM glutamine, and 0.2 mM glutamate (µM scala on the right side). To demonstrate the independency of the biosensor signals each kind of biosensor was addressed subsequently with its analyte in the concentration, which was used in the mixture before.

Summary and Outlook

Disposable multi-parameter biosensor arrays for glucose, lactate, and glutamine/ glutamate in a micro flow-system with nanoliter internal volume were developed as all flexible mass producible devices. These systems were successfully applied for monitoring of cancer cell lines and in ex vivo biomedical applications. The devices are aimed to be part of disposable bioreactors as valuable process analytical technology tools.

References

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Benchmarks	
Construction	Interfaces to FFC ZIF connector, Currently 0.15mm id tube termination
Operating principle	Oxidase enzymes and hydrogen peroxide oxidation @ Platinum @ +450mV vs internal Ag/AgCl
Sensitivity	Glucose: 0.8nA/mM, L-lactate: 2.0nA/mM, Glutamine: 1 nA/mM, Glutamate: 0.5 nA/mM
Dynamic range	Glucose: >25mM, L-lactate: >15mM (low levels of oxygen will reduce linear range)
Operational stability	Typically >2 weeks Decreased mainly by: higher analyte concentration and less oxygen
Daily variation	<5% in sensitivity
Storage	Desiccated @ 4°C. Freezing not adverse. Humidity matters more than temperature.
Interferences	Very low sensitivity even to Acetaminophen further minimized due to difference measurement
Flow cell pressure drop	700µl/min.bar
Sample composition considerations	Reference electrode relies on the presence and moderate variability of chloride ions. Typical HCO3-/CO2 system is optimal

Company

Jobst Technologies GmbH, a Germany based private company located in Freiburg's Biotech park, is unrivalled competence leader in bioanalytical monitoring applications with OEM products in clinical routine and biotechnology as well as with his own products for R& D applications. B2B contract development together with participation in EC research projects provides permanent extension of the company's technology and product portfolio.

Jobst Technologies is a technology orientated enterprise offering its core competencies in the overlap between micro systems technology, (bio)electrochemical analytics, and microfluidics both as service and products to his customers.