Micro Biosensor Systems for Cellular Monitoring

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Even so, in 1885, Roux did first *in vitro* cultivation of embryonic egg cells, it was in the mid of last century, when animal cell cultures became routine laboratory technique. Since that time cell biologists made a lot of progress to establish *in vitro* models, also with different mammalian cultures, allowing research on cell physiology and metabolism as well as behaviour of the cells to different chemical compounds, e.g. for drug tests. Later on, cell culturing was used to exploit the cells, as it is done with tissue engineering. Nowadays further improvement led to the possibility of cell therapy.

Along with the progress in cell culturing, the need of peri-cellular monitoring of multiple parameters is continuously increasing. In contrast to single-shot measurements as can be performed by taking out a sample and usage of an analyzer, the monitoring allows to track the temporal behaviour of these parameters. Especially with adherent cell cultures, there is an important field and market for micro sensors to obtain sensor readings from as close to the cell layer as possible.

There are multiple motivations to use cell culture monitoring systems.

- Basic research: By gaining new insight in the transient variation of several parameters, cellular behaviour and the under-laying pathways can be investigated. Thereby cell culture monitoring is tremendously enhancing the field of cellular research.
- Pharma technology: To obtain reproducible results, cell cultures have to be standardized, what would be impossible without the monitoring of all the relevant peri-cellular parameters. Especially in the field of tissue engineering and cell therapy, cell culture monitoring is indispensable to allow patient safety and quality control.
- Pharma screening: During drug screening a combination of sensor signals could be used as indicating parameter for cellular metabolism or even vitality.
- Biotechnology: Further, the monitoring of cell cultures allows the further control of the *in vitro* experiment, e.g. by finding optimal time for medium exchange et cetera.

As wide as the variety of motivations is, the number of parameters to monitor is huge and different depending on the application. The most important parameters to monitor are oxygen tension, glucose, lactate, ammonium, glutamine and alcohol concentration. Depending on the application NO and neuro-transmitter, as well as pH can be of interest.

All these parameters could be classified whether they have a source **and** sink inside the cell culture or just have a sink **or** source. Glucose for example is normally a priori inside the cell culture medium. There is no source generating new glucose, only the metabolism of cells acts as sink for the glucose. Therefore the glucose concentration is continuously decreasing over time. In contrast lactate has only a source, as it is the end product of metabolism, leading to a continuous increase in lactate level. All these parameters with sink **or** source always show monotonous behaviour but usually demand for sensors with a huge measuring range.

The oxygen tension is an example for a parameter with source **and** sink. The cellular respiration acts as sink. The dissolution of oxygen from gas atmosphere into the cell culture medium is an infinite source for oxygen. As the cellular respiration itself depends on the oxygen tension, the systems are usually unpredictable. The pericellular oxygen tension is a very critical parameter because dependent on the oxygen tension, different metabolic pathways could be activated.

The presentation will focus on an overview about the different parameters and give some example for micro biosensor systems from research as well as some commercial available systems.