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Lab-on-a-Chip Technology for Continuous Glucose Monitoring

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Abstract

The demand for continuous glucose monitoring systems is greater than ever. The microelectromechanical systems (MEMS) approach has the advantage of being relatively easy to upscale to a commercial level; the preferred MEMS technique would be to run several detectors at once and, through the improved statistics, get a both more accurate and more reliable device than is currently available. Lab-on-a-chip technology may be seen as a further development of MEMS technology for analytical sensors. Lab-on-a-chip systems may be used to obtain improvements on several important characteristics of a sensor system: remove or decrease cross-sensitivity, improve sensor stability, improve accuracy, and/or improve response time compared to similar laboratory-equipment methods.

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As Mugweru and colleagues[1] point out, the demand for continuous glucose monitoring systems (CGMS) is greater than ever. With only a limited number of players currently on the market, this is an area of ever-increasing interest.

The CGMS market is not uniform but is subdivided based on usage and performance demands; the main dividing line is between diabetes treatment and intensive care unit (ICU) tight glycemic control (TGC) treatment.

Possibly the largest single market is the diabetes home usage segment, where the main foci are cost and convenience. This means that any device for this market must be noninvasive or minimally invasive. For hospital use, cost efficiency and convenience are of course still important, but in addition there is an added weight on the accuracy of the device.

The device described in this article most probably falls within the minimally invasive diabetes treatment category, which means that it will be competing with current state-of-the-art devices available on the market today, such as the GlucoDay® S (A. Menarini Diagnostics), which utilizes a microdialysis catheter to sample glucose, and the Guardian® REAL-Time (Medtronic, Inc.), which is based on readings from a glucose oxidase-covered electrode.

The authors also mention some of the other techniques utilized to measure glucose in a noninvasive manner, for example, the Symphony™ (Sontra Medical Corporation),

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Abbreviations: (CGMS) continuous glucose monitoring systems, (ICU) intensive care unit, (MEMS) microelectromechanical systems, (TGC) tight glycemic control

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utilizing sonophoresis to sample glucose, and GlucoTrack™ (Integrity Applications), using transdermal measurements of ultrasound, conductivity, and heat capacity to estimate the glucose level.

When comparing the presented technology with the techniques used by competitors, one would normally look for clinical accuracy and expected lifetime of the device in question. However, as data on these issues have not been presented, a comparison with existing devices is difficult. The microelectromechanical systems (MEMS) approach has the advantage of being relatively easy to upscale to large volumes, and the MEMS technique would also enable having several detectors at once and, through improved statistics, potentially obtain a more accurate and reliable device than is currently available.

It is, however, questionable if the device described here could be used during TGC treatment of ICU patients where the paramount demand is accuracy. One problem here is the measurement technique; the measured glucose value is representative for the subcutaneous tissue but is linked only indirectly to the blood glucose level and the increased response time because of this is problematic in this setting.

Sampling directly in the bloodstream is more attractive because of the low response time and high accuracy that can be achieved. Currently there are not many continuous devices that sample in the bloodstream (such as the Nikkiso STG22), but several companies are testing new technologies for introduction to the ICU CGMS market. Most of these are based on different variations of venous catheter sampling coupled with different detection methods.

Microelectromechanical systems technology is good for reliable and inexpensive electrode fabrication, as shown by the authors. However, this technology may be taken much further in the direction of more or less sophisticated lab-on-a-chip sensor systems.

Lab-on-a-chip technology makes many additional tools available for a miniaturized analytical sensor system. One being better reproducibility than in many macroscopic systems due to the inherent ability to dose and mix several analytes and to control the timing of reaction kinetics.

Miniaturization in itself brings along sampling techniques, such as microdialysis or analysis on very small droplets. On top of this comes the possibility of doing sample pretreatment by the addition of complex binders or other methods of masking off potential cross-sensitivity species. Automated flow control may also be used to obtain self-reconditioning of a sensor system, which brings a sensor surface (e.g., electrode, ion-sensitive field effect transistor, optical window, surface acoustic wave surface) back to a well-known condition. Further, flow control may be used to do real self-calibration by exposing the in-system sensor to one or more reference liquids.

Lab-on-a-chip system opportunities may be used to obtain improvements on several important characteristics of a sensor system: remove or decrease cross-sensitivity, improve sensor stability, improve accuracy, and/or improve response time compared to similar laboratory-equipment methods.

Unfortunately, all these beautiful features do not come free. Lab-on-a-chip systems tend to be complex to build and even more complex to operate for an extended period of time in "the real world" outside the research and development laboratory.

One challenge is the choice of a sampling method that optimizes small sampling volume, fast response time, and high accuracy at the same time. The flow-chip material itself is a challenge as well. Robustness, low-cost manufacturing, and compatibility with MEMS fabrication have to be considered. Many systems have been based on silicon and glass, but polymer technology has progressed significantly and must be expected to be the preferred material for most applications.

Another inherent challenge linked to lab-on-a-chip systems is to design flow systems with air bubble tolerance and proper mixing/dispersion characteristics. Because of the small dimensions, surface tension forces become much more dominant compared to gravity or inertial forces, and current good practice on the benchtop may not work at all in a lab-on-a-chip system. To solve these problems, experience is mandatory, but new computer-based modeling tools are also helping out in this respect.

Finally, microflow control demands highly accurate pumps, low dead volume valves, and sophisticated mechatronics assembly methods. This is where the jump from the research and development laboratory to the real world often becomes a "giant leap." Every application has its own requirements, and one will have to select the best one for exactly the application at hand.

Microelectromechanical systems technology has much to offer in the area of analytical chemistry. Mugweru and co-workers[1] demonstrate some of the opportunities by making multiple MEMS-fabricated electrodes for

glucose measurements. Further work in this area is very much encouraged. In particular, it could be of interest to demonstrate experimentally the improvement of sensor accuracy and possible self-detection of fouling electrodes using multiple electrodes and advanced statistical analysis of the multiple sensor signals.

References:

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