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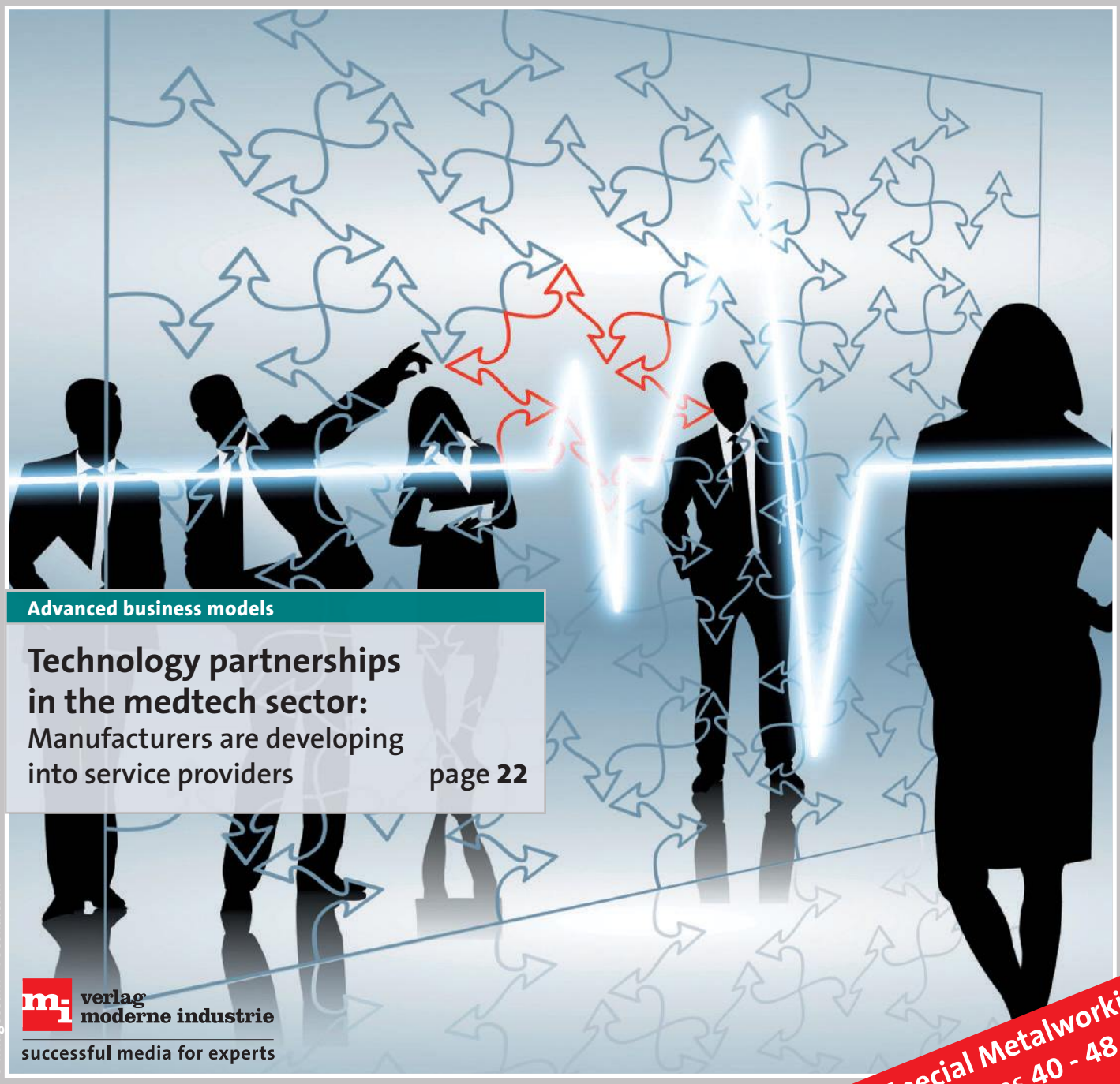

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In the clutches of microfluidic systems

Increasingly smaller sample quantities are required to obtain reliable diagnostic results. As a result, measuring equipment is also getting downsizing. A mobile analysis laboratory based on lab-on-a-chip technology able to detect microorganisms shows how process integration and automation can cut hardware costs without adversely impacting on quality and speed.

There is an obvious trend in diagnostics towards increasingly small sample quantities. Manufacturers of measuring technology, microfluidics and pump technologies continue to push ahead with miniaturizing their devices, penetrating new fields as they do so. Mobile labs cost less than classic lab analysis thanks to the reduced amount of apparatus, and they consume less material, too. According to the VDE Innovation Monitor, most innovation stimuli for a wide range of applications in medical technology come from micro engineering and nanotechnologies. According to many experts, microfluidic integration of laboratory processes is well on the way to replacing time-consuming methods with fast, automated on-si-

Valve clusters: valves clustered in groups are high-performance, compact alternatives to conventional solutions.

Photo: Provenion

te analysis. Compact, highly-integrated devices are required which are simple to operate and can identify and reliably analyse a wide range of parameters. For users it is important to gain access to lab-on-a-chip technology as quickly and simply as possible without putting their own development too much at risk.

Microfluidic systems are always in demand when fluids have to be transported, mixed or analysed within a very small space – whether biomolecules in water or blood cells or bacteria in tissue fluid. The potential of lab-on-a-chip technology is illustrated clearly by a current example from the field of drinking water analytics.

Lab-on-a-chip technology

The brief was highly delicate and by no means run-of-the-mill: a highly sensitive, portable analysis device was to be developed to monitor drinking water. The development consortium was made up of leading protagonists including representatives of research institutes, molecular biologists, software specialists and mechatronics experts. The main focus of online drinking water monitoring is the early detection of pathogenic contamination without significant expenditure in terms of personnel and logistics. The project stems from concerns on the part of the EU Commission that the drinking water supply could be the target of bioterrorist attacks during large-scale political or sporting events. Reliable and fast detection of such attacks is currently difficult. The new analysis device is to use a lab-on-a-chip technology to allow virtually continuous monitoring of the flow of drinking water directly at the endangered supply nodes.

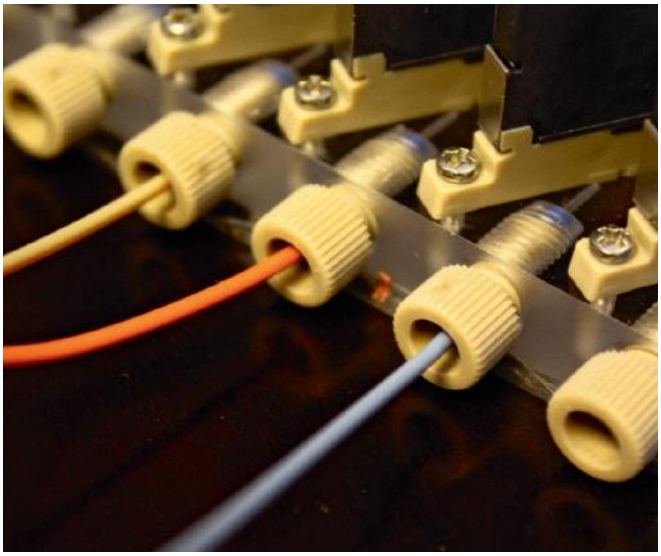
Development engineers are involved from the company Provenion based in Kirchseeon near Munich. Their med-

Photo: Provenion

Shrinkage without loss: this device increases the concentration of the water components by means of tangential ultrafiltration in hollow fibre filters, reducing the components of 32 litres of water to a volume of just 20 millilitres.

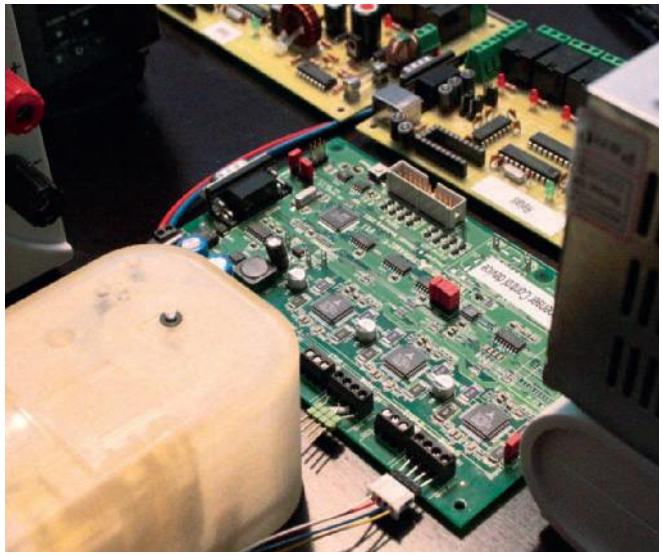
German Summary

Der Trend in der Diagnostik zu immer kleineren Probenmengen ist unübersehbar. Die Hersteller von Messtechnik, Mikrofluidik und Pumptechniken treiben die Miniaturisierung ihrer Geräte weiter voran und erschließen darüber neue Einsatzfelder. Das mobile Labor kostet wegen des geringen apparativen Aufwands weniger als eine klassische Laboranalyse und verbraucht weniger Material. Laut VDE-Innovationsmonitor gehen von den Mikro- und Nanotechnologien die größten Innovationsimpulse für viele medizintechnische Anwendungen aus. Der deutschsprachige Beitrag ist nachzulesen auf www.meditec.mi-verlag.de/medi0411flui



Photos: Provenion

Fully automatic and non-contact: the various reagents required for the detection protocol no longer have to be pipetted by hand but are fed to the detection chip in tiny quantities of ten microliters.



Electronically controlled: lab-on-a-chip technology with its excellent analysis results can no longer be realized without control electronics and software.

tech expertise ranges from mechatronics and system engineering to filter and extraction methods, fluid handling and microfluidics, integrated processing technologies for DNA hybridization and signal preparation and processing on silicon and polymer substrates. "One aspect which had not been clarified at all was how to obtain drinking water samples," says project manager Christoph Zeis of Provenion, "as nobody knew what quantity of water was required and how it had to be prepared so as obtain reliable results on a microfluidic lab-on-a-chip system."

The focus is on three main areas

In addition to determining the overall layout of the devices and the component specifications, development work is focusing on three main areas relating to the microfluidic concept: the device for water sampling and pre-concentration, a valve cluster for up to six analysis valves as a low-cost alternative to multi-port selector valves, and a dispenser with a mixer unit for tiny quantities of ten microliters, allowing automatic and non-contact dispensing of various reagents to the detector chip.

In order to obtain sound and precisely reproducible measurement results the developers started by defining the required water sampling quantity per analysis, then reducing the sample quantity to an acceptable minimum by means of intricate measures. In particular the combination of cell lysis and DNA isolation in a single simultaneous process stage and the development of a 2-stage system to pre-concentrate the drinking water samples reduced the volume of the required water sample by several decades, with the 2-stage pre-concentration system making the most significant contribution at a factor of 40.

This device, developed by Provenion under the name of "inline separator", uses a hollow fibre ultrafiltration module for each filtration stage in which the concentration of all water components including bacteria, viruses and other germs is significantly increased - the figure given by the company is a factor of 1600. Expressed in absolute figures, the components of at least 32 litres of water are therefore compressed to around 20 millilitres in just two times 25 minutes. The technique of tangential filtration is used here (cross-flow filtration), since this is the only way to ensure blockage-free, continuation operation of the system, as well as providing a much higher and reliable rate of efficiency as compared to conventional dead-end filtration.

Compact, highly-integrated devices are required which are simple to operate

Process integration of the thermal and chemical breakdown of the cells – the so-called cell lysis – in direct combination with the simultaneously occurring isolation of DNA molecules has proven to be considerably more economical than conventional processes. Conversion to a single, flowing process reduces processing time as well as increasing DNA yield in spite of the reduced sample volume. "Process integration allows us to increase detection probability while using less hardware and cutting costs at the same time," says Zeis.

The microfluidic part of the sample analysis feeds the released DNA material, reproduced by means of polymerase chain reaction (PCR) to the detector chip. This operates according to the principle of chemoluminescence. As soon as a specific DNA molecule docks onto the capture molecules anchored on the chip surface, a light reaction is triggered. This requires the application of several other reagents to the detector chip in very small quantities of around ten microliters. This is possible due to an automatic dispenser, which prevents contamination by means of non-contact sample transfer. In addition, the dispenser has a mixer chamber. This is important since two of the reagents are mixed immediately before release: the mixture does not have long term stability.

Andreas Beuthner ←