

DNA tests could soon be conducted on handheld devices based on Siemens' *quicklab*. A prototype with its channels and reaction chambers is shown in the large image. The small picture at right illustrates a vision of a future quick test.

ISIT, Siemens and Infineon were nominated for the German Future Prize 2004.

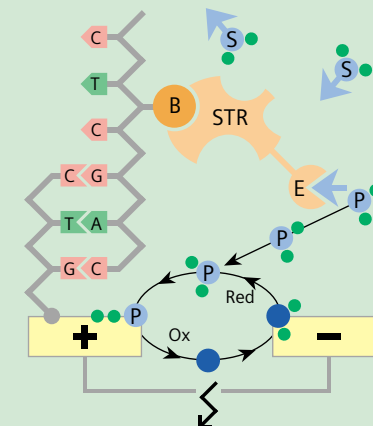
One Card. At the heart of *quicklab*, which was developed by Siemens, is a miniature laboratory the size of a credit card that automatically extracts DNA or proteins from a drop of blood or other bodily fluid and emits the diagnostic information as an electrical signal. "In the last six months, we've pressed forward with the development of the DNA analysis in particular," says Gumbrecht. As

economically efficient," says Birkle. The non-reusable cards will cost only a fraction of a laboratory test.

And for the same reason, researchers are relying on existing technologies wherever possible. For instance, they are using the gold contacts of a conventional chip card as electrodes, because gold is the ideal base for the "receptors" — synthetically produced biomolecules that pick out specific DNA sequences or proteins from a sample. The binding of enzymes and the decomposition of a



THE CATCHER IN THE CHIP



If the DNA sequence tested for is contained in the sample, it binds with the receptor on the gold electrode. The DNA marked with biotin (B) acts as a docking point for the enzyme alkaline phosphatase (Str/E), which releases a molecule (P) from the substrate (S). P releases two electrons at the positive electrode. After that, it migrates to the negative electrode, receives two electrons again and shuttles back to the positive electrode. Because of P's migration, an electric current flows between the electrodes — this is the actual proof that a matching DNA sequence was found. Otherwise, there is no pairing of the DNA with the receptor; no substrate molecule P and no electrons are released, and therefore no current is measured.

The Pocket Laboratory

Molecular diagnostics is becoming increasingly important in the identification of illnesses. The latest biosensors and a new technology platform known as *quicklab* are expected to make many medical tests faster, simpler and less expensive.

Runny nose, a cough, a worn-out feeling and fever: Is it dangerous influenza or just a cold? Often only a laboratory test can provide the answer — but once the sample is transported to the lab, it takes an average of two days for a doctor to get the results. That delays treatment, which can have a serious impact in the case of viral infections.

"Our *quicklab* system performs a test in just under an hour," says Dr. Walter Gumbrecht, an expert in the Power & Sensor Systems department at Siemens Corporate Technology (CT) in Erlangen, Germany. "And we'll be able to make it even faster than that."

The new *quicklab* molecular diagnostic system will allow family doctors to do rapid

tests in their own offices. It's suitable for both genetic material (DNA) and proteins — a feature that makes it ideal for a broad range of applications. It can be used to track down pathogens that cause infectious diseases and to detect allergies, hereditary diseases and incompatibilities when medicine is prescribed or transplants are performed. In the future, there will be quick tests for every medical requirement.

The foundation for *quicklab* was laid in the years 2000 to 2003 by the German Federal Ministry of Research's SiBAnaT project (Silicon Chip System for Biochemical Analysis Technology). SiBAnaT involved the cooperation of Siemens, the Fraunhofer Institute for Silicon Technology (ISIT), Infineon Technologies AG, november AG and Eppendorf Instrumente GmbH.

The high value of the above mentioned innovations was also recognized by the jury for the German President's Award in the field of technology and innovation: For the "Lab on a Chip — Electric Biochip Technology,"

part of this effort, his working group designed a microfluidic system composed of channels, chambers and pumps. Capillary forces draw a microliter of an injected drop of blood into a channel. Water is pumped in to dissolve chemicals present there, which break down the cells in minutes. Water is pumped in again to rinse the constituents through a chamber in which the DNA is extracted and held. There, the tiny initial quantity of DNA is reproduced on a large level and marked with biotin molecules. Afterward, the DNA reaches a chamber that contains the biosensor.

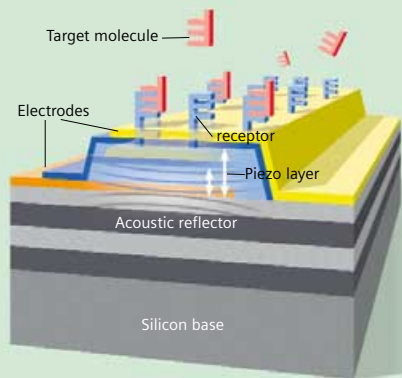
"We've combined existing technologies into an innovative platform," says Dr. Siegfried Birkle, head of the Power & Sensor Transducer Systems unit. For example, the researchers succeeded in placing dry forms of all of the enzymes and reagents on the inner walls of the reaction spaces. The *quicklab* cards must have a shelf life of at least six months at room temperature to ensure that the general practitioner can always keep them in stock. "The system is designed to be

WEIGHING DNA — VIBRATIONS REVEAL ILLNESSES



A micropipette (left) deposits a nano-liter of a biomolecular solution on a test sensor array. A sputter system for the piezo layer of the sensor (right).

Researchers are working on a sensor that is compatible with the *quicklab* system and is likewise capable of electric read-outs — the micro-balance sensor, which is being developed by Dr. Reinhard Gabl of the Materials & Microsystems department at Siemens Corporate Technology (CT) in Munich. In contrast to the electro-chemical sensor, here the conversion into an electrical signal does not take place via a linked enzymatic reaction. That means the molecule being detected doesn't have to be specially marked either, which makes the sensor even more economical. The receptor rests on a vibrating base, which is the actual sensor element. When a DNA or protein sample binds to the sensor, the frequency of this oscillator changes. "In a sense, we use this to register the change in weight due to the bound molecule," says Gabl. The sensor is constructed of several layers (graphic below). The fundamental oscillation is produced in a piezo-ceramic with the help of an alternating current. The surface is coated with a very thin layer of gold, "because for gold there is an established coupling chemistry," says Dr. Hans-Dieter Feucht of the Erlangen, Germany CT labs. Feucht ensures that the receptors bind onto the surface of the sensor with pinpoint precision. That requires a few tricks, because the molecules are in a solution. To make sure they don't disperse at the sensor, Feucht had plastic rings ten micrometers high mounted on its surface. Into these rings, a pipetting robot injects a few billionths of a liter of the receptor solution — aided by cameras with automatic image processing. Thanks to its high operating frequency, the micro-balance system is more sensitive than conventional piezo oscillators. The sensor therefore functions with very small measuring areas, which makes it cheaper. "In three years, at the earliest, it will enter product development," Gabl estimates. Before then, he still has to develop a transverse oscillator. Currently, the sensor simply oscillates up and down, which results in a significant dampening of the signal when measurements are made in liquids. "The future transverse oscillator, on the other hand, shakes like a pudding," says Gabl. "That reduces the dampening."



Principle of the micro-balance sensor. An electrical voltage causes the resonator — the piezo layer — to oscillate. When a target molecule binds with a receptor according to the lock-and-key principle, it changes the frequency of resonance because of its weight. This change is then translated into an electrical signal and processed further.

substrate ultimately give rise to an electric current that the researchers can record with a read-out device (see box p. 75).

The system is so sensitive that even the smallest deviations in genes can be detected. In a DNA test, the DNA sample and the receptors fit together like a lock and key. "When we slowly raise the temperature, the precisely matching molecules remain bound longer than those which differ in some constituent," says Gumbrecht. In the past, analysis of individual mutations of this kind, which play a key role in many illnesses, was possible only with expensive laboratory equipment.

Expensive Lenses Not Needed. In large part, it is the electric detection which is responsible for the compact and inexpensive design. This makes it possible for the researchers to forgo the light sources, lenses and filters of a conventional optical detection system, in which the biomolecules are marked with fluorescent dyes. "In about a year we'll have a prototype," says Gumbrecht. In the meantime, he wants to make the system more user-friendly, simplify the process of acquiring the sample and make further progress with miniaturization.

In the long run, there may be no need for the card reader at all, because it could be replaced by a highly integrated microchip — with an electronic evaluation unit, sensors for various questions and organic LEDs that display the result directly on the card. Gumbrecht's vision is as follows: Just as diabetics now measure their indicators at home, patients could one day use rapid tests to check the course of treatment for their illnesses. Pressing one's thumb on a fine pin on the card would be enough to start an analysis of the drop of blood.

Dr. Mohammad Naraghi, who oversees business development at Siemens Medical Solutions, is already looking into the first potential applications. He has great confidence in the system. "A drop goes in and information comes out," says Naraghi. "So far no one has successfully implemented such a comprehensive integrated approach — but that's the vision we're all pursuing."

■ Michael Lang