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### NMR Technology Comes to the Lab on a Chip

A breakthrough in the technology of nuclear magnetic resonance (NMR), one of the most powerful analytic tools known to science, is opening the door to new applications in microfluidic chips, devices for studying super-tiny amounts of fluids. A team of scientists with Lawrence Berkeley National Laboratory (Berkeley Lab) and the University of California, Berkeley, has demonstrated a means by which NMR can be made compatible with microfluidic "lab-on-a-chip" devices. This demonstration holds great promise for biomedical research, the detection of biohazards and toxic chemicals, and other endeavors in which the chemical composition of a fluid must be determined.

"Our novel methodology bypasses the longstanding problem of optimizing the two basic steps of NMR, signal encoding and detection, by physically separating them, and, at the same time, adds an important dimension to the study of fluid flow dynamics with the possibility of time-of-flight measurements," said Alexander Pines, a leading authority on NMR technology.

The technique in which NMR signal encoding and detection are carried out independently (in a conventional NMR setup, the two actions take place within a single device) is called remote NMR detection. In a paper published in the online edition of the Proceedings of the National Academy of Sciences (PNAS), Pines and his collaborators describe the use of remote NMR to study the flow of gases through microfluidic devices.

"Remote detection of the NMR signal overcomes the sensitivity limitation of NMR and enables spatially resolved imaging in addition to time-of-flight measurements," said chemist Christian Hilty, a member of Pines' research group and the principal author of the PNAS paper. "Our approach also offers the unique advantage of being non-invasive. We can use it to measure microfluidic flow without the introduction of foreign tracer particles. This is important for the design and the operation of microfluidic devices."

Co-authoring the PNAS paper with Hilty and Pines were Erin McDonnell, Josef Granwehr, Kimberly Pierce and Song-I Han, all of whom at the time of the study held joint appointments with Berkeley Lab and UC Berkeley.

NMR is a phenomenon involving a property found in the atomic nuclei of almost all molecules called "spin," which gives rise to a magnetic moment, meaning the nuclei act as if they were bar magnets with a north and south pole. When a sample is exposed to a strong external magnetic field, these "bar magnets" attempt to align their axes along the lines of magnetic force. The alignment is not exact, resulting in a wobbly rotation about the magnetic field lines that is unique for each type of nuclei.

If, while exposed to the magnetic field, the nuclei in a sample are also subjected to a sequence of radiofrequency (rf) pulses, they will absorb

and re-emit energy at characteristic frequencies. This is called the signal "encoding" phase of NMR. In the detection phase, the frequencies of these encoded signals are measured to obtain a NMR spectrum. This spectrum will feature distinct peaks of varying height that, like a set of fingerprints, can be used to identify the sample's chemical structure.

While NMR has long been a powerful tool for studying the chemical composition of macroscopic samples, its application to microfluidic chip devices has been hampered by low sensitivity. When atomic nuclei align their axes along the lines of a magnetic field, the nuclear spin of some will point "up" while that of others will point "down." Obtaining an NMR signal depends upon an excess of nuclei in a sample with spins pointing in one direction or the other, but the natural population difference in a typical fluid sample, even under a powerful magnetic field, is usually no more than one in 100,000 at room temperature.

To overcome this low spin polarization so they can measure gas flow, Pines and his research group have been injecting their samples with xenon whose atomic nuclei have been hyperpolarized by laser light. Hyperpolarized xenon boosts the NMR sensitivity of a sample by at least four orders of magnitude and xenon being inert, does not interfere with the other sample constituents as it is carried along in the flow.

When working with microfluidic samples of gas, Pines and his collaborators apply their NMR encoding technique to the hyperpolarized xenon. With its long spin-relaxation time (several minutes), hyperpolarized xenon is well suited for transporting the encoded NMR information to a separate site for detection. By staging the encoding and detection phases at separate sites, each site can be customized to obtain optimal results.

Microfluidic devices are essentially miniaturized chemistry laboratories, featuring a series of micrometer-sized channels etched into a chip in which nanoliter-sized samples of fluids can be analyzed. Such analyses can provide a wealth of information for biomedical and analytical chemistry studies. Because of their incredibly small sample sizes, thousands of times smaller in volume than a typical droplet, microfluidic "labs on a chip" are highly prized for providing rapid analysis at relatively low costs.

According to Hilty and Pines, their NMR remote detection technology is ready to be applied to any existing microfluidic device, so long as the fluid is transported to the detection site within the spin relaxation time of encoded NMR information.

Another limiting factor is the relatively high cost of a NMR spectrometer. Pines and his research group are working on the development of alternative, less expensive means of detecting encoded NMR signals, like a magnetometer. According to Hilty, preliminary results on this line of research have been promising.



Hilty is a member of the Alexander Pines research group and principal author of a paper in which it was demonstrated that NMR spectroscopy can be used with microfluidic "lab-on-a-chip" devices.