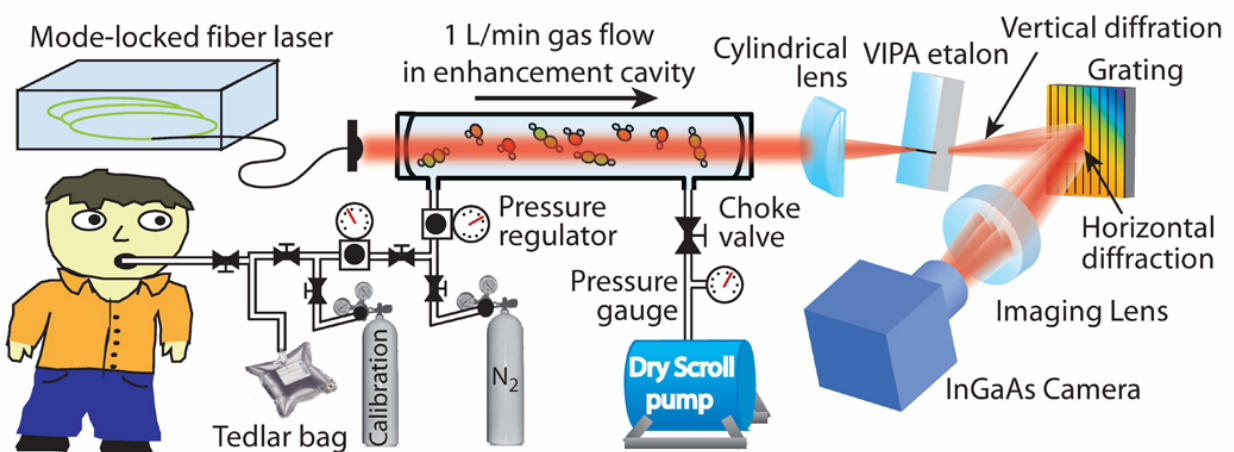# News Coverage

of the

JILA Breathalyzer

February – March 2008

Compiled By:

NIST Public Affairs Office

Laser could provide breath test for cancer, asthma
By Maggie Fox

BOULDER, Colo.—A new laser analyzer might be able to help doctors detect cancer, asthma or other diseases by sampling a patient's breath, researchers reported on Tuesday.

The device uses mirrors to bounce the laser's light back and forth until it has touched every molecule a patient exhales in a single breath, the team reported in the journal Optics Express.

This can help detect minute traces of compounds that can point to various diseases, including cancer, asthma, diabetes and kidney malfunction, they said.

"This technique can give a broad picture of many different molecules in the breath all at once," Jun Ye, who led the research at the University of Colorado, said in a statement.

Ye's team at a joint institute of the National Institute of Standards and Technology and the university developed a new technique, called cavity-enhanced direct optical frequency comb spectroscopy.

When animals and people breathe out, they exhale not only gases that are not needed, such as carbon dioxide, but also compounds that result from the metabolism of cells.

"To date, researchers have identified over 1,000 different compounds contained in human breath," Ye's team wrote in the report, published on the Internet ">here

Some point to abnormal function—such as methylamine, produced in higher amounts by liver and kidney disease, ammonia produced when the kidneys are failing or elevated acetone caused by diabetes.

People with asthma may produce too much nitric oxide, exhaled in the breath, while smokers produce high levels of carbon monoxide.

Last February, a team at the Cleveland Clinic in Ohio reported they could use a mass spectrometer breath test to detect lung cancer in patients. Tumor cells produce compounds called volatile organic compounds at higher levels than healthy cells.

In 2006, researchers found dogs could be trained to smell cancer on the breath of patients with 99 percent accuracy.

Ye's team used their method to analyze the breath of several student volunteers and found they could detect trace signatures of ammonia, carbon monoxide, and methane in breath.

Their volunteers breathed into an optical cavity, which is a space between two mirrors. When a pulsed laser light was shone into this space, it bounced back and forth multiple times, striking all the molecules in the sample, Ye's team said.

Spectrometry analysis showed which frequencies of light were absorbed, in turn an indirect measure of which molecules were in the sample.

Additional pickups of the Reuters story include:

ABC News
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Biology News Net (Canada)
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Zee News (India)

February 25, 2008

Laser Screen Detects Diseases in Breath

A special technique that uses laser light to sample a person's breath can detect molecules that may be markers for a number of diseases, a U.S. study says.

This approach, called cavity-enhanced direct optical frequency comb spectroscopy, may one day help doctors screen patients for diseases such as asthma, cancer, kidney failure and diabetes, according to the team of scientists at JILA, a joint institute of the National Institute of Standards and Technology and the University of Colorado at Boulder.

"This technique can give a broad picture of many different molecules in the breath all at once," lead researcher Jun Ye said in a prepared statement.

Optical frequency comb spectroscopy was developed in the 1990s. This study describes the potential use of the technology in detecting disease.

Each breath exhaled by a person contains more than a thousand different molecules, some of which may be indicators of disease. For example, excess levels of methylamine may indicate liver or kidney disease, ammonia may be a sign of renal failure, elevated acetone levels may indicate diabetes, and nitric oxide levels can be used to diagnose asthma.

In this study, Ye and colleagues used the technique to analyze the breaths of several volunteers. They exhaled into an optical cavity (a space between two mirrors) and a pulsed laser light was then aimed into the optical cavity. The laser light bounced back and forth between the mirrors, covering a distance of several kilometers by the time it exited the optical cavity. During this time, the laser light struck all the molecules within the cavity.

The technology was able to detect a wide range of molecules, the scientists said. The findings, published in the current issue of *Optics Express*, suggest this technique, which still needs to be evaluated in clinical trials, may offer a low-cost, rapid and noninvasive method of health screening, the researchers said.

This article also appeared on the Forbes Magazine Web site.

Scientists Develop Breathalyzer for Disease
Just Breathe Into a Tube to See Whether You Have Cancer, Scientists Say
By LEE DYE

University of Colorado at Boulder physics doctoral student Michael Thorpe holds a detection chamber next to a novel laser apparatus at JILA. Thorpe and JILA's Jun Ye led a new study showing how scientists can use laser light to detect faint breath molecules that may be biomarkers for disease.

(Courtesy JILA, NIST, University of Colorado at Boulder)

It may soon be possible to walk into your doctor's office and breathe into a small device that will tell you if you are in the earliest stage of a wide range of diseases from lung cancer to asthma to kidney failure.

Early detection is the key to survival when it comes to many medical problems, and the first place some diseases show up is in the breath.

Scientists have just revealed that they have produced a machine that can identify single molecules that are associated with specific diseases, and all that's required is a little breath.

"It's very noninvasive," said physicist Jun Ye, leader of the research team that is working on the technology. "There's nothing to be scared of. No blood test, just a breath test."

Ye is a research fellow at JILA, a joint institute of the National Institute of Standards and Technology and the University of Colorado at Boulder. Ye and research assistant Michael Thorpe, doctoral student Matthew Kirchner and former graduate student David Balslev-Clausen described their work in the Feb. 18 online edition of *Optics Express*, published by the Optical Society of America.

It has been well established that people exhale a complex mixture of gases, including oxygen, nitrogen, carbon dioxide, and others, Ye told ABCNEWS.com. In fact, more than 1,000 different compounds are contained in human breath. But along with those common gases and compounds, people also exhale certain molecules that are considered "biomarkers" indicating specific conditions, such as diseases.

"If you go to the medical literature you will see tons of studies that correlate certain diseases with particular molecules found in the breath," he said. "One common example is nitrous oxide, which is associated with asthma."

Recognizing that fact, scientists for some time now have been trying to develop the technology to identify those molecules in the breath, thus detecting a disease that may not show up anyplace else. Several techniques have been advanced, but Ye said they all fall short because of the old needle-in-the-haystack problem.

Normal breath consists of trillions of molecules, only a few of which are actual biomarkers. And finding just one isn't enough. There needs to be a pattern consisting of several different types of biomarkers that are all associated with a particular medical problem.

What's necessary, he said, is to create a device that will find a few molecules in a sea of background noise consisting of trillions of harmless molecules. He calls it "seeing the forest all at once, but also seeing individual trees extremely clearly."

And that, he said, is exactly what his team has accomplished.

The technology builds on the device that won a Nobel Prize in 2005, called optical frequency comb. Ye and his group applied the technology to spectroscopy, which is used to identify distinct molecules by their emission and absorption of light.

The heart of Ye's machine, which is about the size of a microwave oven, is a cavity between two curved mirrors. Laser pulses are shot into the cavity and reflect back and forth between the mirrors tens of thousands of times, bombarding any molecules in their way, before finally escaping. To test the device, the researchers recruited several students and had them breathe into the cavity.

The bouncing laser beam interacted with the billions of exhaled molecules, identifying the entire composition of the breath. The findings were very precise, Ye said. One of the participants was a smoker, and his test revealed five times the normal level of carbon monoxide.

The beauty of the system, Ye said, is the fact that it sees the entire spectrum, not just a few specific molecules. And that's important because a single molecule would mean little.

"If you have asthma, your breath will have nitrous oxide, but nitrous oxide does not necessarily mean you have asthma," he said. "But if you see several different molecules all at once, and they are associated with asthma, then you have found a real fingerprint of a certain disease."

The technology is still in its infancy, and for now it appears to be limited to diseases that somehow involve the lungs. But Ye thinks that could change, and the applications could broaden, as the technology develops further.

The device can also differentiate between different isotopes, like carbon 12 and carbon 13, and oxygen 16 and oxygen 17, and changes in those ratios could also indicate the presence of a disease. The idea, Ye said, is to build a system that will allow the earliest possible detection in the least invasive manner at a price that everyone can afford.

The technology can now identify a single molecule among billions. The next goal will be to find a single molecule among trillions. That would broaden its application even further.

The researchers built their machine at their institute, located on the University of Colorado campus, at an estimated cost of $50,000. That, of course, does not include the millions spent on earlier research, or the cost of their time.

"Once it's mass produced, the cost could be quite low," Ye said. "It could be put into every doctor's clinic so people could walk in and do painless breath tests and then walk away. They would get results in a day or so."

Of course, all of this is based on lab research, and an experiment with a few college students. The technology has not been tested yet in the medical field. But Ye's office phones were ringing constantly during the interview, and some of the calls were from companies interested in moving the technology from the laboratory to the marketplace.

Bad Breath: Laser 'Breathalyzer' May Detect Potential Diseases in an Exhale

The term "bad breath" usually means your mouth smells bad. But excess ammonia compounds in an exhale may also signal liver and kidney disease, elevated acetone levels can indicate diabetes and nitric oxide levels can imply asthma. By blasting a person's breath with a laser light, scientists can now detect molecules that may indicate the presence of such diseases.

Scientists have a developed a way to use laser light to detect faint molecules in breath that may indicate diseases such as asthma.

(Jupiter Images Corporation)

CU-Boulder physics doctoral student Michael Thorpe holds a chamber that detects molecules in breath next to a novel laser apparatus he helped develop.

(JILA, NIST, University of Colorado-Boulder)

When breathing, people inhale a complex mixture of gases, including nitrogen, oxygen, carbon dioxide, water vapor and traces of other gases like carbon monoxide, nitrous oxide and methane, said Jun Ye, an adjoint professor of physics at University of Colorado-Boulder who leads the research. Exhaled breath contains less oxygen, more carbon dioxide and a rich collection of more than a thousand types of other molecules, most of which are present in only trace amounts, he says.

Laser light can detect and distinguish specific molecules because different molecules vibrate and rotate at distinct frequencies that depend on their composition and structure, Ye said. He likens the concept to different radio stations broadcasting on separate radio frequencies.

Current breath analysis for biomarkers is a noninvasive and low-cost procedure, but the approaches are limited because the equipment is either not selective enough to detect a diverse set of rare markers or not sensitive enough to detect particular trace amounts of molecules exhaled in human breath. The new technique, known as optical frequency comb spectroscopy, "has the potential to be low-cost, rapid and reliable, and is sensitive enough to detect a much wider array of biomarkers all at once for a diverse set of diseases," Ye said.

The optical frequency comb is a very precise laser for measuring different colors, or frequencies, of light. Each comb line, or "tooth," is tuned to a distinct frequency of a particular molecule's vibration or rotation, and the entire comb covers a broad spectral range—much like a rainbow of color—that can identify thousands of different molecules.

When many breath molecules are detected simultaneously, highly reliable, disease-specific information can be collected, said Ye. Asthma, for example, can be detected much more reliably when carbonyl sulfide, carbon monoxide and hydrogen peroxide are all detected simultaneously with nitric oxide.

To test the technology, Ye's team from JILA—a joint institute of the National Institute of Standards and Technology and CU-Boulder—had several volunteer students breathe into a space between two curved mirrors and then directed sets of ultrafast laser pulses into the cavity. As the light pulses ricocheted around the cavity tens of thousands of times, the researchers determined which frequencies of light the molecules soaked up. That told them which molecules, and how much, were present in the breath.

They detected trace signatures of gases like ammonia, carbon monoxide and methane from the samples of volunteers. In one measurement, they detected carbon monoxide in a student smoker that was five times higher compared to a nonsmoking student.

The researchers described their work in an article in the Feb. 18 online edition of *Optics Express*.

The project was supported by the National Science Foundation and other government and non-profit agencies.

—By Jim Scott/CU-Boulder and Leslie Fink/NSF

Laser can detect diseases in your breath

Device identifies compounds that may indicate cancer, asthma, study shows

By Steve Mitchell

A new laser technique could enable doctors to detect certain diseases, such as lung cancer or asthma, simply by analyzing a patient's breath.

A new study shows the laser system can identify trace levels of compounds that may be signs of disease in breath samples, and companies and investors have already expressed interest in developing the device for routine use in doctor's offices, said Jun Ye, a physicist at JILA, a joint institute of the National Institute of Standards and Technology and the University of Colorado at Boulder, who led the research.

The advantages of the laser technique — known as optical frequency comb spectroscopy — is that it would provide a painless and non-invasive way of detecting certain diseases. In addition, it could enable physicians to detect some conditions earlier when they may be more easily treated, Ye said.

With each breath, we exhale a variety of chemicals. The predominant compounds are carbon dioxide and oxygen, but a typical exhalation will also contain more than a thousand other chemicals in very tiny amounts, some of which can indicate disease. For example, ammonia could be a sign of kidney failure, while nitric oxide can indicate asthma.

Breath analysis systems have been around for several years, but a common problem with previous methods is they could only detect one or a few types of compounds in the breath. This doesn't provide enough information to determine if a person has a specific disease because they could have elevated levels of a single compound for other reasons, Ye said.

But the new laser technique provides a way to assess the levels of many different compounds in the breath at once, offering a more accurate picture of whether a person has a particular disease. "It's like seeing the entire forest, rather than just individual trees," Ye said.

In the study, which was published in this week's Optics Express, Ye's team had human volunteers breathe into the laser system. The device reliably detected trace levels of methane, carbon monoxide and carbon dioxide in the breath samples. The device was able to detect higher levels of carbon monoxide in the breath of a smoker compared to a non-smoking participant. The device also distinguished ammonia — an indicator of kidney failure — from water, which can be a tricky issue because of the similarity of the compounds.

The next step is larger trials to show the technique can accurately diagnose diseases.

The technique would be most useful for detecting lung problems, such as lung cancer and asthma, because these conditions create changes in the body that show up in the breath, Ye said. It also could be used for digestive problems because these can lead to alterations in the composition of the breath.

Immediate results

To use the device, a person breathes into a tube into which a laser is shining. Mirrors positioned around the tube reflect the laser signal to enhance detection of compounds. The laser signal bounces off the different chemicals in the breath sample, and the device is able to detect the unique light signals of specific compounds.

"It's almost like a radio," Ye said. "Each molecule has a unique set of frequencies, like a certain radio station, so the device can easily identify them."

The results are nearly instantaneous, he said. So there's no need to wait for an analysis to be processed, as there is with a blood test.

Dr. John Hunt, a pediatrician at the University of Virginia in Charlottesville who has been involved in breath analysis research for more than 15 years, said the study results were promising but a lot of kinks need to be worked out before the laser technique could be used in patients. He said it still remains to be shown that the technique provides reproducible results and that the breath chemicals it detects can be used to accurately determine whether a person has a specific disease or not.

"It's an interesting early study with a very long way to go," said Hunt.

More personalized treatment

He noted that the laser system has the potential to improve the treatment of some conditions, such as asthma, which have numerous different causes. Being able to analyze all the different compounds in the breath simultaneously may help pinpoint the specific cause of a person's asthma and enable physicians to develop a personalized treatment instead of treating each patient exactly the same, Hunt said.

So far, Ye said, at least one physician and two companies, including a local Colorado firm and one in Germany have contacted him about their interest in developing his laser technique for use in patients.

The system may have other important applications as well. Ye said the Los Alamos National Laboratory in New Mexico has said they're interested in developing the technique for use in airport security screenings to detect explosives or nuclear material in the ambient air. And the Jet Propulsion Laboratory in Pasadena, Calif., is considering whether it could be used on remote locations, such as the surface of Mars, to detect the composition of the air in these environments.

Steve Mitchell is a science and medicine writer in Washington, D.C. His articles have appeared in a variety of newspapers, magazines and Web sites, including UPI, Reuters Health, The Scientist and WebMD.

Asthma, cancer diagnoses may be just a breath away.

By Bill Scanlon

Detecting asthma or cancer could be only a breath away, with help from powerful laser lights.

Colorado scientists have found that by blasting laser light at a person's breath, they can detect molecules that could be markers of asthma or cancer.

The technique is powerful enough to sort through all the molecules in human breath, and is sensitive enough to distinguish rare molecules that may be biomarkers for disease, said Jun Ye, a fellow at the University of Colorado's Joint Institute for Laboratory Astrophysics.

The process is called optical frequency comb spectroscopy, Ye and his colleagues at CU and the National Institute of Standards and Technology, wrote in the on-line edition of Optics Express.

When people breathe, they inhale a mix of gases — nitrogen, oxygen, carbon dioxide, water vapor and trace amounts of other gases such as carbon monoxide, nitrous oxide and methane, said Ye, who also is a scientist with NIST in Boulder.

The air people exhale contains less oxygen, more carbon dioxide and more than 1,000 types of other molecules, mostly in trace amounts.

Dentists know that bad breath can indicate dental problems.

Similarly, too much methylamine can be a signal of liver and kidney disease, Ye said.

Excess ammonia can indicate renal failure; too much acetone could mean diabetes; more than expected nitric oxide could indicate asthma.

A more reliable diagnosis of asthma could be made if carbon dioxide, carbonyl sulfide and hydrogen peroxide all are detected along with nitric oxide. The comb can detect all those molecules, and their relative quantity.

Ye worked with CU graduate assistant Michael Thorpe, doctoral student Matthew Kirchner and former graduate student David Balslev-Clausen on the project.

The optical frequency comb was developed in the 1990s by CU's John Hall and Theodor W. Hansch of the Max-Planck Institute, who shared the 20005 Nobel Price in physics.

Ye's group was the first to apply the frequency combs to spectroscopy — the analysis of the light emitted or absorbed by matter.

The comb is a precise laser. for measuring different frequencies of light, Ye said. Each tooth on the comb line is tuned to measure a different frequency. Each molecule vibrates and rotates at a distinct frequency, and the comb can distinguish among them all, Ye said.

To test their technique, the scientists asked several CU students to breathe into a space between two curved mirrors. The scientists then blasted ultra-fast laser pulses into the cavity formed by the mirrors.

The light pulses ricocheted around the cavity tens of thousands of times. The scientists detected which light frequencies were absorbed, learning which molecules were present — and at what quantities — by the amount of light they absorbed.

They detected trace signatures of gases like ammonia, carbon monoxide and methane in the volunteers.

One volunteer, who was a smoker, had five times the level of carbon monoxide compared to non-smoking students.

Current breath-analysis techniques don't use equipment sensitive enough to detect many of the rare biomarkers or those in tiny trace amounts, Ye said.

The new technique could be a "low-cost, rapid and reliable" diagnostic tool for a wide variety of diseases, he said.

The U.S. Air Force, Agilent Technologies, NIST, the National Science Foundation and CU were among those that funded the study.

Breath of Life

By LANCE VAILLANCOURT

The space-aged breathalyzer that researchers from <u>CU and the National Institute of Standards and Technology (NIST)</u> have been working on could conceivably measure the precise blood-alcohol level of a drunken reveler from across Farrand Field—but, thankfully, the mind-boggling technology will instead be applied toward analyzing human breath for the detection and diagnosis of certain diseases.

According to a recent release backed by a study published in the Feb. 18 edition of "Optics Express," by blasting a person's breath with laser light, CU and NIST scientists have shown that they can detect molecules that may be biomarkers for diseases such as asthma or cancer.

"When breathing," stated the release, "people inhale and exhale a complex mixture of gases Š and just as bad breath can indicate dental problems, excess methylamine may signal liver and kidney disease, ammonia may be a sign of renal failure, elevated acetone levels can indicate diabetes and nitric oxide levels can be used to diagnose asthma."

<u>Jun Ye, a fellow of JILA and NIST and Adjoint Professor of Physics at CU</u> who led the research for the technology, stated that the capabilities of laser and spectrometer instruments used in the detection of disease indicating molecules in the breath are nearly limitless.

"Imagine every molecule you can think of as a little radio station that is broadcasting its own frequency," said Ye. "Whereas old technology could only pick up one radio station at a time and scan through them to pick up different broadcasts—the new technology allows scientists to tune into all radio stations all at once. Not only that, but we can also tune in very sensitively so that we can pick up one molecule out of a billion others."

That sensitivity and selectivity allows scientists to look at one's breath entirely, according to Ye, and at the same time pick out a minute amount of trace molecules that may be associated with the preliminary stages of a certain disease.

"The main drive is to develop a very low cost and yet extremely robust technique for non-invasive diagnosis of disease," he said.

Researches such as <u>Ye, CU graduate assistant Michael Thorpe, CU doctoral student Matthew Kirchner and former CU graduate student David Balslsev-Clausen</u>—who teamed described their research in the "Optics Express" paper—hope that the technology will soon be introduced to medical market as an affordable alternative to more invasive diagnostic procedures.

Imagine walking into a medical clinic and being told to 'Please breath into this machine for one minute," and then—in the next minute—being told precisely what diseases you might have.

"It could conceivably replace things like blood tests," speculated Jim Scott, CU Spokesman for this stage of team's research. "You wouldn't have to send out your blood to undergo testing for days at a time if you could detect signals molecularly through somebody's breath."

Typically one would have blood drawn or perhaps even undergo minor surgery to detect problems with lung cancer, kidney and liver problems. According to Ye, any of those internal organs will be reflected in breath patterns and breath composition as they begin to malfunction.

Furthermore, "optical frequency comb spectroscopy"—as the technology has been dubbed— allows scientists more diagnostic accuracy by locating several of the disease-indicating molecules in the breath at one time.

Whereas the presence of certain molecules in the breath may indicate the presence of disease, such as elevated levels of nitric oxide being a symptom of asthma, Ye described the ability to identify multiple biomarkers at the same time as the ability to detect the "fingerprint" of certain diseases.

"When you see tens of [disease-indicating] molecules all at once," he said, "not only do you have a single tree-but you have the entire forest in front of you. Then you can make a highly confident diagnosis of certain disease—and that's the goal—being able to see the whole tree and the whole forest at the same time, and making a more informed diagnosis.

Since the optical frequency comb was developed in the 1990s by Ye's JILA, NIST and CU-Boulder colleague John L. "Jan" Hall and Theodor W. Hänsch of Germany's Max-Planck Institute (who shared the 2005 Nobel Prize in physics with Roy J. Glauber for their work), Ye's group has pioneered the application of frequency combs to spectroscopy, or the analysis of light emitted or absorbed by matter.

Ye went on to describe that the technology could also be applied toward procedures relating to homeland security, such as providing the ability to detect hazardous and explosive molecules in airports. When asked about the likelihood of Police also employing the advanced technology for DUI tests, Ye was amused.

"Sure it would work," he said. "It would work very well for that process, but it would probably do a lot more than they need it for."

Laser light may be able to detect diseases on the breath

University of Colorado at Boulder physics doctoral student Michael Thorpe holds a detection chamber next to a novel laser apparatus at JILA. Thorpe and JILA's Jun Ye led a new study showing how scientists can use laser light to detect faint breath molecules that may be biomarkers for disease.

Credit: JILA, NIST, University of Colorado at Boulder

By blasting a person's breath with laser light, scientists from the National Institute of Standards and Technology and the University of Colorado at Boulder have shown that they can detect molecules that may be markers for diseases like asthma or cancer.

While the new technique has yet to be tested in clinical trials, it may someday allow doctors to screen people for certain diseases simply by sampling their breath, according to the research team from JILA, a joint institute of NIST and CU-Boulder. "This technique can give a broad picture of many different molecules in the breath all at once," said Jun Ye, a fellow of JILA and NIST who led the research.

CU-Boulder graduate research assistant Michael Thorpe, Ye, CU-Boulder doctoral student Matthew Kirchner and former CU graduate student David Balslev-Clausen describe the research in a paper that appeared in the Feb. 18 online edition of *Optics Express*, the free, open-access journal published by the Optical Society of America. Known as optical frequency comb spectroscopy, the technique is powerful enough to sort through all the molecules in human breath and sensitive enough to distinguish rare molecules that may be biomarkers for specific diseases, said Ye.

When breathing, people inhale a complex mixture of gases, including nitrogen, oxygen, carbon dioxide, water vapor and traces of other gases like carbon monoxide, nitrous oxide and methane, said Ye, an adjoint professor of physics at CU-Boulder. Exhaled breath contains less oxygen, more carbon dioxide and a rich collection of more than a thousand types of other molecules, most of which are present only in trace amounts.

Just as bad breath can indicate dental problems, excess methylamine may signal liver and kidney disease, ammonia may be a sign of renal failure, elevated acetone levels can indicate diabetes and nitric oxide levels can be used to diagnose asthma, Ye said.

When many breath molecules are detected simultaneously, highly reliable, disease-specific information can be collected, said Ye. Asthma, for example, can be detected much more reliably when carbonyl sulfide, carbon monoxide and hydrogen peroxide are all detected simultaneously with nitric oxide.

While current breath analysis using biomarkers is a noninvasive and low-cost procedure, approaches are limited because the equipment is either not selective enough to detect a diverse set of rare biomarkers or not sensitive enough to detect particular trace amounts of molecules exhaled in human breath, Ye said.

"The new technique has the potential to be low-cost, rapid and reliable, and is sensitive enough to detect a much wider array of biomarkers all at once for a diverse set of diseases," he said. The optical frequency comb is a very precise laser for measuring different colors, or frequencies, of light, said Ye. Each comb line, or "tooth," is tuned to a distinct frequency of a particular molecule's vibration or rotation, and the entire comb covers a broad spectral range—much like a rainbow of colors—that can identify thousands of different molecules.

Laser light can detect and distinguish specific molecules because different molecules vibrate and rotate at certain distinct resonant frequencies that depend on their composition and structure, he said. He likened the concept to different radio stations broadcasting on separate radio frequencies.

The optical frequency comb was developed in the 1990s by Ye's JILA, NIST and CU-Boulder colleague John L. "Jan" Hall and Theodor W. Hänsch of Germany's Max-Planck Institute, who shared the 2005 Nobel Prize in physics with Roy J. Glauber for their work.

Ye's group has pioneered the application of frequency combs to spectroscopy, or the analysis of light emitted or absorbed by matter. The technique allows for many different gases to be detected all at once with high sensitivity through their interaction with light from such "combs," demonstrated by Thorpe, Ye and colleagues in the journal *Science*, in 2006.

To test the technology, Ye's team had several CU-Boulder volunteer students breathe into an optical cavity—a space between two curved mirrors—and then directed sets of ultrafast laser pulses into the cavity. As the light pulses ricocheted around the cavity tens of thousands of times, the researchers determined which frequencies of light were absorbed, indicating which molecules—and their quantities—were present by the amount of light they absorbed.

Ye and his colleagues detected trace signatures of gases like ammonia, carbon monoxide and methane from the samples of volunteers. In one measurement, they detected carbon monoxide in a student smoker that was five times higher compared to a nonsmoking student, Ye said.

Laser Breath Test Could Detect Disease

Ed Sutherland

Boulder, CO—Researchers have found they can use a laser to detect molecules from exhaled breath which could indicate diseases such as asthma or cancer. <u>Government and University of Colorado at Boulder scientists</u> say the technique could assist doctors in disease-prevention.

Known as cavity-enhanced direct optical frequency comb spectroscopy, the technique checks the more than 1,000 molecules exhaled by humans for signs of disease.

While analyzing breath can indicate dental problems or alcohol consumption, scientists found high levels of methylamine, for instance, is a sign of possible liver or kidney disease, for instance.

The scientists used students to test the system, findings of which were published in the Optical Society of America's *Optics Express*.

February 19, 2008

Asthma, Cancer Detected By Breath Analysis
By Matthew Williams

Scientists from the National Institute of Standards and Technology and the University of Colorado at Boulder discovered that if a person's breath is tested with a laser light, it can detect molecules related to diseases like asthma or cancer.

According Jun Ye, the leader of the research team from JILA, a joint institute of NIST and CU-Boulder, the technique will offer a bigger picture for the molecules in just one breath.

When people breathe, a mixture of gases is inhaled like nitrogen, oxygen, carbon dioxide, water vapor and traces of gases like carbon monoxide, nitrous oxide and methane.

Exhaling, we eliminate less oxygen, more carbon dioxide and over thousand of molecules, which are there in trace amounts.

So, excess methylamine may indicate liver problems and kidney disease, while ammonia may show a sign of renal failure. Also Ye says that high levels of acetone can point to diabetes and nitric oxide levels may show signs of asthma.

According to Ye, information about a disease may be gathered if breath molecules are identified simultaneously.

For example asthma may be detected when carbonyl sulfide, carbon monoxide and hydrogen peroxide are traced altogether with nitric oxide.

Ye says that the equipment is not that selective in order to choose a set of rare biomarkers or it cannot trace particular amounts of molecules which are exhaled in the human breath.

Ye said: "The new technique has the potential to be low-cost, rapid and reliable, and is sensitive enough to detect a much wider array of biomarkers all at once for a diverse set of diseases," medicalnewstoday.com reports.

The technique was tested on a group of volunteer students who had to breathe into an optical cavity while sets of ultra fast lasers were transmitted into it. They found that the technique permits for many gases to be analyzed at the same time and to diagnose a disease.

The report can be found in the February edition of *Optic Express*.

February 20, 2008

Laser Light Can Detect Potential Diseases Via Breath Samples

By blasting a person's breath with laser light, scientists from the National Institute of Standards and Technology and the University of Colorado at Boulder have shown that they can detect molecules that may be markers for diseases like asthma or cancer.

While the new technique has yet to be tested in clinical trials, it may someday allow doctors to screen people for certain diseases simply by sampling their breath, according to the research team from JILA, a joint institute of NIST and CU-Boulder.

"This technique can give a broad picture of many different molecules in the breath all at once," said Jun Ye, a fellow of JILA and NIST who led the research.

CU-Boulder graduate research assistant Michael Thorpe, Ye, CU-Boulder doctoral student Matthew Kirchner and former CU graduate student David Balslev-Clausen describe the research in a paper that appeared in the Feb. 18 online edition of *Optics Express*, the free, open-access journal published by the Optical Society of America. Known as optical frequency comb spectroscopy, the technique is powerful enough to sort through all the molecules in human breath and sensitive enough to distinguish rare molecules that may be biomarkers for specific diseases, said Ye.

When breathing, people inhale a complex mixture of gases, including nitrogen, oxygen, carbon dioxide, water vapor and traces of other gases like carbon monoxide, nitrous oxide and methane, said Ye, an adjoint professor of physics at CU-Boulder. Exhaled breath contains less oxygen, more carbon dioxide and a rich collection of more than a thousand types of other molecules, most of which are present only in trace amounts.

Just as bad breath can indicate dental problems, excess methylamine may signal liver and kidney disease, ammonia may be a sign of renal failure, elevated acetone levels can indicate diabetes and nitric oxide levels can be used to diagnose asthma, Ye said.

When many breath molecules are detected simultaneously, highly reliable, disease-specific information can be collected, said Ye. Asthma, for example, can be detected much more reliably when carbonyl sulfide, carbon monoxide and hydrogen peroxide are all detected simultaneously with nitric oxide.

While current breath analysis using biomarkers is a noninvasive and low-cost procedure, approaches are limited because the equipment is either not selective enough to detect a diverse set of rare biomarkers or not sensitive enough to detect particular trace amounts of molecules exhaled in human breath, Ye said.

"The new technique has the potential to be low-cost, rapid and reliable, and is sensitive enough to detect a much wider array of biomarkers all at once for a diverse set of diseases," he said.

The optical frequency comb is a very precise laser for measuring different colors, or frequencies, of light, said Ye. Each comb line, or "tooth," is tuned to a distinct frequency of a particular molecule's vibration or rotation, and the entire comb covers a broad spectral range—much like a rainbow of colors—that can identify thousands of different molecules.

Laser light can detect and distinguish specific molecules because different molecules vibrate and rotate at certain distinct resonant frequencies that depend on their composition and structure, he said. He likened the concept to different radio stations broadcasting on separate radio frequencies.

The optical frequency comb was developed in the 1990s by Ye's JILA, NIST and CU-Boulder colleague John L. "Jan" Hall and Theodor W. Hänsch of Germany's Max-Planck Institute, who shared the 2005 Nobel Prize in physics with Roy J. Glauber for their work.

Ye's group has pioneered the application of frequency combs to spectroscopy, or the analysis of light emitted or absorbed by matter. The technique allows for many different gases to be detected all at once with high sensitivity through their interaction with light from such "combs," demonstrated by Thorpe, Ye and colleagues in the journal *Science*, in 2006.

To test the technology, Ye's team had several CU-Boulder volunteer students breathe into an optical cavity—a space between two curved mirrors—and then directed sets of ultrafast laser pulses into the cavity. As the light pulses ricocheted around the cavity tens of thousands of times, the researchers determined which frequencies of light were absorbed, indicating which molecules—and their quantities—were present by the amount of light they absorbed.

Ye and his colleagues detected trace signatures of gases like ammonia, carbon monoxide and methane from the samples of volunteers. In one measurement, they detected carbon monoxide in a student smoker that was five times higher compared to a nonsmoking student, Ye said.

February 19, 2008

NIST working on "Deathalyzer"

A researcher working for the National Institute of Standards and Technology has demonstrated an optical technique for identifying tiny amounts of a broad range of molecules in the breath, potentially enabling a fast, low-cost screening tool for disease.

In this approach, NIST researchers analyze human breath with "frequency combs," which are generated by a laser specially designed to produce a series of very short, equally spaced pulses of light. Each pulse may be only a few millionth billionths of a second long. The laser generates light as a series of very narrow frequency peaks equally spaced, like the teeth of a comb, across a broad spectrum.

The tool sounds like yet another example of a Star Trek-like device making its reality debut. On Star Trek, Tricorders had multiple functions but the medical version used by Bones McCoy could scan a body and help diagnose and heal injured or sick patients.

To test frequency combs, student volunteers exhaled breath that entered an optical cavity where it was "combed" by the light pulses. By detecting which colors of light were absorbed and in what amounts—essentially looking for light absorbed near the "teeth" of the comb— the researchers could detect specific molecules and their concentrations, NIST said. According to researchers over 1000 different compounds contained in human breath have already been identified.

For example, a student smoker who participated in the experiment had a level of carbon monoxide that was five times greater than a nonsmoker in the experiment, NIST said. The optical comb approach allows the researchers to simultaneously analyze a very broad spectrum, covering many possible molecular compounds, with high precision, frequency resolution and sensitivity.

The technique is in early phases, and would require clinical trials before it could become available at a doctor's office, but it could lead to one of the first widespread applications of frequency combs, NIST said in a release.

"For example, nitric oxide can indicate asthma, but it also appears in breath with many other lung diseases, including chronic obstructive pulmonary disease, cystic fibrosis and bronchiectasis. However, if we simultaneously monitor nitric oxide, carbon monoxide, hydro-peroxide, nitrites, nitrates, pentane, and ethane, all important biomarkers for asthma, we can be much more certain for a definitive diagnosis of this important disease," said Jun Ye, a physicist at JILA, a joint institute of the NIST and the University of Colorado at Boulder.

Existing methods for detecting trace amounts of molecules from the breath are either bulky, slow, limited to specific molecules, unable to distinguish very well between multiple compounds or inaccurate at measuring their concentrations, NIST said.

February 19, 2008

Lasers blast bated breath and find disease
Scientists using laser light to detect potential diseases via breath samples, says new study

By blasting a person's breath with laser light, scientists from the National Institute of Standards and Technology and the University of Colorado at Boulder have shown that they can detect molecules that may be markers for diseases like asthma or cancer.

While the new technique has yet to be tested in clinical trials, it may someday allow doctors to screen people for certain diseases simply by sampling their breath, according to the research team from JILA, a joint institute of NIST and CU-Boulder. "This technique can give a broad picture of many different molecules in the breath all at once," says Jun Ye, a fellow of JILA and NIST who led the research.

CU-Boulder graduate research assistant Michael Thorpe, Ye, CU-Boulder doctoral student Matthew Kirchner and former CU graduate student David Balslev-Clausen describe the research in a paper that appeared in the Feb. 18 online edition of *Optics Express*, the free, open-access journal published by the Optical Society of America. Known as optical frequency comb spectroscopy, the technique is powerful enough to sort through all the molecules in human breath and sensitive enough to distinguish rare molecules that may be biomarkers for specific diseases, says Ye.

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Just as bad breath can indicate dental problems, excess methylamine may signal liver and kidney disease, ammonia may be a sign of renal failure, elevated acetone levels can indicate diabetes and nitric oxide levels can be used to diagnose asthma, Ye says.

When many breath molecules are detected simultaneously, highly reliable, disease-specific information can be collected, says Ye. Asthma, for example, can be detected much more reliably when carbonyl sulfide, carbon monoxide and hydrogen peroxide are all detected simultaneously with nitric oxide.

While current breath analysis using biomarkers is a noninvasive and low-cost procedure, approaches are limited because the equipment is either not selective enough to detect a diverse set of rare biomarkers or not sensitive enough to detect particular trace amounts of molecules exhaled in human breath, Ye says.

"The new technique has the potential to be low-cost, rapid and reliable, and is sensitive enough to detect a much wider array of biomarkers all at once for a diverse set of diseases," he says.

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Ye and his colleagues detected trace signatures of gases like ammonia, carbon monoxide and methane from the samples of volunteers. In one measurement, they detected carbon monoxide in a student smoker that was five times higher compared to a nonsmoking student, Ye says.

Laser Light Might Be Newest Way to Detect Disease

Kathy Walsh, Reporter:

Scientists at the University of Colorado atoulder have discovered a way to spot some diseases by blasting a person's breath with laser light. It has the potential to be cheap, quick and reliable.

The laser tests normal breath for biomarkers for diseases like asthma or cancer.

Mike Thorpe, University of Colorado Graduate Research Assistant:

"You're using kind of the molecules in your breath to determine something about your current state."

Walsh:

In a month long study, volunteers breathed into what is called a "detection chamber." Scientists then used a technique called "optical frequency comb spectroscopy." They blasted the breath with ultra fast invisible laser pulses that can recognize individual molecules. That information was recorded on a camera, allowing researchers to actually see what was in the breath on a computer.

Thorpe:

"Researchers have already identified more than 1,000 of these molecules that exist on your breath, and they pertain to your metabolism, or maybe disease, or just the state of your health in general."

Walsh:

In one of the student volunteers, a smoker, they found carbon monoxide levels five times higher than those in a nonsmoking student. Other studies already show they can detect asthma or ulcers by the presence of certain gases. This one offers a much broader range.

Thorpe:

"In the future hopefully we'll be able to tell things about kidney failure, liver failure, cancer and diabetes."

Walsh:

CU is excited about what their research could mean for health care.

Thorpe:

"I hope it means a cheaper method for health screening," Thorpe said. "That would be the ultimate goal."

Walsh:

The new technique has yet to be tested in clinical trails, but CU is already getting calls from entrepreneurs hoping to get in on this promising laser technology.

Kathy Walsh, CBS 4.

February 20, 2008

Remote Patient Monitoring?—Don't Hold Your Breath

Scientists from the <u>National Institute of Standards and Technology</u> and the University of Colorado at Boulder have shown that by blasting a person's breath with laser light they can detect molecules that may be markers for diseases like asthma or cancer.

While the new technique has yet to be tested in clinical trials, it may someday allow doctors to screen people for certain diseases simply by sampling their breath, according to the research team from <u>JILA, a joint institute of NIST and CU-Boulder</u>. "This technique can give a broad picture of many different molecules in the breath all at once," said <u>Jun Ye, a fellow of JILA and NIST who led the research</u>.

<u>CU-Boulder graduate research assistant Michael Thorpe, Ye, CU-Boulder doctoral student Matthew Kirchner and former CU graduate student David Balslev-Clausen</u> describe the research in a paper that appeared in the Feb. 18 online edition of *Optics Express*, the free, open-access journal published by the Optical Society of America. Known as optical frequency comb spectroscopy, the technique is powerful enough to sort through all the molecules in human breath and sensitive enough to distinguish rare molecules that may be biomarkers for specific diseases, said Ye.

Whether this technology can be miniaturized to the level where it could be incorporated into a mobile phone's handset remains to be seen. If it can then it will no doubt open up a large market for the remote diagnosis of diseases and medical conditions.

Laser light detects disease on the breath

Scientists could soon be diagnosing disease by using laser spectroscopy to analyze the gas molecules in a patient's breath.

An optical spectroscopy technique that uses a laser to detect molecules in the breath could help to diagnose diseases such as asthma or cancer. According to U.S. researchers, they have improved a technique, known as cavity-enhanced direct optical frequency comb (OFC) spectroscopy, to be more sensitive and cover a larger spectral bandwidth.
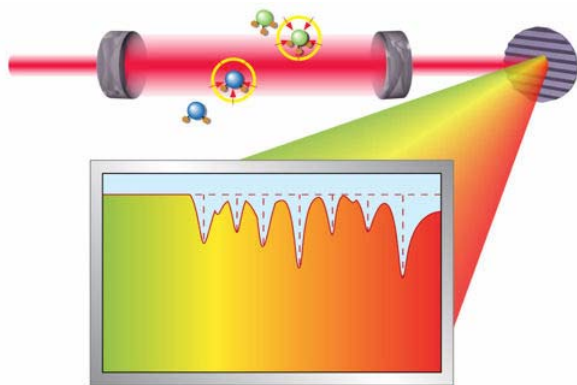
The spectroscopy technique uses many frequencies of laser light to identify trace amounts of atoms and molecules. Each chemical absorbs light at characteristic frequencies, whose pattern forms a signature, or fingerprint, for identifying it.

Image Credit: Jeffrey Fal

"With our current system we can detect many tens of molecules with sensitivities near the 1 part per billion level," Michael Thorpe, a researcher from JILA, a joint venture between the National Institute of Standards and Technology and the University of Colorado, both United States, told optics.org. "In the next 5-10 years I expect detection capability will extend further to the mid-infrared and the spectral bandwidth will increase to detect thousands of molecules simultaneously."

Why frequency combs?

OFC technology uses a mode-locked laser to create broad spectral coverage. "Unlike single frequency laser systems, a frequency comb can detect many different molecules at the same time," commented Thorpe. "What's more, it is superior to mass spectrometer systems because it is better at distinguishing individual molecules, performs more rapid detections and is relatively inexpensive."

Whilst the idea of using frequency combs is not new, it has only recently been extended thanks to the availability of user friendly mode-locked femtosecond (fs) fiber lasers. "These lasers can now be used to produce robust frequency combs capable of continuous operation without user intervention," commented Thorpe.

Thorpe's team uses a mode-locked erbium-doped fiber laser that generates 100 fs pulses and covers a spectrum between 1.5-1.7 μm. By coupling these pulses into an optical enhancement cavity and using a virtually imaged phased array (VIPA) detector, a high spectral resolution of 800 MHz is achieved. "It is this unique combination of optical components that provides broad spectral coverage, high sensitivity and high resolution for analyzing complex gas samples," explained Thorpe.

Light detects breath molecules

The pulses of laser light were fired into an optical cavity, which contained the breath sample. The laser beam bounces back and forth within the cavity allowing the light to sample the entire volume. This increases the light-molecule interaction time, which in turn increases the sensitivity. By comparing the light coming out of the cavity with the light that went in, the JILA team could determine which frequencies of light were absorbed and by how much.

"Light transmitted from the cavity is dispersed into a two-dimensional pattern and imaged onto a camera by the VIPA spectrometer," explained Thorpe. "Computer databases and software compares the recorded spectrum against known molecular spectra to determine the quantities of the individual molecules contained in the gas sample."

Looking to the future

Apart from disease diagnosis via breath analysis, the approach could be useful for applications such as: monitoring of atmospheric greenhouse gases and analyzing ice core samples for climate studies and detecting impurities in gases used to manufacture semiconductors.

The team expects clinical trials to be carried out in the next couple of years and plans to explore new laser systems, new types of optical cavities and new methods of detecting the transmitted light. "To reach its full potential, the device's spectral bandwidth and the number of molecules available for detection need to be increased by an order of magnitude," concluded Thorpe. "I'm fairly confident that the next generation system is just over the horizon."

Marie Freebody is a reporter for Optics & Laser Europe and optics.org.

Breath may help in diagnosing any disease

BOULDER, Colo., USA—Your breath can reveal more than what you ate or drank, it may provide a very inexpensive method of diagnosing any disease you might be suffering from, researchers say.

The breath potentially contains trace of more than 1000 compounds even though you might see only water vapor coming out of your mouth on a cold winter day, they say.

A team of researchers led by Jun Ye has demonstrated that an optical technique for simultaneously identifying tiny amount of a broad range of molecules in breath has the potential of enabling a fast, low cast screen tool for disease.

"It is exciting to imagine the potential of analysing all major biomarkers in one's breath at once," says Ye, a physicist at JILA, a joint institute of National Institute of Standards and Technology (NIST) and the University of Colorado at Boulder.

Giving an example, he says nitric oxide can indicate asthma, but it also appears in breath with many other lung diseases, including chronic obstructive pulmonary disease, cystic fibrosis and bronchiectasis.

"However, if we simultaneously monitor nitric oxide, carbon monoxide, hydro-peroxide, nitrites, nitrates, pentane, and ethane, all important biomarkers for asthma, we can be much more certain for a definitive diagnosis of this important disease," he adds.

Existing methods for detecting trace amounts of molecules from the breath, the researchers say, are either bulky, slow, limited to specific molecules, unable to distinguish very well between multiple compounds or inaccurate at measuring their concentrations.

This article appeared in The Hindu (India), New India Press, Daily News and Analysis (India), Zee News (India), The Times of India, The Economic Times (India), PakTribune (Pakistan), and Press TV (Iran).

Laser Screen Detects Diseases in Breath

A special technique that uses laser light to sample a person's breath can detect molecules that may be markers for a number of diseases, a U.S. study says.

This approach, called cavity-enhanced direct optical frequency comb spectroscopy, may one day help doctors screen patients for diseases such as asthma, cancer, kidney failure and diabetes, according to the team of scientists at JILA, a joint institute of the National Institute of Standards and Technology and the University of Colorado at Boulder.

"This technique can give a broad picture of many different molecules in the breath all at once," lead researcher Jun Ye said in a prepared statement.

Optical frequency comb spectroscopy was developed in the 1990s. This study describes the potential use of the technology in detecting disease.

Each breath exhaled by a person contains more than a thousand different molecules, some of which may be indicators of disease. For example, excess levels of methylamine may indicate liver or kidney disease, ammonia may be a sign of renal failure, elevated acetone levels may indicate diabetes, and nitric oxide levels can be used to diagnose asthma.

In this study, Ye and colleagues used the technique to analyze the breaths of several volunteers. They exhaled into an optical cavity (a space between two mirrors) and a pulsed laser light was then aimed into the optical cavity. The laser light bounced back and forth between the mirrors, covering a distance of several kilometers by the time it exited the optical cavity. During this time, the laser light struck all the molecules within the cavity.

The technology was able to detect a wide range of molecules, the scientists said. The findings, published in the current issue of *Optics Express*, suggest this technique, which still needs to be evaluated in clinical trials, may offer a low-cost, rapid and noninvasive method of health screening, the researchers said.

Laser Detects Diseases in Your Breath!
By Stefan Anitei

You don't even have to say something. Just a laser beam, and the doc tells you what you have and ever have had. A new study, made at the National Institute of Standards and Technology and the University of Colorado at Boulder, and published in the journal Optics Express, shows how molecules from the breath, markers for diseases like asthma or cancer, can be "read" using lasers.

"Known as optical frequency comb spectroscopy, the technique is powerful enough to sort through all the molecules in human breath and sensitive enough to distinguish rare molecules that may be biomarkers for specific diseases. Exhaled breath contains a rich collection of more than a thousand types of other molecules, most of which are present only in trace amounts. Just as bad breath can indicate dental problems, excess methylamine may signal liver and kidney disease, ammonia may be a sign of renal failure, elevated acetone levels can indicate diabetes and nitric oxide levels can be used to diagnose asthma," said lead researcher Jun Ye, of NIST and an adjoint professor of physics at CU-Boulder.

"When many breath molecules are detected simultaneously, highly reliable, disease-specific information can be collected. Asthma, for example, can be detected much more reliably when carbonyl sulfide, carbon monoxide and hydrogen peroxide are all detected simultaneously with nitric oxide. While current breath analysis using biomarkers is a noninvasive and low-cost procedure, approaches are limited because the equipment is either not selective enough to detect a diverse set of rare biomarkers or not sensitive enough to detect particular trace amounts of molecules exhaled in human breath. The new technique has the potential to be low-cost, rapid and reliable, and is sensitive enough to detect a much wider array of biomarkers all at once for a diverse set of diseases. The optical frequency comb is a very precise laser for measuring different colors, or frequencies, of light," said Ye.

The laser can be programmed for differentiating frequencies of a particular molecule's vibration, on a broad spectral range that can detect thousands of molecules.

"Laser light can detect and distinguish specific molecules because different molecules vibrate and rotate at certain distinct resonant frequencies that depend on their composition and structure," said Ye.

The research team tested the technique on subjects located into an optical cavity (a space between two curved mirrors), and sets of ultrafast laser pulses scanned the cavity. The researchers found traces of gases like ammonia, carbon monoxide and methane from the subjects' breath.

"In one measurement, we detected carbon monoxide in a student smoker that was five times higher compared to a nonsmoking student," said Ye.

Science and health briefs

CHEMISTRY In the air

A laser and a sample of a person's breath might be all you need to tell whether a person has asthma or cancer. Scientists at <u>JILA, a joint research institute of the National Institute of Standards and Technology and the University of Colorado</u>, say they can detect molecules in the breath that may be markers for such diseases.

The technique, called cavity-enhanced direct optical frequency comb spectroscopy, may one day allow doctors to screen people for certain diseases simply by sampling their breath.

Every time we exhale, we blow out a mixture with less oxygen, more carbon dioxide and a rich collection of more than a thousand types of other molecules — most of which are present only in trace amounts. Some of these trace breath molecules are biomarkers of disease.

Your Health This Week
This week, Dr. Sydney Spiesel discusses a new tool for diagnosing illness by scent.

Sniffing out illness—literally
By Sydney Spiesel

Problem: The folklore of medicine is full of stories of master practitioners who would walk into a room, sniff, and make a diagnosis. Hippocrates, for example, is said to have diagnosed diabetes from the characteristic sweet odor of ketones on the breath. Most doctors these days would also be able to diagnose out-of-control diabetes, as well as liver or kidney failure, based on breath scent. Dogs can be trained to recognize bladder cancer by sniffing the urine of patients, and there are claims that honeybees can be trained similarly to detect tuberculosis. But subtler olfactory clues would probably escape us and our animal helpers. To take advantage of this neglected method of diagnosis, we need to either train doctors' noses using the same tools that are used to train wine tasters or turn to a mechanical nose.

History: Doctors and biomedical engineers have been working on building such a nose since the 1970s. Considerable progress has been made, but until now the required machinery has been too complex, too huge, too expensive, and too narrowly focused to be clinically practical (though one electronic nose was pretty accurate in its ability to diagnose lung cancer from traces of volatile materials in exhaled air).

New method: Enter a recent report about a new and still experimental machine, developed in the laboratories of NIST, formerly the National Bureau of Standards, which marks a turning point in breath analysis. This machine makes use of new laser technology that, in effect, sweeps a huge range of wavelengths of light from ultraviolet to deep infrared through a cavity containing the patient's exhaled air. Computer analysis of the pattern of light frequencies absorbed by materials in the exhaled air can, in principle, be used to detect diseases like asthma, cancer, and liver and kidney failure. The machine is small—about the size of a microwave—and should be simpler, sturdier, and much cheaper than its predecessors. It should also be much more flexible, with the ability to identify a vastly expanded range of breath ingredients.

Caveat: The caveat—a serious one—is that this machine has not yet been tested on real patients with real diseases, though it has been used to detect the same breath ingredients in well people as would identify illness.

Conclusion: Additional development will surely be required before the new electronic nose will be ready for clinical work, but this machine is the first system that looks as if it can be put to practical use. If it lives up to its promise, it will probably turn out to be an extraordinarily powerful new tool for diagnosing serious illness.

Winds of change
A new kind of breathalyzer

Just over 50 years ago Robert Borkenstein, then a little-known forensic scientist, invented the breathalyzer, allowing instant analysis of alcohol levels in the blood from a sample of breath. It turns out, though, that a person's breath may reveal a great deal more about him than simply whether or not he is fit to drive. It could also help doctors diagnose illnesses.

Every breath that is exhaled contains trace amounts of at least 1,000 compounds. Yet mass spectrometry, electronic noses and the other ways of detecting these compounds tend to be too slow or too imprecise. Mass spectrometry, for example, can have difficulty identifying a single component from within a mixture of many molecules.

Michael Thorpe and his colleagues at the National Institute of Standards and Technology, and the University of Colorado, both in Boulder, have been looking for something better. This month in an online journal called *Optics Express*, they demonstrate a technique that may simultaneously—and quickly—identify tiny amounts of many different substances in the breath.

They use something called an optical "frequency comb", which is a precise tool for measuring different frequencies of light—made possible by advances in ultra-fast lasers. The frequency comb is generated by a laser that produces a series of very short, equally spaced pulses of light (like the teeth of a comb) across a broad spectrum of frequencies.

The team "combed" breath samples from volunteers with the light pulses. Each molecule has its own light-absorption spectrum, so by analyzing which colors of light were absorbed, and in what amounts, the team could work out which chemicals were present and in what concentrations. The breath of one student smoker, for example, contained a level of carbon monoxide five times greater than the breath of the non-smokers.

Some diseases and conditions can cause small changes to the breath. Excess methylamine can, for example, signal liver and kidney disease. Ammonia may be a sign of renal failure and elevated acetone levels can indicate diabetes. Nitric oxide is a sign of asthma and other lung diseases, such as chronic obstructive pulmonary disease, cystic fibrosis and bronchiectasis (the abnormal widening of airways). However, simultaneously monitoring nitric oxide, carbon monoxide, hydro-peroxides, nitrites, nitrates, pentane and ethane in the breath, would allow a much more definitive diagnosis of asthma.

The technique is a long way from the doctor's surgery—it has not yet been through clinical trials. But as a new kind of breathalyzer, more selective and sensitive than any existing device, it promises to become a fast, cheap screening tool. In addition, lots more markers of disease in the breath no doubt remain to be discovered.

What the researchers delicately forget to mention is that the breath is not the only source of biological aromas suitable for chemical analysis. Perhaps not what Borkenstein had in mind when he created the breathalyzer, but another way of sniffing out the truth.

New device aids in disease detection

By Chris Waisnor

A new laser breath analyzer could give doctors the ability to quickly detect and monitor diseases, and one local pathologist said the device might revolutionize diagnostics.

Developed at the University of Colorado at Boulder, the device uses mirrors to bounce lasers off every molecule in a person's exhaled breath.

It can then detect molecular compounds that could indicate the presence of diseases such as asthma and cancer.

The project was developed within JILA, a joint institute of the National Institute of Standards and Technology (NIST) and the University of Colorado at Boulder.

Ben Stein wrote in the NIST press release for the project that previous efforts were too slow, inaccurate and detected a much smaller number of molecules.

Because of these qualities, detecting the presence of a certain compound didn't necessarily prove a patient had a certain disease.

"To be effective, you have to see a lot of [molecules] at once," Stein said.

This is done through the use of frequency combs. Frequency combs are ultra-short pulses of light that all originate from one source.

By analyzing light absorption, frequency combs are able to efficiently detect as many as 1,000 compounds in someone's breath.

"It's always important to look at anything that is less invasive to a patient," said Dr. Gordon C. Handte, a pathologist at Mount Nittany Medical Center and J.C. Blair Memorial Hospital.

Handte emphasized the importance of convenience for medical tests and detection, saying there will probably be more patient-friendly devices in the future. He added that a lot of research is conducted every year to find simpler and easier forms of testing.

"If you think about it, it's common to look at certain genetic markers for diseases, so it's not surprising that you can try something similar by analyzing someone's breath," Handte said. "I don't think the technology is going to have a big impact for a while, but eventually, it will."

Michael Thorpe, one of the main researchers on the project, said only two diseases have been FDA-approved for discovery through the laser. Asthma has been linked to breathing out nitric oxide, and septic ulcers have been linked to exhaling high levels of carbon dioxide, he said.

Calling the technology a "young field," Thorpe added that other relationships between exhaled compounds and diseases are being researched.

Possibilities include the link between ammonia and kidney failure, acetone and diabetes, and ethane and cancer.

In an experiment where student volunteers breathed into the laser, one student smoker was found to have five times as much carbon monoxide in his breath as a nonsmoker.

Dr. Jun Ye, the leader of the research team, told Stein that using the laser to analyze someone's breath is "like seeing the trees and the entire forest at the same time."

JILA team's disease device

A Nobel-Prize-related tool that could potentially detect trace amounts of over 1,000 compounds, some of which provide early warning signs of disease, is described in a recent paper* by a team led by <u>Jun Ye, a physicist at JILA, a joint institute of the National Institute of Standards and Technology (NIST) and the University of Colorado at Boulder</u>.

The device has demonstrated an optical technique for identifying simultaneously minute amounts of a broad range of molecules in the breath, potentially enabling a fast, low-cost screening tool for disease.

"It's exciting to imagine the potential of analyzing all major biomarkers in one's breath at once," Ye said last month. "For example, nitric oxide can indicate asthma, but it also appears in breath with many other lung diseases, including chronic obstructive pulmonary disease, cystic fibrosis and bronchiectasis. However, if we simultaneously monitor nitric oxide, carbon monoxide, hydroperoxide, nitrites, nitrates, pentane, and ethane, all important biomarkers for asthma, we can be much more certain for a definitive diagnosis of this important disease."

Existing techniques for detecting trace amounts of molecules from human breath are, according to officials, either bulky, slow, limited to specific molecules, unable to distinguish very well between multiple compounds or inaccurate at measuring their concentrations.

The new approach used by the JILA researchers analyzes human breath with 'frequency combs,' an optical tool that was cited in the 2005 Nobel Prize in Physics shared by <u>JILA fellow Jan Hall</u>.

Frequency combs are created by a laser designed especially to generate a series of very short, equally spaced pulses of light. Each pulse may last only a few billionths of a second and the laser generates light as a series of very narrow frequency peaks spaced equally, similar to the teeth of a comb, across a broad spectrum.

In experiments, student volunteers exhaled into an optical cavity where it was 'combed' by the light pulses. By detecting which colors of light were absorbed and in what amounts, the JILA researchers could detect specific molecules and their concentrations.

For example, a student smoker who took part had a level of carbon monoxide that was five times greater than a non-smoker in the experiment.

The optical comb approach permits researchers to analyze simultaneously a very broad spectrum that covers many possible molecular compounds with high precision, frequency resolution and sensitivity. Although the JILA technique is still in its early phases and would need clinical trials before it could be used in a doctor's office, the approach could become one of the first widespread applications of frequency combs.

Human breath analysis via cavity enhanced optical frequency comb spectroscopy is described by M. Thorpe, D. Balslev-Clausen, M. Kirchner and J. Ye in the Feb.18 issue of Optics Express.