ANIKA BANK

"As soon as they're alone, they vibrate and radiate"

Ferenc Krausz is the founder of attophysics, a science that seeks to observe and control processes on an ultrashort time scale. His current research has a very specific goal: Krausz is hoping to use attosecond laser pulses to finally win the battle against cancer.

What question did you actually set out to answer?
My goal is to discover how electrons move in microscopic systems. Aside from that, I didn't have any specific objective or even any practical application in mind when I first started out. I've always enjoyed doing basic research. I like the fact that it isn't just a matter of pursuing one particular question that you can check off when you're done. Basic research produces findings that could potentially be of use in science, engineering, technology and – in the long term – in medicine and in various aspects of our daily lives. But of course nobody really knows in advance where exactly those uses will lie! At the moment we're trying to work out why it might be useful to observe how electrons actually move.

You can really observe electrons? Even though they're so tiny and incredibly fast?
Yes. That's the challenge we set ourselves – to trace those kind of ultrafast movements. We want to capture that motion as if we were taking a snapshot. That's far from simple, of course, because electrons are 1,000 times lighter than atoms, which makes them about 1,000 times faster.
It's a bit like how scientists are striving to see ever tinier structures by using increasingly powerful microscopes. The difference is that we're dealing with the fourth dimension of time. We're attempting to exert control over ultrashort time scales, to zoom in on smaller and smaller intervals of time in order to observe very fast processes. That takes us into the realm of the attosecond, which is one quintillionth of a second. An attosecond is a nano part of a nanosecond, in other words zero point zero zero zero zero zero zero zero zero zero zero zero zero zero zero zero zero zero one second!

What do you learn by breaking down time into such tiny fractions?
For a start, that electrons are hugely important. They are key players in electricity, biology, chemistry and physics. For example, if we want to make modern electronics faster, we need to understand the motion of electrons in nanostructured materials. The same applies to our efforts to understand how diseases emerge on the most fundamental level, because chemical and, of course, biochemical reactions are essentially an interchange of electrons. Attophysics has given us an extremely accurate observation tool – and now we are spoilt for choice as to what to use it for first! Recently we've been zooming out a few orders of magnitude from electrons to focus our attention on molecules, looking at blood tests and the early detection of diseases, particularly cancer. Now that we've laid the technical foundations, we're seeing how doors are

opening up to whole new realms and potential applications.

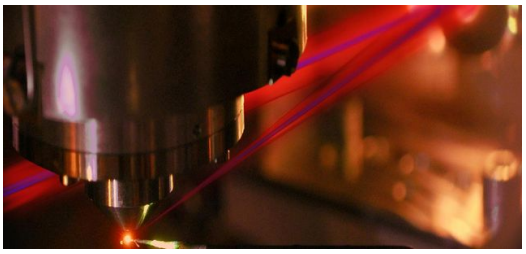
An attosecond is extremely short – just one quintillionth of a second, or 0.0000000000000000001 seconds.
second □ nanosecond □ attosecond (each arrow indicates a shift to a unit a billion times smaller)

How do you intend to detect cancer?
Our method is based on the fact that molecules vibrate in many different ways. Each molecule has a unique vibration frequency, and we have set ourselves the task of finding an accurate and reliable method of measuring the amplitude, frequency and phase of these vibrations. One of the keys to detecting diseases at an early stage is the ability to measure tiny changes between two blood samples taken at different times. In the early stages of a disease, the concentration of different molecules in the blood only changes by a minimal amount.

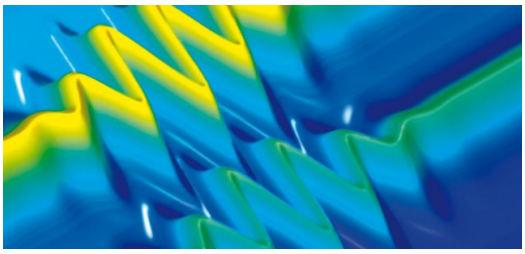
Surely we already have blood tests which can do that…?
Well, we've been using measurements based on conventional IR spectroscopy for around 20 years, but they simply aren't sensitive enough. And detection methods based on selected biomarkers have also turned out to be less specific than we need.

So what are you doing differently?
We're not looking for individual molecular biomarkers. Instead, we're looking at the bigger picture – at all the molecules in the "soup". The advantage of our approach is that we don't need to know in advance which molecule could be crucial to determining how a disease develops. What we're able to do is to pick up the molecular changes between two blood samples, however small those changes may be. We pass those findings onto medical experts who can then decide on the next steps to take.

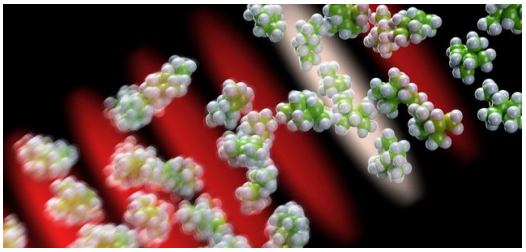
How is that technically possible?
We can use attosecond measurement techniques not only to capture the motion of electrons, but also to probe light waves. That latter ability means we can detect the light waves that molecules emit when they are suddenly made to vibrate by an ultrashort light pulse – and we can do that with greater sensitivity than ever before. That provides us with information on tiny changes in the molecular composition of blood, which can potentially be interpreted as signs of disease.



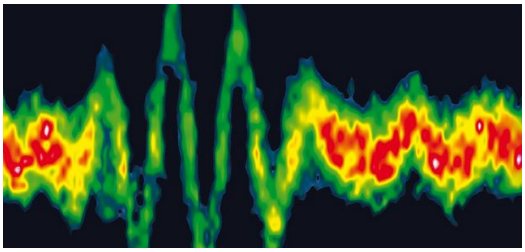
In this illustration, the blue attosecond pulse can be clearly distinguished from the red infrared beam. They strike the sample of gas atoms at slightly different times, enabling the particle detector to capture the electrons. (Image: Thorsten Naeser | Christian Hackenberger)



This approach has yielded the first measurement of electron motion in a solid. Two electrons escaped from the atom, one faster than the other. (Image: Barbara Ferus)



The laser beam strikes the molecules from the top right. The vibrating molecules appear as a blur in the bottom left. (Illustration: Alexander Gelin)



Throwing light on light: a red light wave captured by an attosecond camera. (Image: Eleftherios Goulielmakis)

The laser plays a major role in your experiments…

Absolutely, we couldn't manage without it. If you want to observe a process in the attosecond realm, you need a fast source of radiation to serve as a camera – and that's exactly what the laser provides. With a good-quality laser like the ones we have here at the institute, you can generate pulses – even high-energy pulses – many thousands of times per second. And in the context of blood tests the laser offers another unbeatable advantage...

Really? What kind of advantage?
Conventional blood testing techniques have always come up against an insurmountable barrier in the accuracy of the measurements. Basically, technical noise originating from the light source caps the sensitivity of the analytical method, so it effectively puts a limit on the smallest change you can detect in the concentration of molecules.
That's why we decided to take a different approach. Instead of exciting the molecules continuously, we excite them very briefly with a broadband infrared laser light. That's what we use to make them vibrate – but what comes out of the excitation source after the pulse is absolute darkness. Even left alone, the molecules continue to vibrate and radiate. That allows us to take a time-delayed measurement of the molecular signal after the excitation stage is over, thereby eliminating the interference that would otherwise be caused by technical noise from the light source. Using this method, we have so far been able to detect concentrations of molecules almost one hundred times smaller than those picked up by conventional infrared spectroscopy. And we think this laser method still has even more potential. We reckon that we will be able to zoom in even closer, improving the sensitivity a hundredfold yet again – in other words eventually making it 10,000 times more sensitive than an infrared spectrometer.

Can you explain how that approach might play out in the future?
We're hoping to use our laser-based blood test to detect cancer and other diseases at an early stage and then monitor the development of the disease closely over the course of the therapy. I could imagine everyone having a few milliliters of their blood tested on a routine basis once a year. Within a matter of minutes, our laser method would detect even the tiniest changes in molecular composition from one sample to the next. The molecular "fingerprint" of each blood sample could then be kept for subsequent comparison – you could compare samples taken at different times, and any changes would be immediately noticeable, and could be the first indication of a disease. Eventually this approach would also end up creating a useful database containing the collected attributes of different diseases. Before that vision can become a reality, however, we will need to work on the technology for a while longer and then test and validate it on thousands of human test subjects.

Is the beam source one of the areas you are working on?
Yes, and not just in an abstract sense; we've spent decades building the kinds of devices that never even existed before. For example, we've been working on our OPCPA system for years. That's the optical parametric chirped pulse amplification system that compresses and amplifies ultrashort laser pulses. We've made a lot of progress in that area.

But now we've discovered a new way of amplifying ultrashort laser pulses. Over the past few years, we've been working with a new high-power femtosecond disk laser oscillator in the near-infrared spectral region. This is still based on disk laser technology as the primary source of the short flashes of light. The difference is that it works using direct frequency broadening and pulse compression.

Essentially, we take relatively long pulses from our primary source and broaden their spectrum using nonlinear optical methods. We do that using a multi-pass arrangement in which a number of mirrors focus the beam of light through a thin piece of glass up to 40 times. Each time it passes through the glass, its spectrum becomes a little bit broader, which is the prerequisite for shorter and shorter pulse durations.

This method can yield a significantly higher level of efficiency. The repetition rate is in the megahertz region, with some 10 million pulses per second, so it's very high. Thanks to this ability to broaden its own spectrum, the pulse can harness over 90 percent of the input energy. That makes extremely short pulses in the ten-femtosecond region available with three to four times the average power – and that's a significant step forward.

We use an additional nonlinear process to transform these pulses into longer wavelengths in order to excite the molecular vibrations. Finally, we scan the resulting molecular signal from these vibrations.

We're delighted to have a prototype of the zero generation of this new measuring device. It's still so new that it doesn't even have a name! Nevertheless, oscillators have already become our workhorses in this new approach to diagnosing cancer – but there's no doubt we will be continuing to develop this technology for the foreseeable future.

TRUMPF Scientific Lasers is a joint venture between the laser manufacturer TRUMPF and Professor Ferenc Krausz. It brings together basic research and industrial ultrashort pulse laser expertise. The company develops high-power, high-energy femtosecond and picosecond lasers based on TRUMPF's disk laser technology.

It sounds like you are making constant advances in your work – does that mean your team is evolving, too?

Right now, our project has a very practical bearing on medicine, so we are currently restructuring our team of physicists to create an interdisciplinary team. We've already added two renowned molecular biologists and a biochemist, plus we have a physicist on our team who specializes in big data management. Handling the enormous quantities of data we produce is a huge challenge. We also need a big dose of energy, perseverance and courage to move forward, as well as plenty of support from our busy colleagues in the world of medicine. We're doing all we can to earn their trust by resolutely pursuing our goals and hopefully achieving the progress we want to make.

Born in 1962, Professor Ferenc Krausz is Director of the Max Planck Institute of Quantum Optics in Munich and Chair of Experimental Physics at LMU Munich. He is regarded as one of the world's leading experimenters in "attoscience", a field of physics that studies electron dynamics and light oscillations that occur on the attosecond scale.

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