A heart attack is usually caused by a build-up of fatty deposits in the coronary arteries. In many cases the patient will have noticed early warning signs such as rapid exhaustion and shortness of breath. A cardiologist can now use an ultrasonic sensor to detect fatty deposits in the coronary arteries.

With the heart pumping away as usual during the examination, the artery containing the sensor is constantly being stretched and compressed in concertina fashion. This results in a collection of shuffled images, which makes measuring the thickness of the deposits a tricky and inaccurate business.

At the faculty of Electrical Engineering, Mathematics, and Informatics, Prof. Henk Koppelaar and his post-doc guest Dr. Xiaoqiang Liu have developed a mathematical model that rearranges the recorded images in the correct sequence to reconstruct the picture of the artery.

BY ASTRID VAN DE GRAAF
The ultrasonic sensor is inserted into the coronary artery using a catheter. Once expanded (bottom picture), the stent remains behind in the blood vessel to make sure the artery does not return to its former, constricted condition.

A stent is a metal structure that can be expanded by means of a balloon in order to stretch a constricted artery. The stent is introduced into the coronary artery using a catheter. Once expanded, the stent remains behind in the blood vessel to ensure the artery does not return to its former condition.

When a patient’s coronary arteries are being examined for strictures, a contrast fluid is first injected, and then an X-ray picture is taken of the blood vessels around the heart (angiography). However, the contrast fluid only shows the shape of the flowing blood. Any sudden blockages, such as clots, can be observed very well using IVUS, intravascular ultrasound.

Ultrasonic vision When a patient’s coronary arteries are being examined for strictures, a contrast fluid is first injected, and then an X-ray picture is taken of the blood vessels around the heart (angiography). However, the contrast fluid only shows the shape of the flowing blood. Any sudden blockages, such as clots, can be observed very well using IVUS, intravascular ultrasound.

Ultrasonic waves with a frequency of 20-40 MHz can penetrate sufficiently deeply into the tissue to produce a clear image of both the interior and exterior walls of the blood vessels.

In search of sharp fat contours

To make the apertures available to the blood (lumen) in the coronary arteries, the cardiologist uses a contrast fluid that shows up on X-ray images. The disadvantage of this type of X-ray technique is that, although the lumen becomes visible, it does not show the amount of plaque adhering to the vascular walls, which is a measure of the severity of the arteriosclerosis. The intravascular ultrasound (IVUS) technique was developed to make the plaque visible by making ultrasound images of the coronary arteries from the inside. A miniature sensor is introduced through a catheter into the blood flow of the coronary arteries. Images B–E were generated using the IVUS method. As it turns out, the X-ray images appear to indicate constrictions of the same severity, indicated by the arrows. However, the images B–D and C–E clearly show (as has been measured in D and E) that the plaque at point B is worse than at point C. The red circle indicates the available aperture (lumen). The area between the green and red circle indicates plaque.

“Suppose you’re driving along a road in the centre of town and your job is to photograph every house in the street. The road is very bumpy, so you are constantly being thrown backwards and forwards in your seat, as if you were riding the surf. In the meantime, you’re taking pictures of all the houses. Unfortunately, the houses are not numbered, and you do not have a GPS to tell you exactly where you are. In spite of all this, you have to somehow get the pictures of the houses laid out in the right order to see what the street looks like.”

Using this analogy, Henk Koppelaar, professor of knowledge-based systems at the department of Mediamatics at TU Delft, tries to explain the complex task facing him and his colleague, Dr. Xiaoqiang Liu of the Chinese Dônghua University.

Fatty deposits In this case, the bumpy road is a coronary artery. There are three of these surrounding the human heart. Their task is to supply a constant flow of oxygen to the heart’s muscles. The heartbeat takes on the role of the surf, with the coronary arteries following each and every motion of the heart as it expands and contracts, a cycle that gets repeated 60 times a minute on average. Riding this roller-coaster is our camera – actually an ultrasonic sensor – looking for fatty deposits in the artery. Arteriosclerosis, as it is officially known, is still the number one cause of death in our society.

The growth of plaques starts at the age of sixteen, as Dr. Nico Bruining, a Cardiology department researcher at the Thorax Centre of the Erasmus University in Rotterdam, explains. “The exact cause remains unclear,” Bruining says. “The interior wall of our arteries is lined with a very smooth layer to prevent damage to the thrombocytes as they flow along it, as this would cause them to clot together. Even so fatty deposits, or plaques, manage to stick to the walls. The build-up can be very smooth, but there can also be volcano-shaped mounds, like pimples.”

“Strangely enough, everyone tends to look at the most complex solution first. As is so often the case, the solution lies in restriction.”

These are inflammations of the artery’s inner wall. When the pimple erupts, its scab is released to flow with the blood into the artery, where it can cause a blockage, resulting in a coronary.

In addition, the fatty substance (pus) released in the process is immediately detected by the thrombocytes, which then clot together to form a thick wall that can block the artery (thrombosis). If this occurs at the beginning of the coronary arteries close to the aorta, the result is a massive heart attack. Severe arterial strictures are often presaged by symptoms such as shortness of breath and lack of stamina.”

Sawteeth The ultrasonic sensor is inserted into the coronary artery using a catheter. Entering through the patient’s groin, the physician first inserts a guide tube up to the entry point of the coronary artery. Through the tube, he then pushes a guide wire some 10 to 14 cm into the artery. The ultrasonic sensor...
Before Bruining went to see Koppelaar in Delft, he had been working on the synchronisation of ultrasound images using an electrocardiogram (ECG), a recording of the patient’s heartbeat. The highest peak in the ECG (known as the R top) occurs when the heart’s ventricle has just filled with blood (the end-diastolic situation). The R top represents the electric pulse that makes the left ventricle ejects its blood content. Based on an average heart rate of 60 beats per minute, the top occurs once every second. At the R top moment, the catheter will always be at the same distance from the beginning of the coronary artery, though its location since the last top will have shifted by 0.5 mm as a result of the automatic retraction. Between the R top moments the sensor is being swept all over the place by the pumping action of the heart. By placing just the R top images in sequence (i.e. 1 in every 25 images), a subset of images can be constructed that provides a reasonably accurate image of the plaques inside the blood vessel, sufficient for a contour detector to do some additional calculations on the intermediate positions.

Multitasking The solution sounds simple, but it did require a heavy-duty multitasking system to complete the calculations. Bruining: “You have to be able to find the R top moment in the images. The problem is that a heartbeat is far from regular; each one differs slightly from the next. One may span 1000 milliseconds, the next 975, another 1125, and so on. In addition, you need all sorts of filters to weed out noise, artefacts, and signal delays, and then link the results to the IVUS readings.” The synchronisation method is not very widespread, because it is very complicated and extends the length of the examination, which adversely affects the patient. In addition, large quantities of data from a great many patients were recorded without any synchronisation, but still have to be analysed. Therefore the group went in search of a method that could be used to post-process the data in order to correct any catheter motion artefacts. The Intelligate model software for the multitasking system was developed by a student of Koppelaar, Sebastiaan de Winter, under the supervision of Dr. Ronald Hamers of Curad b.v., a company developing software for the analysis of cardiovascular images. For some years now, Hamers has been spending one day each week on Bruining’s research project. Bruining: “It was primarily a pragmatic solution. We dearly wanted to use the full set of ultrasound images, and so we had to be able to tell where the catheter was all through the heartbeat. To do so, we first of all had to convert the motion process into a mathematical model.”

Coronary artery Hamers had provided Dr. Liu with a motion picture of a beating coronary artery produced by means of bi-plane angiography. This uses X-ray images taken from two different directions to produce a 3-D reconstruction of the blood vessel. When you piece all these images together, what you get is not an uninterrupted view of the vascular interior, but something rather more like a sawtooth pattern. A contour detector, a piece of software that visualises the vascular wall, is useless in these circumstances, since there is no way of telling where the boundaries between the vascular wall and the plaques lie; they could be at the tops of the sawteeth, at their base, or anywhere in the middle.” For the treatment of a patient this makes it very difficult to accurately measure the thickness of the plaques, which is necessary in order to assess the effect of a possible intervention, such as the insertion of a stent, which is a metal brace that forces the blood vessel open, or the prescription of medication to reduce the plaque thickness. But for medical research into new methods of treatment, too, the inaccuracy of the plaque measurement means that the number of subjects tested for each study has to be much higher. “There is quite a difference between having to test 100 patients for a research project rather than 1000,” Bruining says.

To find out where the constrictions due to the plaques are located in the coronary arteries, the data have to be reprocessed, a time-consuming job that, still produced anything but perfect results even though it was carried out by experienced staff.

Subset Before Bruining went to see Koppelaar in Delft, he had been working on the synchronisation of ultrasound images using an electrocardiogram (ECG), a recording of the patient’s heartbeat. The highest peak in the ECG (known as the R top) occurs when the heart’s ventricle has just filled with blood (the end-diastolic situation). The R top represents the electric pulse that makes the left ventricle ejects its blood content. Based on an average heart rate of 60 beats per minute, the top occurs once every second. At the R top moment, the catheter will always be at the same distance from the beginning of the coronary artery, though its location since the last top will have shifted by 0.5 mm as a result of the automatic retraction. Between the R top moments the sensor is being swept all over the place by the pumping action of the heart. By placing just the R top images in sequence (i.e. 1 in every 25 images), a subset of images can be constructed that provides a reasonably accurate image of the plaques inside the blood vessel, sufficient for a contour detector to do some additional calculations on the intermediate positions.

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Expressed as a volume.

To avoid the problem visualised in the previous figure, a method was developed to select only
those images made at a certain point during the heartbeat cycle, i.e. the moment just before
the heart ejects the blood from its ventricles, known as the end-diastolic phase. Once the end-
diastolic images have been identified and selected, a new reconstruction can be made, the result
of which is shown in the lower panel. The algorithm was developed at the Erasmus Medical Centre
in collaboration with the group of Prof. Koppelaar and has been named Intelligenta. The vascular
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readings.

Hamers: “A 15 frames per second movie gives us some idea of how the shape of
the blood vessel changes in time. We gave this to Liu and asked her whether she
would be able to quantify it.”
Liu started by delving into a stack of medical textbooks and attending a number
of heart inspections in hospital to understand what actually goes on. Her result
was a 3-D simulation of the way the coronary artery moved. It looked like a fat
string of spaghetti spiralling back and forth in space every second, which is a
fine mathematical description of what takes place, but did not help much to get
the pictures in the right position.
Koppelaar: “Strangely enough, everyone tended to look at the most complex
solution first, i.e. a three-dimensional heart. So did we, since it is the most
tangible image and appears to provide the best insight. Many groups all around
the world are currently working on complete mechanistic models of the heart,
but as is so often the case, the solution lies in simplicity.”

**Inner tube**  Liu and Koppelaar still had to make the conversion from an
artery encircling a pumping heart to a mathematical model that arranges the
images in the correct order.

Koppelaar: “In fact, it takes a non-medical person to come up with a solution.
A coronary artery is nothing more than a bicycle inner tube that expands
and contracts, lengthens and shortens. This was to be our second attempt to
produce a virtual two-dimensional simulation model that would describe the
way the coronary artery works. All we had to do was apply a suitable relative
coordinates system that would enable us to string the ultrasound image
together.”
For this purpose, Koppelaar wrote a computer program that reconstructs the
expanding and contracting motion of the coronary artery. To visualise the
process, he used marker lines that move to and fro from the centre, where the
elastic deformation caused by the heart is at its greatest, like a longitudinal
sound wave.

“The difference between the expanded and contracted states can be up to 5 mm,
so if we did not apply the correction to the image position, we could be out by as
much as ten times,” Koppelaar says.

**Reference point**  “And then came the day when we noticed how the
doctors applied a small rubber ring to guide the sensor. That was the turning
point for us. The ring provides the reference point for all our ultrasound images,
reducing the problem to a one-dimensional relative translation,” Liu recalls
with relief.

The trick required to arrange the ultrasound images in the correct order had
now become relatively simple: just add the periodical longitudinal motion of
the blood vessel, which consists of sinus functions, to those of the uniformly
receding sensor. Using this reconstruction, an automatic contour detector can
easily map the thickness and position of the plaques.
Koppelaar: “Our third model worked perfectly. Of course, it is not as if our
model will suddenly stop people dying, but it will affect the quality of life as a
whole. Since the Thorax Centre looks at ivus image information from all over
the world, its impact on research into new therapies and treatment is huge.
In the Netherlands alone, every year, thousands of people are examined using
ivus. According to Bruining, the Netherlands are ahead of the pack in this
respect.

“This is because we do many of the ivus measurements ourselves. These
measurements are very expensive and are not covered by insurance. A sensor can
cost up to 1200 euro and for reasons of safety it is discarded straight after use.
Hence about 80% of the inspections are funded through manufacturer’s studies
into newly-developed intervention techniques or medication. The remainder is
paid by the hospital itself.”

**Real time**  The first step has been done. What remains is for the model to
be validated through long-term monitoring studies using information from the
database.
Hamers: “Liu’s current model is still too narrowly defined. It fits our patient
data set too well. We now want to take a small step back in order to extract a
basic validity from it that will enable us to gain even more insight into the
artery motions. Given a robust model we will later be able to analyse the
remaining data as well, and arrange the images in the correct order.”
In addition to this method for distilling the information from the images offline and in retrospect, Bruining already dreams of the next model that will no longer require the multitasking processor, but instead can be implemented on a single microchip. The new measuring equipment will present the images in real time, with instantaneous and fully automatic contour detection. “It will enable us to examine patients and apply treatment at the same time. You will actually be able to oversee the positioning of a stent. Modern stents are more than just a piece of wire gauze. They include a coating of medication that prevents the forming of connective tissue. Since stents are not made to measure, you sometimes need two in a row. It is pretty difficult to position them exactly next to each other. They will often overlap a little, or leave a small gap. The overlap will cause overdosing of the underlying tissue, causing it to mortify (necrosis), while a gap may become the start of a new blockage.”

**Computer tomography** However, instant treatment methods are still a long way in the future. Bruining is continuing his collaboration with TU Delft through the group of Professor Dr. Ir. Michiel Verhaegen of the Delft Centre for Systems & Control at the Faculty of Mechanical Engineering & Marine Technology. The group will also look at non-invasive methods for inspecting blood vessels by means of computer tomography, which uses a rotating X-ray source to produce sectional views (called CT scans) of the body. One of Verhaegen's doctorate students will be investigating the possibility of validating the images using images obtained through angiography. For more information please contact Prof. Dr. Henk Koppelaar, phone +31 (0) 15 278 7373, e-mail h.koppelaar@ewi.tudelft.nl, or Dr. Nico Bruining, phone +31 (0) 10 463 3934, e-mail nbruining@erasmusmc.nl, or Dr. X. Liu, e-mail liuxq@dhu.edu.cn.