



NWO

Eminent Talent

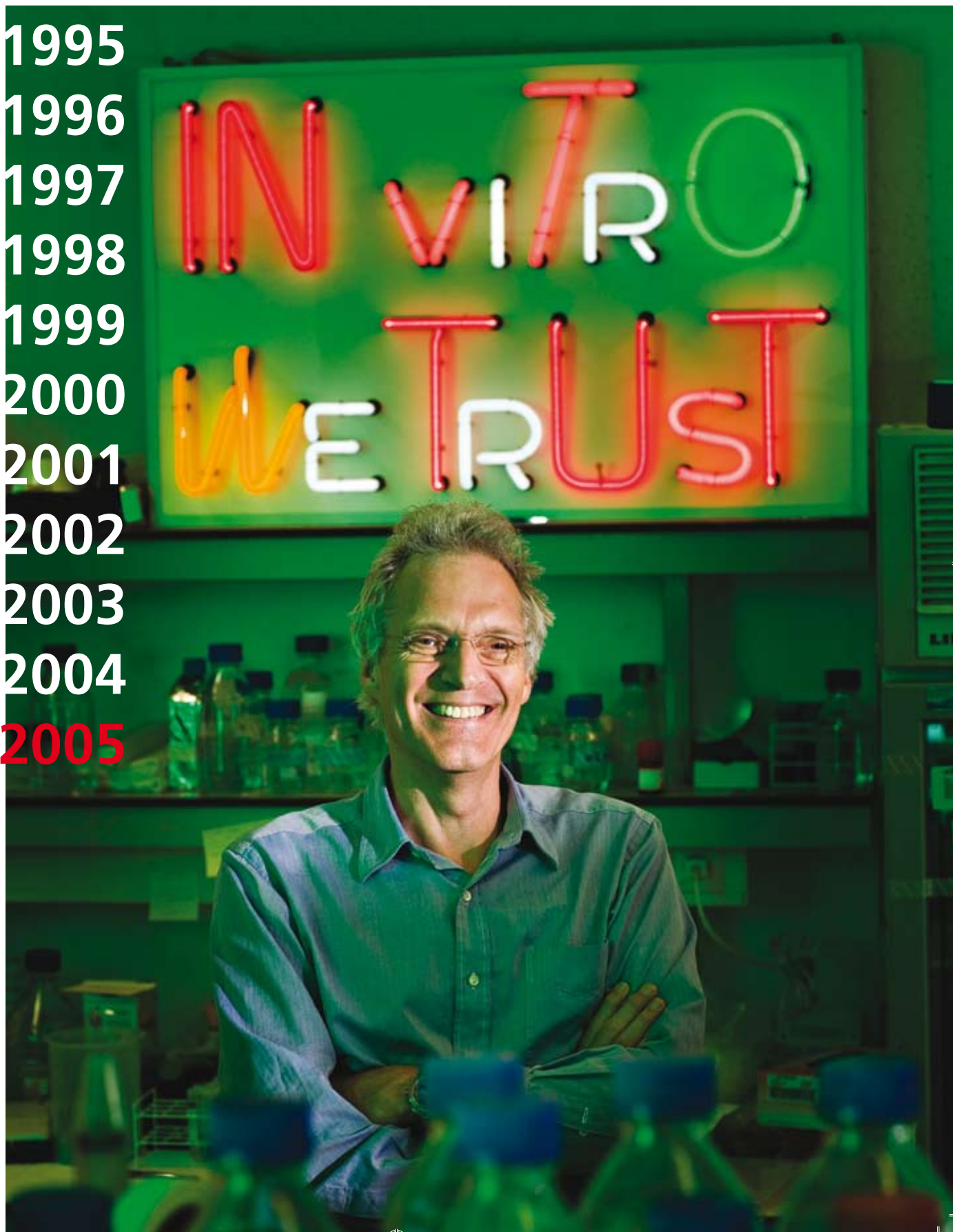
2005: The eleventh year

Netherlands Organisation for Scientific Research



Prof. R. (René) Bernards (1953), head Molecular Carcinogenesis at the Netherlands Cancer Institute (NKI) Amsterdam, part-time professor at Utrecht University. Uses molecular techniques to study genetic processes in cancer cells in order to expose stereotypical genetic patterns. Cancer will then be reduced from a fatal disease to a chronic condition, which will not obstruct a reasonable quality of life.

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Reducing cancer to a chronic condition

“Look”, points René Bernards cheerfully, “this is where it all happens”. On a somewhat neglected corridor at the Netherlands Cancer Institute (NKI) in Amsterdam, Bernards and his team are tracking down the genetic secrets of cancer. Some of the bare doors provide access to rooms where advanced robots screen genetic material day and night to find genes which promote the spread of cancer.

Bernards’ room is small and sober. The linoleum where he sits, behind an enormous monitor, was so badly worn due to his chair rolling backwards and forwards that a new piece has recently been laid there. “My wife is a psychologist and she has diagnosed characteristics of ADHD in me. I cannot concentrate on a single problem for too long. This restlessness is partly due to the continuous influx of new e-mails; some of these are extremely original and valuable, whereas others consist of ten lines of poorly thought-out ideas full of typing errors”, says Bernards explaining the worn out linoleum.

The renowned cancer researcher is immune to luxury. “Sobriety does not distract; it fits in with the Dutch tradition of frugality and spending your money wisely.” Therefore a visitor to NKI or Bernards’ own company Agendia, a building further up, will not be greeted with marble facades, smoked-glass desks and thick-piled carpet. Bernards would rather spend his budget on experiments, equipment and personnel. **“I am constantly aware of our supporters who drop their hard-earned euros in the collecting box of the Dutch Cancer Society. They want the problem of cancer to be solved.”**

And solving that problem is what drives Bernards to work 80 hours a week. “We want to do for cancer what has been done for AIDS – reduce it from a fatal, lethal condition to a chronic illness which does not obstruct a reasonable quality of life.” Bernards believes this will be achieved within 25 years. “We are now switching from the use of classical cytostatics to highly-targeted drugs. In other words, we are shifting from rough remedies with many side effects to therapeutics which exert an effect on a single protein, responsible for the hyperactive cell divisions of a certain type of cancer in a specific group of patients.”

Bernards believes that this will also lead to considerable improvements in diagnostics. “Better tests will be able to more accurately predict whether, for example, someone will still develop metastases after the successful removal of the tumour. That will lead to a more targeted approach and a much more effective use of different drugs. At the same time the life expectancy of cancer patients will increase.”

René Bernards works on the boundary between diagnostics and therapeutics. And with success. First of all it must be clear which genes are responsible for the ‘derailments’ in the cell. In 2004, Bernards’ research group made the so-called RNA interference technique – which had already mapped much larger groups of genes in worms and fruit flies – suitable for research in humans as well. Five different oncogenes were immediately detected. The next step is the development of molecular medicines which target the protein concerned. “Just like the phenomenal new drug Gleevec that reduces the number of abnormal blood cells in patients with chronic myeloid leukaemia (CML) and sometimes even completely normalises the blood picture. We will certainly make more of this type of drug. With such ‘personalised medicines’ we will give those antisocial cancer cells a jolly good kick up the backside”, says Bernards enthusiastically.





The RNAi technique is sometimes explained as a volume knob that 'turns down' the activity of genes so that their role in cell processes can be more easily seen. At NKI robots can now simultaneously examine some 8000 different genes. The so-called microarray technique also delivers a wealth of information. A microarray is a DNA chip to which pieces of DNA from 25,000 human genes have been applied. "Using this we can measure which genes in the cancer tissue are active and expose stereotypical gene patterns", says Bernards.

In 2002, this led to a pattern of 70 genes involved in breast cancer metastases among women who initially had a successful removal of the tumour. "That was a breakthrough, because it is now possible to treat such women in a more targeted manner."

However the pharmaceutical world did not see any point in investing money in research to develop this advanced lab test into a robust routine test. "That would take 10 years", they said. This rejection evoked a latent 'Really? We'll see if that's the case' reaction in Bernards, a 'can do' mentality which Bernards saw in many Americans during his seven-year stay in the United States.

To cut a long story short, Bernards and several associates founded the company Agendia and within two years the 'Mammaprint' breast cancer test was available. Bernards: **"Thanks to our pirate mentality we can now see from the fingerprints of the breast cancer concerned, whether or not metastases will develop.** And we will continue to look for other specific mechanisms until the entire complex has been exposed."

Bernards' company – which already employs 25 people – is now developing similar tests for certain forms of lung cancer and colon cancer. It will not be long before the same pharmaceutical giants who initially misjudged Bernards' discovery, buy up his business. This does not bother the researcher. He, and shareholder NKI, will be all the richer from the sale.

Yet that will not lead to a plush office. "I will carry on with the chase." No, René Bernards is quite happy doing groundbreaking research in his unassuming office at NKI.





Prof. P. (Peter) Hagoort (1954), professor Cognitive Neuroscience at the FC Donders Centre for Cognitive Neuroimaging, Radboud University Nijmegen. Expert in language and speech processing by the brain and neuroimaging. Thinks that communication between areas in the brain is more important than the precise location of the brain activity.

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Brain images of language

“Although the brain is gradually revealing more of its secrets, I do not regard this as a desecration of the human mind. On the contrary, my fascination and admiration for the human mind has only increased as a result of this. After all if a doctor investigates the ribs of a beautiful woman, the investigation does not detract from her beauty.” Peter Hagoort is a cognitive neuroscientist who investigates the functioning of the brain. His speciality is language, but as director of the F.C. Donders Centre of the Radboud University Nijmegen, Hagoort also manages 120 researchers, technicians, and students who are investigating many other aspects of the brain.

“Language has always fascinated me”, says Hagoort, who after studying both biology and psychology focused on psychology. “I helped to produce the school newspaper and was on the editorial committee of various newsletters. And with other students I discussed literature and poetry. During a practical placement in Suriname I was a temporary correspondent for the Dutch newspaper Trouw. Then I learnt to write under pressure.”

Hagoort could just as easily have become a journalist or equally a medic, historian or economist. “How your life unfolds is to a large degree determined by chance events. Yet I believe that what I am doing now, suits me best.” As a student researcher, Hagoort came into contact with aphasia patients. Their language disorders fascinated him and became the basis for a Ph.D. thesis about the temporal aspects of understanding and processing language and speech.

Yet Hagoort only really became hooked, once it was possible to image what happened in the brain during the understanding of language. Initially researchers did that by registering electrical signals on the outside of the head (the EEG). Later MRI and other imaging techniques were used. These techniques reveal, in increasingly greater detail, what happens in the brain when it is performing a certain task.

“It became apparent that not one area in the brain is involved in the completion of a task, but a network of multiple areas. The communication patterns between the areas are probably at least as important as the activity in the areas concerned.” Now one of the important questions is whether certain parts of the brain are solely capable of carrying out a unique task, such as understanding the spoken word, or whether they know a trick – such as the recognition of patterns – which they can apply to various tasks: understanding, seeing, reasoning.

And language researchers want to know how the brain retrieves a single word from a database of 40,000 to 60,000 words in our memory, combines that with the words heard earlier in a sentence, subsequently brings these together to a larger entity and finally provides an interpretation. Hagoort: “The brain combines incoming signals with other signals and information previously stored. That happens in a moment.” As an illustration Hagoort touches his computer. In a common accent from The Hague it says: ‘In my free time I like to listen to piano music from Chopin.’ When you hear this, the pattern of activity that arises in the brain is different from when a voice with a Wassenaar (posh) accent says the same sentence, explains Hagoort. **“Clearly the brain doubts whether common**

Harry from The Hague listens to Chopin.”



What happens in the brain is determined by genetic and biological factors and by the information and experiences which our mind has received and stored. "As the brain needs a far longer period of time to reach maturity than other organs, it is more strongly influenced by the environment. That is why there are large differences between people in terms of skills and qualities. This can also imply that the one quality is often at the expense of the other."

For example, you have people who like to take risks, who more frequently exhibit risky behaviour and sometimes end up in the criminal world. There are also people who take as few risks as possible, and the chances of them becoming a criminal are almost nil. However as a society we cannot permit ourselves to exclude the risk seekers; these are often the creative types. **And as it becomes possible to visualise more and more of the brain, the discussion about what is and is not normal is hotting up."**

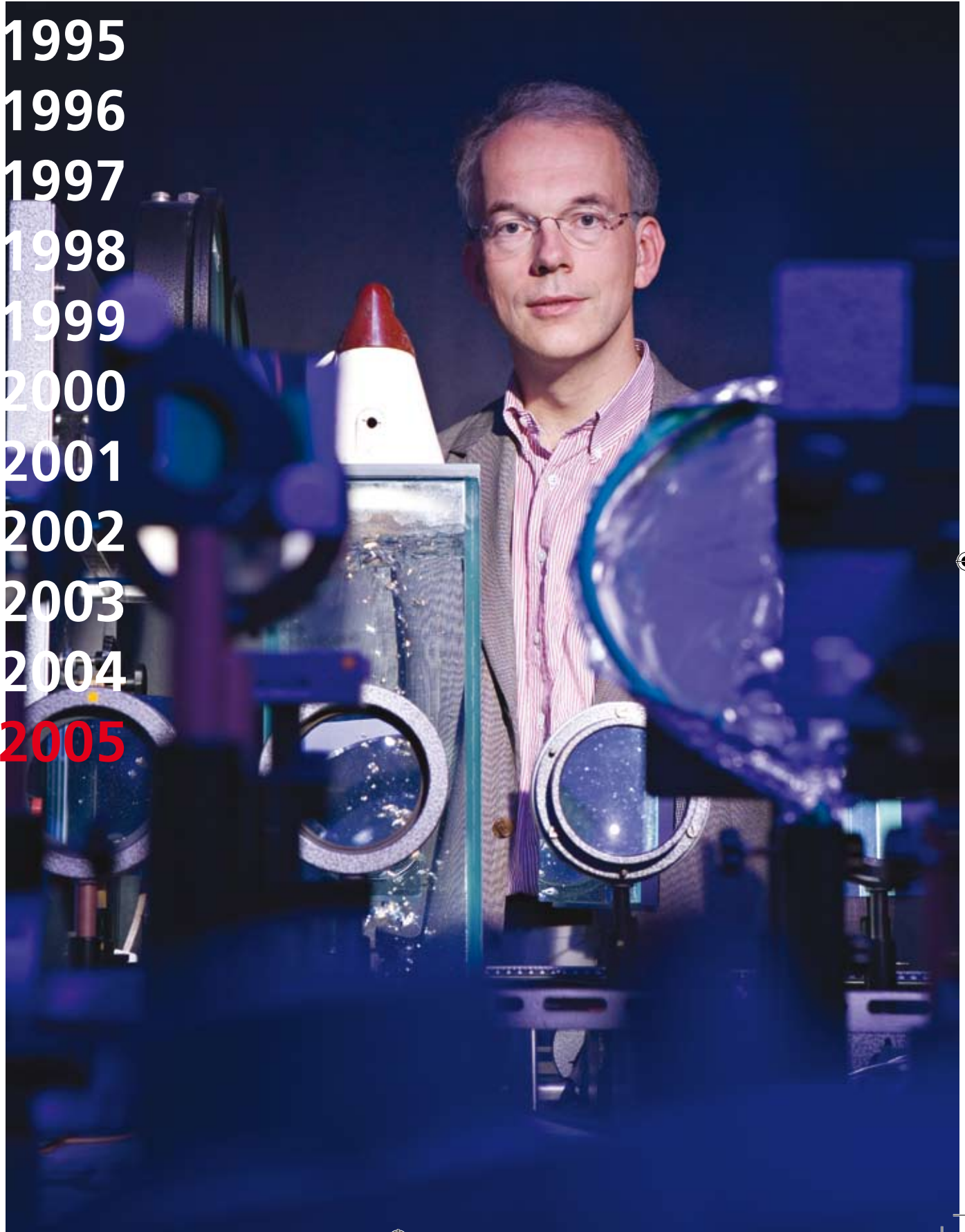
These are just some of the intriguing questions arising from our increased knowledge about how the brain develops and functions. **"Lectures on the brain and language are real crowd pullers"**, states Hagoort from experience. "I find it important to organise events that attract the general public. In the 'Science and Technology Week' we performed experiments with the audience in a theater, watching the scanning of subjects 5 miles away in an MRI-scanner. People find that fascinating because it illustrates how you undertake a scientific voyage of discovery and reveals something of the uncertainties and pieces of the puzzle involved. We need to show people that science is more than just solving certain problems; it is a voyage of discovery."





Prof. D. (Detlef) Lohse (1963), professor for Physics of Fluids, University of Twente, and specialist in the study of flow patterns, turbulence and granular media. Thinks that no real innovations are possible without fundamental research.

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Inspired by bubbles

Detlef Lohse is a passionate investigator. His subject is physics of fluids. The birth of what became Lohse's most famous publication is symbolic for the scientist's determination. "In 1990 a researcher in Mississippi discovered that ultrasonic sound could cause a small air bubble in water to emit light", says Lohse in his study at the green campus of the University of Twente. This phenomenon – termed sonoluminescence – was a complete mystery. The researcher provided accurate data about the light spectrum, the dynamics of the gas bubble and the sound frequencies. "By chance I heard a lecture about this in the summer of 1994 and it intrigued me. I was convinced that this cannot be a mystery, so physics had to provide an explanation for this phenomenon."

A two-year hunt into the fascinating behaviour of the bubbles followed. "Yes, absolutely impassioned", says Lohse. On an evening in 1996, whilst cleaning my teeth, everything fell into place. "Up until then, all of the researchers had completely overlooked the chemistry in the bubble. Argon accumulating in the bubble is essential for the phenomenon. The ultrasonic sound causes an implosion of the gas bubble. This leads to such high temperatures that all of the molecular gases become unstable and their reaction products disappear into the water. All what remains is the mono-atomic gas argon. At collapse, it is partially ionised due to the high temperature. During the subsequent recombination of electrons and ions, photons are emitted which we observe as blue light."

What started as a piece of curiosity-driven fundamental research, has now led to important applications. "The knowledge from our fundamental research is being applied to develop better and faster ink jet printers. Medical concerns are using our insight to improve the contrast in ultrasound diagnostics with the help of air bubbles. This will make it easier, for example, to observe abnormal structures in heart vessels."

And to round things off we now know how pistol shrimps can disrupt the communication between submarines. Lohse: "This shrimp produces an exploding noise which biologists had assumed was caused by vibrations from the animal's pincers. However, we soon concluded that it was the result of an imploding gas bubble. The explosion is remarkably violent, given the small scale of the animal. The sound wave is powerful enough to kill small fishes in the intermediate vicinity, which the shrimp then eats. It is claimed that the Japanese hid their submarines in such shrimp colonies during the attack on Pearl Harbour in 1941, so that they were not picked up by sonar."

Despite the successful applications of his fundamental work, Lohse expresses concern that the government is more and more frequently requiring science to cooperate with industry. "This is spreading like a virus, also at an international level. People think that such an approach facilitates innovative technology. Yet nothing could be further from the truth. At most this cooperation helps to bring about some improvements in a product. **Real innovation only happens when you give good scientists the freedom to go their own way.** True innovations can only be born in an environment of genuine academic freedom, where the possible applications of research outcomes are not immediately obvious."





Lohse is investing the Spinoza prize in equipment and personnel to find out more about bubbles in fluids at a micro-level and even a nano-level. Moreover, together with his team, Lohse would like to clarify how large the hydrodynamic resistance of liquid between two co-rotating cylinders is. "This resistance is determined by the degree of turbulence and the bubble concentration." And Lohse already knows a direct application for this research. "Using air bubbles to reduce the resistance will enable boats to move through the water with less friction. That could save a lot of energy and fuel oil."

During his childhood in Germany, Lohse always wanted to improve his understanding of how processes in nature proceeded. "Even though I never consciously thought about it, it was always clear that I would become a researcher.

When I was five years old, one of my uncles even predicted that I would become a professor. During my school years I carried out chemistry experiments in the cellar (however I did not create any spectacular explosions nor any bubbles), and I analysed the lead concentration in the village pond and sought explanations for various observations and findings."

Now Lohse has two children aged five and seven. They really enjoy looking at dad's experiments with steel balls dropped on sand, causing a fountain. Or they all look with astonishment in the sandpit at the bubbles that appear if water is thrown into a bucket with dry sand. "Then all three of us stare in awe at that bubbling bucket. We learn to observe carefully."





Prof. A. (Lex) Schrijver (1948), Center for Mathematics and Computer Science (CWI) in Amsterdam and part-time professor of Discrete Mathematics and Optimisation at the University of Amsterdam.
Investigates solutions for problems with complex combinations of possibilities. Believes that many problems can be reduced to a mathematical question.



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Mathematics as a challenge

“Most people find mathematics difficult, and I am no exception”, says Lex Schrijver. An astonishing comment from somebody who has spent his entire life doing mathematics. “But that is what I like about it”, says the 57-year-old professor of discrete mathematics and optimisation a second later. “I want to push back the boundaries. After all an athlete who breaks the world record for the 100 metres, does not say: that was a piece of cake. If that were the case, he could have run even faster still.”

For Schrijver mathematics is a universal language with which complex and colourful problems can be reduced to their simplest level. “Mathematics teaches you to deal with abstractions, with the general applicability of solutions. Once you have got rid of all the frills, the essence of a problem is often mathematical. This abstract approach has, however, increasingly disappeared from mathematical teaching due to the emphasis on descriptive exercises. Because the current view is that everybody at school must be able to learn mathematics, the level has dropped. As a result of this, mathematics is increasingly less viewed as something interesting and something that you could study.”

Low student numbers are one of the problems with which Schrijver, part-time professor at the University of Amsterdam and researcher at the Center for Mathematics and Computer Science (CWI), is confronted. Last year there were only twenty first-year undergraduates. “I would like to bring mathematics and its applications closer together and make mathematics more popular, in particular for high school pupils. **Mathematics is a cheap scientific discipline; one-and-a-half million euros Spinoza prize money is a fortune.** Therefore I will use part of this to invite pupils to the university to get a taste of mathematics research.”

And Schrijver wants to write a book aimed at able high-school pupils, which contains a number of interesting and challenging problems. Another popular book about mathematics? “There are already plenty of superb books about mathematics, but my subject, combinatorial optimisation, is ideally suited for showing high school pupils that mathematics is anything but a dead subject. It can be used to solve appealing problems. I am not claiming that I can solve the problem of the small number of students, but I can contribute to reversing the situation.”

Combinatorial optimisation can be used in everyday situations, states Schrijver. You can tackle problems that need optimal combinations. How do you go about drawing up a good train timetable, how to combine the best train units or how can you find the shortest route between a number of towns (the ‘travelling salesman problem’)?

With the help of analytical geometry such a problem is captured in a collection of vectors. “The art is then to find so-called fast algorithms which calculate the optimal solution from an almost endless number of combinations. By the way, such an algorithm for the problem of the travelling salesman has still not been found.”

As a 12-year-old pupil, Schrijver made timetables for the Amsterdam trams. With his four brothers he cycled according to the timetable, including interconnections and transfer times. “We also wanted to give our friends lifts, but nothing ever came of that. I occasionally solve a puzzle, such as a sudoku, but I am far happier solving practical problems, such as a school timetable.”





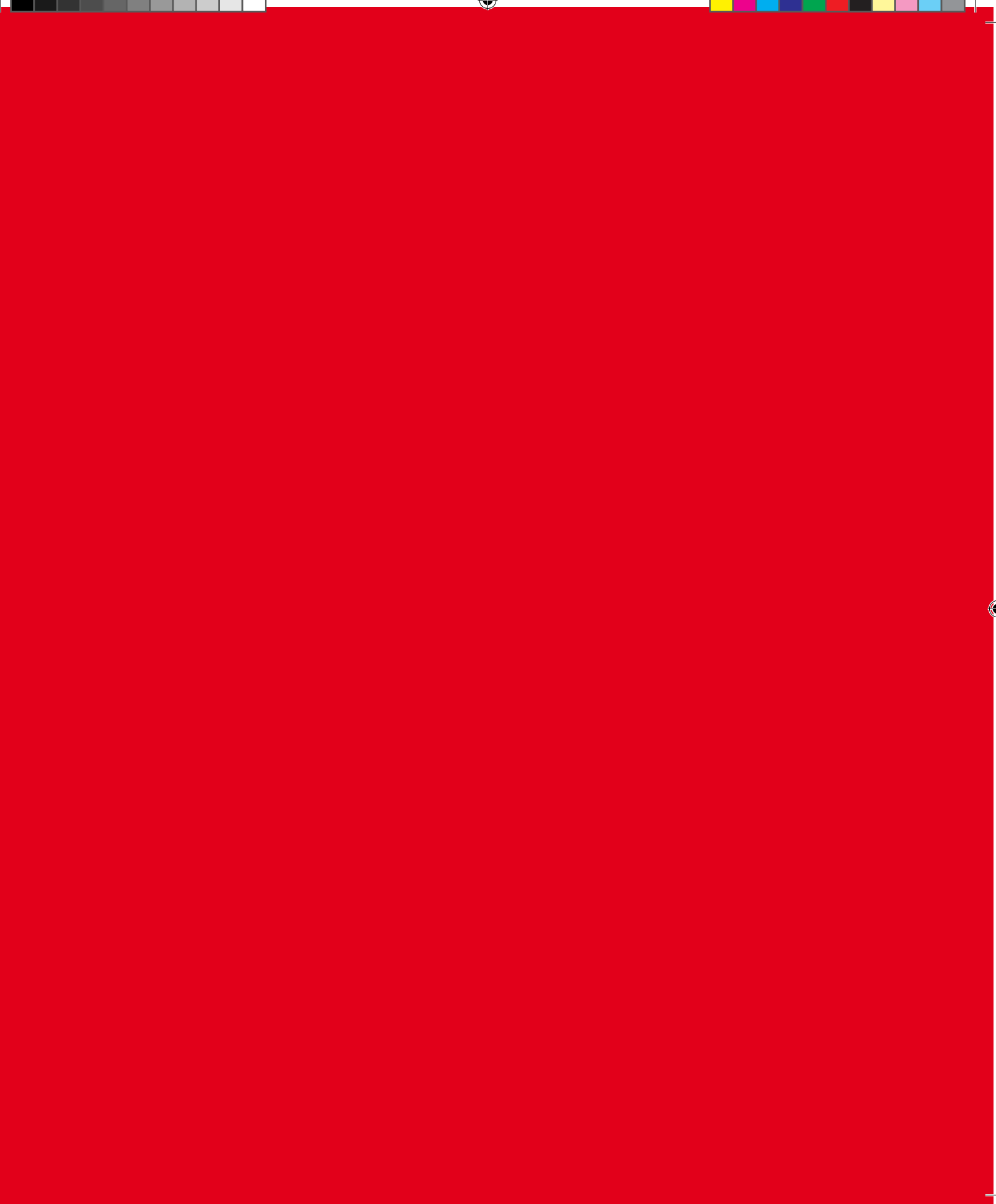
Some problems have tantalised Schrijver for a long time. “You cannot force the solution. Mathematics is not a nine-to-five occupation. You are always mulling things over, on the bike, in the train. **Sometimes I get a brainwave when I get up. But often not.** And so I frequently take an afternoon nap to create extra chances.”

Since the 1970s, Schrijver has been wrestling with a problem that looked simple and for which a simple solution ought to exist: a formula for counting the number of matchings in a network. “After twenty years of regularly working on this problem, I thought: perhaps there is no simple solution after all. Then I became a father and so I scarcely had the time to work on the problem further. Then during one night in 1998, when I was feeding my daughter, I suddenly hit on a solution. I stayed up another hour to briefly work it out and then went back to sleep again.”

Schrijver has also written a three-volume standard work of 1800 pages about his subject area. This was published in 2002. “I spent 20 years writing it and even read articles from the 17th and 18th centuries whilst researching the field. That way I not only got an overview over the subject but I could also see what was missing. I then tried to fill in the gaps, which was extremely inspiring. Finally I endeavoured to write it down in an attractive and succinct manner.”

And that is what attracts Schrijver to mathematics: the elegance, the beauty. “You are often confronted with simple problems for which a simple answer exists. You strive for elegance in the solution, in the proof. Just like in the arts. A beautiful and elegant proof provides new insights. Take, as illustration, the discovery of the wheel. A lot of thought went into that. A simple problem was solved with a simple and universally applicable solution.”







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