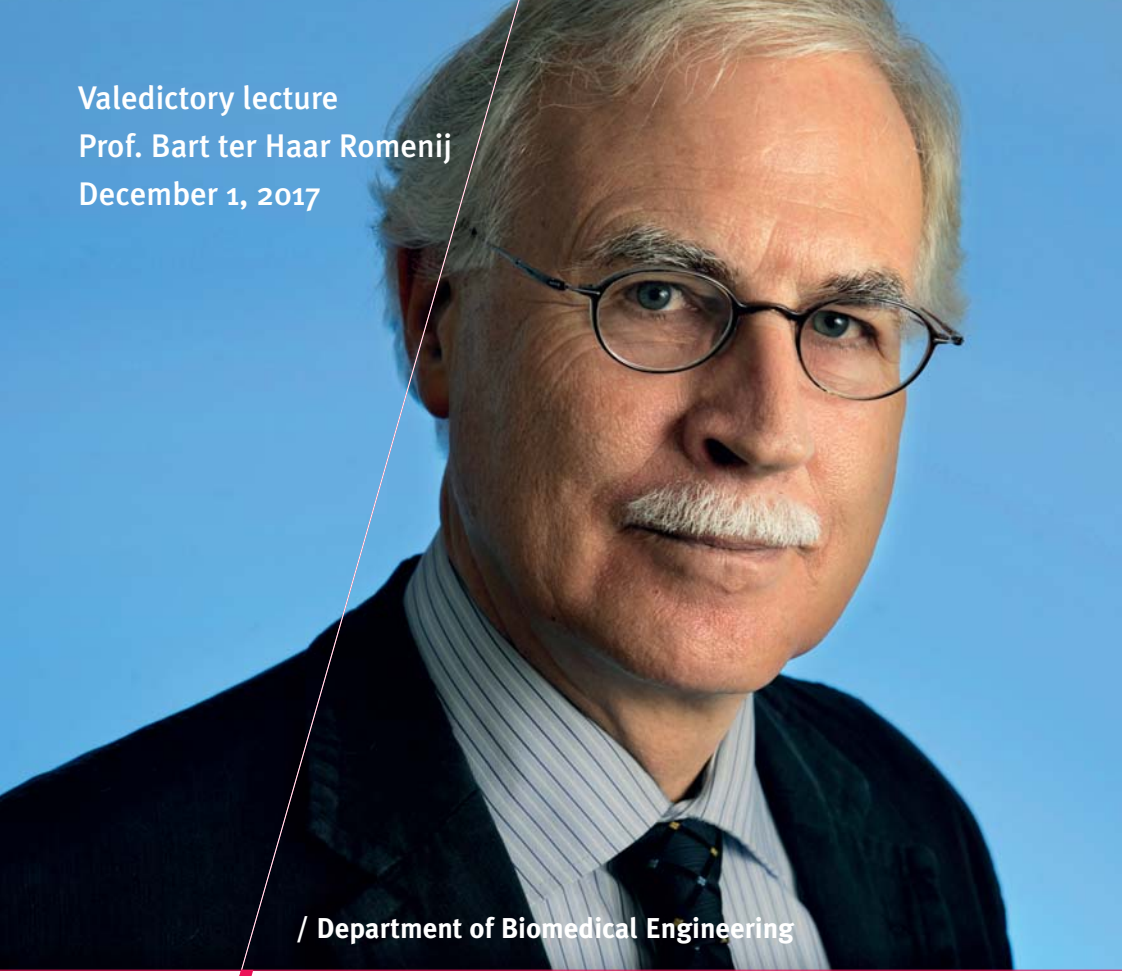
Vision for health



Valedictory lecture
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December 1, 2017

/ Department of Biomedical Engineering

TU/e Technische Universiteit Eindhoven University of Technology

Vision for Health

Where innovation starts

Valedictory lecture Prof. Bart ter Haar Romenij

Vision for Health

Presented on December 1, 2017
at Eindhoven University of Technology

Introduction

Today I will share with you my fascination with my field: brain-inspired medical image analysis. I have worked in this field, bridging biophysics and image analysis, over the last 40 years with much pleasure and satisfaction. The field is in rapid transition, through the recent breakthroughs in artificial intelligence. In this lecture I like to discuss several aspects of the journey, what we learned and accomplished, and what are our challenges.

I first want to sketch the intrinsic scientific approach we have taken over the years, in understandable terms. Problems in medical image analysis are complex. The data are often high-dimensional, multi-modality, very variable and noisy, and the results of the detection, segmentation, registration, quantification or enhancement tasks need to be of the highest quality, as they involve the diagnosis or treatment planning of a patient.

The sketch will involve the fields of computer vision, of scientific visualization, symbolic computing and artificial intelligence. The application areas I have worked in with my team are in computer-aided detection and diagnosis, for many different purposes, such as breast cancer, lung emphysema, cardiac motion, intervention techniques, deep brain stimulation, brain connectivity visualization and diabetic retinopathy, to name a few.

I will give a short overview of the mathematics of multi-scale and multi-orientation differential geometry we have developed, and how it was inspired by state-of-the-art models of our visual perception. On the way, I want to express my sincere gratitude to the many people who inspired me, who trusted me, and who gave me amazing changes and privileges in my scientific and educational endeavors.

Science gains a better understanding if you can teach about it. And I love teaching, and interacting with my students. I feel at my best when I can discuss new ways if we feel we get stuck. I am proud of the many new careers I have seen growing, of which you have seen some amazing examples in the symposium. The biggest reward I could get for a lifelong career of hard work has been to be able to give people the confidence they need to develop their personal skills.

Today, we see that deep learning is taking over, especially in my field with deep convolutional neural networks. It penetrates our field in every nook and cranny, it is disruptive. I am delighted to see this development; it finally works, amazingly well, and about time, too [2]. Can we also understand why it works so well?

Computer-aided diagnosis

Pattern recognition

Let us first look at the task of the field: the detection and quantification of organs, of pathology or changes in pathology. To automatically detect lung tumors, brain tumors, breast cancers, polyps, etc., or quantify blood flow and local cardiac perfusion etc., we need to describe the tissue or tissue boundaries we are looking for: the (scalar field) anatomic, (vector field) dynamic and (tensor field) functional properties. The classical way is through pattern recognition: design sets of features, design a classifier, validate the classes and come to a decision. The features can be plentiful, such as local texture derivatives, Gabor kernels, shape descriptors like curvature, 'roundness' etc., and there is a wide variety of classifiers such as support vector machines, random forests, etc. We interview the doctor to construct our hand-crafted, model-driven geometric reasoning.

Deep learning

While this all worked fine, it was not perfect. In fact, we more or less got stuck and could not reach human performance. The solution, and revolution, was to let the system itself find the features: train them from the data, the more the better, train the classifier. It is all in the data. That is why data is now the most precious resource of all.

The big surprise in 2012 was the jump in performance in a famous image classification challenge, ImageNet Large Scale Visual Recognition Challenge (ILSVRC) with object localization in 150,000 images and 1,000 classes. It made a leap from 74% to 84% correct. Today it is 97.7%! The breakthrough was deep convolutional neural networks (CNNs), with many layers (fig. 1), just as in our visual cascade (fig 2). The stages extract increasingly more complex information, beginning (e.g. for face recognition) with lines and edges, then parts like noses and eyes, then faces, then persons, then groups etc. The learning of the network is an iterative updating process, where the error at the end is back-propagated to the beginning, on the way adjusting the neuronal connections. The amazing effectiveness, and the availability of Big Data, cheap GPU (graphical processing units, 'game cards') parallel processors and clever CNN designs is causing this field to explode. U-nets, deep residual networks, generative adversarial networks,

spatial transformer networks, to name a few. It will impact our whole field in the decade to come: self-driving cars, delivery drones and, of course, electronic doctors. 60 percent of the 800 manuscripts submitted at MICCAI 2017, our largest 'medical image computing and computer-assisted interventions' conference, focused on machine learning. And of those papers, 80 percent use deep learning.

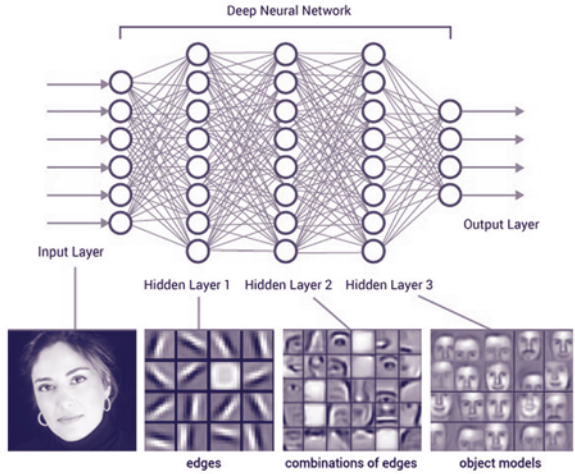

Figure 1

Stages in a deep neural network learn increasingly more complex features, in a larger contextual region.

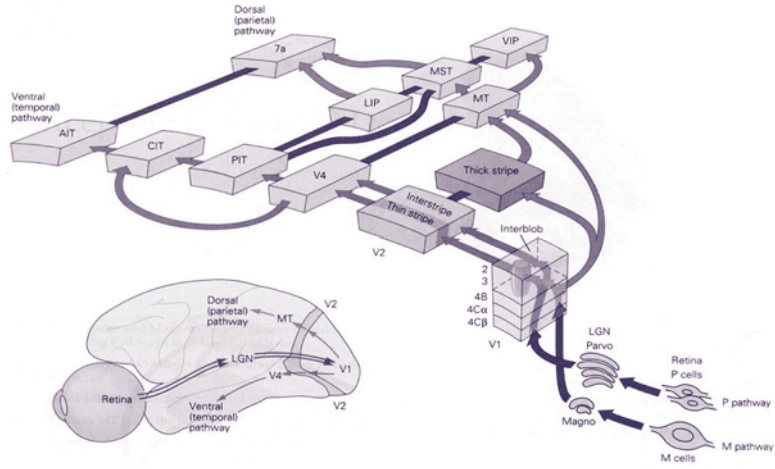

Figure 2

The cascade of processing stages in the human visual system: primary visual cortex V1, V2, V3, V4, MT, etc.

There is a feeling of crisis, relief and new energy in old professors like me, who spent their whole life in 'hand-crafted features', which are now being replaced by 'learned features', as well as with radiologists, who are confronted with patients who Google a lot, and see these networks starting to outperform human experts [1] [2].

Finally, it works! There is virtually no lab anymore in my field of Biomedical Image Analysis that is not converting to deep learning. I am happy to see that my successor, prof. Josien Pluim, is applying deep learning full scale, with effective national and international collaborations, in such important fields as pathology, retinal analysis brain segmentation, and crowd sourcing.
Deep learning is an improvement of artificial neural networks, using more layers, each exploiting more context, and giving a higher level of abstraction. In our field the convolutional neural networks (CNNs) especially have proven to be outstanding performers. However, the magic of DL, actually the mathematics of DL, is not yet fully understood, despite a huge number of labs and top minds working on it. Much is still a black box. In parallel, the developments in today's 'wet' physiological vision science are equally spectacular. But these two worlds are still relatively disjunct. It works two ways: in addition to brain-inspired computing, there is also computer-vision-inspired visual modeling.

In my lecture I want to give you a glimpse where we stand now, combined with a peek into my career path, and a peek into the future. With two central threads: mimicking human vision and translating it into healthcare, which I will illustrate with the work I have done with my PhD students.

The start of a fascinating journey

The title of my lecture is Vision for Health. It all started at Delft University, where I did my Master thesis on eye movements, with prof. Gert van den Brink. We designed an eye-controlled typewriter for fully paralyzed patients, and were able to print 180 characters per minute. Ten systems were built, and set out in revalidation centers. One day, I attended a lecture in Eindhoven by prof. Larry Stark, from UC Berkeley, on his scan-path theory: eye movements teach us a lot about our internal control system. I arranged an externship of 4 months in Berkeley, which was fascinating: doing non-linear pupil motion research, I learned a lot about eye movements, and was a member of the world-famous Bay Area Vision community.

Back in the Netherlands, in the Royal Navy as part of my military service, I worked at TNO-FEL on a far-infrared scanner to detect, even at night, warm people fallen overboard into cold sea water. It was for me the beginning of remote sensing and automated hotspot detection, i.e. pattern recognition.

My PhD at Utrecht University, with prof. Jan Denier van der Gon, was on non-linearities in single muscle fiber control in (my own) upper arm muscles. It was the perfect introduction to neurophysiology. At that same department prof. Jan Koenderink was pioneering mathematical models for vision. He realized that vision is a 'geometry inference engine'. I was captivated by this notion of differential operators, sensorium, psychophysics, and his solid mathematics borrowed from Einstein for shape and motion extraction, color and depth analysis, shape from shading, etc.

Later, during my first years at the AZU Radiology Department, with prof. Paul van Waes, I was able to co-pioneer with Philips and BaZIS the first PACS in Radiology experiences, and learned the physics of medical imaging of CT, MRI, ultrasound etc. at its base. Prof. Stephen Pizer (University of North Carolina, UNC) did a sabbatical year in Utrecht with prof. Koenderink. We became friends, and through a joint Philips grant I was able to visit UNC many times. He donated to us the full image analysis software environment of his PhD students. The first 3D visualization applications were developed With Karel Zuiderveld and Frans Zonneveld. Together with the advent of prof. Max Viergever, who generated major growth in the medical imaging environment, it was a perfect start at AZU and ISI in medical image analysis. With Bram van Ginneken we developed the first applications in X-thorax analysis for TBC screening [18]. Bram is now heading, together with Nico Karssemeijer, the Diagnostic Image Analysis group in Nijmegen, which group is establishing a solid name in deep learning. The focus on mathematics and multi-scale medical image analysis took off when Luc Florack, with a solid background in theoretical physics and differential geometry, joined the team [15] [16].

The visual system / Seeing

We aim to mimic the visual system, and I will provide some basic concepts here. The brain has always inspired the imagination. It has as many neurons (100 billion) as there are trees in the Amazon basin, and each neuron has as many synapses as one tree has leaves (50K). The synapses can grow and shrink, which makes up for the brain's plasticity: learning and forgetting, and adaptation. The brain uses 25% of our body's energy, but with only 25 Watt and the frequencies of firing neurons not exceeding 10 KHz, we can still learn a lot from it. It has always been called 'the last frontier'. The visual system is in the back of our head, and takes up about a quarter of our brain. We are indeed very much a visual machine, 'an image tells more than a thousand words'. Why do we need so many neurons for vision?

Imaging the brain is possible today with sophisticated imaging tools. In addition to the classical anatomical / functional techniques such as histology, MRI, diffusion MRI, functional MRI, CT, US, SPECT and PET, we can do very high resolution functional / anatomical studies with optical imaging techniques (voltage sensitive dyes, calcium intrinsic imaging), and connectivity studies with opto-genetics and polarized light imaging.

The retina is far more complex than we thought [10]. Around 60 distinct types of neurons have been found, in three layers. The first layer establishes 12 photoreceptor pathways, the second connects by 10 types of bipolar cells to the output cells of the retina, the ganglion cells, and the third one creates around 20 specific encodings of the visual world to be sent to the brain. With only a million ganglion cells, and thus fibers to the brain, and 150 million receptors, there is strong convergence, through so-called 'on-center-' and 'off-center-surround' receptive fields. The retina is multi-scale: at each location we have a range of receptive fields with different diameters, increasing with eccentricity.

The main retinal output goes directly to the lateral geniculate nucleus (LGN) in the thalamus, from where pathways radiate to the primary visual cortex. There is also a major stream (75%) back projecting from the primary visual cortex (V1) to LGN.

Onwards from V1 we find a clearly layered hierarchy of processing levels: V1, V2, V3, V4 etc., about 11 levels deep.

In the mid-sixties the Nobel laureates David Hubel and Torsten Wiesel found in V1 the so-called ‘simple’ cells with a strictly ordered receptive field that could be modeled with a Gabor function or the spatiotemporal derivative of a Gaussian. For segmentation, enhancement, registration, motion analysis, depth analysis etc., high-order derivatives of images are abundantly used. It was the basis of our brain-inspired ‘neuro-mathematics’ approach.

Front-end vision

Multi-scale image analysis

However, high order derivatives also amplify noise. One of our early important realizations [15] was that Gaussian derivatives are the only properly regularized derivatives, for discrete data to high order. It was the same as Laurent Schwartz' proposal for tempered distributions ('blur the data a little bit'), for which he received the Field Medal. This allowed us to go to very high derivatives. There are no x- and y-coordinates in vision, so we need an invariant representation. This was accomplished by local gauge coordinates, and tensor contraction invariants, inspired by the famous Feynman diagrams in theoretical physics. As the Gaussian derivatives have a free size parameter, the 'scale', from each image a new stack of images is generated (just as in our visual system), which is called a 'scale-space stack', or simply a 'scale-space'.

Many applications followed. We were able to do deblurring (sharpening) of images, designing many feature detectors as invariant image landmarks (corners, T-junctions) and (dynamic) texture and shape descriptors [16], and applying them in many applications in computer-aided diagnosis, described in the next sections. With Wiro Niessen we explored the first multi-scale applications in radiology [17]. Wiro is now leading the Biomedical Imaging Group Rotterdam. He has been awarded the Simon Stevin Master prize, the highest award for technical-scientific research in the Netherlands, and is the current president of the MICCAI society.

I initiated the Scale-Space in Computer Vision series of conferences in 1989 in Utrecht, which has been held bi-annually ever since. It later merged with the Variational Methods community. This is a fine community, where we met many collaborators who became colleagues for life [5]. It also led to the writing of my book "Front-End Vision and Multi-Scale Image Analysis", which has been reprinted many times, and has been the basis of my longstanding course by the same name. It is still used as course notes by many other image analysis groups abroad. The widely cited 'vesselness' detector by Alex Frangi exploits the results of this differential geometry work, using eigenvectors of the second order Hessian matrix as principal curvatures.

In the nineties, non-linear adaptive scale-space emerged. Intelligent blurring paradigms, where the denoising kernel is made adaptive to the local geometry, i.e. driven by local edge or curvature strength [17]. The results are striking, and today this algorithm is world's most used algorithm for denoising, present in every TV, smartphone and tablet, and digital camera. Stilyan Kalitzin and Joachim Weickert [9] stayed with us as postdocs for two years. Joachim is now professor at Saarland University (and was awarded the prestigious Gottfried Wilhelm Leibniz Prize in 2010, the highest scientific prize in Germany).

I became the chairman and organizer of the EU-NSF funded 'Diffusion' project, a collaboration of 7 EU and 6 US research groups on 'geometry-driven diffusion'. Many key players of the field were on board, such as Jitendra Malik, Pietro Perona, Olivier Faugeras, David Mumford, Stephen Pizer, Tony Lindeberg, Luis Alvarez, Peter Olver, Steven Zucker, Wiro Niessen, Luc van Gool, Joachim Weickert, Mads Nielsen, Guillermo Sapiro, Ben Kimia, etc. I was able to organize 5 international meetings, which were highly stimulating events (fig. 3). I edited a Springer book with chapters by all participating labs [6]. The tutorial chapter by Tony Lindeberg and me [8] is one of the best cited in this field (2690 times).

Figure 3

Participants EU-NSF 'Diffusion' project, CalTech 1993.

We realized that the multi-scale stack has an embedded graph structure, automatically giving a hierarchical decomposition of the image. This led to the initiative of the 'Deep Structure and Scale in Computer Vision' (DSSCV) project (led by Luc Florack and Univ. of Copenhagen), from which we were able to start the fundamental computer vision research in Eindhoven with 3 PhD projects [21] [22] [23]. The so-called 'top-points', singularity points in the deep scale-space, enabled us to do the first content-based image retrieval [22] [23], and hierarchical image editing, by pruning the branches of the tree graph of the deep structure singularities [21], 'think away the ribs'.

Multi-orientation image analysis

The mapping in the primary visual cortex V1 is remarkably well organized. By means of voltage sensitive dyes it was found that the cortical hypercolumns, forming the left and right ocular dominance bands, form so-called 'orientation pinwheels'. This was a striking finding. We realized that this was a way to represent multiple orientations on the same location in a visual domain. As it was also convincingly demonstrated that similar orientations of neighboring pinwheels form functional connections over longer ranges, we started to develop a suite of contextual operators for contour enhancement and contour completion, based on the physics of multi-orientation diffusions [20] [27]. The 'lifting' of orientation into a new domain had many advantages, such as being able to enhance arbitrarily crossing fibers [27] (fig. 4).

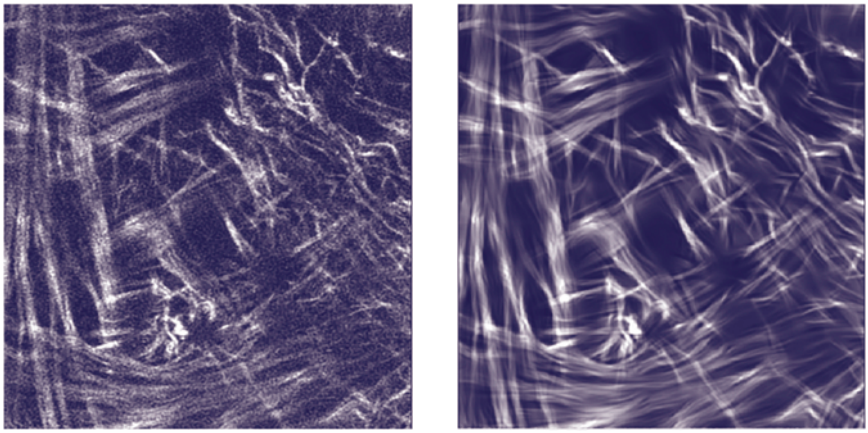

Figure 4

Left: Noisy two-photon laser microscopy image of tissue engineered heart valve tissue.
Right: crossing preserving enhancement, exploiting orientation scores. From [27].

It led to many new mathematical image analysis algorithms in the orientation domain [41]. The optimal and invertible kernels in this orientation space were termed ‘cake kernels’, as we could distill them as ‘pieces of cake’ from a polar frequency spectrum representation. The new representations were called ‘orientation scores’, with special left invariant differential operators.

This caught the attention of the mathematics community, and we joined an FP7-ITN Marie Curie program of the application of sub-Riemannian geometry in vision. Remco Duits received an ERC grant of €1.25m to develop this ‘Lie group theory for Vision’. We collaborated with the international ‘neuro-mathematics’ top of this field (prof. Giovanna Citti, prof. Alessandro Sarti) [43].

Quantitative image analysis and visualization

Computer-Aided Diagnosis

The TU/e Biomedical Image Analysis group started in 2001 from scratch. Not being embedded in a University Medical Center, we focused on the development of innovative algorithms, new visualization techniques and applications for industry.

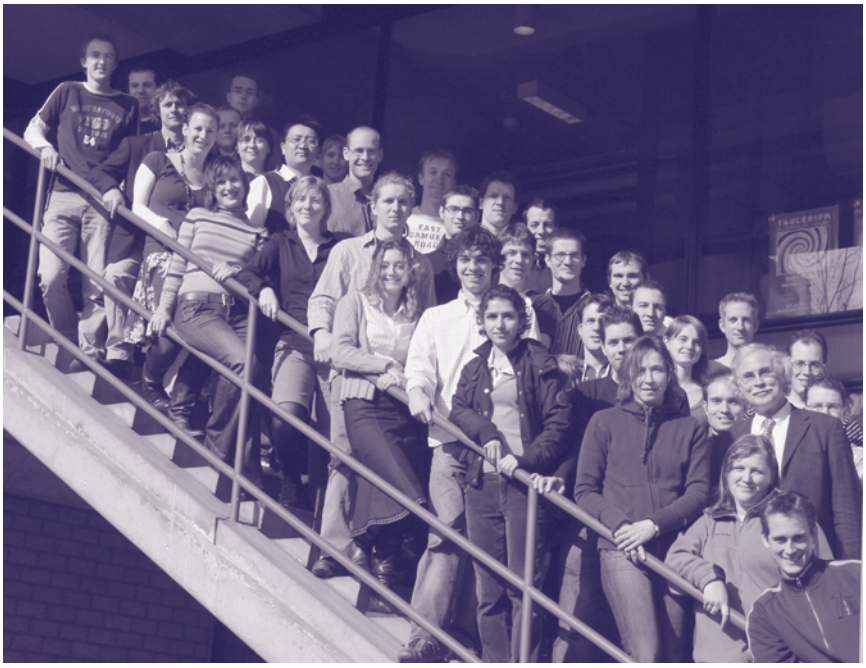

Figure 5

Biomedical Image Analysis, Feb. 2007.

From the start the collaboration with especially the Biomedical NMR lab (Klaas Nicolay), the BME Cardiovascular lab (Frans van de Vosse) and Philips Healthcare flourished (Frans Gerritsen, Marcel Breeuwer). Both profs. Nicolay and Gerritsen passed away far too early. They had contributed substantially to our development. Our clinical partners included Maastricht University Medical Center (UMC), Máxima Medical Center, Kempenhaeghe, Catharina Hospital, Utrecht UMC, Radboud UMC,

King's College London and Shengjing Hospital and He Eye Hospital in Shenyang, China.

The Dutch medical image analysis scene is concentrated, of high quality and rich in application areas, at almost all universities and UMCs. Many of our TU/e MSc students have continued their career in these highly esteemed labs, as well as in many medical imaging companies and new start-ups.

It is extremely effective and mutually beneficial to be a neighbor to such a giant as Philips Healthcare in Best and Philips Research on Eindhoven's High Tech Campus. The group Interventional X-Ray Solutions is one of the largest in Philips Healthcare, with over 750 employees. Everything that can be done through a small access opening in an X-Ray department is called interventional radiology. We worked on the complex problem of 3D reconstructions for through-the-skin interventions [32] (fig. 7), and interactive visualizations and road mapping for neurovascular treatment (fig. 8), multi-modal needle puncture planning and tracking, and stent placement within coronary artery disease, exploiting fusion of real-time C-arm X-ray with pre-treatment CT scans [33]. A collaboration on high density CTA lung images led to pioneering work on automatic embolus detection, using our multi-scale shape operators to detect tiny vascular obstructions [24].

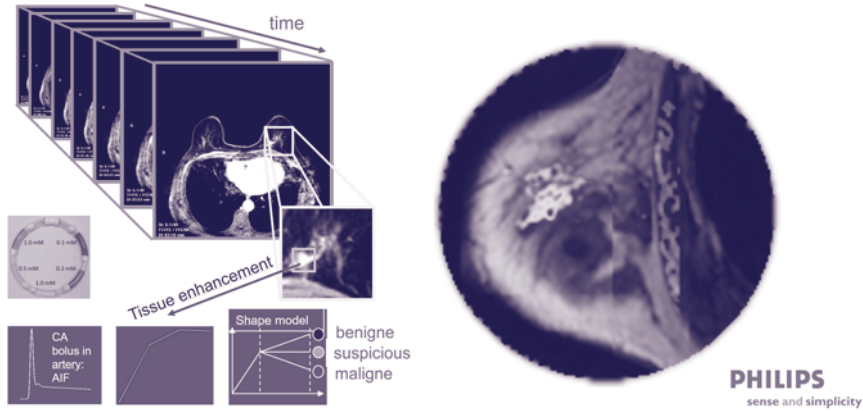

Figure 6

Quantitative dynamic contrast enhancement (DCE) of the breast. From [35]

As MRI got faster, and with the discovery of tagging MRI, an innovative MRI excitation technique similar to illumination with structured light, we were able to begin handling MRI 4D (x-y-z-time) datasets. Data were acquired in international

Figure 7

Radiological interventions are all procedures through a small opening.

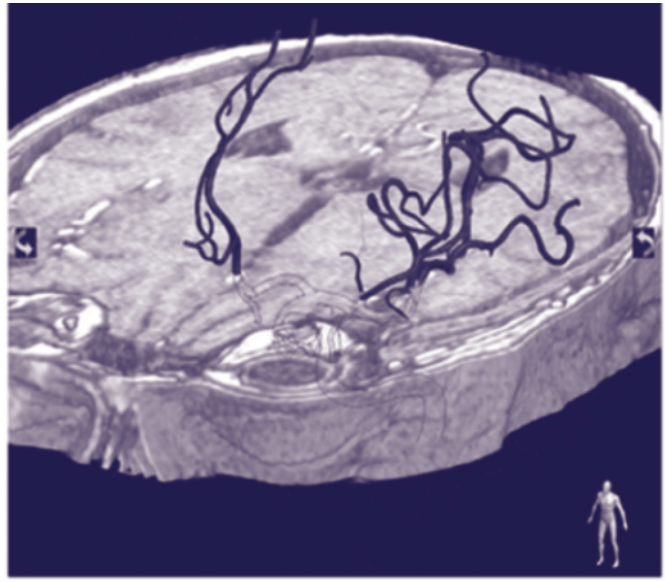

Figure 8

Multi-modality view of CT slab with cone-beam angiography [33].

hospitals (a.o. King's College London), and fully automated quantitative results on cardiac output [38] given to the clinician; this non-invasive, non-radiative and no contrast medium MRI technique showed the location and extent of cardiac infarcted areas [34] . In this study we effectively exploited the multi-scale spatiotemporal differential operators on the optic flow field to find singularities, to develop new dynamic regularization techniques and to convert the hitherto 2D tagging analysis into a true 3D space-time analysis.
With Philips Healthcare and Nijmegen Radboud UMC we developed new techniques and models for quantitative dynamic contrast enhancement (DCE) of the breast (fig. 6) to detect early breast cancer. Angiogenic tumor locations could be found by measuring the increased velocity of the passage of the contrast bolus, and modeling the process with a multi-compartment contrast medium exchange model [35].

Visualization

Proper visualization in medical imaging is crucial. We are visual machines, but not optimized for seeing high-dimensional or tensorial data. Anna Vilanova developed

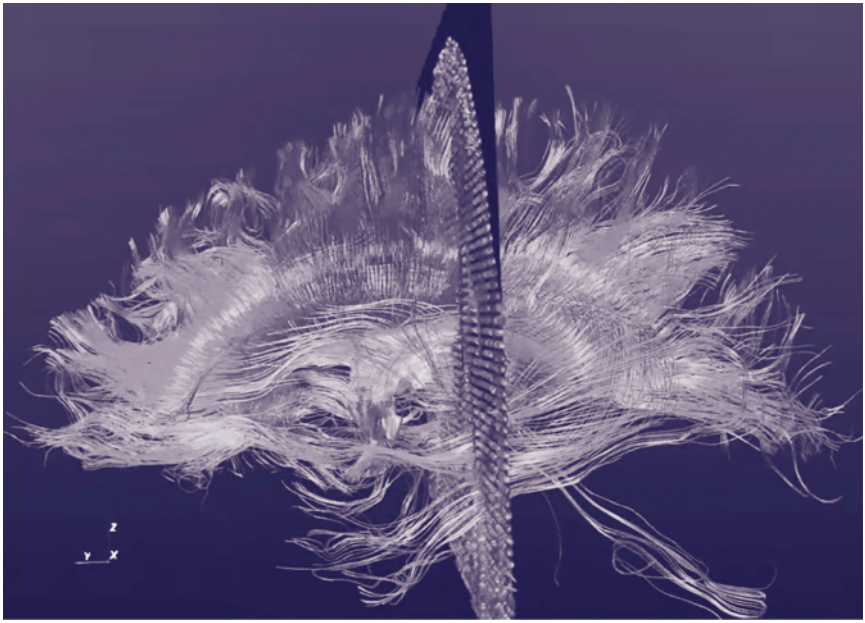

Figure 9

Interactive GPU-based tractography of the corpus callosum. VIST/e software. Note the use of shading (specularities, reflections) based on the physics of rendering hair. VIST/e team led by dr. Anna Vilanova.

the science of visualization by designing a wide range of real-time interactive and highly versatile tools with her PhD students. Starting from research on transfer functions [25], we developed a sophisticated tool for tractography, i.e. visualizing the fiber tracts of brain (and muscle) tissue as measured from diffusion tensor MRI data (fig. 9), as well as their uncertainty [37].

In diffusion tensor imaging (DTI) a 3 x 3 tensor is acquired, representing the local ellipsoid model of water molecule diffusion. The connected main eigenvectors represent the main direction of the local coherent structure. More complex fiber structures can be measured with high angular resolution diffusion imaging (HARDI), measuring 3D voxel diffusion in up to hundreds of directions [30].

We developed a GPU-based visualization package, VIST/e, capable of visualizing real-time and interactively virtually all the parameters from our own research and literature, including shading, shadowing and complex glyphs (fig. 9) [26] [31]. It can be freely downloaded from http://bmia.bmt.tue.nl/software/viste.

Applications were developed for many areas: the study of complex muscle anatomy in mouse hearts (only 7 mm high) and human extremities, in collaboration with the BME NMR Lab, and brain connectivity development in neonates, in collaboration with Máxima Medical Center in Eindhoven. In Maastricht UMC the procedure of deep brain stimulation (DBS) was regularly performed on patients with severe Parkinson's disease. In this neurosurgical procedure a needle, and later a fixed wire, is progressed to the deep subthalamic nucleus in order to elicit inhibition of its uncontrolled firing during a seizure. The problem was that the position of the needle tip had to be very accurate, only to the motor part of the STN and not to its adjacent parts, the adverse effects of which could be serious. The STN was often insufficiently visible on the MRI data. We developed accurate tractography studies, STN subdivision studies with high angular diffusion MRI, and were able to quantify all brain fiber connections to neighboring ganglia and cortex [36], also exploiting the ultra-high field 7T MRI available in Maastricht [40].

In severe epilepsy patients surgical resection of the epileptic focus sometimes remains the ultimate solution. When the medio-temporal area is resected, damage to the underlying optic radiation tracts can lead to severe damage of the visual field. In collaboration with Epilepsy Centre Kempenhaeghe in Heeze we tracked, enhanced and visualized the optic radiation bundle, for safe surgical planning and the prevention of blindness (fig. 10) [11].

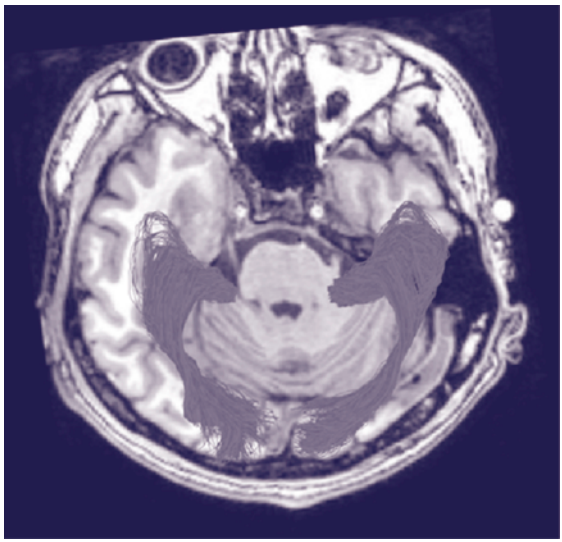

Figure 10

Tractography for planning safe resection surgery in epilepsy [11]. The resection (right) does not cut the optic radiation fibers, preserving full vision.

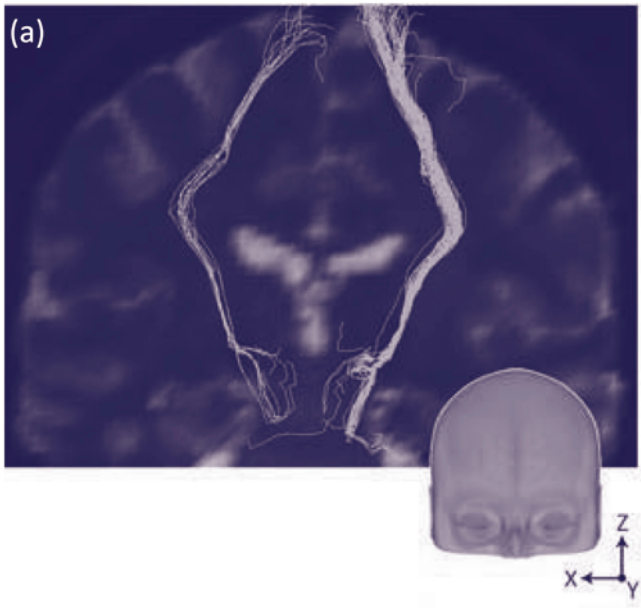

Figure 11

Hyper-direct pathway: streamlines from the right and left STN ending in the motor cortex, not passing through thalamus, caudate, putamen or globus pallidus. From [12].

Tensor images are not only difficult to visualize and interactively explore, such complex 5D tensorial data are also difficult to segment, enhance, register and denoise. Together with the TU/e Mathematics Department and the international DTI community (Harvard, INRIA, EPFL, Univ. Chicago, NeuroSpin, etc.), we developed a wide range of sophisticated tools for this tensorial computer vision. Examples are analytical solutions for 5D HARDI enhancement kernels and numerical solutions for geodesic tracking by considering the diffusion tensor as a local inverse space-deforming metric [29].

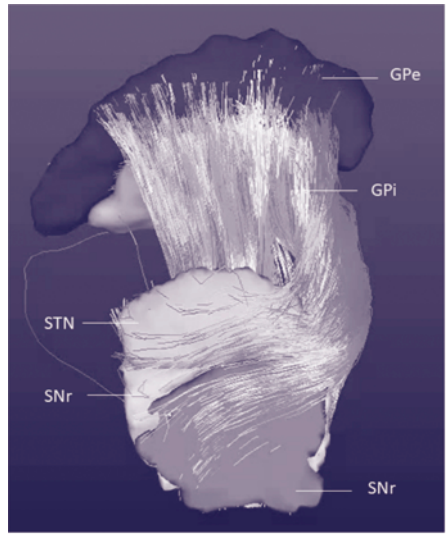

Figure 12

Connections around the subthalamic nucleaus, revealed from a 42 hours MRI scan at 7 Tesla of a human brain specimen. From [40]

In collaboration with Philips and King's College London we were able to develop innovative and interactive 4D flow tools, all running on modern GPU hardware, such as 'particle flow' from 4D velocity encoded MRI data [39] (fig. 13).

In 2012, prof. Wei He, founder and president of He Eye Care, asked for biomedical support to set up a large screening program for diabetes in China. The 11.6% incidence of diabetes in China is of epidemic proportions. This figure, 0% in 1980, is still rising linearly. It is a major source of blindness, as blood vessels start to leak, and the retina as the body's most oxygen-consuming tissue is vulnerable in particular. I decided to become project leader of RetinaCheck, and with funding from NWO, the EU Marie Curie project MaNeT, the European Diabetes foundation

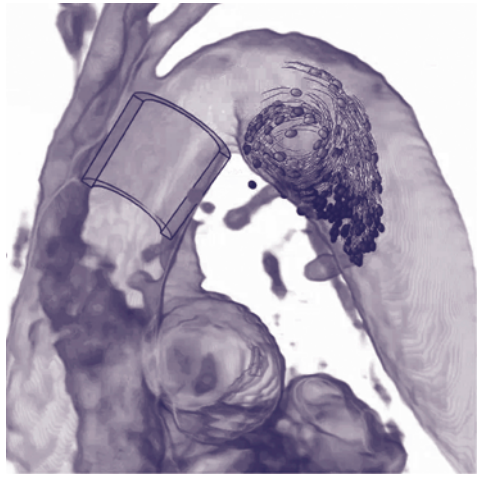

Figure 13

Interactive GPU-based visualization of 4D velocity-encoded MRI particle flow in the human aorta arch. This enables the study of how well heart valves open and close [39].

Figure 14

Retinal image and diabetic metadata acquisition at the Diabetes & Endocrinology Department of Shengjing Hospital, Shenyang, China. Note the tulips on the wall.

and Northeastern University, we managed to form a great team, which produced over 40 scientific papers, and will lead to 4 PhD theses [41] [42] [43] [44].

We have developed multi-scale and multi-orientation algorithms to extract a broad range of quantitative and clinically validated biomarkers, such as vessel tortuosity, arterio-venous ratio, bifurcation branching angle, fractal dimension etc. Clinical validation is done at Shengjing Hospital in Shenyang, China, where we were able to scan the retinas of over 3000 diabetes patients, and collect their extensive diabetic metadata (fig. 14). We have recently developed a residual neural net-based deep learning method, where the training is done at image level, while the detection of exudates is at pixel level [13] [43] (fig. 15).

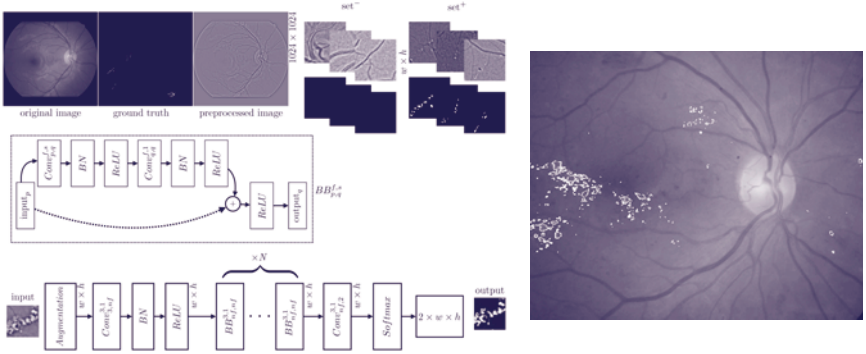

Figure 15

Left: Residual neural network for exudate detection in retinal images. Right: Full segmentation (probability map) of automatic exudate detection (DiaRetDB1 dataset) [13].

RetinaCheck is currently being converted into a promising internationally operating start-up, offering a retinal check as eCloud service, with the help of the TU/e Innovation Center and heathtech incubator NLC in Amsterdam.

Education

Courses

It has always been a joy to teach. A range of courses has been organized, developed and given, together with my staff members, from "Physics of Medical Imaging", Basic Medical Image Analysis, Systems and Models, and many Design Centered Learning topics, to the core 'Front-End Vision and Multi-Scale Image Analysis'. This last course, 3 times awarded best MSc course, is also a national course of the PhD research school ASCI (Advanced School for Computing and Imaging), and is still given annually. The focus of multi-scale and multi-orientation brain-inspired computing for medical imaging applications is now shifting to deep learning, and understanding why it works. This topic has also been invited and taught at many international Summer Schools, such as EMBS, SSIMA (with prof. Fred Bruckstein and Elena Ovreiu), BICV, etc.

I was Program Planning Committee member of the European Congress of Radiology in Vienna from 1997 till 2009, responsible for the 'Golden Mile': the computer vision exhibit at this world's second largest radiological conference with over 22,000 participants and over 250 exhibiting industries. Each year we invited the 12-14 top medical imaging groups in Europe and the world to show their latest medical imaging research. In order to let the students discover and experience this very impressive market, and the professional radiological community, from 2007 till 2013 we organized visits to the ECR with all staff, PhD and MSc students, about 25 people. This was a highlight, always concluded with the famous 'ECR Party'. Another annual highlight was the social event in the Ardennes with the whole BMIA group, with the renowned 'five-minute talks' about 'the other side of you', creating an atmosphere of mutual recognition and respect.

Mathematica

When I started in Eindhoven, I realized that Mathematica was the perfect tool not only to design highly sophisticated algorithms in our research in an efficient way, but also to stimulate students to 'play with the mathematics, design their solution interactively, with lots of interactivity and visual feedback'. It was really nice to see that it worked. Together with Markus van Almsick, hired as expert and 'evangelist', we set up many new Design Centered Learning projects, and wrote most of our

many sophisticated mathematical algorithms in large-scale Mathematica packages. Several of them have found their way into Wolfram's new versions of Mathematica. We were part of the lively international Mathematica community.

We saw the enthusiasm of students using it. It is a high-level language, actually it is the highest level design language. It is a functional programming language instead of an object-oriented programming language. It is today at the level that a careful phrasing of the problem in English virtually gives you the code, in typically very few lines. This has always been my main motivation: let students focus on the mathematics, the structure of the problem, *design* instead of focus on debugging and struggling with endless lines of code.

Matlab has a much larger market share, but I always have felt privileged that my group was special, advanced, using Mathematica as the most sophisticated software available today in its endeavors. We were always generously supported by TU/e (through five-year campus license agreements), and the senior staff of Wolfram Research. My book, Front-End Vision, published in 2004, is written completely in Mathematica, an innovative approach for course notes: everything is interactive, every topic has code to experiment with. I have plans to write a successor, also in Mathematica, on our multi-orientation and deep learning work, and its many medical CAD applications, over the coming years.

Computer vision-inspired vision modeling

We are all going to be profoundly impacted by Artificial Intelligence. New application areas are discovered almost daily, and many new network designs and paradigms are emerging rapidly. Next to brain-inspired computing, there is of 'computer-vision inspired human vision modeling'. However, these worlds have so far been relatively disjunctive. Not many computer scientists know about the recent discoveries of stellate amacrine cells nor do many physiologists know about residual networks or graph cuts.

To make the developments of AI optimally beneficial to our field, health care, it is imperative to understand how it actually works. Numerous labs are focusing on just this. We have only just begun. Among others, the energy efficiency of the brain is stunning, and by far not yet replicated in our implementations. On the other hand, recent breakthroughs in computer vision as evidenced by high citation rates are also just beginning to be tested as models for human vision.

Being 'raised' in both worlds, I recently published a number of observations that may give some new and unconventional thoughts ('conjectures') on both understanding vision, and understanding some of the effectiveness of the perceptual grouping process of deep learning.

The AI revolution has begun, and will profoundly change our medical image analysis field, as it does change numerous other fields. It is comforting to see that the computer assistance finally helps in augmenting our healthcare efforts at the level of human experts or even better, by better recognition, better prediction and better efficiency. It also creates many new challenges, for new paradigms in existing diagnostic protocols, for exploring the many new possibilities when endless data can be combined, and for regulating the availability and ownership of the huge amounts of medical data needed for the AI expert training.

We live in a fascinating time, with many fields in revolutionary development. The best innovations occur at the intersections of fields, and I was happy to learn so much from 'vision' for 'health'.

Thanks

At the end of my lecture, it is time to thank everyone. It will be impossible to be complete, so my apologies in advance.

I have been able to work with very talented students, Master and PhD students, staff members and colleagues. I would especially like to thank all the people that gave me the fantastic opportunities about which I have been able to report. Opportunities that occurred during my whole career.

I started in Utrecht, where my sincere thanks go to my early coaches and inspirers, prof. Paul van Waes, prof. Max Viergever, prof. Jan Koenderink and prof. Stephen Pizer, who believed in me and gave me trust and great chances.

The TU/e Department of Biomedical Engineering was a new department, where we as professors were able to enjoy freedom, and experienced an open and collegial atmosphere. This has been much appreciated. I am proud to see that our BME Department is doubling in size, and is the largest and the best in the Netherlands. I felt appreciated, and was able to develop myself. I loved the teaching. Especially the numerous editions of the Front-End Vision course, with national and international students, was a treat. And so was taking care of the students who studied in our group. Working with young people keeps you young.

My Biomedical Image Analysis group is a troupe to never forget. Luc Florack, Anna Vilanova, Markus van Almsick and Remco Duits, and all postdocs, PhD students and MSc students, with you we joined the international scene, wrote lots of papers and did lots of studies, you made me proud. The relationship with Philips Healthcare was precious and productive, through prof. Frans Gerritsen, who passed away way too soon, prof. Marcel Breeuwer, and Philips staff. The final years in China I and the RetinaCheck team got the essential support of prof. Yan Kang.

Prof. Jan Janssen invited me to Eindhoven, a feat that changed my life. My deep thanks concern the Board of Biomedical Engineering, prof. Frank Baaijens, prof. Peter Hilbers and mr. Rob Debeij. They gave me all support when needed, HR and

management advice, and grant application support. Margret Philips and Rina van Dijck kept us well-organized. The doors of the supporting staff of BME were always open.

It is a pleasure to see that my successor, prof. Josien Pluim, is dedicated to Deep Learning, the group is growing nicely, and I am sure this will blossom over the next decade.

It has been a great and rewarding journey. My greatest award is to see my students blossom. The symposium gave you wonderful examples.

But most of all, I would like to thank my wife and life companion Hetty, who has been my greatest support in all my journeys, in science and in teaching, and, above all, in together exploring our wonderful planet.

Looking back, it was a fascinating time, from the very beginning to the very end. I feel very privileged to have been able to do this as professor. I will continue for some years to come, as TU/e guest, with kicking off RetinaCheck, some continued teaching and publishing, and I can say it one more time: working on my passion: vision for health.

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43. Samaneh Abbasi, “Contextual and deep learning approaches in retinal image analysis”, PhD thesis TU/e, 2017.
44. Fan Huang, “Retinal image analysis for early blindness prevention”, PhD thesis TU/e, scheduled for 2018

* co-promotor

Curriculum Vitae

Prof. Bart ter Haar Romenij was appointed full professor (May 2001) of Biomedical Image Analysis in the Department of Biomedical Engineering at Eindhoven University of Technology (TU/e).

Bart ter Haar Romenij obtained his MSc degree in Applied Physics in 1979 at Delft University of Technology and his Doctoral degree in Biophysics in 1983 at Utrecht University. After being principal physicist and associate professor at Utrecht University Medical Center, he joined TU/e in May 2001. He has become known especially for research (and teaching) on brain-inspired and mathematically well-founded medical image analysis, with applications in computer-aided diagnosis, brain connectivity and retinal image analysis.

Bart ter Haar Romenij has served as president of the NVKF, VvB-BMT and NVPHBV. He initiated the bi-annual conferences on Scale Space and Variational Methods. He is distinguished professor and vice dean at Northeastern University, Shenyang, China, visiting professor at the Chinese Academy of Sciences in Beijing, honorary president of He University Shenyang, and distinguished professor at the National Taiwanese University of Science and Technology. He is a senior member of IEEE, and Fellow of EAMBES. He has supervised 30 PhD theses (6 cum laude) and over 140 MSc theses, published over 220 papers and 12 books and book chapters and holds 2 patents. He is a frequently awarded teacher. He has received the Mathematica Innovator Award and the Friendship Award of Liaoning Province, China.

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