RetinaCheck

Screening for Diabetes Detection and Blindness Prevention in China

Prof. Bart M. ter Haar Romeny, PhD
and full RetinaCheck team
东北大学中荷生物医学与信息工程学院
Sino-Dutch Biomedical and Information Engineering School of Northeastern University  2005-2015
Diabetes is exploding in China
11.6% of the population has diabetes – many don’t know

The RetinaCheck project: a huge preventive screening project

Diabetes: blood vessels start to leak
糖尿病：血管开始出血

Diabetes is leading cause of new blindness
糖尿病是产生失明的主要原因

Computer-Aided Diagnosis (CAD)
计算机辅助诊断：

可以快速和自动的处理大量的图像

→ Screening: 24 million people in Liaoning
筛查程序：辽宁2400万人

Prevention → huge costs savings
预防→可以节约大量的在医疗成本

TU/e
Technische Universiteit Eindhoven
University of Technology
110 million adults in China age 20 or older (over 11% of the country's total population) have diabetes, and 168.2 million adults have pre-diabetes.

The majority of diabetes cases are undiagnosed and untreated.

China has edged ahead of India to become the country with the highest number of diabetes-afflicted people.

Estimated medical costs for diabetes and its complications accounted for 18.2 percent of China's total health expenditure in 2007.
Complementary and strong partners, critical mass

He Shi:
Large coverage

何氏：
覆盖范围广

TU/e:
Brain-inspired new algorithms

TU/e: 大脑启发的创新的算法

NEU-BMIE:
Classification statistics, data analysis

东北大学:
数据分析、数据挖掘和IT系统建设
Fundus Images

Cheap
Easy acquisition
Very high resolution (10-18 Megapixel)
Retina is brain tissue

The retina

A fundus camera

Laser-scan fundus camera
Diabetic retinopathy - a main cause of blindness

Progressive damage to the vascular network:

- Vessel integrity, leakage, micro-bleeds
- Cotton wool spots, exudates
- Optic disc changes
- Tortuosity changes, A/V ratio, bifurcation branching angle, …
- Angiogenesis, proliferative DR

Quantification by modern computer vision algorithms is essential.

Retinal vessels are brain vessels

Fully automatic, quantitative detection

- Vessel tracking

- Microbleeds detection

- Curvature / tortuosity
Fully automatic, quantitative detection = many projects

- Fractal dimension
- Image ‘stitching’
- Bifurcations & angles
- Artery/vein ratio
Diseases associated with retinovascular parameters

Diabetes
Diabetic Retinopathy
Glaucoma
Hypertension
Cardiovascular diseases
Cerebrovascular diseases
Alzheimers disease
Stroke prediction

CRAE (artery width)
CRVE (vein width)
AVR (artery/vein ratio)
Tortuosity
Branch angle
Microbleeds
Fractal dimension
Arterial narrowing
Art. length / diameter ratio
AV nicking

Much more ongoing research

DR prediction
Project lay-out

Retinal modeling
- Vasculature
- Background tissue
- Optic nerve head

Feature extraction
- Curvature
- Caliber
- Bifurcation Geometry
- Number of lesions
- Cup/Disk ratio
- Etc.

Severity grading
- Healthy (R0)
- R1
- R2
- R3

Input retinal image
The RetinaCheck Screening Project

Algorithm design for Computer-Aided Diagnosis

Eindhoven University of Technology

Maastricht University Eye Clinic

Sino-Dutch BMIE School

He Shi Eye Care System

I-Optics

High volume screening

Easy-scan fundus camera

Project Collaboration

Maastricht Study

Retinal background study

Validation study

Shengjing Hospital

ICT infrastructure Cloud PACS

TU/e

TU/e

TU/e
He Eye Care System

Education and Training
He's University
Training Center of He's University
He Postgraduate Institute of Ophthalmology and Visual Sciences
International Remote Training Center

Clinical Services
5 He Eye Hospitals (Shenyang, Dalian, Huhudao, Panjin, Jinzhou)
46 Vision Centers (Shenyang, Dalian, Huhudao)
National Key Eye Center

Research
Shenyang Green Valley Bio-tech Industry Co. Ltd.
National Ophthalmic Pharmaceutical Bio-technology
International Technology Cooperation Base

Industrialization
Shenyang Sunmed Medical Device Co., Ltd
Shenyang Bio Medical Device Co., Ltd
Shenyang He's Pharmaceutical Co., Ltd
Shenyang Silver Sea Medical Products Co., Ltd

Public Eye Care
Blindness Prevention and Treatment
Eye Museum
Children Myopia Prevention and Treatment Base
Culture Regimen Park for Senior Citizen

Eye Care for All
He Shi Eye Care: 1200 employees

Screening program Province of Liaoning: 24 million people.

Project partners:
BMIE
TU/e
He Shi
Maastricht University
i-Optics

Dedicated He University for Ophthalmology, Shenyang
He Eye Hospitals

Fundus image acquisitions:

He Eye Hospital Shenyang
+ 10 He Eye Hospitals in Liaoning
+ 200 Health Centers
+ Rural by bus
Large-scale screening in Liaoning

He Eye Hospitals, Health Centers, rural areas by bus.

Central ‘cockpit’ with storage and Computer-Aided Diagnosis software.
Neusoft Medical Systems, Shenyang

Largest Medical Imaging company in China (> 20,000 employees)

- CT, MRI, PET, US, ICT
- Hospital Information Systems
- Picture Archiving and Communication Systems (PACS)

The RetinaCheck project will install Neusoft’s cloud-based PACS solution.
The official track

Prof. He and prof. Romeny reporting at the Sino-Dutch Science Seminar, 24-03-2014 Beijing
The official track

Signing the NWO-He collaboration agreement, Beijing with Minister Bussemakers 24-03-2014

Prof. Romeny discussing the RetinaCheck project with Minister Schippers, NL ambassador Jacobi, and i-Optics CEO Cammeraat
International team:
- TU/e
- BMIE
- i-Optics
- He Eye Care
- Maastricht University Eye Clinic
- Shengjing Hospital

Four phases:
1. Algorithms and infrastructure
2. Validation
3. Screening
4. Exploitation
Software

- Most complete design language
- Very rapid development
- Notebooks are tutorial, reusable documents, easy sharing
- Full use of Manipulate, CDF interactivity, Image* functions
- Successful choice for design with PhD and MSc students
- RetinaCheck package integrates all functions
- CUDA link for fast massively parallel GPU implementations
Vessel tracking - closely parallel
The arterial-venous ratio

- On diabetic fundus images, arteries are constricted and veins are dilated, which makes the A-V ratio become a remarkable feature for disease detection.

A dilated vein on diabetic retina.
The Arterial-Venous Ratio

- "Due to the different bluegreen-light-absorption ability between oxy-

In the green channel, arteries and veins have different brightness.


Red
Micro-bleeds are among the earliest signs of leaking bloodvessels in diabetic retinopathy.

Behdad Dasht Bozorg, Jiong Zhang, TU/e
Fully automatic micro-anerysm detection

Weighting pixels based on gradient in different orientations and scales

MBs appear as doughnut shapes

Candidate selection (successive thresholding)

Removing candidates inside OD and the bright ones

Selecting the ones with high ARF response
Micro-aneurysm detection: validation and annotation tool

Validation:
Annotation by experts is compared with automatic detection.

Gao Han, BMIE
B.M. ter Haar Romenij, “Learning color receptive fields and color differential structure”. Accepted at IEEE 11th International Conference on Natural Computation (ICNC’15), Dayong, China.
Micro-aneurysm enhancement by vessel removal

Vessels are segmented as elongated structures by orientation scores.

Vessels are removed by inpainting.

ter Haar Romeny, 2015
Image deblurring with progressive blind deconvolution

Nerve patterns now visible

Rana Hanocka,
Tel Aviv University 2015
Optic disk detection
100% success with multi-orientation filters

Method

Variance
Homogeneity

Our method

Success rate

100%
96%
100%

Our method

Scanning Laser Ophthalmoscope
EasyScan (Green channel)

Variance (Automatic), 0.8086462 sec.
Homogeneity (Automatic), 3.855349 sec.
Variance (Fast), 0.3420196 sec.
Homogeneity (Fast), 3.9512350 Sec.

Method

Variance
Homogeneity

Our method

Success rate

38%
100%
28%
Comparison of 6 fundus cameras

- 3Nethra
- Canon CR1
- i-Optics EasyScan
- Nidek AFC 230
- Spectralis HRA OCT
- Topcon
Some patients have cataract (milky lens).

Fully automatic rejection of images if the quality is not sufficient.

Jinghan Feng, TU/e
Wang Cuicui, BMIE
Image entrance quality check

Pattern recognition: calculation of 25 image features + cluster analysis

Black cluster: good quality

Jinghan Feng, TU/e BMIE 2014
Fractal dimension (vessel coverage)

Box dimension
Information dimension
Correlation dimension

\[ \ln[35] = \{ \text{boxDims}, \text{informDims}, \text{corrDims} \} \]

\[ \text{Out}[35] = \{1.46697, 1.51049, 1.51814\} \]
Brain-inspired: Multi-orientation image analysis

- Higher mammals can identify objects in varied orientations.
- This is achieved by simple cells in the primary visual cortex.

1981: Nobel prize in Physiology or Medicine

David Huvel
Torsten Wiesel

Voltage sensitive dye optical imaging of tree shrew cortex
Brain-inspired: Multi-orientation image analysis

Optical dye response at different orientations (monkey V1)

Orientation sensitive cells are organized in a pin-wheel fashion

Cortical column
Brain-inspired: Multi-orientation image analysis

Pinwheel centers are extremely well organized

Calcium fluorescence microscopy

Kenichi Ohki et al., Fukuoka, Japan
Connections exist between similar orientations to far away columns - context

Alexander & van Leeuwen, 2010

Fitzpatrick, Duke University, Nature 2002
Multi-orientation image analysis

For Fourier Transform / Inverse Fourier Transform:
- Sin / Cos
- Orientation Space 2D: New wavelet family
- Orientation Space 3D: Mathieu functions

Exactly invertible orientation transform:

\[
\Phi_n(z, \sigma) = a_n (-\sigma \bar{\sigma})^n e^{-\frac{z^2}{2\sigma^2}},
\]

\[
\Phi_{-n}(z, \sigma) = \bar{a}_n (-\sigma \bar{\sigma})^n e^{-\frac{z^2}{2\sigma^2}}; n \geq 0
\]
Fast implementations on GPU (CUDA)

Graphical Processing Unit (GPU): game computer

Massively parallel, thousands of cores

Song Liang, BMIE
Image background normalization

Removal of inhomogeneous lighting

Samaneh Abbasi, TU/e BMIA, 2015
SLO (scanning laser) image denoising

Nonlinear orientation score transform

Samaneh Abbasi, TU/e BMIA, 2015
Detection of crossings and bifurcations

Rotating filter:
- 3 maxima = bifurcation (yellow)
- 4 maxima = crossing (red)
Quantitative vessel tortuosity (curvature)

Healthy

Diabetic retinopathy
Quantitative vessel tortuosity (curvature)

Based on 1200 images (Messidor)

E. Bekkers, J. Zhang, R. Duits, B. ter Haar Romeny, TU/e BMIA 2015
Angiogenesis (new blood vessel growth)

Detection of curly new vessels with tortuosity

Li Bo, BMIE
Feature selection

- In total, we have extracted 17 retina features from 338 clinical images which includes 220 healthy images and 118 diabetic images (the Maastricht Study).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Health (Mean ± SD)</th>
<th>Diabetes (Mean ± SD)</th>
<th>Feature</th>
<th>Health (Mean ± SD)</th>
<th>Diabetes (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FD</td>
<td>1.58 ± 0.04</td>
<td>1.58 ± 0.03</td>
<td>CRAE-B</td>
<td>154.73 ± 15.63</td>
<td>156.90 ± 12.92</td>
</tr>
<tr>
<td>MTA</td>
<td>0.62 ± 0.18</td>
<td>0.64 ± 0.17</td>
<td>CRAE-C</td>
<td>152.32 ± 15.20</td>
<td>154.36 ± 12.80</td>
</tr>
<tr>
<td>SDTA</td>
<td>0.19 ± 0.10</td>
<td>0.20 ± 0.11</td>
<td>CRVE-B</td>
<td>220.71 ± 20.25</td>
<td>224.22 ± 20.21</td>
</tr>
<tr>
<td>MTV</td>
<td>0.59 ± 0.16</td>
<td>0.61 ± 0.17</td>
<td>CRVE-C</td>
<td>152.32 ± 15.20</td>
<td>154.36 ± 12.80</td>
</tr>
<tr>
<td>SDTV</td>
<td>0.16 ± 0.08</td>
<td>0.17 ± 0.09</td>
<td>AVR-B</td>
<td>0.70 ± 0.06</td>
<td>0.70 ± 0.05</td>
</tr>
<tr>
<td>MTSA</td>
<td>0.83 ± 0.10</td>
<td>0.87 ± 0.25</td>
<td>AVR-C</td>
<td>0.70 ± 0.06</td>
<td>0.70 ± 0.05</td>
</tr>
<tr>
<td>SDTSV</td>
<td>0.23 ± 0.11</td>
<td>0.25 ± 0.13</td>
<td>OptiM</td>
<td>0.68 ± 0.10</td>
<td>0.66 ± 0.09</td>
</tr>
<tr>
<td>MTV</td>
<td>0.80 ± 0.20</td>
<td>0.87 ± 0.25</td>
<td>OptiSD</td>
<td>0.24 ± 0.08</td>
<td>0.20 ± 0.07</td>
</tr>
<tr>
<td>SDTSV</td>
<td>0.20 ± 0.09</td>
<td>0.22 ± 0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rank | feature  
84% |
--- | ---
1  | MTSV
2  | SDTSV
3  | MTSA
4  | MTV
5  | MTA
6  | FD
7  | AVR-C
8  | SDTSV
9  | OptiSD
10 | CRAE-C
11 | AVR-B
12 | SDTA
13 | CRVE-B
14 | SDTV
15 | CRAE-B
16 | CRVE-C
17 | OptiM

Classifiers:
- Support vector machines
- Random Forests
- Learning Vector Quantization
- Neural Networks
- and several others

Huang Fan, MSc

Big Data
RetinaCheck Workstation

Design:
Behdad Dasht Bozorg, TU/e
Kaggle Challenge 2015

Completed • $100,000 • 661 teams

Diabetic Retinopathy Detection

Tue 17 Feb 2015 – Mon 27 Jul 2015 (2 months ago)

Processing of 90,000 retina images.
Classifications in R0, R1, R2, R3 group.
By: Mitko Veta & Behdad Dasht Bozorg.

RetinaCheck arrived at an honorable 17th position (in the top 2.6%).
Validation study at Shengjing Hospital

Validation:
- Which biomarkers are effective?
- Compare different diabetic groups and normals
- Record a large number of metadata:
  - Blood values
  - Urine values
  - Disease duration
  - Medicine use
  - Lifestyle data

Fundus image acquisitions:

Shengjing Hospital, Shenyang Diabetes Department, prof. Han Ping
10-30 patients / day

Fall 2015: 2000 patients scanned
Preparation clinical collaboration

Lectures and discussions at Shengjing Diabetes Department
Preparation clinical collaboration

dr. Li Li, Clinic Head Shengjing
prof. Han Ping, Dept. Head Shengjing
dr. Tos Berendschot, Maastricht Study
prof. Bart Romeny, RetinaCheck
prof. Guo Fan, Head Ophthalmology
Msc Mengmeng Tong, PhD TU/e
The Maastricht Study - Netherlands

The Maastricht Study is the world’s biggest phenotyping study to find relations in diabetes.

- 5000 diabetes patients, 5000 normals
- 30 million euro, 10 years
- dedicated building
  - MRI scans, bone density, kidney US
  - Blood, urine, lifestyle etc.
  - Ophthalmology examinations
- Project leader: dr. Tos Berendschot

With Shengjing Hospital we prepare a Chinese variant of the Maastricht study for Chinese diabetes patients: the “Shengjing Study”.

Workshop planning, Fall 2015
Travel grant requested NWO
The Shengjing Study - China

Dedicated room for RetinaCheck in center Diabetes Dept. Shengjing Hospital

So far:

2450 patients done
- retina images
  - left/right
  - disk/fovea
- full diabetic metadata
Neusoft Cloud PACS
DICOM format

- Big servers at Shengjing and He Shi
- NAS 5 TB
- Patient data security

Statistical data analysis metadata: Wu Huanhui, Tong Mengmeng, Mieke van Triest
Server programming at Shengjing: Tom Lamers
Neusoft Medical Systems: Cloud PACS: prof. Yan Kang
European Diabetes Foundation, EU-CN ‘Lilly’ program, 2013-2014

Partners: TU/e, BMIE, He Shi, Maastricht Eye Clinic
NL+CN: 90.000 € (= 630.000 ¥)
2 SLO laser cameras, 2 postdocs Shenyang, 2 compute servers

NWO-He China-Netherlands Collaboration program 2014-2017

Partners: TU/e + NEU, i-Optics + He Shi
Government matches industrial contribution
NL: 250 K€ + 80 K€ (i-Optics) + 315 K€ = 645.000 € (= 4.515.000 ¥)
CN: 1.800.000 ¥ (He Shi) + 1.800.000 ¥ (900.000 ¥ for NEU)

Chinese Scholarship Council, European Union Marie Curie


Jinghan Feng, Tos Berendschot and Bart M. ter Haar Romeny, *Quality classification of retinal fundus images by image structure clusters and random forests*. Submitted to ICAIP 2015, 18th Int. Conf. on Image Analysis and Processing, Geneva, Italy, 9-11 Sep 2015.


Strong focus: Vision and Brain

一站式视网膜数据采集

One-Stop-Shop retina

Early detection

Fundamental life science, cause of diabetes

更好的治疗和理解大脑

Better treatment, understand the brain

眼科磁共振成像

MRI

Cardio-vascular diseases

心血管疾病

f MRI

功能性磁共振成像

Reduce healthcare costs - 降低医疗成本

自适应光学

Adaptive Optics

心血管疾病

 Early detection

心血管疾病

Basic life science, cause of diabetes

更好的治疗和理解大脑

Better treatment, understand the brain
Opening of the Sino-Euro Vision & Brain Institute
6 November 2013, Shenyang

Sino-Euro Vision & Brain Institute
Zeng Wei (曾维), Party Secretary Province of Liaoning
Prof. He Wei, He University / He Shi Eye Care
Prof. Kang Yan, Northeastern University
Prof. Bart Romeny, TU/e - NEU
Vision and Brain  视觉和脑

MRI of Vision Lab - MRI  视觉实验室

Study of cerebral causes of blindness

Micro-bleeds in the brain (Haacke, Wayne State University 2013)

Optic tract visualization (TU/e 2013)

视神经纤维可视化 (TU/e 2013)

Micro-bleeds in the retina (RetinaCheck)

相关性研究
心血管
Collaborations

Chinese Academy of Sciences Beijing
Eindhoven University of Technology
Haacke MRI Imaging Center
Philips Healthcare / Siemens Healthcare
Maastricht University Eye Clinic
European Diabetes Foundation
Brainnetome, CAS Beijing
Kempenhaeghe Epilepsy Institute NL

合 作：
中国科学院
埃因霍温科技大学
Haacke MRI成像中心
飞利浦医疗 / 西门子医疗
马斯特里赫特大学眼科医院
欧洲糖尿病基金会
Brainnetome
Kempenhaeghe
Collaborations

Prof. Mark Haacke
Detroit, USA
Inventor SWI

Collaboration Brainnetome:
Prof. Tianzi Jiang,
Academy of Sciences, Beijing

Xiangshan Meeting, Beijing 2011
Qi Shouliang, PhD

MRI research at Kempenhaeghe, Netherlands, Aug 2014 - Aug 2015

Grant: Chinese Scholarship Council

Brain networks

The influence of construction methodology on structural brain network measures: a review

Shouliang Qi\textsuperscript{1,3,4}, Stephan Meesters\textsuperscript{2,3}, Klaas Nicolay\textsuperscript{4}, Bart M. ter Haar Romeny\textsuperscript{1,4}, Pauly Ossenblok\textsuperscript{3,4}

\textsuperscript{1}Sino-Dutch Biomedical and Information Engineering School, Northeastern University, Shenyang, China
\textsuperscript{2}Department of Mathematics & Computer Science, Eindhoven University of Technology, Eindhoven, the Netherlands
\textsuperscript{3}Academic Center for Epileptology Kempenhaeghe & Maastricht UMC+, Heeze, the Netherlands
\textsuperscript{4}Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands

Abstract: Structural brain networks based on diffusion MRI and tractography show robust attributes such as small-worldness, hierarchical modularity, and rich-club organization. However, there are large discrepancies in the reports about specific network measures between different studies, which may be due to different construction methodologies. In this review, we will discuss some of the methodologies used and their potential influences on the network measures.
Summer Schools at BMIE 2010-2015

NEU Shenyang:

International Summer School on Biomedical Image Analysis
“The Visual Brain”


Prof. Tianzi Jiang
(Chinese Acad. of Sciences)

Prof. Wei He
(He Shi Eye Care)
Brain-inspired Computer Vision

The last decade has seen an exponential growth of effective computer vision systems in many sectors, such as medical imaging, smart phones and tablets, smart car applications, robotics, satellite imaging, industrial visual inspection and navigation systems.

Computer Vision is the field where images are analyzed by computer, for many purposes, such as recognition, segmentation, enhancement, registration, and quantitative analysis. Medical computer-aided diagnosis systems are developed for a wide range of diseases, in particular for high-volume screening purposes.

Computer-aided diagnosis in medical imaging is not only needed due to the staggering amount of images produced today, but also requires sophisticated and innovative algorithms. The human brain typically still outperforms most of the state-of-the-art algorithms of today. Even while using only 25 watts, and working at low frequencies, it can recognize objects in the scene almost instantly, analyze the contents of very complex scenes effortlessly, and is able to efficiently learn from previous experiences. How can we learn, how to do the bio-mimicking?

The spirit of this one-week Summer School is inspired by the visual brain: one of the most important brain research topic of today. We aim to design powerful image analysis tools and algorithms from inspired by the biology and structure of the brain. We study and discuss in-depth the anatomy, mechanisms and mathematical models of visual perception, and build powerful, modern and innovative applications for computer-aided diagnosis and computer vision. Vision for Vision.

The speakers are well-known researchers in the field of brain-inspired computing:

Prof. Bert ter Haar Romeny
Northeastern University, Shenyang
Eindhoven University, Netherlands

Dr. George Azzopardi
Malta University, Malta
Groningen University, Netherlands

Topics include:
Computer Vision (for robotics, smart car imaging, industrial inspection, navigation maps)
Computer-Aided Diagnosis (retinal image analysis, cancer detection, microscopy, diabetes)
Welcoming banquet, offered by President Xi Jinping and Mrs. Peng Liyuan, to King Willem Alexander and Queen Maxima, 26 Oct. 2015, Beijing
Challenges

Algorithm design → Validation

- Curvature
- AV Ratio
- Micro-aneurysms
- etc.

Rolling out in Chinese hospitals

- ICT infrastructure
- Training
- Workflow

Statistical analysis

- Screening + prediction

Buffalo NeuroImaging Center, NY
Prevention of blindness

Thanks to all hard working members of the RetinaCheck team!
RetinaCheck.org

Screening for Diabetes Detection and Blindness Prevention in China