

Technologies for Digital Life - Radisson Blu Royal Hotel, Bryggen, Bergen, 21.10 2016, 14:00-14:15

<https://www.ntnu.no/dln/technologies-for-digital-life>

In vivo imaging and image analysis

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<http://github.com/arvidl/computational-medicine>

Technologies for Digital Life

- The Centre for Digital Life Norway (DLN) aims to drive the development of a new branch of Norwegian biotechnological research and innovation, by mixing life scientists, mathematicians, statisticians, computer scientists and engineers.
- This will be a key ingredient to scale up the success of **generating predictive models** of biological systems – by using many different types of technologies and methodologies.
- How can we best integrate different technologies and methodologies in **transdisciplinary research** projects?
- Are we equipped for this type of research?

How does “In vivo imaging & image analysis” fit in ?

+ live imaging acquisition

+ image-based modelling

CONCEPTS

TRENDS

INFRASTRUCTURE

SOLUTIONS

Predictive models of biological systems

- Development and use of algorithms, data structures, visualization and communication tools with the goal of computer **modelling** of biological systems.
Includes stochastic and deterministic computer **simulations** and **machine learning** from biological measurements: -omics, images ... Has a **broad mathematical foundation**.
- When deployed commercially, predictive modelling is often referred to as **predictive analytics** (extracting information from data and using it to predict trends and system behavior patterns)
Wikipedia

Transdisciplinary research = team science

- In a transdisciplinary research endeavor, scientists **contribute their unique expertise** but **work outside their own discipline**.
- Strive to **understand the complexities of the whole project**, rather than one part of it.
- Allows investigators to **transcend their own disciplines** to inform one another's work, capture complexity, and **create new intellectual spaces**.



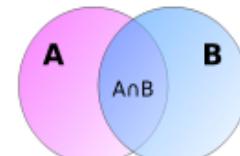
WIKIPEDIA
The Free Encyclopedia

Mathematics is the body of knowledge centered on concepts such as **quantity, structure, space, and change**, and the academic discipline which studies them ...

CONCEPTS

FOUNDATIONS

$$P \Rightarrow Q$$



Mathematical logic

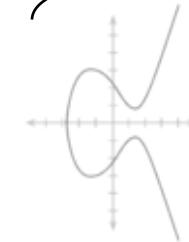
$$\begin{array}{ccc} X & \xrightarrow{f} & Y \\ & \searrow g \circ f & \downarrow g \\ & & Z \end{array}$$

Set theory

Category theory

... being instrumental in **predictive models** of biological systems and “**Digital Life**”

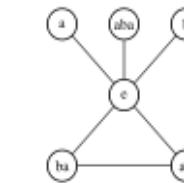
STRUCTURE



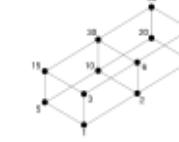
Number theory



Abstract algebra

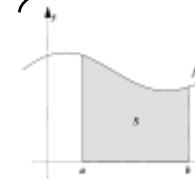


Group theory

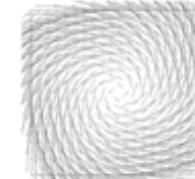


Order theory

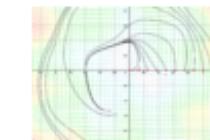
CHANGE



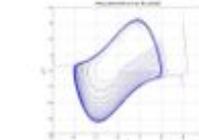
Calculus



Vector calculus



ODEs/PDEs/SDEs

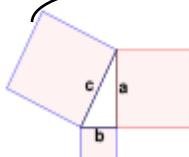


Dynamical systems

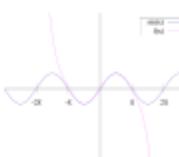


Chaos theory

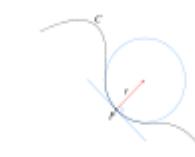
SPACE



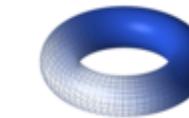
Geometry



Trigonometry



Differential geometry



Topology

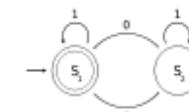


Fractal geometry

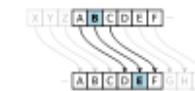
DISCRETE MATHEMATICS

$$\begin{array}{ll} (1, 2, 3) & (1, 3, 2) \\ (2, 1, 3) & (2, 3, 1) \\ (3, 1, 2) & (3, 2, 1) \end{array}$$

Combinatorics



Theory of computation

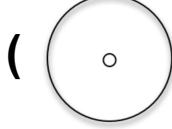


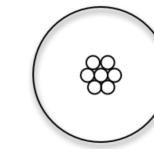
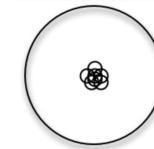
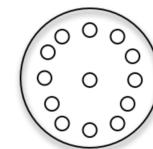
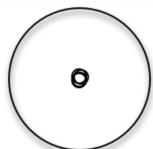
Cryptography



Graph theory

What is the difference?

( Intradisciplinary)

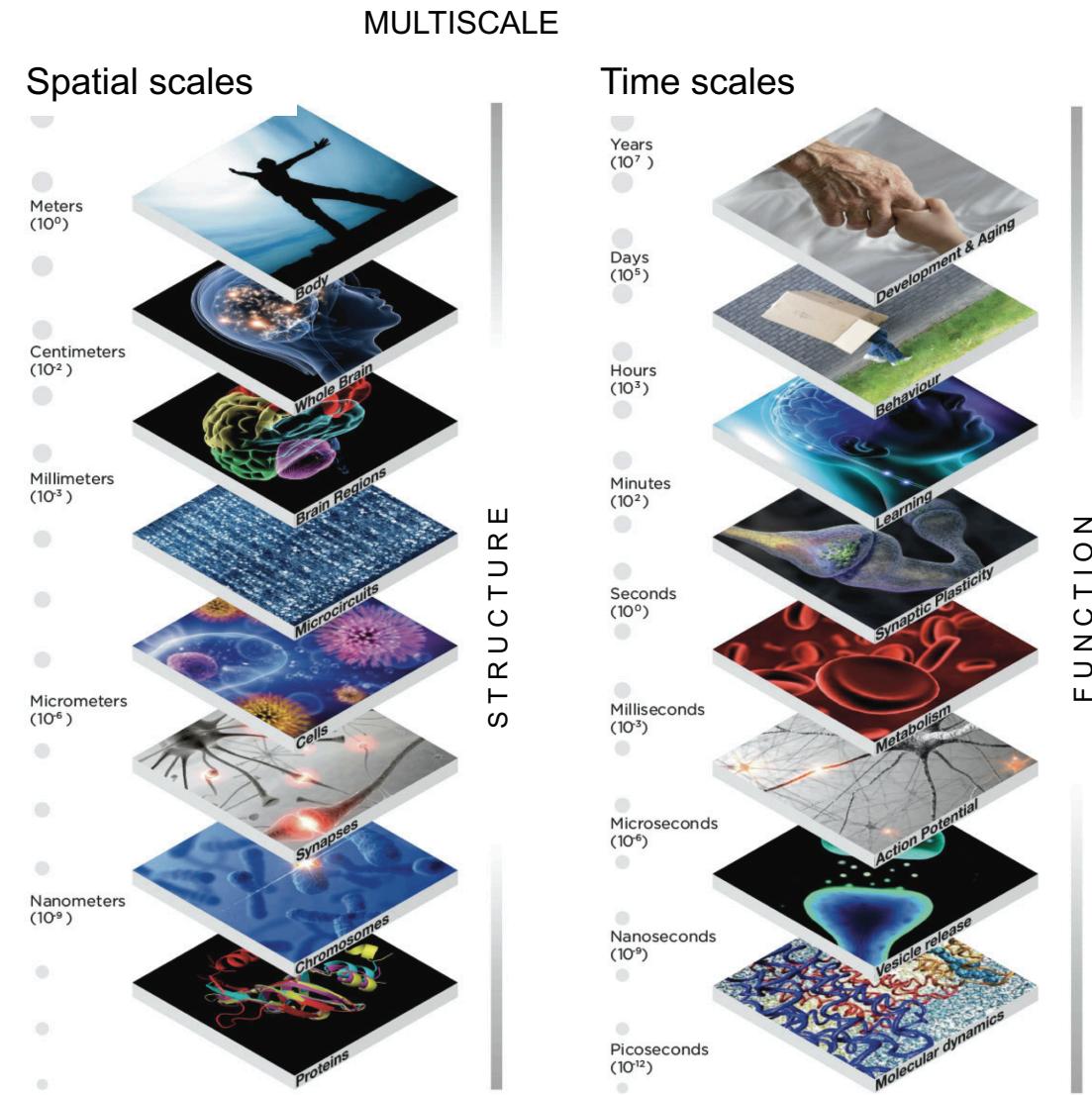
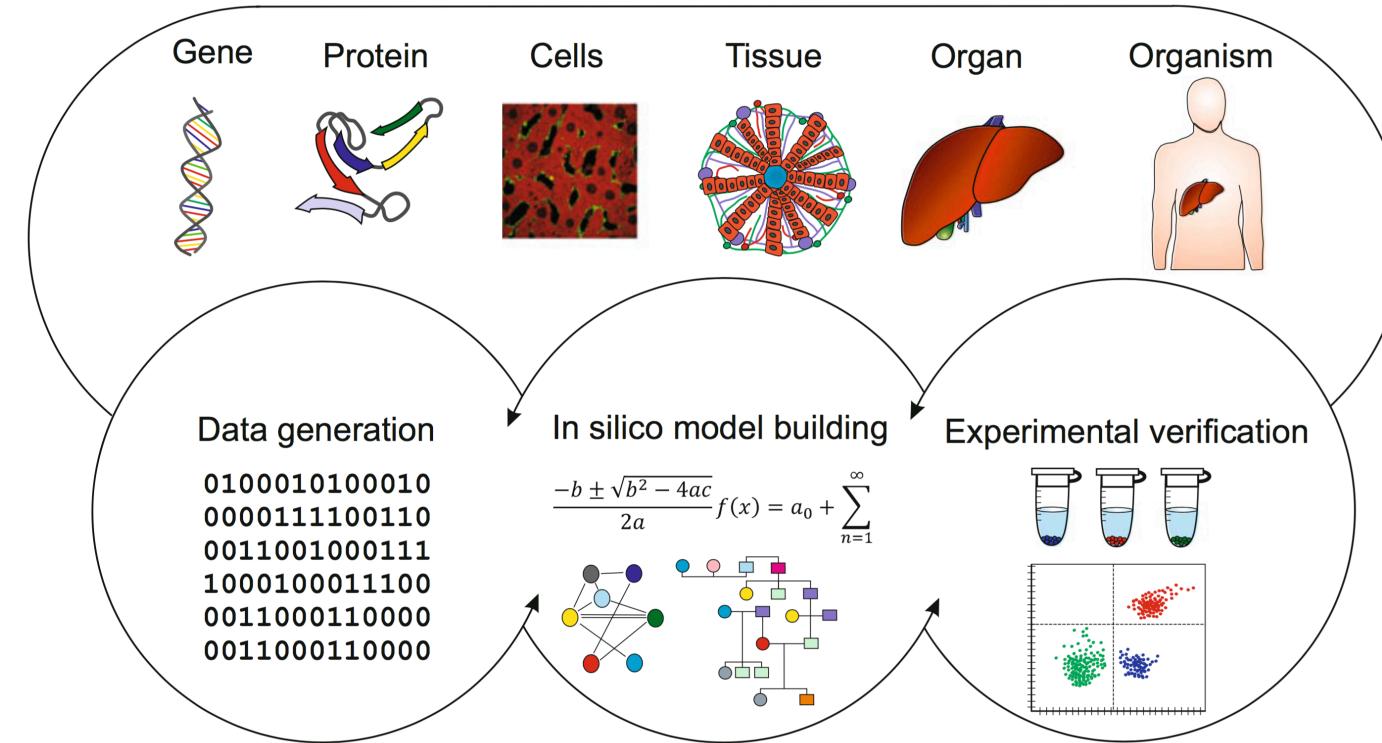


- Transdisciplinary
- Multidisciplinary
- Interdisciplinary
- Crossdisciplinary

research

Transdisciplinary Research	Multidisciplinary Research	Interdisciplinary Research	Crossdisciplinary Research
<p>Collaboration in which exchanging information, altering discipline-specific approaches, sharing resources and integrating disciplines achieves a <u>common scientific goal</u></p> <p>e.g. pharmacokinetic modeling from DCE-MRI measurements for assessment of tumor physiology</p>	<p>Researchers from a variety of disciplines work together at some point during a project, but have separate questions, separate conclusions, and disseminate in different journals.</p> <p>e.g. image co-registration and segmentation</p>	<p>Researchers interact with the goal of transferring knowledge from one discipline to another. Allows researchers to <u>inform each other's work</u> and compare individual findings.</p> <p>e.g. multimodal validation of automated image segmentation</p>	<p>Researchers are <u>viewing one discipline from the perspective of another</u>.</p> <p>e.g. Digital Life in transition to transdisciplinary research ?</p>

Systems biology & medicine and computational imaging



Computational Medicine

It will soon be common for clinical research studies to:

- Collect genetic, transcriptional, proteomic, imaging and clinical data from every patient in large, carefully selected cohorts sharing a specific disease diagnosis.

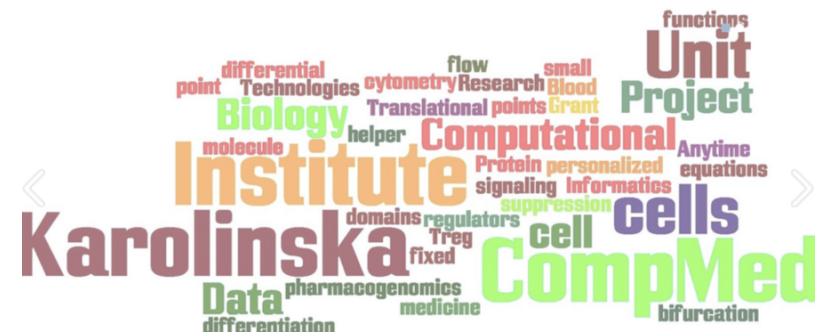
The screenshot shows the homepage of the Johns Hopkins Institute for Computational Medicine (ICM). At the top left is the ICM logo, which consists of a stylized blue 'J' and 'H' intertwined. To the right of the logo is the text 'INSTITUTE for COMPUTATIONAL MEDICINE'. Below this, a paragraph describes the mission: 'Johns Hopkins Institute for Computational Medicine (ICM), a remarkable collaboration between Johns Hopkins School of Medicine and Whiting School of Engineering, is using powerful computational tools to transform the practice of medicine.' A blue button labeled 'More about our mission' is located below the text. At the bottom of the page is a navigation bar with links: 'About ICM', 'People', 'Research Thrusts', 'Portals', 'Seminars', 'Publications', 'Education', and 'Community'. On the right side of the page, there are three circular inset images showing complex, multi-colored 3D data visualizations, likely representing medical or computational models.

Johns Hopkins University

- The challenge of the coming decade will be
 - how best to use these *multi-scale* biomedical data
 - to gain a *quantitative understanding* of disease mechanisms
 - across *hierarchical levels* of biological organization
 - to identify *biological markers* which correlate with different disease states
 - and inter-individual differences in *disease risk*
- Discover more effective *therapeutics targeted to the individual*

<http://www.icm.jhu.edu>

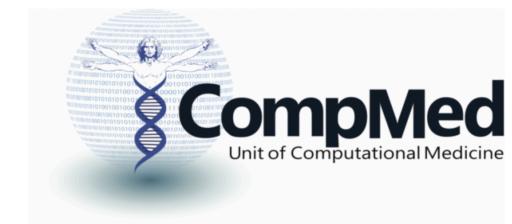
Unit of Computational Medicine - Karolinska Institutet



Uniquely integrated multidisciplinary team of more than 30 scientists from

- pure and applied mathematics
- immunology
- physics
- midwifery
- complexity theory
- cell and molecular biology
- computer science
- pharmacology
- engineering
- medicine

- develop and apply integrative *computational-experimental approaches*
- provide fundamental insights of *life beyond physics*
- enable prediction, prevention and treatment of *diseases*



<http://www.compmed.se>

Data analytics - Machine learning

IEEE TRANSACTIONS ON MEDICAL IMAGING

A PUBLICATION OF
THE IEEE ENGINEERING IN MEDICINE AND BIOLOGY SOCIETY
THE IEEE NUCLEAR AND PLASMA SCIENCES SOCIETY
THE IEEE SIGNAL PROCESSING SOCIETY
THE IEEE ULTRASONICS, FERROELECTRICS, AND FREQUENCY CONTROL SOCIETY

MAY 2016

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Deep learning is a growing trend in general data analysis and has been termed one of the 10 breakthrough technologies of 2013 [1]. Deep learning is an improvement of artificial neural networks, consisting of more layers that permit higher levels of abstraction and improved predictions from data [2]. To date, it is emerging as the leading machine-learning tool in the general imaging and computer vision domains.

SPECIAL ISSUE ON DEEP LEARNING IN MEDICAL IMAGING

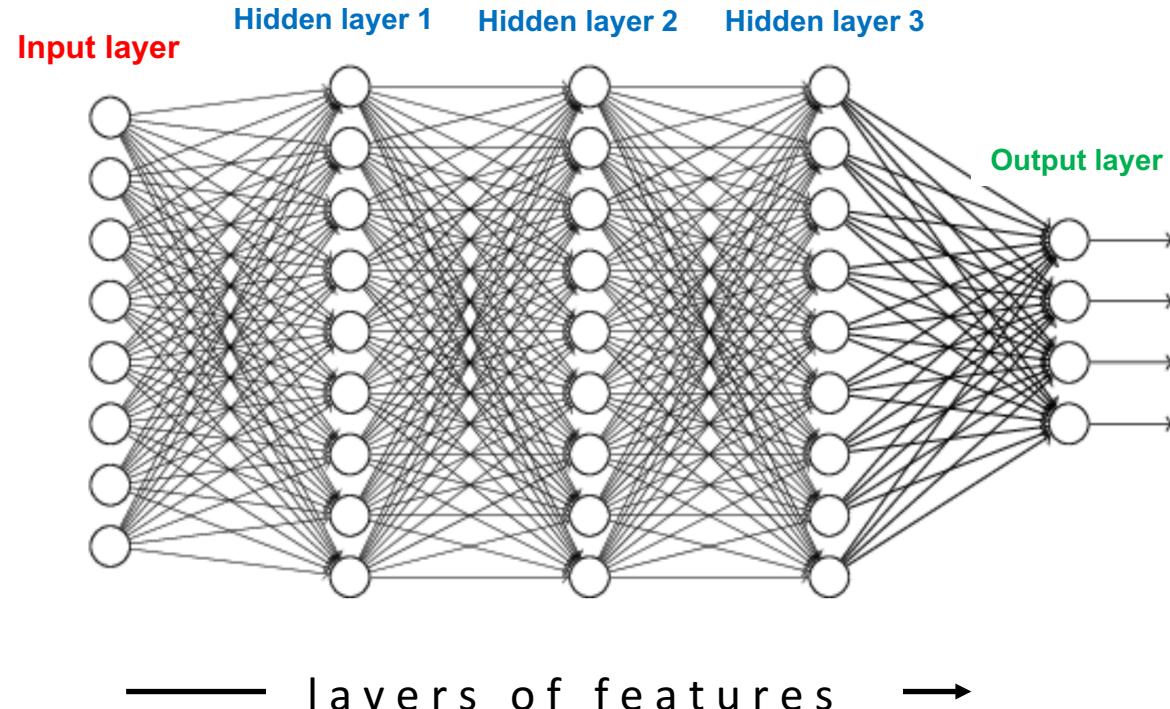
GUEST EDITORIAL

- Deep Learning in Medical Imaging: Overview and Future Promise of an Exciting New Technique *H. Greenspan, B. van Ginneken, and R. M. Summers* 1153

SPECIAL ISSUE PAPERS

- Pulmonary Nodule Detection in CT Images: False Positive Reduction Using Multi-View Convolutional Networks *A. A. A. Setio, F. Ciompi, G. Litjens, P. Gerke, C. Jacobs, S. J. van Riel, M. M. W. Wille, M. Naqibullah, C. I. Sánchez, and B. van Ginneken* 1160
- Improving Computer-Aided Detection Using Convolutional Neural Networks and Random View Aggregation *H. R. Roth, L. Lu, J. Liu, J. Yao, A. Seff, K. Cherry, L. Kim, and R. M. Summers* 1170
- Automatic Detection of Cerebral Microbleeds From MR Images via 3D Convolutional Neural Networks *Q. Dou, H. Chen, L. Yu, L. Zhao, J. Qin, D. Wang, V. C. Mok, L. Shi, and P.-A. Heng* 1182
- Locality Sensitive Deep Learning for Detection and Classification of Nuclei in Routine Colon Cancer Histology Images .. *K. Sirinukunwattana, S. E. A. Raza, Y.-W. Tsang, D. R. J. Snead, I. A. Cree, and N. M. Rajpoot* 1196
- Lung Pattern Classification for Interstitial Lung Diseases Using a Deep Convolutional Neural Network *M. Anthimopoulos, S. Christodoulidis, L. Ebner, A. Christe, and S. Mougiakakou* 1207
- Marginal Space Deep Learning: Efficient Architecture for Volumetric Image Parsing *F. C. Ghesu, E. Krubasik, B. Georgescu, V. Singh, Y. Zheng, J. Hornegger, and D. Comaniciu* 1217
- Deep 3D Convolutional Encoder Networks With Shortcuts for Multiscale Feature Integration Applied to Multiple Sclerosis Lesion Segmentation *T. Brosch, L. Y. W. Tang, Y. Yoo, D. K. B. Li, A. Traboulsi, and R. Tam* 1229

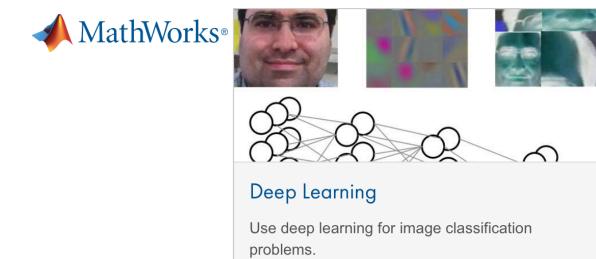
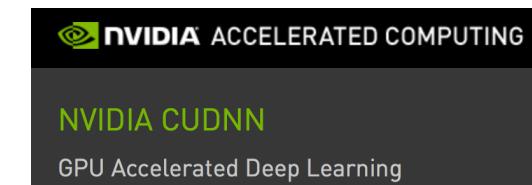
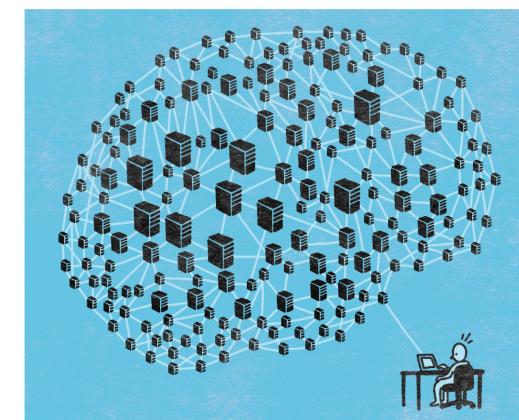
Neural networks - deep learning



Deep learning is a branch of machine **learning** based on a set of algorithms that attempt to model high-level abstractions in data by using multiple processing layers, with complex structures or otherwise, composed of multiple non-linear transformations

Wikipedia

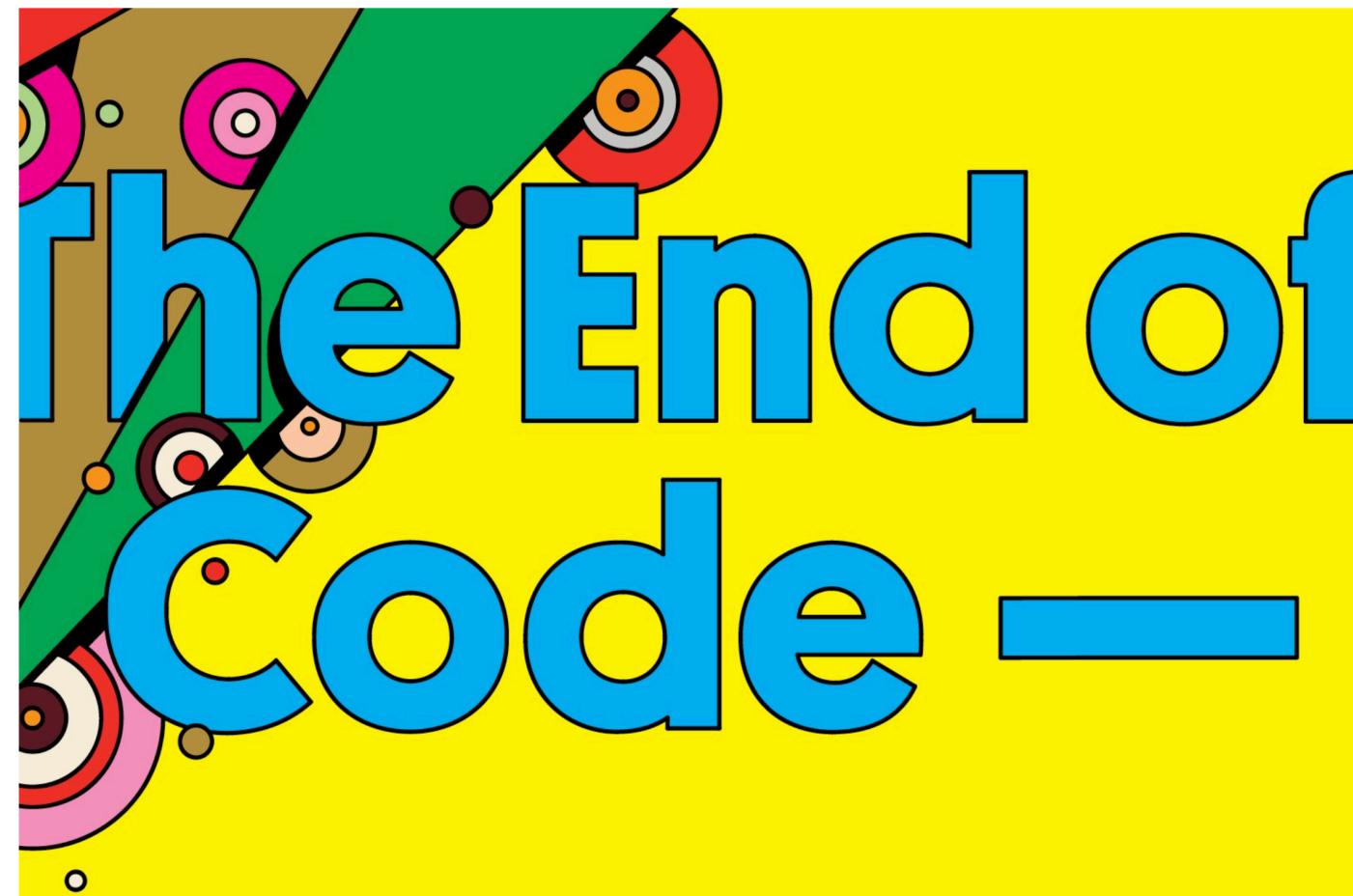
Microsoft releases CNTK, its open source deep learning toolkit, on GitHub



SOON WE WON'T PROGRAM COMPUTERS. WE'LL TRAIN THEM LIKE DOGS

WIRED

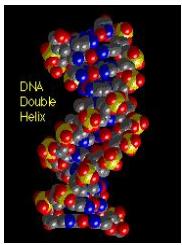
June 2016



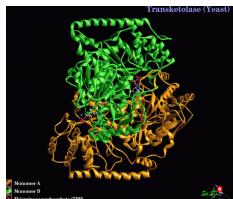
<https://www.wired.com/2016/05/the-end-of-code/>

Imaging infrastructure (in Bergen)

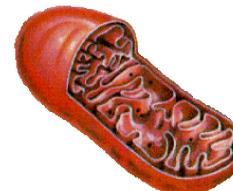
DNA



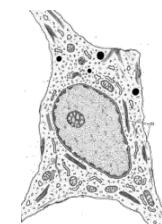
Protein



Organelle



Cell



Microscopy

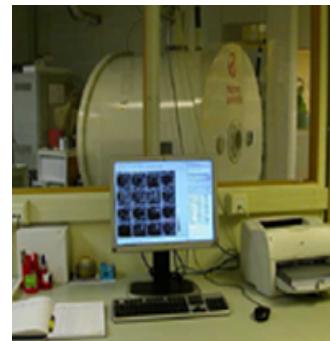
EM



Confocal



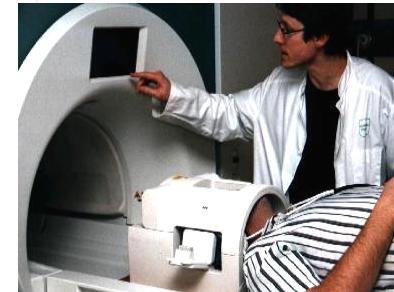
Animal MRI



7 Tesla Bruker Pharmascan

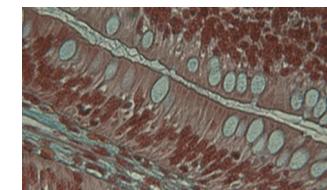
- Superresolution microscopy (STED)
- MRI experts (acquisition + analysis)

Clinical MRI



1 GE + 2 x Siemens 3 Tesla

Tissue

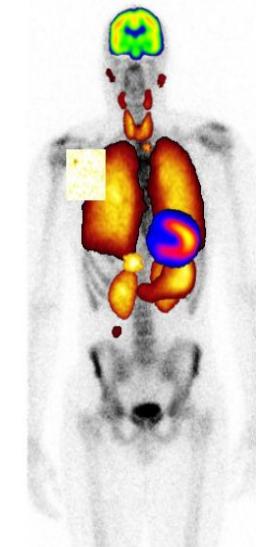


- New visualization center from 2017

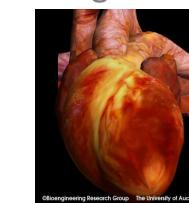
Clinical US



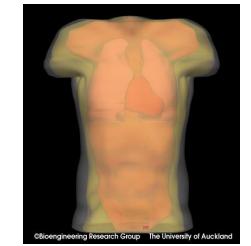
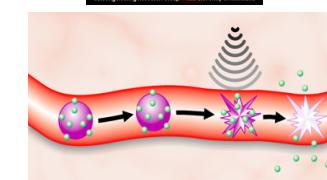
Clinical PET/CT



Organ



Organism

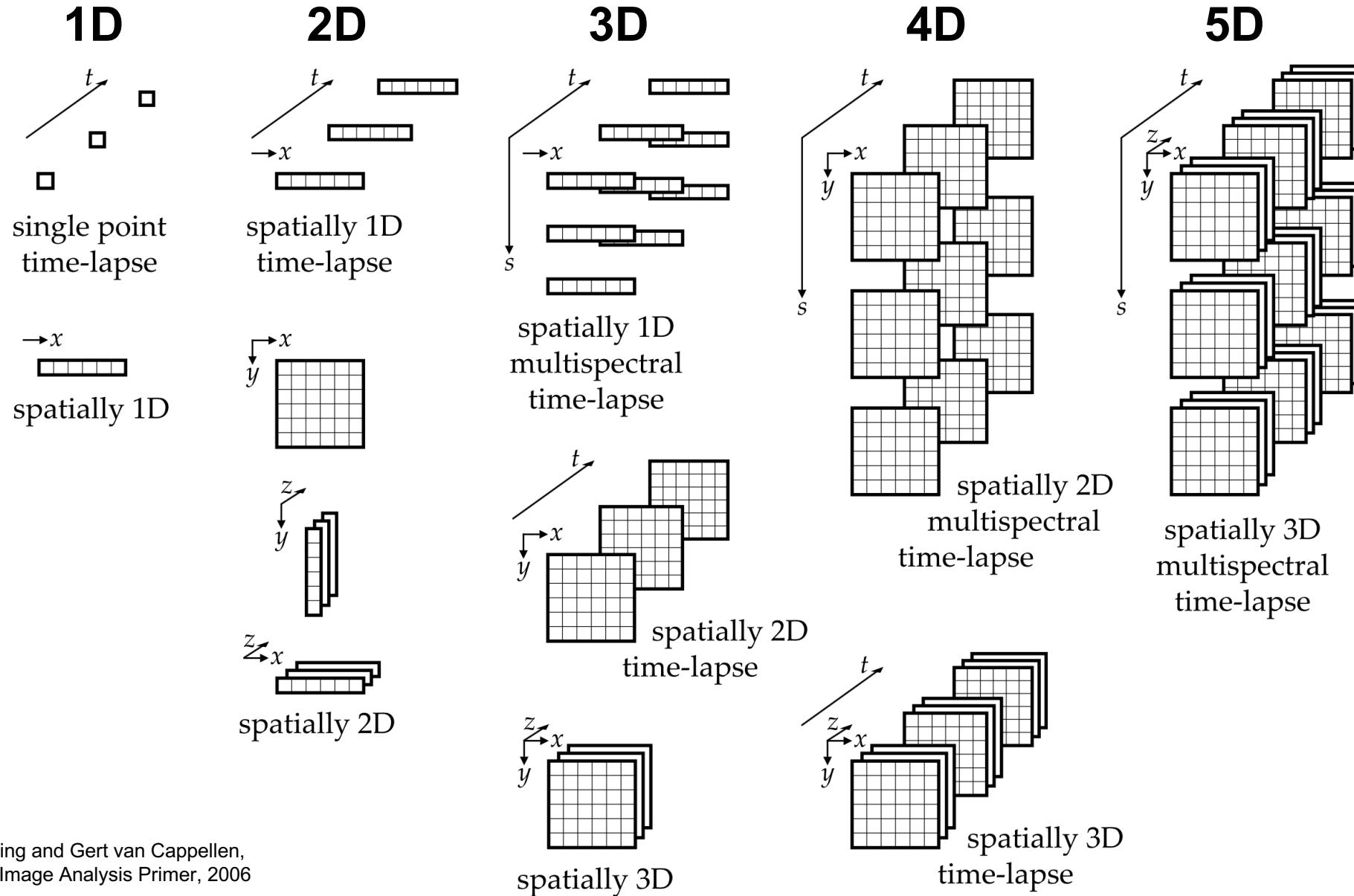


$$\frac{\partial M_x(t)}{\partial t} = \gamma(\mathbf{M}(t) \times \mathbf{B}(t))_x - \frac{M_x(t)}{T_2}$$

$$\frac{\partial M_y(t)}{\partial t} = \gamma(\mathbf{M}(t) \times \mathbf{B}(t))_y - \frac{M_y(t)}{T_2}$$

$$\frac{\partial M_z(t)}{\partial t} = \gamma(\mathbf{M}(t) \times \mathbf{B}(t))_z - \frac{M_z(t) - M_0}{T_1}$$

Images as matrices



From: Erik Meijering and Gert van Cappellen,
Biological Image Analysis Primer, 2006

“Image formation” vs. “Image processing”

Image Formation

object in → image out

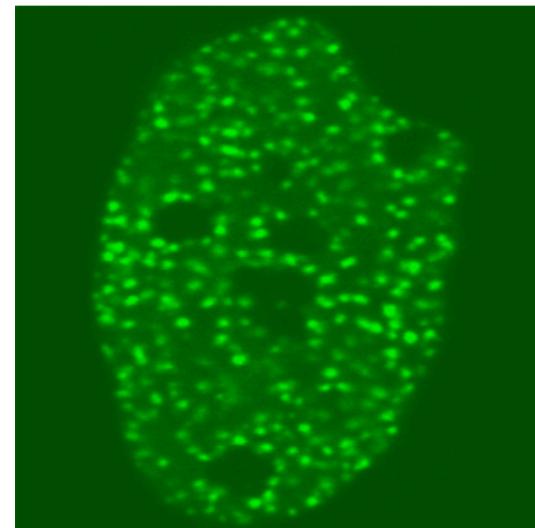
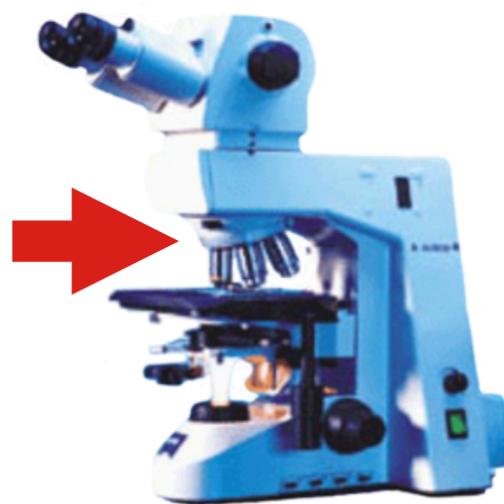
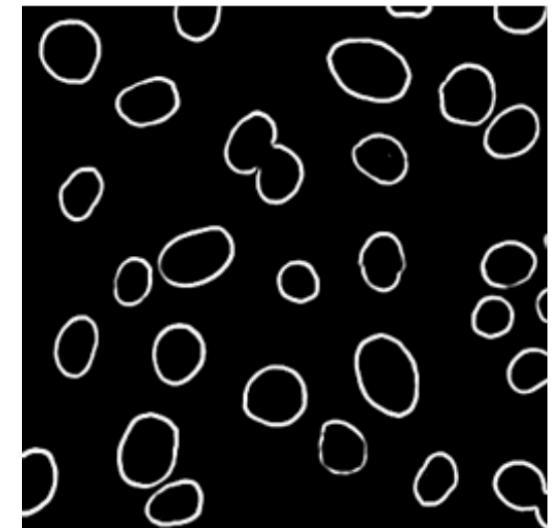
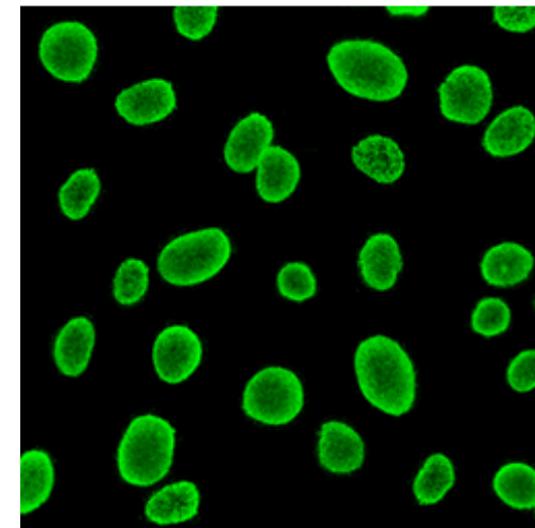


Image Processing

image in → image out

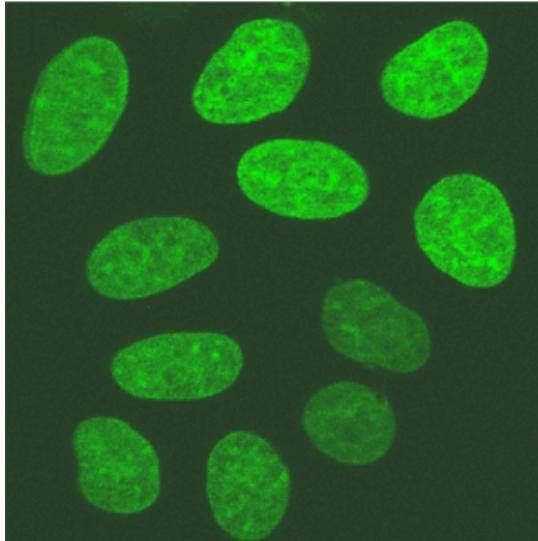


From: Erik Meijering and Gert van Cappellen,
Biological Image Analysis Primer, 2006

“Image analysis” vs. “Computer graphics”

Image Analysis

image in → features out

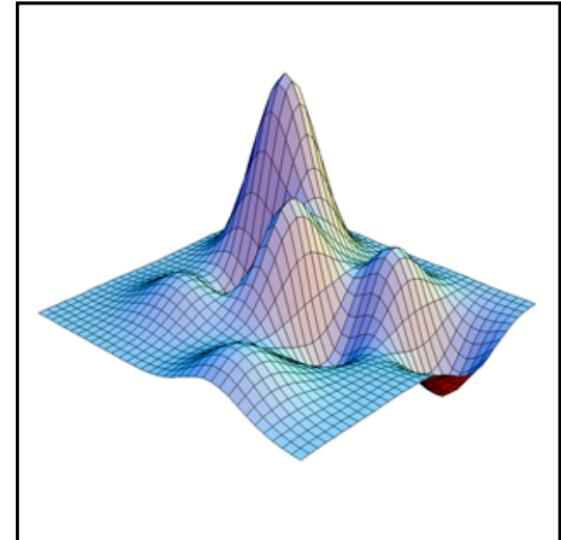


Obj	Area	Perim
1	324.2	98.5
2	406.7	140.3
3	487.1	159.2
4	226.3	67.8
5	531.8	187.6
6	649.5	203.1
7	582.6	196.4
8	498.0	162.9
9	543.2	195.1

Computer Graphics

numbers in → image out

X	Y	I
-3.54	-2.32	0.50
-2.78	-1.90	0.12
-1.15	0.42	3.09
0.45	1.65	5.89
1.83	2.18	7.72
2.98	3.33	2.07
4.21	3.96	-4.58
5.62	4.54	-11.45
7.16	5.02	-3.63

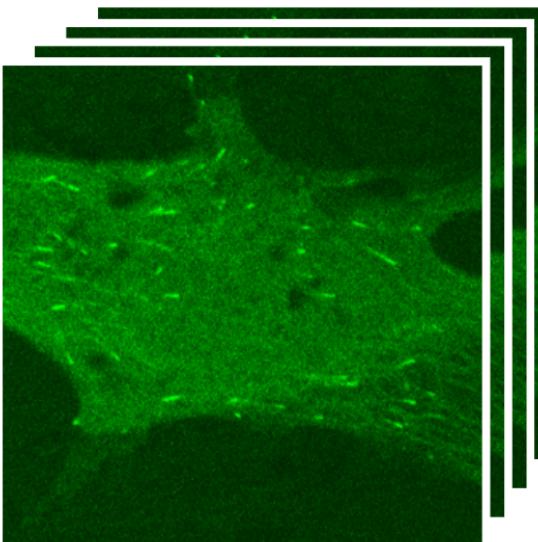


From: Erik Meijering and Gert van Cappellen,
Biological Image Analysis Primer, 2006

“Computer vision” vs. “Visualization”

Computer Vision

image in → interpretation out

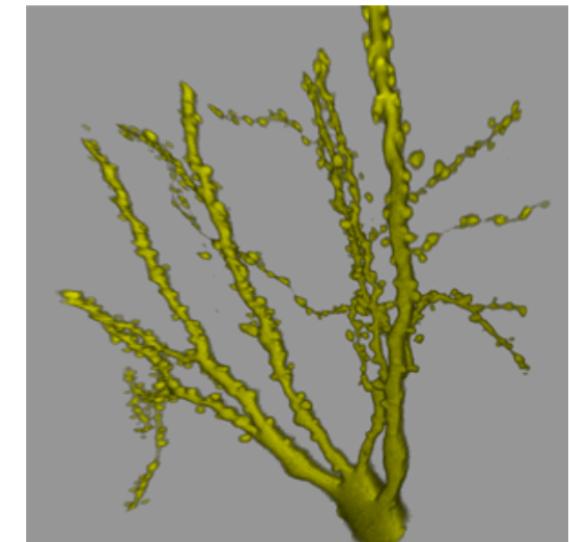
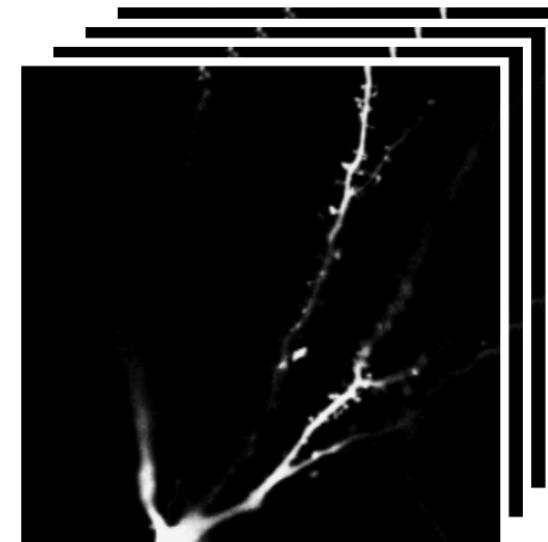


The series shows microtubule growth in a live neuron. The average speed of the distal ends is comparable in the cell body, dendrites, axons, and growth cones.

(Image understanding)

Visualization

image in → representation out



From: Erik Meijering and Gert van Cappellen,
Biological Image Analysis Primer, 2006

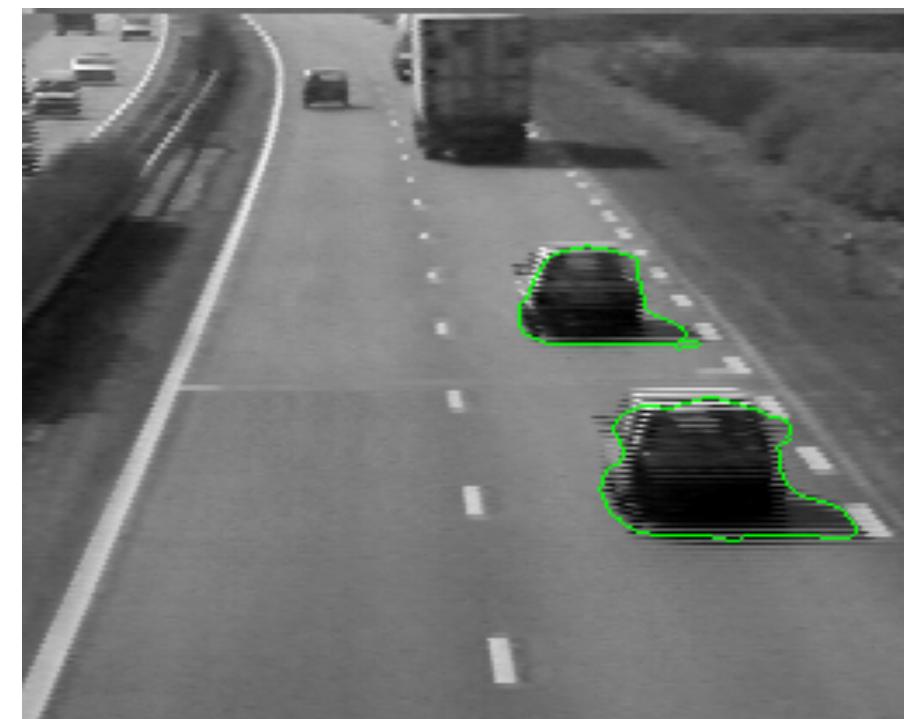
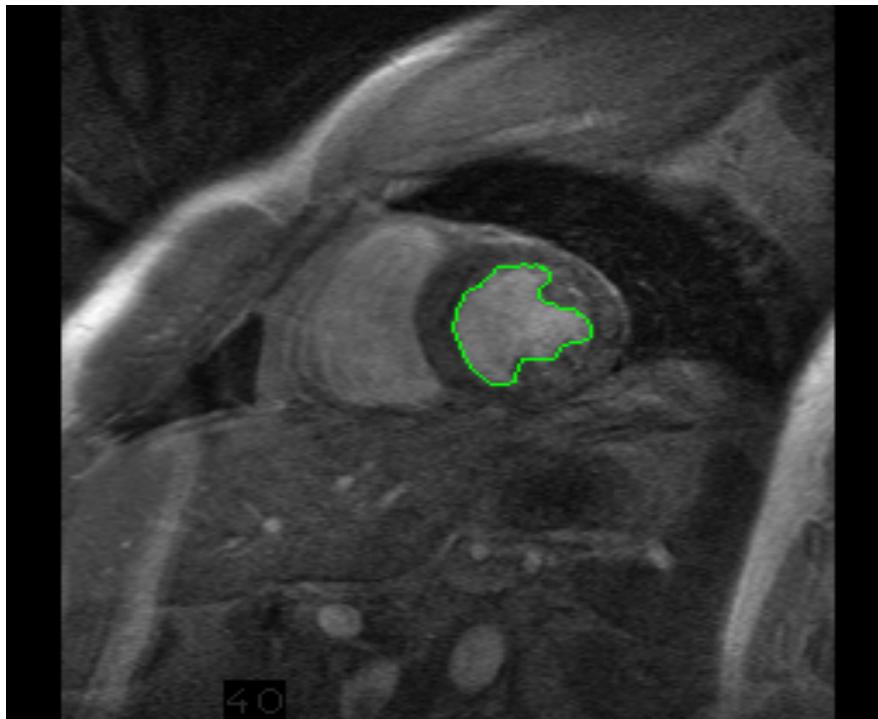
Modeling and image analysis can be **generic** in nature

("active contours")

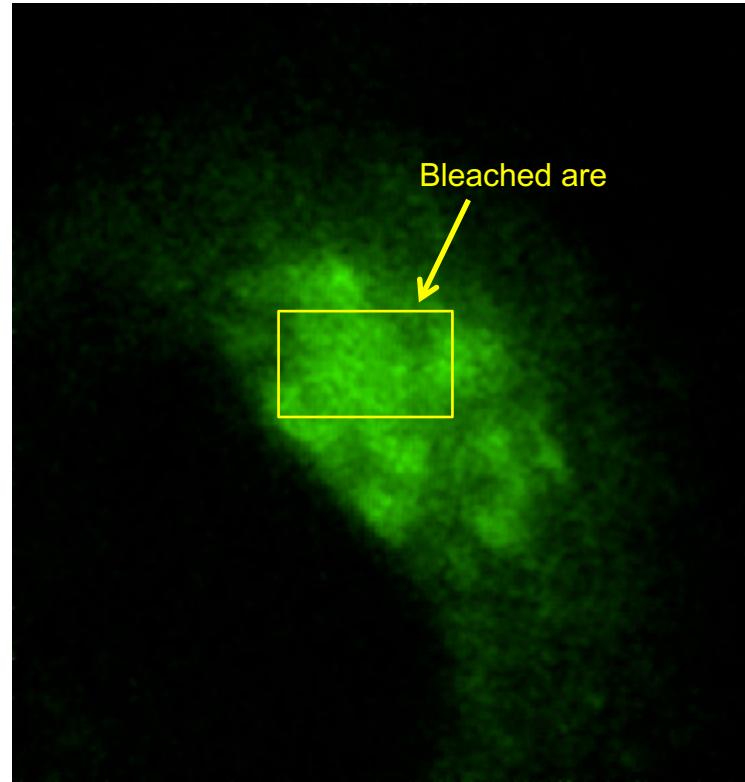
Medical MR imaging



Surveillance engineering

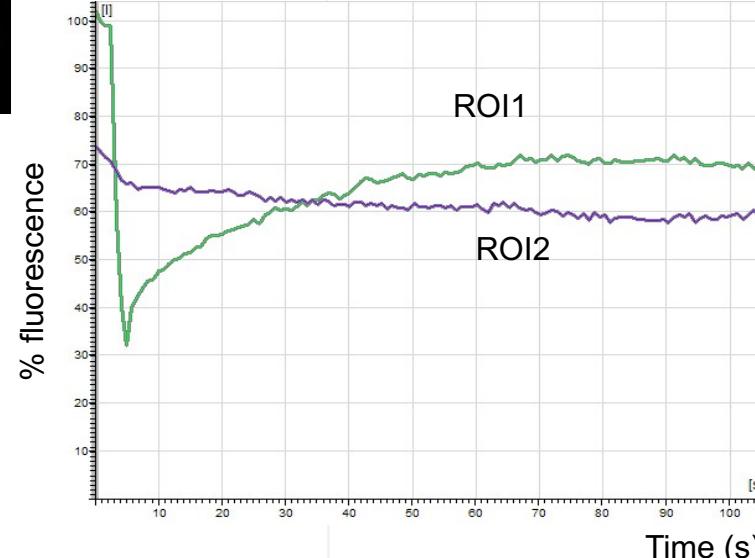
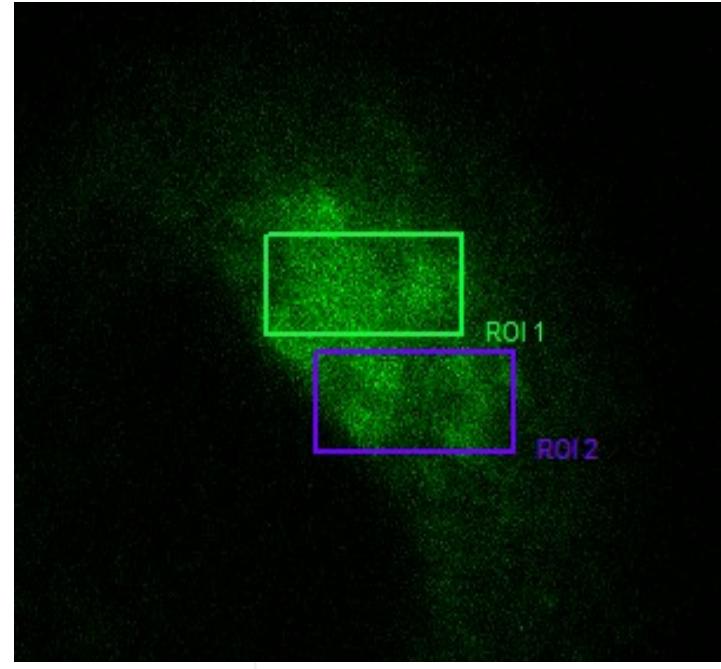


Live cell imaging: FRAP – Fluorescence Recovery After Photobleaching



Photobleaching of GFP in the Golgi area (ROI1) with a high intensity laser.

The recovery of fluorescence in the bleached area is followed.



Measure the dynamics of a molecule over time (diffusional mobility) and chemical changes of molecular species

Image-based modelling:

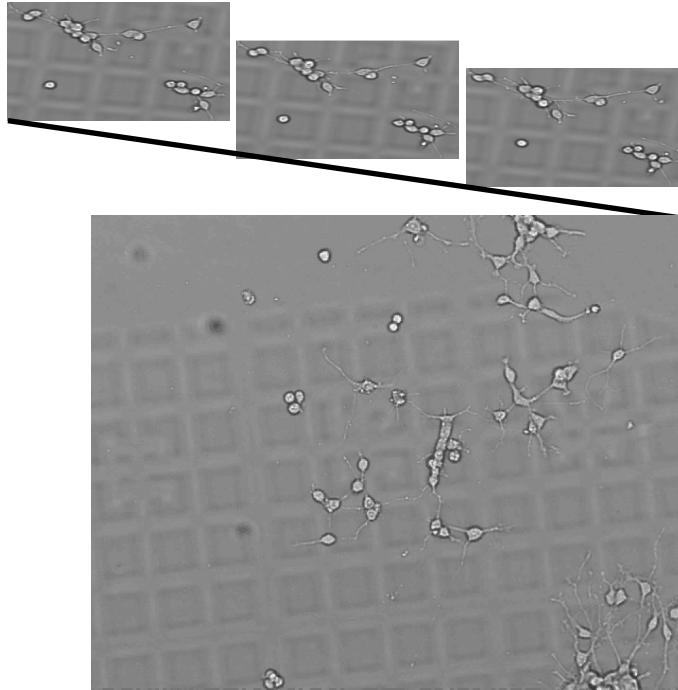
2-compartment model

O - organelle-associated protein

C - cytoplasmic protein

$$\left. \begin{aligned} \frac{dO}{dt} &= k_{in} C - k_{out} O \\ \frac{dC}{dt} &= k_{out} O - k_{in} C \end{aligned} \right\}$$

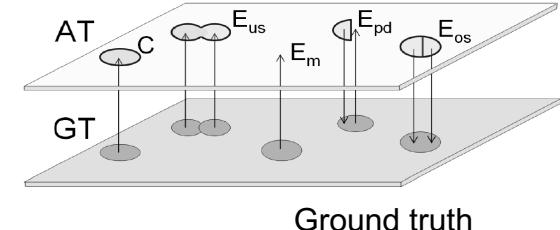
k_x – rate constants



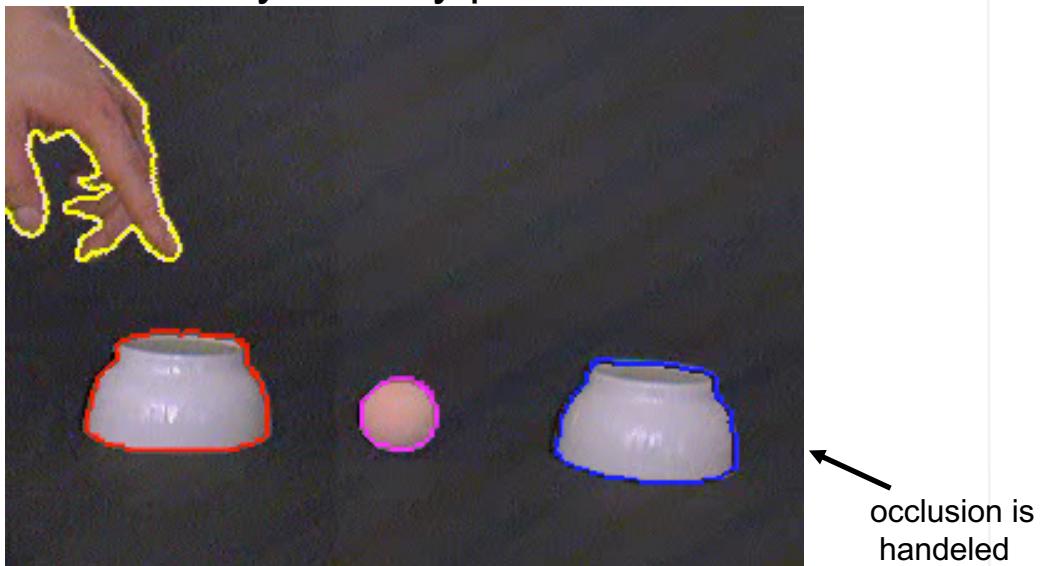
Object tracking

Performance evaluation

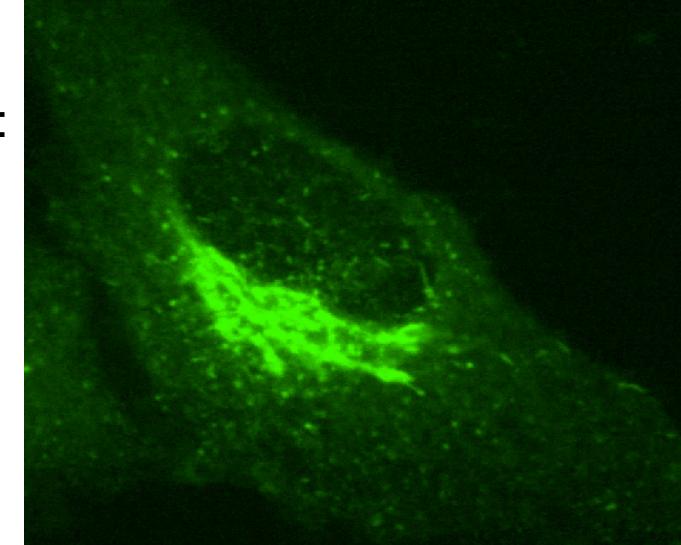
Automatically segmented and tracked



"Easy" - "Toy problem"



Difficult:



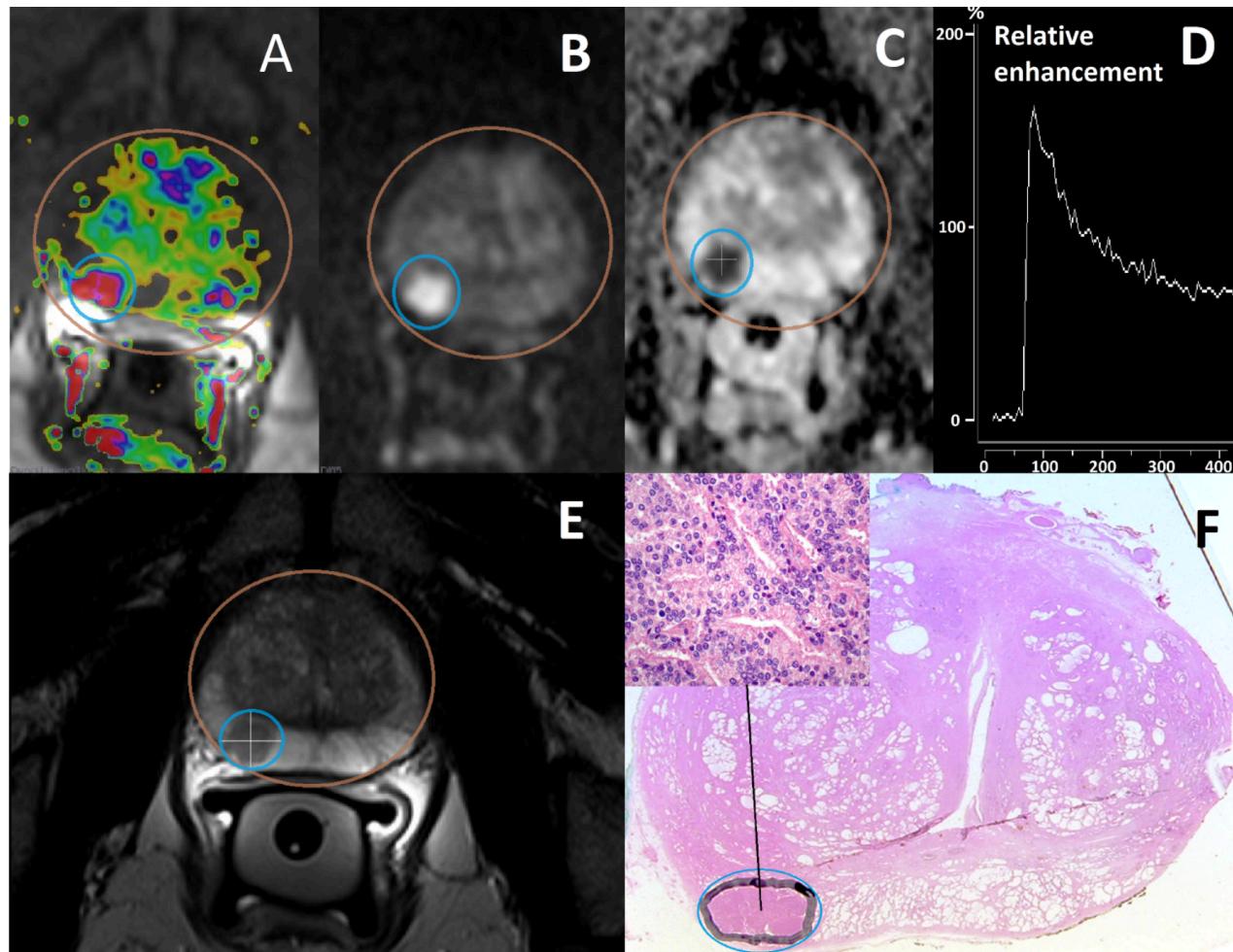
A pipeline for 3D registration of prostate MRI and whole-mount sections

Are Losnegård^{1,6}, Lars A. Reisæter¹, Arvid Lundervold^{2,1}, Ole J. Halvorsen^{4,6},
Christian Beisland^{5,6}, Liv B. Hysing³ and Jarle Rørvik^{6,1}

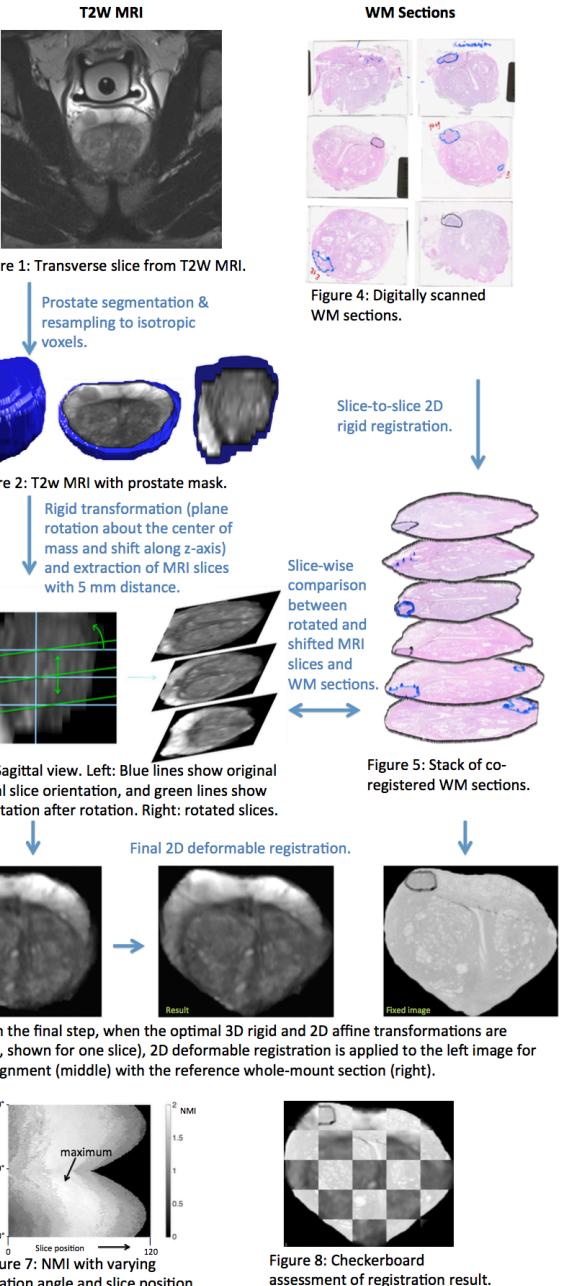
¹Department of Radiology, Haukeland University Hospital, Bergen, Norway; ²Department of Biomedicine, University of Bergen;

³Department of Oncology and Medical Physics, Haukeland University Hospital; ⁴Department of Pathology, Haukeland University Hospital;

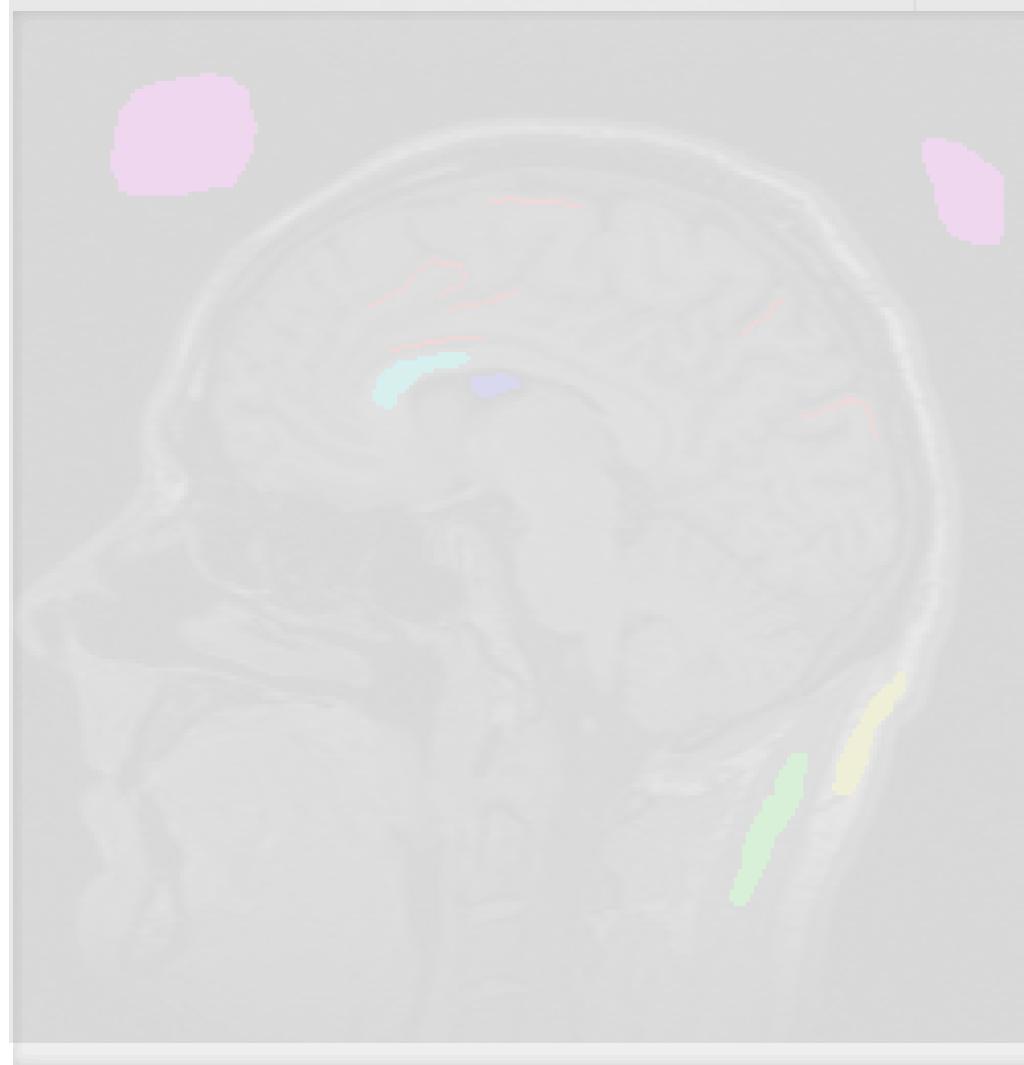
⁵Department of Urology, Haukeland University Hospital; ⁶Department of Clinical Medicine, University of Bergen



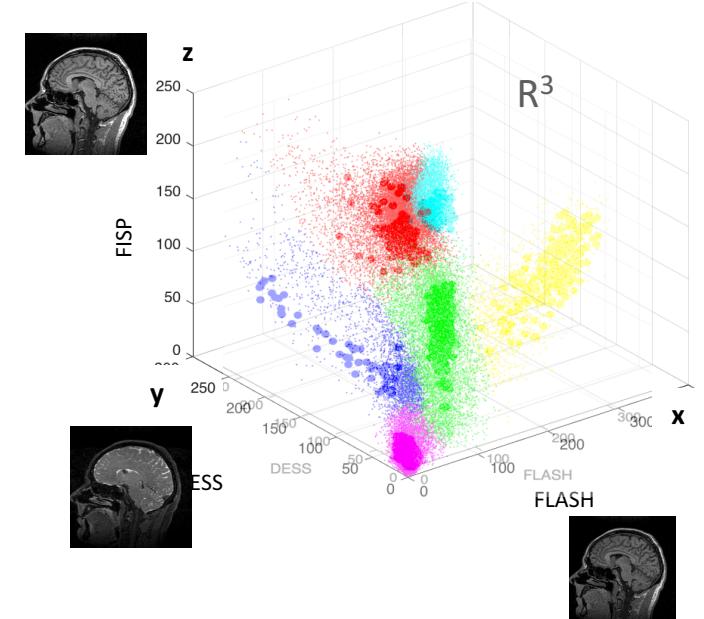
Multi-parametric MRI and histopathological examinations of a prostate (brown circle) with tumor (blue circle).



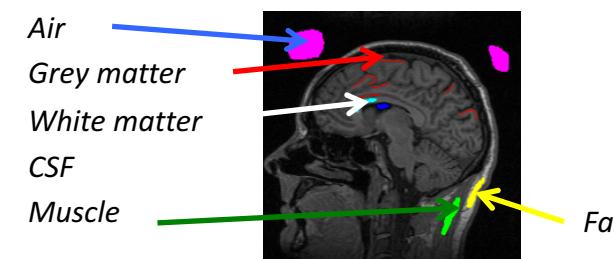
Automated brain tissue classification - kNN



k=7 Nearest Neighbor classification
to six different tissue types of the human head



⇨ Classification of new voxels based on a training set (mask)
made by an expert (**supervised learning**):

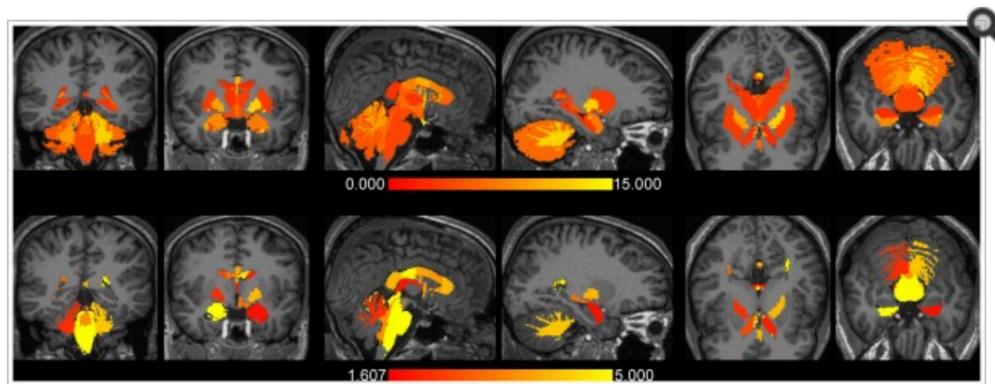


The role of numerical libraries, operating systems and versions

[PLoS One. 2012;7\(6\):e38234. doi: 10.1371/journal.pone.0038234. Epub 2012 Jun 1.](#)

The effects of FreeSurfer version, workstation type, and Macintosh operating system version on anatomical volume and cortical thickness measurements.

[Gronenschild EH¹, Habets P, Jacobs HI, Mengelers R, Rozendaal N, van Os J, Marcelis M.](#)



The differences in subcortical grey matter volumes between FreeSurfer version v4.3.1 and v5.0.0 on a Mac (OSX 10.5).



Freesurfer 5.3 ReleaseNotes

Important Note: It is essential to process all your subjects with the same version of FreeSurfer, on the same OS platform and vendor, and to be completely safe, even the same version of the OS.



« Kids Today Are Not Inattentive

Brains are Different on Macs

By Neuroskeptic | June 14, 2012 7:27 pm

Imagine you're doing a study comparing brain structure in two groups. Halfway through analyzing your data, you upgrade your MacOS. All of the brains you analyze after that will be, say, 5% "bigger". That'll certainly make your data much noisier, and if you happen to analyze most of Group A before Group B, it'll give you a false positive finding.

Reproducible research – Open Science – Open source

TRENDS

/

SOLUTIONS

Computational (bio)medicine
& Software development

GitHub

From Wikipedia, the free encyclopedia

GitHub is a web-based [Git](#) repository hosting service. It offers all of the [distributed revision control](#) and [source code management](#) (SCM) functionality of [Git](#) as well as adding its own features. Unlike [Git](#), which is strictly a [command-line](#) tool, GitHub provides a [Web-based graphical interface](#) and desktop as well as mobile integration. It also provides [access control](#) and several collaboration features such as [bug tracking](#), [feature requests](#), [task management](#), and [wikis](#) for every project.^[3]

GitHub offers both plans for private [repositories](#) and free accounts,^[4] which are usually used to host [open-source](#) software projects.^[5] As of April 2016, GitHub reports having more than 14 million users and more than 35 million repositories,^[6] making it the largest host of source code in the world.^[7]

"Build software better, together "

README.md



Example

The [Medical Imaging Interaction Toolkit](#) (MITK) is a free open-source software system for development of interactive medical image processing software. MITK combines the [Insight Toolkit](#) (ITK) and the [Visualization Toolkit](#) (VTK) with an application framework.

The links below provide high-level and reference documentation targeting different usage scenarios:

- Get a [high-level overview](#) about MITK with pointers to further documentation
- End-users looking for help with MITK applications should read the [MITK User Manual](#)
- Developers contributing to or using MITK, please see the [MITK Developer Manual](#) as well as the [MITK API Reference](#)

See the [MITK homepage](#) for details.

Supported Platforms

MITK is a cross-platform C++ toolkit and officially supports:

- Windows
- MacOS X
- Linux

For details, please read the [Supported Platforms](#) page.

License

Copyright (c) German Cancer Research Center.

MITK is available as free open-source software under a [BSD-style license](#).

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Source Code for Biology and Medicine

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METHODOLOGY | OPEN ACCESS

CellSegm - a MATLAB toolbox for high-throughput 3D cell segmentation

Erlend Hodneland  , Tanja Kögel, Dominik Michael Frei, Hans-Hermann Gerdes and Arvid Lundervold

Source Code for Biology and Medicine 2013 8:16 | DOI: 10.1186/1751-0473-8-16 |

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Received: 27 November 2012 | Accepted: 30 July 2013 | Published: 9 August 2013

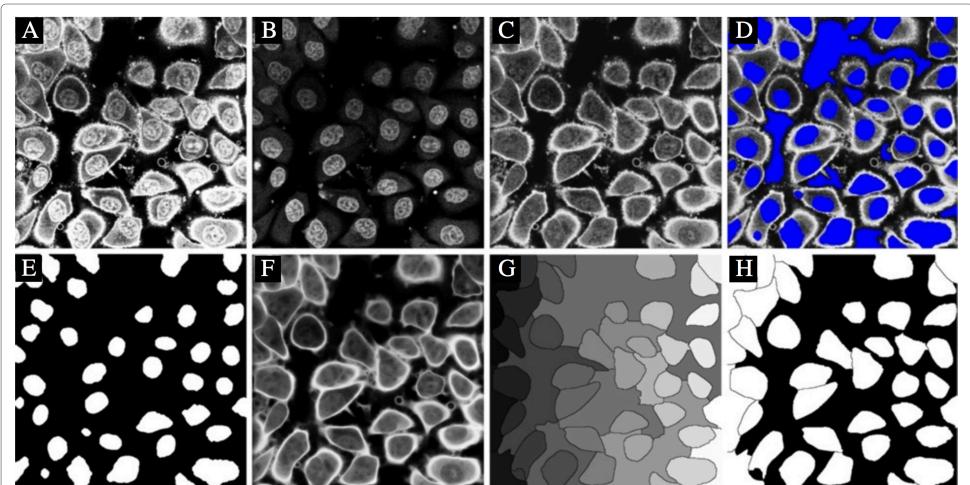


Figure 9 Segmentation of cells using nucleus markers in 2D from Example 7, executed for plane five in the image stack. **A)** Raw surface stain, **B)** raw nucleus stain, **C)** surface stain minus nucleus stain, **D)** markers (blue) derived from the nucleus stain superimposed onto the surface stain, **E)** cell markers, **F)** smoothed segmentation image, from **C**, **G)** watershed image, **H)** detected cell areas.

← Paper

Code
↓



<https://github.com/ehodneland/cellsegm>

An automated MATLAB tool for segmentation of surface stained cells.

Branch: master		New pull request	Create new file	Upload files	Find file	Clone or download
188 commits	1 branch	0 releases	1 contributor			
Latest commit 6ac2ae on Sep 20						
<p>ehodneland Modified gaussian.m and smoothim.m</p> <p>@cellsegm Modified gaussian.m and smoothim.m</p> <p>data Added examples from article</p> <p>examples Fixing bug related to arguments to gaussian. Now stdev is scalar</p> <p>README.txt Minor bug fixes and improved help function. In getminima, fixed bug o...</p> <p>startupcellsegm.m Adding the file for setting the path</p>						
<p>README.txt</p> <pre>% WELCOME TO CELLSEG % Cell segmentation package % =====</pre>						

Sourcecode Examples Testdata

Test-data



The future of bio(medical)imaging and imaging-based modeling...

- **LIVE / IN VIVO IMAGING, SYSTEMS BIOLOGY and SYSTEMS MEDICINE**
- **TRANSDISCIPLINARITY and COMPUTATIONAL APPROACHES**
to the multi-scale nature of molecules, cells, tissues and organs in health and disease

SUMMARY

*Addressing
the challenges:*

△ mindset

△ skillset

△ toolset

- open science

- reproducible
research

