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

Prof. Arvid Lundervold BSc, MD, PhD

Department of Biomedicine, University of Bergen &
Department of Radiology, Haukeland University Hospital, Bergen, Norway

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

Technologies for Digital Life

CENTRE FOR DIGITAL LIFE NORWAY

- 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*

CONCEPTS

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**.

http://www.obesity-cancer.wustl.edu/en/About/What-Is-Transdisciplinary-Research

CONCEPTS

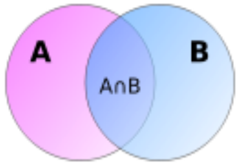
<u>Mathematics</u> is the body of knowledge centered on concepts such as ***quantity, structure, space,*** *and* ***change,*** *and the academic discipline which studies them …*

… being instrumental in ***predictive models*** *of biological systems and* ***"Digital Life"***

FOUNDATIONS

$P \Rightarrow Q$

Mathematical logic

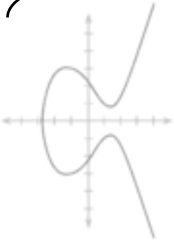


Set theory

$$\begin{tikzcd} X \arrow[r, "f"] \arrow[dr, "g \circ f"'] & Y \arrow[d, "g"] \\ & Z \end{tikzcd}$$

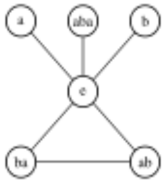
Category theory

STRUCTURE



Number theory

Abstract algebra



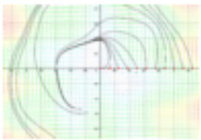
Group theory

Order theory

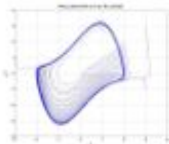
CHANGE

Calculus

Vector calculus



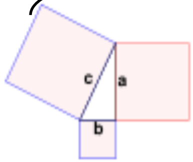
ODEs/PDEs/SDEs



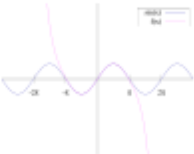
Dynamical systems

Chaos theory

SPACE

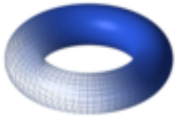


Geometry



Trigonometry

Differential geometry



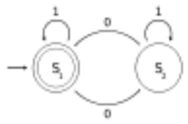
Topology

Fractal geometry

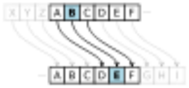
DISCRETE MATHEMATICS

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

Combinatorics



Theory of computation



Cryptography

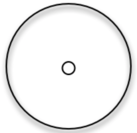
Graph theory

CONCEPTS

What is the difference?

- **Transdisciplinary**
- **Multidisciplinary**
- **Interdisciplinary**
- **Crossdisciplinary**

research

( **Intradisciplinary)**

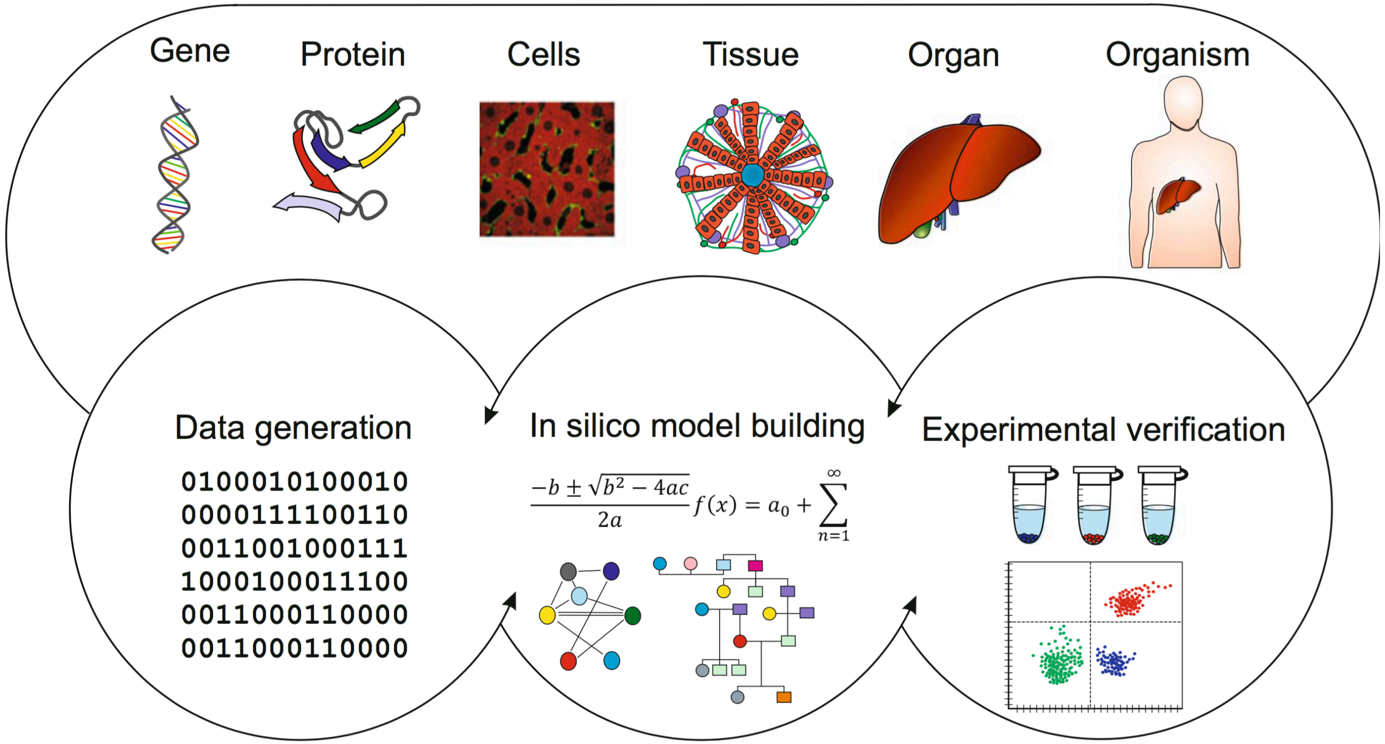
Transdisciplinary Research	Multidisciplinary Research	Interdisciplinary Research	Crossdisciplinary Research
Collaboration in which exchanging information, altering discipline-specific approaches, sharing resources and integrating disciplines achieves a common scientific goal *e.g. pharmacokinetic modeling from DCE-MRI measurements for assessment of tumor physiology*	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. *e.g. image co-registration and segmentation*	Researchers interact with the goal of transferring knowledge from one discipline to another. Allows researchers to inform each other's work and compare individual findings. *e.g. multimodal validation of automated image segmentation*	Researchers are viewing one discipline from the perspective of another. *e.g. Digital Life in transition to transdisciplinary research ?*

http://www.obesity-cancer.wustl.edu/en/About/What-Is-Transdisciplinary-Research

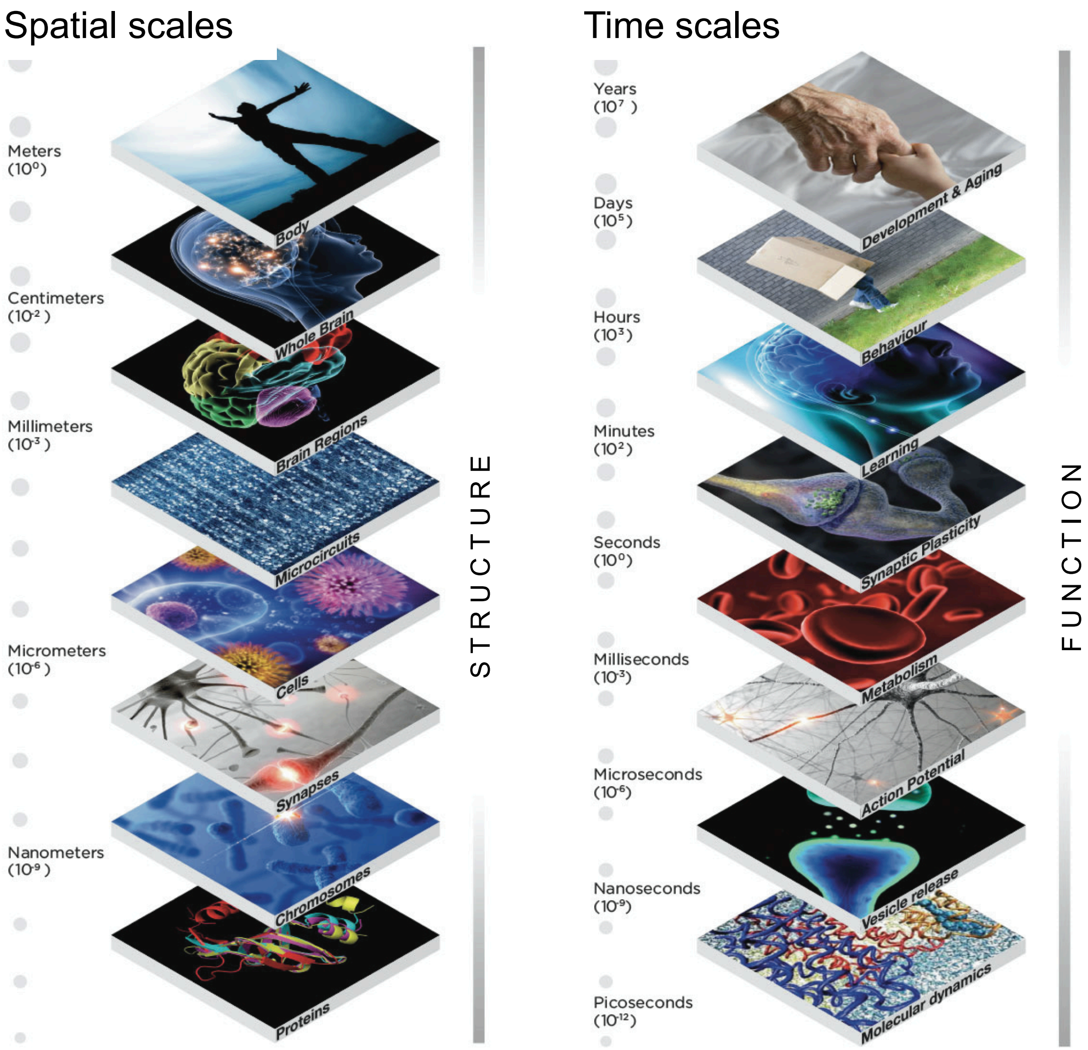
http://www.arj.no/2012/03/12/disciplinarities-2

TRENDS

Systems biology & medicine and computational imaging



MULTISCALE



Ulf Schmitz, Olaf Wolkenhauer (eds) Systems Medicine, Springer, 2016

https://www.humanbrainproject.eu

TRENDS

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.

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

TRENDS

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

TRENDS

Data analytics - Machine learning

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.

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 VOLUME 35 NUMBER 5

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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. Traboulsee, and R. Tam* 1229

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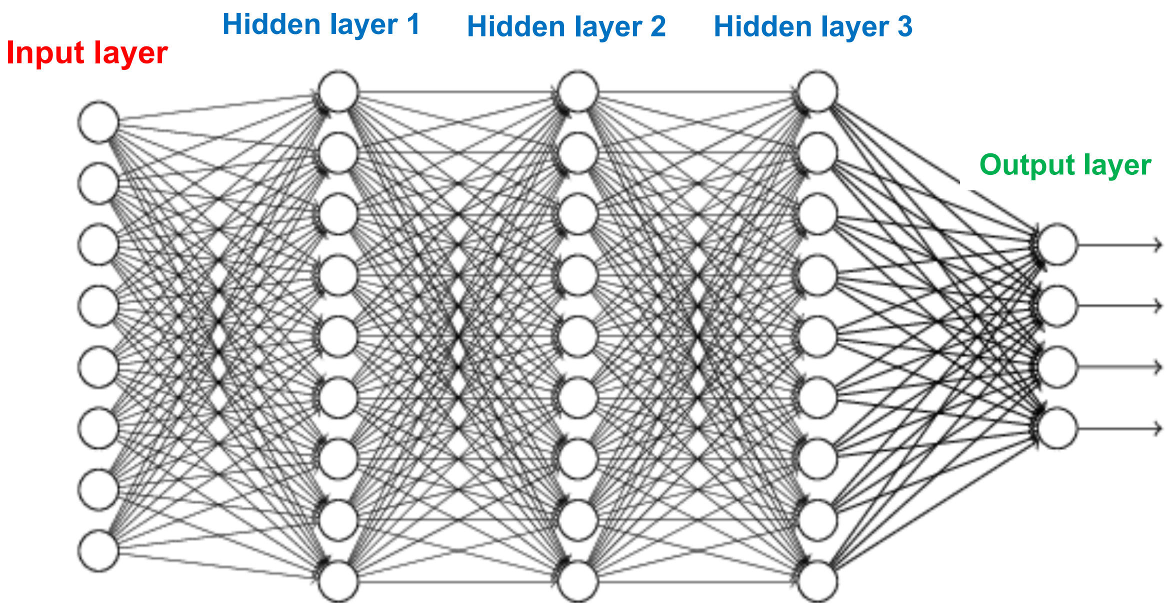
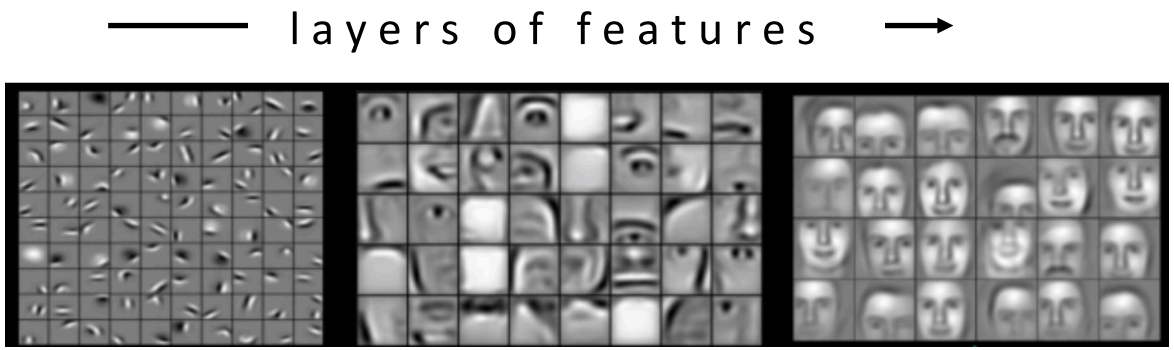
Neural networks - deep learning

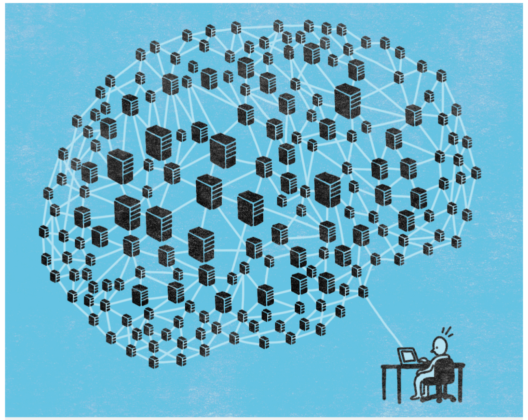


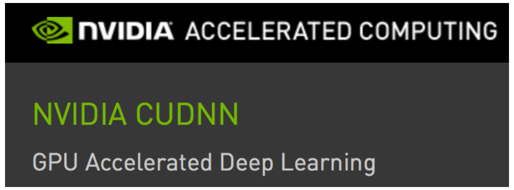


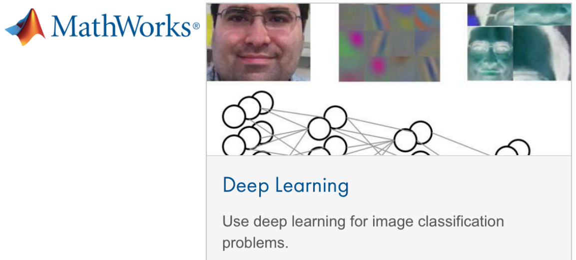
Deep learning is a branch of machine **learning** based on a set of algorithms that attempt to model high-level abstractions in data by using multiple processing layers, with complex structures or otherwise, composed of multiple non-linear transformations

Wikipedia

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







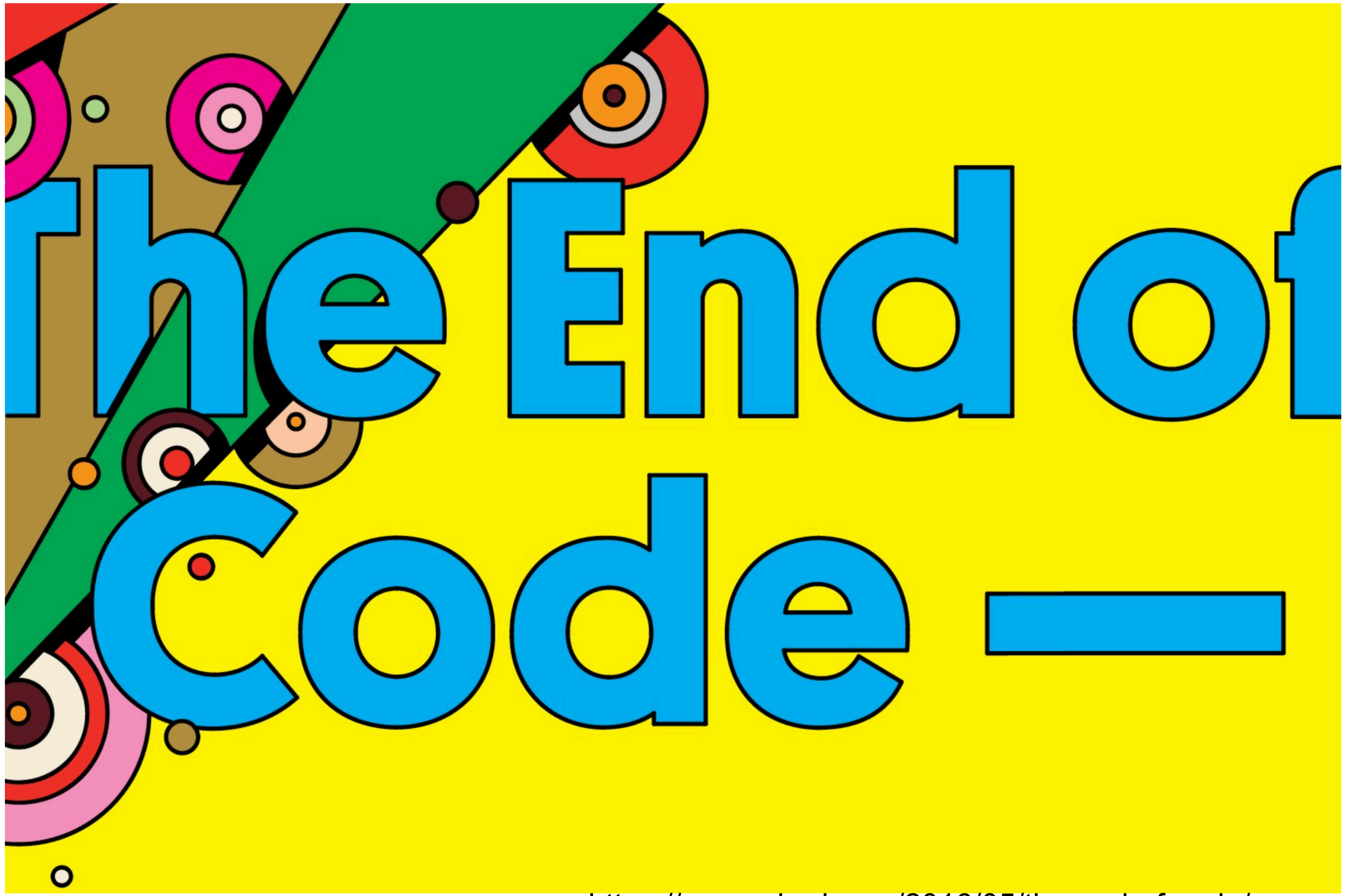
TRENDS

JASON TANZ   BUSINESS   05.17.16   6:50 AM

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/

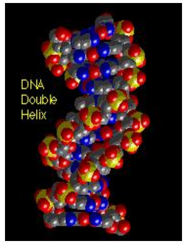
Imaging infrastructure (in Bergen)

INFRASTRUCTURE

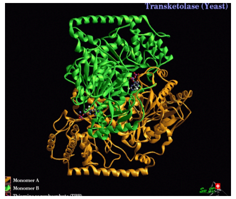
- Superresolution microscopy (STED)
- MRI experts (acquisition + analysis)

- New visualization center from 2017

DNA

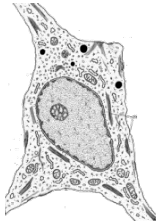


Protein

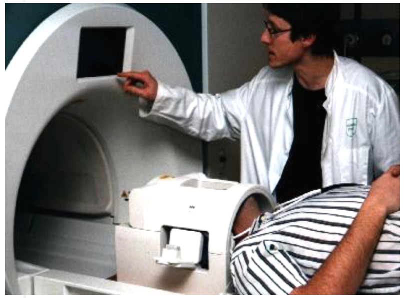


Organelle

Cell



Clinical MRI

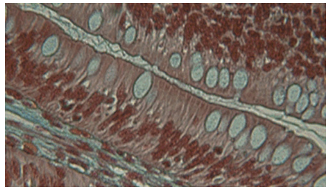


1 GE + 2 x Siemens 3 Tesla

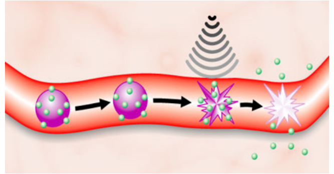
Clinical US

Clinical PET/CT

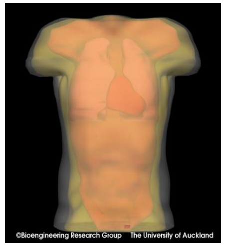
Tissue



Organ

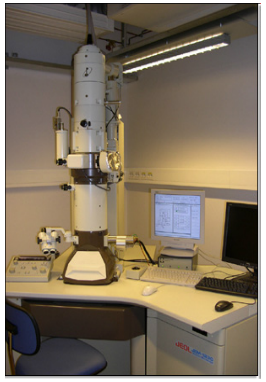


Organism



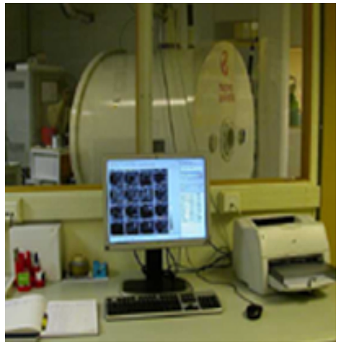
Microscopy

EM



Confocal

Animal MRI

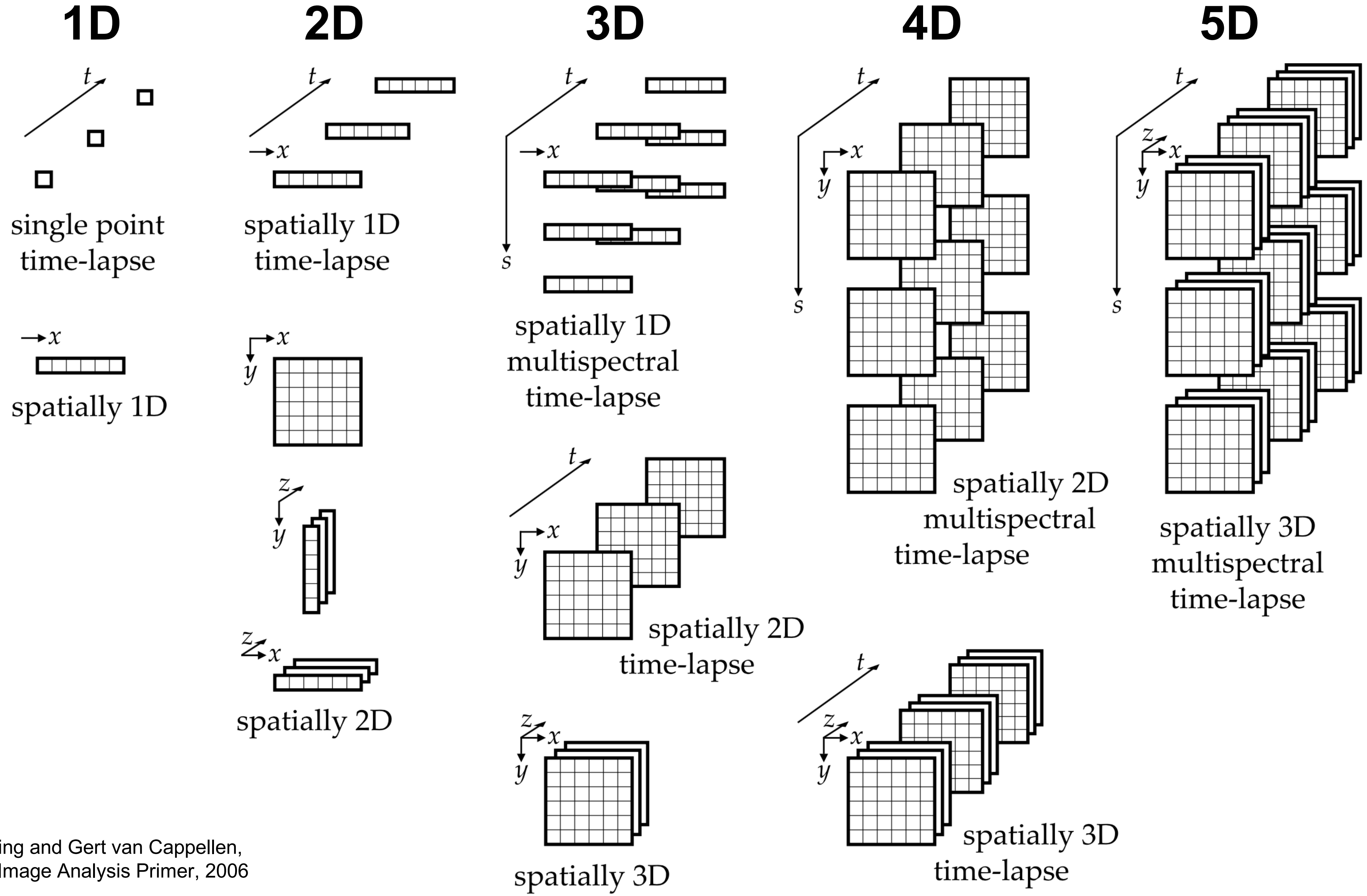


7 Tesla Bruker Pharmascan

$$\frac{\partial M_x(t)}{\partial t} = \gamma(\mathbf{M}(t) \times \mathbf{B}(t))_x - \frac{M_x(t)}{T_2}$$
$$\frac{\partial M_y(t)}{\partial t} = \gamma(\mathbf{M}(t) \times \mathbf{B}(t))_y - \frac{M_y(t)}{T_2}$$
$$\frac{\partial M_z(t)}{\partial t} = \gamma(\mathbf{M}(t) \times \mathbf{B}(t))_z - \frac{M_z(t) - M_0}{T_1}$$

Images as matrices

CONCEPTS



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

http://www.imagescience.org/meijering/publications/download/biap2006.pdf

CONCEPTS

"Image formation" vs. "Image processing"

Image Formation

object in → image out

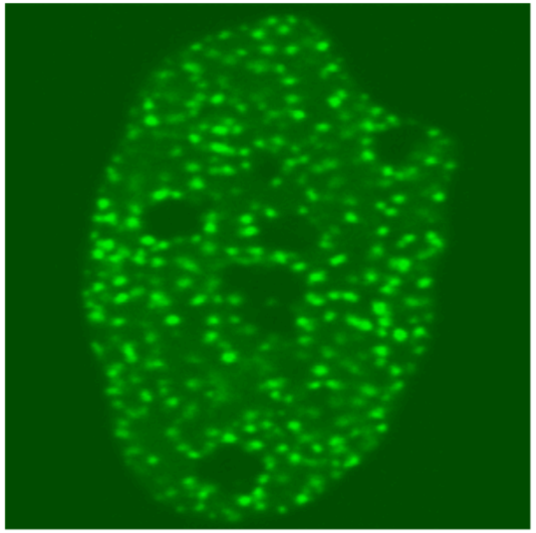
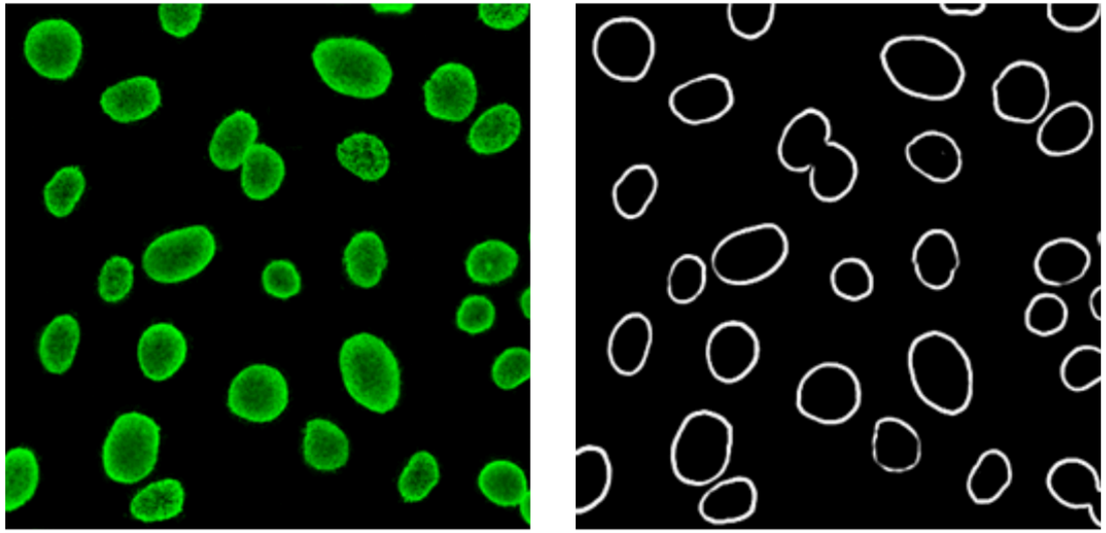


Image Processing

image in → image out



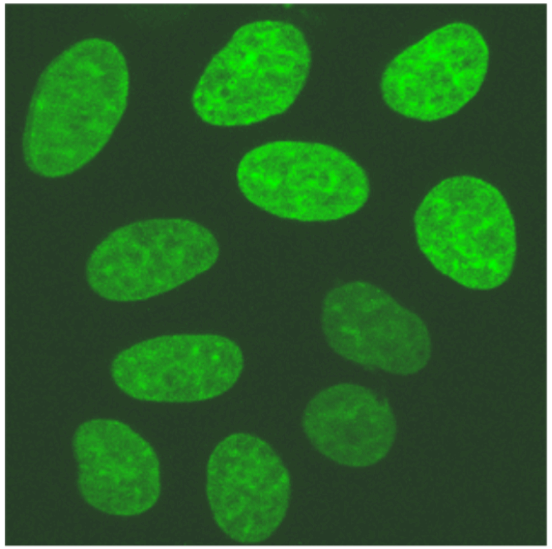
From: Erik Meijering and Gert van Cappellen,
Biological Image Analysis Primer, 2006

http://www.imagescience.org/meijering/publications/download/biap2006.pdf

“Image analysis” vs. “Computer graphics”

Image Analysis

image in ➞ features out

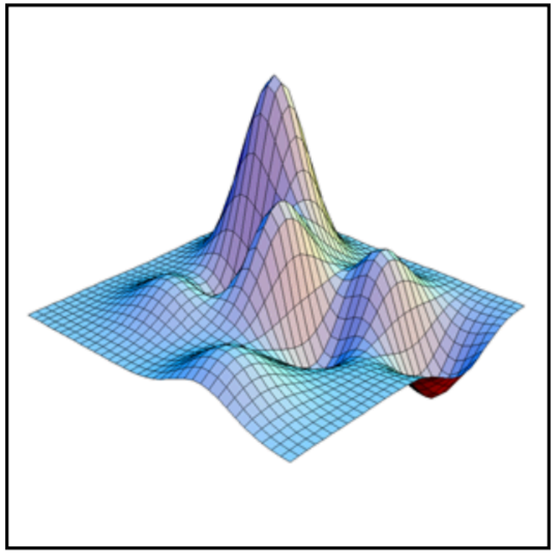


Obj	Area	Perim
1	324.2	98.5
2	406.7	140.3
3	487.1	159.2
4	226.3	67.8
5	531.8	187.6
6	649.5	203.1
7	582.6	196.4
8	498.0	162.9
9	543.2	195.1

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



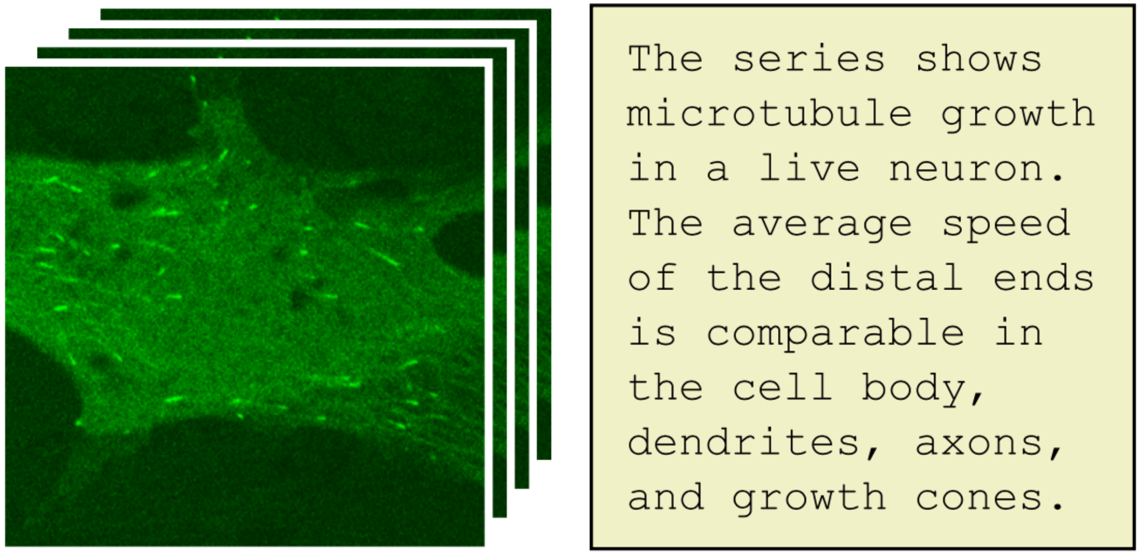
From: Erik Meijering and Gert van Cappellen,
Biological Image Analysis Primer, 2006

http://www.imagescience.org/meijering/publications/download/biap2006.pdf

“Computer vision” vs. “Visualization”

Computer Vision

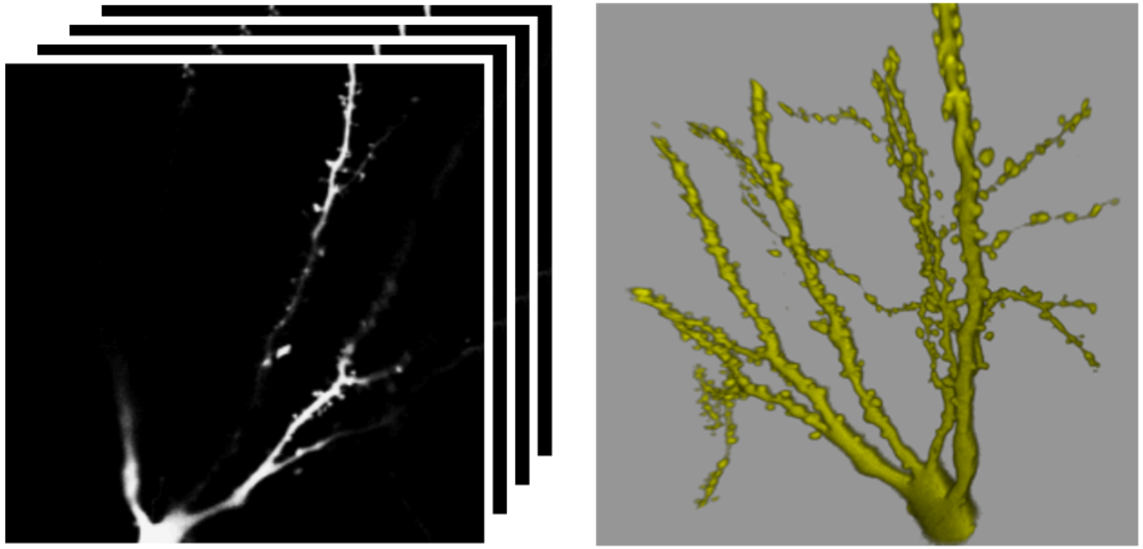
image in → interpretation out



(Image understanding)

Visualization

image in → representation out



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

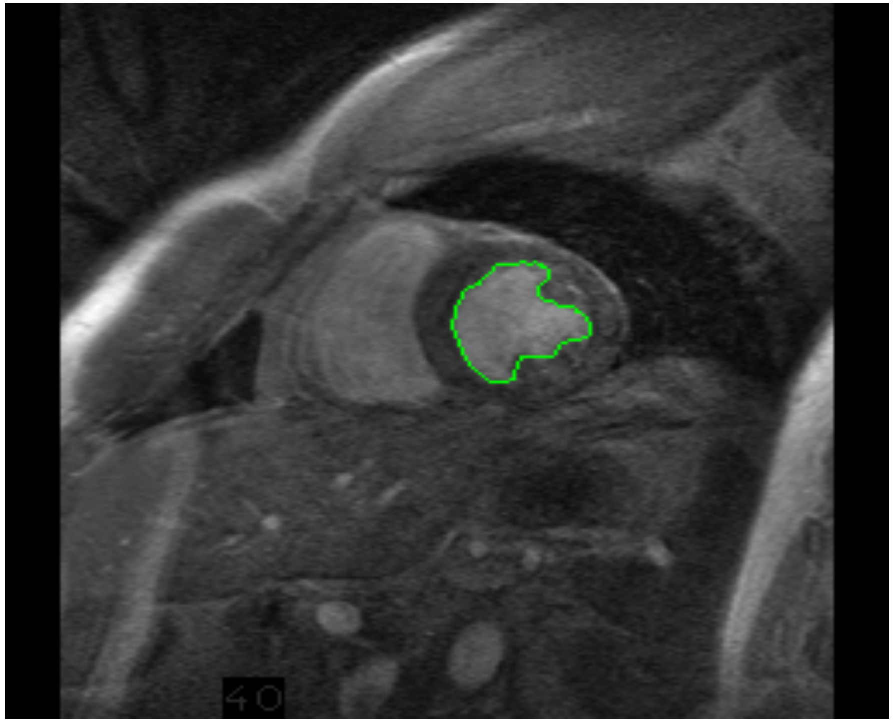
http://www.imagescience.org/meijering/publications/download/biap2006.pdf

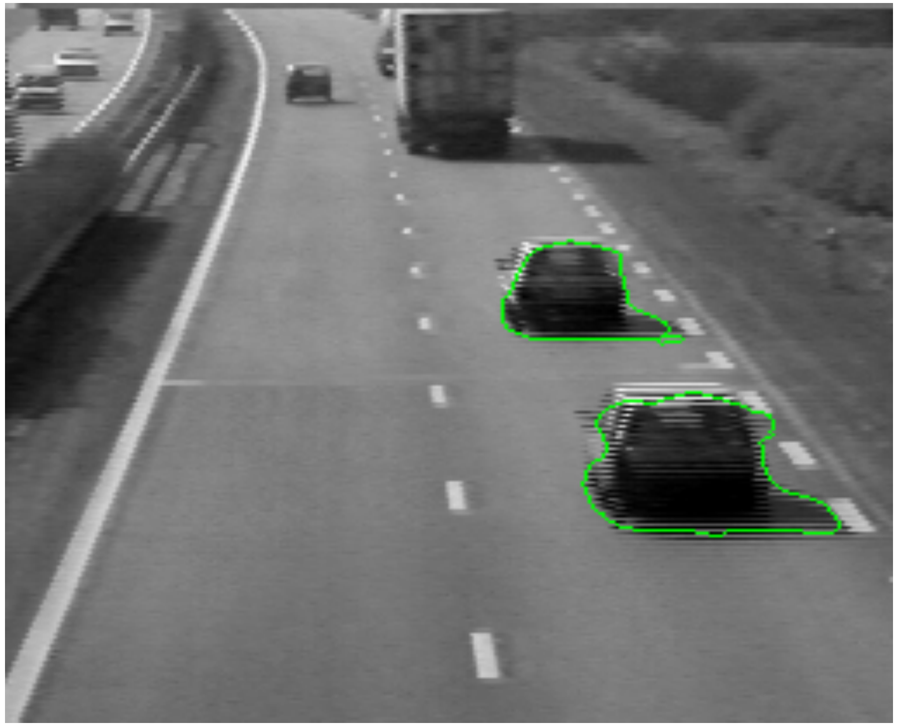
Modeling and image analysis can be **generic** in nature

("active contours")

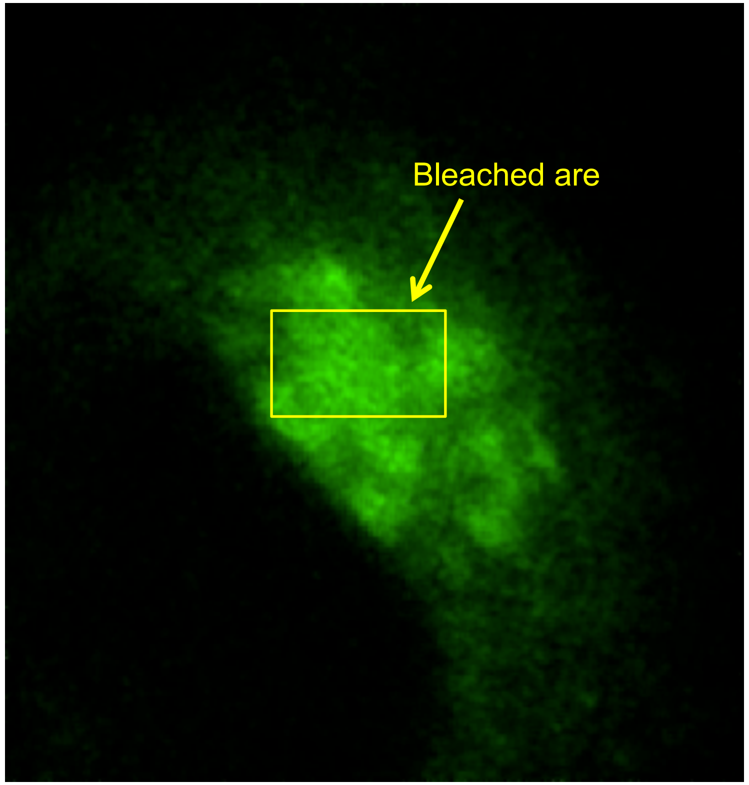
Medical MR imaging

Surveillance engineering



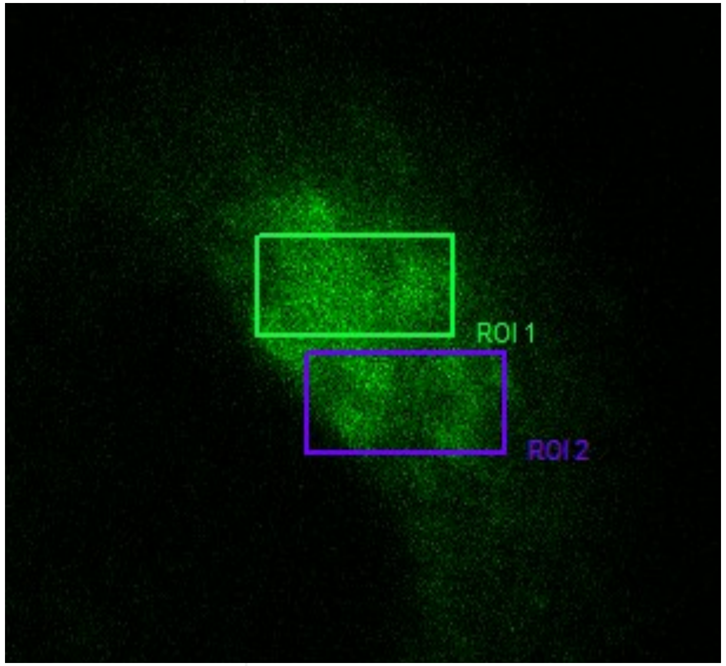


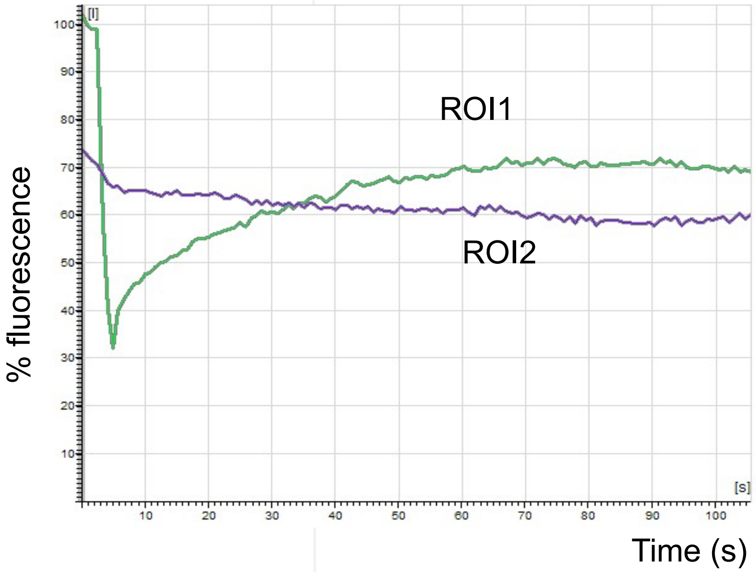
Live cell imaging: **FRAP** – Fluorescence Recovery After Photobleaching



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 ("conservation of mass"):

2-compartment model

O - organelle-associated protein

C - cytoplasmic protein

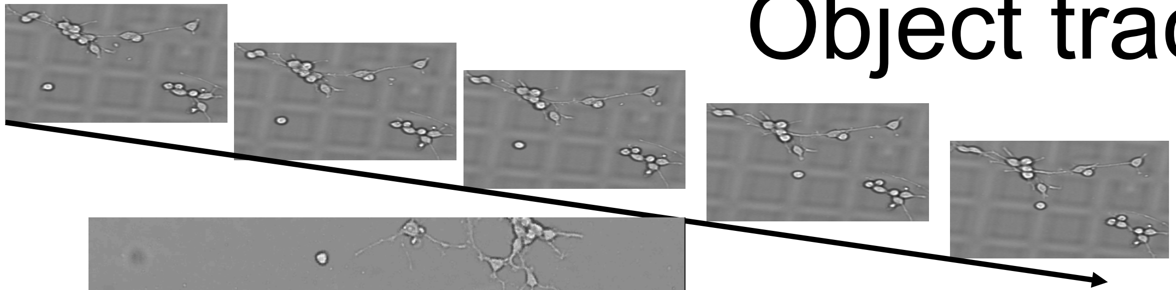
$$\left.\begin{aligned} \frac{dO}{dt} &= k_{in}\,C - k_{out}\,O \\ \frac{dC}{dt} &= k_{out}\,O - k_{in}\,C \end{aligned}\right\}$$

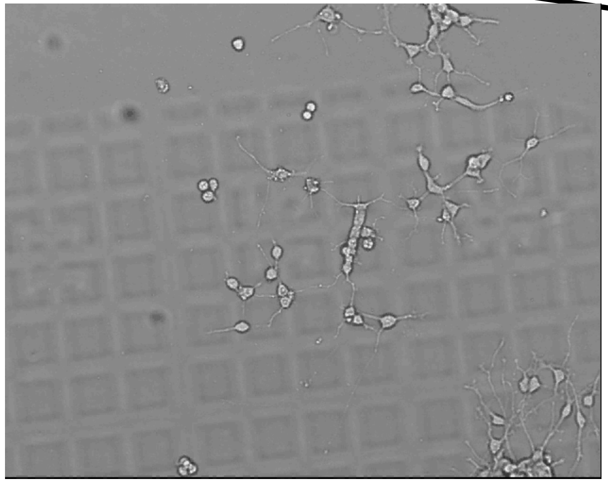
k_x – reate constants

MIC
Molecular Imaging Center

Object tracking

SOLUTIONS





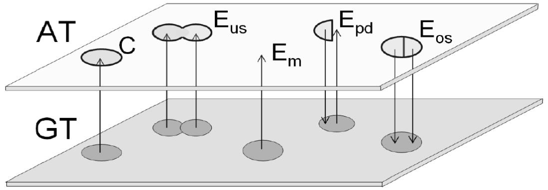
StemCells_amalka_uppsala_thesis_paper1.avi

Time

Moving, dividing and fusing cells on a monolayer

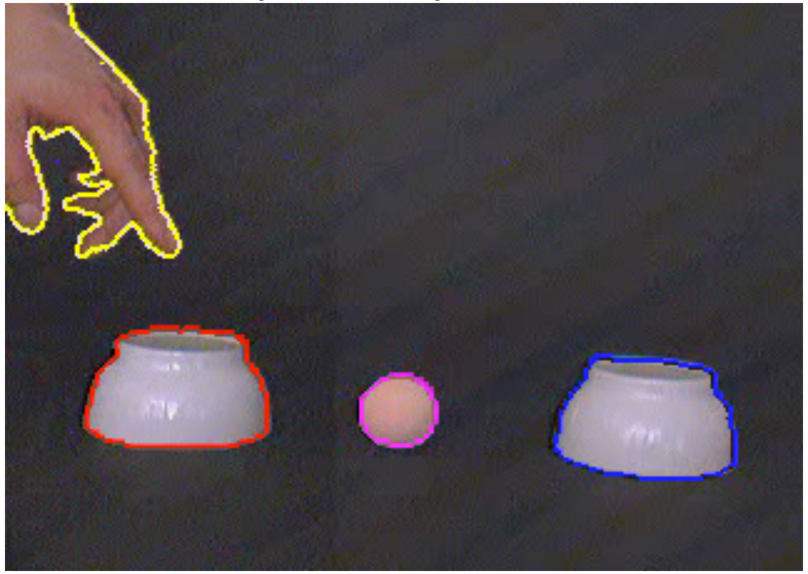
Performance evaluation

Automatically segmented and tracked



Ground truth

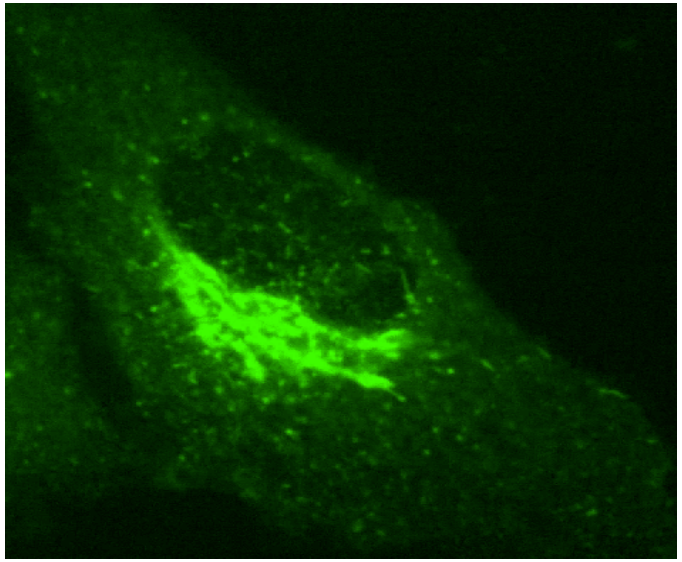
”Easy” - ”Toy problem ”



occlusion is handeled

” Intracellular transport vesicles ”

Difficult:

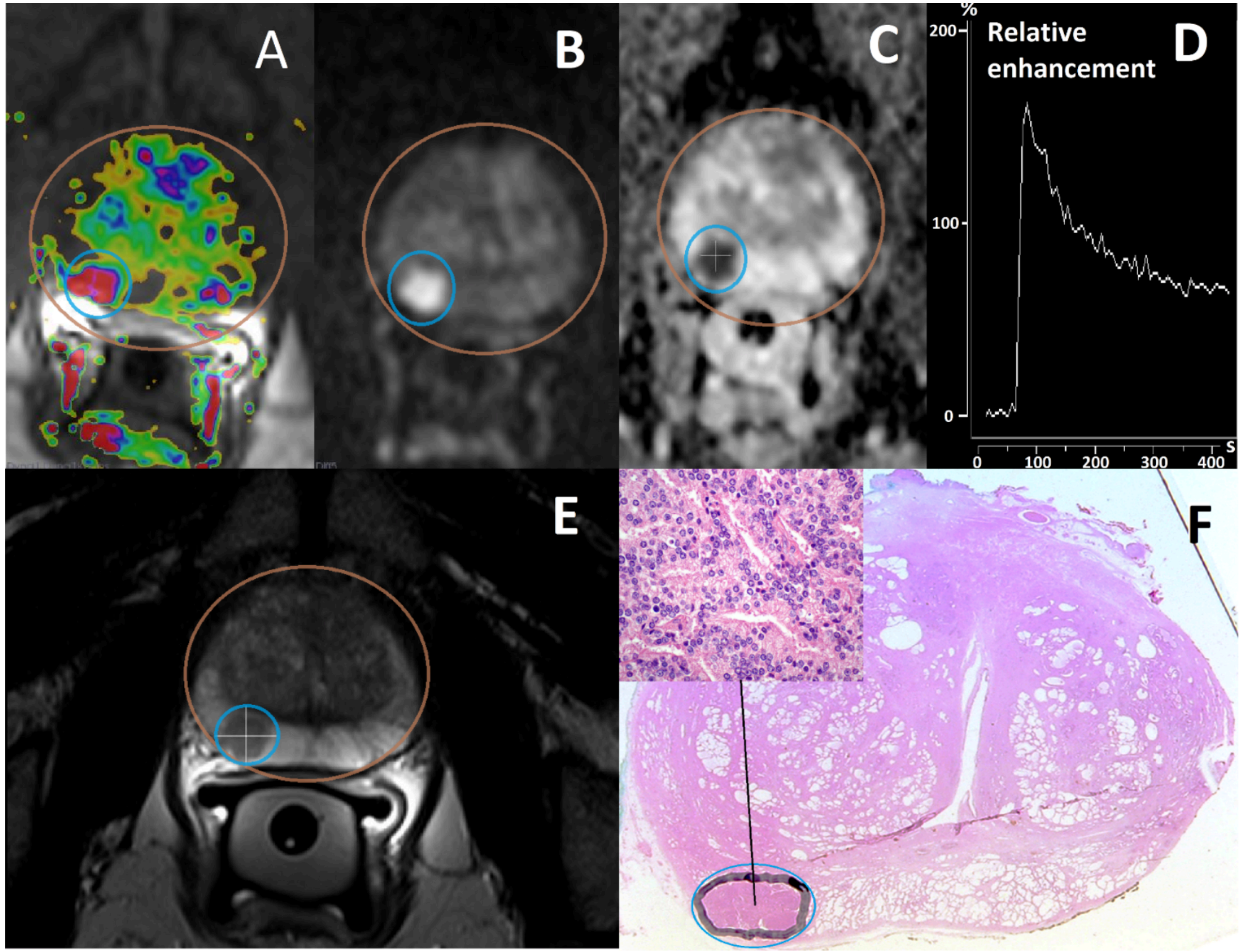


MIC
Molecular Imaging Center

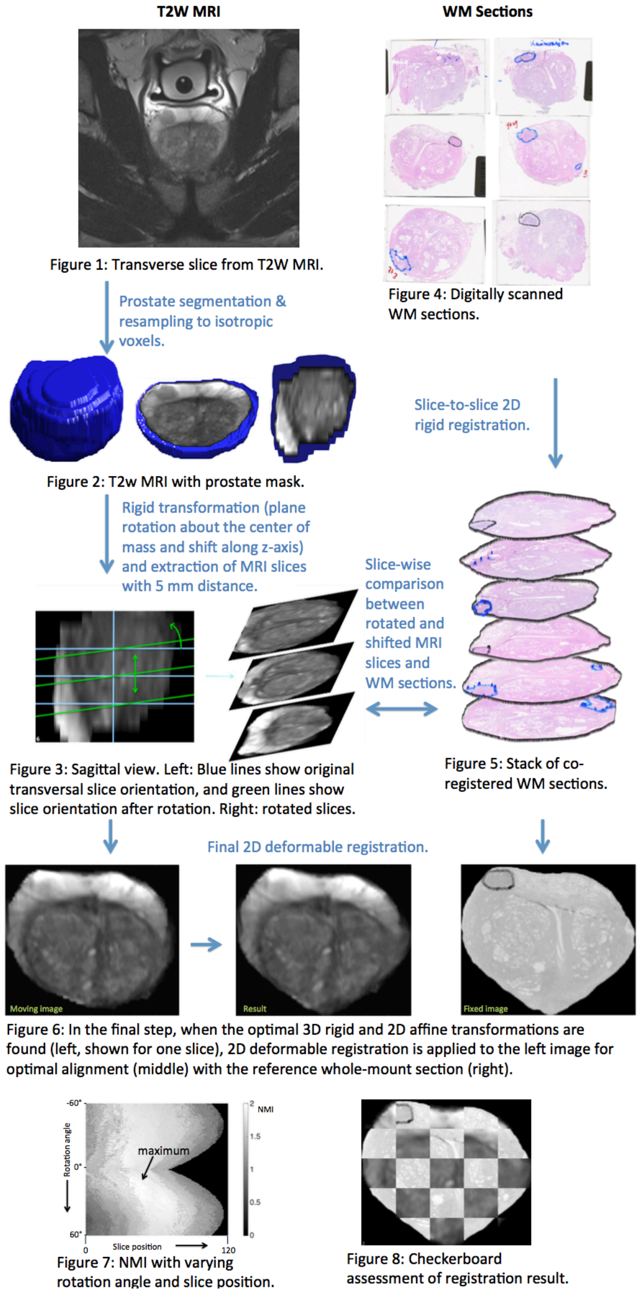
A pipeline for 3D registration of prostate MRI and whole-mount sections

SOLUTIONS

… merging the pathology / optical and the physiological / MRI   view of disease process



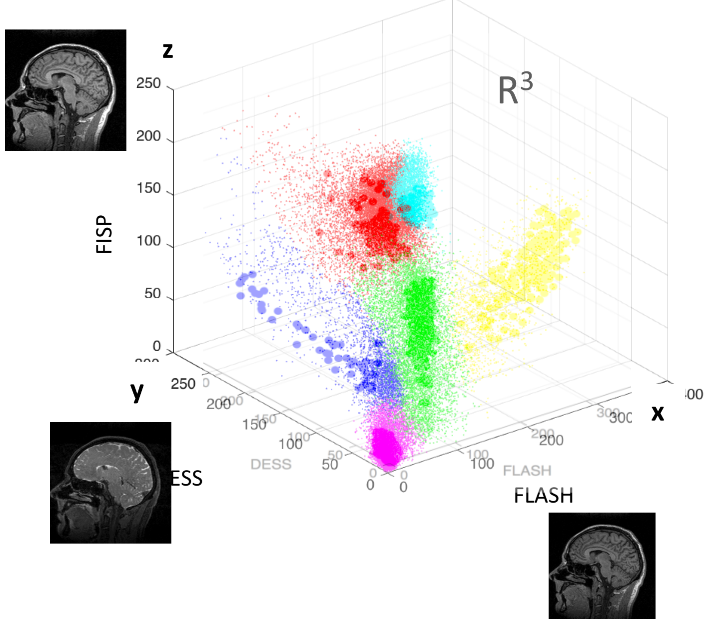
Multi-parametric MRI and histopathological examinations of a prostate (brown circle) with tumor (blue circle).



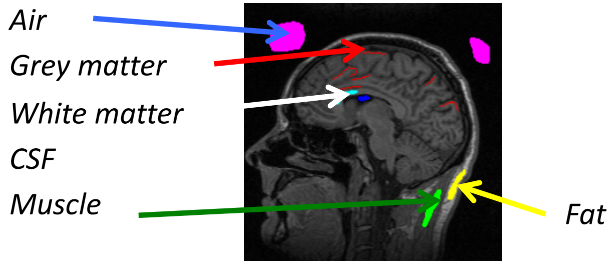
Automated brain tissue classification - kNN

SOLUTIONS

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**):



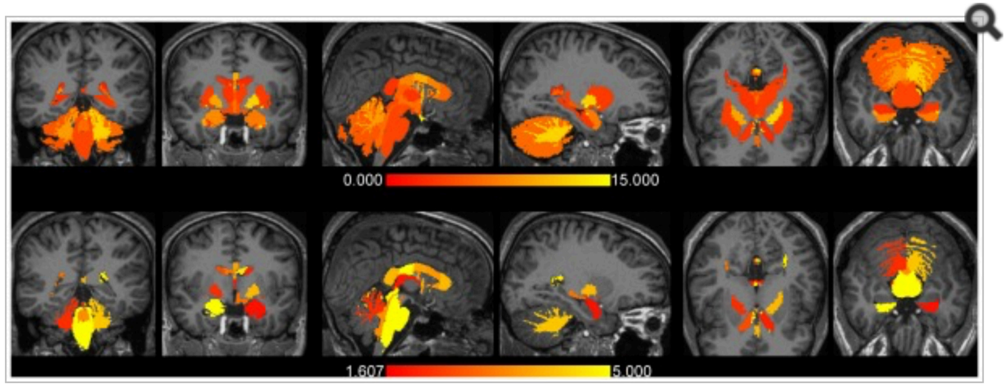
CONCEPTS

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 EH[1], 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

Wiki Documentation | Download | Support | Courses | People | Publications

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.

Neuroskeptic

« 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

MITK

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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SOLUTIONS

Paper

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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

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

Code

https://github.com/ehodneland/cellsegm

GitHub, Inc.

This repository | Search | Pull requests | Issues | Gist

ehodneland / cellsegm

Watch 4 | Star 8 | Fork 12

Code | Issues 0 | Pull requests 0 | Projects 0 | Wiki | Pulse | Graphs

An automated MATLAB tool for segmentation of surface stained cells.

188 commits | 1 branch | 0 releases | 1 contributor

Branch: master | New pull request | Create new file | Upload files | Find file | Clone or download

ehodneland Modified gaussian.m and smoothim.m — Latest commit 6ac2ae2 on Sep 20

@cellsegm	Modified gaussian.m and smoothim.m	a month ago
data	Added examples from article	3 years ago
examples	Fixing bug related to arguments to gaussian. Now stdev is scalar	a year ago
README.txt	Minor bug fixes and improved help function. In getminima, fixed bug o…	3 years ago
startupcellsegm.m	Adding the file for setting the path	3 years ago

README.txt

```
%
%   W E L C O M E   T O   CELLSEGM
%   Cell segmentation package
%
%   ==========================================================================
```

Sourcecode
Examples
Testdata

Test-data

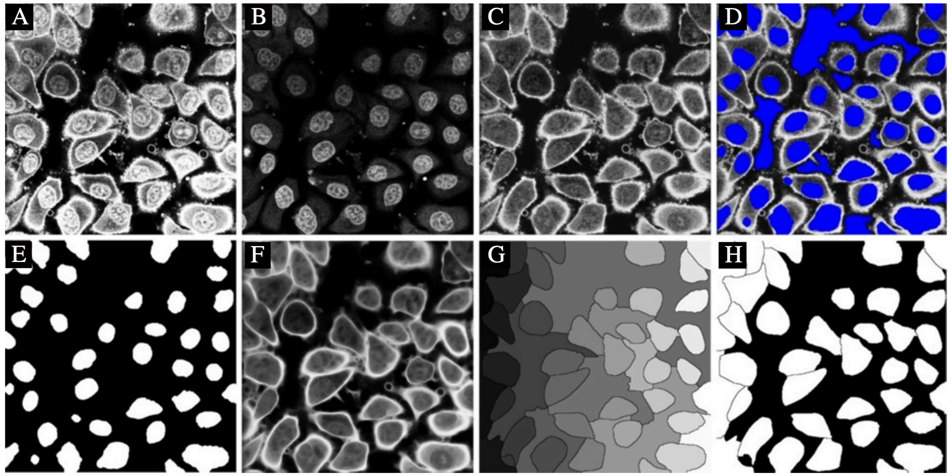


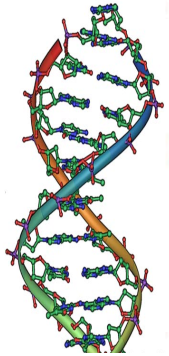
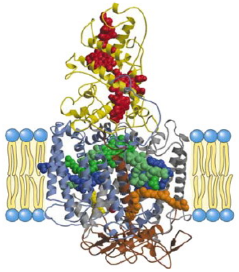
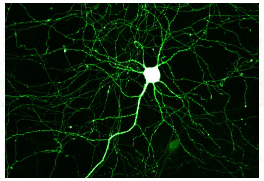
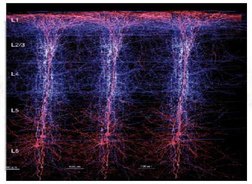
Figure 9 Segmentation of cells using nucleus markers in 2D from Example 7, executed for plane five in the image stack. A) Raw surface stain, **B)** raw nucleus stain, **C)** surface stain minus nucleus stain, **D)** markers (blue) derived from the nucleus stain superimposed onto the surface stain, **E)**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

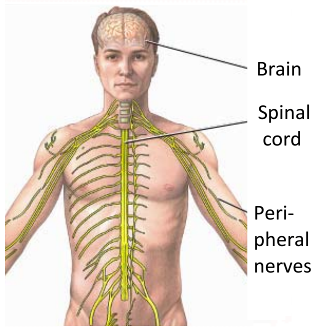
The future of bio(medical)imaging and imaging-based modeling…

- **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

SPACE:

Atom	Protein	Cell	Tissue	Organ	Organ system & organism
10^{-12} m	10^{-9} m	10^{-6} m	10^{-3} m	10^{0} m Anatomy	Physiology



Gene networks	Pathway models	Stochastic models	Ordinary Differential Equations	Continuum models (Partial Differential Equations)	Systems models

TIME:

10^{-6} s	10^{-3} s	10^{0} s	10^{3} s	10^{6} s	10^{9} s
molecular events (ion channel gating)	diffusion cell signalling	motility	mitosis	protein turnover	human lifetime

SUMMARY

Addressing the challenges:

Δ mindset

Δ skillset

Δ toolset

- open science

- reproducible research

- education
- training

DLN PhD school !

From: C. Dollery and R. Kitney, Systems biology: A vision for engineering and medicine, Tech. report, The Academy of Medical Sciences and The Royal Academy of Engineering, London, UK, Feb. 2007.