Advances and Challenges in Dynamic Bioimage Analysis



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Bioimage analysis ingredients







Microscope

Computer

Software

Developments in light microscopy



Resolution improvements

MICRO 1670: Leeuwenhoek ~ 1 µm **1930:** Phase-Contrast 1950: Differential Interference Contrast 1980: Confocal ~ 250 nm 1994: STED ~ 40 nm ~ 100 nm **1997:** 4Pi ~ 70-90 nm 1999: IⁿM 2000: SIM ~ 100 nm 2005: SSIM ~ 50 nm NANO 2006: PALM/STORM ~ 2-25 nm



Developments in light microscopy



Developments in computer hardware

Electronics, Volume 38, Number 8, April 19, 1965

Cramming more components onto integrated circuits

By Gordon E. Moore

• The complexity for minimum component costs has increased at a rate of roughly a factor of two per year (see graph on next page). Certainly over the short term this rate can be expected to continue, if not to increase. Over the longer term, the rate of increase is a bit more uncertain, although there is no reason to believe it will not remain nearly constant for at least 10 years. **9**





singularity.com

Developments in computer hardware



Developments in computer software?



sanantonioeyeinstitute.com

Diversity of cell images



Cell segmentation examples



Thresholds

Features

Watersheds

Deformables

Cell segmentation approaches over time



From 250 technical journal papers describing cell segmentation methods

Meijering, IEEE Signal Processing Magazine, 2012

More powerful methods are needed

Recently proposed concepts

- Graph cuts
- Active masks
- Dynamic programming
- Support vector machines
- Tensor voting schemes
- Bayesian estimation
- Particle filtering
- Markov random fields
- Neural networks



Catalysts for future method development



Improved availability

Community supported software platforms

Improved testability

Standardized test images and measures

Improved comparability

Organization of objective challenges

Community supported software



Images with expert annotation to serve as gold standard





- DIADEM Data Sets http://www.diademchallenge.org/
- Broad Bioimage Benchmark Collection http://www.broadinstitute.org/bbbc/
- UCSB Bio-Segmentation Benchmarking
 http://bioimage.ucsb.edu/research/bio-segmentation
- Cell Centered Database http://ccdb.ucsd.edu/

Cell Image Library

http://www.cellimagelibrary.org/

COMPUTER VISION, GRAPHICS, AND IMAGE PROCESSING 36, 387-391 (1986)

Anything You Can Do, I Can Do Better (No You Can't)...*

KEITH PRICE

Powell Hall MC-0273, Intelligent Systems Group, University of Southern California, Los Angeles, California 90089-0273

Received February 3, 1986; revised March 5, 1986

Computer vision suffers from an overload of written information but a dearth of good evaluations and comparisons. This paper discusses why some of the problems arise and offers some guidelines we should all follow. © 1986 Academic Press, Inc.

INTRODUCTION

Many of the comments in this paper apply to any scientific domain and are not unique to computer vision, but some other research domains have well-defined methods for evaluating research (e.g., in medical research, does it help the patient?).

Organization of objective challenges



Grand Challenges in Biomedical Image Analysis

Every year, thousands of papers are published that describe new algorithms to be applied to medical and biomedical images, and various new products appear on the market based on such algorithms. But few papers and products provide a fair and direct comparison of the newly proposed solution with the state-of-the-art. We believe that such comparisons can help the research community and industry to develop better algorithms. We support the organization of these comparative studies and the dissemination of their results.

Organizing and participating in challenges is not the only way to facilitate better comparisons between new and existing solutions. If it were easy to publish and share your data, and the code you used to evaluate your algorithm's performance on that data, and possibly the algorithm itself, others could directly compare their approach to yours, using the same test data and the same evaluation metrics. With this site we provide tools to make it as easy as possible for you to publish your data and your evaluation for any paper you've written.

Why Challenges? describes the rationale for organizing grand challenges, provides advice for those who want to organize such events, and discusses where we hope the field will move to next.

<u>All Challenges</u> provides an overview of all previous, ongoing and upcoming challenges in biomedical image analysis that we are aware of. Drop us a note if you want your event listed on this overview.

<u>Create your own project</u> explains how you can set up your own challenge site in a matter of minutes, based upon the COMIC platform, open source and <u>hosted on</u> <u>github</u>, that we are developing within an international consortium. The idea is that you can easily reuse all the tools we have developed to set up challenge sites, and instead of a full-blown challenge, you can also create sites for sharing data, evaluation code, and algorithms. We also link to other platforms that offer similar solutions and invite everybody to help us build better platforms.

Bioimage analysis challenges



Particle tracking challenge 2012 Website: http://www.biomedicalimaging.org/2012/ind Event: ISBI, May 2, 2012



Cell Tracking Challenge Website: http://www.codesolorzano.com/celltrackingchallenge/ @ Event: ISBI, April 11, 2013 @



Segmentation of neuronal structures in EM stacks 20 Website: http://www.biomedicalimaging.org/2012/ind challenges/49-contest-workshop-segmentation-of-ne Event: ISBI, May 2, 2012 Overview article: http://ieeexplore.ieee.org/xpl/article Number of submissions: 20



Localization Microscopy Challenge Website: http://bigwww.epfl.ch/smlm/challenge/ Event: ISBI, April 11, 2013 Number of submissions: 25



Mitosis Detection in Breast Cancer Histological Image Website: http://ipal.cnrs.fr/ICPR2012/ & Event: ICPR 2012 & Number of submissions: 17, Latest result: Apr 16, 20:



3D Segmentation of Neurites in EM Images Website: http://brainiac.mit.edu/SNEMI3D/ & Event: ISBI, April 11, 2013 &



3D Deconvolution Microscopy Website: http://bigwww.epfl.ch/deconvolution/challe Event: ISBI, April 11, 2013



Assessment of Mitosis Detection Algorithms 2013 Website: http://amida13.isi.uu.nl/@ Event: MICCAI, September 22, 2013@

Particle Tracking Challenge

Contest Workshop

http://bioimageanalysis.org/track/



Summary

Organizers

Erik Meijering Erasmus MC – University Medical Center Rotterdam, The Netherlands

Jean-Christophe Olivo-Marin Institut Pasteur, Paris, France



Quantitative analysis of dynamic processes in biological cells requires accurate tracking of large numbers of particles in time-lapse microscopy images. The aim of this challenge is to objectively compare the performance of existing and newly developed particle tracking algorithms for this purpose.

The evaluation will be based on synthetic image sequences (with known ground truth) simulating real fluorescence microscopy image data from a range of biological applications. The accuracy and robustness of the algorithms will be evaluated using various particle localization and trajectory consistency error measures.

ISBI 2012 Challenges

This challenge is organized as part of the ISBI 2012 Challenges. It is open to all groups (academic or corporate) developing their own particle tracking methods.

Home

Life is dynamic...



Drosophila embryogenesis



Increasing interest in tracking

Market share (in percent) of papers published on the subject



PubMed, NLM, USA, January 2015

Many tools already available

Vane	4 railable	Platform	Source	Cell	Particle	Multiple	Dimension	Automation	Author or Recorder	Meijering et al. 2012 Methods in Enzymology	
Braincells	Free	Win		V		V	2D	Manual	Gabor Ivancsy	http://pearl.eite.hu/~kyd/	
CellProfiler	Free	Win/Lin/Mac	V	V	V	V	2D	Auto	Carpenter et al. (2006)	http://www.cellprofiler.org/	
CellTrack	Free	Win	V	V		V	2D	Auto	Sacan et al. (2008)	http://db.cse.ohio-state.edu/CellTrack/	
CellTracker	Free	Win		V		V	2D	Semi	Shen et al. (2006)	http://go.warwick.ac.uk/bretschneider/celltracker/	
ClusterTrack	Free	Matlab	V		V	V	2D	Auto	Matov et al. (2010)	http://lccb.hms.harvard.edu/software.html	
DCellIQ	Free	Matlab	V	V		V	2D	Auto	Li et al. (2010)	http://www.cbi-tmhs.org/Dcelliq/	
DIAS	Paid	Win/Mac		V		V	3D	Auto	Wessels et al. (2006)	http://keck.biology.uiowa.edu/	
DiaTrack	Paid	Win		V	\checkmark	\checkmark	3D	Auto	Semasopht (Switzerland)	http://www.semasopht.com/	
DYNAMIK	Free	Matlab	V	V		V	2D	Auto	Mosig et al. (2009)	http://www.picb.ac.cn/sysbio/DYNAMIK/	
FARSIGHT	Free	Win/Lin/Mac	V	\checkmark		V	3D	Auto	Bjomsson et al. (2008)	http://www.farsight-toolkit.org/	
GMinPro	Free	Win			V	V	2D	Auto	Mashanov & Molloy (2007)	http://www.nimr.mrc.ac.uk/gmimpro/	
ICY	Free	Java	\checkmark	V	V	V	3D	Auto	de Chaumont et al. (2011)	http://icy.bioimageanalysis.org/	
Image-Pro Plus	Paid	Win		V	V	\checkmark	3D	Auto	Media Cybernetics (USA)	http://www.mediacy.com/index.aspx?page=IPP	
ImarisTrack	Paid	Win/Mac		V	V	V	3D	Auto	Bitplane (Switzerland)	http://www.bitplane.com/go/products/imaristrack	
LevelSetTracker	Free	Matlab	V	V		V	3D	Auto	Dzyubachyk et al. (2010)	http://celmia.bigr.nl/	
LineageTracker	Free	ImageJ		V		V	2D	Auto	Till Bretschneider	http://go.warwick.ac.uk/bretschneider/lineagetracker/	
ManualTracking	Free	ImageJ	V		V	V	3D	Manual	Fabrice Cordelières	http://rsb.info.nih.gov/ij/plugins/track/track.html	
MetaMorph	Paid	Win		V	\checkmark	V	3D	Auto	Molecular Devices (USA)	http://www.moleculardevices.com/Products/Software.html	
MTrack2	Free	ImageJ	V		\checkmark	V	2D	Auto	Nico Stuurman	http://valelab.ucsf.edu/~nico/Uplugins/MTrack2.html	
MTrackJ	Free	ImageJ	V		V	V	3D	Manual	Erik Meijering	http://www.imagescience.org/meijering/software/mtrackj/	
MTT	Free	Matlab	V		V	V	2D	Auto	Sergé et al. (2008)	http://www.ciml.univ-mrs.fr/lab/he-marguet.htm	
Octane	Free	ImageJ	V		V	\checkmark	2D	Auto	Ji Yu lab	http://www.ccam.uchc.edu/yu/Software.shtml	
Oko-Vision	Paid	Win		V		\checkmark	2D	Semi	Okolab (Italy)	http://www.oko-lab.com/cell_tracking.page	
ParticleTracker	Free	ImageJ	V		V	V	3D	Auto	Sbalzarini et al. (2005)	http://weeman.inf.ethz.ch/ParticleTracker/	
ParticleTracking	Free	IDL	V		V	V	2D	Auto	Crocker & Grier (1996)	http://physics.nyu.edu/grierlab/software.html	
plusTipTracker	Free	Matlab	N		V	V	2D	Auto	Danuser lab	http://lccb.hms.harvard.edu/software.html	
PolyParticleTracker	Free	Matlab	V		V	V	2D	Auto	Rogers et al. (2007)	http://personalpages.manchester.ac.uk/staff/david.kenwright/software.html	
QuimP	Free	ImageJ		V			2D	Auto	Bosgraaf et al. (2009)	http://go.warwick.ac.uk/bretschneider/quimp/	
SpeckleTrackerJ	Free	ImageJ	\checkmark		V	V	2D	Semi	Smith et al. (2011)	http://athena.physics.lehigh.edu/speckletrackerj/	
SpotTracker	Free	ImageJ			V		2D	Auto	Sage et al. (2005)	http://bigwww.epfl.ch/sage/soft/spottracker/	
StarryNite	Free	Win/Lin		V		V	3D	Auto	Murray et al. (2006)	http://waterston.gs.washington.edu/	
TIKAL	Request	Win/Lin			\checkmark	V	3D	Auto	Bacher et al. (2004)	http://ibios.dkfz.de/tbi/	
TLA	Free	Matlab	V	V		V	2D	Auto	Huth et al. (2011)	http://www.informatik.uni-ulm.de/ni/staff/HKestler/tla/	
u-track	Free	Matlab	V		V	\checkmark	2D	Auto	Jaqaman et al. (2008)	http://lccb.hms.harvard.edu/software.html	
Volocity	Paid	Win/Mac		V	\checkmark	V	3D	Auto	Perkin Elmer (USA)	http://cellularimaging.perkinelmer.com/products/volocity/demo/	

Objective comparison of algorithms



Participating methods

Particle detection



Particle linking



- Intensity thresholding
- Centroid calculation
- Convolution with disk
- Wavelet-based detection
- Local maxima finding
- Gaussian model fitting
- LoG / DoG filtering
- Morphological filtering

- Nearest-neighbor linking
- Multiple hypothesis tracking
- Viterbi path searching
- Multi-Kalman filtering
- Dynamic programming
- Interacting multiple motion models
- Simulated annealing energy minimization

Real image data...?



- Most realistic particle appearance and dynamics
- But... no ground truth available... manual annotation?
- Observer variability, subjectivity, incompleteness
- Known from previous evaluations to be inferior

Simulated image data

Most important factors affecting tracking performance?

Particle dynamics	 Random walk Near-constant velocity Switching random Switching directed 	(2D) (2D) (2D) (3D)
Particle density	 Low (≈ 100 particle Medium (≈ 500 particle High (≈ 1000 particle 	es) es) es)
Particle signal	 Bad (SNR ≈ 1) Low (SNR ≈ 2) Critical (SNR ≈ 4) 	

• High (SNR ≈ 7)

Total 48 sequences

- Fluorescence microscopy
- GFP-labeled particles
- Images 512 x 512 pixels
- Stacks of 10 slices
- Length 100 frames
- About 4 GB of data
- Airy or Gaussian PSF
- Poisson noise
- Random processes
- Track length \geq 4 frames
- Mean length ≈ 15 frames
- No particle interaction
- Trajectory ambiguities
- Ground truth known

Simulated image data set



Simulated image data examples



Scenario 1 Random walk (2D)



Scenario 2 Near-constant velocity (2D)



Scenario 3 Switching random (2D)



Scenario 4 Switching directed (3D)

> Density = Medium SNR = 4

Quantitative performance measures





Low density



Mid density



High density



Low density



Mid density



High density

General observations

- Overall trends in good agreement with expectations
- No single method best overall (dynamics, density, SNR)
- Best detection using Gaussian and centroid based methods
- Best linking using motion models and global optimization
- Best methods not necessarily computationally slowest
- Better methods are possible by different combinations
- Much room for improvement remains (detection + linking)
- Fundamentally new concepts (learning-based?) needed
- More detailed analyses in published challenge paper

Objective comparison of particle tracking methods

Nicolas Chenouard^{1-3,25}, Ihor Smal^{4,5,25}, Fabrice de Chaumont^{1,25}, Martin Maška^{6,7,25}, Ivo F Sbalzarini⁸, Yuanhao Gong⁸, Janick Cardinale⁸, Craig Carthel⁹, Stefano Coraluppi⁹, Mark Winter¹⁰, Andrew R Cohen¹⁰, William J Godinez^{11,12}, Karl Rohr^{11,12}, Yannis Kalaidzidis^{13,14}, Liang Liang¹⁵, James Duncan¹⁵, Hongying Shen¹⁶, Yingke Xu¹⁷, Klas E G Magnusson¹⁸, Joakim Jaldén¹⁸, Helen M Blau¹⁹, Perrine Paul-Gilloteaux²⁰, Philippe Roudot²¹, Charles Kervrann²¹, François Waharte²⁰, Jean-Yves Tinevez²², Spencer L Shorte²², Joost Willemse²³, Katherine Celler²³, Gilles P van Wezel²³, Han-Wei Dan²⁴, Yuh-Show Tsai²⁴, Carlos Ortiz de Solórzano⁶, Jean-Christophe Olivo-Marin^{1,26} & Erik Meijering^{4,5,26}

Particle tracking is of key importance for quantitative analysis of intracellular dynamic processes from time-lapse microscopy image data. Because manually detecting and following large numbers of individual particles is not feasible, automated computational methods have been developed for these tasks by many groups. Aiming to perform an objective comparison of methods, we gathered the community and organized an open competition in which participating teams applied their own methods independently to a commonly defined data set

processes is particle tracking. Here, a 'particle' may be anything from a single molecule to a macromolecular complex, organelle, virus or microsphere¹², and the task of detecting and following individual particles in a time series of images is often (somewhat confusingly) referred to as 'single-particle tracking'. As the number of particles may be very large (hundreds to thousands), requiring 'multiple-particle tracking'^{13–15}, manual annotation of the image data is not feasible, and computer algorithms are needed to perform the task.

Mean-squared displacement results



Mean-squared displacement results



Linking as a function of detection performance

Most common linking algorithms

- Multi-Dimensional Assignment (MDA)
- Noniterative Greedy Assignment (NGA)
- Interacting Multiple Models (IMM)
- Linear Assignment Procedure (LAP)
- Greedy Nearest-Neighbor (GNN)

Enhanced ground-truth evaluation data set

- Four motion scenarios (random-walk, linear, mix 2D & 3D)
- Low (~100) and medium (~500 particles) density levels
- False-negative (FN) detection levels 0, 5, 10, 15, 20%
- False-positive (FP) detection levels 0, 10, 20, 30, 40, 50%



240 cases

Linking as a function of detection performance



Linking is much more sensitive to missing than to spurious detections !

MTrackJ2 for advanced particle and cell tracking

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1	1	1	25.5	12.113	5	18	0	0	NA	NA
2	1	2	25.415	12.337	6	34	0.239	0.239	0.239	0.239
3	1	3	25.338	12.55	7	30	0.467	0.467	0.227	0.227
4	1	4	25.325	12.797	8	30	0.714	0.706	0.247	0.247
5	2	1	19,793	23.68	0	20	0	0	NA	NA
6	2	2	19.949	23.881	1	39	0.254	0.254	0.254	0.254
7	2	3	20.095	24.042	2	24	0.472	0.472	0.218	0.218
8	2	4	20.232	24.217	3	25	0.694	0.694	0.222	0.222
9	2	5	20.341	24.373	4	26	0.884	0.883	0.19	0.19
10	2	6	20.409	24.546	5	21	1.07	1.063	0.186	0.186
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2	2	11	19.793	20.661	20.355	0.304	23.68	25,373	24.5	
3	3	21	2.69	7,762	5.06	1.701	16.385	18.309	17.2	
4	4	5	12.542	13.51	13.024	0.358	12.011	12,785	12.4	
5	Б	14	4.996	8.715	6.912	1.176	8.147	9.563	8.71	
6	6	19	10.006	14.122	11.86	1.325	15.08	19.012	16.S	
7	7	13	17 265	19.802	18.341	0.804	5.083	5.57	5.36	
8	в	15	19.352	21.794	20,444	0.829	12.316	14.943	13.8	
9	9	8	6.76	7.835	7.275	0.38	6.603	8.292	7.45	
10	10	8	8.268	9.664	8.893	0.506	11.337	11.747	11.5	

http://www.imagescience.org/meijering/software/mtrackj/



Clear	Revert
Load	Import
Save	Export
Add	Cluster
Hide	Color
Delete	Mave
Merge	Split
Refer	Set
Measure	Record
Filter	Render
Auto	Hand
Options	Display
Qut	Help

To be released soon!

- Fully automated tracking solutions
- Fully manual tracking and track editing
- Customizable track visualization
- Support for multiple file formats



Bioinformatics

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A benchmark for comparison of cell tracking algorithms

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Abstract

Motivation: Automatic tracking of cells in multidimensional time-lapse fluorescence microscopy is an important task in many biomedical applications. A novel framework for objective evaluation of cell tracking algorithms has been established under the auspices of the IEEE International Symposium on Biomedical Imaging 2013 Cell Tracking Challenge. In this article, we present the logistics, datasets, methods and results of the challenge and lay down the principles for future uses of this benchmark. CORRECTED PROOF

This Article

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Bioinformatics (2014) doi: 10.1093/bioinformatics/btu080 First published online: February 12, 2014

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Cell Tracking Challenge

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Arrate Muñoz Barrutia

Carlos III University, Madrid, Spain

Website

http://www.codesolorzano.com/celltrackingchallenge/

Challenge Abstract

Tracking moving cells in time-lapse video sequences is a challenging task, required for many applications in both scientific and industrial settings. Properly characterizing how cells move as they interact with their surrounding environment is key to understanding the mechanobiology of cell migration and its multiple implications in both normal tissue development and many diseases. Our proposal is to leverage on the experience, methods and results of the ISBI'13 and ISBI'14 Cell Tracking Challenges to expand and enrich our comprehensive benchmark for comparison of cell tracking algorithms by attracting new participants, and new submissions. To this end will use our existing dataset repository, which includes 2D and 3D fluorescence, Phase Contrast and Differential Interference Contrast microscopy videos, and realistic simulations of moving nuclei both in 2D and 3D. Furthermore, we will provide new light-sheet microscopy 3D embryonic developmental data, probably the most challenging cell tracking problem existing today.

Summary

Bioimage analysis is a huge challenge!

- Rapid developments in microscopic imaging
- Rapid developments in computer technology
- To be matched by computer vision methods

Recent developments shaping the future

- Improved availability of bioimage analysis methods
- Improved availability of image data and ground truth
- Improved availability of objective comparison results