Computational Pathology

Toby C. Cornish, MD, PhD
Associate Professor of Pathology
University of Colorado SOM
May 21, 2018

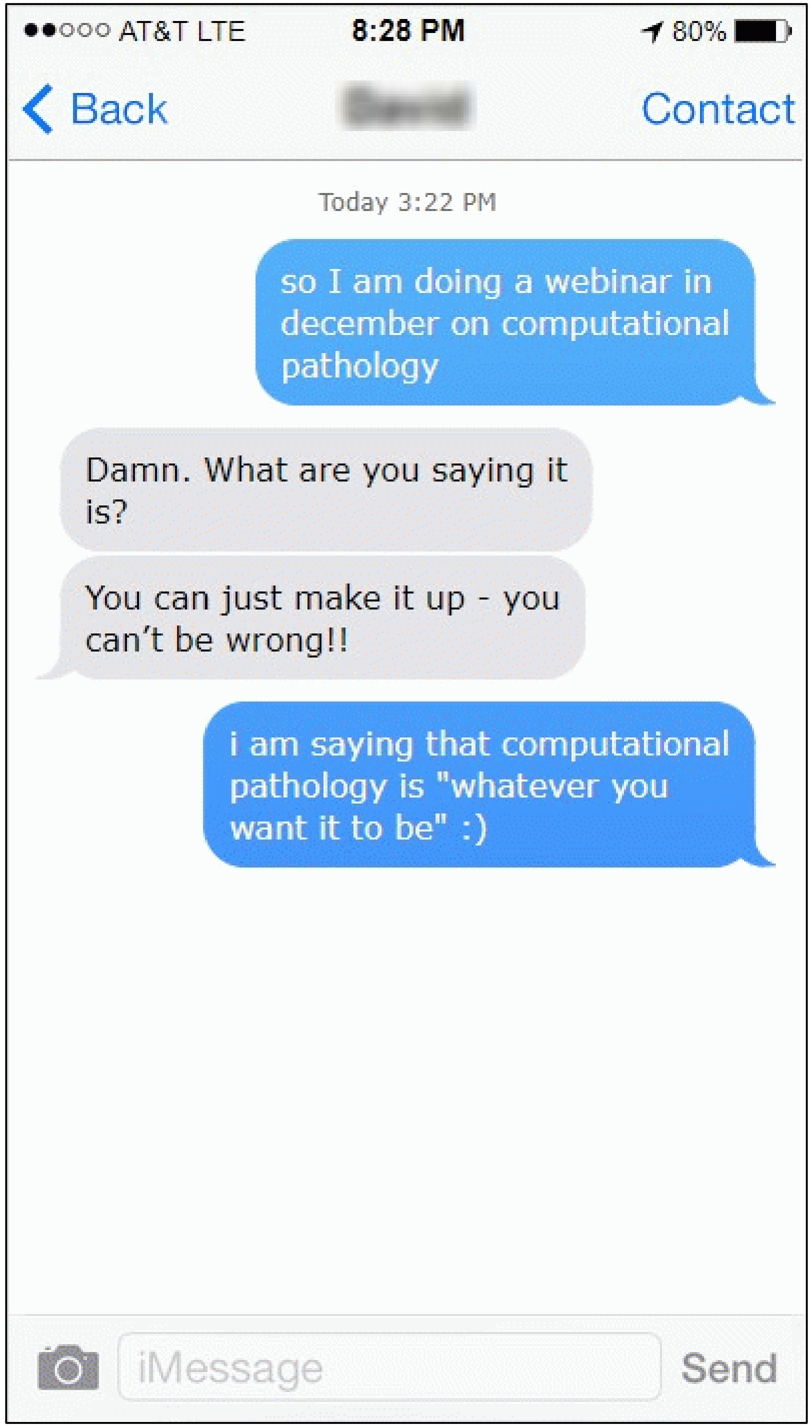
Disclosures

- Leica, Inc. Pathology Imaging Advisory Board

Learning Objectives

- By the end of this activity, the audience should be able to:
    - Define computational pathology (CP)
    - Distinguish (generally) between CP methods and non-CP methods
    - Give examples of data sources used in CP
    - Understand the evolution of CP, including its current state
    - Explain why deep learning has advanced CP
    - List typical use cases for CP in digital pathology
    - Recognize challenges to advancing CP

What is computational pathology?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so I am doing a webinar in december on computational pathology
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You can just make it up - you can't be wrong!!
i am saying that computational pathology is "whatever you want it to be" :)
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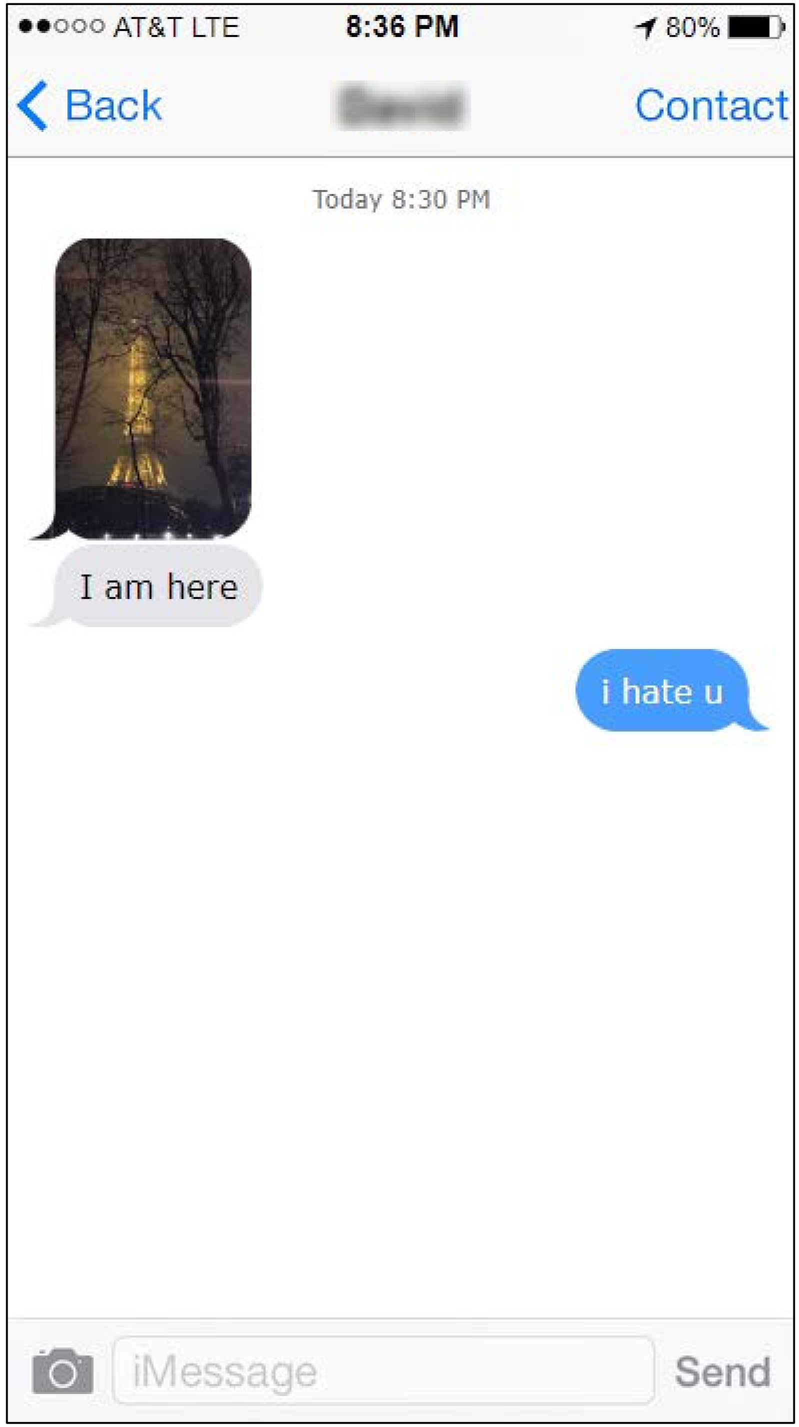
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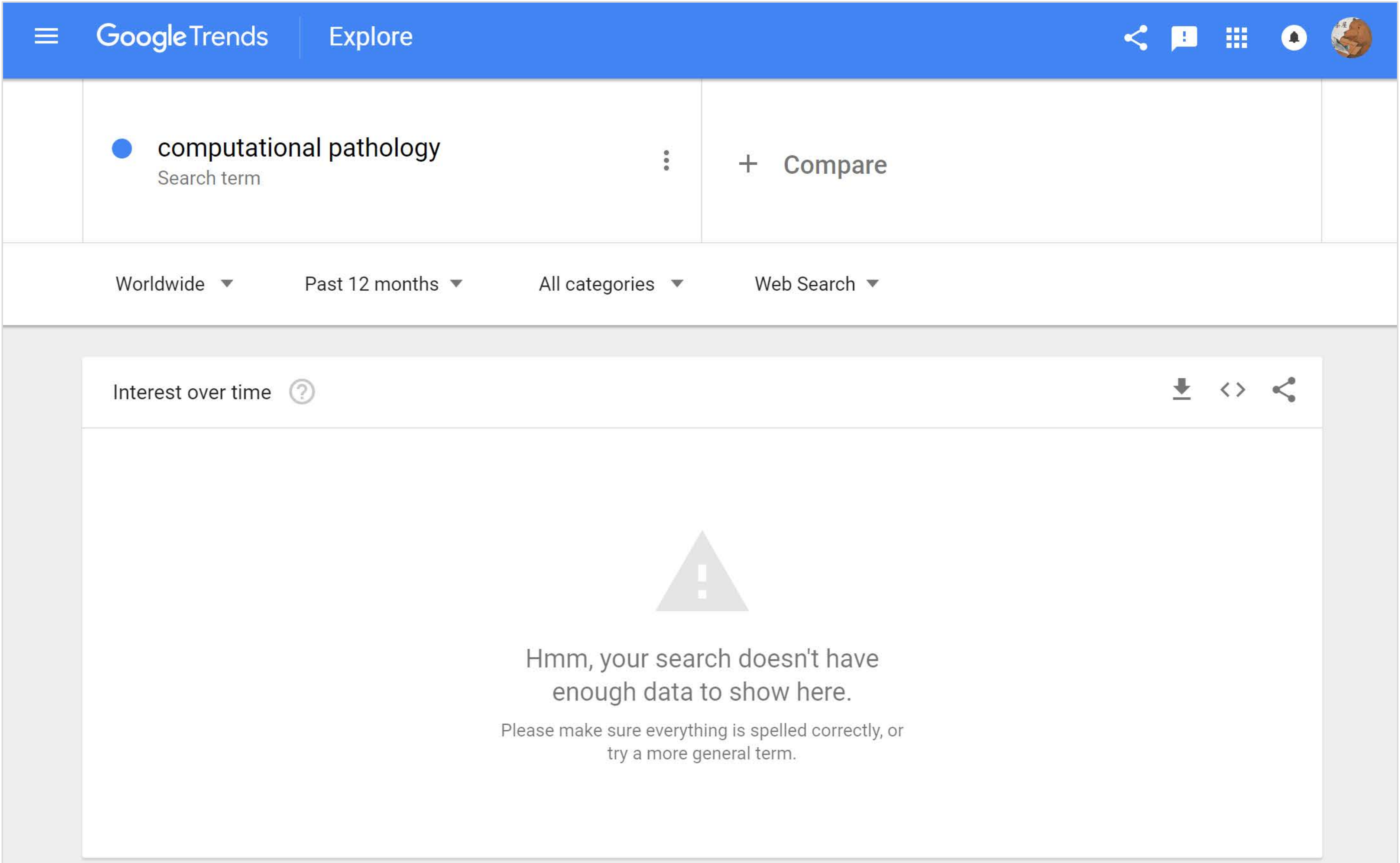
“The beginning of wisdom is to call things by their proper name.”

— Confucius

Why do we have difficulty defining computational pathology?



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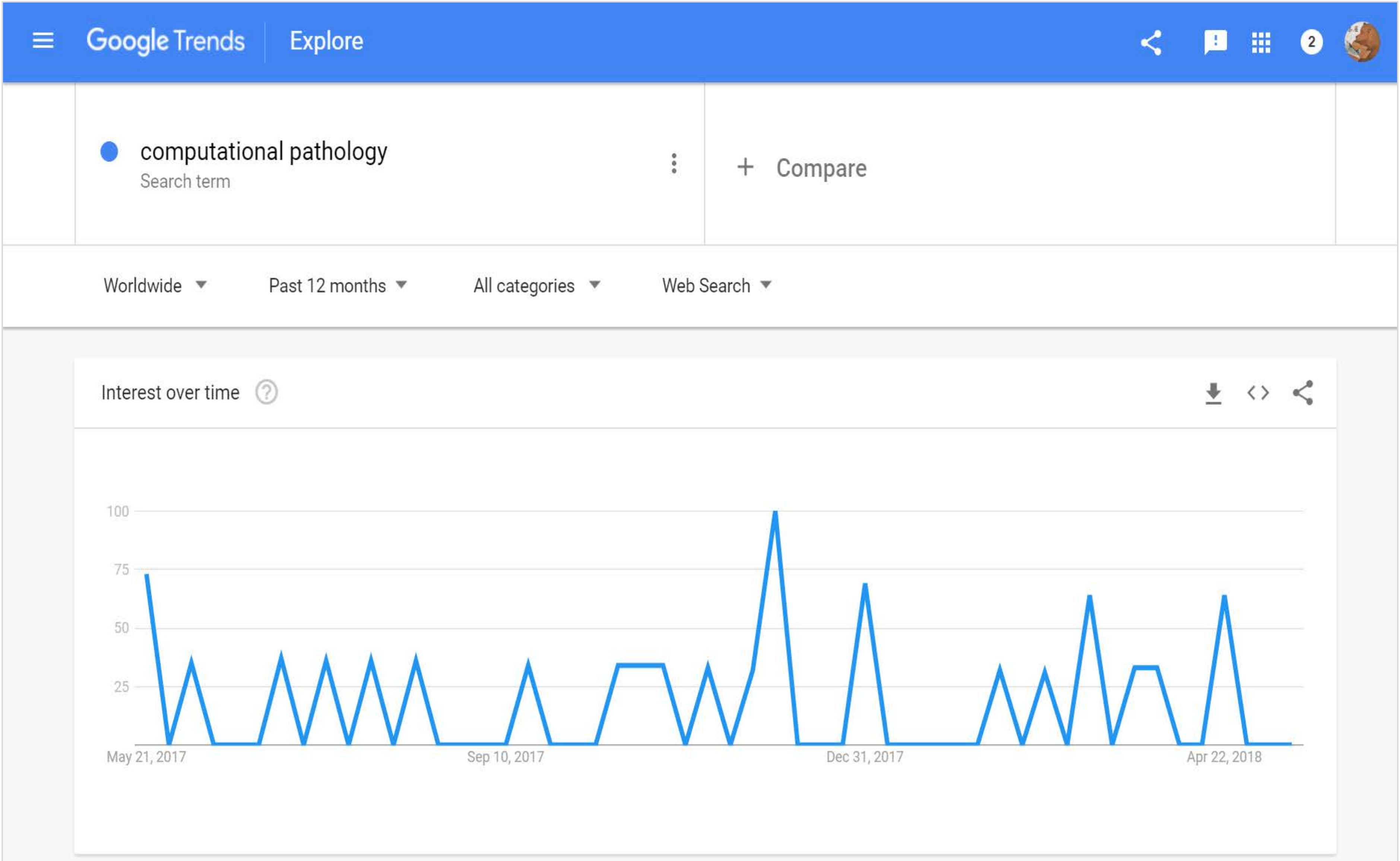

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1. Computational simulation and modeling of the blood-brain barrier pathology.
Shityakov S, Förster CY.
Histochem Cell Biol. 2018 May 2. doi: 10.1007/s00418-018-1665-x. [Epub ahead of print]
Review.
PMID: 29721642
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2. Preparing for a **Computational Pathology** Future Through Informaticians and a Computational Technologist Workforce.
Sirintrapun SJ.
Am J Clin Pathol. 2018 Mar 29;149(5):369-372. doi: 10.1093/ajcp/aqy009. No abstract available.
PMID: 29538613
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3. Computationally-Guided Development of a Stromal Inflammation Histologic Biomarker in Lung Squamous Cell Carcinoma.
Xia D, Casanova R, Machiraju D, McKee TD, Weder W, Beck AH, Soltermann A.
Sci Rep. 2018 Mar 2;8(1):3941. doi: 10.1038/s41598-018-22254-4.
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4. What is mood? A computational perspective.

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"computational pathology"[All Fields]
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Defining “pathology”

- In North America (predominantly), pathology includes both anatomic pathology and clinical pathology (laboratory medicine)

- Elsewhere in the world, pathology is limited to anatomic pathology

Defining "computational"

computational

ADJECTIVE

1 Using or relating to computers.

'the computational analysis of English'

\+ More example sentences

2 Relating to the process of mathematical calculation.

'the exam only really tested computational ability'

\+ More example sentences

https://en.oxforddictionaries.com/definition/computational

Is this computational pathology?

- $INR = (PT\ patient / PT\ normal)^{ISI}$

Definition: Computational *Biology*

- The development and application of data-analytical and theoretical methods, mathematical modeling and computational simulation techniques to the study of biological, behavioral, and social systems.

"NIH working definition of bioinformatics and computational biology". Biomedical Information Science and Technology Initiative. NIH. 17 July 2000.

Computational Pathology Analysis of Tissue Microarrays Predicts Survival of Renal Clear Cell Carcinoma Patients

Thomas J. Fuchs[1,3], Peter J. Wild[2],
Holger Moch[2,3], and Joachim M. Buhmann[1,3]

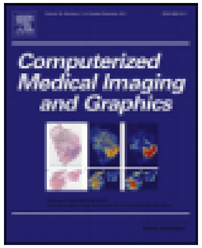
[1] Institute for Computational Science, ETH Zürich, Switzerland
{thomas.fuchs, jbuhmann}@inf.ethz.ch
[2] Institute of Pathology, University Hospital Zürich, University Zürich, Switzerland
[3] Competence Center for Systems Physiology and Metabolic Diseases, ETH Zürich

D. Metaxas et al. (Eds.): MICCAI 2008, Part II, LNCS 5242, pp. 1–8, 2008.

Contents lists available at ScienceDirect

Computerized Medical Imaging and Graphics

journal homepage: www.elsevier.com/locate/compmedimag



Review

Computational pathology: Challenges and promises for tissue analysis

Thomas J. Fuchs [a,b,*], Joachim M. Buhmann [a,b]

[a] Department of Computer Science, ETH Zurich, Universitaetstrasse 6, CH-8092 Zurich, Switzerland
[b] Competence Center for Systems Physiology and Metabolic Diseases, ETH Zurich, Schafmattstr. 18, CH-8093 Zurich, Switzerland

doi:10.1016/j.compmedimag.2011.02.006

Fuchs & Buhmann 2011 Definition

- “Computational Pathology investigates a complete probabilistic treatment of scientific and clinical workflows in general pathology, i.e. it combines experimental design, statistical pattern recognition and survival analysis within a unified framework to answer scientific and clinical questions in pathology.”

Editorial

Computational Pathology

An Emerging Definition

David N. Louis, MD; Georg K. Gerber, MD, PhD; Jason M. Baron, MD; Lyn Bry, MD, PhD; Anand S. Dighe, MD, PhD; Gad Getz, PhD; John M. Higgins, MD; Frank C. Kuo, MD, PhD; William J. Lane, MD, PhD; James S. Michaelson, PhD; Long P. Le, MD, PhD; Craig H. Mermel, MD, PhD; John R. Gilbertson, MD; Jeffrey A. Golden, MD

Arch Pathol Lab Med—Vol 138, September 2014 *Editorial*—Louis et al **1133**

Computational Pathology:

A Path Ahead

Dr. David N. Louis, MD, **Dr. Michael Feldman, MD, PhD**, **Dr. Alexis B. Carter, MD**, **Dr. Anand S. Dighe, MD, PhD**, **Dr. John D. Pfeifer, MD, PhD**, **Dr. Lynn Bry, MD, PhD**, **Dr. Jonas S. Almeida, PhD**, **Dr. Joel Saltz, MD, PhD**, **Dr. Jonathan Braun, MD, PhD**, **Dr. John E. Tomaszewski, MD**, **Dr. John R. Gilbertson, MD**, **Dr. John H. Sinard, MD, PhD**, **Dr. Georg K. Gerber, MD, PhD, MPH**, **Dr. Stephen J. Galli, MD**, **Dr. Jeffrey A. Golden, MD**, and **Dr. Michael J. Becich, MD, PhD**

Published in final edited form as:
Arch Pathol Lab Med. 2016 January ; 140(1): 41–50. doi:10.5858/arpa.2015-0093-SA.

Definition: Computational Pathology

- An approach to diagnosis that incorporates multiple sources of raw data (eg, clinical electronic medical records, laboratory data including “-omics,” and imaging [both radiology and pathology imaging]); extracts biologically and clinically relevant information from these data; uses mathematic models at the molecular, individual, and population levels to generate diagnostic inferences and predictions; and presents this clinically actionable knowledge to customers through dynamic and integrated reports and interfaces, enabling physicians, patients, laboratory personnel, and other health care system stakeholders to make the best possible medical decisions.

Computational Pathology: A Path Ahead. Louis DN, et al. Arch Pathol Lab Med. 2016 Jan;140(1):41-50.

Definition: Computational Pathology

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Computational Pathology: A Path Ahead. Louis DN, et al. Arch Pathol Lab Med. 2016 Jan;140(1):41-50.

Computational Pathology: The Next Wave of Digital Pathology
5:00 pm - 7:30 pm
King's Garden 2/3

5:00 pm - 5:10 pm	Introduction/Opening Remarks	**Anil Parwani, MD, PhD, MBA**
5:10 pm - 5:45 pm	Future of Computational Pathology: Driving Innovation in Pathology Diagnostics	**Thomas J. Fuchs, PhD**
5:45 pm - 6:20 pm	The Nuts and Bolts of Computational Pathology: Considering Costs, Resources, Infrastructure Needs, And Barriers to Adoption	**David McClintock, MD**
6:20 pm - 6:55 pm	Platform for Quantitative Evaluation of Spatial Intratumor Heterogeneity in Multiplexed Fluorescence Images	**Chakra Chennubhotla, PhD**
6:55 pm - 7:25 pm	Computational Cytopathology: Past & Prospective Apps	**Liron Pantanowitz, MD**
7:25 pm - 7:30 pm	Wrap up	**Anil Parwani, MD, PhD, MBA**

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Computational Pathology: A Path Ahead. Louis DN, et al. Arch Pathol Lab Med. 2016 Jan;140(1):41-50.

Data sources: Lab

- Laboratory values
- Anatomic pathology free text reports
- Synoptic / discrete anatomic pathology data
- Molecular and genomic data
- Whole slide images
- Other digital imaging
- *Etc.*

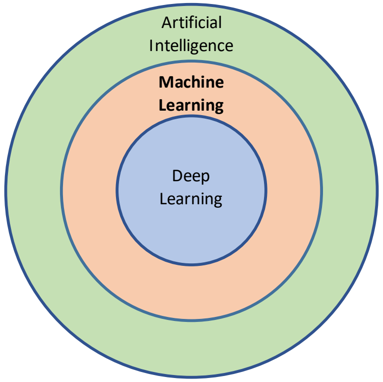
Data sources: Non-lab

- Problem lists
- Medication lists
- Vital signs
- Radiology notes
- Radiology imaging
- Clinical notes
- *Etc.*

Computational pathology and machine learning

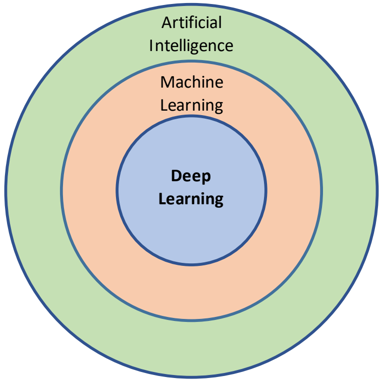
- Definitions of computational pathology include some element "mathematical models" (usually machine learning but potentially some other form of statistical / predictive model)

Machine learning



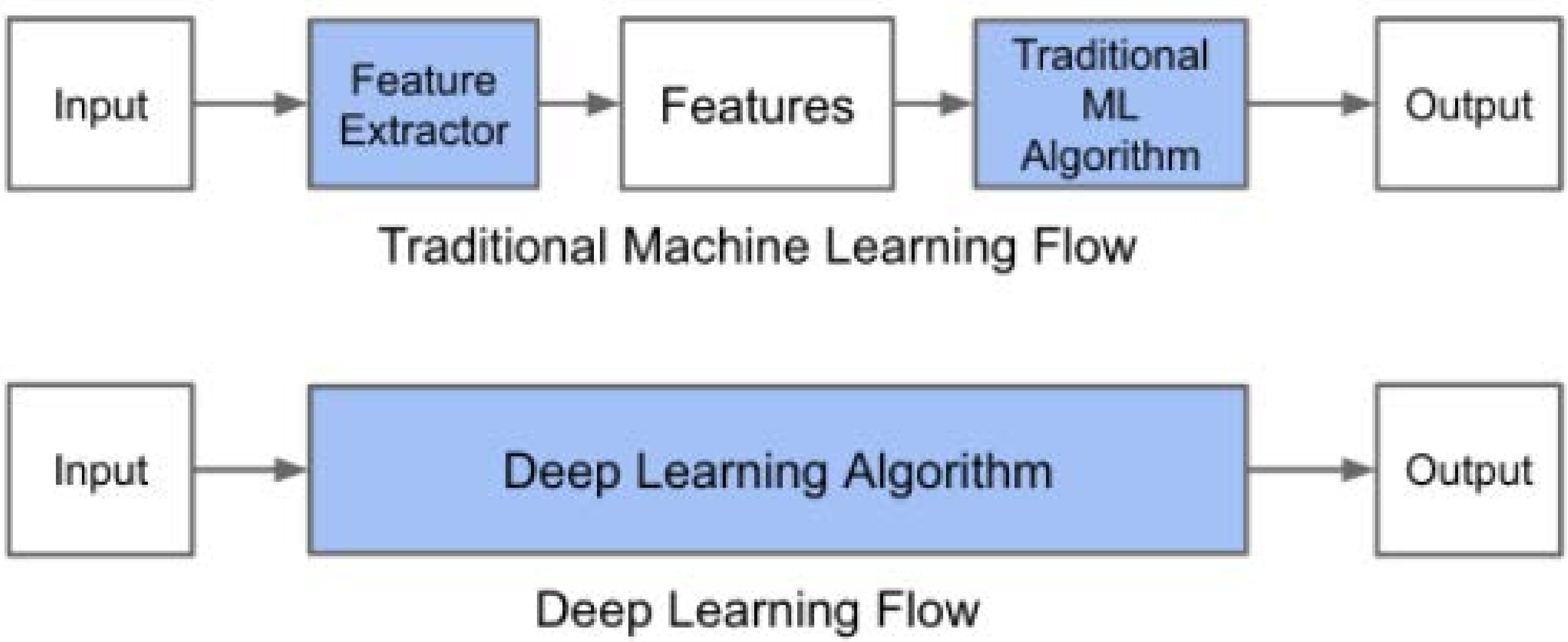
- Machine learning allows computers to predict outcomes from data without being explicitly programmed
- Refines a model that predicts outputs using sample inputs (features) and a feedback loop
- Classical machine learning relies heavily on extracting or selecting salient, which is a combination of art and science ("feature engineering")

Deep learning



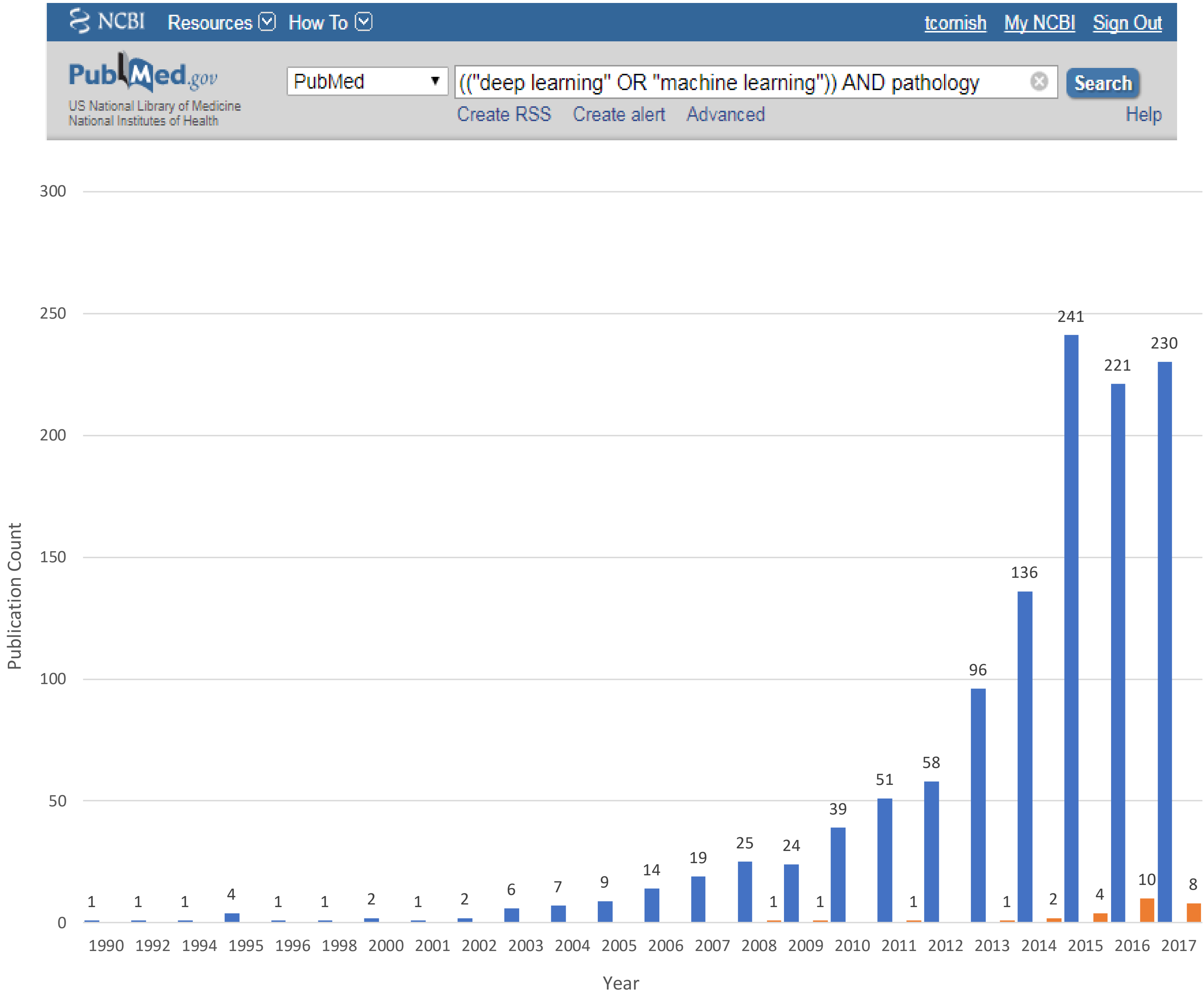
- Avoids the need to define specific features in the data as inputs
- Discovers the features from the raw data provided during training
- Hidden layers in the artificial neural network represent increasingly more complex features in the data
- Convolutional Neural Networks, a type of deep learning, are commonly used for image analysis

Machine learning *v.* deep learning



http://adilmoujahid.com/posts/2016/06/introduction-deep-learning-python-caffe/

The rise of machine learning / deep learning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Machine Learning in Quantitative Histopathology

Peter H. Bartels, Ph.D., F.I.A.C.(hon)
Jean E. Weber, Ph.D.
Lucien Duckstein, Ph.D.

0884-6812/88/1004-0299/$02.00/0
Analytical and Quantitative Cytology and Histology

Accepted for publication April 20, 1988.

However, it has become clear that the complexity of the problem domains in diagnostic cytopathology and histopathology must eventually lead to systems going beyond closed-domain, rule-based production systems and, in fact, must lead to systems capable of autonomous learning.

Bartels, et al. Machine learning in quantitative histopathology. *Anal Quant Cytol Histol*. 1988 Aug;10(4):299-306.

Current state of computational pathology (CP)

- Computational pathology is largely a research endeavor
- Some academic centers are beginning to explore its use in the clinical lab
- Numerous examples of computational pathology applied to digital pathology
- Handful of startups that seem to rely entirely on computational pathology (or the promise of CP)

Areas of application

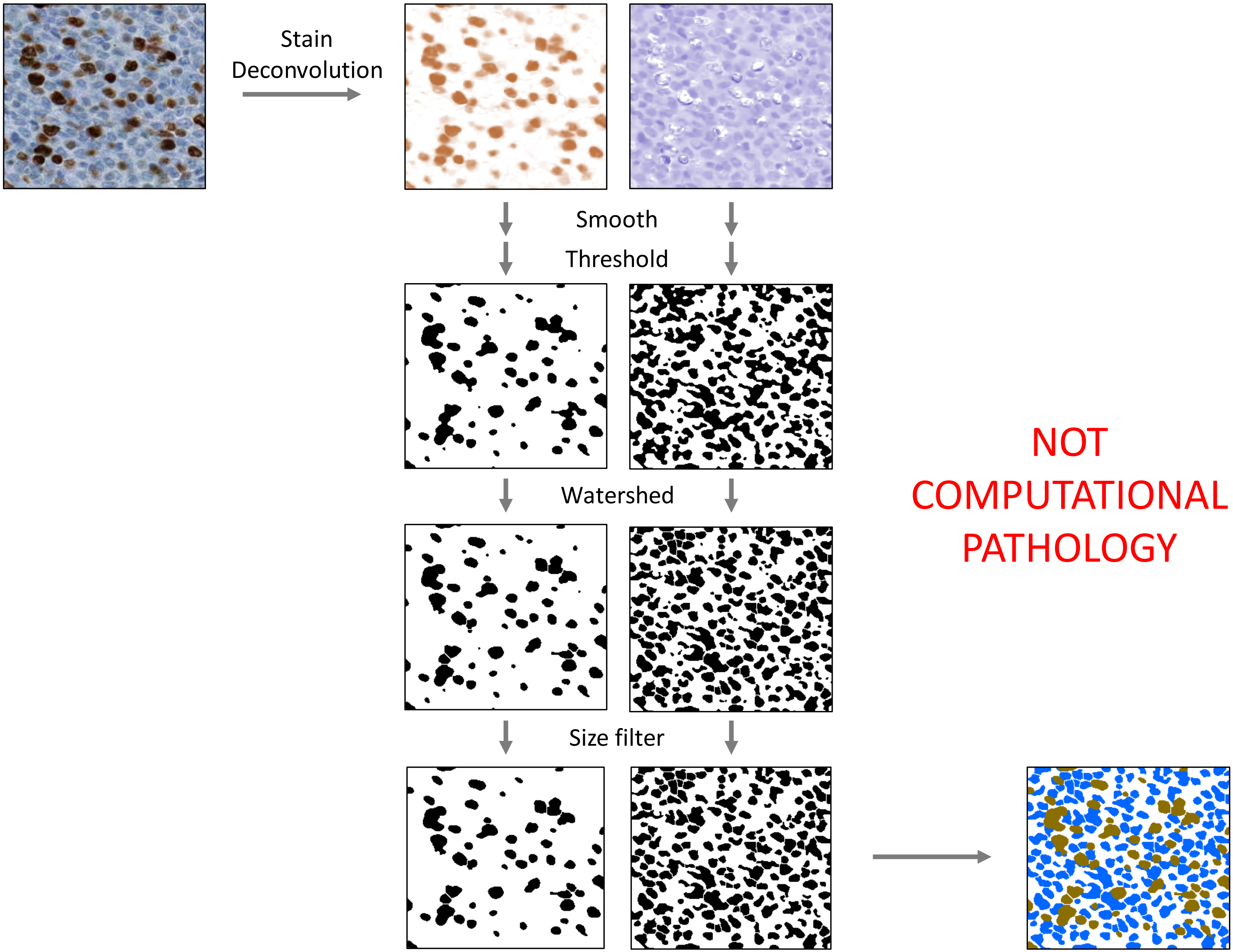
- Clinical decision support
- Test utilization / ordering
- “Surrogate” lab results
- Quality control / error detection
- Therapeutic outcome prediction
- Patient outcome prediction
- **Digital pathology**

CP in Digital Pathology

- CP has been applied to a number of areas:
  - Tissue classification
    - As part of a pipeline (segmentation) or standalone
    - Benign vs. malignant
    - Grading, etc.
  - Screening
  - Diagnosis
  - Prognostication
  - Prediction
  - Object / rare event identification

NOT CP in Digital Pathology

- Conventional task-specific image analysis algorithms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COMPUTATIONAL
PATHOLOGY

Who are the stakeholders in computational pathology?

Stakeholders

- Pathologists
- Clinicians
- Patients
- Population
- Health system
- Hospital administrators
- Payers
- Digital pathology companies

Stakeholders

- Pathologists
- Clinicians
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Pathologist benefits

- Use CP as an adjunct to other traditional tests and methods
- Derive diagnostic, prognostic and predictive information not possible before
- Increase visibility and importance of pathologists in the healthcare enterprise
- Create new billable tests (where applicable)
- "Automate" the boring stuff
- "Automate" the time-consuming stuff
- "Automate" the hard stuff

Patient benefits

- Benefit from new diagnostic, prognostic and predictive information not possible before
- Better use of healthcare resources
- Better care

DP company benefits

- Computational pathology represents a potential “killer app” for digital pathology
- Could drive adoption of DP, especially if new computational methods:
  - Provide diagnostic, prognostic, or predictive information that cannot be produced by other methods
  - Create significant savings in time or money
  - Are companion tests for important therapeutics
  - Augment, but do not displace pathologists
  - Are seamlessly integrated into DP workflows

Challenges for CP in Digital Pathology

- Accumulation of large well-annotated image datasets and related data
- Creation of robust, generalizable models
- Demonstration of value to pathologists, clinicians, administrators
- Overcome stakeholder skepticism
- Insufficient substrate for implementation (i.e. not enough clinical deployment of WSI)
- Lack of CP expertise amongst pathologists

Addressing these challenges

Addressing challenges: value

Original Article

Machine Learning Algorithms for Objective Remission and Clinical Outcomes with Thiopurines

Akbar K. Waljee,[a,b] Kay Sauder,[b] Anand Patel,[c] Sandeep Segar,[c] Boang Liu,[d] Yiwei Zhang,[d] Ji Zhu,[d] Ryan W. Stidham,[b] Ulysses Balis,[e] Peter D. R. Higgins[b]

[a]Department of Veterans Affairs Center for Clinical Management Research, Ann Arbor, MI, USA [b]Division of Gastroenterology, University of Michigan, Ann Arbor, MI, USA [c]Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA [d]Department of Statistics, University of Michigan, Ann Arbor, MI, USA [e]Department of Pathology, University of Michigan, Ann Arbor, MI, USA

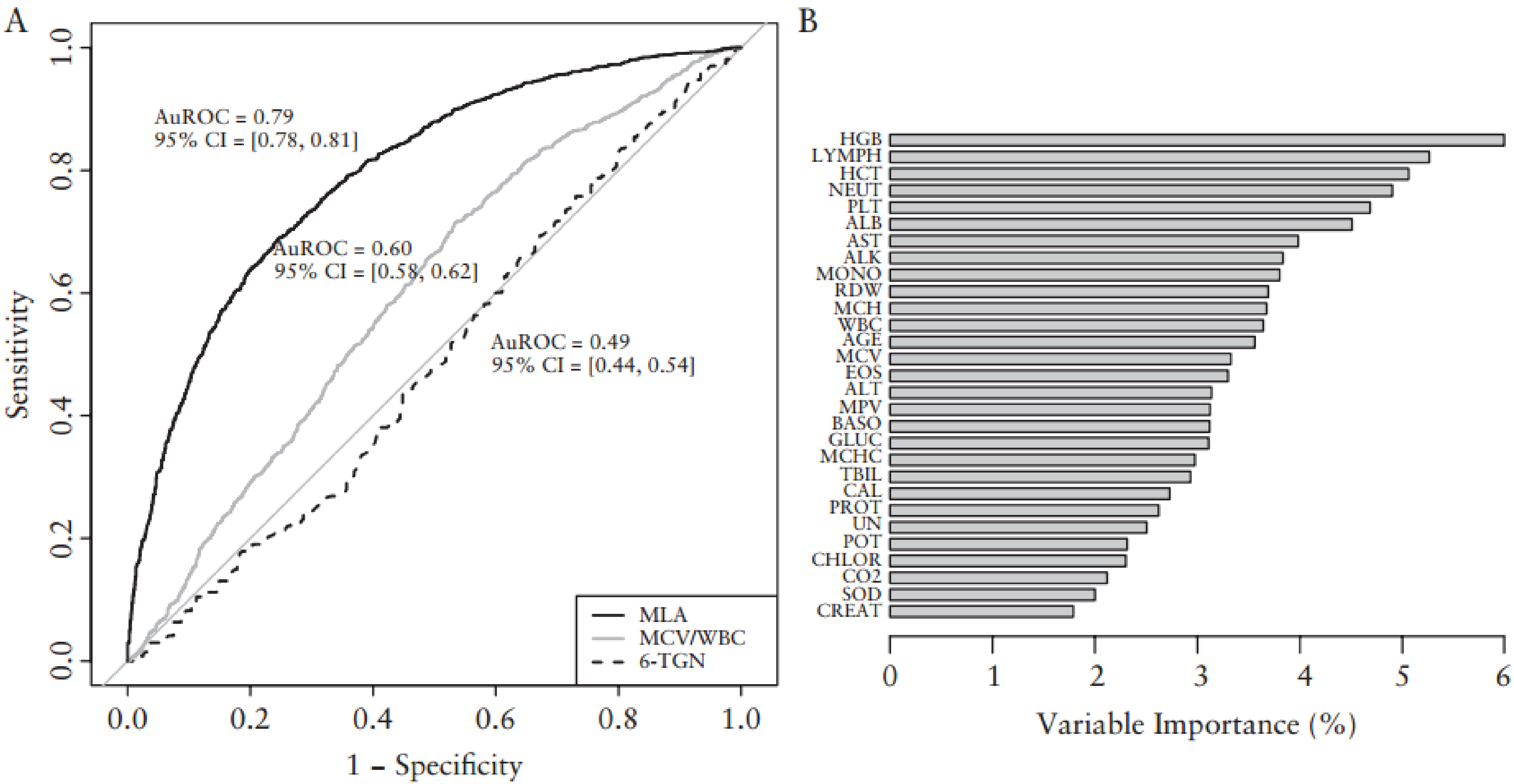
Background

- Thiopurines are immunomodulators for treatment of inflammatory bowel disease (IBD) patients
- Thiopurines have a narrow therapeutic index
- The current lab test for optimizing dosage, 6-thioguanine nucleotide (6-TGN), performs poorly
- Physicians traditionally rely on patterns in CBC and chemistry to monitor clinical response and titrate dosage
- Can machine learning algorithms (MLA) using routine lab tests as input predict objective remission with thiopuines?

Study design

- 1080 patients with 3263 cases
- Three dependent outcomes:
  - Objective remission
  - Non-adherence
  - Preferential shunting to 6-MMP (instead of 6-TGN)
- Independent variables: CBC with Diff, comprehensive chem panel and age
- Random forest machine learning was used to develop algorithms

Result: objective remission

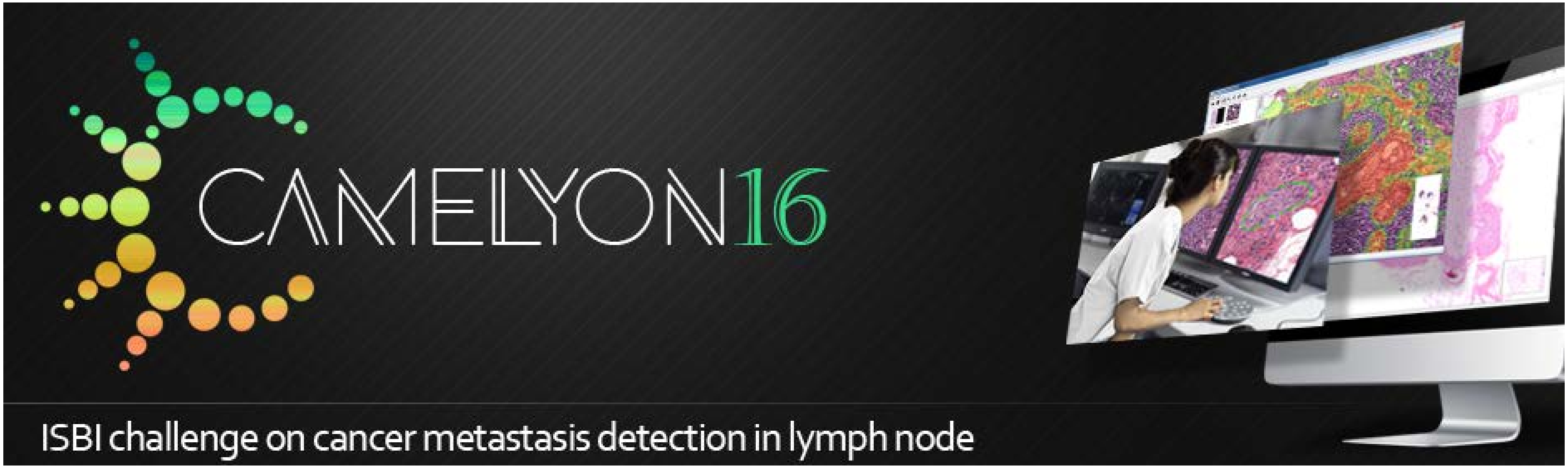


Waljee, et al. 2017

Conclusion

- “This group of three MLAs has been incorporated into daily clinical use using the Soft Laboratory Information system and the EPIC Electronic Medical Record at the University of Michigan, where it has replaced the use of thiopurine metabolite measurement, reducing total expenditures on send-out metabolite testing by $75000 per year at our institution.”

Addressing challenges: skepticism



https://camelyon17.grand-challenge.org/
https://camelyon16.grand-challenge.org/

Design

- Multiple teams competing to develop **algorithms for automated detection and classification of breast cancer metastases in lymph node sections**
- **Slide-based Evaluation**:
  - Classify slides as positive or negative for metastasis
  - The measure used for comparing the algorithms will be area under the ROC curve (AUC)
- **Lesion-based Evaluation**:
  - Free-response receiver operating characteristic (FROC) curve will be used
  - The FROC curve is defined as the plot of sensitivity versus the average number of false-positives per image.

2016 Result (4/1 deadline)

Public Leaderboard 1 - Whole-slide-image classification

- The results are computed on the independent test set.
- Evaluation 1: Teams are ranked based on area under ROC curve (AUC).

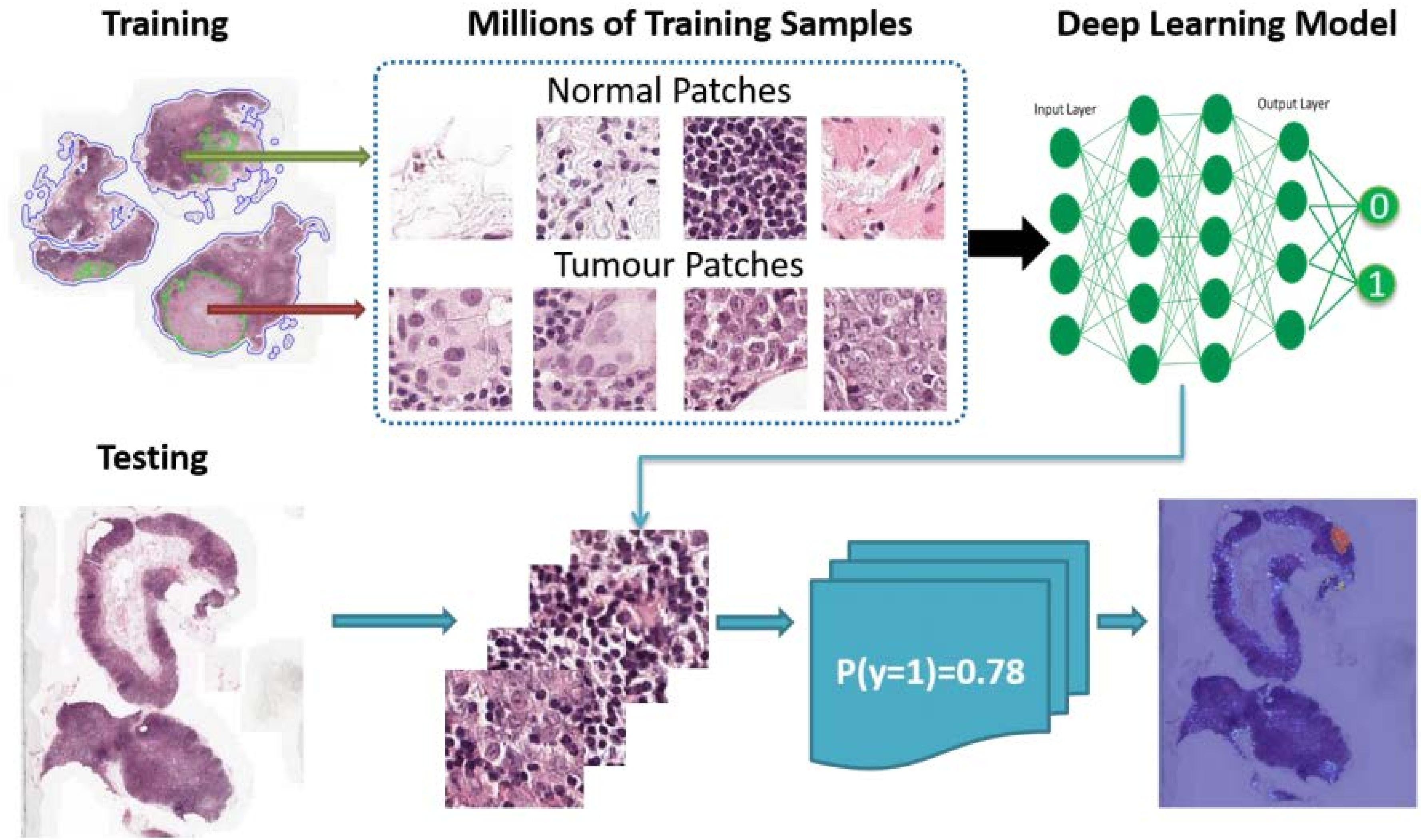
Top-five ranked teams until the challenge event deadline (Apr 1, 2016):

Rank	Team	AUC	Submission date	Description
01	Harvard Medical School and MIT, Method 1	0.9234	01 Apr 2016	
02	EXB Research and Development co., Germany	0.9156	01 Apr 2016	
03	Independent participant, Germany	0.8654	01 Apr 2016	
04	Middle East Technical University, Departments of EEE, NSNT and HS, Turkey	0.8642	01 Apr 2016	
05	NLP LOGIX co., USA	0.8298	01 Apr 2016	

Wang, *et al.* Department of Pathology, Harvard Medical School and Beth Israel Deaconess Medical Center, MIT Computer Science and Artificial Intelligence Laboratory

https://camelyon16.grand-challenge.org/results/

SYSTEM FRAMEWORK



Deep Learning Based Cancer Metastases Detection. Wang, et al. 2016. https://camelyon16.grand-challenge.org/site/CAMELYON16/serve/public_html/Results/Presentations/Camelyon16_BIDMC_CSAIL.pdf/

2016 Result (post deadline)

Leaderboard including all submissions (updated after each new entry):

* Indicates that the team has achieved an AUC value that surpasses the AUC of the pathologist in our study.

Rank	Team	AUC	Submission date	Description
01 *	Harvard Medical School and MIT, Method 2 (updated)	0.9935	06 Nov 2016	
02 *	Harvard Medical School, Gordon Center for Medical Imaging, MGH, Method 3	0.9763	24 Oct 2016	
03	Harvard Medical School, Gordon Center for Medical Imaging, MGH, Method 1	0.9650	07 Sep 2016	
04	The Chinese University of Hong Kong (CU lab, Hong Kong), Method 3	0.9415	29 Aug 2016	
05	Harvard Medical School and MIT, Method 1	0.9234	01 Apr 2016	

https://camelyon16.grand-challenge.org/results/

Addressing challenges: generalizability

IEEE TRANSACTIONS ON MEDICAL IMAGING, VOL. 35, NO. 2, FEBRUARY 2016

Stain Specific Standardization of Whole-Slide Histopathological Images

Babak Ehteshami Bejnordi*, Geert Litjens, Nadya Timofeeva, Irene Otte-Höller, André Homeyer, Nico Karssemeijer, and Jeroen AWM van der Laak

Bejnordi, *et al.*: method

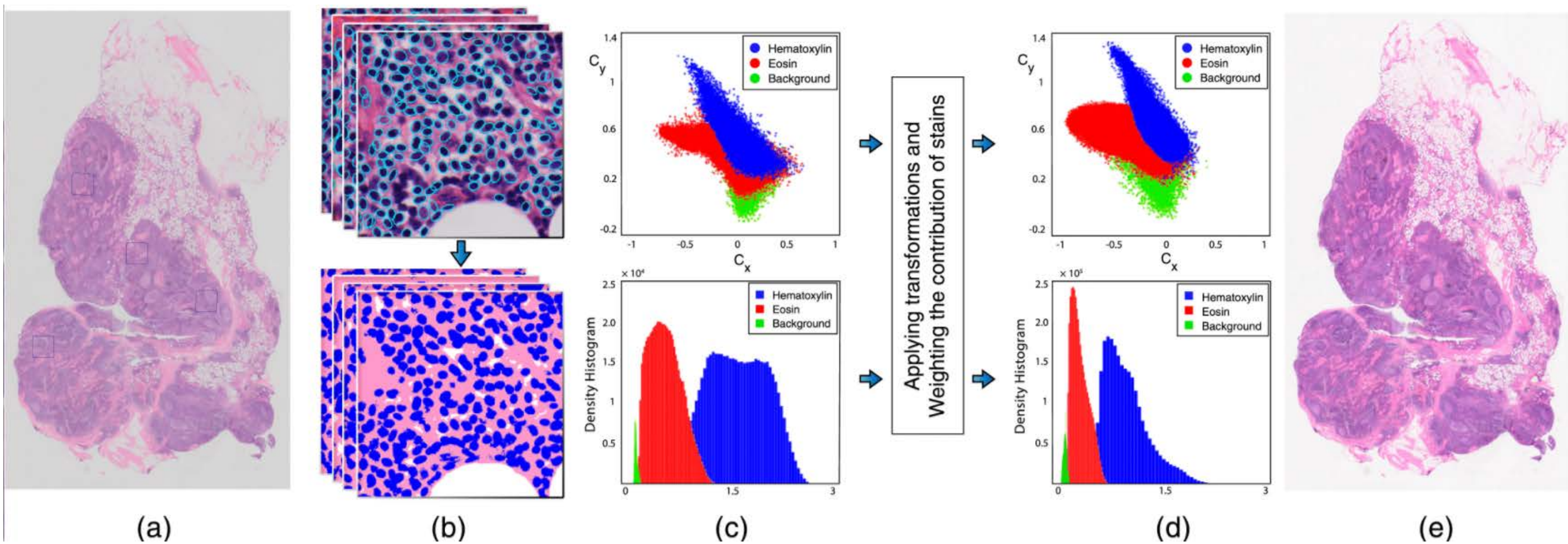
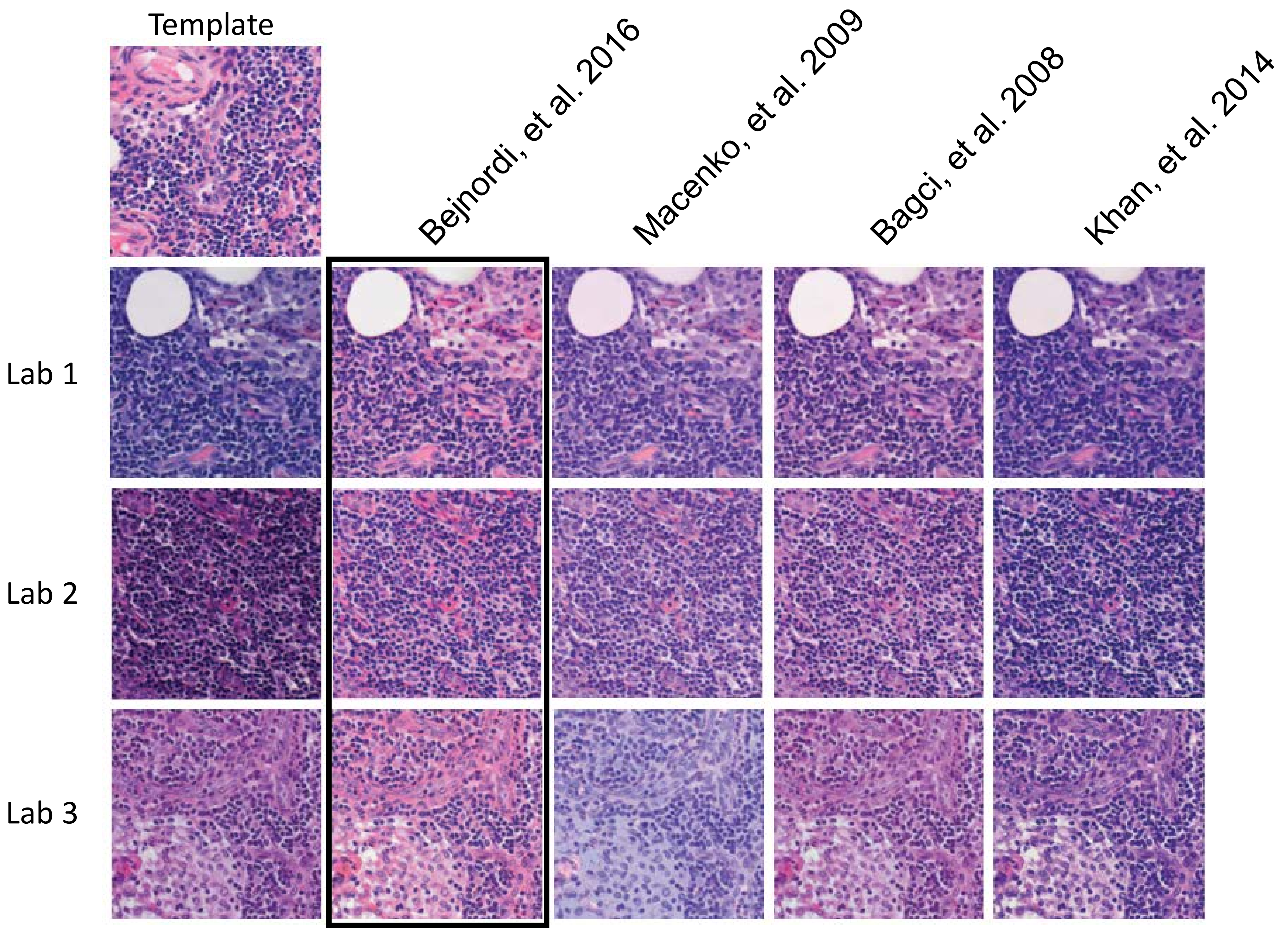


Fig. 1. Illustration of selected steps of the WSICS algorithm. (a) Original WSI of a lymph node tissue section. Several regions containing tissue are randomly selected for automatic extraction of representative samples for the hematoxylin, eosin and background class. (b) The selected regions of interest are classified into: pixels absorbing mostly hematoxylin, pixels absorbing mostly eosin, and background pixels. (c) The chromatic distribution and density histogram of pixels are defined in the *HSD* model to be transformed to match a template WSI. (d) The result of transforming the chromatic and Density distributions after application of weights. (e) Reconstructing the *RGB* image by applying reverse *HSD* transform using the standardized chromatic and density components.

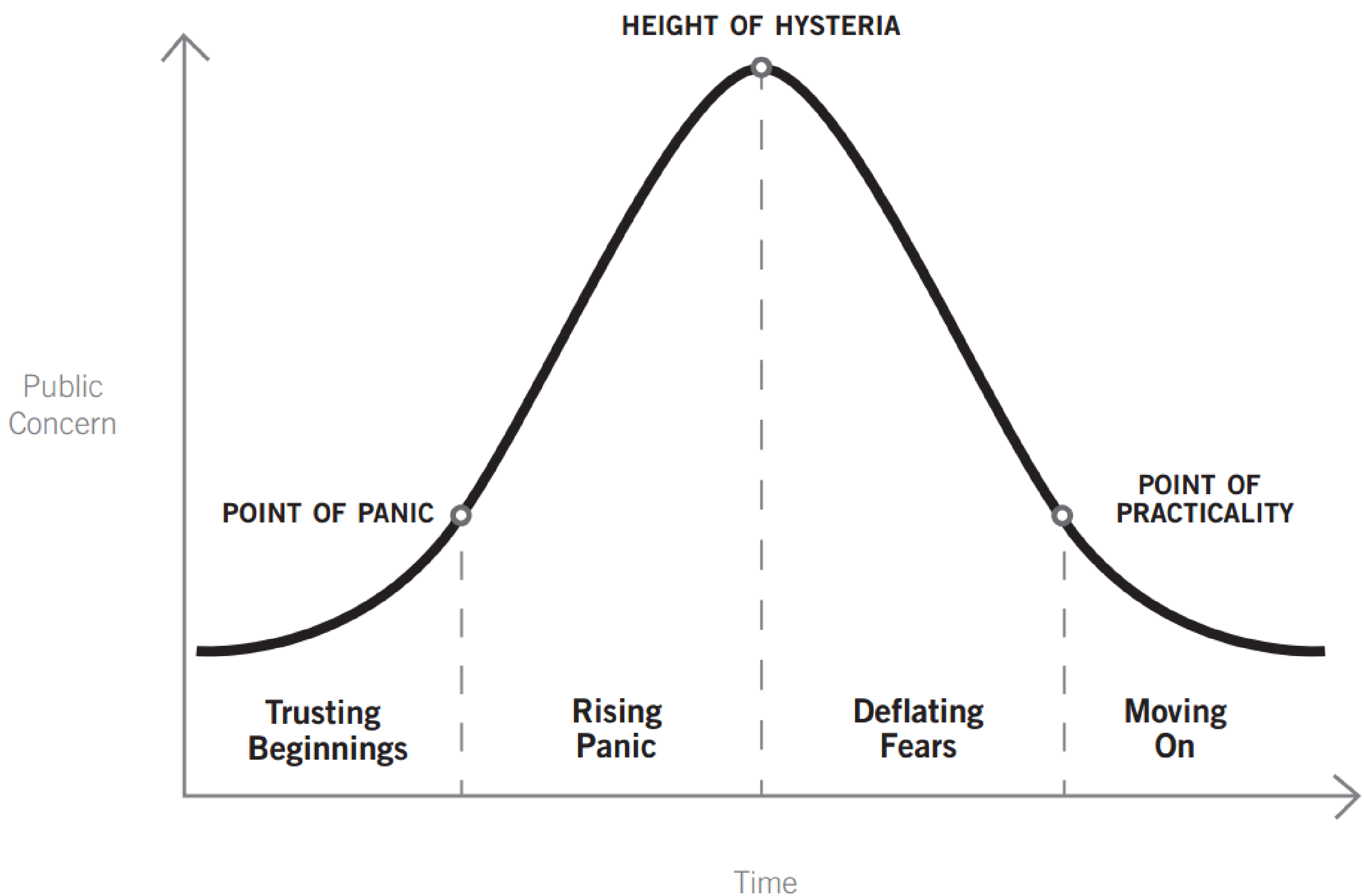

Template
Bejnordi, et al. 2016
Macenko, et al. 2009
Bagci, et al. 2008
Khan, et al. 2014
Lab 1
Lab 2
Lab 3

Other approaches to generalizability

- Use slides from a number of different labs in the training set
- Artificially manipulate the color of the images in the training set to introduce variation
  - e.g. adjust hue, saturation, etc.

Addressing challenges: “technopanic”

“AI Technopanic”



Daniel Castro and Alan McQuinn. 9/10/2015. The Information Technology & Innovation Foundation

Thoughts from another domain…

Kasparov *v.* Deep Blue

- May 11, 1997
- Match result: Deep Blue (W) - Kasparov: 3½ - 2½

https://commons.wikimedia.org/wiki/File:Kasparov-29.jpg
https://www.flickr.com/photos/amitrajit/

What have they been up to since?

Deep Blue

Computer History Museum (CHM), Mountain View, California, US

https://www.flickr.com/photos/amitrajit/

Garry Kasparov

- In June 1998, Kasparov played the first public game of human-computer collaborative chessagainst Veselin Topalov
- Each used a regular computer with off-the-shelf chess software (Kasparov: Fritz 5, Topalov: ChessBase 7.0)
- The match ended in a 3 - 3 tie
- Kasparov called this “advanced chess,” and it has later been called “centaur chess”
- Retired in 2005

“Freestyle” chess

- 2005: the first “freestyle” chess tournament
- Teams could consist of any number of humans or computers
- Some teams consisted of chess grand masters
- The most powerful chess computer at the time was also entered
- The winning team consisted of young, amateur players, Steven Cramton and Zackary Stephen and their computers

"weak human + machine + better process was superior to a strong computer alone and, more remarkable, superior to a strong human + machine + inferior process."

- Garry Kasparov

"The Chess Master and the Computer"
The New York Review of Books, 2/11/2010

http://www.nybooks.com/articles/2010/02/11/the-chess-master-and-the-computer/

Questions?

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