Life Beyond the Pixels

Peter Horvath
FIMM, Institute for Molecular Medicine Finland, Helsinki
BRC, Hungarian Academy of Sciences
Where...? What...? How many...?
Where...? What...? How many...?
Where...? What...? How many...?

Bev Doolittle (1975)
Where...? What...? How many...?

Bev Doolittle (1975)
Where...? What...? How many...?
Where...? What...? How many...?
Where...? What...? How many...?
How fast can you count?

# Human    Computer
How fast can you count?

#  

<table>
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[Image of blue circular objects]
How fast can you count?

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<tr>
<td>3610</td>
<td>😊</td>
<td>1 mp</td>
</tr>
</tbody>
</table>
Human vs. Computer

Human:
- Imprecise
- Slow
- Intelligent

Computer:
- Precise
- Fast
- Dummy 😊
Precise, fast and intelligent
Research activities

- Image quality improvement
  - Flat field, photo bleaching
Research activities

- Image quality improvement
  - Flat field, photo bleaching

- Image segmentation and tracking
  www.celltracker.website

Research activities

- Image quality improvement
  - Flat field, photo bleaching

- Image segmentation and tracking
  - [www.celltracker.website](http://www.celltracker.website)
  - Piccinini, Horvath. Bioinformatics 2016

- Machine learning
  - Phenotypic profiling
Research activities

- Image quality improvement
  - Flat field, photo bleaching

- Image segmentation and tracking
  - www.celltracker.website

- Machine learning
  - Phenotypic profiling

- CL²M (correlative light-light microscopy)
  - High-throughput single cell isolation
Vignetting
Vignetting
Vignetting

![Graph showing vignetting effect with a curve on a plot representing decreasing intensity with distance.]
The CIDRE model

Super resolution relation

Energy minimization simultaneously estimates $v$ and $z$ at all locations

Energy minimization simultaneously estimates $v$ and $z$ at all locations

Fitting energy $E_f$

Quantile-quantile

Low energy when fit

High energy when poor fit

Regularization energy $E_r$

Noisy, weak regularization

Smooth, strong regularization

Zero-light energy $E_z$

$$\frac{\partial}{\partial v(x)} E = \frac{\partial E_f}{\partial v(x)} + \lambda_r \frac{\partial E_r}{\partial v(x)} + \lambda_z \frac{\partial E_z}{\partial v(x)} + \lambda_b \frac{\partial E_b}{\partial v(x)}$$

$$= \sum_{n=1}^{N} \frac{Q_n (Q_n v(x) + b(x) - q_n(x))}{1 + \frac{1}{w(z)} (Q_n v(x) + b(x) - q_n(x))^2}$$

$$+ \lambda_r \sum_{t \in T} \frac{2}{|T|} \nabla^2 G_t \ast v(x) + 2\lambda_z Z_Q (b(x) + v(x) Z_Q - Z_q).$$

Corrected image $l = (I_o - z) / v$
The CIDRE model

Super resolution relation

Tested on 12 different microscopy techniques and largely outperforms the state of the art, highly dominates over calibration techniques.

Usable: Epi Fluo, Bright filed, DIC, PC, STED, Confocal, Outdoor cameras
Applications: HCS, Neurology, Histology, Standard microscopy, …

Implemented in Java (ImageJ), MalLab, CellProfiler, Python

\[
\frac{\partial}{\partial v(x)} E = \frac{\partial E_f}{\partial v(x)} + \lambda_g \frac{\partial E_r}{\partial v(x)} + \lambda_z \frac{\partial E_z}{\partial v(x)} + \lambda_b \frac{\partial E_b}{\partial v(x)}
\]

\[
= \sum_{n=1}^{N} \frac{Q_n \left( Q_n v(x) + b(x) - q_n(x) \right)}{1 + \left( \frac{Q_n v(x) + b(x) - q_n(x)}{\delta_n^2} \right)^2} + \lambda_{\theta} \sum_{t \in T} \frac{2}{|T|} \nabla^2 G_t \ast v(x) + 2 \lambda_z Z_Q (b(x) + v(x)) Z_Q - Z_q.
\]
Image processing

Image processing

Image processing

3 main steps:
- Cell detection (segmentation)
- Cellular compartment identification
- Feature extraction

Image processing I. — cell detection

Banerjee, etal.; Science 2014.
Image processing 1. – cell detection

Image processing I. — cell detection

Image processing I. — cell detection

Image processing II. – compartments
Image processing II. — compartments
Image processing II. — compartments
Image processing II. — compartments
Image processing II. – compartments
Image processing II. – compartments
Image processing III. — feature extraction

- Morphology

- Intensity-based

- Texture
Image processing - Summary
Challenges

**IMAGE SEGMENTATION**

*Label free image reconstruction*

- Koos, et al. *DICTA 2015*

*Complex object modeling*

- Horvath, et al. *PattRec 2009*
Image segmentation with priors

Single-cell tissue analysis

Hundreds of different breast cancer TMA spots

Data courtesy of Prof. J. Lundin
3D extension - GPU

\[ p = 10.6 \]

\[ p = 16.1 \]
3D active surfaces

(a) Surface evolution while segmenting out the pseudohyphae form.

(b) Surface evolution while segmenting out the yeast cell in normal form.
New active contour model

Molnar et al. *IEEE ISVC 2016.*
New active contour model
Size selective droplet analysis
Size selective droplet analysis
Size selective droplet analysis
Size selective droplet analysis
Size selective droplet analysis
2018 Kaggle Data Science Bowl: find nuclei in diverse images

Training data

Test data

40% of all deaths are caused by illnesses like heart disease and cancer.

75% of rare diseases affect children.

30% of affected children with rare diseases die before age 5.

Finding the nucleus helps to...

- locate cells in varied conditions to enable faster cures
- free biologists to focus on solutions
- improve throughput for research and insight
- reduce time-to-market for new drugs—currently 10 years
- increase # of compounds for experiments
- improve health and increase quality of life

Source: https://www.kaggle.com/c/data-science-bowl-2018#description
Image style transfer learning

Image style transfer learning

Cell images

Original

Fake
Cell images

Original

Fake
Cell images

Original

Fake
Tissue images
Tissue images
Image-to-image translation with conditional adversarial networks

www.nucleAlzer.org
Cytoplasm segmentation using Mask-RCNN
Cytoplasm segmentation using Mask-RCNN
Cytoplasm segmentation using Mask-RCNN
Cytoplasmin segmentation using Mask-RCNN
Cytoplasm segmentation using Mask-RCNN
Astrocyte detection at the level of human performance using deep learning

Suleymanova, Balassa, Saarma, Horvath: A deep convolutional neural network approach for astrocyte detection. *Scientific Reports* 2018
Remember! Image processing. What next?
Remember! Image processing. What next?
SINGLE CELL-BASED CLASSIFICATION FOR HCA
Smith et al.: *Nature Meth.* 2015
Badertscher et al.: *Cell Rep.* 2015
Ungricht et al.: *JCB* 2015
Bouther et al.: *Oncotarget* 2014
Meier et al.: *J. Virology* 2014
Kiss et al.: *PLoS One* 2014
Smith et al.: *J. of Biomol Screening* 2014
Palazzolo, Horvath Wong; *PLoS One* 2012
Misselwitz, Horvath et al.; *PLoS Pathogens* 2012
Huotari, Horvath et al.; *PNAS* 2012
Yamauchi, Horvath et al.; *PLoS Pathogens* 2011
Horvath, Wild et al.; *J. of Biomol Screening* 2011
Laurell, Beck et al.; *Cell* 2011
Wild, Horvath et al.; *PLoS Biol* 2010
Turgay, Ungricht et al.; *EMBO journal* 2010

Advanced Cell Classifier is a data analyzer program to evaluate cell-based high-content screens and tissue section images developed at the Biological Research Centre, Szeged and FIMM, Helsinki (formerly at ETH Zurich). The basic aim is to provide a very accurate analysis with minimal user interaction using advanced machine learning methods. ACC was used to analyze some of the first large whole genome scale RNAi screens and all together for more than 300,000,000 images and several billion single cell-based machine learning decisions.
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The basic aim is to provide a very accurate analysis with minimal user interaction using advanced machine learning methods.
Training the machine

Training the machine

Training the machine
Training the machine

Automated classification

Future: lets WEB and deeplearn

Anne Carpenter
Broad Institute

**CYTO CLASSIFIER UI**

Develop an interactive and beautiful user interface
Technology used: React, D3js

**TO PROJECT**

**BROWSER-BASED MACHINE LEARNING**

Build fast and easy-to-use machine learning for science
Technology used: tensorflow.js

**TO PROJECT**

**PARTICIPANTS**

ETHzürich  
BROAD Institute  
FIMM

**CYTO.AI**
Classical data processing
Classical data processing
Classical data processing
Classical data processing

Data → Expert → Results
Classical data processing

Data → Expert → -Slow -Subjective
Classical data processing

Data

Expert

- Slow
- Subjective

Software

Results
Classical data processing

Data \rightarrow Expert \rightarrow \textbf{-Slow} \rightarrow \textbf{-Subjective}

Expert \rightarrow Data \rightarrow \textbf{Software} \rightarrow \textbf{Results}
Classical data processing

- Data
- Expert
- Slow
- Subjective

Expert

Software developer

Data

Software

Results
Classical data processing

- Slow
- Subjective

Data → Expert → Results

Expert → Software developer

Data → Software → Results

- Indirect
Intelligent data processing/mining
Intelligent data processing/mining

Goal: Most effective combination and usage of available information and the knowledge of field expert
Intelligent data processing/mining

Software developer

Data

Software

Results
Intelligent data processing/mining

- **Data**
- **Software developer**
- **Expert/information**
- **Software**
- **Results**
Intelligent data processing/mining

Software developer

Data

Software

Machine learning

Artificial intelligence

Results
Intelligent data processing/mining

Software developer

Data

Software

Results

Machine learning

Artificial intelligence

Data

Results
Intelligent data processing/mining

Software developer

Data

Software

Program

Machine learning

Artificial intelligence

Results

Results

Data

Expert/information
Intelligent data processing/mining

Software developer

Data

Software

Program

Machine learning
Artificial intelligence

Results

Expert/information

Results

Data
Intelligent data processing/mining

Machine learning
Artificial intelligence

Interactive machine learning algorithms
TWO MAJOR QUESTIONS WE FORGOT TO ASK!

Is my analysis the most accurate?
Did I entirely discover my data? Or partially?
Active learning for HCS
Active learning for HCS

Aim
Active learning for HCS

Aim

- More precise and faster analysis
Active learning for HCS

Aim
- More precise and faster analysis
- Using less human resources
Active learning for HCS

Aim

- More precise and faster analysis
- Using less human resources
- Asking more intelligent questions
Active learning for HCS

Aim

- More precise and faster analysis
- Using less human resources
- Asking more intelligent questions
Results

Results

1 - Negative cell
2 - Nucleoplasmic acc.
3 - Nucleolar acc.
4 - Mitotic
5 - No tet

1 - Non infected
2 - Infected (early)
3 - Infected (mid)
4 - Infected (late)
5 - Infected (collapsed)

Phenotype finder

### Results

#### a) Manually Selected

<table>
<thead>
<tr>
<th>Normal</th>
<th>Rounded Up</th>
<th>Elongated</th>
<th>Multinucleated</th>
<th>Overexpressed Tubules</th>
<th>Overexpressed Membraned</th>
<th>Collapsed Membrane</th>
<th>Cytoplasm Absent</th>
<th>Apoptotic</th>
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#### b) Automatically Identified by Using Find Similar Cells

Caie et al. High-Content Phenotypic Profiling of Drug Response Signatures across Distinct Cancer Cells
Tell me your neighbor I tell what you are

Major concept
Beyond single cell-based discrete decisions

REGRESSION MODELS FOR HCA
Localization of Late Endosome/Lysosomes

Helenius lab; ETH Zurich

Normal

Dynein/Dynactin kd

Lack of retrograde motility

Localization of Late Endosome/Lysosomes

Helenius lab; ETH Zurich

PACKED

Control

Dynactin kd

SCATTERED

Regression models for HCA

- Problem: Discrete decisions
Problem: Discrete decisions
Regression models for HCA

- Problem: Discrete decisions

Type A

Type B

A or B?
Regression models for HCA

- **Problem**: Discrete decisions

- **Solution**: Comparison

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<td><img src="image" alt="Type B" /></td>
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Regression models for HCA

- **Problem:** Discrete decisions

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<td><img src="2" alt="Type B" /></td>
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<td><img src="4" alt="Type A" /></td>
<td><img src="5" alt="Type B" /></td>
<td><img src="6" alt="A or B?" /></td>
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- **Solution:** Comparison
Regression models for HCA

- **Problem:** Discrete decisions

- **Solution:** Comparison

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Regression models for HCA

- **Problem:** Discrete decisions

- **Solution:** Comparison

Type A | Type B | A or B ?
Regression models for HCA

- **Problem:** Discrete decisions

- **Solution:** Comparison

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- ![Comparison Image](image4.png)
Regression plane concept
Further results - Semliki Forest virus genome-wide screen

Balistreri, Horvath, Helenius.
Cell Host and Microbe.
Further results - Semliki Forest virus genome-wide screen

Balistreri, Horvath, Helenius. Cell Host and Microbe.
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Balistreri, Horvath, Helenius. *Cell Host and Microbe.*
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Balistreri, Horvath, Helenius. *Cell Host and Microbe.*
Results

Plate bEZ01-3A

Balistreri, Horvath, et al.
Cell Host and Microbe

Scrambled
Lipid droplet phenotype analysis

MORE COMPLEX DECISIONS
Lipid droplet phenotype analysis

Based on: Surakka, ..., S. Timonen, V. Pietiäinen, ... et al.; The impact of low-frequency and rare variants on lipid levels. Nature Genetics
Lipid droplet phenotype analysis

Based on: Surakka, ..., S. Timonen, V. Pietiäinen, ... et al; The impact of low-frequency and rare variants on lipid levels. Nature Genetics
Lipid droplet phenotype analysis

Based on: Surakka, ..., S. Timonen, V. Pietiäinen, ... et al.; The impact of low-frequency and rare variants on lipid levels. *Nature Genetics*
Using supervised classification
Using supervised classification
Using supervised classification
Using supervised classification

😊 Hard decisions, undefined/artificial boundaries 😞
A. Szkalïsity, etal: A novel concept for high-content screen analysis using multi-parametric regression models to predict continuous cellular processes; KEPAF15
2D regression plane concept

- Can we predict/learn more than one property of the cells?
Can we predict/learn more than one property of the cells?

Yes, we can!
Can we predict/learn more than one property of the cells?

- Yes, we can!

I do not want to talk/analyze in terms of image processing quantities (jargon) but based on visual observations.
A. Szkalisy, et al.: A novel concept for high-content screen analysis using multi-parametric regression models to predict continuous cellular processes; KEPAF15
Results
A. Szkalisity, etal: A novel concept for high-content screen analysis using multi-parametric regression models to predict continuous cellular processes; KEPAF15
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A. Szkalisity, et al.: A novel concept for high-content screen analysis using multi-parametric regression models to predict continuous cellular processes; KEPAF15
Childhood acute lymphoblastic leukemia

Prof. MD Bourquin  Children’s Hospital Zurich

Drug and treatment strategy testing using high-content screening
Biology idea

Untreated population

XY gene or drug

Bone marrow cells

Boutter, Horvath, Bourquin; Oncotarget 2014.
Detection of cells

Boutter, Horvath, Bourquin; Oncotarget 2014.
UNET deep learning (prelim)
UNET deep learning (prelim)
UNET deep learning (prelim)
UNET deep learning (prelim)
Image-based personalized and translational medicine
Personalized precision medicine

- Primary drug testing
  - ~550 oncology drugs
  - Cell lines
  - Patient samples

Bioinformatics

Imaging

Microscopy screening

Saeed et al. – European Urology (2017)
Pediatric brain tumors – 3D

Effective drug

Apoptotic control drug

Heike Peterziel, Olaf Witt, Sina Oppermann, KiTZ, Heidelberg, collaboration
Advancing 3D single-cell based screening

Pipeline:
- Spheroid generation
- Spheroid picker
- Imaging
- Image analysis
Spheroid generation

- InSphero GravityPLUS Kit
- SphericalPlate5D
- Homogenous size (200-300 µm)

Source: © InSphero AG

Source: © Kugelmeiers AG
Spheroid picker

- Deep learning detection

- Diameter: 195µm, Roundness: 0.51, Status: No

- Diameter: 201µm, Roundness: 0.71, Status: OK

- Diameter: 230µm, Roundness: 0.87, Status: OK

- Diameter: 235µm, Roundness: 0.84, Status: OK

- Diameter: 195µm, Roundness: 0.51, Status: No
3D large organoid imaging

- SCALE tissue clearing
- Leica SP8 DLS
- 3D imaging
**Image analysis**

- **3DCellAnnotator**
- Active surface-based 3D compatible tool
- Segmenting and phenotyping single cells

<table>
<thead>
<tr>
<th>3D VIEWER</th>
<th>POINT SELECTION</th>
<th>SEGMENTATION</th>
<th>ANNOTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="3D Viewer" /></td>
<td><img src="image2.png" alt="Point Selection" /></td>
<td><img src="image3.png" alt="Segmentation" /></td>
<td>Mitotic cell</td>
</tr>
<tr>
<td>Add a new class</td>
<td>Annotate the selected object</td>
<td>Import classes</td>
<td>Import masks</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td>Export classes</td>
</tr>
<tr>
<td>Export masks</td>
</tr>
</tbody>
</table>
Can we learn more? How?

SINGLE-CELL
CAMI: Computer Aided Microscopy Isolation

APPLICATIONS
1. Cerebral cortex

1. Cerebral cortex

1. Cerebral cortex

1. Cerebral cortex

3. Resolving ccRCC heterogeneity (report)

Immunofluorescent images of a representative patient-derived cell culture (ccRCC) taken with the Operetta automated microscope (blue – nucleus, green – cytoplasm, red – cell membranes).

In collaboration with Hella Bolck, Peter Schraml, and Holger Moch; University of Zurich
Patient samples

Primary ccRCC with rhabdoid differentiation

Corresponding patient-derived cell culture
Resolving ccRCC heterogeneity

Patient-derived cell culture (ccRCC) taken with automated microscope (blue – nucleus, green – cytoplasm, red – cell membranes). Five subclasses of morphologically distinct cells were defined and are depicted here.
Definition of morphologically distinct cells in primary ccRCC

grade01_02 subclasses for grade01_02
nucleus: grade01_02
cytoplasm: clear or slightly dense

grade03_04 subclasses for grade03_04
nucleus: grade03_04
cytoplasm: cytoplasms with different color intensities and textures
AutoPatch: single cell system

In collaboration with Tamás Gábor, Vígh László
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