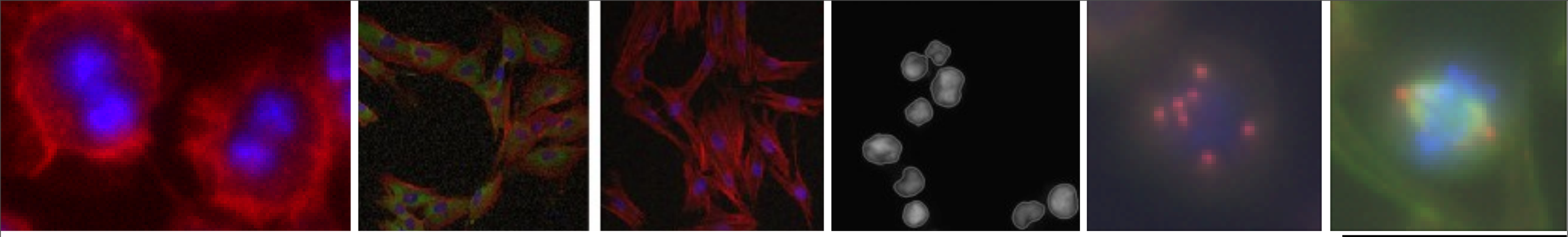


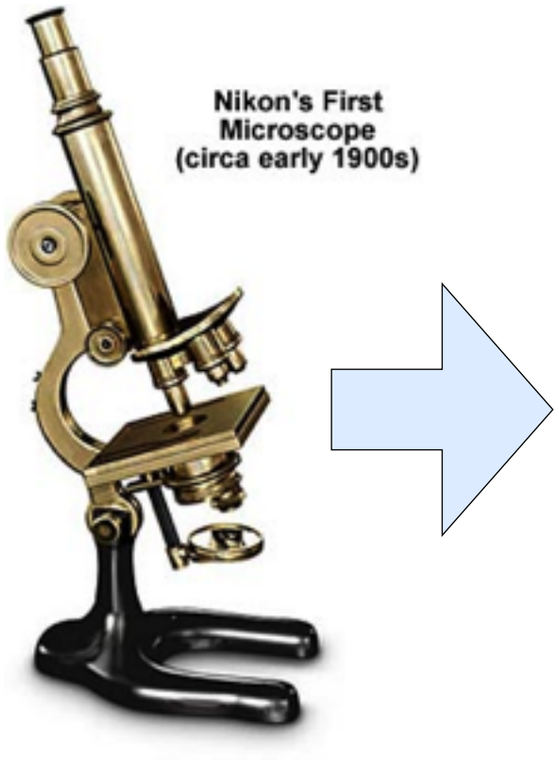
# Automatic quantification of subtle cellular phenotypes in microscopy-based high-throughput experiments

Vebjorn Ljosa
Broad Institute of MIT and Harvard
Cambridge, MA, USA

With other members of the Imaging Platform and numerous collaborators

Fourth International Workshop on Machine Learning in Systems Biology (MLSB)
Edinburgh, Scotland 2010-10-16

van Leeuwenhoek's
microscope
(late 1600s)




modern robotic microscope

More relevant for
systems biology

More in need of
machine learning



2

Image data are exciting.

You should join us in working on them.

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# Outline

1. The Imaging Platform at the Broad Institute
2. CellProfiler – image-analysis software
3. Iterative training of a boosting classifier for a particular (possibly rare) cellular phenotype
4. Large-scale training of a classifier for subtle phenotype changes
5. Comparing heterogeneous populations of cells perturbed by small molecules or RNA inhibition
6. Discovering latent "phenotypes" by learning to scale image features using linear regression and a topic model


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HARVARD

# The Broad Institute's unusual organization

Faculty member + lab

Imaging platform

Faculty member + lab

Chemical biology platform

Sequencing platform

Faculty member + lab

Faculty member + lab

[phdcomics.com]

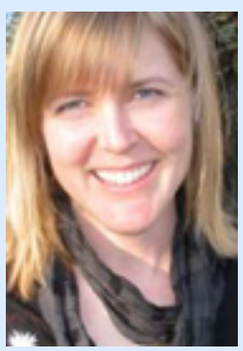
# The Imaging Platform at the Broad Institute

## Anne Carpenter

Director

### Methods development

Vebjorn Ljosa



Carolina Wählby

### Image assay development

Mark Bray

David Logan

Kate Madden

### Software engineering

Lee Kamentsky

Adam Fraser



7

# Outline

1. The Imaging Platform at the Broad Institute
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# CellProfiler—why was new software needed?

## Assay-specific pre-packaged commercial software

Fast

Poor results on crowded cells or unusual cell types

Designed for standard assays

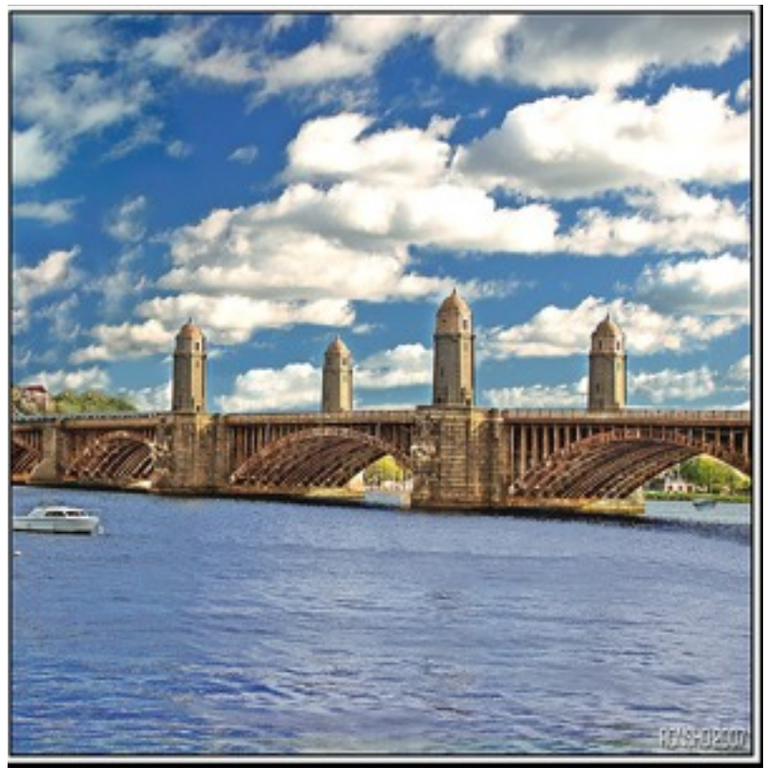
Cell adhesion
Neurite outgrowth
Micronucleus formation
Protein translocation
Cell cycle analysis
Adipogenesis
Reporter gene analysis
Cell viability
Apoptosis
Cell migration

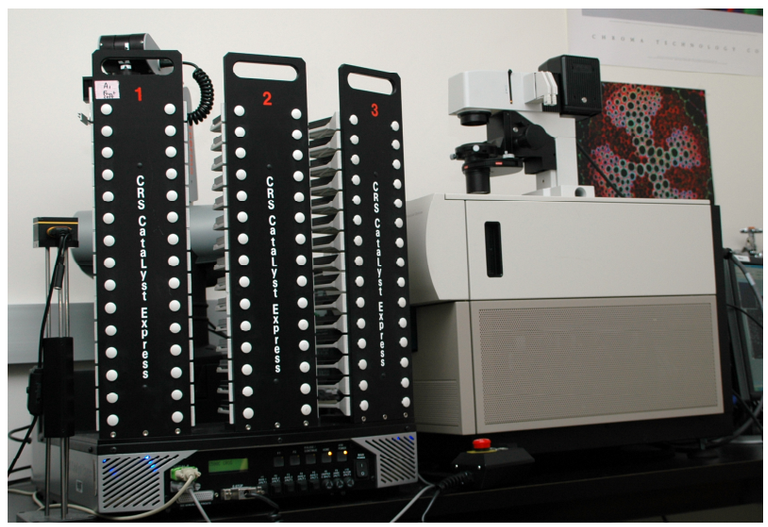
Often inflexible

Proprietary methods

Expensive

CellProfiler™
cell image analysis software






## Published raw source code

Advanced algorithms

Heavily customized, not generalizable

Requires programming skills + a lot of time to adapt to new situations

Rarely applied outside the originating lab

```
function [rgOut, varargout] = ImDAPI2Rg(imDAPIin,
LoGDim, LoGHW, MinArea)

wiendim=[5 5];

rgLoG=fspecial('log',LoGDim,LoGHW);
imLoGout=imfilter(double(imDAPIin),rgLoG);
imLoGoutW=wiener2(imLoGout,wiendim);
rgNegCurve=imLoGoutW<-1;

%set outsides
rgNegCurve([1 end],1:end)=1;
rgNegCurve(1:end,[1 end])=1;

%Throw out noise, label regions
rgArOpen=bwareaopen(rgNegCurve,MinArea,4);
```

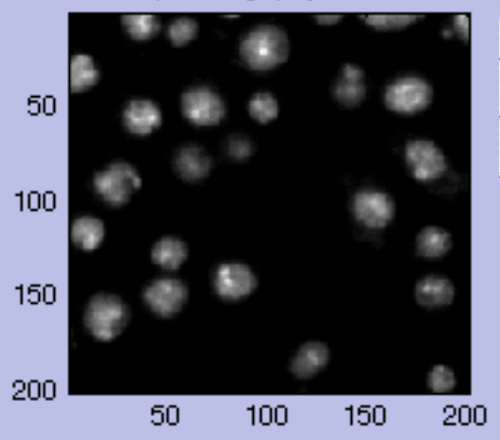
# CellProfiler™

cell image analysis software

Figure 5: IdentifyPrimAutomatic Display, cycle #3

File Edit View Insert Tools Desktop Window Help CellProfiler Image To

Input Image, cycle # 3




Identified Nuclei

Outlined Nuclei

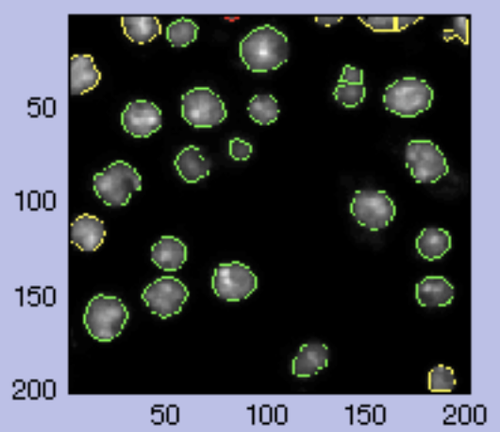
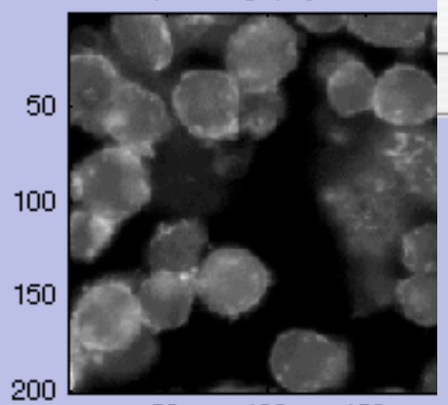


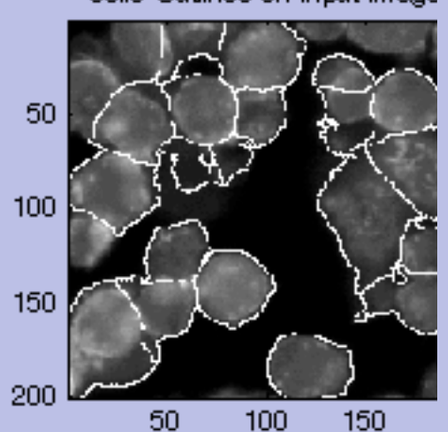

Figure 6: IdentifySecondary Display, cycle #3

File Edit View Insert Tools Desktop Window Help CellProfiler Image To

Input Image, cycle # 3




Cells Outlines on Input Image




Threshold: 0.041

objects

ects that you want to measure? Cells

asm

use

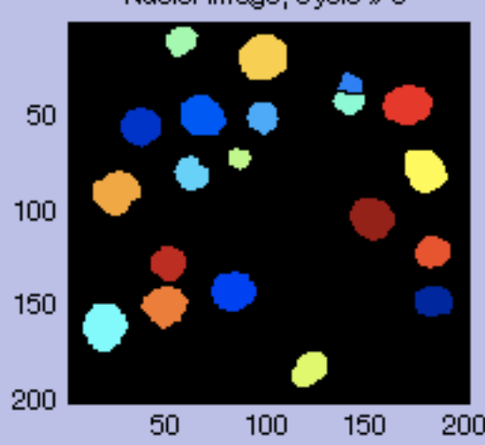
use

use

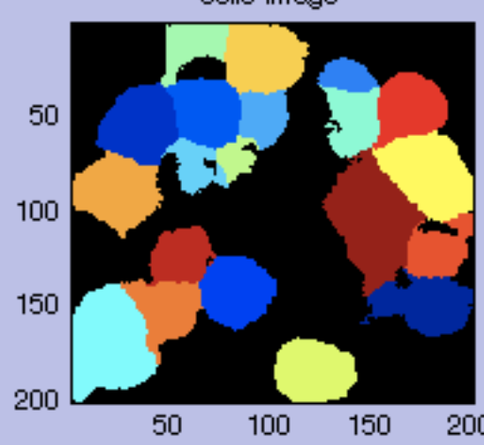
Figure 7: IdentifyTertiarySubregion Display, cycle #3

File Edit View Insert Tools Desktop Window Help CellProfiler Image To

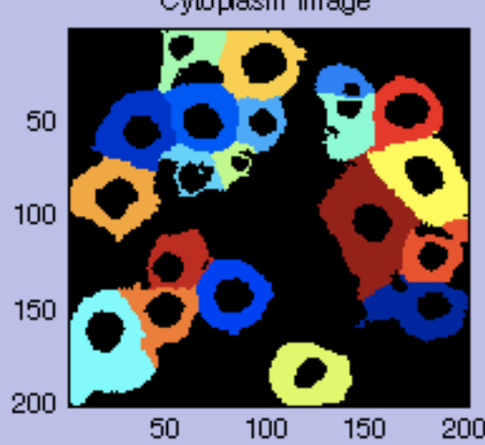
Nuclei Image, cycle # 3



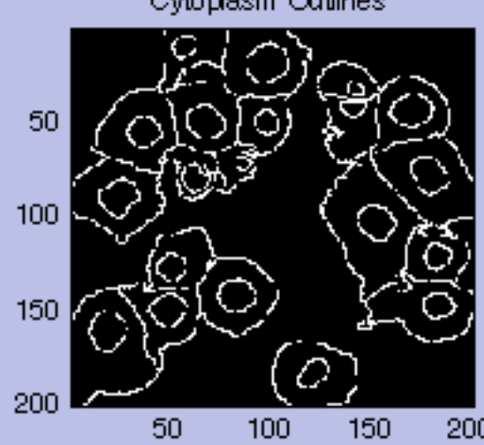

Cells Image




Cytoplasm Image




Cytoplasm Outlines




Browse...

Browse...

lyze images

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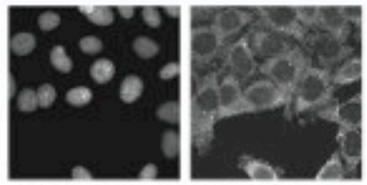
C s

# Typical CellProfiler pipeline



original images

Image processing modules

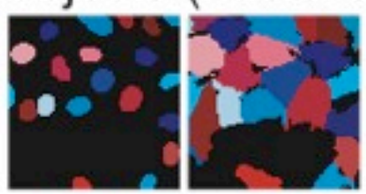
processed images

Illumination correction modules

illumination-corrected images

Object identification modules

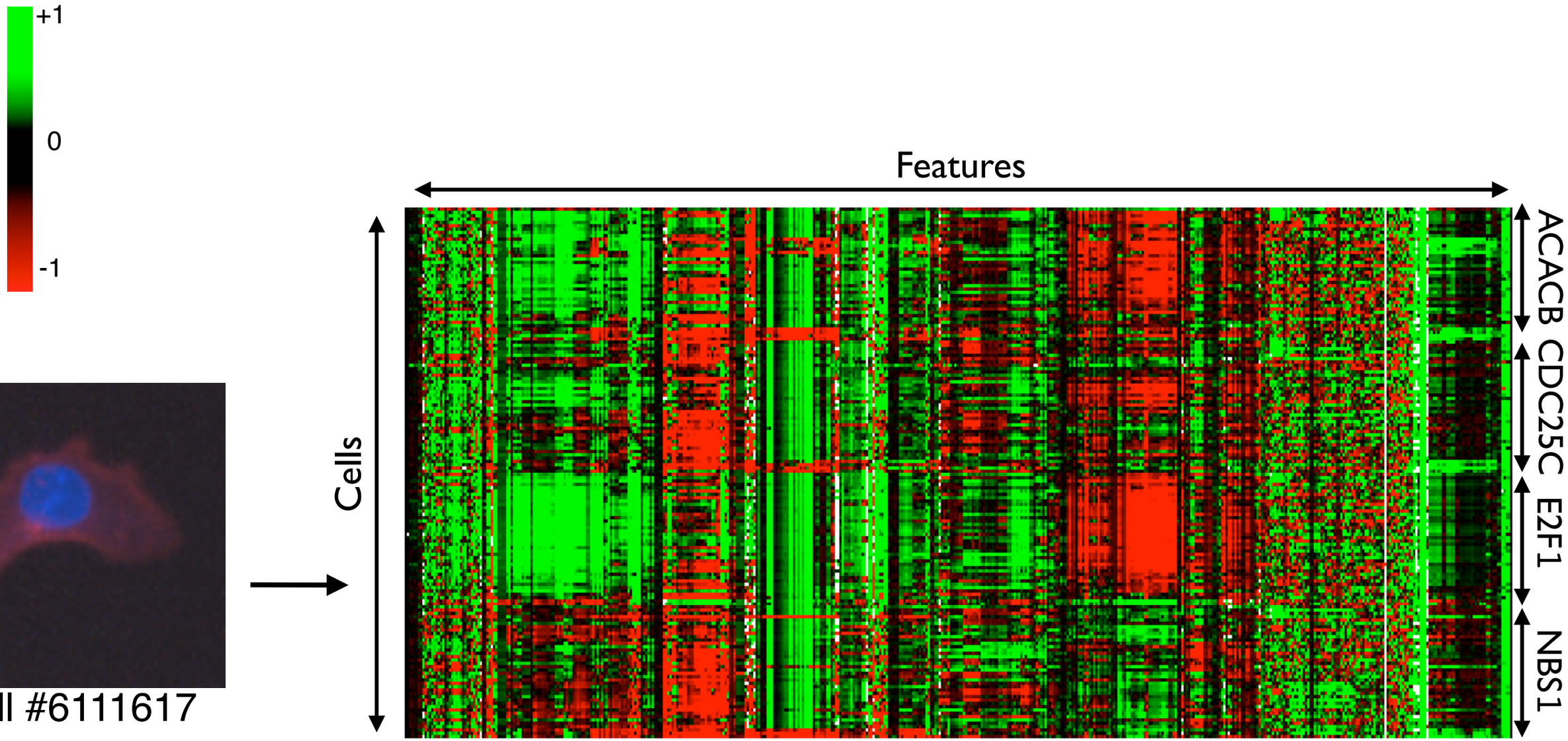
identified objects (nuclei and cells)



Measurement modules

measurements for every cell in every image (number, location, size, shape, intensity, texture) can be analyzed by:
1. built-in CellProfiler data tools
2. exporting to spreadsheet
3. exporting to database

# Measure everything first, ask questions later




cell #6111617

"Cytological profile": collection of measurements describing the appearance of a cell

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Data plot: Noa Shefi



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# Successful image-based assays

## Phenotypes:

Cell count
Cell size
DNA content
Nuclear speckles
Cytoplasm/nucleus localization
Membrane localization
Protein or phospho-protein levels
Metastasis
Wound healing
Metaphase
Anaphase/telophase
Prophase
Shape/texture
Crescent-shaped nuclei
Peas-in-a-pod
Cells-on-the-move
Long projections
Crooked projections
Hyphae-like fingers
Actin at contractile ring/cell junctions
Internal actin
Actin circles
Large spread cells
Phospho-histone H3 nuclear dots
Bi/multinucleate

## Cell types:

Drosophila Kc167 cells
Drosophila S2R+ cells
Drosophila epithelial tissue
Drosophila embryo
Human HT29 cells
Human A549 cells
Human TOV21G cells
Human H1299 lung carcinoma cells
Human biopsied prostate gland tissue
Human adult mesenchymal stem cells
Mouse NIH/3T3 cells
Mouse neural precursor cells derived from embryos
Mouse lung tissue sections
Mouse isolated germ cells
Rat H9c2 cells
C. elegans worms (preliminary)
Neurons (preliminary)
S. cerevisiae cells
Yeast colonies
Yeast growth patches
Array grids

# www.cellprofiler.org

CellProfiler cell image analys

http://www.cellprofiler.org/

**CellProfiler**
cell image analysis software

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CellProfiler Analyst
Download

**CellProfiler** is free open-source software designed to enable biologists without training in computer vision or programming to quantitatively measure phenotypes from thousands of images automatically. See our papers on analyzing cell images and non-cell images.

**CellProfiler Analyst** is free open-source s for exploring and analyzing large, high-dim image-derived data. It includes machine le tools for identifying complex and subtle phenotypes. See our papers on data visua and machine learning.

**CellProfiler News**

**March 29, 2010 — CellProfiler 2.0 Released**

Our image analysis software CellProfiler has been completely redesigned and written in Python, and is available download. New features include a sparkling new graphical interface, a test mode for experimenting with module improved algorithms and more.

**Monday, December 7, 2009 — CellProfiler Analyst 2.0 Released**

Our data exploration tool CellProfiler Analyst has been re-released and is available for download here. The softw boasts our most current advances to our Classifier tool as well as tools for visualizing and plotting data from Ce

Old news...

**Broad Bioimage Benchmark Collection (BBBC)**

The Broad Bioimage Benchmark Collection (BBBC) is a collection of freely available microscopy image sets fo developing and testing image analysis algorithms.

CellProfiler cell image analys

http://www.cellprofiler.org/examples.shtml

**CellProfiler**
cell image analysis software

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## Examples

The best way to learn how to use CellProfiler and CellProfiler Analyst is to download our examples and try it out!

**CellProfiler example images and pipelines (jump to CellProfiler Analyst example)**

**How do I get started?**

Download example images along with pipelines so you can get immediate hands-on experience in using CellProfiler.

1. Select an example from the pipeline list below where the cell type (or object type) resembles yours. You can move your mouse over an image below to see an example of the CellProfiler analysis, or click to see an expanded view.
2. Download the example images and pipeline from the list below and run it in CellProfiler to see how it works.
3. Try the pipeline on your own images.
4. Adjust the pipeline to identify objects properly in your images. This most often includes changing the size range of the objects. See the Tutorials page for step by step instructions.
5. Still stuck? See if your question has been answered on the forum.

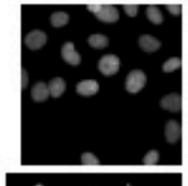
Please note that each example links to a compressed ZIP file containing the following:

1. CellProfiler pipelines, in both version 1.0 (.mat) and version 2.0 (.cp) formats.
2. Example images which are to be used as input for the pipeline.

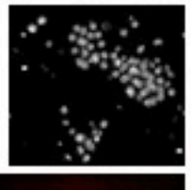
**Basic Pipelines**

These pipelines are made for simple cellular and tissue image assays, and include some basic measurements.

- **Human cells:** Human HT29 cells are fairly smooth and elliptical. This pipeline demonstrates how to accurately identify these cells and how to measurements cellular parameters such as morphology, count, intensity and texture.
  [Download] (0.3 MB)

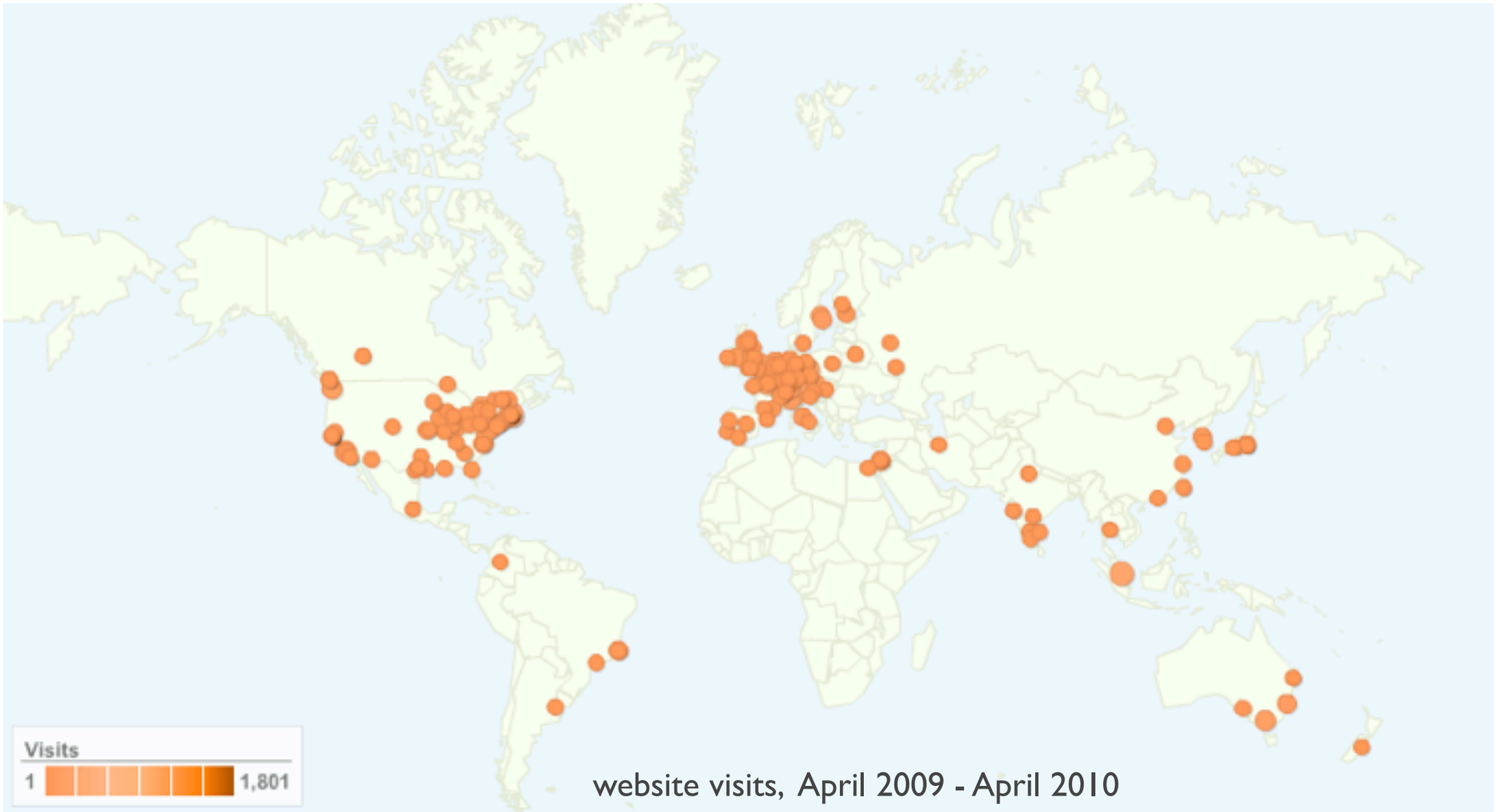


- **Fruit fly cells:** In comtrast to the HT29 cells, Drosophila Kc167 cells are a highly textured and clumpy cell type. This pipeline demonstrates how to identify these clumpy cells and obtain morphological, intensity and texture measurements.
  [Download] (4 MB)



- **Tumors:** A simple pipeline that identifies and counts tumors in a mouse lung, and then measures their size.
  [Download] (0.9 MB)

# CellProfiler around the world




website visits, April 2009 - April 2010

CellProfiler is downloaded 400x/month, 11,000x total (~50% USA, 90% non-profit institutions).

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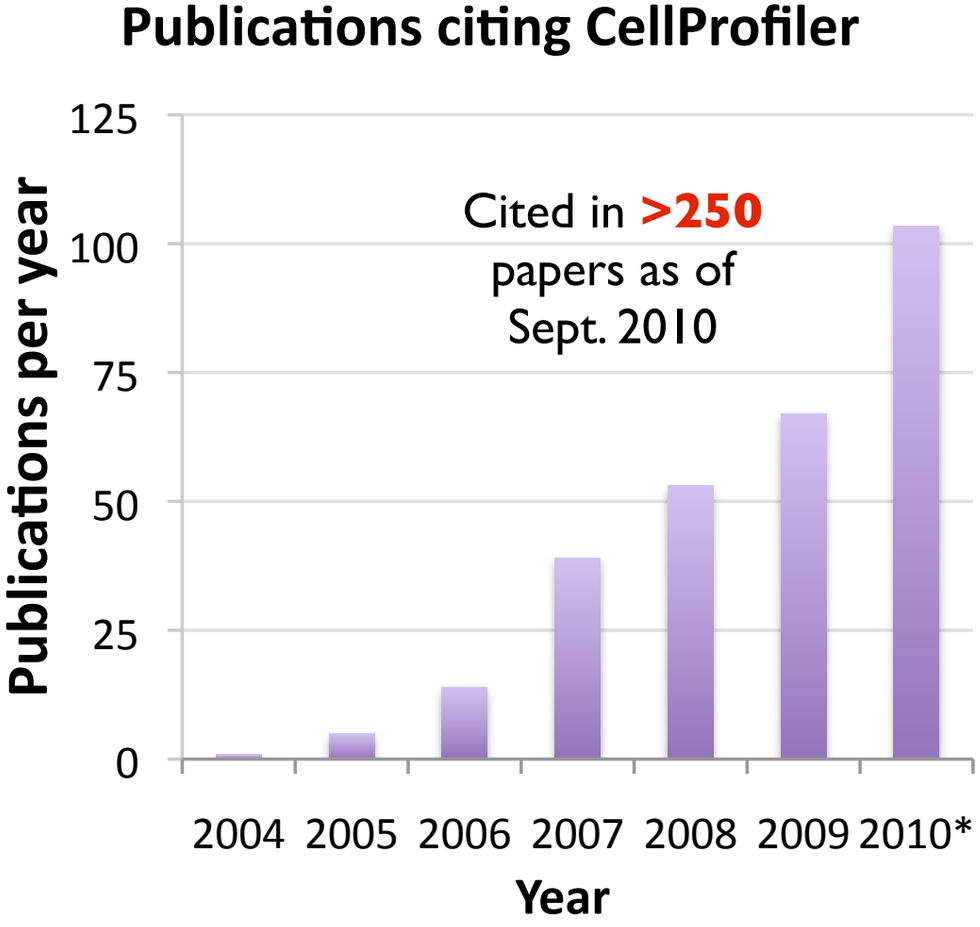
# The CellProfiler project

free, at www.CellProfiler.org




| Selected high-throughput screens using CellProfiler | |
|---|---|
| Root lab, *Cell*, 2006 | Screen for cell cycle regulators |
| Alon lab, *Nature Methods*, 2006 | High-throughput analysis of protein dynamics |
| Neefjes lab, *Nature*, 2007 | Screen for levels of Salmonella typhimurium infection |
| Raff lab, *PLoS Biology*, 2008 | Screen for centriole duplication and mitotic PCM recruitment |
| Carpenter lab, *PNAS 2009* & *BMC Bioinformatics* 2008 | Screens for > 15 diverse phenotypes in human and *Drosophila* cells |
| Shokat lab, *Cancer Cell*, 2008 | Screen for PI3K inhibitor resistance mutations in *S. cerevisiae* |
| Pelkmans lab, *Nature*, 2009 | High-throughput infection assay |
| Ausubel lab, *ACS Chem Bio*, 2009 | Screen for inhibitors of infection by *E. faecalis* |

CellProfiler's is the 5th most-accessed *Genome Biology* paper of all time

# Experiments we have completed recently

| Biological process/ phenotype | Laboratory | Samples tested | Number of fields of view (images) processed |
|---|---|---|---|
| Meiosis | Terry Orr-Weaver (Whitehead) | RNAi | 84,000 |
| Mitochondria | Vamsi Mootha (HMS/MGH) | chemicals | 100,000 |
| Morphology | AstraZeneca | chemicals | 109,200 |
| Cell cycle | AstraZeneca | chemicals | 109,200 |
| Breast cancer/Heregulin | Eric Lander (Broad) | RNAi | 144,798 |
| Tuberculosis | Deb Hung (Broad) | chemicals | 164,000 |
| Glioma | David Sabatini & Bill Hahn (Whitehead, Harvard, Dana-Farber) | RNAi | 286,000 |
| Polyploidy: AMKL | John Crispino (Northwestern University) | chemicals, some RNAi | 530,000 |
| Hematopoetic stem cells | David Scadden and Stuart Schreiber (HMS, MGH, Broad) | chemicals, some RNAi | 465,448 |
| Leukemic stem cells | Gary Gilliland (BWH/HMS) | chemicals, some RNAi | 1,040,098 |
| Hepatotoxicity | Sangeeta Bhatia (MIT) | chemicals | 1,135,093 |

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4. Large-scale training of a classifier for subtle phenotype changes
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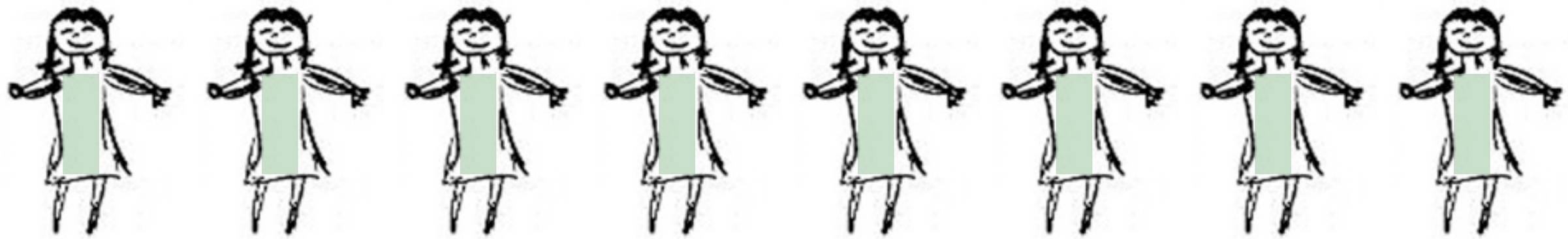
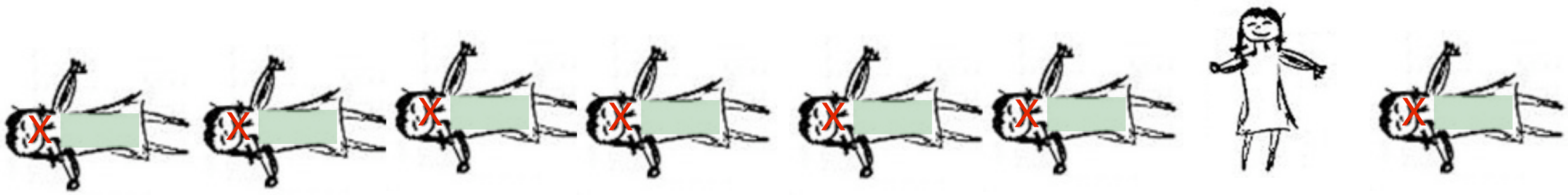
6. Discovering latent "phenotypes" by learning to scale image features using linear regression and a topic model

# Screens



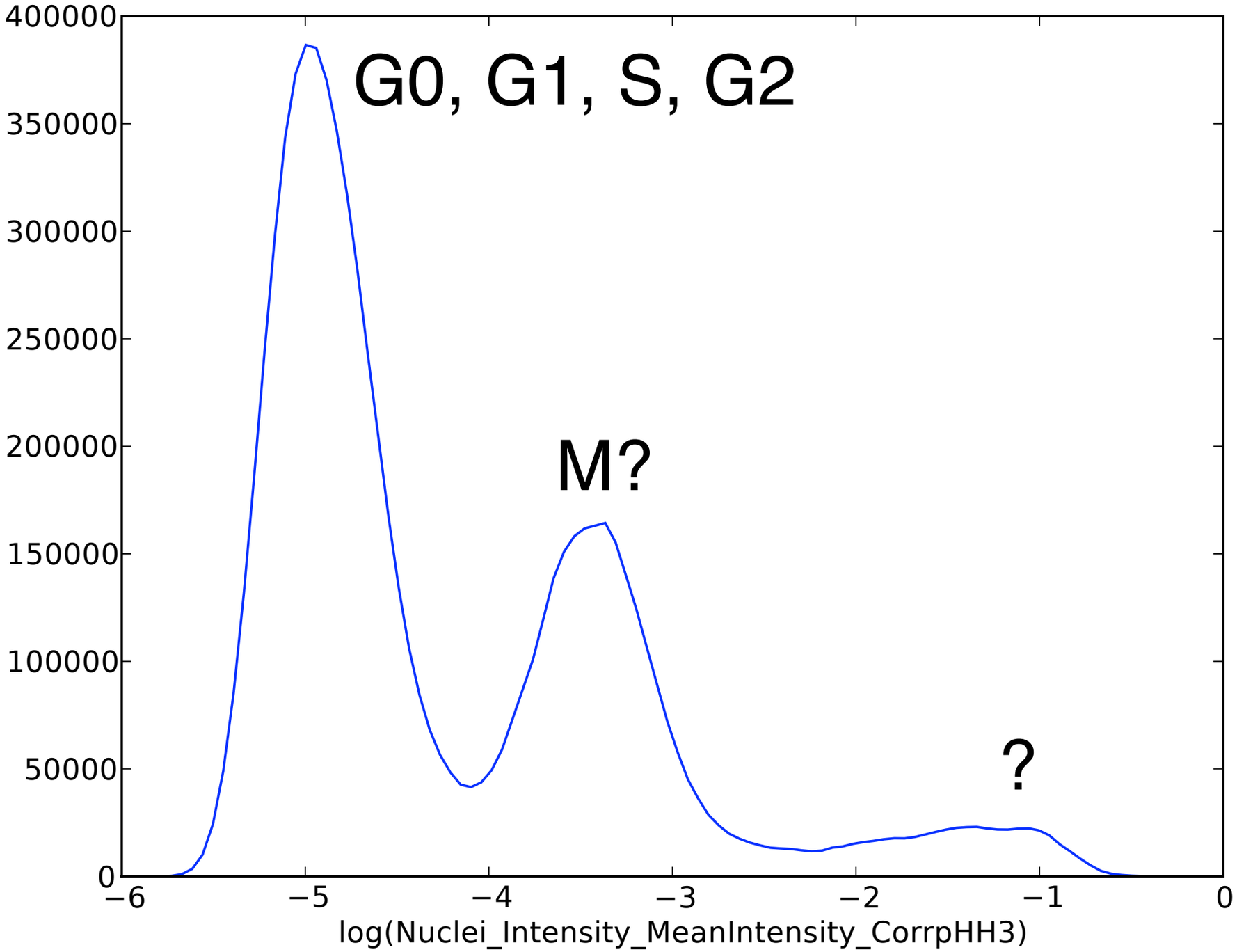
Thousands of samples

Add thousands of chemicals or RNAi agents, each one in a different sample



Hit

# Phosphorylated histone H3 – Mean

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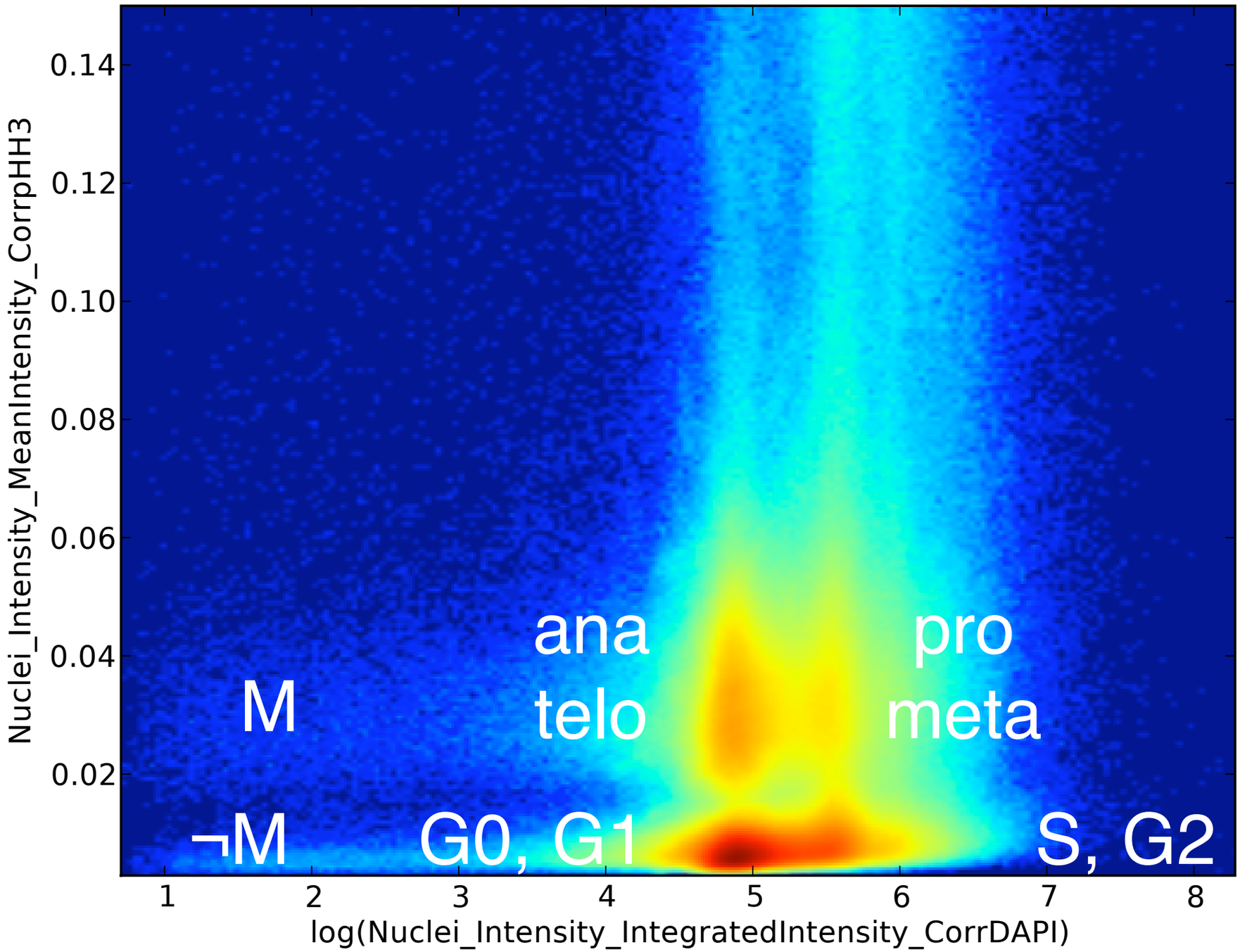
# DAPI and mean pHH3

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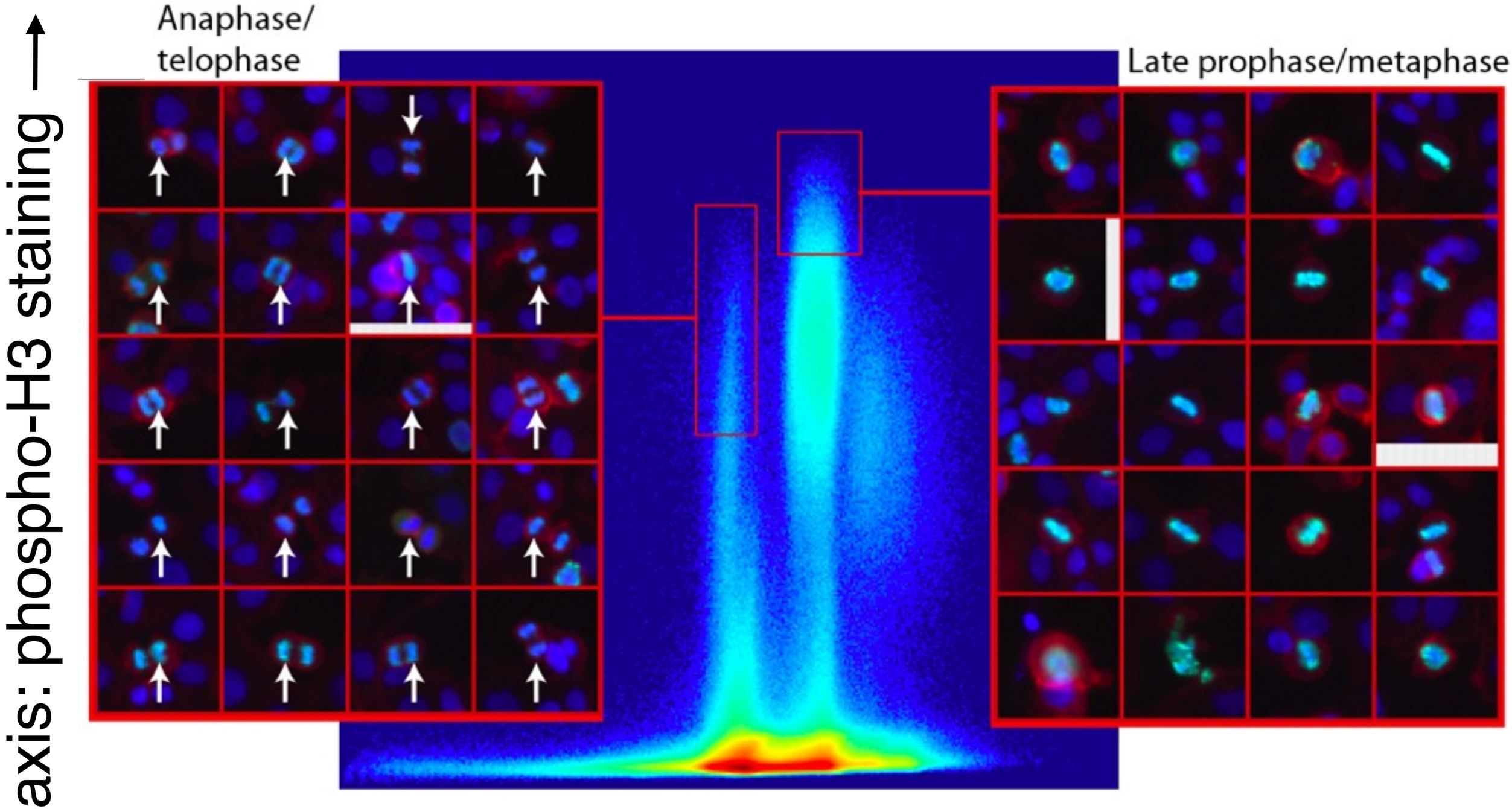
# “Simple” phenotypes: one or two features is enough





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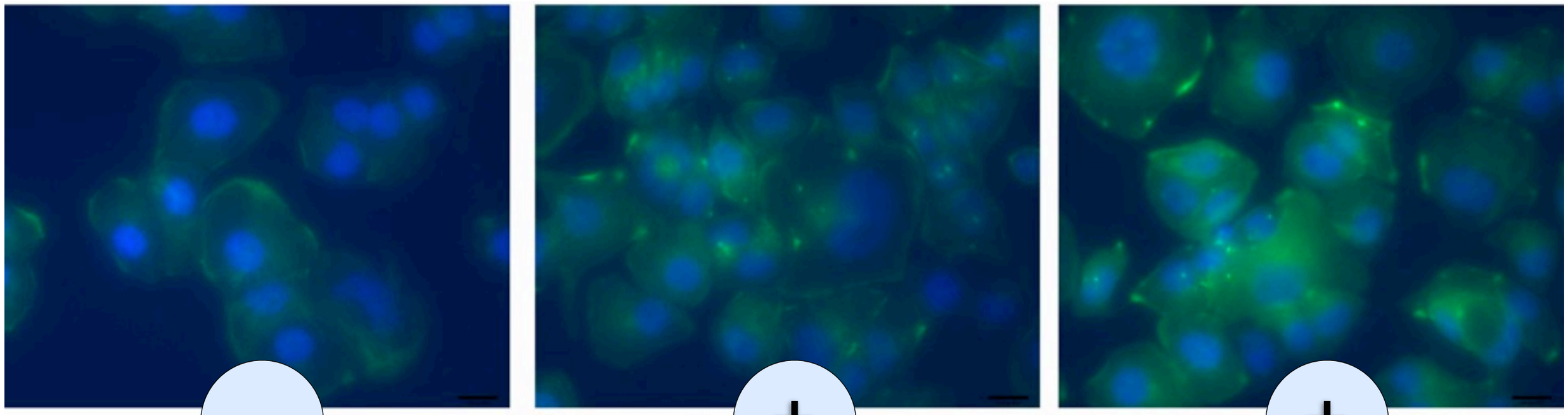
# Example of complex phenotype: motile T47D cells

Normal T47D cells

Features associated with cell motility: lamellipodia, filopodia, polarized cell shape, F-actin nucleation at filapodia, less clumping



−

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+

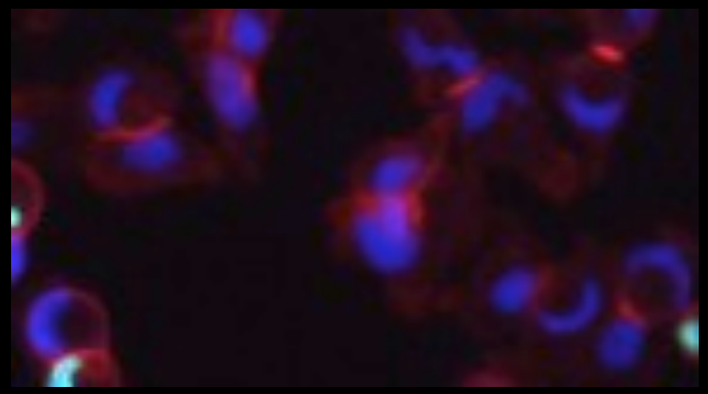
Inducable by HRG

# Challenges

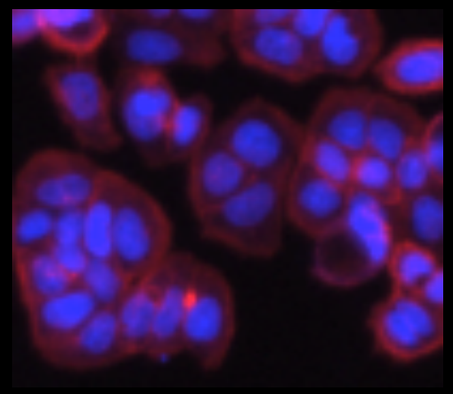
- How to get and crossvalidate with rare phenotypes?
- How to make classifier interpretable by biologist?
- Normalization of features?
- Dimensionality reduction?
- Prevent overfitting?
- Avoid having to tune parameters?

# Rare phenotypes: HT29 colon cancer cells

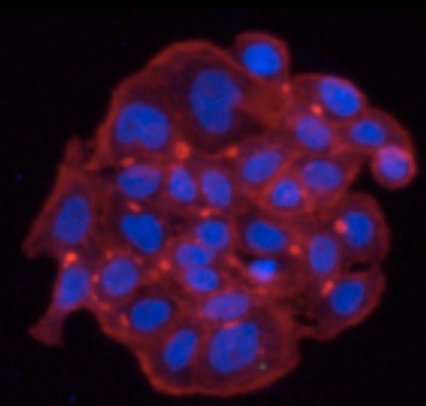
Crescent-shaped nuclei



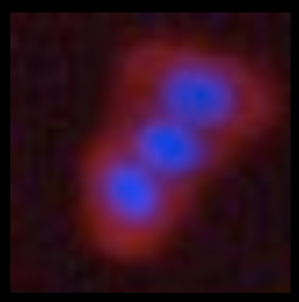
Control cells (HT29)



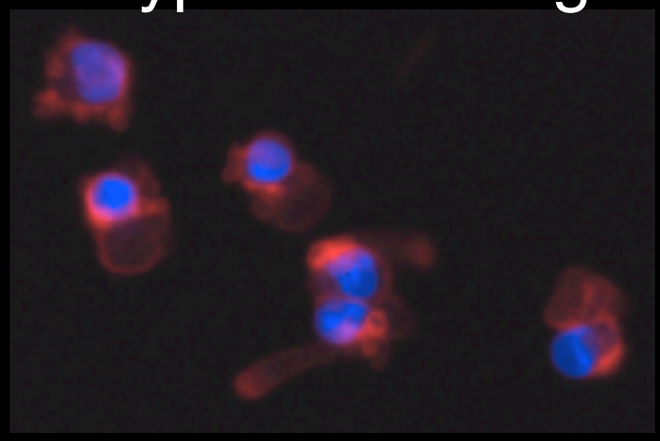
Actin at contractile ring/cell junctions



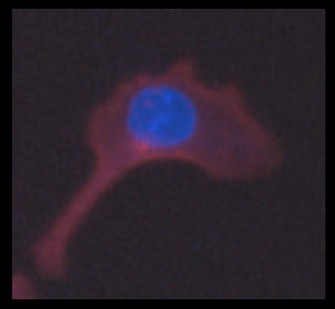
Peas-in-a-pod



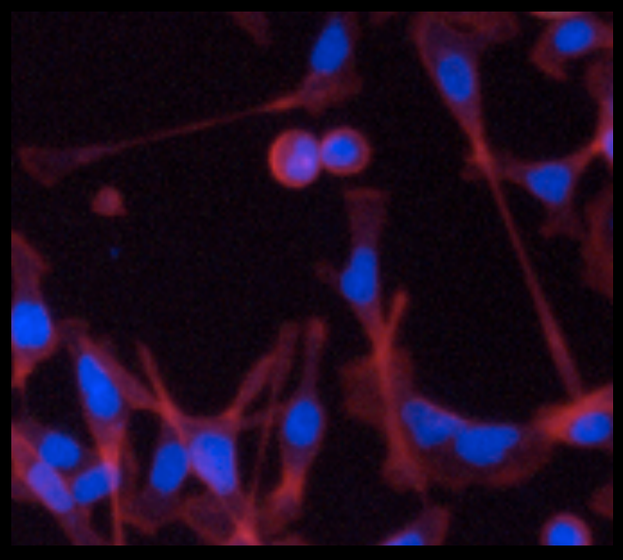
Hyphae-like fingers



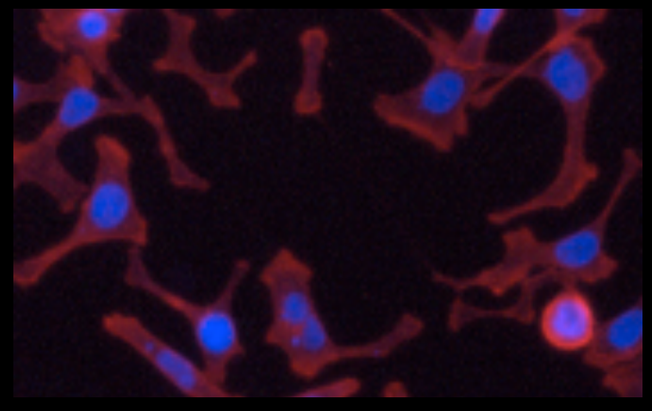
Cells-on-the-move



Long projections



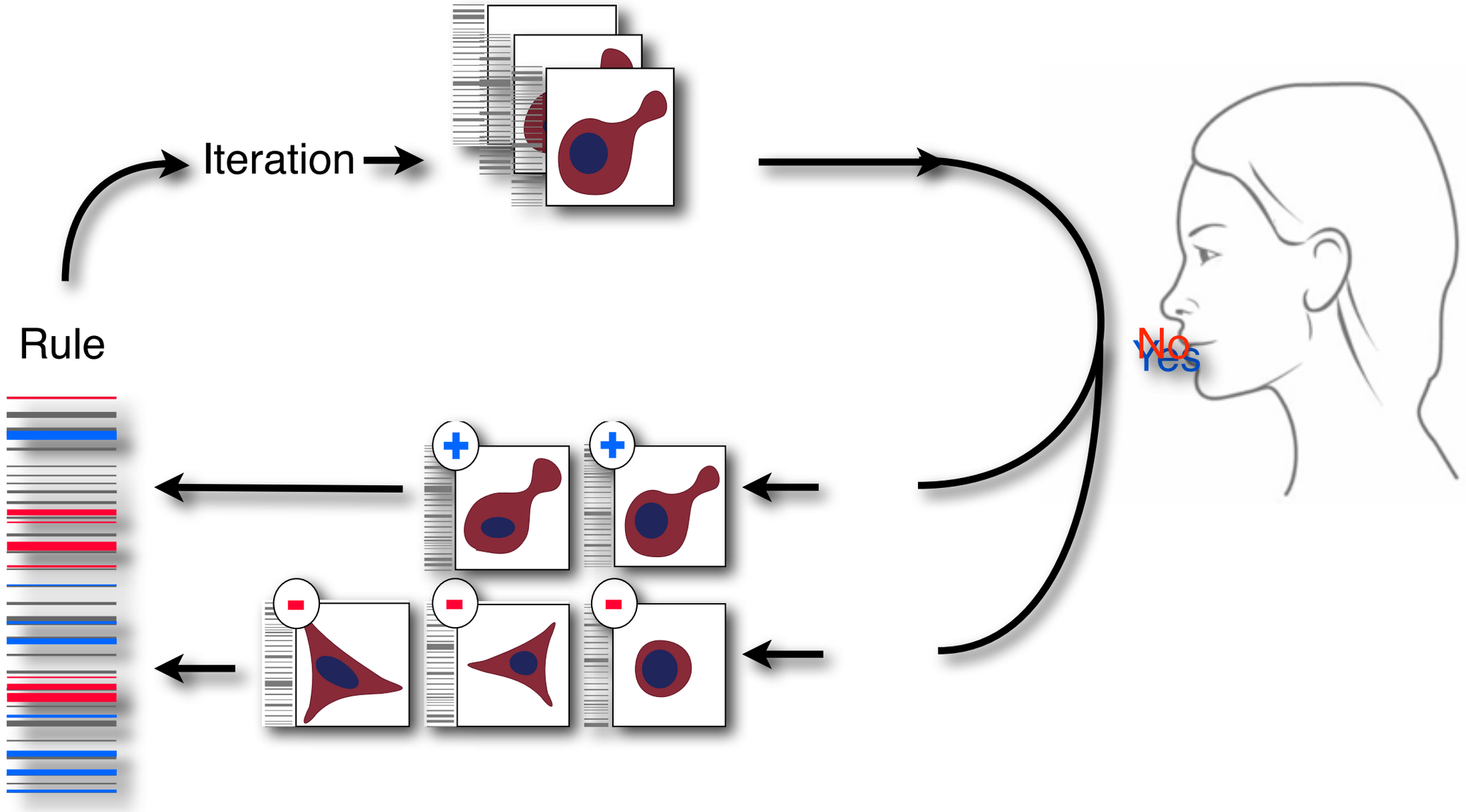
Crooked projections





[Jones et al., PNAS, 2009]

# Iterative machine learning




CellProfiler Analyst
data exploration software

[Jones et al., PNAS, 2009]

Using gentle boosting [Friedman et al., 1998]

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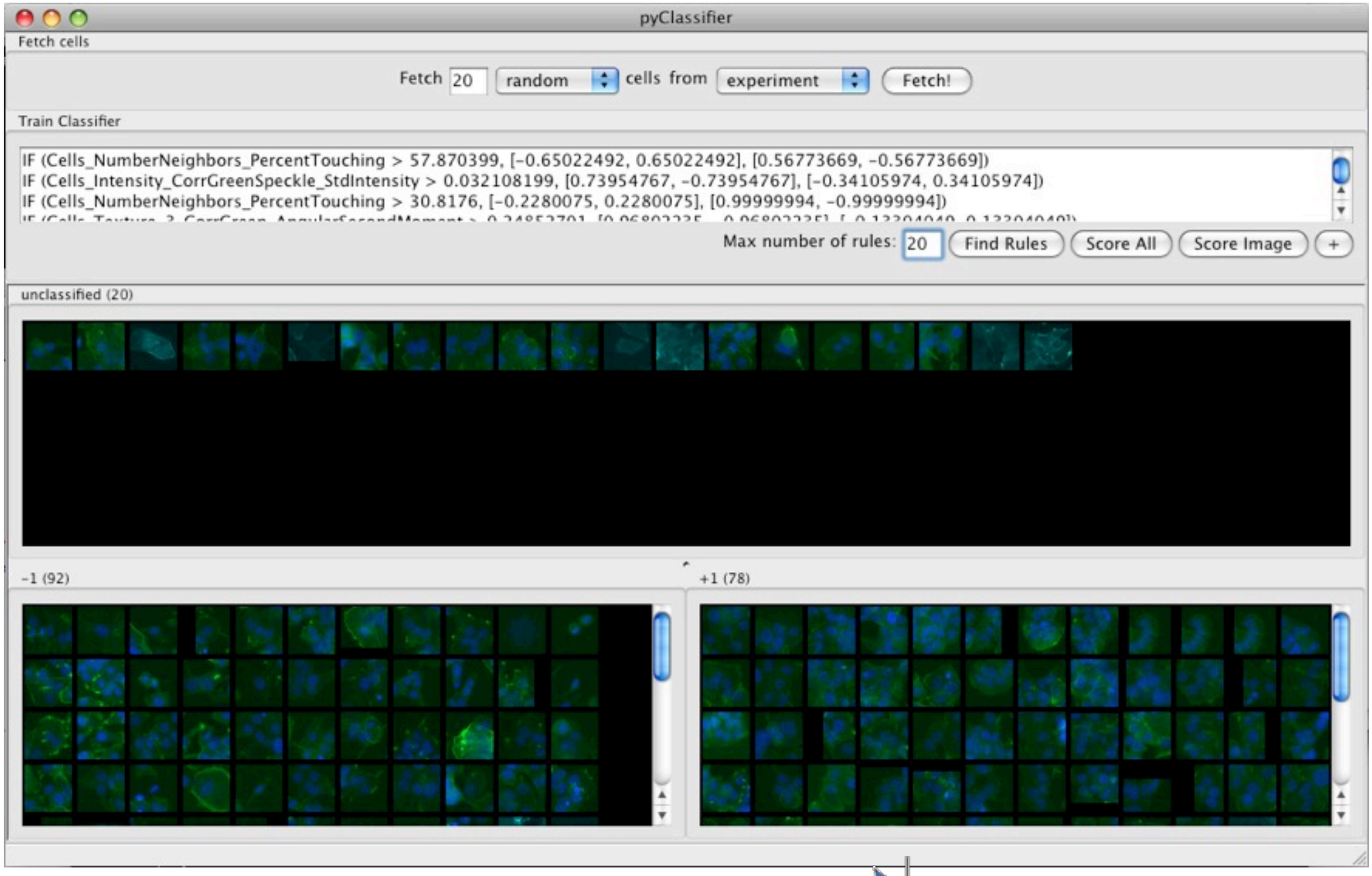
# Incorporated into CellProfiler Analyst

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CellProfiler Analyst
data exploration software



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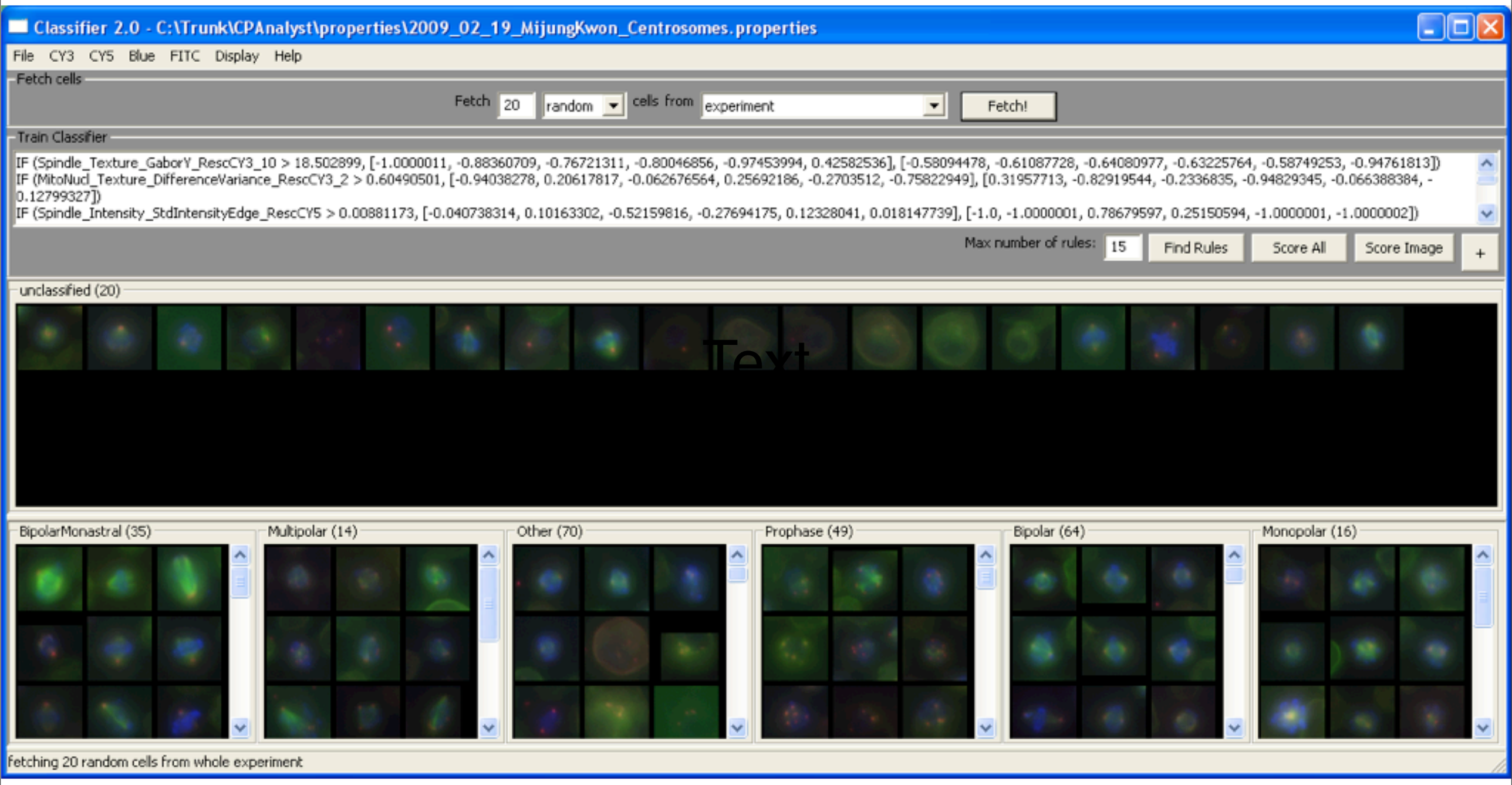
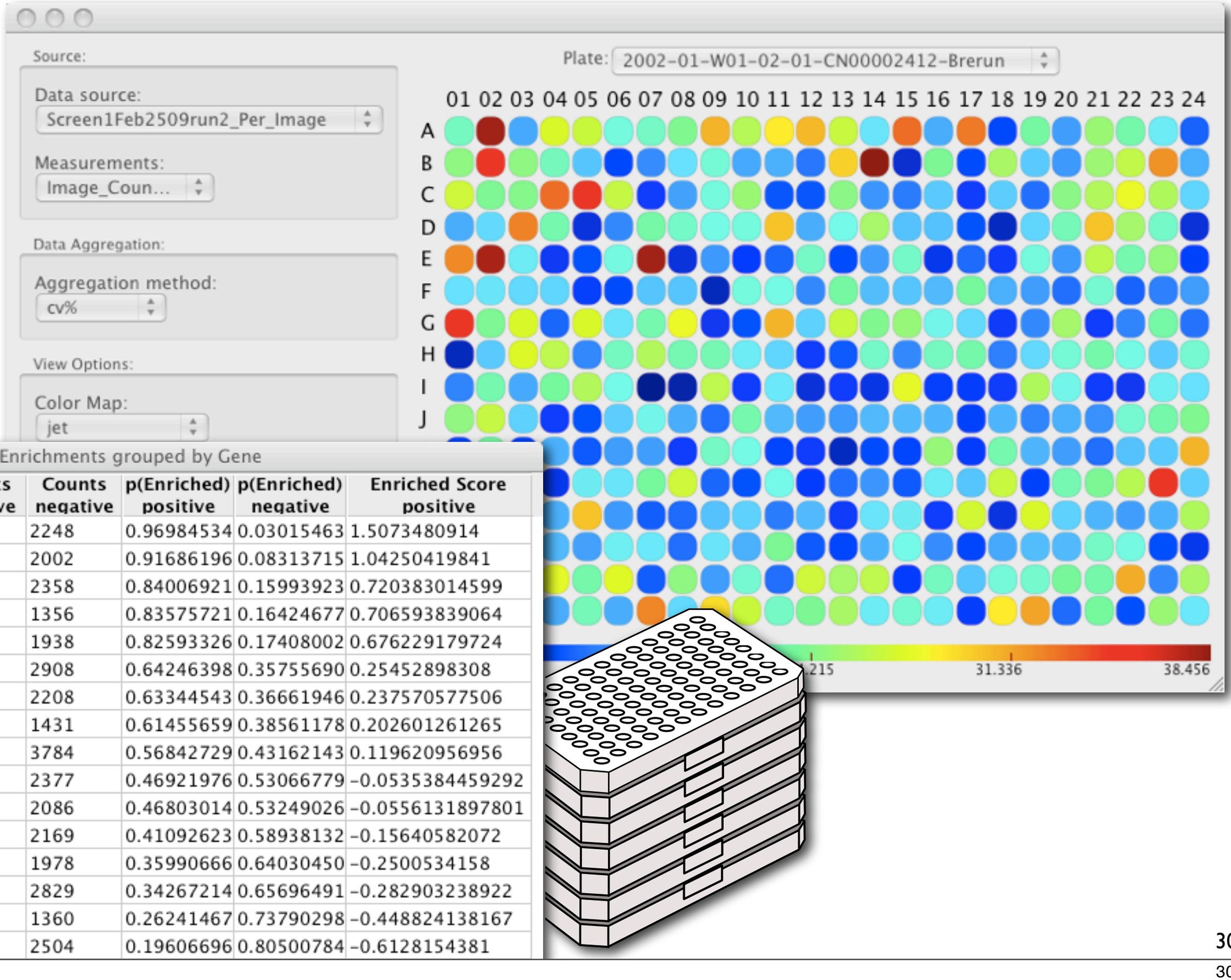
# Rules for distinguishing HRG-stimulated T47D cells

(IF MeanSpeckles_AreaShape_Area > 12.000000, 0.827550, -0.350258) +
(IF Cells_AreaShape_FormFactor > 0.449767, -0.331746, 0.706321) +
(IF CellMembrane_Texture_3_CorrGreen_DifferenceVariance > 0.718124, 0.593955, -0.198424) +
(IF Cells_Intensity_CorrGreenSpeckle_MaxIntensity > 0.370382, 0.787301, -0.204062) +
(IF CellMembrane_Intensity_CorrGreenSpeckle_MinIntensityEdge > 0.001284, 0.275866, -0.500179) +
(IF Cells_Texture_3_CorrGreen_SumEntropy > 1.710600, -0.199515, 0.700658) +
(IF Nuclei_AreaShape_Perimeter > 96.669000, -0.177882, 0.788582) +
(IF Cells_Texture_3_CorrGreen_GaborY > 0.147318, -0.215618, 0.613682) +
(IF Cells_Intensity_CorrGreenSpeckle_StdIntensity > 0.033557, 0.742323, -0.169222) +
(IF Cells_Intensity_CorrGreenSpeckle_StdIntensityEdge > 0.009328, -0.118830, 0.956272)

# Multiple classes



# QC and Tracking Down Hits




Enrichments grouped by Gene

| gene | Counts positive | Counts negative | p(Enriched) positive | p(Enriched) negative | Enriched Score positive |
|---|---|---|---|---|---|
| NME1 | 179 | 2248 | 0.96984534 | 0.03015463 | 1.5073480914 |
| PRPS2 | 140 | 2002 | 0.91686196 | 0.08313715 | 1.04250419841 |
| TK1 | 146 | 2358 | 0.84006921 | 0.15993923 | 0.720383014599 |
| PMS1 | 86 | 1356 | 0.83575721 | 0.16424677 | 0.706593839064 |
| GALK1 | 119 | 1938 | 0.82593326 | 0.17408002 | 0.676229179724 |
| MAPK13 | 148 | 2908 | 0.64246398 | 0.35755690 | 0.25452898308 |
| Gabra2 | 112 | 2208 | 0.63344543 | 0.36661946 | 0.237570577506 |
| PHKG2 | 72 | 1431 | 0.61455659 | 0.38561178 | 0.202601261265 |
| MAP2K3 | 181 | 3784 | 0.56842729 | 0.43162143 | 0.119620956956 |
| STK19 | 105 | 2377 | 0.46921976 | 0.53066779 | -0.0535384459292 |
| Gabra1 | 92 | 2086 | 0.46803014 | 0.53249026 | -0.0556131897801 |
| MAP2K6 | 91 | 2169 | 0.41092623 | 0.58938132 | -0.15640582072 |
| Gpr12 | 79 | 1978 | 0.35990666 | 0.64030450 | -0.2500534158 |
| PDXK | 112 | 2829 | 0.34267214 | 0.65696491 | -0.282903238922 |
| MAPK11 | 48 | 1360 | 0.26241467 | 0.73790298 | -0.448824138167 |
| Gabra3 | 84 | 2504 | 0.19606696 | 0.80500784 | -0.6128154381 |



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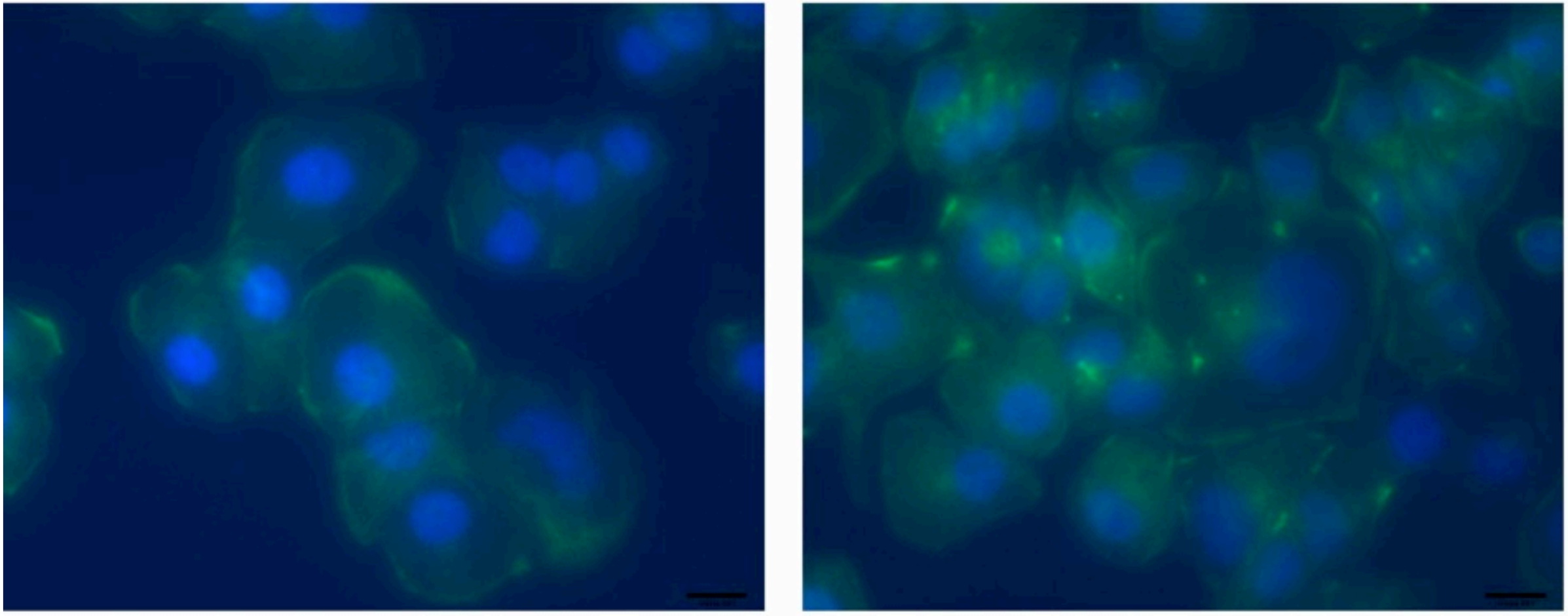
# The phenotype of motile T47D cells

Normal T47D cells

Features associated with cell motility: lamellipodia, filopodia, polarized cell shape, F-actin nucleation at filopodia, less clumping



Unstimulated

Stimulated by heregulin

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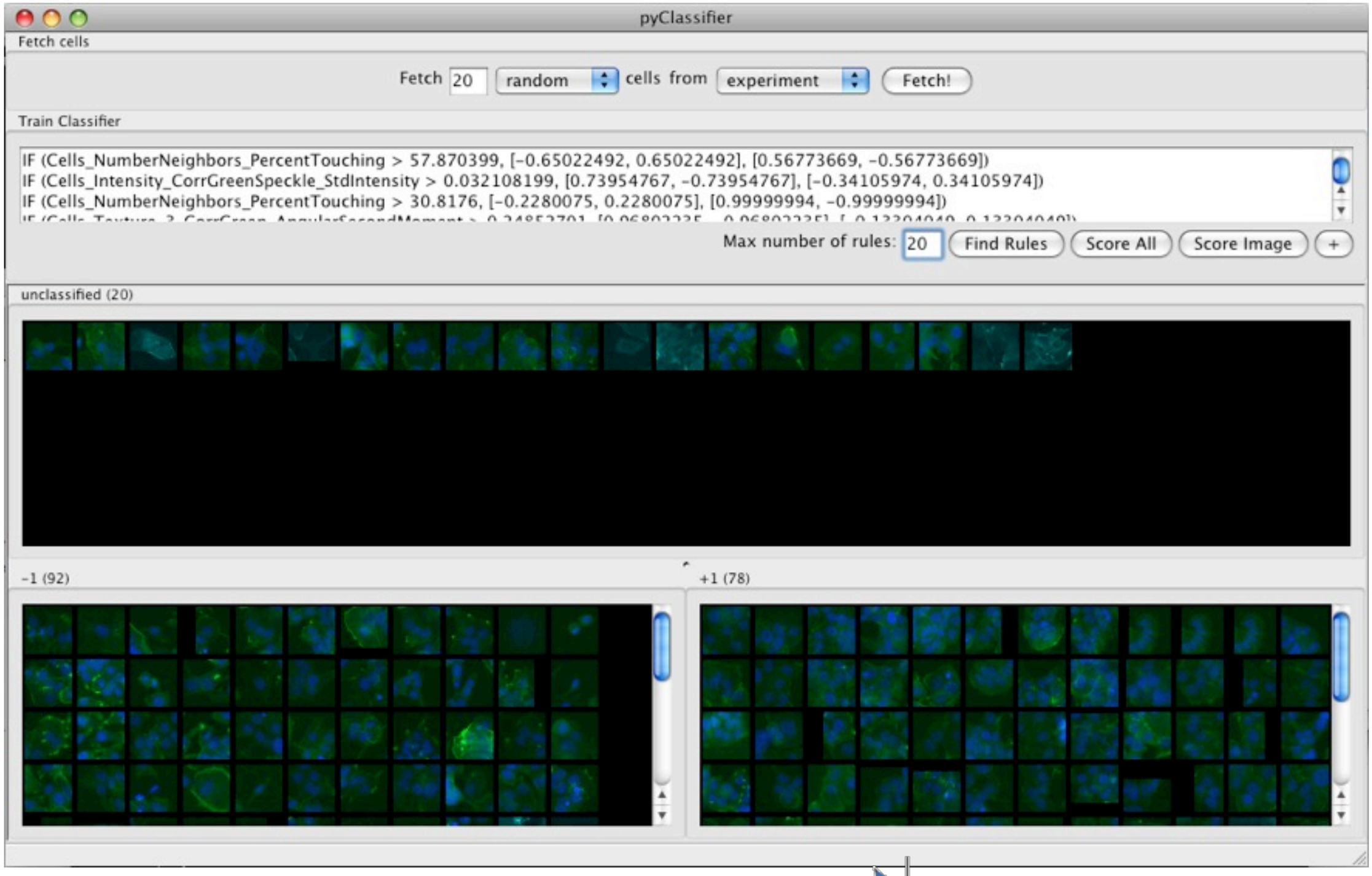
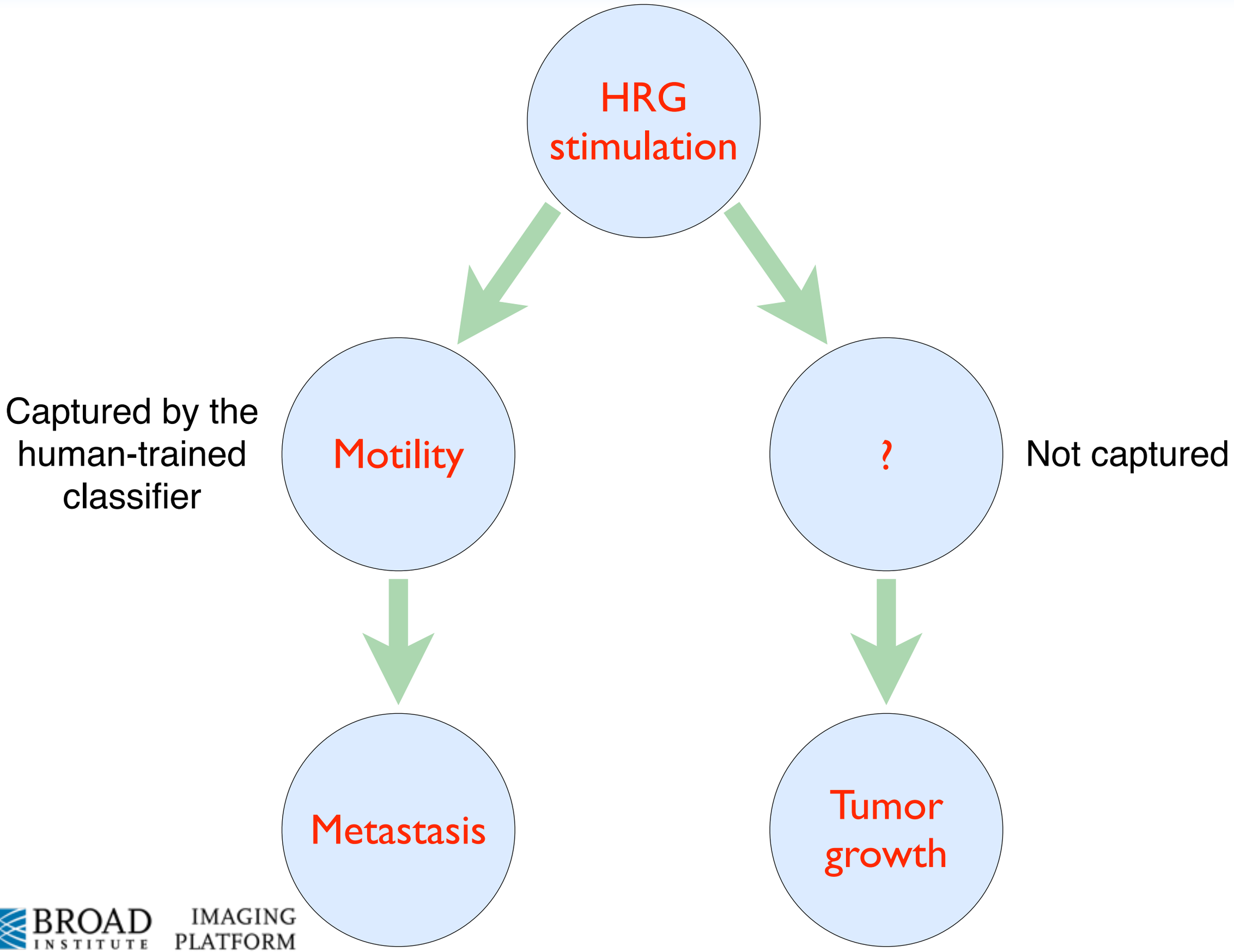
# Built training set of ~300 cells



# Why cut out the human?

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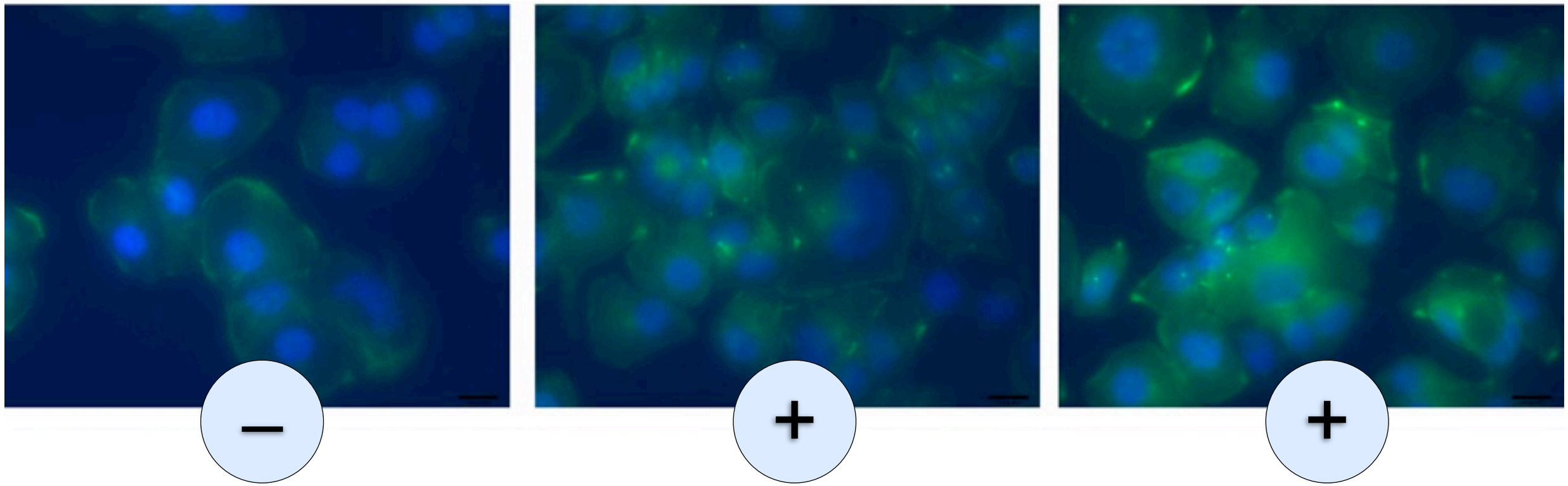
# Labeling for automatic training set

Replicate 1

Replicate 2

Replicate 3



−

+

+

Unstimulated

Stimulated by heregulin

45 % motile cells

55 % motile cells

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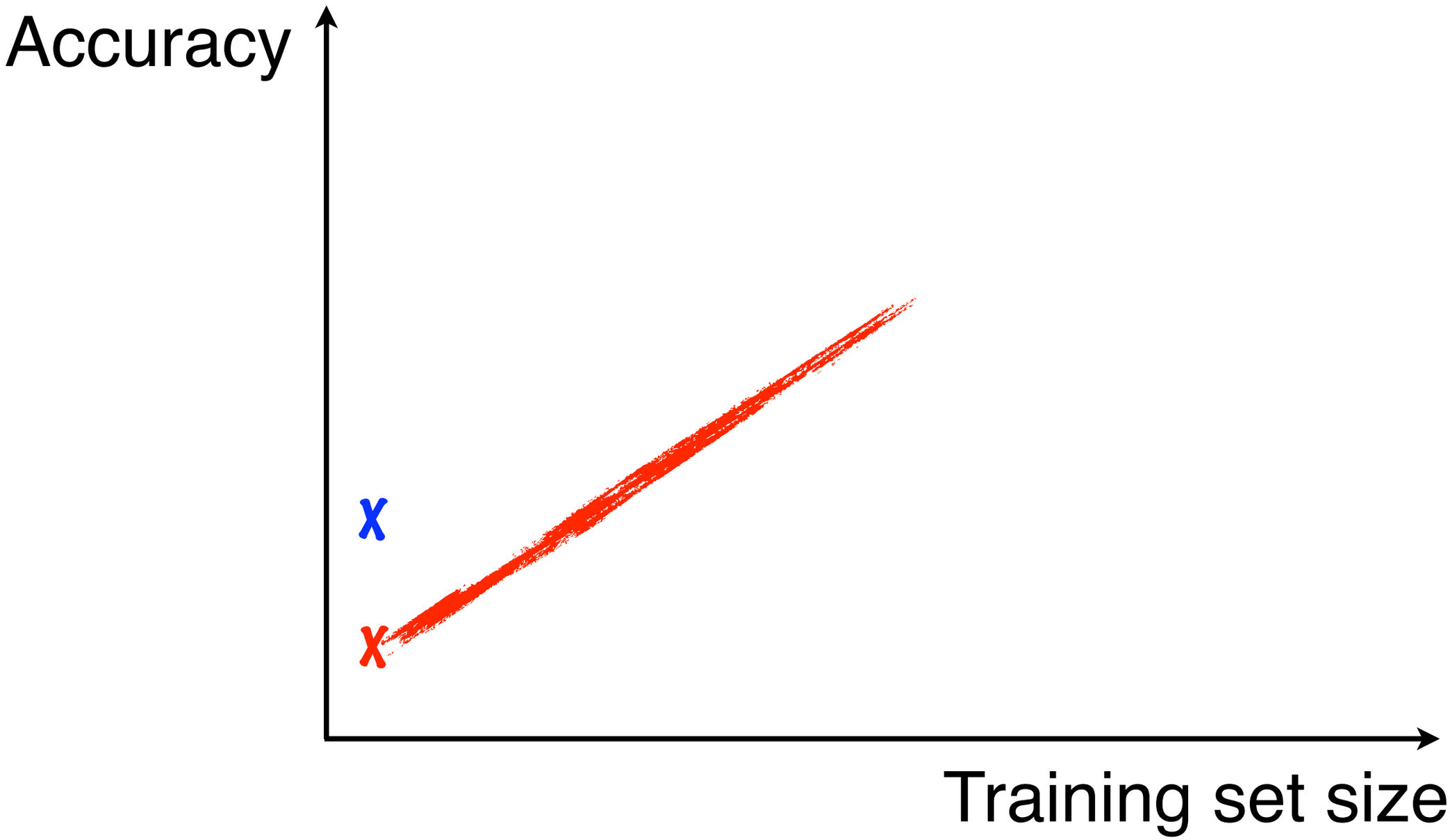
# Two ways to improve the classifier




See [Banko & Brill, 2001]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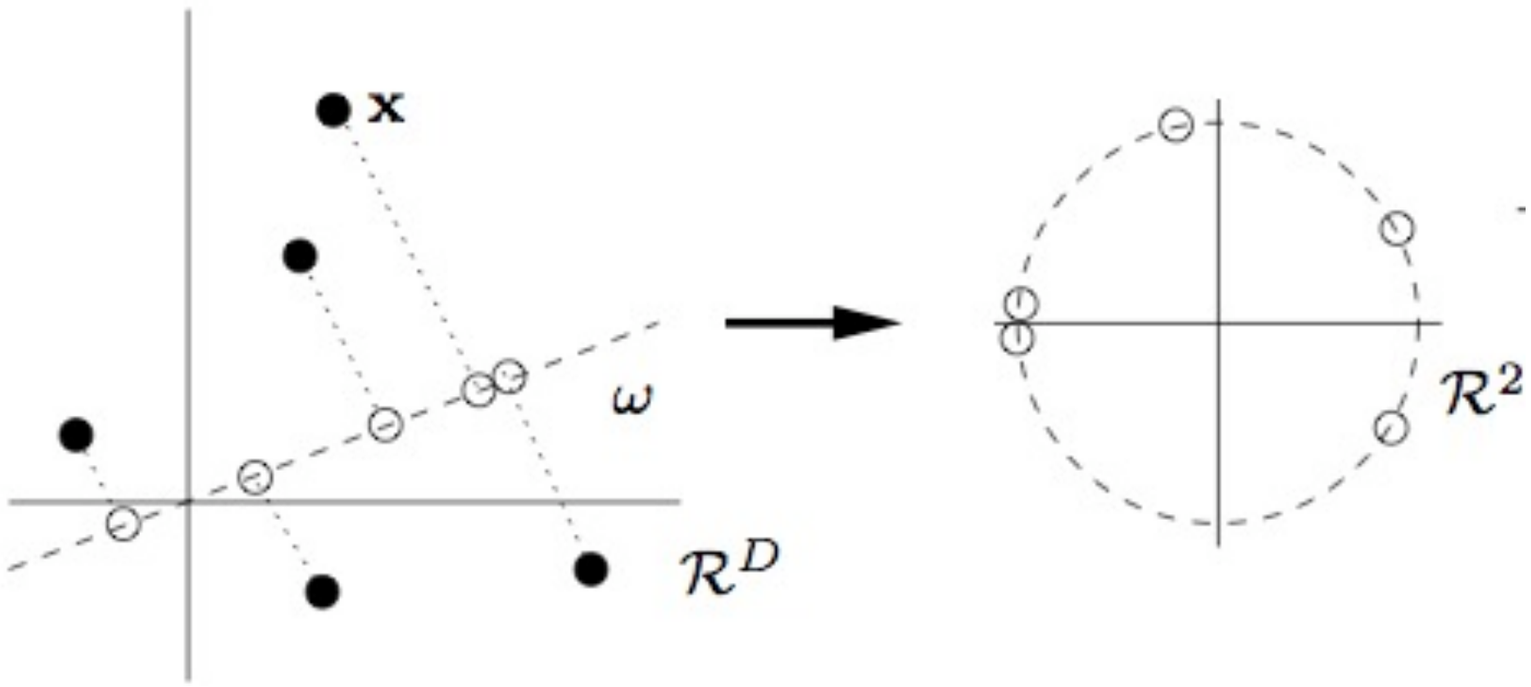
# Random Fourier features

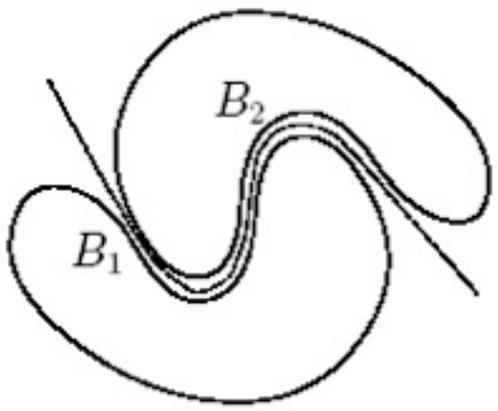
$$\cos(\omega' \mathbf{x} + b)$$




| Kernel Name | $k(\Delta)$ | $p(\omega)$ |
|---|---|---|
| Gaussian | $e^{-\frac{\|\Delta\|_2^2}{2}}$ | $(2\pi)^{-\frac{D}{2}} e^{-\frac{\|\omega\|_2^2}{2}}$ |
| Laplacian | $e^{-\|\Delta\|_1}$ | $\prod_d \frac{1}{\pi(1+\omega_d^2)}$ |
| Cauchy | $\prod_d \frac{2}{1+\Delta_d^2}$ | $e^{-\|\Delta\|_1}$ |

[Rahimi and Recht, NIPS, 2007]

# Random features




$\mathbf{x}$ $\mathbf{y}$

Original data

The kernel trick

$k(\mathbf{x}, \mathbf{y})$

Kernel function

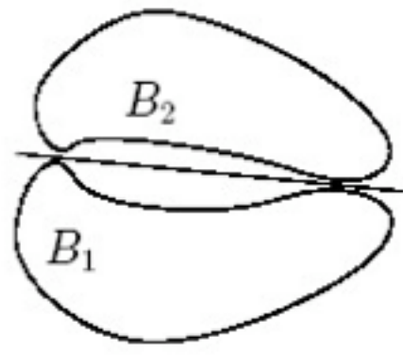
$\langle \phi(\mathbf{x}), \phi(\mathbf{y}) \rangle \approx \mathbf{z}(\mathbf{x})'\mathbf{z}(\mathbf{y})$

Inner product used, e.g., by SVM.

Random features
[Rahimi and Recht, NIPS, 2007]

$\mathbf{z}(\mathbf{x})$ $\mathbf{z}(\mathbf{y})$

Datapoints in a fairly low-dimensional space (a few hundred dimensions) spanned by random Fourier bases

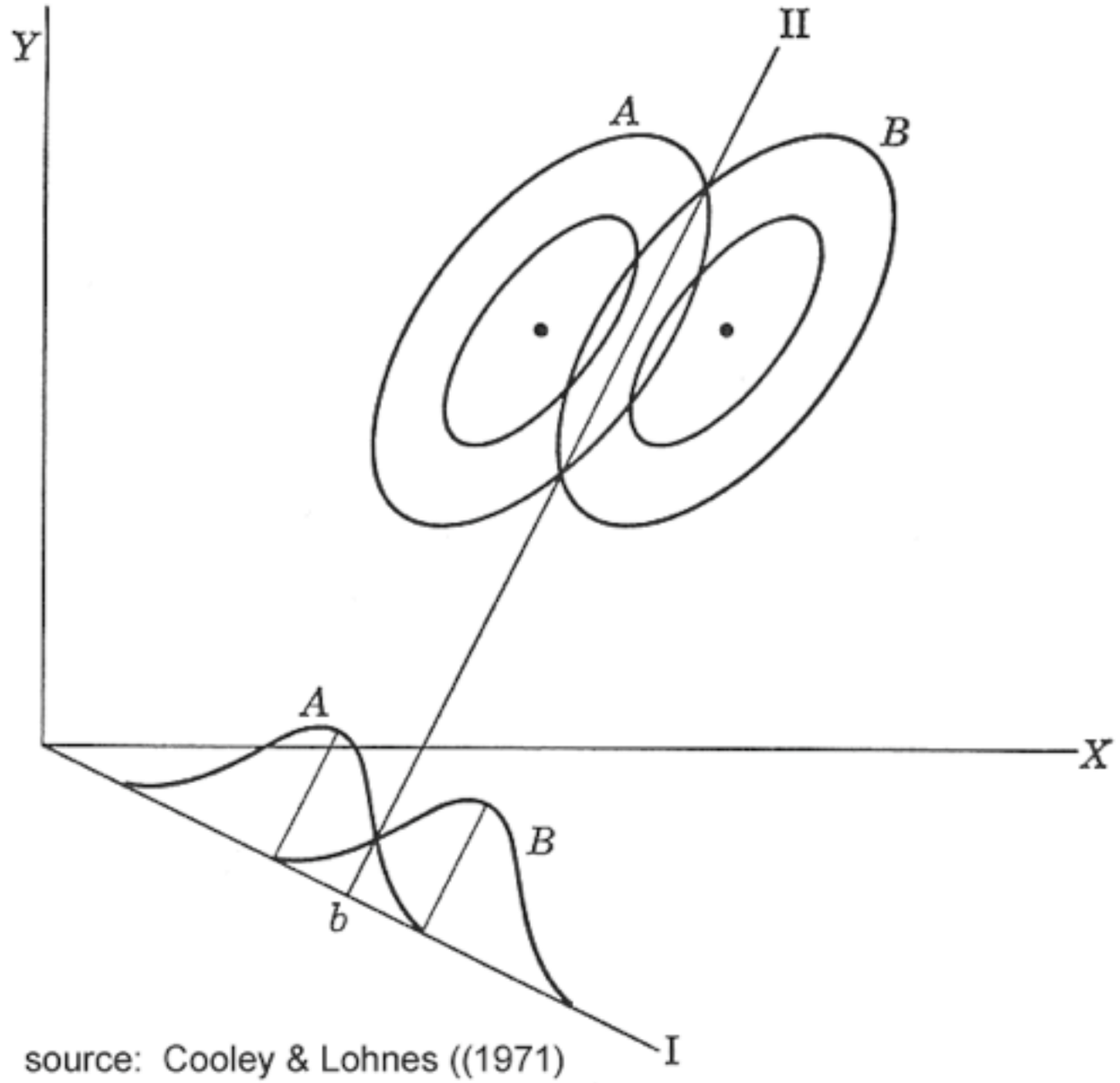


# Linear discriminant on random features

7.6 million training cells,
130 measurements

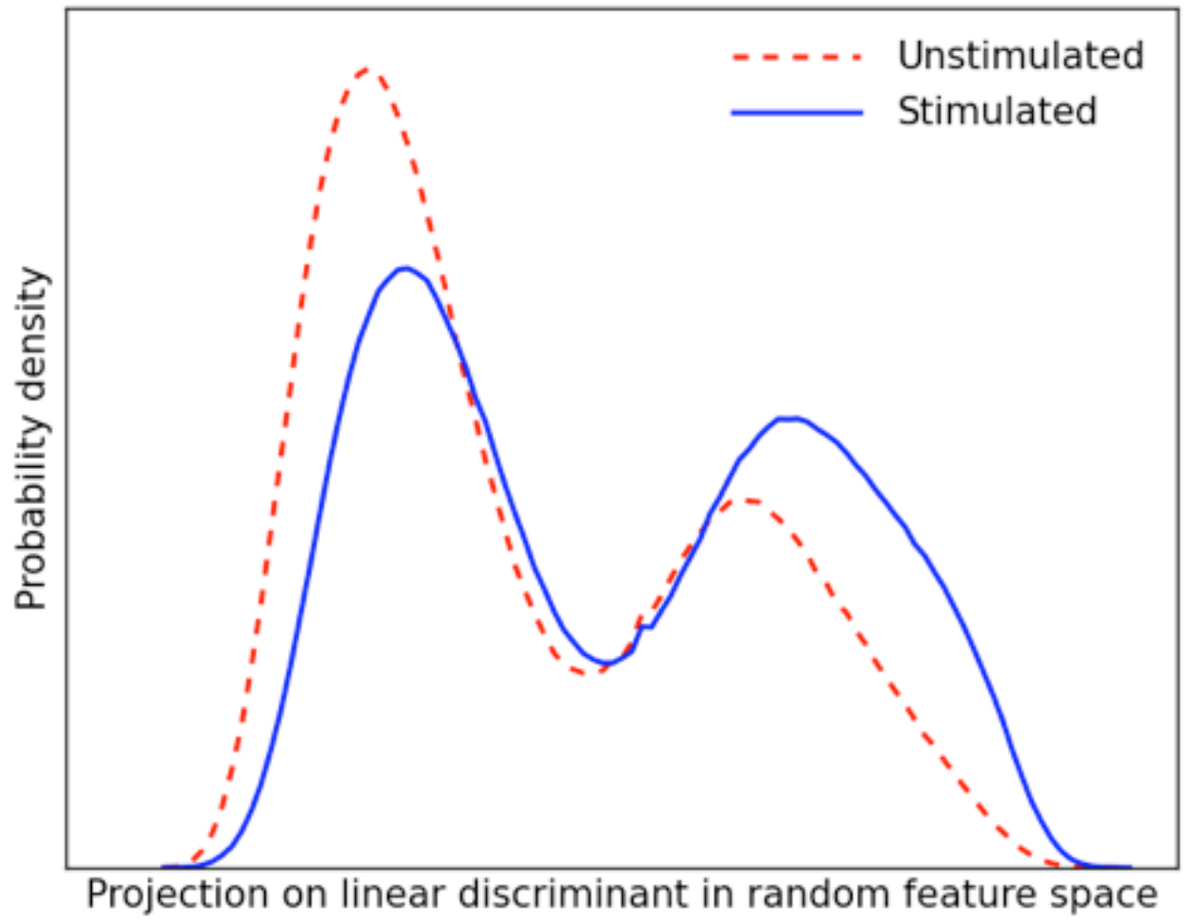
Mapped into 250-dimensional random feature space

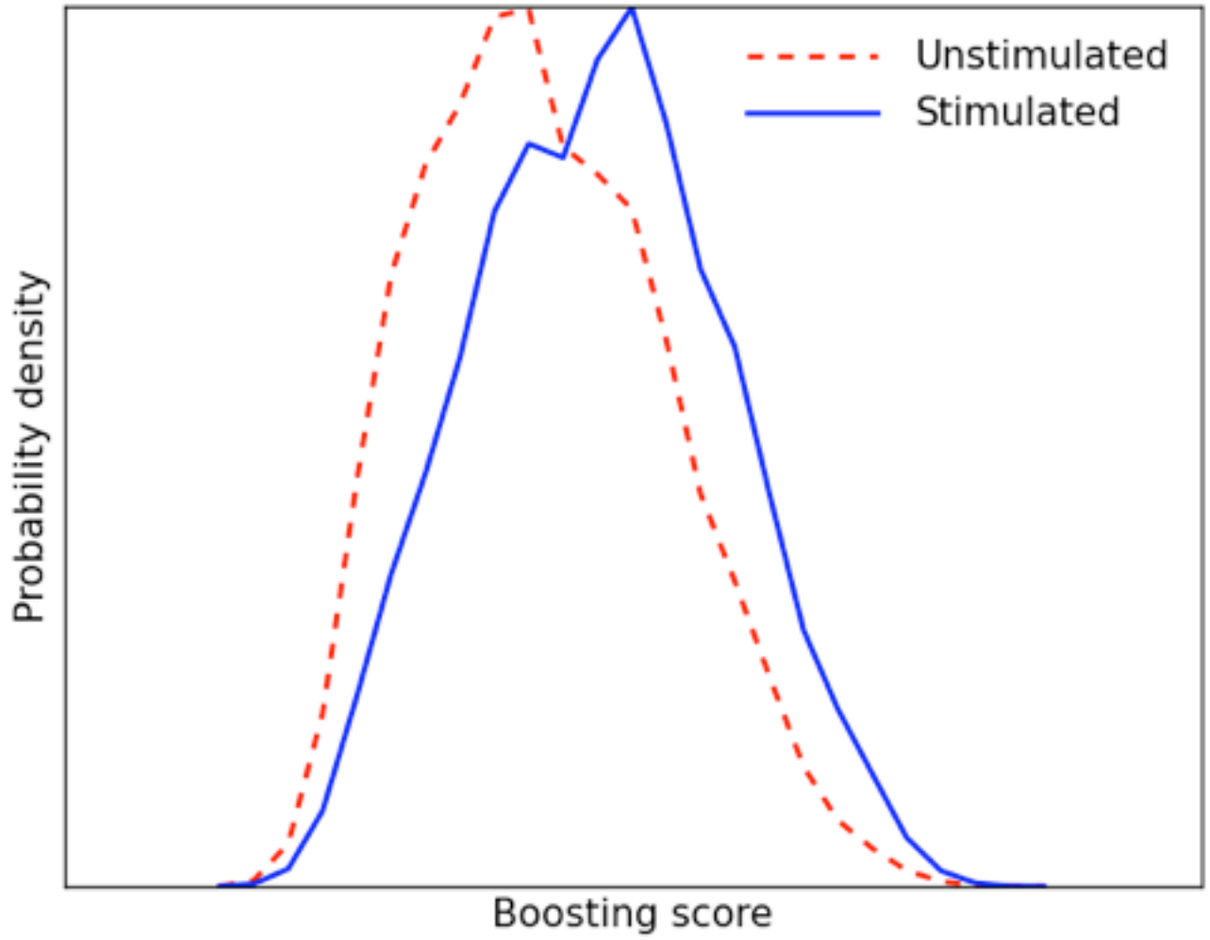
Trained Fisher's linear discriminant




source: Cooley & Lohnes ((1971)

# Automatic vs. hand training



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# Expected likelihood kernel

$$k(A, B) = \int \Pr(x|A)\ \Pr(x|B)\, \mathrm{d}x$$

[Jebara et al., 2004]

$z(x)$ projection of x into random-feature space

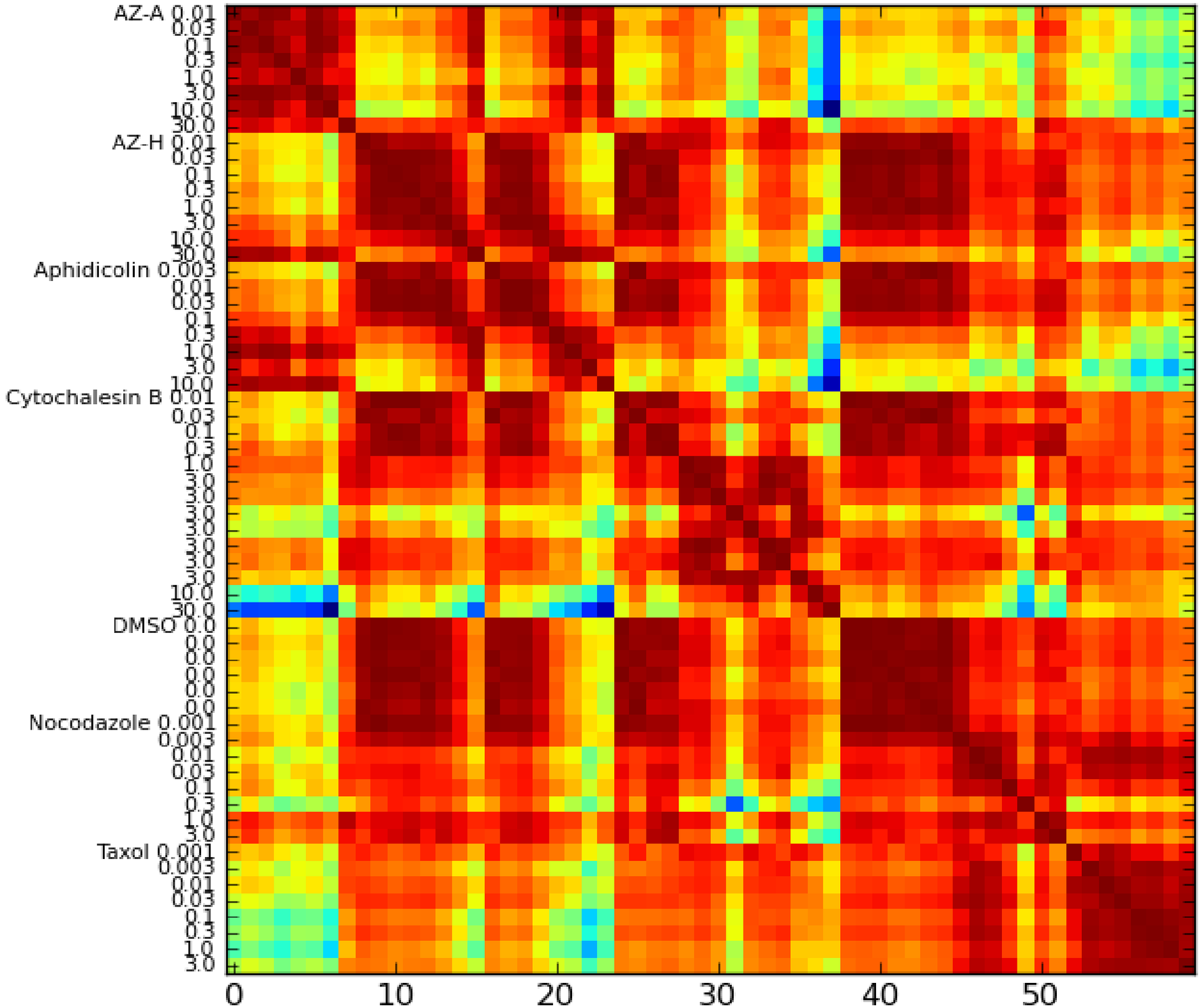
$$\langle z(a), z(b) \rangle \approx k(a, b)$$

$$v_A = \frac{1}{|A|} \sum_{x \in A} z(x)$$

$$\langle v_A, v_B \rangle \approx \frac{1}{|A||B|} \sum_{x \in A, y \in B} \mathrm{e}^{-(x-y)^2/2}$$

$$\approx \int \Pr(x|A) \Pr(x|B) \, \mathrm{d}x$$

# Correlation coefficient of dot products



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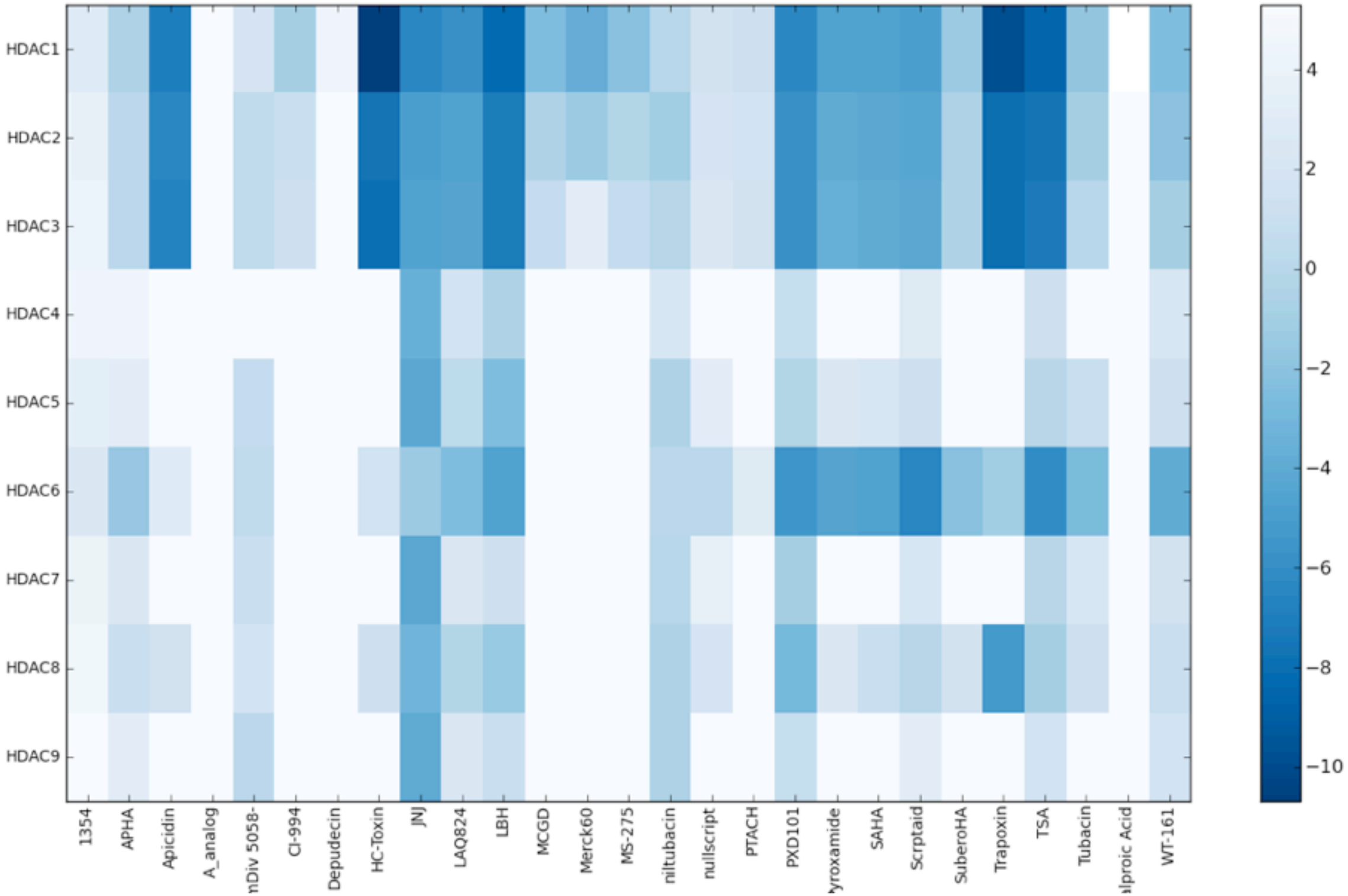
# Histone deacetylases

- 11 enzymes
- Component of chromatin-regulating complexes
- Also target many non-histone proteins
- Broad relevance to cell signaling and cell state
- Induce differentiation and inhibit proliferation in cancer models
- Inhibitors used clinically for cutaneous T-cell lymphoma, others in trials for other cancers

# Screening question: find specific HDAC inhibitors

Inhibition potency data from biochemical assays

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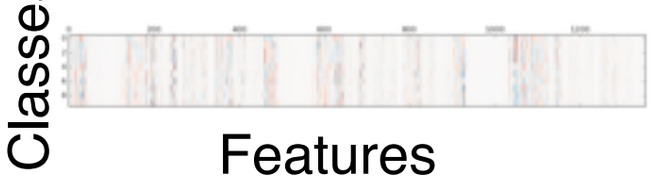
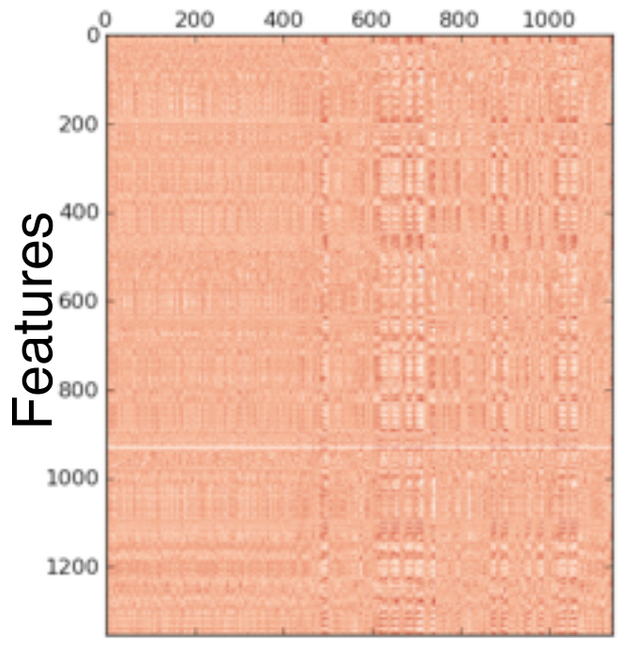
# Training

T X = K

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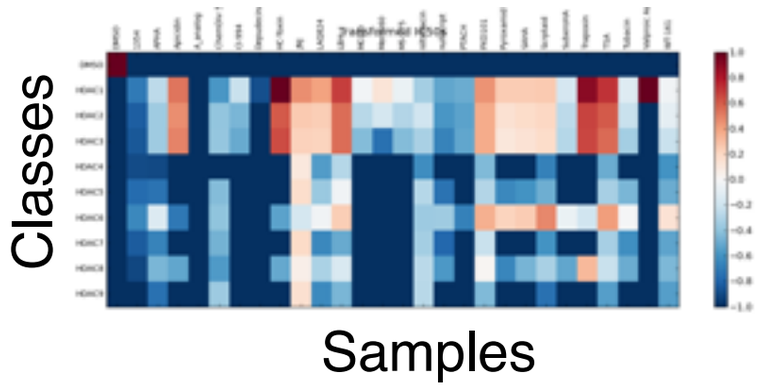


$$T = K X^{-1}$$

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Schematic



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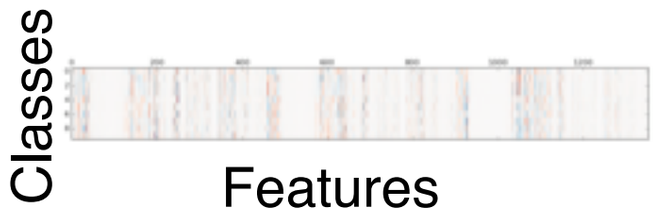
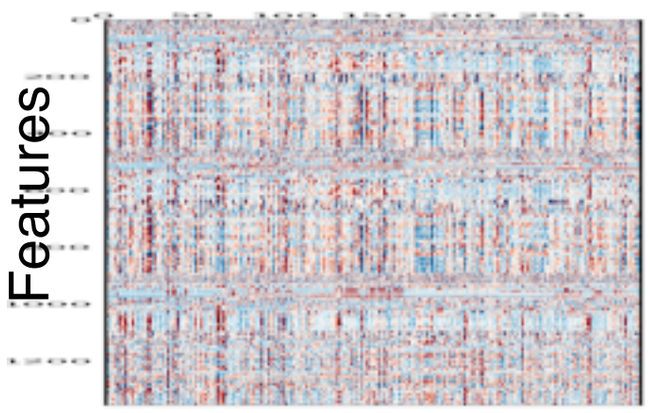
# Testing

T X = K’

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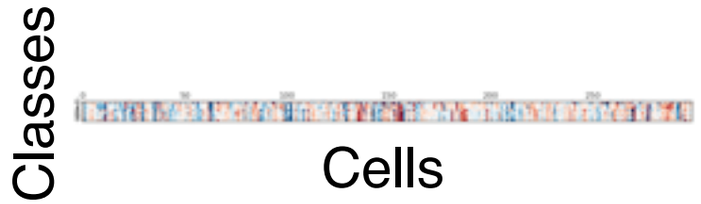


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Schematic



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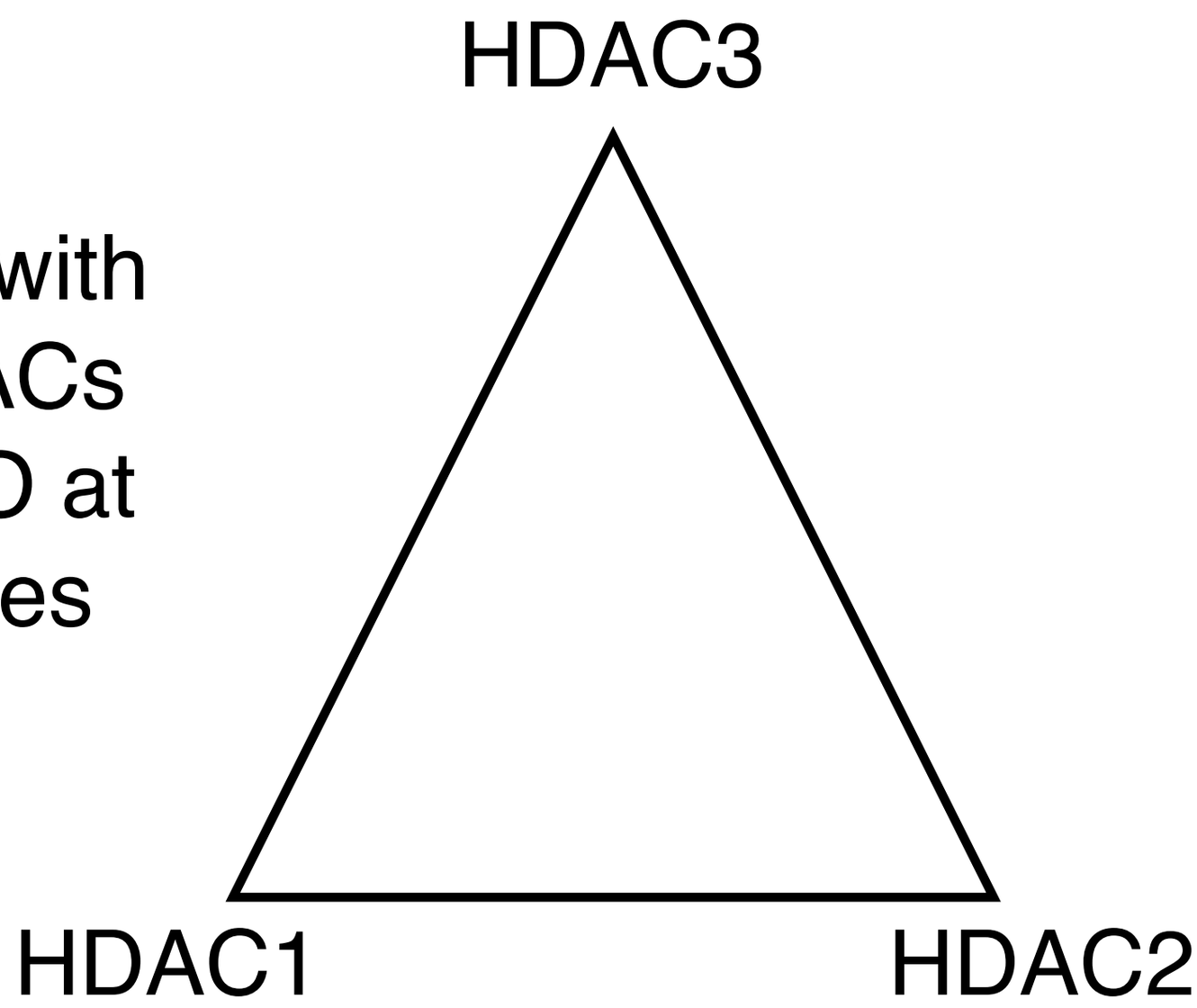
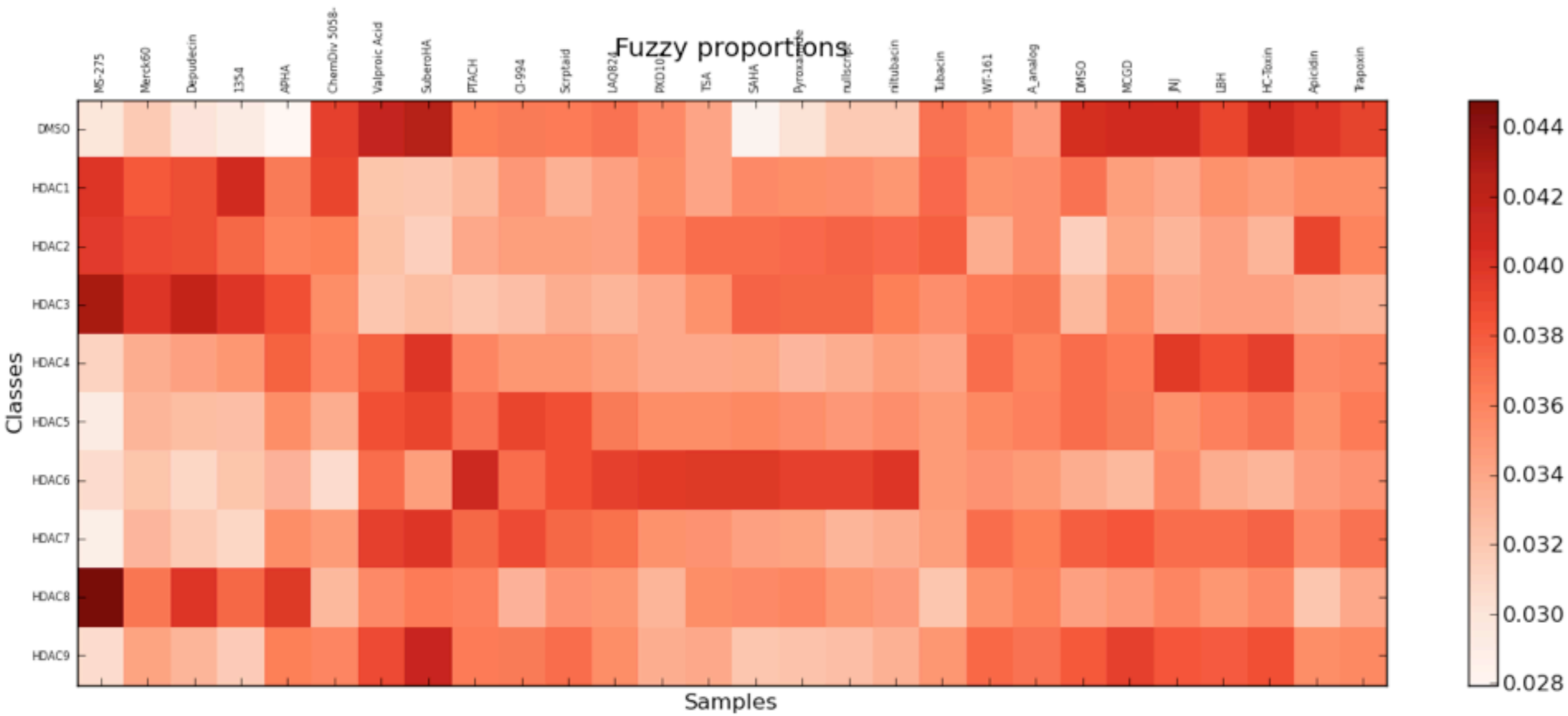
# Convert scores to soft labels by logistic transform

9-simplex with the 9 HDACs and DMSO at the vertices



# Proportions of cells for each topic

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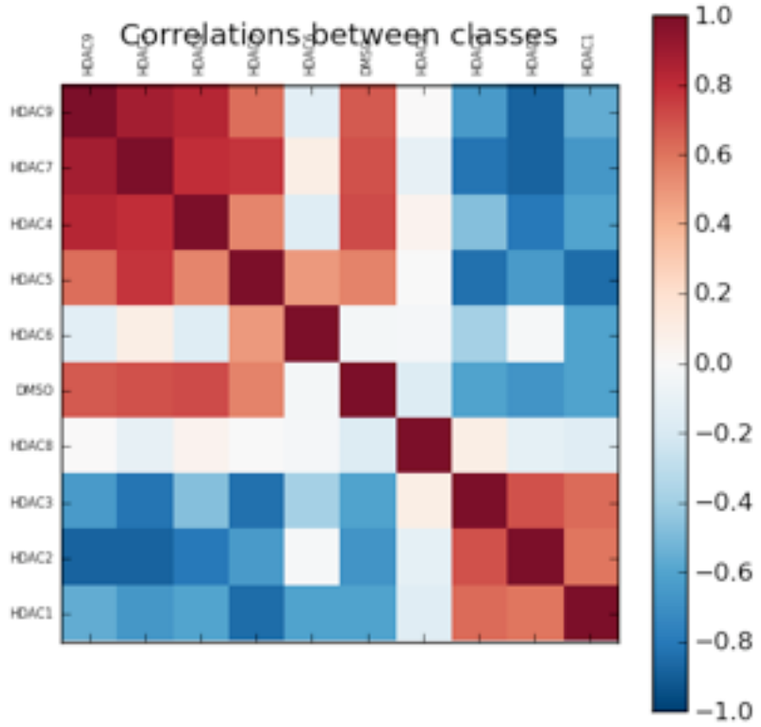
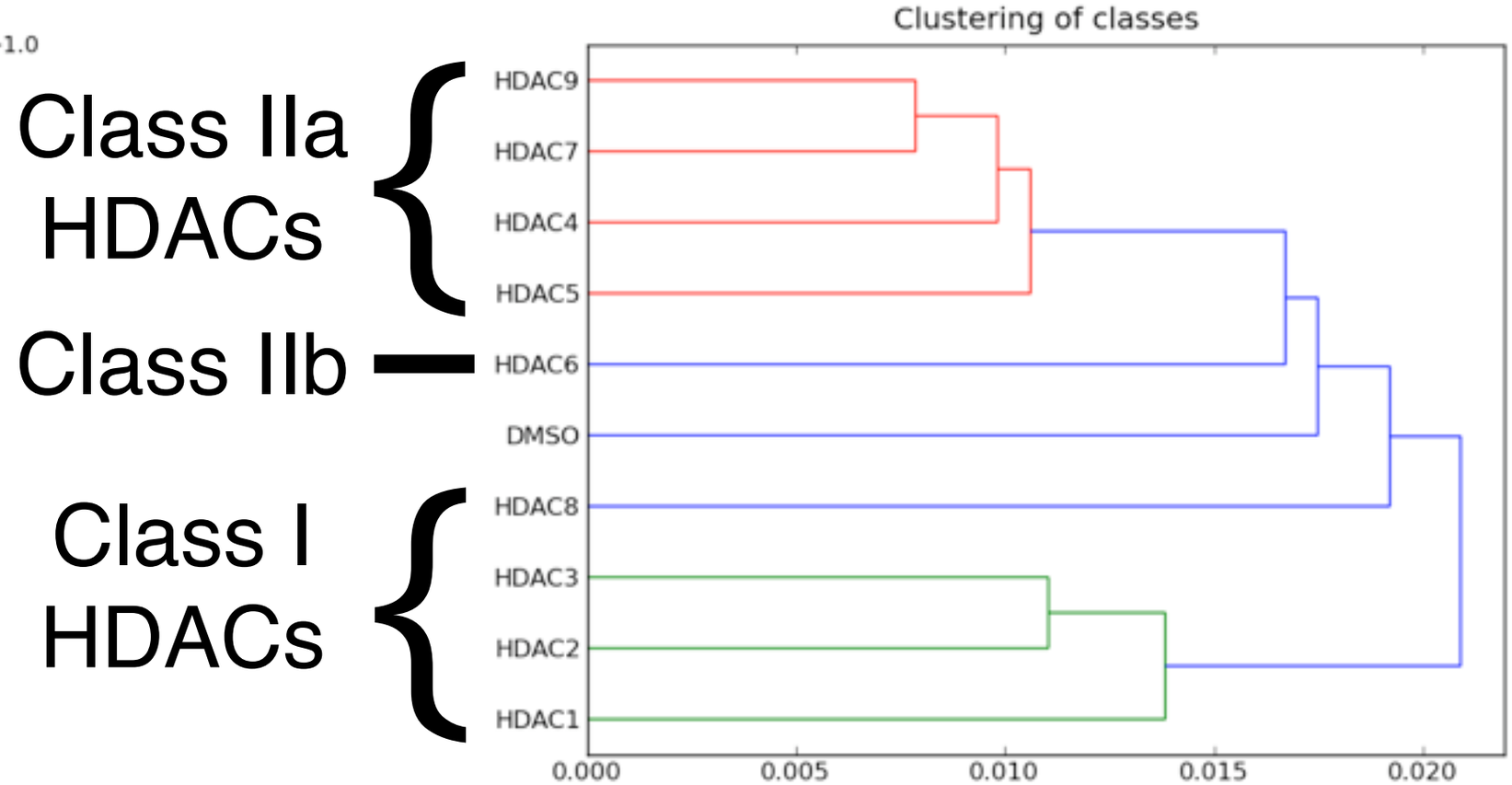
# Correlations between classes match HDAC phylogeny




Class IIa HDACs

Class IIb

Class I HDACs

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# Thank you!

**Imaging Platform and alumni:**
Mark Bray
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Kate Madden
Tejas Shah
Carolina Wählby

**Collaborators:**
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Neil Carragher
Paul Clemons
Emma Cooke
Christopher Denz
Piyush Gupta
Sigrun Gustafsdottir
Tom Houslay
Melissa Kemp
Angela Koehler
Mijung Kwon
Melissa Passino
Eric Lander
Aly Shamji

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