Alpha Divergence for Feature Pruning and Indexing of Large Biological Databases

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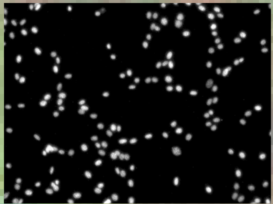
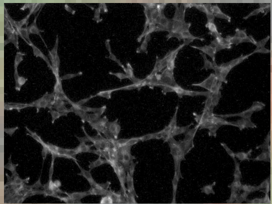
Outline

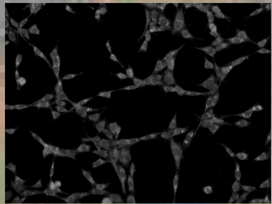
1. Indexing Application: Large-Scale Cellular Imagery Database
2. Statistical Framework: Alpha-Divergence for Indexing
3. Application Cellular Imagery
4. Summary, Open Issues

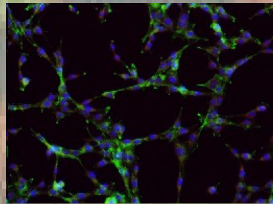
Cellular Imaging with Fluorescence Microscopy

- Can label and image several distinct cell components

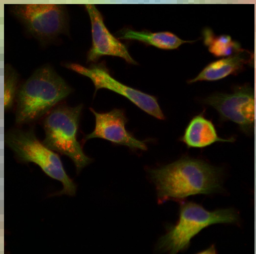

Nucleii

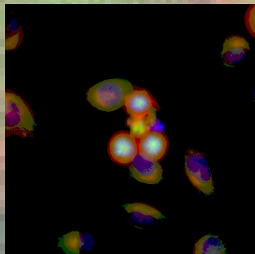

Actin


Mitochondria


Composite

- Can measure biological effect of drugs by tracking changes vs. dose


Before


After

Large-Scale Cellular Imagery Database

- Combinatorial Biology: large biological effects database

  ~ 30 cell lines (heart, liver, cervix, prostate, lung, etc.)

  ~ 30 labels/markers (nucleus, membranes, cytoskeleton)

  ~ 10000 compounds (pharmacopia)

  ~ 100 images (4 replicates $\times$ 5 doses $\times$ 5 timepoints)

  $\Rightarrow\ 10^{10}$ images (300M multi-color image sets)

- Objectives:
  - Catalog biological effects of known compounds
  - Infer properties of novel compounds by comparison to known drugs

Methodology

- Combinatorial Biology $\Rightarrow$ Imaging Experiments
- High-Throughput Cellular Imaging $\Rightarrow$ Image Responses

$$\left\{\left(X^k, Y^k\right), k = 1, \ldots, K\right\}$$

X^k are images, $Y^k \in \mathcal{Y}$ are labels assigned by experiment protocol

- Image Responses $\Rightarrow$ Response Signatures (feature vectors)

$$Z^k = Z(X^k)$$

- Response Signatures $\Rightarrow$ Biological Effects

$$Z^k = Z(X^k) \sim f(z|Y^k)$$

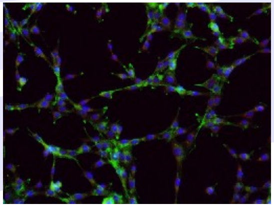
f a feature density (likelihood) conditioned on label Y^k

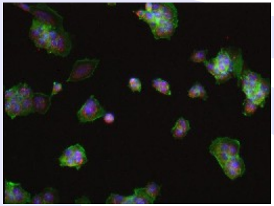
$\Rightarrow$ Biological Similarity? $X^1 \sim X^2$ if $f(z^1|Y^1) \sim f(z^2|Y^2)$

Comparison of Biological Effects

- Define a Cell Imaging Experiment
  $\mathcal{E}_k = \{\, Y^k \sim$ treatment k :
  n cell lines $\times$ m labels $\times$ p time points $\times$ q replicates $\}$
- Can we infer biological effects by comparing experiments?

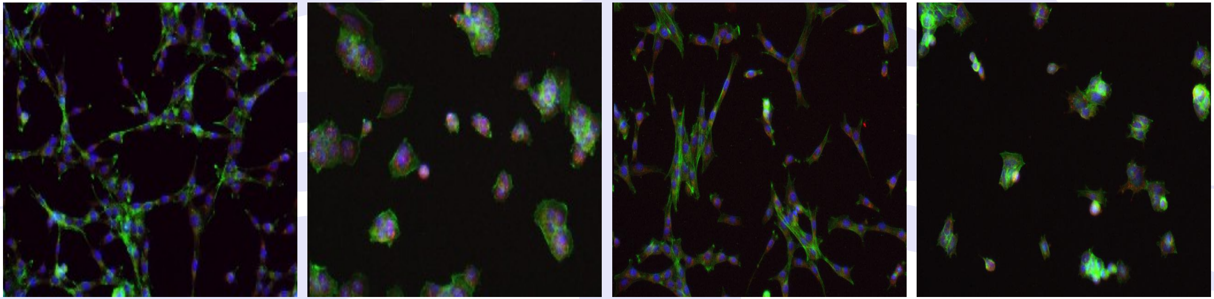
$Y^k \in \mathcal{Y} \stackrel{\text{def}}{=} \{$ Apoptosic (cell death), Normal (blank)$\}$
$\mathcal{E}_{\text{Blank}} = \{$ “Blank” : 400 imgs of untreated 3T3 cells $\}$
$\mathcal{E}_{\text{Apop}} = \{$ “Pos. Control” : 90 imgs of 3T3 w/ Paclitaxel$\}$


Blank


Pos. Control

Apoptosis Experiment

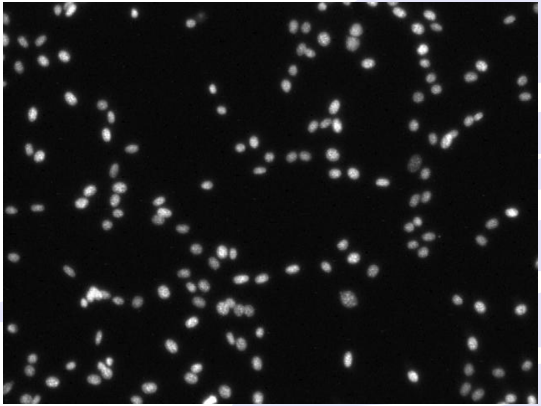
- Collected 1000 images of 10 different compounds, $\mathcal{E}_k, k = 1, \ldots, 10$
  - 3 known apoptosis inducers, 7 known non-apoptotic agents
  - Imaged 3T3 cells treated with various compound doses
- Objective: Classify compounds according to effect (apoptosis inducer?) (classify: $\mathcal{E}_k \sim \mathcal{E}_{\text{Blank}}$ or $\mathcal{E}_k \sim \mathcal{E}_{\text{Apop}}$)



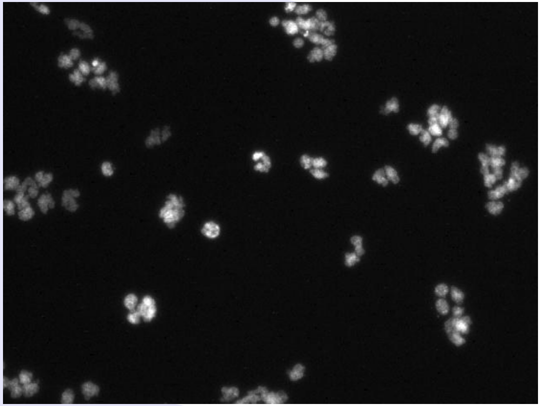
Blank | Pos. Control | Penicillin G | Vinblastine

Apoptosis Effects: Nucleus

- Nuclear Fragmentation (“blebbing”) and Condensation



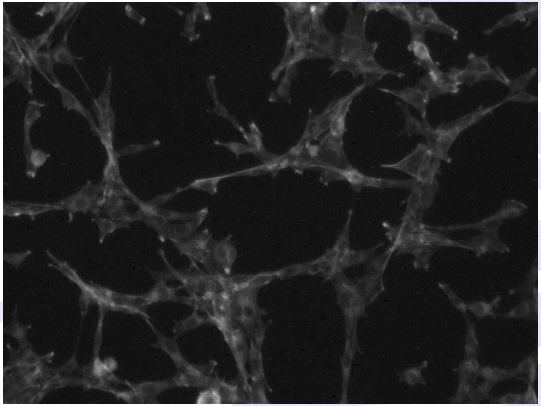
Normal



Apoptosis

Apoptosis Effects: Actin Filaments

- Actin Reorganization



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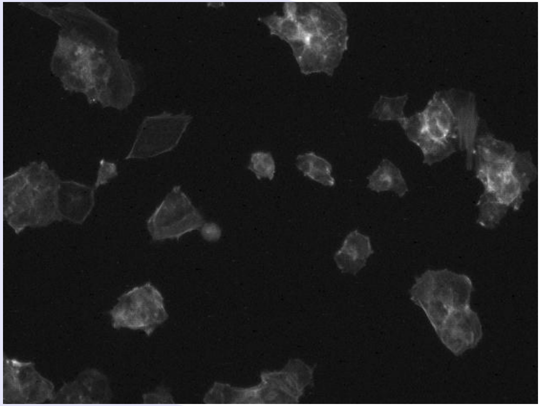
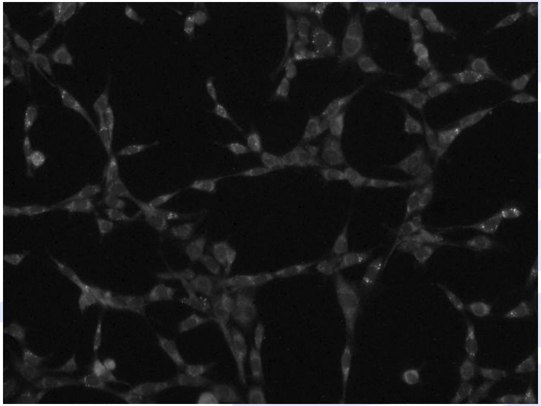


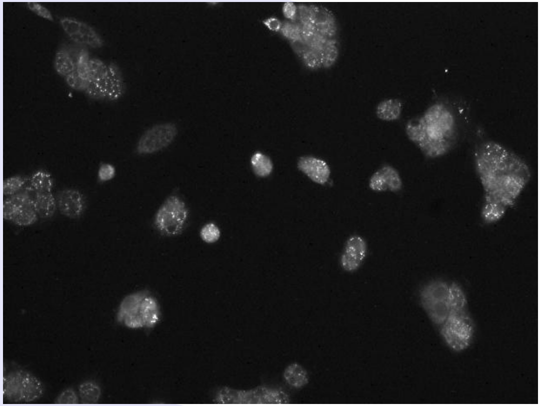
Apoptosis

Apoptosis Effects: Mitochondria

- Mitochondrial Disintegration



Normal



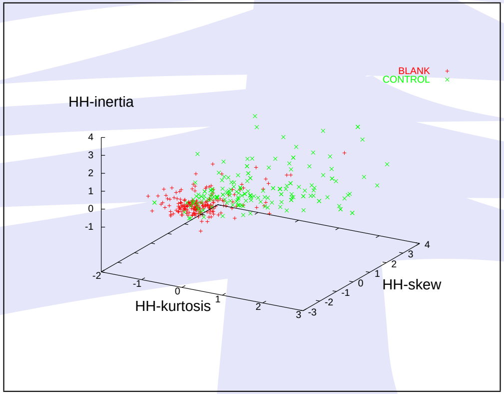
Apoptosis

Feature Extraction

- Top 12 Features:

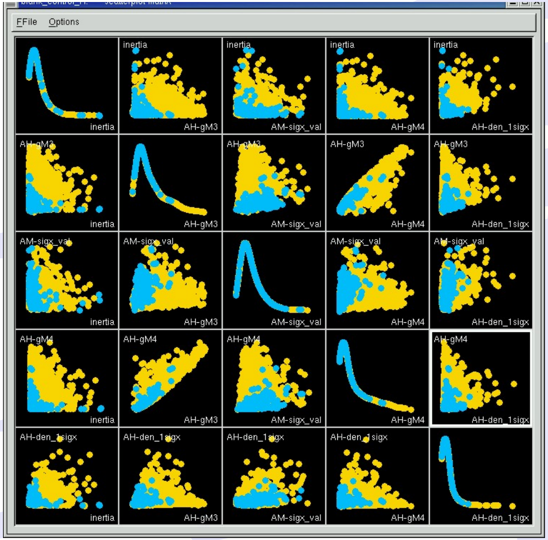
Nucleus	Actin	Mitochondria
H-Mass(Size in pix)	A-Mass(Size in pix)	HM-Coef.Var.
H-Coef.Var.	A-Rot.Inert.	M-2nd X-Mom. Inert.
H-Kurt.	AH-3rd Jt. Cumulant	M-Rot.Inert.
H-Skew	AH-4th Jt. Cumulant	
	AH-2nd Y-Mom. Inert.	

- Graylevel features from Nuclear channel:

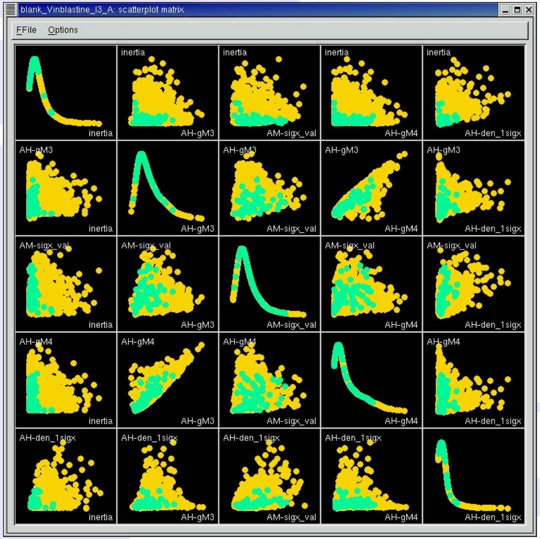


Feature Extraction

- Lattice plot of five selected features
  - Blank vs. Control and Blank vs. Vinblastine scatterplots visually similar



Blank vs. Control



Blank vs. Vinblastine

Candidate Feature Similarity Metrics

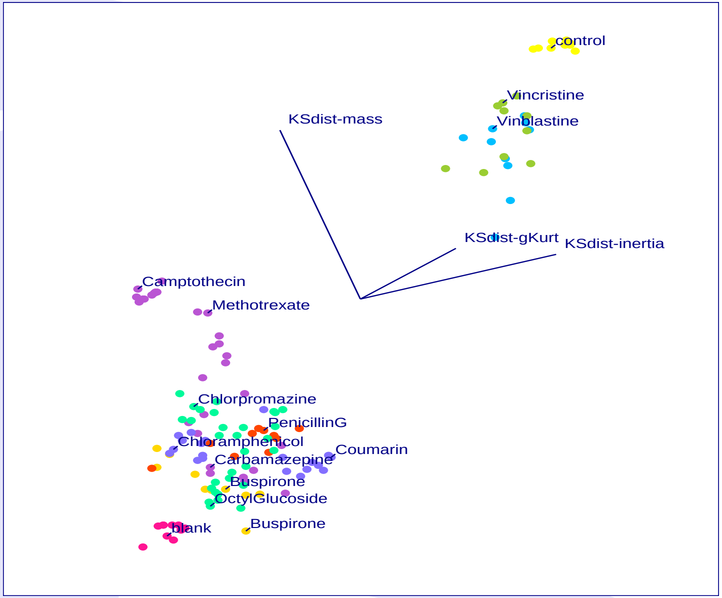
- Univariate: Kolmogorov-Smirnov Distance:
  - Product density approximation: combine several 1D feature scores
- Multivariate: Rényi α-Divergence
  - Computation via second-order approximation of densities
  - Direct computation via minimal graphs

Univariate Distance Measures

Score computed from 1D Kolmogoroff-Smirnoff distance

$$D_b(z) = D_{KS}(f_1(z) \| f_{\text{blank}}(z))$$
$$D_c(z) = D_{KS}(f_1(z) \| f_{\text{control}}(z))$$
$$D_{bc}(z) = D_{KS}(f_{\text{blank}}(z) \| f_{\text{control}}(z))$$

$$\text{Score}(z) = (D_b(z) - D_c(z))/D_{bc}(z)$$



Renyi α-Divergence

Define: $f_i = f(z|Y^i), f_0 = f(z|Y^0)$

The Rényi α-divergence of fractional order $\alpha \in [0,1]$ [Renyi:61, 70]

$$\begin{aligned} D_\alpha(f_i \| f_0) &= \frac{1}{\alpha - 1} \ln \int f_0 \left(\frac{f_i(z)}{f_0(z)} \right)^\alpha dz \\ &= \frac{1}{\alpha - 1} \ln \int f_i^\alpha(z) f_0^{1-\alpha}(z) dz \end{aligned}$$

Note: $D_\alpha(f_i \| f_0) = D_\alpha(Y^i \| Y^0)$ is indexed by Y^i and Y^0.

Renyi α-Divergence: Special Cases

α-Divergence vs. Batthacharrya-Hellinger distance

$$D_{\frac{1}{2}}(f_i \,\|\, f_0) = \ln\left(\int \sqrt{f_i(z)\, f_0(z)}\, dz\right)^2$$

$$D_{BH}(f_i \| f_0) = \int \left(\sqrt{f_i(z)} - \sqrt{f_0(z)}\right)^2 dz$$

$$= 2\left(1 - \int \sqrt{f_i f_0}\, dz\right)$$

α-Divergence vs. Kullback-Leibler divergence

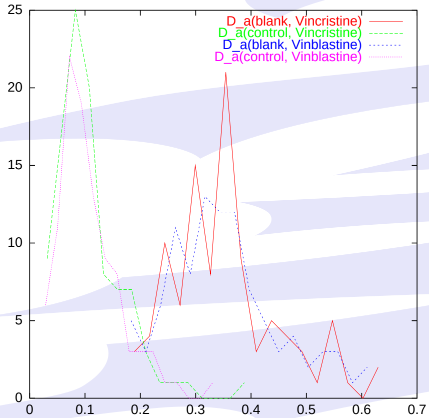
$$\lim_{\alpha \to 1} D_\alpha(f_i, f_0) = \int f_0(z) \ln \frac{f_0(z)}{f_i(z)}\, dz \tag{1}$$

Renyi α-Divergence via Approximation

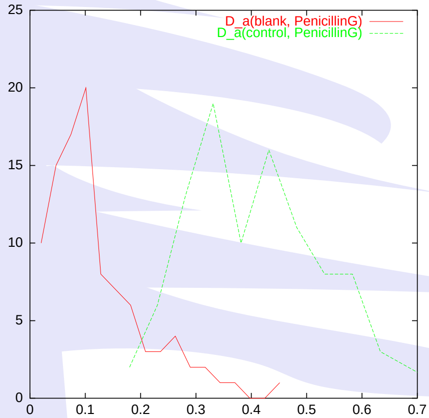
- Compute D_α using second-order approximation:

$$D^u_\alpha(f(x;\mu_1,\Lambda_1)\|f(x;\mu_0,\Lambda_0)) = \underbrace{-\frac{1}{2}\ln\frac{|\Lambda_0|^\alpha|\Lambda_1|^{1-\alpha}}{|\alpha\Lambda_0+(1-\alpha)\Lambda_1|}}_{\text{Term A}} + \underbrace{\frac{\alpha(1-\alpha)}{2}\Delta\mu^T(\alpha\Lambda_0+(1-\alpha)\Lambda_1)^{-1}\Delta\mu}_{\text{Term B}}$$

where $\Delta\mu = \mu_1 - \mu_0$.



$D_\alpha(\text{Vin}*\|\text{Blank})$ vs. $D_\alpha(\text{Vin}*\|\text{Control})$



$D_\alpha(\text{Penicillin G}\|\text{Blank})$ vs. $D_\alpha(\text{Penicillin G}\|\text{Control})$

Experiment Results

- Compounds used in Experiment

Training Data	Test Data
Negative Blank, Penicillin G	**Non-Apoptotic** Chloramphenicol, Buspirone, Sodium Azide, Carbamezapine, Octyl Glucoside, Carbon Tetrachloride
Positive Paxlitaxel (pos. control)	**Apoptotic** Methotrexate, Vincristine, Vinblastine

- Correctly classified Vincristine and Vinblastine as apoptosis inducers
- Methotrexate did not penetrate the 3T3 cells with the experiment protocol we used → did not induce apoptosis.

Summary and Ongoing Issues

- Successful Comparison of Biological Experiments
  - Similarity of cell image changes $\Leftrightarrow$ similarity of biological effect
- Rényi Divergence via 2nd Order Approximation
  - Reasonable fit for nuclear features (unimodal, symmetric)
  - Will be an issue for other feature densities (skew, multimodal)
- Open Questions:
  - What is the appropriate feature set for cellular imagery analysis?
  - Does image similarity imply biological similarity?