Learning Good Representations for Learning, Part II

Summary:

- 1. Representing images: Edges (with Ben Allen)
- 2. Representing general features: incorporating prior knowledge (Charles DeLisi, Yue Fan)

Invariance (e.g. translation-invariance) in representating images is good for many purposes, including

Image Compression: fewer numbers needed to store image

Image Classification: fewer numbers to confuse classifier (in identifying image)!

So good compression and good classification share an important common goal: fewer numbers to represent the image.

Widely studied way to store and analyze images with fewer numbers: keep only line/edge information:



Rea Gardner, New Yorker

Now-classic method (1980's): edge detection

Image:



Multiscale edges:





Multiscale edges:







Mathematically - can blur image by convolving with Gaussian:

$$f(x) \to f_{\sigma}(x) = f(x) * g_{\sigma}(x) = \int_{-\infty}^{\infty} f(x-y)g_{\sigma}(y)dy;$$

$$g_\sigma(x) = rac{1}{\sqrt{2\pi}\sigma}e^{-x^2/2\sigma^2}.$$



www.borisfx.com

Technically, find edges as zero crossings of





blurred image $f_{\sigma}(x)$



edge locations: multiscale zeroes of $\frac{d^2}{dx^2}f_{\sigma}(x)$ (various scales σ)



Upper left: original image; upper right reconstructed image (S. Mallat, 1992)

Stephane Mallat (1992) reconstructed images from edge information using (instead of Gaussian function)

 $g(x) = \operatorname{cubic} \mathsf{B}$ spline.

Marr conjecture: an image is uniquely determined by its Gaussian multiscale edges.

1 dimensional version: slices of images (like functions above) are uniquely determined from their edge information.

Some significant work:

- Logan (1977) (band-limited images f(x))
- Curtis, Shitz, Oppenheim (1987) (band-limited signals f(x))
- Yuille, Poggio (1987); polynomial signals f(x) in multiple dimensions; less edge information needed
- Hummel, Monoit (1989) (knowledge of gradient of f(x))
- Meyer (1994) (counterexample -false if infinite extent)



A 1-D image intensity map and its Gaussian edges (of blurred function); scale = blurring level

Theorem: Assume a signal f(x) representing the intensity (brightness) of an image at point x. Assume we know only the edges of f(x) for a fixed infinite sequence of blurring scales σ₁, σ₂,... (not converging to 0). Then this sequence of zeroes
(a) uniquely determines f(x) if it decays exponentially at infinity, i.e., if |f(x)| ≤ Ce^{-k|x|}.
(b) does not uniquely determine f(x) generally if it

decays at most algebraically, i.e., $|f(x)| \ge C|x|^{-l}$ for some l > 0.

(c) However, if the scale sequence $\sigma_i \rightarrow 0$

(i.e., $f_{\sigma_i} \rightarrow f$!), the zeroes generally do not determine the image f(x) uniquely for any decay rate of f. Conclusion: knowing edges of a blurred image f(x) for a any sequence of blurring levels determines f(x) uniquely, unless the blurrings $\sigma_1, \sigma_2, \ldots$ approach 0 (i.e. almost no blurring at all).

Conclusion: An image is determined by its (multiscale) edges if the image intensity f(x) decays exponentially (e.g. is bounded in extent!).

Conclusion: There are images which decay algebraically arbitrarily fast (i.e., like $|f(x)| \le C|x|^{-l}$ for any l > 0) but which are not determined by their edges.

Extends Meyer result showing that non-decaying (infinite extent) functions are not determined by their edges.

Proof of Theorem: For our one dimensional case write

$$f(x) = \sum_{k=1}^{\infty} a_k \delta^{(k)}(x),$$

where $\delta(x)$ is the delta function:



http://en.citizendium.org/wiki/Dirac_delta_function

$$\delta(x) = \lim_{\sigma o 0} g_\sigma(x) = \lim_{\sigma o 0} rac{1}{(2\pi)^{1/2}\sigma} e^{-x^2/(2\sigma)}$$

Idea: First term $a_0\delta(x)$ of series represents 'monopole moment' of f, i.e., for large blurring σ , to first order

$$a_0\delta(x)*g_\sigma(x) \approx f(x)*g_\sigma(x),$$

i.e., for very large blurrings σ , this approximates the Gaussian function $f_{\sigma}(x) = f(x) * g_{\sigma}(x)$ which looks like



Second (first derivative) term $a_1\delta^{(1)}(x)$ of series gives next order of approximation - $a_1\delta^{(1)}(x)*g_{\sigma}(x)$ includes 'dipole moment' term to the blurred $f_{\sigma}(x)$, asymptotically of the form (derivative of Gaussian)







If $\sigma \to \infty$,

- Each term $a_k \delta^{(k)} * g_\sigma(x)$ in series for f_σ has a different rate of decay
- Each *a_k* in turn corresponds to one term in an asymptotic series giving rate of convergence of the edges of *f_σ*) toward an asymptote as *σ_k* → ∞.
- This convergence rate of the zeroes determines a_k and thus f(x) through solution of the moment problem.

Caveat: the edges of the 'sharp' blurrings $f_{\sigma}(x)$ as $\sigma \rightarrow 0$ are *not* sufficient to determine *f*; an infinite set of blurrings σ_i away from 0 is needed!

Learning Good Representations for Classifying Cancer Subtypes

(with C. DeLisi, Y. Fan, S. Kim, R. Raphael)

Below:

- I. Machine learning approaches
- II. Applications to Cancer

1. Machine learning methods in computational biology

Example: microarray-based inference

A microarray produces approximately 20k biomarkers describing a tissue sample:





Result: for each subject tissue sample *s*, obtain feature vector

$$\Phi(s) = \mathbf{X} = (x_1, \dots, x_{20,000})$$

= vector of gene expression levels

Machine learning methods If this is an ovarian cancer tissue sample:

Questions:

- (a) What type of cancer is it?
- (b) What is prognosis if untreated?
- (c) What will be the reaction to standard chemotherapies?

Goals:

- 1. Differentiate two different but similar cancers.
- 2. Determine the future course of the cancer
- 3. Determine what chemical agents the cancer will respond to
- 4. Understand genetic origins and pathways of cancer

Machine learning methods Basic difficulties: few samples (e.g., 30-200); high dimension (e.g., 5,000 - 100,000).

Curse of dimensionality - too few samples and too many parameters (dimensions) to fit them.

2. SVM as a tool

Method: Support vector machine (SVM)

Procedure: look at feature space F in which $\Phi(s)$ lives, and differentiate examples of one and the other cancer with a hyperplane:

SVM as a tool



Train machine: take n = 50 subjects with different responses to a particular therapy T, and locate their feature vectors in the space F, labeling them red (unresponsive) or green (responsive).

SVM as a tool

Find separating hyperplane, and use this plane to separate feature vectors of future subjects into 'responsive' and 'unresponsive'.

There are a number of other *machine learning methods* which are able to discriminate feature vectors $\Phi(s)$ with respect to prognosis, response to therapies, etc.

Data obtained in collaboration with TCGA (the Cancer Genome Atlas).

3. The principle: more is more

Machine learning

Past: too many variables spoil the statistics; < 50 variables was typical requirement

Present: more is better

Machine learning allows massive integration of relationship information:

Machine learning

Relationship information on a gene level:

- protein-protein interactions
- co-expression
- gene ontology relationships
- pathway correlations
- epigenetic information (methylation,

phosphorylation)

Machine learning in study of cancer allows seamless combination of many different data types.

Method: kernel matrices

Machine learning

Kernel trick: incorporate relational information into a kernel matrix: for genes g_i and g_j :

$$\mathbf{K}_{ij} = K(g_i, g_j) =$$
'closeness' of g_i and g_j

as measured by, e.g.,

- protein-protein interactions
- coexpression
- gene ontology
- pathway connections

Each type of gene relation gives a different kernel matrix.
Machine learning

To integrate information in kernel matrices $\mathbf{K}^{(1)}$, $\mathbf{K}^{(2)}, \dots, \mathbf{K}^{(n)}$, we add them:

$$\mathbf{K} = \mathbf{K}^{(1)} + \ldots + \mathbf{K}^{(n)}.$$

incorporates all of these measures into one.

No matter what the source of prior information in kernel matrix $\mathbf{K}^{(i)}$, it is automatically integrated with other sources by kernel addition.

Information types (for example, in The Cancer Genome

Machine learning

Atlas, TCGA) contain:

Gene expression (microarray)
Single nucleotide polymorphism (SNP) information
Methylation, epigenetic information
Gene copy numbers
micro-RNA (miRNA) data

Noisy Biomarkers 4. Problem: biomarkers are noisy!

Microarray for example is non-self-replicating:



Human liver vs. human liver: 3875/22,283 (17%) Human heart vs. human heart: 4026/22,283 (18%) Human liver vs. human heart: 6963/14,159 (49%) Human liver vs. human liver: 5129/14,159 (36%) Human heart vs. human heart: 1204/18,006 (6%) Human liver vs. human heart: 2595/9970 (26%) Human liver vs. human liver: 318/9778 (3%) Human heart vs. human heart: 454/9772 (5%)

Human liver vs. human heart: 8572/11,904 (72%) Human liver vs. human liver: 2811/11,904 (24%) Human heart vs. human heart: 3515/11,904 (30%)

How to clean up the noise? Use the same methods as denoising functions in Euclidean space.



Figure: smoothing of gene copy number arrays using wavelet denoising. Huang, et al. http://www.biomedcentral.com/content/pdf/1471-2164-9-S2-S17.pdf

What methods help in denoising functions on Euclidean spaces?

- 1. Local averaging (Haar wavelet denoising) above
- 2. Smoothing using convolutions $f(x) \rightarrow f * g(x)$, where $g(x) = \frac{1}{\sqrt{2\pi}} e^{-x^2/2}$ is say a Gaussian kernel.
- 3. More generally, smoothing using kernel regression:

$$f(x) \to \sum_{i} \alpha_i K(x, x_i) + b$$

4. Spectral smoothing - filtering high spectral components of a function:



http://www.scilab.org/product/man/DesignEllipticFilter.html

and many other modes.

Rapaport, Vert, et al. (2007) have used spectral methods for denoising gene expression arrays.

Euclidean denoising on gene space

5. How to transfer Euclidean space methods to gene space?

One can use similar methods for denoising gene expression arrays, and more generally machine learning (ML) feature vectors.

Gene expression arrays: Given a gene expression feature vector $\mathbf{x} = (x_1, x_2, ..., x_n)$, we can view it as a function on its indices $G = \{1, 2, ..., n\}$ or equivalently the genes $g_1, ..., g_n$.

Euclidean denoising on gene space

Purpose: if index set G has a distance measure (e.g. a metric or network structure), and thus a notion of when two points i, j in G are 'close', then we will try to use this metric structure similarly to Euclidean metric to eliminate noise.

In Euclidean space denoising of a function $f(\mathbf{x})$ is done using continuity, i.e.,

 $|f(\mathbf{x}) - f(\mathbf{y})|$ small when $d(\mathbf{x}, \mathbf{y})$ is small.

Euclidean denoising on gene space In ML denoising can be done when we expect

|f(i) - f(j)| small when d(i, j) is small,

where d is a distance measure on indices i, j (e.g. genes)

Genes in a network: if index *i* represents gene g_i and *j* represents gene g_j , and if nodes g_i and g_j are close in the gene network, we believe their expressions x_i and x_j should be close to each other.

Euclidean denoising on gene space Note this is an unsupervised method which can regularize feature vectors for any classifier (e.g., SVM, random forest, k-nearest neighbors, etc.)

Formalities

6. More formally:

Given distance structure (e.g., metric or network) on the index set *G* (e.g. genes) of a basis for a feature space *F*, so that $\mathbf{x} \in F$ is

$$\mathbf{X} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{bmatrix}$$

with index $G = \{1, 2, ..., n\}.$

Formalities

View features $x_i = f(i) = f(g_i)$ as a function on the indices *i*.

Model features (e.g. gene expressions)

$$x_i = f(g_i) = f_1(g_i) + \epsilon(g_i),$$

where ϵ_i represents noise, and $f_1(g_i)$ is the 'true' expression signal.



Base space G for feature vector $\mathbf{x} = f(g)$ (gene network) Lu, et al. http://www.nature.com/msb/journal/v3/n1/full/msb4100138.html

7. Example: local averaging noise reduction

Using the protein-protein interaction (PPI) gene network as an example: consider differentiation of metastatic and non-metastatic breast cancer (Wang; van de Vijver).

Wang data set:

93 metastatic 183 non-metastatic

van de Vijver data set:

79 metastatic 216 non-metastatic

How to predict metastasis?

Strategy - regularize the feature vectors before the classification begins.

Regularizer for feature vectors: clustering using PPI network and then averaging over clusters

Classifier: SVM

Results:

Area under ROC curve improved by 5% to 20%

No. Clusters	Wang			van de Vijver			
	AUROC	AUPRC	ACC90	AUROC	AUPRC	ACC90	
64	0.658	0.450	0.470	0.687	0.371	0.472	
	(0.014)	(0.019)	(0.027)	(0.014)	(0.015)	(0.024)	
128	0.680	0.462	0.477	0.705	0.399	0.520	
	(0.015)	(0.021)	(0.023)	(0.013)	(0.019)	(0.023)	
256	0.692	0.475	0.526	0.689	0.398	0.490	
	(0.019)	(0.026)	(0.029)	(0.016)	(0.022)	(0.030)	
512	0.684	0.487	0.502	0.686	0.375	0.489	
	(0.019)	(0.031)	(0.029)	(0.021)	(0.023)	(0.038)	
1024	0.708	0.500	0.527	0.712	0.403	0.520	
	(0.019)	(0.032)	(0.029)	(0.019)	(0.026)	(0.026)	
2048	0.730	0.522	0.567	0.500	0.270	0.311	
	(0.017)	(0.029)	(0.024)	(0.038)	(0.026)	(0.026)	
RAW	0.534	0.362	0.430	0.660	0.346	0.535	
	(0.044)	(0.032)	(0.035)	(0.027)	(0.028)	(0.020)	

Performance of local averaging of microarray data locally averaged in PPI network

8. Performance using support vector regression:

In Euclidean space: replace noisy gene expression function by a regularized one based on support vector regression (here x = g represents a variable gene in base space gene network)

$$f(x) \rightarrow f(x) = \sum_{i=1}^{n} \alpha_i K(x, x_i) + b$$

for selected points (centers) $\{x_i\}_i$, where K(x, y) is a kernel which gives a metric between genes x and y.

Example: Local averaging Example: in our gene space kernel

K(x,y) = graph diffusion kernel

(heat kernel on gene network graph).

Regularized function f(x) = f(g) is optimizer of objective fn.

$$f = \underset{f(g)}{\operatorname{argmin}} \sum_{j} L(f(g_j), z_j) + \lambda \|f\|_K^2,$$

where $g_j = j^{th}$ gene f(g) = f(x) = fn. on genes (regularized expressions), $z_j = \text{ original measured expression on gene } j$ $L(f(g_j), z_j) = (|f(g_j) - z_j| - \epsilon)^+$ = loss function (difference between measured and regularized gene expression) $\lambda = \text{regularization parameter}$

Example: Local averaging $||f||_K =$ norm of f with respect to kernel K

Regularization done within clusters of genes, grouped by similar expressions in the training set

No. Clusters	Wang			van de Vijver			
	AUROC	AUPRC	ACC90	AUROC	AUPRC	ACC90	
1	0.618	0.405	0.456				
	(0.013)	(0.014)	(0.024)				
64	0.672	0.503	0.476	0.706	0.441	0.468	
	(0.018)	(0.025)	(0.033)	(0.017)	(0.025)	(0.032)	
128	0.698	0.519	0.52	0.738	0.456	0.527	
	(0.018)	(0.026)	(0.032)	(0.017)	(0.024)	(0.035)	
256	0.716	0.526	0.565	0.741	0.465	0.536	
	(0.017)	(0.024)	(0.030)	(0.017)	(0.025)	(0.033)	
512	0.71	0.515	0.567	0.746	0.478	0.552	
	(0.016)	(0.023)	(0.027)	(0.015)	(0.026)	(0.030)	
1024	0.701	0.494	0.558	0.74	0.48	0.536	
	(0.015)	(0.022)	(0.027)	(0.013)	(0.025)	(0.022)	
2048	0.676	0.47	0.521	0.718	0.441	0.532	
	(0.019)	(0.026)	(0.031)	(0.015)	(0.026)	(0.018)	
RAW	(0.54)	0.364	0.434	0.661	0.351	0.535	
	(0.040)	(0.030)	(0.035)	(0.023)	(0.026)	(0.020)	

Support vector regression performance (expression clustering followed by regression in each cluster)

There are other potential gene metrics based on gene networks derived gene ontology (GO), gene copy number information (in cancer), etc.

Now consider a smoothing transformation T on f(g) to smooth out noise:

Mapping $f(g) \to T(f(g))$ gives $T(f(g)) = T(f_1(g)) + T(\epsilon(g)).$

Transformation $T(f_1(g))$ will differ from the true expression $f_1(g)$, so we have introduced bias

If k regularization parameter (cluster size)

Example: Local averaging loss of signal through bias increase: (*) $f_1 - T(f_1)$ (increases with k)

However, the smoothing $T(\epsilon(g))$ of noise ϵ will quench it: averaging over k genes will reduce $\epsilon \rightarrow \frac{1}{\sqrt{k}}\epsilon$

Gain in signal through variance decrease (**) $\epsilon - \frac{1}{\sqrt{k}}\epsilon$ (decreases with k)

For some value of regularization parameter k the bias loss in (*) is balanced by the variance gain in (**).

This is the usual bias-variance dilemma - when do we quench so much noise (**) that the increase (*) in bias is overcome?

Principle: local averaging eliminates noise.

The Gaussian Copula 9. Use of the Copula

Above in a feature space F, we want to discriminate between feature vectors **x** which represent metastatic vs. non-metastatic cancers.

The Gaussian Copula Use of SVM involves finding a *discriminant function*

$$f(\mathbf{X}) = \mathbf{W} \cdot \mathbf{X} + b$$

which maps feature vector $\mathbf{x} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x \end{bmatrix}$ into

positive/negative number depending on whether cancer is metastatic/nonmetastatic.

Denote such an $f(\mathbf{x})$ to be a *discriminant*.

Consider microarray $\mathbf{x} = \mathbf{X}$ to be a random vector, randomly selected from metastatic patients.

Let
$$\mathbf{X} = \begin{bmatrix} X_1 \\ X_2 \\ \vdots \\ X_n \end{bmatrix}$$
 be a random variable representing a random metastatic microarray,

Let
$$\mathbf{X}' = \begin{bmatrix} X'_1 \\ X'_2 \\ \vdots \\ X'_n \end{bmatrix}$$

be a random variable representing a random nonmetastatic array.

For each X_i , let $F_i(x) = P(X_i \le x)$ be the *empirical* distribution function of X_i , obtained from the *non-metastatic* data set.

Let $F'_i(x)$ [NOT a derivative] represent the same for the vector **X**'. Define the vector function

$$\mathbf{F}(\mathbf{X}) = \begin{bmatrix} F_1(X_1) \\ F_2(X_2) \\ \vdots \\ F_n(X_n) \end{bmatrix}$$

which composes each random variable X_i with its own disribution function F_i .

Then it is known that the feature map **F** maps **X** into an array of standard uniform random variables.

Similarly define \mathbf{F}' so that $\mathbf{F}'(\mathbf{X}')$ has uniform components if \mathbf{X}' represents a random metastatic microarray.

The maps \mathbf{F}, \mathbf{F}' are known as *uniform copulas*.
The Gaussian CopulaLetting $\phi(x)$ be the cumulative distribution function of thestandard Gaussian, for any vector $\begin{bmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_n \end{bmatrix}$, define

$$\Psi(\mathbf{X}) = \phi^{-1}(\mathbf{F}(\mathbf{X})),$$

where ϕ acts componentwise. Similarly define

$$\Psi'(\mathbf{X}') = \phi^{-1}(\mathbf{F}'(\mathbf{X}')).$$

The feature maps Ψ, Ψ' therefore map each component of **X**, **X**', respectively into standard Gaussian distributions.

The maps Ψ, Ψ' are know as *normal copulas*.

These maps take arbitrarily distributed features into features all of which have standard normal distributions.

These can be used to find a likelihood $L(\mathbf{x})$ and $L'(\mathbf{x})$ representing the respective probabilities that a given microarray \mathbf{x} comes from

(a) the non-metastatic population of microarrays, or(b) the metastatic population of microarrays

Notes:

 Conventional linear discriminant analysis (LDA) or quadratic discriminant analysis (QDA) for binary classification often assume features have approximately multivariate normal distributions.

- **2.** Hence such methods are sub-optimal when the data in fact are not normal and may be heavy-tailed.
- **3.** This method (after application of the feature maps Ψ, Ψ') guarantees that at least the marginals of the feature vectors (e.g. $\Psi(\mathbf{x})$) are in fact normal (e.g. if \mathbf{x} is from the non-metastatic population).

The Gaussian Copula The form of the discriminant is

$$f(\mathbf{x}) = \frac{L(\mathbf{x})}{L(\mathbf{x})} =$$

$$J_1(x_1) \dots J_d(x_d) e^{\mathbf{z}^T (\Sigma^{-1} - 1)\mathbf{z} - \mathbf{z}'^T (\Sigma'^{-1} - 1)\mathbf{z}'/2} \left(\frac{\det \Sigma}{\det \Sigma'}\right)^{1/2}$$

where

 $T/(\mathbf{v})$

$$J_i(x) = rac{ ext{empirical density of } X_i ext{ at location } x}{ ext{empirical density of } X'_i ext{ at location } x}$$

= Jacobian of i^{th} coordiante of map from Ψ to Ψ' feature space.

$$\mathbf{Z}=\Psi(\mathbf{X}); \ \mathbf{Z}'=\Psi'(\mathbf{X}'),$$

and

 $\boldsymbol{\Sigma} = \text{empirical covariance matrix of } \boldsymbol{X}$

 $\Sigma' =$ empirical covariance matrix of **X**'.

Results:

The Gaussian Copula Accuracies: Normally distributed data:

		2-D					10-D					
Case	Size\ Method	Е	1	Q	s	т	Е	L	Q	s	т	
I	100	71	71	75	72	75	69	69	72	65	82	
	1000	75	75	75	75	75	79	79	81	79	82	
	10000	76	76	76	76	76	80	82	82	81	82	
п	100	76	76	77	75	79	80	82	83	81	93	
	1000	79	79	79	79	79	91	90	92	91	92	
	10000	79	80	79	80	79	92	93	93	92	93	
ш	100	83	83	85	84	85	91	91	94	90	98	
	1000	85	85	85	85	85	96	96	97	95	97	
	10000	85	85	85	85	85	97	98	98	98	98	
IV	100	89	89	90	89	91	97	96	97	96	99	
	1000	90	90	90	90	90	98	98	99	98	99	
	10000	90	90	90	90	90	99	99	100	100	100	

- E = empirical normalization method
- J = empirical normalization using underlying Jacobian
- Q = quadratic discriminant (assuming normality)
- S = SVM
- T = Optimal Bayes method based on knowledge of underlying densities

Accuracies: (Heavy-tailed) t_1 -distributed data

Case	Size\ Method	2-D					10-D				
		E	٦	Q	5	т	E	з	Q	s	т
1	100	56	59	52	53	64	58	57	52	60	71.0
	1000	61	62	50	51	64	65	60	51	59	71
	10000	63	63	50	48	64	66	59	50	66	71
п	100	74	77	54	66	80	81	80	68	83	89
	1000	77	79	51	67	80	85	84	51	87	89
	10000	79	79	50	59	80	86	84	50	89	89
ш	100	80	82	58	79	86	85	85	81	90	93
	1000	84	84	52	77	85	89	88	55	91	93
	10000	85	85	49	84	86	90	89	49	92	93
IV	100	84	86	64	83	89	88	87	88	91	94
	1000	87	88	52	82	89	91	91	62	94	94
	10000	87	87	51	87	89	92	90	50	93	95

- E = empirical normalization method
- J = empirical normalization using underlying Jacobian
- Q = quadratic discriminant (assuming normality)
- S = SVM

T = Optimal Bayes method based on knowledge of underlying densities

Accuracies: Benchmark Breast and Prostate cancer data (Prostate is cancer/no cancer only); CRF denotes Convergent Random Forest algorithm (Bienkowska)

	QDA (Q)	CRF	SVM (S)	Emp (E)
Prostate	94	95	93	94
Breast	79	84	68	89