Learning structure in gene expression data using deep architectures, with an application to gene clustering

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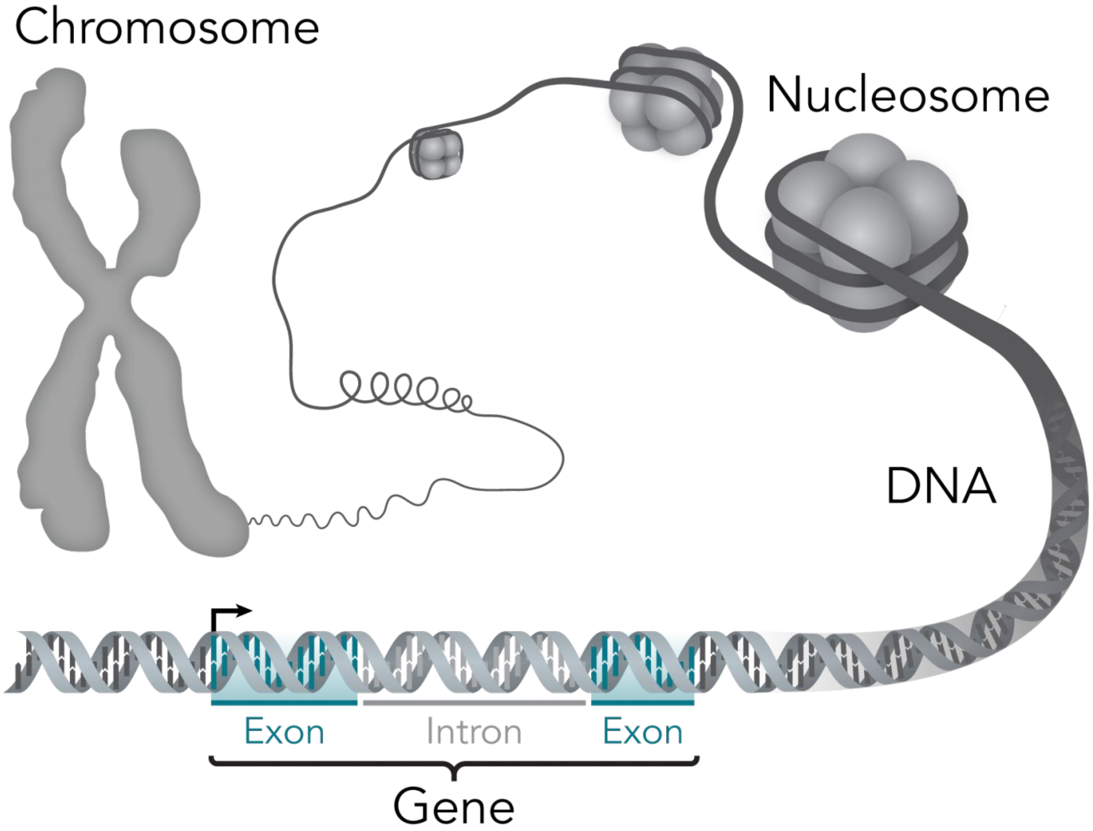
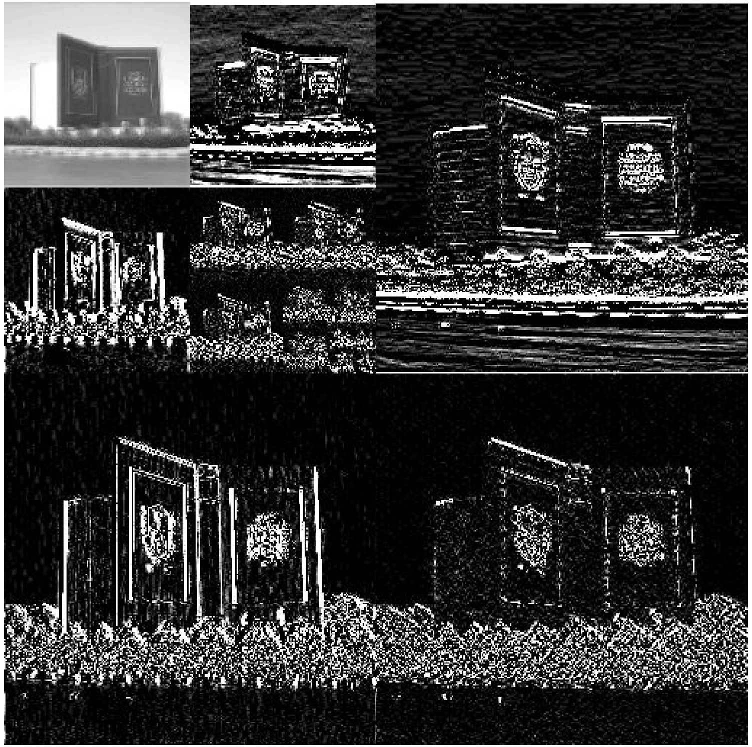
Gene Expression



Previous Work

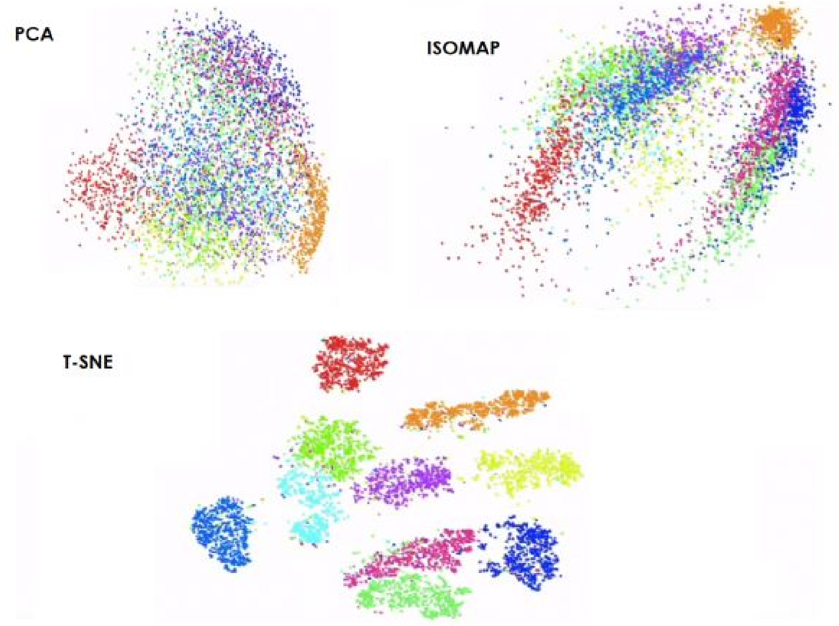


- Wavelet transformations
- Missing Value Imputation
  - Bayesian approach
  - Least Squares approach
- PCA
  - Did not improve cluster quality
- Autoencoder used to featurize breast cancer data

Motivation

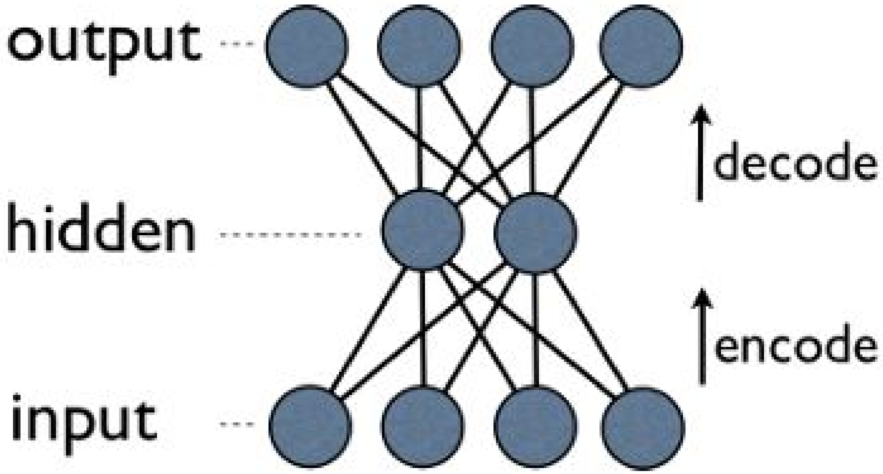
- **Objective**: Learn interesting patterns in the input distribution of gene expression profiles using deep networks with denoising autoencoders

- No microarray data denoising
- Learn and generalize
- Clustering

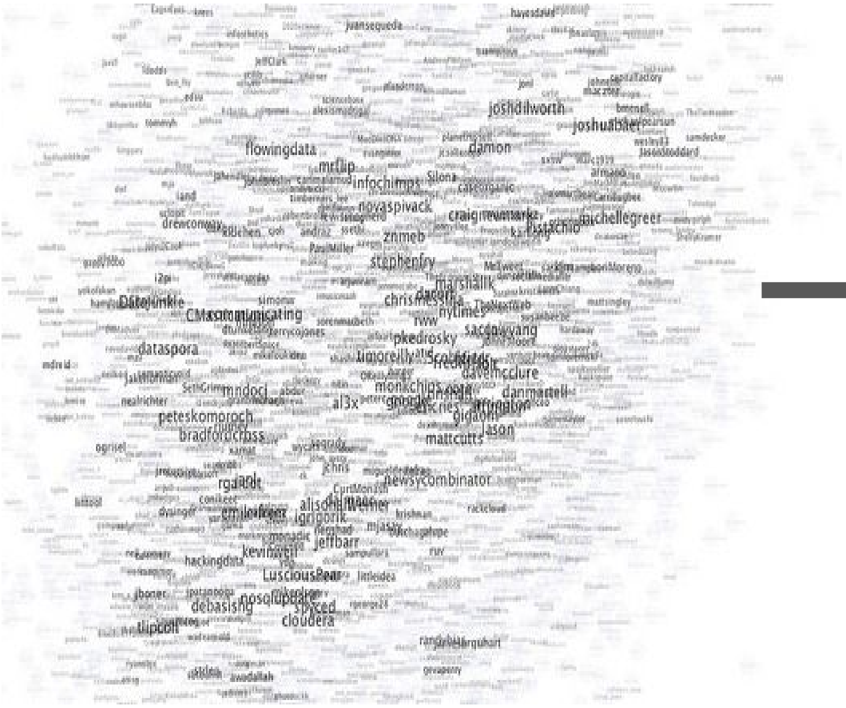


What is an Auto-encoder?

- Tries to learn $h_{W,b}(x) \simeq x$, so that the output $\hat{x}$ is close to x
- Typically, learn **lower dimension representation** of features i.e. hidden layers have lower dimension than input
- In some cases, hidden layers **can** have higher dimension, with an **additional sparse** (regularization) constraint, like KL divergence

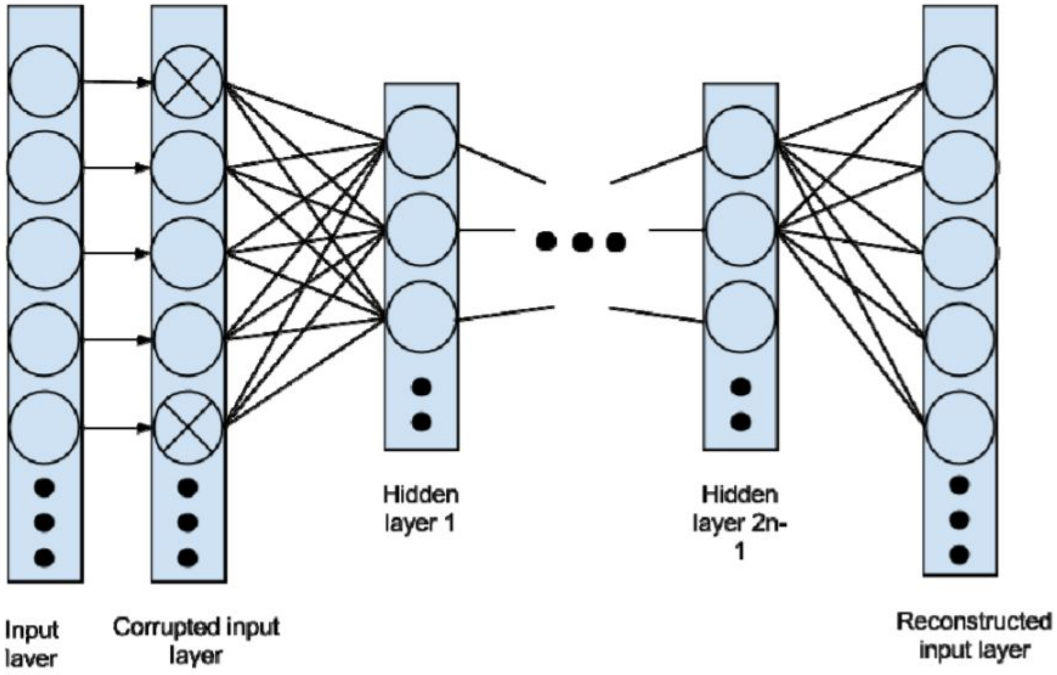


Why Autoencoders?



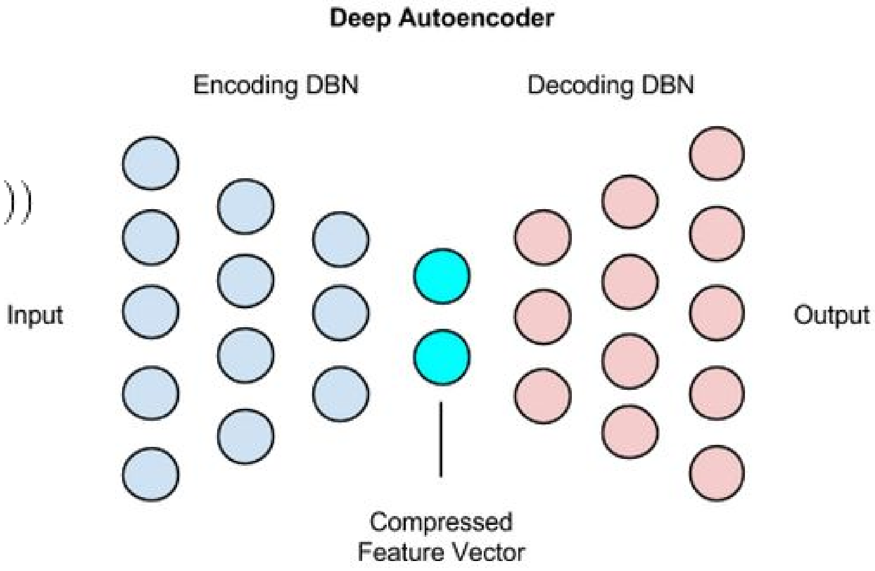
Additions to Vanilla Autoencoder

- Two additional changes are made to the vanilla autoencoders.
  - Stacking Autoencoders
  - Denoising Autoencoders



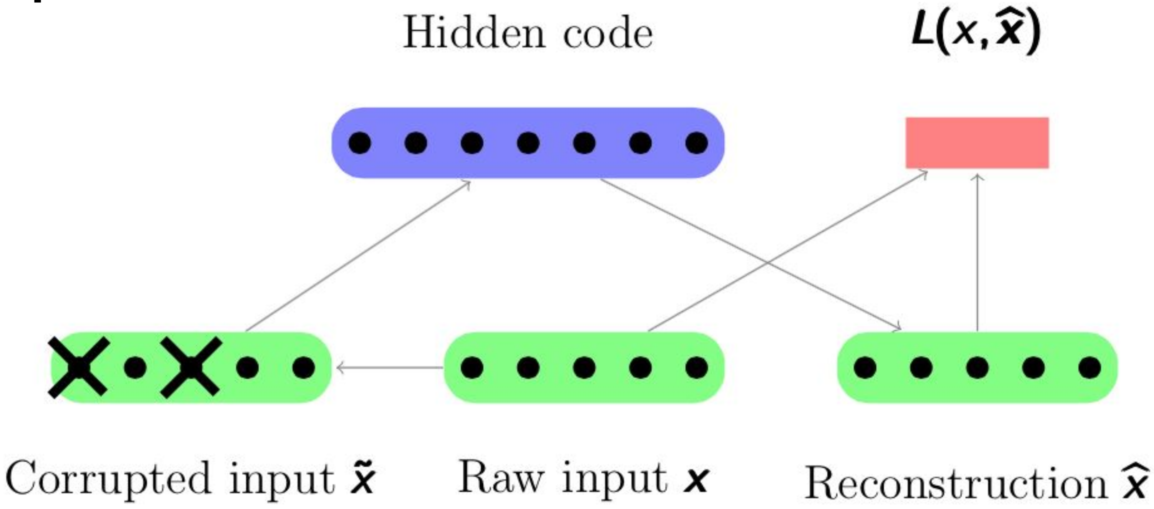
Deep Autoencoders

- Sigmoid layers present in between each layer, for non-linearities
- $\text{Transformation matrix} = f_1(W_1 * f_2(W_2 \ldots))$



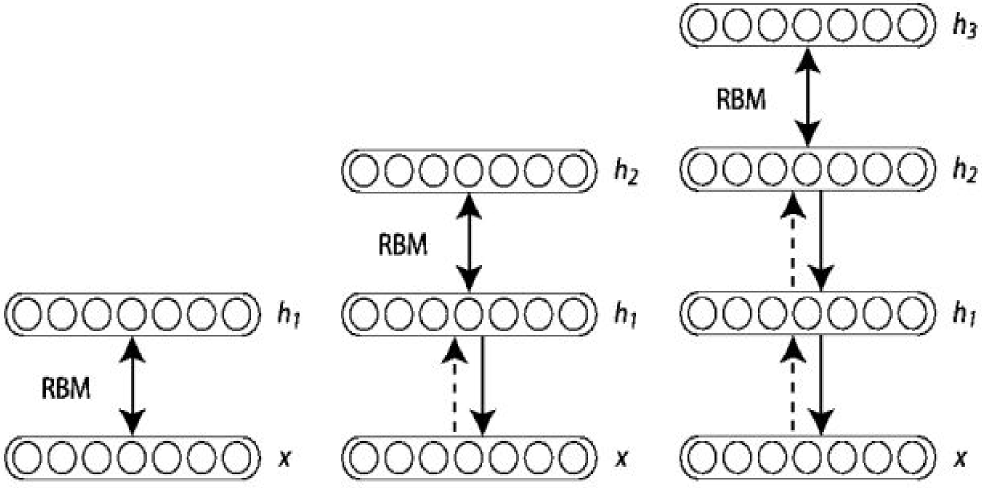
Denoising Autoencoders

- To **avoid learning an identity mapping**, two methods are usually used:
    - **Lower dimensionality** for the **hidden layer**
    - Train with **corrupt input**
- 2 Types of noise used:
    - Gaussian
    - Masking



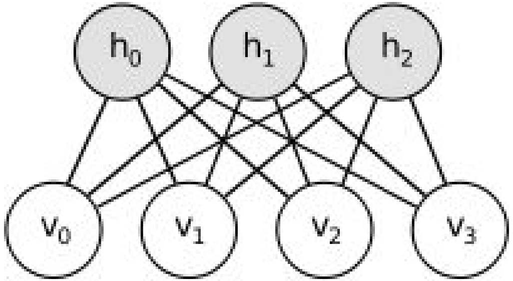
What were the improvements made?

- The authors decided to **stack multiple hidden layers** for the autoencoders
- The **training was done greedily**, training 1 layer at a time and minimizing the reconstruction error each time.
- By adding noise and stacking the layers, the encoders are able to generalize properties and learn interesting features.
- Similar to how **Deep Belief Network** is trained



Restricted Boltzmann Machine (RBM)

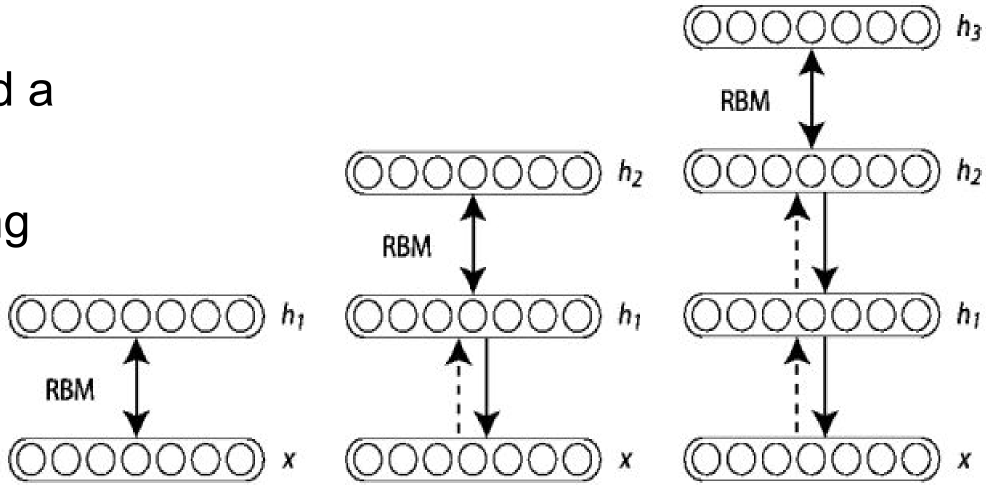
- Has a **visible layer** and a **hidden layer**, neither of which are connected to nodes from its own layer
- RBM is a **generative model**, tries to capture the probability distribution of the sample
- The **visible layer emulates the samples**
- As a result, the **hidden layer learns interesting features** of the samples
- The training is done to **minimize the "energy" equation**.



$$E = -\left(\sum_{i<j} w_{ij}\, s_i\, s_j + \sum_{i} \theta_i\, s_i\right)$$

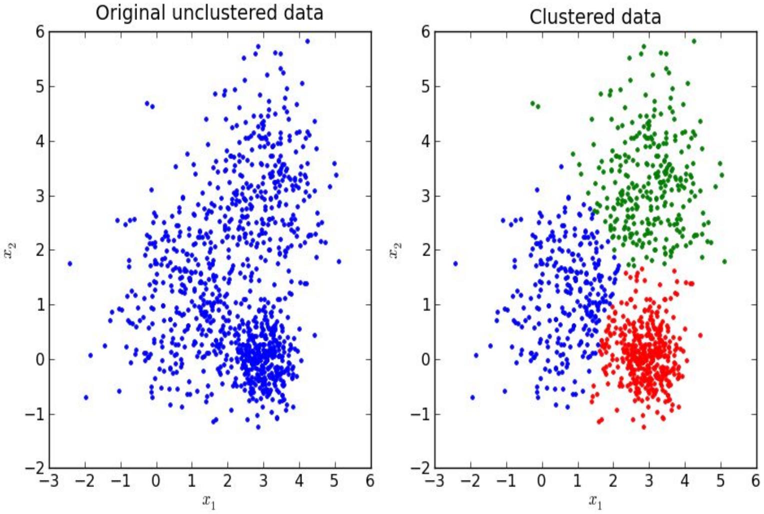
Deep Belief Network

- Another method to **preprocess the data**
- Created using stacking **multiple layers of RBM**
- Visible layers are taken as the inputs, and the Hidden layers are taken as the outputs to the next layer.
- **Training** is done layer by layer, and a global-parameter turning at the end
- Each layer of RBM learns interesting features of the first visible layer



Unsupervised Clustering: K-means

- **Cluster** the lower-dimensional points so that similar points are together. Centroids can be treated as “representative” points.
- Assign random (k < n) points as centroids. **Assign clusters based on the closest centroid** and then update centroid as mean of the vectors in that cluster.
- Helps find non-readily apparent patterns

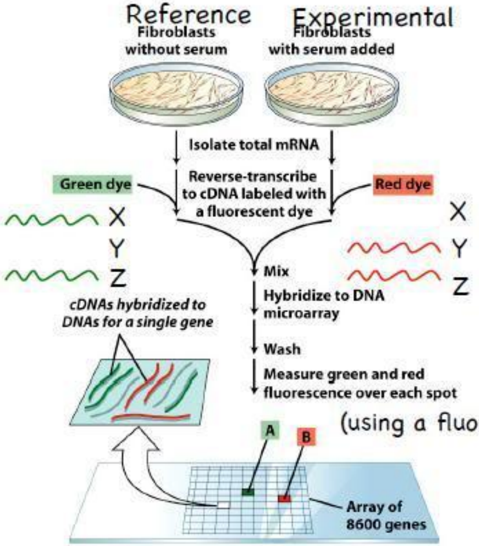


Yeast Cell Cycle Datasets

- Gupta et al. evaluated their autoencoder-based methodology on two yeast cell cycle data sets (Yeung et al. 2001)
- **Two data sets** derived from gene expression data for **6000 genes across 17 time points**; of 6000 total genes, **380 genes identifiably peak in expression** during a single phase of mitotic cell cycle
- Expression data **normalized**, with mean 0 and variance 1

DNA Microarrays

DNA microarray analysis of gene expression


Reference
Fibroblasts without serum
Experimental
Fibroblasts with serum added
Isolate total mRNA
Reverse-transcribe to cDNA labeled with a fluorescent dye
Green dye
Red dye
X
Y
Z
X
Y
Z
Mix
Hybridize to DNA microarray
Wash
Measure green and red fluorescence over each spot
cDNAs hybridized to DNAs for a single gene
A
B
Array of 8600 genes

(using a fluorescence scanner)

A If a spot is green, expression of that gene decreases in cells after serum addition

B If a spot is red, expression of that gene increases in cells after serum addition

Small region of a microarray representing expression

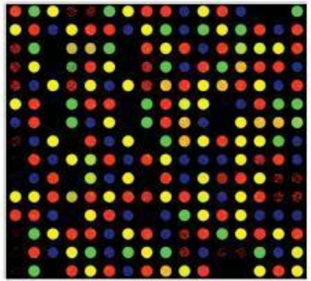


Figure 5-29b
Molecular Cell Biology, Sixth Edition
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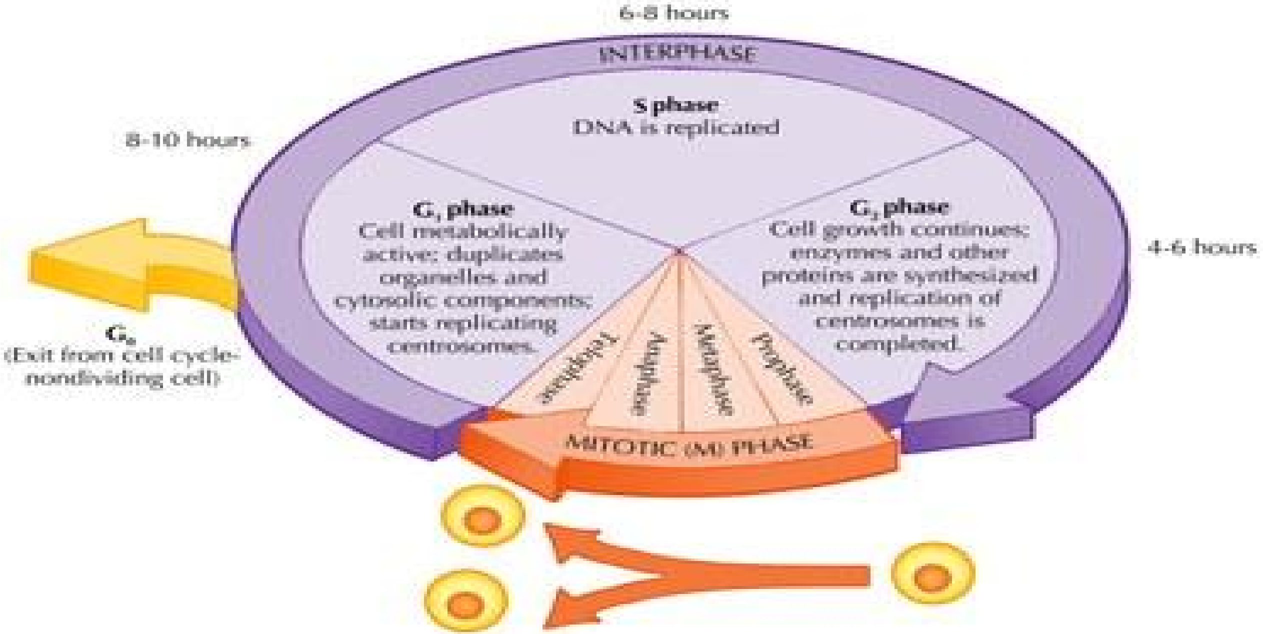
Yeast Mitotic Cell Cycle


6-8 hours
INTERPHASE
S phase
DNA is replicated
8-10 hours
G_1 phase
Cell metabolically active; duplicates organelles and cytosolic components; starts replicating centrosomes.
G_2 phase
Cell growth continues; enzymes and other proteins are synthesized and replication of centrosomes is completed.
4-6 hours
G_0
(Exit from cell cycle-nondividing cell)
Telophase
Anaphase
Metaphase
Prophase
MITOTIC (M) PHASE

Hyper-parameter Tuning

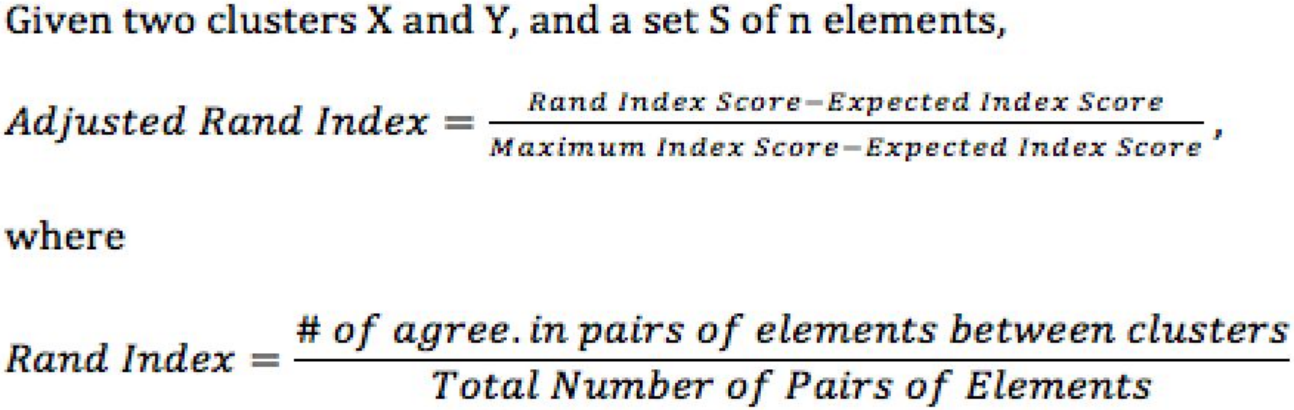
- **Hidden Layer Size** and **Corruption Level** contributed the most to the **variance** in results
- Performance of all hyper-parameter combinations considered in selection of parameter values
- Selected parameter values based on **“best results”** (validation set?)
- Number of hyper-parameters vs. dataset size

Parameters	Values Used
Batch Size	4,8,12
Number of Training Epochs	2000, 5000
Number of Hidden Nodes	Number between 4-17
Corruption Level	0, 0.05, 0.1, 0.15, 0.2
Learning Rate	0.05, 0.1

Evaluation Criteria

Adjusted Rand Index

- Quantitative measure of the **similarity in composition between two clusters**
- The “corrected-for-chance” version of the Rand Index
- Used to **assess performance of auto-encoder based clusters**, as compared to “gold-standard” cluster labels



Given two clusters X and Y, and a set S of n elements,

$$Adjusted\ Rand\ Index = \frac{Rand\ Index\ Score - Expected\ Index\ Score}{Maximum\ Index\ Score - Expected\ Index\ Score},$$

where

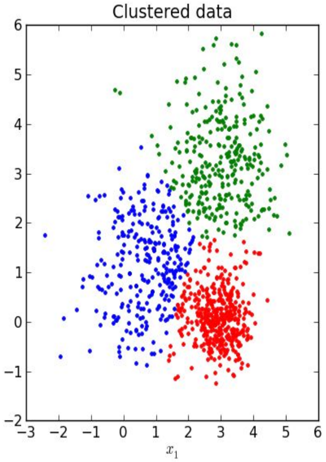
$$Rand\ Index = \frac{\#\ of\ agree.in\ pairs\ of\ elements\ between\ clusters}{Total\ Number\ of\ Pairs\ of\ Elements}$$

Clustering Algorithms and Implementation

Clustering

- K-means and spectral clustering

SciPy

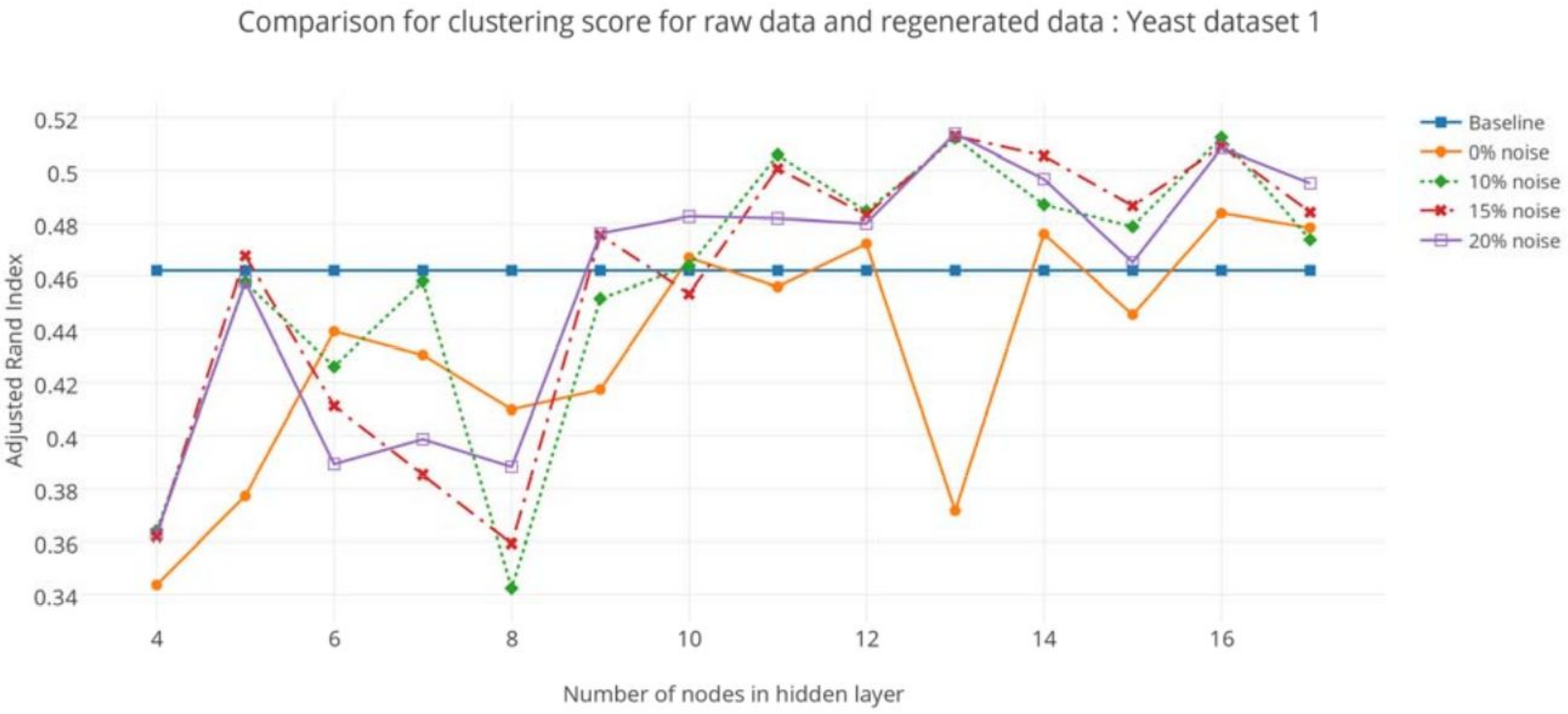


Implementation

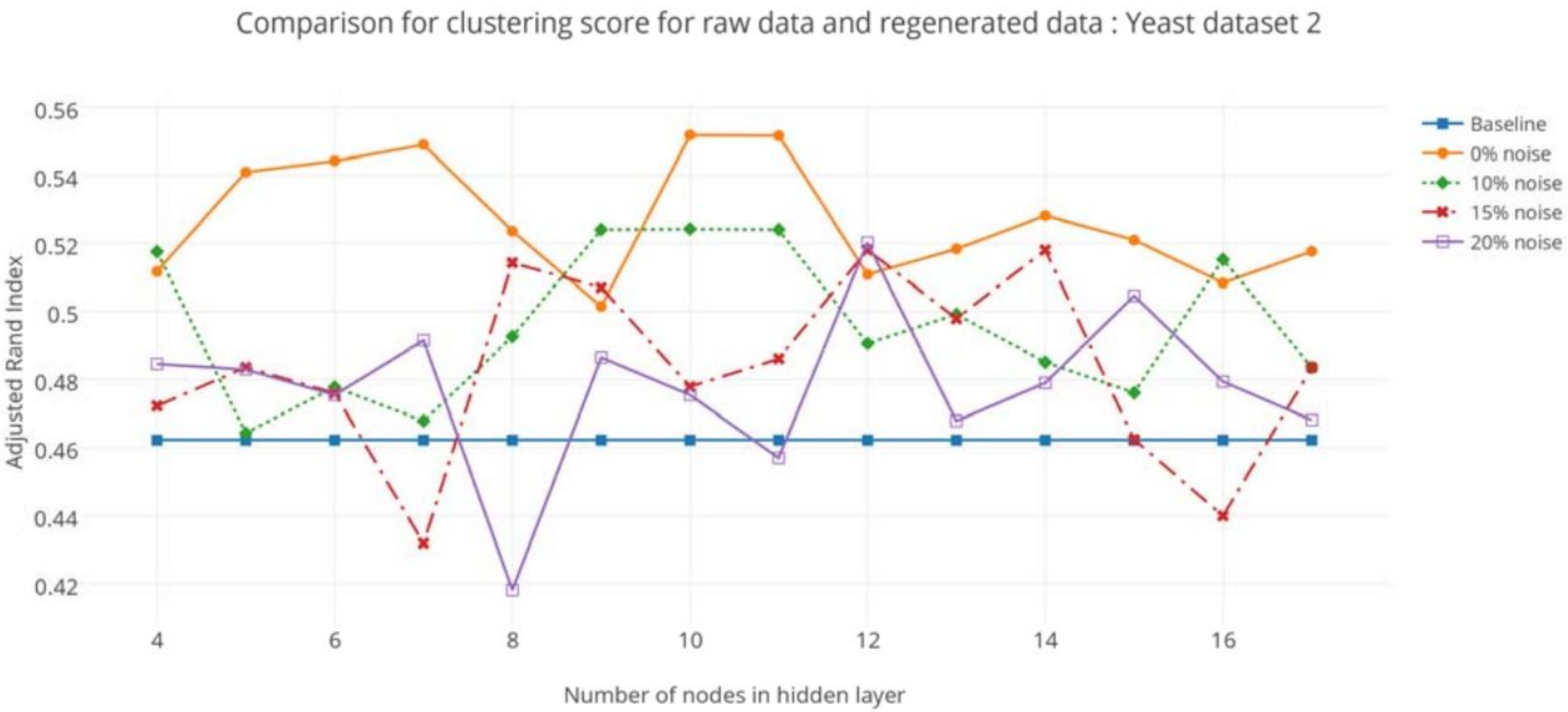
- Single hidden layer used, as opposed to three hidden layers, based largely on computation time, but also superior performance

theano

Experimental Results



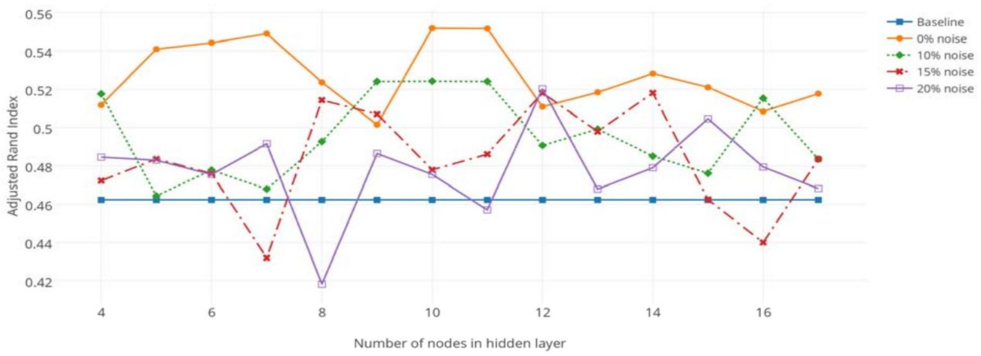
Experimental Results



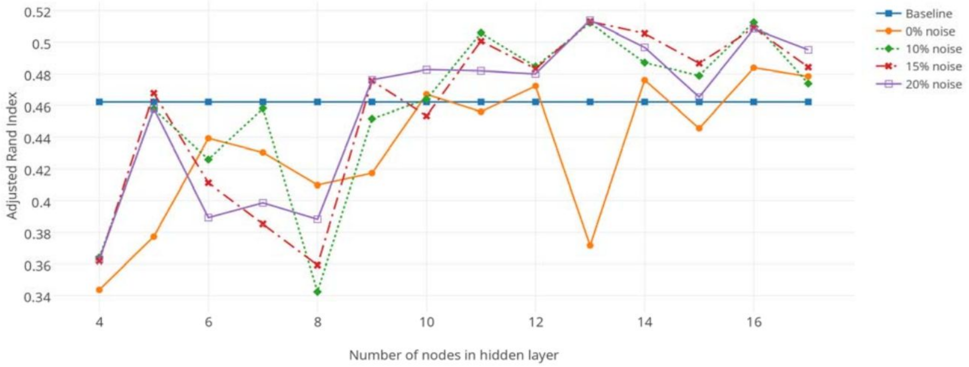
Shortcomings

- Will this generalize?
- Clustering
- Weak Evidence

Comparison for clustering score for raw data and regenerated data : Yeast dataset 2



Comparison for clustering score for raw data and regenerated data : Yeast dataset 1



Questions?