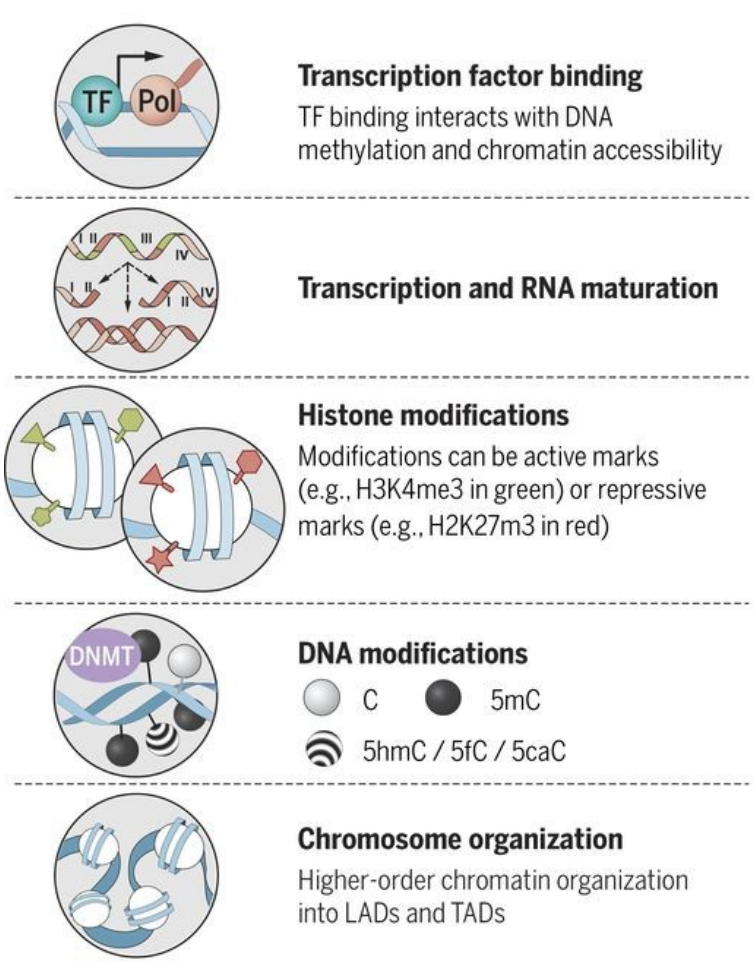
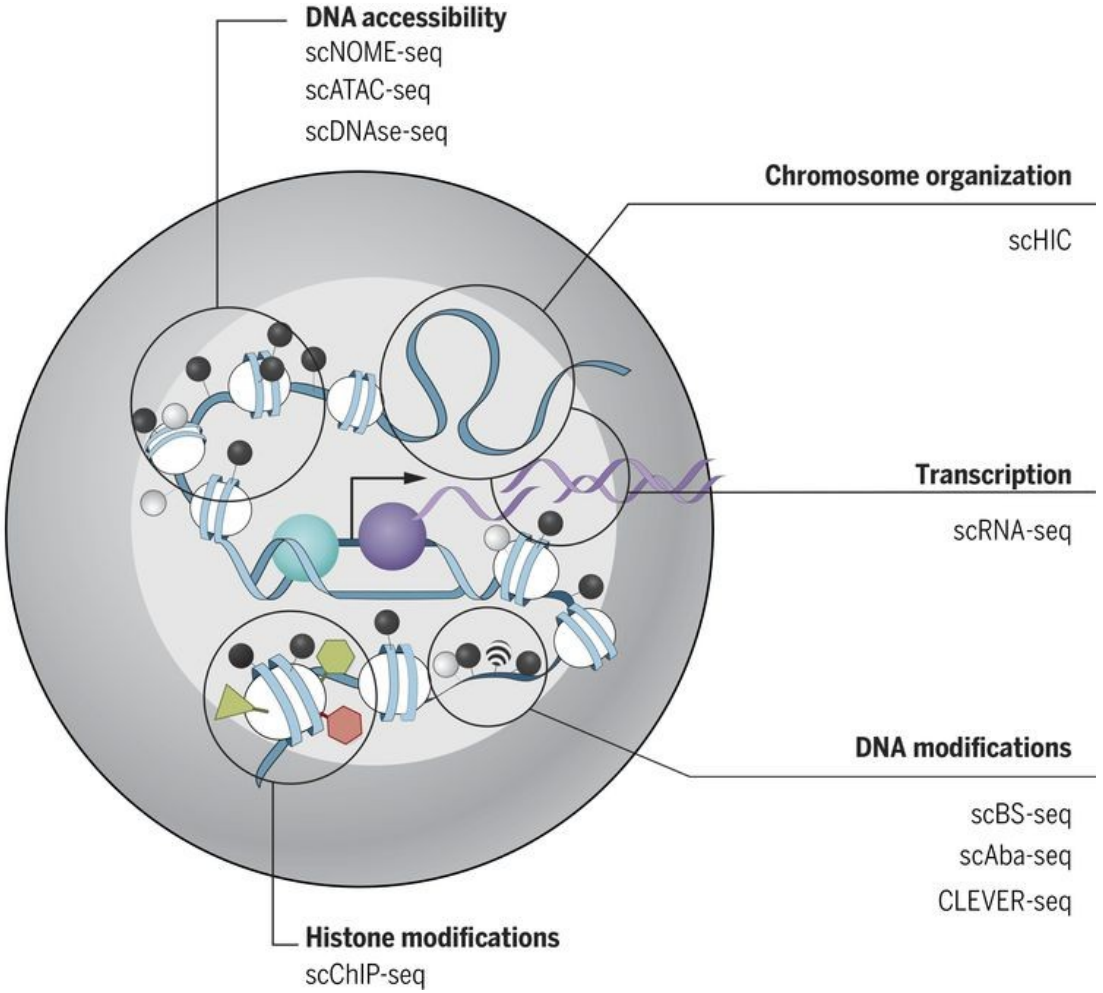
Deep Learning for Omics Integration

OMICs Integration and Systems Biology course

Nikolay Oskolkov, NBIS SciLifeLab

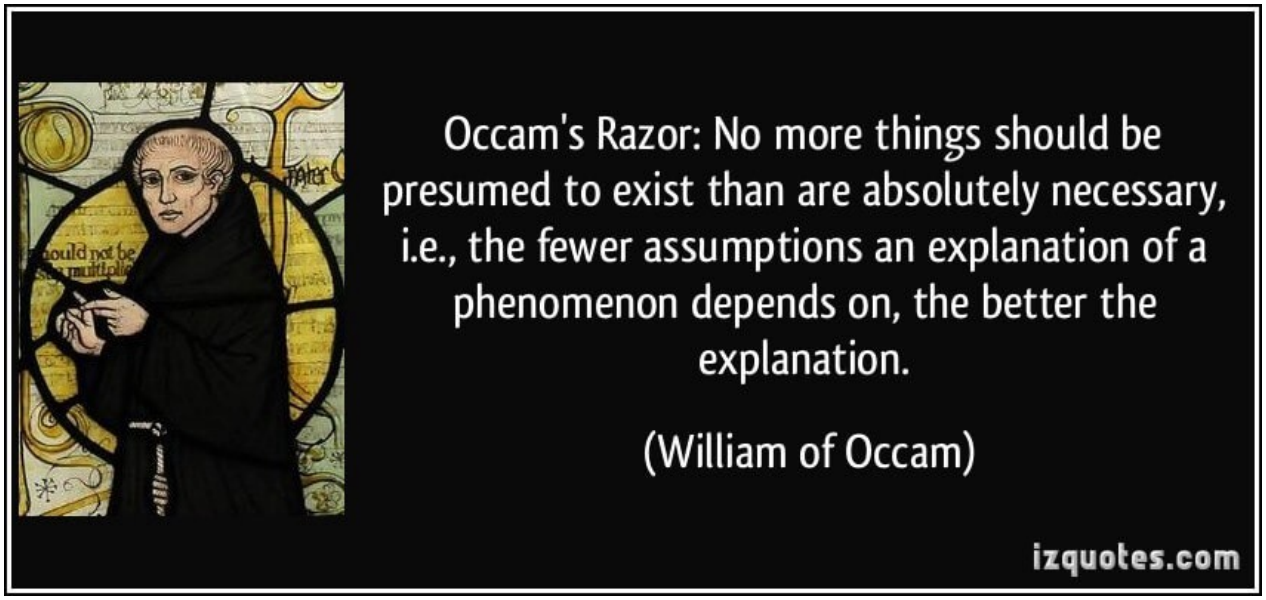
Lund, 09.02.2023





Chellenges of Applying Deep Learning

- Difficult to apply to real Life Science projects (NGS: tabular data)
- Lack of data in Life Sciences (exceptions: single cell, microscopy)
- Apply only if Deep Learning better than simpler methods



Why don’t neural networks always work?

Statistics vs. Machine Learning

You are viewing Fredrik Strand's screen View Options

Rodriguez et al compared AI with 101 radiologists – AI was as good as radiologists

JNCI JOURNAL of the NATIONAL CANCER INSTITUTE

Article Navigation

Stand-Alone Artificial Intelligence for Breast Cancer Detection in Mammography: Comparison With 101 Radiologists FREE

Alejandro Rodriguez-Ruiz, Kristina Lång, Albert Gubern-Merida, Mireille Broeders, Gisella Gennaro, Paola Clauser, Thomas H Helbich, Margarita Chevalier, Tao Tan, Thomas Mertelmeier ... Show more

Author Notes

JNCI: Journal of the National Cancer Institute, Volume 111, Issue 9, September 2019, Pages 916–922, https://doi.org/10.1093/jnci/djy222

Published: 05 March 2019 **Article history**

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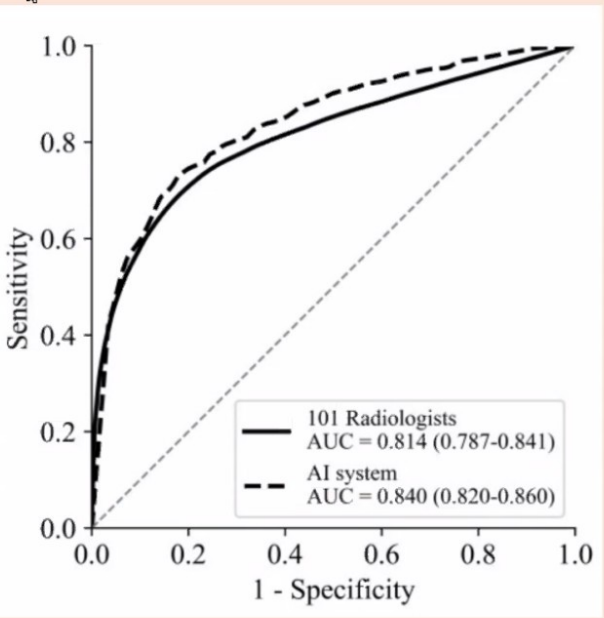


Nikolay Oskolkov

Kristin Scott

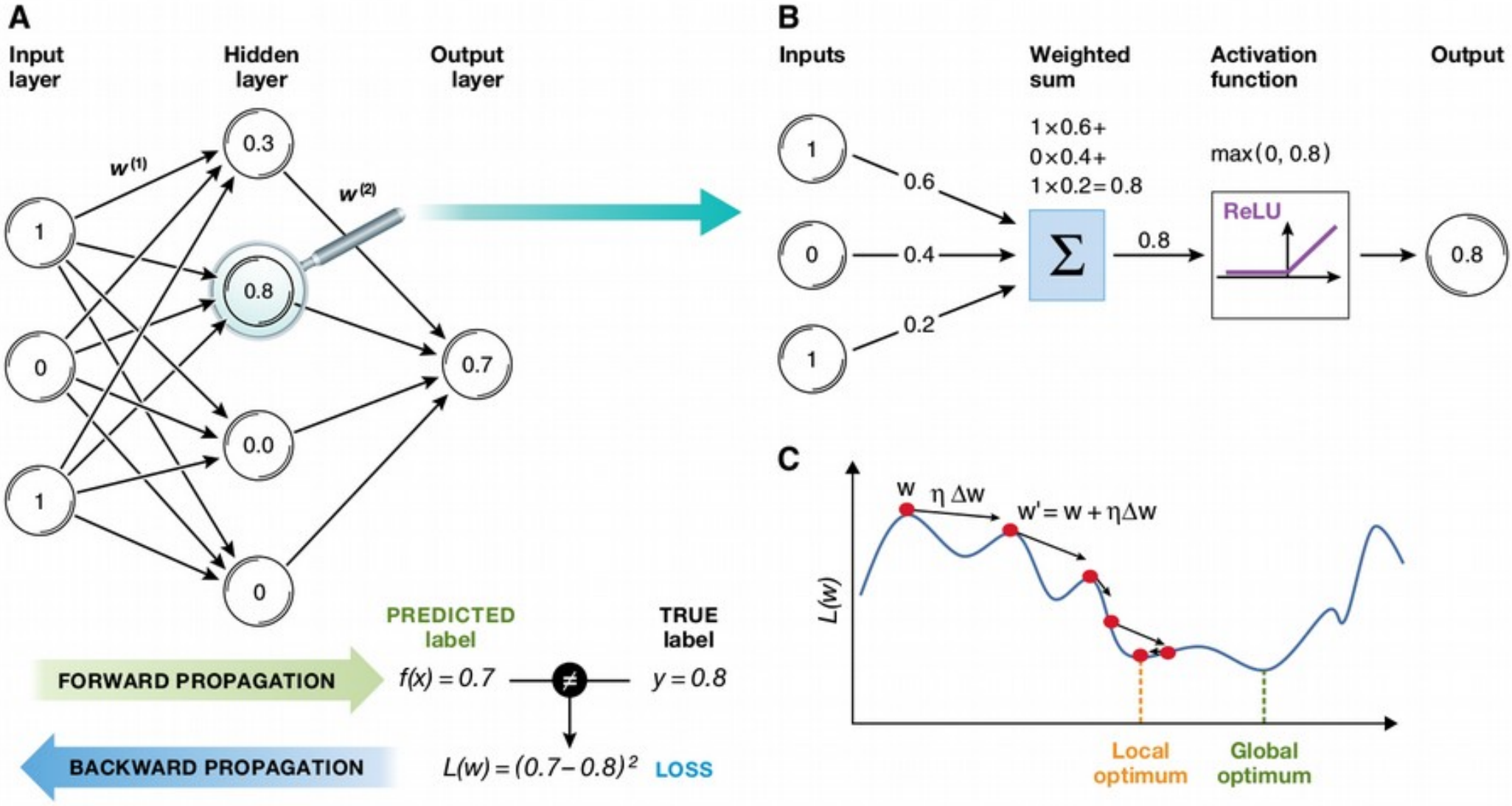
Einar Heiberg

Amanda Spet...

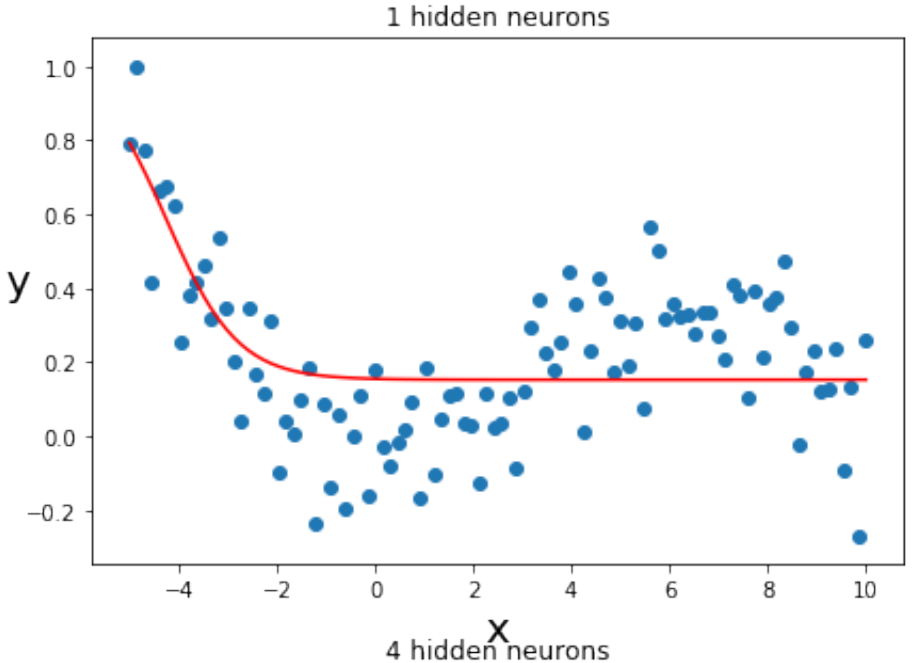
Unmute Stop Video Participants 71 Chat Share Screen Record Leave

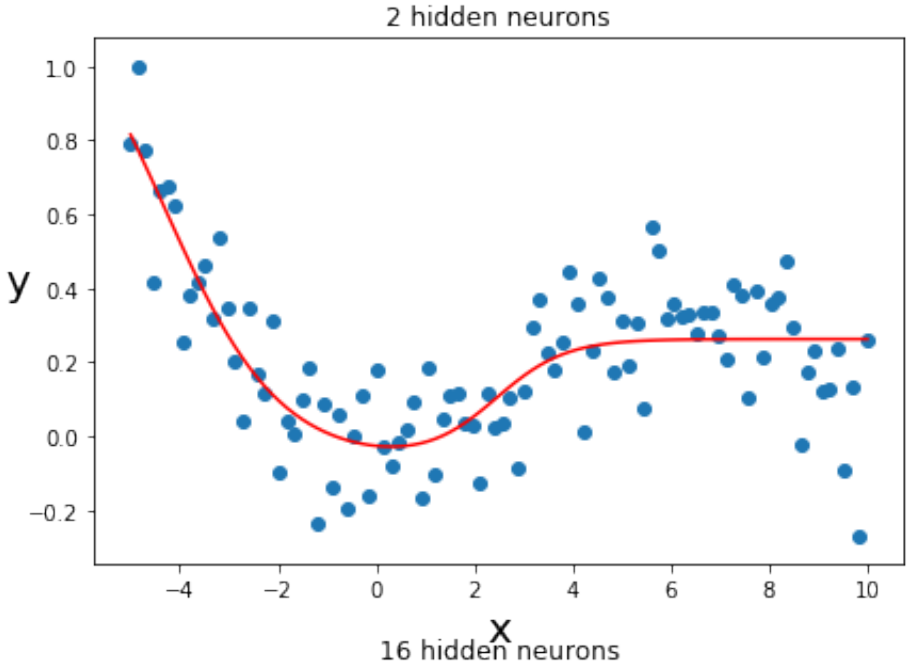
Why do you compare AI against radiologists?
You should compare it against simpler models

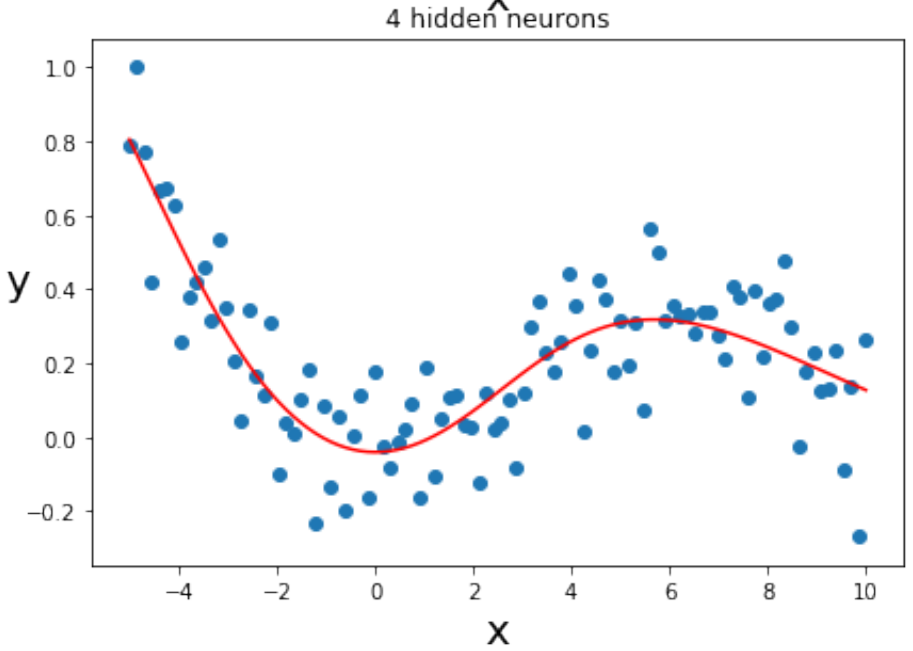
Artificial Neural Networks (ANN)

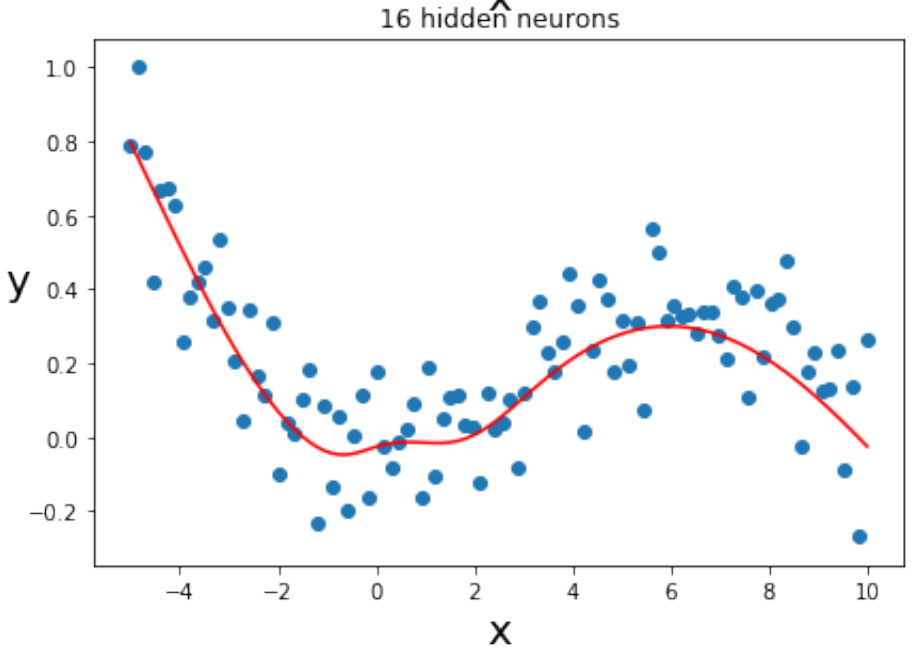


ANN: Universal Approximation Theorem

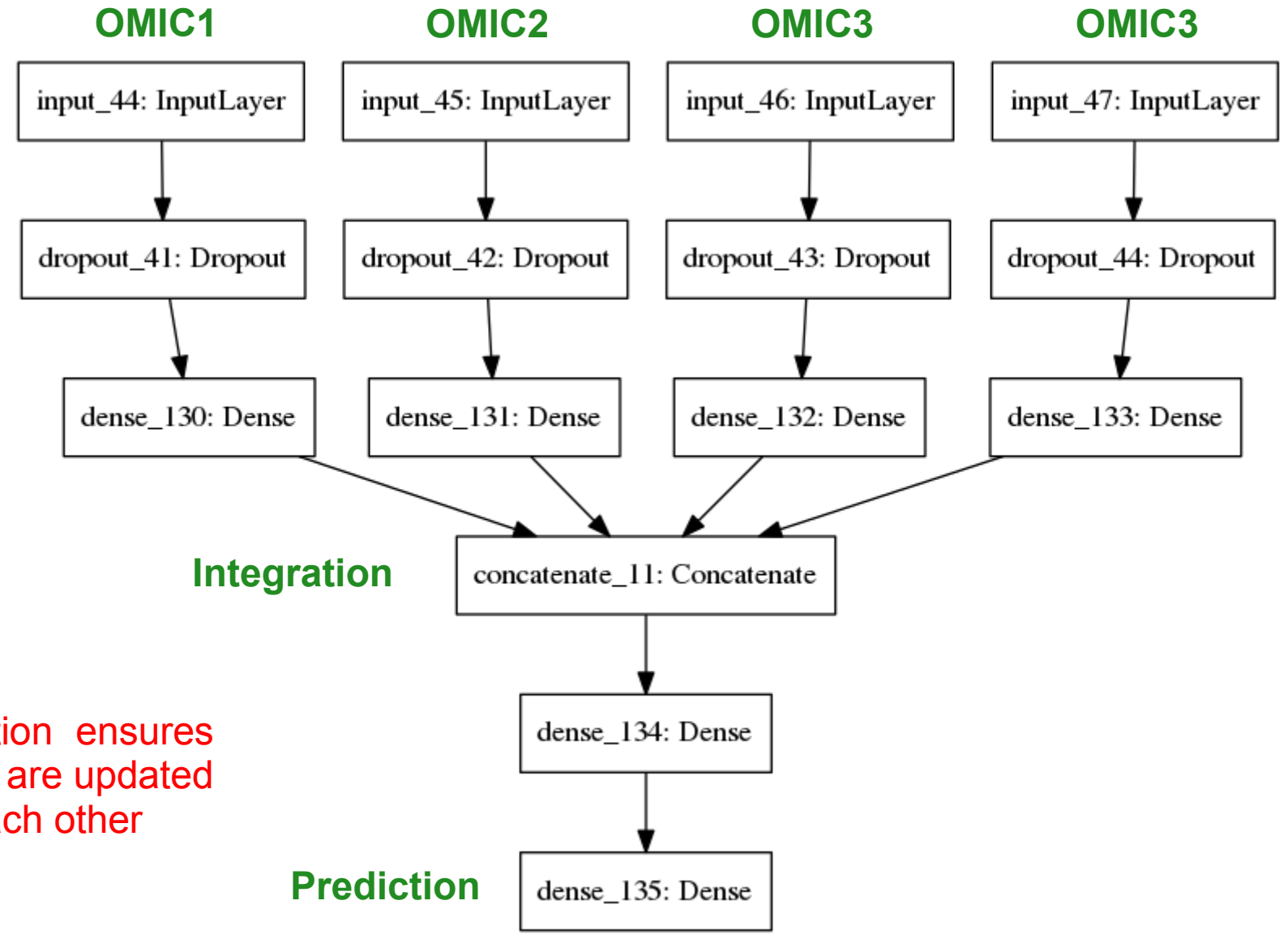






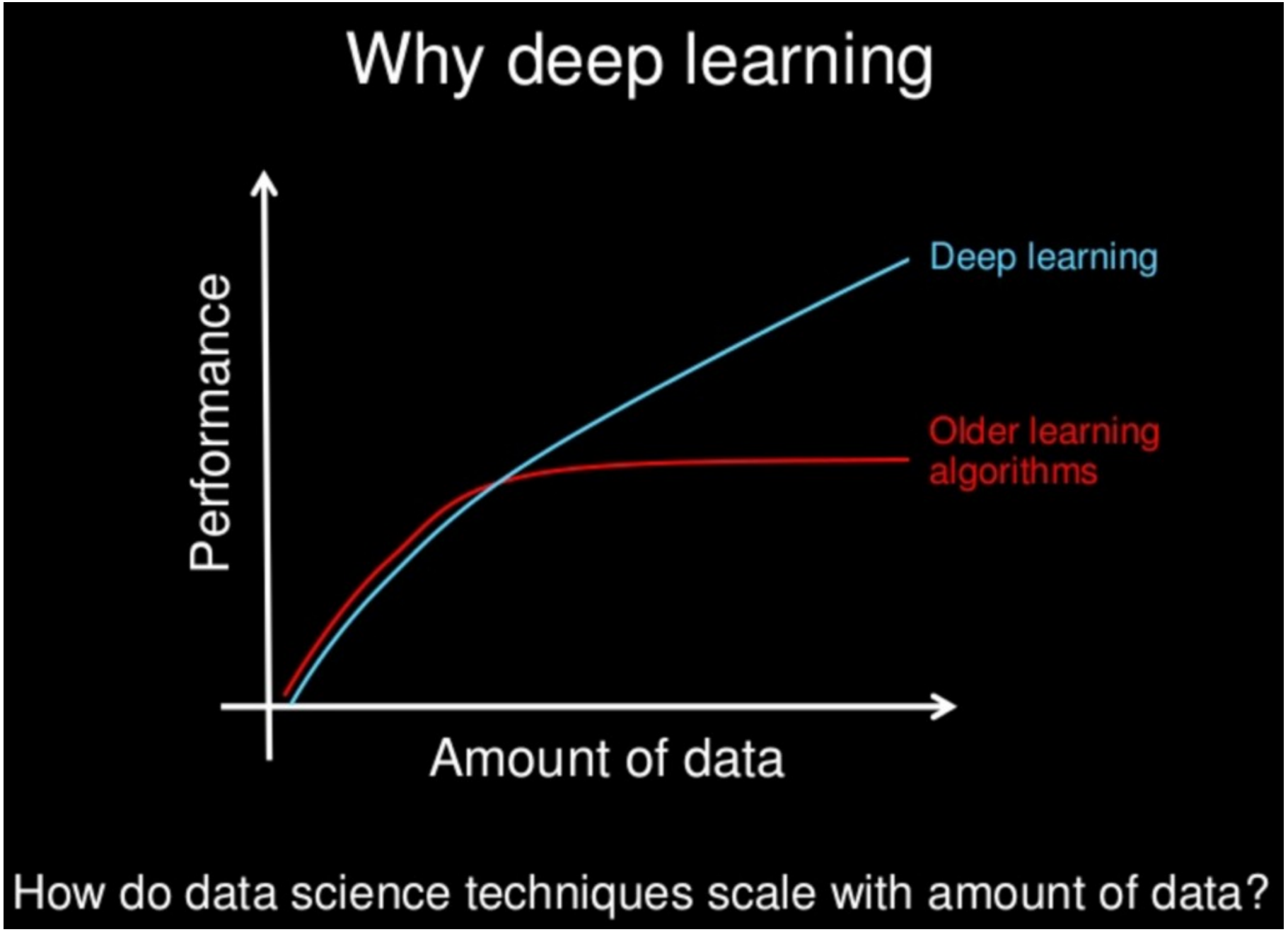


Supervised Deep Learning for Omics Integration



Back propagation ensures that all weights are updated in context of each other

Why to Use Deep Learning?



Big Data in Single Cell

CAREERS BLOG 10X UNIVERSITY

10X GENOMICS SOLUTIONS & PRODUCTS RESEARCH & APPLICATIONS EDUCATION & RESOURC

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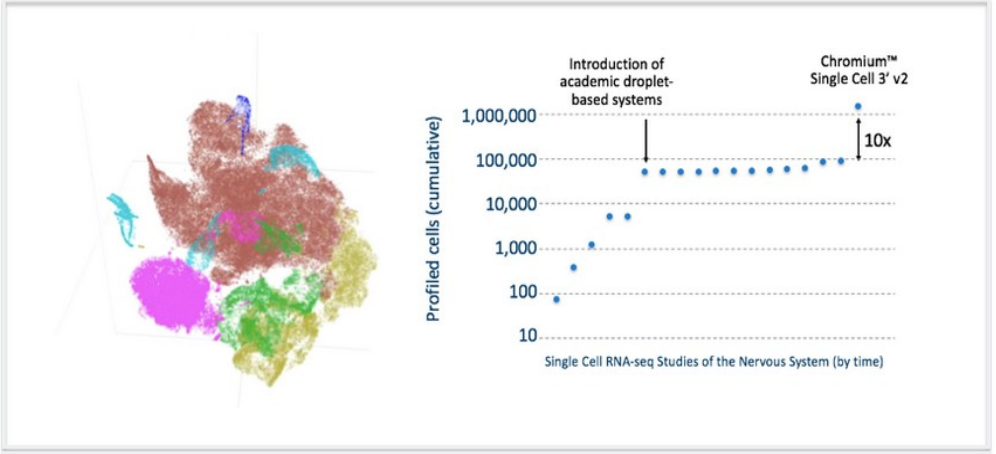


Our 1.3 million single cell dataset is ready to download

0 KUDOS

POSTED BY: grace-10x, on Feb 21, 2017 at 2:28 PM

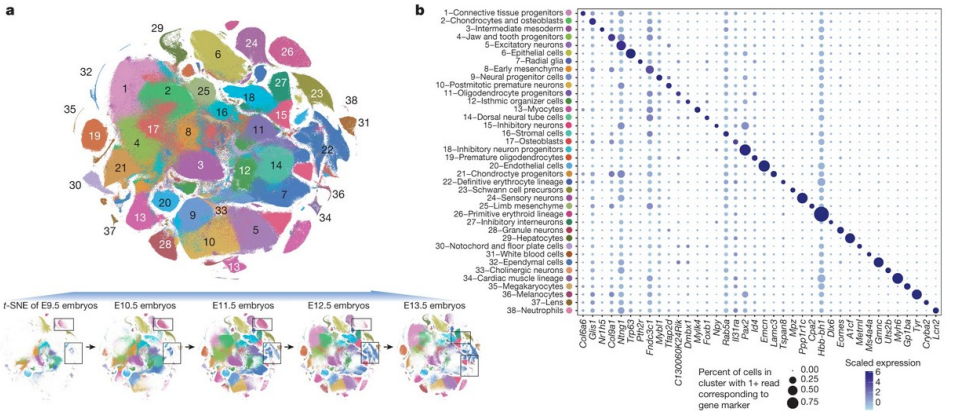
At ASHG last year, we announced our 1.3 Million Brain Cell Dataset, which is, to date, the largest dataset published in the single cell RNA-sequencing (scRNA-seq) field. Using the Chromium™ Single Cell 3' Solution (v2 Chemistry), we were able to sequence and profile 1,308,421 individual cells from embryonic mice brains. Read more in our application note Transcriptional Profiling of 1.3 Million Brain Cells with the Chromium™ Single Cell 3' Solution.

Watch out Underfitting!
Paradise for Deep Learning!

MENU nature

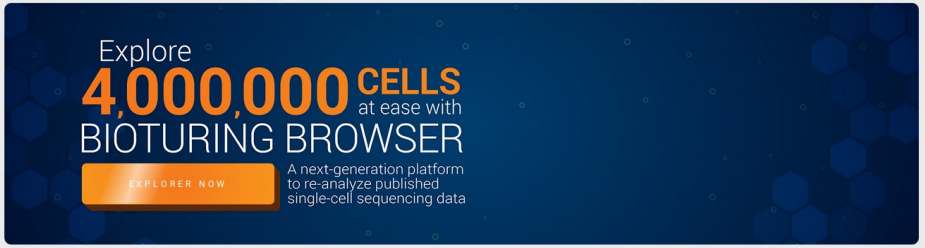
Fig. 2: Identifying the major cell types of mouse organogenesis.

From: The single-cell transcriptional landscape of mammalian organogenesis



a, t-SNE visualization of 2,026,641 mouse embryo cells (after removing a putative doublet cluster), coloured by cluster identity (ID) from Louvain clustering (in **b**), and annotated on the basis of marker genes. The same t-SNE is plotted below, showing only cells from each stage (cell numbers from left to right: n = 151,000 for E9.5; 370,279 for E10.5; 602,784 for E11.5; 468,088 for E12.5; 434,490 for E13.5). Primitive erythroid (transient) and definitive erythroid (expanding) clusters are boxed. **b**, Dot plot showing expression of one selected marker gene per cell type. The size of the dot encodes the percentage of cells within a cell type in

BioTuring Solutions Resources



Single Cell Analysis

5,500,000 cells will be indexed into BioTuring Single-cell Data Repository this September

by biomembers · August 30, 2019

Human Cell Atlas, single-cell data

We are glad to announce that we will upsize the current single-cell database in BioTuring Single-cell Browser to 5,500,000 cells this September. With this release, we will double the current number of publications indexed in BioTuring Single-cell Browser, and cross the number of cells hosted on available public single-cell data repositories like Human Cell Atlas (HCA) and Broad Institute's Single-cell Portal.

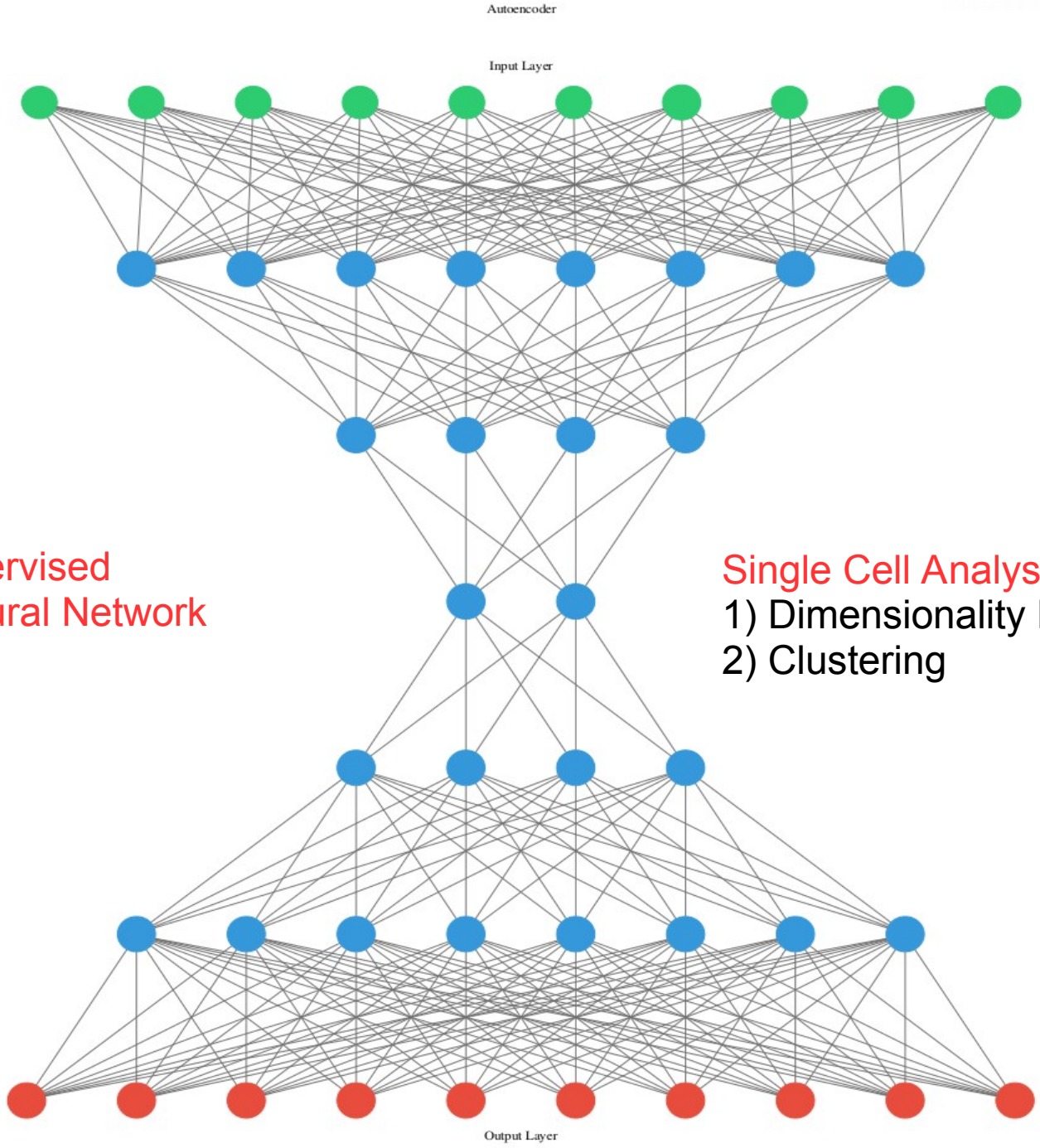
Search

RECENT POSTS

A new tool to interactively visualize single-cell objects (Seurat, Scanpy, SingleCellExperiments, ...)
September 26, 2019

5,500,000 cells will be indexed into BioTuring Single-cell Data Repository this September
August 30, 2019

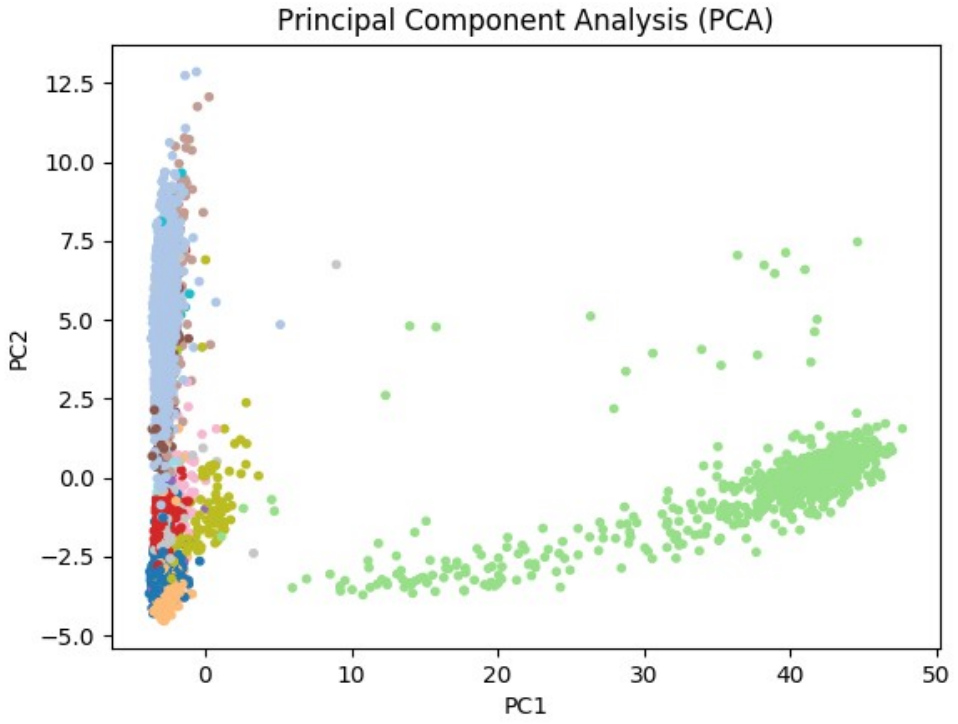
Why Autoencoder for Single Cell?

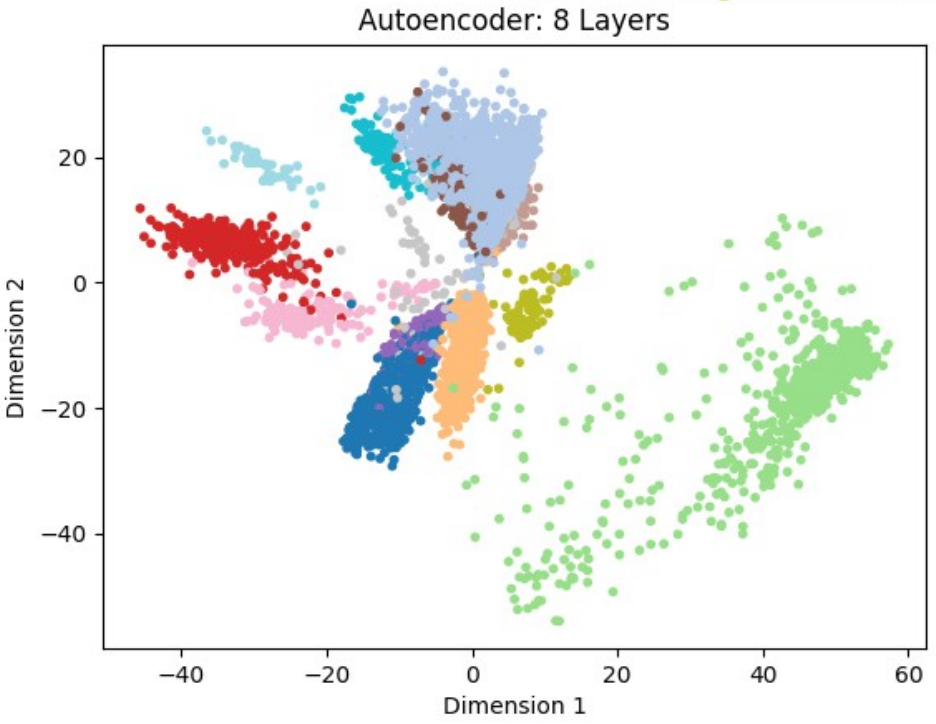


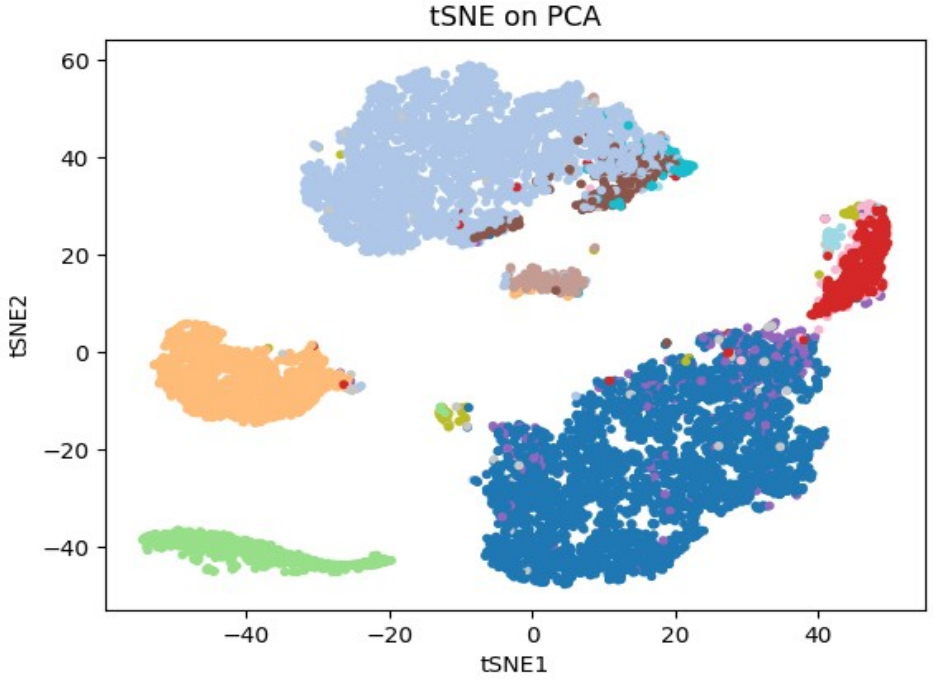
Unsupervised
Artificial Neural Network

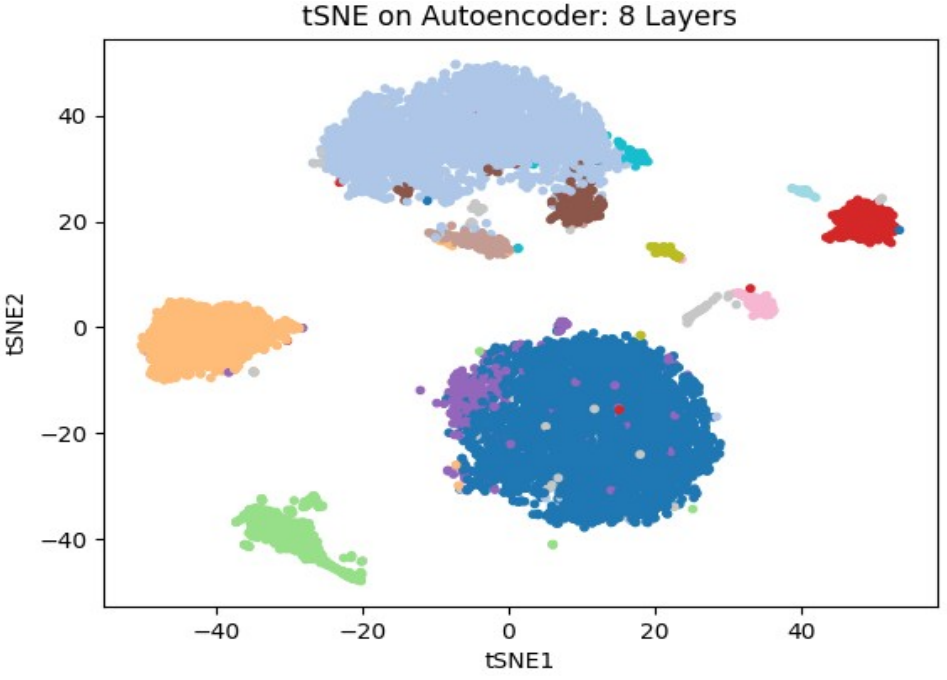
Single Cell Analysis is Unsupervised
1) Dimensionality Reduction
2) Clustering

CITE-seq: Dimensionality Reduction scRNAseq, 8 617 cells

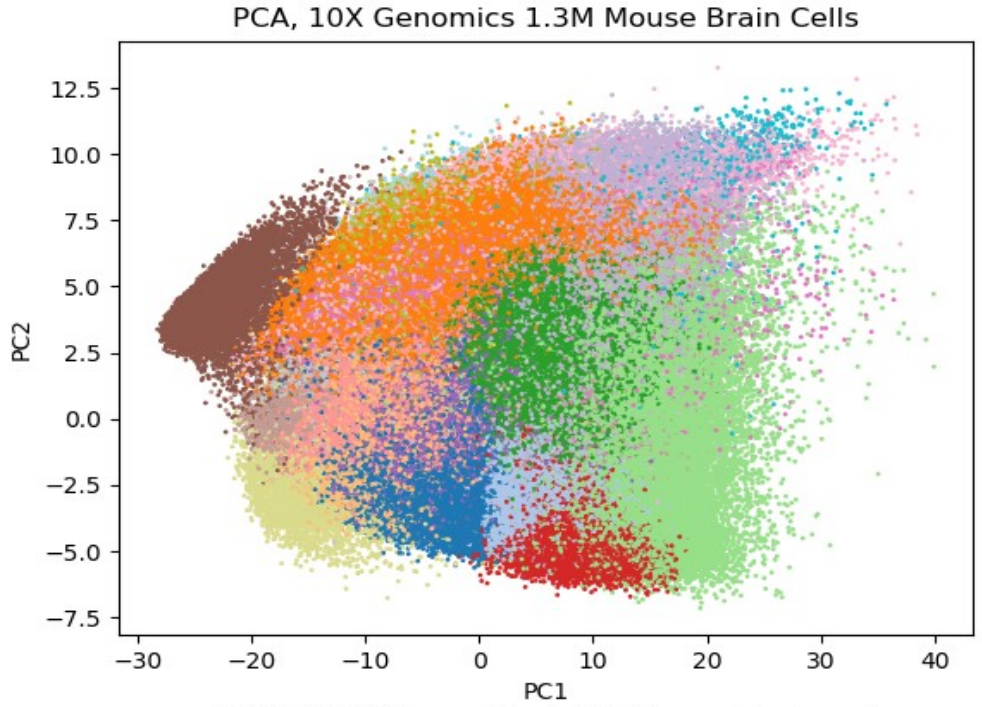


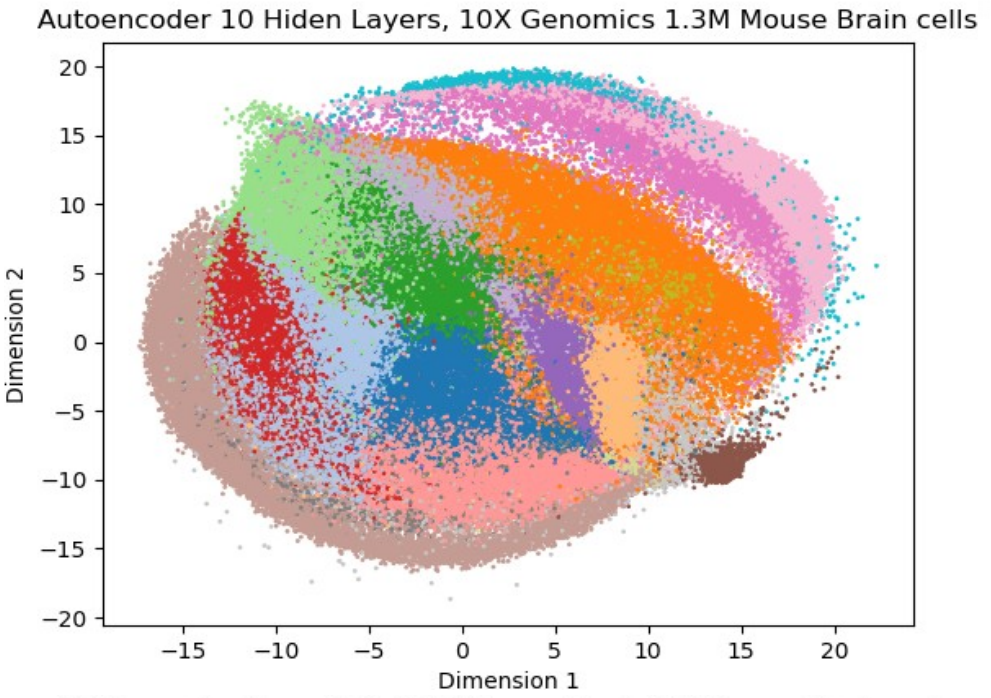


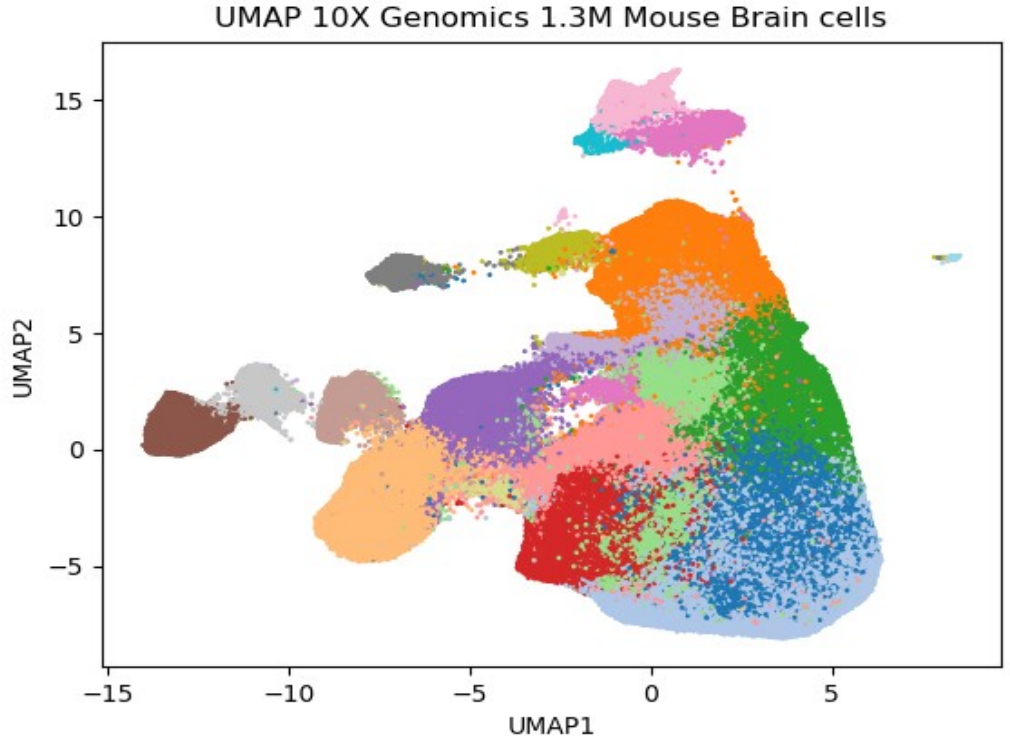


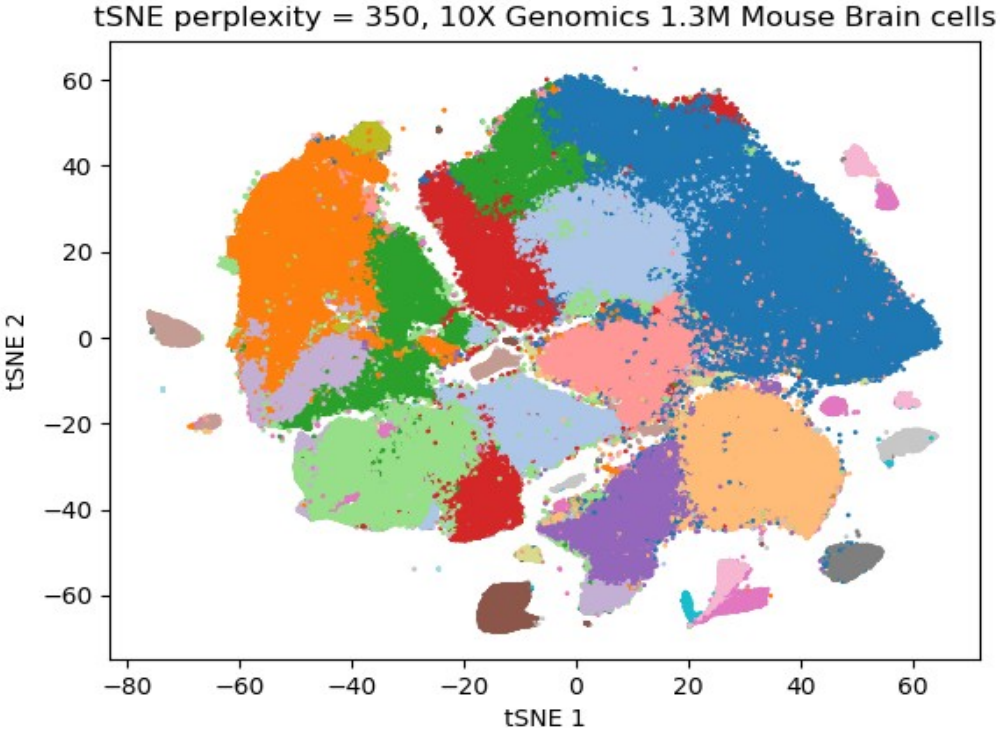


10X Genomics Mouse Brain: scRNAseq, 1.3M cells

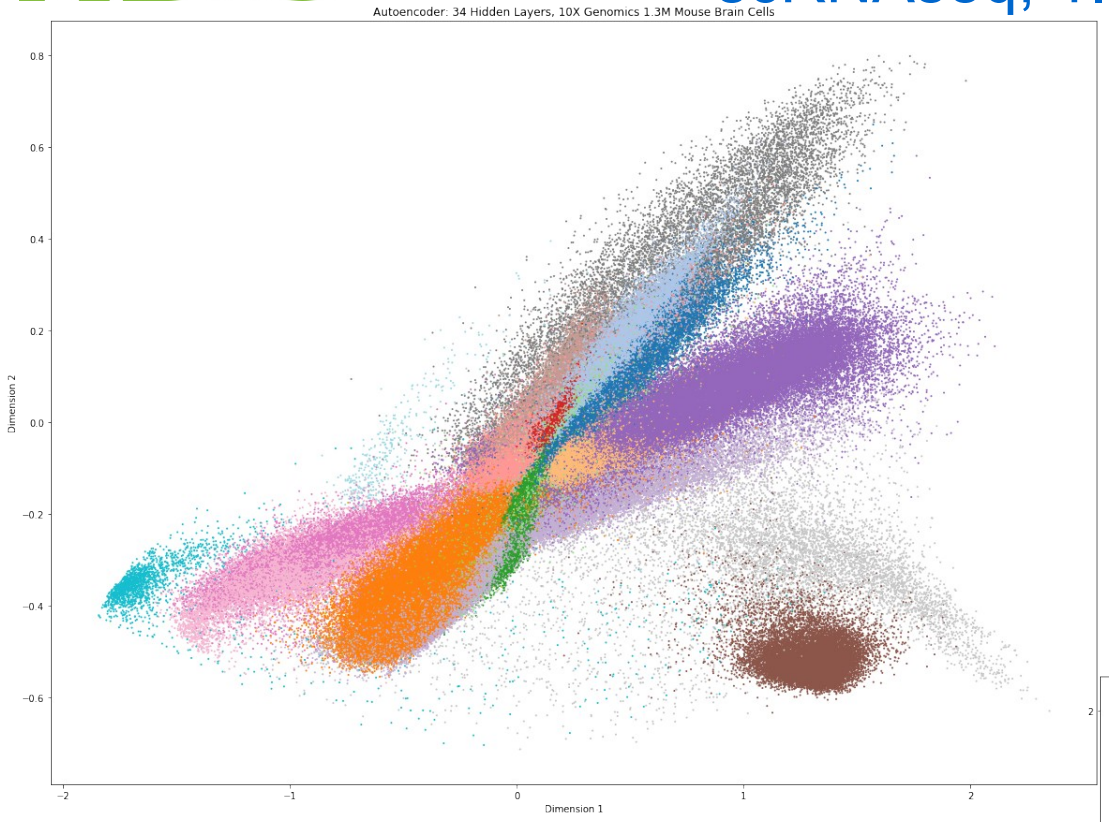






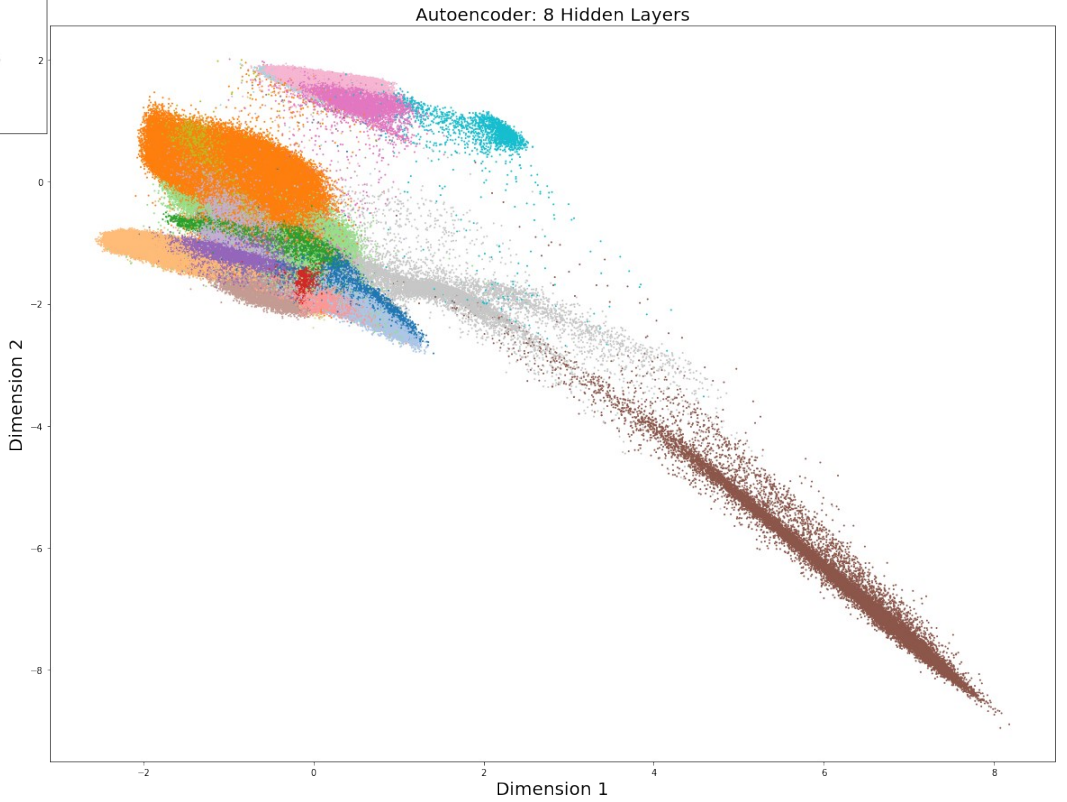


10X Genomics Mouse Brain: scRNAseq, 1.3M cells

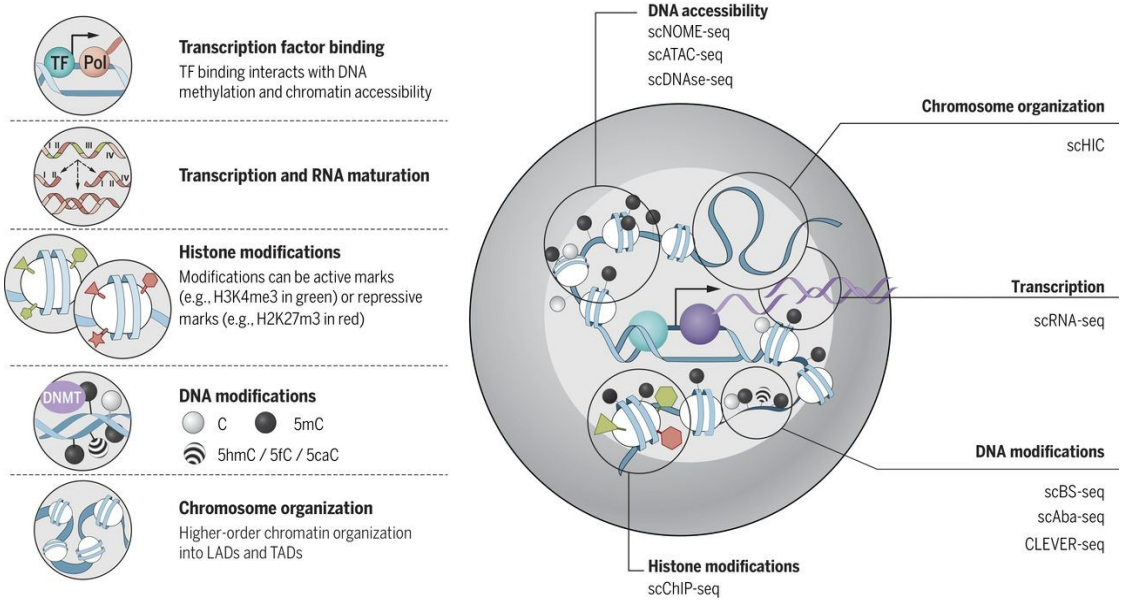


Autoencoders are good for non-linear pre- dimension reduction, the bottleneck can be fed to tSNE / UMAP

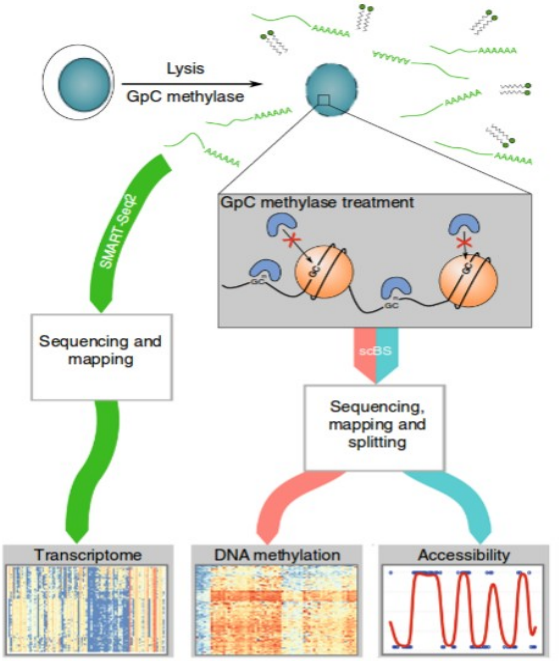
Autoencoder itself perhaps is not that great for visualization of scOmics



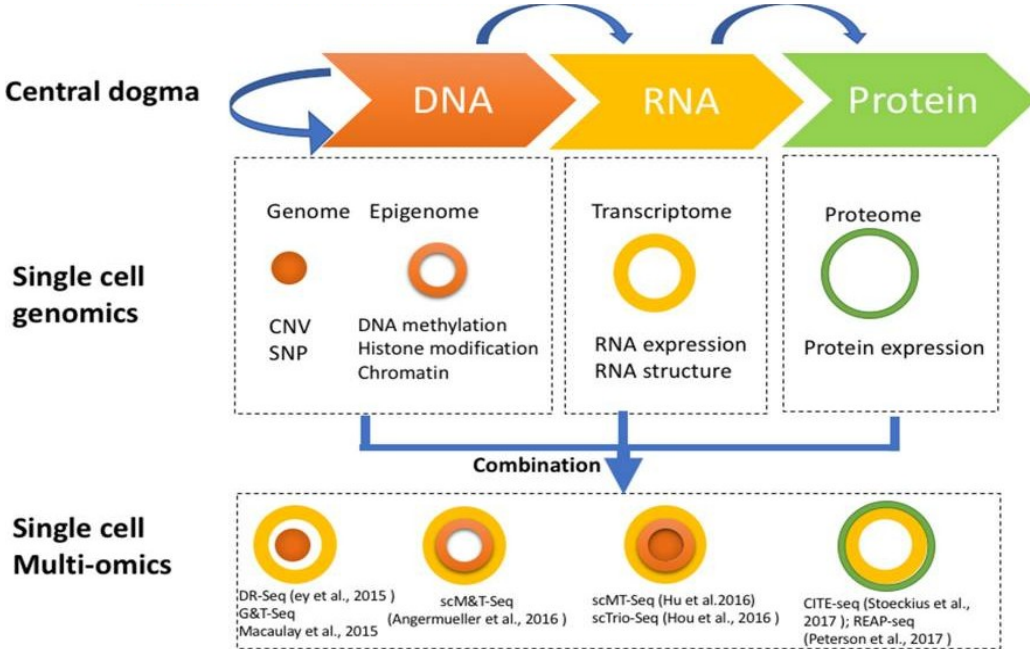
Multimodal scOMICs Technologies



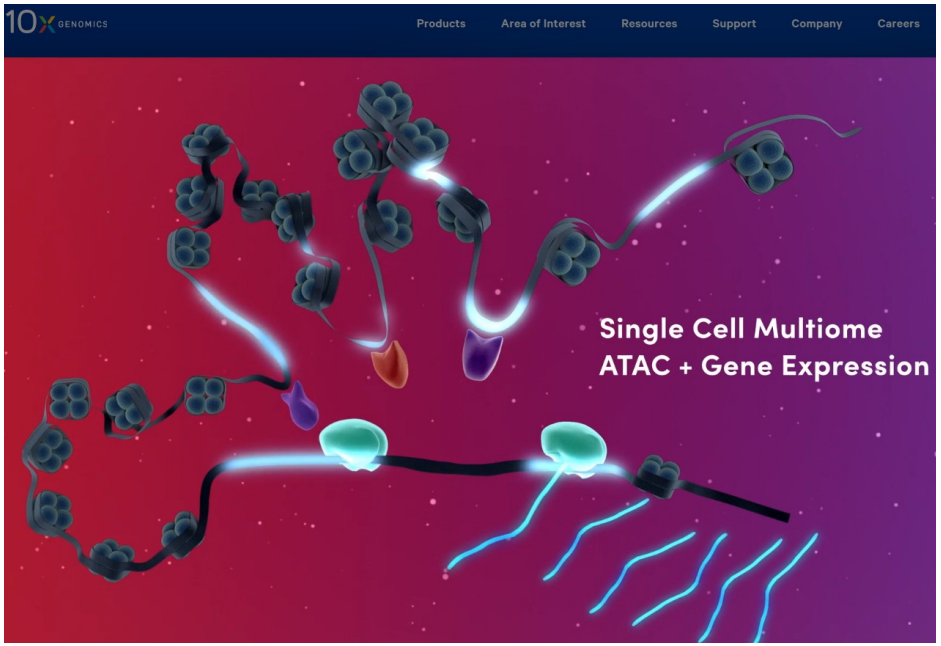
Kelsey et al., 2017, Science 358, 69-75



Clark et al., 2018, Nature Communications 9, 781

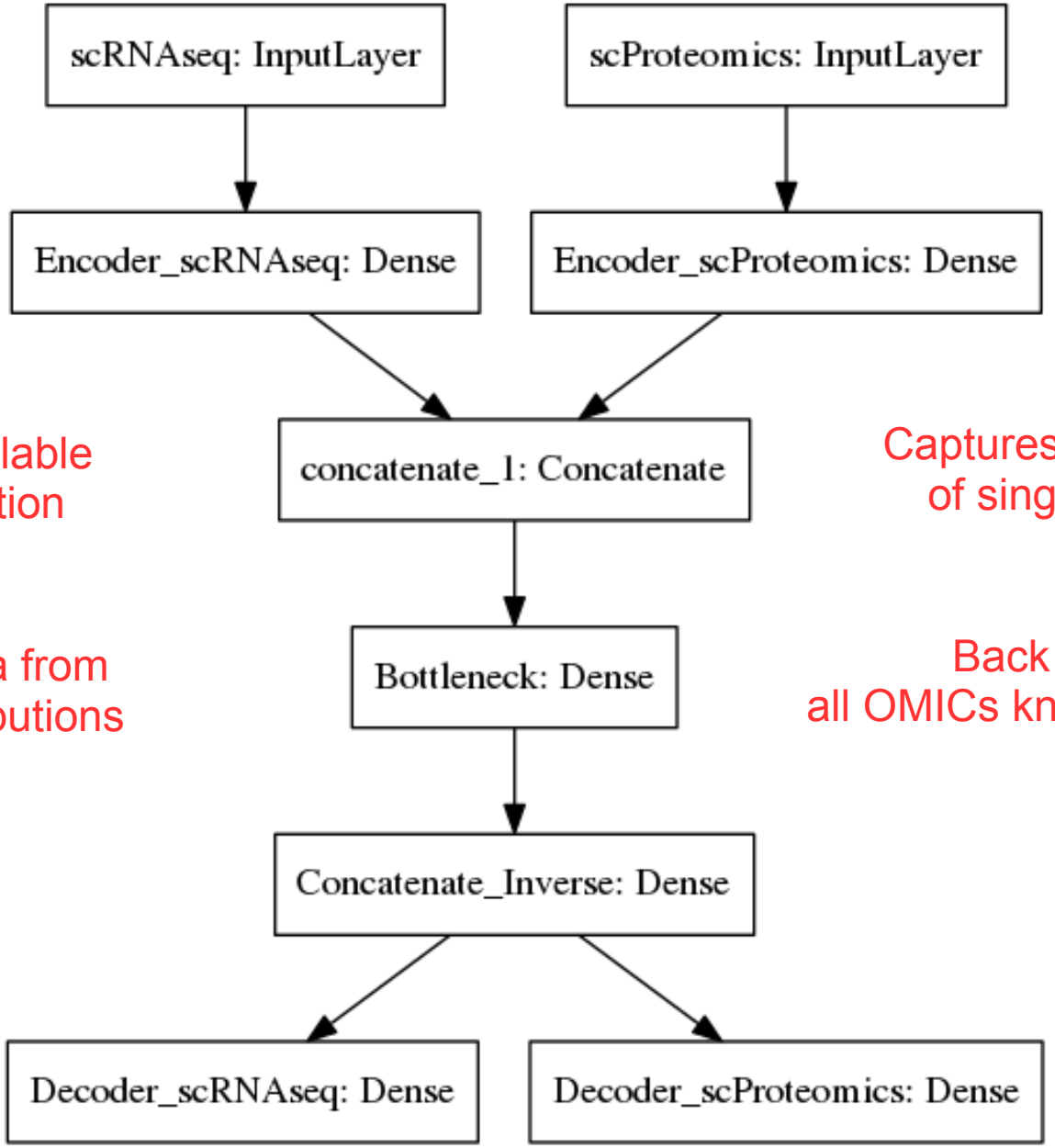


Hu et al., 2018, Frontier in Cell and Developmental Biology 6, 1-13



10X Genomics Multiome ATAC + Gene Expression

CITE-seq: Data Integration
Autoencoder



Flexible and scalable OMICs integration

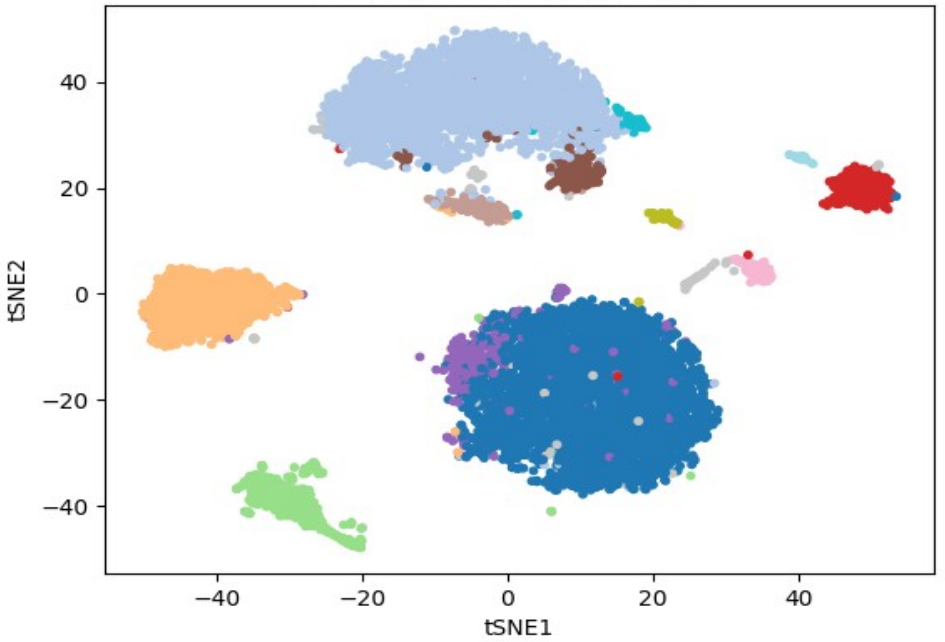
Captures non-linearity of single cell data

Combine data from different distributions

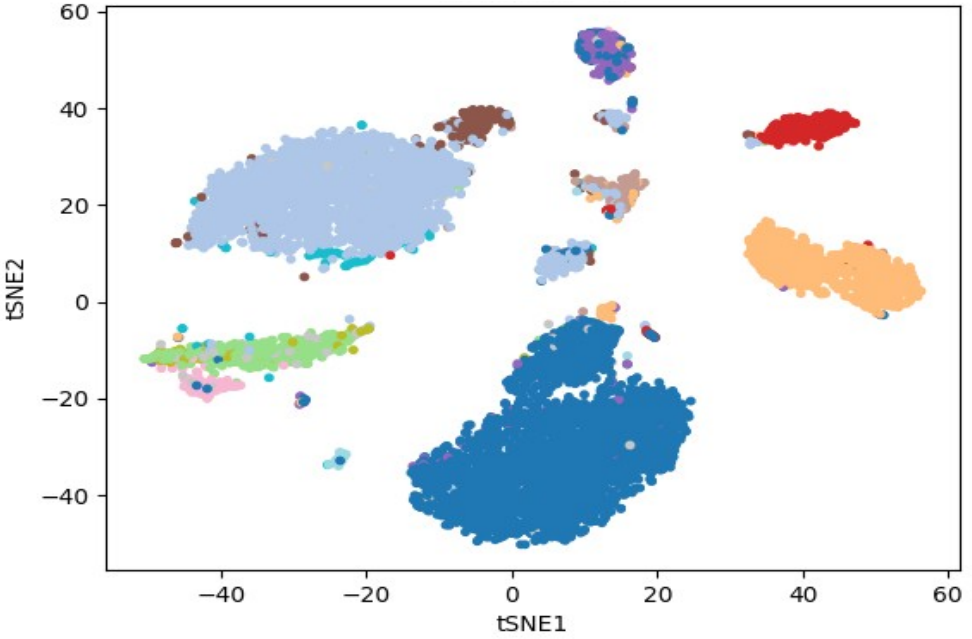
Back Propagation: all OMICs know about each other

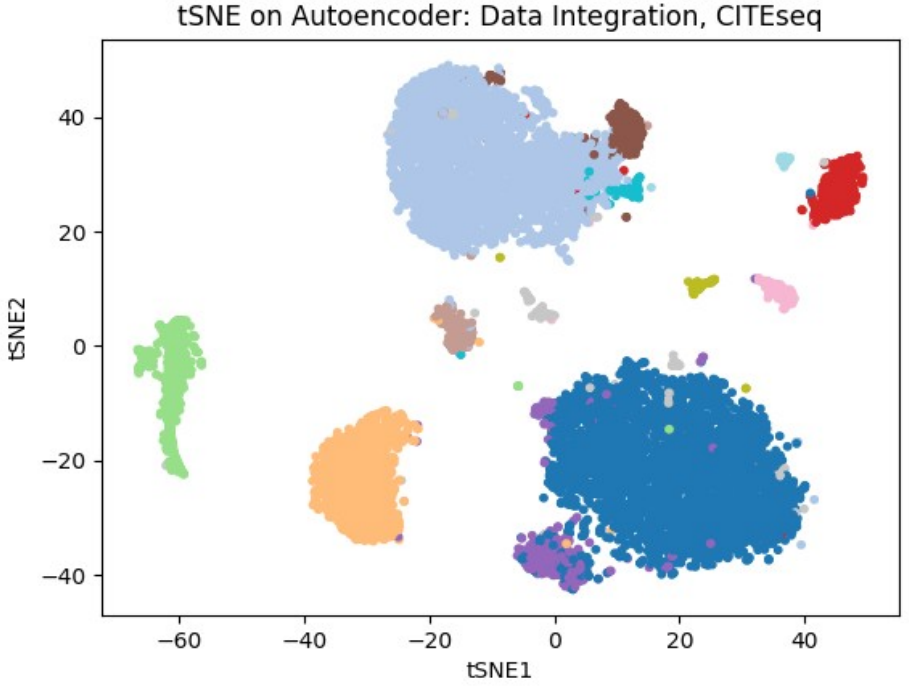
CITE-seq: Data Integration
scRNAseq + scProteomics, 8 617 cells

scRNAseq



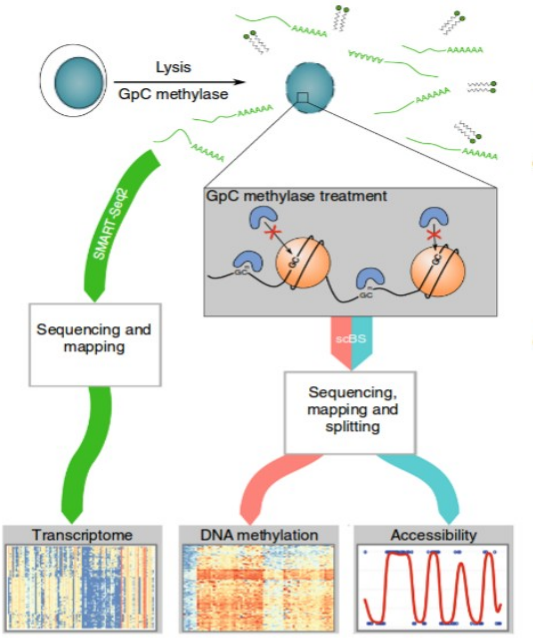
scProteomics



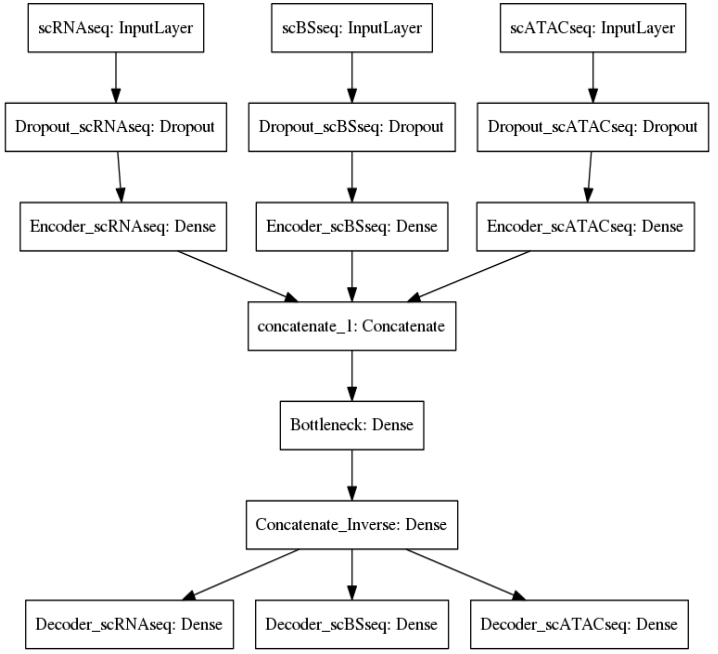


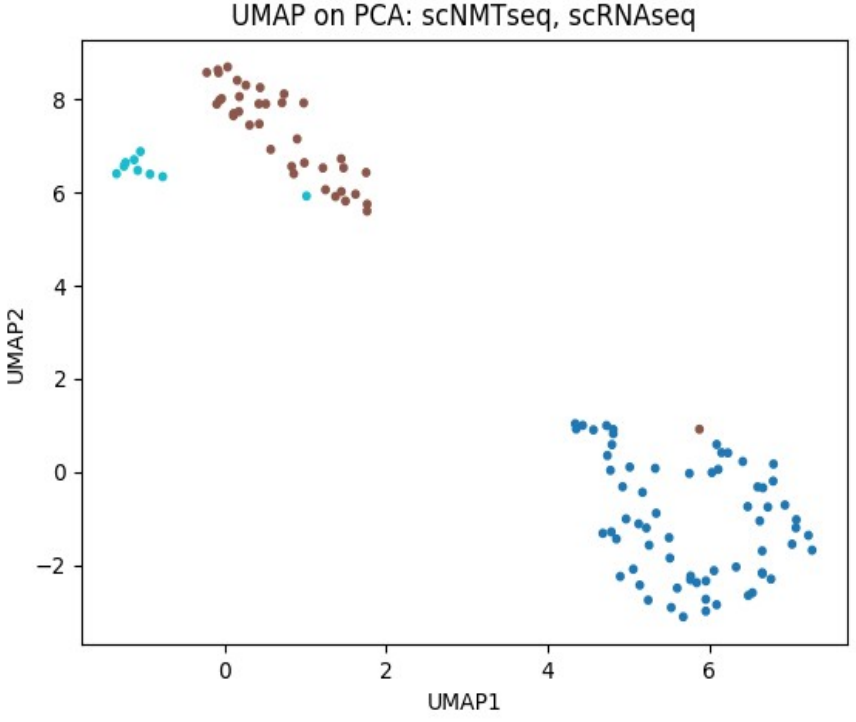
scNMT-seq: Data Integration

scRNAseq + scBSseq + scATACseq, 120 cells

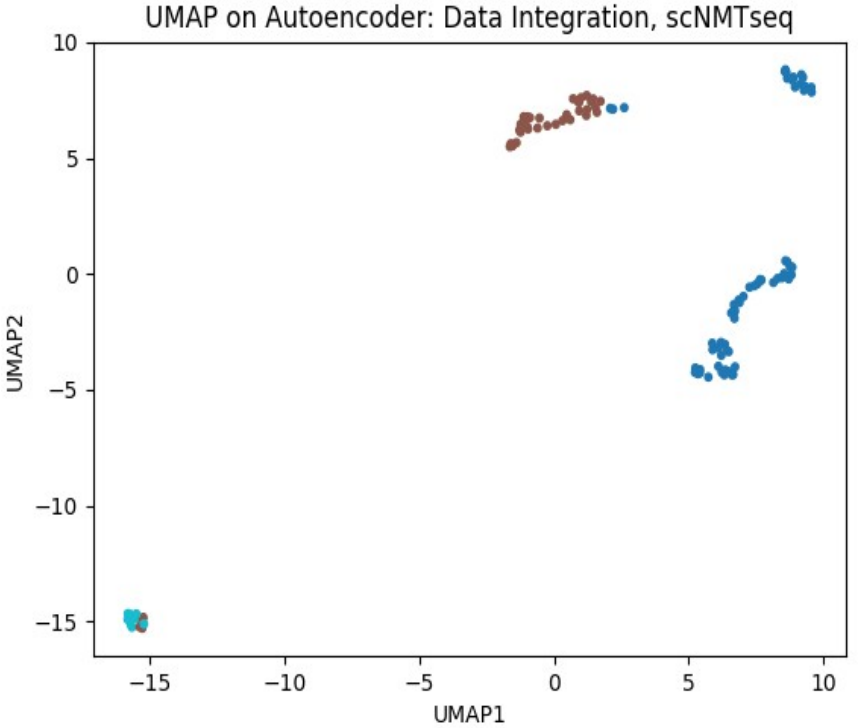


scNMTseq: Clark et al., 2018, Nature Communications 9, 781

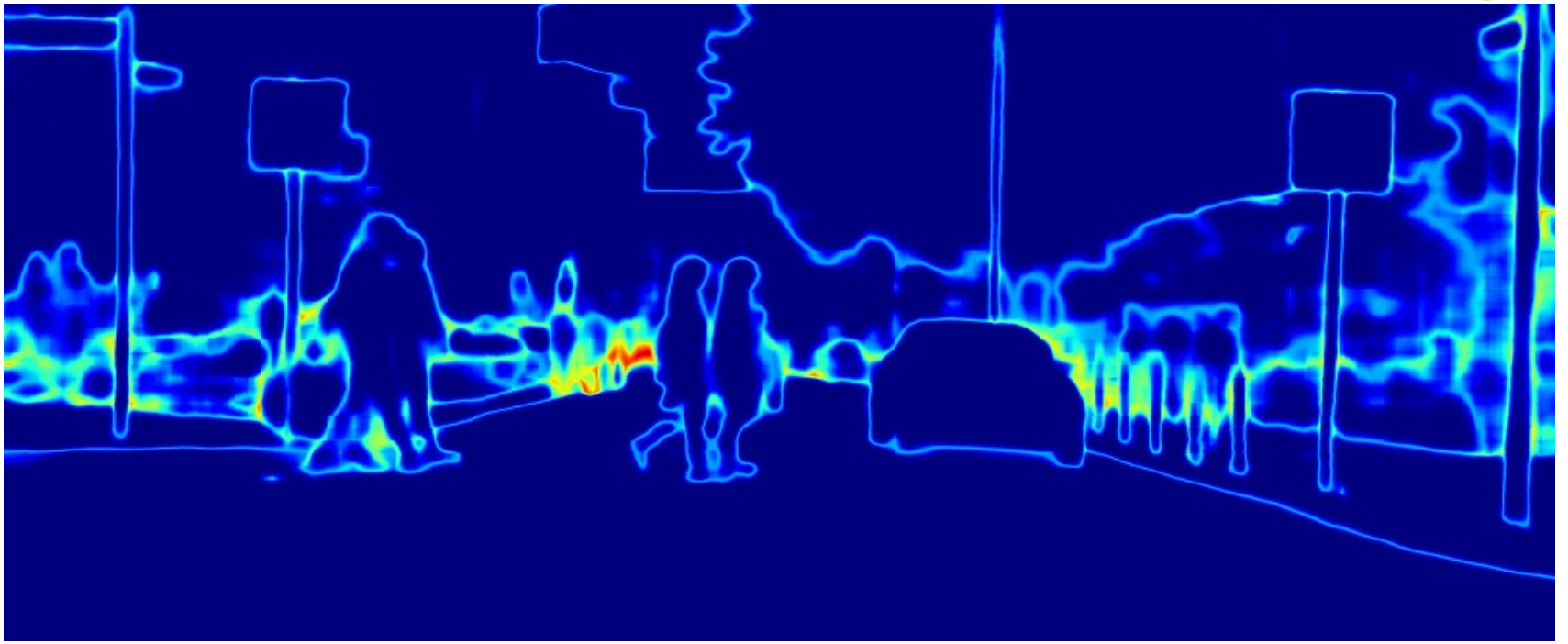




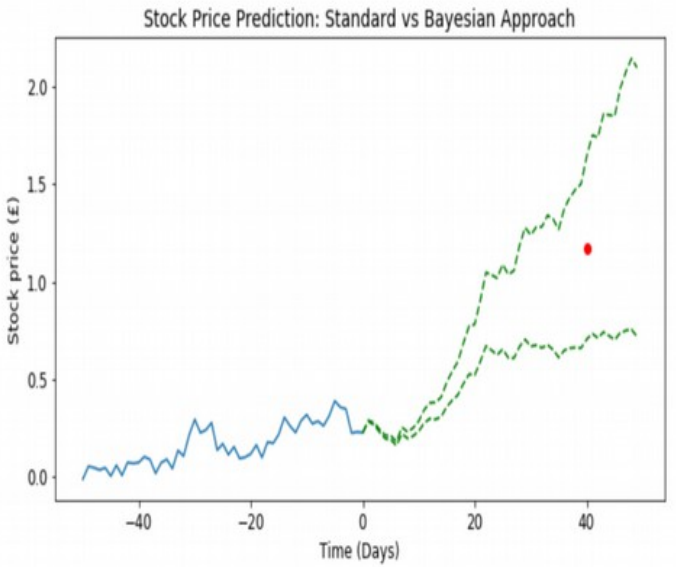
From Single To Multi-OMICs

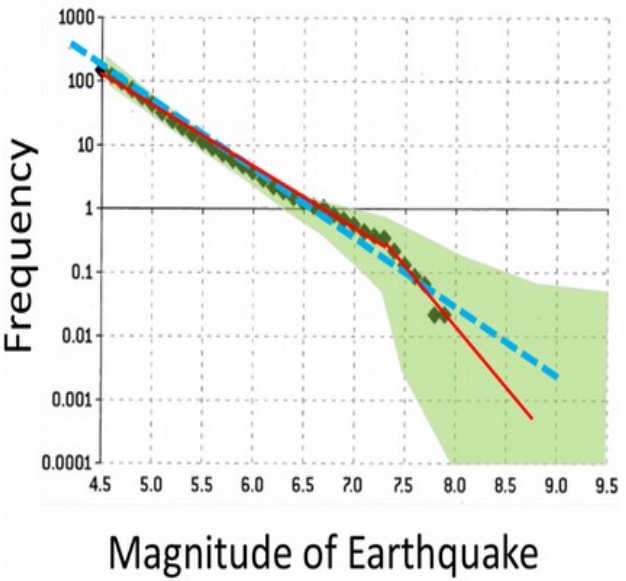


Deep Learning is not Good Enough



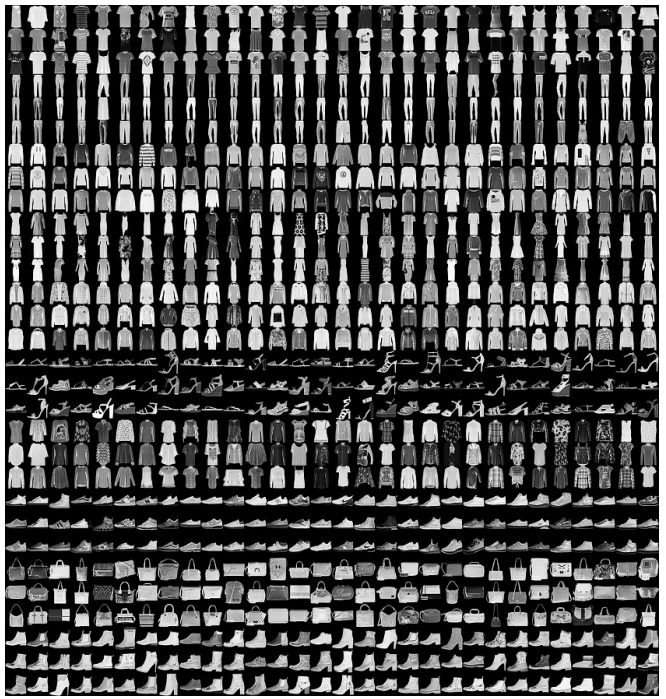
Intelligence is to know how much you do not know





Frequentist Image Recognition

Fashion MNIST



```
In [24]: # normalize inputs from 0-255 to 0.0-1.0
X_train = X_train.reshape(X_train.shape[0], 1, 28, 28).astype('float32')
X_test = X_test.reshape(X_test.shape[0], 1, 28, 28).astype('float32')
X_train = X_train / 255.0
X_test = X_test / 255.0

In [25]: # one hot encode outputs
y_train = np_utils.to_categorical(y_train)
y_test = np_utils.to_categorical(y_test)
num_classes = y_test.shape[1]
print(num_classes)

10

In [27]: # Create the model
model = Sequential()
model.add(Conv2D(32, (3, 3), input_shape=(1, 28, 28), padding='same', activation='relu',
                 kernel_constraint=maxnorm(3)))
model.add(Dropout(0.2))
model.add(Conv2D(32, (3, 3), padding='same', activation='relu',
                 kernel_constraint=maxnorm(3)))
model.add(MaxPooling2D(pool_size=(2, 2)))
model.add(Flatten())
model.add(Dense(512, activation='relu', kernel_constraint=maxnorm(3)))
model.add(Dropout(0.5))
model.add(Dense(num_classes, activation='softmax'))

# Compile model
epochs = 25
lrate = 0.01
decay = lrate/epochs
sgd = SGD(lr=lrate, momentum=0.9, decay=decay, nesterov=False)
model.compile(loss='categorical_crossentropy', optimizer=sgd, metrics=['accuracy'])
print(model.summary())
```

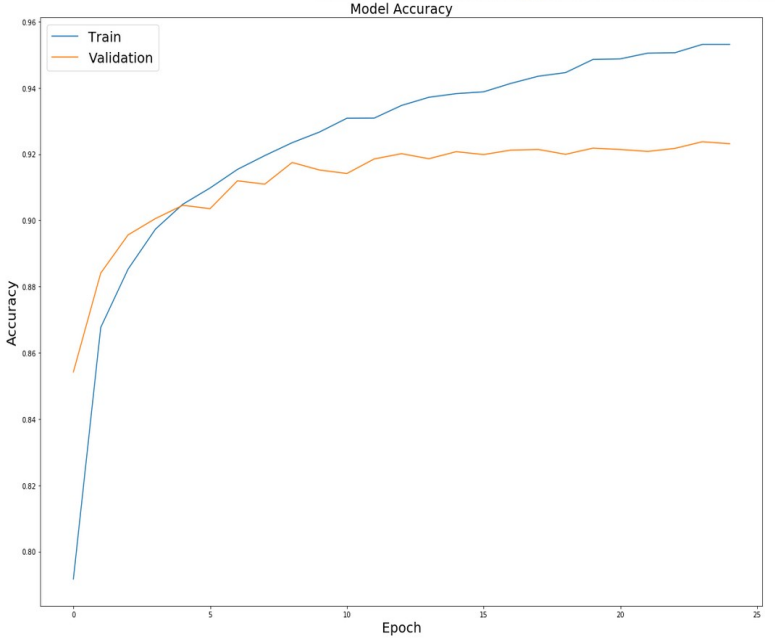
Layer (type)	Output Shape	Param #
conv2d_8 (Conv2D)	(None, 32, 28, 28)	320
dropout_7 (Dropout)	(None, 32, 28, 28)	0
conv2d_9 (Conv2D)	(None, 32, 28, 28)	9248
max_pooling2d_4 (MaxPooling2	(None, 32, 14, 14)	0
flatten_4 (Flatten)	(None, 6272)	0
dense_7 (Dense)	(None, 512)	3211776
dropout_8 (Dropout)	(None, 512)	0
dense_8 (Dense)	(None, 10)	5130

Total params: 3,226,474
Trainable params: 3,226,474
Non-trainable params: 0

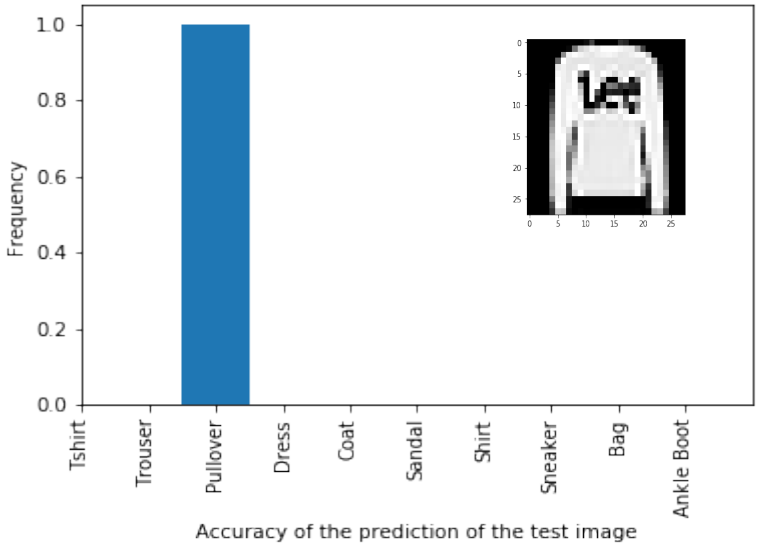
None

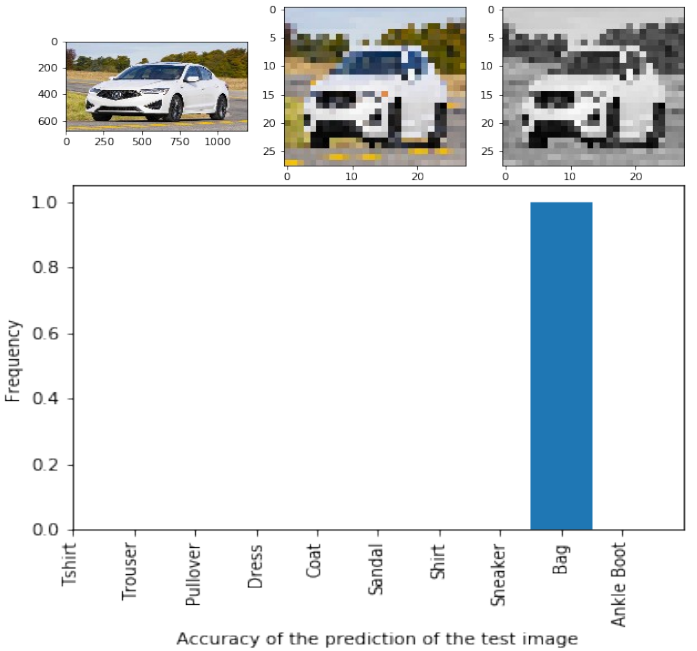
```
In [28]: # Fit the model
#model.fit(X_train, y_train, validation_data=(X_test, y_test), epochs=epochs, batch_size=32)
history = model.fit(X_train, y_train, epochs = epochs, verbose = 1, validation_split = 0.25,
                    batch_size = 32, shuffle = True)

Train on 45000 samples, validate on 15000 samples
Epoch 1/25
45000/45000 [==============================] - 1158s 26ms/step - loss: 0.5762 - acc: 0.7917 - val_loss: 0.39
73 - val_acc: 0.8542
Epoch 2/25
45000/45000 [==============================] - 1124s 25ms/step - loss: 0.3643 - acc: 0.8676 - val_loss: 0.31
27 - val_acc: 0.8841
Epoch 3/25
45000/45000 [==============================] - 1158s 26ms/step - loss: 0.3129 - acc: 0.8853 - val_loss: 0.28
25 - val_acc: 0.8956
Epoch 4/25
45000/45000 [==============================] - 1609s 36ms/step - loss: 0.2813 - acc: 0.8973 - val_loss: 0.27
27 - val_acc: 0.9005
Epoch 5/25
45000/45000 [==============================] - 902s 20ms/step - loss: 0.2618 - acc: 0.9048 - val_loss: 0.258
8 - val_acc: 0.9045
Epoch 6/25
45000/45000 [==============================] - 936s 21ms/step - loss: 0.2451 - acc: 0.9098 - val_loss: 0.256
4 - val_acc: 0.9035
Epoch 7/25
```



Prediction





Bayesian Image Recognition

PyMC3, Edward, TensorFlow Probability

```
In [8]:
x_train = x_train.reshape((x_train.shape[0],D))
x_test = x_test.reshape((x_test.shape[0],D))
print(x_train.shape)
print(x_test.shape)
```

```
(60000, 784)
(10000, 784)
```

```
In [9]:
from keras.utils import to_categorical
y_train = to_categorical(y_train)
y_test = to_categorical(y_test)
print(y_train.shape)
print(y_test.shape)
```

```
(60000, 10)
(10000, 10)
```

```
In [10]:
ed.set_seed(314159)
N = 100    # number of images in a minibatch.
D = D      # number of features.
K = 10     # number of classes.

# Create a placeholder to hold the data (in minibatches) in a TensorFlow graph.
x = tf.placeholder(tf.float32, [None, D])
# Normal(0,1) priors for the variables. Note that the syntax assumes TensorFlow 1.1.
w = Normal(loc=tf.zeros([D, K]), scale=tf.ones([D, K]))
b = Normal(loc=tf.zeros(K), scale=tf.ones(K))
# Categorical likelihood for classication.
y = Categorical(tf.matmul(x, w) + b)
```

```
In [11]:
# Contruct the q(w) and q(b). in this case we assume Normal distributions.
qw = Normal(loc=tf.Variable(tf.random_normal([D, K])),
            scale=tf.nn.softplus(tf.Variable(tf.random_normal([D, K]))))
qb = Normal(loc=tf.Variable(tf.random_normal([K])),
            scale=tf.nn.softplus(tf.Variable(tf.random_normal([K]))))
```

```
In [12]:
def generator(arrays, batch_size = N):
    starts = [0] * len(arrays)  # pointers to where we are in iteration
    while True:
        batches = []
        for i, array in enumerate(arrays):
            start = starts[i]
            stop = start + batch_size
            diff = stop - array.shape[0]
            if diff <= 0:
                batch = array[start:stop]
                starts[i] += batch_size
            else:
                batch = np.concatenate((array[start:], array[:diff]))
                starts[i] = diff
            batches.append(batch)
        yield batches
cifar10 = generator([x_train, y_train], N)
```

```
In [13]:
# We use a placeholder for the labels in anticipation of the traning data.
y_ph = tf.placeholder(tf.int32, [N])
# Define the VI inference technique, ie. minimise the KL divergence between q and p.
inference = ed.KLqp({w: qw, b: qb}, data={y: y_ph})
# Initialse the infernce variables
inference.initialize(n_iter=50000, n_print=100, scale={y: float(x_train.shape[0]) / N})
# We will use an interactive session.
sess = tf.InteractiveSession()
# Initialise all the vairables in the session.
tf.global_variables_initializer().run()
# Let the training begin. We load the data in minibatches and update the VI infernce using each new batch.
for _ in range(inference.n_iter):
    X_batch, Y_batch = next(cifar10)
    #X_batch = X_batch.reshape(N,-1)
    # TensorFlow method gives the label data in a one hot vetor format. We convert that into a single label.
    Y_batch = np.argmax(Y_batch, axis=1)
    info_dict = inference.update(feed_dict={x: X_batch, y_ph: Y_batch})
    inference.print_progress(info_dict)
```

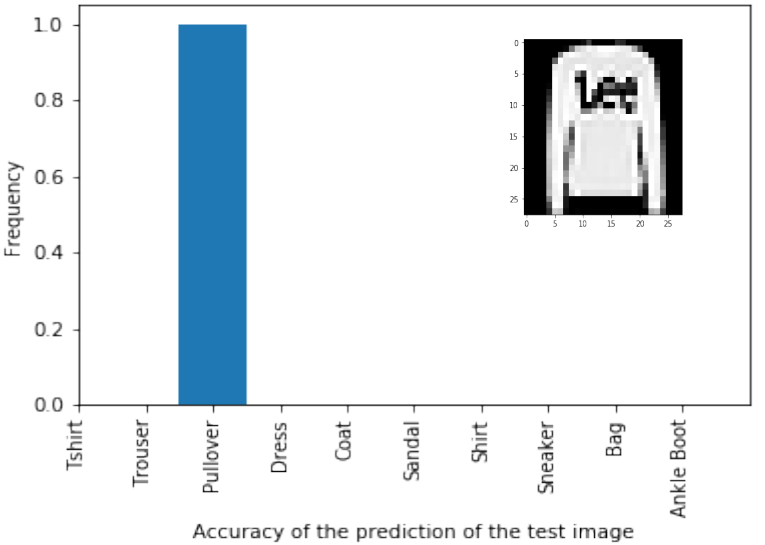
```
50000/50000 [100%] ██████████████████████████████ Elapsed: 221s | Loss: 85453.266
```

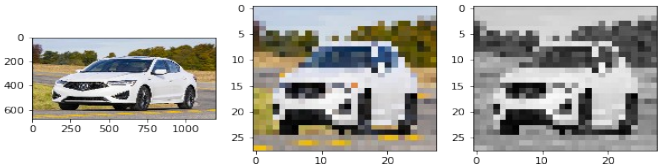
```
In [14]:
# Generate samples the posterior and store them.
n_samples = 100
prob_lst = []
samples = []
w_samples = []
b_samples = []
for _ in range(n_samples):
    w_samp = qw.sample()
    b_samp = qb.sample()
    w_samples.append(w_samp)
    b_samples.append(b_samp)
    # Also compute the probabiliy of each class for each (w,b) sample.
    prob = tf.nn.softmax(tf.matmul(x_test, w_samp) + b_samp)
    prob_lst.append(prob.eval())
    sample = tf.concat([tf.reshape(w_samp,[-1]),b_samp],0)
    samples.append(sample.eval())
```

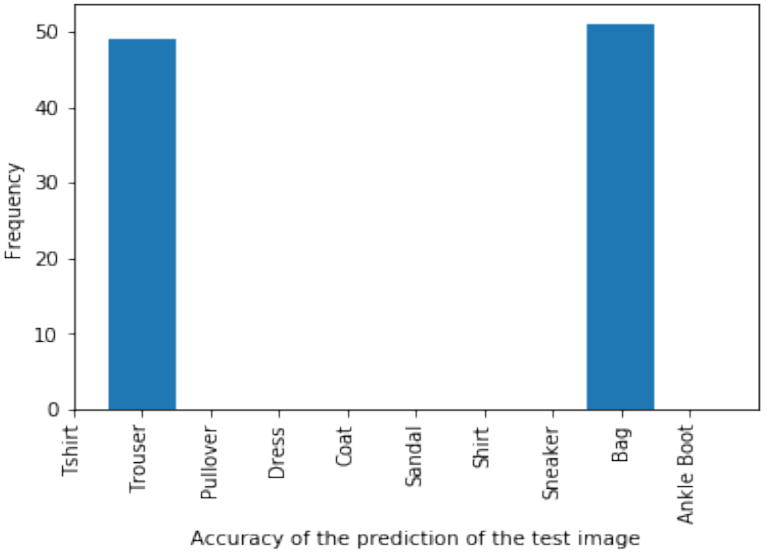
```
In [15]:
# Compute the accuracy of the model.
# For each sample we compute the predicted class and compare with the test labels.
# Predicted class is defined as the one which as maximum probability.
# We perform this test for each (w,b) in the posterior giving us a set of accuracies
# Finally we make a histogram of accuracies for the test data.
accy_test = []
for prob in prob_lst:
    y_trn_prd = np.argmax(prob, axis=1).astype(np.float32)
    acc = (y_trn_prd == np.argmax(y_test, axis=1)).mean()*100
    accy_test.append(acc)

plt.hist(accy_test)
plt.title("Histogram of prediction accuracies in the CIFAR10 test data")
plt.xlabel("Accuracy")
plt.ylabel("Frequency")
plt.show()
```

Prediction

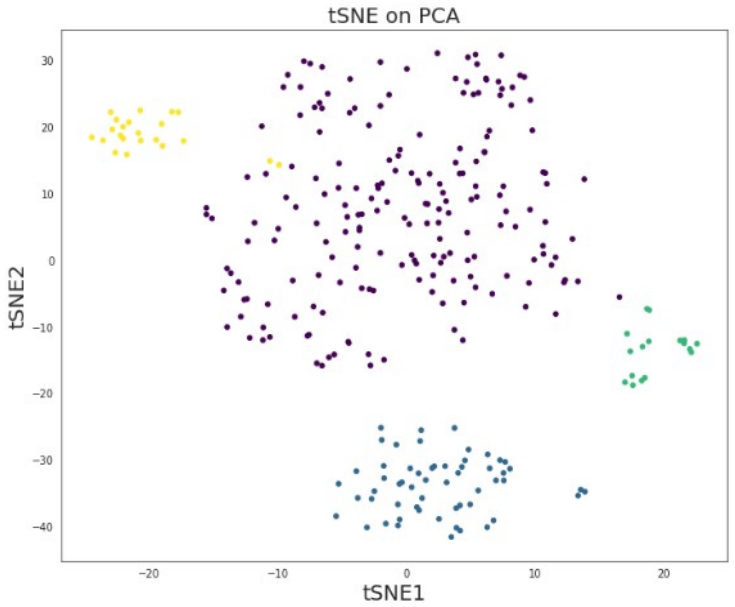


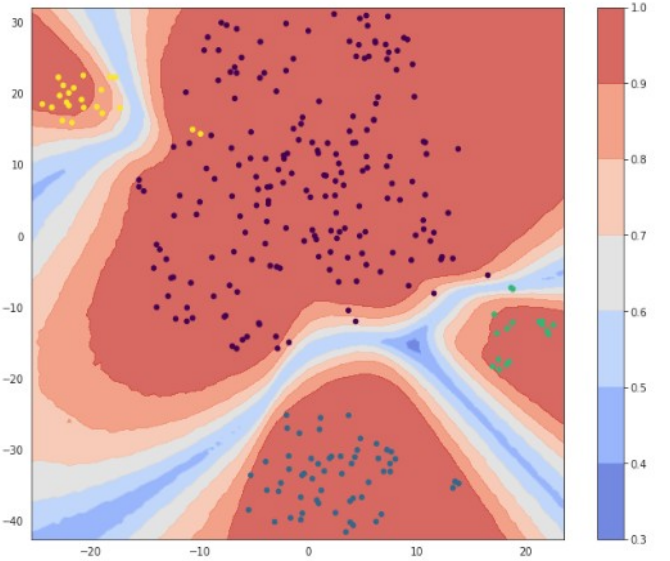


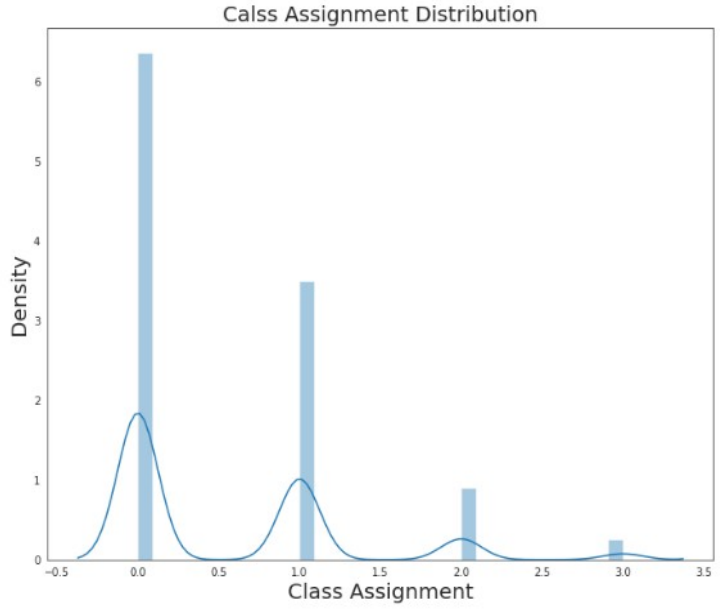


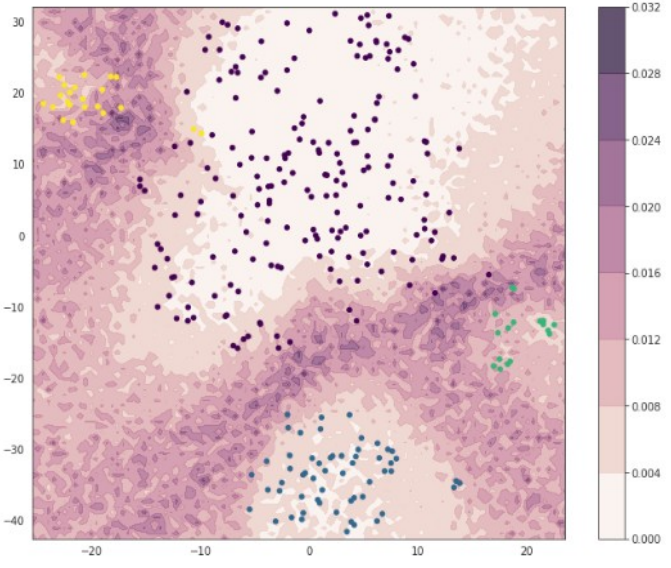
Bayesian Deep Learning for Single Cell

Superior for predictions on unseen data









Bartoschek et al. 2018, Nature Communications, 9, 5150

PyMC3

Uncertainties are crucial for Clinical Diagnostics

National Bioinformatics Infrastructure Sweden (NBIS)

Knut och Alice Wallenbergs Stiftelse

Vetenskapsrådet

Lunds Universitet