Bayesian Deep Learning Applications in Biomedicine

BayesLund 2019

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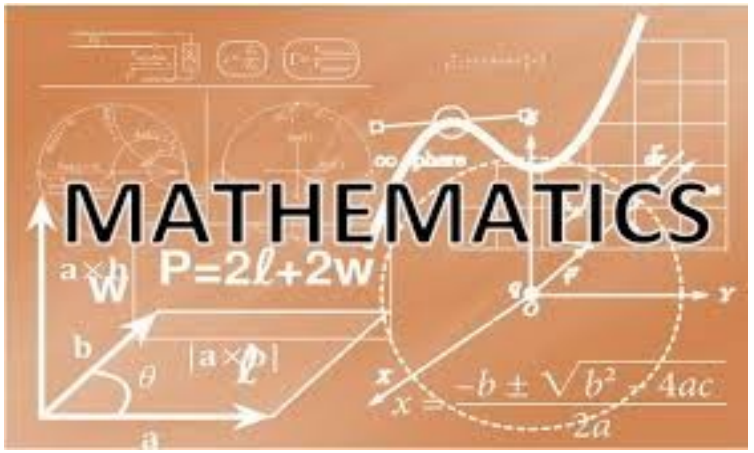
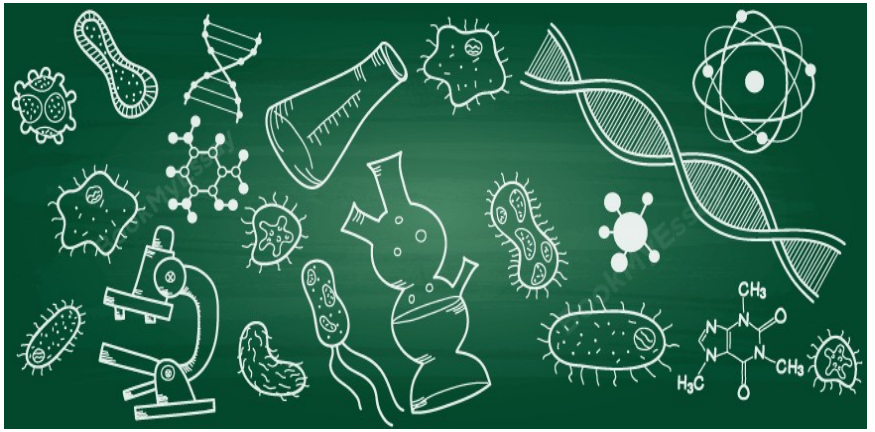
Lund, 07.05.2019

Bioinformatics in the Bayesian way

Bioinformatics Connects Sciences

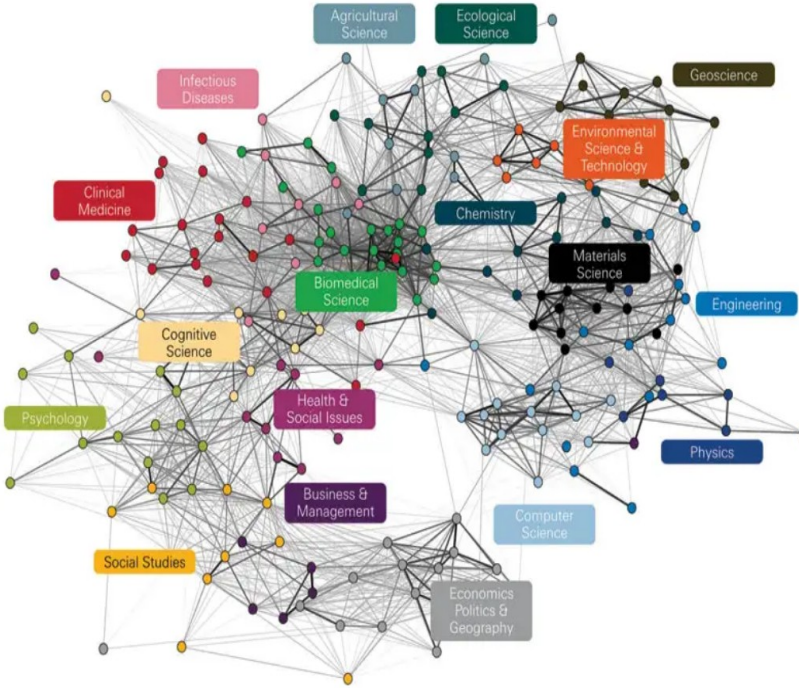




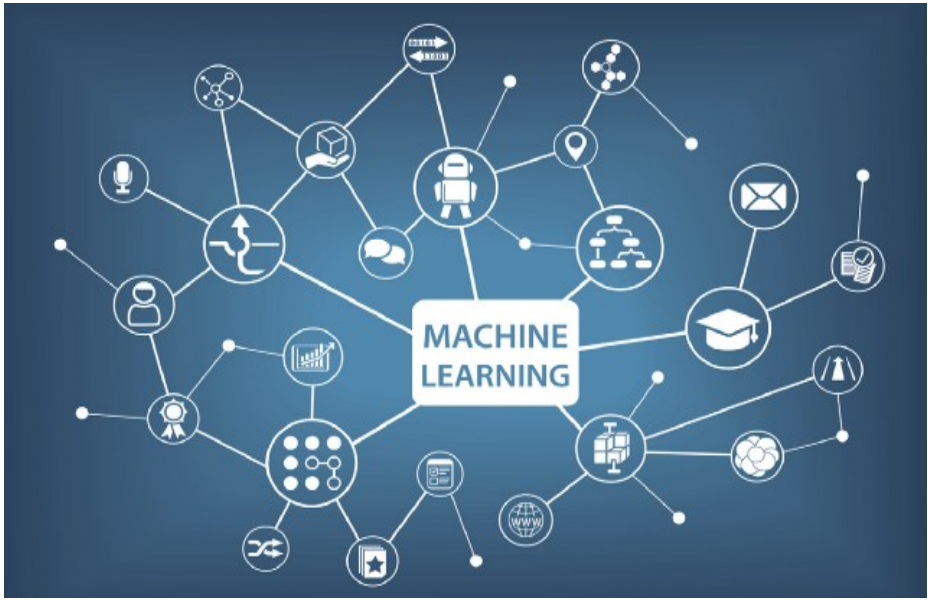
Why am I excited to be at BayesLund?

Diverse Audience

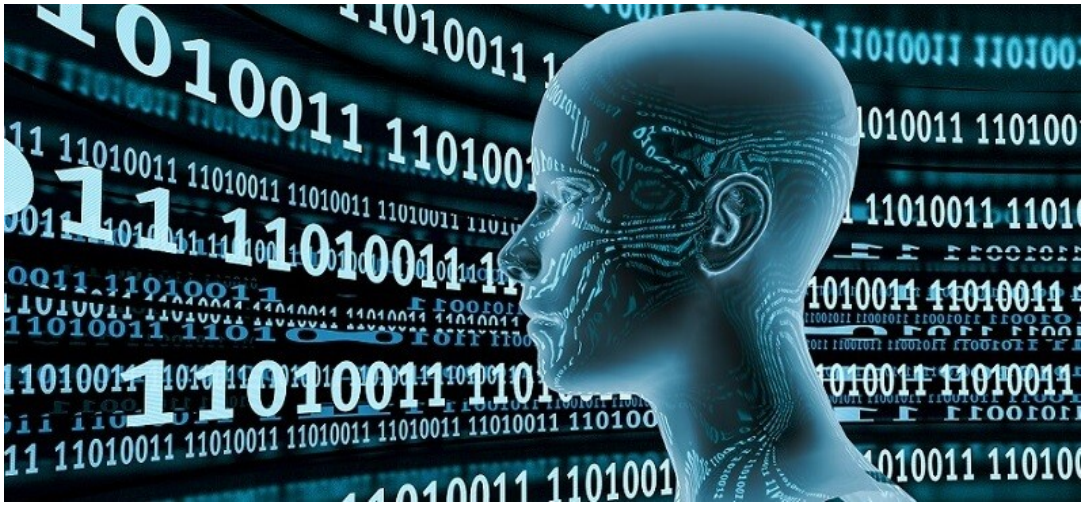
Different Sciences



Machine Learning for Everyone

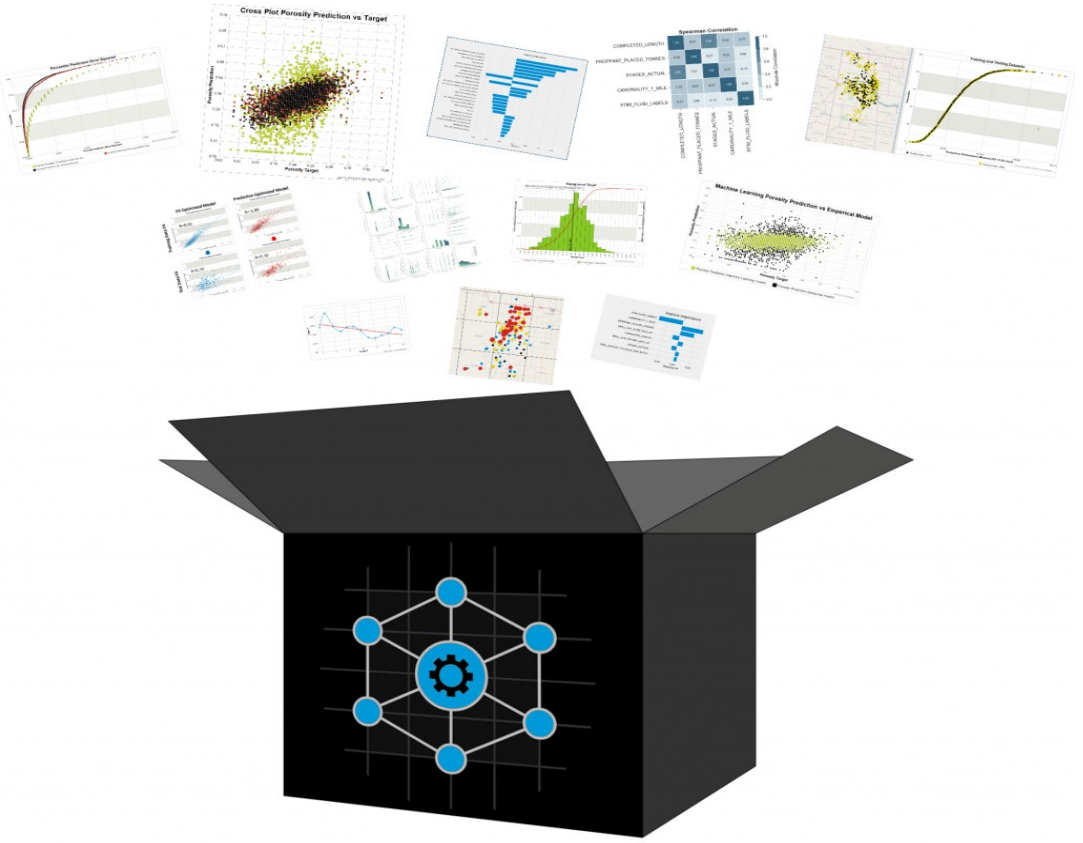


Stereotypes about Machine Learning



Machine Learning has nothing to do with machines

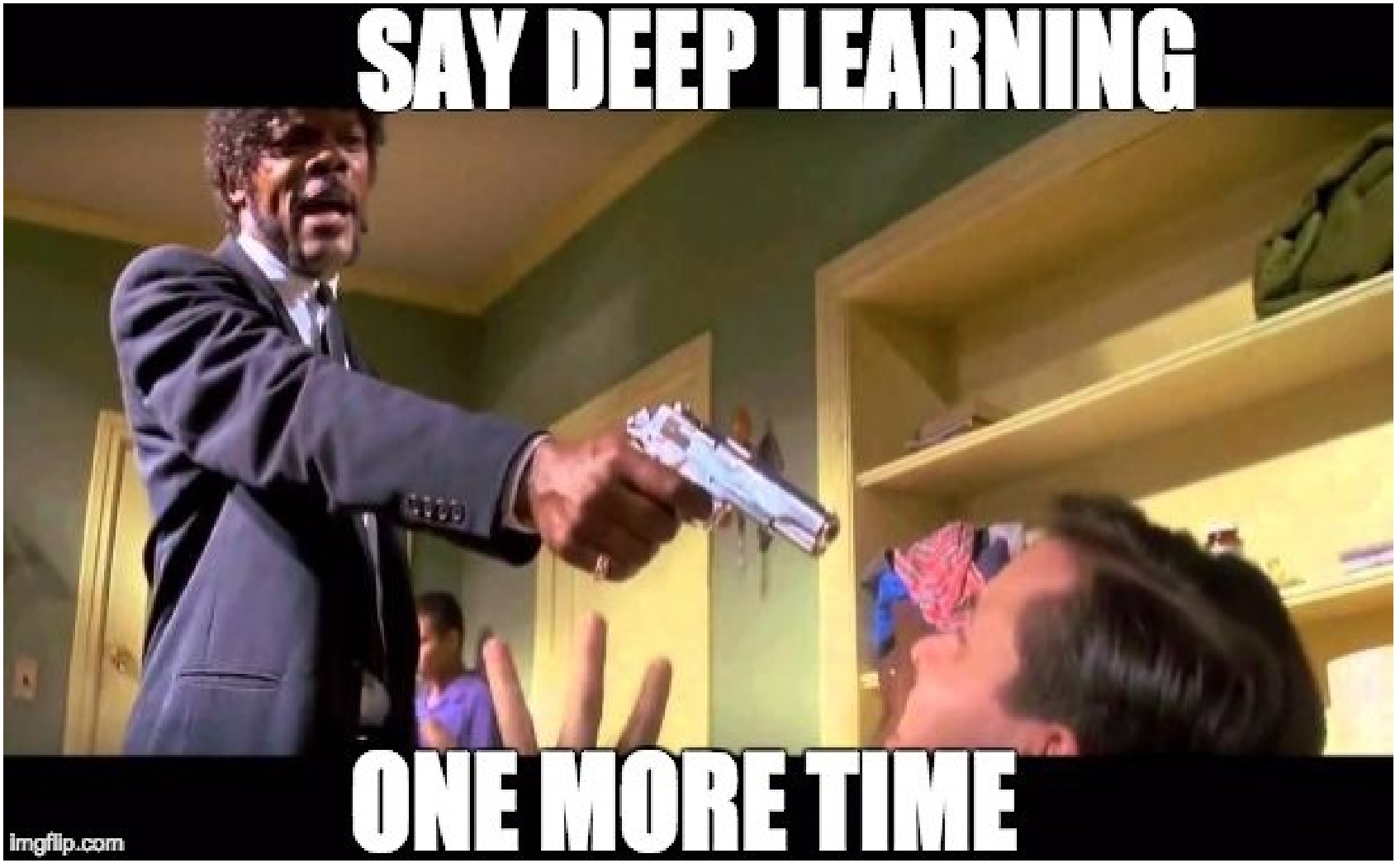
… but mathematics



Machine Learning is not a black box

… because it selects biomarkers

Why such a hype about Deep Learning?

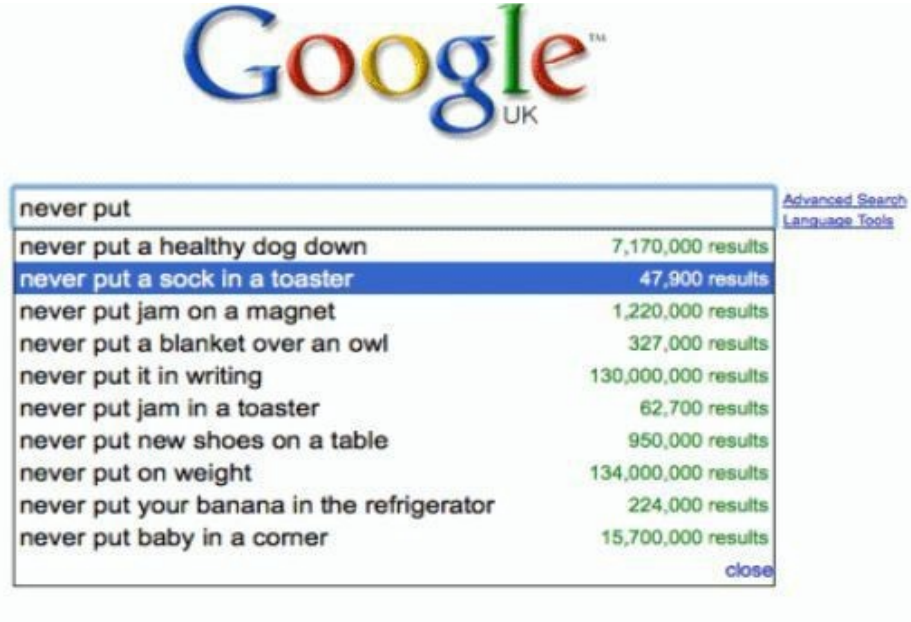


Because Deep Learning delivers state-of-the-art results

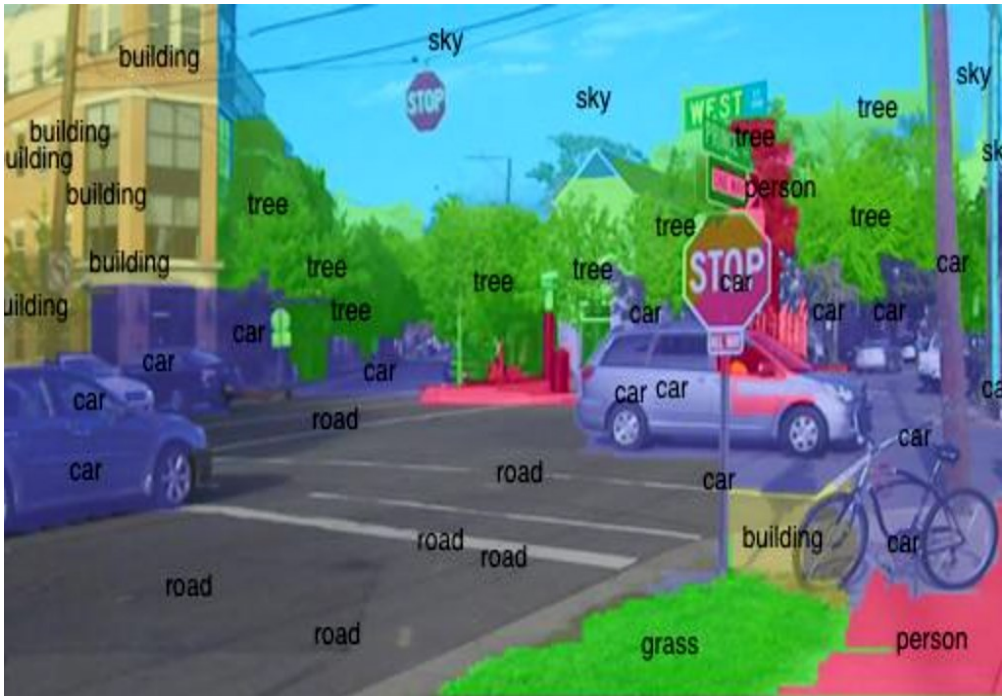
Promises of Deep Learning for Society

Self-Driving Cars

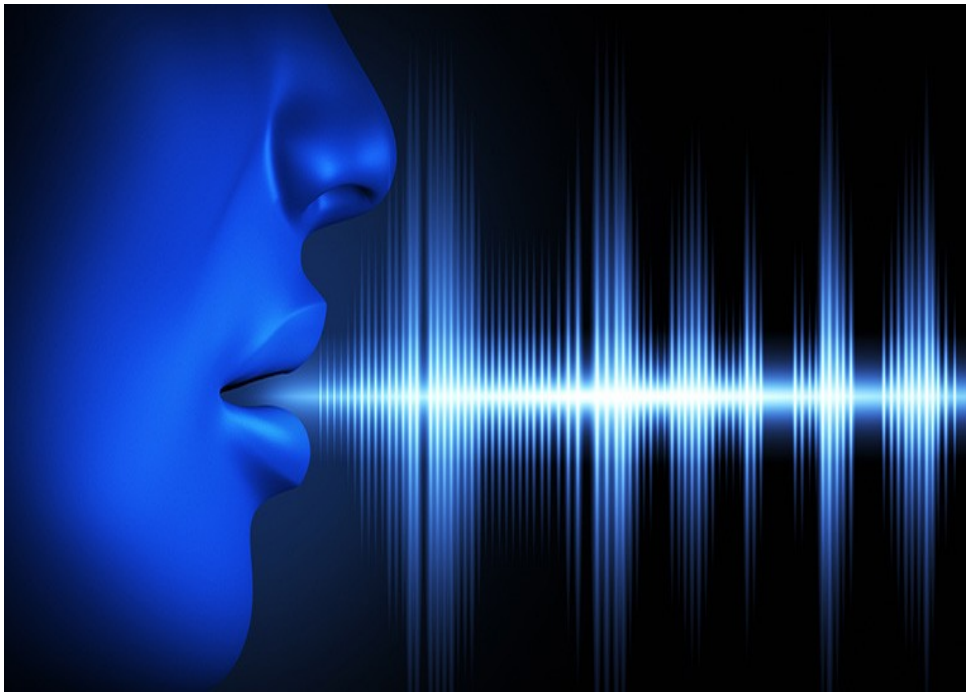
Natural Language Processing



Computer Vision



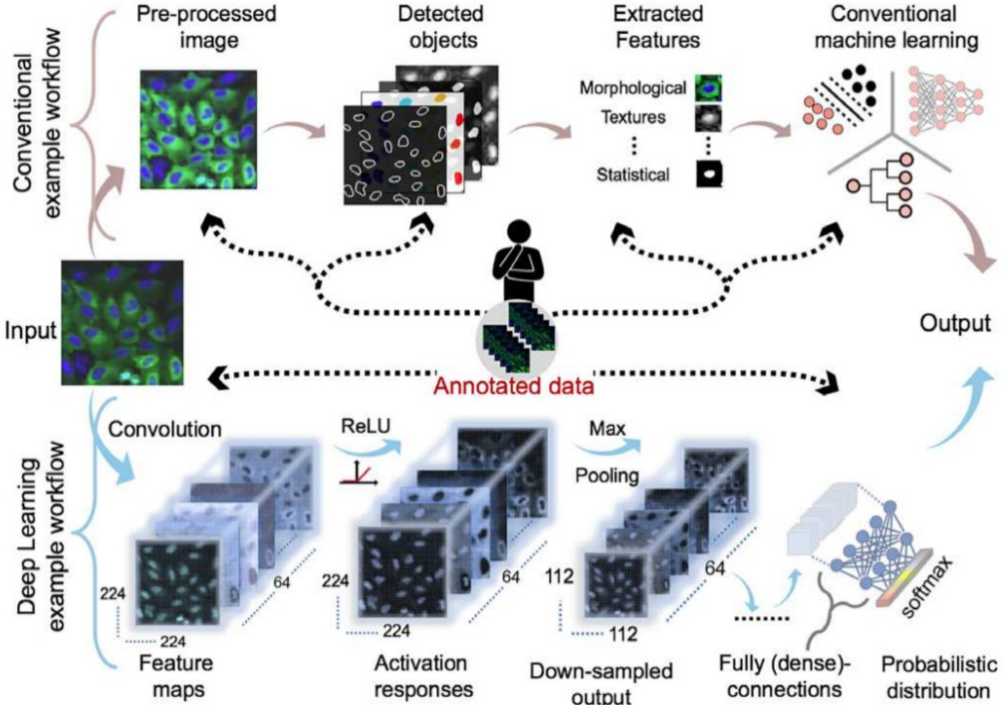
Speech Recognition

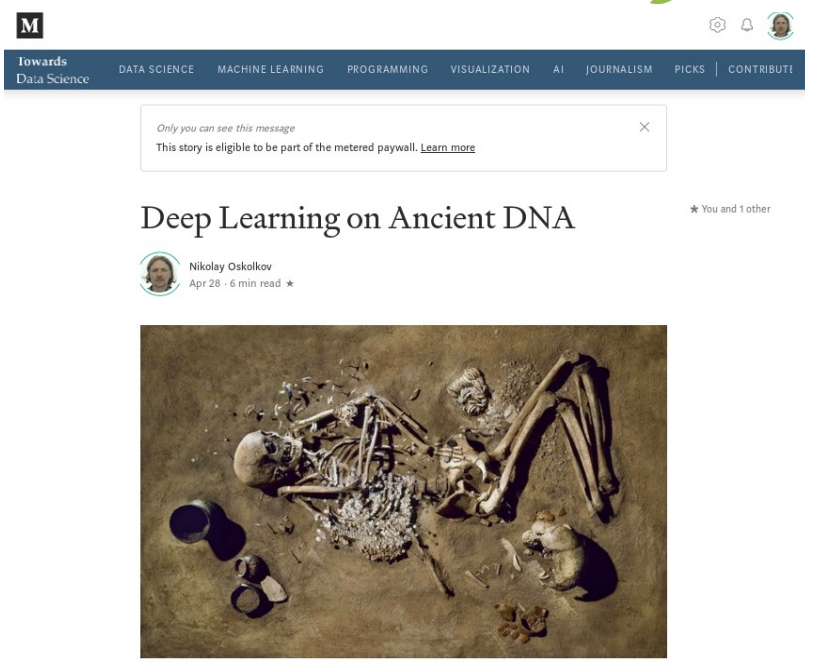


Promises of Deep Learning for Life Sciences

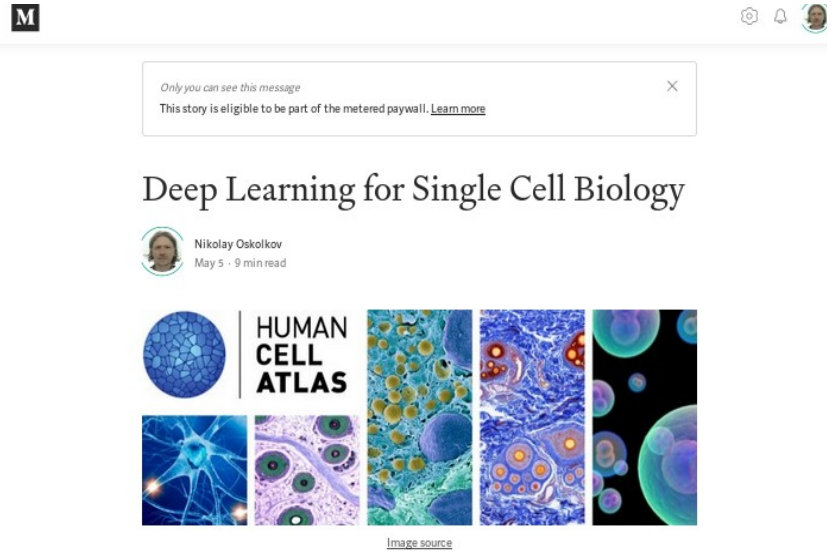
Clinical Diagnostics

Image Cytometry





Reconstructing the Human Past with Deep Learning



Resolving cellular architectures by Deep Learning

Deep Learning is not The Only Tool

P is the number of features (genes, proteins, genetic variants etc.)
N is the number of observations (samples, cells, nucleotides etc.)

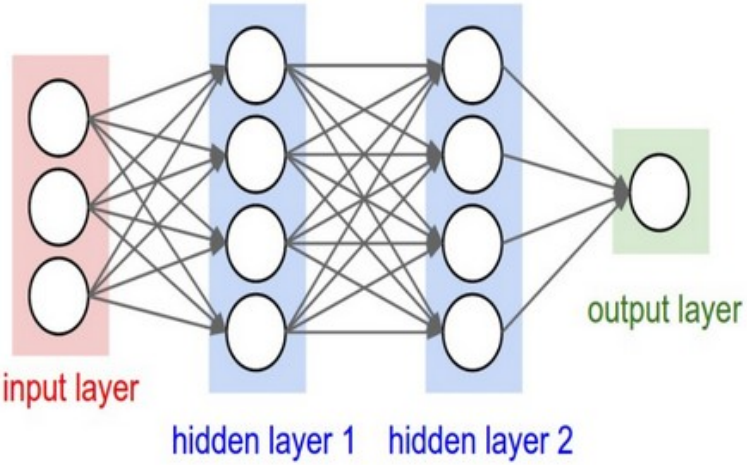
Bayesianism

P >> N

Frequentism

P ~ N

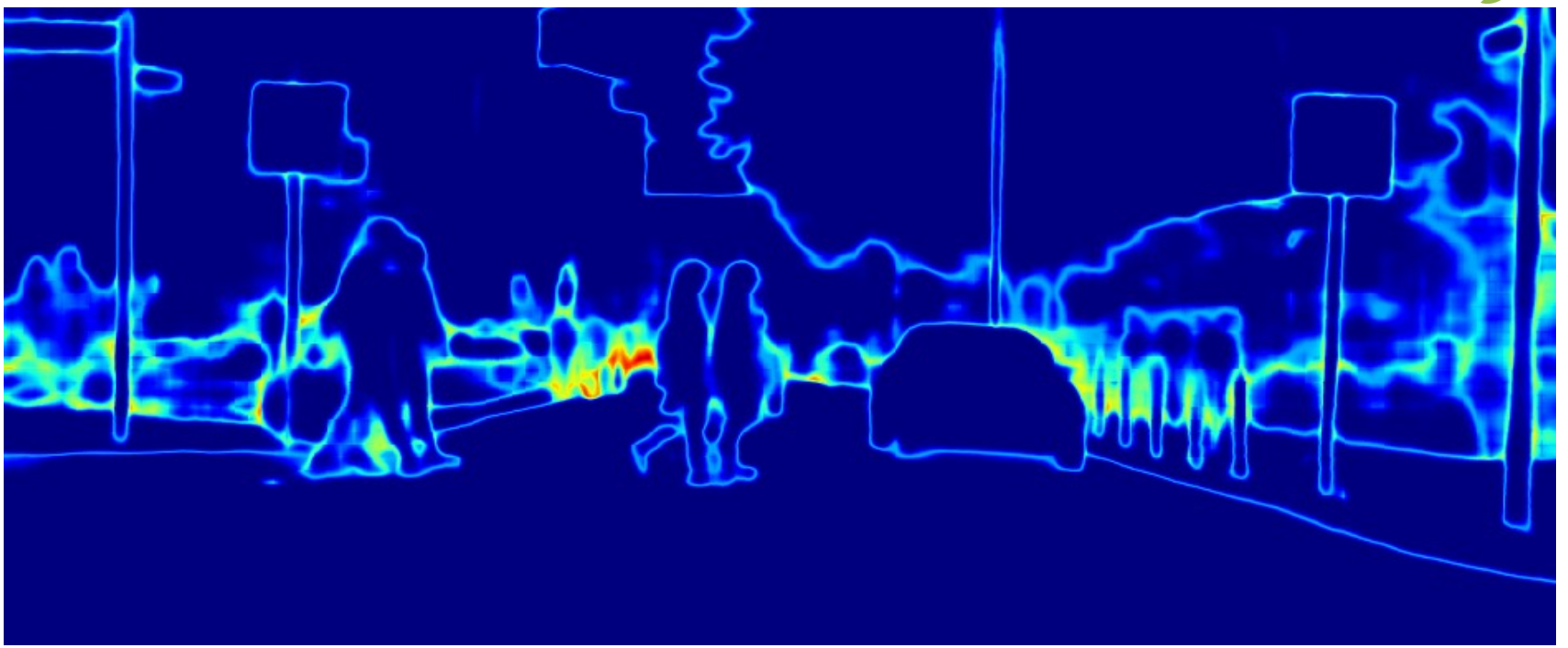
Deep Learning



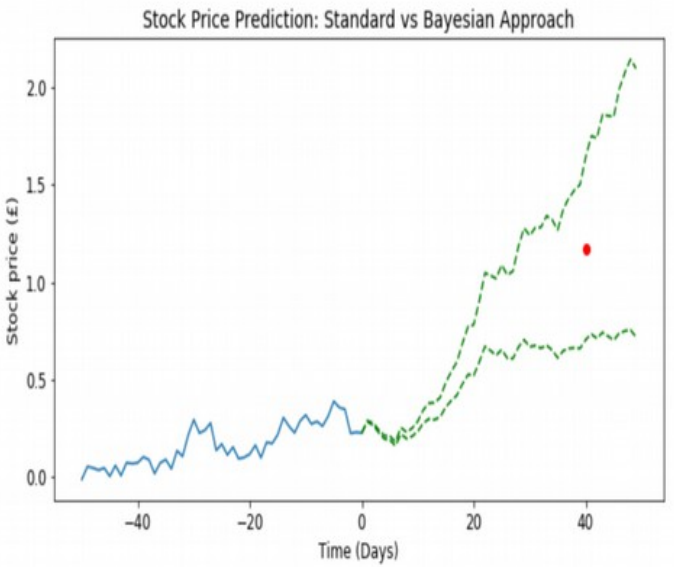
P << N

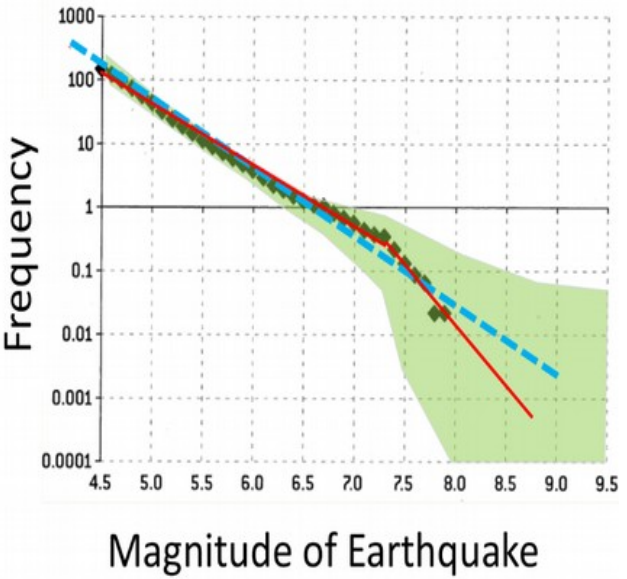
Amount of Data

Deep Learning is not Good Enough

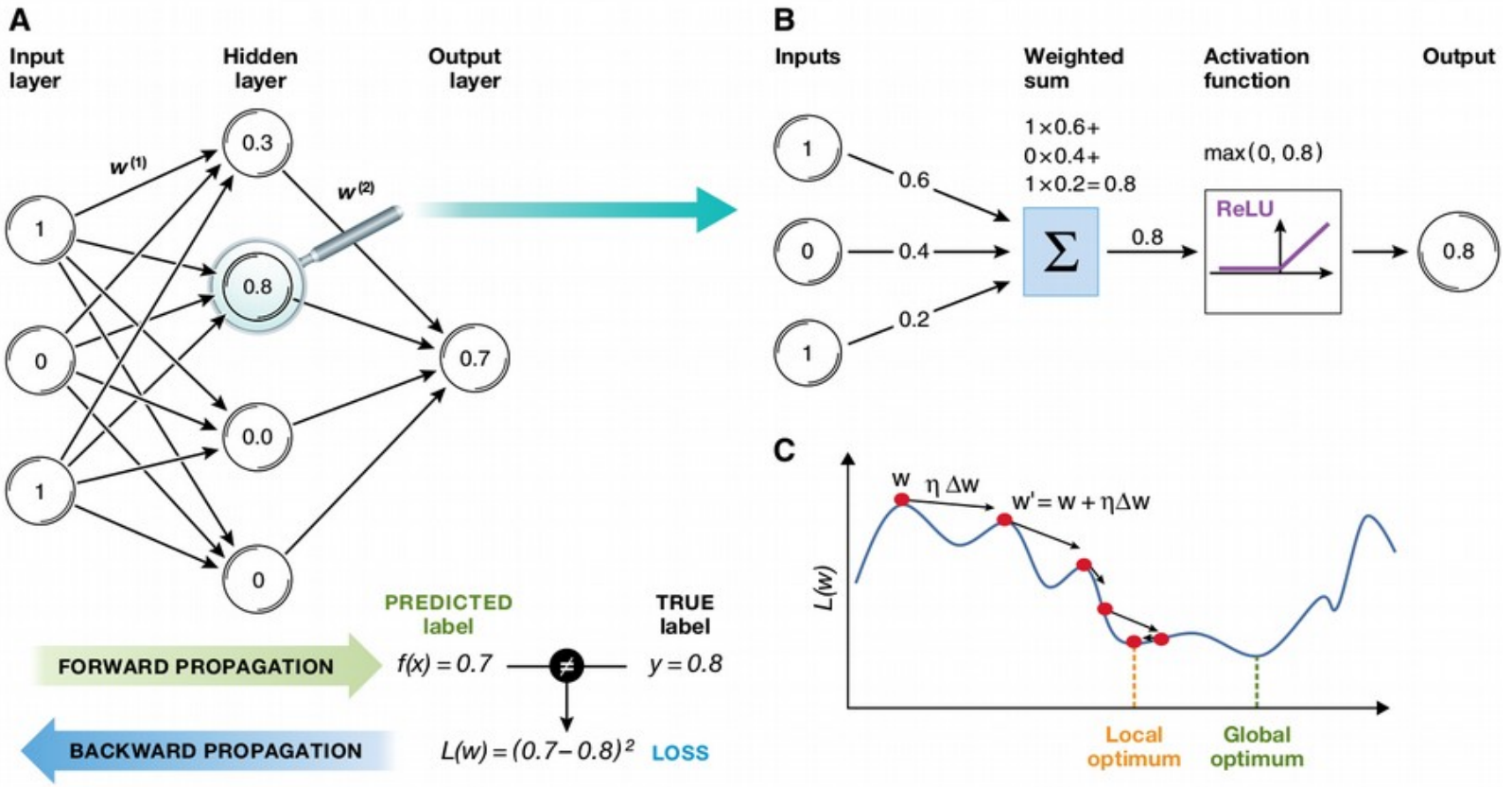


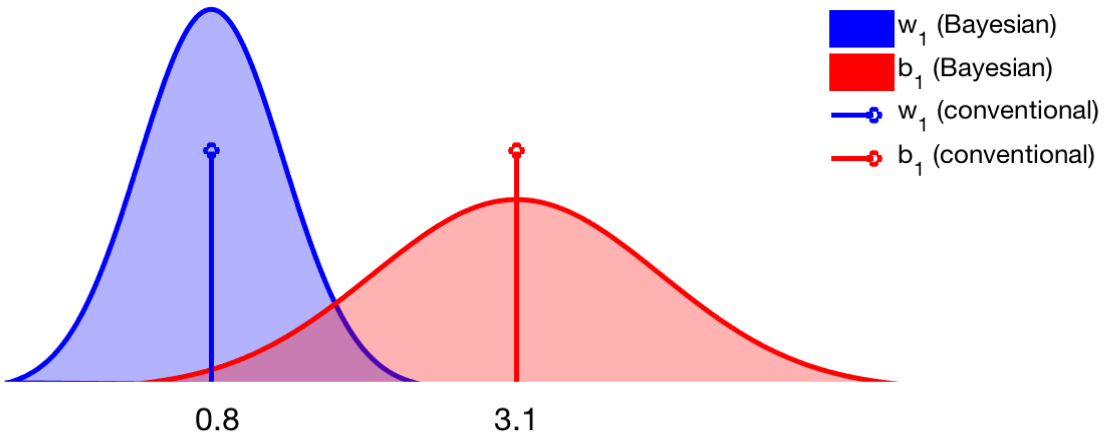
Intelligence is to know how much you do not know





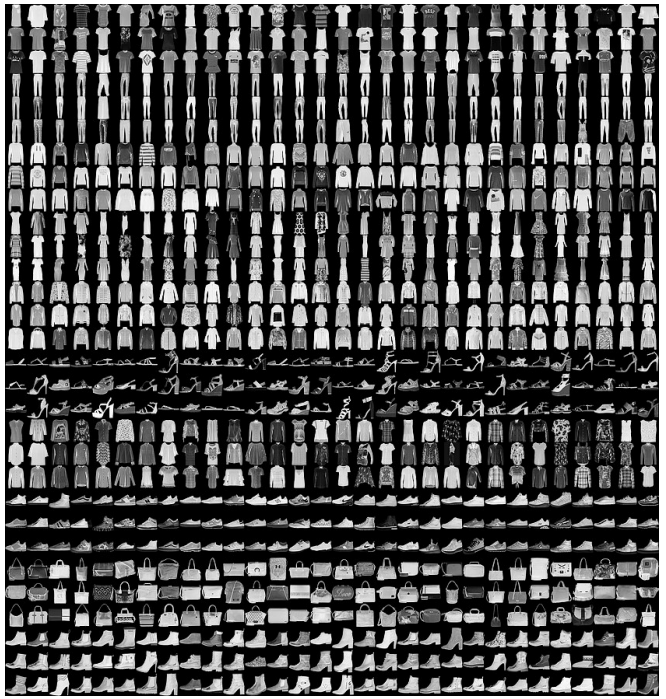
What is Bayesian Deep Learning?





Frequentist Image Recognition

Fashion MNIST



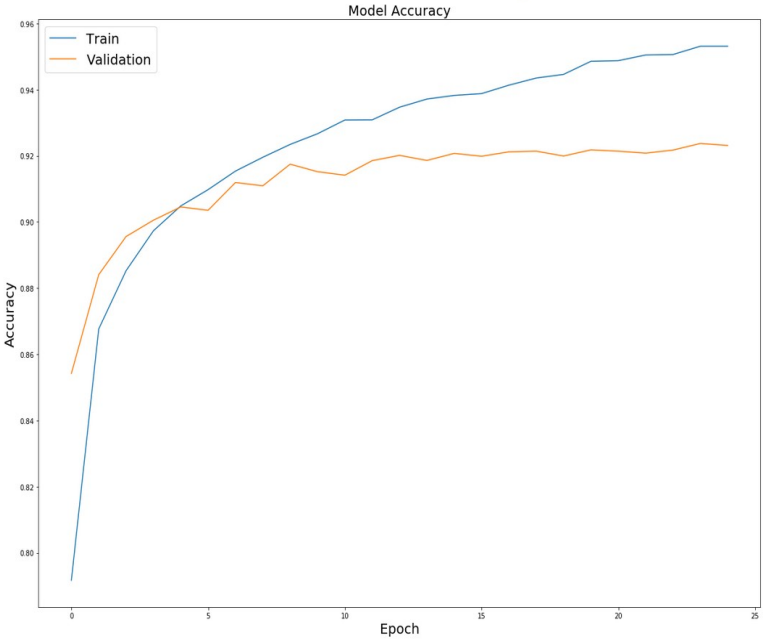
```
In [24]: # normalize inputs from 0-255 to 0.0-1.0
X_train = X_train.reshape(X_train.shape[0], 1, 28, 28).astype('float32')
X_test = X_test.reshape(X_test.shape[0], 1, 28, 28).astype('float32')
X_train = X_train / 255.0
X_test = X_test / 255.0

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

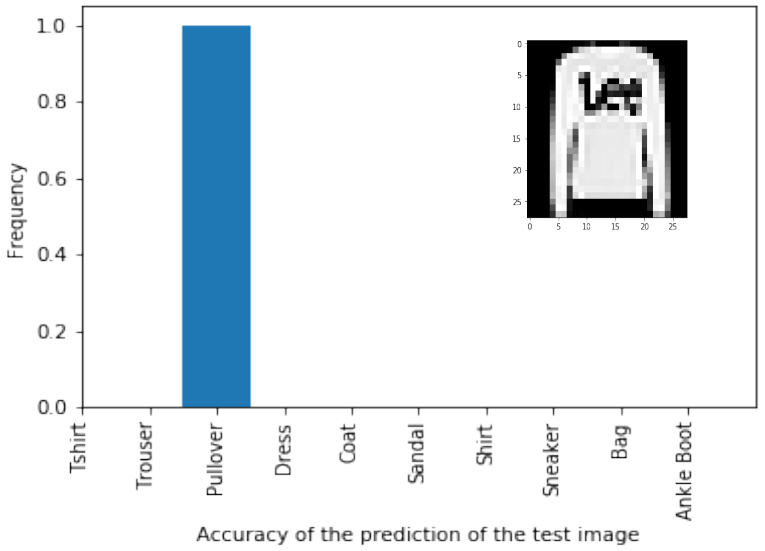
Total params: 3,226,474
Trainable params: 3,226,474
Non-trainable params: 0

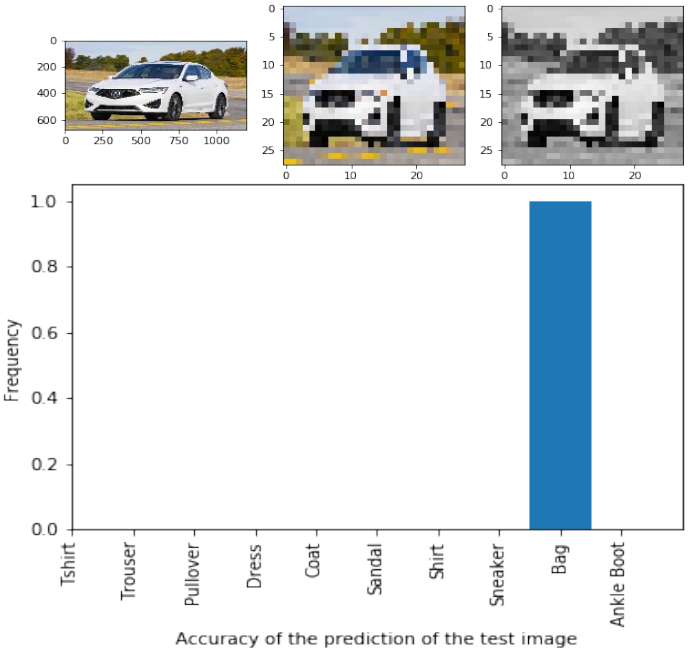
None

```
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



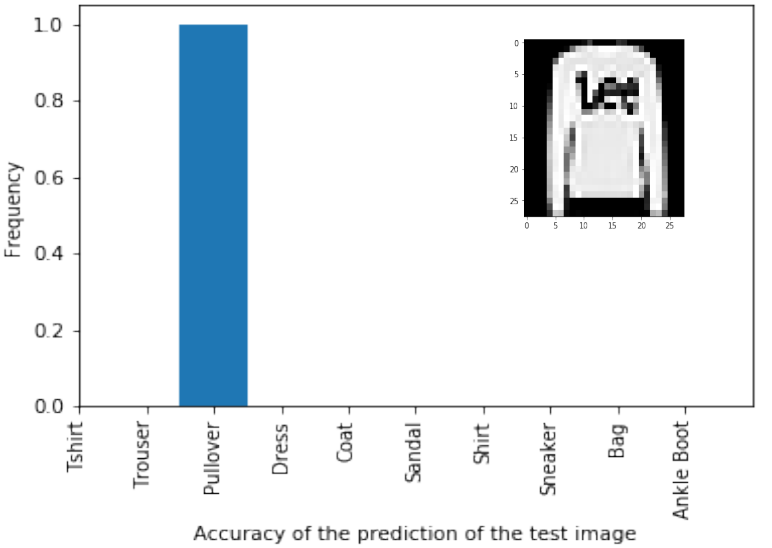


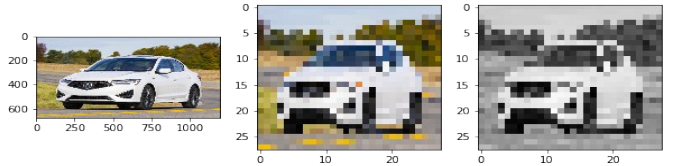
Bayesian Image Recognition

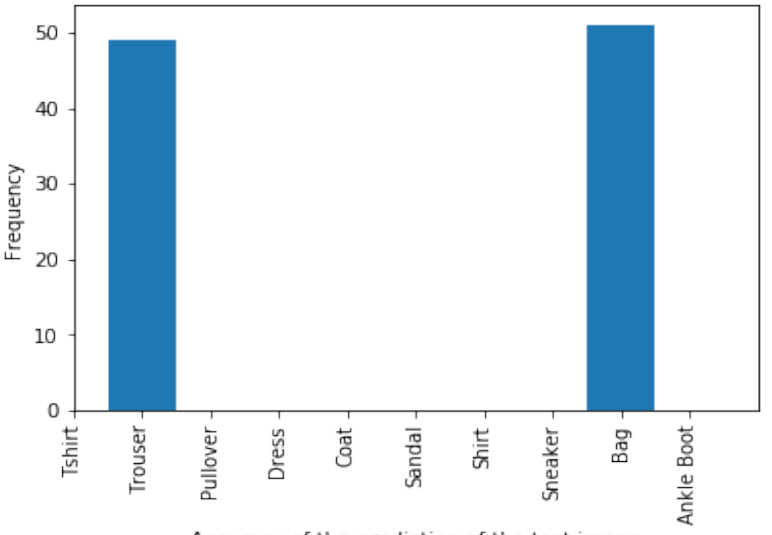
PyMC3, Edward, TensorFlow Probability

```
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})
         # Initialise 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







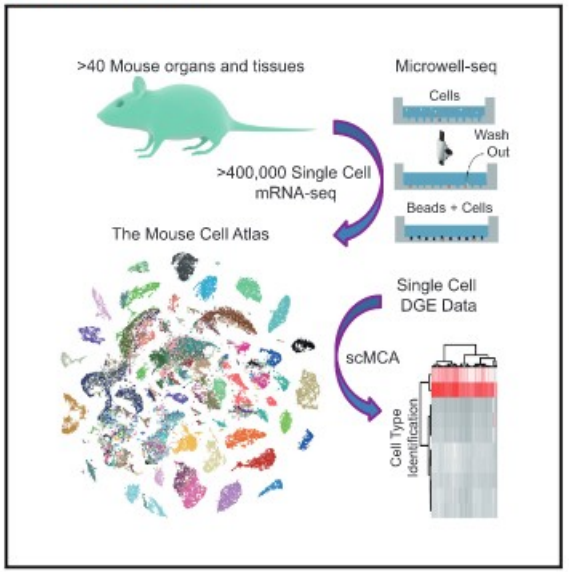
Biomedical Big Data in Single Cell

Resource

Cell

Mapping the Mouse Cell Atlas by Microwell-Seq

Graphical Abstract



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In Brief

Development of Microwell-seq allows construction of a mouse cell atlas at the single-cell level with a high-throughput and low-cost platform.

Highlights

- Development of Microwell-seq, a high-throughput and low-cost scRNA-seq platform
- Construction of a single-cell mouse cell atlas (scMCA) covering major cell types
- Characterization of cellular heterogeneity with minimal batch effect
- Characterization of cross-tissue cellular network at the single-cell level

Data Resources

GSE108097

Han et al., 2018, Cell 172, 1091–1107
February 22, 2018 © 2018 Elsevier Inc.
https://doi.org/10.1016/j.cell.2018.02.001

CellPress

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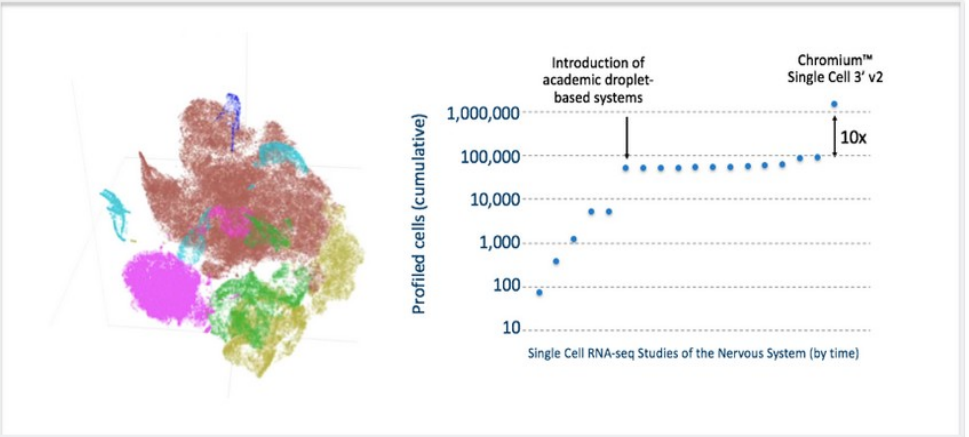


Our 1.3 million single cell dataset is ready to download

0 KUDOS

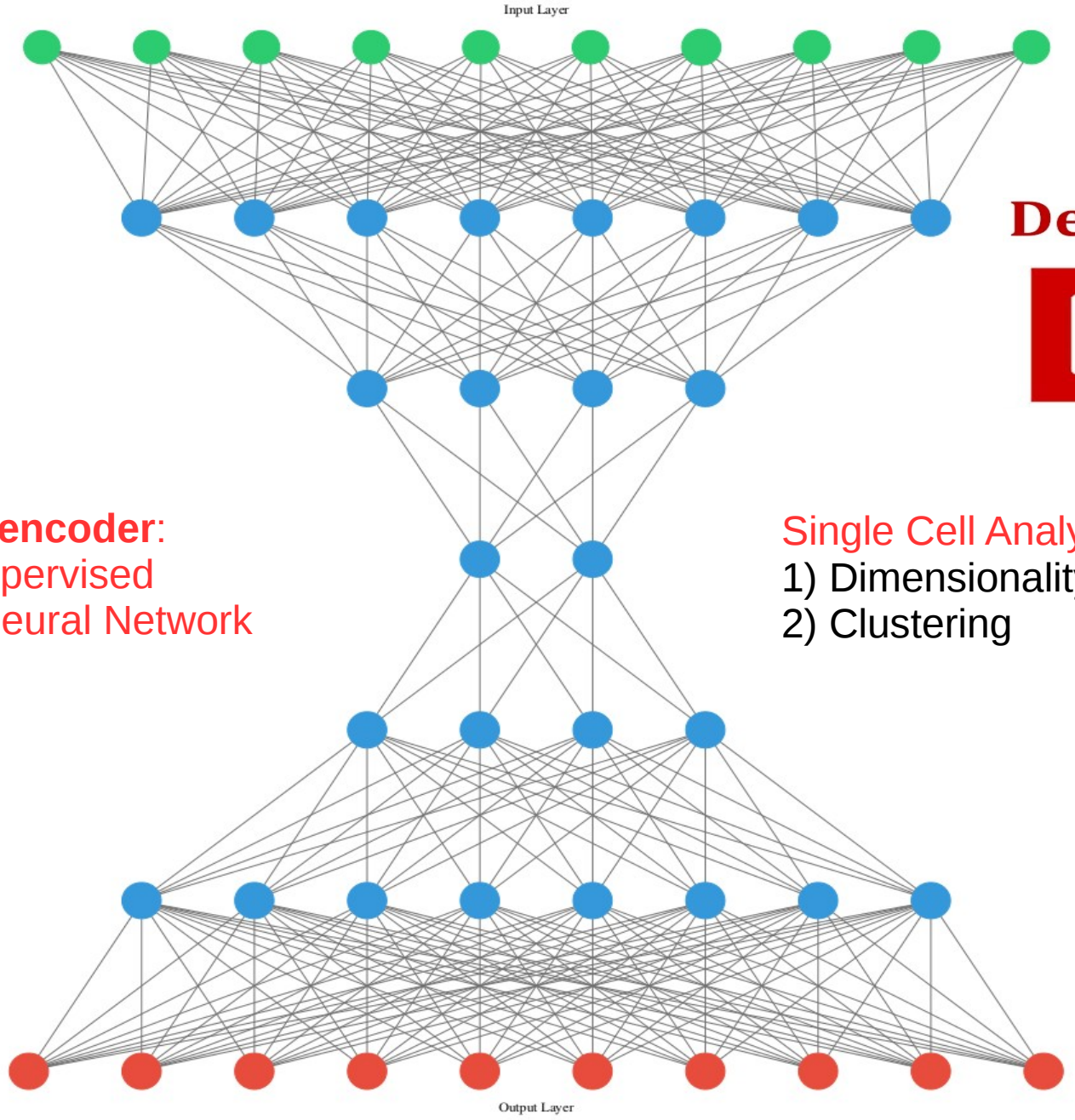
POSTED BY: grace-10x, on Feb 21, 2017 at 2:28 PM

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.

Paradise for Deep Learning!

Deep Learning for Single Cell

Non-Linearity of Single Cells OMICs



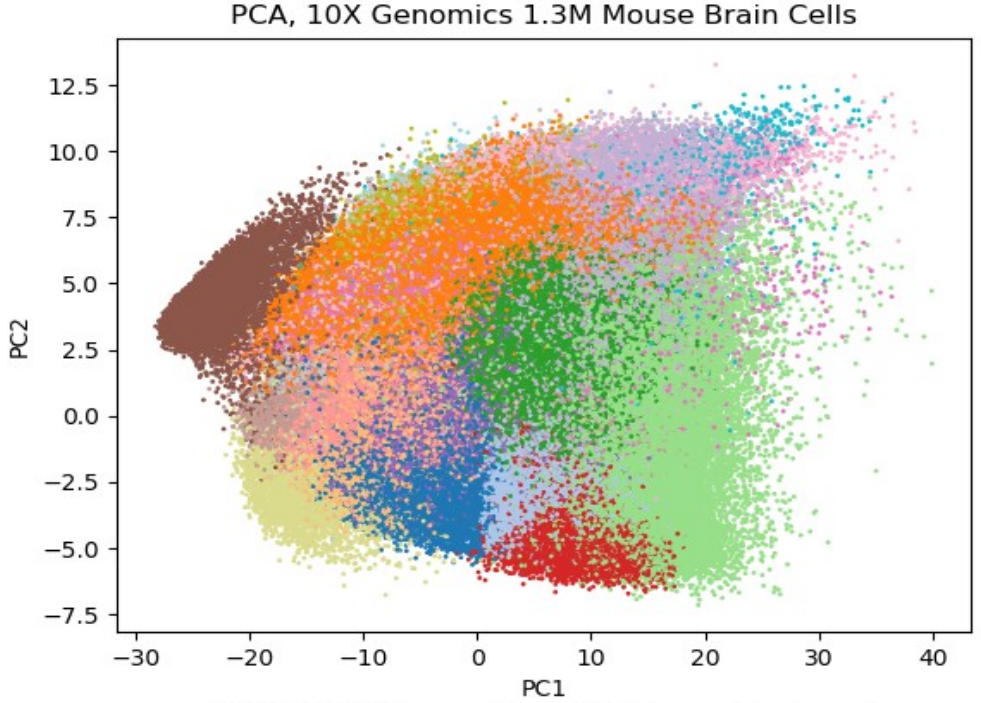
Autoencoder:
Unsupervised
Artificial Neural Network

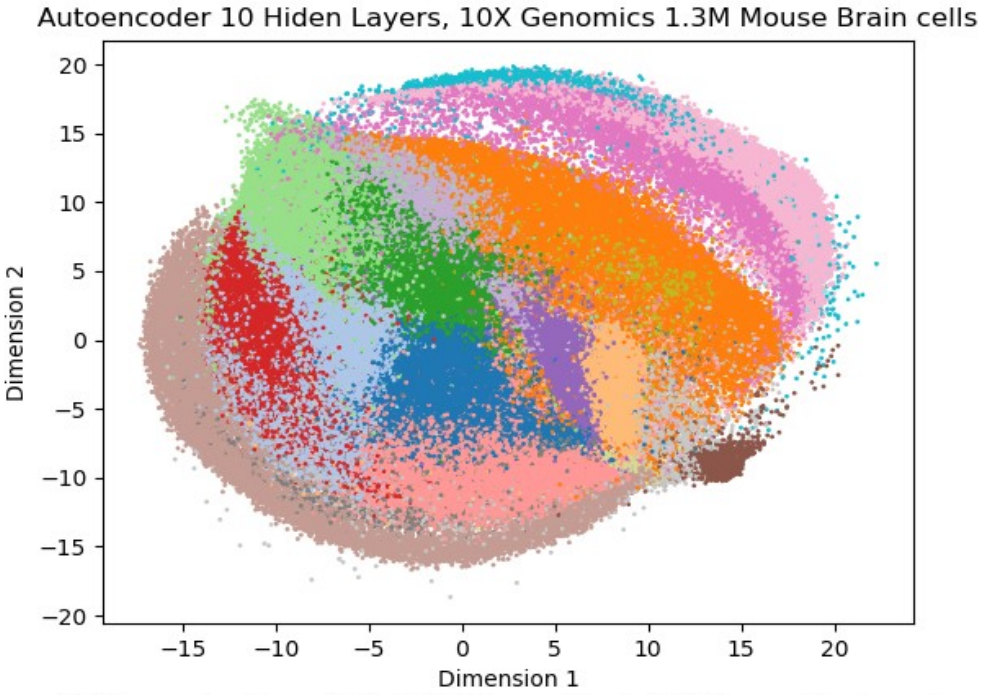
Deep Learning

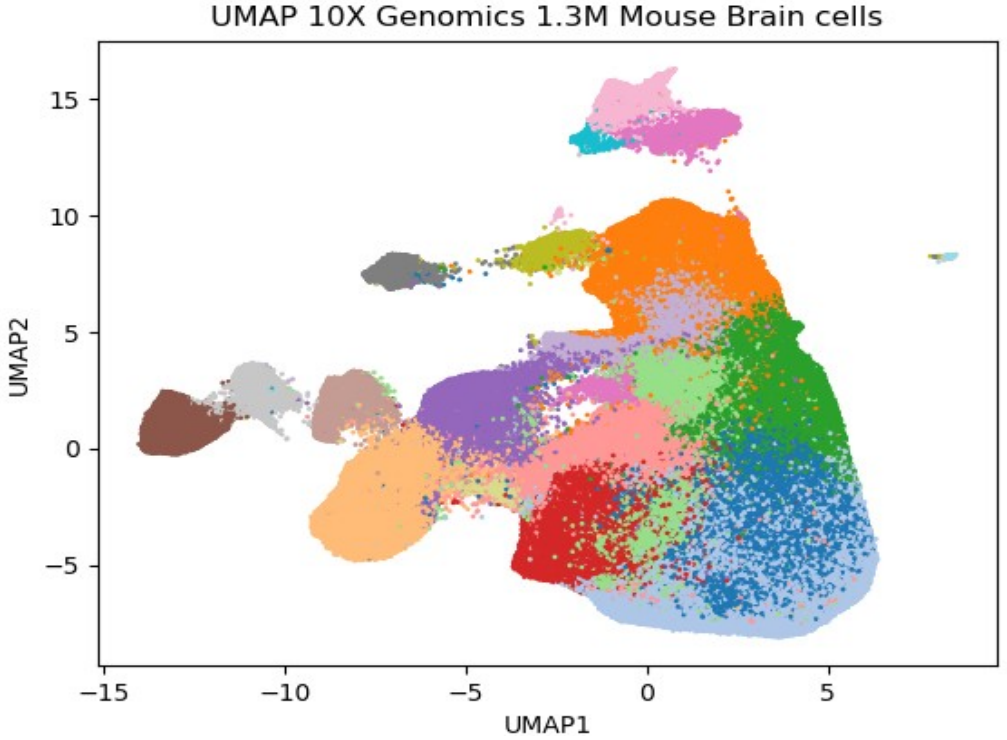
K + TensorFlow

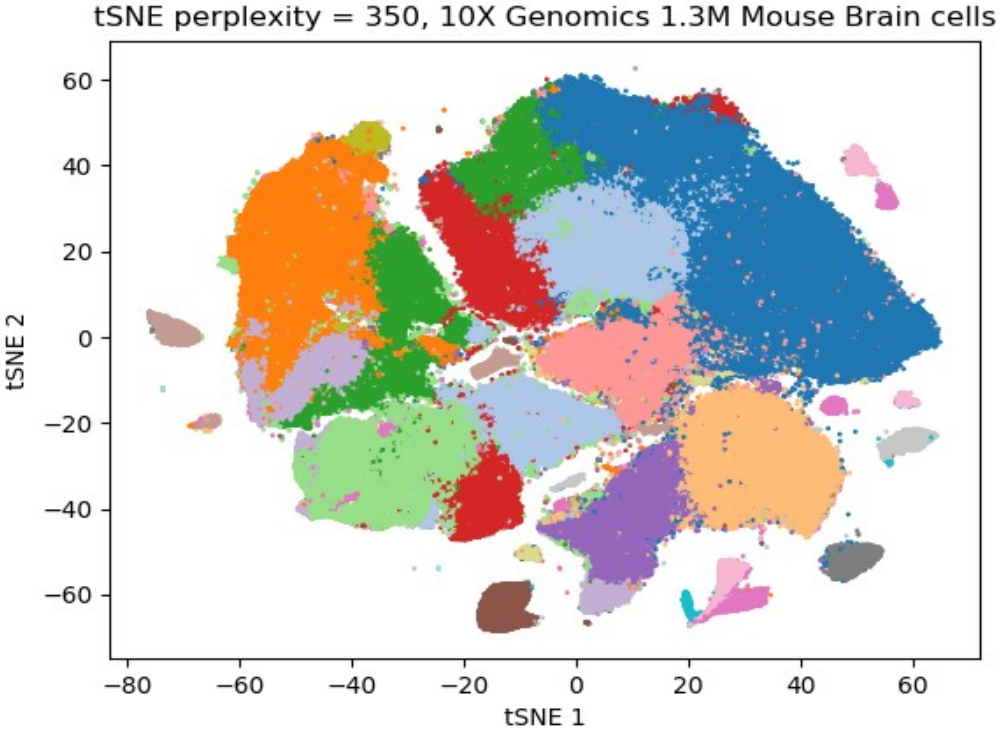
Single Cell Analysis is Unsupervised
1) Dimensionality Reduction
2) Clustering

10X Genomics Mouse Brain: scRNAseq, 1.3M cells

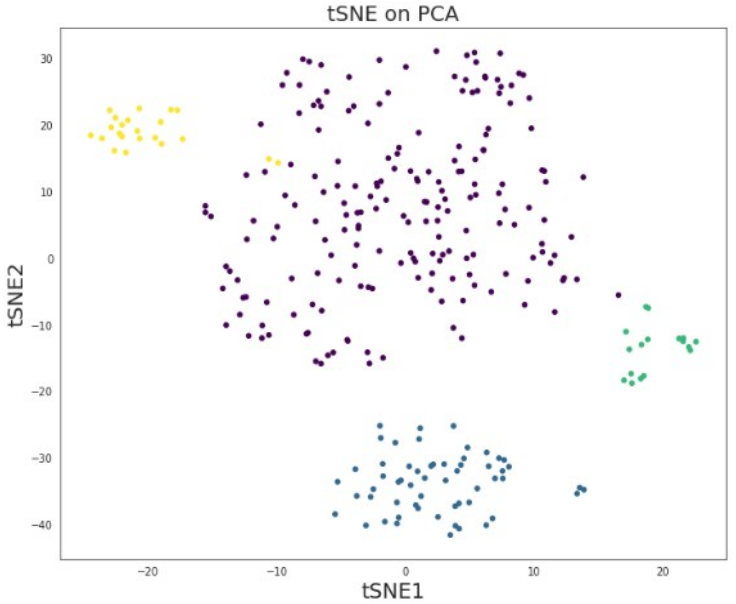


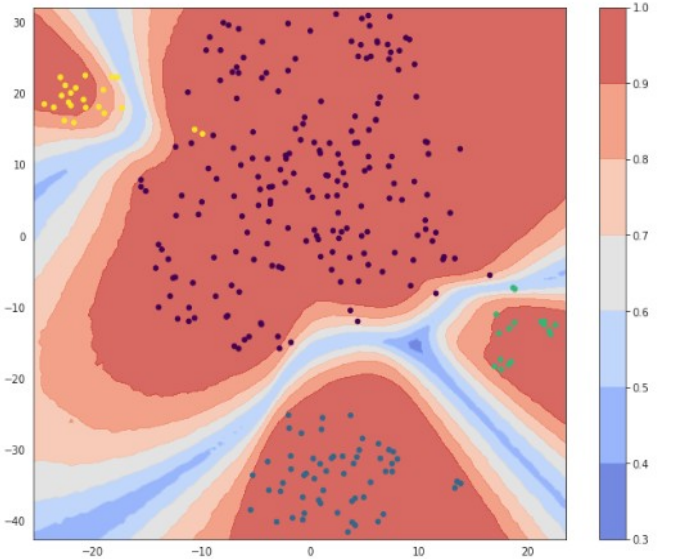


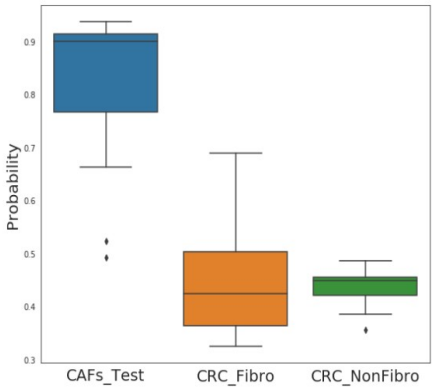


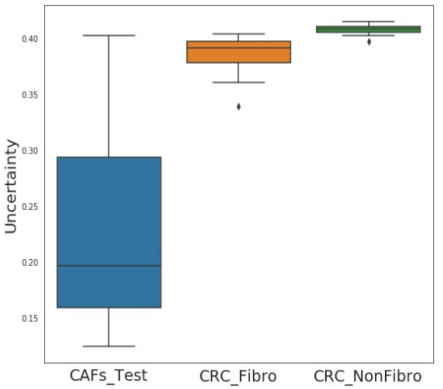


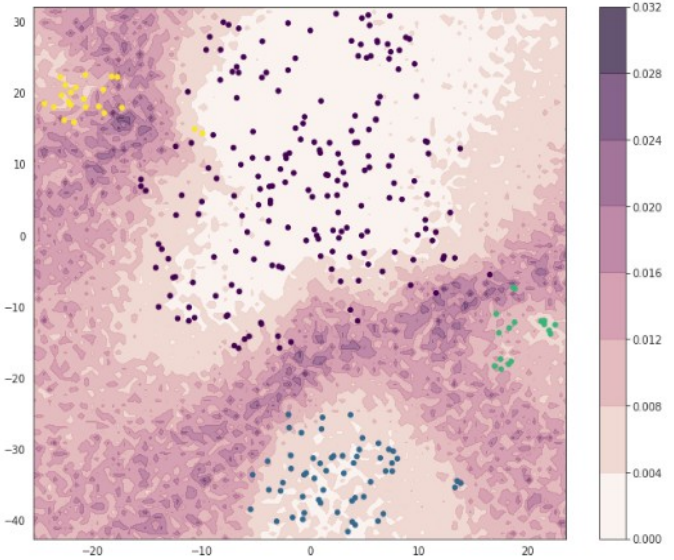
Bayesian Deep Learning on Cancer Associated Fibroblasts (CAFs)











```
In [64]: from scipy.stats import mannwhitneyu
         stat, p = mannwhitneyu([np.max(i) for i in np.array(prob_crc_fibro_list).mean(axis=0)],
                                [np.max(i) for i in np.array(prob_crc_all_cells_minus_fibro_list).mean(axis=0)])
         print('Statistics = %.3f, p = %.3f' % (stat, p))

         Statistics = 123.000, p = 0.235

In [65]: from scipy.stats import mannwhitneyu
         stat, p = mannwhitneyu([np.max(i) for i in np.array(prob_crc_fibro_list).std(axis=0)],
                                [np.max(i) for i in np.array(prob_crc_all_cells_minus_fibro_list).std(axis=0)])
         print('Statistics = %.3f, p = %.10f' % (stat, p))

         Statistics = 8.000, p = 0.0000014045
```

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

Superior for predictions on unseen data

National Bioinformatics Infrastructure Sweden (NBIS)

Knut och Alice Wallenbergs Stiftelse

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