BCB726

Lecture 1

October 20, 2025

Welcome and Logistics

- 10 meetings here in MEJ 3116 on Mondays and Wednesdays from 11-12:15pm until Monday November 19
- Lectures will be taught primarily by Natalie, Alex, and Dhuvi (your TA!)
- Class notes and schedule on our course page `https://github.com/natalies-teaching/BCB726_Fall2025` and we will also use canvas for homework submissions and discussions
- Components of final grade.
  - Two homework assignments (20% each, 40% in total). These will be practical and focused on implementation
  - 60 % will be based on class attendance. You must attend 8/10 lectures. If you need to miss class please communicate with me as soon as possible

Topics and what to expect

- First half of course $\rightarrow$ more classical topics and ML fundamentals
  - classical unsupervised and supervised learning
  - components of the optimization problems happening under the hood
  - practical considerations (e.g. cross-validation, bootstrapping, data leakage) to keep in mind when training your models to facilitate robust scientific discovery.
- Second half of course $\rightarrow$ more modern ML topics
  - Deep learning basics, explainability, large language models
- Implementation: we will use standard libraries such as scikit-learn and pytorch. You will use modal notebooks for GPU computing.

Resources

- Office hours with Dhuvi (time TBD). Dhuvi's email $\rightarrow$ dkarthikeyan1@.unc.edu
- Textbooks/ free resources listed on our course page
  - Murphy book (all encompassing, CS-y, practical, and implementation focused) : `https://probml.github.io/pml-book/book1.html`

Some motivating applications of ML in biomedicine....

Creating diagnostic predictors of disease

Ideally, we want to train models of disease status based on samples from donors in a training or *discovery cohort* and evaluate the model on a completely independent validation (v) cohort. A model that performs well on an independent cohort suggests having discovered a diagnostic for future studies.

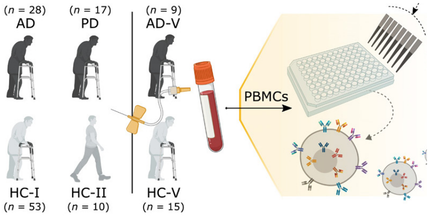


Figure: from Phongpreecha *et al.* Science Advances. 2020

ML approaches can be used to make hypotheses about biological mechanisms

A trained model can be used to evaluate how cell-type specific contributions to a donor's phenotype. This example is related to aging and therefore highlights cell-types that are likely to have a pro-aging effect.

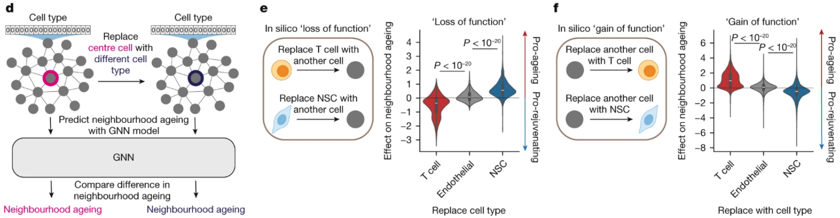


Figure: from Sun *et al.* Nature. 2025.

Vocabulary for discussing machine learning problems

- Data matrix ($\mathbf{X}$) is an array of N **data instances** $\times$ d **features** measured about these data instances. We often say this matrix, $\mathbf{X} \in \mathbb{R}^{N \times d}$
  - Example : If we are measuring 20K (features) in 100 mice (data instances), this would produce a matrix $\mathbf{X} \in \mathbb{R}^{100 \times 20K}$
- Response variable or target variable, $\mathbf{Y} \in \mathbb{R}^{N \times 1}$ is the vector of labels for each of our N data instances
  - $\mathbf{Y} \in \mathbb{R}^{100 \times 1}$ could be the ages of each of the 100 mice.

Vocabulary for discussing ML problems (continued)

- Parameters : This is the collection of learnable values that help to translate the *input features* to the target variable.
  - Example : regression coefficients (β), which provide a weight for each input feature. When you fit a regression model, you are trying to learn an appropriate β so that $\mathbf{X}\beta$ approximates $\mathbf{Y}$ as closely as possible.
- Hyperparameters : additional parameters that dictate how to set up the model (e.g. a regularization parameter)
- **Training** refers to optimizing the parameters (e.g. specifying the model) on a collection of data instances.
- Inference or Prediction: Can the model be used in a useful way after it has been trained on a collection of unseen data instances.

Types of learning

- **Supervised** : Leverage labels of data instances to learn parameters. We are training by showing several instances of a predicted data input and what the output label is.
  - diagnostic test trained to predict treatment response based on an omic modality from many donors
  - training a model to predict protein structure from sequence
  - training a model to predict age based on methylation signatures in the blood.
- **Unsupervised** : Looking for patterns across data instances based on features. Usually involves clustering or dimensionality reduction.
  - Clustering cells based on gene or protein expression patterns to identify cell-types
  - Dimensionality reduction (e.g. PCA) of donors based on a large number of measured omics features to identify subgroups of donors. Then investigate sub-groups to find drivers of variation.

Unsupervised learning example

Dimensionality reduction refers to the fact that cells here, which were originally in a $\sim$ 20K dimensional space are represented in two-dimensions. **Clustering** refers to the computationally-determined partitioning of data points (cells), based on all measured features. Often we actually first reduce the dimensionality of cells to do the clustering [1].

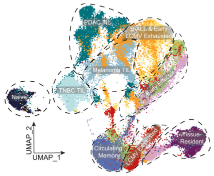


Figure: from Green *et al.* Immunity. 2025

[1] You should not be clustering in the 2d UMAP or tSNE space

Regression as another supervised learning example

Models of age were trained with supervision (e.g. using ages of donors) from single-cell measurements. The model can be used to predict the age in a new donor.

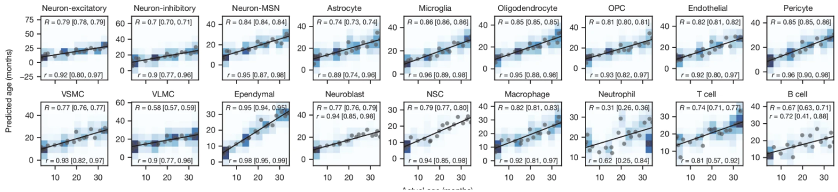
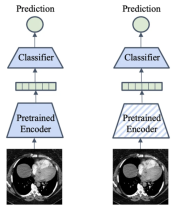


Figure: from Sun *et al.* 2025. Shown here are predicted ages under cell-type specific *aging clocks*, or machine learning models of age.

How do we create features about our data instances

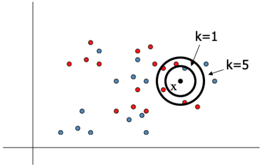
- **Feature engineering.** We define or measure features about each data instance that we suspect are important for differentiating classes in the data
  - Canonical example : omics features measured for each data instance.
  - Summaries of the data : for example, counts across cell-types.
- **Feature learning:** Learning representations of the data.
  - Here, features represent mathematically abstract dimensions that were trained to be helpful for some task, such as, classification



(e) End-to-end Fine-tuning **(f) Extract feature for classifier**

The simplest way to label data : *k*-nearest neighbors classification

If we have an unlabeled point, x, we can simply classify x, according to the labels of its k nearest neighbors. The higher k is, the less of a possibility we have of making a prediction based on noise.



[2]

Figure: In this example, we see that we would make different predictions for the black point, depending on if we had used 1 or 5 nearest neighbors.

[2] from `https://people.csail.mit.edu/dsontag/courses/ml12/slides/lecture10.pdf`

Advantages and disadvantages of this simple approach

- If the data are well separated, then a kNN classifier should do a great job.
- The query time could be expensive.
  - We need a distance metric to quantify the distance of a point in the high-dimensional space to every other point.
  - Then, we need to use these distances to determine the k nearest neighbors.
  - What k should we use?
- This leads us to consider more sophisticated approaches that can be used to learn how to classify or label points in the data.

Mapping data input to label

- Classifiers and regression models specify a set of rules of take input data and map it to a label
- Consider a simple linear classifier, f as, $f(x, W) = Wx + b$
  - x is the data instance
  - w is the weights for the map

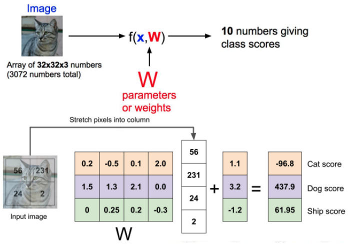


Figure: [3]

[3] from `https://cs231n.stanford.edu/slides/2017/cs231n_2017_lecture3.pdf`.

Training and evaluating the model

- What happens if we train and test the model on the same data?
- The model would effectively memorize the data , but not generalize.
- **Overfitting** is when a complex model with many parameters effectively memorizes the data.

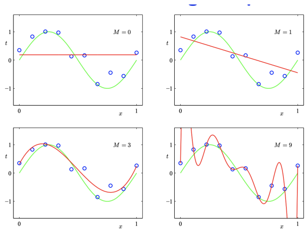


Figure: Higher degree polynomials have increased capacity to overfit the data. [4]

[4] from `https://www.cs.mcgill.ca/~dprecup/courses/ML/Lectures/ml-lecture02.pdf`

Adopting a proper training/testing procedure

- In an ideal setting with enough data points, we would like to divide the data into three disjoint components :
  - **Training:** A set of data points that will be used to learn model parameters.
  - **Validation:** A subset of the training set that can be used to select hyperparameters
  - **Testing:** A never before seen set of data points used to quantify how well the model generalizes and can predict in a new setting.
- For a **classification** task where we are predicting discrete labels, the simplest *metric of success* is **accuracy**, or the fraction of **testing** data points with a correctly predicted label.

What happens across different train/test splits?

Different train/test splits can cause variability in the trained models and lead to varying test-set accuracies. Hence, good to *bootstrap* and compute a mean or median across train/test splits or cross validation folds (more on that later!).

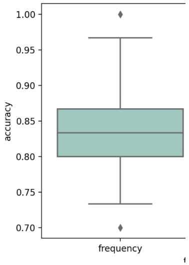
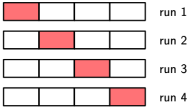


Figure: Each point in the boxplot is the accuracy obtained in an individual train/test split.

Cross validation - common for small datasets in biology

- Divide the dataset into K chunks. Train model K times. In the i-th iteration, train with all of the data except points in the i-th fold and test on data points in the i-th fold.
- Report mean accuracy across folds.



[5]

Figure: Colored instances representing testing chunks of the data across 4 cross-validation folds.

[5] from Pattern recognition and machine learning textbook (Bishop)

Leave-one-out cross validation (LOOCV)

- Realistically in biology, we often have super small datasets (< 30 data points)
- We can make as many folds as there are datapoints. So, for N datapoints, we would essentially be doing N fold cross validation.
- For data point, i, train the model with all N datapoints, *except* i. Test the model on datapoint i.
- Evaluate accuracy as the fraction of datapoints with the correctly predicted label from the iteration where they were in the test set.

Loss functions

- **Loss function:** A quantity that we define, which reflects how well the current model explains explains the labels (either discrete or continuous) on our training data.
- The loss function implements 'book-keeping' for quantifying how much predictions of training images violate their true labels

cat	**3.2**	1.3	2.2
car	5.1	**4.9**	2.5
frog	-1.7	2.0	**-3.1**

[6]

Figure: How do we quantify how good these predictions are? Each number in the matrix the output given by the linear model for $f(x, W) = Wx + b$.

[6] from `https://cs231n.stanford.edu/slides/2017/cs231n_2017_lecture3.pdf`.

Loss function notation

- Consider your dataset of data points and labels $\{(x_i, y_i)\}_{i=1}^{N}$
  - x_i is image i, y_i is the label for image i.
- The loss function for the linear model in our example is computed across all data points as, $L = \frac{1}{N}\sum_i L_i(f(x_i, W), y_i)$
- **Mean squared error loss is common for regression when we are predicting continuous outputs:** $\frac{1}{N}\sum_{i=1}^{N}(y_i - [Wx_i + b])^2$

Coming back to out example...

Since this is classification, we need to compare the values predicted by $f(x, W) = Wx + b$.

cat	**3.2**	1.3	2.2
car	5.1	**4.9**	2.5
frog	-1.7	2.0	**-3.1**

[7]

Figure: Each number in the matrix the output given by the linear model for $f(x, W) = Wx + b$.

[7] from `https://cs231n.stanford.edu/slides/2017/cs231n_2017_lecture3.pdf`.

Hinge loss

- Consider our example of the 3 images and their predicted scores across cat, car, and frog classes
- We will define $s = f(x_i, W)$ as the model evaluated for image x_i under weights, W.

Then the loss is,

$$L_i = \sum_{j \neq y_i} \begin{cases} 0 & \text{if } s_{y_i} \geq s_j + 1 \\ s_j - s_{y_i} + 1 & \text{otherwise} \end{cases}$$

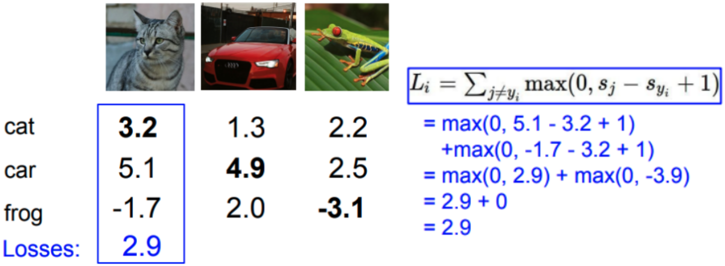
$$= \sum_{j \neq y_i} \max\left(0, s_j - s_{y_i} + 1\right)$$

Intuition of what this is doing...

$$L_i = \sum_{j \neq y_i} \begin{cases} 0 & \text{if } s_{y_i} \geq s_j + 1 \\ s_j - s_{y_i} + 1 & \text{otherwise} \end{cases}$$
$$= \sum_{j \neq y_i} \max\left(0, s_j - s_{y_i} + 1\right)$$

- Since we are summing over instances where $j \neq y_i$, then we are incurring a penalty if the predicted score for image i of being in class j, (s_j) is larger than the score for its actual class label, (s_{y_i}).
- Otherwise, we add 0 if the score for the predicted class (s_{y_i}) is larger than for the class j. In a perfect world, where our classifier predicted correctly, we would have a 0 for the evaluated loss function.

Computing the loss for the cat image



cat	**3.2**	1.3	2.2
car	5.1	**4.9**	2.5
frog	-1.7	2.0	**-3.1**
Losses:	2.9		

$$\boxed{L_i = \sum_{j \neq y_i} \max(0, s_j - s_{y_i} + 1)}$$

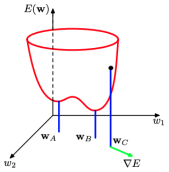
= max(0, 5.1 - 3.2 + 1)
+max(0, -1.7 - 3.2 + 1)
= max(0, 2.9) + max(0, -3.9)
= 2.9 + 0
= 2.9

[8]

[8] from `https://cs231n.stanford.edu/slides/2017/cs231n_2017_lecture3.pdf`

Finding the best model parameters via the loss function

- Let $E(\mathbf{w})$ be the error function evaluated for a particular set of parameters, $\mathbf{w}$.
- Ideally, we want to walk in a productive direction so that $\nabla E(w) = 0$. So, we make small steps in the direction of $-\nabla E(w)$.



[9]

Figure: Geometric view of loss function, $E(\mathbf{w})$. w_A is a local minimum, w_B is a global minimum. At a point, W_C the gradient is given by $\nabla E(\mathbf{w})$.

[9] Pattern Recognition and Machine Learning. Chris Bishop.

Recap and next time

- Today $\rightarrow$ training/testing, cross validation, feature engineering vs feature learning, loss functions,
- Next time $\rightarrow$ statistics vs ML, optimization for ML, introduction to Modal notebooks.