MACHINE LEARNING IN SYSTEMS BIOLOGY I

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INTRODUCTION

WHAT IS MACHINE LEARNING?

'A computer program is said to learn from experience E with respect to some class of tasks T and performance measure P if its performance at tasks in T, as measured by P, improves with experience E'
- Tom M. Mitchell [Mit97]

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2002	Torch first release (open source library)
2006	Geoffrey Hinton coins 'Deep Learning' [HOT06]
>2006	Companies such as Netflix, Facebook, Microsoft, Google fund projects/prizes in and use machine learning/artificial intelligence

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8. Apply model to problems, learn more

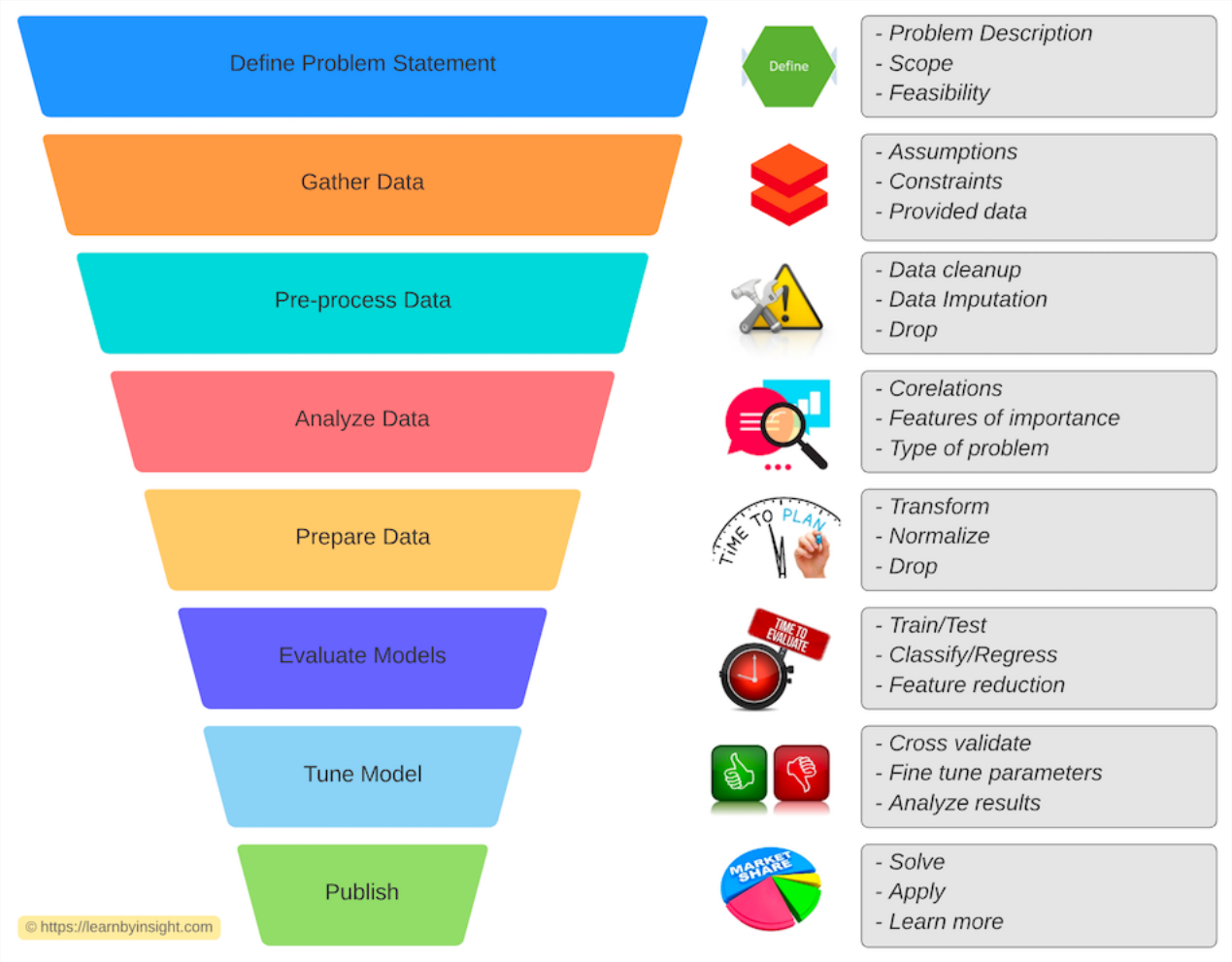

Figure 1: Machine Learning workflow [Mew20]

CONCEPTS

UNSUPERVISED AND SUPERVISED LEARNING

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This section follows [GKMJ21].

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- Can have huge performance benefits compared to unsupervised learning

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- Validation: Use seperate dataset to test model.

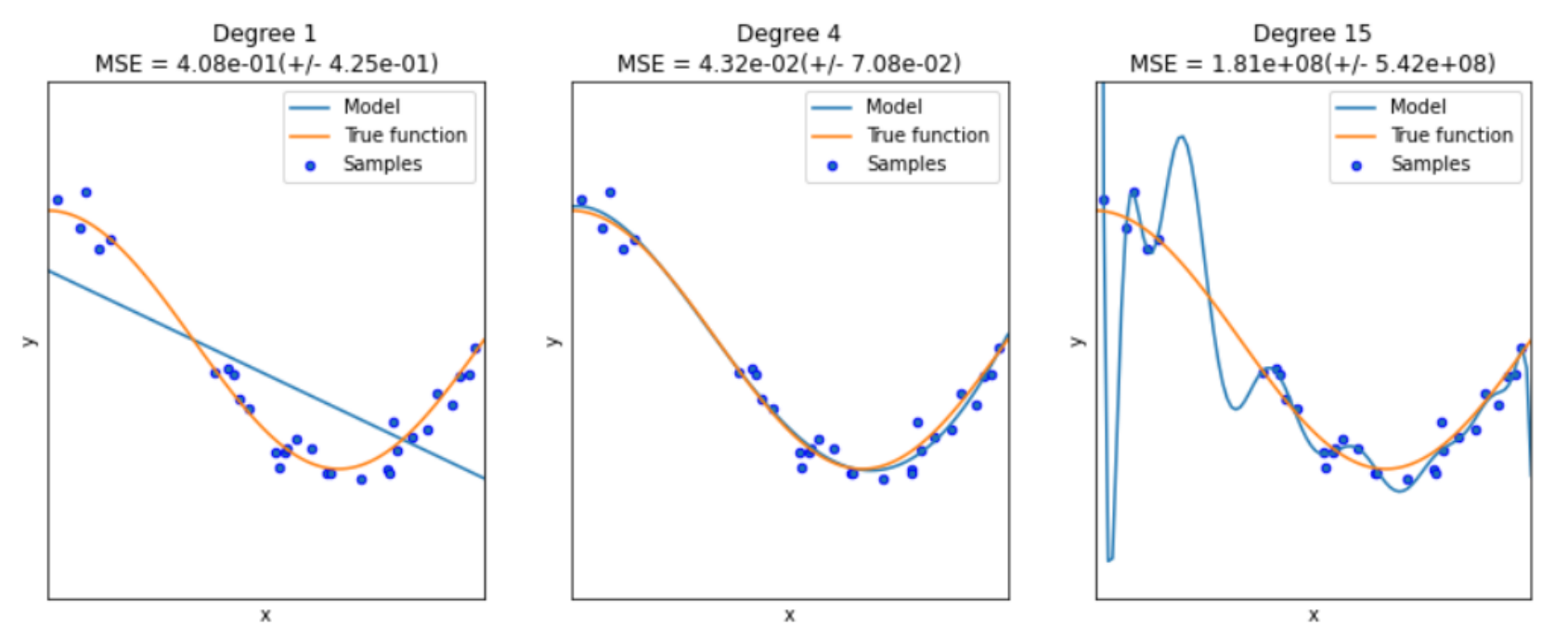

Figure 2: Underfitting, Optimal Fitting and Overfitting [Tri20]

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MACHINE LEARNING TECHNIQUES

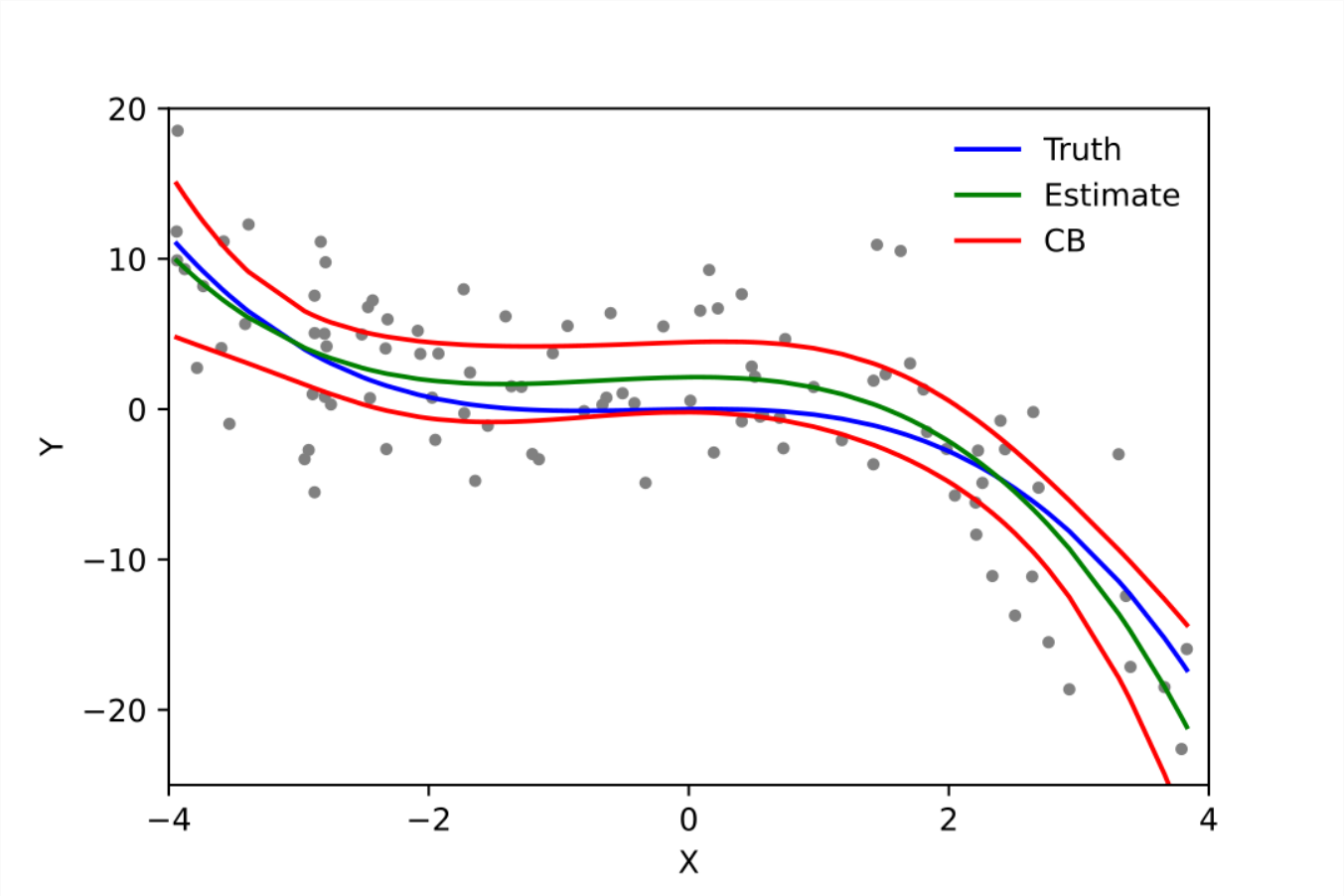

Figure 3: Polynomial Regression [Skb09]

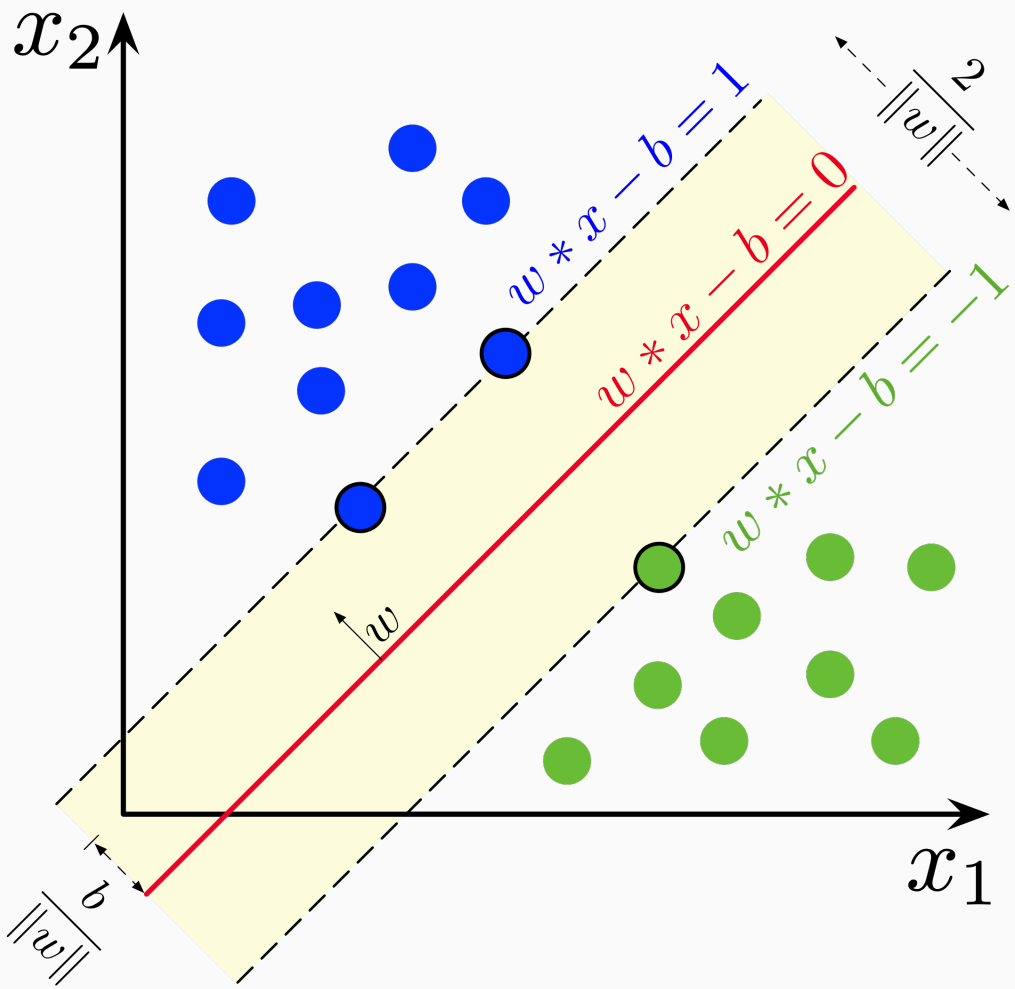

Figure 4: Support Vector Machine [Lar18]

TRADITIONAL MACHINE LEARNING TECHNIQUES

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TRADITIONAL MACHINE LEARNING TECHNIQUES

- Traditional machine learning routines should be preferred over neural networks
- Deep learning can be powerful (and trendy)

  However, currently still limited in applicability

  Requires lots of data $\Rightarrow$ often not present
- Traditional Methods are faster to develop and test

  They typically expect same number of features with each datapoint

  $\Rightarrow$ Padding and Windowing are methods to circumvent this

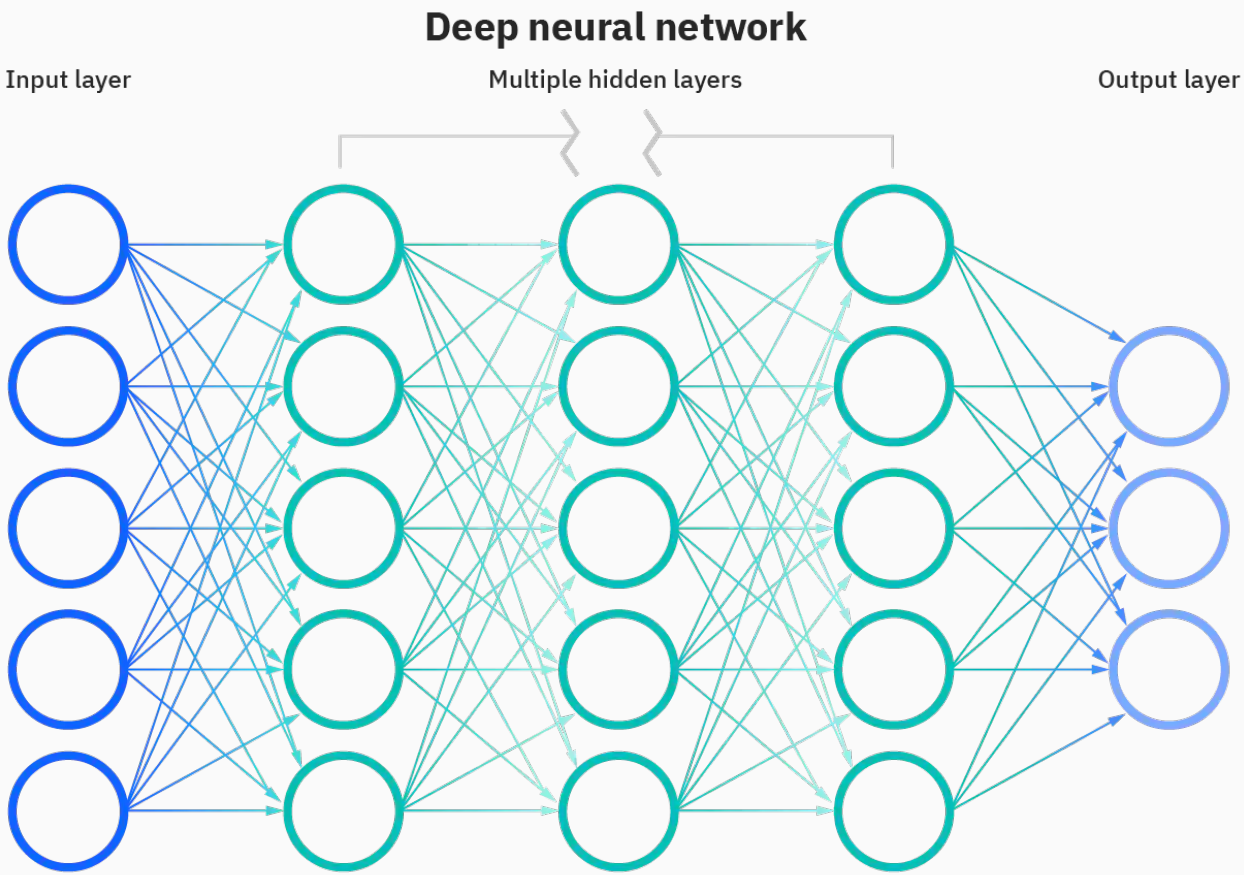

Figure 5: Standard, fully connected neural network [Edu20]

- Universal function approximators
- No guarantee that model will yield accurate predictins for new data
- Question: Is the trained model optimal?
- Neurons are at the heart of Neural Networks

  They apply a function to the input variables x_i to obtain output y by multiplying with learnable weight w_i.

$$y = \sigma\left(\sum_{i=1}^{n} w_i x_i + b\right) \tag{1}$$

- Multiple layers $\Rightarrow$ iterate this procedure

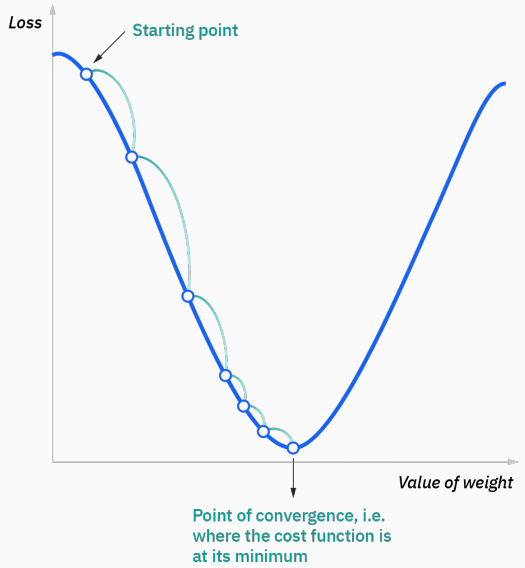

Figure 6: Iterative approach to finding a local optimum of the cost function. It penalizes or rewards good/bad results. An example can be given by the mean squared error [Edu20].

$$\text{MSE} = \frac{1}{2m} \sum_{i=1}^{m} (\hat{y} - y)^2 \tag{2}$$

BIOLOGICAL APPLICATIONS

BIOLOGICAL APPLICATIONS I

Input data	Example prediction tasks	Recommended models	Challenges
Gene sequence	DNA accessibility[14] 3D genome organization[58] Enhancer–promoter interactions[40]	1D CNNs RNNs Transformers	Repetitive regions in genome Sparse regions of interest Very long sequences
Protein sequence	Protein structure[23,55] Protein function[132] Protein–protein interaction[133]	2D CNNs and residual networks using co-variation data Multilayer perceptrons with windowing Transformers	Metagenome data stored in many places and therefore hard to access Data leakage (from homology) can make validation difficult
Protein 3D structure	Protein model refinement[134] Protein model quality assessment[135] Change in stability upon mutation[136]	GCNs using molecular graph 3D CNNs using coordinates Traditional methods using structural features Clustering	Lack of data, particularly on protein complexes Lack of data on disordered proteins
Gene expression	Intergenic interactions or co-expression[137] Organization of transcription machinery[138]	Clustering CNNs Autoencoders	Unclear link between co-expression and function High dimensionality High noise

Figure 7: Different applications in Biological contexts. I

BIOLOGICAL APPLICATIONS I

Mass spectrometry	Detecting peaks in spectra[139] Metabolite annotation[140]	CNNs using spectral data Traditional methods using derived features	Lack of standardized benchmarks[141] Normalization[a] required between different datasets
Images	Medical image recognition[24,62] Cryo-EM image reconstruction[60,142] RNA-sequencing profiles[143]	2D CNNs and residual networks Autoencoders Traditional methods using image features	Systematic differences in data collection affect prediction Hard to obtain large datasets of consistent data
Molecular structure	Antibiotic activity[73] Drug toxicity[54] Protein-ligand docking[39] Novel drug generation[144]	GCNs using molecular graph Traditional methods or multilayer perceptrons using molecular properties RNNs using text-based representations of molecular structure such as SMILES Autoencoders	Experimental data available for only a tiny fraction of possible small molecules
Protein–protein interaction network	Polypharmacology side effects[77] Protein function[145]	GCNs Graph embedding	Interaction networks can be incomplete Cellular location affects whether proteins interact High number of possible combinations

Figure 8: Different applications in Biological contexts. II

Questions?

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