Linear Regression in Pharmacology

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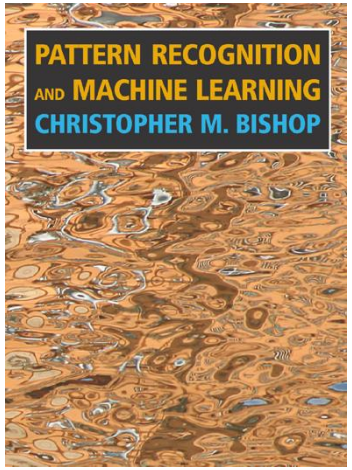
Pharmacology Department

Applying Statistical Learning to Drug Discovery and Clinical Data

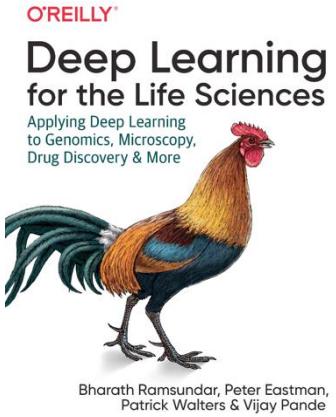
Machine learning algorithms



Pattern Recognition and Machine Learning

by Christopher M. Bishop

✓Chapter 3: Linear Model for Regression



Deep Learning for the Life Sciences

by Bharath Ramsundar, Peter Eastman, and Vijay S. Pande

✓Chapter 2: Introduction to Deep Learning

Prerequisite: Calculus I

Course structure

- **Weekly Lectures:**
  Introduce core ML concepts in Pharmacology applications
- **Python Lab:**
  Weekly Hands-on coding to implement algorithms and visualize data
- **Quizzes (30%):**
  Focus on understanding *when and why* to use each ML algorithm
- **Project (40%): :**
  Build an end-to-end ML pipeline for a real Pharmacology dataset
- **Exam (30%): :**
  Assess both conceptual understanding and practical application

Machine learning algorithms

What we will cover today's lecture

- Why Machine Leaning
- QSAR
- QSAR and Linear Regression
- Example and Exercise

Why LR in Pharmacology

- Pharmacology is data-rich
- Need to predict potency, toxicity, and Pharmacokinetics.
- Machine Learning (ML) enables:
  - Discovery of hidden patterns
  - Quantitative prediction of biological activity
  - Linking chemical structure → pharmacological behavior
- Next is Deep Learning

What is QSAR

QSAR (Quantitative Structure–Activity Relationship):
A mathematical model that relates molecular **structure** to biological **activity**

- **Hansch & Fujita (1964):**
- Led to famous **multivariate regression models** in pharmacology
- First linear equation:

$$\log\left(\frac{1}{c}\right) = a * logP + b * \sigma + c * MW + d$$

What is QSAR

QSAR in Practice: A Simple Example

Predicting Inhibitor Potency (pIC_{50}) for a Protease Target

Compound	Mol. Wt. (Da)	LogP	pIC_{50} (activity)
A	250	2.1	6.2
B	280	2.8	6.9
C	310	3.2	7.1
D	340	3.9	7.5
E	320	3.2	??

Question: Can we build a model to predict pIC_{50} for new compounds?

Machine learning algorithms

Supervised learning

- Data include **input features** and known **output labels**
  - Model learns a mapping: $f(x) \rightarrow y$
- Goal: **predict or estimate** outcomes for new data
- Examples in pharmacology:
  - Predicting IC_{50} (regression)
  - Classifying compounds as toxic/non-toxic (classification)

Algorithms:
Linear Regression, Logistic Regression, Decision Trees, Neural Networks

Unsupervised learning

- Data have **no predefined labels**
  - Model finds hidden structure or patterns
- Goal: **group** or **reduce** data complexity
- Examples in pharmacology:
  - Clustering compounds by chemical similarity
  - Grouping patients by response profile
  - Dimensionality reduction of molecular descriptors (e.g., PCA)

Algorithms:
k-Means, Hierarchical Clustering, PCA, Autoencoders

Mathematics Recap

Vector and Matrix

$$x = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{bmatrix} \qquad A = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}$$

Matrix

$$xA = \begin{bmatrix} x_1 & x_2 \end{bmatrix} \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} x_1 a_{11} + x_2 a_{21} & x_1 a_{12} + x_2 a_{22} \end{bmatrix}$$

$$B = \begin{bmatrix} a & b \\ c & d \end{bmatrix} \qquad (B)^{-1} = \frac{1}{ad - bc} \begin{bmatrix} d & -b \\ -c & a \end{bmatrix}$$

$$B^T = \begin{bmatrix} a & c \\ b & d \end{bmatrix}$$

Linear Regression

Chapter 3

Linear Regression:

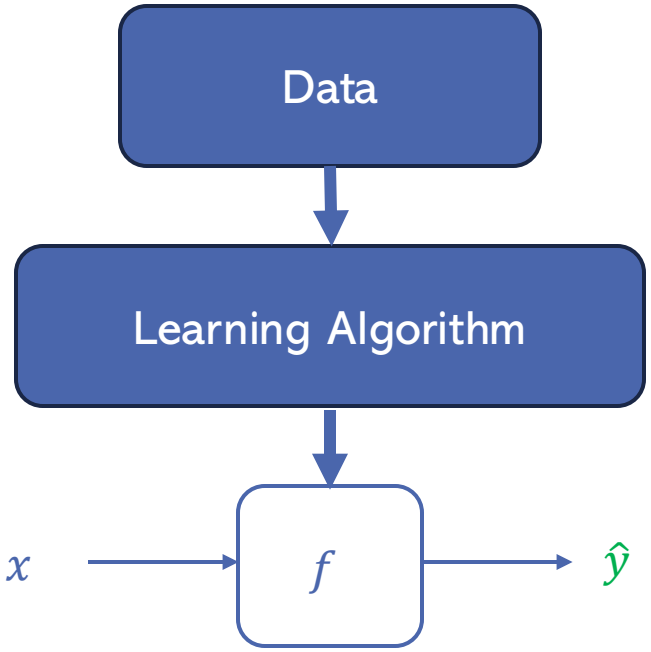
Training set: Data used to train the model

Compound	Mol. Wt. (Da)	LogP	pIC_{50} (activity)
A	250	2.1	6.2
B	280	2.8	6.9
C	310	3.2	7.1
D	340	3.9	7.5
…	…	…	…
E	320	3.2	??

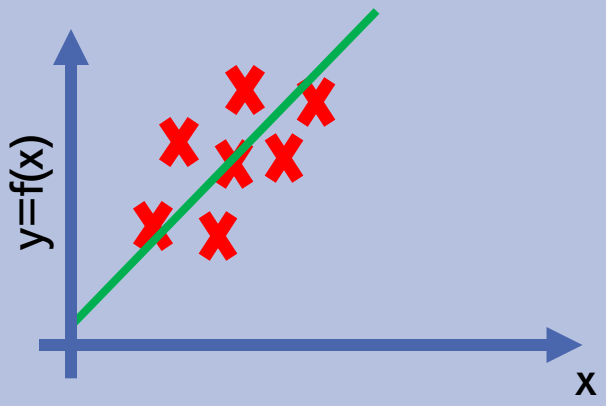
x : Input (features)

y: output (target)

Linear Regression



How to represent f



One size variable

$$f_{w,b}(x) = wx + b$$

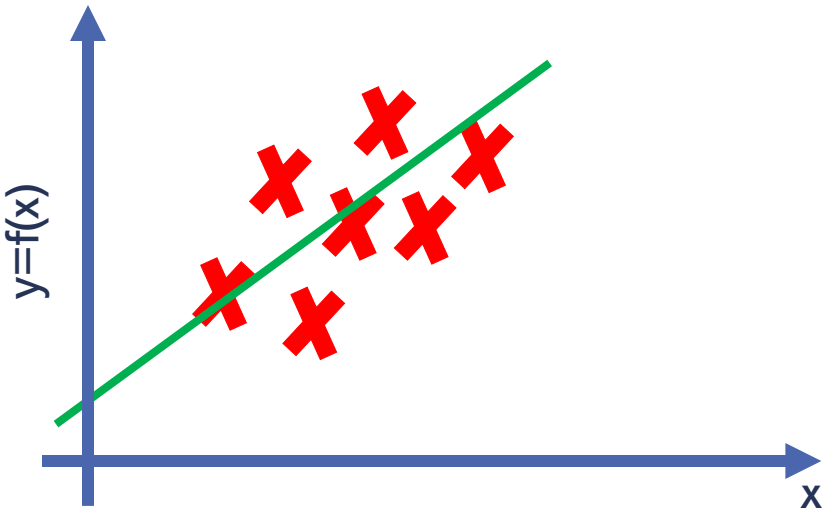
Multi variable

$$f_{w,b}(x) = w_0 + w_1x_1 + w_2x_2 + w_3x_3 =$$

$$w_0 + \sum_{i=0}^{3} w_i x_i$$

Linear Regression: Model

Cost Function $J(w,b)$ { Measures the average squared difference between predicted $(\hat{y})$ and actual (y) values. The goal is to find parameters w, b that **minimize this error**.



$\hat{y} = f_{w,b}(x^{(i)})$

$f_{w,b}(x) = w_0 + wx^{(i)}$

$$J(w) = \frac{1}{2m}\sum_{i=0}^{m}(\hat{y}^{(i)} - y^{(i)})^2$$

With :

$$\hat{y} = f_{w,b}(x^{(i)}) = w_0 + wx^{(i)}$$

Find the parameters w and b that **minimize the cost function $J(w,b)$**

Closed Form (Normal Equation)

To minimize the $J(w)$ take the derivative with respect to w and set it to zero:

$$\frac{\partial J}{\partial w} = \left(\frac{1}{m}\right)\Phi^{\mathrm{T}}(\Phi w - y) = 0$$

Where:

$$\hat{y} = wx + b$$

$$\hat{y} = w_1 x + w_0 = [w_0\, w_1]\begin{bmatrix}1\\ x\end{bmatrix} = w\phi$$

Simplify

$$\phi^T \phi w = \phi^T y$$

Now solve w

$$w = (\phi^T \phi)^{-1} \phi^T y$$

This is called the **Normal Equation,** it gives the exact, closed-form solution.

Note:

- Requires invertible $\phi^T \phi w$ (issue with multicollinearity).
- Gradient Decent will be use for higher dimension (Training)

The Coefficient of Determination

Measures how well our regression line fits the data

$$R^2 = 1 - \left(\frac{SS_{res}}{SS_{tot}}\right)$$

$SS_{res} = \sum(y_i - \hat{y_i})^2$ → unexplained variation (residuals)

$SS_{tot} = \sum(y_i - \overline{y_i})^2$ → total variation in data

Interpretation:

- $R^2 = 1 \rightarrow$ Perfect fit (model explains all variation)
- $R^2 = 0 \rightarrow$ Model explains none of the variation
- Example: $R^2 = 0.85$ means the model explains **85% of the change** in the response.

Recap

- QSAR

$$\hat{Y} = \log\left(\frac{1}{c}\right) = a * logP + b * \sigma + c * MW + d$$

- Linear Regression

$$\hat{y} = w_1 x + w_0 = [w_0\ w_1]\begin{bmatrix}1\\ x\end{bmatrix} = w\phi$$

$$J(w) = \frac{1}{2m}\sum_{i=0}^{m}(\hat{y}^{(i)} - y^{(i)})^2$$

- How to compute the coefficients
  - Normal Equation

$$w = (\phi^T\phi)^{-1}\phi^T y \quad \text{and} \quad R^2 = 1 - \left(\frac{SS_{res}}{SS_{tot}}\right)$$

Normal Function Example:

Fit Linear model to

No.	x	y
1	1	2
2	2	3
3	3	5

$$X = \begin{bmatrix} 1 & 1 \\ 1 & 2 \\ 1 & 3 \end{bmatrix} \qquad y = \begin{bmatrix} 2 \\ 3 \\ 5 \end{bmatrix}$$

$$w = (X^T X)^{-1} X^T y$$

$$X^T X = \begin{bmatrix} 3 & 6 \\ 6 & 14 \end{bmatrix} \qquad X^T y = \begin{bmatrix} 10 \\ 23 \end{bmatrix}$$

$$(X^T X)^{-1} = \frac{1}{6} \begin{bmatrix} 14 & -6 \\ -6 & 3 \end{bmatrix}$$

$$w = \begin{bmatrix} 0.33 \\ 1.5 \end{bmatrix} \qquad y = 0.33 + 1.5x$$

$$R^2 = 0.964$$

Lab Exercise 1

Predicting Drug-Induced Heart Rate Response Using Multi-Feature Regression

	Dose (mg/kg)	Weight (kg)	Age (years)	Response (Δ bpm)
1	3.62	74.3	42.49	9.05
2	7.66	56.82	37.21	21.94
3	6.12	52.6	62.29	17.46
4	5.19	87.96	41.05	16.55
5	2.09	88.63	37.64	2.71
6	2.09	82.34	49.42	5.51
7	1.41	62.18	31.34	-3.75
8	7.06	53.91	61.1	21.69
9	5.21	77.37	28.35	14.66

Develop a multiple linear regression model that predicts the heart rate response (Δ bpm) based on the following independent variables:

- Dose (mg/kg): Drug dosage per kilogram of body weight
- Weight (kg): Subject's total body mass
- Age (years): Subject's age

The goal is to **quantify the contribution of each factor** to the observed pharmacological response and interpret the coefficients in a biological context.

Lab Exercise 1

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$$\hat{Y} = \mathrm{w}_0 + w_1 * \mathrm{Dose} + w_2 * Weight + w_3 * Age$$

$$w = (\phi^T \phi)^{-1} \phi^T y$$

Solution:

$$\hat{Y} = -3.231 + 3.410 * \mathrm{Dose} + 0.003 * Weight - 0.023 * Age \text{ and } R^2 = 0.99$$

Link to Google Colab

Next session

- Gradient Decent
- Python
- Python implementation of the LR
  - Normal Equation
- Non-Linear LR
  - Gaussian (Radial Basis) Regression
  - Logarithmic and Exponential Models
  - Generalized Linear Models (GLMs)
  - Sigmoidal / Logistic Regression (Hill Equation)

Appendix A

QSAR Parameters

$$\log\left(\frac{1}{c}\right) = a * logP + b * \sigma + c * MW + d$$

Symbol	Description	Pharmacological Interpretation
C	Molar concentration required to produce a defined biological effect	Inversely related to potency (lower C → higher activity)
log(1/C)	Activity term (higher = more active)	Used as dependent variable (Y)
log P	Partition coefficient (lipophilicity between octanol and water)	Measures hydrophobicity; affects membrane permeability and receptor binding
σ (sigma)	Hammett substituent constant	Represents electronic effects of substituents on the aromatic ring (electron-withdrawing or -donating)
MW	Molecular weight	Captures steric or size-related contribution to activity
a, b, c	Regression coefficients	Quantify how each property influences activity (sign and magnitude indicate direction and strength)
d	Intercept	Baseline biological activity independent of descriptors

Linear Regression: Model

We want to find the best-fitting line that predicts $\hat{y}$ from x:

$$\hat{y} = wx + b$$
$$\hat{y} = w_1 x + w_0 = [w_0\ w_1] \begin{bmatrix} 1 \\ x \end{bmatrix}$$

or, in vector/matrix form (for many samples and features):

$$\hat{y} = w\phi$$

Where

- ϕ= design matrix (rows = samples, columns = features, plus 1 for intercept),
- w = weights (parameters),
- $\hat{y}$ = predicted values.

Gradient Descent (When D or N is large)

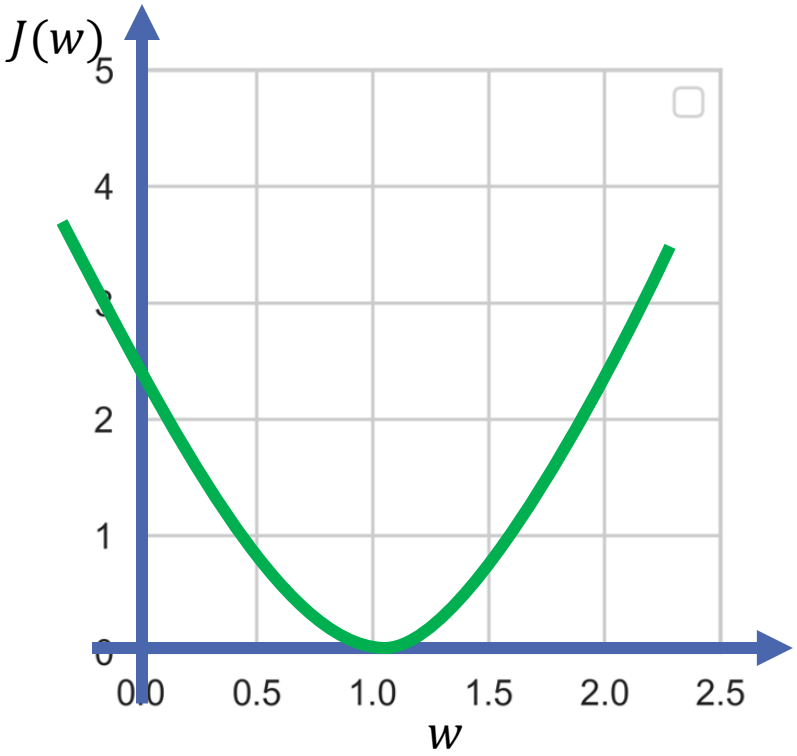
This **iterative optimization** steps is called Gradient Decent Instead of computing the $(\phi^T\phi)^{-1}\phi^T y$, it **updates weights step-by-step** by following the gradient (slope) of the cost function:

$$w := w - \alpha \frac{\partial J}{\partial w}$$

where α is the **learning rate.**

$$\frac{\partial J}{\partial w} = \left(\frac{1}{m}\right) \Sigma \left(\hat{y}^{(i)} - y^{(i)}\right) x^{(i)}$$

- Scales to streaming data; no matrix inversion.
- Learning rate α controls convergence speed/stability.
- Batch / stochastic / mini-batch variants.



Gradient Descent (When D or N is large)