BCB 726: *Machine Learning for Computational Biology*

The Three Cultures of Data

October 22nd, 2025

“Cultures”?

Statistical Modeling: The Two Cultures

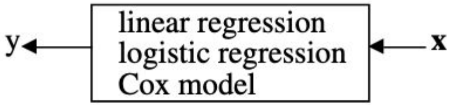
Leo Breiman

Abstract. There are two cultures in the use of statistical modeling to reach conclusions from data. One assumes that the data are generated by a given stochastic data model. The other uses algorithmic models and treats the data mechanism as unknown. The statistical community has been committed to the almost exclusive use of data models. This commitment has led to irrelevant theory, questionable conclusions, and has kept statisticians from working on a large range of interesting current problems. Algorithmic modeling, both in theory and practice, has developed rapidly in fields outside statistics. It can be used both on large complex data sets and as a more accurate and informative alternative to data modeling on smaller data sets. If our goal as a field is to use data to solve problems, then we need to move away from exclusive dependence on data models and adopt a more diverse set of tools.

The Data Modeling Culture

The analysis in this culture starts with assuming a stochastic data model for the inside of the black box. For example, a common data model is that data are generated by independent draws from

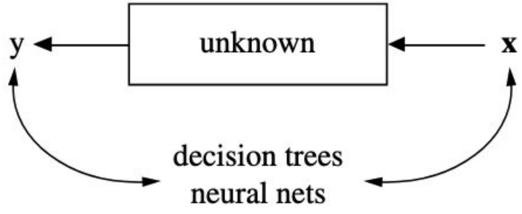
response variables = f(predictor variables,
random noise, parameters)



Model validation. Yes–no using goodness-of-fit tests and residual examination.
Estimated culture population. 98% of all statisticians.

The Algorithmic Modeling Culture

The analysis in this culture considers the inside of the box complex and unknown. Their approach is to find a function $f(\mathbf{x})$—an algorithm that operates on $\mathbf{x}$ to predict the responses $\mathbf{y}$. Their black box looks like this:



Model validation. Measured by predictive accuracy.
Estimated culture population. 2% of statisticians, many in other fields.

The Three Cultures of Data

- **Statistics**
- **Machine Learning**
- **Deep Learning**

…and a lot of other ones we won't talk about:

Bayesian Statistics, Statistical Learning, Econometrics, Cybernetics, Control Theory, Signal Processing, Inverse Problems, Operations Research, Causal Inference, Actuarial Science, &c

What do I mean by <u>culture</u>?

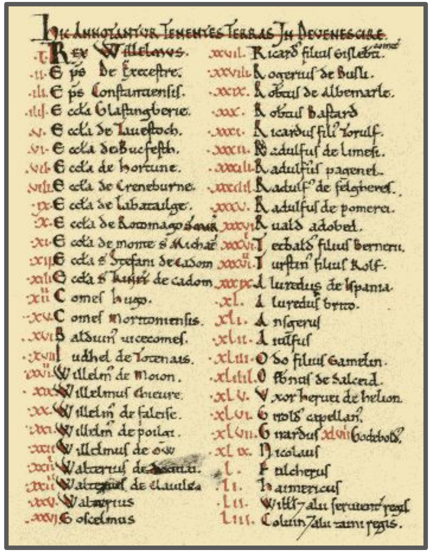
A community of researchers with socially determined assumptions about:

- What is the goal of distilling data into a mathematical model?
- What are the important properties of a data infused mathematical model?

…who then teach classes and write textbooks, creating a socially constructed aura of "the right way to work with data"

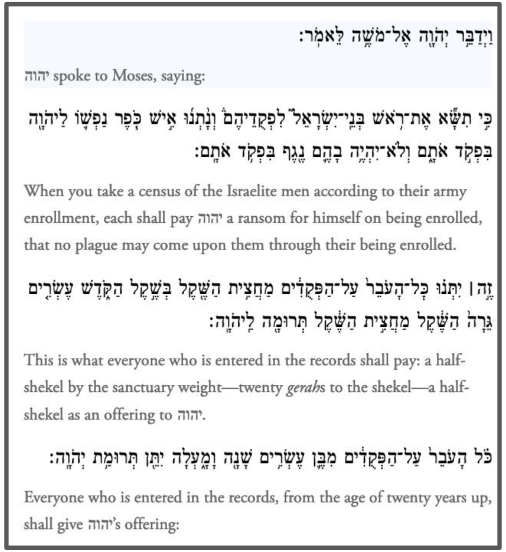
A historical interlude

Measurement & estimation aren't new...



William The Conqueror's
Domesday Book of 1086

"What did I just conquer?"



וַיְדַבֵּר יְהֹוָה אֶל־מֹשֶׁה לֵּאמֹר׃

יהוה spoke to Moses, saying:

כִּי תִשָּׂא אֶת־רֹאשׁ בְּנֵי־יִשְׂרָאֵל לִפְקֻדֵיהֶם וְנָתְנוּ אִישׁ כֹּפֶר נַפְשׁוֹ לַיהֹוָה בִּפְקֹד אֹתָם וְלֹא־יִהְיֶה בָהֶם נֶגֶף בִּפְקֹד אֹתָם׃

When you take a census of the Israelite men according to their army enrollment, each shall pay יהוה a ransom for himself on being enrolled, that no plague may come upon them through their being enrolled.

זֶה ׀ יִתְּנוּ כׇּל־הָעֹבֵר עַל־הַפְּקֻדִים מַחֲצִית הַשֶּׁקֶל בְּשֶׁקֶל הַקֹּדֶשׁ עֶשְׂרִים גֵּרָה הַשֶּׁקֶל מַחֲצִית הַשֶּׁקֶל תְּרוּמָה לַיהֹוָה׃

This is what everyone who is entered in the records shall pay: a half-shekel by the sanctuary weight—twenty *gerahs* to the shekel—a half-shekel as an offering to יהוה.

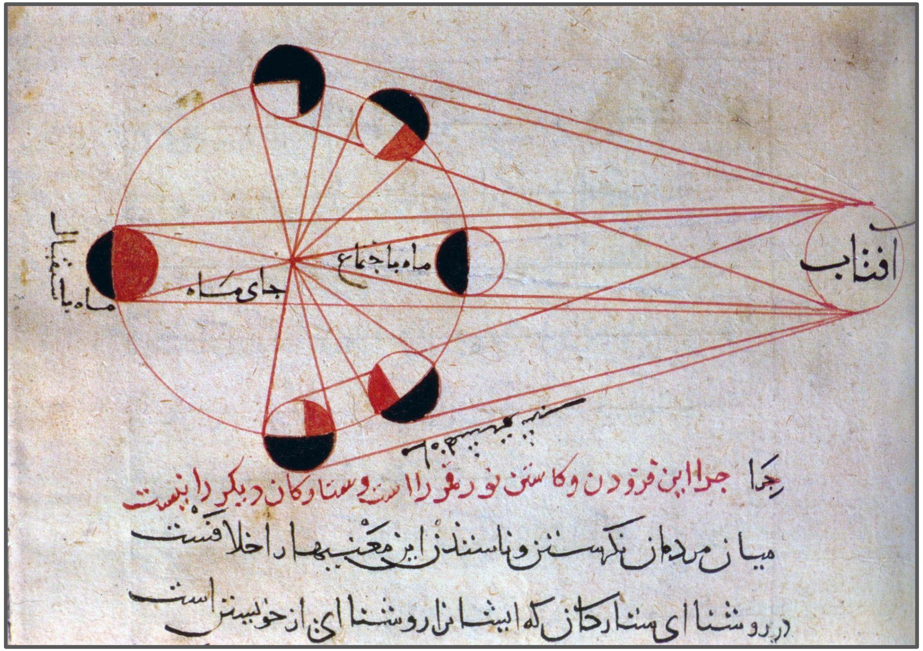
כֹּל הָעֹבֵר עַל־הַפְּקֻדִים מִבֶּן עֶשְׂרִים שָׁנָה וָמָעְלָה יִתֵּן תְּרוּמַת יְהֹוָה׃

Everyone who is entered in the records, from the age of twenty years up, shall give יהוה's offering:

Beginning of the Torah portion *Ki Tisa*, Moses asked to take a census and collect a tax

Sparks of mathematical modeling of measurement in pre-modern science

- Interplay between **observation** & strong **inductive** priors
- Abstract models <u>but</u> often more descriptive than mathematical
- Validated by agreement with observation <u>but</u> also:
  - Elegance / aesthetics
  - Great “masters”
  - Theology & philosophy



Abu-Rayhan al-Biruni’s *Al-Tafhim li Awa'il Sana'at al-Tanjim* (Book on the Elements of Astrology)

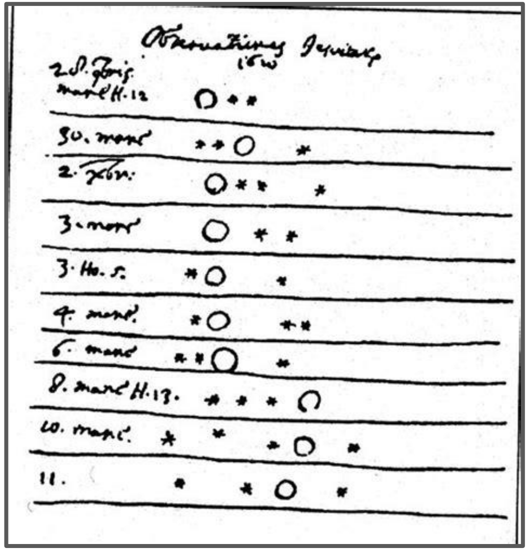
Modern science = empiricism

- 1600s science narrowed “natural philosophy” to:
  - **Collect data**
  - **Build mathematical models** (repeat)

“the Universe – which stands continually open to our gaze, but it cannot be understood unless one first learns to comprehend the language and interpret the characters in which it is written. It is written in the language of mathematics” – Galileo in The Assayer

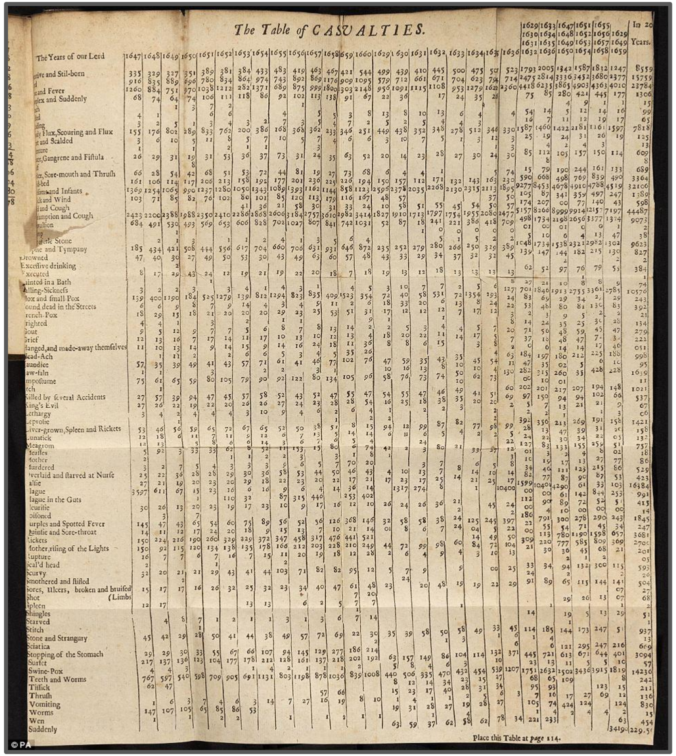
IL SAGGIATORE
Nel quale
Con bilancia esquisita e giusta
si ponderano le cose contenute
nella
LIBRA ASTRONOMICA E FILOSOFICA
DI LOTARIO SARSI SIGENSANO
Scritto in forma di lettera
All'Illmo et Reuermo Mons.re D.
VIRGINIO CESARINI
Accº Linceo Mº di Camera di N.S.
Dal Sig.r
GALILEO GALILEI
Accº Linceo Nobile Fiorentino
Filosofo e Matematico Primario
del
Ser.mo Gran Duca di Toscana
IN ROMA MDCXXIII
Appresso Giacomo Mascardi
F. Villamoena Fecit.

Galileo Gallilei’s “The Assayer”



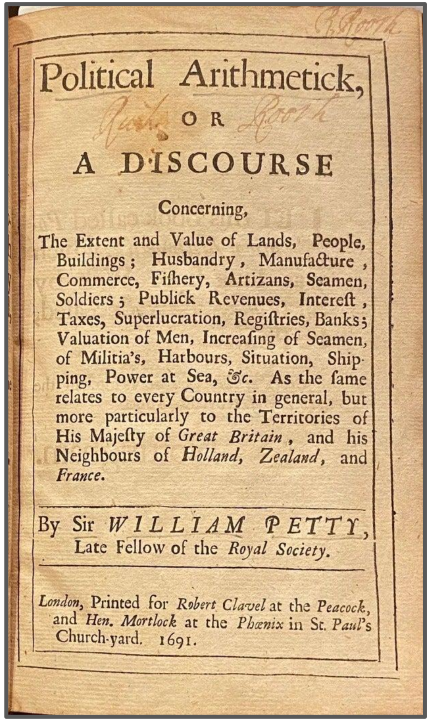
Galileo’s notebook observing moons of Jupiter (interpreted as evidence for refuting geocentrism)

Statistics = seeing like a state



The Table of CASUALTIES.

Table from John Graunt's *Natural and Political Observations Made Upon the Bills of Mortality* (1662)



Political Arithmetick,
OR
A DISCOURSE
Concerning,
The Extent and Value of Lands, People, Buildings; Husbandry, Manufacture, Commerce, Fishery, Artizans, Seamen, Soldiers; Publick Revenues, Interest, Taxes, Superlucration, Registries, Banks; Valuation of Men, Increasing of Seamen, of Militia's, Harbours, Situation, Shipping, Power at Sea, &c. As the same relates to every Country in general, but more particularly to the Territories of His Majesty of *Great Britain*, and his Neighbours of *Holland*, *Zealand*, and *France*.

By Sir *WILLIAM PETTY*,
Late Fellow of the *Royal Society*.

London, Printed for *Robert Clavel* at the *Peacock*, and *Hen. Mortlock* at the *Phœnix* in St. *Paul's* Church-yard. 1691.

William Petty's *Political Arithmetic* (1691)

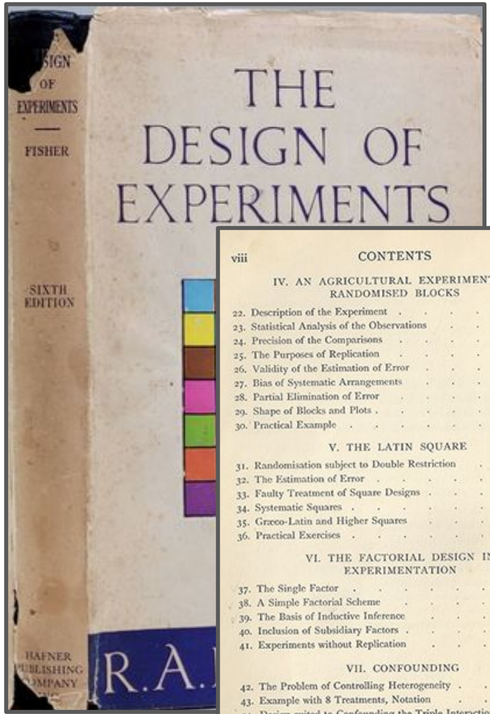
Statistics

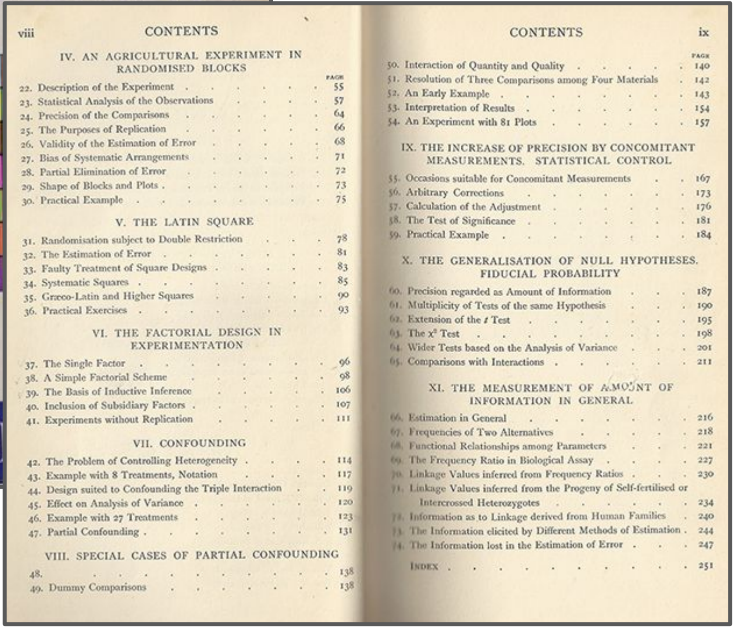
So, what is classical statistics?

- <u>There is some real world quantity</u>
  - …how do we finite noisy measurements into a robust estimate of the “true” value?

- <u>We have a mathematical model of reality</u>
  - …how do rigorously we use finite noisy measurements to reject (or conditionally accept) the model?

1920s/30s: statistics infiltrates science





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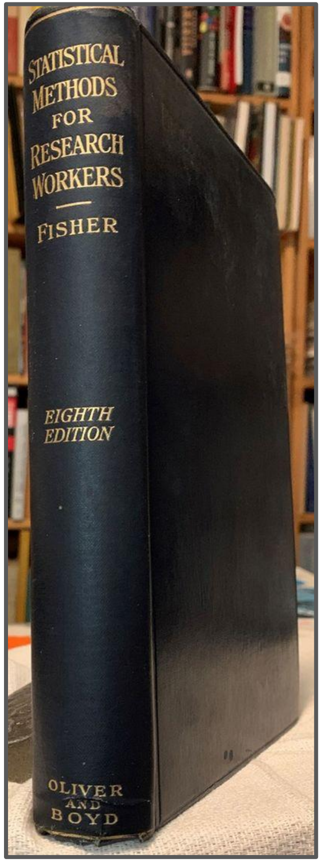

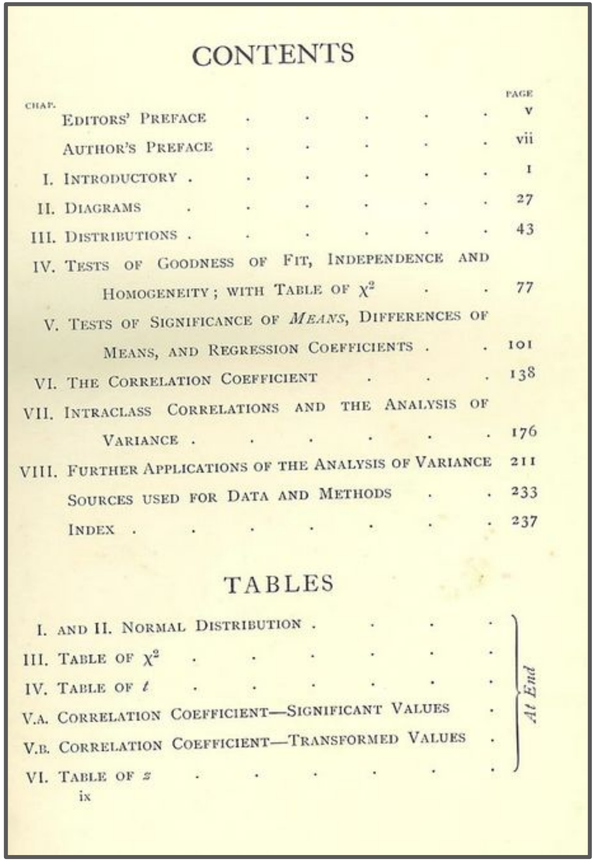
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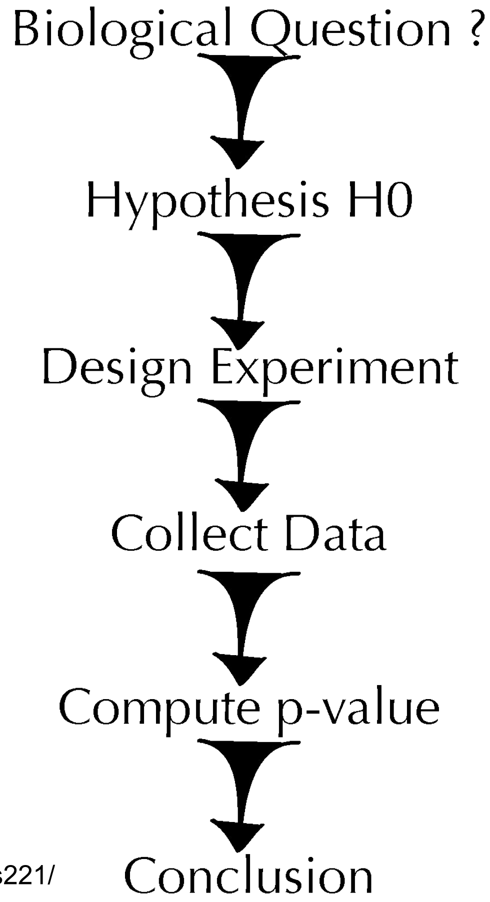
TABLES

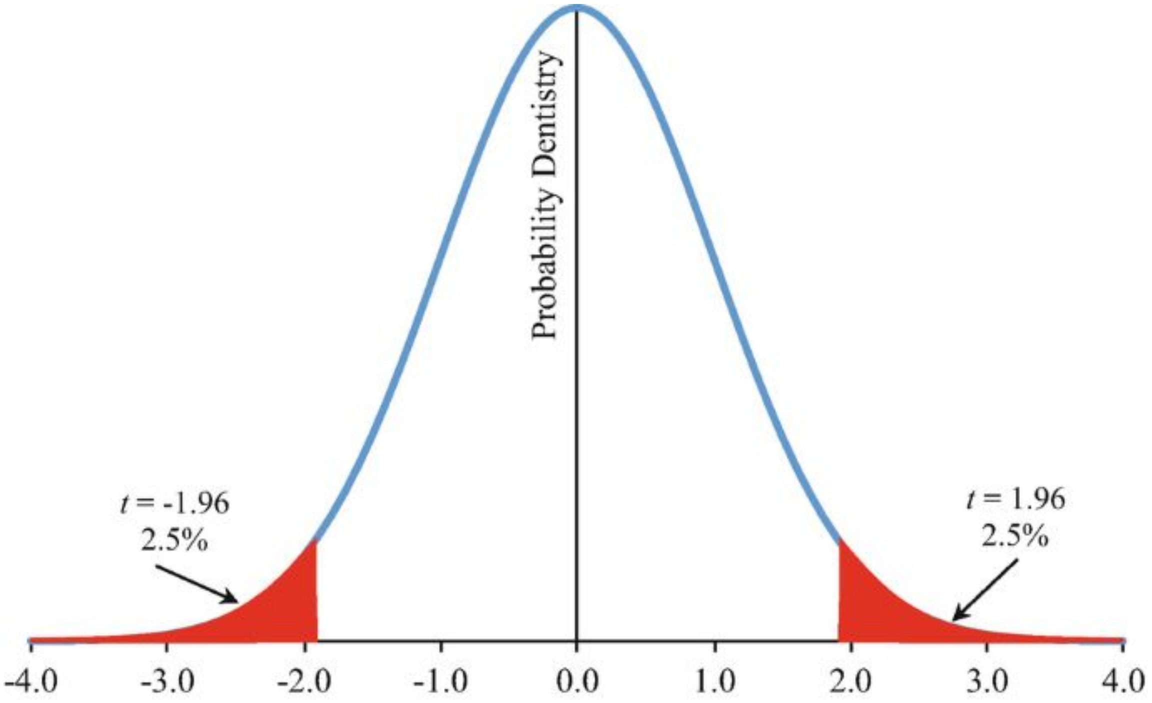
Tools of classical statistics

- Experimental design
- Inference & estimators
  - consistent, unbiased, efficient
- Confidence intervals
- Statistical hypothesis testing (Neyman-Pearson)
- Null hypothesis models (Fisher)
- Their unholy marriage: NHST



https://web.stanford.edu/class/bios221/

Null Hypothesis Significance Testing



Teaching Null Hypothesis Significance Testing (NHST) in the Health Sciences: The Significance of Significance

Exploratory Data Analysis: You're allowed to look at your data

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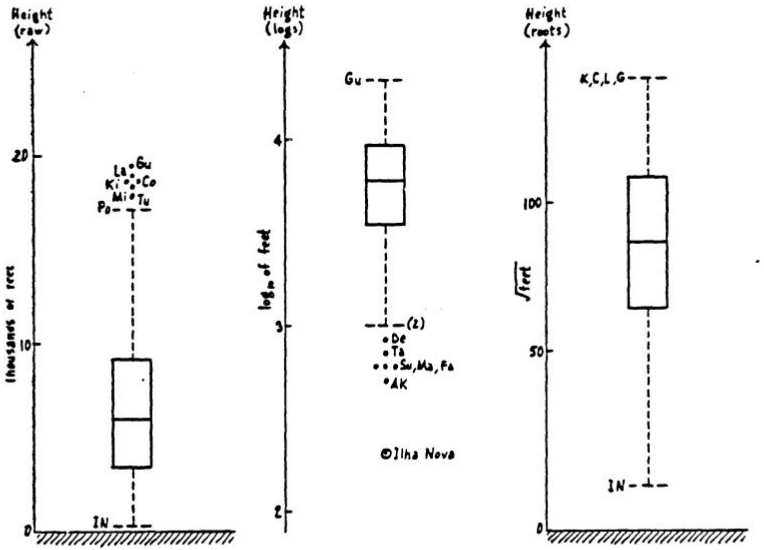
Exploratory Data Analysis: Past, Present, and Future

John W. Tukey[1]

Technical Report No. 302
Princeton University, 408 Fine Hall, Washington Road, Princeton, NJ 08544-1000

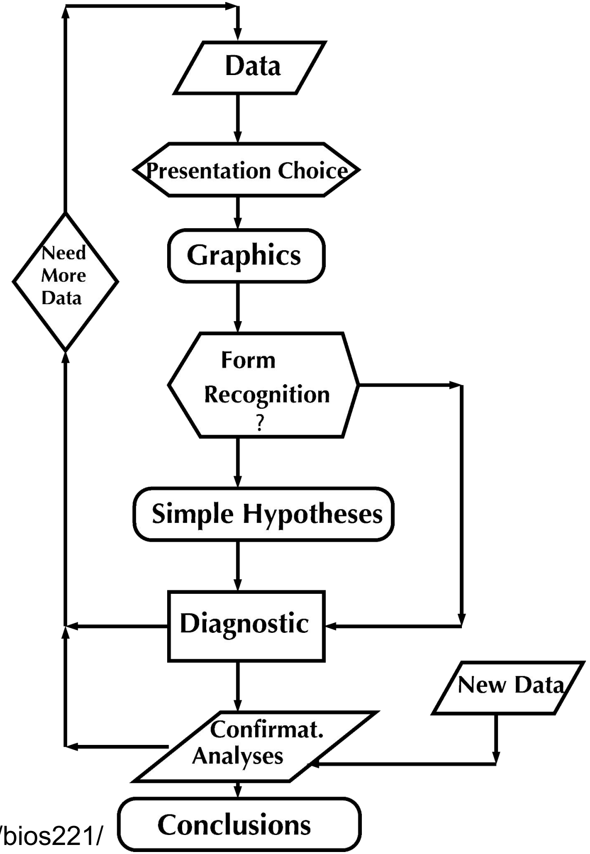
Abstract

The 1971-1977 early formulation of Exploratory Data Analysis, in terms of (a) results of some of its techniques and considerations which underlay, at various depths, the choices realized in the books. The 1991–1995 development of Exploratory Analysis of Variance, described in its simplest (two-way table) form and barely sketched in general. Discussion of the changes in apparent philosophy caused by the need to communicate more complicated things, notches, hints, the likely impact on a revised edition of Exploratory Data Analysis 1977. Dreams and targets for what might happen in 1996–2005, with emphasis on Exploratory Regression and the combined use of multiple description.



Exploratory Data Analysis: workflow

- Emphasis on visualization
- Look at residuals of your model
  - ...you can even try different models!
- Does it make sense?
- ...classical stats left for "confirmatory analyses"



https://web.stanford.edu/class/bios221/

Machine Learning

ML: a different lineage

VOL. LIX. No. 236.] [October, 1950

MIND

A QUARTERLY REVIEW

OF

PSYCHOLOGY AND PHILOSOPHY

I.—COMPUTING MACHINERY AND INTELLIGENCE

BY A. M. TURING

1. *The Imitation Game.*

I PROPOSE to consider the question, 'Can machines think?' This should begin with definitions of the meaning of the terms 'machine' and 'think'. The definitions might be framed so as to reflect so far as possible the normal use of the words, but this attitude is dangerous. If the meaning of the words 'machine' and 'think' are to be found by examining how they are commonly used it is difficult to escape the conclusion that the meaning and the answer to the question, 'Can machines think?' is to be sought in a statistical survey such as a Gallup poll. But this is absurd. Instead of attempting such a definition I shall replace the question by another, which is closely related to it and is expressed in relatively unambiguous words.

The new form of the problem can be described in terms of a game which we call the 'imitation game'. It is played with three people, a man (A), a woman (B), and an interrogator (C) who may be of either sex. The interrogator stays in a room apart from the other two. The object of the game for the interrogator is to determine which of the other two is the man and which is the woman. He knows them by labels X and Y, and at the end of the game he says either 'X is A and Y is B' or 'X is B and Y is A'. The interrogator is allowed to put questions to A and B thus:

C: Will X please tell me the length of his or her hair?

Now suppose X is actually A, then A must answer. It is A's

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Massachusetts Institute of Technology
Lincoln Laboratory

HEURISTIC ASPECTS OF THE ARTIFICIAL INTELLIGENCE PROBLEM

by

M. L. Minsky

Group Report 34-55 17 December 1956

HEURISTIC ASPECTS OF THE ARTIFICIAL INTELLIGENCE PROBLEM*

M. L. Minsky

Introduction

In this report we will discuss, from a heuristic point of view, some of the problems encountered in the design of what might be called "intelligent" machines. We will attempt to indicate, in a few words, the nature of the domain of problems with which we are concerned here.

I do not feel that it would be at all useful to try to lay down an absolute definition of "intelligence" or even of "intelligent behavior". For the things we are trying to accomplish are always related to some set of ad hoc ground rules, problems, and resources. There are certain kinds of performances which, if exhibited by a man, we could all agree embody, or reflect, intelligence. For some purposes we might be able to agree to regard the same performances, in a machine, as "intelligent". But while this convention may be useful in some kinds of discourse, its use in analysis is precluded, for the most part, by two serious faults. First it would constitute a direct evasion of any concise specification of the kinds of activity we are looking for. And then, it seems wrong in spirit; we can often find very simple machines which, for certain tasks, exhibit performances which, if done by a man, we would have to call "intelligent". Now since we just don't want to confer such a dignity on absurdly simple machines,

* In this paper, which is part of some notes for a book in preparation, the arguments are, for the most part, highly condensed. Details are regularly omitted, particularly those of the mathematical models we have in mind. It is hoped, nevertheless, that it will serve as an introduction to some ideas and techniques that are representative of what is developing in the rapidly growing field of heuristic machines and programs.

ML = symbolic AI isn't working and it seems like AIs need to work with data

- Information Retrieval
- Natural Language Processing
- Computer Vision
- Speech Recognition
- ...and a base of techniques that mix:
  - *Computer Science*
  - *Optimization*
  - *Signal Processing*

Deep Learning: let's imitate the brain to get to AI?

A LOGICAL CALCULUS OF THE IDEAS IMMANENT IN NERVOUS ACTIVITY

WARREN S. MCCULLOCH and WALTER H. PITTS

Because of the "all-or-none" character of nervous activity, neural events and the relations among them can be treated by means of propositional logic. It is found that the behavior of every net can be described in these terms, with the addition of more complicated logical means for nets containing circles; and that for any logical expression satisfying certain conditions, one can find a net behaving in the fashion it describes. It is shown that many particular choices among possible neurophysiological assumptions are equivalent, in the sense that for every net behaving under one assumption, there exists another net which behaves under the other and gives the same results, although perhaps not in the same time. Various applications of the calculus are discussed.

INTRODUCTION

THEORETICAL neurophysiology rests on certain cardinal assumptions. The nervous system is a net of neurons, each having a soma and an axon. Their adjunctions, or synapses, are always between the axon of one neuron and the soma of another. At any instant a neuron has some threshold, which excitation must exceed to initiate an impulse. This, except for the fact and the time of its occurrence, is determined by the neuron, not by the excitation. From the point of excitation the impulse is propagated to all parts of the neuron. The velocity along the axon varies directly with its diameter, from less than one meter per second in thin axons, which are usually short, to more than 150 meters per second in thick axons, which are usually long. The time for axonal conduction is consequently of little importance in determining the time

Machine Learning

- Forget models of reality!
- ...let's just do function approximation instead.
- Data is some set of featurized vectors x
  - can have labels (or not)
- Learn functions parameterized by weights
  - minimize a loss function however you can
  - control model complexity to avoid overfitting
- Evaluate predictive accuracy on held-out data

Deep Learning

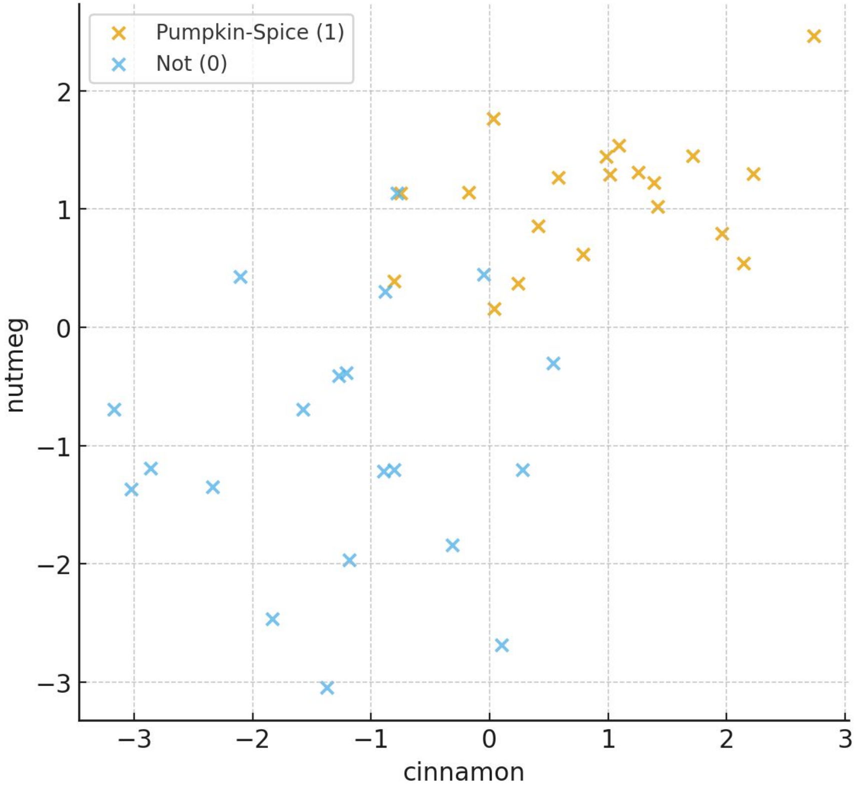
Like machine learning but…

- terminology inspired by brains
    - “neurons”
    - “layers”
- make the models as big as possible
    - surprisingly, overfitting doesn’t matter
- train arbitrary compute graphs with gradient descent

A Pumpkin Flavored Example

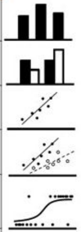
Is it a Pumpkin Spice Latte?

```python
import numpy as np
import pandas as pd
from sklearn.model_selection import train_test_split
from sklearn.metrics import roc_auc_score, log_loss, accuracy_score, brier_score_loss

rng = np.random.default_rng(0)

# Tiny, overlapping 2D Gaussians (avoid separation)
n_per = 20
ps_mean = np.array([ 0.8,  0.8])  # Pumpkin-Spice: higher cinnamon/nutmeg
no_mean = np.array([-0.8, -0.8])  # Not
cov = np.array([[1.0, 0.2],
                [0.2, 1.0]])

X_ps = rng.multivariate_normal(ps_mean, cov, size=n_per)
X_no = rng.multivariate_normal(no_mean, cov, size=n_per)
X = np.vstack([X_ps, X_no])
y = np.hstack([np.ones(n_per), np.zeros(n_per)])

df = pd.DataFrame(X, columns=["cinnamon","nutmeg"]).assign(psl=y.astype(int))

# Shared train/test split; *all* cultures use the same training data
X_train, X_test, y_train, y_test = train_test_split(
    df[["cinnamon","nutmeg"]].values, df["psl"].values,
    test_size=0.4, random_state=0, stratify=df["psl"].values
)
```



Statistics Flavored Logistic Regression

Dependent variable	Explanatory variables	Model type
Quantitative	1 qualitative with k levels	1-way ANOVA
	Several qualitative	Multi-way ANOVA
	1 or several quantitative	Linear regression
	Mixture of qualitative & quantitative	ANCOVA
Qualitative	1 or several quantitative or qualitative	Logistic regression
Counts with many zeros	1 or several quantitative or qualitative	Log-linear regression



Link: which modeling method to choose?

```python
import numpy as np, pandas as pd, statsmodels.api as sm
from sklearn.metrics import roc_auc_score, log_loss, accuracy_score, brier_score_loss, confusion_matrix

# === Fit ridge (your code) ===
Xtr_sm = sm.add_constant(X_train)
logit = sm.Logit(y_train, Xtr_sm)
res_ridge = logit.fit_regularized(alpha=1.0, L1_wt=0.0)  # try alpha in {0.1, 1, 10}

# === Coef table ===
terms   = res_ridge.model.exog_names
beta    = np.asarray(res_ridge.params)
coef_tbl = pd.DataFrame({"term": terms, "coef": beta, "odds_ratio": np.exp(beta)}).round(3)
print("=== Coefficients (ridge) ===")
print(coef_tbl.to_string(index=False))
```

Inspect everything!

```python
# === Coef table ===
terms  = res_ridge.model.exog_names
beta   = np.asarray(res_ridge.params)
coef_tbl = pd.DataFrame({"term": terms, "coef": beta, "odds_ratio": np.exp(beta)}).round(3)
print("=== Coefficients (ridge) ===")
print(coef_tbl.to_string(index=False))

# === Helper: unpenalized log-likelihood at given beta ===
def loglik_logit(beta, X, y):
    z = X @ beta
    # numerically stable log-sigmoid pieces
    # log(sigmoid(z)) = -softplus(-z); log(1-sigmoid(z)) = -softplus(z)
    ll = (y * (-np.log1p(np.exp(-z))) + (1 - y) * (-np.log1p(np.exp(z)))).sum()
    return float(ll)

# Train diagnostics (unpenalized LL evaluated at penalized beta)
n, k = Xtr_sm.shape
ll_full = loglik_logit(beta, Xtr_sm, y_train)

# Null (intercept-only) model log-likelihood
p0 = y_train.mean()
ll_null = (y_train*np.log(p0) + (1-y_train)*np.log(1-p0)).sum()

deviance   = -2.0 * ll_full
mcfadden_r2 = 1.0 - (ll_full / ll_null)
aic = 2*k - 2*ll_full      # using unpenalized LL
bic = np.log(n)*k - 2*ll_full

print("\n=== Train diagnostics (evaluated at penalized estimates) ===")
print(f"Log-likelihood (full): {ll_full:.3f}")
print(f"Log-likelihood (null): {ll_null:.3f}")
print(f"Deviance:              {deviance:.3f}")
print(f"McFadden R^2:          {mcfadden_r2:.3f}")
print(f"AIC (k={k}):            {aic:.3f}")
print(f"BIC (k={k}):            {bic:.3f}")
print("Note: AIC/BIC use the unpenalized log-likelihood at the penalized β̂; exact penalty-aware ICs require effective df.")

# === Test-set metrics ===
Xte_sm = sm.add_constant(X_test, has_constant='add')
proba  = res_ridge.predict(Xte_sm)
pred   = (proba >= 0.5).astype(int)

auc   = roc_auc_score(y_test, proba)
lloss = log_loss(y_test, proba, labels=[0,1])
acc   = accuracy_score(y_test, pred)
brier = brier_score_loss(y_test, proba)
tn, fp, fn, tp = confusion_matrix(y_test, pred).ravel()
sens = tp / (tp + fn) if (tp+fn) else np.nan   # recall, TPR
spec = tn / (tn + fp) if (tn+fp) else np.nan   # TNR

print("\n=== Test metrics ===")
print(f"AUC:     {auc:.3f}")
print(f"LogLoss: {lloss:.3f}")
print(f"Acc:     {acc:.3f}")
print(f"Brier:   {brier:.3f}")
print(f"Confusion: TP={tp}, FP={fp}, TN={tn}, FN={fn}")
print(f"Sensitivity (TPR): {sens:.3f}")
print(f"Specificity (TNR): {spec:.3f}")
```

```
Optimization terminated successfully    (Exit mode 0)
            Current function value: 0.2645366576404406
            Iterations: 17
            Function evaluations: 17
            Gradient evaluations: 17
=== Coefficients (ridge) ===
 term  coef  odds_ratio
const 0.000       1.000
   x1 0.983       2.673
   x2 2.029       7.606

=== Train diagnostics (evaluated at penalized estimates) ===
Log-likelihood (full): -3.337
Log-likelihood (null): -16.636
Deviance:              6.674
McFadden R^2:          0.799
AIC (k=3):           12.674
BIC (k=3):           16.208
Note: AIC/BIC use the unpenalized log-likelihood at the penalized β̂; exact penalty-aware ICs require effective df.

=== Test metrics ===
AUC:     1.000
LogLoss: 0.250
Acc:     0.875
Brier:   0.089
Confusion: TP=8, FP=2, TN=6, FN=0
Sensitivity (TPR): 1.000
Specificity (TNR): 0.750
```

Machine Learning

```
from sklearn.pipeline import Pipeline
from sklearn.preprocessing import StandardScaler
from sklearn.linear_model import LogisticRegression

pipe = Pipeline([
    ("scaler", StandardScaler()),
    ("logreg", LogisticRegression())
])
pipe.fit(X_train, y_train)

pred_probs = pipe.predict_proba(X_test)[:,1]
pred_labels  = (proba_ml >= 0.5).astype(int)

print("AUC:", round(roc_auc_score(y_test, pred_probs), 3))
print("Accuracy:", round(accuracy_score(y_test, pred_labels), 3))
```

```
AUC: 1.0
Accuracy: 0.812
```

Deep Learning

```python
import torch
from torch import nn
import numpy as np
from sklearn.metrics import roc_auc_score, log_loss, accuracy_score

# Assume X_train, y_train, X_test, y_test are NumPy arrays
torch.manual_seed(0)

# Tensors
Xtr = torch.tensor(X_train, dtype=torch.float32)
ytr = torch.tensor(y_train, dtype=torch.float32).view(-1, 1)
Xte = torch.tensor(X_test,  dtype=torch.float32)
yte = torch.tensor(y_test,  dtype=torch.float32).view(-1, 1)

# Model: linear -> sigmoid (returns probabilities in (0,1))
model = nn.Sequential(
    nn.Linear(Xtr.shape[1], 1),
    nn.Sigmoid()
)

# Loss takes probabilities because we already applied Sigmoid
loss_fn = nn.BCELoss()
opt = torch.optim.SGD(model.parameters(), lr=0.1)

# Train (full-batch for simplicity)
for _ in range(200):
    p = model(Xtr)                    # predicted probabilities
    loss = loss_fn(p, ytr)
    opt.zero_grad()
    loss.backward()
    opt.step()

# Evaluate
with torch.no_grad():
    pred_probs = model(Xte).numpy().ravel()   # probabilities directly
pred_labels = (pred_probs >= 0.5).astype(int)

print("AUC:",      round(roc_auc_score(y_test, pred_probs), 3))
print("Accuracy:", round(accuracy_score(y_test, pred_labels), 3))
```

```
AUC: 1.0
Accuracy: 0.812
```

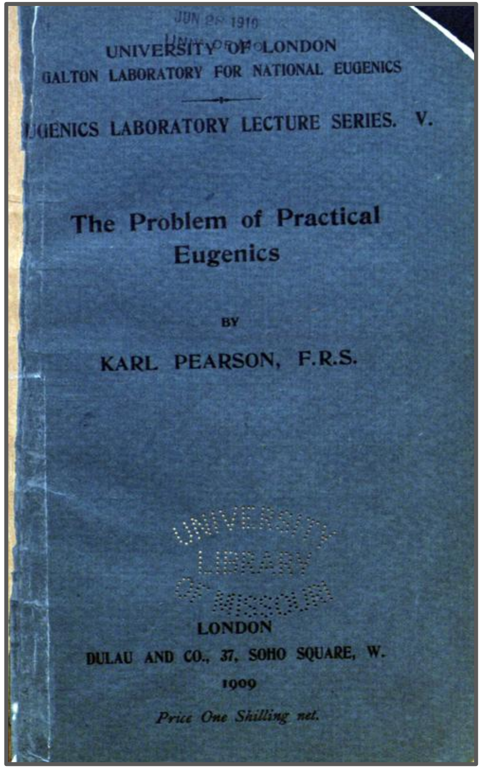

```python
# Model: linear -> sigmoid (returns probabilities in (0,1))
model = nn.Sequential(
    nn.Linear(Xtr.shape[1], 1),
    nn.Sigmoid()
)
```

Fin

Side note: 2/4 “fathers” of statistics were <u>very</u> into eugenics

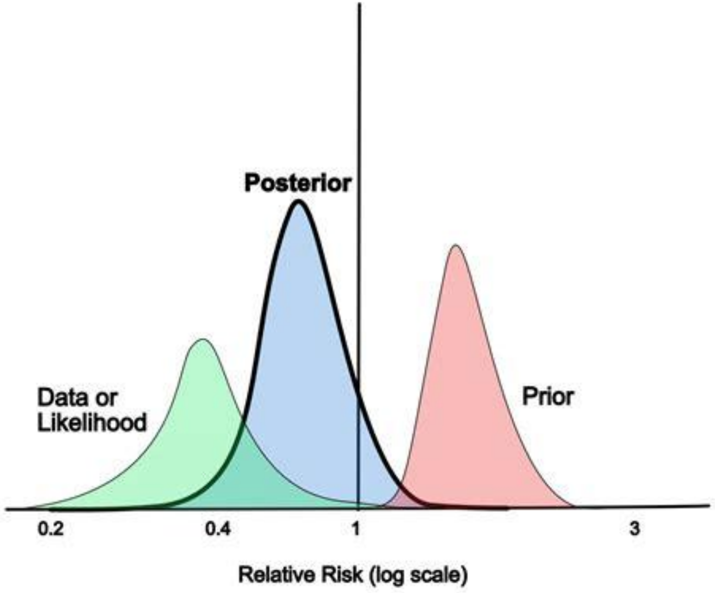
“...eugenics urges us to simplify our lives, and to simplify our needs; the only luxury worth having is that of a worthy human environment. We must be ready to sacrifice social success, at the call of nobler instincts.” -R. A. Fisher

“History shows me one way, and one way only, in which a high state of civilization has been produced, namely, the struggle of race with race, and the survival of the physically and mentally fitter race.” -Karl Pearson



Bayesian Statistics

- Why are we accepting or rejecting a hypothesis?
- Why do we think there’s a single “true” value to parameters?
- Inference should give us a full probability distribution



https://www.thebottomline.org.uk/blog/ebm/bayesian-statistics/