Machine Learning for Scientific Discovery

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Data61 | CSIRO, Canberra

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Faculté Informatique et Communications, EPFL
- NICTA merger
- Part of CSIRO, focus on ICT
- Approx 1000 researchers, PhD students and university staff
Applications - Optimization - Models

Mathematical Model

\[ \min_{w,b} \frac{1}{2} \|w\|^2 + C \sum_{i=1}^{n} \xi_i \]

s.t. \[ y_i(\langle w, x_i \rangle + b) \geq 1 - \xi_i \]

Numerical Optimization

Prediction Task

freq

\[ AV \]

mldata.org

mloss.org

Python
What is machine learning?

Machine learning is about prediction

<table>
<thead>
<tr>
<th>Examples/features</th>
<th>$x_1, \ldots, x_n \sim X$</th>
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<tbody>
<tr>
<td>Labels/annotations</td>
<td>$y_1, \ldots, y_n \sim Y$</td>
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<tr>
<td>Predictor</td>
<td>$f_w(x) : X \rightarrow Y$</td>
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</table>

Estimate best predictor = training

Given data $(x_1, y_1), \ldots, (x_n, y_n)$, find a predictor $f_w(\cdot)$.

- No mechanistic model of the phenomenon
- There is relatively large amounts of data (examples, $x$ usually $\mathbb{R}^d$)
- The outcomes (labels, $y$ usually binary) are well defined

Prediction ≠ understanding

How can we use prediction to help with scientific research?
Today: focus on the predictor

\[ f_W(x) : \mathcal{X} \to \mathcal{Y} \]

**Label: Finding black holes**

- Exist physical models, we directly use images
- There is relatively large amounts of data (examples)
- Object localisation with crowd labels

**Feature: Finding genetic associations**

- No mechanistic model of the phenomenon
- High dimensional low sample size
- Stability of feature selection

**Predictor: Finding good experiments**

- Partial mechanistic model of the phenomenon
- Estimate the expected information gain

Discuss challenges to applying machine learning
Not standard binary classification

\[ f_w(x) : \mathcal{X} \rightarrow \mathcal{Y} \]
Finding black holes

Goal: Automate radio cross-identification, a problem in astronomy

Too much data
- Collaboration with ANU, ANTF, CAASTRO
- Square kilometer array (South Africa and Australia)

Labelled by non-experts
- Convert object localisation to binary classification
- Deal with label noise
Radio cross-identification

Optical  Infrared  X-ray  Radio

Images of Centaurus A at different wavelengths.
The real data

The same patch of sky in both radio (left) and infrared (right)
Localisation as binary classification

Galaxy catalogue as candidates
Could scan a patch across the sky

Classify pairs of images

positive

negative

Features: Neural network image features, fluxes, radial distance

https://github.com/chengsoonong/crowdastro
Crowdsourcing labels

Radio Galaxy Zoo:
citizen science project to cross identify radio galaxies

About 100,000 of 177,000 image pairs labelled.

- 5 volunteers per pair for compact sources
- 20 volunteers per pair for complex sources
How to find black holes

Prior catalogues

- Heuristic rules + expert human effort
  Norris et. al. 2006
- Annotation based on physical models
  Fan et. al. 2015
- Use set where both agree as gold standard

Many labels to one binary label

- Logistic regression from `sklearn`
- Majority vote
- EM style algorithm to estimate ground truth
  Raykar et. al. 2010, Yan et. al. 2010

Latent variable model

- Noisy labels = ground truth + biased coin flip
Conclusion: Features meaningful, but pipeline can be improved.
Side note about label noise

Latent variable
Assume that there is a hidden ground truth label, and model it.
Alger, Banfield, Ong, (in preparation)

Learning with label noise
During training, pretend that labels are noiseless, and assume that
the learning algorithm takes care of it.
Menon, van Rooyen, Ong, Williamson, ICML 2015

Model evaluation
How do we measure performance without ground truth?
What are good features?

\[ f_w(x) : \mathcal{X} \rightarrow \mathcal{Y} \]
Case-control studies
A cohort of sick individuals (cases) and healthy individuals (controls) are genotyped and their corresponding binary phenotype are recorded.

We use the framework of hypothesis testing

Hypothesis testing Given a case control study, test whether a particular SNP is associated with the phenotype.

Good biomarker? If difference is statistically significant

⇒

SNP is associated with the phenotype.
Genome Wide Interaction Search (GWIS)
Consider the association of all pairs of genotypes to phenotypes

Large search space
- 5000 individuals, 500,000 SNPs (WTCCC)
- Need to tabulate 125 billion contingency tables

Classification based analysis
- Focus on SNPs in case control studies
- New statistical tests
- Consider specificity and sensitivity
- Gain over univariate ROC
- CPU (≈ days) and GPU (≈ hours)
- Store the top 1 million pairs

Web service
Goudey,...,Ong,...,Kowalczyk, BMC Genomics, 2013
Interpreting p-values

Is $10^{-10}$ probability of association very significant?

**Quote**

... but a reliable method of procedure. In relation to the test of significance, we may say that a phenomenon is experimentally demonstrable when we know how to conduct an experiment which will rarely fail to give us a statistically significant result.


**Stability of scoring**

We consider p-values as a score of association.

- How stable is this score if we repeat the experiment?
- How do we combine scores?

**Challenges**

- Scores available for only the top-k examples
- Scores from different sources not calibrated
Multiple ways to represent ranks

- Ordered list of $n$ objects selected from $\Omega$
- List of values $[1, \ldots, n]$ (the ranks of the object)
- Normalised ranks $\in (0, 1)$
- Permutation mapping $R : \Omega \rightarrow (0, 1)$
Measuring Overlap

Motivation
Given a set of replicated experiments, how do we measure overlap?

Examples
- Perform repeated splits of the data
- Experiments on different cohorts
- Multiple sources of information

Challenges
- Scores available for only the top-k examples
- Scores from different sources not calibrated
Set based overlap

Running example (6 objects)

\[ A = [a, b, c, d, e, f] \]
\[ B = [a, b, e, f, c, d] \]

Jaccard Index

\[ \text{overlap} = \frac{|A \cap B|}{|A \cup B|} \]

Measuring stability

- Easy to compute
- Works for top-k lists
  Consider the top-3 lists from above:

\[ \text{Jaccard index} = \frac{|\{a, b\}|}{|\{a, b, c, e\}|} = \frac{1}{2} \]

- Ignores the order given by scores
Spearman’s ρ

Similar to Pearson’s correlation for the measure of dependence

Spearman’s ρ is a correlation measure between ranked lists

\[
\rho(A, B) := \frac{\sum_i (r_A^{(i)} - \bar{r}_A)(r_B^{(i)} - \bar{r}_B)}{\sqrt{\sum_i (r_A^{(i)} - \bar{r}_A)^2 \sum_i (r_B^{(i)} - \bar{r}_B)^2}}
\]

Running example:

\[
\rho([a, b, c, d, e, f], [a, b, e, f, c, d]) = 0.543
\]

(Jaccard index = 1)

Need the same elements in A and B

\[
\rho([a, b, c], [a, b, e])?
\]
**Spearman’s $\rho$ on top $k$ lists**

**Simple idea**
Define Spearman’s $\rho$ for top $k$ lists

**Key observation**
Any elements in list $A$ that do not appear in list $B$ must have a rank higher than the number of elements in $B$

**Running example (top-3)**

$$A = [a, b, c, d, e, f] \quad \text{and} \quad B = [a, b, e, f, c, d]$$

$$A_3 = [a, b, c] \quad \text{and} \quad B_3 = [a, b, e]$$

$$A_3^{B_3} = [a, b, c, e] \quad \text{and} \quad B_3^{A_3} = [a, b, e, c]$$

Spearman’s $\rho = \rho(A_3^{B_3}, B_3^{A_3}) = 0.8$
Extend the list
We expand lists $A$ and $B$ to complete rankings over the same set of elements, denoting them as $A^B \rightarrow$ and $B^A \rightarrow$ respectively.

The missing values in the extension are given the average rank.

Running example (top-4)

$$A_4 = [a, b, c, d] \quad \text{and} \quad B_4 = [a, b, e, f]$$

$$A_4^B \rightarrow = [1, 2, 3, 4, 5.5, 5.5] \quad \text{and} \quad B_4^A \rightarrow = [1, 2, 5.5, 5.5, 3, 4]$$

Makes no assumption about the order of the unranked objects

Other possible imputation approaches
- Optimistic
- Worst case

Bedő, Rawlinson, Goudey, Ong, PLoS ONE, 2014
Frank copula (sample)
Spearman’s $\rho$
Simulate two cohorts by splitting

Cross validation stability for raWTC-GSS

Spearman's $\rho$

Top $k$ GWIS pairs

Bedő, Rawlinson, Goudey, Ong, PLoS ONE, 2014
Measuring Overlap

Motivation

Given a set of replicated experiments, how do we measure overlap?

Challenges

- Scores available for only the top-k examples
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Model

- Ranked list: Instead of just using set intersection, we can use the scores from GWIS to order the results
- top k: Traditional methods (Spearman’s $\rho$) requires ranks for the whole list. We have incomplete information, but we know our ranks are the top ones.

Multivariate: Textbook Spearman’s $\rho$ is for computing correlation between two ranks. We want to compute the correlation between multiple ranked lists.

Bedő, Ong, JMLR (to appear)
Multiple replicates

Cross validation stability for raWTC-GSS

- Optimistic
- Empirical
- Bivariate

Spearman's $\rho$

Top $k$ GWIS pairs

$10^1$ $10^2$ $10^3$ $10^4$ $10^5$
*-Seq

dsRNA-Seq
FRAG-Seq
SHAPE-Seq
PARTE-Seq
PARS-Seq
DMS-Seq

Nucleo-Seq
DNAse-Seq
Sono-Seq
ChIA-PET-Seq
FAIRE-Seq
NOMe-Seq
ATAC-Seq

GRO-Seq
Quartz-Seq
CAGE-Seq
Nascent-Seq
Cel-Seq
3P-Seq

https://liorpachter.wordpress.com/seq/
Integrating different sources of data

Association Study

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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Sequence Analysis

Variation
- SNP
- Structural
- Methylation
- Expression
- ...

ID3023
ID4454
ID7675
ID2283
Rank aggregation

Modeling using Spearman’s correlation

Stability of feature selection
How to measure overlap?

\[ \rho(R_1, \ldots, R_d) \]

Rank aggregation
How to combine different sources of information?

Macintyre, Yepes, Ong, Verspoor, PeerJ, 2014
Optimal aggregator: geometric mean

How to combine different sources of information?
We maximise multivariate correlation

$$R^* = \arg \max_R \rho(R, R_1, R_2, \ldots, R_d).$$

**Theorem** The aggregator that maximises multivariate Spearman’s correlation is the product of the normalised ranks.

Use the geometric mean

**NOT pairwise correlation**
Instead of decomposing the association into a combination of pairwise similarities $\rho(R, R_1), \rho(R, R_2), \ldots, \rho(R, R_d)$.

**Learning weighting of experts**
We can also do supervised learning to rank

Bedő, Ong, JMLR (to appear)
What are good biomarkers?

Genome Wide Association Studies
- Which mutations are associated with tall poppies?
- Identify biomarkers with hypothesis tests

Finding stable biomarkers
- Split cohort into two (cross validation)
- Investigate rank correlation between scores

Integrating information via ranks
- Multivariate Spearman correlation using copulas
- Geometric mean is the optimal aggregator
What to measure?

\[ f_w(x) : X \rightarrow Y \]
Use predictor to identify good candidates

- Annotate top-k items
- Confidence interval improves performance
- Explore - exploit tradeoff

Krause, Ong, NIPS 2011

Finding black holes and redshifts

- Machine learning to classify images
- Show 10 candidates to expert daily

Collaboration with ANU, ANTF, CAASTRO

Glucose metabolism in Yeast

- Multiple possible models
- Design biological experiments that maximise information gain

Collaboration of ETHZ with SystemsX Switzerland
What is a model?

Bergman insulin dependent glucose metabolism model.
TOR pathway

The diagram illustrates the TOR pathway with key components including Rapamycin, Fpr1, Tor1/2, Tip41, Tap42, Sit4, Pph21/22, and Cdc55/Tpd3. Rapamycin interacts with Fpr1, which in turn affects Tor1/2. Tip41 and Tap42 are also crucial in this pathway, with interactions involving Sit4 and Pph21/22. The pathway highlights the regulation of various targets such as Gln3, Msn2, and eIF2a.
Finding good models

*a priori* belief state

- high uncertainty (low gain)

*a posteriori* belief state

- high uncertainty

+ data update (high gain)

- low uncertainty
Optimised experimental design

Measurements
Experiments produce readouts $y(t_i)$, grouped into datasets $Y_\pi$ for an experiment $\pi$.

Bayes rule
For a particular model $f$, (taking care of parameters)

$$p(f|Y_\pi) = \frac{p(Y_\pi|f)p(f)}{p(Y_\pi)}$$

Information gain
We want to take measurements that change model probabilities

$$D_{KL}[p(f|Y_\pi)||p(f)] = \sum_{f \in \mathcal{F}} p(f|Y_\pi) \log_2 p(f|Y_\pi)/p(f)$$

Marginalise over possible outcomes
Maximise expected information gain (tough computational problem)

$$\arg\max_{\pi} \mathbb{E}_{Y_\pi} D_{KL}[p(f|Y_\pi)||p(f)]$$
What is a biomarker?

How to measure?
Use adaptive experimental design to identify important time series.
Busetto et. al. Near-optimal experimental design for model selection in systems biology, 2013

What to measure?
Combine various sources of information for robust decision making.
Macintyre et. al. Associating disease-related genetic variants in intergenic regions to the genes they impact, 2014

Where to measure?
Use expert domain knowledge to construct dynamical models.
Brodersen et. al. Generative embedding for model-based classification of fMRI data, 2011
A more philosophical section...

\[ f_w(x) : X \rightarrow Y \]

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- There is relatively large amounts of data (examples)
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**Predictor: Finding good experiments**
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Discuss challenges to applying machine learning
Mathematical Model

\[
\min_{w,b} \frac{1}{2} \|w\|^2 + C \sum_{i=1}^{n} \xi_i
\]

s.t. \( y_i (\langle w, x_i \rangle + b) \geq 1 - \xi_i \)

Numerical Optimization

Prediction Task

freq

2-mers

freq

AV

Mathematical Model

min

\( w, b \)

1

2

\[ w \]

+ \( C \)

\[ n \]

\[ i = 1 \]

\[ \xi_i \]

s.t.

\[ y_i (\langle w, x_i \rangle + b) \geq 1 - \xi_i \]

\( f(x_{t+1}) \)

\[ x_{t+1} \]

\[ a < b \]
Scoring candidates - ABCDE

Active Learning
- Choose a particular example to label using heuristics
- Annotator assumed to provide ground truth

Bandits
- Select a choice from a set of actions
- Simple algorithms with theoretical guarantees
- Manage uncertainty with repeated sampling

Choice theory
- Aggregate set of ranks into one ordering
- Economics and social science, impossibility theorems

Designing Experiments
- Choose a set of trials to measure
- Optimisation algorithms with theoretical analysis
- Information theory, real random variables
ML Open Source Software

Wider adoption of methods

- Domain experts can use machine learning core
- Available for teaching

Scientific reproducibility

- Fair comparison of methods
- Access to scientific tools

Community growth

- “Given enough eyeballs, all bugs are shallow”
- Combination of advances

mloss.org  mldata.org
Plug and Pray

Machine Learning Open Source Software
Do We Need Hundreds of Classifiers to Solve Real World Classification Problems?
jmlr.org/papers/v15/delgado14a.html
Spoiler: No

Usability and Reproducibility
(too much) focus on new algorithms
Documentation, modularity issues
Literate programming
yihui.name/knitr jupyter.org
Scientific computing workflows
galaxyproject.org

Dream: App Bazaar for data science
Bumpy road to data science

Two classes of objects

Data
images, counts, raw sensor data, output of simulation, results

Analysis
visualisation, user interface, predictors, observational statistics

Multi-sided platform

- Decentralised architecture, not walled garden
- Enable direct interaction between data owner and analytics system
- Network effect: each new entrant benefits from whole network

Not just tech people
Domain experts, data managers, project management
Wish list

We need an open federated framework for scientific discovery

- Provenance, trust and reliability
- Management of legal rights
- Uncertainty propagation
- Confidentiality and privacy
- Complex workflows
- Late binding ontologies
- Cross organisation, jurisdiction, technical boundaries
- Decouple technique from problem
- No proprietary control
- *-as-a-service
One more challenge

McCulloch and Pitts, 1943

Multilayer perceptron

Deep neural networks
One more challenge

McCulloch and Pitts, 1943
Multilayer perceptron
Deep neural networks
Today’s ML systems

How to analyse two systems?
Prediction $\neq$ understanding
How can we use prediction to help with scientific research?

Three extensions

- Not standard binary classification $f_w(x) : X \rightarrow Y$
- What are good features? $f_w(x) : X \rightarrow Y$
- What to measure? $f_w(x) : X \rightarrow Y$

Plug and pray

- Software, software, software
- Build the road and rail for data science
- Understand combinations of machine learning components
Prediction ≠ understanding
How can we use prediction to help with scientific research?

Three extensions

- Not standard binary classification: $f_W(x) : X \rightarrow Y$
- What are good features? $f_W(x) : X \rightarrow Y$
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Plug and pray

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Please make your research open

www.ong-home.my
Copulas

Intuition
For continuous random variables, copulas model the dependence component after discounting for univariate marginal effects.

Probabilistic definition
Let $U_1, \ldots, U_d$ be real random variables $\sim U([0, 1])$. A copula function $C : [0, 1]^d \rightarrow [0, 1]$ is a joint distribution

$$C_\theta(u_1, \ldots, u_d) = P(U_1 \leq u_1, \ldots, U_d \leq u_d)$$

The same Gaussian copula function
Copulas and Spearman’s $\rho$

Spearman’s $\rho$ can be expressed in terms of the copula

$$\rho(A, B) = 12 \int_{[0,1]^2} C(u, v) dudv - 3$$

Empirical copula

$$C_n(u, v) = \frac{1}{|\Omega|} \sum_{x \in \Omega} 1 \left( R(x) \leq u, S(x) \leq v \right)$$

Why do the math?

- Unclear how to extend formula for Spearman’s correlation.
- Multivariate distributions $\Rightarrow$ multivariate copula.


Multivariate Spearman’s $\rho$

A multivariate extension of Spearman’s $\rho$

For a $d$ dimensional set of random variables $\mathbf{u}$, the multivariate Spearman’s $\rho$ is given by

$$\rho(R_1, \ldots, R_d) = Q(C, \pi) = h(d) \left( 2^d \int_{[0,1]^d} \pi(\mathbf{u}) \, dC(\mathbf{u}) - 1 \right),$$

where

$$h(d) = \frac{d + 1}{2^d - (d + 1)}.$$

Empirical multivariate Spearman’s corelation

$$\rho_n(R_1, \ldots, R_d) = h(d) \left[ \frac{2^d}{n} \sum_x \prod_{j=1}^d R_j(x) - 1 \right].$$

No negative correlation

As the number of dimensions increases, the lower bound of Spearman’s $\rho$ tends to zero.