Potential Application of Machine Learning in Regulatory Setting

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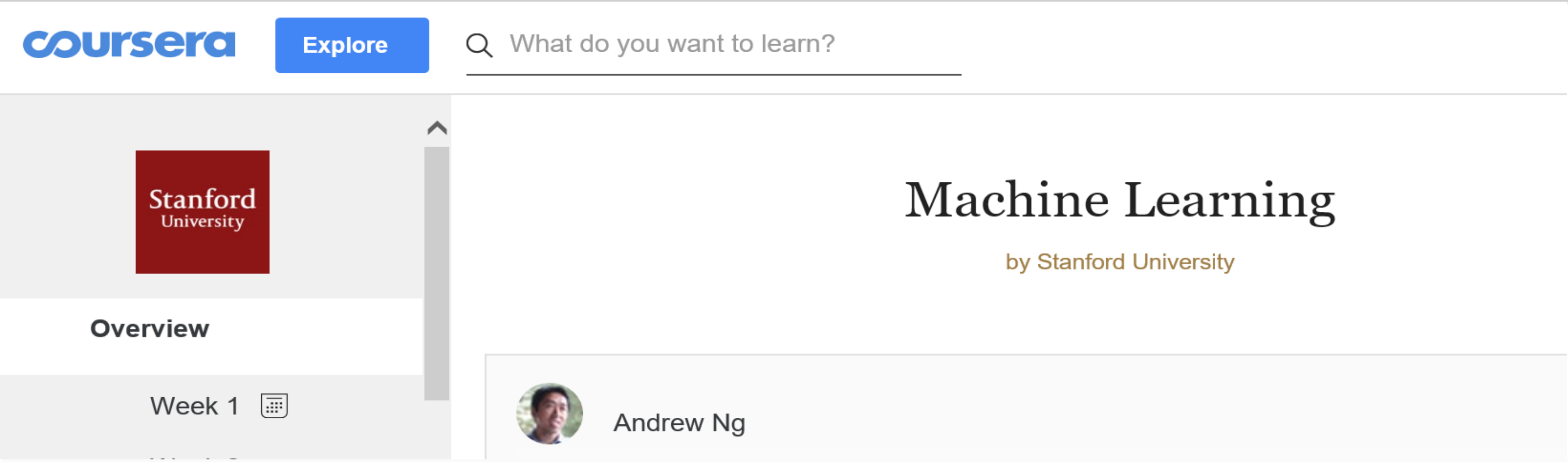
Outline

- Background
- Examples of ML submissions to the FDA
- Examples of ML use at the FDA
- Challenges and future directions

What is Machine Learning (ML)?

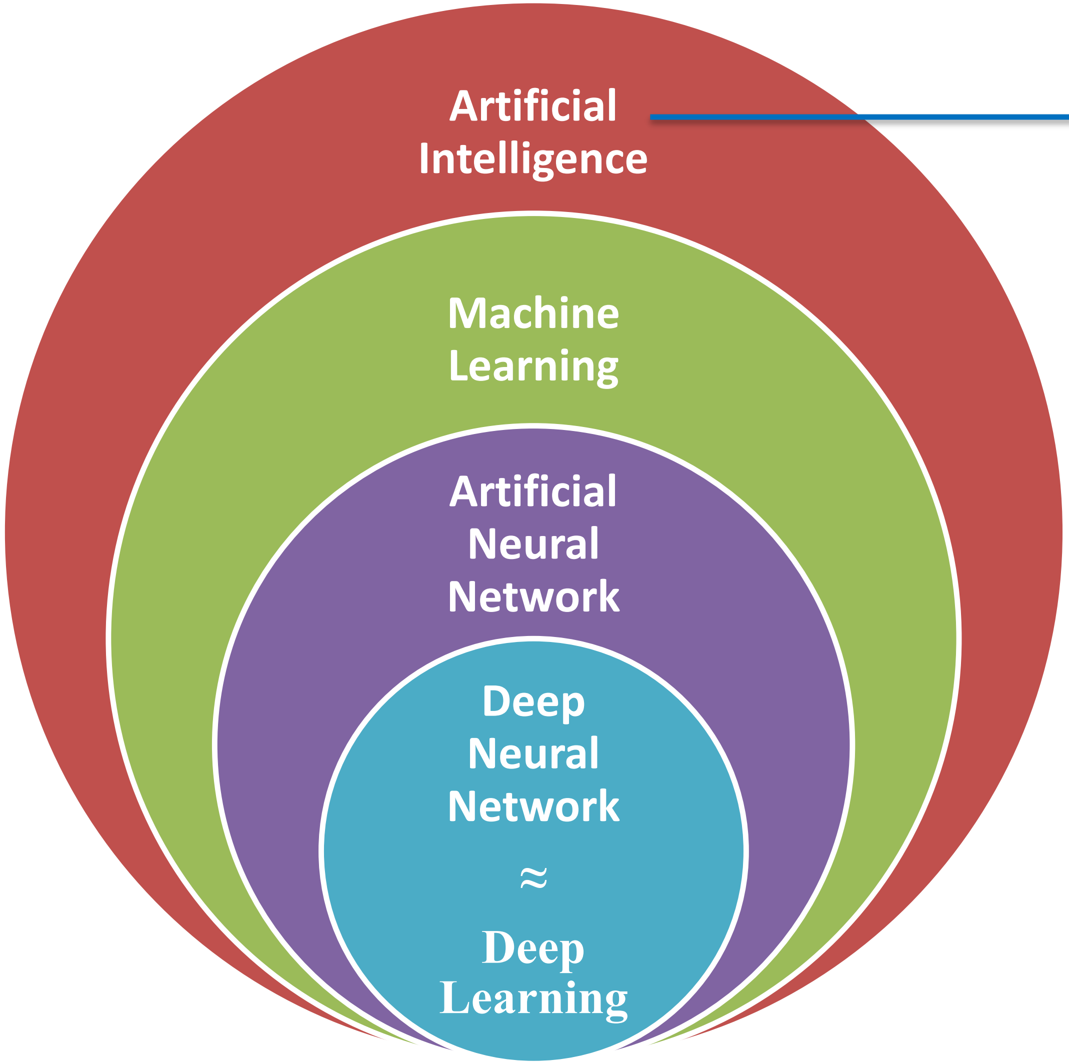


Two definitions of Machine Learning are offered. Arthur Samuel described it as: "the field of study that gives computers the ability to learn without being explicitly programmed." This is an older, informal definition.

Tom Mitchell provides a more modern definition: "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."

https://www.coursera.org/learn/machine-learning/home/welcome

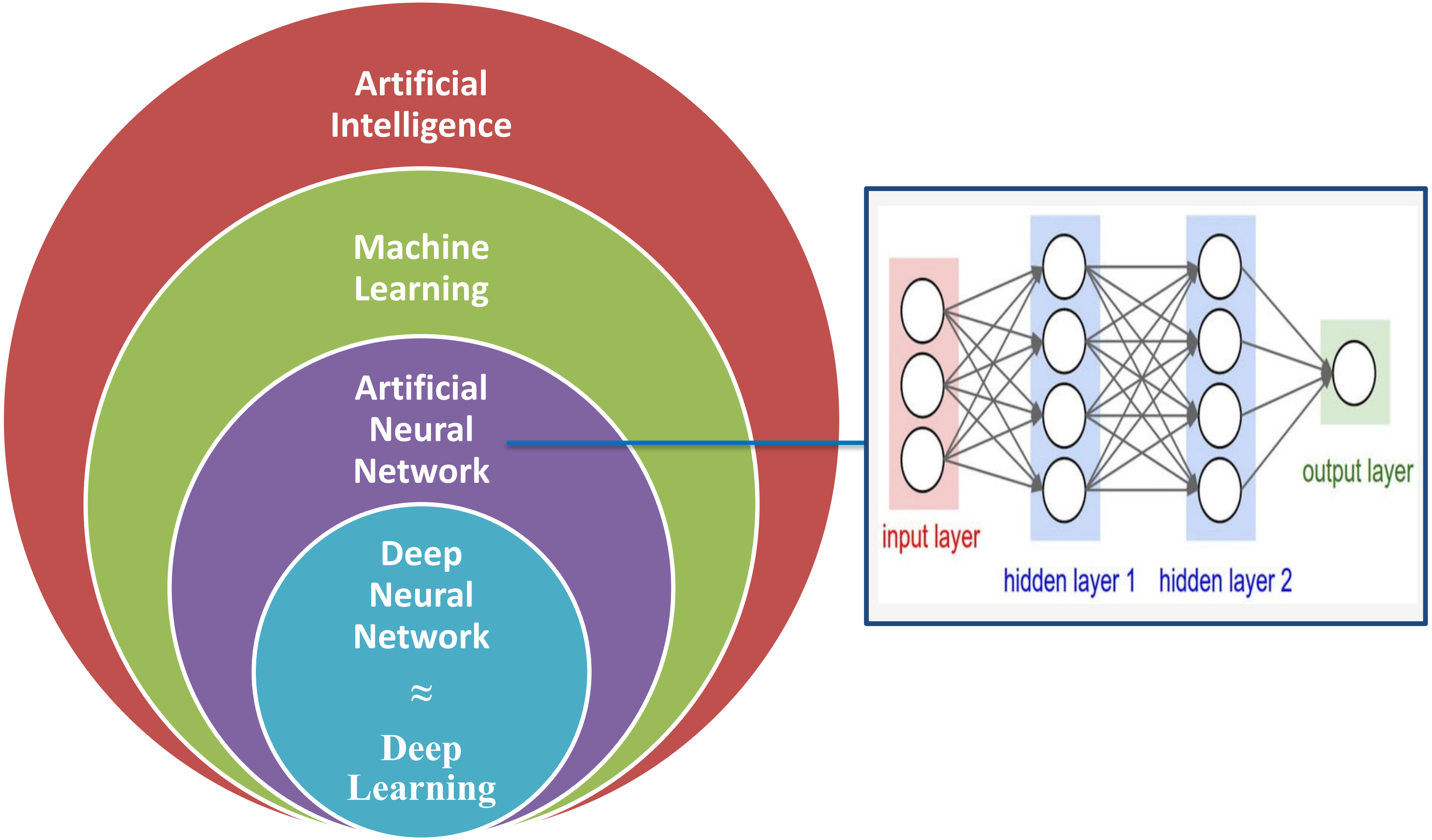
Machine Learning and Related terminology



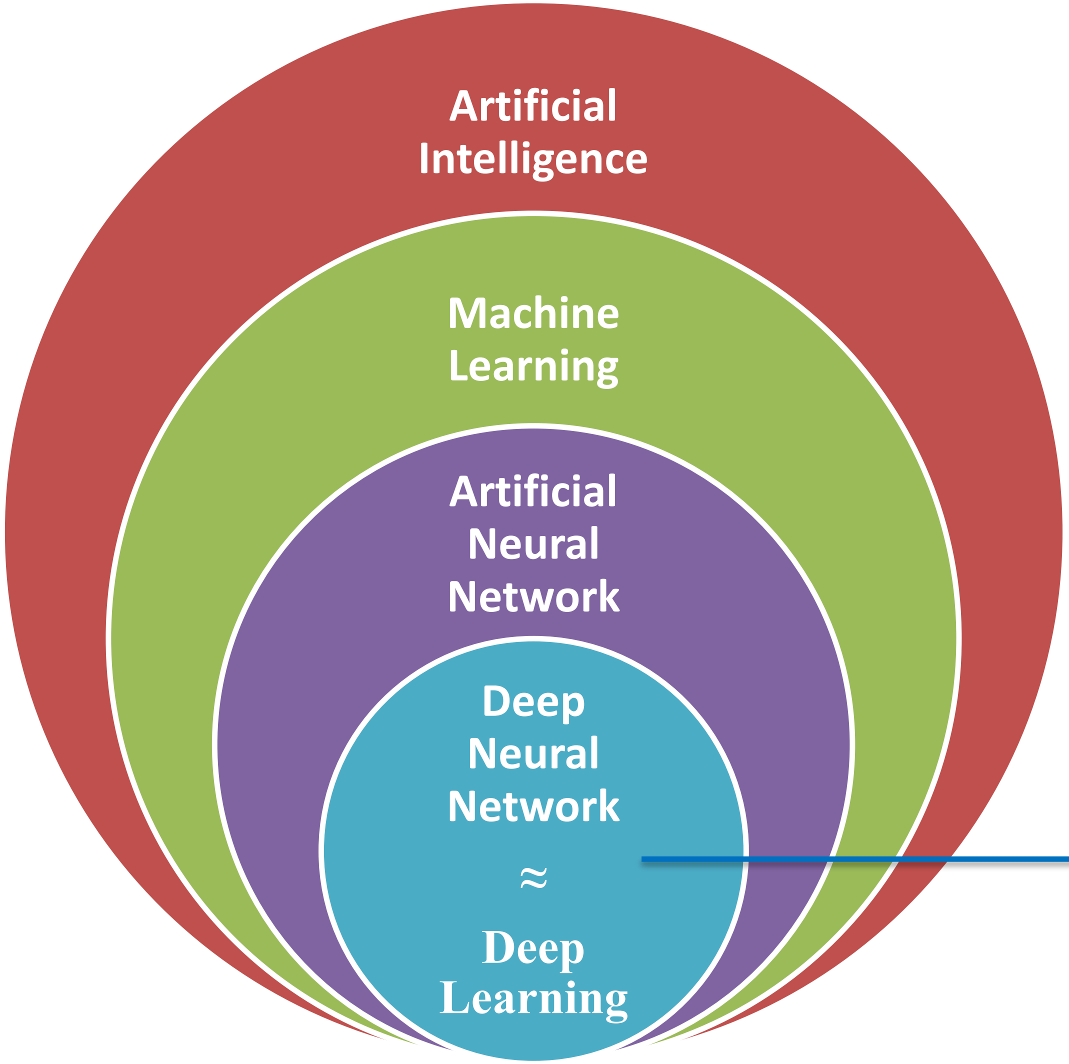
The field of computer science dedicated to solving cognitive problems commonly associated with human intelligence, such as learning, problem solving, and pattern recognition.

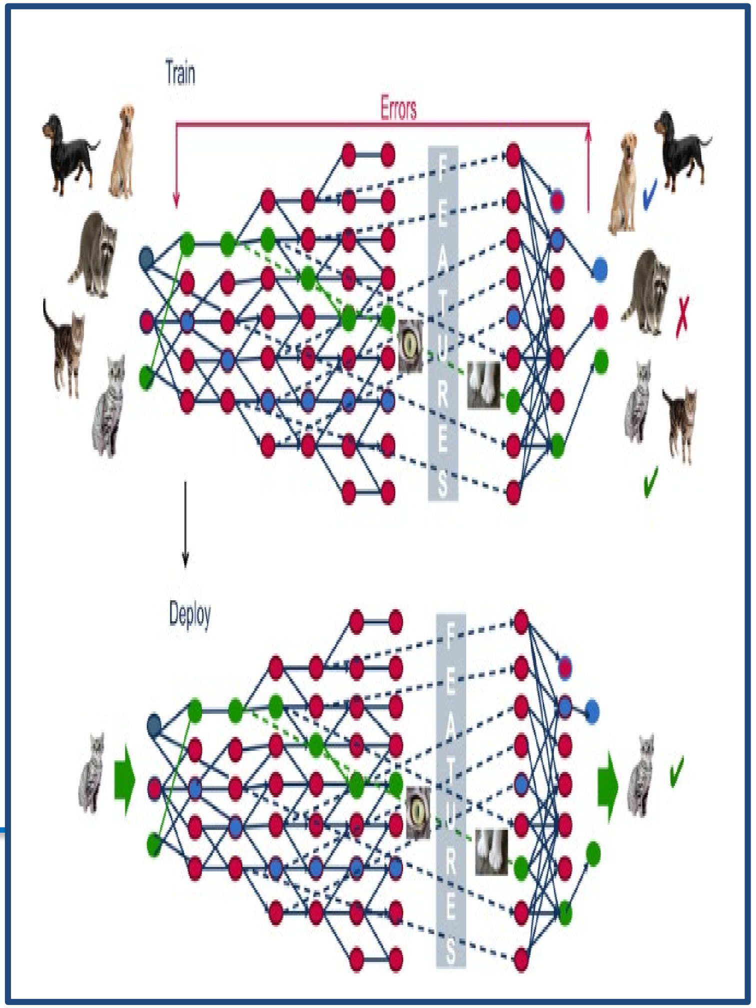
https://aws.amazon.com/machine-learning/what-is-ai/

Machine Learning and Related terminology

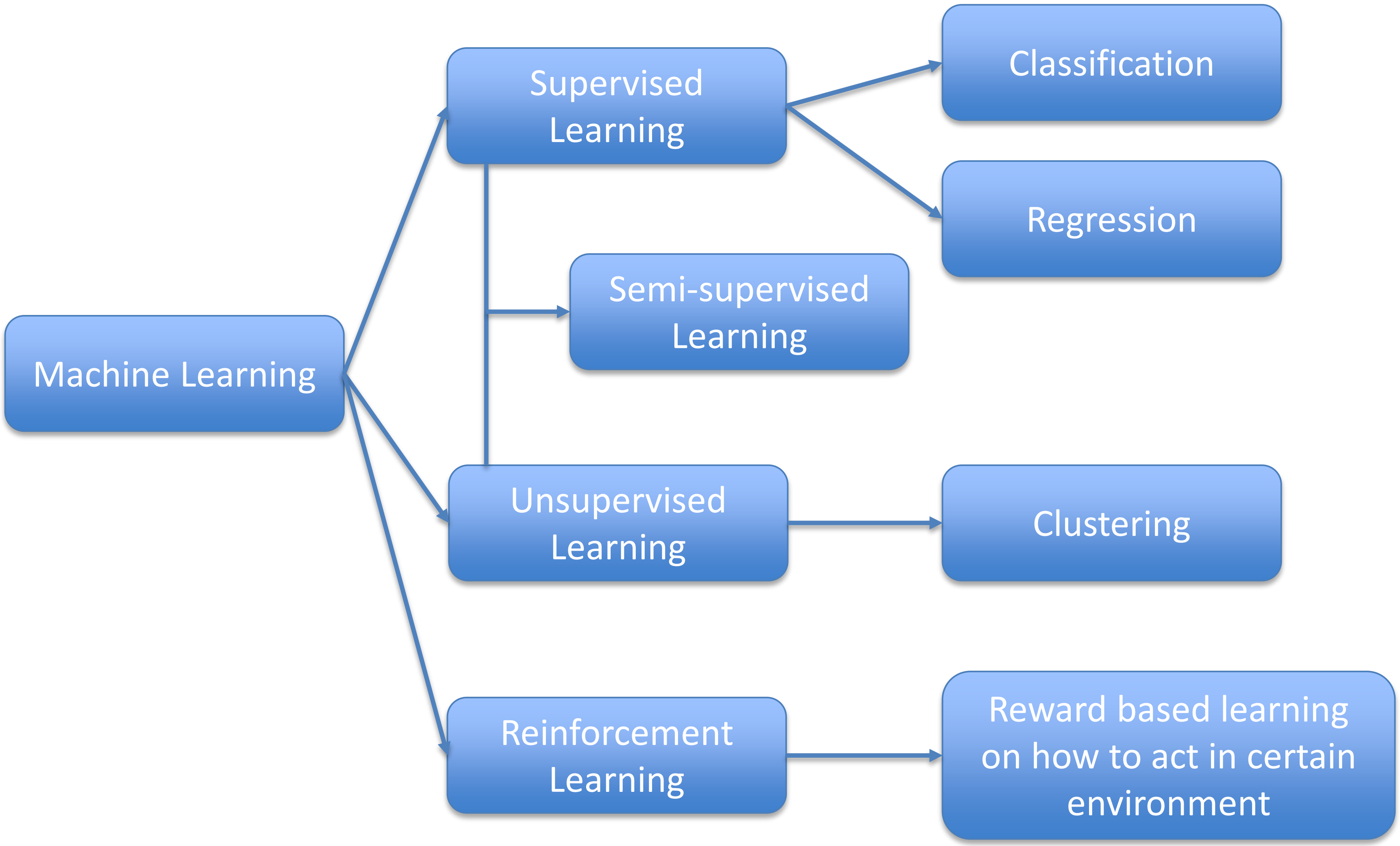


Machine Learning and Related terminology

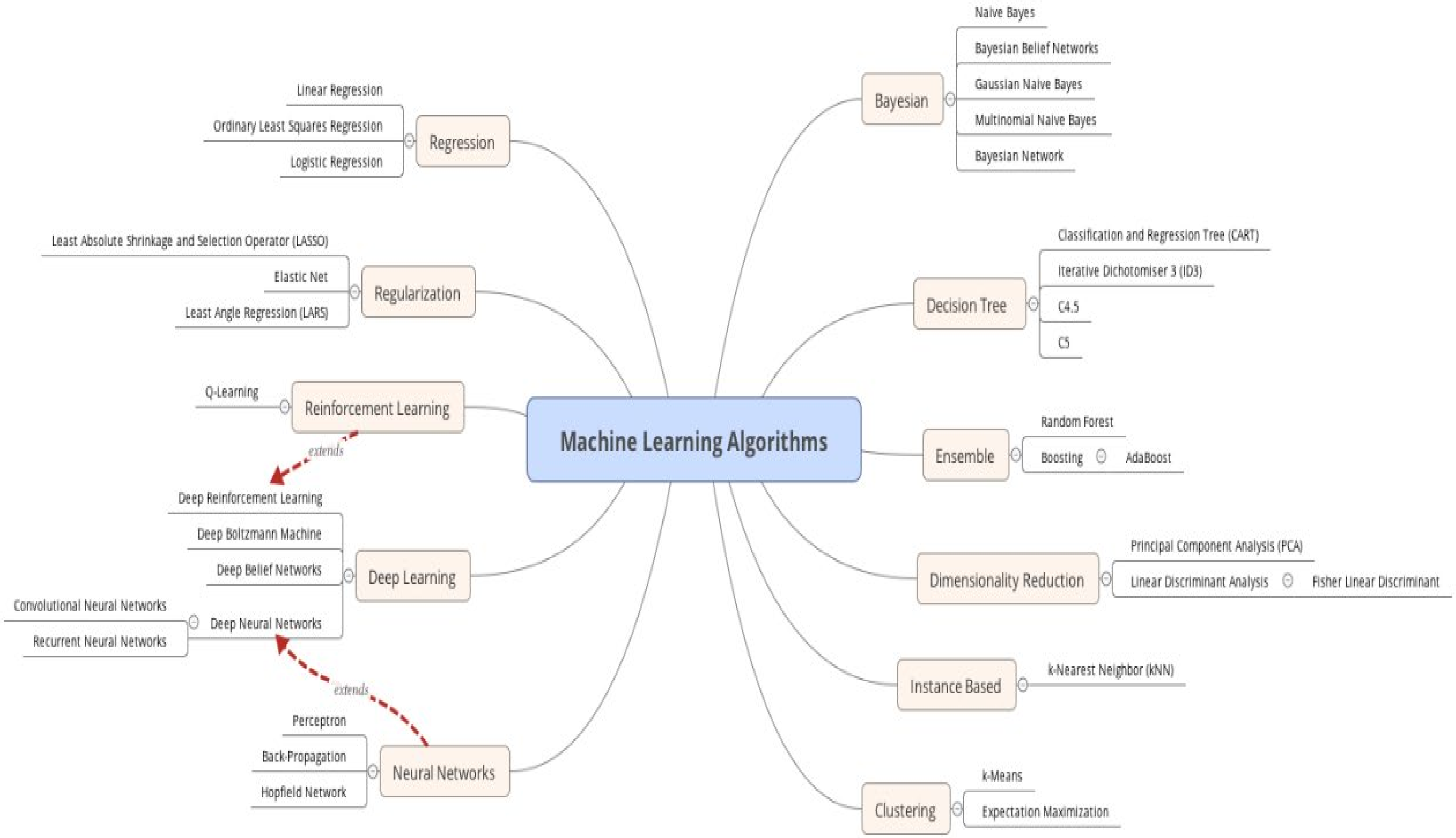




Types of Machine Learning



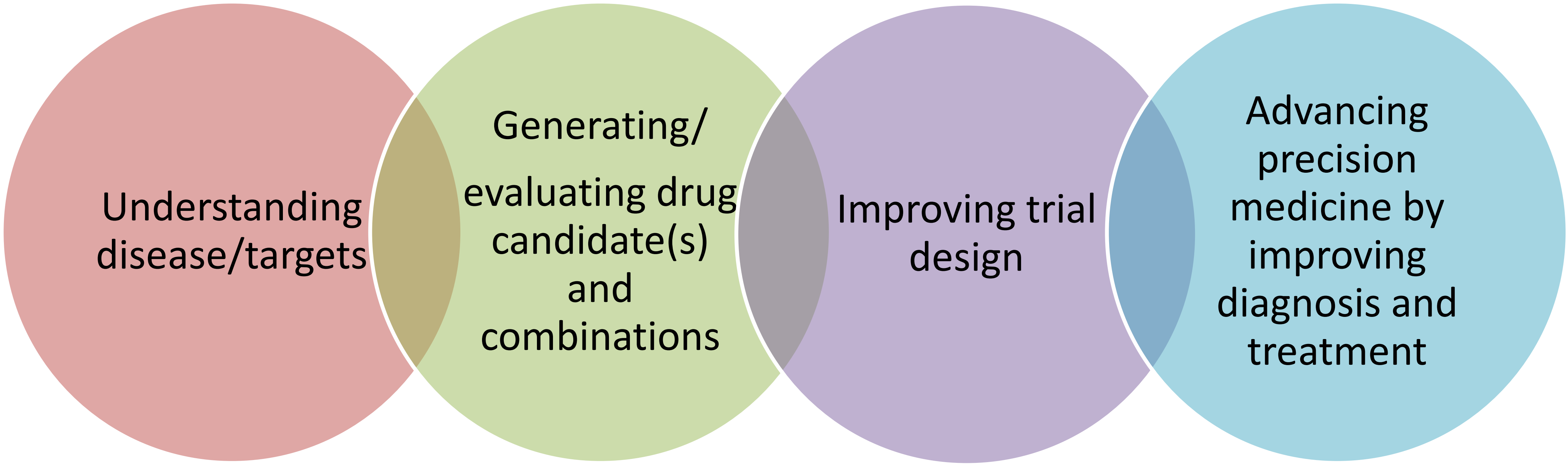
Machine Learning Algorithms



http://web.cs.ucla.edu/~shi.feng/Machine_Learning.html

The Potential Use of ML in Drug Development

Aggregating data, synthesizing information, seeking patterns and optimizing decisions



Examples of ML Submissions to the FDA

- ML-based diagnostic tools
- ML-based pharmacometrics analyses
- ML-based disease models as a drug development tool (randomization aid, patient enrichment, virtual control)
- ML to predict drug response based on baseline factors (e.g., genomic/ proteomic data)
- ML applied to claims and electronic medical records to identify drug abuse related problems in post marketing setting
- ML applied to imaging data to predict drug response

Examples of Use of Machine Learning at the FDA

- Resource allocation
  - Prediction of workflow
- Review and research
  - Machine-learning-based quantitative structure-activity relationship (QSAR)
  - Investigation of AI/ML in the interpretation of adverse event reports
  - Pharmacometric/statistical analyses
    - Covariate identification
    - Exposure-Response analyses
  - Imaging data and precision medicine

Prediction of the first ANDA Submission for New Chemical Entities (NCEs) Utilizing ML Methodology

- Objectives: Prioritize research efforts, product-specific guidance (PSG) development and resource allocation
- Formulate the prediction question:

$$\text{Time to first ANDA submission} \sim f(\text{product, regulatory, pharmacoeconomic})$$

- Methods of analysis:
  – Cox regression model
  – Machine-learning based method: Random Survival Forest (RSF)
- Results and Conclusions:
  – The RSF model outperforms the Cox regression model in prediction.
  – This approach can be expanded to other prediction tasks, e.g., predicting the number of ANDAs submitted.

https://www.fda.gov/downloads/Drugs/NewsEvents/UCM582150.pdf

Investigation of AI/ML in the Interpretation of Adverse Event Reports

Phase 1

- IBM reviewers trained to perform causality assessments
- Manually scored 300 FAERS/VAERS reports (pilot)
- ~900 FAERS reports already scored by DPV staff
- 5,350 FAERS/VAERS reports scored by IBM

Phase 2

- IBM Watson uploaded to CBER HIVE
- Machine learning model training with subset of FAERS/VAERS reports
- Expert input provided by FDA (key words, phrases, etc.)
- Uploaded CDC vaccine information sheet data

Phase 3

- Evaluated IBM Watson with remaining scored reports

– To investigate the ability of NLP/ML techniques to assess safety reports received in FAERS and VAERS

– To ensure efficient triage to FDA reviewers, potentially leading to better safety surveillance and improved protection of public health.

https://www.fda.gov/downloads/Drugs/NewsEvents/UCM621740.pdf

Identifying Predictors for All-Cause Mortality in Diabetic Patients in the ACCORD Trial Using RSF

- **Background:** The ACCORD trial was terminated early due to an unexpected increase in mortality with intensive vs. standard glucose-lowering treatment.
- **Methods:**
  - A total of 240 variables including demographic, clinical and laboratory data, and their change from baseline during follow-up, were analyzed as potential predictors of mortality, using RSF.
  - The top 20 predictors, identified by RSF, were included in a Cox proportional hazards model with stepwise selection to validate the results.
- **Conclusion:**
  - Some markers (e.g., urinary biomarkers, loop diuretic use and age) emerged as important predictors of mortality.
  - RSF is a rapid and flexible approach to identify potential outcome predictors among a large number of variables.

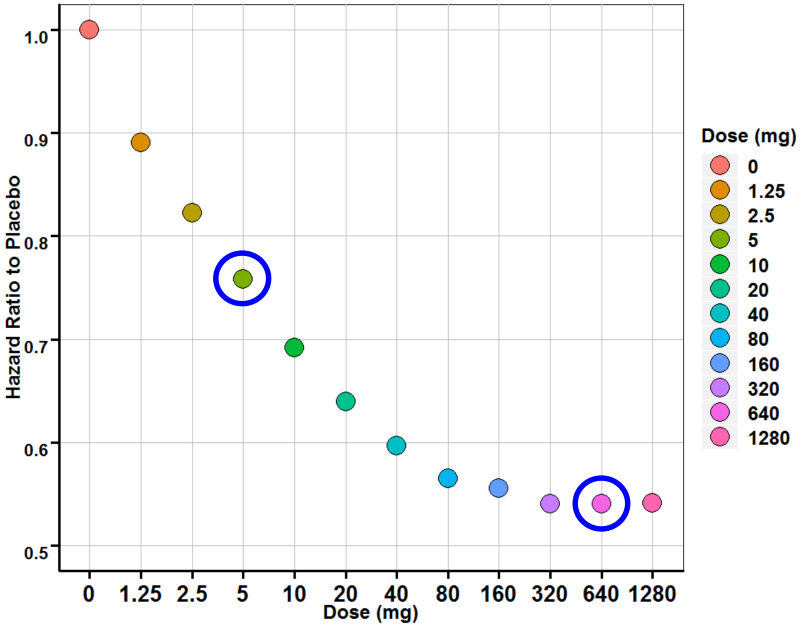
https://www.ahajournals.org/doi/abs/10.1161/circ.136.suppl_1.18043

Exposure Response Analysis using Machine Learning

A simulation study

Slide curtesy of Dr. Chao Liu

Question: How do we know if further efficacy could be achieved by increasing dose given data from only one dose level were available?



Option A: Combining ML prediction & causal inference tools

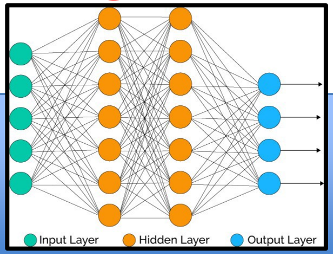
Option B: Apply ML toolbox for approximating the ground truth

Estimate the causal effects of exposure on response in a highly nonlinear system

Option A: Combining ML Prediction & Causal Inference Tools

Inverse-Probability Weighting + Marginal Structural Model

Propensity Score Estimation



- ***Prediction problem***
- ***Nonlinear with interactions***

Generate Weighted Population

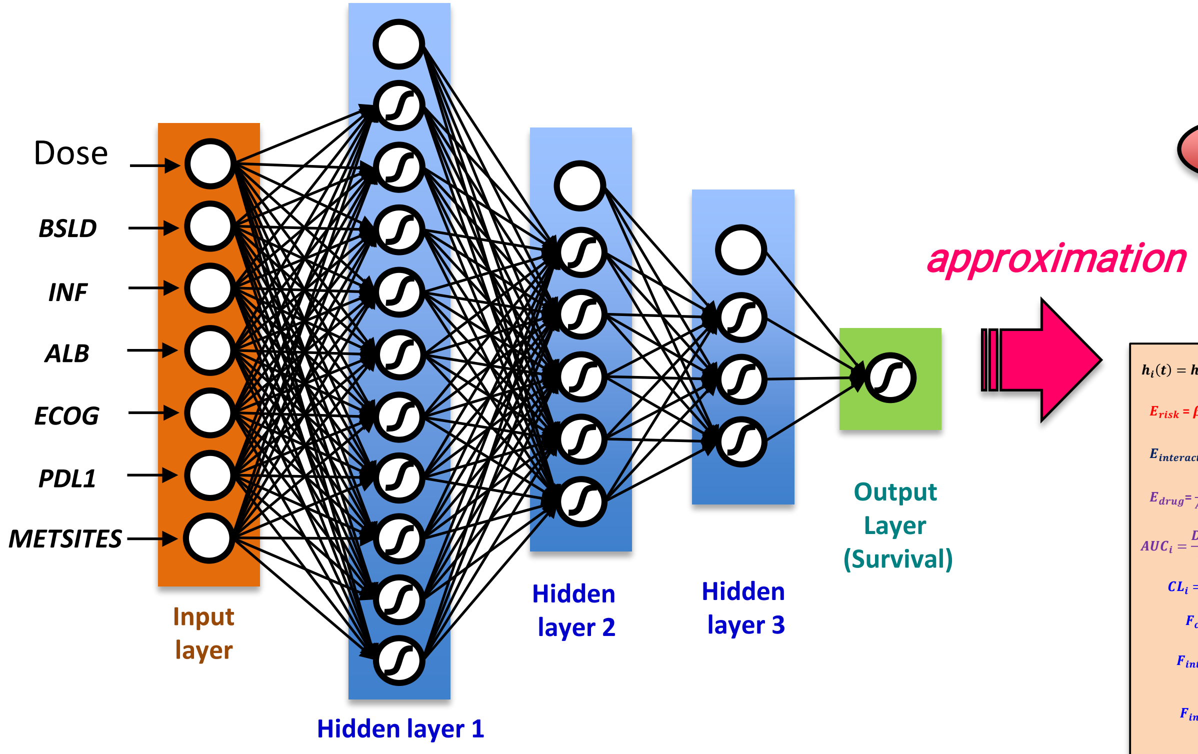
- ***Association between confounders and exposure removed in the weighted samples***

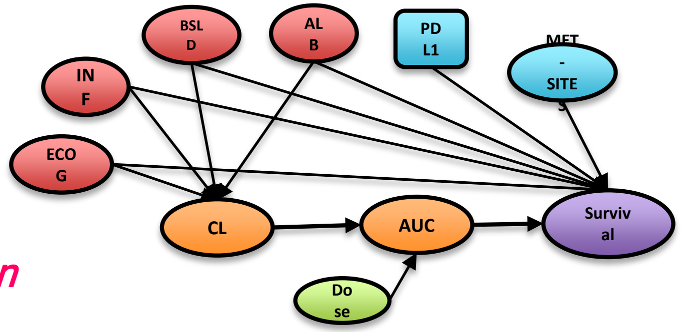
Inference on Causality

- ***Average treatment effects (ATE) estimated using marginal structural model (MSM)***

Option B: Apply ML to Approximate the Ground Truth

Neural network: A universal function approximator





$$h_i(t) = h_0 \cdot exp\left(E_{risk} + E_{interaction} + E_{drug} + \eta_{i'}\right)$$

$$E_{risk} = \beta_{ECOG} \cdot ECOG + \beta_{Met} \cdot \sqrt{Met} + \beta_{BSLD} \cdot glogis(BSLD) + \beta_{ALB} \cdot log(ALB)^2 + \frac{\beta_{max} \cdot INF}{INF + \beta_{EC50} \cdot INF}$$

$$E_{interaction} = \beta_{INF-BSLD} \cdot log(BSLD)^{log(INF)}$$

$$E_{drug} = \frac{E_{max} \cdot AUC^{\gamma}}{AUC^{\gamma} + EC50_i^{\gamma}} \qquad E_{max} = TVE_{max} \cdot \tau_{ECOG}{}^{ECOG} \cdot \tau_{PDL1}{}^{PDL1} \cdot (BSLD - 60)_+{}^{\tau_{BSLD}} + \omega_i$$

$$AUC_i = \frac{Dose}{CL_i}$$

$$CL_i = TVCL \cdot e^{F_{cov} + F_{interaction-1} + F_{interaction-2} + \eta_i}$$

$$F_{cov} = l_{m_{INF}}(INF) + l_{m_{BSLD}}(BSLD) - l_{m_{ALB}}(ALB) + ECOG \cdot \tau_{ECOG}$$

$$F_{interaction-1} = log(INF) \cdot log\left(\frac{1}{ALB}\right) \cdot \tau_{INT-1} + log(BSLD) \cdot log(INF) \cdot \tau_{INT-1} + log\left(\frac{1}{ALB}\right) \cdot log(BSLD) \cdot \tau_{INT-1}$$

$$F_{interaction-2} = \cdot ECOG \cdot \tau_{INT-2} \cdot \left(\sqrt{\frac{INF}{70}} + \sqrt{\frac{BSLD}{55}} + \sqrt{\frac{2.5}{ALB}}\right)$$

$$l_{m_x}(x) = I_{x<m_x} \cdot x \cdot \tau_{low} + I_{x \geq m_x} \cdot \tau_{high}$$

Simulation Study Conclusions

- In a strong nonlinear system, linear model may provide biased estimate on E-R relationship, even all confounders were adjusted

- Estimation of E-R relationship could be more robust with causal inference toolbox if machine learning was applied in its prediction steps

- Neural Network has the potential to recover the heterogeneous E-R relationships by approximating the ground truth

Use of Machine Learning for Imaging Data to Advance Precision Medicine

- Machine learning/computer vision is a great tool to unlock the power of imaging data
  - Detection, characterization, staging of the disease
  - Prediction and assessment of treatment response
- Progress has been made in the fields in radiomics and radiogenomics
- Opportunities:
  - Incremental improvements to current practice
  - New paradigms that did not exist before
- Examples:
  - Novel metrics for response assessment
  - Predictive imaging biomarkers for drug response

A Radiomics Imaging Biomarker to Predict Response to Immunotherapy Agents

THE LANCET
Oncology

ARTICLES | VOLUME 19, ISSUE 9, P1180-1191, SEPTEMBER 01, 2018

A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study

Roger Sun, MD * • Elaine Johanna Limkin, MD * • Maria Vakalopoulou, PhD • Laurent Dercle, MD •
Stéphane Champiat, MD • Shan Rong Han, MD • et al. Show all authors • Show footnotes

Published: August 14, 2018 • DOI: https://doi.org/10.1016/S1470-2045(18)30413-3 • Check for updates

Interpretation

The radiomic signature of CD8 cells was validated in three independent cohorts. This imaging predictor provided a promising way to predict the immune phenotype of tumours and to infer clinical outcomes for patients with cancer who had been treated with anti-PD-1 and PD-L1. Our imaging biomarker could be useful in estimating CD8 cell count and predicting clinical outcomes of patients treated with immunotherapy, when validated by further prospective randomised trials.

A Proposal of Using Machine Learning and Imaging Data to Facilitate Precision Treatment

- Establish a platform/procedure for imaging data submission/storage at the FDA
- Combine imaging data with other data (e.g.., clinical data, liquid biopsy data)
- Develop algorithm(s) that can predict each patient's response to treatment and support treatment decisions
- Seek industry and academia collaborators

Challenges and Future Directions in the Application of ML in Drug Development

- The expectation needs to be fit-for-purpose and risk-based.
- Validation of the algorithms
- Generalizability
  - Issues with biased training data/underrepresented population (especially with high-dimensional data)
  - Training data should be unbiased and diverse/inclusive
  - Methods need to be developed for performance guarantee
- Transparency/interpretability
  - Black box nature of some algorithms
  - Methods are being developed to improve interpretability
- Deep learning is data hungry
  - ML+ Real world data (e.g., electronic medical records, patient-generated data/wearables)
  - Data sharing/precompetitive collaboration

FDA-Stanford/UCSF CERSI Machine Learning Fellowship (Recruiting now!)

- FDA-Stanford/UCSF CERSI machine learning fellowship (Recruiting now!)
  https://www.zintellect.com/Opportunity/Details/FDA-CDER-2019-0355

Office of Clinical Pharmacology

Artificial Intelligence,Machine Learning, Mobile Health, Real World Evidence, and other Innovative Data Analytics

The OCP Innovative Data Analytics Program seeks to support advances in drug development, regulatory research and review that can facilitate precision treatment in various therapeutic areas.

- Other opportunities: Harvard-FDA INFORMED Post-Doctoral Fellowship in Artificial Intelligence and Machine Learning
  https://spark.adobe.com/page/5ehro94b1FpGv/

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