New computational approaches for cancer therapeutics

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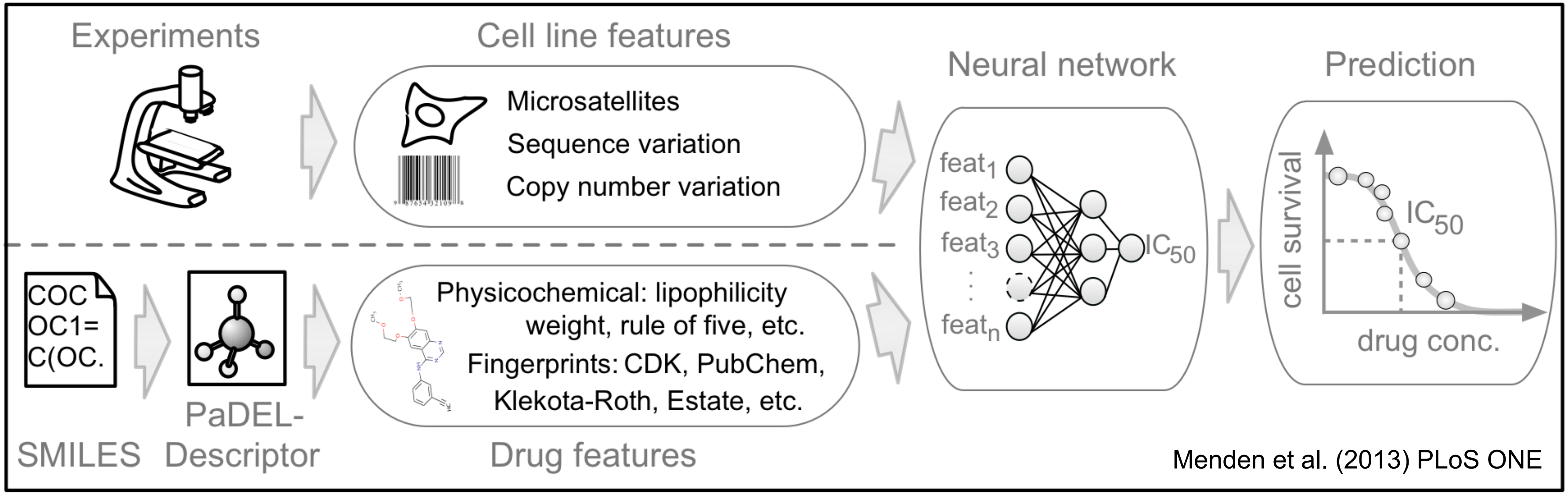
The dose response prediction problem

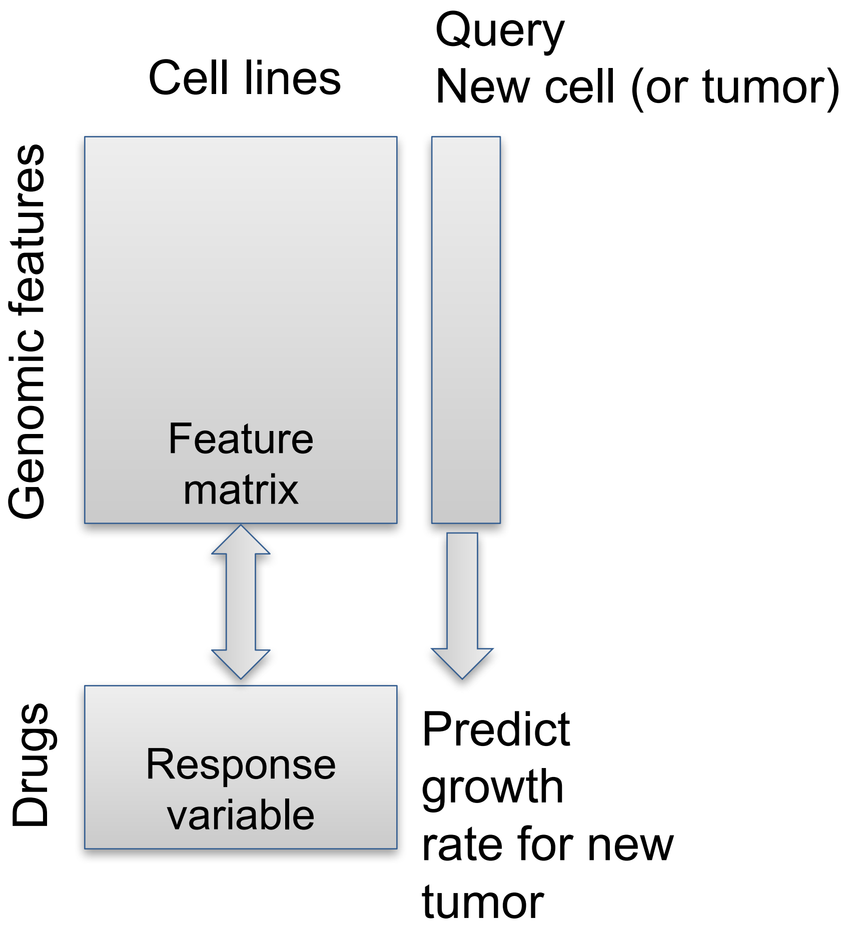
Problem motivated by NCI's Molecular Profiling-Based Assignment of Cancer Therapy (MPACT) clinical trial study



Menden et al. (2013) PLoS ONE

Presents a challenging data driven modeling problem with large input feature dimensions

Focusing on two prediction problems



Cell lines

Query
New cell (or tumor)

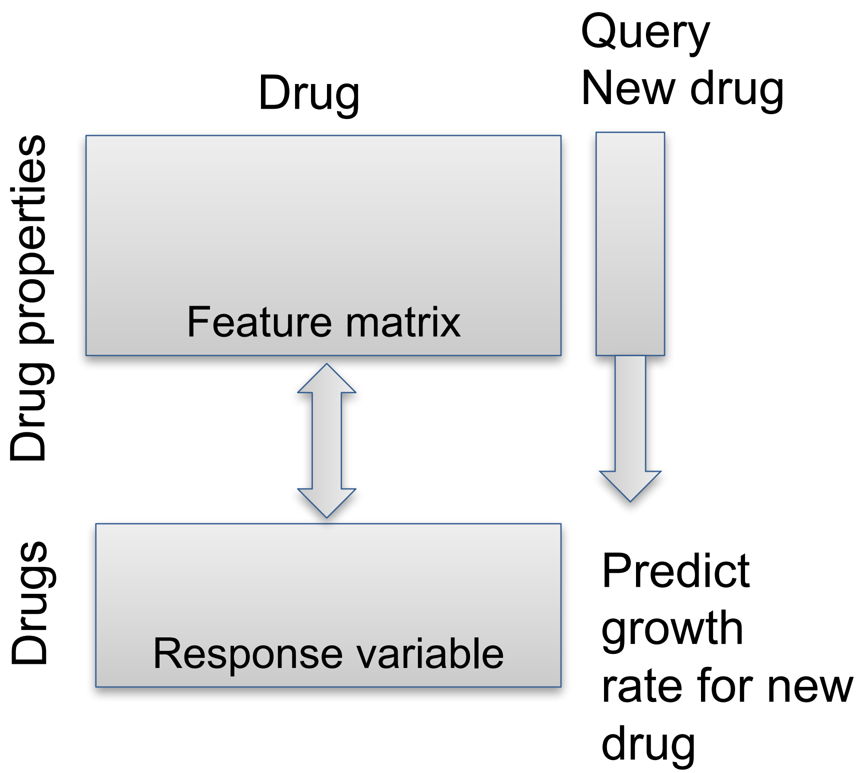
Genomic features

Feature matrix

Drugs

Response variable

Predict growth rate for new tumor



Drug

Query
New drug

Drug properties

Feature matrix

Drugs

Response variable

Predict growth rate for new drug

Investigating the use of unsupervised feature learning

Big Data Hypothesis:
larger unlabeled collections of observations: tumors, normal tissue, chemical compounds can be used to learn descriptive features
GDC: includes gene expression for 11,574 tumors (and related normal tissue)
ChEMBL: public repository of 1.6 million compounds

Transfer Learning Hypothesis:
models (or encodings) of smaller subsets of features can be transferred to smaller pre-clinical trial data to improve accuracy of dose response predictions
cell line models applied to patient derived tumor models

Mechanisms of Action Hypothesis:
feature learning can help inform and be informed by biological models

Experimental data for model evaluation

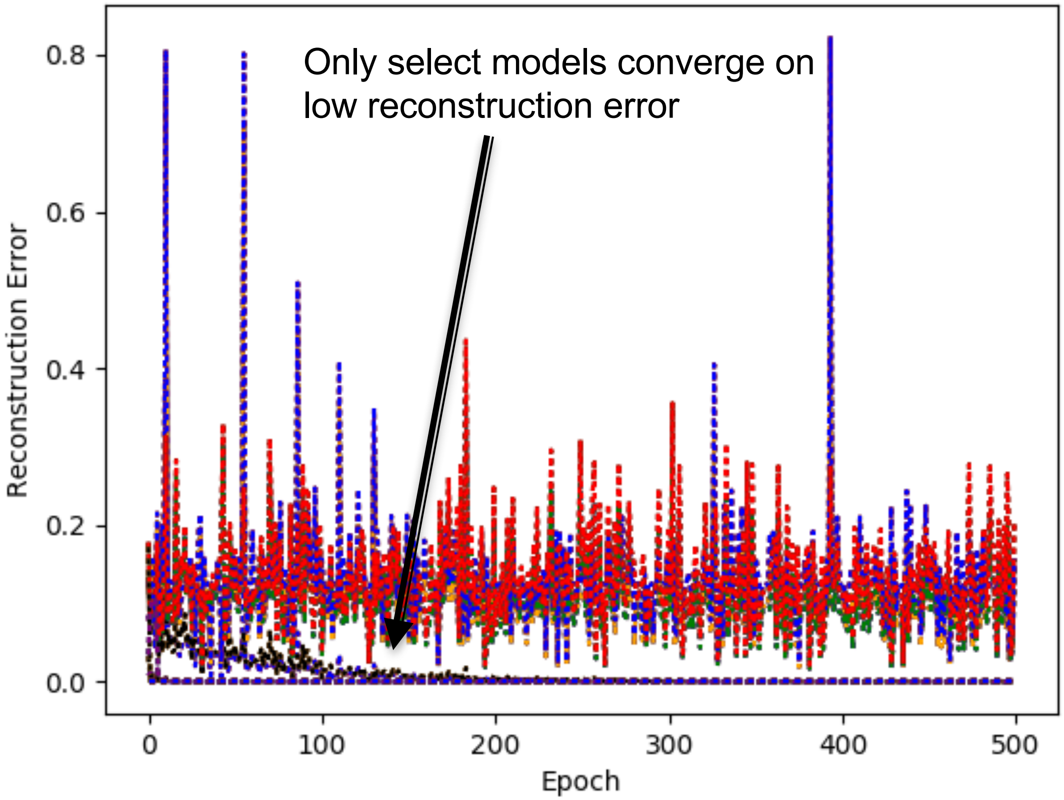
- NCI-60: 60 cell lines
  - Each cell line has microarray gene expression, protein, miRNA, SNP, (RNAseq in progress).
  - 5-dose response measurements for 52,672 compounds.
    - Size of individual cell culture measured after an initial 24 hour incubation period ("Time Zero"). ~5K – 40K cells depending on cell/tumor type.
    - Size of cell culture growth measured after 48 hours with initial compound treatment and without compound treatment (control)
    - Ratio reports change in tumor size relative to control.
      - 0 -> drug has no impact on tumor growth
      - -100 -> tumor exhibits large reduction in size
      - 100 -> tumor exhibits large increase in size

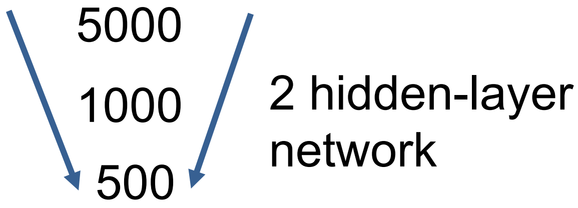
- Other labeled datasets being examined:
  - CCLE, GDSC: Additional cell line repositories, with more (~1K) cell lines but future drugs tested.
  - Ultimate goal is application to new patient derived tumors being established at Frederick National Laboratory (NCI).

Scalable deep learning tools used to explore feature representation space

- Learn 500 dimension feature representation on 50K chemical compounds from 5000 dimension input feature: ~6 hours x 24 cores x 16 nodes x 104 runs = ~239,616 CPU hours

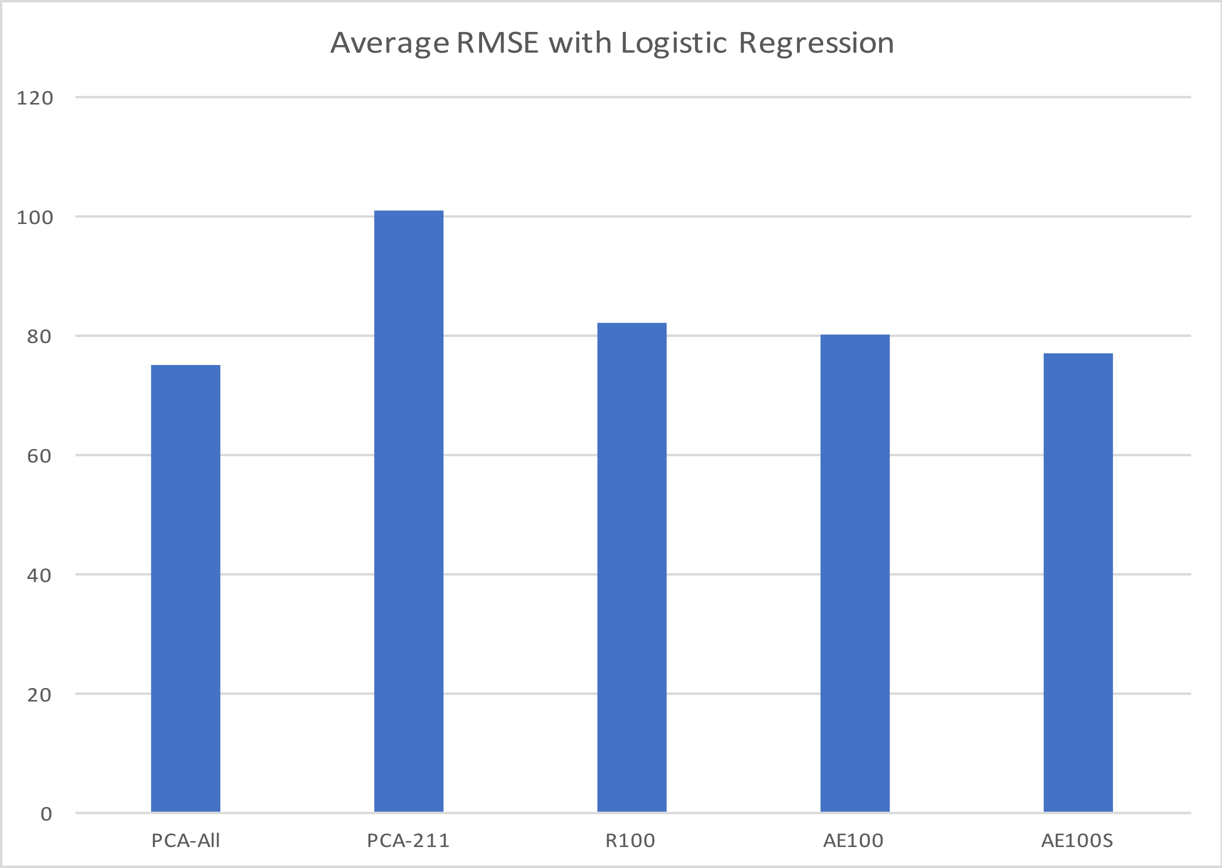
Experiments run using Livermore Big Artificial Neural Network (LBANN)

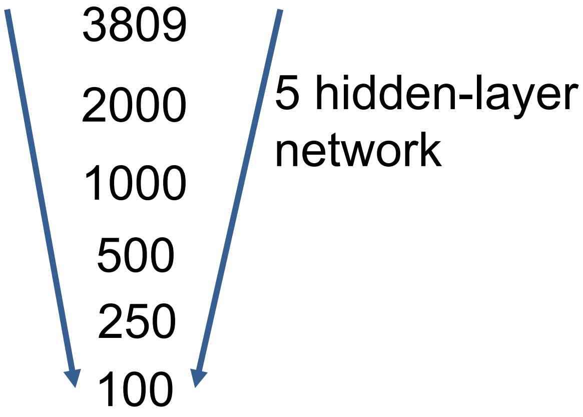




Initial use of autoencoder indicated potential to find low reconstruction error but results were sensitive to the choice of parameters

Autoencoders show potential to retain information for downstream prediction





3809

2000

1000

500

250

100

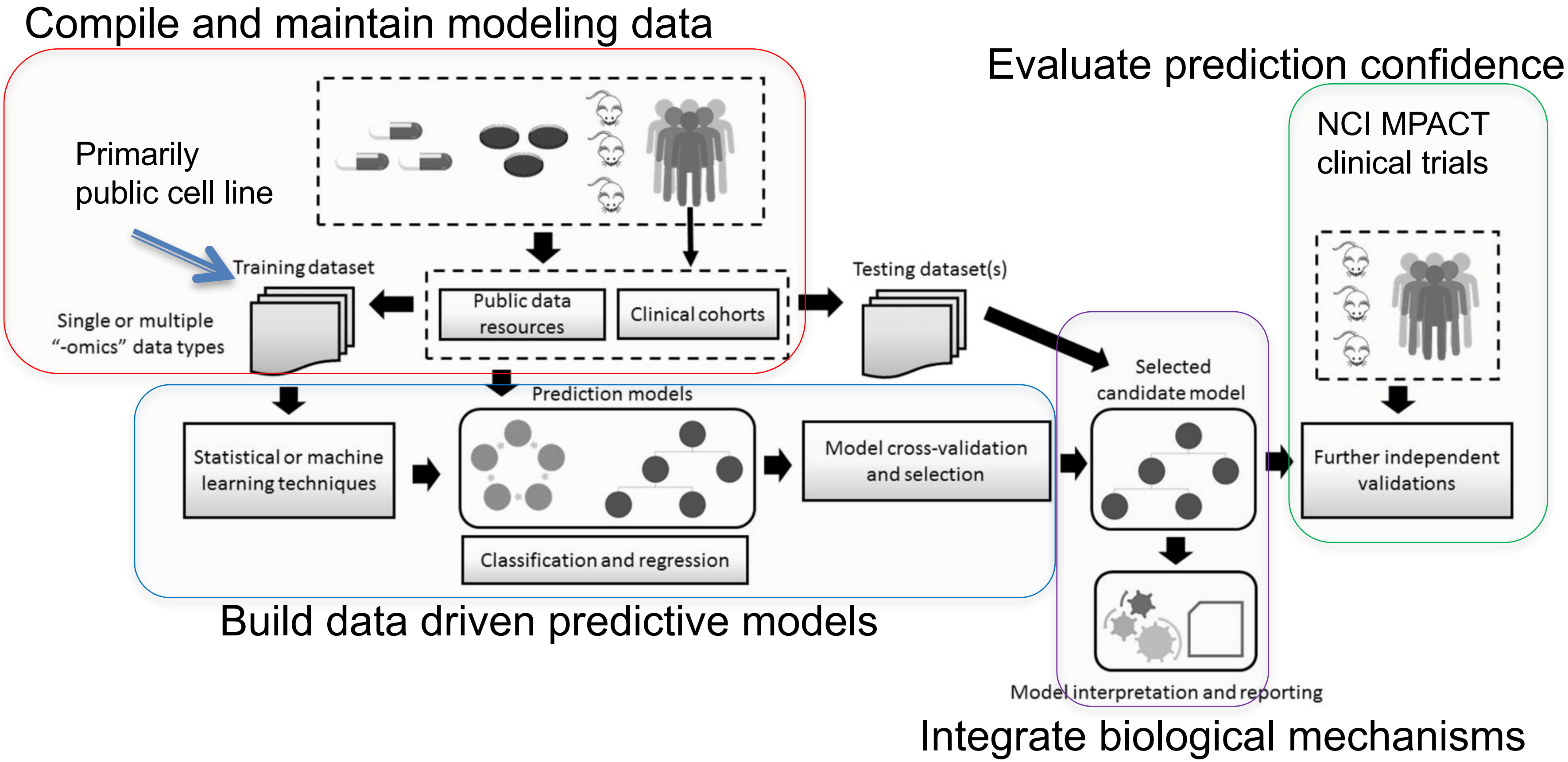
5 hidden-layer network

1. Unlabeled training: 24,789 (samples) x 3,809 features
2. Build logistic regression model on single concentration dose response using a single cell line.
3. Test response prediction on ~2K held out compounds for 6 representative cell lines. Labeled training: ~14k-16k examples.

Next steps

- Evaluate feature learning with larger unlabeled dataset - ChEMBL's 1.6 million compound library
- Evaluate response prediction on novel compound classes, not just near neighbors.
- Incorporate new molecular features, such as gene expression and SNPs
- Explore methods to guide model complexity reduction and integrate models with biological knowledge (no time to discuss today)

Framework for developing predictive models


Compile and maintain modeling data

Primarily public cell line

Evaluate prediction confidence

NCI MPACT clinical trials

Build data driven predictive models

Integrate biological mechanisms

Training dataset
Single or multiple "-omics" data types
Public data resources
Clinical cohorts
Testing dataset(s)
Selected candidate model
Prediction models
Statistical or machine learning techniques
Model cross-validation and selection
Further independent validations
Classification and regression
Model interpretation and reporting

Francisco Azuaje Brief Bioinform 2016;bib.bbw065

Improve drug treatment selection for patient
Increase understanding of drug efficacy mechanisms

Cancer pilot is a multi-laboratory effort

— Rick Stevens (Lead), Fangfang Xia, Maulik Shukla (ANL)

— Yvonne Evrand, Susan Holbeck (NCI / Frederick)

— Jason Gans, Judith Cohn, John Hodge (LANL)

— Adam Zemla, Marisa Torres (LLNL)

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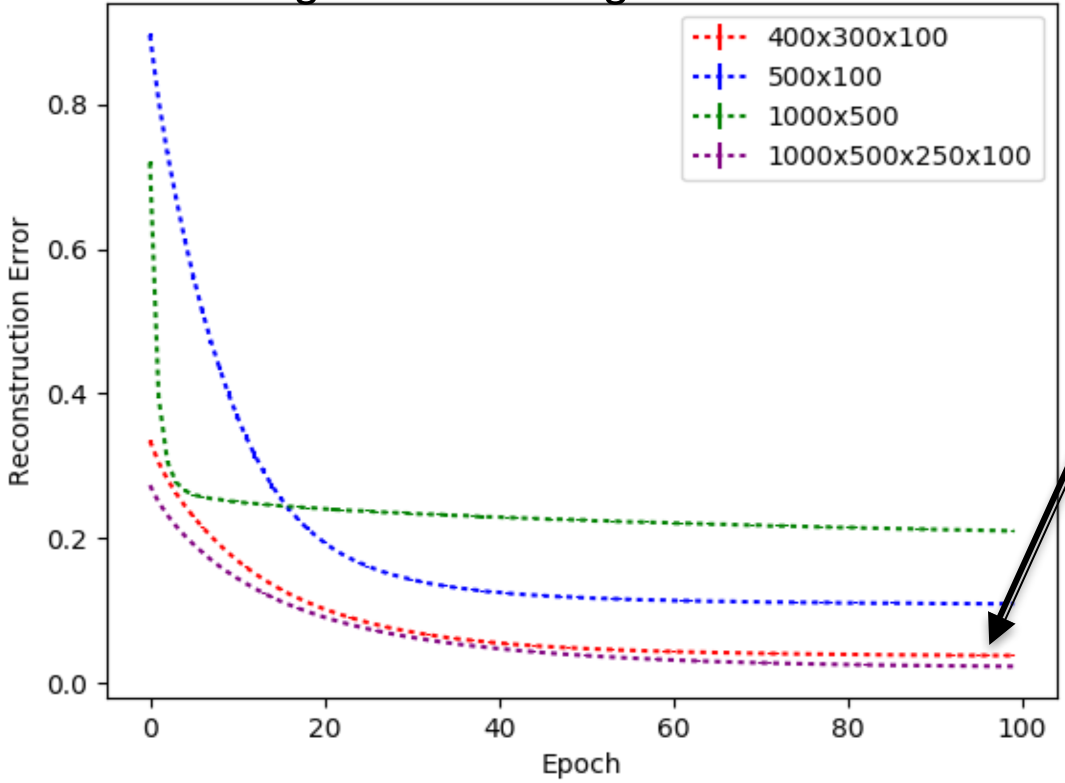
Deeper networks show potential to learn novel feature encoding

- Gene expression feature encoding (5-fold cross validation)

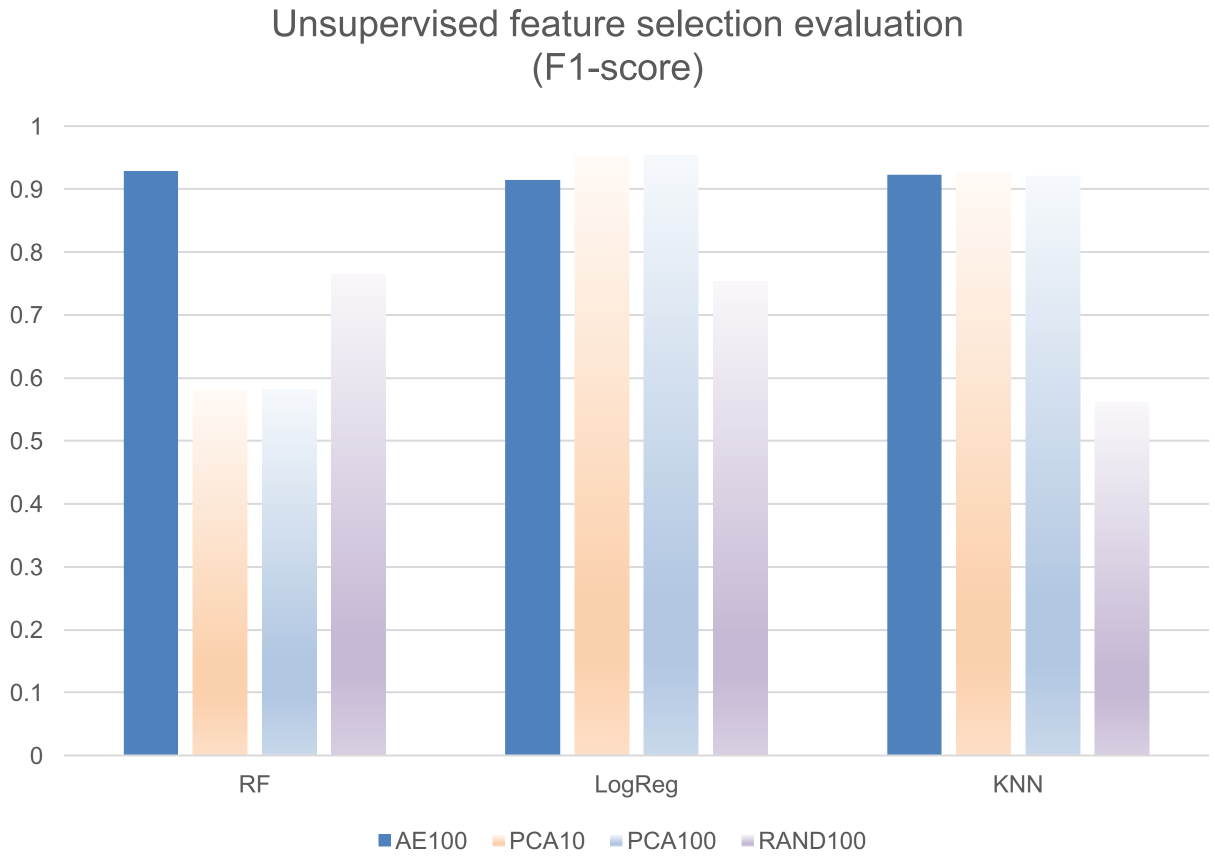
Experiments run using Livermore Big Artificial Neural Network (LBANN)



Deeper network converges on lower error rate

Data size of 60,483 features x 11,574 examples presents a computational challenge

Non-linear feature encoding improves performance in some conditions



Prediction models:
RF=random forest
LogReg=logistic regression
KNN=k nearest neighbor

AE=autoencoder
PCA=prinicipal components analysis
RAND=random feature selection

Indicates potential to find more robust molecular features with auotencoder