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Machine Learning in Predictive Toxicology: An Overview and Case Study

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A frequent problem in toxicology….

- We have a large number of chemicals to screen for potential risk
- We want to know about hazard or toxicity that is *hard* to measure for all these chemicals (expensive, slow, unethical…)
  - We have some previously-measured examples of this information for some chemicals
- We have information that is *easier* to measure (rapid, inexpensive)
  - Molecular structure
  - *In vitro* bioactivity in high-throughput screening assays
- We don't have a clear idea of how the "hard" info relates to the "easy" info
  - no mechanistic model
- How can we use the available "easy" data to *predict* the "hard-to-measure" data?

Idakwo et al. 2018; Wang et al. 2020

Machine learning: Computational algorithms that can infer patterns from data

Data			
Target/ response	**Features**		
y1	**x1**	**x2**	**…**
[value1]	[value1]	[value1]	…
[value2]	[value2]	[value2]	…
…	…	…	…

Target/response (y): what we want to predict (e.g. toxicity or hazard)
Features (x1, x2…): Information available to predict response (e.g. structure, *in vitro* HTS bioactivity, etc.)

Two categories of patterns to be inferred

Supervised: Infer relationship between target and features. Goal: predict target from features.

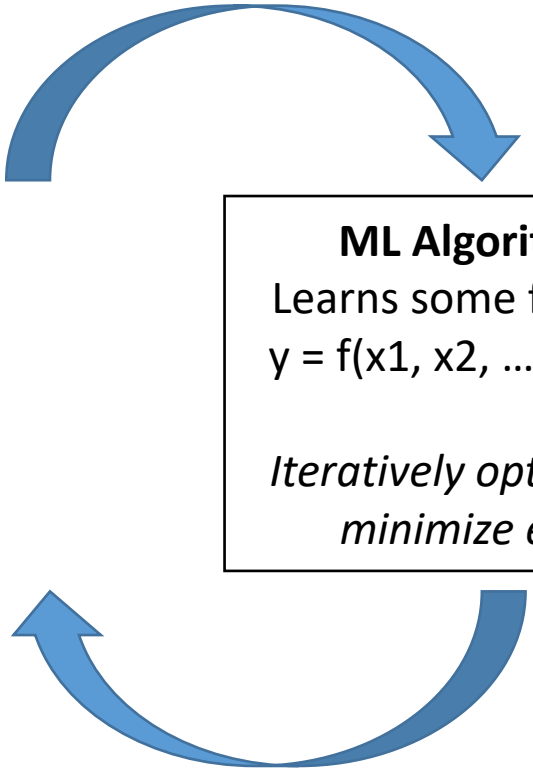
Data			
Target/ response	**Features**		
y1	**x1**	**x2**	**…**
[value1]	[value1]	[value1]	…
[value2]	[value2]	[value2]	…
…	…	…	…

Unsupervised: No target to predict. Infer descriptive patterns in features (e.g., clustering)

Data		
Features		
x1	**x2**	**…**
[value1]	[value1]	…
[value2]	[value2]	…
…	…	…

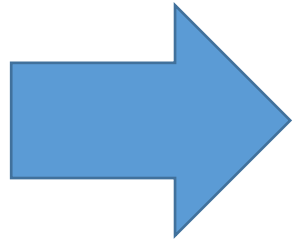
Training a ML model

Training data			
Target/ response	**Features (predictors)**		
y1	**x1**	**x2**	**…**
[value1]	[value1]	[value1]	…
[value2]	[value2]	[value2]	…
…	…	…	…



ML Algorithm:
Learns some function
y = f(x1, x2, …) + error

Iteratively optimize to minimize error



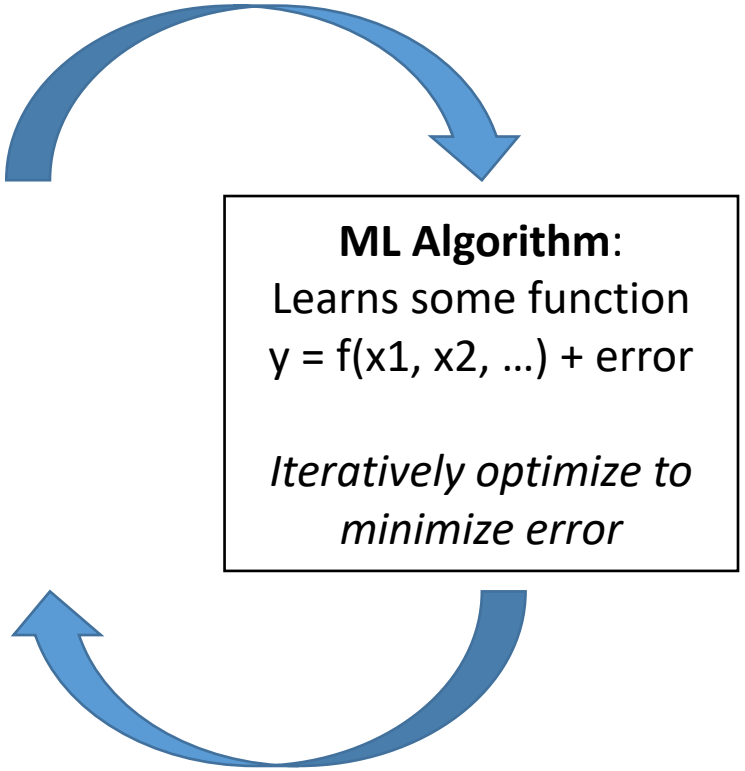
MODEL
y = f (x1, x2, …)

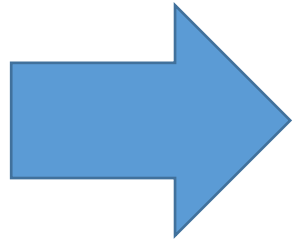
Algorithms can include:

- k nearest neighbors
- decision trees
- support vector machine
- naïve Bayes
- random forest
- artificial neural networks
- etc.

Training a ML model

Training data			
Target/ response	Features (predictors)		
y1	x1	x2	…
[value1]	[value1]	[value1]	…
[value2]	[value2]	[value2]	…
…	…	…	…



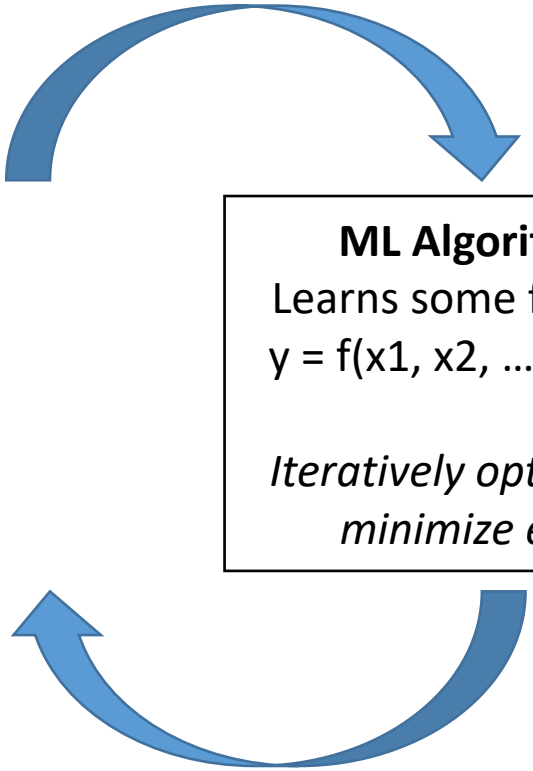


MODEL
y = f (x1, x2, …)

Regression model: y is numeric & continuous (e.g. LD50)
Classification model: y is categorical (e.g. hepatic toxicity yes/no)

Training a ML model

Training data			
Target/ response	**Features (predictors)**		
y1	**x1**	**x2**	**…**
[value1]	[value1]	[value1]	…
[value2]	[value2]	[value2]	…
…	…	…	…



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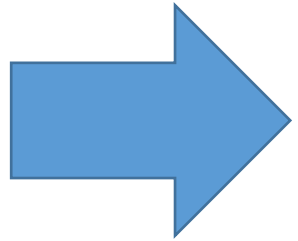
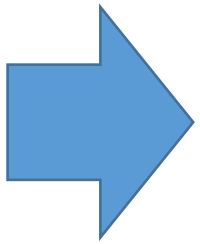


MODEL
y = f (x1, x2, …)

Classification model: Usually predicts *probability* of category
Usually dichotomized as "prob of category A > 50% → model predicts category A"
But threshold can be tuned – not necessarily 50%!

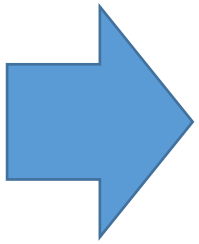
Evaluating performance of a ML model

Test data			
Target/ response	Features (predictors)		
y	x1	x2	…
[value1]	[value1]	[value1]	…
[value2]	[value2]	[value2]	…
…	…	…	…



MODEL

y = f (x1, x2, …)



y_pred
[value1]
[value2]
…

Metric: Error between predicted & observed y

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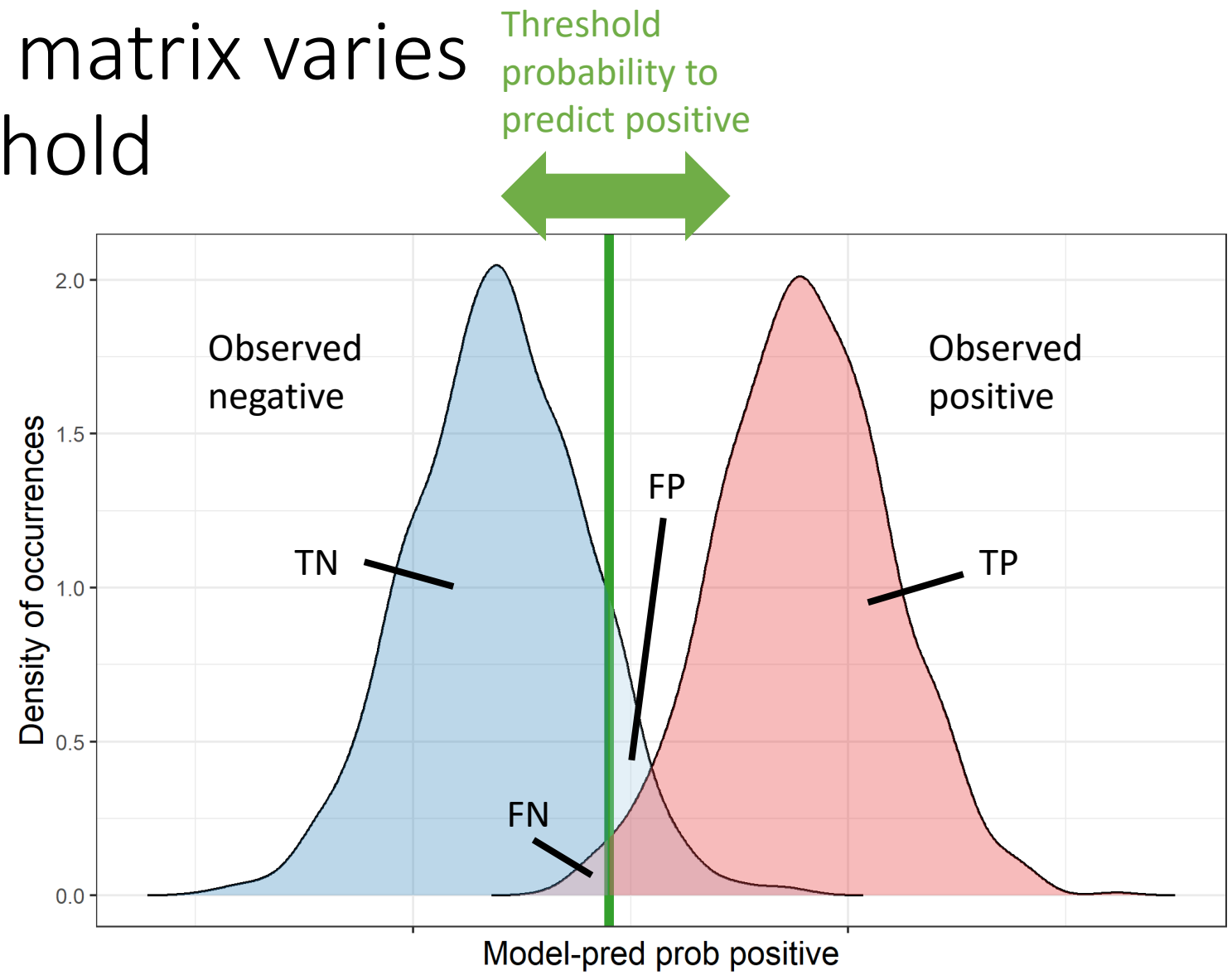
Error metrics for (binary) classification models: *confusion matrix*

	Predicted negative	Predicted positive
Observed negative	True negatives (TN)	False positives (FP)
Observed positive	False negatives (FN)	True positives (TP)

Accuracy: (TN + TP) / (TN + TP + FN + FP)
Sensitivity (true positive rate, TPR): TP/(TP + FN)
Specificity (true negative rate, TNR): TN/(TN + FP)
Balanced Accuracy: (Sensitivity + Specificity)/2
Positive Predictive Value (PPV): TP / (TP + FP)
False Discovery Rate: 1 – PPV
[…lots more!]

Confusion matrix varies with threshold



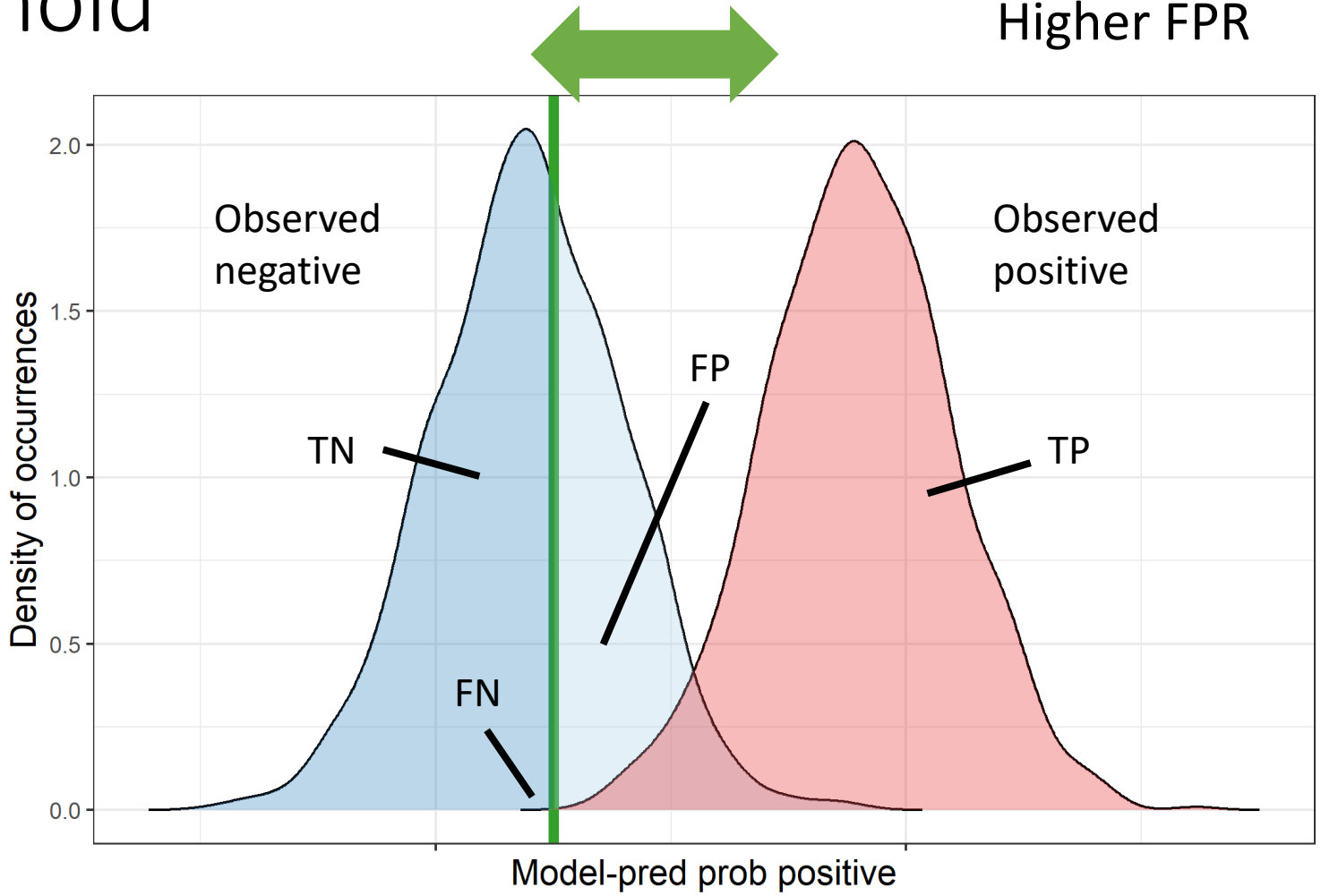
More separation between peaks = more informative model

(synthetic example data)

Confusion matrix varies with threshold

Threshold probability to predict positive

Lower threshold =
Higher TPR
Higher FPR

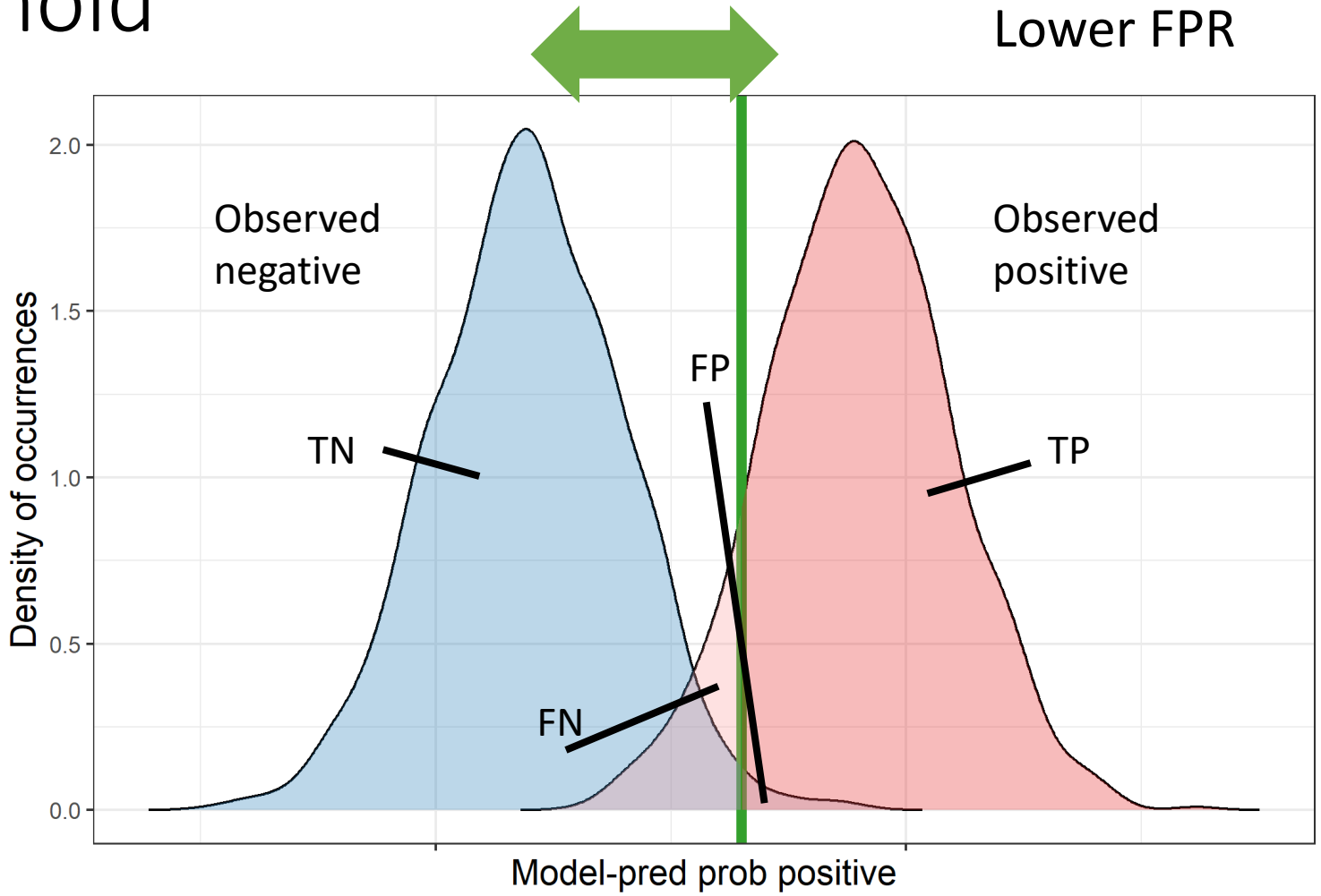


(synthetic example data)

Confusion matrix varies with threshold

Threshold probability to predict positive

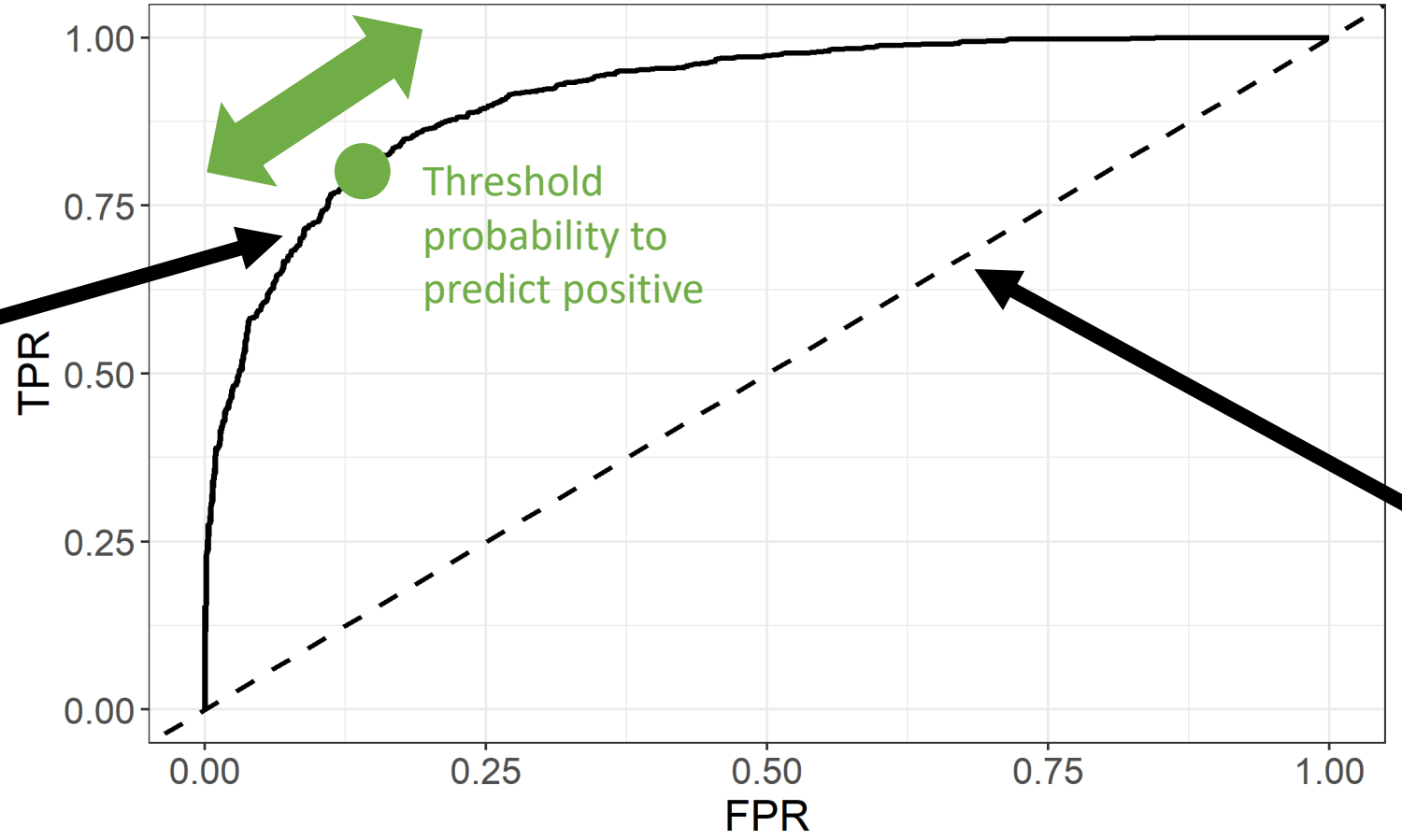
Higher threshold =
Lower TPR
Lower FPR



(synthetic example data)

Area under receiver-operator characteristic (ROC) curve tells us about separation between peaks & model performance over all thresholds

Trained model AUC = 0.91 (for this fake example)



Perfectly uninformative model (no separation between peaks) AUC = 0.5

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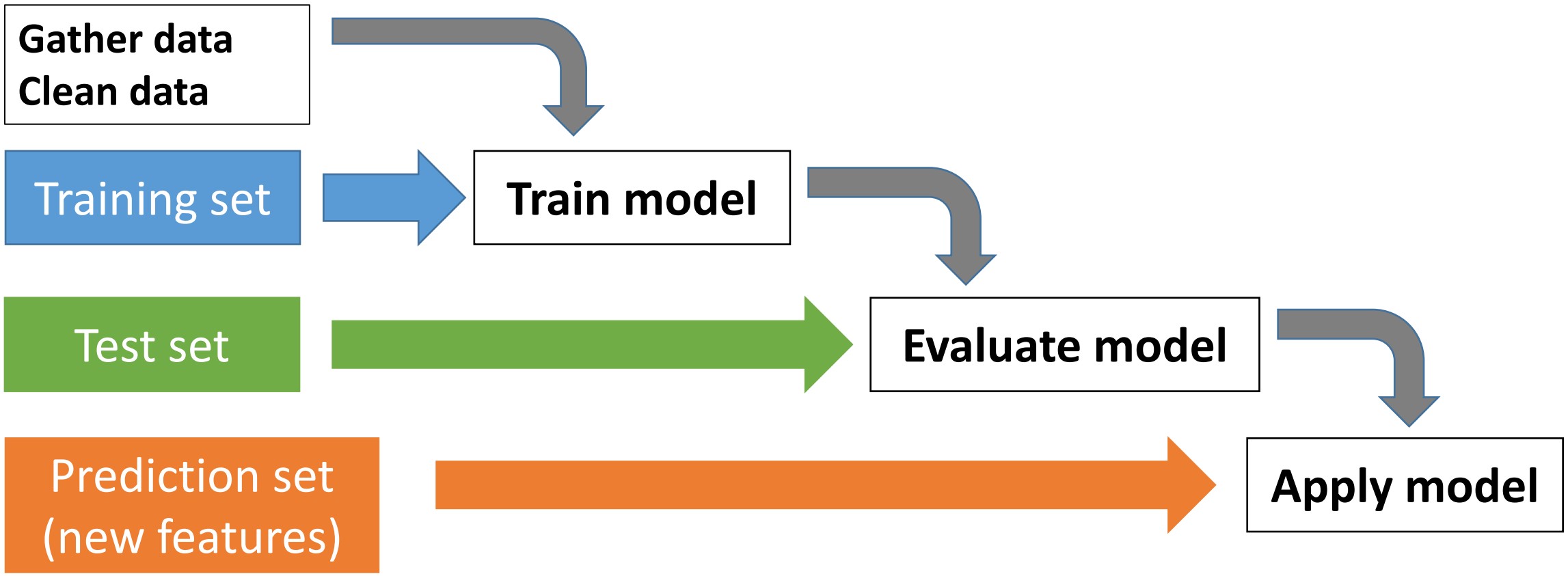
Summary of machine-learning model process



Challenge in classification models for predictive toxicology: *imbalanced data*

From Mansouri et al. 2020: ComPARA training set
(response = *in vitro* androgen activity in ToxCast, yes/no)

Table 1. Training set chemicals for binding, agonist and antagonist data sets.

Number of	Binding	Agonist	Antagonist
Actives	198	43	159
Inactives	1,464	1,616	1,366
Total	1,662	1,659	1,525

88% inactive for binding

97% inactive for agonism

90% inactive for antagonism

Problem:

A ML model that simply predicted "inactive" for *everything* would have a 97% accuracy rate for agonism!

Many toxicology-related data sets are imbalanced like this (Idakwo et al. 2018; Wang et al. 2020)

How can we build a ML model that properly predicts the minority class?

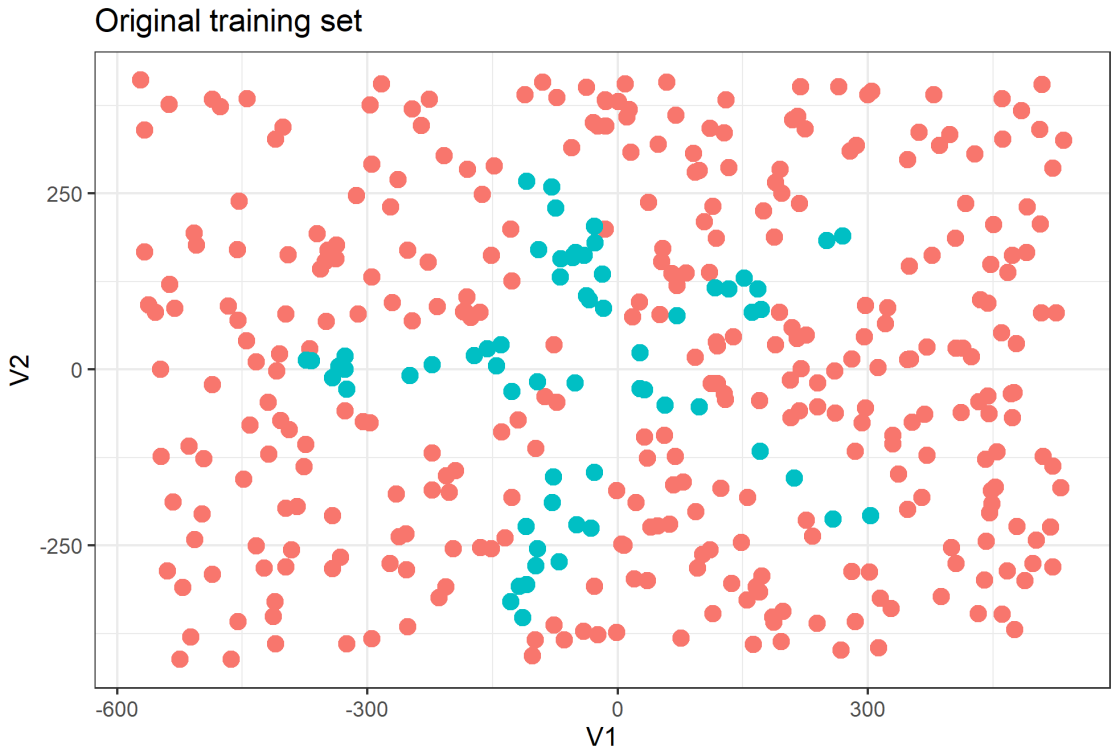
Strategies to address imbalanced training data

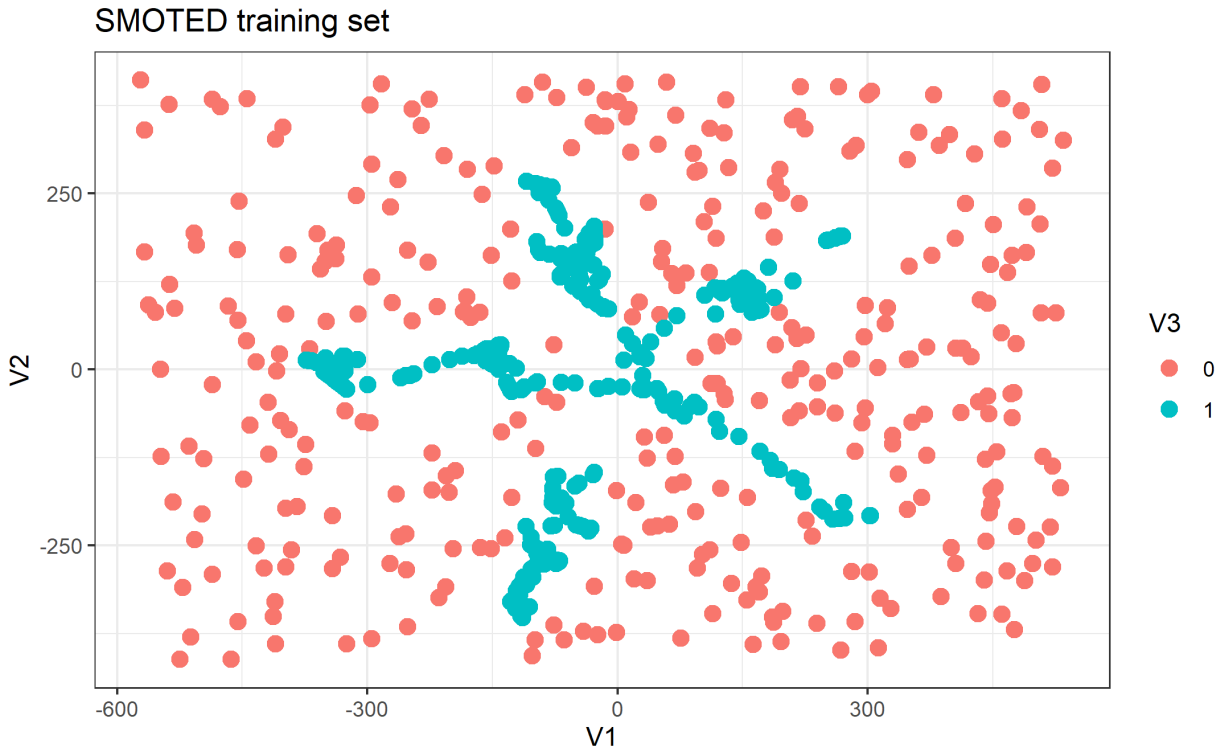
(Branco et al., 2016)

- Algorithm-based: Make the model less sensitive to imbalance
  - *Boosting*: iteratively correct misidentified instances in the training class
  - *Bagging:* trains multiple versions of the model on subsets or bootstrap-resampled versions of the data set
  - *Cost function*: During model training, weight errors more heavily for minority-class examples
- Sampling-based: Pre-process training data to balance out the classes
  - *Undersampling*: Remove some majority-class examples
  - *Oversampling*: Repeat some minority-class examples
  - Interpolate between minority-class examples & nearest neighbors: e.g. SMOTE (Synthetic Minority Over-sampling TEchnique) (Chawla et al., 2002)
  - Generative Adversarial Networks (GAN): train a second ML model to generate synthetic minority data (Douzas & Bacao, 2018; Green et al. 2021)

Example of SMOTE

"clover" data from https://sci2s.ugr.es/keel/datasets.php (Alcalá-Fdez et al. 2011)





Drawback: SMOTE can blur boundaries by interpolating to majority-class near neighbors

It turns out that ML algorithms and imbalanced data strategies perform very differently for different data sets

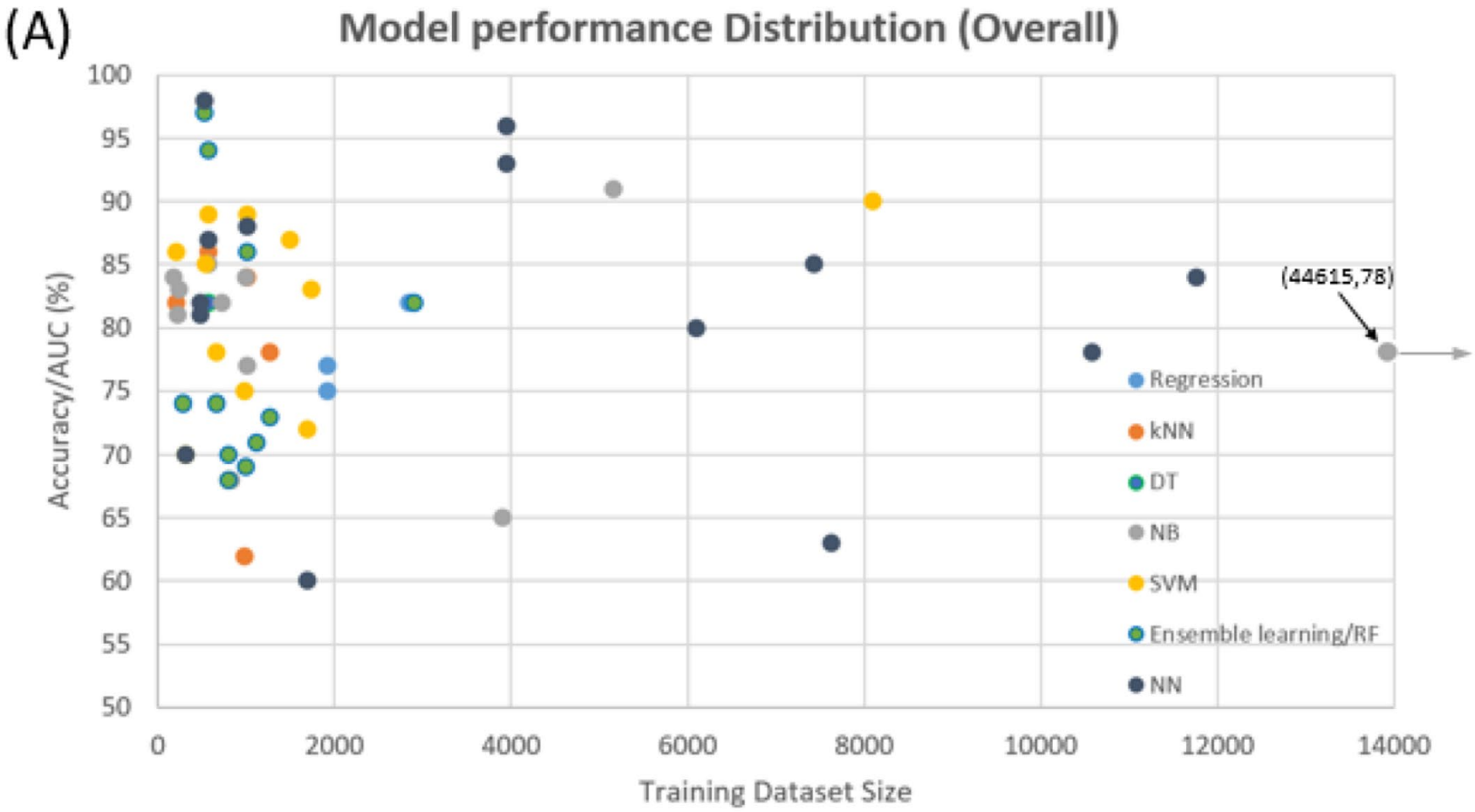
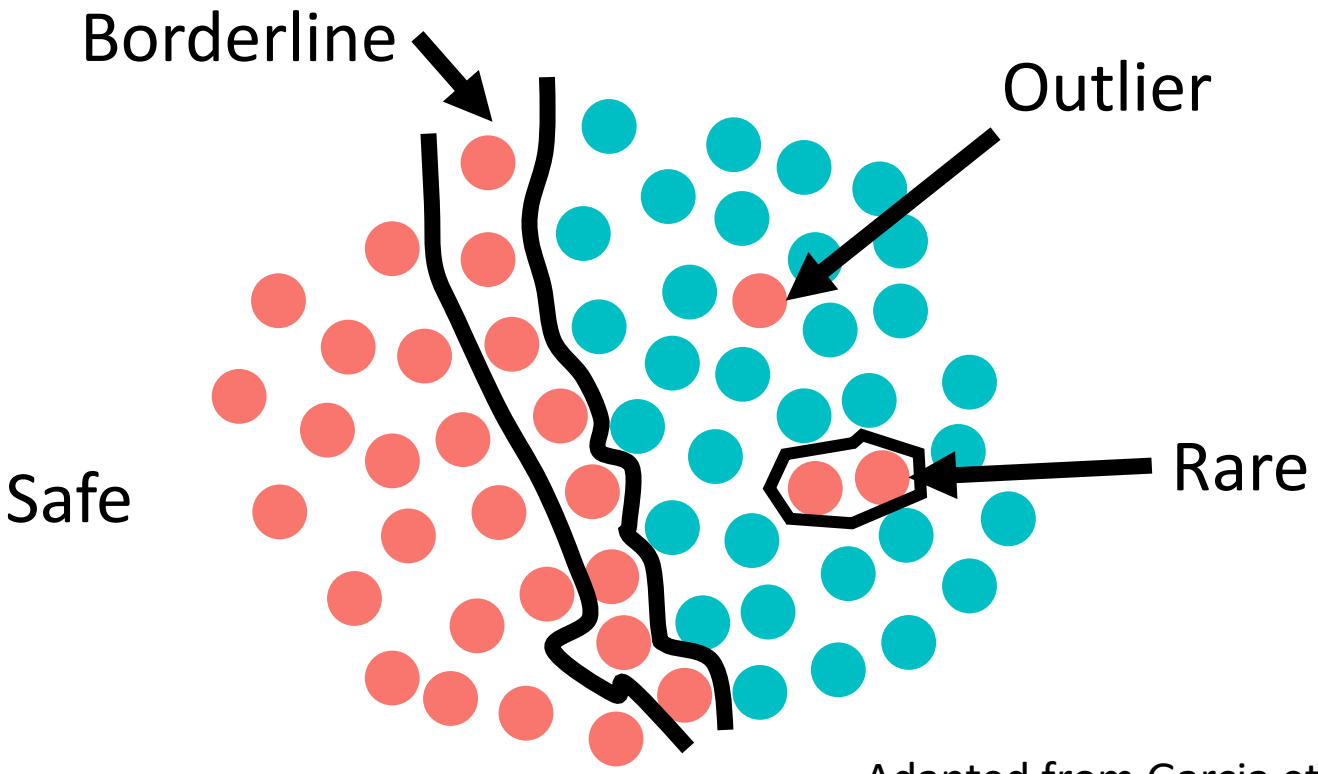


Figure 9A from Wang et al. 2020 (literature review of ML methods in predictive toxicology)

Variability in model performance *not* explained by training dataset size or by ML algorithm used

Authors suspect dataset-specific effects

ML research: performance depends on frequency of 4 different types of data points (Napierla & Stefanowski 2015; Garcia et al. 2020; Stefanowski 2016)



Napierla & Stefanowski 2015:

Undersampling seems to work better for borderline examples

SMOTE seems to work better for outlier & rare examples

Adapted from Garcia et al. (2020)

Suggestion: Develop a more systematic approach to characterize these “data difficulty factors” in predictive toxicology datasets

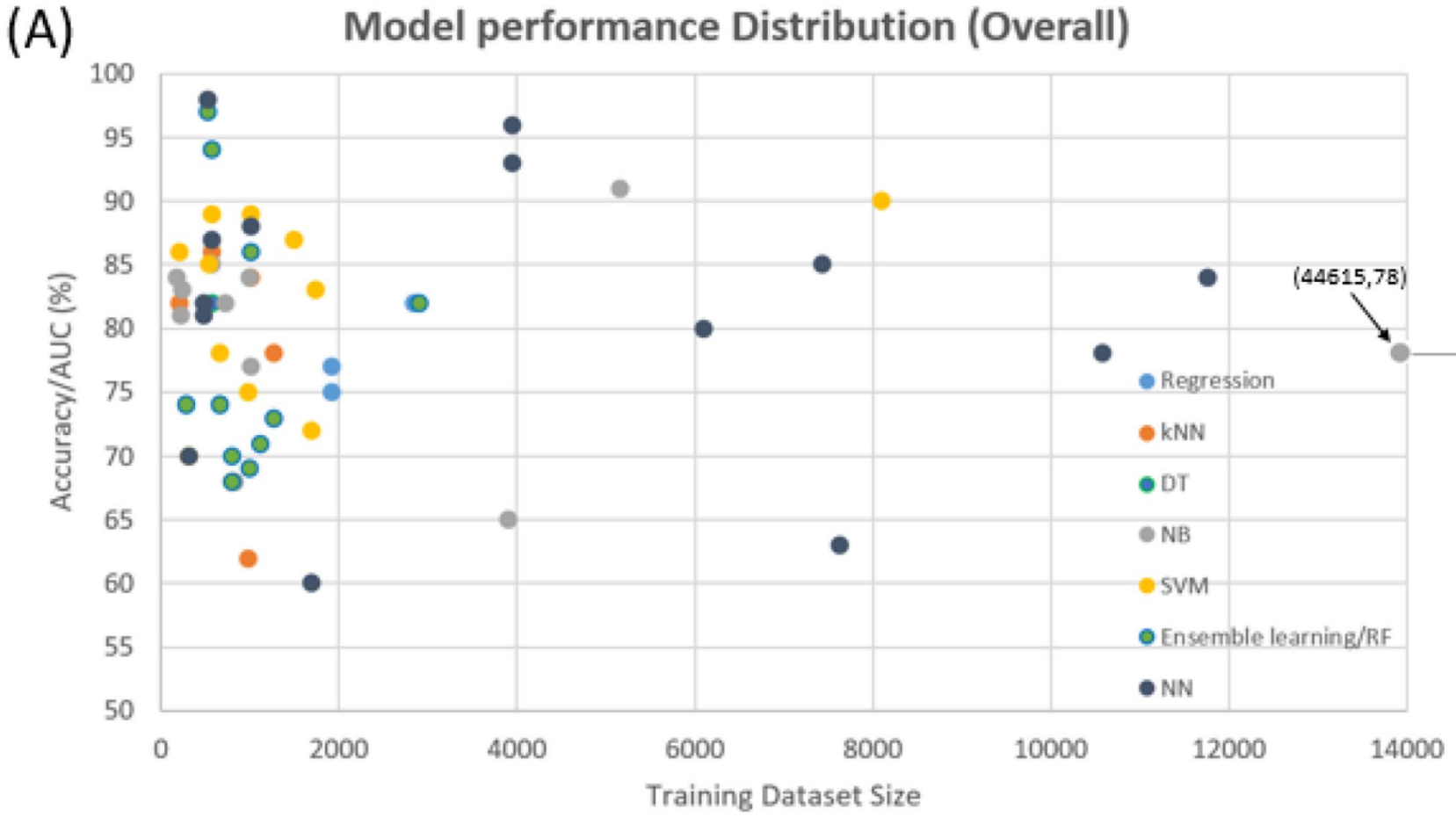


Figure 9A from Wang et al. 2020 (literature review of ML methods in predictive toxicology)

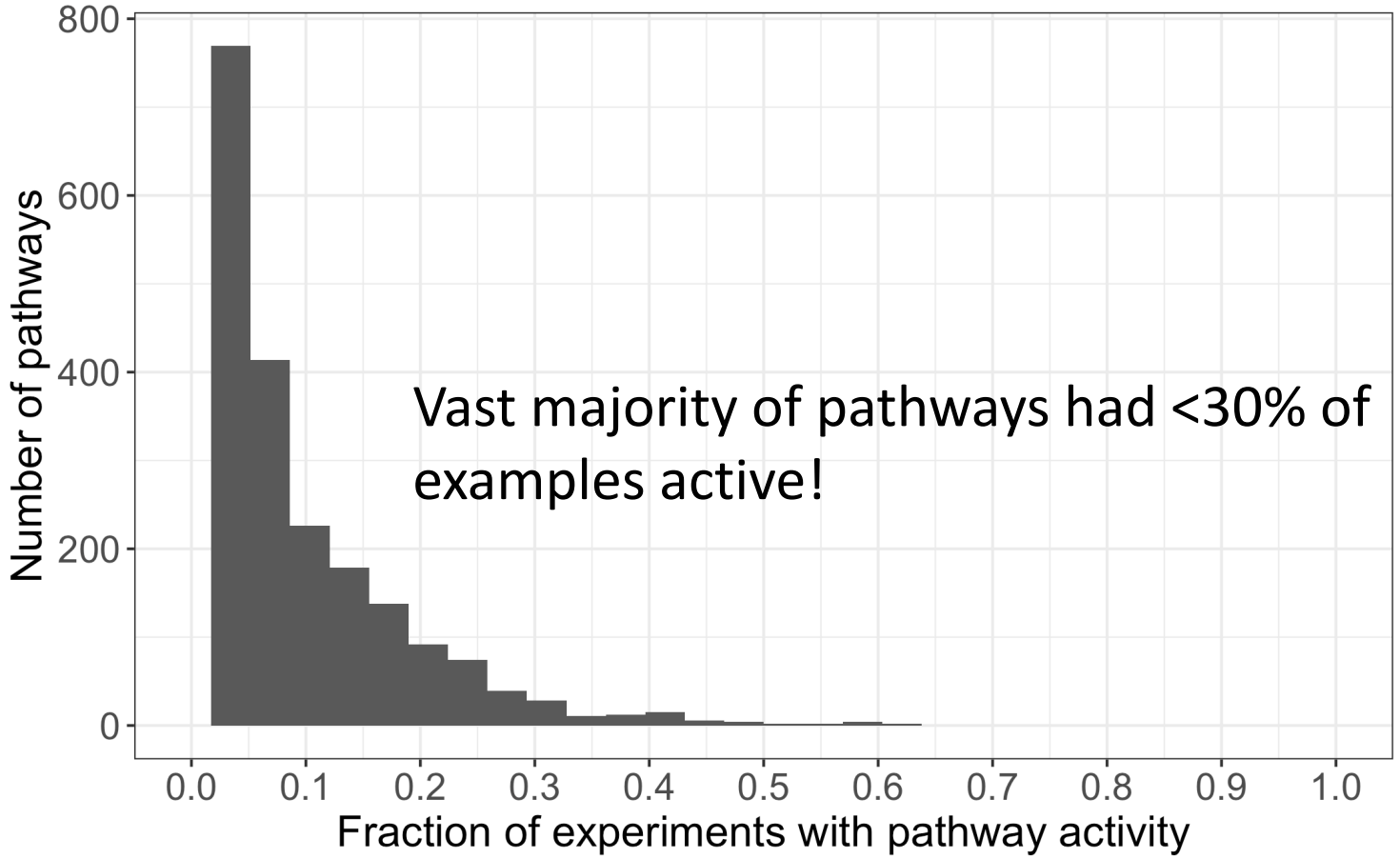
Could it be color-coded by proportion of safe, borderline, rare, and outlier data?

Could we identify “best practices” based on these dataset characteristics?

Case study: Machine learning for *in vitro-in vivo* extrapolation (Ring, Rager, et al. 2021)

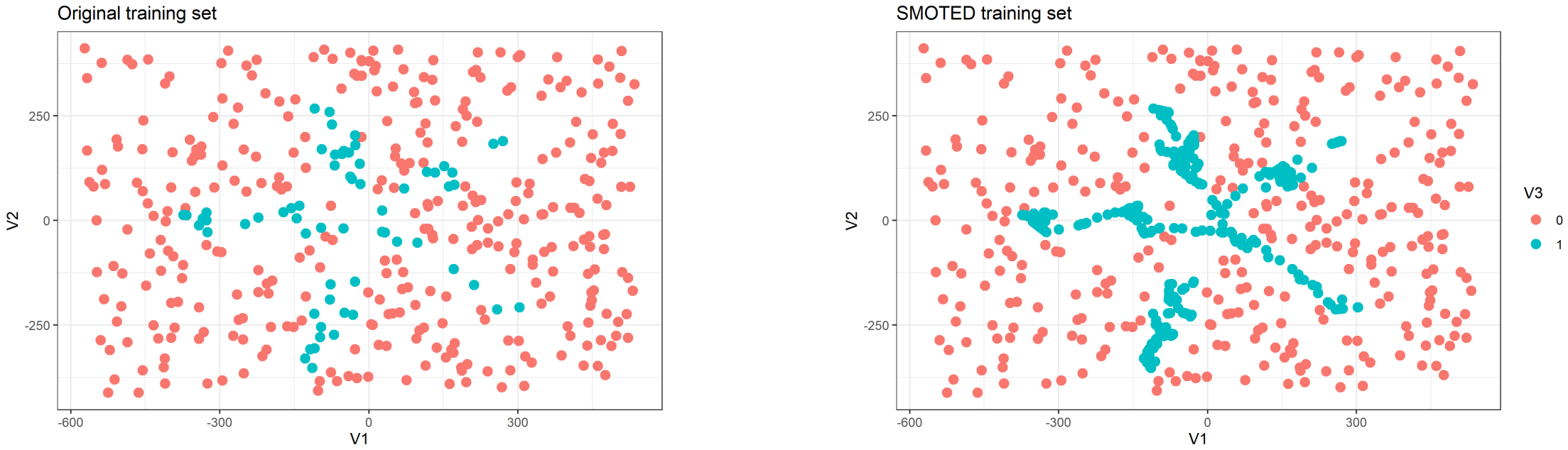
- Target: *in vivo* pathway-level transcriptomic activity in rat liver for a given chemical & dose (DrugMatrix and TG-Gates datasets)
- Features:
  - *in vitro* ToxCast bioactive concentration (AC50)
  - phys-chem properties
  - *in vivo* dose
  - toxicokinetic model predictions of body concentration at *in vivo* dose

Challenge: Highly imbalanced data



Approach to imbalanced data: SMOTE (Ring, Rager, et al. 2021)

(Illustration of SMOTE on example data from earlier, not our actual data)

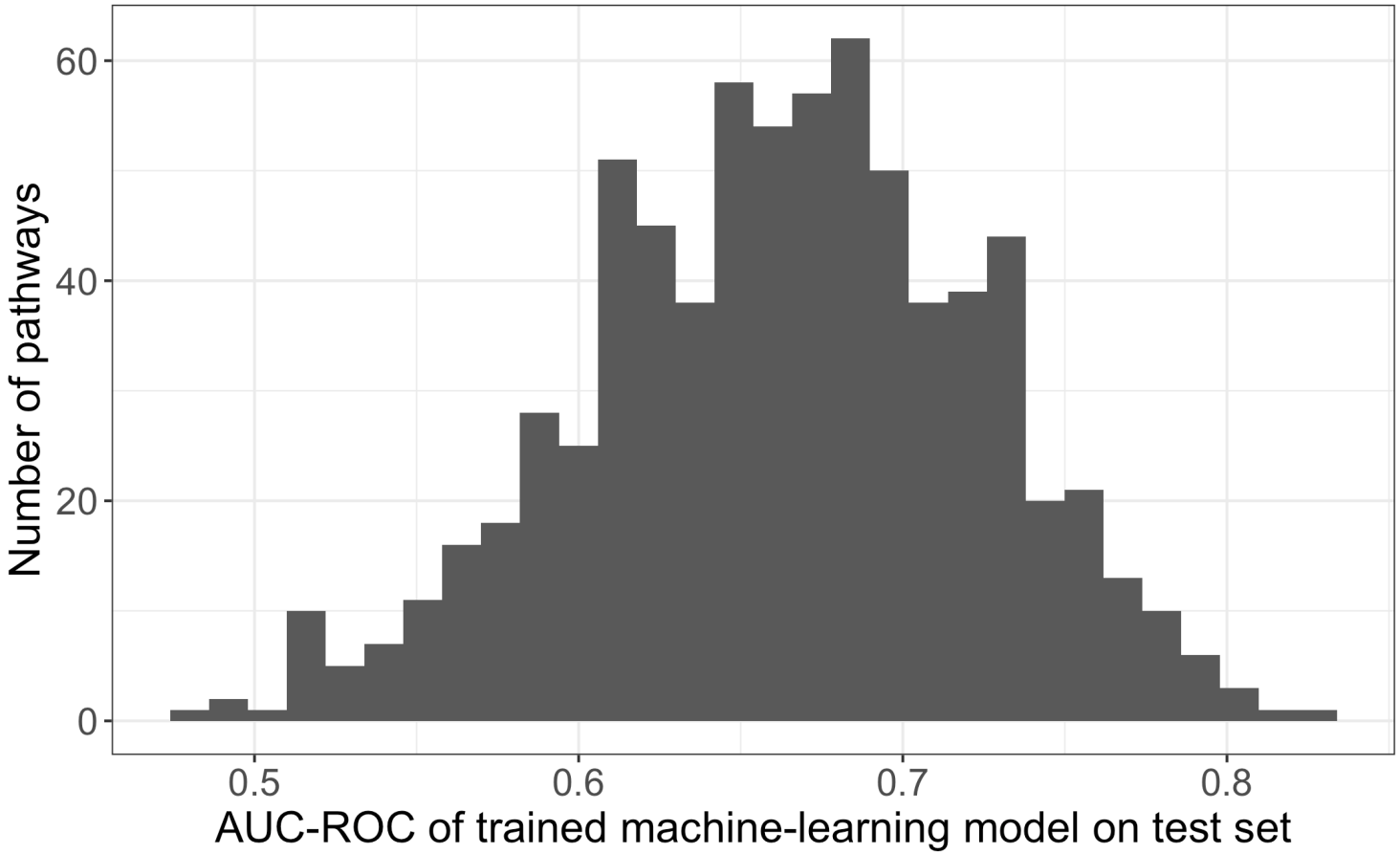


High-dimensional feature set: *in vitro* bioactivity for 144 Tox21 assays

We did not evaluate “data difficulty factors” in this analysis

Result: Pathway models with decent AUC-ROC

(Ring, Rager, et al. 2021)



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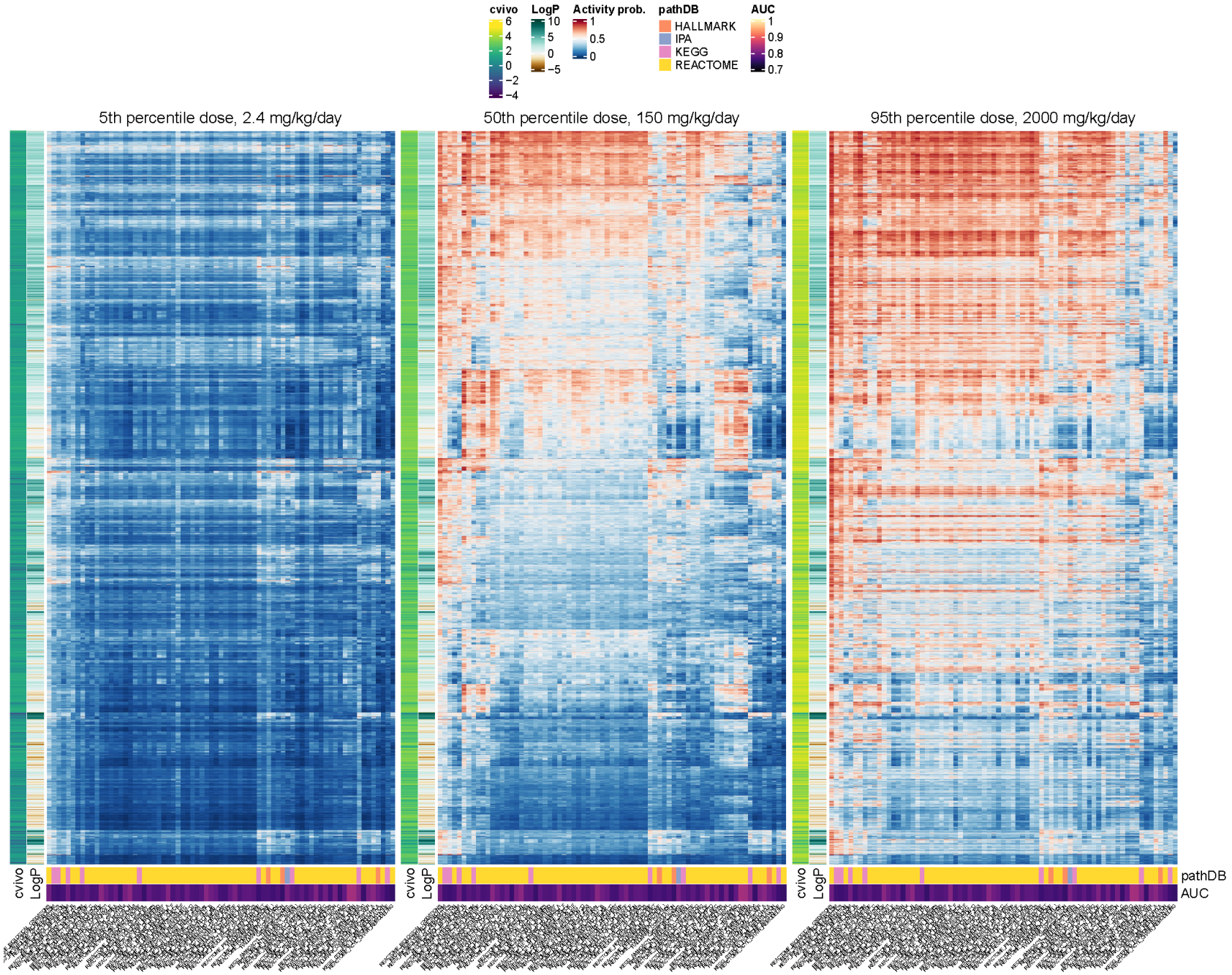
Result: Apply models to predict pathway activity for 6617 Tox21 chemicals at a range of doses (Ring, Rager, et al. 2021)



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Summary

- Machine learning is a powerful tool for predictive toxicology
- But its performance is affected by dataset-specific characteristics
  - Imbalanced data
  - Safe, borderline, rare, and outlier data points
- Strategies to address imbalanced data exist & are fairly successful
  - e.g. SMOTE, GAN
  - but dataset-specific characteristics affect these strategies as well
- Suggestion: Develop a more systematic approach to characterizing “data difficulty factors”
- Case study: Machine learning for *in vitro-in vivo* extrapolation
  - Applying SMOTE to address highly imbalanced training data

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