Sample-Specific Models for Interpretable Analysis with Applications to Disease Subtyping

May 5, 2022
Banff International Research Station

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Why does interpretability matter?

“Death by Round Numbers”

With


Rich Caruana — Microsoft Research


Mark Nunnally — NYU Langone Health


Manolis Kellis — Massachusetts Institute of Technology

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Elevated creatinine levels are an indicator of renal failure, so we expect mortality risk to increase with creatinine.

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Mortality Odds Ratio

Creatinine (mg/dL)

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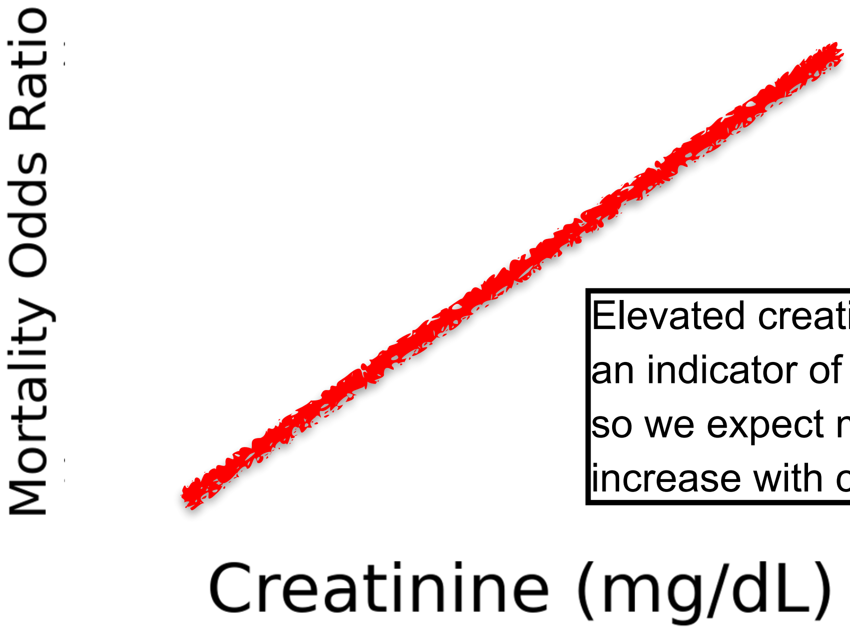

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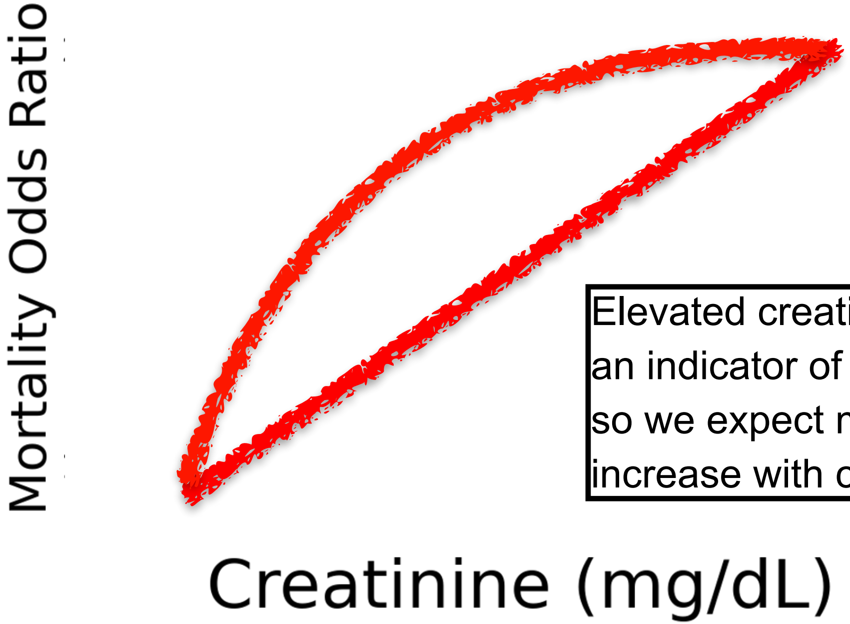

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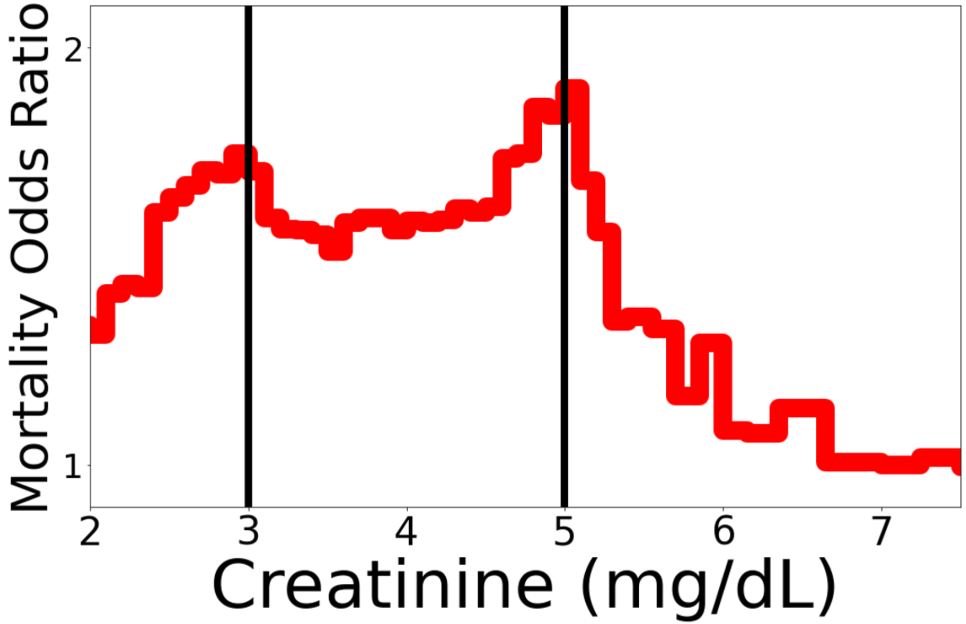

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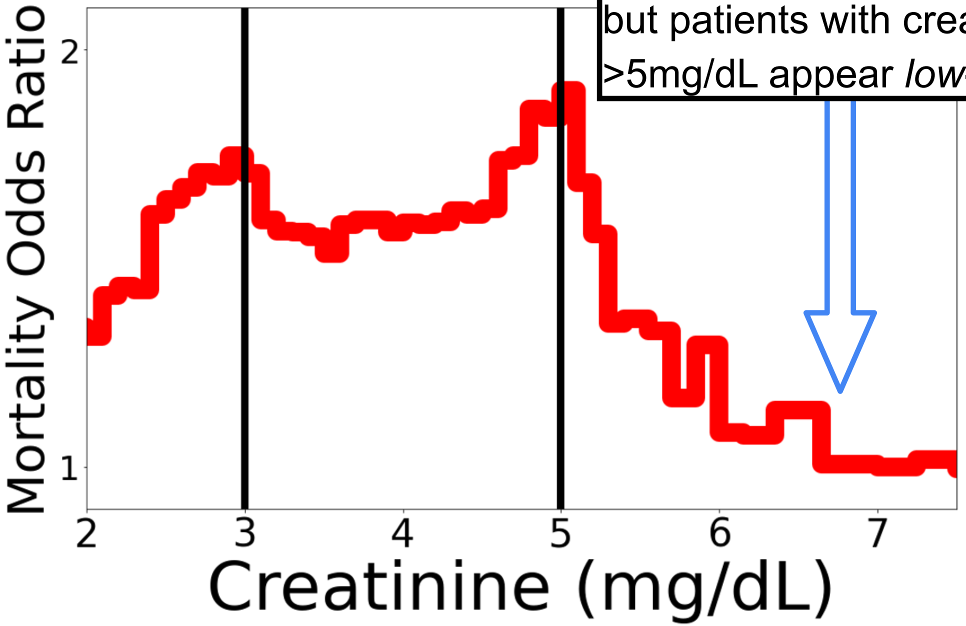

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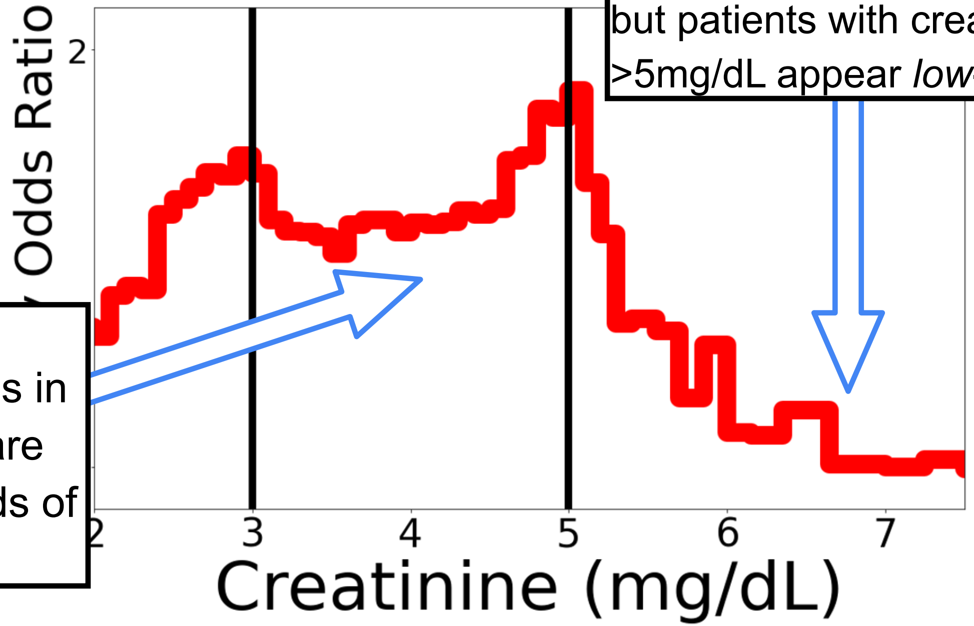

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Concave risk curve suggests that changes in physician behaviors are triggered by thresholds of 3 and 5 mg/dL.

Many examples of confounding revealed by interpretability

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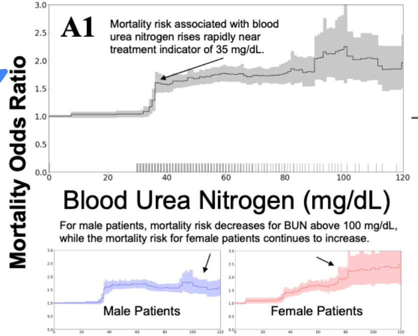
- Risk jumps, then flattens at BUN 35 mg/dL



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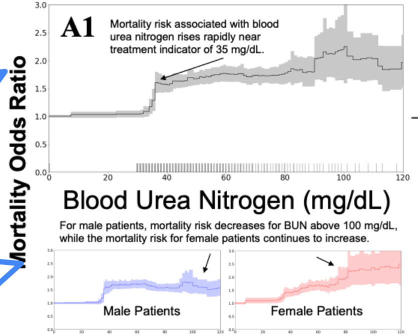
- Risk decreases for men BUN>100 mg/dL, but for women risk continues climbing



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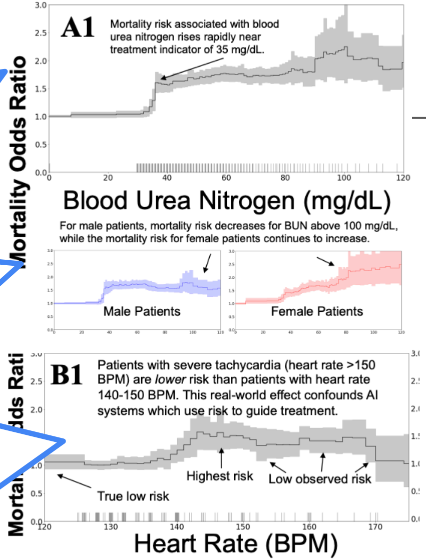
- Severe tachycardia is good?



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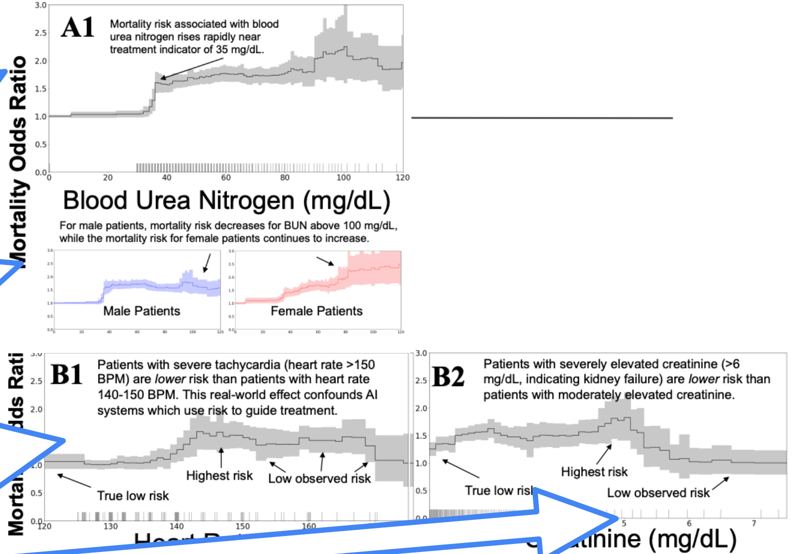
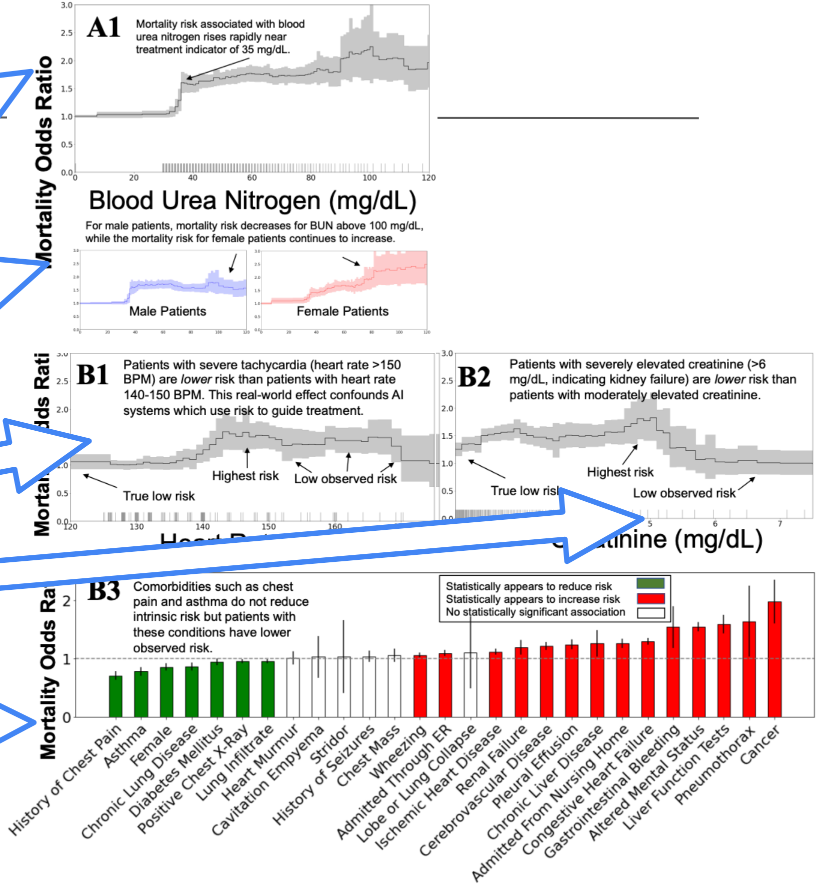


Many examples of confounding revealed by interpretability

- Risk jumps, then flattens at BUN 35 mg/dL
- Risk decreases for men BUN>100 mg/dL, but for women risk continues climbing
- Severe tachycardia is good?
- Elevated creatinine is good?
- History of chest pain, asthma, chronic lung disease are good?



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Interpretability turns these confounding **problems** into **opportunities**

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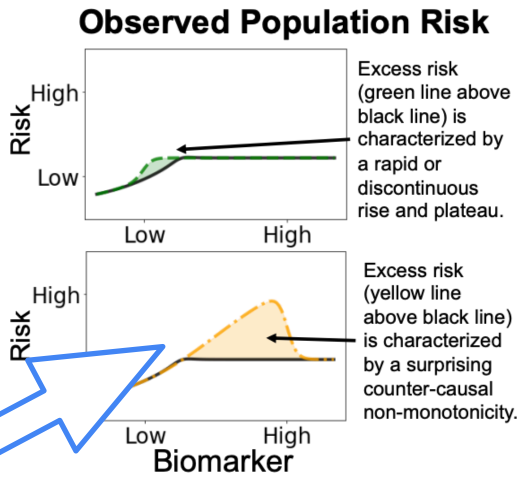

Finding these risk patterns

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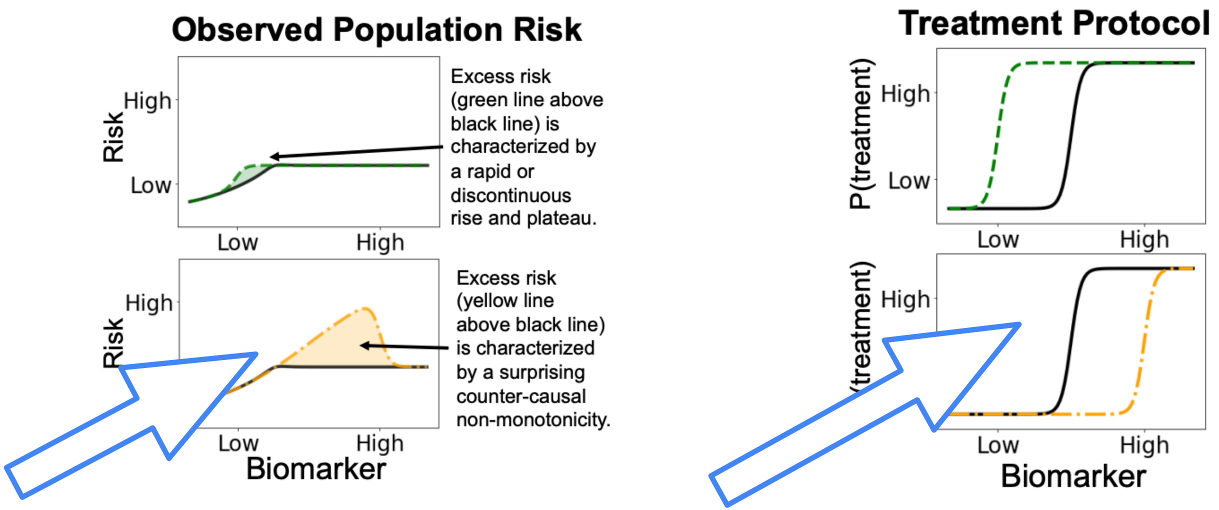

Finding these risk patterns

suggests the underlying protocols could be improved

What if interactions matter?

If interactions do matter…Black-box Models?

Fit black-box model
with non-linear
decision surface

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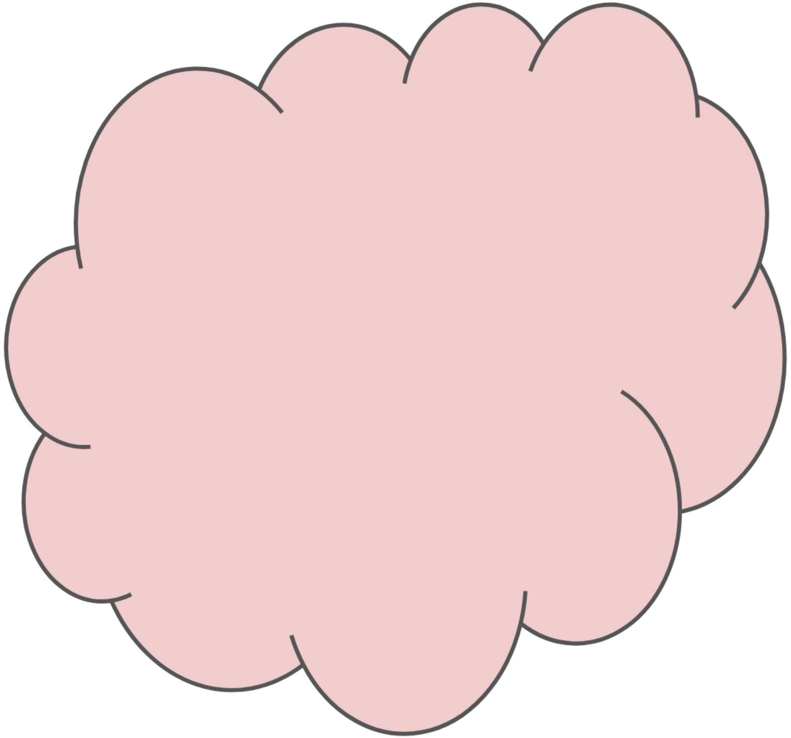
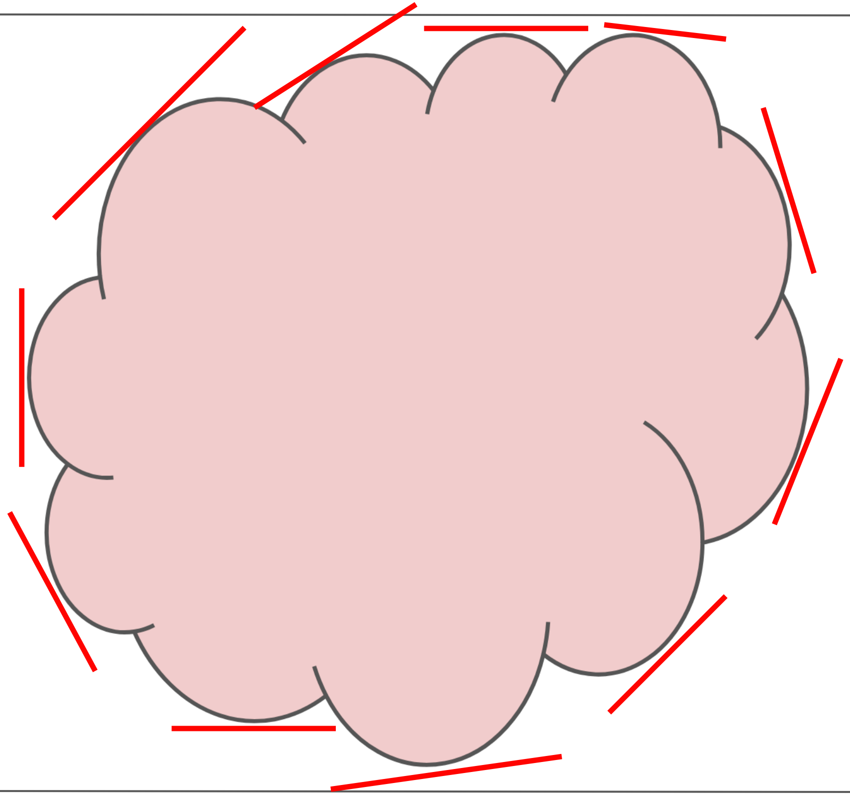
Fit black-box model with non-linear decision surface



If interactions do matter…Black-box Models?

Fit black-box model with non-linear decision surface

Then interpret with locally-linear models



LIME, Ribeiro et al. 2016

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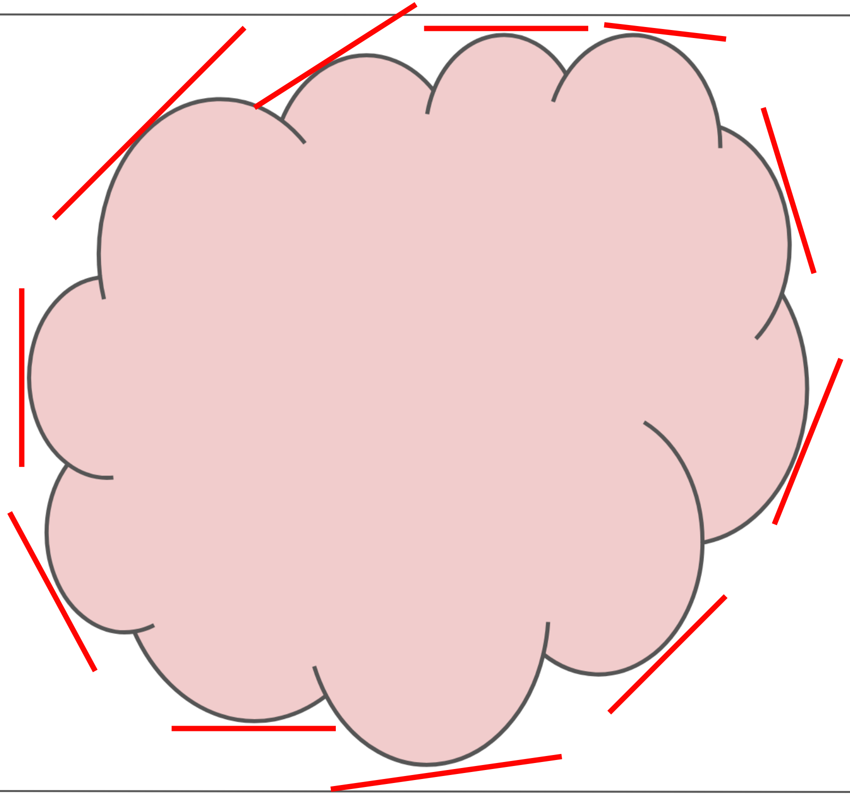
Locally-Linear Models Sacrifice Nothing?

ReLU NNs are both **universal approximators**

AND

Piecewise-linear



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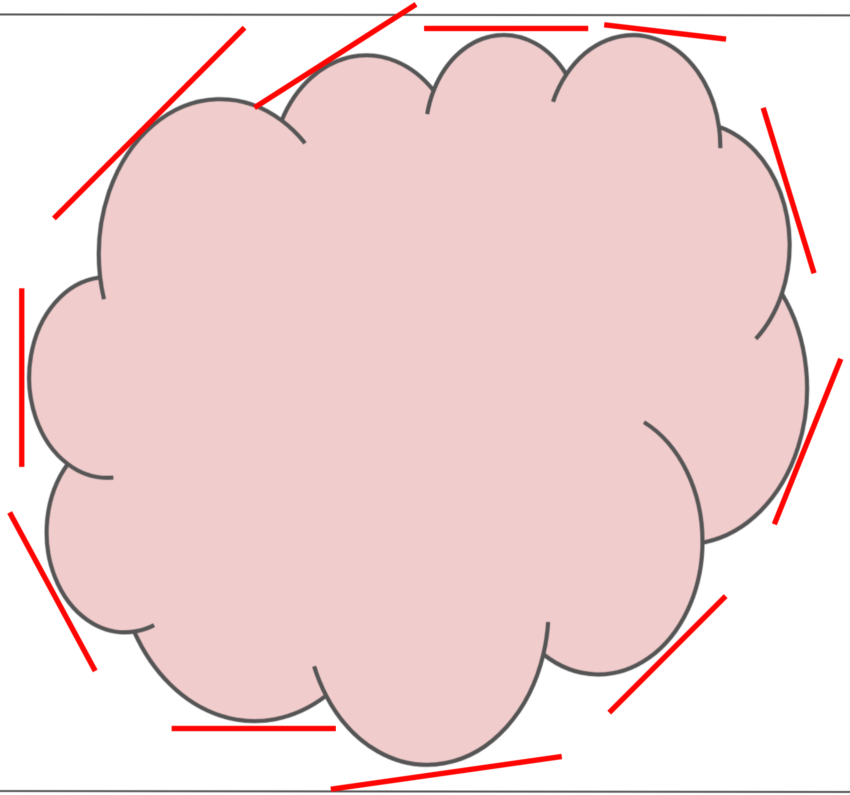
So what's the point of the black-box model?



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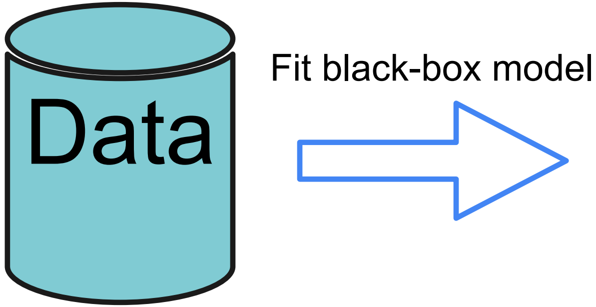

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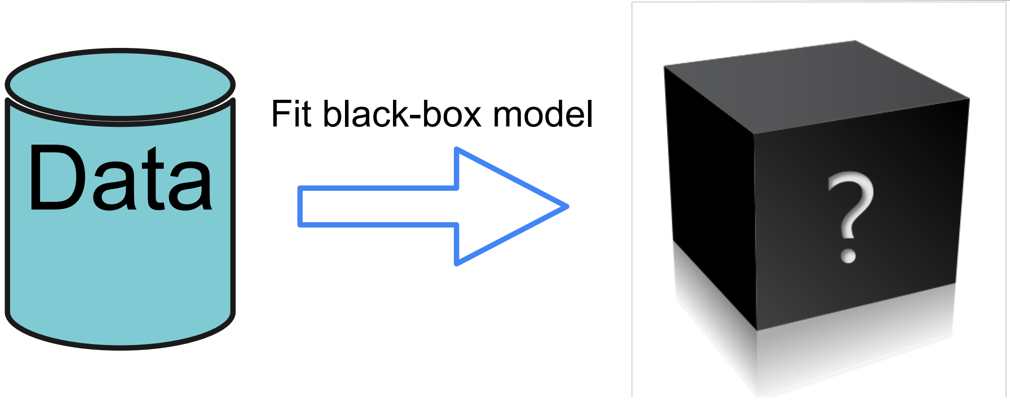

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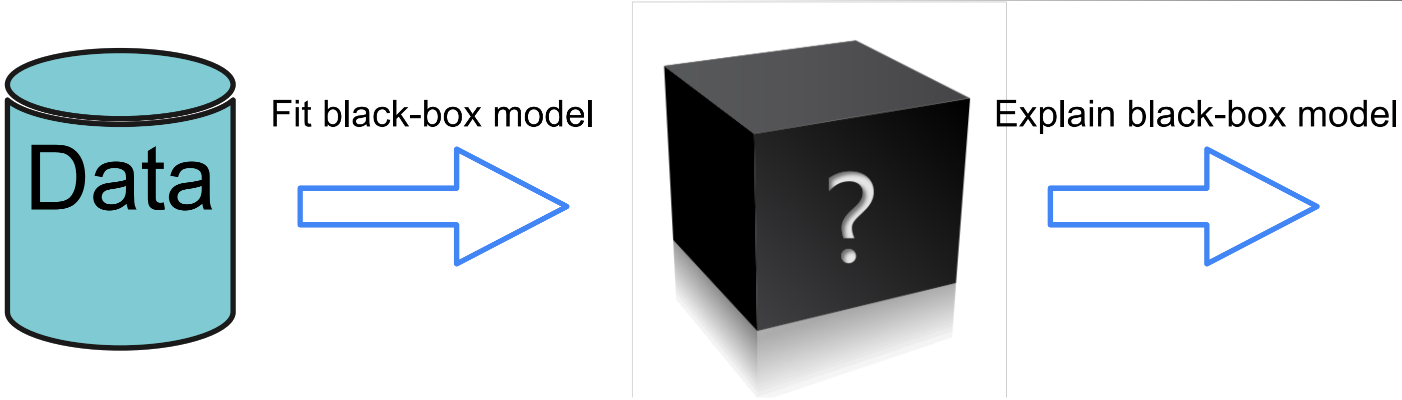

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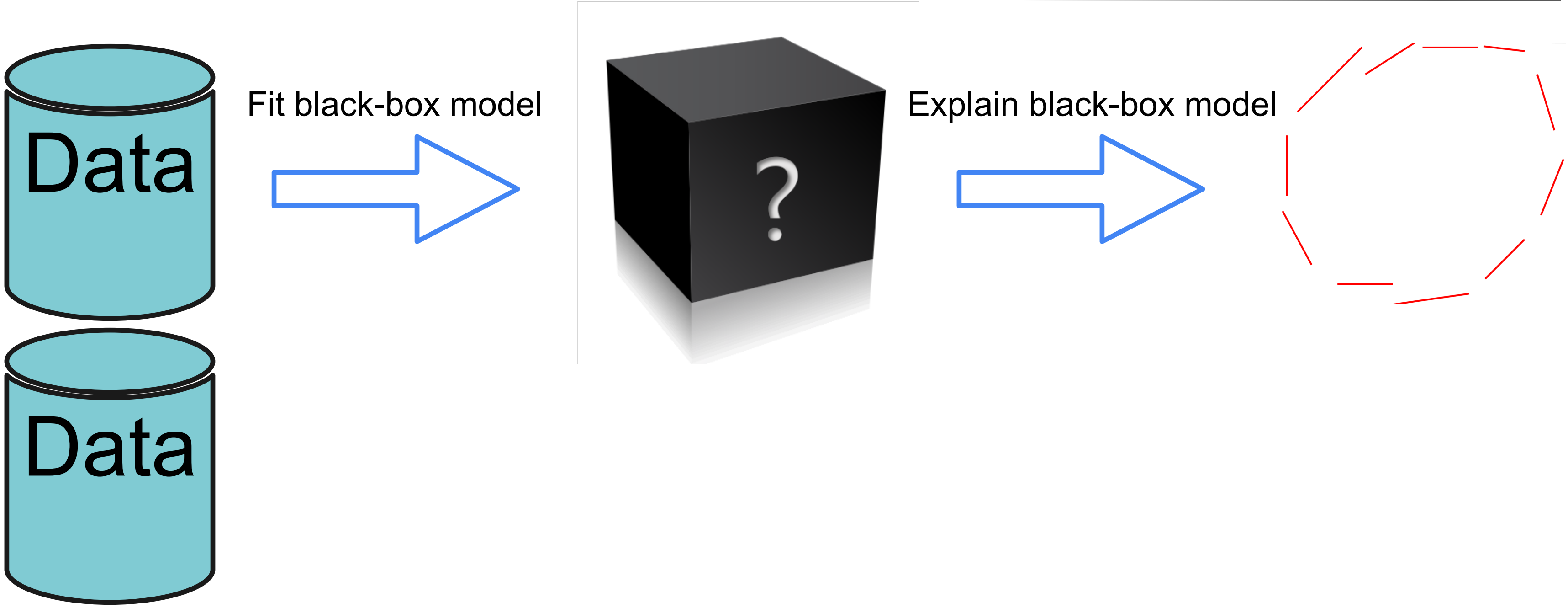

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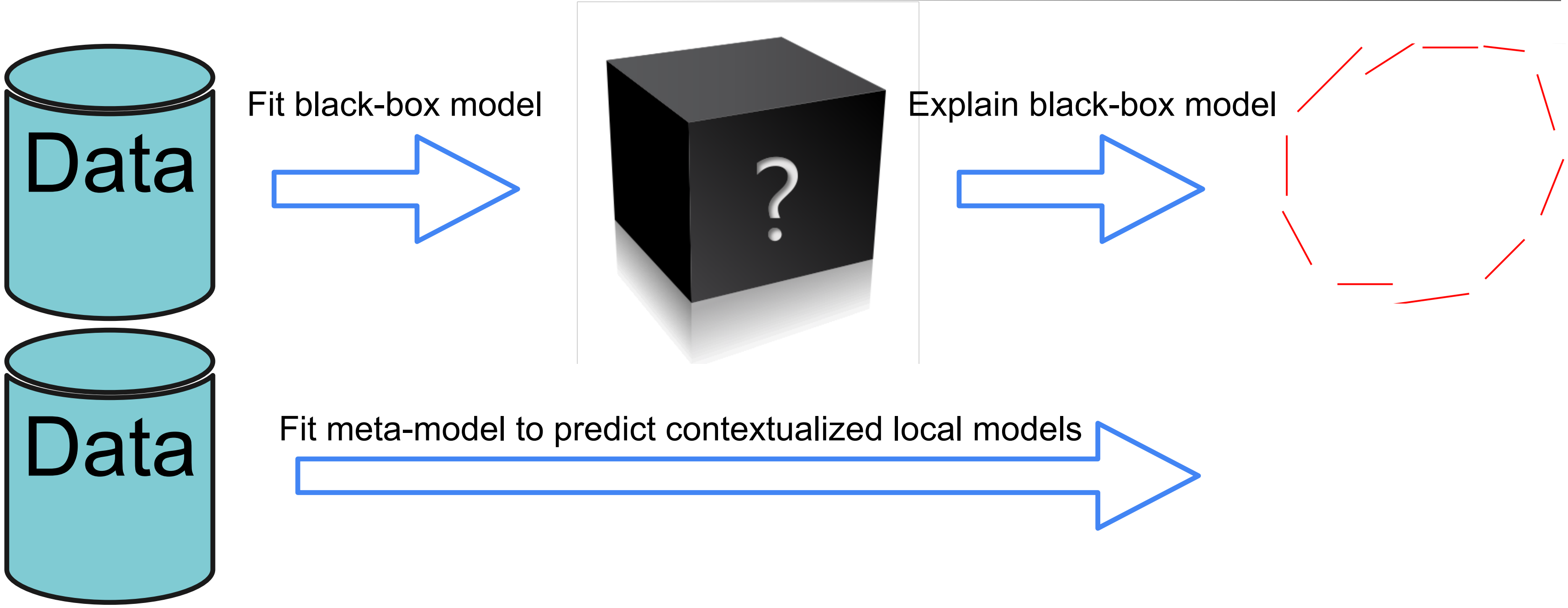

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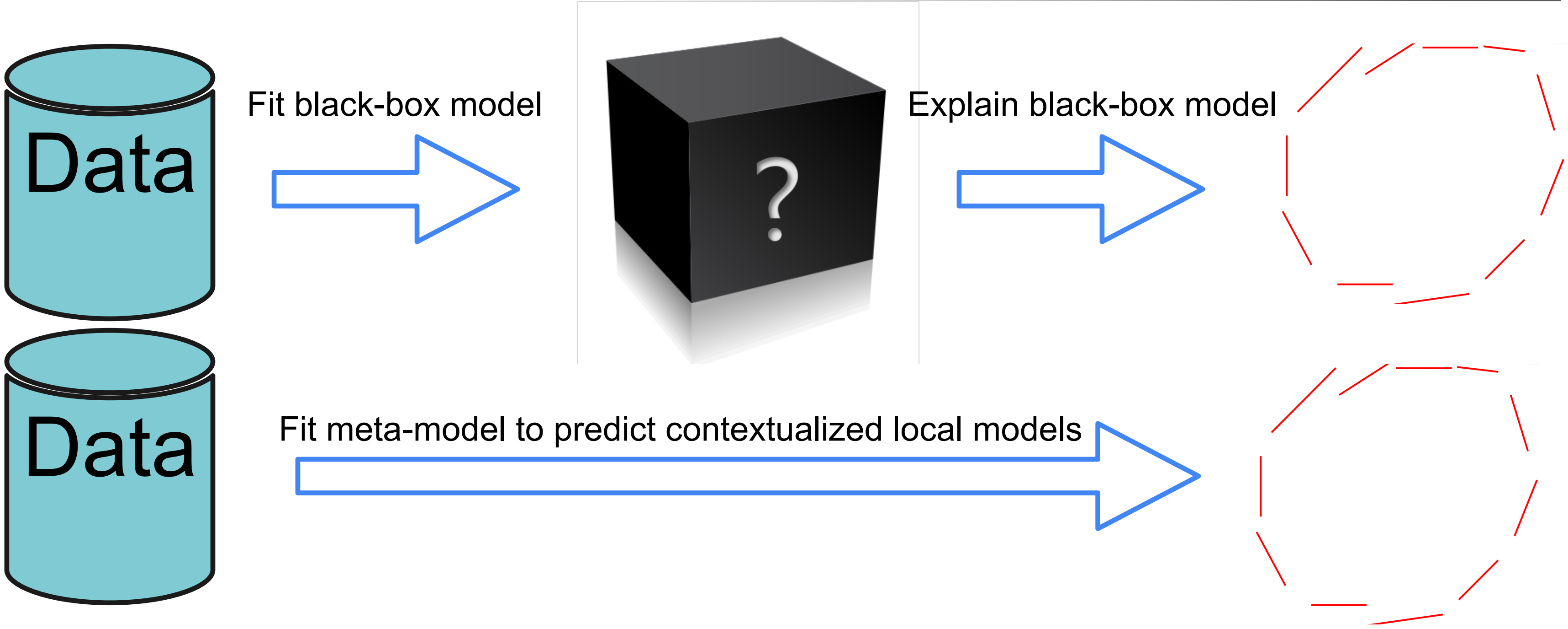

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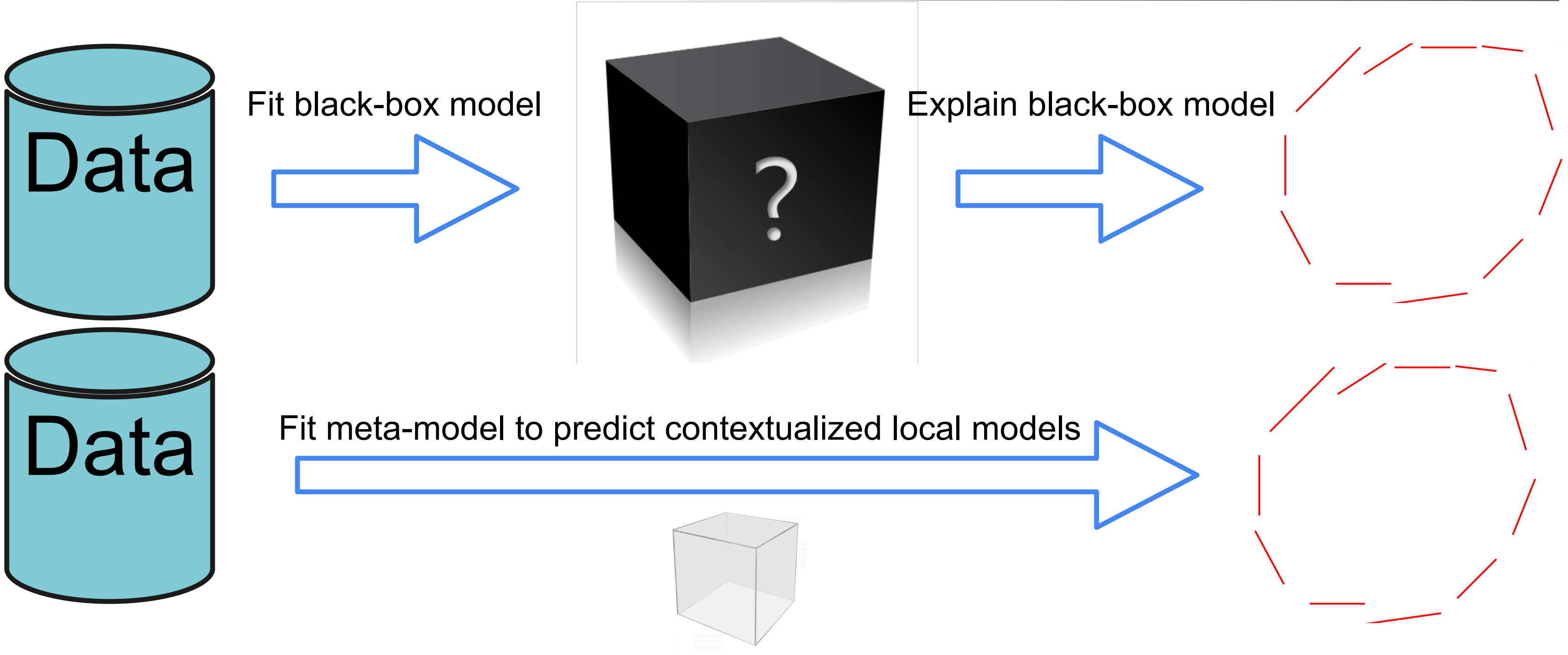

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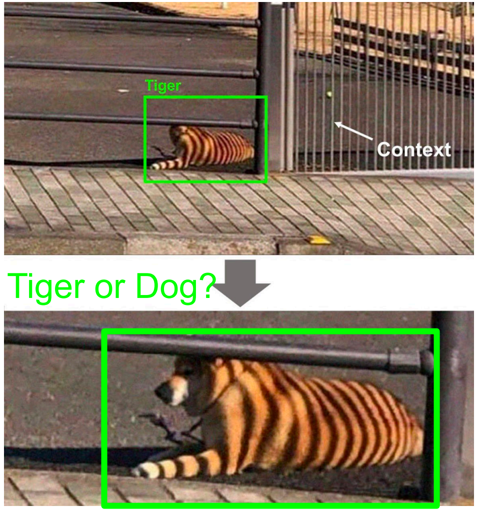
What are local models? 3 Philosophies:

1 Local models are incorrect, obscured by context factors



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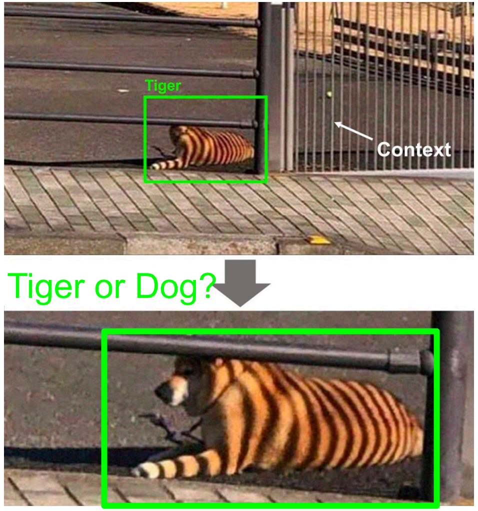

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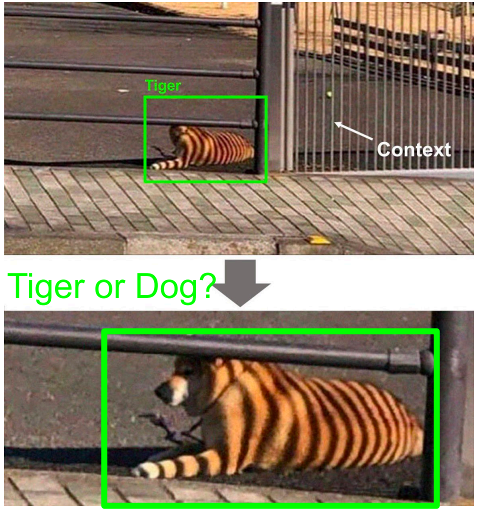

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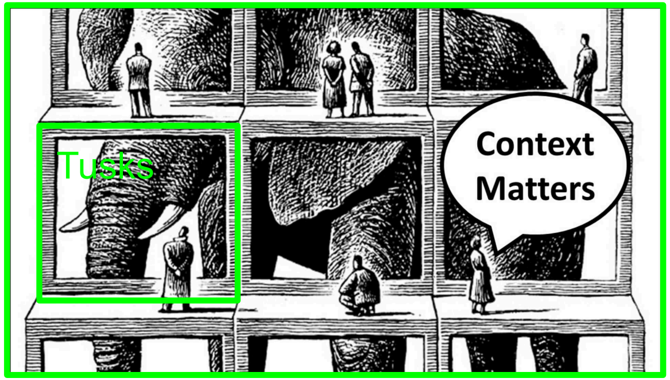

Elephant

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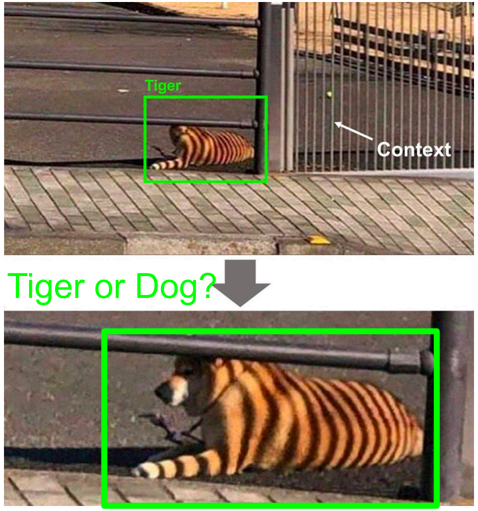

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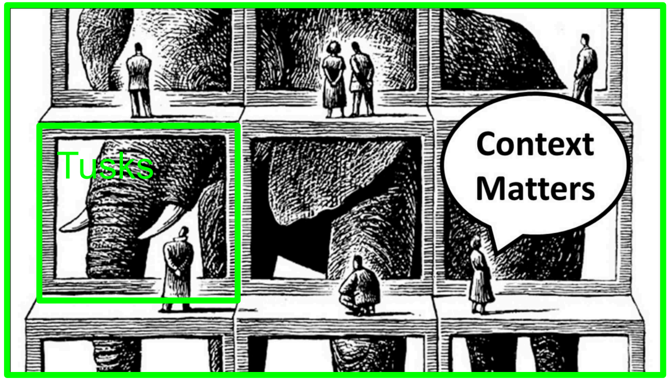

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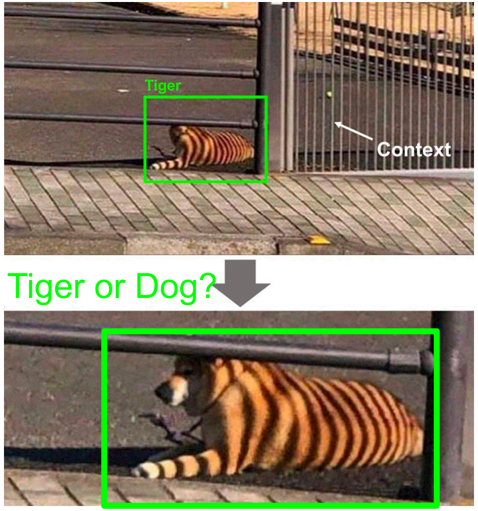

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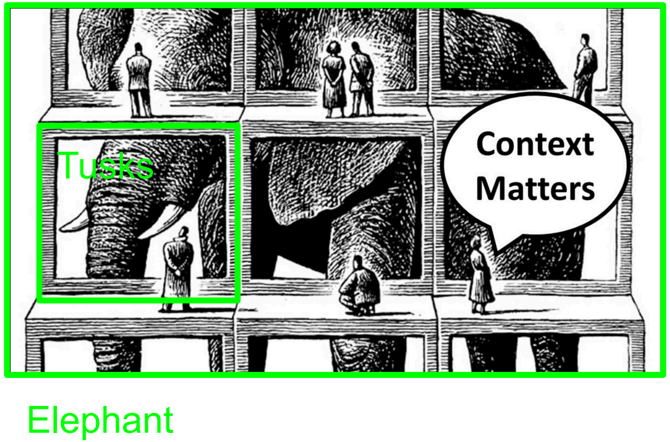

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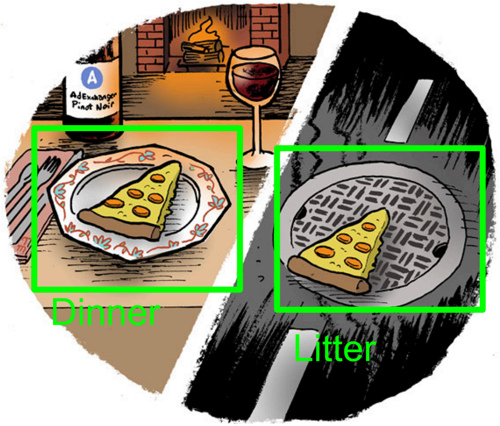

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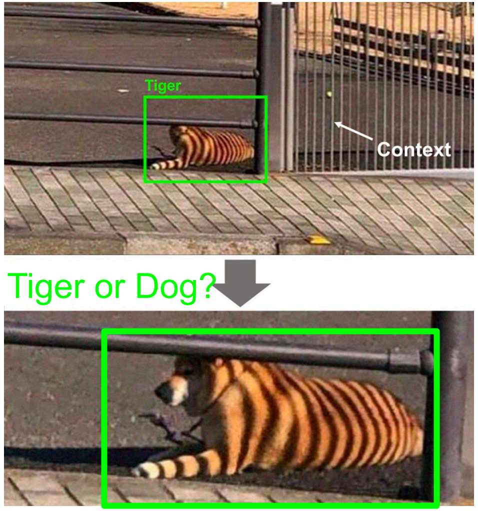

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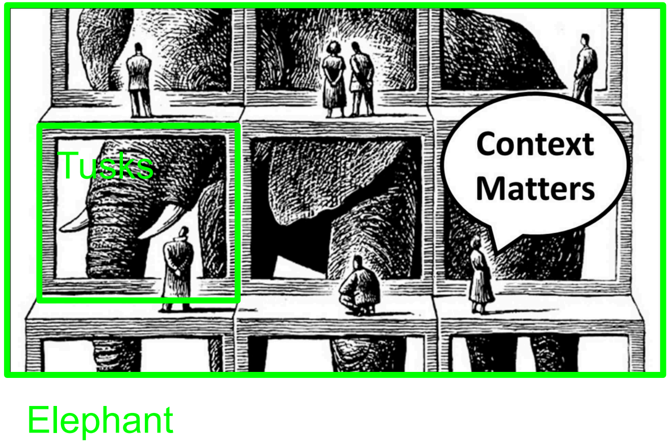

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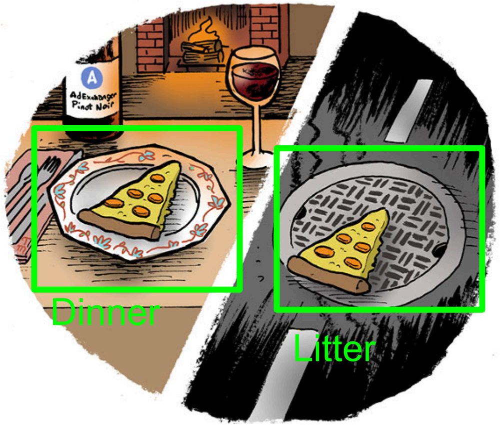

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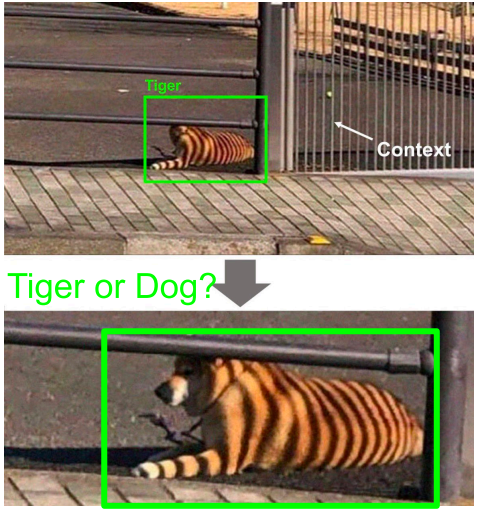

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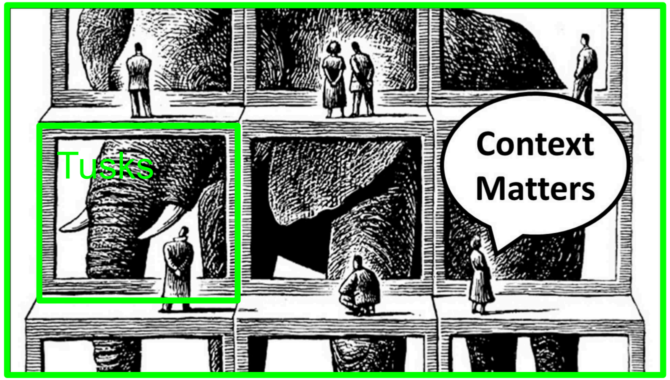

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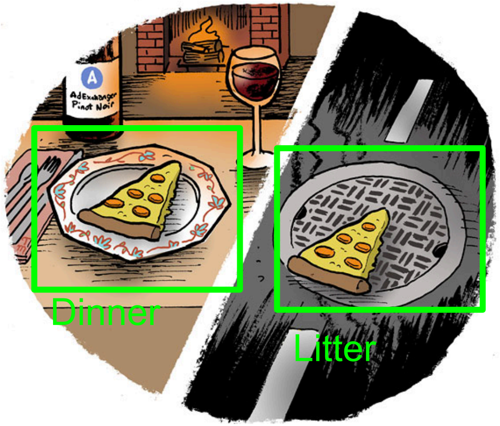

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Contextualized
Heterogeneous Modeling Toolbox

Trevor Hastie and Rob Tibshirani got here first too…

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$$Y = \beta X + \epsilon, \text{ where } \beta = C\phi$$

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- Let's put it on modern ML steroids
    - If we can solve technical problems: dimensionality, stability, etc
    - Then backprop allows us to make *any* model class contextualized

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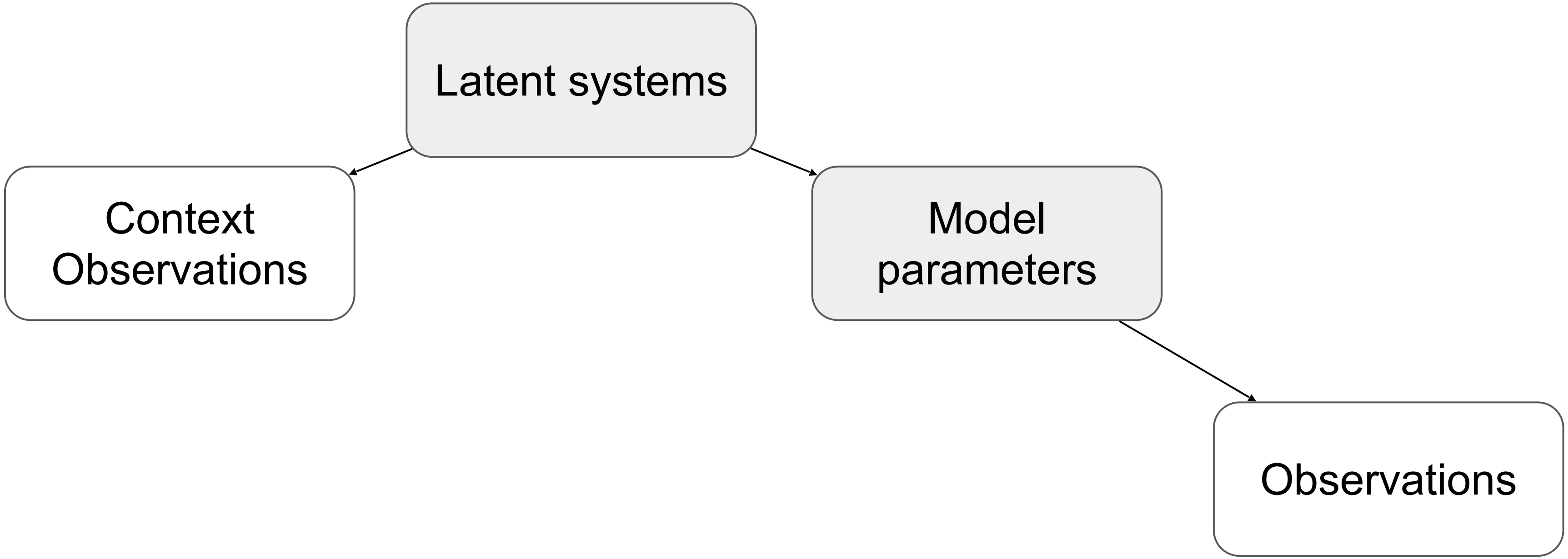
Our Solution:
Contextualized Machine Learning

Contextualized Machine Learning



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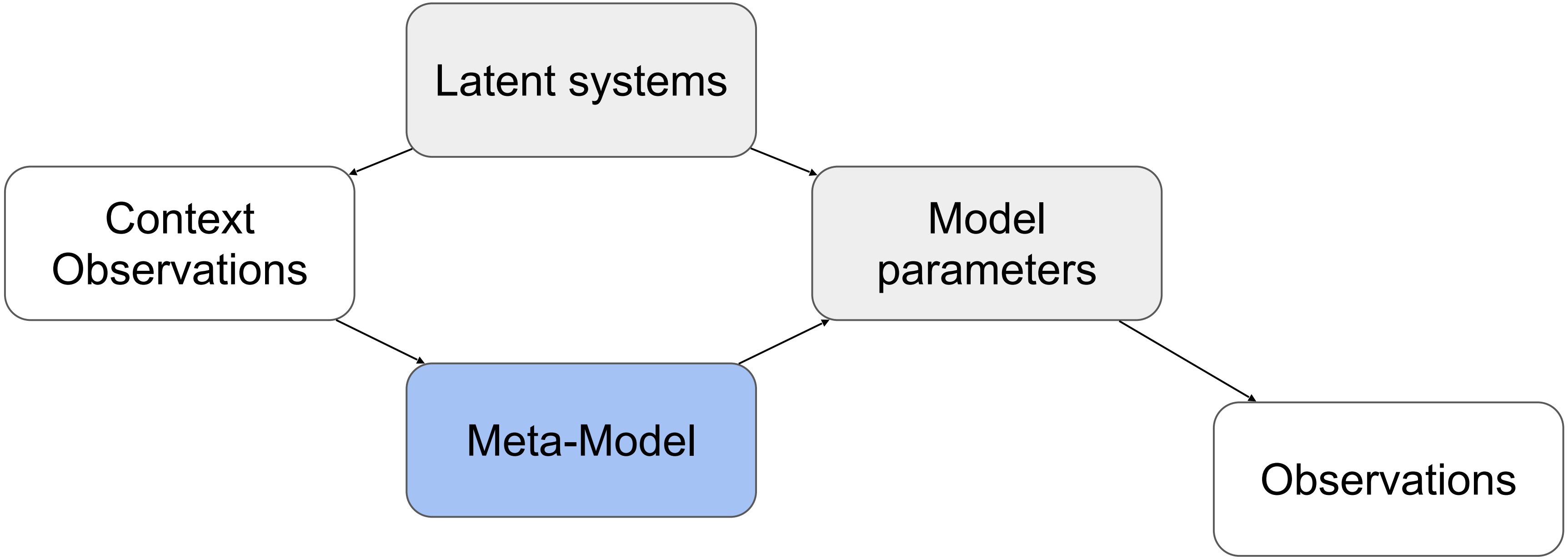

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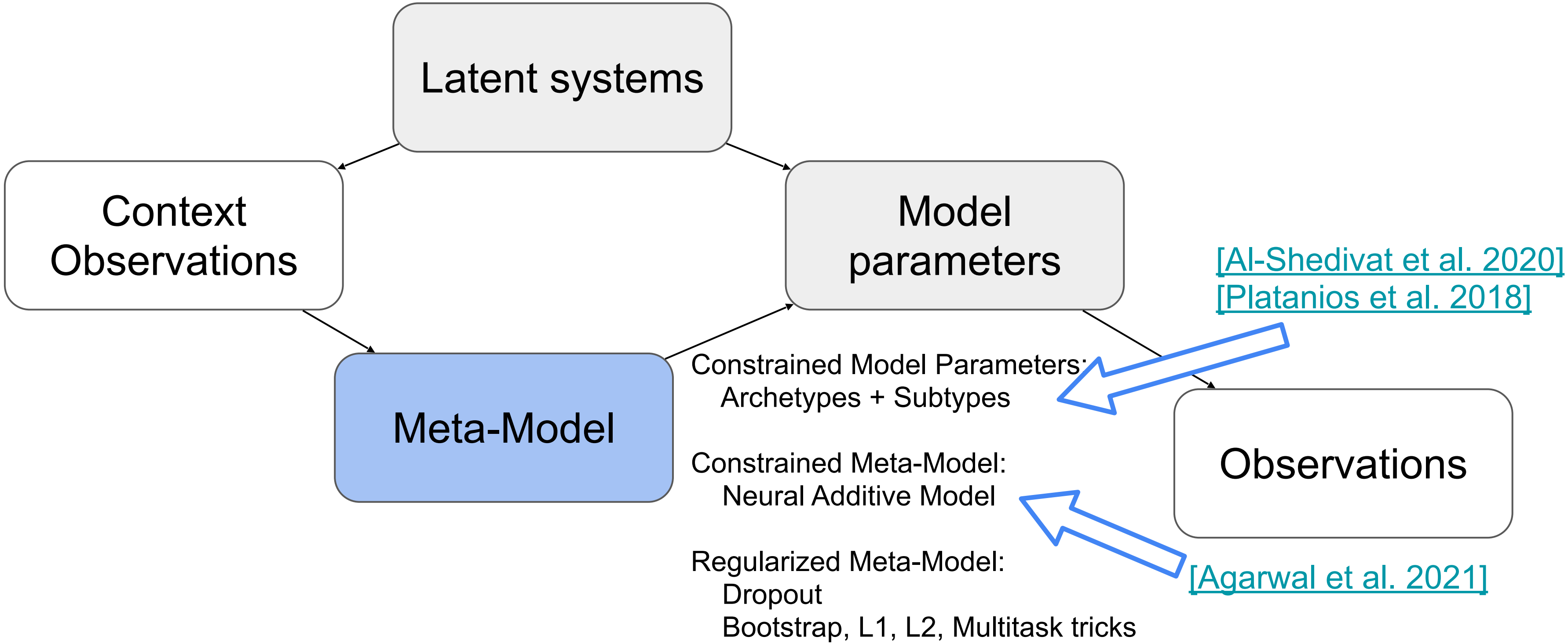

Toy Example: Heterogeneous Treatment Effects

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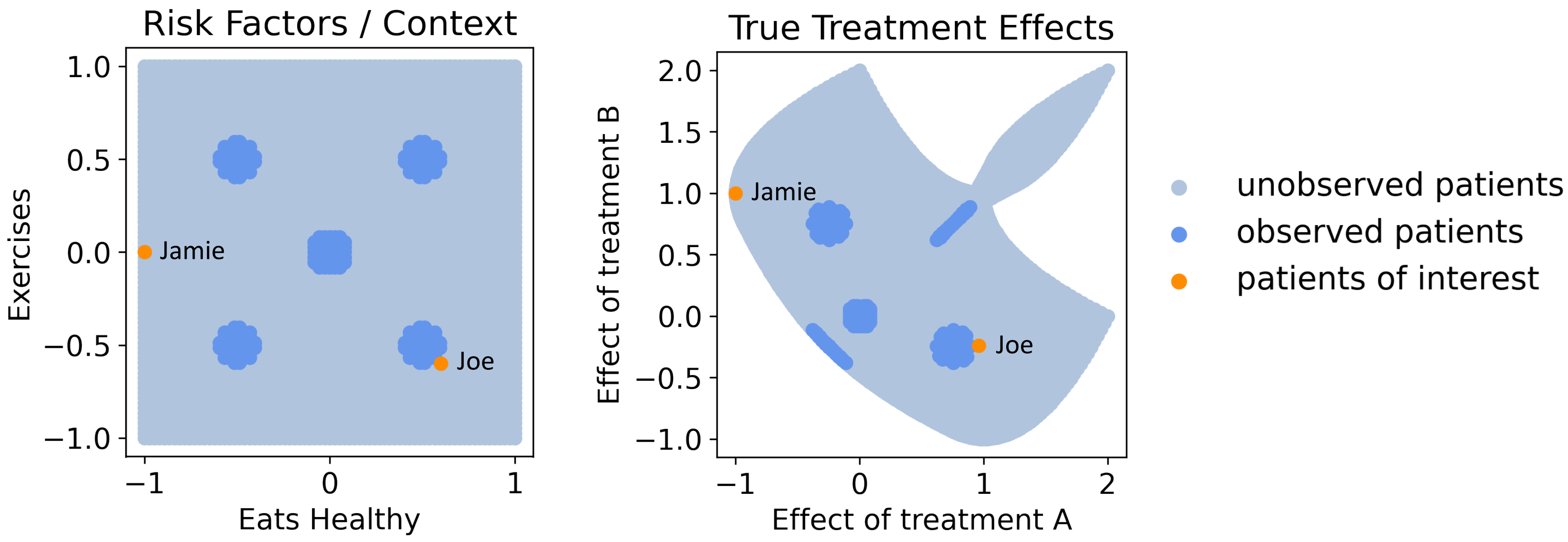

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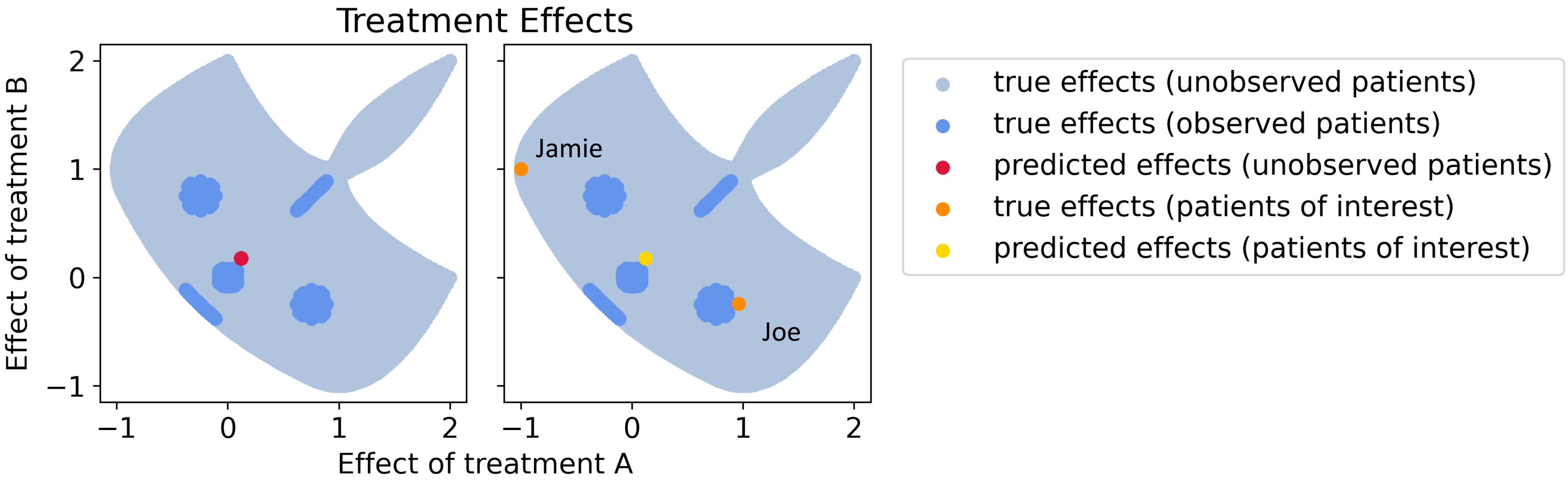
Population Model: No Heterogeneity

Learn a single (population) model by solving $Y = X\hat{\beta} + \hat{\mu}$



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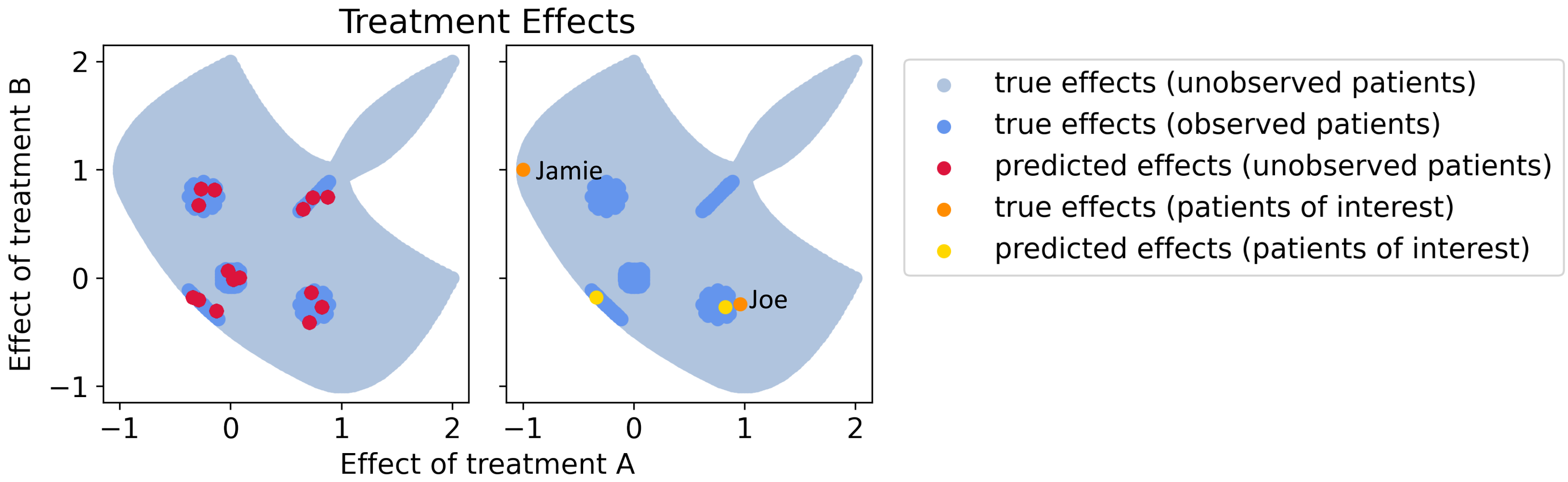
Cluster-Based Models: Limited Heterogeneity

Cluster C, then for each cluster solve $Y_c = X_c\,\hat{\beta}_c + \hat{\mu}_c$



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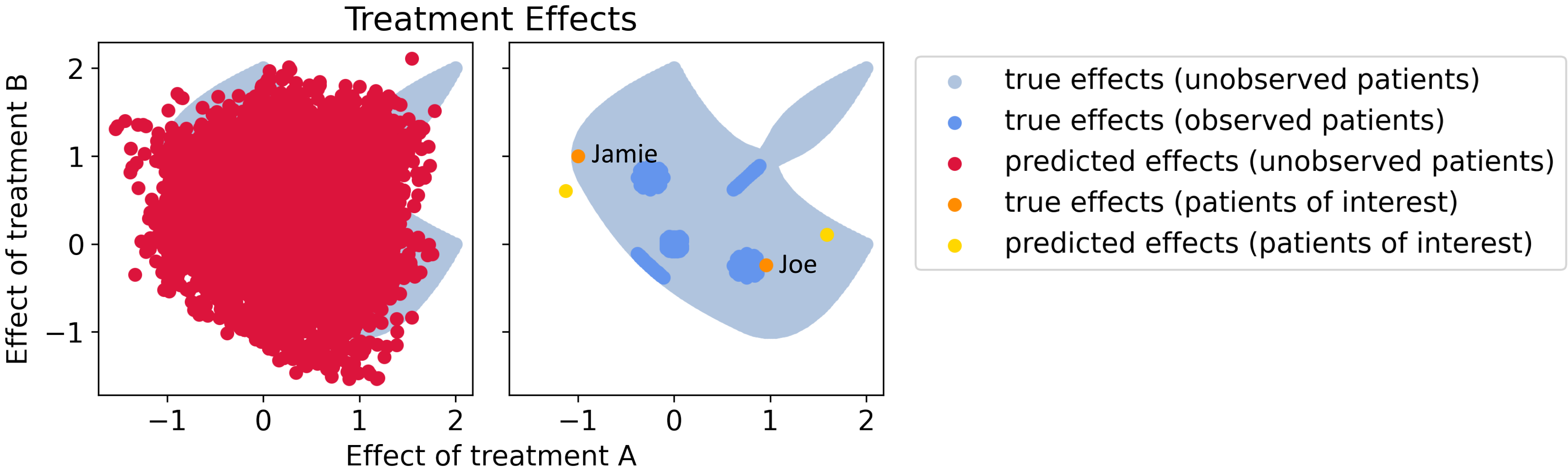
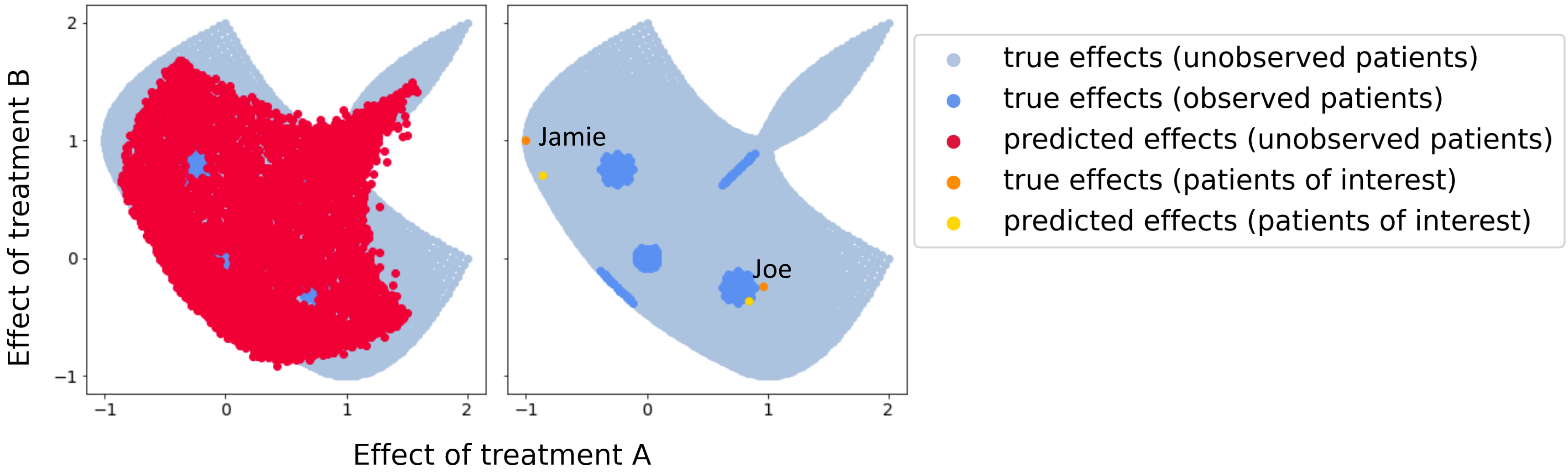
Implicit Models: Unorganized

$$Y = \Phi(C, X) \rightarrow \hat{\beta} = \frac{\partial \Phi}{\partial X}$$



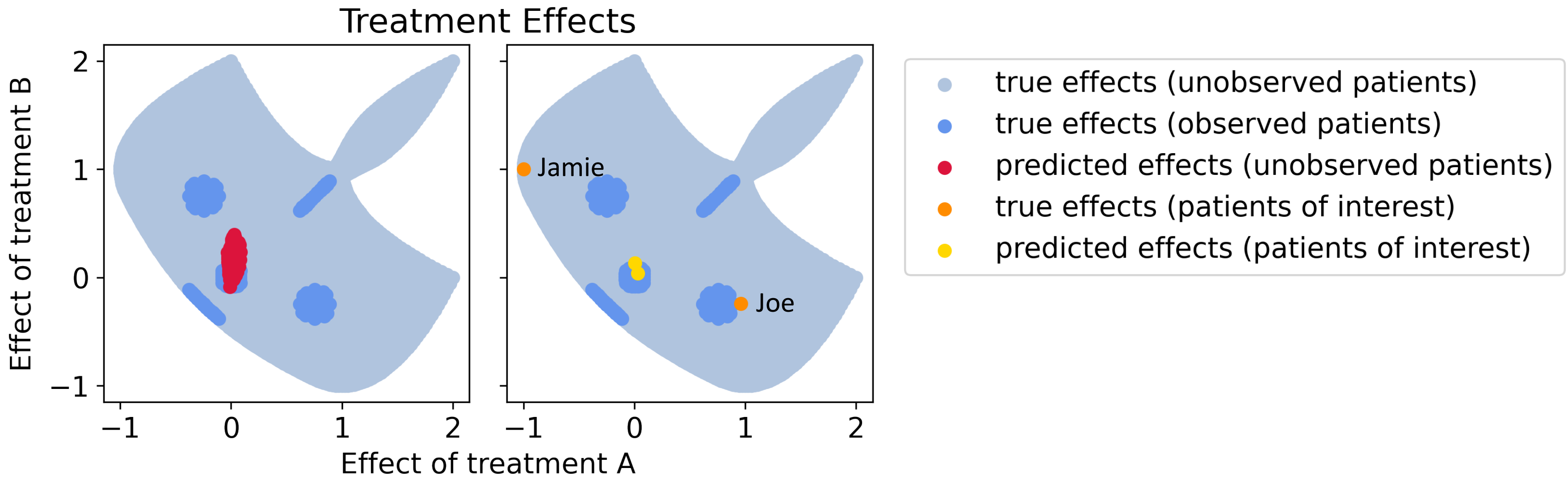
Context Encoder: Generalizability by Learning Latent Structure

$$Y = X\ \beta_{\Phi}(C,\ \epsilon) + \mu_{\Phi}(C,\ \epsilon)$$



In the worst case, context encoders recapitulate the population model

$$Y = X\,\beta_{\Phi}(\epsilon) + \mu_{\Phi}(\epsilon) \rightarrow Y = X\hat{\beta} + \hat{\mu}$$



Contextualized

Heterogeneous Modeling Toolbox

contextualized.ml



With Caleb Ellington, Eric Xing, Manolis Kellis

Carnegie Mellon University
MOHAMED BIN ZAYED UNIVERSITY OF ARTIFICIAL INTELLIGENCE
Massachusetts Institute of Technology

Contextualized Regression in Contextualized.ML

sklearn-like interface:

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from contextualized.easy import ContextaulizedRegressor
model = ContextualizedRegressor()
model.fit(C, X, Y)
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PyTorch

Common keywords:
- n_bootstraps
- n_archetypes
- link function
- meta-model type
- multitask sharing strategy

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Making predictions:

```
Y_hats = model.predict(C_test, X_test)
beta_hats, mu_hats = model.predict_params(C_test)
```

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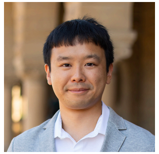
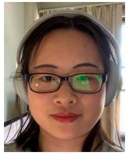
Disease Subtyping Vignette 1: Alzheimer's Disease

With Yosuke Tanigawa, Na Sun, Carles Boix, Leyla Akay, Manolis Kellis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Contextualized Analysis Reveals Personalized Markers of Alzheimer's Disease

Data
- 430 patients with single-cell RNA-seq of post-mortem brain samples
- Aggregated to pseudo cell-sorted (cell type), flattened for each patient
- Extensively pre-processed for QC
- Context: demographics, clinical factors
- Outcome: AD / Healthy

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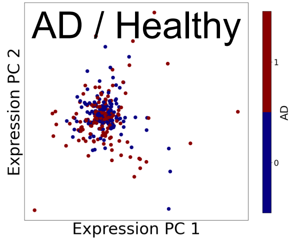
Raw Gene expression doesn't separate patients



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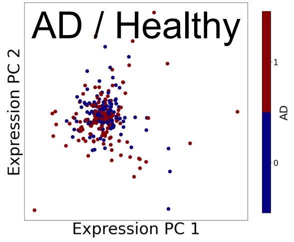

Personalized Regression Improves Predictive Performance

Tests AUCs:
- Population Model: 0.67
- Personalized Models: 0.78

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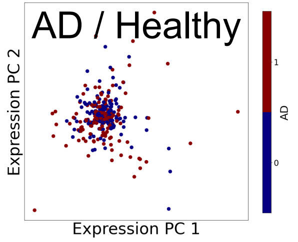

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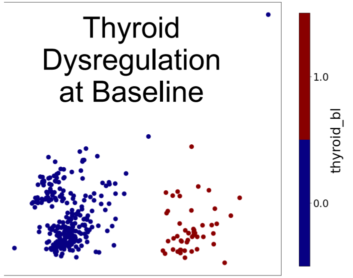

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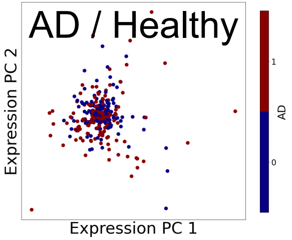

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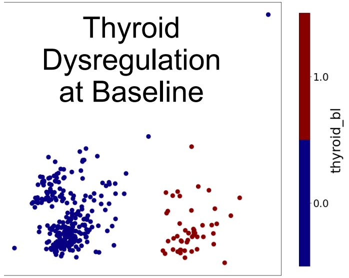

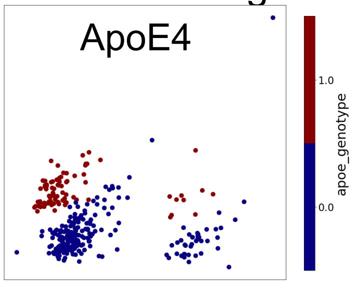

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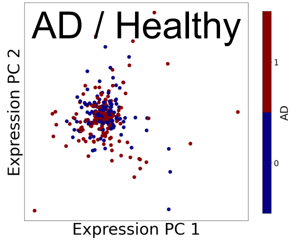

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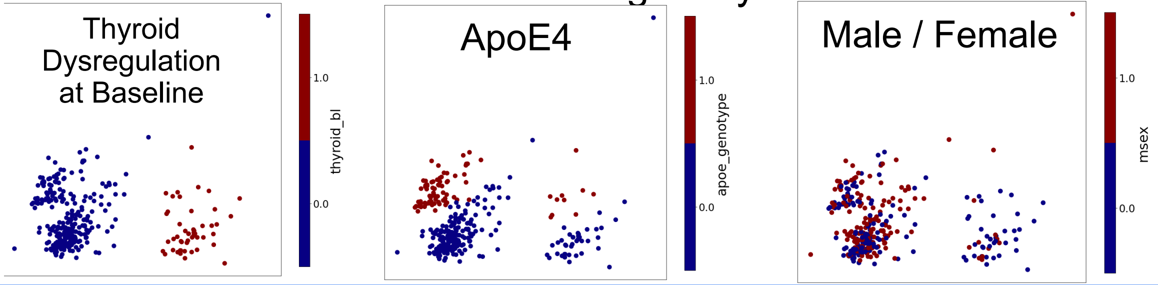

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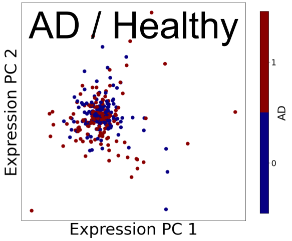

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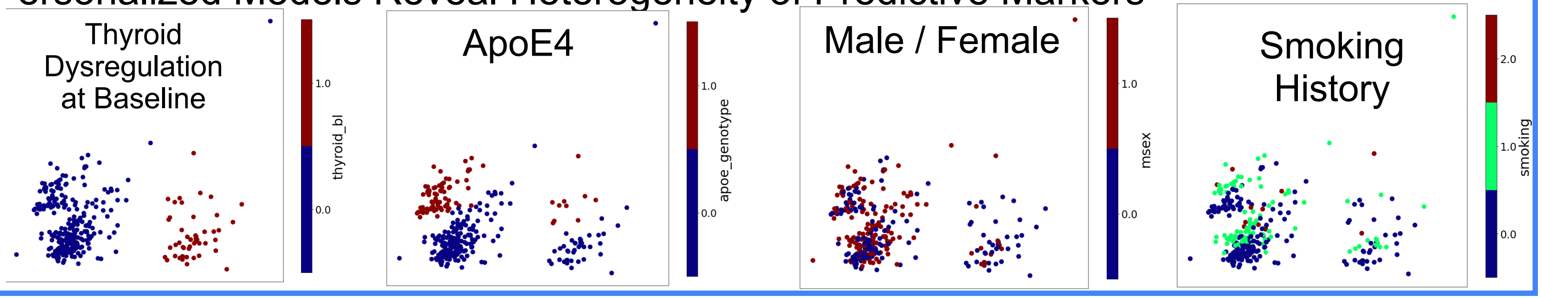

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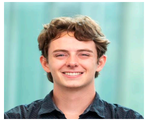
Disease Subtyping Vignette 2: Personalized Treatment Benefits in Covid-19

With Mark Nunnally, Yin Aphinyanaphongs, Caleb Ellington, Rich Caruana






Personalized Treatment Benefits in Covid-19

Tree-based EBMs are **great** at modeling healthcare data, but not differentiable. Can we combine EBM benefits with contextualized treatment estimation?

Solution:

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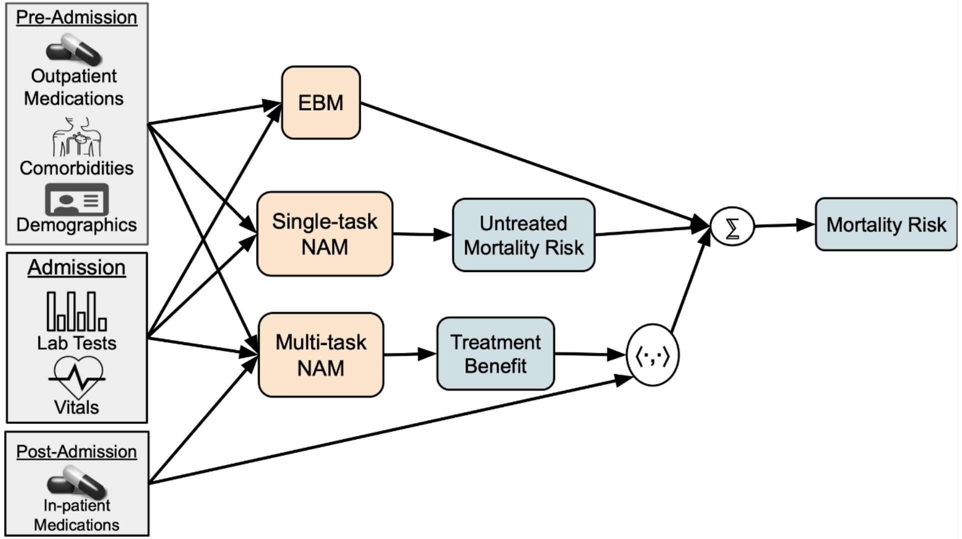

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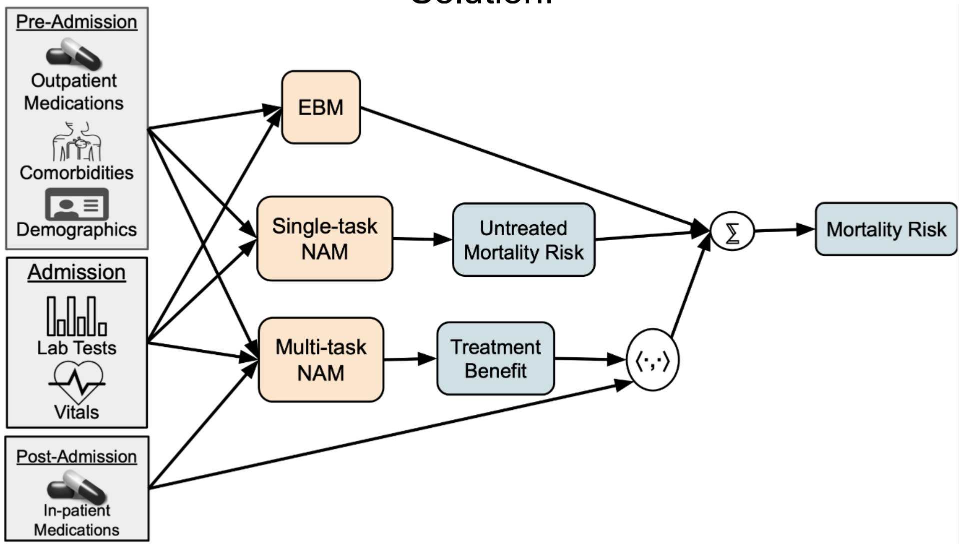
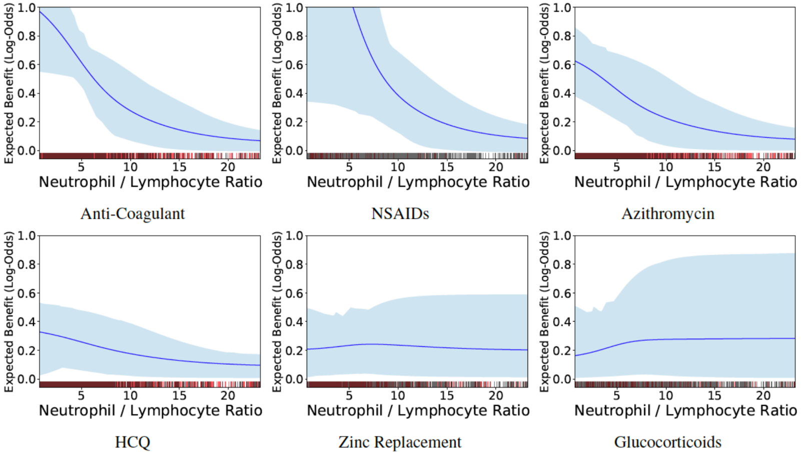


Reveals that treatment effectiveness changes based on inflammation and thrombosis factors:



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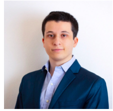
Disease Subtyping Vignette 3:
Discriminative Subtypes of Lung Cancer

With Maruan Al-Shedivat, Amir Alavi, Jennifer Williams, Sami Labbaki, Eric Xing

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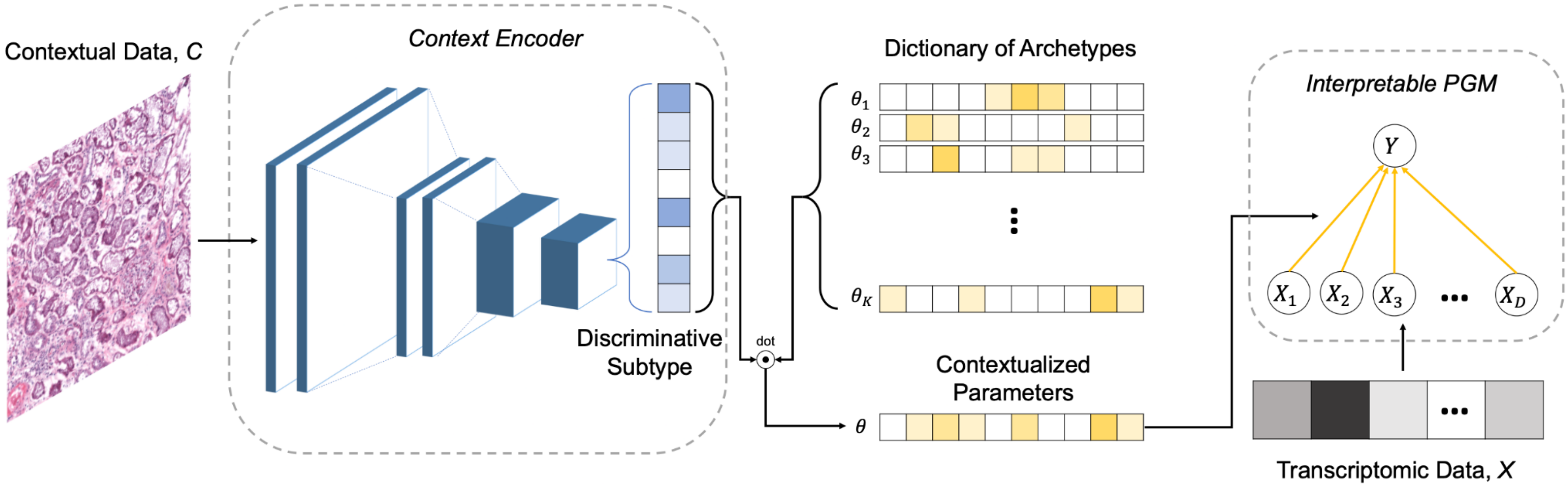
Discriminative Subtypes Connect Histopathology and Transcriptomics

3-way Classification Task: Adenocarcinoma / Squamous Cell Carcinoma / Healthy



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Discriminative Subtypes Reveal Biological Patterns

Sample-specific models improve classification performance on held-out (test) patients

Model (Data)	Accuracy (%)	Macro F1
CEN (H+T)	**96.18**	**96.97**
Concatenated (H+T)	95.32	93.65
Ensemble (H+T)	94.61	90.23
Logistic Regression (T)	94.05	91.40
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Transcriptomic Archetypes focus on biologically-relevant processes

Archetype	**Term ID**	**Term Name**	**P-Val**
1	KEGG:04071	Sphingolipid signaling pathway	0.037
	KEGG:04310	Wnt signaling pathway	0.049
6	REAC:R-HSA-6802952	Signaling by BRAF and RAF fusions	0.039
8	TF:M06732	Factor: ZNF304	0.023
12	REAC:R-HSA-8939236	RUNX1 regulates transcription of genes involved in differentiation of HSCs	0.022
	GO:0010629	negative regulation of gene expression	0.039
13	TF:M09657_1	Factor: Smad4	0.004
15	GO:0071385	cellular response to glucocorticoid stimulus	0.013
17	REAC:R-HSA-400206	Regulation of lipid metabolism by PPARα	0.018
18	TF:M04726_1	Factor: REST	0.001
19	TF:M05327_1	Factor: WT1	0.025
21	TF:M01224_1	Factor: P50:RELA-P65	0.034
25	TF:M09611_0	Factor: ER81	0.003
26	KEGG:04215	Apoptosis - multiple species	0.006
28	GO:0051240	positive regulation of multicellular organismal process	0.006
30	REAC:R-HSA-4791275	Signaling by WNT in cancer	0.045

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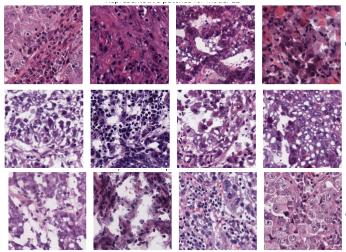
Archetypal Models connect Transcriptomics to Morphology

RUNX1

SMAD4

WNT



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Disease Subtyping Vignette 4:
Contextualized Network Inference

With Caleb Ellington, Bryon Aragam, Eric Xing, Manolis Kellis




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Context-Specific Bayesian Networks

- Bayesian Networks (BNs) are directed acyclic graphs (DAGs) which factorize joint distributions into sets of parent and children nodes.

- Context-Specific BNs use context C to allow the parameters and/or structure of the BNs to vary:

$$P(X, C) = \int_W dW \, P(X|W) P(W|C) P(C),$$

- where $P(X|W) = \mathrm{BN}(X|W)$

Context-Specific Bayesian Networks

Assume that context-specific BNs lie on a subspace measured by a latent variable $Z \in \mathbb{R}^k$ with $C \perp (X, W) \mid Z$. Then

$$P(W \mid X, C) \propto P(X \mid W) \int_Z dZ P(W \mid Z) P(Z \mid C)$$

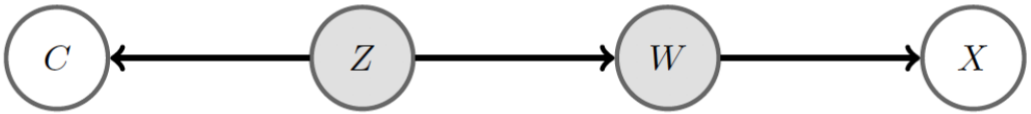

Figure 2: Graphical Model. Contextual covariates C and observations X are observed, while subtype Z and BN parameters W are latent.

How can we define tractable $P(W \mid Z), P(Z \mid C)$?

Context-Specific Bayesian Networks

Solution: Model context-specific BN parameters as the output of a smooth function:

$$P(X \mid C) = \text{BN}(X \mid \phi_\theta(C))$$

Challenge: How to ensure that learned ϕ_θ outputs BNs?

Difficult because BNs are directed ***acyclic*** graphs (DAGs) — a global constraint which must consider all entries in the adjacency matrix *simultaneously* and thus is not naturally amenable to local gradient-based updates.

Solution: Smooth DAG-ness regularizer

[Zheng et al 2018] showed that "DAG"-ness can be encoded as a smooth function:

$$\mathrm{tr}\left(e^{W \cdot W}\right)$$

NOTEARS: Non-combinatorial Optimization via Trace Exponential and Augmented lagRangian for Structure learning

NOTEARS-Optimized Mixtures of Archetypal DAGs (NOTMAD)

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Define the DAG for sample i as:

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Archetype Networks

Sample Subtype

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Archetype Networks

Sample Subtype

Giving us the optimization:

$$\arg\min_{\theta, W_{1:k}} \sum_{i=1}^{n} \frac{\alpha}{2}(X^i - X^i\phi_\theta(C^i))^2 + \beta \text{tr}\left(e^{\phi_\theta(C^i)\cdot\phi_\theta(C^i)}\right) + \sum_{k=1}^{K} \gamma |W_k|_1$$

Data Likeliihood (Squared Error) DAG-ness Archetype Sparsity

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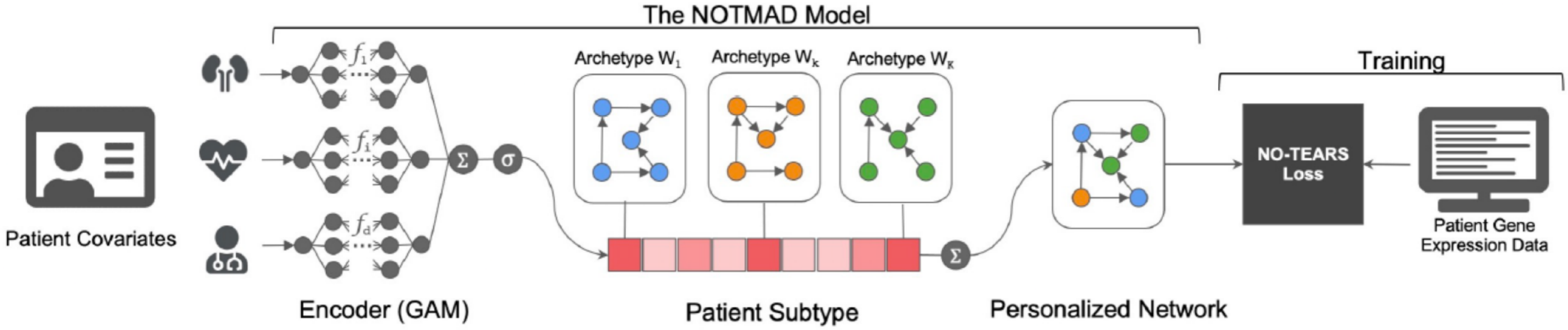
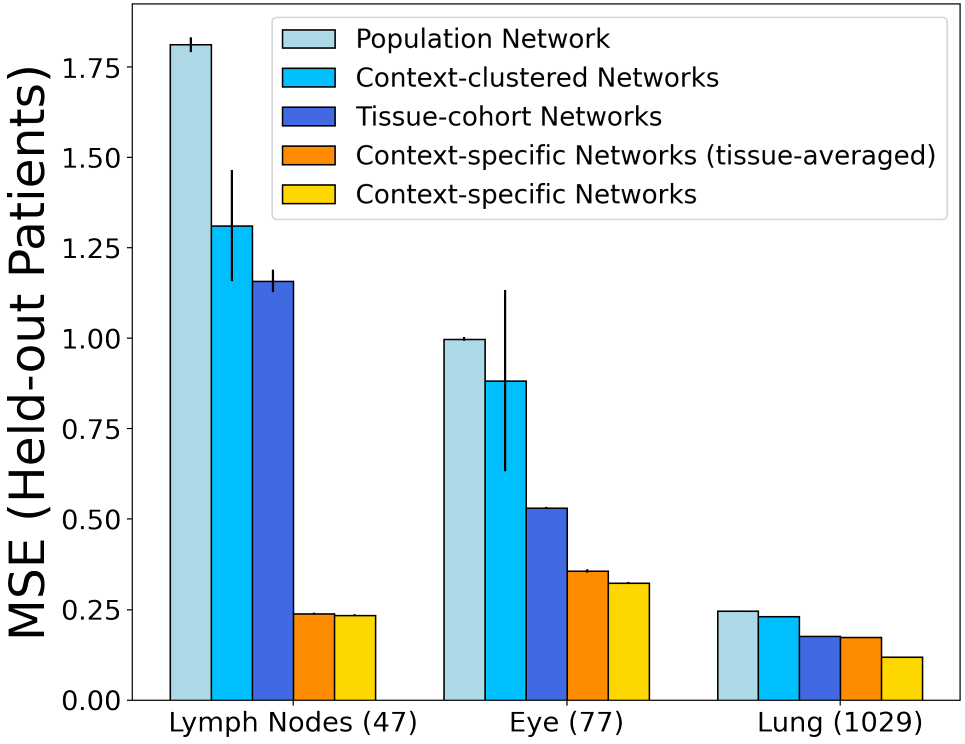
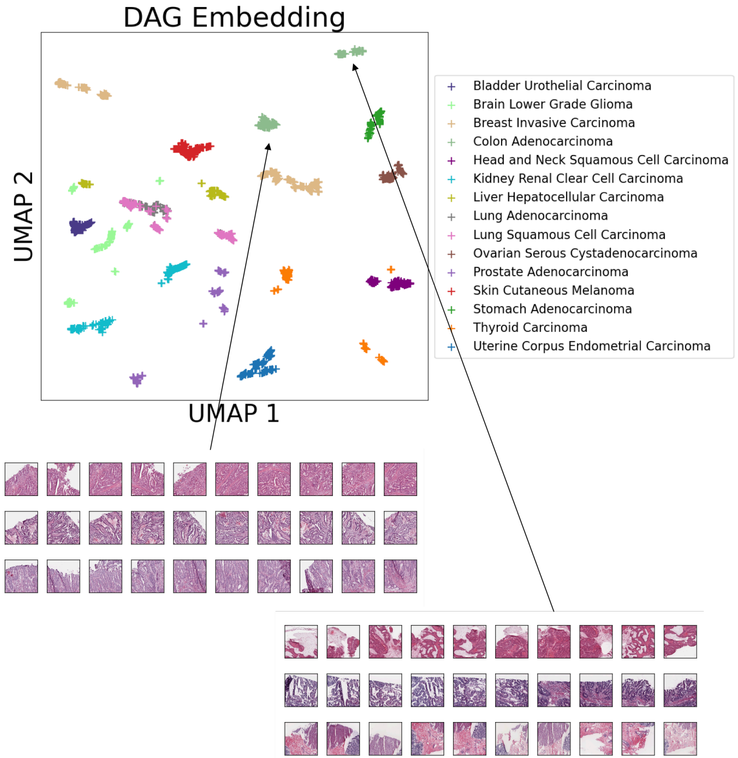


Personalized Networks allow us to ask about gene network heterogeneity

- The Cancer Genome Atlas
- Context: patient demographics, immune cell proportions
- Network data: bulk RNA-seq
- Plot: samples grouped by cancer tissue-of-origin, (#) indicates the number of samples from that tissue in the training set
- Lower MSE (mean squared error) is better

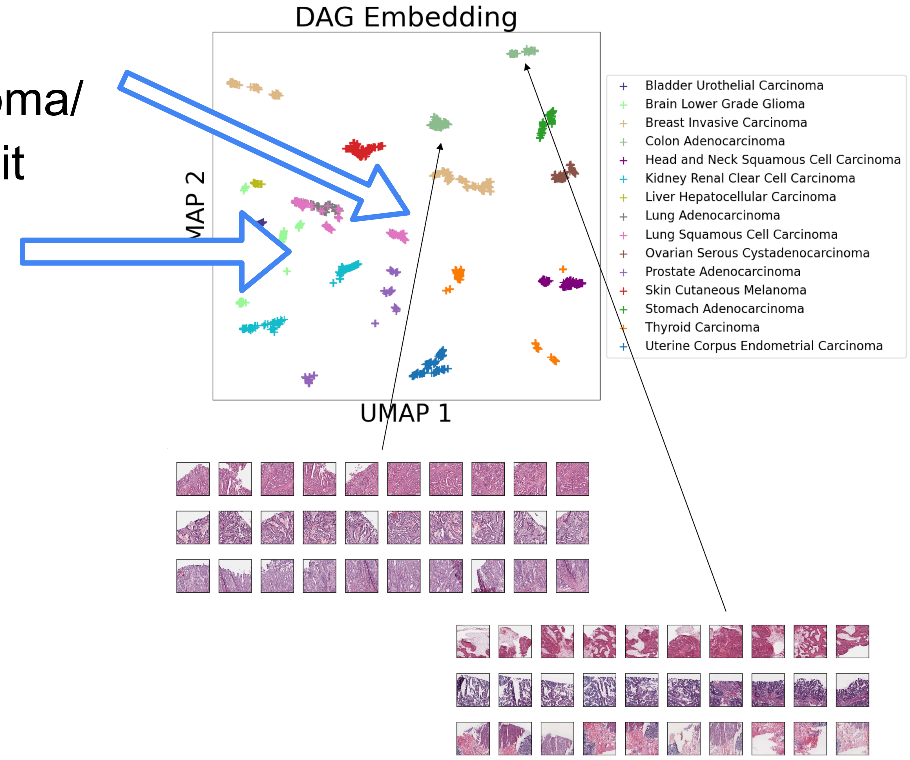


Sample Networks Cluster According to Medical Heterogeneity



Sample Networks Cluster According to Medical Heterogeneity

- Recovers Lung Adenocarcinoma/ Squamous cell carcinoma split



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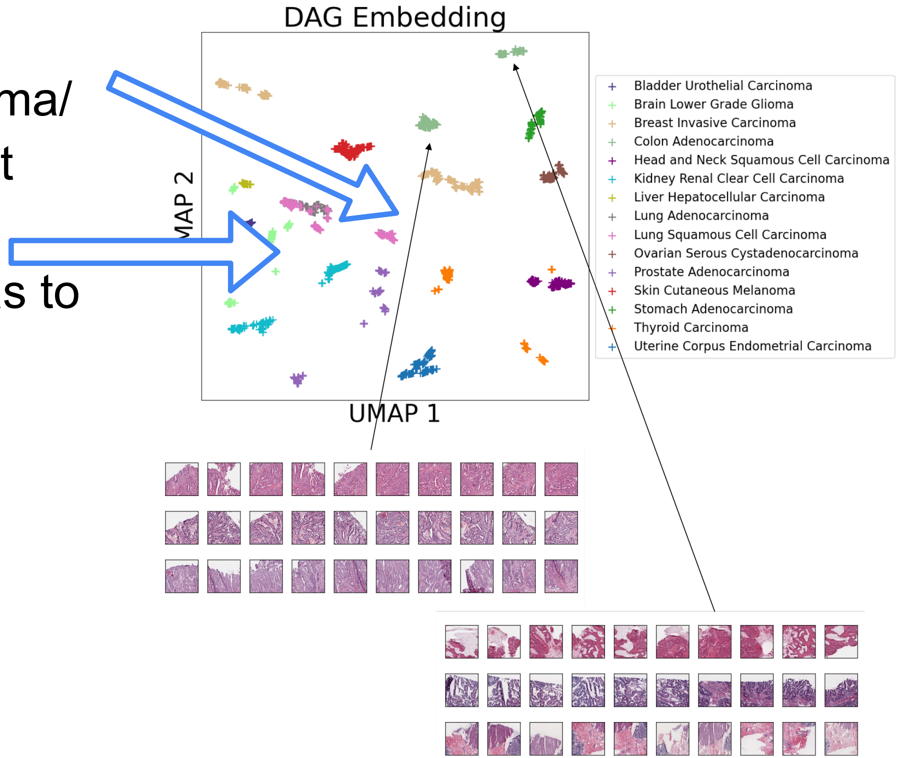
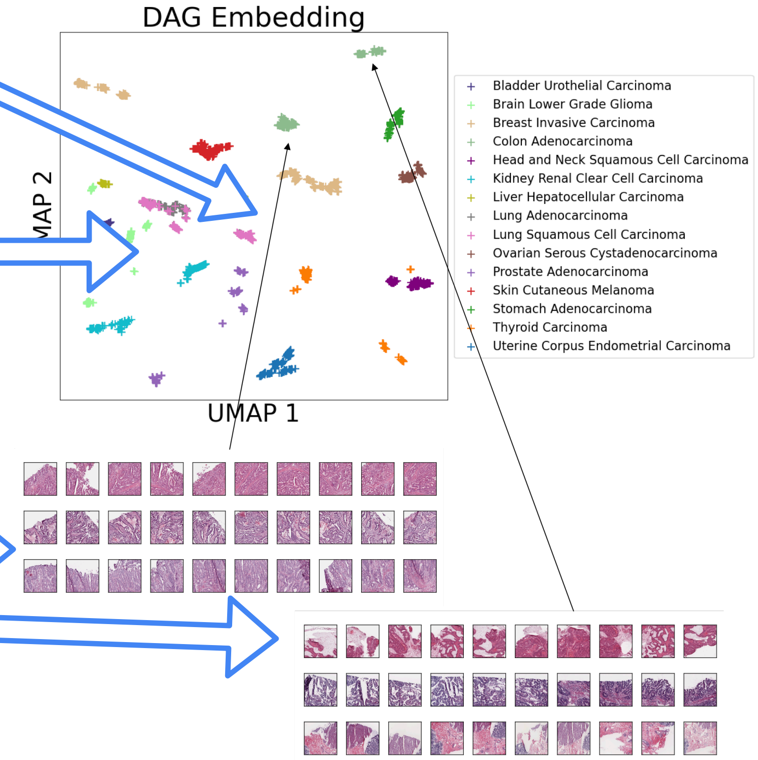


Sample Networks Cluster According to Medical Heterogeneity

- Recovers Lung Adenocarcinoma/ Squamous cell carcinoma split
  - Identifies a subset of squamous cell carcinomas to be molecularly similar to adenocarcinomas
- Identifies two clusters of colon adenocarcinomas which correspond to morphologically-distinct tumors



Contextualized

Heterogeneous Modeling Toolbox

contextualized.ml



With **Caleb Ellington**, Eric Xing, Manolis Kellis

Carnegie Mellon University

MOHAMED BIN ZAYED UNIVERSITY OF ARTIFICIAL INTELLIGENCE

Massachusetts Institute of Technology

Thank you!

- Computational Biology Lab @MIT
  - **Manolis Kellis**
  - Jackie Yang
  - Yosuke Tanigawa
- Microsoft Research
  - **Rich Caruana**
  - Anthony Platanios
  - Harsha Nori
- SAILING Lab @CMU
  - **Eric Xing**
  - Caleb Ellington
  - Maruan Al-Shedivat
  - Bryon Aragam

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Demos online
Pull requests/issues welcome
blengeri@mit.edu

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