Curating Combinations to Fight Cancer

Predicting Efficacy of Anticancer Drug Combinations


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1. CONTEXT

Objective: Identify promising anti-cancer drug combinations.

Why?

1) Save **time** & **money**.

There exist 100 million possible drug combinations to test. *In-vitro* testing is not tractable.

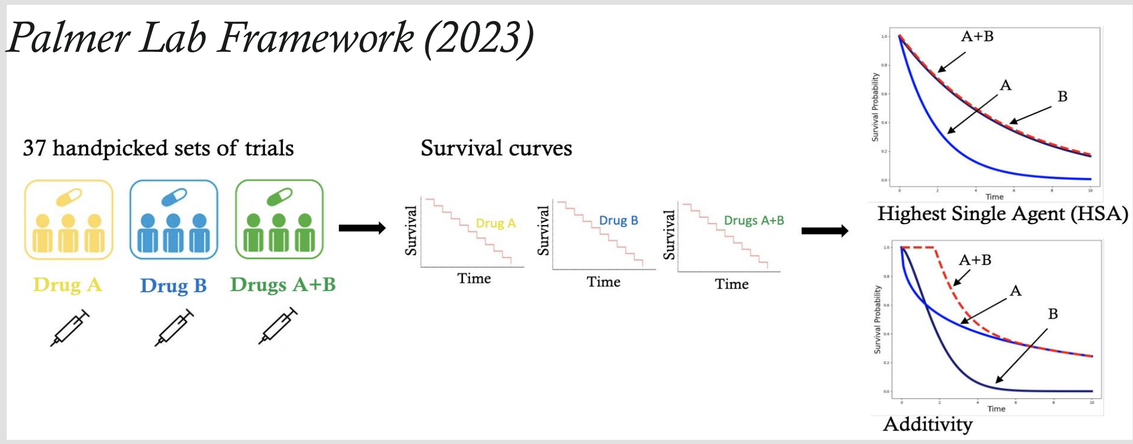
2) Make **robust** decisions.

Cancer cells used for *in-vitro* tests are not representative of the diversity of the human genome, but clinical trials are.

How? Leverage deep learning to forecast the survival of patients under drugs (A+B), informed by their clinical information.

Background: Recent research suggests additivity can predict efficacy of combination therapies for advanced cancer.

Palmer Lab Framework (2023)



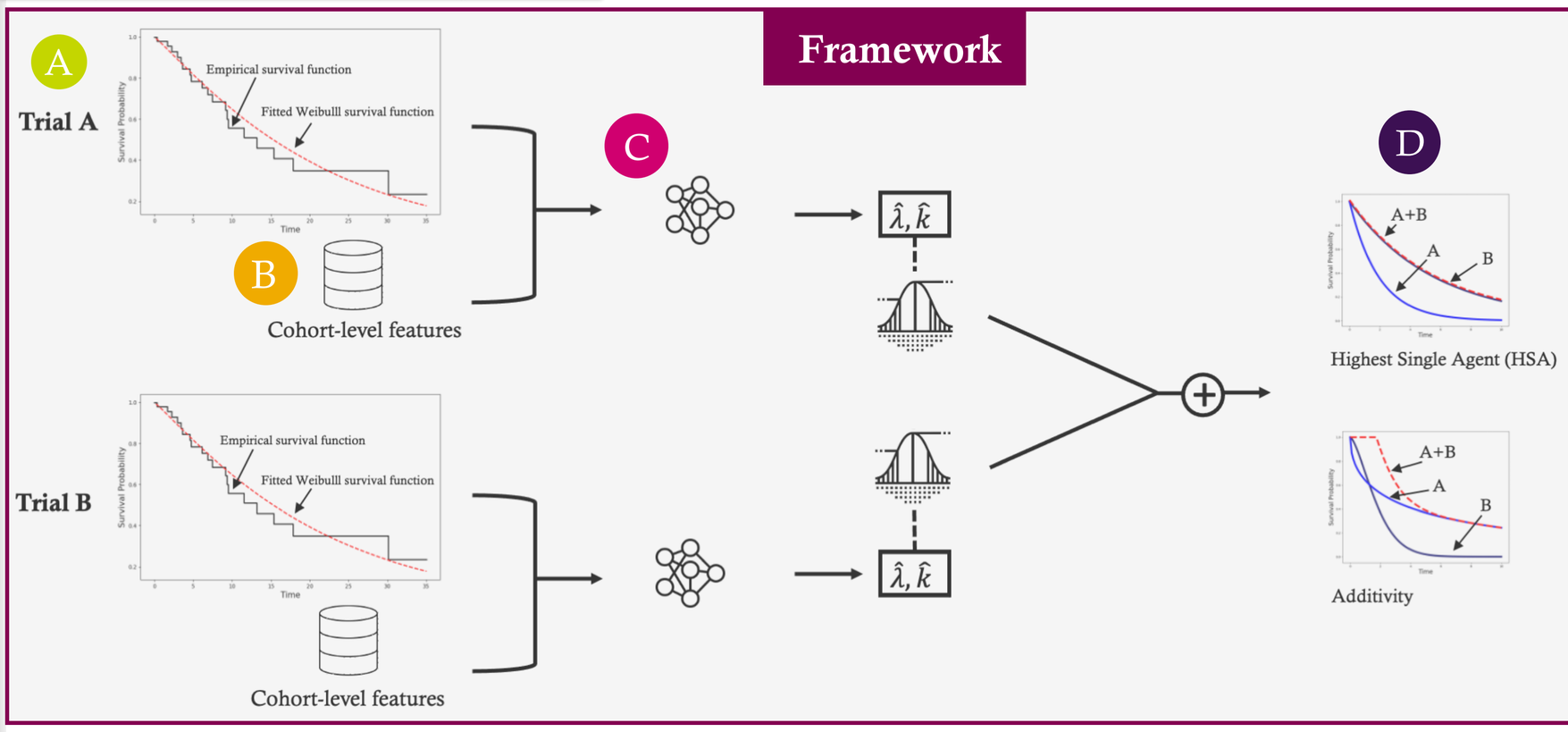
Limitations: Model only applies to trials which have same characteristics (i.e. dose, disease severity, patient demographics) but this is seldom the case.

Problem Statement

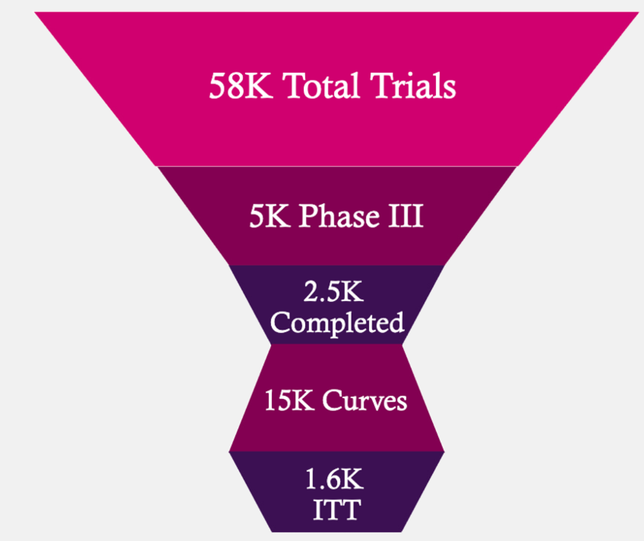
Given time-survival observations of a trial, can we predict the survival for patients with different clinical backgrounds?

2. METHODOLOGY

Framework



Data Curation



A Data Preprocessing

- Represent empirical survival curves as parametric survival functions to restrict size of input tensor.
- Experiment with Exponential and Weibull survival distribution.
- Standardize survival values between 0 and 1 and normalize using Min and Max of training set.

B Feature Engineering

Methodical Feature Extraction: Obtain value from unclean, textual data. Pivotal step for the success of modeling methods.

Result: Cohort characteristics now include tumor stage, trial phase, line of therapy, trial modality, cancer spread, etc.

C Model Creation

Preliminary Model: Multi-output linear regression for benchmarking the metric and gaining intuition.

Neural Network: Experiments with architecture and hyperparameters.

- Weighted Loss Function
- Learning Rate Decay
- Batching by Drug Type

D Final Evaluation

Input: Parameters λ, k for a pair of adjusted trial survival functions.

Prediction: Forecast the drug combination survival with the Palmer Lab methodology.

Output: Compute the error of the survival prediction against the observed ground-truth survival of the combination therapies.

3. RESULTS AND IMPACT

Model	Average KL Divergence (Additivity)	Average MAE (Additivity)	Average RMSE (Additivity)
Baseline	0.091	16.91	19.58
Linear Regression	0.089	16.54	19.36
Exponential 5.0	0.133	18.87	23.09
Weibull 5.0	0.083	15.93	18.39
Weibull 6.0	0.079	13.89	16.27

Baseline: Compute the error between combination predictions on non-adjusted curves (without taking into account prognostic background) and the observed combinations.

Analysis: Modeling survival with a Weibull function improves on the baseline by 13.2 %. Modeling survival with an Exponential function falls short of the baseline, because an immoderate assumption is made on constant hazard rate.

Impact

- Pioneered **first** AstraZeneca model to estimate combination efficacy of any two clinical trial arms.
- Improved ability to make combination predictions by **13.2%** by incorporating prognostic factors.
- Model has potential applications in patient selection and supporting physician prognoses.

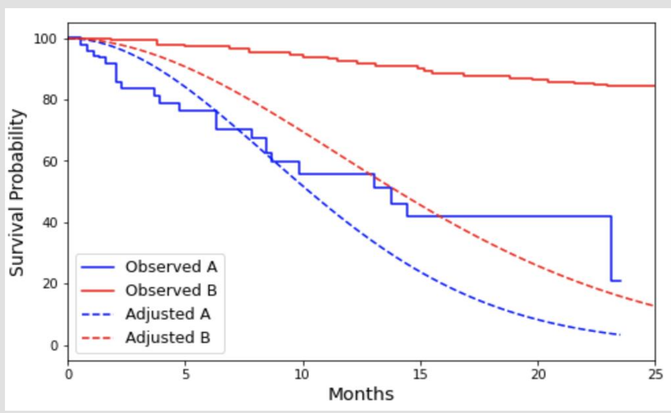
Example Application

Trial A: Dexamethasone and Bortezomib on Stage III patients

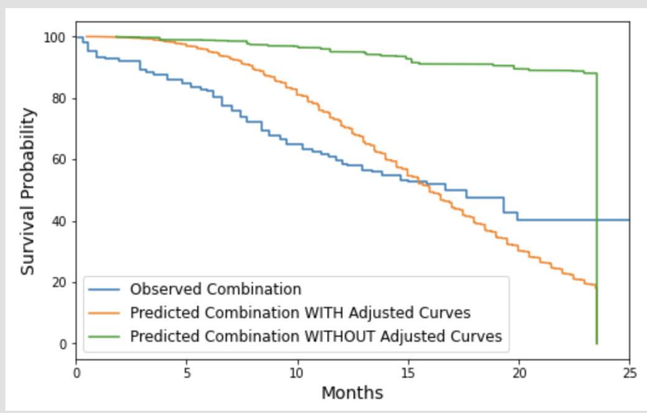
Trial B: Daratumumab on Stage I patients

Trial A+B: Combination of the two therapies on Stage IV patients

Observed and Adjusted Monotherapy Survival



Observed and Predicted Combination Survival



Future Work

- Incorporate features missing from dataset including age, gender, dosage and most importantly, toxicity.
- Experiment with representation of drug as a feature, including as an embedding
- Estimate combination efficacy directly via a neural network.