Deep Bayesian Neural Networks for improved Treatment Assignment in Precision Oncology. A Contextual Bandit Problem.

Niklas Rindtorff[1,2,6,7], Ming Yu Lu[1,5,#], Nisarg Patel[1,2,4,#], HuaHua Zheng[1,3,#], Kun-Hsing Yu[1], Alexander D'Amour[8]

[1]Harvard Medical School, Department of Biomedical Informatics, Boston, MA
[2]Broad Institute of MIT and Harvard, Cambridge, MA, USA
[3]Harvard T.H. Chan School of Public Health, Department of Biostatistics, Boston, MA
[4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
[5]Laboratory for Computational Physiology, Massachusetts Institute of Technology, MA, USA
[6]German Cancer Research Center (DKFZ), Division Signaling and Functional Genomics, Heidelberg, Germany
[7]Heidelberg University, Medical Faculty Heidelberg, MD/PhD Program
[8]Google Brain, Cambridge, MA
[#]In alphabetical order

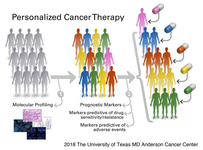
Please share!

Problem - Contextual Bandit in Precision Oncology programs

The goal of precision medicine is providing the right treatment to the right patient at the right time. Despite a number of successes, assigning patients to adequate treatments remains a challenge until today. The current best practice in precision oncology is to base the treatment decision on published and frequently used therapeutic protocols that consider the patient's clinical characteristics and cancer biomarkers. For example, based on the status of a single mutation, such as a BRAF V600E, a treatment decision can be made.

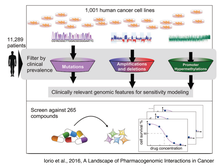
Current therapeutic protocols in precision oncology evaluate one biomarker and one targeted therapeutic at a time. This limits the ability to make high-confidence clinical decisions in a real world scenario with a large number of biomarkers to measure and potential treatments to choose from. The current limitations include:

(I) high selectiveness
(II) high unsystematic compassionate use
(III) limited continuous development
(IV) limited predictive availability

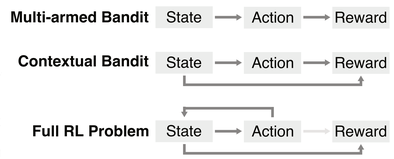


We hypothesized that, if framed as a contextual bandit problem, neural network based agents can outperform current clinical therapeutic assignment mechanisms. Potentially, this could allow a less selective, more systematic, continuously evolving practice of precision oncology, which balances exploration and exploitation of treatment strategies.

To this end we prepared a public dataset of drug vulnerability measurements from >1000 cancer cell lines for benchmarking of contextual bandit agents. The dataset contains genomic information for every cell line and complete drug response observations.

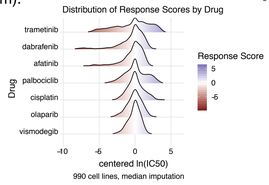


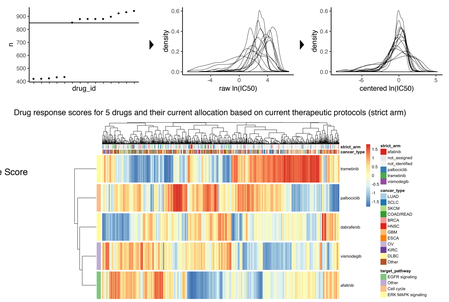
The bandit problem's roots are in the rows of "one-armed bandit" slot machines seen in casinos. Each machine has a different probability of a payout and your goal is to maximize the total payout. You are limited by both the total number of bandits you can pull in a fixed period of time and uncertainty regarding which machine will deliver the best payout. The bandit problem here involves a tradeoff between exploration and exploitation



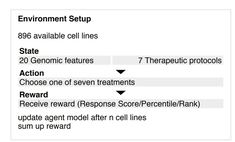
Methods - Dataset synthesis

Next to data pre-processing, we searched clinical guidelines and trial protocols to identify FDA approved targeted therapeutics that have genetic biomarkers of an evidence level >2A. We defined a set of therapeutic protocols that follow a "IF gene X is altered THEN administer drug Y" structure (strict arm).

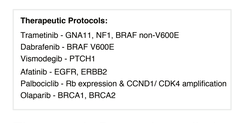




Methods - Experimental Design



896 cancer cell lines are matched to one of seven available treatments subsequently. Each action is followed by a reward.

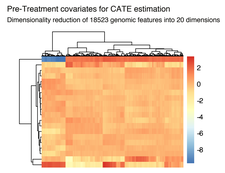


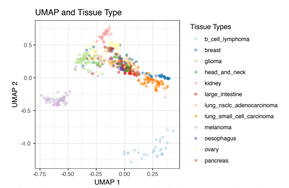
Therapeutic Protocols applied to genomic data

To guide treatment decision making, the agent is provided with 20 genomic features (right) and prior knowledge (bottom left), formalized in one-hot encoded current therapeutic protocols.

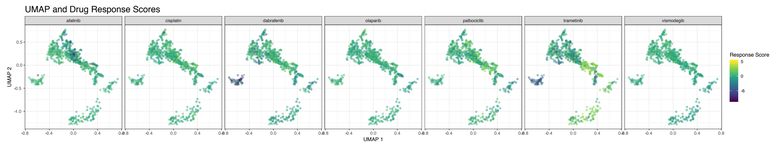
Based on this information the agent chooses one of seven treatments and received a reward proportional to the drug response.

The agent's model is updated iteratively. We compared multiple models and reward functions.

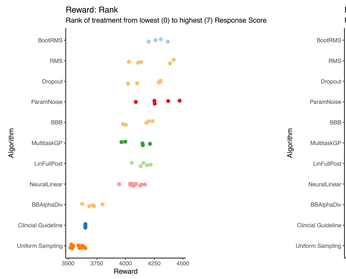


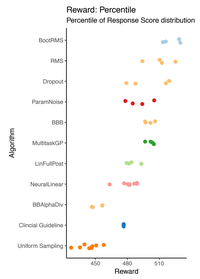


Treatment covariates were summarized using uniform manifold approximation and projection (UMAP). The Treatment covariates included tissue type, mutation status, CNVs and gene expression. UMAP recovered tissue type while not directly recovering overall drug sensitivities.



Results - Contextual Bandit Agents outperform current therapeutic protocols in-silico

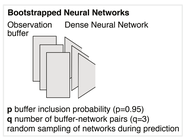


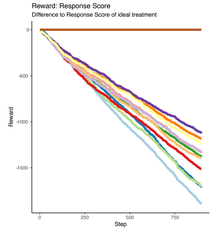


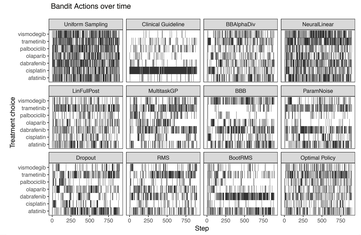
We further evaluated alternative reward functions, such as the rank of each treatment option (from 1 to 7) or the percentile of the Response Score (from 0 to 1).

We evaluated different classes of models in the our contextual bandit environment. Strict adherence to current clinical guidelines, as codified in the therapeutic protocols, consistently outperformed random allocation of treatments. However, most models were able to outperform agents that adhered to therapeutic protocols only.

Three Neural Network algorithms, bootstrapped-, greedy and Dropout based networks, consistently scored higher rewards compared to linear methods or Gaussian Processes, independent of the reward function.



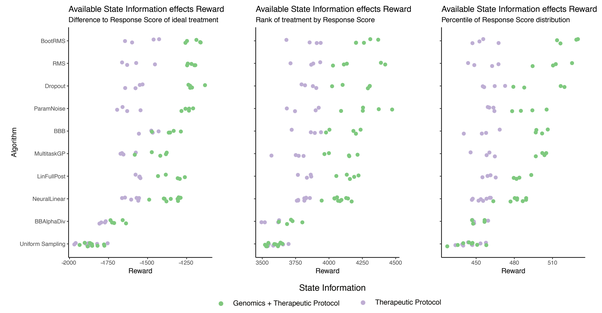




Results - Agent Performance depends on genomic features

Next, we evaluated the agent performance in a scenario with only therapeutic protocol assignments as state information. Most agents performed systematically better in environments with available genomic information, independent of reward function.

Additional experiments with only genomic data as state information confirmed this observation (data not shown).



Conclusion

Assignment mechanisms in precision oncology programs can be framed as a contextual bandit problem.

When provided with genomic information and expert knowledge, contextual bandit agents outperform current clinical standards in an in-vitro cancer drug response dataset, in scenarios with three different reward functions. The availability of genomic information increases the performance of most agents.

Among the most successful agents were bootstrapped or simple dense neural networks that acted greedily. In principle, both bootstrapped and dropout networks add uncertainty information by sampling from multiple related models.

This study has several limitations including: (I) In-vitro drug response data of cancer models has limited transferability into a clinical context, (II) The response scores are on average lower in treatments vs. controls, (III) Cisplatin is a limited reference treatment for all considered cancer types.

In the future, we plan to validate our findings in alternative in-vitro drug response datasets, PDX experiments and pre-clinical Organoid model data. In addition, we plan to subsample the available genomic information and measure the impact on model performance.

We would like to stimulate an open discussion about the limitations and potential benefits of AI guided treatment assignments in precision oncology program to minimize collective treatment regret. We acknowledge that further analysis needs to focus on avoidable regret on a per-patient level.

References

Iorio et al., 2016, A Landscape of Pharmacogenomic Interactions in Cancer
Riquelme, Tucker and Snoek, 2018, Deep Bayesian Bandits Showdown
Osband et al., 2016, Deep Exploration via Bootstrapped DQN

https://github.com/NiklasTR/oncoassign

@Niklas_TR, @Mingyu07550306, @nxpatel, @kunhsingyu, @alexdamour
niklas_rindtorff@hms.harvard.edu