

Deep neural networks with knockoff features identify nonlinear causal relations and estimate effect sizes in complex biological systems

By: Hyun Jung (HJ) Park, PhD

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Learning the causal structure helps identify risk factors, disease mechanisms, and candidate therapeutics among multiple clinical features for complex diseases. Recently, deep neural network models have been proposed to characterize the non-linear associations in the causal structure. However, they cannot identify the causal relationships of different nonlinearity and estimate their effect size accordingly, limiting the clinical application. To overcome these limitations, we developed the first computational method that learns both linear and nonlinear causal relations and estimates their effect size using a deep-neural network approach coupled with the knockoff framework [9], named causal Directed Acyclic Graphs using deep-learning Variable SElection (DAG-deepVASE). Using simulation data of diverse scenarios and molecular/clinical data of various contexts, we demonstrated that DAG-deepVASE consistently outperforms existing methods in identifying known and novel causal relations. In the analyses, we also illustrate how identifying nonlinear causal relations and estimating their effect size help understand the complex disease pathobiology, which is not possible using other methods.

After validating the use of DAG-deepVASE, we applied this to address an emerging problem in immunotherapy, which is low reproducibility in identifying gut bacteria predicting the therapy response for advanced cutaneous melanoma. Melanoma is the most aggressive and deadly of skin cancers. Immune checkpoint inhibitors (ICI) have induced long-term clinical responses in a subset of melanoma patients. The gut microbiome is a major tumor-extrinsic regulator of the clinical response in addition to tumor-intrinsic factors, such as the host immune system. Multiple studies have identified distinct gut microbial signatures in ICI responders (R) vs. non-responders (NR). However, there are inconsistencies among published microbial signatures for the response, which has impeded their further clinical applications. To identify statistically significant and thus clinically relevant microbiome signatures that predict ICI response, we extended DAG-deepVASE and revealed that the neural network model helps identify reproducible gut bacteria for ICB response.



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Dr. Park is an assistant professor of Human Genetics in the University of Pittsburgh's School of Public Health. As a computational biologist, he seeks to identify novel therapeutic targets for human diseases from a comprehensive understanding of biology. To achieve this goal, he uses quantitative techniques designed to overcome various challenges in the efforts. To comprehensively decode dynamics in each biological layer, he applies big data analysis techniques (e.g., signaling processing or information-theoretic measures) on NGS data, such as WES, WGS, RNA-Seq, miRNA-Seq, CHIP-Seq, methyl-Seq, and single-cell RNA-Seq.

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