

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

By: Hyun Jung (HJ) Park PhD

...ical features for complex diseases. Recently, deep neural network models have been proposed to characterize associations in the causal structure. However, they cannot identify the causal relationships of different nonlinearity and estimate their effect sizes, limiting the clinical application. To overcome these limitations, we developed the first method that learns both linear and nonlinear causal relations and estimates their effect sizes. This approach, coupled with the knockoff framework [9], named causal Directed Acyclic Graphs using deep learning Variable Selection (DAGdeepVASE). Using simulation data of diverse scenarios and molecular/clinical data of various contexts, we demonstrated that DAGdeepVASE consistently outperforms existing methods in identifying known and novel causal relations. In the analyses, we also show 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 DAGdeepVASE, we applied this to address a long-standing problem in immunotherapy, which is low reproducibility in identifying gut bacteria predicting the therapy response for advanced cutaneous melanoma. Melanoma is the most aggressive 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 application. We identified statistically significant and thus clinically relevant microbiome signatures that predict ICI response, we extended DAGdeepVASE and revealed that the neural network model helps identify reproducible gut bacteria for ICB response.

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