A causal discovery approach for streamline ion channels selection to improve drug-induced TdP risk assessment

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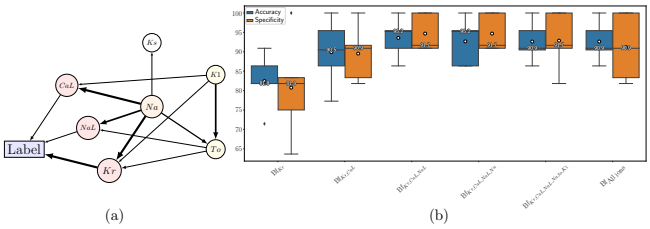
Context: Torsade de Pointes (TdP) is an extremely serious drug-induced cardiac side effect, which can provoke ventricular fibrillation and lead to sudden death. TdP is related to abnormal repolarizations in single cells, and the minimum set of ion channels needed to correctly assess TdP risk is still an open question. Discovering causal relations between drug-induced ionic channels' perturbations could shed new light on the underlined mechanisms leading to TdP, and drive variable selection to improve TdP-risk assessment tools.

Method: In this work, we propose to apply the causal discovery method ICA-Linear Non-Gaussian Acyclic Model (ICA-LiNGAM) to uncover the relations across the 7 ion channels identified by the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative as potentially related to the induction of TdP: I_{Kr}, I_{Na}, I_{NaL}, I_{CaL}, I_{K1}, I_{Ks} and I_{to}. We consider 109 drugs of known torsadogenic risk (51 unsafe) listed by CredibleMeds.

Results: I_{Kr}, I_{NaL} and I_{CaL} resulted in being directly related to the TdP-risk label node. In addition, our method suggests that I_{Na} perturbations could potentially have a high impact on proarrythmic risk induction. Our causality-based results were further confirmed by independently performing binary drug risk classification, which shows that the combination of the 3 selected ions maximizes the classification accuracy and specificity, outperforming state-of-the-art approaches which uses other ion channels combinations.

Conclusions: The proposed causal approach can bring valuable insights on the downstream effects of ion channels' perturbation, and the obtained causal graph can further be deployed to infer the safety of new compounds.



(a) (b)

Figure 1: (a) Causal graph generated by ICA-LiNGAM. (b) Independent binary classification performance, following causal prescriptions for ion selection.