Assessing ion channel blockade and electromechanical biomarkers' interrelations through a novel Multi-Channel Causal Variational Autoencoder

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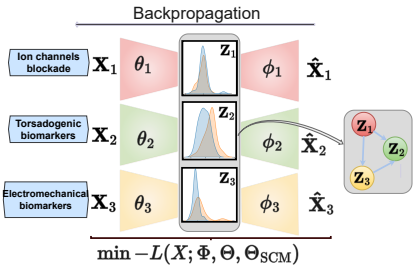
Aim: Knowing the impact of causal relationships between ion channel blockade and electromechanical biomarkers is essential to improve drug-induced torsades de pointes (TdP)-risk assessment. Apart from common purely electric torsadogenic indices, mechanical biomarkers may provide additional proarrhythmic information, but the impact and interrelationships between those variables need to be assessed to guide feature selection for classification methods. Variational Autoencoders (VAE) offer a reliable framework for learning disentangled representations from complex data distributions and can handle a variety of data types and structures. Causal discovery strives to reveal causal links between observed variables, thereby providing a better understanding and insight into the phenomenon under investigation. Nevertheless, establishing causal relationships between heterogeneous multichannel observations is far from straightforward. **Method:** We propose a novel VAE architecture, Multi-Channel Causal Variational Autoencoder (*MC²VAE*), to identify mutual relationships between ion channel blockades, torsadogenic biomarkers, and electromechanical biomarkers, considered here as three distinct channels, *i.e.* three distinct sources of information for drug-induced TdP risk. Our approach for causal disentanglement from multi-channel data is designed to search for a linear causal structure between the generated latent variables, shifting the problem of causal discovery from a heterogeneous multichannel space to a compact lower-dimensional one, while encoding and decoding operations are proper to each modality to better adapt to their own specificities. **Conclusion:** Our approach interestingly suggests the existence of hidden (latent) causal relationships between the three considered sets of biomarkers, providing a rationale for including mechanical biomarkers in TdP-risk assessment approaches. Further, MC²VAE is able to quantify the strengths of the identified causal relationships, opening up a viable avenue for actionable interventions on the established graph.



MC²VAE schematic architecture.