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A Multiplex Molecular Digital Twin of the Brain for Tracking Evolutionary Conservation in Substance Use Disorders

Understanding how addiction-related brain mechanisms are conserved or diverge across evolution is essential for interpreting cross-species models and identifying robust therapeutic targets. We present a brain-focused extension of MENTOR-EV, a scalable, multiplex-network-native molecular digital twin framework for tracking the evolution of mechanistic organization, applied in a pan-substance use disorder context.

We construct large multiplex networks centered on human neural biology, including whole-brain, tissue-specific, and cell type-specific multiplexes. Each multiplex integrates hundreds of complementary network layers, including functional association networks, brain-derived predictive expression networks, protein-protein interactions, and transcription factor regulatory networks. Within each multiplex, we compute Random Walk with Restart (RWR) embeddings for every gene and hierarchically cluster genes based on their global topological context, yielding data-driven mechanistic modules without reliance on predefined pathways.

To examine pan-SUD organization, multi-omic signals from methamphetamine, opioid, cocaine, and nicotine use disorders are projected onto these brain multiplexes. This enables identification of conserved addiction-relevant modules spanning synaptic signaling, neuroimmune processes, mitochondrial energetics, transcriptional regulation, and neuromodulatory circuits. We then integrate comparative genomics data across multiple species to quantify mechanistic conservation at the module level. Ortholog presence matrices, ordered by RWR-derived dendrogram structure and phylogenetic distance, reveal modules that are deeply conserved across vertebrates and invertebrates.

This framework demonstrates that addiction-relevant biology is often conserved at the level of network architecture even when individual genes differ. By combining multiplex network inference, evolutionary profiling, and pan-SUD integration, MENTOR-EV provides a scalable strategy for identifying evolutionarily stable brain mechanisms most likely to translate across species and inform therapeutic development.

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