

A Structural Systems Biology Platform for Pan-SUD Drug Repurposing and Effective Binding Discovery

This poster describes a structural systems biology strategy to identify druggable mechanisms in substance use disorders (SUDs) by integrating multiplex network biology with protein-level modeling. Rather than focusing on isolated targets, we begin with mechanistic modules derived from multi-omic signals projected onto a multiplex-network-driven molecular digital twin of normal human biology. Proteins within prioritized modules are then evaluated for structural druggability using complementary artificial intelligence and biophysics-based approaches.

We apply fragment-based pocket similarity screening, sequence-based deep learning models, and structure-aware diffusion models to identify candidate ligand-binding sites across module proteins, including sites not previously annotated as druggable. Because the diversity of protein folds and binding pockets is constrained, FDA-approved drugs may interact with evolutionarily unrelated proteins that nonetheless share structural features. By systematically scanning conserved pocket geometries and sequence-level determinants of binding, we identify off-target and repurposing opportunities beyond canonical receptor targets.

Top-ranked protein–ligand pairs are refined using enhanced-sampling molecular dynamics simulations to assess binding stability and predicted affinity. Consensus predictions from orthogonal methods are reintegrated into network-defined modules to evaluate pathway coherence and potential effects on protein–protein interaction networks central to addiction biology. This structural layer extends systems pharmacology beyond gene-level annotation and enables structure-informed repositioning of FDA-approved compounds and can be passed as input to RealOmics and MENTOR-IA for further prioritization.

In a pan-SUD context, this framework highlights convergent modules targeted by existing drugs, including alpha-1 adrenergic antagonists and glucagon-like peptide-1 receptor agonists. GLP-1 receptor agonists map to modules spanning metabolic regulation, neuroimmune signaling, and reward circuitry. Real-world data demonstrate reduced alcohol consumption among GLP-1 receptor agonist initiators, consistent with network-based predictions across alcohol, nicotine, opioid, and stimulant pathways. Together, these results show that structure-informed, network-anchored analyses can uncover shared, druggable mechanisms and prioritize clinically actionable candidates across substance use disorders.

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