

Systems Biology and Network Analysis: From Multi-omics Integration to Biological Mechanisms

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1. Session Introduction: Systems Biology and Network Analysis

Recent advances in multi-omics technologies have generated unprecedented volumes of data, offering new opportunities to decode the complex interplay between molecular components and biological mechanisms. This session, *Systems Biology and Network Analysis: From Multi-omics Integration to Biological Mechanisms*, brings together innovative computational approaches that span transcriptomics, proteomics, metabolic modeling, and network biology. The selected papers exemplify how systems-level analysis can reveal interpretable, mechanistically grounded insights into disease processes, therapeutic strategies, and biological regulation.

The session is anchored in the belief that bridging molecular interactions with cellular and tissue-level phenomena is essential for understanding disease mechanisms and developing personalized interventions. The contributions in this session reflect the growing synergy between network biology and machine learning, particularly in areas such as dynamic network inference, drug repurposing, and multi-modal data integration.

2. Session Summary

This session includes an invited talk, five peer-reviewed papers selected for oral presentation by the session chairs, and one poster presentation selected by the conference organizers. The studies featured in this session focus on the development of computational methods that leverage multi-omics data—including transcriptomics, proteomics, and network biology—to investigate complex biological mechanisms. These contributions exemplify the session’s emphasis on systems-level modeling, mechanistic interpretation, and translational relevance.

2.1. *Session Papers*

The following papers will be presented at the Systems Biology and Networks Session:

Tasnina et al. address a critical gap in network biology by introducing a path-based provenance tracing framework for diffusion algorithms. Their metrics—path-based effective diffusion and diffusion betweenness—quantify how scores propagate through biological networks, revealing the global structure exploited by diffusion algorithms. Applied to SARS-CoV-2 interactors and human protein networks, their work provides a new lens for interpreting network-based predictions, directly supporting the session’s goal of mechanistic transparency in AI-driven models.

Zhou et al. present REPEL, a graph augmentation method that improves protein function prediction by introducing random repelling forces in network embeddings. Evaluated on yeast and *E. coli* networks, REPEL outperforms existing methods such as Mashup, deepNF, and BIONIC. This contribution illustrates how uniform perturbation can denoise embeddings and enhance robustness, aligning with the session’s interest in scalable, generalizable methods for functional annotation across biological networks.

Blair et al. introduce NORSP, a novel algorithm for identifying sparse perturbation sets capable of transitioning biological systems between steady states. By combining network propagation with supervised learning, NORSP enables biologically feasible control strategies across transcriptomic and metabolic models. This contribution aligns with the session’s focus on systems-level modeling and experimental design, offering a scalable framework for hypothesis generation and therapeutic prioritization.

Chen and Wang introduce a transcriptomic signature-based framework built on the Genomas system, designed to analyze over 1,300 disease–condition pairs. Their work constructs a disease similarity network that successfully recovers known comorbidities while revealing unexpected cross-category relationships. By combining gene-level and pathway-level similarities, the study underscores the value of interpretable multi-omics integration for generating mechanistic hypotheses. Their focus on rare diseases, including autism spectrum disorder, highlights the promise of network-based methodologies in advancing precision medicine.

Orlenko et al. present a random-walk-based learning framework aimed at drug repurposing for Alzheimer’s disease. Leveraging Hetionet and AlzKB, they generate network-informed gene embeddings and apply a multi-objective AutoML strategy to rank candidate genes. Their approach illustrates how integrating knowledge graphs with network-derived metrics can reveal both established and previously unrecognized biological connections—reflecting the session’s broader emphasis on data-driven strategies for drug discovery and the importance of

transparent, interpretable modeling.

The poster presentation by Rajagopalan et al. introduces DRIVE-KG, a heterogeneous knowledge graph framework designed to integrate multi-omics data for variant–phenotype association discovery in complex and understudied diseases such as endometriosis. By combining biological knowledge from diverse sources and applying graph-based machine learning, the authors uncover novel SNP–phenotype associations and demonstrate improved patient classification performance compared to traditional genetic risk scores. This work exemplifies the session’s goals by showing how graph-based integration of multi-modal data can advance precision medicine, particularly in historically underdiagnosed conditions.

Together, these papers reflect the session’s commitment to advancing systems biology through computational innovation. They demonstrate how network-based methods can integrate multi-omics data, generate testable hypotheses, and provide mechanistic insights into disease and biology. By bridging molecular and cellular scales, and combining network biology with machine learning, this session contributes to the broader goals of precision medicine, translational research, and biological discovery.

3. Acknowledgments

Gurkan Bebek is supported by an NIH NIA grant (1R21AG074287). Iman Hajirasouliha is supported by an NIH NIGMS grant (R35GM138152) and an Irma T. Hirschl/Monique Weill-Caulier Trust Research Award.