Higher-Order Dynamics in Protein Interaction Networks

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***Abstract*— Network analysis is a powerful tool for studying the dynamics of cellular processes. Graph-based models are limited, however, in that these models consider only pairwise relationships. Higher-order interactions are well-characterized in biology, including protein complex formation and feedback or feedforward loops. These higher-order relationships are better represented by a hypergraph as a generalized network model. Here, we present an approach to analyzing dynamic gene expression data using a hypergraph model and quantify network heterogeneity via Forman-Ricci curvature. We observe, on a global level, increased curvature in pluripotent stem cells and cancer cells. Further, we use local curvature to conduct pathway analysis in a melanoma dataset, finding increased curvature in several oncogenic pathways and decreased curvature in tumor suppressor pathways. We compare this approach to a graph-based model and a differential gene expression approach.**

***Index Terms*— cellular dynamics, protein interaction network, higher-order interaction, hypergraph, network geometry, cellular differentiation, cancer**

I. Overview

Cells are complex dynamic systems wherein gene expression into specific protein levels and resulting interactions shape cell phenotype. For example, in differentiation, stem cells evolve into specialized differentiated cells, requiring expression of certain molecular pathways that provide the cell with specialized function. In order to study such dynamic cellular processes, we analyze gene expression data (single-cell RNA-seq) from stem cell and cancer experiments.

Protein-protein interaction (PPI) networks model the interactome as a network, where each protein is represented by a vertex and interactions with other proteins are represented by edges. However, the standard graph model considering only pairwise edges is limited to binary interactions, whereas higher-order interactions are well known in biology (protein complex formation, molecular pathways, etc.).

Entropy ("randomness") and the related geometric property of Ricci curvature ("flatness") can describe the dynamics of a system, including robustness [1], [2]. In PPI networks, these properties can be discretized to measure local heterogeneity in the network. In this regard, global network entropy and Forman-Ricci curvature have been shown to indicate cellular pluripotency ("stemness"), where the magnitudes of these values decrease upon differentiation [3], [4].

This work was funded by NSF grant ECCS-1749937 and AFOSR grant FA955018-1-0130.

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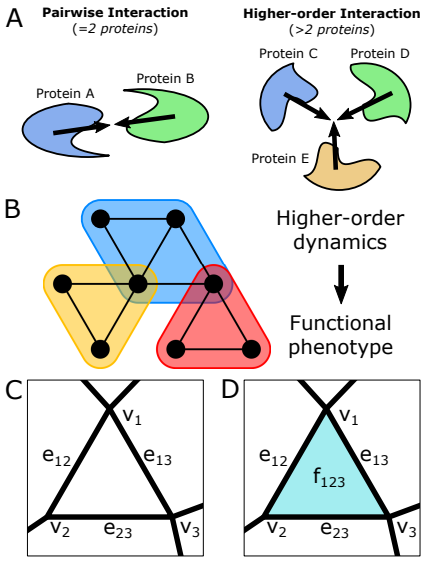

Fig. 1. Hypergraph model of higher-order protein interactions. A: Illustration of two types of protein interactions: pairwise (binary) interaction between 2 proteins, and higher-order interaction between >2 proteins. B: Schematic of hypergraph model, representing higher-order relationships (shaded bubbles) among multiple proteins (vertices). C: Graph model of three adjacent vertices, representing only pairwise relationships. D: 2-dimensional model with a face considered among the three adjacent vertices, representing a shared higher-order relationship.

Here, we present and characterize a higher-order model of PPI networks based on a 2-dimensional simplicial complex, identifying triangular faces representing feedforward and feedback connectivity. We apply geometric network analysis using this higher-order model to explore cell differentiation and cancer datasets.

We find Forman-Ricci curvature in the hypergraph model reflects cellular pluripotency, with larger magnitude of negative curvature in stem cells, decreasing with differentiation. Further, curvature is increased in cancer, indicating a more "stem-like" state in cancer. Pathway analysis demonstrates the capacity of Forman-Ricci curvature to identify molecular pathway functionality in pathologic processes like cancer.

References

[1] K.-T. Sturm, "On the geometry of metric measure spaces," *Acta mathematica*, vol. 196, no. 1, pp. 65–131, 2006.

[2] J. Lott and C. Villani, "Ricci curvature for metric-measure spaces via optimal transport," *Annals of Mathematics*, pp. 903–991, 2009.

[3] A. E. Teschendorff and T. Enver, "Single-cell entropy for accurate estimation of differentiation potency from a cell's transcriptome," *Nature communications*, vol. 8, no. 1, pp. 1–15, 2017.

[4] K. A. Murgas, E. Saucan, and R. Sandhu, "Quantifying cellular pluripotency and pathway robustness through forman-ricci curvature," in *International Conference on Complex Networks and Their Applications*. Springer, 2021, pp. 616–628.