IDENTIFICATION OF RNASEL AND ROCK1 AS GEOMETRIC BOTTLENECKS IN MULTIPLE MYELOMA VIA DISCRETE RICCI CURVATURE ANALYSIS

A. Mustafa[1]

1.MBBS, Faculty of Medicine, Al-Neelain University, Khartoum, Sudan.

INTRODUCTION

High-resolution sequencing has revolutionized multiple myeloma (MM) research; however, methods capable of revealing global functional coordination remain scarce. This study employs Ollivier-Ricci curvature (ORC), an extended notion of Ricci curvature on a Riemannian manifold. Applying ORC to apoptotic signaling pathways in MM may enable the detection of negatively curved edges acting as geometric bottlenecks. These topologically fragile, nonredundant points may serve as promising therapeutic targets, providing novel perspectives on the geometric resilience of the apoptotic pathway in MM beyond conventional coexpression analyses

METHOD

RNA-seq data from 859 patients were obtained from the Genomic Data Commons Multiple Myeloma Research Foundation-CoMMpass cohort, with more than 160 apoptotic genes sourced from MSigDB. Coexpression networks were established via Spearman correlation and scale-free topology optimization to generate a topological overlap matrix . This network was sparsified via percentile thresholding and transformed into a topological distance framework for the computation of ORC analyses. Key bottleneck genes were ranked using a score integrating the average magnitude and proportion of a gene's negatively curved connections. Finally, the therapeutic potential of these structural vulnerabilities was validated through ligand-based druggability assessments using the DepMap portal to identify actionable targets within the MM apoptotic pathway.

RESULTS

Ricci curvature analysis of the apoptotic pathway identified only *ROCK1*, *SLC20A1*, *BAX*, *RNASEL*, *DAP3*, *DFFA*, and GSR with negative curvature, marking systemic bottlenecks. Visualization of the negative curvature backbone highlighted critical nonredundant signaling bridges. Integrating DepMap assessments identified *RNASEL* and *ROCK1* as actionable, ligand-based druggable targets. These results demonstrate that the analysis of geometric vulnerabilities may offer a new strategy for identifying therapeutic candidates in MM.

CONCLUSIONS

Ricci curvature analysis uncovers signaling bottlenecks in the apoptotic pathway that are typically masked by conventional statistical methods. These findings prioritize *RNASEL* and *ROCK1* as ligand-based druggable vulnerabilities for MM.

TABLES AND FIGURES

1. Data Cleaning & Exploration

i. Handle infinite and missing values
ii. Remove columns with zero standard deviation
iii. Generate baseline heatmap visualization (clustermap)

2. Weighted Gene Co-Expression Analysis (WGCNA)

I. Filter low-variance genes (keep top 75% by variance)
II. Compute Spearman correlation matrix
III. Select soft threshold β (best scale-free topology fit, R^2>0.7)
IV. Build signed adjacency matrix: $((1+corr)/2)^{\beta}$
V. Compute Topological Overlap Matrix (TOM)
VI. Perform hierarchical clustering on topological dissimilarity matrix (1−TOM)

3. Co-Expression Network Construction

I. Apply adaptive edge threshold to TOM (90th percentile)
II. Build graph (nodes = genes, edges = significant TOM weights)

4. Geometric Vulnerability Analysis (Ollivier-Ricci Curvature)

I. Convert TOM edge weight to distance: 1/(weight+ε)
II. Compute Ollivier-Ricci curvature for every edge
III. Extract edges with negative curvature (structural bottlenecks)
IV. Calculate a bottleneck score for each node: (mean negative curvature) × (fraction of negative incident edges)
V. Rank genes by bottleneck score

5. Druggability Assessment & Target Identification

VII. Cross-reference top bottleneck genes with DepMap database
VIII. Identify actionable, ligand-based druggable targets

Figure 1: Methodology Flow Diagram

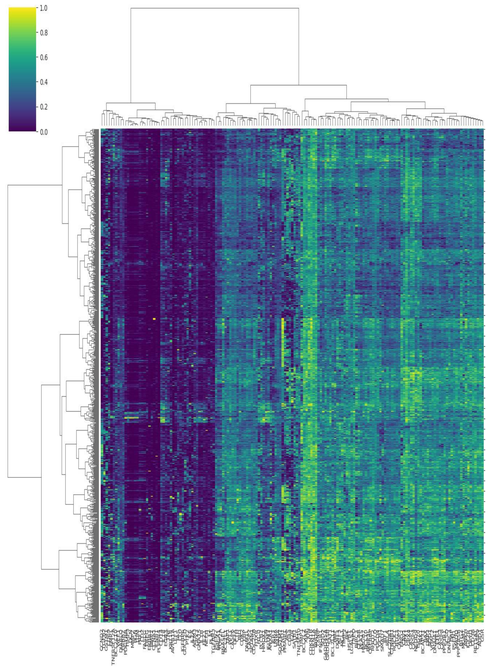

Figure 2: Heatmap of the apoptotic pathway gene expression in multiple myeloma

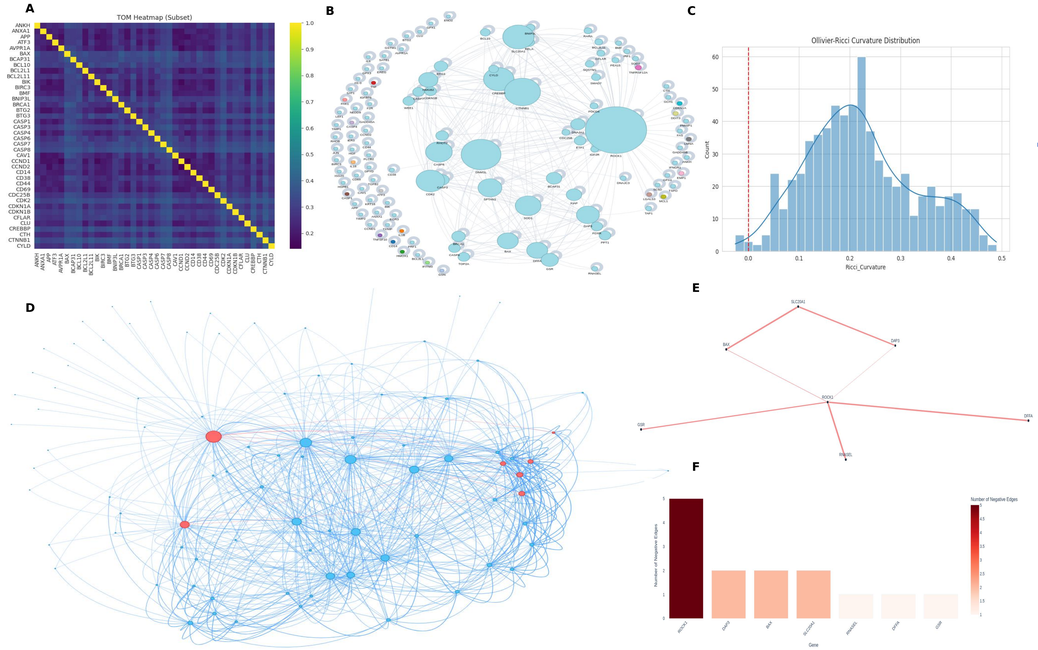

Figure 3: Co-expression network construction and geometric vulnerability analysis. **(A)** Topological Overlap Matrix (TOM) heatmap for a subset of genes, where lighter colors (yellow) indicate higher similarity and co-expression. **(B)** Gene co-expression network derived from WGCNA. Node sizes are scaled according to their degree of connectivity within the network. **(C)** Distribution of Ollivier-Ricci curvature values across all network edges. The red dashed vertical line marks a curvature of zero; the small tail to the left represents edges with negative curvature. **(D)** Global network topology. Edges and corresponding nodes that exhibit negative Ricci curvature (falling below the zero threshold in panel C) are highlighted in red, identifying them as structural bottlenecks, whereas the positive connections remain blue. **(E)** An isolated network detailing the specific interactions between genes with negative curvature edges. **(F)** Bar chart ranking the identified bottleneck genes based on their negetive curvature.

CONTACT INFORMATION

Alamin Mustafa, MBBS, Faculty of Medicine, Al-Neelain University, Khartoum, Sudan.
Email: alamin900005@gmail.com

REFERENCES

Simhal AK, Weistuch C, Murgas K, Grange D, Zhu J, Oh JH, Elkin R, Deasy JO. ORCO: Ollivier-Ricci Curvature-Omics—an unsupervised method for analyzing robustness in biological systems. Bioinformatics. 2025 Mar;41(3):btaf093.

Agourakis DC, Gerenutti M. Ollivier–Ricci Curvature Reveals Geometric Phase Transitions in Biomedical Networks: From Ontologies to Aging Comorbidity. medRxiv. 2026 Mar 16:2026-03.

Lin Y, Lu L, Yau ST. Ricci curvature of graphs. Tohoku Mathematical Journal, Second Series. 2011 Dec 30;63(4):605-27.

Zheng X, Zhang Z, Zhang X, Jin N, Zhang Y. Ricci-GraphDTA: A graph neural network integrating discrete Ricci curvature for drug–target affinity prediction. Journal of Molecular Graphics and Modelling. 2025 Sep 13:109170.