Comprehension of Multiple Molecular Pathways using 3D Networks

Suresh K. Bhavnani[1] **PhD, Justin Drake**[1] **BS, Bryant Dang**[1] **BS, Shyam Visweswaran**[2] **MD, Juan P. Olano**[3] **MD**
[1]Inst. for Translational Sciences, [3]Dept. of Pathology, UTMB; [2]Dept. of Biomedical Informatics, Univ. of Pittsburgh

Abstract

Many infectious diseases such as rickettsioses trigger multiple concurrent pathways including those related to innate immune response, and the repair of tissue damage. While bipartite networks can help to infer such complex pathways from patterns of co-expressed genes or proteins, the two dimensional (2D) network layouts are often too dense to reveal sub-topologies in the data. We therefore analyzed rickettsioses patients and cytokines using 3D stereo network layouts to explore if they could help in comprehending more complex relationships among multiple pathways. The results suggest that (1) the extra degree of freedom offered by 3D layouts revealed sub-topologies that helped to infer how the two pathways might be connected, and (2) the 3D stereo enabled comprehension of the network due to reduced node occlusions and disorienting rotations that plague viewing of non-stereo 3D networks.

Introduction

Human biological response to a wide range of infections typically involves the activation of multiple pathways such as innate immune response, and repair to endothelial damage. To address this complexity, researchers have used multivariate methods such as bipartite networks to help infer such pathways based on how genes or proteins are co-expressed. However, while 2D network layouts are powerful in revealing overall topologies, they are often too dense to reveal sub-topologies, which could conceal important information about the relationship among the pathways. We therefore posed the question: *Can 3D network layouts help to infer the relationship among multiple biological pathways?*

Method

As shown in Figure 1, a recent bipartite network analysis[1] of 26 cytokines and 85 rickettsioses patients revealed a cluster of 5 highly co-expressed cytokines (red nodes) across the patients. A domain expert inferred that these cytokines were members of two pathways: (a) PDGF with other cytokines was involved in endothelial tissue repair; (b) IL-17, GM-CSF, and G-CSF were involved in immune pro-inflammatory response. Furthermore, although he inferred that these two pathways could be connected by a growth factor such as GM-CSF or G-CSF, or indirectly with MIP-1β, the 2D network was too dense to reveal more details about the sub-topology within the cluster. We therefore re-analyzed the data using (1) the Fruchterman-Reingold 3D layout algorithm in Pajek, and (2) 3D stereo which helps in comprehending occluded nodes without rotating the network (which often results in disorientation[2]).

Results and Conclusion

As shown in Figure 2, the 3D network revealed a sub-topology of two clusters: Cluster-1 indeed included PDGF and MIP-1β, while Cluster-2 included IL-17 and GM-CSF. Furthermore, G-CSF was in-between these two clusters, suggesting that if patients highly expressed Cluster-1 and Cluster-2, they were more likely to express G-CSF than if either cluster was highly expressed alone. Because the expression of G-CSF appears dependent on both clusters, this pattern implies that G-CSF could be involved in both the PDGF and IL-17 pathways. This sub-topology was verified by (but was not discoverable through[1]) hierarchical clustering. Furthermore, the comprehension of this layout was aided by the stereo which reduced node occlusions and the resulting disorienting rotations. Future research should confirm that the relationship among multiple pathways is easier to comprehend through 3D stereo networks, with the goal of accelerating translational insights.

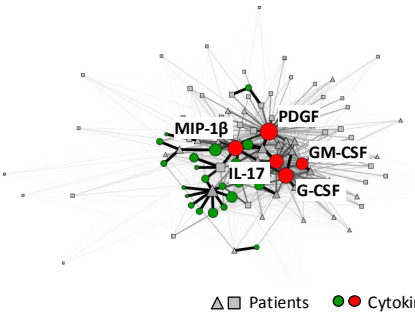

Figure 1. 2D Network Layout

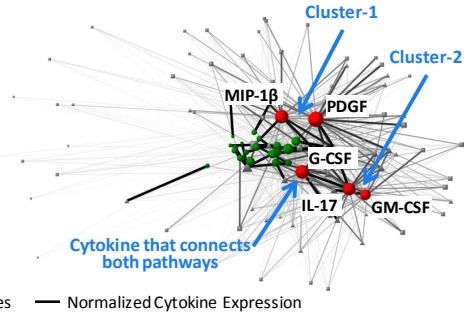

Figure 2. 3D Network Layout

Acknowledgements

Funded by IHII, UTMB.

References

1. Bhavnani S.K., et al. How Cytokines Co-occur across Rickettsioses Patients: From Bipartite Visual Analytics to Mechanistic Inferences of a Cytokine Storm. *AMIA Summit on Translational Bioinformatics* (in press).
2. Bhavnani, S.K., et al. Discovering Hidden Relationships between Renal Diseases and Regulated Genes through 3D Network Visualizations. *BMC Research Notes*, 3, 296 (2010).