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A Topology-Enabled Patient Connectivity Network to Bridge the Molecular-To-Phenotype Gap in Cholestasis

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Abstract : Cholestasis is characterized by the accumulation of toxic bile salts and lipids in the organism. The variety in causes (genetic, immunologic, environmental) and nature (benign, transient, chronic, progressive) combined with the need for early diagnosis and rapid clinical decisions emphasizes the need for good diagnostic strategies to improve patient outcomes. In a current diagnostic analysis of cholestasis, mass-spectrometry metabolomics is a widely adopted tool to enhance clinical decisions at point-of-care, thanks to a short turnaround in measurement times while performing comprehensive molecular profiling of patient material. However, this comes at the cost of difficult-to-identify yet actionable knowledge, often buried within large and heterogenous omics data. Here, we demonstrate how topological data analysis can overcome this challenge in large metabolomics datasets of patients with twenty categories of Metabolic Disorders and overlapping clinical manifestations. To elucidate the complexity of disease progression in three cholestasis patients, we applied topological data analysis to direct-infusion mass spectrometry data collected from 190 plasma samples, including 67 controls, at the University Medical Center in Utrecht, Netherlands. Using the Mapper algorithm and filter function defined as a two-component projection based on Principal Component Analysis, we constructed a topological graph of connected patients, termed a Patient Connectivity Network (PCN). With incorporated clinical and molecular information, PCN revealed the topological shape of causes and severity of cholestasis and transitions in patients' conditions. In conclusion, topology based PCN provides a holistic view of cholestasis state dynamics that has the potential to support and expedite clinical decisions.

Keywords : mass spectrometry-based metabolomics, patient connectivity network, topological data analysis, unmet clinical needs in Cholestasis
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