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TITLE: ZONAR: A Probabilistic Framework for Liver Zonation Mapping Integrating Spatial Omics and Anatomical Regularization

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ABSTRACT: Liver zonation is determined by the intrinsic distances of hepatocytes to the nearest portal and central veins. Inferring these three-dimensional distances from two-dimensional tissue sections is heavily biased by unobserved out-of-plane vessels. Conversely, purely data-driven omics methods are vulnerable to batch effects and circular reasoning. We introduce ZONAR (ZONation via Anatomical Regularization), a probabilistic framework that overcomes these limitations by combining geometric landmarks with spatial omics data to produce anatomically anchored zonation estimates, which allows us to detect liver metabolic shifts in cholestasis and its treatment from high-resolution imaging mass spectrometry data. Operating on a Delaunay graph of hepatocytes, ZONAR estimates the zonation coordinate via Maximum A Posteriori (MAP) estimation. The framework combines a molecular likelihood derived from dimension-reduced MALDI-MSI meta-features modeled as smooth functions using penalized splines, a geometry-based Gaussian observation model that quantifies local trust in distance-derived zonation ratios, and a Gaussian Markov Random Field smoothness prior that enforces spatial coherence. Applying ZONAR to mouse liver sections analyzed by MALDI-MSI demonstrated its ability to anchor the zonation field and correct for geometric drift caused by missing landmarks. In a case study analyzing zonation in a mouse liver model of bile duct ligation-induced cholestasis, ZONAR effectively quantified the degradation and blurring of normal metabolic zonation profiles associated with chronic cholestatic injury. By separating spatial priorities from molecular probabilities, this framework provides a solid basis for cross-sample measurement of metabolic gradients in spatial omics studies.

BRIEF SPEAKER BIO: Michael A. Debebe is a PhD student in Biostatistics at the University of Cologne, where his research focuses on spatial omics and dose-response analysis. He holds bachelor's and master's degrees in Statistics and Data Science from Uppsala University. During his graduate studies, he completed a one-year integration at Boehringer Ingelheim's Biostatistics and Data Science department, investigating combination dose-response models.