# Hidden Loops in Cancer: Persistent Homology Framework for PDAC Transcriptional State Discovery

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Pancreatic ductal adenocarcinoma (PDAC) has a five-year survival rate of 12%, driven in part by unresolved mechanisms of therapeutic resistance. While single-cell RNA sequencing has advanced tumor profiling, standard trajectory inference methods assume linear or branching progression and fail to capture recurrent cellular states. Here, we apply persistent homology from topological data analysis to uncover higher-order transcriptional structure in PDAC. Single-cell transcriptomic data from 10,699 ductal cells across 20 PDAC patients were analyzed. Topological features were evaluated, and cells within detected loops were assigned geodesic circular pseudotime. Cyclic gene expression was quantified, followed by pathway and drug-gene interaction analyses. We identified a statistically significant one-dimensional topological loop comprising 158 PDAC-specific ductal cells (persistence = 2.457; p = 0.038), detected at 46-fold finer resolution than conventional clustering. Circular pseudotime analysis revealed 54 cyclic genes, suggesting the presence of a coordinated transcriptional program exhibiting cyclic dynamics. Notably, GABRP, a known PDAC oncogenic driver, was present within this gene set but has not previously been characterized as part of a cyclic transcriptional program. Drug–gene interaction analysis identified 135 interactions between FDA-approved drugs and loop-associated genes. These findings demonstrate that PDAC exhibits a tumor-specific cyclic transcriptional program linked to phase-dependent therapeutic vulnerability. Our results show that topological methods can uncover dynamic cellular states inaccessible to standard analyses and provide a framework for temporally targeted treatment strategies.

**Awards Won:**