Topological Data Analysis of Pulmonary Vascular Networks

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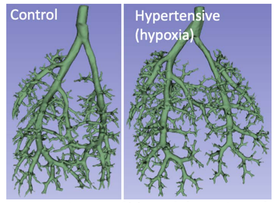
Pulmonary Hypertension

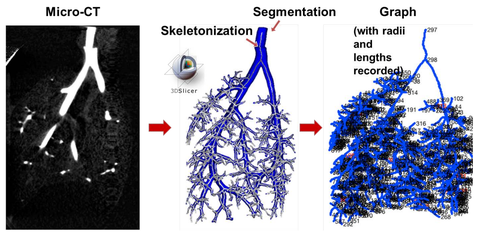


Cardiovascular disease (CVD) is the leading cause of mortality, globally claiming an estimated 17.9 million lives per year. One CVD with no known cure is pulmonary hypertension (PH), defined as high blood pressure above 25 mmHg in the main pulmonary artery (Hambly et. al., 2016).

PH is often accompanied by vascular remodeling, wherein the large vessels dilate and the small vessels constrict. This study uses topological data analysis (TDA) to analyze data from control and hypertensive subjects. TDA provides insight into the structural differences between vascular networks. Since PH is a chronic and progressive disease, recognizing the distinguishing features of a hypertensive network can facilitate diagnosis and improve treatment.

Data

This study examines micro-CT images of six male C57BL6/J mice, three experimental and three control. Experimental mice are placed in a hypoxic chamber with FiO_2 reduced by half for ten days to induce PH. The lungs of the mice are extracted, ventilated, rinsed, and perfused with perfluorooctyl bromide at pressures of *6.3*, *7.4*, *13.0*, and *17.4 mmHg*. The lungs are then rotated in a micro-CT scanner to obtain 360-degree planar images for each pressure. The images are converted into 3D volumetric data.

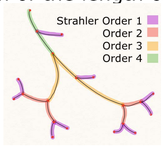


We isolate the pulmonary arterial network using the open-source image analysis program, 3D Slicer. We then extract skeletonizations and spatial graphs with vessel radii and lengths recorded. Micro-CT images are provided by Naomi Chesler (UC Irvine).

Modeling

Arterial networks are modeled with geometric rooted trees, where the direction corresponds to the blood flow (Chambers et. al., 2020). Each edge corresponds to a vessel, with a length and radius, and each vertex in $\mathbb{R}^3$ corresponds to a branching point, the root or an outlet.

The **length** of the arterial tree is the sum of the length of all edges. The **depth** of a tree is the maximum number of edges in any path from root to leaf. A related branching complexity measure is **Strahler order** (Strahler 1957).



The **length to radius ratio** (LRR) in a tree can be modeled by the function, $f(r) = c_1 e^{-c_2 r}$, where r is edge radius. The network is mostly bifurcating, so we compute branching ratios α and β denoting how the two daughter vessels relate to their parent.

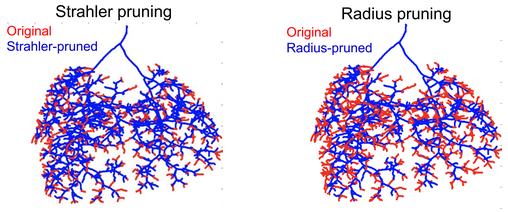
Pruning Techniques

As a consequence of the imaging technique, rooted trees of mice with PH contain more edges than the rooted trees of control mice.

To remove the edges that correspond to vessels visible only in the arterial trees of hypertensive subjects, we use pruning techniques based on radius thresholding and Strahler order.

Radius thresholding: The hypertensive trees are pruned by removing pairs of leaves whose radii fall below a certain threshold. The threshold is increased, and the process is continued until the average radius of the hypertensive trees is close to that of the control.

Strahler order: Edges of Strahler order 1 are removed until the desired Strahler order of the root vessel is achieved.

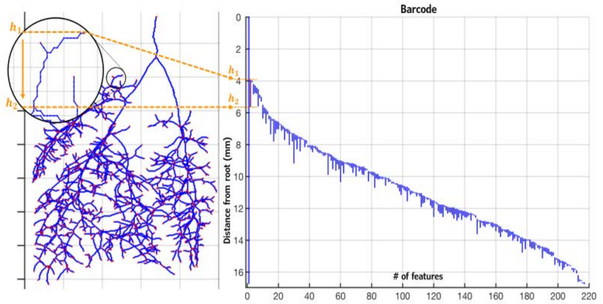


Example of pruned hypertensive tree

Topological Data Analysis (TDA)

Persistent homology is a TDA method that computes the homology of a filtered simplicial complex from the data. In particular, persistent homology in degree zero, H_0, determines the number of **connected components** of the rooted tree at a given filtration parameter, h_i.

In this study, we use **height filtration** defined by a distance, h_i, from the root. The zeroth persistent homology, H_0 , of a geometric rooted tree then counts the number of trees obtained from our rooted tree by considering points and edges less than h_i away from the root.



Persistence in degree zero with respect to the height filtration is represented by a **barcode** where the length, l_j, of each bar, b_j, is the difference between the height where a connected component appears and the height when it merges with another connected component. The sum of the length of all bars in the barcode, $\sum_j l_j$, is the **upwards complexity (UC)** of the tree.

Results

		Number of edges		UC		Tree length		Depth		Strahler order of root	LRR	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	C1	C2
Original	Ctrl	1018	151	1648	423	10314	1351	26.3	1.53	6	529	0.00057
	Hyp	2196	778	3659	1369	17674	4937	33.3	4.04	7	371	0.0015
Radius pruning	Hyp	1022	404	1678	54	9366	4120	31.7	3.51	6	514	0.00025
Strahler pruning	Hyp	1519	530	2601	950	13024	3511	32.3	4.04	6	435	0.0008

Results

Among the numerical descriptors this study introduced, upwards complexity, edge radii, depth and the Strahler order of a geometric tree modelling the arterial networks show the greatest promise in distinguishing hypertension. Upwards complexity, edge radii, and depth were higher in the hypertensive group and length to radius ratio was lower in the hypertensive group. These results persisted after pruning both according to the radii and Strahler order.

Additional numerical descriptors such as number of edges and tree length were higher in the original hypertensive trees, but through pruning methods became comparable to the control. Analysis of these comparable networks suggests the differences in numerical descriptors are relevant and are not a consequence of imaging.

Discussion

This is a proof-of-concept study, aimed at developing methods for analyzing and comparing arterial tree networks to discover definitive biological differences between those with and without PH. We explore the potential of TDA tools combined with Strahler order and other graph statistics to capture differences between arterial networks of control and hypertensive mice. To the best of our knowledge, this is the first application of the powerful TDA framework to study pulmonary arterial networks. Our results provide a set of numerical descriptors to differentiate these networks and suggest that arterial trees do remodel in patients with hypertension.

In the future, we aim to perform this analysis on a larger data set and on human subjects. As hypertension starts at the smallest vessels, we will compute persistence in degrees 0, 1 and 2 with respect to alpha filtration to detect differences in the arterial networks not accessible to current imaging techniques.

References

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