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► **To cite this version:**

Inoue Megumi, Bordeu Ignacio, Hallou Adrien, Hernandez-Garzon Edwin, Yorick Gitton, et al..
Branching Morphogenesis in Human Lung Development. Les Treilles Workshop: Developmental Bi-
ology in the 21st C., Jul 2023, LES TREILLES, France. hal-04237976

HAL Id: hal-04237976

<https://cnrs.hal.science/hal-04237976>

Submitted on 13 Oct 2023

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Branching Morphogenesis in Human Lung Development

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INTRODUCTION

Human lung development begins as an outgrowth of the foregut endoderm at around 4 post-conceptual weeks (PCW) and continues into toddlerhood. Past studies of human airway development have been restricted to the first few weeks due to technical limitations. Here, we study the airway tree in the left and right lungs between 5-12 PCW. What is the statistical, morphological, and cellular organization of the branching epithelium in early human lung development? We use whole-mount immunostaining, tissue clearing, and light-sheet microscopy to acquire 3D image datasets of the airway epithelium. In the adult human lungs, we map bronchopulmonary segments known in adult lungs to the developing lung. We develop an image processing pipeline to extract a "skeleton" of the branching tree which allows us to quantify and analyze the airway. To elucidate the balance between stereotypic and stochastic influences on the large-scale architecture of the human airway, we study the statistical features of the branching network across a critical period of branching morphogenesis.

METHODS

Sample Preparation and Imaging

Fetal lungs are obtained from our biobank within the Human Developmental Cell Atlas (HuDeCA) Initiative funded by INSERM (approved by the French Biomedicine Agency and the Ministry for Research). Tissue is fixed and dissected, bleached, epitopes blocked, then incubated with primary and secondary antibodies. Airway is stained with epithelial marker E-cadherin or Epcam. We clear the tissue with iDISCO+ and image with Miltenyi's Blaze light-sheet microscope.

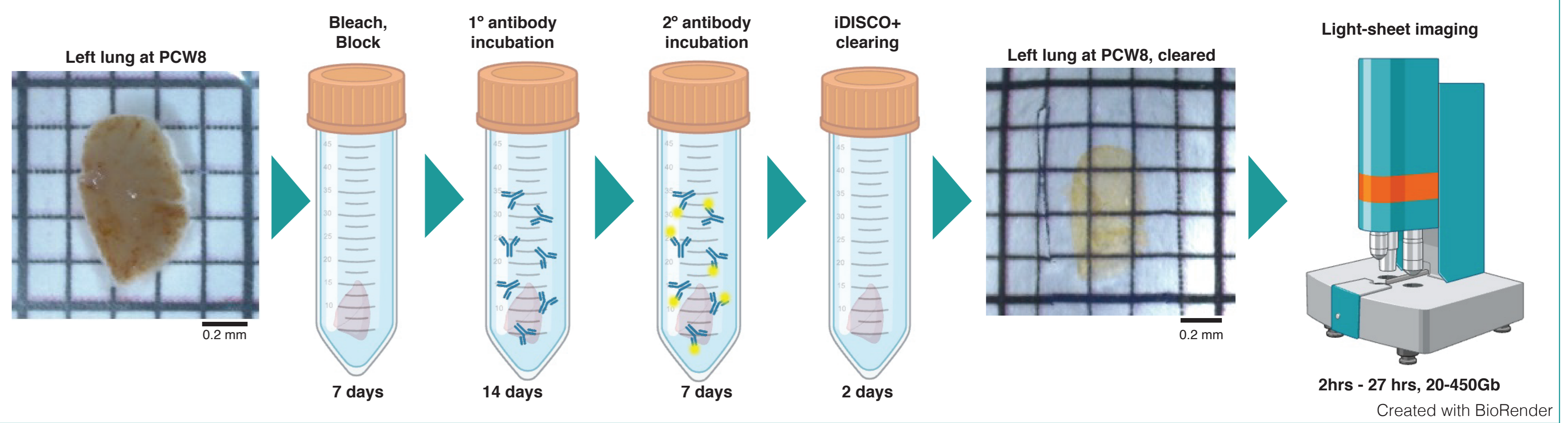
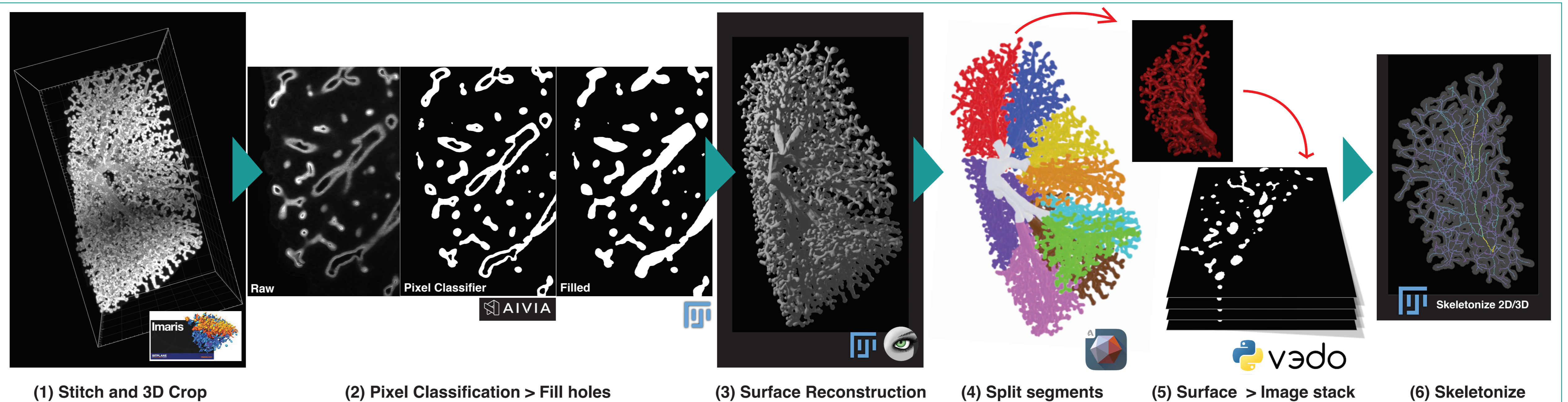
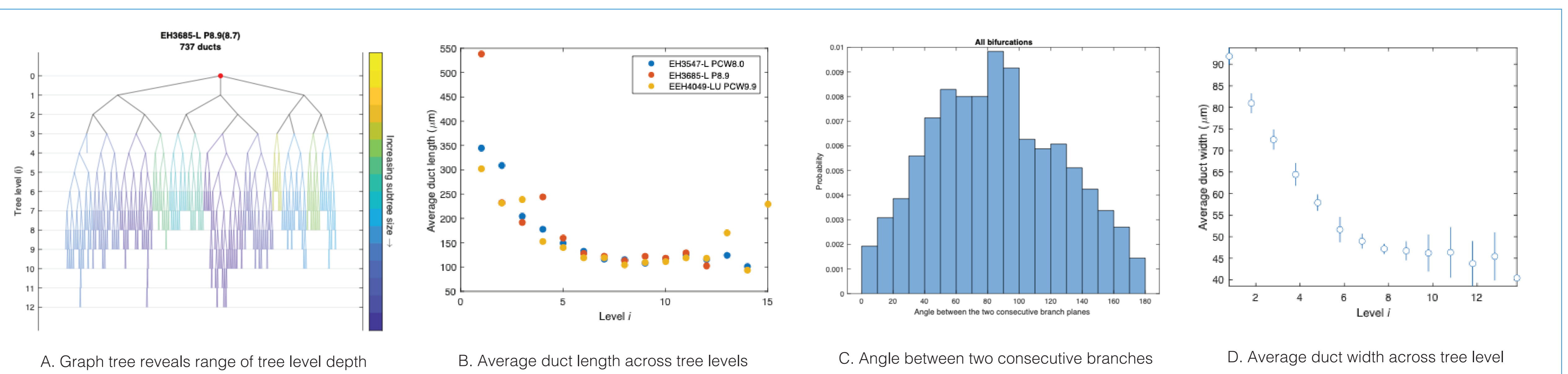


Image Processing

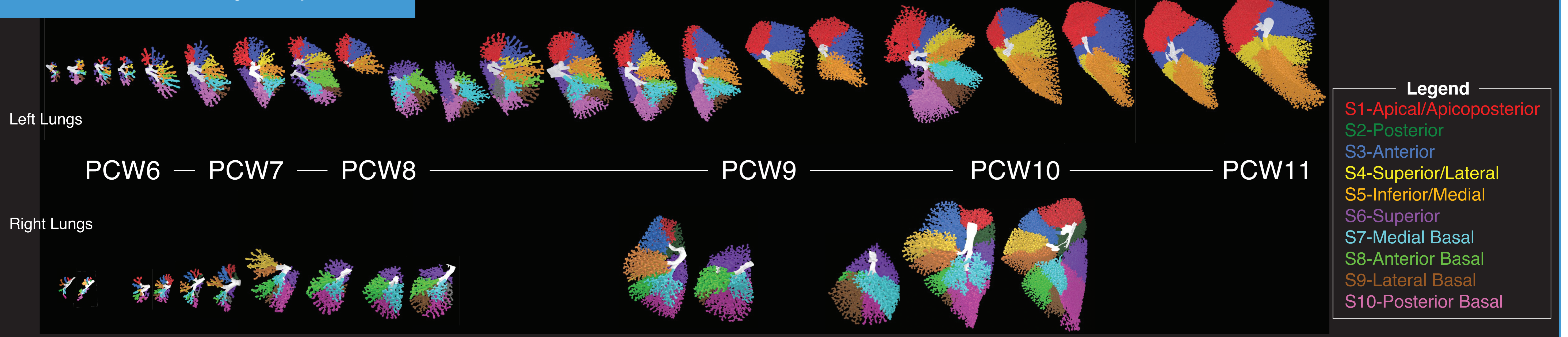


RESULTS

Network Analysis



A Reference for human lung development



Left Upper Lobe average number of branches and maximal tree levels across developmental age.

Age (PCW)	# of branches	Max tree level (Trachea=0)
PCW5 (n=2)	23.5	7.5
PCW6 (n=1)	39	9
PCW7 (n=0)	-	-
PCW8 (n=5)	423.6	14.8
PCW9 (n=9)	1843.3	19.3
PCW10 (n=3)	4306.3	21

Variations across branches in the Left Upper Lobe.

Branch	Variations (%)
B1and2, Apico-posterior (n=20)	15
B3, Anterior (n=20)	15
B4, Superior (or Lateral) (n=20)	35
B5, Inferior (or Medial) (n=20)	35
B6, Superior (n=15)	0
B7, Medial Basal (n=15)	30
B8, Anterior Basal (n=15)	30
B9, Lateral Basal (n=15)	20
B10, Posterior Basal (n=15)	46

Work in Progress: DL for Image Segmentation of PCW11+ Lungs

