Vasculature System as Common Coordinate Framework to Visualize and Interlink Human Functional Tissue Units

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Abstract

Several international efforts are collaborating to comprehensively map the human body at cellular resolution. One major challenge is to create a Common Coordinate to Framework (CCF) to reproducibly define any location in the human body. While most human anatomical atlases map the human body into a 3D *cartesian* coordinate system, this approach cannot accommodate the diversity of human body geometry which varies by sex, race, BMI and changes significantly over a person's lifespan. In this paper, we adopt vasculature as a CCF to visualize the positions of selected Functional Tissue Units (FTUs) and their corresponding Anatomical Structures (AS) and Cell Types (CT). We also propose a novel way to layout the VCCF using bubble-tree layouts to automatically visualize FTUs and their corresponding anatomically indistinguishable CTs.

Introduction

An average adult human body contains about 37 trillion cells with their specialized functions and characteristics [14]. Several international efforts are collaborating to map these cells into a human reference atlas. Examples are the National Institutes of Health's Human Biomolecular Atlas Program (HuBMAP) and the Chan Zuckerberg funded Human Cell Atlas (HCA) initiative. In March 2020, a joint NIH-HCA meeting was organized that brought together experts from multiple consortia to develop Anatomical Structures, Cell Types and Biomarkers (ASCT+B) tables. The tables capture the partonomy of anatomical structures, cell types, and major biomarkers (e.g., gene, protein, lipid, or metabolic markers).

To create a "Google Map" of the human body, these anatomical structures (AS) and cell types (CT) need to be mapped to their respective position in a single coordinate system called a Common Coordinate Framework (CCF).

In this paper, we explore using the vasculature as a CCF (called VCCF) to map the human body down to the cellular level. The idea is to use known vascular pathways through the body as an

axis in a coordinate system that can describe the position of AS and CT in the tissue surrounding the vasculature [17]. Specifically, we describe how the VCCF can be used to map 10 functional tissue units from 9 organs.

Mapping Functional Tissue Units to ASCT+B Tables

We define a functional tissue unit (FTU) as a unit consisting of a three-dimensional volume of cells centered around a capillary, such that each cell in this volume is within diffusion distance from vasculature cells in the same block [6]. In regards to the vasculature CCF, we can think of an FTU as the zip code for a region of interest in which a specific population of cells resides and in well defined spatial structure and the capillaries are the street address of the FTU. Some positional information may be lost in this method by simplifying the vascular pathways. For example, there are approximately one million renal corpuscles in the kidney. Treating them as a single structure potentially masks the differences in renal corpuscle at the superior and inferior renal poles. However, as we learn more about the biomolecular profiles of these pathways, we can iteratively refine the vascular CCF over time by splitting pathways into any subtypes that are discovered [17].

Ten FTUs were identified and their anatomical structures (AS) and cell types (CT) were mapped to the ASCT+B tables [5][9]. The spatially explicit cell population layouts for 10 FTUs were mapped in 2D, see **Fig. 1** for schematics of all 10 FTUs.

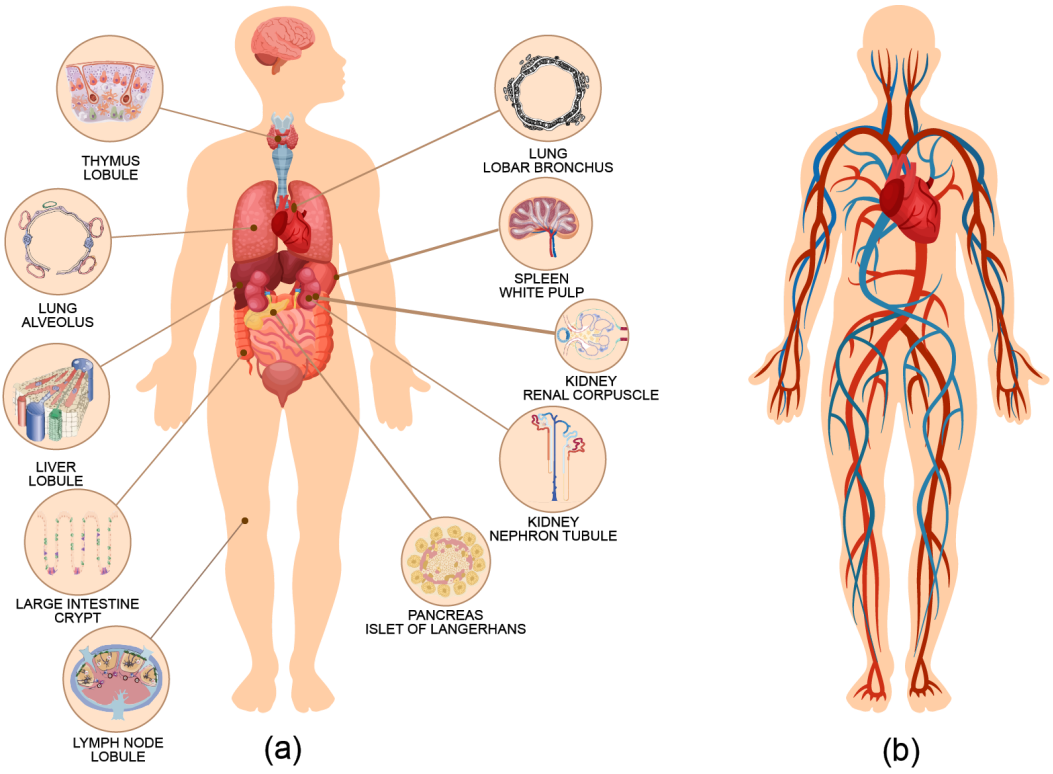

Figure 1. Human body with 10 functional tissue units (FTUs). a. Schematics of 10 FTUs and their anatomical positions. **b.** Human vasculature system.

Note that FTUs are at different levels of abstraction--some consist of only AS, others have only CTs, some have ASs and CTs, see **Table 1**.

Table 1. Number of AS and CT for each FTU.

No.	Organ	FTU	#Unique AS	#Unique CT	Source
1	Kidney	Renal Corpuscle	10	5	[8]
2	Kidney	Nephron Tubule	15	0	[8]
3	Lung	Alveolus	3	4	[7]
4	Large Intestine	Crypt	1	4	[4]
5	Pancreas	Islet of Langerhans	1	10	[4]
6	Spleen	White Pulp	5	1	[12]
7	Liver	Lobule	7	8	[1]
8	Lymph Node	Lobule	1	3	[3]
9	Thymus	Lobule	8	5	[13]
10	Lung	Lobar Bronchus	5	6	[7]

Linking FTUs via the Vasculature

For each FTU, we identified the main vessel that connects the FTU to the vasculature. Using the vasculature ASCT+B table, we then identified 103 vessels connecting all 10 FTUs from the heart to the FTUs and vice versa. Each vessel can be categorized as one of these six types: (1) artery, (2) arteriole, (3) capillary, (4) sinusoid, (5) venule, or (6) vein. At the time of this writing, only renal corpuscle, nephron tubule, large intestine crypt, and alveolus have their nearest capillaries identified in the 2nd release of the ASCT+B tables. A special case is the liver lobule,

as the vascular exchanges between the blood and hepatocytes are facilitated by sinusoids instead of capillaries. A listing of the 10 FTUs and their respective nearest connecting vessels are listed in **Table 2**. Note that for some FTUs, their nearest capillaries are not identified yet, such as for spleen white pulp and thymus lobule.

Table 2. FTUs and their major connecting vessels

No.	FTU	Nearest Vessel in ASCT+B	UBERON/ FMA ID
1	renal corpuscle	glomerular capillary	UBERON:0004212
2	nephron tubule (cortex)	peritubular capillary	UBERON:0005272
3	nephron tubule (medulla)	vasa recta of kidney	FMA:72006
3	alveolus	pulmonary capillary	UBERON:0016405
4	large intestine crypt	short branch of vasa recta of colon	N/A
5	pancreas islet of Langerhans	dorsal pancreatic artery	UBERON:0001264
6	spleen white pulp	spleen central arteriole	UBERON:0002106
7	liver lobule	liver sinusoid	UBERON:0002107
8	popliteal lymph node lobule	popliteal artery	UBERON:0000978
9	thymus lobule	thymic artery	UBERON:0002370
10	left superior lobar bronchus	superior left bronchial artery	UBERON:0002048

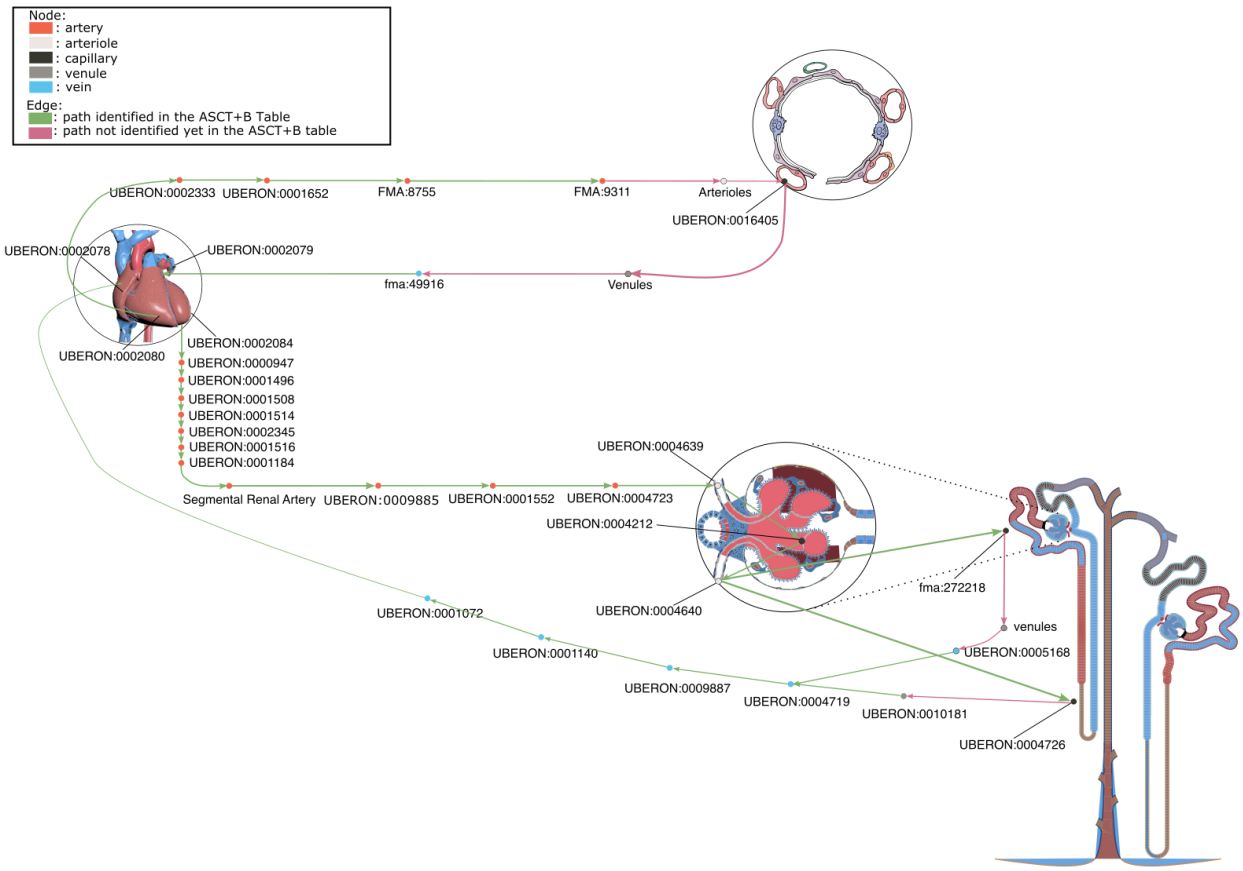

Figure 2. Exemplary pathway from heart organ to one FTU in lung and the two FTUs in kidney

The pathway from heart to lung and kidney is exemplarily shown in **Fig. 2**. The nodes represent the vessels and are color coded based on their types (artery, arteriole, capillary, sinusoid, venule, or vein). For each vessel we provide the Uberon or FMA ontology ID. The vascular pathways form loop that extend out through the arteries, gradually taper off to cellular levels as they approach the FTUs, and return from the FTU back to the heart. These vascular paths act as axes that describe the position of the FTUs. Note that some paths between heart and the FTUs are not identified yet in the ASCT+B table and are color-coded in pink. These paths should be added in the 3rd release due April 1, 2022.

Combining VCCF with Bubble-tree Map to Visualize AS and CT Partonomy in an FTU

As of December 2021, the ASCT+B tables contain 2,582 ASs and 898 CTs. Some of these CTs have different functionalities and biomarkers, but are not anatomically distinguishable; imposing challenges on visualizing them in two-dimensional medical illustrations. Moreover, HuBMAP is an ongoing project, revisions to the ASCT+B table are expected in the future. Updating a

medical illustration with new information is not a small task, especially when dealing with thousands of ASs and CTs. In **Fig. 3**, we adopt bubble-tree layouts [2] [11] to automatically visualize ASs and CTs in FTUs. A bubble-tree layout visualizes the ASs and CTs as a nested hierarchy. The algorithm reads the ASCT+B table and generates a layout where cells are enclosed by the most detailed AS; these detailed AS are grouped and enclosed by ever more general, macro-scale AS. Whenever the ASCT+B table changes, the layout can be automatically regenerated.

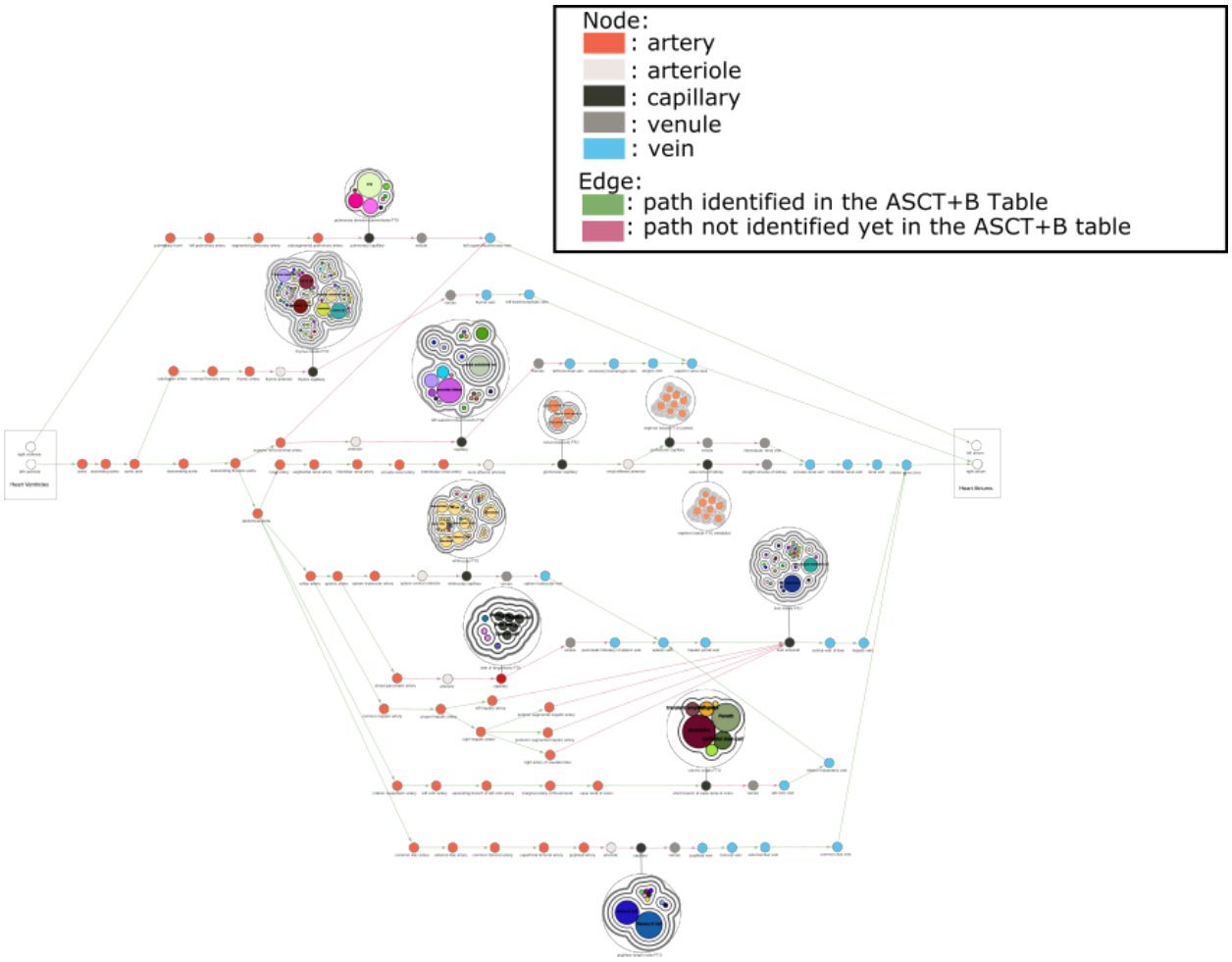

Figure 3. Bubble-tree layout of the 10 FTUs. High resolution SVG is available at [8]

Just like in **Fig. 2**, the nodes in **Fig. 3** represent the vessels and are color coded based on their types (artery, arteriole, capillary, sinusoid, venule, or vein). The paths between heart and the FTUs that are not identified yet are also color coded in pink. However, instead of medical illustration, we represent the FTUs with bubble-tree layout. **Fig. 4** depicts the bubble-tree layout of an alveolus on the left. Note that it clearly distinguishes between two types of capillary endothelial cells, which are anatomically indistinguishable in the medical illustration on right. Both types of capillary endothelial cells are enclosed in a circle as they are under the hierarchy of pulmonary capillary (UBERON:0016405) in the ASCT+B table. The size of each circle

represents the number of cells for each CT based on the CZI dataset [16]. **Table 3** compares the CTs depicted on the bubble-tree layout and on the 2D FTU illustration.

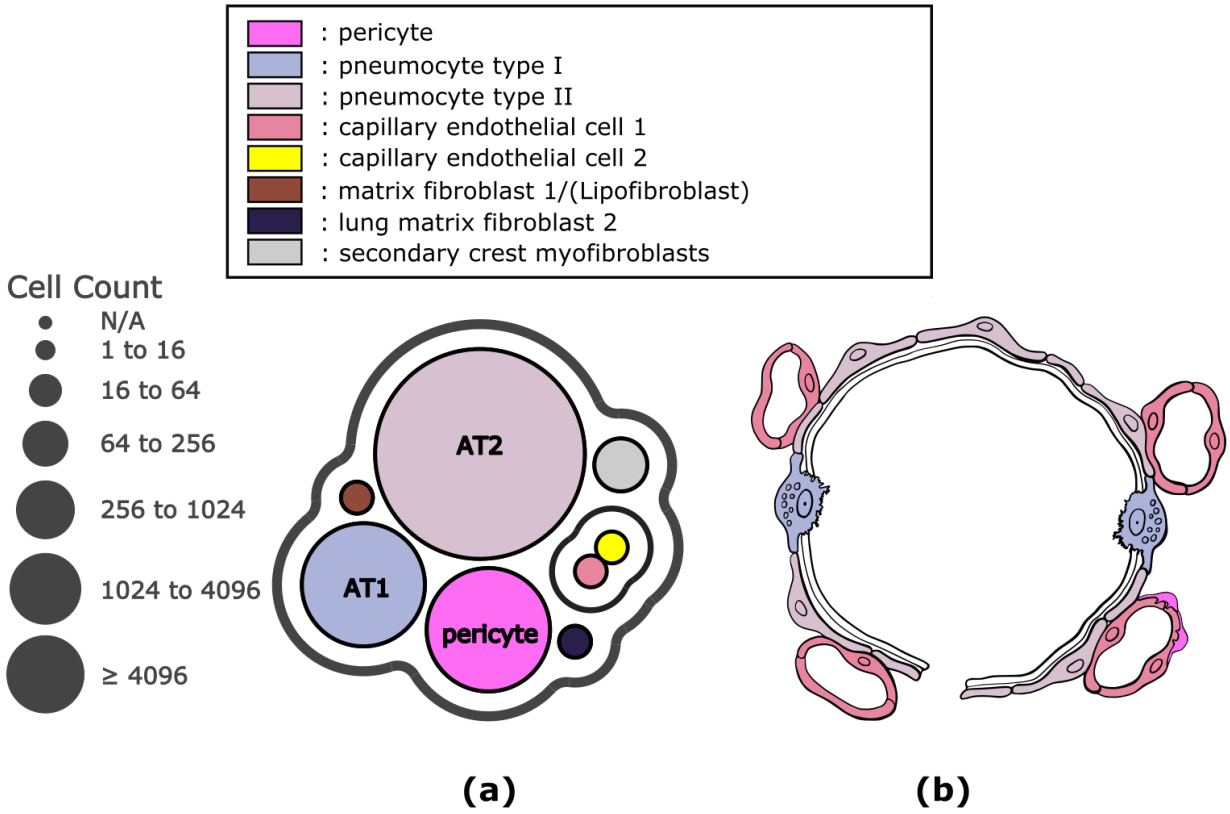

Figure 3. Pulmonary alveolar parenchyma. a. Bubble-tree layout of the pulmonary alveolar parenchyma. **b.** FTU illustration. High resolution SVG is available at [9].

Table 3. Comparison of cell types on the bubble-tree layout and on the 2D FTU illustration

CT	Cell Counts	Depicted on the FTU Illustration?
pericyte	213	Yes
pneumocyte type I	211	Yes
pneumocyte type II	9,146	Yes
capillary endothelial cell 1	N/A	Yes
capillary endothelial cell 2	N/A	No
matrix fibroblast 1/(Lipofibroblast)	N/A	No
lung matrix fibroblast 2	N/A	No
secondary crest myofibroblasts	10	No

Next Steps and Future Directions

Begin of December 2021, the teams at Indiana University and Harvard Medical School are in the process of identifying the vasculature pathway from the heart to the 10 initial FTUs listed in **Table 1**. Some of these vessels do not yet have a standardized name in medical ontologies, so a framework has been developed to come up with new names for these vessels.
Other than for VCCF, building this information could benefit other scientific applications such as understanding microvascular diseases.

The VCCF will need to be continually updated in terms of coverage and quality. Coverage depends on identifying new FTUs and their corresponding ASs and CTs. Quality depends on complete identification of the vasculature path and accurate definition of the FTUs. For example, there are different models of FTU for the liver: the popular hexagonal model of liver lobule and the choleohepaton model [15]. A survey with organ experts will be conducted in the future to improve the FTUs and VCCF.

Summary

In this paper, we present a draft VCCF that connects 10 FTUs and their corresponding ASs and CTs to the heart organ. We also propose to lay out the VCCF using bubble-tree layouts that automatically visualize FTUs and their corresponding anatomically indistinguishable CTs. While many vessels in the vasculature pathway are yet to be identified, this work has helped refine and make progress on the missing vessels in the VCCF and register them in the Uber-anatomy ontology (UBERON).

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