Creating a map of the human blood vasculature: anatomical level and beyond

Griffin M Weber, MD, PhD
Department of Biomedical Informatics
Harvard Medical School
weber@hms.harvard.edu

Avinash Boppana
PhD Student
MIT
asboppana@gmail.com

Vasculature domain experts: Sujin Lee, Rajeev Malhotra, Marc Halushka

Funding from NIH Award OT2OD026671
Create a map of all the **cells** in the human body

Create a map of all the **blood vessels**

Create a map of all the **buildings** in a country

Create a map of all the **roads**
Create a map of all the **buildings** in the country

Describing a building's location

42.302708, -71.072105  Latitude-Longitude Coordinate System

49 Oldfields Rd  Road-based
Boston, MA 02121  Coordinate System

Can we describe the location of cells based on position relative to a nearby blood vessel?
Cells need to be near blood vessels to receive oxygen and nutrients

Buildings need to be near roads so that people and packages can get to them
Creating a map of roads by starting with the highways

Average Daily Long-Haul Truck Traffic on the National Highway System: 2015

Note: Major flows include domestic and international freight moving by truck on highway segments with more than twenty-five FAF trucks per day and between places typically more than fifty miles apart.


https://interestingengineering.com/the-complex-history-of-the-us-interstate-highway-system
Back Bay

Downtown

https://www.zumper.com/blog/best-neighborhoods-in-boston-for-newcomers/

https://www.75statestreetgarage.com/nearby-destinations/financial-district/

Vascular Common Coordinate Framework (VCCF)

Vascular Common Coordinate Framework (VCCF)

Complexity of the VCCF

Body Worlds?

Eduard Weber 1978
VCCF Construction – UBERON "Top-Down" Approach

arterial blood vessel [378]
artery [361]
--systemic a. [197]
--respiratory system a.
arteriole [7]
aorta
=====
kidney arterial
respiratory arterial

venous blood vessel [322]
vein [297]
--systemic v. [62]
-----craniocervical region v. [51]
--thoracic cavity v.
-----vena cava
--thoracic v. [10]
--vein of abdomen [16]
venule [2]
venous sinus
=====
coronary sinus
renal venous

capillary [21]
continuous
fenestrated
--sinusoid
-----hepatic sinusoid
-----spleenic sinusoid
=====
kidney
--glomerular
--peritubular
respiratory
--pulmonary
coronary
liver

blood vessel [778]

head [140]
trunk [125]
appendage [83]

respiratory system [29]

brain [21]

main bronchus
trachea
(lung)
cerebral

limb [79]

thoracic segment
abdominal segment

lung
abdomen
pelvis

forelimb
hindlimb

kidney
liver

arm
manus
leg
pes

upper arm
lower arm
manus digit
upper leg
lower leg
pedal digit

"is_a" relationships

720 items in arterial/venous/capillary classes
439 items in body part blood vessel classes

[N] = number of vessels in subtree
VCCF Construction – UBERON "Bottom-Up" Approach
Connecting 747 Individual Vessels in UBERON

UBERON Only
- Connected vessels
- Unconnected vessels

UBERON + Manually Added Links
- Left ventricle - arteries
- Right atrium - veins
- Left atrium - pulmonary veins
- Right ventricle - pulmonary arteries

294 "part_of", "branching_part_of", "develops_from", and "tributary_of" relations
Visualizing branching connections for quality checks
Review Process

Subject matter experts
  • Marc Halushka – Vascular pathology (Johns Hopkins)
  • Rajeev Malhotra – Vascular biology (Mass General Hospital, Harvard)
  • Sujin Lee – Vascular surgery (Mass General Hospital, Harvard)

Merge process
  • Kept change if made by both MH and RM+SL
  • Kept change if made one and the other made no change
  • Manually reviewed if each made a different change

Cleanup
  • Misspellings, standardizing dashes, duplicates
  • Paired vessels, anastomoses, variants

Publish
  • 869 vessels; 19 levels of depth; 371 vessels (43%) in UBERON
  • Construct HuBMAP Anatomical Structures, Cell Types, Biomarker (ASCT+B) table
  • References to Wikipedia, Radiopaedia, Gray's Anatomy (1858); Netter (1981)
  • Saved additional information we collected into an "extended" VCCF data table
Connections to other organ ASCT+B tables

https://docs.google.com/spreadsheets/d/1RNNywmOjb2MmWFFC62VlG08mSQKnspusuSlqsPiiGbl8/edit#gid=0

<table>
<thead>
<tr>
<th>BodyPart</th>
<th>Vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>abdominal cavity</td>
<td>6</td>
</tr>
<tr>
<td>abdominal cavity;thoracic cavity</td>
<td>2</td>
</tr>
<tr>
<td>abdominal wall</td>
<td>7</td>
</tr>
<tr>
<td>adrenal gland</td>
<td>7</td>
</tr>
<tr>
<td>arm</td>
<td>25</td>
</tr>
<tr>
<td>brain</td>
<td>65</td>
</tr>
<tr>
<td>brainstem</td>
<td>2</td>
</tr>
<tr>
<td>cerebellum</td>
<td>6</td>
</tr>
<tr>
<td>clitoris</td>
<td>2</td>
</tr>
<tr>
<td>diaphragm</td>
<td>13</td>
</tr>
<tr>
<td>ear</td>
<td>12</td>
</tr>
<tr>
<td>esophagus</td>
<td>4</td>
</tr>
<tr>
<td>eye</td>
<td>21</td>
</tr>
<tr>
<td>face</td>
<td>57</td>
</tr>
<tr>
<td>foot</td>
<td>32</td>
</tr>
<tr>
<td>hand</td>
<td>25</td>
</tr>
<tr>
<td>head</td>
<td>48</td>
</tr>
<tr>
<td>heart</td>
<td>21</td>
</tr>
<tr>
<td>heart chamber</td>
<td>4</td>
</tr>
<tr>
<td>kidney</td>
<td>26</td>
</tr>
<tr>
<td>large intestine</td>
<td>20</td>
</tr>
<tr>
<td>larynx</td>
<td>2</td>
</tr>
<tr>
<td>leg</td>
<td>48</td>
</tr>
<tr>
<td>liver</td>
<td>20</td>
</tr>
<tr>
<td>lung</td>
<td>38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BodyPart</th>
<th>Vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>neck</td>
<td>39</td>
</tr>
<tr>
<td>nose</td>
<td>1</td>
</tr>
<tr>
<td>ovary</td>
<td>5</td>
</tr>
<tr>
<td>pancreas</td>
<td>4</td>
</tr>
<tr>
<td>pancreas;small intestine</td>
<td>10</td>
</tr>
<tr>
<td>pelvis</td>
<td>65</td>
</tr>
<tr>
<td>penis</td>
<td>11</td>
</tr>
<tr>
<td>pituitary gland</td>
<td>2</td>
</tr>
<tr>
<td>rectum</td>
<td>3</td>
</tr>
<tr>
<td>scrotum</td>
<td>2</td>
</tr>
<tr>
<td>shoulder</td>
<td>14</td>
</tr>
<tr>
<td>small intestine</td>
<td>12</td>
</tr>
<tr>
<td>spinal cord</td>
<td>41</td>
</tr>
<tr>
<td>spleen</td>
<td>7</td>
</tr>
<tr>
<td>stomach</td>
<td>10</td>
</tr>
<tr>
<td>stomach;small intestine</td>
<td>1</td>
</tr>
<tr>
<td>testis</td>
<td>6</td>
</tr>
<tr>
<td>thoracic cavity</td>
<td>13</td>
</tr>
<tr>
<td>thoracic wall</td>
<td>77</td>
</tr>
<tr>
<td>thymus</td>
<td>2</td>
</tr>
<tr>
<td>thyroid gland</td>
<td>9</td>
</tr>
<tr>
<td>urinary bladder</td>
<td>6</td>
</tr>
<tr>
<td>uterus</td>
<td>7</td>
</tr>
<tr>
<td>vagina</td>
<td>8</td>
</tr>
</tbody>
</table>
Connections to other organ ASCT+B tables

https://docs.google.com/spreadsheets/d/1RNNywmojb2MmWFFC62VlGo8mSQKnspsuSlqsPiiGbl8/edit#gid=0

<table>
<thead>
<tr>
<th>BodyPart</th>
<th>BodyPartURI</th>
<th>Vessel</th>
<th>VesselType</th>
<th>VesselURI</th>
<th>VesselIFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>abdominal cavity</td>
<td>UBERON 0003684</td>
<td>abdominal aorta</td>
<td>artery</td>
<td>UBERON 001516</td>
<td>fma3789</td>
</tr>
<tr>
<td>abdominal cavity</td>
<td>UBERON 0003684</td>
<td>celiac artery</td>
<td>artery</td>
<td>UBERON 001640</td>
<td>fma50737</td>
</tr>
<tr>
<td>abdominal cavity</td>
<td>UBERON 0003684</td>
<td>inferior mesenteric artery</td>
<td>artery</td>
<td>UBERON 001163</td>
<td>fma14750</td>
</tr>
<tr>
<td>abdominal cavity</td>
<td>UBERON 0003684</td>
<td>inferior mesenteric vein</td>
<td>vein</td>
<td>UBERON 0001215</td>
<td>fma15351</td>
</tr>
<tr>
<td>abdominal cavity</td>
<td>UBERON 0003684</td>
<td>superior mesenteric artery</td>
<td>artery</td>
<td>UBERON 001162</td>
<td>fma14749</td>
</tr>
<tr>
<td>abdominal cavity</td>
<td>UBERON 0003684</td>
<td>superior mesenteric vein</td>
<td>vein</td>
<td>UBERON 0001158</td>
<td>fma14332</td>
</tr>
<tr>
<td>abdominal cavity, thoracic cavity</td>
<td>UBERON 0003684, UBERON 0002224</td>
<td>aorta</td>
<td>artery</td>
<td>UBERON 000547</td>
<td>fma3734</td>
</tr>
<tr>
<td>abdominal cavity, thoracic cavity</td>
<td>UBERON 0003684, UBERON 0002224</td>
<td>inferior vena cava</td>
<td>vein</td>
<td>UBERON 001072</td>
<td>fma10561</td>
</tr>
<tr>
<td>abdominal wall</td>
<td>UBERON 0003697</td>
<td>inferior epigastric artery</td>
<td>artery</td>
<td>UBERON 001354</td>
<td>fma20666</td>
</tr>
<tr>
<td>abdominal wall</td>
<td>UBERON 0003697</td>
<td>inferior epigastric vein</td>
<td>vein</td>
<td>UBERON 0007354</td>
<td>fma21162</td>
</tr>
<tr>
<td>abdominal wall</td>
<td>UBERON 0003697</td>
<td>musculophrenic artery</td>
<td>artery</td>
<td>UBERON 000632</td>
<td>fma10645</td>
</tr>
<tr>
<td>abdominal wall</td>
<td>UBERON 0003697</td>
<td>superficial epigastric artery</td>
<td>artery</td>
<td>UBERON 0034964</td>
<td>fma20734</td>
</tr>
<tr>
<td>abdominal wall</td>
<td>UBERON 0003697</td>
<td>superficial epigastric vein</td>
<td>vein</td>
<td>UBERON 0014692</td>
<td>fma44318</td>
</tr>
<tr>
<td>abdominal wall</td>
<td>UBERON 0003697</td>
<td>superior epigastric artery</td>
<td>artery</td>
<td>UBERON 0017153</td>
<td>fma10646</td>
</tr>
<tr>
<td>abdominal wall</td>
<td>UBERON 0003697</td>
<td>superior epigastric vein</td>
<td>vein</td>
<td>UBERON 0017155</td>
<td>fma4731</td>
</tr>
<tr>
<td>adrenal gland</td>
<td>UBERON 0002389</td>
<td>inferior suprarenal artery</td>
<td>artery</td>
<td>UBERON 0012056</td>
<td>fma92824</td>
</tr>
<tr>
<td>adrenal gland</td>
<td>UBERON 0002389</td>
<td>left middle suprarenal artery</td>
<td>artery</td>
<td>UBERON 0014756</td>
<td></td>
</tr>
<tr>
<td>adrenal gland</td>
<td>UBERON 0002389</td>
<td>left suprarenal vein</td>
<td>vein</td>
<td>UBERON 0035463</td>
<td>fma14349</td>
</tr>
<tr>
<td>adrenal gland</td>
<td>UBERON 0002389</td>
<td>middle suprarenal artery</td>
<td>artery</td>
<td>UBERON 0012173</td>
<td>fma14753</td>
</tr>
<tr>
<td>adrenal gland</td>
<td>UBERON 0002389</td>
<td>right middle suprarenal artery</td>
<td>artery</td>
<td>UBERON 0014755</td>
<td></td>
</tr>
<tr>
<td>adrenal gland</td>
<td>UBERON 0002389</td>
<td>right suprarenal vein</td>
<td>vein</td>
<td>UBERON 0035435</td>
<td>fma14343</td>
</tr>
<tr>
<td>adrenal gland</td>
<td>UBERON 0002389</td>
<td>superior suprarenal artery</td>
<td>artery</td>
<td>UBERON 0001198</td>
<td>fma14683</td>
</tr>
</tbody>
</table>
Merging Paired Vessels and Sets of Vessels

- **abdominal aorta**
  - **left renal artery**
  - **right renal artery**

**ForBranchesSee**

- **renal artery**
  - **anterior inferior segmental renal artery**
  - **anterior superior segmental renal artery**
  - **interlobar renal artery**
  - **segmental renal artery**
    - **anterior inferior segmental renal artery**
    - **anterior superior segmental renal artery**
  - **inferior segmental renal artery**
  - **posterior segmental renal artery**
  - **superior segmental renal artery**

**MergedVessel**
Selecting a Vessel Direction and Removing Loops

BranchesFrom side of vessel is side closer to the heart based on blood flow direction
Variants (Many Examples)

Internal Iliac Artery

Liver Arteries

Anterior Communicating Artery Complex

Mesenteric Vasculature


https://www.sciencedirect.com/science/article/pii/S2211568413003781#fig0010

https://www.jocn-journal.com/article/S0967-5868(20)31460-0/fulltext

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036491/
Variants - Spinal Arteries

Branches From

Anastomoses

Kanazawa, 2019, Anatomical Science International, 95:97-103
### Vascular Smooth Muscle Cells:
- α-Smooth muscle actin
- SM22α
- Calponin
- Myocardin
- H-caldesmon
- Smoothelin
- Telokin
- Meta-vinculin
- Desmin
- CRBP-1
- Matrix gla protein
- Smemb

### Fibroblasts in the vascular adventitial layer:
- Responsible for depositing abundant collagen fibrils around vessels
- Fibroblast specific protein 1 (FSP-1)
- Discoidin domain receptor 2 (DDR2)
- Collagen1a1
- Enolase 2
- Gli1
- Patched-1 and Patched-2
- Tcf21

### Pericytes (periendothelial/subendothelial location):
- Proximity to capillaries
- Express PDGFRβ, NG2 (chondroitin sulfate proteoglycan 4), CD146, CD13, and Desmin, but none of these are specific for pericytes.

### Vascular progenitor cells in the adventitial layer:
- Stem cell antigen-1 (Sca1)
- CD34 (non-specific)

### Cardiac Endocardium:
- Challenging since different types of progenitor cells (e.g., precardiac mesoderm and vascular endothelium)
- VE-Cadherin (CD144)
- PECAM-1 (CD31)
- FLK1 (non-specific marker)

### Specific Subpopulations of Endothelial Cells:
- Blood Brain Barrier: alkaline phosphatase (TNAP), γ-glutamyltranspeptidase (GGT), monoamine oxidase (MAO), lack of leukocyte adhesion molecules (i.e., VCAM, ICAM), lack of thrombomodulin
- Sinusoidal (liver, spleen, bone marrow) that have minimal basement membrane and lack classical tight junctions: lack of thrombomodulin (CD141) and CD34; presence of E-selectin (CD62E) under normal conditions, expression of VAP-1, Stabilin-1, L-SIGN
- Lymphatic Endothelial Cells: Flt-4 (VEGFR-3), Desmoplakin, LYVE-1, lack CD34
- High Endothelial Venule: VAP-1, VAP-2, MECA79

### Vascular Cell Types and Biomarkers (From Rajeev Malhotra)


Currently in Extended VCCF Table

- Vessel name
- Branches from
- Male or female
- Anastomoses
- Part of the body supplies or drains [roughly]
- Branching sequence [mostly]
- Paired and sets of vessels

Still in development

- Anatomical variants and prevalence
- Vessel geometry (length and diameter)
- Cell types and biomarkers
- Microvasculature (branching depth, branching angle, diameter, length, number)

https://docs.google.com/spreadsheets/d/13g01Jtz0jYNrKZx7eF6njWtkMf5O6JNSwwWvzpqGyZqE/edit#gid=144480668
Thank you!