ApiNATOMY: Towards Multiscale Views of Human Anatomy

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Abstract. Physiology experts deal with complex biophysical relationships, across multiple spatial and temporal scales. Automating the discovery of such relationships, in terms of physiological meaning, is a key goal to the physiology community. ApiNATOMY is an effort to provide an interface between the physiology expert's knowledge and all ranges of data relevant to physiology. It does this through an intuitive graphical interface for managing semantic metadata and ontologies relevant to physiology. In this paper, we present a web-based ApiNATOMY environment, allowing physiology experts to navigate through circuitboard visualizations of body components, and their cardiovascular and neural connections, across different scales. Overlaid on these schematics are graphical renderings of organs, neurons and gene products, as well as mathematical models of processes semantically annotated with this knowledge.

1 Introduction

Knowledge of physiology is extensive and complex. To provide software support for using and manipulating physiology data, formalization of the knowledge is required. An *ontology* consists of a set of terms, and their relations, representing a specific domain of knowledge. They are created and maintained by knowledge domain experts, and are used as computer-readable taxonomies by software tools to support knowledge management activities in that domain. When knowledge is formalised in this way, it is possible to record explicit descriptions of data elements in the relevant domain using ontologies; this is the process of semantic annotation or the generation of *semantic metadata*.

For example, physiology experts deal with complex biophysical operations across multiple spatial and temporal scales, which they represent in terms of the transfer of energy from one form to another and/or from one anatomical location to another. Different kinds of descriptions of these biophysical operations are produced by different disciplines in biomedicine. For instance, (i) a medical doctor may describe the mechanism by which a stone in the ureter causes damage in the kidney; (ii) a pharmacologist may depict the process by which a drug absorbed from gut transits to the hip joints where it reduces inflammation; (iii) a molecular geneticist may trace the anatomical distribution of the expression of a particular gene to understand the cause of a skeletal malformation; and, (iv) a

bio-engineer may build a mathematical model to quantify the effect of hormone production by the small intestine on the production of bile by the liver. These descriptions take diverse forms, ranging from images and free text (e.g., journal papers) to models bearing well-defined data (e.g., from clinical trials) or sets of mathematical equations (which might be used as input for a simulation tool).

The physiology community is investing considerable effort in building ontologies for the annotation and semantic management of such resources. For example, a number of reference ontologies have been created to represent gene products [3], chemical entities [4], cells [5] and gross anatomy [6]. Together, these ontologies consist of hundreds of thousands of terms, such that the volume of semantic metadata arising from resource annotation is considerable.

Unfortunately, conventional technology for the visualization and management of ontologies and metadata is not usefully accessible to physiology experts, as they involve unfamiliar, abstract technicalities. Having to become technically proficient with such technology is a burden few physiology experts can bear without losing touch with their long term goals. Rather, domain experts should be able to manage data based on a familiar perspective, in which its meaning is made explicit in terms of the expert's own knowledge; a long standing challenge in knowledge engineering.

In this paper, we present ApiNATOMY, a web-based environment that allows physiology experts to navigate through circuitboard visualizations of body components, and their cardiovascular and neural connections, across different scales. It supports a plugin infrastructure to overlay graphical renderings of organs, neurons and gene products on these schematics, in support of biomedical knowledge management use cases discussed in the next section.

The remainder of the paper is structured as follows: Section 2 gives an overview of the ontology-, metadata- and data-resources that we focused on for the ApiNATOMY prototype, and outline key use-case scenarios that motivate our work. Sections 3 and 4 then discuss the visualization techniques we applied to arrange and display those resources. Section 5 provides some insight into the implementation of the prototype. Finally, Sections 6 and 7 offer an overview of related efforts in the field, and conclude the paper with a discussion of the anticipated implications of our tool, as well as planned future work.

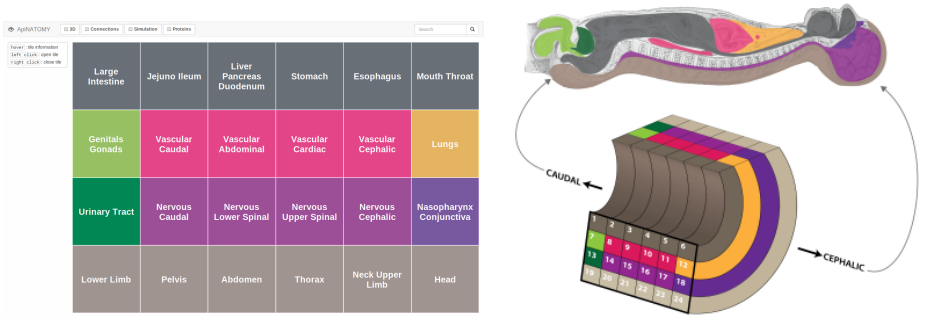
2 Use Cases and Data Resources

In this section, we briefly discuss a core use case for the ApiNATOMY application: the generation of interactive schematics in support of genomics and drug discovery studies. We introduce some of the key ontology- and data-resources required in this case. In so doing, we set the stage for an exposition of our early-stage results in the ApiNATOMY application effort.

The domains of genomics and drug discovery are heavily dependent on physiology knowledge, as both domains take into account the manufacture of proteins in different parts of the body and the transport of molecules that interact with those proteins, such as drugs, nutrients, and other proteins. We aim to provide

an interactive, schematic overview of data resources important to these domains. This includes gene expression data (e.g., [7]), and data on the transport routes taken by molecular interactors (e.g., [8]). Such data may be usefully depicted in the form of a physiology *circuitboard*.

In ApiNATOMY, a physiology circuitboard schematic consists of an *anatomical treemap* and an overlay of *process graphs*. Our earlier prototypes [9,10] presented treemaps of the Foundational Model of Anatomy (FMA) ontology [6]. Nesting of one treemap tile inside another indicated that the term associated with the child tile is either a mereotopological *part* or a *subclass* of the term associated with the parent tile. Our newest prototype also adopts this convention.



(a) Initial view of ApiNATOMY

(b) Longitudinal section through the male human body, justifying the layout

Fig. 1. The main 24-tile layout of the ApiNATOMY circuitboard

The ApiNATOMY graphical user interface (Figure 1(a)) supports user interaction with circuitboard schematics via point-and-click navigation of the treemap content. The upper level of the anatomical treemap is arranged to resemble the longitudinal section through the middle of the human body (Figure 1(b)). Each of the organs in the plan is composed of multiple tissues and sub-organs. The GUI supports data filtering across multiple levels and contextual zooming into selected areas.

This type of interaction extends also to the overlayed process graphs. These graphs project routes of blood flow processes linking different regions of the human body —using data generated in [11]—, as well as transport processes along neurons of the central nervous system (i.e., the brain and spinal cord) — using data obtained via the Neuroscience Information Framework [12].

The ApiNATOMY GUI is built from inception as a three-dimensional environment. This facilitates interaction not only with 3D renderings of the circuit boards themselves, but also with a wide range of geometry/mesh formats for volumetric models of biological structure across scales. For instance, it is already possible to overlay Wavefront `.obj` data from BodyParts3D [13] as well as `.swc` data provided by `neuromorpho.org` [14]. Easy access to such visual resources is

critical to the understanding of long-range molecular processes in genomics and drug discovery research.

In the next two sections, we discuss our techniques for constraining treemap layouts to generate stable anatomical treemaps (Section 3.1), designing and overlaying physiological communication routes for the cardiovascular and neural systems (Sections 3.2 and 3.3), and depicting three-dimensional models of organs and protein architecture diagrams for the anatomical overview of gene expression data (Section 4).

3 Visualizing Ontologies and Connectivity Data

In this section we discuss our considerations in the visualization of ontological hierarchies using treemaps, and connectivity data using graph overlays.

3.1 Treemaps

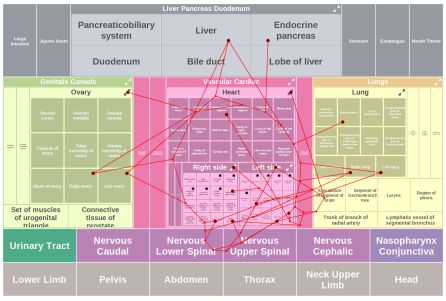
Treemaps [15] visualize hierarchical data by using nested shapes in a space-filling layout. Each shape represents a geometric region, which can be subdivided recursively into smaller regions. The standard shape is a rectangle. Nodes in a treemap, also called *tiles*, represent individual data items. Node size, color and text label can be used to represent attributes of the data item. In interactive environments such as ApiNATOMY, it is possible to navigate between different layers and zoom into selected tiles [16].

We do not use node size to represent information. We focus on tile color and *position*. Tiling algorithms used for typical applications of treemaps (e.g., visualizing the structure of a computer file system) do not usually associate tile positions with any characteristic of the data, and as such, it does not matter if tiles shift around arbitrarily. But this is not the case in our scenario. As shown in Figure 1, relative tile positions are quite relevant, and should be kept stable while the user filters data and zooms in and out. Otherwise, their perception of the data could be easily disrupted. Moreover, the user should be able to enforce constraints on (relative) tile positions to make the treemap views structurally resemble body regions. Hence, we developed a stable and customizable *tiling algorithm* that arranges tiles according to a given template [10].

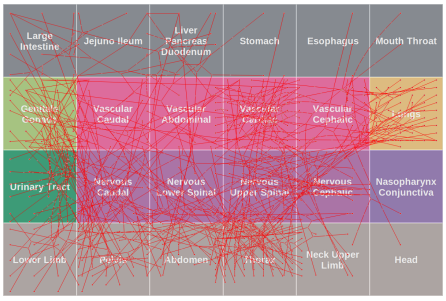
The schematic body plans created using template-based treemaps can be seen in Figure 1. Figure 1(a) shows the top level 24 tile body anatomy plan. The choice of this layout is explained by Figure 1(b), which shows how it can conceptually wrap around the longitudinal axis of the human body. The treemap layout is controlled by the (default) templates and remains stable during navigation.

3.2 Process Graphs

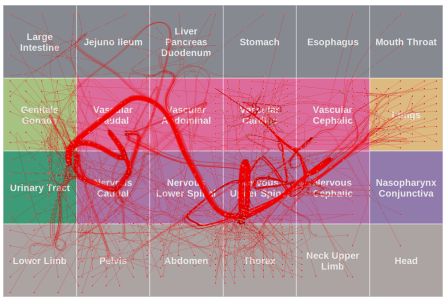
With the treemap-based body plans as background, we overlay the schematic representation of *body systems* such as circulatory, respiratory, or nervous systems. Body systems are essentially graphs with nodes corresponding to body



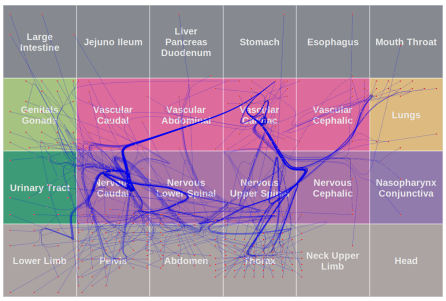
(a) Selected blood vessel connections



(b) Arterial connections from left ventricle



(c) Bundled connections from left ventricle



(d) Bundled connections to right atrium

Fig. 2. Overlaying cardiovascular connections. A straightforward approach works well when the number of connections is limited (a). When many connections need to be displayed, we quickly lose overview (b). This is mitigated by employing edge-bundling techniques (c,d).

parts (treemap tiles) or entities inside of body parts (e.g., proteins, cells), and edges corresponding to organ system compounds such as blood vessels or nervous connections that pass through such body parts or sub-parts. They may also contain auxiliary nodes that are not represented on the treemap but still carry important biomedical information.

Body systems are intrinsically complex and require efficient data visualization techniques to help avoid clutter induced by the large amount of graph edges and their crossings. Our users need to trace individual connections of body systems, as well as view large parts at once. Edge bundling techniques [17,18,19] have been proposed to improve perception of large, dense graphs. Such techniques generally rely on edge rerouting strategies that are either solely targeted at improving visual perception (by using the positions of nodes) or exploit the relationships among connectivity data as guidelines for a more natural allocation of graph edges and nodes. Our application requires a mixture of these techniques.

If there are too many edges to get a clear overview of the data —as in Figure 2(b), which shows the full connectivity graph for the left ventricle (7101) on the top-level body plan— we can apply hierarchical edge bundling techniques that use path structure to bundle common sub-paths. The result for the left

ventricle is shown in Figure 2(c), which gives a much nicer overview. The result for the right atrium is shown in Figure 2(d).

After a one-time pre-processing to import data from available external sources, we store connectivity data in a convenient format. A user can interact with and edit this data using the tool.

3.3 Analyzing the Connectivity Data: an Example

Consider the blood vessels in the human body. Our initial dataset on this is a graph based on the FMA ontology, and consists of approximately 11,300 edges and over 10,000 distinct nodes. In this graph, an edge represents a flow process over an unbranched blood-vessel segment. Nodes represent blood vessel junctions and end-points. Samples of records from the dataset are shown in Table 1.

Segment	T.	FMA	Node 1	Node 2	Description
121a	2	62528	62528_2	62528_4	Arterioles in Microcirculation segment of Wall of left inferior lobar bronchus
121c	2	62528	62528_4	62528_5	Capillaries in Microcirculation segment of Wall of left inferior lobar bronchus
121v	2	62528	62528_3	62528_5	Venules in Microcirculation segment of Wall of left inferior lobar bronchus
⋮	⋮	⋮	⋮	⋮	⋮
8499	1	69333	8498_0	62528_2	Arterial Segment 8499 of Trunk of left second bronchial artery from origin of supplying terminal segment to the arteriolar side of the Wall of left inferior lobar bronchus MC
9547	3	66699	9546_0	62528_3	Venous Segment 9547 of Trunk of left bronchial vein from origin of supplying terminal segment to the venular side of the Wall of left inferior lobar bronchus MC

Table 1. Vascular connectivity data from the FMA ontology. The first column is a unique segment identifier. The second shows the type of a segment (1: arterial, 2: microcirculation, 3: venous, and 4: cardiac chamber). The third contains FMA IDs. The fourth and fifth contain identifiers of the two connected nodes.

A *microcirculation (MC)* is represented by three edges connected in series: one representing tissue arterioles, a second for the bed of capillaries, and a third for the venules. In Table 1, the anatomical entity in which the MC is embedded is 62528 ("Wall of left inferior lobar bronchus"). The topology of its MC segment connectivity is as follows:

$$62528\_2 \xrightarrow{121a} 62528\_4 \xrightarrow{121c} 62528\_5 \xleftarrow{121v} 62528\_3.$$

MC segment 121a is supplied with blood by the arterial segment 8499, and MC segment 121v is drained of blood by the venous segment 9547.

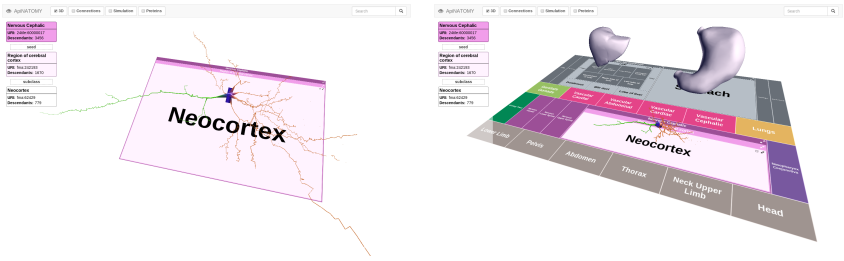
The accurate and comprehensible visualization of the cardiovascular system requires complex pre-processing; a biomedical expert in our team identified about 12 rules for the extraction of relevant data from the full dataset. For illustration purpose, Figure 2 shows only paths connecting MCs of the walls of the heart (i.e., wall of left ventricle, left atrium, right ventricle or right atrium) to MCs belonging to the sub-organs of the tiles in our upper level 24 tile body plan. To obtain this view, we looked for the shortest paths — due to the way the data is represented in the initial data set, cycles are possible. For example, the path from the left ventricle to the wall of left inferior lobar bronchus MC is $7101 \rightarrow 2406 \rightarrow \cdots \rightarrow 8499 \rightarrow 62528$, and the path from there to the right atrium is $7096 \leftarrow 771 \leftarrow \cdots \leftarrow 9546 \leftarrow 9547 \leftarrow 62528$.

The first and the last IDs in this path correspond to the tiles in the treemap, while the intermediate IDs will be represented using auxiliary nodes with undefined coordinates. One of the issues we encountered is the need to determine optimal positions for these nodes. Since several paths can have common sub-paths, as shown in Figure 2(a), the intermediate nodes should be positioned so as to minimize the overall path length. This motivates our application of the *sticky force-directed graph visualization* method [20,21] in which a sub-set of nodes have fixed coordinates, and the coordinates of the other nodes is determined by simulating imaginary forces applied by their edges.

4 Visualizing Models and Metadata

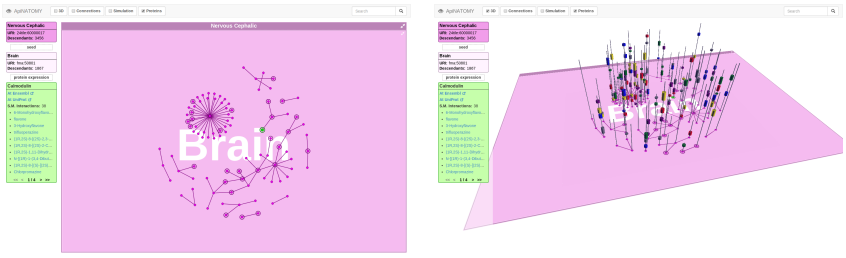
The entities in the ApiNATOMY ontologies have various data associated with them, to which they are explicitly linked via semantic metadata annotations. This includes static and dynamic 3D models of body organs and their subsystems. For instance, we extract and display neuronal reconstructions and associated metadata from `http://neuromorpho.org` [14]. Figure 3(a) shows a sample neuron model associated with the neocortex (reached through "Nervous Cephalic" → "Region of cerebral cortex" → "Neocortex"). ApiNATOMY allows users to show multiple 3D objects together in their proper context. For example, Figure 3(b) shows a screenshot including the "Neocortex" neuron, as well as 3D models of the "Liver" and "Stomach", retrieved from BodyParts3D [13].

ApiNATOMY also supports the visualization of protein- and drug-interaction networks (Figure 4(a)) that are represented as graphs on top of treemap tiles. We are in the process of acquiring and integrating relevant data from the Ensembl genomic database [22]. In Ensembl, gene models are annotated automatically using biological sequence data (e.g. proteins, mRNA). We query this database to extract genes, transcripts, and translations with related protein features, such as PFAM domains. ApiNATOMY generates diagrams of protein-interactions and positions them on tiles where the corresponding genes are expressed. For easy access, protein diagrams are able to represent domain features in the form of color-coded 3D shapes extending from the circuitboard (Figure 4(b)).



(a) A neuron in the "Neocortex" (b) Multiple 3D models in context

Fig. 3. Visualizing static 3D models



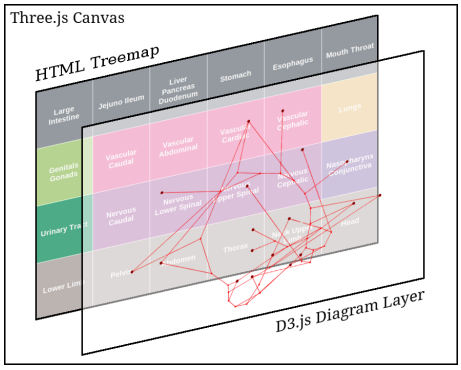
(a) Protein interactions in 2D (b) Protein features in 3D

Fig. 4. Visualizing protein expression, protein interaction and protein features

5 Implementation

In this section we discuss a number of implementation aspects of ApiNATOMY. For maximum compatibility across operating systems as well as handheld devices, the whole application is written in Javascript. The main framework in use is AngularJS, which provides a Model-View-Controller architecture, as well as two-way databinding. Connectivity- and protein-protein interaction diagrams (Figures 2 and 4(a)) are generated using D3.js, and all 3D functionality (Figures 3 and 4(b)) is implemented using Three.js, which provides a convenient abstraction layer over WebGL.

The circuit-board is rendered with essentially three layers, which are shown in Figure 5. The treemap is generated with plain HTML. On top of this, a partly transparent diagram layer is rendered by D3.js. The positions of the tiles and the positions of the diagram nodes are synchronized with AngularJS two-way databinding. When 3D mode is activated, Three.js takes control of both layers. Besides rendering 3D objects with WebGL, it can manipulate HTML elements using CSS 3D transforms. When using both rendering engines in conjunction, Three.js can keep WebGL and HTML perfectly synchronized. Together with AngularJS two-way databinding, we get very fine control of positioning. This is demonstrated particularly well in Figure 4(b). To render `.swc` neuron files (Figure 3), ApiNATOMY uses SharkViewer, an open source Three.js library developed by the Howard Hughes Medical Institute [23].



Able to Control Position:

Three.js Canvas ⟶ HTML Treemap

Three.js Canvas ⟶ D3.js Layer

Able to Add Content:

HTML Treemap ⟶ D3.js Layer

HTML Treemap ⟶ Three.js Canvas

D3.js Layer ⟶ Three.js Canvas

Fig. 5. The three layers of circuitboard visualization and their interaction.

A separate module keeps track of the entity under focus. Whenever the mouse hovers over a specific tile or object, it is highlighted and its hierarchical information is shown in the left side-panel (Figures 3 and 4). Clicking on the object fixes this focus, allowing the user to interact with the information in the side-panel.

This direct feedback has another purpose. An ontology need not necessarily be a tree. In the FMA ontology, for example, different branches may join, making it a directed acyclic graph. A treemap, however, is only meant for visualizing trees. We compensate for this by allowing the same entity to be represented by more than one tile at the same time. To reinforce this intuition, all such tiles are highlighted in unison when the mouse hovers over any one of them. Only one visible tile per entity may be opened up to show its children. Such a tile is considered 'active', and only active tiles participate in the visualization of cross-tile connectivity data.

6 Rationale for our approach and related work in anatomy and physiology knowledge visualization

The need for the multi-scale visualization and analysis of human body systems is well recognized by biomedical communities. For example, the 3D Multiscale Physiological Human initiative deals with combinations of physiological knowledge and computational approaches to help scientists in biomedicine to improve diagnostics and treatments of various disorders [24,25]. In addition, numerous anatomy-related taxonomies and databases have been created and are widely used by researchers in the biomedical field [26]. While various generic visualization techniques can be used to display biomedical ontologies [2], to the best of our knowledge, ApiNATOMY is the first systematic approach to integrate such knowledge in one extensible and configurable framework.

Among the most effective taxonomy visualization techniques are space-filling diagrams, and in particular, treemaps. de Bono et al. [9] describes limitations of existing treemapping tools for biomedical data visualization. To overcome these limitations, we introduced a generic method to build custom templates which

is applied in our tool to control layout of ApiNATOMY body tissues. Among the advantages of the proposed treemapping method are customizable layouts, visualization stability and multi-focus contextual zoom. The detailed comparison of our method with existing treemaping algorithms can be found in [10]. Burch and Diehl [27] discuss the ways to display multiple hierarchies and conclude that overlaying connectors on top of treemaps is the most visually attractive and easy to follow approach. Among the alternative options they considered are separate, linked and colored tree diagrams, sorted and unsorted matrices and sorted parallel coordinate views. Regarding the way to layout the connectors, two naive methods were considered: straight connections and orthogonal connections.

Our application requires multiple taxonomies consisting of thousands of items to be displayed on relatively small screens of handhold devices. We employ the same visualization technique with more advanced treemapping and connector layout algorithms. Due to the potentially large amount of vascular connectivity data, we employ the hierarchical edge bundling technique [17] that results in an intuitive and realistic depiction of blood flow across a treemap-based plan of the human body. In contrast to the scenarios in the aforementioned work, not every node in our vascular connection dataset has a corresponding node in the treemap. Thus, force-directed graph drawing method [28] is added to the scene to find optimal positions of intermediate junctions on the paths that connect the root of the taxonomy (i.e. in the heart) with its leaves (body tissues shown as treemap tiles). The variation of the force-bundling method suitable for our application is known as sticky force-directed placement [20] which allows to fix the positions of certain nodes and allocate other nodes to achieve mechanical equilibrium between forces pulling the free nodes towards fixed positions.

Other potentially useful methods did not provide the desired result. The first approach we tried consists of applying the force-directed edge bundling method [29] to bundle entire paths among the heart chambers and body tissues, but this does not reflect the hierarchical structure of vascular connectivity graph. The second approach, force-based edge bundling over a graph produced by sticky force-directed node allocation algorithm results into unnatural distortion of short edges towards each other. Other edge-bundling methods(e.g., [18,19,30]) operate on graphs with known node positions and thus would produce visualizations on our data that suffer from similar problems.

7 Conclusions and Future Work

The core goal for ApiNATOMY is to put clinicians, pharmacologists, basic scientists and other biomedical experts in direct control of physiology knowledge management (e.g. in support of integrative goals outlined in [31]). As the domain of physiology deals with processes across multiple anatomical scales, the schematic ApiNATOMY approach provides a more flexible and customizable depiction of process participants, and the routes they undertake, compared to conventional methods of anatomy navigation that constrain visualization to regional views of very detailed and realistically proportioned 3D models (such as

Google Body [32]). In this paper, we presented our initial results in the development of a generic tool that creates an interactive topological map of physiology communication routes. These routes are depicted in terms of (i) treemaps derived from standard reference anatomy ontologies, as well as (ii) networks of cardiovascular and neural connections that link tiles within these treemaps. These topological maps, also known as circuitboard schematics, set the stage for the visual management of complex genomic and drug-related data in terms of the location of gene products and the route taken by molecules that interact with them. While the implementation of our tool is still in its early stages, we have already started taking steps in preparation for future developments, supporting:

- the visually-enhanced construction of mathematical models in systems biology (e.g., as discussed in [33]),
- the collaborative graphical authoring of routes of physiology communication (e.g., brain circuits) and, crucially,
- the automated discovery of transport routes given (i) a fixed- location receptor and (ii) its corresponding ligand, found elsewhere in the body.

Above all, our aim is to ensure that ApiNATOMY is easy to use for biomedical professionals, and available across a wide range of platforms, to foster collaborative exchange of knowledge both within, and between, physiology communities.

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