Model Formulation

Modeling Functional Neuroanatomy for an Anatomy Information System

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Abstract
Objective: Existing neuroanatomical ontologies, databases and information systems, such as the Foundational Model of Anatomy (FMA), represent outgoing connections from brain structures, but cannot represent the “internal wiring” of structures and as such, cannot distinguish between different independent connections from the same structure. Thus, a fundamental aspect of Neuroanatomy, the functional pathways and functional systems of the brain such as the pupillary light reflex system, is not adequately represented. This article identifies underlying anatomical objects which are the source of independent connections (collections of neurons) and uses these as basic building blocks to construct a model of functional neuroanatomy and its functional pathways.

Design: The basic representational elements of the model are unnamed groups of neurons or groups of neuron segments. These groups, their relations to each other, and the relations to the objects of macroscopic anatomy are defined. The resulting model can be incorporated into the FMA.

Measurements: The capabilities of the presented model are compared to the FMA and the Brain Architecture Management System (BAMS).

Results: Internal wiring as well as functional pathways can correctly be represented and tracked.

Conclusion: This model bridges the gap between representations of single neurons and their parts on the one hand and representations of spatial brain structures and areas on the other hand. It is capable of drawing correct inferences on pathways in a nervous system. The object and relation definitions are related to the Open Biomedical Ontology effort and its relation ontology, so that this model can be further developed into an ontology of neuronal functional systems.

Introduction
Functional Anatomy is concerned with anatomical entities grouped together to perform a physiological function. In Functional Neuroanatomy, a typical example is the visual system. Neuroanatomy textbooks are usually illustrated with drawings similar to the ones in Figure 1 which exhibit an important peculiarity of Functional Neuroanatomy: the main focus is not on single anatomical entities, such as in the musculoskeletal system, but on collections of uniform entities, neurons, which are considered its functional units. In textbook illustrations they are usually visualized as blobs. In the text, however, adequate expressions such as “a collection of neurons within the lateral geniculate body projects to a collection of neurons within area 17” are unusual. Such expressions are precise, but clumsy. Instead, the same scenario is expressed as “the lateral geniculate body projects into the area 17.” This compromise, however, obscures some detail—especially when the anatomical entities being described are constituted, in reality, by several qualitatively different collections of neurons.

A symbolic representation of anatomy—especially for didactic purposes—should represent facts on a comprehensible, but detailed level, and yield output on the level of object names. To this end, we here diligently define both levels, and establish the transition rules between them. The model presented here is derived from an approach that had been implemented in the early anatomy e-learning system “Anatom-Tutor”\(^1\) and is put into the context of current ontologies such as the Foundational Model of Anatomy (FMA).

Background
Representations of Anatomy and Neuroanatomy and Their Respective Focus
The organization of the nervous system of various species is currently represented in several large systems. NeuroNames is a nomenclature of human and macaque brain structures,
designed as a tool for indexing digital databases of neuroscience information. It was started in the late 80's as a MacIntosh hypercard stack and has since been developed into a web-accessible database. Its primary objects are anatomical entities identified by names.

The Foundational Model of Anatomy (FMA) is a frame-based ontology, originally designed to represent the macroscopic anatomy of the human thorax. It was assumed that this would cover all complexities of anatomy, and in this way the model could later be easily extended to other body areas and to other granularity levels such as cellular and subcellular structures. When incorporating neuroanatomy from NeuroNames, the authors themselves encountered diverse problems with this approach. The Foundational Model was further enhanced to accommodate so-called input/output relationships in order to represent the flow of information through the nervous system. The corresponding slots “Gets Input From” and “Sends Output To” are, however, not restricted in terms of domain and range constraints. For example, the class “organ region” has this slot. Most neuroanatomical objects are listed under this class, but also others such as “auricle of heart” and “segment of tooth.” Furthermore, it is not distinguishable whether two connections which an object exhibits are collaterals or whether they originate in different populations of neurons within the object. Therefore, an important subfield of neuroanatomy, viz. functional neuroanatomy, which is concerned with pathways and systems, cannot readily be represented in the FMA in its current form.

Brain Architecture Management System (BAMS) and Brainmaps.org are web accessible repositories and digital atlases on neuroanatomy, containing each a compilation from different atlases and for different species. Both contain data on connections, and in both, like in the FMA, collaterals cannot be distinguished from axons originating in different neuron populations.

Other web accessible anatomy information resources: Kim et al. have recently conducted a review of 40 online resources on anatomy, most of them aimed at education. Six of them are dedicated to Neuroanatomy, four of which still in service (see Table A1 in the online appendix, available at http://www.jamia.org). None of them contains explicit information on functional systems. Other recent neuroanatomy teaching systems are Brain Project/3D-Brain 2.0 and BrainTrain. Like the other resources cited above, these do not represent neural connections in functional systems.

In summary, the aforementioned neuroanatomical systems address nomenclature, hierarchical taxonomy, part-of hierarchy, connections, cytoarchitecture, and different mappings of the cortex. In all of them the primary objects of representation are macroscopic, morphologically-defined anatomical

**Figure 1.** A. Pupillary light reflex (crossover connections not shown). a: group of neuron cell bodies in the retina. b: group of axons. c: branching of the axons. d: branch leading to the pretectal nucleus. e: connection to a group of cell bodies in the parvocellular oculomotor nucleus. f: fibers running in the oculomotor nerve. g: connection to a group of cell bodies in the ciliary ganglion. h: termination in the sphincter muscle of iris. B. Accommodation reflex (crossover connections not shown). a: group of neuron cell bodies in the retina. b: group of axons. c: connection in the lateral geniculate body. d: connections within the area-17, and subsequent connection to a group of cell bodies in the pretectal nucleus. e: connection to a group of cell bodies in the parvocellular oculomotor nucleus. f: fibers running in the oculomotor nerve. g: connection to a group of cell bodies in the ciliary ganglion. h: termination in the ciliary muscle. C. The pathways combined. An anatomy information system must represent at least all the information illustrated in this picture: Two different pathways involving different groups of neurons in the pretectal nucleus, the parvocellular oculomotor nucleus and the ciliary ganglion. 1: nasal half of the right retina. 2: temporal half of the right retina. 3: optic nerve. 4: optic chiasm. 5: optic tract. 6: lateral geniculate body. 7: Brodmann area 17 (area striata, primary visual cortex). 8: pretectal nucleus. 9: parvocellular oculomotor nucleus. 10: ciliary ganglion. 11: ciliary muscle. 12: sphincter muscle of iris. All drawings by the authors in the style of textbook illustrations.
structures. Their main disadvantage is their inability to represent internal subgroups of neurons and their connections, the “internal wiring” of neuroanatomical objects.

Formal Ontologies

Both terms and relations in an ontology have to be well-defined so that automated reasoning becomes feasible and yields meaningful results (see Smith et al., 2005). Recently the Open Biomedical Ontologies (OBO) consortium has compiled the OBO ontology library, a repository of controlled vocabularies developed for shared use across different biological and medical domains. Smith et al. reviewed the definition and use of relations in these ontologies and found, that even the most basic relations part-of and is-a are not always used in consistent fashion both within and between ontologies. The authors then proceeded to define an “ontology of relations,” which we will use here as a starting point.

Defining Anatomical Objects as Counts, Collections, Mass, etc.

The idea proposed in this paper is to define the basic concepts of functional neuroanatomy in terms of groups of uniform objects. This idea is related to the works of Bittner, Rector et al., who suggested the description of the relation between collectives of uniform objects and each of their single constituents as has-granular-part, a subrelation of has-part.

Functional Anatomy

Johansson et al. have introduced “pure structural anatomy” and “pure functional anatomy” as perspectives on anatomy. They argue that there are two ways to draw boundaries between spatial parts of the body: structural and functional. After defining the functional parts the authors state: “A part-of relation between such spatial-functional entities goes parallel to a sub-function relation among the functions associated to the spatial-functional entities”. Niggemann outlined a similar perspective with respect to neuroanatomy, from the point of view of knowledge representation. He argued that the spatial dimension is not even necessary in order to define a “functional object” (however, this topic is beyond the scope of this article).

Example: The Visual System

Our model is introduced using the visual system as an example. We concentrate on the reflex systems of the pupillary light reflex and the accommodation reflex (Fig 1). Both reflex arcs involve a group of neurons in the paravascular oculomotor nucleus which send their signals (efferences) to a group of neurons in the ciliary ganglion (e, f, g in Figures 1A and 1B). Important to note is that the two reflex arcs involve two different groups of neurons in the pretectal nucleus, the paravascular oculomotor nucleus and the ciliary ganglion.

The sentence “The paravascular oculomotor nucleus sends output to the ciliary ganglion” is correct in both reflexes, but this information alone is not sufficient to distinguish between the two reflex arcs. We need a way to represent different connections within the structures, such as they are depicted in Fig. 1C. In general, we want to represent the most detailed information available. For this purpose we introduce a model which represents groups of neurons, as well as groups of neuronal cell bodies and groups of neuronal axons with their myelin sheaths.

Model Formulation

The model we are proposing addresses specific aspects of Neuroanatomy. This model is meant to be useful under many perspectives: both on an instance (token, individual, particular) and a class (type, concept, universal) level, and—from a philosophical perspective—both under a “conceptualist” and a “realist” point of view. The model of anatomical groups is introduced in an atemporal way, as we intend to model one idealized, prototypical, “normal” instance of a human nervous system at one specific point in time. This is the perspective taken e.g., in anatomical atlases, which introduce general “classes” such as “flat bone” but then describe every bone in the body as one instance of such a class. We introduce the terms GROUP and INDIVIDUAL with the relations has-member and member-of. From the OBO relations ontology we choose the following ones as primitive relations in our model: part-of, located-in, adjacent, instance-of, is-a. (New terms which we introduce as names of classes/universals are printed in small caps, such as FUNCTIONAL-GROUP. We consider relations between instances only, they are printed in italics.)

Analyzing the Underlying Structures

In order to express “groups of neurons” and “groups of neuron parts,” we start with a brief inspection of the underlying particulars, the neurons themselves. We do this on the “cell” and “subcellular” levels of granularity. Here we look at a neuron and its relevant segments, and then define the basic relations of adjacency and efference. Afterwards, we can transpose these definitions into the higher granularity level of groups, which lies between the “cell” and the “tissue” granularity levels.

Nerve cells (neurons) are the individual information processors of the neural system. Figure 2 depicts a typical neuron. It has a long process, the axon, which conducts electric signals to target cells (targets can be other neurons or effectors such as muscle cells). Every axon is part of some neuron. Most axons are covered by a myelin sheath which consists of cells or parts thereof. An axon together with its myelin sheath is called a fiber. Fibers can be partitioned into segments according to the Ranvier’s nodes in the myelin sheath. The segment of a fiber between two nodes is called the internodal segment. The terminals of the fiber form part of the conducting connection to the target cell. The connection or synapse overlaps the source neuron as well as the target cell. The central part of the neuron which includes the cytoplasm, cell nucleus and the surrounding plasma mem-

Figure 2. Schematic depiction of a neuron. 1: cell body, 2: axon, 3: schwann’s cell, 4: ranvier’s node, 5: branching of the axon, 6: terminals.
brane but excludes the axon, dendrites (see below) and any other neurites is called the cell body. Many neurons also have dendrites: protuberances to which synapses connect and which conduct the excitation to the cell body. In this functional model, it is irrelevant whether a terminal connects to a dendrite or directly to the cell body, we therefore abstract from this detail.

**Definition (R-Segment, Fiber-Segment)**

The smallest functional segment of a fiber is an internodal segment together with its following node; we will give it the name R-Segment. We also need to define fiber segments of arbitrary length: A Fiber-Segment is one R-Segment or a sequence of connected R-Segments, possibly ended with a terminal.

This definition is needed when we want to express the meaning of sentences like: “The fibers originating in the retina run through the optic nerve”. This can be translated as “Each of the fibers has some Fiber-Segment as part which is spatially located-in the optic nerve”.

**Definition (Neuron-Structure)**

We define as Neuron-Structure all sections of a neuron introduced in the previous description and definition.

**Relations Between Neuron-Structures**

The relations between the cell-structure-level objects serve as an orientation for defining relations between group objects.

**Definition (Efferent-to, Afferent-to, Direct-efferent-to, Direct-afferent-to)**

Neuron-Structures pass electrical excitation:

A Neuron-Structure is in relation efferent-to another one, if and only if it passes signals to it. Efferent-to is a transitive relation. Direct-efferent-to is a subrelation of efferent-to, it additionally requires spatial adjacency and therefore is not transitive. The same holds for the inverse, afferent-to and direct-afferent-to.

A neuron is in relation direct-efferent-to another one, if and only if it has as a part a terminal, which is direct-efferent-to, the second neuron.

**From Neuron-Structures to Groups**

Now the transition is made from Neuron-Structures to groups. To achieve this, we will define an equivalent in the group level for each object and each relation on the Neuron-Structure level (Fig. 3). We uniformly name all group objects with the postfix “-group”.

**Functional-Group** is the common subsumer of all groups that can be derived from the Neuron-Structures defined above, together with groups of neurons themselves. It can be defined more generally by use of the criteria of a common connection pattern or participation in a common function. Fig. 4 shows a taxonomy of the classes defined in this section.

**Definition (Functional-Group)**

A Functional-Group is a collection of neurons or neuron segments of the same type, such that:

a) all members of the group share a common connection pattern (they are recipients of input from the same source or have output/efference to the same target or any combination thereof)

b) 1) all share a given location, or

2) the group as a whole is bearer of a (sub-) function, all its members are capable of contributing to the group’s function

c) the group contains (his-member) all individuals which share these properties.

A Functional-Group is therefore a kind of “ObjectAggregate” as defined in the Basic Formal Ontology (BFO)21,22 as “An independent continuant that is a mereological sum of separate objects and possesses non-connected boundaries”. Similarly, the definition of Functional-Group is consistent with Simons’ notation of “group.”23

**Relations between Functional-Groups**

We define two sets of relations between Functional-Groups. One describes relations with respect to signal conduction, the other with respect to their members.
Definition (Relations with Respect to Connections)
The same relations that are defined for Neurons and Neuron-Structures can be used between Functional-Groups:

efferent-to/efferent-to: We define efferent-to as the transitive relation which represents signal passing. A Functional-Group \(g_1\) is in relation efferent-to to another Functional-Group \(g_2\) if and only if for every member \(m_1\) of \(g_1\), there is a member \(m_2\) of \(g_2\) such that \(m_1\) efferent-to \(m_2\), efferent-to is the inverse relation.

direct-efferent-to/direct-afferent-to: Similarly, the non-transitive relations direct-efferent-to/direct-afferent-to can be derived from the underlying Neuron-Structures: A Functional-Group \(g_1\) is in relation direct-efferent-to to another Functional-Group \(g_2\) if and only if for every member \(m_1\) of \(g_1\), there is a member \(m_2\) of \(g_2\) such that \(m_1\) direct-efferent-to \(m_2\), direct-afferent-to is the inverse relation.

Definition (Mereological Relations)
subgroup-of: A Functional-Group \(g_1\) is subgroup-of another Functional-Group \(g_2\) if and only if every member of \(g_1\) is also member of \(g_2\). Thus the subgroup-of relation corresponds to a part-of relation between groups.

overlap: A Functional-Group \(g_1\) overlaps another Functional-Group \(g_2\) if and only if there is at least one member of \(g_1\) which is also member of \(g_2\).

equal: Two Functional-Groups are equal if and only if they have exactly the same members.

sum: A Functional-Group \(g_1\) is sum of Functional-Groups \(g_2\) and \(g_3\) if and only if every member of \(g_1\) is also member of \(g_2\) or \(g_3\) and both \(g_2\) and \(g_3\) are subgroups of \(g_1\).

Subclasses of Functional-Group
Definition (Group of Complete Neurons: Neuron-Group)
A group of neurons will be called Neuron-Group.

Definition (Group of Cell-Bodies: Cell-Body-Group)
A Cell-Body-Group is a group of cell bodies, all of which share a common function or common connections. Therefore, looking at functions and subfunctions or at connections in different levels of granularity leads to different formations of Cell-Body-Groups.

Definition (Group of Fibers: Fiber-Group)
Fiber-Group refers to a group of complete fibers (axons with myelin sheath if applicable) from cell bodies to terminals. Note that a complete fiber is a (maximal) Fiber-Segment, such that Fiber-Group must be considered a subtype of Fiber-Segment-Group.

On the group level like on the Neuron-Structure level we need to define a smallest (functional) segment of a Fiber-Group. We derive this from the smallest (functional) segment of a fiber, the R-Segment. So we can define:

Definition (Group of R-Segments: Atomic-Fiber-Segment-Group)
An Atomic-Fiber-Segment-Group is a group of parallel R-Segments within the same Fiber-Group.

Definition (Group of Fiber-Segments: Fiber-Segment-Group)
A Fiber-Segment-Group is a collection of parallel Fiber-Segments.
Validation through Example

Proof of Completeness, Correctness, Novelty and Advantage

In this section we will prove that the Functional-Group model is a valid and useful extension to models such as the FMA or BAMS. We use the example of the visual system to illustrate the steps of the proof.

Claim: Augmenting a current model such as the FMA with the Functional-Group model

1. does not lead to any loss in information or capabilities
2. adds functionality which these models currently do not have

In order to prove that the Functional-Group model can indeed add functionality to current models, we choose the FMA as an example and take the following steps:

1. We show that the current FMA can be transformed into the Functional-Group enhanced format. Especially, we show that
   a) this process can be reverted, which proves that no information is lost in the conversion (completeness)
   b) the classes which are automatically added correctly reflect anatomical reality (correctness)

2. We prove that in the Functional-Group enhanced FMA, additional information (namely internal wiring) can be stored
   a) which could not be stored in the original FMA (novelty)
   b) which allows inferences that could not be drawn in the original FMA (advantage)

The complete proof is given in the online appendix. Here we outline the main steps.

1. Transformation of the FMA into a Functional-Group enhanced format

The transformation mainly involves

1. Augmentation of the class hierarchy by the classes defined in section IV
2. Processing of all “Sends Output To” links

The result is illustrated in Fig. 5A and B: The information contained in the former “Sends Output To” links (Fig. 5A) is now represented by Functional-Groups contained in the objects and their efferent-to connections (Fig. 5B). The detailed proof also shows that the original information can be recovered from the extended form. The process corresponds to redefining the relation “Sends Output To” as in Definition (receives-input-from, sends-output-to) in section IV.

Completeness: As we have only added classes, nothing is lost in this step. The original information in the “Sends Output To” links can be recovered, proving that no information is lost.

Correctness: As outlined in section IV, the new classes by design correctly reflect anatomical entities. Since the procedure introduces new objects (the individual Functional-Groups and their relations), we must prove that these reflect anatomical reality. It is a fundamental truth in neuroanatomy, that every neuronal signal

![Figure 5. Two-step augmentation of FMA models by Functional-Group information. A. A situation as it occurs in the original FMA: macroscopic anatomical objects (FMA classes) are linked by “Sends Output To” links. These links can (by design) not carry any additional information. B. Each “Sends Output To” link has been replaced by a Neuron-Group. This replacement can be done automatically. It does not yet add any information. C. The structure of the new model allows collators to add Neuron-Groups and direct-efferent-to links between Terminal-Groups and Cell-Body-Groups in one macroscopic object. This way, different pathways can be kept apart.](http://jamia.oxfordjournals.org/)
macroscopic anatomical objects. In the extension however, the connections are represented by objects within the macroscopic anatomical objects (FUNCTIONAL-GROUPS) which can again be linked to each other (direct-efferent-to). Therefore, internal connections within a macroscopic anatomical object can only be represented in the extension.

Advantage: Representing internal connections is a basic step for distinguishing known pathways from candidate pathways (see next paragraph).

2. Known Pathways and Functional Systems

The FUNCTIONAL-GROUP extension allows one to distinguish between complex known pathways and candidate pathways, and to represent complete functional systems such as the accommodation reflex system as in Fig. 1C.

Novelty: In current models such as FMA or BAMS, candidate pathways can be generated by recursively following “Sends Output To” links. It is not guaranteed that these candidates represent any anatomical or physiological reality. In contrast, the addition of the “internal wiring” of direct-efferent-to links between TERMINAL-GROUPS and CELL-BODY-GROUPS where these are known, allows the enhanced model to discern different functional systems.

Advantage: Known pathways can be represented and can be searched and followed, and they can be discerned from candidate pathways. One of the most important kind of entities in functional neuroanatomy, functional systems, can now be represented. A detailed example of how the system follows a known pathway is given in section “Following pathways in the FUNCTIONAL-GROUP model versus FMA and BAMS” in the online appendix.

3. “White matter” pathway information

The resulting pathway structures can also represent the path that a connection takes through “white matter” structures (those that primarily contain axons or parts thereof). Fig 1 shows the structures through which fibers from the retina pass on their way to the lateral geniculate body (numbers 3–5 in Fig. 1C). With the FUNCTIONAL-GROUP extension, this information is now explicitly represented so that an information system can output information like “fibers from the retina run through the optic nerve, the optic chiasm, and the optic tract.” This is equivalent to the statement “each of the Fibers has a Fiber-Segment as part which is spatially located-in the optic nerve, the optic chiasm, and the optic tract.” Details are given in the online appendix.

Novelty: The “Continuous With” relation of the original FMA is not constrained to objects of neuroanatomy; it is also used to link blood vessels, tendons etc. Therefore, the “white matter” pathway information can only be correctly represented using the FUNCTIONAL-GROUP extension.

Advantage: An anatomical information system containing this information can be used to reason about and to teach structure-function relationships such as consequences of lesions to white matter structures.

In summary, we have shown that the FUNCTIONAL-GROUP extended FMA can store information and draw conclusions, which the design of the original FMA does not allow. This proves claim 2 and completes the proof that the FUNCTIONAL-GROUP model is a valid and useful extension of the FMA.

Discussion

The FUNCTIONAL-GROUP model has been designed to address the topology of neural connections as a specific aspect of Neuroanatomy. So far we have presented a basic form of the model. Three aspects need further attention: The usability of the model with incomplete information, the specific phenomenon of the cross-connection of pathways, and the addition of more aspects of neuronal connections such as the transmitters involved.

Use with Incomplete Information, and Aggregation of Scientific Results

The steps described in the section “Validation Through Example” illustrate how incomplete information is handled: when embedded in a “host system” such as the FMA, it is first set up to reconstruct that system’s “Sends Output To” information. That information is necessarily incomplete because information about internal wiring is lacking. In this stage, candidate pathways are found by assuming links from every incoming to every outgoing connection of an object. When scientific results about internal connections become available, these can be added to the model as described in the step “Adding new information,” thus enabling the model to represent known pathways and distinguish those from candidate ones.

The Cross Connection of the Pathways

Bright light causes a constriction of the pupil but not simultaneously an accommodation reaction. However, looking at nearby objects also leads to a constriction of the pupil. This observation is a subject matter of physiology and, as such, not directly represented in a neuroanatomical model. Together with the general axiom that in the nervous system there is no function without connection, we can conclude that “there is some connection from at least one CELL-BODY-GROUP involved in the accommodation pathway to at least one other that is involved in the pupillary reflex pathway.” This first-order logic statement can not be represented in the FUNCTIONAL-GROUP model (nor can it be represented in one of the other models mentioned). As soon as it is known which MACROSCOPIC-NEUROANATOMICAL-ENTITY contains this cross situation, the situation can be modeled, for example by adding a collateral from an incoming connection belonging to the accommodation reflex to the CELL-BODY-GROUP of the pupillary light reflex, or by establishing other internal wiring as the scientific results suggest.

Scope and Possible Extension: More Detailed Description of Signal Transmission

Apart from the visual system, this approach has been successfully tested with representations of the vestibular system, the auditory system, the accessory nerve system, long corticofugal tracts of the motoric systems, the extrapyramidal motoric system, the central limbic continuum, ascending reticular tracts, efferent connections of the cerebellum and thalamo-cortical connections.

In its basic form, as presented here, the model only represents the “bare” connections from terminal to target cell. It does not represent dendrites, different kinds of synapses, or different neurotransmitters. In a more advanced form, our model can be expanded to cover such details. The existing objects can then be enriched with attributes such as “adrenergic,” and new intermediate objects can be introduced...
between synapse and target cell bodies in order to represent dendrites. Further extensions can express characteristics of signal conduction in the fibers and modulations thereof by axo-axonal synapses.

**Conclusion**

We have proposed a model based on groups of cells or cell parts, which serves to represent neuronal connections between brain structures in more detail than it has been thus far possible. The model is capable of drawing valid inferences on pathways in a nervous system. In combination with an ontology of functions, the group-oriented model of functional neuroanatomy can be the starting point for a comprehensive ontology of functional pathways in nervous systems, and can thus augment the Foundational Model of Anatomy when used in an anatomy information system.

**References**