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Review

The neuron classification problem

*Mihail Bota, Larry W. Swanson**

Department of Biological Sciences, University of Southern California, 3641 Watt Way, Los Angeles, CA 90089-2520, USA

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ABSTRACT

A systematic account of neuron cell types is a basic prerequisite for determining the vertebrate nervous system global wiring diagram. With comprehensive lineage and phylogenetic information unavailable, a general ontology based on structure–function taxonomy is proposed and implemented in a knowledge management system, and a prototype analysis of select regions (including retina, cerebellum, and hypothalamus) presented. The supporting Brain Architecture Knowledge Management System (BAMS) *Neuron ontology* is online and its user interface allows queries about terms and their definitions, classification criteria based on the original literature and "Petilla Convention" guidelines, hierarchies, and relations—with annotations documenting each ontology entry. Combined with three BAMS modules for neural regions, connections between regions and neuron types, and molecules, the *Neuron ontology* provides a general framework for physical descriptions and computational modeling of neural systems. The knowledge management system interacts with other web resources, is accessible in both XML and RDF/OWL, is extendible to the whole body, and awaits large-scale data population requiring community participation for timely implementation.

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* *Corresponding author.*
E-mail address: lswanson@usc.edu (L.W. Swanson).

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1. Introduction

The first requirement for understanding how a machine or system works is a list of parts and account of how they are connected. Systematic classification of animals, and their parts and relationships, is a cornerstone of biology pioneered by Aristotle 2300 years ago. General approaches today emphasize organizing principles of time and lineage elaborated by Darwin for species evolution and Baer for embryonic development in the 19th century (Russell, 1916). Histology and cell type classification have benefited especially from lineage analysis, as exemplified by differentiation of the embryonic trilaminar plate or adult hematopoietic stem cells (Standring, 2005).

One glaring exception is the vertebrate nervous system, a uniquely intricate biological network coordinating and controlling fundamental bodily mechanisms assuring survival of individuals and their species through integrated reflex and voluntary responses. Here lineage analysis has contributed relatively little beyond identifying two daughter cell types (neurons and glia) generated from embryonic neuroepithelial stem cells and their regionalization patterns in neural plate, tube, and crest (Brown et al., 2001). Qualitative estimates suggest the adult mammalian nervous system is constructed ontogenetically from 2500 to 5000 classes of neurons generating 25,000–100,000 stereotyped axonal macroconnections between them (Bota et al., 2003). Compared to the relatively simple invertebrate, *C. elegans*, where the lineage and structure of all 302 adult neurons are established (Sulston et al., 1983; White et al., 1986), only relatively crude lineage data will be available any time soon for the mammalian nervous system. Instead, there is not even a satisfactory definition of neuron cell type, with terms like “class”, “subclass”, “type”, and “subtype” often used interchangeably without proper definition (Cook, 1998; Masland, 2004). Obviously, a systematic account of neuron cell types is a prerequisite for establishing the nervous system's basic wiring diagram and determining the functional significance of molecular mechanisms in specific circuit elements.

1.1. *A general solution*

Research extending back to Aristotle indicates the vertebrate nervous system is an elongated bilateral structure parceled into distinct gray matter regions interconnected by fiber (“white matter”) tracts (Swanson, 2003) (Fig. 1a, left)—a necessary macroscopic level of description equivalent to using maps for geographic localization or discussing the heart physically in terms of four contractile chambers and a

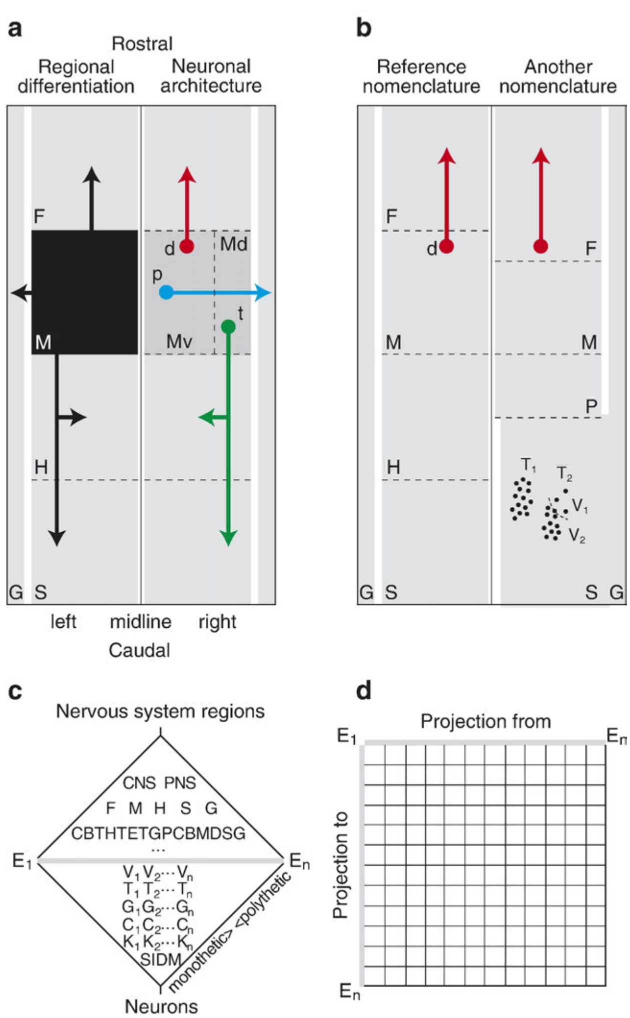

Fig. 1 – A systematic account of nervous system parts and connections. (a) Schematically the vertebrate nervous system has right and left halves with rostral and caudal ends, divided into gray matter regions (G, F, M, H, S) interconnected by fiber tracts (black arrows from black box region M, left half). Each region is actually characterized by a set of neuron types (d, p, t for region M, right half) with a stereotyped pattern of axonal projections forming the tracts, and typically also a neuron-type set generating strictly intraregional axon connections (local interneurons, not shown; see panel b right half). Mathematically, the number of projection possibilities is given by the combinations of axons and axon collaterals between pairs of neuron types from different regions. Let $X=\{A_i,\ldots,A_k\}$ the set of gray matter regions, each having $n_j; j\overline{1,k}$ neuron types. The number of neuron type pairs connected by axons or axon collaterals is $P=\sum_{i=1}^{k}\sum_{j=1}^{k} n_i n_j; i\neq j$ and the number of possible combinations is $C=\sum_{i=1}^{P}\frac{P!}{(P-i)!i!}$. Experimentally, physical connections are established currently with anterograde and retrograde tracer methods, which may help subdivide regions (Md, Mv). (b) Historically, disagreement is common about region boundaries, profoundly affecting description and interpretation of experimental results; here in a reference nomenclature neuron type d projects from region M to F, whereas in another nomenclature the same neuron type is described as having local connections in region F. (c) A complete ontology of nervous system regions and neuron types could be represented as two reference hierarchies meeting at the lowest level of each (see text and example in Fig. 3). (d) Finally, the global nervous system connection matrix is defined by data for each neuron type (or region) in a complete reference nomenclature (entities E_1–E_n) taken from (c).

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