Review

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Towards the automatic classification of neurons

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The classification of neurons into types has been much debated since the inception of modern neuroscience. Recent experimental advances are accelerating the pace of data collection. The resulting growth of information about morphological, physiological, and molecular properties encourages efforts to automate neuronal classification by powerful machine learning techniques. We review state-of-the-art analysis approaches and the availability of suitable data and resources, highlighting prominent challenges and opportunities. The effective solution of the neuronal classification problem will require continuous development of computational methods, high-throughput data production, and systematic metadata organization to enable cross-laboratory integration.

Data descriptors to classify neuronal types

Neuronal type classification is an increasingly hot topic, but its history began with neuroscience itself [1]. Researchers routinely refer to pyramidal, stellate, granule, bipolar, or basket cells, but these names are often insufficient to describe neuronal diversity even within limited brain areas. Realizing this issue, both the European Human Brain Project and the American BRAIN initiatives identified cell type classification among their first priorities [2,3]: 'to complete a comprehensive cell census of the human brain'. The ultimate endeavor is to link neuronal types with behavior, computation, and eventually cognition. Prominent international efforts proposed initial guidelines to help to organize the growing body of knowledge [4]. However, manual classification attempts are ill-equipped to deal with big data. The magnitude and complexity of neuronal classification demands high-throughput technologies.

Neuroscience and computer science are mature to tackle neuronal classification by powerful mathematical approaches. Several recent studies have leveraged modern computational methodologies to considerably advance the state-of-the-art [5–26]. Increasing integration of machine learning techniques with microscopic, chemical, and functional methods has already pushed bioinformatics to new heights [27]. While neuroscience is rapidly transitioning to digital data [28,29], the principles behind automatic classification algorithms remain often inaccessible to neuroscientists, limiting the potential for breakthroughs.

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Neurons are typically characterized by their morphology, physiology, and biochemistry (Figure 1). These principal experimental approaches reflect the most-prominent available techniques, namely microscopic imaging, electrical recording, and molecular analysis. These investigation domains also constitute proxies for key attributes of neuronal identity: axonal and dendritic structures establish the means for network connectivity; neuronal expression profiles provide a window onto developmental origins; and electrophysiological properties underlie signal processing. Furthermore, these features are intimately intertwined. The macromolecular machinery sculpts both neuronal excitability and circuitry, and these together define computational functions. The difficulty of the problem increases even further when considering systematic differences between species, across brain areas, and throughout development. However, even for the most common animal models, for well-defined regions of the nervous systems, and confined age ranges or developmental stages, the available information on neuronal identity has so far failed to yield a broadly agreed-upon approach to neuronal classification.

Much as 'parts lists' precede 'exploded diagrams' in assembly-kit manuals, the objective identification of neuronal types is essential to understanding their functional interactions [30–32]. After formally introducing automatic neuronal classification, we review exemplary progress, from foundational breakthroughs to recent trends, that provide useful pointers to available informatics tools. We then highlight current opportunities and challenges in neuronal classification before discussing the transformative prospects of forthcoming big data.

Automatic neuronal classification

The term 'classification' is often used with two related but distinct meanings when referring to neuronal types. In the narrower sense, neuronal classification is the process of dividing a group of neurons into known classes, as exemplified by the task of distinguishing between excitatory and inhibitory cells. The second usage of the term encompasses the above classification proper as well as the identification of the classes themselves, a step sometime referred to as categorization. This broader connotation implies the definition of distinct neuronal types and the simultaneous assignment of neurons to each type.

This work reviews the automatic classification of neurons from quantitative measurements. The emphasis on minimized human intervention complements qualitative

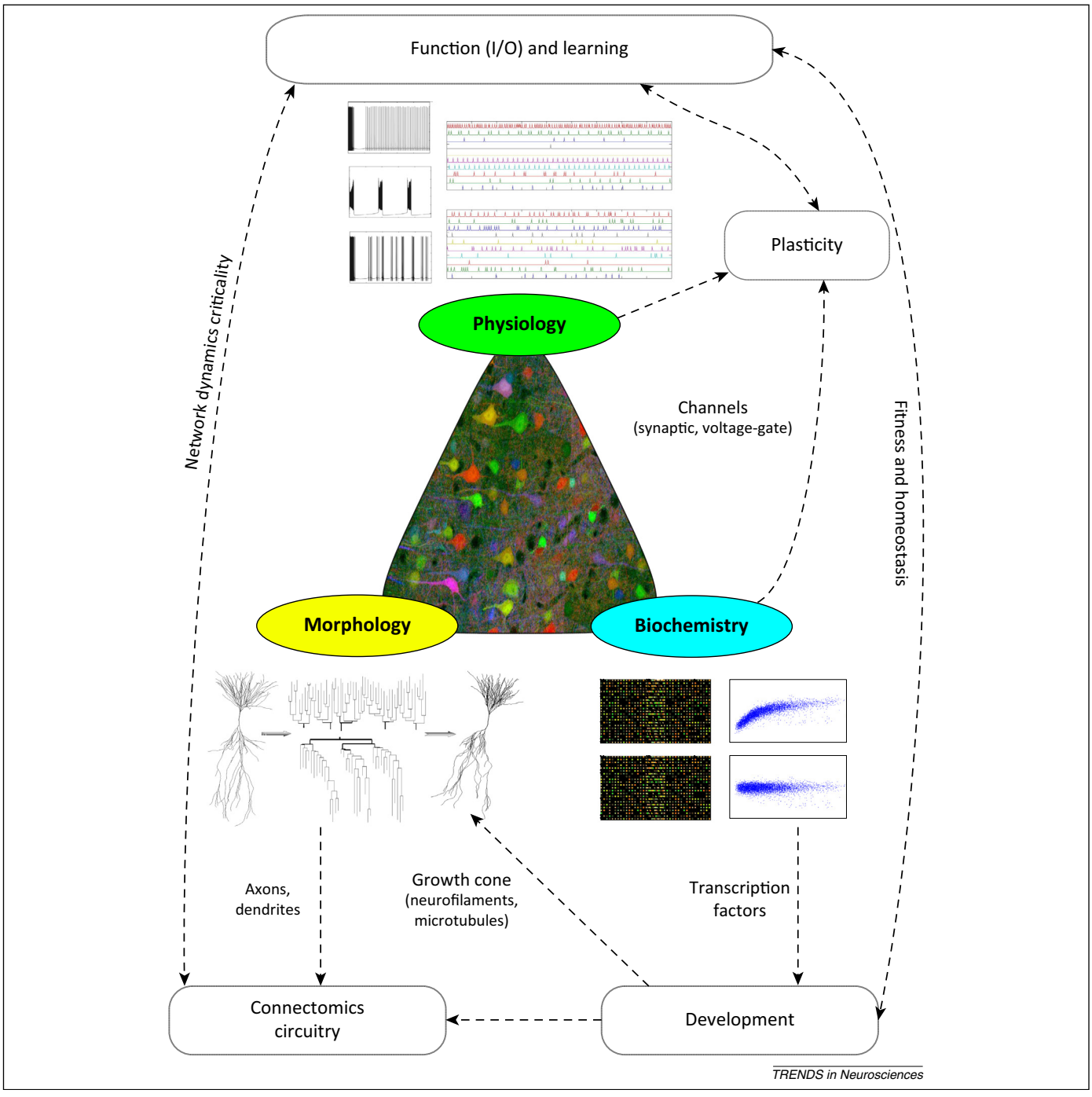

Figure 1. Basic dimensions of neuronal characterization: morphology (yellow), physiology (green), and biochemistry (blue). These feature domains are tightly interrelated with other fundamental aspects of neural identity, such as connectivity, development, and plasticity.

descriptions of neuronal types based on expert knowledge (e.g., [33]) as well as computational models of the biophysical mechanisms differentiating between neuronal types (e.g., [34]). Automatic classification is primarily data-driven and hence largely blind to the researcher.

Formally, a neuronal classification dataset D (see Box 1 for a glossary of machine learning terms) consists of a set of k observed neurons, each described by $(n + 1)$ variables. The first n variables, known as predictive variables, are measurements on the neurons. The last variable, referred to as the class variable, specifies the neuronal type. A classifier is a function γ assigning labels to observations:

$$\gamma : (x_1, \ldots, x_n) \rightarrow 1, 2, \ldots, m,$$

where the n-dimensional vector $\boldsymbol{x} = (x_1, \ldots, x_n)$ contains the values for all measurements of a particular neuron, and $\{1, 2, \ldots, m\}$ are the possible neuronal classes. The real class of the given neuron, usually denoted c, is a value in that range. The assumed (but unknown) joint probability distribution $p(x_1, \ldots, x_n, c)$ underlying the observations can be estimated from the sample $\{(\boldsymbol{x}^1, c^1), \ldots, (\boldsymbol{x}^k, c^k)\}$, where superscripts refer to neurons, and subscripts to measurements of those neurons.